Characterizing the Effect of CD388 Prophylactic Treatment on Influenza Viral Dynamics

Krish Penumarthi, Avir Sankara, and Hana M. Dobrovolny
Department of Physics and Astronomy, Texas Christian University, Fort Worth, USA

Background

- Influenza A virus (IAV) is a major public health concern; its rapid mutation rate reduces the effectiveness of vaccines and antivirals.
- CD388 is a novel long-acting neuraminidase inhibitor conjugate being evaluated as a prophylactic agent.
- Mathematical modeling is increasingly used to predict viral load dynamics and assess prophylactic treatments.
- The goal is to personalize mathematical models to individual patients to optimize treatment timing and dosing.
- We use an ordinary differential equation (ODE) model of influenza dynamics to assess the prophylactic effect of CD388 vs. placebo.

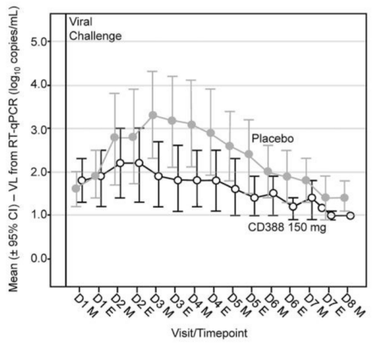
Objective

- Develop an ODE model to quantify within-host influenza dynamics in placebo and CD388-treated patients.
- Fit the model to human challenge study viral load data using nonlinear least squares optimization.
- Estimate biologically meaningful parameters and compare between treatment groups.
- Assess parameter uncertainty through bootstrapping.
- Determine whether there are statistically significant differences between treatment and placebo for any parameters.

Experimental Data

Data is taken from a phase 2a randomized, double-blind, placebo-controlled human challenge study:

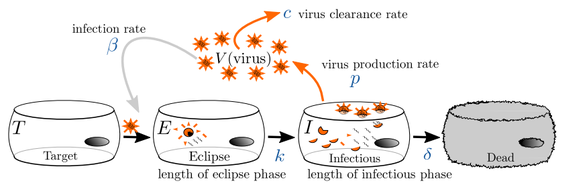
- CD388 is a first-in-class drug–Fc conjugate: multivalent dimers of zanamivir linked to human IgG1 Fc for extended half-life.
- Single subcutaneous dose of CD388 (150 mg) or placebo is given 5 days before intranasal H3N2 challenge.
- Nasopharyngeal swabs is collected twice daily (Days 1–8); viral load is measured by RT-qPCR.
- Mean viral load data extracted from Fig. 2A of Rojas et al. (2025) via WebPlotDigitizer.



[1] Rojas et al. (2025). Prophylactic Efficacy of CD388 in a Human Influenza A/H3N2 Virus Challenge Model. *Clin. Infect. Dis.*

Mathematical Model

The model has four compartments: uninfected target cells (T), eclipse-phase cells (E), productively infected cells (I), and free virus (V).



These processes are modeled using the system of ODEs:

$$\begin{aligned}\frac{dT}{dt} &= -\beta TV \\ \frac{dE}{dt} &= \beta TV - kE \\ \frac{dI}{dt} &= kE - \delta I \\ \frac{dV}{dt} &= pI - cV\end{aligned}$$

We are interested in estimating the following parameters for both treated and untreated patients:

- β – infection rate ($\mathrm{mL\,copies^{-1}\,day^{-1}}$)
- k – eclipse transition rate ($\mathrm{day^{-1}}$)
- δ – infected cell death rate ($\mathrm{day^{-1}}$)
- p – viral production rate ($\mathrm{copies\,cell^{-1}\,day^{-1}}$)
- c – viral clearance rate ($\mathrm{day^{-1}}$)

Fitting the Model to Data

- The model is fit to each group separately by minimizing SSR in $\log_{10}$ space:

$$\mathrm{SSR} = \sum_{i=1}^{n} \left(\log_{10}(V_{\mathrm{data},i}) - \log_{10}(V_{\mathrm{model}}(t_i;\boldsymbol{\theta}))\right)^2$$

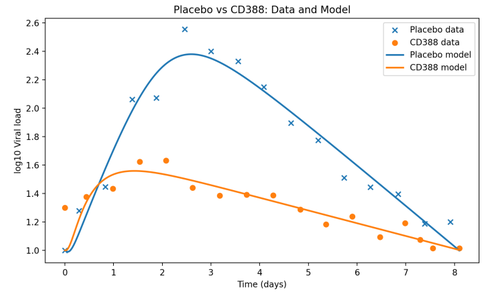
- We used the SciPy `minimize` function with the Nelder-Mead algorithm to find the minimum SSR.
- We assumed initial values for the variables of $T(0) = 1$, $E(0) = 0$, $I(0) = 0$, $V(0) = 10$.

Bootstrapping

- We used bootstrapping to determine the uncertainty in parameter estimates.
- Bootstrapping creates surrogate data sets by shuffling the residual errors and adding them to the model best fit prediction. This creates new data sets that have the same error as the original data set.
- The model is re-fit to the surrogate data to get a alternative set of possible parameter values.
- We use 1000 bootstrap replicates to get a distributions for each parameter value.
- The Mann-Whitney U-test is used to compare parameter estimates for the treated and placebo groups.

Results: Model Fits to Data

The fitted ODE model captures viral dynamics well for both groups ($\mathrm{SSR_{Placebo}} = 0.183$, $\mathrm{SSR_{CD388}} = 0.141$).



Solid lines closely match data for both groups. CD388-treated patients reach a lower peak viral load ($10^{1.56}$ vs. $10^{2.38}$ copies/mL) with ∼21.6% reduction in total viral burden (AUC).

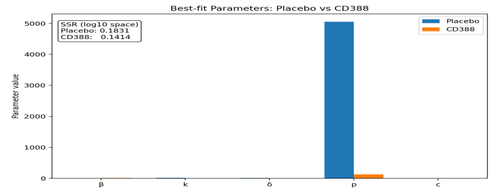
Infection Metrics

Metric	Placebo	CD388
Peak $\log_{10}(V)$	2.380	1.558
Time of peak (days)	2.60	1.43
AUC $\log_{10}(V)$	15.81	12.39
Duration $> 10^1$ (days)	7.98	8.09

Bootstrap uncertainty was estimated by perturbing best-fit parameters in log-space (Gaussian noise, $\sigma = 0.2$) and recomputing infection metrics over 1000 replicates. Welch's t-tests were used to compare AUC and duration distributions between groups.

Results: Model Parameters

Parameter	Placebo	CD388
β (infection)	7.02×10^{-3}	10.0
k (eclipse)	18.5	2.40
δ (death)	9.81	3.51
p (production)	5054	131.4
c (clearance)	0.679	0.207
SSR ($\log_{10}$)	0.1831	0.1414



The most striking difference is viral production rate p, ∼38-fold lower in CD388 patients, consistent with neuraminidase inhibition suppressing viral replication.

Conclusions

- The model captures overall viral dynamics well for both groups.
- CD388 reduces peak viral load by ∼1 $\log_{10}$ unit and total burden (AUC) by ∼21.6%.
- The ∼38-fold reduction in p is consistent with neuraminidase inhibition suppressing viral spread.
- Eclipse duration ($1/k$) is longer under CD388, indicating delayed productive infection onset.
- Individual patient-level fitting would better capture inter-patient variability.

Future Directions

- Perform structural and practical identifiability analysis on the ODE model parameters.
- Implement full data-resampling bootstrap for rigorous confidence intervals.
- Extend the model to include an explicit immune response.
- Apply to individual patient viral load curves to capture inter-patient variability.
- Compare fitted parameters to other neuraminidase inhibitors (e.g., oseltamivir).

SciCom Let's Talk Science

Influenza can cause serious respiratory illness and spreads quickly, so prevention matters. CD388 is a long acting antiviral taken before illness, but its effects on within host virus growth are not fully known. We built a mathematical model that tracks target cells, an eclipse phase, infected cells, and free virus, and fit it to human challenge viral load data for placebo and CD388 groups. The model matches overall data trends and estimates key infection parameters. CD388 lowered peak viral load and reduced total viral burden