Mathematical Modeling of Dengue Disease in Infants

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Topics

- Introduction
- The main objective
- The mathematical model
- Mathematical analysis
- Sensitivity analysis
- Numerical simulations
- Conclusions
- References

Introduction

Dengue fever (DF)

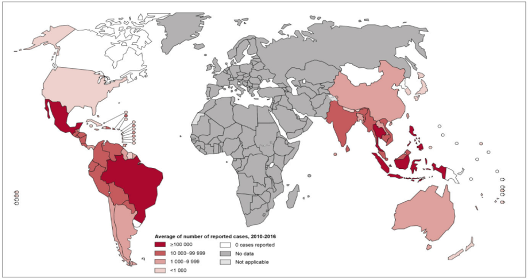
- DF: Classical form;
- Transmitted by infected female mosquito of genus *Aedes* (*A. aegypti* and *A. albopictus)*;
- 4 distinct serotypes of the Virus (DENV-1 – DEN-4).

Dengue control challenges:

1. No vaccine due to the co-circulation of different serotypes;
2. Unplanned and uncontrolled urbanization (Florentino, et al., 2014, 2019);
3. Mosquito resistance by insecticide (Kuniyoshi &, Santos, 2017),
4. Human mobility (Santos, F.L.P., 2017).

Spatial distribution of dengue cases

Distribution of dengue, worldwide, 2016



- Aedes mosquitoes are found in tropical and subtropical climates and urban areas;
- The Americas region reported more than 2.38 million cases in 2016.

WHO

Dengue Hemorrhagic Fever (DHF)

- Severe form: lethal complication;
- Causes serious illnesses and death among children and elderly;
- In infants: The number of cases has been increasing over the last years.

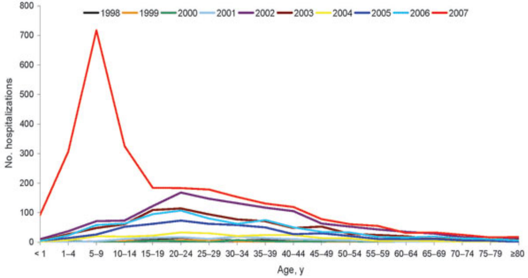


Figure: Number of hospitalizations for DHF, Brazil, 1998–2007.

Dengue Hemorrhagic Fever (DHF)

Can occur basically in two ways:

1. Children and adults: infected with a second serotype of DENV after a primary DENV infection with a different serotype;
2. in infants: with primary DENV infection whose mothers have some immunity to DENV.

Focus: Study DHF in the context of (2).

The objectives

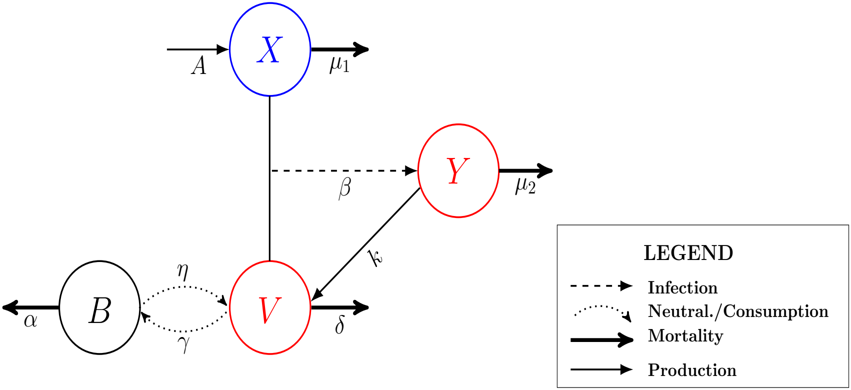
- To Propose and study a new mathematical model that mimics dengue disease in infants with passive immunity.

The Mathematical Model

State variables

- B: Antibodies of the infants: Passive immunity or Primary response of DENV infection by maternal Antibodies.
- X: DENV–uninfected monocytes;
- Y: DENV–infected monocytes;
- V: free immature DENV;

Diagram



X
A
μ_1
Y
β
μ_2
k
B
V
η
γ
α
δ
LEGEND
Infection
Neutral./Consumption
Mortality
Production

Dimensional Nonlinear ODE Model

$$\begin{cases} \dfrac{dB}{dt} = \overbrace{-\alpha\, B}^{\text{Antibody decay}} \quad \overbrace{-\eta\, B\, V}^{\text{DENV neutralization}} \\ \dfrac{dX}{dt} = \overbrace{A - \mu_1\, X}^{\text{Monocytes dynamics}} \quad \overbrace{-\beta\, V\, X}^{\text{DENV infection}} \\ \dfrac{dY}{dt} = \overbrace{-\mu_2\, Y}^{\text{Death of monocytes}} \quad +\beta\, V\, X \\ \dfrac{dV}{dt} = \overbrace{kY}^{\text{DENV production}} \quad \overbrace{-\gamma B\, V}^{\text{Antibody neutralization}} \quad \overbrace{-\,\delta\, V}^{\text{Virus decay}} \end{cases} . \tag{1}$$

Nondimensionalization

Dimensional parameter units:

$$\begin{cases} [\eta] = \frac{1}{[t]} \cdot \frac{1}{[V]}, \ [\alpha] = \frac{1}{[t]}, \ [\beta] = \frac{1}{[t]} \cdot \frac{1}{[V]} \\ \\ [\mu_1] = \frac{1}{[t]}, \ [A] = \frac{[C]}{[t]}, \ [\mu_2] = \frac{1}{[t]} \\ \\ [\gamma] = \frac{1}{[t\ ]} \cdot \frac{1}{[B]}, \quad [k] = \frac{1}{[t]} \cdot \frac{[V]}{[C]}, \quad [\delta] = \frac{1}{[t]} \end{cases}.$$

Nondimensionalization

Let,

$$\begin{cases} B^\star = \dfrac{B\gamma}{\alpha} & \Rightarrow \quad B = \dfrac{B^\star \alpha}{\gamma}, \\ t^\star = t\alpha & \Rightarrow \quad t = \dfrac{t^\star}{\alpha}, \\ X^\star = \dfrac{X\mu_1}{A} & \Rightarrow \quad X = \dfrac{X^\star A}{\mu_1}, \\ Y^\star = \dfrac{Y\mu_1}{A} & \Rightarrow \quad Y = \dfrac{Y^\star A}{\mu_1}, \\ V^\star = \dfrac{V\eta}{\delta} & \Rightarrow \quad V = \dfrac{V^\star \delta}{\eta}. \end{cases} \tag{2}$$

Nondimensional Nonlinear ODE Model

Substituting (2) in the system (1), we obtain:

$$\begin{cases} \dfrac{dB}{dt} &= -\omega BV - B \\ \dfrac{dX}{dt} &= \rho(1-X) - \theta XV \\ \dfrac{dY}{dt} &= \theta XV - \varphi Y \\ \dfrac{dV}{dt} &= \epsilon Y - \omega V - BV \end{cases} . \tag{3}$$

where,

$$\omega = \frac{\delta}{\alpha}, \quad \rho = \frac{\mu_1}{\alpha}, \quad \theta = \frac{\delta\beta}{\alpha\eta}, \quad \varphi = \frac{\mu_2}{\alpha} \ \text{ e } \ \epsilon = \frac{\eta k A}{\delta\alpha\mu_1}. \tag{4}$$

Mathematical Analysis

Equilibrium points

Considering $\frac{dB}{dt} = \frac{dX}{dt} = \frac{dY}{dt} = \frac{dV}{dt} = 0$ in system (3) and solving the associated homogeneous system, we obtain:

$$\begin{cases} \bar{B} & = & 0 \quad \text{or} \quad \bar{V} = -\dfrac{1}{\omega} \\ \bar{X} & = & \dfrac{\rho}{\rho + \theta \bar{V}} \\ \bar{Y} & = & \dfrac{\theta \bar{X} \bar{V}}{\varphi} \\ \bar{V} & = & \dfrac{\epsilon \bar{Y}}{\omega + \bar{B}} \end{cases} . \qquad (5)$$

Equilibrium points

1. If $\bar{B} = 0$, $\bar{X} = \dfrac{\varphi\omega}{\epsilon\theta}$, $\bar{Y} = \dfrac{\rho}{\theta}\left(1 - \dfrac{\varphi\omega}{\epsilon\theta}\right)$ and $\bar{V} = \dfrac{\rho}{\theta}\left(\dfrac{\epsilon\theta}{\varphi\omega} - 1\right)$.
   Then,
   - **The disease–Free Equilibrium (DFE) point:** $S_1 = (0, 1, 0, 0)$.
   - **The infection equilibrium point:**

$$S_2 = \left(0,\ \frac{\varphi\omega}{\theta\epsilon},\ \frac{\rho}{\varphi}\left(1 - \frac{\varphi\omega}{\epsilon\theta}\right),\ \frac{\rho}{\theta}\left(\frac{\epsilon\theta}{\varphi\omega} - 1\right)\right).$$

2. If $\bar{V} = -\dfrac{1}{\omega}$, then

$$S_3 = \left(\frac{\omega(\epsilon\rho\theta - \omega\rho\varphi + \theta\varphi)}{\varphi(\omega\rho - \theta)}, \frac{\rho\omega}{\omega\rho - \theta}, -\frac{\theta\rho}{\varphi(\omega\rho - \theta)}, -\frac{1}{\omega}\right).$$

Positivity

- Let,

$$\mathcal{P}^+ = \left\{ \begin{array}{l} (B,\ X,\ Y,\ V) \in \mathbb{R}^4 : B(0) = B_0 > 0, \\ X(0) = X_0 > 0, Y(0) = Y_0 > 0, V(0) = V_0 > 0 \end{array} \right\}. \quad (6)$$

- All parameters are positive;

Then,

- $S_1 = (0, 1, 0, 0)$ has biological sense;
- S_2 has biological sense, if

$$\mathcal{R}_0 = \frac{\epsilon\theta}{\varphi\omega} > 1;$$

- $\mathcal{R}_0$ is the **Basic Reproduction Number.**
- S_3 has not biological sense, since $\bar{V} = -\frac{1}{\omega} < 0$.

Numerical behaviour of S_3

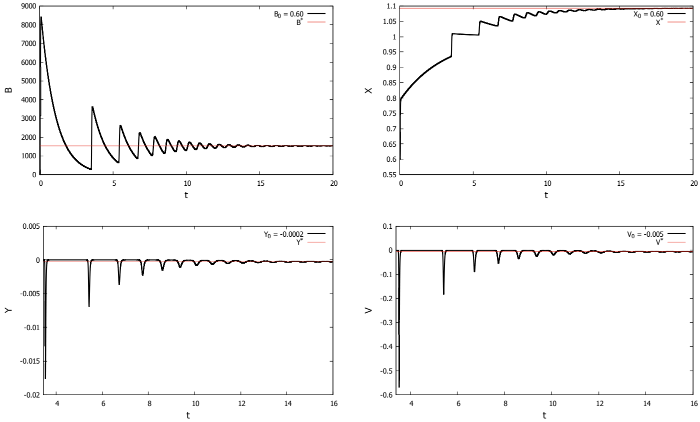


Figure: $B_0 = 0.60$, $X_0 = 0.60$, $Y_0 = -0.0002$, $V_0 = -0.0050$. $\bar{B} \approx 1.52 \times 10^3$, $\bar{X} \approx 1.09$, $\bar{Y} \approx -2.67 \times 10^4$ and $\bar{V} \approx -5.99 \times 10^3$.

The Linear Stability Analysis

The Jacobian matrix J of nondimensional model (3) evaluated on S_1 and S_2 is:

$$J(S_i) = \begin{pmatrix} -(\omega \bar{V} + 1) & 0 & 0 & -\omega \bar{B} \\ 0 & -(\rho + \theta \bar{V}) & 0 & -\theta \bar{X} \\ 0 & \theta \bar{V} & -\varphi & \theta \bar{X} \\ -\bar{V} & 0 & \epsilon & -(\omega + \bar{B}) \end{pmatrix}. \quad (7)$$

The Linear Stability Analysis: S_1

We have

$$J(S_1) = \begin{pmatrix} -1 & 0 & 0 & 0 \\ 0 & -\rho & 0 & -\theta \\ 0 & 0 & -\varphi & \theta \\ 0 & 0 & \epsilon & -\omega \end{pmatrix} \quad (8)$$

In this case, the eigenvalues λ_i, $i = 1, \cdots, 4$, obtained from $\det(J(S_1) - \lambda \mathbf{I}) = 0$ are:

$$\lambda_1 = -1 \text{ e } \lambda_2 = -\rho$$

and

$$\lambda_{3,4} = \frac{1}{2}\left(-(\varphi + \omega) \pm \sqrt{(\varphi + \omega)^2 - 4\left(\varphi\omega - \epsilon\theta\right)}\right).$$

The linear stability Analysis: S_1

If $\varphi\omega - \epsilon\theta > 0$, then

$$\mathcal{R}_0 = \frac{\epsilon\theta}{\varphi\omega} < 1,$$

and thus S_1 is assymptotically stable.

The linear stability Analysis: S_2

Considering $\mathcal{R}_0$, S_2 has the form:

$$S_2 = \left(0, \frac{1}{\mathcal{R}_0}, \ \frac{\rho}{\varphi}\left(1 - \frac{1}{\mathcal{R}_0}\right), \ \frac{\rho}{\theta}(\mathcal{R}_0 - 1)\right).$$

Then,

$$J(S_2) = \begin{pmatrix} -(\omega \bar{V} + 1) & 0 & 0 & 0 \\ 0 & -(\rho + \theta \bar{V}) & 0 & -\theta \bar{X} \\ 0 & \theta \bar{V} & -\varphi & \theta \bar{X} \\ -\bar{V} & 0 & \epsilon & -\omega \end{pmatrix}$$

The Linear Stability Analysis: S_2

Here,

$$\det(J(S_2) - \lambda \mathbf{I}) = (\omega \bar{V} + 1 + \lambda)\mathcal{B} = 0,$$

where $\mathcal{B} = (\rho + \theta \bar{V} + \lambda)(\lambda^2 + \lambda(\varphi + \omega) + \varphi\omega - \epsilon\theta\bar{X}) + \epsilon\theta^2 \bar{X}\bar{V}$.

1. The one solution is

$$\lambda = -\omega \bar{V} - 1$$

2. and also given by

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0,$$

   where

   - $a_1 = \varphi + \omega + \rho\mathcal{R}_0$;
   - $a_2 = \rho\mathcal{R}_0(\varphi + \omega) + \varphi\omega - \dfrac{\epsilon\theta}{\mathcal{R}_0}$;
   - $a_3 = \rho\mathcal{R}_0\varphi\omega - \dfrac{\epsilon\theta\rho}{\mathcal{R}_0}$.

The Linear Stability Analysis: S_2

- All parameters are positives in $\mathcal{P}^+$;
- If $\mathcal{R}_0 > 1$, the *Routh-Hurwitz* conditions for the stability of the linearized system are satisfyied in $\mathcal{P}^+$, since

$$a_1\varphi + \omega + \rho\mathcal{R}_0 > 0,$$

$$a_3 = \rho\mathcal{R}_0\varphi\omega - \frac{\epsilon\theta\rho}{\mathcal{R}_0} = \rho\varphi\omega\big(\mathcal{R}_0 - 1\big) > 0$$

and

$$a_1a_2 - a_3 = \varphi\rho\mathcal{R}_0(\varphi + \omega) + \rho^2\mathcal{R}_0^2(\varphi + \omega) + \omega^2\rho\mathcal{R}_0 + \rho\varphi\omega > 0.$$

Thus,

S_2 is assyntotically stable and S_1 is unstable.

Sensitivity Analysis

Sensitivity Analysis

Linear correlation for ϵ and θ with $\mathcal{R}_0 = \dfrac{\epsilon\theta}{\varphi\omega}$.

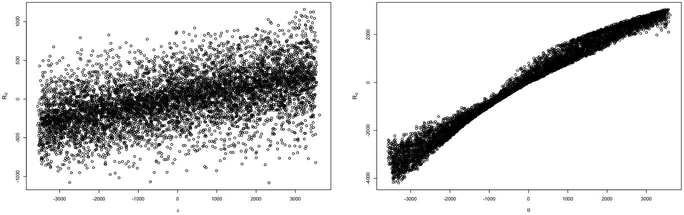


Figure: PRCC = 0.514582 and PRCC = 0.989135, respectively.

Partial Rank Correlation Coefficient (PRCC) method.

Sensitivity Analysis

Linear correlation for ω and φ with $\mathcal{R}_0 = \dfrac{\epsilon\theta}{\varphi\omega}$.

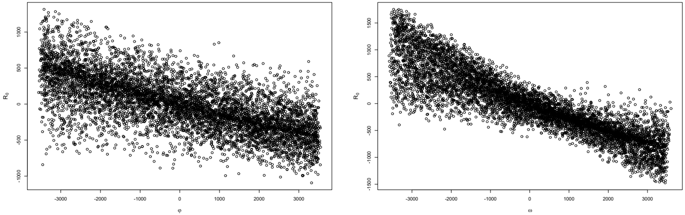


Figure: PRCC = -0.668597 and PRCC = -0.883255, respectively.

Sensitivity Analysis

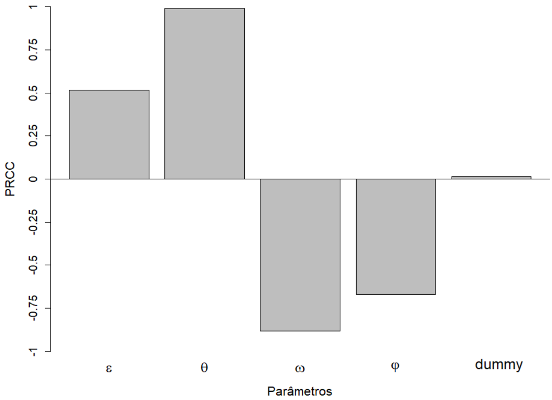


Figure: Parcial correlation coefficient for the ϵ, θ, ω, φ and dummy with $\mathcal{R}_0$.

Numerical Simulations

Numerical Simulations

Table: Parameters for the simulations.

Parameter	**Values** $(\mathcal{R}_0 < 1)$	**Values** $(\mathcal{R}_0 > 1)$
ρ	3.33×10^{-1}	3.33×10^{-1}
ϵ	3.82×10^{4}	3.82×10^{4}
φ	1.16×10^{2}	1.16×10^{2}
θ	4.74×10^{-1}	4.74×10
ω	1.66×10^{2}	1.66×10^{2}

- Age of the infant: 4 - 6 mouths (Castanha *et al.*, 2016);
- $t_0 = 0$: initial time of Dengue infection in the infants;
- Time-step $\Delta t = 10^{-4}$ for the *Runge-Kutta* fourth–order method;
- $\mathcal{R}_0 = \epsilon\theta/\varphi\omega$.

Numerical Simulations: $\mathcal{R}_0 < 1$

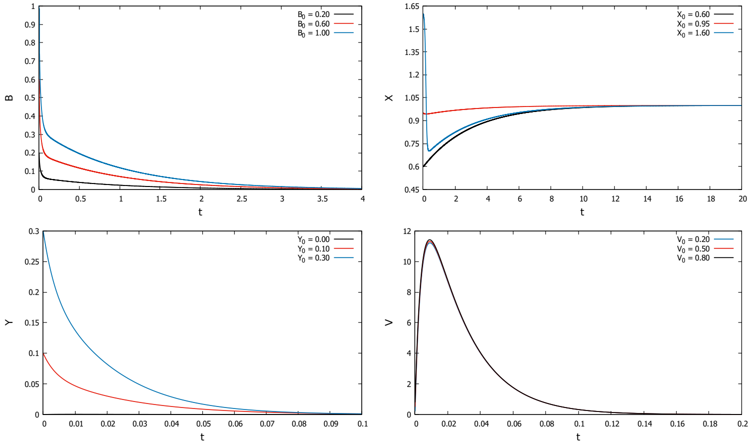


Figure: Convergency of the solution (B, X, Y, V) to the free-disease equilibrium point, $S_1 = (0, 1, 0, 0)$.

Numerical Simulations: $\mathcal{R}_0 > 1$

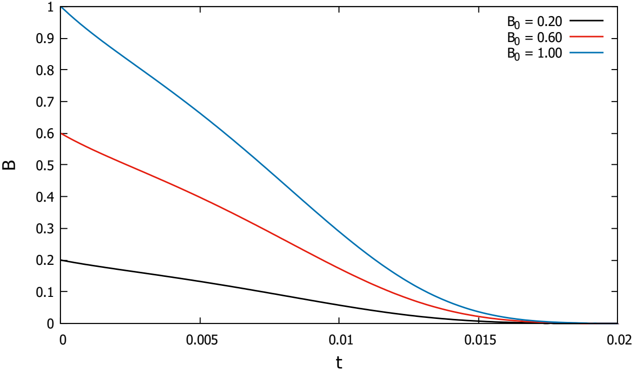


Figure: Convergency of the solution (B, X, Y, V) to the endemic-disease equilibrium point, S_2.; $\bar{B} = 0$.

Numerical Simulations: Scenario $\mathcal{R}_0 > 1$

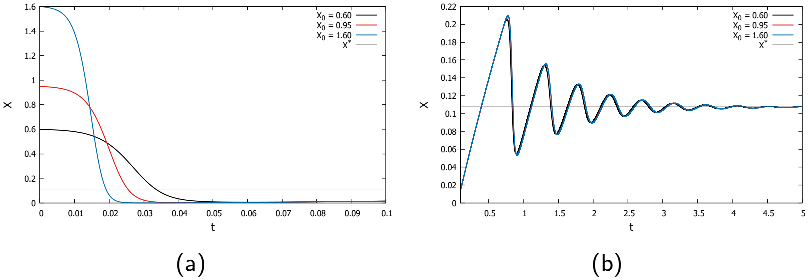
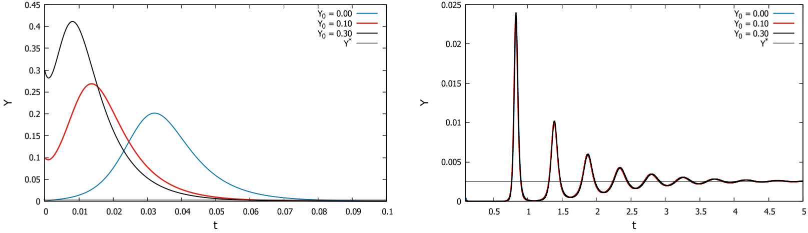


Figure: Population dynamics of the monocytes unfected cells along the time t. (a) $t \in [0,\ 0.1)$; (b) $t \in [0.1,\ 5)$. Initial conditions: $B_0 = 0.60$, $Y_0 = 0.00$, $V_0 = 0.50$. $\bar{X} \approx 1.07 \times 10^{-1}$.

Numerical Simulations: Scenario $\mathcal{R}_0 > 1$



(a) (b)

Figure: Population dynamics of the monocytes infected cells along the time t. (a) $t \in [0,\ 0.1)$; (b) $t \in [0.1,\ 5)$. Initial conditions: $B_0 = 0.60$, $X_0 = 0.60$, $V_0 = 0.50$; $\bar{Y} \simeq 2.5 \times 10^{-3}$.

Numerical Simulations: Scenario $\mathcal{R}_0 > 1$

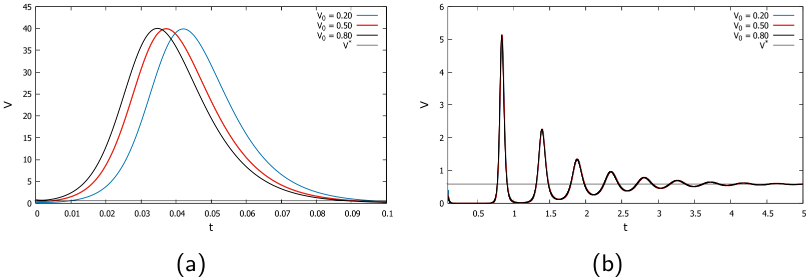


Figure: Population dynamics of the virus along the time t. (a) $t \in [0,\ 0.1)$ e (b) $t \in [0.1,\ 5)$. Initial conditions: $B_0 = 0.60$, $X_0 = 0.60$, $Y_0 = 0.00$; $V^* \simeq 5.84 \times 10^{-1}$.

Conclusions

Conclusions

1. The numerical results of the computational simulations are in agreement with the mathematical analysis performed;
2. The sensitivity analysis showed that the parameter of the infection θ has a strong and positively correlation to the $\mathcal{R}_0$;
3. From the numerical results, the peaks were visualized in the dynamics of Y and V; (Gómez & Yang, 2018) classified these peaks as DHF.
4. From our hypothesis of passive immunity meaning the primary response mediated by maternal antibodies, we can conclude that this peak mean DHF in infants.

Improvements on the Model

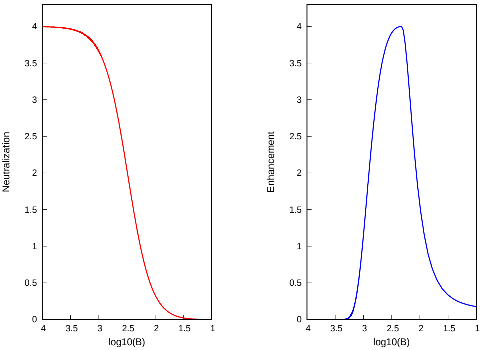
Neutralization and Enhancement as a function of antibodies concentration:

$$N_j(B) = \eta_j + s_j \frac{B^n}{r_j^n + B^n} \mathbb{1}_{B > B_0}, \quad \text{with} \quad j = 1, 2,$$

and

$$E(B) = q \left(e^{-\frac{(B-\epsilon)^2}{2\sigma_1}} \mathbb{1}_{B \leq \epsilon} + e^{-\frac{(B-\epsilon)^2}{2\sigma_2}} \mathbb{1}_{B > \epsilon} \right).$$

Antibodies Neutralization and Enhancement functions



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