Mathematical Modeling of Viral Hemorrhagic Fevers

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1 Introduction

Viral hemorrhagic fevers (VHFs) refer to a group of illnesses that are caused by several distinct families of viruses. They are spread by contact with infected animals, people, or insects. These include the Ebola, Lassa fever, Dengue fever and yellow fever viruses. VHFs have common features: they affect many organs, they damage the blood vessels, and they affect the body's ability to regulate itself. Some VHFs cause mild disease, but some, like Ebola, cause severe disease and death. VHFs are found around the world. Specific diseases are usually limited to areas where the animals that carry them live. For example, Lassa fever is limited to rural areas of West Africa where rats and mice carry the virus.

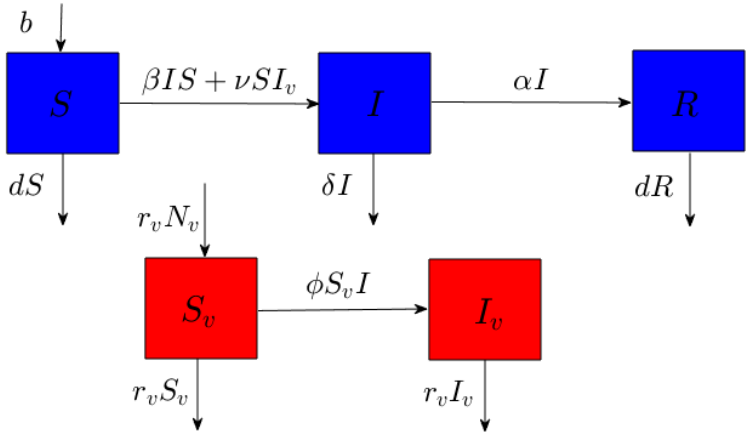
Dengue fever is a mosquito-borne disease. Millions of cases of dengue infection occur worldwide each year. Dengue fever is most common in Southeast Asia, the western Pacific islands, Latin America and Africa. But the disease has been spreading to new areas, including local outbreaks in Europe and southern parts of the United States [3]. Mild dengue fever causes a high fever and flu-like symptoms. The severe form of dengue fever, also called dengue hemorrhagic fever, can cause serious bleeding, a sudden drop in blood pressure (shock) and death.

In this work we develop a compartmental mathematical model to capture the dynamics of VHFs. We simulate the model for Dengue fever and Rift Valley fever (RVF).

2 Model Description

We make the following preliminary assumptions: there is no vertical transmission of the virus, hosts will have full immunity upon recovery, the total host population N is not constant, and the total vector population N_v is constant.

We construct our equations based on the compartmental diagram below.



For our human population, we have

$$\begin{aligned}\frac{dS}{dt} &= b - \beta IS - \nu SI_v - dS \\ \frac{dI}{dt} &= \beta IS + \nu SI_v - (\alpha + \delta)I \\ \frac{dR}{dt} &= \alpha I - dR.\end{aligned}$$

For our vector population, we have

$$\begin{aligned}\frac{dS_v}{dt} &= r_v N_v - \phi S_v I - r_v S_v \\ \frac{dI_v}{dt} &= \phi S_v I - r_v I_v.\end{aligned}$$

The parameters are defined as follows, with units given below.

$$\begin{aligned} b &= \text{human natural birth or recruitment rate} \\ d &= \text{human natural death rate} \\ \beta &= \text{encounter rate with infectious individual} \\ \nu &= \text{encounter rate with infectious vector} \\ \alpha &= \text{recovery rate} \\ \delta &= \text{natural death rate + death rate from infection} \\ r_v &= \text{vector population turnover rate (birth rate - death rate)} \\ \phi &= \text{encounter rate of susceptible vector with infected human} \\ N, N_v &= \text{total human and vector populations, respectively}\end{aligned}$$

$$\begin{aligned}[b] &= \frac{\text{individuals}}{\text{area} \times \text{time}} \\ [\beta] = [\nu] = [\phi] &= \frac{\text{area}}{\text{individuals} \times \text{time}} \\ [d] = [\alpha] = [\delta] = [r_v] &= \frac{1}{\text{time}}\end{aligned}$$

Since our total vector population is constant ($\frac{dN_v}{dt} = 0$), we can reduce our system from 5 equations to 3 by writing $S_v = N_v - I_v$ and by omitting $\frac{dR}{dt}$ (since no other equations depend on R). Hence, we work with the following reduced system in our analysis:

$$\begin{aligned}\frac{dS}{dt} &= b - \beta IS - \nu SI_v - dS \\ \frac{dI}{dt} &= \beta IS + \nu SI_v - (\alpha + \delta)I \\ \frac{dI_v}{dt} &= \phi(N_v - I_v)I - r_v I_v.\end{aligned}$$

3 Model Analysis

3.1 Disease-Free Equilibrium Point (DFE)

The disease-free equilibrium (DFE) point for the reduced system is given by $(\bar{S}, 0, 0)$ with $\bar{S} = \frac{b}{d}$. For the original system, our DFE is $(\frac{b}{d}, 0, 0, \bar{S_v}, 0)$ where $\bar{S_v} = N_v$. Thus, we can have infinitely many DFEs for a given system with set parameters, depending on our initial vector population size.

3.2 Endemic Equilibrium Point (EE)

The EE point satisfies the following:

$$b - \beta IS - \nu SI_v - dS = 0 \tag{3.1}$$
$$\beta IS + \nu SI_v - \alpha I - \delta I = 0 \tag{3.2}$$
$$\phi(N_v - I_v)I - r_v I_v = 0 \tag{3.3}$$

Solving for endemic equilibria poses a difficulty because of the nonlinearity involved. However, we were able to solve this system with the aid of MATHEMATICA to obtain two solutions. The positivity and indeed the existence of endemic equilibria (EE) depends on the model parameters combination but they are very complicated. We attempted using some algebraic analysis (e.g. Descartes rule of signs) to obtain results about the EE but were unable to proceed since the coefficients of the resulting polynomial had indeterminable signs. Using MATLAB to symbolically solve the system with strategically chosen parameter values, we numerically obtained the existence and stability of one endemic equilbrium (see Section 4: Results).

We can, however, realistically consider the case when $\beta = 0$, since oftentimes the viruses causing VHF cannot be transmitted from human to human, only from humans to vectors to humans. We show two examples of this in Section 4 with Dengue fever and Rift Valley fever. When making this assumption, we can solve (3.1) for S in terms of I_v to obtain

$$S = \frac{b}{-\nu I_v - d} < 0$$

since $I_v > 0$ for any biologically existing equilibrium value. Hence, we do not have any endemic equilibria without the existence of human to human transmission.

3.3 Basic Reproduction Number

Using the next generation matrix approach, we can derive the basic reproduction number, R_0, by considering the subsystem given the ODEs for the disease variables, i.e, I, I_v; however, the decomposition of the matrix A into "new infection" and "transition" greatly depends on the interpretation of "new infection". If we consider that new infection could come from both the human and vector populations, then the reproduction number in this case is:

$$R_0^{(1)} = \frac{\beta b}{2d(\alpha+\delta)} + \frac{1}{2}\sqrt{\left(\frac{\beta b}{d(\alpha+\delta)}\right)^2 + \frac{4\nu b\phi N_v}{r_v d(\alpha+\delta)}}.$$

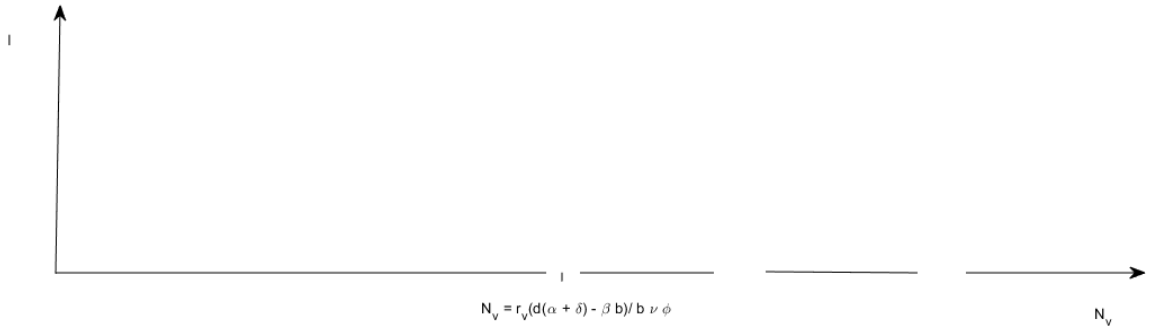
On the other hand, if we consider new infection could only come from the human population alone, then the reproduction number is:

$$R_0^{(2)} = \frac{b}{d(\alpha+\delta)}\left[\beta + \frac{\phi\nu N_v}{r_v}\right]$$

These two reproduction numbers agree at the threshold value, i.e, $R_0^{(1)} = 1 \iff R_0^{(2)} = 1$, (see Appendix A). Hence, in what follows, we shall use $R_0^{(2)}$ to discuss our stability result. In particular, the DFE is locally stable if $R_0^{(2)} < 1 \iff [\beta + \frac{\phi\nu N_v}{r_v}] < \frac{d(\alpha+\delta)}{b}$ and unstable if $R_0^{(2)} > 1$.

3.4 Bifurcation at N_v

The bifurcation diagram with parameter N_v for the $I-$component of the DFE is a horizontal line which is continuous for $N_v < \frac{r_v(d(\alpha+\delta)-\beta b}{\nu\phi b}$ and broken for $N_v > \frac{r_v(d(\alpha+\delta)-\beta b}{\nu\phi b}$. The endemic equilibrium component is not included since we don't have an closed-form expression for it.



4 Results

4.1 Numerical Simulation: Dengue

Since VHF can be caused by a number of different diseases (see introduction), we create our first simulation using dengue fever. According to the World Health Organization (WHO), dengue can only be spread through the trajectory human-vector-human (rather than human to human), so we take β to be zero.

We use parameter values as given in [4]. Here, time t is given in weeks.

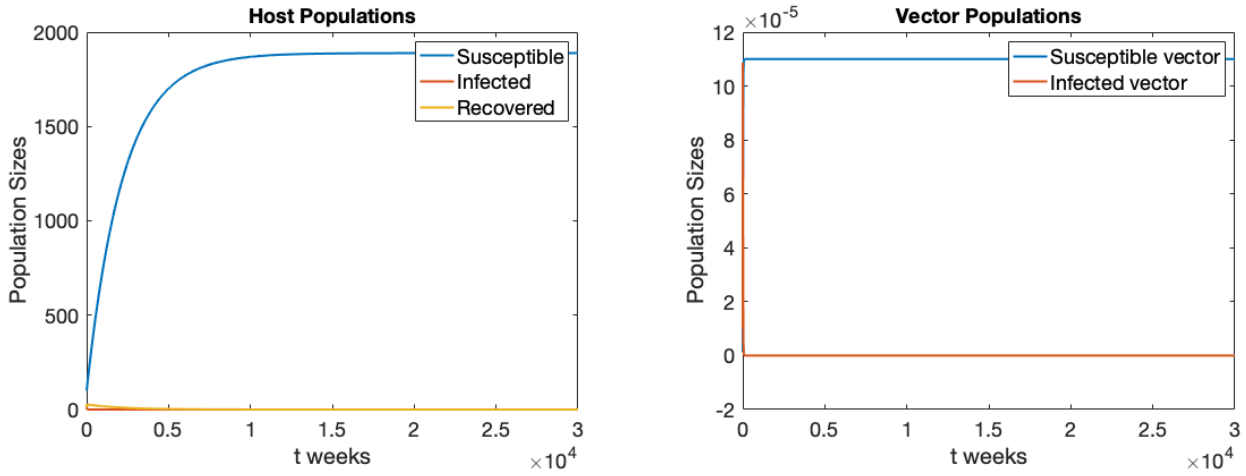


Figure 1: Parameter values: $b = 0.85$, $\beta = 0$, $\nu = 0.375$, $d = 0.00045$, $\alpha = 1.5/2$, $\delta = 0.00045 + (1 - 1.5/2)$, $r_v = 0.1$, $\phi = 0.75$; $S(0) = 100$, $I(0) = 20$, $R(0) = 12$, $S_v(0) = 0.0001$, $I_v(0) = 0.00001$). Reproduction numbers are $R_0^{(1)} = 0.7643$, $R_0^{(2)} = 0.5841$. DFE is (1888.9,0,0,0,0).

Clearly, the solutions do not reach this equilibrium in a practically realistic time period. The simulation had to be run for about 30,000 weeks before the solutions reached that equilibrium. However, since our reproduction numbers are less than 1, our DFE is stable. This case is not very practical since the vector populations have to be almost to the point of nonexistence for the DFE to be stable. Since the disease cannot be spread human to human, this is essentially saying that the disease will only die out when it cannot be spread in the first place. However, this does imply that controlling the mosquito population should be an effective control measure.

4.2 Numerical Simulation: Rift Valley Fever (RVF)

We run simulations with differing parameter values to compare. We use Rift Valley fever (RVF), another cause of VHF, in this simulation. Parameter values used are as given in [7]. Our model over-simplifies RVF, since this virus can also be transmitted via infected livestock, which our model does not consider. We acknowledge this simplification and focus instead on what the differing parameter values of RVF inform us about our model.

The next simulation uses parameter values for Rift Valley Fever (infects humans and livestock; passed through mosquitoes and contact with infected livestock fluids). Parameter values modeled from [7]; t is given in days.

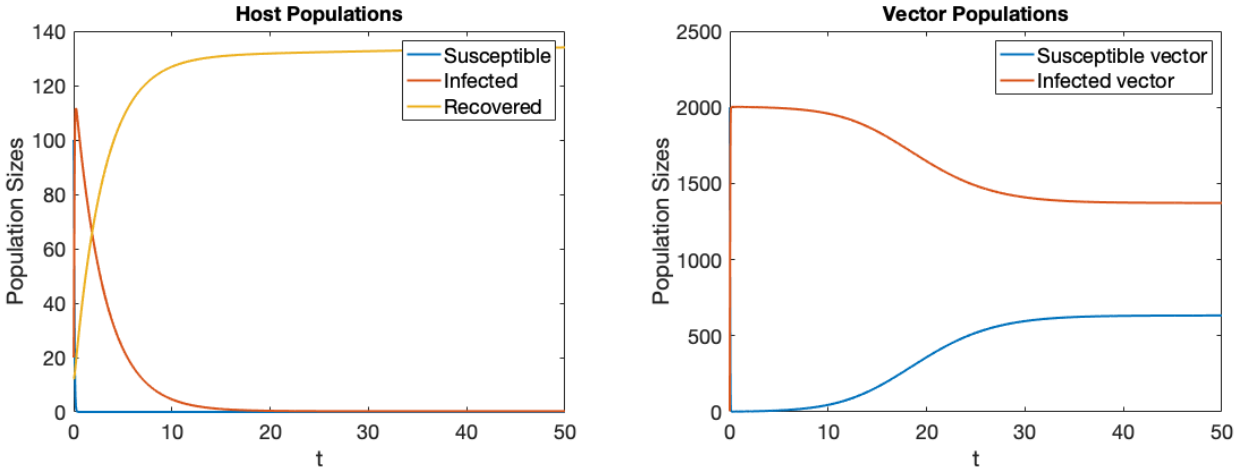


Figure 2: Parameter values: $b = 0.085$, $\beta = 0$, $\nu = 0.01$, $d = 1/(25 * 360)$, $\alpha = (1/3) * 0.99$, $\delta = 1/(25 * 360) + (1/3) * 0.01$, $r_v = 0.1$, $\phi = 0.85$; $S(0) = 100$, $I(0) = 20$, $R(0) = 12$, $S_v(0) = 2000$, $I_v(0) = 5$). Reproduction numbers are $R_0^{(1)} = 625.2960$, $R_0^{(2)} = 391,000$.

Here, we only run the simulation for just under 2 months (t is given in days) in order to better see the dynamics close to zero. Our reproduction numbers are very large, possibly due to the factor of N_v in the reproduction numbers (here, $N_v = 1500$). When we consider that humans infect other humans only through vectors, and humans have a high probability of infecting vectors ($\phi = 0.85$), then the total amount of humans another human can infect via vector transmission is very high. This may account for the dynamics of the infected host population: the infections spike quickly near 0, then die out as the recovered population increases dramatically. While the infected vectors stay stable over that time period, the host population has full immunity and thus cannot be reinfected. Hence, the infected host population stays very close to zero. However, the infected vector population stays very large; this behavior is appropriate considering that very few infected humans are needed to produce many infected mosquitoes.

4.3 Existence & Stability of Endemic Equilibrium

As mentioned in 3.2, the existence and stability of arbitrary endemic equilibria is very difficult. Here, we show the existence and stability of an endemic equilibrium with specific parameter values (for both the original system and the reduced system). In this case, we chose β to be nonzero, a requirement for the existence of an EE (see 3.2). We use the same parameter values as for RVF (so t is given in days) with the exception of having $\beta = 0.5$ and $\nu = 0.1$ to increase the spread of the infection. For the sake of simplicity, we use initial conditions that are close to the values of the EE which we solve for numerically (see below).

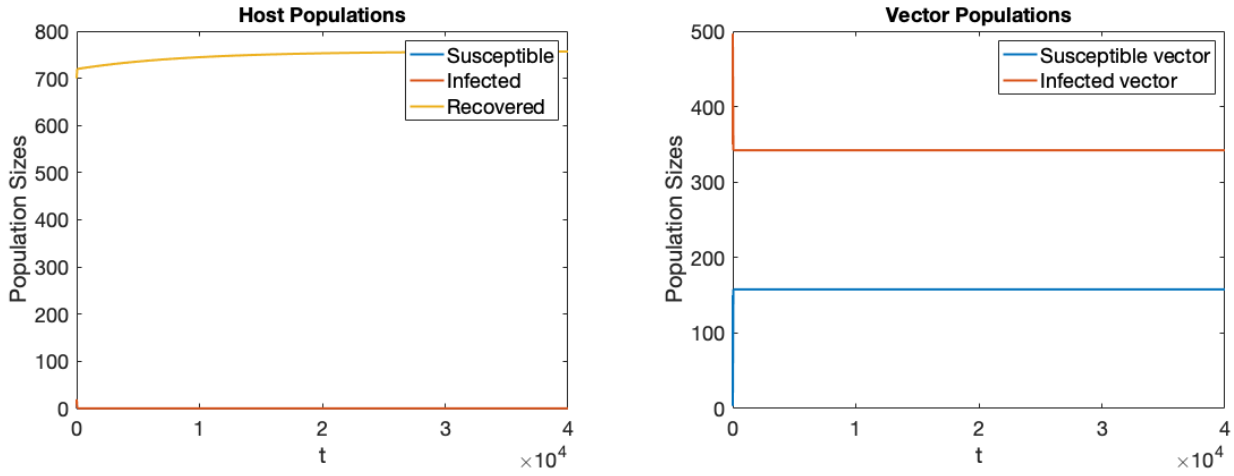


Figure 3: Parameter values: $b = 0.085$, $\beta = 0.5$, $\nu = 0.1$, $d = 1/(25 * 360)$, $\alpha = (1/3) * 0.99$, $\delta = 1/(25 * 360) + (1/3) * 0.01$, $r_v = 0.1$, $\phi = 0.85$; $S(0) = 10$, $I(0) = 10$, $R(0) = 700$, $S_v(0) = 150$, $I_v(0) = 350$). Reproduction numbers are $R_0^{(1)} = 1,715.5$, $R_0^{(2)} = 976,200$.

Solving numerically gave the EE for the reduced system as

$$(0.002475, 0.254914, 757.095184).$$

From this, we can obtain the EE for the original model:

$$(0.002475, 0.254914, 757.095184, 157.889548, 342.110452).$$

We obtain numerically that the eigenvalues of the Jacobian evaluated at this EE all have negative real part, giving local asymptotic stability for this EE.

Again, it takes a very long time for the model to reach this equilibrium (over 100 years). We also have very large reproduction numbers.

5 Modification

5.1 Model Comparison

Compare to the model in [6]. They have a very similar model to ours although they focus exclusively on modeling dengue fever, so they omit the term describing human to human transmission. One adjustment that we will make to our model based on their model is changing our incidence rate from mass action to standard. The system of ODEs in this case is:

Human population

$$\begin{aligned}
\frac{dS}{dt} &= b - \beta\frac{IS}{N} - \nu\frac{SI_v}{N} - dS \\
\frac{dI}{dt} &= \beta\frac{IS}{N} + \nu\frac{SI_v}{N} - (\alpha + \delta)I \\
\frac{dR}{dt} &= \alpha I - dR.
\end{aligned}$$

For our vector population, we have

$$\begin{aligned}
\frac{dS_v}{dt} &= r_v N_v - \phi\frac{S_v I}{N} - r_v S_v \\
\frac{dI_v}{dt} &= \phi\frac{S_v I}{N} - r_v I_v.
\end{aligned}$$

By removing the R and S_v compartments, we also obtain the reduced system

$$\begin{aligned}\frac{dS}{dt} &= b - \beta\frac{IS}{N} - \nu\frac{SI_v}{N} - dS \\ \frac{dI}{dt} &= \beta\frac{IS}{N} + \nu\frac{SI_v}{N} - (\alpha+\delta)I \\ \frac{dI_v}{dt} &= \phi\frac{(N_v - I_v)I}{N} - r_v I_v.\end{aligned}$$

This model is similar to what they had in [6]. However, one major difference is that both their human and vector populations were assumed to be constant, so they were able to do some simplifications involving nondimensionalization. We remark that the analysis of this new model is as complicated, if not more so, as the original system, hence we shall not delve into it.

To make adjustments to our model based off of [6] would be to either 1) over-complicate our model with frequency dependent interaction rates (nondimensionalization does not work to simplify the system as it does in [6] since our host population is not constant), or 2) simplify our model and essentially lead to reproducing their results. We focus instead on extending our model to include partial immunity.

5.2 Extension

In our original model, we assumed full immunity is conferred for VHF from any disease which causes it. We adjust our model here to assume that only partial immunity to VHF is conferred from any given disease causing VHF (e.g. one could be infected with and recover from the VHF caused by Dengue fever, then be reinfected with VHF caused by RVF). This requires modifying the equations $\frac{dS}{dt}$ and $\frac{dR}{dt}$ by adding and subtracting, respectively, the term γR, where γ represents the period of immunity. From this, we note that we can no longer drop the $\frac{dR}{dt}$ equation in the original model since $\frac{dS}{dt}$ now depends on R.

5.2.1 System

Our new system is then

$$\begin{aligned}\frac{dS}{dt} &= b - \beta IS - \nu SI_v - dS + \gamma R \\ \frac{dI}{dt} &= \beta IS + \nu SI_v - (\alpha+\delta)I \\ \frac{dR}{dt} &= \alpha I - (d+\gamma)R.\end{aligned}$$

with our vector system remaining the same.

Clearly, we can see that our DFE remains the same as for the original system.

5.2.2 Reproduction Number

Our reproduction numbers remain the same since the two infected compartments, I and I_v, were not affected by the addition of partial immunity. This makes sense since the presence of partial immunity only affects the number of individuals who can be infected, not the number of infections that one individual can confer in a wholly susceptible population.

Thus, it follows that the analysis on the DFE remains the same as for the original system. We focus then only on the change in EE.

5.2.3 Endemic Equilibrium

We see a substantive change from our original system with respect to the EE. Using the same parameters as in our third simulation for the original model, with the addition of partial immunity parameter

$\gamma = 0.75$ gives Figure 4. The host populations all decrease to the equilibrium value; the infected population decreases much more slowly than in the original model. All host populations reach their steady states much faster than the original model. With t given in days, we see the steady states being reached at about 4 years. The behavior of the vector populations differ in that the infected vector population increases, rather than decreases, to reach its equilibrium, while the susceptible vector population does the opposite.

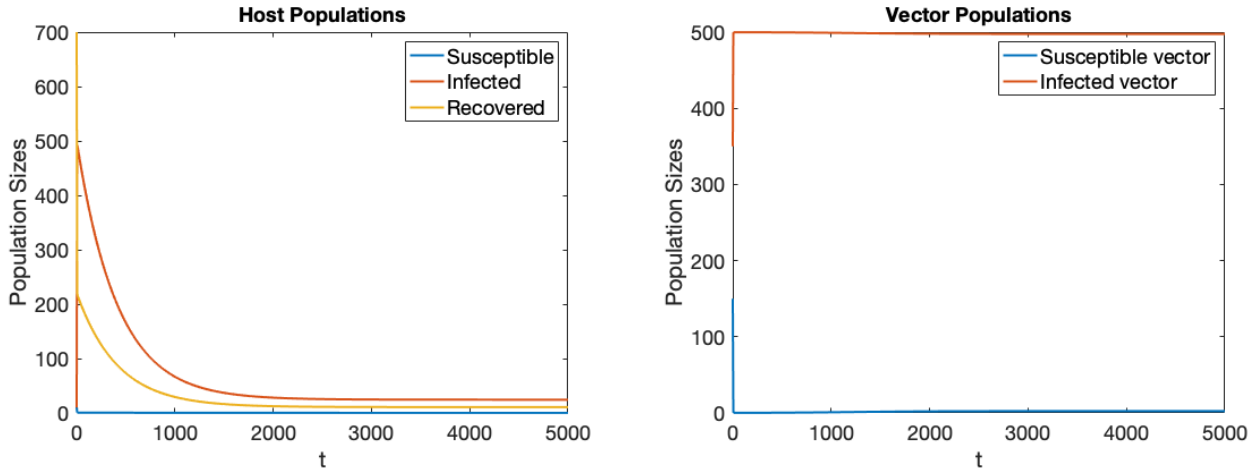


Figure 4: Parameter values: $b = 0.085$, $\beta = 0.5$, $\nu = 0.1$, $d = 1/(25 * 360)$, $\alpha = (1/3) * 0.99$, $\delta = 1/(25 * 360) + (1/3) * 0.01$, $r_v = 0.1$, $\phi = 0.85$,$\gamma = 0.75$; $S(0) = 10$, $I(0) = 10$, $R(0) = 700$, $S_v(0) = 150$, $I_v(0) = 350$). Reproduction numbers are $R_0^{(1)} = 1,715.5$, $R_0^{(2)} = 976,200$.

When solving numerically, we obtained the following equilibria for the reduced and original systems, respectively:

$$(0.131, 24.328, 10.703, 497.594)$$

and

$$(0.131, 24.328, 10.703, 2.406, 497.594).$$

We obtain numerically that the eigenvalues of the Jacobian evaluated at this EE all are negative, giving local asymptotic stability for this EE. Our reproduction numbers remain large, likely for the same reasons as described for the previous RVF simulation.

6 Discussion & Conclusion

The results from our model show that, given the prevalence of mosquito populations in many countries, these diseases will not die out without control measures being taken since the DFE is unstable unless N_v, the total vector population, is very small. Control of the mosquito population seems like a reasonable way to decrease the persistence of the disease. Future adjustments to the model could involve sensitivity analysis to N_v as well as adding a component to account for control measures for the mosquito population.

Additionally, an endemic equilibrium for the whole system cannot be reached if $\beta = 0$, i.e. if human to human transmission is not possible (although we see that the vector populations seem to reach equilibrium). For the simulation run from the original model with $\beta \neq 0$, it took a very long time to reach the endemic equilibrium, primarily because the recovered population grew very slowly (the number of infections decreased rapidly, so the recovered population's growth slowed). This slow growth indicates that, while VHF from RVF may remain endemic, its growth will be very slow and may not cause much issue in the population.

The partial immunity model retained the same dynamics as the original model with respect to the DFE. We had a similar stability result for the EE; however, the dynamics at that particular EE changed dramatically. The susceptible and infected host populations stabilized at a larger value while the recovered population's steady state was much smaller. Also, the infected vector steady state was much larger; subsequently, the susceptible vector population was much smaller (likely due to the increase in susceptible host population allowing the disease to spread more). This model would be better suited than the original model for a region with the presence of multiple viruses causing VHF.

References

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7 Appendices

7.1 Appendix A ($R_0^{(1)}$ Vs $R_0^{(2)}$)

$$R_0^{(1)} = 1$$

$$\iff \frac{\beta b}{2d(\alpha+\delta)} + \frac{1}{2}\sqrt{\left(\frac{\beta b}{d(\alpha+\delta)}\right)^2 + \frac{4\nu b\phi N_v}{r_v d(\alpha+\delta)}} = 1$$

$$\iff \left(\frac{\beta b}{d(\alpha+\delta)}\right)^2 + \frac{4\nu b\phi N_v}{r_v d(\alpha+\delta)} = \left(\frac{\beta b}{d(\alpha+\delta)}\right)^2 + 4 - 4\frac{\beta b}{d(\alpha+\delta)}$$

$$\frac{b}{d(\alpha+\delta)}[\beta + \frac{\phi\nu N_v}{r_v}] = 1 = R_0^{(2)}$$