Modeling the Spatial Spread of Rift Valley Fever in Egypt

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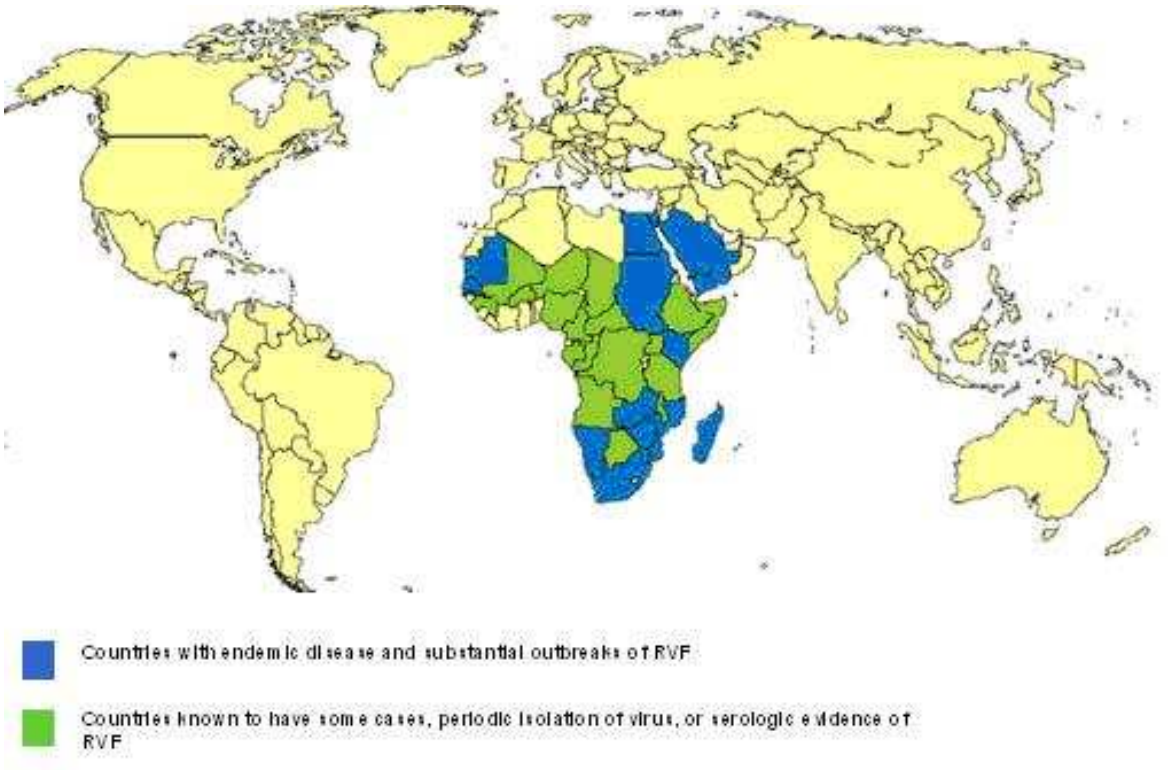
1. Background

- Rift Valley fever (RVF) is a viral zoonosis of domestic animals (such as cattle, sheep, camels and goats) and humans caused by the RVF virus (RVFV), a member of the genus *Phlebovirus* in the Bunyaviridae family.
- The virus is transmitted primarily by the bites of infected female mosquitoes.
- Initially identified in the Rift Valley of Kenya in 1931, outbreaks of RVF have been reported in sub-Saharan Africa, Egypt, Saudi Arabia and Yemen.
- RVF causes high mortality and abortion in domestic animals.

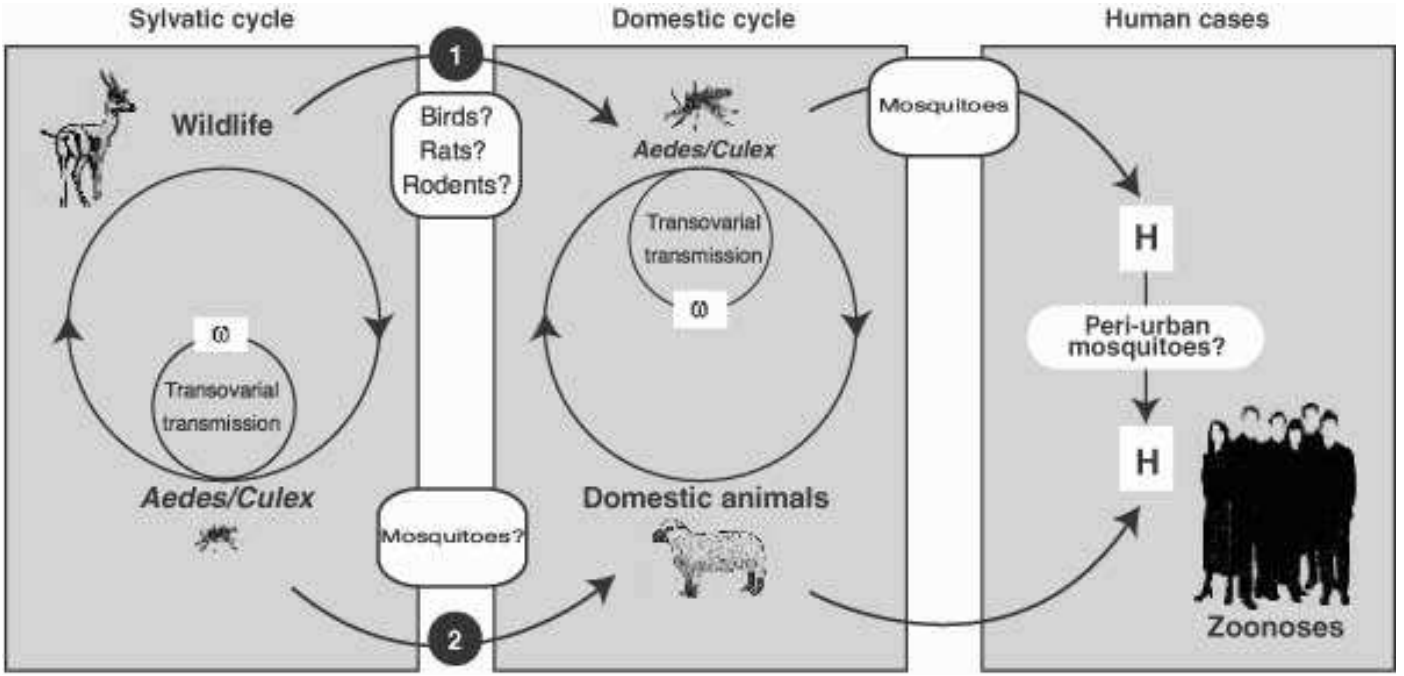
Rift Valley Fever Distribution Map



Source: http://en.wikipedia.org/wiki/Rift_Valley_fever

RVF virus transmission cycle

- Several mosquito species of the genera *Culex* or *Aedes* are known vectors and some *Aedes* spp. can also transmit the virus vertically (mother-to-offspring).



Source: FAO Animal Health Manual No. 15

2. The model

So far little has been done to model and analyze the RVF transmission dynamics.

- Gaff et al., Electr. J. Differential Equations, 2007;
- Mpheshe et al., Acta Biotheor, 2011;
- Xue et al., J. Theoret. Biol., 2012;
- Niu et al., Comput. Math. Method. M., 2012;
- Chitnis et al., J. Biol. Dyn., 2013.

However, these models either do not include spatial effects or are too complicated to perform rigorous mathematical analysis.

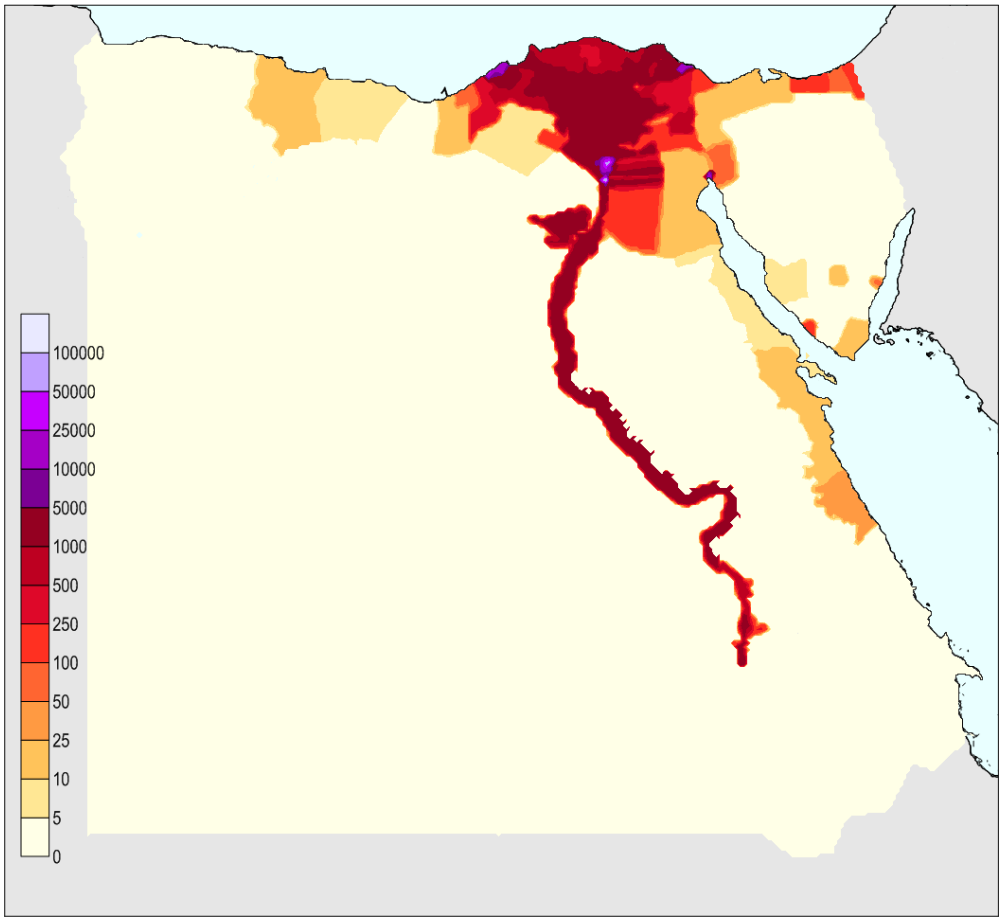
RVF in Egypt

- The first outbreak of RVF in Egypt occurred in the Nile Valley and Delta in 1977. Due to a combination of a lack of experience in dealing with RVF patients and insufficient public health programs, the outbreak caused at least thousands of human infections and hundreds of human deaths.
- Since then, Egypt has been experiencing continued RVF outbreaks among domestic animals which indicates that the RVFV has become enzootic in Egypt.
- It is believed that RVF has been introduced into Egypt from Sudan via sheep transported along Lake Nasser.

RVF in Egypt

- Travel time from north-central Sudan, where RVF is epizootic, to the Aswan area, livestock markets in southern Egypt, is less than 5 days, approximating the incubation period of RVF virus in sheep.
- Egypt is an arid country with most of the population concentrated along the Nile, in the Delta and near the Suez Canal.
- The basic idea is that the imported animals enter southern Egypt from northern Sudan, are moved up the Nile, and then consumed at population centres.

Egyptian Population Density and Distribution 2010



Model assumptions

- For simplicity, we restrict our focus to the disease transmission between domestic animals and mosquitoes.
- The study of field-collected mosquitoes suggests that *Culex pipiens* is the main vector of RVFV in Egypt.
- The movement timescale of animals is relatively short, so we assume no host reproduction during the journey.
- We assume no movement for vector populations because of their limited mobility.
- Assume also logistic growth for vector populations to maintain an equilibrium vector population.
- We use a simple SIRS model for hosts and an SI model for vectors.

Model Equations

Based on the above assumptions, we propose a three-patch model (Sudan-Nile-feast) with animals movement from patch 1 to patch 2 and then from patch 2 to patch 3:

$$
\begin{cases}
\dfrac{dS_1}{dt} = r - \alpha_1 S_1 V_1 - \mu S_1 + \zeta R_1 - \dfrac{c}{d_1} S_1, \\
\dfrac{dI_1}{dt} = \alpha_1 S_1 V_1 - (\mu + \gamma + \delta) I_1 - \dfrac{c}{d_1} I_1, \\
\dfrac{dR_1}{dt} = \gamma I_1 - (\mu + \zeta) R_1 - \dfrac{c}{d_1} R_1, \\
\dfrac{dU_1}{dt} = \xi_1 (U_1 + V_1) - \dfrac{\xi_1 - \nu_1}{M_1} (U_1 + V_1)^2 - \nu_1 U_1 - \beta_1 I_1 U_1, \\
\dfrac{dV_1}{dt} = -\nu_1 V_1 + \beta_1 I_1 U_1,
\end{cases}
\tag{1}
$$

Model Equations-patch 2

$$
\begin{cases}
\dfrac{dS_2}{dt} = \dfrac{c}{d_1} S_1 - \alpha_2 S_2 V_2 - \mu S_2 + \zeta R_2 - \dfrac{c}{d_2} S_2, \\
\dfrac{dI_2}{dt} = \dfrac{c}{d_1} I_1 + \alpha_2 S_2 V_2 - (\mu + \gamma + \delta) I_2 - \dfrac{c}{d_2} I_2, \\
\dfrac{dR_2}{dt} = \dfrac{c}{d_1} R_1 + \gamma I_2 - (\mu + \zeta) R_2 - \dfrac{c}{d_2} R_2, \\
\dfrac{dU_2}{dt} = \xi_2 (U_2 + V_2) - \dfrac{\xi_2 - \nu_2}{M_2} (U_2 + V_2)^2 - \nu_2 U_2 - \beta_2 I_2 U_2, \\
\dfrac{dV_2}{dt} = -\nu_2 V_2 + \beta_2 I_2 U_2,
\end{cases}
\tag{2}
$$

Model Equations-patch 3

$$
\begin{cases}
\dfrac{dS_3}{dt} = \dfrac{c}{d_2} S_2 - \alpha_3 S_3 V_3 - \mu S_3 + \zeta R_3 - \dfrac{c}{d_3} S_3, \\
\dfrac{dI_3}{dt} = \dfrac{c}{d_2} I_2 + \alpha_3 S_3 V_3 - (\mu + \gamma + \delta) I_3 - \dfrac{c}{d_3} I_3, \\
\dfrac{dR_3}{dt} = \dfrac{c}{d_2} R_2 + \gamma I_3 - (\mu + \zeta) R_3 - \dfrac{c}{d_3} R_3, \\
\dfrac{dU_3}{dt} = \xi_3 (U_3 + V_3) - \dfrac{\xi_3 - \nu_3}{M_3} (U_3 + V_3)^2 - \nu_3 U_3 - \beta_3 I_3 U_3, \\
\dfrac{dV_3}{dt} = -\nu_3 V_3 + \beta_3 I_3 U_3.
\end{cases}
\tag{3}
$$

The state variables for the model and their description

S_i	Number of susceptible animals in patch i at time t
I_I	Number of infectious animals in patch i at time t
R_i	Number of recovered animals in patch i at time t
U_i	Number of susceptible mosquitoes in patch i at time t
V_i	Number of infectious mosquitoes in patch i at time t

The parameters for the model and their description

r	Recruitment rate of animals
c	Movement speed of animals
d_i	The length of journey for animals within patch i
μ	Natural death rate for animals
δ	Disease-induced death rate for animals
γ	Recovery rate for animals
ζ	Rate of loss of immunity for animals
ξ_i	Growth rate of mosquitoes in patch i
ν_i	Natural death rate for mosquitoes in patch i
M_i	Carrying capacity for mosquitoes in patch i
α_i	Transmission rate from vector to host in patch i
β_i	Transmission rate from host to vector in patch i

Reduced system

The total number of mosquitoes in patch i at time t, denoted $N_i^v(t)$, satisfies

$$\frac{dN_i^v}{dt} = (\xi_i - \nu_i)N_i^v - \frac{\xi_i - \nu_i}{M_i}(N_i^v)^2, i = 1, 2, 3,$$

and it converges to M_i as $t \to \infty$. Let $1/p_i = d_i/c$ be the average time an animal spent in patch i. System (1)-(3) can be reduced to

$$\begin{cases} \frac{dS_1}{dt} = r - \alpha_1 S_1 V_1 - \mu S_1 + \zeta R_1 - p_1 S_1, \\ \frac{dI_1}{dt} = \alpha_1 S_1 V_1 - (\mu + \gamma + \delta) I_1 - p_1 I_1, \\ \frac{dR_1}{dt} = \gamma I_1 - (\mu + \zeta) R_1 - p_1 R_1, \\ \frac{dV_1}{dt} = -\nu_1 V_1 + \beta_1 I_1 (M_1 - V_1), \end{cases} \quad (4)$$

Reduced system-patch 2 and 3

$$\begin{cases} \dfrac{dS_2}{dt} = p_1 S_1 - \alpha_2 S_2 V_2 - \mu S_2 + \zeta R_2 - p_2 S_2, \\ \dfrac{dI_2}{dt} = p_1 I_1 + \alpha_2 S_2 V_2 - (\mu + \gamma + \delta) I_2 - p_2 I_2, \\ \dfrac{dR_2}{dt} = p_1 R_1 + \gamma I_2 - (\mu + \zeta) R_2 - p_2 R_2, \\ \dfrac{dV_2}{dt} = -\nu_2 V_2 + \beta_2 I_2 (M_2 - V_2), \end{cases} \tag{5}$$

$$\begin{cases} \dfrac{dS_3}{dt} = p_2 S_2 - \alpha_3 S_3 V_3 - \mu S_3 + \zeta R_3 - p_3 S_3, \\ \dfrac{dI_3}{dt} = p_2 I_2 + \alpha_3 S_3 V_3 - (\mu + \gamma + \delta) I_3 - p_3 I_3, \\ \dfrac{dR_3}{dt} = p_2 R_2 + \gamma I_3 - (\mu + \zeta) R_3 - p_3 R_3, \\ \dfrac{dV_3}{dt} = -\nu_3 V_3 + \beta_3 I_3 (M_3 - V_3). \end{cases} \tag{6}$$

3. Main results

Theorem 1. *All forward solutions in* $\mathbb{R}^{12}_+$ *of* (4)-(6) *eventually enter into* $\Omega = \Omega_1 \times \Omega_2 \times \Omega_3$, *where* $\Omega_i = \{(S_i, I_i, R_i, V_i) \in \mathbb{R}^4_+ : S_i + I_i + R_i \leq r \prod_{j=1}^{i} \frac{p_{j-1}}{\mu + p_j}, V_i \leq M_i\}, i = 1, 2, 3$, *and* $p_0 = 1$, *and* Ω *is positively invariant for* (4)-(6).

Disease-free equilibrium

System (4)-(6) has a unique disease-free equilibrium

$$\begin{aligned} E^0 &= (S_1^0, I_1^0, R_1^0, V_1^0, S_2^0, I_2^0, R_2^0, V_2^0, S_3^0, I_3^0, R_3^0, V_3^0) \\ &= \Big(\frac{r}{\mu+p_1}, 0, 0, 0, \frac{rp_1}{(\mu+p_1)(\mu+p_2)}, 0, 0, 0, \frac{rp_1p_2}{(\mu+p_1)(\mu+p_2)(\mu+p_3)}, 0, 0, 0\Big). \end{aligned}$$

Note that system (4)-(6) is in a block-triangular form, the dynamics of patch 1 is independent of patch 2 and patch 3 while the dynamics of patch 2 is independent of patch 3.

The first patch

$E_1^0 = (S_1^0, 0, 0, 0)$ is the unique DFE of subsystem (4).
The basic reproduction number for the first patch equals

$$\mathcal{R}_{10} = \rho(FV^{-1}) = \sqrt{\frac{\alpha_1 S_1^0}{\nu_1} \cdot \frac{\beta_1 M_1}{\mu + \gamma + \delta + p_1}} = \sqrt{\frac{\alpha_1 r}{(\mu + p_1)\nu_1} \cdot \frac{\beta_1 M_1}{\mu + \gamma + \delta + p_1}}.$$

Theorem 2. *The disease-free equilibrium* E_1^0 *of* (4) *is globally asymptotically stable in* Ω_1 *if* $\mathcal{R}_{10} \leq 1$ *and unstable if* $\mathcal{R}_{10} > 1$.

Theorem 3. *If* $\mathcal{R}_{10} > 1$, *then system* (4) *has a unique endemic equilibrium, denoted* $E_1^* = (S_1^*, I_1^*, R_1^*, V_1^*)$, *which is locally asymptotically stable. Moreover, the disease is uniformly persistent in* Ω_1^0, *the interior of* Ω_1, *i.e., there is a constant* $\epsilon > 0$ *such that any solution of* (4) *starting at a point of* Ω_1^0 *satisfies*

$$\liminf_{t \to \infty} (I_1(t), R_1(t), V_1(t)) > (\epsilon, \epsilon, \epsilon).$$

The second patch

- By a simple comparison theorem, we conclude that the disease is uniformly persistent in Ω^0 if it is uniformly persistent in Ω_1^0. Namely, the disease will persist in all three patches if $\mathcal{R}_{10} > 1$.
- If the disease dies out in patch 1, i.e., $\mathcal{R}_{10} \leq 1$, each solution of (4) with nonnegative initial data converges to E_1^0 and the limiting system of (5) is

$$\begin{aligned}
\frac{dS_2}{dt} &= p_1 S_1^0 - \alpha_2 S_2 V_2 - \mu S_2 + \zeta R_2 - p_2 S_2, \\
\frac{dI_2}{dt} &= \alpha_2 S_2 V_2 - (\mu + \gamma + \delta) I_2 - p_2 I_2, \\
\frac{dR_2}{dt} &= \gamma I_2 - (\mu + \zeta) R_2 - p_2 R_2, \\
\frac{dV_2}{dt} &= -\nu_2 V_2 + \beta_2 I_2 (M_2 - V_2).
\end{aligned} \tag{7}$$

- System (7) possesses a unique disease-free equilibrium $E_2^0 = (S_2^0, I_2^0, R_2^0, V_2^0) = (p_1 S_1^0/(\mu + p_2), 0, 0, 0) = (rp_1/((\mu + p_1)(\mu + p_2)), 0, 0, 0)$ and we define the basic reproduction number of patch 2 as

$$\mathcal{R}_{20} = \sqrt{\frac{\alpha_2 S_2^0}{\nu_2} \cdot \frac{\beta_2 M_2}{\mu + \gamma + \delta + p_2}} = \sqrt{\frac{\alpha_2 r p_1}{(\mu + p_1)(\mu + p_2)\nu_2} \cdot \frac{\beta_2 M_2}{\mu + \gamma + \delta + p_2}}.$$

- If $\mathcal{R}_{10} \leq 1$ and $\mathcal{R}_{20} \leq 1$, then the disease goes extinct in the first two patches; if $\mathcal{R}_{10} \leq 1$ and $\mathcal{R}_{20} > 1$, then the disease dies out in the first patch, but persists in the last two patches.

The third patch

- Similarly, if $\mathcal{R}_{10} \leq 1$ and $\mathcal{R}_{20} \leq 1$, we get a limiting system

$$\begin{aligned}
\frac{dS_3}{dt} &= p_2 S_2^0 - \alpha_3 S_3 V_3 - \mu S_3 + \zeta R_3 - p_3 S_3, \\
\frac{dI_3}{dt} &= \alpha_3 S_3 V_3 - (\mu + \gamma + \delta) I_3 - p_3 I_3, \\
\frac{dR_3}{dt} &= \gamma I_3 - (\mu + \zeta) R_3 - p_3 R_3, \\
\frac{dV_3}{dt} &= -\nu_3 V_3 + \beta_3 I_3 U_3,
\end{aligned} \tag{8}$$

- System (8) has a unique disease-free equilibrium $E_3^0 = (S_3^0, I_3^0, R_3^0, V_3^0) = (p_2 S_2^0/(\mu + p_3), 0, 0, 0) = (r p_1 p_2/((\mu + p_1)(\mu + p_2)(\mu + p_3)), 0, 0, 0)$ and we define the basic reproduction number of patch 3 as

$$\mathcal{R}_{30} = \sqrt{\frac{\alpha_3 S_3^0}{\nu_3} \cdot \frac{\beta_3 M_3}{\mu + \gamma + \delta + p_3}} = \sqrt{\frac{\alpha_3 r p_1 p_2}{(\mu + p_1)(\mu + p_2)(\mu + p_3)\nu_3} \cdot \frac{\beta_3 M_3}{\mu + \gamma + \delta + p_3}}.$$

If $\mathcal{R}_{10} \leq 1$, $\mathcal{R}_{20} \leq 1$ and $\mathcal{R}_{30} \leq 1$, then the disease goes extinct in all three patches; if $\mathcal{R}_{10} \leq 1$, $\mathcal{R}_{20} \leq 1$ and $\mathcal{R}_{30} > 1$, then the disease dies out in the first two patches, but persists in the third patch. So, we have the following result:

Theorem 4. *For the full system* (4)-(6)*, if* $\mathcal{R}_{10} > 1$*, the disease persists in all three patches; if* $\mathcal{R}_{10} \leq 1$ *and* $\mathcal{R}_{20} > 1$*, the disease dies out in the first patch, but persists in the remaining two patches; if* $\mathcal{R}_{10} \leq 1$*,* $\mathcal{R}_{20} \leq 1$ *and* $\mathcal{R}_{30} > 1$*, the disease dies out in the first two patches, but persists in the last patch; if* $\mathcal{R}_{10} \leq 1$*,* $\mathcal{R}_{20} \leq 1$ *and* $\mathcal{R}_{30} \leq 1$*, the disease dies out in all three patches and* E_0 *is GAS.*

Theorem 5. *System* (4)-(6) *has a unique endemic equilibrium, denoted* $E^* = (S_1^*, I_1^*, R_1^*, V_1^*, S_2^*, I_2^*, R_2^*, V_2^*, S_3^*, I_3^*, R_3^*, V_3^*)$*, if and only if* $\mathcal{R}_{10} > 1$ *and it is locally asymptotically stable when it exists.*

Model with Permanent Immunity

- Research in RVF indicates that an infection leads to a durable, probably life-long, immunity in animals.
- We may assume that the rate of loss of immunity ζ equals zero and use an SIR model for the host population. In this case, since R_i does not appear in other equations of (4)-(6), system (4)-(6) can be reduced to a 9-dimensional system.
- We can use the second additive compound matrix method (Li and Muldowney, 1996) to prove that the disease dynamics are completely determined by the basic reproduction numbers $\mathcal{R}_{i0}$ for $i = 1, 2, 3$.

The relation between $\mathcal{R}_0$ and model parameters

Recall that

$$\mathcal{R}_{i0}^2 = \frac{\alpha_i r}{\nu_i} \prod_{j=1}^{i} \frac{p_{j-1}}{\mu + p_j} \cdot \frac{\beta_i M_i}{\mu + \gamma + \delta + p_i}, p_i = \frac{c}{d_i}, i = 1, 2, 3, \text{ and } p_0 = 1.$$

- Obviously, $\mathcal{R}_{i0}$ is strictly increasing in α_i, β_i, M_i, r or d_i, and strictly decreasing in ν_i, μ, γ, δ or d_j, $j = 1, \ldots, i-1$.
- An increase in the movement speed, c, will decrease $\mathcal{R}_{10}$. The dependence of $\mathcal{R}_{i0}$ on c becomes more complicated if $i > 1$.

$\mathcal{R}_0^i$ vs c

Proposition 1. *For $i > 1$, there exists some c_i^* such that the basic reproduction number $\mathcal{R}_{i0}$ is strictly increasing in c if $c \in (0, c_i^*)$ and strictly decreasing if $c \in (c_i^*, \infty)$. Furthermore, $(i-1)\mu\underline{d}_i/2 < c_i^* < (i-1)\mu\bar{d}_i$, where $\underline{d}_i = \min_{1\le j\le i} d_j$ and $\bar{d}_i = \max_{1\le j\le i} d_j$.*

Remark 1. The duration of movement in each patch, $1/p_i = d_i/c$, is about a few weeks or months, while the life span of an animal, $1/\mu$, could be a couple of years or even longer. Namely, the timescale of the movement is very short relative to the host population dynamic timescale. So generally speaking, $\mathcal{R}_{i0}$ is decreasing in c and shortening the duration of host movement could reduce the possibility of a disease spread.

Sensitivity analysis

- The normalized forward sensitivity index or elasticity of $\mathcal{R}_{i0}$ to a parameter p is defined as

$$\Upsilon_p^i = \frac{\partial \mathcal{R}_{i0}}{\partial p} \times \frac{p}{\mathcal{R}_{i0}}.$$

- For $i = 1, 2, 3$, we find that $\Upsilon_{\alpha_i}^i = \Upsilon_{\beta_i}^i = \Upsilon_{M_i}^i = \Upsilon_r^i = \frac{1}{2}$, $\Upsilon_{\nu_i}^i = -\frac{1}{2}$, $\Upsilon_\gamma^i > -\frac{1}{2}$ and $\Upsilon_\delta^i > -\frac{1}{2}$. In addition, if $c \gg \mu \bar{d}_i$ then

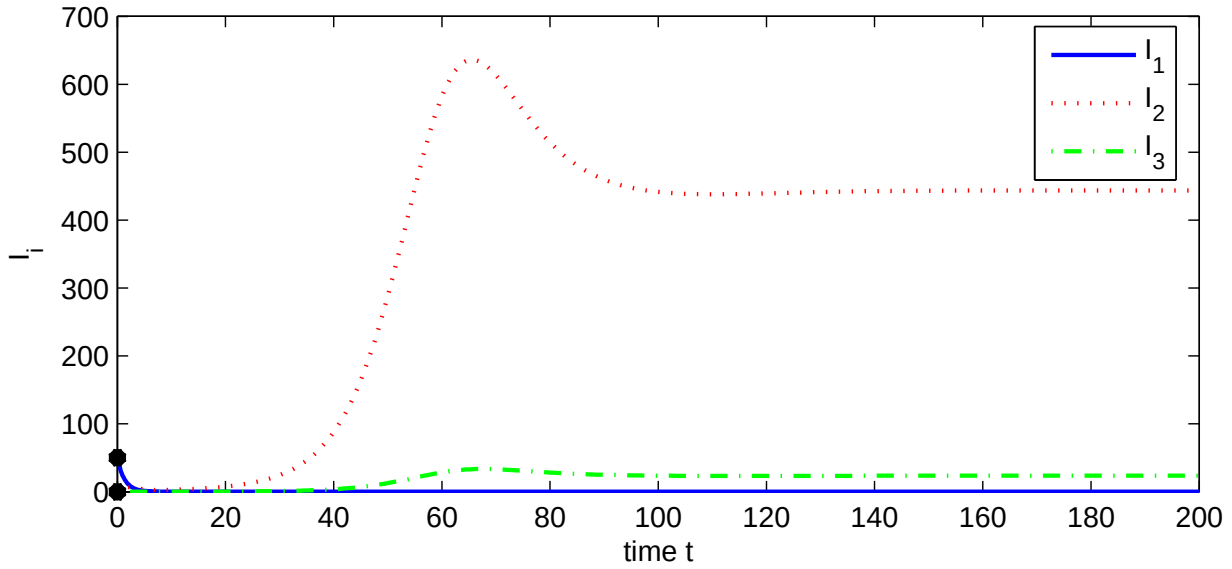
$$\Upsilon_\mu^i > -\frac{1}{2}, \Upsilon_{d_j}^i > -\frac{1}{2}, \text{ for } j = 1, \ldots, i-1, \Upsilon_{d_i}^i > \frac{1}{2}, \text{ and } \Upsilon_c^i < -\frac{1}{2}.$$

- It follows from $\Upsilon_{d_i}^i > -\Upsilon_c^i$ that $\mathcal{R}_{i0}$ is most sensitive to the travel distance in the ith patch, d_i. However, the travel route is usually fixed and thus the most feasible way for fast reducing $\mathcal{R}_{i0}$ is to accelerate livestock transport.

4. Simulations

- Parameter values: $r = 300, \mu = 1.2 \times 10^{-3}, \delta = 0.1, \gamma = 0.4, \zeta = 5 \times 10^{-3}, c = 25, M_1 = 1000, M_2 = 8000, M_3 = 1500, d_1 = 100, d_2 = 800, d_3 = 200, \nu_i = 0.06, \alpha_i = 3 \times 10^{-5}$ and $\beta_i = 8 \times 10^{-5}$ for $i = 1, 2, 3$.
- The respective basic reproduction numbers are $\mathcal{R}_{10} = 0.2522 < 1, \mathcal{R}_{20} = 2.352 > 1$ and $\mathcal{R}_{30} = 0.4672 < 1$.
- To consider hypothetical disease invasion scenarios, we set the initial data such that there is no infected animals or mosquitoes in patch 2 and 3.

$\mathcal{R}_{10} < 1, \mathcal{R}_{20} > 1$ and $\mathcal{R}_{30} > 1$



Numerical solution of system (4) showing I_i vs t. Initial conditions:
$S_1(0) = 1800, I_1(0) = 50, R_1(0) = 100, V_1(0) = 0$ and
$S_2(0) = I_2(0) = R_2(0) = V_2(0) = S_3(0) = I_3(0) = R_3(0) = V_3(0) = 0$.
The disease dies out in patch 1, but persists in patch 2 and 3.

5. Discussion

- We have formulated a simple epidemic patch model aimed at capturing a scenario where animals are imported into Egypt from the south and taken north along the Nile for human consumption, with the risk of a RVF outbreak if some of them are infected.
- We have evaluated the basic reproduction number for each patch and established the threshold dynamics of the model.
- It is suggested that a small number of imported infectious animals from Sudan could result in an outbreak of RVF in Egypt.

- Increasing the recruitment rate of animals, r, or the carrying capacity of mosquitoes, M_i, will increase the basic reproduction number, $\mathcal{R}_{i0}$. So the likelihood of a RVF outbreak is higher when both r and M_i are large.

- The rate r at which animals are fed in might be determined by demand, which would be large during Muslim festival periods.
- For example, millions of animals are imported and slaughtered as each devout Muslim must traditionally slaughter one animal during the celebration of Eid al-Adha (also known as the Feast of Sacrifice). The date of Eid al-Adha varies from year to year as it is linked to the Islamic calendar and more attention should be paid to the transmission of RVFV when the rainy season (more mosquitoes) corresponds to the time of the occurrence of festivals.

Future work

- The global stability of the endemic equilibrium of model (4)-(6) is in general unclear.
- We may want to think about extending the model to a larger and more realistic patch network, and to study how changing the network affects disease spread.
- Seasonal effects on mosquito population and time-dependence of animal importation may also be incorporated.
- Data for disease, vector and animal migration from RVF endemic regions need to be collected so that we can further test the validity of our model.

Question?

Thank you