HIV influence on the transmission dynamics of Mpox

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1. Some facts on Mpox disease

- Mpox (Monkeypox previously) is a viral disease caused by the Mpox virus, a species of the genus Orthopoxvirus (WHO, 2023).
- On 23, July 2022, 13 & 14, August 2024, WHO (2022, 2024), CDC (2024) declared Mpox a Public Health Emergency of International Concern (PHEIC).
- January 2022-August 2024: Over 120 countries reported Mpox with over 100,000 Laboratory-confirmed cases reported and over 200 deaths (WHO, 2024).
- Initially present in animals (e.g. rodents, prairie dogs, mice), the virus has now spread to humans.
- Transmission routes: direct contact with infected animals and contact with skin lesions or bodily fluids (e.g. saliva, seminal).
- Symptoms: rash, fever, sore throat, headache, muscle aches, back pain, low energy, and swollen lymph nodes.
- Correlation between HIV & Mpox : 40%-90% of Mpox cases in USA & Europe are people with HIV (PWH); the co-infection leads to treatment complications (Saldana, 2023).

 

Figure 1: Skin rash/lesion of Mpox infected individuals

2. Model formulation

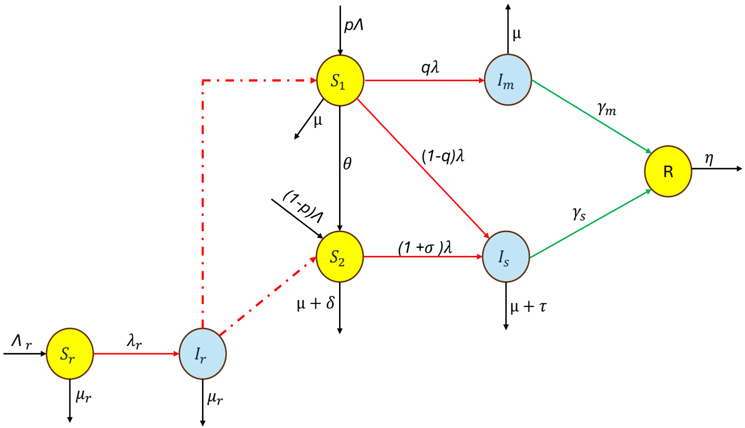

Figure 2: Flow diagram of the Mpox model, with PWH, (1) below

Continuous Model

$$\begin{cases} \dot{S}_1 = p\Lambda - \lambda S_1 - (\mu + \theta)S_1 \\ \dot{S}_2 = (1-p)\Lambda + \theta S_1 - \lambda(1+\sigma)S_2 - (\mu+\delta)S_2 \\ \dot{I}_m = q\lambda S_1 - (\mu + \gamma_m)I_m \\ \dot{I}_s = (1-q)\lambda S_1 + \lambda(1+\sigma)S_2 - (\mu + \gamma_s + \tau)I_s \\ \dot{R} = \gamma_m I_m + \gamma_s I_s - \eta R \\ \dot{S}_r = \Lambda_r - \lambda_r S_r - \mu_r S_r \\ \dot{I}_r = \lambda_r S_r - \mu_r I_r \end{cases} \tag{1}$$

$$\lambda = \frac{\beta_h(I_m + \nu_s I_s)}{N_h} + \frac{\omega I_r}{N_r} \text{ and } \lambda_r = \frac{\beta_r I_r}{N_r} \text{ (Forces of infection).}$$

Table 1: Model variables

Classes	Description
S_1	HIV uninfected individuals susceptible to Mpox infection.
S_2	HIV infected individuals susceptible to Mpox infection.
I_m	Asymptomatic and mild Mpox-infected individuals.
I_s	Severe Mpox cases.
R	Mpox recovered individuals.
S_r	Mpox susceptible rodents.
I_r	Mpox infected rodents.
$N_h(N_r)$	Total population of humans (animals)

Table 2: Parameters description.

Parameter	Description
$\Lambda(\Lambda_r)$	Recruitment constant of human (rodent) population .
p	Proportion of susceptible individuals recruited in S_1.
θ	Exit rate from S_1 to S_2.
$\beta_h(\omega)$	Mpox transmission rate due to contacts with individuals in $I_m(I_r)$.
ν_s	Modification parameter for the infectiousness of individuals in I_s.
β_r	Mpox human transmission rate of Mpox due to rodents.
q	Proportion of individuals in S_1 who develop a mild form of Mpox when infected.
σ	Modification parameter that accounts for the increased susceptibility of the individuals in S_2 as compared to those in S_1.
$\gamma_m(\gamma_s)$	Recovery rate in the compartment $I_m(I_s)$.
δ	Additional death rate in the S_2 compartment due to HIV's infection.
τ	Average additional death rate in I_s due to the severity of Mpox and eventually the co-morbidity of some of these individuals.
$\mu(\mu_r)$	Natural mortality rate of humans (rodents).
η	Mortality rate in compartment R.

Further notation

$$\phi_1 = \mu + \theta,\ \phi_2 = \mu + \delta,\ \phi_3 = \mu + \gamma_m,\ \phi_4 = \mu + \gamma_s + \tau,\ a_1 = p\Lambda,$$
$$a_2 = (1-p)\Lambda,\ a_3 = 1+\sigma,\ a_4 = 1-q;\ a_5 = a_2\phi_1 + \theta a_1,\ a_6 = a_1 a_4 a_3 + a_2 a_3,$$
$$a_7 = a_1 a_4 \phi_2 + a_3 a_5,\ a_8 = \gamma_m q a_1 a_3 \phi_4 + \phi_3 \gamma_s a_6,\ a_9 = \gamma_m q a_1 \phi_2 \phi_4 + \phi_3 \gamma_s a_7,$$
$$a_{10} = a_8 + a_6 \eta \phi_3 + q a_1 \eta \phi_4 a_3,\ a_{11} = a_7 \eta \phi_3 + a_9 + q a_1 \eta \phi_2 \phi_4 + a_2 \eta \phi_3 \phi_4 + a_1 \eta a_3 \phi_3 \phi_4,$$
$$a_{12} = a_1 \eta \phi_2 \phi_3 \phi_4 + a_5 \eta \phi_3 \phi_4,\ a_{13} = \beta_h q a_1 \eta \phi_4 a_3 + a_6 \eta \phi_3 \beta_h \nu_s,$$
$$a_{14} = \beta_h q a_1 \eta \phi_4 \phi_2 + a_7 \eta \phi_3 \beta_h \nu_s,$$
$$b_1 = ((1-q)S_{10} + a_3 S_{20})/\phi_3,\ b_2 = ((1-q)S_{10} + a_3 S_{20})/\phi_4,\ b_3 = ((1-q)S_{10} + a_3 S_{20})/\mu_r,$$
$$b_4 = ((1-q)S_{10} + a_3 S_{20}),\ \phi_5 = \phi_4 \gamma_m q + \phi_3 \gamma_s (1-q),\ \phi_6 = q\phi_4 \mu + (1-q)\phi_3 \mu + \phi_5,$$
$$N_0 = S_{10} + S_{20};\ c_1 = S_{10}/N_0,\ c_2 = S_{20}/N_0;\ c_3 = ((1-q)S_{10} + a_3 S_{20})/N_0.$$

3. Main results: full model

Theorem 1

1. *Model* (1) *is a dynamical system on the biologically feasible and attractive region* Ω*:*

$$\Omega = \Omega_h \times \Omega_r \equiv \{(S_1, S_2, I_m, I_s, R) \in \mathbb{R}^5_+,\ N_h \leq \frac{\Lambda}{\mu}\} \times \{(S_r, I_r) \in \mathbb{R}^2_+,\ N_r \leq \frac{\Lambda_r}{\mu_r}\}.$$

2. *The DFE,* $\mathcal{E}^0 \equiv (S_1, S_2, I_m, I_s, R, S_r, I_r)$*, and the basic reproduction number,* $\mathcal{R}_0$*, are:*

$$\mathcal{E}^0 = \left(\frac{a_1}{\phi_1}, \frac{a_2}{\phi_2} + \frac{a_1\theta}{\phi_1\phi_2}, 0, 0, 0; \frac{\Lambda_r}{\mu_r}, 0\right) \quad (2)$$

$$\mathcal{R}_0 = \max\left\{\frac{q\beta_h S_{10}}{\phi_3 N_0} + \frac{\beta_h \nu_s((1-q)S_{10} + a_3 S_{20})}{\phi_4 N_0},\ \frac{\beta_r}{\mu_r}\right\} \equiv \max\{\mathcal{R}_0^H,\ \mathcal{R}_0^R\} \quad (3)$$

3. *The DFE is locally asymptotically stable whenever* $\mathcal{R}_0 < 1$*, and unstable when* $\mathcal{R}_0 > 1$*.*

Remark 2

From Eq. (3)*, an epidemic can occur if either* $\mathcal{R}_0^H > 1$ *or* $\mathcal{R}_0^R > 1$*. However, the disease can disappear in the animal population, while persisting in the human population (Principle of competitive exclusion). Hence, the investigation of frontier equilibrium.*

Theorem 3

1. *For frontier equilibria:*
   - *If* $\mathcal{R}_0^H > 1$*, Model* (1) *has a unique frontier equilibrium, which is the human-only endemic equilibrium*
   - *If* $\mathcal{R}_0^H < 1$*, it has 0 or two positive frontier equilibria or human-only endemic equilibria.*
2. *For interior equilibria and* $\mathcal{R}_0^R > 1$*, Model* (1) *has at least one interior equilibrium in the following precise manner:*
   - *There is a unique interior equilibrium if* $A_1 A_2 > 0$ *or* $A_1 < 0$ *&* $A_2 > 0$
   - *There exists one or three interior equilibria if* $A_1 > 0$ *&* $A_2 < 0$*.*

   Here the coefficients A_1 *and* A_2 *involved in the algebraic equation,*

$$\mathcal{R}_0^R a_{10}(\lambda^*)^3 + (\lambda^*)^2 A_2 + \lambda^* A_1 - a_{12}\omega(\mathcal{R}_0^R - 1) = 0, \tag{4}$$

are

$$A_1 = \mathcal{R}_0^R a_{12}\left(1 - \mathcal{R}_0^H\right) - \omega a_{11}(\mathcal{R}_0^R - 1) \text{ and } A_2 = \mathcal{R}_0^R(a_{11} - a_{13}) - \omega a_{10}(\mathcal{R}_0^R - 1).$$

For the GAS of equilibria, we introduce an additional threshold $\mathcal{N}$:

$$\mathcal{N}_1 = \frac{(1-q)\beta_h\nu_s + a_3\beta_h\nu_s}{\phi_4},\ \mathcal{N}_2 = \frac{q\beta_h}{\phi_3(1-\mathcal{N}_1)},\ \mathcal{N}_0 = \mathcal{N}_1 + \mathcal{N}_2\ \&\ \mathcal{N} = \max\{\mathcal{N}_0, \mathcal{R}_0^R\}.$$

Theorem 4

The DFE for Model (1) *is globally asymptotically stable (GAS) whenever* $\mathcal{N} < 1$.

Remark 5

1. *Since* $\mathcal{R}_0 \leq \mathcal{N}$, *Theorem 4 implies that global control of Mpox requires more effort. It is clear that when* $\mathcal{R}_0^R < 1$, *the disease dies out in the rodent population. But, this does not guarantee disease elimination in the human population, as positive frontier equilibria may persist. (Remark 2).*
2. *We can use the target reproduction number,* $\mathcal{T}$, *(Shuai et al., 2015), to control the high-risk* S_2 *group of PWH. Under suitable conditions, we have*

$$\text{Either } 1 < \mathcal{R}_0 < \mathcal{T},\ \text{or } \mathcal{T} = \mathcal{R}_0 = 1,\ \text{or } \mathcal{T} < \mathcal{R}_0 < 1.$$

When $\mathcal{T} > 1$, *Mpox can be overcome by only targeting the population in* S_2: S_2*-control is sufficient if a proportion* $1 - \frac{1}{\mathcal{T}}$ *of susceptible in* S_2 *is controlled.*

4. Model with only human-to-human transmission

Without the spillover event from rodents to humans, Model (1) becomes

$$\begin{cases} \dot{S}_1 = p\Lambda - \lambda S_1 - (\mu + \theta)S_1, \\ \dot{S}_2 = (1-p)\Lambda + \theta S_1 - \lambda(1+\sigma)S_2 - (\mu+\delta)S_2, \\ \dot{I}_m = q\lambda S_1 - (\mu + \gamma_m)I_m, \\ \dot{I}_s = (1-q)\lambda S_1 + \lambda(1+\sigma)S_2 - (\mu + \gamma_s + \tau)I_s, \\ \dot{R} = \gamma_m I_m + \gamma_s I_s - \eta R, \\ \lambda = (\beta_h(I_m + \nu_s I_s))/N_h. \end{cases} \tag{5}$$

Interior equilibria are found by solving the quadratic equation

$$A(\lambda^*)^2 + B\lambda^* + C\left(1 - \mathcal{R}_0^H\right) = 0;\ A = a_{10}, \quad B = (a_{11} - a_{13}) \quad \text{and} \quad C = a_{12}. \tag{6}$$

Theorem 6

1. *Model (5) always admits a unique disease-free equilibrium* $E_0 = (S_{10}, S_{20}, 0, 0, 0)$.
2. *If* $\mathcal{R}_0^H > 1$, *Model (5) has a unique endemic equilibrium* E^*.
3. *The critical number* $\mathcal{R}_0^{H^*} := 1 - \frac{B^2}{4AC}$ *is such that for* $\mathcal{R}_0^H \in (\mathcal{R}_0^{H^*}, 1)$, *Model (5) possesses 2 endemic equilibria if, and only, if* $B < 0$.

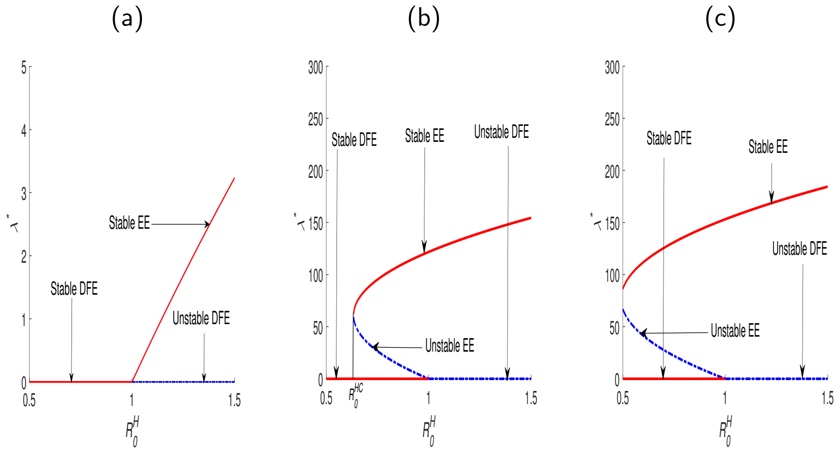

Figure 3: $\mathcal{R}_0^H$ is the basic reproduction number for Model (5). The model can exhibit different bifurcation behaviors (Banasiak, Ouifki, 2020): (a) forward, (b) backward , and (c) full backward

Theorem 7

1. *In the absence of the PWH group, the DFE of Model* (5) *is GAS when* $\mathcal{R}_0^H < 1$.
2. *In the general case, the DFE of Model* (5) *is GAS provided that* $\mathcal{N}_0 < 1$.
3. *If* $\mathcal{R}_0^H > 1$ *but close to 1, the unique endemic equilibrium* E^* *of System (5) is locally asymptotically stable. Moreover, System (5) undergoes a trans-critical/forward bifurcation at* $\mathcal{R}_0^H = 1$.

5.Model calibration: Case of the USA

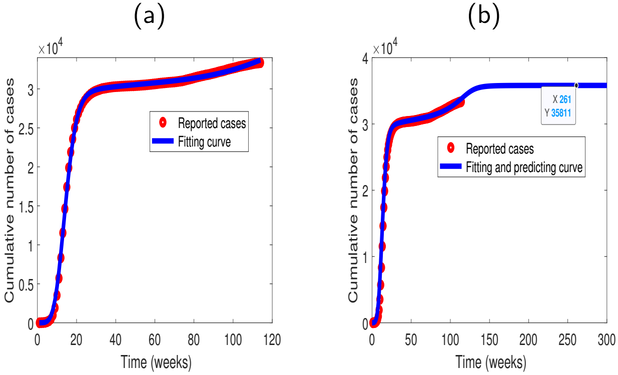

Figure 4: Calibration of Model (1) to the weekly cumulative Mpox cases in the USA from the beginning of the outbreak (10 May 2022) to 09 July 2024 (114 weeks) using the initial conditions: $S_1(0) = 340,334,045$, $S_2(0) = 1,200,000$, $I_m(0) = 0$, $I_s(0) = 1$, $R(0) = 0$, $S_r(0) = 150,000,000$. (a): Model calibration. (b): Predicting curve up to 2028. The predicting curve suggests that towards May 2027, Mpox will be overcome with 35,811 cases.

6. Nonstandard Finite Difference Scheme

Mickens, (1994, 2021), Anguelov, JL (2001, 2020), etc.

$$\begin{cases} \dfrac{S_1^{n+1}-S_1^n}{\varphi} = p\Lambda - \lambda^n S_1^{n+1} - (\mu+\theta)S_1^{n+1}, \\ \dfrac{S_2^{n+1}-S_2^n}{\varphi} = (1-p)\Lambda + \theta S_1^{n+1} - \lambda^n a_3 S_2^{n+1} - (\mu+\delta)S_2^{n+1}, \\ \dfrac{I_m^{n+1}-I_m^n}{\varphi} = q\lambda^n S_1^{n+1} - (\mu+\gamma_m)I_m^{n+1}, \\ \dfrac{I_s^{n+1}-I_s^n}{\varphi} = (1-q)\lambda^n S_1^{n+1} + \lambda^n a_3 S_2^{n+1} - (\mu+\gamma_s+\tau)I_s^{n+1}, \\ \dfrac{R^{n+1}-R^n}{\varphi} = \gamma_m I_m^{n+1} + \gamma_s I_s^{n+1} - \eta R^{n+1}, \\ \dfrac{S_r^{n+1}-S_r^n}{\varphi} = \Lambda_r - \lambda_r^n S_r^{n+1} - \mu_r S_r^{n+1}, \\ \dfrac{I_r^{n+1}-I_r^n}{\varphi} = \lambda_r^n S_r^{n+1} - \mu_r I_r^{n+1}, \end{cases} \tag{7}$$

$$\lambda^n = \frac{\beta_h(I_m^n + \nu_s I_s^N)}{N_h^n} + \frac{\omega I_r^n}{N_r^n},\ \lambda_r^n = \frac{\beta_r I_r^n}{N_r^n} \tag{8}$$

$$\varphi \equiv \varphi(h) = \frac{1-e^{-kh}}{k} = h + \mathcal{O}(h^2),\ \text{with } k \geq \mu+\delta+\eta. \tag{9}$$

Theorem 8

1. *The NSFD (7) is dynamically consistent with respect to the structural properties stated in Theorem 1. More precisely, this NSFD is a discrete dynamical system on the same region Ω irrespective of the size of Δt.*
2. *For $\mathcal{R}_0 \neq 1$ and k properly defined, the NSFD scheme is elementary stable in the sense of (Anguelov and JL, 2001): the fixed points of the scheme (7) are exactly the equilibrium points of Model (1), and their stability properties are the same as those of the continuous model. More precisely, the DFF is locally asymptotically stable whenever $\mathcal{R}_0 < 1$ and unstable for $\mathcal{R}_0 > 1$.*

7. Numerical simulations

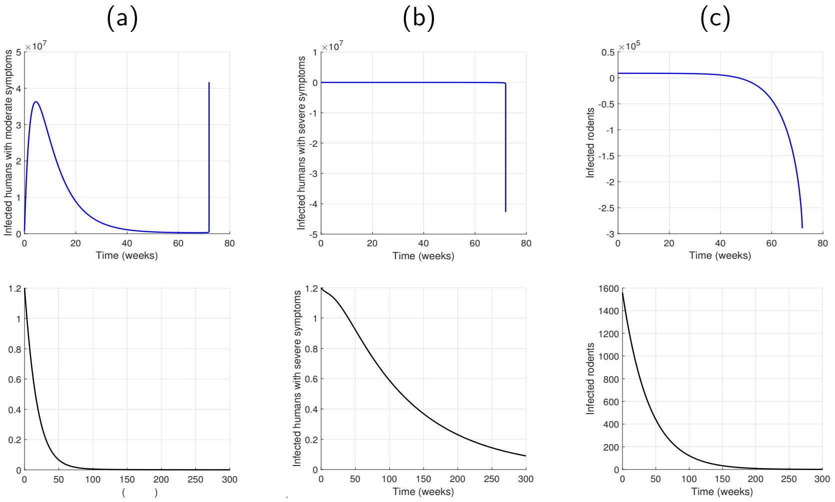

Figure 5: Unlike the ode 45 (top), the NSFD scheme is a discrete dynamical system on the biologically feasible region $\Omega = \Omega_h \times \Omega_r \subset \mathbb{R}_+^5 \times \mathbb{R}_+^2$ of the continuous model

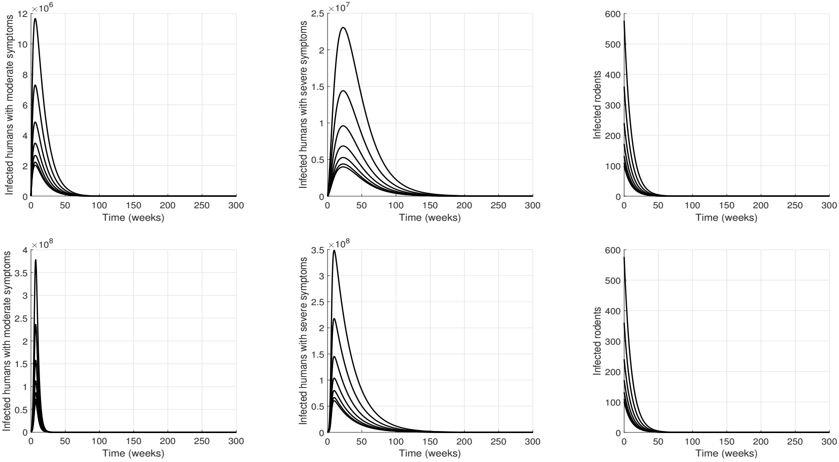

Figure 6: GAS of the DFE for Model (1) when $\mathcal{R}_0 := \max\{\mathcal{R}_0^R, \mathcal{R}_0^H\} < 1$ and an additional explicit threshold $\mathcal{N}$ is less than 1 (top) or larger than 1 (bottom).

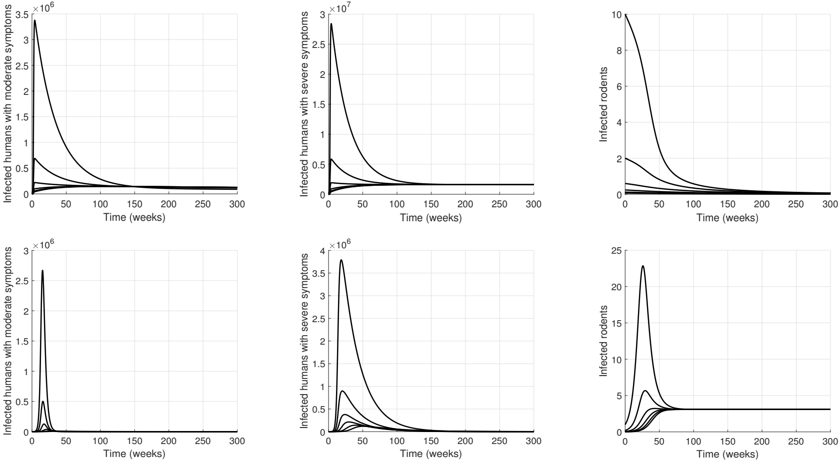

Figure 7: Frontier equilibria: The disease persists in the human population and disappears in the rodent population (top). It disappears in the human population, but persists in the rodent population (bottom).

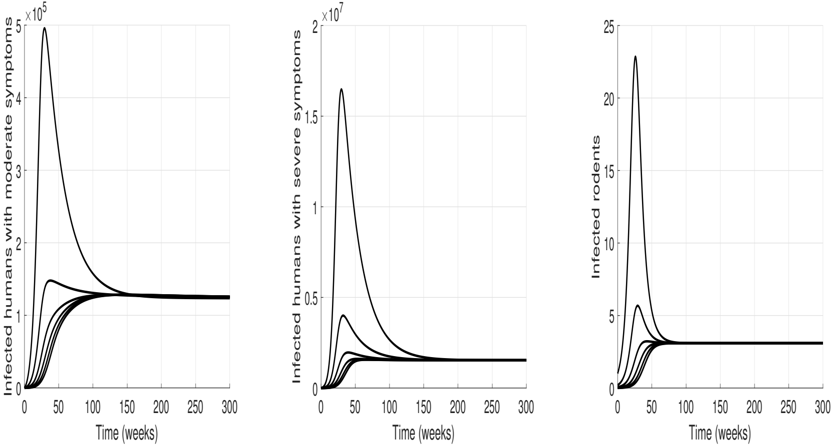

Figure 8: Stability of the interior equilibrium when $\mathcal{R}_0^R > 1$.

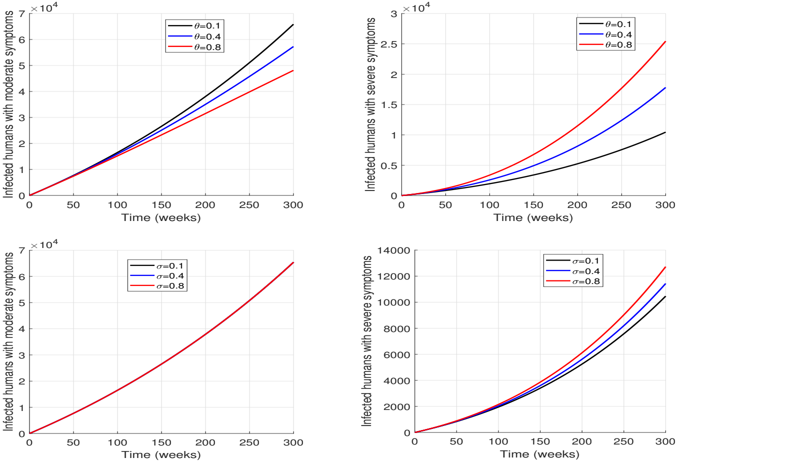

Figure 9: Influence of the parameters, σ, of increased susceptibility in S_2 and, θ of exiting from S_1 to S_2.

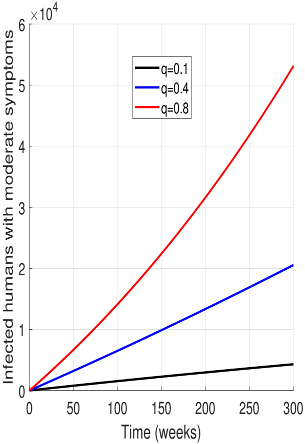

Figure 10: Influence of the parameter, q, proportion of S_1 with mild Mpox

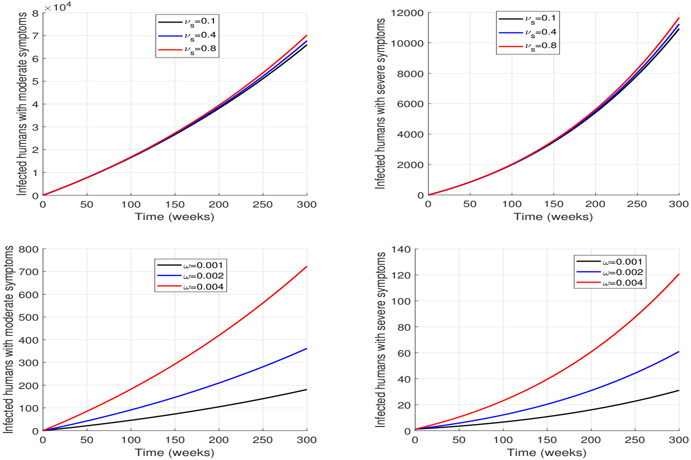

Figure 11: Influence of the the modification parameters, ν, for I_s and, ω, for I_r.

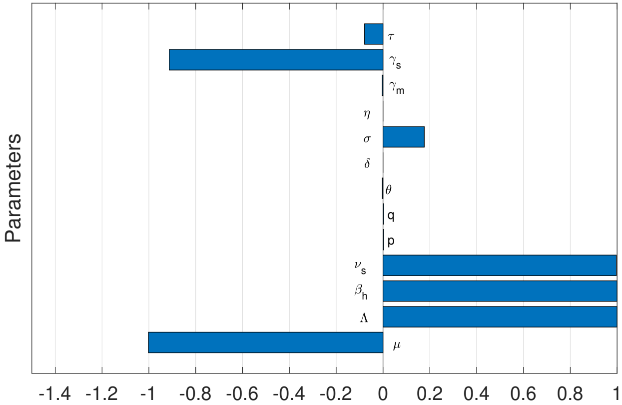

Figure 12: Local sensitivity indices of $\mathcal{R}_0$.

8. Conclusion

We proposed a model that allows individuals without HIV to develop a severe or moderate form of Mpox, while individuals with HIV only exhibit the severe form of the disease when infected.

- We did a thorough quantitative, qualitative, computational, and statistical analysis.
- We identified two threshold values, which, if kept below one, ensure the elimination of the disease in both the human-only and human-rodent populations
- The NSFD scheme we proposed supported the theory and revealed that rodent-to-human Mpox transmission is highly sensitive to the number of Mpox cases.

Future work include:

- The development of an HIV-Mpox co-infection model to investigate how the dynamics of one disease influence the dynamics of the other.
- Deeper study of the target reproduction number as threshold value that should be controlled to manage the disease by focusing on PWH.