Microsporidia MB infection as a Biocontrol Strategy against Malaria

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Outline

1. Overview

- Malaria is a mosquito-borne disease caused by a parasite of the genus plasmodium.
- It spreads to humans through the biting of infected mosquitoes who have become infected with the disease after biting an infected person.
- People with malaria often experience fever, chills, diarrhea, abdominal pain, fatigue, muscle or joint pain, nausea and vomiting, headache,.... Left untreated, they can develop more severe complications such as anemia, breathing problems, ..., which can lead to death.
- Multiple medicines and means are used to prevent and treat malaria (Artemisinin and Chloroquine for instance).
- Each year, around 290 million people are infected with malaria, and more than 400,000 die, mostly in Africa.
- The prevention of malaria is mostly based on avoiding bites of mosquitoes. This can be achieved by the use of mosquito nets and the use insecticides.
- Anopheles and plasmodium have become resistant to insecticides and treatments, respectively.

1. Overview

- Researchers are thinking about the control of malaria transmission by biological agents that could influence the ability of anopheles to transmit the disease.
- This strategy has been experimented for the control of some vector-borne diseases like dengue, chikungunya, zika, ... It is found that the wolbachia bacteria boost the mosquito's immune response to insects, making it more difficult for dengue and some other viruses to grow inside them.
- The World Mosquito Program (WMP) breeds mosquitoes infected with wolbachia in insectaries and releases them into communities where they breed with wild mosquitoes and produce offspring that are also infected.
- Recently, it has been discovered that anopheles symbiont microsporidia MB blocks malaria transmission in anopheles mosquitoes when they are infected with this bacterium.
- The microsporidia MB are a group of unicellular intracellular parasites closely related to fungi. They can be transmitted vertically and horizontally. The microsporidia MB horizontal transmission, which is the most common, occurs through mating between a virgin anopheles with an infected male.

2. Formulation of the impulsive model and some results

- S_h: Compartment susceptible humans.
- I_h: Compartment of infected humans. The mosquito population is subdivided into a group of females and a group of males. For the female mosquito population, we define
- S_v: Compartment of female mosquitoes which are susceptible both to plasmodium and microsporidia MB;
- I_v: compartment of female mosquitoes, infected with plasmodium, but susceptible to microsporidia;
- R_v: Compartment of female mosquitoes infected with microsporidia. Although microsporidia-positive anopheles females can also become infected with plasmodium, as they can no longer transmit malaria they remain in the compartment R_v of retired female mosquitoes. Microsporidia MB infection can be understood as a preventive treatment against plasmodium in the anopheles population.
- M_n: Compartment of male anopheles susceptible to microsporidia.
- M_p: Compartment of male anopheles infected with microsporidia

Furthermore, we set

$$N_h = S_h + I_h,\ V = S_v + I_v + R_v \text{ and } M = M_n + M_p$$

2. Model formulation

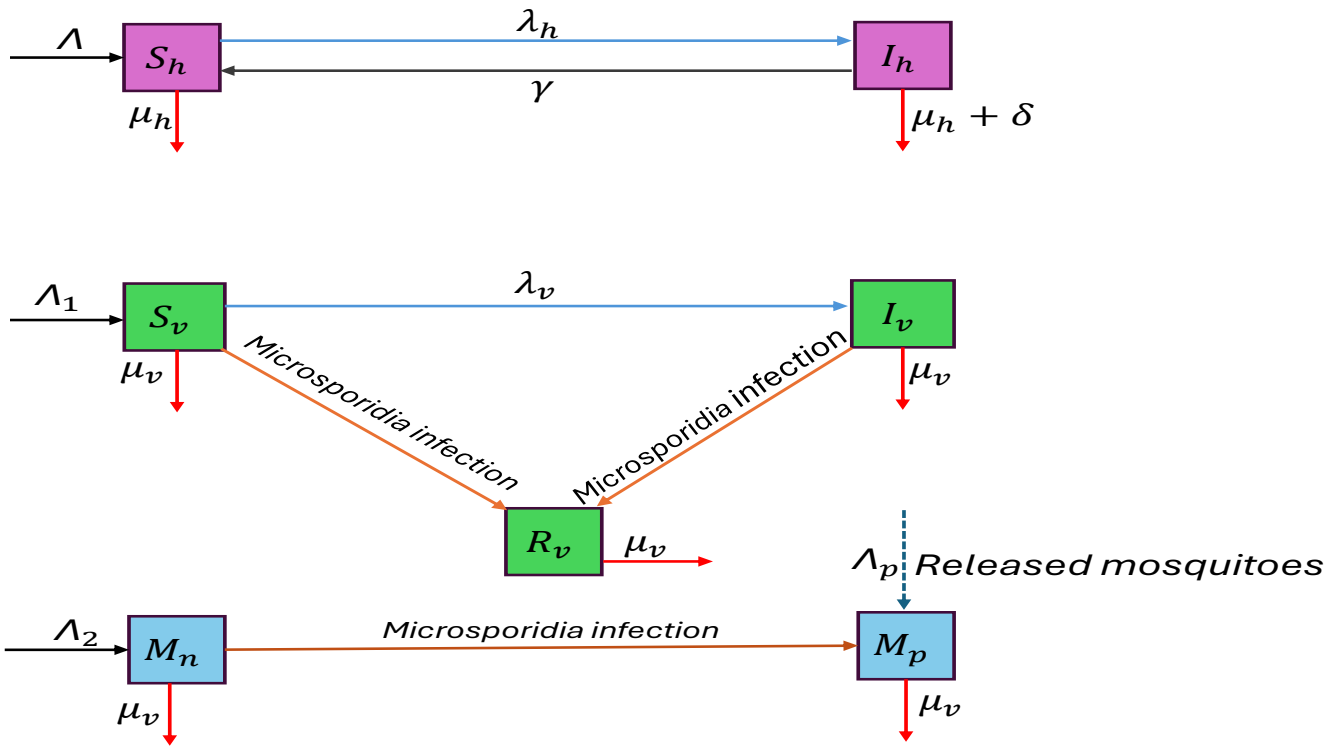

Figure: Flow diagram of Model (1)

2. Model formulation

Set $\lambda_h = \dfrac{p_1\beta I_v}{N_v} =: \dfrac{\beta_1 I_v}{N_v}, \quad \lambda_v = \dfrac{p_2\beta I_h}{N_h} =: \dfrac{\beta_2 I_h}{N_h}$

$$
\begin{cases}
\begin{cases}
\dot{S}_h(t) = \Lambda - \lambda_h S_h + \gamma I_h - \mu_h S_h, \\
\dot{I}_h(t) = \lambda_h S_h - (\mu_h + \delta + \gamma) I_h, \\
\dot{S}_v(t) = \Lambda_1 - \beta_{mv}\dfrac{S_v M_p}{M} - \lambda_v S_v - \mu_v S_v, \quad t > 0 \\
\dot{I}_v(t) = \lambda_v S_v - \beta_{mv}\dfrac{I_v M_p}{M} - \mu_v I_v, \\
\dot{R}_v(t) = \beta_{mv}\dfrac{M_p(S_v + I_v)}{M} - \mu_v R_v, \\
\dot{M}_n(t) = \Lambda_2 - \beta_{vm}\dfrac{M_n R_v}{V} - \mu_v M_n,
\end{cases} \\
\begin{cases}
\dot{M}_p(t) = \beta_{vm}\dfrac{M_n R_v}{V} - \mu_v M_p \qquad t \neq kT \\
M_p(kT^+) = \Lambda_p + M_p(kT), \quad t = kT,\ k \in \mathbb{N}
\end{cases}
\end{cases}
\tag{1}
$$

$M_p(kT^+)$ is the population of male mosquitoes infected with microsporidia just after the release that occurred at time $t = kT, k \in \mathbb{N}$. kT^+ is the momentarily times just after the time t. Each pulse instantaneously releases a fixed number Λ_p of microsporidia MB-positive males in the population.

2. Formulation of the impulsive model and some results

Parameter	Epidemiological interpretation	Values	Units	Range
Λ	Human recruitement constant	$1000/(70 \times 365)$	Ind.day^{-1}	0–100
$\Lambda_1(\Lambda_2)$	Recruitment constant of negative microsporidia MB female (male)	Variable	Mos.day^{-1}	0–5000
β	Mosquitoes biting rate	Variable	-	0–1
$p_1(p_2)$	Transmission probability of malaria to humans(mosquitoes)	1	-	0–1
β_{mv}	Male to female transmission of microsporidia	0.56	day^{-1}	0–1
β_{vm}	Female to male transmission of microsporidia	0.33	day^{-1}	0–1
μ_h	Natural mortality rate of humans	$1/(70 \times 365)$	day^{-1}	0–1
μ_v	Mortality rate of mosquitoes	0.0345	day^{-1}	0–1
γ	Malaria recovery rate	$1/4$	day^{-1}	0–1
δ	Death rate due to malaria	0.001	day^{-1}	0–1
Λ_p	Number of mosquitoes release			
T	Releasing period.			

2. Formulation and analysis of the impulsive model

Theorem 1

If

$$S_h(0^+), I_h(0^+), S_v(0^+), I_v(0^+), R_v(0^+), M_n(0^+), M_p(0^+) \geq 0,$$

$$\text{then } S_h(t), I_h(t), S_v(t), I_v(t), R_v(t), M_n(t), M_p(t) \geq 0, \ \forall\ t > 0.$$

Moreover, System (1) *is uniformly bounded. That is there exists* $\widehat{M} > 0$ *such that for large* t *enough*

$$N_h(t) \leq \max\left(N_h(0), \frac{\Lambda_h}{\mu_h}\right), \quad N_v(t) \leq \max\left(N_v(0), \frac{\Lambda_1}{\mu_v}\right), \quad \text{and} \quad M \leq \widehat{M}.$$

2. Formulation and analysis of the impulsive model

Theorem 2

System (2) *below has a globally asymptotically stable periodic solution.*

$$\widetilde{M}(t) = \frac{\Lambda_2}{\mu_v} + \frac{\Lambda_p e^{-\mu_v (t-kT)}}{1 - e^{-\mu_v T}}, \ \forall \ t \in (kT, (k+1)T].$$

$$\begin{cases} \dot{M}(t) = \Lambda_2 - \mu_v M(t), & t \neq kT \\ M(t^+) = M(t) + \Lambda_p & t = kT \end{cases} \tag{2}$$

3. Mathematical analysis of Model (1) without the release of mosquitoes

For the model to be more mathematically tractable, we consider the particular case where $\Lambda_p = 0$. Although this analysis will not give us insights into the impact of releasing mosquitoes in the control of malaria, it will provide us useful information on the outcome of the disease in an environment of mosquitoes with microsporidia MB.

$$\begin{cases} \dot{S}_h(t) = \Lambda - \lambda_h S_h + \gamma I_h - \mu_h S_h, \\ \dot{I}_h(t) = \lambda_h S_h - (\mu_h + \delta + \gamma) I_h, \\ \dot{S}_v(t) = \Lambda_1 - \beta_{mv} \dfrac{S_v M_p}{M} - \lambda_v S_v - \mu_v S_v, \\ \dot{I}_v(t) = \lambda_v S_v - \beta_{mv} \dfrac{I_v M_p}{M} - \mu_v I_v, \\ \dot{R}_v(t) = \beta_{mv} \dfrac{M_p(S_v + I_v)}{M} - \mu_v R_v, \\ \dot{M}_n(t) = \Lambda_2 - \beta_{vm} \dfrac{M_n R_v}{V} - \mu_v M_n, \\ \dot{M}_p(t) = \beta_{vm} \dfrac{M_n R_v}{V} - \mu_v M_p. \end{cases} \tag{3}$$

3. Mathematical analysis

Set

$$\phi = (\mu_h + \delta + \gamma),\ V^* = \frac{\Lambda_1}{\mu_v},\ \text{ and } \quad M^* = \frac{\Lambda_2}{\mu_v}$$

.

Theorem 3

Model (3) *is a dynamical system on the biologically feasible region* Ω *defined as*

$$\Omega := \Omega_h \times \Omega_{vm} \subset \mathbb{R}^2_+ \times \mathbb{R}^4_+$$

with

$$\Omega_h = \left\{ (S_h, I_h) \in \mathbb{R}^2_+ \,/\, N_h \leq \frac{\Lambda}{\mu_h} \right\}$$

and

$$\Omega_{vm} = \left\{ (S_v, I_v, R_v, M_n, M_p) \in \mathbb{R}^4_+ \,/\ V \leq \frac{\Lambda_1}{\mu_v},\ M \leq \frac{\Lambda_2}{\mu_v} \right\}.$$

3.1 Equilibria of the model

Theorem 4

Model (3) always admits a malaria-microsporidia-free equilibrium (MMFE) $\mathcal{E}_1 = \left(\frac{\Lambda}{\mu}, 0, \frac{\Lambda_1}{\mu_v}, 0, 0, \frac{\Lambda_2}{\mu_v}, 0\right)$. *Furthermore, when*

- $\mathcal{R}_0^M = \frac{\beta_{mv}\beta_{vm}}{\mu_v^2} > 1$, *Model (3) has a malaria-free equilibrium (MFE)*

  $\mathcal{E}_2 = \left(\frac{\Lambda}{\mu}, 0, S_{v2}^*, 0, R_{v2}^*, M_{n2}^*, M_{p2}^*\right)$.

- *When* $\mathcal{R}_0^{VH} = \frac{\beta_1\beta_2}{\phi\mu_v} > 1$, *Model (3) has a microsporidia-free equilibrium (MIFE)*

  $Q_1 = \left(\bar{S}_h, \bar{I}_h, \bar{S}_v, \bar{I}_v, 0, \frac{\Lambda_2}{\mu}, 0\right)$.

- *When* $\mathcal{R}_0^M > 1$, *Model (3) has a unique malaria-microsporidia co-existence equilibrium (EE)* Q_2 *provided that* $\mathcal{R}_0 > 1$, *where*

$$\mathcal{R}_0 = \frac{\beta_1\beta_2 M^*(V^* - R_v^*)}{\phi V^*(\mu_v M^* + \beta_{mv} M_p^*)}, \text{ with } R_v^* = \frac{M^* V^* \mu_v^2(\mathcal{R}_0^M - 1)}{\beta_{vm} M^*(\beta_{mv} + \mu_v)} \text{ and } M_p^* = \frac{M^*\mu_v(\mathcal{R}_0^M - 1)}{(\beta_{mv} + \mu_v) + \mu_v(\mathcal{R}_0^M - 1)}.$$

3.2 Stability of equilibria in the case where $\delta = 0$

The following theorem is due to Vidyasagar (M. A. Aziz-Alaoui et al.).

Theorem 5

Consider the following $\mathcal{C}^1$ system

$$\begin{cases} \dot{x} = f(x), \\ \dot{y} = g(x, y), \\ \text{with an equilibrium point } (x^*, y^*) \text{ i.e } f(x^*) = 0 \text{ and } g(x^*, y^*) = 0. \end{cases} \tag{4}$$

If x^* is globally asymptotically stable (GAS) in $\mathbb{R}^n$ for the system $\dot{x} = f(x)$, and if y^* is GAS in $\mathbb{R}^m$, for the system $\dot{y} = g(x^*, y)$, then (x^*, y^*) is (locally) asymptotically stable for (4). Moreover, if all the trajectories of (4) are forward bounded, then (x^*, y^*) is GAS for (4).

Under the assumption that $\delta = 0$, thanks to Model (3), one has

$$\begin{cases} \dot{N} = \Lambda - \mu N, \\ \dot{V} = \Lambda_1 - \mu_v V, \\ \dot{M} = \Lambda_2 - \mu_v M. \end{cases} \tag{5}$$

Remark

Under the hypothesis $\delta = 0$, $(N^*, V^*, \widetilde{M})$ is GAS for the impulsive system

$$\begin{cases} \begin{cases} \dot{N}_h(t) = \Lambda - \mu N_h(t), & t \geq 0 \\ \dot{V}(t) = \Lambda_1 - \mu_v V(t), & t \geq 0 \end{cases} \\ \begin{cases} \dot{M}(t) = \Lambda_2 - \mu_v M(t), & t \neq kT \\ M(t^+) = M(t) + \Lambda_p & t = kT \end{cases} \end{cases} \tag{6}$$

3.2 Stability of equilibria of Model (3) in the case where $\delta = 0$

The dynamics of Model (3) is the same as that of the reduced system

$$\begin{cases} \dot{I}_h(t) = \dfrac{\beta_1 I_v (N^* - I_h)}{V^*} - \phi I_h, \\ \dot{I}_v(t) = \dfrac{\beta_2 (V^* - I_v - R_v) I_h}{N^*} - \beta_{mv} \dfrac{I_v M_p}{M^*} - \mu_v I_v, \\ \dot{R}_v(t) = \beta_{mv} \dfrac{M_p (V^* - R_v)}{M^*} - \mu_v R_v, \\ \dot{M}_p(t) = \beta_{vm} \dfrac{R_v (M^* - M_p)}{V^*} - \mu_v M_p. \end{cases} \tag{7}$$

Theorem 6

When $\mathcal{R}_0^{VH} < 1$ and $\mathcal{R}_0^{M} < 1$, then the MMFE $\mathcal{E}_1$ is GAS.

3.2 Stability of equilibria in the case where $\delta = 0$

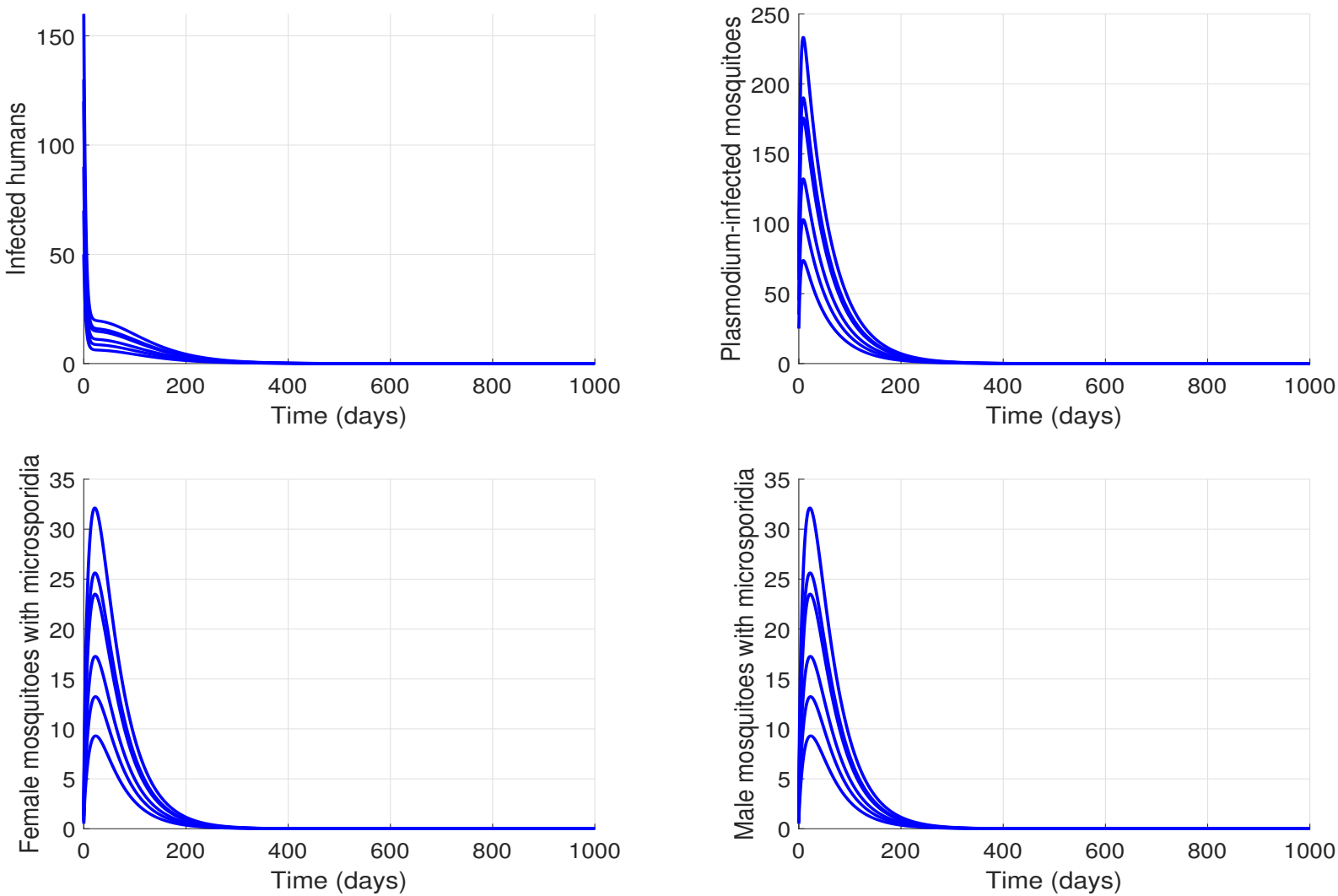

Figure: GAS of $\mathcal{E}_1$

3.2 Stability of equilibria in the case where $\delta = 0$

To prove the stability of the other equilibria, we use the result of Zhao and Jing given below (M. A. Aziz-Alaoui et al.).

Theorem 7

Let $\dot{y} = g(y)$ a differential system, with $g : \mathbb{R}^n_+ \to \mathbb{R}^n$, $n \in \mathbb{N} \setminus \{0\}$ a continuously differentiable map. Assume that:

1. *g is cooperative on $\mathbb{R}^n_+$ and the Jacobian matrix $(\partial g_i/\partial y_j)_{1\leq i,j\leq n}$ is irreducible for every $y \in \mathbb{R}^n_+$.*
2. *$g(0) = 0$ and $g_i(y) \geq 0$ for all $y \in \mathbb{R}^n_+$, with $y_i = 0$, $i = 1, 2, \ldots, n$.*
3. *g is strictly sub-linear on $\mathbb{R}^n_+$. Then,*
   (a) *if the stability modulus $s(J(0))$ of $J(0)$ is nonpositive (where $J(0)$ is the Jacobian matrix at 0), then $y = 0$ is GAS in $\mathbb{R}^n_+$;*
   (b) *if $s(J(0)) > 0$ and $\varphi(t, y_0)$ is the solution for $\dot{y} = g(y)$ initiate at y_0, then either:*
   - *for any $y \in \mathbb{R}^n_+$, $\lim_{t\to\infty} \|\varphi(t, y)\| = +\infty$, or alternatively,*
   - *system $\dot{y} = g(y)$ admits a unique positive steady state $y^* \gg 0$ which is GAS in $\mathbb{R}^n_+ \setminus \{0\}$.*

3.2 Stability of equilibria in the case where $\delta = 0$

Theorem 8

- *If* $\mathcal{R}_0^{VH} < 1$ *and* $\mathcal{R}_0^{M} > 1$, *then the MFE* $\mathcal{E}_2$ *is GAS.*
- *If* $\mathcal{R}_0^{M} < 1$ *then the frontier equilibrium* Q_1 *for System* (3) *is GAS provided that* $\mathcal{R}_0^{VH} > 1$.
- *When* $\mathcal{R}_0^{M} > 1$ *and* $\mathcal{R}_0 > 1$, *the EE* Q_2 *of Model* (3) *is GAS.*

Table: *Conditions for the global asymptotic Stability of the equilibria*

Equilibrium points	$\mathcal{E}_1$	$\mathcal{E}_2$	Q_1	Q_2
Conditions to be GAS	$\mathcal{R}_0^{VH} < 1$ *and* $\mathcal{R}_0^{M} < 1$	$\mathcal{R}_0^{VH} < 1$ *and* $\mathcal{R}_0^{M} > 1$	$\mathcal{R}_0^{VH} > 1$ *and* $\mathcal{R}_0^{M} < 1$	$\mathcal{R}_0^{M} > 1$ *and* $\mathcal{R}_0 > 1$

3.2 Stability of equilibria in the case where $\delta = 0$

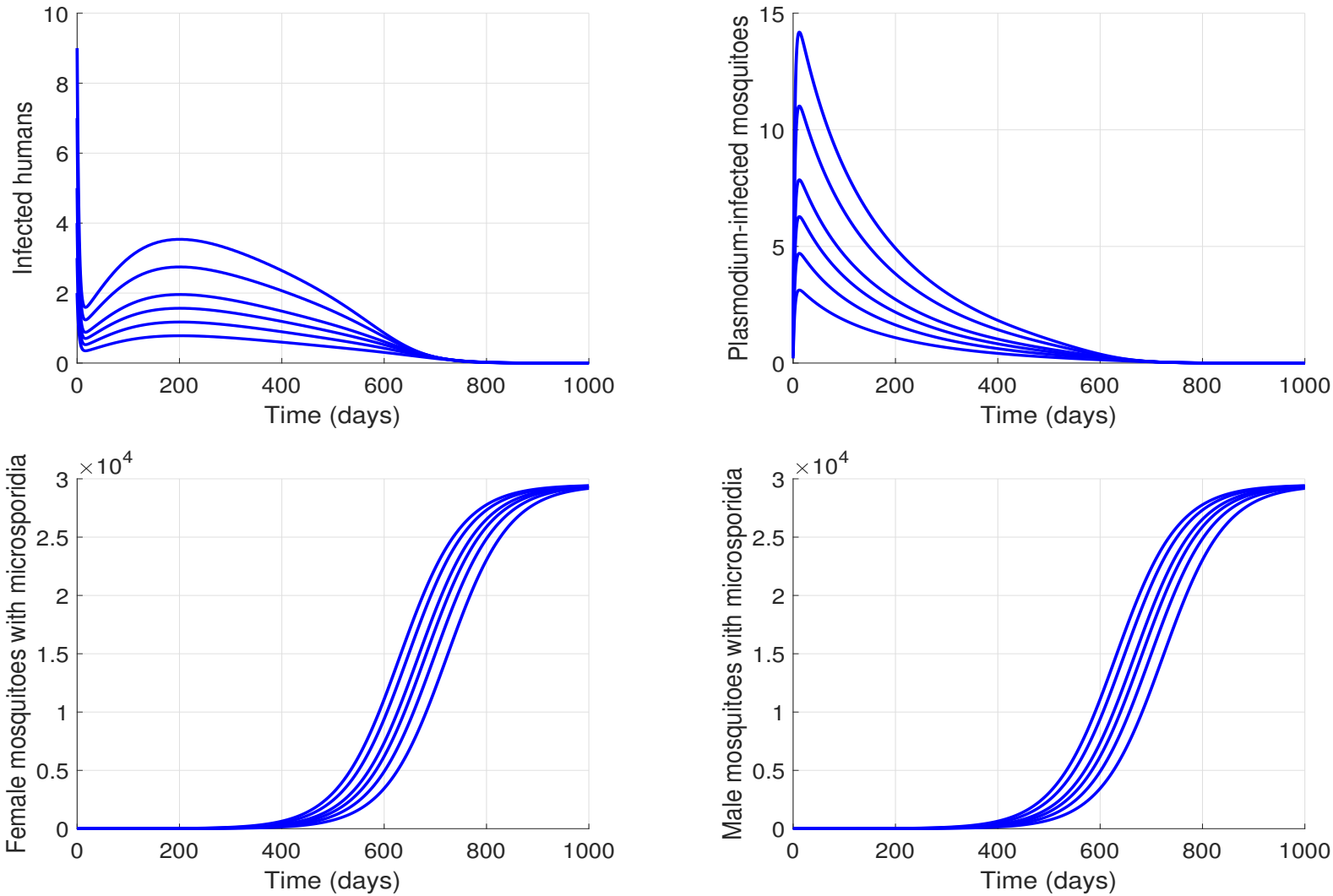

Figure: GAS of $\mathcal{E}_2$

3.2 Stability of equilibria in the case where $\delta = 0$

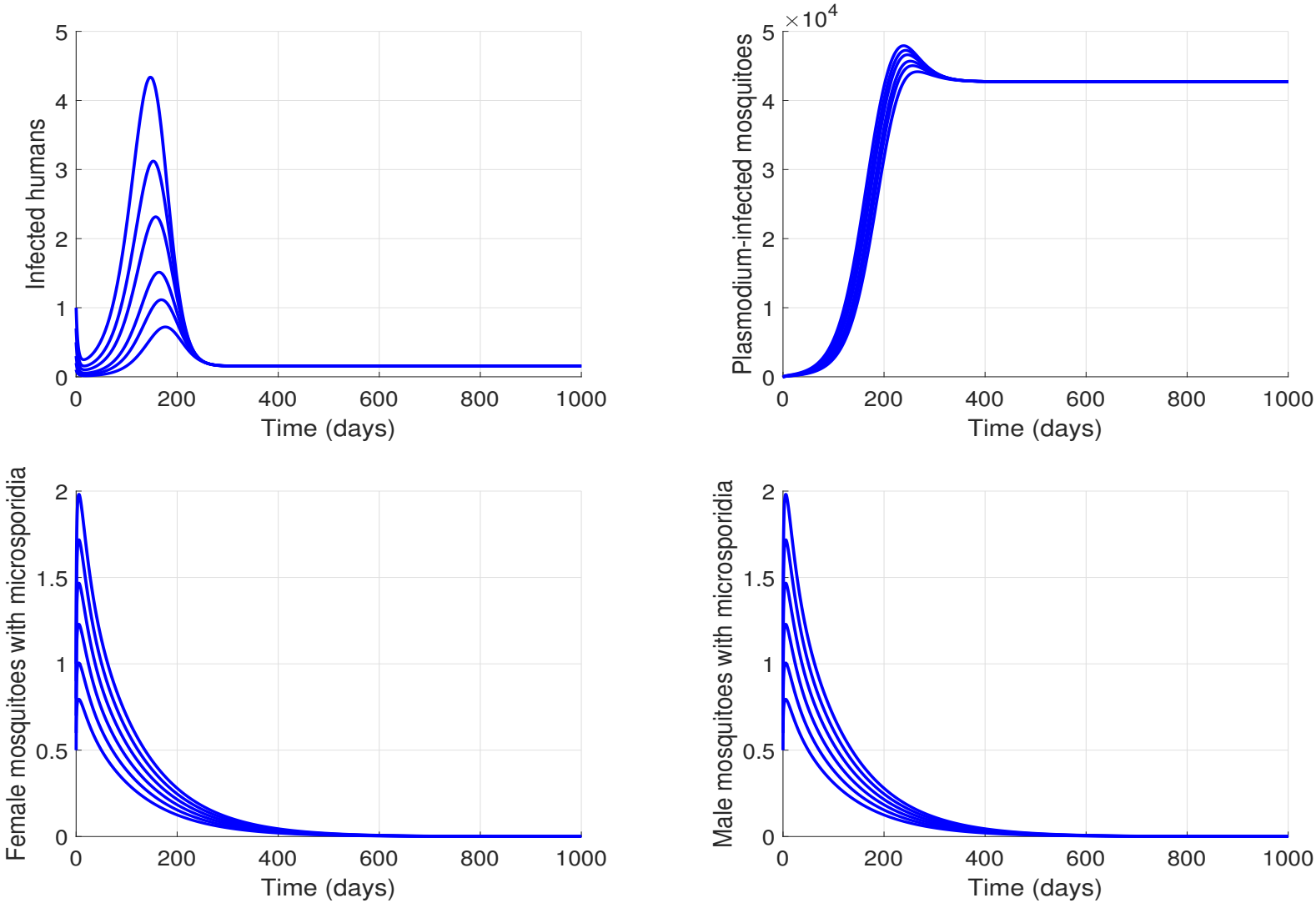

Figure: GAS of $\mathcal{Q}_1$

3.2 Stability of equilibria in the case where $\delta = 0$

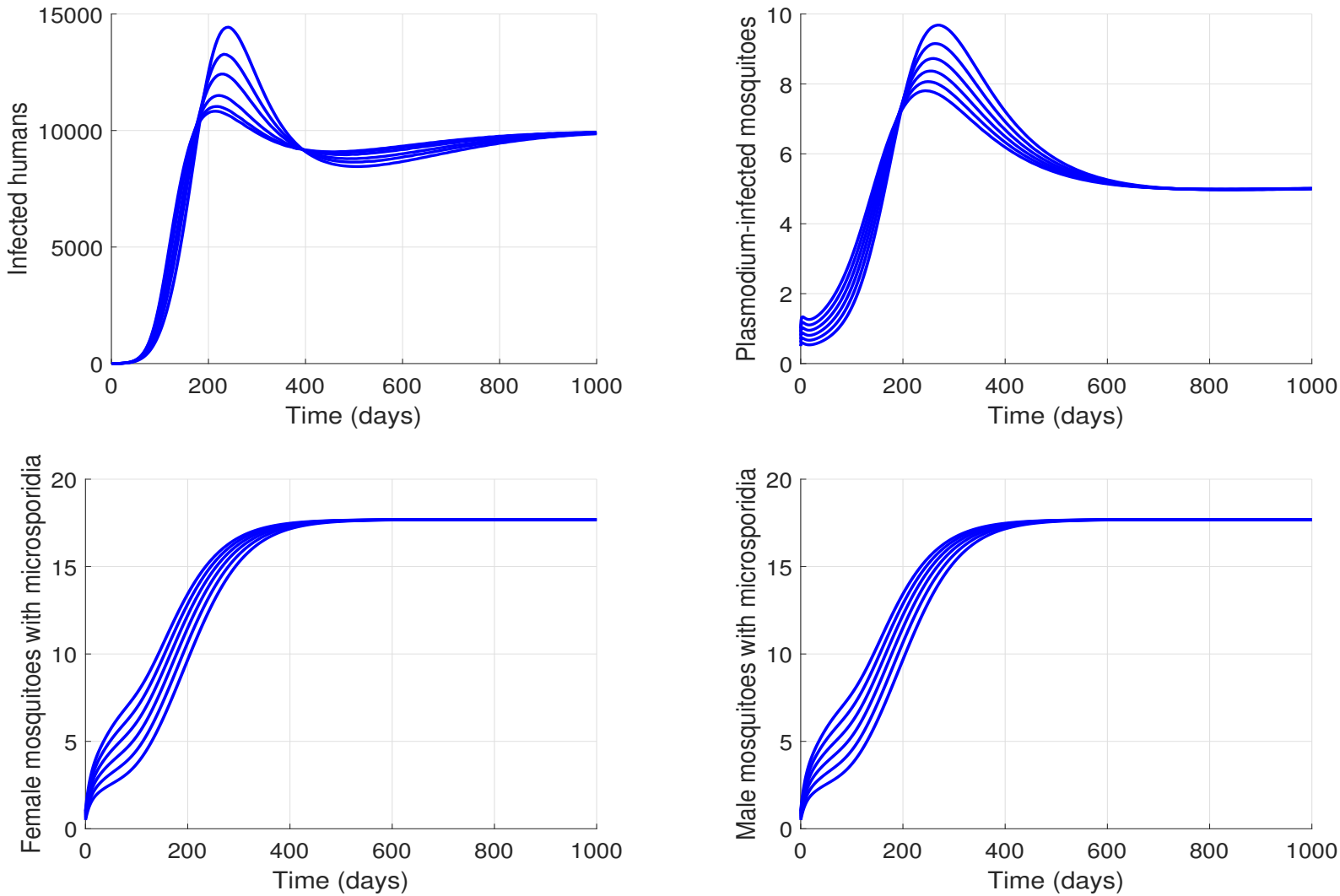

Figure: GAS of $\mathcal{Q}_2$

3.3 Unstability of equilibria ($\delta = 0$)

Theorem 9

- *If* $\mathcal{R}_0^{VH} > 1$ *then the MMFE* $\mathcal{E}_1$ *is unstable.*
- *If* $\mathcal{R}_0^{M} > 1$ *then the frontier equilibrium* Q_1 *is unstable.*
- *If* $\mathcal{R}_0^{VH} > \dfrac{V^*(\mu_v^2 + \beta_{mv} M_{p2}^*)}{\mu_v^2 (V^* - R_{v2}^*))}$ *then the MFE* $\mathcal{E}_2$ *is unstable.*

4. Sensitivity analysis of I_h

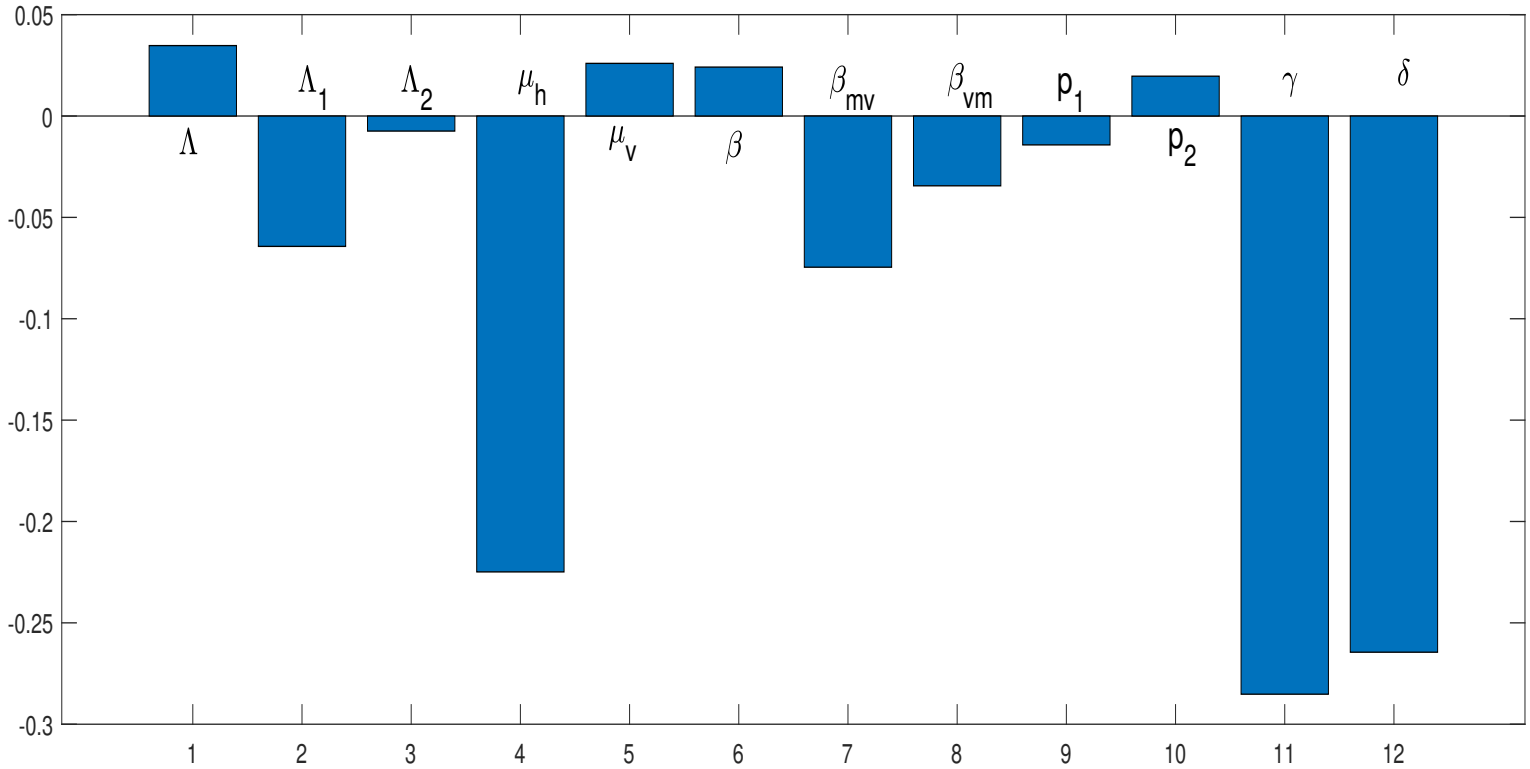

Figure: PRCCs of I_h. The sensitivity of μ_v shows that combining microsporidia MB with insecticides can be counterproductive.

5. Simulations of Model (3)

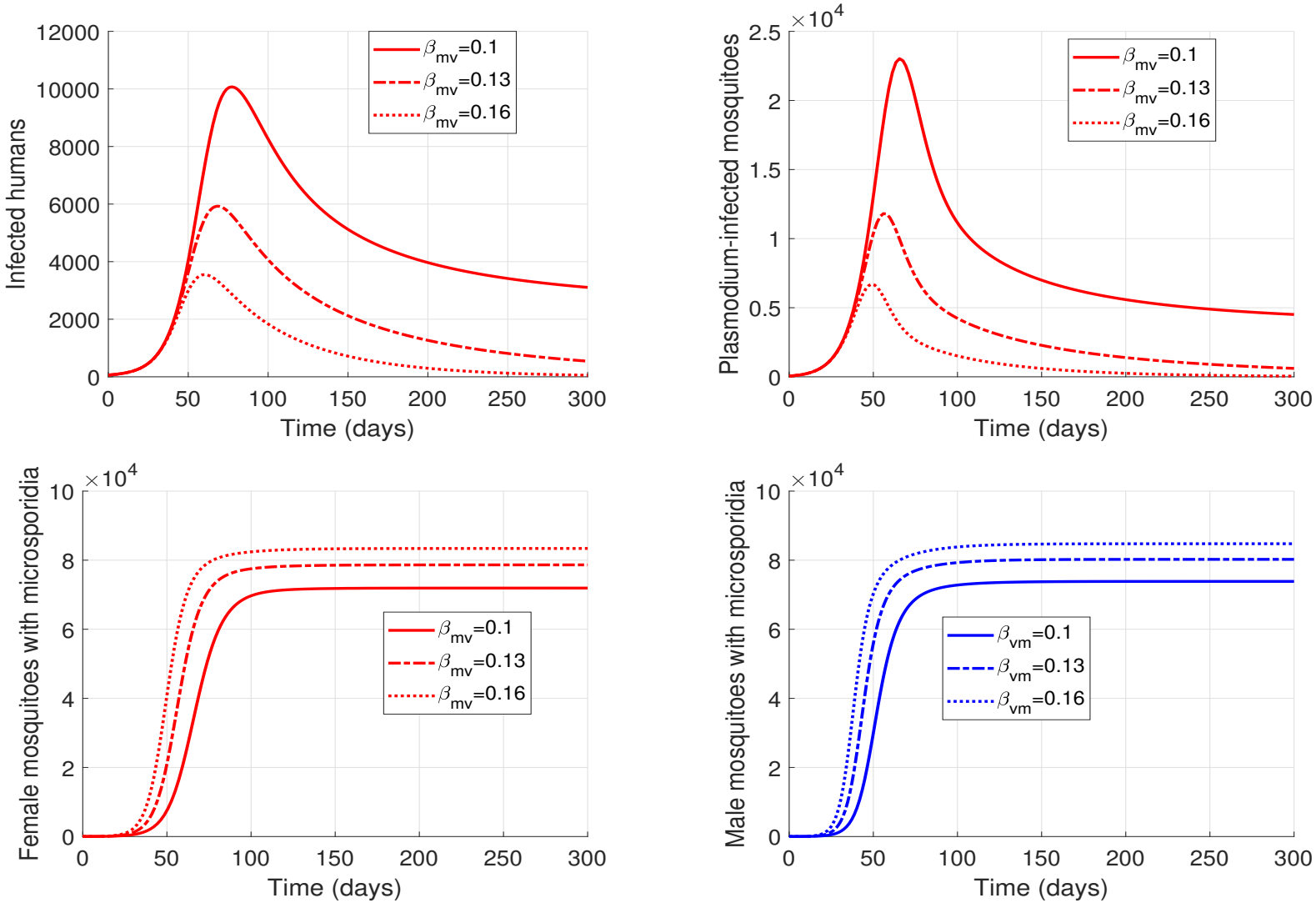

Figure: Influence of the variation of β_{mv}.

5. Simulations of Model (3)

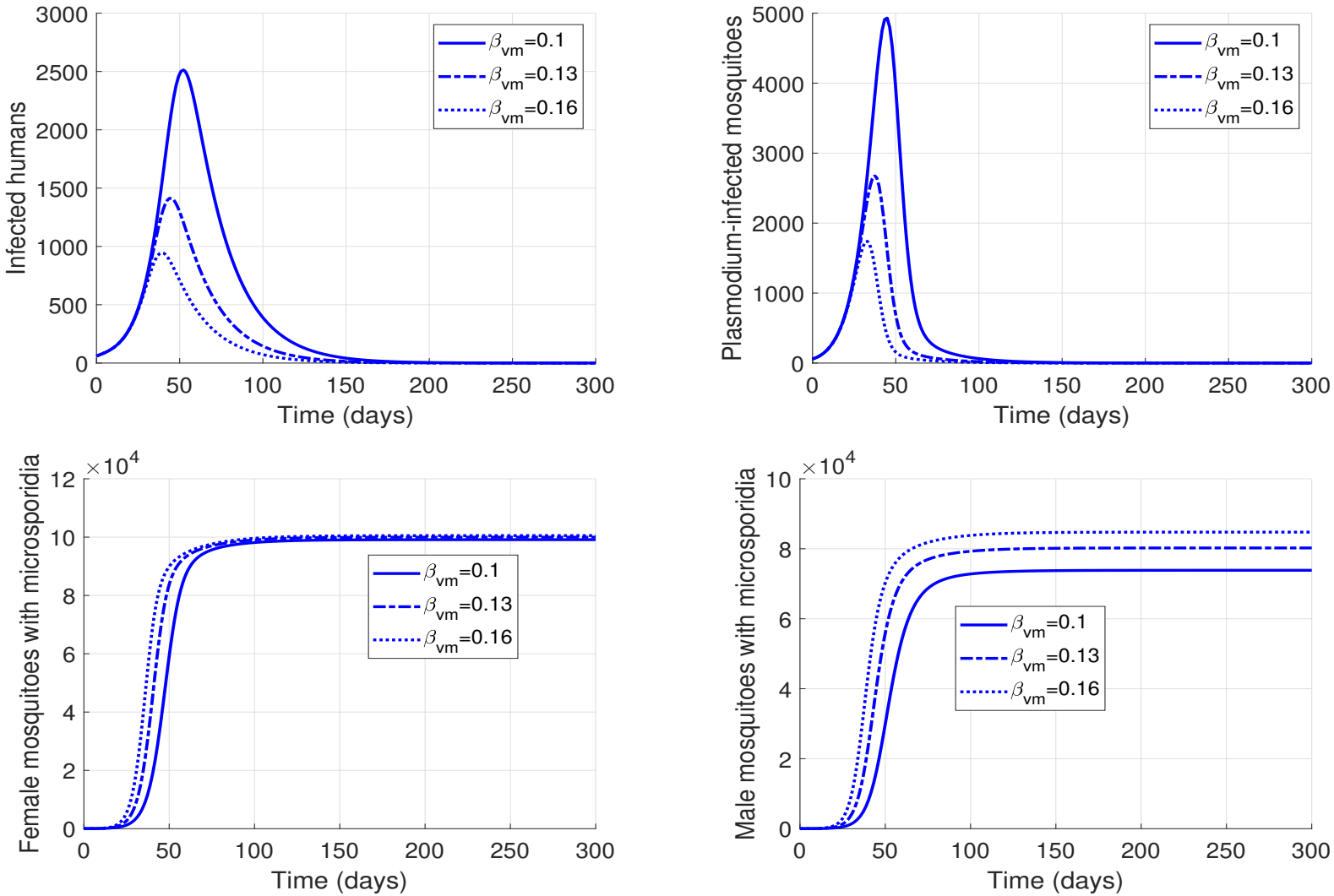

Figure: Influence of the variation of β_{vm}.

6. Simulations of Model (1)

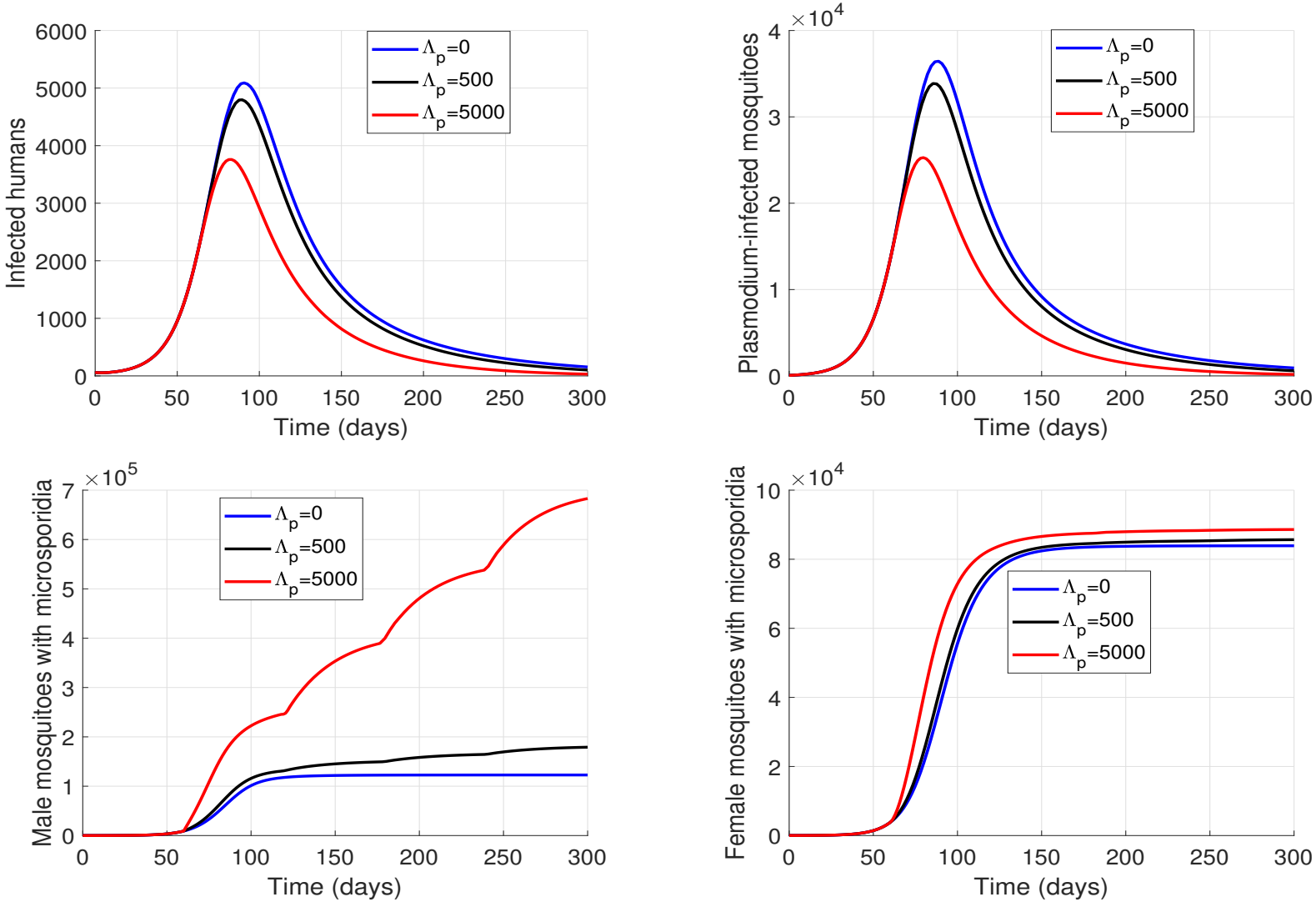

Figure: Impact of releasing male mosquitoes after 60 days, $T = 60$

6. Simulations of Model (1)

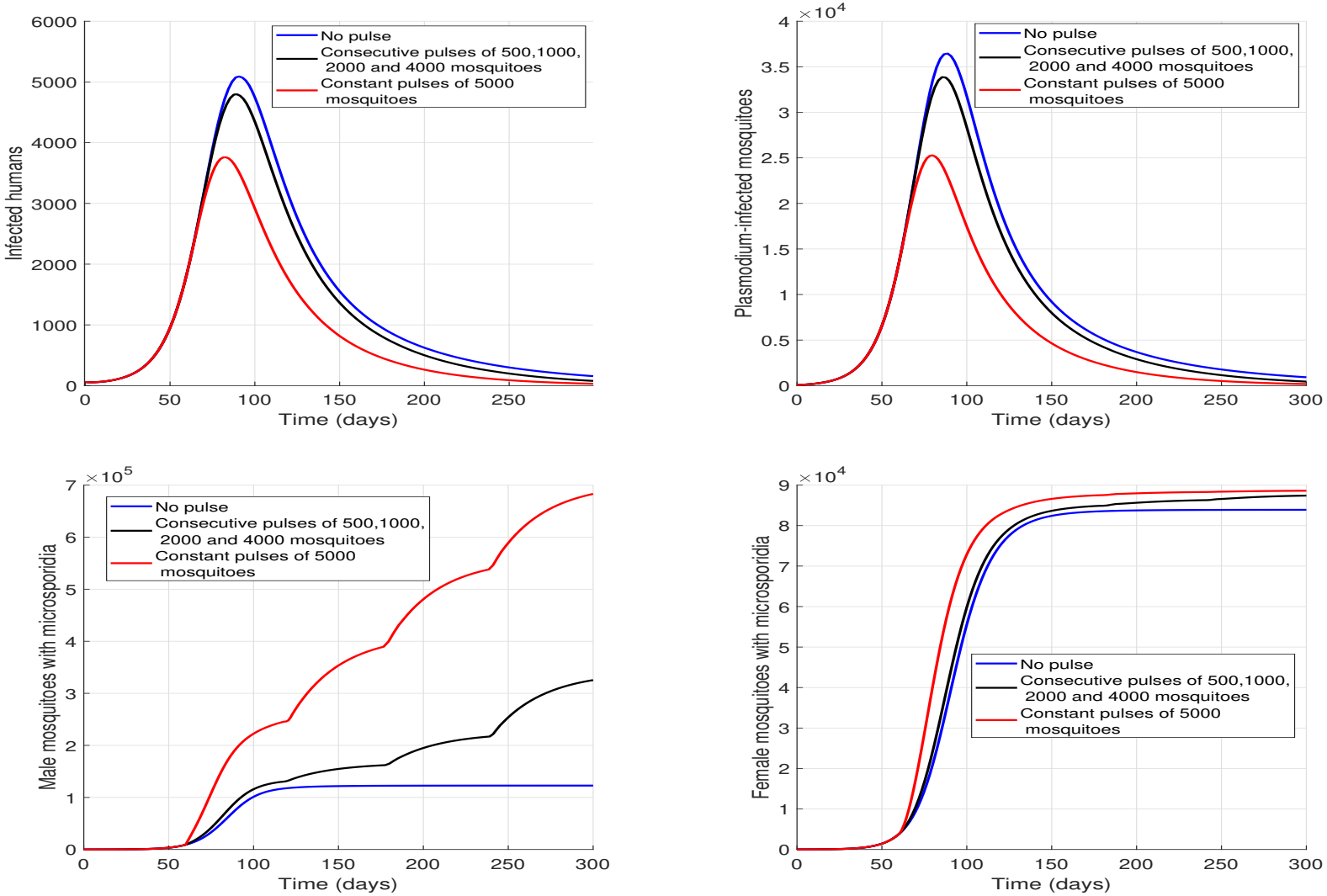

Figure: Here the number of mosquitoes can increase per release

7. Conclusion

- We have found that if the transmission rate of microsporidia MB increases, the population of malaria mosquitoes and humans will conversely decrease. This shows the importance of developing in future a model with periodic transmission rates of microsporidia MB, as the mating rates of mosquitoes could increase during rainy seasons.
- Moreover, malaria decreases as the number of mosquitoes released in each pulse is important, confirming that this control strategy would be a good alternative for the control of malaria.

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