J. Math. Biol.
DOI 10.1007/s00285-011-0418-4

Mathematical Biology

A metapopulation model for malaria with transmission-blocking partial immunity in hosts

Julien Arino · Arnaud Ducrot · Pascal Zongo

Received: 21 September 2009 / Revised: 4 February 2011

Abstract A metapopulation malaria model is proposed using SI and SIRS models for the vectors and hosts, respectively. Recovered hosts are partially immune to the disease and while they cannot directly become infectious again, they can still transmit the parasite to vectors. The basic reproduction number $\mathcal{R}_0$ is shown to govern the local stability of the disease free equilibrium but not the global behavior of the system because of the potential occurrence of a backward bifurcation. Using type reproduction numbers, we identify the reservoirs of infection and evaluate the effect of control measures. Applications to the spread to non-endemic areas and the interaction between rural and urban areas are given.

Keywords Malaria · Reproduction number · Type reproduction number · Metapopulation

Mathematics Subject Classification (2000) 92B05 · 92D30

J. Arino (✉)
Department of Mathematics, University of Manitoba, Winnipeg, MB, R3T 2N2, Canada
e-mail: arinoj@cc.umanitoba.ca

A. Ducrot
IMB UMR CNRS 5251 & INRIA Bordeaux Sud Ouest Anubis, Université de Bordeaux, 33000 Bordeaux, France
e-mail: arnaud.ducrot@u-bordeaux2.fr

P. Zongo
Laboratoire d'Analyse Numérique d'Informatique et de Biomathématique & INRIA Bordeaux Sud Ouest Anubis, Université de Bordeaux & Université de Ouagadougou, 33000 Bordeaux, France
e-mail: Pascal.Zongo@gmail.com

Published online: 26 March 2011

1 Introduction

Malaria is a mosquito-borne infection caused by protozoa of the genus *Plasmodium*, which causes an estimated 1.5–3 million deaths annually, mostly in children (WHO 2005). Here we shall focus on *Plasmodium falciparum*, which is the most commonly encountered parasite responsible for malaria's disease in the tropics. It is also responsible for the largest part of the severe infections and mortalities in these regions. The parasites are transmitted indirectly from human to human by the bite of infected female mosquitoes of the genus *Anopheles*. The distribution of the vector is well known to be highly spatially heterogeneous, even at a city's scale. Despite the obvious role of the spatial heterogeneity of vector distributions (Githeko et al. 2006), this aspect has rarely been taken into account in models; neither has human movement, despite the fact that travel of parasite bearing individuals may induce the translocation of the parasites into other regions.

There are several methods that can be used to describe movement between spatially heterogeneous regions. In this work, we shall use metapopulation theory; see, e.g., Arino (2009). In Ariey et al. (2003), a *patch occupancy* discrete-time metapopulation model is formulated to study the spread of resistance to chloroquine in the pathogen. In Le Menach et al. (2005), the authors consider a metapopulation setting with detailed description of mosquito oviposition behaviour. Metapopulations have been used to model malaria assuming only migration of mosquitoes (Le Menach et al. 2005; Smith et al. 2005). Some authors have taken into account human migration (Auger et al. 2008; Rodríguez and Torres-Sorando 2001). The effect of short term human movement is investigated numerically in Adams and Kapan (2009).

However, the mobility models cited above do not differentiate semi-immune individuals from infectious ones, whereas most malaria models corroborate experimental evidence and show that 60–90% of humans in endemic area are asymptomatic carriers of the parasites (Ducrot et al. 2009; see also Chitnis et al. 2006; Chiyaka et al. 2007; Ngwa and Shu 2000). Recall that in highly endemic region, some acquired partial immunity to the pathogen in humans develops after many years of repeated infections. For an extensive review of the process, see Doolan et al. (2009) and the references therein; see also Artavanis-Tsakonas et al. (2003). Immunity is never perfect and is lost after a prolonged interruption of exposure to the parasites (Aron 1988). However, immunity can be rapidly reacquired when an individual is re-exposed to malaria (Gatton and Cheng 2004). Individuals who have acquired immunity can host and tolerate malaria parasites without developing any clinical symptoms. They may become asymptomatic carriers of parasites in the gametocyte form but the infectivity of these gametocytes to mosquitoes is very low because of so-called *transmission-blocking immunity* (Drakeley et al. 2006; Kaslow 1993). Acquired immunity was first incorporated in a model by Dietz et al. (1974). See also Aron (1988), Chitnis et al. (2006) and Yang (2000) for further studies incorporating immunity. In this work, we call semi-immune an asymptomatic human carrier who is less infectious to mosquitoes than a symptomatic carrier; we thus model transmission-blocking immunity. While these individuals might be reinfected directly, albeit their susceptibility is less than non-immune individuals, we assume here that they must first become susceptible again before this happens.

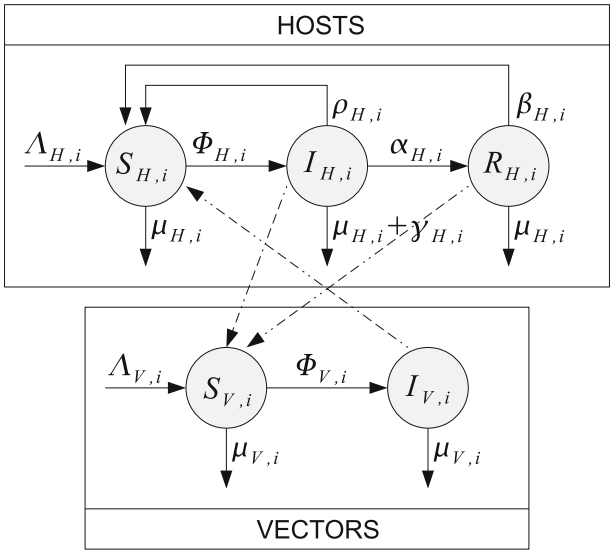

Fig. 1 A schematic of the mathematical model for malaria transmission involving human host and mosquito vector in each patch i, $i = 1, \ldots, n$. The *dotted arrows* show the direction of transmission from human to mosquito (infectious or semi-immune human to susceptible mosquito) or for mosquito to human (infectious mosquito to susceptible human)

The aim of this work is to provide a mathematical model for the spatio-temporal spread of malaria taking into account human movements and, especially, that of asymptomatic carriers; and to study the impact of spatial heterogeneities on control strategies. Underlying questions are the following. How is the heterogeneous local dynamics of malaria transmission affected by the spatial displacement of humans? What is the impact of human migrations from rural to urban areas?

2 The mathematical model

Suppose that space is subdivided into n regions called patches. In each patch $i = 1, \ldots, n$, divide the human population into three subclasses (see Fig. 1): susceptible, infectious and semi-immune, with numbers at time t in these classes given by $S_{H,i}(t)$, $I_{H,i}(t)$ and $R_{H,i}(t)$, respectively. Time-dependence is omitted for these and other state variables in the remainder of the text if this does not lead to ambiguities. Denote $H_i = S_{H,i} + I_{H,i} + R_{H,i}$ the total size of the human population in patch i at time t. Divide the mosquito population in each patch i into two subclasses: susceptible, $S_{V,i}$ and infectious, $I_{V,i}$, and denote $V_i = S_{V,i} + I_{V,i}$ the total mosquito population in patch i at time t. Denote $H = \sum_{i=1}^{n} H_i$ and $V = \sum_{i=1}^{n} V_i(t)$ the total host and vector populations in the system, respectively, at time t.

For $i = 1, \ldots, n$, denote $\Phi_{H,i}$ and $\Phi_{V,i}$ the force of infection from mosquitoes to humans and from humans to mosquitoes, respectively. Assume that $\Phi_{H,i}$ and $\Phi_{V,i}$ depend on the individuals present in patch i and not in another patch $j \neq i$: infection only involves the individuals (vectors and hosts) present in the patch, there is no between-patch infection. Therefore $\Phi_{H,i} = \Phi_{H,i}(S_{H,i}, S_{V,i}, I_{H,i}, R_{H,i}, I_{V,i})$,

$\Phi_{V,i} = \Phi_{V,i}(S_{H,i}, S_{V,i}, I_{H,i}, R_{H,i}, I_{V,i})$. The following forces of infection are found in the literature and will be used here. The first is found for example in Anderson and May (1991), Chiyaka et al. (2007) and Ngwa and Shu (2000) and takes the form

$$\Phi_{H,i} = \tilde{a}_i \sigma_{V_i H_i} \frac{I_{V,i}}{H_i} \tag{F1a}$$

and

$$\Phi_{V,i} = \tilde{a}_i \left(\sigma_{H_i V_i} \frac{I_{H,i}}{H_i} + \widehat{\sigma}_{H_i V_i} \frac{R_{H,i}}{H_i} \right), \tag{F1b}$$

where $\tilde{a}_i$, $\sigma_{V_i H_i}$, $\sigma_{H_i V_i}$, $\widehat{\sigma}_{H_i V_i} \in \mathbb{R}_+$. It is the classic form used in vector-host models, but with the additional infectivity of semi-immune hosts added in (**F1**b). The second form, found for example in Chitnis et al. (2006), is

$$\Phi_{H,i} = \frac{a_{V,i} a_{H,i} V_i}{a_{V,i} V_i + a_{H,i} H_i} \sigma_{V_i H_i} \frac{I_{V,i}}{V_i} \tag{F2a}$$

and

$$\Phi_{V,i} = \frac{a_{V,i} a_{H,i} H_i}{a_{V,i} V_i + a_{H,i} H_i} \left(\sigma_{H_i V_i} \frac{I_{H,i}}{H_i} + \widehat{\sigma}_{H_i V_i} \frac{R_{H,i}}{H_i} \right), \tag{F2b}$$

where $a_{V,i}$, $a_{H,i}$, $\sigma_{V_i H_i}$, $\sigma_{H_i V_i}$, $\widehat{\sigma}_{H_i V_i} \in \mathbb{R}_+$. To explain the difference between **F1** and **F2**, we follow (Chitnis et al. 2006) and refer to that paper for details. Both incidence functions can be written as

$$\Phi_{H,i} = b_{H,i}(H_i, V_i) \sigma_{V_i H_i} \frac{I_{V,i}}{V_i} \tag{Fa}$$

and

$$\Phi_{V,i} = b_{V,i}(H_i, V_i) \left(\sigma_{H_i V_i} \frac{I_{H,i}}{H_i} + \widehat{\sigma}_{H_i V_i} \frac{R_{H,i}}{H_i} \right), \tag{Fb}$$

where $b_{H,i}$ is the number of mosquito bites a human has per unit time and $b_{V,i}$ is the number of humans a mosquito bites per unit time. The general model used in Chitnis et al. (2006) is that the total number of mosquito bites on humans is given by

$$b = b(H_i, V_i) = \frac{a_{H,i} H_i a_{V,i} V_i}{a_{H,i} H_i + a_{V,i} V_i}.$$

Then $b_{H,i} = b/H_i$ and $b_{V,i} = b/V_i$. When the number of humans becomes large or the number of mosquitoes becomes small, $b_{H,i} \to \tilde{a}_i V_i / H_i$ and $b_{V,i} \to \tilde{a}_i$, giving form **F1**. Keeping the general form gives **F2**.

This general formulation make use of a kind of mean between the "availability of humans" to be bitten, $a_{H,i} H_i$, and the maximum number of bites that mosquitoes can

produce per unit of time, $a_{V,i}V_i$. When the number of mosquitoes is large, $V_i \to \infty$, this formulation introduces competition between mosquitoes for "biting space" and the corresponding biting rate reduces to $a_{H,i}H_i$, the availability of humans. On the contrary, when the number of mosquitoes is low, there is no longer competition between mosquitoes for bites and each mosquito that wants to bite can do so because of the relative abundance of humans. The corresponding bitting rate then reduces to $a_{V,i}V_i$.

Parameters of the incidence functions are interpreted in patch $i = 1, \ldots, n$ as follows:

- $\sigma_{H_iV_i}$ is the probability of transmission of the parasite (in gametocyte form) from an infectious human to a susceptible mosquito.
- $\widehat{\sigma}_{H_iV_i}$ is the probability of transmission of the parasite (in gametocyte form) from a semi-immune human to a susceptible mosquito.
- $\sigma_{V_iH_i}$ is the probability of transmission of the parasite (in sporozoite form) from an infectious mosquito to a susceptible human.
- $a_{H,i}$ is the maximum number of mosquito bites a human can receive per unit time.
- $a_{V,i}$ is the number of times one mosquito would "want to" bite humans per unit time.
- $\tilde{a}_i$ is the average number of bites given to humans by each mosquito per unit time.

Assume that humans can move from patch to patch but neglect the movement of mosquitoes, since the latter explore only few kilometers during their lives (see, e.g., Ejercito and Urbino 1951; Russell and Santiago 1934). Assume that the time it takes for humans to travel is small with respect to the incubation period and demographic processes, so humans do not change their epidemiological status during travel. Let m_{ij}^{π}, $\pi = S, I, R$, be the constant rate of travel of humans from patch j to patch i, for all $i, j = 1, \ldots, n$, $i \neq j$. Let $M^{\pi} = [m_{ij}^{\pi}]$, $\pi = S, I, R$, be the travel rate matrices. We shall assume throughout this work that

$$\begin{aligned} &\text{The matrices} \quad M^{\pi}, \pi = S, R, \quad \text{are irreducible.} \\ &m_{ii}^{\pi} = 0, \quad \text{for } \pi = S, I, R \quad \text{and} \quad i = 1, \ldots, n. \end{aligned} \tag{A1}$$

Table 1 summarizes the model parameters and their biological interpretation.

We can now write the model describing the spread of malaria in the patch setting. For notational simplicity, we introduce notation for the total within-patch removal rate from the human infectious class,

$$\epsilon_{H,i} = \alpha_{H,i} + \gamma_{H,i} + \rho_{H,i} + \mu_{H,i},$$

and the total within-patch removal rate from the human semi-immune class,

$$\delta_{H,i} = \beta_{H,i} + \mu_{H,i}.$$

Table 1 Parameters of the model and their meaning, in patch $i = 1, \ldots, n$

Parameters for humans
$\Lambda_{H,i}$: recruitment into the susceptible class
$\alpha_{H,i}$: rate of progression from the infectious to the semi-immune class
$\rho_{H,i}$: rate of recovery from being infectious
$\beta_{H,i}$: rate of recovery from being semi-immune
$\gamma_{H,i}$: disease induced death rate
$\mu_{H,i}$: natural death rate
Parameters for mosquitoes
$\Lambda_{V,i}$: recruitment into the susceptible class
$\mu_{V,i}$: natural death rate

All parameters are positive except $\gamma_{H,i}$ which is nonnegative

Then, for each $i = 1, \ldots, n$, the model takes the form

$$\begin{aligned}
\frac{dS_{H,i}}{dt} &= \Lambda_{H,i} + \beta_{H,i} R_{H,i} + \rho_{H,i} I_{H,i} - \mu_{H,i} S_{H,i} - \Phi_{H,i} S_{H,i} \\
&\quad + \sum_{j=1}^{n} m_{ij}^{S} S_{H,j} - \sum_{j=1}^{n} m_{ji}^{S} S_{H,i}, && \text{(4a)} \\
\frac{dI_{H,i}}{dt} &= \Phi_{H,i} S_{H,i} - \epsilon_{H,i} I_{H,i} + \sum_{j=1}^{n} m_{ij}^{I} I_{H,j} - \sum_{j=1}^{n} m_{ji}^{I} I_{H,i}, && \text{(4b)} \\
\frac{dR_{H,i}}{dt} &= \alpha_{H,i} I_{H,i} - \delta_{H,i} R_{H,i} + \sum_{j=1}^{n} m_{ij}^{R} R_{H,j} - \sum_{j=1}^{n} m_{ji}^{R} R_{H,i}, && \text{(4c)} \\
\frac{dS_{V,i}}{dt} &= \Lambda_{V,i} - \mu_{V,i} S_{V,i} - \Phi_{V,i} S_{V,i}, && \text{(4d)} \\
\frac{dI_{V,i}}{dt} &= \Phi_{V,i} S_{V,i} - \mu_{V,i} I_{V,i}, && \text{(4e)}
\end{aligned}$$

with initial conditions $S_{H,i}(0), S_{V,i}(0) > 0$, $I_{H,i}(0), R_{H,i}(0), I_{V,i}(0) \geq 0$.

We first consider the well-posedness of (4). Let $\Omega = \mathbb{R}_+^{*2n} \times \mathbb{R}_+^{3n}$ (where $\mathbb{R}^* = \mathbb{R} \setminus \{0\}$), and denote points in Ω by $(S, I)^T$, where $S = (S_{H,1}, S_{V,1}, \ldots, S_{H,n}, S_{V,n})$ and $I = (I_{H,1}, R_{H,1}, I_{V,1}, \ldots, I_{H,n}, R_{H,n}, I_{V,n})$. Rewrite system (4) in compact form as

$$\begin{aligned}
\frac{dS}{dt} &= \Psi_1(S, I), && \text{(5a)} \\
\frac{dI}{dt} &= \Psi_2(S, I). && \text{(5b)}
\end{aligned}$$

The following result guarantees the global well-posedness of system (4).

Theorem 1 *For any initial condition* $(S(0), I(0))$ *in* Ω, *system* (4) *has a unique globally defined solution* $(S(t), I(t))$ *which remains in* Ω *for all* $t \geq 0$. *Moreover, the total populations of humans,* $H(t)$, *and mosquitoes,* $V(t)$, *are bounded for all* $t \geq 0$.

Proof The local existence and uniqueness of solutions follows from the regularity of the function $\Psi = (\Psi_1, \Psi_2)$, which is of class C^1 in Ω. It is also easy to see that $\Psi_1(0, I) > 0$ and $\Psi_2(S, 0) \geq 0$. Thus Ω is forward-invariant under system (4). Adding up equations (4a)–(4c) and (4d)–(4e), we obtain equations for the total human and mosquito populations, respectively, in patch $i = 1, \ldots, n$:

$$\frac{dH_i}{dt} = \Lambda_{H,i} - \mu_{H,i} H_i - \gamma_{H,i} I_{H,i} + \sum_{\pi=S,I,R} \left(\sum_{j=1}^{n} m_{ij}^{\pi} \pi_{H,j} - \sum_{j=1}^{n} m_{ji}^{\pi} \pi_{H,i} \right), \tag{6a}$$

$$\frac{dV_i}{dt} = \Lambda_{V,i} - \mu_{V,i} V_i. \tag{6b}$$

From (6a),

$$\begin{aligned} \frac{dH}{dt} &= \sum_{i=1}^{n} (\Lambda_{H,i} - \mu_{H,i} H_i - \gamma_{H,i} I_{H,i}) \\ &\quad + \sum_{i=1}^{n} \left[\sum_{\pi=S,I,R} \left(\sum_{j=1}^{n} m_{ij}^{\pi} \pi_{H,j} - \sum_{j=1}^{n} m_{ji}^{\pi} \pi_{H,i} \right) \right]. \end{aligned}$$

Straightforward computations show that the double sum in the equation above equals zero, and since $I_{H,i} < H_i$, it follows that

$$\sum_{i=1}^{n} \Lambda_{H,i} - \sum_{i=1}^{n} (\mu_{H,i} + \gamma_{H,i}) H_i \leq \frac{dN_h}{dt} \leq \sum_{i=1}^{n} \Lambda_{H,i} - \sum_{i=1}^{n} \mu_{H,i} H_i$$

and thus

$$\sum_{i=1}^{n} \Lambda_{H,i} - \max_{1 \leq i \leq n} \{\mu_{H,i} + \gamma_{H,i}\} N_h \leq \frac{dN_h}{dt} \leq \sum_{i=1}^{n} \Lambda_{H,i} - \min_{1 \leq i \leq n} \{\mu_{H,i}\} N_h.$$

We conclude that for all $t \geq 0$,

$$\min \left\{ \frac{\sum_{i=1}^{n} \Lambda_{H,i}}{\max_{1 \leq i \leq n} \{\mu_{H,i} + \gamma_{H,i}\}}, H(0) \right\} \leq H(t) \leq \max \left\{ \frac{\sum_{i=1}^{n} \Lambda_{H,i}}{\max_{1 \leq i \leq n} \{\mu_{H,i}\}}, H(0) \right\}.$$

Using similar arguments, we show using (6b) that for all $t \geq 0$,

$$\min \left\{ \frac{\sum_{i=1}^{n} \Lambda_{V,i}}{\max_{1 \leq i \leq n} \{\mu_{V,i}\}}, V(0) \right\} \leq V(t) \leq \max \left\{ \frac{\sum_{i=1}^{n} \Lambda_{V,i}}{\min_{1 \leq i \leq n} \{\mu_{V,i}\}}, V(0) \right\}.$$

This completes the proof of the result.

3 Disease-free equilibrium point and basic reproduction number

3.1 Disease-free equilibrium point

A disease-free equilibrium is an equilibrium solution of system (4) at which there is no disease in any of the patches. This corresponds to the solution S^* of the algebraic system $\Psi_1(S,0) = \Psi_2(S,0) = 0$. Denote $S_h^* = (S_{H,1}^*, S_{H,2}^*, \ldots, S_{H,n}^*)^T$, $S_v^* = (S_{V,1}^*, S_{V,2}^*, \ldots, S_{V,n}^*)^T$, $\Lambda_h = (\Lambda_{H,1}, \Lambda_{H,2}, \ldots, \Lambda_{H,n})^T$, $\Lambda_v = (\Lambda_{V,1}, \Lambda_{V,2}, \ldots, \Lambda_{V,n})^T$, $G_h = \mathrm{diag}(\sum_{j=1}^n m_{ji}^S + \mu_{H,i}) - M^S$ and $G_v = \mathrm{diag}(\mu_{V,i})$, $\quad i = 1, \ldots, n$. Then we have the following result.

Theorem 2 *Let* (**A1**) *be satisfied. Then* (4) *has a unique disease-free equilibrium* $(S^*, 0)$ *in* Ω*, with the vector and host components of this equilibrium given by* $S_v^* = G_v^{-1}\Lambda_v$ *and* $S_h^* = G_h^{-1}\Lambda_h$*, respectively.*

Proof Let $(S^*, 0)$ be a disease-free equilibrium of system (4). Then $(S^*, 0)$ satisfies the equilibrium equation $\Psi_1(S^*, 0) = \Psi_2(S^*, 0) = 0$ deduced from (5). This yields the algebraic system $\Lambda_{H,i} - \mu_{H,i} S_{H,i}^* + \sum_{j=1}^n m_{ij}^S S_{H,j}^* - \sum_{j=1}^n m_{ji}^S S_{H,i}^* = 0$ and $\Lambda_{V,i} - \mu_{V,i} S_{V,i}^* = 0$, for $i = 1, \ldots, n$. Rewrite this system in matrix form,

$$\Lambda_h - G_h S_h^* = 0, \tag{7a}$$

$$\Lambda_v - G_v S_v^* = 0. \tag{7b}$$

Solving (7b) gives $S_v^* = G_v^{-1}\Lambda_v = (\Lambda_{V,1}/\mu_{V,1}, \Lambda_{V,2}/\mu_{V,2}, \ldots, \Lambda_{V,n}/\mu_{V,n}) > 0$, because $\mu_{V,i}, \Lambda_{V,i} > 0$ for all $i = 1, \ldots, n$. In order to solve (7a), recall that M^S is assumed to be irreducible. Also observe that G_h has negative off-diagonal entries and positive column sums. It follows that G_h is a nonsingular M-matrix. Then, since $\Lambda_h > 0$, from Berman and Plemmons (1979, Chap. 6, Theorem 2.7), $G_h^{-1} > 0$, giving $G_h^{-1}\Lambda_h > 0$. Therefore there exists a unique solution of (7a) given by $S_h^* = G_h^{-1}\Lambda_h$. So there exists a unique disease free equilibrium $(S^*, 0)$ in Ω for system (4) and the proof is complete.

3.2 Basic reproduction number

The basic reproduction number $\mathcal{R}_0$ is the expected number of secondary cases produced by a typical infective individual introduced into a completely susceptible population, in the absence of any control measure. A general method for computing $\mathcal{R}_0$ is the next generation method (Diekmann et al. 1990; van den Driessche and Watmough 2002). Mathematically, $\mathcal{R}_0$ is the spectral radius of the so-called next generation matrix. We use the method described in van den Driessche and Watmough (2002). Rewrite Ψ_2 in (5b) as $\Psi_2(S, I) = \mathcal{F}(I) - \mathcal{V}(I)$, where $\mathcal{F}(I)$ is the inflow of new individuals into the infected classes,

$$\mathcal{F} = (\Phi_{H,1} S_{H,1}, 0, \Phi_{V,1} S_{V,1}, \ldots, \Phi_{H,n} S_{H,n}, 0, \Phi_{V,n} S_{V,n})^T$$

and $\mathcal{V}(I)$ contains all other flows within and out of the infected classes,

$$\mathcal{V} = -\begin{bmatrix} -\epsilon_2 I_{H,1} + \sum_{j=1}^{n} m_{1j}^{I} I_{H,j} - \sum_{j=1}^{n} m_{j1}^{I} I_{H,1} \\ \alpha_{H,1} I_{H,1} - \delta_{H,1} R_{H,1} + \sum_{j=1}^{n} m_{1j}^{R} R_{H,j} - \sum_{j=1}^{n} m_{j1}^{R} R_{H,1} \\ -\mu_{V,1} I_{V,1} \\ \vdots \\ -\epsilon_{H,n} I_{H,n} + \sum_{j=1}^{n} m_{nj}^{I} I_{H,j} - \sum_{j=1}^{n} m_{jn}^{I} I_{H,n} \\ \alpha_{H,n} I_{H,n} - \delta_{H,n} R_{H,n} + \sum_{j=1}^{n} m_{nj}^{R} R_{H,j} - \sum_{j=1}^{n} m_{jn}^{R} R_{H,n} \\ -\mu_{V,n} I_{V,n} \end{bmatrix}.$$

Let $F = D\mathcal{F}|_{(S^*,0)}$ and $V = D\mathcal{V}|_{(S^*,0)}$ be the Jacobian matrices of the maps $\mathcal{V}(I)$ and $\mathcal{F}(I)$, respectively, evaluated at the disease free equilibrium $(S^*, 0)$. Following van den Driessche and Watmough (2002), the matrix FV^{-1} is well defined, and is the next generation matrix.

We have $\partial\Phi_{H,i}/\partial I_{H,j} = \partial\Phi_{H,i}/\partial R_{H,j} = \partial\Phi_{H,i}/\partial I_{V,j} = 0$, for $j \neq i$, and $\partial\Phi_{V,i}/\partial I_{H,j} = \partial\Phi_{V,i}/\partial R_{H,j} = \partial\Phi_{V,i}/\partial I_{V,j} = 0$, for $j \neq i$. Denote $\Phi_{H,i}^{I_{V,i}} = \partial\Phi_{H,i}/\partial I_{V,i}$, $\Phi_{V,i}^{I_{H,i}} = \partial\Phi_{V,i}/\partial I_{H,i}$ and $\Phi_{V,i}^{R_{H,i}} = \partial\Phi_{V,i}/\partial R_{H,i}$ the partial derivatives evaluated at the disease-free equilibrium $(S^*, 0)$.

The matrices F and V are $3n \times 3n$ matrices that we rewrite as $F = \mathsf{diag}(F_{ii})$, $i = 1, \ldots, n$, where

$$F_{ii} = \begin{bmatrix} 0 & 0 & \Phi_{H,i}^{I_{V,i}} S_{H,i}^{*} \\ 0 & 0 & 0 \\ \Phi_{V,i}^{I_{H,i}} S_{V,i}^{*} & \Phi_{V,i}^{R_{H,i}} S_{V,i}^{*} & 0 \end{bmatrix},$$

and $V = (V_{ij})$, where $V_{ij} = \mathsf{diag}(-m_{ij}^{I}, -m_{ij}^{R}, 0)$, $i \neq j$ and

$$V_{ii} = \begin{bmatrix} \epsilon_{H,i} + \sum_{j=1}^{n} m_{ji}^{I} & 0 & 0 \\ -\alpha_{H,i} & \delta_{H,i} + \sum_{j=1}^{n} m_{ji}^{R} & 0 \\ 0 & 0 & \mu_{V,i} \end{bmatrix}.$$

From van den Driessche and Watmough (2002, Theorem 2), the local stability of the disease-free equilibrium $(S^*, 0)$ is governed by the basic reproduction number $\mathcal{R}_0$, with the disease-free locally asymptotically stable if $\mathcal{R}_0 < 1$ and unstable when $\mathcal{R}_0 > 1$.

The element (ℓ, s) in FV^{-1} is interpreted as the expected number of new infections in compartment ℓ generated by the infected mosquito or human originally introduced

into compartment s. It is of interest to us here to go into more detail about this. Denote $K = FV^{-1}$, and K_{ij} the (i, j) block of size 3×3 of K, i.e., for $1 \leq i, j \leq n$,

$$K_{ij} = \begin{bmatrix} (I_{H,i} \leftarrow I_{H,j}) & (I_{H,i} \leftarrow R_{H,j}) & (I_{H,i} \leftarrow I_{V,j}) \\ (R_{H,i} \leftarrow I_{H,j}) & (R_{H,i} \leftarrow R_{H,j}) & (R_{H,i} \leftarrow I_{V,j}) \\ (I_{V,i} \leftarrow I_{H,j}) & (I_{V,i} \leftarrow R_{H,j}) & (I_{V,i} \leftarrow I_{V,j}) \end{bmatrix},$$

where the notation $Y \leftarrow X$ indicates that individuals from compartment X infect individuals from compartment Y. The matrix K_{ij} thus describes the *next generation* infection of vectors and hosts in patch i by vectors and hosts from patch j.

Because K involves the inverse of the $3n \times 3n$ matrix V, we do not have an explicit expression for it. Information about the structure of the matrix K is useful, though, as it allows to gain a better understanding of the spread of the infection.

Theorem 3 *Elements of the matrix K take, for $i, j = 1, \ldots, n$, the form*

$$K_{ij} = \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ (I_{V,i} \leftarrow I_{H,j}) & (I_{V,i} \leftarrow R_{H,j}) & 0 \end{bmatrix} \quad \text{if } i \neq j, \tag{8a}$$

$$K_{ii} = \begin{bmatrix} 0 & 0 & (I_{H,i} \leftarrow I_{V,i}) \\ 0 & 0 & 0 \\ (I_{V,i} \leftarrow I_{H,i}) & (I_{V,i} \leftarrow R_{H,i}) & 0 \end{bmatrix}. \tag{8b}$$

The proof of Theorem 3 is given in Appendix A. This result is expected since, in a patch, secondary infections cannot result from the direct transmission of the infection between humans or between mosquitoes.

Corollary 1 *Let $\tilde{K}$ be the $n \times n$ block matrix of 2×2 matrices with elements extracted from the matrix K, given for $i, j = 1, \ldots, n$ by*

$$\tilde{K}_{ij} = \begin{bmatrix} 0 & 0 \\ (I_{V,i} \leftarrow I_{H,j}) & 0 \end{bmatrix} \quad \text{if } i \neq j, \tag{9a}$$

$$\tilde{K}_{ii} = \begin{bmatrix} 0 & (I_{H,i} \leftarrow I_{V,i}) \\ (I_{V,i} \leftarrow I_{H,i}) & 0 \end{bmatrix}. \tag{9b}$$

Let $P_K(\lambda)$ and $P_{\tilde{K}}(\lambda)$ be the characteristic polynomials of the next generation matrices K and $\tilde{K}$, respectively. Then we have

$$P_K(\lambda) = (-\lambda)^n P_{\tilde{K}}(\lambda). \tag{10}$$

The proof of Corollary 1 uses basic multilinear algebra manipulations, as it can be easily shown that, for all $n \geq 1$,

$$\det(K - \lambda \mathbb{I}_{3n}) = (-1)^{2n^2} (-\lambda)^n \det(\tilde{K} - \lambda \mathbb{I}_{2n}) = (-\lambda)^n P_{\tilde{K}}(\lambda).$$

Corollary 1 shows that the nonzero eigenvalues of the next generation matrix K are equal to those of matrix $\tilde{K}$. The spectral radius of these matrices remains unchanged. In the sequel, to define $\mathcal{R}_0$, we shall use $\tilde{K}$ instead of K. To simplify notation, we set, for $1 \leq i, j \leq n$,

$$k_{H_j V_i} = (I_{V,i} \hookleftarrow I_{H,j}), \tag{11a}$$

$$k_{H_i V_i} = (I_{V,i} \hookleftarrow I_{H,i}), \tag{11b}$$

$$k_{V_i H_i} = (I_{H,i} \hookleftarrow I_{V,i}). \tag{11c}$$

The element k_{rs} of $\tilde{K}$ represents the expected number of secondary cases in host s generated by a typical primary case in host r, in a completely susceptible population.

One limiting case of interest is when $M^{\pi} = 0$ for $\pi = S, I, R$, i.e., humans do not travel. If $\mathcal{R}_{0i}$ is the basic reproduction number in patch $i = 1, \ldots, n$, then

$$\mathcal{R}_{0i} = \sqrt{k_{V_i H_i} k_{H_i V_i}}, \tag{12}$$

where

$$k_{V_i H_i} = \Phi_{H,i}^{I_{V,i}} \frac{\Lambda_{H,i}}{\mu_{H,i}} \frac{1}{\mu_{V,i}}, \tag{13a}$$

and

$$k_{H_i V_i} = \Phi_{V,i}^{I_{H,i}} \frac{\Lambda_{V,i}}{\mu_{V,i}} \frac{1}{\epsilon_{H,i}} + \Phi_{V,i}^{R_{H,i}} \frac{\Lambda_{V,i}}{\mu_{V,i}} \frac{\alpha_{H,i}}{\epsilon_{H,i}} \frac{1}{\delta_{H,i}}. \tag{13b}$$

Therefore, for the system of isolated patches,

$$\mathcal{R}_0 = \max_{1 \leq i \leq n} \mathcal{R}_{0i}. \tag{14}$$

Note that this does not mean that the disease becomes prevalent in all patches when $\mathcal{R}_0 > 1$. Since the patches are decoupled, the behaviour in a given patch is determined by the value of the local basic reproduction number $\mathcal{R}_{0i}$ in that patch. In fact, when $\min \mathcal{R}_{0i} > 1$ the disease-free equilibrium is unstable (in the classical sense) and on the other hand, if $\mathcal{R}_0 < 1$, then all the patches have a locally asymptotically stable disease-free equilibrium.

4 Existence of a backward bifurcation

Backward bifurcations have been investigated in epidemic models in two main areas: vaccination, where they often arise in the presence of a loss of immunity (Arino et al. 2003), and some vector-host models (Chitnis et al. 2006). Backward bifurcations generally occur when there are several types of infective individuals and that

one or several of these infective classes can flow directly back into the susceptible class.

We do not provide theoretical results concerning the global stability of the disease-free equilibrium $(S^*, 0)$. But we can easily show by using the two incidence functions **F1** and **F2** that, if the disease-induced death rate $\gamma_{H,i} = 0$ for all $i = 1, \ldots, n$, then the point $(S^*, 0)$ is globally asymptotically stable when $\mathcal{R}_0 < 1$ and the backward bifurcation cannot occur. On the other hand, when the disease may induce death in each patch $\gamma_{H,i} \neq 0$ for all $i = 1, \ldots, n$ and when it is sufficiently large, backward bifurcation at $\mathcal{R}_0 = 1$ may occur for this model for one patch using the two incidence functions **F1** and **F2**; see Appendix B for the case of **F1** (computations in the case of **F2** can be done similarly). Thus positive equilibria may exist even when $\mathcal{R}_0 < 1$. Therefore small changes in the parameters (or initial conditions) of the model may imply major changes in the dynamical behavior of the disease. This result can be extended to the case of n weakly connected patches by considering low migration.

Indeed, consider the equilibrium equation written in the formal form $\Psi(M, x) = 0$, indicating the dependence on the travel matrix $M = (M^S, M^I, M^R)$ and where $x = (S, I)$. Isolating the patches (by setting $M = 0$), assume that the equation $\Psi(0, x) = 0$ admits a solution x_0 even when $\mathcal{R}_0(0) < 1$, where we have explicitly written down the dependence of $\mathcal{R}_0$ on M. Such a solution is achieved by assuming that at least one of the isolated patches is in a backward bifurcation situation.

Then connecting the patches with a migration matrix with small entries such that $\mathcal{R}_0(M) < 1$, when the operator $\frac{\partial \Psi}{\partial x}(0, x_0)$ is invertible, one can conclude from the implicit functions theorem that there exists a branch (parametrized by M) of endemic equilibria when the travel matrix M has small enough entries.

In order to check whether the backward bifurcation happened within a realistic range of parameter values or was just an artifact, we performed some numerical simulations in a single patch using incidence function **F2**. Parameters were chosen to represent a typical malaria setting. The reproduction number $\mathcal{R}_0$ was made to vary between 0.7 and 1.5 by varying $a_{V,1}$. Using a value of the disease induced rate $\gamma_{H,1} = 9 \times 10^{-4}$ gave a backward bifurcation, while a lower $\gamma_{H,1} = 9 \times 10^{-5}$ gave a forward bifurcation. Note that a value of $\gamma_{H,1} = 9 \times 10^{-4}$ is not unreasonable: it indicates a case-fatality ratio of the order of 1/1,000, which is in the order of the observed case-fatality ratio: it is estimated that every year, 500 million people become infected with malaria and deaths are between 1.5 and 3 million. Considering the same parameter values in 3 patches connected with small migration rates, we observe the same type of behaviour.

From Fig. 3, the threshold of additional mortality leading to bistability decreases together with $\Lambda_{H,1}$. This implies that bistability regimes can easily be obtained when dealing with patches with relatively low human populations, such as in rural areas. In addition, increasing the influx of mosquitoes $\Lambda_{V,1}$ also decreases the threshold of mortality leading to the presence of a backward bifurcation (Fig. 3). Thus controlling the disease is hard in a region with low human population and high vectorial density. This is in agreement with the situation discussed in Dushoff et al. (1998). Similarly, one can argue that acquired immunity in the human population reduces the risk of a catastrophe (using the terminology of Ludwig et al. 1978).

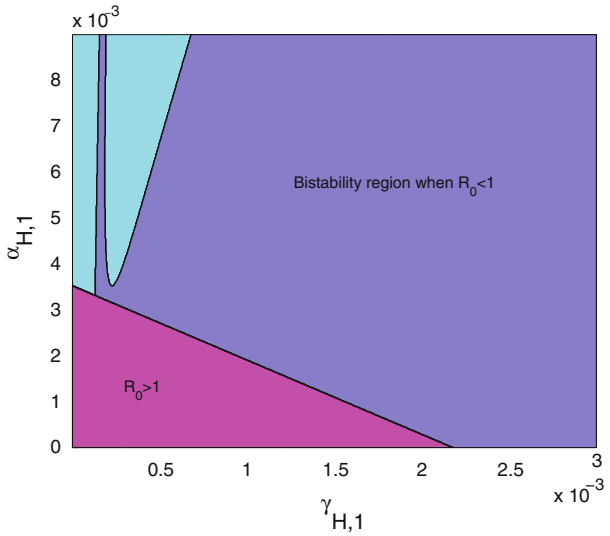

Fig. 2 Bistability region as a function of $\alpha_{H,1}$ and $\gamma_{H,1}$

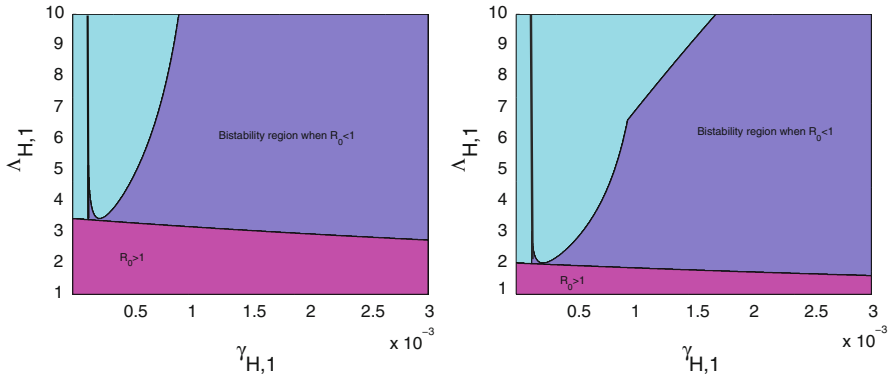

Fig. 3 Bistability region as a function of $\Lambda_{H,1}$ and $\gamma_{H,1}$ for $\Lambda_{V,1} = 1,200$ (*left*) and $\Lambda_{V,1} = 700$ (*right*)

Indeed, an increase in the parameter $\alpha_{H,1}$ increases flux out of the infected human population, without increasing much the flux into the susceptible population because immunity loss happens at a very low rate. This argument implies that in such a case, the disease has much more difficulties to be established. This is also supported by Fig. 2.

Thus, control strategies within patches with small human populations and high vector densities may induce backward bifurcation phenomena that can propagate through to regions with higher human populations by way of the connections between regions due to human movements. As will be discussed in the next section, this situation typically describes the interaction between rural and urban habitats.

5 Infection reservoir and control effort strategy

To control malaria, $\mathcal{R}_0$ must be reduced below 1 or $\mathcal{R}_c$, depending on whether the bifurcation is forward or backward at $\mathcal{R}_0 = 1$, respectively. For the human population, this involves using insecticide-treated bed nets, intermittent prophylactic treatment or a vaccine (if one were to become available); for mosquitoes, control measures involve indoor residual spraying and reduction of breeding sites. It is however difficult and expensive to aim a control at all $2n$ host types within the n patches. (Note that here, we use the term host to express the fact that both humans and mosquitoes are hosts of the plasmodium.) It is much more efficient to target specific (sub-) populations and/or patches. In order to identify those targets where the control would be the most effective, we use a method introduced in Heesterbeek and Roberts (2007) and Roberts and Heesterbeek (2003). We present the theory of type reproduction numbers and extend it to the case $\mathcal{R}_c < 1$, then propose a methodology to identify the different reservoirs of infection and conclude this section by some applications.

5.1 Type reproduction numbers

Consider the following problem: Let J be a subset of the set $\{H_1, V_1, \ldots, H_n, V_n\}$ of host types; can malaria be eradicated by targeting this subset J of host types with some control measure? The technique described in Heesterbeek and Roberts (2007) and Roberts and Heesterbeek (2003) can be used to try to address this problem. We adapt it here to the metapopulation case.

5.1.1 Case where $\mathcal{R}_c = 1$

Consider the threshold quantity T_J, spectral radius of the operator M_J defined by

$$M_J = \mathbb{E}_J^T \tilde{K} (\mathbb{I}_{2n} - (\mathbb{I}_{2n} - \mathbb{P}_J)\tilde{K})^{-1} \mathbb{E}_J \tag{15}$$

where $\mathbb{E}_J$ and $\mathbb{P}_J$, respectively, $(2n) \times \text{cardinal}(J)$ and $(2n) \times (2n)$ projection matrices satisfying $(\mathbb{E}_J)_{jj} = (\mathbb{P}_J)_{jj} = 1$ for $j \in J$ and $(\mathbb{E}_J)_{jj} = (\mathbb{P}_J)_{jj} = 0$ otherwise. (The index j here denotes the position of the elements of J in the set $\{H_1, V_1, \ldots, H_n, V_n\}$.)

It is claimed in Heesterbeek and Roberts (2007) and Roberts and Heesterbeek (2003) that $T_J = \rho(M_J)$ is well defined if the other host types $\{H_1, V_1, \ldots, H_n, V_n\} \setminus J$ cannot by themselves support an epidemic. This means that T_J is well defined if $\rho((\mathbb{I}_{2n} - \mathbb{P}_J)\tilde{K}) < 1$, i.e., if the series $\sum_{j=0}^{\infty} \left((\mathbb{I}_{2n} - \mathbb{P}_J)\tilde{K}\right)^j$ converges (Roberts and Heesterbeek 2003). Therefore, reducing T_J below 1 is sufficient to reduce $\mathcal{R}_0$ below 1 and is achieved by only targeting the subset J of host types. This assumption is valid when the disease free equilibrium is globally asymptotically stable when $\mathcal{R}_0 < 1$.

Let X be a host on a given patch i, i.e., $X = H_i$ or $X = V_i$. If $J = \{X\} \subset \{H_1, V_1, \ldots, H_n, V_n\}$ then T_X is the *type reproduction number* specific to host X and is interpreted as the expected number of cases in individuals of type X, caused either

directly or indirectly by one infected individual of type X in a completely susceptible population (Heesterbeek and Roberts 2007).

For a fixed host type $X \in \{H_1, V_1, \ldots, H_n, V_n\}$, assume that T_X is well defined, i.e., $\rho((\mathbb{I}_{2n} - \mathbb{P}_X)\tilde{K}) < 1$. Consider a malaria control program that aims to reduce the number of susceptible individuals of host type X and assume that this control strategy acts linearly upon k_{YX}, with $Y \in \{H_1, V_1, \ldots, H_n, V_n\}$. Then one can linearly reduce the number of susceptible host type X individuals and a proportion $s_X > 1 - 1/T_X$ of susceptible host type X individuals needs to be protected (by the control) to eliminate malaria in the $2n$ populations.

5.1.2 Case where $\mathcal{R}_c < 1$

Suppose there is a backward bifurcation in the model, i.e., there exists $\mathcal{R}_c$ such that there is no endemic equilibrium when $\mathcal{R}_0 < \mathcal{R}_c < 1$ and two endemic equilibria when $\mathcal{R}_c < \mathcal{R}_0 < 1$. Then redefine M_J as a function of $\mathcal{R}_c$. Note that $\mathcal{R}_c^{-1}\mathcal{R}_0 < 1$. Since $\mathcal{R}_0 = \rho(\tilde{K})$, one has the equivalence $\mathcal{R}_c^{-1}\rho(\tilde{K}) < 1 \Leftrightarrow \rho(R_c^{-1}\tilde{K}) < 1$. Consider a new next generation operator denoted $\mathcal{R}_c^{-1}\tilde{K}$. The elements of $\mathcal{R}_c^{-1}\tilde{K}$ are interpreted in the same way as those of $\tilde{K}$. Redefine T_J by using $\mathcal{R}_c^{-1}\tilde{K}$. Thus, replace $\tilde{K}$ by $R_c^{-1}\tilde{K}$ in the expression of M_J given by Eq. (15). Thus, the series $\sum_{j=0}^{\infty}\left((\mathbb{I}_{2n} - \mathbb{P}_J)\mathcal{R}_c^{-1}\tilde{K}\right)^j$ converges if $\rho((\mathbb{I}_{2n} - \mathbb{P}_J)\mathcal{R}_c^{-1}\tilde{K}) < 1$, i.e., $\rho((\mathbb{I}_{2n} - \mathbb{P}_J)\mathcal{R}_c^{-1}\tilde{K}) < \mathcal{R}_c < 1$ and

$$M_J(R_c) = E_J^T(R_c^{-1}\tilde{K})\left[\mathbb{I}_{2n} - (\mathbb{I}_{2n} - \mathbb{P}_J)(R_c^{-1}\tilde{K})\right]^{-1}\mathbb{E}_J. \tag{16}$$

5.2 Reservoirs of infection

In order to simplify computations, assume that $\mathcal{R}_c = 1$. Similar results can be obtained for $\mathcal{R}_c < 1$.

5.2.1 Malaria control targeting only the human or mosquito populations

Assume that we want to control malaria by targeting a control only to the human population, so define $J_h = \{H_1, H_2 \ldots, H_n\}$. Straightforward computations show that M_{J_h} is given by

$$M_{J_h} = [k_{H_iV_j}k_{V_jH_j}]_{1\leq i,j\leq n}. \tag{17}$$

To simplify notation, set

$$\mathcal{R}_{H_iH_j} = k_{H_iV_j}k_{V_jH_j}. \tag{18}$$

Note that $\rho((\mathbb{I}_{2n} - \mathbb{P}_{J_h})\tilde{K}) = 0 < 1$. Thus $T_{J_h} < 1 \Leftrightarrow \mathcal{R}_0 < 1$. Consequently T_{J_h} can be used as a threshold quantity for the complete system.

Each $\mathcal{R}_{H_iH_j}$ can be interpreted as the expected number of secondary infected humans in patch j that would arise from a single infected human case in patch i, in a situation where all the patches contain a completely susceptible population.

Let us now consider a control targeting the mosquito population. The same arguments can be used. Let us consider $J_v = \{V_1, V_2, \ldots, V_n\}$, so that M_{J_v} is given by

$$M_{J_v} = [k_{V_iH_i}k_{H_iV_j}]_{1\leq i,j\leq n}. \tag{19}$$

To simplify notation, set

$$\mathcal{R}_{V_iV_j} = k_{V_iH_i}k_{H_iV_j} \tag{20}$$

and $\rho((\mathbb{I}_{2n} - \mathbb{P}_{J_v})\tilde{K}) = 0 < 1$. Again, $T_{J_v} < 1 \Leftrightarrow \mathcal{R}_0 < 1$.

5.2.2 Sufficient condition for a patch to be a reservoir of infection

Observe that the matrices M_{J_h} and M_{J_v} have the same diagonal elements. In addition, one can check that M_{J_h} and M_{J_v} have the same eigenvalues. Thus we obtain that $T_{J_h}=T_{J_v}$. Note now that M_{J_h} is a nonnegative matrix. If we set $\mathbb{D} = \mathsf{diag}(\mathcal{R}_{H_\ell H_\ell})$, $\ell = 1, \ldots, n$, then $\mathbb{D} \leq M_{J_h}$. It follows that $\rho(\mathbb{D}) \leq \rho(M_{J_h})$. Then the following inequality holds:

$$\max_{1\leq\ell\leq n} \mathcal{R}_{H_\ell H_\ell} \leq T_{J_h}. \tag{21}$$

Thus, if $T_{J_h} < 1$, then $\max_{1\leq\ell\leq n} \mathcal{R}_{H_\ell H_\ell} < 1$. It follows that if $\min_{1\leq\ell\leq n} \mathcal{R}_{H_\ell H_\ell} \geq 1$, then $T_{J_h} \geq 1$. Therefore, if there exists some patch ℓ in the subset $\{1, 2, \ldots, n\}$ such that $\mathcal{R}_{H_\ell H_\ell} \geq 1$, then patch ℓ is an infection reservoir.

5.2.3 Case of isolated patches

When the patches are disconnected,

$$T_{H_i} = T_{V_i} = \mathcal{R}_{V_iV_i} = \mathcal{R}_{H_iH_i} = \mathcal{R}_{0i}^2. \tag{22}$$

$\mathcal{R}_{0i}^2$ gives the expected number of *humans* infected by a single infected *human* during their entire infectious period (Anderson and May 1991; Ducrot et al. 2009; Ngwa and Shu 2000). This is the definition of the reproduction number originally used for malaria. Moreover $\mathcal{R}_{0i}$ gives the number of *humans or mosquitoes* infected by a single *human* or *mosquito* during their entire infectious period, in a population of *humans* and *mosquitoes* that is entirely susceptible.

5.3 Applications

Here, we study two applications of our model; again, we simplify the computations by assuming that $\mathcal{R}_c = 1$.

5.3.1 Movement from endemic to non-endemic or malaria areas

Malaria transmission due to the colonization of new territories (unpopulated or sparsely populated areas) or intercontinental travel can be studied using a two patch model. In this situation, we have

$$M_{H_1,H_2} = \begin{bmatrix} k_{H_1V_1}k_{V_1H_1} & k_{H_1V_2}k_{V_2H_2} \\ k_{H_2V_1}k_{V_1H_1} & k_{H_2V_2}k_{V_2H_2} \end{bmatrix} = \begin{bmatrix} \mathcal{R}_{H_1H_1} & \mathcal{R}_{H_1H_2} \\ \mathcal{R}_{H_2H_1} & \mathcal{R}_{H_2H_2} \end{bmatrix}.$$

Straightforward computations show that

$$T_{H_1,H_2} = \frac{1}{2}\left(\mathcal{R}_{H_1H_1} + \mathcal{R}_{H_2H_2} + \sqrt{(\mathcal{R}_{H_1H_1} - \mathcal{R}_{H_2H_2})^2 + 4\mathcal{R}_{H_2H_1}\mathcal{R}_{H_1H_2}}\right) = \mathcal{R}_0^2,$$

$$T_{H_1} = \mathcal{R}_{H_1H_1} + \frac{\mathcal{R}_{H_2H_1}\mathcal{R}_{H_1H_2}}{1 - \mathcal{R}_{H_2H_2}} \quad \text{and} \quad \rho((\mathbb{I}_4 - \mathbb{P}_2)\tilde{K}) = \mathcal{R}_{H_2H_2},$$

$$T_{H_2} = \mathcal{R}_{H_2H_2} + \frac{\mathcal{R}_{H_2H_1}\mathcal{R}_{H_1H_2}}{1 - \mathcal{R}_{H_1H_1}} \quad \text{and} \quad \rho((\mathbb{I}_4 - \mathbb{P}_4)\tilde{K}) = \mathcal{R}_{H_1H_1},$$

Let us assume for instance that patch 1 is the non endemic area, i.e., $\mathcal{R}_{H_1H_1} < 1$. It follows that T_{H_2} is well defined and a proportion $s_{H_2} > 1 - 1/T_{H_2}$ of susceptible individuals in patch 2 need to be protected to eradicate malaria in the two patches.

5.3.2 Movement from rural to urban areas

Rapid urbanization plays a key role in human migrations, particularly from rural to urban regions. It is estimated, for example, that urbanization concerns nearly 40% of Africans. An important feature of this type of human movement is also that it is often temporary: individuals from rural areas work in cities, but usually come back to their home villages from time to time.

Consider three patches, with patch 1 a city and patches 2 and 3 villages. We only consider here malaria control targeting the human population, i.e., $J_h = \{H_1, H_2, H_3\}$. The possible combinations of host types to find a subset $J \subset J_h$ such that $\rho((\mathbb{I}_{2n} - \mathbb{P}_J)\tilde{K}) < 1$ are $J \subset \{H_1, H_2, H_3, \{H_1, H_2\}, \{H_1, H_3\}, \{H_2, H_3\}, \{H_1, H_2, H_3\}\}$.

To determine what possible actions can be undertaken to control malaria, we begin by evaluating T_{H_1}, T_{H_2} and T_{H_3}. If none of these quantities is well defined, we evaluate $T_{\{H_1,H_2\}}$, $T_{\{H_1,H_3\}}$ and $T_{\{H_2,H_3\}}$. If in turn none of these quantities is well defined, we evaluate $T_{\{H_1,H_2,H_3\}} = \rho\left(M_{\{H_1,H_2,H_3\}}\right)$, which is always well defined (see Sect. 5.2.1). From (17),

$$M_{\{H_1,H_2,H_3\}} = \begin{bmatrix} \mathcal{R}_{H_1H_1} & \mathcal{R}_{H_1H_2} & \mathcal{R}_{H_1H_3} \\ \mathcal{R}_{H_2H_1} & \mathcal{R}_{H_2H_2} & \mathcal{R}_{H_2H_3} \\ \mathcal{R}_{H_3H_1} & \mathcal{R}_{H_3H_2} & \mathcal{R}_{H_3H_3} \end{bmatrix}.$$

Suppose we want to control malaria by acting on the human population living in patches 2 and 3 and the impact of their immigration into patch 1. We must then evaluate the

type reproduction numbers T_{H_2} and T_{H_3}. Computations show that

$$T_{H_2} = \mathcal{R}_{H_2H_2} + \frac{\mathcal{R}_{H_2H_1}\left(\mathcal{R}_{H_1H_2} + \mathcal{R}_{H_1H_3}\mathcal{R}_{H_3H_2} - \mathcal{R}_{H_1H_2}\mathcal{R}_{H_3H_3}\right)}{(1-\mathcal{R}_{H_1H_1})(1-\mathcal{R}_{H_3H_3}) - \mathcal{R}_{H_3H_1}\mathcal{R}_{H_1H_3}} + \frac{\mathcal{R}_{H_2H_3}\left(\mathcal{R}_{H_3H_2} + \mathcal{R}_{H_3H_1}\mathcal{R}_{H_1H_2} - \mathcal{R}_{H_3H_2}\mathcal{R}_{H_1H_1}\right)}{(1-\mathcal{R}_{H_1H_1})(1-\mathcal{R}_{H_3H_3}) - \mathcal{R}_{H_3H_1}\mathcal{R}_{H_1H_3}}$$

and the infection reservoir other than host 4 is

$$\rho((\mathbb{I}_6 - \mathbb{P}_{H_2})\tilde{K}) = \frac{1}{2}\left(\mathcal{R}_{H_1H_1} + \mathcal{R}_{H_3H_3} + \sqrt{(\mathcal{R}_{H_1H_1} - \mathcal{R}_{H_3H_3})^2 + 4\mathcal{R}_{H_3H_1}\mathcal{R}_{H_1H_3}}\right).$$

If $\rho((\mathbb{I}_6 - \mathbb{P}_{H_2})\tilde{K}) < 1$, then it suffices to protect a proportion $s_{H_2} > 1 - T_{H_2}$ of humans in patch 2 to eliminate malaria.

Similarly,

$$T_{H_3} = \mathcal{R}_{H_3H_3} + \frac{\mathcal{R}_{H_3H_1}\left(\mathcal{R}_{H_1H_3} + \mathcal{R}_{H_1H_2}\mathcal{R}_{H_2H_3} - \mathcal{R}_{H_1H_3}\mathcal{R}_{H_2H_2}\right)}{(1-\mathcal{R}_{H_1H_1})(1-\mathcal{R}_{H_2H_2}) - \mathcal{R}_{H_2H_1}\mathcal{R}_{H_1H_2}} + \frac{\mathcal{R}_{H_3H_2}\left(\mathcal{R}_{H_2H_3} + \mathcal{R}_{H_2H_1}\mathcal{R}_{H_1H_3} - \mathcal{R}_{H_2H_3}\mathcal{R}_{H_1H_1}\right)}{(1-\mathcal{R}_{H_1H_1})(1-\mathcal{R}_{H_2H_2}) - \mathcal{R}_{H_2H_1}\mathcal{R}_{H_1H_2}}$$

and the infection reservoir other than host H_3 is

$$\rho((\mathbb{I}_6 - \mathbb{P}_{H_3})\tilde{K}) = \frac{1}{2}\left(\mathcal{R}_{H_1H_1} + \mathcal{R}_{H_2H_2} + \sqrt{(\mathcal{R}_{H_1H_1} - \mathcal{R}_{H_2H_2})^2 + 4\mathcal{R}_{H_2H_1}\mathcal{R}_{H_1H_2}}\right).$$

Then one needs to protect a proportion $s_{H_3} > 1 - T_{H_3}$ of humans in patch 3 to eliminate malaria over time, provided of course that $\rho((\mathbb{I}_3 - \mathbb{P}_{H_3})\tilde{K}) < 1$.

Now, if $\min\{\rho((\mathbb{I}_6 - \mathbb{P}_{H_3})\tilde{K}), \rho((\mathbb{I}_6 - \mathbb{P}_{H_2})\tilde{K})\} \geq 1$, then T_{H_2} and T_{H_3} are not well defined and we cannot control malaria by acting one and one only of patches 2 and 3. A control can then be applied simultaneously in patches 2 and 3. We evaluate $M_{\{H_2,H_3\}}$:

$$M_{\{H_2,H_3\}} = \begin{bmatrix} \dfrac{\mathcal{R}_{H_2H_1}\mathcal{R}_{H_1H_2}}{1-\mathcal{R}_{H_1H_1}} + \mathcal{R}_{H_2H_2} & \dfrac{\mathcal{R}_{H_2H_1}\mathcal{R}_{H_1H_3}}{1-\mathcal{R}_{H_1H_1}} + \mathcal{R}_{H_2H_3} \\ \dfrac{\mathcal{R}_{H_3H_1}\mathcal{R}_{H_1H_2}}{1-\mathcal{R}_{H_1H_1}} + \mathcal{R}_{H_3H_2} & \dfrac{\mathcal{R}_{H_3H_1}\mathcal{R}_{H_1H_3}}{1-\mathcal{R}_{H_1H_1}} + \mathcal{R}_{H_3H_3} \end{bmatrix}.$$

It follows that $T_{\{H_2,H_3\}} = \rho(M_{\{H_2,H_3\}})$, and the infection reservoir other than humans hosts on patches 2 and 3 is

$$\rho\left((\mathbb{I}_6 - \mathbb{P}_{\{H_2,H_3\}})\tilde{K}\right) = \mathcal{R}_{H_1H_1}.$$

In cities, the human population is generally protected by many control strategies such as insecticide-treated bed nets or intermittent prophylactic treatment, and this can reduce $\mathcal{R}_{H_1H_1}$ to a value below 1. Consequently $T_{H_2H_3}$ can be used as a threshold quantity to control malaria in the three patches, implying that control must act simultaneously on the two villages.

We now turn to a brief numerical exploration of the behaviour of model (4) in the particular case of movement between rural and urban areas. We take parameter values compatible with malaria and use in particular $\gamma_{H,1} = 9.0 \times 10^{-5}$, and use the force of infection **F2**. Take

$$M^R = \begin{bmatrix} 0 & m_{12}^R & m_{13}^R \\ m_{21}^R & 0 & m_{23}^R \\ m_{31}^R & m_{32}^R & 0 \end{bmatrix} = \begin{bmatrix} 0 & 0.07 & 0.08 \\ 0.02 & 0 & 0.000001 \\ 0.01 & 0.000001 & 0 \end{bmatrix}$$

so that the flux of population from the villages to the city is large. In areas where malaria is endemic, the semi-immune class comprises humans over 5 years of age (Gatton and Cheng 2004; Kalipeni 1993; Paul et al. 2007; Smith et al. 2001; Taylor-Robinson 2002). Migration, on the other hand, concerns in majority humans over 15 years of age. Therefore, the migration of susceptible individuals is very low, and we take $M^S = (1/100)M^R$. Since most infected individuals are incapacitated by the symptoms of malaria and cannot travel, we take $M^I = (1/100)M^R$. With the parameter values used, we find $\mathcal{R}_0 = 3.864$ and the system with migration approaches an endemic equilibrium.

We find

$$M_{\{H_1H_2H_3\}} = \begin{bmatrix} 0.949 & 3.513 \times 10^{-5} & 2.673 \times 10^{-5} \\ 16.498 \times 10^{-5} & 3.864 & 4.390 \times 10^{-7} \\ 15.022 \times 10^{-5} & 5.254 \times 10^{-7} & 8.395 \end{bmatrix}$$

and $\mathcal{R}_{H_1H_1} = 0.949 < 1$. It follows that $M_{H_2H_3}$ is well defined, with

$$M_{\{H_2H_3\}} = \begin{bmatrix} 3.864 & 5.268 \times 10^{-7} \\ 6.305 \times 10^{-7} & 8.395 \end{bmatrix},$$

so $T_{\{H_2H_3\}}$ can be used as a threshold quantity. With the parameters used, we find $T_{\{H_2H_3\}} = T_{\{H_1H_2H_3\}} = 8.395$.

6 Conclusion

We formulated a metapopulation model for the spatial spread of malaria. We subdivided space into n patches wherein we modelled malaria transmission between human host and mosquito vector by dividing the human population into three subclasses: susceptible, infectious and semi-immune while the mosquito population is divided in two subclasses: susceptible and infectious. We modeled the spatial spread of malaria

between these n patches via the migration of humans. We showed that there exists a unique disease free equilibrium (DFE). The local stability of the DFE is governed by the basic reproduction number $\mathcal{R}_0$, but the global dynamics of the model is not governed by the latter quantity. Indeed, there can exist a backward bifurcation at $\mathcal{R}_0 = 1$ when the disease induced death rate is large enough, leading to bi-stability when $\mathcal{R}_c < \mathcal{R}_0 < 1$. Note that from the implicit function theorem, the backward bifurcation can be triggered in other patches if it is present in only one patch when there is no travel, at least when migration is initially increases. Bi-stability implies in particular that a control strategy for malaria epidemics may require $\mathcal{R}_0$ to be reduced to below $\mathcal{R}_c < 1$ to eradicate the disease.

The potential presence of a backward bifurcation in a one-patch setting is related to the increase of the number of bites per habitant. As explained in Sect. 4, the occurrence of such a phenomenon is sensitive to a decrease of the total number of humans and to an increase of the total density of vectors. As a consequence, villages are locations that are good candidate for exhibiting bistability dynamics; such dynamics might spill over into urban areas because of human movements. Finally, note that the rate at which individuals acquire immunity has a stabilizing effect on the dynamics of malaria transmission, since it increases the out-flux of infected human. The faster the immunity is reached, the smaller the bistability region.

We then showed how type reproduction numbers could be used in a metapopulation framework and proposed a methodology to identify the different reservoirs of infection. A reservoir of infection is a subpopulation to which applying a (linear) control strategy suffices to eradicate the disease in the whole system. To identify these spatial infection reservoirs, we formulated the type reproduction number specific to each host type in each patch. This was numerically applied with realistic parameters to study the impact of the movement of human population on malaria transmission in different realistic situations: from rural into urban areas and colonization of heretofore unused territories.

Future work will consider the combined effects of transmission blocking immunity and of direct reinfection of the partially immune individuals.

Appendix A: Proof of Theorem 3

The proof of the result uses the algebraic properties of some sets of matrix. We begin by defining the subsets $\mathcal{J}$ and $\mathcal{H}$ of $\mathcal{M}_3(\mathbb{R})$ by

$$\mathcal{J} = \left\{ J(a,b,c,d) = \begin{bmatrix} a & 0 & 0 \\ b & c & 0 \\ 0 & 0 & d \end{bmatrix}, \quad (a,b,c,d) \in \mathbb{R}^4 \right\}$$

and

$$\mathcal{H} = \left\{ H(a,b,c) = \begin{bmatrix} a & 0 & 0 \\ b & c & 0 \\ 0 & 0 & 0 \end{bmatrix}, \quad (a,b,c) \in \mathbb{R}^3 \right\},$$

respectively. The sets $\mathcal{J}$ and $\mathcal{H}$ satisfy the following properties:

(i) $\mathbb{I}_3 = J(1, 0, 1, 1) \in \mathcal{J}$.
(ii) $\mathcal{J}$ and $\mathcal{H}$ are closed under addition and multiplication.
(iii) For all $(J, H) \in \mathcal{J} \times \mathcal{H},\ J \cdot H = H \cdot J \in \mathcal{H}, J + H \in \mathcal{J}$.

Properties (ii)–(iii) are obtained by straightforward computations. Now, introduce

$$\mathcal{G} = \{G \in \mathcal{M}_{3n}(\mathbb{R}) : G_{\ell s} \in \mathcal{H} \text{ for all } \ell \neq s \text{ and } G_{\ell\ell} \in \mathcal{J}\}, \tag{23a}$$

$$U(\mathcal{G}) = \mathcal{G} \cap GL_{3n}(\mathbb{R}). \tag{23b}$$

The following result holds:

Lemma 1 *The set $\mathcal{G}$ forms a subalgebra of the algebra $\mathcal{M}_{3n}(\mathbb{R})$. Moreover the subset $U(\mathcal{G})$ of the invertible elements of $\mathcal{G}$ forms a subgroup of the group of invertible matrices $GL_{3n}(\mathbb{R})$.*

Proof From property (i), we have that $\mathbb{I}_{3n} \in \mathcal{G}$, and from properties (ii)–(iii), $\mathcal{G}$ is closed under linear combination. So it remains to check that the product of two elements of $\mathcal{G}$ is itself an element of $\mathcal{G}$. Let $A = (A_{\ell s})_{1\leq \ell, s\leq n}$ and $B = (B_{\ell s})_{1\leq \ell, s\leq n}$ be two given elements of $\mathcal{G}$, i.e., $A_{\ell s}, B_{\ell s} \in \mathcal{H}$ for all $\ell \neq s$ and $A_{\ell\ell}, B_{\ell\ell} \in \mathcal{J}$. Let $C = (C_{\ell s})_{1\leq \ell, s\leq n}$ be the product of A and B. Let us verify that the matrix C belongs to $\mathcal{G}$.

First we show that for all $\ell = 1, \ldots, n$, $C_{\ell\ell} \in \mathcal{K}$. By definition, for all $\ell, s,\ C_{\ell s} = \sum_{k=1}^{n} A_{\ell k} B_{k s}$. It follows that $C_{\ell\ell} = \sum_{k=1, k\neq\ell}^{n} A_{\ell k} B_{k\ell} + A_{\ell\ell} B_{\ell\ell}$. It is clear that for $k \neq \ell,\ A_{\ell k}, B_{k\ell} \in \mathcal{H}$. Moreover, from property (ii), $A_{\ell k} B_{k\ell} \in \mathcal{H}$ and $\sum_{k=1, k\neq\ell}^{n} A_{\ell k} B_{k\ell} \in \mathcal{H}$. Similarly, $A_{\ell\ell}, B_{\ell\ell} \in \mathcal{J}$, then $A_{\ell\ell} B_{\ell\ell} \in \mathcal{J}$. Consequently $C_{\ell\ell} \in \mathcal{J}$ from property (iii).

Now, for all $\ell \neq s$, we show that $C_{\ell s} = \sum_{k=1}^{n} A_{\ell k} B_{k s} \in \mathcal{H}$. If $k = \ell$, (resp. $k = s$), then $A_{\ell\ell} B_{\ell s} \in \mathcal{H}$ (resp. $A_{\ell s} B_{s s} \in \mathcal{H}$) from property (iii). If $k \neq s$ and $k \neq \ell$, then $A_{\ell k} B_{k s} \in \mathcal{H}$ from property (ii). It follows $C_{\ell s} \in \mathcal{H}$ for all $\ell \neq s$.

The second assertion directly follows from the first one.

We now return to the next generation operator $K = FV^{-1}$. The matrix V belongs to the set $U(\mathcal{G})$. It follows from Lemma 1 that its inverse V^{-1} remains in the set $U(\mathcal{G})$. We conclude the proof of Theorem 3 by straightforward computations of the product FV^{-1}.

Appendix B: Bifurcation analysis for one patch

The aim of this appendix is to study the existence of endemic steady states for the system

$$\begin{cases} \frac{dS_H}{dt} = \Lambda_H + \beta_H R_H + \rho_H I_H - \frac{\tilde{a}_1 \sigma_{VH} I_V S_H}{S_H + R_H + I_H} - \mu_H S_H \\ \frac{dI_H}{dt} = \frac{\tilde{a}_1 \sigma_{VH} I_V S_H}{S_H + R_H + I_H} - \epsilon_H I_H \\ \frac{dR_H}{dt} = \alpha_H I_H - \delta_H R_H \\ \frac{dS_V}{dt} = \Lambda_V - \mu_V S_V - \frac{\tilde{a}_1 (\sigma_{HV} I_H + \widehat{\sigma}_{HV} R_H) S_V}{S_H + R_H + I_H} \\ \frac{dI_V}{dt} = \frac{\tilde{a}_1 (\sigma_{HV} I_H + \widehat{\sigma}_{HV} R_H) S_V}{S_H + R_H + I_H} - \mu_V I_V, \end{cases} \tag{24}$$

the epidemic model under consideration for one patch with force of infection **F1**. (Note that we have dropped the patch index for convenience.) Before stating our main result, let us recall that for the model under consideration, $\mathcal{R}_0$ is given by the following expression

$$\mathcal{R}_0 = \sqrt{\tilde{a}_1^2 \sigma_{VH} \left(\sigma_{HV} + \widehat{\sigma}_{HV} \frac{\alpha_H}{\delta_H} \right) \frac{\Lambda_V \mu_H}{\epsilon_H \Lambda_H \mu_V^2}}, \tag{25}$$

and let us set

$$\begin{aligned} A_2 &= \frac{\epsilon_H I_H^* \gamma_H}{\Lambda_H} \left(\frac{\mu_V \gamma_H}{\mu_H} - \Sigma \right), \\ A_1 &= \Sigma \frac{\Lambda_V \tilde{a}_1 \sigma_{VH}}{\mu_V} - \epsilon_H I_H^* \left(\frac{2\mu_V \gamma_H}{\mu_H} - \Sigma \right), \\ A_0 &= \frac{\Lambda_H \mu_V \epsilon_H I_H^*}{\mu_H} \left(1 - \mathcal{R}_0^2 \right), \end{aligned}$$

wherein

$$\Sigma = \tilde{a}_1 \left(\sigma_{HV} + \widehat{\sigma}_{HV} \frac{\alpha_H}{\delta_H} \right) \quad \text{and} \quad I_H^* = \frac{\Lambda_H}{\mu_H + \gamma_H + \frac{\alpha_H \mu_H}{\delta_H}}.$$

Our main result is summarized in the following theorem, where $\mathcal{R}_0$ refers to (25).

Theorem 4 *System (24) may have up to three biologically plausible equilibria.*

(i) *The disease free equilibrium is always a boundary equilibrium.*
(ii) *When $\mathcal{R}_0 > 1$ the system has a unique positive equilibrium.*
(iii) *When $\mathcal{R}_0 < 1$ then*
- *If $A_2 \leq 0$ there is no positive equilibrium.*
- *If $A_2 > 0$ system (24) has two positive equilibria if and only if*

$$-\frac{A_1}{2A_2} < I_H^* \text{ and } A_1^2 - 4A_2A_0 \geq 0,$$

with the two equilibria coalescing when $A_1^2 - 4A_2A_0 = 0$.

Proof The nontrivial stationary states of system (24) are the positive solutions of the system

$$\begin{cases} V = \frac{\Lambda_V}{\mu_V}, \quad R_H = \frac{\alpha_H}{\delta_H} I_H \\ \Lambda_H + \left(\frac{\beta_H \alpha_H}{\delta_H} + \rho_H \right) I_H - \frac{\tilde{a}_1 \sigma_{VH} I_V S_H}{S_H + (1 + \frac{\alpha_H}{\delta_H}) I_H} - \mu_H S_H = 0 \\ \frac{\tilde{a}_1 \sigma_{VH} I_V S_H}{S_H + \left(1 + \frac{\alpha_H}{\delta_H}\right) I_H} - \epsilon_H I_H = 0 \\ \frac{\tilde{a}_1 \left(\sigma_{HV} + \widehat{\sigma}_{HV} \frac{\alpha_H}{\delta_H} \right) I_H \left(\frac{\Lambda_V}{\mu_V} - I_V \right)}{S_H + (1 + \frac{\alpha_H}{\delta_H}) I_H} - \mu_V I_V = 0. \end{cases} \tag{26}$$

Adding the second and the third equation leads to

$$S_H = \frac{\Lambda_H - \left(\mu_H + \gamma_H + \frac{\alpha_H \mu_H}{\delta_H} \right) I_H}{\mu_H}. \tag{27}$$

Setting

$$I_H^* = \frac{\Lambda_H}{\mu_H + \gamma_H + \frac{\alpha_H \mu_H}{\delta_H}},$$

we obtain that $I_H \in [0, I_H^*)$ and plugging (27) into (26) we obtain that I_H is an intersection point for the curves

$$I_V = \Gamma_1(I_H) = \frac{\Sigma \frac{\Lambda_V}{\mu_V} I_H}{\Lambda_H \frac{\mu_V}{\mu_H} + \left(\Sigma - \frac{\mu_V \gamma_H}{\mu_H} \right) I_H},$$

and

$$I_V = \Gamma_2(I_H) = \frac{\Lambda_H}{\tilde{a}_1 \sigma_{VH} I_H^*} \frac{(\Lambda_H - \gamma_H I_H) I_H}{I_H^* - I_H},$$

where we have set

$$\Sigma = \tilde{a}_1 \left(\sigma_{HV} + \widehat{\sigma}_{HV} \frac{\alpha_H}{\delta_H} \right).$$

On the one hand, if $(S_H, I_H, R_H, S_V, I_V)$ is a positive steady states of system (24) then $I_H \in [0, I_H^*)$ and

$$\Gamma_1(I_H) = \Gamma_2(I_H). \tag{28}$$

On the other, when $I_H \in [0, I_H^*)$ is a solution of (28) then straightforward computations show that it provides a positive solution for the steady state problem.

Thus it remains to discuss the existence of solutions for (28) together with $I_H \in [0, I_H^*)$. The problem is rewritten as follow:

$$I_H \left(A_2 I_H^2 + A_1 I_H + A_0 \right) = 0, \tag{29}$$

with

$$\begin{aligned} A_2 &= \frac{\epsilon_H I_H^* \gamma_H}{\Lambda_H} \left(\frac{\mu_V \gamma_H}{\mu_H} - \Sigma \right), \\ A_1 &= \Sigma \frac{\Lambda_V \tilde{a}_1 \sigma_{VH}}{\mu_V} - \epsilon_H I_H^* \left(\frac{2\mu_V \gamma_H}{\mu_H} - \Sigma \right). \\ A_0 &= \frac{\Lambda_H \mu_V \epsilon_H I_H^*}{\mu_H} \left(1 - \mathcal{R}_0^2 \right). \end{aligned}$$

Considering (29) for $I_H \in (0, I_H^*)$, we obtain the second degree equation

$$f(I_H) = A_2 I_H^2 + A_1 I_H + A_0 = 0.$$

To study this equation, we compute $f(I_H^*)$. To do so, set $\zeta = \mu_H + \gamma_H + \frac{\alpha_H \mu_H}{\delta_H}$, giving

$$\begin{aligned} \frac{\zeta^2}{\Lambda_H} f(I_H^*) &= A_2 \Lambda_H + A_1 \zeta + \frac{\mu_V \epsilon_H I_H^*}{\mu_H} \left(1 - \mathcal{R}_0^2 \right) \zeta^2 \\ &= \epsilon_H \frac{\Lambda_H}{\zeta} \gamma_H \left(\frac{\mu_V \gamma_H}{\mu_H} - \Sigma \right) + \Sigma \frac{\Lambda_V \tilde{a}_1 \sigma_{VH}}{\mu_V} \zeta - \epsilon_H \Lambda_H \left(\frac{2\mu_V \gamma_H}{\mu_H} - \Sigma \right) \\ &\quad + \frac{\mu_V \epsilon_H \Lambda_H \zeta}{\mu_H} - \zeta \tilde{a}_1 \sigma_{VH} \Sigma \frac{\Lambda_V}{\mu_V} \\ &= \epsilon_H \Lambda_H \left(\frac{\gamma_H}{\zeta} \left(\frac{\mu_V \gamma_H}{\mu_H} - \Sigma \right) - \frac{2\mu_V \gamma_H}{\mu_H} + \Sigma + \frac{\mu_V \zeta}{\mu_H} \right) \\ &= \epsilon_H \Lambda_H \left(\frac{\mu_V}{\mu_H} \left(\frac{\gamma_H}{\sqrt{\zeta}} - \sqrt{\zeta} \right)^2 + \Sigma \left(1 - \frac{\gamma_H}{\zeta} \right) \right) > 0. \end{aligned}$$

So, when $\mathcal{R}_0 > 1$ then $f(0) < 0$ and there exists a unique positive equilibrium. When $\mathcal{R}_0 < 1$ then $f(0) > 0$ and the equation $f(I_H) = 0$ has no positive solution in the interval $(0, I_H^*)$ if $A_2 \leq 0$. When $\mathcal{R}_0 < 1$ and $A_2 > 0$ then the equation $f(I_H) = 0$ has two different positive roots in $(0, I_H^*)$ if and only if

$$-\frac{A_1}{2A_2} < I_H^* \quad \text{and} \quad A_1^2 - 4A_2 A_0 > 0,$$

and one root (of multiplicity two) when $-\frac{A_1}{2A_2} < I_H^*$ and $A_1^2 - 4A_2 A_0 = 0$. This completes the proof of the result.

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