The vector-host epidemic model with multiple strains in a patchy environment

Zhipeng Qiu[1*] Qingkai Kong[1] Xuezhi Li[2†] Maia Martcheva[3‡]

[1]*Department of Applied Mathematics, Nanjing University of Science and Technology, Nanjing 210094, P R China*

[2]*Department of Mathematics, Xinyang Normal University, Xinyang 464000, P R China*

[3]*Department of Mathematics, University of Florida, Gainesville, FL 32611-8105,USA*

Abstract Spatial heterogeneity plays an important role in the distribution and persistence of infectious diseases. In this article, a vector-host epidemic model is proposed to explore the effect of spatial heterogeneity on the evolution of vector-borne diseases. The model is a Ross-McDonald type model with multiple competing strains on a number of patches connected by host migration. The multi-patch basic reproduction numbers $\mathcal{R}_0^j, j = 1, 2, \cdots, l$ are respectively derived for the model with l strains on n discrete patches. Analytical results show that if $\mathcal{R}_0^j < 1$, then strain j cannot invade the patchy environment and dies out. The invasion reproduction numbers $\mathscr{R}_i^j, i, j = 1, 2, i \neq j$ are also derived for the model with two strains on n discrete patches. It is shown that the invasion reproduction numbers $\mathscr{R}_i^j, i, j = 1, 2, i \neq j$ provide threshold conditions that determine the competitive outcomes for the two strains. Under the condition that both invasion reproduction numbers are lager than one, the coexistence of two competing strains is rigorously proved. However, the two competing strains cannot coexist for the corresponding model with no host migration. This implies that host migration can lead to the coexistence of two competing strains and enhancement of pathogen genetic diversity. Global dynamics is determined for the model with two competing strains on two patches. The results are based on the theory of type-K monotone dynamical systems.

Keywords: Vector-host disease; Meta-population model; Migration; Multiple strains; K-monotone

*nustqzp@mail.njust.edu.cn

†Corresponding author, E-mail: xzli66@126.com, Tel: 0086(376)6391735, Fax: 0086(376)6391733

‡maia@ufl.edu

1 Introduction

Two characteristics that are main drivers behind the distribution and persistence of infections diseases, are host migration and pathogen variability. Host migration allows the pathogen to invade new areas, and maintains the disease in areas where it would disappear if the area were isolated. Pathogen variability allows the pathogen to persist despite building host immunity, wide-spread treatment and vaccination. These two heterogeneities of transmission have been explored separately in multiple studies. In this article we study them together to gain insight on the impact of spatial heterogeneity on pathogen genetic diversity.

On the one hand, understanding the transmission mechanisms for diseases with multiple strains or serotypes is critical for predicting the persistence and evolution of diseases. Mathematical models have provided a powerful tool to broaden our knowledge into the mechanisms [1, 2] that lead to coexistence or competitive exclusion of multiple strains. The competitive exclusion principle is a classic result in this field, which states that no two species can indefinitely occupy the same ecological niche [3]. Using a multi-strain ODE model, Bremermann and Thieme [4] proved that the principle of competitive exclusion is valid with the strain with the highest reproduction number persisting, while all remaining strains are being eliminated. Castillo-Chavez et al. [5, 6] formulated a simple two-sex epidemiological model that considers the competitive interactions of two strains. They showed that coexistence of two competing strains is not possible except in special and unrealistic circumstances.

However, it is a common phenomenon that multiple strains coexist in nature. For instance, dengue fever has four different serotypes, often coexisting in the same geographical region [1]. The competitive exclusion principle leads to the conclusion that persistent coexistence may only occur if some heterogeneity in the ecological niche is present. Identifying the factors that allow multiple strains to coexist is an important topic in theoretical biology that has been occupying significant attention in the last 20 years. Recent studies have shown that mechanisms, such as superinfection [2, 7], co-infection [8, 9], partial cross-immunity [10], density dependent host mortality [11], different modes of transmission [12], can lead to coexistence of strains. In this paper, we will show that another mechanism, spatial heterogeneity, can also generate the coexistence of multiple competing strains in the same geographical domain.

On the other hand, spatial heterogeneities are believed to play an important role in the distribution and dynamics of infectious diseases [14]. Spatial heterogeneity can be incorporated in epidemic models as a continuous characteristic, in the form of epidemic models with diffusion, or as a discrete characteristic where migration of individuals between discrete geographical regions is considered. The discrete geographical regions can be cities, towns, states, countries or other appropriate community devisions. In recent years, several studies have focused on the transmission dynamics of infectious diseases in patchy environments by using deterministic meta-population epidemic models [15]. Castillo-Chavez and Yakubu [16] discussed a two-patch SIS epidemic model with dispersion governed by discrete equations. Wang and Zhao [17] and Wang and Mulone [18] proposed an epidemic model with population dispersal to describe the dynamics of disease spread between two patches and n patches. Wang and Zhao [19] formulated a time-delayed epidemic model to describe the dynamics of disease spread among patches, an age structure is incorporated in order to simulate the phenomenon that some diseases only occur in the adult population, sufficient conditions are established for global extinction and uniform persistence of the disease. Arino and van den Driessche [20] developed a multi-city epidemic model to analyze the spatial spread of infectious diseases. Dhirasakdanon, Thieme and Driessche [21] established sharp persistence results for multi-city models. All the previous articles consider directly transmitted diseases.

Vector-borne diseases, such as West Nile virus (WNV) and malaria, have reemerged after being nearly eliminated in the 1950s and 1960s [13]. Migration patterns of the hosts, birds and humans, is one of the important reasons that cause the worldwide spread of the vector-borne diseases. Wonham et al. [22] have suggested that the WNV model should be extended biologically to consider bird migration. Rappole *et. al.* [23] have provided some factors supporting the hypothesis that the migrant bird is an introductory host for the spread of WNV. Owen et al. [24] have demonstrated that migrating passerine birds are potential dispersal vehicles for WNV. These studies show that the importance of migration on the distribution and maintainance of infectious diseases can hardly be underestimated. Few articles have considered the effect of host migration among multiple patches on the dynamics of vector-borne diseases. Auger *et. al.* [25] formulate a Ross-MacDonald model on n patches to describe the transmission dynamics of malaria. In a recent study Cosner *et. al.* [26] consider the impact of both short term host movement and long-term host migration on the dynamics of vector-borne diseases. The models in [25, 26] discuss only vector-host diseases represented by a single strain. In this paper, based on the model in [25] we formulate Ross-

MacDonald type model with multiple competing strains on n patches. Competitive exclusion of the strains is the only outcome on a single patch. The main question that we address is whether spatial heterogeneity can generate the coexistence of multiple competing strains in a common heterogenous geographical area.

The remaining parts of this paper are organized as follows. In the next section we formulate the Ross-MacDonald model with multiple competing strains on n patches. In Section 3, we derive the reproduction numbers and investigate the local stability of the model. In Section 4, we consider the threshold dynamics of a two-strain multi-patch version of the model. Section 5 is devoted to the global analysis of the two-strain two-patch version of the model. The paper ends with a brief discussion of the results in section 6.

2 Model description

In this section we formulate a Ross-MacDonald type model to describe the transmission dynamics of a vector borne disease. Vector and host populations occupy n discrete patches linked by host migration. The model also incorporates l competing strains.

To introduce the model let $N_i(t)$ denote the total host population in the i-th patch which is partitioned into $l+1$ distinct epidemiological subclasses: susceptible and infected with strain $j, j = 1, 2, \cdots, l$. The size of the susceptible host population on patch i is denoted by $S_i(t)$. The size of the infected host population with strain j on patch i is denoted by $H_i^j(t), j = 1, 2, \cdots, l$. Let $T_i(t)$ denote the total vector population in the i-th patch. The vector population is also divided into susceptible and infected with strain $j, j = 1, 2, \cdots, l$ subclasses. The size of the susceptible vector population that occupies patch i is denoted by $M_i(t)$. The size of the infected with strain j vector population that occupies patch i is denoted by $V_i^j(t), j = 1, 2, \cdots, l$. We assume that the system which describes the spread of a vector borne disease with l strains in the i-th patch is governed by the following differential equations:

$$\begin{cases} \dfrac{dS_i(t)}{dt} = \nu_i N_i - b_i(\sum_{j=1}^{l} \alpha_j V_i^l)\dfrac{S_i}{N_i} + \sum_{j=1}^{l} \gamma_i^j H_i^j - \nu_i S_i, \\ \dfrac{dH_i^j(t)}{dt} = b_i \alpha_j V_i^j \dfrac{S_i}{N_i} - \gamma_i^j H_i^j - \nu_i H_i^j, \\ \dfrac{dM_i(t)}{dt} = \Lambda_i - b_i(\sum_{j=1}^{l} \beta_j H_i^j)\dfrac{M_i}{N_i} - \mu_i M_i, \qquad\qquad j = 1, 2, \cdots, l. \\ \dfrac{dV_i^j(t)}{dt} = b_i \beta_j M_i \dfrac{H_i^j}{N_i} - \mu_i V_i^j, \\ N_i = S_i + H_i \end{cases} \tag{2.1}$$

Here, b_i is the per capita biting rate of vectors on hosts in the i-th patch; α_j, β_j are the disease transmission probabilities from infected vectors with strain j to uninfected hosts and from infected hosts with strain j to uninfected vectors, respectively; ν_i is the birth and death rate of the hosts; μ_i is the natural death rate of the vectors; γ_i^j is the recovery rate of infected hosts with strain j in the i-th patch, and Λ_i is the recruitment rate of the uninfected vectors (by birth) in the i-th patch.

When the n patches are connected, we assume that only hosts can migrate among the patches since vectors are usually arthropods who typically move only small distances during their lifetime. Let $m_{ji} \geq 0$ denote the per capita rate that susceptible and infected hosts of patch i leave for patch j, where $i \neq j$. Then the dynamics of the hosts and the vectors with migration is governed by the following model:

$$\begin{cases} \dfrac{dS_i(t)}{dt} = \nu_i N_i - b_i(\sum_{j=1}^{l} \alpha_j V_i^j)\dfrac{S_i}{N_i} + \sum_{j=1}^{l} \gamma_i^j H_i^j \\ \qquad\qquad + \sum_{k=1,k\neq i}^{n} m_{ik} S_k - \sum_{k=1,k\neq i}^{n} m_{ki} S_i - \nu_i S_i, \\ \dfrac{dH_i^j(t)}{dt} = b_i \alpha_j V_i^j \dfrac{S_i}{N_i} - \gamma_i^j H_i^j + \sum_{k=1,k\neq i}^{n} m_{ik} H_i^j - \sum_{k=1,k\neq i}^{n} m_{ki} H_i^j - \nu_i H_i^j, \\ \dfrac{dM_i(t)}{dt} = \Lambda_i - b_i(\sum_{j=1}^{l} \beta_j H_i^j)\dfrac{M_i}{N_i} - \mu_i M_i, \\ \dfrac{dV_i^j(t)}{dt} = b_i \beta_j M_i \dfrac{H_i^j}{N_i} - \mu_i V_i^j, \\ N_i = S_i + H_i \end{cases} \tag{2.2}$$

where $i = 1, 2, \cdots, n, j = 1, 2, \cdots, l$.

Adding the first $l + 1$ equations of the system (2.1) gives

$$\frac{dN_i(t)}{dt} = 0,$$

and it follows that the total population size $N_i(t) = N_i^0$ is a constant. Similarly, adding the last $l+1$ equations of the system (2.1) gives

$$\frac{dT_i(t)}{dt} = \Lambda_i - \mu_i T_i.$$

The asymptotic equilibrium values for the T_i are $T_i(t) \to \frac{\Lambda_i}{\mu_i} := \bar{W}_i$ as $t \longrightarrow +\infty$.

By adding the first $l+1$ equations of the system (2.2), we have

$$\frac{dN_i(t)}{dt} = \sum_{j=1, j\neq i}^{n} m_{ij} N_j - \sum_{j=1, j\neq i}^{n} m_{ji} N_i.$$

This system can be rewritten as

$$\frac{dN(t)}{dt} = MN(t), \tag{2.3}$$

where N is the column vector $(N_1, N_2, \cdots, N_n)^T$ and the superscript T denotes transpose. The movement matrix M is defined by $M(i,j) = m_{ij}$ for $i \neq j$ and

$$M(i,i) = -\sum_{j=1, j\neq i}^{n} m_{ji}.$$

We assume that the matrix M is irreducible, that is, the graph of the patches is strongly connected through the movement of hosts. If that is not the case, it follows from [25] that the system (2.2) can be divided into some decoupled subsystems. From article [25] it follows that any trajectory of the system (2.3) remains in the affine hyperplane orthogonal to the vector $(1, 1, \cdots, 1)^T$ and containing the initial condition $N(0)$. In the affine hyperplane the system (2.3) has a positive equilibrium denoted by $\bar{N} = (\bar{N}_1, \bar{N}_2, \cdots, \bar{N}_n)^T$. Moreover, the positive equilibrium $\bar{N}$ is globally asymptotically stable on the affine hyperplane.

Noting that the total host and vector populations for system (2.1) and (2.2) tend to the the asymptotic states as $t \to +\infty$, in this paper we always assume that the system (2.1) and the system (2.2) have reached the asymptotic states. Thus system (2.1) is equivalent to the following system

$$\begin{cases} \dfrac{dH_i^j(t)}{dt} = b_i \alpha_j V_i^j \dfrac{N_i^0 - \sum\limits_{j=1}^{l} H_i^j}{N_i^0} - (\gamma_i^j + \nu_i) H_i^j, \\ \dfrac{dV_i^j(t)}{dt} = b_i \beta_j (\bar{W}_i - \sum\limits_{j=1}^{l} V_i^j) \dfrac{H_i^j}{N_i^0} - \mu_i V_i^j, \end{cases} \tag{2.4}$$

and system (2.2) can be reduced to the system as follows

$$\begin{cases} \dfrac{dH_i^j(t)}{dt} = b_i\alpha_j V_i^j \dfrac{\bar{N}_i - \sum\limits_{j=1}^{l} H_i^j}{\bar{N}_i} \\ \qquad\qquad -\gamma_i^j H_i^j + \sum\limits_{k=1,k\neq i}^{n} m_{ik} H_k^j - \sum\limits_{k=1,k\neq i}^{n} m_{ki} H_i^j - \nu_i H_i^j, \\ \dfrac{dV_i^j(t)}{dt} = b_i\beta_j(\bar{W}_i - \sum\limits_{j=1}^{l} V_i^j)\dfrac{H_i^j}{\bar{N}_i} - \mu_i V_i^j, \end{cases} \tag{2.5}$$

where $i = 1, 2, \cdots, n, j = 1, 2, \cdots, l$.

In the remainder of this article we will analyze the dynamics of the system (2.4) and (2.5) instead of (2.1) and (2.2), respectively, and we will further investigate how spatial heterogeneity affects the dynamics and outbreaks of the vector borne diseases with multiple strains on multiple patches.

3 The reproduction numbers and the local stability

One of the important critical threshold quantities in epidemiological modeling studies is the reproduction number. Epidemiologically, this quantity is defined as the average number of secondary cases (infections) produced by a typical infected individual during the entire period of infection when this infectious individual is introduced into a completely susceptible population [30]. Mathematically, the reproduction number serves as a threshold quantity that often determines the persistence or eradication of the disease [11, 31, 32]. Generally, if the basic reproduction number is less than one, the disease can not establish itself in the population, If the reproduction number is greater than one the disease will be endemic. In this section we derive the reproduction numbers for strain $j, j = 1, 2, \cdots, l$, and then we investigate the local stabilities of the boundary equilibria using these reproduction numbers.

We begin by introducing certain notations that will be used throughout this paper. Let

$$\mathbb{R}_+^{2ln} := \{(I^1, I^2, \cdots, I^l) : H_i^j \geq 0, V_i^j \geq 0, i = 1, 2, \cdots, n, j = 1, 2, \cdots, l\}.$$

We define a subset Ω of $\mathbb{R}_+^{2ln}$ by

$$\Omega = \{(I^1, I^2, \cdots, I^l) \in \mathbb{R}_+^{2ln} : \sum_{j=1}^{l} H_i^j \leq \bar{N}_i, \sum_{j=1}^{l} V_i^j \leq \bar{W}_i, i = 1, 2, \cdots, n\},$$

where

$$I^j = (H_1^j, H_2^j, \cdots, H_n^j, V_1^j, V_2^j, \cdots, V_n^j). \tag{3.1}$$

Let $\varphi(I^1, I^2, \cdots, I^l)$ denote the solution flow generated by (2.5). It is not difficult to see that the flow is positively invariant in Ω. For two vectors $x = (x_1, x_2, \cdots, x_{2n}), z = (z_1, z_2, \cdots, z_{2n}) \in \mathbb{R}^{2n}$ we define an order between them as follows:

$$x \leq z \text{ if } x_i \leq z_i, i = 1, 2, \cdots, 2n.$$

We can easily derive the reproduction number of system (2.4) which gives the isolated reproduction number for strain j in patch i:

$$R_i^j = \sqrt{\frac{b_i^2 \alpha_j \beta_j \bar{W}_i}{(\gamma_i^j + \nu_i)\mu_i N_i^0}}. \tag{3.2}$$

Similar argument as in the proof of Theorem 3.2 and Theorem 4.2 of [5], we can obtain the following theorem.

Theorem 3.1. *For a given $i \in \{1, 2, \cdots, n\}$, the system* (2.4) *has*

*1) if $R_i^j < 1$ for all $1 \leq j \leq l$, then the disease for all strains will eventually die out, i.e., the disease-free equilibrium of the system (*2.4*) is globally asymptotically stable;*

2) if $R_i^j > 1$ for some $1 \leq j \leq l$ and assume that there exists $j^* \in \{1, 2, \cdots, l\}$ such that $R_i^{j^*} > R_i^j$ for all $j = 1, 2, \cdots, l, j \neq j^*$, then

$$\lim_{t\to+\infty} H_i^{j^*}(t) = \frac{[b_i^2 \alpha_{j^*} \beta_{j^*} \frac{\bar{W}_i}{N_i^0} - \mu_i(\gamma_i^{j^*} + \nu_i)]N_i^0}{b_i \beta_{j^*}(\gamma_i^{j^*} + \nu_i + b_i \alpha_{j^*} \frac{\bar{W}_i}{N_i^0})}, \lim_{t\to+\infty} V_i^{j^*}(t) = \frac{[b_i^2 \alpha_{j^*} \beta_{j^*} \frac{\bar{W}_i}{N_i^0} - \mu_i(\gamma_i^{j^*} + \nu_i)]N_i^0}{b_i \alpha_{j^*}(b_i \beta_{j^*} + \mu_i)},$$

and

$$\lim_{t\to+\infty} H_i^j(t) = 0, \lim_{t\to+\infty} V_i^j(t) = 0$$

for all $j = 1, 2, \cdots, l, j \neq j^*$.

The proof of Theorems 3.1 is provided in Appendix A.

Theorem 3.1 implies that if the system (2.5) has no host migration among patches then no more than one strain will persist in the population of patch i, namely the strain with the largest reproduction number in patch i. All strains which have lower basic reproductive rates die out in patch i. In what follows we will prove that coexistence of two competing strains in a common area is possible if the system incorporates host migration among patches. This suggests that host migration, that is spatial heterogeneity, is one of the mechanisms which can lead to the coexistence of multiple competing strains.

We now derive the basic reproduction numbers for system (2.5). Let $c \in \{1, 2 \cdots, l\}$ and

$$\Gamma^c = \{(I^1, I^2, \cdots, I^l) \in \Omega : I^j = 0, j \neq c\}, \tag{3.3}$$

then Γ^c is invariant for system (2.5). The system (2.5) in Γ^c is

$$\begin{cases} \dfrac{dH_i^c(t)}{dt} = b_i\alpha_c V_i^c \dfrac{\bar{N}_i - H_i^c}{\bar{N}_i} - \gamma_i^c H_i^c + \displaystyle\sum_{k=1,k\neq i}^{n} m_{ik}H_k^c - \sum_{k=1,k\neq i}^{n} m_{ki}H_i^c - \nu_i H_i^c, \\ \dfrac{dV_i^c(t)}{dt} = b_i\beta_c(\bar{W}_i - V_i^c)\dfrac{H_i^c}{\bar{N}_i} - \mu_i V_i^c, \qquad i = 1, 2, \cdots, n. \end{cases} \tag{3.4}$$

It is clear that $E_0^c(I^c = 0)$ is the disease-free equilibrium (DFE) of the subsystem (3.4). Noting that the model has 2n infected populations, namely H_i^c and $V_i^c, i = 1, 2, \cdots, n$, it follows that, in the notation of [33], the matrix $\mathscr{F}^c$ and $\mathscr{V}^c$ for the new infection terms and the remaining transfer terms respectively, are given by

$$\mathscr{F}^c = \begin{pmatrix} 0 & \mathscr{F}_{12}^c \\ \mathscr{F}_{21}^c & 0 \end{pmatrix}, \quad \mathscr{V}^c = \begin{pmatrix} \mathscr{V}_{11}^c & 0 \\ 0 & \mathscr{V}_{22}^c \end{pmatrix},$$

where

$$\mathscr{F}_{12}^c = \begin{pmatrix} b_1\alpha_c & 0 & \cdots & 0 \\ 0 & b_2\alpha_c & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & b_n\alpha_c \end{pmatrix}, \mathscr{F}_{21}^c = \begin{pmatrix} b_1\beta_c\frac{\bar{W}_1}{\bar{N}_1} & 0 & \cdots & 0 \\ 0 & b_2\beta_c\frac{\bar{W}_2}{\bar{N}_2} & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & b_n\beta_c\frac{\bar{W}_n}{\bar{N}_n} \end{pmatrix},$$

$$\mathscr{V}_{11}^c = \begin{pmatrix} \hat{\gamma}_1^c & -m_{12} & \cdots & -m_{1n} \\ -m_{21} & \hat{\gamma}_2^c & \cdots & -m_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ -m_{n1} & -m_{n2} & \cdots & \hat{\gamma}_n^c \end{pmatrix}, \mathscr{V}_{22}^c = \begin{pmatrix} \mu_1 & 0 & \cdots & 0 \\ 0 & \mu_2 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & \mu_n \end{pmatrix},$$

and $\hat{\gamma}_i^c = \gamma_i^c + \nu_i + \sum_{k=1,k\neq i}^{n} m_{ki}$.

Results in [33] imply that the basic reproduction number of the subsystem (3.4) is given by

$$\begin{aligned} \mathcal{R}_0^c : &= \rho(\mathscr{F}^c(\mathscr{V}^c)^{-1}) \\ &= \Big\{\rho(diag\{b_1\beta_c\frac{\bar{W}_1}{\bar{N}_1}, b_2\beta_c\frac{\bar{W}_2}{\bar{N}_2}, \cdots, b_n\beta_c\frac{\bar{W}_n}{\bar{N}_n}\}(\mathscr{V}_{11}^c)^{-1}diag\{\frac{b_1\alpha_c}{\mu_1}, \frac{b_2\alpha_c}{\mu_2}, \cdots, \frac{b_n\alpha_c}{\mu_n}\})\Big\}^{\frac{1}{2}} \end{aligned} \tag{3.5}$$

where $\rho(M)$ represents the spectral radius of the matrix M.

Following Smith [34] one can establish that the subsystem (3.4) is strongly concave. Results in [34] also imply that that either the origin of system (2.5) is globally asymptotically stable in Γ^c defined in (3.3), or system (2.5) has a unique equilibrium $E_{I^c}(I^c = \bar{I}^c > 0, I^j = 0, j \neq c)$ such that it is globally asymptotically stable in $\Gamma^c \setminus \{O\}$, where I^c, I^j are defined in (3.1). This conclusion is based on the observation that E_{I^c} is linearly stable in Γ^c, that is

$$A_{11}^c = \begin{pmatrix} \eta_1 & m_{12} & \cdots & m_{1n} & \alpha_c Q_1^H & 0 & \cdots & 0 \\ m_{21} & \eta_2 & \cdots & m_{2n} & 0 & \alpha_c Q_2^H & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \ddots & \vdots \\ m_{n1} & m_{n2} & \cdots & \eta_n & 0 & 0 & \cdots & \alpha_c Q_n^H \\ \beta_c Q_1^V & 0 & \cdots & 0 & Q_1^\beta & 0 & \cdots & 0 \\ 0 & \beta_c Q_2^V & \cdots & 0 & 0 & Q_2^\beta & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & \beta_c Q_n^V & 0 & 0 & \cdots & Q_n^\beta \end{pmatrix}, \tag{3.6}$$

is a stable matrix, where

$$\begin{aligned} &Q_i^V = \frac{b_i(\bar{W}_i - \bar{V}_i^c)}{\bar{N}_i}, \quad Q_i^H = \frac{b_i(\bar{N}_i - \bar{H}_i^c)}{\bar{N}_i}, \quad Q_i^\beta = -\mu_i - \frac{b_i \beta_c \bar{H}_i^c}{\bar{N}_i}, \\ &\eta_i = -\frac{b_i \alpha_c \bar{V}_i^c}{\bar{N}_i} - \gamma_i^c - \sum_{k=1,k\neq i}^{n} m_{ki} - \nu_i, \quad i = 1, 2, \cdots, n. \end{aligned}$$

Simple algebraic calculations imply that system (3.4) has an equilibrium if and only if $\mathcal{R}_0^c > 1$. Thus we have

Theorem 3.2. *If $\mathcal{R}_0^c \leq 1$, then the disease-free equilibrium (DFE) E_0 of the system* (2.5) *is globally asymptotically stable in Γ^c. If $\mathcal{R}_0^c > 1$, then system* (2.5) *has a unique equilibrium $E_{I^c}(I^c = \bar{I}^c > 0, I^j = 0, j \neq c)$ which is globally asymptotically stable in $\Gamma_c \setminus \{O\}$.*

Now we are able to state the main result in this section.

Theorem 3.3. *1) If $\mathcal{R}_0^j \leq 1$ for all $1 \leq j \leq l$, then the DFE E_0 of the system* (2.5) *is globally asymptotically stable in Ω.*

2) If there exists $c \in \{1, 2, \cdots, l\}$ such that $\mathcal{R}_0^c > 1$ and $\mathcal{R}_0^j \leq 1$ for $1 \leq j \leq l, j \neq c$, then the boundary equilibrium $E_{I^c}(I^c = \bar{I}^c > 0, I^j = 0, j \neq c)$ is globally asymptotically stable in $\Omega \setminus \{(I^1, I^2, \cdots, I^l) : I^c = 0\}$.

Proof. For a given $j \in \{1, 2, \cdots, l\}$, it follows from the system (2.5) that

$$\begin{cases} \dfrac{dH_i^j(t)}{dt} \leq b_i \alpha_j V_i^j - \gamma_j H_i^j + \displaystyle\sum_{k=1,k\neq i}^{n} m_{ik} H_k^j - \sum_{k=1,k\neq i}^{n} m_{ki} H_i^j - \nu_i H_i^j, \\ \dfrac{dV_i^j(t)}{dt} \leq b_i \beta_j \dfrac{\bar{W}_i}{\bar{N}_i} H_i^j - \mu_i V_i^j, \qquad i = 1, 2, \cdots, n. \end{cases} \tag{3.7}$$

Let us consider the following differential equations

$$\begin{cases} \dfrac{d\tilde{H}_i^j(t)}{dt} = b_i\alpha_j\tilde{V}_i^j - \gamma_j\tilde{H}_i^j + \displaystyle\sum_{k=1,k\neq i}^{n} m_{ik}\tilde{H}_k^j - \sum_{k=1,k\neq i}^{n} m_{ki}\tilde{H}_i^j - \nu_i\tilde{H}_i^j, \\ \dfrac{d\tilde{V}_i^j(t)}{dt} = b_i\beta_j\dfrac{\bar{W}_i}{\bar{N}_i}\tilde{H}_i^j - \mu_i\tilde{V}_i^j, \qquad i = 1, 2, \cdots, n. \end{cases} \tag{3.8}$$

Since the system (3.8) is a linear system, the global stability of the origin of the system (3.8) is determined by the stability of the matrix $J^j = \mathscr{F}^j - \mathscr{V}^j$. If $\mathcal{R}_0^j \leq 1$, Theorem 2 in [33] implies that the matrix J^j is stable. Then we have $\lim_{t\to+\infty}\tilde{H}_i^j(t) = 0, \lim_{t\to+\infty}\tilde{V}_i^j(t) = 0$ for all $1 \leq i \leq n$. By the comparison principle it then follows that $H_i^j(t) \to 0, V_i^j(t) \to 0$ as $t \to +\infty$ for all $1 \leq i \leq n$.

If $\mathcal{R}_0^j \leq 1$ for all $1 \leq j \leq l$, then we have $\lim_{t\to+\infty}\tilde{H}_i^j(t)) = 0, \lim_{t\to+\infty}\tilde{V}_i^j(t) = 0$ for all $1 \leq i \leq n, 1 \leq j \leq l$. We can easily see that E_0 is locally asymptotically stable in Ω. This fact implies that the disease-free equilibrium E_0 is globally asymptotically stable in Ω if $\mathcal{R}_0^j < 1$ for all $1 \leq j \leq l$.

If there exists $c \in \{1, 2, \cdots, n\}$ such that $\mathcal{R}_0^c > 1$ and $\mathcal{R}_0^j \leq 1$ for $1 \leq j \leq n, j \neq c$, then we have that $\lim_{t\to+\infty}\tilde{H}_i^j(t)) = 0, \lim_{t\to+\infty}\tilde{V}_i^j(t) = 0$ for all $1 \leq i \leq n, 1 \leq j \leq l, j \neq c$. Furthermore, if $(I^1(0), I^2(0), \cdots, I^l(0)) \in \Omega \setminus \{(I^1, I^2, \cdots, I^l) : I^c = 0\}$, by using the comparison principle, we can easily prove that there exists $\varsigma > 0$ such that

$$H_i^c(t) > \varsigma, V_i^c(t) > \varsigma \tag{3.9}$$

for t sufficiently large and all $1 \leq i \leq n$. In this case the limiting system of system (2.5) is subsystem (3.4). Since $\mathcal{R}_0^c > 1$, Theorem 3.2 implies that $E_{I^c}(\bar{I}^c > 0, \bar{I}^j = 0, j \neq c)$ is globally asymptotically stable in $\Gamma^c \setminus \{O\}$. Denote the flows generated by systems (2.5) by $\Psi(t, X)$. Since for any $X \in \Omega \setminus \{(I^1, I^2, \cdots, I^l) : I^c = 0\}$, the orbit $\{\Psi(t, X) : t > 0\}$ is precompact, $\omega_\Psi(X)$the limit set of X, exists. Let ω_Ψ^P be the projection of $\omega_\Psi(X)$ onto Γ^c. then (3.9) implies that $\omega_\Psi^P \in \Gamma^c \setminus \{0\}$. By Theorem 2.3 in [27] we can conclude that the equilibrium $E_{I^c}(\bar{I}^c > 0, \bar{I}^j = 0, j \neq c)$ is a global attractor in $\Omega \setminus \{(I^1, I^2, \cdots, I^l) : I^c = 0\}$. This completes the proof of Theorem 3.3. □

4 Coexistence of two strains on n patches

In this section we consider the case of two strains on n patches. When system (2.5) has only two strains, strain 1 and strain 2, then it can be rewritten as

$$\begin{cases} \dfrac{dH_i^1(t)}{dt} = b_i\alpha_1 V_i^1 \dfrac{\bar{N}_i - H_i^1 - H_i^2}{\bar{N}_i} \\ \qquad\qquad -\gamma_i^1 H_i^1 + \displaystyle\sum_{k=1,k\neq i}^{n} m_{ik}H_k^1 - \sum_{k=1,k\neq i}^{n} m_{ki}H_i^1 - \nu_i H_i^1, \\ \dfrac{dV_i^1(t)}{dt} = b_i\beta_1(\bar{W}_i - V_i^1 - V_i^2)\dfrac{H_i^1}{\bar{N}_i} - \mu_i V_i^1, \\ \dfrac{dH_i^2(t)}{dt} = b_i\alpha_2 V_i^2 \dfrac{\bar{N}_i - H_i^1 - H_i^2}{\bar{N}_i} \\ \qquad\qquad -\gamma_i^2 H_i^2 + \displaystyle\sum_{k=1,k\neq i}^{n} m_{ik}H_k^2 - \sum_{k=1,k\neq i}^{n} m_{ki}H_i^2 - \nu_i H_i^2, \\ \dfrac{dV_i^2(t)}{dt} = b_i\beta_2(\bar{W}_i - V_i^1 - V_i^2)\dfrac{H_i^2}{\bar{N}_i} - \mu_i V_i^2, \end{cases} \quad i = 1, 2\cdots, n. \tag{4.1}$$

In the case when at least one of the reproduction numbers is smaller than one, that is, either $\mathcal{R}_0^1 \leq 1$ or $\mathcal{R}_0^2 \leq 1$, Theorem 3.3 gives the global behavior of system (4.1). Therefore, we only need to consider the case when both $\mathcal{R}_0^1 > 1$ and $\mathcal{R}_0^2 > 1$. When $\mathcal{R}_0^1 > 1, \mathcal{R}_0^2 > 1$, the system (4.1) has the disease-free equilibrium $E_0(0,0)$, which is unstable, as well as the two boundary equilibria $E_{I^1}(\bar{I}^1, 0), E_{I^2}(0, \bar{I}^2)$, where $\bar{I}^j = (\bar{H}_1^j, \bar{H}_2^j, \cdots, \bar{H}_n^j, \bar{V}_1^j, \bar{V}_2^j \cdots, \bar{V}_n^j), j = 1, 2$. In what follows we investigate the local stability of the boundary equilibria $E_{I^1}(\bar{I}^1, 0), E_{I^2}(0, \bar{I}^2)$. To this effect we define two important quantities $\mathscr{R}_1^2, \mathscr{R}_2^1$ as follows

$$\mathscr{R}_1^2 = (\rho(\mathscr{M}_1^2))^{\frac{1}{2}}, \mathscr{R}_2^1 = (\rho(\mathscr{M}_2^1))^{\frac{1}{2}},$$

where

$$\begin{aligned} \mathscr{M}_1^2 &= \Big\{diag\{b_1\beta_2\frac{\bar{W}_1 - \bar{V}_1^1}{\bar{N}_1}, b_2\beta_2\frac{\bar{W}_2 - \bar{V}_2^1}{\bar{N}_2}, \cdots, b_n\beta_2\frac{\bar{W}_n - \bar{V}_n^1}{\bar{N}_n}\} \\ &\qquad \times(\mathscr{V}_{11}^2)^{-1} diag\{b_1\alpha_2\frac{\bar{N}_1 - \bar{H}_1^1}{\bar{N}_1\mu_1}, b_2\alpha_2\frac{\bar{N}_2 - \bar{H}_2^1}{\bar{N}_2\mu_2}, \cdots, b_n\alpha_2\frac{\bar{N}_n - \bar{H}_n^1}{\bar{N}_n\mu_n}\}\Big\}; \\ \mathscr{M}_2^1 &= \Big\{diag\{b_1\beta_1\frac{\bar{W}_1 - \bar{V}_1^2}{\bar{N}_1}, b_2\beta_1\frac{\bar{W}_2 - \bar{V}_2^2}{\bar{N}_2}, \cdots, b_n\beta_1\frac{\bar{W}_n - \bar{V}_n^2}{\bar{N}_n}\} \\ &\qquad \times(\mathscr{V}_{11}^1)^{-1} diag\{b_1\alpha_1\frac{\bar{N}_1 - \bar{H}_1^2}{\bar{N}_1\mu_1}, b_2\alpha_1\frac{\bar{N}_2 - \bar{H}_2^2}{\bar{N}_2\mu_2}, \cdots, b_n\alpha_1\frac{\bar{N}_n - \bar{H}_n^2}{\bar{N}_n\mu_n}\}\Big\}. \end{aligned}$$

and $\mathscr{V}_{11}^j, j = 1, 2$ are defined in Section 3.

Theorem 4.1. *1) If $\mathscr{R}_1^2 > 1$ ($\mathscr{R}_1^2 < 1$) the boundary equilibrium $E_{I^1}(\bar{I}^1, 0)$ is unstable (locally stable).*

2) If $\mathscr{R}_2^1 > 1$ ($\mathscr{R}_2^1 < 1$) the boundary equilibrium $E_{I^2}(0, \bar{I}^2)$ is unstable (locally stable).

Proof. We only prove the first point above, since the second point can be proved in a similar way.

The Jacobian matrix $J(E_{I^1}(\bar{I}^1, 0))$ at $E_{I^1}(\bar{I}^1, 0)$ takes the form

$$J(E_{I^1}(\bar{I}^1, 0)) = \begin{pmatrix} A_{11}^1 & A_{12}^1 \\ 0 & A_{22}^1 \end{pmatrix},$$

where A_{11}^1 has the same form as (3.6) and

$$A_{22}^1 = F_{22}^1 - V_{22}^1,$$

$$F_{22}^1 = \begin{pmatrix} 0 & 0 & \cdots & 0 & \alpha_2 \bar{Q}_1^H & 0 & \cdots & 0 \\ 0 & 0 & \cdots & 0 & 0 & \alpha_2 \bar{Q}_2^H & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & 0 & 0 & 0 & \cdots & \alpha_2 \bar{Q}_n^H \\ \beta_2 \bar{Q}_1^V & 0 & \cdots & 0 & 0 & 0 & \cdots & 0 \\ 0 & \beta_2 \bar{Q}_2^V & \cdots & 0 & 0 & 0 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & \beta_2 \bar{Q}_n^V & 0 & 0 & \cdots & 0 \end{pmatrix},$$

$$V_{22}^1 = \begin{pmatrix} \zeta_1 & -m_{12} & \cdots & -m_{1n} & 0 & 0 & \cdots & 0 \\ -m_{21} & \zeta_2 & \cdots & -m_{2n} & 0 & 0 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \ddots & \vdots \\ -m_{n1} & -m_{n2} & \cdots & \zeta_n & 0 & 0 & \cdots & 0 \\ 0 & 0 & \cdots & 0 & \mu_1 & 0 & \cdots & 0 \\ 0 & 0 & \cdots & 0 & 0 & \mu_2 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & 0 & 0 & 0 & \cdots & \mu_n \end{pmatrix},$$

and

$$\bar{Q}_i^V = \frac{b_i(\bar{W}_i - \bar{V}_i^1)}{\bar{N}_i}, \quad \bar{Q}_i^H = \frac{b_i(\bar{N}_i - \bar{H}_i^1)}{\bar{N}_i}, \quad \eta_i = \gamma_i^2 + \sum_{k=1, k\neq i}^{n} m_{ki} + \nu_i, \quad i = 1, 2, \cdots, n.$$

The stability of the boundary equilibrium $E_{I^1}(\bar{I}^1, 0)$ is determined by the stability of the matrices A_{11}^1 and A_{22}^1. It follows from (3.6) that the matrix A_{11}^1 is stable. We only need to investigate the stability of the matrix A_{22}^1.

Since V_{22}^1 has the Z pattern and it is a strictly row diagonally dominant matrix, we conclude that V_{22}^1 is non-singular M-matrix. It is easy to see that F_{22}^1 is non-negative, then $-A_{22}^1 = V_{22}^1 - F_{22}^1$ has the Z

pattern [33]. Thus,

$$s(A_{22}^1) < 0 \Longleftrightarrow -A_{22}^1 \text{ is a non-singular M-matrix},$$

where $s(A_{22}^1)$ denotes the maximum real part of all the eigenvalues of the matrix A_{22}^1. By results in article [33], we have

$$-A_{22}^1 \text{ is a non-singular M-matrix} \Longleftrightarrow I - F_{22}^1(V_{22}^1)^{-1} \text{ is a non-singular M-matrix.}$$

Since $F_{22}^1(V_{22}^1)^{-1}$ is non-negative, all eigenvalues of $F_{22}^1(V_{22}^1)^{-1}$ have magnitude less than or equal to $\rho(F_{22}^1(V_{22}^1)^{-1})$. So

$$\begin{aligned} I - F_{22}^1(V_{22}^1)^{-1} \text{ is a non-singular M-matrix} \quad &\Longleftrightarrow \quad \rho(F_{22}^1(V_{22}^1)^{-1}) < 1 \\ &\Longleftrightarrow \quad (\rho(\mathscr{M}_1^2))^{\frac{1}{2}} < 1. \end{aligned}$$

Hence, $s(A_{22}^1) < 0$ if and only if $\mathscr{R}_1^2 < 1$. We conclude that the boundary equilibrium $E_{I_1}(\bar{I}_1, 0)$ is locally stable when $\mathscr{R}_1^2 < 1$.

Similarly, we have $s(A_{22}^1) = 0$ if and only if $\mathscr{R}_1^2 = 1$. In addition, $s(A_{22}^1) > 0$ if and only if $\mathscr{R}_1^2 > 1$. Thus, if $\mathscr{R}_1^2 > 1$ then the boundary equilibrium $E_{I^1}(\bar{I}^1, 0)$ is unstable. This concludes the proof. □

Theorem 4.2. *If $\mathscr{R}_2^1 > 1$ and $\mathscr{R}_1^2 > 1$, then there exists an $\varepsilon > 0$ such that for every $(I^1(0), I^2(0)) \in \mathrm{Int}R_+^{4n}$ the solution $(I^1(t), I^2(t))$ of system* (4.1) *satisfies that*

$$\liminf_{t\to+\infty} H_i^j(t) \geq \varepsilon, \liminf_{t\to+\infty} V_i^j(t) \geq \varepsilon$$

for all $i = 1, 2, \cdots, n, j = 1, 2$. Moreover, the system (4.1) *admits at least one (component-wise) positive equilibrium.*

Proof. Define

$$X = \{(I^1, I^2) : H_i^j \geq 0, V_i^j \geq 0, i = 1, 2, \cdots, n, j = 1, 2\},$$

$$X^0 = \{(I^1, I^2) : H_i^j > 0, V_i^j > 0, i = 1, 2, \cdots, n, j = 1, 2\},$$

$$\partial X^0 = X \setminus X^0.$$

To prove the theorem, it suffices to show that (4.1) is uniformly persistent with respect to $(X^0, \partial X^0)$ (see [17]).

First, from system (4.1), we get that both X and X^0 are positively invariant. Clearly, ∂X^0 is relatively closed in X and the system (4.1) is point dissipative. If $(I^1(t), I^2(t))$ are solutions of system (4.1), we define

$$M_\partial = \{(I^1(0), I^2(0)) : (I^1(t), I^2(t)) \in \partial X^0, \forall t \geq 0\}.$$

We can show that

$$M_\partial = B_1 \cup B_2, \tag{4.2}$$

where $B_1 = \{(I^1, I^2) : I^2 \equiv 0\}$ and $B_2 = \{(I^1, I^2) : I^1 \equiv 0\}$. Let $(I^1(0), I^2(0)) \in M_\partial$. To show that (4.2) holds, it suffices to show that $I^1(t) \equiv 0$ or $I^2(t) \equiv 0$ for all $t \geq 0$. We establish this result by contradiction. Suppose the result is not true. Then there exists a $t_1 > 0$ such that, without loss of generality, $H_1^1(t_1) > 0, H_1^2(t_1) > 0$ and $H_i^j(t_1) = 0, i = 2, 3, \cdots, n, j = 1, 2, V_i^j(t_1) = 0, i = 1, 2 \cdots, n, j = 1, 2$ (the other cases can be discussed in the same way). Since

$$\begin{aligned} \frac{dH_i^j(t)}{dt} &\geq -(\gamma_i^j + \sum_{k=1, k\neq i}^{n} m_{ki} + \nu_i) H_i^j, \\ \frac{dV_i^j(t)}{dt} &\geq -\mu_i V_i^j \end{aligned}$$

for all $i = 1, 2 \cdots, n, j = 1, 2$, we can easily see that if there exists a $t_0 > 0$ such that $H_i^j(t_0) > 0$ or $V_i^j(t_0) > 0$ then $H_i^j(t) > 0$ or $V_i^j(t) > 0$ for all $t > t_0$. Let $k \in \{2, 3, \cdots, n\}$. The irreducibility of M implies that there exists a chain from 1 to k, i.e., a sequence $i_1, i_2, \cdots, i_s \in \{1, 2, \cdots, n\}$ with $i_1 = 1$ and $i_s = k$ such that $m_{i_p i_{p+1}} > 0$ for $1 \leq p \leq s-1$. System (4.1) implies that we have

$$\frac{dH_{i_2}^1(t)}{dt}|_{t=t_0} > 0.$$

Then there exists a $t_{i_2}(> t_1)$ such that $H_{i_2}^1(t) > 0$ for all $t > t_{i_2}$. Similarly, there exists a $t_{i_p}(> t_{i_{p-1}}), p = 3, 4, \cdots, s$ such that $H_{i_p}^1(t) > 0$ for all $t > t_{i_p}$. Since k is arbitrary, we can conclude that there exists a $t^1 > 0$ such that $H_i^1(t) > 0$ for all $i = 1, 2, \cdots, n$ and $t > t^1$. From the second equation of system (4.1) we can easily see that there exists a $T^1(> t^1)$ such that $V_i^1(t) > 0$ for all $i = 1, 2 \cdots, n$ and $t > T^1$. As in the previous proof it is also easy to show that if $H_1^2(0) > 0$ there exists a $T^2 > 0$ such that $H_i^2(t) > 0, V_i^2(t) > 0$ for all $i = 1, 2, \cdots, n$ and $t > T^2$. Clearly, we have that $H_i^j(t) > 0, V_i^j(t) > 0, i = 1, 2, \cdots, n, j = 1, 2$ for all $t > \max\{T^1, T^2\}$. This means that $(I^1(t), I^2(t)) \notin \partial X_0$ for all

$t > \max\{T^1, T^2\}$, which contradicts the assumption $(I^1(0), I^2(0)) \in M_\partial$. The contradiction implies that (4.2) holds.

It is clear that there are three equilibria E_0, E_{I^1} and E_{I^2} in M_∂. Since $\mathscr{R}_1^2 > 1$, we can choose $\delta_1 > 0$ small enough such that

$$\begin{aligned} r_1^2 \quad := \quad & \Big(\rho\Big(diag\{b_1\beta_2\frac{\bar{W}_1 - \bar{V}_1^1 - 2\delta_1}{\bar{N}_1}, b_2\beta_2\frac{\bar{W}_2 - \bar{V}_2^1 - 2\delta_1}{\bar{N}_2}, \cdots, b_n\beta_2\frac{\bar{W}_n - \bar{V}_n^1 - 2\delta_1}{\bar{N}_n}\} \\ & \times(\mathscr{V}_{11}^2)^{-1} diag\{b_1\alpha_2\frac{\bar{N}_1 - \bar{H}_1^1 - 2\delta_1}{\bar{N}_1\mu_1}, b_2\alpha_2\frac{\bar{N}_2 - \bar{H}_2^1 - 2\delta_1}{\bar{N}_2\mu_2}, \cdots, b_n\alpha_2\frac{\bar{N}_n - \bar{H}_n^1 - 2\delta_1}{\bar{N}_n\mu_n}\}\Big)\Big)^{\frac{1}{2}} \\ > \quad & 1. \end{aligned}$$

Let us consider the arbitrary positive solution $(I^1(t), I^2(t))$ of system (4.1). Now we can claim that

$$\limsup_{t\to+\infty} \max_i\{H_i^2(t), V_i^2(t)\} > \delta_1.$$

Suppose, for the sake of contradiction, that there is a $T_1 > 0$ such that $H_i^2(t) < \delta_1, V_i^2(t) < \delta_1, i = 1, 2, \cdots, n$, for all $t > T_1$. Noting that

$$\begin{cases} \dfrac{dH_i^1(t)}{dt} \le b_i\alpha_1 V_i^1 \dfrac{\bar{N}_i - H_i^1}{\bar{N}_i} - \gamma_i^1 H_i^1 + \displaystyle\sum_{k=1,k\neq i}^n m_{ik}H_k^1 - \sum_{k=1,k\neq i}^n m_{ki}H_i^1 - \nu_i H_i^1, \\ \dfrac{dV_i^1(t)}{dt} \le b_i\beta_1(\bar{W}_i - V_i^1)\dfrac{H_i^1}{\bar{N}_i} - \mu_i V_i^1, \qquad i = 1, 2, \cdots, n. \end{cases}$$

Since the equilibrium $E_{I^1}(I^1 = \bar{I}^1)$ of system (3.4), where $c = 1$, is globally asymptotically stable, by comparison principle there is a $T_2 > 0$ such that $H_i^1(t) < \bar{H}_i^1 + \delta_1, \hat{V}_i^1(t) < \bar{V}_i^1 + \delta_1, i = 1, 2\cdots, n$, for all $t > T_2$. Then, for $t > \max\{T_1, T_2\}$, we have

$$H_i^1(t) < \bar{H}_i^1 + \delta_1, V_i^1(t) < \bar{V}_i^1 + \delta_1, 0 < H_i^2(t) < \delta_1, 0 < V_i^1(t) < \delta_1$$

for $i = 1, 2, \cdots, n$. Hence, from the third and fourth equations of system (4.1) we have

$$\begin{cases} \dfrac{dH_i^2(t)}{dt} \ge b_i\alpha_2 V_i^2 \dfrac{\bar{N}_i - (\bar{H}_i^1 + 2\delta_1)}{\bar{N}_i} - (\gamma_i^2 + \nu_i + \displaystyle\sum_{k=1,k\neq i}^n m_{ki})H_i^2 + \sum_{k=1,k\neq i}^n m_{ik}H_k^2, \\ \dfrac{dV_i^2(t)}{dt} \ge b_i\beta_2(\bar{W}_i - (\bar{V}_i^1 + 2\delta_1))\dfrac{H_i^2}{\bar{N}_i} - \mu_i V_i^2, \quad i = 1, 2\cdots, n. \end{cases} \tag{4.3}$$

for sufficiently large t. We consider the following auxiliary system

$$\begin{cases} \dfrac{d\tilde{H}_i^2(t)}{dt} = b_i\alpha_2 \tilde{V}_i^2 \dfrac{\bar{N}_i - (\bar{H}_i^1 + 2\delta_1)}{\bar{N}_i} - (\gamma_i^2 + \nu_i + \displaystyle\sum_{k=1,k\neq i}^n m_{ki})\tilde{H}_i^2 + \sum_{k=1,k\neq i}^n m_{ik}\tilde{H}_k^2, \\ \dfrac{d\tilde{V}_i^2(t)}{dt} = b_i\beta_2(\bar{W}_i - (\bar{V}_i^1 + 2\delta_1))\dfrac{\tilde{H}_i^2}{\bar{N}_i} - \mu_i \tilde{V}_i^2, \quad i = 1, 2\cdots, n. \end{cases} \tag{4.4}$$

The coefficient matrix $\tilde{J}_1^2$ of system (4.4) is given by

$$\tilde{J}_1^2 = \begin{pmatrix} \tilde{Q}_1^{\gamma} & \cdots & m_{1n} & \alpha_c \bar{Q}_1^H & 0 & \cdots & 0 & \\ m_{21} & \tilde{Q}_2^{\gamma} & \cdots & m_{2n} & 0 & \alpha_c \bar{Q}_2^H & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \ddots & \vdots \\ m_{n1} & m_{n2} & \cdots & \tilde{Q}_n^{\gamma} & 0 & 0 & \cdots & \alpha_c \bar{Q}_n^H \\ \beta_c \bar{Q}_1^V & 0 & \cdots & 0 & -\mu_1 & 0 & \cdots & 0 \\ 0 & \beta_c \bar{Q}_2^V & \cdots & 0 & 0 & -\mu_2 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & \beta_c \bar{Q}_n^V & 0 & 0 & \cdots & -\mu_n \end{pmatrix},$$

where

$$\tilde{Q}_i^V = \frac{b_i(\bar{W}_i - \bar{V}_i^1 - 2\delta_1)}{\bar{N}_i}, \quad \tilde{Q}_i^H = \frac{b_i(\bar{N}_i - \bar{H}_i^1 - 2\delta_1)}{\bar{N}_i},$$
$$\tilde{Q}_j^{\gamma} = -\gamma_j^i - \mu_i - \sum_{k=1,k\neq j}^{n} m_{kj}, \quad i = 1, 2, \cdots, n; \quad j = 1, 2, \cdot, n.$$

Similar discussion as for the matrices $\hat{J}^j$ implies that the matrices $\tilde{J}_1^2$ are also unstable and their principal eigenvalue is either positive or has a positive real part $\tilde{\lambda}_m > 0$ when $r_1^2 > 1$. Using the linear systems theory, we can establish that all positive solutions of system (4.4) tend to infinity as $t \to \infty$. Then, applying the standard comparison principle, we have that $\tilde{H}_i^2(t) \to +\infty$ and $\tilde{V}_i^2(t) \to +\infty$ as $t \to +\infty$ for all $i = 1, 2 \cdots, n$. This is a contradiction with the assumption that $H_i^2(t) \to 0$ and $V_i^2(t) \to 0$ as $t \to +\infty$ for all $i = 1, 2 \cdots, n$, which leads a contradiction. The contradiction implies that $\limsup_{t\to+\infty} \max_i \{H_i^2(t), V_i^2(t)\} > \delta_1$. Similarly, since $\mathscr{R}_2^1 > 1$, we can choose δ_2 small enough such that

$$\limsup_{t\to+\infty} \max_i \{H_i^1(t), V_i^1(t)\} > \delta_2.$$

By Theorem 3.2 E_{I^1} is global attractor in $B_1 \setminus \{0\}$ and E_{I^2} is global attractor in $B_2 \setminus \{0\}$ for (4.1). By the afore-mentioned arguments, it then follows that the set $\{E_0, E_{I^1}, E_{I^2}\}$ is isolated invariant set in X, and $W^s(E_0) \cap X^0 = \emptyset$, $W^s(E_{I^1}) \cap X^0 = \emptyset$, $W^s(E_{I^2}) \cap X^0 = \emptyset$. Clearly, the set $\{E_0, E_{I^1}, E_{I^2}\}$ is acyclic in ∂X^0, then Theorem 4.6 in [35] leads to the conclusion that the system (4.1) is uniformly persistent with respect to $(X^0, \partial X^0)$. Using Theorem 1.3.7 in [36], as applied to the solution semiflow of system (4.1), we can infer that the system has a positive equilibrium. This completes the proof of Theorem 4.2. □

Theorem 3.1 implies that if the system (4.1) has no host migration among patches then no more than one strain will persist in the population of patch i except in special and unrealistic circumstances. However, it follows from Theorem 4.2 that the coexistence of two competing strains is possible if the system has host migration among dispersal patches. The coexistence occurs on all n patches. This indicates that the host migration, i.e., the spatial heterogeneity, can lead to the coexistence of multiple competing strains.

5 Global behavior of two strains on two patches

Global results for multi-strain or multi-patch systems are rare, so it is of particular interest to further study the asymptotic behavior of the system (4.1). The high dimension of system (4.1) with general n, however, increases the difficulty in obtaining information on the global behavior of the system. To show the main idea and obtain results on the global behavior, which might be obscured by the complicated computation for the higher dimensional case, in this section we will focus on the case $n = 2$. We shall see that the minimum dimension choice for patchy environment enables us to do some more detailed rigorous analysis.

When $n = 2$, the model (4.1) becomes

$$\begin{cases} \dfrac{dH_i^1(t)}{dt} = b_i\alpha_1 V_i^1 \dfrac{\bar{N}_i - H_i^1 - H_i^2}{\bar{N}_i} - \gamma_i^1 H_i^1 + m_{ik}H_k^1 - m_{ki}H_i^1 - \nu_i H_i^1, \\ \dfrac{dV_i^1(t)}{dt} = b_i\beta_1(\bar{W}_i - V_i^1 - V_i^2)\dfrac{H_i^1}{\bar{N}_i} - \mu_i V_i^1, \\ \dfrac{dH_i^2(t)}{dt} = b_i\alpha_2 V_i^2 \dfrac{\bar{N}_i - H_i^1 - H_i^2}{\bar{N}_i} - \gamma_i^2 H_i^2 + m_{ik}H_k^2 - m_{ki}H_i^2 - \nu_i H_i^2, \\ \dfrac{dV_i^2(t)}{dt} = b_i\beta_2(\bar{W}_i - V_i^1 - V_i^2)\dfrac{H_i^2}{\bar{N}_i} - \mu_i V_i^2, \qquad i,k = 1,2, i \neq k. \end{cases} \tag{5.1}$$

Straight forward computation yields that the basic reproduction number for strain $j, j = 1, 2$ over the whole domain can be expressed as

$$\mathcal{R}_0^j = \frac{\sqrt{2}}{2}\sqrt{(R_1^j)^2(1-\chi^j) + (R_2^j)^2(1-\zeta^j) + [((R_1^j)^2(1-\chi^j) - (R_2^j)^2(1-\zeta^j))^2 + 4(R_1^j)^2(R_2^j)^2\chi^j\zeta^j]^{\frac{1}{2}}}$$

and the invasion reproduction number for strain j on patch i can be expressed as

$$\mathscr{R}_i^j = \frac{\sqrt{2}}{2}\sqrt{(\tilde{\mathfrak{R}}_{1i}^j)^2(1-\chi^j) + (\tilde{\mathfrak{R}}_{2i}^j)^2(1-\zeta^j) + \left(((\tilde{\mathfrak{R}}_{1i}^j)^2(1-\chi^j) - (\tilde{\mathfrak{R}}_{2i}^j)^2(1-\zeta^j))^2 + 4(\tilde{\mathfrak{R}}_{1i}^j)^2(\tilde{\mathfrak{R}}_{2i}^j)^2\chi^j\zeta^j\right)^{\frac{1}{2}}},$$

where

$$\chi^j = \frac{\frac{m_{21}}{\gamma_1^j+\nu_1}}{1 + \frac{m_{21}}{\gamma_1^j+\nu_1} + \frac{m_{12}}{\gamma_2^j+\nu_2}}; \zeta^j = \frac{\frac{m_{12}}{\gamma_2^j+\nu_2}}{1 + \frac{m_{21}}{\gamma_1^j+\nu_1} + \frac{m_{12}}{\gamma_2^j+\nu_2}};$$

$$\tilde{\mathfrak{R}}^j_{ki} = \sqrt{\frac{b_k^2\alpha_j\beta_j(\bar{N}_k - \bar{H}^i_k)(\bar{W}_k - \bar{V}^i_k)}{\mu_k(\gamma^j_k + \nu_k)(\bar{N}_k)^2}}, i, j, k = 1, 2, i \neq j.$$

We recall that reproduction numbers of strain j on patch i, $R^j_i, i, j = 1, 2$, are defined in (3.2). From the proof of Theorem 4.1, we have

$$\mathcal{R}^j_0 < 1(\mathcal{R}^j_0 = 1, \mathcal{R}^j_0 > 1) \Leftrightarrow s(J^j_0) < 0(s(J^j_0) = 0, s(J^j_0) > 0),$$

where

$$J^j_0 = \begin{pmatrix} -(\gamma^j_1 + \nu_1 + m_{21}) & m_{12} & b_1\alpha_j & 0 \\ m_{21} & -(\gamma^j_2 + \nu_2 + m_{12}) & 0 & b_2\alpha_j \\ b_1\beta_j\frac{\bar{W}_1}{\bar{N}_1} & 0 & -\mu_1 & 0 \\ 0 & b_2\beta_j\frac{\bar{W}_2}{\bar{N}_2} & 0 & -\mu_2 \end{pmatrix}$$

and $s(J^j_0)$ is the maximum real part of the eigenvalues of the matrix J^j_0. Since J^j_0 is irreducible and has non-negative off-diagonal elements, it follows form Theorem A.5 in [37] that $s(J^j_0)$ is a simple eigenvalue of J^j_0 with a positive eigenvector. Furthermore, since the diagonal elements of $-J$ are positive and its off-diagonal elements are non-positive, it follows from $M-$matrix theory [38] that

$$s(J^j_0) < 0 \Leftrightarrow \begin{cases} J^j_{01} = -(\gamma^j_1 + \nu_1 + m_{21}) < 0, \\ J^j_{02} = (\gamma^j_1 + \nu_1 + m_{21})(\gamma^j_2 + \nu_2 + m_{12}) - m_{12}m_{21} > 0, \\ J^j_{03} = (\gamma^j_1 + \nu_1)(\gamma^j_2 + \nu_2)\mu_1(1 + \dfrac{m_{21}}{\gamma^j_1 + \nu_1} + \dfrac{m_{12}}{\gamma^j_2 + \nu_2})((R^j_1)^2(1 - \chi^j) - 1) < 0, \\ J^j_{04} = (\gamma^j_1 + \nu_1)(\gamma^j_2 + \nu_2)\mu_1\mu_2(1 + \dfrac{m_{21}}{\gamma^j_1 + \nu_1} + \dfrac{m_{12}}{\gamma^j_2 + \nu_2})\times \\ \qquad (1 - (R^j_1)^2(1 - \chi^j) - (R^j_2)^2(1 - \zeta^j) + (R^j_1)^2(R^j_2)^2(1 - \chi^j - \zeta^j)) > 0, \end{cases}$$

where $J^j_{0k}, k = 1, 2, 3, 4$ are the leading principal minors of J^j_0 with k rows. Consequently, a simple calculation yields that

$$\mathcal{R}^j_0 < 1 \Leftrightarrow \begin{cases} \dfrac{(b_i)^2\alpha_j\beta_j\bar{W}_i}{\mu_i\bar{N}_i(\gamma^j_i + \nu_i + m_{ki})} < 1, \quad i, k = 1, 2, i \neq k, \\ (R^j_1)^2(1 - \chi^j) + (R^j_2)^2(1 - \zeta^j) - (R^j_1)^2(R^j_2)^2(1 - \chi^j - \zeta^j) < 1. \end{cases}$$

Using a similar approach, we have

$$\mathscr{R}^j_i < 1 \Leftrightarrow \begin{cases} \dfrac{(b_i)^2\alpha_j\beta_j(\bar{W}_i - \bar{V}^i_i)(\bar{N}_i - \bar{H}^i_i)}{\mu_i(\bar{N}_i)^2(\gamma^j_i + \nu_i + m_{ki})} < 1, \quad k = 1, 2, k \neq i, \\ (\tilde{\mathfrak{R}}^j_{1i})^2(1 - \chi^j) + (\tilde{\mathfrak{R}}^j_{2i})^2(1 - \zeta^j) - (\tilde{\mathfrak{R}}^j_{1i})^2(\tilde{\mathfrak{R}}^j_{2i})^2(1 - \chi^j - \zeta^j) < 1. \end{cases} \tag{5.2}$$

It follows from Theorem 3.3 that the global behavior of system (5.1) is clear in the case when both reproduction numbers are less than one, or at most one reproduction number is greater than one, that is either $\mathcal{R}_0^1 > 1$ or $\mathcal{R}_0^2 > 1$. Hence, in this section we only need to investigate the global dynamics of the model in the case when $\mathcal{R}_0^1 > 1$ and $\mathcal{R}_0^2 > 1$. When $\mathcal{R}_0^1 > 1$ and $\mathcal{R}_0^2 > 1$, the system (5.1) has three boundary equilibria $E_0, E_{I^1}(\bar{I}^1, 0), E_{I^2}(0, \bar{I}^2)$, where $\bar{I}^1 = (\bar{H}_1^1, \bar{H}_2^1, \bar{V}_1^1, \bar{V}_2^1), \bar{I}^2 = (\bar{H}_1^2, \bar{H}_2^2, \bar{V}_1^2, \bar{V}_2^2)$.

We begin by investigating the local dynamics of system (5.1). Any positive equilibrium must satisfy the following algebraic equations

$$\begin{cases} \Gamma_i^j(H_1^1, H_2^1, V_1^1, V_2^1, H_1^2, H_2^2, V_1^2, V_2^2) & := & b_i\alpha_j V_i^j \dfrac{\bar{N}_i - H_i^1 - H_i^2}{\bar{N}_i} \\ & & -(\gamma_i^j + m_{ki} + \nu_i)H_i^j + m_{ik}H_k^j = 0, \\ \Theta_i^j(H_1^1, H_2^1, V_1^1, V_2^1, H_1^2, H_2^2, V_1^2, V_2^2) & := & b_i\beta_j(\bar{W}_i - V_i^1 - V_i^2)\frac{H_i^j}{\bar{N}_i} - \mu_i V_i^j = 0, \end{cases} \tag{5.3}$$

where $i, j, k = 1, 2, i \neq k$. From the second equation in (5.3), we have

$$\begin{cases} V_i^1 = \dfrac{b_i\beta_1\bar{W}_iH_i^1}{b_i\beta_1H_i^1 + b_i\beta_2H_i^2 + \bar{N}_i\mu_i}, \\ V_i^2 = \dfrac{b_i\beta_2\bar{W}_iH_i^2}{b_i\beta_1H_i^1 + b_i\beta_2H_i^2 + \bar{N}_i\mu_i}. \end{cases} \tag{5.4}$$

Then, by substituting (5.4) into the first equation in (5.3), we have

$$\begin{cases} \mathscr{F}_i(H_1^1, H_1^2, H_2^1, H_2^2) = H_i^1\varphi_i(H_i^1, H_i^2) + m_{ik}H_k^1 = 0, \\ \mathscr{G}_i(H_1^1, H_1^2, H_2^1, H_2^2) = H_i^2\psi_i(H_i^1, H_i^2) + m_{ik}H_k^2 = 0, \quad i, k = 1, 2, i \neq k, \end{cases} \tag{5.5}$$

where

$$\varphi_i(H_i^1, H_i^2) = \frac{(b_i)^2\alpha_1\beta_1\bar{W}_i(\bar{N}_i - H_i^1 - H_i^2)}{(b_i\beta_1H_i^1 + b_i\beta_2H_i^2 + \bar{N}_i\mu_i)\bar{N}_i} - (\gamma_i^1 + \nu_i + m_{ki});$$
$$\psi_i(H_i^1, H_i^2) = \frac{(b_i)^2\alpha_2\beta_2\bar{W}_i(\bar{N}_i - H_i^1 - H_i^2)}{(b_i\beta_1H_i^1 + b_i\beta_2H_i^2 + \bar{N}_i\mu_i)\bar{N}_i} - (\gamma_i^2 + \nu_i + m_{ki}), \quad i, k = 1, 2, i \neq k.$$

From (5.5) it follows that

$$\begin{aligned} H_1^1 &= -\frac{1}{m_{21}}H_2^1\varphi_2(H_2^1, H_2^2), \\ H_1^2 &= -\frac{1}{m_{21}}H_2^2\psi_2(H_2^1, H_2^2). \end{aligned} \tag{5.6}$$

Substituting (5.6) into (5.5) yields:

$$\begin{cases} F(H_2^1, H_2^2) := \varphi_2(H_2^1, H_2^2)\varphi_1\Big(-\dfrac{1}{m_{21}}H_2^1\varphi_2(H_2^1, H_2^2), \\ \qquad\qquad -\dfrac{1}{m_{21}}H_2^2\psi_2(H_2^1, H_2^2)\Big) - m_{12}m_{21} = 0, \\ G(H_2^1, H_2^2) := \psi_2(H_2^1, H_2^2)\psi_1\Big(-\dfrac{1}{m_{21}}H_2^1\varphi_2(H_2^1, H_2^2), \\ \qquad\qquad -\dfrac{1}{m_{21}}H_2^2\psi_2(H_2^1, H_2^2)\Big) - m_{12}m_{21} = 0. \end{cases} \tag{5.7}$$

Clearly, $F(\bar{H}_2^1, 0) = 0, G(0, \bar{H}_2^2) = 0$. Equations (5.7) give a 2×2 system which only depends on H_2^1, H_2^2. From (5.4) and (5.6) we can easily see that the system (5.1) has a positive equilibrium $E^{\#}(H_1^{1\#}, H_2^{1\#}, V_1^{1\#}, V_2^{1\#}, H_1^{2\#}, H_2^{2\#}, V_1^{2\#}, V_2^{2\#})$ if and only if (5.7) has a positive solution $(H_2^{1\#}, H_2^{2\#})$ satisfying $\varphi_2(H_2^{1\#}, H_2^{2\#}) < 0, \psi_2(H_2^{1\#}, H_2^{2\#}) < 0$, i.e.,

$$\Big[\frac{(\gamma_2^1 + \nu_2 + m_{12})\bar{N}_2}{b_2\alpha_1\bar{W}_2} + 1\Big] H_2^{1\#} + \Big[\frac{(\gamma_2^1 + \nu_2 + m_{12})\bar{N}_2\beta_2}{b_2\alpha_1\beta_1\bar{W}_2} + 1\Big] H_2^{2\#} > \bar{N}_2\Big[1 - \frac{(\gamma_2^1 + \nu_2 + m_{12})\mu_2\bar{N}_2}{(b_2)^2\alpha_1\beta_1\bar{W}_2}\Big],$$

$$\Big[\frac{(\gamma_2^1 + \nu_2 + m_{12})\beta_1\bar{N}_2}{b_2\alpha_2\beta_2\bar{W}_2} + 1\Big] H_2^{1\#} + \Big[\frac{(\gamma_2^1 + \nu_2 + m_{12})\bar{N}_2}{b_2\alpha_2\bar{W}_2} + 1\Big] H_2^{2\#} > \bar{N}_2\Big[1 - \frac{(\gamma_2^1 + \nu_2 + m_{12})\mu_2\bar{N}_2}{(b_2)^2\alpha_2\beta_2\bar{W}_2}\Big].$$

After extensive algebraic calculations, we can verify that

$$\frac{\partial F}{\partial H_2^1}\Big|_{(H_2^{1\#}, H_2^{2\#})} > 0, \quad \frac{\partial F}{\partial H_2^2}\Big|_{(H_2^{1\#}, H_2^{2\#})} > 0; \quad \frac{\partial G}{\partial H_2^1}\Big|_{(H_2^{1\#}, H_2^{2\#})} > 0, \quad \frac{\partial G}{\partial H_2^2}\Big|_{(H_2^{1\#}, H_2^{2\#})} > 0.$$

To obtain results on the local stability of the endemic equilibrium, we assume the following non-degeneracy assumption (H)

(H) $\frac{F_{H_2^2}(H_2^{1\#}, H_2^{2\#})}{F_{H_2^1}(H_2^{1\#}, H_2^{2\#})} \cdot \frac{G_{H_2^1}(H_2^{1\#}, H_2^{2\#})}{G_{H_2^2}(H_2^{1\#}, H_2^{2\#})} \neq 1.$

Then we have the following result.

Theorem 5.1. *Let $E^{\#}(H_1^{1\#}, H_2^{1\#}, V_1^{1\#}, V_2^{1\#}, H_1^{2\#}, H_2^{2\#}, V_1^{2\#}, V_2^{2\#})$ be a positive equilibrium of system* (5.1) *and let (H) hold. Equilibrium $E^{\#}$ is locally stable if $\frac{F_{H_2^2}(H_2^{1\#}, H_2^{2\#})}{F_{H_2^1}(H_2^{1\#}, H_2^{2\#})} \cdot \frac{G_{H_2^1}(H_2^{1\#}, H_2^{2\#})}{G_{H_2^2}(H_2^{1\#}, H_2^{2\#})} < 1$, and it is unstable if $\frac{F_{H_2^2}(H_2^{1\#}, H_2^{2\#})}{F_{H_2^1}(H_2^{1\#}, H_2^{2\#})} \cdot \frac{G_{H_2^1}(H_2^{1\#}, H_2^{2\#})}{G_{H_2^2}(H_2^{1\#}, H_2^{2\#})} > 1$.*

Proof. The Jacobian matrix $J(E^{\#})$ at $E^{\#}$ takes the form

$$J(E^{\#}) = \begin{pmatrix} A_{11} & A_{12} \\ A_{21} & A_{22} \end{pmatrix},$$

where

$$A_{11} = \begin{pmatrix} -(b_1\alpha_1\frac{V_1^{1\#}}{\bar{N}_1} + \gamma_1^1 + \nu_1 + m_{21}) & m_{12} & b_1\alpha_1\frac{\bar{N}_1 - H_1^{1\#} - H_1^{2\#}}{\bar{N}_1} & 0 \\ m_{21} & -(b_2\alpha_1\frac{V_2^{1\#}}{\bar{N}_2} + \gamma_2^1 + m_{12} + \nu_2) & 0 & b_2\alpha_1\frac{\bar{N}_2 - H_2^{1\#} - H_2^{2\#}}{\bar{N}_2} \\ b_1\beta_1\frac{\bar{W}_1 - V_1^{1\#} - V_1^{2\#}}{\bar{N}_1} & 0 & -(\mu_1 + b_1\beta_1\frac{H_1^{1\#}}{\bar{N}_1}) & 0 \\ 0 & b_2\beta_1\frac{\bar{W}_2 - V_2^{1\#} - V_2^{2\#}}{\bar{N}_2} & 0 & -(\mu_2 + b_2\beta_1\frac{H_2^{1\#}}{\bar{N}_2}) \end{pmatrix};$$

$$A_{12} = \begin{pmatrix} -b_1\alpha_1\frac{V_1^{1\#}}{\bar{N}_1} & 0 & 0 & 0 \\ 0 & -b_2\alpha_1\frac{V_2^{1\#}}{\bar{N}_2} & 0 & 0 \\ 0 & 0 & -b_1\beta_1\frac{H_1^{1\#}}{\bar{N}_1} & 0 \\ 0 & 0 & 0 & -b_2\beta_1\frac{H_2^{1\#}}{\bar{N}_2} \end{pmatrix};$$

$$A_{21} = \begin{pmatrix} -b_1\alpha_2\frac{V_1^{2\#}}{\bar{N}_1} & 0 & 0 & 0 \\ 0 & -b_2\alpha_2\frac{V_2^{2\#}}{\bar{N}_2} & 0 & 0 \\ 0 & 0 & -b_1\beta_2\frac{H_1^{2\#}}{\bar{N}_1} & 0 \\ 0 & 0 & 0 & -b_2\beta_2\frac{H_2^{2\#}}{\bar{N}_2} \end{pmatrix};$$

$$A_{22} = \begin{pmatrix} \begin{matrix} -(b_1\alpha_2\frac{V_1^{2\#}}{\bar{N}_1}+\gamma_1^2 \\ +\nu_1+m_{21}) \end{matrix} & m_{12} & b_1\alpha_2\frac{\bar{N}_1-H_1^{1\#}-H_1^{2\#}}{\bar{N}_1} & 0 \\ m_{21} & \begin{matrix} -(b_2\alpha_2\frac{V_2^{2\#}}{\bar{N}_2}+\gamma_2^2 \\ +m_{12}+\nu_2) \end{matrix} & 0 & b_2\alpha_2\frac{\bar{N}_2-H_2^{1\#}-H_2^{2\#}}{\bar{N}_2} \\ b_1\beta_2\frac{\bar{W}_1-V_1^{1\#}-V_1^{2\#}}{\bar{N}_1} & 0 & -(\mu_1+b_1\beta_2\frac{H_1^{2\#}}{\bar{N}_1}) & 0 \\ 0 & b_2\beta_2\frac{\bar{W}_2-V_2^{1\#}-V_2^{2\#}}{\bar{N}_2} & 0 & -(\mu_2+b_2\beta_2\frac{H_2^{2\#}}{\bar{N}_2}) \end{pmatrix}.$$

Let

$$T = \begin{pmatrix} 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 \\ 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 \\ 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -1 & 0 & 0 \\ 0 & 0 & 0 & 0 & -1 & 0 & 0 & 0 \end{pmatrix},$$

and consider the matrix

$$\tilde{J} = T\begin{pmatrix} A_{11} & A_{12} \\ A_{21} & A_{22} \end{pmatrix}T^{-1}.$$

It is easy to see that if all eigenvalues of $\tilde{J}$ have negative real parts then so do those of $J(E^{\#})$. Note that all off-diagonal elements of $\tilde{J}$ are non-negative. Let $W_i, i = 1, 2\cdots, 8$ be the leading principal minors of

$\tilde{J}$ with i rows. Then straight forward algebraic calculations give

$$\begin{aligned}
(-1)^1 W_1 &= \gamma_2^1 + \nu_2 + m_{12} + b_2\alpha_1 \frac{V_2^{1\#}}{\bar{N}_2} > 0;\\
(-1)^2 W_2 &= (b_2\alpha_1 \frac{V_2^{1\#}}{\bar{N}_2} + \gamma_2^1 + \nu_2 + m_{12})(\mu_1 + b_1\beta_1 \frac{H_1^{1\#}}{\bar{N}_1}) > 0;\\
(-1)^3 W_3 &= (\mu_1 + b_1\beta_1 \frac{H_1^{1\#}}{\bar{N}_1})(\mu_2 b_2\alpha_1 \frac{V_2^{1\#}}{\bar{N}_2} + b_2\beta_1 \frac{H_2^{1\#}}{\bar{N}_2} \times \\
&\qquad (b_2\alpha_1 \frac{V_2^{1\#}}{\bar{N}_2} + \gamma_2^1 + m_{12} + \nu_2) - \mu_2\varphi_2(H_2^{1\#}, H_2^{2\#}))\\
&> 0;\\
(-1)^4 W_4 &= (\mu_2 + b_2\beta_2 \frac{H_2^{2\#}}{\bar{N}_2})(\mu_1 + b_1\beta_1 \frac{H_1^{1\#}}{\bar{N}_1})(\mu_2 b_2\alpha_1 \frac{V_2^{1\#}}{\bar{N}_2} + b_2\beta_1 \frac{H_2^{1\#}}{\bar{N}_2} \times \\
&\qquad \frac{\mu_2}{\mu_2 + b_2\beta_2 \frac{H_2^{2\#}}{\bar{N}_2}}(b_2\alpha_1 \frac{V_2^{1\#}}{\bar{N}_2} + \gamma_2^1 + m_{12} + \nu_2) - \mu_2\varphi_2(H_2^{1\#}, H_2^{2\#}))\\
&> 0;\\
(-1)^5 W_5 &= (\mu_2 + b_2\beta_2 \frac{H_2^{2\#}}{\bar{N}_2})(\mu_1 + \frac{\mu_1}{\mu_1 + b_1\beta_2 \frac{H_1^{2\#}}{\bar{N}_1}} b_1\beta_1 \frac{H_1^{1\#}}{\bar{N}_1})(\mu_2 b_2\alpha_1 \frac{V_2^{1\#}}{\bar{N}_2} + \\
&\quad b_2\beta_1 \frac{H_2^{1\#}}{\bar{N}_2} \frac{\mu_2}{\mu_2 + b_2\beta_2 \frac{H_2^{2\#}}{\bar{N}_2}}(b_2\alpha_1 \frac{V_2^{1\#}}{\bar{N}_2} + \gamma_2^1 + m_{12} + \nu_2) - \mu_2\varphi_2(H_2^{1\#}, H_2^{2\#}))\\
&> 0.
\end{aligned}$$

Furthermore, we apply tricky calculations to conclude that $(-1)^6 W_6 > 0$ and $(-1)^7 W_7 > 0$. The proofs for $(-1)^6 W_6 > 0$ and $(-1)^7 W_7 > 0$ are given in Appendices B and C, respectively. Since $(-1)^i W_i > 0, i = 1, 2, \cdots, 7$, it follows from the well-known M-matrix theory that the stability of the matrix $\tilde{J}$ is determined by the sign of the determinant of $\tilde{J}$. In particular, if $\det(\tilde{J}) > 0$ then the matrix $\tilde{J}$ is stable, and if $\det(\tilde{J}) < 0$ then the matrix $\tilde{J}$ is unstable. In what follows we prove that $\det(J(E^{\#})) = \det(\tilde{J}) > 0$ if and only if

$$\frac{F_{H_2^2}(H_2^{1\#}, H_2^{2\#})}{F_{H_2^1}(H_2^{1\#}, H_2^{2\#})} \cdot \frac{G_{H_2^1}(H_2^{1\#}, H_2^{2\#})}{G_{H_2^2}(H_2^{1\#}, H_2^{2\#})} < 1.$$

Moreover, we prove that $\det(J(E^{\#})) = \det(\tilde{J}) < 0$ if and only if

$$\frac{F_{H_2^2}(H_2^{1\#}, H_2^{2\#})}{F_{H_2^1}(H_2^{1\#}, H_2^{2\#})} \cdot \frac{G_{H_2^1}(H_2^{1\#}, H_2^{2\#})}{G_{H_2^2}(H_2^{1\#}, H_2^{2\#})} > 1.$$

We begin by observing that from the equations (5.3), we have

$$\begin{cases}
\Gamma_i^1(H_1^1, H_2^1, V_1^1, V_2^1, H_1^2, H_2^2, V_1^2, V_2^2) = 0,\\
\Theta_i^j(H_1^1, H_2^1, V_1^1, V_2^1, H_1^2, H_2^2, V_1^2, V_2^2) = 0,\\
\Gamma_i^2(H_1^1, H_2^1, V_1^1, V_2^1, H_1^2, H_2^2, V_1^2, V_2^2) = 0, \quad i, j = 1, 2.
\end{cases}$$

Furthermore, we verify that

$$\det\left(\frac{\partial(\Gamma_2^1, \Theta_1^1, \Theta_2^1, -\Theta_2^2, -\Theta_1^2, \Gamma_1^1, -\Gamma_2^2)}{\partial(H_2^1, V_1^1, V_2^1, -V_2^2, -V_1^2, H_1^1, -H_2^2)}\Big|_{(H_2^{1\#}, V_1^{1\#}, V_2^{1\#}, V_1^{2\#}, V_2^{2\#}, H_1^{1\#}, H_2^{2\#})}\right) = W_7 < 0.$$

The implicit function theorem then implies that there exist continuously differentiable functions $H_i^1(H_1^2)$, $V_i^j(H_1^2), H_2^2(H_1^2), i, j = 1, 2$ defined on a neighborhood Δ of $H_1^{2\#}$ such that

(1) $H_i^1(H_1^{2\#}) = H_i^{1\#}, V_i^j(H_1^{2\#}) = V_i^{j\#}, H_2^2(H_1^{2\#}) = H_2^{2\#}, i, j = 1, 2;$

(2) For $H_1^2 \in \Delta$, the functions $H_i^1(H_1^2), V_i^j(H_1^2), H_2^2(H_1^2), i, j = 1, 2$ satisfy the equations

$$\begin{cases} \Gamma_2^1(H_1^1, H_2^1(H_1^1, H_1^2, H_2^2), V_1^1(H_1^1, H_1^2, H_2^2), V_2^1(H_1^1, H_1^2, H_2^2), \\ \qquad\qquad H_1^2, H_2^2, V_1^2(H_1^1, H_1^2, H_2^2), V_2^2(H_1^1, H_1^2, H_2^2)) \equiv 0, \\ \Theta_i^j(H_1^1, H_2^1(H_1^1, H_1^2, H_2^2), V_1^1(H_1^1, H_1^2, H_2^2), V_2^1(H_1^1, H_1^2, H_2^2), \\ \qquad\qquad H_1^2, H_2^2, V_1^2(H_1^1, H_1^2, H_2^2), V_2^2(H_1^1, H_1^2, H_2^2)) \equiv 0, \quad i, j = 1, 2; \end{cases}$$

(3) For $H_1^2 \in \Delta$, we have

$$\begin{aligned} \frac{\partial V_1^2(H_1^2)}{\partial H_1^2} &= -\frac{\det\left(\frac{\partial(\Gamma_2^1, \Theta_1^1, \Theta_2^1, -\Theta_2^2, -\Theta_1^2, \Gamma_1^1, -\Gamma_2^2)}{\partial(H_2^1, V_1^1, V_2^1, -V_2^2, -H_1^2, H_1^1, -H_2^2)}\right)}{\det\left(\frac{\partial(\Gamma_2^1, \Theta_1^1, \Theta_2^1, -\Theta_2^2, -\Theta_1^2, \Gamma_1^1, -\Gamma_2^2)}{\partial(H_2^1, V_1^1, V_2^1, -V_2^2, -V_1^2, H_1^1, -H_2^2)}\right)} \\ &= -\frac{D_{85}}{W_7}, \\ -\frac{\partial H_1^1(H_1^2)}{\partial H_1^2} &= -\frac{\det\left(\frac{\partial(\Gamma_2^1, \Theta_1^1, \Theta_2^1, -\Theta_2^2, -\Theta_1^2, \Gamma_1^1, -\Gamma_2^2)}{\partial(H_2^1, V_1^1, V_2^1, -V_2^2, -V_1^2, -H_1^2, -H_2^2)}\right)}{\det\left(\frac{\partial(\Gamma_2^1, \Theta_1^1, \Theta_2^1, -\Theta_2^2, -\Theta_1^2, \Gamma_1^1, -\Gamma_2^2)}{\partial(H_2^1, V_1^1, V_2^1, -V_2^2, -V_1^2, H_1^1, -H_2^2)}\right)} \\ &= \frac{D_{86}}{W_7}, \\ \frac{\partial H_2^2(H_1^2)}{\partial H_1^2} &= -\frac{\det\left(\frac{\partial(\Gamma_2^1, \Theta_1^1, \Theta_2^1, -\Theta_2^2, -\Theta_1^2, \Gamma_1^1, -\Gamma_2^2)}{\partial(H_2^1, V_1^1, V_2^1, -V_2^2, -V_1^2, H_1^1, -H_1^2)}\right)}{\det\left(\frac{\partial(\Gamma_2^1, \Theta_1^1, \Theta_2^1, -\Theta_2^2, -\Theta_1^2, \Gamma_1^1, -\Gamma_2^2)}{\partial(H_2^1, V_1^1, V_2^1, -V_2^2, -V_1^2, H_1^1, -H_2^2)}\right)} \\ &= -\frac{D_{87}}{W_7}, \end{aligned}$$

where D_{ij} is the complement minor of order 7 obtained by removing the i-th row and j-th column from the matrix $\tilde{J}$.

On the one hand, substituting the functions $H_i^1(H_1^2), V_i^j(H_1^2), H_2^2(H_1^2), i, j = 1, 2$ for the expression $\Gamma_1^2(H_1^1, H_2^1, V_1^1, V_2^1, H_1^2, H_2^2, V_1^2, V_2^2)$ yields:

$$\Upsilon(H_1^2) := \Gamma_1^1(H_1^1(H_1^2), H_2^1(H_1^2), V_1^1(H_1^2), V_2^1(H_1^2), H_1^2, H_2^2(H_1^2), V_1^2(H_1^2), V_2^2(H_1^2)).$$

By differentiating the function $\Upsilon(H_1^2)$ with respect to H_1^2, we have

$$\begin{aligned}&\frac{\partial\Upsilon(H_1^2)}{\partial H_1^2}|_{H_1^2=H_1^{2\#}}\\&=[b_1\alpha_2\frac{\bar{N}_1-H_1^1-H_1^2}{\bar{N}_1}\frac{\partial V_1^2}{\partial H_1^2}-b_1\alpha_2\frac{V_1^2}{\bar{N}_1}\frac{\partial H_1^1}{\partial H_2^1}+m_{12}\frac{\partial H_2^2}{\partial H_1^2}-(b_1\alpha_2\frac{V_1^2}{\bar{N}_1}+\gamma_1^2+m_{21}+\nu_1)]|_{H_1^2=H_1^{2\#}}\\&=\frac{\det(\tilde{J})}{W_7}.\end{aligned} \tag{5.8}$$

On the other hand, in Appendix C we have obtained continuously differentiable functions $\tilde{H}_1^1(H_1^2,H_2^2)$, $\tilde{H}_2^1(H_1^2,H_2^2)$ from the first equation (5.5). These functions are defined on a neighborhood Δ' of $(H_1^{2\#},H_2^{2\#})$ and satisfy:

$$\tilde{H}_1^1(H_1^{2\#},H_2^{2\#})=H_1^{1\#},\tilde{H}_2^1(H_1^{2\#},H_2^{2\#})=H_2^{1\#}.$$

By substituting $H_2^1=\tilde{H}_2^1(H_1^2,H_2^2)$ into the second equation in (5.5), we obtain

$$\Upsilon'(H_1^2,H_2^2)=H_2^2\psi_2(\tilde{H}_2^1(H_1^2,H_2^2),H_2^2)+m_{21}H_1^2=0.$$

From Appendix C we can see that

$$\frac{\partial\Upsilon'(H_1^2,H_2^2)}{\partial H_2^2}|_{(H_1^{2\#},H_2^{2\#})}<0.$$

The implicit function theorem then implies that there exists a continuously differentiable function $\tilde{H}_2^2(H_1^2)$ defined on a neighborhood $\tilde{\Delta}$ of $H_1^{2\#}$ such that

$$\tilde{H}_2^2(H_1^{2\#})=H_2^{2\#},$$

and

$$\Upsilon'(H_1^2,H_2^2(H_1^2))\equiv 0$$

for all $H_1^2\in\tilde{\Delta}$. Moreover, from Appendix C we have

$$\frac{\partial\tilde{H}_2^2}{\partial H_1^2}|_{H_1^2=H_1^{2\#}}=-\frac{\Upsilon'_{H_1^2}(H_1^{2\#},H_2^{2\#})}{\Upsilon'_{H_2^2}(H_1^{2\#},H_2^{2\#})}>0.$$

Since $F_{H_2^1}(H_2^{1\#},H_2^{2\#})>0$ then by the implicit function theorem there exists a continuously differentiable function $\tilde{H}_2^1(H_2^2)$ defined on a neighborhood Δ' of $H_2^{2\#}$ such that $\tilde{H}_2^1(H_2^{2\#})=H_2^{1\#}$ and $F(\tilde{H}_2^1(H_2^2),H_2^2)\equiv 0$ for $H_2^2\in\Delta'$. Moreover, we have

$$\frac{\partial\tilde{H}_2^1}{\partial H_2^2}|_{H_2^2=H_2^{2\#}}=-\frac{F_{H_2^2}(H_2^{1\#},H_2^{2\#})}{F_{H_2^1}(H_2^{1\#},H_2^{2\#})}<0.$$

By substituting (5.6) and $H_2^1 = \tilde{H}_2^1(H_2^2), H_2^2 = \tilde{H}_2^2(H_1^2)$ into the second equation in (5.5), we obtain

$$\Upsilon(H_1^2) = -\frac{1}{m_{21}}\tilde{H}_2^2(H_1^2))G(\tilde{H}_2^1(\tilde{H}_2^2(H_1^2)), \tilde{H}_2^2(H_1^2)).$$

Differentiating the function $\Upsilon(H_1^2)$ with respect to H_1^2, we have

$$\begin{aligned}&\frac{\partial \Upsilon(H_1^2)}{\partial H_1^2}|_{H_1^2=H_1^{2\#}} \\ &= -\frac{1}{m_{21}}H_2^{2\#}\frac{\partial \tilde{H}_2^2}{\partial H_1^2}|_{H_1^2=H_1^{2\#}}G_{H_2^2}(H_1^{2\#}, H_2^{2\#})\left[1 - \frac{G_{H_2^1}(H_1^{2\#}, H_2^{2\#})}{G_{H_2^2(H_1^{2\#}, H_2^{2\#})}} \cdot \frac{F_{H_2^2}(H_1^{2\#}, H_2^{2\#})}{F_{H_1^2}(H_1^{2\#}, H_2^{2\#})}\right].\end{aligned} \tag{5.9}$$

Hence, we see that

$$\frac{\partial \Upsilon(H_1^2)}{\partial H_1^2}|_{H_1^2=H_1^{2\#}} > 0 \tag{5.10}$$

if and only if

$$\frac{F_{H_2^2}(H_2^{1\#}, H_2^{2\#})}{F_{H_2^1}(H_2^{1\#}, H_2^{2\#})} \cdot \frac{G_{H_2^1}(H_2^{1\#}, H_2^{2\#})}{G_{H_2^2}(H_2^{1\#}, H_2^{2\#})} > 1.$$

Moreover,

$$\frac{\partial \Upsilon(H_1^2)}{\partial H_1^2}|_{H_1^2=H_1^{2\#}} < 0 \tag{5.11}$$

if and only if

$$\frac{F_{H_2^2}(H_2^{1\#}, H_2^{2\#})}{F_{H_2^1}(H_2^{1\#}, H_2^{2\#})} \cdot \frac{G_{H_2^1}(H_2^{1\#}, H_2^{2\#})}{G_{H_2^2}(H_2^{1\#}, H_2^{2\#})} < 1.$$

From equations (5.8), (5.10) and (5.11) we can easily see that $\det(J(E^{\#})) = \det(\tilde{J}) > 0$ if and only if

$$\frac{F_{H_2^2}(H_2^{1\#}, H_2^{2\#})}{F_{H_2^1}(H_2^{1\#}, H_2^{2\#})} \cdot \frac{G_{H_2^1}(H_2^{1\#}, H_2^{2\#})}{G_{H_2^2}(H_2^{1\#}, H_2^{2\#})} < 1,$$

and $\det(J(E^{\#})) = \det(\tilde{J}) < 0$ if and only if

$$\frac{F_{H_2^2}(H_2^{1\#}, H_2^{2\#})}{F_{H_2^1}(H_2^{1\#}, H_2^{2\#})} \cdot \frac{G_{H_2^1}(H_2^{1\#}, H_2^{2\#})}{G_{H_2^2}(H_2^{1\#}, H_2^{2\#})} > 1.$$

This completes the proof of Theorem 5.1. □

We now proceed to investigate the global stability of the system (5.1). Let

$$\begin{aligned}\Lambda = \{(H_2^1, H_2^2) \in \mathbb{R}_+^2 : \varphi_2(H_2^1, H_2^2) < 0, \psi_2(H_2^1, H_2^2) < 0,\\ H_2^1 + H_2^2 \le \bar{N}_2, -H_2^1\varphi_2(H_2^1, H_2^2) - H_2^2\psi_2(H_2^1, H_2^2) \le m_{21}\bar{N}_1\}\end{aligned}$$

and

$$\Omega = \{((I^1, I^2) \in \mathbb{R}_+^8 : I^j \triangleq (H_1^j, H_2^j, V_1^j, V_2^j), H_i^1 + H_i^2 \le \bar{N}_i, V_i^1 + V_i^2 \le \bar{W}_i, i = 1, 2\}.$$

The Jacobian matrix of system (5.1) at each point $(I^1, I^2) \in \Omega$ has the form

$$\begin{pmatrix} A_1(I^1,I^2) & -A_2(I^1,I^2) \\ -A_3(I^1,I^2) & A_4(I^1,I^2) \end{pmatrix},$$

where $A_i(I^1, I^2), i = 1, 2, 3, 4$ are all 4×4 matrices One can verify that all off-diagonal entries of $A_1(I^1, I^2)$ and $A_4(I^1, I^2)$ are non-negative, and $A_2(I^1, I^2)$ and $A_3(I^1, I^2)$ are non-negative matrices. It follows from Smith [39] that the flow $\Phi_t(I^1, I^2)$ generated by (5.1) is type-K monotone in the sense that

$$\Phi_t(\tilde{I}^1, \tilde{I}^2) \geq_K \Phi_t(\hat{I}^1, \hat{I}^2) \text{ whenever } (\tilde{I}^1, \tilde{I}^2) \geq_K (\hat{I}^1, \hat{I}^2) \text{ and } t > 0.$$

Theorem 4.1.2 in [39] implies that almost all solutions of system (5.1) are convergent to the equilibria, and thus the global dynamics of the system (5.1) is completely determined by the equations (5.7). Since the algebraic equations (5.7) are difficult to solve explicitly, in what follows we only consider a special case to show the global stability. We further assume the following hypothesis:

(H') $\{(H_2^1, H_2^2) : F(H_2^1, H_2^2) = 0, H_2^1 \geq 0, H_2^2 \geq 0\} \subset \Lambda$ and $\{(H_2^1, H_2^2) : G(H_2^1, H_2^2) = 0, H_2^1 \geq 0, H_2^2 \geq 0\} \subset \Lambda$.

Straight forward, but tedious algebraic calculations yield that

$$F_{H_2^1}(H_2^1, H_2^2) > 0, F_{H_2^2}(H_2^1, H_2^2) > 0, G_{H_2^1}(H_2^1, H_2^2) > 0, G_{H_2^2}(H_2^1, H_2^2) > 0.$$

Using the implicit function theorem, from the equations (5.7) we can infer that there exist positive, continuously differentiable functions $H_2^2 = f(H_2^1), H_2^1, = g(H_2^2)$ defined on the intervals $[0, \bar{H}_2^1]$ and $[0, \bar{H}_2^2]$, respectively, such that

(1) $f(\bar{H}_2^1) = 0, g(\bar{H}_2^2) = 0$;

(2) For $H_2^1 \in [0, \bar{H}_2^1]$ and $H_2^2 \in [0, \bar{H}_2^2]$, $H_2^2 = f(H_2^1)$ and $H_2^1 = g(H_2^2)$ satisfy $F(H_2^1, f(H_2^1)) \equiv 0$ and $G(g(H_2^2), H_2^2) \equiv 0$;

(3) $\frac{df(H_2^1)}{dH_2^1} = -\frac{F_{H_2^1}(H_2^1, I_2^2)}{F_{H_2^2}(H_2^1, H_2^1)} < 0, \frac{dg(H_2^2)}{dH_2^2} = -\frac{G_{H_2^2}(H_2^1, H_2^2)}{G_{H_2^1}(H_2^1, H_2^2)} < 0.$

The last property above says that $H_2^2 = f(H_2^1), H_2^1 = g(H_2^2)$ are both monotonically decreasing functions on the intervals $[0, \bar{H}_2^1]$ and $[0, \bar{H}_2^2]$ respectively.

Let $\mathscr{H}(H_2^1) = g(f(H_2^1)), H_2^1 \in [\chi, \bar{H}_2^1]$, where

$$\chi = \begin{cases} f^{-1}(\bar{H}_2^2) & if \;\; f(0) > \bar{H}_2^2; \\ 0 & if \;\; f(0) \leq \bar{I}_2^m. \end{cases}$$

In view of the properties of f and g, $\mathscr{H}(H_2^1)$ satisfies $\mathscr{H}'(H_2^1) > 0$ for $H_2^1 \in [\chi, \bar{H}_2^1]$. Suppose the equation $\mathscr{H}(H_2^1) = H_2^1$ has l positive roots in the interval $(\chi, \bar{H}_2^1)$, which we label as $H_{21}^1 < H_{22}^1 < \cdots < H_{2l}^1$. Since each root gives a positive equilibrium of system (5.1), then system (5.1) has l positive equilibria. The corresponding positive equilibria $E_j^*(I_j^{1*}, I_j^{2*}), j = 1, 2, \cdots, l$ of (5.1) are given by

$$(I_j^{1*}, I_j^{2*}) = (H_{1j}^{1*}, H_{2j}^{1*}, V_{1j}^{1*}, V_{2j}^{1*}, H_{1j}^{2*}, H_{2j}^{2*}, V_{1j}^{2*}, V_{2j}^{2*}), j = 1, \cdots, l, \tag{5.12}$$

where

$$H_{2j}^{2*} = f(H_{1j}^{2*}), H_{1j}^{1*} = -\frac{1}{m_{21}} H_{2j}^{1*} \varphi_2(H_{2j}^{1*}, H_{2j}^{2*}), H_{1j}^{2*} = -\frac{1}{m_{21}} H_{2j}^{2*} \psi_2(H_{2j}^{1*}, H_{2j}^{2*}),$$
$$V_{1j}^{1*} = \frac{b_1 \beta_1 \bar{W}_1 H_{1j}^{1*}}{b_1 \beta_1 H_{1j}^{1*} + b_1 \beta_2 H_{1j}^{2*} + \bar{N}_1 \mu_1}, V_{2j}^{1*} = \frac{b_2 \beta_1 \bar{W}_2 H_{2j}^{1*}}{b_2 \beta_1 H_{2j}^{1*} + b_2 \beta_2 H_{2j}^{2*} + \bar{N}_2 \mu_2},$$
$$V_{1j}^{2*} = \frac{b_1 \beta_2 \bar{W}_1 H_{1j}^{2*}}{b_1 \beta_2 H_{1j}^{1*} + b_1 \beta_2 H_{1j}^{2*} + \bar{N}_1 \mu_1}, V_{2j}^{2*} = \frac{b_2 \beta_2 \bar{W}_2 H_{2j}^{2*}}{b_2 \beta_1 H_{2j}^{1*} + b_2 \beta_2 H_{2j}^{2*} + \bar{N}_2 \mu_2},$$

respectively. Moreover, we have

$$(0, \bar{I}^2) \leq_K (I_1^{1*}, I_1^{2*}) \leq_K \cdots \leq_K (I_l^{1*}, I_l^{2*}) \leq_K (\bar{I}^1, 0).$$

For convenience, let $B(E_{I^1}), B(E_{I^2}), B(E_j^*), j = 1, 2 \cdots, l$, denote the basin of attraction of E_{I^1}, E_{I^2}, E_j^* in $\mathbb{R}_+^8$, and $Cl\ U$ denote the closure of U. Note that the flow $\varphi_t(I^1, I^2)$ generated by the system (4.1) is type-K strongly monotone. The following Theorem summarizes the results on existence and stability of the positive equilibria.

Theorem 5.2. *Let $\mathcal{R}_0^1 > 1$, $\mathcal{R}_0^2 > 1$. Let (H) and (H') hold.*

1) If $\mathscr{R}_1^2 > 1, \mathscr{R}_2^1 > 1$, then system (5.1) has an odd number l of positive equilibria given by (5.12). The odd indexed positive equilibria $E_j^*, j = 1, 3, \cdots, l$ are asymptotically stable and $Cl \cup_{j\ odd} B(E_j^*) = \mathbb{R}_+^8$. The boundary equilibria E_{I^1}, E_{I^2} and the even indexed positive equilibria $E_j^*, j = 2, 4, \cdots, l-1$ are unstable. Moreover, if $l = 1$ then E_1^* is globally asymptotically stable in $\mathbb{R}_+^8 \setminus (\Gamma^1 \cup \Gamma^2)$.

2) If $\mathscr{R}_1^2 < 1, \mathscr{R}_2^1 < 1$, then system (5.1) has an odd number l of positive equilibria given by (5.12). The boundary equilibria E_{I^1}, E_{I^2} and the even indexed positive equilibria $E_j^*, j = 2, 4, \cdots, l-1$, are asymptotically stable, and $Cl((\cup_{j\ even} B(E_j^*) \cup B(E_{I^1}) \cup B(E_{I^2})) = \mathbb{R}_+^8$. The odd indexed positive equilibria $E_j^*, j = 1, 3, \cdots, l$ are unstable. Moreover, if $l = 1$ then there exists an unordered separatrix S

containing E_0 and the unique positive equilibrium E^*, and the unordered separatrix S the separates the basins of attraction of the E_{I^1} and E_{I^2}.

3) If $\mathscr{R}_1^2 > 1, \mathscr{R}_2^1 < 1$, then system (5.1) has an even number l of positive equilibria given by (5.12). The boundary equilibrium E_{I^2} and the even indexed positive equilibria $E_j^*, j = 2, 4, \cdots, l$, are asymptotically stable, and $Cl((\cup_{j\ even} B(E_j^*) \cup B(E_{I^2})) = \mathbb{R}_+^8$. The boundary equilibrium E_{I^1} and the odd indexed positive equilibria $E_j^*, j = 1, 3, \cdots, l-1$ are unstable. Moreover, if $l = 0$, i.e., system (5.1) has no positive equilibrium, then E_{I^2} is globally asymptotically stable in $\mathbb{R}_+^8 \setminus \Gamma^1$.

4) If $\mathscr{R}_1^2 < 1, \mathscr{R}_2^1 > 1$, then the system (5.1) has an even number l of positive equilibria given by (5.12). The boundary equilibrium E_{I^1} and the odd indexed positive equilibria $E_j^*, j = 1, 3, \cdots, l-1$, are asymptotically stable, and $Cl((\cup_{j\ odd} B(E_j^*) \cup B(E_{I^1})) = R_+^8$. The boundary equilibrium E_{I^2} and the even indexed positive equilibria $E_j^*, j = 2, 4, \cdots, l$, are unstable. Moreover, if $l = 0$, i.e., system (5.1) has no positive equilibrium, then E_{I^1} is globally asymptotically stable in $\mathbb{R}_+^8 \setminus \Gamma^2$.

In order to prove Theorem 5.2, we need to prove the following lemmas.

Lemma 5.3. *Let assumption (H') hold. Then we have*

$$\mathscr{R}_2^1 > 1 (\mathscr{R}_2^1 < 1) \Leftrightarrow F(0, \bar{H}_2^2) < 0 (F(0, \bar{H}_2^2) > 0).$$

Proof. From the expression of $\varphi_2(H_2^1, H_2^2)$, we have

$$\begin{aligned} \varphi_2(0, \bar{H}_2^2) &= \frac{(b_2)^2 \alpha_1 \beta_1 \bar{W}_2 (\bar{N}_2 - \bar{H}_2^2)}{(b_2 \beta_2 \bar{H}_2^2 + \bar{N}_2 \mu_2) \bar{N}_2} - (\gamma_2^1 + \nu_2 + m_{12}) \\ &= \frac{(b_2)^2 \alpha_1 \beta_1 (\bar{W}_2 - \bar{V}_2^2)(\bar{N}_2 - \bar{H}_2^2)}{\mu_2 (\bar{N}_2)^2} - (\gamma_2^1 + \nu_2 + m_{12}). \end{aligned}$$

Thus,

$$\varphi_2(0, \bar{H}_2^2) < 0 \Leftrightarrow \frac{(b_2)^2 \alpha_1 \beta_1 (\bar{W}_2 - \bar{V}_2^2)(\bar{N}_2 - \bar{H}_2^2)}{\mu_2 (\bar{N}_2)^2 (\gamma_2^1 + \nu_2 + m_{12})} < 1,$$

$$\varphi_2(0, \bar{H}_2^2) > 0 \Leftrightarrow \frac{(b_2)^2 \alpha_1 \beta_1 (\bar{W}_2 - \bar{V}_2^2)(\bar{N}_2 - \bar{H}_2^2)}{\mu_2 (\bar{N}_2)^2 (\gamma_2^1 + \nu_2 + m_{12})} > 1.$$

Substituting $H_2^1 = 0, H_2^2 = \bar{H}_2^2$ into the expression for $F(H_2^1, H_2^2)$ gives

$$
\begin{aligned}
F(0, \bar{H}_2^2) &= \varphi_2(0, \bar{H}_2^2)\varphi_1(0, -\frac{1}{m_{21}}\bar{H}_2^2\psi_2(0, \bar{H}_2^2)) - m_{12}m_{21} \\
&= [\frac{(b_2)^2\alpha_1\beta_1(\bar{W}_2 - \bar{V}_2^2)(\bar{N}_2 - \bar{H}_2^2)}{\mu_2(\bar{N}_2)^2} - (\gamma_2^1 + \nu_2 + m_{12})]\times \\
&\quad [\frac{(b_1)^2\alpha_1\beta_1(\bar{W}_1 - \bar{V}_1^2)(\bar{N}_1 - \bar{H}_1^2)}{\mu_1(\bar{N}_1)^2} - (\gamma_1^1 + \nu_1 + m_{21})] - m_{12}m_{21} \\
&= [(\gamma_2^1 + \nu_2)(\gamma_1^1 + \nu_1) + m_{12}(\gamma_1^1 + \nu_1) + m_{21}(\gamma_2^1 + \nu_2)]\times \\
&\quad [1 - (\tilde{\mathfrak{R}}_{1i}^j)^2(1 - \chi^j) - (\tilde{\mathfrak{R}}_{2i}^j)^2(1 - \zeta^j) + (\tilde{\mathfrak{R}}_{1i}^j)^2(\tilde{\mathfrak{R}}_{2i}^j)^2(1 - \chi^j - \zeta^j)].
\end{aligned}
$$

Here, we have used the fact $\bar{H}_1^2 = -\frac{1}{m_{21}}\bar{H}_2^2\psi_2(0, \bar{H}_2^2)$. We can then conclude that

$$F(0, \bar{H}_2^2) > 0 \Leftrightarrow (\tilde{\mathfrak{R}}_{1i}^j)^2(1 - \chi^j) + (\tilde{\mathfrak{R}}_{2i}^j)^2(1 - \zeta^j) - (\tilde{\mathfrak{R}}_{1i}^j)^2(\tilde{\mathfrak{R}}_{2i}^j)^2(1 - \chi^j - \zeta^j) < 1,$$

$$F(0, \bar{H}_2^2) < 0 \Leftrightarrow (\tilde{\mathfrak{R}}_{1i}^j)^2(1 - \chi^j) + (\tilde{\mathfrak{R}}_{2i}^j)^2(1 - \zeta^j) - (\tilde{\mathfrak{R}}_{1i}^j)^2(\tilde{\mathfrak{R}}_{2i}^j)^2(1 - \chi^j - \zeta^j) > 1.$$

Assumption (H') implies that $\varphi_2(0, \bar{H}_2^2) < 0$. Hence, the conclusions follow immediately from (5.2) □

Similarly, we can establish the following lemma whose proof is omitted.

Lemma 5.4. *Let the assumption (H') hold. Then we have*

$$\mathscr{R}_1^2 > 1 (\mathscr{R}_1^2 < 1) \Leftrightarrow G(\bar{H}_2^1, 0) < 0 (G(\bar{H}_2^1, 0) > 0).$$

Now we are able to prove Theorem 5.2.

Proof of Theorem 5.2. Here we only prove part 1) of the Theorem The other parts can be established similarly except the last conclusion in part 2) which is a corollary of Theorem 1 in paper [40]. We consider the roots of the equation $\mathscr{H}(H_2^1) = H_2^1$ in the interval $[\chi, \bar{H}_2^1]$. If $\mathscr{R}_1^2 > 1$ and $\mathscr{R}_2^1 > 1$ hold, Lemma 5.3 and Lemma 5.4 imply that $F(0, \bar{H}_2^2) < 0, G(\bar{H}_2^1, 0) < 0$, i.e.,$f(0) > \bar{H}_2^2, g(0) > \bar{H}_2^1$. Hence, we can easily see that $\chi = f^{-1}(\bar{H}_2^2) > 0, g(f(\chi)) = 0, g(f(\bar{H}_2^1)) > \bar{H}_2^1$. The non-degeneracy assumption (H) implies that the number l of the roots of the equation $\mathscr{H}(H_2^1) = H_2^1$ in the interval $[\chi, \bar{H}_2^1]$ is odd. Let the roots of the equation $\mathscr{H}(H_2^1) = H_2^1$ in the interval $[\chi, \bar{H}_2^1]$ be $H_{21}^{1*} < H_{22}^{1*} < \cdots < H_{2l}^{1*}$. This means that system (5.1) has exactly l positive equilibria given by (5.12) and three boundary equilibria E_0, E_{I_1}, E_{I_2}.

Moreover, the non-degeneracy assumption (H) also implies that $g'(f(H_{2j}^{1*}))f'(H_{2j}^{1*}) > 1$, i.e.,

$$\frac{F_{H_2^2}(H_{2j}^{1*}, H_{2j}^{2*})}{F_{H_2^1}(H_{2j}^{1*}, H_{2j}^{2*})} \cdot \frac{G_{H_2^1}(H_{2j}^{1*}, H_{2j}^{2*})}{G_{H_2^2}(H_{2j}^{1*}, H_{2j}^{2\#})} < 1$$

in the case when j is odd and $g'(f(H_{2j}^{1*}))f'(H_{2j}^{1*}) < 1$, that is,

$$\frac{F_{H_2^2}(H_{2j}^{1*}, H_{2j}^{2*})}{F_{H_2^1}(H_{2j}^{1*}, H_{2j}^{2*})} \cdot \frac{G_{H_2^1}(H_{2j}^{1*}, H_{2j}^{2*})}{G_{H_2^2}(H_{2j}^{1*}, H_{2j}^{2\#})} > 1$$

in the case when j is even. By Theorem 5.1 the odd indexed positive equilibria E_j^* are locally asymptotically stable and the even indexed positive equilibria E_j^* are unstable. Note that the flow $\varphi_t(I_1, I_2)$ generated by (5.1) is type-K strongly monotone. Since $E_{I_2} <_K E_1^* <_K \cdots <_K E_l^* <_K E_{I_1}$ and E_1^*, E_l^* are both asymptotically stable, it follows from Theorem 2.2.2 in [39] that E_{I_2}, E_{I_1} are both unstable. By Theorem 4.1.2 in [39] we obtain that almost all solutions of system (5.1) are convergent to the equilibria and $Cl \cup_{j\ odd} B(E_j^*) = \mathbb{R}_+^8$. This completes the proof of Theorem 5.2. □

6 Discussion

In this article we study the effect of spatial heterogeneity on the transmission dynamics of a vector-borne diseases with multiple strains and on multiple patches. Based on the Ross-MacDonald multi-patch model analyzed by Auger et al. [25], we formulate an extension multi-patch multi-strain model. Vector-borne diseases, such as malaria, often display heterogeneity of transmission in different locations. High transmission areas neighbor low transmission areas and those are connected by host migration. Vector-borne disease have reemerged as a major public health threat in the last 30-40 years. The reasons for the re-emergence are complex but they involve the evolution of the pathogens to more resilient drug-resistant strains, often persisting in different isolated regions [41]. This suggests that studying the evolution of pathogens in a spatial context (on multiple patches) is an important topic of particular interest. We believe our model here is the first one that studies the impact of spatial heterogeneities on the evolution of pathogens.

We focus on investigating the dynamics of the multi-patch multi-strain Ross-McDonald type model. We define the multi-patch basic reproduction numbers $\mathcal{R}_0^j$ for each strain. Theorem 3.3 shows that if the reproduction number for strain j is less than one then strain j can not invade the patchy environment and dies out over the entire domain. Theorem 3.3 also implies that if the multi-patch basic reproduction numbers for all strains are less than one the disease free equilibrium is globally asymptotically stable and the disease is eliminated from the host and the vector populations. When the multi-patch basic reproduction numbers for all strains are greater than one, each strain can invade into the population when alone, and thus all strains compete for the same resource, the susceptible individuals.

In order to obtain further theoretical results, we systematically analyze the multi-patch multi-strain model on n discrete patches but restricting the number of strains to two. By analyzing the local stability of the single-strain equilibria, we derive the invasion reproduction numbers $\mathscr{R}_i^j, i, j = 1, 2, i \neq j$ for strain j. Applying the theory of uniform persistence of dynamical systems the uniform persistence of two competing strains on the entire domain is rigorously proved in Theorem 4.2 under the condition that both invasion reproduction numbers are lager than one. However, the results of Theorem 3.1 show that if the system has no host migration no more than one strain will persist in the population on a single patch, namely the strain with the largest reproduction number on that patch. Multiple strains may persist, each on a separate patch, but essentially a divide and conquer strategy is adopted. When the patches are linked through migration, the divide and conquer strategy is not an option and all strains whose reproduction number is greater than one are competing. However, Theorem 4.2 and 3.1 indicate that spatial heterogeneity can lead to the coexistence of multiple competing strains on the entire domain. Hence, spatial heterogeneity supports pathogen genetic diversity. This is the main result of this article.

Finally, we examine the global behavior of the model with two competing strains on two patches. Applying the well-known M-matrix theory and the implicit function theorem a complete classification for the local stabilities of positive equilibria is given in Theorem 5.1. We determine that the flow $\Phi_t(I^1, I^2)$ generated by the two-strain two-patch model (5.1) is type-K monotone. By applying the theory of type-K monotone dynamical systems, we provide the global behavior of the two-strain two-patch model in Theorem 5.2 which is completely determined by the algebraic equations (5.7). These results follow from the conditions on the invasion reproduction numbers as well as the non-degeneracy assumption (H) and assumption (H').

There are still many interesting and challenging mathematical questions which need to be studied for the system (2.5). For example, we could not present the complete classification for the dynamics of the system (2.5). The main difficulty stems from the high dimension of the multi-patch multi-strain model. Additionally, the model discussed here can also be extended to incorporate the other ingredients, such as the different incidences and/or different compartmental structures. It is worth noting that the methods applied to study model (5.1) are not applicable to the other general models because the monotonicity of the model (5.1) plays an essential role in our analysis. We leave these investigations for the future.

Acknowledgments

The authors are very grateful to an anonymous referee for his valuable comments and suggestions which led to an improvement of our original manuscript. The research of this paper is supported by the NSF of China grants (No.11271190, No. 11271314, No.10911120387), the Zijin Star Project of Excellence Plan of NJUST and Qinglan Project of Jiangsu Province. The research is also in part supported by NSF (USA) grant DMS-0817789.

Appendix A: Proof of Theorem 3.1.

For any $1 \leq p, q \leq n$, we consider the system

$$\begin{cases} \dfrac{d\hat{H}_i^p(t)}{dt} = b_i\alpha_p\hat{V}_i^p\dfrac{N_i^0 - (\hat{H}_i^p + \hat{H}_i^q)}{N_i^0} - (\gamma_i^p + \nu_i)\hat{H}_i^p, \\ \dfrac{d\hat{V}_i^p(t)}{dt} = b_i\beta_p(\bar{W}_i - (\hat{V}_i^p + V_i^q))\dfrac{\hat{H}_i^p}{N_i^0} - \mu_i\hat{V}_i^p, \\ \dfrac{d\hat{H}_i^q(t)}{dt} = b_i\alpha_q\hat{V}_i^q\dfrac{N_i^0 - (\hat{H}_i^p + \hat{H}_i^q)}{N_i^0} - (\gamma_i^q + \nu_i)\hat{H}_i^q, \\ \dfrac{d\hat{V}_i^q(t)}{dt} = b_i\beta_q(\bar{W}_i - (V_i^p + \hat{V}_i^q))\dfrac{\hat{H}_i^q}{N_i^0} - \mu_i\hat{V}_i^q. \end{cases}$$

If we let $\hat{R}_i^p$ and $\hat{R}_i^q$ be the reproduction numbers for strain p and q, then $\hat{R}_i^p = R_i^p$ and $\hat{R}_i^q = R_i^q$. Since $R_i^j \leq 1$ for all j (which implies $\hat{R}_i^p < 1$ and $\hat{R}_i^q < 1$) it follows from Theorem 4.1.2 in [6] that $H_i^p(t) \to 0, H_i^q(t) \to 0$ and $\hat{V}_i^p(t) \to 0, \hat{V}_i^q(t) \to 0$, as $t \to +\infty$. On the other hand, from the comparison principle, it follows that $H_i^p(t) \leq \hat{H}_i^p(t), H_i^q(t) \leq \hat{H}_i^q(t)$ and $V_i^p(t) \leq \hat{V}_i^p(t), V_i^q(t) \leq \hat{V}_i^q(t)$ for all $t \geq 0$. Thus, the the disease-free equilibrium of the system (2.4) is globally asymptotically stable. This completes the proof of part (1).

2) For any $j \neq j^*$, consider the system

$$\begin{cases} \dfrac{d\hat{H}_i^{j^*}(t)}{dt} = b_i\alpha_{j^*}\hat{V}_i^{j^*}\dfrac{N_i^0-(\hat{H}_i^{j^*}+\hat{H}_i^j)}{N_i^0}-(\gamma_i^{j^*}+\nu_i)\hat{H}_i^{j^*}, \\ \dfrac{d\hat{V}_i^{j^*}(t)}{dt} = b_i\beta_{j^*}(\bar{W}_i-(\hat{V}_i^{j^*}+V_i^j))\dfrac{\hat{H}_i^{j^*}}{N_i^0}-\mu_i\hat{V}_i^{j^*}, \\ \dfrac{d\hat{H}_i^{j}(t)}{dt} = b_i\alpha_{j}\hat{V}_i^{j}\dfrac{N_i^0-(\hat{H}_i^{j^*}+\hat{H}_i^j)}{N_i^0}-(\gamma_i^{j}+\nu_i)\hat{H}_i^{j}, \\ \dfrac{d\hat{V}_i^{j}(t)}{dt} = b_i\beta_{j}(\bar{W}_i-(V_i^{j^*}+\hat{V}_i^j))\dfrac{\hat{H}_i^{j}}{N_i^0}-\mu_i\hat{V}_i^{j}. \end{cases}$$

Let $\hat{R}_i^{j^*}$ and $\hat{R}_i^j$ be the reproduction numbers for strain j^* and j, then $\hat{R}_i^{j^*}=R_i^{j^*}$ and $\hat{R}_i^j=R_i^j$. Hence $\hat{R}_i^{j^*}>\hat{R}_i^j$ and it follows from Theorem 4.1.2 in [6] that $H_i^j(t)\to 0\hat{V}_i^j(t)\to 0$, as $t\to+\infty$. Again, from the comparison principle, it follows that $H_i^j(t)\leq \hat{}H_i^j(t)$ and $V_i^j(t)\leq \hat{V}_i^j(t)$ for all $t\geq 0$. Thus, $\lim_{t\to+\infty} H_i^j(t)=0$, $\lim_{t\to+\infty} V_i^j(t)=0$. Since j is arbitrary, we have

$$\lim_{t\to+\infty} H_i^{j^*}(t)=\frac{[b_i^2\alpha_{j^*}\beta_{j^*}\frac{\bar{W}_i}{N_i^0}-\mu_i(\gamma_i^{j^*}+\nu_i)]N_i^0}{b_i\beta_{j^*}(\gamma_i^{j^*}+\nu_i+b_i\alpha_{j^*}\frac{\bar{W}_i}{N_i^0})}, \lim_{t\to+\infty} V_i^{j^*}(t)=\frac{[b_i^2\alpha_{j^*}\beta_{j^*}\frac{\bar{W}_i}{N_i^0}-\mu_i(\gamma_i^{j^*}+\nu_i)]N_i^0}{b_i\alpha_{j^*}(b_i\beta_{j^*}+\mu_i)},$$

and

$$\lim_{t\to+\infty} H_i^j(t)=0, \lim_{t\to+\infty} V_i^j(t)=0$$

for all $j=1,2,\cdots,l, j\neq j^*$. This completes the proof Theorem 3.1.

Appendix B: Proof of $(-1)^6W_6>0$.

From the equations in (5.3), we have

$$\begin{cases} \Gamma_2^1(H_1^1,H_2^1,V_1^1,V_2^1,H_1^2,H_2^2,V_1^2,V_2^2)=0, \\ \Theta_1^1(H_1^1,H_2^1,V_1^1,V_2^1,H_1^2,H_2^2,V_1^2,V_2^2)=0, \\ \Theta_2^1(H_1^1,H_2^1,V_1^1,V_2^1,H_1^2,H_2^2,V_1^2,V_2^2)=0, \\ \Theta_1^2(H_1^1,H_2^1,V_1^1,V_2^1,H_1^2,H_2^2,V_1^2,V_2^2)=0, \\ \Theta_2^2(H_1^1,H_2^1,V_1^1,V_2^1,H_1^2,H_2^2,V_1^2,V_2^2)=0. \end{cases}$$

It is easy to verify that

$$\det\left(\frac{\partial(\Gamma_2^1,\Theta_1^1,\Theta_2^1,-\Theta_2^2,-\Theta_1^2)}{\partial(H_2^1,V_1^1,V_2^1,-V_2^2,-V_1^2)}\Big|_{(H_2^{1\#},V_1^{1\#},V_2^{1\#},V_1^{2\#},V_2^{2\#})}\right)=W_5<0.$$

Applying the implicit function theorem we conclude that there exist continuously differentiable functions $H_2^1(H_1^1,H_1^2,H_2^2), V_1^1(H_1^1,H_1^2,H_2^2), V_2^1(H_1^1,H_1^2,H_2^2), V_1^2(H_1^1,H_1^2,H_2^2), V_2^2(H_1^1,H_1^2,H_2^2)$ defined on a neighborhood Δ of $(H_1^{1\#},H_1^{2\#},H_2^{2\#})$ such that

(1) $H_2^1(H_1^{1\#}, H_1^{2\#}, H_2^{2\#}) = H_2^{1\#}, V_1^1(H_1^{1\#}, H_1^{2\#}, H_2^{2\#}) = V_1^{1\#}, V_2^1(H_1^{1\#}, H_1^{2\#}, H_2^{2\#}) = V_2^{1\#}$,

$V_1^2(H_1^{1\#}, H_1^{2\#}, H_2^{2\#}) = V_1^{2\#}, V_2^2(H_1^{1\#}, H_1^{2\#}, H_2^{2\#}) = V_2^{2\#}$;

(2) For $(H_1^1, H_1^2, H_2^2) \in \Delta$, $H_2^1(H_1^1, H_1^2, H_2^2), V_1^1(H_1^1, H_1^2, H_2^2), V_2^1(H_1^1, H_1^2, H_2^2), V_1^2(H_1^1, H_1^2, H_2^2)$, $V_2^2(H_1^1, H_1^2, H_2^2)$ satisfy the equations

$$\begin{cases} \Gamma_2^1(H_1^1, H_2^1(H_1^1, H_1^2, H_2^2), V_1^1(H_1^1, H_1^2, H_2^2), V_2^1(H_1^1, H_1^2, H_2^2), \\ \qquad\qquad H_1^2, H_2^2, V_1^2(H_1^1, H_1^2, H_2^2), V_2^2(H_1^1, H_1^2, H_2^2)) \equiv 0, \\ \Theta_i^j(H_1^1, H_2^1(H_1^1, H_1^2, H_2^2), V_1^1(H_1^1, H_1^2, H_2^2), V_2^1(H_1^1, H_1^2, H_2^2), \\ \qquad\qquad H_1^2, H_2^2, V_1^2(H_1^1, H_1^2, H_2^2), V_2^2(H_1^1, H_1^2, H_2^2)) \equiv 0, \quad i, j = 1, 2; \end{cases}$$

(3) For $(H_1^1, H_1^2, H_2^2) \in \Delta$, we have

$$\frac{\partial H_2^1(H_1^1, H_1^2, H_2^2)}{\partial H_1^1} = -\frac{\det(\frac{\partial(\Gamma_2^1, \Theta_1^1, \Theta_2^1, -\Theta_1^2, -\Theta_2^2)}{\partial(H_1^1, V_1^1, V_2^1, -V_1^2, -V_2^2)})}{\det(\frac{\partial(\Gamma_2^1, \Theta_1^1, \Theta_2^1, -\Theta_1^2, -\Theta_2^2)}{\partial(H_2^1, V_1^1, V_2^1, -V_1^2, -V_2^2)})},$$

$$\frac{\partial V_1^1(H_1^1, H_1^2, H_2^2)}{\partial H_1^1} = -\frac{\det(\frac{\partial(\Gamma_2^1, \Theta_1^1, \Theta_2^1, -\Theta_1^2, -\Theta_2^2)}{\partial(H_2^1, H_1^1, V_2^1, -V_1^2, -V_2^2)})}{\det(\frac{\partial(\Gamma_2^1, \Theta_1^1, \Theta_2^1, -\Theta_1^2, -\Theta_2^2)}{\partial(H_2^1, V_1^1, V_2^1, -V_1^2, -V_2^2)})},$$

On the one hand, substituting the functions $H_2^1(H_1^1, H_1^2, H_2^2), V_1^1(H_1^1, H_1^2, H_2^2), V_2^1(H_1^1, H_1^2, H_2^2)$, $V_1^2(H_1^1, H_1^2, H_2^2), V_2^2(H_1^1, H_1^2, H_2^2)$ for the expression $\Gamma_1^1(H_1^1, H_2^1, V_1^1, V_2^1, H_1^2, H_2^2, V_1^2, V_2^2)$ yields that

$$\Upsilon(H_1^1, H_1^2, H_2^2) := \Gamma_1^1(H_1^1, H_2^1(H_1^1, H_1^2, H_2^2), V_1^1(H_1^1, H_1^2, H_2^2), \\ V_2^1(H_1^1, H_1^2, H_2^2), H_1^2, H_2^2, V_1^2(H_1^1, H_1^2, H_2^2), V_2^2(H_1^1, H_1^2, H_2^2)).$$

Differentiating the function $\Upsilon(H_1^1, H_1^2, H_2^2)$ with respect to H_1^1, we have

$$\begin{aligned} &\frac{\partial \Upsilon(H_1^1, H_1^2, H_2^2)}{\partial H_1^1}|_{(H_1^{1\#}, H_1^{2\#}, H_2^{2\#})} \\ &= [m_{21}\frac{\partial H_2^1}{\partial H_1^1} + b_1\alpha_1\frac{\bar{N}_1 - H_1^1 - H_1^2}{\bar{N}_1}\frac{\partial V_1^1}{\partial H_1^1} - (b_1\alpha_1 V_1^1 + \gamma_1^1 + m_{21} + \nu_1)]|_{(H_1^{1\#}, H_1^{2\#}, H_2^{2\#})} \\ &= \frac{W_6}{W_5}. \end{aligned} \tag{6.1}$$

On the other hand, the first equation in (5.5) implies that we have

$$\frac{\partial \mathscr{F}_2}{\partial H_2^1}|_{(H_1^{1\#}, H_2^{1\#}, H_1^{2\#}, H_2^{2\#})} = \varphi_2(H_2^{1\#}, H_2^{2\#}) + H_2^{1\#}\frac{\partial \varphi_2}{\partial H_2^1}|_{(H_2^{1\#}, H_2^{2\#})}.$$

Since $\varphi_2(H_2^{1\#}, H_2^{2\#}) < 0$ and

$$\begin{aligned} \frac{\partial \varphi_2}{\partial H_2^1}|_{(H_2^{1\#}, H_2^{2\#})} &= -\frac{(b_2)^2\alpha_1\beta_1\bar{W}_2[b_2\beta_2 H_2^{2\#} + \mu_2\bar{N}_2 + b_2\beta_1(\bar{N}_2 - H_2^{2\#})]}{(b_2\beta_1 H_2^{1\#} + b_2\beta_2 H_2^{2\#} + \bar{N}_2\mu_2)^2\bar{N}_2} \\ &< 0, \end{aligned}$$

it follows that $\frac{\partial \mathscr{F}_2}{\partial H_2^1}|_{(H_1^{1\#},H_2^{1\#},H_1^{2\#},H_2^{2\#})} < 0$. By the implicit function theorem, there exists a continuously differentiable function $\tilde{H}_2^1(H_1^1, H_1^2, H_2^2)$ defined on a neighborhood Δ' of $(H_1^{1\#}, H_1^{2\#}, H_2^{2\#})$ such that

$$\tilde{H}_2^1(H_1^{1\#}, H_1^{2\#}, H_2^{2\#}) = H_2^{1\#}$$

and

$$\mathscr{F}_2(H_1^1, \tilde{H}_2^1(H_1^1, H_1^2, H_2^2), H_1^2, H_2^2) \equiv 0$$

for $(H_1^1, H_1^2, H_2^2) \in \Delta'$. Moreover, we have

$$\begin{aligned} \frac{\partial \tilde{H}_2^1}{\partial H_1^1}|_{(H_1^{1\#},H_1^{2\#},H_2^{2\#})} &= -\frac{m_{21}}{\varphi_2(H_2^{1\#}, H_2^{2\#}) + H_2^{1\#}\frac{\partial \varphi_2}{\partial H_2^1}|_{(H_1^{1\#},H_1^{2\#},H_2^{2\#})}} \\ &> 0. \end{aligned}$$

Substituting (5.4) and $H_2^1 = \tilde{H}_2^1(H_1^1, H_1^2, H_2^2)$ into the expression $\Gamma_1^1(H_1^1, H_2^1, V_1^1, V_2^1, H_1^2, H_2^2, V_1^2, V_2^2)$, we can obtain

$$\Upsilon(H_1^1, H_1^2, H_2^2) = H_1^1\varphi_1(H_1^1, H_1^2) + m_{12}\tilde{H}_2^1(H_1^1, H_1^2, H_2^2).$$

Differentiating the function $\Upsilon(H_1^1, H_1^2, H_2^2)$ with respect to H_1^1, we have

$$\begin{aligned} &\frac{\partial \Upsilon(H_1^1, H_1^2, H_2^2)}{\partial H_1^1}|_{(H_1^{1\#},H_1^{2\#},H_2^{2\#})} \\ &= [\varphi_1(H_1^1, H_1^2) + H_1^1\frac{\partial \varphi_1}{\partial H_1^1} - m_{12}\frac{m_{21}}{\varphi_2(H_2^1, H_2^2) + H_2^1\frac{\partial \varphi_2}{\partial H_2^1}}]|_{(H_1^{1\#},H_2^{1\#},H_1^{2\#},H_2^{2\#})} \\ &= \frac{1}{\varphi_2(H_2^1, H_2^2) + H_2^1\frac{\partial \varphi_2}{\partial H_2^1}}[\varphi_1(H_1^1, H_1^2)H_2^1\frac{\partial \varphi_2}{\partial H_2^1} + \\ &\qquad \varphi_2(H_2^1, H_2^2)H_2^1\frac{\partial \varphi_1}{\partial H_1^1} + H_1^1H_2^1\frac{\partial \varphi_1}{\partial H_1^1}\frac{\partial \varphi_2}{\partial H_2^1}]|_{(H_1^{1\#},H_2^{1\#},H_1^{2\#},H_2^{2\#})} \\ &< 0 \end{aligned} \tag{6.2}$$

since $\varphi_1(H_1^{1\#}, H_1^{2\#}) < 0, \varphi_2(H_2^{1\#}, H_2^{2\#}) < 0, \frac{\partial \varphi_2}{\partial H_2^1}|_{(H_2^{1\#},H_2^{2\#})} < 0$ and

$$\begin{aligned} &\varphi_1(H_1^{1\#}, H_1^{2\#})\varphi_2(H_2^{1\#}, H_2^{2\#}) - m_{12}m_{21} = 0, \\ &\frac{\partial \varphi_1(H_1^1, H_1^2)}{\partial H_1^1}|_{H_1^{1\#},H_2^{1\#}} = -\frac{(b_1)^2\alpha_1\beta_1\bar{W}_1[b_1\beta_1H_1^2 + \mu_1\bar{N}_1 + b_1\beta_1(\bar{N}_1 - H_1^2)]}{(b_2\beta_1H_1^1 + b_1\beta_1H_1^2 + \bar{N}_1\mu_1)^2\bar{N}_1} < 0. \end{aligned}$$

From (6.1) and (6.2) we can easily see that $(-1)^6W_6 > 0$ since $W_5 < 0$.

Appendix C: Proof of $(-1)^7 W_7 > 0$.

From the equations in (5.3), we have

$$\begin{cases} \Gamma_2^1(H_1^1, H_2^1, V_1^1, V_2^1, H_1^2, H_2^2, V_1^2, V_2^2) = 0, \\ \Theta_1^1(H_1^1, H_2^1, V_1^1, V_2^1, H_1^2, H_2^2, V_1^2, V_2^2) = 0, \\ \Theta_2^1(H_1^1, H_2^1, V_1^1, V_2^1, H_1^2, H_2^2, V_1^2, V_2^2) = 0, \\ \Theta_1^2(H_1^1, H_2^1, V_1^1, V_2^1, H_1^2, H_2^2, V_1^2, V_2^2) = 0, \\ \Theta_2^2(H_1^1, H_2^1, V_1^1, V_2^1, H_1^2, H_2^2, V_1^2, V_2^2) = 0, \\ \Gamma_1^1(H_1^1, H_2^1, V_1^1, V_2^1, H_1^2, H_2^2, V_1^2, V_2^2) = 0. \end{cases}$$

It is easy to verify that

$$\det\Big(\frac{\partial(\Gamma_2^1, \Theta_1^1, \Theta_2^1, -\Theta_2^2, -\Theta_1^2, \Gamma_1^1)}{\partial(H_2^1, V_1^1, V_2^1, -V_2^2, -V_1^2, H_1^1)}\Big|_{(H_2^{1\#}, V_1^{1\#}, V_2^{1\#}, V_1^{2\#}, V_2^{2\#}, H_1^{1\#})}\Big) = W_6 > 0.$$

The implicit function theorem then implies that there exist continuously differentiable functions

$$H_2^1(H_1^2, H_2^2), V_1^1(H_1^2, H_2^2), V_2^1(H_1^2, H_2^2), V_1^2(H_1^2, H_2^2), V_2^2(H_1^2, H_2^2), H_1^1(H_1^2, H_2^2)$$

defined on a neighborhood Δ of $(H_1^{2\#}, H_2^{2\#})$ such that

(1) $H_2^1(H_1^{2\#}, H_2^{2\#}) = H_2^{1\#}, V_1^1(H_1^{2\#}, H_2^{2\#}) = V_1^{1\#}, V_2^1(H_1^{2\#}, H_2^{2\#}) = V_2^{1\#}, V_1^2(H_1^{2\#}, H_2^{2\#}) = V_1^{2\#}, V_2^2(H_1^{2\#}, H_2^{2\#}) = V_2^{2\#}, H_1^1(H_1^{2\#}, H_2^{2\#}) = H_1^{1\#}$;

(2) For $(H_1^2, H_2^2) \in \Delta$, $H_2^1(H_1^2, H_2^2), V_1^1(H_1^2, H_2^2), V_2^1(H_1^2, H_2^2), V_1^2(H_1^2, H_2^2), V_2^2(H_1^2, H_2^2), H_1^1(H_1^2, H_2^2)$ satisfy the equations

$$\begin{cases} \Gamma_i^1(H_1^1(H_1^2, H_2^2), H_2^1(H_1^2, H_2^2), V_1^1(H_1^2, H_2^2), V_2^1(H_1^2, H_2^2), H_1^2, H_2^2, V_1^2(H_1^2, H_2^2), V_2^2(H_1^2, H_2^2)) \equiv 0, \\ \Theta_i^j(H_1^1(H_1^2, H_2^2), H_2^1(H_1^2, H_2^2), V_1^1(H_1^2, H_2^2), V_2^1(H_1^2, H_2^2), H_1^2, H_2^2, V_1^2(H_1^2, H_2^2), V_2^2(H_1^2, H_2^2)) \equiv 0, \end{cases}$$

where $i, j = 1, 2$;

(3) For $(H_1^2, H_2^2) \in \Delta$, we have

$$-\frac{\partial H_2^1(H_1^2, H_2^2)}{\partial H_2^2} = -\frac{\det\Big(\frac{\partial(\Gamma_2^1, \Theta_1^1, \Theta_2^1, -\Theta_1^2, -\Theta_2^2, \Gamma_1^1)}{\partial(-H_2^2, V_1^1, V_2^1, -V_1^2, -V_2^2, H_1^1)}\Big)}{\det\Big(\frac{\partial(\Gamma_2^1, \Theta_1^1, \Theta_2^1, -\Theta_1^2, -\Theta_2^2, \Gamma_1^1)}{\partial(H_2^1, V_1^1, V_2^1, -V_1^2, -V_2^2, H_1^1)}\Big)},$$

$$\frac{\partial V_2^2(H_1^2, H_2^2)}{\partial H_2^2} = -\frac{\det\Big(\frac{\partial(\Gamma_2^1, \Theta_1^1, \Theta_2^1, -\Theta_1^2, -\Theta_2^2, \Gamma_1^1)}{\partial(H_2^1, V_1^1, V_2^1, -V_1^2, -H_2^2, H_1^1)}\Big)}{\det\Big(\frac{\partial(\Gamma_2^1, \Theta_1^1, \Theta_2^1, -\Theta_1^2, -\Theta_2^2, \Gamma_1^1)}{\partial(H_2^1, V_1^1, V_2^1, -V_1^2, -V_2^2, H_1^1)}\Big)},$$

On the one hand, substituting the functions $H_2^1(H_1^2,H_2^2), V_1^1(H_1^2,H_2^2), V_2^1(H_1^2,H_2^2), V_1^2(H_1^2,H_2^2)$, $V_2^2(H_1^2,H_2^2), H_1^1(H_1^2,H_2^2)$ for the expression $\Gamma_2^2(H_1^1,H_2^1,V_1^1,V_2^1,H_1^2,H_2^2,V_1^2,V_2^2)$ yields that

$$\begin{aligned}\Upsilon'(H_1^2,H_2^2) :=\ & \Gamma_2^2(H_1^1(H_1^2,H_2^2), H_2^1(H_1^2,H_2^2),\\ & V_1^1(H_1^2,H_2^2), V_2^1(H_1^2,H_2^2), H_1^2, H_2^2, V_1^2(H_1^2,H_2^2), V_2^2(H_1^2,H_2^2)).\end{aligned}$$

Differentiating the function $\Upsilon'(H_1^2,H_2^2)$ with respect to H_2^2, we have

$$\begin{aligned}&\frac{\partial\Upsilon'(H_1^2,H_2^2)}{\partial H_2^2}|_{(H_1^{2\#},H_2^{2\#})}\\ &= [b_2\alpha_2\frac{V_2^2(H_1^2,H_2^2)}{\bar N_2}\frac{\partial H_2^1}{\partial H_2^2} + b_2\alpha_2\frac{\bar N_2 - H_2^1(H_1^2,H_2^2) - H_2^2}{\bar N_2}\times\\ &\qquad \frac{\partial V_2^2}{\partial H_2^2} - (b_2\alpha_2 V_2^2(H_1^2,H_2^2) + \gamma_2^2 + m_{12} + \nu_2)]|_{(H_1^{2\#},H_2^{2\#})}\\ &= \frac{W_7}{W_6}.\end{aligned} \tag{6.3}$$

On the other hand, the first equation in (5.5) leads to

$$\begin{aligned}\Xi &:= \det(\frac{\partial(\mathscr{F}_1,\mathscr{F}_2)}{\partial(H_1^1,H_2^1)})|_{(H_1^{1\#},H_2^{1\#},H_1^{2\#},H_2^{2\#})}\\ &= \begin{vmatrix} \varphi_1(H_1^{1\#},H_1^{2\#}) + H_1^{1\#}\frac{\partial\varphi_1}{\partial H_1^1}|_{(H_1^{1\#},H_1^{2\#})} & m_{12}\\ m_{21} & \varphi_2(H_2^{1\#},H_2^{2\#}) + H_2^{1\#}\frac{\partial\varphi_2}{\partial H_2^1}|_{(H_2^{1\#},H_2^{2\#})}\end{vmatrix}\\ &= \varphi_1(H_1^{1\#},H_1^{2\#})H_2^{1\#}\frac{\partial\varphi_2}{\partial H_2^1}|_{(H_2^{1\#},H_2^{2\#})} + H_1^{1\#}\varphi_2(H_2^{1\#},H_2^{2\#})\times\\ &\qquad \frac{\partial\varphi_1}{\partial H_1^1}|_{(H_1^{1\#},H_1^{2\#})} + H_1^{1\#}H_2^{1\#}\frac{\partial\varphi_1}{\partial H_1^1}|_{(H_1^{1\#},H_1^{2\#})}\frac{\partial\varphi_2}{\partial H_2^1}|_{(H_2^{1\#},H_2^{2\#})}\\ &> 0\end{aligned}$$

since $\varphi_1(H_1^{1\#},H_1^{2\#}) < 0, \varphi_2(H_2^{1\#},H_2^{2\#}) < 0, \frac{\partial\varphi_2}{\partial H_2^1}|_{(H_2^{1\#},H_2^{2\#})} < 0, \frac{\partial\varphi_1}{\partial H_1^1}|_{(H_1^{1\#},H_2^{1\#})} < 0$ and

$$\varphi_1(H_1^{1\#},H_1^{2\#})\varphi_2(H_2^{1\#},H_2^{2\#}) - m_{12}m_{21} = 0.$$

By the implicit function theorem, there exists a continuously differentiable function $\tilde H_1^1(H_1^2,H_2^2), \tilde H_2^1(H_1^2,H_2^2)$ defined on a neighborhood Δ' of $(H_1^{2\#},H_2^{2\#})$ such that

$$\tilde H_1^1(H_1^{2\#},H_2^{2\#}) = H_1^{1\#}, \tilde H_2^1(H_1^{2\#},H_2^{2\#}) = H_2^{1\#}$$

and

$$\mathscr{F}_i(\tilde H_1^1(H_1^2,H_2^2), \tilde H_2^1(H_1^2,H_2^2), H_1^2, H_2^2) \equiv 0, i = 1,2$$

for $(H_1^2,H_2^2)\in\Delta'$. Moreover, we have

$$\frac{\partial\tilde H_2^1}{\partial H_1^2}|_{(H_1^{2\#},H_2^{2\#})} := -\frac{\Xi_2}{\Xi}, \frac{\partial\tilde H_2^1}{\partial H_2^2}|_{(H_1^{2\#},H_2^{2\#})} := -\frac{\Xi_1}{\Xi},$$

where

$$\Xi_1 = \begin{vmatrix} \varphi_1(H_1^{1\#}, H_1^{2\#}) + H_1^{1\#}\frac{\partial \varphi_1}{\partial H_1^1}|_{(H_1^{1\#},H_1^{2\#})} & 0 \\ m_{21} & H_2^{1\#}\frac{\partial \varphi_2}{\partial H_2^2}|_{(H_2^{1\#},H_2^{2\#})} \end{vmatrix} > 0,$$

$$\Xi_2 = \begin{vmatrix} \varphi_1(H_1^{1\#}, H_1^{2\#}) + H_1^{1\#}\frac{\partial \varphi_1}{\partial H_1^1}|_{(H_1^{1\#},H_1^{2\#})} & H_1^{1\#}\frac{\partial \varphi_1}{\partial H_1^2}|_{(H_1^{1\#},H_1^{2\#})} \\ m_{21} & 0 \end{vmatrix} > 0.$$

Substituting $H_2^1 = \tilde{H}_2^1(H_1^2, H_2^2)$ into the second equation in (5.5), we can obtain

$$\Upsilon'(H_1^2, H_2^2) = H_2^2\psi_2(\tilde{H}_2^1(H_1^2, H_2^2), H_2^2) + m_{21}H_1^2.$$

Differentiating the function $\Upsilon'(H_1^2, H_2^2)$ with respect to H_2^2, we have

$$\begin{aligned}
&\frac{\partial \Upsilon'(H_1^2, H_2^2)}{\partial H_2^2}|_{(H_1^{2\#},H_2^{2\#})} \\
&= \psi_2(H_2^{1\#}, H_2^{2\#}) + H_2^{2\#}[-\frac{\partial \psi_2}{\partial H_2^1}|_{(H_2^{1\#},H_2^{2\#})}\frac{\Xi_1}{\Xi} + \frac{\partial \psi_2}{\partial H_2^2}|_{(H_2^{1\#},H_2^{2\#})}] \\
&= \frac{1}{\Xi}\Big\{[\psi_2(H_2^{1\#}, H_2^{2\#}) + H_2^{2\#}\frac{\partial \psi_2}{\partial H_2^2}|_{(H_2^{1\#},H_2^{2\#})}]\Xi - H_2^{2\#}\frac{\partial \psi_2}{\partial H_2^1}|_{(H_2^{1\#},H_2^{2\#})}\Xi_1\Big\} \\
&= \frac{1}{\Xi}\Big\{\varphi_1(H_1^{1\#}, H_1^{2\#})H_2^{2\#}\psi_2(H_2^{1\#}, H_2^{2\#})\frac{\partial \psi_2}{\partial H_2^2}|_{(H_2^{1\#},H_2^{2\#})} + H_1^{1\#}\frac{\partial \varphi_1}{\partial H_1^1}|_{(H_1^{1\#},H_1^{2\#})}[\varphi_2(H_2^{1\#}, H_2^{2\#})\times \\
&\quad (\psi_2(H_2^{1\#}, H_2^{2\#}) + H_2^{2\#}\frac{\partial \psi_2}{\partial H_2^2}|_{(H_2^{1\#},H_2^{2\#})}) + H_2^{1\#}\psi_2(H_2^{1\#}, H_2^{2\#})\frac{\partial \varphi_2}{\partial H_2^1}|_{(H_2^{1\#},H_2^{2\#})}]\Big\} \\
&< 0,
\end{aligned} \tag{6.4}$$

$$\begin{aligned}
&\frac{\partial \Upsilon'(H_1^2, H_2^2)}{\partial H_1^2}|_{(H_1^{2\#},H_2^{2\#})} \\
&= -H_2^{2\#}\frac{\partial \psi_2}{\partial H_2^1}|_{(H_2^{1\#},H_2^{2\#})}\frac{\Xi_2}{\Xi} + m_{21} \\
&> 0,
\end{aligned} \tag{6.5}$$

since $\varphi_1(H_1^{1\#}, H_1^{2\#}) < 0, \psi_2(H_2^{1\#}, H_2^{2\#}) < 0, \frac{\partial \psi_2}{\partial H_2^2}|_{(H_2^{1\#},H_2^{2\#})} < 0, \frac{\partial \varphi_1}{\partial H_1^1}|_{(H_1^{1\#},H_1^{2\#})} < 0,$ $\frac{\partial \varphi_2}{\partial H_2^1}|_{(H_2^{1\#},H_2^{2\#})} < 0$ and $\Xi > 0$. The facts that

$$\varphi_1(H_1^{1\#}, H_1^{2\#})\varphi_2(H_2^{1\#}, H_2^{2\#}) - m_{12}m_{21} = 0$$

and

$$\frac{\partial \varphi_2}{\partial H_2^1}|_{(H_2^{1\#},H_2^{2\#})}\frac{\partial \psi_2}{\partial H_2^2}|_{(H_2^{1\#},H_2^{2\#})} = \frac{\partial \varphi_2}{\partial H_2^2}|_{(H_2^{1\#},H_2^{2\#})}\frac{\partial \psi_2}{\partial H_2^1}|_{(H_2^{1\#},H_2^{2\#})}$$

were used in the above calculations. From (6.3) and (6.5) we can easily see that $(-1)^7W_7 > 0$ since $W_6 > 0$.

References

[1] M. Martcheva, M. Iannelli, X. Z. Li, Subthreshold coexistence of strains: the impact of vaccination and mutation, Math. Biosci. Eng. 4: 287-317,2007.

[2] Z.L. Feng, J.X. Velasco-Hernández, Competitive exclusion in a vector-host model for the dengue fever, J.Math. Biol. 35: 523-544,1997.

[3] S. A. Levin, Community equilibria and stability, and an extension of the competitive exclusion principle, Am. Naturalist 104: 413-423,1970.

[4] H. J. Bremermann, H. R. Thieme, A competitive exclusion principle for pathogen virulence, J. Math. Biol. 27: 179-190,1998.

[5] C. Castillo-Chavez, W.Z. Huang, J. Li, Dynamics of multiple pathogen strains in heterosexual epidemiological models, in: M. Martelli, K. Cooke, E. Cumberbatch, B. Tang, H. Thieme (Eds.), Differential Equations and Applications to Biology and Industry, World Scientific Publishing Co., Singapore, pp. 288-298,1995.

[6] C. Castillo-Chavez, W.Z. Huang, J. Li, Competitive exclusion in gonorrhea models and other sexually transmitted diseases, SIAM J. Appl. Math. 56: 494-508,1996.

[7] M. Iannelli, M. Martcheva, X. Z. Li, Strain replacement in an epidemic model with super-infection and perfect vaccination, Math. Biosci. 195: 23-46,2005.

[8] M. Martcheva, S.S. Pilyugin, The role of coinfection in multi-disease dynamics, SIAM J. Appl. Math. 66: 843-872,2006.

[9] R. May, M. Nowak, Coinfection and the evolution of parasite virulence, Proc. R. Soc. B. 261:209-215,1995.

[10] C. Castillo-Chavez, H. Hethcote, V. Andreasen, S. Levin, W. M. Liu, Epidemiological models with age structure, proportionate mixing, and cross-immunity, J. Math. Biol. 27: 233-258,1989.

[11] V. Andreasen, A. Pugliese, Viral coexistence can be induced by density dependent host mortality, J. Theor. Biol. 177: 159-165,1995.

[12] T. Dhirasakdanon, H.R. Thieme, Persistence of vertically transmitted parasite strains which protect against more virulent horizontally transmitted strains, Modeling and Dynamics of Infectious Diseases (Z. Ma, Y. Zhou, J. Wu, eds.), World Scientifc, Singapore, pp.187-215,2009.

[13] D. J. Gubler, The global threat of emergent/re-emergent vector-borne diseases, in “Vector Biology, Ecology and Control”, Part II, Springer, pp. 39-62, 2010.

[14] A. L. Lloyd, R. M. May, Spatial heterogeneity in epidemic models, J Theor. Biol. 179:1-11,1996.

[15] J. Arino, R. Jordan, P. van den Driessche, Quarantine in a multi-species epidemics model with spatial dynamics, Math. Biosci. 206: 46-60,2006.

[16] C.Castillo-Chavez, A.A. Yakubu, Dispersal ,disease and life-history evolution, Math. Biosci. 173:35-53,2001.

[17] W. Wang, X. Zhao, An epidemic model in a patchy environment,Math. Biosci. 190:97-112,2004.

[18] W. Wang and G. Mulone, Threshold of disease transmission in a patch environment, J. Math. Anal. Appl. 285:321-335,2003.

[19] W. Wang, X. Zhao, An age-structured epidemic model in a patchy environment, SIAM J. Appl. Math., 65(5):1597-1614, 2005.

[20] J. Arino and P. van den Driessche. A multi-city epidemic model. Math. Popul. Studies, 10(3):175-193,2003.

[21] T. Dhirasakdanon, H.R. Thieme and P. van den Driessche, A sharp threshold for disease persistence in host metapopulations, J. Biol. Dynamics, 1: 363-378, 2007.

[22] M. J. Wonham, T. de-Camino-Beck, M. Lewis, An epidemiological model for West Nile virus: invasion analysis and control applications, Proc. Royal Soc. London, Series B, 1538:501-507,2004.

[23] J.H. Rappole, Z. Hubalek, Migratory birds and West Nile virus, J. Appl. Microbiol. 94: 47-58,2003.

[24] J. Owen, F. Moore, N. Panella, et al, Migrating birds as dispersal vehicles for West Nile virus, EcoHealth, 3: 79-85,2006.

[25] P. Auger, E. Kouokam, G. Sallet, M. Tchuente, B. Tsanou, The Ross-Macdonald model in a patchy environment, Math. Biosci. 216: 123-131,2008.

[26] C. Cosner, J.C. Beier, R.S. Cantrell, D. Impoinvil, L. Kapitanski, M.D. Potts, A. Troyo, S. Ruan, The effects of human movement on the persistence of vector-borne diseases, J Theor. Biol. 258: 550-560,2009.

[27] C. Castillo-Chavez and H. R. Thieme, Asymptotically autonomous epidemic models, in Mathematical Population Dynamics: Analysis of Heterogeneity, Vol. 1, O. Arino, D. Axelrod, M. Kimmel, M. Langlais, eds., Wuerz, Winnipeg, pp.33-50,1995.

[28] H. R. Thieme, Convergence results and a Poincare-Bendixson trichotomy for asymptotically autonomous differential equations, J. Math. Biol. 30:755-763,1992.

[29] H. R. Thieme, Asymptotically autonomous differential equations in the plane, Rocky Mountain J. Math. 4:351-380, 1994.

[30] Diekmann, O., Heesterbeek, J.A.P., Mathematical Epidemiology of Infectious Diseases. Model Building, Analysis and Interpretation, Wiley Series in Mathematical and Computational Biology. Wiley, Chichester, 2000.

[31] Brauer, F., Castillo-Chavez, C., Mathematical Models in Population Biology and Epidemiology, Texts in Applied Mathematics Series, vol. 40. Springer, New York, 2000.

[32] Herbert W. Hethcote, The Mathematics of Infectious Diseases, SIAM Review, 42:599-653,2000.

[33] P. van den Driessche, J. Watmough, Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission, Math. Biosci. 180:29-48,2002.

[34] H.L.Smith. Cooperative systems of differential equations with concave nonlinearities. Nonlinear Anal.:TMA 10:1037-1052,1986.

[35] H. R. Thieme, Persistence under relaxed point-dissipativity with an application to an epidemic model, SIAM J. Math. Anal. 24: 407-435,1993.

[36] X.Q. Zhao, Dynamical Systems in Population Biology, Springer, New York, 2003.

[37] H. L. Smith, P.Waltman, The Theory of the Chemostat. Cambridge University, 1995.

[38] J. Franklin, Matrix Theory, Prentice-Hall. Englewood Cliffs, NJ,1968.

[39] H. L. Smith, Monotone Dynamical Systems: An Introduction to Theory of Competitive and Cooperative Systems, Math. Surveys Monogr., 41, AMS, Providence, RI, 1995.

[40] H. L. Smith, H. R. Thieme, Stable coexistence and Bi-stability for competitive systems on ordered Banached Spaces, J. Diff. Equs. 176: 195-222,2001.

[41] W. Pongtavornpinyo, S. Yeung, I. M. Hastings, A. M. Dondorp, N. P. J. Day, N. J. White, Spread of anti-malarial drug resistance: Mathematical model with implications for ACT drug policies, Malaria J. 7:229-245,2008.