AN AGE-STRUCTURED WITHIN-HOST MODEL FOR MULTI-STRAIN MALARIA INFECTIONS

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Abstract. In this paper we propose an age-structured malaria within-host model taking into account multi-strains interaction. We provide a global analysis of the model depending upon some threshold $\mathcal{T}_0$. When $\mathcal{T}_0 \leq 1$, then the disease free equilibrium is globally asymptotically stable and the parasites are cleared. On the contrary if $\mathcal{T}_0 > 1$, the model exhibits the competition exclusion principle. Roughly speaking, only the strongest strain, according to a suitable order, survives while the other strains go to extinct. Under some additional parameter conditions we prove that the endemic equilibrium corresponding to the strongest strain is globally asymptotically stable.

Key words. structured population, competitive exclusion principle, nonlinear dynamical systems, global stability, *Plasmodium falciparum*, intra-host model.

AMS subject classifications. 35Q92, 34K20, 92D30

1. Introduction. In this paper we consider an age-structured system of equations modelling the blood stage of multi-strain malaria infections. We more specifically focus upon human malaria caused by the protozoa *Plasmodium falciparum*, the most widespread within the tropics and particularly in Sub Saharan Africa.

According to Read and Taylor [42] natural parasitic infections are often diverse, including multiple parasite species and/or distinct genotypes of the same species. Parasites of the Plasmodium genus are no exception. Human infections of multiple strains or species have been widely reported [6, 52] and it may be typical in highly endemic regions [28, 30].

Recently, using quantitative PCR methods, Wacker et al [51] prove and quantify that the interactions between different strains of *P. falciparum* lead to the competitive suppression of the weakest one. This feature was already observed for *P. chabaudi*, the parasite responsible for rodent malaria (see [6] and the references therein). Such a competition has a strong influence on the spread of strains and thus on drug-resistance. According to Wacker et al [51], a deeper understanding of the dynamic of multiple strain *P. falciparum* infection can improve the understanding of the role of parasite interactions in the spread of drug resistant parasites, perhaps suggesting different treatment strategies.

In this work we shall focus on the blood stage of the parasite where the aforementioned competitive suppression has been reported. Before going to the mathematical model, let us briefly review the features of malaria. The life cycle of malaria parasites inside human body consists in two phases: an exoerythrocytic (the liver stage) and an erythrocytic phase (the blood stage). After an infective bite, a mosquito injects the pathogen under the so-called sporozoites form, which rapidly reach the liver cells. An asymptomatic period follows during which parasites mature and multiply asexually within the liver cells, yielding to hepatic schizonts. Once hepatic schitzonts rupture the parasitized cells release the so-called merozoites into the bloodstream, the starting point of the blood stage. During this phase, the merozoites enter uninfected red blood cells (uRBC) to undergo asexual multiplication. After a sequestration period

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of about 48 hours (for *P. falciparum*) the rupture of the parasitized red bood cells (pRBC) occurs releasing 8 to 32 free merozoites into the bloodstream ready to repeat the invasion scheme. The blood stage of the parasites is mainly responsible for the clinical symptoms of the infection. The rupture of pRBC causes clinical fever. Moreover *P. falciparum* infection is the most frequent acquired RBC disorders in the world (see Buffet et al [3] and the references therein), that may also lead to severe symptoms such as anaemia or cerebral malaria.

In this paper we consider an age-structured intra-host model for *P. falciparum* infection with n different strains for the parasites. The age-structure will allow us to have a good description of the pRBC rupture and of the merozoites release phenomenon. These parameters play an important role to describe the strength of a strain and thus have important consequences on spread of the infection. The model we shall consider is an extension of the model proposed by Iggidr et al in [27] by taking into account a continuous age structure. It reads as

$$\begin{cases} \dfrac{dx(t)}{dt} = \Lambda - \mu_x x(t) - x(t) \displaystyle\sum_{j=1}^{n} \beta_j m_j(t); \\ \dfrac{\partial w_j(t,a)}{\partial t} + \dfrac{\partial w_j(t,a)}{\partial a} = -(\mu_j(a) + \mu_x) w_j(t,a); \\ \dfrac{dm_j(t)}{dt} = \displaystyle\int_0^\infty r_j(a)\mu_j(a) w_j(t,a)da - \mu_{m,j} m_j(t) - \delta_j \beta_j x(t) m_j(t); \\ w_j(t,0) = \beta_j x(t) m_j(t); \;\; j \in \{1, 2, \cdots, n\}. \end{cases} \tag{1.1}$$

In (1.1), the RBC population is split into two classes, $x(t)$ denotes the concentration of uRBC at time t, while $w_j(t,a)$ denotes the age-specific concentration of pRBC at time t and parasitized since a time a by a specific j-strain. Finally $m_j(t)$ denotes the concentration of free specific j-merozoites in the blood stream. We briefly sketch the interpretation of the parameters arising in (1.1). Parameters μ_x, $\mu_{m,j}$ respectively denotes the natural death rates for uRBC and for free specific j-merozoites. Function $\mu_j(a)$ denotes the additional death rate of pRBC due to the j-parasites at age a and leading to the rupture. The rupture of pRBC at age a results in the release of an average number $r_j(a)$ of specific j-merozoites into the blood stream; so that pRBC infected by a specific j-strain then produce, at age a, j-merozoites with the rate $r_j(a)\mu_j(a)$. Together with this description, the quantity $\int_0^\infty r_j(a)\mu_j(a)w_j(t,a)da$ corresponds to the number of specific j-merozoites produced by pRBC at time t. Finally the parameter β_j describes the contact rate between uRBC and free specific j-merozoites while Λ denotes the recruitment rate of uRBC from the bone marrow. In the literature the parameter δ_j takes the values $\delta_j = 0$ when the loss of merozoites when they enter a RBC is ignored or takes the value $\delta_j = 1$ when this loss is not ignored. System (1.1) is supplemented together with initial data those properties will described below.

There has been numerous works on pathogen within-host dynamics describing *P. falciparum* infection. The pioneer work of Anderson et al [2], focused on describing parasitaemia, has been further developed in several direction including in particular immune response and oscillations [14, 21–23, 31, 39]. We also refer to the survey paper of Molineaux and Dietz in [41] and the references therein. However all these works do not take into account an important characteristic of *P. falciparum* which is sequestration of merozoites within the pRBC and their ruptures. Such an issue has been considered using discrete age-structured systems of equations (see for instance [15–17, 38]) with constant RBC population assumption. We finally refer to Iggidr et al. [27] for a mathematical study of a discrete age-structured model with varying RBC concentration. Note that in this latter work multi-strain competitive interaction is also considered and the authors derived the so-called competitive exclusion principle. In an other context, let us mention that the one-strain System (1.1) (namely with $n = 1$) has been rigorously and recently studied by Huang et al [24] in the context HIV infection model (and with $\delta = 0$).

Here we will extend these results to (1.1) by proving that this problem exhibits the competitive exclusion principle. This work is organized as follows. In Section 2, we describe the main results that will be proved in this work. Section 3 is devoted to deriving preliminary results and remarks that will be used to study the long term behaviour of the problem. Section 4 is concerned with the proof of the first part of Theorem 2.2 below, that roughly speaking states that when some threshold (explicitly expressed using the parameters of the system) $\mathcal{T}_0 \leq 1$, then all the strains asymptotically die out and the parasites cannot survive. Finally Section 5 deals with the proof of the second part of Theorem 2.2, that roughly speaking say that when $\mathcal{T}_0 > 1$ and under some additional assumptions on the different strains, then the competitive exclusion principle holds true, that is that only the strongest strain (using a suitable order) is asymptotically surviving.

2. Main results. In this section we will state the main results of this work. In order to deal with system (1.1) we first provide a parameter reduction by introducing the following unknown functions $y_j(t,a) = w_j(t,a)e^{\int_0^a \mu_j(l)dl}$. Therefore, by introducing the vector valued functions $\mathbf{y}(t,a) = (y_1(t,a),..,y_n(t,a))^T$, $\mathbf{m}(t) = (m_1(t),..,m_n(t))^T$ as well as the matrices

$$\beta = \text{diag }(\beta_1,..,\beta_n)\,,\ \delta = \text{diag }(\delta_1,..,\delta_n)\,,\ \ E_n = (1,..,1)^T \in \mathbb{R}^n,$$
$$\mu_m = \text{diag }(\mu_{m,1},..,\mu_{m,n})\,,\ \rho(a) = \text{diag }(\rho_1(a),..,\rho_n(a))\,,$$

System (1.1) re-writes as

$$\begin{cases} \dfrac{dx(t)}{dt} = \Lambda - \mu_x x(t) - x(t)E_n^T\beta\mathbf{m}(t); \\ \partial_t \mathbf{y}(t,a) + \partial_a \mathbf{y}(t,a) = -\mu_x \mathbf{y}(t,a); \\ \mathbf{y}(t,0) = \beta x(t)\mathbf{m}(t); \\ \dfrac{d\mathbf{m}(t)}{dt} = \displaystyle\int_0^\infty \rho(a)\mathbf{y}(t,a)da - \mu_m \mathbf{m}(t) - \delta\beta x(t)\mathbf{m}(t); \end{cases} \tag{2.1}$$

supplemented together with initial data

$$\mathbf{y}(0,.) = \mathbf{y}_0(.) \in L^1\left(0,\infty;\mathbb{R}_+^n\right);\ x(0) = x_0 \geq 0;\ \mathbf{m}(0) = \mathbf{m}_0 \in \mathbb{R}_+^n, \tag{2.2}$$

and wherein we have set $\rho_j(a) = r_j(a)\mu_j(a)e^{-\int_0^a \mu_j(l)dl}$ for $j = 1,..,n$. In (2.2), $\mathbb{R}_+^n$ denotes the positive orthant, namely $\mathbb{R}_+^n = \{(x_1,..,x_n)^T \in \mathbb{R}^n :\ x_i \geq 0,\ \forall i = 1,..,n\}$.

In what follow we shall discuss the asymptotic behaviour of System (2.1)-(2.2) and we will make use the following assumption.

ASSUMPTION 2.1. *We assume that, for each $j \in \{1, 2, \cdots, n\}$ functions ρ_j belong to $L_+^\infty(0,\infty,\mathbb{R}_+)$ while $\Lambda > 0$, $\mu_x > 0$, $\mu_{m,j} > 0$, $\delta_j \in \{0, 1\}$ and $\beta_j > 0$.*

As mentioned in the introduction we shall focus on the competitive exclusion principle generated by (2.1). Roughly speaking, to achieve such a goal we will provide an order to separate the different strains of the parasite. Hence let us introduce, for each strain, the quantity $\mathcal{T}_0^i$ defined by

$$\mathcal{T}_0^i = \frac{\beta_i \Lambda}{\mu_x \mu_{mi}} \left(\int_0^\infty \rho_i(a) l(a) da - \delta_i \right), \tag{2.3}$$

as well as $\mathcal{T}_0 = \max_{1 \leq i \leq n} \mathcal{T}_0^i$ and where function $l \equiv l(a)$ is defined by

$$l(a) = e^{-\mu_x a}. \tag{2.4}$$

As it will be seen below (see Theorem 2.2) the situation when $\mathcal{T}_0 \leq 1$ is rather simple because the infection asymptotically dies out. When $\mathcal{T}_0 > 1$ the situation is much more involved. We expect that System (2.1)-(2.2) exhibits the competition exclusion principle, that, roughly speaking, say that in presence of multiple strains only the strongest can asymptotically survive. The parameters $\left\{\mathcal{T}_0^i\right\}_{i=1,..,n}$ (see (2.3)) will be used to quantify the strength of the different strain-specific infection. We will now introduce some definitions. Let us first of all define the set of strains that can potentially survive $\mathcal{S}$ defined by

$$\mathcal{S} = \begin{cases} \left\{ i \in \{1,..,n\} : \ \mathcal{T}_0^i > 1 \right\} \text{ if } \mathcal{T}_0 > 1 \\ \emptyset \text{ if } \mathcal{T}_0 \leq 1 \end{cases}. \tag{2.5}$$

On the set of index $\{1,..,n\}$ we define an order relation by

$$i \trianglelefteq j \ \Leftrightarrow \ \mathcal{T}_0^i \leq \mathcal{T}_0^j \ \text{ and } \ i \vartriangleleft j \ \Leftrightarrow \ \mathcal{T}_0^i < \mathcal{T}_0^j.$$

We would like to emphasize that when parameter δ_j are non-zero, the set of threshold $\left\{\mathcal{T}_0^i\right\}_{i=1,..,n}$ is different from the set of the different strain specific basic reproduction numbers. Indeed the strain $i-$specific basic reproduction number reads as (see Appendix A for the computation):

$$\mathcal{R}_0^i = 1 + \frac{\mu_{m,i}}{\mu_{m,i} + \delta_i \beta_i x_f} \left(\mathcal{T}_0^i - 1 \right) \text{ with } x_f = \frac{\Lambda}{\mu_x}. \tag{2.6}$$

Hence, when $\delta \neq 0$, the above described order may be different from the one induced by the strain specific basic reproduction numbers.

We also denote by $\max^{\vartriangleleft}$ the maximum operator associated to the order $\trianglelefteq$. Note that in general the operator $\max^{\vartriangleleft}$ is multi-valued and is defined by

$$\max{}^{\vartriangleleft}\{i,j\} = \begin{cases} i \text{ if } \mathcal{T}_0^i > \mathcal{T}_0^j \\ j \text{ if } \mathcal{T}_0^j > \mathcal{T}_0^i \\ \{i,j\} \text{ if } \mathcal{T}_0^i = \mathcal{T}_0^j \end{cases}$$

A subset $\{i_1,..,i_p\} \subset \{1,..,n\} := \mathbb{N}_n$ is said to be *strictly ordered* if there exists a permutation σ of $\{1,..,p\}$ such that $i_{\sigma(1)} \vartriangleleft .. \vartriangleleft i_{\sigma(p)}$. Let us notice that on a strictly ordered set, the operator $\max^{\vartriangleleft}$ becomes a single-valued map. Let us also mention that for biological reason, since we aim to deal with competitive exclusion principle for our multi-strain model, it is relevant to assume that the different strain is distinguishable. Hence we shall assume in most parts of this work that, the species that can potentially survive are distinguishable, that is re-formulated by assuming the set $\{i \in \mathbb{N}_n : \ \mathcal{T}_0^i > 1\}$ is strictly ordered.

Before stating our main result let us introduce further notations that correspond to the stationary states of (2.1) (see Proposition 3.4): $x_f = \frac{\Lambda}{\mu_x}$ and for each $k \in \mathcal{S}$ (when $\mathcal{S} \neq \emptyset$) :

$$x_e^k = \frac{x_f}{\mathcal{T}_0^k}; \quad \mathbf{m}_e^k = \frac{\mu_x(\mathcal{T}_0^k - 1)}{\beta_k} \left(\delta_{i,k}\right)_{i=1}^n; \quad \mathbf{y}_e^k(a) = \beta_i x_e^k e^{-\mu_x a} \mathbf{m}_e^k, \tag{2.7}$$

wherein $\delta_{i,j}$ denotes the usual Kronecker symbol.

For technical reason in relation to some computations we shall assume some relation between the parameters. The set $\mathcal{S}$ (when $\mathcal{S} \neq \emptyset$) satisfies condition (Q) if

$$\left(\mathcal{T}_0^i - 1\right) \delta_i \beta_i x_f \leq \mathcal{T}_0^i \mu_{mi}, \ \forall i \in \mathcal{S}. \tag{2.8}$$

Let us first notice that the above condition is always satisfied when $\delta_i = 0$. When $\delta_i > 0$ then the above parameter condition can re-written in term of a limitation of the strain specific basic reproduction numbers (see (2.6)). Indeed, if one sets $\gamma_i = \frac{\delta_i \beta_i x_f}{\mu_{mi}}$ then condition (Q) re-writes as

$$\mathcal{R}_0^i \leq \max\left(1 + \frac{1}{1 + 2\gamma_i}; 1 + \frac{1 + \sqrt{1 + 4\gamma_i}}{2\gamma_i}\right), \ \forall i \in \mathcal{S}.$$

Using the above notations the main result of this work reads as

Theorem 2.2. *Let Assumption 2.1 be satisfied. Let $x_0 \geq 0$, $\mathbf{m}_0 \in \mathbb{R}_+^n$ and $\mathbf{y}_0 \in L^1\left(0, \infty; \mathbb{R}_+^n\right)$ be a given initial data and let us denote by $(x(t), \mathbf{m}(t), \mathbf{y}(t, .))$ the solution of (2.1)-(2.2). Then the following holds true:*

(i) If $\mathcal{J} := \mathcal{S} \cap \left\{k \in \{1, .., n\} : \, m_{0,k} + \int_0^\infty y_{0,k}(a) da > 0\right\} = \emptyset$ then

$$\lim_{t \to \infty} (x(t), \mathbf{m}(t), \mathbf{y}(t, .)) = \left(x_f, 0_{\mathbb{R}^n}, 0_{L^1(0,\infty;\mathbb{R}^n)}\right),$$

wherein the above convergence holds for the topology of $\mathbb{R} \times \mathbb{R}^n \times L^1\left(0, \infty; \mathbb{R}^n\right)$.

(ii) Let us assume that the set $\mathcal{S}$ is strictly ordered and satisfies the parameter condition (Q). If $\mathcal{J} \neq \emptyset$ then, setting $i = \max^{\triangleleft} \mathcal{J}$ and recalling (2.7) one has

$$\lim_{t \to \infty} (x(t), \mathbf{m}(t), \mathbf{y}(t, .)) = \left(x_e^i, \mathbf{m}_e^i, \mathbf{y}_e^i(.)\right),$$

for the topology of $\mathbb{R} \times \mathbb{R}^n \times L^1\left(0, \infty; \mathbb{R}^n\right)$.

The first part of this result applies in particular when $\mathcal{S} = \emptyset$, namely $\mathcal{T}_0 \leq 1$. In that case all the strains asymptotically die out and the parasites cannot persist. Let us notice that the condition $\mathcal{T}_0 \leq 1$ can be re-written in term of basic reproduction $\mathcal{R}_0 := \max\left\{\mathcal{R}_0^i, \, i \in \mathbb{N}_n\right\}$ as $\mathcal{R}_0 \leq 1$. The second part of the above theorem says that when different strains are sufficiently strong to survive, then only the strongest present strain (with respect to the order $\trianglelefteq$) is surviving in the long term.

Remark 2.3. *The parameter condition (Q) seems to be only a technical condition that we cannot overcome. From numerical computations, the equilibrium associated to the strongest strain continue to be globally stable even if condition (Q) is violated.*

We now provided some numerical simulations to illustrate the dynamics of System (1.1) in the case of two strains interactions ($n = 2$) and using the parameter set described in Table 2.1. They highlight the principle of competitive exclusion. According to [7] the sequestration period for the i-strain satisfies $\tau_i \in [44; 52]$(hours). For numerical simulations we set $\tau_1 = 48$ and $\tau_2 = 50$ h while $\mu_i \equiv \mu_i(a)$ is set (following [45]) to

$$\mu_i(a) := 0 \text{ if } a < \tau_i \text{ and } 0.98 \text{ if } a \geq \tau_i.$$

Using contact rate $\beta_1 = \beta_2 = 0.02/24$, Fig. 1 (left) represents the super-imposition of the time evolution of two strains alone, that is without interaction while Fig.1 (right) corresponds to the time evolution of competitive interactions between the two strains. Since the sequestration period for strain 1 is smaller then strain 1 becomes the strongest and it competitively suppresses strain 2. Let us also notice that the shape of these curves are qualitatively close to the experimental situations recently obtained by Wacker et al in [51]. Let us finally emphasis that using the parameter set described in Table 2.1 and 2.2, the weakest strain, namely strain 2, is quickly suppressed after 20 days. This duration plays an important role on the transmission of gametocytes to mosquitoes. Note that such a conclusion has been reached without taking into account the interactions of the different strains during the liver stage of the disease. This could have an influence on the time needed to suppress the weakest strain during the blood stage and thus on the spread of the different strains. This will be studied in a forthcoming work.

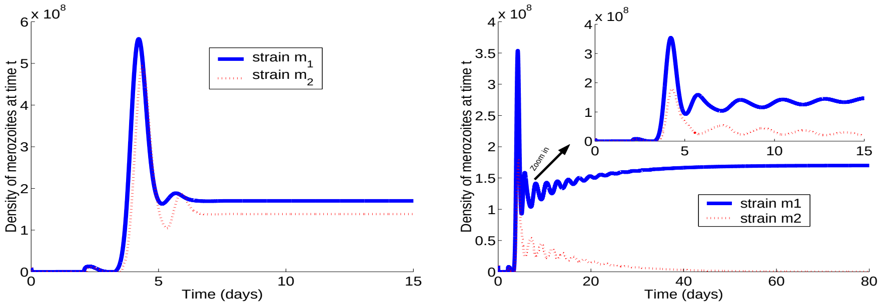

Figure 1: On the left hand-side super-imposed time evolution of the density of merozoites for strain 1 and 2 alone; on the right hand-side competitive suppression of strain 2 when the two strains are mixed. Parameter set for (1.1) is described in Table 2.1 while initial distributions are given in Table 2.2. Here one has $R_0^1 = 4.79$ and $R_0^2 = 3.95$.

Table 2.1
Parameter set for (1.1)

Parameters	Description	Value and Range	References
Λ	Production rate of RBC	1.73×10^6 cell.h^{-1}.ml^{-1}	[1]
β_1; β_2	Infection rate of uRBC	0.02/24 ml.cell^{-1}.h^{-1}	[1]
μ_x	Natural death rate of uRBC	0.00833/24 h^{-1}	[1]
$\mu_{m1}; \mu_{m2}$	Decay rates of malaria parasites	48/24 h^{-1}	[22]
r_1; r_2	Merozoite mean rate produce by pRBC	16	[1]

Table 2.2
Initial values in model (1.1)

Variables	Description	Initial Values	References
$x(0)$	Population of uRBC	5×10^9 cell.ml^{-1}	[1, 4, 22, 38]
$w_1(0, .)$; $w_2(0, .)$	Population of pRBC	0 cell.ml^{-1}	[1, 4, 22, 38]
$m_1(0)$; $m_2(0)$	malaria parasite	10^7 parasite.ml^{-1}	[1, 4, 22, 38]

3. Preliminaries. The aim of this section is to derive preliminary remarks on (2.1)-(2.2). These results include the existence of the unique maximal semiflow bounded dissipative associated to this system. The second part of this section relies on technical material that will be used to prove our stability results.

3.1. Existence of semiflow and basic properties. In this section we shall deal with (2.1)-(2.2) using an integrated semigroup approach. This approach has been introduced by Thieme in [46] in the context of age-structured equations. We also refer to [12, 29, 33, 35, 36] and [47, 49] (see also the references cited therein).

Let us introduce the Banach space $\widehat{X} := \mathbb{R}^n \times L^1(0,\infty;\mathbb{R}^n)$ as well as its positive cone $\widehat{X}_+ = \mathbb{R}^n_+ \times L^1(0,\infty;\mathbb{R}^n_+)$ and the linear operator $\widehat{A} : D(\widehat{A}) \subset \widehat{X} \to \widehat{X}$ defined by

$$D(\widehat{A}) = \{0_{\mathbb{R}^n}\} \times W^{1,1}(0,\infty;\mathbb{R}^n),\ \widehat{A}\begin{pmatrix} 0_{\mathbb{R}^n} \\ \varphi \end{pmatrix} = \begin{pmatrix} -\varphi(0) \\ -\varphi' - \mu_x\varphi \end{pmatrix}. \tag{3.1}$$

Next consider the Banach space X and its positive cone X_+ defined by

$$X = \mathbb{R} \times \mathbb{R}^n \times \widehat{X} \text{ and } X_+ = \mathbb{R}_+ \times \mathbb{R}^n_+ \times \widehat{X}_+,$$

endowed with the usual product norm. Let $A : D(A) \subset X \to X$ be the linear operator defined by

$$D(A) = \mathbb{R} \times \mathbb{R}^n \times D\left(\widehat{A}\right),\quad A = \text{diag}\ \left(-\mu_x, -\mu_m, \widehat{A}\right). \tag{3.2}$$

Note that the domain of operator A is not dense in X because of the identity

$$\overline{D(A)} = \mathbb{R} \times \mathbb{R}^n \times \{0_{\mathbb{R}^n}\} \times L^1(0,\infty;\mathbb{R}^n) \neq X.$$

Finally let us introduce the nonlinear map $F : \overline{D(A)} \to X$ defined by

$$F\left((x,\mathbf{m},0_{\mathbb{R}^n},\mathbf{y})^T\right) = \left(\Lambda - xE_n^T\beta\mathbf{m}, \int_0^\infty \rho(a)\mathbf{y}(a)da - \delta\beta x\mathbf{m}, \beta x\mathbf{m}, 0_{L^1(0,\infty;\mathbb{R}^n)}\right)^T.$$

By identifying $u(t)$ together with $(x(t),\mathbf{m}(t),0_{\mathbb{R}^n},\mathbf{y}(t,.))^T$ and by setting $u_0 = (x_0,\mathbf{m}_0,0_{\mathbb{R}^n},\mathbf{y}_0(.))^T$, one obtains that System (2.1)-(2.2) re-writes as the following non-densely defined Cauchy problem:

$$\frac{du(t)}{dt} = Au(t) + F(u(t))\ t \geq 0 \text{ and } u(0) = u_0 \in \overline{D(A)} \cap X_+. \tag{3.3}$$

We first derive that the above abstract Cauchy problem generates a unique globally defined and positive semiflow. We set $X_0 = \overline{D(A)}$ and $X_{0+} = X_0 \cap X_+$ and the precise result is the following:

THEOREM 3.1. *Let Assumption 2.1 be satisfied. Then there exists a unique strongly continuous semiflow* $\{U(t) : X_{0+} \to X_{0+}\}_{t\geq 0}$ *such that for each* $u_0 \in X_{0+}$, *the map* $u \in C([0,\infty) : X_{0+})$ *defined by* $u = U(.)u_0$ *is a mild solution of (3.3), namely it satisfies*

$$\int_0^t u(s)ds \in D(A) \text{ and } u(t) = u_0 + A\int_0^t u(s)ds + \int_0^t F(u(s))ds,\ \forall t \geqslant 0.$$

Furthermore $\{U(t)\}_{t\geq 0}$ *satisfies the following properties:*

(i) Let $U(t)u_0 = (x(t), \mathbf{m}(t), 0_{\mathbb{R}^n}, \mathbf{y}(t,.))^T$*, then the following Voletrra integral formulation holds true*

$$\mathbf{y}(t,a) = \begin{cases} \mathbf{y}_0(a-t)e^{-\mu_x t} \text{ if } a \geq t \\ \beta x(t-a)\mathbf{m}(t-a)e^{-\mu_x a} \text{ if } a < t \end{cases},$$

coupled with the $x(t)$ *and* $\mathbf{m}(t)$ *equations of (2.1).*

(ii) For each $u_0 \in X_{0+}$ *one has for all* $t \geq 0$*:*

$$x(t) + \int_0^\infty E_n^T \mathbf{y}(t,a)da \leq x_0 + ||E_n^T \mathbf{y}_0||_{L^1} + \frac{\Lambda}{\mu_x},$$

$$E_n^T \mathbf{m}(t) \leq E_n^T \mathbf{m}_0 + \frac{1}{\mu_m^{min}} \left(x_0 + ||E_n^T \mathbf{y}_0||_{L^1} + \frac{\Lambda}{\mu_x} \right) \|\rho\|_{max}.$$

wherein we have set $\mu_m^{min} = \min_{1 \leqslant j \leqslant n} \mu_{m,j}$ *and* $\|\rho\|_{max} = \max_{1 \leqslant j \leqslant n} \|\rho_j\|_{L^\infty}$ *.*

(iii) The semiflow $\{U(t)\}_{t\geq 0}$ *is bounded dissipative and asymptotically smooth.*

Proof. The proof of this result is rather standard. Indeed it is easy to check that operator A satisfies the Hille-Yosida property. Then standard methodologies apply to provide the existence and uniqueness of mild solution for System (2.1)-(2.2). (see for instance [33, 35, 36, 47, 49]).

Next the Voletrra integral formulation is also standard in the context of age-structured equation and we refer to [26, 53] and the references cited therein for more details.

Estimates stated in (ii) directly follow from the system of equations. Let us assume for a moment that $\mathbf{y}_0 \in W^{1,1}(0,\infty;\mathbb{R}^n)$ then adding-up the x-equation together with the y_i-equations yields

$$\frac{d}{dt}\left(x(t) + \int_0^\infty E_n^T \mathbf{y}(t,a)da \right) = \Lambda - \mu_x \left(x(t) + \int_0^\infty E_n^T \mathbf{y}(t,a)da \right);$$

from where one deduces the first estimate of (ii) when $\mathbf{y}_0$ is smooth enough. Then a usual density argument coupled with the continuity of the semiflow with respect to the initial data yields to the conclusion for $\mathbf{y}_0 \in L^1(0,\infty;\mathbb{R}^n_+)$. Then the second estimate directly follows from the first one applied to the m_i-equations.

It remains to prove (iii) and let us notice that the bounded dissipativity of the semiflow $\{U(t)\}_{t\geq 0}$ is a direct consequence of (ii). To prove the asymptotically smoothness, let B be a forward invariant bounded subset of X_{0+}. According to the results in [43] it is sufficient to show that the semiflow is asymptotically compact on B.

Let us consider a sequence of solutions $\left\{ u_p = (x^p; \mathbf{m}^p, 0, \mathbf{y}^p)^T \right\}_{p\geq 0}$ that is equi-bounded in X_{0+} and let consider a sequence $\{t_p\}_{p\geq 0}$ such that $t_p \to +\infty$. Let us show that the sequence $\{u_p(t_p)\}_{p\geq 0}$ is relatively compact in X_{0+}. To do so, we consider the sequence of map $\{w_p(t) = u_p(t+t_p)\}_{p\geq 0}$. Since x_p and $\mathbf{m}_p$ are uniformly bounded in the Lipschitz norm, Arzela-Ascoli theorem implies that, possibly along a sub-sequence, one may assume that $x_p(t+t_p) \to \widehat{x}$ and $\mathbf{m}_p(t+t_p) \to \widehat{\mathbf{m}}(t)$ locally uniformly for $t \in \mathbb{R}$. It remains to deal with the sequence $\{\mathbf{y}^p(t_p,.)\}_{p\geq 0}$. Let us denote by $\widetilde{\mathbf{y}}_p(t,.) = \mathbf{y}_p(t+t_p,.)$. Using the Volterra integral formulation one gets

$$\widetilde{\mathbf{y}}_p(t,a) = \begin{cases} \mathbf{y}_0(a-t+t_p)e^{-\mu_x(t+t_p)} \text{ if } a \geq t+t_p \\ \beta x_p(t-a+t_p)\mathbf{m}_p(t-a+t_p)e^{-\mu_x a} \text{ if } a < t+t_p \end{cases}, \quad (3.4)$$

Finally sine $\beta x_p(t-a+t_p)\mathbf{m}_p(t-a+t_p)e^{-\mu_x a}$ convergences as $p\to\infty$ towards some function $\xi(t,a)=\beta\widehat{x}(t-a)\widehat{\mathbf{m}}(t-a)e^{-\mu_x a}$ locally uniformly, one easily concludes that

$$\mathbf{y}_p(t_p,.)=\widetilde{\mathbf{y}}_p(0,.)\to\beta\widehat{x}(-.)\widehat{\mathbf{m}}(-.)e^{-\mu_x\cdot}\text{ in }L^1\left(0,\infty;\mathbb{R}^n\right).$$

The result follows. □

Now in order to deal with sub-system, it will be also convenient to introduce for each $J\subset\mathbb{N}_n$ the closed subspaces $X^J\subset X$ and $X_0^J\subset X_0$ defined by

$$X^J=\left\{(x,\mathbf{m},\alpha;\mathbf{y})^T\in X:\ m_i+\int_0^\infty y_i(a)da=0,\ \ \forall i\in J\right\}\text{ and }X_0^J=X^J\cap X_0.$$

We also introduce X_{0+}^J, the positive cone of X_0^J defined by $X_{0+}^J=X_0^J\cap X_{0+}$. If $J=\emptyset$ then $X^J=X$, $X_0^J=X_0$ and $X_{0+}^J=X_{0+}$. Recalling definition (3.2), note that $A(D(A)\cap X_0^J)\subset X^J$. In the sequel we shall denote by $A_J:D(A_J)\subset X^J\to X^J$ the linear Hile Yosida operator defined by

$$D(A_J)=D(A)\cap X_0^J,\ \ A_Jx=Ax,\ \ \forall x\in D(A)\cap X_0^J. \tag{3.5}$$

For each $i\in\mathbb{N}_n$ we also consider

$$M_0^i=\left\{(x,\mathbf{m},\alpha;\mathbf{y})^T\in X_{0+}:\ m_i+\int_0^\infty y_i(a)da>0\right\}.$$

Then the following lemma holds true

Lemma 3.2. *For each $J\subset\mathbb{N}_n$ and each $i\in\mathbb{N}_n$, the subsets $X_{0+}^J\subset X_{0+}$ and M_0^i are both positively invariant under the semiflow $\{U(t)\}_{t\geq0}$; in other words*

$$U(t)M_0^i\subset M_0^i\text{ and }U(t)X_{0+}^J\subset X_{0+}^J\ \ \forall t\geq0.$$

Proof. To prove the above result, let $i\in\mathbb{N}_n$ be given. Let $u_0:=(x_0;\mathbf{m}_0;0_{\mathbb{R}^n};\mathbf{y}_0)\in M_0^i$ be given and let us denote for each $t\geq0$, $U(t)u_0:=(x(t);\mathbf{m}(t);0_{\mathbb{R}^n},\mathbf{y}(t,.))^T$ the orbit passing through u_0. Let us set $p_i(t)=m_i(t)+\int_0^\infty y_i(t,a)da$. It comes that $p_i'(t)\geq-\max(\mu_x,\mu_{mi})p_i(0)$. That is

$$m_i(t)+\int_0^\infty y_i(t,a)da\geq e^{-\max(\mu_x,\mu_{mi})t}\left(m_{0i}+\int_0^\infty y_{0i}(a)da\right).$$

This complete the fact that $U(t)M_0^i\subset M_0^i$.
Now, let $u_0\in\partial M_0^i$. Using the Volterra formulation we easily find that $m_i(t)=0$ for all $t\geq0$ and

$$\int_0^\infty y_i(t,a)da=\beta_1\int_0^t x(t-a)m_i(t-a)e^{-\mu_x a}da+e^{-\mu_x t}||y_{0i}||_{L^1}=0.$$

Therefore $U(t)\partial M_0^i\subset\partial M_0^i$ for all $t\geq0$. This ends the proof of the lemma. □

Then coupling Theorem 3.1 together with the results of Hale [18, 19], Hale et al. [20] , one obtains the following proposition:

Proposition 3.3. *Let $J\subset\mathbb{N}_n$ be given. There exists a non-empty compact set $\mathcal{A}_J\subset X_{0+}^J$ such that* *(i)* $\mathcal{A}_J$ *is invariant under the semiflow* $\left\{U_J(t) := U(t)|_{X_{0+}^J}\right\}_{t\geq 0}$.

(ii) The subset $\mathcal{A}_J$ *attracts the bounded sets of* X_{0+}^J *under the semiflow* U_J.

Next the following proposition describes the equilibria of the model.

Proposition 3.4. *Let Assumption 2.1 be satisfied. Assume furthermore that the set* $\mathcal{S}$ *is strictly ordered. Then System (2.1) (or semiflow* $\{U(t)\}_{t\geq 0}$ *provided by Theorem 3.1) has exactly* $1 + \text{card}\,\mathcal{S}$ *stationary states:*

(i) *The disease free equilibrium defined by*

$$u_0^* = \left(x_f; 0_{\mathbb{R}^n}; 0_{\mathbb{R}^n}, 0_{L_1(0,\infty;\mathbb{R}^n)}\right)^T \in X_{0+}^{\mathbb{N}_n}, \quad x_f = \frac{\Lambda}{\mu_x},$$

is an equilibrium of U *and it is the only one when* $\mathcal{S} = \emptyset$.

(ii) *When* $\mathcal{S} \neq \emptyset$ *the semiflow* U *has exactly* card $\mathcal{S}$ *endemic stationary states defined for each* $k \in \mathcal{S}$ *by*

$$u_k^* = \left(x_e^k, \mathbf{m}_e^k, 0_{\mathbb{R}^n}, \mathbf{y}_e^k\right)^T \in X_{0+}^{\mathbb{N}_n\setminus\{k\}} \cap M_0^k,$$

wherein the above quantities are defined in (2.7).

The proof of this result follows from straightforward algebra. The details are left to the reader.

3.2. Technical materials. In this subsection we establish some properties of the entire solutions of System (2.1). These properties will be useful later to derive the asymptotic behaviour of (2.1) especially when $\mathcal{S} \neq \emptyset$.

Our first result is concerned with spectral properties of the linearized semiflow $U_J := U|_{X_{0+}^J}$ for some given subset $J \subset \mathbb{N}_n$ at an given stationary point $u^* \in \partial M_0^J$. Let $u^* = (x^*, \mathbf{m}^*, 0_{\mathbb{R}^n}, \mathbf{y}^*)^T \in X_{0+}^J$ be a given stationary state of the semiflow U_J. The associated linearized equation at the point u^* reads as

$$\frac{du(t)}{dt} = (A_J + B_{u^*})u(t);$$

where A_J is the linear operator defined in (3.5) while $B_{u^*} \in \mathcal{L}\left(X_0^J, X^J\right)$ is the bounded linear operator defined by:

$$B_{u^*}\begin{pmatrix} x \\ \mathbf{m} \\ 0_{\mathbb{R}^n} \\ \mathbf{y} \end{pmatrix} = \begin{pmatrix} -x^* E_n^T \beta \mathbf{m} - x E_n^T \beta \mathbf{m}^* \\ \int_0^\infty \rho(a)\mathbf{y}(a)da - \delta\beta(x^*\mathbf{m} + x\mathbf{m}^*) \\ x^*\beta\mathbf{m} + x\beta\mathbf{m}^* \\ 0_{L^1(0,\infty,\mathbb{R}^n)} \end{pmatrix}$$

Lemma 3.5. *Let* $J \subset \mathbb{N}_n$ *be given. Let us set* $\Omega = \{\lambda \in \mathbb{C} :\ \text{Re}\,(\lambda) > -\mu_x\}$. *Then the spectrum* $\sigma(A_J + B_{u^*}) \cap \Omega$ *only consists in point spectrum and one has*

$$\sigma(A_J + B_{u^*}) \cap \Omega = \left\{\lambda \in \Omega :\ \Delta^J(\lambda, u^*) = 0\right\},$$

where function $\Delta^J(., u^*) : \Omega \to \mathbb{C}$ *is defined by*

$$\Delta^J(\lambda, u^*) = \prod_{i\in\mathbb{N}_n\setminus J} \chi_i(\lambda, x^*),$$

while for each $i \in \mathbb{N}_n$ *and each* $x \in \mathbb{R}$, *function* $\chi_i(.,x) : \Omega \to \mathbb{C}$ *is defined by*

$$\chi_i(\lambda, x) = 1 - \frac{\beta_i x}{\lambda + \mu_{mi}} \left[\int_0^\infty \rho_i(a) e^{-(\lambda+\mu_x)a} da - \delta_i \right]. \tag{3.6}$$

Proof. Let $J \subset \mathbb{N}_n$ be given. Let us denote by A_{0J} the part of A_J in X_0^J. Then it is the infinitesimal generator of a C_0-semigroup on X_0^J denoted by $\{T_{A_{0J}}(t)\}_{t\geq 0}$. Next it is easy to check that the essential growth rate of this semigroup satisfies $\omega_{0,ess}(A_{0J}) \leq -\mu_x$. Then since operator B_{u^*} is compact, the results in [11, 49] apply and provided that the essential growth rate of $\left\{T_{(A_J+B_{u^*})_0}(t)\right\}_{t\geq 0}$, the C_0-semigroup generated by the part of $(A_J + B_{u^*})$ in X_0^J satisfies $\omega_{0,ess}\left((A_J + B_{u^*})_0\right) \leq -\mu_x$. Applying the result in [36] (see also [13] and [54]), the latter inequality ensures that $\Omega \cap \sigma(A_J + B_{u^*})$ is only composed of point spectrum of $(A_J + B_{u^*})$.

It remains to derive the characteristic equation. However this part is also standard and we refer for instance to [5, 32, 37]. □

Our next result relies on properties of the entire solutions of System (2.1)

Lemma 3.6. *Let* $\left\{u(t) = (x(t), \mathbf{m}(t), 0_{\mathbb{R}^n}, \mathbf{y}(t,.))^T\right\}_{t\in\mathbb{R}}$ *be a given entire solution of the semiflow* U. *Then* x *satisfies*

$$\inf_{t\in\mathbb{R}} x(t) > 0. \tag{3.7}$$

Furthermore the following properties holds true:

(i) If there exist $i \in \mathbb{N}_n$ *and* $t_0 \in \mathbb{R}$ *such that* $u(t_0) \in M_0^i$ *then* $m_i(t) > 0$, $\forall t \in \mathbb{R}$ *and* $y_i(t,a) > 0$ *for any* $(t,a) \in \mathbb{R} \times [0,\infty)$.

(ii) Assume that $\mathcal{S} \neq \emptyset$ *and assume there exist* $i \in \mathcal{S}$ *and* $t_0 \in \mathbb{R}$ *such that* $u(t_0) \in M_0^i$. *If* $u(t) \to u^*$ *as* $t \to \infty$ *where* u^* *is an equilibrium point of* U. *Then one has* $u^* \in \left\{u_j^* : i \trianglelefteq j\right\}$.

(iii) For each $i \in \mathbb{N}_n$ *there exist a constant* $M_i > 1$ *such that*

$$\frac{m_i^-(t)}{M_i} e^{-\mu_x a} \leq y_i(t,a) \leq M_i e^{-\mu_x a};\ \forall (t,a) \in \mathbb{R} \times [0,\infty),$$

wherein we have set $m_i^-(t) = \inf_{s\leq t} m_i(s)$.

Proof. Let us first notice that since u is an entire solution then

$$\mathbf{y}(\sigma, a) = \beta x(\sigma - a)\mathbf{m}(\sigma - a)e^{-\mu_x a}\ \ \forall(\sigma, a) \in \mathbb{R} \times [0,\infty). \tag{3.8}$$

This expression directly follows from the Volterra integral formulation in Theorem 3.1.

From the estimates provided in Theorem 3.1 and the x-equation there exists some constant $C > 0$ such that for each $s \in \mathbb{R}$ and $t \geq 0$ one has

$$x(s)e^{-Ct} + \Lambda \int_0^t e^{-C(t-l)} dl \leq x(t+s) \leq x(s) + \frac{\Lambda}{\mu_x}. \tag{3.9}$$

This implies that $\inf_{t\in\mathbb{R}} x(t) > 0$ and complete the proof of (3.7).
We now turn to the proof of (i). Let us argue by contradiction by assuming that there exists $t_1 \in \mathbb{R}$ such that $m_i(t_1) = 0$. Then from the m_i-equation we deduce that $m_i(t) = 0$ for all $t \leq t_1$. Next we infer from (3.8) that $\int_0^\infty y_i(t,a)da = 0$ for any $t \leq t_1$. Hence $m_i(t) + \int_0^\infty y_i(t,a)da \equiv 0$, a contradiction with the existence of t_0. On

the other hand, due to (3.9) and (3.7), if there exists $(t_1, a_1) \in \mathbb{R} \times [0, \infty)$ such that $y_i(t_1, a_1) = 0$ then $m_i(t_1 - a_1) = 0$ and the first part of the argument applies.

Let us now prove (ii). Let us first notice that since $m_i(t_0) + \int_0^\infty y_i(t_0, a)da > 0$, (i) implies that $m_i(t) > 0$ for all $t \in \mathbb{R}$ and $y_i(t, a) > 0$ for all $(t, a) \in \mathbb{R} \times [0, \infty)$. Next consider the function $\Gamma_i(a) = \int_a^\infty \rho_i(s)e^{\mu_x(a-s)}ds$ and note that $\Gamma_i \in L^\infty(0, \infty, \mathbb{R})$ and satisfies $\Gamma_i'(a) - \mu_x\Gamma_i(a) + \rho_i(a) = 0$ *a.e.* $a \geq 0$. Let us introduce the functional

$$\Phi_i[u](t) = \int_0^\infty \Gamma_i(a)y_i(t, a)da + m_i(t),$$

that satisfies (recalling Definition (2.3))

$$\frac{d\Phi_i[u](t)}{dt} = \mu_{mi}m_i(t)\left[\mathcal{T}_0^i\frac{x(t)}{x_f} - 1\right], \quad \forall t \in \mathbb{R}. \tag{3.10}$$

Using this computation we will obtain a contradiction by assuming that $u(t) \to u_j^*$ as $t \to \infty$ for some $j \lhd i$. Indeed for $j = 0$ then $u(t) \to u_0^*$ as $t \to \infty$ implies that $x(t) \to x_f$ as $t \to \infty$. Then since $\mathcal{T}_0^i > 1$ then function $t \mapsto \Phi_i[u](t)$ is not decreasing for t large enough. Hence there exists $t_0 \in \mathbb{R}$ such that $\Phi_i[u](t) \geq \Phi_i[u](t_0)$ for all $t \geq t_0$. Since $\Phi_i[u](t_0) > 0$, this prevents the component (y_i, m_i) to converge to $(0, 0_{L^1})$ as $t \to \infty$. A contradiction with $u(t) \to u_0^*$.
The same argument holds for $j \in \mathcal{S}$ with $j \lhd i$. Indeed in such a case $x(t) \to x_e^j$ as $t \to \infty$ and since

$$\left[\mathcal{T}_0^i\frac{x_e^j}{x_f} - 1\right] = \frac{\mathcal{T}_0^i}{\mathcal{T}_0^j} - 1 > 0,$$

the same arguments apply. This completes the proof of (ii).

Finally note that (iii) directly follows from (3.7) and (3.8). This ends the proof of Lemma 3.6. □

Our next lemma is a computation result will be used in the sequel to perform Lyapunov arguments.

Lemma 3.7. *Let us assume that the same assumptions of Lemma 3.6 are satisfied. Let $h : (0, \infty) \to [0, \infty)$ be the function defined by*

$$h(s) = s - 1 - \ln s. \tag{3.11}$$

Let us assume that there exists $i_0 \in \mathcal{S}$ such that

$$\liminf_{t \to -\infty} m_{i_0}(t) > 0. \tag{3.12}$$

Then;
(i) For each $t \in \mathbb{R}$ one has

$$\left[\int_.^\infty \rho_{i_0}(s)l(s)ds\right] h\!\left(\frac{y_{i_0}(t, .)}{y_{ei_0}^{i_0}(.)}\right) \in L^1(0, \infty, \mathbb{R}). \tag{3.13}$$

(ii) Consider now the map $V_{i_0}[u] : \mathbb{R} \to [0, \infty)$ defined by

$$V_{i_0}[u](t) := W_{i_0}(t) + \sum_{j=1; j\neq i_0}^{p} \int_0^\infty f_j(a)y_j(t, a)da + \sum_{j=1; j\neq i_0}^{p} d_jm_j(t), \tag{3.14}$$

wherein we have set $W_{i_0}(t) = V_x(t) + V_{y_{i_0}}(t) + V_{m_{i_0}}(t)$ *and*

$$V_x(t) = h\left(\frac{x(t)}{x_e^{i_0}}\right); \quad V_{y_{i_0}}(t) = \int_0^\infty \alpha_{i_0}(a)\, h\left(\frac{y_{i_0}(t,a)}{y_{ei_0}^{i_0}(a)}\right) da; \quad V_{m_{i_0}}(t) = d_{i_0}\, h\left(\frac{m_{i_0}(t)}{m_{ei_0}^{i_0}}\right)$$

and

$$d_{i_0} = \frac{\beta_{i_0} m_{ei_0}^{i_0}}{\mu_{mi_0}}; \quad d_j = \frac{\beta_j}{\mu_{mj}}, \quad \textit{with } j \neq i_0; \tag{3.15}$$

$$f_j(a) = \frac{\beta_j}{\mu_{mj}} \int_a^\infty \rho_j(s) e^{-\mu_x(s-a)} ds; \ \textit{and } \alpha_{i_0}(a) = \frac{\beta_{i_0}^2 x_e^{i_0} m_{ei_0}^{i_0}}{\mu_{mi_0}} \int_a^\infty \rho_{i_0}(a) l(a) da. \tag{3.16}$$

Then function $t \mapsto V_{i_0}[u](t)$ *is of the class* C^1 *on* $\mathbb{R}$ *and we have*

$$\begin{aligned} \dot{V}_{i_0}[u](t) = & -\frac{\Theta_{i_0}}{x_e^{i_0} x(t)} \left(x(t) - x_e^{i_0}\right)^2 + \frac{x(t)}{x_e^{i_0}} \sum_{j=1; j\neq i_0}^{p} \left(\frac{\mathcal{T}_0^j}{\mathcal{T}_0^{i_0}} - 1\right) \beta_j m_j(t) \\ & - \int_0^\infty \frac{\beta_{i_0}^2 x_e^{i_0} m_{ei_0}^{i_0}}{\mu_{mi_0}} \rho_{i_0}(a) l(a) \left[h\left(\frac{y_{i_0}(t,a) m_{ei_0}^{i_0}}{y_{ei_0}^{i_0}(a) m_{i_0}(t)}\right) + h\left(\frac{m_{i_0}(t) y_{ei_0}^{i_0}(0)}{m_{ei_0}^1 y_{i_0}(t,0)}\right)\right] da; \end{aligned}$$

with

$$\Theta_{i_0} = \mu_x - \delta_{i_0} \frac{\beta_{i_0}^2 x_e^{i_0} m_{ei_0}^{i_0}}{\mu_{mi_0}}. \tag{3.17}$$

Proof. (i) Let us first remark that (3.13) follows from the estimate provided by Lemma 3.6 (*iii*) as well as (3.12). Indeed function $a \mapsto \int_a^\infty \rho_{i_0}(s) l(s) ds$ satisfies

$$\int_0^\infty a \int_a^\infty \rho_{i_0}(s) l(s) ds ds < \infty.$$

(ii) Next note that function $t \mapsto V_{i_0}[u](t)$ is also well defined for each $t \in \mathbb{R}$ because of (3.7), Lemma 3.6 (*i*) and finally because of $f_j \in L^\infty(0,\infty)$ (see Definition (3.16)).

It now remains to compute the derivation of $t \mapsto V_{i_0}[u](t)$ (that is obviously of the class C^1 on $\mathbb{R}$ since u is an entire solution).

Firstly one has

$$\begin{aligned} \dot{V}_x(t) = & \frac{\Lambda}{x_e^{i_0}} + \mu_x - \mu_x \frac{x(t)}{x_e^{i_0}} - \frac{\Lambda}{x(t)} - \beta_{i_0} m_{ei_0}^{i_0} \frac{y_{i_0}(t,0)}{y_{ei_0}^{i_0}(0)} + \beta_{i_0} m_{i_0}(t) \\ & + \left(1 - \frac{x(t)}{x_e^{i_0}}\right) \sum_{j=1; j\neq i_0}^{p} \beta_j m_j(t). \end{aligned} \tag{3.18}$$

Secondly using the $y_{i_0}-$equation and integration by parts, simple algebra leads to

$$\dot{V}_{y_{i_0}}(t) = \alpha_{i_0}(0) h\left(\frac{y_{i_0}(t,0)}{y_{ei_0}^{i_0}(0)}\right) + \int_0^\infty \alpha_{i_0}'(a) h\left(\frac{y_{i_0}(t,a)}{y_{ei_0}^{i_0}(a)}\right) da.$$

Moreover we infer from the definition of α_{i_0} (see (3.16))

$$\dot{V}_{y_{i_0}}(t) = \int_0^\infty \frac{\beta_1^2 x_e^{i_0} m_{ei_0}^{i_0}}{\mu_{mi_0}} \rho_{i_0}(a) l(a) \left[h\left(\frac{y_{i_0}(t,0)}{y_{ei_0}^{i_0}(0)}\right) - h\left(\frac{y_{i_0}(t,a)}{y_{ei_0}^{i_0}(a)}\right)\right] da. \tag{3.19}$$

Next one can also check that

$$\begin{aligned}\dot{V}_{m_{i_0}}(t) = &\int_0^\infty d_{i_0}\delta_{i_0}\beta_{i_0}x_e^{i_0}\rho_{i_0}(a)l(a)\frac{y_{i_0}(t,a)}{y_{ei_0}^{i_0}(a)}da - \frac{d_{i_0}\mu_{mi_0}}{m_{ei_0}^{i_0}}m_{i_0}(t)\\ &- d_{i_0}\delta_{i_0}\beta_{i_0}x_e^{i_0}\frac{y_{i_0}(t,0)}{y_{ei_0}^{i_0}(0)} - \frac{d_{i_0}}{m_{i_0}(t)}\int_0^\infty \rho_{i_0}(a)y_{i_0}(t,a)da\\ &+ d_{i_0}\delta_{i_0}\beta_{i_0}x(t) + d_{i_0}\mu_{mi_0}.\end{aligned} \tag{3.20}$$

Using the fact that

$$\int_0^\infty \frac{\beta_{i_0}^2 x_e^{i_0}m_{ei_0}^{i_0}}{\mu_{mi_0}}\rho_{i_0}(a)l(a)da - \beta_{i_0}m_{ei_0}^{i_0} - d_{i_0}\delta_{i_0}\beta_{i_0}x_e^{i_0} = 0,$$

we infer from (3.18)-(3.20) that

$$\begin{aligned}\dot{W}_{i_0}(t) =&\frac{\Lambda}{x_e^{i_0}} + \mu_x + d_{i_0}\mu_{mi_0} - 2\frac{\beta_{i_0}^2 x_e^{i_0}m_{ei_0}^{i_0}}{\mu_{mi_0}}K_{i_0} + (d_{i_0}\delta_{i_0}\beta_{i_0}x_e^{i_0} - \mu_x)\frac{x(t)}{x_e^{i_0}}\\ &+ \left(\frac{K_{i_0}\beta_{i_0}^2 x_e^{i_0}m_{ei_0}^{i_0}}{\mu_{mi_0}} - \frac{\Lambda}{x_e^{i_0}}\right)\frac{x_e^{i_0}}{x(t)} + \left(1 - \frac{x(t)}{x_e^{i_0}}\right)\sum_{j=1;j\neq i_0}^{p}\beta_j m_j(t)\\ &- \int_0^\infty \frac{\beta_{i_0}^2 x_e^{i_0}m_{ei_0}^{i_0}}{\mu_{mi_0}}\rho_{i_0}(a)l(a)\left[h\left(\frac{y_{i_0}(t,a)m_{ei_0}^{i_0}}{y_{ei_0}^{i_0}(a)m_{i_0}(t)}\right) + h\left(\frac{m_{i_0}(t)y_{ei_0}^{i_0}(0)}{m_{ei_0}^{i_0}y_{i_0}(t,0)}\right)\right]da.\end{aligned}$$

Since EE_{i_0} is an equilibrium of system (2.1) one gets

$$\begin{aligned}\dot{W}_{i_0}(t) =& -\frac{\Theta_{i_0}}{x_e^{i_0}x(t)}\left(x(t) - x_e^{i_0}\right)^2 + \left(1 - \frac{x(t)}{x_e^{i_0}}\right)\sum_{j=1;j\neq i_0}^{p}\beta_j m_j(t)\\ &- \int_0^\infty \frac{\beta_{i_0}^2 x_e^{i_0}m_{ei_0}^{i_0}}{\mu_{mi_0}}\rho_{i_0}(a)l(a)\left[h\left(\frac{y_{i_0}(t,a)m_{ei_0}^{i_0}}{y_{ei_0}^{i_0}(a)m_{i_0}(t)}\right) + h\left(\frac{m_{i_0}(t)y_{ei_0}^{i_0}(0)}{m_{ei_0}^{i_0}y_{i_0}(t,0)}\right)\right]da,\end{aligned}$$

with Θ_{i_0} defined in (3.17). Using the fact that $f_j'(a) - \mu_x f_j(a) + d_j\rho_j(a) = 0$ for all $a \geq 0$ and $\delta_j d_j + \frac{1}{x_f} - f_j(0) = \frac{1-\mathcal{T}_0^j}{x_f}$, one has

$$\begin{aligned}\dot{V}_{i_0}[u](t) = &-\frac{\Theta_{i_0}}{x_e^{i_0}x(t)}\left(x(t) - x_e^{i_0}\right)^2 + \frac{x(t)}{x_e^{i_0}}\sum_{j=1;j\neq i_0}^{p}\left(\frac{\mathcal{T}_0^j}{\mathcal{T}_0^{i_0}} - 1\right)\beta_j m_j(t)\\ - &\int_0^\infty \frac{\beta_{i_0}^2 x_e^{i_0}m_{ei_0}^{i_0}}{\mu_{mi_0}}\rho_{i_0}(a)l(a)\left[h\left(\frac{y_{i_0}(t,a)m_{ei_0}^{i_0}}{y_{ei_0}^{i_0}(a)m_{i_0}(t)}\right) + h\left(\frac{m_{i_0}(t)y_{ei_0}^{i_0}(0)}{m_{ei_0}^{1}y_{i_0}(t,0)}\right)\right]da.\end{aligned}$$

This ends the proof of the lemma. □

4. Proof of Theorem 2.2 (i)**.** The aim of this section is to prove the first part of Theorem 2.2. By using all the above introduced definitions and notations, this result can be reformulated as follows:

PROPOSITION 4.1. *Let Assumption 2.1 be satisfied. Then the following holds true:*

$$\lim_{t\to\infty} U_{\mathcal{S}}(t)x = u_0^*,$$

for each $x \in X_{0+}^{\mathcal{S}}$ and where $U_{\mathcal{S}}$ denotes the restriction semiflow U at $X_{0+}^{\mathcal{S}}$.

Remember that if $\mathcal{S} = \emptyset$, namely $\mathcal{T}_0 \leq 1$ then $X_{0+}^{\mathcal{S}} = X_{0+}$ and $U_{\mathcal{S}} \equiv U$. This remark means that when $\mathcal{T}_0 \leq 1$ then the disease free equilibrium is globally attractive.

The proof of this result relies on the construction of a suitable Lyapunov functional on the entire solution of $U_{\mathcal{S}}$.

Proof. Let us consider $\mathcal{A}_{\mathcal{S}} \subset X_{0+}^{\mathcal{S}}$ the global compact attractor of $U_{\mathcal{S}}$ provided by Proposition 3.3. Let $x \in \mathcal{A}_{\mathcal{S}}$ be given and let $\{u(t)\}_{t\in\mathbb{R}} \subset \mathcal{A}_{\mathcal{S}}$ be an entire solution of $U_{\mathcal{S}}$ such that $u(0) = x$. Recalling that from Lemma 3.6 (iii), $\inf_{t\in\mathbb{R}} x(t) > 0$, one may consider the functional V defined for each entire solutions by

$$V[u](t) = h\left(\frac{x}{x_f}\right) + \sum_{j=1}^{n} \int_0^\infty f_j(a) y_j(a) da + \sum_{j=1}^{n} d_j m_j,$$

where the positives constants d_j and the functions f_j are defined respectively by (3.15) and (3.16) while function h is given in (3.11).

Next using System (2.1) we obtain

$$\frac{d\,V[u](t)}{dt} = -\mu_x \frac{(x(t) - x_f)^2}{x(t)} - \sum_{j=1}^{n}(d_j \mu_{mj} - \beta_j) m_j(t) - \sum_{j=1}^{n}\left(\delta_j d_j + \frac{1}{x_f}\right)\beta_j x(t) m_j(t)$$
$$+ \sum_{j=1}^{n} d_j \int_0^\infty \rho_j(a) y_j(t,a) da - \sum_{j=1}^{n} \int_0^\infty f_j(a) e^{-\mu_x a} (\partial_a y_j(t,a) e^{\mu_x a} + \mu_x e^{\mu_x a} y_j(t,a)) da.$$

Integrating by part the last integral of the previous equality, using the y_j-boundary condition of (2.1) together with $f_j'(a) - \mu_x f_j(a) + d_j \rho_j(a) = 0$ for all $a \geq 0$, one obtains recalling $\{u(t)\}_{t\in\mathbb{R}} \subset X_{0+}^{\mathcal{S}}$ that

$$\frac{d\,V[u](t)}{dt} = -\mu_x \frac{(x(t) - x_f)^2}{x(t)} - x(t) \sum_{j\in\mathbb{N}_n\setminus\mathcal{S}} \frac{1 - \mathcal{T}_0^j}{x_f} \beta_j m_j(t). \tag{4.1}$$

Hence we infer from the definition of $\mathcal{S}$ that $t \mapsto V[u](t)$ is decreasing along the entire solutions of $U_{\mathcal{S}}$. To conclude our proof let $\{t_n\}_{n\geq 0}$ be an increasing sequence tending to $-\infty$ as $n \to \infty$ and consider the sequence of map $u_n(t) = u(t + t_n)$. Note that one has $V[u_n](t) = V[u](t + t_n)$. Up to a subsequence one may assume that $u_n(t) \to \widehat{u}(t)$ as $n \to \infty$ locally uniformly for $t \in \mathbb{R}$ where $\{\widehat{u}(t)\}_{t\in\mathbb{R}} \subset \mathcal{A}_{\mathcal{S}}$ is an entire solution of $U_{\mathcal{S}}$. Since V is decreasing, one obtains that

$$V\left[\widehat{u}\right](t) \equiv \lim_{t\to-\infty} V[u](t) = \sup_{t\in\mathbb{R}} V[u](t).$$

By setting $\widehat{u} = (\widehat{x}, \widehat{\mathbf{m}}, 0, \widehat{\mathbf{y}})^T$, (4.1) yields to $\widehat{x}(t) \equiv x_f$ while the $x-$equation provides that $\widehat{\mathbf{m}}(t) \equiv 0$ so that $\widehat{\mathbf{y}}(t,.) \equiv 0$. Hence $V\left[\widehat{u}\right](t) \equiv 0$ and $0 \leq V[u](t) \leq 0$ for $t \in \mathbb{R}$ and $u(t) \equiv u_0^*$. This completes the proof of Proposition 4.1.
□

5. Proof of Theorem 2.2 (ii)**.** The aim of this section is to prove Theorem 2.2 (ii). For this reason, we will assume throughout this section that $\mathcal{S} \neq \emptyset$. The proof of this result will follow an induction argument. To be more specific we will study the behaviour of the semiflow $U_{\mathcal{S}\setminus J}$ for each subset $J \subset \mathcal{S}$ using card $J \in \{1, .., \text{card}\,\mathcal{S}\}$ as the induction parameter.

The precise result we will prove in the following:

THEOREM 5.1. *Let us assume that the assumptions of Theorem 2.2 are satisfied. Assume that* $\mathcal{S} \neq \emptyset$. *Then for each* $J \subset \mathcal{S}$ *the semiflow* $\left\{U_{\mathcal{S}\setminus J}(t)\right\}_{t\geq 0}$ *satisfies for each* $x \in X_{0+}^{\mathcal{S}\setminus J}$:

(i) if $\mathcal{J}(x) := J \cap \left\{i \in \mathbb{N}_n : x \in M_0^i\right\} = \emptyset$ *then* $x \in X_{0+}^{\mathcal{S}}$ *and*

$$\lim_{t\to\infty} U_{\mathcal{S}\setminus J}(t)x = u_0^*,$$

(ii) If $\mathcal{J}(x) \neq \emptyset$ *we set* $i = \max^{\lhd} \mathcal{J}(x)$ *and one has*

$$\lim_{t\to\infty} U_{\mathcal{S}\setminus J}(t)x = u_i^*.$$

Let us first notice that point (i) in the above theorem is a direct consequence of Theorem 2.2 (i) (see Proposition 4.1). As a consequence, it is sufficient to prove (ii) and let us notice that Theorem 2.2 (ii) corresponds to Theorem 5.1 with $J = \mathcal{S}$. As mentioned above, the proof of this result relies on an induction argument on card J. In the sequel we shall investigate the case where card $J = 1$ and we will then show how such a property is inherited.

5.1. Case card $J = 1$**.** Let $i \in \mathcal{S}$ be given. For notational simplicity we consider the set $Y_{0+} = X_{0+}^{\mathcal{S}\setminus\{i\}}$ and let us denote by $\left\{V(t) := U_{\mathcal{S}\setminus\{i\}}(t)\right\}_{t\geq 0}$. We also consider the sets

$$N_0 = Y_{0+} \cap M_0^i \text{ and } \partial N_0 = Y_{0+} \setminus N_0 = X_{0+}^{\mathcal{S}}.$$

Before constructing a suitable Lyapunov function to study the asymptotic behaviour of $V(t)x$ for some $x \in N_0$ let us first collect in the following lemma some properties of the semiflow $\{V(t)\}_{t\geq 0}$:

LEMMA 5.2. *Under the assumption of Theorem 5.1, the semiflow* $\{V(t)\}_{t\geq 0}$ *satisfies the following properties:*

(i) It is bounded dissipative and asymptotically smooth; N_0 *and* ∂N_0 *are both positively invariant under* V.

(ii) For each $x \in \partial N_0$ *one has* $V(t)x \to u_0^*$.

(iii) The semiflow V *is uniformly persistent with respect to the pair* $(N_0, \partial N_0)$ *in the sense that there exists* $\varepsilon > 0$ *such that for each* $x \in N_0$:

$$\liminf_{t\to\infty} d\left(U(t)x; \partial N_0\right) \geq \varepsilon.$$

Proof. Note that (i) directly follows from Theorem 3.1 (ii), (iii) and Lemma 3.2 while (ii) directly follows from Theorem 5.1 (i). It remains to prove (iii). To do so we will apply Theorem 4.2 in [20]. Let us first notice that u_0^* is an unstable stationary state with respect to the semiflow V. Indeed as an application of Lemma 3.5 we know that the eigenvalues in Ω of the linearized semiflow V at u_0^* are given the resolution of the equation $\Delta^{\mathcal{S}\setminus\{i\}}(\lambda, u_0^*) = 0$. On the other hand these eigenvalues contain the roots of the equation $\chi_i(\lambda, u_0^*) = 0$ (see (3.6)). Note that function $\chi_i(., u_0^*)$ satisfies

$$\chi_i(0, u_0^*) = 1 - \mathcal{T}_0^i < 0 \text{ and } \lim_{\lambda\to\infty} \chi_i(\lambda, u_0^*) = 1,$$

that ensures the existence of a strictly positive eigenvalue. The instability of u_0^* with respect to V follows.

Applying Theorem 4.2 in [20] to complete the proof of Lemma 5.2 (*iii*) it is sufficient to show that $W^s(\{u_0^*\}) \bigcap N_0 = \emptyset$ wherein we have set $W^s(\{u\}) = \{v \in Y_{0+} : \lim_{t\to+\infty} V(t)v = u\}$. To prove this assertion, let us argue by contradiction by assuming that there exists $x \in W^s(\{u_0^*\}) \bigcap N_0$. Then using the same computations as in Lemma 3.6 (*ii*), since $\mathcal{T}_0^i > 1$ one obtains that the function

$$\Phi[V(t)x] := \int_0^\infty \Gamma_i(a) y_i(t,a) da + m_i(t) \text{ with } \Gamma_i(a) := \int_a^\infty \rho_i(s) e^{a-s} ds,$$

is increasing for t large enough. This prevents the function $(y_i(t,.), m_i(t))$ to converge to $(0_{L^1}, 0)$ and provides a contradiction together with the definition x. This completes the proof Lemma 5.2. □

As a consequence of Lemma 5.2 and Theorem 3.7 in [34](see also the monograph [44]) there exists $\mathcal{B}_0$ a compact subset of N_0 which is a global attractor for the semiflow $\{V(t)\}_{t\geq 0}$ in N_0. To complete the proof of Theorem 5.1 (*ii*) in the case $J = \{i\}$ it remains to prove that $\mathcal{B}_0 = \{u_i^*\}$. This will be achieved by constructing a suitable Lyapunov functional on $\mathcal{B}_0$. This idea has been used by Magal et al [37] and Thieme [48].

Let $\left\{u(t) = (x(t), \mathbf{m}(t), 0_{\mathbb{R}^n}, \mathbf{y}(t,.))^T\right\}_{t\in\mathbb{R}} \subset \mathcal{B}_0$ be a given entire solution of V. We claim that

Claim 5.3. *Function m_i satisfies* $\inf_{t\in\mathbb{R}} m_i(t) > 0$.

Before proving this claim let us complete the proof of Theorem 5.1 for $J = \{i\}$. Using Claim 5.3 and Lemma 3.7, one can consider the functional $V_i[u]$ defined in Lemma 3.7. Defining Θ_i as in (3.17) one has

$$\begin{aligned}\dot{V}_i[u](t) = &-\frac{\Theta_i}{x_e^i x(t)}\left(x(t) - x_e^i\right)^2 + \frac{x(t)}{x_e^i}\sum_{j\in\mathbb{N}_n\setminus\mathcal{S}}\left(\frac{\mathcal{T}_0^j}{\mathcal{T}_0^i} - 1\right)\beta_j m_j(t)\\ &-\int_0^\infty \frac{\beta_i^2 x_e^i m_{ei}^i}{\mu_{mi}}\rho_i(a) l(a)\left[h\left(\frac{y_i(t,a)m_{ei}^i}{y_{ei}^i(a)m_i(t)}\right) + h\left(\frac{m_i(t)y_{ei}^i(0)}{m_{ei}^1 y_i(t,0)}\right)\right] da.\end{aligned}$$

Recalling condition (Q) one obtains that $\Theta_i \geq 0$ so that $t \mapsto V[u](t)$ is a bounded and decreasing map. Finally arguing similarly as the end of the proof of Theorem 2.2 (*i*) yields to $u(t) \equiv u_i^*$.

It now remains to prove Claim 5.3.

Proof. [Proof of Claim 5.3] Let us argue by contradiction by assuming that $\inf_{t\in\mathbb{R}} m_i(t) = 0$. Note that due to Lemma 3.6 (*i*), one has $m_i(t) > 0$. Hence let us for instance assume that $\liminf_{t\to-\infty} m_i(t) = 0$. Consider a sequence $\{t_n\}_{n\geq 0}$ tending to $-\infty$ as $n \to \infty$ such that $m_i(t_n) \to 0$ as $n \to \infty$. Consider the sequence of maps $\{u_n(t) := u(t + t_n)\}_{n\geq 0}$. Then up to a subsequence, one may assume that $u_n(t) \to \widehat{u}(t)$ locally uniformly wherein $\widehat{u}$ is an entire solution of V such that $\widehat{m}_i(0) = 0$. Lemma 3.6 (*i*) ensures that $(\widehat{m}_i(t), \widehat{y}_i(t,.)) \equiv (0, 0_{L^1})$ This prevents $\widehat{u}$ to belong to N_0, a contradiction. A similar argument holds true if one deals with $\liminf_{t\to+\infty} m_i(t) = 0$. This completes the proof of Claim 5.3. □

5.2. Case card $\mathcal{S} \geq 2$ **and** $2 \leq$ card $J \leq$ card $\mathcal{S}$**.** In this section we assume that card $\mathcal{S} \geq 2$. Note that the proof of Theorem 5.1 (*ii*) follows from the above section when card $\mathcal{S} = 1$. Let $J \subset \mathcal{S}$ be a given subset such that card $J \geq 2$. Our induction hypothesis is concerned with the validity of Theorem 5.1 for each subset $J' \subset \mathcal{S}$ such that card $J' <$ card J. Consider now the set $Y_{0+} = X_{0+}^{\mathcal{S}\setminus J}$ as well as the semiflow $V := U_{\mathcal{S}\setminus J}$ on Y_{0+}. Let us denote $i = \max^{\lhd}(J)$ and let us consider

$$N_0 = Y_{0+} \cap M_0^i \text{ and } \partial N_0 = Y_{0+} \setminus N_0.$$

Let us first notice that to prove Theorem 5.1 (ii) for J, it is sufficient to show that

$$\lim_{t\to\infty} V(t)x = u_i^*, \quad \forall x \in N_0. \tag{5.1}$$

Indeed, if $x \in \partial N_0$ then $x \in X_{0+}^{\mathcal{S}\setminus J'}$ with $J' = J \setminus \{i\}$. Since $J' \subset \mathcal{S}$ and card $J' <$ card J then $V(t)x = U_{\mathcal{S}\setminus J'}(t)x$ and the asymptotic behaviour follows from the induction hypothesis.

The proof of this section is rather similar to the one provided in the preceding section. The only difference relies on the proof of the uniform persistence of the semiflow V with respect to the pair $(N_0, \partial N_0)$ because of the dynamics of the semiflow on the boundary ∂N_0. Hence to complete the proof of Theorem 5.1 (ii) for J we will only prove the following lemma. The details are left to the reader.

Lemma 5.4. *The semiflow V is uniformly persistent with respect to the pair $(N_0, \partial N_0)$.*

Proof. The proof of this result is an application of Theorem 4.2 in [20] with a non-trivial dynamics for the boundary semiflow. Let us denote by $J' = J \setminus \{i\}$. Then note that $V|_{\partial N_0} = U_{\mathcal{S}\setminus J'}$. According to Proposition 3.3 let us consider $\mathcal{A}_\partial := \mathcal{A}_{\mathcal{S}\setminus J'}$ the global attractor of the semiflow $V|_{\partial N_0}$. Note that according to the induction hypothesis the following holds true:

$$\bigcup_{x\in\mathcal{A}_\partial} \omega(x) = \{u_0^*\} \cup \bigcup_{j\in J'} \{u_j^*\}.$$

Here for each $x \in Y_{0+}$, $\omega(x)$ denotes the omega-limit set of the point x with respect to the semiflow V. The application of Theorem 4.2 in [20] relies on some properties of the set $\widehat{A}_\partial$ defined by

$$\widehat{A}_\partial = \{u_0^*\} \cup \bigcup_{j\in J'} \{u_j^*\}.$$

Let us first claim:

Claim 5.5. *For each $j \in J' \cup \{0\}$ the stationary point u_j^* is unstable with respect to the semiflow V.*

Proof. [Proof of Claim 5.5] The proof of the above claim relies on Lemma 3.5. Let us notice that for each $j \in J' \cup \{0\}$, function $\chi_i(., u_j^*$ (see (3.6)) satisfies

$$\chi_i(0, u_j^*) = \begin{cases} 1 - \mathcal{T}_0^i \text{ if } j = 0, \\ 1 - \frac{\mathcal{T}_0^i}{\mathcal{T}_0^j} \text{ if } j \in J'. \end{cases}$$

Hence since $i = \max^{\lhd} J$, $\chi_i(0, u_j^*) < 0$ and since $\chi_i(\lambda, u_j^*) \to 1$ as $\lambda \to \infty$, for each $j \in J' \cup \{0\}$ function $\chi_i(., u_j^*)$ has a strictly positive root. The result follows. □

Then we claim that:

Claim 5.6. *For each $(j,k) \in J' \cup \{0\}$ then if $\{u(t)\}_{t\in\mathbb{R}}$ is a non-trivial (that non-constant) entire solution of V such that*

$$\lim_{t\to-\infty} u(t) = u_j^* \text{ and } \lim_{t\to\infty} u(t) = u_k^*,$$

then $j \lhd k$*.*

Proof. [Proof of Claim 5.6] The proof of this claim relies on the application of Lemma 3.6 (ii) as well as a Lyapunov functional like argument.
Let us first consider the case where $j \in J'$. Then applying Lemma 3.6 (ii) we know that $j \unlhd k$. It is therefore sufficient to show that there is no homoclinic connection at u_j^*. Let us argue by contradiction by assuming that

$$\lim_{t\to\pm\infty} u(t) = u_j^*.$$

Then applying once again Lemma 3.6 (ii) we obtain that for each $k \in J'$ such that $k \rhd j$:

$$y_k(t,.) \equiv 0 \text{ and } m_k(t) \equiv 0, \ \ \forall k \in J' \rhd j.$$

Then consider the functional

$$V_j[u](t) = V_x(t) + V_{y_j}(t) + V_{m_j}(t) + \sum_{p=1;p\neq j}^{n} \int_0^\infty f_p(a) y_p(t,a)da + \sum_{p=1;p\neq j}^{n} d_p m_p(t).$$

Using similar arguments and computations (see Lemma 3.7) as the ones provided in the preceding section and using the fact that for each $k \in \mathcal{S} \setminus J'$ and each $k \in J'$ such that $k \rhd j$

$$y_k(t,.) \equiv 0 \text{ and } m_k(t) \equiv 0,$$

one obtains that $u(t) \equiv u_j^*$, a contradiction.

It remains to consider the case $j = 0$ and to show that there is no homoclinic connection at u_0^*. Let us argue by contradiction by assuming that

$$\lim_{t\to\pm\infty} u(t) = u_0^*.$$

Then let us notice that due to Lemma 3.6 (ii) one has

$$y_k(t,.) \equiv 0 \text{ and } m_k(t) \equiv 0, \ \ \forall k \in \mathcal{S}.$$

Then by considering the map

$$V_0[u](t) = h\left(\frac{x}{x_f}\right) + \sum_{j=1}^{n} \int_0^\infty f_j(a) y_j(a)da + \sum_{j=1}^{n} d_j m_j,$$

as well as computations and arguments similar to the proof of Proposition 4.1 one concludes that

$$u(t) \equiv u_0^*,$$

a contradiction that completes the proof of Claim 5.6. □

As a consequence of Claim 5.5 and Claim 5.6, the set $\widehat{A}_\partial$ is isolated and has an acyclic covering. Hence since the semiflow is bounded dissipative and asymptotically smooth, Theorem 4.2 in [20] applies and to complete the proof of Lemma 5.4, it is sufficient to show that $N_0 \cap W^s\left(\{u_j^*\}\right) = \emptyset$ for each $j \in J' \cup \{0\}$. Similarly to the proof in Section 5.1 this latter property directly follows from the functional

$$\Phi\left[V(t)x\right] := \int_0^\infty \Gamma_i(a) y_i(t,a)da + m_i(t) \text{ with } \Gamma_i(a) := \int_a^\infty \rho_i(s) e^{a-s} ds.$$

This completes the proof of Lemma 5.4. □

Appendix A. Basic reproduction rate of system (1.1). Here we follow the methodology of Diekmann and Heesterbeek [8, 9] and Inaba [25] (see also the references cited therein). Let $b_j(t)$ be the density of newly produced $j-$ merozoites at time t. Then from (1.1) one has

$$b_j(t) = \int_0^\infty r(a)\mu_j(a)w_j(t,a)da.$$

Since w_j is given by the resolution of the linearized system (1.1) at the disease free equilibrium, the Volterra formulation of the transport equation yields

$$b_j(t) = \beta_j x_f \int_0^t \rho_j(a)l(a)m_j(t-a)da + \int_t^\infty \rho_{y,j}(a)w_j(0,a)da.$$

On the other hand, it follows from the m_j component of the linearized system (1.1) at the DFE that

$$\dot{m}_j(t) = b_j(t) - (\mu_{m,j} + \delta_j\beta_j x_f)m_j(t),$$

that re-writes as

$$m_j(t) = \int_0^t e^{-(\mu_{m,j}+\delta_j\beta_j x_f)(t-s)}b_j(s)ds + m_j(0)e^{-(\mu_{m,j}+\delta_j\beta_j x_f)t}.$$

As a consequence b_j satisfies the following renewal equation:

$$\begin{aligned} b_j(t) &= \beta_j x_f \int_0^t \left(\int_0^a e^{-(\mu_{m,j}+\delta_j\beta_j x_f)(a-s)}\rho_j(s)l(s)ds\right) b_j(t-a)da \\ &\quad + \beta_j x_f m_j(0)\int_0^t \rho_j(a)l(a)e^{-(\mu_{m,j}+\delta_j\beta_j x_f)(t-a)}da + \int_t^\infty r_j(a)\mu_j(a)w_j(0,a)da. \end{aligned}$$

Due to the above formulation, the $j-$strain specific basic reproduction number $\mathcal{R}_0^j$ is calculated as

$$\mathcal{R}_0^j = \beta_j x_f \int_0^\infty \left(\int_0^a e^{-(\mu_{m,j}+\delta_j\beta_j x_f)(a-s)}\rho_j(s)l(s)ds\right)da;$$

that is

$$\mathcal{R}_0^j = \frac{\beta_j x_f}{\mu_{m,j}+\delta_j\beta_j x_f}\int_0^\infty \rho_j(a)l(a)da.$$

Now let us notice that sgn $\left(\mathcal{R}_0^j - 1\right)$ = sgn $\left(\mathcal{T}_0^j - 1\right)$. Indeed it is easy to check that

$$\mathcal{R}_0^j - 1 = \frac{\mu_{m,j}}{\mu_{m,j}+\delta_j\beta_j x_f}\left(\mathcal{T}_0^j - 1\right).$$

Moreover one can notice that when $\delta_j = 0$ then $\mathcal{R}_0^j = \mathcal{T}_0^j$.

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