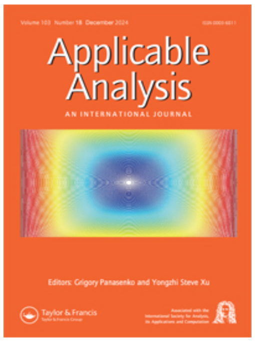

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Quantifying ivermectin's optimal strategy impacts on malaria transmission: a dual-structured mathematical model

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ABSTRACT
Ivermectin (IVM), used alongside mass treatment strategies, has been suggested as a potential tool for reducing malaria transmission. The effectiveness of IVM in shortening vector lifespan depends on the time elapsed between the administration of IVM to the host and the blood meal taken by the vector. This effectiveness is measured by the median effective dose (ED_{50}), the IVM concentration required to kill 50% of mosquitoes after a specific host exposure period. We use a mathematical model structured by human and vector exposure times to IVM and the model's well-posedness is established through semigroups theory. We calculate the basic reproduction number, linking it to epidemiological dynamics, and show steady states bifurcate at $\mathcal{R}_0 = 1$, governed by a constant C_{bif}. We identify the optimal human exposure to IVM and intervention interval to reduce prevalence by 10% to 20%. This depends on the IVM formulation (ED_{50}) and the target number of campaigns in the host population.

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1. Introduction

Vector-borne diseases, such as those transmitted by mosquitoes, account for approximately 17% of the global burden of infectious diseases, posing significant public health challenges worldwide [1, 2]. Estimated to affect 247 million people and cause 619,000 deaths in 2022 [2], malaria is undoubtedly the most serious example of a vector-borne disease, affecting mainly children under 5 years and pregnant women. The disease occurs mainly in sub-Saharan Africa, where 95% of cases are often recorded [2]. The disease is caused by a parasite of the genus *Plasmodium* through the bites of mosquitoes of the genus *Anopheles*. Although two vaccines, RTS,S and R21, have been licensed for malaria, their deployment is still limited, and additional trials are ongoing, particularly for young children under age 5 [3, 4]. Therefore, preventative measures targeting the vector population remain crucial. Traditional methods, such as long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS), are commonly used to reduce mosquito density. However, these approaches offer only short-term solutions due to growing insecticide resistance among mosquitoes, and their environmental impact raises concerns about large-scale implementation [5–7]. It is therefore important to implement other control tools, and ivermectin (IVM) is emerging as a new malaria control tool in that the mosquito's lifespan and refeeding frequency is reduced when it bites a human exposed to IVM [2, 8]. Ivermectin is an endectocide that was first approved in 1981 as a veterinary medicine. This drug is one of the main

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drugs used to control the filarial nematodes *Onchocerca volvulus* and *Wuchereria bancrofti* through mass drug administration to humans in endemic areas. Due to its broad spectrum of activity against nematodes and ectoparasites, its high potency, its long pharmacokinetic persistence in blood and lymph and its safety in vertebrates, it has become one of the best anti-parasitic drugs and can help reduce the burden of malaria [9–11].

The application of mathematical models to disease surveillance data can be used to address scientific hypotheses and policy questions relating to disease control. The first mathematical model of malaria was devised by Ross in 1911 [12] and later performed by Macdonald [13]. Several mathematical modeling studies have explored malaria transmission dynamics, incorporating ivermectin as a control measure. For example, Slater et al. [14, 15] indicate that mass drug administration with IVM can reduce prevalence and morbidity, particularly in regions with shorter transmission seasons, particularly in combination with other tools such as antimalarials and seasonal malaria chemoprevention. Additionally, Zhao et al. [16] support IVM as an efficient tools by analyzing the long-term disease transmission dynamics in Kenya. They use an ordinary differential equation model with delay, considering seasonality and the effect of IVM on controlling the vector population. The existence of a backward bifurcation, as demonstrated in [17], suggests the importance of early intervention when using ivermectin. It also indicates that stopping the spread of the disease requires minimal drug dosage in low initial conditions but higher levels once the disease has taken hold in a population. In addition, Wang and Zhao [18] performed a reaction diffusion model taking into account spatial heterogeneity and the implementation of ivermectin as a therapeutic option and compared it to LLNS and IRS in West Africa. The study shows that treatment plans with or without IVM contribute equally to the number of basic reproductions but have different effects on malaria epidemic levels.

Yet, very few models have specifically addressed the time since exposure to IVM, despite the fact that the impact of IVM on reducing the lifespan and feeding frequency of mosquitoes is highly dependent on the duration since the host's blood meal was exposed to IVM. Here we propose a dual-structured mathematical model that takes into account the time since exposure to IVM in both human and mosquito populations. The model proposed enables the capture of variable IVM formulations, typically characterized by the median effective dose ED_{50}. Furthermore, we conduct a detailed mathematical analysis of the proposed model and derive the basic reproduction number $\mathcal{R}_0$. The expression emphasizes the influence of the aforementioned structural variables on crucial epidemiological traits of the human–vector association, such as vectorial capacity.

In this paper, we first show the well-posedness of the PDE model formulated using the theory of integrated semigroups introduced in [19–22], for which we use a classical fixed point argument combined with some population estimates. Furthermore, we explore the existence of steady states, which signify solutions independent of time. A disease-free equilibrium is consistently present, while the existence of endemic equilibria is explored. To provide information on the endemic equilibrium, we first show its existence using the Krasnoselskii fixed point argument [23, 24]. We demonstrate that, depending on the sign of a constant C_{bif} determined by the model parameters, a bifurcation occurs when the bifurcation parameter, denoted by $\bar{r}_0$, attains the value of 1, resulting in either a Forward or Backward bifurcation [25–27]. In this context, it means that there is a unique (resp. multiple) endemic equilibrium if and only if $\bar{r}_0 > 1$ (resp. $\bar{r}_0 < 1$, but close enough to 1). Utilizing spectral theory, we can ascertain the local stability of the disease-free equilibrium under the condition that $\mathcal{R}_0 < 1$. However, it becomes unstable when $\mathcal{R}_0 > 1$ [28–30].

Numerical simulations enabled us to quantify the impact of IVM administration in the human host population on malaria transmission dynamics across various levels of endemicity. In this work, an IVM intervention campaign is defined by four parameters: the number of campaigns implemented within 1 year, the time between two successive campaigns within a year, the target proportion of humans to be exposed to IVM during a campaign, and the median effective dose of the IVM formulation. A global sensitivity analysis enables us to evaluate the relative significance of these parameters in reducing malaria incidence. Finally, utilizing a specified IVM formulation and the targeted number of campaigns per year, we determine the optimal proportion of humans to be exposed to IVM during an intervention as well as the necessary time intervals between subsequent interventions to achieve a reduction in human prevalence ranging from 10% to 20%. This is of practical importance for identifying the minimum proportion of individuals to be exposed to IVM during a campaign.

This paper is organized as follows. Section 2 introduces the model and the parameters description. In Section 3, we present the main results of the mathematical analysis and the simulations conducted to achieve the objectives of this work. Section 4 discusses the results obtained from our numerical simulations. Finally, details on the proof of the main analytical results are provided in Appendix to complete the document.

2. Description of the model

2.1. Model overview

The model investigates the dynamics of human and mosquito populations interacting with the presence of IVM pressure. Subsequently, both of these populations are subjected to either exposure IVM or no exposure at all. The subscripts h and m are respectively used for human and mosquito populations that remain unexposed to IVM, whereas subscripts h,IVM and m,IVM are employed when these populations are exposed to IVM. At any given time t, the human population exists in four states: susceptible to infection denoted as $S_h(t)$ or $S_{h,\text{IVM}}(t,\tau)$, asymptomatic infection indicated by $A_h(t)$ or $A_{h,\text{IVM}}(t,\tau)$, symptomatic infection denoted as $I_h(t)$ or $I_{h,\text{IVM}}(t,\tau)$, and recovered represented by $R_h(t)$ or $R_{h,\text{IVM}}(t,\tau)$. The variable τ corresponds to the time elapsed since the exposure of human population to IVM. Similarly, the mosquito population exists in two states: susceptible to infection indicated by $S_m(t)$ or $S_{m,\text{IVM}}(t,\eta)$, and infected denoted as $I_m(t)$ or $I_{m,\text{IVM}}(t,\eta)$. The variable η represents the time elapsed since the exposure of mosquito populations to IVM. The total number of humans N_h and mosquitoes N_m is then given by

$$
\begin{aligned}
N_h(t) &= S_h(t) + A_h(t) + I_h(t) + R_h(t) + \int_0^\infty S_{h,\text{IVM}}(t,\tau)\,\mathrm{d}\tau + \int_0^\infty A_{h,\text{IVM}}(t,\tau)\,\mathrm{d}\tau \\
&\quad + \int_0^\infty I_{h,\text{IVM}}(t,\tau)\,\mathrm{d}\tau + \int_0^\infty R_{h,\text{IVM}}(t,\tau)\,\mathrm{d}\tau, \\
N_m(t) &= S_m(t) + I_m(t) + \int_0^\infty S_{m,\text{IVM}}(t,\eta)\,\mathrm{d}\eta + \int_0^\infty I_{m,\text{IVM}}(t,\eta)\,\mathrm{d}\eta.
\end{aligned}
$$

The total number of new infection within human population at time t is given by $S_h(t)\lambda_m(t)$, where $\lambda_m(t)$ is the force of infection from mosquitoes to humans. This force of infection is defined in such a way that

$$
\lambda_m(t) = \frac{\theta\beta_m}{N_h(t)}\left(I_m(t) + \int_0^\infty I_{m,\text{IVM}}(t,\eta)\,\mathrm{d}\eta\right),
$$

where θ is the number of humans bitten by mosquitoes per unit of time and β_m is the probability of parasite transmission from an infected mosquito to a human.

By the same way, the total number of new infection within mosquitoes population at time t is given by $S_m(t)\lambda_h(t)$, where $\lambda_h(t)$ is the force of infection from humans to mosquitoes. This force of infection is defined by

$$
\lambda_h(t) = \frac{\theta\beta_h}{N_h(t)}\left(A_h(t) + I_h(t)\right),
$$

where β_h is the probability of parasite transmission from an infected human to any mosquito for each bite.

Adequate contacts between uninfected humans exposed to IVM and susceptible mosquitoes lead to susceptible mosquitoes newly exposed to IVM. The total number of susceptible mosquitoes that

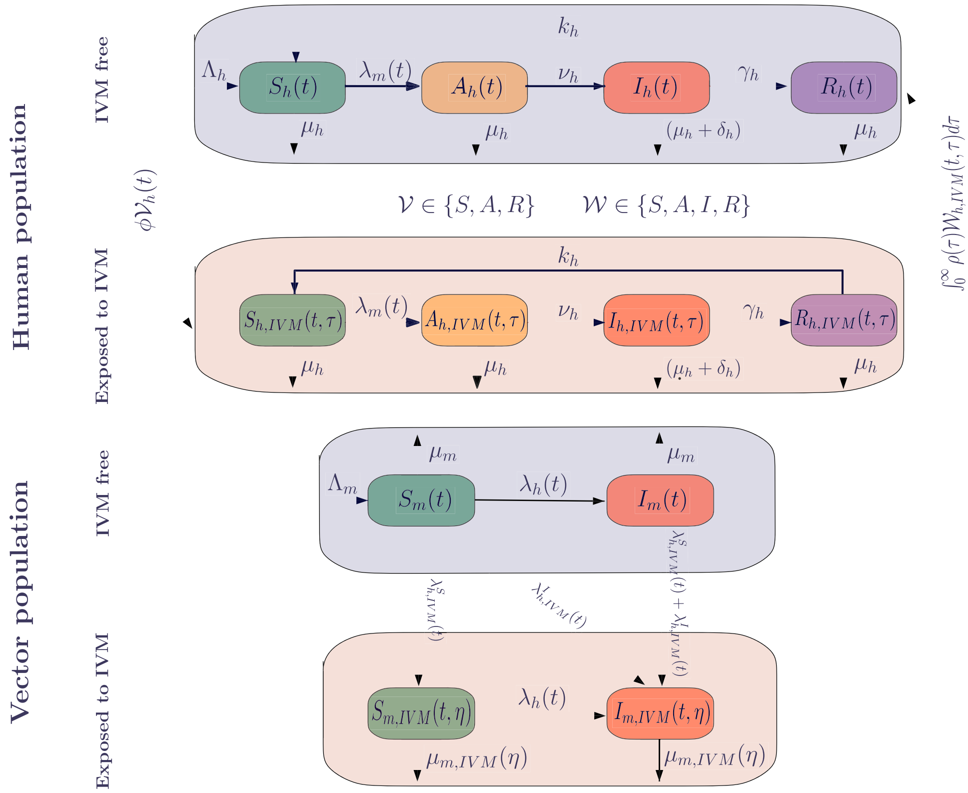

Figure 1. Flow diagram of the nested model. **Human population**: Ivermectin is applied as a preventive measure, i.e. to susceptible, asymptomatic and recovered humans, who are therefore exposed at rate ϕ. Humans exposed to IVM lose their immune system at a rate $\int_0^\infty \rho(\tau)\mathcal{W}_{h,\text{IVM}}(t,\tau)\,d\tau$ $\mathcal{W} \in \{S, A, I, R\}$, where τ represents the time since the exposure of human sub-populations to IVM and $\rho(\tau)$ captures the loss of IVM efficiency. **Vector population**: The vector population exposed to IVM arises when the initial vector population (consisting of susceptible and infectious) bites a human population exposed to IVM. This transition is given by the forces of infection $\lambda^S_{h,\text{IVM}}(t)$ and $\lambda^I_{h,\text{IVM}}(t)$. Thus vector population exposed to IVM has a mortality rate $\mu_{m,\text{IVM}}(\eta)$ which depends on the parameter η representing the time since mosquitoes are exposed to IVM.

have been newly exposed to IVM is determined by $\lambda^S_{h,\text{IVM}}(t)S_m(t)$, where $\lambda^S_{h,\text{IVM}}(t)$ represents the force that describes the exposure of mosquito to IVM without resulting in infections. This quantity is such that

$$\lambda^S_{h,\text{IVM}}(t) = \frac{\theta}{N_h(t)} \int_0^\infty \left(S_{h,\text{IVM}}(t,\tau) + R_{h,\text{IVM}}(t,\tau)\right) \, d\tau.$$

Similarly, the force, indicated as $\lambda^I_{h,\text{IVM}}$, which defines the exposure of mosquitoes to IVM leading to infections, is expressed as

$$\lambda^I_{h,\text{IVM}}(t) = \frac{\theta}{N_h(t)} \int_0^\infty \left(A_{h,\text{IVM}}(t,\tau) + I_{h,\text{IVM}}(t,\tau)\right) \, d\tau.$$

Note that asymptomatic malaria infections are highly prevalent in endemic areas and only a small percentage of asymptomatic infections will exhibit clinical symptoms [31]. This has significant implications for malaria control programs [32].

Finally, the human–mosquito life cycle is shown in Figure 1, and the notations of all variables and parameters are summarized in Table 1.

Table 1. Main notations, state variables and parameters of the model.

Category	Biological meanings	Unit
Notations		
t	Time	Tu
τ	Time since the exposure of human populations to IVM	Tu
η	Time since the exposure of mosquito populations to IVM	Tu
State variables		
S_h	Susceptible humans unexposed to IVM	No unit
A_h	Asymptomatic humans unexposed to IVM	No unit
I_h	Symptomatic humans unexposed to IVM	No unit
R_h	Recovered humans unexposed to IVM	No unit
S_m	Susceptible mosquitoes unexposed to IVM	No unit
I_m	Infectious mosquitoes unexposed to IVM	No unit
$S_{h,\mathrm{IVM}}$	Susceptible humans exposed to IVM	No unit
$A_{h,\mathrm{IVM}}$	Asymptomatic humans exposed to IVM	No unit
$I_{h,\mathrm{IVM}}$	Symptomatic humans and exposed to IVM	No unit
$R_{h,\mathrm{IVM}}$	Recovered humans and exposed to IVM	No unit
$S_{m,\mathrm{IVM}}$	Susceptible mosquitoes and exposed to IVM	No unit
$I_{m,\mathrm{IVM}}$	Infectious mosquitoes and exposed to IVM	No unit
N_h	Total humans population	No unit
N_m	Total mosquitoes population	No unit
	Parameters	Value*;Unit
$\wedge_h$	Recruitment rate for humans	5;Tu^{-1}
μ_h	Natural mortality rate for humans	0.00224;Tu^{-1};
ν_h	Progression rate of asymptomatic humans	1/30;Tu^{-1};
γ_h	Recovery rate for humans	3.704 e^{-2};Tu^{-1};
k_h	Rate of immunity loss for recovered humans	1.469 e^{-2};Tu^{-1};
δ_h	Disease induced death rate for humans	0.0005;Tu^{-1};
$\wedge_m$	Recruitment rate for susceptible vector	100;Tu^{-1};
μ_m	Natural mortality rate for vector unexposed to IVM	0.14;Tu^{-1};
ϕ	IVM injection rate	Variable
$\mu_{m,\mathrm{IVM}}$	Mortality rate for vector exposed to IVM	Equation (17)
ρ	Rate of IVM efficiency loss within the human population exposed to IVM	Equation (18)
θ	The number of human bitten by mosquitoes by unit of time	0.5;Tu^{-1}
β_h	Parasite transmission probability from human to mosquitoes	0.8333;Tu^{-1}
β_m	Parasite transmission probability from mosquitoes to human	0.5;Tu^{-1}
ED_{50}	The median effective dose	Variable
n_c	The number of IVM intervention (Campaign) implemented within one year	Variable
d_c	The duration of an intervention	7;Tu
t_c	The duration between two successive interventions	Variable

Tu, Time unit; h, humans; m, mosquitoes; IVM, ivermectin. * Values of fixed parameters are chosen to fall within a plausible range found in the literature.

2.2. The mathematical model

The interaction dynamics between populations of humans and mosquitoes without exposure to IVM is described as follows:

$$\begin{cases} \dot{S}_h(t) = \Lambda_h + k_h R_h(t) - (\mu_h + \phi(t))\, S_h(t) - \lambda_m(t) S_h(t) + \int_0^{\infty} \rho(\tau) S_{h,\mathrm{IVM}}(t,\tau)\, \mathrm{d}\tau, \\ \dot{A}_h(t) = \lambda_m(t) S_h(t) - (\mu_h + \nu_h + \phi(t))\, A_h(t) + \int_0^{\infty} \rho(\tau) A_{h,\mathrm{IVM}}(t,\tau)\, \mathrm{d}\tau, \\ \dot{I}_h(t) = \nu_h A_h(t) - (\mu_h + \gamma_h + \delta_h)\, I_h(t) + \int_0^{\infty} \rho(\tau) I_{h,\mathrm{IVM}}(t,\tau)\, \mathrm{d}\tau, \\ \dot{R}_h(t) = \gamma_h I_h(t) - (\mu_h + k_h + \phi(t)) R_h(t) + \int_0^{\infty} \rho(\tau) R_{h,\mathrm{IVM}}(t,\tau)\, \mathrm{d}\tau, \end{cases} \tag{1}$$

and

$$\begin{cases} \dot{S}_m(t) = \Lambda_m - \mu_m S_m(t) - \left(\lambda_h(t) + \lambda^S_{h,\mathrm{IVM}}(t) + \lambda^I_{h,\mathrm{IVM}}(t)\right) S_m(t), \\ \dot{I}_m(t) = \lambda_h(t) S_m(t) - \mu_m I_m(t) - \left(\lambda^S_{h,\mathrm{IVM}}(t) + \lambda^I_{h,\mathrm{IVM}}(t)\right) I_m(t). \end{cases} \tag{2}$$

System (1)–(2) basically captures the classical human–mosquito interaction dynamics. Moreover, humans may either recover at a rate of γ_h or succumb to the infection with a rate δ_h. Recovered individuals wane their immunity at rate k_h. The human population is assumed to be consistently replenished at a steady rate Λ_h, which can be attributed to either births or migrations, while individuals also naturally pass away at a rate of μ_h. Asymptomatic infected humans become symptomatic infected at rate ν_h. The human population that has been exposed to IVM since time τ reverts to an unexposed state at a rate $\rho(\tau)$. The parameter ρ reflects the loss of IVM efficiency within the human population exposed to IVM. The mosquitoes are recruited at a rate of Λ_m and naturally perish at a rate of μ_m.

Assume that a fixed proportion ϕ of a human population is exposed to IVM. Therefore, the number of humans newly exposed to IVM (i.e. at $\tau = 0$) is given by

$$\begin{cases} S_{h,\mathrm{IVM}}(t,0) = \phi S_h(t), & A_{h,\mathrm{IVM}}(t,0) = \phi A_h(t), \\ I_{h,\mathrm{IVM}}(t,0) = 0, & R_{h,\mathrm{IVM}}(t,0) = \phi R_h(t). \end{cases} \tag{3}$$

In System (3), it is assumed that symptomatic infections are not subjected to exposure to IVM. The boundary conditions (3) are then coupled with the dynamics of human population exposed to IVM such that:

$$\begin{cases} (\partial_t + \partial_\tau) S_{h,\mathrm{IVM}}(t,\tau) = k_h R_{h,\mathrm{IVM}}(t,\tau) - (\mu_h + \lambda_m(t)) S_{h,\mathrm{IVM}}(t,\tau) - \rho(\tau) S_{h,\mathrm{IVM}}(t,\tau), \\ (\partial_t + \partial_\tau) A_{h,\mathrm{IVM}}(t,\tau) = \lambda_m(t) S_{h,\mathrm{IVM}}(t,\tau) - (\mu_h + \nu_h) A_{h,\mathrm{IVM}}(t,\tau) - \rho(\tau) A_{h,\mathrm{IVM}}(t,\tau), \\ (\partial_t + \partial_\tau) I_{h,\mathrm{IVM}}(t,\tau) = \nu_h A_{h,\mathrm{IVM}}(t,\tau) - (\mu_h + \gamma_h + \delta_h) I_{h,\mathrm{IVM}}(t,\tau) - \rho(\tau) I_{h,\mathrm{IVM}}(t,\tau), \\ (\partial_t + \partial_\tau) R_{h,\mathrm{IVM}}(t,\tau) = \gamma_h I_{h,\mathrm{IVM}}(t,\tau) - (\mu_h + k_h) R_{h,\mathrm{IVM}}(t,\tau) - \rho(\tau) R_{h,\mathrm{IVM}}(t,\tau). \end{cases}$$

Based on the above notations, the dynamics of mosquito newly exposed to IVM (i.e. $\eta = 0$) is given by

$$\begin{cases} S_{m,\mathrm{IVM}}(t,0) = \lambda^S_{h,\mathrm{IVM}}(t) S_m(t), \\ I_{m,\mathrm{IVM}}(t,0) = \lambda^I_{h,\mathrm{IVM}}(t) S_m(t) + \left(\lambda^S_{h,\mathrm{IVM}}(t) + \lambda^I_{h,\mathrm{IVM}}(t)\right) I_m(t), \end{cases}$$

combined with the dynamics of the mosquito population exposed to IVM, as defined by

$$\begin{cases} \left(\partial_t + \partial_\eta\right) S_{m,\mathrm{IVM}}(t,\eta) = -\mu_{m,\mathrm{IVM}}(\eta) S_{m,\mathrm{IVM}}(t,\eta) - \left(\lambda_h(t) + \lambda^I_{h,\mathrm{IVM}}(t)\right) S_{m,\mathrm{IVM}}(t,\eta), \\ \left(\partial_t + \partial_\eta\right) I_{m,\mathrm{IVM}}(t,\eta) = \left(\lambda_h(t) + \lambda^I_{h,\mathrm{IVM}}(t)\right) S_{m,\mathrm{IVM}}(t,\eta) - \mu_{m,\mathrm{IVM}}(\eta) I_{m,\mathrm{IVM}}(t,\eta). \end{cases} \tag{4}$$

Within System (4), the parameter $\mu_{m,\mathrm{IVM}}(\eta)$ accounts for the mortality of the mosquito population that has been exposed to IVM since time η.

Lastly, the initial condition (at $t = 0$) for the mathematical model above is given by

$$\begin{cases} S_h(0) = S_{h0}, \quad A_h(0) = A_{h0}, \quad I_h(0) = I_{h0}, \quad R_h(0) = R_{h0}, \quad S_m(0) = S_{m0}, \quad I_m(0) = I_{m0}, \\ S_{h,\mathrm{IVM}}(0,\tau) = S_{h0,\mathrm{IVM}}(\tau), \quad A_{h,\mathrm{IVM}}(0,\tau) = A_{h0,\mathrm{IVM}}(\tau), \quad I_{h,\mathrm{IVM}}(0,\tau) = I_{h0,\mathrm{IVM}}(\tau), \\ R_{h,\mathrm{IVM}}(0,\tau) = R_{h0,\mathrm{IVM}}(\tau), \quad S_{m,\mathrm{IVM}}(0,\eta) = S_{m0,\mathrm{IVM}}(\eta), \quad I_{m,\mathrm{IVM}}(0,\eta) = I_{m0,\mathrm{IVM}}(\eta). \end{cases}$$

3. Main results

To deal with Models (1)–(4), we introduce vector state variables as follows: $v_h(t) = (S_h(t), R_h(t))^T$; $u_h(t) = (A_h(t), I_h(t))^T$; $v_{h,\mathrm{IVM}}(t,\cdot) = (S_{h,\mathrm{IVM}}(t,\cdot), R_{h,\mathrm{IVM}}(t,\cdot))^T$; $u_{h,\mathrm{IVM}}(t,\cdot) = (A_{h,\mathrm{IVM}}(t,\cdot), I_{h,\mathrm{IVM}}(t,\cdot))^T$, where x^T is the set for the transpose of x. Furthermore, let $e = (1,1)$; $e_1 = (1,0)^T$, $\mathrm{I_d}$ the identity matrix, and as well as the matrices

$$D_h = \begin{pmatrix} \mu_h + \nu_h & 0 \\ -\nu_h & \mu_h + \gamma_h + \delta_h \end{pmatrix}; \quad K_h = \begin{pmatrix} 0 & k_h \\ 0 & -k_h \end{pmatrix}; \quad E_1 = \begin{pmatrix} 1 & 0 \\ 0 & 0 \end{pmatrix}; \quad E_2 = \begin{pmatrix} 0 & 0 \\ 0 & 1 \end{pmatrix}.$$

Consequently, we have

$$\lambda_m(t) = \frac{\theta\beta_m}{N_h(t)}\left(I_m(t) + \int_0^\infty I_{m,\mathrm{IVM}}(t,\eta)\,\mathrm{d}\eta\right), \quad \lambda_h(t) = \frac{\theta\beta_h}{N_h(t)} e u_h(t),$$
$$\lambda^I_{h,\mathrm{IVM}}(t) = \frac{\theta\beta_h}{N_h(t)}\int_0^\infty e u_{h,\mathrm{IVM}}(t,\tau)\,\mathrm{d}\tau, \quad \lambda^S_{h,\mathrm{IVM}}(t) = \frac{\theta}{N_h(t)}\int_0^\infty e v_{h,\mathrm{IVM}}(t,\tau)\,\mathrm{d}\tau,$$

and systems (1)–(4) rewrite as

$$\begin{cases} \dot v_h(t) = \Lambda_h e_1 - \lambda_m(t) E_1 v_h(t) - (\mu_h + \phi)\, v_h(t) + K_h v_h(t) + \gamma_h E_2 u_h(t) \\ \qquad\quad + \int_0^\infty \rho(\tau) v_{h,\mathrm{IVM}}(t,\tau)\,\mathrm{d}\tau, \\ \dot u_h(t) = \lambda_m(t) E_1 v_h(t) - \phi E_1 u_h(t) - D_h u_h(t) + \displaystyle\int_0^\infty \rho(\tau) u_{h,\mathrm{IVM}}(t,\tau)\,\mathrm{d}\tau, \\ \dot S_m(t) = \Lambda_m - \mu_m S_m(t) - \left(\lambda_h(t) + \lambda^S_{h,\mathrm{IVM}}(t) + \lambda^I_{h,\mathrm{IVM}}(t)\right) S_m(t), \\ \dot I_m(t) = \lambda_h(t) S_m(t) - \mu_m I_m(t) - \left(\lambda^S_{h,\mathrm{IVM}}(t) + \lambda^I_{h,\mathrm{IVM}}(t)\right) I_m(t), \end{cases} \tag{5}$$

with

$$\begin{cases} v_{h,\mathrm{IVM}}(t,0) = \phi v_h(t), \\ u_{h,\mathrm{IVM}}(t,0) = \phi E_1 u_h(t), \\ S_{m,\mathrm{IVM}}(t,0) = \lambda^S_{h,\mathrm{IVM}}(t) S_m(t), \\ I_{m,\mathrm{IVM}}(t,0) = \lambda^I_{h,\mathrm{IVM}}(t) S_m(t) + \left(\lambda^S_{h,\mathrm{IVM}}(t) + \lambda^I_{h,\mathrm{IVM}}(t)\right) I_m(t), \\ (\partial_t + \partial_\tau) v_{h,\mathrm{IVM}}(t,\tau) = -\lambda_m(t) E_1 v_{h,\mathrm{IVM}}(t,\tau) - (\mu_h + \rho(\tau) - K_h)\, v_{h,\mathrm{IVM}}(t,\tau) \\ \qquad + \gamma_h E_2 u_{h,\mathrm{IVM}}(t,\tau), \\ (\partial_t + \partial_\tau) u_{h,\mathrm{IVM}}(t,\tau) = \lambda_m(t) E_1 v_{h,\mathrm{IVM}}(t,\tau) - D_h u_{h,\mathrm{IVM}}(t,\tau) - \rho(\tau) u_{h,\mathrm{IVM}}(t,\tau), \\ \left(\partial_t + \partial_\eta\right) S_{m,\mathrm{IVM}}(t,\eta) = -\mu_{m,\mathrm{IVM}}(\eta) S_{m,\mathrm{IVM}}(t,\eta) - \left(\lambda_h(t) + \lambda^I_{h,\mathrm{IVM}}(t)\right) S_{m,\mathrm{IVM}}(t,\eta), \\ \left(\partial_t + \partial_\eta\right) I_{m,\mathrm{IVM}}(t,\eta) = \left(\lambda_h(t) + \lambda^I_{h,\mathrm{IVM}}(t)\right) S_{m,\mathrm{IVM}}(t,\eta) - \mu_{m,\mathrm{IVM}}(\eta) I_{m,\mathrm{IVM}}(t,\eta), \end{cases} \tag{6}$$

supplemented together with the initial data

$$\begin{cases} v_h(0) = v_{h0}, \quad u_h(0) = u_{h0}, \quad S_m(0) = S_{m0}, \quad I_m(0) = I_{m0}, \quad v_{h,\mathrm{IVM}}(0,\tau) = v_{h0,\mathrm{IVM}}(\tau), \\ u_{h,\mathrm{IVM}}(0,\tau) = u_{h0,\mathrm{IVM}}(\tau), \quad S_{m,\mathrm{IVM}}(0,\eta) = S_{m0,\mathrm{IVM}}(\eta), \quad I_{m,\mathrm{IVM}}(0,\eta) = I_{m0,\mathrm{IVM}}(\eta). \end{cases} \tag{7}$$

In the following sections, we examine systems (5)–(7) while operating under the following general assumption.

Assumption 3.1: (1) *The parameters* $\Lambda_j, \mu_j, \beta_j, \nu_h, \gamma_h, \delta_h, k_h, \theta$ *are positive constants for* $j \in \{h, m\}$.

(2) *The functional parameters* $\mu_{m,\text{IVM}}$ *and* ρ *fulfill the conditions:* $\mu_{m,\text{IVM}} \in L^\infty_+(\mathbb{R}_+)$; $\rho \in L^\infty_+(\mathbb{R}_+)$, *and there exist positive constants* μ_{m0} *and* $\bar{\rho}$ *such that* $\mu_{m,\text{IVM}}(z) > \mu_{m0}$ *and* $\rho(z) > \bar{\rho}$ *for all* $z \in \mathbb{R}_+$.
(3) *The initial data is such that* $v_{h0}, u_{h0}, S_{m0}, I_{m0} \geq 0$ *and* $v_{h0,\text{IVM}} \in L^\infty_+(\mathbb{R}^2_+)$, $u_{h0,\text{IVM}} \in L^\infty_+(\mathbb{R}^2_+)$, $S_{m0,\text{IVM}} \in L^\infty_+(\mathbb{R}_+)$, $I_{m0,\text{IVM}} \in L^\infty_+(\mathbb{R}_+)$.

3.1. Existence of semiflow and basic properties

We shall deal with the integrated semigroup approach for non-densely defined operators (e.g. see [21, 22]).

Let us set the spaces

$$\mathcal{X}_h := \mathbb{R}^2 \times L^1(0,\infty,\mathbb{R}^2) \times \mathbb{R}^2 \times L^1(0,\infty,\mathbb{R}^2), \quad \mathcal{X}_m := \mathbb{R} \times L^1(0,\infty,\mathbb{R}) \times \mathbb{R} \times L^1(0,\infty,\mathbb{R}),$$

as well as positive cones

$$\begin{aligned}\mathcal{X}_{h,+} &:= \mathbb{R}^2_+ \times L^1(0,\infty,\mathbb{R}^2_+) \times \mathbb{R}^2_+ \times L^1(0,\infty,\mathbb{R}^2_+),\\ \mathcal{X}_{m,+} &:= \mathbb{R}_+ \times L^1(0,\infty,\mathbb{R}_+) \times \mathbb{R}_+ \times L^1(0,\infty,\mathbb{R}_+).\end{aligned}$$

Let the linear operators $\widehat{\mathcal{A}}_h : D(\widehat{\mathcal{A}}_h) \subset \mathcal{X}_h \longrightarrow \mathcal{X}_h$, and $\widehat{\mathcal{A}}_m : D(\widehat{\mathcal{A}}_m) \subset \mathcal{X}_m \longrightarrow \mathcal{X}_m$ defined as follows:

$$\widehat{\mathcal{A}}_h \begin{pmatrix} 0_{\mathbb{R}^2} \\ \psi_1 \\ 0_{\mathbb{R}^2} \\ \psi_2 \end{pmatrix} = \begin{pmatrix} -\psi_1(0) \\ -\psi_1' - (\mu_h + \rho(\tau))\,\psi_1 \\ -\psi_2(0) \\ -\psi_2' - (D_h + \rho(\tau)\text{I}_\text{d})\,\psi_2 \end{pmatrix}, \quad \widehat{\mathcal{A}}_m \begin{pmatrix} 0_{\mathbb{R}} \\ \psi_1 \\ 0_{\mathbb{R}} \\ \psi_2 \end{pmatrix} = \begin{pmatrix} -\psi_1(0) \\ -\psi_1' - \mu_{m,\text{IVM}}(\eta)\psi_1 \\ -\psi_2(0) \\ -\psi_2' - \mu_{m,\text{IVM}}(\eta)\psi_2 \end{pmatrix},$$

with their domain defined by

$$\begin{aligned} D(\widehat{\mathcal{A}}_h) &:= \{0_{\mathbb{R}^2}\} \times W^{1,1}(0,\infty,\mathbb{R}^2) \times \{0_{\mathbb{R}^2}\} \times W^{1,1}(0,\infty,\mathbb{R}^2),\\ D(\widehat{\mathcal{A}}_m) &:= \{0_{\mathbb{R}}\} \times W^{1,1}(0,\infty,\mathbb{R}) \times \{0_{\mathbb{R}}\} \times W^{1,1}(0,\infty,\mathbb{R}).\end{aligned}$$

Subsequently, consider the Banach space $\mathcal{X} = \mathbb{R}^6 \times \mathcal{X}_h \times \mathcal{X}_m$ and $\mathcal{X}_+ = \mathbb{R}^6_+ \times \mathcal{X}_{h,+} \times \mathcal{X}_{m,+}$ associated with the usual product norm $\|\cdot\|$. Let $\mathcal{A} : D(\mathcal{A}) \subset \mathcal{X} \longrightarrow \mathcal{X}$ be the linear operator defined by

$$\mathcal{A} = \text{diag}\left(-(\mu_h + \phi)\text{I}_\text{d}, -(\phi E_1 + D_h), -\mu_m \text{I}_\text{d}, \widehat{\mathcal{A}}_h, \widehat{\mathcal{A}}_m\right),$$

with $D(\mathcal{A}) = \mathbb{R}^6 \times D(\widehat{\mathcal{A}}_h) \times D(\widehat{\mathcal{A}}_m)$.

Hence, we have

$$\begin{aligned}\overline{D(\mathcal{A})} &= \mathbb{R}^6 \times \{0_{\mathbb{R}^2}\} \times L^1(0,\infty,\mathbb{R}^2) \times \{0_{\mathbb{R}^2}\} \times L^1(0,\infty,\mathbb{R}^2)\\ &\quad \times \{0_{\mathbb{R}}\} \times L^1(0,\infty,\mathbb{R}) \times \{0_{\mathbb{R}}\} \times L^1(0,\infty,\mathbb{R})\\ &:= \mathcal{X}_0 \subset \mathcal{X}.\end{aligned}$$

Hence, the domain of operator $\mathcal{A}$ is not dense in $\mathcal{X}$, and its positive cone is defined by $\mathcal{X}_{0,+} = \mathcal{X}_0 \cap \mathcal{X}_+$. By setting

$$\begin{aligned} u(t) = \big(&v_h(t), u_h(t), S_m(t), I_m(t), 0_{\mathbb{R}^2}, v_{h,\text{IVM}}(t,\cdot),\\ &0_{\mathbb{R}^2}, u_{h,\text{IVM}}(t,\cdot), 0_{\mathbb{R}}, S_{m,\text{IVM}}(t,\cdot), 0_{\mathbb{R}}, I_{m,\text{IVM}}(t,\cdot)\big)^T, \end{aligned} \tag{8}$$

the operator $\mathcal{A}$ is the linear part of systems (5)–(6) while the non-linear part is defined by the map $\mathcal{F}:\mathcal{X}\longrightarrow\mathcal{X}$ such that

$$\mathcal{F}(u(t))=\begin{pmatrix}\Lambda_h e_1-\lambda_m(t)E_1v_h(t)+K_hv_h(t)+\gamma_hE_2u_h(t)+\int_0^\infty\rho(\tau)U_{h,\mathrm{IVM}}(t,\tau)\,\mathrm{d}\tau\\ \lambda_m(t)E_1v_h(t)+\int_0^\infty\rho(\tau)u_{h,\mathrm{IVM}}(t,\tau)\,\mathrm{d}\tau\\ \Lambda_m-\left(\lambda_h(t)+\lambda^S_{h,\mathrm{IVM}}(t)+\lambda^I_{h,\mathrm{IVM}}(t)\right)S_m(t)\\ \lambda_h(t)S_m(t)-\left(\lambda^S_{h,\mathrm{IVM}}(t)+\lambda^I_{h,\mathrm{IVM}}(t)\right)I_m(t)\\ \phi v_h(t)\\ -\lambda_m(t)E_1v_{h,\mathrm{IVM}}(t,\cdot)+\gamma_hE_2u_{h,\mathrm{IVM}}(t,\cdot)+K_hv_{h,\mathrm{IVM}}(t,\cdot)\\ \phi E_1u_h(t)\\ \lambda_m(t)E_1v_{h,\mathrm{IVM}}(t,\cdot)\\ \lambda^S_{h,\mathrm{IVM}}(t)S_m(t)\\ -\left(\lambda_h(t)+\lambda^I_{h,\mathrm{IVM}}(t)\right)S_{m,\mathrm{IVM}}(t,\cdot)\\ \lambda^I_{h,\mathrm{IVM}}(t)S_m(t)+\left(\lambda^S_{h,\mathrm{IVM}}(t)+\lambda^I_{h,\mathrm{IVM}}(t)\right)I_m(t)\\ \left(\lambda_h(t)+\lambda^I_{h,\mathrm{IVM}}(t)\right)S_{m,\mathrm{IVM}}(t,\cdot)\end{pmatrix}. \tag{9}$$

Observe that the non-linear map $\mathcal{F}$ is not well defined (in the strict mathematical sense) on the space $\mathcal{X}_0$, this is due to the quantity N_h in the denominator on forces of infection. To sort this out, we use the same approach as in [27]. More precisely, for any $\epsilon>0$, we introduce the space

$$\mathcal{X}_\epsilon=\left\{\left\{u(t)\in\mathcal{X}_0:\mathcal{T}(u(t))\geq\epsilon\quad\right\}\subset\mathcal{X}_0, \tag{10}$$

where $\mathcal{T}:\mathcal{X}\longrightarrow\mathcal{X}$ is the operator defined by

$$\mathcal{T}(u(t))=\|v_h(t)\|_{\mathbb{R}^2}+\|u_h(t)\|_{\mathbb{R}^2}+\left\|v_{h,\mathrm{IVM}}(t,\cdot)\right\|_{L^1(\mathbb{R}_+,\mathbb{R}^2)}+\left\|u_{h,\mathrm{IVM}}(t,\cdot)\right\|_{L^1(\mathbb{R}_+,\mathbb{R}^2)}.$$

It should be noted that for $\epsilon=0$, the space $\mathcal{X}_\epsilon$ corresponds to $\mathcal{X}_0=\overline{D(\mathcal{A})}$. Hence, define $\mathcal{F}_\epsilon:\mathcal{X}_\epsilon\longrightarrow\mathcal{X}$ by $\mathcal{F}_\epsilon\equiv\mathcal{F}$. Therefore, the abstract Cauchy problem associated with systems (5)–(7) writes

$$\frac{\mathrm{d}u}{\mathrm{d}t}(t)=\mathcal{A}u(t)+\mathcal{F}_\epsilon(u(t)),\ t>0,\quad u(0)=u_0\in\mathcal{X}_{0,+}\text{ for each }\epsilon>0. \tag{11}$$

Theorem 3.2: *Suppose that Assumption 3.1 holds. Then there exists a unique globally defined strongly continuous semiflow $\{U(t)\}_{t\geq0}$ on $\mathcal{X}_+\cap\mathcal{X}_{\bar\epsilon}$ for Problem (11). Where $\bar\epsilon$ is a positive constant such that*

$$\bar\epsilon\in\left(0,\frac{\Lambda_h}{\mu_h+\nu_h+\phi+\gamma_h+\delta_h+k_h+\|\rho\|_{L^\infty}}\right).$$

Furthermore $\{U(t)\}_{t\geq0}$ satisfies the following properties:

(i) *Let*

$$\mu_m^*=\min\left\{\ \mu_m,\left\|\mu_{m,\mathrm{IVM}}\right\|_{L^\infty}\ \right\},$$

for each $u_0=(v_{h0},u_{m0},S_{m0},I_{m0},v_{h0,\mathrm{IVM}},u_{h0,\mathrm{IVM}},S_{m0,\mathrm{IVM}},I_{m0,\mathrm{IVM}})^T\in\mathcal{X}_+\cap\mathcal{X}_{\bar\epsilon}$, one has for all $t\geq0$:

$$N_h(t)\leq N_h(0)\,\mathrm{e}^{-\mu_ht}+\frac{\Lambda_h}{\mu_h}\left(1-\mathrm{e}^{-\mu_ht}\right),\quad N_m(t)\leq N_m(0)\,\mathrm{e}^{-\mu_m^*t}+\frac{\Lambda_h}{\mu_m^*}\left(1-\mathrm{e}^{-\mu_m^*t}\right),$$

$$N_h(t)\geq N_h(0)\,\mathrm{e}^{-(\mu_h+\delta_h)t}+\frac{\Lambda_h}{\mu_h+\delta_h}\left(1-\mathrm{e}^{-(\mu_h+\delta_h)t}\right),$$

$$N_m(t) \geq N_m(0)\,\mathrm{e}^{-(\mu_m+\|\mu_{m,\mathrm{IVM}}\|_{L^\infty})t} + \frac{\Lambda_h}{\mu_m + \|\mu_{m,\mathrm{IVM}}\|_{L^\infty}}\left(1-\mathrm{e}^{-(\mu_m+\|\mu_{m,\mathrm{IVM}}\|_{L^\infty})t}\right).$$

In addition, each sub-population is bounded such that

$$\limsup_{t\to\infty}\|y_h(t)\| \leq \frac{\Lambda_h}{\mu_h}, \quad \text{for } y_h \in \{v_h, u_h, v_{h,\mathrm{IVM}}, u_{h,\mathrm{IVM}}\},$$
$$\limsup_{t\to\infty}\|y_m(t)\| \leq \frac{\Lambda_m}{\mu_m^*}, \quad \text{for } y_m \in \{S_m, I_m, S_{m,\mathrm{IVM}}, I_{m,\mathrm{IVM}}\}.$$

(ii) *Let* $U(t)u_0 = (v_h(t), u_h(t), S_m(t), I_m(t), 0_{\mathbb{R}^2}, v_{h,\mathrm{IVM}}(t,\cdot), 0_{\mathbb{R}^2}, u_{h,\mathrm{IVM}}(t,\cdot), 0_{\mathbb{R}}, S_{m,\mathrm{IVM}}(t,\cdot), 0_{\mathbb{R}}, I_{m,\mathrm{IVM}}(t,\cdot))^T$, *for each* $t > 0$, *then the following Volterra formulation holds true:*

$$v_{h,\mathrm{IVM}}(t,\tau) = \begin{cases} \phi v_h(t-\tau)\exp\left(-\int_0^\tau (\lambda_m(\sigma+t-\tau)E_1 + (\mu_h+\rho(\sigma))\mathrm{I_d} - K_h)\,\mathrm{d}\sigma\right) \\ \quad + \int_0^\tau \gamma_h E_2 u_{h,\mathrm{IVM}}(s+t-\tau, s)\exp\left(-\int_s^\tau (\lambda_m(\sigma+t-\tau)E_1 \right. \\ \quad \left. +(\mu_h+\rho(\sigma))\mathrm{I_d} - K_h)\,\mathrm{d}\sigma\right)\,\mathrm{d}s \quad \forall\, \tau < t, \\ v_{h0,\mathrm{IVM}}(\tau-t)\exp\left(-\int_0^t (\lambda_m(\sigma)E_1 + (\mu_h+\rho(\sigma+\tau-t))\mathrm{I_d} - K_h)\,\mathrm{d}\sigma\right) \\ \quad + \int_0^t \gamma_h E_2 u_{h,\mathrm{IVM}}(s, s+\tau-t)\exp\left(-\int_s^t (\lambda_m(\sigma)E_1 \right. \\ \quad \left. +(\mu_h+\rho(\sigma+\tau-t))\mathrm{I_d} - K_h)\,\mathrm{d}\sigma\right)\,\mathrm{d}s \quad \forall\, t < \tau. \end{cases} \tag{12}$$

$$u_{h,\mathrm{IVM}}(t,\tau) = \begin{cases} \phi E_1 u_h(t-\tau)\exp\left(-\int_0^\tau (D_h + \rho(\sigma)\mathrm{I_d})\,\mathrm{d}\sigma\right) \\ \quad + \int_0^\tau \lambda_m(s+t-\tau)E_1 v_{h,\mathrm{IVM}}(s+t-\tau, s) \\ \quad \exp\left(-\int_s^\tau (D_h+\rho(\sigma)\mathrm{I_d})\,\mathrm{d}\sigma\right)\,\mathrm{d}s \quad \forall\, \tau < t, \\ u_{h0,\mathrm{IVM}}(\tau-t)\exp\left(-\int_0^t (D_h + \rho(\sigma+\tau-t)\mathrm{I_d})\,\mathrm{d}\sigma\right) \\ \quad + \int_0^t \lambda_m(s)E_1 u_{h,\mathrm{IVM}}(s, s+\tau-t) \\ \quad \exp\left(-\int_s^t (D_h+\rho(\sigma+\tau-t)\mathrm{I_d})\,\mathrm{d}\sigma\right)\,\mathrm{d}s \quad \forall\, t < \tau. \end{cases}$$

$$S_{m,\mathrm{IVM}}(t,\eta) = \begin{cases} \lambda^S_{h,\mathrm{IVM}}(t-\eta)S_m(t-\eta) \\ \quad \exp\left(-\int_0^\eta \left(\lambda_h(\sigma+t-\eta) + \lambda^I_{h,\mathrm{IVM}}(\sigma+t-\eta) + \mu_{m,\mathrm{IVM}}(\sigma)\right)\mathrm{d}\sigma\right) \quad \forall\, \eta < t, \\ S_{m0,\mathrm{IVM}}(\eta-t) \\ \quad \exp\left(-\int_0^t \left(\lambda_h(\sigma) + \lambda^I_{h,\mathrm{IVM}}(\sigma) + \mu_{m,\mathrm{IVM}}(\sigma-\eta-t)\right)\mathrm{d}\sigma\right) \quad \forall\, t < \eta. \end{cases}$$

$I_{m,\mathrm{IVM}}(t,\eta)$

$$
= \begin{cases} \Big(\lambda^I_{h,\mathrm{IVM}}(t-\eta)S_m(t-\eta) + \Big(\lambda^S_{h,\mathrm{IVM}}(t-\eta) + \lambda^I_{h,\mathrm{IVM}}(t-\eta)\Big) I_m(t-\eta)\Big) \\ \quad \exp\left(-\int_0^\eta \mu_{m,\mathrm{IVM}}(\sigma)\,\mathrm{d}\sigma\right) \\ \quad + \int_0^\eta \left(\lambda_h(s+t-\eta) + \lambda^I_{h,\mathrm{IVM}}(s+t-\eta)\right) S_{m,\mathrm{IVM}}(s+t-\eta, s) \\ \quad \exp\left(-\int_s^\eta \mu_{m,\mathrm{IVM}}(\sigma)\,\mathrm{d}\sigma\right)\,\mathrm{d}s \quad \forall\, \eta < t, \\ I_{m0,\mathrm{IVM}}(\eta - t)\exp\left(-\int_0^t \mu_{m,\mathrm{IVM}}(\sigma+\eta-t)\,\mathrm{d}\sigma\right) \\ \quad + \int_0^t \left(\lambda_h(s) + \lambda^I_{h,\mathrm{IVM}}(s)\right) S_{m,\mathrm{IVM}}(s, s+\eta-t) \\ \quad \exp\left(-\int_s^t \mu_{m,\mathrm{IVM}}(\sigma+\eta-t)\,\mathrm{d}\sigma\right)\,\mathrm{d}s \quad \forall\, t < \eta. \end{cases} \tag{13}
$$

(iii) *For a mild solution $u \in \mathcal{C}([0,\tau_0], \mathcal{X}_\epsilon \cap \mathcal{X}_+)$ to (11), and for a sequence of initial data $\{u_0^k\}_{k\geq 0} \in D(\mathcal{A})^{\mathbb{N}}$ such that $\lim_{k\to\infty} \|u_0^k - u_0\|_{\mathcal{X}} = 0$, with $k \geq 0$, there exists a unique solution $u^k \in \mathcal{C}^1(\mathbb{R}_+, \mathcal{X}_{\bar\epsilon} \cap \mathcal{X}_+)$ to the system* (11), *with initial data u_0^k such that* $\lim_{k\to\infty} \|u^k - u\|_{\mathcal{X}} = 0$ *so that $u \in \mathcal{C}(\mathbb{R}_+, \mathcal{X}_{\bar\epsilon} \cap \mathcal{X}_+)$.*

The Volterra integral formulation within the framework of age-structured equations is a well-established concept, e.g. see [33] and the associated references. The proof of Theorem 3.2 is given in Section A.1.

3.2. The disease-free steady state and reproduction number

In an infection free population, the disease-free steady of systems (5)–(7), denoted here as E^0, is given by

$$
E^0 = \left(v_h^0, 0_{\mathbb{R}^2}, S_m^0, 0, v_{h,\mathrm{IVM}}^0(\cdot), 0_{L^1(\mathbb{R}_+,\mathbb{R}^2_+)}, S_{m,\mathrm{IVM}}^0(\cdot), 0_{L^1(\mathbb{R}_+,\mathbb{R}_+)}\right)^T, \tag{14}
$$

with

$$
N_h^0 = \frac{\Lambda_h}{\mu_h + \phi(1-\chi_h)}\left(1 + \phi\int_0^\infty \Psi_h(\tau)\,\mathrm{d}\tau\right),
$$

$$
v_h^0 = \left(\frac{\Lambda_h}{\mu_h + \phi(1-\chi_h)}, 0\right)^T, \quad v_{h,\mathrm{IVM}}^0(\tau) = \left(\frac{\phi\Lambda_h\Psi_h(\tau)}{\mu_h + \phi(1-\chi_h)}, 0\right)^T,
$$

$$
S_m^0 = \frac{\Lambda_m}{\mu_m + \lambda_h^0[\phi]}, \quad S_{m,\mathrm{IVM}}^0(\eta) = S_m^0\lambda_h^0[\phi]\Gamma_m(\eta),
$$

and where

$$
\Gamma_m(\eta) = \mathrm{e}^{-\int_0^\eta \mu_{m,\mathrm{IVM}}(s)\,\mathrm{d}s}, \quad \Psi_h(\tau) = \mathrm{e}^{-\int_0^\tau (\mu_h + \rho(s))\,\mathrm{d}s},
$$

$$
\chi_h = \int_0^\infty \rho(\tau)\Psi_h(\tau)\,\mathrm{d}\tau, \quad \lambda_h^0[\phi] = \theta\frac{\phi\int_0^\infty \Psi_h(\tau)\,\mathrm{d}\tau}{1 + \phi\int_0^\infty \Psi_h(\tau)\,\mathrm{d}\tau}.
$$

Furthermore, $\Gamma_m(\eta)$ represents the survival probability that of a mosquito η time after exposure to IVM. Similarly, $\Psi_h(\tau)$ quantifies the probability that a human remains in the IVM class τ-time post exposure. Therefore, the quantity χ_h represents the average rate of loss of IVM efficiency within the human population, and $\lambda_h^0[\phi]$ the rate at which mosquitoes come into contact with IVM (by biting a human) without leading to infections. It is important to emphasize that those parameters are well-defined constants because Assumption 3.1 holds, and particularly we have $\chi_h \leq 1$. We refer to Section A.2 for the computation of the disease-free steady state.

To calculate the basic reproduction number $\mathcal{R}_0$, we employ the next-generation operator methodology, e.g. see [34, 35]. During the initial phase of the epidemic, the population dynamics can be approximated using the linearized equations around the disease-free steady state E^0. As the linearized equation for the infective population does not involve other sub-populations, we establish that the next-generation operator $\mathcal{G}$ is defined from $(\mathbb{R}^2 \times L^1((0,\infty),\mathbb{R}^2)) \times (\mathbb{R} \times L^1((0,\infty),\mathbb{R}))$ to itself by

$$\mathcal{G}\left(\begin{pmatrix}\psi_h \\ \bar{\psi}_h\end{pmatrix} \atop \begin{pmatrix}\varphi_m \\ \bar{\varphi}_m\end{pmatrix}\right) = \begin{pmatrix}\mathcal{A} & \mathcal{B} \\ \mathcal{C} & 0_{\mathbb{R}\times L^1(\mathbb{R}_+,\mathbb{R})}\end{pmatrix}\left(\begin{pmatrix}\psi_h \\ \bar{\psi}_h\end{pmatrix} \atop \begin{pmatrix}\varphi_m \\ \bar{\varphi}_m\end{pmatrix}\right), \tag{15}$$

where the operators $\mathcal{A} : \mathbb{R}^2 \times L^1((0,\infty),\mathbb{R}^2) \to \mathbb{R}^2 \times L^1((0,\infty),\mathbb{R}^2)$, $\mathcal{B} : \mathbb{R} \times L^1((0,\infty),\mathbb{R}) \to \mathbb{R}^2 \times L^1((0,\infty),\mathbb{R}^2)$, and $\mathcal{C} : \mathbb{R}^2 \times L^1((0,\infty),\mathbb{R}^2) \to \mathbb{R} \times L^1((0,\infty),\mathbb{R})$ are as follows:

$$\begin{aligned}
\mathcal{A}\begin{pmatrix}\psi_h \\ \bar{\psi}_h\end{pmatrix} &= \begin{pmatrix}\int_0^\infty \rho(\tau)\Gamma_h(\tau)\bar{\psi}_h(\tau)\,\mathrm{d}\tau \\ 0_{L^1(\mathbb{R}_+,\mathbb{R}^2)}\end{pmatrix}, \\
\mathcal{B}\begin{pmatrix}\varphi_m \\ \bar{\varphi}_m\end{pmatrix} &= \frac{\theta\beta_m}{N_h^0}\left(\frac{\varphi_m}{\mu_m + \lambda_h^0[\phi]} + \int_0^\infty \Gamma_m(\eta)\bar{\varphi}_m(\eta)\,\mathrm{d}\eta\right)\begin{pmatrix}E_1\nu_h^0 \\ E_1\nu_{h,\mathrm{IVM}}^0\end{pmatrix}, \\
\mathcal{C}\begin{pmatrix}\psi_h \\ \bar{\psi}_h\end{pmatrix} &= \frac{\theta\beta_h}{N_h^0}\begin{pmatrix}e(\phi E_1 + D_h)^{-1}\psi_h S_m^0 \\ \left(e(\phi E_1 + D_h)^{-1}\psi_h + \int_0^\infty e\Gamma_h(\tau)\bar{\psi}_h(\tau)\,\mathrm{d}\tau\right) S_{m,\mathrm{IVM}}^0\end{pmatrix},
\end{aligned}$$

with

$$\Gamma_h(\tau) = \mathrm{e}^{-\int_0^\tau (\rho(a)\mathrm{I_d} + D_h)\,\mathrm{d}a}.$$

Note that $\Gamma_h(\tau)$ represents the survival probability that of a human τ time after infection. It is worth noting that the operators $\mathcal{B}$ and $\mathcal{C}$ are referred to as *the net reproduction operators* [34, 35]. The operator $\mathcal{B}$ enables the calculation of the total count of new human infections caused by an infective mosquito population. In contrast, the operator $\mathcal{C}$ calculates the count of new infected mosquitoes resulting from an infective human population. Finally, the operator $\mathcal{A}$ allows in quantifying the overall decrease in IVM efficiency within the human population that has been exposed to IVM.

Consequently, based on the above estimates, $\mathcal{R}_0$ is characterized as the spectral radius of the next-generation operator $\mathcal{G}$, that is

$$\mathcal{R}_0 = r(\mathcal{G}).$$

For a comprehensive understanding of the computation of $\mathcal{G}$, please refer to Section A.3.

An explicit expression of $\mathcal{R}_0$ is quite difficult to obtain within the context of the model developed here. However, without the effect of IVM, the next-generation operator $\mathcal{G}$ rewrites as a 3×3 matrix as follows:

$$\mathcal{G} = \begin{pmatrix} 0_{2\times 2} & \frac{\theta\beta_m}{\mu_m}\begin{pmatrix}1 \\ 0\end{pmatrix} \\ \theta\beta_h \frac{\Lambda_m/\mu_m}{\Lambda_h/\mu_h} e D_h^{-1} & 0 \end{pmatrix}.$$

From which, we find that

$$\mathcal{R}_0^2 = r(\mathcal{G}^2) = \theta^2 \frac{\beta_m\beta_h}{\mu_m}\frac{\Lambda_m/\mu_m}{\Lambda_h/\mu_h}\frac{\mu_h + \nu_h + \gamma_h + \delta_h}{(\mu_h + \nu_h)(\mu_h + \gamma_h + \delta_h)}. \tag{16}$$

The above expression aligns with the $\mathcal{R}_0$ value commonly associated with the classical human–mosquito transmission model, without accounting for ivermectin.

3.3. Threshold dynamics

Here we state the threshold dynamics of systems (5)–(7) in relation to $\mathcal{R}_0$ as follows:

Theorem 3.3: *Let Assumption 3.1 be satisfied.*

(i) *If* $\mathcal{R}_0 < 1$, *the disease-free steady state* E^0 *is the unique equilibrium of systems* (5)–(7).
(ii) *If* $\mathcal{R}_0 > 1$, *alongside the disease-free steady state* E^0, *systems* (5)–(7) *possess at least one positive (or endemic) equilibrium.*
(iii) *The disease-free steady state* E^0 *is locally asymptotically stable when* $\mathcal{R}_0 < 1$ *and it becomes unstable when* $\mathcal{R}_0 > 1$.

Details on the proof of Theorem 3.3 are given in Sections A.4 and A.5.

According to Theorem 3.3, it is established that when $\mathcal{R}_0 > 1$, systems (5)–(7) possess at least one positive equilibrium. Nonetheless, it is important to note that the bifurcation of an endemic equilibrium at $\mathcal{R}_0 = 1$ is typically observed in the context of vector-borne diseases [27, 36].

Let us introduce the parameter,

$$\bar{r}_0 = \theta^2 \beta_h \beta_m \frac{\Lambda_m S_h^0 e M_1 e_1}{\left(\mu_m S_h^0 + \theta \int_0^\infty S_{h,\mathrm{IVM}}^0(\tau)\, \mathrm{d}\tau\right)^2},$$

with M_1 a matrix such that

$$M_1 = \left(\phi E_1 + D_h - \int_0^\infty \phi\rho(\tau)\Gamma_h(\tau)E_1\, \mathrm{d}\tau\right)^{-1} \left(E_1 + \int_0^\infty \int_0^\infty \phi\rho(\tau)\frac{\Gamma_h(\tau)}{\Gamma_h(\sigma)}E_1 l(0,\tau)\, \mathrm{d}\sigma\, \mathrm{d}\tau\right),$$

where $\ell(\lambda,\tau) = \mathrm{e}^{-\int_0^\tau (\lambda E_1 + \mu_h + \rho(\sigma) - K_h)\, \mathrm{d}\sigma}$.

Therefore, we can determine the existence of a positive equilibrium for systems (5)–(7) by proving that there exists a positive value of λ such that

$$\bar{G}(\bar{r}_0, \lambda) = 1,$$

with $\bar{G}$ defined by

$$\bar{G}(\bar{r}_0,\lambda) = \frac{\theta^2\beta_h\beta_m\Lambda_m e M_1 g_1(\lambda)}{\left[\mu_m\left(\lambda e M_1 + e\right) g_1(\lambda) + \lambda e M_1 g_1(\lambda) + g_2(\lambda)\right]\left[\mu_m\left(\lambda e M_1 + e\right) g_1(\lambda) + g_2(\lambda)\right]},$$

wherein

$$\begin{aligned} g_1(\lambda) = \Bigg(&\lambda E_1 + (\mu_h + \phi) I_\mathrm{d} - K_h - \lambda\gamma_h E_2 M_1 - \int_0^\infty \phi\rho(\tau) l(0,\tau)\, \mathrm{d}\tau \\ &- \lambda\int_0^\infty\int_0^\tau \phi\gamma_h\rho(\tau)\frac{l(0,\tau)}{l(0,\sigma)}E_2\Gamma_h(\tau)E_1M_1\, \mathrm{d}\sigma\, \mathrm{d}\tau \\ &-\lambda\int_0^\infty\int_0^\tau\int_0^\sigma \phi\gamma_h\rho(\tau)\frac{l(0,\tau)}{l(0,\sigma)}E_2\frac{\Gamma_h(\sigma)}{\Gamma_h(\varsigma)}E_2 l(0,\varsigma)\, \mathrm{d}\varsigma\, \mathrm{d}\sigma\, \mathrm{d}\tau\Bigg)^{-1} \Lambda_h e_1 \end{aligned}$$

and

$$\begin{aligned} g_2(\lambda) = \theta\beta_h\lambda &\int_0^\infty e\left[\phi\Gamma_h(\tau)E_1M_1 + \int_0^\tau \phi\frac{\Gamma_h(\tau)}{\Gamma_h(\sigma)}E_1 l(0,\tau)\right] g_1(\lambda)\, \mathrm{d}\tau \\ &+\theta\int_0^\infty e\Bigg[\ell(0,\tau)\phi g_1(\lambda) + \gamma_h\lambda\int_0^\tau \phi\frac{\ell(0,\tau)}{\ell(0,\sigma)}E_2\left(\Gamma(\sigma)E_1M_1\right. \end{aligned}$$

$$+\int_0^{\sigma}\frac{\Gamma_h(\sigma)}{\Gamma_h(\varsigma)}E_1 l(0,\varsigma)\,d\varsigma\bigg)g_1(\lambda)\,d\sigma\bigg]\,d\tau.$$

Next, let us also introduce the following bifurcation parameter:

$$C_{\text{bif}} = \frac{S_h^0\,[2\mu_m eM_1 + eM_1 + 2\mu_m eM_2 + 2M_3]\,e_1}{\mu_m S_h^0 + \int_0^\infty \theta S_{h,\text{IVM}}^0(\tau)\,d\tau} - \frac{eM_1M_2e_1}{eM_1e_1},$$

with M_2 and M_3 being matrices such that

$$\begin{aligned}M_2 = \bigg(&\gamma_h E_2 M_1 + \int_0^\infty\int_0^\tau \phi\gamma_h\rho(\tau)\frac{l(0,\tau)}{l(0,\sigma)}E_2\Gamma_h(\tau)E_1M_1\,d\sigma\,d\tau\\ &+\int_0^\infty\int_0^\tau\int_0^\sigma \phi\gamma_h\rho(\tau)\frac{l(0,\tau)}{l(0,\sigma)}E_2\frac{\Gamma_h(\sigma)}{\Gamma_h(\varsigma)}E_2 l(0,\varsigma)\,d\varsigma\,d\sigma\,d\tau - E_1\bigg)\\ &\times\left((\mu_h+\phi)\,I_{\text{d}} - K_h - \int_0^\infty \phi\rho(\tau)l(0,\tau)\,d\tau\right)^{-1}\end{aligned}$$

and

$$\begin{aligned}M_3 = \theta\beta_h&\int_0^\infty e\left[\phi\Gamma_h(\tau)E_1M_1 + \int_0^\tau \phi\frac{\Gamma_h(\tau)}{\Gamma_h(\sigma)}E_1 l(0,\tau)\right]d\tau + \theta\int_0^\infty e\ell(0,\tau)\phi\,d\tau\\ &+\theta\int_0^\infty e\left[\gamma_h\int_0^\tau \phi\frac{\ell(0,\tau)}{\ell(0,\sigma)}E_2\left(\Gamma(\sigma)E_1M_1 + \int_0^\sigma\frac{\Gamma_h(\sigma)}{\Gamma_h(\varsigma)}E_1 l(0,\varsigma)\,d\varsigma\right)d\sigma.\right.\end{aligned}$$

Afterward, the subsequent outcome pertaining to the existence and bifurcation of the positive equilibrium is derived.

Theorem 3.4: *Let Assumption 3.1 be satisfied. Then*

(1) *If* $C_{\text{bif}} > 0$*, there is a backward bifurcation at rate* $\bar{r}_0 = 1$*, i.e. systems* (5)–(7) *admit two positive equilibria for* $\bar{r}_0 < 1$ *close enough to 1.*
(2) *If* $C_{\text{bif}} < 0$*, there is a forward bifurcation at rate* $\bar{r}_0 = 1$*, systems* (5)–(7) *admit a unique positive equilibrium for* $\bar{r}_0 < 1$ *close enough to 1.*

Details on the proof of Theorem 3.4 are given in Section A.6.

In the absence of the effect of IVM, i.e. when $\phi = 0$, the parameter $\bar{r}_0$ becomes

$$\bar{r}_0 = \theta^2\beta_h\beta_m\frac{\Lambda_m eM_1e_1}{\mu_m^2 S_h^0}.$$

In such a configuration, it is important to observe that the bifurcation parameter $\bar{r}_0$ corresponds to the expression of $\mathcal{R}_0^2$ without considering the impact of IVM, as given in (16). Furthermore, in this scenario, the bifurcation parameter rewrites

$$C_{\text{bif}} = -\frac{\Lambda_m}{\mu_m^2}\frac{\mu_h+\nu_h+\gamma_h+\delta_h}{\Lambda_h}\left(1 - \frac{\mu_h^3(1+2\mu_m)\bar{a} + 2\mu_h\mu_m\Lambda_h(1-\bar{a})}{\mu_m\Lambda_h^2(\mu_h+\nu_h)(\mu_h+\gamma_h+\delta_h)}\right),$$

wherein $\bar{a} = \frac{\gamma_h\nu_h}{(\mu_h+\nu_h)(\mu_h+\gamma_h+\delta_h)}$.

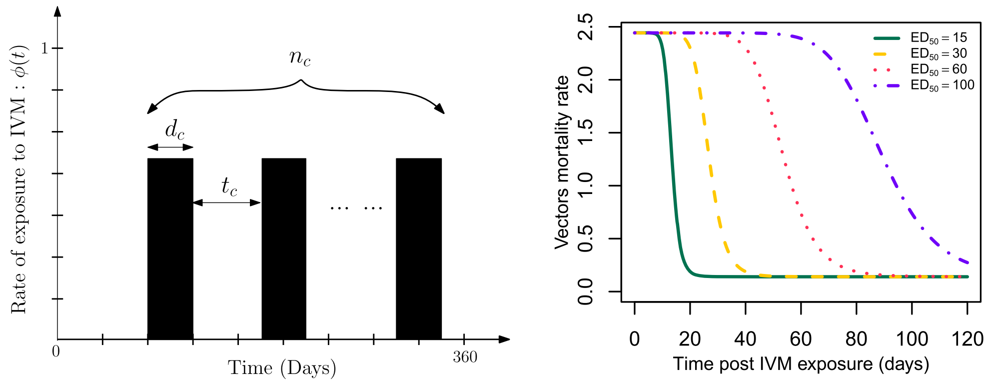

Figure 2. (Left) An ivermectin implementation strategies: n_c the number of interventions implemented within 1 year, d_c the duration of one intervention and t_c the duration between two successive interventions. (Right) The mortality rate $\mu_{m,\mathrm{IVM}}(\eta)$ of vector η-time post exposure to IVM for different values of the median effective dose ED_{50}.

3.4. Model parameters, numerical illustrations and global sensitivity analysis

For numerical illustrations, we consider the majority of parameters in Models (1)–(4) as fixed constants, as outlined in Table 1. However, we treat the natural mortality rate $\mu_{m,\mathrm{IVM}}$ for vectors exposed to IVM, and the rate ρ of IVM efficiency loss within the human population exposed to IVM as variable parameters. Additionally, while assuming the rate ϕ of humans exposure to IVM as a constant helps for the mathematical analysis of the proposed model, it is worth noting that for our numerical illustrations, we consider ϕ as a time-dependent parameter. Taking ϕ as a time-dependent parameter in our numerical illustrations reflects a practical approach, allowing us to capture realistic scenarios and better simulate the dynamic nature of interventions in practical situations.

Model parameters. More precisely, we set the duration of an intervention, denoted as d_c, to a fixed value of 7 days. Based on the number of interventions implemented within 1 year, denoted as n_c, and the duration between two successive interventions, denoted as t_c, we define the rate $\phi(t)$ of human exposure to IVM at time t. The profile of this parameter is illustrated in Figure 2, capturing the dynamic nature of an intervention strategy.

Define $p_{m,\mathrm{IVM}}(\sigma)$ as the proportion of mosquitoes that perish after biting a human exposed to IVM since time σ. We assume that

$$p_{m,\mathrm{IVM}}(\sigma) = \frac{0.9}{1 + \left(\frac{\sigma}{\mathrm{ED}_{50}}\right)^{-10}},$$

where ED_{50} is the median effective dose. Therefore, the mortality rate $\mu_{m,\mathrm{IVM}}(\eta)$ of vector η-time post exposure to IVM is such that Figure 2

$$\mu_{m,\mathrm{IVM}}(\eta) = \mu_m - \log\left(1 - p_{m,\mathrm{IVM}}(\eta)\right), \tag{17}$$

where μ_m is the base line vector mortality rate. Finally, we assume that the rate $\rho(\tau)$ at which the effect of IVM vanishes within a human τ-time post exposure is such that

$$\rho(\tau) = \begin{cases} \alpha, & \tau > \mathrm{ED}_{50}, \\ 0 & \text{elsewhere}. \end{cases} \tag{18}$$

Note that in the above formulation, the overall average duration of time a human is under IVM after exposure is ED_{50}. Specifically, let $J(\tau) = \exp\left(-\int_0^\tau \rho(\sigma)\,\mathrm{d}\sigma\right)$ the probability that a human exposed to IVM remains in such a state τ-time post exposure (excluding other mechanisms like human natural mortality). The average duration of time under the effect of IVM is given by $\int_0^\infty J(\tau)\,\mathrm{d}\tau =$

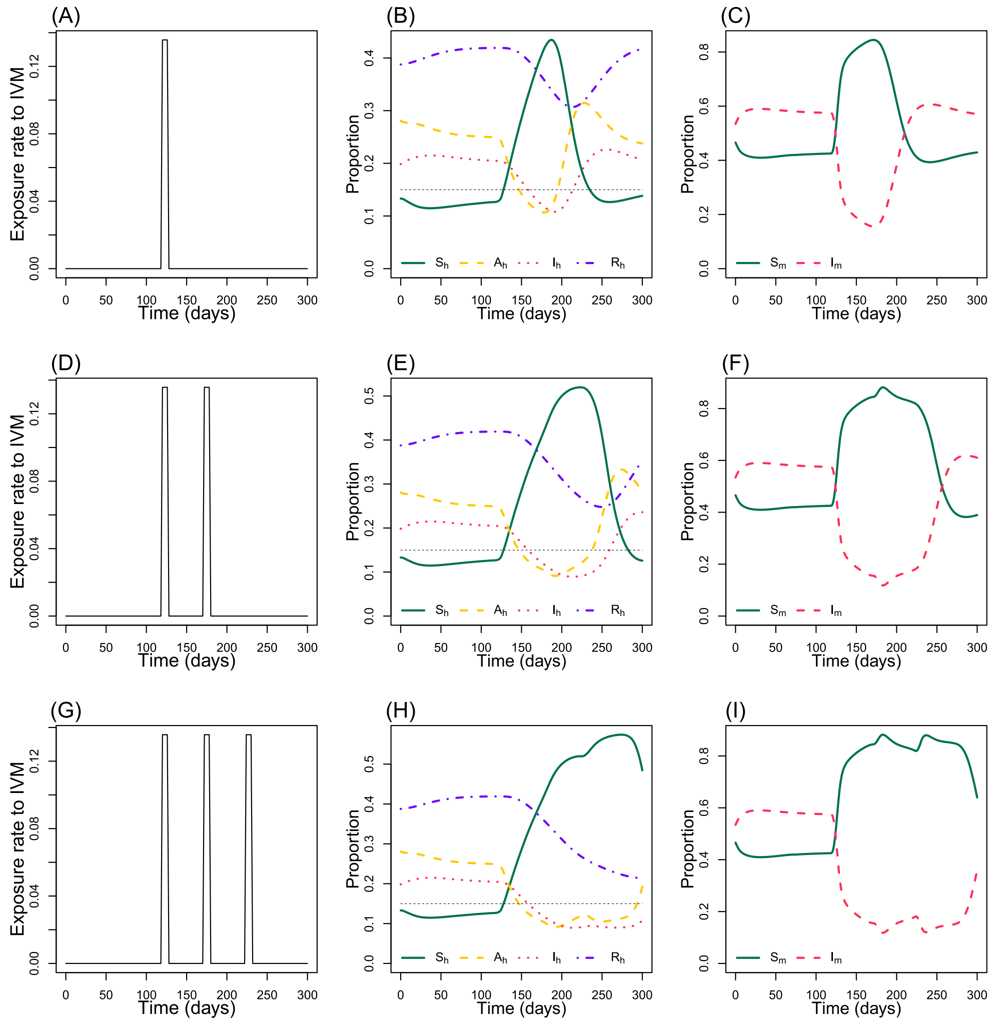

Figure 3. Effect of the IVM strategy on the epidemic outbreak. (A) The IVM campaign consists of 1 cycle, with 45 days between successive cycles, and the IVM formulation is with $ED_{50} = 60$. The campaign begins on day 120 and by the end of each cycle, 95% of the target population is covered by IVM. (B) The impact of the IVM campaign on the human dynamics. (C) The impact of the IVM campaign on the mosquitoes dynamics. (D–F) Similar to panels A–C, but with an IVM campaign of two cycles. (G–I) Similar to panels A–C, but with an IVM campaign of three cycles.

$ED_{50} + 1/\alpha$. We choose, for example, $\alpha = 10$ such that $\int_0^\infty J(\tau)\,d\tau = ED_{50} + 1/\alpha \approx ED_{50}$. The specific value of α becomes less significant as long as the last approximation holds.

Baseline simulated dynamics. We first use models (1)–(4) to describe the outbreak of the epidemics for a given IVM intervention strategy within the human population. We assume $ED_{50} = 60$ days and other parameters defined previously and summarized in Table 1. In each simulated scenario, the IVM intervention starts at $t = 120$ days, and the population dynamics reach a state of epidemiological equilibrium (Figure 3). Each intervention campaign lasts for $d_c = 7$ days, and the time between two successive campaigns is $t_c = 45$ days.

With a single IVM intervention campaign (Figures 3a–c), the prevalence of symptomatic cases is reduced by more than 20%, relative to the prevalence before the intervention. However, this reduction in prevalence is observed for a relatively short duration. The configuration remains essentially unchanged when increasing the number of IVM intervention campaigns to 2 (Figures 3d–f) or 3

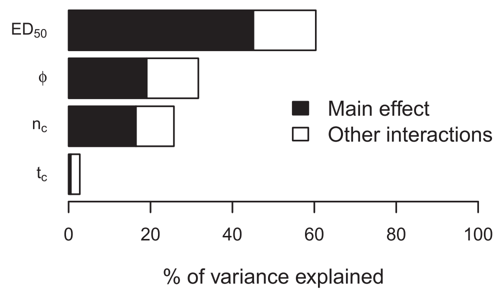

Figure 4. Sensitivity indices of the symptomatic cases $\Delta = \int_0^T [I_h(t) + I_{h,\mathrm{IVM}}(t,\tau)\,\mathrm{d}\tau]\,\mathrm{d}t$, over $T = 300$ days. The shaded parts of bars correspond to the main indices (effect of the factor alone). The complete bars, including both the shaded and unshaded parts, correspond to the effect of the factor in interaction with all other factors.

(Figures 3g–i). Nevertheless, the duration over which the intervention sustains a significant reduction in the prevalence of symptomatic cases substantially increases with the number of intervention campaigns.

Global sensitivity analysis. Global sensitivity analysis aims to assess the relative significance of model parameters by dividing the variance of output variables into components attributed to the primary effects of individual parameters and their interactions of higher orders. In this study, we explore the sensitivity of the symptomatic cases, given by $\Delta = \int_0^T [I_h(t) + I_{h,\mathrm{IVM}}(t,\tau)\,\mathrm{d}\tau]\,\mathrm{d}t$, over a time horizon $T = 300$ days. Initially, the model is assumed at the equilibrium without the effect of IVM. The focus is on evaluating the impact of four parameters: t_c, ED_{50}, ϕ and n_c. The range of variation is detailed in Table 1. To estimate the sensitivity indices, an analysis of variance (ANOVA), inclusive of third-order interactions, is fitted to simulation-generated data. It is essential to highlight that this ANOVA exhibits a high level of fitness, explaining more than 99% of the variance. The implementation of the model and the ANOVA analysis are both conducted with R software (http://www.r-project.org/). The sensitivity analyses reveal that the most influential factor affecting the symptomatic cases Δ is the median effective dose of the IVM formulation (ED_{50}), contributing to 45% of the variance (Figure 4). Followed closely are the target proportion of humans to be exposed to IVM during a campaign (ϕ) and the number of successive IVM campaigns (n_c), accounting for 19% and 16% of the variance respectively.

Optimal IVM campaign. In the context of a specified number n_c of IVM intervention campaigns, practical interest lies in identifying the minimum proportion of individuals to be exposed to IVM during a campaign as well as the corresponding time between two successive cycles t_c. One may aim to achieve, for example, a 10% reduction in prevalence. The effectiveness of such an optimal campaign is closely tied to the formulation of IVM, as captured by the ED_{50}. To attain a 10% reduction in prevalence with $\mathrm{ED}_{50} = 15$ days, a minimum of $n_c = 3$ cycles is required (Figure 5 a). The optimal campaign involves exposing a minimal proportion of around 80% of the population to IVM, with the time between cycles t_c falling within the range of 20–30 days (Figure 5 a). However, even with $n_c = 3$ cycles, identifying an optimal strategy to achieve a reduction of at least 20% in prevalence remains unfeasible with an IVM formulation such that $\mathrm{ED}_{50} = 15$ days (Figure 5 d). When the ED_{50} is set at 30 days, a minimum of $n_c = 2$ cycles is required to discern an optimal IVM strategy for a 10% reduction in prevalence (Figure 5 b). In contrast, achieving a reduction of at least 20% in prevalence demands at least $n_c = 3$ cycles for the identification of an optimal IVM strategy (Figure 5 e). Nevertheless, with a more prolonged effect of IVM featuring $\mathrm{ED}_{50} = 100$ days, achieving an optimal IVM strategy for a 10% or 20% reduction in prevalence is always feasible, even with just $n_c = 1$ cycle (Figure 5 c,f). Moreover, given the prolonged impact of IVM, the minimum percentage of individuals requiring exposure to IVM during a campaign remains relatively small and quite similar for both two and three

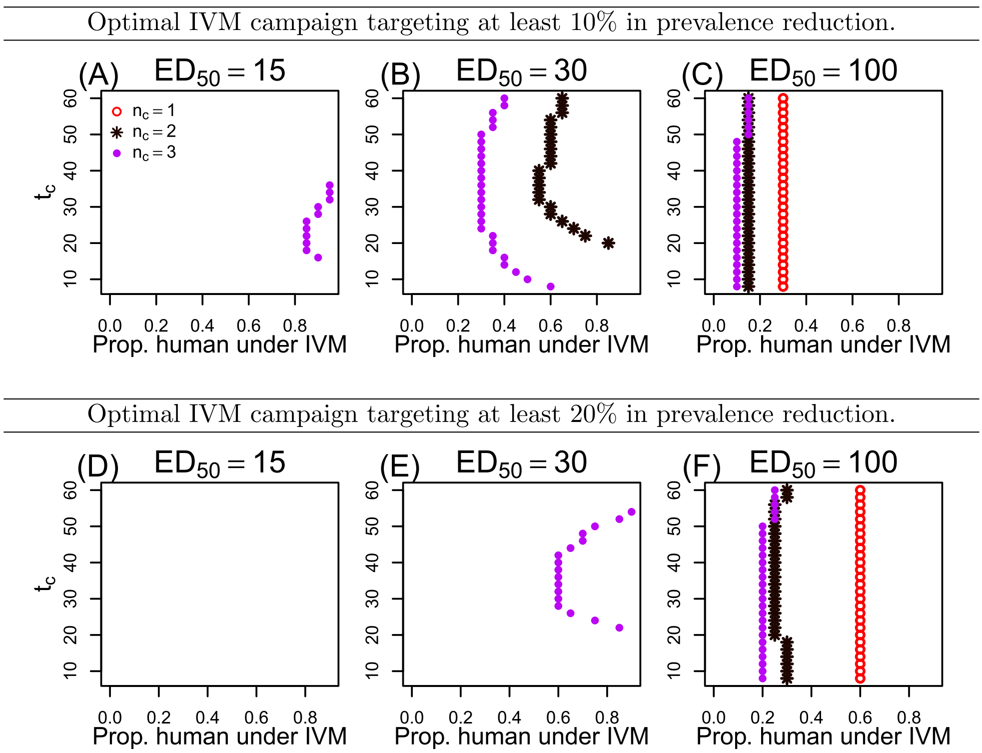

Figure 5. Line 1: Optimizing the IVM campaign to ensure a minimal reduction of 10% in prevalence relative to the prevalence before the intervention. For a fixed number of cycles n_c targeted for the IVM campaign, each figure panel determines whether we can find (i) the minimum proportion of humans to enroll during each IVM campaign to achieve the target prevalence reduction and (ii) the corresponding time between two successive cycles, denoted as t_c. Various IVM formulations are considered, with $ED_{50} \in \{15, 30, 100\}$. **Line 2**: The same as in Line 1 but with the target reduction in prevalence set at 20%.

cycles (Figures 5c,f). This proportion is higher when implementing the optimal IVM campaign with only one cycle (Figures 5c,f).

4. Discussion

IVM can be implemented as public health interventions to mitigate the malaria burden. Here, we explicitly factor in the time since human and vectors are exposed to IVM in the identification of the optimal deployment campaign, i.e. the optimal proportion of humans to be exposed to IVM during an intervention, as well as the time interval between subsequent interventions required to achieve a reduction in human prevalence.

The model formulation enables us to easily capture the variation in the IVM effect based on the duration since exposure. Additionally, diverse IVM formulations, as represented by the median effective dose ED_{50}, can be explored. The presented model enables the characterization of the optimal pairing based on the specific IVM formulation (Figure 5). For a relatively short-lasting effect of the IVM formulation, up to three interventions are necessary to ensure subsequent prevalence reduction. In contrast, a long-lasting effect of the formulation allows for a reduction in the number of interventions needed (Figure 5).

In this paper, we established the mathematical well-posedness of the model using classical integrated semigroups theory. Our analysis highlights the basic reproduction number $\mathcal{R}_0$ of the proposed model as the spectral radius of a next-generation operator given by (A16). This operator comprises components that facilitate (i) the computation of the total count of new human infections caused by

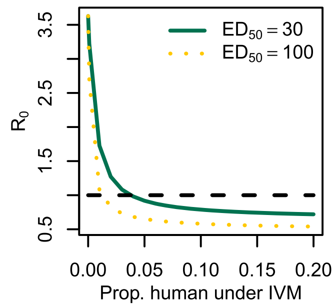

Figure 6. The basic reproduction number $\mathcal{R}_0$ varies with the proportion of humans exposed to IVM. The exposure rate is assumed to be constant within the human host population.

an infective mosquito population, (ii) the count of new infected mosquitoes resulting from an infective human population and (iii) the quantification of the overall decrease in IVM efficiency within the human population exposed to IVM. Due to the structure of the next-generation operator, especially considering the lost efficiency of IVM within the exposed human population, obtaining a more explicit expression for the $\mathcal{R}_0$ within the context of the developed model becomes challenging. Moreover, in our analysis, we uncover two distinct behaviors surrounding $\mathcal{R}_0 = 1$. In the first scenario, characterized by a forward bifurcation, an epidemic is only possible when $\mathcal{R}_0 > 1$. In the second scenario, marked by a backward bifurcation, an epidemic can emerge if $\mathcal{R}_0 < 1$, particularly when $\mathcal{R}_0$ is in close proximity to 1.

While deriving an explicit expression for the $\mathcal{R}_0$ within the framework of the proposed model is challenging, numerical simulations can aid in evaluating the impact of IVM on the $\mathcal{R}_0$. Indeed, assuming intervention campaigns occur at a constant rate ϕ, Figure 6 illustrates that even with a relatively small proportion of humans exposed to IVM, such a campaign could have a positive effect in reducing the malaria burden within a short time period. However, it is important to note that this effect may not necessarily persist for an extended duration, as in practice, IVM campaigns are not consistently maintained at a constant rate within the human host population. Therefore, optimizing IVM campaigns is crucial for ensuring a sustainable deployment and control of the malaria burden. Indeed, as depicted in Figure 5(f), with an IVM formulation where the median effective dose $ED_{50} = 100$ days, an optimal intervention campaign may involve designing $n_c = 2$ cycles, $t_c = 30$ days between two successive cycles, and exposing at least 30% of the target population to IVM. This strategy aims to ensure a minimum of 20% reduction in prevalence. Such an optimal campaign can maintain the reduction in prevalence for a relatively extended time period, especially when increasing the proportion of the targeted human host population to be exposed to IVM (Figure 7).

The size of endemicity plays a crucial role in the implementation of an IVM campaign. For example, consider an IVM strategy consisting of three cycles, with 45 days between each cycle (Figure 8 a). In a moderate endemic setting, this approach can sustainably reduce the prevalence of symptomatic cases by more than 20% compared to the pre-intervention levels (Figure 8 b). However, as endemicity increases, the effectiveness of this strategy diminishes significantly (Figures 8c,d). The model presented here does not consider the chronological age heterogeneity of the human population which is a limitation given that the majority of clinical cases are observed in the younger population [2]. The primary human infectious reservoir is believed to predominantly comprise children aged 5–15 [37, 38]. Furthermore, the production of gametocytes within a human host is closely linked to the time post-infection [39], and mosquito senescence is a crucial factor for a comprehensive understanding of the overall dynamics [27, 40]. Therefore, incorporating additional structuring variables such as the chronological and infection ages of both human and mosquito populations, along with the time since recovery to depict potential waning immunity in humans, would be appropriate for a more realistic quantification of the impact of IVM on malaria transmission. Another potential limitation is the

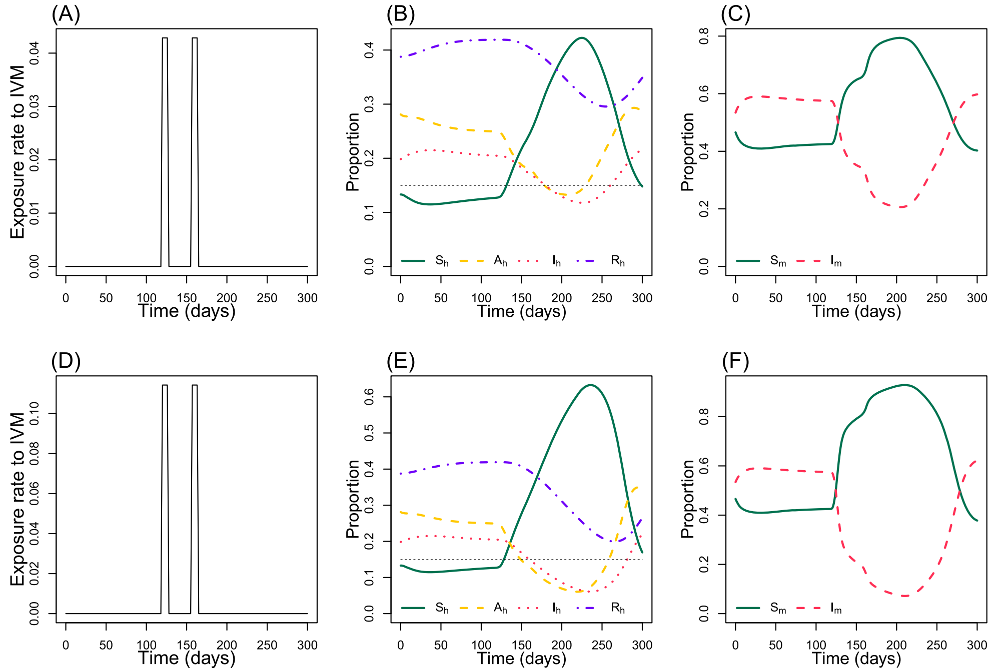

Figure 7. Effect of an optimal campaign to ensure a minimal reduction of 20% in prevalence. Here, the IVM formulation is such that $ED_{50} = 100$ days. An optimal intervention campaign involves two cycles and 30 days between two successive cycles. **Line 1**: 30% of human exposed to IVM. **Line 2**: 80% of human exposed to IVM.

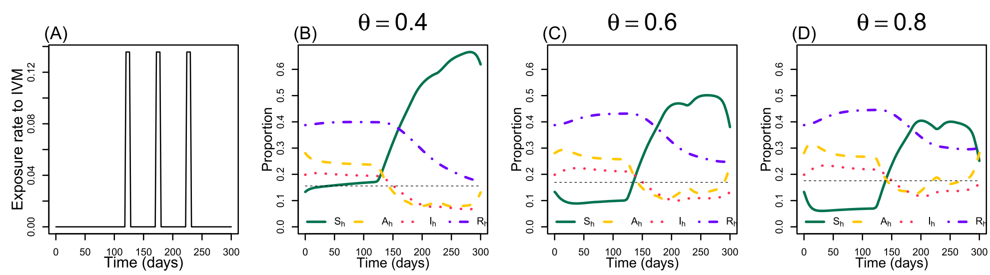

Figure 8. Effect of an IVM strategy on the epidemic outbreak for different endemicities. (A) The IVM campaign consists of 3 cycles, with 45 days between successive cycles, and the IVM formulation is with $ED_{50} = 60$. The campaign begins on day 120 and by the end of each cycle, 95% of the target population is covered by IVM. (B) The impact of the IVM campaign on the outbreak is shown for a mosquito biting rate of $\theta = 0.4$. (C-D) Similar to panel B, but with mosquito biting rates of $\theta = 0.4$ and 0.8 respectively.

absence of gender structure in the model formulation. It can be anticipated that pregnant women may not be exposed to IVM during an intervention campaign.

The primary objective of this study was to quantify ivermectin's impact on malaria transmission and identify key variables for developing a mathematical model in this context. A mathematical model incorporating these key structural variables, along with the use of IVM in combination with other malaria control tools such as mass drug administration, seasonal malaria chemoprevention, and bed nets, will be thoroughly discussed in our ongoing work. To assist national malaria control programs, and building on recent studies [41, 42], we will also design and quantify the impact of real-world scenarios using the developed model.

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Appendix

A.1 Proof of Theorem 3.2: existence and uniqueness of bounded solutions

We first prove that $\mathcal{A}$ is the generator of a locally Lipschitz continuous integrated semigroup. For this, choose

$$\varsigma = \min \{\mu_h, \nu_h, k_h, \gamma_h, \delta_h, \bar{\rho}, \mu_m, \mu_{m0}\},$$

we find that for $\lambda \in \mathbb{C}$ such that $\Re(\lambda) \geq -\varsigma$, we have $\lambda \in \rho(\mathcal{A})$ and using the explicit formula for the resolvent, we have

$$\left\|(\lambda - \mathcal{A})^{-n}\right\| \leq \frac{1}{(\lambda+\varsigma)^n}, \quad \textit{for all } n \in \mathbb{N}.$$

Since the resolvent $\rho(\mathcal{A})$ of $\mathcal{A}$ is non-empty, then $\mathcal{A}$ is closed. Hence, the operator $\mathcal{A}$ is a Hille–Yosida and generates a locally Lipschitz continuous integrated semigroup given by $\{S_{\mathcal{A}}(t)\}_{t\geq 0} \subset \mathcal{L}(\mathcal{X})$. $\mathcal{A}$ is resolvent positive, then $S_{\mathcal{A}}(t)\mathcal{X}_+ \subset \mathcal{X}_+$, which ensures the positivity of the semigroup $\{S_{\mathcal{A}}(t)\}_{t\geq 0}$. Set

$$\alpha = m \max\left\{\ \phi, \max \tfrac{\theta}{\varepsilon}\{\beta_h, \beta_m, 1\}\ \right\}, \tag{A1}$$

$$\tau_0 = \min\left\{\ \frac{1}{2(k_m+\alpha)}, \frac{ln(2)}{\mu_h+\nu_h+\phi+\gamma_h+\delta_h+k_h+\|\rho\|_{L^\infty}+\alpha}\ \right\} > 0, \tag{A2}$$

and let

$$u_0 = \left(v_{h0}, u_{m0}, S_{m0}, I_{m0}, v_{h0,\mathrm{IVM}}, u_{h0,\mathrm{IVM}}, S_{m0,\mathrm{IVM}}, I_{m0,\mathrm{IVM}}\right)^T \in \mathcal{X}_+ \cap \mathcal{X}_{\bar{\epsilon}}, \tag{A3}$$

where

$$m = 2 \sup_{t\in[0,\tau_0]} \|u(t)\|_{\mathcal{X}} \quad \textit{and} \quad \bar{\epsilon} = 2\epsilon.$$

The non-linear part of the models (5)–(6) given by (9) is not necessarily positive and will not be able to ensure the positivity of the semiflow, to adjust this, rewrite problems (5)–(6) as follows:

$$\frac{\mathrm{d}u}{\mathrm{d}t}(t) = \mathcal{A}^\alpha u(t) + \mathcal{F}^\alpha(u(t)), \tag{A4}$$

with $\mathcal{A}^\alpha = \mathcal{A} - \alpha \mathrm{I_d}$ and $\mathcal{F}^\alpha = \mathcal{F}_\epsilon + \alpha \mathrm{I_d}$, so that $\mathcal{F}^\alpha$ is positive.

We prove also that the operator $\mathcal{A}^\alpha$ is resolvent positive. Then the linear operator $\mathcal{A}^\alpha$ is a Hille–Yosida operator and yields a positive locally Lipschitz continuous integrated semigroup, given by $\{S_{\mathcal{A}^\alpha}(t)\}_{t\geq 0} \subset \mathcal{L}(\mathcal{X})$.

Let us introduce

$$\Omega_m = \left\{\ u \in \mathcal{X} : \|u(t)\| \leq m\ \right\}. \tag{A5}$$

Due to (10), it is straightforward to show that $\mathcal{F}^\alpha$ is continuous and for all $m > 0$, there exists $k_m > 0$, such that

$$\left\|\mathcal{F}^\alpha(u_1) - \mathcal{F}^\alpha(u_2)\right\| \leq (k_m + \alpha)\, \|u_1 - u_2\|, \quad \forall\, u_1, u_2 \in \Omega_m \cap \mathcal{X}_\epsilon \cap \mathcal{X}_+, \quad \forall\, t \geq 0, \tag{A6}$$

Define $\{\mathrm{T}_{(\mathcal{A}^\alpha)_0}(t)\}_{t\geq 0}$ the $\mathcal{C}_0$-Semigroup generated by the linear operator $\mathcal{A}_0 : D(\mathcal{A}_0) \subset \mathcal{X} \longrightarrow \mathcal{X}$, that is the part of $\mathcal{A} - \alpha \mathrm{I_d}$ in $\mathcal{X}_0$. It follows that

$$\left\|\mathrm{T}_{(\mathcal{A}^\alpha)_0}(t)u\right\|_{\mathcal{X}} \leq \|u\|_{\mathcal{X}}\ \mathrm{e}^{-(\varsigma+\alpha)t} \quad \text{for each} \quad t \geq 0 \quad \text{and} \quad u \in \mathcal{X}.$$

Let the space

$$\mathcal{Y} := \mathcal{C}^0\left([0,\tau_0], \mathcal{X}_\epsilon \cap \mathcal{X}_+ \cap \Omega_m\right),$$

be endowed with the metric

$$d(u_1,u_2) = \max_{t\in[0,\tau_0]} \|u_1(t) - u_2(t)\|_{\mathcal{X}}, \quad \forall\, u_1, u_2 \in \mathcal{Y}.$$

Define the operator $\mathcal{W} : \mathcal{Y} \longrightarrow \mathcal{C}^0([0,\tau_0],\mathcal{X})$ by

$$\mathcal{W}(u)(t) = \mathrm{T}_{(\mathcal{A}^\alpha)_0}(t)u_0 + \frac{\mathrm{d}}{\mathrm{d}t}(S_{\mathcal{A}^\alpha} * \mathcal{F}^\alpha(u))(t),$$

with $\mathcal{A}^\alpha := \mathcal{A} - \alpha \mathrm{I_d}$ and $\mathcal{F}^\alpha(u) := \mathcal{F}_\epsilon(u) + \alpha u \in \mathcal{X}_+$. With $u_0 \in \mathcal{X}_\epsilon$ and where $*$ stands for the convolution product.

According to [43], the map $t \longmapsto (S_{\mathcal{A}^\alpha} * \mathcal{F}^\alpha(u))(t)$ is continuously differentiable as $\mathcal{F}^\alpha(u) \in \mathrm{L}((0,\tau_0),\mathcal{X})$ (see also [44, 45]). One has

$$\begin{aligned}
\left\|\frac{\mathrm{d}}{\mathrm{d}t}(S_{\mathcal{A}^\alpha} * \mathcal{F}^\alpha(u))(t)\right\|_{\mathcal{X}} &\leq \int_0^t \mathrm{e}^{-(\varsigma+\alpha)(t-s)}\ \left\|\mathcal{F}^\alpha(u)(s)\right\|_{\mathcal{X}}\ \mathrm{d}s \\
&\leq (k_m+\alpha) \sup_{s\in[0,t]} \|u(s)\|_{\mathcal{X}} \int_0^t \mathrm{e}^{-(\varsigma+\alpha)(t-s)}\,\mathrm{d}s \\
&\leq \tau_0(k_m+\alpha) \sup_{s\in[0,t]} \|u(s)\|_{\mathcal{X}} \quad \forall\, t < \tau_0.
\end{aligned}$$

Next, before establishing the contraction of the operator $\mathcal{W}$, we need to show that $\mathcal{W}(\mathcal{Y}) \subset \mathcal{Y}$.

We have first $\mathcal{W}(\mathcal{Y}) \subset C([0,\tau_0],\mathcal{X})$ since $\{\mathrm{T}_{(\mathcal{A}^\alpha)_0}(t)\}_{t\geq 0}$ is a $\mathcal{C}_0$-Semigroup. In addition, using definition of m and τ_0 given by (A2)–(A1) we ensure that $\mathcal{W}(\mathcal{Y}) \subset C([0,\tau_0],\Omega_m)$. Next, according to the following approximation formula (see [43]):

$$\frac{\mathrm{d}}{\mathrm{d}t}(S_{\mathcal{A}^\alpha} * \mathcal{F}^\alpha(u))(t) = \lim_{\lambda\to\infty}\int_0^t \mathrm{T}_{(\mathcal{A}^\alpha)_0}(t-s)\lambda(\lambda-\mathcal{A})^{-1}\mathcal{F}^\alpha(u)(s)\,\mathrm{d}s,$$

and positivity properties of $\mathcal{F}^\alpha$ and $\{S_{\mathcal{A}^\alpha}(t)\}_{t\geq 0}$, we deduce that $\frac{\mathrm{d}}{\mathrm{d}t}(S_{\mathcal{A}^\alpha} * \mathcal{F}^\alpha(u))(t)$ is positive, then $\mathcal{W}(\mathcal{Y}) \subset C([0,\tau_0],\mathcal{X}_+\cap\Omega_m)$. It only remains to show that $\mathcal{W}(u(t)) \in \mathcal{X}_\epsilon$ for each $u \in \mathcal{Y}$ and $t \in [0,\tau_0]$. To do so, we must first observe that $t \longmapsto \mathrm{T}_{(\mathcal{A}^\alpha)_0}(t)u_0$ is a solution of the Cauchy problem

$$\frac{\mathrm{d}u}{\mathrm{d}t}(t) = \mathcal{A}^\alpha u(t), \quad \forall\, t\in[0,\tau_0],\ \textit{with}\ u(0) = u_0 \in \mathcal{X}_{0,+}\ \text{for each}\ \epsilon > 0, \tag{A7}$$

and u_0 is given by (A3).

This means that

$$\int_0^t \mathrm{T}_{(\mathcal{A}^\alpha)_0}(s)u_0\,\mathrm{d}s \in D(\mathcal{A}), \quad \forall\, t\in[0,\tau_0],$$

and

$$\mathrm{T}_{(\mathcal{A}^\alpha)_0}(t)u_0 = u_0 + \mathcal{A}^\alpha\int_0^t \mathrm{T}_{(\mathcal{A}^\alpha)_0}(s)u_0\,\mathrm{d}s \in D(\mathcal{A}), \quad \forall\, t\in[0,\tau_0].$$

Using the Volterra formulation associated with the Cauchy problem (A7), we can give an explicit form to our $\mathcal{C}_0$-Semigroup as follows:

$$\mathrm{T}_{(\mathcal{A}^\alpha)_0}(t)u_0 = \begin{pmatrix} v_{h0}\,\mathrm{e}^{-(\mu_h+\phi+\alpha)\mathrm{I_d}t} \\ u_{h0}\,\mathrm{e}^{-(\phi E_1 + D_h + \alpha\mathrm{I_d})t} \\ S_{m0}\,\mathrm{e}^{-(\mu_m+\alpha)t} \\ I_{m0}\,\mathrm{e}^{-(\mu_m+\alpha)t} \\ 0_{\mathbb{R}^2} \\ 1_{\{t\leq\tau\}}v_{h0,\mathrm{IVM}}(\tau-t)\exp\left(-\int_{\tau-t}^{\tau}(\mu_h+\rho(\sigma)+\alpha)\,\mathrm{I_d}\,\mathrm{d}\sigma\right) \\ 0_{\mathbb{R}^2} \\ 1_{\{t\leq\tau\}}u_{h0,\mathrm{IVM}}(\tau-t)\exp\left(-\int_{\tau-t}^{\tau}(D_h+\rho(\sigma)\mathrm{I_d}+\alpha\mathrm{I_d})\,\mathrm{d}\sigma\right) \\ 0 \\ 1_{\{t\leq\eta\}}S_{m0,\mathrm{IVM}}(\eta-t)\exp\left(-\int_{\eta-t}^{\eta}\left(\mu_{m,\mathrm{IVM}}(\sigma)+\alpha\right)\,\mathrm{d}\sigma\right) \\ 0 \\ 1_{\{t\leq\eta\}}I_{m0,\mathrm{IVM}}(\eta-t)\exp\left(-\int_{\eta-t}^{\eta}\left(\mu_{m,\mathrm{IVM}}(\sigma)+\alpha\right)\,\mathrm{d}\sigma\right) \end{pmatrix}.$$

By setting

$$Q_h = \mu_h + \nu_h + \phi + \gamma_h + \delta_h + k_h + \|\rho\|_{L^\infty} + \alpha,$$

we observe that

$$\mathrm{T}_{(\mathcal{A}^\alpha)_0}(t)u_0 \geq \begin{pmatrix} v_{h0}\,\mathrm{e}^{-Q_h t} \\ u_{h0}\,\mathrm{e}^{-Q_h t} \\ 0_{\mathbb{R}^4} \\ 1_{\{t\leq\tau\}}v_{h0,\mathrm{IVM}}(\tau-t)\,\mathrm{e}^{-Q_h t} \\ 0_{\mathbb{R}^2} \\ 1_{\{t\leq\tau\}}u_{h0,\mathrm{IVM}}(\tau-t)\,\mathrm{e}^{-Q_h t} \\ 0_{\mathbb{R}^4} \end{pmatrix}.$$

Since we know that $\frac{\mathrm{d}}{\mathrm{d}t}(S_{\mathcal{A}^\alpha} * \mathcal{F}^\alpha(u))(t)$ for each $t\in[0,\tau_0]$ is positive then we can compute $\mathcal{T}(u(t))$ as follows:

$$\begin{aligned}
\mathcal{T}(u(t)) &\geq \|v_{h0}\|_{\mathbb{R}^2}\,\mathrm{e}^{-Q_h t} + \|u_{h0}\|_{\mathbb{R}^2}\,\mathrm{e}^{-Q_h t} + \int_t^\infty v_{h0,\mathrm{IVM}}(\tau-t)\,\mathrm{e}^{-Q_h t}\,\mathrm{d}\tau + \int_t^\infty u_{h0,\mathrm{IVM}}(\tau-t)\,\mathrm{e}^{-Q_h t}\,\mathrm{d}\tau \\
&\geq \|v_{h0}\|_{\mathbb{R}^2}\,\mathrm{e}^{-Q_h t} + \|u_{h0}\|_{\mathbb{R}^2}\,\mathrm{e}^{-Q_h t} + \left\|v_{h0,\mathrm{IVM}}\right\|_{L^1(\mathbb{R}_+)}\,\mathrm{e}^{-Q_h t} + \left\|u_{h0,\mathrm{IVM}}\right\|_{L^1(\mathbb{R}_+)}\,\mathrm{e}^{-Q_h t} \\
&\geq \left(\|v_{h0}\|_{\mathbb{R}^4} + \|u_{h0}\|_{\mathbb{R}^4} + \left\|v_{h0,\mathrm{IVM}}\right\|_{L^1(\mathbb{R}_+)} + \left\|u_{h0,\mathrm{IVM}}\right\|_{L^1(\mathbb{R}_+)}\right)\,\mathrm{e}^{-Q_h\tau_0} \\
&\geq \bar{\epsilon}\,\mathrm{e}^{-Q_h\tau_0} \quad \forall\, t\in[0,\tau_0],
\end{aligned}$$

Using the definition of τ_0, it's just so happens that for each $t \in [0, \tau_0]$ and $u \in \mathcal{Y}$ we obtain

$$\mathcal{T}(u(t)) \geq \epsilon.$$

Hence, $\mathcal{W}(\mathcal{Y}) \subset \mathcal{Y}$. Then, for each $(u_1, u_2) \in \mathcal{Y}$, we have the following estimation:

$$\begin{aligned}
\|\mathcal{W}(u_1) - \mathcal{W}(u_2)\|_{\mathcal{Y}} &= \max_{t\in[0,\tau_0]} \|G(u_1(t)) - G(u_2(t))\|_{\mathcal{X}} \\
&= \max_{t\in[0,\tau_0]} \left\| \frac{\mathrm{d}}{\mathrm{d}t}(S_{\mathcal{A}^\alpha} * \left(\mathcal{F}^\alpha(u_1) - \mathcal{F}^\alpha(u_2)\right)(t)\right\|_{\mathcal{X}} \\
&\leq \tau_0(k_m + \alpha) \max_{t\in[0,\tau_0]} \|u_1(t) - u_2(t)\|_{\mathcal{X}} \\
&\leq \tau_0(k_m + \alpha)\|u_1 - u_2\|_{\mathcal{Y}} \\
&\leq \frac{1}{2}\|u_1 - u_2\|_{\mathcal{Y}}.
\end{aligned}$$

It comes that $\mathcal{W}$ is a $\frac{1}{2}$-Shrinking operator. By using the Banach–Picard theorem, there exists a unique mild solution $u \in \mathcal{C}([0, \tau_0], \mathcal{X}_\epsilon \cap \mathcal{X}_+)$ for the system problem (11) such as

$$\int_0^t u(s)\,\mathrm{d}s \in D(\mathcal{A}), \text{ and } u(t) = u_0 + \mathcal{A}\int_0^t u(s)\,\mathrm{d}s + \int_0^t \mathcal{F}_\epsilon\left(u(s)\right)\,\mathrm{d}s, \quad \forall\, t \in [0, \tau_0],$$

and the Volterra formulation given by (12) – (13) holds true. Furthermore, this solution is defined in a continuously differentiable sense and becomes classical: i.e. $u \in \mathcal{C}^1([0, \tau_0], \mathcal{X}_\epsilon \cap \mathcal{X}_+)$. Whenever $u_0 \in D(\mathcal{A})$.

For the estimations in (i), let the total number of humans at time t is given by

$$N_h(t) = \|v_h(t)\|_{\mathbb{R}^2} + \|u_h(t)\|_{\mathbb{R}^2} + \left\|v_{h,\mathrm{IVM}}(t,\cdot)\right\|_{L^1(\mathbb{R}_+,\mathbb{R}^2)} + \left\|u_{h,\mathrm{IVM}}(t,\cdot)\right\|_{L^1(\mathbb{R}_+,\mathbb{R}^2)}.$$

The dynamic of the total human population is given by

$$\dot{N}_h(t) = \Lambda_h - \mu_h N_h(t) - \delta_h E_2\left(u_h(t) + \int_0^\infty u_{h,\mathrm{IVM}}(t,\tau)\,\mathrm{d}\tau\right).$$

Since the solution of the systems (5)–(7) is positive, we have

$$\dot{N}_h(t) \leq \Lambda_h - \mu_h N_h(t), \quad \dot{N}_h(t) \geq \Lambda_h - (\mu_h + \delta_h)N_h(t).$$

Then, by using Gronwall's inequality, we obtain

$$N_h(t) \leq N_h(0)\,\mathrm{e}^{-\mu_h t} + \frac{\Lambda_h}{\mu_h}\left(1 - \mathrm{e}^{-\mu_h t}\right), \tag{A8}$$

supplemented with

$$\mathcal{T}(u(t)) = N_h(t) \geq \mathcal{T}(u_0)\,\mathrm{e}^{-(\mu_h+\delta_h)t} + \frac{\Lambda_h}{\mu_h + \delta_h}\left(1 - \mathrm{e}^{-(\mu_h+\delta_h)t}\right). \tag{A9}$$

By the definition of $\bar{\epsilon}$, we have taken $\bar{\epsilon} \in (0, \frac{\Lambda_h}{\mu_h+\nu_h+\phi+\gamma_h+\delta_h+k_h+\|\rho\|_{L^\infty}})$, we see hat

$$\bar{\epsilon} \leq \frac{\Lambda_h}{\mu_h + \nu_h + \phi + \gamma_h + \delta_h + k_h + \|\rho\|_{L^\infty}} \leq \frac{\Lambda_h}{\mu_h + \delta_h}.$$

So that, we are able to find a constant $\varrho \geq 0$ such as

$$\frac{\Lambda_h}{\mu_h + \delta_h} = \varrho + \bar{\epsilon},$$

It follows that

$$\begin{aligned}
\mathcal{T}(u(t)) &\geq \frac{\Lambda_h}{\mu_h + \delta_h} + \left(\mathcal{T}(u_0) - \frac{\Lambda_h}{\mu_h + \delta_h}\right)\,\mathrm{e}^{-(\mu_h+\delta_h)t}, \\
&\geq \bar{\epsilon} + \varrho\left(1 - \mathrm{e}^{-(\mu_h+\delta_h)t}\right) + \left(\mathcal{T}(u_0) - \bar{\epsilon}\right)\,\mathrm{e}^{-(\mu_h+\delta_h)t}
\end{aligned}$$

Since $\mathcal{T}(u_0) \geq \bar{\epsilon}$ by assumption, we then deduce that $u \in \mathcal{C}^1([0, \tau_0], \mathcal{X}_{\bar{\epsilon}} \cap \mathcal{X}_+)$. From here, we define the operator $\tilde{\mathcal{W}} : \tilde{\mathcal{Y}} \longrightarrow \mathcal{C}^0([0, \tau_0], \mathcal{X})$ by

$$\tilde{\mathcal{W}}(u)(t) = \mathrm{T}_{(\mathcal{A}^\alpha)_0}(t)u_0 + \frac{\mathrm{d}}{\mathrm{d}t}(S_{\mathcal{A}^\alpha} * \mathcal{F}^\alpha(u))(t),$$

for each $u \in \tilde{\mathcal{Y}} := \mathcal{C}^0([0, \tau_0], \mathcal{X}_{\bar{\epsilon}} \cap \mathcal{X}_+ \cap \Omega_m)$. In the similar way, we prove that $\tilde{\mathcal{W}}$ is a $\frac{1}{2}$-shrinking operator with $\tilde{\mathcal{W}}(\tilde{\mathcal{Y}}) \cap \tilde{\mathcal{Y}}$, and we prove by using the Banach–Picard theorem that the Cauchy problem (11) admits a unique mild solution $u \in \mathcal{C}([0, \tau_0], \mathcal{X}_{\bar{\epsilon}} \subset \mathcal{X}_+)$ since $u_0 \in \mathcal{X}_{\bar{\epsilon}}$, and this mild solution becomes classical whenever $u_0 \in D(\mathcal{A})$. We can easily use some classical time extending properties (see, e.g. [46]) to extend the solution over a maximal interval $[0, t_{max}]$ with $t_{max} > 0$.

Moreover, the total number of mosquitoes at time t is given by

$$N_m(t) = S_m(t) + I_m(t) + \int_0^\infty S_{m,\mathrm{IVM}}(t, \eta)\, \mathrm{d}\eta + \int_0^\infty I_{m,\mathrm{IVM}}(t, \eta)\, \mathrm{d}\eta,$$

The dynamic of the mosquito population is given by

$$\dot{N_m}(t) = \Lambda_m - \mu_m (S_m(t) + I_m(t)) - \int_0^\infty \mu_{m,\mathrm{IVM}}(\eta) \left(S_{m,\mathrm{IVM}}(t, \eta) + I_{m,\mathrm{IVM}}(t, \eta)\right) \mathrm{d}\eta,$$

Since the solution of the systems (5)–(7) is positive, we have

$$\dot{N_m}(t) \leq \Lambda_m - \mu_m^* N_m(t), \quad \dot{N_m}(t) \geq \Lambda_m - (\mu_m + \left\|\mu_{m,\mathrm{IVM}}\right\|_{L^\infty})N_m(t),$$

with

$$\mu_m^* = \min\left\{\ \mu_m, \left\|\mu_{m,\mathrm{IVM}}\right\|_{L^\infty}\ \right\}$$

Similarly, using Gronwall's inequality, we have

$$N_m(t) \leq N_m(0)\, \mathrm{e}^{-\mu_m^* t} + \frac{\Lambda_h}{\mu_m^*}\left(1 - \mathrm{e}^{-\mu_m^* t}\right), \tag{A10}$$

supplemented with

$$N_m(t) \geq N_m(0)\, \mathrm{e}^{-(\mu_m + \|\mu_{m,\mathrm{IVM}}\|_{L^\infty})t} + \frac{\Lambda_h}{\mu_m + \left\|\mu_{m,\mathrm{IVM}}\right\|_{L^\infty}}\left(1 - \mathrm{e}^{-(\mu_m + \|\mu_{m,\mathrm{IVM}}\|_{L^\infty})t}\right). \tag{A11}$$

Then, we have

$$\limsup_{t\to\infty} N_h(t) \leq \frac{\Lambda_h}{\mu_h}, \quad \limsup_{t\to\infty} N_m(t) \leq \frac{\Lambda_m}{\mu_m^*}.$$

To prove (iii), we assume that $u_0 \in \mathcal{X}_0$ so that $u \in \mathcal{C}([0, \tau_0], \mathcal{X}_\epsilon \cap \mathcal{X}_+)$ is a mild solution to (11). Since $\overline{D(\mathcal{A})} = \mathcal{X}_0$, it comes that there exists a sequence of initial data $\{u_0^k\}_{k\geq 0} \in D(\mathcal{A})^{\mathbb{N}}$ so that $\lim_{k\to\infty} \|u_0^k - u_0\|_{\mathcal{X}} = 0$. There exists a unique solution $u^k \in \mathcal{C}^1(\mathbb{R}_+, \mathcal{X}_\epsilon \cap \mathcal{X}_+)\ \forall\, k \geq 0$ to our Cauchy problem (11) according to the initial data u_0^k. Hence $t \in [0, \tau_0]$. It follows that

$$\begin{aligned}\left\|u(t) - u^k(t)\right\|_{\mathcal{X}} &= \left\|\mathrm{T}_{(\mathcal{A}^\alpha)_0}(t)u_0 - \mathrm{T}_{(\mathcal{A}^\alpha)_0}(t)u_0^k + \frac{\mathrm{d}}{\mathrm{d}t}(S_{\mathcal{A}^\alpha} * \mathcal{F}^\alpha(u))(t) - \frac{\mathrm{d}}{\mathrm{d}t}(S_{\mathcal{A}^\alpha} * \mathcal{F}^\alpha(u^k))(t)\right\|_{\mathcal{X}} \\ &\leq \left\|u_0 - u_0^k\right\|_{\mathcal{X}} + \frac{1}{2}\max_{s\in[0,\tau_0]} \|u(s) - u^k(s)\|_{\mathcal{X}}, \quad \forall\, t \in [0, \tau_0]\end{aligned}$$

Then, we have

$$\left\|u - u^k\right\|_{\mathcal{Y}} = \max_{t\in[0,\tau_0]} \|u(t) - u^k(t)\|_{\mathcal{X}} \leq 2\left\|u_0 - u_0^k\right\|_{\mathcal{X}} \to 0, \quad \textit{when } k \to \infty.$$

We rewrites $u(t)$ as follows:

$$u(t) = u^k(t) + u(t) - u^k(t).$$

It comes that

$$\mathcal{T}(u(t)) \geq \mathcal{T}(u^k(t)) - \left\|u(t) - u^k(t)\right\|_{\mathcal{X}}. \tag{A12}$$

In the former case, we have

$$\mathcal{T}(u(t)) \geq \bar{\epsilon} - \left\|u(t) - u^k(t)\right\|_{\mathcal{X}},$$

and in the latter case, we obtain

$$\mathcal{T}(u(t)) \geq \mathcal{T}(u_0^k)\, \mathrm{e}^{-(\mu_h+\delta_h)t} + \frac{\Lambda_h}{\mu_h + \delta_h}\left(1 - \mathrm{e}^{-(\mu_h+\delta_h)t}\right) - \left\|u(t) - u^k(t)\right\|_{\mathcal{X}},$$

when k tends for infinity, it comes that $\mathcal{T}(u(t)) \geq \bar{\epsilon}$, whence $u \in \mathcal{C}([0,\tau_0],\mathcal{X}_{\bar{\epsilon}} \cap \mathcal{X}_+)$, and (A9) holds for each $t \in [0,\tau_0]$ respectively.

Likewise (A12), we have

$$\mathcal{T}(u(t)) \leq \mathcal{T}(u^k(t)) + \left\| u(t) - u^k(t) \right\|_{\mathcal{X}}$$
$$\leq \mathcal{T}(u_0^k(t))\, \mathrm{e}^{-\mu_h t} + \frac{\Lambda_h}{\mu_h}\left(1 - \mathrm{e}^{-\mu_h t}\right) + \left\| u(t) - u^k(t) \right\|_{\mathcal{X}},$$

and when k tends for infinity, we observe that the estimation (A3) holds true for each $t \in [0,\tau_0]$. Letting the operator $\overline{\mathcal{T}} : \mathcal{X} \longrightarrow \mathcal{X}$ defined by

$$\overline{\mathcal{T}}(u(t)) = S_m(t) + I_m(t) + \int_0^\infty S_{m,\mathrm{IVM}}(t,\eta)\, \mathrm{d}\eta + \int_0^\infty I_{m,\mathrm{IVM}}(t,\eta)\, \mathrm{d}\eta.$$

We prove the estimations (A10)–(A11) for each u defined by (8). Using what was done earlier we show that this solution u is global, this means that $u \in \mathcal{C}(\mathbb{R}_+,\mathcal{X}_{\bar{\epsilon}} \cap \mathcal{X}_+)$ and each above estimates holds for each $t \geq 0$.

A.2 The computation of the disease-free steady state

Here we derive the disease-free steady state. In equilibrium, the time derivatives are zero and in an infection-free population, the compartments of the symptomatic, the asymptomatic and the recovered are empty. Taking into account that $A_h^0 = I_h^0 = R_h^0 = A_{h,\mathrm{IVM}}^0 = I_{h,\mathrm{IVM}}^0 = R_{h,\mathrm{IVM}}^0 = 0$ and $I_m^0 = I_{m,\mathrm{IVM}}^0 = 0$. All that remains is to solve the following system :

$$\begin{cases} 0 = \Lambda_h - (\mu_h + \phi)\, S_h^0 + \displaystyle\int_0^\infty \rho(\tau) S_{h,\mathrm{IVM}}^0(\tau)\, \mathrm{d}\tau, \\ \dfrac{\mathrm{d}S_{h,\mathrm{IVM}}^0}{\mathrm{d}\tau}(\tau) = -\left(\mu_h + \rho(\tau)\right) S_{h,\mathrm{IVM}}^0(\tau), \quad S_{h,\mathrm{IVM}}^0(0) = \phi S_h^0, \\ 0 = \Lambda_m - \mu_m S_m^0 - \displaystyle\int_0^\infty \theta \frac{S_{h,\mathrm{IVM}}^0(\tau)}{N_h^0}\, \mathrm{d}\tau\, S_m^0, \\ \dfrac{\mathrm{d}S_{m,\mathrm{IVM}}^0}{\mathrm{d}\eta}(\eta) = -\mu_{m,\mathrm{IVM}}(\eta) S_{m,\mathrm{IVM}}(\eta), \quad S_{m,\mathrm{IVM}}^0(0) = S_m^0 \displaystyle\int_0^\infty \theta \frac{S_{h,\mathrm{IVM}}^0(\tau)}{N_h^0}\, \mathrm{d}\tau. \end{cases}$$

This leads to

$$S_{h,\mathrm{IVM}}^0(\tau) = \phi S_h^0\, \mathrm{e}^{-\int_0^\tau (\mu_h + \rho(s))\, \mathrm{d}s}, \quad S_h^0 = \frac{\Lambda_h}{\mu_h + \phi - \int_0^\infty \phi\rho(\tau)\, \mathrm{e}^{-\int_0^\tau (\mu_h+\rho(s))\, \mathrm{d}s}\, \mathrm{d}\tau},$$

$$S_{m,\mathrm{IVM}}^0(\eta) = S_m^0 \int_0^\infty \theta \frac{S_{h,\mathrm{IVM}}^0(\tau)}{N_h^0}\, \mathrm{d}\tau\, \mathrm{e}^{-\int_0^\eta \mu_{m,\mathrm{IVM}}(s)\, \mathrm{d}s}, \quad S_m^0 = \frac{\Lambda_m}{\mu_m + \int_0^\infty \theta \frac{S_{h,\mathrm{IVM}}^0(\eta)}{N_h^0}\, \mathrm{d}\tau}.$$

We rewrite the last relationships as

$$S_h^0 = \frac{\Lambda_h}{\mu_h + \phi(1-\chi_h)}, \quad S_{h,\mathrm{IVM}}^0(\tau) = \frac{\phi\Lambda_h \Psi_h(\tau)}{\mu_h + \phi(1-\chi_h)},$$
$$S_m^0 = \frac{\Lambda_m}{\mu_m + \lambda_h^0[\phi]}, \quad S_{m,\mathrm{IVM}}^0(\eta) = S_m^0 \lambda_h^0[\phi]\Gamma_m(\eta),$$

with

$$\Gamma_m(\eta) = \mathrm{e}^{-\int_0^\eta \mu_{m,\mathrm{IVM}}(s)\, \mathrm{d}s}, \quad \Psi_h(\tau) = \mathrm{e}^{-\int_0^\tau (\mu_h+\rho(s))\, \mathrm{d}s},$$
$$\chi_h = \int_0^\infty \rho(\tau)\Psi_h(\tau)\, \mathrm{d}\tau, \quad \lambda_h^0[\phi] = \theta \frac{\phi\int_0^\infty \Psi_h(\tau)\, \mathrm{d}\tau}{1 + \phi\int_0^\infty \Psi_h(\tau)\, \mathrm{d}\tau}.$$

Thus the disease-free steady state is $E^0 = (v_h^0, 0_{\mathbb{R}^2}, S_m^0, 0, v_{h,\mathrm{IVM}}^0(\cdot), 0_{L^1(\mathbb{R}_+,\mathbb{R}_+^2)}, S_{m,\mathrm{IVM}}^0(\cdot), 0_{L^1(\mathbb{R}_+,\mathbb{R}_+)})^T$, with $v_h^0 = (S_h^0, 0)^T$, $v_{h,\mathrm{IVM}}^0 = (S_{h,\mathrm{IVM}}^0, 0)^T$.

Obviously,

$$\chi_h = \int_0^\infty \rho(\tau)\Psi_h(\tau)\, \mathrm{d}\tau$$
$$= \int_0^\infty \rho(\tau)\, \mathrm{e}^{-\mu_h\tau}\, \mathrm{e}^{-\int_0^\tau \rho(s)\, \mathrm{d}s}\, \mathrm{d}\tau$$

$$\leq \int_0^\infty \rho(\tau)\,\mathrm{e}^{-\int_0^\tau \rho(s)\,\mathrm{d}s}\,\mathrm{d}\tau$$
$$\leq \left(1-\mathrm{e}^{-\int_0^\infty \rho(s)\,\mathrm{d}s}\right)$$
$$\leq 1.$$

This ensures the positivity of E^0.

Note that the total number of humans in an infection free population N_h^0 is given by

$$N_h^0 = \frac{\Lambda_h}{\mu_h+\phi(1-\chi_h)}\left(1+\phi\int_0^\infty \Psi_h(\tau)\,\mathrm{d}\tau\right).$$

A.3 Basic reproduction number

Here we derive the basic reproduction number $\mathcal{R}_0$ of the models (5)–(6). We recall that $(u_h, I_m, u_{h,\mathrm{IVM}}, I_{m,\mathrm{IVM}})$ satisfy the following equations:

$$\begin{cases} \dot{u}_h(t) = \lambda_m(t)E_1 v_h(t) - \phi E_1 u_h(t) - D_h u_h(t) + \int_0^\infty \rho(\tau) u_{h,\mathrm{IVM}}(t,\tau)\,\mathrm{d}\tau, \\ \dot{I}_m(t) = \lambda_h(t)S_m(t) - \mu_m I_m(t) - \left(\lambda^S_{h,\mathrm{IVM}}(t)+\lambda^I_{h,\mathrm{IVM}}(t)\right) I_m(t), \\ (\partial_t+\partial_\tau)u_{h,\mathrm{IVM}}(t,\tau) = \lambda_m(t)E_1 v_{h,\mathrm{IVM}}(t,\tau) - D_h u_{h,\mathrm{IVM}}(t,\tau) - \rho(\tau)u_{h,\mathrm{IVM}}(t,\tau), \\ \left(\partial_t+\partial_\eta\right) I_{m,\mathrm{IVM}}(t,\eta) = \left(\lambda_h(t)+\lambda^I_{h,\mathrm{IVM}}(t)\right) S_{m,\mathrm{IVM}}(t,\eta) - \mu_{m,\mathrm{IVM}}(\eta) I_{m,\mathrm{IVM}}(t,\eta), \\ u_{h,\mathrm{IVM}}(t,0) = \phi E_1 u_h(t), \quad I_{m,\mathrm{IVM}}(t,0) = \lambda^I_{h,\mathrm{IVM}}(t)S_m(t) + \left(\lambda^S_{h,\mathrm{IVM}}(t)+\lambda^I_{h,\mathrm{IVM}}(t)\right) I_m(t). \end{cases} \tag{A13}$$

Let

$$x_h(t) = \left(u_h(t), \begin{pmatrix} 0_{\mathbb{R}^2} \\ u_{h,\mathrm{IVM}}(t,\cdot)\end{pmatrix}\right), \quad x_m(t) = \left(I_m(t), \begin{pmatrix} 0_{\mathbb{R}} \\ I_{m,\mathrm{IVM}}(t,\cdot)\end{pmatrix}\right).$$

Then we have

$$\dot{x}_h(t) = \begin{pmatrix} -\phi E_1 u_h(t) - D_h u_h(t) \\ \begin{pmatrix} -u_{h,\mathrm{IVM}}(t,0) \\ -\partial_\tau u_{h,\mathrm{IVM}}(t,\cdot) - D_h u_{h,\mathrm{IVM}}(t,\cdot) - \rho u_{h,\mathrm{IVM}}(t,\cdot) \end{pmatrix} \end{pmatrix}$$
$$+ \begin{pmatrix} \lambda_m(x_m(t))E_1 v_h(t) + \int_0^\infty \rho(\tau) u_{h,\mathrm{IVM}}(t,\tau)\,\mathrm{d}\tau \\ \begin{pmatrix} \phi E_1 u_h(t) \\ \lambda_m(x_m(t))E_1 v_{h,\mathrm{IVM}}(t,\cdot) \end{pmatrix} \end{pmatrix}$$

$$\dot{x}_m(t) = \begin{pmatrix} -\mu_m I_m(t) - \left(\lambda^S_{h,\mathrm{IVM}}(v_{h,\mathrm{IVM}}(t,\cdot)) + \lambda^I_{h,\mathrm{IVM}}(x_h(t))\right) I_m(t) \\ \begin{pmatrix} -I_{m,\mathrm{IVM}}(t,0) \\ -\partial_\eta I_{m,\mathrm{IVM}}(t,\cdot) - \mu_{m,\mathrm{IVM}}(\cdot) I_{m,\mathrm{IVM}}(t,\cdot) \end{pmatrix} \end{pmatrix}$$
$$+ \begin{pmatrix} \lambda_h(x_h(t))S_m(t) \\ \begin{pmatrix} \lambda^I_{h,\mathrm{IVM}}(x_h(t))S_m(t) + \left(\lambda^S_{h,\mathrm{IVM}}(v_{h,\mathrm{IVM}}(t,\cdot)) + \lambda^I_{h,\mathrm{IVM}}(x_h(t))\right) I_m(t) \\ \left(\lambda_h(x_h(t)) + \lambda^I_{h,\mathrm{IVM}}(x_h(t))\right) S_{m,\mathrm{IVM}}(t,\cdot) \end{pmatrix} \end{pmatrix},$$

with

$$\lambda_m(x_m) = \frac{\theta\beta_m}{N_h}\left(I_m + \int_0^\infty I_{m,\mathrm{IVM}}(\eta)\,\mathrm{d}\eta\right), \quad \lambda_h(x_h) = \frac{\theta\beta_h}{N_h} e u_h,$$
$$\lambda^I_{h,\mathrm{IVM}}(x_h) = \frac{\theta\beta_h}{N_h}\int_0^\infty e u_{h,\mathrm{IVM}}(\tau)\,\mathrm{d}\tau, \quad \lambda^S_{h,\mathrm{IVM}}(v_{h,\mathrm{IVM}}) = \frac{\theta}{N_h(t)}\int_0^\infty e v_{h,\mathrm{IVM}}(\tau)\,\mathrm{d}\tau.$$

Therefore, (x_h, x_m) satisfy the following equations:

$$\begin{cases} \dot{x}_h = \mathcal{A}_h x_h + \mathcal{F}_h(x_h, x_m, v_h, v_{h,\mathrm{IVM}}), \\ \dot{x}_m = \mathcal{A}_m[x_h, v_{h,\mathrm{IVM}}]x_m + \mathcal{F}_m(x_h, x_m, v_{h,\mathrm{IVM}}, S_m, S_{m,\mathrm{IVM}}), \end{cases} \tag{A14}$$

with

$$\mathcal{A}_h x_h = \begin{pmatrix} -\phi E_1 u_h - D_h u_h \\ \begin{pmatrix} -u_{h,\mathrm{IVM}}(0) \\ -\partial_\tau u_{h,\mathrm{IVM}}(\cdot) - D_h u_{h,\mathrm{IVM}}(\cdot) - \rho u_{h,\mathrm{IVM}}(\cdot) \end{pmatrix} \end{pmatrix},$$

$$\mathcal{A}_m[x_h, v_{h,\mathrm{IVM}}]x_m = \begin{pmatrix} -\mu_m I_m - \left(\lambda^S_{h,\mathrm{IVM}}(v_{h,\mathrm{IVM}}(\cdot)) + \lambda^I_{h,\mathrm{IVM}}(x_h)\right) I_m \\ \begin{pmatrix} -I_{m,\mathrm{IVM}}(0) \\ -\partial_\eta I_{m,\mathrm{IVM}}(\cdot) - \mu_{m,\mathrm{IVM}}(\cdot) I_{m,\mathrm{IVM}}(\cdot) \end{pmatrix} \end{pmatrix},$$

$$\mathcal{F}_h(x_h, x_m, v_h, v_{h,\mathrm{IVM}}) = \begin{pmatrix} \lambda_m(x_m) E_1 v_h + \int_0^\infty \rho(\tau) u_{h,\mathrm{IVM}}(\tau)\,\mathrm{d}\tau \\ \begin{pmatrix} \phi E_1 u_h \\ \lambda_m(x_m) E_1 v_{h,\mathrm{IVM}}(\cdot) \end{pmatrix} \end{pmatrix},$$

$$\mathcal{F}_m(x_h, x_m, v_{h,\mathrm{IVM}}, S_m, S_{m,\mathrm{IVM}}) = \begin{pmatrix} \lambda_h(x_h) S_m \\ \begin{pmatrix} \lambda^I_{h,\mathrm{IVM}}(x_h) S_m + \left(\lambda^S_{h,\mathrm{IVM}}(v_{h,\mathrm{IVM}}(\cdot)) + \lambda^I_{h,\mathrm{IVM}}(x_h)\right) I_m \\ \left(\lambda_h(x_h) + \lambda^I_{h,\mathrm{IVM}}(x_h)\right) S_{m,\mathrm{IVM}}(\cdot) \end{pmatrix} \end{pmatrix}.$$

We want to compute the next-generation operator, for this by linearizing system (A14) at the disease-free steady state E^0 given by (14), we have

$$\frac{\mathrm{d}}{\mathrm{d}t}(x_h, x_m) = \mathcal{A}^0(x_h, x_m) + \mathcal{F}^0(x_h, x_m), \tag{A15}$$

with $\mathcal{A}^0 = \mathrm{diag}(\mathcal{A}_h, \mathcal{A}^0_m)$, $\mathcal{F}^0 = (\mathcal{F}^0_h, \mathcal{F}^0_m)$,

$$\mathcal{A}^0_m x_m = \begin{pmatrix} -\mu_m I_m - \lambda^S_{h,\mathrm{IVM}}(v^0_{h,\mathrm{IVM}}(\cdot)) I_m \\ \begin{pmatrix} -I_{m,\mathrm{IVM}}(0) \\ -\partial_\eta I_{m,\mathrm{IVM}}(\cdot) - \mu_{m,\mathrm{IVM}}(\cdot) I_{m,\mathrm{IVM}}(\cdot) \end{pmatrix} \end{pmatrix},$$

$$\mathcal{F}^0_h(x_h, x_m) = \begin{pmatrix} \lambda_m(x_m) E_1 v^0_h + \int_0^\infty \rho(\tau) u_{h,\mathrm{IVM}}(\tau)\,\mathrm{d}\tau \\ \begin{pmatrix} \phi E_1 u_h \\ \lambda_m(x_m) E_1 v^0_{h,\mathrm{IVM}}(\cdot) \end{pmatrix} \end{pmatrix},$$

$$\mathcal{F}^0_m(x_h, x_m) = \begin{pmatrix} \lambda_h(x_h) S^0_m \\ \begin{pmatrix} \lambda^I_{h,\mathrm{IVM}}(x_h) S^0_m + \lambda^S_{h,\mathrm{IVM}}(v^0_{h,\mathrm{IVM}}(\cdot)) I_m \\ \left(\lambda_h(x_h) + \lambda^I_{h,\mathrm{IVM}}(x_h)\right) S^0_{m,\mathrm{IVM}}(\cdot) \end{pmatrix} \end{pmatrix},$$

and

$$\lambda_m(x_m) = \frac{\theta\beta_m}{N^0_h}\left(I_m + \int_0^\infty I_{m,\mathrm{IVM}}(\eta)\,\mathrm{d}\eta\right), \quad \lambda_h(x_h) = \frac{\theta\beta_h}{N^0_h} e u_h,$$

$$\lambda^I_{h,\mathrm{IVM}}(x_h) = \frac{\theta\beta_h}{N^0_h}\int_0^\infty e u_{h,\mathrm{IVM}}(\tau)\,\mathrm{d}\tau, \quad \lambda^S_{h,\mathrm{IVM}}(v_{h,\mathrm{IVM}}) = \frac{\theta}{N^0_h}\int_0^\infty e v_{h,\mathrm{IVM}}(\tau)\,\mathrm{d}\tau.$$

Thus the next-generation operator $\mathcal{G}$ is given by

$$\mathcal{G} = \mathcal{F}^0(-\mathcal{A}^0)^{-1}.$$

For the computation of $\mathcal{G}$, we have first

$$(-\mathcal{A}_h)^{-1}\begin{pmatrix} \psi_h \\ \begin{pmatrix} \psi_0 \\ \psi_{h,\mathrm{IVM}} \end{pmatrix} \end{pmatrix} = \begin{pmatrix} (\phi E_1 + D_h)^{-1}\psi_h \\ \begin{pmatrix} \psi_0 \\ \Gamma_h(\tau)\psi_0 + \int_0^\tau \Gamma_h(\tau)\Gamma_h(-\sigma)\psi_{h,\mathrm{IVM}}(\sigma)\,\mathrm{d}\sigma \end{pmatrix} \end{pmatrix},$$

$$(-\mathcal{A}^0_m)^{-1}\begin{pmatrix} \varphi_m \\ \begin{pmatrix} \varphi_0 \\ \varphi_{m,\mathrm{IVM}} \end{pmatrix} \end{pmatrix} = \begin{pmatrix} \frac{\varphi_m}{\mu_m + \lambda^S_{h,\mathrm{IVM}}(v^0_{h,\mathrm{IVM}}(\cdot))} \\ \begin{pmatrix} \varphi_0 \\ \Gamma_m(\eta)\varphi_0 + \int_0^\eta \Gamma_m(\eta)\Gamma_m(-\sigma)\varphi_{m,\mathrm{IVM}}(\sigma)\,\mathrm{d}\sigma \end{pmatrix} \end{pmatrix},$$

and where

$$\Gamma_h(\tau) = \mathrm{e}^{-\int_0^\tau (\rho(a) I_\mathrm{d} + D_h)\,\mathrm{d}a},$$

$$\Gamma_m(\eta) = \mathrm{e}^{-\int_0^\eta \mu_{m,\mathrm{IVM}}(a)\,\mathrm{d}a}.$$

Set

$$\bar{\varphi}_m(\eta) = \varphi_0 + \int_0^\eta \Gamma_m(-\sigma)\varphi_{m,\mathrm{IVM}}(\sigma)\,\mathrm{d}\sigma,$$

$$\bar{\psi}_h(\tau) = \psi_0 + \int_0^\tau \Gamma_h(-\sigma)\psi_{h,\mathrm{IVM}}(\sigma)\,\mathrm{d}\sigma.$$

We compute $\mathcal{F}_h^0(-\mathcal{A}_h)^{-1}$ and $\mathcal{F}_m^0(-\mathcal{A}_m^0)^{-1}$ respectively by

$$\mathcal{F}_h^0(-\mathcal{A}_h)^{-1}\left[\left(\begin{pmatrix}\psi_h\\ \begin{pmatrix}\psi_0\\ \psi_{h,\mathrm{IVM}}\end{pmatrix}\end{pmatrix},\begin{pmatrix}\varphi_m\\ \begin{pmatrix}\varphi_0\\ \varphi_{m,\mathrm{IVM}}\end{pmatrix}\end{pmatrix}\right)\right] = \mathcal{F}_h^0\left[\left(\begin{pmatrix}(\phi E_1+D_h)^{-1}\psi_h\\ \begin{pmatrix}\psi_0\\ \Gamma_h(\tau)\bar{\psi}_h(\tau)\end{pmatrix}\end{pmatrix},\begin{pmatrix}\frac{\varphi_m}{\mu_m+\lambda^S_{h,\mathrm{IVM}}(v^0_{h,\mathrm{IVM}}(\cdot))}\\ \begin{pmatrix}\varphi_0\\ \Gamma_m(\eta)\bar{\varphi}_m(\eta)\end{pmatrix}\end{pmatrix}\right)\right]$$

$$= \begin{pmatrix}\frac{\theta\beta_m}{N_h^0}\left(\frac{\varphi_m}{\mu_m+\lambda^S_{h,\mathrm{IVM}}(v^0_{h,\mathrm{IVM}}(\cdot))}+\int_0^\infty\Gamma_m(\eta)\bar{\varphi}_m(\eta)\,\mathrm{d}\eta\right)E_1v_h^0+\int_0^\infty\rho(\tau)\Gamma_h(\tau)\bar{\psi}_h(\tau)\,\mathrm{d}\tau\\ \begin{pmatrix}\phi E_1(\phi E_1+D_h)^{-1}\psi_h\\ \frac{\theta\beta_m}{N_h^0}\left(\frac{\varphi_m}{\mu_m+\lambda^S_{h,\mathrm{IVM}}(v^0_{h,\mathrm{IVM}}(\cdot))}+\int_0^\infty\Gamma_m(\eta)\bar{\varphi}_m(\eta)\,\mathrm{d}\eta\right)E_1v^0_{h,\mathrm{IVM}}(\cdot)\end{pmatrix}\end{pmatrix}$$

$$= \left(\mathcal{F}^0_{h,h},\mathcal{F}^0_{h,m}\right)\begin{pmatrix}\begin{pmatrix}\psi_h\\ \bar{\psi}_h\end{pmatrix}\\ \begin{pmatrix}\varphi_m\\ \bar{\varphi}_m\end{pmatrix}\end{pmatrix},$$

with

$$\mathcal{F}^0_{h,h}\begin{pmatrix}\psi_h\\ \bar{\psi}_h\end{pmatrix} = \begin{pmatrix}\int_0^\infty\rho(\tau)\Gamma_h(\tau)\bar{\psi}_h(\tau)\,\mathrm{d}\tau\\ \phi E_1(\phi E_1+D_h)^{-1}\psi_h\\ 0_{L^1}\end{pmatrix},$$

$$\mathcal{F}^0_{h,m}\begin{pmatrix}\varphi_m\\ \bar{\varphi}_m\end{pmatrix} = \begin{pmatrix}\frac{\theta\beta_m}{N_h^0}\left(\frac{\varphi_m}{\mu_m+\lambda^S_{h,\mathrm{IVM}}(v^0_{h,\mathrm{IVM}}(\cdot))}+\int_0^\infty\Gamma_m(\eta)\bar{\varphi}_m(\eta)\,\mathrm{d}\eta\right)E_1v_h^0\\ 0_{\mathbb{R}^2}\\ \frac{\theta\beta_m}{N_h^0}\left(\frac{\varphi_m}{\mu_m+\lambda^S_{h,\mathrm{IVM}}(v^0_{h,\mathrm{IVM}}(\cdot))}+\int_0^\infty\Gamma_m(\eta)\bar{\varphi}_m(\eta)\,\mathrm{d}\eta\right)E_1v^0_{h,\mathrm{IVM}}(\cdot)\end{pmatrix},$$

and

$$\mathcal{F}_m^0(-\mathcal{A}_m^0)^{-1}\left[\left(\begin{pmatrix}\psi_h\\ \begin{pmatrix}\psi_0\\ \psi_{h,\mathrm{IVM}}\end{pmatrix}\end{pmatrix},\begin{pmatrix}\varphi_m\\ \begin{pmatrix}\varphi_0\\ \varphi_{m,\mathrm{IVM}}\end{pmatrix}\end{pmatrix}\right)\right] = \mathcal{F}_m^0\left[\left(\begin{pmatrix}(\phi E_1+D_h)^{-1}\psi_h\\ \begin{pmatrix}\psi_0\\ \Gamma_h(\tau)\bar{\psi}_h(\tau)\end{pmatrix}\end{pmatrix},\begin{pmatrix}\frac{\varphi_m}{\mu_m+\lambda^S_{h,\mathrm{IVM}}(v^0_{h,\mathrm{IVM}}(\cdot))}\\ \begin{pmatrix}\varphi_0\\ \Gamma_m(\eta)\bar{\varphi}_m(\eta)\end{pmatrix}\end{pmatrix}\right)\right]$$

$$= \begin{pmatrix}\frac{\theta\beta_h}{N_h^0}e(\phi E_1+D_h)^{-1}\psi_hS_m^0\\ \begin{pmatrix}\frac{\theta\beta_h}{N_h^0}\int_0^\infty e\Gamma_h(\tau)\bar{\psi}_h(\tau)\,\mathrm{d}\tau\,S_m^0+\lambda^S_{h,\mathrm{IVM}}(v^0_{h,\mathrm{IVM}}(\cdot))\frac{\varphi_m}{\mu_m+\lambda^S_{h,\mathrm{IVM}}(v^0_{h,\mathrm{IVM}}(\cdot))}\\ \left(\frac{\theta\beta_h}{N_h^0}e(\phi E_1+D_h)^{-1}\psi_h+\frac{\theta\beta_h}{N_h^0}\int_0^\infty e\Gamma_h(\tau)\bar{\psi}_h(\tau)\,\mathrm{d}\tau\right)S^0_{m,\mathrm{IVM}}(\cdot)\end{pmatrix}\end{pmatrix}$$

$$= \left(\mathcal{F}^0_{m,h},\mathcal{F}^0_{m,m}\right)\begin{pmatrix}\begin{pmatrix}\psi_h\\ \bar{\psi}_h\end{pmatrix}\\ \begin{pmatrix}\varphi_m\\ \bar{\varphi}_m\end{pmatrix}\end{pmatrix},$$

with

$$\mathcal{F}^0_{m,h}\begin{pmatrix}\psi_h\\ \bar{\psi}_h\end{pmatrix} = \begin{pmatrix}\frac{\theta\beta_h}{N_h^0}e(\phi E_1+D_h)^{-1}\psi_hS_m^0\\ \frac{\theta\beta_h}{N_h^0}\int_0^\infty e\Gamma_h(\tau)\bar{\psi}_h(\tau)\,\mathrm{d}\tau\,S_m^0\\ \left(\frac{\theta\beta_h}{N_h^0}e(\phi E_1+D_h)^{-1}\psi_h+\frac{\theta\beta_h}{N_h^0}\int_0^\infty e\Gamma_h(\tau)\bar{\psi}_h(\tau)\,\mathrm{d}\tau\right)S^0_{m,\mathrm{IVM}}(\cdot)\end{pmatrix},$$

$$\mathcal{F}^0_{m,m}\begin{pmatrix}\varphi_m\\ \bar{\varphi}_m\end{pmatrix} = \begin{pmatrix}0\\ \frac{\theta}{N_h^0}\int_0^\infty ev^0_{h,\mathrm{IVM}}(\tau)\,\mathrm{d}\tau\frac{\varphi_m}{\mu_m+\lambda^S_{h,\mathrm{IVM}}(v^0_{h,\mathrm{IVM}}(\cdot))}\\ 0_{L^1(\mathbb{R}_+,\mathbb{R})}\end{pmatrix}.$$

From where,

$$\mathcal{G}\begin{pmatrix}\begin{pmatrix}\psi_h\\ \bar{\psi}_h\end{pmatrix}\\ \begin{pmatrix}\varphi_m\\ \bar{\varphi}_m\end{pmatrix}\end{pmatrix} = \begin{pmatrix}\mathcal{F}^0_{h,h} & \mathcal{F}^0_{h,m}\\ \mathcal{F}^0_{m,h} & \mathcal{F}^0_{m,m}\end{pmatrix}\begin{pmatrix}\begin{pmatrix}\psi_h\\ \bar{\psi}_h\end{pmatrix}\\ \begin{pmatrix}\varphi_m\\ \bar{\varphi}_m\end{pmatrix}\end{pmatrix}$$

$$
= \begin{pmatrix}
\begin{pmatrix} \int_0^\infty \rho(\tau)\Gamma_h(\tau)\bar{\psi}_h(\tau)\,\mathrm{d}\tau \\ \phi E_1(\phi E_1 + D_h)^{-1}\psi_h \\ 0_{L^1(\mathbb{R}_+,\mathbb{R}^2)} \end{pmatrix} + \begin{pmatrix} \frac{\theta\beta_m}{N_h^0}\left(\frac{\varphi_m}{\mu_m+\lambda^S_{h,\mathrm{IVM}}(v^0_{h,\mathrm{IVM}}(\cdot))} + \int_0^\infty \Gamma_m(\eta)\bar{\varphi}_m(\eta)\,\mathrm{d}\eta\right) E_1 v_h^0 \\ 0_{\mathbb{R}^2} \\ \frac{\theta\beta_m}{N_h^0}\left(\frac{\varphi_m}{\mu_m+\lambda^S_{h,\mathrm{IVM}}(v^0_{h,\mathrm{IVM}}(\cdot))} + \int_0^\infty \Gamma_m(\eta)\bar{\varphi}_m(\eta)\,\mathrm{d}\eta\right) E_1 v^0_{h,\mathrm{IVM}}(\cdot) \end{pmatrix} \\
\begin{pmatrix} \frac{\theta\beta_h}{N_h^0} e(\phi E_1 + D_h)^{-1}\psi_h S_m^0 \\ \frac{\theta\beta_h}{N_h^0}\int_0^\infty e\Gamma_h(\tau)\bar{\psi}_h(\tau)\,\mathrm{d}\tau\, S_m^0 \\ \left(\frac{\theta\beta_h}{N_h^0} e(\phi E_1 + D_h)^{-1}\psi_h + \frac{\theta\beta_h}{N_h^0}\int_0^\infty e\Gamma_h(\tau)\bar{\psi}_h(\tau)\,\mathrm{d}\tau\right) S^0_{m,\mathrm{IVM}}(\cdot) \end{pmatrix} \\
+ \begin{pmatrix} 0_{\mathbb{R}} \\ \frac{\theta}{N_h^0}\int_0^\infty e v^0_{h,\mathrm{IVM}}(\tau)\,\mathrm{d}\tau\, \frac{\varphi_m}{\mu_m+\lambda^S_{h,\mathrm{IVM}}(v^0_{h,\mathrm{IVM}}(\cdot))} \\ 0_{L^1(\mathbb{R}_+,\mathbb{R})} \end{pmatrix}
\end{pmatrix}.
$$

By deleting lines 2 and 5 of the previous relationship corresponding to the initial data, we have

$$
\mathcal{G}\begin{pmatrix} \begin{pmatrix} \psi_h \\ \bar{\psi}_h \end{pmatrix} \\ \begin{pmatrix} \varphi_m \\ \bar{\varphi}_m \end{pmatrix} \end{pmatrix}
= \begin{pmatrix}
\begin{pmatrix} \int_0^\infty \rho(\tau)\Gamma_h(\tau)\bar{\psi}_h(\tau)\,\mathrm{d}\tau \\ 0_{L^1(\mathbb{R}_+,\mathbb{R}^2)} \end{pmatrix} + \begin{pmatrix} \frac{\theta\beta_m}{N_h^0}\left(\frac{\varphi_m}{\mu_m+\lambda^S_{h,\mathrm{IVM}}(v^0_{h,\mathrm{IVM}}(\cdot))} + \int_0^\infty \Gamma_m(\eta)\bar{\varphi}_m(\eta)\,\mathrm{d}\eta\right) E_1 v_h^0 \\ \frac{\theta\beta_m}{N_h^0}\left(\frac{\varphi_m}{\mu_m+\lambda^S_{h,\mathrm{IVM}}(v^0_{h,\mathrm{IVM}}(\cdot))} + \int_0^\infty \Gamma_m(\eta)\bar{\varphi}_m(\eta)\,\mathrm{d}\eta\right) E_1 v^0_{h,\mathrm{IVM}}(\cdot) \end{pmatrix} \\
\begin{pmatrix} \frac{\theta\beta_h}{N_h^0} e(\phi E_1 + D_h)^{-1}\psi_h S_m^0 \\ \left(\frac{\theta\beta_h}{N_h^0} e(\phi E_1 + D_h)^{-1}\psi_h + \frac{\theta\beta_h}{N_h^0}\int_0^\infty e\Gamma_h(\tau)\bar{\psi}_h(\tau)\,\mathrm{d}\tau\right) S^0_{m,\mathrm{IVM}}(\cdot) \end{pmatrix}
\end{pmatrix}.
$$

The next-generation operator $\mathcal{G}$ is then defined from $(\mathbb{R}^2 \times L^1((0,\infty),\mathbb{R}^2)) \times (\mathbb{R} \times L^1((0,\infty),\mathbb{R}))$ to itself by

$$
\mathcal{G}\begin{pmatrix} \begin{pmatrix} \psi_h \\ \bar{\psi}_h \end{pmatrix} \\ \begin{pmatrix} \varphi_m \\ \bar{\varphi}_m \end{pmatrix} \end{pmatrix} = \begin{pmatrix} \mathcal{A} & \mathcal{B} \\ \mathcal{C} & 0_{\mathbb{R}\times L^1(\mathbb{R}_+,\mathbb{R})} \end{pmatrix} \begin{pmatrix} \begin{pmatrix} \psi_h \\ \bar{\psi}_h \end{pmatrix} \\ \begin{pmatrix} \varphi_m \\ \bar{\varphi}_m \end{pmatrix} \end{pmatrix}, \tag{A16}
$$

where

$$
\mathcal{A}\begin{pmatrix} \psi_h \\ \bar{\psi}_h \end{pmatrix} = \begin{pmatrix} \int_0^\infty \rho(\tau)\Gamma_h(\tau)\bar{\psi}_h(\tau)\,\mathrm{d}\tau \\ 0_{L^1(\mathbb{R}_+,\mathbb{R}^2)} \end{pmatrix},
$$

$$
\mathcal{B}\begin{pmatrix} \varphi_m \\ \bar{\varphi}_m \end{pmatrix} = \begin{pmatrix} \frac{\theta\beta_m}{N_h^0}\left(\frac{\varphi_m}{\mu_m+\lambda^S_{h,\mathrm{IVM}}(v^0_{h,\mathrm{IVM}}(\cdot))} + \int_0^\infty \Gamma_m(\eta)\bar{\varphi}_m(\eta)\,\mathrm{d}\eta\right) E_1 v_h^0 \\ \frac{\theta\beta_m}{N_h^0}\left(\frac{\varphi_m}{\mu_m+\lambda^S_{h,\mathrm{IVM}}(v^0_{h,\mathrm{IVM}}(\cdot))} + \int_0^\infty \Gamma_m(\eta)\bar{\varphi}_m(\eta)\,\mathrm{d}\eta\right) E_1 v^0_{h,\mathrm{IVM}}(\cdot) \end{pmatrix},
$$

$$
\mathcal{C}\begin{pmatrix} \psi_h \\ \bar{\psi}_h \end{pmatrix} = \begin{pmatrix} \frac{\theta\beta_h}{N_h^0} e(\phi E_1 + D_h)^{-1}\psi_h S_m^0 \\ \left(\frac{\theta\beta_h}{N_h^0} e(\phi E_1 + D_h)^{-1}\psi_h + \frac{\theta\beta_h}{N_h^0}\int_0^\infty e\Gamma_h(\tau)\bar{\psi}_h(\tau)\,\mathrm{d}\tau\right) S^0_{m,\mathrm{IVM}}(\cdot) \end{pmatrix}.
$$

From the next-generator operator, we deduce that the basic reproduction number $\mathcal{R}_0$ is defined by the spectral radius of $\mathcal{G}$ denotes by

$$
\mathcal{R}_0 = r(\mathcal{G}).
$$

A.4 Proof of Theorem 3.3 (i) and (ii): existence of an endemic equilibrium

We know that any endemic equilibrium

$$
E^* = (x_h^*, x_m^*, v_h^*, v^*_{h,\mathrm{IVM}}, s_m^*, S^*_{m,\mathrm{IVM}})^T
$$

must satisfy the following equations:

$$x_h^* = (-\mathcal{A}_h)^{-1}\,\mathcal{F}_h^*(x_h^*, x_m^*), \tag{A17}$$

$$x_m^* = \left(-\mathcal{A}_m[x_h^*, x_m^*]\right)^{-1}\,\mathcal{F}_m^*(x_h^*, x_m^*), \tag{A18}$$

$$0 = \Lambda_h e_1 - \lambda_m(x_m^*)E_1 v_h^* - (\mu_h + \phi)\, v_h^* + K_h v_h^* + \gamma_h E_2 u_h^* + \int_0^\infty \rho(\tau) v_{h,\mathrm{IVM}}^*(\tau)\,\mathrm{d}\tau,$$

$$v_{h,\mathrm{IVM}}^*(\tau) = \phi v_h^*\,\mathrm{e}^{-\int_0^\tau (\lambda_m(x_m^*)E_1 + (\mu_h+\rho(\sigma))I_{\mathrm{d}})\mathrm{d}\sigma} + \int_0^\tau \gamma_h E_2 u_{h,\mathrm{IVM}}^*(s)\,\mathrm{e}^{-\int_s^\tau (\lambda_m(x_m^*)E_1 + (\mu_h+\rho(\sigma))I_{\mathrm{d}})\mathrm{d}\sigma}\,\mathrm{d}s, \tag{A19}$$

$$S_m^* = \frac{\Lambda_m}{\mu_m + \lambda_h(x_h^*) + \lambda_{h,\mathrm{IVM}}^S(v_{h,\mathrm{IVM}}^*) + \lambda_{h,\mathrm{IVM}}^I(x_h^*)}, \tag{A20}$$

$$S_{m,\mathrm{IVM}}^*(\eta) = \lambda_{h,\mathrm{IVM}}^S(v_{h,\mathrm{IVM}}^*)S_m^*\,\mathrm{e}^{-\int_0^\eta \left(\mu_{m,\mathrm{IVM}}(\sigma) + \lambda_h(x_h^*) + \lambda_{h,\mathrm{IVM}}^I(x_h^*)\right)\mathrm{d}\sigma}. \tag{A21}$$

With

$$\mathcal{A}_m^*[x_h^*, x_m^*]x_m^* = \begin{pmatrix} -\mu_m I_m^* - \left(\lambda_{h,\mathrm{IVM}}^S(h_2(x_m^*, u_{h,\mathrm{IVM}}^*, \tau)) + \lambda_{h,\mathrm{IVM}}^I(x_h^*)\right) I_m^* \\ \begin{pmatrix} -I_{m,\mathrm{IVM}}^*(0) \\ -\partial_\eta I_{m,\mathrm{IVM}}^*(\cdot) - \mu_{m,\mathrm{IVM}}(\cdot)I_{m,\mathrm{IVM}}^*(\cdot) \end{pmatrix} \end{pmatrix},$$

$$\mathcal{F}_h^*(x_h^*, x_m^*) = \begin{pmatrix} \lambda_m(x_m^*)E_1 h_1(u_h^*) + \int_0^\infty \rho(\tau)u_{h,\mathrm{IVM}}^*(\tau)\,\mathrm{d}\tau \\ \begin{pmatrix} \phi E_1 u_h^* \\ \lambda_m(x_m^*)E_1 h_2(x_m^*, u_{h,\mathrm{IVM}}^*, \tau) \end{pmatrix} \end{pmatrix},$$

$$\mathcal{F}_m^*(x_h^*, x_m^*) = \begin{pmatrix} \lambda_h(x_h^*)h_3(x_m^*, x_h^*) \\ \begin{pmatrix} \lambda_{h,\mathrm{IVM}}^I(x_h^*)S_m + \left(\lambda_{h,\mathrm{IVM}}^S(h_2(x_m^*, u_{h,\mathrm{IVM}}^*, \tau)) + \lambda_{h,\mathrm{IVM}}^I(x_h^*)\right) I_m \\ \left(\lambda_h(x_h) + \lambda_{h,\mathrm{IVM}}^I(x_h)\right) h_4(x_m^*, x_h^*, \eta) \end{pmatrix} \end{pmatrix}.$$

With $h_1(u_h^*) = v_h^*$, and $h_2(x_m^*, u_{h,\mathrm{IVM}}^*)$, $h_3(x_m^*, x_h^*)$ and $h_4(x_m^*, x_h^*, \eta)$ are respectively the right-hand side of Equations (A19), (A20) and (A21). Using Equations (A17) and (A18), we have the following fixed point $H(x_h^*, x_m^*)^T = (x_h^*, x_m^*)^T$, where $H(x_h^*, x_m^*)^T = (H_h(x_h^*, x_m^*), H_m(x_h^*, x_m^*))^T$ and $H_h(x_h^*, x_m^*)$; $H_m(x_h^*, x_m^*)$ are respectively the right-hand side of Equations (A17) and (A18). Thus the endemic equilibrium point is fixed point of H given by

$$H(x_h^*, x_m^*)^T = (x_h^*, x_m^*)^T. \tag{A22}$$

Equation (A22) implies that at the endemic steady state, the infected population simply reproductive itself. Therefore we can call H the next-generation operator at the endemic steady state.

Lemma A.1: (i) *H is positive, continue operator. There exists a closed, bounded and convex subset $\mathcal{Z} \subset \mathrm{Y} := (\mathbb{R}^4 \times L^1((0,\infty), \mathbb{R}^2)) \times (\mathbb{R}^2 \times L^1((0,\infty), \mathbb{R}))$ such that $H(\mathcal{Z}) \subset \mathcal{Z}$.*

(ii) *Operator H as Frechet derivative at the point $(x_h^*, x_m^*) \equiv (0,0)$ and $= H'(0,0)$ is positive, compact and nonsupporting operator.*

Proof of Lemma A.1.: (i) The operators H_h, H_m are defined by

$$H_h(x_h^*, x_m^*) := \begin{pmatrix} H_{h1}(x_h^*, x_m^*) \\ H_{h2}(x_h^*, x_m^*) \\ H_{h3}(x_h^*, x_m^*) \end{pmatrix}$$

$$= \begin{pmatrix} \frac{\theta\beta_m}{N_h^*}\left(\frac{\varphi_m^*}{\mu_m + \lambda_{h,\mathrm{IVM}}^{S,I}(x_m^*, x_h^*, \cdot)} + \int_0^\infty \Gamma_m(\eta)\bar{\varphi}_m^*(\eta)\,\mathrm{d}\eta\right) E_1 h_1(u_h^*) + \int_0^\infty \rho(\tau)\Gamma_h(\tau)\bar{\psi}_h^*(\tau)\,\mathrm{d}\tau \\ \begin{pmatrix} \phi E_1(\phi E_1 + D_h)^{-1}\psi_h^* \\ \frac{\theta\beta_m}{N_h^*}\left(\frac{\varphi_m^*}{\mu_m + \lambda_{h,\mathrm{IVM}}^{S,I}(x_m^*, x_h^*, \cdot)} + \int_0^\infty \Gamma_m(\eta)\bar{\varphi}_m^*(\eta)\,\mathrm{d}\eta\right) E_1 h_2(x_m^*, u_{h,\mathrm{IVM}}^*, \cdot) \end{pmatrix} \end{pmatrix},$$

$$H_m(x_h^*, x_m^*) := \begin{pmatrix} H_{m1}(x_h^*, x_m^*) \\ H_{m2}(x_h^*, x_m^*) \\ H_{m3}(x_h^*, x_m^*) \end{pmatrix}$$

$$= \left(\begin{pmatrix} \frac{\theta\beta_h}{N_h^*} e(\phi E_1 + D_h)^{-1} \psi_h^* h_3(x_m^*, x_h^*) \\ \frac{\theta\beta_h}{N_h^*} \int_0^\infty e\Gamma_h(\tau)\bar{\psi}_h^*(\tau)\,\mathrm{d}\tau\, h_3(x_m^*, x_h^*) + \lambda_{h,\mathrm{IVM}}^{S,I}(x_m^*, x_h^*, \cdot) \frac{\varphi_m^*}{\mu_m + \lambda_{h,\mathrm{IVM}}^{S,I}(x_m^*, x_h^*, \cdot)} \\ \left(\frac{\theta\beta_h}{N_h^*} e(\phi E_1 + D_h)^{-1} \psi_h^* + \frac{\theta\beta_h}{N_h^*} \int_0^\infty e\Gamma_h(\tau)\bar{\psi}_h^*(\tau)\,\mathrm{d}\tau \right) h_4(x_m^*, x_h^*, \cdot) \end{pmatrix} \right).$$

With

$$\bar{\varphi}_m^*(\eta) = \varphi_0^* + \int_0^\eta \Gamma_m(-\sigma)\varphi_{m,\mathrm{IVM}}^*(\sigma)\,\mathrm{d}\sigma,$$

$$\bar{\psi}_h^*(\tau) = \psi_0^* + \int_0^\tau \Gamma_h(-\sigma)\psi_{h,\mathrm{IVM}}^*(\sigma)\,\mathrm{d}\sigma,$$

$$\lambda_{h,\mathrm{IVM}}^{S,I}(x_m^*, x_h^*, \cdot) = \lambda_{h,\mathrm{IVM}}^{S}(h_2(x_m^*, u_{h,\mathrm{IVM}}^*, \cdot)) + \lambda_{h,\mathrm{IVM}}^{I}(x_h^*)$$

It is straightforward to see that the operator H is continue and positive. Since the flow of systems (5)–(6) is bounded (Theorem 3.2), we can find an constant $\bar{M} > 0$ such that $\|\bar{\varphi}_m^*\|_{L^1(\mathbb{R}_+,\mathbb{R})} \le \bar{M}$, $\|\bar{\psi}_h^*\|_{L^1(\mathbb{R}_+,\mathbb{R}^2)} \le \bar{M}$, and since we know that

$$\limsup_{t\to\infty} \|y_h(t)\| \le N_h^* \le \frac{\Lambda_h}{\mu_h}, \quad \text{for } y_h \in \{x_h^*, v_h^*, v_{h,\mathrm{IVM}}^*\},$$

$$\limsup_{t\to\infty} \|y_m(t)\| \le \frac{\Lambda_m}{\mu_m}, \quad \text{for } y_m \in \{x_m^*, S_m^*, I_m, S_{m,\mathrm{IVM}}^*\}.$$

We have

$$\|H_{h1}(x_h^*, x_m^*)\|_{L^1(\mathbb{R}_+,\mathbb{R}^2)} \le C_m + \|\rho\|_{L^\infty}\frac{\Lambda_h}{\mu_h}, \quad \|H_{h2}(x_h^*, x_m^*)\|_{L^1(\mathbb{R}_+,\mathbb{R}^2)} \le C_{h1},$$

$$\|H_{h3}(x_h^*, x_m^*)\|_{L^1(\mathbb{R}_+,\mathbb{R}^2)} \le C_m, \quad \|H_{m1}(x_h^*, x_m^*)\|_{L^1(\mathbb{R}_+,\mathbb{R})} \le C_{h2},$$

$$\|H_{m2}(x_h^*, x_m^*)\|_{L^1(\mathbb{R}_+,\mathbb{R})} \le \frac{\theta\beta_h\Lambda_h}{\mu_h} + (\theta + \theta\beta_h)\frac{\Lambda_m}{\mu_m^2}, \quad \|H_{m3}(x_h^*, x_m^*)\|_{L^1(\mathbb{R}_+,\mathbb{R})} \le C_{h2} + \theta\beta_h\bar{M},$$

and where

$$C_m = \theta\beta_m\left(\frac{\Lambda_m}{\mu_m^2} + \bar{M}\right), \quad C_{h1} = \frac{\phi\Lambda_h}{\mu_h}\left\|E_1(\phi E_1 + D_h)^{-1}\right\|_\infty, \quad C_{h2} = \frac{\theta\beta_h\Lambda_h}{\mu_h}\left\|e_1(\phi E_1 + D_h)^{-1}\right\|_{\mathbb{R}^2}.$$

Therefore $\|H(x_h^*, x_m^*)\|_{\mathrm{Y}} \le M$ with

$$M = 2C_m + \|\rho\|_{L^\infty}\frac{\Lambda_h}{\mu_h} + C_{h1} + (\theta + \theta\beta_h)\frac{\Lambda_m}{\mu_m^2} + 2C_{h2} + \theta\beta_h\bar{M}.$$

Setting $\mathcal{Z} = \overline{B_+(0,M)}$ with $\overline{B_+(0,M)} := \{(x_h^*, x_m^*) \in \mathrm{Y} : \|(x_h^*, x_m^*)\|_{\mathrm{Y}} \le M\}$, hence $H(\mathcal{Z}) \subset \mathcal{Z}$.

(ii) Since $h_1(0) = v_h^0$, $h_2(0,0,\cdot) = u_{h,\mathrm{IVM}}^0(\cdot)$, $h_3(0,0) = S_m^0$, $h_4(0,0,\cdot) = S_{m,\mathrm{IVM}}^0(\cdot)$ (the disease-free steady state) and H infinitely Frechet differentiable, the jacobian at the point $(0,0)$ (without initial values) is given by the relation (A16), for instance

$$H'(0,0) = \begin{pmatrix} \mathcal{A} & \mathcal{B} \\ \mathcal{C} & 0_{\mathbb{R}\times L^1(\mathbb{R}_+,\mathbb{R})} \end{pmatrix} = \mathcal{G}.$$

It is straightforward to see that the operator $H'(0,0)$ is positive because the operators $\mathcal{A}, \mathcal{B}, \mathcal{C}$ are also positive and the proof of compactness of the operator $H'(0,0)$ is similar than the proof in Section A.5. We claim that $H'(0,0)$ is irreducible because the associated graph of the matrix is strongly connected, which implies the nonsupporting of the operator $H'(0,0)$. That end the proof of Lemma A.1.

■

Since the previous lemma is satisfied, therefore there exists a unique positive eigenvector ψ corresponding to eigenvalue $\mathcal{R}_0 = r(\mathcal{G})$ of $H'(0,0)$. using the same argument as the Krasnoselskii fixed point theorem [23, 24], it come that if $\mathcal{R}_0 = r(\mathcal{G}) > 1$, then the operator H has at least one positive fixed point $\lambda^* \in \mathrm{Y} \setminus \{0_{\mathrm{Y}}\}$, corresponding to the endemic equilibrium of systems (A13)–(A14) and since $H(0,0) = (0,0)$. This completes the proof of Theorem 3.3(ii).

A.5 Proof of Theorem 3.3(iii): stability of the disease-free steady state E^0

We must first by prove that the operator $\mathcal{F}^0$ given by (A15) is compact.

For this, we first rewrite $\mathcal{F}^0$ as follows :

$$\mathcal{F}^0 = (\mathcal{F}_1^0, \mathcal{F}_2^0, \mathcal{F}_3^0, \mathcal{F}_4^0, \mathcal{F}_5^0, \mathcal{F}_6^0)^T,$$

where $\mathcal{F}_1^0, \mathcal{F}_2^0, \mathcal{F}_4^0, \mathcal{F}_5^0 : \mathcal{X}_0 \longrightarrow \mathbb{R}_+^2$ and $\mathcal{F}_3^0, \mathcal{F}_6^0 : \mathcal{X}_0 \longrightarrow \mathrm{L}^1(\mathbb{R}_+, \mathbb{R}^2)$.

Since the operators $\mathcal{F}_1^0, \mathcal{F}_2^0, \mathcal{F}_4^0$ and $\mathcal{F}_5^0$ have values in $\mathbb{R}_+^2$ and the solutions of our problem are bounded, the only thing left to do is to prove that the operators $\mathcal{F}_3^0$ and $\mathcal{F}_6^0$ are compact. Let h belongs to the set of positive real numbers ($\mathbb{R}_+$), and let $\mathcal{Z}$ be a bounded subset of $\mathcal{X}0$. Consequently, there exists a positive constant m_0 such that for all t in $\mathbb{R}+$, the supremum of the norm of $u(t)$ in $\mathcal{Z}$ is less than or equal to m_0. Let Th represents the translation operator in $\mathrm{L}^1(\mathbb{R}+, \mathbb{R}^2)$, defined as follows:

$$\mathrm{T}_h(\psi) = \psi(\cdot + h).$$

In the former case, we have

$$\begin{aligned}
\left\|\mathrm{T}_h(\mathcal{F}_3^0(u)) - \mathcal{F}_3^0(u)\right\|_{\mathrm{L}^1(\mathbb{R}_+,\mathbb{R}_+^2)} &= \int_0^\infty \lambda_m(x_m) \mid E_1 v_{h,\mathrm{IVM}}^0(\tau + h) - E_1 v_{h,\mathrm{IVM}}^0(\tau) \mid \mathrm{d}\tau \\
&\le \frac{m_0\theta\beta_m}{N_h^0} \int_0^\infty \mid E_1 v_{h,\mathrm{IVM}}^0(\tau + h) - E_1 v_{h,\mathrm{IVM}}^0(\tau) \mid \mathrm{d}\tau \\
&\le \frac{m_0\theta\beta_m}{N_h^0} \left\|E_1 \left(\mathrm{T}_h(v_{h,\mathrm{IVM}}^0) - v_{h,\mathrm{IVM}}^0\right)\right\|_{\mathrm{L}^1(\mathbb{R}_+,\mathbb{R}_+^2)} \longrightarrow 0 \quad \textit{when } h \longrightarrow 0.
\end{aligned}$$

Since $v_{h,\mathrm{IVM}}^0 \in \mathrm{L}^1(\mathbb{R}_+, \mathbb{R}_+^2)$, it comes that

$$\sup_{u\in\mathcal{Z}} \left\|\mathrm{T}_h(\mathcal{F}_3^0(u)) - \mathcal{F}_3^0(u)\right\|_{\mathrm{L}^1(\mathbb{R}_+,\mathbb{R}_+^2)} \longrightarrow 0 \quad \textit{when } h \longrightarrow 0,$$

and in the latter case, according to the Lebesque theorem it comes that

$$\sup_{u\in\mathcal{Z}} \int_c^\infty \mathcal{F}_3^0(u)(\tau)\,\mathrm{d}\tau \le \frac{m_0\theta\beta_m}{N_h^0} \int_c^\infty v_{h,\mathrm{IVM}}^0(\tau)\,\mathrm{d}\tau \to 0 \quad \textit{when } c \longrightarrow +\infty.$$

Therefore, by using the Rietz–Frechet–Kolgomorov criterion (see, e.g. [47]) we deduce the compactness of $\mathcal{F}_3^0(\mathcal{Z})$ in $\mathrm{L}^1(\mathbb{R}_+, \mathbb{R}^2)$ which means that the operator $\mathcal{F}_3^0$ is compact. The proof of the compactness of the operators $\mathcal{F}_6^0$ is done in a similar way. Thus the operator $\mathcal{F}^0$ is compact.

Next, we prove Theorem 3.3(iii), we observe that $\mathcal{A}^0$ is resolvent positive with $s(\mathcal{A}^0) < 0$ and $\mathcal{F}^0$ is a positive pertubation of $\mathcal{A}^0$, There we use the theory developed by Thieme [48] and then $r(\mathcal{F}^0(-\mathcal{A}^0)^{-1}) - 1 := \mathcal{R}_0 - 1$ and $s(\mathcal{A}^0 + \mathcal{F}^0)$ have the same sign. Moreover, $\mathcal{A}^0 + \mathcal{F}^0$ being a generator of uniformly continuous semigroup $\{\mathrm{T}_{(\mathcal{A}^0+\mathcal{F}^0)}(t)\}_{t\ge0}$ so that there exists a constant $M > 0$ such that one has $\|\mathrm{T}_{(\mathcal{A}^0+\mathcal{F}^0)}(t)\|_{\mathcal{L}}(\mathcal{X}) \le M\,\mathrm{e}^{-\varsigma t}$ for each $t \ge 0$. Then we have

$$s(\mathcal{A}^0 + \mathcal{F}^0) = \omega_0(\mathcal{A}^0 + \mathcal{F}^0),$$

(where ω_0 denotes the growth bound with $\omega_0(\mathcal{A}^0 + \mathcal{F}^0) = \lim_{t\to+\infty} \frac{1}{t} ln(\|\{\mathrm{T}_{(\mathcal{A}^0+\mathcal{F}^0)}(t)\}_{t\ge0}\|_{\mathcal{L}(\mathcal{X})})$). Since the operator $\mathcal{F}^0$ is compact, then from [29] we deduce that

$$\left\{\ \lambda \in \sigma(\mathcal{A}^0 + \mathcal{F}^0), \Re(\lambda) \ge -\varsigma\ \right\},$$

is finite and composed (at most) of isolated eigenvalues with finite algebraic multiplicity, where $\sigma(\cdot)$ denotes the spectrum [28]. Consequently, it remains to study the punctual spectrum of $\mathcal{A}^0 + \mathcal{F}^0$. Since $r(\mathcal{F}^0(-\mathcal{A}^0)^{-1}) - 1 := \mathcal{R}_0 - 1$ and $s(\mathcal{A}^0 + \mathcal{F}^0)$ have the same sign, then if $\mathcal{R}_0 > 1$ we have $s(\mathcal{A}^0 + \mathcal{F}^0) < 0$. Thus all the eigenvalues of the operator $\mathcal{A}^0 + \mathcal{F}^0$ have strictly negative real parts, which prove that E^0 is locally asymptotically stable.

Next, we recall that $\lambda \longmapsto r(\mathcal{F}^0(\lambda - \mathcal{A}^0)^{-1})$ is convex and strictly decreasing in $(s(\mathcal{A}^0), +\infty)$. Since $\mathcal{R}_0 = r(\mathcal{F}^0(-\mathcal{A}^0)^{-1}) > 1$, by the intermediate value theorem, there exists $\lambda_0 > 0$ such that $r(\mathcal{F}^0(\lambda_0 - \mathcal{A}^0)^{-1}) = 1$. Therefore we have $s(\mathcal{F}^0 + \mathcal{A}^0 - \lambda_0) = 0$ so that $s(\mathcal{F}^0 + \mathcal{A}^0) = \lambda_0$. Thus we are sure that the spectrum of the operator $\mathcal{A}^0 + \mathcal{F}^0$ admits at least one real positive eigenvalue when $\mathcal{R}_0 > 1$ and in this case the equilibrium E^0 is unstable.

A.6 Proof of Theorem 3.4: bifurcation of an endemic equilibrium

$$\begin{cases}
v_{h,\mathrm{IVM}}(\tau) = \ell(\lambda_m, \tau)\phi v_h + \gamma_h \displaystyle\int_0^\tau \frac{\ell(\lambda_m, \tau)}{\ell(\lambda_m, \sigma)} E_2 u_{h,\mathrm{IVM}}(\sigma)\,\mathrm{d}\sigma, \\
u_{h,\mathrm{IVM}}(\tau) = \phi\Gamma_h(\tau)E_1 u_h + \lambda_m \displaystyle\int_0^\tau \frac{\Gamma_h(\tau)}{\Gamma_h(\sigma)} E_1 v_{h,\mathrm{IVM}}(\sigma)\,\mathrm{d}\sigma, \\
S_{m,\mathrm{IVM}}(\eta) = \lambda_{h,\mathrm{IVM}}^S S_m \Gamma_m(\eta)\,\mathrm{e}^{-(\lambda_h+\lambda_{h,\mathrm{IVM}}^I)\eta}, \\
I_{m,\mathrm{IVM}}(\eta) = (\lambda_{h,\mathrm{IVM}}^S + \lambda_{h,\mathrm{IVM}}^I)(S_m + I_m)\Gamma_m(\eta) - \lambda_{h,\mathrm{IVM}}^S S_m \Gamma_m(\eta)\,\mathrm{e}^{-(\lambda_h+\lambda_{h,\mathrm{IVM}}^I)\eta},
\end{cases} \tag{A23}$$

where $\ell(\lambda_m,\tau)=\mathrm{e}^{-\int_0^\tau(\lambda_m E_1+\mu_h+\rho(\sigma)-K_h)\,\mathrm{d}\sigma}$.

Introduce the linear operator

$$L_{\lambda_m}[w](\tau)=w(\tau)-\lambda_m\gamma_h\int_0^\tau \frac{\Gamma_h(\tau)}{\Gamma_h(\sigma)}E_1\int_0^\sigma \frac{\ell(\lambda_m,\sigma)}{\ell(\lambda_m,\zeta)}E_2 w(\zeta)\,\mathrm{d}\zeta\,\mathrm{d}\sigma,\quad \forall\, w\in L^1.$$

Then by (A23), it comes

$$\begin{cases} u_{h,\mathrm{IVM}}(\tau)=L_{\lambda_m}^{-1}\left[\phi\Gamma_h(\tau)E_1u_h+\left(\lambda_m\int_0^\tau \frac{\Gamma_h(\tau)}{\Gamma_h(\sigma)}E_1\ell(\lambda_m,\sigma)\,\mathrm{d}\sigma\right)\phi v_h\right]:=\bar u(\lambda_m,v_h,u_h,\tau),\\ v_{h,\mathrm{IVM}}(\tau)=\ell(\lambda_m,\tau)\phi v_h+\gamma_h\int_0^\tau \frac{\ell(\lambda_m,\tau)}{\ell(\lambda_m,\sigma)}E_2\bar u(\lambda_m,v_h,u_h,\sigma)\,\mathrm{d}\sigma,\\ S_{m,\mathrm{IVM}}(\eta)=\lambda^S_{h,\mathrm{IVM}}S_m\Gamma_m(\eta)\,\mathrm{e}^{-(\lambda_h+\lambda^I_{h,\mathrm{IVM}})\eta},\\ I_{m,\mathrm{IVM}}(\eta)=(\lambda^S_{h,\mathrm{IVM}}+\lambda^I_{h,\mathrm{IVM}})(S_m+I_m)\Gamma_m(\eta)-\lambda^S_{h,\mathrm{IVM}}S_m\Gamma_m(\eta)\,\mathrm{e}^{-(\lambda_h+\lambda^I_{h,\mathrm{IVM}})\eta}. \end{cases}$$

Therefore,

$$\begin{aligned} \lambda_m&=\frac{\theta\beta_m}{N_h}\left(I_m+(\lambda^S_{h,\mathrm{IVM}}+\lambda^I_{h,\mathrm{IVM}})(S_m+I_m)\overline{\Gamma}_m-\lambda^S_{h,\mathrm{IVM}}S_m\int_0^\infty \Gamma_m(\eta)\,\mathrm{e}^{-(\lambda_h+\lambda^I_{h,\mathrm{IVM}})\eta}\,\mathrm{d}\eta\right),\\ \lambda^I_{h,\mathrm{IVM}}&=\frac{\theta\beta_h}{N_h}\int_0^\infty eL_{\lambda_m}^{-1}\left[\phi\Gamma_h(\tau)E_1u_h+\left(\lambda_m\int_0^\tau \frac{\Gamma_h(\tau)}{\Gamma_h(\sigma)}E_1\ell(\lambda_m,\sigma)\,\mathrm{d}\sigma\right)\phi v_h\right]\mathrm{d}\tau,\\ \lambda^S_{h,\mathrm{IVM}}(t)&=\frac{\theta}{N_h(t)}\int_0^\infty e\left[\ell(\lambda_m,\tau)\phi v_h+\gamma_h\int_0^\tau \frac{\ell(\lambda_m,\tau)}{\ell(\lambda_m,\sigma)}E_2\bar u(\lambda_m,\sigma)\,\mathrm{d}\sigma\right]\mathrm{d}\tau, \end{aligned}\tag{A24}$$

with $\overline{\Gamma}_m=\int_0^\infty \Gamma_m(\eta)\,\mathrm{d}\eta$.

We now deal with the following system:

$$\begin{cases} 0=\Lambda_h e_1-\lambda_m E_1 v_h-(\mu_h+\phi)\,v_h+K_h v_h+\gamma_h E_2 u_h+\int_0^\infty \rho(\tau)v_{h,\mathrm{IVM}}(\tau)\,\mathrm{d}\tau,\\ 0=\lambda_m E_1 v_h-\phi E_1 u_h-D_h u_h+\int_0^\infty \rho(\tau)u_{h,\mathrm{IVM}}(\tau)\,\mathrm{d}\tau,\\ 0=\Lambda_m-\mu_m S_m-\left(\lambda_h+\lambda^S_{h,\mathrm{IVM}}+\lambda^I_{h,\mathrm{IVM}}\right)S_m,\\ 0=\lambda_h S_m-\mu_m I_m-\left(\lambda^S_{h,\mathrm{IVM}}+\lambda^I_{h,\mathrm{IVM}}\right)I_m, \end{cases}$$

with the expression of λ_m, $\lambda^S_{h,\mathrm{IVM}}$ and $\lambda^I_{h,\mathrm{IVM}}$ given by (A24).

Remark A.2: Let's assume λ_m is small enough. Then

$$L_{\lambda_m}[w]=w(\tau)-\lambda_m\gamma_h\int_0^\tau \frac{\Gamma_h(\tau)}{\Gamma_h(\sigma)}E_1\int_0^\sigma \frac{\ell(0,\sigma)}{\ell(0,\zeta)}E_2 w(\zeta)\,\mathrm{d}\zeta\,\mathrm{d}\sigma+\mathcal{O}(\lambda_m^2),$$

and therefore

$$L_{\lambda_m}^{-1}[w](\tau)=w(\tau)-\lambda_m\gamma_h\int_0^\tau \frac{\Gamma_h(\tau)}{\Gamma_h(\sigma)}E_1\int_0^\sigma \frac{\ell(0,\sigma)}{\ell(0,\zeta)}E_2 w(\zeta)\,\mathrm{d}\zeta\,\mathrm{d}\sigma+\mathcal{O}(\lambda_m^2).$$

With the above remark, it follows that

$$\bar u(\lambda_m,v_h,u_h,\tau)\approx\phi\Gamma_h(\tau)E_1u_h+\left(\lambda_m\int_0^\tau \frac{\Gamma_h(\tau)}{\Gamma_h(\sigma)}E_1\ell(0,\sigma)\,\mathrm{d}\sigma\right)\phi v_h.$$

Let's solve the following system:

$$\begin{cases} 0=\Lambda_h e_1-\lambda_m E_1 v_h-(\mu_h+\phi)\,v_h+K_h v_h+\gamma_h E_2 u_h\\ \quad+\int_0^\infty \rho(\tau)\left[\ell(\lambda_m,\tau)\phi v_h+\gamma_h\int_0^\tau \frac{\ell(\lambda_m,\tau)}{\ell(\lambda_m,\sigma)}E_2\bar u(\lambda_m,v_h,u_h,\sigma)\,\mathrm{d}\sigma\right]\mathrm{d}\tau,\\ 0=\lambda_m E_1 v_h-\phi E_1 u_h-D_h u_h+\int_0^\infty \rho(\tau)\bar u(\lambda_m,v_h,u_h,\tau)\,\mathrm{d}\tau, \end{cases}$$

we have

$$u_h=\lambda_m\left(\phi E_1+D_h-\int_0^\infty \phi\rho(\tau)\Gamma_h(\tau)E_1\,\mathrm{d}\tau\right)^{-1}\left(E_1+\int_0^\infty\int_0^\infty \phi\rho(\tau)\frac{\Gamma_h(\tau)}{\Gamma_h(\sigma)}E_1 l(0,\tau)\,\mathrm{d}\sigma\,\mathrm{d}\tau\right)v_h:=\lambda_m M_1 v_h,$$

with

$$M_1=\left(\phi E_1+D_h-\int_0^\infty \phi\rho(\tau)\Gamma_h(\tau)E_1\,\mathrm{d}\tau\right)^{-1}\left(E_1+\int_0^\infty\int_0^\infty \phi\rho(\tau)\frac{\Gamma_h(\tau)}{\Gamma_h(\sigma)}E_1 l(0,\tau)\,\mathrm{d}\sigma\,\mathrm{d}\tau\right).$$

Therefore

$$\begin{cases} v_h=g_1(\lambda_m),\\ u_h=\lambda_m M_1 g_1(\lambda_m).\end{cases} \tag{A25}$$

with

$$\begin{aligned} g_1(\lambda_m)=\Bigg(&\lambda_m E_1+(\mu_h+\phi)I_{\mathrm{d}}-K_h-\lambda_m\gamma_h E_2 M_1-\int_0^\infty \phi\rho(\tau)l(0,\tau)\,\mathrm{d}\tau\\ &-\lambda_m\int_0^\infty\int_0^\tau \phi\gamma_h\rho(\tau)\frac{l(0,\tau)}{l(0,\sigma)}E_2\Gamma_h(\tau)E_1M_1\,\mathrm{d}\sigma\,\mathrm{d}\tau\\ &-\lambda_m\int_0^\infty\int_0^\tau\int_0^\sigma \phi\gamma_h\rho(\tau)\frac{l(0,\tau)}{l(0,\sigma)}E_2\frac{\Gamma_h(\sigma)}{\Gamma_h(\varsigma)}E_2 l(0,\varsigma)\,\mathrm{d}\varsigma\,\mathrm{d}\sigma\,\mathrm{d}\tau\Bigg)^{-1}\Lambda_h e_1.\end{aligned}$$

Moreover, by (A25) it comes

$$N_h=eu_h+ev_h=(e\lambda_m M_1+e)\,g_1(\lambda_m). \tag{A26}$$

Let

$$\begin{aligned} g_2(\lambda_m)&:=\left(\lambda^I_{h,\mathrm{IVM}}+\lambda^S_{h,\mathrm{IVM}}\right)N_h\\ &=\theta\beta_h\lambda_m\int_0^\infty e\left[\phi\Gamma_h(\tau)E_1M_1+\int_0^\tau \phi\frac{\Gamma_h(\tau)}{\Gamma_h(\sigma)}E_1 l(0,\tau)\right]g_1(\lambda_m)\,\mathrm{d}\tau\\ &\quad+\theta\int_0^\infty e\Bigg[\ell(0,\tau)\phi g_1(\lambda_m)+\gamma_h\lambda_m\int_0^\tau \phi\frac{\ell(0,\tau)}{\ell(0,\sigma)}E_2\,(\Gamma(\sigma)E_1M_1\\ &\quad+\int_0^\sigma \frac{\Gamma_h(\sigma)}{\Gamma_h(\varsigma)}E_1 l(0,\varsigma)\,\mathrm{d}\varsigma\Bigg)g_1(\lambda_m)\,\mathrm{d}\sigma\Bigg]\,\mathrm{d}\tau,\end{aligned}$$

By (A25) and (A26), we have

$$\lambda_h=\frac{\theta\beta_h}{N_h}eu_h=\theta\beta_h\frac{e\lambda_m M_1 g_1(\lambda_m)}{(e\lambda_m M_1+e)\,g_1(\lambda_m)}.$$

We also have,

$$\begin{aligned} S_m&=\frac{\Lambda_m}{\mu_m+\lambda_h+\lambda^S_{h,\mathrm{IVM}}+\lambda^I_{h,\mathrm{IVM}}},\\ I_m&=\frac{\lambda_h S_m}{\mu_m+\lambda^S_{h,\mathrm{IVM}}+\lambda^I_{h,\mathrm{IVM}}}\\ &=\frac{\lambda_h\Lambda_m}{\left(\mu_m+\lambda_h+\lambda^S_{h,\mathrm{IVM}}+\lambda^I_{h,\mathrm{IVM}}\right)\left(\mu_m+\lambda^S_{h,\mathrm{IVM}}+\lambda^I_{h,\mathrm{IVM}}\right)}\\ &=\theta\beta_h\frac{\lambda_m\Lambda_m eM_1g_1(\lambda_m)\,(e\lambda_mM_1+e)\,g_1(\lambda_m)}{\left[\mu_m\,(e\lambda_mM_1+e)\,g_1(\lambda_m)+\lambda_m eM_1g_1(\lambda_m)+g_2(\lambda_m)\right]\left[\mu_m\,(e\lambda_mM_1+e)\,g_1(\lambda_m)+g_2(\lambda_m)\right]}.\end{aligned}$$

Therefore,

$$\begin{aligned}\lambda_m&=\frac{\theta\beta_m}{N_h}I_m\\ &=\frac{\theta^2\beta_h\beta_m\lambda_m\Lambda_m eM_1g_1(\lambda_m)}{\left[\mu_m\,(e\lambda_mM_1+e)\,g_1(\lambda_m)+\lambda_m eM_1g_1(\lambda_m)+g_2(\lambda_m)\right]\left[\mu_m\,(e\lambda_mM_1+e)\,g_1(\lambda_m)+g_2(\lambda_m)\right]}.\end{aligned}$$

Since we are interesting for $\lambda_m>0$, the above equality becomes

$$\bar{g}(\lambda_m)=1, \tag{A27}$$

with $\bar{g}$ a function defined from $\mathbb{R}$ to itself by

$$\bar{g}(\lambda_m)=\frac{\theta^2\beta_h\beta_m\Lambda_m eM_1g_1(\lambda_m)}{\left[\mu_m\,(e\lambda_mM_1+e)\,g_1(\lambda_m)+\lambda_m eM_1g_1(\lambda_m)+g_2(\lambda_m)\right]\left[\mu_m\,(e\lambda_mM_1+e)\,g_1(\lambda_m)+g_2(\lambda_m)\right]}.$$

Since

$$g_1(0) = S_h^0 e_1,$$
$$g_2(0) = \int_0^\infty \theta S_{h,\mathrm{IVM}}^0(\tau)\,\mathrm{d}\tau,$$

we have

$$\bar{g}(0) = \frac{\theta^2 \beta_h \beta_m \Lambda_m e M_1 g_1(0)}{\left(\mu_m e g_1(0) + g_2(0)\right)^2}$$
$$= \frac{\theta^2 \beta_h \beta_m \Lambda_m e M_1 e_1 S_h^0}{\left(\mu_m S_h^0 + \theta \int_0^\infty S_{h,\mathrm{IVM}}^0(\tau)\,\mathrm{d}\tau\right)^2} = \theta^2 \beta_h \beta_m \bar{c}_0,$$

with $\bar{c}_0$ a positive constant such that $\bar{c}_0 = \frac{\Lambda_m e M_1 e_1 S_h^0}{(\mu_m S_h^0 + \theta \int_0^\infty S_{h,\mathrm{IVM}}^0(\tau)\,\mathrm{d}\tau)^2}$

Set

$$\bar{r}_0 = \theta^2 \beta_h \beta_m \bar{c}_0.$$

Then, (A27) rewrites as a $\bar{r}_0$-parametric equation

$$\bar{G}(\bar{r}_0, \lambda_m) = 1,$$

with

$$\bar{G}(\bar{r}_0, \lambda) = \frac{(\bar{r}_0/\bar{c}_0)\Lambda_m e M_1 g_1(\lambda)}{\left[\mu_m(\lambda e M_1 + e) g_1(\lambda) + \lambda e M_1 g_1(\lambda) + g_2(\lambda)\right]\left[\mu_m(\lambda e M_1 + e) g_1(\lambda) + g_2(\lambda)\right]}.$$

Note that $\bar{G}(1,0) = 1$ and by the implicit function theorem, it comes

$$\left(\frac{\mathrm{d}\lambda}{\mathrm{d}r_0}\right)_{|(r_0=1,\lambda=0)} = -\frac{\partial_{r_0}\bar{G}(1,0)}{\partial_\lambda \bar{G}(1,0)}.$$

We have

$$\partial_{r_0}\bar{G}(1,0) = \frac{(1/\bar{c}_0)\Lambda_m e M_1 g_1(0)}{\left[\mu_m e g_1(0) + g_2(0)\right]^2} = \frac{(1/\bar{c}_0)\Lambda_m S_h^0 e M_1 e_1}{\left[\mu_m S_h^0 + \int_0^\infty \theta S_{h,\mathrm{IVM}}^0(\tau)\,\mathrm{d}\tau\right]^2} = 1.$$

Furthermore, we rewrite $\bar{G}(r_0, \lambda)$ as

$$\bar{G}(r_0, \lambda) = \frac{(\bar{r}_0/\bar{c}_0)\Lambda_m e M_1 g_1(\lambda)}{\bar{A}(\lambda)\bar{B}(\lambda)},$$

with $\bar{A}(\lambda) = [\mu_m(\lambda e M_1 + e)g_1(\lambda) + \lambda e M_1 g_1(\lambda) + g_2(\lambda)]$ and $\bar{B}(\lambda) = [\mu_m(\lambda e M_1 + e)g_1(\lambda) + g_2(\lambda)]$. It follows that

$$\partial_\lambda \bar{G}(1,0) = (1/\bar{c}_0)\frac{\Lambda_m e M_1 g_1'(0)}{\bar{A}(0)\bar{B}(0)} - (1/\bar{c}_0)\frac{\Lambda_m e M_1 g_1(0)\left[\bar{A}'(0)\bar{B}(0) + \bar{A}(0)\bar{B}'(0)\right]}{\bar{A}(0)^2\bar{B}(0)^2}, \tag{A28}$$

and

$$\bar{A}'(\lambda) = [\mu_m e M_1 + e M_1]\, g_1(\lambda) + [\mu_m(\lambda e M_1 + e) + \lambda e M_1]\, g_1'(\lambda) + g_2'(\lambda),$$
$$\bar{B}'(\lambda) = \mu_m e M_1 g_1(\lambda) + \mu_m(\lambda e M_1 + e) g_1'(\lambda) + g_2'(\lambda).$$

We recall that

$$g_1(\lambda) = \Bigg(\lambda E_1 + (\mu_h + \phi)\, I_\mathrm{d} - K_h - \lambda\gamma_h E_2 M_1 - \int_0^\infty \phi\rho(\tau) l(0,\tau)\,\mathrm{d}\tau$$
$$- \lambda \int_0^\infty \int_0^\tau \phi\gamma_h\rho(\tau)\frac{l(0,\tau)}{l(0,\sigma)} E_2 \Gamma_h(\tau) E_1 M_1\,\mathrm{d}\sigma\,\mathrm{d}\tau$$
$$-\lambda \int_0^\infty \int_0^\tau \int_0^\sigma \phi\gamma_h\rho(\tau)\frac{l(0,\tau)}{l(0,\sigma)} E_2 \frac{\Gamma_h(\sigma)}{\Gamma_h(\varsigma)} E_2 l(0,\varsigma)\,\mathrm{d}\varsigma\,\mathrm{d}\sigma\,\mathrm{d}\tau\Bigg)^{-1} \Lambda_h e_1.$$

$$g_2(\lambda) = \theta\beta_h\lambda \int_0^\infty e\left[\phi\Gamma_h(\tau) E_1 M_1 + \int_0^\tau \phi\frac{\Gamma_h(\tau)}{\Gamma_h(\sigma)} E_1 l(0,\tau)\right] g_1(\lambda)\,\mathrm{d}\tau$$
$$+ \theta \int_0^\infty e\left[\ell(0,\tau)\phi g_1(\lambda) + \gamma_h\lambda \int_0^\tau \phi\frac{\ell(0,\tau)}{\ell(0,\sigma)} E_2 \left(\Gamma(\sigma) E_1 M_1 + \int_0^\sigma \frac{\Gamma_h(\sigma)}{\Gamma_h(\varsigma)} E_1 l(0,\varsigma)\,\mathrm{d}\varsigma\right) g_1(\lambda)\,\mathrm{d}\sigma\right] \mathrm{d}\tau,$$

and therefore

$$\begin{aligned} g_1'(\lambda) = &\Bigg(\gamma_h E_2 M_1 + \int_0^\infty \int_0^\tau \phi\gamma_h\rho(\tau)\frac{l(0,\tau)}{l(0,\sigma)}E_2\Gamma_h(\tau)E_1M_1 \,\mathrm{d}\sigma\,\mathrm{d}\tau \\ &+\int_0^\infty \int_0^\tau \int_0^\sigma \phi\gamma_h\rho(\tau)\frac{l(0,\tau)}{l(0,\sigma)}E_2\frac{\Gamma_h(\sigma)}{\Gamma_h(\varsigma)}E_2 l(0,\varsigma)\,\mathrm{d}\varsigma\,\mathrm{d}\sigma\,\mathrm{d}\tau - E_1\Bigg) \\ &\times\Bigg(\lambda E_1 + (\mu_h+\phi)I_\mathrm{d} - K_h - \lambda\gamma_h E_2 M_1 - \int_0^\infty \phi\rho(\tau)l(0,\tau)\,\mathrm{d}\tau \\ &-\lambda\int_0^\infty \int_0^\tau \phi\gamma_h\rho(\tau)\frac{l(0,\tau)}{l(0,\sigma)}E_2\Gamma_h(\tau)E_1M_1\,\mathrm{d}\sigma\,\mathrm{d}\tau \\ &-\lambda\int_0^\infty \int_0^\tau \int_0^\sigma \phi\gamma_h\rho(\tau)\frac{l(0,\tau)}{l(0,\sigma)}E_2\frac{\Gamma_h(\sigma)}{\Gamma_h(\varsigma)}E_2 l(0,\varsigma)\,\mathrm{d}\varsigma\,\mathrm{d}\sigma\,\mathrm{d}\tau\Bigg)^{-2}\Lambda_h e_1 \\ = &\Bigg(\gamma_h E_2 M_1 + \int_0^\infty \int_0^\tau \phi\gamma_h\rho(\tau)\frac{l(0,\tau)}{l(0,\sigma)}E_2\Gamma_h(\tau)E_1M_1 \,\mathrm{d}\sigma\,\mathrm{d}\tau \\ &+\int_0^\infty \int_0^\tau \int_0^\sigma \phi\gamma_h\rho(\tau)\frac{l(0,\tau)}{l(0,\sigma)}E_2\frac{\Gamma_h(\sigma)}{\Gamma_h(\varsigma)}E_2 l(0,\varsigma)\,\mathrm{d}\varsigma\,\mathrm{d}\sigma\,\mathrm{d}\tau - E_1\Bigg) \\ &\times\Bigg(\lambda E_1 + (\mu_h+\phi)I_\mathrm{d} - K_h - \lambda_m\gamma_h E_2 M_1 - \int_0^\infty \phi\rho(\tau)l(0,\tau)\,\mathrm{d}\tau \\ &-\lambda\int_0^\infty \int_0^\tau \phi\gamma_h\rho(\tau)\frac{l(0,\tau)}{l(0,\sigma)}E_2\Gamma_h(\tau)E_1M_1\,\mathrm{d}\sigma\,\mathrm{d}\tau \\ &-\lambda\int_0^\infty \int_0^\tau \int_0^\sigma \phi\gamma_h\rho(\tau)\frac{l(0,\tau)}{l(0,\sigma)}E_2\frac{\Gamma_h(\sigma)}{\Gamma_h(\varsigma)}E_2 l(0,\varsigma)\,\mathrm{d}\varsigma\,\mathrm{d}\sigma\,\mathrm{d}\tau\Bigg)^{-1} g_1(\lambda), \end{aligned}$$

and

$$\begin{aligned} g_2'(\lambda) = &\theta\beta_h\int_0^\infty e\left[\phi\Gamma_h(\tau)E_1M_1 + \int_0^\tau \phi\frac{\Gamma_h(\tau)}{\Gamma_h(\sigma)}E_1 l(0,\tau)\right]g_1(\lambda)\,\mathrm{d}\tau \\ &+\theta\beta_h\lambda\int_0^\infty e\left[\phi\Gamma_h(\tau)E_1M_1 + \int_0^\tau \phi\frac{\Gamma_h(\tau)}{\Gamma_h(\sigma)}E_1 l(0,\tau)\right]g_1'(\lambda)\,\mathrm{d}\tau + \theta\int_0^\infty e\ell(0,\tau)\phi g_1(\lambda)\,\mathrm{d}\tau \\ &+\theta\int_0^\infty e\left[\gamma_h\int_0^\tau \phi\frac{\ell(0,\tau)}{\ell(0,\sigma)}E_2\left(\Gamma(\sigma)E_1M_1 + \int_0^\sigma \frac{\Gamma_h(\sigma)}{\Gamma_h(\varsigma)}E_1 l(0,\varsigma)\,\mathrm{d}\varsigma\right)g_1(\lambda)\,\mathrm{d}\sigma\right. \\ &\left.+\gamma_h\lambda\int_0^\tau \phi\frac{\ell(0,\tau)}{\ell(0,\sigma)}E_2\left(\Gamma(\sigma)E_1M_1 + \int_0^\sigma \frac{\Gamma_h(\sigma)}{\Gamma_h(\varsigma)}E_1 l(0,\varsigma)\,\mathrm{d}\varsigma\right)g_1'(\lambda)\,\mathrm{d}\sigma\right]\mathrm{d}\tau. \end{aligned}$$

Hence

$$\begin{aligned} g_1'(0) = &\Bigg(\gamma_h E_2 M_1 + \int_0^\infty \int_0^\tau \phi\gamma_h\rho(\tau)\frac{l(0,\tau)}{l(0,\sigma)}E_2\Gamma_h(\tau)E_1M_1 \,\mathrm{d}\sigma\,\mathrm{d}\tau \\ &+\int_0^\infty \int_0^\tau \int_0^\sigma \phi\gamma_h\rho(\tau)\frac{l(0,\tau)}{l(0,\sigma)}E_2\frac{\Gamma_h(\sigma)}{\Gamma_h(\varsigma)}E_2 l(0,\varsigma)\,\mathrm{d}\varsigma\,\mathrm{d}\sigma\,\mathrm{d}\tau - E_1\Bigg) \\ &\times\left((\mu_h+\phi)I_\mathrm{d} - K_h - \int_0^\infty \phi\rho(\tau)l(0,\tau)\,\mathrm{d}\tau\right)^{-1} g_1(0) \\ = &S_h^0 M_2 e_1, \end{aligned}$$

and

$$\begin{aligned} g_2'(0) = &\theta\beta_h\int_0^\infty e\left[\phi\Gamma_h(\tau)E_1M_1 + \int_0^\tau \phi\frac{\Gamma_h(\tau)}{\Gamma_h(\sigma)}E_1 l(0,\tau)\right]g_1(0)\,\mathrm{d}\tau + \theta\int_0^\infty e\ell(0,\tau)\phi g_1(0)\,\mathrm{d}\tau \\ &+\theta\int_0^\infty e\left[\gamma_h\int_0^\tau \phi\frac{\ell(0,\tau)}{\ell(0,\sigma)}E_2\left(\Gamma(\sigma)E_1M_1 + \int_0^\sigma \frac{\Gamma_h(\sigma)}{\Gamma_h(\varsigma)}E_1 l(0,\varsigma)\,\mathrm{d}\varsigma\right)g_1(0)\,\mathrm{d}\sigma\right. \\ = &S_h^0 M_3 e_1, \end{aligned}$$

with

$$M_2 = \left(\gamma_h E_2 M_1 + \int_0^\infty \int_0^\tau \phi\gamma_h\rho(\tau)\frac{l(0,\tau)}{l(0,\sigma)}E_2\Gamma_h(\tau)E_1M_1\,\mathrm{d}\sigma\,\mathrm{d}\tau \right.$$
$$\left. + \int_0^\infty \int_0^\tau \int_0^\sigma \phi\gamma_h\rho(\tau)\frac{l(0,\tau)}{l(0,\sigma)}E_2\frac{\Gamma_h(\sigma)}{\Gamma_h(\varsigma)}E_2 l(0,\varsigma)\,\mathrm{d}\varsigma\,\mathrm{d}\sigma\,\mathrm{d}\tau - E_1\right)$$
$$\times \left((\mu_h+\phi)I_\mathrm{d} - K_h - \int_0^\infty \phi\rho(\tau)l(0,\tau)\,\mathrm{d}\tau\right)^{-1},$$

and

$$M_3 = \theta\beta_h \int_0^\infty e\left[\phi\Gamma_h(\tau)E_1M_1 + \int_0^\tau \phi\frac{\Gamma_h(\tau)}{\Gamma_h(\sigma)}E_1 l(0,\tau)\right]\mathrm{d}\tau + \int_0^\infty \theta S^0_{h,\mathrm{IVM}}(\tau)\,\mathrm{d}\tau$$
$$+\theta\int_0^\infty e\left[\gamma_h\int_0^\tau \phi\frac{\ell(0,\tau)}{\ell(0,\sigma)}E_2\left(\Gamma(\sigma)E_1M_1 + \int_0^\sigma \frac{\Gamma_h(\sigma)}{\Gamma_h(\varsigma)}E_1 l(0,\varsigma)\,\mathrm{d}\varsigma\right)\mathrm{d}\sigma.\right.$$

We then deduce that

$$\bar{A}'(0) = S^0_h\left[\mu_m eM_1 + eM_1 + \mu_m eM_2 + M_3\right]e_1,$$
$$\bar{B}'(0) = S^0_h\left[\mu_m eM_1 + \mu_m eM_2 + M_3\right]e_1.$$

Consequently, (A28) gives

$$\partial_\lambda\bar{G}(1,0) = \frac{(1/\bar{c}_0)\Lambda_m S^0_h eM_1M_2e_1}{\left[\mu_m S^0_h + \int_0^\infty \theta S^0_{h,\mathrm{IVM}}(\tau)\,\mathrm{d}\tau\right]^2} - \frac{(1/\bar{c}_0)\Lambda_m\left(S^0_h\right)^2 eM_1e_1\left[2\mu_m eM_1 + eM_1 + 2\mu_m eM_2 + 2M_3\right]e_1}{\left[\mu_m S^0_h + \int_0^\infty \theta S^0_{h,\mathrm{IVM}}(\tau)\,\mathrm{d}\tau\right]^3}.$$

Therefore, by introducing the following bifurcation parameter:

$$C_\mathrm{bif} = \left(\frac{\mathrm{d}\lambda}{\mathrm{d}\bar{r}_0}\right)^{-1}_{|(\bar{r}_0=1,\lambda=0)}$$
$$= \frac{(1/\bar{c}_0)\Lambda_m\left(S^0_h\right)^2 eM_1e_1\left[2\mu_m eM_1 + eM_1 + 2\mu_m eM_2 + 2M_3\right]e_1}{\left[\mu_m S^0_h + \int_0^\infty \theta S^0_{h,\mathrm{IVM}}(\tau)\,\mathrm{d}\tau\right]^3} - \frac{(1/\bar{c}_0)\Lambda_m S^0_h eM_1M_2e_1}{\left[\mu_m S^0_h + \int_0^\infty \theta S^0_{h,\mathrm{IVM}}(\tau)\,\mathrm{d}\tau\right]^2},$$

it comes that a backward bifurcation occurs at $\bar{r}_0 = 1$ if and only if $C_\mathrm{bif} < 0$, and a forward bifurcation occurs at $\bar{r}_0 = 1$ if and only if $C_\mathrm{bif} > 0$.

However, without the effect of IVM, i.e. when $\phi = 0$, it comes

$$\bar{r}_0 = \theta^2\beta_h\beta_m\frac{\Lambda_m eM_1e_1}{\mu_m^2 S^0_h}.$$

In such a configuration, it is important to observe that the bifurcation parameter $\bar{r}_0$ corresponds to the expression of $\mathcal{R}_0$ without considering the impact of IVM, as given in (16).

Furthermore, without the effect of IVM, the bifurcation parameter C_bif rewrites

$$C_\mathrm{bif} = \frac{(1/\bar{c}_0)\Lambda_m eM_1e_1}{\left[\mu_m S^0_h\right]^3}\left(S^0_h\left[2\mu_m eM_1 + eM_1 + 2\mu_m eM_2\right]e_1 + \mu_m S^0_h\right) - \frac{(1/\bar{c}_0)\Lambda_m eM_1M_2e_1}{\left[\mu_m S^0_h\right]^2}$$
$$= -\frac{\Lambda_m}{\mu_m^2}\frac{\mu_h+\nu_h+\gamma_h+\delta_h}{\Lambda_h}\left(1 - \frac{\mu_h^3(1+2\mu_m)\bar{a} + 2\mu_h\mu_m\Lambda_h(1-\bar{a})}{\mu_m\Lambda_h^2(\mu_h+\nu_h)(\mu_h+\gamma_h+\delta_h)}\right),$$

wherein

$$\bar{a} = \frac{\gamma_h\nu_h}{(\mu_h+\nu_h)(\mu_h+\gamma_h+\delta_h)}.$$