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Bifurcation Thresholds and Optimal Control in Transmission Dynamics of Arboviral Diseases

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Abstract

In this paper, we derive and analyse a model for the control of arboviral diseases which takes into account an imperfect vaccine combined with some other mechanisms of control already studied in the literature. We begin by analyse the basic model without controls. We prove the existence of two disease-free equilibrium points and the possible existence of up to two endemic equilibrium points (where the disease persists in the population). We show the existence of a transcritical bifurcation and a possible saddle-node bifurcation and explicitly derive threshold conditions for both, including defining the basic reproduction number, \mathcal{R}_0 , which determines whether the disease can persist in the population or not. The epidemiological consequence of saddle-node bifurcation (backward bifurcation) is that the classical requirement of having the reproduction number less than unity, while necessary, is no longer sufficient for disease elimination from the population. It is further shown that in the absence of disease-induced death, the model does not exhibit this phenomenon. We perform the sensitivity analysis to determine the model robustness to parameter values. That is to help us to know the parameters that are most influential in determining disease dynamics. The model is extended by reformulating the model as an optimal control problem, with the use of five time dependent controls, to assess the impact of vaccination combined with treatment, individual protection and vector control strategies (killing adult vectors, reduction of eggs and larvae). By using optimal control theory, we establish optimal conditions under which the disease can be eradicated and we examine the impact of a possible combined control tools on the disease transmission. The Pontryagin's maximum principle is used to characterize the optimal control. Numerical simulations, efficiency analysis and cost effectiveness analysis show that, vaccination combined with other control mechanisms, would reduce the spread of the disease appreciably, and this at low cost.

Keywords: Arboviral diseases; Bifurcation; Sensitivity analysis; Optimal control; Pontryagin's Maximum Principle; Efficiency analysis, Cost effectiveness analysis.

AMS Subject Classification (2010): 37N25, 49J15, 92D30.

1 Introduction

Arboviral diseases are affections transmitted by hematophagous arthropods. There are currently 534 viruses registered in the International Catalog of Arboviruses and 25% of them

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have caused documented illness in human populations [15, 35, 30]. Examples of those kinds of diseases are Dengue, Yellow fever, Saint Louis fever, Encephalitis, West Nile fever and Chikungunya. A wide range of arboviral diseases are transmitted by mosquito bites and constitute a public health emergency of international concern. For example, Dengue, caused by any of four closely-related virus serotypes (DEN-1-4) of the genus *Flavivirus*, causes 50–100 million infections worldwide every year, and the majority of patients worldwide are children aged 9 to 16 years [53, 65, 64].

The dynamics of arboviral diseases like Dengue or Chikungunya are influenced by many factors such as human and mosquito behaviours. The virus itself (multiple serotypes of dengue virus [65, 64], and multiple strains of chikungunya virus [22, 46]), as well as the environment, affects directly or indirectly all the present mechanisms of control [5, 13]. Indeed, in the absence of conditions which favour the development of their larvae, eggs of certain *Aedes* mosquitoes (*Aedes albopictus*, for example) enter in diapause phenomenon, allowing the eggs to hatch even after two years [47, 57]. Taking the case of *Aedes* mosquitoes for example, the main control method used in many countries continues to be space spraying of insecticide for adult mosquito control. This strategy must be repeated constantly, its cost is high, and its effectiveness is limited. Also, *Ae. aegypti*, for example, prefers to rest inside houses, so truck or aerial insecticide spraying simply does not reach mosquitoes resting in hidden places such as cupboards [63]. The different types of control mechanisms put in place to reduce the proliferation of vectors responsible for the transmission of pathogens such as arboviruses are listed below..

- (i) Biological control or "biocontrol" is the use of natural enemies to manage vector populations: introduction of parasites, pathogens and predators to target vectors. for example, effective biocontrol agents include predatory fish that feed on mosquito larvae such as mosquitofish (*Gambusia affinis*) and some cyprinids (carps and minnows) and killifish. *Tilapia* also consume mosquito larvae [11]. As biological control does not cause chemical pollution, it is considered as a better method for mosquito control by many people. However, there are limitations on employing biological agents for mosquito control. The agent introduced usually has to be substantial in number for giving desirable effect.
- (ii) Mechanical control consist at the environmental sanitation measures to reduce mosquito breeding sites, such as the physical management of water containers (e.g. mosquito-proof covers for water storage containers, polystyrene beads in water tanks), better designed and reliable water supplies, and recycling of solid waste such as discarded tyres, bottles, and cans [63, 23].
- (iii) Chemical methods [63, 23]:
 - chemical methods against the mosquito's aquatic stages for use in water containers (larviciding –killing of larvae),
 - chemical methods directed against adult mosquitoes, such as insecticide space sprays or residual applications (adulticiding –killing of adult mosquitoes),.
- (iv) Personal protection consist at the use of repellents, vaporizers, mosquito coils, and insecticide treated screens, curtains, and bednets (for daytime use against *Aedes*) [63].

The main problem encountered in the implementation of some of these control mechanisms is the preservation of the ecological systems. For example, in the "biocontrol" mechanism, direct introduction of *tilapia* and *mosquitofish* into ecosystems around the world have had

disastrous consequences [11]. Also, the chemical methods can not be applied in continuous times. Some chemical product like *Deltamethrin* seems to be effective only during a couple of hours [23, 8, 33]. So its use over a long period and continuously, leads to strong resistance of the wild populations of *Aedes aegypti* [19], for example.

For all the diseases mentioned above, only yellow fever has a licensed vaccine. Nevertheless, considerable efforts are made to obtain vaccines for other diseases. In the case of dengue, for example, tests carried out in Asia and Latin America, have shown that the future dengue vaccine will have a efficacy between 30.2% and 77.7%, and this, depending on the serotype [51, 60]. Also, the future dengue vaccine will have an overall efficacy of 60.8% against all forms of the disease in children and adolescents aged 9-16 years who received three doses of the vaccine[54].

As the future vaccines (e.g., dengue vaccine) will be imperfect, it is therefore necessary to combine such vaccines with some control mechanisms cited above, to find the best sufficient combination (in terms of efficacy and costs), which permit to decrease the expansion of these kind of diseases in human communities.

A number of studies have been conducted to study host-vector models for arboviral diseases transmission (see [23, 1, 2, 4, 6, 7, 10, 16, 18, 20, 25, 26, 27, 29, 41, 43, 44, 48, 50]). Some of these works have been conducted to explore optimal control theory for arboviral disease models (see [4, 7, 44, 50, 62]).

In [4], Dipo Aldila and co-workers derive a optimal control problem for a host-vector Dengue transmission model, in which treatments with mosquito repellent are given to adults and children and those who undergo treatment are classified in treated compartments. The only control considered by the authors is the treatment of people with clinical signs of the disease. Blayneh et al. in [7] consider a deterministic model for the transmission dynamics of West Nile virus (WNV) in the mosquito-bird-human zoonotic cycle. They use two control functions, one for mosquito-reduction strategies and the other for personal (human) protection, and redefining the demographic parameters as density-dependent rates. In [44], Moulay et al. derive optimal prevention (individual protection), vector control (Larvae reduction) and treatment strategies used during the Chikungunya Réunion Island epidemic in 2006. Authors in [50] derive the optimal control efforts for vaccination in order to prevent the spread of a Dengue disease using a system of ordinary differential equations (ODEs) for the host and vector populations. Recently, Dias et al. in [62] analyse the Dengue vector control problem in a multiobjective optimization approach, in which the intention is to minimize both social and economic costs, using a dynamic mathematical model representing the mosquitoes' population. This multiobjective optimization approach consists in finding optimal alternated step-size control policies combining chemical (via application of insecticides) and biological control (via insertion of sterile males produced by irradiation).

None of the above mentioned models [4, 7, 44, 50, 62] takes into account the combination of optimal control mechanisms such as vaccination, individual protection, treatment and vector control strategies. In our effort, we investigate such optimal strategies for vaccination combined with individual protection, treatment and two vector controls (adulticiding–killing of adult vectors, and larviciding–killing eggs and larvae), using two systems of ODEs which consist of a complete stage structured model Eggs-Larvae-Pupae for the vectors, and a SEI/SEIR type model for the vector/host population. This provides a new different mathematical perspective to the subject. Furthermore, a efficiency analysis and cost effectiveness analysis, are performed here in order to evaluate the control combination that is most effective in the design of optimal strategies.

We start with the formulation of a model without control which is an modified of the previous models developed in [1, 2]. We compute the net reproductive number \mathcal{N} , as well as the basic reproduction number, \mathcal{R}_0 , and investigate the existence and stability of equilibria.

We prove that the trivial equilibrium is globally asymptotically stable whenever $\mathcal{N} < 1$. When $\mathcal{N} > 1$ and $\mathcal{R}_0 < 1$, we prove that the system exhibit the backward bifurcation phenomenon. The implication of this occurrence is that the classical epidemiological requirement for effective eradication of the disease, $\mathcal{R}_0 < 1$, is no longer sufficient, even though necessary. We show the existence of a transcritical bifurcation and a possible saddle-node bifurcation and explicitly derive threshold conditions for both.

Then, we formulate an optimal control model by adding five control functions: three for human (vaccination, protection against mosquitoes bites and treatment), and two for mosquito-reduction strategies (the use of adulticide to kill adult vectors, and the use of larvicide to increase the mortality rate of eggs and larvae). By Using optimal control theory, we derive the conditions under which it is optimal to eradicate the disease and examine the impact of a possible combination of vaccination, treatment, individual protection and vector control strategies on the disease transmission. The Pontryagin's maximum principle is used to characterize the optimal control. Numerical simulations, efficiency analysis, as well as, the cost effectiveness analysis, are performed to determine the best combination (in terms of efficacy and cost).

The rest of the paper is organized as follows. In section 2, we present the basic transmission model and carry out some analysis by determining important thresholds such as the net reproductive number \mathcal{N} and the basic reproduction number \mathcal{R}_0 , and different equilibria of the model. We then demonstrate the stability of equilibria and carry out bifurcation analysis, by deriving the threshold conditions for saddle–node bifurcation. In Section 3 we present the optimal control problem and its mathematical analysis. Section 4 is devoted to numerical simulations, efficiency analysis and cost effectiveness analysis. A conclusion round up the paper.

2 The basic model and its analysis

The model we propose here is based on the modelling approach given in [1, 2]. For the reader convenience, we briefly recall here main results which are developed in this work.

It is assumed that the human and vector populations are divided into compartments described by time–dependent state variables. The compartments in which the populations are divided are the following ones:

(i) For humans, we consider a SEIR model: Susceptible (denoted by S_h), exposed (E_h), infectious (I_h) and resistant or immune (R_h) which includes naturally-immune individuals. The recruitment in human population is at the constant rate Λ_h , and newly recruited individuals enter the susceptible compartment S_h . Are concern by recruitment people that are totally naive from the disease. Each human compartment, individual goes out from the dynamics at natural mortality rates μ_h . The human susceptible population is decreased following infection, which can be acquired via effective contact with an exposed or infectious vector at a rate

$$\lambda_h = \frac{a\beta_{hv}(\eta_v E_v + I_v)}{N_h}, \quad (1)$$

where a is the biting rate per susceptible vector, β_{hv} is the transmission probability from an exposed/infectious vector (E_v or I_v) to a susceptible human (S_h). The expression of λ_h is obtained as follows. The probability that a vector chooses a particular human or other source of blood to bite can be assumed as $\frac{1}{N_h}$. Thus, a human receives in average $a\frac{N_v}{N_h}$ bites per unit of times. Then, the infection rate per susceptible human is given $a\beta_{hv}\frac{N_v}{N_h}\frac{(\eta_v E_v + I_v)}{N_v}$. In expression of λ_h , the modification parameter $0 < \eta_v < 1$ accounts for the assumed reduction in transmissibility of exposed mosquitoes relative to infectious mosquitoes [1, 2, 29] (see the

references therein for the specific sources). Latent humans (E_h) become infectious (I_h) at rate γ_h . Infectious humans recover at a constant rate, σ or dies as consequence of infection, at a disease-induced death rate δ . Immune humans retain their immunity for life. We denote the total human population by N_h ,

$$N_h = S_h + E_h + I_h + R_h. \quad (2)$$

(ii) Following [43], the stage structured model is used to describe the vector population dynamics, which consists of three main stages: embryonic (E), larvae (L) and pupae (P). Even if eggs (E) and immature stages (L and P) are both aquatic, it is important to dissociate them because, for optimal control point of view, drying the breeding sites does not kill eggs, but only larvae and pupae. Moreover, chemical interventions on the breeding sites have a more great impact on the larval population, but not on the eggs [43]. The number of laid eggs is assumed proportional to the number of females. The system of stage structured model of aquatic phase development of vector is given by (see [43] for details)

$$\dot{E} = \mu_b \left(1 - \frac{E}{\Gamma_E}\right) (S_v + E_v + I_v) - (s + \mu_E)E \quad (3a)$$

$$\dot{L} = sE \left(1 - \frac{L}{\Gamma_L}\right) - (l + \mu_L)L \quad (3b)$$

$$\dot{P} = lL - (\theta + \mu_P)P. \quad (3c)$$

Unlike the authors of [43], we take into account the pupal stage in the development of the vector. This is justified by the fact that they do not feed during this transitional stage of development, as they transform from larvae to adults. So, the control mechanisms can not be applied to them.

With a rate θ , pupae become female adults. Each vector compartment, individuals goes out from the dynamics at natural mortality rates μ_v . The vector susceptible population is decreased following infection, which can be acquired via effective contact with an exposed or infectious human at a rate

$$\lambda_v = \frac{a\beta_{vh}(\eta_h E_h + I_h)}{N_h}, \quad (4)$$

where β_{vh} is the transmission probability from an exposed/infectious human (E_h or I_h) to a susceptible vector (S_v). As well as in the expression of λ_h , the modification parameter $0 < \eta_h < 1$ in the expression of λ_v accounts for the assumed reduction in transmissibility of exposed humans relative to infectious humans [1, 2, 29]. Latent vectors (E_v) become infectious (I_v) at rate γ_v . The vector population does not have an immune class, since it is assumed that their infectious period ends with their death [26]. So, we denote the total adult vector population by N_v ,

$$N_v = S_v + E_v + I_v. \quad (5)$$

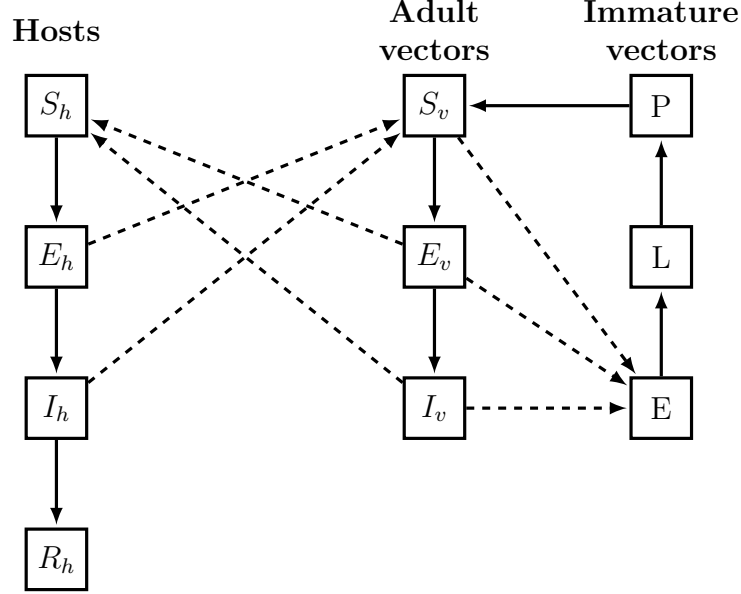


Figure 1: Schematic of the vector-borne epidemic model with development stage of vectors.

Therefore, our basic arboviral disease model reads as

$$\dot{S}_h = \Lambda_h - (\lambda_h + \mu_h)S_h \quad (6a)$$

$$\dot{E}_h = \lambda_h S_h - (\mu_h + \gamma_h)E_h \quad (6b)$$

$$\dot{I}_h = \gamma_h E_h - [\mu_h + \delta + \sigma]I_h \quad (6c)$$

$$\dot{R}_h = \sigma I_h - \mu_h R_h \quad (6d)$$

$$\dot{S}_v = \theta P - \lambda_v S_v - \mu_v S_v \quad (6e)$$

$$\dot{E}_v = \lambda_v S_v - (\mu_v + \gamma_v)E_v \quad (6f)$$

$$\dot{I}_v = \gamma_v E_v - (\mu_v)I_v \quad (6g)$$

$$\dot{E} = \mu_b \left(1 - \frac{E}{\Gamma_E}\right) N_v - (s + \mu_E)E \quad (6h)$$

$$\dot{L} = sE \left(1 - \frac{L}{\Gamma_L}\right) - (l + \mu_L)L \quad (6i)$$

$$\dot{P} = lL - (\theta + \mu_P)P \quad (6j)$$

where the upper dot denotes the time derivative and λ_h and λ_v are given by (1) and (4), respectively. A schematic of the model is shown in Figure 1. The states and parameters are all strictly positive constants and are described in Table 1 and 2, respectively.

Table 1: The state variables of model (6).

Humans		Aquatic Vectors		Adult Vectors	
S_h :	Susceptible	E :	Eggs	S_v :	Susceptible
E_h :	Infected in latent stage	L :	Larvae	E_v :	Infected in latent stage
I_h :	Infectious	P :	Pupae	I_v :	Infectious
R_h :	Resistant (immune)				

Table 2: Description and baseline values/range of parameters of model (6). The baseline values refer to dengue fever transmission.

Parameter	Description	Baseline value/range	Sources
Λ_h	Recruitment rate of humans	2.5 day^{-1}	[29]
μ_h	Natural mortality rate in humans	$\frac{1}{(67 \times 365)} \text{ day}^{-1}$	[29]
a	Average number of bites	1 day^{-1}	[4, 29]
β_{hv}	Probability of transmission of infection from an infected vector to a susceptible human	$0.1, 0.75 \text{ day}^{-1}$	[4, 29]
γ_h	Progression rate from E_h to I_h	$[\frac{1}{15}, \frac{1}{3}] \text{ day}^{-1}$	[23, 55]
δ	Disease-induced death rate	10^{-3} day^{-1}	[29]
σ	Recovery rate for humans	0.1428 day^{-1}	[4, 29]
η_h, η_v	Modifications parameter	$[0, 1)$	[29]
μ_v	Natural mortality rate of vectors	$[\frac{1}{30}, \frac{1}{14}] \text{ day}^{-1}$	[4, 29]
γ_v	Progression rate from E_v to I_v	$[\frac{1}{21}, \frac{1}{2}] \text{ day}^{-1}$	[23, 55]
β_{vh}	Probability of transmission of infection from an infected human to a susceptible vector	$0.1, 0.75 \text{ day}^{-1}$	[4, 29]
θ	Maturation rate from pupae to adult	0.08 day^{-1}	[23, 43, 44]
μ_b	Number of eggs at each deposit	6 day^{-1}	[23, 43, 44]
Γ_E	Carrying capacity for eggs	$10^3, 10^6$	[4, 43]
Γ_L	Carrying capacity for larvae	$5 \times 10^2, 5 \times 10^5$	[4, 43]
μ_E	Eggs death rate	0.2 or 0.4	[44]
μ_L	Larvae death rate	0.2 or 0.4	[44]
μ_P	Pupae death rate	0.4	Assumed
s	Transfer rate from eggs to larvae	0.7 day^{-1}	[44]
l	Transfer rate from larvae to pupae	0.5 day^{-1}	[43]

Remark 1. (i) It is important to note that, in the case of other arboviral diseases (e.g, Chikungunya), the exposed humans and vectors do not play any role in the infectious process, in this case $\eta_h = \eta_v = 0$.

(ii) The model (6) is the same that we studied in a previous work (see model 18 in [2]) to show that the backward bifurcation is caused by the disease-induced death in human. In this previous work, we have just showed that the occurrence of the backward bifurcation is possible in the model without vaccination. In the present work, we give a sufficient and necessary condition, as well as the explicit expressions of the thresholds which governing this phenomenon.

2.1 Basic properties and equilibria

The rates of change of the total populations of humans (2) and adult vectors (5) for the basic arboviral model (6) are,

$$\begin{aligned}\dot{N}_h &= \Lambda_h - \mu_h N_h - \delta I_h, \\ \dot{N}_v &= \theta P - \mu_v N_v.\end{aligned}$$

Therefore, by standard arguments (see [1, 2, 43]) it follows that the feasible region for model (6) is

$$\mathcal{D} = \left\{ (S_h, E_h, I_h, R_h, S_v, E_v, I_v, E, L, P) \in \mathbb{R}_+^{10} : N_h \leq \Lambda_h/\mu_h; E \leq K_E; L \leq K_L; P \leq \frac{lK_L}{k_7}; N_v \leq \frac{\theta l K_L}{k_7 k_8} \right\},$$

where \mathbb{R}_+^{10} represents the non-negative orthant of \mathbb{R}^{10} .

The model is epidemiologically (the state variables have a valid physical interpretation) and mathematically (the system of equations has a unique solution that is bounded and exists for all time) well-posed in the region \mathcal{D} .

For easier readability, we introduce the following quantities,

$$\begin{aligned} k_1 &:= \mu_h; k_3 := \mu_h + \gamma_h; k_4 := \mu_h + \delta + \sigma, k_5 := s + \mu_E; \\ k_6 &:= l + \mu_L; k_7 := \theta + \mu_P; k_8 := \mu_v; k_9 := \mu_v + \gamma_v; k_{10} = \eta_h k_4 + \gamma_h; k_{11} = \eta_v k_8 + \gamma_v, \end{aligned} \quad (7)$$

and (the positive quantity), $k_2 = k_3 k_4 - \delta \gamma_h = \mu_h k_4 + \gamma_h (\mu_h + \sigma)$.

Without disease in the both populations (i.e $\lambda_h = \lambda_v = 0$ or $E_h = I_h = E_v = I_v = 0$), the basic arboviral model (6) have two *disease-free equilibria* given by $\mathcal{E}_0 = (N_h^0, 0, 0, 0, 0, 0, 0, 0, 0, 0)$ which correspond to the trivial equilibrium, and $\mathcal{E}_1 = (N_h^0, 0, 0, 0, N_v^0, 0, 0, E, L, P)$ which correspond to the biological disease-free equilibrium, where

$$\begin{aligned} N_h^0 &= \frac{\Lambda_h}{\mu_h}, \quad N_v^0 = \frac{\Gamma_E \Gamma_L k_5 k_6 (\mathcal{N} - 1)}{\mu_b (\Gamma_{ES} + k_6 \Gamma_L)}, \quad P = \frac{\Gamma_E \Gamma_L k_5 k_6 k_8 (\mathcal{N} - 1)}{\mu_b \theta (\Gamma_{ES} + k_6 \Gamma_L)} \\ L &= \frac{\Gamma_E \Gamma_L k_5 k_6 k_7 k_8 (\mathcal{N} - 1)}{\mu_b \theta l (\Gamma_{ES} + k_6 \Gamma_L)}, \quad E = \frac{\Gamma_E \Gamma_L k_5 k_6 k_7 k_8 (\mathcal{N} - 1)}{s (\mu_b l \Gamma_L \theta + k_5 k_7 k_8 \Gamma_E)}, \end{aligned} \quad (8)$$

and \mathcal{N} is the net reproductive number [2, 43] given by

$$\mathcal{N} = \frac{\mu_b \theta l s}{k_5 k_6 k_7 k_8}. \quad (9)$$

Define the basic reproductive number [21, 59]

$$\mathcal{R}_0 = \sqrt{\frac{a^2 \beta_{hv} \beta_{vh} (\gamma_h + k_4 \eta_h) (\gamma_v + k_8 \eta_v) N_v^0}{k_3 k_4 k_8 k_9 N_h^0}}. \quad (10)$$

We note that,

$$\mathcal{R}_0 = \sqrt{K_{vh} K_{hv}},$$

where,

$$\begin{aligned} K_{vh} &= (K_{vh}^{E_h} + K_{vh}^{I_h}) \\ &= (a) (\beta_{vh}) \left(\frac{N_v^0}{N_h^0} \right) \left(\frac{1}{k_3} \right) \left[(\eta_h) + \left(\frac{\gamma_h}{k_4} \right) \right] \\ &= \frac{a \beta_{vh} (\gamma_h + k_4 \eta_h) N_v^0}{k_3 k_4 N_h^0}, \end{aligned}$$

is the number of vector that one human infects through his/her latent/infectious life time. It is equal to the sum of the number of vector infections generated by an exposed human (near the DFE, \mathcal{E}_1) $K_{vh}^{E_h}$, and the number of vector infections generated by an infectious human (near the DFE) $K_{vh}^{I_h}$. $K_{vh}^{E_h}$ is given by the product of the infection rate of exposed humans ($a \beta_{vh} \eta_h N_v^0 / N_h^0$) and the average duration in the exposed (E_h) class ($1/k_3$). $K_{vh}^{I_h}$ is given by the product of the infection rate of infectious humans ($a \beta_{vh} N_v^0 / N_h^0$), the probability that an exposed human

survives the exposed stage and move to the infectious stage ($\gamma_h/(\mu_h + \gamma_h)$) and the average duration in the infectious stage ($1/(\mu_h + \delta + \sigma)$).

Analogously, we have

$$\begin{aligned} K_{hv} &= K_{hv}^{E_v} + K_{hv}^{I_v} \\ &= (a)(\beta_{hv}) \left(\frac{1}{k_9} \right) \left(\eta_v + \frac{\gamma_v}{k_8} \right) \\ &= \frac{a\beta_{hv}(\gamma_v + k_8\eta_h)}{k_8k_9}, \end{aligned}$$

which is the number of humans that one vector infects through its infectious life time. It is equal to the sum of the number of human infections generated by an exposed vector (near the DFE, \mathcal{E}_1), $K_{hv}^{E_v}$, and the number of human infections generated by an infectious vector (near the DFE), $K_{hv}^{I_v}$. $K_{hv}^{E_v}$ is given by the product of the infection rate of exposed vectors ($a\beta_{vh}\eta_h$) and the average duration in the exposed (E_v) class ($1/(\mu_v + \gamma_v)$). $K_{hv}^{I_v}$ is given by the product of the infection rate of infectious humans ($a\beta_{vh}$), the probability that an exposed human survives the exposed stage and move to the infectious stage (γ_h/k_9) and the average duration in the infectious stage ($1/k_8$). The basic reproduction number is equal to the geometric mean of K_{vh} and K_{hv} because infection from human to human goes through one generation of vectors.

The local asymptotic stability result of equilibria \mathcal{E}_0 and \mathcal{E}_1 is given in the following.

Theorem 1.

- (i) if $\mathcal{N} \leq 1$, the trivial equilibrium \mathcal{E}_0 is locally asymptotically stable in \mathcal{D} ;
- (ii) if $\mathcal{N} > 1$, the trivial equilibrium is unstable and the disease-free equilibrium \mathcal{E}_1 is locally asymptotically stable in \mathcal{D} whenever $\mathcal{R}_0 < 1$.

Proof. See appendix A. □

The epidemiological implication of item (ii) in Theorem 1 is that, in general, when the basic reproduction number, \mathcal{R}_0 is less than unity, a small influx of infectious vectors into the community would not generate large outbreaks, and the disease dies out in time (since the DFE is locally asymptotically stable) [2, 29, 21, 59, 17]. However, we will show in the subsection 2.2 that the disease may still persist even when $\mathcal{R}_0 < 1$.

The global stability of the trivial equilibrium is given by the following result:

Theorem 2. *If $\mathcal{N} \leq 1$, then \mathcal{E}_0 is globally asymptotically stable on \mathcal{D} .*

Proof. See appendix B. □

We now show the existence of endemic equilibria, that is, steady states of model (6) where all state variables are positive. First we introduce:

$$\psi = k_{10}a\mu_h\beta_{vh} - \delta\gamma_hk_8, \tag{11}$$

$$\mathcal{R}_c = \sqrt{\frac{2k_8k_2 + k_{10}a\mu_h\beta_{vh}}{k_3k_4k_8}}, \tag{12}$$

$$\mathcal{R}_{1b} = \frac{1}{k_3k_4} \left(\sqrt{\frac{1}{k_8k_9}} \left| \sqrt{\delta\gamma_h(a\mu_h\beta_{vh}k_{10} + k_2k_8)} - \sqrt{(-k_2\psi)} \right| \right), \tag{13}$$

$$\mathcal{R}_{2b} = \frac{1}{k_3k_4} \left(\sqrt{\frac{1}{k_8k_9}} \left(\sqrt{\delta\gamma_h(a\mu_h\beta_{vh}k_{10} + k_2k_8)} + \sqrt{(-k_2\psi)} \right) \right). \tag{14}$$

Note that (as shown in the Appendix C), when $\mathcal{R}_c < \mathcal{R}_0 < 1$, $\psi \leq 0$ and correspondingly, \mathcal{R}_{1b} and \mathcal{R}_{2b} are real.

With the inequalities,

$$\mathcal{R}_c < \mathcal{R}_0 < \min(1, \mathcal{R}_{1b}), \quad (15a)$$

$$\max(\mathcal{R}_c, \mathcal{R}_{2b}) < \mathcal{R}_0 < 1, \quad (15b)$$

we claim the following result:

Theorem 3. *The number of endemic equilibrium points of the basic arboviral disease model (6) depends on \mathcal{R}_0 as follows:*

(i) For $\mathcal{R}_0 > 1$, the system has a unique endemic equilibrium point.

(ii) For $\mathcal{R}_0 = 1$, the system has

(a) A unique endemic equilibrium point if $\mathcal{R}_c < 1$.

(b) No endemic equilibrium points otherwise.

(iii) For $\mathcal{R}_0 < 1$, the system has

(a) Two endemic equilibrium points if either inequality (15a) or (15b) is satisfied.

(b) A unique endemic equilibrium point if $\mathcal{R}_c < \mathcal{R}_0$ and either $\mathcal{R}_0 = \mathcal{R}_{1b}$ or $\mathcal{R}_0 = \mathcal{R}_{2b}$.

(c) No endemic equilibrium points otherwise.

Proof. See appendix C. □

It is clear that case (iii) (item (a)) of theorem 3 indicate the possibility of backward bifurcation (where the locally-asymptotically stable DFE co-exists with a locally asymptotically stable endemic equilibrium when $\mathcal{R}_0 < 1$) in the model (6). In a previous work (see model 18 in [2]), we just showed that the model exhibited the backward bifurcation phenomenon. In the following, we provide not only a sufficient condition, but also the thresholds which governing this phenomenon.

2.2 Bifurcation analysis

Here, we use the centre manifold theory [31] to explore the possibility of bifurcation in (3) at criticality (i.e. the existence and stability of the equilibrium points bifurcating from \mathcal{E}_1 at $\mathcal{R}_0 = 1$) by studying the centre manifold near the criticality through the approach developed in [59, 24, 14, 12], which is based on general centre manifold theory [31]. To do so, a bifurcation parameter β_{hv}^* is chosen, by solving for β_{hv} from $\mathcal{R}_0 = 1$, giving

$$\beta_{hv}^* = \frac{k_3 k_4 k_8 k_9 N_h^0}{a^2 \beta_{vh} k_{10} k_{11} N_v^0}. \quad (16)$$

Let $J_{\beta_{hv}^*}$ denotes the Jacobian of the system (3) evaluated at the DFE (\mathcal{E}_1) and with $\beta_{hv} = \beta_{hv}^*$.

$$\text{Thus, } J = \begin{pmatrix} -k_1 & 0 & 0 & 0 & 0 & -\beta_{hv}^* \eta_v & -\beta_{hv}^* & 0 & 0 & 0 \\ 0 & -k_3 & 0 & 0 & 0 & \beta_{hv}^* \eta_v & \beta_{hv}^* & 0 & 0 & 0 \\ 0 & \gamma_h & -k_4 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \sigma & -\mu_h & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -\frac{\beta_{vh} \eta_h S_v^0}{N_h^0} & -\frac{\beta_{vh} S_v^0}{N_h^0} & 0 & -k_8 & 0 & 0 & 0 & 0 & \theta \\ 0 & \frac{\beta_{vh} \eta_h S_v^0}{N_h^0} & \frac{\beta_{vh} S_v^0}{N_h^0} & 0 & 0 & -k_9 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \gamma_v & -k_8 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & K_1 & K_1 & K_1 & -K_2 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & K_3 & -K_4 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & l & -k_7 \end{pmatrix},$$

$$\text{with } K_1 = \mu_b \left(1 - \frac{E^*}{K_E}\right), K_2 = k_5 + \frac{\mu_b}{K_E} S_v^0, K_3 = s \left(1 - \frac{L^*}{K_L}\right), \text{ and } K_4 = \left(k_6 + \frac{sE^*}{K_L}\right).$$

Note that the system (6), with $\beta_{hv} = \beta_{hv}^*$, has a hyperbolic equilibrium point, i.e., the linearised system (6) has a simple eigenvalue with zero real part and all other eigenvalues have negative real part (this follows from the loss of stability of the disease-free equilibrium, \mathcal{E}_1 through the transcritical bifurcation). Hence, the centre manifold theory [59, 24, 14, 31, 12] can be used to analyse the dynamics of the model (3) near $\beta_{hv} = \beta_{hv}^*$. The technique in Castillo-Chavez and Song (2004) [14] entails finding the left and right eigenvectors of the linearised system above as follows.

The left eigenvector components of $J_{\beta_{hv}^*}$, which correspond to the uninfected states are zero (see Lemma 3 in [59]). Thus a non-zero components correspond to the infected states. It follows that the matrix $J_{\beta_{hv}^*}$ has a left eigenvector given by $\mathbf{v} = (v_1, v_2, \dots, v_{10})$, where

$$\begin{aligned} v_1 = v_4 = v_5 = v_8 = v_9 = v_{10} = 0; \quad v_2 &= \frac{k_8}{\beta_{hv}^*} v_7; \quad v_3 = \frac{\beta_{vh} S_v^0 (\eta_v k_8 + \gamma_v)}{k_4 k_9 N_h^0} v_7; \\ v_6 &= \frac{(\eta_v k_8 + \gamma_v)}{k_9} v_7, \quad v_7 > 0. \end{aligned} \quad (17)$$

Similarly, the component of the right eigenvector \mathbf{w} are given by

$$\begin{aligned} w_7 > 0, \quad w_{10} > 0, \\ w_1 &= -\frac{\beta_{hv}^* (\eta_v k_8 + \gamma_v)}{\beta_{hv}^*} w_7; \quad w_4 = \frac{\beta_{hv}^* \gamma_h \sigma (\eta_v k_8 + \gamma_v)}{\mu_h \gamma_v k_3 k_4} w_7; \quad w_2 = \frac{\mu_h k_4}{\gamma_h \sigma} w_4; \quad w_3 = \frac{\mu_h}{\sigma} w_4; \\ w_5 &= -\frac{k_8 + \gamma_v}{\gamma_v} w_7 + \frac{k_7 K_2 K_4}{l K_1 K_3} w_{10}; \quad w_6 = \frac{k_8}{\gamma_v} w_7; \quad w_8 = \frac{k_7 K_4}{l K_3} w_{10}; \quad w_9 = \frac{k_7}{l} w_{10}. \end{aligned} \quad (18)$$

Theorem 4.1 in Castillo-Chavez and Song [14] is then applied to establish the existence of backward bifurcation in (6). To apply such a theorem, it is convenient to let f_k represent the right-hand side of the k^{th} equation of the system (3) and let x_k be the state variables whose derivative is given by the k^{th} equation for $k = 1, \dots, 10$. The local bifurcation analysis near the bifurcation point ($\beta_{hv} = \beta_{hv}^*$) is then determined by the signs of two associated constants, denoted by \mathcal{A}_1 and \mathcal{A}_2 , defined by

$$\mathcal{A}_1 = \sum_{k,i,j=1}^{10} v_k w_i w_j \frac{\partial^2 f_k(0,0)}{\partial x_i \partial x_j} \quad \text{and} \quad \mathcal{A}_2 = \sum_{k,i=1}^{10} v_k w_i \frac{\partial^2 f_k(0,0)}{\partial x_i \partial \phi} \quad (19)$$

with $\phi = \beta_{hv} - \beta_{hv}^*$. It is important to note that in $f_k(0,0)$, the first zero corresponds to the disease-free equilibrium, \mathcal{E}_1 , for the system (6). Since $\beta_{hv} = \beta_{hv}^*$ is the bifurcation parameter, it follows from $\phi = \beta_{hv} - \beta_{hv}^*$ that $\phi = 0$ when $\beta_{hv} = \beta_{hv}^*$ which is the second component in $f_k(0,0)$.

Using Eqs. (17) and (18) in Eq. (19), we obtain

$$\mathcal{A}_1 = v_2 \sum_{i,j=1}^{10} w_i w_j \frac{\partial^2 f_2(0,0)}{\partial x_i \partial x_j} + v_6 \sum_{i,j=1}^{10} w_i w_j \frac{\partial^2 f_6(0,0)}{\partial x_i \partial x_j} \quad \text{and} \quad \mathcal{A}_2 = v_2 \sum_{i=1}^{10} w_i \frac{\partial^2 f_2(0,0)}{\partial x_i \partial \phi} \quad (20)$$

It follows then, after some algebraic computations (see the details in appendix D), that

$$\mathcal{A}_1 = \zeta_1 - \zeta_2, \quad (21)$$

where we have set (see the appendix D for details on derivation of this quantity)

$$\begin{aligned} \zeta_1 &= \left\{ 2 \frac{k_7 K_2 K_4}{l K_1 K_3} \frac{a \beta_{vh}}{N_h^0} (\eta_h w_2 + w_3) w_{10} - 2 \frac{a \beta_{vh} S_v^0}{(N_h^0)^2} (\eta_h w_2 + w_3) w_1 \right\} v_6 \\ \zeta_2 &= 2 \frac{a \beta_{hv}^*}{N_h^0} (\eta_v w_6 + w_7) (w_2 + w_3 + w_4) v_2 \\ &\quad + 2 \frac{a \beta_{vh}}{N_h^0} \left\{ \frac{S_v^0}{N_h^0} (\eta_h w_2^2 + (\eta_h + 1) w_2 w_3 + \eta_h w_2 w_4 + \eta_h w_3^2 + w_3 w_4) + \frac{(k_8 + \gamma_v)}{\gamma_v} (\eta_h w_2 + w_3) w_7 \right\} v_6 \end{aligned} \quad (22)$$

According to (17) and (18), we have $\zeta_1 > 0$ and $\zeta_2 > 0$.

We then have

$$\mathcal{A}_2 = \frac{a S_v^0}{N_h^0} (\eta_h w_6 + w_7) v_2.$$

Note that the coefficient \mathcal{A}_2 is always positive. Thus, using Theorem 4.1 in [14], the following result is established.

Theorem 4. *The basic model (6) exhibits a backward bifurcation at $\mathcal{R}_0 = 1$ whenever $\mathcal{A}_1 > 0$ (i.e., $\zeta_1 > \zeta_2$). If the reversed inequality holds, then the bifurcation at $\mathcal{R}_0 = 1$ is forward.*

The direct consequence of Theorem 4 is the following.

Corollary 1. *If $\mathcal{A}_1 < 0$ (i.e., $\zeta_1 < \zeta_2$), then the unique endemic equilibrium point of the basic model (6) is locally asymptotically stable whenever $\mathcal{R}_0 > 1$.*

The backward bifurcation phenomenon is illustrated by numerical simulation of the model with the following set of parameter values (it should be noted that these parameters are chosen for illustrative purpose only, and may not necessarily be realistic epidemiologically): $\Lambda_h = 30$, $\beta_{hv} = 0.008$, $\eta_h = 0.78$, $\eta_v = 0.99$, $\delta = 1$, $\sigma = 0.01428$, $\beta_{vh} = 0.5$, $\gamma_v = 1/14$, $\Gamma_E = 10^4$, $\Gamma_L = \Gamma_E/2$. All other parameters are as in Table 2. In this case the conditions required by Theorem 3, case (iii), are satisfied, as well as $\zeta_1 = 1.0772 \times 10^{-7} > \zeta_2 = 1.0250 \times 10^{-9}$ (so $\mathcal{A}_1 = 1.0669 \times 10^{-7} > 0$) in Theorem 4. Note, in particular, that with this set of parameters, $\mathcal{R}_c = 0.0367 < 1$, $\mathcal{R}_0 = 0.4359 < 1$ (so that $\mathcal{R}_c < \mathcal{R}_0 < 1$). It follows: $d_2 = -5.6537 \times 10^{-8} < 0$, $d_1 = 1.1504 \times 10^{-10} > 0$ and $d_0 = -2.4857 \times 10^{-14} < 0$, so that $d_1^2 - 4d_2d_0 = 7.6134 \times 10^{-21} > 0$. The resulting two endemic equilibria $\mathcal{E}_2 = (S_h^*, E_h^*, I_h^*, R_h^*, S_v^*, E_v^*, I_v^*, E, L, P)$, are:

$$\mathcal{E}_2^* = (16394, 16384, 29, 10092, 6558, 406, 869, 8393, 31334, 3264),$$

which is locally stable and

$$\mathcal{E}_2^{**} = (104660, 104660, 25, 8850, 7530, 97, 206, 8393, 31334, 3264),$$

which is unstable.

The associated bifurcation diagram is depicted in figure 2. This clearly shows the co-existence of two locally-asymptotically stable equilibria when $\mathcal{R}_0 < 1$, confirming that the model (6) undergoes the phenomenon of backward bifurcation.

The occurrence of the backward bifurcation can be also seen in Figure 3. Here, \mathcal{R}_0 is less than the transcritical bifurcation threshold $\mathcal{R}_0 = 1$ ($\mathcal{R}_0 = 0.4359 < 1$), but the solution of the

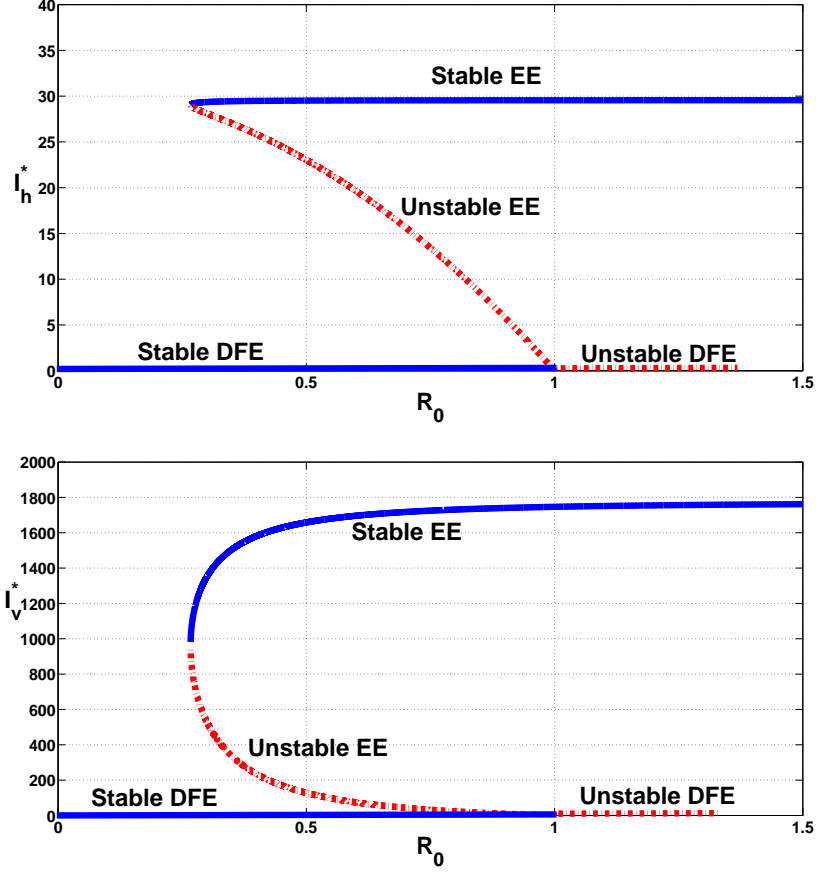


Figure 2: The backward bifurcation curves for model system (6) in the (\mathcal{R}_0, I_h^*) and (\mathcal{R}_0, I_v^*) planes. The parameter β_{hv} varied in the range $[0, 0.0877]$ to allow \mathcal{R}_0 to vary in the range $[0, 1.5]$. Two endemic equilibrium points coexist for values of \mathcal{R}_0 in the range $(0.2671, 1)$ (corresponding to the range $(0.0028, 0.0390)$ of β_{hv}). The notation EE and DFE stand for endemic equilibrium and disease-free equilibrium, respectively. Solid lines represent stable equilibria and dash lines stand for unstable equilibria.

model (6) can approach either the endemic equilibrium point or the disease-free equilibrium point, depending on the initial condition.

We know from Theorem 4 that a backward bifurcation scenario is possible for model (6). Here, we characterize the critical value in terms of a single parameter, the transmission rate β_{hv} , at which the saddle-node bifurcation occurs, i.e. the threshold for the appearance of two endemic equilibria (see Figure 2).

We follow the approach given in [52]. Introducing the quantities,

$$\bar{\beta} = \frac{[a\mu_h\beta_{vh}k_{10} + 2k_2k_8] N_h^0}{a^2\beta_{vh}k_{10}k_{11}N_v^0}, \quad (23)$$

and,

$$\beta_{\pm} = \frac{N_h^0}{k_3k_4k_{10}k_{11}a^2N_v^0\beta_{vh}} \left\{ \sqrt{\delta\gamma_h(a\mu_h\beta_{vh}k_{10} + k_2k_8)} \pm \sqrt{(-k_2\psi)} \right\}^2, \quad (24)$$

we have the following result (see the Appendix E for the proof).

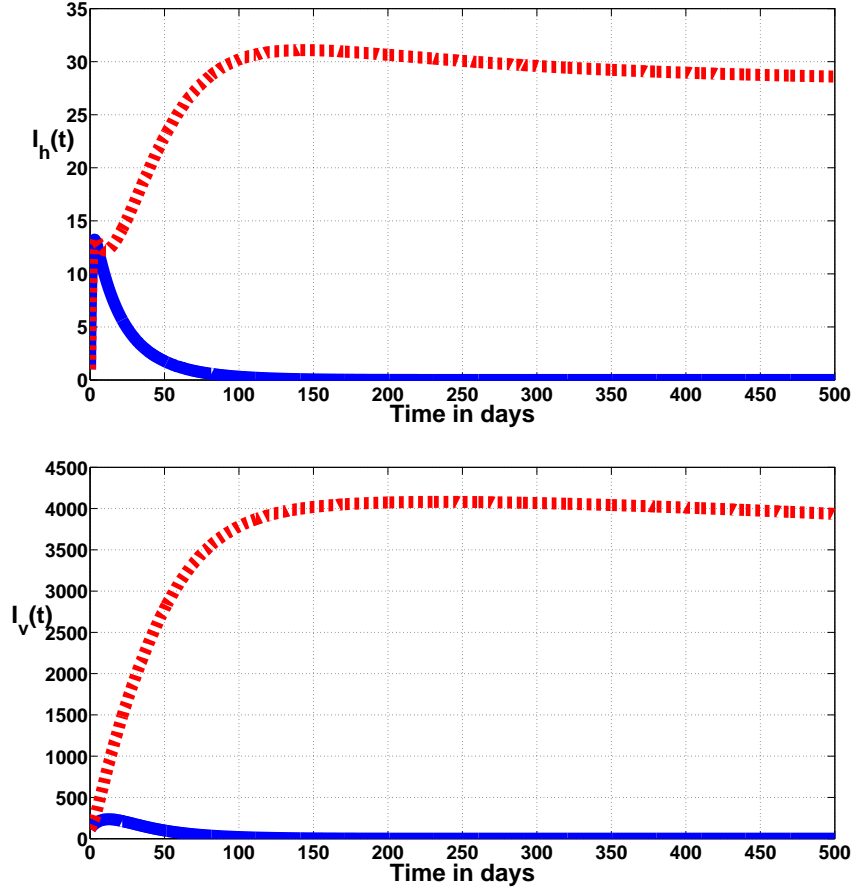


Figure 3: Solutions of model (6) of the number of infectious humans, I_h , and the number of infectious vectors, I_v , for parameter values given in the bifurcation diagram in Figure 2 with $\beta_{hv} = 0.008$, so $\mathcal{R}_0 = 0.4359 < 1$, for two different set of initial conditions. The first set of initial conditions (corresponding to the dotted trajectory) is $S_h = 700$, $E_h = 220$, $I_h = 15$, $R_h = 60$, $S_v = 3000$, $E_v = 400$, $I_v = 120$, $E = 10000$, $L = 5000$ and $P = 3000$. The second set of initial conditions (corresponding to the solid trajectory) is $S_h = 733650$, $E_h = 220$, $I_h = 15$, $R_h = 60$, $S_v = 3000$, $E_v = 400$, $I_v = 120$, $E = 10000$, $L = 5000$ and $P = 3000$. The solution for initial condition 1 approaches the locally asymptotically stable DFE point, while the solution for initial condition 2 approaches the locally asymptotically stable endemic equilibrium .

Theorem 5. *Assume that $\psi < 0$, where ψ is given by (11). Then the backward bifurcation phenomenon takes place in the basic model (6) if and only if*

$$\bar{\beta}_{hv} < \beta_{hv} < \min(\beta_-, \beta_{hv}^*) \quad \text{or} \quad \max(\bar{\beta}_{hv}, \beta_+) < \beta_{hv} < \beta_{hv}^*. \quad (25)$$

The previous analysis is in line with the observation made by Wangari et al. in [61] concerning the bifurcation thresholds of epidemiological models.

2.3 Non-existence of endemic equilibria for $\mathcal{R}_0 < 1$ and $\delta = 0$

In this case, we have the following result.

Theorem 6. *(i) The model (6) without disease-induced death ($\delta = 0$) has no endemic equilibrium when $\mathcal{R}_{0,\delta=0} \leq 1$, and has a unique endemic equilibrium otherwise.*

(ii) The DFE, \mathcal{E}_1 , of model (6) without disease-induced death ($\delta = 0$), is globally asymptotically stable (GAS) in \mathcal{D} if $\mathcal{R}_{0,\delta=0} < 1$.

Proof. See appendix F. □

2.4 Sensitivity analysis

We carried out the sensitivity analysis to determine the model robustness to parameter values. That is to help us to know the parameters that are most influential in determining disease dynamics. Following the approach by Marino *et al.* [42] and Wu *et al.* [66], partial rank correlation coefficients (PRCC) between the basic reproduction number \mathcal{R}_0 and each parameter are derived from 5,000 runs of the Latin hypercube sampling (LHS) method, which is a stratified Monte Carlo sampling method that divides each parameter's range into N equal intervals and randomly draws one sample from each interval [66, 58]. The parameters are assumed to be random variables with uniform distributions with their mean value listed in Table 2.

With these 5,000 runs of LHS, the derived distribution of \mathcal{R}_0 is given in Figure 4. This sampling shows that the mean of \mathcal{R}_0 is 1.9583 and the standard deviation is 1.8439. This implies that for the mean of parameter values given in Table 2, we may be confident that the model predicts an endemic state, since the basic reproduction number is greater than unity. The probability that $\mathcal{R}_0 > 1$ (the disease-free equilibrium is unstable and there is exactly one endemic equilibrium point) is 64.48%.

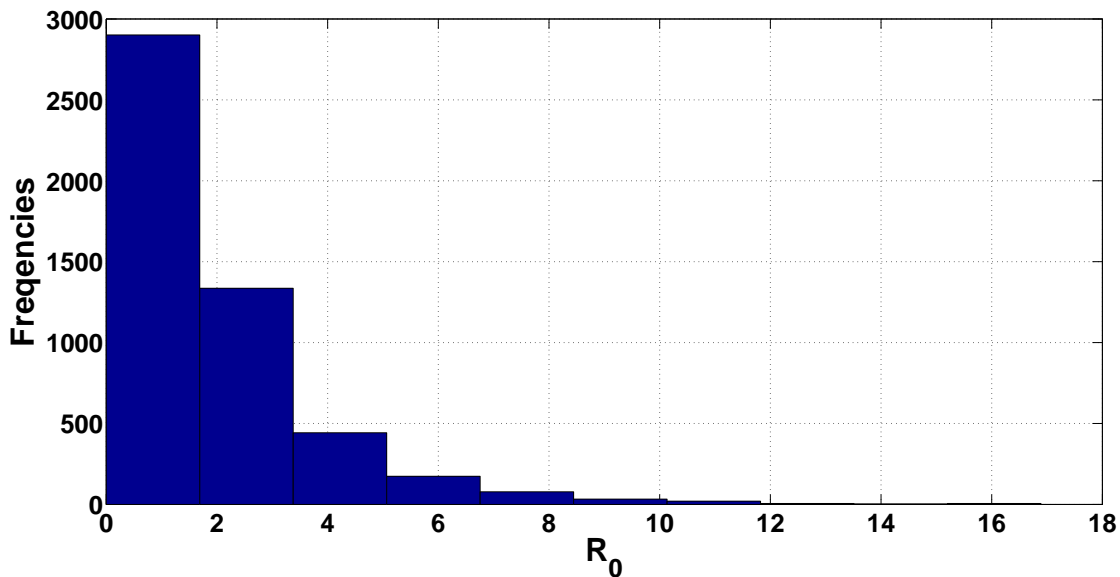


Figure 4: Sampling distribution of \mathcal{R}_0 from 5,000 runs of Latin hypercube sampling. The mean of \mathcal{R}_0 is 1.9583 and the standard deviation is 1.8439. Furthermore, $\mathbb{P}(\mathcal{R}_0 \geq 1) = 64.48\%$.

We also evaluate the probabilities that conditions (i), (ii) and (iii) in Theorem 3 are satisfied. Let us set $\mathbb{P}[X]$ the probability of X , and the sets of parameter values for which ($\mathcal{N} > 1$) is true by Φ_1 , the sets of parameter values for which ($\mathcal{R}_c < \mathcal{R}_0 < \min(1, \mathcal{R}_{1b})$) or ($\max(\mathcal{R}_c, \mathcal{R}_{2b}) <$

$\mathcal{R}_0 < 1$) by Φ_2 , and the sets of parameter values for which $\{(\mathcal{R}_0 = R_{1b}) \text{ or } (\mathcal{R}_0 = R_{2b})\}$ by Φ_3 ,

$$\mathbb{P}[\neg\Phi_1] = \mathbb{P}[\mathcal{N} \leq 1] = 0.0020, \quad (26a)$$

$$\mathbb{P}[\Phi_1] = \mathbb{P}[\mathcal{N} > 1] = 0.9980, \quad (26b)$$

$$\mathbb{P}[\Phi_1 \text{ and } (\mathcal{R}_0 < 1) \text{ and } \Phi_2] = 0.0026, \quad (26c)$$

$$\mathbb{P}[\Phi_1 \text{ and } (\mathcal{R}_0 < 1) \text{ and } \Phi_3] = 0, \quad (26d)$$

$$\mathbb{P}[\Phi_1 \text{ and } (\mathcal{R}_0 < 1) \text{ and } \neg\Phi_2 \text{ and } \neg\Phi_3] = 0.3526, \quad (26e)$$

$$\mathbb{P}[\Phi_1 \text{ and } (\mathcal{R}_0 < 1)] = 0.3552, \quad (26f)$$

$$\mathbb{P}[\Phi_1 \text{ and } (\mathcal{R}_0 \geq 1)] = 0.6448. \quad (26g)$$

Therefore, the probability that the trivial disease-free equilibrium is locally asymptotically stable is 0.0020 (from (26a)), the probability that the disease free equilibrium point is locally asymptotically stable is 0.3552 (from (26f)), the probability that the disease free equilibrium point is locally asymptotically stable and (i) there are no endemic equilibrium points is 35.26% (ii) there are exactly one endemic equilibrium point is 0 (from (26d)), (iii) there are exactly two endemic equilibrium points is 0.0026 (from (26c)). This implies that for the ranges of parameter values given in Table 4, the disease-free equilibrium point is likely to be locally asymptotically stable and the probability of co-existence of a locally asymptotically stable endemic equilibrium point (occurrence of backward bifurcation phenomenon) is very small and insignificant.

We now use sensitivity analysis to analyse the influence of each parameter on the basic reproductive number. From the previously sampled parameter values, we compute the PRCC between \mathcal{R}_0 and each parameter of model (3). The parameters with large PRCC values (> 0.5 or < -0.5) statistically have the most influence [66].

Table 3: Partial Rank Correlation Coefficients between \mathcal{R}_0 and each parameters of model (6).

Parameter	Correlation Coefficients	Parameter	Correlation Coefficients	Parameter	Correlation Coefficients
β_{vh}	0.7345	Γ_L	0.3813	μ_h	0.1717
β_{hv}	0.7285	Γ_E	0.3698	γ_v	0.0872
a	0.6454	s	0.3733	η_v	0.06891
θ	0.6187	μ_P	-0.2565	μ_L	-0.0556
μ_v	-0.5521	η_h	0.2331	μ_b	0.0531
Λ_h	-0.5435	γ_h	-0.2204	μ_E	-0.0022
l	0.5144	σ	-0.1867	δ	0.0003

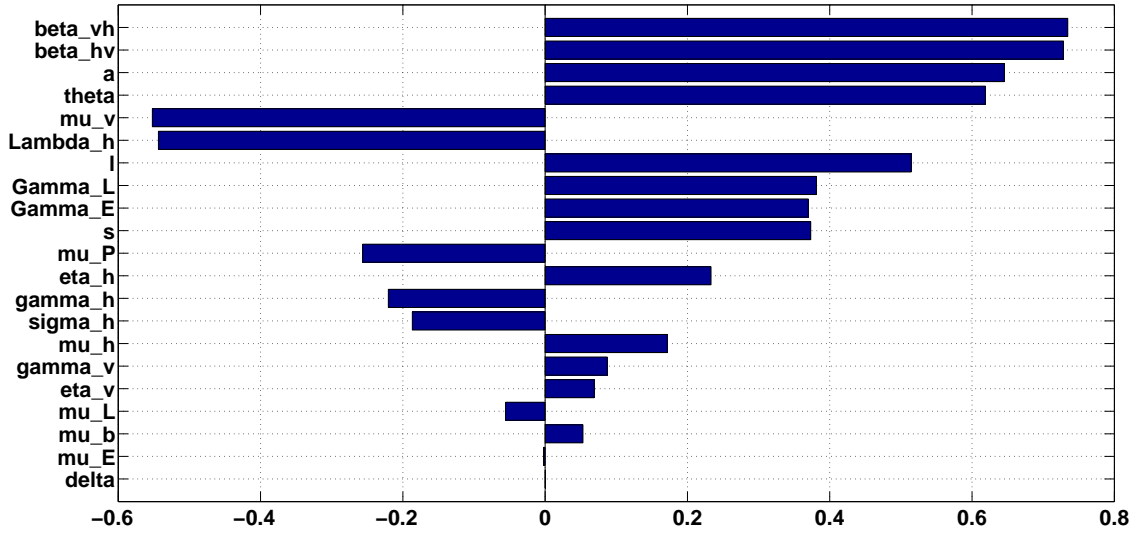


Figure 5: Partial rank correlation coefficients for \mathcal{R}_0

The results, displayed in Table 3 and Figure 5, show that the basic reproduction number \mathcal{R}_0 outcome measures are sensitive to changes in the parameters β_{vh} , β_{hv} , a , θ , μ_v , Λ_h and l .

The sensitivity results suggest that the control of the epidemic of arboviral diseases pass through a combination of immunization against arbovirus, individual protection against vector bites, treatment of infected human, and vector control mechanisms.

3 A Model for Optimal Control

There are several possible interventions in order to reduce or limit the proliferation of mosquitoes and the explosion of the number of infected humans and mosquitoes. In addition of controls used in [44], we add vaccination and the control of adult vectors as control variables to reduce or even eradicate the disease. So we introduce five time dependent controls:

1. The first control $0 \leq u_1(t) \leq 1$ denotes the percentage of susceptible individuals that one decides to vaccinate at time t . A parameter ω associated to the control $u_1(t)$ represents the waning immunity process [50].
2. The second control $0 \leq u_2(t) \leq 1$ represents efforts made to protect human from mosquito bites. It mainly consists to the use of mosquito nets or wearing appropriate clothes [44]. Thus we modify the infection term as follows:

$$\lambda_h^e = (1 - \alpha_1 u_2(t)) \lambda_h, \quad \lambda_v^c = (1 - \alpha_1 u_2(t)) \lambda_v \quad (27)$$

where α_1 measures the effectiveness of the prevention measurements against mosquito bites.

3. The third control $0 \leq u_3(t) \leq 1$ represents efforts made for treatment. It mainly consists in isolating infected patients in hospitals, installing an anti-mosquito electric diffuser in the hospital room, or symptomatic treatments [44]. Thus we modify the recovery rate

such that $\sigma_h^c := \sigma_h + \alpha_2 u_3$. α_2 is the effectiveness of the anti-arboviral diseases drugs with $\alpha_2 = 0.3$ [44]. Note that this control also permit to reduce the disease-induced death.

4. The fourth control $0 \leq u_4(t) \leq 1$ represents mosquitoes adulticiding effort with killing efficacy c_m . Thus the mosquito natural mortality rate becomes $\mu_v^c = \mu_v + c_m u_4(t)$.
5. The fifth control $0 \leq u_5(t) \leq 1$ represents the effect of interventions used for the vector control. It mainly consists in the reduction of breeding sites with chemical application methods, for instance using larvicides like BTI (*Bacillus Thuringensis Israelensis*) which is a biological larvicide, or by introducing larvivore fish. This control focuses on the reduction of the number of larvae, and thus eggs, of any natural or artificial water-filled container [44]. Thus the eggs and Larvae natural mortality rate become $\mu_E^c = \mu_E + \eta_1 u_5(t)$ and $\mu_L^c = \mu_L + \eta_2 u_5(t)$ where η_1, η_2 , represent the chemical eggs and larvae mortality rate, respectively [44].

Note that $0 \leq u_i \leq 1$, for $i = 1, \dots, 5$, means that when the control is zero there is no any effort invested (i.e. no control) and when it is one, the maximum control effort is invested.

Therefore, our optimal control model of arboviral diseases reads as

$$\left\{ \begin{array}{l} \dot{S}_h = \Lambda_h - [(1 - \alpha_1 u_2(t))\lambda_h + \mu_h + u_1(t)] S_h + \omega u_1(t) R_h \\ \dot{E}_h = (1 - \alpha_1 u_2(t))\lambda_h S_h - (\mu_h + \gamma_h) E_h \\ \dot{I}_h = \gamma_h E_h - [\mu_h + (1 - \alpha_2 u_3(t))\delta + \sigma + \alpha_2 u_3(t)] I_h \\ \dot{R}_h = (\sigma + \alpha_2 u_3(t)) I_h + u_1 S_h - (\mu_h + \omega u_1) R_h \\ \dot{S}_v = \theta P - (1 - \alpha_1 u_2(t))\lambda_v S_v - (\mu_v + c_m u_4(t)) S_v \\ \dot{E}_v = (1 - \alpha_1 u_2(t))\lambda_v S_v - (\mu_v + \gamma_v + c_m u_4(t)) E_v \\ \dot{I}_v = \gamma_v E_v - (\mu_v + c_m u_4(t)) I_v \\ \dot{E} = \mu_b \left(1 - \frac{E}{\Gamma_E}\right) (S_v + E_v + I_v) - (s + \mu_E + \eta_1 u_5(t)) E \\ \dot{L} = s E \left(1 - \frac{L}{\Gamma_L}\right) - (l + \mu_L + \eta_2 u_5(t)) L \\ \dot{P} = l L - (\theta + \mu_P) P \end{array} \right. \quad (28)$$

with initial conditions given at $t = 0$.

For the non-autonomous system (28), the rate of change of the total populations of humans and adults vectors is given, respectively, by

$$\left\{ \begin{array}{l} \dot{N}_h = \Lambda_h - \mu_h N_h - (1 - \alpha_2 u_3(t))\delta I_h \\ \dot{N}_v = \theta P - (\mu_v + c_m u_4(t)) N_v \end{array} \right. \quad (29)$$

For bounded Lebesgue measurable controls and non-negative initial conditions, non-negative bounded solutions to the state system exist [40].

The objective of control is to minimize: the number of symptomatic humans infected with arboviruses (that is, to reduce sub-population I_h), the number of vector (N_v) and the number of eggs and larvae (that is, to reduce sub-population E and L , respectively), while keeping the costs of the control as low as possible.

To achieve this objective we must incorporate the relative costs associated with each policy (control) or combination of policies directed towards controlling the spread of arboviral diseases. We define the objective function as

$$J(u_1, u_2, u_3, u_4, u_5) = \int_0^{t_f} \left[D_1 I_h(t) + D_2 N_v(t) + D_3 E(t) + D_4 L(t) + \sum_{i=1}^5 B_i u_i^2(t) \right] dt \quad (30)$$

and the control set

$$\Delta = \{(u_1, u_2, u_3, u_4, u_5) | u_i(t) \text{ is Lebesgue measurable on } [0, t_f], 0 \leq u_i(t) \leq 1, i = 1, \dots, 5\}.$$

The first fourth terms in the integrand J represent benefit of I_h , N_v , E and L populations, describing the comparative importance of the terms in the functional. A high value of D_1 for example, means that it is more important to reduce the burden of disease as reduce the costs related to all control strategies [9]. Positive constants B_i , $i = 1, \dots, 5$ are weight for vaccination, individual protection (human), treatment and vector control effort respectively, which regularize the optimal control. In line with the authors of some studies on the optimal control (see [44, 50, 62, 3, 9, 69, 34, 68]), we choose a linear function for the cost on infection, $D_1 I_h$, $D_2 N_v$, $D_3 E$, $D_4 L$, and quadratic forms for the cost on the controls $B_1 u_1^2$, $B_2 u_2^2$, $B_3 u_3^2$, $B_4 u_4^2$, and $B_5 u_5^2$. This choice can be justified by the following arguments:

- (i) An epidemiological control can be likened to an expenditure of energy, by bringing to the applications of physics in control theory;
- (ii) In a certain sense, minimize u_i is like minimize u_i^2 , because $u_i > 0$, $i = 1, \dots, 5$.
- (iii) The quadratic controls give rise to controls as feedback law, which is convenient for calculations.

We solve the problem using optimal control theory.

Theorem 7. *Let $X = (S_h, E_h, I_h, R_h, S_v, E_v, I_v, E, L, P)$. The following set*

$$\Omega = \left\{ X \in \mathbf{R}^{10} : N_h \leq \frac{\Lambda_h}{\mu_h}; E \leq \Gamma_E; L \leq \Gamma_L; P \leq \frac{l\Gamma_L}{k_7}; N_v \leq \frac{\theta l\Gamma_L}{k_7 k_8} \right\}$$

is positively invariant under system (28).

Proof. On the one hand, one can easily see that it is possible to get,

$$\left\{ \begin{array}{l} \dot{S}_h \geq -(\lambda_h + \mu_h) S_h \\ \dot{E}_h \geq -(\mu_h + \gamma_h) E_h \\ \dot{I}_h \geq -(\mu_h + \delta + \sigma) I_h \\ \dot{R}_h \geq -\mu_h R_h \\ \dot{E} \geq -\left(\frac{\mu_b}{K_E} + s + \mu_E + \eta_1\right) E \\ \dot{L} \geq -\left(\frac{l}{K_L} + l + \mu_L + \eta_2\right) L \\ \dot{P} \geq -(\theta + \mu_P + \eta_3) P \\ \dot{S}_v \geq -(\lambda_v + \mu_v) S_v \\ \dot{E}_v \geq -(\mu_v + \gamma_v) E_v \\ \dot{I}_v \geq -\mu_v I_v \end{array} \right. \quad (31)$$

for $(S_h(0), E_h(0), I_h(0), R_h(0), E(0), A(0), P(0), S_v(0), E_v(0), I_v(0)) \geq 0$. Thus, solutions with initial value in Ω remain nonnegative for all $t \geq 0$. On the other hand, we have

$$\left\{ \begin{array}{l} \dot{N}_h \leq \Lambda_h - \mu_h N_h \\ \dot{N}_v \leq \theta P - \mu_v N_v \\ \dot{E} \leq \mu_b \left(1 - \frac{E}{K_E}\right) (S_v + E_v + I_v) - (s + \mu_E) E \\ \dot{L} \leq s E \left(1 - \frac{L}{K_L}\right) - (l + \mu_L) L \\ \dot{P} \leq l L - (\theta + \mu_P) P \end{array} \right. \quad (32)$$

The right hand side of the inequalities correspond to the transmission model without control, and it is easy to show that solutions remain in Ω . Then using Gronwall's inequality, we deduce that solutions of (28) are bounded. \square

3.1 Existence of an optimal control

The existence of an optimal control can be obtained by using a result of Fleming and Rishel [28].

Theorem 8. *Consider the control problem with system (28).*

There exists $u^ = (u_1^*, u_2^*, u_3^*, u_4^*, u_5^*)$ such that*

$$\min_{(u_1, u_2, u_3, u_4, u_5) \in \Delta} J(u_1, u_2, u_3, u_4, u_5) = J(u_1^*, u_2^*, u_3^*, u_4^*, u_5^*)$$

Proof. To use an existence result, Theorem III.4.1 from [28], we must check if the following properties are satisfied:

- 1- the set of controls and corresponding state variables is non empty;
- 2- the control set Δ is convex and closed;
- 3- the right hand side of the state system is bounded by a linear function in the state and control;
- 4- the integrand of the objective functional is convex;
- 5- there exist constants $c_1 > 0$, $c_2 > 0$, and $\beta > 1$ such that the integrand of the objective functional is bounded below by $c_1 \left(\sum_{i=1}^5 |u_i|^2 \right)^{\frac{\beta}{2}} - c_2$.

In order to verify these properties, we use a result from Lukes [40] to give the existence of solutions for the state system (28) with bounded coefficients, which gives condition 1. Since by definition, the control set Δ is bounded, then condition 2 is satisfied. The right hand side of the state system (28) satisfies condition 3 since the state solutions are bounded. The integrand of our objective functional is clearly convex on Δ , which gives condition 4. There are $c_1 > 0$, $c_2 > 0$ and $\beta > 1$ satisfying $D_1 I_h + D_2 N_v + D_3 E + D_4 L + \sum_{i=1}^5 B_i u_i^2 \geq c_1 \left(\sum_{i=1}^5 |u_i|^2 \right)^{\frac{\beta}{2}} - c_2$, because the states variables are bounded. Thus condition 5 is satisfied. We conclude that there exists an optimal control $u^* = (u_1^*, u_2^*, u_3^*, u_4^*, u_5^*)$ that minimizes the objective functional $J(u_1, u_2, u_3, u_4, u_5)$. \square

3.2 Characterization of an optimal control

The necessary conditions that an optimal control must satisfy come from the Pontryagin's Maximum Principle (PMP) [49]. This principle converts (28)-(30) into a problem of minimizing

point wise a Hamiltonian \mathbb{H} , with respect to $(u_1, u_2, u_3, u_4, u_5)$:

$$\begin{aligned}
\mathbb{H} = & D_1 I_h + D_2 N_v + D_3 E + D_4 L + \sum_{i=1}^5 B_i u_i^2 \\
& + \lambda_{S_h} \{ \Lambda_h - [(1 - \alpha_1 u_2) \lambda_h + \mu_h + u_1] S_h + \omega u_1 R_h \} \\
& + \lambda_{E_h} \{ [1 - \alpha_1 u_2] \lambda_h S_h - (\mu_h + \gamma_h) E_h \} \\
& + \lambda_{I_h} \{ \gamma_h E_h - (\mu_h + (1 - \alpha_2 u_3) \delta + \sigma + \alpha_2 u_3) I_h \} \\
& + \lambda_{R_h} \{ (\sigma + \alpha_2 u_3) I_h + u_1 S_h - (\mu_h + \omega u_1) R_h \} \\
& + \lambda_{S_v} \{ \theta P - [1 - \alpha_1 u_2] \lambda_v S_v - (\mu_v + c_m u_4) S_v \} \\
& + \lambda_{E_v} \{ (1 - \alpha_1 u_2) \lambda_v S_v - (\mu_v + \gamma_v + c_m u_4) E_v \} + \lambda_{I_v} \{ \gamma_v E_v - (\mu_v + c_m u_4) I_v \} \\
& + \lambda_E \left\{ \mu_b \left(1 - \frac{E}{\Gamma_E} \right) (S_v + E_v + I_v) - (s + \mu_E + \eta_1 u_5) E \right\} \\
& + \lambda_L \left\{ s E \left(1 - \frac{L}{\Gamma_L} \right) - (l + \mu_L + \eta_2 u_5) L \right\} \\
& + \lambda_P \{ l L - (\theta + \mu_P) P \}
\end{aligned} \tag{33}$$

where the λ_i , $i = S_h, E_h, I_h, R_h, S_v, E_v, I_v, E, L, P$ are the adjoint variables or co-state variables. Applying Pontryagin's Maximum Principle [49], we obtain the following result.

Theorem 9. *Given an optimal control $u^* = (u_1^*, u_2^*, u_3^*, u_4^*, u_5^*)$ and solutions $(S_h^*, E_h^*, I_h^*, R_h^*, S_v^*, E_v^*, I_v^*, E^*, A^*, P^*)$ of the corresponding state system (28), there exist adjoint variables $\Pi = (\lambda_{S_h}, \lambda_{E_h}, \lambda_{I_h}, \lambda_{R_h}, \lambda_{S_v}, \lambda_{E_v}, \lambda_{I_v}, \lambda_E, \lambda_L, \lambda_P)$ satisfying,*

$$\frac{d\lambda_{S_h}}{dt} = \mu_h \lambda_{S_h} + u_1 (\lambda_{S_h} - \lambda_{R_h}) + (1 - \alpha_1 u_2) \lambda_h \left(1 - \frac{S_h}{N_h} \right) (\lambda_{S_h} - \lambda_{E_h}) + (1 - \alpha_1 u_2) \frac{S_v \lambda_v}{N_h} (\lambda_{E_v} - \lambda_{S_v}) \tag{34}$$

$$\frac{d\lambda_{E_h}}{dt} = \mu_h \lambda_{E_h} + \gamma_h (\lambda_{E_h} - \lambda_{I_h}) + (1 - \alpha_1 u_2) \frac{S_h \lambda_h}{N_h} (\lambda_{E_h} - \lambda_{S_h}) + (1 - \alpha_1 u_2) \frac{S_v}{N_h} (a\beta_{vh} \eta_h - \lambda_v) (\lambda_{S_v} - \lambda_{E_v}) \tag{35}$$

$$\begin{aligned}
\frac{d\lambda_{I_h}}{dt} = & -D_1 + [\mu_h + (1 - \alpha_2 u_3) \delta] \lambda_{I_h} + (\sigma + \alpha_2 u_3) (\lambda_{I_h} - \lambda_{R_h}) + (1 - \alpha_1 u_2) \frac{S_h \lambda_h}{N_h} (\lambda_{E_h} - \lambda_{S_h}) \\
& + (1 - \alpha_1 u_2) \frac{S_v}{N_h} (a\beta_{vh} - \lambda_v) (\lambda_{S_v} - \lambda_{E_v})
\end{aligned} \tag{36}$$

$$\frac{d\lambda_{R_h}}{dt} = \mu_h \lambda_{R_h} + \omega u_1 (\lambda_{R_h} - \lambda_{S_h}) + (1 - \alpha_1 u_2) \frac{S_h \lambda_h}{N_h} (\lambda_{E_h} - \lambda_{S_h}) + (1 - \alpha_1 u_2) \frac{S_v \lambda_v}{N_h} (\lambda_{E_v} - \lambda_{S_v}) \tag{37}$$

$$\frac{d\lambda_{S_v}}{dt} = -D_2 + (\mu_v + c_m u_4) \lambda_{S_v} + (1 - \alpha_1 u_2) \lambda_v (\lambda_{S_v} - \lambda_{E_v}) - \mu_b \left(1 - \frac{E}{\Gamma_E} \right) \lambda_E \tag{38}$$

$$\frac{d\lambda_{E_v}}{dt} = -D_2 + (\mu_v + c_m u_4) \lambda_{E_v} + \gamma_v (\lambda_{E_v} - \lambda_{I_v}) + a\eta_v \beta_{hv} (1 - \alpha_1 u_2) (\lambda_{S_h} - \lambda_{E_h}) \frac{S_h}{N_h} - \mu_b \left(1 - \frac{E}{\Gamma_E} \right) \lambda_E \tag{39}$$

$$\frac{d\lambda_{I_v}}{dt} = -D_2 + (\mu_v + c_m u_4) \lambda_{I_v} + a\beta_{hv} (1 - \alpha_1 u_2) \frac{S_h}{N_h} (\lambda_{S_h} - \lambda_{E_h}) - \mu_b \left(1 - \frac{E}{\Gamma_E} \right) \lambda_E \tag{40}$$

$$\frac{d\lambda_E}{dt} = -D_3 + \left[\frac{\mu_b}{\Gamma_E} N_v + s + \mu_E + \eta_1 u_5 \right] \lambda_E - s \left(1 - \frac{L}{\Gamma_L} \right) \lambda_L \tag{41}$$

$$\frac{d\lambda_L}{dt} = -D_4 - l \lambda_P + \left[\frac{s}{\Gamma_L} E + \mu_L + l + \eta_2 u_5 \right] \lambda_L \tag{42}$$

$$\frac{d\lambda_P}{dt} = (\mu_P + \theta) \lambda_P - \theta \lambda_{S_v} \tag{43}$$

and the transversality conditions

$$\lambda_i^*(t_f) = 0, \quad i = 1, \dots, 10. \quad (44)$$

Furthermore,

$$\begin{aligned} u_1^* &= \min \left\{ 1, \max \left(0, \frac{(S_h - \omega R_h)(\lambda_{S_h} - \lambda_{R_h})}{2B_1} \right) \right\}, \\ u_2^* &= \min \left\{ 1, \max \left(0, \frac{\alpha_1 [\lambda_h S_h (\lambda_{E_h} - \lambda_{S_h}) + \lambda_v S_v (\lambda_{E_v} - \lambda_{S_v})]}{2B_2} \right) \right\}, \\ u_3^* &= \min \left\{ 1, \max \left(0, \frac{\alpha_2 [(1 - \delta)\lambda_{I_h} - \lambda_{R_h}] I_h}{2B_3} \right) \right\}, \\ u_4^* &= \min \left\{ 1, \max \left(0, \frac{c_m [S_v \lambda_{S_v} + E_v \lambda_{E_v} + I_v \lambda_{I_v}]}{2B_4} \right) \right\}, \\ u_5^* &= \min \left\{ 1, \max \left(0, \frac{\eta_1 E \lambda_E + \eta_2 L \lambda_L}{2B_5} \right) \right\}. \end{aligned} \quad (45)$$

Proof. The differential equations governing the adjoint variables are obtained by differentiation of the Hamiltonian function, evaluated at the optimal control. Then the adjoint system can be written as

$$\begin{aligned} \frac{d\lambda_{S_h}}{dt} &= -\frac{\partial \mathbb{H}}{\partial S_h}, & \frac{d\lambda_{E_h}}{dt} &= -\frac{\partial \mathbb{H}}{\partial E_h}, & \frac{d\lambda_{I_h}}{dt} &= -\frac{\partial \mathbb{H}}{\partial I_h}, & \frac{d\lambda_{R_h}}{dt} &= -\frac{\partial \mathbb{H}}{\partial R_h}, \\ \frac{d\lambda_{S_v}}{dt} &= -\frac{\partial \mathbb{H}}{\partial S_v}, & \frac{d\lambda_{E_v}}{dt} &= -\frac{\partial \mathbb{H}}{\partial E_v}, & \frac{d\lambda_{I_v}}{dt} &= -\frac{\partial \mathbb{H}}{\partial I_v}, \\ \frac{d\lambda_E}{dt} &= -\frac{\partial \mathbb{H}}{\partial E}, & \frac{d\lambda_L}{dt} &= -\frac{\partial \mathbb{H}}{\partial L}, & \frac{d\lambda_P}{dt} &= -\frac{\partial \mathbb{H}}{\partial P}, \end{aligned}$$

with zero final time conditions (transversality).

To get the characterization of the optimal control given by (45), we follow [50, 39] and solve the equations on the interior of the control set,

$$\frac{\partial \mathbb{H}}{\partial u_i} = 0, \quad i = 1, \dots, 5.$$

Using the bounds on the controls, we obtain the desired characterization. This ends the proof. \square

4 Numerical simulations and discussion

The simulations were carried out using the values of Table 4. We use an iterative scheme to solve the optimality system. We first solve the state equations (28) with a guess for the controls over the simulated time using fourth order Runge–Kutta scheme. Then, we use the current iterations solutions of the state equation to solve the adjoint equations (34)– (43) by a backward fourth order Runge–Kutta scheme. Finally, we update the controls by using a convex combination of the previous controls and the value from the characterizations (45) (see e.g. [44, 9, 69, 39, 45]). The values chosen for the weights in the objective functional J (see Eq. (30)) are given in Table 5. Table 6 gives the initials conditions of state variables. We simulated the system (28) in a period of twenty days ($t_f = 20$).

As the purpose of our study is to seek the best combination linking vaccination to other control mechanism, we will just determine the best strategy among the strategies listed in Table 7. Therefore, we will distinguished five control strategies at follows:

Table 4: Value of parameters using in numerical simulations.

Parameter	value	Parameter	value	Parameter	value	Parameter	value
μ_v	$\frac{1}{30}$	l	0.5	α_2	0.5	γ_h	$\frac{1}{14}$
a	1	μ_E	0.2	μ_h	$\frac{1}{67*365}$	γ_v	$\frac{1}{21}$
Λ_h	2.5	μ_b	6	θ	0.08	μ_P	0.4
β_{hv}	0.75			σ	0.1428	η_v	0.35
β_{vh}	0.75	ω	0.05	μ_L	0.4	δ	10^{-3}
Γ_E	10000	s	0.7	η_1	0.001	η_2	0.3
Γ_L	5000	η_h	0.35	c_m	0.2	α_1	0.5

Table 5: Numerical values for the cost functional parameters.

Parameters	Value	Source	Parameters	Value	Source
D_1 :	10,000	[44]	B_1	10	Assumed
D_2 :	10,000	[44]	B_2 :	10	[44]
D_3 :	5000	Assumed	B_3 :	10	[44]
D_4 :	1	[44]	B_4 :	10	Assumed
			B_5	10	[44]

Table 6: Initial conditions.

Human states	Initial value	Adult Vector states	Initial value	Aquatic states	Initial value
S_{h_0} :	700	S_{v_0}	3000	E_0	10000
E_{h_0} :	220	E_{v_0}	400	L_0	5000
I_{h_0} :	100	I_{v_0}	120	P_0	3000
R_{h_0} :	60				

Table 7: Description of the different Control strategies.

Strategy	Description
Z_1	Vaccine combined with individual protection, treatment and adulticide
Z_2	Vaccine combined with individual protection, treatment and larvicide
Z_3	Vaccine combined with treatment, adulticide and larvicide
Z_4	Vaccine combined with individual protection, adulticide and larvicide
Z	Combination of the five controls

(i) Vaccination combined with individual protection, treatment and adulticide

With this strategy, only the combination of the control u_1 on vaccination, the control u_2 on individual protection, the control u_3 on treatment and the control u_4 on adulticide, is used to minimise the objective function J (30), while the other control u_5 is set to zero. On figure 7, we observed that the control strategy resulted in a decrease in the number of infected humans (I_h) while an increase is observed in the number of infected humans (I_h) in strategy without control. The use of this combination have also a great impact on the decreasing total vector population (N_v), as well as aquatic vector populations (E and L).

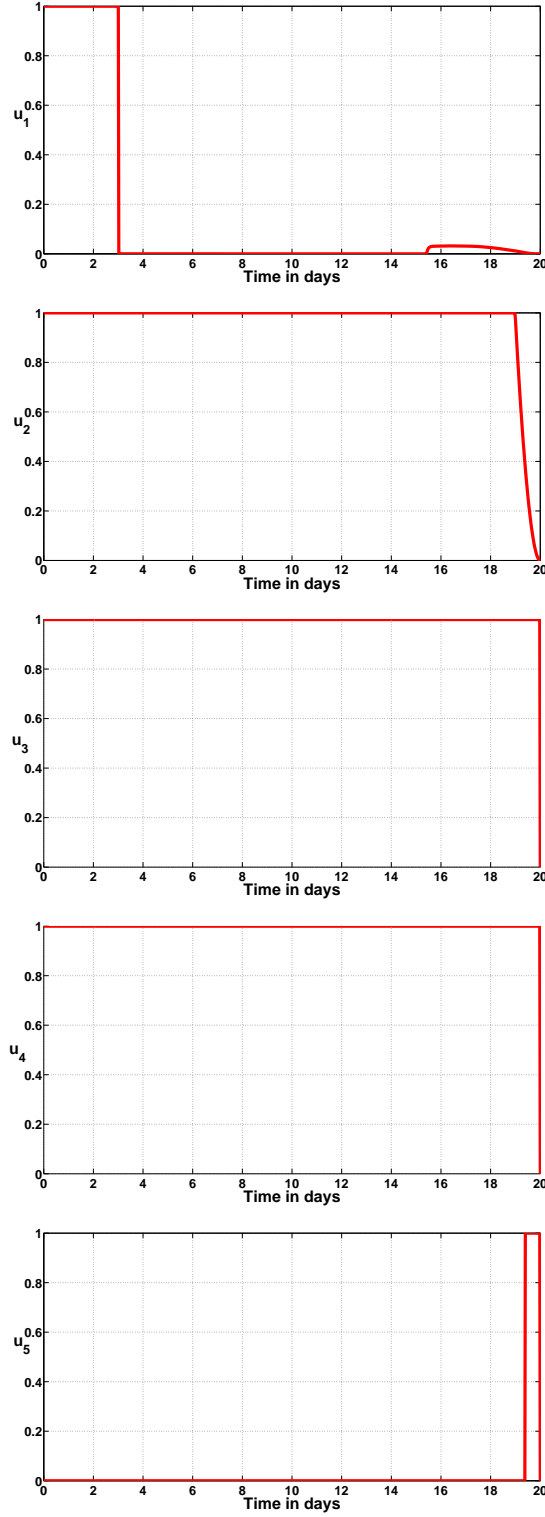


Figure 6: Control functions.

(ii) Vaccination combined with individual protection, treatment and larvicide

With this strategy, only the combination of the control u_1 on vaccination, the control u_2 on individual protection, the control u_3 on treatment and the control u_5 on larvicide, is used to minimise the objective function J (30), while the other control u_4 is set to zero. On figure 8, we observed that the control strategy resulted in a decrease in the number of infected humans

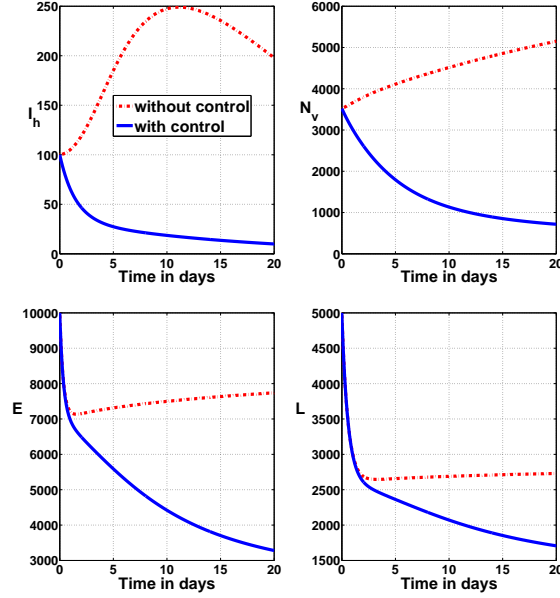


Figure 7: Simulation results of optimal control model (28) showing the effect of using optimal vaccination combined with individual protection, treatment and adulticide ($u_1 \neq 0$, $u_2 \neq 0$, $u_3 \neq 0$, $u_4 \neq 0$).

(I_h) while an increase is observed in the number of infected humans (I_h) in strategy without control. The use of this combination have no impact on the decreasing total vector population (N_v), as well as aquatic vector populations (E and L).

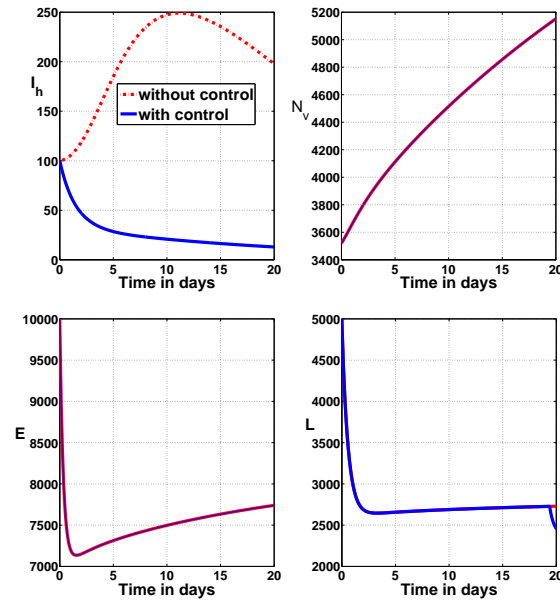


Figure 8: Simulation results of optimal control model (28) showing the effect of using optimal vaccination combined with individual protection, treatment and larvicide ($u_1 \neq 0$, $u_2 \neq 0$, $u_3 \neq 0$, $u_5 \neq 0$).

(iii) Vaccination combined with treatment, adulticide and larvicide

With this strategy, only the combination of the control u_1 on vaccination, the control u_3 on treatment, the control u_4 on adulticide and the control u_5 on larvicide, is used to minimise the objective function J (30), while the other control u_2 is set to zero. On figure 9, we observed that the control strategy resulted in a decrease in the number of infected humans (I_h) while an increase is observed in the number of infected humans (I_h) in strategy without control. The use of this combination have a considerable impact on the decreasing total vector population (N_v), as well as aquatic vector populations (E and L).

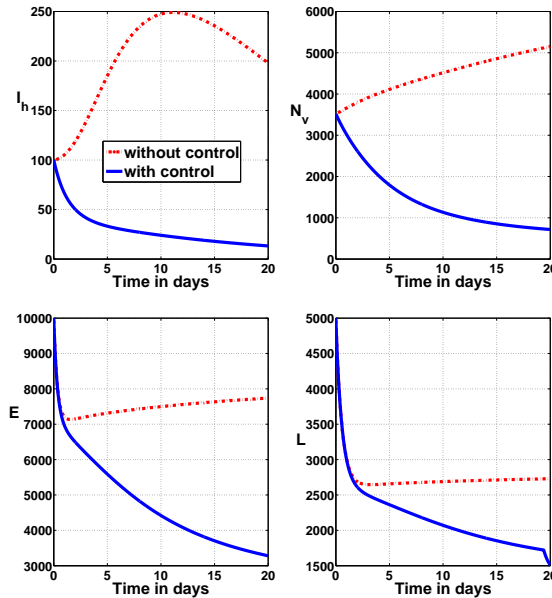


Figure 9: Simulation results of optimal control model (28) showing the effect of using optimal vaccination combined with treatment, adulticide and larvicide ($u_1 \neq 0, u_3 \neq 0, u_4 \neq 0, u_5 \neq 0$).

(iv) Vaccination combined with individual protection, adulticide and larvicide

With this strategy, only the combination of the control u_1 on vaccination, the control u_2 on individual protection, the control u_4 on adulticide and the control u_5 on larvicide, is used to minimise the objective function J (30), while the other control u_3 are set to zero. On figure 10, we observed that the control strategy resulted in a decrease in the number of infected humans (I_h) while an increase is observed in the number of infected humans (I_h) in strategy without control. The use of this combination have a great impact on the decreasing total vector population (N_v), as well as aquatic vector populations (E and L).

(v) The combination of all the five controls

In this strategy, the combination of all the five controls is applied. On figure 11, we observed that combining all the five controls give a better result in a decrease in the number of infected humans (I_h), as well as, the total number of vector population (N_v), and the aquatic vector populations (E and L).

Figures 7, 9, 10, and 11 have the same shape, which it is difficult to say what is the best control strategy. In the following, we make an efficiency analysis and a cost effectiveness analysis to determine the best strategy in terms of efficiency and cost

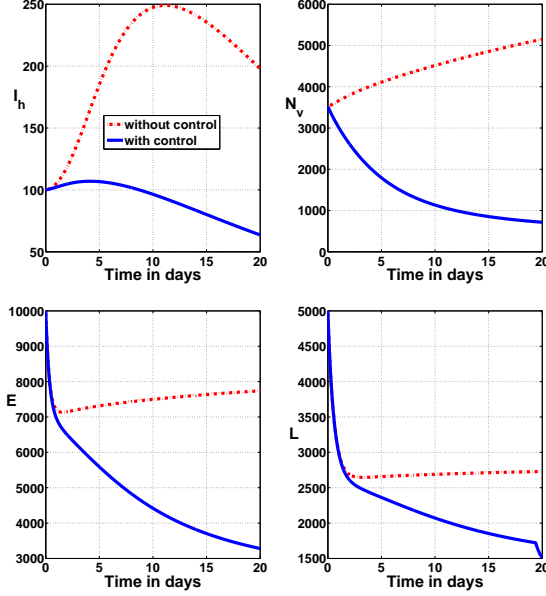


Figure 10: Simulation results of optimal control model (28) showing the effect of using optimal vaccination combined with individual protection, adulticide and larvicide ($u_1 \neq 0$, $u_2 \neq 0$, $u_4 \neq 0$, $u_5 \neq 0$).

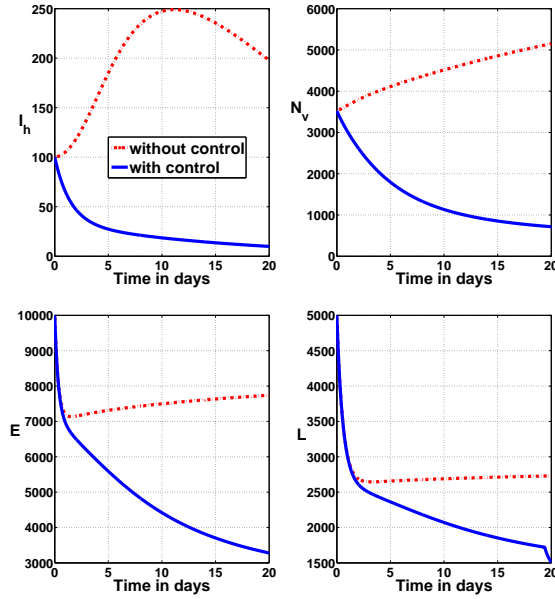


Figure 11: Simulation results of optimal control model (28) showing the effect of using the combination of all the five controls ($u_i \neq 0$, $i = 1, \dots, 5$).

4.1 Efficiency analysis

In line with Yang and Ferreira [67], Dumont and Chiroleu [23], and Carvalho et al. [13], we compare the effects of different strategies applied on the arboviral diseases, by the introduction of the efficiency index, designed by \mathbb{F} . To this aim, we define the variable \mathcal{A} as the area comprised between the curve of the symptomatic infectious human (I_h) population size, for

instance, and the time axis during the period of time from 0 to t_f , as

$$\mathcal{A} = \int_0^{t_h} I_h(t) dt, \quad (46)$$

which measures the cumulated number of infectious human during the time interval $[0, t_f]$ [13, 67]. Hence the efficiency index, \mathbb{F} , be can defined by

$$\mathbb{F} = \left(1 - \frac{\mathcal{A}_h^c}{\mathcal{A}_h^{(0)}} \right) \times 100, \quad (47)$$

where \mathcal{A}_h^c and \mathcal{A}_h^0 are the cumulated number of infectious human with and without the different controlling mechanisms, respectively. So, It follows that the best strategy will be the one whom efficiency index will be the biggest [13, 67].

With the previous simulations, we resume the efficiency index of different strategies in the Tables 8.

Table 8: Table of efficiency index (the case of infected humans).

Strategy	$\mathcal{A}_{I_h} = \int_0^{t_h} I_h(t) dt$	$\mathbb{F}_{I_h} = 100 \times \left(1 - \frac{\mathcal{A}_{I_h}^c}{\mathcal{A}_{I_h}^{(0)}} \right)$	Strategy	$\mathcal{A}_{I_h} = \int_0^{t_h} I_h(t) dt$	$\mathbb{F}_{I_h} = 100 \times \left(1 - \frac{\mathcal{A}_{I_h}^c}{\mathcal{A}_{I_h}^{(0)}} \right)$
No controls	4.1052×10^3	0%	Z_1	490.6350	88.048451%
Z_2	528.9018	87.116296%	Z_3	580.5772	85.857517%
Z_4	1.8391×10^3	55.200721%	Z	490.6350	88.048451%

From table 8, we can conclude that the best strategies are Z_1 and Z.

Remark 2. *The same reasoning (about efficiency analysis) can be done for vector population, by replacing I_h by N_v , and \mathcal{A}_h by \mathcal{A}_{N_v} in Eq. (46) and (47), respectively.*

4.2 Cost Effectiveness Analysis

The analysis of efficiency allowed us to determine the most efficient strategy, regardless of the cost associated with each control. In what follows, we will among the strategies listed in Table 7, determine which one is the most efficient and which can be implemented at lower cost. To this aim, we follow Okosun and co-workers [45], and use cost effectiveness analysis to determine the most cost effective strategy to use the controls of arboviral diseases (Strategies $Z_1 - Z$). To this aim, we calculate the Incremental Cost-Effectiveness Ratio (ICER) which is generally described as the additional cost per additional health outcome (see [45]).

Based on the model simulation results, we rank the strategies in decreasing number of Total number of infectious individuals (see Table 9).

Table 9: Cost Effectiveness of different strategies.

Strategies	Total number of infected individuals	Total infection averted	Total cost(\$)
Z_4	1839	87538	7.6218×10^8
Z_3	581	88796	7.6093×10^8
Z_2	529	88848	1.6452×10^9
Z_1	491	88886	7.6081×10^8
Z	491	88886	7.6081×10^8

The difference between the total number of infectious individuals without control and the total number of infectious individuals with control was used to determine the "total number of infection averted" used in the tables of cost-effectiveness analysis.

We obtain the ICER of strategies (i) and (j) by applying the formula given by equation (48).

$$\begin{aligned}
 ICER(i) &= \frac{Total\ cost(i)}{Total\ infection\ averted(i)} \\
 ICER(j) &= \frac{Total\ cost(j) - Total\ cost(i)}{Total\ infection\ averted(j) - Total\ infection\ averted(i)}
 \end{aligned} \tag{48}$$

Table 10: Strategy Z_4 vs Strategy Z_3 .

Strategies	Total infection averted	Total cost (\$)
Z_4	87538	7.6218×10^8
Z_3	88796	7.6093×10^8

$$\begin{aligned}
 ICER(Z_4) &= \frac{7.6218 \times 10^8}{87538} = 8706.8473 \\
 ICER(Z_3) &= \frac{(7.6093 - 7.6218) \times 10^8}{88796 - 87538} = -993.6407
 \end{aligned} \tag{49}$$

The comparison between $ICER(Z_4)$ and $ICER(Z_3)$ shows a cost saving of \$ 993.6407 for strategy Z_3 over strategy Z_4 . The negative ICER for strategy Z_3 indicates that the strategy Z_4 is "strongly dominated". That is, strategy Z_4 is more costly and less effective than strategy Z_3 . Therefore, strategy Z_4 , the strongly dominated is excluded from the set of alternatives so it does not consume limited resources.

We exclude strategy Z_4 and compare strategy Z_3 with Z_2 . From table 9, we have:

Table 11: Strategy Z_3 vs Strategy Z_2 .

Strategies	Total infection averted	Total cost (\$)
Z_3	88796	7.6093×10^8
Z_2	88848	1.6452×10^9

This leads to the following values for the ICER,

$$\begin{aligned} ICER(Z_3) &= \frac{7.6093 \times 10^8}{88796} = 8569.4175 \\ ICER(Z_2) &= \frac{1.6452 \times 10^9 - 7.6093 \times 10^8}{88848 - 88796} = 17005192 \end{aligned} \quad (50)$$

The comparison between $ICER(Z_3)$ and $ICER(Z_2)$ shows a cost saving of \$ 8569.4175 for strategy Z_3 over strategy Z_2 . That is, strategy Z_2 is more costly and less effective than strategy Z_3 . Therefore, strategy Z_2 , the strongly dominated is excluded.

We then compare strategy Z_3 with Z_1 . From table 9, we have:

Table 12: Strategy Z_3 vs Strategy Z_1 .

Strategies	Total infection averted	Total cost (\$)
Z_3	88796	7.6093×10^8
Z_1	88886	7.6081×10^8

This leads to the following values for the ICER,

$$\begin{aligned} ICER(Z_3) &= \frac{7.6093 \times 10^8}{88796} = 8569.4175 \\ ICER(Z_1) &= \frac{7.6081 \times 10^8 - 7.6093 \times 10^8}{88886 - 88796} = -1333.3333 \end{aligned} \quad (51)$$

The comparison between $ICER(Z_3)$ and $ICER(Z_1)$ shows a cost saving of \$ 1333.3333 for strategy Z_1 over strategy Z_3 . So the strategy Z_3 is "strongly dominated". That is, strategy Z_3 is more costly and less effective than strategy Z_1 . Therefore, strategy Z_3 , the strongly dominated is excluded.

We then compare strategy Z_1 with Z . From table 9, we have

Table 13: Strategy Z_1 vs Strategy Z .

Strategies	Total infection averted	Total cost (\$)
Z_1	88886	7.6081×10^8
Z	88886	7.6081×10^8

From Table 13, it follows that strategy Z_3 is equivalent in term of efficiency and cost at strategy Z .

With these results, we conclude that the strategies Z (combination of the five control) and Z_3 (vaccination u_1 combined with personal protection u_2 , the treatment of individuals with clinical signs of the disease u_3 , killing adult vectors with adulticide, u_4) are most cost-effective that all the strategies studied in this work.

5 Conclusion

In this paper, we derived and analysed a model for the control of arboviral diseases with non linear form of infection and complete stage structured model for vectors, and which takes

into account a vaccination with waning immunity, treatment, individual protection and vector control strategies (adult vectors, eggs and larvae reduction strategies).

We have begun by calculate the net reproductive number \mathcal{N} and the basic reproduction number \mathcal{R}_0 , of the basic model (the model without control), and investigate the existence and stability of equilibria. The stability analysis revealed that for $\mathcal{N} \leq 1$, the trivial equilibrium is globally asymptotically stable. When $\mathcal{N} > 1$ and $\mathcal{R}_0 < 1$, the disease-free equilibrium is locally asymptotically stable. We have found that the model exhibits backward bifurcation. The epidemiological implication of this phenomenon is that for effective eradication and control of diseases, \mathcal{R}_0 should be less than a critical values less than one. We have explicitly derived threshold conditions for saddle-node bifurcation in term of the transmission rate, β_{hv} , as well as the basic reproduction number. Then, we have proved, that the disease-induced death is the principal cause of the backward bifurcation phenomenon in model.

Using data from literature related to the transmission dynamics of dengue fever, we also estimated the probability that the model predicts the existence of multiple endemic equilibrium and of the likely stability of the disease-free equilibrium point, through Latin Hypercube Sampling (LHS). The result showed that the model is in an endemic state, since the mean of \mathcal{R}_0 is greater than unity. Then, using global sensitivity analysis, we have computed the Partial Rank Correlation Coefficients between \mathcal{R}_0 and each parameter of the model. This analysis showed that the basic reproduction number is sensitive to changes in the parameters β_{vh} , the probability of transmission of infection from an infected human to a susceptible vector, β_{hv} , the probability of transmission of infection from an infected vector to a susceptible human, a , the average number of bites, θ , the maturation rate from pupae to adult, μ_v , the natural mortality rate of vector, Λ_h , the recruitment rate of humans and l , the transfer rate from larvae to pupae, which suggested that the control of the epidemic of arboviral diseases pass through a combination of immunization against arbovirus (vaccination of susceptible humans), individual protection against vector bites, treatment of infected human, vector control through chemical interventions (adulticide and larvicide).

We then considered five time dependent controls as a way out, to ensure the eradication of the disease in a finite time. We performed optimal control analysis of the model. In this light, we addressed the optimal control by deriving and analysing the conditions for optimal eradication of the disease and in a situation where eradication is impossible or of less benefit compared with the cost of intervention, we also derived and analysed the necessary conditions for optimal control of the disease.

From the numerical results and efficiency analysis, as well as, cost-effectiveness analysis, we concluded that the optimal strategy to effectively control arboviral diseases is the combination of vaccination, individual protection, treatment, and other mechanisms of vector control (by chemical intervention—the adulticides). However this conclusion must be taken with caution because of the uncertainties around the parameter values and to the budget/resource limitation. It is also important to note that in most of the work which speak of the optimal control of infectious diseases (see e.g. [3, 9, 69, 34, 68]), and particularly the arboviral diseases [4, 7, 44, 50, 62], cost effectiveness analysis, to our knowledge, is not did by the authors. This therefore represents a contribution to the study of optimal control models of arboviral diseases.

In addition, the utilization of a vaccine of small efficacy could have a negative impact on the health of the population. Indeed, for the particular case of dengue, the fact that sequential infections with different strains can cause severe forms of the disease must be taken into account. For instance, it is not currently known if a vaccinated individual, for which the efficacy for a given strain is small, can develop a severe form of the disease when coming into contact with such a strain. Also, its efficiency is higher in children 9-16 years (two thirds are immune) and in individuals who have already been infected. The vaccine appears to contrast against-productive

in younger children without the researchers knowing why. The results of clinical trials - which involved more than 40,000 volunteers- were therefore not lifted all the uncertainties about the impact of the vaccine [38]. Therefore, pending the completion of Phase III trials on the efficacy of the vaccine against dengue (Dengvaxia[®]), and therefore its acceptance by public health organizations such as WHO and the Centre for Disease Control (CDC), it is important to focus on other control mechanisms.

All simulated intervention combinations can be considered cost-effective in the context of available resources for health in countries affected by arboviruses. These results have the potential to help managers control programs against arbovirus infections in high endemicity countries by modifying the implementation of current interventions, or by adding new control mechanisms.

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A Proof of Theorem 1

The Jacobian matrix of $f = (\dot{S}_h, \dot{E}_h, \dot{I}_h, \dot{R}_h, \dot{S}_v, \dot{E}_v, \dot{I}_v, \dot{E}, \dot{L}, \dot{P})^T$ at the Trivial equilibrium is given by

$$Df(\mathcal{E}_0) = \begin{pmatrix} -\mu_h & 0 & 0 & 0 & 0 & -a\beta_{hv}\eta_v & -a\beta_{hv} & 0 & 0 & 0 \\ 0 & -k_3 & 0 & 0 & 0 & a\beta_{hv}\eta_v & a\beta_{hv} & 0 & 0 & 0 \\ 0 & \gamma_h & -k_4 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \sigma & -\mu_h & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\mu_v & 0 & 0 & 0 & 0 & \theta \\ 0 & 0 & 0 & 0 & 0 & -k_9 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \gamma_v & -\mu_v & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \mu_b & \mu_b & \mu_b & -k_5 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & s & -k_6 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & l & -k_7 \end{pmatrix}. \quad (52)$$

The characteristic polynomial of $Df(\mathcal{E}_0)$ is given by:

$$P(\lambda) = (\lambda - \mu_h)^2(\lambda - k_3)(\lambda - k_4)(\lambda - k_9)(\lambda - \mu_v)\phi_1(\lambda)$$

where

$\phi_1(\lambda) = \lambda^4 + A_1\lambda^3 + A_2\lambda^2 + A_3\lambda + A_4$, with

$$A_1 = \mu_v + k_7 + k_6 + k_5, \quad A_2 = (k_7 + k_6 + k_5)\mu_v + (k_6 + k_5)k_7 + k_5k_6, \\ A_3 = ((k_6 + k_5)k_7 + k_5k_6)\mu_v + k_5k_6k_7, \quad A_4 = k_5k_6k_7\mu_v(1 - \mathcal{N}).$$

The roots of $P(\lambda)$ are $\lambda_1 = -\mu_h$, $\lambda_2 = -\mu_h$, $\lambda_3 = -k_3$, $\lambda_4 = -k_4$, $\lambda_5 = -\mu_v$, $\lambda_6 = -k_9$, and the others roots are the roots of $\phi_1(\lambda)$. Since $\mathcal{N} < 1$, it is clear that all coefficients of $\phi_1(\lambda)$ are always positive. Now we just have to verify that the Routh–Hurwitz criterion holds for polynomial $\phi_2(\lambda)$. To this

$$\text{aim, setting } H_1 = A_1, H_2 = \begin{vmatrix} A_1 & 1 \\ A_3 & A_2 \end{vmatrix}, H_3 = \begin{vmatrix} A_1 & 1 & 0 \\ A_3 & A_2 & A_1 \\ 0 & A_4 & A_3 \end{vmatrix}, H_4 = \begin{vmatrix} A_1 & 1 & 0 & 0 \\ A_3 & A_2 & A_1 & 1 \\ 0 & A_4 & A_3 & A_2 \\ 0 & 0 & 0 & A_4 \end{vmatrix} = A_4 H_3.$$

The Routh-Hurwitz criterion of stability of the trivial equilibrium \mathcal{E}^0 is given by

$$\begin{cases} H_1 > 0 \\ H_2 > 0 \\ H_3 > 0 \\ H_4 > 0 \end{cases} \Leftrightarrow \begin{cases} H_1 > 0 \\ H_2 > 0 \\ H_3 > 0 \\ A_4 > 0 \end{cases} \quad (53)$$

We have $H_1 = A_1 > 0$,

$$\begin{aligned} H_2 &= A_1 A_2 - A_3 \\ &= (k_7 + k_6 + k_5) \mu_v^2 + (k_7^2 + (2k_6 + 2k_5)k_7 + k_6^2 + 2k_5k_6 + k_5^2) \mu_v + (k_6 + k_5)k_7^2 \\ &\quad + (k_6 + k_5)^2 k_7 + k_5k_6^2 + k_5^2k_6, \end{aligned}$$

$$\begin{aligned} H_3 &= A_1 A_2 A_3 - A_1^2 A_4 - A_3^2 \\ &= ((k_6 + k_5)k_7^2 + (k_6^2 + 2k_5k_6 + k_5^2)k_7 + k_5k_6^2 + k_5^2k_6) \mu_v^3 + (\mu_b l s \theta + (k_6 + k_5)k_7^2 + (2k_6^2 + 4k_5k_6 + 2k_5^2)k_7^2 \\ &\quad + (k_6^3 + 4k_5k_6^2 + 4k_5^2k_6 + k_5^3)k_7 + k_5k_6^3 + 2k_5^2k_6^2 + k_5^3k_6) \mu_v^2 + ((2k_7 + 2k_6 + 2k_5) \mu_b l s \theta + (k_6^2 + 2k_5k_6 + k_5^2)k_7^3 \\ &\quad + (k_6^3 + 4k_5k_6^2 + 4k_5^2k_6 + k_5^3)k_7^2 + (2k_5k_6^3 + 4k_5^2k_6^2 + 2k_5^3k_6)k_7 + k_5^2k_6^3 + k_5^3k_6^2) \mu_v \\ &\quad + (k_7^2 + (2k_6 + 2k_5)k_7 + k_6^2 + 2k_5k_6 + k_5^2) \mu_b l s \theta + (k_5k_6^2 + k_5^2k_6)k_7^3 + (k_5k_6^3 + 2k_5^2k_6^2 + k_5^3k_6)k_7^2 + (k_5^2k_6^3 + k_5^3k_6^2)k_7 \end{aligned}$$

We always have $H_1 > 0$, $H_2 > 0$, $H_3 > 0$ and $H_4 > 0$ if $\mathcal{N} < 1$. Thus, the trivial equilibrium \mathcal{E}_0 is locally asymptotically stable whenever $\mathcal{N} < 1$.

We assume the net reproductive number $\mathcal{N} > 1$. Following the procedure and the notation in [59], we may obtain the basic reproduction number \mathcal{R}_0 as the dominant eigenvalue of the *next-generation matrix* [21, 59]. Observe that model (6) has four infected populations, namely E_h , I_h , E_v and I_v . It follows that the matrices F and V defined in [59], which take into account the new infection terms and remaining transfer terms, respectively, are given by

$$F = \begin{pmatrix} 0 & 0 & \beta_{hv}\eta_v & \beta_{hv} \\ 0 & 0 & 0 & 0 \\ \frac{\beta_{vh}\eta_v N_v^0}{N_h^0} & \frac{\beta_{vh} N_v^0}{N_h^0} & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \text{ and } V = \begin{pmatrix} k_3 & 0 & 0 & 0 \\ -\gamma_h & k_4 & 0 & 0 \\ 0 & 0 & k_9 & 0 \\ 0 & 0 & -\gamma_v & k_8 \end{pmatrix}.$$

The dominant eigenvalue of the next-generation matrix FV^{-1} is given by (10). The local stability of the disease-free equilibrium \mathcal{E}_1 is a direct consequence of Theorem 2 in [59]. This ends the proof.

B Proof of Theorem 2

Setting $Y = X - TE$ with $X = (S_h, E_h, I_h, R_h, S_v, E_v, I_v, E, L, P)^T$, $A_{88} = \left(k_5 + \mu_b \frac{S_v + E_v + I_v}{K_E} \right)$, and $A_{99} = \left(k_6 + s \frac{E}{\Gamma_L} \right)$. we can rewrite (3) in the following manner

$$\frac{dY}{dt} = \mathcal{B}(Y)Y \quad (54)$$

where

$$\mathcal{B}(Y) = \begin{pmatrix} -(\lambda_h + \mu_h) & 0 & 0 & 0 & 0 & -\frac{a\beta_{hv}\eta_v S_h^0}{N_h} & -\frac{a\beta_{hv} S_h^0}{N_h} & 0 & 0 & 0 \\ \lambda_h & -k_3 & 0 & 0 & 0 & \frac{a\beta_{hv}\eta_v S_h^0}{N_h} & \frac{a\beta_{hv} S_h^0}{N_h} & 0 & 0 & 0 \\ 0 & \gamma_h & -k_4 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \sigma & -\mu_h & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -(\lambda_v + \mu_v) & 0 & 0 & 0 & 0 & \theta \\ 0 & 0 & 0 & 0 & \lambda_v & -k_9 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \gamma_v & -\mu_v & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \mu_b & \mu_b & \mu_b & -A_{88} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & s & -A_{99} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & l & -k_7 \end{pmatrix}.$$

It is clear that $Y = (0, 0, 0, 0, 0, 0, 0, 0, 0, 0)$ is the only equilibrium. Then it suffices to consider the following Lyapunov function $\mathcal{L}(Y) = \langle g, Y \rangle$ where $g = \left(1, 1, 1, 1, 1, 1, 1, \frac{k_8}{\mu_b}, \frac{k_5 k_8}{\mu_b s}, \frac{k_5 k_6 k_8}{\mu_b s l}\right)$. Straightforward computations lead that

$$\begin{aligned} \dot{\mathcal{L}}(Y) &= \langle g, \dot{Y} \rangle \stackrel{\text{def}}{=} \langle g, \mathcal{B}(Y)Y \rangle \\ &= -\mu_h Y_1 - \mu_h Y_2 - (\mu_h + \delta)Y_3 - \mu_h Y_4 - \frac{k_8}{K_E}(Y_5 + Y_6 + Y_7) - \frac{k_5 k_8}{\mu_b K_L} Y_8 Y_9 + \theta \left(1 - \frac{1}{\mathcal{N}}\right) Y_{10}. \end{aligned}$$

We have $\dot{\mathcal{L}}(Y) < 0$ if $\mathcal{N} \leq 1$ and $\dot{\mathcal{L}}(Y) = 0$ if $Y_i = 0$, $i = 1, 2, \dots, 10$ (i.e. $S_h = S_h^0$ and $E_h = I_h = R_h = S_v = E_v = I_v = E = L = P = 0$). Moreover, the maximal invariant set contained in $\{\mathcal{L}|\dot{\mathcal{L}}(Y) = 0\}$ is $\{(0, 0, 0, 0, 0, 0, 0, 0, 0, 0)\}$. Thus, from Lyapunov theory, we deduce that $\{(0, 0, 0, 0, 0, 0, 0, 0, 0, 0)\}$ and thus, \mathcal{E}_0 , is GAS if and only if $\mathcal{N} \leq 1$.

C Proof of Theorem 3

Proof. In order to determine the existence of endemic equilibria, i.e., equilibria with all positive components, say

$$\mathcal{E}^{**} = (S_h^*, V_h^*, E_h^*, I_h^*, R_h^*, S_v^*, E_v^*, I_v^*, E, L, P),$$

we have to look for the solution of the algebraic system of equations obtained by equating the right sides of system (6) to zero.

Solving the equations in the model (6) in terms of λ_h^* and λ_v^* , gives

$$S_h^* = \frac{\Lambda_h}{\mu_h + \lambda_h^*}, \quad E_h^* = \frac{\lambda_h^* S_h^*}{k_3}, \quad I_h^* = \frac{\gamma_h \lambda_h^* S_h^*}{k_3 k_4}, \quad R_h^* = \frac{\sigma \gamma_h \lambda_h^* S_h^*}{\mu_h k_3 k_4}, \quad (55)$$

and

$$\begin{aligned} S_v^* &= \frac{\theta P}{(\lambda_v^* + k_8)}, \quad E_v^* = \frac{\theta P \lambda_v^*}{k_9 (\lambda_v^* + k_8)}, \quad I_v^* = \frac{\gamma_v \theta P \lambda_v^*}{k_8 k_9 (\lambda_v^* + k_8)}, \\ E &= \frac{\mu_b \theta \Gamma_E P}{(k_5 k_8 \Gamma_E + \mu_b \theta P)}, \quad L = \frac{\mu_b \theta s \Gamma_E \Gamma_L P}{k_6 \Gamma_L (k_5 k_8 \Gamma_E + \mu_b \theta P) + s \mu_b \theta \Gamma_E P}, \end{aligned} \quad (56)$$

where P is solution of the following equation

$$f(P) = -k_7 P [\mu_b \theta (s \Gamma_E + k_6 \Gamma_L) P - k_5 k_6 k_8 \Gamma_E \Gamma_L (\mathcal{N} - 1)] = 0 \quad (57)$$

A direct resolution of the above equation give $P = 0$ or $P = \frac{k_5 k_6 k_8 \Gamma_E \Gamma_L (\mathcal{N} - 1)}{\mu_b \theta (s \Gamma_E + k_6 \Gamma_L)}$.

Note that $P = 0$ corresponds to the trivial equilibrium \mathcal{E}_0 . Now we consider $P > 0$ i.e. $\mathcal{N} > 1$. Substituting (55) and (56) into the expression of λ_h^* and λ_v^* and simplifying, lead the non-zero equilibria of the basic model (6) satisfy the quadratic equation

$$k_9\mu_b\Lambda_h(s\Gamma_E + k_6\Gamma_L) [d_2(\lambda_h^*)^2 + d_1\lambda_h^* + d_0] = 0, \quad (58)$$

where d_i , $i = 0, 1, 2$, are given by

$$d_2 = -k_2 [k_{10}a\mu_h\beta_{vh} + k_2k_8] < 0, \quad (59a)$$

$$d_1 = k_3^2k_4^2k_8\mu_h(\mathcal{R}_0^2 - \mathcal{R}_c^2), \quad (59b)$$

$$d_0 = k_3^2k_4^2k_8\mu_h^2(\mathcal{R}_0^2 - 1). \quad (59c)$$

and \mathcal{R}_0 and \mathcal{R}_c are given by (10) and (12), respectively.

This equation may be simply analyzed through the Descartes' rule of signs. First of all, note that d_2 is negative. Therefore the following cases are possible:

1. There is a unique endemic equilibrium if $d_0 > 0$;
2. There is a unique endemic equilibrium if

$$(d_1 > 0 \text{ and } d_0 = 0) \text{ or } (d_1 > 0 \text{ and } d_0 < 0 \text{ and } d_1^2 - 4d_2d_0 = 0); \quad (60)$$

3. There are two endemic equilibria if

$$d_1 > 0 \text{ and } d_0 < 0 \text{ and } d_1^2 - 4d_2d_0 > 0; \quad (61)$$

4. There are no endemic equilibria otherwise.

We observe $d_0 > 0$ is equivalent to $\mathcal{R}_0 > 1$ so statement (i) of Theorem 3 is equivalent to point (a).

When $\mathcal{R}_0 = 1$, $d_0 = 0$. We observe that $d_1 > 0$ is equivalent to $\mathcal{R}_c < \mathcal{R}_0$. Therefore, when $\mathcal{R}_0 = 1$ and $\mathcal{R}_c < 1$, $d_0 = 0$ and $d_1 > 0$, so statement (ii) a) of Theorem 3 follows from statement (b) above. Since the condition $d_0 = 0$ does not appear elsewhere in statements (a), (b), or (c) above, statement (ii) b) of Theorem 3 follows from statement (d) above.

When $\mathcal{R}_0 < 1$, $d_0 < 0$, and when $\mathcal{R}_c < \mathcal{R}_0$, $d_1 > 0$. We also note that for $\mathcal{R}_0 < 1$, when $d_1 > 0$, $\psi \leq 0$ because $\psi > 0$ is equivalent to $d_1 < 0$. Indeed,

$$\begin{aligned} \psi > 0 &\iff k_{10}a\mu_h\beta_{vh} > \delta\gamma_hk_8 \\ &\iff k_{10}a\mu_h\beta_{vh}k_9 + 2k_8k_9k_2 > \delta\gamma_hk_8k_9 + 2k_8k_9k_2 \\ &\iff a^2\beta_{hv}\beta_{vh}k_3k_4k_{10}k_{11}\mu_hN_v^0 - k_3k_4\mu_hN_h^0(k_{10}a\mu_h\beta_{vh}k_9 + 2k_8k_9k_2) < k_3k_4k_8k_9\mu_hN_h^0[(\mathcal{R}_0^2 - 1)k_3k_4 - k_3k_4 + \delta\gamma_h] \\ &\iff a^2\beta_{hv}\beta_{vh}k_3k_4k_{10}k_{11}\mu_hN_v^0 - k_3k_4\mu_hN_h^0(k_{10}a\mu_h\beta_{vh}k_9 + 2k_8k_9k_2) < k_3k_4k_8k_9\mu_hN_h^0[(\mathcal{R}_0^2 - 1)k_3k_4 - k_2] \\ &\iff d_1 < k_3k_4k_8\mu_h[(\mathcal{R}_0^2 - 1)k_3k_4 - k_2] < 0, \text{ since } \mathcal{R}_0 < 1. \end{aligned} \quad (62)$$

Consequently, we show that $d_1^2 - 4d_2d_0 = 0$ is equivalent to,

$$\rho_2R_0^4 + \rho_1R_0^2 + \rho_0 = 0, \quad (63)$$

where

$$\rho_2 = k_3^4k_4^4k_8^2\mu_h^2, \quad (64a)$$

$$\rho_1 = 2k_3^2k_4^2k_8\mu_h^2[k_2(k_{10}a\mu_h\beta_{vh} - k_8\delta\gamma_h) - (k_{10}a\mu_h\beta_{vh} + k_8k_2)\delta\gamma_h], \quad (64b)$$

$$\rho_0 = k_3^2k_4^2k_{10}^2a^2\mu_h^4\beta_{vh}^2. \quad (64c)$$

We again use Descartes' rule of signs to analyse equation (63). The discriminant of (63) is $\Delta_r = \rho_1^2 - 4\rho_2\rho_0$, and can be written

$$\Delta_r = -16k_3^4k_4^4k_8^2k_2\mu_h^4\delta\gamma_h(k_{10}a\mu_h\beta_{vh} + k_8k_2)(k_{10}a\mu_h\beta_{vh} - k_8\delta\gamma_h)$$

Since $\rho_2 > 0$ and $\rho_0 > 0$, equation (63) allows real positive solutions if and only if $\rho_1 < 0$ and $\Delta_r \geq 0$. Now, we express the obtained inequalities in terms of the quantities (11)–(14). To this aim, we note that $\Delta_r \geq 0$ is equivalent to $\psi \leq 0$. From the definition of ψ (11) and ρ_1 (64b), this implies that $\rho_1 < 0$. Therefore, equation (63) has exactly two positive solutions given by (13) and (14). Therefore, statement (iii) b) follows from statement (b) above.

Similarly, $d_1^2 - 4d_2d_0 > 0$, with $d_1 > 0$ and $d_0 < 0$ written in terms of the basic reproduction number, is equivalent to

$$\mathcal{R}_0 < \mathcal{R}_{1b} \quad \text{or} \quad \mathcal{R}_0 > \mathcal{R}_{2b}, \quad (65)$$

so statement (iii) a) follows from statement (c) above.

Finally, statement (iii) c) then follows from statement (d) above. Thus Theorem 3 is established. \square

D Derivation of formula (21)

The local bifurcation analysis near the bifurcation point ($\beta_{hv} = \beta_{hv}^*$) is then determined by the signs of two associated constants, denoted by \mathcal{A}_1 and \mathcal{A}_2 , defined by

$$\mathcal{A}_1 = \sum_{k,i,j=1}^{10} v_k w_i w_j \frac{\partial^2 f_k(0,0)}{\partial x_i \partial x_j} \quad \text{and} \quad \mathcal{A}_2 = \sum_{k,i=1}^{10} v_k w_i \frac{\partial^2 f_k(0,0)}{\partial x_i \partial \phi} \quad (66)$$

with $\phi = \beta_{hv} - \beta_{hv}^*$. It is important to note that in $f_k(0,0)$, the first zero corresponds to the disease-free equilibrium, \mathcal{E}_1 , for the system (6). Since $\beta_{hv} = \beta_{hv}^*$ is the bifurcation parameter, it follows from $\phi = \beta_{hv} - \beta_{hv}^*$ that $\phi = 0$ when $\beta_{hv} = \beta_{hv}^*$ which is the second component in $f_k(0,0)$.

Using Eqs. (17) and (18) in Eq. (19), we obtain

$$\mathcal{A}_1 = v_2 \sum_{i,j=1}^{10} w_i w_j \frac{\partial^2 f_2(0,0)}{\partial x_i \partial x_j} + v_6 \sum_{i,j=1}^{10} w_i w_j \frac{\partial^2 f_6(0,0)}{\partial x_i \partial x_j} \quad \text{and} \quad \mathcal{A}_2 = v_2 \sum_{i=1}^{10} w_i \frac{\partial^2 f_2(0,0)}{\partial x_i \partial \phi}. \quad (67)$$

Let

$$\begin{aligned}
\mathcal{A}_1^{(1)} &= \sum_{i,j=1}^{10} w_i w_j \frac{\partial^2 f_2(0,0)}{\partial x_i \partial x_j} \\
&= w_1 \sum_{i,j=1}^{10} w_j \frac{\partial^2 f_2(0,0)}{\partial x_1 \partial x_j} + w_2 \sum_{i,j=1}^{10} w_j \frac{\partial^2 f_2(0,0)}{\partial x_2 \partial x_j} + w_3 \sum_{i,j=1}^{10} w_j \frac{\partial^2 f_2(0,0)}{\partial x_3 \partial x_j} + w_4 \sum_{i,j=1}^{10} w_j \frac{\partial^2 f_2(0,0)}{\partial x_4 \partial x_j} \\
&+ w_5 \sum_{i,j=1}^{10} w_j \frac{\partial^2 f_2(0,0)}{\partial x_5 \partial x_j} + w_6 \sum_{i,j=1}^{10} w_j \frac{\partial^2 f_2(0,0)}{\partial x_6 \partial x_j} + w_7 \sum_{i,j=1}^{10} w_j \frac{\partial^2 f_2(0,0)}{\partial x_7 \partial x_j} \\
&= w_2 \left(w_6 \frac{\partial^2 f_2}{\partial E_h \partial E_v}(0,0) + w_7 \frac{\partial^2 f_2}{\partial E_h \partial I_v}(0,0) \right) + w_3 \left(w_6 \frac{\partial^2 f_2}{\partial I_h \partial E_v}(0,0) + w_7 \frac{\partial^2 f_2}{\partial I_h \partial I_v}(0,0) \right) \\
&+ w_4 \left(w_6 \frac{\partial^2 f_2}{\partial R_h \partial E_v}(0,0) + w_7 \frac{\partial^2 f_2}{\partial R_h \partial I_v}(0,0) \right) + w_6 \left(w_2 \frac{\partial^2 f_2}{\partial E_v \partial E_h} + w_3 \frac{\partial^2 f_2}{\partial E_v \partial I_h} + w_4 \frac{\partial^2 f_2}{\partial E_v \partial R_h} \right) \\
&+ w_7 \left(w_2 \frac{\partial^2 f_2}{\partial I_v \partial E_h} + w_3 \frac{\partial^2 f_2}{\partial I_v \partial I_h} + w_4 \frac{\partial^2 f_2}{\partial I_v \partial R_h} \right) \\
&= w_2 \left(-\frac{a\beta_{hv}^* \eta_v}{N_h^0} w_6 - \frac{a\beta_{hv}^*}{N_h^0} w_7 \right) + w_3 \left(-\frac{a\beta_{hv}^* \eta_v}{N_h^0} w_6 - \frac{a\beta_{hv}^*}{N_h^0} w_7 \right) \\
&+ w_4 \left(-\frac{a\beta_{hv}^* \eta_v}{N_h^0} w_6 - \frac{a\beta_{hv}^*}{N_h^0} w_7 \right) + w_6 \left(-\frac{a\beta_{hv}^* \eta_v}{N_h^0} w_2 - \frac{a\beta_{hv}^* \eta_v}{N_h^0} w_3 - \frac{a\beta_{hv}^* \eta_v}{N_h^0} w_4 \right) \\
&+ w_7 \left(-\frac{a\beta_{hv}^*}{N_h^0} w_2 - \frac{a\beta_{hv}^*}{N_h^0} w_3 - \frac{a\beta_{hv}^*}{N_h^0} w_4 \right) \\
&= -\frac{a\beta_{hv}^*}{N_h^0} (\eta_v w_6 + w_7) (w_2 + w_3 + w_4) - \frac{a\beta_{hv}^*}{N_h^0} (w_2 + w_3 + w_4) (\eta_v w_6 + w_7) \\
&= -2 \frac{a\beta_{hv}^*}{N_h^0} (\eta_v w_6 + w_7) (w_2 + w_3 + w_4),
\end{aligned}$$

and

$$\begin{aligned}
\mathcal{A}_1^{(2)} &= \sum_{i,j=1}^{10} w_i w_j \frac{\partial^2 f_6(0,0)}{\partial x_i \partial x_j} \\
&= w_1 \sum_{i,j=1}^{10} w_j \frac{\partial^2 f_6(0,0)}{\partial x_1 \partial x_j} + w_2 \sum_{i,j=1}^{10} w_j \frac{\partial^2 f_6(0,0)}{\partial x_2 \partial x_j} + w_3 \sum_{i,j=1}^{10} w_j \frac{\partial^2 f_6(0,0)}{\partial x_3 \partial x_j} + w_4 \sum_{i,j=1}^{10} w_j \frac{\partial^2 f_6(0,0)}{\partial x_4 \partial x_j} \\
&+ w_5 \sum_{i,j=1}^{10} w_j \frac{\partial^2 f_6(0,0)}{\partial x_5 \partial x_j} + w_6 \sum_{i,j=1}^{10} w_j \frac{\partial^2 f_6(0,0)}{\partial x_6 \partial x_j} + w_7 \sum_{i,j=1}^{10} w_j \frac{\partial^2 f_6(0,0)}{\partial x_7 \partial x_j} \\
&= w_1 \left(w_2 \frac{\partial f_6}{\partial S_h \partial E_h}(0,0) + w_3 \frac{\partial f_6}{\partial S_h \partial I_h}(0,0) \right) \\
&+ w_2 \left(w_1 \frac{\partial f_6}{\partial E_h \partial S_h}(0,0) + w_2 \frac{\partial f_6}{\partial E_h^2}(0,0) + w_3 \frac{\partial f_6}{\partial E_h \partial I_h}(0,0) + w_4 \frac{\partial f_6}{\partial E_h \partial R_h}(0,0) + w_5 \frac{\partial f_6}{\partial E_h \partial S_v}(0,0) \right) \\
&+ w_3 \left(w_1 \frac{\partial f_6}{\partial I_h \partial S_h}(0,0) + w_2 \frac{\partial f_6}{\partial I_h \partial E_h}(0,0) + w_3 \frac{\partial f_6}{\partial I_h^2}(0,0) + w_4 \frac{\partial f_6}{\partial I_h \partial R_h}(0,0) + w_5 \frac{\partial f_6}{\partial I_h \partial S_v}(0,0) \right) \\
&+ w_4 \left(w_2 \frac{\partial f_6}{\partial R_h \partial E_h}(0,0) + w_3 \frac{\partial f_6}{\partial R_h \partial I_h}(0,0) \right) + w_5 \left(w_2 \frac{\partial f_6}{\partial S_v \partial E_h}(0,0) + w_3 \frac{\partial f_6}{\partial S_v \partial I_h}(0,0) \right) \\
&= w_1 \left(-\frac{a\beta_{vh}\eta_h S_v^0}{(N_h^0)^2} w_2 - \frac{a\beta_{vh} S_v^0}{(N_h^0)^2} w_3 \right) \\
&+ w_2 \left(-\frac{a\beta_{vh}\eta_h S_v^0}{(N_h^0)^2} w_1 - 2\frac{a\beta_{vh}\eta_h S_v^0}{(N_h^0)^2} w_2 - \frac{a\beta_{vh} S_v^0}{(N_h^0)^2} (\eta_h + 1) w_3 - \frac{a\beta_{vh}\eta_h S_v^0}{(N_h^0)^2} w_4 + \frac{a\beta_{vh}\eta_h}{N_h^0} w_5 \right) \\
&+ w_3 \left(-\frac{a\beta_{vh} S_v^0}{(N_h^0)^2} w_1 - \frac{a\beta_{vh} S_v^0}{(N_h^0)^2} (\eta_h + 1) w_2 - 2\frac{a\beta_{vh}\eta_h S_v^0}{(N_h^0)^2} w_3 - \frac{a\beta_{vh} S_v^0}{(N_h^0)^2} w_4 + \frac{a\beta_{vh}}{N_h^0} w_5 \right) \\
&+ w_4 \left(-\frac{a\beta_{vh}\eta_h S_v^0}{(N_h^0)^2} w_2 - \frac{a\beta_{vh} S_v^0}{(N_h^0)^2} w_3 \right) + w_5 \left(\frac{a\beta_{vh}\eta_h}{N_h^0} w_2 + \frac{a\beta_{vh}}{N_h^0} w_3 \right) \\
&= -\frac{a\beta_{vh}\eta_h S_v^0}{(N_h^0)^2} w_1 w_2 - \frac{a\beta_{vh} S_v^0}{(N_h^0)^2} w_1 w_3 \\
&- \frac{a\beta_{vh}\eta_h S_v^0}{(N_h^0)^2} w_1 w_2 - 2\frac{a\beta_{vh}\eta_h S_v^0}{(N_h^0)^2} w_2^2 - \frac{a\beta_{vh} S_v^0}{(N_h^0)^2} (\eta_h + 1) w_2 w_3 - \frac{a\beta_{vh}\eta_h S_v^0}{(N_h^0)^2} w_2 w_4 + \frac{a\beta_{vh}\eta_h}{N_h^0} w_2 w_5 \\
&- \frac{a\beta_{vh} S_v^0}{(N_h^0)^2} w_1 w_3 - \frac{a\beta_{vh} S_v^0}{(N_h^0)^2} (\eta_h + 1) w_2 w_3 - 2\frac{a\beta_{vh}\eta_h S_v^0}{(N_h^0)^2} w_3^2 - \frac{a\beta_{vh} S_v^0}{(N_h^0)^2} w_3 w_4 + \frac{a\beta_{vh}}{N_h^0} w_3 w_5 \\
&- \frac{a\beta_{vh}\eta_h S_v^0}{(N_h^0)^2} w_2 w_4 - \frac{a\beta_{vh} S_v^0}{(N_h^0)^2} w_3 w_4 + \frac{a\beta_{vh}\eta_h}{N_h^0} w_2 w_5 + \frac{a\beta_{vh}}{N_h^0} w_3 w_5 \\
&= -2\frac{a\beta_{vh}\eta_h S_v^0}{(N_h^0)^2} w_1 w_2 - 2\frac{a\beta_{vh} S_v^0}{(N_h^0)^2} w_1 w_3 - 2\frac{a\beta_{vh}\eta_h S_v^0}{(N_h^0)^2} w_2^2 - 2\frac{a\beta_{vh} S_v^0}{(N_h^0)^2} (\eta_h + 1) w_2 w_3 - 2\frac{a\beta_{vh}\eta_h S_v^0}{(N_h^0)^2} w_2 w_4 \\
&- 2\frac{a\beta_{vh}\eta_h S_v^0}{(N_h^0)^2} w_3^2 - 2\frac{a\beta_{vh} S_v^0}{(N_h^0)^2} w_3 w_4 + 2\frac{a\beta_{vh}\eta_h}{N_h^0} w_2 w_5 + 2\frac{a\beta_{vh}}{N_h^0} w_3 w_5 \\
&= -2\frac{a\beta_{vh}\eta_h S_v^0}{(N_h^0)^2} w_2^2 - 2\frac{a\beta_{vh} S_v^0}{(N_h^0)^2} (\eta_h + 1) w_2 w_3 - 2\frac{a\beta_{vh}\eta_h S_v^0}{(N_h^0)^2} w_2 w_4 - 2\frac{a\beta_{vh}\eta_h S_v^0}{(N_h^0)^2} w_3^2 - 2\frac{a\beta_{vh} S_v^0}{(N_h^0)^2} w_3 w_4 \\
&+ 2\frac{a\beta_{vh}}{N_h^0} \eta_h w_2 w_5 + 2\frac{a\beta_{vh}}{N_h^0} w_3 w_5 - 2\frac{a\beta_{vh} S_v^0}{(N_h^0)^2} \eta_h w_1 w_2 - 2\frac{a\beta_{vh} S_v^0}{(N_h^0)^2} w_1 w_3 \\
&= -2\frac{a\beta_{vh}\eta_h S_v^0}{(N_h^0)^2} w_2^2 - 2\frac{a\beta_{vh} S_v^0}{(N_h^0)^2} (\eta_h + 1) w_2 w_3 - 2\frac{a\beta_{vh}\eta_h S_v^0}{(N_h^0)^2} w_2 w_4 - 2\frac{a\beta_{vh}\eta_h S_v^0}{(N_h^0)^2} w_3^2 - 2\frac{a\beta_{vh} S_v^0}{(N_h^0)^2} w_3 w_4 \\
&+ 2\frac{a\beta_{vh}}{N_h^0} (\eta_h w_2 + w_3) w_5 - 2\frac{a\beta_{vh} S_v^0}{(N_h^0)^2} \eta_h w_1 w_2 - 2\frac{a\beta_{vh} S_v^0}{(N_h^0)^2} w_1 w_3 \\
&= -2\frac{a\beta_{vh}\eta_h S_v^0}{(N_h^0)^2} w_2^2 - 2\frac{a\beta_{vh} S_v^0}{(N_h^0)^2} (\eta_h + 1) w_2 w_3 - 2\frac{a\beta_{vh}\eta_h S_v^0}{(N_h^0)^2} w_2 w_4 - 2\frac{a\beta_{vh}\eta_h S_v^0}{(N_h^0)^2} w_3^2 - 2\frac{a\beta_{vh} S_v^0}{(N_h^0)^2} w_3 w_4 \\
&+ 2\frac{a\beta_{vh}}{N_h^0} (\eta_h w_2 + w_3) \left(-\frac{k_8 + \gamma_v}{\gamma_v} w_7 + \frac{k_7 K_2 K_4}{l K_1 K_3} w_{10} \right) - 2\frac{a\beta_{vh} S_v^0}{(N_h^0)^2} \eta_h w_1 w_2 - 2\frac{a\beta_{vh} S_v^0}{(N_h^0)^2} w_1 w_3 \\
&= -2\frac{a\beta_{vh} S_v^0}{(N_h^0)^2} (\eta_h w_2^2 + (\eta_h + 1) w_2 w_3 + \eta_h w_2 w_4 + \eta_h w_3^2 + w_3 w_4) - 2\frac{a\beta_{vh} (k_8 + \gamma_v)}{\gamma_v N_h^0} (\eta_h w_2 + w_3) w_7 \\
&+ 2\frac{k_7 K_2 K_4}{l K_1 K_3} \frac{a\beta_{vh}}{N_h^0} (\eta_h w_2 + w_3) w_{10} - 2\frac{a\beta_{vh} S_v^0}{(N_h^0)^2} (\eta_h w_2 + w_3) w_1
\end{aligned}$$

It follows then, after some algebraic computations, that

$$\begin{aligned}
\mathcal{A}_1 &= v_2 \left\{ -2 \frac{a\beta_{hv}^*}{N_h^0} (\eta_v w_6 + w_7) (w_2 + w_3 + w_4) \right\} \\
&+ v_6 \left\{ -2 \frac{a\beta_{vh} S_v^0}{(N_h^0)^2} (\eta_h w_2^2 + (\eta_h + 1) w_2 w_3 + \eta_h w_2 w_4 + \eta_h w_3^2 + w_3 w_4) - 2 \frac{a\beta_{vh}(k_8 + \gamma_v)}{\gamma_v N_h^0} (\eta_h w_2 + w_3) w_7 \right. \\
&\quad \left. + 2 \frac{k_7 K_2 K_4}{l K_1 K_3} \frac{a\beta_{vh}}{N_h^0} (\eta_h w_2 + w_3) w_{10} - 2 \frac{a\beta_{vh} S_v^0}{(N_h^0)^2} (\eta_h w_2 + w_3) w_1 \right\} \\
&= v_2 \left\{ -2 \frac{a\beta_{hv}^*}{N_h^0} (\eta_v w_6 + w_7) (w_2 + w_3 + w_4) \right\} \\
&+ v_6 \left\{ -2 \frac{a\beta_{vh} S_v^0}{(N_h^0)^2} (\eta_h w_2^2 + (\eta_h + 1) w_2 w_3 + \eta_h w_2 w_4 + \eta_h w_3^2 + w_3 w_4) - 2 \frac{a\beta_{vh}(k_8 + \gamma_v)}{\gamma_v N_h^0} (\eta_h w_2 + w_3) w_7 \right\} \\
&+ v_6 \left\{ 2 \frac{k_7 K_2 K_4}{l K_1 K_3} \frac{a\beta_{vh}}{N_h^0} (\eta_h w_2 + w_3) w_{10} - 2 \frac{a\beta_{vh} S_v^0}{(N_h^0)^2} (\eta_h w_2 + w_3) w_1 \right\} \\
&= v_6 \left\{ 2 \frac{k_7 K_2 K_4}{l K_1 K_3} \frac{a\beta_{vh}}{N_h^0} (\eta_h w_2 + w_3) w_{10} - 2 \frac{a\beta_{vh} S_v^0}{(N_h^0)^2} (\eta_h w_2 + w_3) w_1 \right\} \\
&+ v_2 \left\{ -2 \frac{a\beta_{hv}^*}{N_h^0} (\eta_v w_6 + w_7) (w_2 + w_3 + w_4) \right\} \\
&+ v_6 \left\{ -2 \frac{a\beta_{vh} S_v^0}{(N_h^0)^2} (\eta_h w_2^2 + (\eta_h + 1) w_2 w_3 + \eta_h w_2 w_4 + \eta_h w_3^2 + w_3 w_4) - 2 \frac{a\beta_{vh}(k_8 + \gamma_v)}{\gamma_v N_h^0} (\eta_h w_2 + w_3) w_7 \right\} \\
&= v_6 \left\{ 2 \frac{k_7 K_2 K_4}{l K_1 K_3} \frac{a\beta_{vh}}{N_h^0} (\eta_h w_2 + w_3) w_{10} - 2 \frac{a\beta_{vh} S_v^0}{(N_h^0)^2} (\eta_h w_2 + w_3) w_1 \right\} \\
&- v_2 \left\{ 2 \frac{a\beta_{hv}^*}{N_h^0} (\eta_v w_6 + w_7) (w_2 + w_3 + w_4) \right\} \\
&- v_6 \left\{ 2 \frac{a\beta_{vh} S_v^0}{(N_h^0)^2} (\eta_h w_2^2 + (\eta_h + 1) w_2 w_3 + \eta_h w_2 w_4 + \eta_h w_3^2 + w_3 w_4) + 2 \frac{a\beta_{vh}(k_8 + \gamma_v)}{\gamma_v N_h^0} (\eta_h w_2 + w_3) w_7 \right\} \\
&= \zeta_1 - \zeta_2,
\end{aligned} \tag{68}$$

where we have set

$$\begin{aligned}
\zeta_1 &= v_6 \left\{ 2 \frac{k_7 K_2 K_4}{l K_1 K_3} \frac{a\beta_{vh}}{N_h^0} (\eta_h w_2 + w_3) w_{10} - 2 \frac{a\beta_{vh} S_v^0}{(N_h^0)^2} (\eta_h w_2 + w_3) w_1 \right\}, \\
\zeta_2 &= v_2 \left\{ 2 \frac{a\beta_{hv}^*}{N_h^0} (\eta_v w_6 + w_7) (w_2 + w_3 + w_4) \right\} \\
&+ v_6 \left\{ 2 \frac{a\beta_{vh} S_v^0}{(N_h^0)^2} (\eta_h w_2^2 + (\eta_h + 1) w_2 w_3 + \eta_h w_2 w_4 + \eta_h w_3^2 + w_3 w_4) \right. \\
&\quad \left. + 2 \frac{a\beta_{vh}(k_8 + \gamma_v)}{\gamma_v N_h^0} (\eta_h w_2 + w_3) w_7 \right\}.
\end{aligned} \tag{69}$$

According to (17) and (18), we have $\zeta_1 > 0$ and $\zeta_2 > 0$.

We then have

$$\begin{aligned}
\mathcal{A}_2 &= v_2 \sum_{i=1}^{10} w_i \frac{\partial^2 f_2(0, 0)}{\partial x_i \partial \phi} \\
&= v_2 \left(w_6 \frac{\partial^2 f_2}{\partial E_v \partial \phi}(0, 0) + w_7 \frac{\partial^2 f_2}{\partial E_v \partial \phi}(0, 0) \right) \\
&= v_2 \left(\eta_h w_6 \frac{aS_v^0}{N_h^0} + w_7 \frac{aS_v^0}{N_h^0} \right) \\
&= \frac{aS_v^0}{N_h^0} (\eta_h w_6 + w_7) v_2.
\end{aligned}$$

E Proof of Theorem 5

We follow the approach given in [52]. At this aim, note that equation (58) may be written as

$$F(\beta_{hv}, \lambda_h) := d_2(\lambda_h^*)^2 + d_1\lambda_h^* + d_0 = 0, \quad (70)$$

where d_2 , d_1 and d_0 are the same coefficients as in (58). Thus, the positive endemic equilibria of model (6) are obtained by solving (70) for positive λ_h^* and substituting the results into (55). Clearly, the coefficient d_2 , of (70), is always negative while d_1 and d_0 may change sign. Therefore, there is a single endemic equilibrium if and only if $d_0 > 0$, which correspond to $\mathcal{R}_0 > 1$. There are two endemic equilibria if and only if $d_0 < 0$, $d_1 > 0$ and $d_1^2 - 4d_2d_0 > 0$. Now, first remember that $d_0 < 0$ (i. e. $\mathcal{R}_0 < 1$) is equivalent to $\beta_{hv} < \beta_{hv}^*$, where β_{hv}^* is given at Eq. (16).

Then, inequality $d_1 > 0$, is equivalent to

$$\beta_{hv} > \bar{\beta} \quad (71)$$

where $\bar{\beta}$ is given by (23).

Finally, equation $d_1^2 - 4d_2d_0 = 0$, in terms of β_{hv} , is equivalent to

$$\alpha_2\beta_{hv}^2 + \alpha_1\beta_{hv} + \alpha_0 = 0, \quad (72)$$

where $\alpha_2 = k_3^2 k_4^2 k_{10}^2 k_{11}^2 a^4 \mu_h^2 (N_v^0)^2 \beta_{vh}^2$, $\alpha_0 = k_3^2 k_4^2 k_{10}^2 a^2 \mu_h^4 (N_h^0)^2 \beta_{vh}^2$, and $\alpha_1 = 2k_3 k_4 k_{10} k_{11} a^2 \mu_h^2 N_h^0 N_v^0 \beta_{vh} [2k_2(k_{10} a \mu_h \beta_{vh} - k_8 \delta \gamma_h) - k_3 k_4 k_{10} a \mu_h \beta_{vh}]$.

Now we compute the discriminant $\Delta := \alpha_1^2 - 4\alpha_2\alpha_0$, to obtain:

$$\Delta = -16k_3^2 k_4^2 k_{10}^2 k_{11}^2 \delta \gamma_h a^4 \mu_h^4 (N_h^0)^2 (N_v^0)^2 \beta_{vh}^2 (k_{10} a \mu_h \beta_{vh} + k_8 k_2) (k_{10} a \mu_h \beta_{vh} - \delta \gamma_h k_8).$$

Equation (72) admits a real solution if and only if $\Delta \geq 0$. This condition is equivalent to

$$\psi := k_{10} a \mu_h \beta_{vh} - \delta \gamma_h k_8 \leq 0 \quad (73)$$

Under condition (73), we conclude that $\alpha_1 < 0$. Thus, Eq. (72) admits exactly two positive solutions which are given by

$$\begin{aligned} \beta_{\pm} &= \frac{-\alpha_1 \pm \sqrt{\Delta}}{2\alpha_2} \\ &= \frac{N_h^0}{k_3 k_4 k_{10} k_{11} a^2 N_v^0 \beta_{vh}} \left\{ \sqrt{\delta \gamma_h (a \mu_h \beta_{vh} k_{10} + k_2 k_8)} \pm \sqrt{(-k_2 \psi)} \right\}^2 \end{aligned}$$

Thus, condition $d_1^2 - 4d_2d_0 > 0$ written in the terms of β_{hv} is equivalent to

$$\beta_{hv} < \beta_- \quad \text{or} \quad \beta_{hv} > \beta_+.$$

and the inequalities (25) then follow.

Remark 3. Note that condition (25) is equivalent to condition (65). Therefore, Theorem 5 is equivalent to Theorem 3.

F Proof of Theorem 6

Considering the model (6) without disease-induced death in human, and applying the same procedure as appendix 3, we obtain that the non-zero equilibria of the basic model (6) satisfy the linear equation

$$(s\Gamma_E + k_6\Gamma_L)(p_1\lambda_h^* + p_0) = 0,$$

where $p_1 = \mu_b\Lambda_h k_9(k_2 a \mu_h \beta_{vh} + k_3 k_8(\mu_h + \sigma))$ and $p_0 = -\mu_h k_3 k_4 k_8 k_9 \mu_b \Lambda_h (\mathcal{R}_{0,\delta=0}^2 - 1)$.

Clearly, $p_1 > 0$ and $p_0 \geq 0$ whenever $R_{0,\delta=0} \leq 1$, so that $\lambda_h^* = -\frac{p_0}{p_1} \leq 0$. Therefore, the model (6) without disease-induced death in human, has no endemic equilibrium whenever $\mathcal{R}_{0,\delta=0} \leq 1$. The above result suggests the impossibility of backward bifurcation in the model (6) without disease-induced death, since no endemic equilibrium exists when $\mathcal{R}_{0,\delta=0} < 1$ (and backward bifurcation requires the presence of at least two endemic equilibria when $\mathcal{R}_{0,\delta=0} < 1$) [29, 56].

To completely rule out backward bifurcation in model (6), we use the direct Lyapunov method to prove the global stability of the DFE. Define the positively-invariant and attracting region

$$\mathcal{D}_1 = \{(S_h, E_h, I_h, R_h, S_v, E_v, I_v, E, L, P) \in \mathcal{D} : S_h \leq N_h^0; S_v \leq N_v^0\}.$$

Consider the Lyapunov function

$$\mathcal{G} = q_1 E_h + q_2 I_h + q_3 E_v + q_4 I_v,$$

where

$$q_1 = \frac{1}{k_3}; \quad q_3 = \frac{\tau_1 S_h^0 k_{11}}{k_3 k_8 k_9}, \quad q_2 = \frac{\tau_1 S_h^0 k_{11} \zeta_2 S_v^0}{k_3 k_8 k_4 k_9}, \quad q_4 = \frac{\tau_1 S_h^0}{k_3 k_8}.$$

and we have set $\tau_1 = \frac{\mu_h \beta_{hv}}{\Lambda_h}$ and $\tau_2 = \frac{\mu_h \beta_{vh}}{\Lambda_h}$. The derivative of \mathcal{G} is given by

$$\begin{aligned} \dot{\mathcal{G}} &= q_1 \dot{E}_h + q_2 \dot{I}_h + q_3 \dot{E}_v + q_4 \dot{I}_v \\ &= q_1(\lambda_h S_h - k_3 E_h) + q_2(\gamma_h E_h - k_4 I_h) + q_3(\lambda_v S_v - k_9 E_v) + q_4(\gamma_v E_v - k_8 I_v) \\ &= q_1 \tau_1 S_h (\eta_v E_v + I_v) - q_3 k_9 E_v + q_4 \gamma_v E_v - q_4 k_8 I_v + q_3 \tau_2 S_v (\eta_h E_h + I_h) - q_1 k_3 E_h + q_2 \gamma_h E_h - q_2 k_4 I_h \\ &= (q_1 \tau_1 S_h \eta_v + q_4 \gamma_v - q_3 k_9) E_v + (q_1 \tau_1 S_h - q_4 k_8) I_v + (q_3 \tau_2 S_v \eta_h + q_2 \gamma_h - q_1 k_3) E_h + (q_3 \tau_2 S_v - q_2 k_4) I_h \\ &\leq (q_1 \tau_1 S_h^0 \eta_v + q_4 \gamma_v - q_3 k_9) E_v + (q_1 \tau_1 S_h^0 - q_4 k_8) I_v + (q_3 \tau_2 S_v^0 \eta_h + q_2 \gamma_h - q_1 k_3) E_h + (q_3 \zeta_2 S_v^0 - q_2 k_4) I_h, \\ &\text{since } S_h \leq S_h^0, S_v \leq S_v^0 \text{ in } \mathcal{D}_1. \end{aligned}$$

Replacing q_i , $i = 1, \dots, 4$, by their value gives after straightforward simplifications

$$\dot{\mathcal{G}} \leq (\mathcal{R}_{0,\delta=0}^2 - 1) E_h$$

We have $\dot{\mathcal{G}} \leq 0$ if $\mathcal{R}_{0,\delta=0} \leq 1$, with $\dot{\mathcal{G}} = 0$ if $\mathcal{R}_{0,\delta=0} = 1$ or $E_h = 0$. Whenever $E_h = 0$, we also have $I_h = 0$, $E_v = 0$ and $I_v = 0$. Substituting $E_h = I_h = E_v = I_v = 0$ in the first, fourth and fifth equation of Eq. (6) with $\delta = 0$ gives $S_h(t) \rightarrow S_h^0 = N_h^0$, $R_h(t) \rightarrow 0$, and $S_v(t) \rightarrow S_v^0 = N_v^0$ as $t \rightarrow \infty$. Thus

$$\begin{aligned} [S_h(t), E_h(t), I_h(t), R_h(t), S_v(t), E_v(t), I_v(t), E(t), L(t), P(t)] &\rightarrow (N_h^0, 0, 0, 0, N_v^0, 0, 0, E, L, P) \\ \text{as } t &\rightarrow \infty. \end{aligned}$$

It follows from the LaSalle's invariance principle [32, 36, 37] that every solution of (6) (when $\mathcal{R}_{0,\delta=0} \leq 1$), with initial conditions in \mathcal{D}_1 converges to \mathcal{E}_1 , as $t \rightarrow \infty$. Hence, the DFE, \mathcal{E}_1 , of model (6) without disease-induced death, is GAS in \mathcal{D}_1 if $\mathcal{R}_{0,\delta=0} \leq 1$.

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