



Stability Analysis and Optimal Control for Yellow Fever Model with Vertical Transmission

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Abstract

In this study, a deterministic model for the transmission dynamics of yellow fever (YF) in a human–mosquito setting in the presence of control measures is constructed and rigorously analyzed. In addition to horizontal transmissions, vertical transmission within mosquito population is incorporated. Analysis of the mosquito-only component of the model shows that the reduced model has a mosquito-extinction equilibrium, which is globally-asymptotically stable whenever the basic offspring number (N_0) is less than unity. The vaccinated and type reproduction numbers of the full-model are computed. Condition for global-asymptotic stability of the disease-free equilibrium of the model when $N_0 > 1$ is presented. It is shown that, fractional dosing of YF vaccine does not meet YF vaccination requirements. Optimal control theory is applied to the model to characterize the controls parameters. Using Pontryagin’s maximum principle and modified forward–backward sweep technique, the necessary conditions for existence of solutions to the optimal control problem is determined. Numerical simulations of the models to assess the effect of fractional vaccine dosing on the disease dynamics and global sensitivity analysis are presented.

Keywords Yellow fever virus · Basic offspring number · Vaccination reproduction number · Metzler matrix · Stability analysis · Optimal control

Introduction

Yellow fever (YF) is an acute viral haemorrhagic fever that is transmitted by mosquitoes of the *Aedes* and *Haemogogus* species. It is endemic in Africa, Central and South America, where approximately one billion people in forty seven countries are at risk. Symptoms of the disease include fever, headache, jaundice, muscle pain, nausea, vomiting and fatigue [5,44,47,48]. In broad terms, YF can either be jungle or urban. Jungle YF occurs in tropical rain-forest. In Africa, it is usually transmitted by *Aedes africanus* while in South America by *Haemagogus* species [6,47,48]. Urban YF is transmitted by *Aedes aegypti*, that it characterized by rapid amplification, capacity for international spread and has devastating effect on public health,

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socio-economic and political life [47]. Once a mosquito is infected, it lives with the disease for the rest of its life and hence they can be considered as the reservoir for the virus. On the other hand, monkeys have brief viremia and can be considered to be amplifying hosts [6].

Unfortunately, the threats posed by YF have largely been forgotten, just a bit more than a century ago, it was a source of terror, decimating populations of cities, destroying economies and driving political chaos. Extensive, repeated epidemics in North American and European port cities during the 18th and 19th centuries spread panic, shutting down affected cities and killing hundreds of thousands of people [47]. Despite the availability of very effective YF vaccine, the disease has however continuously persist in Africa and South America, often with high mortality rate [5]. In general terms, forty seven countries are either YF endemic or have some regions that are YF endemic, thirty four of those countries are in Africa with thirteen in South and Central America. A modeling study based on African data sources estimated that, the burden of YF in the year 2013 was between 84,000 to 170,000 severe cases, and 29,000 to 60,000 deaths [47].

Vertical transmission of YF virus occurs when orally infected female mosquitoes pass the virus to their progeny (transovarial transmission) [13]. First evidence of vertical transmission of YF virus was reported as far back as 1997 [20]. Apart from experimental proof for the vertical transmission of YF, entomological surveys also provide more evidences of vertical transmission of YF virus in mosquitoes. The virus was isolated from wild mosquitoes and recently emerged adults from larvae collected in the field [13]. In fact, during dry seasons (when mosquito breeding is not favorable), YF virus survival can be attributed to vertical transmission from infected female mosquitoes to their eggs, at which point the viral particles are stable for long periods and can be reactivated when the progeny emerges under better conditions [6,45]. Thus, vertical transmission is incorporated in this study.

There is no specific treatment for YF infection, but care to specifically treat cases of dehydration, liver failure, fever and kidney failure is often administered to improve outcomes. Thus, early detection and good supportive treatment in hospitals improve possibility of survival. In the case of bacterial infections, it can also be treated with antibiotics [48]. Mosquito control is an important (perhaps the most important) component of preventing and controlling transmission of vector borne diseases. It requires knowledge of both mosquito biology and local conditions to be used in choosing the best interventions (habitat modification, water management, sanitation or pesticides) on a site-specific basis [42]. In this study, we only consider the use of pesticides, which can be achieved either by the use of adulticides (agents to clear adult mosquitoes) or larvicides (agents aimed at eliminating potential mosquito breeding sites) [42,48]. Adulticides are most often applied as a very fine ultra low-volume (ULV) droplet spray from a truck or aircraft, it is usually organophosphate insecticides and/or synthetic pyrethroids and their combinations [40,42]. Some larvicide agents are specific to mosquitoes and when use according to directions will have relatively little impact on the environment and human health. They can prevent the emergence of adult mosquitoes for up to 1 month, which decreases labour costs [42].

After the isolation of YF in 1927, there were unsuccessful efforts to produce inactivated vaccines in the early twentieth century, thus, subsequent developments focused on live virus products and yield the production of a safe, effective vaccine against YF called the 17D strain (originally developed by Theiler and Smith in 1936) [5,33]. One vaccine dose can provide life-long immunity at an affordable rate of 1 US dollar. Angola was in 2016 hit by an unprecedented outbreak of urban YF which spread to beyond its borders and generates local transmissions. The epidemic creates an urgent need for more than 28 million doses of YF vaccines, the demand exhausted the existing global vaccine supply. It also diverted health authorities from tackling other important public health issues, which impacted on health care

delivery in general [47,48]. In order to ensure adequate supply of vaccine especially in high risk regions, the Eliminate Yellow Fever Epidemics (EYE) strategy, steered by World Health Organization, UNICEF and Gavi, the Vaccine Alliance was inaugurated. The vision of EYE is to have a world without YF epidemics. Its mission is to coordinate international action and help countries at risk of the disease to prevent outbreaks and prepare for the inevitable cases, to minimize suffering, damage and spread through early and reliable detection as well as a rapid and appropriate response. The initiative has three strategic objectives: they include protecting at-risk populations, preventing international spread, and containing outbreaks rapidly [47].

Yellow fever has attracted less modeling studies when compared with other mosquito borne diseases such as malaria, dengue, West Nile and Zika virus. To study population dynamics of *Aedes aegypti* (mosquitoes responsible for YF transmission), Dye [17] proposed an appropriate continuous time model that described a field population of adult *Aedes aegypti* mosquito. Recently, Martorano et al., constructed and analysed a compartmental model for the transmission of YF with vaccination [32], although vertical transmission is not accounted for in their model, both aquatic and non-aquatic stages of mosquito development were considered. An urban YF epidemic model was also formulated and used to study the 2016 YF outbreak in Luanda, Angola by Zhao et al. [50]. Their model successfully fits the time series of weekly reported YF cases and deaths during the epidemic in Angola [50]. Monica et al. [34] looked at a YF model in a human-vector-primate setting with vaccination in human population. To estimate the incubation periods of YF virus in both human and mosquito populations, four statistical models of incubation periods were fitted with historical data in [26].

In this work, we extend the model in [32] by incorporating vertical transmission in mosquito population. In addition to vaccination of susceptible humans, the proposed model also incorporates the use of treated bed nets, larvicides and adulticides in mosquito control. The work is organized as follows: Introduction and short review of relevant literature is presented in “Introduction” section. A deterministic model for the transmission dynamics of YF is constructed and analyzed for its basic dynamical features in “Model Formulation” section. Analyses of the full model is provided in “Analysis of the Full Model” section. Threshold quantities and stability analysis of equilibria are also explored in this section. Optimal control form of the model is presented and analyzed in “YF Model for Optimal Control” section. Sensitivity analysis and numerical simulations are presented in “Sensitivity Analysis and Numerical Simulation” section.

Model Formulation

Following compartmental modeling approach, the total human population at time t , denoted by, $N_H(t)$, is divided into five mutually exclusive compartments of susceptible ($S_H(t)$), vaccinated ($V_H(t)$), exposed ($E_H(t)$), infected ($I_H(t)$) and recovered ($R_H(t)$) humans. So that

$$N_H(t) = S_H(t) + V_H(t) + E_H(t) + I_H(t) + R_H(t).$$

Mosquito population is split into aquatic (immature) and non-aquatic (mature) stages. For mathematical tractability, different development stages of the aquatic mosquito population (eggs, larvae and pupae) are lumped into a single compartment $A(t)$. Furthermore, to incorporate vertical transmission, the aquatic mosquito population are further divided into infectious ($A_I(t)$) and non-infectious ($A_N(t)$) mosquitoes. So that the total mosquito population at the aquatic stage at time t , is given by

$$A(t) = A_I(t) + A_N(t).$$

Similarly, the total mosquito population at non-aquatic stage (adult) at time t , denoted by $N_V(t)$, is sub-divided into susceptible ($S_V(t)$) and infectious ($I_V(t)$) mosquitoes. So that

$$N_V(t) = S_V(t) + I_V(t).$$

Incidence Function

The frequency-dependent (standard) incidence function is the most widely used form of incidence in vector borne disease models. Infection from mosquitoes to humans occur after an infectious mosquito bites a susceptible human at a rate b_{VH} , let ρ_{VH} be a transmission probability from an infectious mosquito to susceptible human, then the infection rate of humans is $\beta_{VH} = \rho_{VH}b_{VH}$. Therefore the force of infection in humans is given by

$$\lambda_H = \rho_{VH}b_{VH} \frac{I_V}{N_V} = \beta_{VH} \frac{I_V}{N_V}. \tag{1}$$

Similarly, let $\beta_{HV} = \rho_{HV}b_{HV}$ be the rate at which susceptible mosquitoes acquire infection from infectious human, where ρ_{HV} is the probability of transmission from an infectious human to a susceptible mosquito and b_{HV} is the biting rate of a susceptible mosquito. Then the force of infection in mosquito population (due to horizontal transmission) is given by

$$\lambda_V = \rho_{HV}b_{HV} \frac{I_H}{N_H} = \beta_{HV} \frac{I_H}{N_H}. \tag{2}$$

Since mosquitoes bite both susceptible and infected humans, for the total number of bites to be conserved, it is assumed that the total number of bites by the mosquitoes must be equal to the total number of bites received by humans (and this depends on the total sizes of the populations of humans and mosquitoes), see [8,10,12,21,22,36]. Thus

$$\beta_{VH}(N_H, N_V)N_H = \beta_{HV}N_V, \text{ so that, } N_V = \frac{\beta_{VH}(N_H, N_V)}{\beta_{HV}}N_H, \tag{3}$$

Substituting Eq. (3) into Eq. (1), we have

$$\lambda_H = \beta_{HV} \frac{I_V}{N_H}. \tag{4}$$

The population of susceptible humans is generated by birth (or immigration) at a constant rate b_H . Fraction of this population are vaccinated at a rate c_V , since the vaccine is not perfect, it wanes at a rate ω_H . This population is decreased through infection at a rate $(1 - r_B\epsilon_B)\lambda_H$ (where r_B is the rate of using treated bed-nets and ϵ_B is the efficacy of bed nets). Natural mortality occurs in all human classes at a rate μ_H . The population of vaccinated humans is generated by vaccination of susceptible individuals at the rate c_V . This population decreases due to waning of vaccine at the rate ω_H , by infection at the rate $(1 - r_B\epsilon_B)(1 - \epsilon)\lambda_H$ (where $0 < \epsilon < 1$ is a vaccine efficacy) and due to natural death. The populations of exposed humans (E_H) is generated by the infection of susceptible (S_H) and vaccinated (V_H) humans at the rates $(1 - r_B\epsilon_B)\lambda_H$ and $(1 - r_B\epsilon_B)(1 - \epsilon)\lambda_H$, respectively. These populations reduces by progressing to infectious class at a rates γ_H , and by natural death. The populations of infectious humans (I_H) is generated by progression of exposed individuals to the infectious class at the rate γ_H . It decreases by recovery at the rate τ_H , natural death and disease-induced death at the rate δ_H . Recovered humans population increases by the recovery of infectious humans at the rate τ_H and decreases due to natural death.

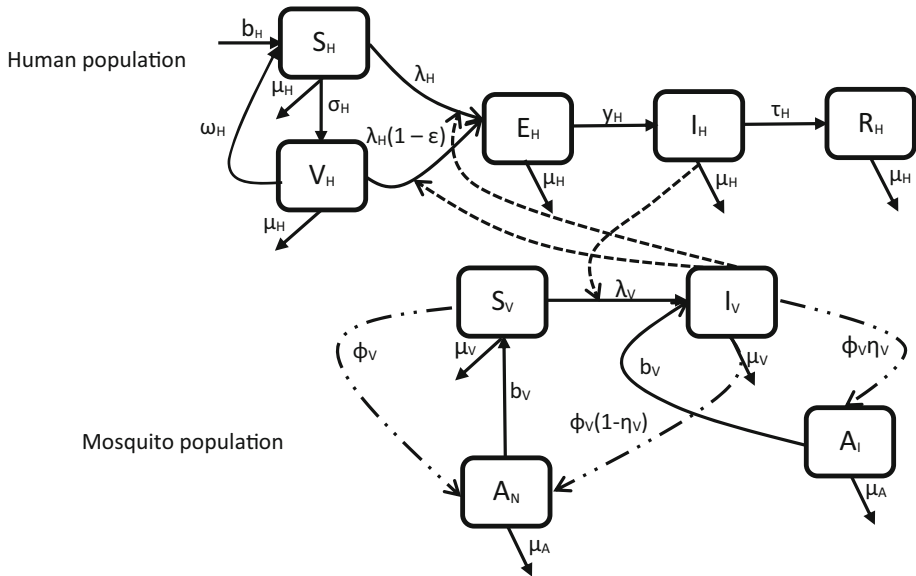


Fig. 1 Schematic diagram of the model (5)

The population of aquatic mosquitoes (eggs, larvae and pupae) increases through oviposition by reproductive mosquitoes (infected and non-infected) at a rate ϕ_V . The aquatic mosquitoes mature to adulthood at a rate b_V , die naturally at a rate μ_A and due to the use of larvicides at a rate $c_L = r_L e_L$ (where r_L is the rate of applying larvicides and e_L is the efficacy of larvicides).

The population of susceptible adult mosquitoes is generated by maturation of non-infectious mosquitoes from the aquatic stage at the rate b_V and decreases by infection and move to infectious class at a rate $(1 - r_{B \in B})\lambda_V$, they die naturally at a rate μ_V and due to the use of adulticides at a rate $c_A = r_A e_A$ (where r_A is the rate of applying adulticides and e_A is the efficacy of adulticides). Finally, The population of infectious adult mosquitoes is generated by maturation of infected mosquitoes from the aquatic stage at the rate b_V and by infection of susceptible mosquitoes. This population is reduced by natural death at the rate μ_V and due to the use of adulticides at a rate c_A .

The time independent YF transmission model with vaccination (and vertical transmission in mosquitoes) is represented by the following system of non-linear ordinary differential equations (a flow diagram of the model is depicted in Fig. 1 and the state variables and parameters of the model are described in Table 1):

$$\text{Humans} \left\{ \begin{aligned} \frac{dS_H}{dt} &= b_H + \omega_H V_H - c_V S_H - \beta_{HV}(1 - r_{B \in B}) \frac{I_V}{N_H} S_H - \mu_H S_H, \\ \frac{dV_H}{dt} &= c_V S_H - \beta_{HV}(1 - r_{B \in B})(1 - \epsilon) \frac{I_V}{N_H} V_H - \omega_H V_H - \mu_H V_H, \\ \frac{dE_H}{dt} &= \beta_{HV}(1 - r_{B \in B}) \frac{I_V}{N_H} S_H + \beta_{HV}(1 - r_{B \in B})(1 - \epsilon) \frac{I_V}{N_H} V_H - \gamma_H E_H - \mu_H E_H, \\ \frac{dI_H}{dt} &= \gamma_H E_H - \delta_H I_H - \tau_H I_H - \mu_H I_H, \\ \frac{dR_H}{dt} &= \tau_H I_H - \mu_H R_H, \end{aligned} \right. \quad (5)$$

$$\text{Mosquitoes} \begin{cases} \frac{dA_N}{dt} = \phi_V \left(1 - \frac{A}{\mathcal{K}}\right) S_V + \phi_V (1 - \eta_V) \left(1 - \frac{A}{\mathcal{K}}\right) I_V - b_V A_N - \mu_A A_N - c_L A_N, \\ \frac{dA_I}{dt} = \phi_V \eta_V \left(1 - \frac{A}{\mathcal{K}}\right) I_V - b_V A_I - \mu_A A_I - c_L A_I, \\ \frac{dS_V}{dt} = b_V A_N - \beta_{HV} (1 - r_{B \in B}) \frac{I_H}{N_H} S_V - \mu_V S_V - c_A S_V, \\ \frac{dI_V}{dt} = \beta_{HV} (1 - r_{B \in B}) \frac{I_H}{N_H} S_V + b_V A_I - \mu_V I_V - c_A I_V. \end{cases}$$

It is assumed that, all the model parameters are positive and initial conditions are non-negative. In addition, let $A_N + A_I = A$ so that

$$\frac{dA}{dt} = \phi_V \left(1 - \frac{A}{\mathcal{K}}\right) [S_V + I_V] - b_V A - \mu_A A - c_L A, \tag{6}$$

which is the standard formulation for aquatic mosquitoes with density dependent and independent death rate, see for instance [15,16].

Lemma 2.1 *The following biologically feasible region of the model (5)*

$$\Omega = \left\{ S_H, V_H, E_H, I_H, R_H, A_N, A_I, S_V, I_V \in \mathbb{R}_+^9 : S_H + V_H + E_H + I_H + R_H \leq \frac{b_H}{\mu_H}, \right. \\ \left. A_N \leq \mathcal{K}, \quad A_I \leq \mathcal{K}, \quad S_V + I_V \leq \frac{\mathcal{K}b_V}{\mu_V + c_A} \right\} \tag{7}$$

is positively-invariant and attracting.

Proof It is easy to see that solution to the system (5) exists locally and it is unique (system (5) is C^1 in \mathbb{R}_+^{10}). Observe that $A_N + A_I \leq \mathcal{K}$, thus $A_N(t) \leq \mathcal{K}$ and $A_I(t) \leq \mathcal{K}$. Therefore by Gronwall’s lemma we have

$$N_H(t) \leq N_H(0)e^{-\mu_H t} + \frac{b_H}{\mu_H} \left(1 - e^{-\mu_H t}\right), \tag{8}$$

$$N_V(t) \leq N_V(0)e^{-(\mu_V + c_A)t} + \frac{\mathcal{K}b_V}{\mu_V + c_A} \left(1 - e^{-(\mu_V + c_A)t}\right),$$

which are bounded and hence solution exists for all $t \geq 0$. In addition, $N_H(t) \leq \frac{b_H}{\mu_H}$ if $N_H(0) \leq \frac{b_H}{\mu_H}$ and $N_V(t) \leq \frac{\mathcal{K}b_V}{\mu_V + c_A}$ if $N_V(0) \leq \frac{\mathcal{K}b_V}{\mu_V + c_A}$. Consequently, solution of the system (5) with initial condition in Ω remains in Ω for all $t > 0$ (the ω -limits set of the system are contained in Ω). \square

Having obtained the positively-invariant and attracting domain for the system (5), it is sufficient to consider the asymptotic properties of dynamics of the flow generated by the system.

Mosquito-Only Equilibria

Consider the mosquito component of the model given by (5) in the absence of interaction with humans. By direct computation, we obtained a threshold termed as the basic offspring

Table 1 Description of the variables and parameters for the model (5)

Var.	Interpretation		
S_H	Susceptible humans		
V_H	Vaccinated humans		
E_H	Exposed humans		
I_H	Infected humans		
R_H	Recovered humans		
A_N	Non-infected aquatic mosquitoes		
A_I	Infected aquatic mosquitoes		
S_V	Susceptible mosquitoes		
I_V	Infected mosquitoes		
N_H	Total human population		
N_V	Total matured mosquitoes		
N_M	Total mosquito population		

Par.	Interpretation	Range	Ref.
c_V	Successful rate of vaccination	0 – 0.043	[32,37,44]
ϵ	Vaccine efficacy	0.8–0.99	[24,33,37]
ω_H	Waning rate of vaccine	(0, 1)	[32]
c_B	Rate of successful use of bed net	0–0.95	[9]
b_H	Recruitment rate of humans	10–800	[4,8]
μ_H	Natural death rate of humans	3×10^{-5} – 6×10^{-5}	[1,21,23,32]
γ_H	Progression rate of exposed humans	0.167–0.3	[26,48,50]
δ_H	Disease induced death rate of humans	0.0001–0.0004	[12,32]
τ_H	Recovery rate of humans	0.25–0.33	[32,48,50]
μ_A	Natural death rate of aquatic mosquito	0.2–0.33	[15,16]
μ_V	Natural death rate of mosquitoes	0.0287–0.25	[1,32,50]
c_L	Mosquito death rate due to larvicides	(0, 1)	Assumed
c_A	Mosquito death rate due to adulticides	(0, 1)	[7,9]
ϕ_V	Mosquito oviposition rate	(1, 50)	[2,15,16]
η_V	Vertical transmission rate	(0, 1)	[13,20]
b_V	Mosquito maturation rate	0.05–0.1	[2,15,16]
\mathcal{K}	Mosquito carrying capacity	5×10^1 – 9.8×10^7	[4,32]
b_{HV}	Biting rate of mosquitoes	0.3–1	[1,15,50]
ρ_{HV}	Transmission probability from I_H to S_V	0.5–1	[1,50]
ρ_{VH}	Transmission probability from I_V to S_H	0.1–0.75	[1,15,50]
β_{VH}	Infection rate of humans	0.03–0.75	[1,50]
β_{HV}	Infection rate of mosquitoes	0.15–1	[1,50]

number (N_0) given by

$$N_0 = \frac{\phi_V b_V}{(b_V + \mu_A + c_L)(\mu_V + c_A)}. \tag{9}$$

It is defined as the average number of offspring produced by a female mosquito in her entire lifespan in the absence of interaction with humans. It can be interpreted as follows. The average time spent by mosquito in the aquatic stage is given by $\frac{1}{b_V + \mu_A + c_L}$, where b_V is the rate at which aquatic mosquitoes mature into an adult mosquito, so that the probability that an aquatic mosquito develops into an adult female mosquito is given by

$$\frac{b_V}{b_V + \mu_A + c_L}. \tag{10}$$

The average life expectancy of an adult female mosquito is given by $\frac{1}{\mu_V + c_A}$, so that the average eggs laid by an adult female mosquito throughout her life span is given by

$$\frac{\phi_V}{\mu_V + c_A}. \tag{11}$$

where ϕ_V is the oviposition rate of a female mosquito. Thus, the product of (10) and (11) gives (9), the basic offspring number of the mosquito-only population model.

The mosquito component of model (5) has an extinction disease-free equilibrium obtained when $N_0 \leq 1$, denoted by \mathcal{E}_0 , given by

$$\mathcal{E}_0 = (A_N^*, A_I^*, S_V^*, I_V^*) = (0, 0, 0, 0),$$

and non-extinction disease-free equilibrium obtained when $N_0 > 1$, denoted by \mathcal{E}_1 , that is given by

$$\mathcal{E}_1 = (A_N^*, A_I^*, S_V^*, I_V^*) = \left[\mathcal{K} \left(1 - \frac{1}{N_0} \right), 0, \frac{b_V \mathcal{K}}{\mu_V + c_A} \left(1 - \frac{1}{N_0} \right), 0 \right].$$

Theorem 2.2 *The mosquito extinction equilibrium, \mathcal{E}_0 , is globally-asymptotically stable (GAS) when $N_0 \leq 1$ and unstable otherwise. The equilibrium \mathcal{E}_1 exists and it is locally-asymptotically stable (LAS) when $N_0 > 1$.*

The proof of the theorem is given in ‘‘Appendix A’’. The epidemiological implication of Theorem (2.2) is that, if the basic offspring number can be brought to a value below unity, then the mosquito population goes to extinction and horizontal transmission can be avoided. It is worth mentioning that this result is not attainable.

Analysis of the Full Model

Disease-Free Equilibria

The disease-free equilibrium of the model given by (5) depends on N_0 . If $N_0 \leq 1$ a mosquito extinction DFE (\mathcal{E}_2) is obtained, while a mosquito persistent equilibrium (\mathcal{E}_3) is obtained when $N_0 > 1$. Thus

$$\mathcal{E}_2 = (S_H^*, V_H^*, E_H^*, I_H^*, R_H^*, A_N^*, A_I^*, S_V^*, I_V^*) = \left(\frac{b_H(\omega_H + \mu_H)}{K_1 \mu_H}, \frac{c_V b_H}{K_1 \mu_H}, 0, 0, 0, 0, 0, 0, 0 \right),$$

and

$$\mathcal{E}_3 = \left(S_H^*, V_H^*, E_H^*, I_H^*, R_H^*, A_N^*, A_I^*, S_V^*, I_V^* \right), \\ = \left[\frac{b_H(\omega_H + \mu_H)}{K_1\mu_H}, \frac{c_V b_H}{K_1\mu_H}, 0, 0, \mathcal{K} \left(1 - \frac{1}{N_0} \right), 0, \frac{\mathcal{K} b_V}{K_5} \left(1 - \frac{1}{N_0} \right), 0, 0 \right],$$

where $K_1 = c_V + \omega_H + \mu_H$, $K_2 = \gamma_H + \mu_H$, $K_3 = \delta_H + \tau_H + \mu_H$, $K_4 = b_V + \mu_A + c_L$ and $K_5 = \mu_V + c_A$.

For the case, when $N_0 < 1$, the associated reproduction number obtained by linearizing the system about \mathcal{E}_2 is given by $R_{vv} = \frac{\phi_V \eta_V b_V}{N_0 K_4 K_5} = \eta_V$. The detail computation is provided in ‘‘Appendix B’’.

Lemma 3.1 *The mosquito extinction DFE given by, \mathcal{E}_2 , is locally-asymptotically stable if the vectorial vertical transmission reproduction number $R_{vv} = \eta_V \leq 1$ and unstable otherwise [46].*

Remark The DFE, \mathcal{E}_2 , can be shown to be globally-asymptotically stable under the same condition. It is worth mentioning that, the mosquito extinction DFE, \mathcal{E}_2 , is less tractable (due to the absence of mosquito in the population).

For the DFE, \mathcal{E}_3 , obtained in the presence of mosquitoes ($N_0 > 1$), the vaccinated reproduction number (R_{0v}) is given by

$$R_{0v} = \frac{\eta_V}{2} + \sqrt{\left(\frac{\eta_V}{2} \right)^2 + \frac{\beta_{HV}^2 S_V^* (1 - c_B)^2 \gamma_H}{N_H^* K_2 K_3 K_5} \left(1 - \frac{V_H^* \epsilon}{N_H^*} \right)}, \tag{12}$$

where $c_B = r_{B \in B}$ is the rate of reducing contact between humans and mosquitoes through the use of bed nets. The threshold quantity, R_{0v} is the average number of new secondary cases that one infected individuals can produce in a totally naive population, where a fraction of the population is vaccinated. The computation of the threshold is presented in ‘‘Appendix C’’.

The disease can be controlled in a community through appropriate measures such as reducing the carrying capacity of mosquito population, use of larvicides, adulticides or repellents to the extent of lowering R_{0v} to a value below unity. Effective mosquito control strives to prevent large swarms of adult mosquitoes in an environment through the application of chemical substances called adulticides. They can be applied either aerially or on the ground. Droplets of the chemicals that make physical contact with mosquitoes usually kill them, while large droplets that missed target and settle on surfaces may cause undesirable harm. To achieve small droplets, adulticides are mostly applied in the air as a very fine ultra low-volume (ULV) droplet spray from a truck or aircraft, it is usually organophosphate insecticides and/or synthetic pyrethroids and their combinations [40,42]. Through aerial or ground applications of larvicides, large population of aquatic mosquitoes can be killed. This method is often more effective and environmentally friendly than the use of adulticides. It should be noted that, larvicides are only administered at identified suspected breeding sites, where they are expected to clear populations of aquatic mosquitoes, conventional larvicides kill aquatic mosquitoes at every stage and therefore, they can be applied whenever necessarily. Some larvicides agents are specific to mosquitoes and when used according to directions will have relatively little impact on the environment and human health. They can prevent the emergence of adult mosquitoes for up to 1 month, which decreases labour costs [47]. In essence, larvicides can be specific for mosquitoes, they have minimal impact on other organisms and often penetrate even dense objects.

Threshold Analysis and Vaccine Impact

Here we analyse the potential impact of a single dose and a fractional dosing of vaccine. Since not all vaccine have positive impact in a population, it is therefore instructive to first of all assess the impact of vaccine.

In the absence of vaccination ($S_H^* = N_H^*$ when $V_H^* = 0$), the vaccinated reproduction reduces to

$$R_{0v} \Big|_{V_H^*=0} = \frac{\eta_V}{2} + \sqrt{\left(\frac{\eta_V}{2}\right)^2 + \frac{\beta_{HV}^2 S_V^* (1 - c_B)^2 \gamma_H}{N_H^* K_2 K_3 K_5}}. \tag{13}$$

Notice that $R_{0v} \leq R_0$ since $\frac{V_H^* \epsilon}{N_H^*} \geq 0$. Thus, vaccination of individuals will have positive impact in the community by reducing the value of the associated reproduction number R_0 .

Furthermore, the impact of vaccination can be analysed qualitatively by differentiating R_{0v} with respect to the fraction of vaccinated individuals (V). It can be shown that

$$\frac{\partial R_{0v}}{\partial V} = \frac{-\beta_{HV}^2 S_V^* (1 - c_B)^2 \gamma_H \epsilon}{2 K_2 K_3 K_5 N_H^* \sqrt{\left[\frac{\eta_V}{2}\right]^2 + \frac{\beta_{HV}^2 S_V^* (1 - c_B)^2 \gamma_H}{(N_H^*)^2 K_2 K_3 K_5} [S_H^* + V_H^* (1 - \epsilon)]}} < 0. \tag{14}$$

Thus, R_{0v} is a decreasing function of V . Since the reproduction number measures disease burden, the vaccination will have a positive impact in disease control.

Standard Dosing

Based on the available clinical data [47], the minimum standard dose administered should preferentially contains 3000 international units (IU)/dose, but no less than 1000 IU/dose. Let $V = \frac{V_H^*}{N_H^*}$ ($V \leq 1$) be the fraction of the vaccinated individuals at steady-state (when standard dose of YF vaccine is issued). Then solving for $R_{0v} = 1$ we obtained

$$V_c = \frac{1}{\epsilon} \left[1 - \frac{\{1 - \eta_V\} N_H^* K_2 K_3 K_5}{\beta_{HV}^2 S_V^* (1 - c_B)^2 \gamma_H} \right]. \tag{15}$$

Thus, for the vaccination to be effective in bringing $R_{0v} < 1$, the fraction of vaccinated individuals (V_c) at steady-state must be greater than the vaccinated threshold ratio ($V > V_c$) defined in Eq. (15). Notice that if $\eta_V = 1$, that is the case when all eggs laid by infected female mosquitoes are infected, then it is highly unlikely for any vaccine coverage to bring R_{0v} to a value less than unity (in this settings) since the critical vaccination rate reduces to $V_c = \frac{1}{\epsilon}$.

Lemma 3.2 *The DFE, \mathcal{E}_3 , of the model (5) is locally-asymptotically stable if $\eta_V < 1$ and $V > V_c$. It is unstable otherwise.*

The proof follows from Theorem 2 of [46] and the fact that $R_{0v} < 1$ if and only if $\eta_V < 1$ and $V > V_c$.

Backward Bifurcation

Consider the model (5) with $N_0 > 1$. We claim the following result (the proof of the Theorem is presented in ‘‘Appendix D’’).

Theorem 3.3 *The yellow fever model (5) undergoes backward bifurcation at $R_{0v} = 1$ whenever the bifurcation coefficient a , given by (D.3) is positive.*

The epidemiological implication of the phenomenon of backward bifurcation is that the classical requirement of $\mathcal{R}_{0v} < 1$ is, although necessary, no longer sufficient for the effective control of the disease in the population [3]. Hence, the presence of backward bifurcation makes the feasibility of the effective control of YF in a population difficult. In the next section, the possible cause(s) of this phenomenon is(are) explored.

Global Asymptotic Stability of \mathcal{E}_3

Here, a global asymptotic stability of the non-extinction equilibrium, (\mathcal{E}_3) , is presented To confirm the absence of backward bifurcation in the model (5) for a special case when disease induced mortality in human is negligible ($\delta_H = 0$). Consider the model (5) with $N_0 > 1$ and $\delta_H = 0$.

Lemma 3.4 *Consider the subset Ω^* of Ω defined in (7) given by*

$$\Omega^* = \left\{ S_H, V_H, E_H, I_H, R_H, A_N, A_I, S_V, I_V \in \mathbb{R}_+^9 : S_H + V_H + E_H + I_H + R_H \leq \frac{b_H}{\mu_H}, \right. \\ \left. A_N \leq \mathcal{K}, \quad A_I \leq \mathcal{K}, \quad S_V + I_V \leq \frac{\mathcal{K}b_V}{\mu_V + c_A}, \right. \\ \left. S_V \leq S_V^* = \frac{\mathcal{K}b_V}{\mu_V + c_A} \left(1 - \frac{1}{N_0} \right), \quad 1 - \frac{1}{N_0} \leq \frac{A}{\mathcal{K}} \right\}.$$

We claim the following result

Theorem 3.5 *The non-extinction equilibrium (\mathcal{E}_3) of the model (5) is globally-asymptotically stable in the positively invariant set Ω^* if $\delta_H = 0$ and $\mathcal{R}_{0v} \leq 1$.*

The proof of the Theorem is presented in ‘‘Appendix E’’. This result shows that, in the absence of disease induced death, the DFE of the model (5) is GAS. Hence, the classical requirement of $\mathcal{R}_{0v} \leq 1$ is necessary and sufficient condition for disease elimination from the community provided $\delta_H = 0$ (thus, YF will be effectively controlled or eliminated from the population if $\mathcal{R}_{0v} \leq 1$). This result is consistent with that in [21], which suggests that disease induced death in humans is the main cause for the emergence of the backward bifurcation phenomenon in this setting.

Fractional Dosing

The best way to stretch vaccine supplies and protect as many people as possible to stop the spread of yellow fever in emergency situations is by using fractional dosing. Based on the available evidence, the Strategic Advisory Group of Experts (SAGE) on Immunization affirms that a fractional dose can be used as part of an exceptional response when there is a large outbreak and a shortage of vaccine [47,48]. In the case of dose fractionation, a smaller amount of antigen would be used per dose in order to increase the number of persons who can be vaccinated with a given quantity of vaccine. Studies show that the yellow fever vaccine given as one fifth of the regular dose, still provides full immunity against the disease for at least 12 months and likely longer [47,48]. This strategy was previously proposed

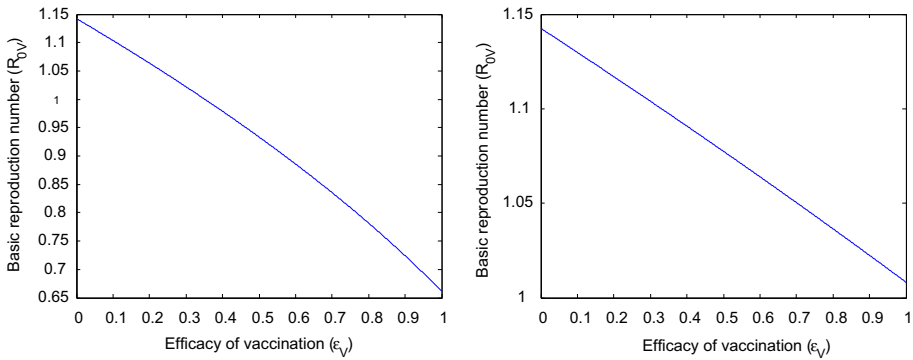


Fig. 2 Vaccinated reproduction number (R_{0v}) as a function of efficacy of vaccination with standard dose and fractionated threefold vaccines

to extend pre-pandemic influenza vaccine supplies [49]. Suppose each dose of vaccination is fractioned into m number of doses, so that the efficacy of the fractioned vaccine (e_{Vf}) becomes $e_{Vf} = \frac{\epsilon}{m}$, then

$$V_{cf} = \frac{m}{\epsilon} \left[1 - \frac{\{1 - \eta_V\} N_H^* K_2 K_3 K_5}{\beta_{HV}^2 S_V^* (1 - c_B)^2 \gamma_H} \right] = m \times V_c > V_c$$

and

$$e_{Vcf} = \frac{m}{V} \left[1 - \frac{\{1 - \eta_V\} N_H^* K_2 K_3 K_5}{\beta_{HV}^2 S_V^* (1 - c_B)^2 \gamma_H} \right] = m \times e_{Vc} > e_{Vc}.$$

Figure 2 shows the simulation of the vaccinated reproduction number as a function of vaccine efficacy with single dose and fractionated threefold. Although when $\epsilon = 0$, all the simulations have the same value of $R_{0v} = R_0$ (about 1.143), the vaccinated reproduction number becomes less than unity when the vaccine efficacy, $\epsilon > 0.4$ (for a single dose), while for threefold fractionated vaccine, a higher vaccine efficacy, ϵ is required to possibly bring R_{0v} to a value below unity. This result is consistent with those in [47], which stated that a fractional YF vaccination does not meet YF vaccination requirements under the International Health Regulations (IHR) (Fig. 3).

Type Reproduction Numbers

For homogeneous population, controlling the basic reproduction number will be sufficient for disease control. In the case of heterogeneous populations (usually vector borne diseases) with more than one host types, control is often targeted at one host. The type-reproduction number (T) is a threshold quantity that correctly determines the critical control effort for a heterogeneous populations [25]. A method that is used to estimate the required effort(s) for controlling disease by targeting a specific sub-population of hosts, under the premise that infection may pass through other sub-populations before causing secondary infections is described in [25,41]. If K is the next generation matrix with large domain and hosts 1, 2 and 3 represent the populations of E_H , A_I and I_V . The type i reproduction number is given by

$$T_i = e^T K (I - (I - P)K)^{-1} e, \tag{16}$$

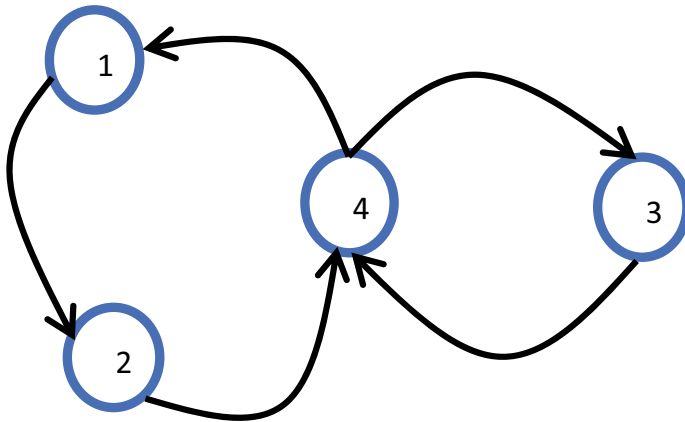


Fig. 3 Connected di-graph associated with the matrix $A_{22}(x)$

where I is an identity matrix, P is a projection matrix and e is a unit vector with all elements equal to zero except the i th. Let

$$K = \begin{pmatrix} 0 & 0 & k_{13} & k_{14} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & k_{33} & k_{34} \\ k_{41} & k_{42} & 0 & 0 \end{pmatrix},$$

where

$$k_{13} = \frac{\beta_{HV} b_V (1 - c_B) [S_H^* + (1 - \epsilon) V_H^*]}{N_H^* K_4 K_5}, \quad k_{14} = \frac{\beta_{HV} (1 - c_B) [S_H^* + (1 - \epsilon) V_H^*]}{N_H^* K_5},$$

$$K_{33} = \eta_V, \quad k_{34} = \frac{\phi_V \eta_V}{N_0 K_5}, \quad k_{41} = \frac{\beta_{HV} S_V^* (1 - c_B) \gamma_H}{N_H^* K_2 K_3}, \quad k_{42} = \frac{\beta_{HV} S_V^* (1 - c_B)}{N_H^* K_3}.$$

Notice that k_{ij} is the expected number of cases of type i produced by one infected individual of type j , so that from (16) the type-reproduction number for exposed humans is

$$T_1 = k_{14} k_{41} + \frac{k_{13} k_{34} k_{41}}{1 - k_{33}}$$

$$= \frac{\beta_{HV}^2 (S_V^*)^2 (1 - c_B)^2}{(N_H^*)^2 K_2^2} + \frac{\beta_{HV}^2 S_V^* (1 - c_B)^2 b_V \gamma_V \phi_V \eta_V [S_H^* + (1 - \epsilon) V_H^*]}{(N_H^*)^2 N_0 K_2 K_3 K_4 K_5^2 (1 - \eta_V)}.$$

Observe that $R_{0v} < 1$ implies

$$\frac{\beta_{HV}^2 S_V^* (1 - c_B)^2 [S_H^* + (1 - \epsilon) V_H^*]}{(N_H^*)^2 K_2 K_5} + \eta_V < 1 \tag{17}$$

Thus $T_1 < 1$ implies $R_{0v} < 1$. Similarly, it can be shown that the infected aquatic mosquito type-reproduction number (T_2) satisfies $T_2 < 1$ and the infectious adult mosquito type-reproduction number (T_3) also satisfies $T_3 < 1$ whenever $R_{0v} < 1$. T_i , ($i = 1, 2, 3$) is the expected number of cases in compartment i caused by one infected individual of type i in a population where fractions of susceptible individuals are vaccinated, the infection might be directly or through chains of infections passing through individuals of other types, it singles out the required control effort when targeting the population of type i [25].

YF Model for Optimal Control

Usually, incidences of YF and other vector borne diseases are seasonality dependent with their peaks during warm and rainy seasons, therefore it is reasonable to integrate time dependent controls in the model, the goal of which is to show the possibility of implementing time dependent controls while minimizing implementation cost.

Let the time dependent effort in preventing human–mosquito contacts through the use of treated bed nets be $u_1(t)$, so that the contact rate between mosquitoes and humans reduces by a factor $(1 - u_1(t))$ where $0 \leq u_1(t) \leq 1$. The effort in vaccinating humans is $u_2(t) : 0 \leq u_2(t) \leq 1$. Similarly, the effort in the application of larvicides is $u_3(t) : 0 \leq u_3(t) \leq 1$, while that of spraying adulticides is $u_4(t) : 0 \leq u_4(t) \leq 1$. For instance, there is no any effort in controlling mosquitoes when $u_3(t) = u_4(t) = 0$, while aquatic and mature mosquitoes die at maximum possible rates c_L and c_A respectively, when $u_3(t) = u_4(t) = 1$. Maximum control is attained by the use of bed nets and vaccination when $u_1(t) = 1$ and $u_2(t) = 1$, respectively and no effort invested when $u_1(t) = u_2(t) = 0$. The autonomous system given by (5) is extended to include the aforementioned time dependent controls. Let $\Phi(t) = \omega_H(1 - u_2(t))$, then the non-autonomous version of the model (5) is given by

$$\left. \begin{aligned} \frac{dS_H}{dt} &= b_H + \Phi(t)V_H - \beta_{HV}(1 - u_1(t))(1 - c_B)\frac{I_V S_H}{N_H} - c_V u_2(t)S_H - \mu_H S_H, \\ \frac{dV_H}{dt} &= c_V u_2(t)S_H - \beta_{HV}u_1(t)(1 - c_B)(1 - \epsilon)\frac{I_V V_H}{N_H} - \Phi(t)V_H - \mu_H V_H, \\ \frac{dE_H}{dt} &= \beta_{HV}(1 - u_1(t))(1 - c_B)\frac{I_V}{N_H} [S_H + (1 - \epsilon)V_H] - \gamma_H E_H - \mu_H E_H, \\ \frac{dI_H}{dt} &= \gamma_H E_H - \delta_H I_H - \tau_H I_H - \mu_H I_H, \\ \frac{dR_H}{dt} &= \tau_H I_H - \mu_H R_H, \end{aligned} \right\} \text{Humans} \tag{18}$$

$$\left. \begin{aligned} \frac{dA_N}{dt} &= \phi_V \left(1 - \frac{A}{K}\right) [S_V + (1 - \eta_V)I_V] - b_V A_N - \mu_A A_N - u_3(t)c_L A_N, \\ \frac{dA_I}{dt} &= \phi_V \eta_V \left(1 - \frac{A}{K}\right) I_V - b_V A_I - \mu_A A_I - u_3(t)c_L A_I, \\ \frac{dS_V}{dt} &= b_V A_N - \beta_{HV}u_1(t)(1 - c_B)\frac{I_H}{N_H} S_V - \mu_V S_V - u_4(t)c_A S_V, \\ \frac{dI_V}{dt} &= \beta_{HV}u_1(t)(1 - c_B)\frac{I_H}{N_H} S_V + b_V A_I - \mu_V I_V - u_4(t)c_A I_V. \end{aligned} \right\} \text{Mosquitoes}$$

Following the non-autonomous system given by (18), an optimal control problem is formulated with the following objective (cost) function.

$$J(u_1(t), u_2(t), u_3(t), u_4(t)) = \int_0^T \left(B_1 E_H + B_2 I_H + B_3 A + B_4 N_V + B_5 c_V S_H + D_1 u_1^2 + D_2 u_2^2 + D_3 u_3^2 + D_4 u_4^2 \right) dt. \tag{19}$$

The interval $[0, T]$ represents the time through which various control measures are implemented. The cost incurred due to human infection of YF (which is proportional to the number of infected individuals) over the period of intervention is given by

$$\int_0^T (B_1 E_H + B_2 I_H) dt,$$

where B_1 and B_2 are positive weight constants associated with exposed and infected humans, respectively. Similarly, the cost due to the presence of mosquitoes in the community, which is proportional to the number of aquatic and adult mosquitoes is given by

$$\int_0^T (B_3 A + B_4 N_V) dt,$$

where B_3 and B_4 are positive weight constants. Because of the short supply of YF vaccine, in order to optimize the available vaccines, there is need to minimize the total number of vaccines used over the period of intervention, thus the integral

$$\int_0^T B_5 c_V(t) S_H dt,$$

which measures the total number of vaccinated individuals during the period of intervention included in the objective functional, with B_5 being a positive weight constant. The positive terms D_1, D_2, D_3 and D_4 are weight constants for efforts in the use of bed nets, vaccination, larvicides and adulticides, respectively, and regularize the optimal control. $D_1 u_1^2, D_2 u_2^2, D_3 u_3^2,$ and $D_4 u_4^2$ describe the cost associated with the aforementioned prevention and control measures. The degree of the cost functions follow from the non-linearity of controls and the convexity of quadratic functions [43]. Similar assumption has been used in optimal control problems in epidemiology, see for instance [7,29,35,39,43] and some of the references therein.

The aim is to minimize the number of infected humans and total mosquito population while optimizing limited vaccines and keeping the cost of vaccination, use of treated nets and application of pesticides low. Therefore we seek to optimize u_1^*, u_2^*, u_3^* and u_4^* such that

$$J(u_1^*, u_2^*, u_3^*, u_4^*) = \min_{u_1, u_2, u_3, u_4} \left\{ J(u_1, u_2, u_3, u_4) \mid u_1, u_2, u_3, u_4 \in \mathcal{G} \right\} \tag{20}$$

where

$$\mathcal{G} = \left\{ (u_1, u_2, u_3, u_4) \mid u_i : [0, T] \longrightarrow [0, 1] \text{ is Lebesgue measurable, } i = 1, 2, 3, 4 \right\}$$

is the control set. The impact of each control does depends on adherence and effort, if for example $u_1 = 1$, production and distribution of bed nets is at maximum, but its impact also depends on c_B , likewise the remaining control functions.

Existence of Optimal Control

The existence of optimal control solution can be established using Theorem 4.1 and Corollary 4.1 of [19].

Theorem 4.1 *There exist an optimal control $u_1^*, u_2^*, u_3^*, u_4^*$ and corresponding solution $S_H^*, V_H^*, E_H^*, I_H^*, R_H^*, A_N^*, A_I^*, S_V^*$ and I_V^* that minimizes $J(u_1, u_2, u_3, u_4)$ over \mathcal{G} .*

Proof Clearly the set of controls and state variables are non-empty and the control set \mathcal{G} is closed and convex. The integrand of the objective functional is convex on \mathcal{G} . Furthermore, the model is linear in the control variables and bounded by a linear system in the state variables, thus, the existence of an optimal control is guaranteed [7,19]. \square

Optimality System

The necessarily conditions that optimal controls and their corresponding states must satisfy are derived using Pontryagin’s Maximum Principle [35,38], where the problem of finding time-dependent control variables $u_1^*(t), u_2^*(t), u_3^*(t)$ and $u_4^*(t)$ that minimize J is equivalent to the problem of minimizing the Hamiltonian function defined as

$$H(t, \mathbf{x}, \mathbf{u}, \lambda) = g(t, \mathbf{x}, \mathbf{u}) + \lambda(t) f(t, \mathbf{x}, \mathbf{u})$$

where $g(t, \mathbf{x}, \mathbf{u})$ is the integrand of the objective functional (19) and $\lambda(t)$ is the adjoint vector such that $\lambda(t) = (\lambda_{S_H}(t), \lambda_{V_H}(t), \lambda_{E_H}(t), \lambda_{I_H}(t), \lambda_{R_H}(t), \lambda_{A_N}(t), \lambda_{A_I}(t), \lambda_{S_V}(t), \lambda_{I_V}(t))$ satisfies

$$\frac{d\lambda_{S_H}}{dt} = -\frac{\partial H}{\partial S_H}, \quad \frac{d\lambda_{V_H}}{dt} = -\frac{\partial H}{\partial V_H}, \quad \dots, \quad \frac{d\lambda_{I_V}}{dt} = -\frac{\partial H}{\partial I_V}.$$

The optimality equation is given by

$$\frac{\partial H}{\partial u_1} = \frac{\partial H}{\partial u_2} = \frac{\partial H}{\partial u_3} = \frac{\partial H}{\partial u_4} = 0,$$

and transversality conditions as $\lambda_{S_H}(T) = \lambda_{V_H}(T) = \dots = \lambda_{I_V}(T) = 0$. Therefore,

$$\begin{aligned} H = & B_1 E_H + B_2 I_H + B_3 A + B_4 N_V + B_5 c_V S_H + D_1 u_1^2 + D_2 u_2^2 + D_3 u_3^2 + D_4 u_4^2 \\ & + \lambda_{S_H} \left[b_H + \Phi(t) V_H - c_V u_2(t) S_H - \beta_{HV} (1 - u_1(t)) (1 - c_B) \frac{I_V}{N_H} S_H - \mu_H S_H \right] \\ & + \lambda_{V_H} \left[c_V u_2(t) S_H - \beta_{HV} (1 - u_1(t)) (1 - c_B) (1 - \epsilon) \frac{I_V}{N_H} V_H - \Phi(t) V_H - \mu_H V_H \right] \\ & + \lambda_{E_H} \left[\beta_{HV} (1 - u_1(t)) (1 - c_B) \frac{I_V}{N_H} \left\{ S_H + (1 - \epsilon) V_H \right\} - \gamma_H E_H - \mu_H E_H \right] \\ & + \lambda_{I_H} \left[\gamma_H E_H - \delta_H I_H - \tau_H I_H - \mu_H I_H \right] + \lambda_{R_H} \left[\tau_H I_H - \mu_H R_H \right] \\ & + \lambda_{A_N} \left[\phi_V \left(1 - \frac{A}{\mathcal{K}} \right) \left[S_V + (1 - \eta_V) I_V \right] - b_V A_N - \mu_A A_N - u_3(t) c_L A_N \right] \\ & + \lambda_{A_I} \left[\phi_V \eta_V \left(1 - \frac{A}{\mathcal{K}} \right) I_V - b_V A_I - \mu_A A_I - u_3(t) c_L A_I \right] \\ & + \lambda_{S_V} \left[b_V A_N - \beta_{HV} (1 - u_1(t)) (1 - c_B) \frac{I_H}{N_H} S_V - \mu_V S_V - u_4(t) c_A S_V \right] \\ & + \lambda_{I_V} \left[\beta_{HV} (1 - u_1(t)) (1 - c_B) \frac{I_H}{N_H} S_V + b_V A_I - \mu_V I_V - u_4(t) c_A I_V \right], \end{aligned} \tag{21}$$

where $\lambda_{S_H}, \dots, \lambda_{I_V}$ are adjoint functions.

Theorem 4.2 *Given an optimal control $(u_1^*, u_2^*, u_3^*, u_4^*)$ and the corresponding state solutions of the non-autonomous system given by (18), there exist adjoint functions satisfying*

$$\frac{d\lambda_{S_H}}{dt} = \mu_H \lambda_{S_H} + u_2(t) c_V [\lambda_{S_H} - \lambda_{V_H}] + \beta_{HV} (1 - u_1(t)) (1 - c_B) [\lambda_{S_H} - \lambda_{E_H}] \frac{I_V}{N_H} + \beta_{HV}$$

$$\begin{aligned}
 & (1 - u_1(t))(1 - c_B)[\lambda_{I_V} - \lambda_{S_V}] \frac{I_H S_V}{(N_H)^2} + \beta_{H_V}(1 - u_1(t))(1 - c_B)[\lambda_{E_H} - \lambda_{S_H}] \\
 & \frac{I_V S_H}{(N_H)^2} + \beta_{H_V}(1 - u_1(t))(1 - c_B)(1 - \epsilon)[\lambda_{E_H} - \lambda_{V_H}] \frac{I_V V_H}{(N_H)^2} - B_5 c_V, \\
 \frac{d\lambda_{V_H}}{dt} &= \mu_H \lambda_{V_H} + \beta_{H_V}(1 - u_1(t))(1 - c_B)[\lambda_{E_H} - \lambda_{S_H}] \frac{I_V S_H}{N_H^2} + \beta_{H_V}(1 - u_1(t))(1 - c_B) \\
 & [\lambda_{I_V} - \lambda_{S_V}] \frac{I_H S_V}{N_H^2} + \beta_{H_V}(1 - u_1(t))(1 - c_B)(1 - \epsilon) \frac{I_V}{N_H} [\lambda_{V_H} - \lambda_{E_H}] + \beta_{H_V} \\
 & (1 - u_1(t))(1 - c_B)(1 - \epsilon)[\lambda_{E_H} - \lambda_{V_H}] \frac{I_V V_H}{N_H^2} - \omega_H(1 - u_2(t))[\lambda_{V_H} - \lambda_{S_H}], \\
 \frac{d\lambda_{E_H}}{dt} &= \mu_H \lambda_{E_H} + \gamma_H[\lambda_{E_H} - \lambda_{I_H}] + \beta_{H_V}(1 - u_1(t))(1 - c_B)[\lambda_{E_H} - \lambda_{S_H}] \frac{I_V S_H}{N_H^2} + \beta_{H_V} \\
 & (1 - u_1(t))(1 - c_B)[\lambda_{I_V} - \lambda_{S_V}] \frac{I_H S_V}{N_H^2} + \beta_{H_V}(1 - u_1(t))(1 - c_B)(1 - \epsilon)[\lambda_{E_H} - \lambda_{V_H}] \\
 & \frac{I_V V_H}{N_H^2} - B_1, \\
 \frac{d\lambda_{I_H}}{dt} &= (\delta_H + \mu_H)\lambda_{I_H} + \tau_H[\lambda_{I_H} - \lambda_{R_H}] + \beta_{H_V}(1 - u_1(t))(1 - c_B)[\lambda_{E_H} - \lambda_{S_H}] \frac{I_V S_H}{N_H^2} + \beta_{H_V} \\
 & (1 - u_1(t))(1 - c_B)[\lambda_{S_V} - \lambda_{I_V}] \frac{S_V}{N_H} + \beta_{H_V}(1 - u_1(t))(1 - c_B)(1 - \epsilon)[\lambda_{E_H} - \lambda_{V_H}] \\
 & \frac{I_V V_H}{N_H^2} + \beta_{H_V}(1 - u_1(t))(1 - c_B)[\lambda_{I_V} - \lambda_{S_V}] \frac{I_H S_V}{N_H^2} - B_2, \\
 \frac{d\lambda_{R_H}}{dt} &= \mu_H \lambda_{R_H} + \beta_{H_V}(1 - u_1(t))(1 - c_B)[\lambda_{E_H} - \lambda_{S_H}] \frac{I_V S_H}{N_H^2} + \beta_{H_V}(1 - (1 - u_1(t)))(1 - c_B) \\
 & [\lambda_{I_V} - \lambda_{S_V}] \frac{I_H S_V}{N_H^2} + \beta_{H_V}(1 - u_1(t))(1 - c_B)(1 - \epsilon)[\lambda_{E_H} - \lambda_{V_H}] \frac{I_V V_H}{N_H^2}, \\
 \frac{d\lambda_{A_N}}{dt} &= (\mu_A + u_3 c_L)\lambda_{A_N} + b_V[\lambda_{A_N} - \lambda_{S_V}] + \frac{\lambda_{A_N} \phi_V (S_V + I_V)}{\mathcal{K}} + \frac{I_V \phi_V \eta_V}{\mathcal{K}} [\lambda_{A_I} - \lambda_{A_N}] \\
 & - B_3, \\
 \frac{d\lambda_{A_I}}{dt} &= (\mu_A + u_3 c_L)\lambda_{A_I} + b_V[\lambda_{A_I} - \lambda_{I_V}] + \frac{\lambda_{A_N} \phi_V (S_V + I_V)}{\mathcal{K}} + \frac{I_V \phi_V \eta_V}{\mathcal{K}} [\lambda_{A_I} - \lambda_{A_N}] \\
 & - B_3, \\
 \frac{d\lambda_{S_V}}{dt} &= (\mu_V + u_4 c_A)\lambda_{S_V} + \beta_{H_V}(1 - u_1(t))(1 - c_B)[\lambda_{S_V} - \lambda_{I_V}] \frac{I_H}{N_H} - \phi_V \left(1 - \frac{A}{\mathcal{K}}\right) \lambda_{A_N} - B_4, \\
 \frac{d\lambda_{I_V}}{dt} &= (\mu_V + u_4 c_A)\lambda_{I_V} + \beta_{H_V}(1 - u_1(t))(1 - c_B)(1 - \epsilon)[\lambda_{V_H} - \lambda_{E_H}] \frac{V_H}{N_H} + \beta_{H_V}(1 - u_1(t)) \\
 & (1 - c_B)[\lambda_{S_H} - \lambda_{E_H}] \frac{S_H}{N_H} + \left(1 - \frac{A}{\mathcal{K}}\right) \phi_V \eta_V [\lambda_{A_N} - \lambda_{A_I}] - \phi_V \left(1 - \frac{A}{\mathcal{K}}\right) \lambda_{A_N} - B_4,
 \end{aligned}$$

with final time condition as $\lambda_i(T) = 0, i = 1, \dots, 9$. In addition, the optimal control $u_j^*, j = 1, 2, 3, 4$ are given by

$$u_1^* = \begin{cases} 0, & \text{if } \left(\frac{\beta_{H_V}(1-c_B)}{2N_H D_1}\right) Q_0 < 1 \\ \left(\frac{\beta_{H_V}(1-c_B)}{2N_H D_1}\right) Q_0, & \text{if } 0 < \frac{\beta_{H_V}(1-c_B)}{2N_H D_1} Q_0 < 1 \\ 1, & \text{if } \left(\frac{\beta_{H_V}(1-c_B)}{2N_H D_1}\right) Q_0 > 0 \end{cases} \tag{22}$$

where $Q_0 = (I_V S_H [\lambda_{S_H} - \lambda_{E_H}] + I_V V_H (1 - \epsilon) [\lambda_{V_H} - \lambda_{E_H}] + I_H S_V [\lambda_{S_V} - \lambda_{I_V}])$, while u_2^* is given by

$$u_2^* = \begin{cases} 0, & \text{if } \frac{(c_V S_H + \omega_H V_H)}{2D_2} [\lambda_{S_H} - \lambda_{V_H}] < 0 \\ \frac{(c_V S_H + \omega_H V_H)}{2D_2} [\lambda_{S_H} - \lambda_{V_H}], & \text{if } 0 < \frac{(c_V S_H + \omega_H V_H)}{2D_2} [\lambda_{S_H} - \lambda_{V_H}] < 1 \\ 1, & \text{if } \frac{(c_V S_H + \omega_H V_H)}{2D_2} [\lambda_{S_H} - \lambda_{V_H}] > 1, \end{cases} \quad (23)$$

also u_3^* is given by

$$u_3^* = \begin{cases} 0, & \text{if } \frac{c_V}{2D_3} (\lambda_{A_N} A_N + \lambda_{A_I} A_I) < 0 \\ \frac{c_V}{2D_3} (\lambda_{A_N} A_N + \lambda_{A_I} A_I), & \text{if } 0 < \frac{c_V}{2D_3} (\lambda_{A_N} A_N + \lambda_{A_I} A_I) < 1 \\ 1, & \text{if } \frac{c_V}{2D_3} (\lambda_{A_N} A_N + \lambda_{A_I} A_I) > 1, \end{cases} \quad (24)$$

and u_4^* is given by

$$u_4^* = \begin{cases} 0, & \text{if } \frac{c_I}{2D_4} [\lambda_{S_V} S_V + \lambda_{I_V} I_V] < 0 \\ \frac{c_I}{2D_4} [\lambda_{S_V} S_V + \lambda_{I_V} I_V], & \text{if } 0 < \frac{c_I}{2D_4} [\lambda_{S_V} S_V + \lambda_{I_V} I_V] < 1 \\ 1, & \text{if } \frac{c_I}{2D_4} [\lambda_{S_V} S_V + \lambda_{I_V} I_V] > 1. \end{cases} \quad (25)$$

Proof The non-autonomous system given by (18) together with the objective functional given by (19) and (20) are converted into a problem of minimizing the Hamiltonian, H , defined by (21). Therefore applying Pontryagin’s Maximum Principle [35,38], the proof follows. \square

Sensitivity Analysis and Numerical Simulation

In this section, global sensitivity analysis using partial rank correlation coefficient (PRCC) for the basic offspring number and vaccinated reproduction number are conducted. Numerical simulations for the optimal control model given by (18) is also presented.

Sensitivity Analysis

Local sensitivity analysis is used to provide direct information on the effect of small parameter perturbation, it evaluates the relative change in a function due to change in a single parameter, where other parameters are kept at constant values. It does not indicate the effect of simultaneous large perturbations in all model parameters. Thus, the need for a more robust form of sensitivity analysis for a multidimensional parameter space. The PRCC is a robust sensitivity measure for a non-linear but monotonic relationships between inputs and output, with little correlation between the inputs [31].

The PRCC of the basic offspring number (N_0) and that of the vaccinated reproduction number (R_{0v}) are computed with parameter ranges as presented in Table 1. The PRCC values

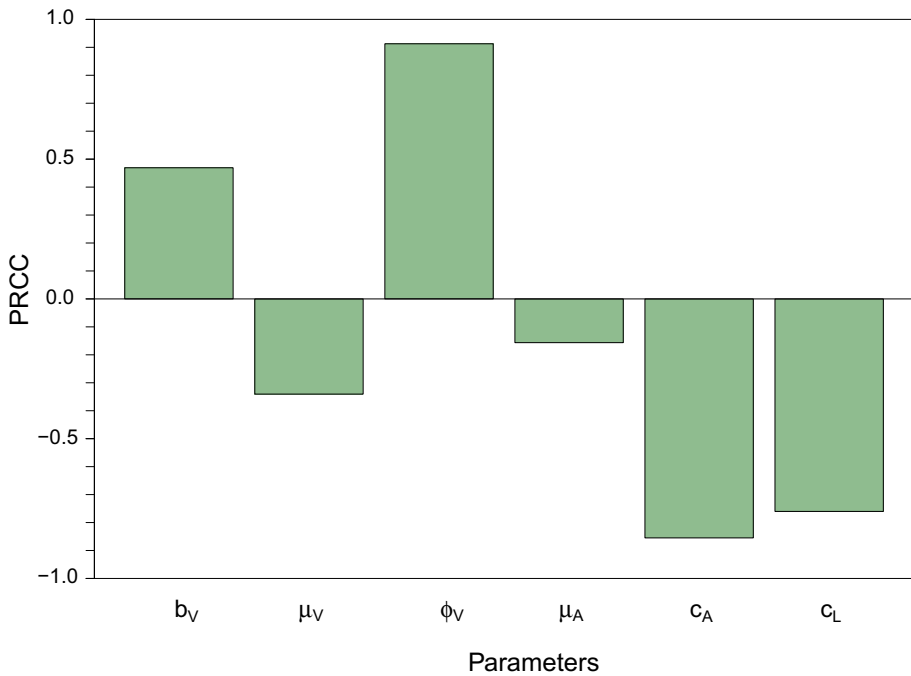


Fig. 4 Partial rank correlation coefficient plots of the various parameters of the model (5) using N_0 as the output function

of the parameters of the YF model, using N_0 as the response function are depicted in Fig. 4. The Fig. show that the top parameters that most influences the values of the threshold quantity, N_0 , are mosquito death rates due to adulticides and larvicides (c_A and c_L , respectively) and the vertical transmission rate (η_V). It can be seen from the figure that c_A and c_L are negatively correlated and ϕ_V is positively correlated to N_0 . On the other hand, R_{0v} is most positively correlated to η_V , which is followed by β_{HV} then \mathcal{K} , and it is most negatively correlated to c_A , c_B and then b_H as presented in Fig. 5.

Numerical Simulations

Using the forward–backward sweep method as described in [30], solution of the optimal control problem can be obtained numerically. An initial guess for the optimal control is used to solve the state system in forward time, after which the guessed optimal control and the obtained solution to the state system are used as input to the adjoint system, which is solved numerically in backward scheme using the transversality condition. The controls are then updated using convex combination of the previous controls and the value from the characterizations.

The following numerical values for the model parameters are used as in Table 1: $b_H = 50$; $\beta_{HV} = 0.375$; $c_B = 0.5$; $\omega_H = 0.01$; $\mu_H = 0.0000421$; $c_V = 0.3$; $\epsilon = 0.95$; $\gamma_H = 0.3$; $\delta_H = 0.0001$; $\tau_H = 0.143$; $b_V = 0.1$; $\phi_V = 50$; $\kappa = 800,000$; $\eta_V = 0.01$; $\mu_A = 0.22$; $\mu_V = 0.29$; $c_A = 0.2$; and $c_L = 0.2$. For the numerical values of the weight constants in the objective functional J , it is important to note that the choices are made only for simulation

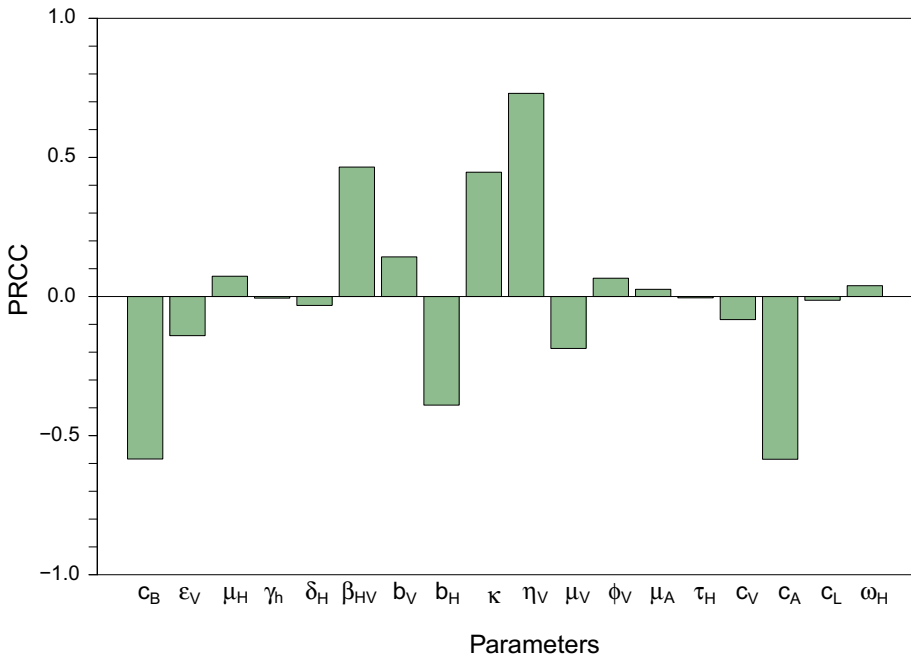


Fig. 5 Partial rank correlation coefficient plots of the various parameters of the model (5) using R_{0v} as the output function

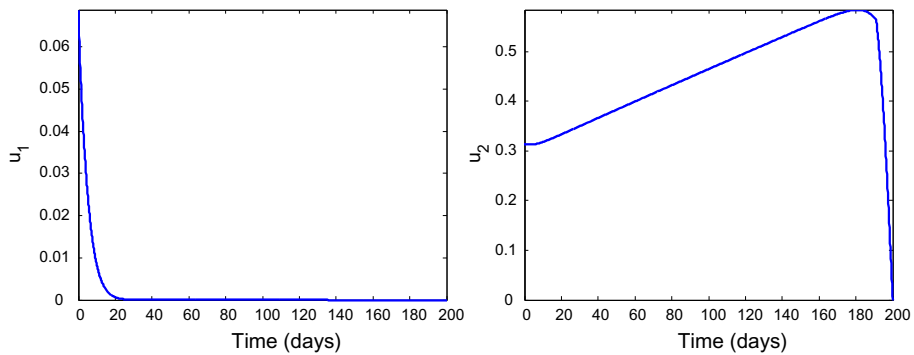


Fig. 6 Simulations of the model (18) showing control profiles U_1 and U_2 for the case when $B_1 = 0.1$; $B_2 = 0.1$; $B_3 = 0.001$; $B_4 = 0.005$; $B_5 = 0.1$; $D_1 = 500$; $D_2 = 500$; $D_3 = 500$; $D_4 = 500$

purposes, different choices were made and simulated. Simulations for 200 days were carried out. Using initial populations of $S_H(0) = 2000$; $V_H(0) = 500$; $E_H(0) = 500$; $I_H(0) = 200$; $R_H(0) = 50$; $A_N(0) = 25,000$; $A_I(0) = 200$; $S_V(0) = 1000$ and $I_V(0) = 500$, impact of control and that of using different weight constants for the objective function is assessed. In order to regularize the objective function, smaller values were chosen for the coefficients of the populations while larger values for the control functions. Two different scenarios for weight constants are considered, in both instances, minimizing the number of infected humans is given more priority over minimizing adult mosquitoes, then aquatic mosquitoes i.e $B_2 \geq B_1 > B_4 > B_3$ but with the same cost ($D_1 = D_2 = D_3 = D_4$), thus we have

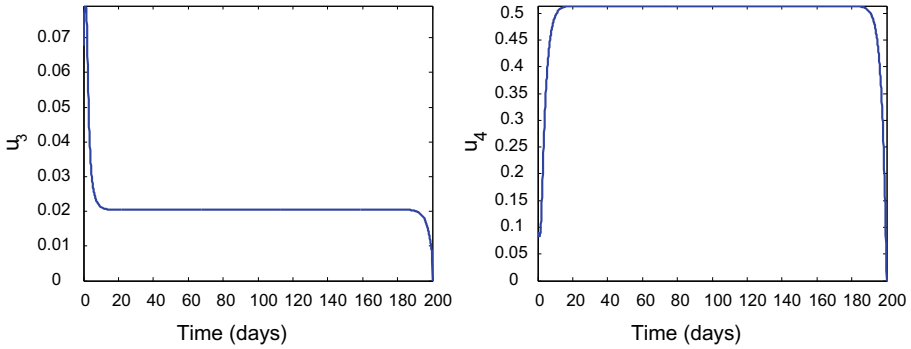


Fig. 7 Simulations of the model (18) showing control profiles U_3 and U_4 for the case when $B_1 = 0.1$; $B_2 = 0.1$; $B_3 = 0.001$; $B_4 = 0.005$; $B_5 = 0.1$; $D_1 = 500$; $D_2 = 500$; $D_3 = 500$; $D_4 = 500$

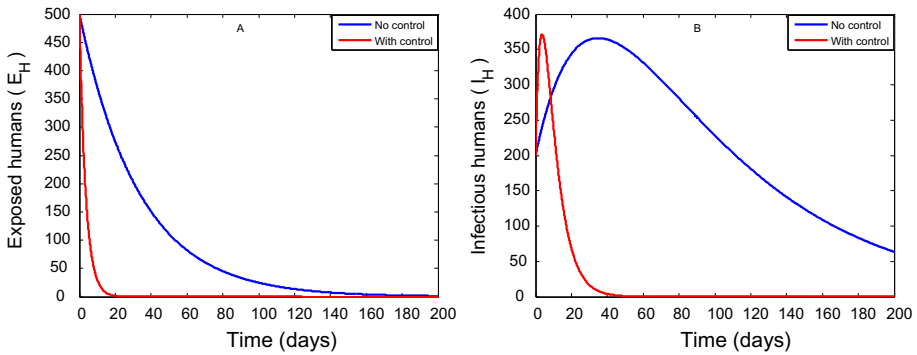


Fig. 8 Simulations of the model (18) showing exposed humans and infected humans for the case when $B_1 = 0.1$; $B_2 = 0.1$; $B_3 = 0.001$; $B_4 = 0.005$; $B_5 = 0.1$; $D_1 = 500$; $D_2 = 500$; $D_3 = 500$; $D_4 = 500$

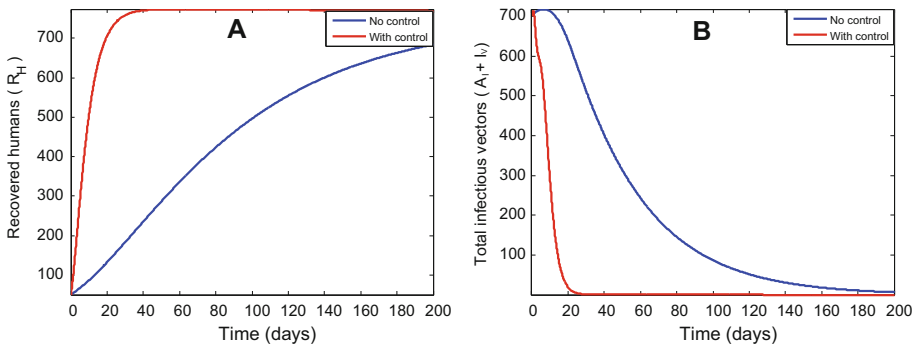


Fig. 9 Simulations of the model (18) showing recovered humans and populations of infected mosquitoes for the case when $B_1 = 0.1$; $B_2 = 0.1$; $B_3 = 0.001$; $B_4 = 0.005$; $B_5 = 0.1$; $D_1 = 500$; $D_2 = 500$; $D_3 = 500$; $D_4 = 500$

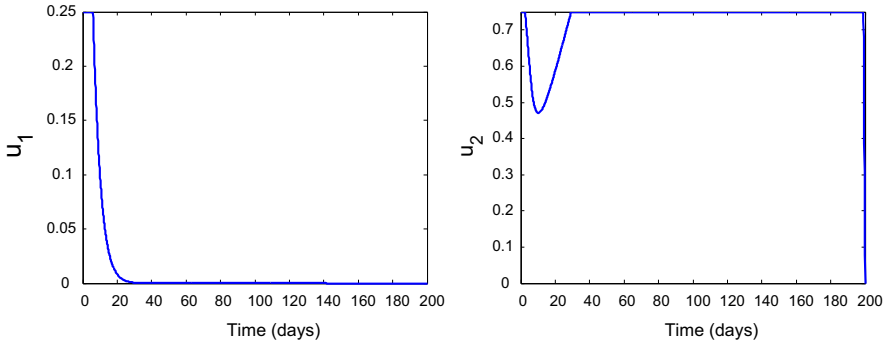


Fig. 10 Simulations of the model (18) showing control profiles U_1 and U_2 for the case when $B_1 = 0.01$; $B_2 = 0.01$; $B_3 = 0.0001$; $B_4 = 0.0005$; $B_5 = 0.1$; $D_1 = 50$; $D_2 = 50$; $D_3 = 50$; $D_4 = 50$

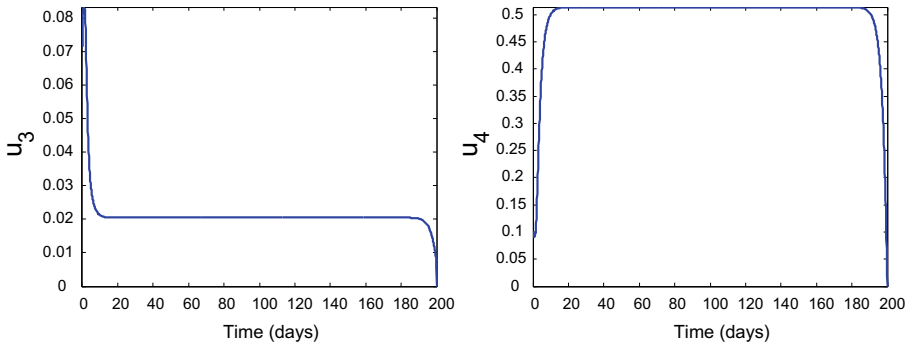


Fig. 11 Simulations of the model (18) showing control profiles U_3 and U_4 for the case when $B_1 = 0.01$; $B_2 = 0.01$; $B_3 = 0.0001$; $B_4 = 0.0005$; $B_5 = 0.1$; $D_1 = 50$; $D_2 = 50$; $D_3 = 50$; $D_4 = 50$

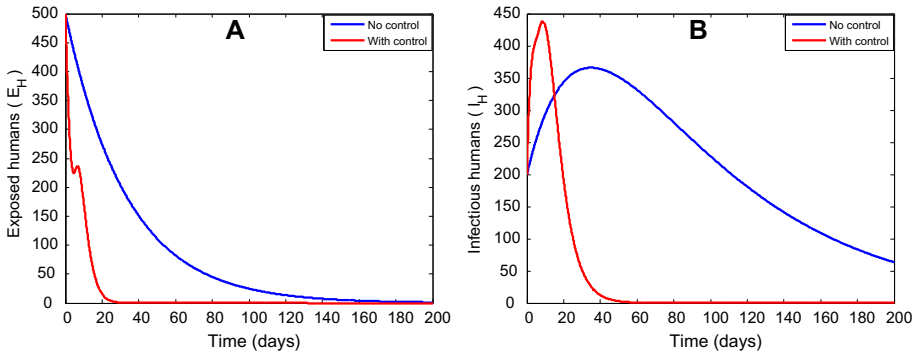


Fig. 12 Simulations of the model (18) showing exposed humans and infected humans for the case when $B_1 = 0.01$; $B_2 = 0.01$; $B_3 = 0.0001$; $B_4 = 0.0005$; $B_5 = 0.1$; $D_1 = 50$; $D_2 = 50$; $D_3 = 50$; $D_4 = 50$

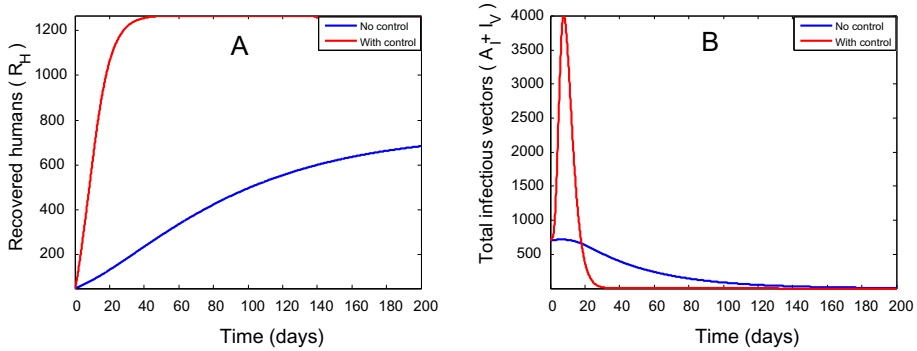


Fig. 13 Simulations of the model (18) showing recovered humans and populations of infected mosquitoes for the case when $B_1 = 0.01$; $B_2 = 0.01$; $B_3 = 0.0001$; $B_4 = 0.0005$; $B_5 = 0.1$; $D_1 = 50$; $D_2 = 50$; $D_3 = 50$; $D_4 = 50$

1. Case 1: Simulations of the optimal control model when $B_1 = 0.1$; $B_2 = 0.1$; $B_3 = 0.001$; $B_4 = 0.005$; $B_5 = 0.1$; $D_1 = 500$; $D_2 = 500$; $D_3 = 500$; $D_4 = 500$ is carried out. Control profiles of the model are presented in Figs. 6 and 7. Simulation of the model for the populations of exposed, infected and recovered humans and infected mosquitoes are depicted in Figs. 8 and 9. Figures 8a, b present simulations of the model for populations of exposed and infected humans with and without control, respectively. The figures show that the populations of exposed and infected humans reaches the DFE at a faster rates with control than without control. Figure 9a shows the population of recovered humans where the population with control is larger than those without control, this may be attributed to the fact that recovery confers permanent immunity. Simulation of the model for the population of infectious mosquitoes (both aquatic and non-aquatic) is presented in Figure 9b.
2. Case 2: In this case, the weight constants are taken to be $B_1 = 0.01$; $B_2 = 0.01$; $B_3 = 0.0001$; $B_4 = 0.0005$; $B_5 = 0.1$; $D_1 = 50$; $D_2 = 50$; $D_3 = 50$; $D_4 = 50$. Similarly, control profiles of the model are depicted in Figs. 10 and 11. The simulation of the model for population of exposed humans shows similar dynamics as that of Case 1 as presented in Fig. 12a. Simulation of model for infected humans, where population with control shoot up before falling to the DFE is presented in Fig. 12b. The population of recovered humans shows wider margin between cases with and without control in this instance compared to Case 1 as depicted in Fig. 13a, also, population of infected mosquitoes sporadically bumps up before reaching DFE as shown in Fig. 13b. Notice that, less effort and less costs are expended (in this case) in comparison to Case 1.

Conclusion

A deterministic model for the transmission dynamics of yellow fever in a population is constructed and rigorously analysed. The model with standard incidence formulation incorporates the use of treated bed nets and vaccination as forms of prevention in humans, while the use of larvicides and adulticides are used in controlling mosquito population. Some of the key results obtained include:

- The mosquito-only model has a threshold quantity called the basic offspring number (N_0) which described the extinction or persistence of mosquito population.
- The model has two disease-free equilibriums, the mosquito-extinction equilibrium (\mathcal{E}_2) which is globally-asymptotically stable (GAS) when the basic offspring number (N_0) is less than unity and the non-mosquito-extinction equilibrium, (\mathcal{E}_3), which is locally-asymptotically stable when $R_{0v} \leq 1$.
- The YF model undergoes the phenomenon of backward bifurcation (a dynamic phenomenon characterized by the co-existence of two stable attractors when the associated reproduction number of the model is less than unity). A condition for the emergence of this phenomenon have been identified.
- The DFE, \mathcal{E}_3 , of the model is shown to be GAS in the positively-invariant region Ω , provided $R_{HV} R_{VH} \frac{N_0 N_H^* (\delta_H + \mu_H)}{(N_0 - 1) b_H} + R_{VV} N_0 < 1$.
- For standard dosing of YF vaccine, a high vaccine efficacy (at-least 40%) would be required to reduce R_{0v} to value below unity.
- Fractional dosing of YF vaccine does not meet YF vaccination requirements of yellow fever elimination. This result is consistent with that of International Health Regulations (IHR). However, the vaccine will always have a positive impact in a community.
- Using Pontryagin’s maximum principle and modified forward–backward sweep technique, the necessary conditions for existence of solutions to the optimal control problem is determined.
- Numerical simulations of the non-autonomous model (with optimal control) using different weight constants show that slight increase in control effort show wide difference in the impact of control.
- Using sensitivity analysis, it is shown that the vaccinated reproduction is most sensitive and positively correlated to the rate of vertical transmission, thus making it the most important parameter to target in controlling the disease.

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Appendix A: Proof of Theorem 2.2

Proof Let $f : \Omega_* \rightarrow \mathbb{R}^4$ be continuous, where $\Omega_* \subseteq \mathbb{R}^n$. Consider a system given by $\dot{x} = f(x)$, we use the following theorem in [2] in the proof of Theorem 2.2 □

Theorem 5.1 [2] *Let $a, b \in \Omega_*$ be such that $a < b$, $[a, b] \subseteq \Omega_*$ and $f(b) \leq 0 \leq f(a)$. Then $\dot{x} = f(x)$ defines a (positive) dynamical system on $[a, b]$. Moreover, if $[a, b]$ contains a unique equilibrium q then q is globally asymptotically stable on $[a, b]$.*

By rewriting the mosquito component of (5) in the form of $\dot{x} = f(x)$ and considering the interval $[a, b] = [0, b] \in \mathbb{R}_+^2$, where $b = (q, \frac{(b_V + \mu_A + c_L)q}{\phi_V})$ with $q > 0$. Clearly $f(a) = f(0) = 0$ while

$$f(b) = \begin{pmatrix} -\frac{q^2}{\kappa} [b_V + \mu_A + c_L] \\ b_V q [1 - \frac{1}{N_0}] \end{pmatrix} < 0 \text{ provided } N_0 \leq 1. \tag{A.1}$$

Therefore $f(b) \leq 0 \leq f(0)$ provided $N_0 \leq 1$, thus by Theorem (5.1), the mosquito component of the system given by (5) defines a positive dynamical system on $[0, b]$, moreover, the equilibrium (\mathcal{E}_0) is GAS on $[0, b]$. Because q is arbitrary, b can be chosen such that its bigger than any $x \in \mathbb{R}_+^2$. Hence the result holds on \mathbb{R}_+^2 . The second part of the proof follows by linearization. \square

Appendix B: Computation of mosquito extinction basic reproduction number

For \mathcal{E}_2 , the matrix of new infection terms and that of transition terms are respectively given by

$$F = \begin{pmatrix} 0 & 0 & 0 & \frac{\beta_{HV}(1-c_B)[S_H^*+V_H^*(1-\epsilon)]}{N_H^*} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{\phi_V \eta_V}{N_0} \\ 0 & \frac{\beta_{HV}(1-c_B)S_V^*}{N_H^*} & 0 & 0 \end{pmatrix}, \tag{B.1}$$

$$V = \begin{pmatrix} K_2 & 0 & 0 & 0 \\ -\gamma & K_3 & 0 & 0 \\ 0 & 0 & K_4 & 0 \\ 0 & 0 & -b_V & K_5 \end{pmatrix}.$$

The next generation matrix with large domain ($K_L = FV^{-1}$) is

$$K_L = \begin{pmatrix} 0 & 0 & \frac{\beta_{HV}b_V(1-c_B)[S_H^*+V_H^*(1-\epsilon)]}{N_H^*K_4K_5} & \frac{\beta_{HV}(1-c_B)[S_H^*+V_H^*(1-\epsilon)]}{N_H^*K_5} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{\phi_V b_V \eta_V}{N_0 K_4 K_5} & \frac{\phi_V \eta_V}{N_0 K_5} \\ 0 & 0 & 0 & 0 \end{pmatrix}, \tag{B.2}$$

Thus using the approach of [14] with an auxiliary matrix E , the NGM (K) is

$$K = E^T K_L E = E^T F V^{-1} E = \begin{pmatrix} 0 & \frac{\beta_{HV}b_V(1-c_B)[S_H^*+V_H^*(1-\epsilon)]}{N_H^*K_4K_5} \\ 0 & \frac{\phi_V \eta_V b_V}{N_0 K_4 K_5} \end{pmatrix}, \tag{B.3}$$

where

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

Therefore the mosquito extinction basic reproduction number, which is the dominant eigenvalue of K is $R_{vv} = \frac{\phi_V \eta_V b_V}{N_0 K_4 K_5} = \eta_V$.

Appendix C: Computation of vaccinated reproduction number

For the case of \mathcal{E}_3 , applying similar method to that of Appendix B, the NGM with large domain K_L is given by

$$\left(\begin{array}{ccc} 0 & 0 & \frac{\beta_{HV}b_V(1-c_B)[S_H^*+V_H^*(1-\epsilon)]}{N_H^*K_4K_5} \quad \frac{\beta_{HV}(1-c_B)[S_H^*+V_H^*(1-\epsilon)]}{N_H^*K_5} \\ 0 & 0 & 0 \quad 0 \\ 0 & 0 & \frac{\phi_V\eta_Vb_V}{N_0K_4K_5} \quad \frac{\phi_V\eta_V}{N_0K_5} \\ \frac{\beta_{HV}S_V^*(1-c_B)\gamma_H}{N_H^*K_2K_3} & \frac{\beta_{HV}S_V^*(1-c_B)}{N_H^*K_3} & 0 \quad 0 \end{array} \right). \tag{B.1}$$

Thus using the approach of [14] with an auxiliary matrix E , the NGM (K) is

$$K = \left(\begin{array}{ccc} 0 & \frac{\beta_{HV}b_V(1-c_B)[S_H^*+V_H^*(1-\epsilon)]}{N_H^*K_4K_5} & \frac{\beta_{HV}(1-c_B)[S_H^*+V_H^*(1-\epsilon)]}{N_H^*K_5} \\ 0 & \frac{\phi_V\eta_Vb_V}{N_0K_4K_5} & \frac{\phi_V\eta_V}{N_0K_5} \\ \frac{\beta_{HV}S_V^*(1-c_B)\gamma_H}{N_H^*K_2K_3} & 0 & 0 \end{array} \right), \tag{B.2}$$

where

$$E = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix}.$$

Thus, the vaccinated reproduction number which is the dominant eigenvalue of K is given by

$$R_{0v} = \frac{\eta_V}{2} + \sqrt{\left(\frac{\eta_V}{2}\right)^2 + \frac{\beta_{HV}^2 S_V^*(1-c_B)^2 \gamma_H}{N_H^* K_2 K_3 K_5} \left(1 - \frac{V_H^* \epsilon}{N_H^*}\right)} \tag{B.3}$$

Appendix D: Proof of Theorem 5.3 Backward bifurcation

Proof We apply a method which is based on the Centre Manifold Theory [11,46] to prove the existence of backward bifurcation for the model (5). Let,

$$(S_H, E_H, I_H, R_H, A_N, A_I, S_V, I_V) = (x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8),$$

so that the total human and mosquito populations are:

$$N_H = x_1 + x_2 + x_3 + x_4, \quad \text{and} \quad N_V = x_5 + x_6 + x_7 + x_8.$$

The transformed model (5) is represented by,

$$\begin{aligned}
 \frac{dx_1}{dt} &= b_H - \sigma x_1 - \left(\frac{\beta_{HV}(1-u)x_9}{x_1+x_2+x_3+x_4+x_5}\right)x_1 - \mu_H x_1, \\
 \frac{dx_2}{dt} &= \sigma x_1 - \left(\frac{\beta_{HV}(1-u)(1-\epsilon)x_9}{x_1+x_2+x_3+x_4+x_5}\right)x_2 - \mu_H x_2, \\
 \frac{dx_3}{dt} &= \beta_{HV}(1-u)x_9\left(\frac{x_1+x_2(1-\epsilon)}{x_1+x_2+x_3+x_4+x_5}\right) - \gamma_H x_3 - \mu_H x_3, \\
 \frac{dx_4}{dt} &= \gamma_H x_3 - \delta_H x_4 - \tau_H x_4 - \mu_H x_4, \\
 \frac{dx_5}{dt} &= \tau_H x_4 - \mu_H x_5, \\
 \frac{dx_6}{dt} &= \phi_V \left(1 - \frac{x_6+x_7}{K}\right) \left(x_8 + (1-\eta_V)x_9\right) - b_V x_6 - \mu_A x_6 - c_L x_6, \\
 \frac{dx_7}{dt} &= \phi_V \left(1 - \frac{x_6+x_7}{K}\right) \eta_V x_9 - b_V x_7 - \mu_A x_7 - c_L x_7, \\
 \frac{dx_8}{dt} &= b_V x_6 - \frac{\beta_{HV}x_4x_8}{x_1+x_2+x_3+x_4+x_5} - \mu_V x_8 - c_A x_8, \\
 \frac{dx_9}{dt} &= \frac{\beta_{HV}x_4x_8}{x_1+x_2+x_3+x_4+x_5} + b_V x_7 - \mu_V x_9 - c_A x_9.
 \end{aligned}
 \tag{D.1}$$

The forces of infections in human and mosquito populations are respectively given by,

$$\beta_{HV}(1-u)x_9\left(\frac{x_1+x_2(1-\epsilon)}{x_1+x_2+x_3+x_4+x_5}\right), \text{ and, } \frac{\beta_{HV}x_4x_8}{x_1+x_2+x_3+x_4+x_5} + b_V x_7.$$

Thus, the Jacobian matrix (J^*) at the DFE with $\beta_{HV} = \beta_{HV}^*$ is,

$$\begin{pmatrix}
 -K_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -Z_{19} \\
 \sigma & -\mu_H & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -Z_{29} \\
 0 & 0 & -K_2 & 0 & 0 & 0 & 0 & 0 & 0 & Z_{39} \\
 0 & 0 & \gamma_H & -K_3 & 0 & 0 & 0 & 0 & 0 & 0 \\
 0 & 0 & 0 & \tau_H & -\mu_H & 0 & 0 & 0 & 0 & 0 \\
 0 & 0 & 0 & 0 & 0 & -K_4 N_0 & -Z_{67} & \frac{\phi_V}{N_0} & \frac{\phi_V(1-\eta_V)}{N_0} & 0 \\
 0 & 0 & 0 & 0 & 0 & 0 & -K_4 & 0 & \frac{\phi_V \eta_V}{N_0} & 0 \\
 0 & 0 & 0 & -\frac{\beta_{HV}^* S_V^* (1-u)}{S_H^* + V_H^*} & 0 & b_V & 0 & -K_5 & 0 & 0 \\
 0 & 0 & 0 & \frac{\beta_{HV}^* S_V^* (1-u)}{S_H^* + V_H^*} & 0 & 0 & b_V & 0 & -K_5 & 0
 \end{pmatrix}.$$

where

$$Z_{19} = \frac{\beta_{HV}^* S_H^* (1-u)}{S_H^* + V_H^*}, Z_{29} = \frac{\beta_{HV}^* V_H^* (1-\epsilon)(1-u)}{S_H^* + V_H^*}, Z_{39} = \frac{\beta_{HV}^* (1-u) [S_H^* + V_H^* (1-\epsilon)]}{S_H^* + V_H^*}, Z_{67} = K_4 \left(1 - \frac{1}{N_0}\right).$$

At $R_{0v} = 1$ we have,

$$\frac{\beta_{HV}^2 S_V^* (1-u)^2 \gamma_H [S_H^* + V_H^* (1-\epsilon)]}{(N_H^*)^2 K_2 K_3 K_5} + \eta_V = 1,
 \tag{D.2}$$

under which we obtained the left eigenvector (v) and the right eigenvector (w) corresponding to the zero eigenvalue given by

$$v_1 = 0, \quad v_2 = 0, \quad v_3 = \frac{Z_{19}\gamma_H}{K_2K_3}v_9, \quad v_4 = \frac{\beta_{HV}^*S_V^*(1-u)}{N_H^*K_3}v_9, \quad v_5 = 0, \quad v_6 = 0,$$

$$v_7 = \frac{b_V}{K_4}v_9, \quad v_8 = 0, \quad v_9 = \frac{K_2K_3K_4}{K_5},$$

and

$$w_1 = -\frac{Z_{19}}{K_1}w_9 \quad w_2 = -\left(\frac{Z_{19}\sigma}{K_1\mu_H} + \frac{Z_{29}}{\mu_H}\right)w_9, \quad w_3 = \frac{(Z_{19} + Z_{29})}{K_2}w_9,$$

$$w_4 = \frac{(Z_{19} + Z_{29})\gamma_H}{K_2K_3}w_9 \quad w_5 = \frac{(Z_{19} + Z_{29})\gamma_H\tau_H}{K_2K_3\mu_H}w_9,$$

$$w_6 = -\left[\frac{(Z_{19} + Z_{29})\beta_{HV}^*S_V^*\gamma_H(1-u)}{N_H^*K_2K_3K_5} + Z_{67}\frac{\eta_V}{K_4} - (1 - \eta_V)\right]\frac{\phi_V w_9}{(N_0)^2 Z_{67}}, \quad w_7 = \frac{\phi_V \eta_V w_9}{N_0 K_4},$$

$$w_8 = -\left[\frac{(Z_{19} + Z_{29})\beta_{HV}^*S_V^*\gamma_H(1-u)N_0}{N_H^*K_2K_3K_5} + Z_{67}\frac{\eta_V}{K_4} - (1 - \eta_V)\right]\frac{K_4 w_9}{N_0 Z_{67}},$$

$$w_9 = \frac{(Z_{19} + Z_{29})\beta_{HV}^*S_V^*\gamma_H(1-u)}{N_H^*K_2K_3K_5}K_4(K_2 + K_3) + K_2K_3(K_4 + \eta_V).$$

Clearly $v_i \geq 0$, $w_1 < 0$, $w_2 < 0$ while w_6 and w_8 can be positive or negative, such choice is justified by Remark 1 of [11] which states; □

Remark 5.2 The requirement that w is non-negative in the theorem is not necessary. When some components in w are negative, we still can apply this theorem, but one has to compare w with the actual equilibrium because the general parametrization of the Centre Manifold before the coordinate change is,

$$W^c = \left\{x_0 + c(t)w + h(c, \phi_V) : v \cdot h(c, \phi_V) = 0, |c| \leq c_0, c(0) = 0\right\},$$

provided that x_0 is a non-negative equilibrium of interest (usually x_0 is the disease-free equilibrium). Hence, $x_0 - \frac{2b\phi_V}{a} > 0$ requires that $w_j > 0$ whenever $x_0(j) = 0$. If $x_0(j) > 0$, then $w(j)$ need not be positive [11].

It can be verified that $vw = 1$, thus all the necessarily conditions for the use of the Center Manifold theory are satisfied, and

$$\mathbf{a} = \sum_{k,i,j=1}^n v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0, 0) = -\frac{2w_5^2 v_9}{(N_H^*)^2 \mathcal{K}} \left\{ G_4 \left[\frac{\eta_V(N_0 - 1)^2 + N_0(1 - \eta_V)}{N_0} \right] + \right.$$

$$\frac{G_0(N_H^*)^2 \mathcal{K}}{S_V^*(N_0 - 1)} \left[G_0 N_0 + \eta_V \left(1 - \frac{1}{N_0}\right) \right] + G_1 \left(K_3 \mu_H + \gamma_H \{ \mu_H + \tau_H \} \right) \left(1 + K_2 K_3 \right.$$

$$\mu_H \left[1 - \frac{V_H^*}{N_H^*} \epsilon \right] + G_2 \gamma_H \epsilon \left[V_H^* + S_H^* G_3 \right] - G_0 G_4 - G_1 \left[S_H^* + G_3 \right] \frac{(K_2 K_3 \mu_H)^2}{N_H^* K_1}$$

$$\left. - \frac{G_0(N_H^*)^2 \mathcal{K}}{S_V^*(N_0 - 1)} (1 - \eta_V) \right\}, \tag{D.3}$$

while

$$\mathbf{b} = \sum_{k,i=1}^n v_k w_I \frac{\partial^2 f_k}{\partial x_I \partial \phi_V}(0, 0) = \frac{2\beta_{HV} S_V^* (1-u)^2 \gamma_H}{N_H^* K_2 K_3} \left[1 - \frac{V_H^*}{N_H^*} \epsilon \right] w_9 v_9 > 0 \quad (D.4)$$

where

$$G_0 = \frac{[\beta_{HV}(1-u)]^2 S_V^* \gamma_H}{N_H^* K_2 K_3 K_5} \left[1 - \frac{V_H^*}{N_H^*} \epsilon \right], \quad G_1 = \frac{[\beta_{HV}(1-u)]^3 S_V^* \mathcal{K} \gamma_H}{(K_2 K_3)^2 \mu_H} \left[1 - \frac{V_H^*}{N_H^*} \epsilon \right]$$

$$G_2 = \frac{[\beta_{HV}(1-u)]^3 S_H^* S_V^* \mathcal{K}}{(N_H^*)^2 K_1 K_2 K_3}, \quad G_3 = \frac{[S_H^* \sigma + V_H^* K_1 (1-\epsilon)]}{\mu_H}, \quad G_4 = \frac{(N_H^*)^2 \phi_V^2 b_V \eta_V}{K_4^2 N_0 (N_0 - 1)}.$$

□

Theorem 5.3 *The yellow fever model (5) undergoes backward bifurcation at $R_{0v} = 1$ whenever the bifurcation coefficient \mathbf{a} , given by (D.3) is positive*

Since the bifurcation coefficient \mathbf{b} is positive, the direction of the bifurcation depends on the sign of \mathbf{a} , which can be positive or negative, and $\mathbf{a} > 0$ means the model (5) may undergoes backward bifurcation at $\mathcal{R}_{0V} = 1$ [11].

Appendix E: Global stability of the DFE (\mathcal{E}_3)

Proof Conditions for global asymptotic stability of the DFE (\mathcal{E}_3) can be found using a method described in [27]. Similar approach was employed in [15,16,28]. Using the property of the DFE, system (5) can be rewritten in a pseudo-triangular form as follows,

$$\begin{aligned} \frac{dS_H}{dt} &= b_H - c_V S_H - \beta_{HV}(1-c_B) \frac{I_V}{N_H} S_H - \mu_H S_H, \\ &= b_H - c_V S_H - \beta_{HV}(1-c_B) \frac{I_V}{N_H} S_H - \mu_H S_H - b_H + c_V S_H^* + \mu_H S_H^*, \quad (E.1) \\ &= -K_1(S_H - S_H^*) - \beta_{HV}(1-c_B) \frac{I_V}{N_H} S_H. \end{aligned}$$

The equation of vaccinated humans is rewritten as

$$\begin{aligned} \frac{dV_H}{dt} &= c_V S_H - \beta_{HV}(1-c_B)(1-\epsilon) \frac{I_V}{N_H} V_H - \mu_H V_H, \\ &= c_V S_H - \beta_{HV}(1-c_B)(1-\epsilon) \frac{I_V}{N_H} V_H - \mu_H V_H - c_V S_H^* + \mu_H V_H^*, \quad (E.2) \\ &= -\mu_H(V_H - V_H^*) + c_V(S_H - S_H^*) - \beta_{HV}(1-c_B)(1-\epsilon) \frac{I_V}{N_H} V_H. \end{aligned}$$

Similarly, the equation of non-infectious aquatic mosquitoes can be rewritten as

$$\begin{aligned} \frac{dA_N}{dt} &= \phi_V \left(1 - \frac{A}{\mathcal{K}} \right) S_V + \phi_V \left(1 - \frac{A}{\mathcal{K}} \right) (1-\eta_V) I_V - b_V A_N - \mu_A A_N - c_L A_N, \\ &= -(A_N - A_N^*) \left(K_4 + \phi_V \frac{S_V}{\mathcal{K}} \right) + \frac{\phi_V}{N_0} (S_V - S_V^*) + \phi_V (1-\eta_V) \left(1 - \frac{A}{\mathcal{K}} \right) I_V \\ &\quad - \phi_V \frac{S_V}{\mathcal{K}} A_I, \end{aligned} \quad (E.3)$$

and

$$\begin{aligned} \frac{dS_V}{dt} &= b_V A_N - \beta_{HV}(1 - c_B) \frac{I_H}{N_H} S_V - \mu_V S_V - c_A S_V, \\ &= -K_5(S_V - S_V^*) + b_V(A_N - A_N^*) - \beta_{HV}(1 - c_B) \frac{I_H}{N_H} S_V. \end{aligned} \tag{E.4}$$

Following the above simplification, the system given by (5) can therefore be re-written in a pseudo-triangular form as

$$\begin{cases} \dot{\mathbf{x}}_1 = A_{11}(\mathbf{x})(\mathbf{x}_1 - \mathbf{x}_1^*) + A_{12}(\mathbf{x})\mathbf{x}_2 \\ \dot{\mathbf{x}}_2 = A_{22}(\mathbf{x})\mathbf{x}_2 \end{cases} \tag{E.5}$$

where $\mathbf{x}_1 = (S_H, V_H, R_H, A_N, S_V)^T$ represents the naive (uninfected) component of the model (5), $\mathbf{x}_2 = (E_H, I_H, A_I, I_V)^T$ represents the infectious part of (5), $\mathbf{x}_1^* = (S_H^*, V_H^*, R_H^*, A_N^*, S_V^*)^T$ is the DFE and

$$\begin{aligned} A_{11}(\mathbf{x}) &= \begin{pmatrix} -K_1 & \omega_H & 0 & 0 & 0 \\ c_V & -\mu_H & 0 & 0 & 0 \\ 0 & 0 & -\mu_H & 0 & 0 \\ 0 & 0 & 0 & -(K_4 + \frac{\phi_V S_V}{\mathcal{K}}) & \frac{\phi_V}{N_0} \\ 0 & 0 & 0 & b_V & -K_5 \end{pmatrix}, \\ A_{12}(\mathbf{x}) &= \begin{pmatrix} 0 & 0 & 0 & -\beta_{HV}(1 - c_B) \frac{S_H}{N_H} \\ 0 & 0 & 0 & -\beta_{HV}(1 - c_B)(1 - \epsilon) \frac{S_H}{N_H} \\ 0 & \tau_H & 0 & 0 \\ 0 & 0 & -\frac{\phi_V S_V}{\mathcal{K}} & \phi_V(1 - \eta_V)(1 - \frac{A}{\mathcal{K}}) \\ 0 & -\beta_{HV}(1 - c_B) \frac{S_V}{N_H} & 0 & 0 \end{pmatrix}, \\ A_{22}(\mathbf{x}) &= \begin{pmatrix} -K_2 & 0 & 0 & \frac{\beta_{HV}(1 - c_B)[S_H + (1 - \epsilon)V_H]}{N_H} \\ \gamma_H & -K_3 & 0 & 0 \\ 0 & 0 & -K_4 & \phi_V \eta_V(1 - \frac{A}{\mathcal{K}}) \\ 0 & \beta_{HV}(1 - c_B) \frac{S_V}{N_H} & b_V & -K_5 \end{pmatrix}. \end{aligned} \tag{E.6}$$

□

Theorem 5.4 Consider (5). Let $\Omega \subset \mathbb{R}_+^{n_1+n_2}$ be a positively-invariant set. If

1. The system (5) is defined on the positively invariant set $\Omega \subset \mathbb{R}_+^{n_1+n_2}$.
2. The sub-system $\dot{\mathbf{x}} = A_{11}(\mathbf{x})(\mathbf{x}_1 - \mathbf{x}_1^*)$ is globally asymptotically stable at the equilibrium \mathbf{x}_1^* .
3. For any $\mathbf{x} \in \Omega$, the matrix $A_{22}(\mathbf{x})$ is Metzler and irreducible.
4. There exists an upper bound matrix \bar{A}_{22} for the set $\bar{\mathcal{M}} = \{A_{22}(\mathbf{x})/\mathbf{x} \in \Omega\}$, with the property that either $\bar{A}_{22} \notin \bar{\mathcal{M}}$ or if $\bar{A}_{22} \in \bar{\mathcal{M}}$ (i.e., $\bar{A}_{22} = \max_{\Omega} \bar{\mathcal{M}}$), then for $\mathbf{x}^* \in \Omega$ such that $\bar{A}_{22} = A_{22}(\mathbf{x}^*)$, then $\mathbf{x}^* \in \mathbb{R}^7 \times \{0\}$ (the DFE sub-manifold contains the points where the maximum is attained).
5. The stability modulus of \bar{A}_{22} satisfies $\alpha(\bar{A}_{22}) \leq 0$.

Then, the associated DFE is GAS in Ω [15,27].

Recall that the model given by (5) is defined on a positively invariant domain given by Ω in (7). Also straightforward computation shows that the eigenvalues of $A_{11}(x)$ are real and negative. Therefore conditions 1 and 2 of (5.4) are satisfied, for condition 3 of (5.4), the following definition is used.

Definition 5.5 A square matrix \mathbf{A} is said to be reducible if it has the form

$$\mathbf{A} = \begin{pmatrix} \mathbf{A}_1 & \mathbf{A}_2 \\ 0 & \mathbf{A}_3 \end{pmatrix} \tag{D.7}$$

where \mathbf{A}_1 and \mathbf{A}_3 are square matrices of order at least 1 or if \mathbf{A} can be transformed into the form (D.7) by simultaneous permutations of rows and columns [18]. It is irreducible otherwise. Alternatively, A square matrix is irreducible if and only if its associated digraph is strongly connected.

Fig. 3 is the associated digraph of the matrix $A_{22}(x)$, and it is clear that it is strongly connected. Thus condition 3 is satisfied. Furthermore, since $S_V \leq \frac{\mathcal{K}b_V}{\mu_V+c_A} = S_V^* \frac{N_0}{N_0-1}$ in Ω , $A \leq \mathcal{K}$, $S_H + (1 - \epsilon)V_H \leq N_H$, and $L_H^* = \frac{b_H}{\delta_H+\mu_H} \leq N_H \leq \frac{b_H}{\mu_H} = N_H^*$ then the matrix

$$\bar{A}_{22}(\mathbf{x}) = \begin{pmatrix} -K_2 & 0 & 0 & \beta_{HV}(1-c_B) \\ \gamma_H & -K_3 & 0 & 0 \\ 0 & 0 & -K_4 & \phi_V \eta_V \\ 0 & \frac{\beta_{HV}(1-c_B)S_V^*N_0}{L_H^*(N_0-1)} & b_V & -K_5 \end{pmatrix}, \tag{D.8}$$

is an upper bound of $A_{22}(x)$. For condition 5 of Theorem (5.4), the following result of [27] is applied.

Lemma 5.6 Let \mathcal{M} be a Metzler matrix which is block decomposed

$$\mathcal{M} = \begin{pmatrix} \mathbb{A} & \mathbb{B} \\ \mathbb{C} & \mathbb{D} \end{pmatrix} \tag{D.9}$$

where \mathbb{A} and \mathbb{D} are square matrices. Then \mathcal{M} is Metzler stable if and only if \mathbb{A} and $\mathbb{D} - \mathbb{C}\mathbb{A}^{-1}\mathbb{B}$ are Metzler stable.

In the case of $\bar{A}_{22}(x)$ defined above, we have

$$\mathbb{A} = \begin{pmatrix} -K_2 & 0 \\ \gamma_H & -K_3 \end{pmatrix}, \quad \mathbb{B} = \begin{pmatrix} 0 & \beta_{HV}(1-c_B) \\ 0 & 0 \end{pmatrix}, \quad \mathbb{C} = \begin{pmatrix} 0 & 0 \\ 0 & \frac{\beta_{HV}(1-c_B)S_V^*N_0}{L_H^*(N_0-1)} \end{pmatrix}, \tag{D.10}$$

$$\mathbb{D} = \begin{pmatrix} -K_4 & \phi_V \eta_V \\ b_V & -K_5 \end{pmatrix}, \quad \mathbb{D} - \mathbb{C}\mathbb{A}^{-1}\mathbb{B} = \begin{pmatrix} -K_4 & \phi_V \eta_V \\ b_V & -K_5 \left[1 - \frac{\beta_{HV}^2(1-c_B)^2 S_V^* N_0 \gamma_H}{L_H^* K_2 K_3 K_5 (N_0-1)} \right] \end{pmatrix}.$$

Therefore, $\mathbb{D} - \mathbb{C}\mathbb{A}^{-1}\mathbb{B}$ is Metzler matrix if

$$\frac{\beta_{HV}^2(1-c_B)^2 S_V^* N_0 N_H^* \gamma_H}{L_H^* K_2 K_3 K_5 (N_0-1) N_H^*} = R_{HV} R_{VH} \frac{N_0 N_H^*}{L_H^* (N_0-1)} < 1 \tag{D.11}$$

and it is stable if

$$K_4 K_5 \left(1 - R_{HV} R_{VH} \frac{N_0 N_H^*}{L_H^* (N_0-1)} - R_{VV} N_0 \right) > 0 \tag{D.12}$$

which implies $R_{HV} R_{VH} \frac{N_0 N_H^*}{L_H^* (N_0-1)} + R_{VV} N_0 \leq 1$.

It should be noted that, condition (D.12) is a generalization of condition (D.11), which is also equivalent to

$$R_{HV}R_{VH} < \frac{L_H^*}{N_H^*} \left(1 - \frac{1}{N_0}\right) < 1, \text{ and } R_{VV} < \frac{1}{N_0} < 1,$$

Hence

$$R_{0v} < \frac{1}{2N_0} + \sqrt{\left(\frac{1}{2N_0}\right)^2 + \frac{L_H^*}{N_H^*} \left(1 - \frac{1}{N_0}\right) \left(1 - \frac{V^*\epsilon}{N_H^*}\right)} < 1.$$

Thus, satisfying condition (D.12) is sufficient for the GAS of the DFE. \square

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