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MODELING VACCINE PREVENTABLE VECTOR-BORNE INFECTIONS: YELLOW FEVER AS A CASE STUDY

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In this paper, we propose and simulate a deterministic model for a vector-borne disease in the presence of a vaccine. The model allows the assessment of the impact of an imperfect vaccine with various characteristics, which include waning protective immunity, incomplete vaccine-induced protection and adverse events. We find three threshold parameters which govern the existence and stability of the equilibrium points. Our stability analysis suggests that the reduction in the mosquito fertility theoretically is the most effective factor of reducing disease prevalence in both low and high transmission areas. To illustrate the theoretical results, the model is simulated by the example of yellow fever. We also perform sensitivity analyses to determine the importance of both vaccine-induced mortality rate and disease-induced mortality rate for determining a control strategy. We found that there is an optimum vaccination rate, above which people die by the vaccination and below which people die by the disease.

Keywords: Mathematical Models; Vaccination; Vector–Borne; Yellow Fever.

1. Introduction

Frequently unnoticed by practicing physicians, arthropod-borne diseases account for a huge proportion of the spectrum of human maladies worldwide, and the problem appears to be growing.[1] Despite the enormous effort of the medical and

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scientific community, controlling disease agents transmitted by arthropod vectors has proven to be difficult.[2–5] The list of emerging and re-emerging infections is enormous but it is worth citing just a few: dengue, malaria, yellow fever, various mosquito-borne encephalitis, leishmaniasis and Lyme disease. Most of the techniques used for the control and eradication of vector-borne diseases were developed in the early 20th century. Rules for source reduction, insecticides, biological control, vaccination, chemotherapy and personal protection were all laid down nearly a century ago.[6] Many of these techniques are still effective, others succeeded initially but failed later for a variety of reasons. Investigators must now incorporate new approaches that will allow them to move to the next level of control to alleviate the effects of vector-borne diseases on human and animal health.[6]

Public health measures to control infectious diseases have relied on the use of vaccines, insecticides and the various types of drugs and, understandingly, most of the literature cited above addresses the evolutionary implications of such control measures.[7]

Vaccination, one of the most successful development in controlling diseases, raises the classical Public Health dilemma of collective versus individual interests: on one hand it is of greatest interest of individuals not to being vaccinated provided that everybody else is protected by the vaccine; on the other hand, it is of greatest interest the entire community that every individual receives the vaccine.[8–17] As all vaccines have adverse effects varying from the simple annoying shot to deaths,[18,19] there would be an optimum level of vaccination that would minimize the negative aspects of vaccination.

In this paper, we present a mathematical model that addresses the effects of vaccination against vector-borne diseases illustrated by the example of yellow fever. This paper is organized as follows. In Sec. 2, we develop the model based on biological features of the transmission of vector-borne diseases where the human and vector populations are in course; Sec. 3 presents the analysis of the trivial and the endemic equilibrium (EE) points, the study is to address the question whether vaccination could ever completely stop the spread of infection in a population and in some rare circumstances could lead to adverse events; Sec. 4 presents the numerical results and epidemiological implications for the case of yellow fever; finally, in Sec. 5 are the conclusion.

2. Model Formulation

The model presented here monitors the temporal dynamics of both human and vector (mosquito) populations. The model is an extension of the model given in Refs. 17, 20 and 21, by incorporating the death induced by the vaccine. The main objective of this study is to carry out a qualitative analysis of the model and determine the impact of a vaccine on the vaccine-induced mortality rate.

It is assumed that the human and vector populations have constant and variable sizes, respectively, and all vectors are born susceptible, so that no vertical transmission is allowed.[22] The total human population size, denoted by $\overline{N}_H$,

is partitioned into four subpopulations of unvaccinated ($\overline{S}_H$), vaccinated ($\overline{V}_H$), infected ($\overline{I}_H$) and recovered ($\overline{R}_H$) humans, so that $\overline{N}_H = \overline{S}_H + \overline{V}_H + \overline{I}_H + \overline{R}_H$. The winged form and aquatic form (comprising eggs, larvae and pupae) are represented by $\overline{N}_M$ and $\overline{S}_E$, respectively. The total population $\overline{N}_M$ is split into uninfected vectors ($\overline{S}_M$), latent vectors ($\overline{L}_M$) and infectious vector, ($\overline{I}_M$), so that $\overline{N}_M = \overline{S}_M + \overline{L}_M + \overline{I}_M$; whereas the total aquatic population is $\overline{S}_E$.

In addition, a homogeneous mixing is incorporated, so that each mosquito has equal chance of either transmitting the virus to the susceptible human in the population or acquiring infection from an infected human. Since $\lambda_H = ab\overline{I}_M$ represents the rate of transmission, the incidence in the human population is given by the mass term $\lambda_H \overline{S}_H/\overline{N}_H$. Likewise, since $\lambda_V = ac\overline{I}_H$ is the rate of infection in the vector population that become infected after biting an infected human, the incidence is given by $\lambda_V \overline{S}_M/\overline{N}_H$.

The model will include the vital dynamics, that is, the natural mortality (μ_H) together with mortality induced by both vaccine (α_v) and disease (α_D), and a positive and constant recruitment rate so that it balances deaths, for the total human population to be of constant size $\overline{N}_H$. The unvaccinated susceptible subpopulation, $\overline{S}_H$ is increased by recruitment at a rate $\prod_E = \mu_H \overline{N}_H + \alpha_D \overline{I}_H + \alpha_v \overline{V}_H$; while the non-infected aquatic forms population follows a classical logistic growth at a rate $\prod_E = r_M \overline{N}_M (1 - \frac{\overline{S}_E}{\kappa_E})$. It is further assumed that the uninfected vector population is generated by emerging from pupae ($c_S \overline{S}_E$).

We assume that all susceptible humans $\overline{S}_H$ are vaccinated at a constant per capita rate, ν_H, where f_H is the degree of vaccine efficacy. From now on we make the realistic assumption that vaccination elicit immune response, but at a certain

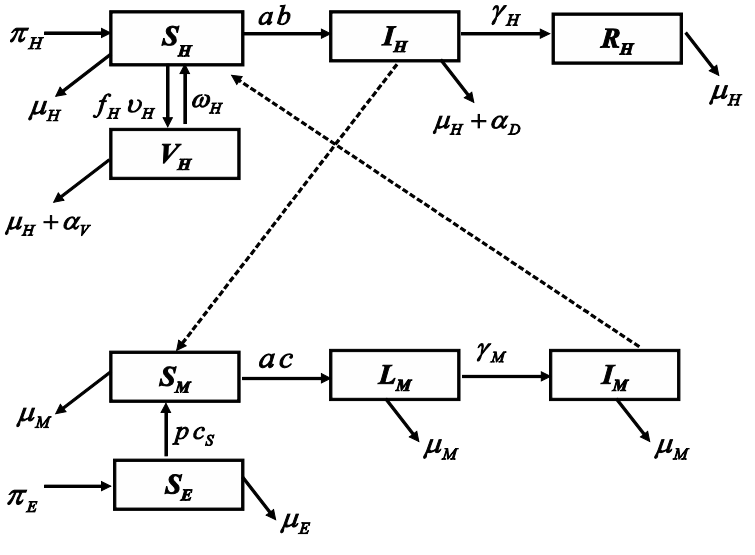


Fig. 1. The flow diagram for the model (2.1).

efficacy, that is, $0 < f_H < 1$. The vaccine-induced immunity is assumed to be lost at per-capita rate, ω_H. In the case $\omega_H = 0$, the vaccine is long lasting, the immunological memory developed against infection does not wane over time; whereas $\omega_H > 0$, implies that vaccine is imperfect and confers a temporary protection for vaccinated humans. Therefore, ω_H is the rate at which the vaccine protection wanes. The vaccinated human population $\overline{V}_H$ is decreased by the waning of vaccine-induced immunity, that is, the vaccinated humans can either reenter the $\overline{S}_H$ class, or die at the natural death and vaccine-induced. Vaccinated individuals engage in increased risk of death compared to unvaccinated individuals. This last point is one of the great interest here.

Furthermore, it is also assumed that the uninfected vectors population ($\overline{S}_M$) is diminished by infection which is acquired by contact with infected humans and by natural death at a rate μ_M. Latent vectors develop symptoms of disease and become infected at rate γ_M. The aquatic population, and infected and latent vectors population die at a rate μ_E and μ_M, respectively.

The flow diagram of the model is depicted in Fig. 1.

Using these assumptions and definitions the model is then governed by the following system of nonlinear ordinary differential equations:

$$\begin{cases} \dfrac{d\overline{S}_M}{dt} = \mu_H \overline{N}_H + \alpha_D \overline{I}_H + (\alpha_v + \omega_H)\overline{V}_H - ab\overline{I}_M \dfrac{\overline{S}_H}{\overline{N}_H} - \mu_H \overline{S}_H - f_H \upsilon_H \overline{S}_H \\ \dfrac{d\overline{V}_H}{dt} = f_H \upsilon_H \overline{S}_H - (\mu_H + \omega_H + \alpha_v)\overline{V}_H \\ \dfrac{d\overline{I}_H}{dt} = ab\overline{I}_M \dfrac{\overline{S}_H}{\overline{N}_H} - (\mu_H + \alpha_D + \gamma_H)\overline{I}_H \\ \dfrac{d\overline{R}_H}{dt} = \gamma_H \overline{I}_H - \mu_H \overline{R}_H \\ \dfrac{d\overline{S}_M}{dt} = c_s \overline{S}_E - \left(\mu_M + ac\dfrac{\overline{I}_H}{\overline{N}_H}\right)\overline{S}_M \\ \dfrac{d\overline{L}_M}{dt} = ac\overline{S}_M \dfrac{\overline{I}_M}{\overline{N}_M} - (\gamma_M + \mu_M)\overline{L}_M \\ \dfrac{d\overline{I}_M}{dt} = \gamma_M \overline{L}_M - \mu_M \overline{I}_M \\ \dfrac{d\overline{S}_E}{dt} = r_M \overline{N}_M \left(1 - \dfrac{\overline{S}_M}{\kappa_E}\right) - (\mu_E + c_s)\overline{S}_E, \end{cases} \tag{2.1}$$

with generic initial conditions $\overline{S}_H(0) \geq 0$, $\overline{V}_H \geq 0$, $\overline{I}_H \geq 0$, $\overline{R}_H \geq 0$, $\overline{S}_M \geq 0$, $\overline{L}_M \geq 0$, $\overline{I}_M \geq 0$, $\overline{S}_E \geq 0$. The total human population given by $\overline{N}_H = \overline{S}_H + \overline{V}_H + \overline{I}_H + \overline{R}_H$ is constant, due to $\frac{d\overline{N}_H}{dt} = 0$; while the total adult vectors population, $\overline{N}_M = \overline{S}_M + \overline{L}_M + \overline{I}_M$ is given by

$$\frac{d\overline{N}_M}{dt} = c_s \overline{S}_E - \mu_M \overline{N}_M. \tag{2.2}$$

Table 1. Model's variables and their biological meaning.

Variable	Description
$\overline{S}_H$	Population of susceptible humans
$\overline{I}_H$	Population of infected humans
$\overline{R}_H$	Population of recovered humans
$\overline{V}_H$	Population of vaccinated humans
$\overline{N}_H$	Population of total human population
$\overline{S}_M$	Population of uninfected vectors
$\overline{L}_M$	Population of latent vectors
$\overline{I}_M$	Population of infected vectors
$\overline{N}_M$	Population of total vectors population
$\overline{S}_E$	Population of aquatic forms

Table 2. Model's parameters and their biological meaning.

Parameter	Description
a	Average daily biting rate
b	Fraction of actually infective bites
μ_H	Humans natural mortality rate
α_V	Vaccine-induced mortality rate for vaccinated humans
α_D	Disease-induced mortality rate for infected humans
γ_H	Humans recovery rate
ω_H	Waning rate of vaccine
υ_H	Vaccination rate
f_H	Vaccine efficacy
γ_M	Vectors latency rate
μ_M	Vectors natural mortality rate
r_M	Oviposition rate
κ_E	Aquatic carrying capacity
μ_E	Aquatic natural mortality rate
c	Vectors susceptibility
c_S	Emerging rate

In order to assess the mortality due to disease and vaccine, the compartments for both disease-induced mortality and vaccine-induced mortality are included in the system (2.1) by

$$\frac{d\overline{\Lambda}_D}{dt} = \alpha_D \overline{I}_H \quad \text{and} \quad \frac{d\overline{\Lambda}_V}{dt} = \alpha_V \overline{V}_H. \tag{2.3}$$

The variables and parameters are described in Tables 1 and 2, respectively.

3. Analysis of the Model

3.1. *Basic properties*

Before analyzing model (2.1), it is instructive to explore its basic qualitative features. Because system (2.1) monitors the dynamics of human, vector and aquatic

populations, all parameters of the model are assumed to be non-negative. Furthermore, it can be shown that all state variables in the system are also non-negative for all time $t \geq 0$. It is a simple matter to show that Eq. (2.1) are well-posed, in the sense, that if the initial data are in the feasible region

$$\Omega = \{(\overline{S}_H, \overline{V}_H, \overline{I}_H, \overline{R}_H, \overline{S}_M, \overline{L}_M, \overline{I}_M, \overline{S}_E) \in R^8 : \overline{S}_H \geq 0, \overline{V}_H \geq 0, \\ \overline{I}_H \geq 0, \overline{R}_H \geq 0, \overline{S}_M \geq 0, \overline{L}_M \geq 0, \overline{I}_M \geq 0, \overline{S}_E \geq 0\},$$

then the solutions will be defined for all time $t \geq 0$ and remain in this region. Since, $\overline{N}_H$ is constant, we write $\lambda_M = ab\overline{I}_M/\overline{N}_H = ab\overline{I}_M$, and the following result can be proven.

Theorem 3.1. *If the initial conditions of system* (2.1) *lie in region* Ω, *then there exists a unique solution for* (2.1) *that remains in* Ω *for all time* $t \geq 0$.

The proof of Theorem 3.1, based on using a standard proof by contradiction,[23] is given in Appendix A.

To simplify the mathematical analysis of this study, and without loss of generality, we can introduce the proportions

$$S_H = \frac{\overline{S}_H}{\overline{N}_H}, V_H = \frac{\overline{V}_H}{\overline{N}_H}, I_H = \frac{\overline{I}_H}{\overline{N}_H}, R_H = \frac{\overline{R}_H}{\overline{N}_H}, S_M = \frac{\overline{S}_M}{k_E}, \\ L_M = \frac{\overline{L}_M}{k_E}, I_M = \frac{\overline{I}_M}{k_E}, N_M = \frac{\overline{N}_M}{k_E}, S_E = \frac{\overline{S}_E}{k_E}.$$

By using the relation $S_H = 1 - V_H - I_H - R_H$, $S_M = N_M - L_M - I_M$, the equation for S_H and S_M in (2.1) can be eliminated and the equation for N_M can be then introduced. Hence, the system (2.1) can be then written as the equivalent seven-dimensional nonlinear system of ordinary differential equations:

$$\begin{cases} \dfrac{dV_H}{dt} = f_H \upsilon_H (1 - V_H - I_H - R_H) - (\mu_H + \omega_H + \alpha_v) V_H \\ \dfrac{dI_H}{dt} = ab \dfrac{\kappa_E}{\overline{N}_H} I_M (1 - V_H - I_H - R_H) - (\mu_H + \alpha_D + \gamma_H) I_H \\ \dfrac{dR_H}{dt} = \gamma_H I_H - \mu_H R_H \\ \dfrac{dL_M}{dt} = acI_H (N_M - L_M - I_M) - (\gamma_M + \mu_M) L_M \\ \dfrac{dI_M}{dt} = \gamma_M L_M - \mu_M I_M \\ \dfrac{dN_M}{dt} = c_s S_E - \mu_M N_M \\ \dfrac{dS_E}{dt} = r_M N_M (1 - S_E) - (\mu_E + c_s) S_E. \end{cases} \tag{3.1}$$

Finally, it is important to point out that the region of biological interest

$$\Omega_1 = \{(V_H, I_H, R_H, L_M, I_M, N_M, S_E) \in R^7 : 0 \leq V_H + I_H + R_H \leq 1,$$
$$0 \leq S_M + L_M + I_M = N_M \leq 1, S_E \leq 1\}$$

is positively invariant under the flow induced by Eq. (3.1), as the vector field on the boundary does not point to the exterior. Since solutions approach, enter or stay in finite time Ω in they are eventually bounded and hence exist for $t \geq 0$. Therefore, the model (3.1) is mathematically and epidemiologically well posed. It is therefore sufficient to consider solutions in Ω_1. In this region, the usual existence and uniqueness results hold for the system. Hence, the model (2.1) will be, from now on, represented by system (3.1) only. In this way, our next result concerns the existence and stability of equilibrium points of system (3.1).

3.2. *The existence of equilibria*

In this section, we present the results of the equilibrium solutions of system (3.1) which are biologically feasible as well as the reproductive number. In Appendix B, it is shown the possible equilibrium solutions the system (3.1) can have. However, it is worth to highlight Eqs. (B.11) and (B.12) given by

$$R_{\text{vac}} = R_0[1 - \rho_{\text{vac}}], \quad \text{where } 0 < \rho_{\text{vac}} = \frac{f_H \nu_H}{f_H \nu_H + \mu_H + \omega_H + \alpha_V} < 1$$

and

$$R_0 = \frac{a^2 bc \gamma_M \kappa_E}{(\mu_H + \alpha_D + \gamma_H)(\mu_M + \gamma_M)\mu_M} \frac{\overline{N}_M}{\overline{N}_H},$$

since, epidemiologically speaking, they state the effort to effectively to control the disease.

Note that since $0 < \rho_{\text{vac}} < 1, R_{\text{vac}} < R_0$, and R_{vac} can be interpreted as the average total number of new infections caused by a single infected individual, introduced into a susceptible population in which some individuals have been vaccinated. Thus, in the absence of vaccination (so that, $v_H = 0$, and hence $\rho_{\text{vac}} = 0$), the vaccination reproductive number R_{vac} reduces to R_0, which is the basic reproduction number (see Refs. 24–29 for more details) in the absence of any control measure.

It is also worth mentioning that from Eq. (B.11) it is possible to evaluate the threshold biting rate, (a^{thres}), by writing

$$R_{\text{vac}} = \left(\frac{a}{a^{\text{thres}}}\right)^2, \tag{3.2}$$

where

$$a^{\text{thres}} = \mu_M \sqrt{\frac{(\mu_H + \alpha_D + \gamma_H)(\mu_M + \gamma_M) r_M}{bc\gamma_M c_s \kappa_E (r_M - r_M^{\text{thres}})(1 - \rho_{\text{vac}})}} \tag{3.3}$$

Notice that $R_{\text{vac}} = 1$, when $a = a^{\text{thres}}$.

In what follows, the analysis present in Appendix B, indicates the possibility of the existence of the following positive equilibrium points for system (3.1):

(1) for $r_M < r_M^{\text{thres}}$, the disease-free equilibrium (DFE) is defined by the human population $P_0^H = (\rho_{\text{vac}}, 0, 0, 0, 0, 0, 0)$,
(2) for $r_M > r_M^{\text{thres}}$ and $R_{\text{vac}} < 1$, the DFE is defined by both human and vector populations, $P_0^{HM} = (\rho_{\text{vac}}, 0, 0, 0, 0, N_M^*, S_E^*)$,
(3) for $r_M > r_M^{\text{thres}}$ and $R_{\text{vac}} > 1$, the EE point is given by $P_1^{HM} = (V_H^*, I_H^*, R_H^*, L_M^*, I_M^*, N_M^*, S_E^*)$,

where

$$V_H^* = \rho_{\text{vac}}\left[1 - \frac{(\mu_H + \gamma_H)}{\mu_H} I_H^*\right], \quad R_H^* = \frac{\gamma_H}{\mu_H} I_H^*, \quad I_H^* = \frac{R_{\text{vac}} - 1}{R_{\text{vac}}\left(1 + \frac{\gamma_H}{\mu_H}\right) + \frac{ac}{\mu_M}},$$

$$L_M^* = \frac{\mu_M}{\gamma_M} I_M^*, \quad N_M^* = \frac{c_s}{\mu_M} S_E^*, \quad S_E^* = \left[1 - \frac{r_M^{\text{thres}}}{r_M}\right],$$

$$I_M^* = \frac{(\mu_H + \alpha_D + \gamma_H) I_H^*}{\frac{ab\kappa_E}{N_H}(1 - \rho_{\text{vac}})\left[1 - \left(1 + \frac{\gamma_H}{\mu_H}\right) I_H^*\right]}. \tag{3.4}$$

Quite apart from this, the existence of the positive equilibrium points for system (3.1) given in Appendix B, can be summarized as follows.

Theorem 3.2. *The model* (3.1) *has the DFE* P_0^H *whenever* $r_M < r_M^{\text{thres}}$. *Otherwise, model* (3.1) *has the DFE* P_0^{HM} *and the EE* P_1^{HM}. *For* $r_M > r_M^{\text{thres}}$, *if* $R_{\text{vac}} < 1$ (*or* $a < a^{\text{thres}}$), *the unique equilibrium that exists is the DFE* P_0^{HM}; *if* $R_{\text{vac}} > 1$ (*or* $a > a^{\text{thres}}$), *the unique equilibrium that exist is the EE* P_1^{HM}.

Having found the scenarios in which there exist the equilibria for system (3.1), it is instructive to analyze whether or not these equilibria are stable under any of these scenarios. Moreover, together with the vaccination rate, v_H, and the reproduction number, R_{vac}, we will see that each scenario can be used as a check for the existence and the stability of all equilibria. This is explored below.

3.3. *Stability of equilibrium points*

In the absence of disease (i.e., $I_H^0 = 0$), model (3.1) has two DFEs given by P_0^H and P_0^{HM}. To establish the stability of both equilibria, the Jacobian of system (3.1) is computed and evaluated at both P_0^H and P_0^{HM}. We will discuss the properties of both equilibrium points making an elementary row-transformation for the Jacobian matrix.

Evaluating the system's Jacobian at P_0^H, the local stability of P_0^H is straightforward evaluated by the five eigenvalues given by $\tau_1 = -\mu_M$, $\tau_2 = -\mu_H$, $\tau_3 = -(\mu_M + \gamma_M)$, $\tau_4 = -(\mu_H + \alpha_D + \gamma_H)$ and $\tau_5 = -(f_H v_H + \mu_H + \alpha_v + \gamma_H)$. The

other eigenvalues are expressed as the roots of the following submatrix,

$$M^{P_0^H} = \begin{bmatrix} -\mu_M & c_s \\ r_M & -(\mu_E + c_s) \end{bmatrix}. \tag{3.5}$$

It is easy to verify that the traces of the matrices $\mathrm{tr}(M^{P_0^H})$ and $\mathrm{tr}(M^{P_0^H})$ are always negative. Moreover, the determinant of the matrix, $\det(M^{P_0^H})$, is positive if and only if $r_M < r_M^{\mathrm{thres}}$. In other words, it means that the two eigenvalues of matrix $M^{P_0^H}$ are either negative or have negative real part whenever $r_M < r_M^{\mathrm{thres}}$.

Therefore, all the eigenvalues of the characteristic equation associated with the system (3.1) at P_0^H have negative real parts if and only if $r_M < r_M^{\mathrm{thres}}$. We state then the following result:

Theorem 3.3. *The DFE P_0^H of the model* (3.1) *exists and it is locally asymptotically stable if $r_M < r_M^{\mathrm{thres}}$. Otherwise, P_0^H is unstable.*

Furthermore, by using the Routh–Hurwitz criteria, it can also be established for system (3.1) that the DFE P_0^{HM} exists and it is locally asymptotically stable. This result is summarized below (the proof is given in Appendix C).

Theorem 3.4. *For $r_M > r_M^{\mathrm{thres}}$ the disease-free equilibrium of the model* (3.1), *P_0^{HM}, exists and it is locally asymptotically stable if $R_{\mathrm{vac}} < 1$. Otherwise, P_0^{HM} is unstable.*

Having found the scenarios in which the DFEs of the model (3.1) exhibit local asymptotic dynamics, to ensure that disease elimination is independent of the initial sizes of the sub-populations, a global stability proof for the DFE, P_0^{HM}, using a comparison theorem is presented in Appendix D.

Theorem 3.5. *For $r_M > r_M^{\mathrm{thres}}$, the DFE P_0^{HM} is globally asymptotically stable whenever $R_{\mathrm{vac}} < 1$.*

It should also be mentioned that the consequence of the above result is that for $R_{\mathrm{vac}} > 1$ the disease will establish itself in the population and, clearly, this is a situation where the disease elimination would depend upon the vaccination. Thus, it will be possible to eliminate the disease from the population whenever the vaccination (although imperfect) results in making (and keeping) $R_{\mathrm{vac}} < 1$.

In this way, it is instructive to determine the elimination conditions in terms of the fraction of the population that are vaccinated at equilibrium. The basic problem is to find out the optimum value of vaccination (υ_H) necessary to eradicate the disease. To find the critical value of υ_H, one sets $R_{\mathrm{vac}} = 1$, and solving Eq. (3.2) for υ_H, the threshold vaccination rate is found to be

$$\upsilon_H^{\mathrm{thres}} = \frac{1}{\varepsilon}(R_0 - 1), \tag{3.6}$$

where $\varepsilon = \frac{f_H}{(\mu_H + \omega_H + \alpha_\upsilon)}$.

Table 3. Conditions of existence and stability of the positive equilibria of model (3.1).

Existence and stability conditions	Positive equilibrium points
$r_M < r_M^{\text{thres}}$	$P_0^H = (V_H^0, 0, 0, 0, 0, 0, 0)$
$r_M > r_M^{\text{thres}}, \upsilon_H > \upsilon_H^{\text{thres}}, R_{\text{vac}} < 1$	$P_0^{HM} = (V_H^0, 0, 0, 0, 0, N_M^*, S_E^*)$
$r_M > r_M^{\text{thres}}, \upsilon_H > \upsilon_H^{\text{thres}}, R_{\text{vac}} > 1$	$P_1^{HM} = (V_H^*, I_H^*, R_H^*, L_M^*, I_M^*, N_M^*, S_E^*)$

It is worth remembering that $R_0 > 0$ whenever $r_M > r_M^{\text{thres}}$. From Eq. (3.6), two scenarios emerge: one for the case where $R_0 < 1$, which implies $\upsilon_H^{\text{thres}} < 0$ and $R_{\text{vac}} < 1$ (from Theorem 3.4, P_0^{HM} is the unique DFE locally asymptotically stable in this case); the other for $R_0 > 1$, which implies in $\upsilon_H^{\text{thres}} > 0$, and either $R_{\text{vac}} < 1$ or $R_{\text{vac}} > 1$. In such scenarios, we can, therefore, conjecture that P_0^{HM} could be globally asymptotically stable for $R_{\text{vac}} < 1$, while P_1^{HM} could be globally asymptotically stable for $R_{\text{vac}} > 1$. Thus, it is necessary to determine the vaccine effort (υ_H) to reduce R_{vac} below one, which corresponds to a decrease in the number of infected humans to ensure the conditions under which the disease dies out or at least reduce its prevalence. Thus, if $\upsilon_H > \upsilon_H^{\text{thres}}$, vaccination will eliminate the disease from the community, that is, R_{vac} will be reduced below one. In contrast, if $\upsilon_H < \upsilon_H^{\text{thres}}$, vaccination will fail to eliminate the disease from the community, that is, R_{vac} could not be reduced below one and the disease will then persist.

In summary, in the light of the aforementioned considerations together with extensive numerical simulations, we can establish the following conjecture for system (3.1):

Conjecture. *For $r_M < r_M^{\text{thres}}$ the DFE P_0^H is globally asymptotically stable. If $r_M > r_M^{\text{thres}}$, then P_0^{HM} is globally asymptotically stable if $\upsilon_H > \upsilon_H^{\text{thres}}$ and $R_{\text{vac}} < 1$; if $\upsilon_H < \upsilon_H^{\text{thres}}$ and $R_{\text{vac}} > 1$, then P_1^{HM} is globally asymptotically stable.*

All the existence and stability results for model (3.1) are summarized in Table 3. The numerical results (see Table 3) show that the unique EE point, to which the simulations did converge, supports the Conjecture above.

4. Numerical Illustration: The Case of Yellow Fever

Yellow fever (YF) is a hemorrhagic fever caused by a *Flavivirus*, family Flaviridae,[30,31] and is characterized by fever, chills, loss of appetite, nausea, muscle pains particularly in the back, and headaches.[32] More than 200,000 infections and 30,000 deaths are reported every year,[32] of which about 90% the cases occur in Africa.[33] In addition, a billion people live in an area of the world where the disease is reported.[32] YF also affects tropical areas of South America, but has never been reported in Asia.[32,34,35] The incidence of YF has been increasing in the last years,[32,36] probably due to fewer people being immune, more people living in cities, people moving

frequently, and changing climate.[32] The probable origin of the disease is Africa, from where it spread to South America through the slave trade in the 17th century.[37–39]

An effective vaccine against YF exists and some countries require vaccinations for travelers.[32] In rare cases (less than one in 200,000–300,000 doses), the vaccination can cause YF vaccine-associated viscerotropic disease (YEL-AVD), which is fatal in 60% of cases, probably due to the genetic morphology of the immune system. Another possible side effect is an infection of the nervous system, which occurs in one in 200,000–300,000 cases, causing YF vaccine-associated neurotropic disease (YEL-AND), which can lead to meningoencephalitis, fatal in less than 5% of cases.[35] In some rare circumstances, however, the fatality rate of vaccine induced diseases can reach alarming proportions, as observed recently by Mascheretti *et al.* (see Ref. 40 for more details), who found 1 death per million doses applied in a Southeastern Brazilian region.[17]

To illustrate the results theoretically contained in this paper, model (3.1) is simulated using baseline parameters values/ranges summarized in Table 4 (unless otherwise stated). The parameter values are mostly taken from the literature,[17] except for vaccine-induced mortality rate for vaccinated humans[41] (α_v). Furthermore, the average daily biting rate (a), vaccination rate (υ_H) and disease-induced mortality rate for infected humans (α_D) are chosen for simulations purposes only, so we can illustrate our theoretical results. From now on, all the simulations are carried out for $r_M > r_M^{\text{thres}}$, in accordance with the fact that both P_0^{HM} and P_1^{HM} play an important role to assess the control of the disease in a community. Note that for the baseline parameters values in Table 4, $r_M^{\text{thres}} = 0.2186$ days^{-1}.

In the previous sections, we obtained the parameter restrictions for disease persistence and eradication. Our stability analysis showed that reducing the mosquito fertility, r_M is "theoretically" the most effective way of reducing disease prevalence

Table 4. YF baseline values for model (3.1).

Parameter	Value	Reference
a	Variable	guessed
b	0.6	17
μ_H	3.5×10^{-5} days^{-1}	17
α_V	2.1×10^{-10} days^{-1}	41
α_D	1.0×10^{-2} days^{-1}	guessed
γ_H	0.143 days^{-1}	17
ω_H	0.1 days^{-1}	17
υ_H	variable (days^{-1})	guessed
f_H	(0–1)	
γ_M	0.143 days^{-1}	17
μ_M	0.09 days^{-1}	17
r_M	50 days^{-1}	17
k_E	1	guessed
μ_E	0.1 days^{-1}	17
c	0.8	17
c_S	0.07 days^{-1}	17

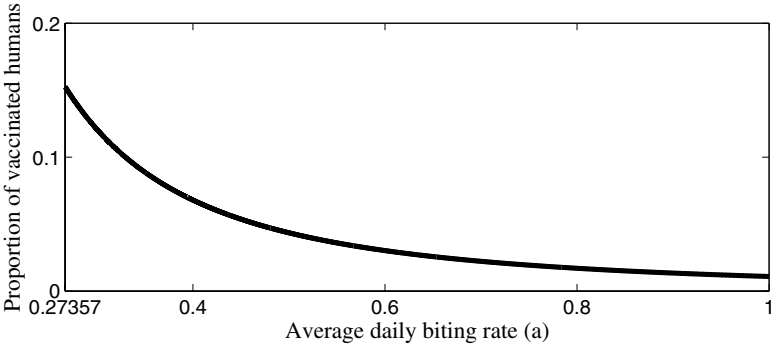
since it has an important effect on disease transmission in both low and high transmission areas (as measured by $R_{\text{vac}} > 1$ and $R_{\text{vac}} \gg 1$, respectively). It is not, however, possible to directly reduce the mosquito fertility. The unique and viable way to reduce effectively r_M, is to reduce the biting rate (using insect repellent or mosquito nets). It is worthwhile here to highlight the fact that $r_M = f(a)$, that is, the mosquitoes need the blood meal (biting hosts) to mature their eggs. In this way, the reduction in the biting rate have, therefore, a positive impact in reducing mosquito fertility. This model, however, does not include this biological reality. In a future work, we will include this fact into a new model.

In addition, to estimate the importance of the biting rate and the number of "effective" mosquito–human contacts, we would need to know the values of other population demographic parameters. For one such example, we expect that strategies that reduce the number of "effective" contacts, such as vaccine, would have effect on the disease prevalence. As a consequence, we should also expect that any change in vaccination rate (υ_H) could have two opposite effects. On one hand, increasing υ_H, the proportion of infected humans decrease, but the number of deaths of vaccinated humans (α_v) would increase. On the other hand, decreasing υ_H increases the number of "effective" contacts between humans and mosquitoes which tends to increase R_{vac} and the proportion of infected humans. These points are of a great deal of interest here.

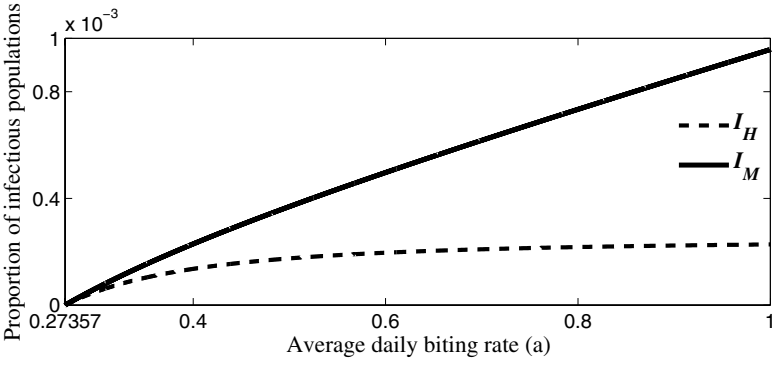
In summary, from now on, we will explore the implications of the biting rate (a), the vaccination rate (υ_H) and the mortality rate for vaccinated humans (α_v) for low and high ($R_{\text{vac}} > 1$ and $R_{\text{vac}} \gg 1$) transmission areas, whenever $r_M > r_M^{\text{thres}}$.

From the discussion above, it is worth mentioning that the vaccinated reproduction number, R_{vac}, increases as both average daily biting rate (a) and vaccine-induced mortality rate in humans (α_v) increase [see Eqs. (3.3), (B.3) and (B.11)]. For $R_{\text{vac}} < 1$ (or $a < a^{\text{thres}}$), P_0^{HM} is globally asymptotically stable. For $R_{\text{vac}} > 1$ and $R_{\text{vac}} \gg 1$ (or $a > a^{\text{thres}}$), the proportion of vaccinated humans (V_H^*) decreases while the proportion of both infected humans and infected vectors ($I_H^* \neq 0, I_M^* \neq 0$) increase. If $\upsilon_H < \upsilon_H^{\text{thres}}$, P_1^{HM} is then globally asymptotically stable. To numerically illustrate this fact, the simulations are carried out for $r_M > r_M^{\text{thres}}, \upsilon_H = 0.00001$ (see Ref. 41), with $\upsilon_H < \upsilon_H^{\text{thres}}$, $a > a^{\text{thres}}$ as increases. The results are shown in Figs. 2(a) and 2(b).

In contrast, the vaccinated reproduction number, $R_{\text{vac}} < 1$, decreases as the vaccination rate (υ_H) increases, showing the benefits of vaccination in the control of the epidemic. Thus, if the average daily biting rate (a) is sufficiently low and it has not overcome its threshold value, a^{thres}, the epidemic is controlled and the vaccine does not have any impact. On the other hand, if $a > a^{\text{thres}}$, then the epidemic could emerge (and persist) and the vaccine will have a positive impact in terms of reducing YF prevalence. Clearly, this is a scenario where vaccination is beneficial to the community. This scenario is illustrated numerically in Fig. 3. The simulations show the profile of populations of both infectious humans and vectors. Thus, if $\upsilon_H < \upsilon_H^{\text{thres}}$, then $I_H^* \neq 0$, $I_M^* \neq 0$; hence P_1^{HM} globally asymptotically



(a)



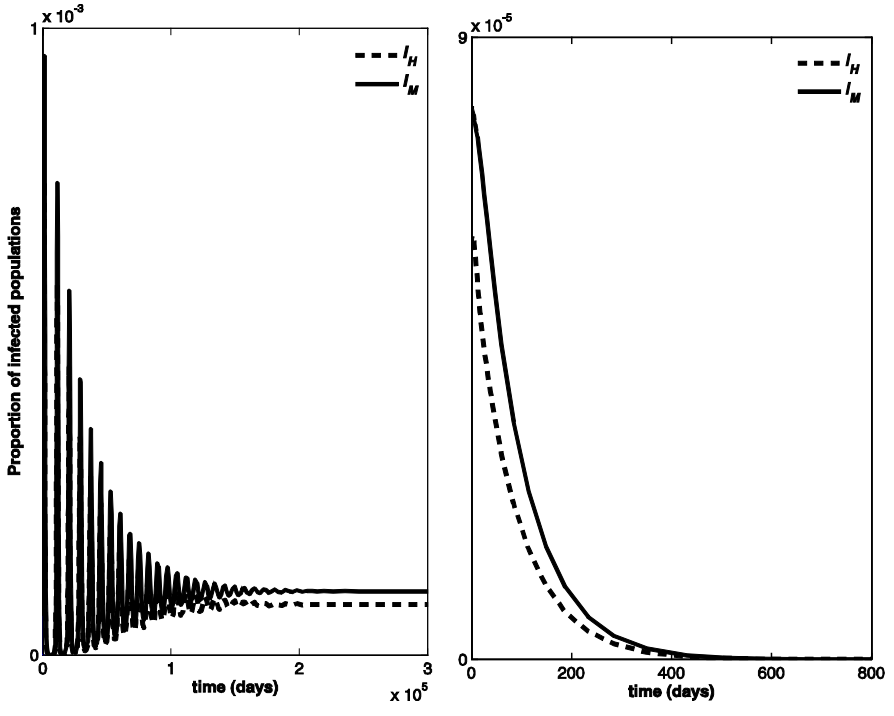
(b)

Fig. 2. Effect of daily biting rate (a) on the prevalence of YF. Simulation of model (3.1) as increases, with $a \geq a^{\text{thres}} = 0.27$ (or $R_{\text{vac}} > 1$). All parameters values used are given in Table 4, except for $f_H = 0.1$ and $\upsilon_H = 0.00001$. (a) The prevalence of vaccinated humans decreases as the average daily biting rate increases. (b) Proportion of both infected humans and mosquitoes populations increase as the average daily biting rate increases.

stable, so that the disease persist into the population [Fig. 3(a)]. If $\upsilon_H > \upsilon_H^{\text{thres}}$, then $I_H^* = 0$, $I_M^* = 0$, hence P_0^{HM} is globally asymptotically stable, so that the disease is eradicated from population [Fig. 3(b)].

However, the challenge is to find out the optimum value of vaccination coverage (υ_H) where there is still high enough control of the disease and, sometimes minimizes the vaccine adverse effects.

Figure 4 illustrates the benefits of vaccination in the control of the epidemic showing that whenever $\upsilon_H > \upsilon_H^{\text{thres}}$, vaccination will have a positive impact in controlling the disease, but in contrast, it can increase mortality in humans due to the vaccine adverse effects. It is possible to find such a condition by simulating the model with increasing values of vaccination rate, υ_H, while keeping the other parameters fixed. As it was expected, we observed that the proportion of vaccinated humans V_H^* always increases, as υ_H increases. Moreover, while $\upsilon_H < \upsilon_H^{\text{thres}}$, $R_{\text{vac}} > 1$



(a) (b)

Fig. 3. For $r_M > r_M^{\text{thres}}, a > a^{\text{thres}}, f_H = 0.1$. The other parameters values used are given in Table 4. Profile of populations of both infected humans (I_H^*) and mosquitoes ((I_M^*)). (a) For $\upsilon_H < \upsilon_H^{\text{thres}}$, the disease persists into the population (P_1^{HM}, is globally asymptotically stable). (b) For $\upsilon_H > \upsilon_H^{\text{thres}}$, the disease is eradicated from population (P_0^{HM} is globally asymptotically stable).

(or $a > a^{\text{thres}}$), and P_1^{HM} is the unique equilibrium globally asymptotically stable, such that both the proportions of infected humans (I_H^*) and the total mortality (μ_{tot}) decrease with increasing values of υ_H. When $\upsilon_H \geq \upsilon_H^{\text{thres}}$, then $R_{\text{vac}} \leq 1$ and $I_H^* = 0$, such that P_0^{HM} is the unique equilibrium globally asymptotically stable, but the total mortality (μ_{tot}) increases with increasing values of υ_H. Therefore, making the vaccine effort slightly above the threshold value $\upsilon_H^{\text{thres}}$, it is still possible to control the disease with a minimum for μ_{tot}. This scenario is due to the smaller contribution from α_v ($\alpha_V \ll \alpha_D$, see Table 4 and sensitivity analysis).

Although the above result is intuitively expected, it is very difficult to reach the vaccination rate υ_H needed to control YF, without a significant increase in the number of deaths of vaccinated humans. In such a situation, it is pertinent to ask, what is the benefit of a limited vaccination? It is known that a low coverage of vaccination still confers protection to each individual vaccinated, who in turn provides some protection to the others, since the vaccinated individual would have

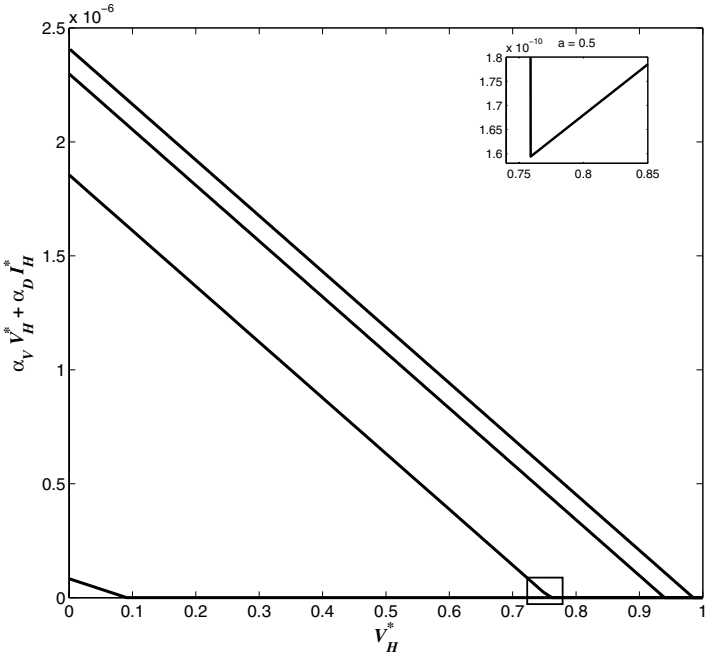


Fig. 4. Effect of vaccination rate (υ_H) on total mortality, $\mu_{\text{tot}} = \alpha_v V_H^* + \alpha_D I_H^*$. Simulations of model (3.1) depicting the total mortality μ_{tot} plotted versus V_H^*, with increasing values of average daily biting rate (a), as υ_H increases. From left to right: $a = 0.3(p^* = 0.034)$; and $a = 0.5(p^* = 0.7585)$; $a = 1.0(p^* = 0.9396)$ and $a = 2.0(p^* = 0.9849)$. All other parameters as in Table 4, with $f_H = 0.1$. The inset shows the case where $a = 0.5$ showing that μ_{tot} decreases if $\upsilon_H < \upsilon_H^{\text{thres}}$, and increases if $\upsilon_H > \upsilon_H^{\text{thres}}$. The optimal proportion of the population that needs to be immunized is indicated by $p^* = 1 - 1/R_0$.

infected is less likely to develop the disease. This is known as herd immunity (see Refs. 22, 42 and 43 for more details).

In this way, using model (3.1) we observe that the effects of vaccination are linear (see Fig. 4), and, even if the vaccination rate, υ_H, is smaller than critical value, this still reduces the level of infection in the population because the proportion of infected humans I_H^* decreases. This implies that it is always better to vaccinate some individuals, even if the vaccination rate υ_H cannot achieve its threshold value, $\upsilon_H^{\text{thres}}$ for eradication. Thus, the degree of protection offered by the vaccine still works to protect the population due to the herd immunity. In such a case, the threshold value can be then be measured by the optimal proportion of the population that needs to be immunized (given immunity) $p^* = 1 - 1/R_0$ which take the same value of the minimum proportion of vaccinated humans ($V_H^{\min}$).

5. Sensitivity Analysis

In this section, we perform the sensitivity analysis of the total mortality, $\mu_{\text{tot}} = \alpha_v V_H^* + \alpha_D I_H^*$ to relevant parameters: the vaccine-induced mortality rate for

vaccinated humans (α_v) and the disease-induced mortality rate for infected humans (α_D). The sensitivity analysis is used to measure the relative change in a variable when a given parameter is varied. To carry out local sensitivity analysis, we use a simple approach to compute the sensitivity index, which is a partial derivative of the output variable with respect to the input parameters (see Refs. 17, 44 and 45 for more details). Measuring the total mortality μ_{tot} sensitive indices is important since the total number of people who will die should be the best indicator to be minimized by any control strategy.

The normalized sensitivity index of μ_{tot} with respect to the $\Omega = \alpha_D = \alpha_v$, at a fixed value $\Omega^0 = \alpha_D^0 = \alpha_v^0$, is given by

$$\frac{\triangle \mu_{\text{tot}}}{\mu_{\text{tot}}} = \frac{\Omega}{\mu_{\text{tot}}} \frac{\partial \mu_{\text{tot}}}{\partial \Omega} \frac{\triangle \Omega}{\Omega} \Bigg| \Omega^0, \tag{5.1}$$

where $\frac{\triangle \Omega}{\Omega} = 0.01$.

The numerical simulations were carried out for $r_M > r_M^{\text{thres}}$, $R_{\text{vac}} > 1$ or $a > a^{\text{thres}}$, where P_1^{HM} is the unique equilibrium locally asymptotically stable. All parameters values used are given in Table 2 (baseline values), except for $v_H = 0.0001$. Applying (5.1) to estimate the sensitivity for the vaccine-induced mortality rate for vaccinated humans (α_v) and the disease-induced mortality rate for infected humans (α_D), we verified that an increase of 1% in the value of α_v augments 2.735301992886937e-8% the value of μ_{tot}, and an increase of 1% in the value of α_D augments 0.006933549243922 the value of μ_{tot}.

6. Summary and Conclusions

In this paper, we have formulated a deterministic model for the transmission of vector-borne infections in a community in the presence of an imperfect vaccine. The model is intended to investigate the existence and stability of the associated equilibria. We found three threshold parameters, which address the restrictions for disease persistence and eradication of YF based on the question whether vaccination could completely interrupt the spread of infection in a community without increasing the number of deaths of vaccinated humans. The main findings of the study are summarized below:

(i) the reduction in the mosquito fertility, r_M, is "theoretically" the most effective factor in reducing disease prevalence since it has an important effect on disease transmission in both low and high transmission areas (as measured by $R_{\text{vac}} > 1$ and $R_{\text{vac}} \gg 1$, respectively),

(ii) if the mosquito fertility is less than the threshold, $r_M < r_M^{\text{thres}}$, then the disease is naturally (without intervention) eradicated from the population (P_0^H is the unique equilibrium globally asymptotically stable),

(iii) if, in contrast, the mosquito fertility is greater than the threshold, $r_M > r_M^{\text{thres}}$ and $a > a^{\text{thres}}$ ($R_{\text{vac}} > 1$ and $R_{\text{vac}} \gg 1$) the disease could be eliminated

from the community if $\upsilon_H > \upsilon_H^{\text{thres}}$ (P_0^{HM} is the unique equilibrium globally asymptotically stable),

(iv) in case $\upsilon_H < \upsilon_H^{\text{thres}}$, the low coverage of vaccination will fail to eliminate the disease from the community, the disease will then persist (P_1^{HM} is the unique equilibrium globally asymptotically stable),

(v) it is still possible to control the disease and minimize the negative aspects of vaccination making the vaccine effort (υ_H) slightly above the threshold value $\upsilon_H^{\text{thres}}$,

(vi) the total mortality μ_{tot} is more sensitive to the disease-induced mortality rate for infected humans than the vaccine-induced mortality rate for vaccinated humans,

(vii) finally, it is important to emphasize that in this model we do not make r_M explicit function of the biting rate. In a future work, we will include this fact into a new model.

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Appendix A. Proof of Theorem 3.1

The Uniqueness and the Positiveness of the Solution.

Proof. Consider the resulting reduced model (2.1). The right-hand sides of system (2.1) are continuous with continuous partial derivatives in Ω, therefore system (2.1) has a unique solution that exists for all time $t \geq 0$. Next we show that $\overline{S}_H$, $\overline{V}_H$, $\overline{I}_H$, $\overline{R}_H$, $\overline{S}_M$, $\overline{L}_M$, $\overline{I}_M$, and $\overline{S}_E$ are positive for $t \in (0, \tau]$. Suppose not, then there must

be a first time $t_1 \in (0, \tau]$ such that $\overline{S}_H(t_1)\overline{V}_H(t_1)\overline{I}_H(t_1)\overline{S}_M(t_1)\overline{L}_M(t_1)\overline{S}_E(t_1) = 0$, which yields

(i) $\overline{S}_H(t_1) = 0$ and $\overline{V}_H(t) \geq 0$, $\overline{I}_H(t) \geq 0$, $\overline{S}_M(t) \geq 0$, $\overline{L}_M(t) \geq 0$, $\overline{S}_E(t) \geq 0$,
(ii) $\overline{V}_H(t_1) = 0$ and $\overline{S}_H(t) \geq 0$, $\overline{I}_H(t) \geq 0$, $\overline{S}_M(t) \geq 0$, $\overline{L}_M(t) \geq 0$, $\overline{S}_E(t) \geq 0$,
(iii) $\overline{I}_H(t_1) = 0$ and $\overline{S}_H(t) \geq 0$, $\overline{V}_H(t) \geq 0$, $\overline{S}_M(t) \geq 0$, $\overline{L}_M(t) \geq 0$, $\overline{S}_E(t) \geq 0$,
(iv) $\overline{S}_M(t_1) = 0$ and $\overline{S}_H(t) \geq 0$, $\overline{V}_H(t) \geq 0$, $\overline{I}_H(t) \geq 0$, $\overline{L}_M(t) \geq 0$ $\overline{S}_E(t) \geq 0$,
(v) $\overline{L}_M(t_1) = 0$ and $\overline{S}_H(t) \geq 0$, $\overline{V}_H(t) \geq 0$, $\overline{I}_H(t) \geq 0$, $\overline{S}_M(t) \geq 0$, $\overline{S}_E(t) \geq 0$, or
(vi) $\overline{S}_E(t_1) = 0$ and $\overline{S}_H(t) \geq 0$, $\overline{V}_H(t) \geq 0$, $\overline{I}_H(t) \geq 0$, $\overline{S}_M(t) \geq 0$, $\overline{L}_M(t) \geq 0$, for $t \in [0, t_1]$.

For case (i),

$$\begin{aligned}\frac{d\overline{S}_H}{dt} &= \mu_H\overline{N}_H + \alpha_D\overline{I}_H + (\alpha_v + \omega_H)\overline{V}_H - (\lambda_M(t) + \mu_H + f_H\upsilon_H)\overline{S}_H \\ &\geq \mu_H\overline{N}_H - (\lambda_M(t) + \mu_H + f_H\upsilon_H)\overline{S}_H,\end{aligned}$$

which can be re-written as

$$\begin{aligned}&\frac{d}{dt}\left[\overline{S}_H(t)\,\exp\left\{\int_0^t \lambda_M(u)du + (\mu_H + f_H\upsilon_H)t\right\}\right] \\ &\qquad \geq \mu_H\overline{N}_H\,\exp\left\{\int_0^t \lambda_M(u)du + (\mu_H + f_H\upsilon_H)t\right\}.\end{aligned}$$

Hence,

$$\begin{aligned}&\overline{S}_H(t_1)\,\exp\left\{\int_0^{t_1} \lambda_M(u)du + (\mu_H + f_H\upsilon_H)t_1\right\} - \overline{S}_H(0) \\ &\qquad \geq \int_0^{t_1} \mu_H\overline{N}_H\,\exp\left\{\int_0^x \lambda_M(\tau)d\tau + (\mu_H + f_H\upsilon_H)x\right\}dx,\end{aligned}$$

and, since $\overline{N}_H$ is constant,

$$\begin{aligned}\overline{S}_H(t_1) \geq\ &\overline{S}_H(0)\,\exp\left\{-\int_0^{t_1} \lambda_M(u)du + (\mu_H + f_H\upsilon_H)t_1\right\} \\ &+ \exp\left\{-\int_0^{t_1} \lambda_M(u)du + (\mu_H + f_H\upsilon_H)t_1\right\} \\ &\times \int_0^{t_1} \mu_H\overline{N}_H\,\exp\left\{\int_0^x \lambda_M(\tau)d\tau + (\mu_H + f_H\upsilon_H)x\right\}dx > 0,\end{aligned}$$

which is in contradiction with $\overline{S}_H(t_1) = 0$. In the same way, we can show that $\overline{V}_H(t_1) \geq 0, \overline{I}_H(t_1) \geq 0$, $\overline{S}_M(t_1) \geq 0$, $\overline{L}_M(t_1) \geq 0$, $\overline{I}_M(t_1) \geq 0$, $\overline{S}_E(t_1) \geq 0$. To sum up, in a similar fashion, it can also be shown that $\overline{S}_H(t)$, $\overline{V}_H(t)$, $\overline{I}_H(t)$, $\overline{R}_H(t)$, $\overline{S}_M(t)$, $\overline{L}_M(t)$, $\overline{I}_M(t)$, $\overline{S}_E(t)$, are positive for $t > 0$. □

Appendix B. Proof of Theorem 3.2. The Existence of Equilibria

Proof. Consider the resulting reduced model (3.1). From the first and third equations of (3.1) with the right-hand side equal to zero, it can be seen that the equilibrium points must satisfy, respectively, the following relations:

$$V_H^{*0} = \rho_{\text{vac}} \left[1 - \frac{(\mu_H + \gamma_H)}{\mu_H} I_H^*\right], \tag{B.1}$$

$$R_H^* = \frac{\gamma_H}{\mu_H} I_H^*, \tag{B.2}$$

where

$$0 < \rho_{\text{vac}} = \frac{f_H v_H}{f_H v_H + \mu_H + \omega_H + \alpha_v} < 1. \tag{B.3}$$

Substituting (B.1) and (B.2) in the second equation of system (3.1), we obtain

$$I_M^* = \frac{(\mu_H + \alpha_D + \gamma_H) I_H^*}{ab\frac{k_E}{N_H}(1 - \rho_{\text{vac}}) \left[1 - \left(1 + \frac{\gamma_H}{\mu_H}\right) I_H^*\right]}. \tag{B.4}$$

From fifth and sixth equations of system (3.1), we obtain

$$L_M^* = \frac{\mu_M}{\gamma_H} I_M^*, \quad 0 < L_M^* < 1, \tag{B.5}$$

and

$$N_M^* = \frac{c_s}{\mu_M} S_E^*. \tag{B.6}$$

Substituting (B.6) in the seventh equation of system (3.1), we get either $S_E^* = 0$ or

$$S_E^* = 1 - \frac{r_M^{\text{thres}}}{r_M}, \tag{B.7}$$

with $r_M^{\text{thres}} = \frac{(\mu_E + c_s)\mu_M}{c_s}$ and $0 \leq S_E^* \leq 1$ From expression (B.7) it follows that

$$S_E^* \geq 0 \Leftrightarrow r_M \geq r_M^{\text{thres}}. \tag{B.8}$$

Substituting (B.5) in the fourth equation of system (3.1), we obtain

$$I_M^* = \frac{acN_M^* I_H^*}{(acI_H^* + \mu_M)\left(1 + \frac{\mu_M}{\gamma_M}\right)}. \tag{B.9}$$

From Eqs. (B.4) and (B.9) we obtain either I_H^* or

$$I_H^* = \frac{R_{\text{vac}} - 1}{R_{\text{vac}}\left(1 + \frac{\gamma_H}{\mu_H}\right) + \frac{ac}{\mu_M}}, \tag{B.10}$$

where

$$R_{\text{vac}} = R_0[1 - \rho_{\text{vac}}], \tag{B.11}$$

and

$$R_0 = \frac{a^2 bc\gamma_M \kappa_E}{(\mu_H + \alpha_D + \gamma_H)(\mu_M + \gamma_M)\mu_M} \frac{\overline{N}_M}{\overline{N}_H}. \tag{B.12}$$

From expression (B.10), it should be noted that for $R_{\text{vac}} > 1$, $I_H^* > 0$. Therefore, for $I_H^* > 0$ the system (3.1) could reach an EE point. Moreover, when $R_{\text{vac}} \to \infty$, $I_H^*(\infty) \to \mu_H/(\mu_H + \gamma_H)$, such that $0 \leq I_H^* \leq I_H^*(\infty)$ implies $V_H^* > 0$ and $I_M^* > 0$ [see Eqs. (B.1) and (B.9)].

In contrast, from Eqs. (A.1), (A.2), (A.5) and (A.9), $I_H^* = 0$ leads to

$$I_M^* = 0, L_M^* = 0, R_H^* = 0, V_H^* = \rho_{\text{vac}}. \tag{B.13}$$

Thus, for $I_H^* = 0$ only the DFE exist for system (3.1). To be more specific, for $S_E^* \neq 0$ and $N_E^* \neq 0$ the trivial equilibrium is described by the population of humans and vectors, whereas for $S_E^* = 0$ and $N_M^* = 0$ the equilibrium is given by the human population. □

Appendix C. Proof of Theorem 3.4. Local Stability of the DFE

Proof. Consider the resulting reduced model (3.1). The local stability of the DFE P_0^{HM}, which is examined by linearizing the system (3.1) around P_0^{HM}, is governed by the Jacobian matrix

$$M^{P_0^{HM}} = \begin{bmatrix} A^{P_0^{HM}} & 0 \\ 0 & B^{P_0^{HM}} \end{bmatrix}, \tag{C.1}$$

where

$$A^{P_0^{HM}} = \begin{bmatrix} -(\mu_H + \gamma_H + \alpha_D) & 0 & \dfrac{ab\kappa_E(1 - V_H^*)}{N_H^*} \\ acN_M^* \left(1 - \dfrac{r_M^{\text{thres}}}{r_M}\right) & -(\gamma_M + \mu_M) & 0 \\ 0 & \gamma_M & -\mu_M \end{bmatrix} \tag{C.2}$$

and

$$B^{P_0^{HM}} = \begin{bmatrix} -\mu_M & c_s \\ r_M(1 - S_E^*) & -r_M N_M^* - (\mu_E + c_s) \end{bmatrix}. \tag{C.3}$$

From (C.3) it is easy to verify that the trace of matrix $\text{tr}(B^{P_0^{HM}})$ is always negative; the determinant of matrix $\det(B^{P_0^{HM}})$ is always positive if and only if

$r_M > r_M^{\text{thres}}$. Therefore, the two eigenvalues of matrix $B^{P_0^{HM}}$ are either negative or have negative real parts if and only if $r_M > r_M^{\text{thres}}$.

Moreover, the characteristic equation of the matrix $A^{P_0^{HM}}$ is given by

$$\Lambda^3 + \eta_2\Lambda^2 + \eta_1\Lambda + \eta_0 = 0, \tag{C.4}$$

where

$$\begin{aligned}
\eta_2 &= \mu_H + \gamma_H + \alpha_D + \mu_M + (\mu_M + \gamma_M)\mu_M,\\
\eta_1 &= (\mu_H + \gamma_H + \alpha_D)(\mu_M + \gamma_M) + (\mu_H + \gamma_H + \alpha_D)\mu_M + (\mu_M + \gamma_M)\mu_M,\\
\eta_0 &= (\mu_H + \gamma_H + \alpha_D)(\mu_M + \gamma_M)\mu_M(1 - R_{\text{vac}}).
\end{aligned} \tag{C.5}$$

By using the Routh–Hurwitz criteria for the polynomial (C.4), it follows that $\eta_2 > 0, \eta_1 > 0, \eta_0 > 0$ if only if $R_{\text{vac}} < 1$ and $\eta_1\eta_2 - \eta_0 > 0$. Thus, the polynomial (C.4) has negative (or has negative real part) roots if $R_{\text{vac}} < 1$. Therefore, all the eigenvalues of the matrix $M^{P_0^{HM}}$ are negative or have negative real parts if and only if $R_{\text{vac}} < 1$ and $r_M > r_M^{\text{thres}}$. □

Appendix D. Proof of Theorem 3.5. Global Stability of the DFE

Proof. Consider the resulting reduced model (3.1). The equations for the variables $I_H, R_H, L_M, I_M, N_M, S_E$ of system (3.1) satisfy the following linear differential inequality

$$\begin{bmatrix} I_H'(t) \\ R_H'(t) \\ L_M'(t) \\ I_M'(t) \\ N_M'(t) \\ S_E'(t) \end{bmatrix} \leq (K - F) \begin{bmatrix} I_H(t) \\ R_H(t) \\ L_M(t) \\ I_M(t) \\ N_M(t) \\ S_E(t) \end{bmatrix}, \tag{D.1}$$

where $' = \frac{d}{dt}$. The matrices K (the non-negative matrix of the infections terms) and F (the non-singular M-matrix of the transitions terms) evaluated at the DFE, P_0^{HM}, are given by

$$K = \begin{bmatrix} 0 & 0 & 0 & K_{14} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ k_{31} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & K_{43} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}, \tag{D.2}$$

where $k_{14} = \frac{abk_E}{\overline{N}_H}(1-\rho_{\text{vac}})$, $k_{31} = ac\frac{c_s}{\mu_M}(1-\frac{r_M^{\text{thres}}}{r_M})$, which is positive for $r_M > r_M^{\text{thres}}$, $k_{43} = \gamma_M$, and,

$$F = \begin{bmatrix} f_{11} & 0 & 0 & 0 & 0 & 0 \\ 0 & f_{22} & 0 & 0 & 0 & 0 \\ 0 & 0 & f_{33} & 0 & 0 & 0 \\ 0 & 0 & 0 & f_{44} & 0 & 0 \\ 0 & 0 & 0 & 0 & f_{55} & 0 \\ 0 & 0 & 0 & 0 & f_{65} & f_{66} \end{bmatrix}, \tag{D.3}$$

where $f_{11} = (\mu_H + \alpha_D + \gamma_H)$, $f_{22} = \mu_H$, $f_{33} = (\gamma_M + \mu_M)$, $f_{44} = f_{55} = \mu_M$, $f_{65} = -r_M(1 - \frac{r_M^{\text{thres}}}{r_M})$ and $f_{66} = \frac{r_M c_s}{\mu_M}(1 - \frac{r_M^{\text{thres}}}{r_M}) + (\mu_E + c_s)$. Following the *next generation operator* approach given in Refs. 26 and 46. R_{vac} is equal to the spectral radius (dominant eigenvalue) of KF^{-1}, i.e., $R_{\text{vac}} = \rho(KF^{-1})$, where KF^{-1} is equal to

$$\begin{bmatrix} 0 & 0 & 0 & \frac{abk_E}{\overline{N}_H}(1-\rho_{\text{vac}}) & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{acN_M}{\mu_H+\alpha_D+\gamma_H} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{\gamma_M}{\gamma_M+\mu_M} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}, \tag{D.4}$$

and its eigenvalues are zero of multiplicity three, and $\phi = \sqrt[3]{R_{\text{vac}}}$ with R_{vac} given by the expression (3.2). Thus, if $R_{\text{vac}} < 1$, then $\rho(KF^{-1}) < 1$ which is equivalent to $K - F$ having all its eigenvalues in the left-half plane.[46,47] It follows that the linear ODE system

$$\overline{y}' = (K - F)\overline{y} \tag{D.5}$$

is stable whenever $R_{\text{vac}} < 1$. Therefore, the solutions $\overline{y}$ approach $(0, 0, 0, 0, N_M^*, S_E^*)$, as $t \to \infty$. Then using a standard comparison theorem (Ref. 48, p. 31),

$$(I_H(t), R_H(t), L_M(t), I_M(t), N_M(t), S_E(t)) \to (0, 0, 0, 0, N_M^*, S_E^*),$$

for $R_{\text{vac}} < 1$. As a consequence, $dv_H(t)/dt \to f_H v_H(1 - V_H) - (\mu_H + \omega_H + \alpha_v)V_H$, which implies $v_H \to \rho_{\text{vac}}$. This proves that

$$(V_H(t), I_H(t), R_H(t), L_M(t), I_M(t), N_M(t), S_E(t)) \to (\rho_{\text{vac}}, 0, 0, 0, 0, N_M^*, S_E^*),$$

and hence, for $r_M > r_M^{\text{thres}}$ the DFE, P_0^{HM} is globally asymptotically stable whenever $R_{\text{vac}} < 1$. □