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MATHEMATICAL ANALYSIS OF A MODEL FOR HIV-MALARIA CO-INFECTION

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Abstract. A deterministic model for the co-interaction of HIV and malaria in a community is presented and rigorously analyzed. Two sub-models, namely the *HIV-only* and *malaria-only* sub-models, are considered first of all. Unlike the HIV-only sub-model, which has a globally-asymptotically stable disease-free equilibrium whenever the associated reproduction number is less than unity, the malaria-only sub-model undergoes the phenomenon of backward bifurcation, where a stable disease-free equilibrium co-exists with a stable endemic equilibrium, for a certain range of the associated reproduction number less than unity. Thus, for malaria, the classical requirement of having the associated reproduction number to be less than unity, although necessary, is not sufficient for its elimination. It is also shown, using centre manifold theory, that the full HIV-malaria co-infection model undergoes backward bifurcation. Simulations of the full HIV-malaria model show that the two diseases co-exist whenever their reproduction numbers exceed unity (with no competitive exclusion occurring). Further, the reduction in sexual activity of individuals with malaria symptoms decreases the number of new cases of HIV and the mixed HIV-malaria infection while increasing the number of malaria cases. Finally, these simulations show that the HIV-induced increase in susceptibility to malaria infection has marginal effect on the new cases of HIV and malaria but increases the number of new cases of the dual HIV-malaria infection.

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1. **Introduction.** HIV/AIDS has killed more than 25 million people since it was first recognized in 1981, making it one of the most destructive epidemics in recorded history (UNAIDS/WHO [45]). It remains one of the leading causes of death in the world, with its effect most devastating in sub-Saharan Africa, where HIV prevalence can range between 12% to 42% (Roseberry, *et al.* [41]). One of the key factors that fuels the high incidence of HIV in sub-Saharan Africa is the dual infection with malaria (Abu-Raddad *et al.* [1]). HIV has been shown to increase the risk of malaria infection and accelerate the development of clinical symptoms of malaria, with the greatest impact in immune-suppressed persons. Conversely, malaria has been shown to induce HIV-1 replication *in vitro* and *in vivo*. A biological explanation for these interactions lies in the cellular-based immune responses to HIV and malaria. Studies have shown that when HIV-infected individuals are attacked by malaria, their body immune system weakens significantly, creating a conducive environment for the HIV virus to replicate (virtually unchallenged), resulting in an increase in the viral load (the amount of HIV virus in the body). Hence, since viral load is correlated with infectiousness [38], such a process (co-infection with malaria) leads to an increase in the number of new HIV cases in the population.

Humans acquire malaria infection from infected female *Anopheles* mosquitoes (after taking blood meal). Of the four mosquito species that infect humans (*P. falciparum, P. vivax, P. ovale,* and *P. malarie*), P. falciparum is the most virulent and potentially lethal to humans. Plasmodium falciparum stimulate release of interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) and the complications of severe falciparum malaria are mostly due to release of these cytokines. The increased levels of such cytokines stimulate the replication of HIV *in vivo* (thus increasing the HIV levels in patients [49]). HIV-1 proviral loads are significantly higher in patients with malaria than those without; and remain higher for at least 4 weeks after treatment [26]. Thus, malaria infection could cause faster progression of HIV-1 disease [34]. A study in rural Tanzania shows a significantly higher prevalence of symptomless malarial parasitemia in HIV-infected adults and higher mortality due to malaria in these individuals [6]. In a large study carried out in Uganda, HIV-1 infection has been found to increase the frequency of clinical malaria and parasite density with tendency to greater parasitemia with advancing immunosuppression [47]. Furthermore, morbidity is higher in HIV-infected individuals [34, 31, 37]. Recent studies of dual HIV-malaria infection confirm and extend earlier findings [26, 47, 20, 28, 35, 39] by showing that co-infection leads to a near one-log increase in viral load in chronic-stage HIV-infected patients during febrile malaria episodes and that HIV infection substantially increases susceptibility to malaria infection [1, 39].

This symbiotic relationship between HIV and malaria is a double blow to sub-Saharan Africa region because of the high prevalence of HIV/AIDS and incidence of malaria [44]. This highlights the need for a robust qualitative assessment of the population-level implications of the immune-mediated interaction of the two diseases [1, 48]. Abu-Raddad *et al.* [1] recently presented a mathematical model to study the transmission dynamics of HIV and malaria co-infection. It quantifies the size of the epidemic synergy between HIV-1 and malaria.

In this study, we formulate and analyse a realistic mathematical model for HIV-malaria co-infection, which incorporates the key epidemiological and biological features of each of the two diseases. The main contribution of this study is in carrying out a detailed qualitative analysis of the resulting model; an activity not carried

out in [1]. It is our view that this study represents the very first modelling work that provides an in-depth analysis of the qualitative dynamics of HIV-malaria co-infection. Additionally, there are some important differences between the model in [1] and the one in this paper. For instance, whilst we used an exponential distribution waiting time to model the exposed class, a discrete time delay was used for the same purpose in [1]. Further, seasonality variations were used in [1] to model the birth rate of mosquitoes, whereas the current study uses a constant birth rate. Mathematically speaking, while the model considered in [1] is non-autonomous, the model considered in the current study is autonomous. Furthermore, unlike in many other modelling studies of HIV transmission dynamics in a population, this study assumes that individuals in the AIDS stage of HIV infection do transmit the disease to susceptible individuals. This is owing to the fact that epidemiologic evidence supports the hypothesis that AIDS patients are capable of, and do engage in, risky sexual behavior defined in terms of inconsistent condom use or having multiple sex partners [30].

It is worth stating that although the acquisition of immunity to malaria is a slow and complex process [4], the effect of partial host immunity on the transmission dynamics of malaria in areas where malaria is endemic can be significant. Such partial immunity, which develops after several years of endemic exposure, results from many factors such as antigenic polymorphism, poor immunogenicity of individual antigens, the ability of the parasite to interfere with the development of immune responses and the interaction of maternal and neonatal immunity [14]. Many infected individuals in endemic areas are asymptomatic (that is, they may harbour large numbers of parasites without exhibiting signs and symptoms of the disease) [2, 5, 14]. In areas of low malaria transmission, immunity develops slowly and malaria affects all age groups [22]. As noted in [33], since HIV infection interferes with cellular immune function, HIV may interfere with the development of partial immunity to malaria, particularly amongst children. This complicates the explicit modelling of the role of partial immunity to malaria in HIV/malaria transmission dynamics.

The paper is organized as follows. The model is formulated in Section 2. The sub-models for HIV and malaria are presented and analyzed in Sections 3 and 4, respectively. The analysis of the full HIV-malaria co-infection model is carried out in Section 5. Numerical simulations and concluding remarks are presented in Section 6.

2. **Model description.** The model sub-divides the total sexually-active human population at time t, denoted by $N_H(t)$, into the following sub-populations of susceptible individuals ($S_H(t)$), individuals exposed to malaria parasite only ($E_M(t)$), individuals with malaria symptoms only ($I_M(t)$), individuals infected with HIV only but display no clinical symptoms of AIDS ($I_H(t)$), HIV-infected individuals (with no symptoms of AIDS) exposed to malaria ($E_{HM}(t)$), individuals dually-infected with HIV and malaria, displaying clinical symptoms of malaria but no AIDS symptoms ($I_{HM}(t)$), HIV-infected individuals displaying AIDS symptoms ($A_H(t)$), AIDS individuals exposed to malaria ($E_{AM}(t)$) and AIDS individuals dually-infected with malaria, and displaying clinical symptoms ($A_{HM}(t)$), so that

$$\begin{aligned} N_H(t) &= S_H(t) + E_M(t) + I_M(t) + I_H(t) + E_{HM}(t) + I_{HM}(t) + A_H(t) \\ &+ E_{AM}(t) + A_{HM}(t). \end{aligned}$$

The total vector (mosquito) population at time t, denoted by $N_V(t)$, is subdivided into susceptible mosquitoes ($S_V(t)$), mosquitoes exposed to the malaria parasite ($E_V(t)$) and infectious mosquitoes ($I_V(t)$), so that

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

It is assumed that susceptible humans are recruited into the population at a constant rate Λ_H. Susceptible individuals acquire HIV infection following effective contact with HIV-infected individuals (at a rate λ_H), and acquire infection with malaria following effective contact with infected mosquitoes (at a rate λ_M). It is assumed that individuals with malaria infection only may recover and return to the susceptible class (at a rate ϕ_1). Further, natural death occurs in all human subpopulations (at a rate μ_H). The force of infection associated with HIV infection, denoted by λ_H, is given by

$$\lambda_H = \frac{\beta_H \left\{ I_H + \eta_{HM} \left(E_{HM} + \theta_{HM} I_{HM} \right) + \eta_A \left[A_H + \eta_{HM} \left(E_{AM} + \theta_{HM} A_{HM} \right) \right] \right\}}{N_H}. \tag{1}$$

In (1), β_H is the effective contact rate for HIV infection (contact sufficient to result in HIV infection), the modification parameter $\eta_{HM} \geq 1$ accounts for the relative infectiousness of individuals asymptomatically-infected with HIV exposed to malaria (E_{HM}) or displaying clinical symptoms of malaria (I_{HM}) in comparison to those with HIV infection alone but with no AIDS symptoms (I_H). In other words, it is assumed that HIV-infected individuals (with no AIDS symptoms) who are also infected with malaria are more infectious than HIV-infected individuals with no AIDS symptoms and no malaria infection (similar comparisons are made for HIV-infected individuals with AIDS symptoms alone in relation to those with AIDS symptoms and malaria infection). Further, the parameter $\theta_{HM} \geq 1$ models the fact that dually-infected individuals with no symptoms of AIDS, but displaying symptoms of malaria (I_{HM}), are more infectious than the corresponding dually-infected individuals who are only exposed to malaria (E_{HM}). Finally, the parameter $\eta_A > 1$ captures the fact that individuals in the AIDS stage of HIV infection are more infectious than HIV-infected individuals displaying no clinical symptoms of AIDS. This is due to the fact that individuals in the AIDS stage have higher viral load compared to other HIV-infected individuals with no AIDS symptoms (this is owing to the aforementioned correlation between HIV viral load and infectiousness).

Similarly, humans acquire malaria infection following effective contact with infected mosquitoes at a rate λ_M, given by,

$$\lambda_M = \beta_M b_M \frac{I_V}{N_H}, \tag{2}$$

where β_M is the transmission probability per bite and b_M is the per capita biting rate of mosquitoes (the form of the disease incidence function is obtained by taking into account "conservation of bites"; that is, the total number of bites made by mosquitoes equals the number of bites received by the human hosts [8]).

Susceptible individuals infected with malaria are moved to the exposed class (E_M) at the rate λ_M, and then progress to the infectious class (I_M), following the development of clinical symptoms (at a rate γ_H). Individuals exposed to malaria can be infected with HIV (at a rate λ_H). That is, individuals in the E_M class are moved into the E_{HM} class upon acquiring HIV infection. Furthermore, individuals

with symptoms of malaria can acquire HIV infection, at a rate $\sigma\lambda_H$, where the parameter $0 < \sigma \leq 1$ models the expected decrease in sexual activity (contact) by individuals with malaria symptoms (because of ill health). Individuals with malaria symptoms recover (at the rate ϕ_1) and suffer disease-induced death (at a rate δ_M).

The population of individuals infected with HIV only (and displaying no symptoms of AIDS) is generated following infection (at the rate λ_H) and by the recovery of malaria infection by those dually-infected with HIV and malaria (at a rate ϕ_2). Individuals in this class acquire malaria infection (at a rate $\vartheta\lambda_M$, where $\vartheta > 1$ accounts for the assumed increase in susceptibility to malaria infection as a result of HIV infection). This population is further decreased following progression to AIDS (at a rate κ). Individuals infected with HIV and exposed to malaria develop symptoms of malaria at a rate $\epsilon\gamma_H$, where $\epsilon \geq 1$ represents the assumption that HIV infected individuals exposed to malaria develop malaria at a faster rate compared to those not infected with HIV.

Individuals in the I_{HM} class die due to malaria (at the rate $\tau\delta_M$, where $\tau \geq 1$ accounts for the increased mortality of the I_{HM} individuals in comparison to individuals with malaria symptoms but not infected with HIV), recover (at a rate ϕ_2) and progress to AIDS (at a rate $\xi\kappa$, where $\xi \geq 1$ represents the assumption that HIV infected individuals dually-infected with malaria progress to AIDS at a faster rate compared to those with HIV only).

The population of individuals with AIDS symptoms only is generated following the progression to AIDS by individuals with HIV only (at the rate κ) as well as the recovery from malaria of individuals with AIDS symptoms and malaria (at a rate ϕ_3). Individuals in this class also acquire malaria infection (at the rate $\vartheta\lambda_M$) and die of AIDS-related illness (at a rate δ_H). Individuals in the class of people with AIDS symptoms exposed to malaria develop symptoms of malaria at the accelerated rate $\epsilon\gamma_H$.

The population of individuals with symptoms of both malaria and AIDS is generated by progression to AIDS by individuals dually-infected with HIV and malaria (at the rate $\xi\kappa$) and the development of malaria symptoms by individuals with AIDS exposed to malaria (at the rate $\epsilon\gamma_H$). This population is diminished by natural death (at the rate μ_H), recovery from malaria infection (at a rate ϕ_3), death due to AIDS (at a rate $\psi\delta_H$, where $\psi > 1$ accounts for the assumed increase in HIV-related mortality due to the dual infection with malaria) and death due to malaria (at the rate $\tau\delta_M$).

Susceptible mosquitoes (S_V) are generated at a constant rate Λ_V, and acquire malaria infection (following effective contacts with humans infected with malaria) at a rate λ_V, where the force of infection λ_V is given by

$$\lambda_V = \beta_V b_M \frac{I_M + \eta_V \left(I_{HM} + \theta_V A_{HM}\right)}{N_H}, \tag{3}$$

where β_V is the transmission probability for mosquito infection, b_M is the biting rate of mosquitoes, $\eta_V \geq 1$ is a modification parameter accounting for the increased likelihood of infection of vectors from humans with dual HIV-malaria infection in relation to acquiring infection from humans with malaria only. The parameter $\theta_V \geq 1$ is similarly defined. Mosquitoes are assumed to suffer natural death at a rate μ_V, regardless of their infection status. Newly-infected mosquitoes are moved into the exposed class (E_V), and progress to the class of symptomatic mosquitoes (I_V) following the development of symptoms (at a rate γ_V).

Putting the above formulations and assumptions together gives the following system of differential equations (where a prime represents differentiation with respect to time).

$$\begin{aligned}
S'_H &= \Lambda_H + \phi_1 I_M - \lambda_H S_H - \lambda_M S_H - \mu_H S_H,\\
E'_M &= \lambda_M S_H - \lambda_H E_M - (\gamma_H + \mu_H) E_M,\\
I'_M &= \gamma_H E_M - \sigma\lambda_H I_M - (\mu_H + \delta_M + \phi_1) I_M,\\
I'_H &= \lambda_H S_H + \phi_2 I_{HM} - \vartheta\lambda_M I_H - (\mu_H + \kappa) I_H,\\
E'_{HM} &= \lambda_H E_M + \vartheta\lambda_M I_H - (\epsilon\gamma_H + \mu_H + \kappa) E_{HM},\\
I'_{HM} &= \sigma\lambda_H I_M + \epsilon\gamma_H E_{HM} - (\mu_H + \tau\delta_M + \phi_2 + \xi\kappa) I_{HM},\\
A'_H &= \kappa I_H + \phi_3 A_{HM} - \vartheta\lambda_M A_H - (\mu_H + \delta_H) A_H,\\
E'_{AM} &= \vartheta\lambda_M A_H + \kappa E_{HM} - (\epsilon\gamma_H + \mu_H + \delta_H) E_{AM},\\
A'_{HM} &= \xi\kappa I_{HM} + \epsilon\gamma_H E_{AM} - (\mu_H + \phi_3 + \tau\delta_M + \psi\delta_H) A_{HM},\\
S'_V &= \Lambda_V - \lambda_V S_V - \mu_V S_V,\\
E'_V &= \lambda_V S_V - (\gamma_V + \mu_V) E_V,\\
I'_V &= \gamma_V E_V - \mu_V I_V.
\end{aligned} \tag{4}$$

The model flow diagram is depicted in Figure 1, and the associated parameters are described in Table 1. Since the model (4) monitors human populations, all associated state variables and parameters are non-negative for all time $t \geq 0$. Further, before analyzing the dynamics of the full model (4), it is instructive to analyze the sub-models (HIV-only and malaria-only) first of all. This is done below.

3. **HIV-only model.** We begin by analysing the HIV-only model (obtained by setting $E_M = I_M = E_{HM} = E_{AM} = A_{HM} = S_V = E_V = I_V = 0$ in (4)) given by,

$$\begin{aligned}
S'_H &= \Lambda_H - \lambda_H S_H - \mu_H S_H,\\
I'_H &= \lambda_H S_H - (\mu_H + \kappa) I_H,\\
A'_H &= \kappa I_H - (\mu_H + \delta_H) A_H,
\end{aligned} \tag{5}$$

where, now, $\lambda_H = \frac{\beta_H (I_H + \eta_A A_H)}{N_H}$ and $N_H = S_H + I_H + A_H$. Consider the region

$$\Omega_H = \Big\{ (S_H, I_H, A_H) \in \mathbb{R}^3_+ : N_H \leq \Lambda_H/\mu_H \Big\}.$$

It can be shown (see, for instance, [42, 43]) that all solutions of the system (5) starting in Ω_H remain in Ω_H for all $t \geq 0$. Thus, Ω_H is positively-invariant (hence, it is sufficient to consider the dynamics of (5) in Ω_H).

The HIV-only model (5) has a DFE given by,

$$\mathcal{E}_{h0} = \Big(S_H, I_H, A_H\Big) = \Big(\frac{\Lambda_H}{\mu_H}, 0, 0\Big). \tag{6}$$

The stability of this equilibrium will be investigated using the *next generation operator* [17, 46]. Using the notation in [46] on the system (5), the matrices F and V, for the new infection terms and the remaining transfer terms are, respectively, given by

$$F = \begin{pmatrix} \beta_H & \beta_H \eta_A \\ 0 & 0 \end{pmatrix} \text{ and } V = \begin{pmatrix} \mu_H + \kappa & 0 \\ -\kappa & \mu_H + \delta_H \end{pmatrix}.$$

It follows that the associated *basic reproduction number* [3, 10, 12, 25], denoted by $\mathcal{R}_H$, is given by

$$\mathcal{R}_H = \rho(FV^{-1}) = \frac{\beta_H(\delta_H + \kappa\eta_A + \mu_H)}{(\kappa + \mu_H)(\delta_H + \mu_H)}, \tag{7}$$

where ρ represents the spectral radius (the dominant eigenvalue in magnitude) of FV^{-1}. Using Theorem 2 of [46], the following result is established.

Lemma 1. *The DFE of the HIV-only model (5) is locally-asymptotically stable (LAS) if $\mathcal{R}_H < 1$, and unstable if $\mathcal{R}_H > 1$.*

The basic reproduction number ($\mathcal{R}_H$) measures the average number of new infections generated by a single infected individual in a completely susceptible population. Thus, Lemma 1 implies that HIV can be eliminated from the community (when $\mathcal{R}_H < 1$) if the initial sizes of the sub-populations of the model are in the basin of attraction of the DFE $\mathcal{E}_{h0}$. To ensure that elimination of the virus is independent of the initial sizes of the sub-populations, it is necessary to show that the DFE is globally-asymptotically stable. The following results can be established (using, for instance, the techniques in [43], where a treatment model for HIV is considered):

Theorem 2. *The DFE of the model (5), given by $\mathcal{E}_{h0}$, is globally-asymptotically stable (GAS) whenever $\mathcal{R}_H \leq 1$.*

Lemma 3. *The HIV-only model has a unique endemic equilibrium if and only if $\mathcal{R}_H > 1$.*

The global stability property of the endemic equilibrium of the HIV-only model is now investigated for a special case.

3.1. **Global stability of the endemic equilibrium for $\delta_H = 0$.** Consider the HIV-only model (5) with $\delta_H = 0$, given by

$$\begin{aligned} S_H' &= \Lambda_H - \lambda_H S_H - \mu_H S_H, \\ I_H' &= \lambda_H S_H - (\mu_H + \kappa) I_H, \\ A_H' &= \kappa I_H - \mu_H A_H. \end{aligned} \tag{8}$$

The system (8), for the special case above, has the same unique endemic equilibrium as the HIV-only model (5), but with $\delta_H = 0$. Let,

$$\Omega_{H0} = \Big\{(S_H, I_H, A_H) \in \Omega_h : I_H = A_H = 0\Big\} \text{ and } \mathcal{R}_{H1} = \mathcal{R}_H|_{\delta_H=0}.$$

We claim the following

Theorem 4. *The endemic equilibrium of the HIV-only model with $\delta_H = 0$ is GAS in $\Omega_H \setminus \Omega_{H0}$ whenever $\mathcal{R}_{H1} > 1$.*

Proof. It can be shown, as for the case of Lemma 3, that the unique endemic equilibrium for this case exists only if $\mathcal{R}_{H1} > 1$. Further, $N_H = \Lambda_H/\mu_H$ as $t \to \infty$. Thus, using $S_H = \Lambda_H/\mu_H - I_H - A_H$ and substituting in (8) gives the following limiting system

$$\begin{aligned} I_H' &= \lambda_H(\Lambda_H/\mu_H - I_H - A_H) - (\mu_H + \kappa)I_H, \\ A_H' &= \kappa I_H - \mu_H A_H. \end{aligned} \tag{9}$$

Using the Dulac's multiplier $1/I_H A_H$, it follows that

$$\begin{aligned} & \frac{\partial}{\partial I_H}\left[\frac{\beta_H(I_H + \eta_A A_H)}{I_H A_H \Lambda_H/\mu_H}(\Lambda_H/\mu_H - I_H - A_H) - \frac{(\kappa+\mu_H)}{A_H}\right] \\ + & \frac{\partial}{\partial A_H}\left(\frac{\kappa}{A_H} - \frac{\mu_H}{I_H}\right) \\ = & -\left[\frac{\beta_H \mu_H}{\Lambda_H} + \frac{\beta_H \eta_A \mu_H}{\Lambda_H I_H^2}\left(1 - \frac{A_H}{\Lambda_H/\mu_H}\right) + \frac{\kappa}{A_H^2}\right] \\ < & \ 0 \qquad \text{since} \qquad A_H \le \Lambda_H/\mu_H \ \text{ in } \ \Omega_H. \end{aligned}$$

Thus, by Dulac's criterion, there are no periodic orbits in $\Omega_H \setminus \Omega_{H0}$. Since Ω_H is positively invariant, and the endemic equilibrium exists whenever $\mathcal{R}_{H1} > 1$, then it follows from the Poincaré-Bendixson Theorem [40] that all solutions of the limiting system originating in Ω_H remain in Ω_H for all t. Further, the absence of periodic orbits in Ω_H implies that the unique endemic equilibrium of the special case of the HIV-only model is GAS whenever $\mathcal{R}_{H1} > 1$. □

It may be possible to show, using a regular perturbation argument (as in [8]), that the above proof holds for $\delta_H > 0$, but small.

In summary, the model with HIV alone has a globally-asymptotically stable disease-free equilibrium whenever $\mathcal{R}_H \le 1$, and a unique endemic equilibrium whenever $\mathcal{R}_H > 1$. The unique endemic equilibrium is globally-asymptotically stable for the special case $\delta_H = 0$ if $\mathcal{R}_{H1} > 1$. The dynamics of the malaria-only model is now studied.

4. **Malaria-only model.** Consider the malaria-only model (obtained by setting $I_H = E_{HM} = I_{HM} = A_H = E_{AM} = A_{HM} = 0$ in (4)), given by

$$\begin{aligned} S_H' &= \Lambda_H + \phi_1 I_M - \lambda_M S_H - \mu_H S_H, \\ E_M' &= \lambda_M S_H - (\gamma_H + \mu_H) E_M, \\ I_M' &= \gamma_H E_M - (\mu_H + \delta_M + \phi_1) I_M, \\ S_V' &= \Lambda_V - \lambda_V S_V - \mu_V S_V, \\ E_V' &= \lambda_V S_V - (\gamma_V + \mu_V) E_V, \\ I_V' &= \gamma_V E_V - \mu_V I_V, \end{aligned} \tag{10}$$

where, now, $\lambda_M = \beta_M b_M \dfrac{I_V}{N_H}$, $\lambda_V = \beta_V b_M \dfrac{I_M}{N_H}$ and $N_H = S_H + E_M + I_M$. The model is a slight modification of the dengue transmission model in [21].

Consider the region

$$\Omega_M = \Big\{ (S_H, E_M, I_M, S_V, E_V, I_V) \in \mathbb{R}_+^6 : N_H \leq \Lambda_H/\mu_H, N_V \leq \Lambda_V/\mu_V \Big\}.$$

It can be shown that the region Ω_M is positively-invariant (so that it is sufficient to consider the dynamics of the model (10) in Ω_M).

4.1. **Local stability of the disease-free equilibrium.** The DFE of the malaria-only model (10) is given by,

$$\mathcal{E}_{M0} = \Big(S_H, E_M, I_M, S_V, E_V, I_V \Big) = \Big(\frac{\Lambda_H}{\mu_H}, 0, 0, \frac{\Lambda_V}{\mu_V}, 0, 0 \Big). \tag{11}$$

Here, the associated next generation matrices are given by

$$F = \begin{pmatrix} 0 & 0 & 0 & b_M \beta_M \\ 0 & 0 & 0 & 0 \\ 0 & \frac{b_M \beta_V \Lambda_V \mu_H}{\Lambda_H \mu_V} & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

$$V = \begin{pmatrix} \gamma_H + \mu_H & 0 & 0 & 0 \\ -\gamma_H & \delta_M + \mu_H + \phi_1 & 0 & 0 \\ 0 & 0 & \gamma_V + \mu_V & 0 \\ 0 & 0 & -\gamma_V & \mu_V \end{pmatrix},$$

so that,

$$\mathcal{R}_M = \rho(FV^{-1}) = \sqrt{\frac{b_M^2 \beta_M \beta_V \gamma_H \gamma_V \mu_H \Lambda_V}{\Lambda_H \mu_V^2 (\gamma_H + \mu_H)(\gamma_V + \mu_V)(\delta_M + \mu_H + \phi_1)}}. \tag{12}$$

Thus, using Theorem 2 of [46], we have established the following result.

Theorem 5. *The DFE of the malaria-only model (10) is LAS if $\mathcal{R}_M < 1$, and unstable if $\mathcal{R}_M > 1$.*

4.2. **Existence of backward bifurcation.** It is shown from Theorem 5 that the DFE of the malaria-only model is LAS if $\mathcal{R}_M < 1$. However, this equilibrium may not be GAS in Ω_M for $\mathcal{R}_M < 1$, owing to the possibility of backward bifurcation, where the stable DFE co-exists with a stable endemic equilibrium when $\mathcal{R}_M < 1$ (see, for instance, [9, 13, 18, 19, 21, 23, 32, 29, 42, 43] and the references therein for further discussion on backward bifurcation). The public health implication of backward bifurcation is that the classical requirement of having the basic reproduction number less than unity, although necessary, is no longer sufficient for disease control. The possibility of the backward bifurcation phenomenon in the system (10) is investigated below.

Solving the malaria-only model at an arbitrary equilibrium, denoted by $\mathcal{E}_{M1} = (S_H^*, E_M^*, I_M^*, S_V^*, E_V^*, I_V^*)$, gives,

$$\begin{cases} S_H^* = \frac{(\gamma_H+\mu_H)(\delta_M+\mu_H+\phi_1)\Lambda_H}{\mu_H(\lambda_M^*+\mu_H)(\delta_M+\mu_H+\phi_1)+\gamma_H(\delta_M(\lambda_M^*+\mu_H)+\mu_H(\lambda_M^*+\mu_H+\phi_1))}, \\ E_M^* = \frac{(\delta_M+\mu_H+\phi_1)\lambda_M^*\Lambda_H}{\mu_H(\lambda_M^*+\mu_H)(\delta_M+\mu_H+\phi_1)+\gamma_H(\delta_M(\lambda_M^*+\mu_H)+\mu_H(\lambda_M^*+\mu_H+\phi_1))}, \\ I_M^* = \frac{\gamma_H\lambda_M^*\Lambda_H}{\mu_H(\lambda_M^*+\mu_H)(\delta_M+\mu_H+\phi_1)+\gamma_H(\delta_M(\lambda_M^*+\mu_H)+\mu_H(\lambda_M^*+\mu_H+\phi_1))}, \\ S_V^* = \frac{\Lambda_V}{\lambda_V^*+\mu_V}, \quad E_V^* = \frac{\lambda_V^*\Lambda_V}{(\gamma_V+\mu_V)(\lambda_V^*+\mu_V)}, \quad I_V^* = \frac{\gamma_V\lambda_V^*\Lambda_V}{\mu_V(\gamma_V+\mu_V)(\lambda_V^*+\mu_V)}, \end{cases} \tag{13}$$

where,

$$\lambda_M^* = \frac{b_M\beta_M I_V^*}{S_H^* + E_M^* + I_M^*}, \tag{14}$$

and,

$$\lambda_V^* = \frac{b_M\beta_M I_M^*}{S_H^* + E_M^* + I_M^*}. \tag{15}$$

Substituting (13) and (15) into (14) shows that the endemic equilibria of the malaria-only model (10) satisfy the following polynomial (in terms of λ_M^*)

$$\lambda_M^*\left[A\left(\lambda_M^*\right)^2 + B\lambda_M^* + C\right] = 0, \tag{16}$$

where,

$$\begin{aligned} A &= \Lambda_H\mu_V(\gamma_V+\mu_V)(\gamma_H+\delta_M+\mu_H+\phi_1)A_1, \\ B &= \Lambda_H\mu_V(\gamma_H+\mu_H)(\gamma_V+\mu_V)(\delta_M+\mu_H+\phi_1)B_1 \\ &\quad -b_M^2\beta_M\beta_V\gamma_H\gamma_V\Lambda_V\Big[\gamma_H(\delta_M+\mu_H)+\mu_H(\delta_M+\mu_H+\phi_1)\Big], \\ C &= \Lambda_H\mu_V^2(\gamma_V+\mu_V)(\gamma_H+\mu_H)^2(\delta_M+\mu_H+\phi_1)^2(1-\mathcal{R}_M^2), \end{aligned}$$

with,

$$\begin{aligned} A_1 &= b_M\beta_V\gamma_H + \mu_V(\gamma_H+\delta_M+\mu_H+\phi_1), \\ B_1 &= b_M\beta_V\gamma_H + 2\mu_V(\gamma_H+\delta_M+\mu_H+\phi_1). \end{aligned}$$

The root $\lambda_M^* = 0$, of (16), corresponds to the DFE $\mathcal{E}_{M0}$ (whose stability has already been analyzed). For backward bifurcation to occur, multiple non-zero (endemic) equilibria must exist. It follows from (16) that the non-zero equilibria of the model satisfy

$$f(\lambda_M^*) = A\left(\lambda_M^*\right)^2 + B\lambda_M^* + C = 0, \tag{17}$$

so that the quadratic (17) can be analyzed for the possibility of multiple equilibria. It is worth noting that the coefficient A is always positive and C is positive (negative) if $\mathcal{R}_M$ is less than (greater than) unity, respectively. Hence, we have established the following result.

Theorem 6. *The malaria-only model (10) has*

(i) precisely one unique endemic equilibrium if $C < 0$ (i.e., $\mathcal{R}_M > 1$),
(ii) precisely one unique endemic equilibrium if $B < 0$, and $C = 0$ or $B^2 - 4AC = 0$,
(iii) precisely two endemic equilibria if $C > 0$ (i.e., $\mathcal{R}_M < 1$), $B < 0$ and $B^2 - 4AC > 0$,
(iv) no endemic equilibrium otherwise.

The possible presence of two endemic equilibria (Case (*iii*)) above indicates the possibility of backward bifurcation in the model (10). This is explored further below, using the Centre Manifold theory [11, 13, 18, 46]. To apply this theory, the following simplification and change of variables are made first of all. Let $S_H = x_1, E_M = x_2, I_M = x_3$, $S_V = x_4$, $E_V = x_5$ and $I_V = x_6$, so that $N_H = x_1 + x_2 + x_3$ and $N_V = x_4 + x_5 + x_6$. Further, by using vector notation $\mathbf{x} = (x_1, x_2, x_3, x_4, x_5, x_6)^T$, the malaria-only model (10) can be written in the form $\frac{d\mathbf{x}}{dt} = F(\mathbf{x})$, with $F = (f_1, f_2, f_3, f_4, f_5, f_6)^T$, as follows:

$$\begin{aligned}
\frac{dx_1}{dt} &= f_1 = \Lambda_H + \phi_1 x_3 - \lambda_M x_1 - \mu_H x_1,\\
\frac{dx_2}{dt} &= f_2 = \lambda_M x_1 - (\gamma_H + \mu_H)x_2,\\
\frac{dx_3}{dt} &= f_3 = \gamma_H x_2 - (\mu_H + \delta_M + \phi_1)x_3,\\
\frac{dx_4}{dt} &= f_4 = \Lambda_V - \lambda_V x_4 - \mu_V x_4,\\
\frac{dx_5}{dt} &= f_5 = \lambda_V x_4 - (\gamma_V + \mu_V)x_5,\\
\frac{dx_6}{dt} &= f_6 = \gamma_V x_5 - \mu_V x_6,
\end{aligned} \tag{18}$$

with,

$$\lambda_M = \frac{\beta_M b_M x_6}{x_1 + x_2 + x_3} \text{ and } \lambda_V = \frac{\beta_V b_M x_3}{x_1 + x_2 + x_3}.$$

The method entails evaluating the Jacobian of the system (18) at the DFE $\mathcal{E}_{M0}$, denoted by $J(\mathcal{E}_{M0})$. This gives:

$$J(\mathcal{E}_{M0}) = \begin{pmatrix} -\mu_H & 0 & \phi_1 & 0 & 0 & -J_1 \\ 0 & -J_2 & 0 & 0 & 0 & J_1 \\ 0 & \gamma_H & -J_3 & 0 & 0 & 0 \\ 0 & 0 & -J_4 & -\mu_V & 0 & 0 \\ 0 & 0 & J_4 & 0 & -J_5 & 0 \\ 0 & 0 & 0 & 0 & \gamma_V & -\mu_V \end{pmatrix},$$

where,

$$\begin{aligned} J_1 &= \beta_M b_M,\ J_2 = \gamma_H + \mu_H,\ J_3 = \mu_H + \delta_M + \phi_1, \\ J_4 &= (\beta_V b_M \Lambda_V \mu_H)/(\mu_V \Lambda_H), J_5 = \gamma_V + \mu_V. \end{aligned}$$

Consider, next, the case when $\mathcal{R}_M = 1$. Suppose, further, that $\beta_M = \beta^*$ is chosen as a bifurcation parameter. Solving for β_M from $\mathcal{R}_M = 1$ gives

$$\beta_M = \beta^* = \frac{\Lambda_H \mu_V^2 (\gamma_H + \mu_H)(\mu_H + \delta_M + \phi_1)(\mu_V + \gamma_V)}{b_M^2 \beta_V \gamma_H \gamma_V \mu_H \Lambda_V}.$$

It follows that the Jacobian ($J(\mathcal{E}_{M0})$) of (18) at the DFE, with $\beta_M = \beta^*$, denoted by J_{β^*}, has a simple zero eigenvalue (with all other eigenvalues having negative real part). Hence, the Centre Manifold theory [11] can be used to analyze the dynamics of the model (18). In particular, the theorem in [13] (see also [11, 18, 46]), reproduced below for convenience, will be used to show that the model (18) (or, equivalently, (10)) undergoes backward bifurcation at $\mathcal{R}_M = 1$.

Theorem 7. Castillo-Chavez and Song [13]

Consider the following general system of ordinary differential equations with a parameter ϕ

$$\frac{dx}{dt} = f(x, \phi), \quad f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}^n \text{ and } f \in \mathbb{C}^2(\mathbb{R}^n \times \mathbb{R}),$$

where 0 *is an equilibrium point of the system (that is,* $f(0, \phi) \equiv 0$ *for all* ϕ*) and*

1. $A = D_x f(0,0) = \left(\frac{\partial f_i}{\partial x_j}(0,0)\right)$ *is the linearization matrix of the system around the equilibrium* 0 *with* ϕ *evaluated at* 0*;*
2. *Zero is a simple eigenvalue of* A *and all other eigenvalues of* A *have negative real parts;*
3. *Matrix* A *has a right eigenvector* w *and a left eigenvector* v *corresponding to the zero eigenvalue.*

Let f_k *be the* k*th component of* f *and*

$$\begin{aligned} a &= \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0), \\ b &= \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0), \end{aligned}$$

then the local dynamics of the system around the equilibrium point 0 *is totally determined by the signs of* a *and* b*. Particularly, if* $a > 0$ *and* $b > 0$*, then a backward bifurcation occurs at* $\phi = 0$*.*

In order to apply the above theorem, the following computations are necessary (it should be noted that we are using β^* as the bifurcation parameter, in place of ϕ in Theorem 7).

Eigenvectors of J_{β^*}: For the case when $\mathcal{R}_M = 1$, it can be shown that the Jacobian of (18) at $\beta_M = \beta^*$ (denoted by J_{β^*}) has a right eigenvector given by $\mathbf{w} = [w_1, w_2, w_3, w_4, w_5, w_6]^T$, where,

$$\begin{aligned}
w_1 &= \frac{\phi_1 w_3 - \beta^* b_M w_6}{\mu_H},\\
w_2 &= \frac{\beta^* b_M w_6}{\gamma_H + \mu_H},\\
w_3 &= \frac{\gamma_H w_2}{\mu_H + \delta_M + \phi_1},\\
w_4 &= \frac{-(\beta_V b_M \mu_H \Lambda_V w_3)}{\Lambda_H \mu_V^2},\\
w_5 &= \frac{\mu_V w_6}{\gamma_V},\\
w_6 &= w_6.
\end{aligned}$$

Further, J_{β^*} has a left eigenvector $\mathbf{v} = [v_1, v_2, v_3, v_4, v_5, v_6]$, where,

$$\begin{aligned}
v_1 &= 0,\\
v_2 &= v_2,\\
v_3 &= \frac{\gamma_H + \mu_H}{\gamma_H},\\
v_4 &= 0,\\
v_5 &= \frac{\gamma_V v_6}{\gamma_V + \mu_V},\\
v_6 &= \frac{\beta^* b_M v_2}{\mu_V}.
\end{aligned}$$

Computations of a and b: It can be shown, after some algebraic manipulations (involving computing the associated non-zero partial derivatives of F (at the DFE) to be used in the expression for a in Theorem 7), that

$$a = \frac{-2 b_M \mu_H v_5 w_3 w_4 \beta_V (\nabla - 1)}{\Lambda_H},$$

where,

$$\nabla = \frac{v_2 w_6 \mu_H \Lambda_H \beta_M (w_2 + w_3) + v_5 w_3 \mu_H \Lambda_V \beta_V (w_1 + w_2 + w_3)}{v_5 w_3 w_4 \mu_V \Lambda_H \beta_V},$$

and,

$$b = v_2 w_6 b_M > 0.$$

Hence, it follows (from Theorem 7 above) that the malaria-only model (10) undergoes backward bifurcation at $\mathcal{R}_M = 1$ whenever

$$a = \frac{-2 b_M \mu_H v_5 w_3 w_4 \beta_V (\nabla - 1)}{\Lambda_H} > 0. \tag{19}$$

This result is summarized below.

Theorem 8. *The malaria-only model (10) undergoes a backward bifurcation at $\mathcal{R}_M = 1$ whenever inequality (19) holds.*

The backward bifurcation phenomenon is illustrated (Figure 2) by simulating the malaria-only model system (10) with the following set of parameter values (note that the parameters are chosen in order to illustrate the backward bifurcation, and may not all be realistic epidemiologically (see [32] for some comments on whether or not backward bifurcation, in the context of TB disease, can occur with realistic parameter values)): $\Lambda_H = 0.00099, \Lambda_V = 0.0089, \beta_M = 0.07833, \beta_V = 0.0057233, b_M = 0.58, \gamma_H = 100, \gamma_V = 0.981, \mu_H = 0.00049139, \mu_V = 0.009, \phi_1 = 0.00656, \delta_M = 0.0013945392$. Using the above set of parameter values, it follows that $\mathcal{R}_M = 0.9823256562$ and $a = 0.3354$ with $b = 0.58$ (so that the inequality (19) is satisfied).

Although the phenomenon of backward bifurcation has been observed in numerous epidemiological settings, such as those for behavioural responses to perceived risk, multi-groups, vaccination, TB dynamics with exogenous re-infection (see [13, 18, 19, 21, 23, 32, 29, 42, 43] and the references therein), this is, probably, the first time such a phenomenon has been established in malaria transmission dynamics (Garba et al. [21] also established backward bifurcation in dengue disease, another vector-borne disease).

Finally, it is worth stating that, unlike in the HIV-only model, the DFE of the malaria-only model ($\mathcal{E}_{M0}$) is not globally-asymptotically stable when the associated reproductive number ($\mathcal{R}_M$) is less than unity, owing to the phenomenon of backward bifurcation. Consequently, this study shows that the control of malaria spread in a population when $\mathcal{R}_M < 1$ will depend on the initial sizes of the sub-populations of the malaria-only model (10).

5. Analysis of the HIV-malaria model.

5.1. Local stability of the disease-free equilibrium.

Having analysed the dynamics of the two sub-models, the full HIV-malaria model (4) is now considered. Its DFE is given by,

$$\begin{aligned} \mathcal{E}_0 &= \Big(S_H, E_M, I_M, I_H, E_{HM}, I_{HM}, A_H, E_{AM}, A_{HM}, S_V, E_V, I_V\Big) \\ &= \Big(\frac{\Lambda_H}{\mu_H}, 0, 0, 0, 0, 0, 0, 0, 0, \frac{\Lambda_V}{\mu_V}, 0, 0\Big). \end{aligned} \tag{20}$$

It is easy to show, using the next generation method (as in Sections 3 and 4), that the associated reproduction number for the full HIV-malaria model (4) (denoted by $\mathcal{R}_{HM}$) is given by

$$\mathcal{R}_{HM} = \max\{\mathcal{R}_H, \mathcal{R}_M\}, \tag{21}$$

so that the following results follows from Theorem 2 of [46].

Theorem 9. *The DFE of the HIV-malaria model (4), given by (20), is LAS if* $\mathcal{R}_{HM} < 1$, *and unstable if* $\mathcal{R}_{HM} > 1$.

Like in the case of the malaria-only model (10), the full HIV-malaria model (4) also undergoes backward bifurcation. We claim the following (see Appendix A for proof)

Theorem 10. *The full model (4) undergoes backward bifurcation at* $\mathcal{R}_{HM} = 1$ *whenever inequality (23) is satisfied.*

The backward bifurcation phenomenon of the full HIV-malaria model (4) is illustrated by depicting time series plots, based on simulating the transformed model (22) with various initial conditions, showing convergence to either the DFE ($\mathcal{E}_0$) or an endemic equilibrium (Figure 3). With the parameter values used in these simulations, the coefficient a in the inequality (23) is given by $a = 0.0006$ (and b is always positive).

6. **Numerical simulations and concluding remarks.** In order to illustrate some of the analytical results in this paper, numerous numerical simulations of the full model (4) were carried out, using a set of parameter values given in Table 1. Figure 4 illustrates the solution profiles of the populations of symptomatic individuals infected with malaria only (I_M), HIV only (I_H), both diseases (I_{HM}) and the symptomatic mosquito population (I_V), using various initial conditions. Simulating the model using the parameter values in Table 1 with $\beta_V = 0.2$ and $\beta_H = 0.0001$ (so that $\mathcal{R}_H = 0.3076$, $\mathcal{R}_M = 0.4065$ and $\mathcal{R}_{HM} = 0.4065 < 1$) shows convergence to the disease-free equilibrium (Fig. 4), in line with Theorem 7. Similarly, choosing $\beta_H = 0.001$ and $\beta_V = 0.9$ (so that, $\mathcal{R}_H = 3.0765$, $\mathcal{R}_M = 0.8624$ and $\mathcal{R}_{HM} = 3.0765$) shows convergence to an endemic equilibrium (Fig. 5). Although the stability analysis of the endemic equilibrium of the HIV-malaria model (4) has not been carried out in this study, this result is certainly expected (since the DFE is unstable in this case, and, typically, the disease persists when the reproduction threshold ($\mathcal{R}_{HM}$) exceeds unity; as is the case in these particular simulations).

Simulations for the case where the two reproduction numbers exceed unity are carried out and depicted in Figure 6. These figures illustrate that for $\mathcal{R}_H$ and $\mathcal{R}_M$ greater than unity, there is always co-existence of the two diseases no matter which of the reproduction numbers is greater. Further, the simulations illustrate that the population of symptomatic individuals infected with malaria only (I_M) always has a higher steady-state value than that of the population of individuals in the HIV class I_H for $1 < \mathcal{R}_M > \mathcal{R}_H$, $1 < \mathcal{R}_H < \mathcal{R}_M$ and $\mathcal{R}_M = \mathcal{R}_H$ (it should be stated that in each of the pictures depicted in Figure 6, the steady-state value of the population of individuals in the I_H class is non-zero). In other words, these simulations suggest that, for the set of parameter values used, there would always be more cases of malaria at steady-state than cases of HIV infection in the community.

The effect of reduction in sexual activity by individuals with malaria symptoms (I_M) exposed to HIV is monitored by varying the parameter σ. Figure 7B shows

that while the cumulative number of new cases of malaria infection increases with decreasing σ, the cumulative number of new cases of HIV (Fig. 7A) and that of the mixed (HIV-malaria) infection (Fig. 7C) decrease as σ decreases from 1 to 0. That is, as individuals with symptoms of malaria decrease their risk of acquiring HIV infection (by decreasing their effective contact rate $\sigma\lambda_H$, with $0 < \sigma \leq 1$), the cumulative number of new cases of HIV and the mixed infection decrease; while the cumulative number of new cases of malaria rises.

Simulations were carried out to monitor the effect of the assumed increase in susceptibility to malaria infection in individuals infected with HIV, by varying the associated parameter ϑ. The simulations, depicted in Figure 8, show that such an increase in susceptibility has marginal effect on the number of new cases of HIV (alone) and malaria infection (since the curves in Figure 8A and Figure 8B seem to, generally, coincide). However, for the case of the mixed infection, Figure 8C shows significant increase in the number of new cases as malaria susceptibility is increased by about 10-fold (the increase in the number of new cases remains constant as ϑ is increased further).

The effect of increase in AIDS-related mortality in individuals dually-infected with HIV and malaria (with symptoms of malaria) is also monitored, by varying ψ. Figure 9 shows an increase in HIV mortality as ψ increases and a decrease in mortality for individuals with the dual infection. This parameter seems to have no effect on the mortality of individuals infected with malaria only (albeit it shows a marginal decrease in mortality as ψ increases).

In summary, a deterministic compartmental model for the transmission dynamics of HIV and malaria in a given community is designed and rigorously analyzed. The model considered the epidemiologic synergy between sexually transmitted HIV and malaria in the context of Abu-Raddad *et al.* [1]. The HIV-only and malaria-only models were qualitatively examined, first of all. The main theoretical results obtained are as follows:

(i) The HIV-only model has a globally-asymptotically stable disease-free equilibrium whenever a certain epidemiological threshold ($\mathcal{R}_H$) is less than unity (see also [42, 43]); and unstable if this threshold exceeds unity;
(ii) The HIV-only model has a unique endemic equilibrium whenever the aforementioned threshold exceeds unity. For the case where no AIDS-related mortality is considered, this endemic equilibrium is globally-asymptotically stable whenever it exists;
(iii) Unlike the HIV-only model, the malaria-only model undergoes the phenomenon of backward bifurcation, where the associated stable disease-free equilibrium co-exists with a stable endemic equilibrium when the corresponding reproduction number ($\mathcal{R}_M$) is less than unity;
(iv) The full HIV-malaria model is shown to have a locally-asymptotically stable disease-free equilibrium when its reproductive threshold is less than unity, and unstable if the threshold exceeds unity. It also undergoes the phenomenon of backward bifurcation under certain conditions;

Numerical simulations of the full HIV-malaria model show the following:

(a) The two diseases co-exist whenever the reproduction number of each of the two diseases exceed unity (regardless of which number is larger);
(b) The number of new cases of malaria at steady state seems to always exceeds that of HIV;

(c) The assumed reduction in sexual activity of individuals with malaria symptoms results in decrease in the number of new cases of HIV and the mixed HIV-malaria infection, while increasing the number of new cases of malaria;
(d) The HIV-induced increase in susceptibility to malaria infection has marginal effect on the number of new cases of HIV, but significantly increases the number of new cases of the dual HIV-malaria infection.

This study provides the first in-depth mathematical analysis of a comprehensive model for the transmission dynamics of HIV and malaria in a population. There are a number of ways this study can be extended, including incorporating preventive and therapeutic strategies for HIV (such as the use of anti-retroviral therapy, condom use, voluntary HIV testing and screening) and malaria (such as the use of treatment and prophylactic drugs, vector-reduction strategies and personal protection against mosquito bites) and the acquisition of malaria immunity for adults in malaria-endemic settings, following repeated exposure (the latter would be somewhat of a daunting task since both diseases affect the immune system). It would also be interesting to consider the possible consequences of HIV-Malaria co-infection in mother-to-child transmission of HIV.

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Appendix A: Proof of Theorem 10.

Proof. The proof is also based on using the Centre Manifold theory on the HIV-malaria model (4). As in Section 4.2, let $S_H = x_1, E_M = x_2, I_M = x_3, I_H = x_4, E_{HM} = x_5, I_{HM} = x_6, A_H = x_7, E_{AM} = x_8, A_{HM} = x_9, S_V = x_{10}, E_V = x_{11}$, and $I_V = x_{12}$, so that $N_H^c = x_1 + x_2 + x_3 + x_4 + x_5 + x_6 + x_7 + x_8 + x_9$ and $N_M^c = x_{10} + x_{11} + x_{12}$. Further, by adopting the same vector notation as in Section 4.2 with $\mathbf{x} = (x_1, x_2, \cdots, x_{12})^T$, the model (4) can be written in the form $\frac{d\mathbf{x}}{dt} = F(\mathbf{x})$, where $F = (f_1, f_2, \cdots, f_{12})^T$, as follows:

$$\frac{dx_1}{dt} = f_1 = \Lambda_H + \phi_1 x_3 - \lambda_H^c x_1 - \lambda_M^c x_1 - \mu_H x_1,$$

$$\frac{dx_2}{dt} = f_2 = \lambda_M^c x_1 - \lambda_H^c x_2 - K_1 x_2,$$

$$
\begin{aligned}
\frac{dx_3}{dt} &= f_3 = \gamma_H x_2 - \sigma\lambda_H^c x_3 - K_2 x_3,\\
\frac{dx_4}{dt} &= f_4 = \lambda_H^c x_1 + \phi_2 x_6 - \vartheta\lambda_M^c x_4 - K_3 x_4,\\
\frac{dx_5}{dt} &= f_5 = \lambda_H^c x_2 + \vartheta\lambda_M^c x_4 - K_4 x_5,\\
\frac{dx_6}{dt} &= f_6 = \sigma\lambda_H^c x_3 + \epsilon\gamma_H x_5 - K_5 x_6,\\
\frac{dx_7}{dt} &= f_7 = \kappa x_4 + \phi_3 x_9 - \vartheta\lambda_M^c x_7 - K_6 x_7,\\
\frac{dx_8}{dt} &= f_8 = \vartheta\lambda_M^c x_7 - K_7 x_8 + \kappa x_5,\\
\frac{dx_9}{dt} &= f_9 = \xi\kappa x_6 + \epsilon\gamma_H x_8 - K_8 x_9,\\
\frac{dx_{10}}{dt} &= f_{10} = \Lambda_V - \lambda_V^c x_{10} - \mu_V x_{10},\\
\frac{dx_{11}}{dt} &= f_{11} = \lambda_V^c x_{10} - K_9 x_{11},\\
\frac{dx_{12}}{dt} &= f_{12} = \gamma_V x_{11} - \mu_V x_{12},
\end{aligned}
\tag{22}
$$

where,

$$
\begin{aligned}
K_1 &= \gamma_H + \mu_H, K_2 = \mu_H + \delta_M + \phi_1, K_3 = \mu_H + \kappa, K_4 = \epsilon\gamma_H + \mu_H + \kappa,\\
K_5 &= \mu_H + \tau\delta_M + \phi_2 + \xi\kappa, K_6 = \mu_H + \delta_H, K_7 = \epsilon\gamma_H + \mu_H + \delta_H,\\
K_8 &= \mu_H + \phi_3 + \tau\delta_M + \psi\delta_H,\ K_9 = \mu_V + \gamma_V,
\end{aligned}
$$

and,

$$
\begin{aligned}
\lambda_H^c &= \beta_H \frac{\{x_4 + \eta_{HM}(x_5 + \theta_{HM}x_6) + \eta_A[x_7 + \eta_{HM}(x_8 + \theta_{HM}x_9)]\}}{N_H^c},\\
\lambda_M^c &= \frac{\beta_M b_M}{N_H^c} x_{12},\\
\lambda_V^c &= \frac{\beta_V b_M}{N_H^c}\left[x_3 + \eta_V(x_6 + \theta_V x_9)\right].
\end{aligned}
$$

It can be shown, by computing the eigenvalues of the associated Jacobian of the system (22) at the DFE (denoted by $J(\mathcal{E}_0)$), that $\mathcal{R}_{HM} = \max\{\mathcal{R}_H, \mathcal{R}_M\}$ as before. For convenience, we re-write

$$\mathcal{R}_H = \frac{\beta_H(\delta_H + \kappa\eta_A + \mu_H)}{K_3K_6} \quad \text{and} \quad \mathcal{R}_M = \sqrt{\frac{b_M^2\beta_M\beta_V\gamma_H\gamma_V\mu_H\Lambda_V}{\Lambda_H\mu_V^2K_1K_2K_9}}.$$

Consider the case when $\mathcal{R}_{HM} = 1$ (that is, $\mathcal{R}_M < \mathcal{R}_H = 1$). Suppose, further, that $\beta_H = \beta^*$ is chosen as a bifurcation parameter. Solving for β_H from $\mathcal{R}_H = 1$ gives

$$\beta_H = \beta^* = \frac{K_3K_6}{(\delta_H + \kappa\eta_A + \mu_H)}.$$

Eigenvectors of J_{β^*}:

For the case when $\mathcal{R}_{HM} = 1$, it can be shown that the matrix $J(\mathcal{E}_0)$ evaluated at $\beta_H = \beta^*$, denoted by J_{β^*}, has a right eigenvector given by

$$\mathbf{w} = [w_1, w_2, w_3, w_4, w_5, w_6, w_7, w_8, w_9, w_{10}, w_{11}, w_{12}]^T,$$

where,

$$\begin{aligned}
w_1 &= \frac{\phi_1 w_3 - \beta^* w_4 - \beta^*\eta_A w_7 - \beta_M b_M w_{12}}{\mu_H},\\
w_2 &= w_2,\\
w_3 &= \frac{\gamma_H w_2}{K_2},\\
w_4 &= w_4,\\
w_5 &= 0,\\
w_6 &= 0,\\
w_7 &= \frac{\kappa w_4}{K_6},\\
w_8 &= 0,\\
w_9 &= 0,
\end{aligned}$$

$$\begin{aligned} w_{10} &= -\frac{\beta_V b_M \mu_H \Lambda_V w_3}{\Lambda_H \mu_V^2}, \\ w_{11} &= \frac{\mu_V w_{12}}{\gamma_V}, \\ w_{12} &= \frac{K_1 w_2}{\beta_M b_M}. \end{aligned}$$

Further, the matrix J_{β^*} has a left eigenvector

$$\mathbf{v} = [v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9, v_{10}, v_{11}, v_{12}],$$

where,

$$\begin{aligned} v_1 &= 0, \\ v_2 &= v_2, \\ v_3 &= \frac{K_1 v_2}{\gamma_H}, \\ v_4 &= v_4, \\ v_5 &= \frac{\beta^* \eta_{HM} v_4 + \epsilon \gamma_H v_6 + \kappa v_8}{K_4}, \\ v_6 &= \frac{(\beta^* \eta_{HM} \theta_{HM} + \phi_2) v_4}{K_5} + \frac{\beta_V b_M \eta_V \mu_H \Lambda_V v_{11}}{\Lambda_H \mu_V K_5} + \frac{\xi \kappa v_9}{K_5}, \\ v_7 &= \frac{\beta^* \eta_A v_4}{K_6}, \\ v_8 &= \frac{\beta^* \eta_A \eta_{HM} v_4 + \epsilon \gamma_H v_9}{K_7}, \\ v_9 &= \frac{\beta^* \eta_A \eta_{HM} \theta_{HM} \Lambda_H \mu_V v_4 + \Lambda_H \mu_V \phi_3 v_7 + \beta_V b_M \eta_V \mu_H \Lambda_V \theta_V v_{11}}{\Lambda_H \mu_V K_8}, \\ v_{10} &= 0, \\ v_{11} &= \frac{K_2 v_3 \Lambda_H \mu_V}{\beta_V b_M \mu_H \Lambda_V}, \\ v_{12} &= \frac{\beta_M b_M v_2}{\mu_V}. \end{aligned}$$

Computations of a and b :

It can be shown, after some tedious manipulations, that

$$
\begin{aligned}
a &= -\frac{2\mu_H}{\Lambda_H^2\mu_V}(v_4w_4^2\beta_H\Lambda_H\mu_V + v_{11}w_3^2\beta_V b_M\mu_H\Lambda_V \\
&+ v_{11}w_1w_3\beta_V b_M\mu_H\Lambda_V + v_{11}w_2w_3\beta_V b_M\mu_H\Lambda_V + v_{11}w_3w_4\beta_V b_M\mu_H\Lambda_V \\
&+ v_{11}w_3w_7\beta_V b_M\mu_H\Lambda_V + v_2w_2w_4\beta_H\Lambda_H\mu_V + v_2w_2w_7\beta_H\eta_A\Lambda_H\mu_V \\
&+ v_2w_2w_{12}\beta_M b_M\Lambda_H\mu_V + v_2w_3w_{12}\beta_M b_M\Lambda_H\mu_V + v_2w_4w_{12}\beta_M b_M\Lambda_H\mu_V \\
&+ v_2w_7w_{12}\beta_M b_M\Lambda_H\mu_V + v_3w_3w_4\sigma\beta_H\Lambda_H\mu_V + v_3w_3w_7\sigma\beta_H\eta_A\Lambda_H\mu_V \\
&+ v_4w_2w_4\beta_H\Lambda_H\mu_V + v_4w_2w_7\beta_H\eta_A\Lambda_H\mu_V + v_4w_3w_4\beta_H\Lambda_H\mu_V \\
&+ v_4w_3w_7\beta_H\eta_A\Lambda_H\mu_V + v_4w_4w_{12}\vartheta\beta_M b_M\Lambda_H\mu_V + v_4w_7^2\beta_H\eta_A\Lambda_H\mu_V \\
&- v_5w_2w_4\beta_H\Lambda_H\mu_V - v_5w_2w_7\beta_H\eta_A\Lambda_H\mu_V - v_5w_4w_{12}\vartheta\beta_M b_M\Lambda_H\mu_V \\
&- v_6w_3w_4\sigma\beta_H\Lambda_H\mu_V - v_6w_3w_7\sigma\beta_H\eta_A\Lambda_H\mu_V + v_7w_7w_{12}\vartheta\beta_M b_M\Lambda_H\mu_V \\
&- v_8w_7w_{12}\vartheta\beta_M b_M\Lambda_H\mu_V - v_{11}w_3w_{10}\beta_V b_M\Lambda_H\mu_V + v_4w_4w_7\beta_H\Lambda_H\mu_V \\
&+ v_4w_4w_7\beta_H\Lambda_H\mu_V\eta_A),
\end{aligned}
$$

and,

$$b = v_4w_4 + v_4w_7\eta_A > 0.$$

Thus, it follows from Theorem 7 that the full HIV-malaria model (4) undergoes backward bifurcation at $\mathcal{R}_{HM} = 1$ whenever

$$a > 0. \tag{23}$$

□

TABLE 1. Model parameters and their interpretations

Parameter	Symbol	Value	Source
Recruitment rate of humans	Λ_H	5×10^{-2} day^{-1}	Assumed
Recruitment rate of mosquitoes	Λ_V	6 day^{-1}	[15]
Natural death rate of humans	μ_H	3.9×10^{-5} day^{-1}	[8]
Natural death rate of mosquitoes	μ_V	0.1429 day^{-1}	[16]
HIV-induced death rate	δ_H	9.13×10^{-4} day^{-1}	[36]
Malaria-induced death rate	δ_M	3.454×10^{-4} day^{-1}	[16]
Effective contact rate for HIV infection	β_H	Variable	Variable
Transmission probability for malaria in humans	β_M	0.8333 day^{-1}	[16]
Transmission probability for malaria in vectors	β_V	(0,1)	-
Biting rate of mosquitoes	b_M	(0.25, 1) day^{-1}	Assumed
Modification parameters	η_A, η_{HM}, ξ	1.4, 1.5, 1.002	Assumed
Modification parameters	$\theta_{HM}, \sigma, \tau$	1.002, 1.00, 1.001	Assumed
Modification parameters	$\epsilon, \vartheta, \psi$	1.02, 1.002, 1.002	Assumed
Recovery rate of humans from malaria	ϕ_1, ϕ_2, ϕ_3	0.00556, 0.002, 0.0005	Assumed
Modification parameters	η_V, θ_V	1.5, 1.5	Assumed
Rate of progression to AIDS stage	κ	0.000548 day^{-1}	Assumed
Rate at which humans exposed to malaria develop clinical symptoms	γ_H	0.08333 day^{-1}	[16]
Rate at which vectors exposed to malaria develop symptoms	γ_V	0.1 day^{-1}	[16]

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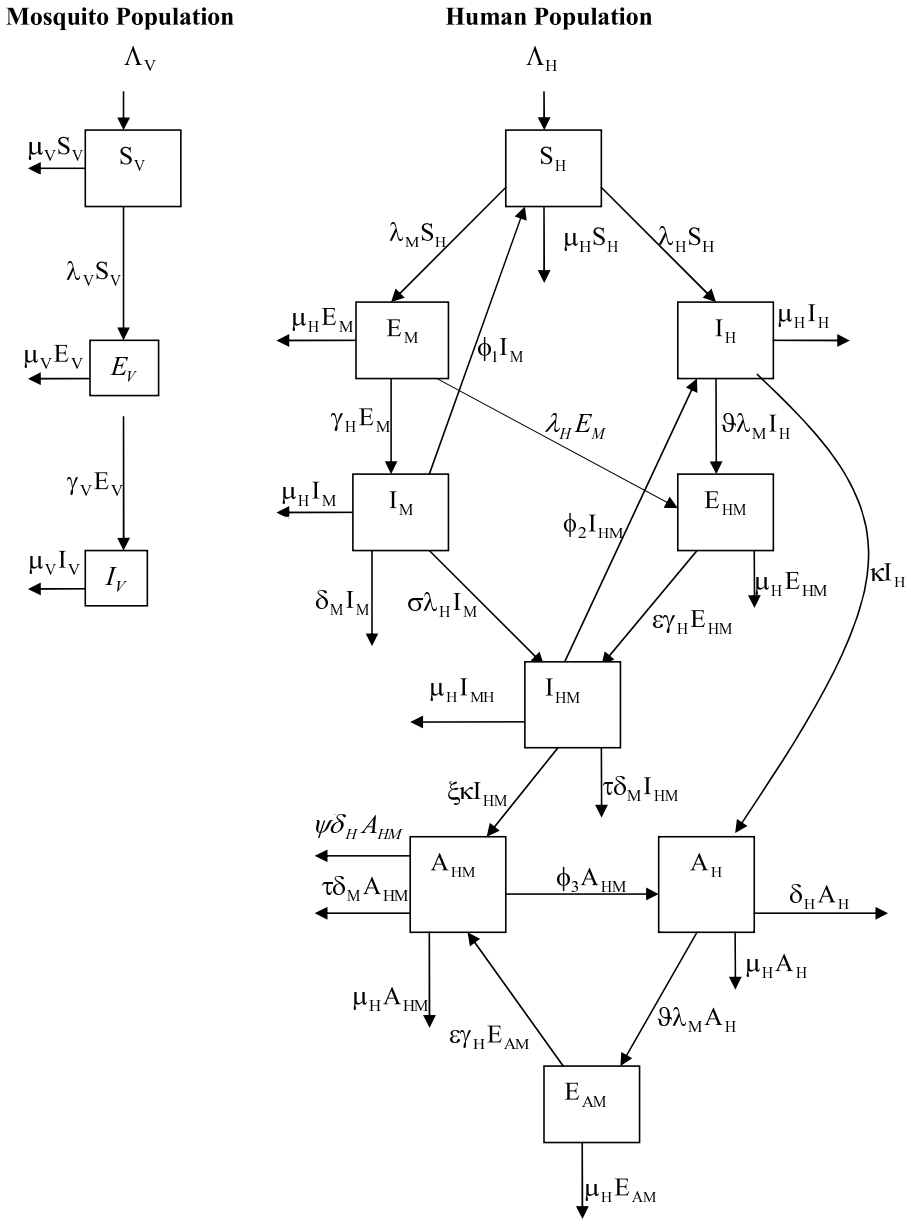

FIGURE 1. Flowchart of the HIV/malaria model (4)

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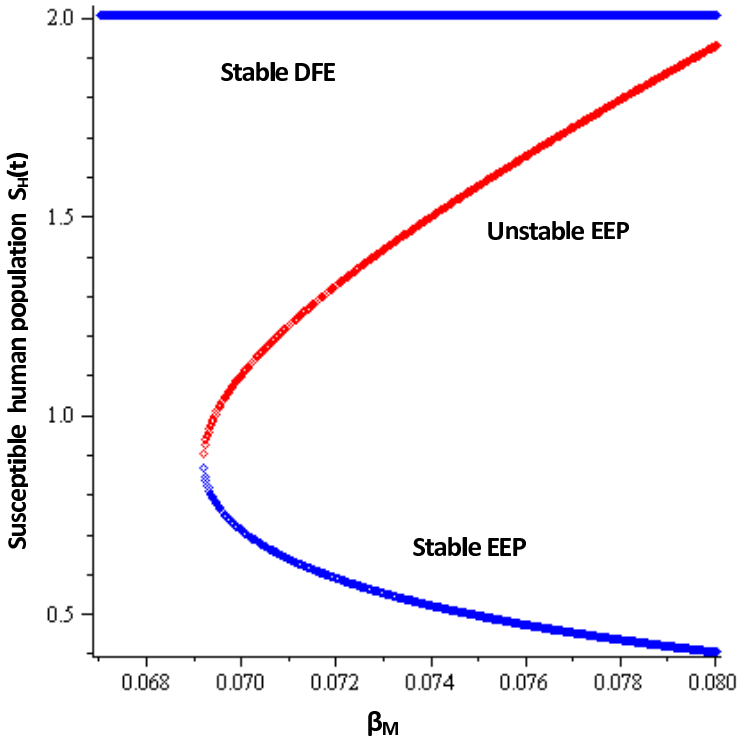

FIGURE 2. Bifurcation diagram for the malaria-only model (10) using: $\Lambda_H = 0.00099, \Lambda_V = 0.0089, \beta_V = 0.0057233, b_M = 0.58, \gamma_H = 100, \gamma_V = 0.981, \mu_H = 0.00049139, \mu_V = 0.009, \phi_1 = 0.00656, \delta_M = 0.0013945392$ and various values of β_M (with these parameter values and β_M range, $a > 0$ and $b > 0$).

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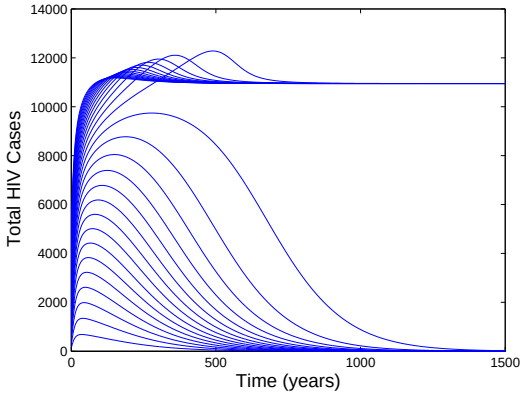
(A)



(B)

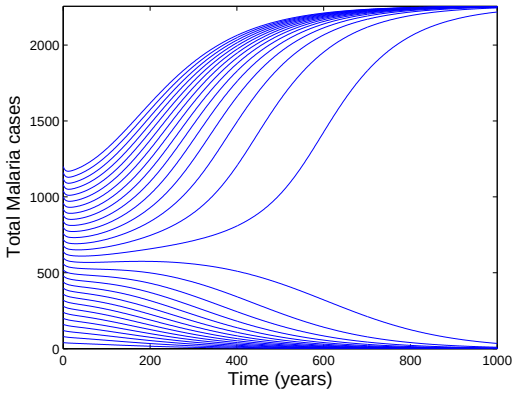


FIGURE 3. Simulations of the HIV-malaria model (22) with different initial conditions illustrating the phenomenon of backward bifurcation. Parameter values used are: $\Lambda_H = 1000, \Lambda_V = 100, \gamma_H = 1, \gamma_V = 0.981, \mu_H = 0.00049139, \mu_V = 0.009, \phi_1 = 0.002, \phi_2 = 0.004, \phi_3 = 0.006, \delta_M = 0.1, \delta_H = 0.1, \beta_V = 0.005723, b_M = 0.58, \beta_M = 3.3, \kappa = 1, \epsilon = 1.02, \eta_A = 1, \eta_{HM} = 1, \theta_{HM} = 1, \eta_V = 1, \theta_V = 1, \vartheta = 1.002, \tau = 1.001, \xi = 1.002, \sigma = 1, \psi = 1.002, \beta_H = 0.0015$. (A) Total HIV cases, (B) Total malaria cases.

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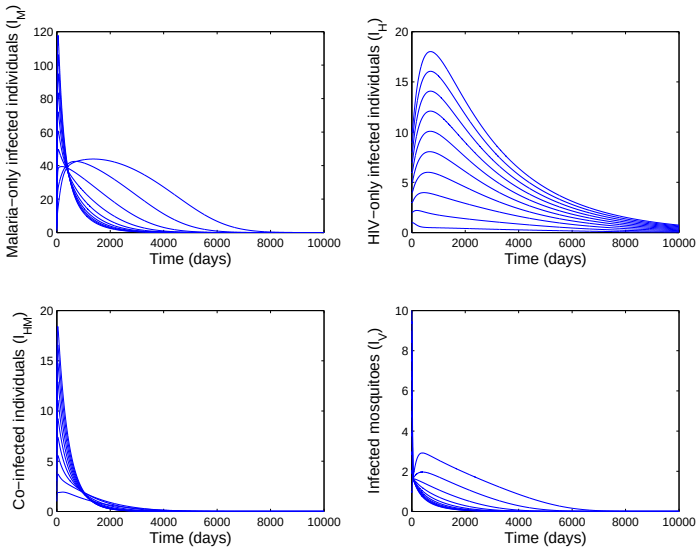

FIGURE 4. Simulations of the model (4) showing plots of individuals with malaria symptoms only (I_M), individuals with HIV only but no AIDS symptoms (I_H), individuals with mixed infection (I_{HM}) and infected mosquitoes (I_V) for the case $\mathcal{R}_{HM} < 1$, using various initial conditions. Parameter values used are as in Table 1 with $\beta_V = 0.2$ and $\beta_H = 0.0001$ (so that $\mathcal{R}_H = 0.3076$, $\mathcal{R}_M = 0.4065$ and $\mathcal{R}_{HM} = 0.4065$)

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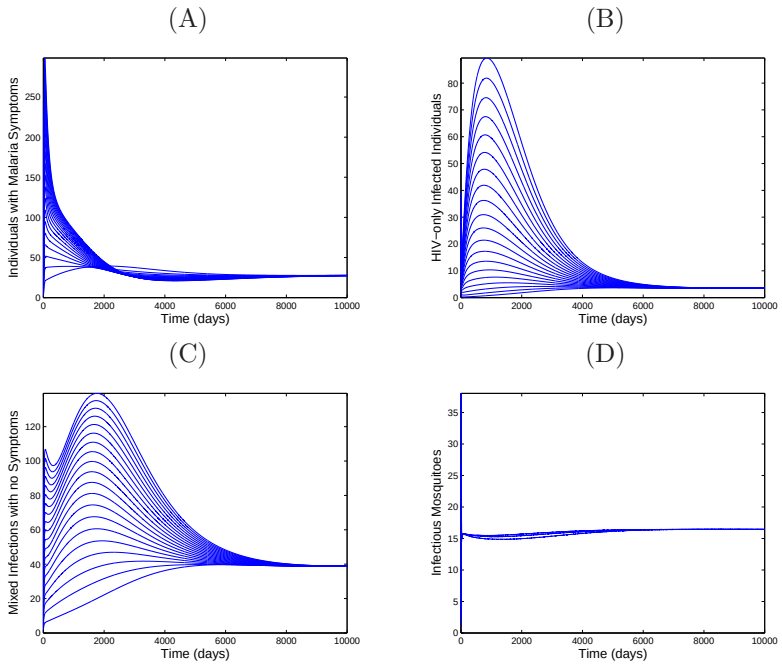

FIGURE 5. Simulations of the model (4) showing plots for (A) individuals with malaria symptoms only (I_M), (B) individuals with HIV only but no AIDS symptoms (I_H), (C) individuals with mixed infection (I_{HM}) and (D) infectious mosquitoes (I_V) for the case $\mathcal{R}_{HM} > 1$, using various initial conditions. Parameter values used are as in Table 1 with $\beta_V = 0.9$ and $\beta_H = 0.001$ (so that, $\mathcal{R}_H = 3.0765$, $\mathcal{R}_M = 0.8624$ and $\mathcal{R}_{HM} = 3.0765$)

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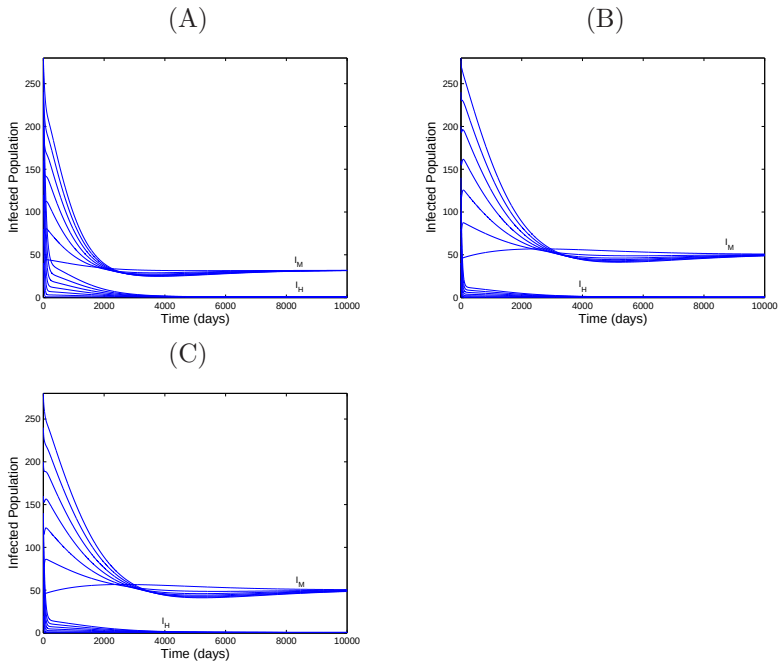

FIGURE 6. Simulations of the model (4) showing plots of individuals with malaria symptoms only (I_M) and those with HIV infection only but without AIDS symptoms (I_H) as a function of time, using various initial conditions. Parameters as in Table 1. (A) $\mathcal{R}_H > \mathcal{R}_M > 1$ ($\beta_V = 0.25$, $b_M = 1$, $\beta_H = 0.001$; so that $\mathcal{R}_H = 3.0765$, $\mathcal{R}_M = 1.8180$ and $\mathcal{R}_{HM} = 3.076$). (B) $\mathcal{R}_M > \mathcal{R}_H > 1$ ($\beta_V = 0.9$, $b_M = 1$, $\beta_H = 0.0007$; so that $\mathcal{R}_H = 2.1535$, $\mathcal{R}_M = 3.4495$ and $\mathcal{R}_{HM} = 3.4495$). (C) $\mathcal{R}_H = \mathcal{R}_M = \mathcal{R}_{HM} > 1$ ($\beta_V = 0.35076$, $\beta_H = 0.0007$; so that $\mathcal{R}_H = \mathcal{R}_M = \mathcal{R}_{HM} = 2.1535$)

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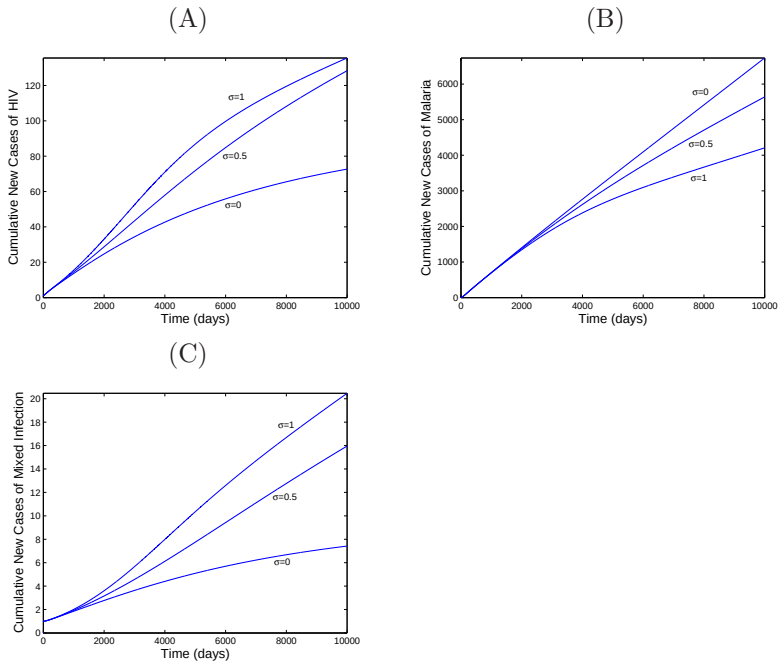

FIGURE 7. Simulations of the model (4) showing the effect of reduction in sexual activity (σ) by individuals with malaria symptoms exposed to HIV. The figures give the cumulative number of new cases of (A) HIV, (B) malaria and (C) the mixed infection, as a function of time. The parameter values used are as in Table 1, with $\beta_V = 0.9$, $b_M = 0.25$, $\beta_H = 0.0007$ and varying values of σ.

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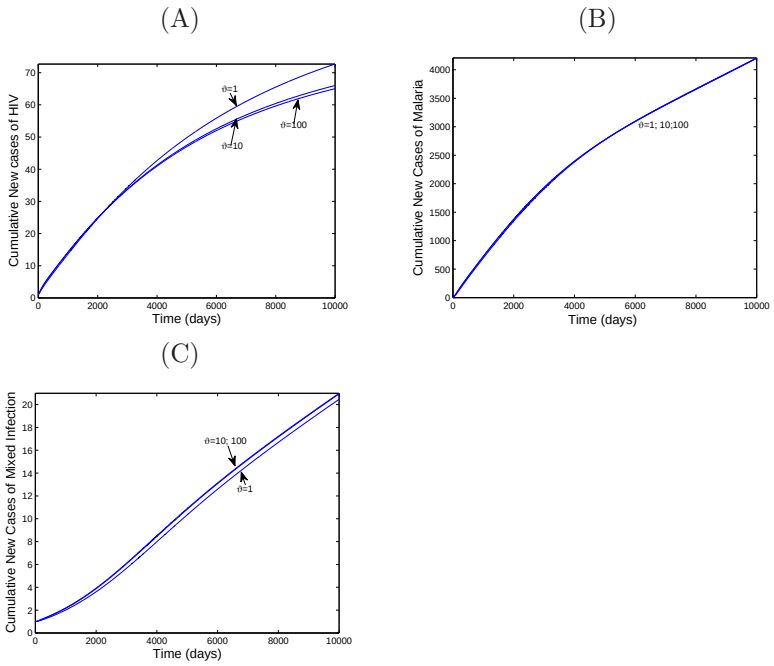

FIGURE 8. Simulations of the model (4) showing the effect of increase in susceptibility to malaria infection in individuals with HIV infection (ϑ). The figures give the cumulative number of new cases of (A) HIV, (B) malaria and (C) the mixed infection, as a function of time. The parameter values used are as in Table 1, with $\beta_V = 0.9$, $b_M = 0.25$, $\beta_H = 0.0007$ and varying values of ϑ.

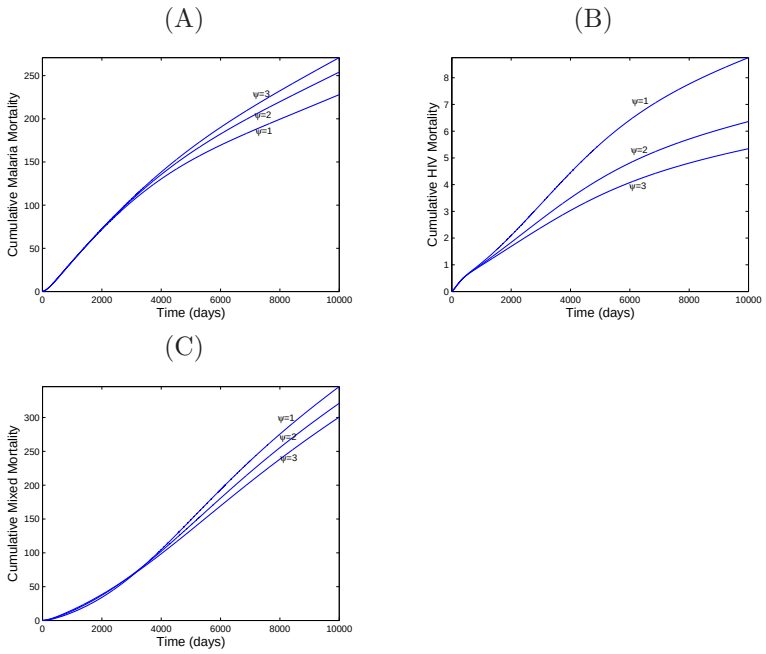

FIGURE 9. Simulations of the model (4) showing the effect of increase in HIV mortality in individuals dually-infected with HIV and malaria (ψ). The figures give the cumulative number of new cases of (A) HIV, (B) malaria and (C) the mixed infection, as a function of time. The parameter values used are as in Table 1, with $\beta_V = 0.9$, $b_M = 0.25$, $\beta_H = 0.0007$ and varying values of ψ.