

A Mathematical Model of HIV and Malaria Co-Infection in Sub-Saharan Africa

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Abstract

Malaria and HIV are two of the most deadly diseases in Africa. Combined they account for 4 million deaths each year, and according to the Center for Disease Control and Prevention (CDC), there is an estimated 5 percent increase in malaria deaths due to HIV infection in Sub-Saharan Africa. Since the co-infections was recorded, malaria has seen a 28 percent increase in its prevalence. Malaria associated death rates have nearly doubled for those with co-infections. We introduce a system of differential equations linking the host-vector system of malaria with co-infection with HIV. We use data from Sub-Saharan Africa in general and Malawi in particular where co-infections from both disease in order to motivate and guide the behavior of our model. We discovered that when parameter ρ is alter it will effect the way the diseases interact with each

other as well as separately.

1 Introduction

The Sub-Saharan region of Africa has many endemic diseases including malaria and HIV, which are two of the most deadliest diseases of our time [7]. The geographic overlap of these diseases (see Figures 1 and 2) in Sub-Saharan Africa facilitates co-infections with HIV and malaria [15]. Since both diseases are endemic and the length of infection for both diseases can be several years, the burden of co-infection is a real and pressing problem.

Malaria is an old disease that has been well studied since the late 1800's by Ross [14]. Despite over 100 years of study and advanced biological, medical, and mathematical understanding, we have yet to come to a viable solution for this disease that has already killed hundreds of millions of individuals. HIV/AIDS, by contrast, is a relatively new disease that has only been studied since the 1980's. Like malaria, HIV has received considerable attention from the scientific community and continues to kill millions while we search for a cure. While AIDS (last HIV stage) is characterized by the process of opportunistic infections, malaria is not typical in this regard. The co-infection between HIV/AIDS and malaria is not well understood. It is our hope that through our model the joint effects of co-infections are better understood.

The prevalence of HIV in east and south Africa is about 30 percent. From about one quarter to one third of the malaria patients are infected because of a weakened immune system caused by HIV infection [9]. On the other hand, malaria increases the viral load in HIV patients but this effect may be reversed with malaria treatment [7]. Because of the increase in viral loads in HIV patients from malaria, HIV transmission is thought to become twice as likely to be passed on to a noninfected individual [15].

In this study we propose a mathematical model for the joint dynamics of HIV and malaria co-infections. Our model is given by a set of six differential equations (which we later reduce to four). The details of the co-infection are very complicated, yet, we have

managed to model the effects of co-infections in a simple setting (a detailed discussion is deferred to Section 2). The remainder of the paper is organized as follows: below we give a brief discussion of HIV/AIDS and malaria. In Section 2 we analyze the stability of our model and find the basic reproductive number of our model, using the next generator operator approach. In Section 3, we discuss some simplifying assumptions, reduce our model to a system of four equations, and carry out the corresponding stability analysis. In Section 4, we examine the model in the absence of malaria and also in the absence of HIV. In Section 5, we discuss our conclusions, list avenues for potential future work and acknowledgements are in section 6. Finally we include mathematical derivations of R_0 and Matlab code in the Appendix.

1.1 HIV/AIDS

HIV has killed an estimated 25 million individuals world wide [1]. Since it was discovered in 1981, HIV has become one of the leading causes of death, globally, affecting mostly impoverished people already suffering from poor nutrition and health[15]. HIV stands for human immunodeficiency virus; it is a virus that attacks the immune system. While HIV does not kill, it causes the immune system to become defenseless against other opportunistic diseases it could normally fight off. An estimated 25 million people are infected with HIV each year in Africa [15].

1.2 Malaria

According to the CDC, malaria was first discovered centuries ago by the Chinese in 2700 BC. However it was in the late 1800's when Ross made his ground breaking discoveries that led to our understanding of the mechanics behind malaria infection [8]. Malaria is a mosquito borne disease and kills about 1 to 2 million people a year, of which most are children [11]. If left untreated malaria attacks the liver and moves through the bloodstream infecting every organ it can until the body shuts down leading to death. In Africa an estimated 350 million individuals are infected with the disease [1]. Although malaria is

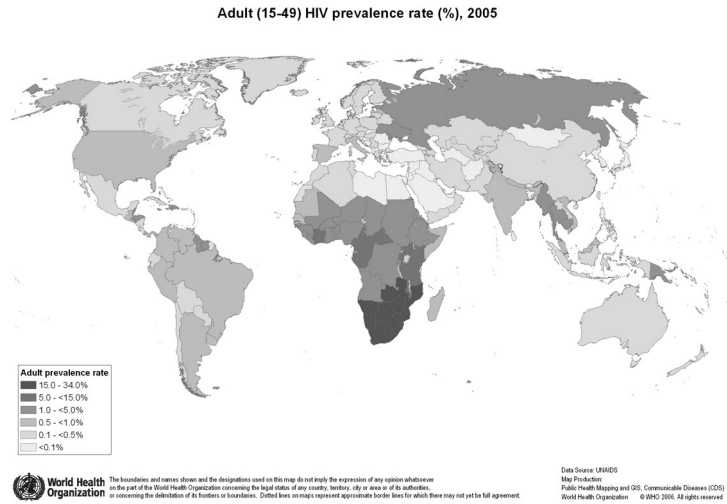


Figure 1: Global Prevalence of HIV according to WHO

[17]

treatable, the drugs can be too expensive or too difficult to distribute to the general public in countries where it is endemic. Like HIV it affects mostly impoverished people and, like HIV, it is a contributor to the impoverishment of many countries in Sub-Saharan Africa.

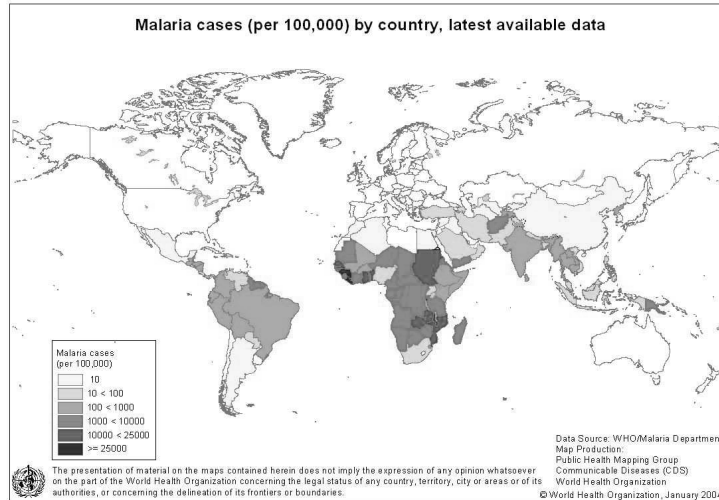


Figure 2: Global Prevalence of Malaria according to WHO

[17]

2 Full Model

There are many challenges in the derivation of an HIV/malaria co-infection model. HIV has many methods of transmission; the principles being: heterosexual and homosexual contact, intravenous needle sharing and mother to child transmission. The age group most affected by each method of transmission varies widely. Malaria is transmitted by a vector (mosquito), but the exact species varies from region to region. Mostly children die from malaria. For simplification we assume that our susceptible population is the general population that is at risk to getting an HIV infection at a rate proportional to the density of HIV infected people. Similarly, our susceptible population is also assumed to be at risk to get malaria at a rate proportional to the density of infected mosquitoes.

We divide the total human population, N , into 4 different classes: S , represents the susceptible class; I_M , represents infectious malaria class; I_H , represents infectious HIV class; I_{HM} , represents infectious with both HIV and malaria class; the total mosquito population, N_V , is divided into 2 different classes: V , represents the susceptible vector

class; and I_V , represents the infectious vector class;

It is known that there is an incubation period for malaria [1], but since we are interested in long term dynamics we ignore any latent or exposed classes. We also assume the total vector population is constant, but since death is a major concern for people infected with HIV or malaria, we do include disease induced mortality for people. Thus, the human population is not assumed to be constant, in fact Malawi has an estimated growth rate of 2.6 percent. Instead we assume a constant recruitment rate in the S class. We also assume susceptible people can not simultaneously get infected with malaria and HIV since the transmission mechanics are completely different for the two diseases. To get to the I_{HM} class a person must first enter either the I_H or the I_M class. However, a person in the I_{HM} class can transmit both diseases. Furthermore, since a person's immune system is compromised, that person has a higher probability of transmission given a "contact" has occurred. Here a "contact" is any process that can transmit an infection. We model this with an amplification factor ρ_i , where i depends on classes involved in the transmission.

We arrive at the following system of equations for the Full Model:

$$\begin{aligned}
\frac{dS(t)}{dt} &= \Lambda - \beta_{VM} \frac{I_V(t)}{N_V} S(t) - \beta_H \frac{I_H(t)}{N} S(t) - \rho_1 \beta_H \frac{I_{HM}(t)}{N} S(t) + \gamma I_M(t) - \alpha S(t) \\
\frac{dI_M(t)}{dt} &= \beta_{VM} \frac{I_V(t)}{N_V} S(t) - \beta_H \frac{I_H(t)}{N} I_M(t) - \rho_2 \beta_H \frac{I_{HM}(t)}{N} I_M(t) - \gamma I_M(t) - (\mu_M + \alpha) I_M(t) \\
\frac{dI_{HM}(t)}{dt} &= \rho_3 \beta_{VM} \frac{I_V(t)}{N_V} I_H(t) - \gamma k I_{HM}(t) - (\mu_{HM} + \alpha) I_{HM}(t) \\
\frac{dI_H(t)}{dt} &= \beta_H \frac{S(t)}{N} I_H(t) + \rho_1 \beta_H \frac{S(t)}{N} I_{HM}(t) - \rho_3 \beta_{VM} \frac{I_V(t)}{N_V} I_H(t) + \gamma k I_{HM}(t) - (\mu_H + \alpha) I_H(t) \\
\frac{dV(t)}{dt} &= \mu_V N_V - \beta_{MV} \frac{I_M(t)}{N} V(t) - \rho_4 \beta_{MV} \frac{I_{HM}(t)}{N} V(t) - \mu_V V(t) \\
\frac{dI_V(t)}{dt} &= \beta_{MV} \frac{I_M(t)}{N} V(t) + \rho_4 \beta_{MV} \frac{I_{HM}(t)}{N} V(t) - \mu_V I_V(t)
\end{aligned}$$

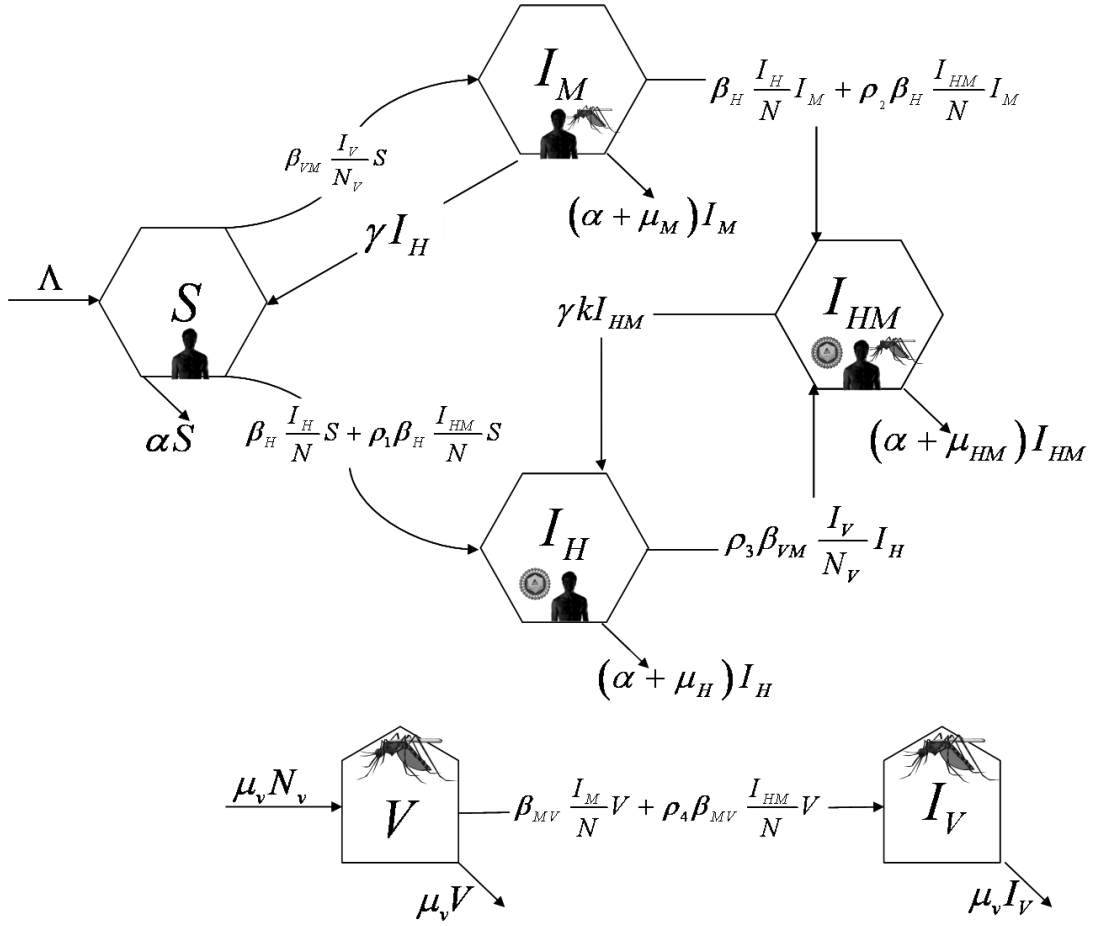


Figure 3: Full Model. Note there are two modes of transmission from the classes I_M to I_{HM} , S to I_H , and V to I_V

Where parameter definitions are given in Table 1, note that the rates relating to the human population have been rescaled by the initial total population for numerical stability.

Table 1: Parameter Definitions

Parameter	Definition	Malawi	Sub-Saharan Africa	Ref
Λ	Human recruitment rate	0.00039	0.00038	Approx
β_H	Effective contact rate for HIV infection	0.0005	0.0005	Approx
β_{MV}	Rate of infection of people infected by mosquitoes	0.0030	0.12	Approx
β_{VM}	Rate of humans which become infected following bite of an infectious mosquitoes	0.12	0.0030	Approx
γ	per capita recovery rate for humans from malaria	0.00001	0.00001	Approx
k	reduction factor of the recovery rate for malaria HIV co-infection	$\frac{1}{2}$	$\frac{1}{2}$	Approx
N	Total Population of Humans	12800000	767000000	[10]
μ_H	Rate of mortality of humans infected with HIV	$2.3*10^{-4}$	$2.3*10^{-4}$	[10]
μ_M	Rate of mortality of humans infected with Malaria	$3.454*10^{-4}$	$3.454*10^{-4}$	[3]
μ_{HM}	Rate of mortality of humans infected with HIV and Malaria	$1.4*10^{-3}$	$1.4*10^{-3}$	Approx
μ_V	Vector daily natural mortality rate	0.1429-0.0714	0.167	[3], [1]
α	per capita mortality rate of humans	$6.0883*10^{-5}$	$5.7078*10^{-5}$	[10]
$\rho_{i=1,2,3,4}$	Amplification factor	4,4,4,4	4,4,4,4	Approx

2.1 Local Stability of the Full Model

The disease free equilibrium (DFE) is straight forward to calculate by setting the infectious classes (I_M, I_H, I_{HM}, I_V) equal to zero:

$$DFE = (S^o, I_M^o, I_H^o, I_{HM}^o, V^o, I_V^o) = \left(\frac{\Lambda}{\alpha}, 0, 0, 0, N_V, 0\right)$$

This implies that the population, in the absence of diseases, will reach a demographic equilibrium. It remains to study the stability of this equilibrium point.

The basic reproductive number represents the average number of secondary infectious caused by a “typical” infectious individual in a mostly susceptible population. It is the threshold parameter that usually determines the stability of the DFE. We use the next

generation operator approach [5] to arrive at the following R_0

$$R_0 = \max \{R_{0H}, R_{0M}\}$$

where

$$R_{0H} = \frac{\beta_H}{\mu_H + \alpha}$$

and

$$R_{0M} = \sqrt{\frac{\beta_{MV}\beta_{VM}}{\mu_v(\mu_M + \gamma + \alpha)}}.$$

A formal proof is deferred to the Appendix. R_{0H} represents the rate at which HIV is transmitted (β_H) times the average time spent in the HIV class ($\frac{1}{\mu_H + \alpha}$). R_{0M} , represents the square root of the transmission rate from human to vector (β_{MV}) times the average time spent in the infectious vector class ($\frac{1}{\mu_v}$) times the transmission rate from vector to human (β_{VM}) times the average time spent in the infectious malaria class ($\frac{1}{\mu_M + \gamma + \alpha}$). There is a square root in this term because malaria is a two step process, meaning for an infected individual to infect another individual a mosquito must transmit the disease.

We then arrive at the following theorem: If $R_0 < 1$, the DFE is locally asymptotically stable. The DFE of the Full Model is unstable if $R_0 > 1$ see Appendix for a proof.

We remind the reader that our goal is to understand the dynamics of HIV and malaria co-infections using the simplest possible model. While R_0 gives us insight, physical intuition, and the numerical solutions indicate there should be a co-infection equilibrium (CE). Unfortunately, our model is too complicated to arrive at an explicit solution for the CE. Previous work [1] and numerical solution (see Figure 4) pose a possible answer: the mosquito population is on a fast time scale relative to the dynamics of the human population. We use this difference in time scale to simplify our model.

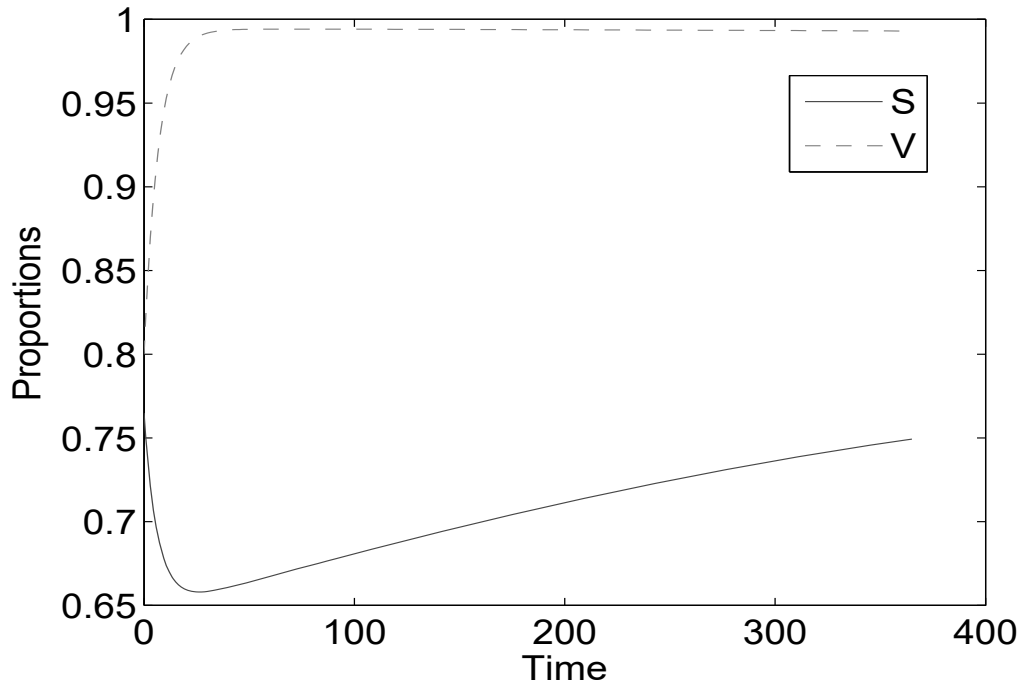


Figure 4: The dynamics of the vectors are on a much faster time scale than the dynamics of the humans.

3 Reduced Model

We reduce our full model to a system of 4 nonlinear equations as follows: First we note that the birth rate going into the vector classes is equal to the mortality rate going out of them, that is the total vector population is constant. Hence, we set $V = N_V - I_V$. Furthermore, we assume that the vector dynamics are fast relative to the humna dynamics, allowing us to make the pseudo steady state approximation. That is we assume that the vector system is at a steady state and substitute for V to get:

$$I_V^* = \frac{\beta_{MV} N_V (I_M + \rho_4 I_{HM})}{\beta_{MV} I_M + \rho_4 \beta_{MV} I_{HM} + \mu_V N}$$

Where I_V^* is the equilibrium value of the I_V class, this is simply a rational function of I_M and I_{HM} . Using the fact that the vector dynamics go a lot faster than human dynamics lead to the following reduced model:

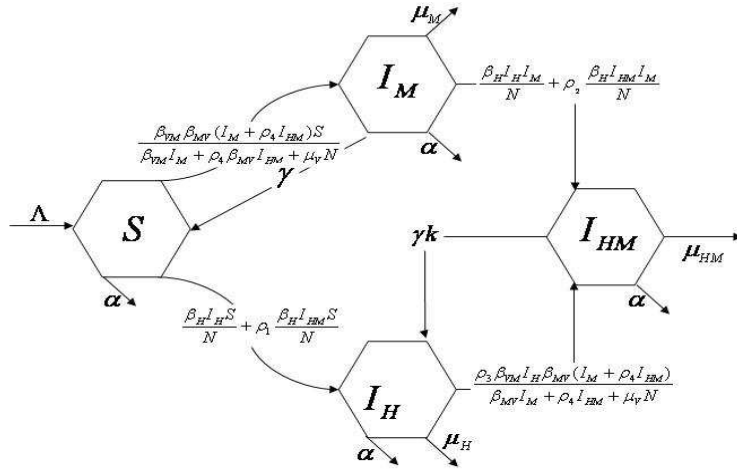


Figure 5: Reduced Model. The vector population is assumed to reach its equilibrium much faster than the human population.

$$\begin{aligned}
\frac{dS(t)}{dt} &= \Lambda - \frac{\beta_{VM}\beta_{MV}(I_M+\rho_4 I_{HM})S}{\beta_{MV}I_M+\rho_4\beta_{MV}I_{HM}+\mu_V N} - \frac{\beta_H I_H S + \rho_2 \beta_H I_{HM} S}{N} + \gamma I_M - \alpha S \\
\frac{dI_M(t)}{dt} &= \frac{\beta_{VM}\beta_{MV}(I_M+\rho_4 I_{HM})S}{\beta_{MV}I_M+\rho_4\beta_{MV}I_{HM}+\mu_V N} - \frac{\beta_H I_H I_M + \rho_1 \beta_H I_{HM} I_M}{N} - \mu_M I_M - \gamma I_M - \alpha I_M \\
\frac{dI_H(t)}{dt} &= \frac{\beta_H I_H S + \rho_2 \beta_H I_{HM} S}{N} - \frac{\rho_3 \beta_{VM} I_H \beta_{MV} (I_M + \rho_4 I_{HM})}{\beta_{MV} I_M + \rho_4 \beta_{MV} I_{HM} + \mu_V N} - \mu_H I_H + k\gamma I_{HM} - \alpha I_H \\
\frac{dI_{HM}(t)}{dt} &= \frac{\beta_H I_H I_M + \rho_1 \beta_H I_{HM} I_M}{N} + \frac{\rho_3 \beta_{VM} I_H \beta_{MV} (I_M + \rho_4 I_{HM})}{\beta_{MV} I_M + \rho_4 \beta_{MV} I_{HM} + \mu_V N} - \mu_{HM} I_{HM} - k\gamma I_{HM} - \alpha I_{HM}
\end{aligned}$$

3.1 Local Stability of the Reduced Model

The disease free equilibrium of the Reduced Model (DFER) can be derived from the DFE and carries the analogous interpretation.

$$DFER = (S^o, I_M^o, I_H^o, I_{HM}^o) = \left(\frac{\Lambda}{\alpha}, 0, 0, 0\right)$$

Similarly the stability analysis and R_0 calculations follow directly from that of the Full Model.

$$R_0 = \max \{R_{0H}, R_{0M}\}$$

$$R_{0H} = \frac{\beta_H}{\mu_H + \alpha}$$

$$R_{0M} = \sqrt{\frac{\beta_{MV}\beta_{VM}}{\mu_v(\mu_M + \gamma + \alpha)}}$$

Where R_{0H} and R_{0M} have the same biological interpretations as before. It was our hope that the reduced model would lend itself to an analytical calculation of the coexistence equilibrium point. However, even with the use of a computer algebra system we were unable to get an analytical form for it. Instead we employ numerical solutions and single disease models to gain insight into our problem of co-infection.

4 Single Disease Vs Co-Infection

To evaluate the effects of co-infection in our model we look at the case of only a single disease for comparison. The HIV only model is a simple SI model obtained by setting the infectious malaria classes (I_M , I_{HM} and I_V) to zero. The dynamics of this model are known, the DFE is stable when $R_{0H} < 1$ and there is a stable HIV only endemic equilibrium when $R_{0H} > 1$ [5]. Figure 6 is the phase portrait of the HIV only model with the parameters from Malawi. Similarly the malaria only model is obtained by setting I_H and I_{HM} to zero. It is a vector-host SI model with essentially the same dynamics as the SI model. Figure 7 shows the phase portrait of the malaria only model with the parameters from Malawi.

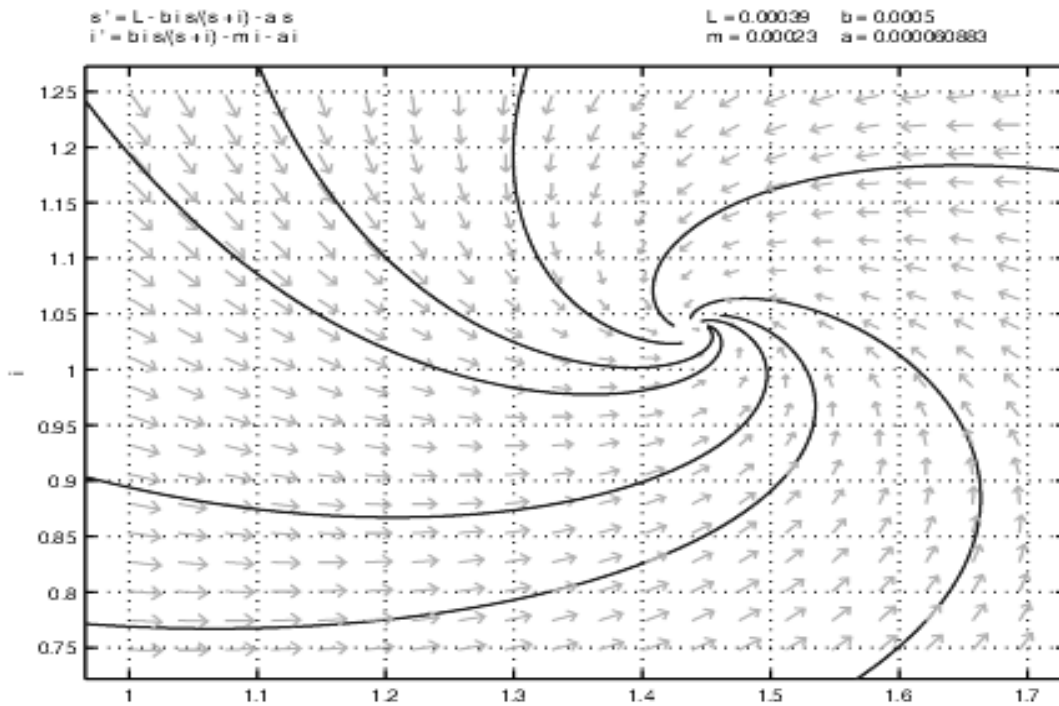


Figure 6: $L = \Lambda$, $m = \mu_H$, $b = \beta_H$, $a = \alpha$

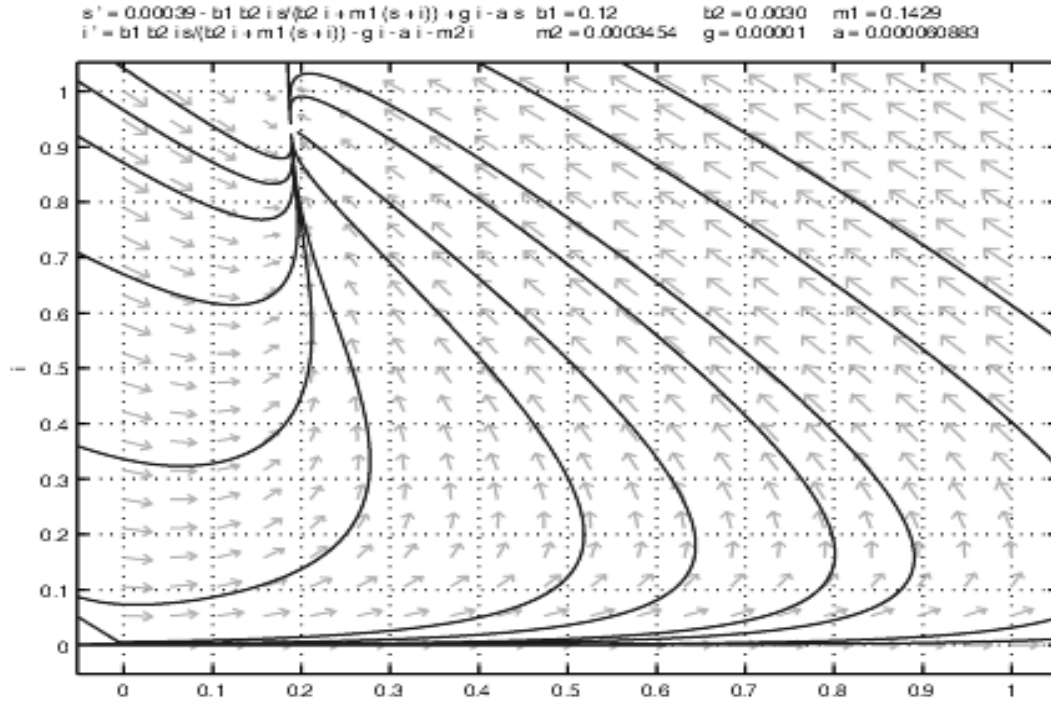


Figure 7: $L = \Lambda = 0.00039$, $m_1 = \mu_V$, $m_2 = \mu_M$, $b_1 = \beta_{VM}$, $b_2 = \beta_{MV}$, $a = \alpha$, $N = S + I_M$

4.1 Comparison with Co-Infection: Mortality

HIVInsite estimates that additional mortality due to co-infection may increase by less than 5 percent to 118 percent. Figure 8 compares the total deaths calculated from that HIV only model, malaria only model, and Full Model. These deaths are calculated with varying ρ where $\rho_i = \rho$ for $i = 1, 2, 3, 4$, we make the assumption that all the (ρ_i) 's are equal for simplicity. Since the HIV and malaria only models do not have any co-infections, they are constant with respect to ρ . With $\rho = 1$ (there is no additional infectivity due to co-infection) the increased deaths due to co-infection was approximately 3 percent and with ρ at approximately thirty, the number of deaths double, agreeing with the HIVInsite estimate.

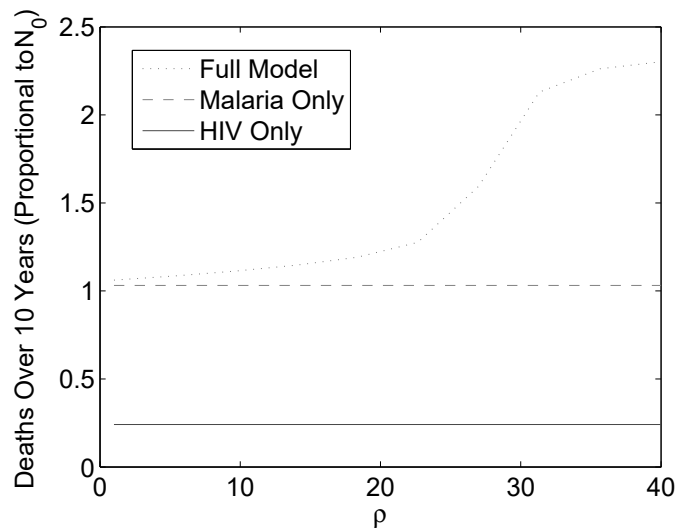


Figure 8: Death Due to Diseases

Since it is not known what the additional infectivity due to co-infection is, we plotted the diseases induced deaths vs ρ in Figure 9. For ρ small there was very little increased mortality, but if ρ was larger than 25 then co-infection deaths dominate total deaths.

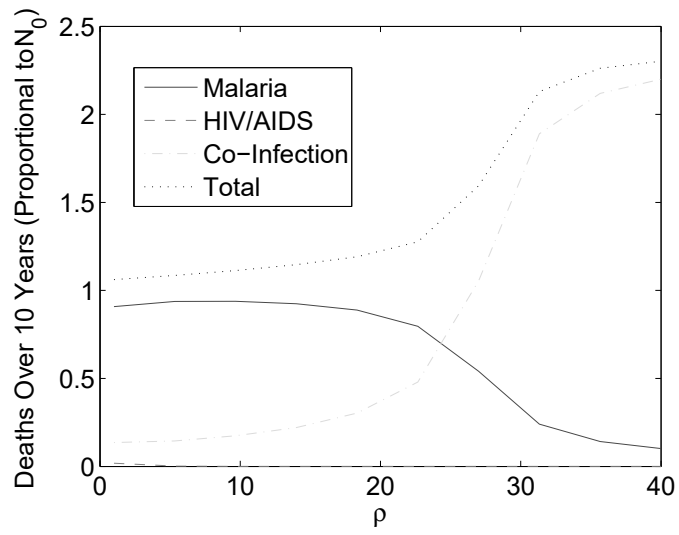


Figure 9: Total deaths are dominated by co-infection deaths when ρ is larger than 25 in the Full Model.

4.2 Sensitivity Analysis

Table 2: Sensitivity Index for HIV and Malaria

R_0	Parameter	$\frac{\partial R_0}{\partial parameter} \frac{parameter}{R_0}$	Values for Malawi	Values for Sub-Saharan Africa
R_{0H}	β_H	1	1	1
R_{0H}	μ_H	$-\frac{\mu_H}{\mu_H + \alpha}$	-0.6969230846	-0.8011759871
R_{0H}	α_1	$-\frac{\alpha}{\mu_H + \alpha}$	-0.3030769154	-0.1988240130
R_{0M}	β_{MV}	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2}$
R_{0M}	β_{VM}	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2}$
R_{0M}	μ_V	$-\frac{1}{2}$	$-\frac{1}{2}$	$-\frac{1}{2}$
R_{0M}	μ_M	$-\frac{1}{2} * \frac{\mu_M}{\mu_M + \gamma + \alpha}$	-0.2631486722	-0.03384629978
R_{0M}	γ	$-\frac{1}{2} * \frac{\gamma}{\mu_M + \gamma + \alpha}$	-0.1904666128	-0.4605605355
R_{0M}	α	$\frac{1}{2} * \frac{\alpha}{\mu_M + \gamma + \alpha}$	-0.04638471514	-0.005593164735

Getting reliable data is a ubiquitous problem in mathematical biology. While we were able to find many of the parameters in Table 1, some parameters were estimated. Thus we would hope our estimate of R_0 is not very sensitive to parameter values. We perform a sensitivity analysis on R_0 with respect to our parameters [3]. The sensitivity index S is defined as:

$$S = \frac{\text{partial}R_0}{\text{partial}P} * \frac{P}{R_0}$$

where P is the parameter of interest.

The sensitivity index is a local estimate of the best way to reduce R_0 . The larger magnitude of the sensitivity index, the more 'sensitive' R_0 is with respect to that parameter. For example if we know R_0 is dominated by HIV infection, then a 10 percent decrease in the transmission rate corresponds, roughly, to a 10 percent decrease in R_0 . However a 10 percent decrease in the death rate corresponds to a 7 percent increase in R_0 for Malawi and an 8 percent increase for Sub-Saharan Africa. Then we are interested in the indices with the largest magnitude, thus if R_0 is dominated by R_{0H} , we want to control β_H . On

the other hand, if R_0 is dominated by R_{0M} , then we want to control β_{VM} , β_{MV} , or μ_V .

5 Conclusion

A model for the co-infection of HIV and malaria was constructed and analyzed. We started with a simple system of six equations which we reduced to four. We observed it was not necessary to explicitly model the vector population to capture the dynamics of co-infection. Although there is an increase in mortality due to co-infection, this increase is not pronounced until the amplification factor is approximately 25. In fact, if we assume there is no additional infectivity due to co-infection, the increased mortality is only 3 percent. However, the mortality nearly doubles when the increased infectivity is 30. The biological integrations between the malaria parasite and HIV are not fully understood, but it is conceivable that the parasite or viral load can increase by an order of magnitude due to co-infection. Future studies should include fitting parameters to data. An investigation of the co-infection at a cellular level would also be interesting. In our framework we did not include treatment for simplicity, but treatment is a major component of any approach to a solution of the HIV and malaria epidemics.

6 Acknowledgments

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A Calculation of R_0

The next generation operator method is a systematic way to calculate R_0 [10]. R_0 is defined as the spectral radius of the next generation matrix. First we separate the classes into two groups, infectious and non-infectious. Vector \mathcal{F} is composed of the new infection terms of the infectious classes.

$$\mathcal{F} = \begin{bmatrix} \frac{\beta_{VM}vI s}{M} \\ \frac{\beta_H i_H s + \rho_2 \beta_H i_{HM} s}{N} \\ 0 \\ \frac{\beta_{MV}i_M v + \rho_4 \beta_{MV}i_{HM} v}{N} \end{bmatrix}$$

The vector \mathcal{V} is composed of the remaining terms of the infectious classes.

$$\mathcal{V} = \begin{bmatrix} \frac{\beta_H i_H i_M + \rho_1 \beta_H i_{HM} i_M}{N} + \mu_M i_M + \gamma i_M + \alpha i_M \\ \frac{\rho_3 \beta_{VM} i_H v I}{M} + \mu_H i_H - k\gamma i_{HM} + \alpha i_H \\ -\frac{\beta_H i_H i_M + \rho_1 \beta_H i_{HM} i_M}{N} - \frac{\rho_3 \beta_{VM} i_H v I}{M} + \mu_{HM} i_{HM} + k\gamma i_{HM} + \alpha i_{HM} \\ \mu_V v I \end{bmatrix}$$

\mathbf{F} and \mathbf{V} are the Jacobians of \mathcal{F} and \mathcal{V} with respect to the infectious classes, respectively. Then the next generation matrix is defined as $\mathbf{V}^{-1}\mathbf{F}$ evaluated at the DFE, and R_0 is the dominant eigenvalue of this matrix.

$$\mathbf{V}^{-1}\mathbf{F} = \begin{bmatrix} 0 & 0 & 0 & \frac{\beta_{VM}\Lambda}{\alpha M\mu_V} \\ 0 & \frac{\beta_H}{\mu_H + \alpha} & \frac{\beta_H k\gamma}{(\mu_H + \alpha)(\mu_{HM} + k\gamma + \alpha)} + \frac{\rho_2 \beta_H}{\mu_{HM} + k\gamma + \alpha} & 0 \\ 0 & 0 & 0 & 0 \\ \frac{\beta_{MV} M \alpha}{\Lambda (\mu_M + \gamma + \alpha)} & 0 & \frac{\rho_4 \beta_{MV} M \alpha}{\Lambda (\mu_{HM} + k\gamma + \alpha)} & 0 \end{bmatrix}$$

For the Reduced Model we have

$$\mathcal{F} = \begin{bmatrix} \frac{\beta_{VM}\beta_{MV}(i_M + \rho_4 i_{HM})s}{\beta_{MV}i_M + \rho_4\beta_{MV}i_{HM} + \mu_V N} \\ \frac{\beta_H i_H s + \rho_2 \beta_H i_{HM} s}{N} \\ 0 \end{bmatrix}$$

$$\mathcal{V} = \begin{bmatrix} \frac{\beta_H i_H i_M + \rho_1 \beta_H i_{HM} i_M}{N} + \mu_M i_M + \gamma i_M + \alpha i_M \\ \frac{\rho_3 \beta_{VM} i_H \beta_{MV} (i_M + \rho_4 i_{HM})}{\beta_{MV} i_M + \rho_4 \beta_{MV} i_{HM} + \mu_V N} + \mu_H i_H - k\gamma i_{HM} + \alpha i_H \\ -\frac{\beta_H i_H i_M + \rho_1 \beta_H i_{HM} i_M}{N} - \frac{\rho_3 \beta_{VM} i_H \beta_{MV} (i_M + \rho_4 i_{HM})}{\beta_{MV} i_M + \rho_4 \beta_{MV} i_{HM} + \mu_V N} + \mu_{HM} i_{HM} + k\gamma i_{HM} + \alpha i_{HM} \end{bmatrix}$$

Then the next generation matrix is

$$\mathbf{V}^{-1}\mathbf{F} = \begin{bmatrix} \frac{\beta_{VM}\beta_{MV}}{\mu_V(\mu_M + \gamma + \alpha)} & 0 & \frac{\beta_{VM}\beta_{MV}\rho_4}{\mu_V(\mu_{HM} + k\gamma + \alpha)} \\ 0 & \frac{\beta_H}{\mu_H + \alpha} & \frac{\beta_H k\gamma}{(\mu_H + \alpha)(\mu_{HM} + k\gamma + \alpha)} + \frac{\rho_2 \beta_H}{\mu_{HM} + k\gamma + \alpha} \\ 0 & 0 & 0 \end{bmatrix}$$

Note R_{0M} is now

References

- [1] Abdu-Raddad L. J., Patnaik P., and Kublin J.G., Dual infection with HIV and Malaria fuels the spread of both diseases in Sub-Saharan Africa, *Science*, 314, 1603, (2006), DOI: 10.1126/science.1132338.
- [2] Anderson R.M., *The Population Dynamics of Infectious Diseases: Theory and Applications*, (1982), pp. 139-178.
- [3] Arriola L.M., and Hyman J.M., Being Sensitive to Uncertainty, *Science and Engineering*, vol. 9(2), (2007)
- [4] Bowman C., Gumel A.B., van den Driessche P., Wu J., and Zhu H., A Mathematical Model for Assessing control Strategies Against West Nile virus, *Bull. Math. Biol.*, 67, 1107-1133, (2005).
- [5] Brauer F., Castillo-Chávez C., *Mathematical Models in Population Biology and Epidemiology*, Springer, New York, (2000).
- [6] Castillo-Chávez C., Feng Z., Huang W., On the Computation of R_0 and its Role on Global Stability in Mathematical Approaches for emerging and re-emerging infectious diseases, Part I, *IMA*, 125, Springer-Verlag, New York, pp. 224-250.
- [7] Castillo-Chávez C., Levin S.A., Shoemaker C.A., *Mathematical Approaches to Problems in Resource Management and Epidemiology*, New York, (1987), pp. 220-248.
- [8] Center for Disease Control (CDC). July 1, 2007. World Wide Web.
<http://www.cdc.gov/malaria/facts.htm>
<http://www.cdc.gov/hiv/facts.htm>
- [9] Chitnis N., Cushing J.M., and Hyman J.M., Bifurcation Analysis of a Mathematical Model for Malaria Transmission, *SIAM J. Appl. Math.*, 67(1), 24-45, (2006).

- [10] Corbett EL et al, AIDS In Africa III: HIV-1/AIDS and the Control of other Infectious Diseases in Africa. Lancet 2002; 359: 2177-87.
- [11] Driessche P., Watmough J., Reproduction Numbers and Sub-Threshold Endemic Equilibria for Compartmental Models of Disease Transmission, *Mathematical Biosciences* 180, 29-48, (2002).
- [12] HIV Insite, World Wide Web.
<http://www.hivinsite.com>
- [13] Holmberg S, McNabb S, Aral S. HIV, Sexually Transmitted Diseases, Tuberculosis, and Malaria: Resurgence and Response. *Emerg Infect Dis.* (2004).
- [14] Ross R., *The Prevention of Malaria*, London, (1911).
- [15] Ross R., *Studies on Malaria*, London, (1928).
- [16] Saul, A., Zooprophylaxis or zoopotential: The outcome of Introducing Animals on Vector Transmission is highly Dependent on the Mosquito Mortality while searching. *Malar. J.*,2, 32-50, (2003).
- [17] The World Health Organization(WHO), *Malaria and HIV Interaction and their Implications for Public Health Policy*, (2004).