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**COLLEGE OF BIOLOGICAL AND PHYSICAL
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SCHOOL OF MATHEMATICS

**MATHEMATICAL MODELLING OF HIV AND
MALARIA CO-INFECTION DYNAMICS**

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**A project submitted to the school of mathematics in partial
fulfillment for a degree of Master of Science in Applied
Mathematics**

Declaration

I the undersigned declare that this project report is my original work and to the best of my knowledge has not been presented for the award of a degree in any other University.

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This project report has been submitted for examination with my approval as the supervisor.

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Statement

This dissertation has been submitted in partial fulfillment of requirement for a master of science degree at the University of Nairobi and is deposited in the University Library to be made available to the borrowers under the rules of the Library.

Dedication

I dedicate this work to my parents, Mr and Mrs Oketch for the care and support they gave and still give me.

Acknowledgment

I wish to convey my sincere appreciation to the following people, whose assistance and guidance led to the completion of this project:

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Abstract

We formulate a mathematical model using system of differential equations to understand the co-dynamics of two diseases HIV and Malaria. The entire human population is divided into four compartments and mosquito population into two. The model is analysed and steady state conditions are derived. It is shown that the disease free equilibrium is locally stable and globally unstable if the basic reproduction number R_0 is less than unity. Numerical sensitivity analysis show that R_0 is most sensitive to β_1 and Λ_h , the contact rate of of susceptible humans with HIV infected individuals and recruitment rate into susceptible population.

Chapter 1

INTRODUCTION

1.1 GENERAL INTRODUCTION

In Sub-Saharan region of Africa there are many endemic diseases such as Human Immunodeficiency Virus (HIV) and malaria which are the two most deadly diseases of our time. 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 pressing problem despite the development of antibiotics and vaccines.

According to global report at Geneva(2004),40 Million people worldwide are infected with HIV and due to this disease about 20 Million people have died in the last two decades. The disease HIV is untreatable and only with the help of the Antiretroviral therapy(ART),life span of an infected person can be increased and can remain healthy before acquiring full blown AIDS [6].

Malaria is an old disease that has been well studied since the late 1800s by Ross[5].HIV by contrast is a relatively new disease that has only been studied since 1980s.HIV like Malaria has received considerable attention from the scientific community and continue to kill millions while we search for cure.While HIV is characterized by the process of opportunistic infections, malaria is not typical in this regard. Although the co-infection between HIV and malaria is not well understood, available evidence show that about one quarter to one third of malaria patients are infected because of a weakened immune system caused by HIV infection. On the other hand ,malaria increases the viral load in HIV patients but this effect may be reversed with malaria treatment. According to the Centre for Disease Control and preven-

tion (CDC) there is an estimated 5% increase in malaria deaths due to HIV infection in Sub-Saharan Africa [7]. Malaria and HIV are common among poorest populations, pregnant women, and children under the age of 5 years.

1.1.1 HIV

Human Immunodeficiency Virus was discovered in 1981 and it has become one of the leading causes of death globally affecting mostly impoverished people already suffering from poor nutrition and health. HIV is a sub microscopic virus parasite that survive and reproduces inside the cells of host organism. While HIV does not kill, it attacks the immune system causing it to become defenseless against other opportunistic diseases it could normally fight off. Its effect is most devastating in Sub-Saharan Africa, where HIV prevalence ranges between 12% to 42% [10].

HIV infects and destroys CD4+T cells which are responsible for some specific immune responses. And with time as the infection progresses it goes on damaging human immune system and makes infected human more vulnerable for catching other infections. Malaria and TB are two most opportunistic diseases affecting an HIV patient. A person infected with HIV develops symptomatic malaria more easily because of low CD4+T cells count [38]. As per WHO report, by the end of 2011 there were 34.2 million people living with HIV infection and in the same year 1.7 million people died of AIDS. HIV is found in the blood, sexual and body fluids of an infected person. The transmission of HIV occurs when a sufficient quantity of contaminated body fluid such as blood, semen and vaginal secretions pass from a carrier (infected) of the virus to another person (susceptible) [27], [26]. It has many methods of transmission; the principles being: heterosexual and homosexual contacts, intravenous needle sharing and mother to child transmission.

HIV has shown a high degree of prevalence in populations all over the world. It is common in individuals aged 15 years and above. This is because they are more sexually active. HIV has a long latency period that is, it takes considerable time before the body's immune system can no longer generate the immune response required to suppress HIV leading to an intensified replication of the virus. The symptoms of HIV vary depending on the phase of the infection. HIV infection can be classified into the following stages [32]:

1.1.2 Primary infection(Early HIV symptoms)

This stage lasts for two weeks. Infected individuals may have no visible symptoms at all, although it is common to develop a brief flue like illness. The symptoms may include headache, fever, loss of appetite, sweating, swell of lymph nodes, sore throat and skin rashes on chest or abdomen.

1.1.3 Latency stage(The asymptomatic stage)

This stage can last for an average of 3 years and the infected person do not show any signs or symptoms of the disease.

1.1.4 The symptomatic HIV infection

This is the stage where a lot of symptoms such as diarrhoea, heavy weight loss, fever, cough, fatigue, pneumococcal pneumonia, shortness of breath, herpes simplex and herpes zoster begin to manifest because the immune system is severely damaged by the virus.

1.1.5 Progression from HIV to AIDS

This is the final stage when the immune system is extremely weakened. As a result side infections take the opportunity to infect AIDS patient. This is when the patient develops full blown AIDS and might eventually die.

1.1.6 MALARIA

Malaria was first discovered centuries ago by the Chinese in 2700BC, according to CDC. However it was until the late 1800s when Ross made his ground breaking discoveries that led to our understanding of the mechanisms behind malaria infection and transmission. Malaria remains one of the most prevalent and lethal human infection worldwide.

It is caused by the *protozoa plasmodium* transmitted to vertebrates by female genus Anopheles mosquitoes when they feed on human blood. There are four species of the parasite namely ;*plasmodium falciparum*, *plasmodium vivax* ,*plasmodium ovale* and *plasmodium malariae* which infect humans ,of the four species,*plasmodium falciparum* is the most virulent and potentially

lethal to humans[36].It is responsible for the greatest number of deaths and clinical cases and is the most wide spread in the tropics.Its infection can lead to serious complications affecting the brain ,lungs, kidney and other organs.The malaria parasites are transmitted to the human host through a bite by an infected female anopheles mosquito.Clinical symptoms such as fever, pains, chills,severe headache, diarrhoea, loss of appetite, nausea, vomiting, back pain and increased sweating may develop a few days after an infected mosquito bite [34].

According to KEMRI 2015,Malaria is the leading cause of morbidity and mortality in Kenya.25 million out of 34 million Kenyans are at risk of malaria.It accounts for 30-50% of all outpatient attendance and 20% of all admissions to health facilities.Malaria is also estimated to cause 20% of deaths in children under the age of five [12].The most vulnerable group to malaria infections are pregnant women and children under five years of age.This is because pregnancy lowers the mothers immunity to malaria making them more susceptible to infection.Like HIV it is a contributor to the impoverishment of many countries in Africa.Although malaria is treatable, the drugs can be too expensive or too difficult to distribute to the general public in countries where it is endemic.The incidence of malaria has been on the rise in the recent past due to increasing parasite drug-resistance and mosquito insecticide-resistance.This has also been associated with climate change [11].

The Plasmodium Life Cycle and Vector Feeding Cycle

The RossMacdonald model is a basic quantitative description of the Plasmodium life cycle and the vector feeding cycle.The parasite enters the mosquito during a blood meal and the mosquito becomes infectious 10 to 16 days later,after the parasite develops into sporozoites.In the meantime, the mosquito will have fed several times and most infected mosquitoes will die before they become infectious.Mosquitoes that survive to become infectious can then give several infectious bites before they die [30].

Human infections begin during the mosquito blood meal when sporozoites enter the skin.Parasites are not obvious in the blood until about 11 days later.A human with a *P. falciparum* infection is not infectious until a fraction of the blood-stage parasites become gametocytes and then mature, 8 to 10 days later.Untreated or improperly treated infections last about 200 days on average, though some infections can last more than a year. As long as

the blood-stage parasites persist, some gametocytes will be produced. The number of mosquitoes that will become infectious depends, in part, on the number of mosquitoes that bite humans, the rate at which parasites develop, and the longevity of the mosquitoes [8].

1.1.7 HIV-MALARIA CO-INFECTION

In sub-Saharan Africa, infection with HIV and malaria are among the greatest health problems. An estimated 25.3 million persons are currently infected with HIV, and more than 70% of the population lives in areas of intense malaria transmission, where almost 300 million episodes of clinical malaria are reported each year. Although co-infection with HIV and malaria is probably very common, and understanding if and how the two infections interact could be important for the control of both diseases, few studies have been conducted on this potential association.

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). Since viral load is correlated with infectiousness such a process (co-infection with malaria) leads to an increase in the number of new HIV cases in the population [20].

HIV infection appears to increase both the susceptibility to and the severity of malaria infection. Most of our understanding of the interaction between malaria and HIV comes from studies performed in Africa, primarily involving infection with *P. falciparum*. International literature suggests that HIV-infected patients appear to be more susceptible to acquiring malaria infection particularly if they are pregnant [31]. In regions with unstable malaria transmission, HIV infection is a risk factor for severe malaria in both young children and adults [18]. HIV infection is presumably also a risk factor for severe malaria in young children in regions of heavy transmission, but firm data are lacking. In contrast, HIV infection appears to only modestly increase the risk of parasitemia and clinical malaria in semi-immune adults in regions of holoendemicity. Although the risk increases with decreasing CD4+ T cell counts, malaria is less strongly associated with HIV-related immunosuppression than are other opportunistic infections. Acquired immunity plays an important role in the clearance of drug-resistant parasites. HIV infection

has also been associated with an increased risk of re-infection with malaria after successful treatment. This may be a result of HIV-mediated weakening of immune responses to liver stage parasites. The additional possibility that Anopheles mosquitoes are more likely to bite those HIV related febrile illnesses should not be discounted. HIV infection alters the predictive value of fever in the empirical diagnosis of malaria; the common practice of empirically treating febrile adults for malaria likely leads to overestimation and overtreatment of malaria [25].

In regions of high malarial endemicity, the specific immunity that women of childbearing age have developed is compromised by pregnancy. HIV infection is associated with increased incidence of peripheral and placental parasitemia, clinical malaria, and maternal anemia during pregnancy. Similarly, co-infection is associated with an increased risk of low birth weight, preterm birth, intrauterine growth retardation and postnatal infant mortality. It remains unclear whether malaria infection increases the risk of mother-to-child transmission of HIV infection [29]. With regard to the effects of malaria on HIV infection, *P. falciparum* infection is associated with an increased viral burden in peripheral and placental blood. Malaria-driven increases in HIV replication may well accelerate the course of HIV disease which in turn could facilitate the sexual transmission of HIV infection. In addition treatment of severe anemia due to malaria is a common indication for blood transfusion. As a result, malaria is an important risk factor for the acquisition of HIV infection by children in regions where the blood supply is not well screened .

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 [21]. In another 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 [22] . Furthermore, morbidity is higher in HIV-infected individuals. Recent studies of dual HIV-malaria infection confirm and extend earlier findings 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 [3][23]. This symbiotic relationship between HIV and malaria is a double blow to sub-Saharan Africa region because of the high prevalence of HIV and incidence of malaria. This highlights the need for a robust qualitative assessment of the population-level implications of the immune-mediated interaction of the two diseases [3] [24]. Understanding of

the human immune response to malaria and HIV leads us to expect that either infection might influence the clinical course of the other. Many other types of infections are associated with at least a transient increase in HIV viral load. Hence it is logical to expect malaria to do the same and potentially to accelerate HIV disease progression. On the other hand, the control of malaria parasitaemia is immune mediated, and this prevents most malarial infections from becoming clinically apparent in semi-immune adults in endemic areas [10]. The immune deficiency caused by HIV infection should, in theory, reduce the immune response to malaria parasitaemia and therefore increase the frequency of clinical attacks of malaria. So HIV infection affects the clinical presentation, severity and response to treatment of malaria cases. The clinical impact of these interactions varies depending on the intensity of malaria transmission in the area (and consequent level of host immunity) and the individual affected (e.g. adult, child or pregnant woman) [11]. However, in different malaria HIV co-endemic countries there has been little or no research conducted regarding this topic. The aim of this article is, therefore, to review existing information about HIV malaria interactions, the effect of malaria on HIV transmission and progression and the implications related to prevention and treatment of co-infection.

1.2 Problem Statement

HIV and malaria continue to pose a great threat in the Sub-Saharan Africa, with their death rate and prevalence on the rise, together they accounted for 3 million deaths worldwide in 2007. Such alarming statistics may retard the milestones so far achieved in meeting the Millennium Development Goals 4 and 6 whose targets are to improve child survival and reversing the high prevalence of diseases such as HIV/AIDS and malaria (MDGs, 2011) respectively. Therefore this study aims at formulating and analysing a mathematical model that explains HIV-Malaria co-infection dynamics.

1.3 Objective of the study

The general objective of this study is to develop and analyze a mathematical model for the transmission of HIV-malaria co-infection. The specific objectives are;

- i) To establish a mathematical model for HIV-malaria showing the co-infection.
- ii) To determine the stability of the disease free equilibrium point.
- iii) To determine the most sensitive parameters to R_0 .

1.4 Significance of the study

The outcomes of this study will help the government and NGO's to establish policies, programmes and optimal plan to for control of the diseases by taking into account the aspect of treatment for HIV-malaria co-infection. It will help the society in general to have an understanding of how co-infection of HIV-malaria can be controlled through treatment of infectives with ARV and antimalarial drugs thus reducing the disease burden. It will also add more knowledge to the existing literature on HIV and malaria co-infection and help researches to do more research on this diseases. This study will also add to existing body of knowledge on mathematical application in the field of epidemiology.

Chapter 2

LITERATURE REVIEW

Abu-Raddad et al.(2006) [3],proposed the first compartmental model for the co-infection of HIV and malaria.Their study was an extended version of Anderson which consisted of twenty non-linear ordinary differential equations,eighteen of which described the host population(Human)and two represented the vector population.They modelled the sexually active population and calculated the size of the epidemiological synergy between HIV and malaria.They divided the total population into sexual risk populations,the general population(low risk)and the core population(high risk).They modeled the mosquito population through an SI model with a delay presenting the incubation period in the mosquito and also they account for the seasonal variations in the mosquito population.Their study quantifies the epidemic synergy between HIV-1 and malaria.The synergy in this case is the net effect of the presence of heightened viral load,enhanced susceptibility to malaria mortality in advanced HIV patients.In another study they estimated that the interaction of malaria and HIV in one Kenyan district alone had caused 980,000 excess malaria episodes and 8,500 excess HIV infection since the emergence of HIV in 1980's.In areas endemic for malaria,it is estimated that at least 25% of pregnant women are infected and morbidity is found among the adolescents and those co-infected with HIV.

Barley et al.(2007) [7],constructed and analyzed a model for the co-infection of HIV and malaria.They started with a simple system of six equations which they reduced to four.They observed that it was not necessary to explicitly model the vector population to capture the dynamics of co-infection.They observed that there is an increase in mortality due to co-

infection. Even though the biological interactions between the malaria parasite and HIV are not fully understood, it is conceivable that the parasite or viral load can increase by an order of magnitude due to co-infection. They further suggested that in future work, treatment should be included in the model.

Shah et al. (2014) [2], Formulated a model for HIV-malaria co-infection. They divided the entire human population into six compartments with an objective to compare the trends between HIV only class and HIV with malaria class and also between AIDS class and AIDS with malaria class. Their results showed that the most sensitive parameter to the co-infection is mosquito death rate. This means that mosquito population has to be kept as minimum as possible. They also observed that after catching HIV infection, population does not stay there in that compartment for long, it catches other infection (malaria in this case) and move to the co-infected class. Their results showed that the life span of a patient co-infected with HIV and malaria is shorter, and that co-infected people may drive malaria from smaller scale to larger one as they develop clinical malaria faster giving more mosquitoes a chance get infected. They suggested that for a healthier future we need to control mosquito population as well as HIV infected population.

Mukandavire et al. (2009) [1], Formulated and analyzed a realistic mathematical model for HIV-malaria co-infection. They carried out a detailed qualitative analysis of the resulting model an activity that was not done in the model by [3]. This provides the first modeling work that provides an in-depth analysis of the qualitative dynamics of HIV-malaria co-infection. In addition to that there are some important differences between their model and the model done by [3]. For instance, [1] used an exponential distribution waiting time to model the exposed class while [3] used a discrete time delay for the same purpose. Further, seasonality variations were used in [3] to model mosquitoes birth rate whilst a constant birth rate was used in [1]. Their main theoretical results were as follows:

- i) The HIV-only model has a globally asymptotically stable disease free equilibrium whenever a certain epidemiological threshold (R_H) is less than unity and is unstable if this threshold exceeds unity.
- ii) The HIV only model has a unique endemic equilibrium whenever the aforementioned threshold exceeds unity.

- iii) The malaria model undergoes backward bifurcation, where the associated stable disease free equilibrium co-exists with stable endemic equilibrium when the corresponding reproduction number R_h is less than unity.
- iv) The full HIV-malaria model has a locally asymptotically stable disease free equilibrium when its reproductive threshold is less than unity and unstable if the threshold exceeds unity.

Singh et al.(2013) [6],Formulated a mathematical model to analyze the stability of Malaria-mTB-HIV/AIDS co-infection.Their study was an extended version of [16](co-infection of mTB and HIV/AIDS).They added one compartment of malaria in the form of co-infection of malaria-mTB-HIV/AIDS.Their study revealed the following:

- i) The co-infection equilibrium points (malaria-HIV),(mTB-HIV) and (malaria-mTB-HIV) are always locally stable.
- ii) Susceptible population enhances the infection rate. The disease becomes endemic due to immigration because immigrating population is susceptible population.
- iii) It is also found that higher temporary recovery rates increase the population of susceptible individuals. The infection may be controlled by reducing the susceptible population. Thus to reduce susceptible population, the permanent recovery is essential.
- iv) The number of HIV infected cases increases due to the presence of other diseases, particularly malaria and mTB, separately and altogether. It is noticed that the HIV infection can be slowed down by treating malaria and mTB, effectively.

Hochman et al.[37](2009)established that HIV and malaria have similar global distributions. Annually, 500 million people are infected and 1 million die because of malaria, 33 Million have HIV and 2 million die from it every year. This motivated them to study the impact of HIV and malaria co-infection. They found that minor effects of one infection on the other disease would significantly have an impact on public health for people at risk of co-infection. They mentioned that recent work suggests that those with HIV have more frequent episodes of symptomatic malaria. Malaria increases

HIV plasma viral load and decrease CD+4T cells. Additionally HIV infected people have an increase in viremia during episodes of parasitemia, leading to potential increase in risk of HIV transmission.

In a study carried out by AIDS 2001, Vol 15 on HIV, malaria parasite and acute febrile malaria episodes [31]. They found out that co-infection with HIV and malaria parasites was associated with occurrence of acute febrile episodes, and that single infection with either HIV or malaria was not, suggesting that there is an important interaction between these two infections in Ugandan adults. Specifically the anti-toxic immunity to malaria which protects persons with parasitemia from clinical manifestation of the disease, is suppressed by HIV resulting in clinical manifestation. In a cohort study of HIV infected individuals, the incidences of clinical malaria was found to have increased with decreasing CD4 cell counts and in a population based cohort, HIV infected individuals had a significantly higher risk of having parasitemia and developing clinical malaria than HIV negative individuals.

Chapter 3

MODEL DESCRIPTION AND ANALYSIS.

3.1 Historical background

Epidemiology is the study of the distribution and determinants of diseases both infectious and non infectious. Originally the term was used to refer only to the study of epidemic infectious diseases but it is now applied more broadly to other diseases as well [25]. Mathematical models have been used extensively in research into the epidemiology of HIV-malaria co-infection, to help improve our understanding of major contributing factors in a given epidemic [28]. The goal of any modelling exercise is to extract as much information as possible from available data and provide an accurate representation of both the knowledge and uncertainty about the epidemic.

3.2 Model formulation

In this section we formulate the model with the objective to see the transmission dynamics of HIV-malaria co-infection. For simplicity in formulating our model the following assumptions are taken into account.

- i) Our susceptible human population is general population that is at risk of getting an HIV infection at a rate proportional to the density of HIV infected people and our susceptible vector population is at risk of getting malaria at a rate proportional to density of infected mosquitoes.

- ii) There is no vertical transmission, all recruitments are birth without disease and no infective immigrant, and all parameters are positive.
- iii) Susceptible people cannot simultaneously get infected with malaria and HIV since the transmission dynamics are different.
- iv) A person in the I_{HM} class can transmit both diseases. Further since a persons immune system is compromised, that person has a higher probability of transmission given a contact has occurred. A contact here refers to any process that can transmit a disease.

The model sub-divides the total human population at time t , denoted by $N_h(t)$, into the following sub-populations of Susceptible $S(t)$ who are not yet infected with HIV or malaria, infectious malaria class $I_M(t)$, infectious HIV class $I_H(t)$ and HIV-Malaria infectious class (infected with both HIV and malaria) $I_{HM}(t)$.

Thus we have

$$N_h(t) = S(t) + I_M(t) + I_H(t) + I_{HM}(t) \quad (3.1)$$

The other important population is the total mosquito population at time t , denoted by N_v which is sub-divided into sub-populations of susceptible vector class S_V , and infectious vector class I_V .

Thus we have

$$N_v(t) = S_V(t) + I_V(t) \quad (3.2)$$

Description of the Model

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 and HIV-Malaria co-infected individuals (at a rate β_1), and acquire malaria infection following effective contact with infected mosquitoes (at a rate β_2). It is assumed that individuals with malaria infection only may recover and return to the susceptible class (at a rate γ_1). Further, natural death occurs in all human sub-populations (at a rate μ_h).

HIV infected individuals acquire malaria infection following effective contact with infected mosquitoes (at a rate β_3) and malaria infected individuals acquire HIV infection following effective contact with HIV infected and HIV-malaria co-infected individuals (at a rate β_4). The modification parameter ρI_{HM} accounts for the relative infectiousness of individuals dually infected

with HIV-Malaria. Individuals in the I_{HM} class die due to the diseases (at a rate δ), this is because there is an increase in mortality due to co-infection in comparison to individuals infected with malaria only or HIV only.

Susceptible mosquitoes are generated at a constant rate Λ_V and acquire malaria infection following effective contact with humans infected with malaria and HIV-malaria co-infected individuals (at a rate β_5). Mosquitoes are assumed to suffer natural death at a rate μ_V , regardless of their infection status.

Human and Vector population Model

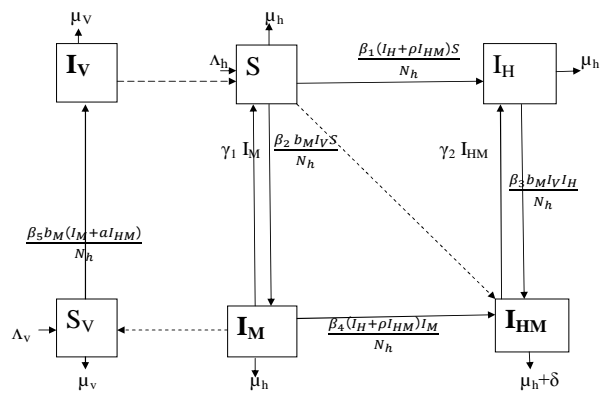


Figure 3.1: Compartment

The model equations are as follows,

$$\left\{ \begin{array}{l}
 \frac{dS(t)}{dt} = \Lambda_h - \frac{\beta_1(I_H + \rho I_{HM})S}{N_h} - \frac{\beta_2 b_M I_V}{N_h} + \gamma_1 I_M - \mu_h S \\
 \frac{dI_H(t)}{dt} = \frac{\beta_1(I_H + \rho I_{HM})S}{N_h} - \frac{\beta_3 b_M I_V I_H}{N_h} + \gamma_2 I_{HM} - \mu_h I_H \\
 \frac{dI_M(t)}{dt} = \frac{\beta_2 b_M I_V}{N_h} - \frac{\beta_4(I_H + \rho I_{HM})I_M}{N_h} - (\gamma_1 + \mu_h)I_M \\
 \frac{dI_{HM}(t)}{dt} = \frac{\beta_3 b_M I_V I_H}{N_h} + \frac{\beta_4(I_H + \rho I_{HM})I_M}{N_h} - (\gamma_2 + \delta + \mu_h)I_{HM} \\
 \frac{dS_V(t)}{dt} = \Lambda_V - \frac{\beta_5 b_M (I_M + \rho I_{HM})S_V}{N_h} - \mu_v S_V \\
 \frac{dI_V(t)}{dt} = \frac{\beta_5 b_M (I_M + \rho I_{HM})S_V}{N_h} - \mu_v I_V
 \end{array} \right. \quad (3.3)$$

Table 3.1: **Definition of variables and Parameters**

	Description.
S	Number of susceptible human population at time t .
I_H	Number of HIV infected humans at time t .
I_M	Number of malaria infected humans at time t .
I_{HM}	Number of HIV-malaria co-infected humans at time t .
S_V	Number of susceptible vectors(mosquitoes) at time t .
I_V	Number of infectious vectors(mosquitoes) at time t .
N_h	Total human population at time t .
N_v	Total vector population at time t .
β_1	Per capita contact rate of susceptible humans with HIV infected and HIV-Malaria infected individuals.
β_2	Per capita contact rate of susceptible humans with infected mosquitoes.
β_3	Per capita contact rate of HIV infected individuals with infected mosquitoes.
β_4	Per capita contact rate of malaria infected individuals with HIV infected and HIV-Malaria infected individuals
β_5	Per capita contact rate of Susceptible mosquitoes with malaria infected and HIV-Malaria co-infected individuals.
Λ_h	Human recruitment rate.
Λ_v	Mosquito recruitment rate.
γ_1	Per capita recovery rate of humans from malaria.
γ_2	The recovery rate of malaria infection by those dually-infected with HIV and malaria.
ρ	Average effective contact rate between humans and HIV-malaria co-infected individuals.
b_M	Mosquito biting rate.
δ	HIV-malaria induced death
μ_h	Natural mortality rate for human.
μ_v	Natural mortality rate for the vector.

3.3 Positivity and boundedness of solution

The system above (3.3) describes the human and mosquito populations and therefore it can be shown that the associated state variables are non-negative

for all $t > 0$ and that the solutions of the model(3.3) with positive initial data remains positive for all time $t > 0$. We show that all feasible solutions are uniformly bounded in a proper subset $\Omega = \Omega_h + \Omega_v$.

Proof

To show that all feasible solutions are uniformly bounded in a proper subset Ω , we split the model (3.3) into the human component N_h , and the mosquito component N_v .

Let $\Omega_h = \{(S, I_H, I_M, I_{HM}) \in \mathbb{R}_+^4\}$ be any solution of the system with non-negative initial conditions.

Taking the time derivative of N_h along a solution path of the model (3.3) gives

$$\frac{dN_h}{dt} \leq \Lambda_h - \mu_h N_h - \delta I_{HM}$$

Then

$$\frac{dN_h}{dt} + \mu_h N_h \leq \Lambda_h \tag{3.4}$$

The integrating factor for equation(3.4) is $(IF) = \exp^{\int \mu_h dt}$

Multiply both sides of (3.4) by $\exp^{\mu_h t}$ gives

$$\begin{aligned} \exp^{\mu_h t} \frac{dN_h}{dt} + \mu_h N_h \exp^{\mu_h t} &\leq \Lambda_h \exp^{\mu_h t} \\ \frac{d}{dt}(N_h \exp^{\mu_h t}) &\leq \Lambda_h \exp^{\mu_h t} \end{aligned} \tag{3.5}$$

Integrating both sides of equation(3.5) we have

$$N_h \exp^{\mu_h t} \leq \frac{\Lambda_h}{\mu_h} \exp^{\mu_h t} + C \tag{3.6}$$

where C is the constant for integration. Dividing equation (3.12) by $\exp^{\mu_h t}$ gives

$$N_h \leq \frac{\Lambda_h}{\mu_h} + C \exp^{-\mu_h t}$$

Using the initial conditions $t = 0, N_h(0) = N_{ho}$ we get

$$N_{ho} - \frac{\Lambda_h}{\mu_h} \leq C,$$

$$N_h \leq \frac{\Lambda_h}{\mu_h} + \left(N_{ho} - \frac{\Lambda_h}{\mu_h} \right) \exp^{-\mu_h t}$$

Applying the theorem of differential inequality [35] we get

$$0 \leq N_h \leq \frac{\Lambda_h}{\mu_h} \text{ as } t \rightarrow \infty$$

This shows that N_h is bounded and all the feasible solutions of the human only component of model(3.3) starting in the region Ω_h approach, enter or stay in the region where

$$\Omega_h = \{(S, I_H, I_M, I_{HM}) \in \mathbb{R}_+^4 : N_h \leq \frac{\Lambda_h}{\mu_h}\}$$

Similarly the feasible solution set of the mosquito population

$$\Omega_v = \{(V, I_V) \in \mathbb{R}_+^2 : N_v \leq \frac{\Lambda_v}{\mu_v}\}$$

Thus it follows from above that N_h and N_v are bounded and all the possible solutions of the model starting in Ω will approach, enter or stay in the region $\Omega = \Omega_h \times \Omega_v$ for all $t > 0$. Thus Ω is positively invariant and the model (3.3) is biologically meaningful and mathematically well posed in the domain Ω .

3.4 Stability analysis

3.4.1 Disease free equilibrium

The total human population N_h is calculated as,

$$N_h(t) = S(t) + I_H(t) + I_M(t) + I_{HM}(t)$$

Therefore on algebraic simplification we get the following,

$$\frac{dN_h}{dt} = \Lambda_h - \mu_h N_h - \delta I_{HM} \quad (3.7)$$

And the vector population N_V is similarly calculated as,

$$N_v(t) = S_V(t) + I_V(t)$$

Thus we get,

$$\frac{dN_V}{dt} = \Lambda_V - \mu_V N_V \quad (3.8)$$

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 and substitute in the system (3.3) above,

$$\frac{dS}{dt} = \frac{dI_H}{dt} = \frac{dI_M}{dt} = \frac{dI_{HM}}{dt} = \frac{dS_V}{dt} = \frac{dI_V}{dt} = 0$$

the system reduces to,

$$0 = \Lambda - \mu_h S$$

and

$$0 = \Lambda_V - \mu_V S_V$$

Therefore the disease free equilibrium(DFE) is given by

$$E_0 = (S, 0, 0, 0, S_V, 0) = \left(\frac{\Lambda_h}{\mu_h}, 0, 0, 0, \frac{\Lambda_V}{\mu_V}, 0 \right)$$

3.4.2 The Basic Reproduction number

R_o is defined as the expected number of secondary cases produced by a single(typical)infection in a completely susceptible population. The next generation matrix is a systematic way to calculate R_o . R_o is the spectral radius of the next generation matrix. First we separate the classes into two groups, infectious and non infectious.

The rate of appearance of new infection in the infectious classes gives the

following:

$$F = \begin{bmatrix} \frac{(\beta_1 I_H + \rho \beta_1 I_{HM}) S}{N_h} \\ \frac{\beta_2 b_M I_V S}{N_h} \\ \frac{\beta_3 b_M I_V I_H}{N_h} + \frac{\beta_4 (I_H + \rho I_{HM}) I_M}{N_h} \\ \frac{(\beta_5 b_M I_M + \beta_5 \rho I_{HM}) S_V}{N_h} \end{bmatrix}$$

Using the linearization method, the associated matrix at DFE and after taking partial derivatives gives us;

$$F = \begin{bmatrix} \frac{\beta_1 \Lambda_h}{\mu_h N_h} & 0 & \frac{\rho \beta_1 \Lambda_h}{\mu_h N_h} & 0 \\ 0 & 0 & 0 & \frac{b_M \beta_2 \Lambda_h}{\mu_h N_h} \\ 0 & 0 & 0 & 0 \\ 0 & \frac{b_M \beta_5 \Lambda_V}{\mu_V N_h} & \frac{\rho b_M \Lambda_V \beta_5}{\mu_h N_h} & 0 \end{bmatrix}$$

The transfer of individuals out of infectious classes is given by,

$$V = \begin{bmatrix} \frac{b_M \beta_3 I_V I_H}{N_h} - \gamma_2 I_{HM} + \mu_h I_H \\ (\gamma_1 + \mu_h) I_M \\ (\gamma_2 + \delta + \mu_h) I_{HM} \\ \mu_h I_V \end{bmatrix}$$

After taking partial derivatives and evaluating at disease free equilibrium we get the following matrix,

$$V = \begin{bmatrix} \mu_h & 0 & -\gamma_2 & 0 \\ 0 & \gamma_1 + \mu_h & 0 & 0 \\ 0 & 0 & \gamma_2 + \delta + \mu_h & 0 \\ 0 & 0 & 0 & \mu_V \end{bmatrix}$$

We now use the Gauss-Jordan method of matrix inversion to find the inverse of matrix V as,

$$V^{-1} = \begin{bmatrix} \frac{1}{\mu_h} & 0 & \frac{\gamma_2}{\mu_h(\gamma_2 + \delta + \mu_h)} & 0 \\ 0 & \frac{1}{\gamma_1 + \mu_h} & 0 & 0 \\ 0 & 0 & \frac{1}{\gamma_2 + \delta + \mu_h} & 0 \\ 0 & 0 & 0 & \frac{1}{\mu_V} \end{bmatrix}$$

Therefore we obtain the following matrix

$$FV^{-1} = \begin{bmatrix} \frac{\beta_1 \Lambda_h}{\mu_h^2 N_h} & 0 & \frac{\Lambda_h \beta_1 (\gamma_2 + \rho \mu_h)}{\mu_h^2 N_h (\gamma_2 + \delta + \mu_h)} & 0 \\ 0 & 0 & 0 & \frac{b_M \beta_2 \Lambda_h}{\mu_h \mu_V N_h} \\ 0 & 0 & 0 & 0 \\ 0 & \frac{b_M \Lambda_V \beta_5}{\mu_V N_h (\gamma_1 + \mu_h)} & \frac{\rho b_M \Lambda_V \beta_5}{\mu_V N_h (\gamma_2 + \delta + \mu_h)} & 0 \end{bmatrix}$$

The eigenvalues of FV^{-1} are:

$$K_1 = 0, K_2 = \frac{\Lambda_h \beta_1}{\mu_h^2 N_h}, K_3, K_4 = \pm \sqrt{\frac{b_M^2 \Lambda_h \Lambda_V \beta_2 \beta_5}{\mu_V^2 \mu_h N_h^2 (\gamma_1 + \mu_h)}}$$

It follows that the basic reproduction number which is given by the largest eigenvalue for the system(3.3) for HIV -malaria co-infection is

$$R_0 = \{R_{HIV}, R_{MAL}\}$$

$$R_{0HM} = \left\{ \frac{\Lambda_h \beta_1}{\mu_h^2 N_h}, \sqrt{\frac{b_M^2 \Lambda_h \Lambda_V \beta_2 \beta_5}{\mu_V^2 \mu_h N_h^2 (\gamma_1 + \mu_h)}} \right\}$$

Where

$$R_{0_{HIV}} = \frac{\Lambda_h \beta_1}{\mu_h^2 N_h}$$

$$R_{0_{MAL}} = \sqrt{\frac{b_M^2 \Lambda_h \Lambda_V \beta_2 \beta_5}{\mu_V^2 \mu_h N_h^2 (\gamma_1 + \mu_h)}}$$

$R_{0_{HIV}}$ is a measure of the average number of secondary HIV infections in humans caused by a single infective human introduced into an entirely susceptible population. Similarly $R_{0_{MAL}}$ is a measure of the average number of secondary malaria infections in humans or mosquito population caused by a single infective human or mosquito introduced into an entirely susceptible population. 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.

3.4.3 Local stability analysis of the DFE

Theorem *The disease free equilibrium of the system is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$*

Now to determine the local stability of E_0 , we find the Jacobian of system (3.3) as, .

$$J = \begin{bmatrix} \frac{\beta_1 S}{N_h} - \mu_h & 0 & \frac{\rho \beta_1 S}{N_h} + \gamma_2 & 0 \\ 0 & -(\gamma_1 + \mu_h) & 0 & \frac{b_M \beta_2 S}{N_h} \\ 0 & 0 & -(\gamma_2 + \delta + \mu_h) & 0 \\ 0 & \frac{b_M \beta_5 S_V}{N_h} & \frac{\rho b_M \beta_5 S_V}{N_h} & -\mu_V \end{bmatrix}$$

The Jacobian at E_0

$$J(E_0) = \begin{bmatrix} \frac{\Lambda_h \beta_1}{\mu_h N_h} - \mu_h & 0 & \frac{\rho \beta_1 \Lambda_h}{\mu_h N_h} + \gamma_2 & 0 \\ 0 & -(\gamma_1 + \mu_h) & 0 & \frac{b_M \Lambda_h \beta_2}{\mu_h N_h} \\ 0 & 0 & -(\gamma_2 + \delta + \mu_h) & 0 \\ 0 & \frac{b_M \Lambda_V \beta_5}{\mu_V N_h} & \frac{\rho b_M \Lambda_V \beta_5}{\mu_V N_h} & -\mu_V \end{bmatrix}$$

The trace of $J(E_0) < 0$ if $\frac{\Lambda_h \beta_1}{\mu_h N_h} < \mu_h$ and

$$\det J(E_0) = (\gamma_2 + \delta + \mu_h) \left(\mu_h - \frac{\Lambda_h \beta_1}{\mu_h N_h} \right) \left[\mu_V (\gamma_1 + \mu_h) - \frac{b_M^2 \Lambda_V \Lambda_h \beta_2 \beta_5}{\mu_V \mu_h N_h^2} \right]$$

In order to get a condition for $\det J(E_0) > 0$,

$$\det J(E_0) = (\gamma_2 + \delta + \mu_h) \left(\mu_h - \frac{\Lambda_h \beta_1}{\mu_h N_h} \right) \left[\mu_V (\gamma_1 + \mu_h) - \frac{b_M^2 \Lambda_V \Lambda_h \beta_2 \beta_5}{\mu_V \mu_h N_h^2} \right] > 0$$

$$\mu_h - \frac{\Lambda_h \beta_1}{\mu_h N_h} > 0$$

$$\mu_h \left[1 - \frac{\Lambda_h \beta_1}{\mu_h^2 N_h} \right] > 0$$

$$\mu_h [1 - R_{0_{HIV}}] > 0$$

Therefore

$$R_{0_{HIV}} < 1$$

and

$$\mu_V (\gamma_1 + \mu_h) - \frac{b_M^2 \Lambda_V \Lambda_h \beta_2 \beta_5}{\mu_V \mu_h N_h^2} > 0$$

$$\frac{b_M^2 \Lambda_V \Lambda_h \beta_2 \beta_5}{\mu_V \mu_h N_h^2} < \mu_V (\gamma_1 + \mu_h)$$

$$\frac{b_M^2 \Lambda_V \Lambda_h \beta_2 \beta_5}{\mu_V^2 \mu_h N_h^2 (\gamma_1 + \mu_h)} < 1$$

Therefore

$$R_{0_{MAL}} < 1$$

If the trace is negative and the determinant is positive, then the eigenvalues will both be negative and the equilibrium point will be stable. However, in any other case the equilibrium point will be unstable. From the conditions established above it is clear that $R_{0_{HIV}} < 1$ and $R_{0_{MAL}} < 1$ therefore the disease free equilibrium E_0 is locally asymptotically stable such that the infection does not persist in the population and under this condition the endemic equilibrium does not exist. It is unstable for $R_0 > 1$.

3.4.4 Global stability analysis of the DFE

The global asymptotic stability (GAS) of the disease-free state of the model is investigated using the theorem by Castillo-Chavez et.al [33]. We rewrite the model as,

$$\frac{dX}{dt} = F(X, Y)$$

$$\frac{dY}{dt} = G(X, Y), G(X, 0) = 0$$

Where $X = (S, S_V)$ and $Y = (I_H, I_M, I_{HM}, I_V)$ with X denoting the number of uninfected population and Y denoting the the number of infected and co-infected population.

The disease free equilibrium $E_0 = (X_0, 0)$, $X_0 = \left(\frac{\Lambda_h}{\mu_h}, \frac{\Lambda_V}{\mu_V} \right)$

The conditions H_1 and H_2 below must be met to guarantee global asymptotic stability.

H_1 : For $\frac{dX}{dt} = F(X_0, 0)$, X_0 is globally asymptotically stable.

H_2 : $G(X, Y) = AY - \hat{G}(X, Y)$, $\hat{G}(X, Y) \geq 0$ for $(X, Y) \in \Omega$

Where $A = D_Y G(X_0, 0)$ is an M-matrix (the off diagonal elements of A are non-negative) and Ω is the region where the model makes biological sense. If the model satisfies the conditions H_1 and H_2 then the following result stated in the theorem below holds.

Theorem *The fixed point $E_0 = (X_0, 0)$ is a globally asymptotically stable equilibrium of system (3.3) provided that $R_{HM} < 1$ and the conditions stated in H_1 and H_2 are satisfied.*

Proof

From the model system (3.7) we have,

$$F(X, 0) = \begin{bmatrix} \Lambda_h - \mu_h S \\ \Lambda_V - \mu_V S_V \end{bmatrix}$$

$$G(X, Y) = AY - \hat{G}(X, Y)$$

Where,

$$A = \begin{bmatrix} \beta_1 - \mu_h & 0 & \rho\beta_1 + \gamma_2 & 0 \\ 0 & -(\gamma_1 + \mu_h) & 0 & \beta_2 \\ 0 & 0 & -(\gamma_2 + \delta + \mu_h) & 0 \\ 0 & \beta_5 & \rho\beta_5 & -\mu_v \end{bmatrix}$$

and

$$\hat{G}(X, Y) = \begin{bmatrix} \hat{G}_1(X, Y) \\ \hat{G}_2(X, Y) \\ \hat{G}_3(X, Y) \\ \hat{G}_4(X, Y) \end{bmatrix} = \begin{bmatrix} \beta_1(I_H + \rho I_{HM}) \left(1 - \frac{S}{N_h}\right) + \frac{b_M \beta_3 I_V I_H}{N_h} \\ b_M \beta_2 I_V \left(1 - \frac{S}{N_h}\right) + \frac{\beta_4 (I_H + \rho I_{HM}) I_M}{N_h} \\ -\frac{b_M \beta_3 I_V I_H}{N_h} - \frac{\beta_4 (I_H + \rho I_{HM}) I_M}{N_h} \\ \beta_5 b_M (I_M + \rho I_{HM}) \left(1 - \frac{S_V}{N_h}\right) \end{bmatrix}$$

Notice that the matrix A is an M-Matrix since all its off-diagonal elements are non-negative, where as to establish the result of global stability of E_0 , we need to prove $\hat{G}(X, Y) \geq 0$ but here $\hat{G}_3(X, Y) < 0$. This implies that the DFE (E_0) is not globally stable when $R_{HM} < 1$.

3.5 Numerical Sensitivity Analysis

We perform a sensitivity analysis on R_0 with respect to our parameters. This is to determine the relation of model parameters to disease transmission (ref). In determining how best to reduce human mortality and morbidity due to HIV and malaria, it is necessary to know the relative importance of the different factors responsible for its transmission and prevalence.

The sensitivity index S is defined as;

$$S = \frac{\partial R_0}{\partial P} \times \frac{P}{R_0}$$

where P is the parameter of interest.

The sensitivity index is a local estimate of the best way to reduce R_0 .

We have taken parameter values from published studies and government websites. For some parameters we pick realistically feasible values.

Table 3.2: **Sensitivity index for HIV and Malaria**

R_0	Parameter	Sensitivity Index
R_{0HIV}	β_1	1
	Λ_h	1
	μ_h	-0.53170
R_{0MAL}	β_2	0.5
	β_5	0.5
	b_m	0.5
	Λ_h	0.5
	Λ_V	0.5
	μ_h	-0.169692308
	μ_v	-0.5
	γ_1	-0.4630560

From table (3.2) it shows that R_0 is sensitive to the following parameters $\beta_1, \beta_2, \beta_5, \Lambda_h, \Lambda_V$. When each one of them increases keeping other parameters constant they increase the value of R_0 because they have positive indices. However the most sensitive parameters are β_1 and Λ_h , the contact rate of of susceptible humans with HIV infected individuals and recruitment rate into susceptible population. Therefore to reduce co-infection we need to control β_1 and reduce susceptible population by finding a permanent recovery to the diseases.

3.6 Numerical simulations.

The DFE equilibrium is globally unstable in this case, therefore the diseases will persist in the population when R_{HM} exceeds unity. Thus the endemic equilibrium exists. The scarcity of data on HIV-malaria co-infection limits our ability to calibrate our analytical results, but for the purpose of illustration, other parameter values are estimated to vary within realistic means and are given in Table 3.3 .

Table 3.3: **Parameters Values**

Parameter	Values.
β_1	0.86
β_2	0.833
β_3	0.1
β_4	0.001
β_5	0.09
Λ_h	0.0384
Λ_v	0.12
γ_1	0.0035
γ_2	0.047
ρ	0.6
b_M	0.2
δ	2.5
μ_h	0.008
μ_v	0.033

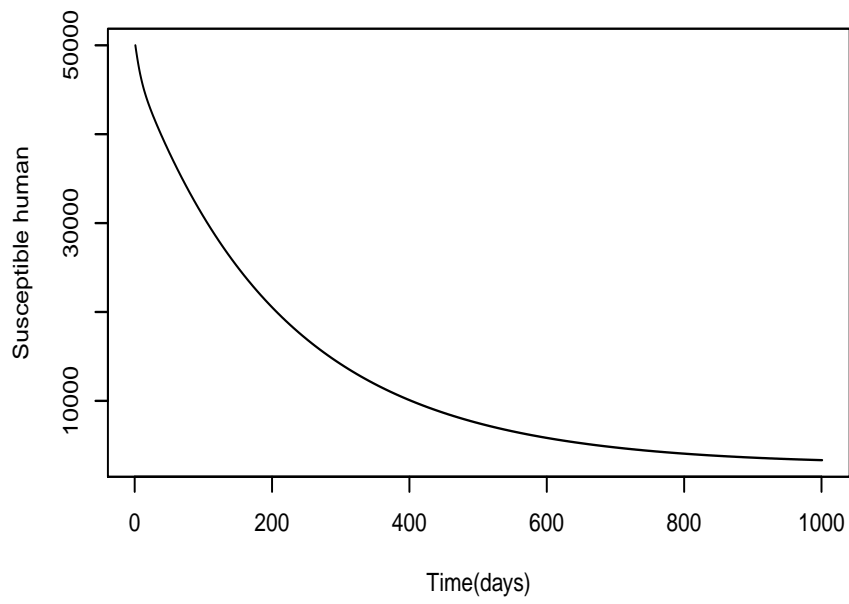


Figure 3.2: Susceptible human vs time

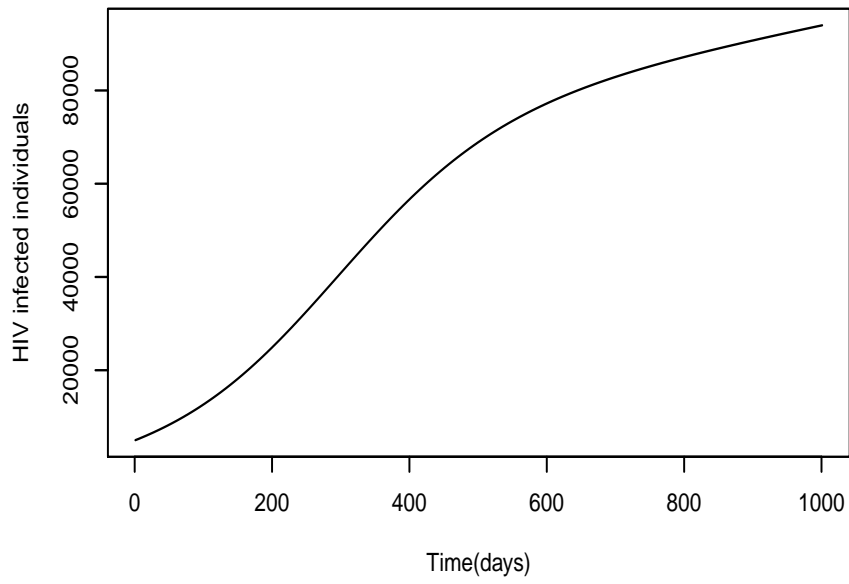


Figure 3.3: HIV infected human vs time

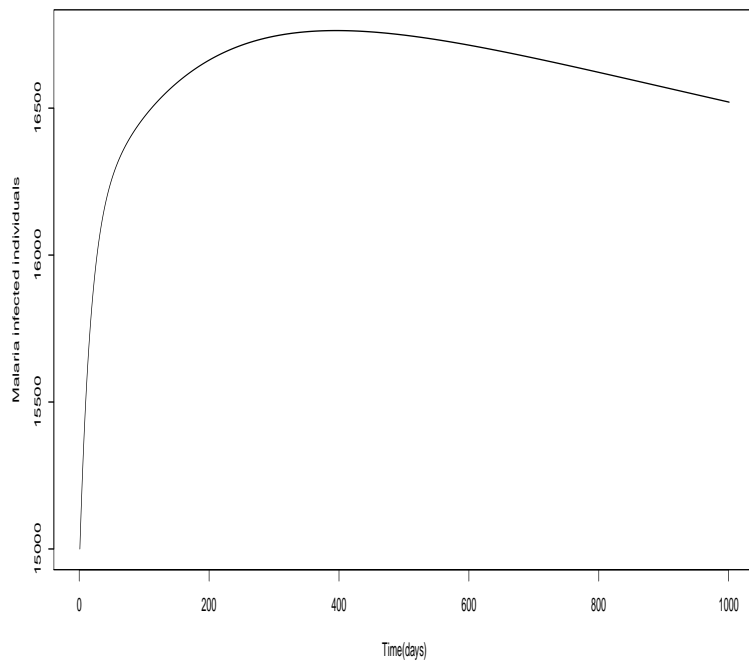


Figure 3.4: Malaria infected human vs time

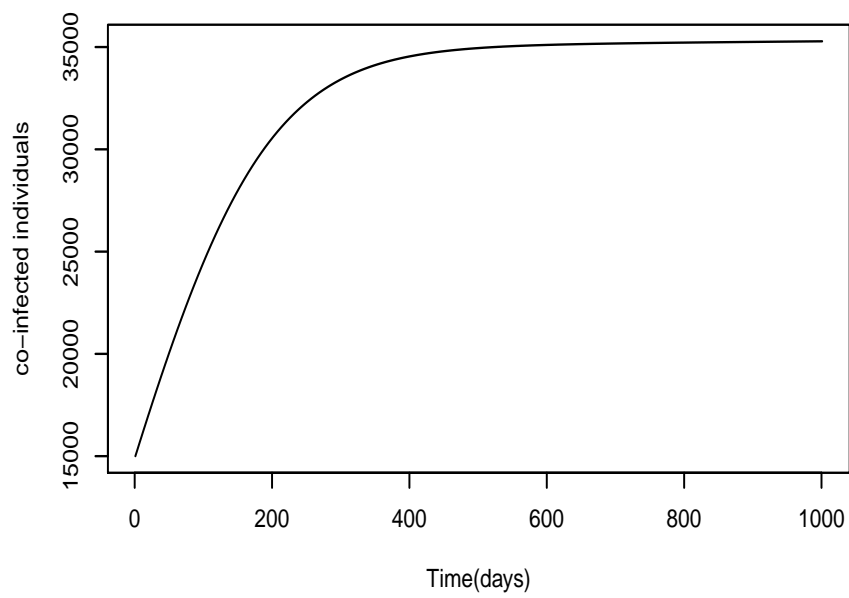


Figure 3.5: Co-infected human vs time

Discussion

The simulation results shows(Figure 3.2)shows that the Susceptible population decreases with time to finally reach equilibrium point.

From (Figure 3.3) the HIV infected population increases with time until it reaches endemic equilibrium point where the disease persists in the population.

Figure (3.4) Malaria infected populations increases with time due to increase in mosquitoes biting rate.It then slowly decreases until it reaches its equilibrium.This is because some individuals recover and join the susceptible population.

Figure(3.5)The co-infected human population increase with time until endemic equilibrium position (i.e. the position where HIV-Malaria persist) is reached.

The simulations illustrate that the population of individuals infected with malaria only always has a higher steady-state value than that of the population of individuals in the HIV class.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.

Chapter 4

CONCLUSION, RECOMMENDATION AND FUTURE WORK.

4.1 Summary

A deterministic model for the dynamics of HIV and malaria co-infection is presented and analysed. We establish the basic reproduction number R_{HM} , which is the expected number of secondary infections produced by an infective in a completely susceptible population. The theoretical results observed are as follows;

- i) The HIV-malaria model is shown to have a locally asymptotically stable disease free equilibrium when $R_{HM} < 1$.
- ii) The DFE is globally asymptotically unstable.

The numerical results show that there is an increase in mortality due to co-infection.

4.2 Recommendation

HIV and Malaria eradication still remains a challenge in developing countries. Thus there is need to strengthen existing control strategies in order to reduce or guard against incidences of co-infection by keeping the prevalence of each disease at low levels. In this regard we recommend that Malaria and HIV program should strengthen the awareness and education campaigns

with a lot of emphasis on the importance of sleeping under insecticide treated mosquito nets, prompt recognition of symptoms, correct disease diagnosis, HIV screening and early commencement of ARV treatment.

4.3 Future work

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 for malaria such as the use of treatment and prophylactic drugs, vector-reduction strategies and personal protection against mosquito bites by use insecticide treated mosquito nets. It would also be interesting to add exposed class for malaria and AIDS class for human population.

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