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Mathematical Malaria Model Focusing on the Effects of Partial Immunity, Strong Immunity, Drug Resistance and Intensive Treatment

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Abstract: Malaria is a public health problem that has affected many countries across the continent. To address this problem, a malaria mathematical model on assessing the impact of strong and weak immunity was investigated. In addition to that drug resistance and intensive treatment analysis was also analyzed between human and mosquito population by the use of appropriate and standard procedures. A malaria model was developed where strong immunity, and weak immunity parameters were incorporated. A variable of drug resistance was also incorporated to describe the rates of transmission of human and mosquito populations. The basic reproductive number was derived using the Next Generation Matrix Method. The stability of the basic reproductive number was checked by use of the Jacobian Matrix. The disease Free equilibrium was found to be locally asymptotically stable as the basic reproductive number is less than one and unstable if greater than one. The results were found that increased immunity, and intensive treatment helped reduce the number of infections and increased recoveries. This study will be useful to the government and non governmental organizations because they will do intensive treatment to those who have resistance malaria infections and low immunity. The government will also give immune boosters so that drug resistance can stop and increase immunity hence leading to high recoveries. The mathematical malaria modelers will use this study as reference in their research.

Keywords: Numerical Simulation, Malaria, Mathematical Modeling, Immunity, Drug Resistance, and Intensive Treatment

1. Introduction

Epidemics of vector borne diseases are usually serious threats globally where malaria is among the deadliest parasitic diseases by Zhao et al. [1]. When an adult female anopheles mosquito infected with malaria bites human blood, it transmits the infection by Fortin et al. [2]. An estimation of 241, 000, 000 malaria cases, 627, 000 deaths in 2020 were reported and 14, 000, 000 cases, 69, 000 deaths had been reported in 2019 in eighty five endemic malaria countries across the world by World Health Organization 2021 [3]. Symptoms of malaria are cold, fevers and sweat which are severe, they are accompanied by pains in joint and abdomen, extreme fatigue, headache and vomiting by Gbenga et al. [4].

To reduce the malaria disease cases in the world, several mathematical models have been developed where the first model was done by Ross et al. [5]. According to their research, if malaria could be reduced to a certain threshold then it could not be an endemic in the world. Later the model was modified by George et al. [6] by including higher infection. They showed that number of mosquitoes reduction had a little elimination on malaria epidemiology in endemic areas by George et al. [6]. Several models have been dedicated in order to come up with strategies that can eliminate malaria but, it continues to be an endemic in Sub Saharan Africa by Bakary et al. [7]. Therefore, there is need to develop new models and more research on malaria mathematical models by Bakary et al. [7]. Tchoumi et al.

[8] developed a model with numerical simulations for malaria transmission dynamics with differential susceptibility and partial immunity. Therefore, understanding how immunity, drug resistance could impact dynamics of malaria and control strategies is important in predicting the its dynamics. Eckhoff et al. [9] did a mathematical model on malaria parasite diversity and transmission intensity and how it affected the development of parasitological immunity.

A mathematical model analysis of competitive dynamics and aggressive treatment in the evolution of drug resistance in malaria parasites was done by Song et al. [10]. In their study they found out that aggressive treatment on drug resistant reduced the malaria infections. They recommended exploring the underlying issue of drug resistance and providing theoretical support for more effective drug treatment strategies by Song et al. [10]. Onifade et al. [11], did a research on the impact of drug resistance and treatment on malaria transmission dynamics. The result of their simulations revealed that to effectively control the widespread drug resistance, it was crucial for the policy makers to ensure that the individuals who become resistant from a particular treatment should be introduced to another treatment to ensure proper healing from the malaria infection by Onifade et al. [11]. Haringo et al. [12], developed a mathematical model with media awareness and treatment interventions. In this study, they found out that media awareness and treatment utilized the control of malaria infections. Olutimo et al. [13], did a malaria mathematical transmission model on the effect of environmental immunity between vector and host population where they developed and analyzed it. The conclusion of their study was that acquired environmental immunity due to nutrition, and medicinal herbs increased the recovery rates and lowered the infected class. Furthermore, Tumwiine et al. [14], found out that drug resistance against antimalarial drugs was a major hindrance to malaria control. The reports of drug resistance of Plasmodium falciparum have been increasing since 2012 across the globe as done by Wurtz et al. [15]. Mathematical models have been used to successfully understand the transmission of infectious diseases by Collins 2020 et al. [16], Collins 2021 et al. [17], Collins 2014 et al. [18], Herdicho et al. [19], Ibrahim et al. [20], Ojo et al. [21], Koella et al. [22], and Tien et al. [23].

In this paper, a deterministic malaria mathematical model was developed with six compartments. The impact of partial immunity, strong immunity, drug resistance and intensive treatment is analyzed using the proposed model which has not been done before. Drug resistance is considered as a model variable that varies with time. The people with low immunity after they decline normal treatment and become resistant must be introduced to another intensive treatment and immune boosters for them to recover. This paper is organized as follows; in Section 2, is the Susceptible S_{ho}, Infected I_{ho}, drug resistant Re_{ho}, recovered humans, R_{ho}, Susceptible S_{mo}, and infected mosquitoes I_{mo} malaria mathematical model with six compartments. Section 3, is the analysis of the mathematical model which include positivity and boundedness, invariant region, basic reproductive number, Disease Free Equilibrium and Endemic Equilibrium. Section 4, is the mathematical numerical simulations and section 5, are the conclusions and recommendations.

2. Research Methodology

2.1. Mathematical Malaria Model and Description

The $S_{ho}I_{ho}Re_{ho}R_{ho}S_{mo}I_{mo}$ model was an extension of the mathematical malaria model done by Ndendya et al. [24] where these researchers only looked at effect of environmental immunity in their research. Their model was a Susceptible, infected recovered humans, and susceptible, infected mosquitoes; $SIRSI$, but this study is a $S_{ho}I_{ho}Re_{ho}R_{ho}S_{mo}I_{mo}$ where strong immunity, weak immunity, drug resistance and intensive treatment were incorporated. This makes it different from other researches that have been done before. The variables and the parameters of the malaria mathematical model figure 1 are described below, where; S_{ho} is the number of the susceptible human population, I_{ho} is the number of human population who are infected with malaria, Re_{ho} is the is the infected human population who are resistant to antimalarial drugs, and R_{ho} is the recovered human population. Additionally S_{mo} is the total number of susceptible mosquito population and I_{mo} is the total number of infected mosquito population. $N_{ho}(t)$ is the total number of human population at time t given by; $N_{ho}(t) = S_{ho}(t) + I_{ho}(t) + Re_{ho}(t) + R_{ho}(t)$ and $N_{mo}(t)$ is the total number of mosquito population at time t given by $N_{mo}(t) = S_{mo}(t) + I_{mo}(t)$.

$\mathbf{\Lambda}_{ho}$ is the birth rate of humans, while $\mathbf{\Lambda}_{mo}$ is the birth rates of mosquitoes. Susceptible mosquitoes increase by natural births at a rate of $\mathbf{\Lambda_{ho}}$ and when the recovered human population lose immunity at a rate of γ. They decrease due to natural deaths at a rate μ and $\pi_{\mathbf{moho}}$ which is the rate at which susceptible humans become infected. Infected humans increase at a rate $\pi_{\mathbf{moho}}$ while they decrease by natural and induced deaths at rates μ and σ respectively. Additionally, they decrease when they are given medication and gain strong immunity at a rate $\alpha\rho$. Finally, they decrease when infected human population with weak immunity become resistant to drugs at a rate (1-α)ρ.

Resistant to drugs human population increase at a rate (1-α)ρ after infected to malaria with weak immunity become resistant to drugs. They decrease due to disease induced and natural death rates denoted as σ and μ respectively. Finally they decrease at a rate τ due to intensive treatment and taking of immune boosters. The recovered human population increase after infectious humans are treated and take immune boosters to gain strong immunity. They also increase after the infected who are resistant to drugs are treated with stronger antimalarial drugs and given immune boosters. They decrease due to natural deaths and loss of immunity at rates μ and γ respectively. Mosquitoes become susceptible after biting human blood from infectious humans (I_{ho}) or from infected humans who are resistant to drugs Re_{ho}. Susceptible

mosquitoes increase due to natural births at a rate $\mathbf{\Lambda_{mo}}$. They decrease after natural deaths of mosquitoes $\mu_{\mathbf{mo}}$ and when they move to infected mosquitoes compartment at a rate $\pi_{\mathbf{homo}}$.

Infected mosquitoes increase at a rate $\pi_{\mathbf{homo}}$ and decrease at $\mu_{\mathbf{mo}}$ which is the death rate. γ is the rate at which the recovered human population lose immunity and become susceptible to malaria infections. $\beta_{\mathbf{ho}}$ is the contact rate of human beings while $\beta_{\mathbf{mo}}$ is the contact rate of the mosquitoes. b is the biting rate of the mosquitoes, while ν is the relative infectivity from the infected human population resistant to antimalarial drugs. Mathematical Model Assumptions include:

1. All newborns are susceptible to malaria infections (both humans and mosquitoes). 2. Humans and mosquito population are constant. 3. All compartments have natural death rates where μ is for the humans while $\mu_{\mathbf{mo}}$ is for the mosquitoes. 4. Mosquitoes do not have immune category because majority die after malaria infections. 5. Humans lose immunity after recovery at a rate γ and become susceptible again.

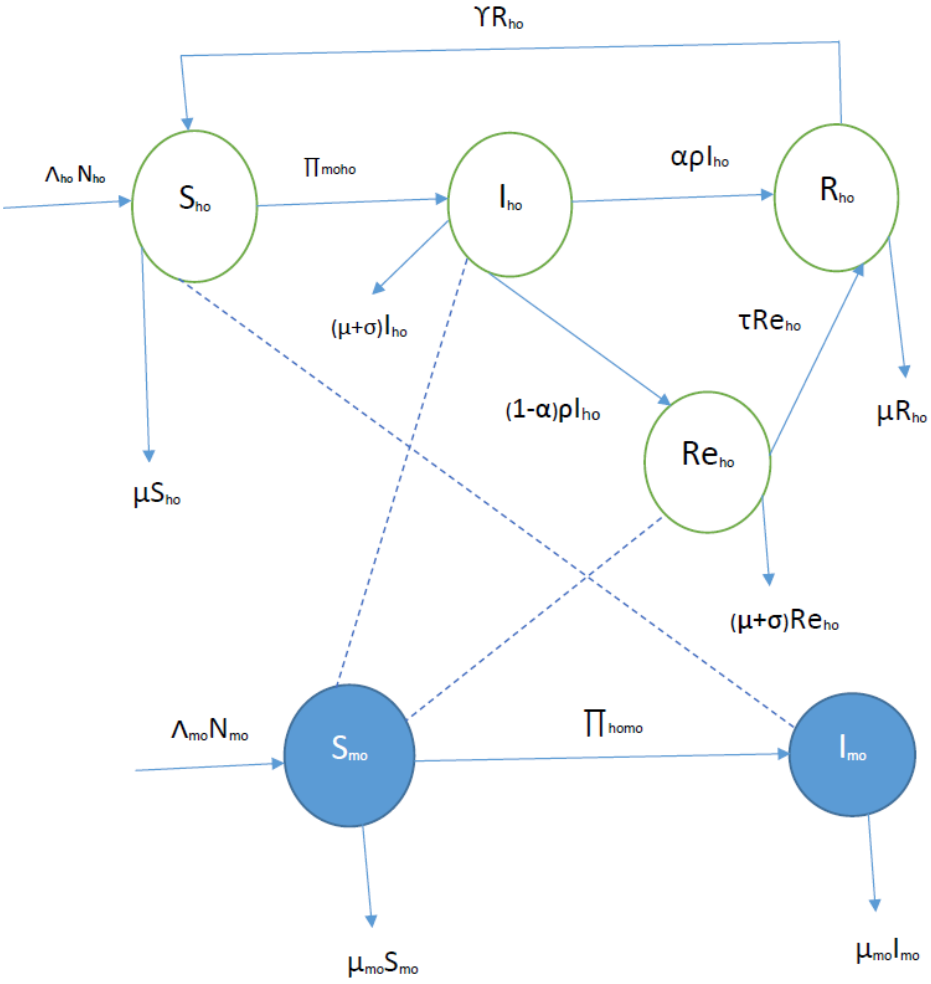

Figure 1. *Mathematical Malaria Model.*

2.2. Mathematical Malaria Model Equations

The following are the Equations for the $S_{ho}I_{ho}Re_{ho}R_{ho}S_{mo}I_{mo}$ Mathematical malaria Model;

$$\frac{dS_{ho}}{dt} = \mathbf{\Lambda_{ho}}N_{ho} + \gamma R_{ho} - \pi_{\mathbf{moho}} - \mu S_{ho}. \quad (1)$$

$$\frac{dI_{ho}}{dt} = \pi_{\mathbf{moho}} - (1-\alpha)\rho I_{ho} - \alpha\rho I_{ho} - (\mu+\sigma)I_{ho}. \quad (2)$$

$$\frac{dRe_{ho}}{dt} = (1-\alpha)\rho I_{ho} - \tau Re_{ho} - (\mu+\sigma)Re_{ho}. \quad (3)$$

$$\frac{dR_{ho}}{dt} = \alpha\rho I_{ho} + \tau Re_{ho} - \gamma R_{ho} - \mu R_{ho}. \quad (4)$$

$$\frac{dS_{mo}}{dt} = \mathbf{\Lambda_{mo}}N_{mo} - \pi_{\mathbf{homo}} - \mu_{\mathbf{mo}}S_{mo}. \quad (5)$$

$$\frac{dI_{mo}}{dt} = \pi_{\mathbf{homo}} - \mu_{\mathbf{mo}}I_{mo}. \quad (6)$$

Let $\pi_{\mathbf{moho}} = \frac{b\beta_{\mathbf{ho}}S_{ho}I_{mo}}{N_{mo}}$ and $\pi_{\mathbf{homo}} = \frac{b\beta_{\mathbf{mo}}S_{mo}(I_{ho}+\nu Re_{ho})}{N_{ho}}$. Where ho represents human population and mo is the mosquito population.

2.2.1. Description of Mathematical Model Variables and Parameters

$\mathbf{\Lambda_{ho}}$ is the Recruitment of susceptible humans by birth.

$\mathbf{\Lambda_{mo}}$ is Constant total recruitment rate of susceptible mosquitoes by birth.

μ is Natural death rate of humans.

$\mu_{\mathbf{mo}}$ is Natural death rate of mosquitoes.

$\beta_{\mathbf{ho}}$ is Transmission probability from infected vector to susceptible humans

$\beta_{\mathbf{mo}}$ is the transmission probability from infected humans to susceptible mosquito.

b is the average biting rate of mosquitoes on humans per day.

$\pi_{\mathbf{moho}}$ is Susceptible humans become infected rate.

$\pi_{\mathbf{homo}}$ is Susceptible mosquitoes become infected rate.

$\alpha\rho$ is Infected humans recover due to strong immunity rate.

$(1-\alpha)\rho$ is weak immunity resist drugs rate.

σ is Induced death rate.

$\rho_{\mathbf{m}}$ is Death rate of mosquitoes.

τ is Recovery rate due to intensive treatment.

S_{ho} is Susceptible human Population.

I_{ho} is Infected human population.

Re_{ho} is Human population resistant to drugs.

R_{ho} is Recovered human Population.

S_{mo} is Susceptible mosquito Population.

I_{mo} is Infected mosquito population.

3. Analysis of the Mathematical Model

3.1. Mathematical Model Basic Properties

The mathematical model figure 1 monitors the changes of human and mosquito populations. To prove that the solutions of the system in figure 1 with initial non-negative conditions remains non-negative for all $t > 0$, the following theorem applies;

Theorem: Given that the initial conditions of mathematical model figure 1 are; $S_{ho}(0) > 0, I_{ho}(0) > 0, Re_{ho}(0) > 0, R_{ho}(0) > 0, S_{mo}(0) > 0$, and $I_{mo}(0) > 0$, the solutions $S_{ho}(t), I_{ho}(t), Re_{ho}(t), R_{ho}(t), S_{mo}(t)$, and $I_{ho}(t)$ are non-negative for all $t > 0$.

Proof: Assume that; $\widehat{t}$ = sup $[t > 0; S_{ho}(t) > 0, I_{ho}(t) > 0, Re_{ho}(t) > 0, R_{ho}(t) > 0, S_{mo}(t) > 0, I_{mo}(t) > 0] \in [0, t]$. Thus $\widehat{t} > 0$, and it follows directly from equation 1 of the mathematical model figure 1 that;

$$\frac{dS_{ho}}{dt} \geq \mathbf{\Lambda_{ho}} N_{ho} + \gamma R_{ho} - (\pi_{\mathbf{moho}} + \mu S_{ho}). \tag{7}$$

Using the integrating factor to solve the inequality (7), we obtain; $\frac{d}{dt}[S_{ho}(t)exp[\mu t + \int_0^t \pi_{\mathbf{moho}} dS]] \geq \mathbf{\Lambda_{ho}} N_{ho} exp[\mu t + \int_0^t \pi_{\mathbf{moho}} dS]$. When both sides are integrated we get; $S_{ho}(t)exp[\mu t + \int_0^{\widehat{t}} \pi_{\mathbf{moho}} dS] \geq \int_0^{\widehat{t}} \mathbf{\Lambda_{ho}} exp[\mu\widehat{t} + \int_0^{\widehat{t}} \pi_{\mathbf{moho}}(Z)]d\widehat{t} + B$, where B is the integrating constant. Hence, $S(\widehat{t}) > 0 \forall \widehat{t} > 0$. For the second equation of the model figure 1, it gives;

$$\frac{dI_{ho}}{dt} \geq \pi_{\mathbf{moho}} - (1-\alpha)\rho I_{ho} - \alpha\rho I_{ho} - (\mu+\sigma)I_{ho} \geq -[(1-\alpha)\rho + \alpha\rho + \mu + \sigma]I_{ho}. \tag{8}$$

Which yields; $I_{ho}(t) \geq I_{ho} exponential[(1-\alpha)\rho + \alpha\rho + \mu + \sigma]t > 0$. The third equation of the mathematical model figure 1 gives;

$$\frac{dRe_{ho}}{dt} \geq (1-\alpha)\rho I_{ho} - \tau Re_{ho} - (\mu+\sigma)Re_{ho} \geq -(\tau+\mu+\sigma)Re_{ho}. \tag{9}$$

Where; $Re_{ho}(t) \geq Re_{ho} exponential(\tau+\mu+\sigma)t > 0$. The fourth equation is;

$$\frac{dR_{ho}}{dt} \geq \alpha\rho I_{ho} + \tau Re_{ho} + \gamma R_{ho} - \mu R_{ho} \geq -(\gamma+\mu)R_{ho}. \tag{10}$$

Where $R_{ho}(t) \geq R_{ho} exponential[(\gamma+\mu)t] > 0$. The fifth equation of our mathematical model figure 1 gives;

$$\frac{dS_{mo}}{dt} \geq \mathbf{\Lambda_{mo}} N_{mo} - \pi_{\mathbf{homo}} - \mu_{\mathbf{mo}} S_{mo} \geq -(\pi_{\mathbf{homo}} + \mu_{\mathbf{mo}})S_{mo}. \tag{11}$$

Which results to; $S_{mo}(t) \geq S_{mo} exponential(\pi_{\mathbf{homo}} + \mu_{\mathbf{mo}})t > 0$. Finally the sixth equation of the mathematical model system figure 1 is;

$$\frac{dI_{mo}}{dt} \geq \pi_{\mathbf{homo}} - \mu_{\mathbf{mo}} I_{mo} \geq -\mu_{\mathbf{mo}} I_{mo}. \tag{12}$$

which yields; $I_{mo}(t) \geq I_{mo} exponential - (\mu_{\mathbf{mo}})t > 0$. Therefore all the solutions of this mathematical model figure 1 with non-negative initial conditions will remain non-negative for all time $t > 0$.

3.2. Invariant Region

Total human and mosquito population is shown here to be bounded for all time $t > 0$. Mathematical model figure 1 is therefore analyzed in a biological interest region $\mathbf{\Omega}$.

Theorem: The $\mathbf{\Omega}$ which is the feasible region is thus defined by:

$\mathbf{\Omega_{ho}} = [S_{ho}(t), I_{ho}(t), Re_{ho}(t), R_{ho}(t) \epsilon R_4^+ | 0 \leq N_{ho} \leq$

$max[N_{ho}(0), \frac{\mathbf{\Lambda_{ho}} N_{ho}}{\mu}]]$. $\mathbf{\Omega_{mo}} = [S_{mo}(t), I_{mo}(t) \epsilon R_2^+ | 0 \leq N_{mo} \leq max[N_{mo}(0), \frac{\mathbf{\Lambda_{mo}} N_{mo}}{\mu_{\mathbf{mo}}}]]$. With initial conditions $S_{ho}(0) \geq 0, I_{ho}(0) \geq 0, Re_{ho}(0) \geq 0, R_{ho}(0) \geq 0, S_{mo}(0) \geq 0$, and $I_{mo}(0) \geq 0$ is invariant positively and attracting with respect to mathematical model figure 1 for all $t > 0$.

Proof: From mathematical model figure 1, the total human and mosquito populations give;

$$\frac{dN_{ho}(t)}{dt} = \mathbf{\Lambda_{ho}} N_{ho} + \gamma R_{ho} - \pi_{\mathbf{moho}} - \mu N_{ho}(t). \quad (13)$$

$$\frac{dN_{mo}(t)}{dt} = \mathbf{\Lambda_{mo}} N_{mo} - \pi_{\mathbf{homo}} - \mu_{\mathbf{mo}} N_{mo}(t). \quad (14)$$

Since I_{mo}, I_{ho}, and R_{ho} are non-negative hence, $N_{ho}(t) \leq N_{ho}(0) exp^{-\mu t} + \frac{\mathbf{\Lambda_{ho}} N_{ho}}{\mu}(1 - exp^{-\mu t})$ and $N_{mo}(t) \leq N_{mo}(0) exp^{-\mu_{\mathbf{mo}} t} + \frac{\mathbf{\Lambda_{mo}} N_{ho}}{\mu_{\mathbf{mo}}}(1 - exp^{-\mu_{\mathbf{mo}} t})$. In general, $N_{ho}(t) \leq \frac{\mathbf{\Lambda_{ho}} N_{ho}}{\mu}$ and $N_{mo}(t) \leq \frac{\mathbf{\Lambda_{mo}} N_{mo}}{\mu_{\mathbf{mo}}}$, if $N_{ho}(0) \leq \frac{\mathbf{\Lambda_{ho}} N_{ho}}{\mu}$ and $N_{mo}(t) \leq \frac{\mathbf{\Lambda_{mo}} N_{mo}}{\mu_{\mathbf{mo}}}$. Therefore, $N_{ho}(t)$ and $N_{mo}(t)$ are bounded above. Subsequently, $S_{ho}(t), I_{ho}(t), Re_{ho}(t), R_{ho}(t), S_{mo}(t)$, and $I_{mo}(t)$ are bounded above. Thus in $\mathbf{\Omega}$, mathematical model figure 1 is well posed. Therefore, to study the dynamics of the mathematical model figure 1 in $\mathbf{\Omega}$ is well sufficient.

3.3. Disease Free Equilibrium and the Basic Reproductive Number

In the absence of malaria disease, ($I_{ho} = Re_{ho} = R_{ho} = I_{mo} = 0$). Mathematical model figure 1 has a disease free equilibrium given by; $E_0 = (S_{ho}^0, 0, 0, 0, S_{mo}^0, 0) = (\frac{\mathbf{\Lambda_{ho}} N_{ho}}{\mu}, 0, 0, 0, \frac{\mathbf{\Lambda_{mo}} N_{mo}}{\mu_{\mathbf{mo}}}, 0)$. Next generation technique was applied by Irunde et al. [25], Korobeinikov et al. [26] where the basic reproductive number R_0 is the result of spectral radius of $FV^{-1} = R_0 = \rho(FV^{-1})$.

$$F = \begin{bmatrix} 0 & 0 & \frac{\mathbf{\Lambda_{ho}} N_{ho} b \beta_{\mathbf{ho}}}{N_{mo} \mu} \\ 0 & 0 & 0 \\ \frac{\mathbf{\Lambda_{mo}} N_{mo} b \beta_{\mathbf{mo}}}{N_{ho} \mu_{\mathbf{mo}}} & \frac{\mathbf{\Lambda_{mo}} N_{mo} b \beta_{\mathbf{mo}} \upsilon}{N_{ho} \mu_{\mathbf{mo}}} & 0 \end{bmatrix}. \quad and \quad V = \begin{bmatrix} -\alpha\rho - \mu + \rho(\alpha - 1) - \sigma & 0 & 0 \\ \rho(1 - \alpha) & -\mu - \sigma - \tau & 0 \\ 0 & 0 & -\mu_{\mathbf{mo}} \end{bmatrix}.$$

Therefore FV^{-1} is;

$$FV^{-1} = \begin{bmatrix} 0 & 0 & \frac{\mathbf{\Lambda_{ho}} N_{ho} b \beta_{\mathbf{ho}}}{N_{mo} \mu \mu_{\mathbf{mo}}} \\ 0 & 0 & 0 \\ A & \frac{\mathbf{\Lambda_{mo}} N_{mo} b \beta_{\mathbf{mo}} \upsilon}{N_{ho} \mu_{\mathbf{mo}} (\mu + \sigma + \tau)} & 0 \end{bmatrix}.$$

$$A = \frac{\mathbf{\Lambda_{mo}} N_{mo} b \beta_{\mathbf{mo}} \upsilon (\alpha\rho - \rho)}{N_{ho} \mu_{\mathbf{mo}} (\mu_{\mathbf{2}} + \mu\rho + 2\mu\sigma + \mu\tau + \rho\sigma + \rho\tau + \sigma^2 + \sigma\tau)} + \frac{\mathbf{\Lambda_{mo}} N_{mo} b \beta_{\mathbf{mo}}}{N_{ho} \mu_{\mathbf{mo}} (-\mu - \rho - \sigma)}$$

Eigenvalues include:

$$-b\sqrt{\frac{-\mathbf{\Lambda_{ho}} \mathbf{\Lambda_{mo}} \beta_{\mathbf{ho}} \beta_{\mathbf{mo}} (\alpha\rho\upsilon - \mu - \rho\upsilon - \sigma - \tau)}{\mu(\mu + \rho + \sigma)(\mu + \sigma + \tau) {\mu_{\mathbf{mo}}}^2}}. \quad or \quad b\sqrt{\frac{-\mathbf{\Lambda_{ho}} \mathbf{\Lambda_{mo}} \beta_{\mathbf{ho}} \beta_{\mathbf{mo}} (\alpha\rho\upsilon - \mu - \rho\upsilon - \sigma - \tau)}{\mu(\mu + \rho + \sigma)(\mu + \sigma + \tau) {\mu_{\mathbf{mo}}}^2}}$$

which is the basic reproductive number because it is the most dominant eigen value.

3.4. Local Stability of the Disease Free Equilibrium

Using the basic reproductive number, the theorem 2 by Van et al. [31], follows that the disease free equilibrium is locally asymptotically stable whenever $R_0 < 1$ and unstable when $R_0 > 1$. The Jacobian Matrix is evaluated at E_0 and it is obtained as;

$$J(E_0) = \begin{bmatrix} -\mu & 0 & 0 & \gamma & 0 & \frac{-b\beta_{\mathbf{ho}} S_{ho}}{N_{mo}} \\ 0 & -(1-\alpha)\rho - \alpha\rho - (\mu + \sigma) & 0 & 0 & 0 & \frac{b\beta_{\mathbf{ho}} S_{ho}}{N_{mo}} \\ 0 & (1-\alpha)\rho & -\tau - (\mu + \sigma) & 0 & 0 & 0 \\ 0 & \alpha\rho & \tau & -\gamma - \mu & 0 & 0 \\ 0 & 0 & -\mu_{\mathbf{mo}} & 0 & -\mu_{\mathbf{mo}} & 0 \\ 0 & \frac{b\beta_{\mathbf{mo}} S_{mo}}{N_{ho}} & \frac{b\beta_{\mathbf{mo}} S_{mo} \upsilon}{N_{ho}} & 0 & \frac{b\beta_{\mathbf{mo}} S_{mo}}{N_{ho}} & -\mu_{\mathbf{mo}} \end{bmatrix}.$$

The eigen values of the Jacobian matrix at the Disease Free Equilibrium must be real parts which are negative for the Disease free Equilibrium to be locally asymptotically stable. Therefore, the eigen values include; $\lambda_1 = -\mu, \lambda_{\mathbf{2}} = -(1-\alpha) - \alpha\rho - (\mu + \sigma), \lambda_{\mathbf{3}} = -\tau - (\mu + \sigma), \lambda_{\mathbf{4}} = -\gamma - \mu$ and $\lambda_{\mathbf{5}} = -\mu_{\mathbf{mo}}$. Since all the eigen values of the Jacobian

matrix at the Disease Free Equilibrium are negative, then the Disease Free Equilibrium is locally asymptotically stable.

3.5. Global Stability at the Disease Free Equilibrium

Theorem: The disease free equilibrium point for the malaria model figure 1 is globally asymptotically stable if $R_0 < 1$.

Proof: To proof global stability at the disease free equilibrium, the approach by Castillo et al. [32] is used. The total population is divided in to uninfected and diseased population. The malaria model is then written as; $\frac{dX}{dt} = F(X, X_1)$, and $\frac{dX_1}{dt} = G(X, X_1), G(X, 0) = 0$ where $X = S_{ho}, R_{ho}, S_{mo} \epsilon \top_+^3$, represents the number of uninfected human and mosquito population is represented by $X_1 = [I_{ho}, Re_{ho}, I_{mo}] \epsilon \top_+^2$, represents the diseased human and mosquito populations. The disease free equilibrium is then denoted as $E_0 = (X_0, 0)$. It is important to prove the two criteria;

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

b). $\hat{G}(X, X_1) = JX_1 - \hat{G}(X, X_1), G(X, X_1) \geq 0$, for all $(X, X_1) \epsilon \psi$ where $J = G(X_0, 0)$ is a Metzler meaning the off diagonal S of J are not negative and ψ is biologically meaningful region of the model.

Case (i):

Consider the uninfected class;

$$X^1(t) = \frac{d}{dt}\begin{bmatrix} S_{ho} \\ R_{ho} \\ S_{mo} \end{bmatrix} = \begin{bmatrix} \mathbf{\Lambda_{ho}} N_{ho} + \gamma R_{ho} - \pi_{\mathbf{moho}} - \mu S_{ho} \\ \alpha\rho I_{ho} + \tau Re_{ho} - \gamma R_{ho} - \mu R_{ho} \\ \mathbf{\Lambda_{mo}} N_{mo} - \pi_{\mathbf{homo}} - \mu_{\mathbf{mo}} S_{mo} \end{bmatrix}.$$

At the disease free equilibrium when $X_1 = 0$, that is $I_{ho} = Re_{ho} = I_{mo} = 0$, the uninfected population becomes;

$$\frac{d}{dt}\begin{bmatrix} S_{ho} \\ R_{ho} \\ S_{mo} \end{bmatrix} = \begin{bmatrix} \mathbf{\Lambda_{ho}} N_{ho} - \mu S_{ho} \\ 0 \\ \mathbf{\Lambda_{mo}} N_{mo} - \mu_{\mathbf{mo}} S_{mo} \end{bmatrix}.$$

Integrating the system above by use of the separation of variables gives; $S_{ho}(t) = \frac{\mathbf{\Lambda_{ho}} N_{ho}}{\mu} + (S_{ho}(0) - \frac{\mathbf{\Lambda_{ho}} N_{ho}}{\mu}) e^{-\mu t}$, $S_{mo}(t) = \frac{\mathbf{\Lambda_{mo}} N_{mo}}{\mu_{\mathbf{mo}}} + (S_{mo}(0) - \frac{\mathbf{\Lambda_{mo}} N_{mo}}{\mu_{\mathbf{mo}}}) e^{-\mu_{\mathbf{mo}} t}$, so that $t \to \infty$, $S_{ho}(t) \to \frac{\mathbf{\Lambda_{ho}} N_{ho}}{\mu}$, $R_{ho}(t) \to 0$, $S_{mo}(t) \to \frac{\mathbf{\Lambda_{mo}} N_{mo}}{\mu_{mo}}$. Regardless of the values of $S_{ho}(0), R_{ho}(0), S_{mo}(0)$, then $X_0 = (\frac{\mathbf{\Lambda_{ho}} N_{ho}}{\mu}, 0, \frac{\mathbf{\Lambda_{mo}} N_{mo}}{\mu_{\mathbf{mo}}})$ is globally asymptotically stable for the subsystem $F(X, 0)$.

Case (ii):

It is also necessary to prove that $\hat{G}(X, X_1) = JX_1 - G(X, X_1), \hat{G}(X, X_1) \geq 0$. Therefore the system is globally asymptotically stable at the disease free equilibrium if $R_0 < 1$.

3.6. Endemic Equilibrium

The endemic equilibrium of the mathematical model figure 1 are steady states where malaria may persist in the population. This happens when one of the infected classes in the malaria mathematical model figure 1 is not empty. In each compartment, the rate of change in the populations is zero at equilibrium; hence the right hand side is set to be zero that is;

$0 = \mathbf{\Lambda_{ho}} N_{ho} - \gamma R^*_{ho} - \frac{b\beta_{\mathbf{ho}} S^*_{ho} I^*_{mp}}{N_{mo}} - \mu S^*_{ho}$,
$0 = \frac{b\beta_{\mathbf{ho}} S^*_{ho}}{N_{ho}} - (1 - \alpha\rho I^*_{ho} - \alpha)\rho I^*_{ho} - (\mu + \sigma) I^*_{ho}$,
$0 = (1 - \alpha)\rho I^*_{ho} - \tau Re^*_{ho} - (\mu + \sigma) Re^*_{ho}$,
$0 = \alpha\rho I^*_{ho} + \tau Re^*_{ho} - \gamma R^*_{ho} - \mu R^*_{ho}$.
$0 = \mathbf{\Lambda_{mo}} N_{mo} - \frac{b\beta_{\mathbf{ho}} S^*_{ho} I^*_{mo}}{N_{mo}} - \mu_{\mathbf{mo}} S^*_{mo}$,
$0 = \frac{b\beta_{\mathbf{ho}} S^*_{ho} I^*_{mo}}{N_{mo}} - \mu_{\mathbf{mo}} I^*_{mo}$.

$S^*_{ho}, I^*_{ho}, Re^*_{ho}, R^*_{ho}, S^*_{mo}$, and I^*_{mo} are solved and endemic equilibrium occurs when the state variables take the form shown below;

$$S^*_{ho} = \frac{N_{mo}(\mathbf{\Lambda_{ho}} N_{ho} + \gamma R^*_{ho})}{b\beta_{\mathbf{ho}} I^*_{mo} - \mu N_{mo}}. \tag{15}$$

$$I^*_{ho} = \frac{b\beta_{\mathbf{ho}} S^*_{ho} I^*_{mo}}{[(1 - \alpha)\rho + \alpha\rho + (\mu + \sigma)] N_{mo}}. \tag{16}$$

$$Re^*_{ho} = \frac{(1 - \alpha)\rho I^*_{ho}}{\tau + \mu + \sigma}. \tag{17}$$

$$R^*_{ho} = \frac{\alpha\rho I^*_{ho} + \tau Re^*_{ho}}{\gamma + \mu}. \tag{18}$$

$$S^*_{mo} = \frac{N_{ho} \mathbf{\Lambda_{mo}} N_{mo}}{b\beta_{\mathbf{mo}}(I^*_{ho} + \upsilon Re^*_{ho})}. \tag{19}$$

$$I^*_{mo} = \frac{b\beta_{\mathbf{mo}} S^*_{mo}(I^*_{ho} + \upsilon Re^*_{ho})}{N_{ho}\mu_{\mathbf{mo}}}. \tag{20}$$

By substituting the values above in to the force of infections which include; $\pi_{\mathbf{moho}} = \frac{b\beta_{\mathbf{ho}} S_{ho} I_{mo}}{N_{mo}}$. And $\pi_{\mathbf{homo}} = \frac{b\beta_{\mathbf{mo}} S^*_{mo}(I^*_{ho} + \upsilon Re_{ho})}{N_{ho}}$. Where we obtain a quadratic equation; $\pi_{\mathbf{homo}}(V_2 {\pi_{\mathbf{homo}}}^2 + V_1 \pi_{\mathbf{homo}} + V_0) = 0$. And the case $\pi_{\mathbf{homo}} = 0$ corresponds to the trivial equilibrium. For the possibility of multiple equilibrium, this study is interested in analyzing the following quadratic equation; $V_2 {\pi_{\mathbf{homo}}}^2 + V_1 \pi_{\mathbf{homo}} + V_0 = 0$. Hence, we have established the results below;

Theorem: The malaria model figure 1 admits precisely;

a). One unique endemic equilibrium if $R_0 > 1$, or if $R_0 = 0$, and $V_1 < 0$,

b). two endemic equilibrium if $R_0 < 1$, $-\frac{V_1}{V_2} > 0$, and $V_1^2 - 4V_2V_0 > 0$,

c). no endemic equilibrium otherwise.

3.7. Global Stability at the Endemic Equilibrium Point

Theorem; If $R_0 > 1$, then the malaria model figure 1 has a unique equilibrium point which is globally asymptotically

stable.

Proof; Using the Lyapunov function technique as a suitable method by Chitnis et al. [27], the global stability of the endemic equilibrium point of figure 1 was established. It was formed using the general formula; $B = \sum_{i=1}^{6} c_i(y_i - y_i^* \ln y_i) = c_1(y_1 - y_1^* \ln y_1) + c_2(y_2 - y_2^* \ln y_2) + c_3(y_3 - y_3^* \ln y_3) + c_4(y_4 - y_4^* \ln y_4) + c_5(y_5 - y_5^* \ln y_5) + c_6(y_6 - y_6^* \ln y_6)$. Note that c_i is a constant which is positive, y_i is the population of the i^{th} compartment and y_i^* is the endemic equilibrium point. So, we differentiate B with respect to time to get; $\frac{dB}{dt} = c_1(1 - \frac{S_{ho}^*}{S_{ho}})\frac{dS_{ho}}{dt} + c_2(1 - \frac{I_{ho}^*}{I_{ho}})\frac{dI_{ho}}{dt} + c_3(1 - \frac{Re_{ho}^*}{Re_{ho}})\frac{dRe_{ho}}{dt} + c_4(1 - \frac{R_{ho}^*}{R_{ho}})\frac{dR_{ho}}{dt} + c_5(1 - \frac{S_{mo}^*}{S_{mo}})\frac{dS_{mo}}{dt} + c_6(1 - \frac{I_{mo}^*}{I_{mo}})\frac{dI_{mo}}{dt}$. Substituting the malaria model equations of figure 1 to the above equations we get; $\frac{dB}{dt} = c_1(1 - \frac{S_{ho}^*}{S_{ho}})[\mathbf{\Lambda_{ho}} N_{ho} + \gamma R_{ho} - \pi_{\mathbf{moho}} - \mu S_{ho}] + c_2(1 - \frac{I_{ho}^*}{I_{ho}})[\pi_{\mathbf{moho}} - (1-\alpha)\rho I_{ho} - \alpha\rho I_{ho} - (\mu + \sigma)I_{ho}] + c_3(1 - \frac{Re_{ho}^*}{Re_{ho}})[(1-\alpha)\rho I_{ho} - \tau Re_{ho} - (\mu + \sigma)Re_{ho}] + c_4(1 - \frac{R_{ho}^*}{R_{ho}})[\alpha\rho I_{ho} + \tau Re_{ho} - \gamma R_{ho} - \mu R_{ho}] + c_5(1 - \frac{S_{mo}^*}{S_{mo}})[\mathbf{\Lambda_{mo}} N_{mo} - \pi_{\mathbf{homo}} - \mu_{\mathbf{mo}} S_{mo}] + c_6(1 - \frac{I_{mo}^*}{I_{mo}})[\pi_{\mathbf{homo}} - \mu_{\mathbf{mo}} I_{mo}]$. Additionally, with the help of Lyapunov technique by Maliyon et al. [28], function $\phi(S_{ho}, I_{ho}, Re_{ho}, R_{ho}, S_{mo}, I_{mo})$ is not positive $i.e$, $\phi(S_{ho}, I_{ho}, Re_{ho}, R_{ho}, S_{mo}, I_{mo}) \leq 0$ for all $\phi(S_{ho}, I_{ho}, Re_{ho}, R_{ho}, S_{mo}, I_{mo})$, and it is zero only when $S_{ho} = S_{ho}^*$, $I_{ho} = I_{ho}^*$, $Re_{ho} = Re_{ho}^*$, $R_{ho} = R_{ho}^*$, $S_{mo} = S_{mo}^*$, and $I_{mo} = I_{mo}^*$ so that $\frac{dB}{dt} = 0$. Recalling the Lyapunov stability conditions that if; $B(S_{ho}, I_{ho}, Re_{ho}, R_{ho}, S_{mo}, I_{mo}) > 0 \forall (S_{ho}, I_{ho}, Re_{ho}, R_{ho}, S_{mo}, I_{mo}) \in \mathbf{\Omega} \backslash$ [Unique equilibrium point], then, Unique equilibrium point = [S_{ho}^*, I_{ho}^*, Re_{ho}^*, R_{ho}^*, S_{mo}^*, I_{mo}^*] is locally asymptotically stable.

3.8. Sensitivity Analysis

The sensitivity analysis of the basic reproduction number are determined here as used by Wedajo et al. [29], and it measures the initial malaria disease transmission. Sensitivity analysis enables the measurement of the change in a state variable in relation to parameter changes by Olutimo et al. [13]. The normalized forward sensitivity index of a variable in relation to parameter change is a ratio of variables change to the change of parameter. In table 2, the parameter values are used for sensitivity analysis and also for numerical results in simulations. $X_r^{pe} = \frac{\partial pe}{\partial r} \times \frac{r}{pe}$ is the formula for normalized forward sensitivity index of the variable pe to a parameter r. Change will occur in pe as ∂pe, where r is any of the parameters. For the malaria infections, sensitivity analysis of the effective reproduction number (pe), will be done to investigate the parameters that are more sensitive to the malaria mathematical model figure 1. Also it is done to investigate the right way to intervene the rate of malaria disease transmission in the population. The most sensitive and negative parameters were α, and τ. If these values were increased and other parameters held constant, the malaria disease would reduce. The other parameters which are positive, if they are increased and the other parameters held constant, then the malaria infections would increase in the human population.

Table 1. *This is the table style in LaTeX.*

Variables	Value	Reference
$\mathbf{\Lambda_{ho}}$	2.5	[28]
$\mathbf{\Lambda_{mo}}$	125	[29]
μ	0.00006	[30]
$\mu_{\mathbf{mo}}$	0.067	[30]
$\beta_{\mathbf{ho}}$	0.2	[30]
$\beta_{\mathbf{mo}}$	0.09	[30]
b	3.9	Variable
a	0.5	[29]
γ	0.000056	Assumed
α	0.005	[30]
$(1-\alpha)\rho$	0.0005	Assumed
σ	0.0095	[30]
Υ	0.00067	Variable
τ	0.00045	Assumed
N_{ho}	100	[30]
N_{mo}	30	[30]

4. Numerical Simulations

The parameter values that have been used in this study are estimates from other researchers as shown in table 2. The initial conditions are; $N_{mo} = 300, N_{ho} = 1000, S_{ho} = 1000, I_{ho} = 500, Re_{ho} = 250, R_{ho} = 50, S_{mo} = 300$ and $I_{mo} = 150$. The initial conditions of the state variables are arbitrary chosen mostly to show a certain behavior of the mathematical model.

4.1. Human Dynamics Against Time in Months

From figure 2, the human population in the exposed class drop rapidly due to malaria infections, natural deaths, and the remaining move to the infected class. In the infected class, there is an increase due to the movement of the susceptible class to the infected class. Then a rapid drop due to disease induced death rates and natural deaths. The rest move to the recovery and those who have low immunity become resistant to drugs and move to resistant to drugs class. The resistant to drugs increase rapidly due to movement of the infected class to the resistant to drugs because of low immunity. Then they drop rapidly due to movement to recovery and death rates due to malaria infections and natural deaths. The recovered population increase rapidly due to movement from infected then to recovered due to medication and high immunity. Also, they increase due to movement from drugs resistant population after intensive treatment and due to taking immune boosters to the recovered human population.

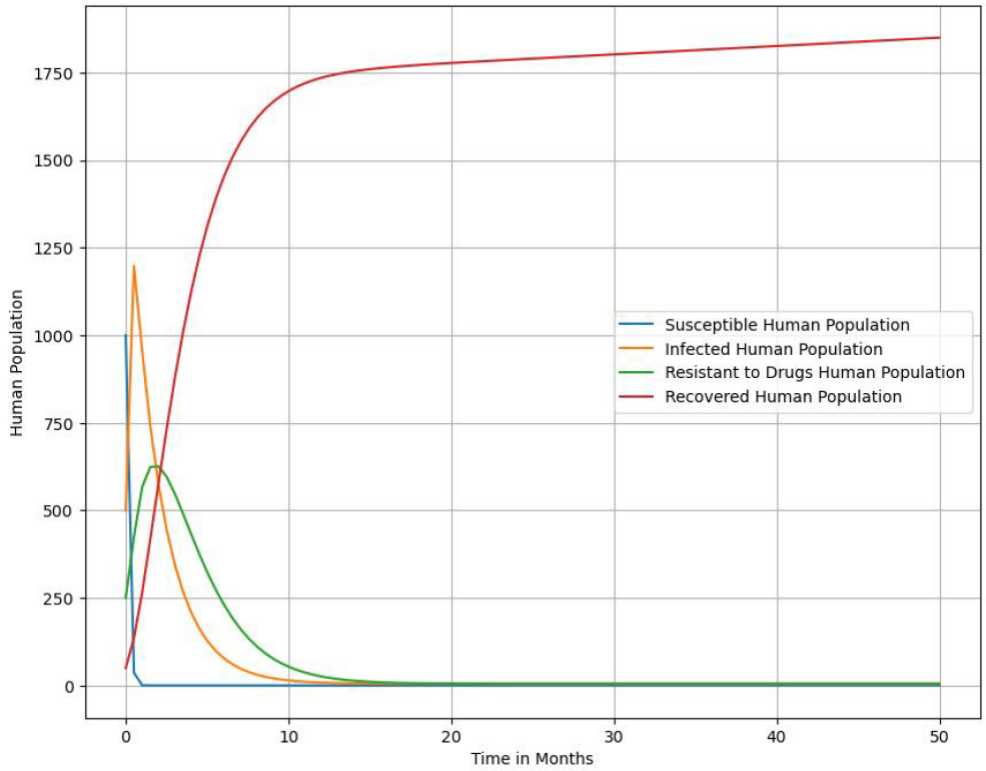

Figure 2. *Human population against time in months.*

4.2. Mosquito Dynamics Against Time in Months

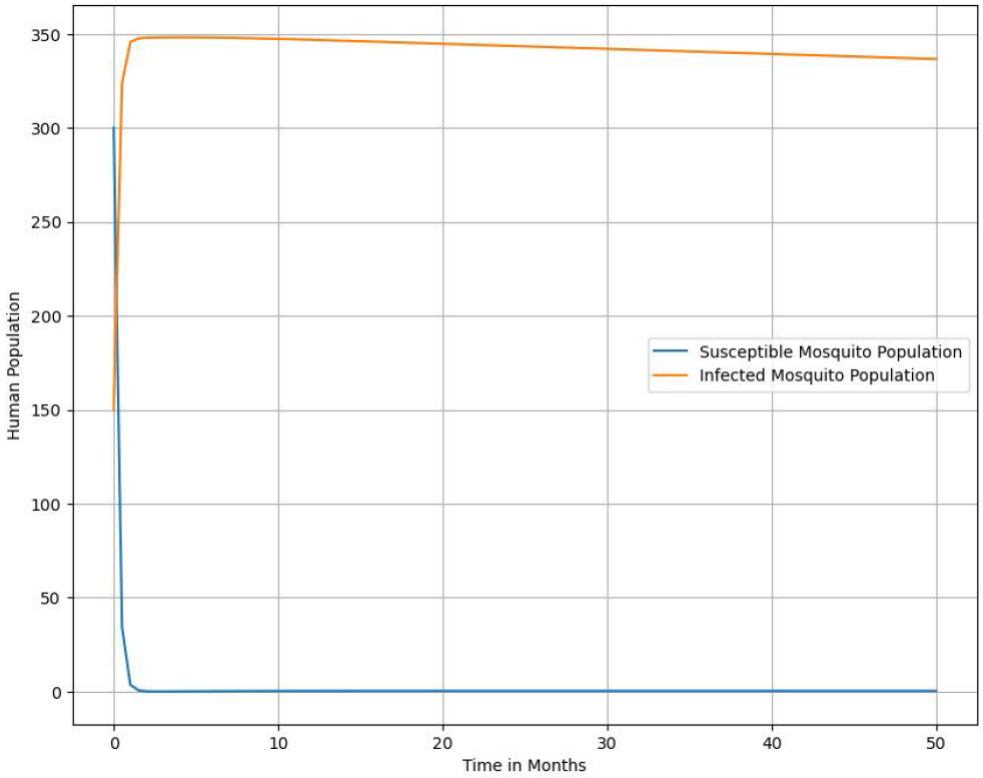

Figure 3. *Mosquito population against time in months.*

In figure 3 is mosquito population against time in months where susceptible mosquito population decreases rapidly with time due to natural deaths and movement to infectious class. Also, the infected mosquito class increase rapidly with time due to the movement from susceptible class and then drop due to natural deaths.

4.3. Dynamics of Various Values of α on Infected and Recovered Human Population

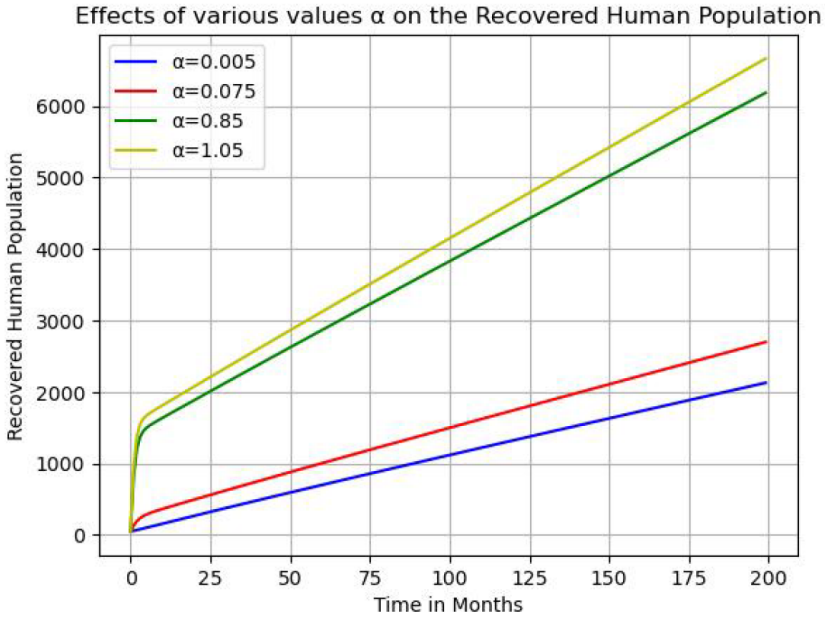

Figure 4. *Plot of Infected human population against time in months on the dynamics of varying values of α.*

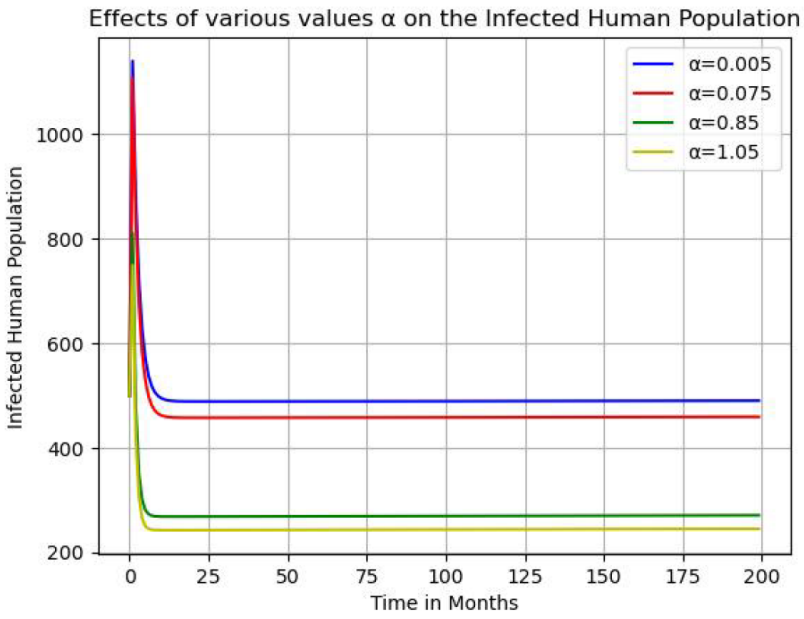

Figure 5. *Plot of Infected human population against time in months on the dynamics of varying values of α.*

In figure 4 shows that the higher the value of α that is the higher the immunity level, the higher the number of individuals who recover from malaria and the lower the immunity level, the lower the level of recoveries. In figure 5, the higher the level of immunity, the lower the number of infectives, and the lower the rate of immunity, the higher the rate of infectives. Therefore there is need for immune boosters so that the recoveries can increase and infected decrease in the community.

4.4. Dynamics of Various Values of τ on Both Resistant to Drugs and Recovered Human Population

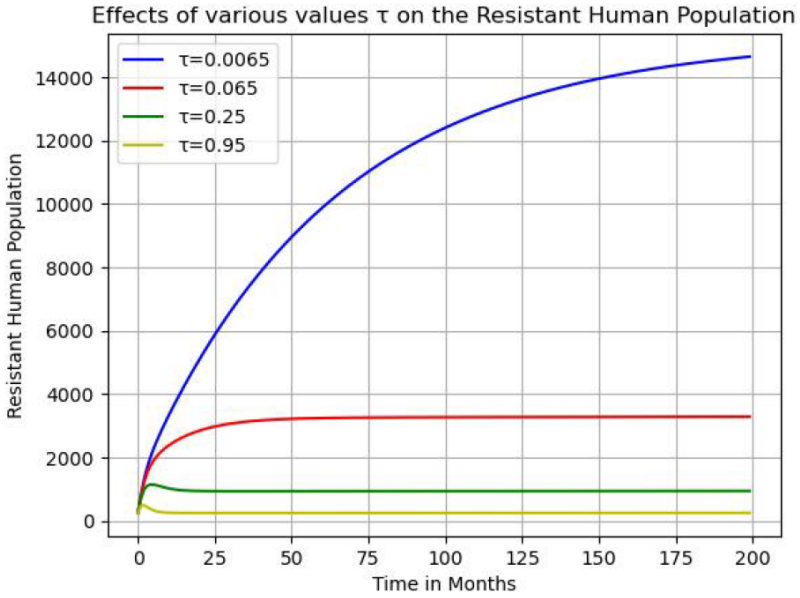

Figure 6. *Plot of human population who have resistent drugs against time in months.*

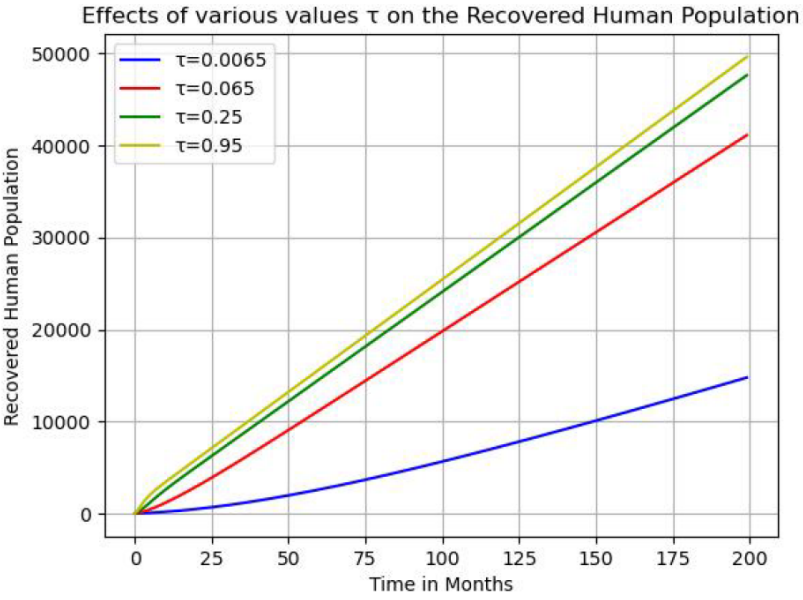

Figure 7. *Plot of Recovered human population against time in months.*

In figure 6 shows clearly that when intensive treatment and intake of immune boosters is high, then the number of those resistant to drugs decrease. Also, when the rate of intensive treatment and intake of immune boosters is low, then the number of those resistant to drugs is very high. In figure 7 shows the higher the rate of intensive treatment and intake of immune boosters, the higher the number of recoveries. Likewise, the lower the rate of intensive treatment and intake of immune boosters, the lower the number of recoveries. Therefore, there is need for intensive treatment and high intake of immune boosters for those who resist drugs in order for recoveries to increase.

4.5. Dynamics of Various Values of γ on Both Resistant to Drugs and Recovered Human Population

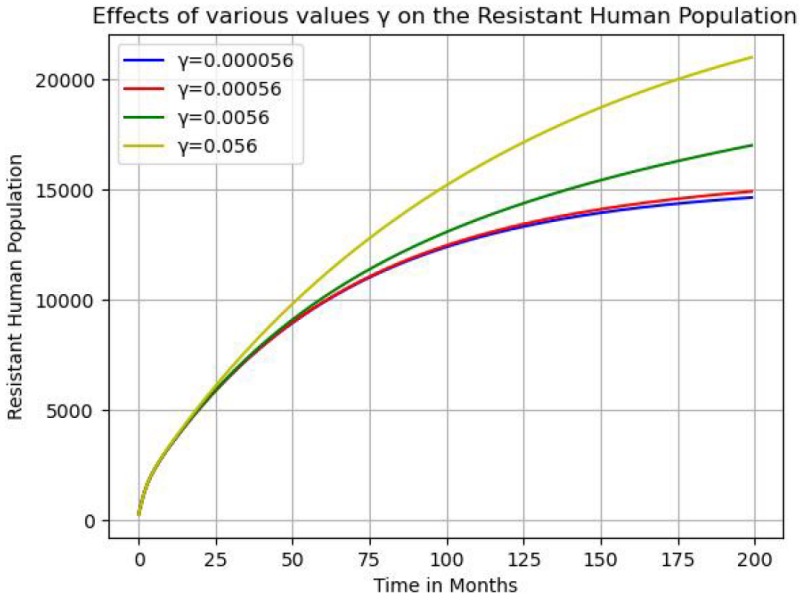

Figure 8. *Plot of human population who have resistent drugs against time in months on the dynamics of varying values of γ.*

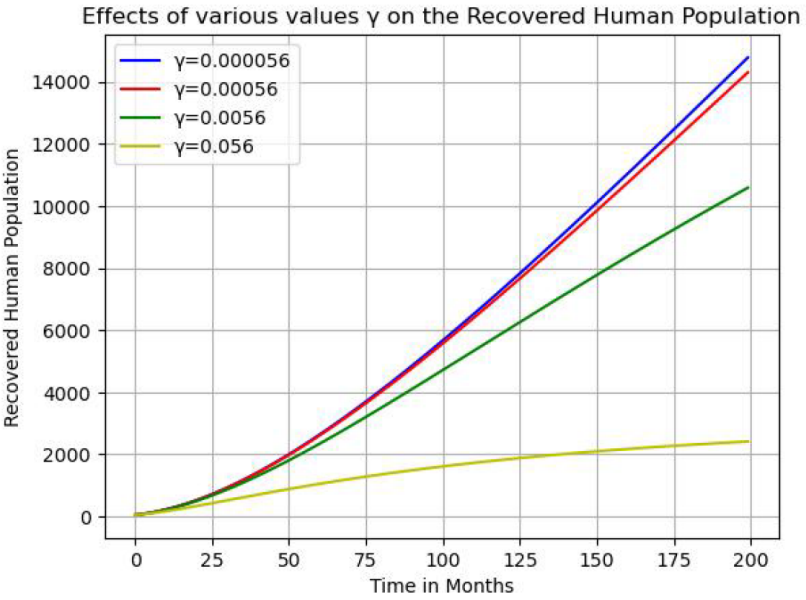

Figure 9. *Plot of Recovered human population against time in months on the dynamics of varying values of γ.*

Figure 8 shows the higher the loss of immunity the high the number of those who resist drugs and the lower the rate of immunity, the lower the number of those who are resistant to drugs. In figure 9 shows clearly that the higher the rate of immunity, the higher the number of those who recover and the lower the rate of immunity, the lower the number of those who recover.

5. Conclusion and Recommendation

The main objective of this study was mathematical malaria model focusing on the effects of immunity, drug resistance, and intensive treatment on the human population who become resistant to drugs. Mathematical model basic properties like positivity boundedness was performed and the system mathematical figure 1 was found to be positively bounded. Basic reproductive number was done using the next generation

matrix where it was found that the most dominant value was the most positive. The Jacobian matrix was used to get the disease free equilibrium where it was found to be locally asymptotically stable wherever $R_0 < 1$ and unstable $R_0 > 1$. Additionally, global stability at the endemic equilibrium was obtained using the Lyapunov function. Again, sensitivity analysis of the basic reproductive number was performed to get the most sensitive parameters which were γ, α, and τ. Numerical simulations were done to investigate effects of immunity, drug resistance, and intensive treatment as shown in figures $2, 3, 4, 5, 6, 7, 8$, and 9. The results showed that low immunity decreases recoveries and increases malaria infections. Also, high immunity increases recoveries and decreases malaria infections. Finally, when intensive treatment decreases those who are resistant to antimalarial drugs increase. Then when intensive treatment increases, recovered human population also increases. This study recommends that the society to be provided with immune boosters, free malaria testing, and free medication especially in areas which are highly endemic because malaria is difficult to eliminate.

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Author Contributions

Grace Maithya: Writing original draft, Conceptualization, Methodology, Analysis and Simulation.
Virginia Kitetu: Review, Editing, and Supervision.
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Conflicts of Interest

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