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MATHEMATICAL MODEL FOR TRANSFUSION TRANSMITTED MALARIA (TTM)

ONUORAH MARTINS O.[1] AND BABANGIDA BALA G.[2]
[1] Department of Physical Sciences Kampala International University, Uganda.
[2]Department of Mathematics, and Statistics Islamic University, in Uganda.

Abstract

In this paper, a deterministic mathematical model for transfusion transmitted malaria with sterilizing immunity is developed. The model, which consist of seven mutually exclusive compartments for human and mosquito populations has a disease free equilibrium (DFE) which is locally asymptotically stable whenever a certain epidemiological threshold, the *basic reproductive numbe*r (R_0) is less than unity. Further analysis shows that the model exhibits phenomena of backward bifurcation where the stable DFE coexist with endemic equilibrium which means that making (R_0) less than unity alone does not guaranty the control of malaria in the community. Numerical simulation of the model underscores the significance of inclusion of the new force of infection for human population. To the best of our knowledge, this is the first mathematical model of malaria to incorporate transmission by transfusion.

Key Words: Stability, Equilibrium, sterilizing immunity, Susceptible, Exposed.

Introduction

Malaria is a serious and sometimes fatal disease caused by a parasite that commonly infects a certain type of mosquito which feeds on human [1]. In 2016, an estimated 216 million cases of malaria occurred worldwide compared with 237 million cases in 2010, and 211 million cases in 2015. Most of these cases were in WHO African region (90%), followed by WHO East Asia Region (7%), and WHO East Mediterranean Region (2%) [2]. There was also an estimated 445,000 deaths from malaria globally in same 2016 compared to 446,000 deaths in 2015 and Su-Saharan Africa accounted for 80% of this global figure [2].

In 2016, all countries in WHO European rejoin reported zero indigenous cases of malaria, while Kyrgyzstan and Seri Lanka were certified malaria free [2], on the other hand, the United State of America eradicated malaria in 1951. Malaria remains endemic to Su-Saharan Africa with pregnant women and children at the greatest risk of contracting while Plasmodium Falciparum being the most active parasite [2]. Usually, people get malaria by being bitten by an infected female Anopheles mosquito. Because the malaria parasite is found in the red blood cells, the parasite can be transmitted through blood transfusion, organ transplant or the shared use of needles or syringes contaminated with blood.

An estimated US$2.7 billion was invested in malaria control and elimination efforts by governments of malaria endemic countries and international partners in 2016. This sum was spent on insecticide treated mosquito net (ITNs), rapid diagnostic test (RDTs), Artemisinin-based combination therapy (ACT), intermittent preventive treatment in pregnancy (IPTP), etc. [2]. From the 2017 and previous world malaria report, there has not been mention of intervention or clear cut programs to mitigate the second mode of transmission, transfusion transmission.

Meanwhile on a global scale, malaria is remains one of the most commonly transmitted infection [3] and (TTM) studies carried out in the Sub-Saharan Africa especially in countries most hit by the malaria menace has shown significant evidence in (TTM). Although international policies recommend that blood transfusion should be screened for transfusion infection, malaria screening is not performed in most malaria endemic countries, given rise to high risk of (TTM) [4]. With exception of anecdotal

Corresponding Author: Onuorah, M. O., Email: martins.onuorah@kiu.ac.ug. Tel +256702916837

of transfusion-transmitted African trypanosomiasis, transmission of protozoa in African through transfusion is largely confined to malaria [5]. Education and in-service training for healthcare workers in endemic region is recommended as a means to improve (TTM) knowledge in [6]. A recent studies found that the prevalence of malaria infection among blood donors was 27.54 %, with overall prevalence of asymptomatic malaria to be 10.17% which account for 47.36 % of all malaria infection [7]. Another study conducted in a malaria endemic area; Doula-Cameroon reported individual median residual risk of TTM as 5.59 per 10,000 or 2.64 per 1,000units of blood transfused every year [8]. The study confirmed presence of *P falciparum* as one of the most prevalent transfusion transmitted infections in the region. They conclude by saying that the residual risk of TTM is high among blood recipients, urging to conduct in malaria endemic areas, a cost benefit analysis of systematically screening blood units for malaria parasites before transfusion versus systematically treating the recipients after transfusion. For other articles that have shown significant TTM in malaria endemic areas, see [9 – 12].

Mathematical models of malaria abound in the literature, [13 – 23]. But mathematical models that account for TTM are rather scant. A generic model for estimating the transfusion transmission risk from a group of traveling donors that visited emerging infectious disease risk area was developed and analyzed in [24]. The model was applied to the outbreaks of Chikungunya virus in Italy in 20017 and Q fever in the Netherlands in 2007 – 2009. This paper extends previous studies by incorporating additional force of infection of human due to transfusion and sterilizing immunity as is common in malaria endemic population.

The model equations

The SEIRS and SEI epidemiological models where individuals in a community without any form of immunity are classified into susceptible, exposed, infected, and recovered compartments will be adopted for this study. The model assumed a homogenous mixing of the human and mosquito populations where susceptible individuals acquire infection upon a bite by an infectious mosquito and susceptible mosquito also acquire infection while taking a blood meal from an infected human. It's assumed also that a proportion of the susceptible individual have some kind of sterilizing immunity as a result of their long stay in the malaria endemic area. The interaction of human and mosquito is represented by the following system of nonlinear differential equations;

$$\frac{dS_H(t)}{dt} = \Lambda_H + \psi R_H - \frac{\alpha_1 S_H I_M}{N_H} + \frac{\alpha_3 S_H I_H}{N_H} - (\rho + \mu_1) S_H, \tag{1}$$

$$\frac{dE(t)}{dt} = \frac{\alpha_1 S_H I_M}{N_H} + \frac{\alpha_2 S_H I_H}{N_H} - (\sigma_1 + \mu_1) E_H, \tag{2}$$

$$\frac{dI_H(t)}{dt} = \sigma_1 E_H - (\gamma + \mu_1 + \delta_1) I_H, \tag{3}$$

$$\frac{dR_H(t)}{dt} = \gamma I_H + \rho S_H - (\psi + \mu_1) R_H, \tag{4}$$

$$\frac{dS_M(t)}{dt} = \Lambda_M - \frac{\alpha_2 S_M I_H}{N_H} - \mu_2 S_M, \tag{5}$$

$$\frac{dE_M(t)}{dt} = \frac{\alpha_2 S_M I_H}{N_H} - (\sigma_2 + \mu_2) E_M, \tag{6}$$

$$\frac{dI_M(t)}{dt} = \sigma_2 E_M - (\mu_2 + \delta_2) I_M , \quad (7)$$

where $S_H(t), E(t), I_H(t), R(t), S_M(t), E_M(t), I_M(t)$ denote the number of Susceptible Human, Exposed Human, Infectious Human, Susceptible Mosquito and Infected Mosquito population at time t respectively. And $N_H(t) = S_H(t) + E(t) + I_H(t) + R(t)$ and $N_M(t) = S_M(t) + E_M + I_M$. The meaning and values of the model parameters are given in the table below.

Parameter	Meaning	Value	Reference
Λ_H	Recruitment rate of human	$2.5\, day^{-1}$	[25]
Λ_M	Recruitment rate of mosquito	$5000\, day^{-1}$	[26]
b_2	Biting rate of infectious mosquito	$0.5\, day^{-1}$	[25]
β_1	Transmission probability from mosquito to human	$0.75\, day^{-1}$	[25]
β_2	Transmission probability from human to mosquito	$0.75\, day^{-1}$	[25]
α_1	Infection rate of human	$0.35\, day^{-1}$	[25]
α_2	Infection rate of mosquito	$0.75\, day^{-1}$	[25]
α_3	Transmission probability from human to human	$0.23\, day^{-1}$	Assumed
δ_1	Death rate of Human due to malaria	$0.0232\, day^{-1}$	[27]
δ_2	Death rate of mosquito due to malaria	$0.07\, day^{-1}$	[27]
σ_1	Progression rate from exposed to infected human	$0.0588\, day^{-1}$	[27]
σ_2	Progression rate from exposed to infected mosquito	$0.0017\, day^{-1}$	[28]
γ	Recovery rate of human	$0.0035\, day^{-1}$	[28]
μ_1	Natural death rate of Human	$0.00009132\, day^{-1}$	[27]
μ_2	Natural death rate of Mosquito	$0.066667\, day^{-1}$	[27]
ρ	The rate at which susceptible human acquired sterilizing immunity	$0.0002\, day^{-1}$	Assumed
ψ	Loss of immunity	$0.000136098\, day^{-1}$	Assumed

Table 1. Model parameters and their values.

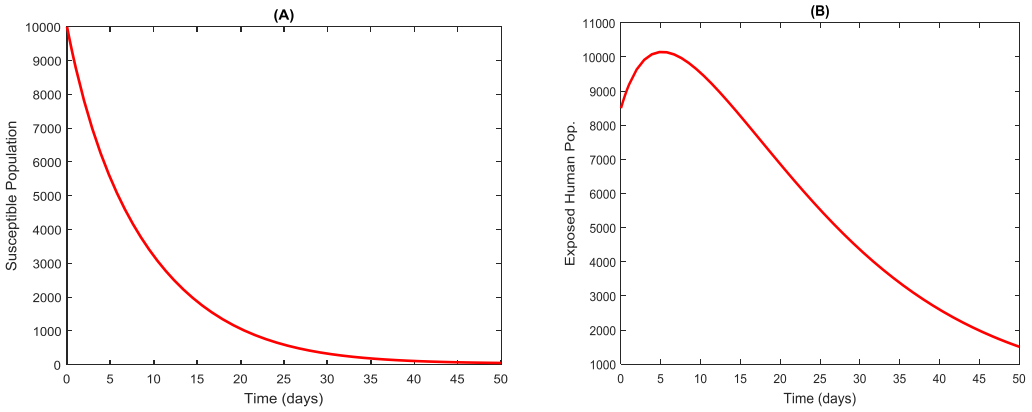

Figure 1(A). A Plot of the susceptible human population with time. The susceptible human population is continuously decreasing with time, this is due to increase in the number of exposed which leaves the compartment as a result of infection. The curve approaches zero because of the inclusion of transmission by transfusion, which means that malaria will always remain in the endemic region as a result of non-serious measure to mitigate transfusion transmission

Figure 1(B). A plot of exposed human population with time. The curve increases with time and then slopes down as a result individuals in this compartment moves to the infected compartment at the expiration of their exposed period.

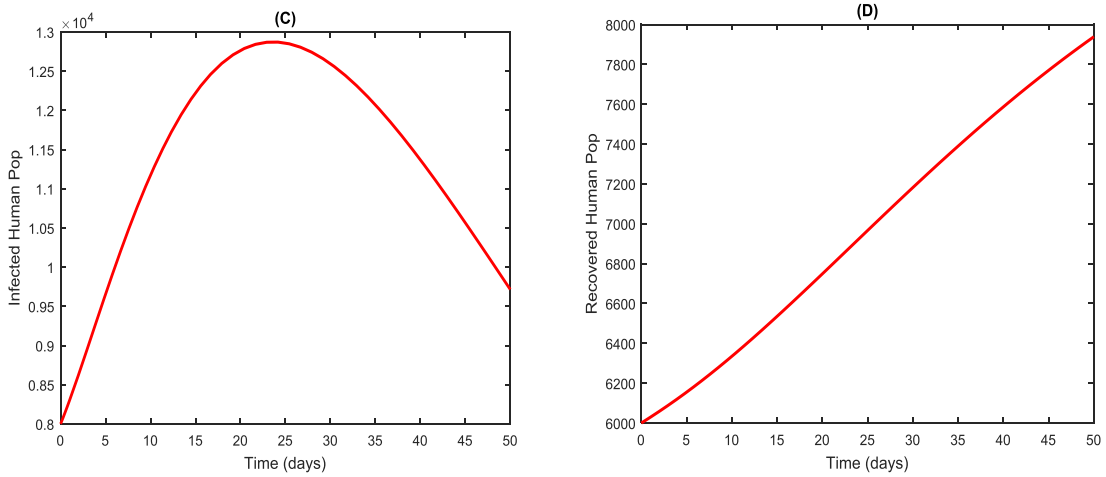

Figure 1(C). A plot of infected human population with time. The curve increases initially, then slopes down as members recover from the infection. The tendency for the curve to touch zero on the time axis is very slim, which means malaria can hardly be eliminated in the community.

Figure 1(D). A plot of the recovered human population with time. The curve is on the increase as infected individuals recover. Parameter values for the figure are as shown in table 1.

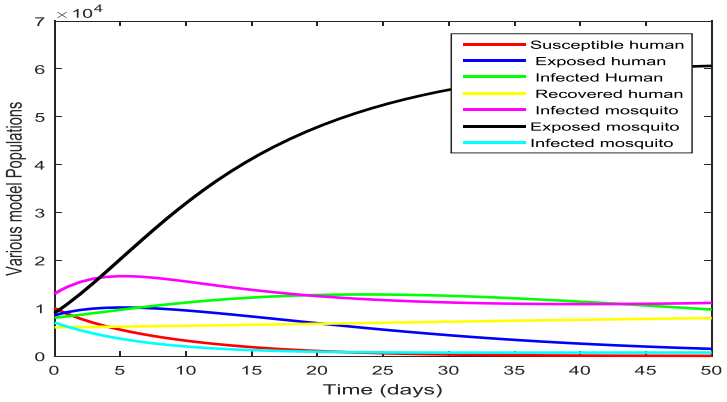

Figure 2. A plot showing the human and mosquito populations, with parameter values as shown in table1.

Basic Properties

In this section, the basic dynamical features of the model (1) to (7) will be explored. We Claim the following:

2.1 Lemma 1

$$D=\left\{(S_H,E_H,I_H,R_H,S_M,E_M,I_M)\in R_+^7 : S_H+E+I_H+R\le\frac{\Lambda_H}{\mu_1};S_M+E_M+I_M\le\frac{\Lambda_M}{\mu_2}\right\},$$

is positively invariant and attracting with respect to the basic model equations (1) to (7).

Proof

Adding equations (1) to (4) gives

$$\frac{dN_H}{dt}=\Lambda_H-\delta_1 I_H-\mu_1 N_H \tag{7}$$

Also, adding equations (5) and (7) gives

$$\frac{dN_M}{dt}=\Lambda_M-\delta_2 I_M-\mu_2 N_M \tag{8}$$

Since $\frac{dN_H}{dt}<\Lambda_H-\mu_1 N_H$, and $\frac{dN_M}{dt}<\Lambda_M-\mu_2 N_M$, it follows that $\frac{dN_H}{dt}<0$ and $\frac{dN_M}{dt}<0$ if,

$N_H(t)>\frac{\Lambda_H}{\mu_1}$ and $N_M(t)>\frac{\Lambda_M}{\mu_2}$ respectively

Thus a standard comparison theorem [29], can be used to show that

$N_H(t)<N_H(0)e^{-\mu_1(t)}+\frac{\Lambda_H}{\mu_1}\left[1-e^{-\mu_1(t)}\right]$ and $N_M(t)<N_M(0)e^{-\mu_2(t)}+\frac{\Lambda_M}{\mu_2}\left[1-e^{-\mu_2(t)}\right]$. In particular,

$N_H(t)\le\frac{\Lambda_H}{\mu_1}$ and $N_M(t)\le\frac{\Lambda_M}{\mu_2}$ if $N_H(0)\le\frac{\Lambda_H}{\mu_1}$ and $N_M(0)\le\frac{\Lambda_M}{\mu_2}$ Thus, D is positively invariant. Further, if

$N_H(t)>\frac{\Lambda_H}{\mu_1}$ and $N_M(t)>\frac{\Lambda_M}{\mu_2}$ then either the solution enters D in finite time or $N_H(t)$ approaches $\frac{\Lambda_H}{\mu_1}$, and

$N_M(t)$ approaches $\frac{\Lambda_M}{\mu_2}$ and the infected variables E_H, I_H, I_M approaches zero. Hence, all solutions R_+^6 eventually enters

D. Thus in D, the basic model (1) to (6) is well posed epidemiologically and mathematically [30]. Hence, it is sufficient to study the dynamics of the model equations in D

Analysis of the model

3.1 Disease free Equilibrium

Disease free equilibrium is equilibrium where there is no infection. Therefore, the infected classes will be zero that means that the whole population will be susceptible. To find the disease free equilibrium of our model equations (1) to (6), we equate the rate of change of our state variables to zero i.e.

$$\frac{dS_H(t)}{dt}=\frac{dE_H(t)}{dt}=\frac{dI_H(t)}{dt}=\frac{dR_H(t)}{dt}=\frac{dS_M(t)}{dt}=\frac{dE_M(t)}{dt}=\frac{dI_M(t)}{dt}=0$$

And solving the resulting algebra we have

$$E_0=\left(S_H^*,E^*,I_H^*,R_M^*,S_M^*,E_M,I_M^*\right)=\left(\frac{\Lambda_H(\psi+\mu_1)}{(\psi+\mu_1)(\rho+\mu_1)-\rho},0,0,\frac{\rho\Lambda_H}{(\psi+\mu_1)(\rho+\mu_1)-\rho},\frac{\Lambda_M}{\mu_2},0,0\right) \tag{9}$$

The stability of this disease free equilibrium given by equation (9) will be analyzed via the basic reproductive number

3.2 The Basic Reproductive Number (R_0)

One of the most important concerns about any infectious disease is its ability to invade a population. Many epidemiological models have a disease free equilibrium (DFE) at which the population remains in the absence of the disease. These models usually have a threshold parameter, known as the basic reproductive number R_0 such that when $R_0 < 1$, then the DFE is locally asymptotically stable, and the disease cannot invade the population, but if $R_0 > 1$,then the DFE is unstable and invasion is always possible see [31].

We define the basic reproductive number R_0 as the number of secondary infections that one infective individual would create over the duration of the infectious period provided that everyone else is susceptible. Our model is suited for a heterogeneous population in which the vital and epidemiological parameter for an individual may depend on such factors as the stage of the disease, spatial position, etc. however, we assume that the population can be broken into homogeneous subpopulation or compartment such that individual in a given compartment are indistinguishable from one another.

We use the next generation matrix approach as seen in [32] to derive our Basic Reproductive Number R_0. Numerous other articles [33, 34, 35] are devoted to the calculation of basic reproductive number R_0 for different models of various diseases.

Here, the basic reproductive number R_0 is the spectral radius (dominant eigenvalue) of the product matrix FV^{-I}, i.e $R_0 = \rho(FV^{-I})$

Our model has three Infective compartments namely the Exposed Human E_H, Infected Human, I_H Infected Mosquito I_M Exposed compartments. It follows that the matrices F and V for the new infective terms and remaining transfer terms respectively are given below. Where the entries of F and V are partial derivatives of $f_i(x)$ and $v_i(x)$. For our model, F and V are given below.

$$F = \begin{bmatrix} 0 & \frac{\alpha_3 S_H^*}{N_H} & 0 & \frac{\alpha_1 S_H^*}{N_H} \\ 0 & 0 & 0 & 0 \\ 0 & \frac{\alpha_2 S_M^*}{N_M} & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} \tag{10}$$

$$V = \begin{bmatrix} (\sigma_1 + \mu_1) & 0 & 0 & 0 \\ -\sigma_1 & (\gamma + \mu_1 + \delta_1) & 0 & 0 \\ 0 & 0 & (\sigma_2 + \mu_2) & 0 \\ 0 & 0 & -\sigma_2 & (\mu_2 + \delta_2) \end{bmatrix} \tag{11}$$

$$V^{-1} = \begin{bmatrix} \frac{1}{\sigma_1 + \mu_1} & 0 & 0 & 0 \\ \frac{\sigma_1}{(\sigma_1 + \mu_1)(\gamma + \mu_1 + \delta_1)} & \frac{1}{(\gamma + \mu_1 + \delta_1)} & 0 & 0 \\ 0 & 0 & \frac{1}{\sigma_2 + \mu_2)} & 0 \\ 0 & 0 & \frac{\sigma_2}{(\sigma_2 + \mu_2)(\mu_2 + \delta_2)} & \frac{1}{(\mu_2 + \delta_2)} \end{bmatrix}$$

$$FV^{-1} = \begin{bmatrix} \frac{S_H^* \alpha_3 \sigma_1}{(\sigma_1 + \mu_1)(\gamma + \mu_1 + \delta_1) N_H^*} & \frac{S_H^* \alpha_3}{(\gamma + \mu_1 + \delta_1) N_H^*} & \frac{S_H^* \alpha_1 \sigma_2}{(\sigma_2 + \mu_2)(\mu_2 + \delta_2) N_M^*} & \frac{S_H^* \alpha_1}{(\mu_2 + \delta_2)} \\ 0 & 0 & 0 & 0 \\ \frac{S_M^* \alpha_2 \sigma_1}{(\sigma_1 + \mu_1)(\gamma + \mu_1 + \delta_1) N_M^*} & \frac{S_M^* \alpha_2}{(\gamma + \mu_1 + \delta_1) N_M^*} & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

$$R_0 = \frac{(\sigma_2+\mu_2)(\mu_2+\delta_2)\alpha_3\sigma_1 N_M^* S_H^* + \sqrt{\begin{matrix}\left((\sigma_2+\mu_2)(\mu_2+\delta_2)\alpha_3\sigma_1 N_M^* S_H^*\right)^2 \\ +4(\sigma_1+\mu_1)(\gamma+\mu_1+\delta_1)(\sigma_2+\mu_2)(\mu_2+\delta_2)N_M^* N_H^* \alpha_1\alpha_2\sigma_1\sigma_2 S_M^* S_H^*\end{matrix}}}{2(\sigma_1+\mu_1)(\gamma+\mu_1+\delta_1)(\sigma_2+\mu_2)(\mu_2+\delta_2)N_M^{**} N_H^{**}}$$

(12)

Interpretation of R_0

Susceptible mosquito acquire infection following effective contact with an infected human I_H. The number of mosquito infections generated by an infectious human is given by the product of the infectious rate of infectious human α_2, the probability that an exposed human survives the exposed stage and move to the infectious compartment $\frac{\sigma_1}{(\sigma_1+\mu_1)}$ and the average duration of the infectious period $\frac{1}{(\gamma+\mu_1+\delta_1)}$. The average number of new mosquito infections generated by one infected human, $S_H^* \frac{\alpha_2\sigma_1}{(\gamma+\mu_1+\delta_1)(\sigma_1+\mu_1)}$ (13)

Similarly, susceptible human acquire infection either following effective contact with infected mosquito or being transfused with an infected human blood. The number of human infections generated by an infected mosquito is the product of the infectious rate of infected mosquito $\frac{\alpha_1}{N_H^*}$, the probability that an exposed mosquito survived the exposed stage and moved the infectious compartment $\frac{\sigma_2}{(\sigma_2+\mu_2)}$, and the average duration in the infectious compartment. $\frac{1}{(\mu_2+\delta_2)}$. Thus the average number of new human infections generated by one infectious mosquito, $R_{MH} = S_M^* \frac{\sigma_2\alpha_1}{(\mu_2+\delta_2)(\sigma_2+\mu_2)N_H^*}$.

(14)

Further, the number of human infections generated by an infectious human is the product of the infectious rate of human $\frac{\alpha_3}{N_H^*}$, the probability that an exposed human survives the exposed period and move to the infectious compartment $\frac{\sigma_1}{(\sigma_1+\mu_1)}$, and the average duration of the infectious period $\frac{1}{(\gamma+\mu_1+\delta_1)}$. Thus, the average number of new human infections generated by one infectious human, $R_{HH} = S_H^* \frac{\sigma_1\alpha_3}{(\gamma+\mu_1+\delta_1)(\sigma_1+\mu_1)N_H^*}$ (15)

From (13), (14) and (15), (12) can be written as $R_0 = \frac{1}{2}\left[R_{HH} + \sqrt{(R_{HH})^2 + 4R_{HM}R_{MH}}\right]$.

Where $\sqrt{R_{HM}R_{MH}}$ is the R_0 for mosquito $\Leftrightarrow$ human transmission only, the $\frac{1}{2}$ and 4 that appear in the expression results from averaging two modes of transmission, mosquito and human based. The square root accounts for the generation of two populations while the square in $(R_{HH})^2$ is to balance the mosquito $\Leftrightarrow$ human transmission

Theorem 1 The disease free equilibrium is locally asymptotically stable when $R_0 < 1$ and unstable when $R_0 > 1$.

Proof The local stability of the disease free equilibrium is a direct consequence of [32] and shows that the model equations (1) to (7) satisfies five assumptions $A_1 - A_5$ in [32], and that ends

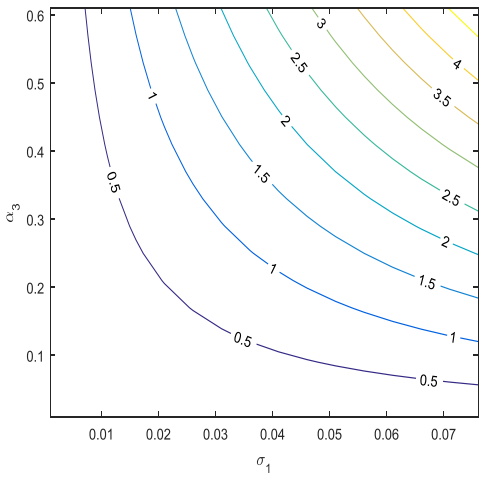

Figure 3

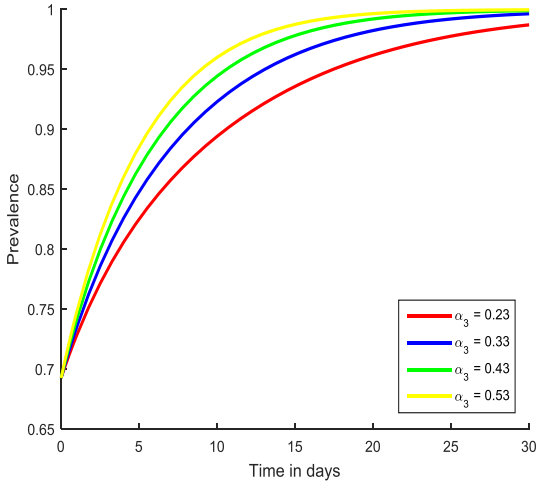

figure 4

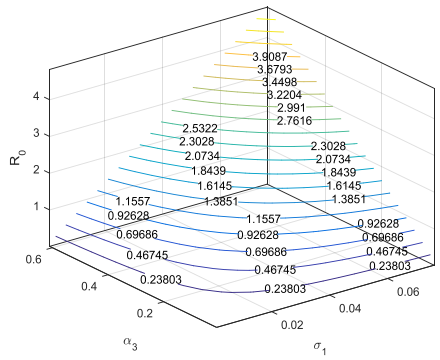

Figure 3. Simulation of the model showing a 2D contour plot of the basic reproductive number R_0 as a function of human to human infection rate α_3, and progression rate from exposed to infectious human σ_1, parameter values are as shown in table 1.

Figure 4: simulation of the prevalence of TTM as function of the human to human infection rate α_3.

The above figure underscores the long neglected transfusion transmitted malaria. The prevalence of the diseases is seen to increase with increase in contact rate due to transfusion.

Figure 5: Simulation of the model showing a 3D contour plot of the basic reproductive number R_0 as a function of human to human infection rate α_3, and progression rate from exposed to infectious human σ_1, parameter values are as shown in table 1.

3.3 **Global stability of disease free equilibrium**

To ascertain the global stability of the disease free equilibrium (DFE) we adopt the approach of [32, 36, 37]. Consider the infected compartment of the model equations (1) to (7)

$$\frac{dE(t)}{dt} = \frac{\alpha_1 S_H I_M}{N_H} + \frac{\alpha_2 S_H I_H}{N_H} - (\sigma_1 + \mu_1)E$$

$$\frac{dI_H(t)}{dt} = \sigma_1 E - (\gamma + \mu_1 + \delta_1)I_H \qquad (16)$$

$$\frac{dE_M(t)}{dt} = \frac{\alpha_2 S_M I_H}{N_H} - (\sigma_2 + \mu_2)I_M$$

$$\frac{dI_M(t)}{dt} = \sigma_2 E_M - (\mu_2 + \delta_2)I_M$$

let F_i be the rate of appearance of new infections in compartment i and $V_i = V_i^- - V_i^+$ be the difference between the rate of transfer of individual out of and into compartment i by all other means, we can write (16) in terms of $F_i - V_i$ (rate of transfer in compartment i), taking the Jacobian of F_i and V_i as F and V respectively, we have:

$$\begin{bmatrix} \dot{E}_H \\ \dot{I}_H \\ \dot{E}_M \\ \dot{I}_M \end{bmatrix} = (F-V) \begin{bmatrix} \dot{E}_H \\ \dot{I}_H \\ \dot{E}_M \\ \dot{I}_M \end{bmatrix} - \begin{bmatrix} 0 \\ \gamma_1 I_H \\ 0 \\ \gamma_2 I_M \end{bmatrix} \quad (17)$$

thus,

$$\begin{bmatrix} \dot{E}_H \\ \dot{I}_H \\ \dot{E}_M \\ \dot{I}_M \end{bmatrix} < (F-V) \begin{bmatrix} \dot{E}_H \\ \dot{I}_H \\ \dot{E}_M \\ \dot{I}_M \end{bmatrix}$$

We write equations (1) to (7) as $Df(x_i)$ for $i = 1,2,...,n$ where $i = 1,2,...,m$ are components in the infectious compartments, and $m < n$. Using E_0 as the DFE which is locally asymptotically stable and considering conditions (i) to (v) in Lemma 1 in [32] we rewrite the Jacobian matrix of (1) to (7) at E_0 as a block matrix;

$$J_{E_0} = \begin{bmatrix} \Delta_1 & 0 \\ \Delta_2 & \Delta_3 \end{bmatrix} \quad (18)$$

Δ_1 is a non - singular matrix (F – V) and Δ_3 has eigenvalues with negative real parts. Based on the [32], inequality (17) is stable when $R_0 < 1$. And it follows from [34, 37] that as $t \to \infty$, then $(E_H, I_H, E_M, I_M), t \to E_0$ which implies that E_0 is globally asymptotically stable (GAS)

3.4 Existence of endemic equilibrium

This is an equilibrium state where at least one of the infected compartments is non-zero. In order to find the Endemic equilibrium for our model equations (1) to (7), the following steps are taken. We let $E_1 = \left(S_H^{**}, E_M^{**}, I_H^{**}, R_M^{**}, S_M^{**}, E_M^{**}, I_M^{**}\right)$ represent any arbitrary point of the Endemic Equilibrium of our model equations (1) to (7), further, let;

$$\lambda_H^{**} = \frac{(\alpha_1 I_M^{**} + \alpha_3 I_H^{**})}{N_H^{**}} \text{ and } \lambda_M^{**} = \frac{(\alpha_2 I_H^{**})}{N_H^{**}} \quad (19)$$

Further we let

$$\left.\begin{aligned} K_1 = \rho + \mu_1, K_2 = \sigma_1 + \mu_1, K_3 = \gamma + \mu_1 + \delta_1, K_4 = \psi + \mu_1, \\ K_5 = \mu_2, K_6 = \sigma_2 + \mu_2, K_7 = \mu_2 + \delta_2 \end{aligned}\right\} \quad (20)$$

Such that the right hand side of our basic model (1) to (7) becomes

$$\left.\begin{aligned} &\Lambda_H + \psi R_H^{**} - \lambda_H^{**} S_H^{**} - K_1 \lambda S_H^{**} = 0 \\ &\lambda_H^{**} S_H^{**} - K_2 E_H^{**} = 0 \\ &\sigma_1 E_H^{**} - K_3 I_H^{**} = 0 \\ &\gamma I_H^{**} + \rho S_H^{**} - K_4 R_H^{**} = 0 \\ &\Lambda_M - \lambda_M^{**} S_M^{**} - K_5 S_M^{**} = 0 \\ &\lambda_M^{**} S_M^{**} - K_6 E_M^{**} = 0 \\ &\sigma_2 E_M^{**} - K_7 I_M^{**} = 0 \end{aligned}\right\} \quad (21)$$

Solving (21) we have;

$$\left.\begin{aligned}
S_H^{**} &= \frac{\Lambda_H\left[\rho\gamma\sigma_1(K_1+\lambda_H^{**})-\psi K_1(\gamma\lambda_H^{**}\sigma_1K_4+\rho)\right]}{\lambda_H^{**}\rho K_1\gamma\sigma_1}\\
E_H^{**} &= \frac{\Lambda_H\left[\rho\gamma\sigma_1(K_1+\lambda_H^{**})-\psi K_1(\gamma\lambda_H^{**}\sigma_1K_4+\rho)\right]}{\rho\gamma\sigma_1K_1K_2}\\
I_H^{**} &= \frac{\Lambda_H\left[\rho\gamma\sigma_1(K_1+\lambda_H^{**})-\psi K_1(\gamma\lambda_H^{**}\sigma_1K_4+\rho)\right]}{\rho\gamma K_1K_2K_3}\\
R_H^{**} &= \frac{(K_2K_3\rho-\lambda_H^{**}\gamma\sigma_1)\Lambda_H\left[\rho\gamma\sigma_1(K_1+\lambda_H^{**})-\psi K_1(\gamma\lambda_H^{**}\sigma_1K_4+\rho)\right]}{\rho\gamma K_1K_2K_3K_4}\\
S_M^{**} &= \frac{\Lambda_M}{\lambda_M^{**}-K_5}\\
E_M^{**} &= \frac{\lambda_M^{**}K_7\sigma_2\Lambda_M}{\sigma_2(\lambda_M^{**}-K_5)K_6K_7}\\
I_M^{**} &= \frac{\lambda_M^{**}\sigma_2\Lambda_M}{(\lambda_M^{**}-K_5)K_6K_7}
\end{aligned}\right\} \quad (22)$$

Substituting (22) into (19) we have;

$$\lambda_m^{**} = \frac{\alpha_2\Lambda_H\left[\rho\gamma\sigma_1(K_1+\lambda_H^{**})-\psi K_1(\gamma\lambda_H^{**}\sigma_1K_4+\rho)\right]}{\rho\gamma K_1K_2K_3N_H^{**}} \quad (23)$$

and

$$\lambda_H^{**} = \frac{\alpha_1\lambda_M^{**}\sigma_2\Lambda_M}{N_H^{**}(\lambda_M^{**}-K_5)K_6K_7} + \frac{\alpha_3\Lambda_H\left[\rho\gamma\sigma_1(K_1+\lambda_H^{**})-\psi K_1(\gamma\lambda_H^{**}\sigma_1K_4+\rho)\right]}{N_H^{**}\rho\gamma K_1K_2K_3} \quad (24)$$

Substituting (23) into (24) it can be shown that the non-zero equilibrium of the model equation is described by the quadratic equation in terms of (λ_H^{**}) given below

$$A(\lambda_H^{**})^2 + B\lambda_H^{**} + C = 0 \quad (25)$$

where

$$A = \alpha_2\Lambda_H\gamma^2\sigma_1(\rho-\psi K_1K_4)K_6K_7\rho K_1K_2K_3,$$

$$B = (N_H^{**})^2K_6K_7\gamma\rho^2K_1^2K_2K_3 - \alpha_1\Lambda_M\sigma_2\alpha_2\Lambda_H\gamma^2\sigma_1(\rho-\psi K_1K_4)K_1K_2K_3N_H^{**} - \alpha_3\Lambda_H\gamma\sigma_1(\rho-\psi K_1K_4),$$

$$C = \gamma^2K_2^2K_3^2K_5(N_H^{**})^2 + \alpha_2\Lambda_H\rho^2K_1^2(\gamma\sigma_1-\psi)K_2K_3N_H^{**} + \alpha_2\Lambda_H\rho K_1(\gamma\sigma_1-\psi).$$

Thus, the positive endemic equilibrium of the model (1) to (7) can be obtained by solving (25) and substituting into (22). It can be seen that the coefficient A of (25) is always positive while C is positive if R_0 is less than unity and negative if R_0 greater than unity. Thus the following result is claimed.

Theorem 2. The basic model given by (1) to (7) is characterized by

one unique endemic equilibrium if $B<0,$ and $C=0$ or $B^2-4AC=0,$

one unique endemic equilibrium if $C<0 \Leftrightarrow R_0>1,$

two endemic equilibrium if $C>0, B<0$ and $B^2-4AC>0,$

no endemic equilibrium otherwise.

Case (iii) above suggest the possibility of backward bifurcation where local stability of DFE co-exist with endemic equilibrium even when $R_0<1$. This prompted the bifurcation analysis.

3.5 Local stability of Endemic Equilibrium and Bifurcation analysis

To prove that the endemic equilibrium (22) of the model (1) to (7) is locally asymptotically stable, we perform bifurcation analysis at the DFE using the Centre Manifold theorem as described in [38].

In order to apply this theorem, we first make the following change of variables. Let

$S_H = x_1, E_H = x_{2,}, I_H = x_3 = R_H = x_4, S_M = x_5, E_M = x_6, I_M = x_7$, so that $N_H = x_1 + x_{2,} + x_3 + x_4$ and $N_M = x_5 + x_6 + x_7$ further, using the vector notation, $X = (x_1, x_{2,}, x_3 x_4, x_5, x_6, x_7)^T$.

Then our model equations (1) to (7) can be written in the form

$\frac{dx}{dt} = (f_1, f_{2,}, f_3, f_4, f_5, f_6, f_7)^T$, such that:

$$\frac{dx_1}{dt} = f_1 = \Lambda_H + \psi x_4 - \frac{\alpha_1 x_1 x_7 + \alpha_3 x_1 x_3}{x_1 + x_{2,} + x_3 + x_4} - k_1 x_1$$

$$\frac{dx_2}{dt} = f_2 = \frac{\alpha_1 x_1 x_7 + \alpha_3 x_1 x_3}{x_1 + x_{2,} + x_3 + x_4} - k_2 x_2$$

$$\frac{dx_3}{dt} = f_3 = \sigma_1 x_2 - k_3 x_3$$

$$\frac{dx_4}{dt} = f_4 = \gamma x_3 + \rho x_1 - k_4 x_4$$

$$\frac{dx_5}{dt} = f_5 = \Lambda_M - \frac{\alpha_2 x_5 x_3}{x_1 + x_{2,} + x_3 + x_4} - k_5 x_5 \qquad (26)$$

$$\frac{dx_6}{dt} = f_6 = \frac{\alpha_2 x_5 x_3}{x_1 + x_{2,} + x_3 + x_4} - k_6 x_6$$

$$\frac{dx_7}{dt} = f_7 = \sigma_2 x_6 - k_7 x_7$$

From (11b), (20) and (26)

Suppose that ϕ^* is taken as the bifurcation parameter, where $\phi^* = \alpha_3$, and considering where the basic reproductive number $R_0 = 1$, then solving for ϕ in R_0, we have;

$$\alpha_3 = \frac{2K_2K_3K_6K_7N_M^{**}N_H^{**}}{\left(K_6K_7\sigma_1N_M^*S_H^*\right)^2 + 4K_2K_3K_6K_7N_M^{**}N_H^{**}\alpha_1\alpha_2\sigma_1\sigma_2S_M^*S_H^*}$$

then linearizing (26) at DFE point E_0 when $\phi = \phi^*$ gives the Jacobian J_0^* which has a trivial zero eigenvalues, while the rest eigenvalues has negative real part.

$$J_0^* = \begin{bmatrix} -K_1 & 0 & -\frac{x_1^*\alpha_3^*}{x_1^*+x_4^*} & \psi & 0 & 0 & -\frac{\alpha_1 x_1^*}{x_1^*+x_4^*} \\ 0 & -K_2 & \frac{x_1^*\alpha_3^*}{x_1^*+x_4^*} & 0 & 0 & 0 & \frac{\alpha_1 x_1^*}{x_1^*+x_4^*} \\ 0 & \sigma_1 & -K_3 & 0 & 0 & 0 & 0 \\ \rho & 0 & \gamma & -K_4 & 0 & 0 & 0 \\ 0 & 0 & -\frac{\alpha_2 x_5^*}{x_1^*+x_4^*} & 0 & -K_5 & 0 & 0 \\ 0 & 0 & \frac{\alpha_2 x_5^*}{x_1^*+x_4^*} & 0 & 0 & -K_6 & 0 \\ 0 & 0 & 0 & 0 & 0 & \sigma_2 & -K_7 \end{bmatrix}$$

The theorem is produced below for convenience.

Theorem 3 Consider the following general system of ordinary differential equations with a parameter ϕ.

$$\frac{dx}{dt} = f(x,\phi): R^n \times R \to R^n \quad \text{and} \quad f \varepsilon C^2(R^n \times R) \qquad (30)$$

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

(A1) $A = D_x f(0,0) = \left(\frac{\partial f_i}{dx_j}(0,0)\right)$ is the linearization matrix of the system (30) around the equilibrium 0 with ϕ evaluated at 0;

(A2) Zero is a simple eigenvalues of A and other eigenvalues of A have negative real parts;

(A3) Matrix A has a right eigenvector w and left eigenvector v (each corresponding to zero eigenvalues). Let f_k be the kth component of f and;

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

then, the local dynamics of the system (30) around equilibrium point 0 is totally determined by the signs of a and b, particularly,

$a > 0, b > 0,$ when $\phi < 0$ with $|\phi| << 1$ 0 is locally asymptotically stable and there exists a positive unstable equilibrium;

when $0 < \phi << 1$, 0 is unstable and there exists a negative, locally asymptotically stable equilibrium;

(ii) $a < 0, b < 0,$ when $\phi < 0$ with $|\phi| << 1$, 0 is unstable; when $0 < \phi << 1$, 0 is locally asymptotically stable equilibrium and there exists a positive unstable equilibrium;

(iii) $a < 0, b > 0,$ when ϕ changes from negative to positive, 0 changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable

Eigenvectors

The Jacobian J_0^* has right eigenvector associated with the trivial eigenvalues zero given by

$w = [w_1, w_2, w_3, w_4, w_5, w_6, w_7]^T$.

$$\left.\begin{aligned}
-K_1 w_1 - \frac{x_1^* \alpha_3^*}{x_1^* + x_4^*} w_3 + \psi w_4 - \frac{\alpha_1 x_1^*}{x_1^* + x_4^*} w_7 &= 0 \\
-K_2 w_2 + \frac{x_1^* \alpha_3^*}{x_1^* + x_4^*} w_3 + \frac{\alpha_1 x_1^*}{x_1^* + x_4^*} w_7 &= 0 \\
\sigma_1 w_2 - K_3 w_3 &= 0 \\
\rho w_1 + \gamma w_3 - K_4 w_4 &= 0 \\
-\frac{\alpha_2 x_5^*}{x_1^* + x_4^*} w_3 - K_5 w_5 &= 0 \\
\frac{\alpha_2 x_5^*}{x_1^* + x_4^*} w_3 - K_6 w_6 &= 0 \\
\sigma_2 w_6 - K_7 w_7 &= 0
\end{aligned}\right\} \qquad (27)$$

Solving (27), we have;

$$\left.\begin{aligned}
w_1 &= -\frac{x_1^* \alpha_3^*}{K_1 (x_1^* + x_4^*)} (w_3 + w_7) + \frac{\psi w_4}{K_1}, \\
w_2 &= \frac{\alpha_1 x_1^*}{K_2 (x_1^* + x_4^*)} (w_3 + w_7), \\
w_3 &= w_3 > 0, \\
w_4 &= \frac{\rho w_1 + \gamma w_3}{K_4}, \\
w_5 &= -\frac{\alpha_2 x_5^*}{(x_1^* + x_4^*) K_5} w_3, \\
w_6 &= \frac{\alpha_2 x_5^*}{(x_1^* + x_4^*) K_6} w_3, \\
w_7 &= \frac{\sigma_2 w_6}{K_7}.
\end{aligned}\right\} \qquad (28)$$

Similarly the left eigenvalues of J_0^* corresponding to the trivial eigenvalue zero is $v = [v_1, v_2, v_3, v_4, v_5, v_6, v_7]$.

$$\left.\begin{aligned} -K_1 v_1 + \rho v_4 &= 0 \\ -K_2 v_2 + \sigma_1 v_3 &= 0 \\ -\frac{x_1^* \alpha_3^*}{x_1^* + x_4^*} v_1 + \frac{x_1^* \alpha_3^*}{x_1^* + x_4^*} v_2 - K_3 v_3 + \gamma v_4 - \frac{\alpha_2 x_5^*}{x_1^* + x_4^*} v_5 + \frac{\alpha_2 x_5^*}{x_1^* + x_4^*} v_6 &= 0 \\ \psi v_1 - K_4 v_4 &= 0 \\ -K_5 v_5 &= 0 \\ \sigma_2 v_7 - K_6 v_6 &= 0 \\ -\frac{\alpha_1 x_1^*}{x_1^* + x_4^*} v_1 + \frac{\alpha_1 x_1^*}{x_1^* + x_4^*} v_2 - K_7 v_7 &= 0 \end{aligned}\right\} \quad (29)$$

By solving (29), we have;

$$v_1 = \frac{\rho v_4}{-K_1},$$

$$v_2 = \frac{\sigma_1 v_3}{K_2},$$

$$v_3 = v_3 > 0$$

$$v_4 = \frac{\psi v_1}{K_4},$$

$$v_5 = 0,$$

$$v_6 = \frac{\sigma_2 v_7}{K_6},$$

$$v_7 = \frac{\alpha_1 x_1^*}{K_7 (x_1^* + x_4^*)}(v_1 - v_2).$$

Computation of a and b

Since $-\rho$ for $k = 5,$ then $k = 1,2,3,4,6,7$ should be considered. That is, the following functions will be used to find a and b from the system.

$$f_2 = \frac{\alpha_1 x_1 x_7 + \phi^* x_1 x_3}{x_1 + x_{2,} + x_3 + x_4} - k_2 x_2$$

$$f_6 = \frac{\alpha_2 x_5 x_3}{x_1 + x_{2,} + x_3 + x_4} - k_6 x_6$$

But at DFE $N_H = S_H + R_H = \frac{\Lambda_H (\rho + (\psi + \mu_1))}{(\psi + \mu_1)(\rho + \mu_1) - \rho}$

Hence, the associated non-zero partial of f at the DFE for $f = f_2, f_6$ are given by;

$$\frac{\partial^2 f_2}{\partial x_1 x_7} = \frac{\alpha_1 (\psi + \mu_1)(\rho + \mu_1) - \rho}{\Lambda_H \left(\rho + (\psi + \mu_1)\right)}, \frac{\partial^2 f_2}{\partial x_1 x_3} = \frac{\phi^* (\psi + \mu_1)(\rho + \mu_1) - \rho}{\Lambda_H \left(\rho + (\psi + \mu_1)\right)}, \frac{\partial^2 f_6}{\partial x_5 x_3} = \frac{\alpha_2 (\psi + \mu_1)(\rho + \mu_1) - \rho}{\Lambda_H \left(\rho + (\psi + \mu_1)\right)}$$

$$\frac{\partial^2 f_2}{\partial \phi x_3} = \frac{\Lambda_H (\psi + \mu_1)}{(\psi + \mu_1)(\rho + \mu_1) - \rho}$$ Therefore,

$$a = v_2 w_1 w_7 \frac{\alpha_1(\psi+\mu_1)(\rho+\mu_1)-\rho}{\Lambda_H\left(\rho+(\psi+\mu_1)\right)} + v_2 w_1 w_3 \frac{\phi^*(\psi+\mu_1)(\rho+\mu_1)-\rho}{\Lambda_H\left(\rho+(\psi+\mu_1)\right)} + v_6 w_5 w_3 \frac{\alpha_2(\psi+\mu_1)(\rho+\mu_1)-\rho}{\Lambda_H\left(\rho+(\psi+\mu_1)\right)}$$ and

$$= \frac{(\psi+\mu_1)(\rho+\mu_1)-\rho}{\Lambda_H\left(\rho+(\psi+\mu_1)\right)}\left[v_2 w_1\left(w_7\alpha_1 + w_3\phi^*\right) + v_6 w_5 w_3 \alpha_2\right]$$

$$b = v_6 w_3 \frac{\Lambda_H(\psi+\mu_1)}{(\psi+\mu_1)(\rho+\mu_1)-\rho} > 0$$

As a corollary to the above when $a > 0, b > 0,$ the bifurcation at $\phi = 0$ is subcritical (backward bifurcation)

Conclusion

The model in this paper represents the transmission of malaria between the mosquito and human population. Two major assumption were made;

That transmission from human to human via blood transfusion is significant in malaria endemic regions as pointed out by relevant literatures here cited.

The model also assumed that susceptible human in same endemic areas develops a sterilizing immunity as a result of their long stay in such communities. This second assumption is quite different from what is common in the literature where human acquire immunity upon recovery from infection.

The model has a DEF that's is locally and globally stable and an endemic equilibrium which coexist with DEF even when $R_0 < 1$, thus suggesting the phenomena of backward bifurcation. Contour map of the basic reproductive number R_0 as function of the transmission rate (human to human) α_3 and the progression rate from exposed human to infected human σ_1 shows the range of values of α_3 for which R_0 is ≤ 1 and ≥ 1 figure 3 and figure 4. Simulation of the prevalence as a function α_3 is also given in figure 5 while figures I and 2 respectively depicts the four human subpopulations and the various populations of the model.

Reference

[1] World Health Organization (2016). World malaria report http://www.who.int/malaria/publications/world-malaria-report-2016/report/en/ (Retrieved December 2017)

[2] World Health Organization (2017). World malaria report 2017. Geneva Licence: CC BY-NC-SA 3.0 IGO. Available online https://creativecommons.org/licenses/by-nc-sa/3.0/igo). (Retrieved December 2017)

[3] Kitchen, A. D., Vox, S., Chiodini, P. L. (2006). Malaria and blood transfusion. *PubMed*. DOI:10.1111/j.1423-0410.2006.00733.x

[4] Owusu-Ofori, A.K., Parry, C., Bates, I (2010) Transfusion-transmitted malaria in countries where malaria is endemic: a review of the literature from sub-Saharan Africa. Clin Infect Dis 51: 1192-1198.

[5] Evan, M. B, Marion, V., and Edward, M. (2011) Blood Transfusion Safety in Africa: A Literature Review of Infectious Disease and Organizational Challenges transfuse med rev 26(2) 164-180 doi: 10.1016/j.tmrv.2011.07.006**.**

[6] Owusu-Ofori, A., Gadzo, D., and Bates, I (2016) Transfusion-transmitted malaria: donor prevalence of parasitaemia and a survey of healthcare workers knowledge and practices in a district hospital in Ghana. *Malaria Journal*201615:234 https://doi.org/10.1186/s12936-016-1289-3.

[7] Mogtomo, M. L. K., Foko, L. P. K, Okoubalimba, E. V. A, Enyegue, E. E .and Ngane, A. R. N. (2016) High Risk of Transfusion-Transmitted Malaria (TTM) from Student Blood Donors Living in the Town of Douala, Cameroon. J Clin Infect Dis Pract 1:108. doi: 10.4172/2476-213X.1000108.

[8] Ebongho, C. O., Dongho, E. N and Moukoko, C. E. (2017). Residual risk of transmission transmitted malaria in a malaria endemic sub-Saharan African setting. *Translational Medicine Communication*. http//doi.org10.1186/s4123-9.

[9] Oladeinde, B. H., Omoregie, R., Osakue, E. O., and Onaiwu, O. T. (2014) Asymptomatic Malaria among Blood Donors in Benin City Nigeria. Iranian J Parasitol 9: 415-422.

[10] Okocha, E. C., Ibeh, C. C., Ele, P. U., Ibeh, N. C. (2005). The prevalence of malaria parasitaemia in blood donors in a Nigerian teaching hospital. J Vector Borne Dis 42: 21- 24.

[11] Agboola, T. F., Ajayi, M. B., Adeleke, M. A, Gyang, P. V (2010) Prevalence of malaria parasite among blood donors in Lagos University teaching hospital, Lagos Nigeria. Ann Bio Res 1: 72-75.

[12] Erhabor O, Awah I, Uko, K. E, Charles, A. T. (2007) The prevalence of Plasmodia parasitaemia among donors in the Niger delta of Nigeria. Trop Doct 37: 32-34.

[13] Chitnis N, Cushing, J. M., Hyman, J. M. (2006) Bifurcation analysis of a mathematical model for malaria transmission. *SIAM J Appl Math*. 67:24-45

[14] Koella, J. C, Antia, R. (2003) Epidemiological models for the spread of anti-malarial resistance. *Malar J*, 2:3.

[15] Ngwa, G. A, Shu, W. S. (2000). A mathematical model for endemic malaria with variable human and mosquito populations. *Math Comput Model*, 32:747-763.

[16] Torres-Sorando L, Rodriguez, D. J. Models of spatio-temporal dynamics in malaria. *Ecol Model* 1997, 104:231-240.

[17] Filipe, J. A. N., Riley, E. M., Darkeley, C. J., Sutherland, C. J., Ghani, A. C. (2007). Determination of the processes driving the acquisition of immunity to malaria using a mathematical transmission model. *PLoS Comput Biol*., 3:2569-2579

[18] Yang, H. M. (2000). Malaria transmission model for different levels of acquired immunity and temperature-dependent parameters (vector). *Revista de Saúde Pública*, 34:223-231.

[19] Bakary, T., Boureima, S., and Sado, T. (2017). A Mathematical Model of Malaria Transmission with Structured Vector Population and Seasonality *Journal of Applied Mathematics* Volume 2017.

[20] Bakere, E. A., and Nwozo, C. R. (2015). Mathematical analysis of the dynamics of malaria disease transmission. *International Journal of Pure and Applied Mathematics*. 99 (4).

[21] Bai, Z., Peng, R., and Zhao, X. Q. (2017). A reaction-diffusion malaria model with seasonality and incubation period. *J. Math Biol*. doi: 10.1007/s00285-017-1193-7. [Epub ahead of print].

[22] Wang, X., and Zhao, X. Q. (2017). A climate-based malaria model with the use of bed nets. *J Math Biol.* doi: 10.1007/s00285-017-1183-9. [Epub ahead of print]

[23] Mojeeb, A. E. O., Isaac, K. A. (2017) Simple Mathematical Model for Malaria Transmission *Journal of Advances in Mathematics and Computer Science.* 25(6): 1-24.

[24] Oei, W, Janssen, M. P, van der Poel, C. L, van Steenbergen, J. E, Rehmet, S. Kretzschmar, M. E. E.(2013) Modeling the transmission risk of emerging infectious. Transfusion 53(7):1421-8. doi: 10.1111/j.1537-2995.2012.03941.x.

[25] Garba, S. M., Gumel, A. B., Abu Bakar, . M. R. (2009). Backward bifurcation in dengue transmission dynamics. Mathematical Bioscience DOI: 10.1016/j.mbs.2008.05.002

[26] Chitnis, N., Hyman, J. M and Cushing, J. M (2008), "Determining important parameters in the spread of malaria through the sensitivity analysis of a mathematical model", *Math. Bio.*, Volume 70, pp 1272-1296.

[27] Blayneh, K., Cao, Y., and Kwon, H. (2009), "Optimal Control of Vector-borne Diseases: Treatment and Prevention", *Discrete and Continuous Dynamical Systems Series B*, Volume 11, No.3.

[28] Esteva, L. and Vargas, C. (1998). Analysis of a dengue disease transmission model. *Mathematical Biosciences.* 150: 131-151.

[29] Lakshmikantham, V. S., Leela and Martynyuk, A. A., (1989). Stability Analysis of Nonlinear Systems. Marcel Dekker, Inc., New York and Basel.

[30] Hethcote, H. W., (2000). The mathematics of infectious diseases. *SIAM Review*.42: 599- 653.

[31] Hethcote, H.W. (1978). An Immunization Model for Heterogeneous Population. *Theoretical Population Biology* 14(1978) 338-349

[32] Driessche, V. P., and Wathmough, J. (2002). Reproductive Number and Sub-Threshold Endemic Eqilibria for Compartment Modelling of Disease Transmission. *Mathematics Bioscience 180:29-48.*

[33] Dietz, K. (1993). The Estimation of basic reproductive number R_0 for infectious disease, *Statistical Methods in Medical Research*, 2, 23-41.

[34] Roberts, M. G. and Heesterbeek J. A. P. (2003). A new method for estimating the efforts require to control an infectious disease, *proceeding of the Royal Society of London Series* B, 270 pp. 1359-1364.

[35] Diekmann O., J. A., Heesterbeek, J. A. P. and Metz, J.(1990). On the definition and computation of basic reproductive ratio R_0 in the model for infectious disease in a heterogeneous population, *Journal of Mathematical Biology*, 28, 365-382.

[36] Musekwa, S., Nyabadza, C. Chiyaka, C, Das, P. Tripathi, A., Mukandavira, Z. (2011) Modelling and analysis of the effctes of malnutrition in the spread of cholera. *Mathematical and computer modelling* .53(1583).

[37] Nampal, H., Luboobi, L. S., Mugisha, J. T. Y., and Obua, C. (2013). Mathematical modelling of liver enzyme elevation in HIV mono-infection. Mathematical Biosciences.

[38] Castill- Chavez, C., and Song, B. (2004). *Dynamical Model of Tuberculosis and Applications*. Lournal of Mathematical Bioscience and Engineering, 1(2), 361-404.