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Dynamical Model of Malaria Infection and S-gene Frequency in the Presence of Treatment: Picard's Existence and Uniqueness of Solution

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Abstract:- Malaria remains one of the major public health problems. However, heterozygous individuals for S-gene experience some protection from malaria infections. Various explanations of the mechanism of this protection have been offered, but the investigation of the effects of malaria treatment among individuals of different genotypes is not common. In this research, the interaction between the dynamics of malaria and S-gene frequency in the presence of malaria treatment was examined. The aim was to examine the effect of malaria treatment and the frequencies of A-gene and S-gene on malaria infection. To achieve this, a mathematical model was developed.

It was shown that the mathematical model which represents the physical system is both epidemiologically feasible and mathematically well posed. This is done by carrying out a classical qualitative proof of the existence and uniqueness of solution to the governing equation of the physical system. It was concluded that it is sufficient to study the dynamics of the model in the defined region, D.

Keywords:- *Malaria, S-gene frequency, Treatment, Mathematical model, Existence and Uniqueness of Solution.*

I. INTRODUCTION

Malaria, an infectious disease, is caused by the parasites of the genus *plasmodium* from the protozoa group. It can be transmitted from an individual to another through bites of infected female *anopheles* mosquitoes, which is the vector of malaria. Four different species of parasite exists which lead to malaria infection among humans. These are: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae* and *Plasmodium ovale*. In Africa and South East Asia, *Plasmodium falciparum* is the most common cause of malaria and is responsible for approximately 80% of all cases with approximately 90% deaths [1]. It has the ability to attack all red blood cells and causes them to clamp together thereby blocking vessels in vital organs and enlargement of the spleen makes it a common species [2].

The signs and symptoms of malaria typically begin 7-30 days after infection. Initial manifestations of the disease, common to all malaria species, are similar to flu-like symptoms [3], and can resemble other conditions such as sepsis, gastroenteritis and viral diseases [4]. The signs and symptoms may include headache, fever, shivering, joint pain, vomiting, haemolytic anaemia, jaundice, haemoglobin in the urine, retina damage, and convulsion [5]. Malaria has several serious complications. Among these is the development of respiratory distress which occurs in up to 25% of adults, 40% of children and up to 29% of pregnant women with severe *P. falciparum* malaria [6] Malaria in pregnant women is an important cause of stillbirths, infant mortality, abortion and low birth weights [7] particularly in *P. falciparum* infection but also with *P. vivax* [8].

Following a laboratory test confirming the existence of the parasite, malaria is treated using medications such as chloroquine, sulfadoxine-pyrimethamine (Fansidar), mefloquine (Lariam) and quinine, artemisinin-based combination therapy (ACT) and intravenous therapy (I.V), etc. It is remarkable to note that malaria vaccine has not been discovered yet. Therefore control measures depend on treatment and some other strategies like:

i. Using Dichloro-Diphenyl Trichloroethane (DDT) on mosquitoes;
ii. administering anti-malaria drugs to people who are travelling to malaria endemic areas;
iii. Using mosquito treated nets, especially for children and pregnant women [9,10].

Despite the use of all these control measures, malaria is still persistent in most African countries. This is attributed to: favourable condition of temperature, resistance of malaria parasite to anti-malaria drugs and resistance of mosquito to insecticides such as DDT.

Furthermore, the presence of the recessive sickle-cell gene (S-gene) in the heterozygous form also has its effect. It has been established that the S-gene provide protection against malaria infection [11]. The AS individuals have protection against malaria infection because:

i. Sickled red blood cells have low oxygen tension, and this is not favourable to the survival of the parasite.
ii. Their red blood cells are sickled in shape and this leads to the leakage of nutrients, such as potassium, which are needed for the survival of the parasites.
iii. Sickled red blood cells are being destroyed continuously by the spleen (within 10–20 days), and this happens together with the parasites.

A number of works has been done on the dynamical spread and control of malaria with/without immunity; on modelling the dynamics with different age groups; and so on. Literature on models of S-gene alone is not common; however the selective advantage of this gene towards malaria infection has been investigated by some researchers. It has been established that in the absence of malaria infection, the S-gene is disadvantaged and its frequency reduces in the population. [11]. Jones, in a review, examined the prediction of sickle cell gene frequency and its selective advantage towards heterozygous individuals in malaria endemic areas. He predicted, using the Hardy-Weinberg law, the expected gene frequency at equilibrium, with a known frequency of the parental population. He assumed an infinitely large isolated population where there was neither emigration nor immigration, so that mating was random, meiosis was normal and there was no mutation from one allele to another [11].

In the present study, a new model was formulated to get a better insight into the dynamical transmission and control of malaria in individuals with AA and AS genotypes.

The rest of this work is organized as follows: a full description of the model is given in Section II. Section III shows a domain where the model is epidemiologically feasible and mathematically well posed by carrying out a qualitative description of the existence and uniqueness of solution of the mathematical model. The concluding remark is given in Section IV.

II. MODEL FORMULATION

To study the existence and uniqueness of solution for the transmission and control dynamics of malaria infection in hosts of AA and AS genotypes, the mathematical model formulated by Adeyemi [12] is employed, which is an extension of the work of Feng and his colleagues [13]. This is described as follows:

Let S_1 and S_2 be the susceptible population for AA and AS individuals respectively, and let I_1 and I_2 be the infected population for AA and AS individuals respectively. Furthermore let R_1 and R_2 be the recovered population for the AA and AS individuals respectively, and finally, let m be the proportion of mosquitoes with plasmodium (which transmits malaria). The proportions of individuals who are of AS and AA genotypes in the population are

$$w = \frac{S_2 + I_2 + R_2}{N} \quad \text{and} \quad (1-w) = \frac{S_1 + I_1 + R_1}{N}, \qquad (1a)$$

respectively, where $N = S_1 + I_1 + R_1 + S_2 + I_2 + R_2$ (1*b*)
is the total human population density. The frequency of the S-gene is $q = \frac{w}{2}$, and the frequency of the A-gene is denoted as $p = 1 - q$.

Let $b(N)$ denote the human per-capita birth rate, possibly density dependent, with a constant per-capita natural mortality of μ. Individuals are recruited in the respective susceptible classes S_1 and S_2 by birth. When a mosquito carrying plasmodium parasite bite a susceptible human, there is a risk that the parasite will be passed unto the human and the person moves to the respective infected class I_1 or I_2. The transmission of malaria between human and mosquito is governed by some basic epidemiological parameters. The human biting rate is denoted a, and the average life of an infected mosquito is $1/\delta$, where δ is the mosquito death rate and it is assumed that there is no mosquito mortality due to presence of parasite. The probability that a human of genotype i (i = 1, 2) develop parasitaemia (i.e. the presence of parasite in the blood) from a bite is denoted θ_i, and it is assumed that $\theta_1 \geq \theta_2$. The probability that a mosquito acquires plasmodium from biting an individual of genotype i is denoted by ϕ_i (with $\phi_1 \geq \phi_2$). It is considered that AS individual may die faster than AA individuals from causes other than malaria and excess rate of mortality is ν. The mortality rate of human of genotype AA, μ_1, is assumed to be equal to the natural mortality, μ, while that of individuals of AS is given by $\mu_2 = \mu + \nu$, where ν is the extra mortality due to Sickle-cell complications.

An infected individual from I_i, either recover spontaneously (to join the recovered population at a rate γ_i, with $\gamma_1 \leq \gamma_2$), or die at a rate α_i, which is the disease-induced death rate ($\alpha_1 > \alpha_2$). Then infected individuals from I_i recover due to treatment at a rate σ_i and move to the respective compartment R_i. Recovered individuals have partial immunity but still inhabit some parasite in their blood stream and can be passed onto the mosquitoes, though with a reduced probability. Immunity is lost at a rate κ_i and

individuals become susceptible again. However, new infections boost the immune system thereby developing a solid immunity.

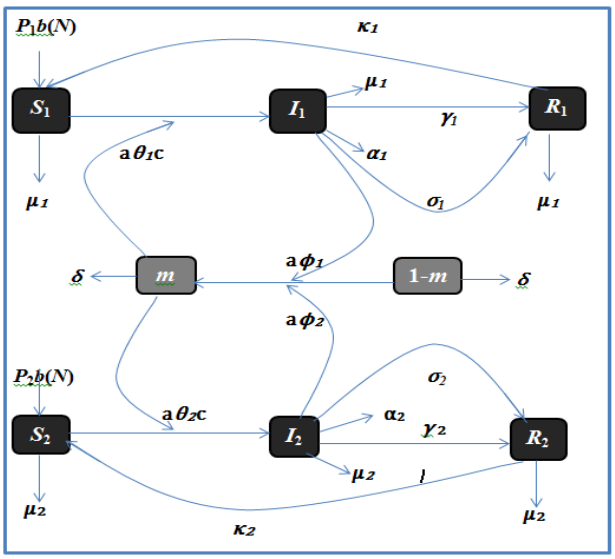

***Fig.* 1:** *Schematic diagram showing the dynamics of Malaria and Sickle-cell gene*

In addition to the above, some assumptions were made. First, it was assumed that the ratio of mosquito to human would need to be justified. Secondly, the fraction of each genotype born into the population is denoted P_i (i = 1, 2), and defined by: $P_1 = p^2$ and $P_2 = 2pq$.

The Fig. 1 shows the dynamics of the model with the inflow and outflow of individuals of both AA and AS in each compartment.

The model is mathematically formulated as a system of coupled ordinary differential equations as:

$$\begin{aligned}
\frac{dS_1}{dt} &= P_1 b(N)N - \mu_1 S_1 - a\theta_1 cmS_1 + \kappa_1 R_1 \\
\frac{dS_2}{dt} &= P_2 b(N)N - \mu_2 S_2 - a\theta_2 cmS_2 + \kappa_2 R_2 \\
\frac{dI_1}{dt} &= a\theta_1 cmS_1 - (\mu_1 + \gamma_1 + \alpha_1 + \sigma_1)I_1 \\
\frac{dI_2}{dt} &= a\theta_2 cmS_2 - (\mu_2 + \gamma_2 + \alpha_2 + \sigma_2)I_2 \qquad (2) \\
\frac{dR_1}{dt} &= (\gamma_1 + \sigma_1)I_1 - (\mu_1 + \kappa_1)R_1 \\
\frac{dR_2}{dt} &= (\gamma_2 + \sigma_2)I_2 - (\mu_2 + \kappa_2)R_2 \\
\frac{dm}{dt} &= (1-m)\left(a\varphi_1 \frac{I_1}{N} + a\varphi_2 \frac{I_2}{N}\right) - \delta m;
\end{aligned}$$

with $S_1(t_0) = S_{1_0}$, $S_2(t_0) = S_{2_0}$, $I_1(t_0) = I_{1_0}$, $I_2(t_0) = I_{2_0}$, $R_1(t_0) = R_{1_0}$, $R_2(t_0) = R_{2_0}$, $m(t_0) = m_0$. (3)

where $b(N)$ is the density dependent per capital birth rate defined by $b(N) = b\left(1 - \frac{N}{K}\right)$, with b the maximum birth rate constant when the population size is small and K is the approximate density dependent reduction in the birth rate (carrying capacity).

In order to reduce the number of parameters, we introduce the notations $\beta_{hi} = a\theta_i c$ and $\beta_{mi} = a\varphi_i$, (where i = 1, 2), which are the transmission coefficients from mosquitoes to humans of genotype i and from humans of genotype i to mosquitoes respectively. Then we have:

$$\begin{aligned}
\frac{dS_1}{dt} &= P_1 b(N)N - \mu_1 S_1 - \beta_{h1} mS_1 + \kappa_1 R_1 \\
\frac{dS_2}{dt} &= P_2 b(N)N - \mu_2 S_2 - \beta_{h2} mS_2 + \kappa_2 R_2 \\
\frac{dI_1}{dt} &= \beta_{h1} mS_1 - (\mu_1 + \gamma_1 + \alpha_1 + \sigma_1)I_1 \\
\frac{dI_2}{dt} &= \beta_{h2} mS_2 - (\mu_2 + \gamma_2 + \alpha_2 + \sigma_2)I_2 \qquad (4) \\
\frac{dR_1}{dt} &= (\gamma_1 + \sigma_1)I_1 - (\mu_1 + \kappa_1)R_1 \\
\frac{dR_2}{dt} &= (\gamma_2 + \sigma_2)I_2 - (\mu_2 + \kappa_2)R_2 \\
\frac{dm}{dt} &= (1-m)\left(\beta_{m1} \frac{I_1}{N} + \beta_{m2} \frac{I_2}{N}\right) - \delta m
\end{aligned}$$

with $S_1(t_0) = S_{10}$, $S_2(t_0) = S_{20}$, $I_1(t_0) = I_{10}$, $I_2(t_0) = I_{20}$, $R_1(t_0) = R_{10}$, $R_2(t_0) = R_{20}$, $m(t_0) = m_0$.

***Table* 1:** *Description of Variables and parameters used in the model*

Parameters	Description	Notes
i = 1	Individuals with AA genotype	
i = 2	Individuals with AS genotype	
S_i	Number of susceptible humans with genotype i	
I_i	Number of infected humans with genotype i	
R_i	Number of recovered humans with genotype i	
m	Fraction of mosquitoes with plasmodium parasite	
N	Total human population	
w	Frequency of AS individuals	$w = \frac{S_2 + I_2 + R_2}{N}$
q	Frequency of the S-gene	For simplicity, $w = q$
P_1	Fraction of the total birth of humans with AA genotype	$P_1 = 1 - w - \frac{w^2}{4}$
P_2	Fraction of the total birth of humans with AS genotype	$P_2 = w\left(1 - \frac{w}{2}\right)$

K	Density dependent reduction in the birth rate	K > N
$b(N)$	Per capita birth rate of humans, with b, the maximum birth rate constant	$b(N)=b\left(1-\frac{N}{K}\right)$
a	Biting rate per human per mosquito	
c	Ratio of mosquitoes to human	
θ_i	Probability that a human of genotype i acquires plasmodium per bite	$\theta_1 \geq \theta_2$
ϕ_i	Probability that a mosquito acquires plasmodium from biting an infected human of genotype i	$\phi_1 \geq \phi_2$
μ_i	Human natural death rate	$\mu_i = \mu_i + \nu$
α_i	Malaria induced death rate for human of genotype i	$\alpha_1 > \alpha_2$
ν	Extra death rate due to sickle-cell complications	
γ_i	Spontaneous Recovery rate from malaria for genotype i	$\gamma_1 \leq \gamma_2$
σ_i	Recovery rate from malaria for genotype i due to treatment	$\sigma_1 = \sigma_2$
κ_i	Immunity loss rate for genotype i	$\kappa_1 = \kappa_2$

III. EXISTENCE AND UNIQUENESS OF SOLUTION

The following result is provided, which guarantee that the malaria model governed by system (4) is epidemiologically feasible and mathematically well-posed in a region D.

***Theorem* 1: Picard's Theorem** [14,15]**:**

Suppose $y' = f(t,y), \quad y(t_0) = y_0$ (5)

is a given system of ordinary differential equation and suppose $f(t, x)$ is continuous and satisfies Lipchitz condition in the closed and bounded domain $\|x-x_0\| \leq \varphi, \ \|t-t_0\| \leq \tau$. Let $\|f(t,x)\| \leq M$. Then the initial value problem (5) has a unique solution in the interval $\|t-t_0\|$, where $h = \min\left\{\tau, \varphi/M\right\}$.

***Theorem* 2:** Consider the model equation (4).

Define $x = [S_1, S_2, I_1, I_2, R_1, R_2, m]^T$ and

$f(x) = [f_1(t,x), f_2(t,x), f_3(t,x), f_4(t,x), f_5(t,x), f_6(t,x), f_7(t,x)]^T$

where

$$f_1(t,x) = \frac{dS_1}{dt} = P_1 b(N)N - \mu_1 S_1 - \beta_{h1} m S_1 + \kappa_1 R_1, \quad S_1(t_0) = S_{10}$$

$$f_2(t,x) = \frac{dS_2}{dt} = P_2 b(N)N - \mu_2 S_2 - \beta_{h2} m S_2 + \kappa_2 R_2, \ S_2(t_0) = S_{20}$$

$$f_3(t,x) = \frac{dI_1}{dt} = \beta_{h1} m S_1 - (\mu_1 + \gamma_1 + \alpha_1 + \sigma_1) I_1, \quad I_1(t_0) = I_{10}$$

$$f_4(t,x) = \frac{dI_2}{dt} = \beta_{h2} m S_2 - (\mu_2 + \gamma_2 + \alpha_2 + \sigma_2) I_2, \quad I_2(t_0) = I_{20} \quad (6)$$

$$f_5(t,x) = \frac{dR_1}{dt} = (\gamma_1 + \sigma_1) I_1 - (\mu_1 + \kappa_1) R_1, \quad R_1(t_0) = R_{10}$$

$$f_6(t,x) = \frac{dR_2}{dt} = (\gamma_2 + \sigma_2) I_2 - (\mu_2 + \kappa_2) R_2, \quad R_2(t_0) = R_{20}$$

$$f_7(t,x) = \frac{dm}{dt} = (1-m)\left(\beta_{m1}\frac{I_1}{N} + \beta_{m2}\frac{I_2}{N}\right) - \delta m, \quad m(t_0) = m_0;$$

so that the system of equation in vector-valued functional form now becomes

$$x' = f(t,x) = f(x), \quad x(t_0) = x_0. \quad (7)$$

Define

$$D = \left\{x = (S_1, S_2, I_1, I_2, R_1, R_2, m) : S_1, S_2, I_1, I_2, R_1, R_2, m \leq 1\right\} \quad (8)$$

and let $\|x-x_0\| \leq \varphi, \ \|t\| \leq \tau$;

with $t_0 = 0$, $x_0 = (S_{1_0}, S_{2_0}, I_{1_0}, I_{2_0}, R_{1_0}, R_{2_0}, m_0)$.

Then the model equation (4) has a unique solution in the domain $\|x-x_0\| \leq \varphi$ and $\|t\| \leq \tau$, where $h = \min\left\{\tau, \varphi/M\right\}$.

***Proof*:** Using the Picard's Theorem 1, it will be established that the model equation (4) has a unique solution in D, by proving that:

(i) $f(t, x)$ is continuous in D;
(ii) $f(t, x)$ satisfies Lipchitz conditions in D; and
(iii) $f(t, x)$ is bounded in D (i.e. $|f(t, x)| \leq M$).

(i) Each component $f_i(t,x), i = 1,2,...,7$ of $f(t, x)$ in (6) is a continuous function of the variable $x = (S_1, S_2, I_1, I_2, R_1, R_2, m)^T$. This follows from the assumptions in the model. Therefore the vector-valued function $f(t, x)$ is continuous in D.

(ii) The Lipchitz condition is established by showing that each component $f_i(t,x), i = 1,2,...,7$ of $f(t, x)$ satisfies Lipchitz conditions in D.

Let $x^* = (S_1^*, S_2^*, I_1^*, I_2^*, R_1^*, R_2^*, m^*)^T$. Then

$$f(x^*) = (f_1(x^*), f_2(x^*), f_3(x^*), f_4(x^*), f_5(x^*), f_6(x^*), f_7(x^*))^T$$

.

Now, noting that $S_1, S_2, I_1, I_2, R_1, R_2, m \leq 1$; and $N = 1$,

we have:

$$\left|f_1(x)-f_1(x^*)\right|=\left|\left[P_1b(N)N-(\mu_1+\beta_{h1}m)S_1+\kappa_1R_1\right]-\left[P_1b(N)N-\left(\mu_1+\beta_{h1}m^*\right)S_1^*+\kappa_1R_1^*\right]\right|$$

$$=\left|(-\mu_1)\left(S_1-S_1^*\right)+(-\beta_{h1})\left[S_1\left(m-m^*\right)+m^*\left(S_1-S_1^*\right)\right]+\kappa_1\left(R_1-R_1^*\right)\right|$$

$$\le\mu_1\left|S_1-S_1^*\right|+\beta_{h1}\left|S_1\right|\left|m-m^*\right|+\beta_{h1}\left|m\right|\left|S_1-S_1^*\right|+\left|\kappa_1\right|\left|R_1-R_1^*\right|$$

$$=(\mu_1+\beta_{h1})\left|S_1-S_1^*\right|+0\left|S_2-S_2^*\right|+0\left|I_1-I_1^*\right|+0\left|I_2-I_2^*\right|+\kappa_1\left|R_1-R_1^*\right|+0\left|R_2-R_2^*\right|+\beta_{h1}\left|m-m^*\right|.$$

$$\Rightarrow\left|f_1(x)-f_1(x^*)\right|\le L_1\left\|x-x^*\right\|.$$

Where $L_1=\max\left\{l_{1_1},l_{2_1},l_{3_1},l_{4_1},l_{5_1},l_{6_1},l_{7_1}\right\}$, and $l_{1_1}=(\mu_1+\beta_{h1})$, $l_{2_1}=l_{3_1}=l_{4_1}=0$, $l_{5_1}=\kappa_1$, $l_{6_1}=0$, $l_{7_1}=\beta_{h1}$

Are constants depending on the model parameters.

Similarly,

$$\left|f_2(x)-f_2(x^*)\right|=\left|\left[P_2b(N)N-(\mu_2+\beta_{h2}m)S_2+\kappa_2R_2\right]-\left[P_2b(N)N-\left(\mu_2+\beta_{h2}m^*\right)S_2^*+\kappa_2R_2^*\right]\right|$$

$$=\left|(-\mu_2)\left(S_2-S_2^*\right)+(-\beta_{h2})\left[S_2\left(m-m^*\right)+m^*\left(S_2-S_2^*\right)\right]+\kappa_2\left(R_2-R_2^*\right)\right|$$

$$\le\mu_2\left|S_2-S_2^*\right|+\beta_{h2}\left|S_2\right|\left|m-m^*\right|+\beta_{h2}\left|m\right|\left|S_2-S_2^*\right|+\left|\kappa_2\right|\left|R_2-R_2^*\right|$$

$$=0\left|S_1-S_1^*\right|+(\mu_2+\beta_{h2})\left|S_2-S_2^*\right|+0\left|I_1-I_1^*\right|+0\left|I_2-I_2^*\right|+0\left|R_1-R_1^*\right|+\kappa_2\left|R_2-R_2^*\right|$$

$$+\beta_{h2}\left|m-m^*\right|.$$

$$\Rightarrow\left|f_2(x)-f_2(x^*)\right|\le L_2\left\|x-x^*\right\|.$$

where $L_2=\max\left\{l_{1_2},l_{2_2},l_{3_2},l_{4_2},l_{5_2},l_{6_2},l_{7_2}\right\}$, and $l_{1_2}=0$, $l_{2_2}=(\mu_2+\beta_{h2})$, $l_{3_2}=l_{4_2}=l_{5_2}=0$, $l_{6_2}=\kappa_2$, $l_{7_2}=\beta_{h2}$

are constants depending on the model parameters.

$$\left|f_3(x)-f_3(x^*)\right|=\left|\left[\beta_{h1}mS_1-(\mu_1+\gamma_1+\alpha_1+\sigma_1)I_1\right]-\left[\beta_{h1}m^*S_1^*-(\mu_1+\gamma_1+\alpha_1+\sigma_1)I_1^*\right]\right|$$

$$=\left|\beta_{h1}\left[S_1\left(m-m^*\right)+m^*\left(S_1-S_1^*\right)\right]+\left[-(\mu_1+\gamma_1+\alpha_1+\sigma_1)\left(I_1-I_1^*\right)\right]\right|$$

$$\le\beta_{h1}\left|S_1\right|\left|m-m^*\right|+\beta_{h1}\left|m^*\right|\left|S_1-S_1^*\right|+(\mu_1+\gamma_1+\alpha_1+\sigma_1)\left|I_1-I_1^*\right|$$

$$=\beta_{h1}\left|S_1-S_1^*\right|+0\left|S_2-S_2^*\right|+(\mu_1+\gamma_1+\alpha_1+\sigma_1)\left|I_1-I_1^*\right|+0\left|I_2-I_2^*\right|+0\left|R_1-R_1^*\right|$$

$$+0\left|R_2-R_2^*\right|+\beta_{h1}\left|m-m^*\right|.$$

$$\Rightarrow\left|f_3(x)-f_3(x^*)\right|\le L_3\left\|x-x^*\right\|.$$

where $L_3=\max\left\{l_{1_3},l_{2_3},l_{3_3},l_{4_3},l_{5_3},l_{6_3},l_{7_3}\right\}$,and $l_{1_3}=\beta_{h1}$, $l_{2_3}=0$, $l_{3_3}=(\mu_1+\gamma_1+\alpha_1+\sigma_1)$, $l_{4_3}=l_{5_3}=l_{6_3}=0$,

$l_{7_3}=\beta_{h1}$ are constants depending on the model parameters.

$$\left|f_4(x)-f_4(x^*)\right|=\left|\left[\beta_{h2}mS_2-(\mu_2+\gamma_2+\alpha_2+\sigma_2)I_2\right]-\left[\beta_{h2}m^*S_2^*-(\mu_2+\gamma_2+\alpha_2+\sigma_2)I_2^*\right]\right|$$

$$=\left|\beta_{h2}\left[S_2\left(m-m^*\right)+m^*\left(S_2-S_2^*\right)\right]+\left[-(\mu_2+\gamma_2+\alpha_2+\sigma_2)\left(I_2-I_2^*\right)\right]\right|$$

$$\le\beta_{h2}\left|S_2\right|\left|m-m^*\right|+\beta_{h2}\left|m^*\right|\left|S_2-S_2^*\right|+(\mu_2+\gamma_2+\alpha_2+\sigma_2)\left|I_2-I_2^*\right|$$

$$=0\left|S_1-S_1^*\right|+\beta_{h2}\left|S_2-S_2^*\right|+0\left|I_1-I_1^*\right|+(\mu_2+\gamma_2+\alpha_2+\sigma_2)\left|I_2-I_2^*\right|+0\left|R_1-R_1^*\right|$$

$$+0\left|R_2-R_2^*\right|+\beta_{h1}\left|m-m^*\right|.$$

$$\Rightarrow\left|f_4(x)-f_4(x^*)\right|\le L_4\left\|x-x^*\right\|.$$

where $L_4 = \max\{l_{1_4}, l_{2_4}, l_{3_4}, l_{4_4}, l_{5_4}, l_{6_4}, l_{7_4}\}$, and $l_{1_4} = 0,\ l_{2_4} = \beta_{h2},\ l_{3_4} = 0,\ l_{4_4} = (\mu_2 + \gamma_2 + \alpha_2 + \sigma_2),$
$l_{5_4} = l_{6_4} = 0,\ l_{7_4} = \beta_{h1}$ are constants depending on the model parameters.

$$\begin{aligned}
\left|f_5(x) - f_5(x^*)\right| &= \left|\left[(\gamma_1 + \sigma_1) I_1 - (\mu_1 + \kappa_1) R_1\right] - \left[(\gamma_1 + \sigma_1) I_1^* - (\mu_1 + \kappa_1) R_1^*\right]\right| \\
&= \left|(\gamma_1 + \sigma_1)\left(I_1 - I_1^*\right) + \left[-(\mu_1 + \kappa_1)\left(R_1 - R_1^*\right)\right]\right| \\
&\le (\gamma_1 + \sigma_1)\left|I_1 - I_1^*\right| + (\mu_1 + \kappa_1)\left|R_1 - R_1^*\right| \\
&= 0\left|S_1 - S_1^*\right| + 0\left|S_2 - S_2^*\right| + (\gamma_1 + \sigma_1)\left|I_1 - I_1^*\right| + 0\left|I_2 - I_2^*\right| + (\mu_1 + \kappa_1)\left|R_1 - R_1^*\right| \\
&\quad + 0\left|R_2 - R_2^*\right| + 0\left|m - m^*\right|.
\end{aligned}$$

$$\Rightarrow \left|f_5(x) - f_5(x^*)\right| \le L_5 \left\|x - x^*\right\|.$$

where $L_5 = \max\{l_{1_5}, l_{2_5}, l_{3_5}, l_{4_5}, l_{5_5}, l_{6_5}, l_{7_5}\}$, and $l_{1_5} = l_{2_5} = 0,\ l_{3_5} = (\gamma_1 + \sigma_1),\ l_{4_5} = 0,\ l_{5_5} = (\mu_1 + \kappa_1),$
$l_{6_5} = l_{7_5} = 0$ are constants depending on the model parameters.

$$\begin{aligned}
\left|f_6(x) - f_6(x^*)\right| &= \left|\left[(\gamma_2 + \sigma_2) I_2 - (\mu_2 + \kappa_2) R_2\right] - \left[(\gamma_2 + \sigma_2) I_2^* - (\mu_2 + \kappa_2) R_2^*\right]\right| \\
&= \left|(\gamma_2 + \sigma_2)\left(I_2 - I_2^*\right) + \left[-(\mu_2 + \kappa_2)\left(R_2 - R_2^*\right)\right]\right| \\
&\le (\gamma_2 + \sigma_2)\left|I_2 - I_2^*\right| + (\mu_2 + \kappa_2)\left|R_2 - R_2^*\right| \\
&= 0\left|S_1 - S_1^*\right| + 0\left|S_2 - S_2^*\right| + 0\left|I_1 - I_1^*\right| + (\gamma_2 + \sigma_2)\left|I_2 - I_2^*\right| + 0\left|R_1 - R_1^*\right| \\
&\quad + (\mu_2 + \kappa_2)\left|R_2 - R_2^*\right| + 0\left|m - m^*\right|.
\end{aligned}$$

$$\Rightarrow \left|f_6(x) - f_6(x^*)\right| \le L_6 \left\|x - x^*\right\|.$$

where $L_6 = \max\{l_{1_6}, l_{2_6}, l_{3_6}, l_{4_6}, l_{5_6}, l_{6_6}, l_{7_6}\}$, and $l_{1_6} = l_{2_6} = l_{3_6} = 0,\ l_{4_6} = (\gamma_2 + \sigma_2),\ l_{5_6} = 0,$
$l_{6_6} = (\mu_2 + \kappa_2),\ l_{7_6} = 0$ are constants depending on the model parameters.

$$\begin{aligned}
\left|f_7(x) - f_7(x^*)\right| &= \left|\left[(1-m)\left(\beta_{m1}\frac{I_1}{N} + \beta_{m2}\frac{I_2}{N}\right) - \delta m\right] - \left[\left(1-m^*\right)\left(\beta_{m1}\frac{I_1^*}{N} + \beta_{m2}\frac{I_2^*}{N}\right) - \delta m^*\right]\right| \\
&= \left|\left[(1-m)\beta_{m1}\frac{I_1}{N} + (1-m)\beta_{m2}\frac{I_2}{N} - \delta m\right] - \left[\left(1-m^*\right)\beta_{m1}\frac{I_1^*}{N} + \left(1-m^*\right)\beta_{m2}\frac{I_2^*}{N} - \delta m^*\right]\right| \\
&= \left|\left[\beta_{m1}\frac{I_1}{N} + \beta_{m1}m\frac{I_1}{N} + \beta_{m2}\frac{I_2}{N} + \beta_{m2}m\frac{I_2}{N} - \delta m\right] - \left[\beta_{m1}\frac{I_1^*}{N} + \beta_{m1}m^*\frac{I_1^*}{N} + \beta_{m2}\frac{I_2^*}{N} + \beta_{m2}m^*\frac{I_2^*}{N} - \delta m^*\right]\right| \\
&= \left|\frac{\beta_{m1}}{N}\left(I_1 - I_1^*\right) + \left(-\frac{\beta_{m1}}{N}\right)\left[I_1\left(m - m^*\right) + m^*\left(I_1 - I_1^*\right)\right] + \frac{\beta_{m2}}{N}\left(I_2 - I_2^*\right)\right. \\
&\qquad \left. + \left(-\frac{\beta_{m2}}{N}\right)\left[I_2\left(m - m^*\right) + m^*\left(I_2 - I_2^*\right)\right] + \left[-\delta\left(m - m^*\right)\right]\right| \\
&\le \left|\frac{\beta_{m1}}{N}\left|I_1 - I_1^*\right| + \frac{\beta_{m1}}{N}\left|I_1\right|\left|m - m^*\right| + \frac{\beta_{m1}}{N}\left|m^*\right|\left|I_1 - I_1^*\right| + \frac{\beta_{m2}}{N}\left|I_2 - I_2^*\right| + \frac{\beta_{m2}}{N}\left|I_2\right|\left|m - m^*\right|\right. \\
&\qquad \left. + \frac{\beta_{m2}}{N}\left|m^*\right|\left|I_1 - I_1^*\right| + \delta\left(m - m^*\right)\right| \\
&= 2\beta_{m1}\left|I_1 - I_1^*\right| + 2\beta_{m2}\left|I_2 - I_2^*\right| + (\beta_{m1} + \beta_{m2} + \delta)\left|m - m^*\right| \\
&= 0\left|S_1 - S_1^*\right| + 0\left|S_2 - S_2^*\right| + 2\beta_{m1}\left|I_1 - I_1^*\right| + 2\beta_{m2}\left|I_2 - I_2^*\right| + 0\left|R_1 - R_1^*\right| + 0\left|R_2 - R_2^*\right| \\
&\qquad + (\beta_{m1} + \beta_{m2} + \delta)\left|m - m^*\right|.
\end{aligned}$$

$$\Rightarrow \left|f_7(x) - f_7(x^*)\right| \le L_7 \left\|x - x^*\right\|.$$

where $L_7 = \max\left\{l_{1_7}, l_{2_7}, l_{3_7}, l_{4_7}, l_{5_7}, l_{6_7}, l_{7_7}\right\}$, and $l_{1_7} = l_{2_7} = 0,\ l_{3_7} = 2\beta_{m1},\ l_{4_7} = 2\beta_{m2},\ l_{5_7} = l_{6_7} = 0,$

$l_{7_7} = (\beta_{m1} + \beta_{m2} + \delta)$ are constants depending on the model parameters.

Therefore, $\|f(x) - f(x^*)\| \le L\|x - x^*\|$, where $L = \max\{L_1, L_2, L_3, L_4, L_5, L_6, L_7\}$.

Thus $f(t, x)$ satisfies the Lipchitz condition.

(iii) Now, to obtain the bound of $f(t, x)$ and, we note that $S_1, S_2, I_1, I_2, R_1, R_2, m \le 1$; and $N = 1$, and so,

$$\begin{aligned}|f_1(x)| &= |P_1 b(N)N - (\mu_1 + \beta_{h1} m)S_1 + \kappa_1 R_1| \\ &\le P_1 b(N)N + \mu_1 |S_1| + \beta_{h1} |m||S_1| + \kappa_1 |R_1| \\ &\le P_1 b + (\mu_1 + \beta_{h1} + \kappa_1) \\ &= M_1.\end{aligned}$$

$$\Rightarrow |f_1(x)| \le M_1.$$

$$\begin{aligned}|f_2(x)| &= |P_2 b(N)N - (\mu_2 + \beta_{h2} m)S_2 + \kappa_2 R_2| \\ &\le P_2 b(N)N + \mu_2 |S_2| + \beta_{h2} |m||S_2| + \kappa_2 |R_2| \\ &\le P_2 b + (\mu_2 + \beta_{h2} + \kappa_2) \\ &= M_2.\end{aligned}$$

$$\Rightarrow |f_2(x)| \le M_2.$$

$$\begin{aligned}|f_3(x)| &= |\beta_{h1} m S_1 - (\mu_1 + \gamma_1 + \alpha_1 + \sigma_1) I_1| \\ &\le \beta_{h1} |m||S_1| + (\mu_1 + \gamma_1 + \alpha_1 + \sigma_1)|I_1| \\ &\le \beta_{h1} + (\mu_1 + \gamma_1 + \alpha_1 + \sigma_1) \\ &= M_3.\end{aligned}$$

$$\Rightarrow |f_3(x)| \le M_3.$$

$$\begin{aligned}|f_4(x)| &= |\beta_{h2} m S_2 - (\mu_2 + \gamma_2 + \alpha_2 + \sigma_2) I_2| \\ &\le \beta_{h2} |m||S_2| + (\mu_2 + \gamma_2 + \alpha_2 + \sigma_2)|I_2| \\ &\le \beta_{h2} + (\mu_2 + \gamma_2 + \alpha_2 + \sigma_2) \\ &= M_4.\end{aligned}$$

$$\Rightarrow |f_4(x)| \le M_4.$$

$$\begin{aligned}|f_5(x)| &= |(\gamma_1 + \sigma_1) I_1 - (\mu_1 + \kappa_1) R_1| \\ &\le (\gamma_1 + \sigma_1)|I_1| + (\mu_1 + \kappa_1)|R_1| \\ &\le (\gamma_1 + \sigma_1) + (\mu_1 + \kappa_1). \\ &\quad M_5.\end{aligned}$$

$$\Rightarrow |f_5| \le M_5.$$

$$\begin{aligned}|f_6(x)| &= |(\gamma_2 + \sigma_2) I_2 - (\mu_2 + \kappa_2) R_2| \\ &\le (\gamma_2 + \sigma_2)|I_2| + (\mu_2 + \kappa_2)|R_2| \\ &\le (\gamma_2 + \sigma_2) + (\mu_2 + \kappa_2). \\ &\quad M_6.\end{aligned}$$

$$\Rightarrow |f_6| \le M_6.$$

$$\begin{aligned}|f_7(x)| &= \left|(1-m)\left(\beta_{m1}\frac{I_1}{N} + \beta_{m2}\frac{I_2}{N}\right) - \delta m\right| \\ &= \left|(1-m)\beta_{m1}\frac{I_1}{N} + (1-m)\beta_{m2}\frac{I_2}{N} - \delta m\right| \\ &= \left|\beta_{m1}\frac{I_1}{N} + \beta_{m1} m\frac{I_1}{N} + \beta_{m2}\frac{I_2}{N} + \beta_{m2} m\frac{I_2}{N} - \delta m\right| \\ &\le \frac{\beta_{m1}}{N}|I_1| + \frac{\beta_{m1}}{N}|m||I_1| + \frac{\beta_{m2}}{N}|I_2| + \frac{\beta_{m2}}{N}|m||I_2| + \delta|m| \\ &\le 2\beta_{m1} + 2\beta_{m1} + \delta \\ &= M_7.\end{aligned}$$

$$\Rightarrow |f_7(x)| \le M_7.$$

Therefore, $\|f(x)\| \le M$,

where $M = \max\{M_1, M_2, M_3, M_4, M_5, M_6, M_7\}$.

i.e. $f(t, x)$ is bounded.

Hence, by (i), (ii) and (iii) above, there exists a unique continuous solution for the IVP (2) (or equivalently, (4)), in the domain $\|x - x_0\| \le \varphi$ and $\|t - t_0\| \le \tau$,

where $h = \min\left\{\tau, \varphi/M\right\}$.

This completes the proof.

IV. CONCLUSION

This research paper considered a mathematical model that investigates the effect of malaria treatment and sickle-cell gene frequency on the dynamics of malaria among AA and AS genotype individuals. The coupled system of non-linear ordinary differential equations represents an important mathematical model, of a physical system. This is shown by carrying out a classical qualitative proof of the existence and uniqueness of solution to the governing equation of the physical system. In other words, the mathematical model which represents the physical system is both epidemiologically feasible and mathematically well posed. Hence, it is sufficient to study the dynamics of the model in the defined region, *D*.

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REFERENCES

[1] World Health Organization (WHO); WHO Global Malaria Programme (2014): World Malaria Report 2014, http://www.who.int/malaria/publication/wmr-2014-full-report.

[2] C. Chiyaka, J.M. Tchuenche, W. Garira, S. Dube. Tranmission Model of Endemic Human Malaria in a Partially Immune Population; *Mathematical and Computer Modelling*, 46(5-6), 2007: 806-822.

[3] A. Bartoloni, L. Zammarchi. Clinical Aspect of Uncomplicated and Severe Malaria; *Mediterranean Journal of Haematology and Infectious Diseases*, 4(1), 2012. p.26.

[4] B. Nadjm, R.H. Behrens. Malaria – An update for Physicians; *Infectious Diseases Clinics of North America*, 26(2), 2012. pp.243-259.

[5] N.A. Beare, T.E. Taylor, S.P. Harding, S. Lewallen, M.E. Molyneux. Malarial Retinopathy: A Newly Established Diagnosis Sign in Severe Malaria; *American Journal of Tropical Medicine and Hygiene*, 75(5), 2006. pp.790-797.

[6] W.R. Taylor, J. Hanson, G.D. Turner, N.J. White, A.M. Dondorp. Respiratory Manifestations of Malaria; *Chest*, 142(2), 2012. pp.492-505.

[7] T.K. Hartman, S.J. Rogerson, P.R. Fischer. The Impact of Maternal Malaria on New-borns; *Annals of Tropical Paediatrics*, 30(4), 2010. pp.271-282.

[8] M.J. Rijken, R. McGreadry, M.E. Boel, R. Poespoprodjo, N. Singh, D. Syafruddin, S. Rogerson, F. Nosten. Malaia in Pregnancy in the Asia-Pacific Regions; *Lancet Infectious Diseases*, 12(1), 2012. pp.75-88.

[9] J.C. Koella. Review on the Use of Mathematical Models of Malaria Transmission; *Acta tropica*, 49, 1999. pp.1-25.

[10] T. Marijani. Modelling Drug Resistance in malaria; Master's Dissertation, *Stellenbosch University, South Africa*. 2009.

[11] T.R. Jones. Quantitative Aspect of the Relationship between Sickle-cell Gene and Malaria; *Parasitology Today*, 13, 1997. pp.107-111.

[12] M. O. Adeyemi. The Interaction between the Dynamics of Malaria Infection and Sickle-cell Gene Frequency in the Presence of Treatment; Master's Dissertation, *LAUTECH, Ogbomoso, Nigeria*. 2018.

[13] Z. Feng, D.L. Smith, F.E. McKenzie, S.A. Levin. Coupling Ecology and Evolution: Malaria and the S-gene across Time Scales; *Mathematical Biosciences*, 1(5), 2004. pp.1-19.

[14] I.J.M. Udoo, R.A. Kimbir and R.M. Odekunle. Existence and Uniqueness of Solution of an HIV/AIDS Model Considering Counselling, Vaccination and Antiretroviral Therapy; *Mathematical Theory and Modelling*, 5(11), 2015. Pp.92–105.

[15] E. A. Coddington and N. Levinson. Theory of Ordinary Differential Equations. McGraw-Hill, New York. 1955.