Mathematical Modelling for the Effect of Malaria on the Heterozygous and Homozygous Genes

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ABSTRACT

This paper models the effect of malaria on the homozygous for the normal gene (AA), heterozygous for sickle cell gene (AS) and homozygous for sickle cell gene (SS) using the first order ordinary differential equation. The Diseases Free Equilibrium (DFE) was obtained and used to compute the basic reproduction Number R_o. The local stability of the (DFE) was analyzed.

KEYWORDS*: - heterozygous, homozygous, sickle cell diseases, plasmodium, genotype.*

Introduction.

The sickle cell gene is caused by a single amino acid mutation (valine instead of glutamate at the 6th position) in the beta chain of the hemoglobin gene. Inheritance of this mutated gene from both parents leads to sickle cell disease and people with this disease have shorter life expectancy. On the contrary, individuals who are carriers for the sickle cell disease (with one sickle gene and one normal hemoglobin gene, also known as sickle cell trait) have some protective advantage against malaria. As a result, the frequencies of sickle cell carriers are high in malaria-endemic areas. It was found that that the sickle cell trait provides 60% protection against overall mortality. Most of this protection occurs between 2-16 months of life, before the onset of clinical immunity in areas with intense transmission of malaria.

The natural history of malaria involves cyclical infection of humans and female *Anopheles* mosquitoes. In humans, the parasites grow and multiply first in the liver cells and then in the red cells of the blood. The infected mosquito carries the disease from one human to another (acting as a “vector”), while infected humans transmit the parasite to the mosquito, in contrast

to the human host, the mosquito vector does not suffer from the presence of the parasites (CDC, 2018).

Methodology

Model Formulation.

In modelling diseases using Ordinary Differential Equation, Akinwande (2018) precludes an assumption of vertical transmission, in which those who recover from infection are returned into the Susceptible class making room for possible re-infection as in the case of malaria fever and some other diseases.

In modelling theeffect of malaria on the heterozygous and homozygous genes, the total population is subdivided in to four main subgroup namely the susceptible homozygous(AA) $S_1(t)$, the infected homozygous(AA) $I_1(t)$, the Susceptible heterozygous(AS) $S_2(t)$, infected heterozygous(AS) $I_2(t)$, the Susceptible homozygous(SS) $S_3(t)$, the infected homozygous(SS) $I_3(t)$, $M_1(t)$ the non-plasmodium carrier mosquito and $M_2(t)$ the plasmodium carrier mosquito. People enter the susceptible class through birth and recovery from the infected class and leaves the susceptible class through infection, natural death and death due infection. It was assumed in this work that infants are not infected with malaria from birth and that the mosquito are non-plasmodium carrier from birth they become infected through contact with infected human. The transmission dynamics of malaria as it affects the heterozygous and homozygous sickle cell genes is given by the equations 1-8 below

$$\frac{dS_1}{dt} = \omega_1\beta_1 + \theta_1\beta_2 + \gamma_1 I_1 - \alpha_1 S_1 M_2 - (\mu_1 + \delta_1) S_1 \qquad 1$$

$$\frac{dI_1}{dt} = \alpha_1 S_1 M_2 - \gamma_1 I_1 - (\mu_1 + \delta_1) I_1 \qquad 2$$

$$\frac{dS_2}{dt} = \omega_2\beta_1 + \theta_2\beta_2 + \rho_1\beta_3 + \gamma_2 I_2 - \alpha_1 S_2 M_2 - (\mu_1 + \delta_2) S_2 \qquad 3$$

$$\frac{dI_2}{dt} = \alpha_1 S_2 M_2 - \gamma_2 I_2 - (\mu_1 + \delta_2) I_2 \qquad 4$$

$$\frac{dS_3}{dt} = \theta_3\beta_2 + \rho_2\beta_3 + \gamma_3 I_3 - \alpha_1 S_3 M_2 - (\mu_1 + \delta_3) S_3 \qquad 5$$

$$\frac{dI_3}{dt} = \alpha_1 S_3 M_2 - \gamma_3 I_3 - (\mu_1 + \delta_3) I_3 \qquad 6$$

$$\frac{dM_1}{dt} = \beta_4 - \alpha_3 M_1 (I_1 + I_2 + I_3) - \mu_2 M_1 \quad 7$$

$$\frac{dM_2}{dt} = \alpha_3 M_1 (I_1 + I_2 + I_3) - \mu_2 M_2 \qquad 8$$

Notation and definition of variables and parameter

S_1(t) Number of susceptible AA

I_1(t) Number of Infected AA

S_2(t) Number of susceptible AS

I_2(t) Number of Infected AS

S_3(t) Number of susceptible SS

I_3(t) Number of Infected SS

M_1(t) Number of non-plasmodium carrier mosquitoes

M_2(t) Number of plasmodium carrier mosquitoes

β_1 normal birth rate in human (AA)

β_2 normal birth rate in human (AS)

β_3 normal birth rate in human (SS)

β_4 normal birth rate in mosquitoes

μ_1 normal death rate in human

μ_1 normal and induced death rate in mosquitoes

δ_1 death due to infection in AA

δ_2 death due to infection in AS

δ_3 death due to infection in SS

α_1 infection rate from mosquitoes to human

α_2 infection rate from infected human to mosquitoes

γ_1 recovery rate in AA

γ_2 recovery rate in AS

γ_3 recovery rate in SS

θ_1 proportion of birth of AA by AS

θ_2 proportion of birth of AS by AS

θ_3 proportion of birth of SS by AS

ω_1 proportion of birth of AA by AA

ω_2 proportion of birth of AS by AA

ρ_1 proportion of birth of AS by SS

ρ_2 proportion of birth of SS by SS

Note that i) $\omega_1 + \omega_2 = 19$

ii) $\theta_1 + \theta_2 + \theta_3 = 1$ 10

iii) $\rho_1 + \rho_2 = 1$ 11

Existence of Equilibrium State of the Model

At equilibrium,

$$\frac{dS_1}{dt} = \frac{dI_1}{dt} = \frac{dS_2}{dt} = \frac{dI_2}{dt} = \frac{dS_3}{dt} = \frac{dI_3}{dt} = \frac{dM_1}{dt} = \frac{dM_2}{dt} = 0 \quad 12$$

Let

$$\left(S_1, S_2, S_3, \mathrm{I}_1, \mathrm{I}_2, \mathrm{I}_3, \mathrm{M}_1, \mathrm{M}_2\right) = \left(S_1^0, S_2^0, S_3^0, \mathrm{I}_1^0, \mathrm{I}_2^0, \mathrm{I}_3^0, \mathrm{M}_1^0, \mathrm{M}_2^0\right) \quad 13$$

Be arbitrary equilibrium points, therefore the system 1 – 8 becomes

$$\frac{dS_1^0}{dt} = \omega_1\beta_1 + \theta_1\beta_2 + \gamma_1 I_1^0 - \alpha_1 S_1^0 M_2^0 - \left(\mu_1 + \delta_1\right) S_1^0 \quad 14$$

$$\frac{dI_1^0}{dt} = \alpha_1 S_1^0 M_2^0 - \gamma_1 I_1^0 - \left(\mu_1 + \delta_1\right) I_1^0 \quad 15$$

$$\frac{dS_2^0}{dt} = \omega_2\beta_1 + \theta_2\beta_2 + \rho_1\beta_3 + \gamma_2 I_2^0 - \alpha_1 S_2^0 M_2^0 - \left(\mu_1 + \delta_2\right) S_2^0 \quad 16$$

$$\frac{dI_2^0}{dt} = \alpha_1 S_2^0 M_2^0 - \gamma_2 I_2^0 - \left(\mu_1 + \delta_2\right) I_2^0 \quad 17$$

$$\frac{dS_3^0}{dt} = \theta_3\beta_2 + \rho_2\beta_3 + \gamma_3 I_3^0 - \alpha_1 S_3^0 M_2^0 - \left(\mu_1 + \delta_3\right) S_3^0 \quad 18$$

$$\frac{dI_3^0}{dt} = \alpha_1 S_3^0 M_2^0 - \gamma_3 I_3^0 - \left(\mu_1 + \delta_3\right) I_3^0 \quad 19$$

$$\frac{dM_1^0}{dt} = \beta_4 - \alpha_3 M_1^0 \left(I_1^0 + I_2^0 + I_3^0\right) - \mu_2 M_1^0 \quad 20$$

$$\frac{dM_2^0}{dt} = \alpha_3 M_1^0 \left(I_1^0 + I_2^0 + I_3^0\right) - \mu_2 M_2^0 \quad 21$$

Let

$$\mu_1 + \partial_1 = A_1, \mu_1 + \partial_2 = A_2, \mu_1 + \partial_3 = A_3 \quad 22$$

$$\omega_1\beta_1 + \theta_1\beta_2 + \gamma_1 I_1^0 - \alpha_1 S_1^0 M_2^0 - A_1 S_1^0 = 0 \quad 23$$

$$\alpha_1 S_1^0 M_2^0 - \gamma_1 I_1^0 - A_1 I_1^0 = 0 \quad 24$$

$$\omega_2\beta_1 + \theta_2\beta_2 + \rho_1\beta_3 + \gamma_2 I_2^0 - \alpha_1 S_2^0 M_2^0 - A_2 S_2^0 = 0 \quad 25$$

$$\alpha_1 S_2^0 M_2^0 - \gamma_2 I_2^0 - A_2 I_2^0 = 0 \quad 26$$

$$\theta_3\beta_2 + \rho_2\beta_3 + \gamma_3 I_3^0 - \alpha_1 S_3^0 M_2^0 - A_3 S_3^0 = 0 \quad 27$$

$$\alpha_1 S_3^0 M_2^0 - \gamma_3 I_3^0 - A_3 I_3^0 = 0 \quad 28$$

$$\beta_4 - \alpha_3 M_1^0 \left(I_1^0 + I_2^0 + I_3^0 \right) - \mu_2 M_1^0 = 0 \quad 29$$

$$\alpha_3 M_1^0 \left(I_1^0 + I_2^0 + I_3^0 \right) - \mu_2 M_2^0 = 0 \quad 30$$

Let

$$I_1^0 = I_2^0 = I_3^0 = 0 \quad 31$$

$$\omega_1 \beta_1 + \theta_1 \beta_2 - \alpha_1 S_1^0 M_2^0 - A_1 S_1^0 = 0 \quad 32$$

$$\alpha_1 S_1^0 M_2^0 = 0 \quad 33$$

$$\omega_2 \beta_1 + \theta_2 \beta_2 + \rho_1 \beta_3 - \alpha_1 S_2^0 M_2^0 - A_2 S_2^0 = 0 \quad 34$$

$$\alpha_1 S_2^0 M_2^0 = 0 \quad 35$$

$$\theta_3 \beta_2 + \rho_2 \beta_3 - \alpha_1 S_3^0 M_2^0 - A_3 S_3^0 = 0 \quad 36$$

$$\alpha_1 S_3^0 M_2^0 = 0 \quad 37$$

$$\beta_4 - \mu_2 M_1^0 = 0 \quad 38$$

$$-\mu_2 M_2^0 = 0 \quad 39$$

From 39 $M_2^0 = 0,$ 40

From 38 $M_1^0 = \dfrac{\beta_4}{\mu_2}$ 41

From 32 $S_1^0 = \dfrac{\omega_1 \beta_1 + \theta_1 \beta_2}{A_1}$ 42

From 34 $S_2^0 = \dfrac{\omega_2 \beta_1 + \theta_2 \beta_2 + \rho_1 \beta_3}{A_2}$ 43

From 36 $S_3^0 = \dfrac{\theta_3 \beta_2 + \rho_2 \beta_3}{A_3}$ 44

Thus, the DFE $\left(E^0\right)$ exists at the points

$$E^0 = \left(S_1^0, S_2^0, S_3^0, \mathrm{I}_1^0, \mathrm{I}_2^0, \mathrm{I}_3^0, \mathrm{M}_1^0, \mathrm{M}_2^0\right)$$
$$= \left(\frac{\omega_1\beta_1 + \theta_1\beta_2}{A_1}, \frac{\omega_2\beta_1 + \theta_2\beta_2 + \rho_1\beta_3}{A_2}, \frac{\theta_3\beta_2 + \rho_2\beta_3}{A_3}, 0, 0, 0, \frac{\beta_4}{\mu_2}, 0\right) \quad 45$$

Computation of Basic Reproduction Number (R_o)

Somma et al (2017) applied next generation matrix operation to compute the Basic reproduction Number of the model as used by Diekmann et al(1990) and improved by Driessche (2002). The effective basic reproduction number is the largest Eigenvalue or spectral radius of (FV^{-1}). The basic reproduction number of the model is given as the largest eigenvalue or spectral radius of FV^{-1}.

$$FV^{-1} = \left\{\left[\frac{\partial F_i(\mathrm{E}^0)}{\partial x_i}\right]\left[\frac{\partial V_i}{\partial x_i}\right]^{-1}\right\} \quad 46$$

Where F_i is the rate of appearance of new infection in compartment i, V_i is the transfer of infections from one compartment i to another and E^0 is the Disease-Free Equilibrium.

$$f_i = \begin{pmatrix} f_1 \\ f_2 \\ f_3 \\ f_4 \end{pmatrix} = \begin{pmatrix} \alpha_1 S_1^0 M_2^0 \\ \alpha_1 S_2^0 M_2^0 \\ \alpha_1 S_3^0 M_2^0 \\ \alpha_3 M_1^0 (\mathrm{I}_1^0 + \mathrm{I}_2^0 + \mathrm{I}_3^0) \end{pmatrix} \quad 47$$

Differentiating (47) partially with respect to time gives

$$F = \begin{bmatrix} 0 & 0 & 0 & \alpha_1 S_1^0 \\ 0 & 0 & 0 & \alpha_1 S_2^0 \\ 0 & 0 & 0 & \alpha_1 S_3^0 \\ \alpha_3 M_1^0 & \alpha_3 M_1^0 & \alpha_3 M_1^0 & 0 \end{bmatrix} \quad 48$$

$$F=\begin{bmatrix} 0 & 0 & 0 & \dfrac{\alpha_1(\omega_1\beta_1+\theta_1\beta_2)}{A_1} \\ 0 & 0 & 0 & \dfrac{\alpha_1(\omega_2\beta_1+\theta_2\beta_2+\rho_1\beta_3)}{A_2} \\ 0 & 0 & 0 & \dfrac{\alpha_1(\theta_3\beta_2+\rho_2\beta_3)}{A_3} \\ \dfrac{\alpha_3\beta_4}{\mu_2} & \dfrac{\alpha_3\beta_4}{\mu_2} & \dfrac{\alpha_3\beta_4}{\mu_2} & 0 \end{bmatrix} \quad 49$$

$$\begin{aligned} K_1 &= \omega_1\beta_1+\theta_1\beta_2, \\ \mathrm{K}_2 &= \omega_2\beta_1+\theta_2\beta_2+\rho_1\beta_3, \\ \mathrm{K}_3 &= \theta_3\beta_2+\rho_2\beta_3, \\ \mathrm{K}_4 &= \frac{\beta_4}{\mu_2} \end{aligned} \quad 50$$

$$F=\begin{bmatrix} 0 & 0 & 0 & \dfrac{\alpha_1K_1}{A_1} \\ 0 & 0 & 0 & \dfrac{\alpha_1K_2}{A_2} \\ 0 & 0 & 0 & \dfrac{\alpha_1K_3}{A_3} \\ \alpha_3K_4 & \alpha_3K_4 & \alpha_3K_4 & 0 \end{bmatrix} \quad V=\begin{bmatrix} A_1 & 0 & 0 & 0 \\ 0 & A_2 & 0 & 0 \\ 0 & 0 & A_3 & 0 \\ 0 & 0 & 0 & \mu_2 \end{bmatrix} 52$$

$$\det V = A_1A_2A_3\mu_2 \quad 53$$

$$AdjV=\begin{bmatrix} A_2A_3\mu_2 & 0 & 0 & 0 \\ 0 & A_1A_3\mu_2 & 0 & 0 \\ 0 & 0 & A_1A_2\mu_2 & 0 \\ 0 & 0 & 0 & A_1A_2A_3 \end{bmatrix} \quad 54$$

$$V^{-1}=\frac{AdjV}{\det V}=\begin{bmatrix} \dfrac{1}{A_1} & 0 & 0 & 0 \\ 0 & \dfrac{1}{A_2} & 0 & 0 \\ 0 & 0 & \dfrac{1}{A_3} & 0 \\ 0 & 0 & 0 & \dfrac{1}{\mu_2} \end{bmatrix} \quad 55$$

$$FV^{-1}=\begin{bmatrix} 0 & 0 & 0 & \frac{K_1\alpha_1}{A_1\mu_2} \\ 0 & 0 & 0 & \frac{K_2\alpha_1}{A_2\mu_2} \\ 0 & 0 & 0 & \frac{K_3\alpha_1}{A_3\mu_2} \\ \frac{K_4\alpha_3}{A_1} & \frac{K_4\alpha_3}{A_2} & \frac{K_4\alpha_3}{A_3} & 0 \end{bmatrix} \quad 56$$

The characteristics equation of (56), gives

$$\left|FV^{-1}-\lambda I\right|=0 \quad 57$$

$$\begin{vmatrix} -\lambda & 0 & 0 & \frac{K_1\alpha_1}{A_1\mu_2} \\ 0 & -\lambda & 0 & \frac{K_2\alpha_1}{A_2\mu_2} \\ 0 & 0 & -\lambda & \frac{K_3\alpha_1}{A_3\mu_2} \\ \frac{K_4\alpha_3}{A_1} & \frac{K_4\alpha_3}{A_2} & \frac{K_4\alpha_3}{A_3} & -\lambda \end{vmatrix}=0 \quad 58$$

$$-\lambda\left[-\lambda(\lambda^2-\frac{\alpha_1\alpha_3\,\mathrm{K}_3\mathrm{K}_4}{A_3^2\mu_2})\right]-0+\frac{\alpha_1 K_1}{A_1\mu_2}(0)=0 \quad 59$$

$$\lambda^2-\frac{\alpha_1\alpha_3\,\mathrm{K}_3\mathrm{K}_4}{A_3^2\mu_2}=0 \quad 60$$

$$\lambda=\pm\sqrt{\frac{\alpha_1\alpha_3\,\mathrm{K}_3\mathrm{K}_4}{A_3^2\mu_2}} \quad 61$$

$$\lambda_1=0,\lambda_2=-\sqrt{\frac{\alpha_1\alpha_3\,\mathrm{K}_3\mathrm{K}_4}{A_3^2\mu_2}},\lambda_3=+\sqrt{\frac{\alpha_1\alpha_3\,\mathrm{K}_3\mathrm{K}_4}{A_3^2\mu_2}} \quad 62$$

λ_3 is the spectral radius of $\rho\left(FV^{-1}\right)$

$$R_0=\sqrt{\frac{\alpha_1\alpha_3\,\mathrm{K}_3\mathrm{K}_4}{A_3^2\mu_2}} \quad 63$$

Concluding Remarks

The Disease-Free Equilibrium exists and it is equal to

$$E^0 = \left(S_1^0, S_2^0, S_3^0, \mathrm{I}_1^0, \mathrm{I}_2^0, \mathrm{I}_3^0, \mathrm{M}_1^0, \mathrm{M}_2^0\right)$$

$$= \left(\frac{\omega_1\beta_1 + \theta_1\beta_2}{A_1}, \frac{\omega_2\beta_1 + \theta_2\beta_2 + \rho_1\beta_3}{A_2}, \frac{\theta_3\beta_2 + \rho_2\beta_3}{A_3}, 0, 0, 0, \frac{\beta_4}{\mu_2}, 0\right) \quad 64$$

The Disease-Free Equilibrium is locally asymptotically stable if Basic reproduction Number $R_0 \leq 1$ and unstable otherwise.

If $R_0 < 1$ then

$$\frac{\alpha_1\alpha_3 \mathrm{K}_3\mathrm{K}_4}{A_3^2\mu_2} < 1 \quad 65$$

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