Deterministic Malaria Transmission Model with Acquired Immunity

J. Labadin, C. Kon M. L. and S. F. S. Juan

***Abstract*— This paper focuses on the development of a deterministic Malaria transmission model by considering the recovered population with and without immunity. A transmission model is found to be useful in providing a better understanding on the disease and the impact towards the human population. In this research, two possibilities were taken into account where one possibility is that infectious humans do not gain immunity while another possibility is that infectious humans will gain temporary immunity. The mathematical model is developed based on the SEIR model which has susceptible S_H, exposed E_H, infectious I_H and recovered R_H classes. The system of equations which were obtained were solved numerically and results were simulated and analyzed. The analysis includes the impact of the different values of the average duration to build effective immunity on the infectious humans. We observed that when the value of q, per capita rate of building effective immunity is increased, the maximum number of infected humans decreased. Hence, if an effective immunity can be build in a short period of time for those who recover from the disease, the number of cases could be reduced.**

***Index Terms*—mathematical modeling, malaria, transmission model, differential equations, immunity**

I. Introduction

Malaria is one of the most common infections in the world today. It is commonly caused by four species of protozoan parasites of the genus *Plasmodium : P.falciparum, P.vivax, P.ovale* and *P.malariae* [1]. Malaria is transmitted through the vectors, *Anopheles* mosquitoes and not directly from human to human. The disease infects humans of all ages and can be lethal. According to the World Health Organization (WHO) in year 2007, about 40% of the world's population, mostly those living in the poorest countries, are at risk of malaria. Of the 2.5 billion people at risk, more than 500 million become severely ill with malaria every year and more than 1 million die from the effects of the disease.

At present, malaria is endemic in most tropical countries including America, Asia and Africa. It remains a public health concern in many countries in South East Asia. Apart from the four common species mentioned above, simian malaria, *P.inui, P.cynomolgi,* and *P.knowlesi* are also known to cause the disease in humans [2]. Cases of malaria in the Kapit division Sarawak has been detected to be caused by *P.knowlesi* [3]. This malaria parasite which infects long-tailed and pig-tailed macaque monkeys in nature had accounted for half of the cases studied in the Kapit division [3].

Mathematical models for transmission dynamics of malaria are useful in providing a better knowledge of the disease, to plan for the future and consider appropriate control measures. Models have played great roles in the development of the epidemiology of the disease. The study on malaria using mathematical modeling originated from the works of Ross [3]. According to Ross, if the mosquito population can be reduced to below a certain threshold then malaria can be eradicated. MacDonald did some modification to the model and included superinfection [4]. He showed that reducing the number of mosquitoes have little effect on epidemiology of malaria in areas of intense transmission. Dietz et al [5] added two classes of humans in their mathematical model, namely those with low recovery rate (more infections, greater susceptibility) and high recovery rate (less infections, less susceptibility). Compartmental models of malaria and differential equations are constructed to model the disease [7,8,13,14,20]. Chitnis et al [13] did a bifurcation analysis of a malaria model. Malaria transmission model which incorporate immunity in the human population had been studied [7,8,14]. Epidemiological models on the spread of anti-malarial resistance were also constructed [15].

In this paper, we present the malaria transmission model in Section II, where we took into account two possibilities: one is where infectious humans do not gain any immunity and the other, who have temporary immunity. After which, the model is simulated and the impact of changing the rate to build effective immunity and other parameters are studied numerically in Section III. We based our work on Malaria cases in general and not specifically on particular parasite genus. Finally, concluding remarks are discussed in Section IV.

II. Model Formulation

A malaria transmission model has been produced based on the epidemiology aspects of the disease. The compartmental model is as shown in Fig. 1. The human population is divided into the SEIR compartmental model which consists of four

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J. Labadin is a senior lecturer in the Department of Computational Science and Mathematics, Faculty of Computer Science and Information Technology, Universiti Malaysia Sarawak, 94300 Kota Samarahan, Sarawak, Malaysia (phone: +60 82 583775; fax: +60 82 583764; e-mail: ljane@fit.unimas.my).

C. Kon M. L. is a postgraduate student in the Department of Computational Science and Mathematics, Faculty of Computer Science and Information Technology, Universiti Malaysia Sarawak, 94300 Kota Samarahan, Sarawak, Malaysia (e-mail: cynkonml@hotmail.com) . C. Kon M. L. Master candidature was supported by Zamalah Postgraduate UNIMAS.

S. F. S. Juan is a lecturer in the Department of Computational Science and Mathematics, Faculty of Computer Science and Information Technology, Universiti Malaysia Sarawak, 94300 Kota Samarahan, Sarawak, Malaysia (e-mail: sfsjuan@fit.unimas.my).

classes: susceptible S_H, exposed E_H, infectious I_H and recovered R_H. Blood meal taken by an infectious female Anopheline mosquito on a susceptible individual will cause sporozoites to be injected into the human bloodstream and will be carried to the liver. The individual will then move to the exposed class E_H. This will decrease the susceptible population S_H. Exposed humans are those who have parasites in them and the parasites are in asexual stages. They are without gametocytes and are not capable of transmitting the disease to susceptible mosquitoes. After the latent period, humans who are exposed will be transferred to the infectious class as they are with gametocytes in their blood stream making them infectious to female *Anopheles* mosquitoes. The infectious humans will recover after some time, gain immunity and move to the recovered with temporary immunity class or they can be susceptible again. This is because continuous exposure is necessary to ensure immunity is built [7]. Those who have recovered have immunity against the disease for a certain period. Acquired immunity exists but the mechanisms are yet to be fully apprehended [22]. As the immunity is temporary, it will fade off after a period of time [7]. Thus, the recovered humans will return to the susceptible class. Every class of human population is decreased by density-dependent and independent death and emigration except for the infectious class which has disease-induced death as an addition.

For the vector mosquitoes, the three compartments represent susceptible S_M, exposed E_M, and infectious I_M. There is no recovered class for the vector as mosquitoes never recover [13]. They are regulated by mortality [8]. Susceptible mosquitoes that feed on infectious or recovered human would have taken gametocytes in blood meal but do not have sporozoites in their salivary glands yet, thus this means they are entering into the exposed class. After fertilization, sporozoites are produced and migrate to the salivary glands ready to infect any susceptible host, the vector is then considered as infectious. The three compartments for the vector mosquitoes are reduced by density-dependent and independent death and emigration.

In the malaria model which has been constructed here, the total number of mosquito bites is restricted by total mosquito population whereas in [13] the total bites on humans is dependent on both human and mosquito population. In our model, the mosquito-human interaction follows the classic model as mentioned in Hethcote's review [9]. The differential equations which describe the dynamics of malaria in human and mosquito populations are formulated based from the compartmental diagram described in Figure 1. The descriptions for the variables used in the model are shown in Table 1 and parameters in Table 2.

The following assumptions are made to characterize the model:

(i) All newborns are susceptible to the disease.
(ii) The infectious period of mosquitoes ends when they die.
(iii) The lifespan of the mosquitoes does not depend on infection.
(iv) Human hosts recover from infection (without immunity) and move right back to susceptible state OR gain temporary immunity before losing it and returning to the susceptible class.
(v) Duration of building effective immunity is right after the duration of recovery from the disease.
(vi) Recovered humans are still able to transmit the disease but at a lower rate.
(vii) Duration of latent period and immune period are constant.
(viii) Human and mosquito populations are not constant.

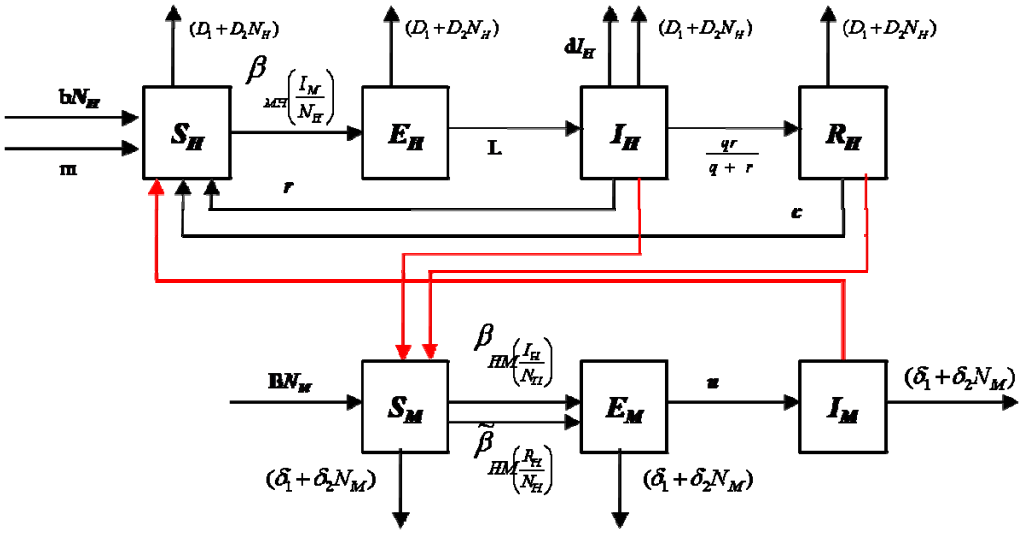

Figure 1: The compartmental model of the Malaria transmission of host human and vector mosquito

Following the compartmental model in Figure 1 and according to the Balance Law, the differential equations describing the transmission of the disease are as follows:

$$\frac{dS_H}{dt} = m + bN_H + cR_H - \beta_{MH}\left(\frac{I_M}{N_H}\right)S_H + rI_H - (D_1 + D_2N_H)S_H \tag{1}$$

$$\frac{dE_H}{dt} = \beta_{MH}\left(\frac{I_M}{N_H}\right)S_H - LE_H - (D_1 + D_2N_H)E_H \tag{2}$$

$$\frac{dI_H}{dt} = LE_H - \frac{qr}{q+r} I_H - rI_H - dI_H - (D_1 + D_2 N_H) I_H \quad (3)$$

$$\frac{dR_H}{dt} = \frac{qr}{q+r} I_H - cR_H - (D_1 + D_2 N_H) R_H \quad (4)$$

$$\frac{dS_M}{dt} = BN_M - \beta_{HM}\left(\frac{I_H}{N_H}\right) S_M - \tilde{\beta}_{HM}\left(\frac{R_H}{N_H}\right) S_M - (\delta_1 + \delta_2 N_M) S_M \quad (5)$$

$$\frac{dE_M}{dt} = \beta_{HM}\left(\frac{I_H}{N_H}\right) S_M + \tilde{\beta}_{HM}\left(\frac{R_H}{N_H}\right) S_M - uE_M - (\delta_1 + \delta_2 N_M) E_M \quad (6)$$

$$\frac{dI_M}{dt} = uE_M - (\delta_1 + \delta_2 N_M) I_M \quad (7)$$

Assumption (i) and (viii) above implies that the total human population, N_H is the summation of all the four human population compartments in Figure 1. This means that $N_H = S_H + E_H + I_H + R_H$. Also from assumption (viii), the total mosquito population, N_M is the summation of the three mosquito population compartments i.e. $N_M = S_M + E_M + I_M$. Thus, the rates of change of the total human population and the mosquito population are

$$\frac{dN_H}{dt} = m + bN_H - dI_H - (D_1 + D_2 N_H) N_H \quad , \quad (8)$$

$$\frac{dN_M}{dt} = BN_M - (\delta_1 + \delta_2 N_M) N_M \, , \quad (9)$$

respectively.

Table I. Description of variables for transmission model

Variable	Description
S_H	number of susceptible human hosts at time t
E_H	number of exposed human hosts at time t
I_H	number of infectious human hosts at time t
R_H	number of recovered human with temporary immunity at time t
S_M	number of susceptible mosquito vectors at time t
E_M	number of exposed mosquito vectors at time t
I_M	number of infectious mosquito vectors at time t
N_H	total human population
N_M	total mosquito population

Table II. Description of parameters for transmission model

Parameter	Description
b	per capita birth rate of humans (per time)
m	immigration rate of humans (per time)
B	per capita birth rate of mosquitoes (per time)
L	per capita rate of progression of human from exposed class to infectious class (per time)
$1/L$	average duration of latent period in humans
u	per capita rate of progressions of mosquitoes from exposed class to infectious class (per time)
$1/u$	average duration of latent period in mosquitoes
q	per capita rate of building effective immunity (per time)
$1/q$	average duration to build effective immunity
c	per capita rate of loss of immunity in human (per time)
$1/c$	average duration of immune period
r	per capita rate of recovery (per time)
$1/r$	average duration of recovery from disease
d	per capita rate of disease-induced death in human (per time)
e	proportion of bites on man that produces an infection (from mosquito ➔ human)
E	proportion of bites on man that causes infection in mosquitoes (from infectious human ➔ susceptible mosquito)
$\tilde{E}$	proportion of bites on man that causes infection in mosquitoes (from recovered human ➔ susceptible mosquito)
F	average number of bites per mosquito (per time)
D_1	density-independent death and emigration rate for humans (per time)
D_2	density-dependent death and emigration rate for humans (per time)
δ_1	density-independent death and emigration for mosquitoes (per time)
δ_2	density-dependent death and emigration for mosquitoes (per time)

All parameters of the model are assumed to be non-negative. The total populations are assumed to be positive for $t = 0$.

β_{MH} is the average number of mosquito bites which causes transmission of disease (from infectious mosquito ➔susceptible human) per mosquito (per time)

$$\beta_{MH} = eF \quad (10)$$

β_{HM} is the average number of mosquito bites which causes transmission of disease (from infectious human ➔ susceptible mosquito) per mosquito (per time)

$$\beta_{HM} = EF \quad (11)$$

$\tilde{\beta}_{HM}$ is the average number of mosquito bites which causes transmission of disease (from recovered human ➔ susceptible mosquito) per mosquito (per time)

$$\tilde{\beta}_{HM} = \tilde{E}\ F \quad (12)$$

I. MODEL ANALYSIS

The system of equations (1)-(9) is nonlinear coupled ordinary differential equations which need to be solved numerically. This is easily achievable given that the initial values for all the variables are specified and the parameter values indicated

appropriately. As mentioned before, there is numerous clinical research works on Malaria was done. Thus, for the purpose of simulating our model, we have taken the parameters values from various sources as cited accordingly:

$m = 1.217 \times 10^{-3}$ [18], $b = 2.417 \times 10^{-3}$ [18], $B = 4.227$ [17], $L = 3.0438$ [12], $u = 3.04375$ [17], $c = 8.333 \times 10^{-2}$ [9], $d = 1 \times 10^{-7}$ [6], $e = 1.2 \times 10^{-2}$ [16], $\delta_1 = 3.623$ [13], $\delta_2 = 6.722 \times 10^{-7}$ [13], E = 4.7×10^{-1} [11], $\tilde{E} = 2.35\text{x } 10^{-1}$ [10], $F = 7.609$ [11], $D_1 = 4.808 \text{ x } 10^{-4}$ [19], $D_2 = 1.000 \text{ x } 10^{-5}$ [13], $q = 8.333 \times 10^{2}$, $r = 5.558 \times 10^{-2}$ [21], where the unit of time is in month.

From the cases studied in [10], the number of cases with immunity is half of the cases without immunity. Hence, we took the probability of transmission from recovered human to susceptible mosquito, $\tilde{E}$ as half of that of from infectious human to susceptible mosquito, E.

Our model considered some infectious humans recover without any gain of immunity [7, 20] and some do acquire immunity. Here, we considered the average duration to build effective immunity. Our analysis includes the impact of the different values of the average duration to build effective immunity, $1/q$, on the infectious human population, I_H. This analysis is required since the actual mechanism of acquired immunity is yet to be understood [22, 23]. The value for q is not available and thus, we prescribed with a value which best fit on actual cases (see figure 4 later).

To run our simulation, we have prescribed the initial condition as S_H=18000, E_H = 0, I_H =40, R_H =35, S_M = 9000, E_M =0 and I_M =1000. Figure 2 shows the predicted human populations in the susceptible, infectious and recovered cases given the initial values above. We can see that Malaria is contagious based from the gradient of the susceptible curve. By the third month, the disease has infected half of the human population. This may be a possibility if there is no intervention to curb the spread of the disease. The outbreak reached its peak around the fifth month and then gradually decreases. From this simulation, we also observe that the disease prevails, that is as time progresses the infectious population seems to arrive to a limiting value. In order to study whether the disease will prevail or not, the basic reproduction number needs to be obtained which is not covered in this paper. The numerical results are verified by finding the steady state equilibrium points analytically for the human populations and then compare them with the numerical results.

The steady state equilibrium points are reached when the differential equations do not change with time. Therefore, to find steady state, we set all the differential equations (1-9) to zero. That is,

$$\frac{dS_H}{dt} = \frac{dE_h}{dt} = \frac{dI_h}{dt} = \frac{dR_h}{dt} = \frac{dS_M}{dt} = \frac{dE_m}{dt} = \frac{dI_m}{dt} = \frac{dN_H}{dt} = \frac{dN_M}{dt} = 0 \quad (13)$$

Having solved (13) we get the equilibrium point which is denoted by E_e below

$$E_e = (S_H^*, E_H^*, I_H^*, R_H^*, S_M^*, E_M^*, I_M^* N_H^*, N_M^*), \quad (14)$$

where

$$N_M^* = \frac{B - \delta_1}{\delta_2}, 0$$

$$N_H^* = \frac{b - D_1 + \sqrt{(D_1 - b)^2 - 4 D_2 (d I_H^* - m)}}{2 D_2},$$

$$E_M^* = \frac{(\delta_1 + \delta_2 N_M^*) I_M^*}{u},$$

$$S_M^* = \frac{(u + B)(\delta_1 + \delta_2 N_M^*) I_M^* N_H^*}{u \left[\beta_{HM} (I_H^*) + \tilde{\beta}_{HM} (R_H^*)\right]},$$

$$R_H^* = \frac{l I_H^*}{c + D_1 + D_2 N_H^*},$$

$$E_H^* = \frac{(l + r + d + D_1 + D_2 N_H^*) I_H^*}{L},$$

$$S_H^* = \frac{(L + D_1 + D_2 N_H^*) E_H^* N_H^*}{\beta_{MH} I_M^*}.$$

Notice that the functions for N_H*, R_H*, E_H* and S_H* are depending on I_H*. Thus, to check our numerical results, we take the value obtain for I_H* numerically and substitute it into the functions N_H*, R_H*, E_H* and S_H* in equation (14). Together with the prescribed values of all parameters involved, we can then calculate the value for N_H*, R_H*, E_H* and S_H*. These values are compared with the numerical results and we found them to be agreeable.

Numerical comparison of our model and that of Chitnis *et al*. [13] had been done in our previous work [24]. The paper [24] presented the differences and analysis between Chitnis model and ours.

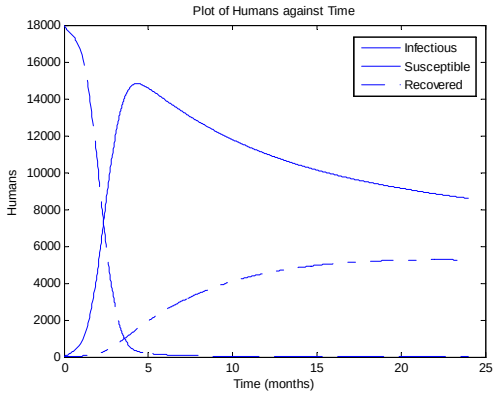

Figure 2: The predicted human populations for infectious, susceptible and recovered over time in months.

As mentioned earlier, one of the parameter which is still unknown is the average duration to build effective immunity $1/q$. Figure 3 shows the sensitivity of the parameter q towards the total infectious humans.

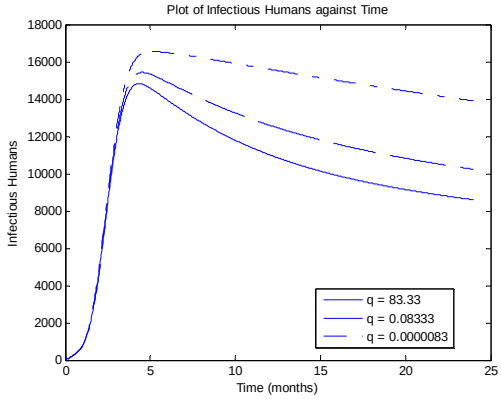

Figure 3: The total infectious humans when the value for per capita rate of building effective immunity per month varies.

It is observed that when the value for q is increased, the maximum number of infected humans decreased. This shows that if the average duration of acquiring immunity is small then the infected population is reduced significantly. Since this parameter is not available yet from the clinical research for Malaria, then we will use the actual incidences of Malaria in Malaysia to predict this value. Figure 4 depicts this result. Here, we found that the best value for q is 83.33. This means that the average duration to build effective immunity is approximately 9 hours after an infectious person has recovered from the disease.

As mentioned by Doolan *et al.* [23], the understanding of the rate of onset of acquired immunity is not clear. This is because of disagreements over relationship between exposure to infection, antigenic polymorphism and naturally acquired immunity [25]. However, with the understanding of naturally acquired immunity, experimental induced immunity against malaria can be duplicated to protect those who are exposed to the disease.

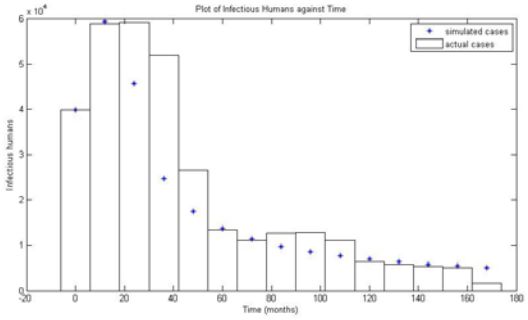

Figure 4: Yearly cases of Malaria in Malaysia from the year 1993 to 2007 (bar chart) and the predicted values (♦)

II. Conclusion

A malaria transmission model had been formulated and analyzed numerically. We can clearly see in our numerical analysis, that if the ability to build effective immunity is fast for those who recover from the disease, the number of cases can be reduced. We compared our simulation results with the actual malaria incidences in Malaysia (1993-2007) which is taken from Vector-Borne Diseases Section, Disease Control Division, Department of Public Health, Ministry of Health Malaysia. We performed our simulation in the absence of immunity and gradually increase the value of q, per capita rate of building effective immunity to estimate the value which is suitable. The value for q is found to be 83.333 which means the average duration to build effective immunity is approximately 9 hours after an infectious person has recovered from the disease. Therefore, after a person has recovered from the disease, safety precautions should still be taken for the first half of the day as the person can still be susceptible to Malaria. Also, the knowledge of the onset of acquired immunity can contribute to the research on the mechanism of the immunity and to develop effective vaccines for Malaria. Hence, malaria morbidity can be controlled by immunological means.

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