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Simulation of Mathematical Modeling of Malaria with Vaccination

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ABSTRACT
Objectives
General Objectives. To formulate and analyse malaria with vaccination.
Specific Objectives.
Formulation of malaria model with vaccination.
Estimation of model parameters
Numerical solution
To clarify the importance of vaccination through model parameters discussion.

Methodology: We build a model through a flowchart diagram. We simulate data which helps to find the parameter values that makes the model to fit to the data in order to verify the validity or adequacy of the model. We use the least squares method to estimate model parameters and interpretation of it. We analyze the model by computing the basic reproduction number R0, the disease-free equilibrium point and endemic point. And also discuss the behavior of numerical solution. We solve the model numerically using MATLAB software. Numerical solutions of the model are presented in graphical way that allows to visualize the model predictions.

Results: Model has shown that the vaccination rates reduce the basic reproduction number, which means that the vaccination are involved in eradicating malaria from the population. To control the spread of malaria disease, we introduced the herd immunity strategy which is concerned about immunizing a large number of people in population and take protective measures for the rest including children and also pregnancy women. Thus, we calculated the herd immunity threshold which is 0.0517, this value means that 5.17% of susceptible people has to be immunized to control the spread of plasmodium parasite. Our model was fitted to simulated data which implies that the model can be used to control the transmission of malaria and to predict the mechanism of prevention by vaccination, it has shown that the vaccination strategy involves in eliminating malaria.

Unique contribution: Malaria is an infectious disease that has become very common and is becoming more widespread in an uncontrolled way throughout Africa, as well as the whole world, due to the bite of the female anopheles' mosquito which spreads the plasmodium. In an attempt to eradicate this deadly disease, a massive response needs to be mounted by governments to enlighten the public about the prevalence of malaria and also provide remedy for treatment of it. On this issue, over the last few decades there have been millions of dollars and much efforts put into the fight against Plasmodium falciparum malaria but unfortunately there is still no registered vaccine against it. Is the vaccination the best strategy to reduce the number of peoples dying from malaria? Many researchers worked on different model and they did not introduce the vaccination, in my model Introduce the vaccination to see if it is the best strategies to eradicate the number of people dying from malaria

KEYWORDS: Basic reproduction number, Disease free equilibrium, Herd immunity, Malaria, Vaccination.

INTRODUCTION

Malaria is a contagious parasitic disease caused by a parasitic organism called plasmodium, it means it is transmitted between humans through bites of female Anopheles mosquitoes and also from person to person by a female Anopheles mosquito. It has been more than six decades to develop effective vaccines. Malaria discovered by **(cox, 2012)**was the first to notice parasites in the blood of a patient suffering from malaria. Malaria is a mosquito borne infection caused by protozoa of the genus plasmodium. Four species of the parasite, namely: plasmodium falciparum, plasmodium vivax, plasmodium ovale and plasmodium malaria infect humans. The parasites are transmitted indirectly from human to human by the bite of infectious female mosquitoes of the genus Anopheles.

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The biology of the four species of plasmodium is generally similar and consists of two distinct phases: a sexual stage at the mosquito host and an asexual stage at the human host. Studies of inactivated sporozoite immunization reported in showed an apparently beneficial effect of combining induction of cellular and humoral immune responses against malaria of domestic fowl (**(Paul F. Russell, 1992**)Around the same time, Freund was developing a powerful adjuvant that showed promising efficacy in malaria studies. However, today, there is still no licensed vaccine against malaria or any other parasitic disease of humans and no deployed subunit vaccine for any parasitic disease of livestock

(D. P. Knox, 2006). Nonetheless, the continuing unacceptable impact of malaria morbidity and mortality, amounting to over 800 000 deaths and some 250 million clinical episodes annually

(al, 2015), has led to a variety of sustained efforts to develop effective malaria vaccine candidates. In the last decade in particular, the development of vaccine candidates for malaria has accelerated considerably and one candidate has recently reached the stage of a large-scale phase III trial while other potentially complementary approaches are showing increasing promise. In this project, I focus on finding the vaccine that suit best strategy to reduce the number of 86 people dying from malaria.

Mathematical Modeling In this section, talk about mathematical modeling and its process, as well as how mathematical models appeared in epidemiology. Mathematical modelling is a way of changing the real-life problem or situation into the mathematical language with the purpose of making the problem simple to understand, analyze and solve for future predictions and decision making. There different types of mathematical model, deterministic and stochastic model. Deterministic models are mathematical models by which the predicted outputs are precisely determined using parameter values and initial conditions. Whereas the stochastic are such models which possess the distribution of possible outcomes **(Peter Henderson, 2020)**

Step of Modeling

Model formulation: To formulate a mathematical model we have first to recognize the objectives of our model then define accordingly the variables and parameters of the model system. The second thing is to make assumptions for the model in order to get an insight of how the model will operate. We also have to design a flow diagram that allows the system. Visualization in a pictorial way that makes the model easy to understand. A flow diagram consists of boxes joined by arrows, the boxes represent physical features in the system while the arrows show how these features are related. Moreover, we have to choose the appropriate equations which govern the system and solve them analytically and numerically to support analysis **(Courchamp, 2008)**

The model analysis: After forming a model we make a study of its behavior by varying model parameters and checking the changes of model output. In this step, we use parameter estimation from existing data **(Courchamp, 2008)**

We Testing the model: In testing we have to check that the model assumption and predictions meet physical features of the problem. We also have to assess the model structure if it is simple and well understood in order to allow the model to be accessible for future users **(Courchamp, 2008)**

Using the model: After validation of the model, we can use that model for in predictions, planning and decision making **(Courchamp, 2008)**

Model validation.

Validation is the process of determining the model accuracy for the real-world situations based on the modeler's purpose. To validate the model, the analysis of model residuals (errors)is needed. Residuals (ei) are defined as the difference between observed data (yi) and expected data ($\bar{y\imath}$). The following assumptions have to be fulfilled in order to say that the model is valid i. (ei) are normally distributed which is represented by the bell shape of the histogram plot of the residuals (errors). Also, the normality occurs if the normal probability plot or quantiles plot (sample quantile vs theoretical quantile) of residuals is a straight line **(Ecotoxicology, 2009)** ii. (ei) have mean zero, this indicated by the random oscillation having mean zero, around zero on residuals plot (residuals against time)

(David M. Eddy, 2012). iii. (ei) have the same variance. An equal variance is represented by the absence of outliers (extreme observations) and the horizontal band (from left to right) of errors on residuals plot **(David M. Eddy, 2012).** iv. (ei) have to be independent. The independent of error terms the independence of error terms called residuals is shown by the analysis of auto correlation plots. We define auto correlation function as the measure of correlation between observation of the same variable which are separated by K time units. Mathematically the auto correlation function at lag k with N observations is given by

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$R_k=\sum_i^{n-k}\frac{(yi-\overline{yi})(yi-\overline{yi})}{\sum_n^k yi-\overline{yi}}$ Where Y is denoted by the sample mean of observation (y). On the auto correlation plot, the X-axis represents lags at which the auto correlation are computed, while the Y-axis represents the auto correlation. The auto correlation plots determine the randomness and independence in a data set. If there is a random scattering in auto correlation plot, it indicates the lack of autocorrelation which means that the error term for the lag (k) is independent with the error term of the different **(David M. Eddy, 2012).**

MODEL OF MALARIA IN FORM OF SEIR EPIDEMIC MODEL

Example of researcher **(Nita H. Shah, 2013),** who worked on SEIR model of malaria, he said that the population of our model is divided into four compartments: Susceptible humans S(t), Exposed human E(t), Infectious humans I(t) and Removed humans R(t). The interactions between the four compartments are as follow:

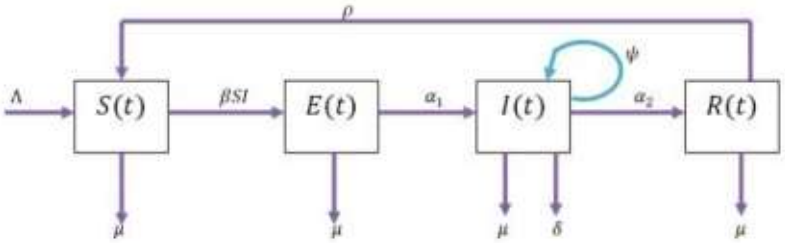

Figure 1: SEIR Epidemic model

The model is given by the system of ODE's as:

$dS\ dt = \Lambda - \beta SI - \mu s + \rho R$

$dE = \beta SI - (\Lambda + \mu)\ E\ dI$

$dt = \Lambda_1 I - (\alpha 2 + \mu + \delta)\ I + \Psi I$

$dR\ dt = \Lambda_2 I - (\mu + \rho)\ R$

Table 1: The parameter description of Malaria in form of SEIR Epidemic model

Parameter	Parameter Description
Λ	Input flow of the susceptible
β	Infection rate
α_1	Developing rate of exposed humans
α_2	Recover rate of humans
μ	Natural death rate
δ	Induced death rate
Ψ	Newborn's birth rate entered compartment I

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(Nita H. Shah, 2013) computed basic reproduction number (R_0) which has the largest eigenvalue, and he end up by concluding that the disease is invade the population if there is no decision measure taken by the government.

MODEL OF MALARIA WITH VACCINATION

Model modeled by **(Nita H. Shah, 2013)** and other different researchers were lucking the mosquito population and they did not check whether the vaccination can stop malaria infectious disease.

I introduce the vaccination which is the best strategy to stop malaria infectious disease. The following model introduces the mathematical model that address as the following question:

• What fraction of the population must be successfully vaccinated to eradicate the infectious agent? Here we have a model that will help us to answer the above questions. The following model can be applied with the aim of finding a vaccination that will help us to eradicate an infectious agent.

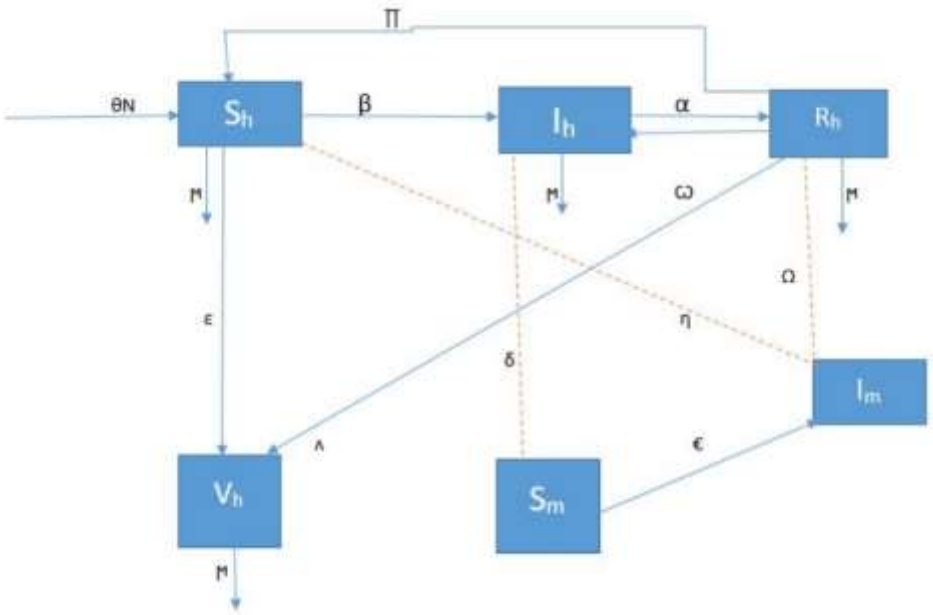

Figure 2: Model of Malaria with Vaccination

The model is given by system of ODE's:

$dS_h = \theta N + \pi R_h - \beta S_h - \varepsilon S_h - \eta S_h I_m - \mu S_h$

$dI_h = \beta Sh + \omega R_h - \alpha I_h + \delta S_m I_h - \mu I_h$

$dR_h = \alpha I_h - \omega R_h - \Lambda R_h - \pi R_h - \Omega R_h I_m - \mu R_h$

$dI_m = S_m + \eta S_h I_m + \Omega R_h I_m$

$dS_m = S_m - \delta S_m Ih$

$dV_h = \varepsilon S_h + \Lambda R_h - \mu V_h$

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The parameter description of malaria model with vaccination is given by:

Table 2: The parameter description of malaria model

Parameter	Description of parameter
α	Infection rate of human
β	Treatment rate
ω	Relapse rate of human
Λ	Vaccination rate from recovered human to vaccination human
δ	Contact rate between susceptible mosquitoes and infectious population
η	Contact rate between susceptible population and infectious mosquitoes
θ	Recruitment rate
ε	Proportion rate of susceptible successfully vaccinated
μ	Natural death rate
Ω	Contact rate between recovered human and Infected mosquitoes
Π	Recovery rate of human
ϵ	Infection rate of human

Stability Analysis. In this part, we study the behavior of our model by changing the scale of variable, finding the disease-free equilibrium and endemic equilibrium point. We computer the basic reproduction number which shows us the spread of malaria disease.

Model rescaling. To study the analysis of the model we have first to rescale the model variable because the compartments can have a large size which is difficult to analyze, therefore it is important to use the rescaled of variables:

Hence the model becomes:

$dS_h = \theta + \pi R_h - \beta S_h - \varepsilon S_h - \eta S_h I_m - \mu S_h$

$dI_h = \beta S_h + \omega R_h - \alpha I_h + \delta s_m I_h - \mu I_h$

$dR_h = \alpha I_h - \omega R_h - \Lambda R_h - \pi R_h - \Omega R_h I_m - \mu R_h$

$dI_m = \varepsilon s_m + \eta S_h I_m + \Omega R_h I_m$

$ds_m = \varepsilon s_m - \delta s_m I_h$

$dV_h = \varepsilon S_h + \Lambda R_h - \mu V_h$

Equilibrium Point.

An equilibrium point is the point $x*R$ at which the derivative vanishes the differential equations $dx\ dt\ |x=x* - f(t, x*) = 0$. In epidemiology, we consider two types of equilibrium point which are disease free equilibrium ($I_h = 0$) and ($I_m = 0$) and endemic equilibrium point ($I_h \neq 0$) and ($I_m \neq 0$). The disease-free equilibrium is defined as the state where the disease is absent in the population while endemic equilibrium point is the point at which there is a disease in the population. Hence, the equilibrium point of our model system is computed by letting $dS_h dt = 0$, $dI_h dt = 0$, $dR_h = 0$, $ds_m\ dt = 0$, $dI_m\ dt = 0$, $dV_h\ dt = 0$

Stability of disease-free equilibrium

To make a study of the disease-free state, we have to analyses the model around disease free equilibrium E_O. We compute the Jacobian matrix at E_O., then find eigenvalues of the Jacobian matrix which helps to analyse the stability of equilibrium point. If all eigenvalues are real and negative then the disease-free equilibrium is asymptotically stable. Whereas the disease-free equilibrium is said to be unstable if eigenvalues have distinct signs (one positive, others negative). If there are complex eigenvalues with the negative real part then the disease-free equilibrium is stable and unstable otherwise. For an n dimension vector function **(etal., 2018)**

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Since we have assumed that all parameters are positive, thus $\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5$ and λ_6 all are negative. Then E_0, can be stable if λ_6, is also negative, which means that the infection will be eradicated **(etal., 2018)**,But for $\lambda_6 = \omega - \mu$ if $\omega > \mu$, thenλ_6 become positive, so disease free equilibrium is not stable. It will be stable if the value of λ_6 is negative, λ_6 to be negative is where ω and μ are both negative. Then the value of λ_6 will become $\lambda_6 = -(\omega + \mu)$ which negative. This implies that E_0 will be stable. By conclusion $\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5$ and λ_6 will became both negative which means disease free equilibrium is stable. Therefore, the infection will be eradicated in the population.

STABILITY ANALYSIS OF ENDEMIC EQUILIBRIUM POINT

The stability of endemic point is determined by eigenvalues of the Jacobian matrix at endemic 509 equilibrium points.

$$\lambda_1 = -\beta - \varepsilon - \eta\left(\frac{\theta - \frac{\Pi\alpha}{(\omega+\Pi+\Lambda-\Omega+\mu)}}{\eta\frac{(\alpha-\mu)}{\beta+\omega}} + \frac{1}{\eta}(\varepsilon - \beta + \mu)\right) - \mu$$

$$\lambda_2 = -\alpha - \mu$$

$$\lambda_3 = -\omega - \Pi - \Lambda + \Omega\left(\frac{\theta - \frac{\Pi\alpha}{(\omega+\Pi+\Lambda-\Omega+\mu)}}{\eta\frac{(\alpha-\mu)}{\beta+\omega}} + \frac{1}{\eta}(\varepsilon - \beta + \mu)\right) - \mu$$

$$\lambda_4 = \epsilon + \delta\left(\frac{\theta - \frac{\Pi\alpha}{(\omega+\Pi+\Lambda-\Omega+\mu)}}{\eta\frac{(\alpha-\mu)}{\beta+\omega}} + \frac{1}{\eta}(\varepsilon - \beta + \mu)\right)$$

$$\lambda_5 = \Omega\left(\frac{\alpha}{(\alpha + \pi + \Lambda - \Omega + \mu)}\right)$$

$$\lambda_6 = -\mu$$

$$\lambda_1 = -\beta - \varepsilon - \eta\left(\frac{\theta - \frac{\Pi\alpha}{(\omega+\Pi+\Lambda-\Omega+\mu)}}{\eta\frac{(\alpha-\mu)}{\beta+\omega}} + \frac{1}{\eta}(\varepsilon - \beta + \mu)\right) - \mu$$

$$\lambda_2 = -\alpha - \mu$$

$$\lambda_3 = -\omega - \Pi - \Lambda + \Omega\left(\frac{\theta - \frac{\Pi\alpha}{(\omega+\Pi+\Lambda-\Omega+\mu)}}{\eta\frac{(\alpha-\mu)}{\beta+\omega}} + \frac{1}{\eta}(\varepsilon - \beta + \mu)\right) - \mu$$

$$\lambda_4 = \epsilon + \delta\left(\frac{\theta - \frac{\Pi\alpha}{(\omega+\Pi+\Lambda-\Omega+\mu)}}{\eta\frac{(\alpha-\mu)}{\beta+\omega}} + \frac{1}{\eta}(\varepsilon - \beta + \mu)\right)$$

$$\lambda_5 = \Omega\left(\frac{\alpha}{(\alpha + \pi + \Lambda - \Omega + \mu)}\right)$$

$$\lambda_6 = -\mu$$

The endemic point of E_0 will be stable if $\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5$ and λ_6 are real and negative. But in this model the endemic point of disease-free equilibrium the value of eigenvalue is real with distinct signs it means that the endemic equilibrium point is saddle point unstable which means that malaria will remain in the population if there are no measures taken to eradicate it.

BASIC REPRODUCTION NUMBER

The basic reproduction number indicates the number of people who can be contaminated by one infected person. **(Richards, 1923),** explains how to determine R_0 using next-generation matrix G = F V, R_0 is the absolute value of largest eigenvalue of matrix G and it is denoted by $R_0 = \rho F\ V - 1$

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$$\lambda_1 = \frac{\eta\theta\omega}{[(\alpha+\mu)(\omega+\pi+\Lambda-\mu)]-(\alpha\gamma)(\beta+\mu+\varepsilon)}$$

$\lambda_2 = 0$

$\lambda_3 = 0$

Since all parameter are positive, then $R_0 = \frac{\eta\theta\omega}{[(\alpha+\mu)(\omega+\pi+\Lambda-\mu)]-(\alpha\gamma)(\beta+\mu+\varepsilon)}$ which the largest eigen value. Once this $(\eta\theta\omega) > [(\alpha+\mu)(\omega+\pi+\Lambda-\mu)]-(\alpha\gamma)(\beta+\mu+\varepsilon)$, R_0 will became positive ($R_0 > 1$) which means the disease-free equilibrium is unstable, then the disease is epidemic so it will invade the population. Once $[(\alpha+\mu)(\omega+\pi+\Lambda-\mu)]-(\alpha\gamma)(\beta+\mu+\varepsilon) > (\eta\theta\omega)$ R_0 will became negative ($R_0 < 1$) which means that the disease-free equilibrium is stable then the disease is eradicated in the population. If $[(\alpha+\mu)(\omega+\pi+\Lambda-\mu)]-(\alpha\gamma)(\beta+\mu+\varepsilon) = (\eta\theta\omega)$ then $R_0 = 1$ which means the disease is endemic, so one infected mosquito can infect only one person

NUMERICAL SIMULATION

The numerical simulation of system is done by using MATLAB software and also it helps us to display the results in the graphical representation that allows us to analyse and interpret the predicted model solutions. Parameter estimation. To find predicted results, we have to estimate the parameter value, so that the model can fit the simulated data. In this section, we use Least Square method for parameters estimation. The method consists of finding the estimators which minimize errors (the sum of square of difference between response or dependent variable with fitted response) (Sorenson). Consider the nonlinear model in matrix form with n observations: $Y = f(X, \beta) + \varepsilon$, where Y: $n \times 1$ vector of response or variable of interest, X: $n \times m$ matrix representing the independent variables, β: $m \times 1$ vector of model parameters or coefficients and C: $n \times 1$ vector of errors. Hence the estimator of β is b which minimizes the objective function (Sum squared errors) $Q = \sum_{i=1}^{n} (yi - f(Xij, \beta j))$ Where $\hat{\beta}$ is found by solving for $\hat{\beta}$ equation

$$\frac{\partial Q}{\partial \beta}\Big|_{\beta=\hat{\beta}} = 0.$$

The initial parameter values and estimated values, the initial values of variables are 0.003, 0.002, 0.0003, 0.01, 0.0005, 0.03, 0.03, 0.03, 0.0001, 0.02, 0.02, 0.01 SVIR respectively.

Table 2: Numerical simulation of SVIR Model

Parameter	Initial value	Estimated value
Infection rate (α)	0.0005	0.0005
Treatment rate (β)	0.002	0.0025
Relapse rate of human (Ω)	0.01	0.0104
Vaccination rate (ʌ)	0.03	0.0328
Contact rate between susceptible mosquitoes and Infected population (δ)	0.01	0.0102
Contact rate between susceptible population and Infected mosquitoes (η)	0.0001	0.0001
Recruitment rate (θ)	0.003	0.0032
Proportional rate of susceptible successful vaccinate (ε)	0.003	0.0315
Natural death rate (ᴘ)	0.02	0.0295
Contact rate between recovered human and Infected mosquitoes (Ω)	0.03	0.0328
Recovery rate of human (∏)	0.0003	0.0003
Infection rate of human (€)	0.02	0.0293

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Numerical solutions.
In this section we present the numerical solutions of our model.

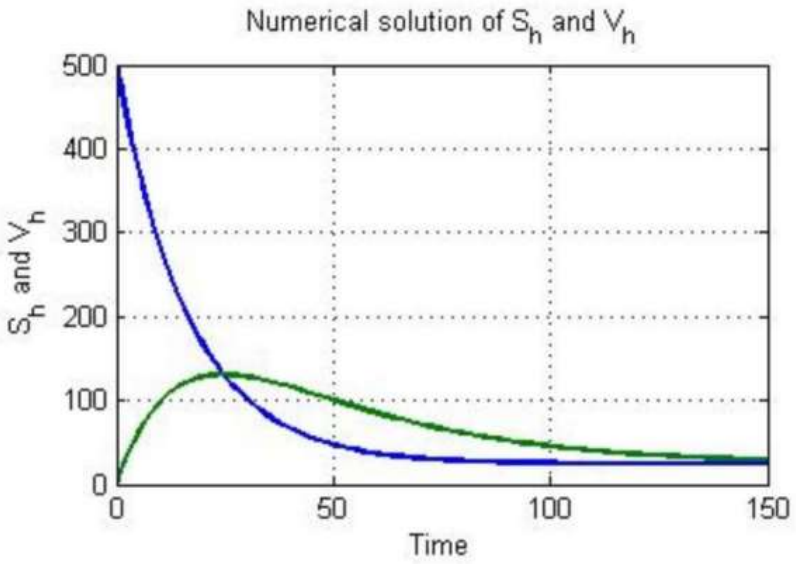

Figure 3: Behaviour of susceptible human and vaccinated portion infection process

This figure represents the behaviour of susceptible human and the vaccinated portion during infection process. The number of susceptible peoples starts decreasing due to the fact that some of them have direct contact with Infected people then they move to Infected class, while others get immunization and move to the class of vaccinated peoples. Other hand the vaccinated people increase because there is presence of newborns and also decreases because some of the people can die naturally or due to other disease.

FITNESS OF THE MODEL
To see if the model will be useful in prediction, we have to check if the model fits the collected or simulated data. In this project, we use simulated data.

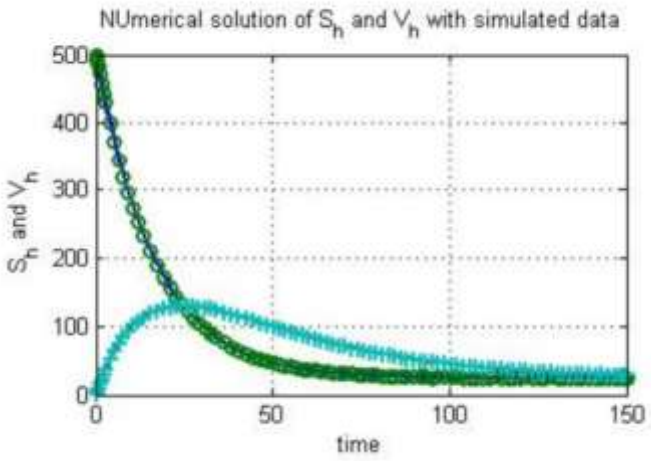

Figure 4: Figure shows the model fits the simulated data

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This Figure indicates the how our model fits the simulated data. As you can see the model fits very well the data because there are no outliers but and also show us how the number of susceptible decreases slowly by slowly due to the vaccination have taken to the people, and also the vaccinated people decrease due to the people die with other natural diseases. Another to know the portion of people needed to be vaccinated we have to compute the herd immunity. From the basic reproduction number, we can derive the Herd immunity threshold as follows H =1- $\frac{1}{R0}$ = 0.0517 637 This value means that 5.17% of susceptible people has to be immunized to control the spread of plasmodium parasite

CONCLUSION AND RECOMMENDATION FUTURE WORK

Conclusion

Mathematical modeling can be used as a tool for disease control strategy and predict the next outbreak which allows taking measures for prevention and treatment. In this project, we developed a mathematical model of malaria with vaccination. An SVIR model was utilized to propose the vaccination which can be used in immunization of those who are susceptible to malaria and those who are cured malaria simultaneously used as treatment of infected people. In fact, we hope that the proposed vaccination and treatment strategy will be helpful to control the spread malaria infection. We have analyzed our model by studying the stability of disease-free equilibrium, endemic equilibrium point and by computing the basic reproduction number R0. The result found after simulating data and estimation of parameter values show that disease free equilibrium is stable while endemic equilibrium point is saddle point unstable which means that malaria infection exits and spread in the population. We got the estimated value of basic reproduction number R_0 = 1.05456 which indicates that a single infected person can infect approximately one person, and malaria will be lower spread if a lot of number of peoples continue to take vaccination. It has shown that the vaccination rates reduce the basic reproduction number, which means that the vaccination are involved in eradicating malaria from the population. To control the spread of malaria disease, we introduced the herd immunity strategy which is concerned about immunizing a large number of people in population and take protective measures for the rest including children and also pregnancy women. Thus, we calculated the herd immunity threshold which is 0.0517, this value means that 5.17% of susceptible people has to be immunized to control the spread of plasmodium parasite. Our model was fitted to simulated data which implies that the model can be used to control the transmission of malaria and to predict the mechanism of prevention by vaccination, it has shown that the vaccination strategy involves in eliminating malaria.

Recommendation

After analyzing the result of our model and understanding how malaria infection spread, we recommend the following to eradicate malaria in the population irrespective some of the practices implemented by governments such as spreading of mosquito nets and spraying of insecticides. All people have to be educated on malaria infection. The infected people must know how to take drugs before malaria attack them or they must know how to take vaccination before being infected. In general, everyone must have the basic information on malaria. He should have early detection and treatment. If someone have malaria signs like fever should go to the hospital to consult the doctor to be treated and thereafter, she/ he should not forget to take the vaccination of malaria disease. Health centers have to make a regular checkup in villages in order to identify people who have malaria or who do not have it so as to give them the vaccination before they.

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