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Stability Analysis Model of *Plasmodium vivax* from *Anopheles* in Human Infection using SIDR Population Compartment with Treatment RTS-S/AS01 Vaccine in Yogyakarta

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Abstract

As the world population grows, many urban and rural area become the nest of malaria. Malaria is one of the most dangerous diseases for human beings and can be fatal. Malaria is caused by *Plasmodium* derived from the parasite protozoa class that multiplies in human blood cells. Malaria transmission occurs through the bite of *Anopheles* female mosquito that has been infected by *Plasmodium vivax*. The transmission process through the female *Anopheles* mosquito can be represented in mathematical model with the SIDR population approach. So far, research on mosquito breeding and spread of this type of disease only uses a mathematical model with the SIR population approach. Update from this research is to add populations of dormant species, populations that allow a person to positively heal or not. In this research the quantitative method is used that utilizes history data to create new model to be applied along with treatment that determined the RTS-S/AS01 vaccine does influence to prevention and reduction of infected population. The results obtained based on the model and graph is the treatment of RTS-S/AS01 vaccine which can reduce the number of infected population. Therefore, it can be concluded that the RTS-S/AS01 vaccine can prevent the spread of malaria disease. The objective of this study is to examine the spread of malaria and provide the solutions that malaria can be prevented from spreading using the RTS-S/AS01 vaccine.

Keywords: *Anopheles*, *Plasmodium vivax*, SIDR, Stability Analysis.

Introduction

Indonesia as one of the developing countries is vulnerable and still at risk of malaria. In 2009 there were about 2 million cases of clinical malaria and 350 thousand cases which were confirmed positive. While in 2010, it increased to 1.75 million cases and 311 thousand of which are confirmed positively. In fact, up to the last year, there was an outbreak and an increase in malaria cases in 8 provinces, 13 regencies, 15 sub-districts and 30 villages with positive malaria cases of 1256 patients and 74 deaths. This number has increased compared to 2009, where only the outbreak in 7 provinces and districts, 7 districts and 10 villages with the number of 1107 patients with 23 deaths [1].

From several cases of malaria above, then came the various studies that construct a mathematical model for malaria. The spread of malaria is usually illustrated by the Ross-MacDonald model. The Ross-MacDonald model is a model that only suitable for the spread of malaria by female *Anopheles* mosquitoes infected with *Plasmodium falciparum* with the possibility of the disease not recurring [1]. For the mathematical model of malaria transmission by female *Anopheles* mosquitoes infected with *Plasmodium vivax* it is necessary to have a limited scope, the distribution model depends only on the human population and the mosquito [2]. In determining most mathematical models according to biological developments until now it takes a cycle of transmission from humans to diseases caused by this parasite. Sporozoite phase

occurs when mosquitoes bite human and then it infects to the liver and becomes merozoite phase. The form of merozoite then enters the human bloodstream and infects the red blood cells. Sporozoites that are still present in the liver form a hypnozoite that can last very long even for years so it will cause a recurrence [3].

Therefore, in order to model the pattern of data that has the effect of the dispersion varies, the SIDR population approach can be used. In this study, researchers focused more on places that are susceptible to malaria attacks and attention is not given to time therefore this causes the time variable which cannot affect the model [4].

MATERIALS AND METHODS

Data Collection

Data for this research is the number of malaria cases in Yogyakarta that has been obtained directly from the Ministry of Health of the Republic of Indonesia in 2003 until 2013 and data surveyed are focused in Yogyakarta area in 2017.

Modeling of Infection Pat

Broadly speaking, the mathematical model of *Plasmodium vivax* malaria illustrates the path of disease spread from susceptible populations group to the infected populations, the infected populations who are able to survive from the disease will recover but will recur if the hypnozoite which is also sporozoites that are still present in the liver active again, entering the dormant group [5]. The subsequent infected populations who are able to withstand the disease will recover and enter the recovered group and have permanent immunity to malaria. There is a period of time before the population becomes infected in malaria.

SIDR modeling is done by determining the following variables:

(a) Susceptible is a group of healthy populations but infected with malaria.
(b) Infected is a group of infected populations and can recover from malaria [6].
(c) Dormant is a group of populations who can recover but can recur.
(d) Recovered is a group of populations who have recovered from malaria with vaccines.

Interpretation Model

Result of modeling the spread of Malaria disease with SIDR compartment is then interpreted into the differential equation obtained from the process of making model analysis in order to be more easily understood. The obtained SIDR model is then used to predict the number of malaria patients to be treated with the RST-S/AS01 vaccine starting in April 2017.

RESULTS AND DISCUSSION

The model discussed in this paper is the SIDR model in which the population is divided into four distinct population classes of susceptible, symptomatic infective, dormant and recovered populations with differential equations [7].

Malaria is caused by *Plasmodium* derived from the parasite protozoa class that multiplies in human blood cells. Malaria transmission occurs through the bite of *Anopheles* female mosquito that has been infected by *Plasmodium vivax*. The transmission process through the female *Anopheles* mosquito can be represented in a mathematical model with the SIDR population approach. So far, research on mosquito breeding and the spread of this type of disease only uses a mathematical model with the SIR population approach. Update from this research is to add populations of dormant species, populations that allow a person to be positively recovered or not. Malaria disease model with SIDR compartment can be formulated as follows:

Model endemic virus *Plasmodium vivax* with quarantine:

$$\frac{ds}{dt} = \delta - \alpha s(t) i_s(t) - \mu s(t),\ s(0) > 0 \text{ (Eq.1)}$$

$$\frac{di_s}{dt} = \beta p e(t) - \theta i_s(t) - \mu i_s(t),\ i_s(0) > 0 \text{ (Eq.2)}$$

$$\frac{dd}{dt} = \theta i(t) - \rho d(t) - \mu d(t),\ d(0) > 0 \text{ (Eq.3)}$$

$$\frac{dr}{dt} = \rho d(t) - \mu r(t),\ r(0) > 0 \text{ (Eq.4)}$$

$$N(t) = s(t) + +i_s(t) + d(t) + r(t) \text{ (Eq.5)}$$

A. Assumption

1. Malaria virus infection occurs internally in the human body.
2. Changes in the population remain, so the rate of birth is equal to the rate of death.
3. The population of each district/city in Indonesia is equal to the number of human population in Sleman district, Yogyakarta.
4. The percentage of adding the number of human beings per compartment is the same.
5. No other microorganisms attack humans other than the malaria virus.
6. The rate of recovery is constant.
7. Any infected quarantined will recover.
8. Viral deaths are ignored.
9. All infected humans have symptoms of malaria disease.
10. Variables:
    Susceptible is a group of healthy populations but infected with malaria.
    Infected is a group of infected populations and can recover from malaria. Dormant is a group of populations who can recover but can recur.
    Recovered is a group of populations who have recovered from malaria with vaccines.
11. Free viruses multiply in population infected with rate of α (virus transmission rate).
12. The rate of recovery from infected to recovered is the same as quarantine to recovered.
13. In the model, all parameters of positive value with the immune system (p) are in the interval $0 < p < 1$.

B. The Point of Free-Disease Equilibrium

By taking $\frac{dS}{dt} = 0, \frac{dI_s}{dt} = 0$, the author managed to get the equilibrium point of the model [8]. If take $i^0 = 0$, the disease-free equilibrium point will be obtained, where in this state all populations enter the

susceptible population and no infected population can spread the disease. So the free equilibrium point of the human population is $E_1 = (s^0, i_s^0, d^0) = (\frac{\delta}{\mu}, 0,0)$.

C. The Point of Epidemic Equilibrium

If taken $i^0 \neq 0$, it can be shown that the point of disease (bacteria) is free where there are infective humans that can spread the disease and cause endemic [9]. So that the epidemic equilibrium point in the human population is $E_2 = (s^*, i_s^*, d^*)$ with:

$s^* = \frac{\beta\theta p+\beta\mu p+\theta\mu+\mu^2}{\alpha\beta p}$ (Eq. 6)

$i_s^* = \frac{-\alpha\beta\delta p+\beta\theta\mu p+\beta\mu^2 p+\theta\mu^2+\mu^3}{(\beta\theta p+\beta\mu p+\theta\mu+\mu^2)\alpha}$ (Eq.7)

$d^* = -\frac{\theta(-\alpha\beta\delta p+\beta\theta\mu p+\beta\mu^2 p+\theta\mu^2+\mu^3)}{\alpha(\beta\theta\mu p+\beta\theta p\rho+\beta\mu^2 p+\beta\mu p\rho+\theta\mu^2+\theta\mu\rho+\mu^3+\mu^2\rho)}$ (Eq. 8)

Consequently the equilibrium point for the mathematical model of the *Plasmodium vivax* transmission process in humans has two equilibrium points:

1. The disease-free equilibrium point

   $E_1 = (s^0, i_s^0, d^0) = (\frac{\delta}{\mu}, 0,0)$ (Eq. 9)

2. Epidemic equilibrium point

   $E_2 = (s^*, i_s^*, d^*)$ (Eq. 10)

D. Basic Reproduction Number (R_0)

To determine the basic reproduction rate is to assume $I_s^* > 0$ [10]. Based on equilibrium point, the epidemic E_2 is obtained:

$\frac{-\alpha\beta\delta p+\beta\theta\mu p+\beta\mu^2 p+\theta\mu^2+\mu^3}{(\beta\theta p+\beta\mu p+\theta\mu+\mu^2)\alpha} > 0$ (Eq.11)

$-\alpha\beta\delta p + \beta\theta\mu p + \beta\mu^2 p + \theta\mu^2 + \mu^3 > 0$ (Eq. 12)

$\frac{(\beta\mu p+\mu^2)(\theta+\mu)}{\alpha\beta\delta p} > 1$(Eq. 13)

Defined $R_0 = \frac{(\beta\mu p+\mu^2)(\theta+\mu)}{\alpha\beta\delta p}$

Based on the value of R_0,

1. If $R_0 \leq 1$ then the quarantine model equation system has one equilibrium point, i.e. the equilibrium-free equilibrium point $E_1 = (s^0, i_s^0, d^0)$.
2. If $R_0 > 1$ then the quarantine model equation system has two equilibrium points, i.e. the equilibrium point of disease E_1 and the equilibrium point of free disease $E_2 = (s^*, i_s^*, d^*)$.

I. FREE DISEASE EQUILIBRIUM ANALYSIS

Given a Jacobian matrix on human populations:

$$J = \begin{bmatrix} -\alpha i_s - \mu & 0 & -\alpha s & 0 \\ \alpha i_s & -\beta p - \mu & \alpha s & 0 \\ 0 & -\beta p & -\theta - \mu & 0 \\ 0 & 0 & \theta & -\rho - \mu \end{bmatrix}$$ (Eq. 14)

$$J(E_1) = \begin{bmatrix} -\mu & 0 & -\alpha\frac{\delta}{\mu} & 0 \\ 0 & -\beta p - \mu & \alpha\frac{\delta}{\mu} & 0 \\ 0 & -\beta p & -\theta - \mu & 0 \\ 0 & 0 & \theta & -\rho - \mu \end{bmatrix} \text{ (Eq. 15)}$$

The eigen value is obtained from $\det(J(E_1) - \lambda I) = 0$, the characteristic equation is obtained:

$$-\frac{(-\mu-\lambda)(\rho+\mu+\lambda)(\beta\mu^2 p\theta+\alpha\beta\delta p+\beta\lambda\mu p+\lambda\mu^2\theta+\mu^3\theta+\lambda^2\mu+\lambda\mu^2)}{\mu} \quad \text{(Eq. 16)}$$

So obtained eigen value as follows:

$\lambda_1 = -\mu$ (Eq. 17)

$\lambda_2 = -\rho - \mu$ (Eq. 18)

$\lambda_3 = \frac{1}{2}\frac{(-\beta\mu p-\mu^2\theta-\mu^2+\sqrt{F})}{\mu}$ (Eq. 19)

$\lambda_4 = -\frac{1}{2}\frac{(\beta\mu p+\mu^2\theta+\mu^2+\sqrt{F})}{\mu}$ (Eq. 20)

With $F = \beta^2\mu^2p^2 - 2\beta\mu^3p\theta + \mu^4\theta^2 - 4\alpha\beta\delta\mu p + 2\beta\mu^3p - 2\mu^4\theta + \mu^4$.

The equilibrium point of a system is said to be stable if the roots of the characteristic equation of a matrix have eigen values with a real negative part.

Lemma 1.

1. If $\lambda < 0$ then the equilibrium point E_1 of the model equations system is stable asymptotically.
2. If $\lambda > 0$ then the equilibrium point E_1 of the model equation system is unstable.

Evidence:

From the above equation, the eigen value $\lambda_1 = -\mu$, whereas it is known that μ is positive, so the real part of the first eigen value is negative.

From the above equation, the eigen value $\lambda_2 = -\rho - \mu$, whereas it is known that ρ is positive therefore the real part of the second eigen value is negative.

Because the values of all compartments are positive, whereas the values of the first and second eigen are negative,$(-\beta\mu p - \mu^2\theta - \mu^2) = \sqrt{(-\beta\mu p - \mu^2\theta - \mu^2)^2} > \sqrt{\beta^2\mu^2p^2 - 2\beta\mu^3p\theta + \mu^4\theta^2 - 4\alpha\beta\delta\mu p + 2\beta\mu^3p - 2\mu^4\theta + \mu^4}$, so the eigen values of λ_3 and λ_4 are either negative or are complex numbers with real numbers negative.

II. FREE DISEASE EQUILIBRIUM ANALYSIS

Next author will look for the Jacobian matrix in the human population at the equilibrium point $E_2 = (s^*, i_s^*, d^*)$:

$$J(E_2) = \begin{bmatrix} A & 0 & B & 0 \\ B & -\beta p - \mu & \alpha(\frac{\beta\theta p + \beta\mu p + \theta\mu + \mu^2}{\alpha\beta p}) & 0 \\ 0 & -\beta p & -\theta - \mu & 0 \\ 0 & 0 & \theta & -\rho - \mu \end{bmatrix} \text{ (Eq.21)}$$

With:

$$A = -\alpha(\frac{-\alpha\beta\delta p + \beta\theta\mu p + \beta\mu^2 p + \theta\mu^2 + \mu^3}{(\beta\theta p + \beta\mu p + \theta\mu + \mu^2)\alpha}) - \mu \text{ (Eq.22)}$$

$$B = -\alpha(\frac{\beta\theta p + \beta\mu p + \theta\mu + \mu^2}{\alpha\beta p}) \text{ (Eq.23)}$$

$$C = \alpha(\frac{-\alpha\beta\delta p + \beta\theta\mu p + \beta\mu^2 p + \theta\mu^2 + \mu^3}{(\beta\theta p + \beta\mu p + \theta\mu + \mu^2)\alpha}) \text{ (Eq.24)}$$

The eigen value is obtained from $\det(J(E_2) - \lambda I) = 0$, the characteristic equation is obtained:

According to Routh-Hurwitz criteria, it is said to be asymptotically local if the eigen value of the real part is negative [11]. By looking for characteristic and qualifying equations:

1. $b_1, b_2, b_3 > 0$
2. $b_1 b_2 - b_3 > 0$

From the above result, the author has used Maple 18 software to show the evidence that E_2 is stability asymptotically with qualifying Routh-Hurwitz criteria, and author get characteristic equation with b_1, b_2, b_3 and $b_0 > 0$ and $b_1 b_2 - b_3 > 0$ so it it can be concluded that E_2 is asymptotic stability equilibrium [12].

III. NUMERIC SIMULATION

Thus the model equation has the solution which real part is negative. So it can be concluded that E_1 is a local asymptotic stable point [13].

With the help of Maple 18 software using parameter values $\delta = 0.72$, $\mu = 0.72$, $\beta = 1.03$, $p = 0.08$, $\rho = 0.78$, $\theta = 0.3$ and $p = 0.08$. Simulation model with quarantine is done for case $R_0 > 0$, taken $\alpha = 0.002$. Result of simulation with initial value $(80.738, 41.61, 41.756, 23.798)$.

From the parameter above, the result is $R_0 = 4966.31 > 0$ with $E_1 = \left(\frac{\delta}{\mu}, 0,0\right) = (1,0,0)$ and $E_2 = (s^*, i_s^*, d^*) = (33.72, 359.928, 71.986)$. The graphic can be show as follows:

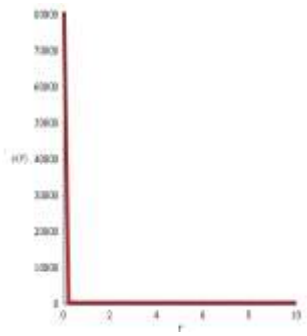

Figure 1

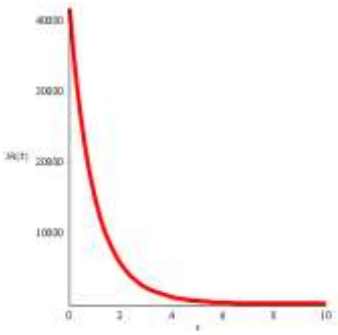

Figure 2

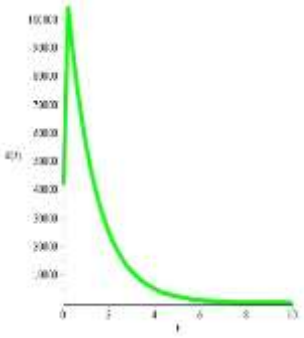

Figure 3

Figure 1 shows a susceptible chart. It appears that the growth rate of susceptible cell population decreases. This happens because the susceptible cell population is infected with the virus and enters the infectious group. At the rate of susceptible cell growth, it is seen that this population will not change at a particular time *t*. In such circumstances, the system is in equilibrium.

Figure 2 shows the exposed chart. The exposed cell proportion is ascending and descending. This increase is due to infected susceptible cells and eventually become infectious cell groups. But then the infectious cell goes down to the point where the movement of the infected cell is unchanged or in equilibrium. Figure 3 shows the infected graph decreased at a certain time *t*.

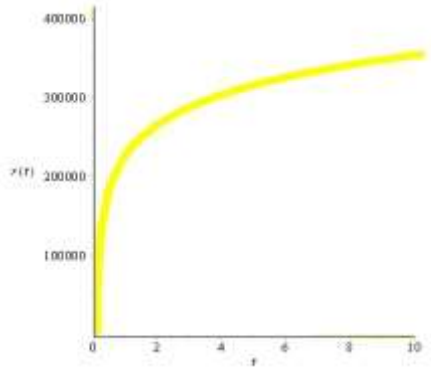

Figure 4 Recovered in 10 years

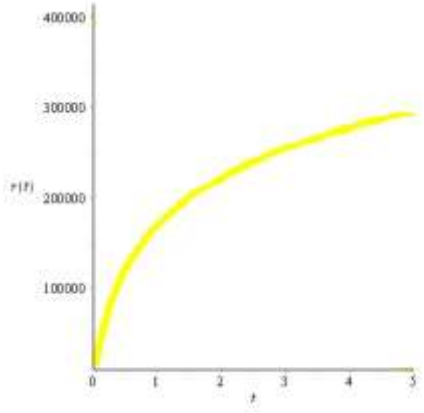

Figure 5 Recovered in 5 years

Figure 4 shows the recovered chart in 10 years. The recovered cell proportion is increasing very fast. This decrease is due to the absence of additional susceptible cells into infected cells. These infected cells will continue to fall down to where the infectious cell growth rate is unchanged or in equilibrium.

Figure 5 shows the recovered chart in 5 years where recovered cell proportion is increasing slowly. This decrease occurs because the infected cells also decreased. The population of this virus will continue to decrease to the extent that the growth rate of the virus does not change or in a state of equilibrium. Based on numerical results, virus population in equilibrium is 0 at a certain time *t*, meaning the infected has switched to recovered.

CONCLUSION

From the results of the malaria model chart with RTS-S/AS01 treatment vaccine, it is seen that the graphs have not significant differences but from the model charts with treatment we know that the proportion of the population recovered with treatment is much less than the population symptomatic infected. So it can be concluded that the treatment with RTS-S/AS01 compartment in malaria gave a positive effect to prevent the spread of malaria disease in human beings. The conclusion that can be drawn from the above result is the mathematical model of human malaria disease with RTS-S/AS01 treatment is better than the previous population in symptomatic infected.

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