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Optimal control mathematical model of Zika Virus

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Abstracts

This study aims to describe the transmission of the Zika virus a mathematical model that was introduced by Ding, Tao, and Zhu (2016). Based on the analysis, obtained a disease-free equilibrium point, then the stability is seen from the basic reproduction number. The basic reproduction numbers show supporting factors and inhibitors of transmission of Zika virus. Then looking for optimal control, the principle is to control transmission of the Zika virus through reducing interactions between mosquitoes and humans, transmission from infected mosquitoes to susceptible humans, and estimates of mosquito deaths by being given insecticides. With the optimal control solution obtained, it produces a strategy to prevent and control the Zika virus and does not incur expensive costs.

Keywords: Zika virus, optimal control, mathematical model, equilibrium point

1. Introduction

Based on [1], [2] Zika virus is an outbreak of mosquitoes caused by the Zika virus, which was first discovered in the study of yellow fever in 1947 in monkey saliva. This virus was first known to infect humans in Uganda and Tanzia in 1952. Then extraordinary events appeared in Asia, Africa, the Western Pacific Region, the last in America and was first reported in 2007 in the Pacific.

Zika virus is transmitted through the bite of the aedes mosquito which is also transmitted by dengue fever, cikungunya and Yellow fever. In a poster issued [3] that the symptoms of people with this disease have the same symptoms as dengue fever, cikungunya and yellow fever, generally appear after 2-3 days of incubation period and last for 2-7 days. The symptoms of the disease have been explained by [1], [4] that the symptoms are accompanied by a rash, fever, conjunctivity, weakness or weakness, headaches and others.

During the extraordinary events in French Polynesia in 2013-2014 there was an increase in cases of Guillaine Barre Syndrome (GBS) and other neurological disorders known to be associated with the Zika virus. In addition, extraordinary events occurring in America have found a relationship between the Zika virus and neurological disorders.

After it was found that there was a relationship between the increase in Zika virus and the incidence of microcephalus in newborns, other neurological disorders, and the high potential for spread, on February 1, 2016 the WHO determined Zika virus as a warning to the World Health Emergency of International Concern (PHEIC), which means the problem of Zika virus is a global public health problem that requires international cooperation [1].

The many interesting studies that exist in the analysis of the Zika virus, there are still puzzles and complex problems. Thus, this problem is an important problem to increase public understanding of the dynamics of Zika virus transmission, and then to take effective steps to eliminate and treat this disease.

2. Experiments Procedure

Zika has been modeled by Chunxiao Ding, Nana Tao, and Yuanguo Zhu (2016). The mathematical model of this problem is a method to overcome the transmission of the Zika virus. This study, a mathematical model developed to develop the dynamics of transmission of the Zika virus. After several analyzes were used, the researcher solved the optimal control problem to find effective steps and improvements for the Zika virus and inexpensive costs. The researchers concluded that there were three effective strategies for spreading the Zika virus:

a. Reducing direct interaction with mosquitoes using clothing, mosquito nets, curtains so that a person's endurance improves.
b. Reducing the level of transmission from mosquitoes to humans by increasing endurance (autoimmunity).
c. Increase the mortality rate of mosquitoes by eradicating nests using insecticides.

This study introduces an epidemic model that published the dynamics of Zika virus transmission, calculates the equilibrium point and calculates basic reproduction numbers (R_0) from the 4-dimensional Zika virus model, then provides an optimal control system using the generated Zika virus model, finding optimal controls, and finding the results from this study.

3. Result and Discussion

Model Formulation

Mathematical model of Zika virus transmission involves the human population and mosquitoes. The total human population is denoted by N_h, and the total population of mosquitoes is symbolized by N_m. The human population divided into two classes, namely susceptible individuals (H_s) and infected individuals (H_i). The population of mosquitoes is divided into 2 classes, namely susceptible mosquitoes (M_s), and infected mosquitoes (M_i).

This study uses the ODE Mathematical Model from [4] to find out how transmission of the Zika virus,

$$\begin{cases} \frac{dH_s}{dt} = L_h - b_{mh}g_{mh}M_iH_s - d_hH_s \\ \frac{dH_i}{dt} = b_{mh}g_{mh}M_iH_s - d_hH_i \\ \frac{dM_s}{dt} = L_m - b_{hm}g_{hm}M_sH_i - d_mM_s \\ \frac{dM_i}{dt} = b_{hm}g_{hm}M_sH_i - d_mM_i \end{cases} \quad (1)$$

In which L_h is the level of recruitment H_s, Λ_m is the level of recruitment M_s, d_h is the natural death rate of humans, d_m is the natural death rate of mosquitoes, b_{mh} is the level of contact between humans and mosquitoes, g_{mh} is the rate of transmission from infected mosquitoes to susceptible humans, b_{hm} is the level of contact between humans and mosquitoes, g_{hm} is the rate of transmission from infected humans to susceptible mosquitoes. Obviously, the level of contact between humans and mosquitoes is the same $b_{mh} = b_{hm}$. But the level of transmission is difficult between M_i to H_s and H_i to M_s.

Equilibrium Point and Basic Reproduction Number (R_0)

Equilibrium Point

System (1) has a disease-free equilibrium point. Disease-free equilibrium points are infections in humans (H_i) and infections in mosquitoes (M_i) are zero. In other word there is no disease in the population. Disease-free equilibrium points for the model of Zika virus transmission in the system (1) are obtained

$$\frac{dH_s}{dt}=\frac{dH_i}{dt}=\frac{dM_s}{dt}=\frac{dM_i}{dt}=0 \qquad (2)$$

Based on (2) the following equations are obtained

$$\Lambda_h - b_{mh}g_{mh}M_iH_s - d_hH_s = 0 \qquad (3)$$

$$b_{mh}g_{mh}M_iH_s - d_hH_i \qquad (4)$$

$$\Lambda_m - b_{hm}g_{hm}M_sH_i - d_mM_s \qquad (5)$$

$$b_{hm}g_{hm}M_sH_i - d_mM_i \qquad (6)$$

If substituted into equation (3), then obtained $H_s=\frac{\Lambda_h}{d_h}$. Subsequently, substituting $H_i=0$ into equation (5) is obtained $M_s=\frac{\Lambda_m}{d_m}$. Thus, a disease-free equilibrium point is obtained

$$E_0=(H_s,H_i,M_s,M_i)=\left(\frac{\Lambda_h}{d_h},0,\frac{\Lambda_m}{d_m},0\right).$$

The Basic Reproduction Number

The basic reproduction number according to [5] is a number that states the average number of infective individuals secondary to contracting primary infective individuals that take place in susceptible populations. Then the biological interpretation of the basic reproduction number (R_0) is the average number of humans infected caused by some people who are infected during a certain period of infection. Next, a model is given on the system (1). The decline in the basic reproduction ratio is done by first grouping the subpopulations into x and y compartments, namely:

$$x=\begin{pmatrix}H_i\\M_i\end{pmatrix},\ y=\begin{pmatrix}H_s\\M_s\end{pmatrix}$$

So that a model can be formed

$$\frac{dx}{dt}=\begin{bmatrix}b_{mh}g_{mh}M_iH_s - d_hH_i\\ b_{hm}g_{hm}M_sH_i - d_mM_i\end{bmatrix} \qquad (7)$$

$$\frac{dy}{dt}=\begin{bmatrix}\Lambda_h - b_{mh}g_{mh}M_iH_s - d_hH_s\\ \Lambda_m - b_{hm}g_{hm}M_sH_i - d_mM_s\end{bmatrix} \qquad (8)$$

Furthermore, equation in (7) can be written as

$$\frac{dx}{dt}=F(x,y)-V(x,y)$$

By *F* declaring new infections that occur and *V* stating the development of disease, death and healing. So, obtained

$$F(x,y)=\begin{bmatrix}F_1(x,y)\\F_2(x,y)\end{bmatrix}=\begin{bmatrix}b_{mh}g_{mh}M_iH_s\\b_{hm}g_{hm}M_sH_i\end{bmatrix}$$

$$V(x,y)=\begin{bmatrix}V_1(x,y)\\V_2(x,y)\end{bmatrix}=\begin{bmatrix}d_hH_i\\d_mM_i\end{bmatrix}$$

So, we make the Jacobian matrix

$$J_{1(x,y)}=\begin{bmatrix}\frac{\partial F_1}{\partial H_i}(x,y) & \frac{\partial F_1}{\partial M_i}(x,y)\\ \frac{\partial F_2}{\partial H_i}(x,y) & \frac{\partial F_2}{\partial M_i}(x,y)\end{bmatrix}=\begin{bmatrix}0 & b_{mh}g_{mh}H_s\\ b_{hm}g_{hm}M_s & 0\end{bmatrix}$$

$$J_{2(x,y)}=\begin{bmatrix}\frac{\partial V_1}{\partial H_i}(x,y) & \frac{\partial V_1}{\partial M_i}(x,y)\\ \frac{\partial V_2}{\partial H_i}(x,y) & \frac{\partial V_2}{\partial M_i}(x,y)\end{bmatrix}=\begin{bmatrix}d_h & 0\\ 0 & d_m\end{bmatrix}$$

The disease-free equilibrium point that has been obtained from system (1) is $E_0=\left(\frac{\Lambda_h}{d_h},0,\frac{\Lambda_m}{d_m},0\right)$. Thus, the matrix *F* and *V* are obtained

$$F=J_{1(E_0)}=\begin{bmatrix}0 & b_{mh}g_{mh}\frac{\Lambda_h}{d_h}\\ b_{hm}g_{hm}\frac{\Lambda_m}{d_m} & 0\end{bmatrix}$$

$$V=J_{2(E_0)}=\begin{bmatrix}d_h & 0\\ 0 & d_m\end{bmatrix}$$

The Next Generation Matrix (NGM) for system (1) is

$$M = FV^{-1}$$

$$= \begin{bmatrix} 0 & \beta_{mh}\gamma_{mh}\dfrac{\Lambda_h}{\delta_h}\dfrac{1}{\delta_m} \\ \beta_{hm}\gamma_{hm}\dfrac{\Lambda_m}{\delta_m}\dfrac{1}{\delta_h} & 0 \end{bmatrix}$$

The eigenvalue of the matrix M is obtained from the following equation:

$$\det(M - \lambda I) = 0$$

$$\Leftrightarrow \ \lambda^2 = \left(\beta_{mh}\gamma_{mh}\frac{\Lambda_h}{\delta_h}\frac{1}{\delta_m}\right)\left(\beta_{hm}\gamma_{hm}\frac{\Lambda_m}{\delta_m}\frac{1}{\delta_h}\right)$$

So that the matrix M eigenvalue is obtained

$$\lambda = \sqrt{\left(\beta_{mh}\gamma_{mh}\frac{\Lambda_h}{\delta_h}\frac{1}{\delta_m}\right)\left(\beta_{hm}\gamma_{hm}\frac{\Lambda_m}{\delta_m}\frac{1}{\delta_h}\right)}$$

Thus, the basic reproduction number values obtained for the system (1) are

$$R_0 = \sqrt{\left(\beta_{mh}\gamma_{mh}\frac{\Lambda_h}{\delta_h}\frac{1}{\delta_m}\right)\left(\beta_{hm}\gamma_{hm}\frac{\Lambda_m}{\delta_m}\frac{1}{\delta_h}\right)}$$

The parameters in the basic reproduction number (R_0) contain two elements, first, $\beta_{mh}\gamma_{mh}\dfrac{\Lambda_h}{\delta_h}$ which means that the average human is infected by one mosquito, and $\dfrac{1}{\delta_m}$ is the average age of the mosquito. Second, $\beta_{hm}\gamma_{hm}\dfrac{\Lambda_m}{\delta_m}$ shows the average infected mosquito caused by one human, and $\dfrac{1}{\delta_h}$ is the average age of humans.

Theoretically, the basic reproduction number (R_0) is the threshold value that can determine the outbreak of Zika virus or Zika virus is extinct. If $R_0 > 1$ that means the disease will endemic in certain areas, and if $R_0 < 1$ means the disease will become extinct.

Optimal Control

The researcher tried to find Zika virus control measures and minimize total costs. The control parameters used are three, first, $\mu_1(t)$ meaning the descent scale in the level of efficient direct interaction between mosquitoes and humans by using clothes dividers, mosquito nets, curtains. Second, the control parameter $\mu_2(t)$ means showing the rate of transmission from mosquitoes infected with the Zika virus to susceptible humans. Third, the parameter $\mu_3(t)$ is an estimate of the growth of the death rate of mosquitoes by eradicating mosquito nests using insecticides.

The objective function:

$$J(\mu_1,\mu_2,\mu_3) = \min\left\{\int_0^T \left(a_1 N_h + a_2 H_i + \sum_{j=1}^{3} b_j(\mu_j)^2\right) dt\right\} \quad (9)$$

Constraints function:

$$\begin{cases} \dfrac{dH_s}{dt} = \Lambda_h - (\beta_{mh} - \mu_1)(\gamma_{mh} - \mu_2)M_i H_s - \delta_h H_s \\ \dfrac{dH_i}{dt} = (\beta_{mh} - \mu_1)(\gamma_{mh} - \mu_2)M_i H_s - \delta_h H_i \\ \dfrac{dM_s}{dt} = \Lambda_m - \beta_{hm}\gamma_{hm}M_s H_i - (\delta_m + \mu_3)M_s \\ \dfrac{dM_i}{dt} = \beta_{hm}\gamma_{hm}M_s H_i - (\delta_m + \mu_3)M_i \end{cases} \quad (10)$$

where a_1 is the quarantine cost for all people in the infected area, a_2 is the cost of treatment for the infected humans, b_j is the weight standing for the cost of the control intervention strategy, N_h is the total human population, $a_1 N_h$ is the total cost for human investigation of the Zika, $a_2 H_i$ is an infected human population, and in this study is an emphasis that researchers try to minimize, and $\sum_{j=1}^{3} b_j(\mu_j)^2$ is the total cost generated by control measures implementing.

Solving the problem of optimal control equations above will be used the Hamiltonian method. The steps according to [6] use the Hamiltonian method to find control functions $(U^*(t))$ that meet the equation $\dot{X}(t) = f(X,U,t)$ by minimizing the behavior index

$$J = h(X(t_1),t_1) + \int_{t_0}^{t_1} g(X,U,t)dt$$

The steps for completing the Hamiltonian method are as follows:

1. Form a Hamiltonian, that is $H(X,U,\lambda,t) = g(X,U,t) + \lambda f(X,U,t)$
2. Complete the control equation $\frac{\partial\left(H(X,U,\lambda,t)\right)}{\partial(U)} = 0$, to obtain $U^* = U^*(X,\lambda,t)$
3. Get a Hamiltonian $H^*(X,\lambda,t) = H(X,U^*,\lambda,t)$
4. Complete the $2n$ equation

$$\begin{cases} \dot{X}(t) = \dfrac{\partial\left(H^*(X,\lambda,t)\right)}{\partial \lambda} & \text{Persamaan "state"} \\ \dot{\lambda}(t) = -\dfrac{\partial\left(H^*(X,\lambda,t)\right)}{\partial X} & \text{Persamaan "co-state"} \end{cases}$$

With boundary conditions given by the initial state and the final state.

5. Substitute the results of step 4 inward U^* to obtain the optimal control sought

Based on the completion steps of the Hamiltonian method to obtain optimal control sought from functions (9) and (10) are:

1. Form the Hamiltonian function equation H from the optimal control problem as,

$$H(t,X,U,\lambda) = L + \lambda_1\frac{dH_s}{dt} + \lambda_2\frac{dH_i}{dt} + \lambda_3\frac{dM_s}{dt} + \lambda_4\frac{dM_i}{dt}$$

$$\begin{aligned} H(t,X,U,\lambda) = & \left(\alpha_1 N_h + \alpha_2 H_i + \beta_1\mu_1^2 + \beta_2\mu_2^2 + \beta_3\mu_3^2\right) \\ & + \lambda_1\left(\Lambda_h - (\beta_{mh} - \mu_1)(\gamma_{mh} - \mu_2)M_i H_s - \delta_h H_s\right) \\ & + \lambda_2\left((\beta_{mh} - \mu_1)(\gamma_{mh} - \mu_2)M_i H_s - \delta_h H_i\right) \\ & + \lambda_3\left(\Lambda_m - \beta_{hm}\gamma_{hm}M_s H_i - (\delta_m + \mu_3)M_s\right) \\ & + \lambda_4\left(\beta_{hm}\gamma_{hm}M_s H_i - (\delta_m + \mu_3)M_i\right) \end{aligned}$$

Where $X = (H_s, H_i, M_s, M_i)$, $U = (\mu_1, \mu_2, \mu_3)$, $\lambda = (\lambda_1, \lambda_2, \lambda_3, \lambda_4)$ and L is a lagrangian function,

$$L = \alpha_1 N_h + \alpha_2 H_i + \sum_{j=1}^{3}\beta_j\mu_j^2 .$$

2. Resolve control issues $\frac{\partial\left(H(t,X,U,\lambda)\right)}{\partial(U)} = 0$, can be written into

$$\frac{\partial H\left(H(t,X,U,\lambda)\right)}{\partial \mu_1} = 0,$$

$$\frac{\partial H\left(H(t,X,U,\lambda)\right)}{\partial \mu_2} = 0$$

and $\frac{\partial H\left(H(t,X,U,\lambda)\right)}{\partial \mu_3} = 0$,

to obtain $U^* = U^*\left(t,X,\lambda\right)$.

Furthermore, obtained

$$\begin{cases} 2\beta_1\mu_1 + (\lambda_1 - \lambda_2)(\gamma_{mh} - \mu_2)M_i H_s = 0 \\ 2\beta_2\mu_2 + (\lambda_1 - \lambda_2)(\beta_{mh} - \mu_1)M_i H_s = 0 \\ 2\beta_3\mu_3 - \lambda_3 M_s - \lambda_4 M_i = 0 \end{cases}$$

To find U^* in equation (13) can use the method of elimination and substitution, obtained and can be simplified to be,

$$\begin{cases} \mu_1^* = \dfrac{2\beta_2(\lambda_1 - \lambda_2)\gamma_{mh}M_i H_s + \left((\lambda_1 - \lambda_2)M_i H_s\right)^2\beta_{mh}}{\left((\lambda_1 - \lambda_2)M_i H_s\right)^2 - 4\beta_1\beta_2} \\ \mu_2^* = \dfrac{2\beta_1(\lambda_1 - \lambda_2)\beta_{mh}M_i H_s + \left((\lambda_1 - \lambda_2)M_i H_s\right)^2\gamma_{mh}}{\left((\lambda_1 - \lambda_2)M_i H_s\right)^2 - 4\beta_1\beta_2} \\ \mu_3^* = \dfrac{\lambda_3 M_s + \lambda_4 M_i}{2\beta_3} \end{cases}$$

3. Get the Hamiltonian

$$\begin{aligned} H^*(t,X,U^*,\lambda) = & \\ & \left(\alpha_1 N_h + \alpha_2 H_i + \beta_1\mu_1^{*2} + \beta_2\mu_2^{*2} + \beta_3\mu_3^{*2}\right) \\ & + \lambda_1\left(\Lambda_h - (\beta_{mh} - \mu_1^*)(\gamma_{mh} - \mu_2^*)M_i H_s - \delta_h H_s\right) \\ & + \lambda_2\left((\beta_{mh} - \mu_1^*)(\gamma_{mh} - \mu_2^*)M_i H_s - \delta_h H_i\right) \\ & + \lambda_3\left(\Lambda_m - \beta_{hm}\gamma_{hm}M_s H_i - (\delta_m + \mu_3^*)M_s\right) \\ & + \lambda_4\left(\beta_{hm}\gamma_{hm}M_s H_i - (\delta_m + \mu_3^*)M_i\right) \end{aligned}$$

4. Form the equation of state and the adjoint (co-state) of H^*
   a. Equation situation, obtained

$$\dot{X}(t) = \frac{\partial\left(H^*(X,\lambda,t)\right)}{\partial \lambda}$$

$$\begin{cases} H_s' = \Lambda_h - (\beta_{mh} - \mu_1^*)(\gamma_{mh} - \mu_2^*)M_i H_s - d_h H_s \\ H_i' = (\beta_{mh} - \mu_1^*)(\gamma_{mh} - \mu_2^*)M_i H_s - d_h H_i \\ M_s' = \Lambda_m - \beta_{hm}\gamma_{hm}M_s H_i - (d_m + \mu_3^*)M_s \\ M_i' = \beta_{hm}\gamma_{hm}M_s H_i - (d_m + \mu_3^*)M_i \end{cases}$$

b. The adjoint (co-state) equation, obtained

$$\dot{\lambda} = -\frac{\partial\left(H^*(X,\lambda,t)\right)}{\partial X}$$

Can be written to be

$$\lambda_1' = -\frac{\partial H}{\partial H_s}, \lambda_2' = -\frac{\partial H}{\partial H_i}, \lambda_3' = -\frac{\partial H}{\partial M_s}, \lambda_4' = -\frac{\partial H}{\partial M_i}$$

Furthermore, obtained

$$\begin{cases} \lambda_1' = (\lambda_1 - \lambda_2)(\beta_{mh} - \mu_1)(\gamma_{mh} - \mu_2)M_i - \alpha_1 + \lambda_1 d_h \\ \lambda_2' = -(\alpha_1 - \alpha_2) + (\lambda_3 - \lambda_4)\beta_{hm}\gamma_{hm}M_s + \lambda_2 d_h \\ \lambda_3' = (\lambda_3 - \lambda_4)\beta_{hm}\gamma_{hm}H_i + \lambda_3(d_m + \mu_3) \\ \lambda_4' = (\lambda_3 - \lambda_4)\beta_{hm}\gamma_{hm}H_s + \lambda_3(d_m + \mu_3) \end{cases}$$

5. Substitute the results of step 4 inward to obtain the optimal control sought. Furthermore, obtained

$$\begin{cases} \mu_1^* = \dfrac{2b_2(\lambda_1' - \lambda_2')\gamma_{mh}M_i'H_s' + \left((\lambda_1' - \lambda_2')M_i'H_s'\right)^2 \beta_{mh}}{\left((\lambda_1' - \lambda_2')M_i'H_s'\right)^2 - 4b_1b_2} \\ \mu_2^* = \dfrac{2b_1(\lambda_1' - \lambda_2')\beta_{mh}M_i'H_s' + \left((\lambda_1' - \lambda_2')M_i'H_s'\right)^2 \gamma_{mh}}{\left((\lambda_1' - \lambda_2')M_i'H_s'\right)^2 - 4b_1b_2} \\ \mu_3^* = \dfrac{\lambda_3'M_s' + \lambda_4'M_i'}{2b_3} \end{cases} \quad (11$$

It can be obtained the completion of optimal control in equation (23). Based on theoretical analysis, researchers can conclude the following strategies for prevention, and control of the Zika virus:

a. Reducing the level of contact between mosquitoes and humans by using clothes, mosquito nets, curtains.
b. Reducing transmission rates from mosquitoes to humans by increasing autoimmunity.
c. Increase the death rate of mosquitoes by eradicating mosquito nests using insecticides.

4. Conclusion

a. Based on the Mathematical model that has been obtained, it is found that the disease- free equilibrium point is

$$E_0 = (H_s, H_i, M_s, M_i) = \left(\frac{\Lambda_h}{d_h}, 0, \frac{\Lambda_m}{d_m}, 0\right)$$

b. Disease-free equilibrium points are stable local asymptotic based on basic reproduction number (R_0) if $R_0 < 1$, and when endemic-equilibrium points will exist and are stable local asymptotic. The basic reproduction numbers produced from the Mathematical model show supporting factors and inhibitors of transmission of Zika virus.

c. A proven strategy for preventing, and controlling the Zika virus at a low cost is first, reducing the level of contact between mosquitoes and humans by using clothes, mosquito nets, curtains. Second, reducing transmission rates from mosquitoes to humans by increasing autoimmunity. Third, increasing the death rate of mosquitoes by eradicating mosquito nests using insecticides.

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References

[1] Kemenkes RI, *Pedoman Pencegahan dan Pengendalian penyakit virus Zika*, no. Oktober. Kementrian Kesehatan Republik Indonesia, 2017.

[2] WHO, “zika vir,” 2018. [Online]. Available: www.who.int/en/news-room/facts-sheets/detail/zika-virus.

[3] WHO, “Zika Virus Disease-Get the Fact,” 2016. [Online]. Available: www.searo.who.int/entity/indonesia/areas/ntd/who_zikavirus_factsheet_ino160202.pdf?

[4] C. Ding, N. Tao, and Y. Zhu, “A mathematical model of Zika virus and its optimal control,” *Chinese Control Conf. CCC*, vol. 2016–Augus, no. October, pp. 2642–2645, 2016.

[5] S. R. R. Yuliani, “Analisis Penyebaran Penyakit Diare Sebagai Salah Satu

Penyebab Kematian Balita Menggunakan Model Matematika SIS," Universitas Negeri Yogyakarta, 2016.

[6] Subiono, *Sistem Linear dan Kontrol Optimal*. Surabaya: Subiono Jurusan Matematika ITS Surabaya, 2013.

[7] Padilah, N.P., Solekhudin, I. *Model Epidemi pada Tanaman.* Yogyakarta: Universitas Gajah Mada, 2015.

[8] Sari, L.R. Model Matematika Infeksi Virus Hepatitis B dengan Adsorpsi*.* *Jurnal Matematika Integratif*, 13(2), 123-130. doi:10.24198/jmi.v13.n2.13665.123-130, 2017.

[9] Travel Advisory [Online]. Available: www.kemlu.go.id/canberra/id/berita-agenda/info-penting/Pages/travel%2520advisory.docx&ved=2ahUKEwjfyvXg_MPfAhWIK48KHQNGCcMQFjACegQICRAB&usg=AOvVaw3Bk6Rq2pOwoaEDNCbB_Rso