MATHEMATICAL MODEL OF SEASONAL INFLUENZA EPIDEMIC IN CENTRAL JAVA WITH TREATMENT ACTION

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Abstract: In this paper, we discussed a mathematical model of seasonal influenza epidemic with treatment action. We got parameters from survey at some district in central java in our research previously. The parameters include incubation period, infection period with treatment and without treatment, and reinfection period. we analysed about the existence of the equilibrium points and their stability. We also determined the basic reproduction number of the model. Lastly, we do a numerical simulation to show the dynamics of the system based on the parameters value that we got at our research previously.

AMS Subject Classification: 37N25, 92B05, 74H15

Key Words: seasonal influenza, basic reproduction number, equilibrium point, local asymptotically stable

1. Introduction

Influenza is a disease that attacks the respiratory tract. Influenza commonly known as flu is caused by an RNA virus of the family Orthomyxoviridae. This virus infects poultries and mammals. The common symptoms of this disease include headache, aches or pains in muscles or joints, feverishness, fatigue,

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cough, sore throat, and nasal congestion (see [9]). Children also may develop croup or bronchiolitis. Younger children may have febrile seizures or sepsis like symptoms (see [7]).

Influenza virus (especially swine flu or avian influenza) is one of viruses that kill millions of people in the world in every year (see [4]). Kohno et al ([9]) stated that pandemic H1N1 and avian influenza virus infection have resulted in more deaths than seasonal influenza virus infection among younger patients with no comorbidities. In this paper, we assume that seasonal influenza doesn't cause the deaths.

The spreading virus from an infected person is started one day before the symptoms are visible. The virus will be released about 5 until 7 days or maybe at longer time. The number of virus that was spread was connected with the body temperature. The higher temperature cause more number of released virus. Kett and Loharikar ([7]) state that the influenza viruses are spread primarily via large-particle respiratory droplet transmission between individuals or by contact with contaminated surfaces. The influenza virus can spread by three principal ways i.e. direct infection that is caused by sneezing person, infection through air, and direct contacts with the infected person as handshake.

In [2], The influenza viruses were divided into three types i.e. type A, B, and C. Influenza viruses of type A have very big influences in human life. These viruses can merge their gen with virus strains in animal population and produce new viruses or mutation viruses. Hence, the recovered human can possibly be infected again by the new viruses. In the Reality, The infected human will require treatment as a form of healing action of this viral infection. The treatment is done by providing medicine or hospitalization. Heinonen et al ([6]) stated that giving oseltamivir to infected children ages 1-3 at time before 24 hours after flu symptoms gave very large results. Oseltamivir is the only suitable medicine used for children younger than 15 years. Aoki et al ([1]) also mentioned that The diagnosis and treatment can maximizes the impact of oseltamivir therapy faster. Research conducted by Aoki et al ([1]) was involving 1426 patients between the ages of 12-70 years who show symptoms of influenza in about 48 hours. the research was done by giving oseltamivir 75 mg twice daily for 5 days. Early administration of drugs would increase the effectiveness of the drug in this case reduce the period of infection. A mutation of influenza virus can produce virus resistant to oseltamivir (see [5]). These mutations result pathogenic contagious virus and deadly virus. de Jong ([3]) mentions the need for other drugs to exterminate the resistant virus so the treatment action will be effective.

Kharis and Arifudin ([8]) researched in 2015 which involved 233 toddlers,

225 child, 229 adults, and 220 elderly in central java province. The results were toddler have same incubation period, same infection period, and same reinfection period with child, adult, and elderly. It was similar between child and adult, and between adult and elderly, but there was a significant difference of average infection period with treatment between child and elderly. The treatment also were effective to all of human age criteria.

In this paper, we will discuss mathematical model of seasonal influenza with treatment. In this model, we didn't divide the human population into four age group because from ([8]), there were globally no difference in parameters value such as incubation period, infection period with treatment or without treatment, and reinfection period between age group.

2. Model Formulation

We use some assumptions to develop the model. The first assumption is that the human population can be separated into 5 classes (compartments), i.e. susceptible human (S), the infected human by seasonal influenza virus (I), the treated human (T_h), and the recovered human (R). We assume that the recruitment of new individual in population has constant rate and the new individual is susceptible human. The other assumptions is the natural death rate is same for all classes. The transfer diagram between compartments can be seen in Fig 1.

The parameters A in Fig 1 represent the recruitment rate. The natural death rate is represented by the parameter μ . Transfer rate from class S to I is defined by $H(N)\frac{S}{N}\frac{I}{N}$ where $H(N)$ is the value of contact function as the function of total population. The parameter α represents the healed rate without treatment. The proportional of the infected person who will be treated is represented by p . The parameter γ represents the healed rate with treatment. From ([8]), we can get the information that treatments are effective to shorter the infection periods so $\gamma > \alpha$. The parameter θ is represented the rate of recovered person who lost their immunity. All variables and parameters in this model are assumed to be non negative.

Based on the transfer diagram which is shown in Fig 1, we will show the formulation of the SITRS epidemic model which is a 4-dimensional system of

Figure 1: Transfer diagram of seasonal influenza epidemic model with treatment.

ODE as system (1).

$$\begin{aligned}
 \frac{dS}{dt} &= A + \theta R - \mu S - H(N) \frac{S}{N} \frac{I}{N} \\
 \frac{dI}{dt} &= H(N) \frac{S}{N} \frac{I}{N} - [(1-p)\alpha + p + \mu] I \\
 \frac{dT_h}{dt} &= pI - (\mu + \gamma) T_h \\
 \frac{dR}{dt} &= \alpha(1-p)I + \gamma T_h - (\mu + \theta)R, \\
 N &= S + I + T_h + R.
 \end{aligned} \tag{1}$$

Factually, influenza can spread quickly among human so we define the value of $H(N) = \beta N^2$ where β is the probability of infectious contact happening. Hence, the system (1) can be changed into system (2)

$$\begin{aligned}
 \frac{dS}{dt} &= A + \theta R - \mu S - \beta SI \\
 \frac{dI}{dt} &= \beta SI - [(1-p)\alpha + p + \mu] I \\
 \frac{dT_h}{dt} &= pI - (\mu + \gamma) T_h \\
 \frac{dR}{dt} &= \alpha(1-p) I + \gamma T_h - (\mu + \theta) R, \\
 N &= S + I + T_h + R.
 \end{aligned} \tag{2}$$

From system (2), we can get the equation $\frac{dN}{dt} = A - \mu N$. We will substitute N to change S in system (2) and we get the system (3).

$$\begin{aligned}
 \frac{dN}{dt} &= A - \mu N \\
 \frac{dI}{dt} &= \beta(N - I - T_h - R)I - [(1-p)\alpha + p + \mu] I \\
 \frac{dT_h}{dt} &= pI - (\mu + \gamma) T_h \\
 \frac{dR}{dt} &= \alpha(1-p) I + \gamma T_h - (\mu + \theta) R.
 \end{aligned} \tag{3}$$

3. System Dynamics

The equilibrium value of N is $N = \frac{A}{\mu}$. Hence, we can define the domain of system (2) such as

$$\Gamma = \left\{ (N, I, T_h, R) \in \mathbb{R}_+^4 \mid 0 < I + T_h + R \leq N \leq \frac{A}{\mu} \right\},$$

where $\mathbb{R}_+^4$ is the non negative area in $\mathbb{R}^4$.

In Theorem 1, we showed the existence of the equilibria of system (3).

Theorem 1. Let $R_0 = \frac{\beta A}{\mu[(1-p)\alpha + p + \mu]}$.

Let $\mathbf{P}_0 = (N, I, T_h, R) = \left(\frac{A}{\mu}, 0, 0, 0 \right)$ and

$$\mathbf{P}_1 = (N, I, T_h, R) = \left(\frac{A}{\mu}, I^*, T_h^*, R^* \right),$$

where:

$$\begin{aligned} I^* &= \frac{(\mu + \theta)(\mu + \gamma) [(1 - p)\alpha + p + \mu] (R_0 - 1)}{\beta [(\mu + \theta)(\mu + \gamma) + \alpha(1 - p)(\mu + \gamma) + (\mu + \gamma + \theta)p]} \\ T_h^* &= \frac{p(\mu + \theta) [(1 - p)\alpha + p + \mu] (R_0 - 1)}{\beta [(\mu + \theta)(\mu + \gamma) + \alpha(1 - p)(\mu + \gamma) + (\mu + \gamma + \theta)p]} \\ R^* &= \frac{[\alpha(1 - p)(\mu + \gamma) + \gamma p] [(1 - p)\alpha + p + \mu] (R_0 - 1)}{\beta [(\mu + \theta)(\mu + \gamma) + \alpha(1 - p)(\mu + \gamma) + (\mu + \gamma + \theta)p]} \end{aligned}$$

1. If $R_0 < 1$ then system (3) has only one equilibrium point i.e. non endemic equilibrium point $\mathbf{P}_0$.
2. if $R_0 > 1$ then system (3) has two equilibrium points i.e. $\mathbf{P}_0$ and the endemic equilibrium point $\mathbf{P}_1$.

Proof. To prove the existence of the equilibria, we made the left side of system (3) be equal to zero. System that will be analyzed is given at system (4)

$$\begin{aligned} A - \mu N &= 0 \\ [\beta(N - I - T_h - R) - [(1 - p)\alpha + p + \mu]] I &= 0 \\ pI - (\mu + \gamma) T_h &= 0 \\ \alpha(1 - p)I + \gamma T_h - (\mu + \theta)R &= 0 \end{aligned} \quad (4)$$

From the first equation of system (4), we get $N = \frac{A}{\mu}$.

From the second equation of System (4), we obtain

$$I = 0 \vee \beta(N - I - T_h - R) = (1 - p)\alpha + p + \mu \quad (5)$$

The case of $I = 0$: Substitute $I = 0$ into the third and the fourth equation of system (4), we get $T_h = 0$ and $R = 0$.

Hence, we obtain the non endemic equilibrium point $\mathbf{P}_0 = (N, I, T_h, R) = (\frac{A}{\mu}, 0, 0, 0)$.

The case of $I \neq 0$: From the third and the fourth equation of system (4), we get

$$T_h = \frac{p}{\mu + \gamma} I \quad \text{and} \quad R = \frac{\alpha(1 - p)(\mu + \gamma) + \gamma p}{(\mu + \theta)(\mu + \gamma)} I \quad (6)$$

We substitute (6) to (5), we get

$$\begin{aligned} I^* &= \frac{[\beta A - \mu [(1 - p)\alpha + p + \mu]] (\mu + \theta)(\mu + \gamma)}{\beta \mu [(\mu + \theta)(\mu + \gamma) + \alpha(1 - p)(\mu + \gamma) + (\mu + \gamma + \theta)p]} \\ \text{or} \quad I^* &= \frac{(\mu + \theta)(\mu + \gamma) [(1 - p)\alpha + p + \mu] (R_0 - 1)}{\beta [(\mu + \theta)(\mu + \gamma) + \alpha(1 - p)(\mu + \gamma) + (\mu + \gamma + \theta)p]} \end{aligned} \quad (7)$$

We substitute (7) to (6) and we will obtain

$$T_h^* = \frac{p(\mu + \theta) [(1-p)\alpha + p + \mu] (R_0 - 1)}{\beta [(\mu + \theta)(\mu + \gamma) + \alpha(1-p)(\mu + \gamma) + (\mu + \gamma + \theta)p]}$$

$$R^* = \frac{[\alpha(1-p)(\mu + \gamma) + \gamma p] [(1-p)\alpha + p + \mu] (R_0 - 1)}{\beta [(\mu + \theta)(\mu + \gamma) + \alpha(1-p)(\mu + \gamma) + (\mu + \gamma + \theta)p]}.$$

From calculating process above, I^* , T_h^* , and R^* were positive if $R_0 > 1$.

Hence, we obtain the endemic equilibrium point

$$\mathbf{P}_1 = (N, I, T_h, R) = \left(\frac{A}{\mu}, I^*, T_h^*, R^* \right),$$

where

$$I^* = \frac{(\mu + \theta)(\mu + \gamma) [(1-p)\alpha + p + \mu] (R_0 - 1)}{\beta [(\mu + \theta)(\mu + \gamma) + \alpha(1-p)(\mu + \gamma) + (\gamma + \mu + \theta)p]}$$

$$T_h^* = \frac{p(\mu + \theta) [(1-p)\alpha + p + \mu] (R_0 - 1)}{\beta [(\mu + \theta)(\mu + \gamma) + \alpha(1-p)(\mu + \gamma) + (\gamma + \mu + \theta)p]}$$

$$R^* = \frac{[\alpha(1-p)(\mu + \gamma) + \gamma p] [(1-p)\alpha + p + \mu] (R_0 - 1)}{\beta [(\mu + \theta)(\mu + \gamma) + \alpha(1-p)(\mu + \gamma) + (\gamma + \mu + \theta)p]}.$$

□

In Theorem 2, we analysed the stability of the equilibria of system (3).

Theorem 2. Let $R_0 = \frac{\beta A}{\mu [(1-p)\alpha + p + \mu]}$, $\mathbf{P}_0$ and $\mathbf{P}_1$ was given in Theorem 1

1. If $R_0 < 1$ then $\mathbf{P}_0$ is locally asymptotically stable.
2. if $R_0 > 1$ then $\mathbf{P}_0$ is unstable and $\mathbf{P}_1$ is locally asymptotically stable.

Proof. The jacobian matrix of system (3) is given below

$$J(\mathbf{P}) = \begin{bmatrix} -\mu & 0 & 0 & 0 \\ \beta I & \beta(N - 2I - T_h - R) - [\alpha(1-p) + p + \mu] & -\beta I & -\beta I \\ 0 & p & -(\mu + \gamma) & 0 \\ 0 & \alpha(1-p) & \gamma & -(\mu + \theta) \end{bmatrix}$$

where $\mathbf{P} \in \Gamma$.

Stability Analysis of $\mathbf{P}_0$: The value of $\mathbf{P}_0$ was substituted to $J(\mathbf{P})$ and we will get

$$J(\mathbf{P}_0) = \begin{bmatrix} -\mu & 0 & 0 & 0 \\ 0 & \beta \frac{A}{\mu} - [\alpha(1-p) + p + \mu] & 0 & 0 \\ 0 & p & -(\mu + \gamma) & 0 \\ 0 & \alpha(1-p) & \gamma & -(\mu + \theta) \end{bmatrix}$$

The eigen values of $J(\mathbf{P}_0)$ are

$$\lambda_1 = -\mu, \lambda_2 = -(\mu + \gamma), \lambda_3 = -(\mu + \theta),$$

dan

$$\lambda_4 = \frac{\beta A - \mu [\alpha(1-p) + p + \mu]}{\mu} = [\alpha(1-p) + p + \mu] (R_0 - 1)$$

Hence, λ_1, λ_2 , and λ_3 are negative. λ_4 is negative if $R_0 < 1$ and positive if $R_0 > 1$.

Finally, The equilibrium point $\mathbf{P}_0$ is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

Stability Analysis of $\mathbf{P}_1$: Stability analysis of $\mathbf{P}_1$ was only done while $R_0 > 1$ because this $\mathbf{P}_1$ was exist when $R_0 > 1$.

The value of $\mathbf{P}_1$ was substituted to $J(\mathbf{P})$ and we will get

$$J(\mathbf{P}_1) = \begin{bmatrix} -\mu & 0 & 0 & 0 \\ \beta I^* & k & -\beta I^* & -\beta I^* \\ 0 & p & -(\mu + \gamma) & 0 \\ 0 & \alpha(1-p) & \gamma & -(\mu + \theta) \end{bmatrix}$$

$$\begin{aligned} \text{where } k &= \beta(N^* - 2I^* - T_h^* - R^*) - [\alpha(1-p) + p + \mu] \\ &= \frac{(\mu + \gamma)(\mu + \theta)(A - 2\mu) - \mu[p(\mu + \theta) + \alpha(1-p)(\mu + \gamma) + \gamma p]}{\mu(\mu + \gamma)(\mu + \theta)} \beta I^* \end{aligned}$$

The characteristic equation of matrix $J(\mathbf{P}_1)$ is

$$\frac{1}{\mu(\mu + \gamma)(\mu + \theta)} (\lambda + \mu)(a_3 \lambda^3 + a_2 \lambda^2 + a_1 \lambda + a_0) = 0 \quad (8)$$

where

$$\begin{aligned} a_3 &= \mu(\mu + \gamma)(\mu + \theta) \\ a_2 &= \mu(\mu + \gamma)(\mu + \theta)(\beta I^* + 2\mu + \gamma + \theta + p) \\ a_1 &= \mu^2(\mu + \gamma)(\mu + \theta) [(\alpha(1-p) + p + \mu)(R_0 - 1) + (\mu + \gamma + \theta)] \\ &\quad + I^* \beta \mu [(\mu + \gamma)(\theta \alpha(1-p) + (\mu + \theta)(\mu + \gamma + \theta)) + p \gamma \theta] \\ a_0 &= (\mu + \gamma)^2 (\mu + \theta)^2 \mu [\alpha(1-p) + p + \mu] (R_0 - 1) \end{aligned}$$

From equation (8) we get $\lambda = -\mu < 0$ from $\lambda + \mu = 0$.

Focus on the equation

$$a_3 \lambda^3 + a_2 \lambda^2 + a_1 \lambda + a_0 = 0 \quad (9)$$

Proof that equation (9) satisfied Routh-Hurwitz criteria if $R_0 > 1$.

Parameter	Average Value (day/days)
Incubation period	3.2
Infection period without treatment	10.2
Infection period with treatment	5.5
Reinfection period	26.8

Table 1: The value of parameter in influenza epidemic in Central Java province

Because the parameters have non negative value, $R_0 > 1$ and $I^* > 0$ then a_0, a_1, a_2 , and a_3 are positive.

By simple calculation we got $a_2a_1 - a_3a_0 = \mu(\mu + \gamma)(\mu + \theta)(\beta I^* + 2\mu + \gamma + \theta + p) [\mu^2(\mu + \gamma)(\mu + \theta)(\mu + \gamma + \theta) + I^*\beta\mu[(\mu + \gamma)(\theta\alpha(1 - p) + (\mu + \theta)(\mu + \gamma + \theta)) + p\gamma\theta]] + \mu^2(\mu + \gamma)^2(\mu + \theta^2)[\alpha(1 - p) + p + \mu](R_0 - 1)(\mu^2 + \beta I^* + p - \gamma\theta)$.

Hence, $a_2a_1 - a_3a_0 > 0$ if $R_0 > 1$ and $\mu^2 + \beta I^* + p > \gamma\theta$.

Because the maximum value of γ and θ are 1, and The value of $I^* > 1$ so we can get $\beta I^* > 1$. Hence $\beta I^* > \gamma\theta$ and finally $\mu^2 + \beta I^* + p > \gamma\theta$.

Hence, $a_3\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0 = 0$ satisfy Routh-Hurwitz criteria. In other word, all of roots of the equation (9) have negative real part.

The conclusion of the stability analysis of $\mathbf{P}_1$ is If $R_0 > 1$ then the point $\mathbf{P}_1$ is locally asymptotically stable. $\square$

4. Parameter Value Estimation

* We researched 233 toddlers, 225 child, 229 adults, and 220 elderly in central java province in 2015. We get the parameters value estimation as given in Table 1

Proportion of person taking treatment was 96% or 0.96 From the parameters value of table, we can calculate the parameter value of mathematics model. The value of α was gotten from infection period without treatment, γ was gotten from infection period with treatment, and θ was gotten from reinfection period. In this paper the value of μ was gotten from expected life period of Indonesian i.e. 65 years and the value of A was gotten from the number of person enter the population (from birth or immigration) every 9 months or 270 days. The complete parameters value in model was given in Table 2. From the parameters

Parameter	Value	Information
A	$\frac{1}{9 \times 30} = 0.0037$	assumed
μ	$\frac{1}{65 \times 365} = 0.00004$	assumed
β	$0 < \beta \leq 1$	the range of probability
α	0.098	Infection period without treatment
γ	0.182	Infection period with treatment
θ	0.037	Reinfection period
p	0.96	Proportion of person taking treatment

Table 2: The value of parameter in model

Figure 2: Plot $N(t)$ while $R_0 < 1$.

value on Table 2, we got $R_0 > 1$ if $\beta \geq 0.02$. Hence, Seasonal influenza usually become an epidemic in Central Java Province although there is no death caused of this infection.

5. Simulation of $R_0 < 1$

We made simulation using the parameters value in Table 2 with the value of $\beta = 0.01$. The simulation graphics were given at Figure 2 until Figure 5

Figure 3: Plot $I(t)$ while $R_0 < 1$.

Figure 4: Plot $T_h(t)$ while $R_0 < 1$.

Figure 5: Plot $R(t)$ while $R_0 < 1$.

From Figure 2 until Figure 5, we got that if $R_0 < 1$ then the value of N, I, T_h , and R tend to the value of every term of $P_0 = (N, I, T_h, R) = (92.5, 0, 0, 0)$. From Figure 3, we got that this epidemic will be extinct if the value of R_0 can be made less than one. Plot of direction field around $I(t), T_h(t)$, and $R(t)$ were given at Figure 6 and Figure 7

From Figure 6 and Figure 7, we can see that all solution with initial value near equilibrium tend to equilibrium value.

6. Simulation of $R_0 > 1$

We made simulation using the parameters value in Table 2 with the value of $\beta = 0.1$. The simulation graphics were given at Figure 8 until Figure 11

From Figure 8 until Figure 11, we got that if $R_0 > 1$ then the value of N, I, T_h , and R tend to the value of every term of $P_1 = (N, I, T_h, R) = (92.5, 2.56, 13.53, 66.76)$. From Figure 9, we got that this epidemic will stay in population for longer time. Plot of direction field around $I(t), T_h(t)$, and $R(t)$ were given at Figure 12 and Figure 13.

From Figure 12 and Figure 13, we can see that all solution with initial value near equilibrium tend to equilibrium value.

Figure 6: Direction field around $I(t)$ and $T_h(t)$ while $R_0 < 1$.

Figure 7: Direction field around $T_h(t)$ and $R(t)$ while $R_0 < 1$.

Figure 8: Plot $N(t)$ while $R_0 > 1$.

Figure 9: Plot $I(t)$ while $R_0 > 1$.

Figure 10: Plot $T_h(t)$ while $R_0 > 1$.

Figure 11: Plot $R(t)$ while $R_0 > 1$.

Figure 12: Direction field around $I(t)$ and $T_h(t)$ while $R_0 > 1$.

Figure 13: Direction field around $T_h(t)$ and $R(t)$ while $R_0 > 1$.

7. Conclusion

From analysis above, we got the reproduction ratio (R_0) of this model. From the value of parameters and the formula of R_0 , we got that the seasonal influenza usually become an epidemic in Central Java Province although there is no death caused of this infection. Because of that, there were needed some preventive actions to reduce the probability of this epidemic spread wider.

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