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Optimal Countermeasure Control on Influenza Spread Model in the Emergence of Drug Resistance

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Abstract: ***The model studied in this article is an optimal control model for the spread of flu with respect to the class that are resistant to standard anti-flu drugs. The non-endemic equilibrium point and reproduction number are obtained based on the studied system. In the model given control, u_1, efforts to prevent contact between peoples who are still healthy; the control, u_2, effectively reduced the number of peoples in the I_s the class, and the control, u_3, effectively decreased the number of peoples in the I_r the class. The system of co-the state equations obtained corresponds to the system of the state, equations. Control, u_1, can prevent peoples from being infected with flu. The control, u_2, effectively reduced the number of peoples in the I_s the class, and the control, u_3, effectively decreased the number of peoples in the I_r the class.***

Keywords: influenza spread model, equilibrium point, the basic reproduction number, resistance to standard anti-influenza drugs, optimal control

1. Introduction

Flu is a disease that attacked humans centuries ago, but the cause was newly discovered in the early 20th century; the group the virus is now known as Flu type A, B, and C viruses [1]. Several mathematical researchers have studied mathematical models for combating the spread of the flu. Chong (2014) has reviewed and developed a semi-saturated dynamics system of the spread of avian flu in human and avian populations [2]. Study of a mathematical model that explains the spread of flu A virus infection in the human respiratory tract [3]. Modeling to determine the change of show parameters, with a simulation of the transmission flow of flu A H1N1 in China [4]. Sungchasit (2022) analyzes global stability in the Respiratory syncytial virus transmission model [5]. Hill (2019) examines the spread of seasonal flu with a modeling approach to determine human immunity to the disease [6]. Modeling a flu epidemic to analyze the worldline solidness of the balance point with discrete time [7]. The factors of human mobility on the increased transmission of flu [8].

Mathematical modeling to analyze the flow of flu A virus spread by taking into account medicate resistance factors [9]. Baba (2021) examined a flu strain model that pays attention to non-resistance and resistance, where non-resistant strains can mutate into resistant strains. [10]. Fahlena (2022) analyzed the dynamics of the coinfection of two pathogens in respiratory diseases and flu [11]. Pinky (2022) studied epidemic models of respite virus and found that co-circulation of SARS-CoV-2 and RSV caused the strongest significant influence on the spread of SARS-CoV-2 [12].

Modeling studies and analysis on the spread of flu by vaccinating healthy peoples can prevent and reduce the spread of the disease [13, 14, 15]. Kim (2017) analyzed mathematical models and optimal control strategies to reduce the 2009 flu A/H1N1 in the Republic of Korea [16]. Optimal control and modeling of swine flu pandemic transmission dynamics were analyzed using a deterministic model [17]. Optimal control and dynamic analysis of the COVID-19 transmission system [18].

The system in this paper is a development of the Sungcasit model [5] by paying attention to exposed the classes. The equilibrium point and reproduction number are analyzed based on the formulated model, which is a deterministic model. Furthermore, optimal control is given in prevention and treatment efforts to reduce the number of peoples infected with the flu.

2. Literature Survey

The studied model is divided into six the class; the susceptible the class, namely peoples who are still healthy peoples, denoted *S*. Healthy peoples vaccinated against flu enter the vaccination the class, denoted *V*[9]. Healthy peoples come in contact with flu-infected peoples and become infected and are still passive or latent into the exposed the class denoted by *E* [7]. Peoples who are actively infected but are still sensitive to standard anti-flu drugs can transmit the disease to peoples who are still healthy and enter the I_s class. Peoples who are actively infected and are resistant to common anti-flu drugs can transmit the disease to peoples who are still healthy and enter the I_r class. Peoples who are vaccinated and immune, peoples infected with flu treated and recovered, enter the recovered the class denoted by *R* [9].

The model assumption being studied, peoples who enter the population only enter the susceptible the class. Peoples who are vaccinated are only the classified peoples who are still healthy. Each the class experiences natural death, and infected peoples resistant to standard anti-flu drugs may die. Vaccinated peoples may enter the recovered the class, but peoples who are not immune and have contact with flu-infected peoples may become infected. Peoples in the I_s and I_r classes are treated to be cured of flu disease. After a few days, the recovered the class peoples may again be sensitive to flu disease. The flow of transfers between the classes of

the model studied is described in the schematic diagram in Figure 1.

The model studied in the paper is like the following equation:

$$\begin{aligned}\frac{dS}{dt} &= \eta N + \tau R - \frac{(\beta_1 I_s + \beta_2 I_r)S}{N} - (\theta + \mu)S \\ \frac{dV}{dt} &= \theta S - (1-\varphi)\left(\frac{(\beta_1 I_s + \beta_2 I_r)V}{N}\right) - (r+\mu)V \\ \frac{dE}{dt} &= \frac{(\beta_1 I_s + \beta_2 I_r)S}{N} + (1-\varphi)\left(\frac{(\beta_1 I_s + \beta_2 I_r)V}{N}\right) \\ &\quad - (\alpha + \gamma + \mu)E \end{aligned} \quad (1)$$

$$\begin{aligned}\frac{dI_s}{dt} &= \alpha E - (\delta + r_1 + \mu)I_s \\ \frac{dI_r}{dt} &= \gamma E + \delta I_s - (d + r_2 + \mu)I_r \\ \frac{dR}{dt} &= rV + r_1 I_s + r_2 I_r - (\tau + \mu)R,\end{aligned}$$

with $N(t) = S(t) + V(t) + E(t) + I_s(t) + I_r(t) + R(t)$

Changes in the number of population units of time are obtained,

$$\frac{dN}{dt} = (\eta - \mu)N - d. \quad (2)$$

3. Method

The methods used in this study include: literature review, analysis and simulation. The following lemmas and theorems are presented.

Lemma 1

The solution of equation (1) is bounded for all $t\epsilon[0, t_f]$

Proof:

Based on equation system (1) $\frac{dN}{dt} = \eta N - \mu N$,obtained

$0 \le lim_{t\to\infty} \sup N(t) \le \frac{\eta N}{\mu}$

so all solutions of equation system (1) are bounded for all $t\epsilon[0, t_f]$. Parameters in the system > 0 and $S(0) > 0, V(0) \ge 0, E(0) > 0, I_s(0) \ge 0, I_r(0) \ge 0, R(0) \ge 0$.

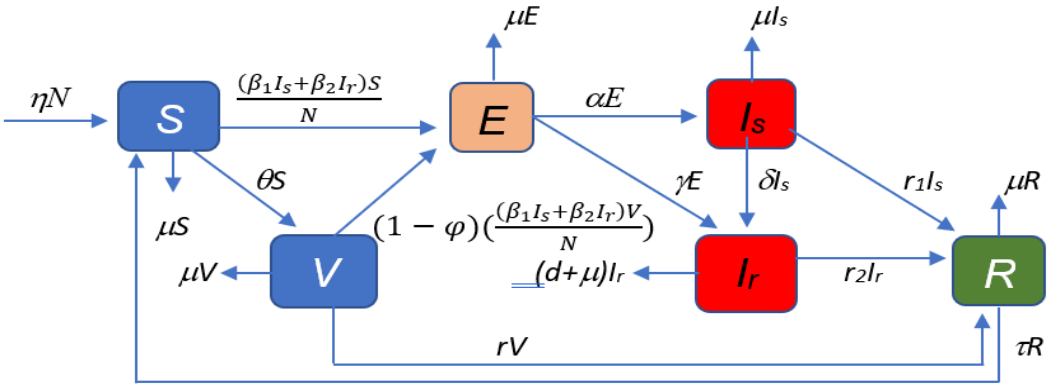

Figure 1: The dynamics of the spread of the flu

Table 1: Notations, descriptions, parameter values, and references were used.

Notations	Description	Values (day^{-1})	Reference
η	Recruitment rate	0.0381	[9]
τ	Resusceptible rate from the class R		
β_1	The contact rate between the peoples of I_s with S or V the class	0.00102	[9]
β_2	The contact rate between the peoples of I_r with S or V the class	0.00026	[9]
θ	Vaccination rates from S to V the class	0.000273	[9]
μ	The natural death rate of each the class	0,000042	estimated
φ	Vaccine strength rate to prevent V the class from becoming infected	0,00526	[17]
r	The rate at which the vaccinated people's immunity enters the R the class	0,005	[17]
α	Displacement rate from E the class to I_s	0,08	estimated
γ	Displacement rate from E the class to I_r	0,03	estimated
δ	Displacement rate from $I_s$the class to I_r	0,06	[17]
r_1	The recovery rate from $I_s$to R the class	0.1998	[9]
r_2	Cure rate from I_r to R the class	0.0714	estimated
d	The death rate due to illness in the I_r the class	0.021	[9]

Based equation system (1) the non-endemic equilibrium point of the flu disease system is obtained with conditions $E(t) = I_s(t) = I_r(t) = L(t) = 0$ and $\frac{dS}{dt} = \frac{dV}{dt} = \frac{dE}{dt} = \frac{dI_s}{dt} = \frac{dI_r}{dt} = \frac{dR}{dt} = 0$, obtained as follows,

$$E_{ne} = (S_1, V_1, 0,0,0, R_1), \quad (3)$$

with $S^* = \frac{\eta N(r+\mu)(\tau+\mu)}{\mu((r+\mu)(\tau+\mu)+(r+\tau+\mu)\theta)}$,

$V^* = \frac{\theta\eta N(\tau+\mu)}{\mu((r+\mu)(\tau+\mu)+(r+\tau+\mu)\theta)}$, $R^* = \frac{\eta r\theta N}{\mu((r+\mu)(\tau+\mu)+(r+\tau+\mu)\theta)}$.

Reproduction Number

A tool that can determine whether a disease is increasing or decreasing is the reproduction number, which is the expectation if one peoples enters a susceptible subpopulation denoted by R_0, to seek reproduction number with the next

generation matrix approach. The first step determines R_0, which determines the F_1 matrix, namely the Jacobian matrix in the S the class that is in connection with infected peoples at the E_1 equilibrium point,

$$F_1 = \begin{bmatrix} 0 & \frac{\beta_1 S^*}{N} + (1-\varphi)\left(\frac{\beta_1 V^*}{N}\right) & \frac{\beta_2 S^*}{N} + (1-\varphi)\left(\frac{\beta_2 V^*}{N}\right) & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}.$$

The next step is to determine the V_1 matrix, which is the matrix of Jacobian the the classes who returned and were not in contact with infected peoples,

$$V_1 = \begin{bmatrix} \alpha+\gamma+\mu & 0 & 0 & 0 \\ -\alpha & \delta+r_1+\mu & 0 & 0 \\ -\gamma & -\delta & d+r_2+\mu & 0 \\ 0 & -r_1 & -r_2 & \tau+\mu \end{bmatrix}.$$

Proof

Based on the system of equations (1), the Jacobian matrix of E_{ne} as follows:

$$J(E_{ne}) = \begin{bmatrix} -(\theta+\mu) & 0 & 0 & -\beta_1 q_1 & -\beta_2 q_1 & \tau \\ 0 & -(r+\mu) & 0 & -\beta_1 q_2 & -\beta_2 q_2 & 0 \\ 0 & 0 & -q_3 & \beta_1 q_1 + \beta_1 q_2 & \beta_2 q_1 + \beta_2 q_2 & 0 \\ 0 & 0 & \alpha & -q_3 & 0 & 0 \\ 0 & 0 & \gamma & \delta & -q_4 & 0 \\ 0 & r & 0 & r_1 & r_2 & -(\tau+\mu) \end{bmatrix}$$

with $q_1 = \frac{\eta N(r+\mu)(\tau+\mu)}{\mu((r+\mu)(\tau+\mu)+(r+\tau+\mu)\theta)}$, $q_2 = \frac{(1-\varphi)\theta\eta(\tau+\mu)}{\mu((r+\mu)(\tau+\mu)+(r+\tau+\mu)\theta)}$, $q_3 = \alpha+\gamma+\mu$, $q_4 = \delta+r_1+\mu$, $q_5 = d+r_2+\mu$. The characteristic equation of the Jacobian matrix, is obtained,

$f(\xi) = (\xi_1+\theta+\mu)(\xi_2+\tau+\mu)(\xi_3+r+\mu)g(\xi)$, with $g(\xi) = \xi^3 + c_1\xi^2 + c_2\xi + c_3$,

Based on the characteristic equation for ξ_j, j = 1, 2, 3 will be negative if $c_i > 0$, i = 1, 2, 3, $R_0 < 1$. Numerical calculations are obtained, with the parameter values used in Table 1, c_1 = 0.003528, c_2 = 0,000741, c_3 = 0,00000168, and fulfill $c_1c_2 > c_3$. This is Routh-Hurwitz's criteria so that the endemic point is locally asymptotically stable of equation system (1).

Optimal Countermeasures Control of Flu Spread Model

Flu prevention is given through counseling and treatment. Control u_1, namely providing counseling in an effort to prevent contact between peoples who are infected with the flu and those who are still healthy. The control, u_2, is an effort to increase the effectiveness of treatment for people who recover with standard cold medicines, namely by giving multivitamins. The control, u_3, is an effort to increase the effectiveness of treatment for flu-infected peoples who are already resistant to standard anti-flu drugs, namely by giving multivitamins and flu drug combinations.

Based on the system of equations (1) and given control, u_1, u_2, dan u_3, equation (5) is obtained:

$$\frac{dS}{dt} = \eta N + \tau R - \frac{(1-u_1)(\beta_1 I_s + \beta_2 I_r)S}{N} - (\theta+\mu)S$$

$$\frac{dV}{dt} = \theta S - (1-\varphi)(1-u_1)\left(\frac{(\beta_1 I_s+\beta_2 I_r)V}{N}\right) - (r+\mu)V$$

$$\frac{dE}{dt} = \frac{(1-u_1)(\beta_1 I_s+\beta_2 I_r)S}{N} + (1-\varphi)(1-u_1)\left(\frac{(\beta_1 I_s+\beta_2 I_r)V}{N}\right) - (\alpha+\gamma+\mu)E \quad (5)$$

$$\frac{dI_s}{dt} = \alpha E - (\delta + r_1(1+u_2) + \mu)I_s$$

Characteristics of polynomials of $\det(\lambda I_3 - FG^{-1}) = 0$ is reproduction number from the system of equations (1), that is, the spectral radius $\rho(FV^{-1})$, the basic production number, which is given by,

$$R_0 = \frac{(k_1+(1-\varphi)k_2)(\alpha\beta_1 k_5 + \alpha\beta_2\delta + \beta_2\gamma k_4)}{k_3 k_4 k_5}, \quad (4)$$

with $k_1 = \frac{\eta(r+\mu)(\tau+\mu)}{\mu((r+\mu)(\tau+\mu)+(r+\tau+\mu)\theta)}$, $k_2 = \frac{\theta\eta(\tau+\mu)}{\mu((r+\mu)(\tau+\mu)+(r+\tau+\mu)\theta)}$, $k_3 = \alpha+\gamma+\mu$, $k_4 = \delta + r_1 + \mu$, $k_5 = d + r_2 + \mu$.

Theorem 1

The non-endemic equilibrium point of equation system (1) is locally asymptotically stable if $R_0 < 1$.

$$\frac{dI_r}{dt} = \gamma E + \delta I_s - (d + r_2(1+u_3) + \mu)I_r$$

$$\frac{dR}{dt} = rV + r_1(1+u_2)I_s + r_2(1+u_3)I_r - (\tau+\mu)R.$$

The optimal prevention $(1-u_1)$ and treatment $(1+u_2)$ dan $(1+u_3)$ control of the spread of flu, constructed functional performance index J. It helps effort to heal those who are sick by providing controls, u_1, u_2 and u_3, that is:

$J = min_{u_1,u_2,u_3} \int_0^{t_f} (Q_1E(t) + Q_2I_s(t) + Q_3I_r(t) + C1u12t+C2u22t+C3u32(t))dt,$ (6)

where Q_1, Q_2, and Q_3 arepositive weight corresponding to each administration, the number of infected E, I_s and I_r subpopulations and cost of controls u_1, u_2 dan u_3 are reduced costs with the help of the functional performance index. We find an optimal control, u_1^*, u_2^* dan u_3^* such that

$J(u_1^*, u_2^*, u_3^*) = min\{J(u_1, u_2, u_3), (u_1, u_2, u_3) \in \boldsymbol{U}\}$,

where control set $U = \{(u_1, u_2, u_3) | u_j(t) \in (0,1), j = 1,2,3$ and u_jLebesgue measurable on (0,1). The problem control set solved using Pontryagin's maximum principle [16, 17, 18], defined functional Hamiltonian for optimal control, taking $Y = (S, V, E, I_s, I_r, R)$, $U = (u_1, u_2, u_3)$, and $\xi = (\xi_1, \xi_2, \xi_3, \xi_4, \xi_5, \xi_6)$, then we have

$$H(Y,U,\xi) = Q_1E(t) + Q_2I_s(t) + Q_3I_r(t) + C_1u_1^2(t) + C_2u_2^2(t) + C_3u_3^2(t) + \xi_1(\eta N + \tau R - (1-u_1)(\beta_1 I_s + \beta_2 I_r)S/N - (\theta+\mu)S) + \xi_2(\theta S - (1-\varphi)(1-u_1)(\beta_1 I_s + \beta_2 I_r)V/N - (r+\mu)V)$$

$$+\xi_3\left((1-u_1)(\beta_1 I_s+\beta_2 I_r)\frac{S}{N}+(1-\varphi)(1-u_1)(\beta_1 I_s+\beta_2 I_r)\frac{V}{N}-(\alpha+\gamma+\mu)E\right)$$
$$+\xi_4(\alpha E-(\delta+r_1(1+u_2)+\mu)I_s)+\xi_5(\gamma E+\delta I_s-(d+r_2(1+u_3)+\mu)I_r)$$
$$+\xi_6(rV+r_1(1+u_2)I_s+r_2(1+u_3)I_r-(\tau+\mu)R) \quad (7)$$

Applying the Hamiltonian equation (7), we get Theorem 2.

Theorem 2

Let the optimal controls u_1^*, u_2^*, u_3^* *and solutions* $S^*, V^*, E^*, I_s^*, I_r^*, R^*$ *of the corresponding equation system* (5), *there are co-the state variables* $\xi_1, \xi_2, \xi_3, \xi_4, \xi_5, \xi_6$ *satisfying the following equations system*:

$$\xi_1' = \frac{(\xi_1-\xi_3)(1-u_1)(\beta_1 I_s+\beta_2 I_r)}{N}+(\xi_1-\xi_2)\theta+\xi_1\mu$$
$$\xi_2' = \frac{(\xi_2-\xi_3)(1-u_1)(1-\varphi)(\beta_1 I_s+\beta_2 I_r)}{N}+(\xi_2-\xi_6)r+\xi_2\mu$$
$$\xi_3' = -Q_1+(\xi_3-\xi_4)\alpha+(\xi_3-\xi_5)\gamma+\xi_3\mu$$
$$\xi_4' = -Q_2+\frac{(\xi_1-\xi_3)(1-u_1)\beta_1 S+(\xi_1-\xi_3)(1-u_1)(1-\varphi)\beta_1 V}{N}+(\xi_4-\xi_5)\delta+(\xi_4-\xi_6)(1+u_2)r_1+\xi_4\mu \quad (8)$$
$$\xi_5' = -Q_3+\frac{(\xi_1-\xi_3)(1-u_1)\beta_2 S+(\xi_1-\xi_3)(1-u_1)(1-\varphi)\beta_2 V}{N}+(\xi_5-\xi_6)(1+u_3)r_2+\xi_5(d+\mu)$$
$$\xi_6' = (\xi_6-\xi_1)\tau+\xi_6\mu.$$

with the transversality conditions $\xi_j(t_f)=0$, *j = 1, 2, 3, 4, 5, 6,of* **U** *andconditions need to be optimal, can be written*

$$u_1^* = \frac{(\xi_3-\xi_1)(\beta_1 I_s+\xi_2 I_r)S+(\xi_3-\xi_1)(1-\varphi)(\beta_1 I_s+\xi_2 I_r)V}{2C_1 N},\ u_2^* = \frac{(\xi_4-\xi_6)r_1 I_s}{2C_2},\ u_3^* = \frac{(\xi_5-\xi_6)r_2 I_r}{2C_3}. \quad (9)$$

Proof

The system of co-the state differential equations, obtained using the Hamiltonian *H* equations [16, 17, 18] with the transfersality condition,

$$\xi_1' = -\frac{\partial H}{\partial S} = \frac{(\xi_1-\xi_3)(1-u_1)(\beta_1 I_s+\beta_2 I_r)}{N}+(\xi_1-\xi_2)\theta+\xi_1\mu$$
$$\xi_2' = -\frac{\partial H}{\partial V} = \frac{(\xi_2-\xi_3)(1-u_1)(1-\varphi)(\beta_1 I_s+\beta_2 I_r)}{N}+(\xi_2-\xi_6)r+\xi_2\mu$$
$$\xi_3' = -\frac{\partial H}{\partial E} = -Q_1+(\xi_3-\xi_4)\alpha+(\xi_3-\xi_5)\gamma+\xi_3\mu$$
$$\xi_4' = -\frac{\partial H}{\partial I_s} = -Q_2+\frac{(\xi_1-\xi_3)(1-u_1)\beta_1 S+(\xi_1-\xi_3)(1-u_1)(1-\varphi)\beta_1 V}{N}+(\xi_4-\xi_5)\delta+(\xi_4-\xi_6)(1+u_2)r_1+\xi_4\mu$$
$$\xi_5' = -\frac{\partial H}{\partial I_r} = -Q_3+\frac{(\xi_1-\xi_3)(1-u_1)\beta_2 S+(\xi_1-\xi_3)(1-u_1)(1-\varphi)\beta_2 V}{N}+(\xi_5-\xi_6)(1+u_3)r_2+\xi_5(d+\mu)$$
$$\xi_6' = -\frac{\partial H}{\partial R} = (\xi_6-\xi_1)\tau+\xi_6\mu$$

The optimal control equation system is obtained by applying the necessary conditions for optimal control to the Hamiltonian equation *H*, we get

$\frac{\partial H}{\partial u_1}=0$, obtained

$$u_1^* = \frac{(\xi_3-\xi_1)(\beta_1 I_s+\xi_2 I_r)S+(\xi_3-\xi_1)(1-\varphi)(\beta_1 I_s+\xi_2 I_r)V}{2C_1 N},$$

$\frac{\partial H}{\partial u_2}=0$, obtained

$u_2^* = \frac{(\xi_4-\xi_6)r_1 I_s}{2C_2}$, and

$\frac{\partial H}{\partial u_3}=0$, obtained

$u_3^* = \frac{(\xi_5-\xi_6)r_2 I_r}{2C_3}$.

4. Results

The solution to the system of equations (5) is solved by a numerical method, the fourth order Runge-Kutta method, by providing initial values. The next step is to provide the initial values for the co-the state variables, which are solved by the fourth order Runge-Kutta method, to obtain a solution to the equation of the state.

By using the parameter values in Table 1, with the initial values of the classes *S(0)* = 10000000, *V(0)* = 500000, *E(0)* = 3000, $I_s(0)$ = 2000, $I_r(0)$ = 1000, and *R(0)* = 0, with weights Q_1 = 100, Q_2 = 200, Q_3 = 300, C_1 = 400, C_2 = 500, C_3 = 600. Solution of equation (5) with u_1^* and no control.

Figures 2 and 3 show that control u_1^*, can prevent flu infection in peoples who are still healthy from the initial time until t = 60 days.

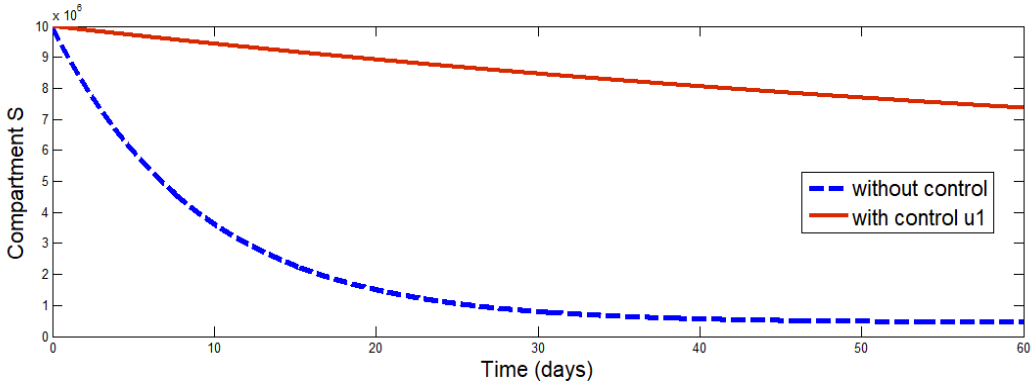

Figure 2: The dynamics spread of *S* with control, u_1^*, and no controls

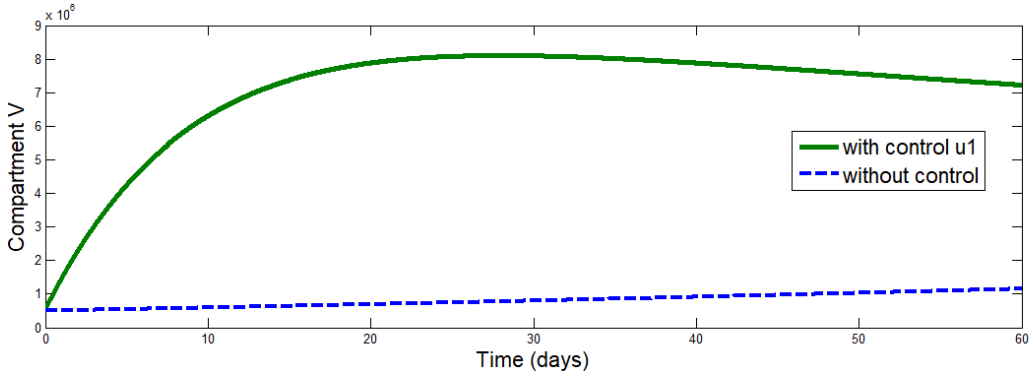

Figure 3: The dynamics spread of V with control u_1^*, and no controls

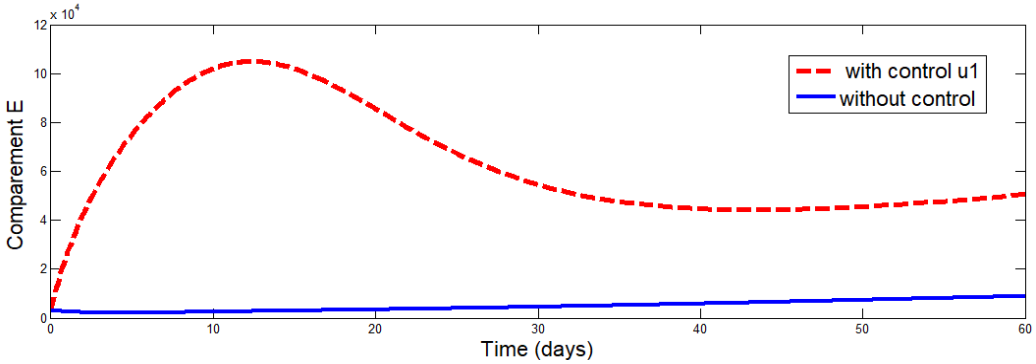

Figure 4: The dynamics spread of E with control, u_1^*, and no controls

Based on Figure 4, control, u_1^*, can reduce the class E peoples from baseline to t = 60 days.

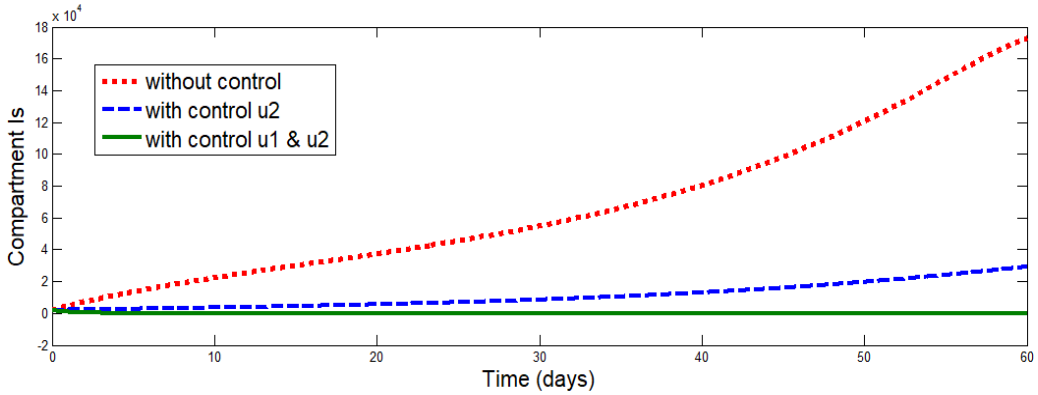

Figure 5: The dynamics spread of I_s with controls u_2^*, u_1^*andu_2^*, and no controls

Based on Figure 5, the control, u_1^*, was effective in reducing flu disease compared to no control from baseline to t = 60 days. The controls, u_1^*, and u_2^*, more effective in reducing the number of I_s compared to the control, u_2^*, only from baseline to t = 60 days.

Based on Figure 6, the control, u_3^*, was effective in reducing I_r compared to no control from baseline to t = 60 days. The controls, u_1^* and u_3^*, were slightly more effective in reducing the number of peoples I_s compared to control, u_1^*, only from baseline to t = 60 days.

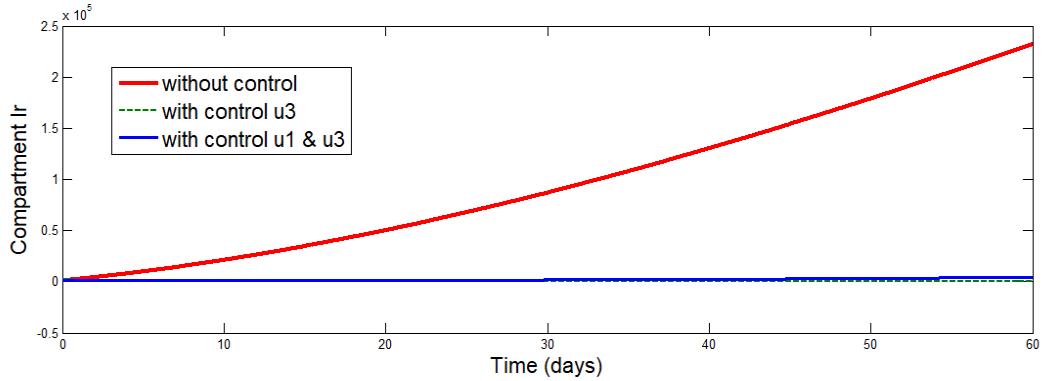

Figure 6: The dynamics spread of I_r with controls u_3^*, u_1^*&u_3^* and no controls

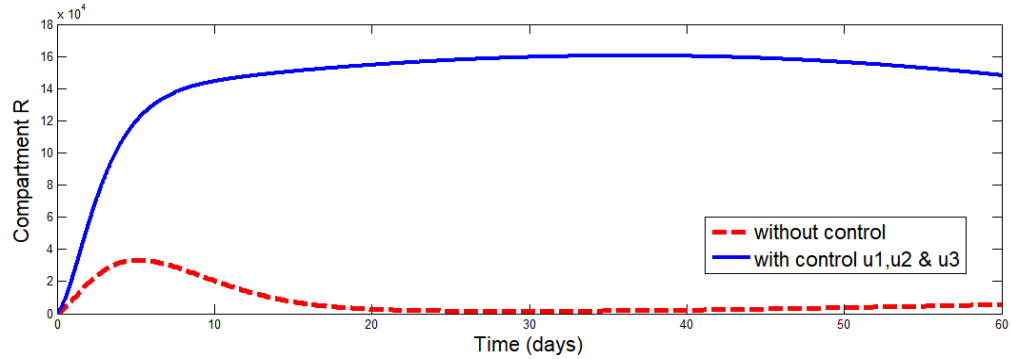

Figure 7: The dynamics spread of R with controls u_1^*, u_2^*, u_3^* and no controls

Based on Figure 7, the controls, u_1^*, u_2^*, and u_3^*, are more effective in increasing the number of R compared to no control from the initial time to time t = 60 days.

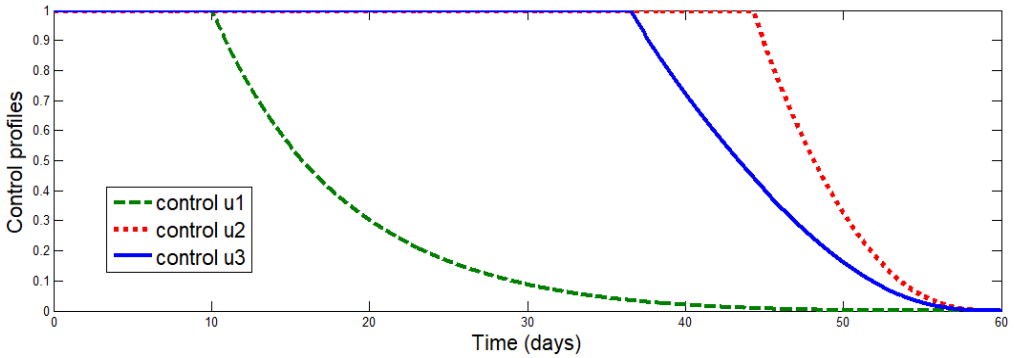

Figure 8: The profile of the optimal controls u_1^*, u_2^*&u_3^*

Based on Figure 8, control profiles u_1^*, u_2^*&u_3^*, optimal control, u_1^* from t = 0 until t = 10 days, from t = 10 days to t = 60 days decreased because peoples who are still healthy already understand how to prevent flu infection. Optimal control, u_2^* from t = 0 until t = 36 days, from t = 36 days until t = 60 days, decreased the number of I_s the class because they had been treated and recovered from flu. Optimal control, u_3^* from t = 0 until t = 46 days, from t = 46 days to t = 60 days, decreased the number of in I_r the class because they had been treated with combination drugs and recovered from flu.

5. Conclusion

The model under study was developed from the article by Sungcasit [5] by paying attention to exposed the classes so that a model of the transmission of flu was obtained, like the system of equations (1). Based on the system of equations (1), the non-endemic equilibrium point is obtained, and the stability analysis of the non-endemic and reproduction number is obtained. In the system of equation (1) is given controls, u_1^*, u_2^*, and u_3^* as in the system of equations (5).

Based on the Hamiltonian equation (7), a system of co-the state equations (8) is obtained, which corresponds to a system of the state equations (5). In the numerical simulation, control, u_1^*, can prevent peoples from getting infected with the flu. Control, u_2^* effectively reduced the number of the I_s class peoples compared to no control. Control, u_3^* effectively reduced the number of peoples in the I_r class compared to no control. Controls u_1^* andu_2^* more effectively reduce the number of the I_s class peoples than control u_2^*. Controls u_1^* andu_3^* are more effective in reducing the number of the I_r class peoples than the control, u_3^* *only*.

6. Future Scope

This research study can be developed by adding the parameters of recruitment into the infected compartment and adding the parameters of reinfection of the recovered subpopulation. To increase the effectiveness of vaccination can also add to the control of vaccination. The spread of influenza can also be studied in fractional form. The population in this study is closed. The results of this study can be used as a reference for research in the epidemic field.

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