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OPTIMAL CONTROL OF MATHEMATICAL MODEL OF DIPHTHERIA SPREADING

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Abstract
This article examines the optimal control model for the spread of diphtheria disease. Diphtheria is an infectious disease caused by the bacterium Corynebacterium diphtheriae. This model is divided into six compartments, namely populations of susceptibles (S), latent (L), infected with symptoms (I_s), infected without symptoms (I_a), recovered with full immunity (R_f) and recovered with partial immunity (R_p). Two optimal controls are applied in the model, namely vaccination and treatment. The problem of optimal control is solved using Pontryagin's minimal principle, which consists of solving a set of necessary conditions that must be satisfied by the optimal control and its associated state. The numerical method used to solve the optimal control problem is the forward-backward sweep method. Based on the results of numerical simulations, both controls should be administered in large numbers and continuously from the beginning of observation to reduce the number of diphtheria-infected populations and control the spread of diphtheria.

Keywords: Mathematical model of diphtheria spread, optimal control problem, state, forward-backward sweep.

INTRODUCTION

The development of increasingly sophisticated technology has meant that the field of mathematics is also developing rapidly. For example, mathematical modeling is not only oriented to minor problems in everyday life but can also be used to discover how an infectious disease spreads. A mathematical model is a set of equations that express the behavior of a problem that occurs based on assumptions [1]. Diphtheria is an infectious disease caused by the bacterium *Corynebacterium diphtheriae*. The main symptoms of this disease are a sore throat, low fever, and swollen glands in the neck. In severe cases, the toxin can cause myocarditis or peripheral neuropathy. The disease is transmitted directly through physical contact or inhalation of aerosol secretions from an infected person's cough or sneeze [2,3]. Based on Centers for Disease Control (CDC) recommendations [4], infants and children under the age of 7 are recommended to receive the DTaP or DT vaccine. In contrast, older children and adults receive the Tdap and Td vaccines. Diphtheria is treated by giving diphtheria antitoxin and antibiotics, relieving symptoms and eradicating bacteria to speed up healing [5].

The number of diphtheria cases in Indonesia was reported to be 775 cases in 2013, decreased in 2014, and increased again in 2015 and 2016. In 2017, the number of reported diphtheria cases in Indonesia was 954 cases, with 44 deaths, so the Ministry of Health (Kemenkes) has declared the outbreak of this diphtheria disease Kejadian Luar Biasa (KLB). In 2019, the number of diphtheria cases decreased slightly; as of May 2020, there were 129 diphtheria cases. Based on data from the Ministry of Health, patients with diphtheria outbreaks that occurred throughout 2017 mostly never received the vaccine, and the age range of the sufferers was quite diverse. A diphtheria outbreak in 2017 and the prevalence of

diphtheria disease in Indonesia, which is still relatively high to date, proves that diphtheria is a real threat to the community, so preventive measures are needed to avoid the occurrence of future diphtheria outbreaks 6,7,8].

Several previous studies modeling the problem of diphtheria spread include Islam et al.[9] in 2022, the SLIR model was developed by assuming the latent population as asymptomatic diphtheria-infected individuals and this latent population cannot transmit diphtheria. In 2017, Sornbundit et al.[10] developed a SIR epidemic model to determine the spread of diphtheria in 77 provinces of Thailand. In the same year Puspita et al.[11] studied the mathematical model of diphtheria spread using the SIQR model developed from the epidemic model of infectious disease spread developed by Hethcote [12]. Suryani and Yuenita [13] used the MSEIR model by paying attention to the saturated incidence rate to determine the spread of diphtheria in Indonesia. In 2004, Cheuvart et al. [14] performed mathematical models to determine how long the vaccine could last to prevent diphtheria. In 2020, Aryani and Widyaningsih[15] studied the SVIR model developed by Liu et al.[16] and added vaccination efforts to suppress the spread of diphtheria in Indonesia.

This study was developed from the SLIR model studied by Islam et al.[9] namely dividing the infected population into infected with symptoms and infected without symptoms, dividing the recovered population into recovered with full immunity and recovered with partial immunity, and assuming the population recovered can be reinfected. The model in this study also maintains optimal control in the form of vaccinations for susceptible populations and treatment for infected populations.

METHOD

The method used in this research is a literature review conducted at Hasanuddin University Faculty of Mathematics, which took place from February to July 2022. The data used are secondary. The steps in this study are to identify problems, build models, formulate optimal control problems, solve optimal control problems, and perform numerical simulations using Matlab 2015a.

RESULT AND DISCUSSION

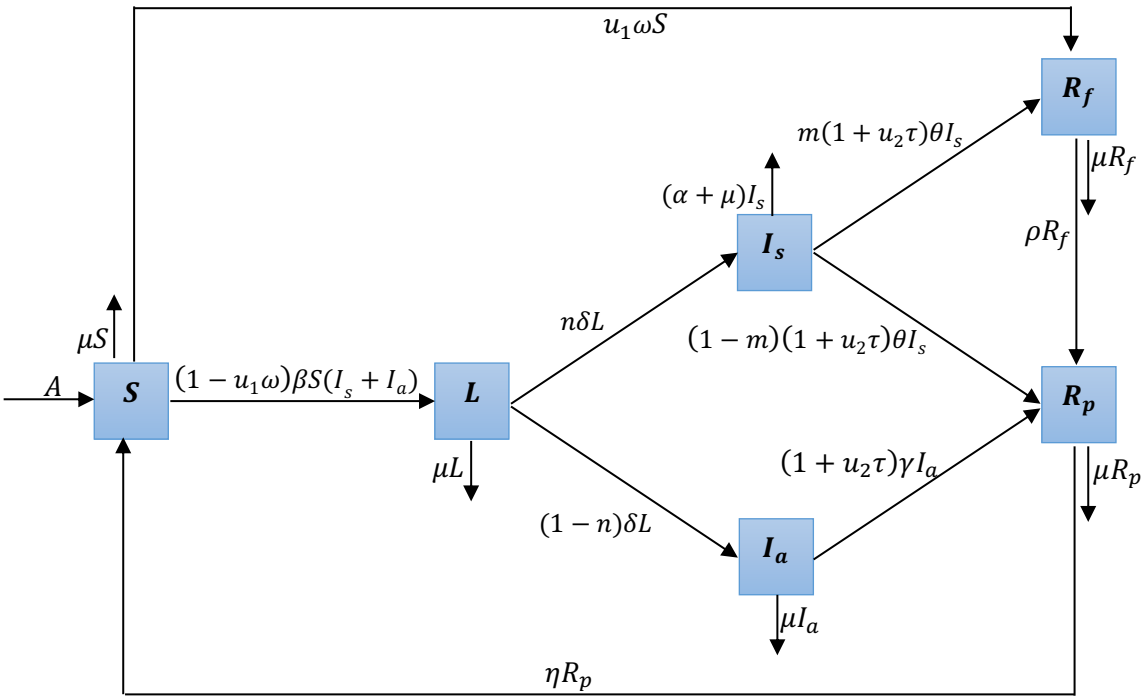
The model developed in this study is divided into six compartments, *namely susceptibles (S), latent (L), infected with symptoms (I_s), infected without symptoms (I_a), recovered with full immunity (R_f), dan recovered with partial immunity (R_p)*. The assumptions underlying the relationship between each compartment in the schematic model of diphtheria spread in Figure 1 are:

1. Every born and migrated person is assumed to be healthy and susceptible to diphtheria infection and enters the compartment for the susceptible population (S) with an input of A individual per unit time.
2. It is assumed that only one disease spreads in the population, namely diphtheria.
3. The population reduction in each compartment due to natural deaths is assumed to be μ per unit time.
4. The susceptible population (S) decreases due to the interaction between the susceptible population (S) and the infected population with symptoms (I_s) and the infected population without symptoms (I_a), so that the population from the compartment of the susceptible individuals (S) to the latent compartment (L) at a rate of β per unit time.
5. It is assumed that by providing controls such as vaccination $u_1(t)$ can reduce the susceptible population infected with diphtheria. The vaccinated susceptible population will acquire full

immunity so that it moves to the recovered with full immunity (R_f) compartment at a rate of $u_1\omega$ per unit time.

6. The latent population (L) moves to the symptomatic or asymptomatic infected population after the incubation period is complete at a rate of δ per unit time.
7. The proportion n infected population is the infected population but showing no symptoms, while the opposite proportion $(1-n)$ is the infected population with symptoms.
8. The decrease in the population infected with symptoms in the infected with symptoms (I_s) compartment occurred due to deaths from diphtheria at a rate of α per unit time.
9. It is assumed that the infected with symptoms (I_s) compartment has a natural recovery rate of θ per unit time. The proportion of m indicates the population recovered from diphtheria has full immunity and moves to the recovered with full immunity (R_f) compartment and the proportion $(1-m)$ shows the population recovered from diphtheria with partial natural immunity and moved to the Recovered with partial immunity (R_p) compartment.
10. The infected without symptoms (I_a) compartment is an infected population without symptoms and can transmit disease, and the recovered population from this compartment only has partial natural immunity at a rate of γ per unit time.
11. Since immunity does not last forever, the level of immunity will decrease over time and eventually be exhausted, allowing the population infected with the disease to be still reinfected. The population of the compartment recovered with full immunity (R_f) decreases at a rate of ρ per unit time due to reduced vaccine immunity, and similarly, the population in the compartment recovered with partial immunity (R_p) decreases at a rate of η per unit time due to exhausted immunity.
12. The control $u_2(t)$ is the proportion of the population infected with symptoms (I_s) and the population infected without symptoms (I_a) who are given treatment to accelerate the recovery rate of the infected population and reduce the mortality rate due to diphtheria infection.

Figure 1. Schematic model of diphtheria spreading with vaccination and treatment control.



Based on the schematic model of diphtheria spreading in Figure 1, the following system of differential equations is obtained:

$$\frac{dS}{dt} = A + \eta R_p - (1-u_1\omega)\beta S(I_s+I_a) - u_1\omega S - \mu S,$$

$$\begin{aligned}
\frac{dL}{dt} &= (1-u_1\omega)\beta S(I_s+I_a) - \delta L - \mu L,\\
\frac{dI_s}{dt} &= (1-n)\delta L - (1+u_2\tau)\theta I_s(t) - (\alpha+\mu)I_s(t),\\
\frac{dI_a}{dt} &= n\delta L - (1+u_2\tau)\gamma I_a - \mu I_a,\\
\frac{dR_f}{dt} &= m(1+u_2\tau)\theta I_s + u_1\omega S - \rho R_f - \mu R_f.\\
\frac{dR_p}{dt} &= (1-m)(1+u_2\tau)\theta I_s + (1+u_2\tau)\gamma I_a + \rho R_f - \eta R_p - \mu R_p.
\end{aligned} \tag{1}$$

It is assumed that the initial conditions are $S(0) > 0$, $L(0) > 0$, $I_s(0) > 0$, $I_a(0) > 0$, $R_f(0) > 0$, $R_p(0) > 0$, and all parameters in equation (1) are positive. The description of the variables and parameter values used in the diphtheria spread model can be seen in Table 1.

Table 1 Description of variables and parameter values in the diphtheria spreading model

Variables/ Parameters	Description	Values	Unit	Reference
S	The population susceptible to diphtheria infection.	-	Individual	-
L	The latent population is still in the incubation period.	-	Individual	-
I_s	Infected population with symptoms.	-	Individual	-
I_a	Infected population without symptoms.	-	Individual	-
R_f	Recovered population with full immunity.	-	Individual	-
R_p	Recovered population with partial immunity.	-	Individual	-
A	Input rate of natural birth and migration.	200	Individual/ day.	[6]
μ	Average natural death rate.	0.002	1 / day.	[6]
β	The average rate of interaction between the susceptible population and the infected population.	0.0000097	1 / (Individual × day).	[6]
δ	Average individual displacement rate from L to I_s or I_a.	0.143	1 / day.	[6]
θ	The average natural cure rate I_s.	0.071428	1 / day.	[13]
α	The average death rate caused by diphtheria infection	0.0054	1 / day.	[6]
γ	The average natural cure rate I_a.	0.00555	1 / day.	Assumption
ρ	Average individual displacement rate from R_f to R_p.	0.0001826	1 / day.	[13]
η	Average individual displacement rate from R_p to S.	0.0001826	1 / day.	[13]
n	Proportion of population I_a.	0.8	-	[13]
$(1-n)$	Proportion of population I_s.	0.2	-	[13]
m	Proportion of population R_f.	0.9	-	[13]
$(1-m)$	Proportion of population R_p.	0.1	-	[13]
u_1	Vaccination proportion.	0-1	-	-
u_2	Treatment proportion.	0-1	-	-
ω	Vaccination effectiveness.	1	-	Assumption
τ	Treatment effectiveness.	0.9	-	Assumption

Review the following optimal control problem for the diphtheria disease spread model:

$$J = \min_{(u_1,u_2)} \int_{t_0}^{t_f} \left(C_1 L(t) + C_2 I_s(t) + C_3 I_a(t) + \frac{C_4}{2} u_1^2(t) + \frac{C_5}{2} u_2^2(t) \right) dt$$

with constraint

$\dot{S} = A + \eta R_p - (1 - u_1\omega - u_2\sigma)\beta S I_s - u_1 \omega S - \mu S,$

$\dot{L} = (1 - u_1\omega - u_2\sigma)\beta S I_s - \delta L - \mu L,$

$\dot{I}_s = (1-n)\delta L - (1 + u_3\tau)\theta I_s - (\alpha + \mu) I_s,$

$\dot{I}_a = n\delta L - (1 + u_3\tau)\gamma I_a - \mu I_a,$

$\dot{R}_f = m(1 + u_3\tau)\theta I_s + u_1\omega S - \rho R_f - \mu R_f,$

$\dot{R}_p = (1-m)(1 + u_3\tau)\theta I_s + (1 + u_3\tau)\gamma I_a + \rho R_f - \eta R_p - \mu R_p.$

The control $u_1(t)$ is a vaccine administered to a susceptible population, and the control function $u_1(t)$ is defined in the range $0 \le u_1(t) \le 1$ for all $t \in [t_0, t_f]$. The control $u_2(t)$ is antitoxin and antibiotic treatment administered to the disease-infected population, both symptomatic and asymptomatic, and the control function $u_2(t)$ is defined in the range $0 \le u_2(t) \le 1$ for all $t \in [t_0, t_f]$. C_1 is the weight value of the objective function to reduce the number of people exposed to diphtheria but still in the incubation phase, C_2 is the weighted value of the objective function to reduce the number of infected with symptoms, C_3 is the weighted value of the objective function to reduce the number of infected individuals without symptoms, C_4 is the weight value of the objective function for the control $u_1(t)$, and C_5 is the weight value of the objective function for the control$u_2(t)$.

The optimal control problem is solved to minimize the diphtheria-infected population with minimal cost of implementing u_1 and u_2 controls, or we will find the control function $(u_1^*, u_2^*) \epsilon U$ such that the objective function $J(u_1^*, u_2^*) < J(u_1, u_2)$ for all $(u_1, u_2) \epsilon U$. Based on the principle of Pontryagin [17], the first step to solving an optimal control problem is to determine the general form of the Hamiltonian of the objective function,

$$H = f\big(t, x(t), u(t)\big) + \lambda^T(t) g\big(t, x(t), u(t)\big),$$

$$\begin{aligned} H = & \left(C_1 L(t) + C_2 I_s(t) + C_3 I_a(t) + \frac{C_4}{2} u_1^2(t) + \frac{C_5}{2} u_2^2(t) \right) \\ & + \lambda_1 \big(A + \eta R_p - (1 - u_1\omega - u_2\sigma)\beta S I_s - u_1 \omega S - \mu S \big) \\ & + \lambda_2 \big((1 - u_1\omega - u_2\sigma)\beta S I_s - \delta L - \mu L \big) \\ & + \lambda_3 \big((1-n)\delta L - (1 + u_3\tau)\theta I_s - (\alpha + \mu) I_s \big) \\ & + \lambda_4 (n\delta L - (1 + u_3\tau)\gamma I_a - \mu I_a) \\ & + \lambda_5 \big(m(1 + u_3\tau)\theta I_s + u_1\omega S - \rho R_f - \mu R_f \big) \\ & + \lambda_6 \left((1-m)(1 + u_3\tau)\theta I_s + (1 + u_3\tau)\gamma I_a + \rho R_f - \eta R_p - \mu R_p \right), \end{aligned} \quad (2)$$

when $\boldsymbol{\lambda} = (\lambda_1 \quad \lambda_2 \quad \lambda_3 \quad \lambda_4 \quad \lambda_5 \quad \lambda_6)^T$ is a Lagrange multiplier.

Based on the Hamiltonian function in equation (2), the state equation is obtained with the following conditions:

$$\dot{\boldsymbol{x}} = \frac{\partial H}{\partial \boldsymbol{\lambda}} = \left(\frac{\partial H}{\partial \lambda_1} \quad \frac{\partial H}{\partial \lambda_2} \quad \frac{\partial H}{\partial \lambda_3} \quad \frac{\partial H}{\partial \lambda_4} \quad \frac{\partial H}{\partial \lambda_5} \right)^T \quad , \boldsymbol{x}(t_0) = \boldsymbol{x}_0,$$

$$\dot{\boldsymbol{x}} = \left(\dot{S} \quad \dot{L} \quad \dot{I}_s \quad \dot{I}_a \quad \dot{R}_f \quad \dot{R}_p \right)^T \quad , \boldsymbol{x}(t_0) = \boldsymbol{x}_0.$$

The costate equation is also obtained from equation (2),

$$\dot{\boldsymbol{\lambda}} = -\frac{\partial H}{\partial \boldsymbol{x}} = \left(-\frac{\partial H}{\partial S} \quad -\frac{\partial H}{\partial L} \quad -\frac{\partial H}{\partial I_s} \quad -\frac{\partial H}{\partial I_a} \quad -\frac{\partial H}{\partial R_f} \quad -\frac{\partial H}{\partial R_p} \right)^T,$$

$$\dot{\boldsymbol{\lambda}} = \left(\dot{\lambda}_1 \quad \dot{\lambda}_2 \quad \dot{\lambda}_3 \quad \dot{\lambda}_4 \quad \dot{\lambda}_5 \quad \dot{\lambda}_6 \right)^T,$$

where

$\dot{\lambda}_1 = (\lambda_1 - \lambda_2)(1 - u_1\omega)\beta(I_s + I_a) + (\lambda_1 - \lambda_5)u_1\omega + \lambda_1\mu,$

$\dot{\lambda}_2 = -C_1 + (\lambda_2 - \lambda_3(1-n) - \lambda_4 n)\delta + \lambda_2\mu,$
$\dot{\lambda}_3 - C_2 + (\lambda_1 - \lambda_2)(1-u_1\omega)\beta S + \big(\lambda_3 - \lambda_5 m - \lambda_6(1-m)\big)(1+u_3\tau)\theta + \lambda_3(\alpha+\mu),$
$\dot{\lambda}_4 = -C_3 + (\lambda_1 - \lambda_2)(1-u_1\omega)\beta S + (\lambda_4 - \lambda_6)(1+u_3\tau)\gamma + +\lambda_4\mu,$
$\dot{\lambda}_5 = (\lambda_5 - \lambda_6)\rho + \lambda_5\mu,$
$\dot{\lambda}_6 = (\lambda_6 - \lambda_1)\eta + \lambda_6\mu.$
The transversality condition is $\boldsymbol{\lambda}(t_f) = 0$.

Optimal conditions are obtained from the stationary conditions $\frac{\partial H}{\partial u} = \left(\frac{\partial H}{\partial u_1} \quad \frac{\partial H}{\partial u_2}\right)^T = (0 \quad 0)^T$,

$$u_1 = \frac{(\lambda_2 - \lambda_1)\omega\beta S(I_s + I_a) + (\lambda_1 - \lambda_5)\omega S}{C_4},$$

$$u_2 = \frac{(\lambda_3 - \lambda_5 m - \lambda_6(1-m))\tau\theta I_s + (\lambda_4 - \lambda_6)\tau\gamma I_a}{C_5}.$$

In this way, the optimal control conditions are obtained:

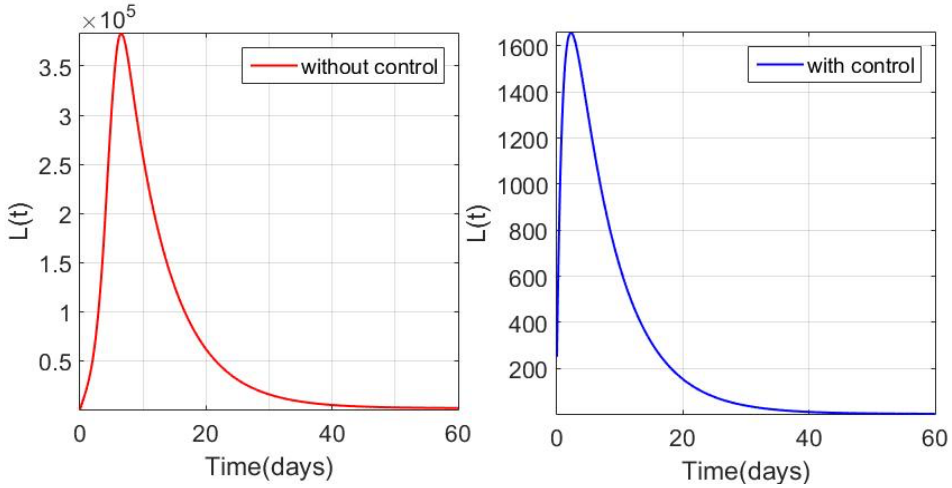
$$u_1{}^* = min\left\{max\left\{0, \frac{(\lambda_2 - \lambda_1)\omega\beta S(I_s + I_a) + (\lambda_1 - \lambda_5)\omega S}{C_4}\right\}, 1\right\},$$

$$u_2{}^* = min\left\{max\left\{0, \frac{\big(\lambda_3 - \lambda_5 m - \lambda_6(1-m)\big)\tau\theta I_s + (\lambda_4 - \lambda_6)\tau\gamma I_a}{C_5}\right\}, 1\right\}$$

The numerical simulation is performed by the Matlab2015a application and uses the forward-backward sweep method as the numerical method. The solution $\boldsymbol{x}(t)$ is obtained by forward Runge-Kutta, and $\boldsymbol{\lambda}(t)$ is obtained using the backward Runge-Kutta method. The time interval $[t_0, t_f]$with $t_0 = 0$ and $t_f = 60$ days. It is assumed that the initial condition of the variable $S(0) = 579384$ individuals, $L(0) = 250$ individuals, $I_s(0) = 2526$ individuals, $I_a(0) = 1000$ individuals, $R_f(0) = 1000$ individual, and $R_p(0) = 1000$ individuals. The weight value of the objective function to be minimized is $C_1 = C_2 = C_3 = C_4 = C_5 = C_6 = 1$.

Figure 2 shows the comparison of latent population change with control and without control. The latent population with no control experienced a large increase, while the latent population with control experienced a small increase until it peaked and thereafter decreased and was stable until the end of the observation time. The increase in the latent population indicates that the infected susceptible population is increasing, while the decrease in the latent population occurs because the incubation period for diphtheria, which ranges from 2 to 5 days, has ended. The small increase in the latent population with controls was due to the control of susceptible individuals, so the number of infected susceptible individuals became smaller.

Figure 2. Graph of latent population change over time ($t = 60$ days)



The population infected with the symptoms in Figure 3 that was controlled decreased, while those that were not controlled experienced a significant increase. The increase in the uncontrolled symptoms infected population was directly proportional to the increase in the uncontrolled latent population. The greater the increase in the uncontrolled latent population, the greater the increase in the uncontrolled symptom-infected population. The decline in the uncontrolled symptoms infected population is due to deaths from infectious diseases and natural remedies. The decrease in the infected population with symptoms brought under control occurs due to the provision of control treatment so that the healing process can be accelerated and the death rate of the population due to infectious diseases can be reduced.

Figure 3. Graph of *Infected with symptoms population* change over time ($t = 60$ days)

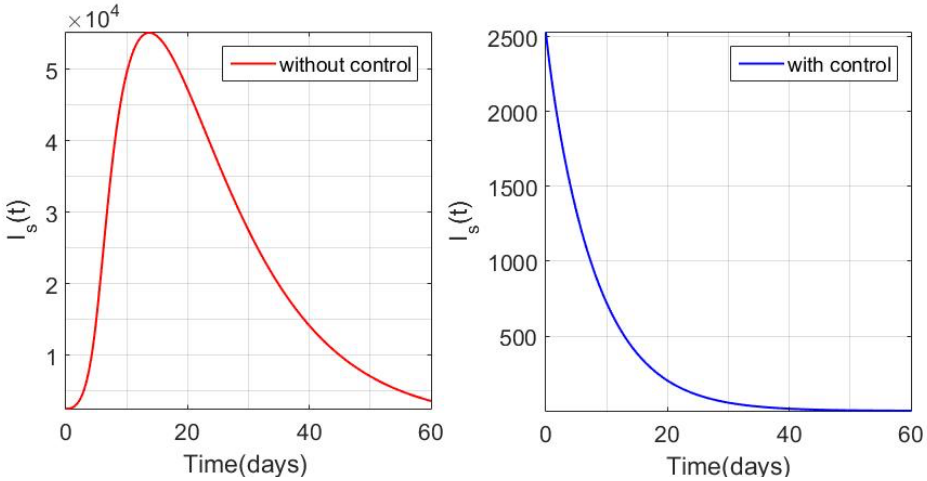
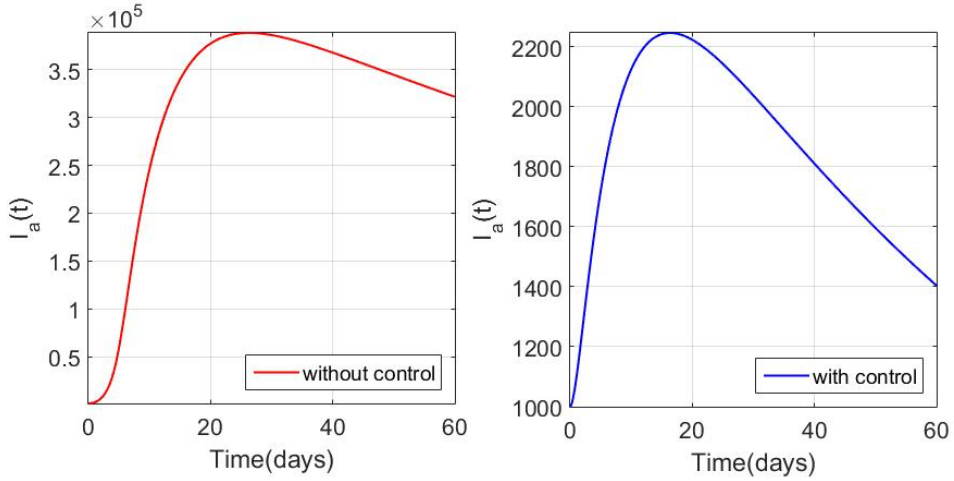


Figure 4. Graph of *Infected without symptoms* population change over time ($t = 60$ days)

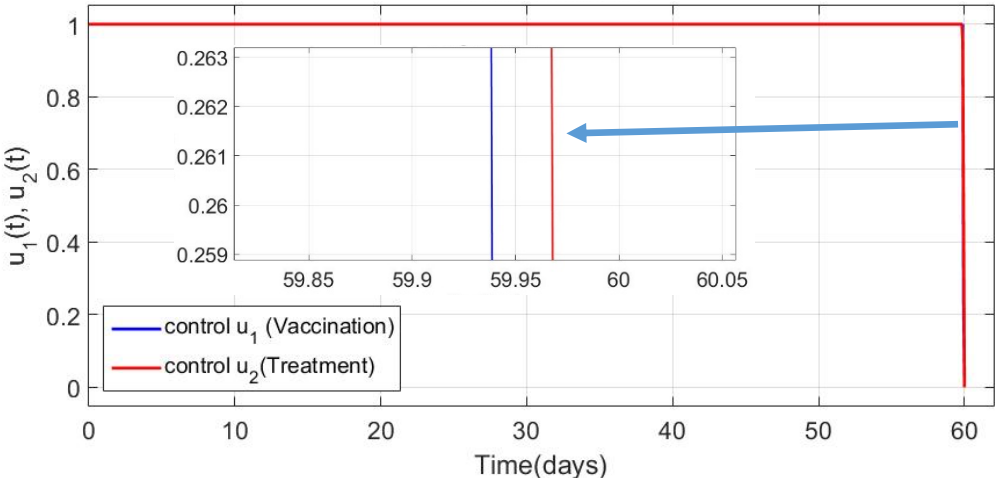


The two asymptomatic infected populations in Figure 4, the control and no control, experienced an increase, but there was a significant difference in the increase between the two populations. This pattern happened because the susceptible population received vaccination control at the beginning, so the infected susceptible population decreased. As a result, the asymptomatic infected population being controlled was also reduced, and treatment control was given again so that the asymptomatic infected population was reduced due to an accelerated healing process.

The values of $u_1(t)$ and $u_2(t)$ reach optimal values from the early observation, which means that vaccination for susceptible populations and treatment for infected populations must be given in large quantities from the beginning. Figure 5. shows that the values of $u_1(t)$ and $u_2(t)$ are equal to one and the only change on the 59th day before dropping significantly to zero at the end of the observation period. It means that for optimal suppression of the rate of spread of diphtheria disease, the $u_1(t)$ vaccine

must be administered continuously, while the $u_2(t)$ treatment must be continuously administered if there is a diphtheria-infected population showing symptoms and no symptoms.

Figure 5. Comparison graph of changes in vaccination control $u_1\ (t)$ and treatment control $u_2(t)$



CONCLUSIONS AND SUGGESTIONS

The SLIR model was developed by dividing the infected *population* (I) into *infected with symptoms* (I_s) and *infected without symptoms* (I_a), dividing the *recovered population* (R) into *recovered with full immunity* (R_f) and *recovered with partial immunity* (R_p). This study also applies optimal controls such as vaccination for susceptible populations and treatment for symptomatic and asymptomatic infected populations. The results of numerical simulations show that the number of symptomatic and asymptomatic diphtheria infections can be reduced by controlling vaccination and treatment. The control values u_1 and u_2, which are maximal from the beginning to the end of the observation, indicate that vaccination and treatment efforts must be given continuously in large quantities.

It is hoped that further research will be able to examine the model of diphtheria disease spread by considering the age limit of the susceptibles population and adding controls other than vaccination and treatments such as mask use and activity restrictions.

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