Model Analysis of Diphtheria Disease Transmission with Vaccination, Quarantine, and Hand-Washing Behavior

Nur Rahmi[1], Muh. Isbar Pratama[2]
[1]Mathematics, Department of Science, Institut Teknologi Bacharuddin Jusuf Habibie, Indonesia
[2]Mathematics, Department of Mathematics, Universitas Negeri Makassar, Indonesia
nurrahmi@ith.ac.id[1], isbarpratama@unm.ac.id[2]

ABSTRACT

Recently, diphtheria outbreaks occur in many countries. According to the latest data from the World Health Organization, the number of registered cases and incidence of diphtheria in 2021 will be 8,638 cases worldwide. Diphtheria is generally an acute respiratory infection with most infections being asymptomatic or having a relatively slight clinical course. However, many sufferers are afflicted by breathing obstruction. In this study, we developed and analyzed the diphtheria spread model by considering transmission by contact with an exposed and infected individual, progression for vaccinated exposed individuals becoming infected, quarantine for both exposed and infected people, and hand-washing behavior. Besides that, we proved the stability analysis around the equilibrium points and did the numerical simulations of models. The results of this study show that the model system has two steady states, namely disease-free equilibrium and endemic equilibrium. The disease-free equilibrium is stable if the basic reproduction number is less than one, either is unstable. The endemic equilibrium exists and is stable if the basic reproduction number is greater than one. The numerical simulations show that there is a significant effect of vaccination, quarantine, and hand-washing behavior for infected numbers, respectively. Vaccination, quarantine, and hand-washing behavior could significantly reduce the basic reproductive and the infected number. Whereas vaccination for exposed people could increase the basic reproductive and the infected number.

——————————— ◆ ———————————

A. INTRODUCTION

Recently, diphtheria outbreaks occur in many countries. According to the latest data from World Health Organization, the number of diphtheria registered cases and incidence in 2021 is 8,638 cases worldwide. Thousands of cases of diphtheria are currently reported annually from several countries with many outbreaks (World Health Organization, 2022). In Indonesia, various regions reported the incidence of diphtheria in various age ranges, which is potentially spread among toddlers and infants (Klausa Bontang, 2023). Diphtheria cases in 2021 have spread to almost all regions of Indonesia. The number of diphtheria cases in Indonesia in 2021 is 235 cases, and the number of deaths is 25 cases, with a CFR of 11%. This is because in the last 2 years from 2020-2021, the coverage of complete basic immunization in infants has dropped dramatically. The decline in immunization coverage was caused by the COVID-19 pandemic. There are around 1.7 million babies who have not received basic immunizations during the

2019-2021 period (Dinas Kominfo Provinsi Jawa Timur, 2022; UNICEF Indonesia, 2022). However, diphtheria is still a world problem that needs to be resolved.

Diphtheria is an acute respiratory infection caused by *Corynebacterium diphtheria* with most infections being asymptomatic or having a relatively slight clinical course. It takes two to five days for symptoms and signs to appear in sufferers. However, many sufferers are afflicted by breathing obstruction (World Health Organization, 2017; World Health Organization, 2023). Bacterial transmission can move from droplets or contact with an infected object of an infected person (Centers for Disease Control and Prevention, 2022). The highest risk factors are unvaccinated, visiting or living in an endemic country, living in densely populated and unhealthy areas, weak immunity due to disease or age (infants, children, and the elderly), or being in contact with the exposed or the infected individual. (Dr. Cameron Troup, 2023). Exposed individuals are all individuals who are in close contact for at least 15 minutes at a distance of fewer than two meters during the estimated duration of infection (Tang, et al., 2020). The time for the exposed individuals to transmit the infection to others is up to four weeks (Anderson, 2022).

To eradicate diphtheria disease, vaccination is a strategy. The most effective way to prevent diphtheria disease is a fully three-dose-diphtheria vaccination. (World Health Organization, 2017). Besides that, hand hygiene and quarantine interventions are essential strategies to reduce diphtheria spread. (McGuinness, et al., 2018; Truelove, et al., 2020). Fortunately, mathematical models have great roles in the field of health which can describe the dynamics of some of the factors or variables related to biological phenomena (Cassidy, et al., 2019; Alridha, Al-Jilawi, & Alsharify, 2022; Ratti, 2018). Hence, a mathematical model of the dynamics of the spread of diphtheria is needed as well to make a rational recommendation to public health, policy or decision makers, and program implementers.

Studies about the diphtheria model have been carried out (Chao, et al., 2021; Tosepu, Gunawan, Effendy, Ahmad, & Farzan, 2018; Valek & Tegeder, 2021). For the diphtheria disease transmission model, Sornbundit et al. (2017) offered a diphtheria model by considering asymptomatic infectious, full natural-acquired immunity, and partial natural-acquired immunity of carrier, individuals with full vaccine-induced immunity, and individual with partial vaccine-induced immunity. Izzati & Andriani (2021) discussed the SEIQR model by considering the rate of natural immunity of the exposed individuals in the spread of diphtheria. While other studies about the diphtheria disease model with the quarantine of exposed individuals analyzed the global stability and parameter estimation (Adewale, et al., 2017; Islam, Ahmed, Rahman, Karim, & Amin, 2022). Therefore, this study aims to construct and analyze the diphtheria spread model by considering transmission by contacting an exposed or infected individual, progression for vaccinated exposed individuals, quarantine for both exposed and infected people, and hand-washing behavior.

B. METHODS

The systematic steps used in this study are described as follows:

1. Study of Literature

   Researchers conducted studies on diphtheria from various journals, in the medical and mathematics fields. In this step, we identified variables related to the problem under study.

2. Mathematical Modeling

   First, make assumptions for the diphtheria transmission model. Model assumptions are built based on literature review studies, especially from medical references. Then, construct the model by modifying several diphtheria models by considering the assumptions.

3. Determine the solution area of the model

   Determine the solution area of the model by finding the maximum and minimum values of the total population.

4. Determine Disease-Free Equilibrium Point and Basic Reproduction Number

   The disease-free equilibrium point can be found by setting free disease in the population, which means, there are no exposed and infected numbers in the population. Then, determine the basic reproduction number of the model to explain the stability behavior (Diekman, Heesterbeek, & Metz, 1990). The basic reproduction number can be determined using the method of the next-generation matrix (Driessche & Watmough, 2002).

5. Determine Endemic Equilibrium Point

   Considering the model system with the number of infected people as not null then solving the system of equations.

6. Stability Analysis

   First, determine Jacobian Matrix for the system. Then, determine Jacobian Matrix for disease-free equilibrium and endemic equilibrium points. After that, find the characteristic polynomials for both Jacobian matrices. Then, the stability is determined by identifying the eigenvalues of characteristic polynomials. The basic reproduction number is considered in the process.

7. Numerical Simulations

   Numerical simulations were carried out on the model using maple18 software to show the dynamics of the spread of diphtheria with vaccination, quarantine, and hand-washing behavior. The parameter values used in the simulation come from a journal article related to the diphtheria model Izzati & Andriani (2021) and from Indonesian population and health data (Countrymeter, 2023; Kementerian Kesehatan RI, 2017). Besides that, we make assumptions on several other parameters and variations in parameter values of vaccination, quarantine, and hand-washing behavior to show the effect of each variable on the system in simulation.

C. RESULT AND DISCUSSION

1. Mathematical Model

A new model of the spread of diphtheria was constructed which refers to the model SEIQR by considering transmission by contact with exposed individuals, vaccinated exposed individuals, quarantine for both exposed and infected individuals, and hand-washing behavior. Let the total population $N(t)$ be divided into five compartments i.e. susceptible, exposed, infected, quarantine, and recovered. While the assumptions are explained as follows:

a. The total human population is not constant.

b. Individuals who are newly born/enter the population are susceptible to diphtheria.

c. Susceptible individuals can become exposed through contact with exposed or infected persons.

d. Vaccination of vulnerable individuals can make them recover.

e. Vaccination of exposed individuals makes acceleration being infected.

f. Quarantine is carried out for exposed and infected individuals.

g. Infected individuals are being treated through the quarantine process.

h. Hand-washing behavior reduces the risk of transmission from exposed and infected individuals.

i. Diphtheria disease can cause death in the sufferer.

j. Individuals who have recovered will not be re-infected because of their immune systems.

Based on the assumptions built, the diphtheria transmission model is given as follows:

$$\frac{dS}{dt} = \Lambda - \beta(1-h)IS - r\beta(1-h)ES - (\mu+v)S,$$

$$\frac{dE}{dt} = \beta(1-h)SI + r\beta(1-h)SE - (q_1+b+v_1+\mu)E,$$

$$\frac{dI}{dt} = (b+v_1)E - (\mu+\alpha+q_2)I, \tag{1}$$

$$\frac{dQ}{dt} = q_1E + q_2I - (\mu+\alpha+\gamma)Q$$

$$\frac{dR}{dt} = vS + \gamma Q - \mu R$$

with the initial condition $S(0) \geq 0,\ E(0) \geq 0,\ I(0) \geq 0,\ Q(0) \geq 0,\ R(0) \geq 0$.

All the used parameters $\Lambda, \beta, r, h, \mu, v, v_1, b, \alpha, q_1, q_2, \gamma$ are non-negative constants. Λ is the recruitment rate by natural birth and immigration, β is the infections transmission rate (as the number of people a single case can infect in a day), r is the reduction of infection transmission by the exposed individuals, h is hand-washing behavior rate, μ is the natural mortality rate, v is per capita rate at which susceptible individuals are vaccinated, v_1 is per capita rate at which exposed individuals are vaccinated, b is the rate of progression of exposed becoming infected, γ is per capita rate at which quarantine individuals are recovered, α is diphtheria disease-induced death rate, q_1 and q_2 are the rates of quarantine for exposed and infected populations, respectively. Next, we have verified that system (1) is bounded, by following Lemma 1.

Lemma 1. If N_0 is the total population at $t = 0$. Then the set $\Delta = \{(S, E, I, Q, R) \in \mathbb{R}_+^5 : 0 \leq S + E + I + Q + R \leq \frac{\Lambda}{\mu} + N_0$ is the positively invariant region for the system (1).

Proof. Let $N = S + E + I + Q + R$, based on system (1) we have

$$\frac{dN}{dt} = \Lambda - \mu N - \alpha(I + Q)$$

since $\alpha(I + Q)$ is non-negative, thus

$$\frac{dN}{dt} + \mu N \leq \Lambda$$

Using the integration factor we have

$$N \leq \frac{\Lambda}{\mu} + N_0 e^{-\mu t}.$$

Since $0 \leq e^{-\mu t} \leq 1$ for $t \geq 0$, thus

$$N \leq \frac{\Lambda}{\mu} + N_0,$$

or

$$S + E + I + Q + R \leq \frac{\Lambda}{\mu} + N_0.$$

Finally, for $t \geq 0$ and since $S(t), E(t), I(t), Q(t),$ dan $R(t)$ are non-negative, then we have

$$0 \leq S + E + I + Q + R \leq \frac{\Lambda}{\mu} + N_0. \qquad \blacksquare$$

Consider system (1). Note that equations for $S(t)$, $E(t)$, $I(t)$, $Q(t)$ are independent of $R(t)$. Therefore, in the next section, we just focus on the following reduced system (2) below.

$$\frac{dS}{dt} = \Lambda - \beta(1 - h)IS - r\beta(1 - h)ES - (\mu + v)S,$$

$$\frac{dE}{dt} = \beta(1 - h)SI + r\beta(1 - h)SE - (q_1 + b + v_1 + \mu)E,$$

$$\frac{dI}{dt} = (b + v_1)E - (\mu + \alpha + q_2)I, \qquad (2)$$

$$\frac{dQ}{dt} = q_1 E + q_2 I - (\mu + \alpha + \gamma)Q$$

2. Epidemic Dynamic Analysis

The equilibrium point is reached when $\frac{dS}{dt} = \frac{dE}{dt} = \frac{dI}{dt} = \frac{dQ}{dt} = 0$. In epidemic conditions, we derived the disease-free equilibrium point of system (2) by assumption $E = I = 0$. Based on model assumptions of (1), we get the number of quarantine people also null since exposed and infected people don't exist. Therefore, the disease-free equilibrium point is given by

$$X^0(S^0, E^0, I^0, Q^0) = \left(\frac{\Lambda}{\mu + v}, 0, 0, 0\right).$$

To find the basic reproduction number, we determine the next-generation matrix of the system, as follows:

$$F = \begin{bmatrix} r\beta(1 - h)\dfrac{\Lambda}{\mu + v} & \beta(1 - h)\dfrac{\Lambda}{\mu + v} & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix},$$

$$V = \begin{bmatrix} (q_1 + b + v_1 + \mu) & 0 & 0 \\ -(b + v_1) & (\mu + \alpha + q_2) & 0 \\ -q_1 & -q_2 & (\mu + \alpha + \gamma) \end{bmatrix}$$

After that, the disease-free equilibrium point, X^0, is substituted into F and V. Matrix FV^{-1} is given by

$$FV^{-1} = \begin{bmatrix} a_{11} & a_{12} & a_{13} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix},$$

$$a_{11} = \frac{\Lambda}{\mu + v} \left(\frac{r\beta(1 - h)}{q_1 + b + v_1 + \mu} + \frac{\beta(1 - h)(b + v_1)}{(\mu + \alpha + q_2)(q_1 + b + v_1 + \mu)} \right)$$

$$a_{12} = \frac{\Lambda\beta(1 - h)}{(\mu + v)(\mu + \alpha + q_2)},$$

$$a_{13} = 0$$

The dominant eigenvalue of FV^{-1} is the basic reproduction number which is

$$R_0 = \frac{\Lambda}{(\mu + v)} \left(\frac{r\beta(1 - h)}{q_1 + b + v_1 + \mu} + \frac{\beta(1 - h)(b + v_1)}{(\mu + \alpha + q_2)(q_1 + b + v_1 + \mu)} \right) \qquad (3)$$

The biological explanation of the basic reproduction number is given as follows. The expression $\Lambda/(\mu + v)$ is the number of susceptible in the disease-free equilibrium. The expression $(b + v_1)$ is the progression of an exposed person to become infected. The expressions $(q_1 + b + v_1 + \mu)$ and $(\mu + \alpha + q_2)$ are population reduction rates of exposed and infected people, respectively. The expressions $r\beta(1 - h)$ and $\beta(1 - h)$, are the infectious rate of susceptible contact with exposed and infected people, respectively. The expressions $r\beta(1 - h)/(q_1 + b + v_1 + \mu)$ and $\beta(1 - h)(b + v_1)/(\mu + \alpha + q_2)(q_1 + b + v_1 + \mu)$ are the number of new cases per unit of time caused by contact with an exposed and infected people, respectively.

Theorem 1. The disease-free equilibrium of the system (2), X^0 is locally asymptotically stable if $R_0 < 1$, and unstable when $R_0 \geq 1$.

Proof. Based on system (2) we have Jacobian Matrix at disease-free equilibrium $J(X^0)$.

$$J(X^0) = \begin{bmatrix} -(\mu + v) & -\frac{\Lambda r\beta(1 - h)}{\mu + v} & -\frac{\Lambda\beta(1 - h)}{\mu + v} & 0 \\ 0 & \frac{\Lambda r\beta(1 - h)}{\mu + v} - (q_1 + b + v_1 + \mu) & \frac{\Lambda\beta(1 - h)}{\mu + v} & 0 \\ 0 & b + v_1 & -(\mu + \alpha + q_2) & 0 \\ 0 & 0 & q_2 & -(\mu + \alpha + \gamma) \end{bmatrix}$$

and the characteristic polynomial of the matrix J_{X_0} is

$$(\lambda + \mu + v)(\lambda + \mu + \alpha + \gamma)\left(\left(\lambda - \frac{\Lambda r\beta(1-h)}{\mu+v} + q_1 + b + v_1 + \mu\right)(\lambda + \mu + \alpha + q_2) - \right.$$

$$\left.\left(\frac{\Lambda\beta(1-h)}{\mu+v}\right)(b + v_1)\right) = 0 \qquad (4)$$

Noted that two of the eigenvalues are negative, i.e. $\lambda_1 = -(\mu + v)$ and $\lambda_2 = -(\mu + \alpha + \gamma)$. Meanwhile, the two others (λ_3 and λ_4) are derived by solving the equation below

$$c_0\lambda^2 + c_1\lambda + c_2 = 0, \qquad (5)$$

with

$$c_0 = 1,$$

$$c_1 = (q_1 + b + v_1 + \mu) + (\mu + \alpha + q_2) - \frac{\Lambda r\beta(1-h)}{\mu + v},$$

$$= (q_1 + b + v_1 + \mu)(1 - R_0) + (\mu + \alpha + q_2) + \frac{\Lambda\beta(1-h)(b + v_1)}{\mu + \alpha + q}$$

$$c_2 = (q_1 + b + v_1 + \mu)(\mu + \alpha + q_2) - \frac{\Lambda\beta(1-h)}{\mu + v}\left((b + v_1) + r(\mu + \alpha + q_2)\right)$$

$$= (q_1 + b + v_1 + \mu)(\mu + \alpha + q_2)(1 - R_0)$$

Consider equation (5). For $R_0 < 1$, we have c_1 and $c_2 > 0$. According to Vieta's formula (Wolfram MathWorld, 2023) for quadratic polynomials, we gained $\lambda_3 + \lambda_4 < 0$ and $\lambda_3 \lambda_4 > 0$, so that it can be ascertained that the other two eigenvalues are also negative. Thus, we know that if $R_0 < 1$, all the eigenvalues of Jacobian Matrix J_{X_0} are negative. Therefore, if $R_0 < 1$, the disease-free equilibrium X_0 is locally asymptotically stable.

Secondly, based on equation (5), $R_0 > 1$ causes $c_2 < 0$, so that $\lambda_3 \lambda_4 < 0$. The product of two eigenvalues can be negative if and only if the two eigenvalues differ in sign. Consequently, there is a positive eigenvalue. So, disease-free equilibrium X_0 is unstable.

Further, if $R_0 = 1$ then $c_1 > 0$ and $c_2 = 0$. This causes the eigenvalue equation (5) to be $\lambda^2 + c_1\lambda = 0$. Then, we obtained one eigenvalue that is zero and another one that is negative, for example, if $\lambda_3 = 0$, then λ_4 will be negative. Hence, there is a non-negative eigenvalue so that disease-free equilibrium X_0 is also unstable. In conclusion, disease-free equilibrium point X_0 is locally asymptotically stable when $R_0 < 1$, and unstable when $R_0 \geq 1$. ∎

3. Endemic Dynamics

In endemic conditions, where exposed and infected as not null we have endemic equilibrium X^* which is given by

$$X^* = (S^*, E^*, I^*, Q^*),$$

where

$$S^* = \frac{(\mu + \alpha + q)(q_1 + b + v_1 + \mu)}{\beta(1 - w)(b + v_1 + r(\mu + \alpha + q))} = \frac{\Lambda}{R_0(\mu + v)}$$

$$E^* = \frac{\Lambda - (\mu + v)S^*}{b + v_1 + \mu} = \frac{\Lambda(R_0 - 1)}{R_0(b + v_1 + \mu)}$$

$$I^* = \frac{(b + v_1)E^*}{(\mu + \alpha + q)} = \frac{\Lambda(b + v_1)(R_0 - 1)}{R_0(b + v_1 + \mu)(\mu + \alpha + q)} \tag{6}$$

$$Q^* = \frac{qI^*}{(\mu + \alpha + \gamma)} = \frac{q\Lambda(b + v_1)(R_0 - 1)}{R_0(b + v_1 + \mu)(\mu + \alpha + q)(\mu + \alpha + \gamma)}$$

Based on system (6), if $R_0 < 1$, then all the subpopulation numbers of X^* are negative (biologically nonfeasible). Besides that, $R_0 = 1$ causes $E^* = I^* = Q^* = 0$. Consequently, the equilibrium point will be back to the disease-free equilibrium point, which was already discussed in the previous section. Thus, a unique positive endemic exists for system (2) if and only if $R_0 > 1$. Furthermore, we derived the following theorem to show that if $R_0 > 1$, then the endemic equilibrium X^* is locally asymptotically stable.

Theorem 2. If $R_0 > 1$, the endemic equilibrium X^* is locally asymptotically stable.
Proof. Based on the system (2) we have Jacobian Matrix at endemic equilibrium state X^*, $J(X^*)$ given

$$J(X^*) = \begin{bmatrix} -(\mu + v)R_0 & -\dfrac{\Lambda r\beta(1 - h)}{R_0(\mu + v)} & -\dfrac{\Lambda\beta(1 - h)}{R_0(\mu + v)} & 0 \\ (\mu + v)R_0 & \dfrac{\Lambda r\beta(1 - h)}{R_0(\mu + v)} - (q_1 + b + v_1 + \mu) & \dfrac{\Lambda\beta(1 - h)}{R_0(\mu + v)} & 0 \\ 0 & b + v_1 & -(\mu + \alpha + q_2) & 0 \\ 0 & q_1 & q_2 & -(\mu + \alpha + \gamma) \end{bmatrix}$$

Consider the 4th column $J(X^*)$. It shows one negative eigenvalue, $-(\mu + \alpha + \gamma)$. Then, the other eigenvalues can be found from the reduction sub-matrix, $J_1(X^*)$ below

$$J_1(X^*) = \begin{bmatrix} -R_0(\mu + v) & -\dfrac{\Lambda r\beta(1 - h)}{R_0(\mu + v)} & -\dfrac{\Lambda\beta(1 - h)}{R_0(\mu + v)} \\ R_0(\mu + v) & \dfrac{\Lambda r\beta(1 - h)}{R_0(\mu + v)} - (q_1 + b + v_1 + \mu) & \dfrac{\Lambda\beta(1 - h)}{R_0(\mu + v)} \\ 0 & b + v_1 & -(\mu + \alpha + q_2) \end{bmatrix}$$

Characteristic matrix for $J_1(X^*)$, given by

$$Char\left(J_1(X^*)\right) = \begin{bmatrix} \lambda + R_0(\mu + v) & \dfrac{\Lambda r\beta(1 - h)}{R_0(\mu + v)} & \dfrac{\Lambda\beta(1 - h)}{R_0(\mu + v)} \\ -R_0(\mu + v) & \lambda - \dfrac{\Lambda r\beta(1 - h)}{R_0(\mu + v)} + (q_1 + b + v_1 + \mu) & -\dfrac{\Lambda\beta(1 - h)}{R_0(\mu + v)} \\ 0 & b + v_1 & (\mu + \alpha + q_2) \end{bmatrix}$$

To simplify the entries of the matrix, let:

$$\xi_1 = R_0(\mu + v)$$
$$\xi_2 = \frac{\Lambda r\beta(1 - h)}{R_0(\mu + v)}$$
$$\xi_3 = (q_1 + b + v_1 + \mu)$$
$$\xi_4 = (\mu + \alpha + q_2)$$
$$\xi_5 = \frac{\Lambda r\beta(1 - h)}{R_0(\mu + v)}(b + v_1)$$

Where $\xi_1, \xi_2, \xi_3, \xi_4, \xi_5 \geq 0$

Hence, the characteristic polynomial of the matrix $J_1(X^*)$ is

$$(\lambda + \xi_1)((\lambda - \xi_2 + \xi_3)(\lambda + \xi_4) - (\lambda + \xi_1)\xi_5 + (\lambda + \xi_4)(\xi_2\xi_1 + \xi_5\xi_1)) = 0$$

$$\Rightarrow \lambda^3 + (\xi_4 + \xi_1 - \xi_2 + \xi_3)\lambda^2 + (\xi_1\xi_3 - \xi_1\xi_2 + \xi_1\xi_4 + \xi_3\xi_4 - \xi_2\xi_4 - \xi_5 + \xi_2\xi_1 + \xi_5\xi_1)\lambda$$
$$+ (\xi_1\xi_4(-\xi_2 + \xi_3) - \xi_1\xi_5 + \xi_4\xi_2\xi_1 + \xi_4\xi_5\xi_1) = 0$$

Consider the basic reproduction number (R_0) in equation (3). Notice that

$$\frac{\xi_2\xi_4 + \xi_5}{\xi_3\xi_4} = 1$$

$$\Rightarrow \xi_3 - \xi_2 = \frac{\xi_5}{\xi_4}$$

Hence, we get,

$$\Rightarrow \lambda^3 + \left(\xi_4 + \xi_1 + \frac{\xi_5}{\xi_4}\right)\lambda^2 + \left(\xi_1\left(\frac{\xi_5}{\xi_4}\right) + \xi_1\xi_4 + \xi_4\left(\frac{\xi_5}{\xi_4}\right) - \xi_5 + (\xi_2 + \xi_5)\xi_1\right)\lambda + (\xi_1\xi_4\left(\frac{\xi_5}{\xi_4}\right)$$
$$+ \xi_1(\xi_4\xi_2 + \xi_4\xi_5 - \xi_5) = 0$$

$$\Rightarrow \lambda^3 + \left(\xi_4 + \xi_1 + \frac{\xi_5}{\xi_4}\right)\lambda^2 + \left(\xi_1\left(\frac{\xi_5}{\xi_4}\right) + \xi_1\xi_4 + (\xi_2 + \xi_5)\xi_1\right)\lambda + + \xi_1(\xi_4\xi_2 + \xi_4\xi_5) = 0 \qquad (7)$$

From equation (7) it is easy to check that all coefficients in the characteristic polynomial are positive. Based on the Routh-Hurwitz criterion (Edelstein-Keshet, 2005) for third order polynomial (7) we derived all the eigenvalues are negative. Further, from equation (6) I^* is positive if and only if $R_0 > 1$. In conclusion, when $R_0 > 1$, the endemic equilibrium point X^* is locally asymptotically stable. ∎

Biologically, the results from theorem 1 and theorem 2 mean that diphtheria disease only can be eradicated in the population when $R_0 < 1$.

4. Numerical Simulations

We do numerical simulations using Maple 18 to check the stability of the equilibrium points and to show the effect of vaccination, quarantine, and hand-washing behavior on diphtheria spread. In this simulations we vary the values of parameters $v, v_1 \, q_1, q_2, h$. The following shows the parameter values used in the simulation, as shown in Table 1.

Table 1. Model parameters and values

Parameter	Value	References
Λ	0.15448/day	Assumed
μ	0.0000194/day	(Countrymeter, 2023)
α	0.1	(Kementerian Kesehatan RI, 2017)
β	0.57	(Izzati & Andriani, 2021)
r	0.5	Assumed
b	0.143	(Kementerian Kesehatan RI, 2017)
γ	0.5	Assumed

It is assumed that the initial condition of the variable $S(0) = 100$; E(0)= 0.01; I(0)=0.235; Q(0)=0.001 (in thousand people). While, various parameters value of $v, v_1 \, q_1, q_2, h$ and the basic reproduction numbers in simulations are shown in Table 2 and Figure 1.

Table 2. Parameter Values and the Basic Reproduction Numbers in Simulations

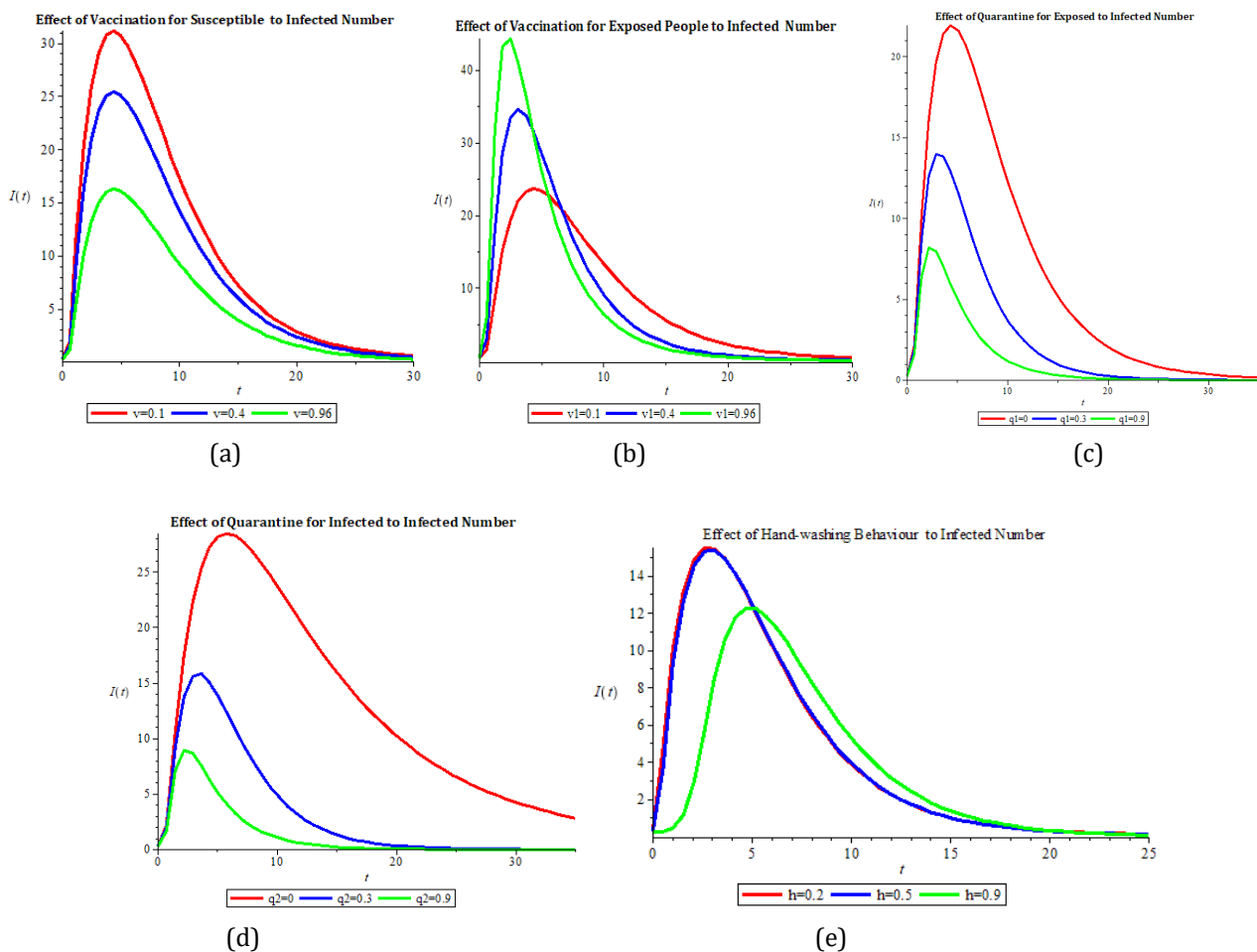| Parameter	Effect of Vaccination for Susceptible			Effect of Vaccination for Exposed			Effect of Quarantine for Exposed			Effect of Quarantine for Infected			Effect of Hand-washing Behavior		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
v	0.1	0.4	0.96	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
v_1	0.1	0.1	0.1	0.1	0.4	0.96	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
q_1	0.1	0.1	0.1	0.1	0.1	0.1	0	0.3	0.9	0.1	0.1	0.1	0.1	0.1	0.1
q_2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0	0.3	0.9	0.2	0.2	0.2
h	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.2	0.5	0.9
R_0	1.01	0.25	0.11	0.17	0.16	0.15	0.24	0.11	0.05	0.38	0.14	0.1	0.45	0.28	0.06

Figure 1. (a) The effect of vaccination for susceptible to infected number, (b) The effect of vaccination for exposed to infected number, (c) The effect of quarantine for exposed to infected number, (d) The effect of quarantine for infected to infected number, and (e) The effect of hand-washing behavior to infected number

The effect of vaccination for susceptible, vaccination for exposed, quarantine for exposed, quarantine for infected, also hand-washing behavior to the infected numbers can be observed in Figure 1 as well the value of parameters used in scenarios 1-3, 4-6, 7-9, 10-12, and 13-15 are shown in Table 2. We can find that, the greater the value of v the lower the value of R_0 and also the lower the value of the infected number. Similarly, the greater the value of q_1, q_2, and h the lower the value of R_0 and also the lower the value of the infected number. On the other hand,

the greater the value of v_1 the greater the value of R_0, and also the greater the value of the infected number.

When the basic reproduction number is less than one, the disease-free equilibrium is locally asymptomatically stable and the endemic equilibrium doesn't exist. When the basic reproduction number is greater than one, the endemic equilibrium is locally asymptomatically stable. It means that diphtheria disease can disappear when the parameter is suppressed until the basic reproduction number is less than one. The numerical simulations show that there is a significant effect of vaccination, quarantine, and hand-washing behavior for infected numbers, respectively. Vaccination, quarantine, and hand-washing behavior could significantly reduce the basic reproductive and the infected numbers. Whereas vaccination for exposed people could increase the basic reproductive and the infected numbers. The smaller the basic reproduction number, the faster the diphtheria disease will disappear from the population.

D. CONCLUSION AND SUGGESTIONS

The mathematical model of diphtheria transmission by considering vaccination, quarantine, and hand-washing behavior is already constructed. The analysis result proof of the epidemic and endemic stability. When the basic reproduction number is less than one, the disease-free equilibrium is locally asymptomatically stable and the endemic equilibrium doesn't exist. When the basic reproduction number is greater than one, the endemic equilibrium is locally asymptomatically stable. It means that diphtheria disease can disappear when the parameter is suppressed until the basic reproduction number is less than one. Besides that, the numerical simulations show that vaccination for susceptible, quarantine, and hand-washing behavior could significantly reduce the basic reproductive and the infected numbers. Whereas vaccination for exposed people could increase the basic reproductive and the infected numbers. Hence, the smaller the basic reproduction number, the faster the diphtheria disease will disappear from the population. Thus, policies on vaccination, quarantine, and dissemination of hand-washing behavior, as well as monitoring of the exposed people are highly recommended to be carried out to reduce the spread of diphtheria in the population.

REFERENCES

Adewale, S. O., Ajao, S. O., Olopade, I. A., Adeniran, G. A., Ajao, S. O., & Mohammed, I. T. (2017, May). Mathematical Analysis of Quarantine on the Dynamical Transmission of Diphtheria Disease. *International Journal of Science and Engineering Investigations, 6*(64).

Alridha, A. H., Al-Jilawi, A. S., & Alsharify, F. H. (2022). Review of Mathematical Modeling Techniques with Applications. *Iraqi Journal for Computer Science and Mathematics*, 135-144. doi:https://doi.org/10.52866/ijcsm.2022.01.01.015

Anderson, A. (2022, July 7). *A to Z Guides: Reference: What to Know About Diphtheria*. Retrieved from WebMD: https://www.webmd.com/a-to-z-guides/what-to-know-diphtheria-causes#091e9c5e822e9965-1-2

Cassidy, R., Singh, N. S., Schiratti, P.-R., Semwanga, A., Binyaruka, P., Sachingongu, N., . . . Josephine, K. (2019). Mathematical modeling for health systems research: a systematic review of system dynamics and agent-based models. *Health Services Research*. doi:https://doi.org/10.1186/s12913-019-4627-7

Centers for Disease Control and Prevention. (2022, September 9). *About diphtheria: Causes and How It Spreads*. Retrieved January 16, 2023, from Centers for Disease Control and Prevention: https://www.cdc.gov/diphtheria/about/causes-transmission.html

Chao, T., Lu, L., Zhang, L., Huang, R., Liu, Z., Zhou, B., . . . Liang, Y. (2021, August). An inducible model for specific neutrophil depletion by diphtheria toxin in mice. *Science China Life Science, 64*(8), 1227–1235. doi:https://doi.org/10.1007/s11427-020-1839-3

Countrymeter. (2023, January 15). *Indonesia Population (LIVE)*. Retrieved January 16, 2023, from Countrymeters: https://countrymeters.info/en/Indonesia

Diekman, O., Heesterbeek, J. A., & Metz, J. A. (1990). On the Definition and Computation of The Basic Reproduction Ratio in The Model of Infectious Disease in Heterogeneous Populations. *Journal of Mathematical Biology, 2*(1), 265–382.

Dinas Kominfo Provinsi Jawa Timur. (2022, August 26). *Berita: Dinas Kominfo Provinsi Jawa Timur*. Retrieved from kominfo.jatimprov.go.id: https://kominfo.jatimprov.go.id/berita/klb-difteri-masyarakat-desa-gili-ketapang-ikuti-ori-difteri

Dr. Cameron Troup, M. (2023). *Bacterial Diseases. Diphtheria: Causes, Pathophysiology, Symptoms, Risk Factors, Complications, Diagnosis and Treatment*. Retrieved from Scope Heal: https://scopeheal.com/diphtheria/

Driessche, P. V., & Watmough, J. (2002). Reproduction numbers and subthreshold. *Math-Biosci, 180*, 29-48.

Islam, Z., Ahmed, S., Rahman, M., Karim, M., & Amin, M. (2022). Global Stability Analysis and Parameter Estimation for a Diphtheria Model: A Case Study of an Epidemic in Rohingya Refugee Camp in Bangladesh. *Computational and Mathematical Methods in Medicine, 2022*. doi: https://doi.org/10.1155/2022/6545179

Izzati, N., & Andriani, A. (2021). Dynamical analysis of diphtheria epidemic model with natural immunity. *Journal of Physics: Conference Series*. doi:10.1088/1742-6596/1869/1/012117

Kementerian Kesehatan RI. (2017). *Buku Pedoman Pencegahan dan Pengendalian Difteri.* Indonesia: Kementerian Kesehatan RI. Retrieved January 16, 2023, from https://sehatnegeriku.kemkes.go.id/wp-content/uploads/2018/01/buku-pedoman-pencegahan-dan-penanggulangan-difteri.pdf

Klausa Bontang. (2023, January 6). *News: Waspada Difteri, RSUD Bontang Tangani 4 Kasus pada Anak*. Retrieved from Klausa Bontang Web site: https://www.klausabontang.news/2023/01/06/waspada-difteri-rsud-bontang-tangani-4-kasus-pada-anak/

McGuinness, S. L., Barker, S. F., O'Toole, J., Cheng, A. C., Forbes, A. B., Sinclair, M., & Leder, K. (2018, August). Effect of hygiene interventions on acute respiratory infections in childcare, school and domestic settings in low- and middle-income countries: a systematic review. *Tropical Medicine & International Health, 23*(8), 816-833. doi:10.1111/tmi.13080

Ratti, I. (2018). A review on mathematical modeling of infectious diseases. *IOSR Journal of Engineering (IOSRJEN)*, 17-19.

Sornbundit, K., Triampo, W., & Modcang, C. (2017). Mathematical modeling of diphtheria transmission in Thailand. *Computers in Biology and Medicine*, 162-168.

Tang, B., Xia, F., Tang, S., Bragazzi, N. L., Li, Q., Sun, X., & Liang, J. (2020, June). The effectiveness of quarantine and isolation determine the trend of the COVID-19 epidemics in the final phase of the current outbreak in China. *International Journal of Infectious Disease : IJID : official publication of the International Society for Infectious Diseases, 95*, 288-293. doi:10.1016/j.ijid.2020.03.018

Tosepu, R., Gunawan, J., Effendy, D. S., Ahmad, O. A., & Farzan, A. (2018, December 27). The outbreak of diphtheria in Indonesia. *The Pan African Medical Journal, 31*(49). doi:https://doi.org/10.11604/pamj.2018.31.249.16629

Truelove, S. A., Keegan, L. T., Moss, W. J., Chaisson, L. H., Macher, E., Azman, A. S., & Lessler, J. (2020, June 24). Clinical and Epidemiological Aspects of Diphtheria: A Systematic Review and Pooled Analysis. *Clinical Infectious Disease, 71*(1), 89-97.

UNICEF Indonesia. (2022, April 18). *Press Release: Cakupan Imunisasi Anak Rendah Akibat COVID-19, Pemerintah Atasi dengan Bulan Imunisasi Anak Nasional*. Retrieved from UNICEF Indonesia: https://www.unicef.org/indonesia/id/press-releases/cakupan-imunisasi-anak-rendah-akibat-covid-19-pemerintah-atasi-dengan-bulan

Valek, L., & Tegeder, I. 2. (2021). Failure of Diphtheria Toxin Model to Induce Parkinson-Like Behavior in Mice. *International journal of molecular sciences, 22*(17). doi:https://doi.org/10.3390/ijms22179496

World Health Organization. (2017, November 27). *Newsroom: Questions and Answers: Diphtheria*. Retrieved from World Health Organization Web site: https://www.who.int/news-room/questions-and-answers/item/diphtheria

World Health Organization. (2022). *Data: GHO: Data: Indicators: Diphtheria - number of reported cases*. Retrieved from World Health Organization Web site: https://www.who.int/data/gho/data/indicators/indicator-details/GHO/diphtheria---number-of-reported-cases

World Health Organization. (2023). *Diphtheria*. Retrieved from World Health Organization Web site: https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/vaccine-standardization/diphtheria