

Dynamics of Cholera Transmission with Hyperinfectious State of Bacteria

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Abstract

Cholera is an infection of the small intestine caused by the gram-negative bacterium, *Vibrio cholerae*. The mathematical models discussed in this study is a model of the cholera transmission with hyperinfectious state of bacteria. This study aims to modify the cholera model by involving hyperinfectious state of bacteria and taking into account the effect of vaccination, treatment and water sanitation. Then we performed the stability analysis around equilibrium point. There are two equilibria, namely disease free and endemic equilibrium. The results of model analysis shows that the number of each subpopulation of humans and bacteria is asymptotically stable around disease free equilibrium if the basic reproduction number is less than one, and asymptotically stable around the positive endemic equilibrium if the basic

reproduction number is greater than one. Numerical analysis is given to justify the theorem from mathematical analysis and to see the effect of parameters variation (i.e. vaccination, treatment and water sanitation) to the number of infected humans.

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1. Introduction

Cholera is a severe water-borne infectious disease caused by the bacterium *Vibrio cholerae*. The last few years have witnessed many cholera outbreaks in developing countries, including India (2007), Congo (2008), Iraq (2008), Zimbabwe (2008–2009), Vietnam (2009), Kenya (2010), Haiti (2010–2011), and Cameroon (2010–2011) [20]. In 2014 a total of 190,549 cases of cholera reported to WHO by 42 countries, 55% of the cases were from Africa, 30% from Asia and 15% of Hispaniola. There are as many as 2,231 cholera caused deaths reported by 24 countries: 1,882 deaths occur in Africa, 42 in Asia, and 307 in Hispaniola. Cholera cases and deaths reported only represent a small portion of the actual cases. Allegedly there are more than 2 million cases and nearly one hundred thousand deaths due to cholera every year [17]. Based on the description, cholera remains a major health problem in the world. Therefore, we need to develop mathematical model of cholera disease that can describe the dynamics of cholera transmission.

The bacterium *Vibrio cholerae* can enter the body through consumed food or beverages. At the infecting time, these bacteria produce *enterotoxin* which results the discharge of body fluids in large numbers, so that without proper treatment, an infected individual can be passed. After getting infected, cholera sufferers will shed *Vibrio cholerae* together with their feces. Freshly shed bacteria from the human gastrointestinal tract has high infectivity, which is called hyperinfectious. But the hyperinfectious bacteria decays in a matter of hours into a lower infectious state. It means that hyperinfectious bacteria can only be ingested if there are meeting (i.e. using the same river or toilet on the same day) between susceptible with infected individuals. Thus, hyperinfectivity of bacteria is the key to understanding the nature of the spread of cholera from human-to-human [7].

Since the pioneering work of Edward Jenner on smallpox [10], vaccination has been a commonly used method for diseases control [11, 12, 13] and works by reducing the number of susceptible individuals in a population. For cholera disease, oral cholera vaccine (OCV) has been proposed as an effective adjunct in endemic and epidemic settings [2, 16]. Besides that, sanitation interventions, such as chlorination, have long been recognized as effective prevention measures against cholera and other diarrheal diseases [8, 9]. Many public health scientists believe that sustained improvements in access to safe water and sanitation can eliminate transmission of cholera, citing interventions used throughout South and Central America in the 1990s [14, 15]. In the other hand, treatment is the most important thing to eradicate the disease. Therefore, vaccination, treatment, and sanitation interventions can play an important role in decreasing the burden of cholera.

A lot of research work has been done on the cholera transmission dynamics [1, 4, 5, 19]. For example, Codeco [1] in 2001 has modeled the cholera transmission that explicitly accounted for the environmental element, i.e. the *V. cholerae* concentration in the water supply, into a regular SIR epidemiological model. The infection force was modeled by a logistic function to represent the saturation effect. Hartley, Morris and Smith [4] in 2006 examined the model of the spread of cholera involving hyperinfectious state of bacteria. Wang and Modnak [5] presented a model of the spread of cholera route of transmission of the environment-to-human and human-to-human by inserting control variables: vaccination, treatment, and water sanitation.

Here, we developed the cholera model of Hartley *et al.* [4] by considering vaccination, treatment, and water sanitation as control strategies. We assumed the total human population is not constant. Furthermore, our goal is to analyze the equilibrium and the stability of the modified model. The paper is organized into four sections. The first section is the background and purpose of this paper. The second section describes the formulation of the model used. The third section describes the model analysis. The fourth section performs the numerical analysis. The conclusions are provided in section five.

2. Model Description and Formulation

The total human population is divided into three compartments depending on the epidemiological status of individuals. These compartments include: Susceptible, $S(t)$, infected, $I(t)$, and Recovered, $R(t)$. The concentration of bacteria in the environment is divided into two compartments, namely hyperinfectious bacteria, $B_H(t)$, and less infectious bacteria, $B_L(t)$.

The underlying assumptions establishing this model are as follows. The total human population is not constant. Susceptible population increases by the rate of new comers, Λ . The number of human population decreases by natural death at the rate μ . Vaccination is introduced to the susceptible population at the rate ν , so that νS individuals per time are removed from the susceptible population and subsequently are added to the recovered population. Infections, I , are caused by ingesting water contaminated with B_H hyperinfectious bacteria per ml or B_L less infectious bacteria per ml. Ingestion of hyperinfectious bacteria occurs at the rate β_H , while ingestion of less infectious bacteria occurs at the rate β_L . The relationship between infection rates and the density of cholera is described by a saturating function with κ_L and κ_H are less infectious and hyperinfectious bacteria concentration that yields 50% chance of catching cholera, respectively. Treatment is given to individuals who are infected at the rate a . Sanitation leads to the death of *V. cholerae* bacteria at the rate w . Cholera can be recovered without certain strategies at the rate θ . Cholera causes deaths in the sufferer at the rate d . Individuals who have recovered from the disease, will not be reinfected because of their immune system. Infected human contribute to subpopulation of hyperinfectious bacteria at the rate ξ . Hyperinfectious bacteria can naturally become less infectious at the rate χ . Bacterial natural death rate

is μ_p . Based on the assumptions, the model of cholera transmission is given by

$$\begin{aligned}\frac{dS}{dt} &= \Lambda - \beta_H S \frac{B_H}{\kappa_H + B_H} - \beta_L S \frac{B_L}{\kappa_L + B_L} - \mu S - vS, \\ \frac{dI}{dt} &= \beta_H S \frac{B_H}{\kappa_H + B_H} + \beta_L S \frac{B_L}{\kappa_L + B_L} - (\theta + \mu + a + d)I, \\ \frac{dR}{dt} &= vS + (\theta + a)I - \mu R, \\ \frac{dB_H}{dt} &= \xi I - \chi B_H - wB_H, \\ \frac{dB_L}{dt} &= \chi B_H - \mu_p B_L - wB_L,\end{aligned}\tag{2.1}$$

with $S(0) \geq 0$, $I(0) \geq 0$, $R(0) \geq 0$, $B_H(0) \geq 0$, $B_L(0) \geq 0$.

In this system, the parameter Λ , μ , v , θ , a , d , β_L , β_H , κ_L , κ_H , ξ , χ , μ_p , w are all non-negative constants. Furthermore, we have proven that the system (2.1) is bounded, by following Lemma 2.1.

Lemma 2.1. The set $\Omega = \{(S, I, R, B_H, B_L) \in R_+^5 : 0 \leq S + I + R \leq \frac{\Lambda}{\mu} + N_0 \text{ and } 0 \leq B_H + B_L \leq \frac{\xi}{w} \left(\frac{\Lambda}{\mu} + N_0 \right) + B_0\}$ is the positive bounded region of model system (2.1), where N_0 and B_0 are total human population and bacterial population at $t = 0$, respectively.

Proof. Let $N = S + I + R$, based on system (2.1) we have

$$\frac{dN}{dt} = \Lambda - \mu N - dI.$$

Because dI is non-negative, thus

$$\frac{dN}{dt} + \mu N \leq \Lambda.\tag{2.2}$$

Inequality (2.2) is solved by using integrating factor, thus

$$N \leq \frac{\Lambda}{\mu} (1 - e^{-\mu t}) + N_0 e^{-\mu t}.$$

Because $S(t)$, $I(t)$, and $R(t)$ are non-negative and $0 \leq e^{-\mu t} \leq 1$ for all $t \geq 0$, then we obtain

$$0 \leq S + I + R \leq \frac{\Lambda}{\mu} + N_0.\tag{2.3}$$

Next, let $B = B_H + B_L$, then based on system (2.1) we have

$$\frac{dB}{dt} = \xi I - wB - \mu_p B_L.\tag{2.4}$$

Because $\mu_p B_L$ is non-negative, then based on inequality (2.3) and equation (2.4) we get

$$\frac{dB}{dt} + wB \leq \xi \left(\frac{\Lambda}{\mu} + N_0 \right). \tag{2.5}$$

The solution of inequality (2.5) is

$$B \leq \frac{\xi \Lambda}{\mu w} + \frac{\xi N_0}{w} + \left(B_0 - \frac{\xi \Lambda}{\mu w} \right) e^{-wt},$$

with $B_0 = B(0)$. Because for all $t \geq 0$, $B_H(t)$ and $B_L(t)$ are non-negative and $0 \leq e^{-\mu t} \leq 1$ then we have

$$0 \leq B_H + B_L \leq \frac{\xi}{w} \left(\frac{\Lambda}{\mu} + N_0 \right) + B_0. \tag{2.6}$$

Based on inequality (2.3) and (2.6) we get

$$0 \leq S + I + R \leq \frac{\Lambda}{\mu} + N_0$$

and

$$0 \leq B_H + B_L \leq \frac{\xi}{w} \left(\frac{\Lambda}{\mu} + N_0 \right) + B_0.$$

■

3. Model Analysis

The model system (2.1) is analyzed qualitatively to get insights into its dynamical features which give better understanding of the dynamics of cholera disease transmission.

3.1. Epidemic Dynamics

The disease free equilibrium (DFE) of model system (2.1) is given by

$$E_0 (S^0, I^0, R^0, B_H^0, B_L^0) = \left(\frac{\Lambda}{\mu + v}, 0, \frac{v\Lambda}{\mu(\mu + v)}, 0, 0 \right).$$

To explain the stability behaviors of the equilibrium points, we need to compute the basic reproduction number of model, R_0 . This disease-threshold quantity, R_0 , measure the average number of secondary infections caused by an infectious individual during his or her entire period of infectiousness [18]. We calculated the basic reproduction number by using the next generation operator approach by van den Driessche and Watmough [3]. The next generation matrix is given by:

$$F = \begin{bmatrix} 0 & \frac{\beta_H S \kappa_H}{(\kappa_H + B_H)^2} & \frac{\beta_L S \kappa_L}{(\kappa_L + B_L)^2} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}, \quad V = \begin{bmatrix} \theta + \mu + a + d & 0 & 0 \\ -\xi & \chi + w & 0 \\ 0 & -\chi & \mu_P + w \end{bmatrix}.$$

Next, DFE E_0 is substituted into F and V so that we obtain FV^{-1} as follows.

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

with

$$\begin{aligned} a_{11} &= \frac{\Lambda\xi(\beta_H\kappa_L(\mu_P + w) + \beta_L\chi\kappa_H)}{\kappa_H\kappa_L(\mu + v)(\theta + \mu + a + d)(\chi + w)(\mu_P + w)}, \\ a_{12} &= (\theta + \mu + a + d)(\chi + w) + (\chi + w)(\mu_P + w), \\ a_{13} &= (\theta + \mu + a + d)(\chi + w)(\mu_P + w) - \frac{\beta_L\Lambda\chi\xi}{\kappa_L(\mu + v)} - \frac{\beta_H\Lambda\xi}{\kappa_H(\mu + v)}(\mu_P + w). \end{aligned}$$

The basic reproduction number is the dominant eigenvalue of FV^{-1} , thus we get

$$R_0 = \frac{\Lambda\xi}{(\mu + v)(\theta + \mu + a + d)} \left(\frac{\beta_H}{\kappa_H} \frac{1}{(\chi + w)} + \frac{\beta_L}{\kappa_L} \frac{\chi}{(\chi + w)} \frac{1}{(\mu_P + w)} \right). \quad (3.7)$$

The biological meaning of this results are as follow. The term $\Lambda/(\mu + v)$ is the number of susceptible population in disease free equilibrium. The term $\xi/(\theta + \mu + a + d)$ is the average amount of hyperinfectious bacteria shed per individual. The term β_H/κ_H and β_L/κ_L are the number of new cases per unit time generated by hyperinfectious and less infectious bacteria, respectively. The term $1/(\chi + w)$ and $1/(\mu_P + w)$ are the expected times that bacteria remain in the hyperinfectious and less infectious states, respectively, before they decay. The term $\chi/(\chi + w)$ is the product of the transition rate of hyperinfectious to less infectious state and the expected times that bacteria remain in the less infectious states. Finally, $\Lambda\xi/(\mu + v)(\theta + \mu + a + d)$ and $\Lambda\xi\chi/(\mu + v)(\theta + \mu + a + d)(\chi + w)$ are the average total amount of hyperinfectious and less infectious bacteria, respectively, shed into the environment. Thus, the first term in the parenthesis is associated with the number of new infections caused by hyperinfectious bacteria, and the second term is associated with new infections caused by less infectious bacteria. The stability of system (2.1) is depend on the basic reproduction number. Here, we state theorems regarding the local asymptotically stability of the disease free equilibrium, E_0 , and endemic equilibrium, E^* .

Theorem 3.1. The DFE of the system (2.1), E_0 is locally asymptotically stable when $R_0 < 1$, and unstable when $R_0 > 1$.

Proof. Jacobian matrix for DFE E_0, J_{E_0} given

$$J_{E_0} = \begin{bmatrix} -(\mu + v) & 0 & 0 & -\frac{\beta_H \Lambda}{\kappa_H(\mu + v)} & -\frac{\beta_L \Lambda}{\kappa_L(\mu + v)} \\ 0 & -(\theta + \mu + a + d) & 0 & \frac{\beta_H \Lambda}{\kappa_H(\mu + v)} & \frac{\beta_L \Lambda}{\kappa_L(\mu + v)} \\ v & \theta + a & -\mu & 0 & 0 \\ 0 & \xi & 0 & -(\chi + w) & 0 \\ 0 & 0 & 0 & \chi & -(\mu_P + w) \end{bmatrix}$$

and the characteristic polynomial of the matrix J_{E_0} is

$$(\lambda + \mu)(\lambda + \mu + v) \left[-(\lambda + \theta + \mu + a + d)(\lambda + \chi + w)(\lambda + \mu_P + w) + \frac{\beta_L \Lambda \chi \xi}{\kappa_L(\mu + v)} + \frac{\beta_H \Lambda \xi}{\kappa_H(\mu + v)} + (\lambda + \mu_P + w) \right] = 0 \tag{3.8}$$

Thus, there are five eigenvalues and two of them are negative, that are $\lambda_1 = -(\mu + v)$ and $\lambda_2 = -\mu$. Meanwhile the three other eigenvalues are derived by solving the cubic equation below

$$\lambda^3 + a_1 \lambda^2 + a_2 \lambda + a_3 = 0, \tag{3.9}$$

with

$$\begin{aligned} a_1 &= \theta + \mu + a + d + \chi + \mu_P + 2w, \\ a_2 &= (\theta + \mu + a + d)(\chi + w) + (\chi + w)(\mu_P + w) \\ &\quad + (\theta + \mu + a + d)(\mu_P + w) - \frac{\beta_H \Lambda \xi}{\kappa_H(\mu + v)}, \\ a_3 &= (\theta + \mu + a + d)(\chi + w)(\mu_P + w) - \frac{\beta_L \Lambda \chi \xi}{\kappa_L(\mu + v)} - \frac{\beta_H \Lambda \xi}{\kappa_H(\mu + v)}(\mu_P + w). \end{aligned}$$

The roots of the equation (3.9) are the other eigenvalues of characteristic polynomial (3.8) namely $\lambda_3, \lambda_4, \lambda_5$. Based on the roots properties of cubic equation, we gained that the roots of equation (3.9) satisfy the following equations.

$$\begin{aligned} \lambda_3 + \lambda_4 + \lambda_5 &= -a_1, \\ \lambda_3 \lambda_4 + \lambda_3 \lambda_5 + \lambda_4 \lambda_5 &= a_2, \\ \lambda_3 \lambda_4 \lambda_5 &= -a_3. \end{aligned} \tag{3.10}$$

Because $a_1 > 0$, then the sum of the three eigenvalues is negative. This denote one of them must be negative, let $\lambda_3 < 0$. Furthermore, to check the equilibrium stability, we just need to notice the negativity of λ_4 and λ_5 . Based on equation (3.7), $R_0 < 1$ yields $a_2 > 0$ and $a_3 > 0$. Thus, based on equations (3.10) the eigenvalues satisfy:

$$\lambda_3(\lambda_4 + \lambda_5) + \lambda_4 \lambda_5 > 0, \tag{3.11}$$

and

$$\lambda_3\lambda_4\lambda_5 < 0. \quad (3.12)$$

Because $\lambda_3 < 0$ and condition (3.12) is satisfied, then we get

$$\lambda_4\lambda_5 > 0. \quad (3.13)$$

Based on condition (3.13) and (3.11) we get

$$\lambda_4 + \lambda_5 < 0. \quad (3.14)$$

Conditions (3.13) and (3.14) can be satisfied if and only if $\lambda_4 < 0$ and $\lambda_5 < 0$. Thus, we know that all the eigenvalues are negative. Therefore, if $R_0 < 1$, then DFE E_0 is locally asymptotically stable.

Further, we will show that if $R_0 > 1$, then DFE E_0 is unstable. Based on equation (3.7), $R_0 > 1$ causes $a_3 < 0$, so that from equation (3.10) the product of the three eigenvalues is positive. Then, because λ_3 is negative, so, we get $\lambda_4 \lambda_5 < 0$. It means that there is a positive eigenvalue. So, DFE of the system (2.1), E_0 is unstable. Finally, DFE of the system (2.1), E_0 is locally asymptotically stable when $R_0 < 1$, and unstable when $R_0 > 1$. ■

3.2. Endemic dynamics

The endemic equilibrium of the model system (2.1) is denoted by

$$E^* = (S^*, I^*, R^*, B_H^*, B_L^*),$$

with

$$S^* = \frac{\Lambda - (\theta + \mu + a + d) I^*}{\mu + v}, \quad (3.15)$$

$$I^* = \frac{S^*}{\theta + \mu + a + d} \left(\frac{\beta_H \xi I^*}{\kappa_H (\chi + w) + \xi I^*} + \frac{\beta_L \chi \xi I^*}{\kappa_H (\mu_P + w) (\chi + w) + \chi \xi I^*} \right), \quad (3.16)$$

$$R^* = \frac{vS^* + (\theta + a) I^*}{\mu}, \quad (3.17)$$

$$B_H^* = \frac{\xi I^*}{(\chi + w)}, \quad (3.18)$$

$$B_L^* = \frac{\chi \xi I^*}{(\mu_P + w) (\chi + w)}. \quad (3.19)$$

First, we show the existence of positive endemic equilibrium of system (2.1) which is given as the following Theorem 3.2.

Theorem 3.2. A unique positive endemic equilibrium E^* of system (2.1) exists if and only if $R_0 > 1$.

Proof. Substituting equations (3.15), (3.18), and (3.19) into the second equation of system (2.1), we can derive

$$A_1 I^{*3} + B_1 I^{*2} + C_1 I^* + D_1 = 0, \tag{3.20}$$

with

$$A_1 = -(\theta + \mu + a + d)\chi\xi^2 \left(\frac{\beta_H + \beta_L}{\mu + v} + 1 \right),$$

$$B_1 = \frac{\Lambda\chi\xi^2(\beta_H + \beta_L)}{\mu + v} - \frac{\xi(\theta + \mu + a + d)[\beta_H\kappa_L(\mu_P + w)(\chi + w) + \beta_L\kappa_H\chi(\chi + w)]}{\mu + v} - \xi\kappa_L(\theta + \mu + a + d)(\mu_P + w)(\chi + w) - \kappa_H\chi\xi(\theta + \mu + a + d)(\chi + w),$$

$$C_1 = \frac{\Lambda\xi[\beta_H\kappa_L(\mu_P + w)(\chi + w) + \beta_L\kappa_H\chi(\chi + w)]}{\mu + v} - \kappa_H\kappa_L(\theta + \mu + a + d)(\mu_P + w)(\chi + w)^2,$$

$$D_1 = 0.$$

Based on the roots properties of cubic equation, the roots of equation (3.20) satisfy:

$$I_1^* + I_2^* + I_3^* = -\frac{B_1}{A_1}, \tag{3.21}$$

$$I_1^* (I_2^* + I_3^*) + I_2^* I_3^* = \frac{C_1}{A_1}, \tag{3.22}$$

$$I_1^* I_2^* I_3^* = -\frac{D_1}{A_1}. \tag{3.23}$$

Because $D_1 = 0$, then at least there is a zero root, let $I_1^* = 0$. Furthermore, based on equation (3.7) $R_0 > 1$ causes $C_1 > 0$. So, the left side of equation (3.22) is negative. Thus $I_2^* I_3^* < 0$. Therefore, a positive root I^* exists in this case. Consequently, B_H^* , B_L^* , S^* , and R^* are uniquely determined and positive.

Contrary, based on equation (3.7) if $R_0 < 1$, then $C_1 < 0$. Because A_1 is negative and $C_1 < 0$, then the value of equation (3.22) is positive. Next, because $I_1^* = 0$, then we have $I_2^* I_3^* > 0$. Meanwhile, based on equation (3.7), $R_0 < 1$ causes

$$\frac{\Lambda\xi^2\chi\beta_H}{(\mu + v)} - \xi\chi\kappa_H(\theta + \mu + a + d)(\chi + w) < 0, \tag{3.24}$$

and

$$\frac{\Lambda\xi^2\chi\beta_L}{(\mu + v)} - \xi\kappa_L(\theta + \mu + a + d)(\mu_P + w)(\chi + w) < 0. \tag{3.25}$$

From inequality (3.24) and (3.25) we get

$$\frac{\Lambda \xi^2 \chi (\beta_H + \beta_L)}{(\mu + v)} - \xi \chi \kappa_H (\theta + \mu + a + d) (\chi + w) - \xi \kappa_L (\theta + \mu + a + d) (\mu_P + w) (\chi + w) < 0,$$

So that, $B_1 < 0$ and then we have $I_1^* + I_2^* + I_3^* < 0$. Because $I_1^* = 0$, then $I_2^* + I_3^* < 0$. Thus, we get $I_2^* < 0$ and $I_3^* < 0$, which is biologically nonfeasible. Therefore, a positive endemic equilibrium doesn't exist. By the same way, we can prove that if $R_0 = 1$, then equation (3.20) have two zero roots and a negative root, which is also biologically nonfeasible. So, a unique positive endemic exists for the system (2.1) if and only if $R_0 > 1$. ■

Based on Theorem 3.2, if $R_0 < 1$, then all endemic equilibria E^* are negative (biologically nonfeasible). The following theorem declare that if $R_0 > 1$, then endemic equilibrium E^* is locally asymptotically stable. This theorem is established by proving that if $R_0 = 1$, then bifurcation occurs. Bifurcation is qualitative change of equilibrium stability of system because of varying parameter value.

Theorem 3.3. When $R_0 > 1$, the endemic equilibrium of system (2.1), E^* , is locally asymptotically stable.

Proof. We utilize Theorem 4.1 in [6]. Let

$$\varphi = \frac{\beta_H \Lambda \xi}{\kappa_H (\mu + v)} (\mu_P + w) + \frac{\beta_L \Lambda \chi \xi}{\kappa_L (\mu + v)} - (\theta + \mu + a + d) (\chi + w) (\mu_P + w).$$

Based on equation (3.7), $R_0 = 1$ causes $\varphi = 0$. Consider Jacobian matrix for DFE, J_{E_0} . DFE E_0 have a zero eigenvalue and four negative eigenvalues when $R_0 = 1$ or $\varphi = 0$. The zero eigenvalue has right eigenvector $(u_1, u_2, u_3, u_4, u_5)$ and left eigenvector $(v_1, v_2, v_3, v_4, v_5)$, with

$$\begin{aligned} u_1 &= -\frac{(\theta + \mu + a + d)(\chi + w)(\mu_P + w)}{(\mu + v)\xi\chi} u_5, \\ u_2 &= \frac{(\chi + w)(\mu_P + w)}{\xi\chi} u_5, \\ u_3 &= \frac{(\mu + v)(\theta + a)(\chi + w)(\mu_P + w) - v(\theta + \mu + a + d)(\chi + w)(\mu_P + w)}{(\mu + v)\xi\chi} u_5, \\ u_4 &= \frac{(\mu_P + w)}{\chi} u_5, \end{aligned}$$

$$\begin{aligned}
 u_5 &> 0, \\
 v_1 &= v_3 = 0, \\
 v_2 &= \frac{\kappa_L(\mu + v)(\mu_P + w)}{\beta_L \Lambda} v_5, \\
 v_4 &= \frac{\kappa_L(\theta + \mu + a + d)(\mu + v)(\mu_P + w)}{\xi \beta_L \Lambda} v_5, \\
 v_5 &> 0.
 \end{aligned}$$

Defined

$$\begin{aligned}
 a &= \sum_{k,i,j=1}^5 v_k u_i u_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(E_0, 0), \\
 b &= \sum_{k,i=1}^5 v_k u_i \frac{\partial^2 f_k}{\partial x_i \partial \varphi}(E_0, 0),
 \end{aligned}$$

$$x_1 = S, \quad x_2 = I, \quad x_3 = R, \quad x_4 = B_H, \quad x_5 = B_L,$$

with

$$f_1 = \frac{dS}{dt}, \quad f_2 = \frac{dI}{dt}, \quad f_3 = \frac{dR}{dt}, \quad f_4 = \frac{dB_H}{dt}, \quad f_5 = \frac{dB_L}{dt}.$$

Based on system (2.1) we derive

$$\begin{aligned}
 a &= 2v_2 u_1 u_4 \frac{\partial^2 f_2}{\partial x_1 \partial x_4}(E_0, 0) \\
 &= 2 \left(\frac{\kappa_L(\mu + v)(\mu_P + w)}{\beta_L \Lambda} v_5 \right) \left(-\frac{(\theta + \mu + a + d)(\chi + w)(\mu_P + w)}{(\mu + v)\xi \chi} u_5 \right) \\
 &\quad \left(\frac{\mu_P + w}{\chi} u_5 \right) \frac{\beta_H}{\kappa_H}, \\
 b &= \frac{v_2 u_2}{(\chi + w)(\mu_P + w)} + \frac{v_2 u_4}{\xi(\mu_P + w)} + \frac{v_2 u_5}{\xi \chi} \\
 &\quad + \frac{v_4 u_2 \kappa_h \kappa_L (\mu + v)^2}{\beta_H \Lambda (\mu_P + w) \kappa_L (\mu + v) + \beta_L \Lambda \chi \kappa_h (\mu + v)} + \frac{v_4 u_4}{(\theta + \mu + a + d)(\mu_P + w)} \\
 &\quad + \frac{v_5 u_4 \kappa_L (\mu + v)(\theta + \mu + a + d)(\mu_P + w)}{\beta_L \Lambda \xi - \kappa_L (\mu + v)(\theta + \mu + a + d)(\mu_P + w)} + \frac{v_5 u_5}{(\theta + \mu + a + d)(\chi + w)}.
 \end{aligned}$$

Because $u_2, u_4, u_5, v_2, v_4, v_5 > 0$, then we obtain $a < 0$ and $b > 0$. Consequently, case (iv) is the only one applicable for the system (2.1). This means that when φ changes from $\varphi < 0$ to $\varphi > 0$, DFE E_0 changes from stable to unstable and endemic equilibrium E^* changes from negative to positive and becomes locally asymptotically stable. Therefore, if $R_0 > 1$, then endemic equilibrium E^* is locally asymptotically stable. ■

Table 1: Model parameters and value

Parameter	Value	References
Λ	10/day	[19]
μ	0.0000548/day	[19]
d	0.015/day	[19]
μ_p	0.0333/day	[4]
β_L	0.2143/day	[4]
κ_L	10^6 cell/ml	[4]
κ_H	1428.5714 cell/ml	[4]
θ	0.2/day	[4]
ξ	10/day	[4]
χ	0.2/day	[4]

4. Numerical Simulation

In this section, our objectives were to justify the stability properties of the equilibrium points based on the theorem in section 3 and to see the influence of parameter variations in dynamics system. Numerical simulation of system (2.1) are carried out using a set of parameter values given in Table 1. Here, we used software *Maple 13* to perform the simulation.

In this case, the dynamics of human population and bacteria were analyzed by varying controlled parameters, that are the rate of ingestion of hyperinfectious bacteria (β_H), the rate of vaccination (v), the rate of treatment (a), and the death rate of bacteria because of sanitation water (w). The dynamics of human populations and the bacteria is observed when $R_0 < 1$ and $R_0 > 1$. In this case R_0 is the basic reproduction number defined in equation (3.7). The initial value used is $S(0) = 1000000$, $I(0) = 10$, $R(0) = 0$, $B_H(0) = 1000000$, $B_L(0) = 1000000$.

First simulation is when $R_0 < 1$. We set the parameter value as given in table 1 with $\beta_H = 0.1$, $v = 0.2$, $a = 0.05$, $w = 0.05$ so that the condition $R_0 < 1$ is satisfied. It is found that there is a disease free equilibrium $E_0(S^0 = 49.98630375$, $I^0 = 0$, $R^0 = 182431.7655$, $B_H^0 = 0$, $B_L^0 = 0)$ with eigen value $\lambda_1 = -0.0000548$, $\lambda_2 = -0.2000548$, $\lambda_3 = -0.44457759138$, $\lambda_4 = -0.0686827432$, $\lambda_5 = -0.08690893442$, which are all negative. It means that E_0 stable when $R_0 < 1$. Thus, Theorem 3.1 was justified. Dynamics of human and bacterial population when $R_0 < 1$ is performed in Figure 1.

Figure 1 shows that the curve S , I , R , B_H , B_L asymptotically approaching the disease free equilibrium point E_0 . Curve I that describes the infected population, at the beginning of simulation, was contained in the population. In short time the curve increased, but after a certain time, it decreased and towards to zero and stable. Similarly occur to curve B_H and B_L , the two curves of bacteria initially increased, but over time B_H and B_L decline until raises zero and stablized. The simulation results are consistent with Theorem 3.1 that if $R_0 < 1$, then the disease free equilibrium point E_0 is asymptotically stable, and

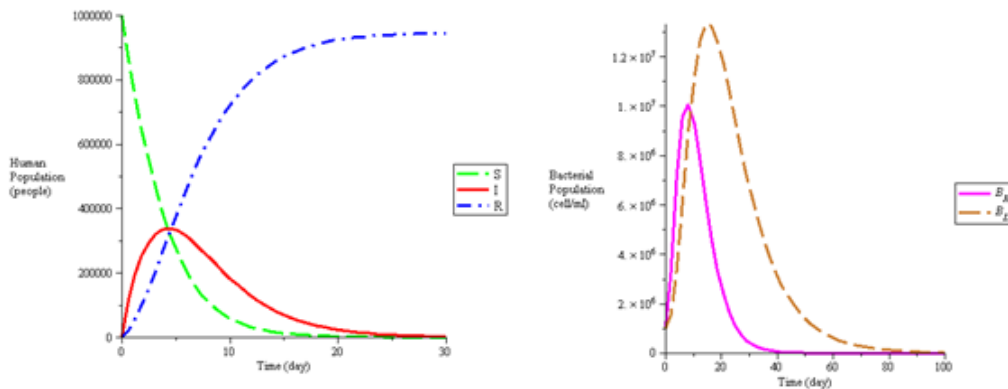


Figure 1: Dynamics of human and bacterial population when $R_0 < 1$.

by Theorem 3.2 that is if $R_0 < 1$, then there is not positive endemic equilibrium point. These results indicate that if the parameters of the model are setting to get $R_0 < 1$, then the cholera could be extinct because the population system will be stable at a disease free equilibrium point.

Next, we performed simulation when $R_0 > 1$. We set the parameter value as given in table 1 with $\beta_H = 0.1$, $v = 0.02$, $a = 0.05$, $w = 0.05$ so that the condition $R_0 > 1$ is satisfied. It is found that there is a disease free equilibrium $E_0(S^0 = 498.6337435, I^0 = 0, R^0 = 181983.1181, B_H^0 = 0, B_L^0 = 0)$ with eigen value $\lambda_1 = -0.0000548$, $\lambda_2 = -0.2000548$, $\lambda_3 = 0.8481379864$, $\lambda_4 = 0.3337531835$, $\lambda_5 = -0.0839699713$, which are not all negative. It means that disease free equilibrium E_0 is not stable when $R_0 > 1$. Thus, Theorem 3.1 was justified, that is disease free equilibrium E_0 is asymptotically stable if and only if $R_0 < 1$. Dynamics of human and bacterial population when $R_0 > 1$ is performed in Figure 2.

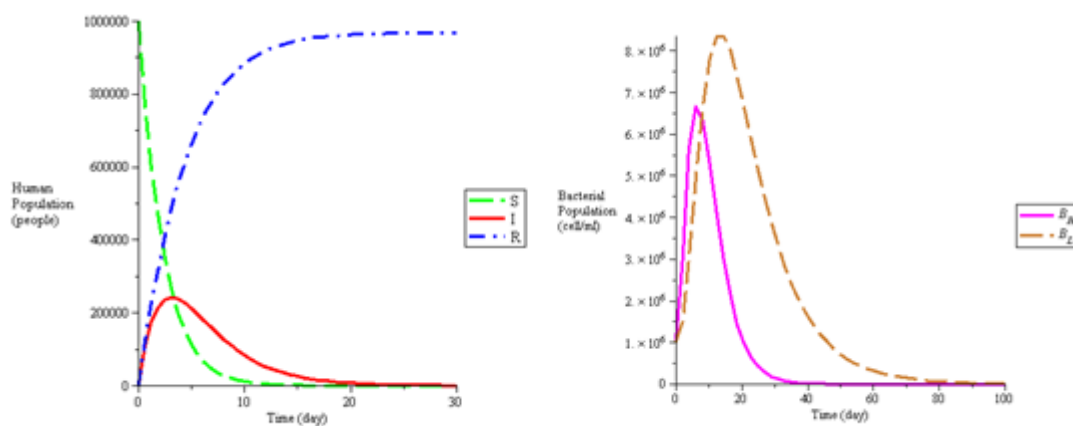


Figure 2: Dynamics of human and bacterial population when $R_0 > 1$.

Figure 2 shows that the curve S, I, R, B_H, B_L asymptotically approaching the en-

demographic equilibrium point E^* . Curve I that describes the infected population, at the beginning of simulation, was contained in the population, in short time the curve increased, but after a certain time decreased, but did not reach the zero point, and then stabilized. Similarly occur to curve B_H and B_L , the two curves of bacteria initially increased, but over time B_H and B_L declined but did not reach the zero point, and then stabilized to positive point. In this case the system is stable at endemic equilibrium. The simulation results are consistent with Theorem 3.1 that is the disease free equilibrium point E_0 is asymptotically stable if and only if $R_0 < 1$, so that when $R_0 > 1$ E_0 is unstable. It is also in accordance with Theorem 3.2 and Theorem 3.3 that if $R_0 < 1$, then there is a positive endemic equilibrium point and it is locally asymptotically stable. These results indicate that if the parameters of the model (2.1) are setting to get $R_0 > 1$, then the cholera disease could not be extinct, otherwise the disease will always exist in the population.

Furthermore, the effect of parameters variation to human infected is shown in the following Figure 3. We varying the rate of ingestion of hyperinfectious bacteria (β_H), vaccination rate (v), treatment rate (a), and the rate of bacterial death because of sanitation (w).

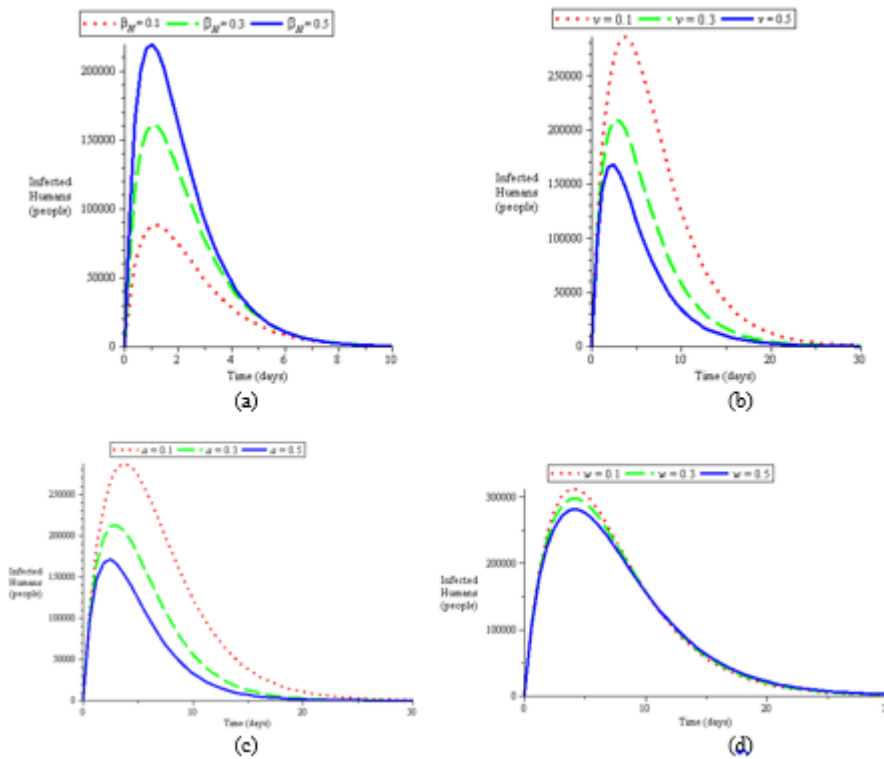


Figure 3: Effect of parameter variation to infected humans. (a) effect of the rate of ingestion of hyperinfectious bacteria. (b) effect of vaccination rate. (c) effect of treatment rate. (d) effect of bacterial death caused of sanitation.

Variations of β_H value associated with hygienic behavior of community and frequency of meetings between susceptible with infected individuals (ex; using the same river or toilet on the same day). When people behave less hygienic and there have been many meetings between susceptible and infected individuals, then β_H value will be great. Based on Figure 3a we can see that increasing of the rate of hyperinfectious bacteria which are ingested (β_H) causes the number of infected humans rise. This is because the greater the value of β_H , the greater the value of R_0 , which means more difficult to overcome the outbreak of cholera. It means that to control cholera we should consider hygienic behavior of community and public sanitation facility. Contrastly, Figure 3b, 3c, and 3d show that the increasing of vaccination rate (v), the treatment rate (a), sanitation rate (w), causes the number of infected humans is on the wane. This is because the higher the value of v , a or w , the lower value of R_0 , thus helping reduce the rate of spread of cholera disease. Therefore, we offered any program to control cholera should consider vaccination, treatment, and sanitation.

5. Conclusions

In this study we have modified mathematical model of the spread of cholera. The model takes into account the presence of hyperinfectious state of bacteria and the influence of vaccination, treatment, and sanitation. Model analysis shows that the model of cholera transmission has two equilibria, that are the disease free equilibrium and endemic equilibrium. A unique positive endemic equilibrium exists if and only if the basic reproduction number is greater than one. The number of individual subpopulations of humans and bacteria is locally asymptotically stable around the disease free equilibrium if and only if the basic reproduction number is less than one, and locally asymptotically stable around endemic equilibrium when the basic reproduction number is greater than one.

Numerical simulation results indicate that the increase of ingestion of hyperinfectious bacteria will accelerate the outbreak of disease. While the increase in the rate of vaccination, treatment, and sanitation will suppress the disease outbreak. Therefore, we offered any program to control cholera should consider vaccination, treatment, and sanitation.

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