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THE ROLE OF HOUSEFLIES IN CHOLERA TRANSMISSION

SHAIMAA AL-SHANFARI, IBRAHIM M. ELMOJTABA*, NASSER ALSALTI

Department of Mathematics, College of Science, Sultan Qaboos University, Al-Khod 123, Muscat, Oman

Abstract. In this paper, we propose and analyse a mathematical model that describes the dynamics of Cholera. The main aim of this model is to investigate the role of houseflies in the transmission of Cholera. Our analysis showed that the disease free equilibrium is globally asymptotically stable whenever the basic reproduction number is less than unity; and unstable otherwise; and our model posses only one endemic equilibrium which is locally asymptotically stable whenever basic reproduction number is greater than unity. Our sensitivity analysis showed that the basic reproduction number is very sensitive to ingesting vibrios rate from aquatic environment by vectors, the rate of contribution to V. cholera in the aquatic environment and the death rate of vector and death rate of vibrios in aquatic environment which indicates that the vector (i.e. the houseflies) play a very important role in the transmission procedure.Numerically, we shown that the rate of water contamination by infectious people shedding V. cholera into the environment has no impact in the infection because it depends on both bacteria shedding of the infected individuals and the level of sanitation in the environment and since the environment is safe, then it is obviously has no effects. In addition, if the contact rate of vectors with contaminated water is high in the presence of increased contribution of each infected vector to the aquatic environment then cholera will persist in the population. Therefore, to obtain a significant and effective control, the contribution of each infected vector to the aquatic environment and the rate of exposure to contaminated water must be reduced.

Keywords: Cholera model; basic reproduction number; bifurcation analysis; sensitivity analysis.

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*Corresponding author

E-mail address: elmojtaba@squ.edu.om

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1. INTRODUCTION

Enteric diseases are considered to be one of the greatest threat to human race, since it causes mortality of millions of people as well as huge impact on social and economic aspects of populations [15]. Enteric diseases are defined as infections caused by viruses or bacteria that enter the body through the mouth or intestinal system, primarily as a result of eating, drinking and/or digesting contaminated foods or liquids. Cholera is a waterborne enteric disease which has a main symptom; acute, watery diarrhea that caused by a bacterium (gram-negative rod), *Vibrio cholerae*. It can be developed to severe watery diarrhoea with vomiting. If people are not treated promptly, they can lose large amounts of fluid and salts which lead to severe dehydration and death within hours [22]. The species *V. cholerae* is subdivided into serogroups, which are toxigenic (O1 & O139) and non-toxigenic (non-O1) [10]. Strains that have the potential to cause epidemic cholera and thus are of public health significance belong to serogroups O1 or O139 and produce cholera toxin (CT) [24, 22]. In its most severe form, cholera is one of the rapid lethal infectious diseases which can lead to death within hours, especially in places where drinking water is unprotected from faecal contamination. These characteristics of cholera have yielded a reputation that cause fear. However, with appropriate treatment, mortality can be kept low.

In 2014, 190549 cases were notified from 43 countries with 55% in Africa and 2231 deaths were reported in that year [27]. In 2015, a total of 172454 cholera cases were reported in 42 countries, 41% of which in Africa, 37% in Asia and 21% in Hispaniola (Central American island) [26]. In the same period, 1304 deaths were reported [26]. During 2016, 132 121 cases were reported from 38 countries, including 2420 deaths [26]. The year 2017 was remarkable for cholera because it marked 200 years since the onset of the first recognized cholera pandemic in 1817, while the current seventh pandemic continues as the longest ever recorded [25]. Globally, in 2017, 71 countries provided data on cholera with 34 countries reported a total of 1 227 391 cases and 5654 deaths and the remaining countries reported no cases. 84% of all suspected cases reported were in Yemen with a total of 1 032 481 cases and 2261 death [25].

The prevalence of cholera depends on numerous environmental and biological variables, including seasonal environmental drivers, host immunity and infectivity of the bacteria [9, 24].

Cholera is usually transmitted through faecally contaminated water, hands or food, and remains an ever-present risk in many countries. New outbreaks can occur where water supply, sanitation, food safety, and hygiene are insufficient. The dynamics of cholera is much more complex as it involves multiple interactions between the human host, other organisms, and the environment [24]. The transmission of cholera include both indirect (i.e., environment-to-human) and direct (i.e., human-to-human) routes [24]. The indirect exposure occurs when people ingest water or food from the environment that is contaminated by the vibrios. The direct transmission may occur when the vibrios are transmitted from an infected person directly to a healthy person by close contacts (such as shaking hands or hugging) or by eating food prepared or consumed by individuals with dirty hands [9, 23, 21]. Some studies show that the infected person or vector typically shed vibrios in their stool for only 1 day, at approximately 10^3 vibrios per gram of stool [24]. Therefore, vectors (e.g. house flies) can play an important role in the transmission of the cholera. The mechanism of transmitting cholera infection from house flies (Musca domestica fly [14]) among humans is such that the flies feed, crawl and lay eggs on human food [14, 28, 11].

To understand the complex dynamics of cholera, several mathematical models have been developed [6, 9, 17, 23]. Capasso and Paveri-Fontana [6] described cholera model by two equations of dynamics of infected people and the dynamic of aquatic population. Then Codeco [9] extended their work by including additional equation of susceptible population in order to study the long term behaviour of cholera and he explored the role of V. cholera in aquatic environment in the persistence of the outbreak. His results emphasis the importance of the aquatic reservoir which depends on the sanitary conditions of the community and seasonal variations of contact rates force a cyclical pattern of cholera outbreaks. Hartley et al. [17] modified Codeco's model by incorporating laboratory observations that passage of V.cholera through the gastrointestinal tract results in a short lived, hyper-infectious state. He found that the incorporation of hyper-infectious state into his model gives a superior fit with the observed epidemic pattern of cholera which help to prove the clinical relevance of laboratory observations regarding the hyper-infectious state, and highlight the significance of human-to-human versus environment-to-human transmission in the generation of epidemic and pandemic disease. Mukandavire et

al. [23] proposed a model to study the 2008-2009 cholera outbreak in Zimbabwe. The model explicitly considered both human-to-human and environment-to-human transmission pathways. The results in this work demonstrated the importance of the human-to-human transmission in cholera epidemics, especially in such places as Zimbabwe, a land-locked country in the middle of Africa.

The model proposed here is an extension of Mukandavire work [23]. The formulation of the model starts by considering two host populations i.e. human and vector populations. The new contribution is the division of the environment into two sub-environments according to the concentration of cholera vibrios. The V. cholerae is associated with contaminated water and food such as rivers, dams, wells, and ponds [9, 23]. In contrast, there are some places in the environment such that it can be considered as uncontaminated and safe places (households and market places). Fundamental in our assumption is that people are well informed of the development and severity of the disease outbreak, thus will take action to reduce contact with other individuals and/or the contaminated environment. However, they can get infection from safe places as the vectors can transmit the infection to them..

2. MODEL FORMULATION

To formulate the model we consider two host populations, human population (N_h) and vector population (N_v). Since the model incorporates the indirect environmental transmission, we add the dynamics of the concentration of free living Cholera vibrios in safe and unsafe environments. Let the human host population be divided into the following, susceptible individuals $S_h(t)$,those who are infected with cholera $I_h(t)$, and those who are recovered and have permanent immunity $R_h(t)$. This implies:

$$N_h = S_h(t) + I_h(t) + R_h(t)$$

Similarly, let the vector population have two categories, susceptible vector $S_v(t)$, and infected vector $I_h(t)$, such that

$$N_v = S_v(t) + I_v(t)$$

The total population for humans and vectors are assumed to be a constant, which is a reasonable assumption for a relatively short period of time and for low-mortality diseases such as cholera.

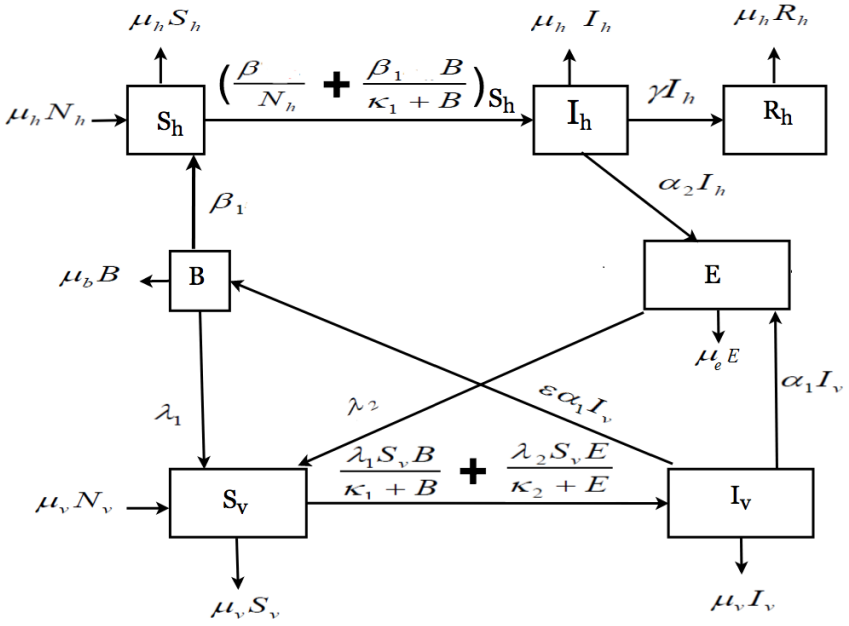

FIGURE 1. Model flow diagram.

Let also $B(t)$ and $E(t)$ denote the concentration of the vibrios in safe and unsafe environment respectively. The following Compartmental model (Figure (**??**)) describes the dynamics of the model, in which, it is assumed that the susceptible individuals acquire infection with cholera by human-to-human contact at per capita $\frac{\beta I_h}{N_h}$ or due to the environment-to-human transmission represented by logistic function. The vector get the infection from unsafe environment then it transmit it to safe environment.

$$
\begin{aligned}
\frac{dS_h}{dt} &= \mu_h N_h - \frac{\beta S_h I_h}{N_h} - \frac{\beta_1 S_h B}{\kappa_1 + B} - \mu_h S_h \\
\frac{dI_h}{dt} &= \frac{\beta S_h I_h}{N_h} + \frac{\beta_1 S_h B}{\kappa_1 + B} - (\gamma + \mu_h) I_h \\
\frac{dR_h}{dt} &= \gamma I_h - \mu_h R_h \\
\frac{dS_v}{dt} &= \mu_v N_v - \frac{\lambda_1 S_v B}{\kappa_1 + B} - \frac{\lambda_2 S_v E}{\kappa_2 + E} - \mu_v S_v \\
\frac{dI_v}{dt} &= \frac{\lambda_1 S_v B}{\kappa_1 + B} + \frac{\lambda_2 S_v E}{\kappa_2 + E} - \mu_v I_v \\
\frac{dB}{dt} &= \varepsilon\alpha_1 I_v - \mu_b B \\
\frac{dE}{dt} &= \alpha_1 I_v + \alpha_2 I_h - \mu_e E
\end{aligned}
\tag{1}
$$

with

$$\frac{dN_h}{dt} = 0$$
$$\frac{dN_v}{dt} = 0$$

Note that we have considered the infection through contact with environmental free Cholera vibrios. As it is the case for most models involving free-living pathogens in the environment [9, 23, 17, 30], the environmental-related forces of infection,e.g. $\frac{\beta_1 S_h B}{\kappa_1 + B}$, is modelled using Michealis-Menten or Holling type II functional responses. The constants κ_1, κ_2 represent the minimum amount of vibrios in the environment capable of ensuring 50% chance of contracting the disease.

The parameters used for system (1) and their biological interpretations are giving in Table (1).

Symbol	Parameter
μ_h	Natural human birth and death rate
β	Contact rate from human to human
β_1	Rates of ingesting vibrios from the safe environment to human
λ_1	Rates of ingesting vibrios from the safe environment to vectors
λ_2	Rates of ingesting vibrios from the aquatic environment to vector
γ	Rate of recovery from cholera
μ_v	Death rate of vector
μ_b	Death rate of vibrios in safe environment
μ_e	Death rate of vibrios in aquatic environment
ε	Modification parameter
α_1	Rate of contribution to V. cholera in the both environments by vectors
α_2	Rate of contribution to V. cholera in the safe environment by human

TABLE 1. Cholera model parameters

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3. THEORETICAL ANALYSIS OF THE MODEL

3.1. Basic properties.

3.1.1. *Positivity and boundedness of solutions.* For model (1) to be epidemiological meaningful, it is important to prove that all state variables are non-negative at all time. That is, solutions of the system (1) with non-negative initial data will remain non-negative for all time $t > 0$. This yields to the following theorem [5].

Theorem 3.1. *Let the initial data $S_h(0);I_h(0);R_h(0);S_v(0);I_v(0);B(0);E(0)$ be non-negative. Then a solution $S_h(t);I_h(t);R_h(t);S_v(t);I_v(t);B(t);E(t)$ of the model (1) are non-negative for all $t > 0$, when it exists.*

Proof. Suppose $S_h(0) > 0$. The first equation of system (1) is to

$$\frac{d}{dt}(S_h(t)\rho(t)) = \mu_h N_h \rho(t)$$

where $\rho(t) = exp(\int_0^t \frac{\beta I_t(x)}{N_h} + \frac{\beta_1 B(x)}{\kappa_1 + b(x)} + \mu_h dx) > 0$ is the integration factor. Hence integrating the last relation with respect to t we get:

$$S_h(t)\rho(t) - S_h(0) = \int_0^t \mu_h N_h \rho(t) dt$$

so that the division of both sides by $\rho(t)$ yields

$$S_h(t) = [S_h(0) + \int_0^t \mu_h N_h \rho(t) dt]\rho^{-1}(t) > 0$$

The same arguments can be used to prove $S_v(t) > 0, I_h(t), R_h(t), I_v(t), B(t), E(t) \geq 0$ for all $t > 0$ □

The dynamics of model (1) is dynamical system in the biological feasible compact set

$$\Gamma = \{(S_h, I_h, R_h, S_v, I_v, B(t), E(t)) \in \Re_+^7, 0 < S_h + I_h + R_h \leq N_h, 0 < S_v + I_v \leq N_v\}$$

3.1.2. *Basic Reproductive Number.* The disease-free equilibrium (DFE) for the cholera model (1) is given by

$$P_0 = (S_h^0, 0, 0, S_v^0, 0, 0, 0) \tag{2}$$

where $S_h^0 = N_h$ and $S_v^0 = N_v$

To compute the basic reproduction number of the model, we use the standard method of the next generation matrix developed in [29, 12] by separating the infected states form the uninfected states. Here, the associated next generation matrices are given by:

$$T = \begin{bmatrix} \beta & 0 & \frac{\beta_1 N_h}{\kappa_1} & 0 \\ 0 & 0 & \frac{\lambda_1 N_h}{\kappa_1} & \frac{\lambda_2 N_h}{\kappa_2} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

and

$$\Sigma = \begin{bmatrix} -(\gamma+\mu_h) & 0 & 0 & 0 \\ 0 & -\mu_v & 0 & 0 \\ 0 & \varepsilon\alpha_1 & -\mu_b & 0 \\ \alpha_2 & \alpha_1 & 0 & -\mu_e \end{bmatrix}$$

The expression of the basic reproductive number is given by:

$$R_0 = \frac{D + \sqrt{D_1}}{2\kappa_2(\gamma+\mu_h)\mu_e\kappa_1\mu_v\mu_e} \tag{3}$$

where:

$$\begin{aligned} D &= d + f \\ d &= ((\lambda_2\gamma + \lambda_2\mu_h)\mu_e N_v\kappa_1 + (\lambda_1\varepsilon\gamma + \lambda_1\varepsilon\mu_h)\mu_e N_v\kappa_2)\alpha_1 \\ f &= \beta\mu_e\kappa_1\kappa_2\mu_v\mu_b \\ D_1 &= (d-f)^2 + 4\kappa_1\kappa_2\mu_e\mu_v\mu_b N_h N_v\alpha_1\alpha_2\varepsilon\beta_1\lambda_2(\gamma+\mu_h) \end{aligned}$$

Using Theorem 2 in [29], the following result is established:

Lemma 3.2. *The DFE of system (1) is locally asymptotically stable (LAS) whenever* $R_0 < 1$, *and unstable whenever* $R_0 > 1$.

Lemma 3.2 implies that the cholera can be eliminated from the community when $R_0 < 1$ and the initial sizes of the host populations in the model are in the basin of attraction of the DFE. However, to guarantee that the disease will be eliminated independently of the initial sizes of

host populations, the DFE must be global asymptotically stable (GAS) of the DFE when $R_0 < 1$ as showing in the following theorem.

Theorem 3.3. *The DFE P_0 of system (1) is GAS if $R_0 < 1$ in the compact set Γ.*

Proof. Using theorem Castillo-Chavez et al. in [7] model (1) can be written in the form:

$$\begin{aligned} \frac{dX}{dt} &= F(X,Z) \\ \frac{dZ}{dt} &= G(X,Z) = G(X,0) = 0 \end{aligned}$$

where X and Z denote the uninfected and infected compartments respectively, that is,$X = (S_h, R_h, S_v)$ and $Z = (I_h, I_v, B, E)$ We begin by showing condition i of Castillo-Chavez et al. in [2] as

$$F(X,0) = \begin{bmatrix} \mu_h N_h - \mu_h S_h \\ -\mu_h R_h \\ \mu_v N_v - \mu_v S_v \end{bmatrix}$$

and solving these three ordinary differential equations gives

$$R_h(t) = R_h(0)e^{-\mu_h t} \tag{4}$$

$$S_h(t) = N_h - (N_h - S_h(0))e^{-\mu_h t} \tag{5}$$

$$S_v(t) = N_v - (N_v - S_v(0))e^{-\mu_v t} \tag{6}$$

Thus, $R_h(t) \longrightarrow 0$, $S_h(t) \longrightarrow N_h$ and $S_v(t) \longrightarrow N_v$ as $t \longrightarrow \infty$, regardless of the values of initial conditions. Thus, P_0 is globally asymptotically stable. Next, applying Castillo-Chavez et al. Theorem to cholera model (1) to show condition ii:

$$G(X,Z) = \begin{bmatrix} \beta \frac{S_h I_h}{N_h} + \frac{\beta_1 S_h B}{\kappa_1 + B} - (\gamma + \mu_h) I_h \\ \frac{\lambda_1 S_v B}{\kappa_1 + B} + \frac{\lambda_2 S_v E}{\kappa_2 + E} - \mu_v I_v \\ \varepsilon \alpha_1 I_v - \mu_b B \\ \alpha_1 I_v + \alpha_2 I_h - \mu_e E \end{bmatrix}$$

and

$$A = \begin{bmatrix} \beta - (\gamma + \mu_h) & 0 & \frac{\beta_1 N_h}{\kappa_1} & 0 \\ 0 & -\mu_v & \frac{\lambda_1 N_v}{\kappa_1} & \frac{\lambda_2 N_v}{\kappa_2} \\ 0 & \varepsilon\alpha_1 & -\mu_v & 0 \\ \alpha_2 & \alpha_1 & 0 & -\mu_e \end{bmatrix}$$

which is clearly an M-matrix. Meanwhile, we find

$$\hat{G}(X,Z) = \begin{bmatrix} \beta(1 - \frac{S_h}{N_h})I_h + \frac{\beta_1 N_h B}{\kappa_1} - \frac{\beta_1 S_h B}{\kappa_1 + B} \\ \frac{\lambda_1 N_v B}{\kappa_1} - \frac{\lambda_1 S_v 1 B}{\kappa_1 + B} + \frac{\lambda_2 N_v E}{\kappa_2} - \frac{\lambda_2 S_v E}{\kappa_2 + E} \\ 0 \\ 0 \end{bmatrix}$$

and since $0 \leq S_h \leq N_h$ and $0 \leq S_v \leq N_v$, then it follows that $\hat{G}(X,Z) \geq 0$ Thus, P_0 is GAS whenever $R_0 < 1$. □

3.2. Existence of Endemic Equilibrium of Model (1). In this section, we investigate the existence of other equilibrium points, i.e. possible boundary equilibrium points and interior equilibria. First, we assume that there is an equilibrium such that $I_v = 0$, then from the sixth equation in model (1), $B = 0$ and substituting these values in the fifth equation yields $E = 0$. it follows from the other equations that $I_h = R_h = 0$. Thus, this equilibrium point is disease free. Similarly, if an equilibrium of (1) is such that $B = 0$, then from the sixth equation in model (1), $I_v = 0$ and same substitutions yield to $E = I_h = R_h = 0$. Therefore, this equilibrium point is disease free as well. Next, if the equilibrium of (1) is such that E = 0, then from the last equation of model (1) $I_h = -\frac{\alpha_2}{\alpha_1} I_v$ which have no biological meaning. Hence, $I_h = I_v = 0$ and introducing these values in the third and sixth equations of cholera model leads to the $R_h = B = 0$, and once more, the corresponding equilibrium is disease free. On the other hand, assume disease absent in the human population i.e. $I_h = 0$, then it is follows fron second equation of model (1) that the cholera vibrios concentration $B = 0$, and hence, we have $I_v = R_h = E = 0$. Thus, the full system is disease free. Note that, the non existence of boundary equilibria is due to the fact the disease transmission is one way" (that is, from vectors to humans and not the other way round). As a result, we have proven the following result:

Lemma 3.4. *System (1) has no other boundary equilibrium than the disease-free equilibrium.*

This lemma is considered as an important result because it eliminates the possibility for the model (1) to have non-trivial equilibriums on the boundary . Therefore, the cholera model (1) could have a unique interior (endemic) equilibrium with the disease being present in all the populations under consideration [20]. This lemma with the existence and uniqueness of interior equilibrium for system (1) related sub-models suggested in [4, 20, 19, 5], yields to the following conjecture [20]

Conjecture 3.5. *Assume that $R_0 > 1$ for system (1). Then there exists a unique interior (endemic) equilibrium.*

The endemic equilibrium of the model is denoted by $P_e = (S_h^*, I_h^*, R_h^*, S_v^*, I_v^*, B^*, E^*)$ and it satisfies the following:

$$\begin{aligned} S_h^* &= N_h - \frac{(\mu_h+\gamma)I_h^*}{\mu_h} \\ R_h^* &= \frac{\gamma I_h^*}{\mu_h} \\ S_v^* &= N_v - I_v^* \\ B^* &= \frac{\varepsilon\alpha_1 I_v^*}{\mu_b} \\ E^* &= \frac{\alpha_1 I_v^* + \alpha_2 I_h^*}{\mu_e} \end{aligned} \tag{7}$$

$$AI_h^{*2} + BI_h^* + C = 0 \tag{8}$$

where

$$\begin{aligned} A &= \frac{-\beta(\gamma+\mu_h)}{\mu_h N_h} \\ B &= \beta - \frac{(\gamma+\mu_h)\beta_1\alpha_1\varepsilon I_v^*}{\mu_h(\varepsilon\alpha_1 I_v^* + \kappa_1\mu_b)} - (\gamma+\mu_h) \\ C &= \frac{(\gamma+\mu_h)\beta_1\alpha_1\varepsilon I_v^* N_h}{\varepsilon\alpha_1 I_v^* + \kappa_1\mu_b} \end{aligned}$$

$$A_0 I_v^{*3} + B_0 I_v^{*2} + C_0 I_v^* + D_0 = 0 \tag{9}$$

where

$$\begin{aligned}
A_0 &= -\alpha_1^2\varepsilon(\lambda_1+\lambda_2+\mu_v)\\
B_0 &= -\alpha_1(-N_v\varepsilon(\lambda_1+\lambda_2)\alpha_1+(\lambda_2\alpha_2I_h^*+(\lambda_1+\mu_v)(\kappa_2\mu_e+\alpha_2I_h^*))\varepsilon+\mu_b\kappa_1(\lambda_2+\mu_v))\\
C_0 &= (N_v((\lambda_2\alpha_2I_h^*+\lambda_1(\kappa_2\mu_e+\alpha_2I_h^*))\varepsilon+\lambda_2\kappa_1\mu_b)\alpha_1-\mu_b(\lambda_2\alpha_2I_h^*+\mu_v(\kappa_2\mu_e+\alpha_2I_h^*))\kappa_1)\\
D_0 &= \lambda_2N_v\alpha_2I_h^*\kappa_1\mu_b
\end{aligned}$$

The endemic equilibrium is LAS whenever $R_0>1$ [4,5] and this will be shown numerically at a later stage.

3.3. Bifurcation analysis of the model. To study the possibility of backward bifurcation, we use the theorem in Castillo-Chavez and Song [8]. Introducing $x_1=S_h, x_2=I_h, x_3=R_h, x_4=S_v, x_5=I_v, x_6=B, x_7=E$, the system (1) becomes:

$$\begin{aligned}
x_1' &= \mu_hN_h-\frac{\beta x_1x_2}{N_h}-\frac{\beta_1x_1x_6}{\kappa_1+x_6}-\mu_hx_1=f_1\\
x_2' &= \frac{\beta x_1x_2}{N_h}+\frac{\beta_1x_1x_6}{\kappa_1+x_6}-(\gamma+\mu_h)x_2=f_2\\
x_3' &= \gamma x_2-\mu_hx_3=f_3\\
x_4' &= \mu_vN_v-\frac{\lambda_1x_4x_6}{\kappa_1+x_6}-\frac{\lambda_2x_4x_7}{\kappa_2+x_7}-\mu_vx_4=f_4\\
x_5' &= \frac{\lambda_1x_4x_6}{\kappa_1+x_6}+\frac{\lambda_2x_4x_7}{\kappa_2+x_7}-\mu_vx_5=f_5\\
x_6' &= \varepsilon\alpha_1x_5-\mu_bx_6=f_6\\
x_7' &= \alpha_1x_5+\alpha_2x_2-\mu_ex_7=f_7
\end{aligned}\tag{10}$$

Consider the case when $R_0=1$ and suppose that $\phi=\lambda_2$ is chosen as a bifurcation parameter. Then, R_0can be seen, in terms of the parameter $\lambda_2=\lambda_2^*=\frac{(N_v\alpha_1\varepsilon\lambda_1\kappa_1\mu_v\mu_b)(\beta-(\gamma+\mu_h))\kappa_2\mu_e}{\alpha_1N_v(\mu_b(-\beta+(\gamma+\mu_h))\kappa_1+\alpha_2\beta_1\mu_h\varepsilon)}$. The Jacobian of the system (10) at the disease-free equilibrium is given by the following:

$$J = \begin{bmatrix} -\mu_h & -\beta & 0 & 0 & 0 & -\frac{\beta_1 N_h}{\kappa_1} & 0 \\ 0 & \beta-(\gamma+\mu_h) & 0 & 0 & 0 & \frac{\beta_1 N_h}{\kappa_1} & 0 \\ 0 & \gamma & -\mu_h & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\mu_v & 0 & -\frac{\lambda_1 N_v}{\kappa_1} & -\frac{\lambda_2 N_v}{\kappa_2} \\ 0 & 0 & 0 & 0 & -\mu_v & \frac{\lambda_1 N_v}{\kappa_1} & \frac{\lambda_2 N_v}{\kappa_2} \\ 0 & 0 & 0 & 0 & \varepsilon\alpha_1 & -\mu_b & 0 \\ 0 & \alpha_2 & 0 & 0 & \alpha_1 & 0 & -\mu_e \end{bmatrix}$$

3.3.1. *Calculation of the eigenvectors of J_ϕ.* It can be shown that the Jacobian of the system (10) at $\Phi = \lambda_2$ (denoted by J_ϕ) has a right eigenvector given by $W = (w_1, w_2, w_3, w_4, w_5, w_6, w_7)^T$, where

$$\begin{aligned} w_1 &= -\frac{(\gamma+\mu_h)}{\mu_h} w_2 \\ w_2 &= w_2 \\ w_3 &= \frac{\gamma}{\mu_h} w_2 \\ w_4 &= -\frac{N_v(\lambda_1\kappa_2 w_6 + \phi\kappa_1 w_7)}{\kappa_1\kappa_2\mu_v} \\ w_5 &= \frac{\mu_b(-\beta+\gamma+\mu_h)\kappa_1}{\beta_1 N_h \varepsilon\alpha_1} w_2 \\ w_6 &= \frac{(-\beta+\gamma+\mu_h)\kappa_1}{\beta_1 N_h} w_2 \\ w_7 &= \frac{\alpha_2 w_2 + \alpha_1 w_5}{\mu_e} \end{aligned} \tag{11}$$

and a left eigenvector given by $V = (v_1, v_2, v_3, v_4, v_5, v_6, v_7)$, where

$$\begin{aligned} v_1 &= v_3 = v_4 = 0 \\ v_2 &= \frac{\alpha_2}{-\beta+\gamma+\mu_h} v_7 \\ v_5 &= v_5 \\ v_6 &= \mu_v v_5 - \alpha_1 v_7 \\ v_7 &= \frac{\phi N_v}{\kappa_2\mu_e} v_5 \end{aligned} \tag{12}$$

3.3.2. *Computation of a and b:* From system (10), it can be shown that:

$$
\begin{aligned}
\frac{\partial^2 f_1}{\partial x_1 \partial x_2} &= \frac{\partial^2 f_1}{\partial x_2 \partial x_1} = -\frac{\beta}{N_h} \\
\frac{\partial^2 f_1}{\partial x_1 \partial x_6} &= \frac{\partial^2 f_1}{\partial x_6 \partial x_1} = -\frac{\beta_1}{\kappa_1} \\
\frac{\partial^2 f_1}{\partial x_6^2} &= \frac{2\beta_1 N_h}{k_1^2} \\
\frac{\partial^2 f_2}{\partial x_1 \partial x_2} &= \frac{\partial^2 f_2}{\partial x_2 \partial x_1} = \frac{\beta}{N_h} \\
\frac{\partial^2 f_2}{\partial x_1 \partial x_6} &= \frac{\beta_1}{\kappa_1} \\
\frac{\partial^2 f_4}{\partial x_4 \partial x_6} &= \frac{\partial^2 f_4}{\partial x_6 \partial x_4} = -\frac{\lambda_1}{\kappa_1} \\
\frac{\partial^2 f_4}{\partial x_4 \partial x_7} &= \frac{\partial^2 f_4}{\partial x_7 \partial x_4} = -\frac{\phi}{\kappa_2} \\
\frac{\partial^2 f_4}{\partial x_6^2} &= \frac{2\lambda_1 N_v}{\kappa_1^2} \\
\frac{\partial^2 f_4}{\partial x_7^2} &= \frac{2\phi N_v}{\kappa_2^2} \\
\frac{\partial^2 f_5}{\partial x_6 \partial x_4} &= \frac{\lambda_1}{\kappa_1} \\
\frac{\partial^2 f_5}{\partial x_6^2} &= -\frac{2\lambda_1 N_v}{\kappa_1^2} \\
\frac{\partial^2 f_5}{\partial x_7 \partial x_4} &= \frac{\phi}{\kappa_2} \\
\frac{\partial^2 f_5}{\partial x_7^2} &= -\frac{2\phi N_v}{\kappa_2^2}
\end{aligned} \tag{13}
$$

and

$$
\begin{aligned}
\frac{\partial^2 f_4}{\partial x_7 \partial \phi} &= -\frac{N_v}{\kappa_2} \\
\frac{\partial^2 f_5}{\partial x_7 \partial \phi} &= \frac{N_v}{\kappa_2}
\end{aligned} \tag{14}
$$

and all the other second-order partial derivatives are equal to zero. Thus, we can compute the coefficient a and b defined in (thereom 4.1 in [8]), that is,

$$a = v_2 w_1 [2w_2 \frac{\beta}{N_h} + w_6 \frac{\beta_1}{\kappa_1}] + v_5 [w_4 (w_6 \frac{\lambda_1}{\kappa_1} + w_7 \frac{\phi}{\kappa_2}) - \frac{2\lambda_1 N v}{\kappa_1^2} w_6^2 - \frac{2\phi N v}{\kappa_2^2} w_7^2] \tag{15}$$

and since $w_1 \& w_4$ are negative,then $a < 0$. and

$$b = v_5 w_7 \frac{N_v}{\kappa_2} > 0 \tag{16}$$

Therefore, we have the following result:

Theorem 3.6. *The direction of the bifurcation of system (10) (or system (1)) at $R_0 = 1$ is forward. Since the bifurcation parameter changes from negative to positive, then the DFE changes its stability from stable to unstable. Therefore, a negative unstable equilibrium becomes positive and locally asymptotically stable*

Theorem 3.6 proves that the unique endemic point is locally asymptotically stable.

4. Sensitivity Analysis (SA) of the Basic Reproduction Number with Respect to the Model Parameters

One of the most important concerns about the infectious disease is its ability to invade a population. The useful and valuable quantity which helps determine whether or not an infectious disease can spread through a population is basic reproduction number (R_0) [29, 7]. R_0 measures whether a disease can persist in a population. When R_0 is less than 1, on average each infected individual infects less than one individual, and the disease will die out. In contrast, when R_0 exceeds unity there is an exponential rise in the number of cases over time, and an epidemic results [29, 7]. Therefore, we studied the sensitivity analysis of the basic reproduction number, with respect to the model parameters in order to discover parameters that have a high impact on R_0 and should be targeted by intervention strategies. There are many ways of conducting sensitivity analysis, all resulting in a slightly different sensitivity ranking [18]. We used the normalized forward sensitivity index which is also called elasticity. The normalized forward sensitivity index of a variable with respect to a parameter is defined as the ratio of the relative

change in the R_0 to the relative change in the parameter [3, 16, 18]. It is given by:

$$S_p^{R_0} = \frac{\partial R_0}{\partial p}\frac{p}{R_0} \tag{17}$$

Given the explicit formula (3) for R_0, one can easily derive an analytical expression for the sensitivity of R_0 with respect to each parameter that comprise it. The obtained values are described in Table 2, which presents the sensitivity indices for the baseline parameter values for $R_0 < 1$ and $R_0 > 1$ given in Table (4).

Symbol	Value	Source
μ_h	$0.00004d^{-1}$	[30]
β	$0.000105 - 0.000111$	[23]
β_1	$.055 - 0.094$	[23]
κ_1	$10^6 cells/mL$	Assumed
κ_2	$10^6 cells/mL$	[23]
λ_1	$0.0056 - 0.097$	Assumed
λ_2	$0.0057 - 0.1$	Assumed
γ	$(5d)^{-1}$	[23]
μ_v	$0.189d^{-1}$	[13]
μ_b	$(30d)^{-1}$	Assumed
μ_e	$(30d)^{-1}$	[23]
ε	$0.001 - 0.01$	Assumed
α_1	12 cells $mL^{-1}d^{-1}$ per vector	Assumed
α_2	10 cells $mL^{-1}d^{-1}$ per person	[23]

TABLE 2. Parameter values

Parameter	Sensitivity index ($R_0 < 1$)	Sensitivity index ($R_0 > 1$)
β	+0.00004	+0.00001
β_1	+0.004	+0.002
γ	$-0.4e-2$	+0.008
κ_1	$-0.1e-1$	$-0.8e-2$
κ_2	-0.99	-0.98
λ_1	+0.009	+0.005
λ_2	+0.987	+0.992
α_1	+0.996	+0.997
α_2	+0.004	+0.003
μ_h	$-8.2e-7$	$-5.8e-7$
μ_v	-0.995	-0.997
μ_b	$-0.13e-1$	$-0.79e-2$
μ_e	-0.987	-0.992
ε	+0.012	+0.008

TABLE 3. Parameter values for sensitivity analysis

The sensitivity analysis results indicate that both the environment-to-human and human-to-human transmission pathways are sensitive, and important, in determining the cholera infections as all the parameters will affect the system either positively or negatively. The sensitivity index tells the quantitative changes produced by a small variation in a parameter. The most influential parameters are the ingesting vibrios rate from aquatic environment by vectors (λ_2) and rate of contribution to V. cholera in the aquatic environment α_1) which have positive impact in the value of R_0 in which the impact will be greater if $R_0 > 1$. For example, $S_{\lambda_2}^{R_0} = 0.989$ means that increasing λ_2 by 10% increases R_0 by 9.87%. Death rate of vector (μ_v) and death rate of vibrios in aquatic environment (μ_e) also have strong negative influence in the value of R_0 which occurs more in endemic case. Note that the recovery rate has negative influence when $R_0 < 1$ such that if it increases then the disease dies out. However, it has positive influence when $R_0 > 1$ because in endemic case the disease persist.

5. NUMERICAL SIMULATION

In this section, we perform a numerical simulation of model system (1) to confirm our analytical results and to illustrate the asymptotic behaviour of the model. At this stage, we solve the model numerically with three sets of initial conditions with total human population is 10000 and vector population is 30000. We choose a set of parameter values in model system (1) according to Table 4 where some of the parameter's values were obtained from literature, and some of them were assumed or made varying in order to study their role.

The GAS of the disease-free equilibrium P_0 demonstrated in Theorem 3.2 and the existence and stability of a unique endemic equilibrium as stated in Conjecture 1 for the model is shown on Figure 2 and Figure 3, respectively.

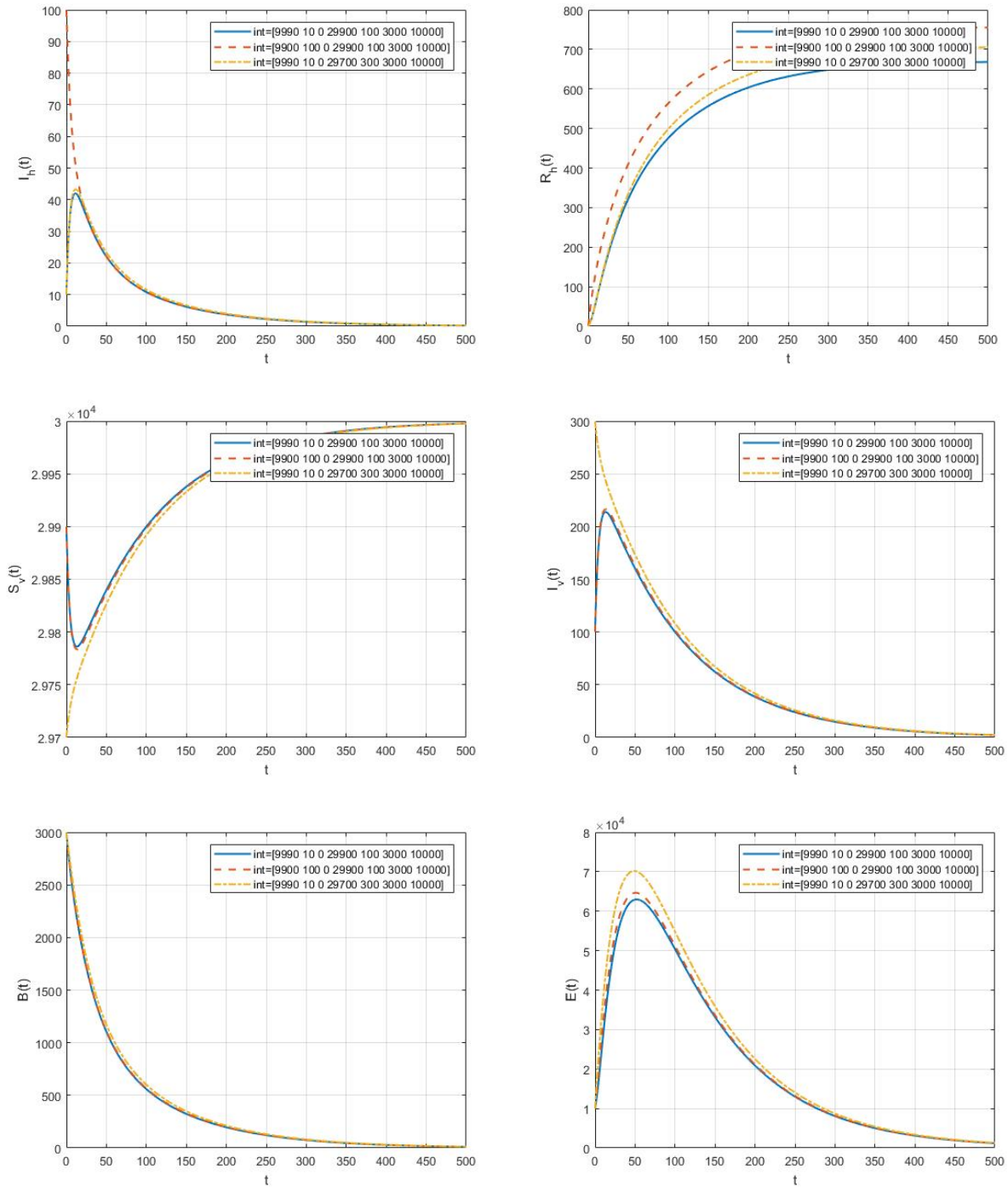

FIGURE 2. GAS of the model disease-free equilibrium with R_0 is 0.69

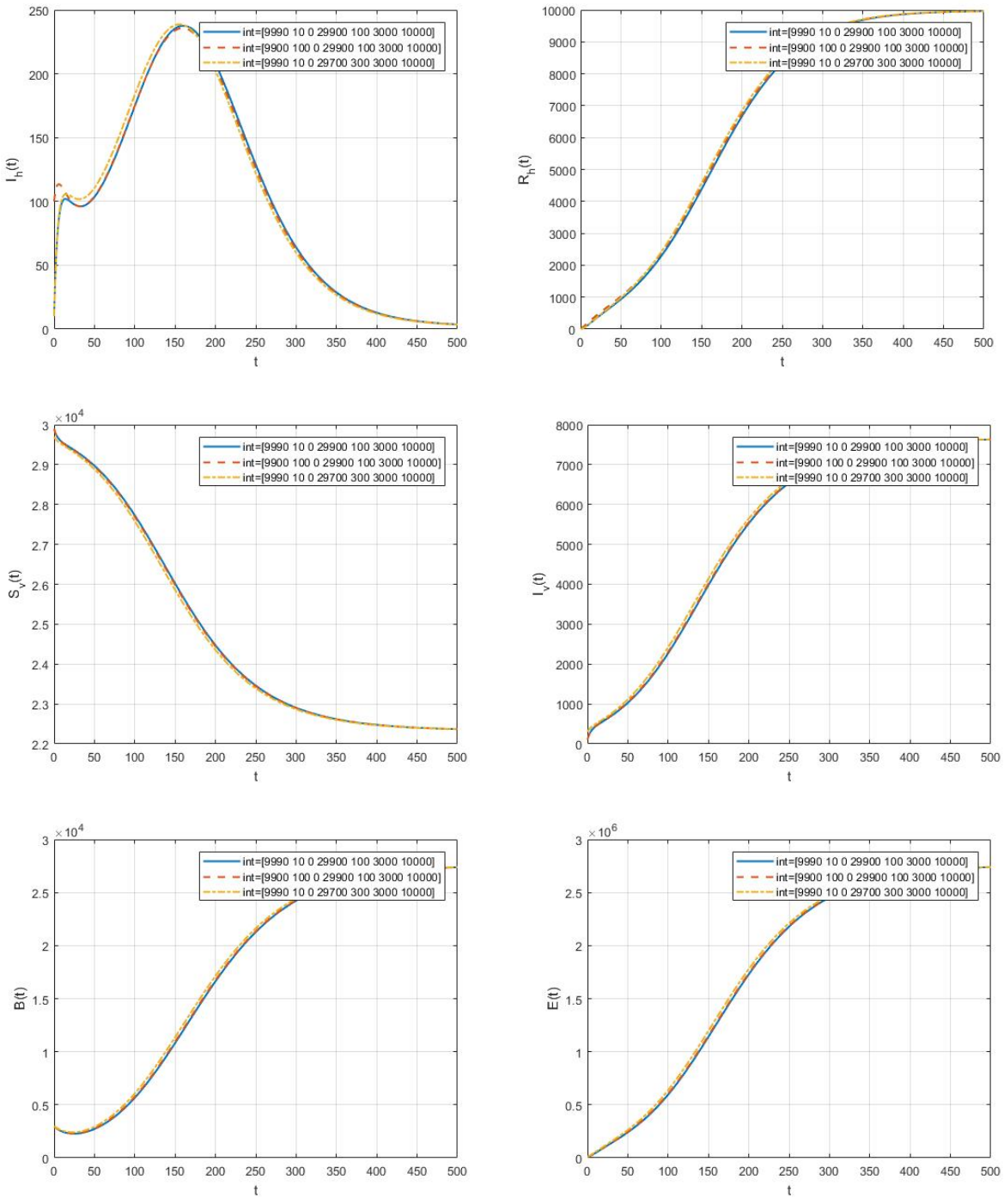

FIGURE 3. GAS of the model endemic equilibrium with R_0 is 1.8

Varying the values of β_1, λ_1 and λ_2 (the ingesting vibrios rate from the safe environment to human, vectors, and ingesting vibrios rate from the unsafe environment to vectors respectively)

Numerical simulation shows that the increase in the value of β_1 leads to an increase in the number of both infected human and infected vector with the effect is more in human population as seen in Figure 4.

It can be seen from Figure 5 that the effect of varying the values of λ_1 affects the infected human and vector populations positively with more effect in vector population which is something predictable. On the other hand, the impact of increasing the value of λ_2 on the infection of human population occurs after some time. In addition, after ingesting a sufficient dose of V. cholera vibrios by vectors then the infection starts to persist and hence the cholera transmission can become endemic. Consequently,the basic reproductive number is significantly increased over unity and hence this will affect the vector population (Figure 6).

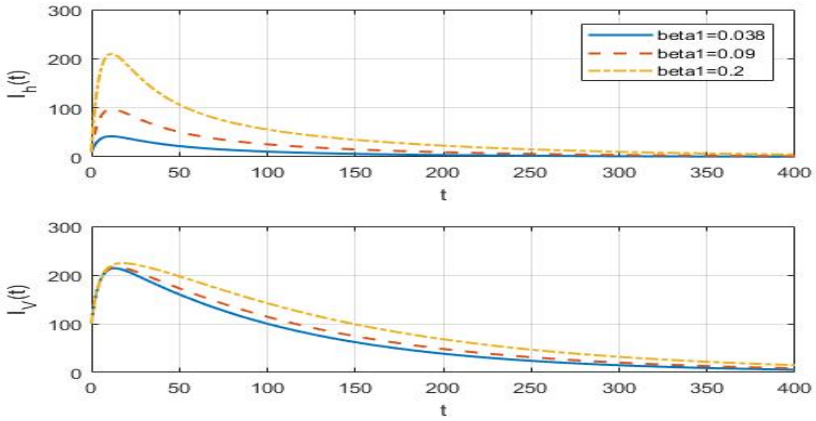

FIGURE 4. Simulation results for different values of β_1.

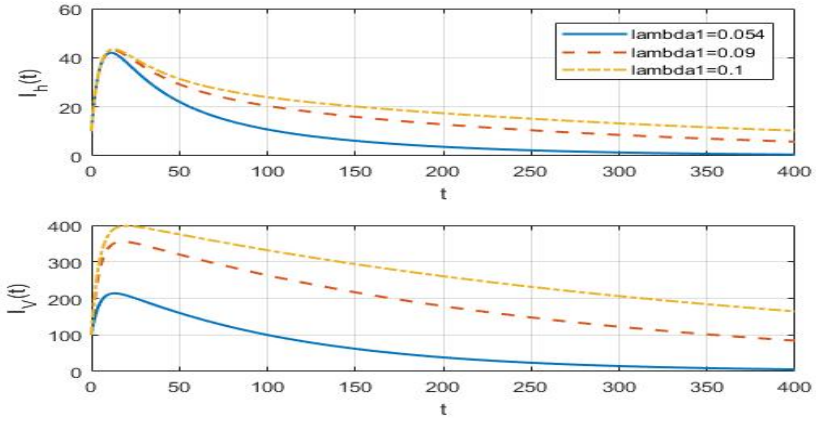

FIGURE 5. Simulation results for different values of λ_1.

Varying the values of α_1, α_2(Rate of contribution to V. cholera in the aquatic and safe environment respectively)

It is clear from Figure 7 that,the impact of increasing the values of α_1 leads to increase the number of infected human and vectors. However, results (Figure 8) show that there is no relationship between α_2 and the fraction of infected humans and vectors.

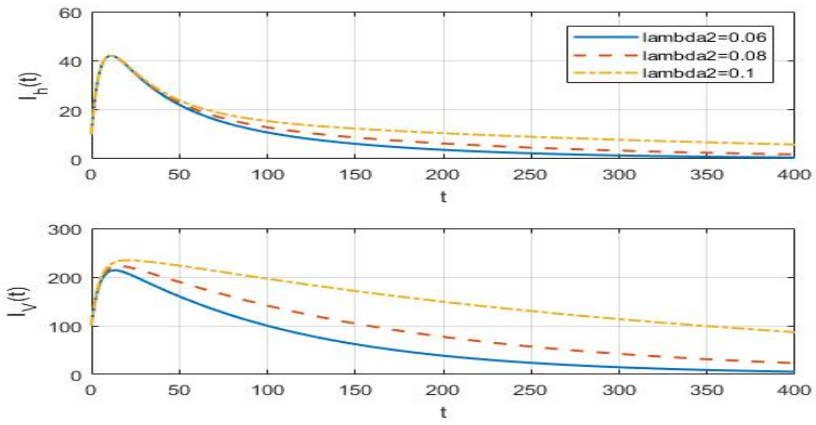

FIGURE 6. Simulation results for different values of λ_2.

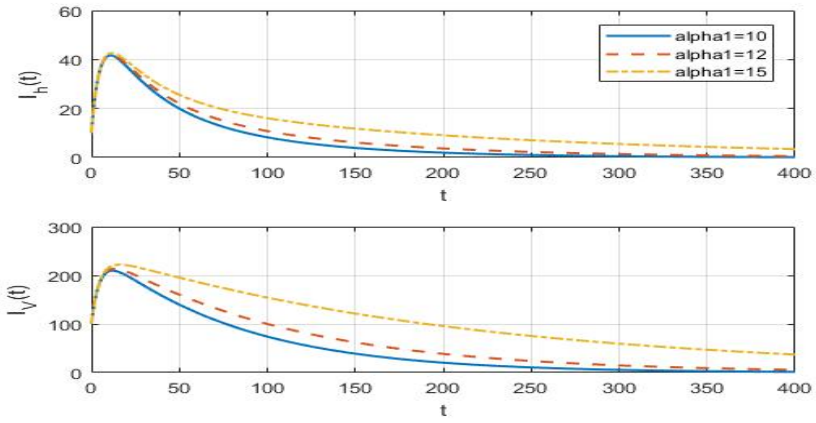

FIGURE 7. Simulation results for different values of α_1.

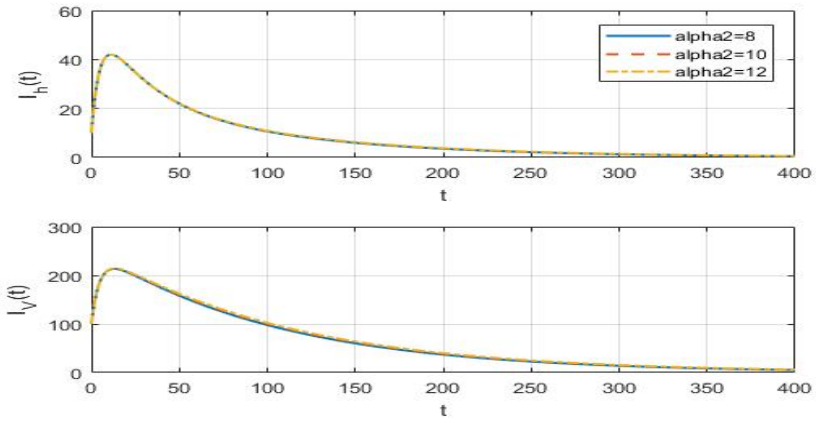

FIGURE 8. Simulation results for different values of α_2.

6. Conclusion

We develop a general model for the dynamics of cholera that incorporates an indirect transmission of V. cholera to yhe environmental reservoir. The proposed model divided the environment into two sub-environments according to the concentration of V. cholera. Our analysis of the model showed that the disease free equilibrium is globally asymptotically stable when R_0 is less than unity; and unstable when R_0 is greater than unity, and our system posses only one endemic equilibrium and we showed that it is locally asymptotically stable when R_0 is greater than unity since the direction of the bifurcation is forward.

Our sensitivity analysis showed that R_0 is sensitive to all of model parameters either positively or negatively, and the most influential has been the ingesting vibrios rate from aquatic environment by vectors, the rate of contribution to V. cholera in the aquatic environment and the death rate of vector and death rate of vibrios in aquatic environment which indicates that the best control strategy is by eliminating vector populations and by sanitizing the aquatic environment. Numerical simulations were used to examine the effect of all of the parameters of the model. The results showed that β_1, λ_1 and α_1 have a positive effects in disease transmission as the increase in their values contribute significantly to the spread of the cholera infections in the system. Also, the simulations showed that the rate of water contamination by infectious people shedding V. cholera into the environment (α_2) has no impact in the infection because it depends on both bacteria shedding of the infected individuals and the level of sanitation in the environment and since the environment is safe, then it is obviously has no effects. In addition, if the contact rate of vectors with contaminated water (λ_2) is high in the presence of increased contribution of each infected vector to the aquatic environment (α_1) then cholera will persist in the population. Therefore, to obtain a significant and effective control, the contribution of each infected vector to the aquatic environment and the rate of exposure to contaminated water must be reduced. Moreover, to reduce the epidemic's peak other interventions are needed.

Conflict of Interests

The author(s) declare that there is no conflict of interests.

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