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COST-EFFECTIVENESS ANALYSIS OF A CHOLERA MODEL WITH AWARENESS PROGRAMS AND LIMITED RESOURCES

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Abstract. In this paper, we developed a mathematical model to describe the dynamics of Cholera with awareness programs under limited resources. The model was fully analysed and the threshold for the eradication of the disease was given. It was proven that the model undergoes a backward bifurcation under certain conditions. The model is then extended to include optimal controls, namely: vaccination of susceptible individuals, killing of vectors, and water sanitation. Numerical simulations for the application of a single control, combinations of two controls and all three controls were given. Cost-effectiveness analysis was carried out in order to determine the most cost-effective control strategies, which was found to be the combination of vaccination and water sanitation.

Keywords: cholera; awareness programs; limited resources; basic reproduction number; stability analysis; optimal control; cost-effectiveness analysis.

2010 AMS Subject Classification: 92B05, 34C23.

1. INTRODUCTION

Cholera is a notable public health problem in many major parts of the world which can kill tens of thousands of individuals [25, 12, 36, 37]. Symptoms include severe acute watery diarrhea. However, it is possible to be a carrier of cholera without exhibiting symptoms since most infected people do not show symptoms for 1-10 days after infection, even though *Vibro.*

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cholerae is present in their faeces and they can shed back into the environment and infect other people. On the other hand, among people who develop symptoms, the major have mild or moderate symptoms, while rare cases develop acute watery diarrhea with severe dehydration. Cholera is acquired through direct or indirect transmission either through physical contact with an infected host or contact with a contaminated environment [9, 4, 38, 6]. Also, Cholera can be obtained by vector transmission when a living organism carries an infectious agent on its body (mechanical) or as an infection host itself (biological), to a new host [30, 28, 2]. Despite recent progress in the provision of clean water and good sewage systems especially in developed countries, cholera is still endemic in many developing countries and remains a considerable public health problem with approximately 1.3 to 4.0 million cases, and 21 000 to 143 000 cholera-related deaths annually worldwide[24].

Several mathematical models have been published in order to describe the dynamics of Cholera [9, 4, 38, 6, 25, 12, 30, 28, 2]. The first mathematical model was published in 1927 by Kermack and McKendrick [35]. The model includes three compartmental classes for susceptible state S, infected people I and recovered individuals R. Capasso [33] proposed a model which was introduced in 1973 to describe the Cholera epidemics in Italy. Then Codeco [4] in 2001 extend Capasso's model and explicitly accounted for the Vibro Cholerae concentration in the water supply which represents the environmental component into a basic SIR model and he modeled the incidence by a logistic function to represent the saturation effect. Hartley et al. in 2006 extended Codeco's model by adding a hyperinfectious state of the pathogen, representing the "explosive" infectivity of freshly shed Vibro Cholerae, based on the laboratory observations [7]. Codeco's model also modified by Joh et al. in 2009 [14] by assuming that there is an explicit incorporation of a minimum infectious dose of pathogen to cause infection. Mukandavire et al. [38] proposed a model to study the 2008-2009 Cholera outbreak in Zimbabwe in which they explicitly considered both human-to-human and environment-to-human transmission pathways. Tien et.al. in 2010 [17] published a SIWR model which also included the water state pathogen concentration in water reservoir. Their model included the dual transmission pathways, with bilinear incidence rates employed for both the environment-to-human and human-to-human infection transmission. Moreover, Neilan et. al. [29] modified the Cholera

model proposed by Hartley [7] and added three control measures into the model. Misra et. al. in 2012 citemisra2012modeling proposed a delay mathematical model for the control of cholera epidemic by assuming that the disease spreads through carriers, which makes the human food contaminated by transporting bacteria from the environment. Recently, Al-Shanfari et.al. [30] proposed a mathematical model that describes the dynamics of Cholera by investigating the role of houseflies in the transmission of Cholera which carry Vibro Cholerae on its body and transfer it from unsafe environment to safe environment. These models differ from each other in some aspects, however, the recovery rate is assumed to be a constant in most of these models.

Farai et.al. in 2019 studied the transmission dynamics of cholera in the presence of limited resources by including a nonlinear recovery rate [10]. In real application, recovery rate depends on many factors. The first factor is the number of infectious individuals seeking treatment. Recovery rate also depends on the availability of health resources to the public which are considered very sufficient for the infectious disease [1, 10, 16, 5]. The resources of the health system includes the number of health care workers (physicians, nurses, pharmacists, etc.), number of hospital beds and medicines and the effectiveness and efficiency of the treatment. In many developing countries, resources of treatment are very limited. So assuming constant recovery rate cannot reflect the real cure rate and the nonlinear recovery rate is normally developed to account for the role of the availability of medical resources.

The awareness programs play an important role in the transmission of the infectious disease. Obviously, awareness can reduce the opportunity and probability of contact transmission among the alerted susceptible populations, which in turn helps to control and prevent the disease from further spreading. In recent time, information about the outbreaks is spreading quickly because of the significant use in social media and the increase the travel around the world. Awareness can have a reflective effect on the actual epidemic dynamics. It can have a positive influence on the disease spread [27, 14, 22, 26, 32]. For instance, in Mexico (2009) the media coverage of transmissibility and mortality rate associated with the virus of swine influenza strongly influenced by behavioral changes and hence it helped to control the epidemic [14]. Also, awareness can lead to negative consequences such as in Romania (2007-2012) although the implementation of two HPV vaccination programs was started, the uptake of vaccination remained low and

the programs were failed because the information about the side effects and insufficient testing of the vaccine was negatively spread [26].

In this study, in order to understand the impact of awareness programs on the spread and control of cholera, a mathematical model will be proposed to capture the dynamics of the effect of awareness programs. The awareness about the disease will alert the aware individuals so that they isolate themselves, reducing the contact with the infected and avoid unsafe environments. Hence, the probability of contracting infection for individuals in aware class is less than those who are in unaware class.

The rest of this paper is organised as follows; in section 2 we present the model formulation and analysis, in section 3 we move on to present the numerical simulations and bifurcation analysis of the model, in section 4 we study the optimal control analysis and cost-effectiveness, and finally, in section 5 we draw the conclusion of our studies.

2. Model Formulation

We use the model in [30] and divide human population into five compartments: aware susceptible $S_{hu}(t)$, uaware susceptible $S_{ha}(t)$, aware infectious $I_{hu}(t)$, unaware infectious $I_{ha}(t)$, and recovered $R_h(t)$. The vector population is divided into two compartments: susceptible $S_v(t)$, infectious $I_v(t)$. Furthermore, we consider two compartments $B(t)$ and $E(t)$ that reflects the bacterial concentration at time t in safe and unsafe environments respectively. It is assumed that the disease spreads due to the direct contact between susceptible and infective and by indirect transmission either by vectors or by ingesting environmental vibrios from unsafe environment. Also, it is considered that due to the awareness, aware susceptible individuals avoid being in contact with the unsafe environment.

Also, we incorporate aspects of limited resources in the model by assuming that the recovery rate (γ) depends on both the number of infectious individuals (I_h) and the hospital bed-population ratio ($b > 0$) such that, it is a function of both b and I_h. The recovery rate $\gamma(b, I_h)$ is thus given as follows:

$$\gamma(b, I_h) = \gamma_0 + (\gamma_1 + \gamma_0)\frac{b}{I_h + b} \tag{2.1}$$

where γ_1 is the maximum per capita recovery rate due to the sufficient health care resource and few infectious individuals as well as the inherent property of a specific disease, γ_0 is the minimum per capita

recovery rate due to the function of basic clinical resources [5]. These assumptions are translated into the following mathematical model:

$$
\begin{aligned}
\frac{dS_{hu}}{dt} &= \mu_h N_h - \frac{\beta S_{hu}(I_{hu}+I_{ha})}{N_h} - \frac{\beta_1 S_{hu}\hat{B}}{\kappa_1+\hat{B}} - \frac{\beta_2 S_{hu}\hat{E}}{\kappa_2+\hat{E}} - (\mu_h+\delta)S_{hu} \\
\frac{dS_{ha}}{dt} &= \delta S_{hu} - \frac{\varepsilon_1\beta S_{ha}(I_{hu}+I_{ha})}{N_h} - \frac{\varepsilon_2\beta_1 S_{ha}\hat{B}}{\kappa_1+\hat{B}} - \mu_h S_{ha} \\
\frac{dI_{hu}}{dt} &= \frac{\beta S_{hu}(I_{hu}+I_{ha})}{N_h} + \frac{\beta_1 S_{hu}\hat{B}}{\kappa_1+\hat{B}} + \frac{\beta_2 S_{hu}\hat{E}}{\kappa_2+\hat{E}} - (\mu_h+\gamma_0+(\gamma_1+\gamma_0)\frac{\hat{b}}{I_{hu}+\hat{b}})I_{hu} \\
\frac{dI_{ha}}{dt} &= \frac{\varepsilon_1\beta S_{ha}(I_{hu}+I_{ha})}{N_h} + \frac{\varepsilon_2\beta_1 S_{ha}\hat{B}}{\kappa_1+\hat{B}} - (\mu_h+\gamma_0+(\gamma_1+\gamma_0)\frac{\hat{b}}{I_{ha}+\hat{b}})I_{ha} \\
\frac{dR_h}{dt} &= (\gamma_0+(\gamma_1+\gamma_0)\frac{\hat{b}}{I_{hu}+\hat{b}})dI_{hu} + (\gamma_0+(\gamma_1+\gamma_0)\frac{\hat{b}}{I_{ha}+\hat{b}})I_{ha} - \mu_h R_h \\
\frac{dS_v}{dt} &= \mu_v N_v - \frac{\lambda_1 S_v\hat{B}}{\kappa_1+\hat{B}} - \frac{\lambda_2 S_v\hat{E}}{\kappa_2+\hat{E}} - \mu_v S_v \\
\frac{dI_v}{dt} &= \frac{\lambda_1 S_v\hat{B}}{\kappa_1+\hat{B}} + \frac{\lambda_2 S_v\hat{E}}{\kappa_2+\hat{E}} - \mu_v I_v \\
\frac{d\hat{B}}{dt} &= \varepsilon\alpha_1 I_v - \mu_b\hat{B} \\
\frac{d\hat{E}}{dt} &= \alpha_1 I_v + \alpha_2 I_{hu} - \mu_e\hat{E}
\end{aligned}
\tag{2.2}
$$

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
β_2	Rates of ingesting vibrios from the unsafe environment to human
γ_0	Minimum per capita recovery rate
γ_1	Maximum per capita recovery rate
b	Hospital bed-population ratio
λ_1	Rates of ingesting vibrios from the safe environment to vectors
λ_2	Rates of ingesting vibrios from the aquatic environment to vector
μ_v	Death rate of vector
μ_b	Death rate of vibrios in safe environment
μ_e	Death rate of vibrios in aquatic (unsafe) environment
ε, ε_1, ε_2	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 unsafe environment by human

TABLE 1. Cholera model parameters

3. ANALYSIS OF THE MODEL

3.1. Non-dimensionalization of the model. Our system of equations has different dimensions with respect to the human population, vector population and V. cholerae. To make system (2.2) dimensionless, the following substitutions are made: $S_h = s_h N_h$, $I_h = i_h N_h$, $R_h = r_h N_h$, $S_v = s_v N_v$, $I_v = i_v N_v$, $\hat{B} = BN_h$, $\hat{E} = EN_h$ and $\hat{b} = bN_h$ with $s_h + i_h + r_h = 1$ and $s_v + i_v = 1$. The new system becomes:

$$
\begin{aligned}
\frac{ds_{hu}}{dt} &= \mu_h - \beta s_{hu}(i_{hu}+i_{ha}) - \frac{\beta_1 s_{hu} B}{\kappa_1 + B} - \frac{\beta_2 s_{hu} E}{\kappa_2 + E} - (\mu_h + \delta) s_{hu} \\
\frac{ds_{ha}}{dt} &= \delta s_{hu} - \varepsilon_1 \beta s_{ha}(i_{hu}+i_{ha}) - \frac{\varepsilon_2 \beta_1 s_{ha} B}{\kappa_1 + B} - \mu_h s_{ha} \\
\frac{di_{hu}}{dt} &= \beta s_{hu}(i_{hu}+i_{ha}) + \frac{\beta_1 s_{hu} B}{\hat{\kappa_1} + B} + \frac{\beta_2 s_{hu} E}{\kappa_2 + E} - (\gamma_0 + (\gamma_1 + \gamma_0)\frac{b}{i_{hu}+b}) i_{hu} - \mu_h i_{hu} \\
\frac{di_{ha}}{dt} &= \varepsilon_1 \beta s_{ha}(i_{hu}+i_{ha}) + \frac{\varepsilon_2 \beta_1 s_{ha} B}{\kappa_1 + B} - (\gamma_0 + (\gamma_1 + \gamma_0)\frac{b}{i_{ha}+b}) i_{ha} - \mu_h i_{ha} \\
\frac{dr_h}{dt} &= (\gamma_0 + (\gamma_1 + \gamma_0)\frac{b}{i_{hu}+b}) i_{hu} + (\gamma_0 + (\gamma_1 + \gamma_0)\frac{b}{i_{ha}+b}) i_{ha} - \mu_h r_h \\
\frac{ds_v}{dt} &= \mu_v - \frac{\lambda_1 s_v B}{\kappa_1 + B} - \frac{\lambda_2 s_v E}{\kappa_2 + E} - \mu_v s_v \\
\frac{di_v}{dt} &= \frac{\lambda_1 s_v B}{\kappa_1 + B} + \frac{\lambda_2 s_v E}{\kappa_2 + E} - \mu_v i_v \\
\frac{dB}{dt} &= \varepsilon \alpha_0 i_v - \mu_b B \\
\frac{dE}{dt} &= \alpha_0 i_v + \alpha_2 i_{hu} - \mu_e E
\end{aligned}
\tag{3.1}
$$

where $\alpha_0 = \frac{\alpha_1 N_v}{N_h}$. Equation of r_h is not needed in the model analysis since $r_h = 1 - s_{hu} - s_{ha} - i_{hu} - i_{ha}$.

The feasible region for model (3.1) is $\Gamma = \Gamma_h \times \Gamma_v \subset \Re_+^7 \times \Re_+^2$, where

$\Gamma_h = \{(s_{hu}, s_{ha}, i_{hu}, i_{ha}, r_h, B, E) \in \Re_+^7 : 0 < s_{hu} + s_{ha} + i_{hu} + i_{ha} + r_h \leq 1\}$,

and $\Gamma_v = \{(s_v, i_v) \in \Re_+^2 : 0 < s_v + i_v \leq 1\}$.

The set Γ is compact. To show that Γ is positively invariant set, i.e., all the variables of model (3.1) stay non-negative if it starts with non-negative initial data, we rewrite model (3.1) as $x_i = F_i(x)$ with $i = 1...9$, then it is obvious that $F_i(x) \geq 0$ and hence Γ is positively invariant set. We assume that all parameters are positive and the initial conditions of system (2.2) are given

by: $s_{hu}(0) = s_{hu0} > 0, s_{ha}(0) = s_{ha0} > 0, i_{hu}(0) = i_{hu0} > 0 \geq 0, i_{ha}(0) = i_{ha0} > 0 \geq 0, r_h(0) = r_{h_0} \geq 0, s_v(0) = s_{v_0} \geq 0, i_v(0) = i_{v_0} \geq 0, B(0) = B_0 \geq 0, E(0) = E_0 \geq 0$

The C^1 smoothness of the right side of system (3.1) implies the local existence and uniqueness of the solution with the initial values in $\Re^{9+}$.

3.2. Equilibria and the basic reproduction number. Obviously, model (3.1) admits a unique disease-free equilibrium DFE ξ^0. A positive equilibrium of (3.1) in the interior of Γ, if one exists, is called an endemic equilibrium EE, and denoted by $\xi^* = (s^*_{hu}, s^*_{ha}, i^*_{hu}, i^*_{ha}, i^*_h, B^*, E^*)$. Here $s^*_{hu}, s^*_{ha}, i^*_{hu}, i^*_{ha}, i^*_h, B^*, E^* > 0$.

Finding Disease-Free Equilibrium Point (DFE):

The disease-free equilibrium (DFE) of model (3.1)is:

$$\xi^0 = (\frac{\mu_h}{\mu_h + \delta}, \frac{\delta}{\mu_h + \delta}, 0, 0, 1, 0, 0, 0) \tag{3.2}$$

The basic reproduction number, R_0, is a threshold parameter that allows us to predict whether the disease will die out or persist. Here, we used the constant term of characteristic equation method to find R_0 since the next generation matrix failed to find its value.

The Jacobian matrix at the DFE is given by:

$$J(\xi^0) = \begin{bmatrix} -\Pi_1 & 0 & -\Pi_2 & -\Pi_2 & 0 & 0 & -\Pi_3 & -\Pi_4 \\ \delta & -\mu_h & -\Pi_5 & -\Pi_5 & 0 & 0 & -\Pi_6 & 0 \\ 0 & 0 & \Pi_2 - \Pi_7 & \Pi_2 & 0 & 0 & \Pi_3 & \Pi_4 \\ 0 & 0 & \Pi_5 & \Pi_5 - \Pi_7 & 0 & 0 & \Pi_6 & 0 \\ 0 & 0 & 0 & 0 & -\mu_v & 0 & -\Pi_8 & -\Pi_9 \\ 0 & 0 & 0 & 0 & 0 & -\mu_v & \Pi_8 & \Pi_9 \\ 0 & 0 & 0 & 0 & 0 & \varepsilon\alpha_0 & -\mu_b & 0 \\ 0 & 0 & \alpha_2 & 0 & 0 & \alpha_0 & 0 & -\mu_e \end{bmatrix}$$

with $\Pi_1 = \mu_h + \delta, \Pi_2 = \frac{\beta\mu_h}{\mu_h+\delta}, \Pi_3 = \frac{\beta_1\mu_h}{(\mu_h+\delta)\kappa_1}, \Pi_4 = \frac{\beta_2\mu_h}{(\mu_h+\delta)\kappa_2}, \Pi_5 = \frac{\varepsilon_1\beta\delta}{\mu_h+\delta}, \Pi_6 = \frac{\varepsilon_2\beta_1\delta}{(\mu_h+\delta)\kappa_1}$, $\Pi_7 = \mu_h + \gamma_1, \Pi_8 = \frac{\lambda_1}{\kappa_1}, \Pi_9 = \frac{\lambda_2}{\kappa_2}$.

The characteristic equation of model (3.1) around the DFE is given by

$$(\lambda+\mu_v)(\lambda+\mu_h)(\lambda+\delta+\mu_h)(\lambda^5+c_4\lambda^4+c_3\lambda^3+c_2\lambda^2+c_1\lambda+c_0)=0$$

where, c_0 is given by:

$$\begin{aligned} c_0 &= (\Pi_7{}^2\mu_b\mu_e\mu_v+((\Pi_9(\Pi_2+\Pi_5)\mu_b+\varepsilon(\Pi_3\Pi_9\alpha_2+\Pi_8(\Pi_2+\Pi_5)\mu_e))\alpha_0+\mu_b\mu_v\alpha_2\Pi_4)\Pi_7 \\ &\quad +\varepsilon\Pi_4\Pi_5\Pi_8\alpha_0\alpha_2)(1-R_0) \end{aligned}$$

and R_0 is given by:

(3.3)
$$R_0=\frac{\alpha_0(\varepsilon\Pi_8\mu_e+\Pi_9\mu_b)\Pi_7{}^2+(\varepsilon\alpha_0\alpha_2\Pi_3\Pi_9+\mu_b\mu_v(\Pi_4\alpha_2+\mu_e(\Pi_2+\Pi_5)))\Pi_7+\varepsilon\alpha_0\alpha_2(\Pi_2\Pi_6\Pi_9+\Pi_4\Pi_5\Pi_8)}{\Pi_7{}^2\mu_b\mu_e\mu_v+(\Pi_9(\Pi_2+\Pi_5)\mu_b+\varepsilon(\Pi_4\alpha_2+\mu_e(\Pi_2+\Pi_5))\Pi_8)\alpha_0\Pi_7+\alpha_2\Pi_5(\varepsilon\Pi_3\Pi_9\alpha_0+\Pi_4\mu_b\mu_v)}$$

The disease-free equilibrium (3.2) is locally asymptotically stable if and only if all roots of the characteristic equation (3.2) has negative real parts which holds if and only if $c_0>0$ [15]. Obviously $c_0>0$ iff $R_0<1$.

3.3. Existence of EE. The literature showed that the study of global stability of cholera disease is difficult to be addressed because of the incorporation of the environmental components [18]. Thus, the question is whether the cholera disease will reach the equilibrium in long-term dynamics. The EE of (3.1) satisfy:

(3.4)
$$\begin{aligned} s_{hu} &= \frac{\mu_h(\alpha_0 i_v+\kappa_1\mu_b)(\alpha_0 i_v+\alpha_2 i_{hu}+\mu_e\kappa_2)}{D_2 i_{hu}{}^2+D_1 i_{hu}-D_0} \\ s_{ha} &= \frac{\delta s_{hu}(\kappa_1+B)}{B\beta\varepsilon_1 i_{ha}+B\beta\varepsilon_1 i_{hu}+\beta\varepsilon_1 i_{ha}\kappa_1+\beta\varepsilon_1 i_{hu}\kappa_1+\varepsilon_2\beta_1 B+\mu_h B+\mu_h\kappa_1} \\ s_v &= 1-i_v \\ B &= \frac{\alpha_0 i_v}{\mu_b} \\ E &= \frac{\alpha_0 i_v+\alpha_2 i_{hu}}{\mu_e} \end{aligned}$$

where

$$
\begin{aligned}
D_2 &= \beta\,\alpha_2 i_v \alpha_0 + \mu_b \beta\,\alpha_2 \kappa_1 \\
D_1 &= \left(i_v\left(\beta\, i_{ha} + \delta + \beta_1 + \beta_2 + \mu_h\right)\alpha_0 + \mu_b\left(\beta\, i_{ha} + \delta + \beta_2 + \mu_h\right)\kappa_1\right)\alpha_2 + \beta\,\left(\alpha_0 i_v + \mu_e \kappa_2\right)\left(\alpha_0 i_v + \kappa_1 \mu_b\right) \\
D_0 &= {i_v}^2\left(\beta\, i_{ha} + \delta + \beta_1 + \beta_2 + \mu_h\right)\alpha_0{}^2 + \left(\mu_b\left(\beta\, i_{ha} + \delta + \beta_2 + \mu_h\right)\kappa_1 + \kappa_2 \mu_e\left(\beta\, i_{ha} + \delta + \beta_1 + \mu_h\right)\right) i_v \alpha_0 \\
&\quad + \kappa_1 \kappa_2 \mu_b \mu_e\left(\beta\, i_{ha} + \delta + \mu_h\right)
\end{aligned}
$$

and

$$A_4 i_{hu}^4 + A_3 i_{hu}^3 + A_2 i_{hu}^2 + A_1 i_{hu} + A_0 = 0 \tag{3.5}$$

where

$$
\begin{aligned}
A_4 &= \alpha_2\beta\,\left(\alpha_0 i_v + \kappa_1 \mu_b\right)\left(\gamma_0 + \mu_h\right) \\
A_3 &= (i_v({\mu_h}^2 + ((b + i_{ha} - 1)\beta + \beta_1 + \beta_2 + \delta + \gamma_0)\mu_h + (b\gamma_1 + \gamma_0\, i_{ha})\beta + \gamma_0\,(\beta_1 + \beta_2 + \delta))\alpha_0 + \kappa_1({\mu_h}^2 \\
&\quad + ((b + i_{ha} - 1)\beta + \beta_2 + \delta + \gamma_0)\mu_h + (b\gamma_1 + \gamma_0\, i_{ha})\beta + \gamma_0\,(\beta_2 + \delta))\mu_b)\alpha_2 + \beta\,(\alpha_0 i_v + \mu_e \kappa_2) \\
&\quad (\alpha_0 i_v + \kappa_1 \mu_b)(\gamma_0 + \mu_h) \\
A_2 &= {\alpha_0}^2 {i_v}^2(((b + i_{ha} - 1)\mu_h + b\gamma_1 + \gamma_0\, i_{ha})\beta + (\gamma_0 + \mu_h)(\beta_1 + \beta_2 + \delta + \mu_h)) + i_v \alpha_0(((\alpha_2(\gamma_1 + \mu_h) i_{ha} \\
&\quad + (\kappa_1 \mu_b + \mu_e \kappa_2)\gamma_1 + \mu_h(\kappa_1 \mu_b + \mu_e \kappa_2 - \alpha_2))b + ((\kappa_1 \mu_b + \mu_e \kappa_2)\gamma_0 + \mu_h(\kappa_{1n} \mu_b + \mu_e \kappa_2 - \alpha_2)) \\
&\quad i_{ha} - \mu_h(\kappa_1 \mu_b + \mu_e \kappa_2))\beta + \alpha_2(\gamma_1 + \mu_h)(\beta_1 + \beta_2 + \delta + \mu_h)b + (\kappa_1 \mu_b + \mu_e \kappa_2)(\gamma_0 + \mu_h)\delta \\
&\quad + (\kappa_2 \gamma_0\, \mu_e + \mu_h(\mu_e \kappa_2 - \alpha_2))\beta_1 + (\gamma_0\, \mu_b \kappa_1 + \mu_h(\kappa_1 \mu_b - \alpha_2))\beta_2 + \mu_h(\kappa_1 \mu_b + \mu_e \kappa_2)(\gamma_0 + \mu_h)) \\
&\quad + \mu_b \kappa_1(((\alpha_2(\gamma_1 + \mu_h) i_{ha} - \mu_h \alpha_2 + \mu_e \kappa_2(\gamma_1 + \mu_h))b + (-\mu_h \alpha_2 + \mu_e \kappa_2(\gamma_0 + \mu_h)) i_{ha} - \mu_e \mu_h \kappa_2)\beta + \alpha_2 \\
&\quad (\gamma_1 + \mu_h)(\beta_2 + \delta + \mu_h)b + \mu_e \kappa_2(\gamma_0 + \mu_h)\delta + \mu_h(-\beta_2 \alpha_2 + \mu_e \kappa_2(\gamma_0 + \mu_h \\
A_1 &= ({i_v}^2({\mu_h}^2 + ((i_{ha} - 1)\beta + \beta_1 + \beta_2 + \delta + \gamma_1)\mu_h + \gamma_1\,(\beta\, i_{ha} + \delta + \beta_1 + \beta_2))\alpha_0{}^2 - i_v((-\kappa_1 \mu_b - \mu_e \kappa_2){\mu_h}^2 \\
&\quad + (-((i_{ha} - 1)\beta + \beta_2 + \delta + \gamma_1)\mu_b \kappa_1 - \mu_e((i_{ha} - 1)\beta + \beta_1 + \delta + \gamma_1)\kappa_2 + \alpha_2(\beta\, i_{ha} + \beta_1 + \beta_2))\mu_h \\
&\quad - (\kappa_1(\beta\, i_{ha} + \delta + \beta_2)\mu_b + \mu_e \kappa_2(\beta\, i_{ha} + \delta + \beta_1))\gamma_1)\alpha_0 - \kappa_1(-\kappa_2 \mu_e {\mu_h}^2 - \mu_e((\gamma_1\, i_{ha} + i_{ha} - 1) \\
&\quad \beta + (\delta + 1)\gamma_1 + \delta)\kappa_2 + \alpha_2(\beta\, i_{ha} + \beta_2))\mu_b)b - {i_v}^2 \mu_h(\beta\, i_{ha} + \beta_1 + \beta_2)\alpha_0{}^2 - (\mu_b(\beta\, i_{ha} + \beta_2)\kappa_1 + \kappa_2 \mu_e \\
&\quad (\beta\, i_{ha} + \beta_1))i_v \mu_h \alpha_0 - \beta\, i_{ha} \kappa_1 \kappa_2 \mu_b \mu_e \\
A_0 &= -\left({i_v}^2\left(\beta\, i_{ha} + \beta_1 + \beta_2\right)\alpha_0{}^2 + i_v\left(\beta\,\left(\kappa_1 \mu_b + \mu_e \kappa_2\right) i_{ha} + \beta_2 \kappa_1 \mu_b + \kappa_2 \mu_e \beta_1\right)\alpha_0 + \beta\, i_{ha} \kappa_1 \kappa_2 \mu_b \mu_e\right) b \mu_h
\end{aligned}
$$

$$B_4 i_{ha}^4 + B_3 i_{ha}^3 + B_2 i_{ha}^2 + B_1 i_{ha} + B_0 = 0 \tag{3.6}$$

$$\begin{aligned}
B_4 &= \varepsilon_1 \beta^2 (\alpha_0 i_v + \kappa_1 \mu_b)^2 (\gamma_0 + \mu_h)(\alpha_0 i_v + \alpha_2 i_{hu} + \mu_e \kappa_2) \\
B_3 &= (\alpha_0 i_v + \kappa_1 \mu_b)\beta((i_v{}^2(\mu_h{}^2 + (b\beta + 2\beta i_{hu} + \delta + \gamma_0 + \beta_1 + \beta_2)\mu_h + 2\beta\gamma_0 i_{hu} + \gamma_0(\beta_1 + \beta_2 + \delta) \\
&\quad + b\beta\gamma_1)\alpha_0{}^2 + i_v((\alpha_2 i_{hu} + \kappa_1\mu_b + \mu_e\kappa_2)\mu_h{}^2 + (2\beta\alpha_2 i_{hu}{}^2 + (2\beta\mu_b\kappa_1 + \alpha_2\gamma_0 + (b\beta + \delta + \beta_1 + \beta_2)\alpha_2 \\
&\quad + 2\beta\kappa_2\mu_e)i_{hu} + \mu_b(b\beta + \delta + \gamma_0 + \beta_2)\kappa_1 + \kappa_2\mu_e(b\beta + \delta + \gamma_0 + \beta_1))\mu_h + 2\alpha_2\beta\gamma_0 i_{hu}{}^2 + (2\kappa_1\beta\gamma_0\mu_b \\
&\quad + ((\beta_1 + \beta_2 + \delta)\alpha_2 + 2\beta\kappa_2\mu_e)\gamma_0 + b\alpha_2\beta\gamma_1)i_{hu} + \mu_b(\gamma_0(\beta_2 + \delta) + b\beta\gamma_1)\kappa_1 + ((\beta_1 + \delta)\gamma_0 + b\beta\gamma_1) \\
&\quad \kappa_2\mu_e)\alpha_0 + \kappa_1\mu_b((\alpha_2 i_{hu} + \mu_e\kappa_2)\mu_h{}^2 + (2\beta\alpha_2 i_{hu}{}^2 + (\alpha_2\gamma_0 + (b\beta + \delta + \beta_2)\alpha_2 + 2\beta\kappa_2\mu_e)i_{hu} \\
&\quad + \kappa_2\mu_e(b\beta + \delta + \gamma_0))\mu_h + 2\alpha_2\beta\gamma_0 i_{hu}{}^2 + ((\alpha_2(\beta_2 + \delta) + 2\beta\kappa_2\mu_e)\gamma_0 + b\alpha_2\beta\gamma_1)i_{hu} + \kappa_2\mu_e(b\beta\gamma_1 + \delta \\
&\quad \gamma_0)))\varepsilon_1 + (i_v(\beta_1\varepsilon_2 + \mu_h)\alpha_0 + \kappa_1\mu_b\mu_h)(\gamma_0 + \mu_h)(\alpha_0 i_v + \alpha_2 i_{hu} + \mu_e\kappa_2)) \\
B_2 &= (\mu_h{}^3 + ((\varepsilon_1 + 1)(b + i_{hu})\beta + (\varepsilon_2 + 1)\beta_1 + \beta_2 + \delta + \gamma_0)\mu_h{}^2 + (2(b + 1/2\, i_{hu})\varepsilon_1 i_{hu}\beta^2 + (((\beta_1 \\
&\quad + \beta_2 + \delta + \gamma_0)\varepsilon_1 + \beta_1\varepsilon_2 + \gamma_0)i_{hu} + ((\beta_1 + \beta_2 + \delta + \gamma_1)b - \delta)\varepsilon_1 + b(\beta_1\varepsilon_2 + \gamma_1))\beta + ((\varepsilon_2 + 1)\beta_1 + \beta_2 \\
&\quad + \delta)\gamma_0 + \beta_1\varepsilon_2(\beta_1 + \beta_2 + \delta))\mu_h + 2(b\gamma_1 + 1/2\,\gamma_0 i_{hu})\varepsilon_1 i_{hu}\beta^2 + ((\beta_1 + \beta_2 + \delta)\varepsilon_1 + \beta_1\varepsilon_2)(b\gamma_1 + \gamma_0 i_{hu})\beta \\
&\quad + \beta_1\varepsilon_2\gamma_0(\beta_1 + \beta_2 + \delta))i_v{}^3\alpha_0{}^3 + ((\alpha_2 i_{hu} + 2\kappa_1\mu_b + \mu_e\kappa_2)\mu_h{}^3 + ((\varepsilon_1 + 1)(\alpha_2 i_{hu} + 2\kappa_1\mu_b + \mu_e\kappa_2) \\
&\quad (b + i_{hu})\beta + ((\varepsilon_2 + 1)\beta_1 + 2\beta_2 + 2\delta + 2\gamma_0)\kappa_1\mu_b + ((\varepsilon_2 + 1)\beta_1 + \beta_2 + \delta + \gamma_0)\alpha_2 i_{hu} + \kappa_2((\varepsilon_2 + 1)\beta_1 + \\
&\quad \delta + \gamma_0)\mu_e)\mu_h{}^2 + (2(b + 1/2\, i_{hu})(\alpha_2 i_{hu} + 2\kappa_1\mu_b + \mu_e\kappa_2)\varepsilon_1 i_{hu}\beta^2 + (\alpha_2((\beta_1 + \beta_2 + \delta + \gamma_0)\varepsilon_1 + \beta_1\varepsilon_2 \\
&\quad + \gamma_0)i_{hu}{}^2 + (((\beta_1 + 2\beta_2 + 2\delta + 2\gamma_0)\varepsilon_1 + \beta_1\varepsilon_2 + 2\gamma_0)\kappa_1\mu_b + (((\beta_1 + \beta_2 + \delta + \gamma_1)b - \delta)\alpha_2 + \mu_e\kappa_2 \\
&\quad (\beta_1 + \delta + \gamma_0))\varepsilon_1 + \alpha_2(\beta_1\varepsilon_2 + \gamma_1)b + \mu_e\kappa_2(\beta_1\varepsilon_2 + \gamma_0))i_{hu} + (((\beta_1 + 2\beta_2 + 2\delta + 2\gamma_1)b - 2\delta)\varepsilon_1 \\
&\quad + b(\beta_1\varepsilon_2 + 2\gamma_1))\kappa_1\mu_b + \kappa_2(((\beta_1 + \delta + \gamma_1)b - \delta)\varepsilon_1 + b(\beta_1\varepsilon_2 + \gamma_1))\mu_e)\beta + \alpha_2(((\varepsilon_2 + 1)\beta_1 + \beta_2 + \delta)\gamma_0 \\
&\quad + \beta_1\varepsilon_2(\beta_1 + \beta_2 + \delta))i_{hu} + (((\varepsilon_2 + 1)\beta_1 + 2\beta_2 + 2\delta)\gamma_0 + \beta_1\varepsilon_2(\beta_2 + \delta))\mu_b\kappa_1 + \kappa_2\mu_e(((\varepsilon_2 + 1)\beta_1 + \delta)\gamma_0 \\
&\quad + \beta_1\varepsilon_2(\beta_1 + \delta)))\mu_h + 2(b\gamma_1 + 1/2\,\gamma_0 i_{hu})(\alpha_2 i_{hu} + 2\kappa_1\mu_b + \mu_e\kappa_2)\varepsilon_1 i_{hu}\beta^2 + (((\beta_1 + 2\beta_2 + 2\delta)\varepsilon_1 \\
&\quad + \beta_1\varepsilon_2)\kappa_1\mu_b + \alpha_2((\beta_1 + \beta_2 + \delta)\varepsilon_1 + \beta_1\varepsilon_2)i_{hu} + \kappa_2((\beta_1 + \delta)\varepsilon_1 + \beta_1\varepsilon_2)\mu_e)(b\gamma_1 + \gamma_0 i_{hu})\beta + \gamma_0(\kappa_1(\beta_2 \\
&\quad + \delta)\mu_b + \alpha_2(\beta_1 + \beta_2 + \delta)i_{hu} + \mu_e\kappa_2(\beta_1 + \delta))\beta_1\varepsilon_2)i_v{}^2\alpha_0{}^2 + 2((\mu_e\kappa_2 + \alpha_2 i_{hu} + 1/2\,\kappa_1\mu_b)\mu_h{}^3 + ((\varepsilon_1 + 1) \\
&\quad (\mu_e\kappa_2 + \alpha_2 i_{hu} + 1/2\,\kappa_1\mu_b)(b + i_{hu})\beta + 1/2\,\kappa_1(\beta_2 + \delta + \gamma_0)\mu_b + 1/2((\varepsilon_2 + 1)\beta_1 + 2\beta_2 + 2\delta + 2\gamma_0) \\
&\quad \alpha_2 i_{hu} + 1/2((\varepsilon_2 + 1)\beta_1 + 2\delta + 2\gamma_0)\kappa_2\mu_e)\mu_h{}^2 + (2(b + 1/2\, i_{hu})\varepsilon_1(\mu_e\kappa_2 + \alpha_2 i_{hu} + 1/2\,\kappa_1\mu_b)i_{hu}\beta^2 \\
&\quad + (1/2\,\alpha_2((\beta_1 + 2\beta_2 + 2\delta + 2\gamma_0)\varepsilon_1 + \beta_1\varepsilon_2 + 2\gamma_0)i_{hu}{}^2 + (1/2\,\mu_b((\beta_2 + \delta + \gamma_0)\varepsilon_1 + \gamma_0)\kappa_1 + \\
&\quad (((1/2\,\beta_1 + \beta_2 + \delta + \gamma_1)b - \delta)\alpha_2 + 1/2\,\mu_e\kappa_2(\beta_1 + 2\delta + 2\gamma_0))\varepsilon_1 + 1/2\,\alpha_2(\beta_1\varepsilon_2 + 2\gamma_1)b + 1/2\,\mu_e\kappa_2 \\
&\quad (\beta_1\varepsilon_2 + 2\gamma_0))i_{hu} + 1/2(((\beta_2 + \delta + \gamma_1)b - \delta)\varepsilon_1 + b\gamma_1)\mu_b\kappa_1 + 1/2\,\kappa_2(((\beta_1 + 2\delta + 2\gamma_1)b - 2\delta)\varepsilon_1
\end{aligned}$$

$$+b(\beta_1\varepsilon_2+2\gamma_1))\mu_e)\beta+1/2\,\alpha_2(((\varepsilon_2+1)\beta_1+2\beta_2+2\delta)\gamma_0+\beta_1\varepsilon_2(\beta_2+\delta))i_{hu}+1/2\,\kappa_1\gamma_0(\beta_2+\delta)\mu_b$$
$$+1/2\,(((\varepsilon_2+1)\beta_1+2\delta)\gamma_0+\delta\beta_1\varepsilon_2)\kappa_2\mu_e)\mu_h+2\,(b\gamma_1+1/2\,\gamma_0 i_{hu})\varepsilon_1(\mu_e\kappa_2+\alpha_2 i_{hu}+1/2\,\kappa_1\mu_b)i_{hu}\beta^2$$
$$+1/2\,(\kappa_1\varepsilon_1(\beta_2+\delta)\mu_b+\alpha_2((\beta_1+2\beta_2+2\delta)\varepsilon_1+\beta_1\varepsilon_2)i_{hu}+((\beta_1+2\delta)\varepsilon_1+\beta_1\varepsilon_2)\kappa_2\mu_e)(b\gamma_1+\gamma_0 i_{hu})\beta$$
$$+1/2\,\gamma_0\beta_1\varepsilon_2(\alpha_2(\beta_2+\delta)i_{hu}+\mu_e\kappa_2\delta))\kappa_1\mu_b i_v\alpha_0+((\alpha_2 i_{hu}+\mu_e\kappa_2)\mu_h{}^3+((\varepsilon_1+1)(\alpha_2 i_{hu}+\mu_e\kappa_2)(b+$$
$$i_{hu})\beta+\alpha_2(\beta_2+\delta+\gamma_0)i_{hu}+\mu_e\kappa_2(\delta+\gamma_0))\mu_h{}^2+(2\,(b+1/2\,i_{hu})\varepsilon_1(\alpha_2 i_{hu}+\mu_e\kappa_2)i_{hu}\beta^2$$
$$+(\alpha_2((\beta_2+\delta+\gamma_0)\varepsilon_1+\gamma_0)i_{hu}{}^2+((((\beta_2+\delta+\gamma_1)b-\delta)\alpha_2+\mu_e\kappa_2(\delta+\gamma_0))\varepsilon_1$$
$$+b\alpha_2\gamma_1+\mu_e\kappa_2\gamma_0)i_{hu}+\kappa_2(((\delta+\gamma_1)b-\delta)\varepsilon_1+b\gamma_1)\mu_e)\beta+\gamma_0(\alpha_2(\beta_2+\delta)i_{hu}+\mu_e\kappa_2\delta))\mu_h+(2\,(b\gamma_1$$
$$+1/2\,\gamma_0 i_{hu})(\alpha_2 i_{hu}+\mu_e\kappa_2)i_{hu}\beta+(b\gamma_1+\gamma_0 i_{hu})(\alpha_2(\beta_2+\delta)i_{hu}+\mu_e\kappa_2\delta))\varepsilon_1\beta)\kappa_1{}^2\mu_b{}^2$$

$$\begin{aligned}
B_1 \;=\;& ((\mu_h{}^3+(i_{hu}(\varepsilon_1+1)\beta+(\varepsilon_2+1)\beta_1+\beta_2+\delta+\gamma_1)\mu_h{}^2+(\varepsilon_1 i_{hu}{}^2\beta^2+((\varepsilon_1+1)\gamma_1+(\beta_1+\beta_2+\delta)\\
&\varepsilon_1+\beta_1\varepsilon_2)\beta\, i_{hu}-\varepsilon_1\delta\beta+((\varepsilon_2+1)\beta_1+\beta_2+\delta)\gamma_1+\beta_1\varepsilon_2(\beta_1+\beta_2+\delta))\mu_h+\gamma_1(\beta\,\varepsilon_1 i_{hu}+\beta_1\\
&\varepsilon_2)(\beta\, i_{hu}+\delta+\beta_1+\beta_2))i_v{}^3\alpha_0{}^3+i_v{}^2((\alpha_2 i_{hu}+2\,\kappa_1\mu_b+\mu_e\kappa_2)\mu_h{}^3+(\alpha_2\beta\,(\varepsilon_1+1)i_{hu}{}^2+\\
&(2\,\beta\,\mu_b(\varepsilon_1+1)\kappa_1+\kappa_2\mu_e(\varepsilon_1+1)\beta+((\varepsilon_2+1)\beta_1+\beta_2+\delta+\gamma_1)\alpha_2)i_{hu}+((\varepsilon_2+1)\beta_1+2\beta_2+2\delta+2\gamma_1\\
&)\kappa_1\mu_b+((\varepsilon_2+1)\beta_1+\delta+\gamma_1)\kappa_2\mu_e)\mu_h{}^2+(\varepsilon_1\beta^2 i_{hu}{}^3\alpha_2+(2\,\kappa_1\varepsilon_1\beta\,\mu_b+\kappa_2\varepsilon_1\beta\,\mu_e+((\varepsilon_1+1)\\
&\gamma_1+(\beta_1+\beta_2+\delta)\varepsilon_1+\beta_1\varepsilon_2)\alpha_2)\beta\, i_{hu}{}^2+(\mu_b\beta\,((2\,\varepsilon_1+2)\gamma_1+(\beta_1+2\beta_2+2\delta)\varepsilon_1+\beta_1\varepsilon_2)\kappa_1+\\
&(\kappa_2\mu_e(\varepsilon_1+1)\gamma_1+(-\alpha_2\delta+\mu_e\kappa_2(\beta_1+\delta))\varepsilon_1+\beta_1\varepsilon_2\kappa_2\mu_e)\beta+(((\varepsilon_2+1)\beta_1+\beta_2+\delta)\gamma_1+\beta_1\varepsilon_2\\
&(\beta_1+\beta_2+\delta))\alpha_2)i_{hu}+\mu_b(-2\,\varepsilon_1\delta\beta+((\varepsilon_2+1)\beta_1+2\beta_2+2\delta)\gamma_1+\beta_1\varepsilon_2(\beta_2+\delta))\kappa_1+\kappa_2\mu_e\\
&(-\varepsilon_1\delta\beta+((\varepsilon_2+1)\beta_1+\delta)\gamma_1+\beta_1\varepsilon_2(\beta_1+\delta)))\mu_h+(\varepsilon_1\beta^2 i_{hu}{}^3\alpha_2+(2\,\kappa_1\varepsilon_1\beta\,\mu_b+\kappa_2\\
&\varepsilon_1\beta\,\mu_e+((\beta_1+\beta_2+\delta)\varepsilon_1+\beta_1\varepsilon_2)\alpha_2)\beta\, i_{hu}{}^2+(\mu_b((\beta_1+2\beta_2+2\delta)\varepsilon_1+\beta_1\varepsilon_2)\beta\,\kappa_1+\\
&((\beta_1+\delta)\varepsilon_1+\beta_1\varepsilon_2)\kappa_2\mu_e\beta+\beta_1\alpha_2\varepsilon_2(\beta_1+\beta_2+\delta))i_{hu}+(\kappa_1(\beta_2+\delta)\mu_b+\mu_e\kappa_2(\beta_1+\delta)\\
&)\varepsilon_2\beta_1)\gamma_1)\alpha_0{}^2+\kappa_1((2\,\alpha_2 i_{hu}+\kappa_1\mu_b+2\,\mu_e\kappa_2)\mu_h{}^3+(2\,\alpha_2\beta\,(\varepsilon_1+1)i_{hu}{}^2+(\beta\,\mu_b(\varepsilon_1+1\\
&)\kappa_1+2\,\kappa_2\mu_e(\varepsilon_1+1)\beta+((\varepsilon_2+1)\beta_1+2\beta_2+2\delta+2\gamma_1)\alpha_2)i_{hu}+\kappa_1(\beta_2+\delta+\gamma_1)\mu_b+((\varepsilon_2+1)\beta_1+2\\
&\delta+2\gamma_1)\kappa_2\mu_e)\mu_h{}^2+(2\,\varepsilon_1\beta^2 i_{hu}{}^3\alpha_2+(\kappa_1\varepsilon_1\beta\,\mu_b+2\,\kappa_2\varepsilon_1\beta\,\mu_e+((2\,\varepsilon_1+2)\gamma_1+(\beta_1+2\beta_2+2\delta\\
&)\varepsilon_1+\beta_1\varepsilon_2)\alpha_2)\beta\, i_{hu}{}^2+(\mu_b((\varepsilon_1+1)\gamma_1+\varepsilon_1(\beta_2+\delta))\beta\,\kappa_1+(2\,\kappa_2\mu_e(\varepsilon_1+1)\gamma_1+(-2\\
&\alpha_2\delta+\kappa_2\mu_e(\beta_1+2\delta))\varepsilon_1+\beta_1\varepsilon_2\kappa_2\mu_e)\beta+(((\varepsilon_2+1)\beta_1+2\beta_2+2\delta)\gamma_1+\beta_1\varepsilon_2(\beta_2+\delta))\alpha_2)
\end{aligned}$$

$$
\begin{aligned}
& i_{hu}+\mu_b(-\varepsilon_1\delta\beta+\gamma_1(\beta_2+\delta))\kappa_1+\kappa_2\mu_e(-2\varepsilon_1\delta\beta+((\varepsilon_2+1)\beta_1+2\delta)\gamma_1+\delta\beta_1\varepsilon_2))\mu_h+\\
& (2\varepsilon_1\beta^2{i_{hu}}^3\alpha_2+(\kappa_1\varepsilon_1\beta\mu_b+2\kappa_2\varepsilon_1\beta\mu_e+((\beta_1+2\beta_2+2\delta)\varepsilon_1+\beta_1\varepsilon_2)\alpha_2)\beta{i_{hu}}^2+(\varepsilon_1\beta\mu_b(\beta_2+\delta)\kappa_1+\\
& ((\beta_1+2\delta)\varepsilon_1+\beta_1\varepsilon_2)\kappa_2\mu_e\beta+\beta_1\alpha_2\varepsilon_2(\beta_2+\delta))i_{hu}+\delta\beta_1\varepsilon_2\kappa_2\mu_e)\gamma_1)\\
& \mu_b i_v\alpha_0+{\kappa_1}^2{\mu_b}^2((\alpha_2 i_{hu}+\mu_e\kappa_2)\mu_h{}^3+(\alpha_2\beta(\varepsilon_1+1){i_{hu}}^2+(\kappa_2\mu_e(\varepsilon_1+1)\beta+\alpha_2(\beta_2+\delta+\gamma_1))i_{hu}+\mu_e\\
& \kappa_2(\delta+\gamma_1))\mu_h{}^2+(\varepsilon_1\beta^2{i_{hu}}^3\alpha_2+(\kappa_2\varepsilon_1\beta\mu_e+((\varepsilon_1+1)\gamma_1+\varepsilon_1(\beta_2+\\
& \delta))\alpha_2)\beta{i_{hu}}^2+((\kappa_2\mu_e(\varepsilon_1+1)\gamma_1-\varepsilon_1\delta(-\mu_e\kappa_2+\alpha_2))\beta+\alpha_2\gamma_1(\beta_2+\delta))i_{hu}-\kappa_2\\
& \delta\mu_e(\beta\varepsilon_1-\gamma_1))\mu_h+\varepsilon_1(\beta{i_{hu}}^2\alpha_2+(\kappa_2\beta\mu_e+\alpha_2(\beta_2+\delta))i_{hu}+\mu_e\kappa_2\delta)\gamma_1 i_{hu}\beta))b-\mu_h\delta(\alpha_0 i_v+\alpha_2 i_{hu}\\
& +\mu_e\kappa_2)(\alpha_0 i_v+\kappa_1\mu_b)(i_v(\beta\varepsilon_1 i_{hu}+\beta_1\varepsilon_2)\alpha_0+\beta i_{hu}\varepsilon_1\kappa_1\mu_b)\\
B_0 \;=\;& -\delta\mu_h(\alpha_0 i_v+\alpha_2 i_{hu}+\mu_e\kappa_2)(\alpha_0 i_v+\kappa_1\mu_b)b(i_v(\beta\varepsilon_1 i_{hu}+\beta_1\varepsilon_2)\alpha_0+\kappa_1\varepsilon_1\beta i_{hu}\mu_b)
\end{aligned}
$$

$$C_3 i_v^3+C_2 i_v^2+C_1 i_v+C_0=0 \tag{3.7}$$

$$
\begin{aligned}
C_3 &= {\alpha_0}^2(\lambda_1+\lambda_2+\mu_v)\\
C_2 &= \alpha_0((-\lambda_1-\lambda_2)\alpha_0+(\alpha_2 i_{hu}+\kappa_1\mu_b)\lambda_2+i_{hu}(\lambda_1+\mu_v)\alpha_2+\kappa_1\mu_b\mu_v+\mu_e\kappa_2(\lambda_1+\mu_v))\\
C_1 &= ((-\lambda_1\alpha_2-\alpha_2\lambda_2)\alpha_0+(\alpha_2\lambda_2+\mu_v\alpha_2)\kappa_1\mu_b)i_{hu}+(-\kappa_1\mu_b\lambda_2-\lambda_1\mu_e\kappa_2)\alpha_0+\mu_v\mu_e\kappa_2\kappa_1\mu_b\\
C_0 &= -\alpha_2 i_{hu}\kappa_1\lambda_2\mu_b
\end{aligned}
$$

We can clearly note that, $A_4>0$ and $A_0<0$ always hold, therefore, there exist at least one positive solution for equation (3.5). Also, we can clearly note that, $B_4>0$, $B_3>0$ and $B_0<0$ always hold, therefore, there exist at least one positive solution for equation (3.6). Moreover, $C_3>0$ and $C_0<0$ always hold, therefore, there exist at least one positive solution for equation (3.7). Hence, by applying the Descartes rule of signs on equations (3.5), (3.6) and (3.7), the following result is established:

Theorem 3.1. *The model (3.1) has:*

case (i) if $A_3>0$

- *a unique endemic equilibrium if* $A_2A_1>0$, $B_2B_1>0$ *and* $C_2C_1>0$.
- *a unique endemic equilibrium if* $A_2>0$, $B_2>0$, $C_2>0$ *and* $A_1<0$, $B_1<0$, $C_1<0$.

- *more then one endemic equilibria otherwise.*

case (ii) if $A_3 < 0$

- *a unique endemic equilibrium if* $A_2 < 0$, $A_1 < 0$, $B_2B_1 > 0$ *and* $C_2C_1 > 0$.
- *a unique endemic equilibrium if* $A_2 < 0$, $B_2 > 0$, $C_2 > 0$ *and* $A_1 < 0$, $B_1 < 0$, $C_1 < 0$.
- *more then one endemic equilibria otherwise.*

3.4. Bifurcation. We establish conditions for the existence of backward bifurcation following Theorem 4.1 proven in [3]. We shall make the following change of variables: $x_1 = s_{hu}, x_2 = s_{ha}, x_3 = i_{hu}, x_4 = i_{ha}, x_5 = s_v, x_6 = i_v, x_7 = B, x_8 = E$. We now use the vector notation $X = (x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8)^T$. Then, system (3.1) can be written in the form $\frac{dX}{dt} = F(t, x(t)) = (f_1, f_2, f3, f_4, f_5, f_6, f_7, f_8)^T$ where,

$$
\begin{aligned}
\frac{dx_1}{dt} &= \mu_h - \beta x_1(x_3 + x_4) - \frac{\beta_1 x_1 x_7}{\kappa_1 + x_7} - \frac{\beta_2 x_1 x_8}{\kappa_2 + x_8} - (\mu_h + \delta)x_1 = f_1 \\
\frac{dx_2}{dt} &= \delta x_1 - \varepsilon_1 \beta x_2(x_3 + x_4) - \frac{\varepsilon_2 \beta_1 x_2 x_7}{\kappa_1 + x_7} - \mu_h x_2 = f_2 \\
\frac{dx_3}{dt} &= \beta x_1(x_3 + x_4) + \frac{\beta_1 x_1 x_7}{\hat{\kappa_1} + x_7} + \frac{\beta_2 x_1 x_8}{\kappa_2 + x_8} - (\gamma_0 + (\gamma_1 + \gamma_0)\frac{b}{x_3 + b})x_3 - \mu_h x_3 = f_3 \\
\frac{dx_4}{dt} &= \varepsilon_1 \beta x_2(x_3 + x_4) + \frac{\varepsilon_2 \beta_1 x_2 x_7}{\kappa_1 + x_7} - (\gamma_0 + (\gamma_1 + \gamma_0)\frac{b}{x_4 + b})x_4 - \mu_h x_4 = f_4 \\
\frac{dx_5}{dt} &= \mu_v - \frac{\lambda_1 x_5 x_7}{\kappa_1 + x_7} - \frac{\lambda_2 x_5 x_8}{\kappa_2 + x_8} - \mu_v x_5 = f_5 \\
\frac{dx_6}{dt} &= \frac{\lambda_1 x_5 x_7}{\kappa_1 + x_7} + \frac{\lambda_2 x_5 x_8}{\kappa_2 + x_8} - \mu_v x_6 = f_6 \\
\frac{dx_7}{dt} &= \varepsilon \alpha_0 x_6 - \mu_b x_7 = f_7 \\
\frac{dx_8}{dt} &= \alpha_0 x_6 + \alpha_2 x_3 - \mu_e x_8 = f_8
\end{aligned}
$$

Taking $\Phi = \beta$, where Φ is the bifurcation parameter, we assume $R_0 = 1$ and then find the bifurcation parameter $\beta = \frac{(\delta+\mu_h)\left(\mu_e \kappa_2 {\mu_h}^2 + (\mu_e(\delta+\gamma_1)\kappa_2 + \alpha_2\beta_2)\mu_h + \delta\,\gamma_1\,\kappa_2\mu_e\right)(\gamma_1+\mu_h)}{\mu_e(\delta+\mu_h)(\delta\,\varepsilon_1+\mu_h)(\gamma_1+\mu_h)\kappa_2 + \delta\,\alpha_2\beta_2\varepsilon_1\mu_h}$

The Jacobian matrix, after linearizing model system (3.1) around the disease-free equilibrium ξ^0 is

$$J(\xi^0)=\begin{bmatrix}
-\mu_h-\delta & 0 & -\frac{\Phi\mu_h}{\delta+\mu_h} & -\frac{\Phi\mu_h}{\delta+\mu_h} & 0 & 0 & -\frac{\beta_1\mu_h}{(\delta+\mu_h)\kappa_1} & -\frac{\beta_2\mu_h}{(\delta+\mu_h)\kappa_2}\\
\delta & -\mu_h & -\frac{\varepsilon_1\Phi\delta}{\delta+\mu_h} & -\frac{\varepsilon_1\Phi\delta}{\delta+\mu_h} & 0 & 0 & -\frac{\varepsilon_2\beta_1\delta}{(\delta+\mu_h)\kappa_1} & 0\\
0 & 0 & \frac{\Phi\mu_h}{\delta+\mu_h}-\mu_h-\gamma_1 & \frac{\Phi\mu_h}{\delta+\mu_h} & 0 & 0 & -\frac{\beta_1\mu_h}{(\delta+\mu_h)\kappa_1} & -\frac{\beta_2\mu_h}{(\delta+\mu_h)\kappa_2}\\
0 & 0 & \frac{\varepsilon_1\Phi\delta}{\delta+\mu_h} & \frac{\varepsilon_1\Phi\delta}{\delta+\mu_h}-\mu_h-\gamma_1 & 0 & 0 & \frac{\varepsilon_2\beta_1\delta}{(\delta+\mu_h)\kappa_1} & 0\\
0 & 0 & 0 & 0 & -\mu_v & 0 & -\frac{\lambda_1}{\kappa_1} & -\frac{\lambda_2}{\kappa_2}\\
0 & 0 & 0 & 0 & 0 & -\mu_v & \frac{\lambda_1}{\kappa_1} & \frac{\lambda_2}{\kappa_2}\\
0 & 0 & 0 & 0 & 0 & \varepsilon\alpha_0 & -\mu_b & 0\\
0 & 0 & \alpha_2 & 0 & 0 & \alpha_0 & 0 & -\mu_e
\end{bmatrix}$$

It can be shown that $J(\xi^0)$, has a right eigenvector is given by $w=(w_1,w_2,w_3,w_4,w_5,w_6,w_7,w_8)^T$, where

$$\begin{aligned}
w_1 &= -\frac{w_3(\mu_h+\gamma_1)}{\mu_h+\delta}\\
w_2 &= \frac{\delta w_1}{\mu_h}-\frac{(\beta\varepsilon_1(w_3+w_4)\kappa_1+\beta_1\varepsilon_2 w_7)\delta}{(\mu_h+\delta)\kappa_1\mu_h}\\
w_3 &= w_3\\
w_4 &= \frac{\left(w_3\left({\mu_h}^2+(-\beta+\delta+\gamma_1)\mu_h+\delta\gamma_1\right)\kappa_2-w_8\mu_h\beta_2\right)\kappa_1-\beta_1\kappa_2\mu_h w_7}{\kappa_1\kappa_2\beta\mu_h}\\
w_5 &= \frac{\alpha_2 w_3\kappa_1\lambda_2\mu_b}{\varepsilon\alpha_0\kappa_2\lambda_1\mu_e-\kappa_1\kappa_2\mu_b\mu_e\mu_v+\alpha_0\kappa_1\lambda_2\mu_b}\\
w_6 &= \frac{\mu_b w_7}{\varepsilon\alpha_0}\\
w_7 &= -\frac{\alpha_2 w_3\varepsilon\alpha_0\kappa_1\lambda_2}{\varepsilon\alpha_0\kappa_2\lambda_1\mu_e-\kappa_1\kappa_2\mu_b\mu_e\mu_v+\alpha_0\kappa_1\lambda_2\mu_b}\\
w_8 &= \frac{\alpha_2\kappa_2 w_3(\varepsilon\alpha_0\lambda_1-\kappa_1\mu_b\mu_v)}{\varepsilon\alpha_0\kappa_2\lambda_1\mu_e-\kappa_1\kappa_2\mu_b\mu_e\mu_v+\alpha_0\kappa_1\lambda_2\mu_b}
\end{aligned} \tag{3.8}$$

Further, the left eigenvector of $J(\xi^0)$ is given by $v=(v_1,v_2,v_3,v_4,v_5,v_6,v_7,v_8)^T$, where

$$\begin{aligned}
v_1 &= v_2=v_5=0\\
v_3 &= v_3\\
v_4 &= \frac{v_3\beta\mu_h}{{\mu_h}^2+\delta\gamma_1\mu_h+\delta(\gamma_1-\varepsilon_1\beta)}\\
v_6 &= \frac{(\delta\kappa_2\mu_e+\kappa_2\mu_e\mu_h)v_8}{(\mu_h+\delta)\lambda_2}-\frac{v_3\beta_2\mu_h}{(\mu_h+\delta)\lambda_2}\\
v_7 &= \frac{(\delta\kappa_2\mu_e\mu_v+\kappa_2\mu_e\mu_h\mu_v-\delta\alpha_0\lambda_2-\alpha_0\lambda_2\mu_h)v_8-\beta_2\mu_h\mu_v v_3}{(\mu_h+\delta)\lambda_2\varepsilon\alpha_0}\\
v_8 &= v_8
\end{aligned} \tag{3.9}$$

We compute a and b in order to apply Theorem 4.1 in [3]. For system (3.8), the associated non-zero partial derivatives of F at the disease-free equilibrium are as follows:

$$\begin{aligned}
\frac{\partial^2 f_1}{\partial x_1 \partial x_3} &= \frac{\partial^2 f_1}{\partial x_1 \partial x_4} = \frac{\partial^2 f_1}{\partial x_3 \partial x_1} = \frac{\partial^2 f_1}{\partial x_4 \partial x_1} = -\beta^* \\
\frac{\partial^2 f_1}{\partial x_1 \partial x_7} &= \frac{\partial^2 f_1}{\partial x_7 \partial x_1} = -\frac{\beta_1}{\kappa_1} \\
\frac{\partial^2 f_1}{\partial x_1 \partial x_8} &= \frac{\partial^2 f_1}{\partial x_8 \partial x_1} = -\frac{\beta_2}{\kappa_2} \\
\frac{\partial^2 f_3}{\partial x_1 \partial x_3} &= \frac{\partial^2 f_3}{\partial x_1 \partial x_4} = \frac{\partial^2 f_3}{\partial x_3 \partial x_1} = \frac{\partial^2 f_3}{\partial x_4 \partial x_1} = \beta^* \\
\frac{\partial^2 f_3}{\partial x_1 \partial x_7} &= \frac{\partial^2 f_3}{\partial x_7 \partial x_1} = \frac{\beta_1}{\kappa_1} \\
\frac{\partial^2 f_3}{\partial x_1 \partial x_8} &= \frac{\partial^2 f_3}{\partial x_8 \partial x_1} = \frac{\beta_2}{\kappa_2} \\
\frac{\partial^2 f_2}{\partial x_2 \partial x_3} &= \frac{\partial^2 f_2}{\partial x_2 \partial x_4} = \frac{\partial^2 f_2}{\partial x_3 \partial x_2} = \frac{\partial^2 f_2}{\partial x_4 \partial x_2} = -\varepsilon_1 \beta^* \\
\frac{\partial^2 f_2}{\partial x_2 \partial x_7} &= \frac{\partial^2 f_2}{\partial x_7 \partial x_2} = -\frac{\varepsilon_2 \beta_1}{\kappa_1} \\
\frac{\partial^2 f_4}{\partial x_2 \partial x_3} &= \frac{\partial^2 f_4}{\partial x_2 \partial x_4} = \frac{\partial^2 f_4}{\partial x_3 \partial x_2} = \frac{\partial^2 f_4}{\partial x_4 \partial x_2} = \varepsilon_1 \beta^* \\
\frac{\partial^2 f_5}{\partial x_5 \partial x_7} &= \frac{\partial^2 f_5}{\partial x_7 \partial x_5} = -\frac{\lambda_1}{\kappa_1} \\
\frac{\partial^2 f_5}{\partial x_5 \partial x_8} &= \frac{\partial^2 f_5}{\partial x_8 \partial x_5} = -\frac{\lambda_2}{\kappa_2} \\
\frac{\partial^2 f_6}{\partial x_5 \partial x_7} &= \frac{\partial^2 f_6}{\partial x_7 \partial x_5} = \frac{\lambda_1}{\kappa_1} \\
\frac{\partial^2 f_6}{\partial x_5 \partial x_8} &= \frac{\partial^2 f_6}{\partial x_8 \partial x_5} = \frac{\lambda_2}{\kappa_2} \\
\frac{\partial^2 f_1}{\partial x_7^2} &= \frac{2\beta_1 \mu_h}{(\mu_h + \delta)\,{\kappa_1}^2} \\
\frac{\partial^2 f_2}{\partial x_7^2} &= \frac{2\varepsilon_2 \beta_1 \delta}{(\mu_h + \delta)\,{\kappa_1}^2} \\
\frac{\partial^2 f_3}{\partial x_7^2} &= -\frac{2\beta_1 \mu_h}{(\mu_h + \delta)\,{\kappa_1}^2} \\
\frac{\partial^2 f_4}{\partial x_2 \partial x_7} &= \frac{\partial^2 f_4}{\partial x_7 \partial x_2} = \frac{\varepsilon_2 \beta_1}{\kappa_1}
\end{aligned}$$

$$
\begin{aligned}
\frac{\partial^2 f_4}{\partial x_7^2} &= -\frac{2\varepsilon_2\beta_1\delta}{(\mu_h+\delta)\,{\kappa_1}^2} \\
\frac{\partial^2 f_5}{\partial x_7^2} &= \frac{2\lambda_1}{{\kappa_1}^2} \\
\frac{\partial^2 f_6}{\partial x_7^2} &= -\frac{2\lambda_1}{{\kappa_1}^2} \\
\frac{\partial^2 f_1}{\partial x_8^2} &= \frac{2\beta_2\mu_h}{(\mu_h+\delta)\,{\kappa_2}^2} \\
\frac{\partial^2 f_3}{\partial x_8^2} &= -\frac{2\beta_2\mu_h}{(\mu_h+\delta)\,{\kappa_2}^2} \\
\frac{\partial^2 f_5}{\partial x_8^2} &= \frac{2\lambda_2}{{\kappa_2}^2} \\
\frac{\partial^2 f_6}{\partial x_8^2} &= -\frac{2\lambda_2}{{\kappa_2}^2} \\
\frac{\partial^2 f_1}{\partial x_3\partial\beta^*} &= \frac{\partial^2 f_1}{\partial x_4\partial\beta^*} = -\frac{\mu_h}{\mu_h+\delta} \\
\frac{\partial^2 f_2}{\partial x_3\partial\beta^*} &= \frac{\partial^2 f_2}{\partial x_4\partial\beta^*} = -\frac{\varepsilon_1\delta}{\mu_h+\delta} \\
\frac{\partial^2 f_3}{\partial x_3\partial\beta^*} &= \frac{\partial^2 f_3}{\partial x_4\partial\beta^*} = \frac{\mu_h}{\mu_h+\delta} \\
\frac{\partial^2 f_4}{\partial x_3\partial\beta^*} &= \frac{\partial^2 f_4}{\partial x_4\partial\beta^*} = \frac{\varepsilon_1\delta}{\mu_h+\delta}
\end{aligned}
$$

It thus follows that:

$$
\begin{aligned}
a &= v_3\left((2w_1w_3+2w_1w_4)\beta^* + \frac{2w_1w_7\beta_1}{\kappa_1} + \frac{2w_1w_8\beta_2}{\kappa_2} - \frac{2w_7^2\beta_1\mu_h}{(\mu_h+\delta)\kappa_1^2} - \frac{2w_8^2\beta_2\mu_h}{(\mu_h+\delta)\kappa_2^2}\right) \\
&+ v_4\left((2w_2w_3+2w_2w_4)\varepsilon_1\beta^* + \frac{2w_2w_7\varepsilon_2\beta_1}{\kappa_1} - \frac{2w_7^2\varepsilon_2\beta_1\delta}{(\mu_h+\delta)\kappa_1^2}\right) \qquad (3.10) \\
&+ v_6\left(\frac{2w_5w_7\lambda_1}{\kappa_1} + \frac{2w_5w_8\lambda_2}{\kappa_2} - \frac{2w_7^2\lambda_1}{\kappa_1^2} - \frac{2w_8^2\lambda_2}{\kappa_2^2}\right) \\
b &= \left(w_3+w_4\right)\left(\frac{v_3\mu_h}{\mu_h+\delta} + \frac{v_4\varepsilon_1\delta}{\mu_h+\delta}\right)
\end{aligned}
$$

Here the coefficient b is obviously positive and the coefficient a will decide the backward bifurcation of the model (3.8). In particular the backward bifurcation in the model would occur

if the coefficient a is positive. Therefore, since there is a possibility for the model to exhibits backward bifurcation, then, reducing R_0 below unity is not sufficient to control the cholera epidemic.

4. NUMERICAL SIMULATION

We perform some numerical simulations of system (3.1) to see the effects of awareness programs parameters $(\delta, \varepsilon_1, \varepsilon_2)$.

We list the values for the parameters in the system in Table (**??**) with the initial conditions $s_{hu}(0) = 0.7, s_{ha}(0) = 0.1, i_{hu}(0) = 0.1, i_{ha}(0) = 0.1, r(0) = 0.0, s_v(0) = 0.95, i_v(0) = 0.05, B(0) = 0.4, E(0) = 0.4$.

Our results in figures(1, 2, 3) illustrate that awareness program lowers the outbreak size definitely and decreases the severity of the cholera outbreak.

Parameter	Value	Unit	Reference
μ_h	0.00004	day^{-1}	[19]
β	$0.000105 - 0.000111$	day^{-1}	[38]
β_1	$.055 - 0.094$	day^{-1}	[38]
β_2	$.055 - 0.094$	day^{-1}	Assumed
γ_0	$(0.15, ...)$	–	[10]
γ_1	$(\gamma_0, 0.09)$	–	[10]
b	$(0, 20)$	–	[10]
κ_1	$10^5 cells/mL$	Cells L^{-1}	[30]
κ_2	$10^5 - 10^7 cells/mL$	Cells L^{-1}	[4, 13]
λ_1	$0.0056 - 0.097$	day^{-1}	[30]
λ_2	$0.0057 - 0.1$	day^{-1}	[30]
μ_v	$0.189d^{-1}$	day^{-1}	[11]
μ_b	$(30d)^{-1}$	day^{-1}	[30]
μ_e	$(30d)^{-1}$	day^{-1}	[38]
ε, ε_1, ε_2	$0.001 - 0.01$	day^{-1}	Assumed
α_0	$1 - 150$	Cells $mL^{-1}day^{-1}$ per vector	[30]
α_2	$1 - 150$	Cells $mL^{-1}day^{-1}$ per person	[38, 10]

TABLE 2. Parameter values

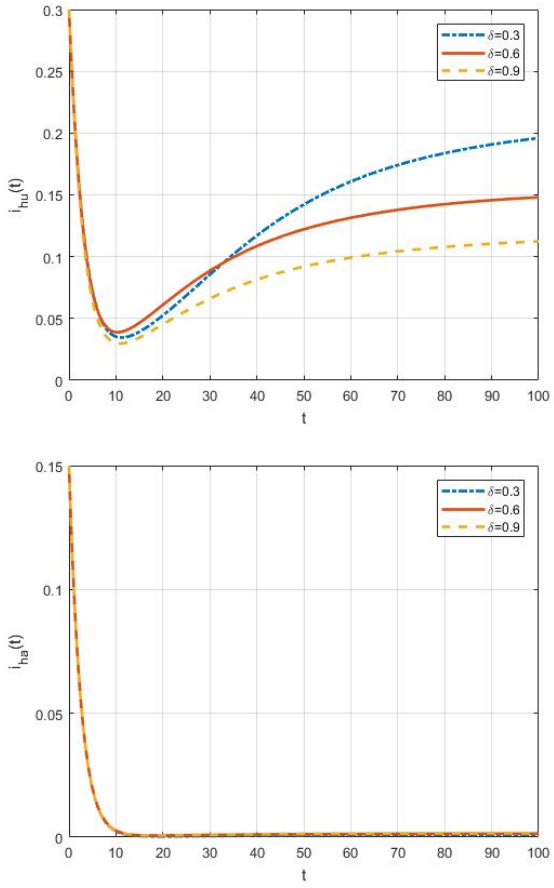

FIGURE 1. Effect of Delta in the infection

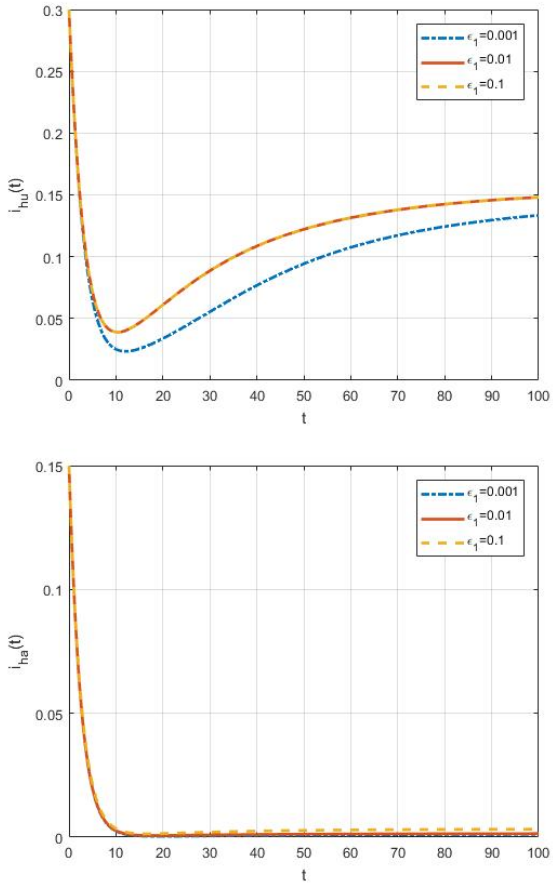

FIGURE 2. Effect of ε_1 in the infection

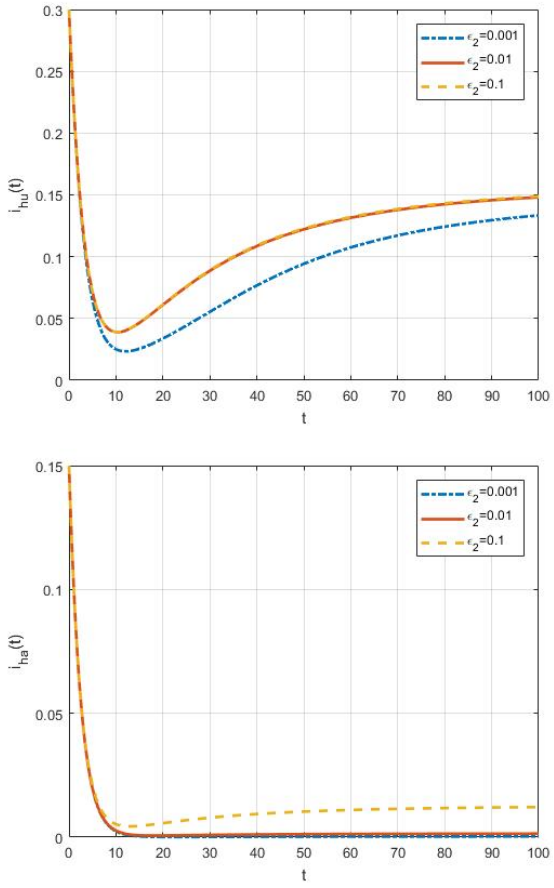

FIGURE 3. Effect of ε_2 in the infection

The limited resource parameter b, is varied in Figure (4). It is shown that as b is increased, the human infection population decrease. This means that increasing the number of hospital-beds during an outbreak, will give a high opportunity for the disease to persist. Hence, the number of hospital beds plays an important role in controlling the spread of infectious diseases.

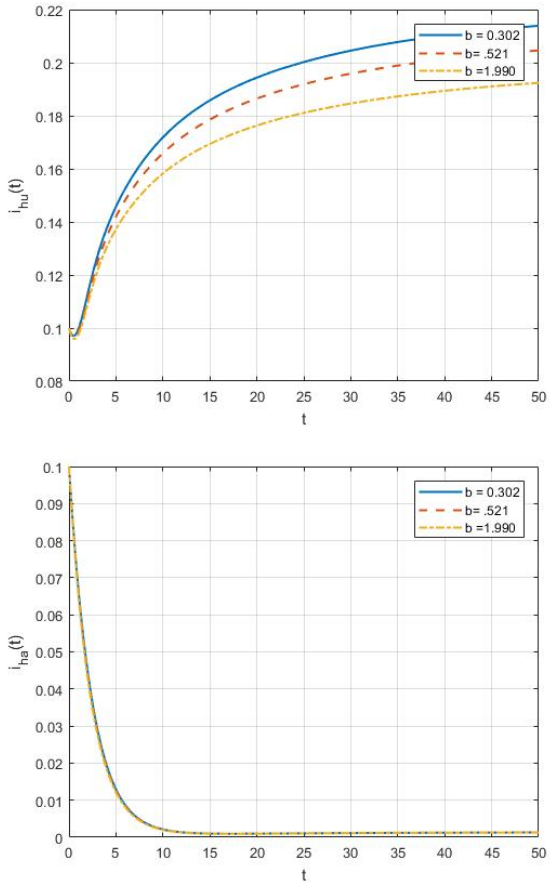

FIGURE 4. Varying limited resources b for $R_0 > 1$

5. EXTENDED MODEL WITH OPTIMAL CONTROL

Optimal control theory is a powerful tool to make decisions involving complex dynamical systems. Optimal control theory is a tool to find an optimal path or value that gives either maximum or minimum points of functions. Optimal control is a set of ordinary differential equations describing the paths of the control variables that minimize the cost functions. Studies have indicated that epidemiological models may give some fundamental rules to public health practitioners to compare the effectiveness of different potential management strategies. We

introduce three time dependent control variables $u_1(t)$, $u_2(t)$ and $u_3(t)$ in the model (3.1). $u_1(t)$ represents vaccination of susceptible individuals, $u_2(t)$ represents the killing of vectors, and $u_3(t)$ represents water sanitation. The control functions $u_1(t)$, $u_2(t)$ and $u_3(t)$ are bounded and Lebesgue integrable functions. Vaccination is introduced to the susceptible populations at a rate of $u_1(t)$, so that $u_1(t)s_{hu}(t)$ and $u_1(t)s_{ha}(t)$ individuals per time are removed from the susceptible classes and added to the recovered class. The elimination of the vector populations is applied to the infected people at a rate of $u_2(t)$. Water sanitation leads to the death of vibrios at a rate of $u_3(t)$. As a result, we obtain the following dynamical system:

$$
\begin{aligned}
\frac{ds_{hu}}{dt} &= \mu_h - \beta s_{hu}(i_{hu}+i_{ha}) - \frac{\beta_1 s_{hu}B}{\kappa_1+B} - \frac{\beta_2 s_{hu}E}{\kappa_2+E} - (\mu_h+\delta+u_1)s_{hu} \\
\frac{ds_{ha}}{dt} &= \delta s_{hu} - \varepsilon_1\beta s_{ha}(i_{hu}+i_{ha}) - \frac{\varepsilon_2\beta_1 s_{ha}B}{\kappa_1+B} - (\mu_h+u_1)s_{ha} \\
\frac{di_{hu}}{dt} &= \beta s_{hu}(i_{hu}+i_{ha}) + \frac{\beta_1 s_{hu}B}{\hat{\kappa_1}+B} + \frac{\beta_2 s_{hu}E}{\kappa_2+E} - (\gamma_0+(\gamma_1+\gamma_0)\frac{b}{i_{hu}+b})i_{hu} - \mu_h i_{hu} \\
\frac{di_{ha}}{dt} &= \varepsilon_1\beta s_{ha}(i_{hu}+i_{ha}) + \frac{\varepsilon_2\beta_1 s_{ha}B}{\kappa_1+B} - (\gamma_0+(\gamma_1+\gamma_0)\frac{b}{i_{ha}+b})i_{ha} - \mu_h i_{ha} \\
\frac{dr_h}{dt} &= u_1(s_{hu}+sha)(\gamma_0+(\gamma_1+\gamma_0)\frac{b}{i_{hu}+b})i_{hu} + (\gamma_0+(\gamma_1+\gamma_0)\frac{b}{i_{ha}+b})i_{ha} - \mu_h r_h \\
\frac{ds_v}{dt} &= \mu_v - \frac{\lambda_1 s_v B}{\kappa_1+B} - \frac{\lambda_2 s_v E}{\kappa_2+E} - (\mu_v+u_2)s_v \\
\frac{di_v}{dt} &= \frac{\lambda_1 s_v B}{\kappa_1+B} + \frac{\lambda_2 s_v E}{\kappa_2+E} - (\mu_v+u_2)i_v \\
\frac{dB}{dt} &= \varepsilon\alpha_0 i_v - \mu_b B \\
\frac{dE}{dt} &= \alpha_0 i_v + \alpha_2 i_{hu} - (\mu_e+u_3)E
\end{aligned}
\tag{5.1}
$$

A control scheme is assumed to be optimal if it minimizes the objective functional:

$$
\begin{aligned}
J(u_1,u_2,u_3) &= \int_0^{t_f} \Big[i_{hu}(t) + i_{ha}(t) + s_v(t) + i_v(t) + \frac{a_1}{2}u_1^2(t) \\
&+ \frac{a_2}{2}u_2^2(t) + \frac{a_3}{2}u_3^2(t) \Big] dt
\end{aligned}
\tag{5.2}
$$

Here the parameters c_i and a_i $(i = 1,2,3)$, with appropriate units, define the balancing cost factors for control strategies. We introduced the quadratic terms to show nonlinear costs which

are arising at high intervention levels [**?**, 31, 29].Hence, we want to minimize the objective function (5.2) subject to the system (5.1). For this purpose, we have to find the values of $u_1(t), u_2(t)$ and $u_3(t)$ which minimize the objective functional (5.2), i.e. to find u_1^*, u_2^* and u_3^* such that

$$J(u_1^*, u_2^*, u_3^*) = \min_{u_1,u_2,u_3 \in \Omega} J(u_1, u_2, u_3) \tag{5.3}$$

where u_1, u_2, u_3 are Lebesgue measurable and the control set Ω is defined as:

$$\Omega = \{u_i(t), u_i(t) : [0, t_f] \to [0,1], i = 1,2,3\} \tag{5.4}$$

Note that, , the conditions for the existence of optimal control are satisfied since the control set Ω is closed and convex, and the integrand of the objective functional (5.2) is convex [31].
To find the optimal control solution, we will use the Pontryagin's Maximum/Minimum principle [34]. We define the adjoint functions λ_i where $i = s_{hu}, s_{ha}, i_{hu}, i_{ha}, s_v, i_v, B, E$ and associated with the state equations for $s_{hu}, s_{ha}, i_{hu}, i_{ha}, s_v, i_v, B$ and E, respectively. We then form the Hamiltonian, H, by multiplying each adjoint function with the right-hand side of its corresponding state equation, and adding each of these products to the integrand of the objective functional. As a result, we obtain

$$\begin{aligned}
H = {} & i_{hu} + i_{ha} + s_v + i_v + 1/2\, a_1 {u_1}^2 + 1/2\, a_2 {u_2}^2 + 1/2\, a_3 {u_3}^2 \\
& + \lambda_{s_{hu}}(\mu_h - \beta\, s_{hu}(i_{hu} + i_{ha}) - \frac{\beta_1 s_{hu} B}{\kappa_1 + B} - \frac{\beta_2 s_{hu} E}{\kappa_2 + E} - (\mu_h + \delta) s_{hu} - u_1 s_{hu}) \\
& + \lambda_{s_{ha}}(\delta\, s_{hu} - \varepsilon_1 \beta\, s_{ha}(i_{hu} + i_{ha}) - \frac{\varepsilon_2 \beta_1 s_{ha} B}{\kappa_1 + B} - \mu_h s_{ha} - u_1 s_{ha}) \\
& + \lambda_{i_{hu}}(\beta\, s_{hu}(i_{hu} + i_{ha}) + \frac{\beta_1 s_{hu} B}{\kappa_1 + B} + \frac{\beta_2 s_{hu} E}{\kappa_2 + E} - (\gamma_0 + \frac{(\gamma_1 - \gamma_0) b}{b + i_{hu}} + \mu_h) i_{hu}) \\
& + \lambda_{i_{ha}}(\varepsilon_1 \beta\, s_{ha}(i_{hu} + i_{ha}) + \frac{\varepsilon_2 \beta_1 s_{ha} B}{\kappa_1 + B} - (\gamma_0 + \frac{(\gamma_1 - \gamma_0) b}{b + i_{ha}} + \mu_h) i_{ha}) \\
& + \lambda_{s_v}(\mu_v - \frac{\lambda_1 s_v B}{\kappa_1 + B} - \frac{\lambda_2 s_v E}{\kappa_2 + E} - \mu_v s_v - u_2 s_v) + \lambda_{i_v}(\frac{\lambda_1 s_v B}{\kappa_1 + B} + \frac{\lambda_2 s_v E}{\kappa_2 + E} - \mu_v i_v - u_2 i_v) \\
& + \lambda_B(\varepsilon\, \alpha_0 i_v - \mu_b B) + \lambda_E(-\mu_e E - E u_3 + \alpha_0 i_v + \alpha_2 i_h)
\end{aligned} \tag{5.5}$$

Theorem 5.1. *Given an optimal control quintuple (u_1^*, u_2^*, u_3^*) and solutions $s_{hu}^*, s_{ha}^*, i_{hu}^*, i_{ha}^*, i_v^*, B^*$ and E^* of the corresponding state system (5.1) that minimizes $J(u_1^*, u_2^*, u_3^*)$*

over Ω. *Then there exists adjoint variables* $\lambda_{s_{hu}}, \lambda_{s_{ha}}, \lambda_{i_{hu}}, \lambda_{i_{ha}}, \lambda_{i_v}, \lambda_B$, *and* λ_E *satisfying*

$$\frac{d\lambda_i}{dt} = -\frac{\partial H}{\partial i} \tag{5.6}$$

and with transversality conditions $\lambda_i(t_f) = 0$ *where* $i = a_{hu}, s_{ha}, i_{hu}, i_{ha}, i_v, B$ *and* E *with the control quadruple* (u_1^*, u_2^*, u_3^*) *is given by:*

$$\begin{aligned} u_1^* &= min\left(1, max\left(\frac{\lambda_{s_{ha}} s_{ha} + \lambda_{s_{hu}} s_{hu})}{a_1}, 0\right)\right) \\ u_2^* &= min\left(1, max\left(\frac{\lambda_{i_v} i_v + \lambda_{s_v} s_v)}{a_2}, 0\right)\right) \\ u_3^* &= min\left(1, max\left(\frac{\lambda_E E}{a_3}, 0\right)\right) \end{aligned} \tag{5.7}$$

Proof. The adjoint equations and the transversality conditions are obtained from the Pontryagin's Maximum Principle, such that

$$\begin{aligned}
\frac{d\lambda_{s_{hu}}}{dt} &= -\lambda_{s_{hu}}(-\beta\,(i_{hu}+i_{ha}) - \frac{\beta_1 B}{\kappa_1+B} - \frac{\beta_2 E}{\kappa_2+E} - \mu_h - \delta - u_1) \\
&\quad -\lambda_{s_{ha}}\delta - \lambda_{i_{hu}}(\beta\,(i_{hu}+i_{ha}) + \frac{\beta_1 B}{\kappa_1+B} + \frac{\beta_2 E}{\kappa_2+E}) \\
\frac{d\lambda_{s_{ha}}}{dt} &= -\lambda_{s_{ha}}\left(-\varepsilon_1\beta\,(i_{hu}+i_{ha}) - \frac{\varepsilon_2\beta_1 B}{\kappa_1+B} - \mu_h - u_1\right) - \lambda_{i_{ha}}\left(\varepsilon_1\beta\,(i_{hu}+i_{ha}) + \frac{\varepsilon_2\beta_1 B}{\kappa_1+B}\right) \\
\frac{d\lambda_{i_{hu}}}{dt} &= -1 + \lambda_{s_{hu}}\beta\, s_{hu} + \lambda_{s_{ha}}\varepsilon_1\beta\, s_{ha} - \lambda_{i_{hu}}(\beta\, s_{hu} + \frac{(\gamma_1-\gamma_0)b i_{hu}}{(b+i_{hu})^2} - \gamma_0 - \frac{(\gamma_1-\gamma_0)b}{b+i_{hu}} - \mu_h) \\
&\quad -\lambda_{i_{ha}}\varepsilon_1\beta\, s_{ha} \\
\frac{d\lambda_{i_{ha}}}{dt} &= -1 + \lambda_{s_{hu}}\beta\, s_{hu} + \lambda_{s_{ha}}\varepsilon_1\beta\, s_{ha} - \lambda_{i_{hu}}\beta\, s_{hu} \\
&\quad -\lambda_{i_{ha}}(\varepsilon_1\beta\, s_{ha} + \frac{(\gamma_1-\gamma_0)b i_{ha}}{(b+i_{ha})^2} - \gamma_0 - \frac{(\gamma_1-\gamma_0)b}{b+i_{ha}} - \mu_h) \\
\frac{d\lambda_{s_v}}{dt} &= -1 - \lambda_{s_v}\left(-\frac{\lambda_1 B}{\kappa_1+B} - \frac{\lambda_2 E}{\kappa_2+E} - \mu_v - u_2\right) - \lambda_{i_v}\left(\frac{\lambda_1 B}{\kappa_1+B} + \frac{\lambda_2 E}{\kappa_2+E}\right) \\
\frac{d\lambda_{i_v}}{dt} &= -1 - \lambda_{i_v}(-\mu_v - u_2) - \lambda_B\varepsilon\,\alpha_0 - \lambda_E\,\alpha_0 \\
\frac{d\lambda_B}{dt} &= -\lambda_{s_{hu}}\left(-\frac{\beta_1 s_{hu}}{\kappa_1+B} + \frac{\beta_1 s_{hu} B}{(\kappa_1+B)^2}\right) - \lambda_{s_{ha}}\left(-\frac{\varepsilon_2\beta_1 s_{ha}}{\kappa_1+B} + \frac{\varepsilon_2\beta_1 s_{ha} B}{(\kappa_1+B)^2}\right) \\
&\quad -\lambda_{i_{hu}}\left(\frac{\beta_1 s_{hu}}{\kappa_1+B} - \frac{\beta_1 s_{hu} B}{(\kappa_1+B)^2}\right) - \lambda_{i_{ha}}\left(\frac{\varepsilon_2\beta_1 s_{ha}}{\kappa_1+B} - \frac{\varepsilon_2\beta_1 s_{ha} B}{(\kappa_1+B)^2}\right) \\
&\quad -\lambda_{s_v}\left(-\frac{\lambda_1 s v}{\kappa_1+B} + \frac{\lambda_1 s_v B}{(\kappa_1+B)^2}\right) - \lambda_{i_v}\left(\frac{\lambda_1 s v}{\kappa_1+B} - \frac{\lambda_1 s_v B}{(\kappa_1+B)^2}\right) + \lambda_B\mu_b \\
\frac{d\lambda_E}{dt} &= -\lambda_{s_{hu}}\left(-\frac{\beta_2 s_{hu}}{\kappa_2+E} + \frac{\beta_2 s_{hu} E}{(\kappa_2+E)^2}\right) - \lambda_{i_{hu}}\left(\frac{\beta_2 s_{hu}}{\kappa_2+E} - \frac{\beta_2 s_{hu} E}{(\kappa_2+E)^2}\right) - \\
&\quad \lambda_{s_v}\left(-\frac{\lambda_2 s_v}{\kappa_2+E} + \frac{\lambda_2 s_v E}{(\kappa_2+E)^2}\right) - \lambda_{i_v}\left(\frac{\lambda_2 s_v}{\kappa_2+E} - \frac{\lambda_2\, s_v)E}{(\kappa_2+E)^2}\right) - \lambda_E(-\mu_e - u_3)
\end{aligned} \tag{5.8}$$

The characterizations of the optimal controls u_1,u_2 and u_3,are based on the conditions

$$\begin{aligned} \frac{\partial H}{\partial u_1} &= 0 \\ \frac{\partial H}{\partial u_2} &= 0 \\ \frac{\partial H}{\partial u_3} &= 0 \end{aligned} \tag{5.9}$$

Solving equation (5.9) for (u_1^*, u_2^*, u_3^*) gives the characterization (5.7). □

5.1. Numerical illustrations. The optimal control problem consists of the state system (5.1) with initial conditions, the adjoint equations (5.8) with the transversality conditions, and equations (5.7) to characterize the optimal controls. Forward-Backward Sweep Method [31] is applied in order to solve it numerically.

Cost coefficients are fixed within the integral expression (5.2) and the optimal schedule of the three controls over $T = 100$ days is simulated for the human populations with the initial guess for the state variables $(s_{hu}(0), s_{ha}(0), i_{hu}(0), i_{ha}(0), r_h(0), s_v(0), i_v(0), B(0), E(0)) = (0.3, 0.2, 0.3, 0.15, 0.05, 0.7, 0.3, 0.4, 0.6)$. Hence we will see the effects of the following:

- Single optimal control scheme.
- Two optimal control schemes.
- All the control schemes.

5.1.1. *Optimal Application of A Single Control.* The optimal control problem can be reformulated to show the effects of each optimal control method when it used alone. Assuming just one of the three control methods is applicable by setting the other two controls to zero. It is clear from figures (5, 6, 7) that each single optimal scheme is advantageous and effective to reduce the number of aware infected individuals. The use of vaccination only (figure 5) or sanitation only (figure 7) reduce the number of unaware infected at the onset of the infection. However, the effect of using vector elimination alone remains optimal for the entire infection's period for unaware infected (figure 6).

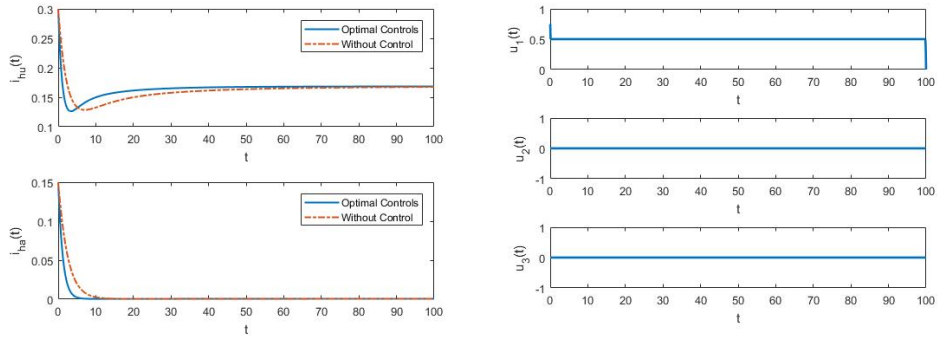

FIGURE 5. Left: Effect of vaccination only on the total number of infected humans. Right: The optimal controls.

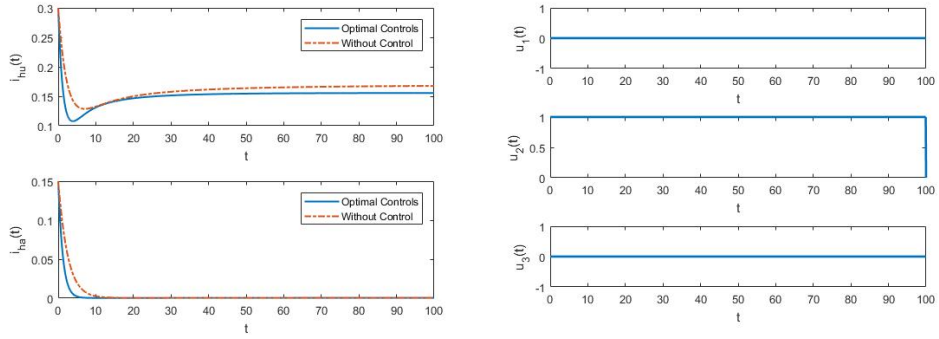

FIGURE 6. Left: Effect of vector elimination only on the total number of infected humans. Right: The optimal controls.

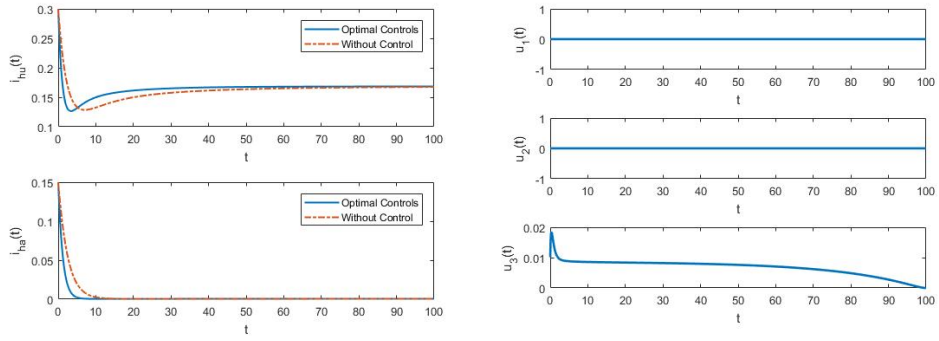

FIGURE 7. Left: Effect of sanitation only on the total number of infected humans. Right: The optimal controls

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5.1.2. *Optimal Application of Two Controls.* In this section, we illustrate the effects of using two optimal schemes in the absence of the third one. It can be seen form figures (8, 9, 10) that, all the method the number of aware infected individuals effectively while the effects on unaware infected vary. The infection level of unaware people has been significantly reduced due to vaccination and vector elimination (figure (8)). Using vector elimination and water sanitation schemes reduce number of unaware infected at the beginning of the infection period (figure (9)) but then the number if unaware infected will increase. Also, it can be seen from figure (10) using vaccination and water sanitation schemes have effects only at the onset of the infections.

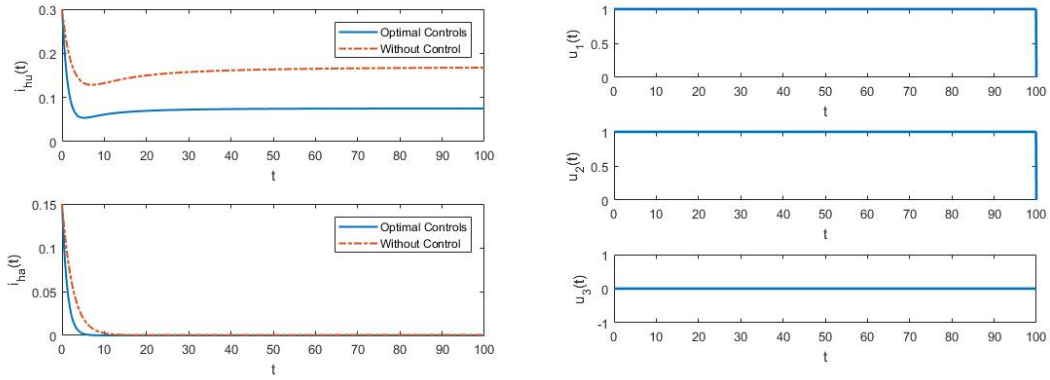

FIGURE 8. Left: Effect of vaccination and vector elimination on the total number of infected humans. Right: The optimal controls.

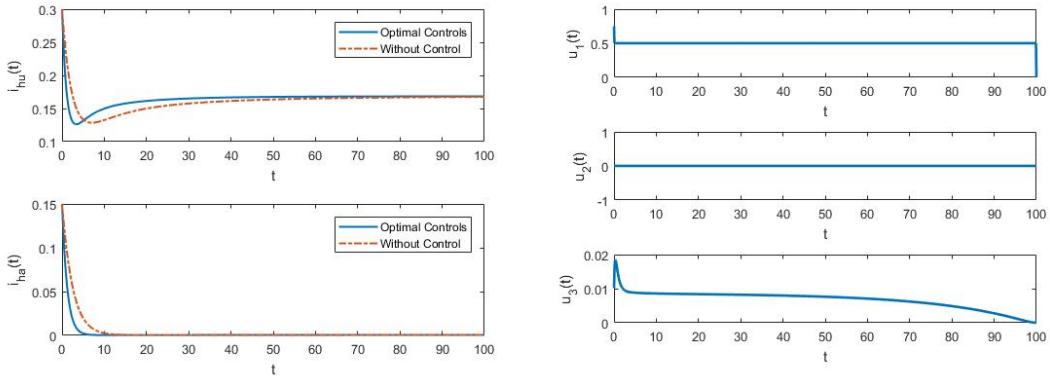

FIGURE 9. Left: Effect of vaccination and water sanitition on the total number of infected humans. Right: The optimal controls.

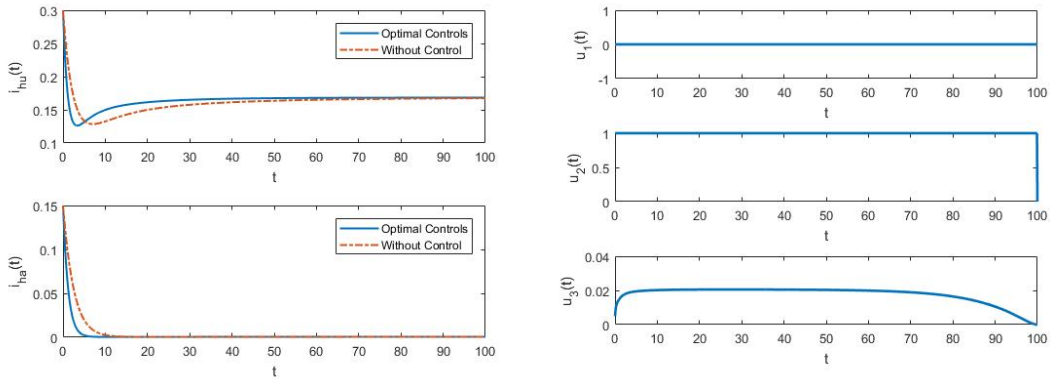

FIGURE 10. Left: Effect of vector elimination and water sanitition on the total number of infected humans. Right: The optimal controls.

5.1.3. *Optimal Application of All Controls.* Here we use all the three controls vaccination, vector elimination and water sanitation to optimize the objective function. The simulation results in figure 11 illustrates that the number of unaware infected human is low in case of control compared with the case of no control but not optimal because u_3 is plunged to 0.011 and then it falls to zero while the two others control takes it upper bound. On the other hand, the three controls are useful in order to reduce the number of aware infected.

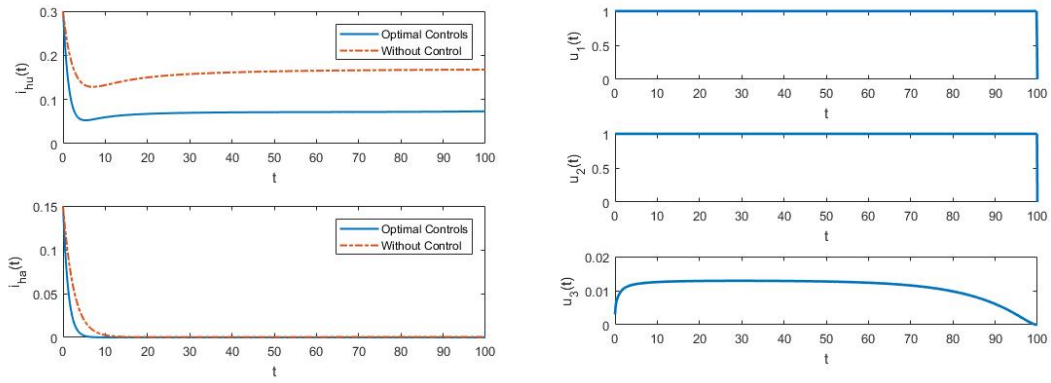

FIGURE 11. Left: Effect of all controls on the total number of infected humans. Right: The optimal controls.

6. COST-EFFECTIVENESS ANALYSIS

Cost-Effectiveness Analysis calculates the costs and effects gains of alternative interventions by providing a method for organizing interventions for a given set of resource constraints. It identifies which control profile that have the potential which gives the optimal improvement in health with less cost.1 [21, 20]. A variety of methods have been used in applied cost-effectiveness studies to estimate the costs and effects of different interventions.

6.1. Efficacy function. The efficacy function is given by:

$$E(t) = \frac{i_h(0) - i_h^*(0)}{i_h(0)} \tag{6.1}$$

where $i_h(0)$ is the values of infected human obtained at the endemic equilibrium of the system (5.1) before the introduction of interventions (i.e. $u_1 = 0; u_2 = 0; u_3 = 0$), and $i_h^*(0)$ is the values of infected human obtained at the endemic equilibrium of the system (5.1) after the introduction of the corresponding intervention.

Using the above formula (6.1), the efficacy of each intervention is given by the following computations:

Intervention	$E_{i_{hu}}(t)$	$E_{i_{ha}}(t)$
All Controls	0.5640	1
u_1 Only	-0.0030	9.98E-03
u_2 Only	0.0739	2.08E-01
u_3 Only	-0.0030	9.98E-03
u_1 and u_2	0.5533	1
u_1 and u_3	0.1007	2.08E-01
u_2 and u_3	-0.0030	9.98E-03

TABLE 3. The efficacy of each intervention

The values of efficacy in table (6.1) indicate that using all controls is the most effective intervention to minimize the number of unaware infected individuals with effectiveness of 56% followed by using vaccination and vector elimination intervention with with effectiveness of 55%. However, the differences between the efficacy of theses two interventions is only 1%. It

is observed from table (6.1) that, the most effective way to control aware infected is either by using all controls or using vaccination with vector elimination since they have the same efficacy value 100%.

6.2. Infection Averted Ratio. The infection averted ratio is given by:

$$IAR(t) = \frac{Number\ of\ infection\ averted}{Numbetr\ of\ recovered} \tag{6.2}$$

where number of infection averted is the difference of infected human obtained at the endemic equilibrium of the system (5.1) before the introduction of interventions and the number of infected human obtained at the endemic equilibrium of the system (5.1) after the introduction of the corresponding intervention.

Using the above formula (6.2), the IAR of each intervention is given by table (6.2).

Intervention	$IAR_{i_{hu}}(t)$	$IAR_{i_{ha}}(t)$
All Controls	0.1317	0.0007
u_1 Only	-0.0104	0.0001
u_2 Only	0.2713	0.0023
u_3 Only	-0.0104	0.0001
u_1 and u_2	0.1295	0.0007
u_1 and u_3	0.0.3781	0.0024
u_2 and u_3	-0.0104	0.0001

TABLE 4. The IAR of each intervention

Comparing the results obtained in table (6.2), it is clear that the most cost-effective intervention is the combination of vaccination with water sanitation for both unaware and aware infected individuals. Then, it is followed by using vector elimination only for both infected classes. However it is also clear from the table that the differences between the IAR of theses two interventions is very small.

6.3. Incremental Cost-Effectiveness Ratio. Incremental cost-effectiveness ratio is used to compare the differences between the costs and health outcomes of two intervention strategies

that compete for the same resources. It is generally described as the additional cost per additional health outcome [23]. The ICER numerator includes the differences in intervention costs (total cost TC), while, the denominator is the difference in health outcomes (infections averted (A_i)). We start the analysis by ranking the total infections averted of the control interventions in increasing order. Next, we define and calculate the ICERs as follows:

$$\begin{aligned} ICER_{i_{hu}}(u_1\ only) &= \frac{TC(u_1\ only)}{IA_{i_{hu}}(u_1\ only)} = -82.125 \\ ICER_{i_{hu}}(u_3\ only) &= \frac{TC(u_3\ only) - TC(u_1\ only)}{IA_{i_{hu}}(u_3\ only) - IA_{i_{hu}}(u_1\ only)} = \infty \end{aligned}$$

The remaining calculations of ICER for both aware and unaware infected population are given in table (6.3).

Strategy (i_{hu})	$IA_{i_{hu}}$	TC	$ICER_{i_{hu}}$	Strategy (i_{ha})	$IA_{i_{ha}}$	TC	$ICER_{i_{ha}}$
no strategy	0	0	−	no strategy	0	0	−
u_1 Only	-0.0008	0.0657	-82.125	u_3 Only	5.83×10^{-6}	0	0
u_3 Only	-0.0008	0	∞	u_2 Only	5.83×10^{-6}	2018	∞
u_2 and u_3	-0.0008	0.0001	-9.2234×10^{14}	All Controls	5.83×10^{-6}	0.0003	∞
u_2 Only	0.0121	0.2018	15.6357	u_2 and u_3	0.0001	0.0001	-2
u_1 and u_3	0.0165	0.0001	-45.8410	u_1 and u_2	0.0001	0.3093	∞
u_1 and u_2	0.0926	0.3093	4.0631	u_1 only	0.0005	0.0657	-609
All Controls	0.0943	0.0003	-181.7647	u_1 and u_3	0.0005	0.0001	∞

TABLE 5. The $ICER_{i_{hu}}$ and $ICER_{i_{hu}}$ of each intervention

It is observed from table (6.3), for unaware infected, using water sanitation has unlimited costs , The lower $ICER_{i_{hu}}$ is obtained form using all controls. This is an indication that using all controls strongly dominate using water sanitation (u_3) only. Hence, the water sanitation (u_3) only strategy is ruled out from the set of alternatives strategies. It is also observed from table (6.3) that for aware infected individuals four strategies have unlimited costs which dominate the other strategies. therefore, we ruled them out from the set of alternatives strategies. Hence, we can get the following values of the ICERs in table (6.3).

Strategy (i_{hu})	$IA_{i_{hu}}$	TC	$ICER_{i_{hu}}$	Strategy (i_{ha})	$IA_{i_{ha}}$	TC	$ICER_{i_{ha}}$
no strategy	0	0	–	no strategy	0	0	–
u_1 Only	-0.0008	0.0657	-82.125	u_3 Only	5.83×10^{-6}	0	0
u_2 and u_3	-0.0008	0.0001	6.0505×10^{17}	u_2 and u_3	0.0001	0.0001	1
u_2 Only	0.0121	0.2018	15.6357	u_1 Only	0.0005	0.0657	164
u_1 and u_3	0.0165	0.0001	-45.8410				
u_1 and u_2	0.0926	0.3093	4.0631				
All Controls	0.0943	0.0003	-181.7647				

TABLE 6. The $ICER_{i_{hu}}$ and $ICER_{i_{hu}}$ of each intervention

From the calculations in table (6.3), we can see that using vector elimination (u_2) and water sanitation (u_3) strategy is more costly and less effective than other strategies therefore, it excluded from the control's strategies of unaware infected. Also, the calculations show that for aware infected using vaccination (u_1 only) is strongly dominated Therefore, it is ruled out from the set of alternatives so it does not consume limited resources. Hence, we recalculate ICER for the remaining strategies (table (6.3)).

Strategy (i_{hu})	$IA_{i_{hu}}$	TC	$ICER_{i_{hu}}$	Strategy (i_{ha})	$IA_{i_{ha}}$	TC	$ICER_{i_{ha}}$
no strategy	0	0	–	no strategy	0	0	–
u_1 Only	-0.0008	0.0657	-82.125	u_3 Only	5.83×10^{-6}	0	0
u_2 Only	0.0121	0.2018	10.5504	u_2 and u_3	0.0001	0.0001	1
u_1 and u_3	0.0165	0.0001	-45.8410				
u_1 and u_2	0.0926	0.3093	4.0631				
All Controls	0.0943	0.0003	-181.7647				

TABLE 7. The $ICER_{i_{hu}}$ and $ICER_{i_{hu}}$ of each intervention

Table (6.3) indicates that a cost saving of 10.5504 for using vector elimination (u_2 only) over the other strategies for unaware infected which implies that this strategy is exclude from further considerations. In addition, Table (6.3) shows that water sanitation (u_3 only) is the most cost-effective strategy for the aware infected.

Strategy (i_{hu})	$IA_{i_{hu}}$	TC	$ICER_{i_{hu}}$
no strategy	0	0	–
u_1 Only	−0.0008	0.0657	−82.125
u_1 and u_3	0.0165	0.0001	−3.7919
u_1 and u_2	0.0926	0.3093	4.0631
All Controls	0.0943	0.0003	−181.7647

TABLE 8. The $ICER_{i_{hu}}$ and $ICER_{i_{hu}}$ of each intervention

Strategy (i_{hu})	$IA_{i_{hu}}$	TC	$ICER_{i_{hu}}$
no strategy	0	0	–
u_1 Only	−0.0008	0.0657	−82.125
u_1 and u_3	0.0165	0.0001	−3.7919
All Controls	0.0943	0.0003	0.0026

TABLE 9. The $ICER_{i_{hu}}$ and $ICER_{i_{hu}}$ of each intervention

Strategy (i_{hu})	$IA_{i_{hu}}$	TC	$ICER_{i_{hu}}$
no strategy	0	0	–
u_1 Only	−0.0008	0.0657	−82.125
u_1 and u_3	0.0165	0.0001	−3.7919

TABLE 10. The $ICER_{i_{hu}}$ and $ICER_{i_{hu}}$ of each intervention

Repeating the entire process, we can determine the next most cost and less effective strategy for unaware infected population. Thus, we found that the combination of vaccination and vector elimination (u_1 and u_2) is the next more costly and less effective strategy; then it is followed by using all controls strategy (tables (6.3) and (6.3)). From table (6.3), it is concluded that using vaccination (u_1 only) has the least ICER and therefore is more cost-effective control strategy for unaware infected population.

7. CONCLUSION

The main contribution of this work is that we have developed a cholera model with two distinct groups (aware and unaware) in the susceptible and infected classes. The disease dynamics is formulated by presuming a general representation for both the direct transmission and the pathogen shedding, and the interaction between environmental vibrios and human vibrios. In addition, we study a nonlinear recovery rate which gives us more insight into the dynamics of the disease transmission in resource limited health settings. We consider a parameter b representing the number of available hospital bed over the human population. The model exhibits disease-free equilibrium which is locally asymptotically stable. Then we study the existence of endemic equilibrium. The numerical results show that dynamics of cholera infection decreases as the number of hospital beds and awareness programs increase. Therefore, in order to eliminate the disease, effort must be targeted to increasing hospital resources as well as media coverage.

Then, we applied optimal control theory to cholera model. We introduced three time-dependent control variables into the model and investigated the associated benefits of different control strategies using cost-effectiveness analysis. Using efficacy analysis, we found that the control strategy utilizing all three control variables is the most efficient strategy to eliminate cholera from both aware and unaware infected populations. On the other hand, IAR analysis of cost-effectiveness showed that the most effective way to eliminate the disease is by using vaccination and water sanitation for both aware and unaware infected populations. ICER analysis showed that vaccination only is the most effective strategy to control cholera for aware infected population, while, using water sanitation only for is the best way to control the disease for unaware infected population. Therefore, we can conclude that, the most efficient and cost-effective control strategy for the entire population is the strategy involving vaccination and water sanitation.

CONFLICT OF INTERESTS

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

REFERENCES

[1] A. Abdelrazec, J. Belair, C. Shan, and H. Zhu. Modelling the spread and control of dengue with limited public health resources. Math. Biosci. 145 (2016), 271-136.

[2] A.K. Misra, S.N. Mishra, A.L. Pathak, P. Misra, and R. Naresh. Modelling the effect of time delay in controlling the carrier dependent infectious disease-cholera. Appl. Math. Comput. 218 (2012), 11547-11557.

[3] C.C. Chavez, B. Song. Dynamical models of tuberculosis and their applications. Math. Biosci. Eng. 1(2004), 361-404.

[4] C. Torres Codeco. Endemic and epidemic dynamics of cholera: the role of the aquatic reservoir. BMC Infect. Dis. 1 (2001), 1.

[5] C. Shan, H. Zhu. Bifurcations and complex dynamics of an sir model with the impact of the number of hospital beds. J. Differ. Equ. 257 (2014), 1662-1688.

[6] D. Heyman. Cholera and other vibroses. Control of Communicable Diseases Manual 20th Edition ed. Washington DC: American Public Health Association, 2015: 102-114.

[7] D. M. Hartley, J. G. Morris Jr, and D. L. Smith. Hyperinfectivity: a critical element in the ability of v. cholerae to cause epidemics, PLoS Med. 3(2005), e7.

[8] E. Asano, L. J. Gross, S. Lenhart, L. A. Real. Optimal control of vaccine distribution in a rabies metapopulation model. Math. Biosci. Eng. 5 (2008), 219.

[9] E.J. Nelson, J. B. Harris, J. G. Morris Jr, S. B. Calderwood, and A.Camilli. Cholera transmission: the host, pathogen and bacteriophage dynamic. Nat. Rev. Microbiol. 7 (2009), 693.

[10] F. Nyabadza, J. Mawunyo Aduamah, and J. Mushanyu. Modelling cholera transmission dynamics in the presence of limited resources. BMC Res. Notes, 12 (2019), 475.

[11] I. M. ELmojtaba, S. Biswas, J. Chattopadhyay. Global dynamics and sensitivity analysis of a vector-host-reservoir model. Sultan Qaboos Univ. J. Sci. 21 (2016), 120-138.

[12] J. G. Morris, J. B. Kaper, M. M. Levine. Cholera. Clinic. Microbiol. Rev. 8 (1995), 48-86.

[13] J. B. H. Njagarah, C.B. Tabi. Spatial synchrony in fractional order metapopulation cholera transmission. Chaos Solitons Fractals, 117 (2018), 37-49.

[14] J. H. Jones, M. Salathe. Early assessment of anxiety and behavioral response to novel swine-origin in uenza a (h1n1). PLoS one, 4 (2009), e8032.

[15] J. Li, D. Blakeley, R. J. Smith. The failure of R_0. Comput. Math. Meth. Med. 2011 (2011), Article ID 527610.

[16] J. Mushanyu, F. Nyabadza, G. Muchatibaya, P. Mafuta, and G. Nhawu. Assessing the potential impact of limited public health resources on the spread and control of typhoid. J. Math. Biol. 77 (2018), 647-670.

[17] J. H. Tien and D. JD Earn. Multiple transmission pathways and disease dynamics in a waterborne pathogen model. Bull. Math. Biol. 72 (2010), 1506-1533.

[18] J. P. Tian, J. Wang. Global stability for cholera epidemic models. Math. Biosci. 232 (2011), 31-41.

[19] J. Wang, C. Modnak. Modelling cholera dynamics with controls. Canad. Appl. Math. Quart. 19 (2011), 255-273.

[20] K. A. Freedberg, J. A. Scharfstein, G. R. Seage III, E. Losina, M. C. Weinstein, D. E. Craven, A. D. Paltiel. The cost-effectiveness of preventing aids-related opportunistic infections. JAMA, 279 (1998), 130-136.

[21] K. Fiscella, P. Franks. Cost-effectiveness of the transdermal nicotine patch as an adjunct to physicians' smoking cessation counseling. JAMA, 275 (1996), 1247-1251.

[22] K. E. Nelson, C. M. Williams, N. M.H. Graham, A. Balows. Infectious disease epidemiology theory & practice, 2001.

[23] K. O. Okosun, O. Rachid, and N. Marcus. Optimal control strategies and cost-effectiveness analysis of a malaria model. BioSystems, 111 (2013), 83-101.

[24] M. Ali, A. R. Nelson, A. Lena Lopez, and D. A. Sack. Updated global burden of cholera in endemic countries. PLoS Negl. Trop. Dis. 9 (2015), e0003832.

[25] M. Halpern, Y.B. Broza, S. Mittler, E. Arakawa, and M. Broza. Chironomid egg masses as a natural reservoir of vibrio cholerae non-o1 and non-o139 in freshwater habitats. Microbial Ecol. 47 (2004), 341-349.

[26] M. A. Penta and A. Baban. Mass media coverage of hpv vaccination in romania: a content analysis. Health Educ. Res. 29 (2014), 977-992.

[27] N. Ferguson. Capturing human behaviour. Nature, 446 (2007), 733-733.

[28] R. Fotedar. Vector potential of house ies (musca domestica) in the transmission of vibrio cholerae in india. Acta Tropica, 78 (2001), 31-34.

[29] R. L. Miller Neilan, E. Schaefer, H. Gaff, K. Renee Fister, and S. Lenhart. Modelling optimal intervention strategies for cholera. Bull. Math. Biol. 72 (2010), 2004-2018.

[30] S. Al-Shanfari, I. M. ELmojtaba, and N. Al-Salti. The role of house flies in cholera transmission. Commun. Math. Biol. Neurosci. 2019 (2019), Article ID. 31.

[31] S. Lenhart and J. T. Workman. Optimal control applied to biological models. CRC Press, 2007.

[32] S. Samanta, S. Rana, A. Sharma, A. K. Misra, and J. Chattopadhyay. Effect of awareness programs by media on the epidemic outbreaks: A mathematical model. Appl. Math. Comput. 219 (2013), 6965-6977.

[33] V. Capasso and S.L. Paveri-Fontana. A mathematical model for the 1973 cholera epidemic in the european mediterranean region. Rev. Depidemiol. Sante Publ. 27 (1979), 121-132.

[34] W. H. Fleming and R. W. Rishel. Deterministic and stochastic optimal control, volume 1. Springer Science & Business Media, 2012.

[35] W. O. Kermack and A. G. McKendrick. A contribution to the mathematical theory of epidemics. Proceedings of the royal society of London. Series A, Containing papers of a mathematical and physical character, 115 (1927), 700-721.

[36] World Health Organization. Weekly epidemiological record. Weekly Epidemiological Record, 2015, 90(40):517-544.

[37] World Health Organization. Weekly epidemiological record. Weekly Epidemiological Record, 91 (2016), 432-440.

[38] Z. Mukandavire, S. Liao, J. Wang, H. Gaff, D. L. Smith, and J. Glenn Morris. Estimating the reproductive numbers for the 2008-2009 cholera outbreaks in Zimbabwe. Proc. Nat. Acad. Sci. 108 (2011), 8767-8772.