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Master Project in Mathematics

Optimal Control Problem for Cholera Epidemiology

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Victor O. L Anyuo

School of Mathematics
College of Biological and Physical sciences
Chiromo, off Riverside Drive
30197-00100 Nairobi, Kenya

Master of Science Project

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               University of Nairobi

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Abstract

Optimal control is vital in determining control policies for diseases that are infectious. A *SIR*-model with vaccination and sanitation is considered. The extant and local stability analysis of (DFE) disease-free equilibrium point is considered and its basic reproduction number (R_o) is derived. We also investigate the existence of singular control and its local optimality with an aim to find an optimal combinations of sanitation and vaccination to minimize infectious individuals (force of infection), bacteria concentration and the costs associated with the strategies.Majority of the projects done on *SIR*- models dealt with the quadratic costs function in respect to control variables. In this thesis, we consider L^1- type objective function that is linear in the control variables. We applied PMP in the characterization of the levels of optimal of the applied strategies that satisfy the necessary optimality conditions. From the computation it is shown that both the optimal controls can be singular.

Keywords: *SIR* Epidemic Models, Singular Optimal Control, PMP, Basic reproduction number, disease-free equilibrium, local stability analysis, vaccination, sanitation.

Declaration and Approval

I the undersigned declare that this project report is my original work and to the best of my knowledge, it has not been submitted in support of an award of a degree in any other university or institution of learning.

——————————————————   ——————————————————
Signature   Date

Victor O. L Anyuo
Reg No. I56/86894/2016

In my capacity as a supervisor of the candidate, I certify that this report has my approval for submission.

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Signature   Date

Dr Nelson Owuor Onyango
School of Mathematics,
University of Nairobi,
Box 30197, 00100 Nairobi, Kenya.
E-mail: onyango@uonbi.ac.ke

Dedication

This project is dedicated to my late parents Mr. and Mrs. Anyuo, my grandmother Mrs. Dorca Ghati, my late brother Kevin and to my siblings David, Resley and Linda, my extended family and to all who inspired me. Most importantly I dedicate this project to the Almighty God for always guiding and strengthening me.

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Acknowledgments

1 Introduction

1.1 Background of the Study

Since 1950s, focus has been on controlling and eliminating organisms that causes disease and due to introduction of different control strategies such antibiotics , vaccinations, treatments, sanitation and education involvements brought a positive impact in combating diseases. However, different factors such as medicine resistant by the microorganisms, environmental evolution and urbanization changes has led to new infections and re-emergence of existing diseases such as cholera which continued to erupt occasionally.

The application of mathematical modeling in epidemiology provides deeper insight in understanding the epidemic features to the spreading law and control measures of the epidemic.

Global incidence of cholera has been significantly reduced through various applications of control strategies such as vaccination, sanitation, treatment and education though it still remains an important public health problem. Cholera being a critical diarrhoeal infection that is brought by the taking of contaminated food or water with the bacterium **Vibrio cholerae**.

According to WHO (2018), about 1.4 million to 5.1 million incidences of cholera and around 145,000 deaths arose due to cholera outbreak. The cholera dynamics is also influenced by the interactions between pathogen,environment and human, as stated by Nelson et al. (2009), which lead to two major pathways which are environment-human (vertical) and human to human (horizontal) transmissions. The number of cholera cases has continued to be on the rise as reported by WHO. In 2016; from 38 countries about 2,420 deaths from 132,121 cases were reported. Due to limitations in surveillance systems, the figures may on the lower side.

Mathematical modeling provides a deeper knowledge into the underlying structures for the spread of diseases and suggesting controls/interventions that are effective. As Hethcote (2000) stated that successful eradication depends on available medical infrastructure and the capacity to discern the structure in transmitting the diseases and also the execution of optimal control interventions and policy implementations.

Optimal control theory is therefore applied widely in the controll of the spread of infectious diseases and also in decision making processes. In their work,Gaff and Schaefer

(2009) used the application of optimal control to consider different variations of standard models in epidemiology and they also computed optimal interventions numerically thus also investigating the responsivity of the optimal solutions. According to Kirschner et al. (1997), they applied the optimal strategies process to determine the optimal strategy (treatment) for dispensing drugs.

This thesis, we include the two optimal strategies in our *SIR*-model involving L^1 - type objective function which are linear in the control variables. We address on how to optimally combine the two strategies such that the force of infection is controlled while the cost of implementing the strategies is also minimized.

1.2   Problem Statement

Cholera is described as one of the most infectious diseases in humans. Even though the incidence has been reduced globally through application of different control strategies, it still remains a public health problem.

In Kenya as per Press release on disease outbreak by the Ministry of Health dated 11th June,2018 showed that a total of 4,954 cases of cholera with 75 deaths were reported since the beginning of the year with a total of 19 counties affected. This categorically shows that Cholera still remains an important public health problem in Kenya that needs to be tackled.

Although, there have been a number of work over the years on Cholera, but the emphasis has been on a quadratic objective (L^2) functions in measuring the cost of control strategies and to reduce the number of infections. L^2 objective function leads to continuous control functions that are difficult to administer in real life situation. This situation therefore motivated us to apply the *SIR* differential equation to effectively model and analyze the disease by combining vaccination and sanitation of a L^1 - type objective function.

1.3   Objectives

The overall objective:

- To theoretically investigating and proof the existence and local optimality of singular control.

The following are the specific objectives:

- To investigate the role of the combined (R_0) Basic Reproductive Number.

- To ascertain stability analysis and equilibrium point (DFE) of the model.

- Studying the effect of the two strategies in the spread of the disease.

1.4 Significance of Study

Cholera epidemiology has been extensively studied especially in developed countries. However, few studies have been done in developing countries like Kenya, hence there are no enough mathematical publication looking at cholera epidemics in Kenya. Also, there is little control programme against the spread of the cholera. Therefore, this thesis will assist decision makers to see the need to implement vaccination and sanitation programme against cholera transmission. This work can also be used by scientists to develop appropriate models for a particular disease and to guide public health professionals to make better strategies for controlling the disease.

2 Literature

2.1 Introduction

Infectious disease is a global health problem and more works are being done by different scientists to develop mathematical models that offers consequential role in describing the transmission dynamics of the diseases and effects of various programs that can be used to control the outbreak.

2.2 Literature Relevant to this Thesis

Mathematical modeling is a vital tool in analyzing the infectious disease dynamics. Many models that have been formulated and analyzed do explain the transmission of cholera dynamics.

In 1979, Capasso and Paveri-Fontana (1979) proposed a mathematical model where they studied cholera epidemic which occurred in the region of Mediterranean in 1973. This model had components which included the pathogen concentration in water, y_1, and the persons infected, y_2. This model was then represented as:

$$\begin{cases} \frac{dy_1}{dt} = -a_{11}y_1 + a_{12}y_2 \\ \frac{dy_2}{dt} = g(y_1) - a_{22}y_2 \end{cases} \quad (1)$$

where $a_{ij}'s$ are positive constants and the function g (y_1) is the rate of an incidence of an infection and a linear function. Codeço (2001), extended the above model and she considered the role of environment (water) reservoir in cholera endemic maintenance and she introduced the susceptible compartment in the population of the model. Thus the model had three components as shown:

$$\begin{cases} \dot{S} = d(N-S) - b\frac{D}{P+B}S \\ \dot{I} = b\frac{D}{P+B}S - cI \\ \dot{D} = fI - nD \end{cases} \quad (2)$$

where I and S represents the infected and susceptible individuals respectively, D is the **vibrios** concentration in the aquatic environment. N represents total human population, d represents the birth/death rate that occurs naturally, c stands for the rate of recovery , f represents shedding rate to the environment by infected person, and n is the rate of

decay of **vibrios**, *b* being the rate of contact rate with the infected environment and P is the concentration of the pathogens that yields a chance of 50% of an individual to be infected. This model only assumed the environment- human mode of transmission just as stated by Capasso and Paveri-Fontana (1979). According to Hartley et al. (2005), where they modified Codecco's work and they included the hyperinfectious of the bacterium in the model and they emphasized on the importance of horizontal transmission.

In their work, Mukandavire et al. (2011), clarified the work done by Hartley et al. (2005) in studying the 2008 to 2009 Zimbabwe cholera outbreak and in this model,they explored two types of cholera transmission that is human to human (horizontal) and environment to human transmissions:

$$\begin{cases} \frac{dS}{dt} & = \mu N - \beta_1 \frac{B}{K+B} S - \beta_2 SI - \mu S \\ \frac{dI}{dt} & = \beta_1 \frac{B}{K+B} S - \beta_2 SI - (\gamma + \mu) I \\ \frac{dR}{dt} & = \gamma I - \mu R \\ \frac{dB}{dt} & = \xi I - \sigma B \end{cases} \tag{3}$$

where β_1 is the rate at which human get infected from the contaminated water and β_2 is the rate at which the bacterium is transmitted between persons. Wang and Modnak (2011), extended the model to involve three interventions which are sanitation, treatment and vaccination and their computed analysis showed that, these controls measures applied are closely linked and that the power of one measure as an optimal strategy depended on its relative cost and the setting in the population.

Yusuf and Benyah (2012) presented Optimal intervention for treatment and vaccination for an *SIR* model, where they applied on a variable size of the population and formulated the optimal problem for the controls. The main goal was to get combined optimal interventions to minimizing the force of infection and weight (cost) in a particular strategy. Their analysis showed that disease-free equilibrium (DFE) was stable asymptotically when the basic reproduction number (R_0) is less than one while the endemic equilibrium exist when basic reproduction ratio (R_0) is greater than one. In conclusion, the results indicate that if it is more expensive in vaccinating than treating, then resources should be put more to treat until the prevalence reduces significantly. This option,though gives rise to infected persons since the susceptible are prone to the disease. If treating is quite expensive then more resources are put in vaccinating. This drastically led to decrease in the susceptible and infectives. If the two intervention measures are equally costly, then the optimal way to eradicate the outbreak is to put more resources in vaccination control and less resources in treatmenting so that the epidemic is pushed below a threshold then we apply more of treatment strategy.

According to Gaff and Schaefer (2009), they indicated that mathematical models are used in investigating dynamics and the control of infectious diseases. They considered the

variations of standard SEIR, SIR and SIRS models in determining the sensitivity of these models to various parameter values. In their conclusion,they stated that Optimal control theory was applied to give the most strategy that reduced the number of infected individuals while efficiently balancing the two strategies applied with various weight scenarios.

Therefore in Optimal control we determine the control and state trajectories for a dynamic system in a period of time and at the same time minimizing the objective function.Based on dynamics models by Hethcote (2009) and Hethcote (2000), various strategic control schedules have been studied by applying techniques in the optimal. [Lenhart and Workman (2007), Silva and Torres (2012)]. Most of done journals assume a L^2 objective in measuring the weight of control strategy applied. According to Schättler et al. (2014), L^2-type are not suitable in biological approach because they lead to continuous control functions that are difficult to administer in practical applications. Therefore we study sanitation and vaccination schedules in the *SIR* model by applying L^1-objective.

3   Methodology

3.1   Introduction

This chapter is mainly concerned with developing a *SIR* model to control cholera transmission in Kenya, understanding threshold conditions for the cholera outbreak and also to describing the stability of a local steady-state solutions.

3.2   Model Formulation

With an aim to gain deeper insight of the cholera disease outbreak, different mathematical models have been done for example [Neilan et al. (2010), and Codeço (2001)]. Effective strategies have been designed basing on these works;assumptions, variables and parameters have been simplified in formulating models in epidemiology with an aim in predicting and understanding the spread of cholera outbreak and therefore to evaluate different control measures to be applied. Furthermore, mathematical model provides an ideal results such as basic reproductive number , contact rate and other numerical thresholds.

The most common methods for interventions in infectious diseases include either removal or vaccination of susceptible individuals or the application of treatments or quarantine to infected individuals.

The parameter which governs the spread of diseases in these models is known as basic reproductive number R_o. If $R_o < 1$, then the disease dies out from the population since the rate of disease being transmitted is less than an individual on average, ideally implying no new transmissions. Secondly, if $R_o > 1$, this will lead to the cholera outbreak. We therefore apply Pontryagin's Maximum Principle in formulating an optimal control problem , optimal characterization and to attain the optimality system.

3.2.1   The mathematical model

The goal is to develop a model for cholera that involves detailed biological concepts and also to narrate for the intervention strategies. We use this model of an epidemic, imposing vaccination and sanitation on it and then determine an optimal strategy for rolling out

the control strategies. We do this optimization for the case of *SIR* model with simple constraints. Being that the control variables is linear in Hamiltonian function and applying PMP gives either singular, bang-bang or a combination of the two.

SIR model Assumptions

The *SIR* model is applied in order to analyze the compartments (susceptible, infected and recovered) in a population. The assumptions to be used include:

- The population of individuals varies.

- Gender,age and social status, does not affect the probability of one being infected.

- Immunity is not inherited.

- The model has constant population size (i.e., there is no extra disease-induced mortality.

- Vaccination is introduced to the susceptible population

- Water sanitation leads to death of ***vibrios***

Let *S(t)* represent susceptibles at time *t*, *I(t)* represents the infectious persons at *t* and *R(t)* represents the recovered persons in time *t*. We also denote the total number of individuals by , *N (t) = S(t) + I(t) + R(t)* and assume that all births enter the susceptibles class *S(t)*.
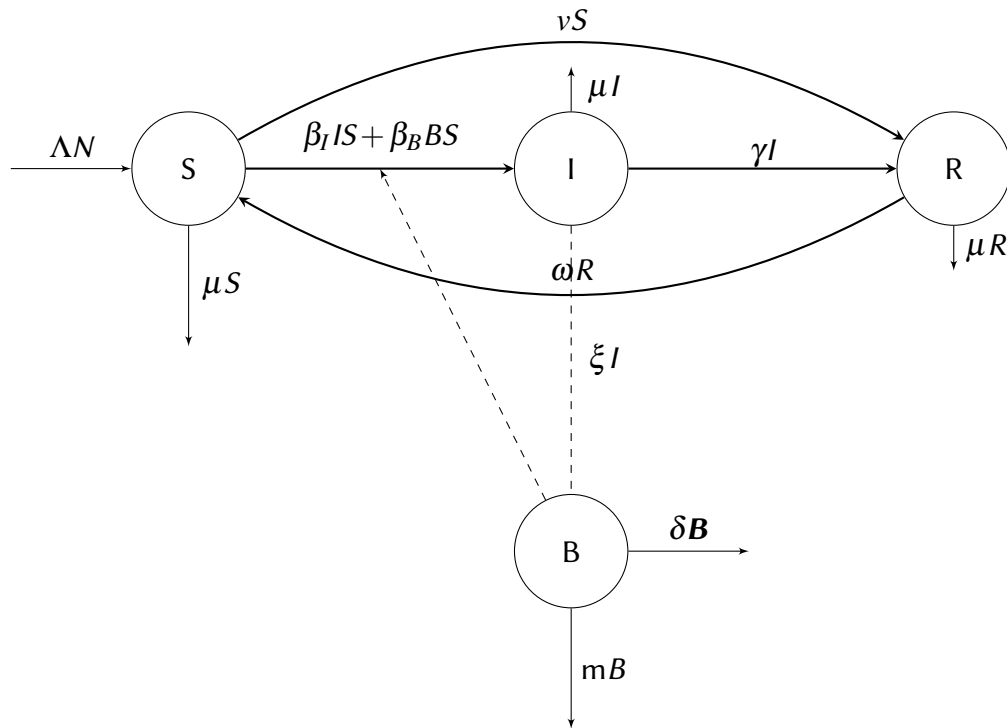
Figure 1. Simplified diagram of cholera transmission and its control model

The model parameters are defined:

- Λ - recruitment rate,

- β_B - transmission rate from environment to human,

- β_I - transmission rate from human to human,

- μ - rate of natural mortality,

- γ - rate of recovery,

- v(t) - rate of vaccination,

- m(t) - sanitation rate,

- B(t) - bacterial concentration in water,

- ξ - shedding rate of bacteria by infectious population,

- ω - rate at which recovered humans are susceptibles,

- δ - bacterial death rate,

3.2.2 The SIR Model Equation

From the stated assumptions, defined state variables and chosen parameters and the above compartmental diagram, the system of differential equations describing the dynamics of Cholera outbreak in Kenya are formulated below with their existing conditions:

$$\begin{cases} \dot{S} = \Lambda N - (\mu + v + \beta_I I + \beta_B B)S(t) + \omega R(t), & S(0) = S_0 \geq 0 \\ \dot{I} = (\beta_I I + \beta_B B)S(t) - (\gamma + \mu + \xi)I(t), & I(0) = I_0 \geq 0 \\ \dot{R} = \gamma I(t) - \mu R(t) - \omega R(t) + v(t)S(t), & R(0) = R_0 \geq 0 \\ \dot{B} = \xi I(t) - (m + \delta)B(t), & B(0) = B_0 \geq 0 \end{cases} \qquad (4)$$

The above solution model is biologically feasible for all times. The solution domain is

$$\Omega = \left[(S, I, R, B) \in \mathfrak{R}_+^4 : S \geq 0, I \geq 0, R \geq 0, B \geq 0, R + I + S = N \right]$$

Since $R = N - S - I$, we consider a new differential equation of the system (4)

$$\begin{cases} \dot{S} = \Lambda N - (\mu + v + \beta_I I + \beta_B B)S(t) + \omega R(t), & S(0) = S_0 \geq 0 \\ \dot{I} = (\beta_I I + \beta_B B)S(t) - (\gamma + \mu + \xi)I(t), & I(0) = I_0 \geq 0 \\ \dot{N} = \Lambda N(t) - \mu N(t) - \xi I(t), & N(0) = N_0 \geq 0 \\ \dot{B} = \xi I(t) - mB(t) - \delta B(t), & B(0) = B_0 \geq 0 \end{cases} \qquad (5)$$

3.3 Equilibrium point and Local Stability

To determine the model stability, we need to obtain the equilibrium points of equation (5) of the model when the right-hand side of a equation(5)s is set to zero.

Equilibrium points

The ordinary differential equation (5) has two equilibrium points:

- **In disease-free equilibrium (DFE)** the disease is absent in the population. In absence of the disease, this implies that $I = B = 0$ and is obtained by setting $\frac{dS}{dt} = \frac{dI}{dt} = \frac{dB}{dt} = 0$

$$\dot{S} = 0 = \Lambda N - (\mu + v + \beta_I I + \beta_B B)S(t) + \omega R(t),$$

$$0 = \Lambda N - (\mu + v)S$$

$$S_0 = \frac{\Lambda N}{(\mu + v)}$$

$$DFE = (S_0, I_0, B_0,) = (\frac{\Lambda N}{(\mu + v)}, 0, 0)$$

- **Endemic equilibrium (E)** is a point where the disease spreads in the population.

$$E^1 = (S^*, I^*, B^*)$$

where

$$B^* = \frac{\xi I^*}{m + \delta} \tag{6}$$

$$S^* = \frac{(m + \delta)(\gamma + \mu + \xi)}{(m + \delta)\beta_I + \beta_B \xi} \tag{7}$$

$$I^* = \frac{\Lambda N[(m + \delta)\beta_I + \beta_B \xi] - (\mu + v)(m + \delta)(\gamma + \mu + \xi)}{(\delta + \mu + \xi)[(m + \delta)\beta_I + \beta_B \xi]} \tag{8}$$

The Model's Basic Reproductive Number

The model's basic reproduction number (R_0), as shown by Kermark and Mckendrick (1927), to be average number of Secondary infections that occurs if an infectious person is brought into a population of the susceptible.

Inorder to analyze equilibrium points, we need to find the (R_0). It is a vital parameter that sets the threshold in the epidemiological study of a disease to help in the prediction of an outbreak and for the evaluation of applied interventions. Therefore, the disease stability depends on R_0.

Therefore, for a local asymptotic stability to occur in a disease-freee equilibrium, R_0 < 1 and the endemic is unstable, this means that the disease is dying out of the population. WhenR_0 > 1, indicates that an infected person causes more additional infection , giving rise to the outbreak,thus endemic will be stable, whereas we have unstable DFE. When R_0 = 1, then the outbreak becomes constant within the population.

To compute R_0 on the system equation(5), we introduce next generation method from which the biggest value of the spectral radius of FV^{-1} gives the R_0.

- **F** - Rate at which new infected enter compartment i

- **V** - Denotes the rate of transferring individuals into and out of compartment i

$$\mathbf{F} = \begin{bmatrix} \beta_B BS + \beta_I IS \\ 0 \end{bmatrix} \quad \mathbf{V} = \begin{bmatrix} (\gamma + \mu + \xi)I \\ (\delta + m)B - \xi I \end{bmatrix}$$

F and **V** are put in form of vectors as **x**= (I , **B**)

$$\mathbf{F} = \begin{bmatrix} \beta_I S_o & \beta_B S_o \\ 0 & 0 \end{bmatrix} \quad \mathbf{V} = \begin{bmatrix} (\gamma + \mu + \xi) & 0 \\ -\xi & (\delta + m) \end{bmatrix}$$

Therefore V^{-1} is given as

$$V^{-1} = \frac{1}{(\delta + m)(\mu + \xi + \gamma)} \begin{bmatrix} (\delta + m) & 0 \\ \xi & (\mu + \xi + \gamma) \end{bmatrix}$$

$$FV^{-1} = \begin{bmatrix} \beta_I S_0 & \beta_B S_0 \\ 0 & 0 \end{bmatrix} \begin{bmatrix} \frac{1}{(\mu+\xi+\gamma)} & 0 \\ \frac{\xi}{(\mu+\xi+\gamma)(m+\delta)} & \frac{1}{(m+\delta)} \end{bmatrix} = \begin{bmatrix} \frac{\beta_I S_0}{(\mu+\xi+\gamma)} + \frac{\beta_B S_0 \xi}{(\mu+\xi+\gamma)(m+\delta)} & \frac{\beta_B S_0}{(m+\delta)} \\ 0 & 0 \end{bmatrix}$$

From the characterization equation, the basic reproduction number of the system is as

$$R_0^c = \rho(FV^{-1}) = \frac{\beta_I S_0}{(\gamma + \mu + \xi)} + \frac{\beta_B S_0 \xi}{(\gamma + \mu + \xi)(\delta + m)}$$

Replacing $S_0 = (\frac{\Lambda N}{(\mu+v)})$. The basic reproductive number there becomes

$$R_0^c = \frac{\beta_I \Lambda N}{(\mu + \xi + \gamma)(v + \mu)} + \frac{\beta_B \Lambda N \xi}{(\mu + \xi + \gamma)(m + \delta)(v + \mu)} \equiv R_I + R_B$$

Where R_B is the partial basic reproductive number induced by induced by environment-human and R_I is partial basic reproductive number induced by human to human transmission.

Disease Free Equilibrium (DFE) Local Stability

Here we investigate the linear local stability of the our model by applying equation(5) through computing its Jacobian matrix.

Theorem. DFE is said to be locally asymptotically stable if $R_0 < 1$ otherwise unstable if $R_0 > 1$.

The computed eigenvalues from Jacobian matrix gives the solutions of the equations characteristic:

$$[\mathbf{J} - \lambda I] = 0$$

If the computed eigenvalues are all negatives, then we conclude that the disease free equilibrium is asymptotically stable.

Proof: The characteristic equation of the system is obtained from equation (5) and thus given by:

$$J = \begin{bmatrix} -(\mu+v)-\lambda_1 & -\beta_I \frac{\Lambda N}{(\mu+v)} & -\beta_B \frac{\Lambda N}{(\mu+v)} \\ 0 & \beta_I \frac{\Lambda N}{(\mu+v)} - (\gamma+\mu+\xi) - \lambda_2 & \beta_B \frac{\Lambda N}{(\mu+v)} \\ 0 & \xi & -(m+\delta)-\lambda_3 \end{bmatrix} \tag{9}$$

Taking one of the eigenvalues to be $-(\mu+v)$, we apply Routh Hurwitz criterion as shown by Li and Wang (1998), by checking the signs of the eigenvalues of the reduced matrix as shown:

$$\begin{bmatrix} \beta_I \frac{\Lambda N}{(\mu+v)} - (\gamma+\mu+\xi) & \beta_B \frac{\Lambda N}{(\mu+v)} \\ \xi & -(m+\delta) \end{bmatrix}$$

obtaining determinant:

$$-(m+\delta)[\beta_I \frac{\Lambda N}{(\mu+v)} - (\gamma+\mu+\xi)] - \beta_B \frac{\Lambda N \xi}{(\mu+v)}$$

Making the determinant to be positive, we have:

$$(\delta+m)\beta_I \frac{\Lambda N}{(v+\mu)} + \beta_B \frac{\Lambda N \xi}{(v+\mu)} < (\delta+m)(\xi+\mu+\gamma)$$

diving both sides by $(m+\delta)(\xi+\mu+\gamma)$ gives:

$$\frac{\beta_I \Lambda N}{(\xi+\mu+\gamma)(\mu+v)} + \frac{\beta_B \Lambda N \xi}{(\xi+\mu+\gamma)(\delta+m)(v+\mu)} < 1$$

but

$$R_0^c = \frac{\beta_I \Lambda N}{(\gamma+\mu+\xi)(\mu+v)} + \frac{\beta_B \Lambda N \xi}{(\gamma+\mu+\xi)(\delta+m)(v+\mu)}$$

Thus

$$R_0^c < 1$$

This therefore means that the model is linearly stable and hence there is no epidemic.

3.4 Optimal Control Strategies

The objective is to choose a combined strategy of vaccination and sanitation $(v^*(t), m^*(t))$ in such a way to minimize the value of objective function,force of infection and also to minimize the cost of strategies. According to Maurer and De Pinho (2014), they suggested that a L^2 function is not recommended for biological or biomedical problems/models.

Therefore, we take into account to apply L^1 cost function that appears to be linear in the Hamiltonian and interventions used.
The objective function, J given as:

$$J(v, m) = \int_{t_0}^{t_f} [a_0 I(t) + a_1 v S(t) + a_2 m B(t)] dt \qquad (10)$$

- $a_0 I(t)$ - This term represents the infected population.

- $a_1 v S(t)$ - This term, where a_1 is a positive parameter associated with the control $v(t)$, represents the weight of vaccination within the susceptible.

- $a_2 m B(t)$ - This term, where a_2 is a positive parameter associated with the control m(t), represents the cost of sanitation applied to the environment.

With $a_0 > 0$, $a_1 > 0$ and $a_2 > 0$, the infected group is to be minimized I by reducing force of infection and at the same time reducing the weights of vaccination v(t) and sanitation m(t). The intervention function v(t) bounded between 0 and 1 ($0 \le v(t) \le 1$)(represents the fraction of susceptible that needs to be vaccinated). When v(t) tends towards 1, then its failure is low but with high cst implementation.(if the value $v^*(t) = 1$ it characterizes an effective vaccine but most of these cholera vaccines have low protective efficacy of around 85%. This then indicates that the upper bound of this control is hardly attainable).Sanitation is denoted by $m(t)$ and is scaled between $0 \le m(t) \le 1$. We reduce the rate of vibro ingestion by putting more effort on sanitation, thereby reducing the transmission rate of cholera(if $m^*(t) = 1$ would signify no transmission of pathogens, especially if there is good sanitation).

3.4.1 The solution of Basic Optimal Control Problem of the Model.

The necessary optimality conditions

We take into account to minimize our objective function $J(v,m)$ with respect to v and m subject to the conditions and constraints. The general procedure of optimal control process in an epidemiological model involves the following processes:

- identifying permissible controls applicable to the model

- setting up the objective function with controls

- constructing the Hamiltonian

- evaluating costate variable (adjoint functions)

- identifying the threshold controls that minimise the Hamiltonian

The basic optimal control problem in compact contains:

$$OCP = \begin{cases} & = \int_{t_0}^{t_f} [a_0 I(t) + a_1 v S(t) + a_2 m B(t)] dt \\ \dot{S} & = \Lambda N - (\mu + v + \beta_I I + \beta_B B) S(t) + \omega R(t), S(0) = S_0 \geq 0 \\ \dot{I} & = (\beta_I I + \beta_B B S) S(t) - (\gamma + \mu + \xi) I(t), I(0)=I_0 \geq 0 \\ \dot{N} & = (\Lambda - \mu) N - \xi I = N_0 \geq 0 \\ \dot{B} & = \xi I(t) - (m + \delta) B(t), B(0)=B_0 \geq 0 \\ & 0 \leq m(t) \leq 1 \\ & 0 \leq v(t) \leq 1 \end{cases} \tag{11}$$

The vector form of equation (11) is given by:

$$\frac{dX}{dt} = \mathbf{f(X)}$$

where

$$\mathbf{X} = (S, I, N, B)^T$$

and we simplify the control double by $u^* = (v, m)$ Therefore we consider the linear system of ODE:

$$\dot{x} = f(\mathbf{x}) + g_1(\mathbf{x})\mathbf{v} + g_2(\mathbf{x})\mathbf{m} \tag{12}$$

$$f(\mathbf{x}) = \begin{bmatrix} \Lambda N - (\beta_I I + \beta_B B + \mu) S(t) + \omega R(t) \\ (\beta_I I + \beta_B B) S(t) - (\mu + \xi + \gamma) I(t) \\ \Lambda N - \xi I - \mu N \\ -\delta B(t) + \xi I(t) \end{bmatrix} \tag{13}$$

$$g_1(\mathbf{x}) = \begin{bmatrix} -S \\ 0 \\ 0 \\ 0 \end{bmatrix} \tag{14}$$

$$g_2(\mathbf{x}) = \begin{bmatrix} 0 \\ 0 \\ 0 \\ -m \end{bmatrix} \tag{15}$$

We denote the integrand of our objective by $L(\mathbf{x}, \mathbf{m}, \mathbf{v}) = a_0 I(t) + a_1 v S(t) + a_2 m B(t)$. We therefore analyze the necessary optimality conditions of the PMP. Since we are minimizing equation (5), the standard Hamiltonian function is given by:

$$H = H(\mathbf{x}, \mathbf{m}, \mathbf{v}, \lambda)$$

$$H = L(\mathbf{x}, \mathbf{m}, \mathbf{v}) + \lambda \left(f(\mathbf{x}) + g_1((\mathbf{x})v) + g_2((\mathbf{x})m) \right)$$

$$H = a_0 I(t) + a_1 v S(t) + a_2 m B(t) + \lambda_S \frac{dS(t)}{dt} + \lambda_I \frac{dI(t)}{dt} + \lambda_N \frac{dN(t)}{dt} + \lambda_B \frac{dB(t)}{dt} \tag{16}$$

The adjoint equations formed are:

$$\begin{cases} \dot{\lambda_S} &= -a_1 v(t) + \lambda_S [\beta_I I(t) + \beta_B B(t) + \mu + v(t)] - \lambda_I [\beta_I I(t) + \beta_B B(t)] \\ \dot{\lambda_I} &= -a_0 + \lambda_S \beta_I S(t) - \lambda_I [\beta_I S(t) - (\gamma + \mu + \xi)] + \lambda_N \xi - \lambda_B \xi \\ \dot{\lambda_N} &= -\lambda_S \Lambda - \lambda_N [\Lambda - \mu] \\ \dot{\lambda_B} &= -a_2 m(t) + \lambda_S \beta_B S(t) - \lambda_I \beta_B S(t) + \lambda_B [m + \delta] \end{cases} \tag{17}$$

The Optimality condition (M) reads,

$$H = \min_{v,m} [a_0 I(t) + a_1 v(t) S(t) + a_2 m(t) B(t) + \lambda_S \frac{dS(t)}{dt} + \lambda_I \frac{dI(t)}{dt} + \lambda_N \frac{dN(t)}{dt} + \lambda_B \frac{dB(t)}{dt}] \tag{18}$$

Since H is linear in the controls, therefore to compute the minimum condition for the equation (18) for the Hamiltonian, we differentiate the Hamiltonian with the respect to the vaccination (v) and sanitation (m) to obtain the switching functions and then we take int the account the switching functions $\Phi_v(t)$ and $\Phi_m(t)$ and seperate the minimization problem into two to enable easy solution of the problem as

$$\Phi_v(t) = H_v = a_1 S - \lambda_S S$$

and

$$\Phi_m(t) = H_m = a_2 B - \lambda_B B$$

The control is said to be bang-bang if the switching function $\Phi_i(t) = 0$ is not contained over a period of time but happens at finitely many different points. Bang-bang occurs at the extreme values of the control set. Banb-bang is said to be a piecewise constant function that switches only between the lower and upper boundaries. Secondly, the control is said to be singular, if the switching function $\Phi_i(t) = 0$ and its derivatives vanish over an open interval. The switch times are times when the optimal control switches from lower to upper boundary or vice-versa or switches to singular control. Lenhart and Workman (2007), stated that a bang- bang problem must be proven analytically before being solved

numerically by applying forward-backward sweep method.

Ledzewicz and Schättler (2002) stated that if $\Phi_i(t)$ and its derivatives vanish over an open interval, then it is referred as singular control. We theoretically investigate the existence and local optimality of singular control for the our as shown by Ledzewicz and Schättler (2011).
We synthesize the Optimal controls by analyzing the switching functions. If $\phi(\iota) = 0$ but $\dot{\phi}(\iota) \neq 0$ then the control has a switch at time ι.
In this thesis, we analyze the existence and local optimality of singular controls.
The controls being linear in the Hamiltonian , the minimum condition, therefore, requires

$$
v^*(t) = \begin{cases} 0 & if \quad \Phi_v(t) > 0 \\ 1 & if \quad \Phi_v(t) < 0 \\ singular & if \quad \Phi_v(t) = 0 \end{cases} \quad and \quad m^*(t) = \begin{cases} 0 & if \quad \Phi_m(t) > 0 \\ 1 & if \quad \Phi_m(t) < 0 \\ singular & if \quad \Phi_m(t) = 0 \end{cases} \quad \textbf{(19)}
$$

Singular Extremals

To investigate the singular case, let $\Phi_i(t) = 0$ on some interval. Taking into consideration that the minimum condition of Hamiltonian equation (18) does not determine the value of the controls, but we have to differentiate the switching functions of the the singular controls until that point of time where control value shows in the derivative,for example,say $\Phi^{(k)}(t)$, then using the results obtained from the derivative to solve for the controls and we therefore define the singular optimal control if the value falls between 0 and 1. According to Krener (1977), he stated that for an input single system which is linear in the control,k=2r, where r is defined as an order of singular arc which either varies with time over an interval but when it becomes a constant it forms part of the necessary condition for optimality of a singular arc of order r, therefore termed as Generalized Legendre-Clebsch condition that is given as

$$
(-1)^r \frac{\partial}{\partial u} \frac{d^{2r}}{dt^{2r}} \frac{\partial H}{\partial u} \geq 0
$$

along the extremals.$\frac{\partial H}{\partial u} = \Phi$ is the switching function.
We differentiate the relations $\Phi_i(t) = 0$. Where i = v, m

$$
\dot{\Phi}_i = 0
$$

and we further compute the singular control value if it is not present in the first equation by obtaining the 2r derivative that will yield the optimal control.

$$
\frac{d^{2r}}{dt^{2r}}(\Phi_i(t))
$$

Examining the Generalized Legendre-Clebsch condition (GLC) for the singular control to be optimal, the derivative of $\frac{d^{2r}}{dt^{2r}}(\Phi_i(t))$ with respect to control needs to be negative as stated by Krener (1977).

Theorem 1 : For **vaccination** we obtain:

$$\Phi_v(t) = a_1 S - \lambda_S S$$

$$\dot{\Phi}_v = \lambda_I S[\beta_I I + \beta_B B] - \lambda_S S(\mu + \beta_I I + \beta_B B)$$

From $\Phi_v(t) = a_1 S - \lambda_S S = 0$ we get $\lambda_S = a_1$. Substituting this into the derivative , we obtain

$$\dot{\Phi}_v = \lambda_I S[\beta_I I + \beta_B B] - a_1 S(\mu + \beta_I I + \beta_B B)$$

To compute the singular control, we additionally check on the second derivatives $\frac{d^2}{dt^2}\Phi_v = \ddot{\Phi}_v = 0$

$$\ddot{\Phi}_v = \lambda_I \dot{S}[\beta_I I + \beta_B B] + \dot{\lambda_I} S[\beta_I I + \beta_B B] + \lambda_I S[\beta_I \dot{I} + \beta_B \dot{B} - a_1 \dot{S}(\mu + \beta_I I + \beta_B B) - a_1 S(\mu + \beta_I \dot{I} + \beta_B \dot{B})]$$

$$= \lambda_S S \beta_I(\beta_I IS + \beta_B BS) + (\lambda_I \beta_B S - a_1 \beta_B S)(\xi I - mB - \delta B) + (\lambda_I \beta_I I + \lambda_I \beta_B B - a_1 \mu - a_1 \beta_I I - a_1 \beta_I S)$$
$$(\Lambda N - \mu S - \beta_I IS - \beta_B BS + \omega R) - \beta_I IS(a_0 - \lambda_N \xi - a_1 \xi) + \beta_B BS(-a_0 + \lambda_I \beta_I(\gamma + \mu + \xi) - \lambda_N \xi - a_1 \xi)$$
$$+ a_1 \beta_I S((\gamma + \mu + \xi) - (\beta_I IS + \beta_B BS)) - vS(\lambda_I \beta_I SI + \lambda_I \beta_B SB - a_1 \mu - a_1 \beta_I IS - a_1 \beta_B SB)$$

The equation above is written in the form:

$$\ddot{\Phi_v}(t) = \Psi_v(t)v(t) + \Psi_1(t)$$

Therefore

$$v_{sing} = -\frac{\Psi_1}{\Psi_v}$$

and $\Psi_v \neq 0$

Let

$$\Psi_v = S(\lambda_I \beta_I SI + \lambda_I \beta_B SB - a_1 \mu - a_1 \beta_I IS - a_1 \beta_B SB)$$

and

$$\Psi_1 = \lambda_S S \beta_I(\beta_I IS + \beta_B BS) + (\lambda_I \beta_B S - a_1 \beta_B S)(\xi I - mB - \delta B) + (\lambda_I \beta_I I + \lambda_I \beta_B B - a_1 \mu - a_1 \beta_I I$$
$$- a_1 \beta_I S)(\Lambda N - \mu S - \beta_I IS - \beta_B BS + \omega R) - \beta_I IS(a_0 - \lambda_N \xi - a_1 \xi) + \beta_B BS(-a_0 + \lambda_I \beta_I(\gamma + \mu + \xi) - \lambda_N \xi - a_1 \xi)$$
$$+ a_1 \beta_I S((\gamma + \mu + \xi) - (\beta_I IS + \beta_B BS))$$

For the singular vaccination control to be optimal, then the Generalized Legendre-Clebsch Condition (GLC) inequality holds as stated below:

$$\frac{\partial}{\partial v}[\frac{d^2}{dt^2}\Phi_v] = -S(\lambda_I\beta_I SI + \lambda_I\beta_B SB - a_1\mu - a_1\beta_I IS - a_1\beta_B SB)$$

Therefore, the equation belows shows the control characterization:

$$v^*(t) = \begin{cases} 0 & if & \Phi_v(t) > 0 \\ 1 & if & \Phi_v(t) < 0 \\ singular & if & \Phi_v(t) = -\frac{\Psi_1(t)}{\Psi_v(t)} \end{cases} \tag{20}$$

Thus, the control is optimal at t only if $\Psi_v(t) = 0$ and $0 \leq -\frac{\Psi_1}{\Psi_v} \leq 1$

Theorem 2 : Sanitation
Let us assume that m*(t) is singular

$$\Phi_m = a_2 B - \lambda_B B = 0$$

Obtaining the derivative:

$$\dot{\Phi}_m = \lambda_I\beta_B BS - \lambda_S\beta_B BS - \lambda_B\delta B$$

Replacing $\lambda_B = a_2$ to the derivative

$$\dot{\Phi}_m = \lambda_I\beta_B BS - \lambda_S\beta_B BS - a_2\delta B$$

considering the control variable m does not surface in the first derivative, we check on the second derivative

$$\frac{d^2}{dt^2}\Phi_m = \ddot{\Phi}_m = 0$$

$$\ddot{\Phi}_m = \dot{S}(\lambda_I\beta_B B - \lambda_S\beta_B B) + \dot{B}(\lambda_I\beta_B S - \lambda_S\beta_B S - a_2\delta) + \beta_B SB(\dot{\lambda}_I - \dot{\lambda}_S)$$

we obtain

$$\ddot{\Phi}_m = -mB(\lambda_I\beta_B S - \lambda_S\beta_B S - a_2\delta B) + (\lambda_I\beta_B S - \lambda_S\beta_B S)(\xi I + \Lambda N + \omega R) + \beta_B BS(a_0 + a_1 v + \lambda_S\beta_I S - \lambda_I\beta_I S + \lambda_S\beta_B S + \lambda_I\beta_B B + \lambda_I I(\gamma + \mu + \xi) + \lambda_N\xi - a_2\xi + a_2\xi\delta + \lambda_S\beta_B SB\delta)$$

The equation aboveis thus written in the form:

$$\ddot{\Phi}_m(t) = \Psi_m(t)m(t) + \Psi_2(t) = 0$$

Therefore

$$m_{sing} = -\frac{\Psi_2}{\Psi_m}$$

and $\Psi_v \neq 0$

Let

$$\Psi_m = B(\lambda_I \beta_B S - \lambda_S \beta_B S - a_2 \delta B)$$

and

$$\Psi_2 = (\lambda_I \beta_B S - \lambda_S \beta_B S)(\xi I + \Lambda N + \omega R) + \beta_B B S(a_0 + a_1 v + \lambda_S \beta_I S$$
$$- \lambda_I \beta_I S + \lambda_S \beta_B S + \lambda_I \beta_B B + \lambda_I I(\gamma + \mu + \xi) + \lambda_N \xi - a_2 \xi + a_2 \xi \delta + \lambda_S \beta_B S B \delta)$$

For the singular sanitation control to be optimal, then the Generalized Legendre-Clebsch Condition (GLC) inequality holds as stated below:

$$\frac{\partial}{\partial m}[\frac{d^2}{dt^2}\Phi_m] = -B(\lambda_I \beta_B S - \lambda_S \beta_B S - a_2 \delta B)$$

Therefore, the control characterization is given as

$$m^*(t) = \begin{cases} 0 & if & \Phi_m(t) > 0 \\ 1 & if & \Phi_m(t) < 0 \\ singular & if & \Phi_m(t) = -\frac{\Psi_2(t)}{\Psi_m(t)} \end{cases} \tag{21}$$

Thus, the control is optimal at t only if $\Psi_m(t) = 0$ and $0 \leq -\frac{\Psi_1}{\Psi_m} \leq 1$

Proposition: From the two theorems, it shows that there exist a singular controls for vaccination and sanitation that are optimal.

4 Analysis

4.1 Introduction

We use the model in chapter three to analyze clinical cholera data in Kenya. In this thesis, we check on the theoretical aspect but for numerical simulations, we use MATLAB software and a fourth order Runge-Kuta method.

4.2 Parameter Estimation

The value of parameter for the model are shown below:

Table 1. Parameters and Values

Parameters	Symbol	Values	Source
Recruitment rate	Λ	0.4108 x 10^{-6}/day	WHO 2018 Kenya
Death rate	μ	0.4108 x 10^{-6}/day	WHO 2018 Kenya
Total population	N	10000	Assumed
Transmission rate from environment	β_B	0.214/day	Hartley et al. (2006)
Transmission rate from human-human	β_I	0.021/day	Hartley et al. (2006)
Recovery rate	γ	0.2/day	Hartley et al. (2006)
Bacterial concentration in water	B	10^6 cells/ml	Codeço (2001)
Shedding rate of bacteria by human	ξ	10 cells/ml-day	Hartley et al. (2006)
Bacterial decay rate in the environment	δ	0.033/day	Codeço (2001)
Rate at which recovered are susceptible	ω	0.005/day	Neilan et al. (2010)

4.3 The Model's Basic Reproductive Number

The model's basic reproductive number is given by:

$$R_0^c = \frac{\beta_I \Lambda N}{(\gamma + \mu + \xi)(\mu + v)} + \frac{\beta_B \Lambda N \xi}{(\gamma + \mu + \xi)(\delta + m)(\mu + v)}$$

From the parameter values given in Table1., we estimate that

$$R_0^c = \frac{\Lambda N}{(\gamma + \mu + \xi)(\mu + v)}[\beta_I + \frac{\beta_B \xi}{(\delta + m)}]$$

$$R_0^c = \frac{0.040275}{(4.108x10^{-5}+v)}\left[0.021+\frac{2.14}{(0.033+m)}\right]$$

From the results presented, it shows that varying the values of v and m will alter the number of suscepible and infected persons.

For instance, if $v = m = 0$, then $R_0^c = 63,598.308 > 1$. This implies that endemic equilibrium is stable. This implies that if there is no vaccination (v) and sanitation (m), then the disease will continue spreading thus more infected population.

If $m = v = 1$, then $R_0^c = 0.084278 < 1$, implies that the disease free equilibrium is locally stable. Thus the disease will drastically disappear in the population.

In summary, R_0^c decreases as the parameters v and m increases.

4.4 Equilibrium point and Stability

Stability analysis of DFE

From the Jacobian matrix eqn.(8)

$$J = \begin{bmatrix} -(\mu+v)-\lambda_1 & -\beta_I\frac{\Lambda N}{(\mu+v)} & -\beta_B\frac{\Lambda N}{(\mu+v)} \\ 0 & \beta_I\frac{\Lambda N}{(\mu+v)}-(\gamma+\mu+\xi)-\lambda_2 & \beta_B\frac{\Lambda N}{(\mu+v)} \\ 0 & \xi & -(m+\delta)-\lambda_3 \end{bmatrix}$$

$$J = \begin{bmatrix} -(0.00004108+v)-\lambda_1 & -\frac{0.0086268}{(0.00004108+v)} & -\frac{0.0879112}{(0.00004108+v)} \\ 0 & \frac{0.0086268}{(0.00004108+v)}-10.200-\lambda_2 & \frac{0.0879112}{(0.00004108+v)} \\ 0 & 10 & -(m+0.033)-\lambda_3 \end{bmatrix} = 0$$

Thus, $\lambda_1 = -(0.00004108+v)$ is one of the eigenvalues and the other two are the roots of,

$$\lambda^2+\left[\frac{0.008627}{(0.0000411+v)}+m-10.167\right]\lambda-\left(\frac{0.008627}{(0.0000411+v)}-10.2\right)(m+0.033)-\frac{0.879112}{(0.0000411+v)}=0$$

applying quadratic formula to obtain eigenvalues:

$$\lambda_{2,3} = \frac{-w\pm\sqrt{w^2-4rk}}{2r}$$

where

$$w = \frac{0.008627}{(0.0000411+v)}+m-10.167$$

$$k = \left(\frac{0.008627}{(0.0000411+v)}-10.2\right)(m+0.033)-\frac{0.879112}{(0.0000411+v)}$$

$$r = 1$$

DFE is to be asymptotically stable if all the eigenvalues are negative. Hence the DFE is locally asymptotically stable as long as $R_0^c < 1$, whereas it is unstable if $R_0^c > 1$

4.5   Numerical Simulation of the Model

There are many numerical analysis methods that are being used compute the initial value problems, such as Runge-Kutta or adaptive schemes, and boundary value problems, such as shooting methods. Any of these methods could be used to analyse the optimality system and thus singular problem in the model.

The combination of the state systems, adjoint systems and optimal interventions characteritics are part of optimality system which is solved numerically through application of Forward-Backward Sweep Method as stated by Lenhart and Workman (2007).

Begin with the guessing the initial status for the control, we then solve the state system forward in time and then applying the new values of state to compute the adjoint values of the system which is then computed backward in time. We then update the control by using a convex combination of the old control values and the new control values from the charcterization. The iteration should be done until convergence is achieved.

5 Conclusions and Recommendations

5.1 Conclusions

In this thesis, we studied optimal intergration of sanitation and vaccination strategies to minimize the infectious individuals (force of infection), bacteria concentration and the costs associated with the strategies. We have constituted the analysis of optimal control problem for our *SIR*-model with sanitation and vaccination. We have established the condition for the local stability of our model, basic reproductive number and also applied Pontryagin's Maximum Principle to characterize the interventions and derived the optimality of the system. We also analyzed the singular control structures though we still desire to check on the feasible concatenations with bang-bang controls. Based on our analysis we found out that the two optimal controls are singular.

The mathematical behavior indicated that when $R_0^c < 1$, disease-free equilibrium point is locally asymtotically stable and when $R_0^c > 1$ the endemic equilibrium point was also asymptotically stable.

Major Findings: The major contributions to this work was the ability to prove the singularity of the optimal controls and the effects of vaccination and sanitation in the spread of the disease.

5.2 Future Research

In future work, there is need to investigate the numerical analysis of the model to confirm the singularity of the controls and the combined strategies to minimize the force of infection and also to give the least weight/cost of the strategies.

5.3 Recommendations

Public health authorities can use the formulated model to understand the spread and control of cholera outbreak. The *SIR* model can help policy makers/public health agencies to better understand on how to optimize the allocation of vaccines and to put more effort on sanitation so as to respond to the dynamics of cholera. We also recommend for the numerical analysis to determine the structure of a feasible concatenations with bang-bang control in order to determine an optimal synthesis of controlled trajectories.

Appendix
MATLAB Codes to be used in Numerical Analysis

```
function y = cap1_singular_back_forw

test = -1;

tf=20;
delta = 0.001;
M = 1000;
t = linspace(0,tf,M+1);
h = tf/M;
h2 = h/2;


Lambda=0.00004108;
mu=0.00004108;
betab=0.214;
beta1=0.021;
gamma=0.2;
xi=10;
d=0.033;
a0=10;
a1=1;
a2=2;
R=50;
omega=0.005;


S=zeros(1,M+1);
I=zeros(1,M+1);
N=zeros(1,M+1);
B=zeros(1,M+1);

v = zeros(1,M+1);
m = zeros(1,M+1);

lambdaS = zeros(1,M+1);
lambdaI = zeros(1,M+1);
lambdaN = zeros(1,M+1);
lambdaB = zeros(1,M+1);



S(1) = 9500;
I(1) = 450;
N(1) = 10000;
B(1) = 10^6;
```

```
while(test < 0)

    oldv = v;
    oldm = m;
    oldS = S;
    oldI = I;
    oldN = N;
    oldB = B;
    oldlambdaS = lambdaS;
    oldlambdaI = lambdaI;
    oldlambdaN = lambdaN;
    oldlambdaB = lambdaB;


for i = 1:M

m1S = Lambda*N(i)-mu*S(i)-v(i)*S(i)-beta1*I(i)*S(i)-betab*B(i)*S(i)-omega*R
m1I = beta1*I(i)*S(i)+betab*B(i)*S(i)-(gamma+mu+xi)*I(i);
m1N = (Lambda-mu)*N(i)-xi*I(i);
m1B = xi*I(i)-(m(i)+d)*B(i);


m2S = Lambda*(N(i)+h2*m1N)-(mu+(0.5*(v(i)+v(i+1))))*(S(i)+h2*m1S)-
beta1*(I(i)+h2*m1I)*(S(i)+h2*m1S)-betab*(B(i)+h2*m1B)*(S(i)+h2*m1S)-omega*R;
m2I = beta1*(I(i)+h2*m1I)*(S(i)+h2*m1S)+betab*(B(i)+h2*m1B)*(S(i)+h2*m1S)-
(gamma+mu+xi)*(I(i)+h2*m1I);
m2N = (Lambda-mu)*(N(i)+h2*m1N)-xi*(I(i)+h2*m1I);
m2B = xi*(I(i)+h2*m1I)-((0.5*(m(i)+m(i+1)))+d)*(B(i)+h2*m1B);


m3S = Lambda*(N(i)+h2*m2N)-(mu+(0.5*(v(i)+v(i+1))))*(S(i)+h2*m2S)-beta1*(I(i)+
h2*m2I)*(S(i)+h2*m2S)-betab*(B(i)+h2*m2B)*(S(i)+h2*m2S)-omega*R;
m3I = beta1*(I(i)+h2*m2I)*(S(i)+h2*m2S)+betab*(B(i)+h2*m2B)*(S(i)+h2*m2S)-
(gamma+mu+xi)*(I(i)+h2*m2I);
m3N = (Lambda-mu)*(N(i)+h2*m2N)-xi*(I(i)+h2*m2I);
m3B = xi*(I(i)+h2*m2I)-((0.5*(m(i)+m(i+1)))+d)*(B(i)+h2*m2B);


m4S = Lambda*(N(i)+h2*m3N)-(mu+v(i+1))*(S(i)+h2*m3S)-beta1*(I(i)+h2*m3I)*
(S(i)+h2*m3S)-betab*(B(i)+h2*m3B)*(S(i)+h2*m3S)-omega*R;
m4I = beta1*(I(i)+h2*m3I)*(S(i)+h2*m3S)+betab*(B(i)+h2*m3B)*(S(i)+h2*m3S)-
(gamma+mu+xi)*(I(i)+h2*m3I);
m4N = (Lambda-mu)*(N(i)+h2*m3N)-xi*(I(i)+h2*m3I);
m4B = xi*(I(i)+h2*m3I)-(m(i+1)+d)*(B(i)+h2*m3B);


S(i+1) = S(i) + (h/6)*(m1S + 2*m2S + 2*m3S + m4S);
I(i+1) = I(i) + (h/6)*(m1I + 2*m2I + 2*m3I + m4I);
N(i+1) = N(i) + (h/6)*(m1N + 2*m2N + 2*m3N + m4N);
B(i+1) = B(i) + (h/6)*(m1B + 2*m2B + 2*m3B + m4B);

end
```

```
for i = 1:M
    j = M + 2 - i;

n1S = -a1*v^2(j)+lambdaS(j)*(beta1*I(j)+betab*B(j)+mu+v(j))-lambdaI(j)*
(beta1*I(j)+betab*B(j));
n1I = -a0+lambdaS(j)*beta1*S(j)-lambdaI(j)*(beta1*S(j)-(gamma+mu+xi)*I(j)
lambdaN(j)*xi-lambdaB(j)*xi;
n1N = -lambdaS(j)*Lambda-lambdaN(j)*(Lambda-mu);
n1B = -a2*m^2(j)+lambdaS(j)*betab*S(j)-lambdaI(j)*betab*S(j)+
lambdaB(j)*(m(j)+d);

n2S = -a1*v^2(j)+(lambdaS(j)-h2*n1S)*(beta1*(0.5*(I(j)+I(j-1)))+betab*
(0.5*(B(j)+B(j-1))+mu+v(j)))-(lambdaI(j)-h2*n1I)*(beta1*(0.5*(I(j)+
I(j-1)))+betab*(0.5*(B(j)+B(j-1))));
n2I = -a0+(lambdaS(j)-h2*n1S)*beta1*(0.5*(S(j)+S(j-1)))-
(lambdaI(j)-h2*n1I)*(beta1*(0.5*(S(j)+S(j-1)))-(gamma+mu+xi)*(0.5*(I(j)+
I(j-1))))-(lambdaB(j)-h2*n1B)*xi+(lambdaN(j)-h2*n1N)*xi;
n2N = -(lambdaS(j)-h2*n1S)*Lambda-(lambdaN(j)-h2*n1N)*(Lambda-mu);
n2B = -a2*m^2(j)+(lambdaS(j)-h2*n1S)*betab*(0.5*(S(j)+S(j-1)))-
(lambdaI(j)-h2*n1I)*betab*(0.5*(S(j)+S(j-1)))
+(lambdaB(j)-h2*n1B)*(m(j)+d);

n3S = -a1*v^2(j)+(lambdaS(j)-h2*n2S)*(beta1*(0.5*(I(j)+I(j-1)))+
betab*(0.5*(B(j)+B(j-1)))+mu+v(j))-(lambdaI(j)-h2*n2I)*(beta1*
(0.5*(I(j)+I(j-1)))+betab*(0.5*(B(j)+B(j-1))));
n3I = -a0+(lambdaS(j)-h2*n2S)*beta1*(0.5*(S(j)+S(j-1)))-(lambdaI(j)
-h2*n2I)*(beta1*(0.5*(S(j)+S(j-1)))-(gamma+mu+xi)*
(0.5*(I(j)+I(j-1))))-(lambdaB(j)-
h2*n2B)*xi+(lambdaN(j)-h2*n2N)*xi;
n3N = -(lambdaS(j)-h2*n2S)*Lambda-(lambdaN(j)-h2*n2N)*(Lambda-mu);
n3B = -a2*m^2(j)+(lambdaS(j)-h2*n2S)*betab*(0.5*(S(j)+S(j-1)))-
(lambdaI(j)-h2*n2I)*betab*(0.5*(S(j)+S(j-1)))
+(lambdaB(j)-h2*n2B)*(m(j)+d);

n4S = -a1*v^2(j)+(lambdaS(j)-h2*n3S)*(beta1*I(j-1)+
betab*B(j-1)+mu+v(j))-(lambdaI(j)-h2*n3I)*
(beta1*I(j-1)+betab*B(j-1));
n4I = -a0+(lambdaS(j)-h2*n3S)*beta1*S(j-1)-(lambdaI(j)-h2*n3I)*
(beta1*S(j-1)-(gamma+mu+xi)*I(j-1))-(lambdaB(j)-h2*n3B)*xi+
(lambdaN(j)-h2*n3N)*xi;
n4N = -(lambdaS(j)-h2*n3S)*Lambda-(lambdaN(j)-h2*n3N)*(Lambda-mu);
n4B = -a2*m^2(j)+(lambdaS(j)-h2*n3S)*betab*S(j-1)-(lambdaI(j)-h2*n3I)
*betab*S(j-1)+(lambdaB(j)-h2*n3B)*(m(j)+d);

lambdaS(j-1) = lambdaS(j) - h/6*(n1S + 2*n2S + 2*n3S + n4S);
lambdaI(j-1) = lambdaI(j) - h/6*(n1I + 2*n2I + 2*n3I + n4I);
lambdaN(j-1) = lambdaN(j) - h/6*(n1N + 2*n2N + 2*n3N + n4N);
lambdaB(j-1) = lambdaB(j) - h/6*(n1B + 2*n2B + 2*n3B + n4B);
```

```
end

v1 = -(lambdaS*beta1*S*(beta1*I*S+betab*B*S)+(lambdaI*betab*S-a1*betab*S)*
(xi*I-m*B-d*B)+(lambdaI*I*beta1+lambdaI*B*betab-a1*mu-a1*beta1*I-
a1*beta1*S)(Lambda*N-mu*S-beta1*I*S-betab*B*S+omega*R)-beta1*I*S*
(a0-lambdaN*xi-a1*xi)+betab*B*S*(a0-lambdaI*I*(gamma+mu+xi)-lambdaN*xi-
a1*xi)+a1*beta1*S*((gamma+mu+xi)-(beta1*I*S+betab*B*S)))/
(S*(lambdaI*beta1*I*S+lambdaI*betab*B*S-a1*mu*S-
a1*beta1*I*S-a1*betab*B*S));
v = 0.5*(v1 + oldv);

m1 = -((lambdaI*betab*S-lambdaS*betab*S)(xi*I+Lambda*N+omega*R)+betab*B*
S*(-a0+a1*v+lambdaS*beta1*S-lambdaI*beta1*S-lambdaS*beta1*I+
lambdaS*betab*S+lambdaI*betab*B+lambdaI*I*(gamma+mu+xi)+lambdaN*xi-
a2*xi+a2*xi*d*I+lambdaS*betab*d*S*B))/(B*(lambdaI*betab*S-
lambdaS*betab*S-a2*d*B)) ;
m = 0.5*(m1 + oldm);

J=sum((a0*I+a1*v^2*S+a2*m^2*B)*(t(i+1)-t(i)));




temp1 = delta*sum(abs(v)) - sum(abs(oldv - v));
temp2 = delta*sum(abs(m)) - sum(abs(oldm - m));
temp3 = delta*sum(abs(S)) - sum(abs(oldS - S));
temp4 = delta*sum(abs(I)) - sum(abs(oldI - I));
temp5 = delta*sum(abs(N)) - sum(abs(oldN - N));
temp6 = delta*sum(abs(B)) - sum(abs(oldB - B));
temp7 = delta*sum(abs(lambdaS)) - sum(abs(oldlambdaS - lambdaS));
temp8 = delta*sum(abs(lambdaI)) - sum(abs(oldlambdaI - lambdaI));
temp9 = delta*sum(abs(lambdaN)) - sum(abs(oldlambdaN - lambdaN));
temp10 = delta*sum(abs(lambdaB)) - sum(abs(oldlambdaB - lambdaB));

test = min(temp1, min(temp2, min(temp3, min(temp4, min(temp5, min(temp6,
min(temp7, min(temp8, min(temp9, temp10)))))))));
end

y(1,:) = t;
y(2,:) = S;
y(3,:) = I;
y(4,:) = N;
y(5,:) = B;
y(6,:) = lambdaS;
y(7,:) = lambdaI;
y(8,:) = lambdaN;
y(9,:) = lambdaB;
y(10,:) = v;
```

```
y(11,:) = m;
y(12,:) = J;

figure(1)
subplot(4,1,1);plot(y(1,:),y(2,:),'LineWidth',2)
subplot(4,1,1);xlabel('Time')
subplot(4,1,1);ylabel('S')
subplot(4,1,2);plot(y(1,:),y(3,:),'LineWidth',2)
subplot(4,1,2);xlabel('Time')
subplot(4,1,2);ylabel('I')
subplot(4,1,3);plot(y(1,:),y(4,:),'LineWidth',2)
subplot(4,1,3);xlabel('Time')
subplot(4,1,3);ylabel('N')
subplot(4,1,4);plot(y(1,:),y(10,:),'LineWidth',2)
subplot(4,1,4);xlabel('Time')
subplot(4,1,4);ylabel('v')
subplot(4,1,4);plot(y(1,:),y(11,:),'LineWidth',2)
subplot(4,1,4);xlabel('Time')
subplot(4,1,4);ylabel('m')
```

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