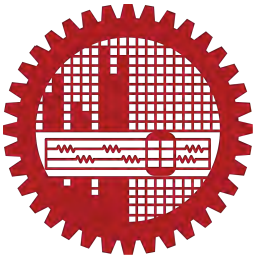
DEVELOPING A MATHEMATICAL MODEL FOR OPTIMAL COST-EFFECTIVE TREATMENT STRATEGIES APPLIED TO A DIPHTHERIA OUTBREAK

The thesis submitted to the
Department of Mathematics, BUET, Dhaka-1000
in partial fulfilment of the requirements for the degree of

MASTER OF SCIENCE
IN
MATHEMATICS

By
MD. ZAHURUL ISLAM
Student No. 1018092502F
Registration No. 1018092502F, Session: October 2018



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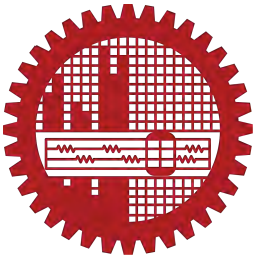

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The thesis entitled " **DEVELOPING A MATHEMATICAL MODEL FOR OPTIMAL COST-EFFECTIVE TREATMENT STRATEGIES APPLIED TO A DIPHTHERIA OUTBREAK"** Submitted by **Md. Zahurul Islam**, Student No. 1018092502F, Registration No. 1018092502F, Session: October-2018 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Master of Science in Mathematics on 22th December, 2020.

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Declaration of Authorship

I, Md. Zahurul Islam, declare that the work contained in this thesis entitled " DEVELOPING A MATHEMATICAL MODEL FOR OPTIMAL COST-EFFECTIVE TREATMENT STRATEGIES APPLIED TO A DIPHTHERIA OUTBREAK" was done by me, under the supervision of Dr. Md. Mustafizur Rahman, Professor, Bangladesh University of Engineering and Technology (BUET), Dhaka-1000 for the award of the degree of Master of Science and this work has not been submitted elsewhere for a degree.

Signed: Zahurul

Date: 22/12/2020

Dedication

This work is dedicated

to

My Family

Abstract

In this study, we seek to apply a system of nonlinear ordinary differential equations to analyze how the dynamics of primary infection affect the proliferation of Diphtheria. We prove existence, uniqueness, positivity, and boundedness of the solution. Also investigate the qualitative behavior of the models, and find a threshold parameter that guarantee the asymptotic stability of the equilibrium points, which is known as basic reproduction number. The parameters are introduced in different terms of equations of the model are determined by fitting to match daily cases data sets using nonlinear least-squares method. The aim of this work is to determine the optimal control of treatment and vaccination administration schemes useful in controlling the epidemic situation especially in poorly resourced settings. The optimal treatments represent the efficacy of vaccination and treatment inhibiting diphtheria infection and preventing new infections with an objective functional which minimizes the infected populations and minimizes the systematic cost based on the percentage effect of the treatment strategies. The existence and the uniqueness of the optimal pair are discussed. A characterization of the optimal controls via adjoint variables is established. We obtain an optimality system that we solve numerically by a iterative Forward-Backward Sweep method. We also discuss cost-effective treatment strategy to obtain the least cost-effective objective function.

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Zahurul

(Md. Zahurul Islam)

Date: 22/12/2020

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Chapter 1

Introduction

1.1 Introduction

Humanity has been plagued with infectious diseases for years. The mechanisms of transmission are known for most diseases; generally, diseases such as influenza, measles, rubella, and chickenpox that are transmitted by virus confer immunity against reinfection, while diseases such as diphtheria, tuberculosis, meningitis, and gonorrhea that are transmitted by bacteria confer no immunity against reinfection. Other diseases, such as malaria, are transmitted not directly from human to human but by vectors (usually insects), which are agents that are infected by humans and then transmit the disease to other humans. West Nile virus has mosquitoes as its vectors and birds as its hosts. For sexually transmitted diseases with the heterosexual transmission, each sex acts as a vector and the disease is transmitted back and forth between the sexes.

Infectious diseases have been a significant cause of death and illness throughout the world. Tens of millions of lives have been lost to them. Some of these diseases include the Spanish influenza virus of the early 20th century, which swept through Africa, America, Asia, and Europe with a death toll of over 30 million people, the 1348 Black Death Bubonic Plague in Europe which killed over 40 million people within five years. In recent times, measles, malaria, tuberculosis, and AIDS, among others, are causing millions of deaths on a yearly basis. UNAIDS reports that an average of 1.8 million people became newly infected with HIV, 36.9 million people are living with HIV in 2016, while over 75 million people have become infected

with HIV since the start of the epidemic in 1981. 1 million people died of AIDS-related diseases in 2016, while over 30 million deaths have resulted from AIDS-related illness since the start of the epidemic. Technological advancements have brought about a remarkable fight against these diseases. Antiretroviral drugs have been made available for people living with HIV. In 2010, 7.7 million were able to access antiretroviral therapy, 17.1 million in 2015, and 20.9 million as of June 2017, which reveals excellent appreciable progress in combating this virus and invariably reducing AIDS-related death [51].

However, while some infectious diseases have been kept under control due to technological advances, others are still ravaging lives, the reason being the diversity of the pathogens coupled with their ability to mutate and adapt to changing environments and the complexity of their transmission mechanisms. Infectious diseases impacts are usually devastating, they hamper the survival rate of children, especially in underdeveloped countries; they also impede opportunities for economic growth and development. Hence, there is a need for a global perspective that accounts for biocomplexity, all the interrelated factors that contribute to the evolution and survival of infectious agents. In order to achieve this, individuals from various fields such as biologists, ecologists, chemists, epidemiologists, mathematicians, statisticians, and atmospheric scientists must work collaboratively in order to shed more light on how these diseases can be eradicated or their impact minimized.

Transmission of infectious diseases occurs through several means that can be categorized into two major routes, direct and indirect transmission. Direct transmission involves the transmission from infected people to uninfected people through close contacts. Their medium includes body fluids such as blood, semen, breast milk, etc., or through the shaking of hands with or touching an infected individual. Indirect transmission involves transmission by non-human infectious agents such as mosquitoes, tsetse flies, contaminated food or water, which serve as intermediate hosts for the disease and later transmit the disease to humans.

The incidence rate of diseases describes the transmission of the disease. An infectious disease that spreads rapidly to a large number of people in a given population for a short period of time is known as an epidemic. An infectious disease that persists in the community or population is known as an endemic disease while a pandemic is an epidemic of infectious disease that has spread through human populations across a large region (several continents, or even worldwide).

Scientists have used mathematical models, which involve the use of mathematical equations and formulas to represent real-life problems, solved and made remarkable predictions based on the solutions obtained from the problems. Epidemiologists (scientists that study infectious diseases) have played a vital role in investigating the transmission dynamics of some of these diseases and have been able to come up with recommendations for different intervention strategies which have helped to control the spread of some of these diseases.

1.2 Diphtheria Disease

In 1613, Spain experienced the first epidemic of diphtheria. In 1735, a diphtheria epidemic swept through England. Before 1826, diphtheria was known by different names across the world. In England, it was known as Boulogne sore throat, as it spread from France. In 1826, Pierre Bretonneau gave the disease the name diphthérite (from Greek diphthera "leather") describing the appearance of pseudomembrane in the throat. In 1856, Victor Fourgeaud described an epidemic of diphtheria in California. In 1883, Edwin Klebs identified the bacterium causing diphtheria and named it Klebs-Loeffler bacterium. The club shape of this bacterium helped Edwin to differentiate it from other bacteria. Over a period of time, it was called Microsporon diphtheriticum, Bacillus diphtheriae, and Mycobacterium diphtheriae. The current nomenclature is Corynebacterium diphtheriae. Friedrich Loeffler was the first person to cultivate C. diphtheriae in 1884. He used Koch's postulates to prove the association between C. diphtheriae and diphtheria. He also showed that the bacillus produces an exotoxin. In 1895, H. K. Mulford Company of Philadelphia started production and testing of diphtheria antitoxin in the United States.

1.3 Diphtheria Epidemic

Diphtheria is fatal in between 5% and 10% of cases. In children under five years and adults over 40 years, the fatality rate may be as much as 20%. In 2013, it resulted in 3,300 deaths, down from 8,000 deaths in 1990. In 2018, countries reported more than 16,000 cases of diphtheria to the World Health Organization, and there are likely many more cases.

During 1990-1995, more than 140,000 cases and 4000 death have been reported worldwide to the Regional Office of World Health Organization (WHO) for Europe [5, 16, 43]. The number of cases has changed over the course of the last 2 decades, specifically throughout developing countries. Better standards of living, mass immunization, improved diagnosis, prompt treatment, and more effective health care have led to a decrease in cases worldwide. However, although outbreaks are rare, they still occur worldwide, especially in developed nations such as Germany among unvaccinated children. In Nazi Germany contagious diseases such as diphtheria were among the leading causes of morbidity; they increased "after the mid-1920s, doubled again between 1932 and 1937, and reached extremely high levels during the war only to decline rapidly thereafter". Diphtheria remains a problem in a number of low-income countries with poor immunization coverage. Several outbreaks have been reported in sub-Saharan Africa (e.g. Nigeria and Madagascar) since 2000. Bangladesh experienced recently an outbreak in a large refugee camp for the Rohinga in 2017. Currently, India, Indonesia, and Nepal have the highest number of diphtheria cases in Asia [19]. Even in countries with rather good immunization coverage, such as Thailand and Iran, outbreaks of 157 and 513 cases respectively, have occurred in recent years. In 2014, for example, 22 cases of confirmed diphtheria were reported in the European Union, and about half of these cases were in Latvia [7]. A large-scale diphtheria epidemic had been reported in the Rohingya refugee camp in Bangladesh which is temporarily located in Cox's Bazar. As of December 26, 2017, the cumulative number of 2,526 cases and 27 deaths were reported [57]. In this thesis, we worked with the data of the Rohingya refugee camp in Bangladesh. It will help the health department of the government to control such a diphtheria outbreak if it further occurs.

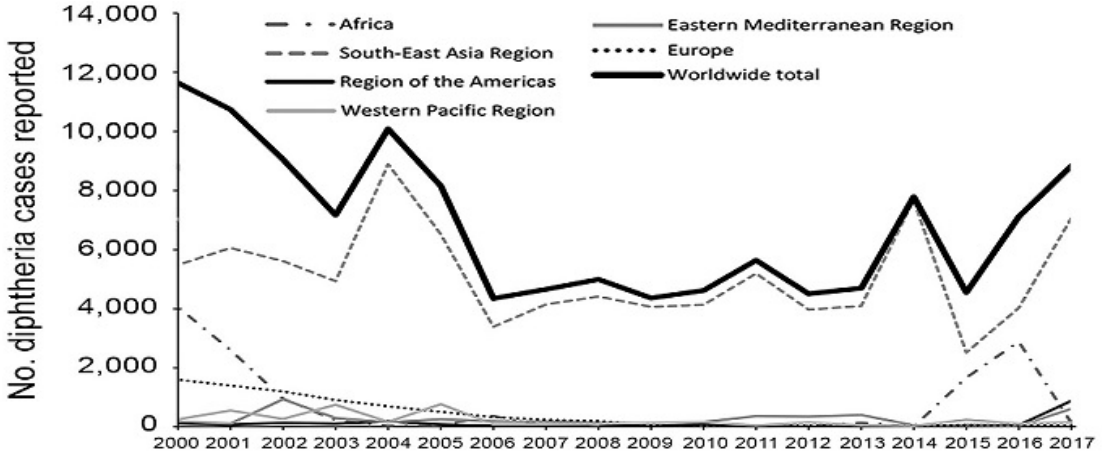

Figure. 1.1. Worldwide Diphtheria Outbreak 2000 to 2017.

1.4 Infection of Diphtheria

1.4.1 Disease Transmission

Human-to-human transmission of diphtheria typically occurs through the air when an infected individual coughs or sneezes. Breathing in particles released from the infected individual leads to infection. Contact with any lesions on the skin can also lead to transmission of diphtheria, but this is uncommon. Indirect infections can occur, as well. If an infected individual touches a surface or object, the bacteria can be left behind and remain viable. Also, some evidence indicates diphtheria has the potential to be zoonotic, but this has yet to be confirmed. Corynebacterium ulcerans has been found in some animals, which would suggest zoonotic potential.

1.4.2 Signs and symptoms

The symptoms of diphtheria usually begin two to seven days after infection. Symptoms of diphtheria include fever of 38 °C (100.4 °F) or above, chills, fatigue, bluish skin coloration (cyanosis), sore throat, hoarseness, cough; headache, difficulty swallowing, painful swallowing, difficulty breathing, rapid breathing, foul-smelling and bloodstained nasal discharge, and lymphadenopathy. Within two to three days, diphtheria may destroy healthy tissues in the respiratory system. The dead tissue forms a thick, gray coating that can build up in the throat or nose. This thick gray coating is called a "pseudomembrane". It can cover tissues in the nose, tonsils, voice box, and throat, making it very hard to breathe and swallow. Symptoms can also include cardiac arrhythmias, myocarditis, and cranial and peripheral nerve palsies.

1.4.3 Mechanism

Diphtheria toxin is produced by C. diphtheriae only when infected with a bacteriophage that integrates the toxin-encoding genetic elements into the bacteria. Diphtheria toxin is a single, 60-kDa-molecular weight protein composed of two peptide chains, fragment A and fragment B, held together by a disulfide bond. Fragment B is a recognition subunit that gains the toxin entry into the host cell by binding to the EGF-like domain of heparin-binding EGF-like growth factor on

the cell surface. This signals the cell to internalize the toxin within an endosome via receptor-mediated endocytosis. Inside the endosome, the toxin is split by a trypsin-like protease into its individual A and B fragments. The acidity of the endosome causes fragment B to create pores in the endosome membrane, thereby catalysing the release of fragment A into the cell's cytoplasm.

Fragment A inhibits the synthesis of new proteins in the affected cell by catalyzing ADP-ribosylation of elongation factor EF-2—a protein that is essential to the translation step of protein synthesis. This ADP-ribosylation involves the transfer of an ADP-ribose from NAD+ to a diphthamide (a modified histidine) residue within the EF-2 protein. Since EF-2 is needed for the moving of tRNA from the A-site to the P-site of the ribosome during protein translation, ADP-ribosylation of EF-2 prevents protein synthesis.

ADP-ribosylation of EF-2 is reversed by giving high doses of nicotinamide (a form of vitamin B3), since this is one of the reaction's end products, and high amounts drive the reaction in the opposite direction.

1.4.4 Treatment

The disease may remain manageable, but in more severe cases, lymph nodes in the neck may swell, and breathing and swallowing are more difficult. People in this stage should seek immediate medical attention, as obstruction in the throat may require intubation or a tracheotomy. Abnormal cardiac rhythms can occur early in the course of the illness or weeks later, and can lead to heart failure. Diphtheria can also cause paralysis in the eye, neck, throat, or respiratory muscles. Patients with severe cases are put in a hospital intensive care unit and given a diphtheria antitoxin (consisting of antibodies isolated from the serum of horses that have been challenged with diphtheria toxin). Since antitoxin does not neutralize toxin that is already bound to tissues, delaying its administration increases risk of death. Therefore, the decision to administer diphtheria antitoxin is based on clinical diagnosis, and should not await laboratory confirmation.

Antibiotics have not been demonstrated to affect healing of local infection in diphtheria patients treated with antitoxin. Antibiotics are used in patients or carriers to eradicate C. diphtheriae and prevent its transmission to others. The Centers for Disease Control and Prevention recommends either:

- Metronidazole
- Erythromycin is given (orally or by injection) for 14 days (40 mg/kg per day with a maximum of 2 g/d), or
- Procaine penicillin G is given intramuscularly for 14 days (300,000 U/d for patients weighing $<$ 10 kg and $600,000U/d$ for those weighing $>$ 10 kg); patients with allergies to penicillin G or erythromycin can use rifampin or clindamycin.

In cases that progress beyond a throat infection, diphtheria toxin spreads through the blood and can lead to potentially life-threatening complications that affect other organs, such as the heart and kidneys. Damage to the heart caused by the toxin affects the heart's ability to pump blood or the kidneys' ability to clear wastes. It can also cause nerve damage, eventually leading to paralysis. About 40% to 50% of those left untreated can die.

1.4.5 Prevention

Quinvaxem is a widely administered pentavalent vaccine, which is a combination of five vaccines in one that protect babies from diphtheria, among other common childhood diseases. Diphtheria vaccine is usually combined at least with tetanus vaccine (Td) and often with pertussis (DTP, DTaP, TdaP, Tdap) vaccines, as well.

1.5 Literature Review

The recent outbreak of Diphtheria Disease has led researchers to develop mathematical models to help understand the dynamic of the virus and the appropriate intervention techniques which have to be put in place in order to be able to combat the disease effectively. Dittmann et al. [43] applied the control strategies of epidemic diphtheria in the USSR, Zakikhany and Efstratiou [20] analyzed on the current problems and new challenges of Diphtheria in Europe, Atkinson et al. [52] in their work discussed about the Epidemiology, risk factors, vaccine details, vaccination schedule and use of vaccine, Torrea et al. [29] discussed the mathematical modeling of a diphtheria epidemic in the refugee camps and Ilahi and Widiana [10] analyzed the effectiveness of vaccine in the outbreak of diphtheria do with

mathematical model and simulation. It was done by controlling the vaccination aimed at decreasing the infected population and minimizing the treatment cost. Matsuyama et al. [40] analyzed the uncertainity and sensitivity of basic reproduction number of diphtheria outbreak in Rohingya refugee camp in Bangladesh. In this thesis, we develope a deterministic model to describe the effects of vaccination and treat-ment on the diphtheria outbreak. Further apply optimal control in the model and analyzed cost-effectiveness to control the Diphtheria outbreak.

In this thesis, a modified susceptible-exposed-infectious-recovered (SEIR) deterministic nonlinear system of equations are used to model the dynamics of Diphtheria disease. In addition to infectious individuals, which are known to be the major carriers of infectious diseases, this model incorporate the effect of the transmission of the disease by deceased infectious individuals, since they also contribute to the transmission of the disease to the susceptible population. Chapter 2 is devoted to mathematical preliminaries that are relevant to this thesis. Chapter 3 is devoted to model formulation, steady state analysis, boundedness and positivity of the solution of the of the model. The disease free and endemic equilibrium point are discussed and also presented their positivity and stability. The next generation matrix is used to compute the basic reproduction number $\mathcal{R}_0$ for the model. The infected cases data provided in [40] are fitted to the Diphtheria epidemic model and estimate the parameter value and numerical discussion of stability analysis are discussed. Chapter 4 deals with optimal control applied to the Diphtheria epidemic model. Mathematical analysis and numerical analysis of the model are carried out in this Chapter. Optimal control strategies and coast-effective analysis are also discussed here. And finally Chapter 5 focuses on the conclussion and the future work.

Chapter 2

Mathematical Preliminaries

2.1 Introduction

This chapter presents some basic mathematical theories and methodologies that will be used in this thesis. The material in this chapter is based on references [9] and [46].

Mathematical modeling can be defined as the use of mathematical signs, symbols, and equations to represent a real-life situation in order to make it (real-life problem) easier to understand, solve, and to infer a reasonable conclusion from the solution of the problem. Mathematical models of infectious diseases have been used as a tool to study and understand the dynamics of diseases, make predictions about future outbreaks of the disease, and suggest intervention measures that have to be implemented in order to control the disease. Mathematical models can be classified in various ways:

- Static versus dynamic models. Static models are time-independent while dynamic models are time-dependent.
- Continuous versus discrete time models. Continuous time models are models in which the independent variable is continuous,$e.g$, $\frac{dx}{dt} = ax$, while discrete time models are models used for life phenomena in which the independent variables are observed at discrete intervals, e.g, $x_{t+1} = ax_t$.
- Stochastic versus deterministic models. Stochastic models are models in which probabilistic concepts are used and distributions of possible behaviors

are presented, while deterministic models are models in which the behavior of a population is determined completely by its history and by the rules which describe the model.

- Homogeneous versus detailed models. A detailed model involves the spatial or physiological distribution of each state variable specification while homogeneous models regard state variables as having the same spatial or physiological distribution.

The tools used are ordinary differential equations (ODEs), partial differential equations (PDE), delay differential equations (DDE), stochastic differential equations (SDE), integral equations, Markov chains, game theory, etc.

2.2 Ordinary Differential Equations

Material of this section is obtained from [47].
Ordinary differential equations (ODEs) are equations that involve the derivatives of one or more dependent variables with respect to an independent variable. In compartmental disease models, the independent variable is time t, the rate of transfer between compartments are expressed mathematically by the derivatives of the compartments with respect to time, with an underlying assumption that the number of individuals in a compartment is a differentiable function with respect to time. The formulation of models as ordinary differential equations follows the assumption that the behavior of a population can be determined completely by its history and the rules that govern the models. A first order ordinary differential equation is defined as

$$\frac{d}{dt}x(t) = f(t, x(t)) \tag{2.1}$$

where $t \in \mathbb{R}$ is an independent variable, $x(t)$ is a dependent variable (unknown function) and $f : \mathbb{R}^n \to \mathbb{R}^n$ is a vector field. Equation (2.1) is known as a non-autonomous ordinary differential equation. When no ambiguity arises, $\frac{d}{dt}x(t)$ is often written as x' so that equation (2.1) is written as

$$x' = f(t, x). \tag{2.2}$$

where the dependece of $x(t)$ on t is also omitted unless this gives rise to ambiguities. If f does not depend explicitly on time, then equation (2.2) is called autonomous

and takes the form

$$x' = f(x) \tag{2.3}$$

and the general solution is

$$x(t) = \int_{t_0}^{t} f(\tau)d\tau \tag{2.4}$$

For $f_i : \mathbb{R}^n \to \mathbb{R}$ and $x_i \in \mathbb{R}^n$, a system of ordinary defferential equations is defined when $n > 1$; otherwise, for $n = 1$ the equation is scalar. In applications, a particular solution, which requires initial conditions, is usually sought for, rather then a general solution.

Definition 2.1. (**Initial Value Problem**) A first order ODE together with an initial condition

$$x' = f(t, x) \tag{2.5a}$$

$$x(t_0) = x_0 \tag{2.5b}$$

is called an **initial value problem**. The initial condition $x(t_0) = x_0$ represents the position of the objects at some initial time t_0. Solutions of a system of ordinary differential equations are sought for within a given initial (say $\mathbb{I}$) that contains t_0, so that the solution curves passes through the point $(t_0, x(t_0))$.
A solution of an initial value problem is a differentiable function $x(t)$ such that

1. $x'(t) = f(t, x(t))$ for all t in an interval containing t_0 where $x(t)$ is defined and
2. $x(t_0) = x_0$

Thus, the solution can be expressed in integral form as

$$x(t) = x_0 + \int_{t_0}^{t} f(\tau, x(\tau))d\tau \tag{2.6}$$

The system of ODEs to be analysed in this thesis is autonomous and takes the form $x' = f(x)$ with $x \in \mathbb{R}^7_+$ and $f : \mathbb{R}^7_+ \to \mathbb{R}^7_+$

2.3 Existence and uniqueness of solutions

In this section, we state some basic theorems describing general properties of solutions of differential equations. Material of this section can be found in [25] and [23].

Definition 2.2. (*Well-posedness*) System (2.2) is well-posed if solutions exists, are unique, and for systems describing populations, remain bounded and non-negative for all non-negative initial conditions.

Theorem 2.3. ***(Cauchy-Lipschitz)*** *Consider the differential equation 2.2 with $x \in \mathbb{R}^n$ and suppose that $f \in C^1$. Then there exists a unique solution of (2.2) such that $x(t_0) = x_0$ where $t_0 \in \mathbb{R}^n$ and $x_0 \in \mathbb{R}^n$, defined on the largest interval $t_0 \in \boldsymbol{I}$ on which $f \in C^1$*

Theorem 2.4. *Let f and its partial derivatives $\left(\dfrac{\partial f_i}{\partial x_j}\right)$ in equation (2.2) be continuous in $\mathbb{R}^n$ and let $x_0 \in \mathbb{R}$ and $t_0 \in \mathbb{R}$. Then there is an interval $|t - t_0| < h$ in which there exists a unique solution $x(t) = \phi(t)$ of the system that also satisfies the initial conditions.*

Definition 2.5. (**Flow**) Consider system (2.2). The flow $\phi(t, x_0)$ of 2.2 represents the solution of (2.2) over time given an initial condition, provided that the solutions to the differential equation exixts and are unique.

2.4 Equilibria of epidemic model

Definition 2.6. An equilibrium solution of (2.3) is a solution $\bar{x} \in \mathbb{R}^n$ such that $f(\bar{x}) = 0$, i.s. a solution which does not change with time. The term "*equilibrium point*" can be used interchangeably with the following: "*fixed point*", "*sthationary point", singularity point", "critical point", or " steady state".*

There are two steady states which are usually sought after in any epidemiological model; the disease-free equilibrium (DFE) and the endemic equilibrium (EE).
The disease-free equilibrium is the state where the population is completely free from infection: the implication is that all infected compartments are zero and the total population comprises only susceptible or immune individuals. The endemic equilibrium is the state where the infection remains in the population, so there is

a positive number of infectious individuals at equilibrium.

Definition 2.7. (**Stable and unstable equilibrium point**) [46] Let $\phi(t)$ be the flow of (2.3), assumed to be defined for all $t \in \mathbb{R}$. An equilibrium solution $\bar{x}$ of (2.4) is said to be locally stable if for all $\epsilon > 0$, there exists $\delta = \delta(\epsilon) > 0$ such that for all $x \in \mathcal{N}_\delta(\bar{x})$ and $t \geq 0$, there holds

$$\phi_t(x) \in \mathcal{N}_\epsilon(\bar{x}).$$

Definition 2.8. (**Asymptotically stable equilibrium point**) Let $\psi(t)$ be the flow of (2.3) is (locally) asymptotically stable if there exists $\delta > 0$ such that for all $x \in \mathcal{N}_\delta(\bar{x})$, there holds

$$\lim_{t\to\infty} \phi(t) = \bar{x}$$

.

2.4.1 Linearization

The information used here are obtained from [46] and [47].

The behaviour of System (2.3) near a hyperbolic equilibrium point $\bar{x}$ is linked to the behaviour of the linearized system

$$x' = Df(\bar{x})(x - \bar{x}) \tag{2.7}$$

about the same equilibrium, where

$$J(\bar{x}) = Df(\bar{x}) = \begin{pmatrix} \frac{\partial f_1}{\partial x_1}(\bar{x}) & \frac{\partial f_1}{\partial x_2}(\bar{x}) & \cdots & \frac{\partial f_1}{\partial x_n}(\bar{x}) \\ \frac{\partial f_2}{\partial x_1}(\bar{x}) & \frac{\partial f_2}{\partial x_2}(\bar{x}) & \cdots & \frac{\partial f_2}{\partial x_n}(\bar{x}) \\ \vdots & \vdots & \ddots & \vdots \\ \frac{\partial f_n}{\partial x_1}(\bar{x}) & \frac{\partial f_n}{\partial x_2}(\bar{x}) & \cdots & \frac{\partial f_n}{\partial x_n}(\bar{x}) \end{pmatrix} \tag{2.8}$$

matrix $Df(\bar{x})$ is the Jacobian matrix of (2.3) evaluated at the equilibrium point $\bar{x}$.

Definition 2.9. (**Hyperbolic fixed point**) Let $x = \bar{x}$ be a fixed point of $x' = f(x),\ x \in \mathbb{R}^n$. Then $\bar{x}$ is called a hyerbolic fixed point if none of the eigenvalues of

$Df(\bar{x})$ have zero real part. A hyperbolic fixed point is called a saddle if some, but not all of the eigenvalues have positive real part, then the hyperbolic fixed point is called an unstable node or source.

Definition 2.10. A non-hyperbolic fixed point is a fixed point having the real part of some of the eigenvalues associated to the linearized system equal to zero, that is, these eigenvalues are purely imaginary. (Such fixed point is said to be a center if the system is linear).

Definition 2.11. (*Homeomoephism*) Let D be a space. A map $h : D \to D$ is a homeomorphism if h is a continuius bijection whose inverse is continuous.

Definition 2.12. (*Topologically conjugate*) Let $\phi(t, x)$ and $\psi(t, x)$ be two flows on a space D. ϕ and ψ are *topologically conjugate* if there exists an *homeomorphism* $h : D \to D$ such that

$$h \; o \; \phi(t, x) = \psi(t, x) \; o \; h(x)$$

for all $x \in D$ and all $t \in \mathbb{R}$.

Theorem 2.13. ***(Hartman and Grobman)*** *[46] Assume that $\bar{x} \in \mathbb{R}^n$ is a hyperbolic equilibrium (all eigenvalues of the Jacobian matrix evaluated at $\bar{x}$ have non-zero real part). Then, in a small neighbourhood of $\bar{x}$, the non-linear system behaves in a similar manner as the linearized system.*

2.5 The basic reproduction number and stability analysis

The basic reproduction number $\mathcal{R}_0$ is defined as the expected number of secondary infections caused by the introduction of an infectious individual into a totally susceptible population. This number forms the basis of any epidemiological study because it helps to predict the future occurrence of any infection under consideration. Stability analysis of steady states of the model shall be carried out through the application of the next-generation matrix in order to determine $\mathcal{R}_0$. In determining $\mathcal{R}_0$, there must be a distinction between new infections and all other changes in the population [37]. Let $x = (x_1, x_2, ..., x_r)^T$ be r homogeneous compartments in a heterogeneous population, with each $x_i \geq 0$ the number of individuals in each compartment. Let the first m compartments correspond to the

infected individuals (disease) compartments while the rest n compartments make up the uninfected compartments, where $r = m + n$. We define X_s to be the set of all disease-free states, that is,

$$X_s = \{x \geq 0 \mid x_i = 0,\ i = 1, ..., m\}.$$

Let

$$x' = f_i(x) = \mathcal{F}_i(x) - \mathcal{V}_i(x),\ i = 1, ..., n \tag{2.9}$$

represent the dynamics of the infected compartments, where $\mathcal{F}_i(x)$ and $\mathcal{V}_i = \mathcal{V}_i^-(x) - \mathcal{V}_i^+(x)$ are continuously differentiable functions, with $\mathcal{F}_i(x)$ the appearance rate of new infections in compartment i, $\mathcal{V}_i^+(x)$ the transfer rate of individuals into compartment i by all other means and $\mathcal{V}_i^-(x)$ the transfer rate of individual out of compartment i. Each of these functions is assumed to be differentiable at least twice in each variable. The disease transmission defined in (2.9) is made up of non-negative initial conditions, that is, $\mathcal{F}_i(x) \geq 0, \mathcal{V}_i^-(x) \geq 0$, and $\mathcal{V}_i^+(x) \geq 0$ for all $i = 1, ..., n$,
The Jacobian matrices of $\mathcal{F}_i(x)$ and $\mathcal{V}_i(x)$ are evaluated at the disease free equilibrium point $\bar{x}$, giving

$$F = \left[\frac{\partial \mathcal{F}_i}{\partial x_k}(\bar{x})\right] \quad \text{and } V = \left[\frac{\partial \mathcal{V}_i}{\partial x_k}(\bar{x})\right],\ \ 1 \leq i,\ k \leq m \tag{2.10}$$

where F and V are $m \times n$ matrices, F is a non-negative and V is a non-singular matrix. The basic reproduction number $\mathcal{R}_0$ is evaluated as

$$\mathcal{R}_0 = \rho(FV^{-1}) \tag{2.11}$$

where ρ denotes the spectral radius of the matrix (FV^{-1}). The following result is proved in [38], which we closely follow.

Theorem 2.14. *The disease free is locally asymptotically stable if* $\mathcal{R}_0 < 1$ *and unstable if* $\mathcal{R}_0 > 1$.

For the computation of the basic reproduction number using the next generation matrix, the following assumptions need to be satisfied.
The functions $\mathcal{F}_i(x)$ and $\mathcal{V}_i$ involve the direct transfer of individuals, hence they are non-negative. Thus

(i) If $x \geq 0$, then $\mathcal{F}_i(x),\ \mathcal{V}_i^+(x),\ \mathcal{V}_i^-(x) \geq 0$ for $i = 1, ..., n$.
If a compartment is empty, then there can be no transfer of individuals out of the compartment by whatever means. Thus

(ii) If $x_i = 0$ then $\mathcal{V}_i^-(x) = 0$ for $i = 1, ..., n$.
Consider the disease transmission model given in (2.9) with $\mathcal{F}_i(x), i = 1, ..., n$, satisfying the two conditions above. If $X_i = 0$, then $\mathcal{F}_i(x) \geq 0$ and hence, the non-negative cone is positively invariant. For each non negative initial condition, there is a unique, non-negative solution.

The next condition arises from the fact that the incidence of infection for the uninfected compartment is zero:

(iii) $\mathcal{F}_i = 0$ if $j > m$.

To ensure that the disease free subspace is invariant, we assume that if the population is free of disease, then the population will remain free of disease. That is, there is no immigration of infectious. This condition is stated as follows:

(iv) If $x \in X_s$ then $\mathcal{F}_i(x) = 0$ and $\mathcal{V}_i^+(x) = 0$ for $i = 1, ..., m$.

The remaining condition is based on the derivatives of f near a DFE. For our purpose, we define a DFE of (1) to be a (locally asymptotically) stable equilibrium solution of the disease free model, i.e., (1) restricted to X_s. Note that we need not assume that the model has a unique DFE. Consider a population near the DFE $\bar{x}$. If the population remains near the DFE (i.e., if the introduction of a few infectious individuals does not result in an epidemic), then the population will return to the DFE according to the linearized system

(v) $x' = Df(x_0)(x - x_0)$,

where $Df(x_0)$ is the derivative $\left[\frac{\partial f_i}{\partial x_k}\right]$ evaluated at the DFE, $\bar{x}$ (i.e., the Jacobian matrix). Here and in what follows, some derivatives are one sided, since $\bar{x}$ is on the domain boundary. We restrict our attention to systems in which the DFE is stable in the absence of new infection. That is, if $\mathcal{F}(x)$ is set to zero, then all eigenvalues of $Df(x_0)$ have negative real parts.

2.6 Stability Analysis

The Hartman-Grobman theorem tells us that, in a neighborhood of a hyperbolic equilibrium point, we can get a qualitative idea of the behavior of solutions of the non-linear system by studying its corresponding linear system. Thus, we can determine whether solution trajectories approach or move away from the equilibrium point over time, that is, we can determine the stability of equilibria in the system (2.3) without finding explicit solutions.

Theorem 2.15. *Let $\bar{x}$ be an equilibrium point of the autonomous system (2.3), where $f \in C^1$ in a neighbourhood of $\bar{x}$.*

(i) If all the eigenvalues of $J = Df(\bar{x})$ have negative real part, then $\bar{x}$ is locally asymptotically stable equilibrium point.

(ii) If $J = Df(\bar{x})$ has at least one eigenvalue with positive real part, then $\bar{x}$ is an unstable equilibrium point.

2.6.1 Lyapunov functions and Lasalle's invariance Principle

Lyapunov functions and LaSalle's Invariance Principle are some of the methods often used to establish the global stability property of an equilibrium point.

Definition 2.16. A point $x_0 \in \mathbb{R}^n$ is called an ω-limit point of $x \in \mathbb{R}^n$ and denoted by $\omega(x)$, if there exists a sequence $\{t_i\}$ such that

$$\phi(t_i, x) \to x_0 \quad \text{as} \quad t_i \to \infty.$$

Definition 2.17. A pointi $x_0 \in \mathbb{R}^n$ is called an α-limit point of $x \in \mathbb{R}^n$ and denoted by $\alpha(x)$, if there exists a sequence $\{t_i\}$ such that

$$\phi(t_i, x) \to x_0 \quad \text{as} \quad t_i \to -\infty.$$

Definition 2.18. The set of all ω-limit points of a flow is called the ω-limit set. Similarly, the set of all α-limit points of a flow is called the α-limit set.

Definition 2.19. Let $S \subset \mathbb{R}^n$ be a set. Then S is said to be invariant under the flow generated by (2.3) if for any $x_0 \in S$, we have $x(0, x_0) \in S$ for all $t \in \mathbb{R}$.
If the region is restricted to positive times (i.s., $t \geq 0$),then S is said to be a **positively-invarriant set** (this implies that solutions in the positive invariant set remains there for all time). The set is **nagatively-invariant** if solutions remain there when we go backward in time.

Definition 2.20. A function $V : \mathbb{R}^b \to \mathbb{R}$ is said to be a **positive-definite** function if:

- $V(x) > 0$ for all $x \neq 0$.
- $V(x) = 0$ if and only if $x = 0$.

Theorem 2.21. *(**Lyapunov**) [23] Consider the autonomous system defined by (2.3). Let $\bar{x}$ be a fixed point of (2.3) and let $V : U \to \mathbb{R}$ be a C^1 function defined on some neighbourhood U of $\bar{x}$ such that*

(i) $V(\bar{x}) = 0$ *and* $V(x) > 0$ *if* $x \neq \bar{x}$.

(ii) $\frac{d}{dt}V(x) \leq 0$ *in* U-$\{\bar{x}\}$.
Then $\bar{x}$ is stable. Moreover, if

(iii) $\frac{d}{dt}V(x) < 0$ *in* U-$\{\bar{x}\}$.
Then $\bar{x}$ is asymptotically stable.

Any function V that satisfies the conditions from Theorem 2.21 is said to be a Lyapunov function.

Theorem 2.22. *(**LaSalle's Invariance Principle**) Consider system (2.3). Let*

$$S = \left\{ x \in \bar{U} : \ \frac{d}{dt}V(x) = 0 \right\} \tag{2.14}$$

and let M be the largest invariant set of (2.3) in S. If V is a lyapunov function on U and $\gamma^+(x_0)$ is a bounded orbit of (2.3) which lies in S, then the ω-limit set of $\gamma^+(x_0)$ belongs to M (that is, $x(t, x_0) \to M$ as $t \to \infty$)

- $\gamma^+(x_0)$: *part of solution trajectory where $t \geq t_0$ (positive orbit).*
- $\gamma^+(x_0)$: *part of solution trajectory where $t \leq t_0$ (negaitive orbit).*

Corollary 2.23. *If* $V(x) \to \infty$ *as* $|x| \to \infty$ *and* $\frac{dV}{dt} < 0$ *on* $\mathbb{R}^n$*, then every solution of (2.3) is bounded and approaches the largest invariant set* M *of (2.3) in the set where* $\frac{dV}{dt} = 0$*. In particular, if* $M = \{0\}$*, then the solution* $x = 0$ *is globally asymptotically stable (GAS).*
Subsequently $V' = \frac{dV}{dt}$.

2.6.2 Global stability analysis

The global stability analysis will be studied using references [30, 31, 59]. A general compartmental disease transmission model can be written as

$$\begin{aligned} i' &= \mathcal{F}(i,u) - \mathcal{V}(i,u) \\ u' &= g(i,u) \end{aligned} \tag{2.12}$$

with $g = (g_1, ..., g_n)^T$. Here $i = (i_1, ..., i_m)^T \in \mathbb{R}^m$ and $u = (u_1, ..., u_n)^T \in \mathbb{R}^n$ represent the populations in disease compartments and non-disease compartments, respectively. $\mathcal{F}$ and $\mathcal{V}$ are as defined in (2.10). If the basic reproduction number $\mathcal{R}_0 \leq 1$ the disease will die out, while the disease persists at a positive level if $\mathcal{R}_0 > 1$. Global stability results for many disease models are non-trivial. Endemic equilibrium global stability results in particular, normally become challenging due to the complexity and high dimension of disease models. Diphtheria and other epidemic disease models among others require the incorporation of their pathogen into their models. This accounts for the complexity of such models compared to other disease models that are transmitted directly by human. As was explained in the aboce section, Lyapunov functions are commonly used to establish global stability results for infectious diseases models. The following Lyapunov function

$$V = \sum_{i=1}^{n} c_i \left(x_i - x_i^* - x_i^* ln \frac{x_i}{x_i^*} \right) \tag{2.13}$$

originated from the first integral of a Lotka-Volterra system, is used as a general Lyapunov function in some mathematical biology literature. Suitable values for c_i have to be determined such that V' along solutions of the model is nonpositive.

2.6.3 Global stability of DFE: A matrix-theoretic method

Material from [59] will be used in the analysis of the global stability analysis of the DFE. Define

$$f(i,u) := (F-V)i - \mathcal{F}(i,u) + \mathcal{V}(i,u) \tag{2.15a}$$

$$i' := (F-V)i - f(i,u) \tag{2.15b}$$

where $f(0,u) = 0$ is the DFE of (2.12). Equation (2.15a) represents the dynamics of diseased compartments of a general compartmental disease model. Let $w^T \geq 0$ be the left eigenvector of the nonnegative matrix $V^{-1}F$ corresponding to the eigenvalue $\rho(V^{-1}F) = \rho(FV^{-1}) = \mathcal{R}_0$. The following result provides a method for constructing a Lyapunov function for 2.12, using the Perron eigenvector.

Theorem 2.24. *Let F, V be defined as in (2.10) and $f(i,u)$ be defined as in (2.15a). If $f(i,u) \geq 0$ in $\Gamma \subset \mathbb{R}^{n+m}_+, F \geq 0, V^{-1} \geq 0$, and $\mathcal{R}_0 \leq 1$, then the function $Q = w^T V^{-1} i$ is a Lyapunov function for the model (2.12) on Γ.*

Proof. Differentiating Q along solutions of (2.12) gives

$$\begin{aligned} Q' = w^T V^{-1} i' =& w^T V^{-1}((F-V)if(i,u)) \\ =& w^T V^{-1}(F-V)i - w^T V^{-1} f(i,u) \\ =& w^T V^{-1}(\mathcal{R}_0 - 1) - w^T V^{-1} f(\mathcal{S},\mathcal{I}) \end{aligned}$$

Since $w^T \geq 0, V^{-1} \geq 0$ and $f(i,u) \geq 0$ in Γ, this implies $w^T V^{-1}(\mathcal{R}_0 - 1) - w^T V^{-1} f(\mathcal{S},\mathcal{I}) \leq 0$. If $\mathcal{R}_0 \leq 1$, then $Q' \leq 0$ in Γ, and thus Q is a Lyapunov function for system 2.12. □

The Lyapunov function constructed in Theorem 2.24 can be used to prove global stability of DFE as well as uniform persistence and thus establish the existence of an EE. The result below provides a scenario in which assumptions can be conveniently checked for disease models.

Theorem 2.25. *Let F, V and $f(i,u)$ be defined as in (2.10) and (2.15a), respectively, and let $\Gamma \subset \mathbb{R}^{n+m}_+$ be compact such that $(0,u_0) \in |Gamma$ and Γ is positively invariant with respect to (2.12). Suppose that $f(i,u) \geq 0$ with $f(i,u_0) = 0$ in Γ,*

$F \geq 0, V^{-1} \geq 0$ and $V^{-1}F$ is irreducible. Assume that the disease-free system $u_0 = g(0, u)$ has a unique equilibrium $u = u_0 > 0$ that is GAS in $\mathbb{R}^m_+$. Then the following results hold for (2.12):

(i) if $\mathcal{R}_0 < 1$, then the DFE ε_0 is GAS in Γ.

(ii) if $\mathcal{R}_0 > 1$, then ε_0 is unstable and system (2.12) is uniformly persistent and there exists at least one EE.

If $f(i, u_0) = 0$ in $\Gamma, F \geq 0, V^{-1} \geq 0$ and FV^{-1} is reducible then this theorem cannot be used to establish the global stability of the disease free equilibrium point.

This result was used to study global stability for some disease models in the following references [13, 60].

2.7 Parameter Estimation

The mathematical analysis of models is very useful for understanding asymptotic behaviors and longtime qualitative outcomes, While the outcomes of a model critically depends on the values of the model parameters. Since models are confronted with disease data, an accurate estimation of parameter values is essential for reliable quantitative predictions within a finite time interval. For estimation of multiple parameters, a systematic approach for the fitting is desirable. Different tecniques was used for estimating the parameters in [24, 39, 61]. In this section, we discuss one of the most commonly used method for parameter estimation, which is nonlinear least square (NLS) method.

2.7.1 Nonlinear Least Square Method

In this least-squares approach, we assume that the time coordinates of the data are exact, but their corresponding y-coordinates (infections) may be noisy or distorted. We fit the solution curve through the data so that the sum of the squares of the vertical distances from the data points to the point on the curve is as small

as possible. This distance is commonly known as least squares error. Next we illustrate how to use NLS method to estimate unknown parameters

Step 1. Data Collection
In particular, suppose we are fitting the virions $C(t)$, with the given data

$$\{(t_1, \widehat{C}_1), (t_2, \widehat{C}_2), ..., (t_n, \widehat{C}_n)\}.$$

Step 2. NLS fitting
So the basic problem is to identify the set parameters θ such that the following sum-of-squares error (SSE) is as small as possible:

$$\underset{\min \theta}{SSE} = \sum_{i=1}^{n} \left\{C(t_i, \theta) - \widehat{C}(t_i)\right\}^2,$$

where $C(t_i, \theta)$ represents the virus concentration at time t_i with parameter θ and $\widehat{C}(t_i)$ represents the data value at time t_i. Such a problem is clearly a nonlinear least-squares problem, since the dependence of a solution on the parameter θ is through a highly nonlinear system of differential equations.

Step 3. Solve the NLS problem numerically
We use a Matlab functions *fminsearch* which takes the least-squares error function $SSE(\theta)$ and an initial guess of the parameter value θ_0, and uses a direct search routine to find a minimum value of least-squares error.

2.8 Optimal Control Method

In an optimal control problem for ordinary differential equations, we use $u(t)$ for the control and $x(t)$ for the state variables. The state variable satisfies a differential equation which depends on the control variable:

$$x'(t) = g(t, x(t), u(t))$$

where x' denote the derivative with respect to time t. Both $u(t)$ and $x(t)$ affect the goal, as the control function changes, the solution to the differential equation will also change. The basic optimal control problem consists of finding a piecewise continuous control $u(t)$ and the associated state variable $x(t)$ to maximize or minimize the given objective functional depending on the situation. Let us consider

the former for this case, i.e.,

$$\text{Maximize } J(u) = \int_0^T f(t, x(t), u(t))$$

subject to

$$x'(t) = g(t, x(t), u(t)) \tag{2.16}$$

where $x(0) = x_0$ and $x(T)$ is free.

We assume that the controls are piecewise continuous functions with values in a set. The principal technique for such an optimal control problem is to solve a set of necessary conditions that an optimal control and corresponding state must satisfy. Next we presented a brief derivation of the necessary conditions. That is, if $u(t)$, $x(t)$ is an optimal pair, then these conditions will hold. These necessary conditions for optimal control theory for ODEs was developed by Pontryagin and his collaborators around 1950. They developed the key idea of introducing the adjoint function to attach the differential equation to the objective functional. This idea is similar to Lagrange multipliers that attach the constraints when finding the maximum of a function in multi-dimensional calculus subject to some equation constraints. The following theorem (known as Pontryagin's Maximum Principle), provide necessary conditions for the optimal control using the Hamiltonian [44].

Theorem 2.26. *(Pontryagin's Maximum Principle) If u^* and x^* are optimal for equation (2.16), subject to the ODEs defining the given dynamical system, then there exists a piecewise differentiable adjoint variable $\lambda(t)$ such that*

$$H(t, x^*, u(t), \lambda(t)) \leq H(t, x^*, u^*(t), \lambda(t))$$

for each control u at each time t, where the Hamiltonian H is

$$H = f(t, x(t), u(t)) + \lambda(t) g(t, x(t), u(t))$$

and

$$\lambda'(t) = -\frac{\partial H(t, x^*, u^*(t), \lambda(t)}{\partial x},$$
$$\lambda(T) = 0.$$

where f is the integrand of the objective functional and g, the right hand side of the given dynamical system. The optimal control u^* must maximize the Hamiltonian.

Chapter 3

The Diphtheria Epidemic Model

3.1 Introduction

Material from references [34], and [24, 34, 47] are used in this section.
In order to understand the dynamics of infectious diseases, models are often formulated. To achieve this, we divide the population under study into compartments and make assumptions about the nature and rates of transfer from one compartment to another. Diseases that confer permanent immunity have a different compartmental structure from diseases without immunity. The term SIR describes a disease which confers immunity against reinfection, indicating that movement of individuals is from the susceptible compartment S to the infectious compartment I and to the removed compartment R. The term susceptible-infectious-susceptible (SIS) describes a disease with no immunity, movement is from the susceptible compartment S to the infectious compartment I and back to the susceptible compartment. Other possibilities include susceptible-exposed-infectious-recovered (SEIR) and susceptible-exposed-infectious-susceptible (SEIS) models, each having exposed period between being infected and becoming infectious and susceptible-infectious-recovered-susceptible (SIRS) model describes disease with temporary immunity after recovery from the infection. Differential equations are used to describe the rates of transfer between compartments, with time being the independent variable [34]. In our thesis we develop a model for the spread of diphtheria in population using latent compartment L instead of exposed in SEIR model. Therefore our proposed model become SLIR instead of SEIR.

3.2 Mathematical Model

Assuming the total population at time t, denoted by $N(t)$, which is subdivided into four classes: Susceptible (S(t)), Latent (asymptotic) stage (L(t)), individual infected with diphtheria in the active stage (I(t)), recovered individuals infected with diphtheria (R(t)), that is , we assume that the recovered individuals are also infectious. All recruitment is into the susceptible class, and occurs at a constant rate λ. The natural death rate is μ. The infectious class has an additional death rate due to deases with rate α. The time before latent individuals become infectious is assumed to satisfy an exponential distribution, with mean waiting time $\frac{1}{\delta}$. Thus, individuals leave class L for class I at rate δL. Infectious individuals are treated with constant rate γ, entering the recovered class. Susceptible individuals acquire diphtheria infection from individuals with active diphtheria at rate βSI, where β is the disease transmission coefficient. A fraction l, of susceptible individuals who acquire diphtheria infection moves to the latent diphtheria class (L), at rate $l\beta SI$ and the remaining fraction, $(1-l)$ moves to the active diphtheria class (I). It is assumed that individuals in the latent class do not transmit infection.

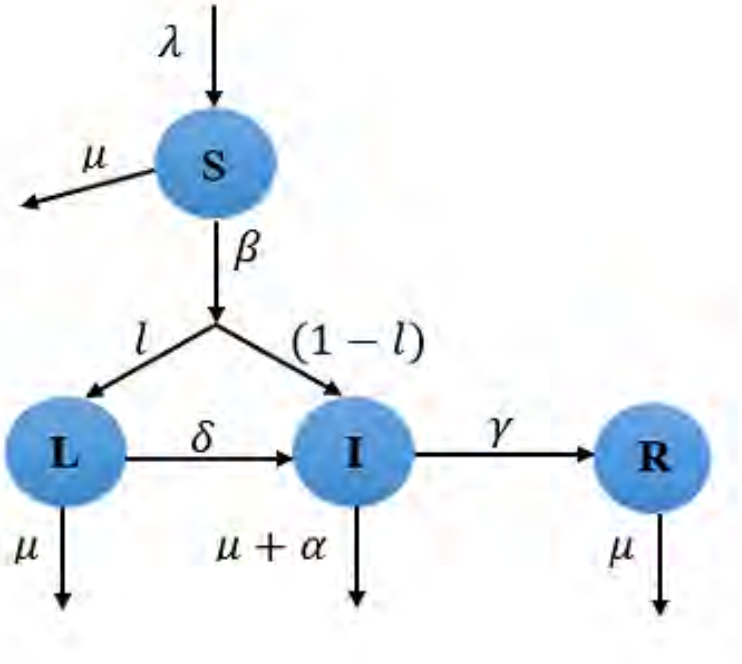

Figure. 3.1. Diagram interaction of each compartment.

Combining all the aforementioned assumptions, the model for the transmission dynamics of diphtheria is given by the following system of differential equations:

$$\begin{cases} \dfrac{dS(t)}{dt} = \lambda - \beta S(t)I(t) - \mu S(t) \\ \dfrac{dL(t)}{dt} = l\beta S(t)I(t) - (\mu + \delta)L(t) \\ \dfrac{dI(t)}{dt} = (1-l)\beta S(t)I(t) + \delta L(t) - (\mu + \gamma + \alpha)I(t) \\ \dfrac{dR(t)}{dt} = \gamma I(t) - \mu R(t) \end{cases} \tag{3.1}$$

subsidiary conditions :

$$S(0) = S_0 > 0, \quad L(0) = L_0 \geq 0, \quad I(0) = I_0 \geq 0, \quad R(0) = R_0 \geq 0 \tag{3.2}$$

3.3 Basic Properties of the Model

In order to retain the biological validity of the model, we must prove that solutions to the system of differential equations exist and they are positive and bounded for all values of time.

Theorem 3.1. *(Existence of Solution). Let $S_0, L_0, I_0, R_0 \in \mathbb{R}$ be given. There exists $t_0 > 0$ and continuously differentiable functions $\{S, , L, I, R : [0, t_0) \to \mathbb{R}\}$ such that the 4-tuples (S, L, I, R) satisfies (3.1) and $(S, L, I, R)(0) = (S_0, L_0, I_0, R_0)$.*

Proof of Theorem 3.1. The Picard-Lindelöf Theorem narrated that for the initial value problem $y'(t) = g(y(t)),\ y(t_0) = y_0, t \in [t_0 - \epsilon, t_0 + \epsilon]$, if g is locally Lipschitz in y and continuous in t, then for some value $\epsilon > 0$, there exists a unique solution $y(t)$ to the initial value problem within the range $[t_0 - \epsilon, t_0 + \epsilon]$. Since the system of ODEs is independent, it suffices to show that the function $\mathbf{g} : \mathbb{R}^4 \to \mathbb{R}^4$ defined by

$$\mathbf{g}(\mathbf{y}) = \begin{pmatrix} \lambda - \beta SI - \mu S \\ l\beta SI - (\mu + \delta)L \\ (1-l)\beta SI + \delta L - (\mu + \gamma + \alpha)I \\ \gamma I - \mu R \end{pmatrix}$$

is locally Lipschitz in its $\mathbf{y}$ argument. The Jacobian matrix

$$\nabla \mathbf{g}(\mathbf{y}) = \begin{pmatrix} -\beta I - \mu & 0 & -\beta S & 0 \\ l\beta I & -(\mu+\delta) & l\beta S & 0 \\ (1-l)\beta I & \delta & (1-l)\beta S - (\mu+\gamma+\alpha) & 0 \\ 0 & 0 & \gamma & -\mu \end{pmatrix}$$

is linear in $\mathbf{y} \in \mathbb{R}^4$. Thus, $\nabla \mathbf{g}(\mathbf{y})$ is continuous on a closed interval and differentiable on an open interval $I \in \mathbb{R}^4$. By the Mean Value Theorem, we know

$$\frac{|\mathbf{g}(\mathbf{y_1}) - \mathbf{g}(\mathbf{y_2})|}{|\mathbf{y_1} - \mathbf{y_2}|} \leq |\nabla \mathbf{g}(\mathbf{y}^*)|$$

for some $\mathbf{y}^* \in I$. By letting $|\nabla \mathbf{g}(\mathbf{y}^*)| = K$, we obtain $|\mathbf{g}(\mathbf{y_1}) - \mathbf{g}(\mathbf{y_2})| \leq K|\mathbf{y_1} - \mathbf{y_2}|$ for all $\mathbf{y_1}, \mathbf{y_2} \in I$ and therefore $\mathbf{g}(\mathbf{y})$ is locally bounded for every $\mathbf{y} \in \mathbb{R}^4$. Hence, $\mathbf{g}$ has a continuous, bounded derivative on any compact subset of $\mathbb{R}^4$ and so $\mathbf{g}$ is locally Lipschitz in $\mathbf{y}$. By the Picard-Lindelöf Theorem, there exists a unique solution, $y(t)$, to the ordinary differential equation $y'(t) = g(y(t))$ with initial value $y(0) = y_0$ on $[0, t_0]$ for some time $t_0 > 0$. □

Theorem 3.2. *The proposed model (3.1) is invariant in the non-negative orthant* $\mathbb{R}^4_+$.

Proof of Theorem 3.2. Let $Y = (S, L, I, R)^T$, then model (3.1) will takes the form

$$\frac{dY(t)}{dt} = LY + C, \tag{3.3}$$

where

$$L = \begin{pmatrix} -(\beta I(t) + \mu) & 0 & 0 & 0 \\ l\beta I(t) & -(\mu+\delta) & 0 & 0 \\ (1-l)\beta I(t) & \delta & -(\mu+\gamma+\alpha) & 0 \\ 0 & 0 & \gamma & -\mu \end{pmatrix}$$

$$C = \begin{pmatrix} \lambda \\ 0 \\ 0 \\ 0 \end{pmatrix}$$ Here, $C \geq 0$ and all of the off-diagonal elements of matrix L are non-negative. Hence L is a Metzler matrix and the system (3.1) is positive invariant in $\mathbb{R}^4_+$. □

Theorem 3.3. *Any solution* (S, L, I, R) *of the model (3.1) with conditions (3.2) is positive for all* $t > 0$.

Proof of Theorem 3.3. Since, R.H.S. of the model (3.1) is differentiable, therefore, connecting it with Cauchey problem covenants the existence of a unique maximal solution. The solution of the first equation of system (3.1) can be figured alternatively as

$$\frac{dS(t)}{dt} + \big(\beta I(t) + \mu\big)S(t) = \lambda \tag{3.4}$$

The solution of equation (3.4) is

$$S(t) = S_0\ e^{\{-(\mu t + \int_0^t \beta I(x)\,dx\}} + e^{\{-(\mu t + \int_0^t \beta I(x)\,dx)\}} \times \int_0^t \lambda\ e^{\{\mu y + \int_0^t \beta I(u)\,du\}}\,dy \tag{3.5}$$

for all $t > 0$. It is cleared that the RHS of equation (3.5) is non-negative, i.s. , $S(t) > 0$ for all $t > 0$. In the same way, solution of the second, third and fourth equation of model (3.1) are of the form

$$L(t) = L_0\ e^{\{-(\mu+\delta)t\}} + e^{\{-(\mu+\delta)t\}} \times \int_0^t l\beta S(y)I(y)\ \ e^{\{(\mu+\delta)y\}}\,dy \tag{3.6}$$

$$\begin{aligned} I(t) = I_0\ e^{\{-((\mu+\gamma+\alpha)t - \int_0^t (1-l)\beta S(x)\,dx)\}} + e^{\{-((\mu+\gamma+\alpha)t - \int_0^t (1-l)\beta S(x)\,dx)\}} \\ \times \int_0^t \delta L(y)\ \ e^{\{(\mu+\gamma+\alpha)y - \int_0^t (1-l)\beta S(u)\,du\}}\,dy \end{aligned} \tag{3.7}$$

$$R(t) = R_0\ e^{\{-\mu t\}} + e^{\{-\mu t\}} \times \int_0^t \gamma I(y)\ \ e^{\{\mu y\}}\,dy \tag{3.8}$$

which show that all $L(t), I(t)$ *and* $R(t)$ are non-negative for all $t > 0$ □

Theorem 3.4. *(Boundedness). Assume the initial conditions of (3.1) satisfy* $S_0 > 0, L_0 > 0, I_0 > 0$, *and* $R_0 > 0$. *If the unique solution provided by Theorem 3.1 exists on the interval* $[0, t_0]$ *for some* $t_0 > 0$, *then the functions* $S(t), L(t), I(t)$ *and* $R(t)$ *will be bounded and remain positive for all* $t \in [0, t_0]$.

Proof of Theorem 3.4. We assume that $S(t), L(t), I(t)$ and $R(t)$ initially have positive values. From the previous theorem, there exists a $t > 0$ such that the solution exists on $[0, t]$. Let us denote by T^* the largest time for which all populations remain positive, or more precisely

$$T^* = \sup\{t > 0 : S(s), L(s), I(s), R(s) > 0,\ \forall s \in [0, t]\}.$$

Since each initial condition is nonnegative and the solution is continuous, there must be an interval on which the solution remains positive, and we see that $T^* > 0$. Then on the interval $[0, T^*]$ we estimate each term. We can place lower bounds on L, I, and R instantly

$$\frac{dL(t)}{dt} = l\beta S(t)I(t) - (\mu + \delta)L(t) \geq -(\mu + \delta)L(t),$$

since the decay terms are linear, that concludes

$$\begin{aligned} \frac{dL(t)}{L(t)} &\geq -(\mu + \delta)dt \\ ln(L(t)) + lnC &\geq -(\mu + \delta)t \\ L(t) &\geq Ce^{-(\mu+\delta)t} \end{aligned}$$

Applying initial condition we get

$$\begin{aligned} L(0) &\geq C \\ \Rightarrow L(t) &\geq L(0)e^{-(\mu+\delta)t} > 0, \end{aligned}$$

for $t \in [0, T^*]$. Again,

$$\frac{dI(t)}{dt} = (1 - l)\beta S(t)I(t) + \delta L(t) - (\mu + \gamma + \alpha)I(t) \geq -(\mu + \gamma + \alpha)I(t),$$

since the decay terms are linear, that concludes

$$I(t) \geq I(0)e^{-(\mu+\gamma+\alpha)t} > 0,$$

for $t \in [0, T^*]$. Further,

$$\begin{aligned} \frac{dR(t)}{dt} &= \gamma I(t) - \mu R(t) \geq -\mu R(t), \\ \text{i.e. } R(t) &\geq R(0)e^{-\mu t} > 0 \end{aligned}$$

for $t \in [0, T^*]$. Similarly, we can place an upper bound on $\frac{dS}{dt}$ so that

$$\begin{aligned} \frac{dS(t)}{dt} &= \lambda - \beta S(t)I(t) - \mu S(t) \leq \lambda, \\ \text{i.e. } S(t) &\leq S(0) + \lambda t \leq C(1 + t), \end{aligned}$$

where the constant C depends on the upper bound of λ and $S(0)$. Next, we sum

the equations for L, I, and R, and by positivity of these functions and place bounds on this sum. Using the upper bound on $S(t)$, we find

$$\begin{aligned}\frac{d}{dt}(L+I+R) &= \beta S(t)I(t) - \mu L(t) - (\mu+\alpha)I(t) - \mu R(t),\\ &\leq \beta C(1+t)I(t) + \mu L(t) + (\mu+\alpha)I(t) + \mu R(t),\\ &\leq C_2(1+t)(L+I+R), \quad \text{where } \; C_2 \geq \max\{\beta C, \mu, (\mu+\alpha)\},\\ \text{i.e. } (L+I+R)(t) &\leq C_3 e^{t^2}\end{aligned}$$

for $t \in [0, T^*]$, where $C_3 > 0$ depends upon $C_2, L(0), I(0)$, and $R(0)$ only. Since $L(t), I(t)$ and $R(t)$ are positive, we can place an upper bound on both L, I and R by

$$C_3 e^{t^2} \geq (L+I+R)(t) \geq L(t)$$

,

$$C_3 e^{t^2} \geq (L+I+R)(t) \geq I(t),$$

and

$$C_3 e^{t^2} \geq (L+I+R)(t) \geq R(t).$$

With these bounds in place, we can now examine $S(t)$ and bound it from below using

$$\begin{aligned}\frac{dS}{dt} &= \lambda - \beta SI - \mu S \geq -\beta SI - \mu S \geq -\mu S - \beta C_3 e^{t^2} S,\\ &\geq -C_4(1+e^{t^2})S, \quad \text{where } \; C_4 \geq \max\{\beta C_3, \mu\},\\ \Rightarrow \frac{dS}{dt} &+ C_4(1+e^{t^2})S \geq 0,\\ \text{i.e. } S(t) &\geq S(0)e^{-C_4\int_0^t (1+e^{\tau^2}d\tau)} > 0\end{aligned}$$

for $t \in [0, T^*]$. Thus, the values of S, L, I and R stay strictly positive for all of $[0, T^*]$, including at time T^*. By continuity, there must exist a $t > T^*$ such that $T(t), I(t)$, and $V(t)$ are still positive. This contradicts the definition of T^*, and shows that $S(t), L(t), I(t)$ and $R(t)$ are strictly positive on the entire interval $[0, t]$. Moreover, on this same interval, all of the functions remain bounded, so the interval of existence can be extended further. In fact, the bounds on S, L, I, and R derived above hold on any compact time interval. Thus, we may extend the time interval on which the solution exists to $[0, t]$ for any $t > 0$ and from the above argument, the solutions remain both bounded and positive on $[0, t]$. □

3.4 Equilibria of the Syatem

In order to fully understand the dynamics of the basic model, it is necssary to study the equilibrium points.

Definition 3.5. Consider the differential equation $y'(t) = f(y(t), t)$, a point $y(t)$ is an equilibrium point if $y'(t) = f(y(t), t) = 0$ for all $t \in \mathbb{R}$

In our case, an equilibrium point is the constant solution of (3.1) so that if the system begins at such a value, it will remain there for all time. In other words, the cell numbers are unchanging; so, the rate of change for each compartment is zero. By setting the right-hand side of (3.1) to zero, we get

$$\lambda - \beta SI - \mu S = 0 \tag{3.9}$$

$$l\beta SI - (\mu + \delta)L = 0 \tag{3.10}$$

$$(1 - l)\beta SI + \delta L - (\mu + \gamma + \alpha)I = 0 \tag{3.11}$$

$$\gamma I - \mu R = 0 \tag{3.12}$$

and solving the resulting equations for S, L, I and R, we find that there exists exactly two equilibria which are biologically meaningful. We can categorize these points to be when the Diphtheria bacteria is either extinct from the body, i.e., $L = I = R = 0$, or when the disease persists within the populations ($L \neq 0, I \neq 0, R \neq 0$) as t grows large.

We begin by solving for the nonlinear interaction term in the equations (3.10), (3.11) and (3.12) that gives

$$l\beta SI = (\mu + \delta)L$$

$$(1 - l)\beta SI + \delta L = (\mu + \gamma + \alpha)I$$

$$\gamma I = \mu R$$

which implies

$$I\big((1 - l)(\mu + \delta)\beta S + \delta l\beta S - (\mu + \delta)(\mu + \gamma + \alpha)\big) = 0$$

Thus, either $I = 0$ or $S = \frac{(\mu+\delta)(\mu+\gamma+\alpha)}{((1-l)\mu+\delta)\beta}$. Using $I = 0$ in the equation (3.10), (3.11) and (3.12) gives $L = 0, R = 0$ and $S = \frac{\lambda}{\mu}$. Hence, the ordered multiple

$$(S, L, I, R) = (\frac{\lambda}{\mu}, 0, 0, 0)$$

This particular equilibrium point is also known as disease extinction, since there are no infected cell. We will refer to this point as $E^0 = (S^0, L^0, I^0, R^0)$. In the latter case, $S = \frac{(\mu+\delta)(\mu+\gamma+\alpha)}{((1-l)\mu+\delta)\beta}$ and substituting this value of S into equation (3.9) and (3.12) yeilds $I = \frac{\lambda(\delta+(1-l)\mu)}{(\mu+\delta)(\mu+\gamma+\alpha)} - \frac{\mu}{\beta}$ and $R = \frac{\gamma\lambda(\delta+(1-l)\mu)}{\mu(\mu+\delta)(\mu+\gamma+\alpha)} - \frac{\gamma}{\beta}$ and further substitution shows $L = \frac{l\lambda}{(\mu+\delta)} - \frac{l\mu(\mu+\gamma+\alpha)}{\beta(\delta+(1-l)\mu)}$. Thus, a second equilibrium exists at the point

$$\begin{aligned}(S, L, I, R) = \Bigg(& \frac{(\mu+\delta)(\mu+\gamma+\alpha)}{((1-l)\mu+\delta)\beta}, \ \frac{l\lambda}{(\mu+\delta)} - \frac{l\mu(\mu+\gamma+\alpha)}{\beta(\delta+(1-l)\mu)}, \\ & \frac{\lambda(\delta+(1-l)\mu)}{(\mu+\delta)(\mu+\gamma+\alpha)} - \frac{\mu}{\beta}, \ \frac{\gamma\lambda(\delta+(1-l)\mu)}{\mu(\mu+\delta)(\mu+\gamma+\alpha)} - \frac{\gamma}{\beta}\Bigg)\end{aligned}$$

Since there are distinct presence of bacteria particles and infected cells, we refer to this point as viral persistence and abbreviate the point as $E^* = (S^*, L^*, I^*, R^*)$.

In terms of biology, we can say E^0 is the case in which an infection exists for a short period of time, then is removed from the population by nature means. The disease does not persist. The second case, where the system of equations tends to E^*, denoted that situation where the population is unable to clear the infection naturally. If this ends up being the case, than after a certain period of time, the Diphtheria infection model loses its applicability as the infection takes a deeper hold on population. More complex models, which consider effects of macrophages, cytotoxic immune response (CLT), or spatial dependence are then required to describe the spread of Diphtheria within the bode and its development towards Diphtheria outbreak.

If the system (3.1) takes on the value of a equilibrium point at any time, it will remain at the point for all remaining time, otherwise the system need not necessarily obtain these values. However, the system may approach the equilibrium point, move away from the equilibrium point, or cycle between specific values. In order to accurately determine the behavior and thus how the system will interact with the equilibrium we must undergo a stability analysis for the system.

3.5 Basic Reproduction Number

The basic reproduction number ($\mathcal{R}_0$) is used to measure the transmission potential of a disease. It is the average number of secondary infections produced by a typical case of an infection in a population where everyone is susceptible. Applying the next generation method which is discussed in Chapter 2 to the model (3.1), and since we are only concerned with persons that spread the infection, we only neeed to model the latend compaertment L, and infected compaertment I. Let us define the model dynamics using the equations

$$\begin{aligned}\frac{dL(t)}{dt} &= l\beta SI - (\mu+\delta)L \\ \frac{dI(t)}{dt} &= (1-l)\beta SI + \delta L - (\mu+\gamma+\alpha)I\end{aligned}$$

For this system, at the disease free equilibrium point

$$F_i(x) = \begin{pmatrix} l\beta SI \\ (1-l)\beta SI \end{pmatrix}$$

$$F = \begin{pmatrix} 0 & l\beta S^0 \\ 0 & (1-l)\beta S^0 \end{pmatrix}$$

and

$$V_i(x) = \begin{pmatrix} (\mu+\delta)L \\ (\mu+\gamma+\alpha)I - \delta L \end{pmatrix}$$

$$V = \begin{pmatrix} \mu+\delta & 0 \\ -\delta & \mu+\gamma+\alpha \end{pmatrix}$$

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

$$FV^{-1} = \begin{pmatrix} \frac{l\delta\beta S^0}{\mu(\mu+\gamma+\alpha)(\mu+\delta)} & \frac{l\beta S^0}{\mu(\mu+\gamma+\alpha)} \\ \frac{(1-l)\delta\beta S^0}{\mu(\mu+\gamma+\alpha)(\mu+\delta)} & \frac{(1-l)\beta S^0}{\mu(\mu+\gamma+\alpha)(\mu+\delta)} \end{pmatrix}$$

The dominant eigenvalue of FV^{-1} is given by expression

$$\mathcal{R}_0 = \frac{\beta(\delta+\mu-l\mu)S^0}{(\alpha+\gamma+\mu)(\delta+\mu)}$$

Putting $S^0 = \frac{\lambda}{\mu}$, we obtain,

$$\mathcal{R}_0 = \frac{\lambda\beta\big(\delta + (1-l)\mu\big)}{\mu(\alpha+\gamma+\mu)(\delta+\mu)}$$

and it is the basic reproduction number for the system (3.1).

The basic reproduction number $\mathcal{R}_0$ is the average number of the secondary infections produced when one single bactria is introduced into a host where every $S - person$ is susceptible [18]. Note that our model $\mathcal{R}_0$ above is a product of the average number of target person per unit time (in the presence of natural death) and the rate of the disease transmission by an infective person. It is indeed a threshold quantity that helps to determine whether an outbreak of the disease dies out or spreads in a body. Later we will see, when $\mathcal{R}_0 < 1$, the disease die out without any medical interventions but when $\mathcal{R}_0 > 1$, the disease becomes endemic and this necessittates the introduction of some control measures in order to curtail the situation.

Remark 3.6. Using basic reproduction number $\mathcal{R}_0$ the infected equilibrium point become

$$(S^*, L^*, I^*, R^*) = \left\{ \frac{(\mu+\delta)(\mu+\gamma+\alpha)}{((1-l)\mu+\delta)\beta}, \frac{l\lambda(\mathcal{R}_0-1)}{(\mu+\delta)\mathcal{R}_0}, \frac{\mu}{\beta}(\mathcal{R}_0-1), \frac{\gamma}{\beta}(\mathcal{R}_0-1) \right\}.$$

3.6 Global Stability of the Equilibria

Before proceeding with the global stability analysis for the model (3.1), we present some inequalities developed in [48], which will be used in the proofs. To begin with, we consider the function $H(x) = x - 1 - \ln(x)$. Note that $H(x) \geq 0, \forall x$ and that $H(x) = 0$ if and only if $x = 1$.
Let $x_1, x_2, \cdots, x_n$ be positive numbers. Then,

$$1 - x_i + \ln(x_i) = -H(x_i) \leq 0, \quad i = 1, 2, \cdots, n.$$

Summing over $i = 1$ to n, from above equation we obtain

$$n - \sum_{i=1}^{n} x_i + \ln\left(\prod_{i=1}^{n} x_i\right) \leq 0.$$

Choosing $x_i = \dfrac{p_i}{q_i}$, where $p_i > 0$, $q_i > 0$ for $i = 1$ to n, it followes that

$$n - \sum_{i=1}^{n} \frac{p_i}{q_i} + \ln\left(\prod_{i=1}^{n} \frac{p_i}{q_i}\right) \leq 0.$$

If $p_1, p_2, \cdots, p_n = q_1, q_2, \cdots, q_n$, then $\prod_{i=1}^{n} \dfrac{p_i}{q_i} = 1$ which leads to

$$n - \sum_{i=1}^{n} \frac{p_i}{q_i} \leq 0 \tag{3.13}$$

Theorem 3.7. *If $\mathcal{R}_0 \leq 1$, then the non-infective equilibrium (E^0) is globally asymptotically stable and the disease dies out.*

Proof of Theorem 3.7. To investigate the global stability of E^0, consider the following Lyapunov function

$$U(t) = S^0\left[\frac{S(t)}{S^0} - 1 - \ln\left(\frac{S(t)}{S^0}\right)\right] + \frac{\delta}{(1-l)\mu + \delta}L(t) + \frac{\mu + \delta}{(1-l)\mu + \delta}I(t).$$

$$\frac{dU}{dt} = \left(1 - \frac{S^0}{S}\right)S' + \frac{\delta}{(1-l)\mu + \delta}L' + \frac{\mu + \delta}{(1-l)\mu + \delta}I'.$$

Notice that U is nonnegative, and U is identically zero if and only if it is evaluated at the non-infective equilibrium point $(S^0, L^0, I^0, R^0) = \left(\dfrac{\lambda}{\mu}, 0, 0, 0\right)$. We compute the derivative along trajectories and find

$$\begin{aligned}
\frac{dU}{dt} =& \left(1 - \frac{S^0}{S}\right)\Big[\lambda - \beta SI - \mu S\Big] + \frac{\delta}{(1-l)\mu + \delta}\Big[l\beta SI - (\mu + \delta)L\Big] \\
&+ \frac{\mu + \delta}{(1-l)\mu + \delta}\Big[(1-l)\beta SI + \delta L - (\mu + \gamma + \alpha)I\Big] \\
=& (\lambda - \mu S)\left(1 - \frac{S^0}{S}\right) + \beta S^0 I - \frac{(\mu + \delta)(\mu + \gamma + \alpha)}{\mu(1-l) + \delta}I
\end{aligned}$$

After using the definition of S^0, we are left with

$$\begin{aligned}
\frac{dU}{dt} &= (\lambda - \mu S)\left(1 - \frac{\lambda}{\mu S}\right) + \frac{(\mu + \delta)(\mu + \gamma + \alpha)}{\mu(1-l) + \delta}\left(\frac{\lambda\beta(\mu(1-l) + \delta}{\mu(\mu + \delta)(\mu + \gamma + \alpha)} - 1\right) \\
&= -\frac{(\lambda - \mu S)^2}{\mu S} + \frac{(\mu + \delta)(\mu + \gamma + \alpha)}{\mu(1-l) + \delta}(\mathcal{R}_0 - 1)
\end{aligned}$$

Thus, under the assumption that $\mathcal{R}_0 \leq 1$, we see that $\frac{dU}{dt} \leq 0$ for all positive values of S, L, I, and R, and the global asymptotic stability follows by LaSalle's Invariance Principle [17]. Therefore the system (3.1) is globally asymptotically stable for $\mathcal{R}_0 \leq 1$. □

Theorem 3.8. *If $\mathcal{R}_0 > 1$, then the endemic equilibrium (E^*) is globally asymptotically stable and the disease persists.*

Proof of Theorem 3.8. For the disease persistent equilibrium, none of the end values are zero, so we denote this steady state by (S^*, L^*, I^*, R^*) and define a Lyapunov function as

$$U(t) = \left(S - S^* - S^* ln\left(\frac{S}{S^*}\right)\right) + B_1\left(L - L^* - L^* ln\left(\frac{L}{L^*}\right)\right) + B_2\left(I - I^* - I^* ln\left(\frac{I}{I^*}\right)\right) + B_3\left(R - R^* - R^* ln\left(\frac{R}{R^*}\right)\right)$$

where B_1, B_2 and B_3 are positive constants to be determined. This type of Layapunov function has been mentioned in [3, 12, 28, 58].

The positive equilibrium $E^* = (S^*, L^*, I^*, R^*)$ satisfies the following equations.

$$\begin{aligned} \lambda &= \beta S^* I^* + \mu S^* \\ (\mu + \delta) L^* &= l\beta S^* I^* \\ (\mu + \gamma + \alpha) &= (1 - l)\beta S^* I^* + \delta L^* \\ \mu R^* &= \gamma I^* \end{aligned} \tag{3.14}$$

We can now write the time derivative of U as

$$\begin{aligned} U' =& \left(1 - \frac{S^*}{S}\right) S' + B_1\left(1 - \frac{L^*}{L}\right) L' + B_2\left(1 - \frac{I^*}{I}\right) I' + B_3\left(1 - \frac{R^*}{R}\right) R' \\ =& \left(1 - \frac{S^*}{S}\right)\left[\lambda - \beta SI - \mu S\right] + B_1\left(1 - \frac{L^*}{L}\right)\left[l\beta SI - (\mu + \delta)L\right] + B_2\left(1 - \frac{I^*}{I}\right) \\ & \left[(1 - l)\beta SI + \delta L - (\mu + \gamma + \alpha)I\right] + B_3\left(1 - \frac{R^*}{R}\right)\left[\gamma I - \mu R\right] \end{aligned}$$

$$
\begin{aligned}
=& -\mu\frac{(S-S^*)^2}{S} + \beta S^* I^*\left(1-\frac{S^*}{S}\right) + SI\big[-\beta + B_1 l\beta + B_2(1-l)\beta\big] \\
&+ I\big[-B_2(\mu+\gamma+\alpha) + B_3\gamma + \beta S^*\big] + L\big[-B_1(\mu+\delta) + B_2\delta\big] \\
&+ T\big[-B_3\mu\big] - B_1 l\beta SI\frac{L^*}{L} + B_1 l\beta S^* I^* - B_2(1-l)\beta SI^* \\
&- B_2\delta L\frac{I^*}{I} + B_2(1-l)\beta S^* I^* + B_2\delta L^* - B_3\gamma I\frac{R^*}{} + B_3\gamma I^*
\end{aligned}
\tag{3.15}
$$

Now the positive constants B_1, B_2 and B_3 are chosen such that the coefficients of SI, ST, I, T and L are equal to zero, that is,

$$
\begin{aligned}
&-\beta + B_1 l\beta + B_2(1-l)\beta = 0 \\
&-B_2(\mu+\gamma+\alpha) + B_3\gamma + \beta S^* = 0 \\
&-B_1(\mu+\delta) + B_2\delta = 0 \\
&-B_3\mu = 0
\end{aligned}
\tag{3.16}
$$

Solving the above equations yeilds

$$
B_1 = \frac{\delta}{\mu+\delta}B_2, \qquad B_2 = \frac{\mu+\delta}{(1-l)\mu+\delta} \quad \textit{and} \quad B_3 = 0
$$

Now, replacing the above expressions of B_1, B_2 and B_3 in equation (3.15), we have

$$
\begin{aligned}
=& -\mu\frac{(S-S^*)^2}{S} + 2B_1 l\beta S^* I^* + 2B_2(1-l)\beta S^* I^* - B_1 l\beta S^* I^*\frac{S^*}{S} - B_2(1-l)\beta S^* I^*\frac{S^*}{S} \\
&- B_1 l\beta SI\frac{L^*}{L} - B_2(1-l)\beta SI^* + B_2\delta L^*\left(1-\frac{L}{L^*}\frac{I^*}{I}\right) + B_3\gamma I^*\left(1-\frac{I}{I^*}\frac{T^*}{T}\right)
\end{aligned}
$$

For convenience, we introduce new variables $x = \frac{S}{S^*}, y = \frac{L}{L^*}, z = \frac{I}{I^*}$and $u = \frac{T}{T^*}$ to eliminate S, L, I, T.

$$
\begin{aligned}
U' =& -\mu\frac{(S-S^*)^2}{S} + B_2(1-l)\beta S^* I^*\left(2-\frac{1}{x}-x\right) + B_1 l\beta S^* I^*\left(2-\frac{1}{x}-\frac{xz}{y}\right) \\
&+ B_2\delta L^*\left(1-\frac{y}{z}\right) + B_3\gamma I^*\left(1-\frac{z}{u}\right)
\end{aligned}
\tag{3.17}
$$

Multiplying second equation of (3.14) by B_1 and the third equation of (3.16) by L^* yields

$$
\begin{aligned}
B_1(\mu+\delta)L^* =& B_1 l\beta S^* I^* \\
B_1(\mu+\delta)L^* =& B_2\delta L^*
\end{aligned}
$$

Hence, it follows that

$$-B_1 l\beta S^* I^* + B_2\delta L^* = 0$$

Multiplying the above equation by $F_1(x)$, where $X = (x, y, z, u)$ and $F_1(X)$ a function to be determined later yields

$$-B_1 l\beta S^* I^* F_1(x) + B_2\delta L^* F_1(x) = 0 \tag{3.18}$$

Multiplying the fourth equation of (3.14) by B_3 and the fourth equation of (3.16) by T^* yields

$$\begin{aligned} B_3\mu T^* =& B_3\gamma I^* \\ B_3\mu T^* =& 0 \end{aligned}$$

Hence, it follows that

$$B_3\gamma I^* = 0$$

Multiplying the above equation by $F_2(x)$, where $X = (x, y, z, u)$ and $F_2(X)$ a function to be determined later yields

$$B_3\gamma I^* F_2(X) = 0 \tag{3.19}$$

From (3.15) using (3.18) and (3.19) yields

$$\begin{aligned} U' =& -\mu\frac{(S-S^*)^2}{S} + B_2(1-l)\beta S^* I^*\left(2 - \frac{1}{x} - x\right) + B_1 l\beta S^* I^*\left(2 - \frac{1}{x} - \frac{xz}{y} - F_1(X)\right) \\ &+ B_2\delta L^*\left(1 - \frac{y}{z} + F_1(X)\right) + B_3\gamma I^*\left(1 - \frac{z}{u} + F_2(X)\right) \end{aligned} \tag{3.20}$$

The function $F_1(X)$ and $F_2(X)$ are now chosen such that the coefficients of L^* and I^* are equals to zero. In this case, we obtain

$$\begin{aligned} F_1(X) =& \frac{y}{z} - 1 \\ F_2(X) =& \frac{z}{u} - 1 \end{aligned}$$

Then equation (3.20) becomes

$$U' = -\mu\frac{(S-S^*)^2}{S} + B_2(1-l)\beta S^* I^*\left(2-\frac{1}{x}-x\right) + B_1 l\beta S^* I^*\left(2-\frac{1}{x}-\frac{xz}{y}-\frac{y}{z}+1\right)$$

$$= -\mu\frac{(S-S^*)^2}{S} + B_2(1-l)\beta S^* I^*\left(2-x-\frac{1}{x}\right) + B_1 l\beta S^* I^*\left(3-\frac{1}{x}-\frac{y}{z}-\frac{xz}{y}\right) \tag{3.21}$$

which is less than or equal to zero by the arithmetic meam-geometric mean inequality, with equality if and if $S = S^*, y = z = u$. Thus, we have $H' \leq 0$ with equality only if $S = S^*$ and $\frac{L}{L^*} = \frac{I}{I^*} = \frac{R}{R^*}$. By LaSalle,s Invariance Principle [17], the omega limit set of each solution lies in an invariant set contained in $\Omega = \{(S, L, I, R) : S = S^*, \frac{L}{L^*} = \frac{I}{I^*} = \frac{R}{R^*}\}$.Since S must be containt at S^*, S' is zero. This implies that $I = I^*$ thus, $L = L^*$ and $R = R^*$. Thus , the only invariant set in Ω is the singleton $\{E_1\}$. This shows that each solution which intersects $\mathbb{R}^4_{+0}$ $\{L = I = T = 0\}$ limits to the endemic equilibrium E_1 , which implies that the endemic equilibrium E^* of the system (3.1) is globally asymptotically stable on $\mathbb{R}^5_{+0}$ $\{L = I = T = 0\}$. □

3.7 Parameter Estimation

Here we use Non-linear Least Square Method (NLSM) which is discribed in Chapter 2. There are seven parameters in our model which have to estimate. Among these parameters, natural death rate μ, recruitment rate of susceptible class λ and disease induced death rate α are obtained from the given data given in [40]. So, the rest of them disease transmission rate β, the fraction l of the susceptible class S(t) which moves to the latent class L(t), the rate δ which leaves from the latent class L(t) for the infected class I(t) and the recovered rate γ have to be estimeted, therefore $\theta = (l, \beta, \delta, \gamma)$. Thus, we assumed the initial parameter values for estimation which is $\omega_0 = (\lambda, \mu, \alpha, l, \beta, \delta, \gamma) = (10, 0.002, 0.0054, 0.5, 0.000065, 0.0001, 0.005)$ and the initial condition $(S_0, L_0, I_0, R_0) = (5000, 250, 1, 1000)$ is assumed. With these initial value of the parameters and initial conditions, the unknown parameters value are obtained from the above discribed NLS method which is given in folowing table

Table. 3.1. Description of parameter and values of the Diphtheria model.

Parameter	Description	Value	Reference
λ	recruitment rate of susceptible class	10 $person\ d^{-1}$	Obtained from data
μ	natural death rate	0.002 $person\ d^{-1}$	Obtained from data
α	disease induced death rate	0.0054 $person\ d^{-1}$	Obtained from data
β	disease transmission rate	0.000081 $person\ d^{-1}$	Estimated
l	the fraction of S(t) which moves to L(t)	0.23	Estimated
γ	recovered rate	0.036 $person\ d^{-1}$	Estimated
δ	the rate which leaves L(t) for I(t)	0.0001 $person\ d^{-1}$	Estimated

3.8 Numerical Results

To farther investigate the attitude of the model (3.1), we directed various numerical simulations using the estimates obtained in Table 3.1. The results obtained for the stability of the disease extinction and the infectious persistence steady states are also numerically illustrated in this section. For this intention, we consider two sets of parameter corresponding to the cases of stability of the infectious persistence steady state where $\mathcal{R}_0 > 1$ and disease extinction steady state where $\mathcal{R}_0 < 1$. Both the models are numerically solved using Runge-Kutta 4th order method.

Firstly, figures 3.2 and 3.3 represent the disease dynamic of the infected population $I(t)$. We can see that upon initiation of infection, the population of the infected class (I-class) increases significantly and it reaches the peak. After achieving the peak, this class decays until it reaches a steady state.

Using the parameter values from table 3.1, the value of R_0 turns out to be $R_0 = 7.29 > 1$ and thereby indicating that the infected steady state is asymptotically stable. For this purpose, we choose three different initial conditions of (S_0, L_0, I_0, R_0) as $IC1 = (5000, 250, 1, 1000), IC2 = (4500, 200, 2, 950)$, and $IC3 = (6000, 400, 20, 1500)$.

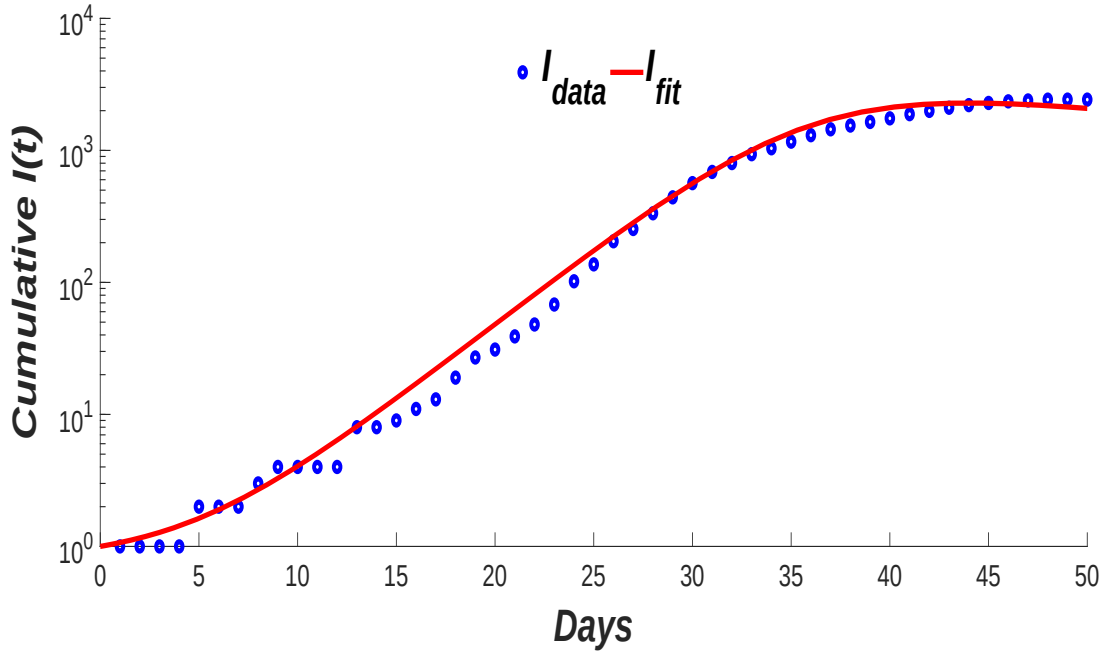

Figure. 3.2. The Diphtheria Model simulation in log scale

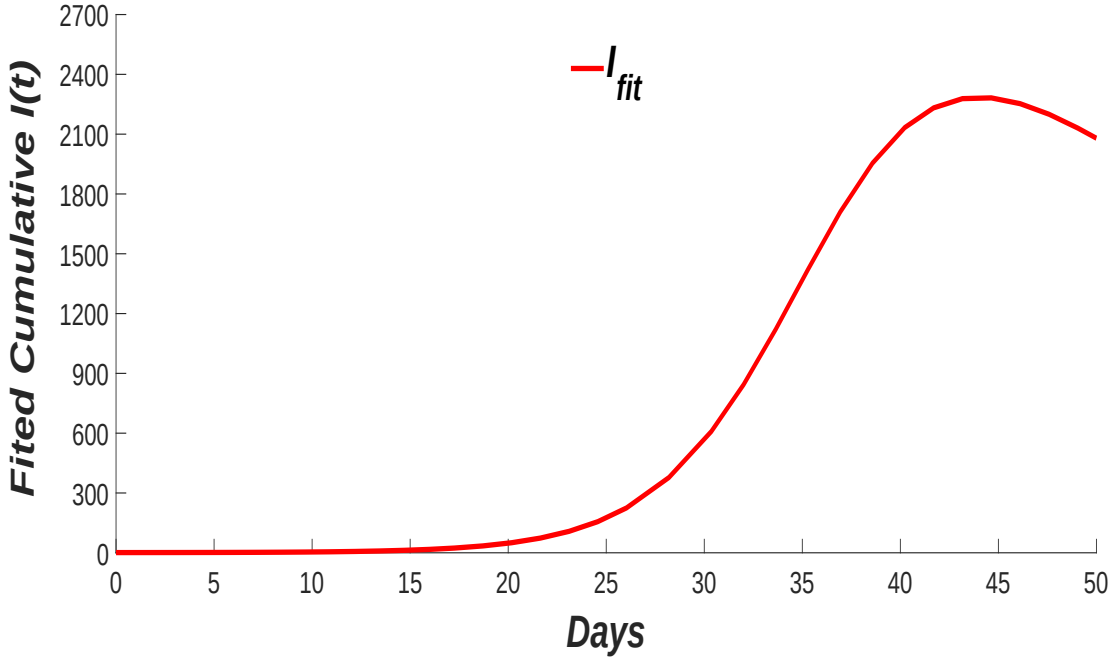

Figure. 3.3. The Diphtheria Model

In figure 3.4, we can see that the infected population is sharply increasing and reaches at a pick point. After that it is decreasing smoothly and converges to approximately 155.25 for all initial condition. Which indicates that there is a disease in the populations and we need to apply treatment in the infected populations. In figure 3.5, it is observed that the latently infected population is also sharply increasing and reaches at a pick point. After that is gradually decreasing and

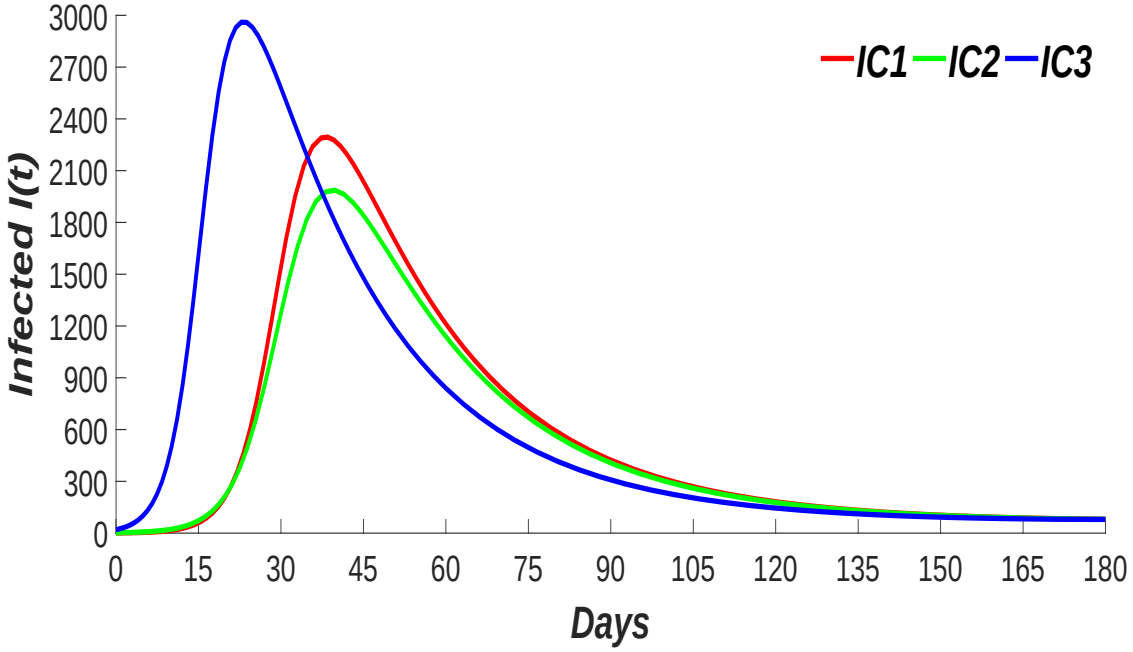

Figure. 3.4. Dynamics of the infected class of Diphtheria Model for $\mathcal{R}_0 = 7.29 > 1$ within 180 days with three different intial condition

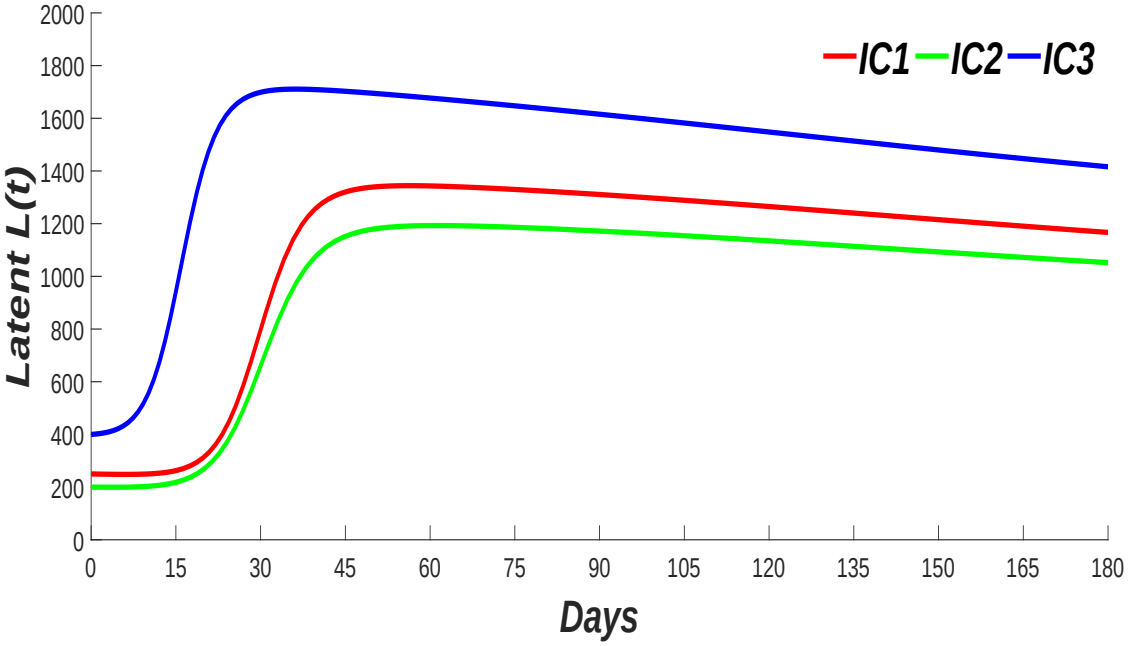

Figure. 3.5. Dynamics of the latent class of Diphtheria Model for $\mathcal{R}_0 = 7.29 > 1$ within 180 days with three different intial condition

tends to converge for all initial conditions but do not converge within 180 days. It means that there is no endemic equilibrium point in 180 days which indicates that we need to apply vaccination to the susceptible population to reduce latently infected and acute infected populations.

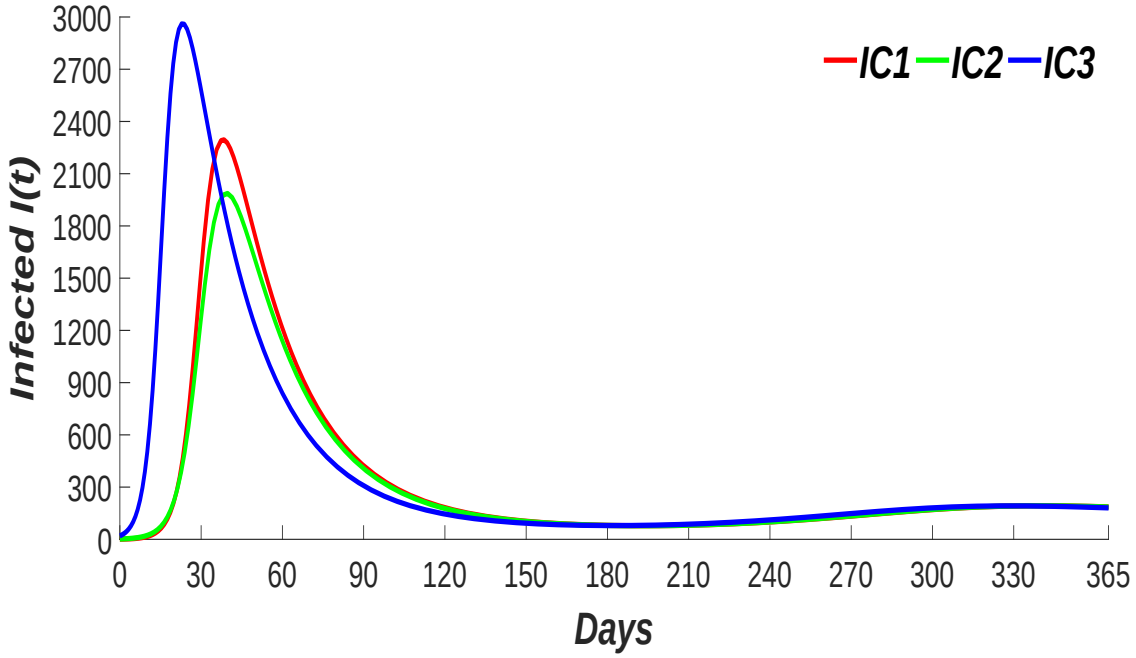

Figure. 3.6. Dynamics of the infected class of Diphtheria Model for $\mathcal{R}_0 = 7.29 > 1$ within 365 days with three different intial condition

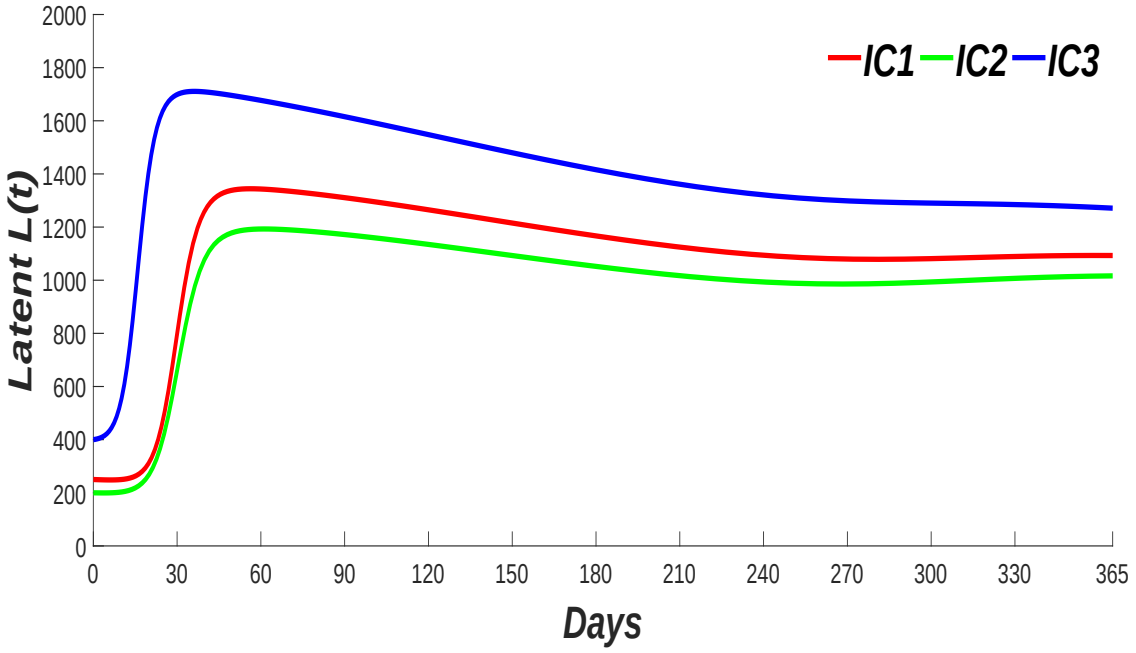

Figure. 3.7. Dynamics of the latent class of Diphtheria Model for $\mathcal{R}_0 = 7.29 > 1$ within 365 days with three different intial condition

In figure 3.6, we can see that the infected population converges to approximately 155.25 for all initial condition within 365 days as in figure 3.4. After that it further gradually increasing within next 30 days which indicates that there shall be a second wave in the populations. From figure 3.7, the latently infected population

is still decreasing more gradually and tends to converge but did not converge within 365 days. It means that the endemic equilibrium point will found after long time. For disease-free equilibrium we assume the values of disease transmission rate β and the acute infection rate δ which leaves from latently infected population different values from Table 3.1. Here we assume $\beta = 0.0000041$ and $\delta = 0.02$. Therefore, we evaluate the basic reproduction rate $\mathcal{R}_0 = 0.463 < 1$. For this purpose we choose the same initial conditions as before.

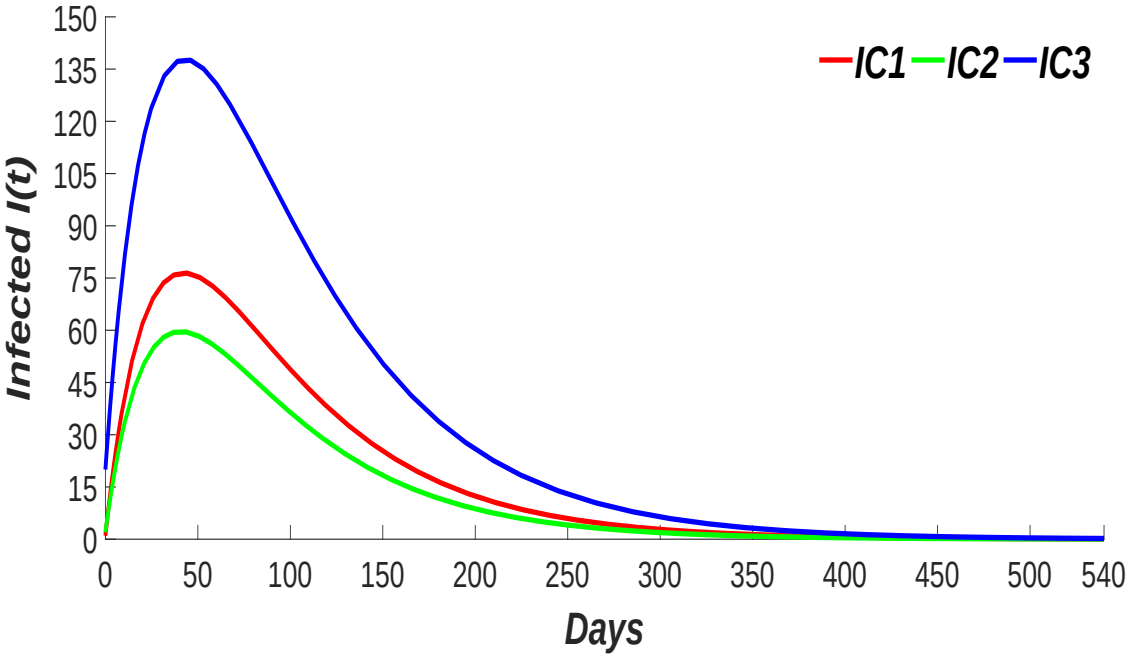

Figure. 3.8. Dynamics of the infected class of Diphtheria Model for $\mathcal{R}_0 = 0.463 < 1$ within 540 days with three different intial condition

In figure 3.8, we can see that the infected population is increasing sharply and reaches at a pick point as like figure 3.4 and 3.6 but after that it is more gradually decreasing than figure 3.4 and 3.6 and converges to 0 within 18 months. That means there is no infection in the populations after 540 days without applying treatment. In figure 3.9, we can see that the latently infected population is gradually decreasing and converges to 0 within 540 days. That means the latently infection is removed from the populations after 540 days without applying treatment. But 540 days is a long time to increase the disease induced death rate of the populations. So we need to apply treatment to control the outbreak. Further, in figure 3.10, we illustrate the contour plot of $\mathcal{R}_0$ for various values of disease transmition rate β and acute infection rate δ. Here we see that the disease transmition rate β is more sensitive than acute infection rate δ. Hence we need to apply contol in the susceptible class $S(t)$ and the infected class $I(t)$. We discuss details about

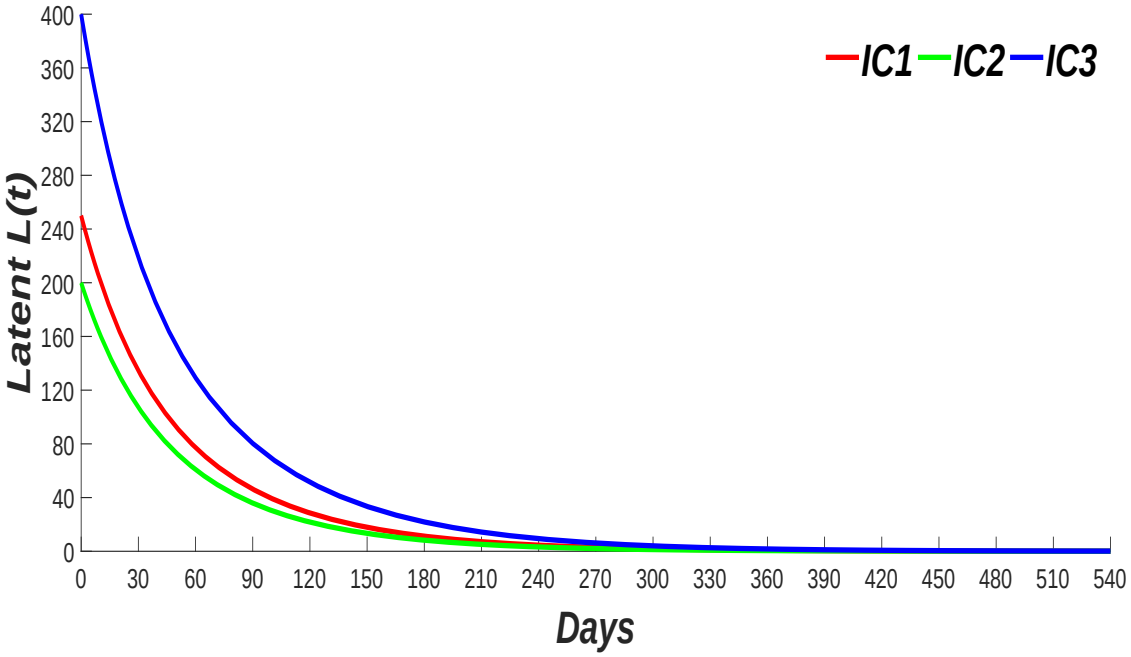

Figure. 3.9. Dynamics of the latent class of Diphtheria Model for $\mathcal{R}_0 = 0.463 < 1$ within 540 days with three different intial condition

the Optimal controls and Coast-Effective Treatment Stategies in the next chapter.

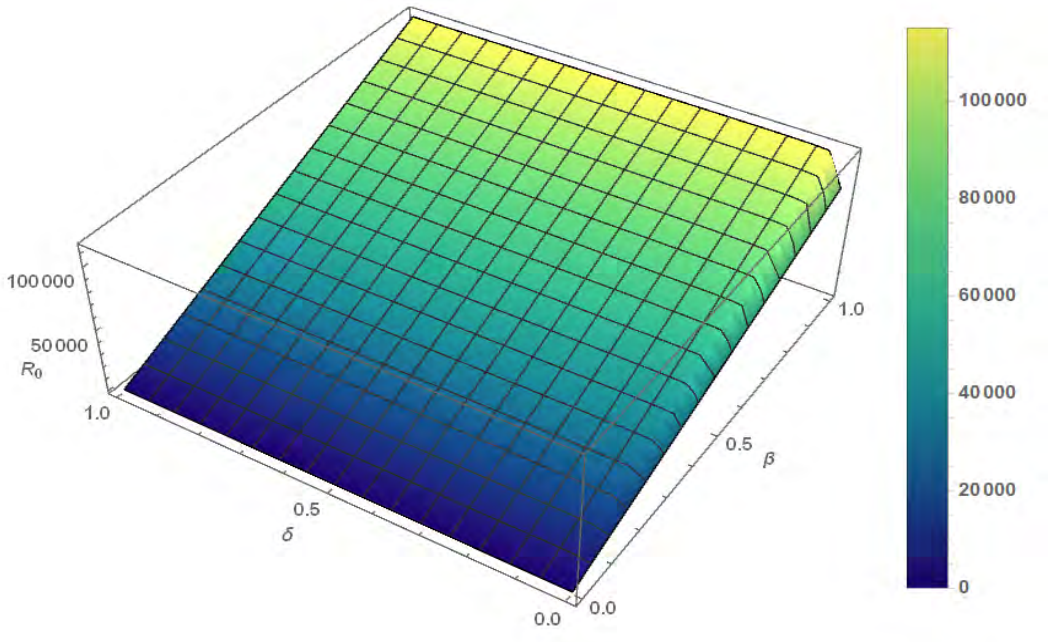

Figure. 3.10. Contour plot of $\mathcal{R}_0$ for various values of β and δ

Chapter 4

Optimal Controls and Cost-Effective Treatment Strategies for Diphtheria Epidemic

4.1 Introduction

The control theoretic concepts have been considered important in a wide variety of disciplines. Since, too large dosage may not be desirable for patients while too small dosage may be ineffective as therapy for the recommended therapeutic agents. Optimal treatment strategies can decrease the possibility of diphtheria transmission, pharmaceutical side effects, and expensive medication burden. To avoid complication due to toxic effects of the drug, adequate amounts of drug in a body compartment should be maintained. To avoid the hazard of side effect of drug dose, our main aim is to find out the optimal drug dosage. Here the drug input is the control and it is through the knowledge of their size that one has a partial way of influencing the drug response behavior among patients.

Diphtheria-Tetanus-Pertussis (DTP) vaccine is administered to prevent Diphtheria infected individuals to control the epidemic outbreak. The individuals which are already infected need to treatment of Diphtheria. Various administration schemes are used to improve patients' lives and at the same time suppressing development

of drug resistance, reduce evolution of new bacterial strains, minimize serious side effects and also reduce the costs of drugs. The main purpose of this chapter is to develop a mathematical framework that deduce an optimal control administration scheme useful in improving the Diphtheria outbreak especially in poor resourced settings.

4.2 Mathematical Model with Treatment

There are two way to control the diphtheria epidemic which are mostly used to reduce the sucseptible and infected populations and increage the recovered populations. To reduce susceptible populations the mass vaccination need to apply to the populations and to reduce the death rate of the infected population treatment should be applied to the infected populations. Both procedure thus diminish the spread of the Diphtheria outbreak. The primary attention of this chapter is to establish an optimal methodology for administering vaccination therapies to fight Diphtheria outbreak which specifically minimize of susceptible populations and also minimize of the systemic cost.

If we let, $u_1(t)$ represents the applied vaccination as a function of time, then β will be modified to become $(1-u_1(t))\beta$ and it is meant to take into account the effectiveness of the delivery. If we also let $u_2(t)$ be the applied treatment, then the parameter δ will be modified to become $(1-u_2(t))\delta$. Hence the state system becomes

$$\begin{cases} \dfrac{dS(t)}{dt} = \lambda - \beta S(t)I(t) - \mu S(t) - u_1(t)S(t), \\ \dfrac{dL(t)}{dt} = l\beta S(t)I(t) - (\mu+\delta)L(t), \\ \dfrac{dI(t)}{dt} = (1-l)\beta S(t)I(t) + \delta L(t) - (\mu+\gamma+\alpha)I(t) - u_2(t)I(t), \\ \dfrac{dR(t)}{dt} = \gamma I(t) - \mu R(t) + u_1(t)S(t) + u_2(t)I(t), \\ \dfrac{dN(t)}{dt} = \lambda - \mu N(t) - \alpha I(t). \end{cases} \tag{4.1}$$

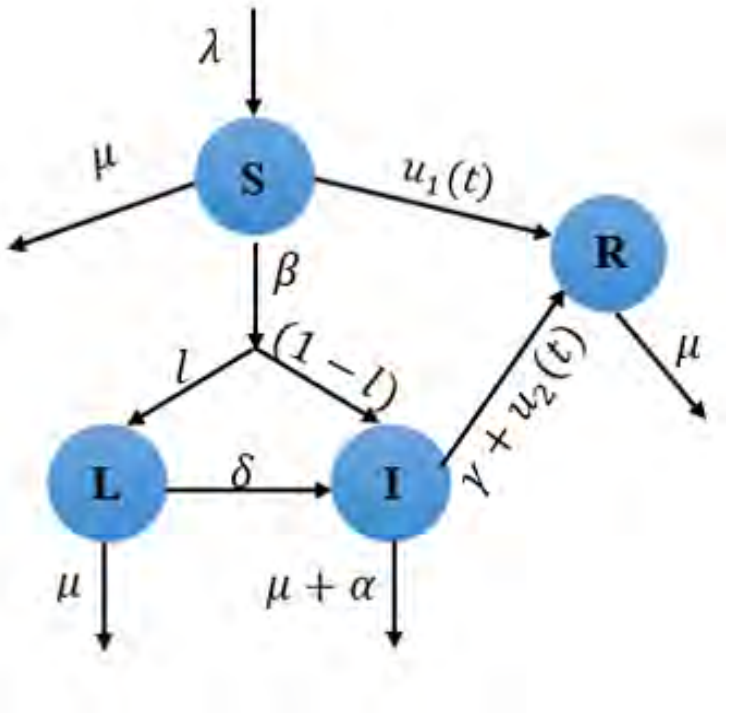

Figure. 4.1. Diagram interaction of each compartment

With initial conditions

$$\begin{gathered} S(0) = S_0,\ L(0) = L_0,\ I(0) = I_0,\ R(0) = R_0,\ N(0) = N_0 \\ \text{and } S(t),\ L(t),\ I(t),\ R(t),\ N(t) \text{ are free at final time } T_f. \end{gathered} \tag{4.2}$$

The optimal controls $0 \leq u_1(t),\ u_2(t) \leq 1$ represent percentage effects of vaccination which apply on susceptible population and treatment therapy on the infected populations. A schematic representation of the model (4.1) is given in figure 4.1.

4.3 Qualitative Study of the Model

Now we must prove that solutions to the system of differential equations (4.1) exists and they are positive as well as bounded for all values of time in order to retain the biological validity of the model,

Theorem 4.1. *(Positivity) Let $t_0 > 0$, In the model (4.1), if the initial conditions satisfy $S_0 > 0, L_0 > 0, I_0 > 0$ and $R_0 > 0$, then for all $t \in [0, t_0]$ the functions $S(t), L(t), I(t)$ and $R(t)$ will be remain positive in $\mathbb{R}^4_+$.*

Proof of Theorem 4.1. Since all of the parameters used in the system are positive, we can place lower bounds on each of the equations given in the model. Thus,

$$\begin{aligned}
\frac{dS(t)}{dt} &= \lambda - \beta S(t)I(t) - \mu S(t) - u_1(t)S(t) \geq -\beta S(t)I(t) - \mu S(t) - u_1(t)S(t),\\
\frac{dL(t)}{dt} &= l\beta S(t)I(t) - (\mu+\delta)L(t) \geq -\mu L(t),\\
\frac{dI(t)}{dt} &= (1-l)\beta S(t)I(t) + \delta L(t) - (\mu+\gamma+\alpha)I(t) - u_2(t)I(t) \geq -\mu I(t),\\
\frac{dR(t)}{dt} &= \gamma I(t) - \mu R(t) + u_1(t)S(t) + u_2(t)I(t) \geq -\mu R(t),
\end{aligned}$$

Through basic differential equations methods we can resolve the inequalities and produce:

$$\begin{aligned}
\frac{dS(t)}{dt} &\geq S(0)e^{-\mu t - k\int_0^{T_f}(\beta I(t)+u_1)Vdt},\\
\frac{dL(t)}{dt} &\geq L(0)e^{-\mu t} > 0,\\
\frac{dI(t)}{dt} &\geq I(0)e^{-\mu t} > 0,\\
\frac{dR(t)}{dt} &\geq R(0)e^{-\mu t} > 0.
\end{aligned}$$

Thus, for all $t \in [0, t_0]$ the functions $S(t), L(t), I(t)$ and $R(t)$ will be positive and remain in $\mathbb{R}^4_+$. □

The boundedness of solutions to system (4.1-4.2) for finite time interval is needed to investigate the existence of an optimal control of our model, now we examining the priori boundedness of the state solutions.

Theorem 4.2. *(Boundedness) Given $(u_1, u_2) \in U$, there exists bounded solutions for the problems (4.1-4.2).*

Proof of Theorem 4.2. The state variables we consider here represent supersolutions for given problems (4.1-4.2). From the given equations we have

$$(S+L+I)'(t) = \lambda - \mu S - u_1 S - \mu L - \delta L - \mu I - \gamma I - \alpha I - u_2 I \leq \lambda - \mu S - \mu L - \mu I.$$

Now, using $X(t) = S(t) + L(t) + I(t)$ we get

$$X'(t) \leq \lambda - \mu X,$$

which implies that

$$\lim_{t\to\infty} \sup X(t) \leq \frac{\lambda}{\mu},$$

The upper bound for X is also the upper bound for S, L, and I. Lastly

$$R'(t) = \gamma I(t) - \mu R(t) + u_1(t)S(t) + u_2(t)I(t) \leq \gamma I(t) \leq \frac{\gamma\lambda}{\mu},$$

which leads to

$$R(t) \leq \frac{\gamma\lambda T_f}{\mu} \in \mathbb{R}_+, \quad \text{for all } t \in [0, T_f].$$

Since $(u_1(t), u_2(t)) \in U$, then, along with $S(t), L(t), I(t)$ and $R(t)$ are bounded above. Via a maximum principle [26] theory for first-order nonlinear differential equations, we obtain the solutions to the problems (4.1-4.2) bounded for all $t \in [0, t_0]$ and lies in the compact set

$$\mathbb{D} = \left\{ (S, L, I, R) \in \mathbb{R}^4_+ : S, L, I \leq \frac{\lambda}{\mu}, R \leq \frac{\gamma\lambda T_f}{\mu} \right\},$$

where $\mathbb{R}^4_+ = \{(S, L, I, R) : S \geq 0, L \geq 0, I \geq 0, R \geq 0\}$. □

Theorem 4.3. *(Existence of Solution) Let $t_0 > 0$, In the model (4.1), if the initial conditions satisfy $S_0 > 0, L_0 > 0, I_0 > 0$ and $R_0 > 0$, then for all $t \in \mathbb{R}$ the functions $S(t), L(t), I(t)$ and $R(t)$ will exist in $\mathbb{R}^4_+$.*

Proof of Theorem 4.3. In the case of our model the system of ODEs are defined by the function $\mathbf{f} : \mathbb{R}^4 \to \mathbb{R}^4$ as

$$\mathbf{f}(\mathbf{y}) = \begin{pmatrix} \lambda - \beta SI - \mu S - u_1 S \\ l\beta SI - (\mu + \delta)L \\ (1-l)\beta SI + \delta L - (\mu + \gamma + \alpha)I - u_2 I \\ \gamma I - \mu R + u_1 S + u_2 I \end{pmatrix}$$

Note that $\mathbf{f}$ has a continuous derivative on $\mathbb{R}^4$ and thus, $\mathbf{f}$ is locally Lipschitz in $\mathbb{R}^4$. Hence, by the Fundamental Existence and Uniqueness Theorem as well as the theorems proved on positivity and boundedness of solutions, we know that there exists a unique, positive, and bounded solution to the ordinary differential equations given in (4.1-4.2). □

4.4 Optimal Control Problem

Our main objective is to miniimize the benefit based on the infected population I and the systemic cost based on the percentage effect of the treatment and vaccination is being minimized (toxic side effects being avoided as much as possible and not causing death). The objective functional is defined as,

$$J(u_1, u_2) = \int_0^{T_f} \left[I(t) + \left(\frac{A_1}{2} u_1^2(t) + \frac{A_2}{2} u_2^2(t) \right) \right] dt, \tag{4.3}$$

where $I(t)$ is the benefit based on the infected populations and the other terms are systemic costs of the treatments. The benefit of treatment is based on the decrease of infected populations and systemic costs of drugs are minimized. The positive constants A_1 and A_2 represent desired weight on the benefit and cost, and u_1^2, u_2^2 reflect the effectivity of the treatment [14]. The cost function is assumed to be nonlinear, basing on the fact that there is no linear relationship between the effects of treatment on infected populations hence the choice of a quadratic cost function. We impose a condition for treatment time, $t \in [0, T_f]$, that monitors global effects of these phenomena; treatment lasts for a given period of time because Diphtheria can transmit and develop resistance to treatment after some finite time frame. The time $t = 0$ is the time when treatment is initiated and time $t = T_f$ is the time when treatment is stopped.

The control set U is defined as

$$U = \left\{ u_1, u_2 \text{ are Lebesgue measurable, } 0 \leq u_1(t), u_2(t) \leq 1, t \in [0, T_f] \right\}.$$

So we seek an optimal control pair, u_1^*, u_2^* such that

$$J(u_1^*, u_2^*) = \min_{u_1, u_2 \in U} J(u_1, u_2), \tag{4.4}$$

subject to state constraints (4.1-4.2).

The basic framework of this problem is to prove the existence of the optimal control, characterize the optimal control and establish uniqueness of the optimality system.

4.5 Existence of an Optimal Control Pair

Using the fact that the solution to each state equation is bounded (see Theorem 4.2). Now, the existence of an optimal control for the state system is analyzed using the theory developed by Fleming and Rishel in [53].

Theorem 4.4. *Given the objective functional*

$$J(u_1, u_2) = \int_0^{T_f} \left[I(t) + \left(\frac{A_1}{2} u_1^2(t) + \frac{A_2}{2} u_2^2(t) \right) \right] dt,$$

where $U = \{(u_2(t), u_2(t))$*, piecewise continuous such that* $0 \leq u_1(t), u_2(t) \leq 1\}$ *for all* $t \in [0, T_f]$ *subject to equations of system (4.1-4.2) with* $S(0) = S_0$*,* $L(0) = L_0$*,* $I(0) = I_0$ *and* $R(0) = R_0$*, then there exists an optimal control pair* u_1^**,* u_2^* *such that*

$$J(u_1^*, u_2^*) = \min\{J(u_1, u_2) | (u_1, u_2) \in U\}.$$

Proof of Theorem 4.4. To prove this theorem, we follow the requirments from Theorem 4.1 and Corollary 4.1 developed by Fleming and Rishel in [53] and verify them. Let $\mathbf{f}(t, \mathbf{X}, \mathbf{u})$ be the right-hand side of (4.1-4.2) for $0 \leq t \leq T_f$ where $\mathbf{X} \in \mathbb{R}^4$, $\mathbf{u} \in \mathbb{R}^2$ where $\mathbf{X} = (S, L, I, R)$ and $\mathbf{u} = (u_1, u_2)$. Accordng to [53], the following coditions are needed to satisfy for the existence:

(i) The class of all initial conditions with an optimal control pair u_1, u_2 in the admissible control set along with each state equation being satisfied is not empty. That is

$$|\mathbf{f}(t, 0, 0)| \leq C, \quad |\mathbf{f}_{\mathbf{X}}(t, \mathbf{X}, \mathbf{u})| \leq C(1 + |\mathbf{u}|) \text{ and } |\mathbf{f}_{\mathbf{u}}(t, \mathbf{X}, \mathbf{u})| \leq C.$$

(ii) The admissible control set U is closed and convex.

(iii) Each right hand side of equations of system (4.1-4.2) is continuous, is bounded above by a sum of the bounded control and the state, and can be written as a linear function of an optimal control pair u_1, u_2 with coefficients depending on time and the state variables. That is

$$\mathbf{f}(t, \mathbf{X}, \mathbf{u}) = \boldsymbol{\alpha}(t, \mathbf{X}) + \boldsymbol{\gamma}(t, \mathbf{X})\mathbf{u} \text{ and } |\mathbf{f}(t, \mathbf{X}, \mathbf{u})| \leq C_1(1 + |\mathbf{X}| + |\mathbf{u}|).$$

(iv) The integrand of the functional $J(u_1, u_2)$ is convex on the admissible control set and is bounded above by $C_2 - C_1|\mathbf{u}|^\beta$, where $C_1,\ C_2$ are positive constants and $\beta > 1$.

In order to verify the theorem we write the right hand side of equations of system (4.1-4.2) as

$$\mathbf{f}(t, \mathbf{X}, \mathbf{u}) = \begin{pmatrix} \lambda - \beta SI - \mu S - u_1 S \\ l\beta SI - (\mu + \delta)L \\ (1-l)\beta SI + \delta L - (\mu + \gamma + \alpha)I - u_2 I \\ \gamma I - \mu R + u_1 S + u_2 I \end{pmatrix}$$

It is easy to see that $\mathbf{f}(t, \mathbf{X}, \mathbf{u})$ is of class C^1 and $|\mathbf{f}(t, 0, 0)| = \lambda$ and we have

$$|\mathbf{f}_{\mathbf{X}}(t, \mathbf{X}, \mathbf{u})| = \left| \begin{pmatrix} a_{11} & 0 & -\beta S & 0 \\ l\beta I & -(\mu + \delta) & l\beta S & 0 \\ (1-l)\beta I & \delta & a_{33} & 0 \\ u_1 & 0 & \gamma + u_2 & -\mu \end{pmatrix} \right|$$

where $a_{11} = -\beta I - \mu - u_1,\ a_{33} = -(1-l)\beta S - (\mu + \gamma + \alpha) - u_2$ and

$$|\mathbf{f}_{\mathbf{u}}(t, \mathbf{X}, \mathbf{u})| = \left| \begin{pmatrix} -S & 0 \\ 0 & 0 \\ 0 & -I \\ S & I \end{pmatrix} \right|$$

Since S, L, I and R are bounded, then there exits a constant C such that

$$|\mathbf{f}(t, 0, 0)| \leq C, \quad |\mathbf{f}_{\mathbf{X}}(t, \mathbf{X}, \mathbf{u})| \leq C(1 + |\mathbf{u}|) \text{ and } |\mathbf{f}_{\mathbf{u}}(t, \mathbf{X}, \mathbf{u})| \leq C.$$

By definition, U is closed. Take any controls $u_1, u_2 \in U$ and $\theta \in [0, 1]$. Then

$$\theta u_1 + (1 - \theta)u_2 \geq 0,$$

with $\theta u_1 \leq \theta$ and $(1 - \theta)u_2 \leq (1 - \theta)$. Then

$$\theta u_1 + (1 - \theta)u_2 \leq \theta + (1 - \theta) = 1,$$

i.e $0 \leq \theta u_1 + (1-\theta)u_2 \leq 1$, for all $u_1, u_2 \in U$ and $\theta \in [0,1]$. Therefore, U is convex and condition (ii) is satisfied. The right hand side of system (4.1-4.2) is continuous, bilinear in the control and it can be written as:

$$\mathbf{f}(t, \mathbf{X}, \mathbf{u}) = \boldsymbol{\alpha}(t, \mathbf{X}) + \boldsymbol{\gamma}(t, \mathbf{X})\mathbf{u}.$$

Where

$$\boldsymbol{\alpha}(t, \mathbf{X}) = \begin{pmatrix} \lambda - \beta SI - \mu S \\ l\beta SI - (\mu + \delta)L \\ (1-l)\beta SI + \delta L - (\mu + \gamma + \alpha)I \\ \gamma I - \mu R \end{pmatrix}, \ \boldsymbol{\gamma}(t, \mathbf{X}) = \begin{pmatrix} -S & 0 \\ 0 & 0 \\ 0 & -I \\ S & I \end{pmatrix}$$

are vector-valued functions of $\mathbf{X}$. and the boundedness of solutions gives

$$|\mathbf{f}(t, \mathbf{X}, \mathbf{u})| \leq C_1(1 + |\mathbf{X}| + |\mathbf{u}|),$$

where C_1 depends on the coefficients of the system. Hence, satisfies condition (iii).

In order to verify the convexity of the integrand of our objective functional, J we show that

$$(1-\epsilon)J(t, \mathbf{X}, \mathbf{u}) + \epsilon J(t, \mathbf{X}, \mathbf{v}) \leq J(t, \mathbf{X}, (1-\epsilon)\mathbf{u} + \epsilon\mathbf{v})$$

for $0 < \epsilon < 1$ and $J(t, \mathbf{X}, \mathbf{u}) = I + \Big(\frac{A_1}{2}u_1^2 + \frac{A_2}{2}u_2^2\Big)$.

Now

$$\begin{aligned}
&(1-\epsilon)J(t, \mathbf{X}, \mathbf{u}) + \epsilon J(t, \mathbf{X}, \mathbf{v}) - J(t, \mathbf{X}, (1-\epsilon)\mathbf{u} + \epsilon\mathbf{v}) \\
&\quad = (1-\epsilon)\Big[I + \Big(\frac{A_1}{2}u_1^2 + \frac{A_2}{2}u_2^2\Big)\Big] + \epsilon\Big[I + \Big(\frac{A_1}{2}v_1^2 + \frac{A_2}{2}v_2^2\Big)\Big] \\
&\qquad - \Big[I + \frac{A_1}{2}\big((1-\epsilon)u_1 + \epsilon v_1\big)^2 + \frac{A_2}{2}\big((1-\epsilon)u_2 + \epsilon v_2\big)^2\Big] \\
&\quad = -\frac{A_1}{2}\Big[\Big((1-\epsilon)u_1 + \epsilon v_1\Big)^2 - (1-\epsilon)u_1^2 - \epsilon v_1^2\Big] \\
&\qquad - \frac{A_2}{2}\Big[\Big((1-\epsilon)u_2 + \epsilon v_2\Big)^2 - (1-\epsilon)u_2^2 - \epsilon v_2^2\Big] \\
&\quad = \frac{A_1}{2}\Big(\sqrt{\epsilon(1-\epsilon)}u_1 - \sqrt{\epsilon(1-\epsilon)}v_1\Big)^2 + \frac{A_2}{2}\Big(\sqrt{\epsilon(1-\epsilon)}u_2 - \sqrt{\epsilon(1-\epsilon)}v_2\Big)^2 \\
&\quad = \frac{A_1}{2}\epsilon(1-\epsilon)(u_1 - v_1)^2 + \frac{A_2}{2}\epsilon(1-\epsilon)(u_2 - v_2)^2 \geq 0.
\end{aligned}$$

Since A_1, $A_2 > 0$, $J(t, \mathbf{I}, \mathbf{u})$ is convex in U. Finally we need to show that $J(t, \mathbf{I}, \mathbf{u}) \leq C_2 - C_1|\mathbf{u}|^\beta$, where $C_1 > 0$ and $\beta > 1$. For our case

$$J(t, \mathbf{I}, \mathbf{u}) = I + \left(\frac{A_1}{2}u_1^2 + \frac{A_2}{2}u_2^2\right) \geq C_2 - C_1|\mathbf{u}|^2,$$

where C_2 depends on the upper bound on infected population, and $C_1 > 0$ since A_1, $A_2 > 0$ and $\beta = 2$. So we conclude that there exists an optimal control pair.

□

4.6 The Optimality Conditions

The Pontryagin's Maximum Principle [22] provides necessary conditions for an optimal control problem. This principle converted the problem of finding a control which minimizes the objective function J subject to the state system (4.1-4.2) to the problem of maximizing the Hamiltonian H, pointwisely with respect to u_1 and u_2. So it is sufficient to derive the Hamiltonian H instead of deriving the objective function J defined in (4.3) in order to characterize the optimal controls u_1^* and u_2^*. The Hamiltonian is defined from the formulation of the objective function as follows:

$$H = I(t) + \left(\frac{A_1}{2}u_1^2(t) + \frac{A_2}{2}u_2^2(t)\right) + \sum_{i=1}^{4} \lambda_i(t)F_i,$$

where F_i is the right hand side of the differential equation of i-th state variable. By applying Pontryagin's Maximum Principle [22] we obtain the following theorem.

Theorem 4.5. *There exists an optimal control $u^* = (u_1^*, u_2^*)$ and corresponding solution $S(t), L(t), I(t)$ and $R(t)$, that maximizes $J(u_1, u_2)$ over U. Furthermore, there exists adjoint functions $\lambda_1(t), \lambda_2(t), \lambda_3(t)$ and $\lambda_4(t)$ satisfying the equations*

$$\begin{cases} \lambda_1'(t) = \lambda_1(t)\left(\beta I(t) + \mu + u_1(t)\right) - \lambda_2(t)l\beta I(t) - \lambda_3(t)(1-l)\beta I(t) - \lambda_4(t)u_1(t) \\ \lambda_2'(t) = \lambda_2(t)(\mu + \delta) - \lambda_3(t)\delta \\ \lambda_3'(t) = -1 + \lambda_1(t)\beta S(t) - \lambda_2(t)l\beta S(t) - \lambda_3\left((1-l)\beta S(t) - (\mu + \alpha + \gamma) - u_2(t)\right) \\ \qquad\qquad - \lambda_4(t)(\gamma + u_2(t)) \\ \lambda_4'(t) = \lambda_4(t)\mu \end{cases} \tag{4.5}$$

with transversality conditions

$$\lambda_i(T_f) = 0, \ \ i = 1, 2, \cdots, 4 \tag{4.6}$$

Moreover, the optimal control is given by

$$u_1^*(t) = \min\left(\max\left(0, \frac{1}{A_1}\Big(\lambda_1(t) - \lambda_4(t)\Big)S(t)\right), 1\right) \tag{4.7}$$

and

$$u_2^*(t) = \min\left(\max\left(0, \frac{1}{A_2}\Big(\lambda_3(t) - \lambda_4(t)\Big)I(t)\right), 1\right) \tag{4.8}$$

Proof of Theorem 4.5. The adjoint equations and transversality conditions can be obtained by using Pontryagin's Maximum Principle such that

$$\begin{aligned}
\lambda_1'(t) &= -\frac{\partial H}{\partial T}, & \lambda_1(T_f) &= 0,\\
\lambda_2'(t) &= -\frac{\partial H}{\partial I}, & \lambda_2(T_f) &= 0,\\
\lambda_3'(t) &= -\frac{\partial H}{\partial L}, & \lambda_3(T_f) &= 0,\\
\lambda_4'(t) &= -\frac{\partial H}{\partial V}, & \lambda_4(T_f) &= 0.
\end{aligned}$$

Since $S(t), L(t), I(t)$ and $R(t)$ do not have fixed values at the final time T_f, the values of the associated adjoints $\lambda_1(t), \lambda_2(t), \lambda_3(t)$ and $\lambda_4(t)$ at the final time are zero. The optimal control u_1^* and u_2^* on the interior of the control set can be solved from the optimality conditions,

$$\left.\frac{\partial H}{\partial u_1}\right|_{u_1=u_1^*} = 0, \quad \text{and} \quad \left.\frac{\partial H}{\partial u_2}\right|_{u_2=u_2^*} = 0.$$

That is

$$\frac{\partial H}{\partial u_1} = -A_1 u_1 - \lambda_1(t)S(t) + \lambda_4(t)\Big)S(t) = 0,$$

and

$$\frac{\partial H}{\partial u_2} = A_2 u_2 - \lambda_3(t)I(t) + \lambda_4 I(t) = 0.$$

By using the bounds on the controls, we get

$$u_1^* = \begin{cases} 0, & \text{if } \dfrac{\partial H}{\partial u_1^*} < 0 \\ \dfrac{1}{A_1}\Big(\lambda_1(t) - \lambda_4(t)\Big)S(t), & \text{if } \dfrac{\partial H}{\partial u_1^*} = 0 \\ 1 & \text{if } \dfrac{\partial H}{\partial u_1^*} > 0. \end{cases}$$

In compact notation

$$u_1^*(t) = \min\left(\max\left(0, \frac{1}{A_1}\Big(\lambda_1(t) - \lambda_4(t)\Big)S(t)\right), 1\right).$$

Again, we get

$$u_2^* = \begin{cases} 0 & \text{if } \dfrac{\partial H}{\partial u_2^*} < 0, \\ \dfrac{1}{A_2}\Big(\lambda_3(t) - \lambda_4(t)\Big)I(t), & \text{if } \dfrac{\partial H}{\partial u_2^*} = 0 \\ 1 & \text{if } \dfrac{\partial H}{\partial u_2^*} > 0. \end{cases}$$

In compact notation

$$u_2^*(t) = \min\left(\max\left(0, \frac{1}{A_2}\Big(\lambda_3(t) - \lambda_4(t)\Big)I(t)\right), 1\right).$$

□

In addition, the second derivative of the Hamiltonian H with respect to $u_1(t)$ and $u_2(t)$ are negative, indicating a maximum at $u^* = (u_1^*, u_2^*)$. That is

$$\frac{\partial^2 H}{\partial u_i^2} = -A_i \leq 0, \quad i = 1, 2 \quad \text{since} \quad A_i \geq 0$$

We point out that the optimality system consists of the state system (4.1) with the initial conditions (4.2), adjoint system (4.5) with transversality conditions (4.6), and optimality condition (4.7-4.8). Thus, we have the following optimality system at $u^*(t) = (u_1^*(t), u_2^*(t))$:

$$
\begin{cases}
\dfrac{dS(t)}{dt} = \lambda - \beta S(t)I(t) - \mu S(t) - u_1(t)S(t) \\
\dfrac{dL(t)}{dt} = l\beta S(t)I(t) - (\mu+\delta)L(t) \\
\dfrac{dI(t)}{dt} = (1-l)\beta S(t)I(t) + \delta L(t) - (\mu+\gamma+\alpha)I(t) - u_2(t)I(t) \\
\dfrac{dR(t)}{dt} = \gamma I(t) - \mu R(t) + u_1(t)S(t) + u_2(t)I(t) \\
\lambda_1'(t) = \lambda_1(t)\left(\beta I(t) + \mu + u_1(t)\right) - \lambda_2(t)l\beta I(t) - \lambda_3(t)(1-l)\beta I(t) - \lambda_4(t)u_1(t) \\
\lambda_2'(t) = \lambda_2(t)(\mu+\delta) - \lambda_3(t)\delta \\
\lambda_3'(t) = -1 + \lambda_1(t)\beta S(t) - \lambda_2(t)l\beta S(t) - \lambda_3\left((1-l)\beta S(t) - (\mu+\alpha+\gamma) - u_2(t)\right) \\
\qquad\qquad - \lambda_4(t)(\gamma + u_2(t)) \\
\lambda_4'(t) = \lambda_4(t)\mu \\
\qquad S(0), L(0), I(0), R(0) \geq 0 \\
\qquad \lambda_i(T_f) = 0, \ i = 1, 2, \cdots, 4
\end{cases}
\tag{4.9}
$$

where the controls $u_1^*(t)$ and $u_2^*(t)$ are given by (4.7) and (4.8) respectively.

4.7 Uniqueness of the Optimality System

Since the state system moves forward in time and the adjoint system moves backward in time, we have a challenge with uniqueness. To prove uniqueness of solutions of the optimality system for the small time interval, we use the following theorems [14].

Theorem 4.6. *The function* $u^*(c) = \min(\max(c, a), b)$ *is Lipschitz continuous in* c*, where* $a < b$ *are some fixed positive constants.*

Proof of Theorem 4.6. Consider c_1, c_2 real numbers and a, b as fixed positive constants. We will show that the Lipschitz continuity holds in all possible cases for $\max(c, a)$. Similar arguments hold for $\min(\max(c, a), b)$ as well.

(i) $c_1 \geq a$, $c_2 \geq a$: $|\max(c_1, a) - \max(c_2, a)| = |c_1 - c_2|$.

(ii) $c_1 \geq a$, $c_2 \leq a$: $|\max(c_1, a) - \max(c_2, a)| = |c_1 - a| \leq |c_1 - c_2|$.

(iii) $c_1 \leq a,\ c_2 \geq a$: $|\max(c_1, a) - \max(c_2, a)| = |a - c_2| \leq |c_1 - c_2|$.

(iv) $c_1 \leq a,\ c_2 \leq a$: $|\max(c_1, a) - \max(c_2, a)| = |a - a| = 0 \leq |c_1 - c_2|$.

Hence $|\max(c_1, a) - \max(c_2, a)| \leq |c_1 - c_2|$ and we have Lipschitz continuity of u^* in c. □

Theorem 4.7. *For sufficiently small final time (T_f), bounded solutions to the optimality system (4.9), are unique.*

Proof of Theorem 4.7. Suppose $(S, L, I, R, \lambda_1, \lambda_2, \lambda_3, \lambda_4)$ and $(\overline{S}, \overline{L}, \overline{I}, \overline{R}, \overline{\lambda_1}, \overline{\lambda_2}, \overline{\lambda_3}, \overline{\lambda_4})$ are two non-identical solutions of our optimality system (4.9). To show that the two solutions are equivalent, it is convenient to make a change of variables.
Let $S = e^{mt}x_1, L = e^{mt}x_2, I = e^{mt}x_3, R = e^{mt}x_4, \lambda_1 = e^{-mt}y_1, \lambda_2 = e^{-mt}y_2,$
$\lambda_3 = e^{-mt}y_3, \lambda_4 = e^{-mt}y_4, \overline{S} = e^{mt}\overline{x_1}, \overline{L} = e^{mt}\overline{x_2}, \overline{I} = e^{mt}\overline{x_3}, \overline{R} = e^{mt}\overline{x_4},$
$\overline{\lambda_1} = e^{-mt}\overline{y_1}, \overline{\lambda_2} = e^{-mt}\overline{y_2}, \overline{\lambda_3} = e^{-mt}\overline{y_3}, \overline{\lambda_4} = e^{-mt}\overline{y_4}.$
where $m > 0$ is a positive constant to be chosen later. With the new variables the optimality conditions become

$$
\begin{aligned}
u_1^* &= \min\left(\max\left(0, \frac{x_1(y_1 - y_4)}{A_1}\right), 1\right),\\
u_2^* &= \min\left(\max\left(0, \frac{x_3(y_3 - y_4)}{A_2}\right), 1\right),\\
\overline{u_1^*} &= \min\left(\max\left(0, \frac{\overline{x_1}\ (\overline{y_1} - \overline{y_4})}{A_1}\right), 1\right),\\
\overline{u_2^*} &= \min\left(\max\left(0, \frac{\overline{x_3}\ (\overline{y_3} - \overline{y_4})}{A_2}\right), 1\right).
\end{aligned}
$$

For the first equation of system (4.9) we substitute $S = e^{mt}x_1$ and get

$$\dot{x}_1 + mx_1 = \lambda e^{-mt} - \beta e^{mt} x_1 x_3 - \mu x_1 - u_1^* x_1$$

and for $\overline{S} = e^{mt}\ \overline{x_1}$ we have

$$\dot{\overline{x_1}} + m\ \overline{x_1} = \lambda e^{-mt} - \beta e^{mt}\ \overline{x_1}\ \overline{x_3} - \mu\ \overline{x_1} - \overline{u_1^*}\ \overline{x_1}.$$

Subtracting the expression for $\overline{S}$ from the expression for S we have

$$\dot{x_1} - \dot{\overline{x_1}} + m(x_1 - \overline{x_1}) = -\beta e^{mt}(x_1 x_3 - \overline{x_1}\ \overline{x_3}) - \mu(x_1 - \overline{x_1}) - (u_1^* x_1 - \overline{u_1^*}\ \overline{x_1}).$$

Multiplying by $(x_1 - \overline{x_1})$ and integrating from $t = 0$ to $t = T_f$ we have

$$\begin{aligned}\frac{1}{2}(x_1 - \overline{x_1})^2(T_f) + (m+\mu)\int_0^{T_f}(x_1 - \overline{x_1})^2 dt \\ = -\beta\int_0^{T_f} e^{mt}(x_1 x_3 - \overline{x_1}\ \overline{x_3})(x_1 - \overline{x_1})dt - \int_0^{T_f}(u_1^* x_1 - \overline{u_1^*}\ \overline{x_1})(x_1 - \overline{x_1})dt\end{aligned} \tag{4.10}$$

In order to simplify the right-hand expressions of (4.10), we need some elementary inequalities.

By the elementary inequality $(a+b)^2 \le 2(a^2+b^2)$, we have

$$\begin{aligned}(x_1 y_1 - \overline{x_1}\ \overline{y_1})^2 &= (x_1 y_1 - x_1\overline{y_1} + x_1\overline{y_1} - \overline{x_1}\ \overline{y_1})^2 \\ &= [x_1(y_1 - \overline{y_1}) + \overline{y_1}(x_1 - \overline{x_1})]^2 \\ &\le \max\{2x_1^2, 2\overline{y_1}^2\}[(x_1 - \overline{x_1}) + (y_1 - \overline{y_1})]^2 \\ &\le C[(x_1 - \overline{x_1})^2 + (y_1 - \overline{y_1})^2],\end{aligned}$$

where C depends on bounds for $x_1, \overline{y_1}$. Another common expression can be used repeatedly,

$$\begin{aligned}(xy - \overline{x}\ \overline{y})(w - \overline{w}) &= (xy - \overline{x}y + \overline{x}y - \overline{x}\ \overline{y})(w - \overline{w}) \\ &= y(x - \overline{x})(w - \overline{w}) + \overline{x}(y - \overline{y})(w - \overline{w}) \\ &\le y^2(x - \overline{x})^2 + \overline{x}^2(y - \overline{y})^2 + 2(w - \overline{w})^2 \\ &\le C[(x - \overline{x})^2 + (y - \overline{y})^2 + (w - \overline{w})^2],\end{aligned}$$

where C depends on bounds for $\overline{x}, y$.
Based on the above arguments and theorem 4.6, we find

$$\begin{aligned}
&\int_0^{T_f} (u_1^* x_1 - \overline{u_1^*}\ \overline{x_1})(x_1 - \overline{x_1})dt \\
&\quad \leq C_1 \int_0^{T_f} \left[(u_1^* - \overline{u_1^*})^2 + (x_1 - \overline{x_1})^2\right] dt \\
&\quad = \int_0^{T_f} \left[\frac{1}{A_1^2}\left(x_1(y_1 - y_4) - \overline{x_1}\ (\overline{y_1} - \overline{y_4}\right) + (x_1 - \overline{x_1})^2\right] dt \\
&\quad \leq C_1' \int_0^{T_f} \left[(x_1 - \overline{x_1})^2 + (y_1 - \overline{y_1})^2 + (y_4 - \overline{y_4})^2\right] dt.
\end{aligned}$$

Also,

$$\begin{aligned}
&\beta \int_0^{T_f} e^{mt}(x_1 x_3 - \overline{x_1}\ \overline{x_3})(x_1 - \overline{x_1})dt \\
&\qquad \leq B_1 e^{mT_f} \int_0^{T_f} \left[(x_1 - \overline{x_1})^2 + (x_3 - \overline{x_3})^2\right] dt
\end{aligned}$$

Substituting above relations in equation (4.10), it becomes

$$\begin{aligned}
&\frac{1}{2}(x_1 - \overline{x_1})^2(T_f) + (m + \mu) \int_0^{T_f} (x_1 - \overline{x_1})^2 dt \\
&\qquad \leq B_1 e^{mT_f} \int_0^{T_f} \left[(x_1 - \overline{x_1})^2 + (x_3 - \overline{x_3})^2\right] dt \\
&\qquad + C_1' \int_0^{T_f} \left[(x_1 - \overline{x_1})^2 + (y_1 - \overline{y_1})^2 + (y_4 - \overline{y_4})^2\right] dt
\end{aligned} \tag{4.11}$$

where the contant B_1 and C_1' obtained above are dependent on the system coefficients as well as the bounds on the state and adjoint variables. For the second, third and fourth equation of system (4.9) we substitute $L = e^{mt} x_2$ and $\overline{L} = e^{mt}\ \overline{x_2}$, $I = e^{mt} x_3$ and $\overline{I} = e^{mt}\ \overline{x_3}$, and $R = e^{mt} x_4$ and $\overline{R} = e^{mt}\ \overline{x_4}$ respectively then we get

$$\begin{aligned}
&\frac{1}{2}(x_2 - \overline{x_2})^2(T_f) + (m + \mu + \delta) \int_0^{T_f} (x_2 - \overline{x_2})^2 dt \\
&\qquad \leq B_2 e^{mT_f} \int_0^{T_f} \left[(x_1 - \overline{x_1})^2 + (x_2 - \overline{x_2})^2 + (x_3 - \overline{x_3})^2\right] dt
\end{aligned} \tag{4.12}$$

$$\begin{aligned}
&\frac{1}{2}(x_3-\overline{x_3})^2(T_f)+(m+\mu+\gamma+\alpha)\int_0^{T_f}(x_3-\overline{x_3})^2dt\\
&\quad\le B_3\ e^{mT_f}\int_0^{T_f}\Big[(x_1-\overline{x_1})^2+(x_3-\overline{x_3})^2\Big]dt\\
&\qquad+C_2'\int_0^{T_f}\Big[(x_2-\overline{x_2})^2+(x_3-\overline{x_3})^2+(y_3-\overline{y_3})^2+(y_4-\overline{y_4})^2\Big]dt
\end{aligned}\tag{4.13}$$

$$\begin{aligned}
&\frac{1}{2}(x_4-\overline{x_4})^2(T_f)+(m+\mu)\int_0^{T_f}(x_4-\overline{x_4})^2dt\\
&\quad\le C_3'\int_0^{T_f}\Big[(x_1-\overline{x_1})^2+(x_3-\overline{x_3})^2+(x_4-\overline{x_4})^2+(y_1-\overline{y_1})^2+(y_3-\overline{y_3})^2\\
&\qquad+(y_4-\overline{y_4})^2\Big]dt
\end{aligned}\tag{4.14}$$

For the fifth equation of system (4.9) we substitute $\lambda_1 = e^{-mt}y_1$ and $\overline{\lambda_1} = e^{-mt}\ \overline{y_1}$, we get,

$$-\dot{y}_1+my_1=-\beta e^{mt}y_1x_3-\mu y_1-u_1^*y_1+l\beta e^{mt}y_2x_3+(1-l)\beta e^{mt}y_3x_3$$

and

$$-\dot{\overline{y_1}}+m\ \overline{y_1}=-\beta e^{mt}\ \overline{y_1}\ \overline{x_3}-\mu\ \overline{y_1}-u_1^*\ \overline{y_1}+l\beta e^{mt}\ \overline{y_2}\ \overline{x_3}+(1-l)\beta e^{mt}\ \overline{y_3}\ \overline{x_3}$$

Subtracting the expression for $\overline{\lambda_1}$ from the expression for λ_1 , then multiplying by $(y_1-\overline{y_1})$ and integrating from $t=0$ to $t=T_f$ we have,

$$\begin{aligned}
&\frac{1}{2}(y_1-\overline{y_1})^2(0)+(m+\mu)\int_0^{T_f}(y_1-\overline{y_1})^2dt\\
&\qquad\le B_4e^{mT_f}\int_0^{T_f}\Big[(y_1-\overline{y_1})^2+(x_1-\overline{x_1})^2\Big]dt\\
&\qquad+\ B_5e^{mT_f}\int_0^{T_f}\Big[(y_2-\overline{y_2})^2+(x_3-\overline{x_3})^2\Big]dt\\
&\qquad+\ B_6e^{mT_f}\int_0^{T_f}\Big[(y_3-\overline{y_3})^2+(x_3-\overline{x_3})^2\Big]dt\\
&\qquad+C_7\int_0^{T_f}\Big[(u_1^*-\overline{u_1^*})^2+(y_1-\overline{y_1})^2\Big]dt
\end{aligned}$$

$$\begin{aligned}
&\leq B_4 e^{mT_f} \int_0^{T_f} \Big[(y_1-\overline{y_1})^2+(x_1-\overline{x_1})^2\Big]dt \\
&+ \ B_5 e^{mT_f} \int_0^{T_f} \Big[(y_2-\overline{y_2})^2+(x_3-\overline{x_3})^2\Big]dt \\
&+ \ B_6 e^{mT_f} \int_0^{T_f} \Big[(y_3-\overline{y_3})^2+(x_3-\overline{x_3})^2\Big]dt \\
&+ C_4' \int_0^{T_f} \Big[(x_1-\overline{x_1})^2+(y_1-\overline{y_1})^2+(y_4-\overline{y_4})^2\Big]dt
\end{aligned} \tag{4.15}$$

Similarly for the sixth, seventh and eighth equation of system (4.9) we substitute $\lambda_2 = e^{-mt}y_2$ and $\overline{\lambda_2} = e^{-mt}\ \overline{y_2}$, $\lambda_3 = e^{-mt}y_3$ and $\overline{\lambda_3} = e^{-mt}\ \overline{y_3}$, and $\lambda_4 = e^{-mt}y_4$ and $\overline{\lambda_4} = e^{-mt}\ \overline{y_4}$ respectively, then we get,

$$\begin{aligned}
&\frac{1}{2}(y_2-\overline{y_2})^2(0)+(m+\mu+\delta)\int_0^{T_f}(y_2-\overline{y_2})^2dt \\
&\qquad\qquad \leq C_5' \int_0^{T_f} \Big[(y_2-\overline{y_2})^2+(y_3-\overline{y_3})^2\Big]dt
\end{aligned} \tag{4.16}$$

$$\begin{aligned}
&\frac{1}{2}(y_3-\overline{y_3})^2(0)+(m+\mu+\gamma+\alpha)\int_0^{T_f}(y_3-\overline{y_3})^2dt \\
&\qquad \leq B_7 e^{mT_f} \int_0^{T_f} \Big[(x_1-\overline{x_1})^2+(y_1-\overline{y_1})^2+(y_3-\overline{y_3})^2\Big]dt \\
&\qquad + \ B_8 e^{mT_f} \int_0^{T_f} \Big[(x_1-\overline{x_1})^2+(y_2-\overline{y_2})^2+(y_3-\overline{y_3})^2\Big]dt \\
&\qquad + C_6' \int_0^{T_f} \Big[(x_3-\overline{x_3})^2+(y_3-\overline{y_3})^2+(y_4-\overline{y_4})^2\Big]dt \\
&\qquad + C_7' \int_0^{T_f} \Big[(y_3-\overline{y_3})^2+(y_4-\overline{y_4})^2\Big]dt
\end{aligned} \tag{4.17}$$

$$\frac{1}{2}(y_4-\overline{y_4})^2(0)+(m+\mu)\int_0^{T_f}(y_4-\overline{y_4})^2dt = 0 \tag{4.18}$$

where $B_i(i = 1, 2, ...9)$ and $C_j(j = 1, 2, ..7)$ depend on the coefficients and the bounds of the state variables and co-state variables.

We obtain total eight integral equations and to show uniqueness, the integral equations are combined. Adding all the eight estimates gives

$$\frac{1}{2}(x_1-\overline{x_1})^2(T_f)+\frac{1}{2}(x_2-\overline{x_2})^2(T_f)+\frac{1}{2}(x_3-\overline{x_3})^2(T_f)+\frac{1}{2}(x_4-\overline{x_4})^2(T_f)+$$
$$\frac{1}{2}(y_1-\overline{y_1})^2(0)+\frac{1}{2}(y_2-\overline{y_2})^2(0)+\frac{1}{2}(y_3-\overline{y_3})^2(0)+\frac{1}{2}(y_4-\overline{y_4})^2(0)+(m+\mu)$$
$$\int_0^{T_f}(x_1-\overline{x_1})^2dt+(m+\mu+\delta)\int_0^{T_f}(x_2-\overline{x_2})^2dt+(m+\mu+\gamma+\alpha)\int_0^{T_f}(x_3-$$
$$\overline{x_3})^2dt+(m+\mu)\int_0^{T_f}(x_4-\overline{x_4})^2dt+(m+\mu)\int_0^{T_f}(y_1-\overline{y_1})^2dt+(m+\mu+\delta)$$
$$\int_0^{T_f}(y_2-\overline{y_2})^2dt+(m+\mu+\gamma+\alpha)\int_0^{T_f}(y_3-\overline{y_3})^2dt+(m+\mu)\int_0^{T_f}(y_4-\overline{y_4})^2dt$$
$$\leq B_1e^{mT_f}\int_0^{T_f}\Big[(x_1-\overline{x_1})^2+(x_3-\overline{x_3})^2\Big]dt+C_1'\int_0^{T_f}\Big[(x_1-\overline{x_1})^2+(y_1-\overline{y_1})^2+$$
$$(y_4-\overline{y_4})^2\Big]dt+B_2e^{mT_f}\int_0^{T_f}\Big[(x_1-\overline{x_1})^2+(x_2-\overline{x_2})^2+(x_3-\overline{x_3})^2\Big]dt+B_3\ e^{mT_f}$$
$$\int_0^{T_f}\Big[(x_1-\overline{x_1})^2+(x_3-\overline{x_3})^2\Big]dt\quad+C_2'\int_0^{T_f}\Big[(x_2-\overline{x_2})^2+(x_3-\overline{x_3})^2+(y_3-\overline{y_3})^2$$
$$+(y_4-\overline{y_4})^2\Big]dt+C_3'\int_0^{T_f}\Big[(x_1-\overline{x_1})^2+(x_3-\overline{x_3})^2+(x_4-\overline{x_4})^2+(y_1-\overline{y_1})^2+$$
$$(y_3-\overline{y_3})^2+(y_4-\overline{y_4})^2\Big]dt+B_4e^{mT_f}\int_0^{T_f}\Big[(y_1-\overline{y_1})^2+(x_1-\overline{x_1})^2\Big]dt+\ B_5e^{mT_f}$$
$$\int_0^{T_f}\Big[(y_2-\overline{y_2})^2+(x_3-\overline{x_3})^2\Big]dt+B_6e^{mT_f}\int_0^{T_f}\Big[(y_3-\overline{y_3})^2+(x_3-\overline{x_3})^2\Big]dt+C_4'$$
$$\int_0^{T_f}\Big[(x_1-\overline{x_1})^2+(y_1-\overline{y_1})^2+(y_4-\overline{y_4})^2\Big]dt+C_5'\int_0^{T_f}\Big[(y_2-\overline{y_2})^2+(y_3-\overline{y_3})^2\Big]dt$$
$$+B_7e^{mT_f}\ \int_0^{T_f}\Big[(x_1-\overline{x_1})^2+(y_1-\overline{y_1})^2+(y_3-\overline{y_3})^2\Big]dt+B_8e^{mT_f}\ \int_0^{T_f}\Big[(x_1-\overline{x_1})^2$$
$$+(y_2-\overline{y_2})^2+(y_3-\overline{y_3})^2\Big]dt+C_6'\int_0^{T_f}\Big[(x_3-\overline{x_3})^2+(y_3-\overline{y_3})^2+(y_4-\overline{y_4})^2\Big]dt$$
$$+C_7'\int_0^{T_f}\Big[(y_3-\overline{y_3})^2+(y_4-\overline{y_4})^2\Big]dt$$

Thus from the above expression, using the non-negativity of the variable expressions evaluated at the initial and the final time and simplifying the inequality

$$\Big[(m+\mu)-(B_1+B_2+B_3+B_7+B_8+B_9)e^{mT_f}-(C_1'+C_3'+C_4')\Big]\int_0^{T_f}(x_1-\overline{x_1})^2dt$$
$$+\Big[(m+\mu+\delta)-B_2e^{mT_f}-C_2'\Big]\int_0^{T_f}(x_2-\overline{x_2})^2dt+\Big[(m+\mu+\gamma+\alpha)-(B_1+B_2$$
$$+B_3+B_5+B_6)e^{mT_f}-(C_2'+C_3'+C_6')\Big]\int_0^{T_f}(x_3-\overline{x_3})^2dt+\Big[(m+\mu)-C_3'\Big]$$
$$\int_0^{T_f}(x_4-\overline{x_4})^2dt+\Big[(m+\mu)-(B_4+B_7)e^{mT_f}-C_1'+C_3'+C_4')\Big]\int_0^{T_f}(y_1-\overline{y_1})^2dt$$
$$+\Big[(m+\mu+\delta)-(B_5+B_8)e^{mT_f}-C_5'\Big]\int_0^{T_f}(y_2-\overline{y_2})^2dt+\Big[(m+\mu+\gamma+\alpha)-$$
$$(B_6+B_7+B_8+B_9)e^{mT_f}-(C_2'+C_3'+C_5'+C_6'+C_7')\Big]\int_0^{T_f}(y_3-\overline{y_3})^2dt+$$
$$\Big[(m+\mu)-(C_1'+C_2'+C_3'+C_4'+C_6'+C_7'\Big]\int_0^{T_f}(y_4-\overline{y_4})^2dt+\leq 0 \tag{4.19}$$

Here all the coefficients of all integrals in (4.19) are non-negative if we choose a sufficiently large m and sufficiently small T_f.
For example, if we fix

$$m > B_1+B_2+B_3+B_7+B_8+B_9+C_1'+C_3'+C_4'-\mu$$

and

$$e^{mT_f} < \frac{(m+\mu)-(C_1'+C_3'+C_4')}{B_1+B_2+B_3+B_7+B_8+B_9}$$

i.s

$$T_f < \frac{1}{m}\ ln\frac{(m+\mu)-(C_1'+C_3'+C_4')}{B_1+B_2+B_3+B_7+B_8+B_9}$$

then the coefficient $(m+\mu)-(B_1+B_2+B_3+B_7+B_8+B_9)e^{mT_f}-(C_1'+C_3'+C_4')$ for the integral $\int_0^{T_f}(x_1-\overline{x_1})^2dt$ will be non-negative. Similar arguments apply to remaining integral terms, we can obtain all of the other m_s and T_fs. Take the maximum of all of the m_s used as m and the minimum of the T_fs used as T_f, then the coefficient of each integral term in (4.19) is non-negative. This implies that

$$x_1=\overline{x_1},\ x_2=\overline{x_2},\ x_3=\overline{x_3},\ x_4=\overline{x_4},\ y_1=\overline{y_1},\ y_2=\overline{y_2},\ y_3=\overline{y_3},\ y_4=\overline{y_4}$$

and

$$S = \overline{S},\ L = \overline{L},\ I = \overline{I},\ R = \overline{R},\ \lambda_1 = \overline{\lambda_1},\ \lambda_2 = \overline{\lambda_2},\ \lambda_3 = \overline{\lambda_3},\ \lambda_4 = \overline{\lambda_4}$$

Hence the solution of (4.9) is unique for small time. This ends the proof.

4.8 Numerical Result

Numerical solutions to the optimality system comprising of the state equation (4.1), adjoint equation (4.5), control characterizations equation (4.6) and corresponding initial/final conditions are carried out using the forward-backward sweep method (implemented in MATLAB) and the parameters set in Table 3.1. The algorithm starts with an initial guess for the optimal controls and the state variables are then solved forward in time using Rung Kutta method of the fourth order. Then the state variables and initial control guess are used to solve the adjoint equation (4.5) backward in time with given final condition (4.6), employing the backward fourth order Runge Kutta method. The controls $u_1(t)$ and $u_2(t)$ are then updated and used to solve the state and then the adjoint system. This iterative process terminates when the current state, adjoint, and control values converge sufficiently [35].

In this section, we use numerical simulations to support the analytical results previously established and to provide examples about the dynamics of diphtheria disease. We use the following initial conditions $\{S(0), L(0), I(0), R(0)\} = \{60000, 250, 1000, 1000\}$ and the value of the parameters are estimated in the previous chapter given in Table 3.1. In the previous chapter, we see that the basic reproduction number $\mathcal{R}_0 = 7.29$ which indicates that the disease is very much infectious. For this reason here we use bigger initial contions of the state variable S and I from the previous chapter. Comparing this value with the previous chapter it seems approximately after 40 days.

Figure 4.2, 4.3, 4.4, and 4.5 represent the disease dynamics of the state variables with control and without control. Here we use the controls in susceptible class $S(t)$ and infected class $I(t)$. Comparing with-control with without-control, figure 4.2 and 4.4 illustrate the significant change of these classes and figure 4.3 and

4.5 illustrate the impact on the latent class $L(t)$ and recovered class $R(t)$ of this changing.

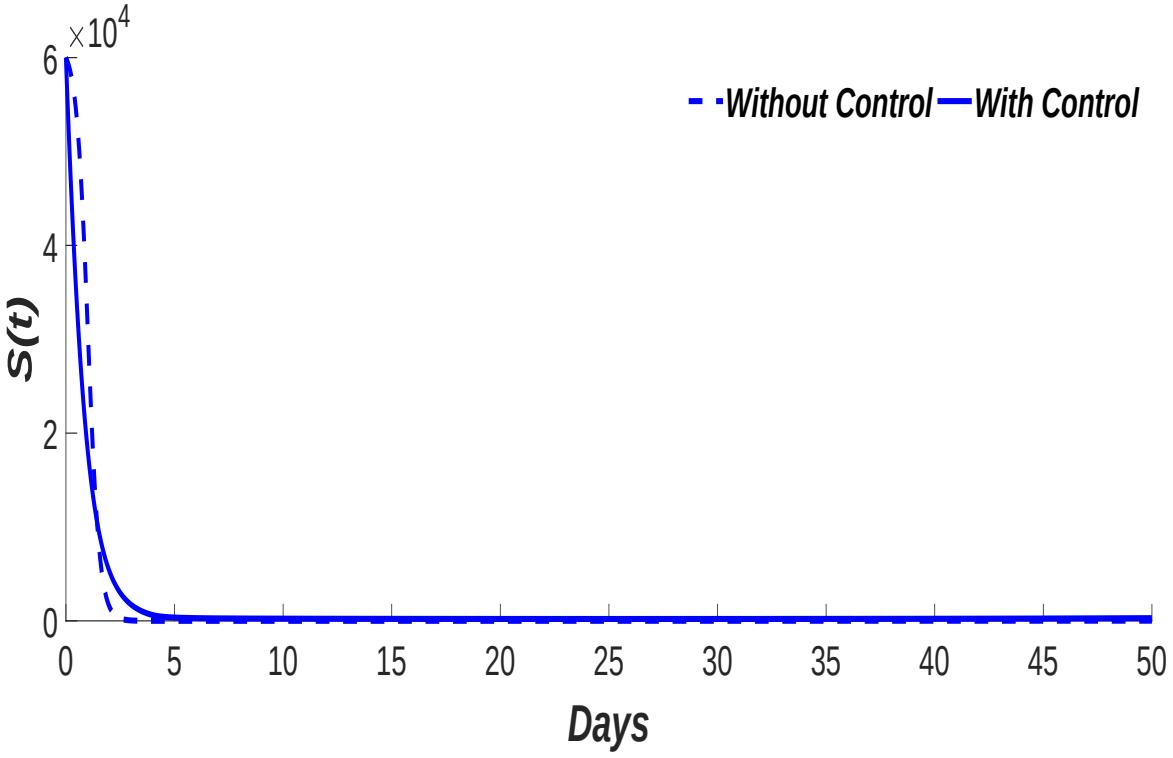

Figure. 4.2. Diphtheria disease dynamics of Susceptible population with control and without control

4.8.1 Treatment strategies

To illustrate the effect of different optimal control strategies on the spread of disease in a population, we will consider the following combination of time-dependent controls making up three control strategies A-C:

Strategy A (Only Vaccination): In this strategy, we only use of vaccination to the population and no use of treatment to the population. Hence for the **Strategy A**, the controls $u_1(t) = 1$ and $u_2(t) = 0$.

Strategy B (Only Treatment): In this strategy, we only use of treatment to the population and no use of vaccination to the population. Hence for the **Strategy B**, the controls $u_2(t) = 1$ and $u_1(t) = 0$.

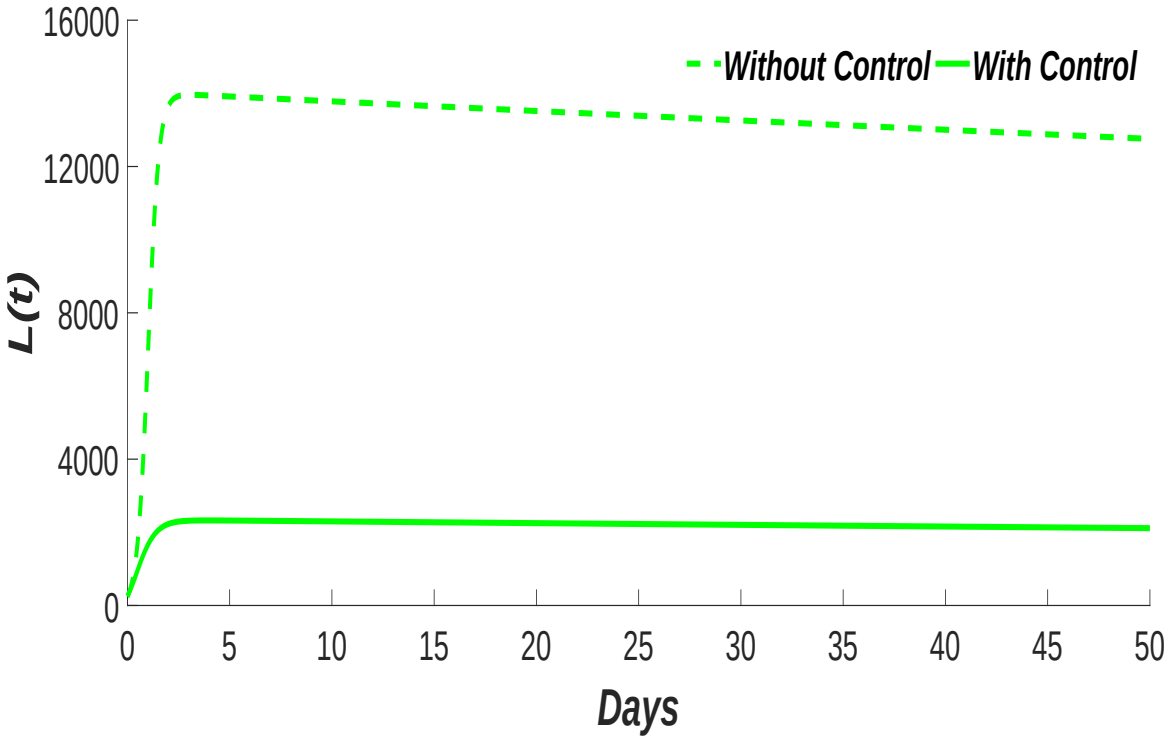

Figure. 4.3. Diphtheria disease dynamics of Latent population with control and without control

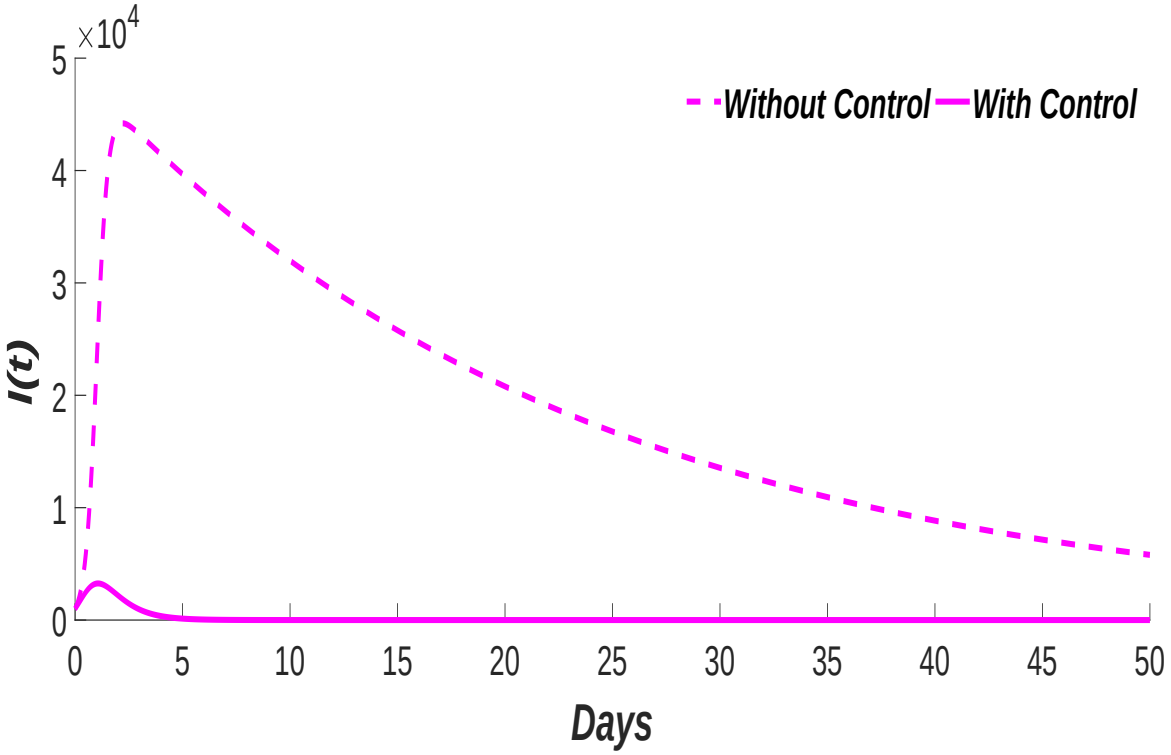

Figure. 4.4. Diphtheria disease dynamics of Infected population with control and without control

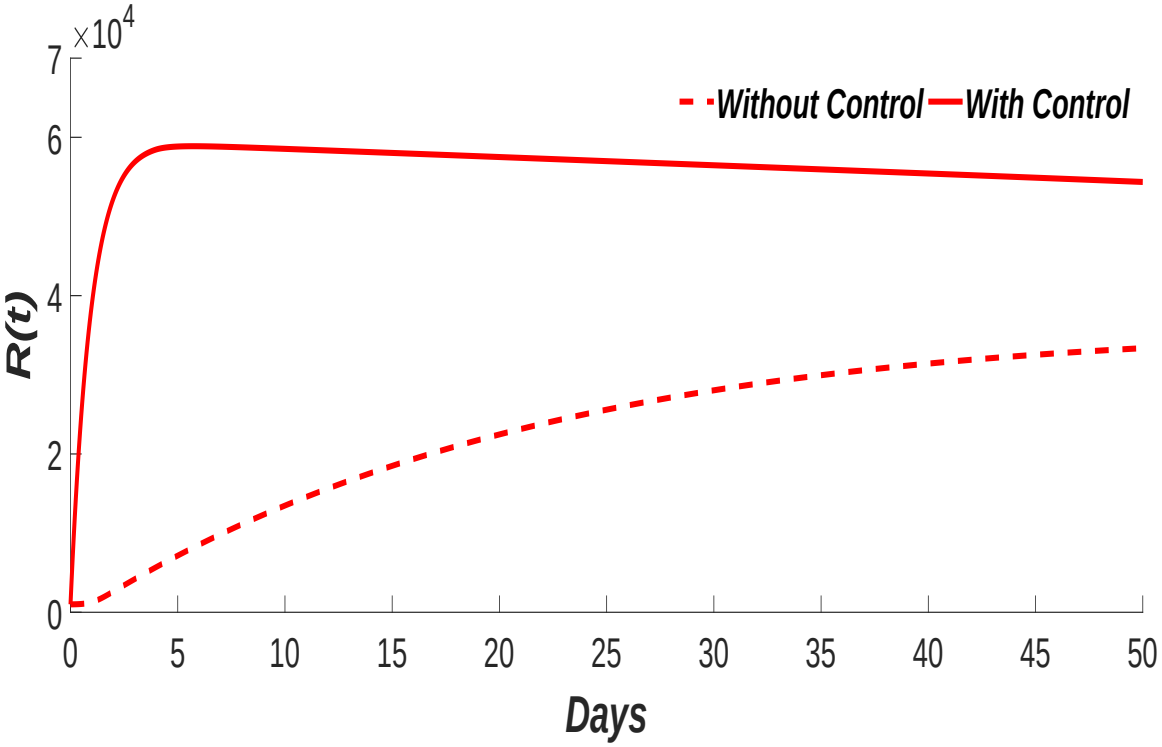

Figure. 4.5. Diphtheria disease dynamics of Recovered population with control and without control

Strategy C (Both Vaccination and Treatment) : Here we use both vaccination and treatment to the population. Therefore for the **Strategy C**, the controls $u_1(t) = u_2(t) = 1$.

Now we are applying the three different control strategies on the state variables to obtain the best strategy by comparing the results of these strategies. Figures 4.6, 4.7, 4.8, and 4.9 represent the different effects of these strategies. From these figure we observed that the strategy C (combined control) feedback the best result.

For Strategy A figure 4.10 illustrates that, if we use only vaccination to the population we need to apply it 100% from first 38 days. After that it should be gradually decreasing and finaly after 50 days it should be closed. For Strategy B figure 4.11 illustrates that if we use only treatment to the population we have to apply it 100% from first 11 days. After that it should be decreasing sharply till 14th day and then should apply 55% till 47th day then it further decreasing sharply and finaly after 50 days it should be closed. For Strategy C, figure 4.12 illustrates that if we use both controls to the population then we have to apply vaccination 100% from first 4 days. After that it should be decreasing sharply to 10% till 7th day and then it should be gradually decreasing and finaly after 50 days it should be

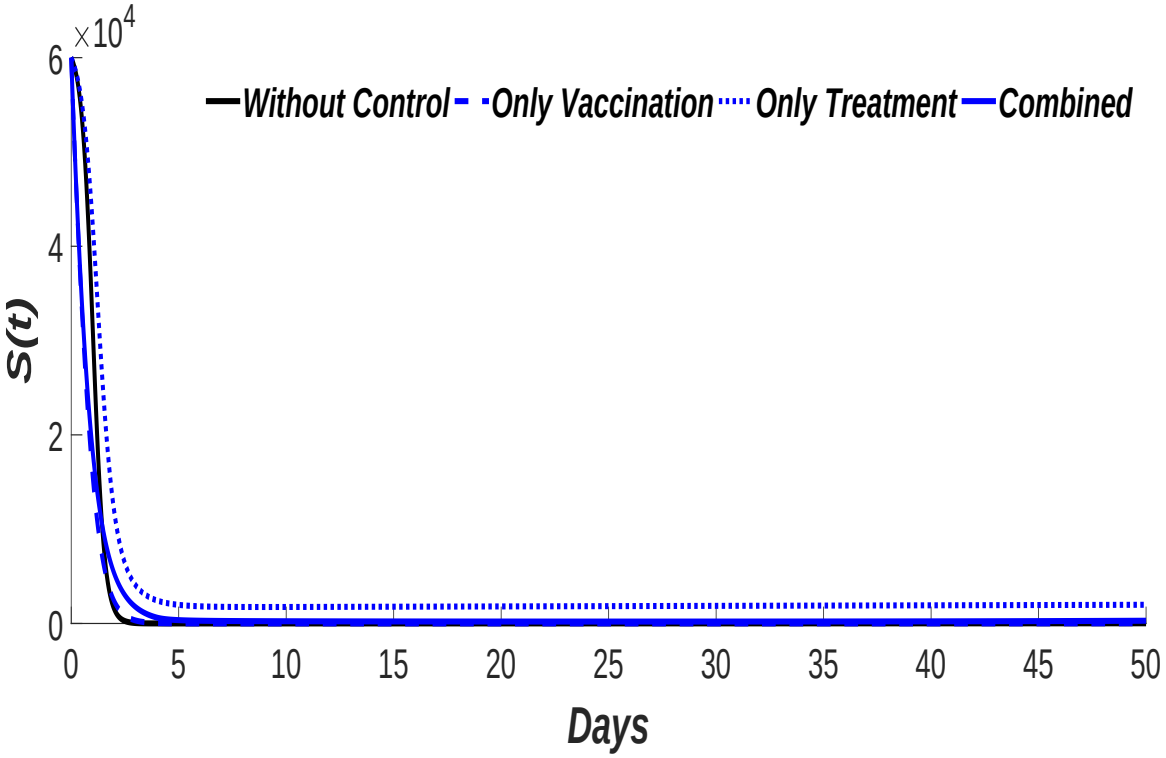

Figure. 4.6. Disease dynamics of Susceptible population in different Strategies and without control

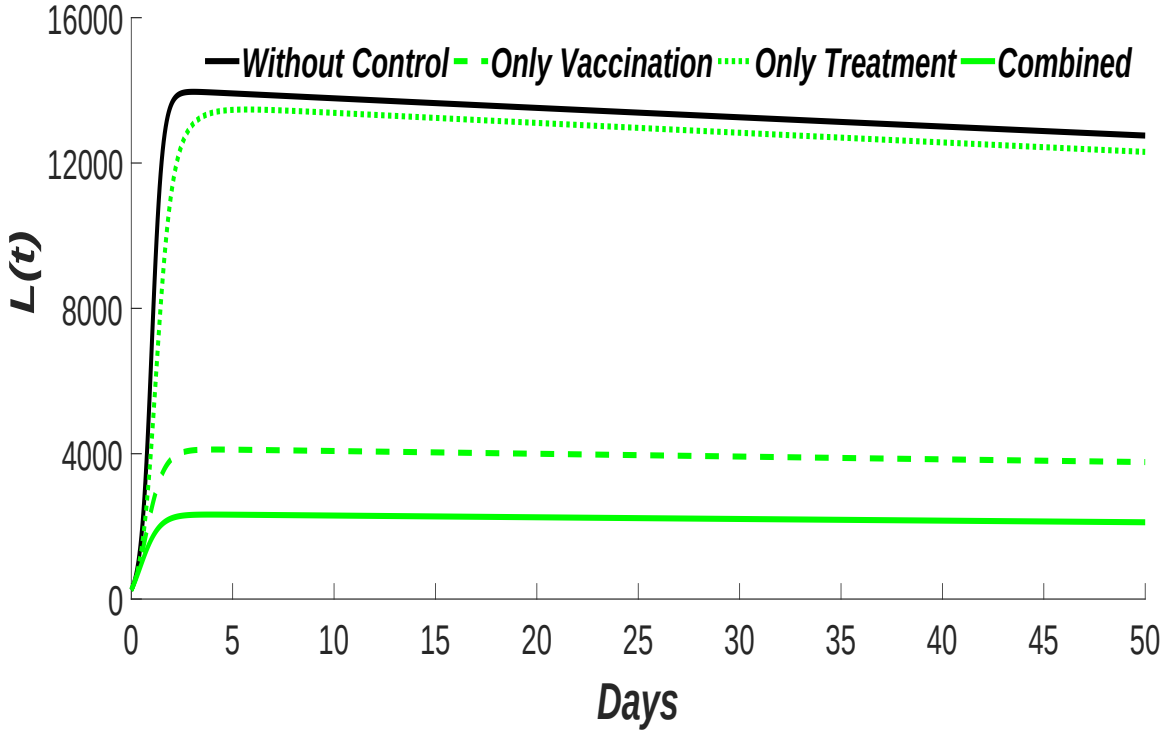

Figure. 4.7. Disease dynamics of Latent population in different Strategies and without control

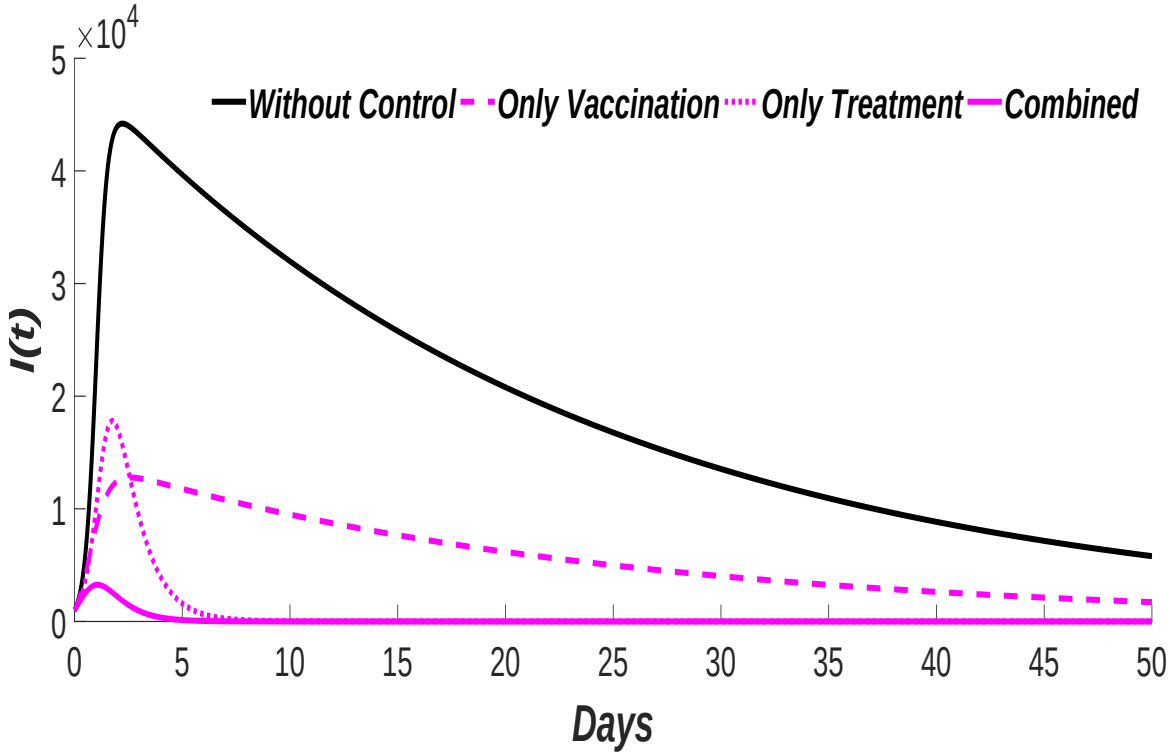

Figure. 4.8. Disease dynamics of Infected population in different Strategies and without control

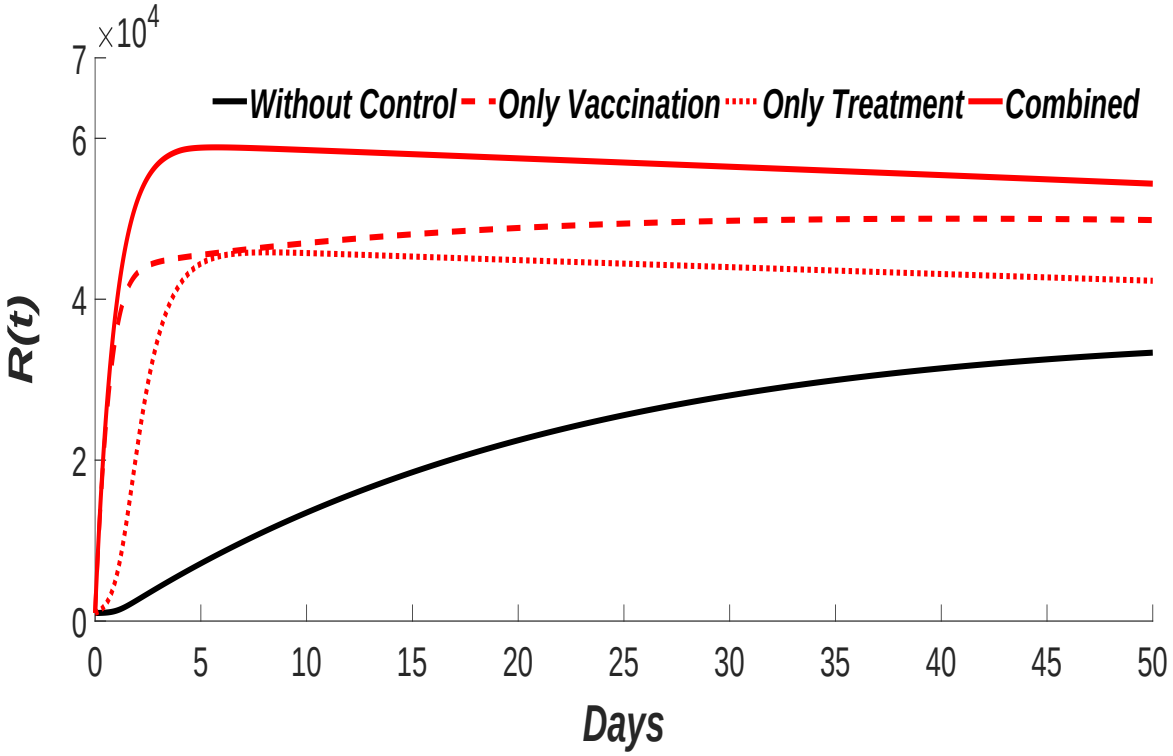

Figure. 4.9. Disease dynamics of Recovered population in different Strategies and without control

closed. While using both controls figure 4.13 illustrates the simulation results of the control treatment. Here it indicates that we should apply treatment 100% to the population from 1st 8 days and then it should be decreasing till 11th day to 35% and further gradually decreasing to 27% till 15th dayand then it should be continuing till 43th day and lastly it should be gradually decreasing to 0% to the final day.

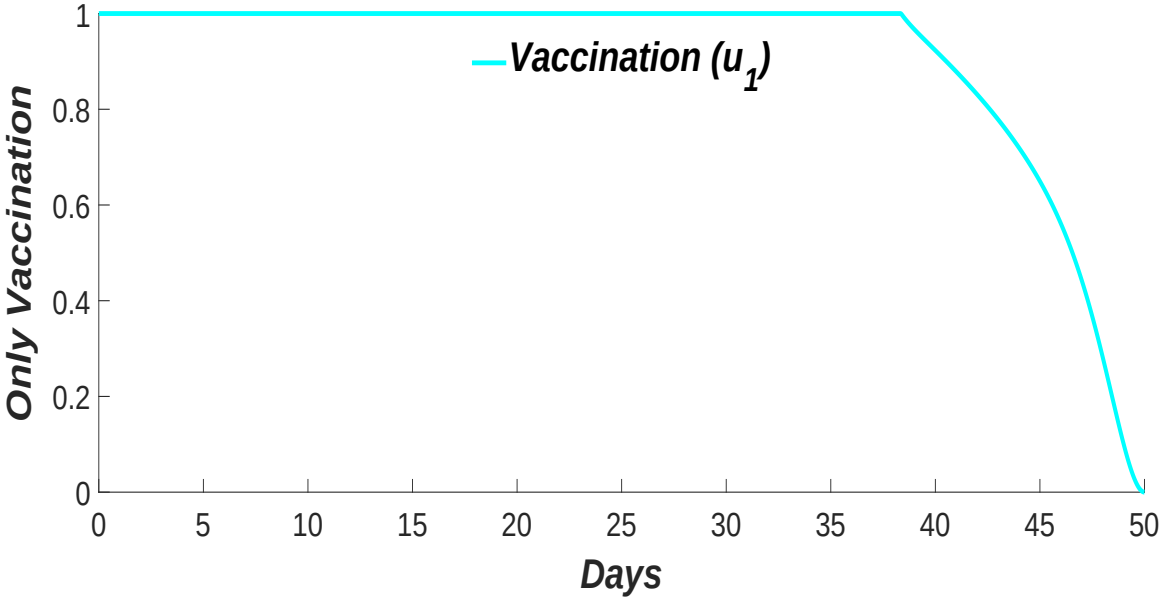

Figure. 4.10. Simulation results of the control $u_1(t)$ while using only vaccination

4.9 Cost-effectiveness analysis

Next, we have performed a cost-effectiveness analysis. In order to justify the costs associated with health intervention(s) or strategy (strategies) such as treatment, or vaccination the associated benefits are usually evaluated using cost-effectiveness analysis [8]. In this section we will consider three approaches, the infection averted ratio (IAR), the average cost-effectiveness ratio (ACER) and the incremental cost-effectiveness ratio (ICER).

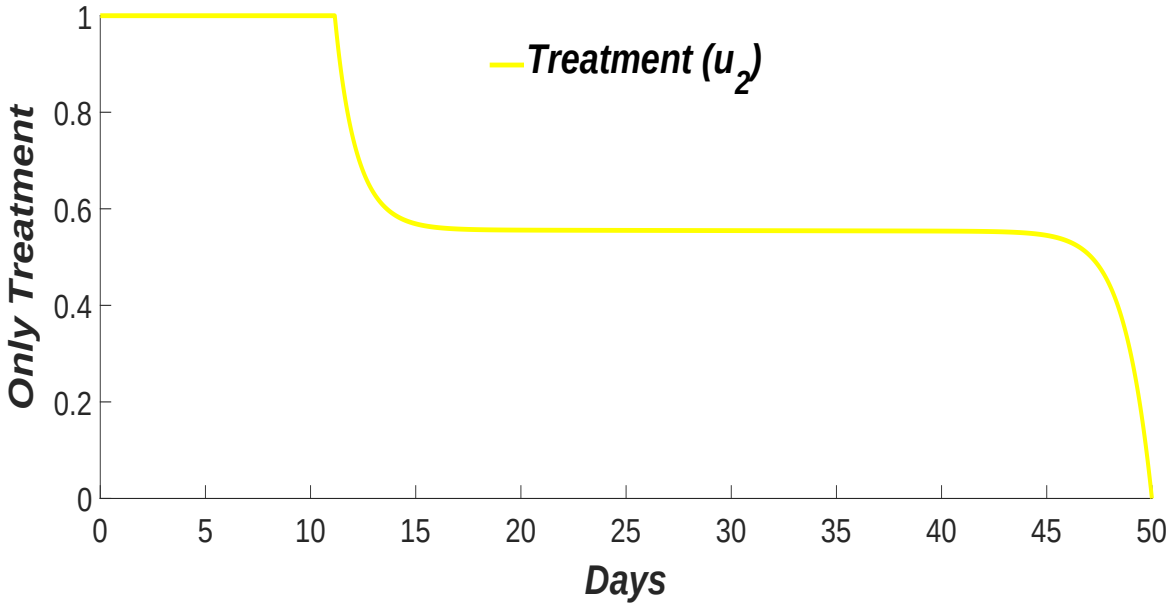

Figure. 4.11. Simulation results of the control $u_2(t)$ while using only treatment

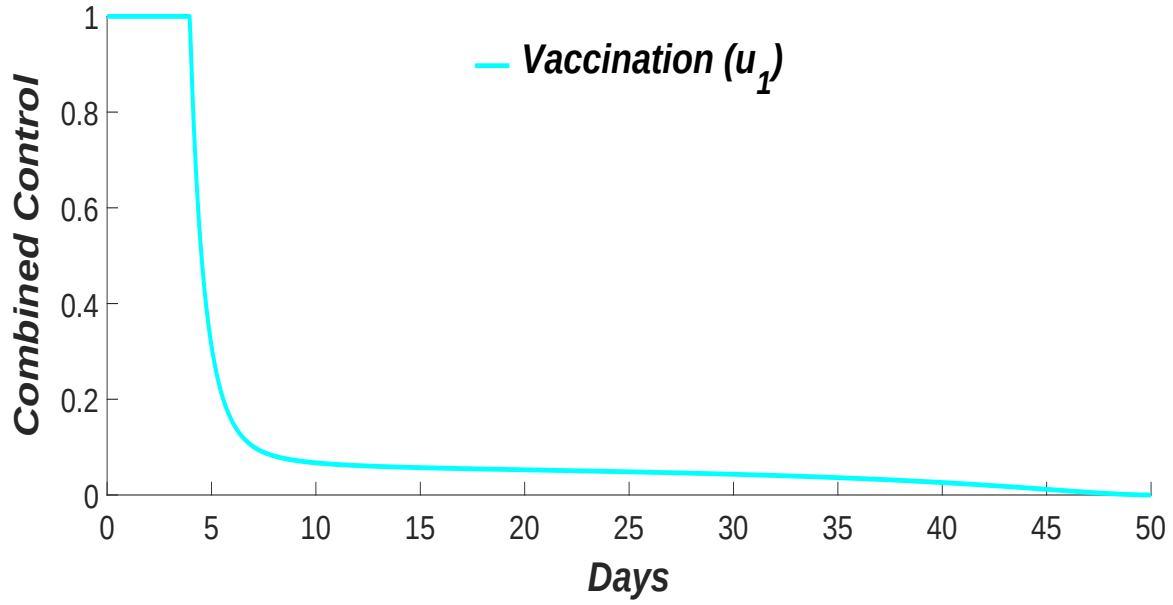

Figure. 4.12. Simulation results of the control $u_1(t)$ while using both controls

4.9.1 Infection averted ratio

The infection averted ratio (IAT) is stated as

$$\text{IAR} = \frac{\text{Number of infection averted}}{\text{Number of recovered}} \tag{4.20}$$

The number of infection averted above is given as the difference between the total infectious individuals without control and the total infectious individuals

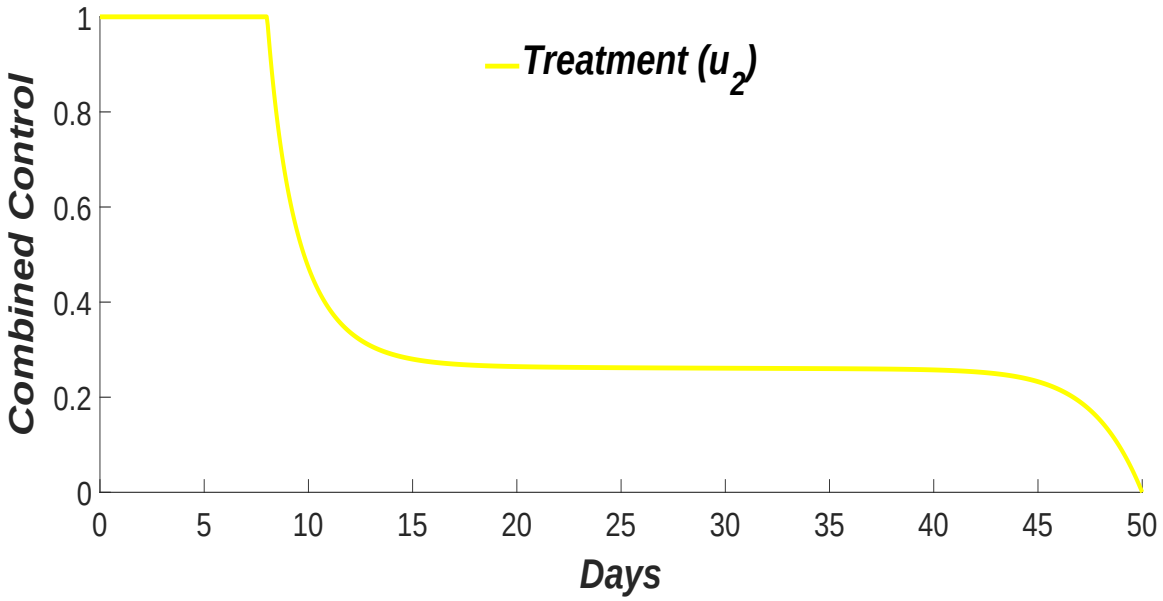

Figure. 4.13. Simulation results of the control $u_2(t)$ while using both controls

with control. The strategy with the highest ratio is the most effective. Using the parameter values in Table 3.1, the IAR for each intervention strategy was determined. Figure 4.14 shows the IAR for the three strategies implemented (see also Table 4.1. Strategy B involving only treatment ($u_1(t) = 0$ and $u_2(t) = 1$) that means applying only treatment produced the highest ratio and was therefore the most effective. This is followed by Strategy C involving the combination of both vaccination and treatment ($u_1(t) = u_2(t) = 1$). Strategy A involving only vaccination ($u_1(t) = 1, u_2(t) = 0$) use was the least effective, this in part was due to the low number of infection averted using this strategy (see Table 4.1).

4.9.2 Average Cost-Effectiveness Ratio (ACER)

Next, we considered the average cost-effectiveness ratio (ACER) which deals with a single intervention, evaluating it against the no intervention baseline option. ACER is calculated as

$$\text{ACER} = \frac{\text{Total cost produced by the intervention}}{\text{Total number of infection averted}} \tag{4.21}$$

Figure 4.15 shows that the most cost-effective strategy is strategy C, followed by Strategy B and Strategy A is the least cost-effective (see also Table 4.1).

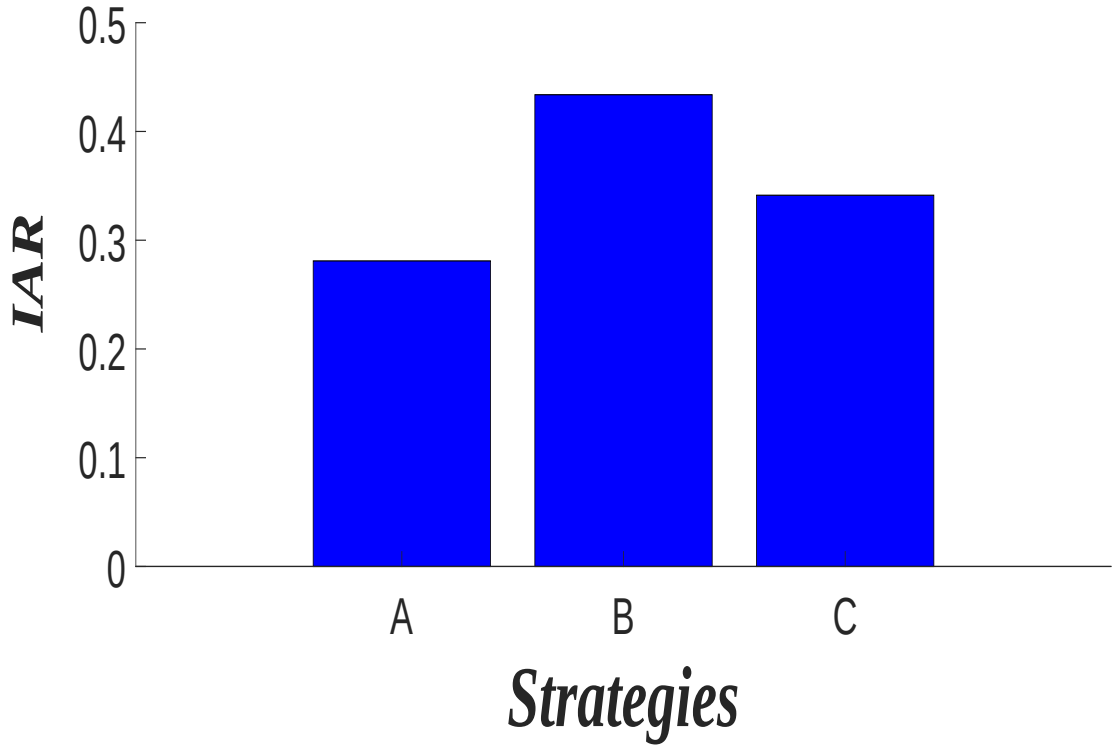

Figure. 4.14. IAR plots indicating the effect of the control strategies A, B, and C

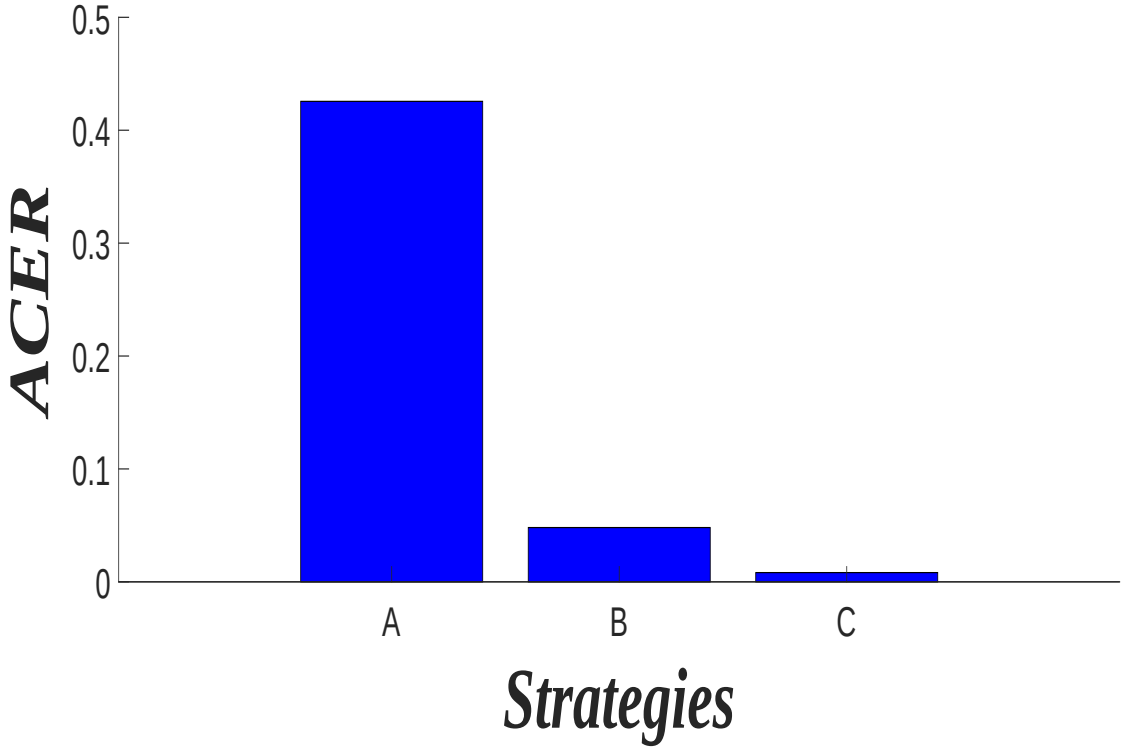

Figure. 4.15. ACER plots indicating the effect of the control strategies A, B, and C

Table. 4.1. Total infection averted, Total cost, IAR and ACER.

Strategies	**Total infection averted**	**Total cost**	IAR	ACER
Strategy A	13498205	5744411	0.280958	0.425569
Strategy B	18357955	882587.1	0.433781	0.048077
Strategy C	19083531	156317.7	0.341351	0.008191

To further investigate the cost-effectiveness of the various control strategies, we evaluated the incremental cost-effectiveness ratio (ICER).

4.9.3 Incremental Cost-Effectiveness Ratio

Disease control and eradication in a community can be both labor intensity and expensive. Thus, to determine the most cost-effective strategy to use, it is imperative to carry out a costeffectiveness analysis. To achieve this, the differences between the various costs and health outcomes of implementing these different interventions are compared by calculating the incremental cost-effectiveness ratio (ICER). The ICER is the additional cost per additional health outcome and we assume that the costs of the various control interventions are directly proportional to the number of controls deployed. To compare competing intervention strategies (usually two or more) incrementally, one intervention is compared with the next-less-effective alternative [8]. Thus, the ICER is calculated as

$$\text{ICER} = \frac{\text{Difference in infection averted costs in strategies i and j}}{\text{Difference in total number of infection averted in strategies i and j}} \tag{4.22}$$

The ICER numerator includes (where applicable) the differences in the costs of disease averted or cases prevented, the costs of intervention(s), and the costs of averting productivity losses among others. The ICER denominator on the other hand is the differences in health outcomes which may include the total number of infections averted or the number of susceptibility cases prevented.

To implement the ICER, we simulate the model using the various interventions strategies. Using these simulation results, we rank the control strategies in increasing order of effectiveness based on infection averted, we have that Strategy C averted the least number of infections, followed by Strategy A, Strategy D, and

Strategy B which averted the most number of infections.
The ICER is computed as follows:

$$\text{ICER(A)} = \frac{5744411}{13498205} = 0.425569$$
$$\text{ICER(B)} = \frac{882587.1 - 5744411}{18357955 - 13498205} = -1.00043$$
$$\text{ICER(C)} = \frac{156317.7 - 882587.1}{19083531 - 18357955} = -1.00096$$

Table. 4.2. Incremental cost-effectiveness raio in increasing order of total infection averted

Strategies	**Total infection averted**	**Total cost**	ICER
Strategy A	13498205	5744411	0.425569
Strategy B	18357955	882587.1	-1.00043
Strategy C	19083531	156317.7	-1.00096

A look at Table 4.2 shows, since ICER for strategy A is positive, the comparison shows a cost saving of 0.425569 for Strategy A over Strategy B and Strategy C. The lower ICER for Strategy B and Strategy C indicate that, Strategy B and Strategy C strongly dominate Strategy A. This implies that Strategy A will be more expensive to implement compare to Strategy B and Strategy C; thus, Strategy A is excluded from further analysis. Hence, we obtain the following numerical computations given in Table 4.3 by excluding Strategy A and comparing the remaining strategies.

Table. 4.3. Incremental cost-effectiveness raio in increasing order of total infection averted

Strategies	**Total infection averted**	**Total cost**	ICER
Strategy B	18357955	882587.1	-1.00043
Strategy C	19083531	156317.7	-1.00096

Table 4.3 shows that Strategy B and Strategy C have negative ICER value. Which indicates that Strategy B and Strategy C in Table 4.3 are cost-effective, but the Strategy C has the least negative ICER value which simply implies that Strategy C is more cost -effective compare to Strategy B.

Repeating the entire process, we can determine the next most cost-effective strategy. Thus, we found that Strategy B is the next cost-effective strategy after Strategy C.

From the result, it is concluded that Strategy C (combination of both control variables u_1 and u_2) has the least ICER and therefore is more cost-effective than both of the Strategy B and Strategy A for control of only treatment and vaccination respectively. This result agrees with the results obtaining in Figure 4.16 for the objective functional for the the control strategies A, B, and C.

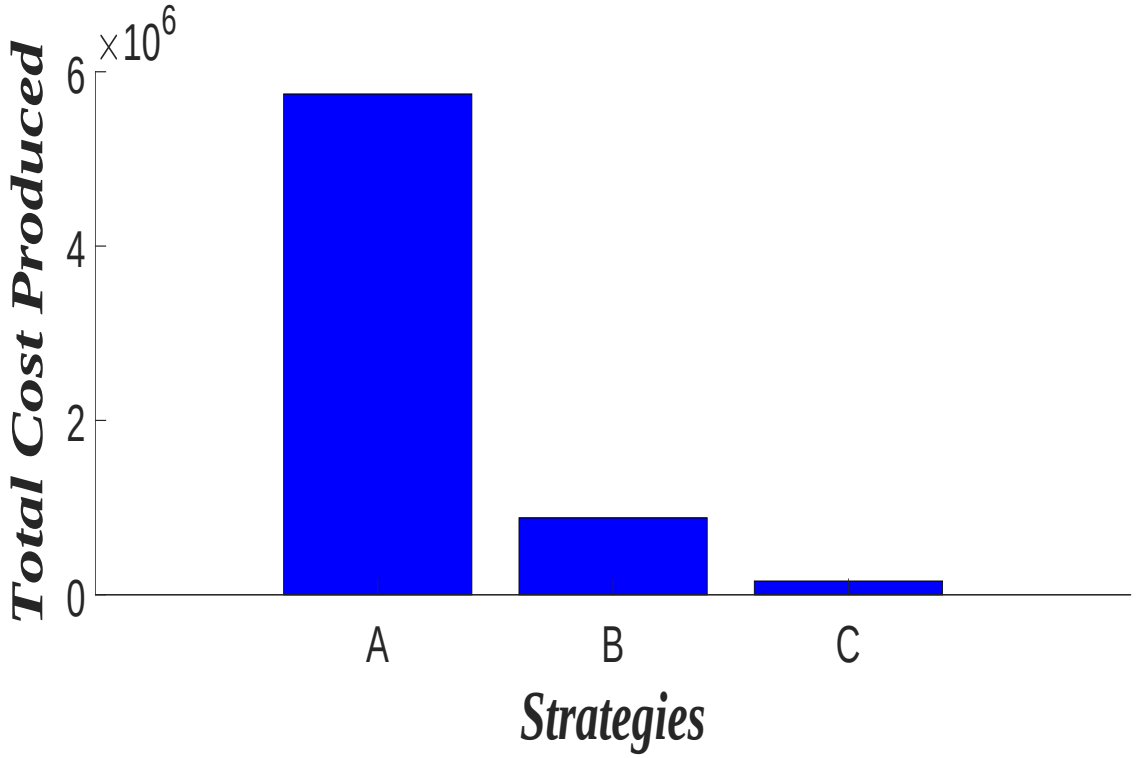

Figure. 4.16. Total Cost plots indicating the effect of the control strategies A, B, and C

Chapter 5

Conclusion and Future Works

In this study, we sought to learn more about Diphtheria by introducing and analyzing mathematical models of immune system dynamics in the presence of vaccination therapy. We began by developing and analyzing several models for Diphtheria infection and, using data from Diphtheria infected individuals, compared the models to determine which best fit the data for long time dynamics. We proved existence, uniqueness, positivity, and boundedness for the models and derived the conditions on basic reproduction number that guarantees the asymptotic stability of the equilibria. Our model determined that during primary infection the interaction between the populations plays a key role in characterizing Diphtheria infection. Our model, which included a latent compartment, maintained the greater basic reproduction number which suggests that the modified model was the best at capturing the long term dynamics and behavior of the infection. In addition to examining untreated systems, we also examined how treatment impacts the proliferation of Diphtheria. In doing so, we used asymptotic stability analyses to define treatment thresholds in order to eliminate the virus and clear the infection. Additionally, we were able to estimate necessary drug efficacy of treatment for infected patients and estimate necessary vaccine efficacy of vaccination for susceptible populations and apply optimal control theory to prove the existence of the optimal treatment solution. This would allow health sector of the country to controll a Diphtheria outbreak. Furthermore, our findings illustrate that combination therapy (strategy C) can provide the more effective strategy than individual treatment (strategy B) and vaccination (strategy A) which indicates that it is with much lower coast. The values of the objective function at the optimal control shows that the greatest effects do occur when vaccination

is initiated earliest. Also, results of the numerical simulations indicate that the rate of recovred populations increased and infected population decreased due to treatment parameter.

Some of the possible future directions of this work are briefly outlined below.

1. In many literature [2], to make the production of S-populations desensity dependent, the logistic growth has been considered during the chronic infection of Diphtheria. To trace out long term disease infectious from the beginning the proliferation rate of susceptible S-populations can be considered to be a logistic growth function.

$$\begin{cases} \dfrac{dS(t)}{dt} = \lambda + rS(t)\left(1 - \dfrac{S(t)}{S_{max}}\right) - \beta S(t)I(t) - \mu S(t), \\ \dfrac{dL(t)}{dt} = (1-l)\beta S(t)I(t) - (\mu + \delta)L(t), \\ \dfrac{dI(t)}{dt} = l\beta S(t)I(t) + \delta L(t) - (\mu + \alpha + \gamma)I(t), \\ \dfrac{dR(t)}{dt} = \gamma I(t) - \mu R(t). \end{cases}$$

2. Our mathematical descriptions have generally been limited to nonlinear ordinary differential equations describing the average behavior throughout the whole populations under the assumption that the environment is well-mixed or spatially-homogeneous. Unfortunately, such an assumption is not valid during infection or at sites of viral entry [50]. So the propagation of Virus cells into the body not only depends on time but also to the space. Proposed spatial model:

$$\begin{cases} \dfrac{\partial S}{\partial t} = \lambda - \beta S(x,t)I(x,t) - \mu S(x,t), \\ \dfrac{\partial L}{\partial t} = (1-l)\beta S(x,t)I(x,t) - (\mu + \delta)L(x,t), \\ \dfrac{\partial I}{\partial t} = q\Delta I(x,t) + l\beta S(x,t)I(x,t) + \delta L(x,t) - (\mu + \gamma + \alpha)I(x,t), \\ \dfrac{\partial R}{\partial t} = \gamma I(x,t) - \mu R(x,t). \end{cases}$$

   Here, $d > 0$ is the diffusion coefficients of virions with Δ being the Laplacian operator.

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