

MATHEMATICAL MODEL FOR CO-INFECTION OF PNEUMONIA AND TYPHOID
FEVER DISEASE WITH OPTIMAL CONTROL

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ABSTRACT

Pneumonia has claimed and continues to claim the lives of millions of people worldwide. Also, its effect on countrys and households cannot be ignored since most of the people that get infected and/or die from the diseases are usually future generation childrens. The impact of Pneumonia worsened in the presence of opportunistic infections like Typhoid fever. Thus, firms need to get involved in the fight against Pneumonia and its co-infection with these opportunistic infections. This thesis presents three detailed deterministic mathematical models that are aimed at describing the dynamics of Pneumonia and its co-infection with Typhoid fever. The first model is a general one that describes the dynamics of Pneumonia. The model is qualitatively analyzed to determine conditions for successful campaign against Pneumonia. Numerical simulations are also carried out and various combinations of interventions strategies are compared to determine the most cost-effective strategy that should be employed for the campaign against the disease. It is observed that the strategy that adopts prevention and treatment is most cost-effective in the fight against the spread of the disease. The second model considers dynamics of the Typhoid fever. This model is qualitatively analyzed to determine conditions for eradication of the disease. Numerical simulations and comparison of various intervention schemes revealed that the most cost-effective scheme that should be adopted for a successful campaign against the disease is one that implements prevention and treatment strategies. The third model considers the dynamics of co-infection of Pneumonia and Typhoid fever diseases The model is also qualitatively analyzed and numerically simulated. It is revealed that a successful campaign against the co-infection of the two diseases will have to include preventative measure for Typhoid fever and treatment for Pneumonia.

DECLARATION

I declare that *MATHEMATICAL MODEL FOR CO-INFECTION OF PNEUMONIA AND TYPHOID FEVER DISEASE WITH OPTIMAL CONTROL* is my own work, that it has not been submitted before for any degree or examination at any other university, and that all sources I have used or quoted have been indicated and acknowledged by complete references.

Name Surname

Month Year

Signed

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This work was successful with the help from the Almighty God. Glory be to his name . I would like to express my sincere gratitude and appreciation goes to my first supervisor Professor Oluwole Daniel Makinde, who painstakingly guided and directed the study at the time he could barely make any time for anything beside his work. I must admit that without him this step was difficult to reach. Your guidance during the Program was par excellence and it is my hope that you will continue to lend your vast experience and knowledge to me even after this program. God will pay you back and I will always pray that he blesses them abundantly as he continue helping other students. I also wish to thank my second supervisor Prof. David Malonza, Your unwavering support and advice during the program cannot be over appreciated. I was not be in this step with out the help of Prof. Malonza. My special thanks should go to my beloved family. I thank God for my lovely wife Ruth Bireda, she was always there for me regardless of all the difficulties we passed through during my studies. I will always thank God for your true love and care. To our beloved kids Adonai Getachew and Edom Getachew, I thank you very much for tolerating my absence when I was away from you. Thank you for your happiness through which I got peace to study without worry. Lastly, but not least, I would like to express my gratitude to my brothers Mr. Asfaw Teshome, Mr. Zayede Teshome and Mr. Belachew Teshome and all my best friends, that supported and encouraged me when I needed it the most.

DEDICATION

I sentimentally would like to dedicate this work to the memories of my Mother and Father. I pray that God gives them eternal life. May their soul rest in peace. Amen.

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List of Publications

Part of this thesis has been published in the form of the following research papers to international journals.

1. Getachew Teshome Tilahun, Oluwole Daniel Makinde and David Malonza. Modelling of Pneumonia Disease dynamics with Optimal control and cost-effectiveness analysis. Taylor and Francis, *Journal of Biological Dynamics*(Review Process is completed and author correction is done).
2. Getachew Teshome Tilahun, Oluwole Daniel Makinde and David Malonza. Modelling of Typhoid fever dynamics with Optimal control and cost-effectiveness analysis. Elsevier , *Journal of Biosystems* (under review).
3. Getachew Teshome Tilahun, Oluwole Daniel Makinde and David Malonza. Co-dynamics of Pneumonia and Typhoid fever with cost-effective optimal control analysis. Elsevier Journal, *Applied Mathematics and Computation* (Review Process is completed and author correction is done).

Chapter 1

INTRODUCTION

1.1 Basic Information about Pneumonia

Pneumonia is a life-threatening infection of the lower respiratory tract that affects children and adults around the world and is a leading cause of death of all infectious disease [WHO 2014]. Hippocrates described this disease before 2,500 years and Dr. William Osler who studied this disease in his entire life, called pneumonia, which means "captain of death" due to the reason that the great loss of human being by this disease (Osler, 2006).

1.1.1 Cause of Pneumonia

According to world healthy organization (WHO), Pneumonia is caused by different factors including pathogens, the environment, health systems, and health-seeking behaviours. Pathogenic Organisms that cause Pneumonia are Bacteria, Viruses, Fungi and Parasites.

Bacteria

Among the four micro-organisms Bacteria is the main cause of Pneumonia [WHO], specifically *Streptococcus pneumoniae*. Another type of pneumonia named as *Klebsiella pneumoniae* and *Hemophilus influenzae* is occurred most of the time for peoples who have chronic obstructive pulmonary disease or individuals that are addicted to alcohol. *Mycoplasma pneumoniae* is also caused by bacteria and most of the time occur during summer(hot) season and

it will continue for some months. Another types of bacteria responsible for pneumonia are Legionella pneumoniae (often found in contaminated water supplies and air conditioners), Chlamydia pneumonia and also Pneumocystis carinii pneumonia is a form of pneumonia that usually affects the two lungs and attack people who have a weak immune system (Dunn, 2005). The bacteria can also be carried in the mouth or flora of nasopharynx of a healthy person without causing any harm (Pessoa, 2010). Such people are referred to as carriers. For carriers, the bacteria can find its way to the lungs and invade to cause the infection. This is possible when the immunity of the individual is lowered otherwise they may continue for years with out showing the symptom of the disease but they may transmit the bacteria to other people.

Viruses

Viral pneumonias are pneumonias that caused by viruses and most of the time they do not respond to antibiotics. Some of the virus that are responsible for the cause of viral pneumonia are influenza virus (flu), parainfluenza, rhino-virus and respiratory syncytial virus (RSV)(Orin, 2005). Herpes simplex virus also cause pneumonia for persons who have significant burns, cancer patient and infants. (Behera, 2010)

Fungi

Fungal pneumonia is a pneumonia that are caused by fungi but this pneumonia is not common but it may affect individuals with low immune system due to different reasons. It is caused by Histoplasma capsulatum, blastomyces, Cryptococcus neoformans, Pneumocystis jiroveci (pneumocystis pneumonia), and Coccidioides immitis. (Orin, 2005).

Parasites

Different Parasites like, Plasmodium malariae, Strongyloides stercoralis, Toxoplasma gondii, and Ascaris lumbricoides can affect human lungs by releasing toxic substances which may result Pneumonia WHO.

1.1.2 Symptom of Pneumonia

Symptoms of pneumonia for individuals in which their is younger than 65 may come suddenly if the pneumonia is caused by bacteria. Pneumonia symptom most of the time starts after or during upper respiratory infections due to flu or cold (Singh and Aneja, 2011). The symptom of Pneumonia varies in age but most common symptoms may include: Cough, chest wall, feel pain due to coughing or breathing in often producing mucus and this mucus may be tinged with blood, rusty or green , fever, Shaking, chills. Fast, often shallow, breathing and the feeling of being short of breath, fast heartbeat, feeling very tired or weak, nausea and vomiting and diarrhea (Singh and Aneja, 2011). Symptoms of pneumonia that are not caused by bacteria may not come suddenly and are usually not as bad as symptoms due to bacterial pneumonia because of this, many people don't realize that, they have been affected by non-bacterial pneumonia, because they feel good until it worsen. Children symptoms varies according their age, most of the time for more than one month of age, symptoms may include having little or no energy, feeding poorly, grunting, or having a fever. In some conditions other disease with symptoms similar to pneumonia include bronchitis and tuberculosis citepWo2006. As a result of this clinical diagnosis of pneumonia is difficult and going for Pneumonia lab test is recommended.

1.1.3 Diagnosis of Pneumonia

A chest X-ray, which is almost always done to check for changes in the lungs that may mean presence of pneumonia. But an X-ray does not always show whether you have pneumonia, especially if it is done when you first get sick citepWo2006. In some cases, the X-ray results may: Suggest the type of organism (bacterial, viral, or fungal) causing pneumonia, show complications of pneumonia, such as infection of the heart muscle or the sac surrounding the heart, show conditions that may occur with pneumonia, such as fluid in the chest cavity or a collapsed lung, reveal another condition, such as heart failure, lung cancer, or acute bronchitis. Figure 1.1.1 shows chest X- ray film of a person who suffered from pneumonia.

This chest X-ray shows an area of lung inflammation indicating the presence of pneumo-

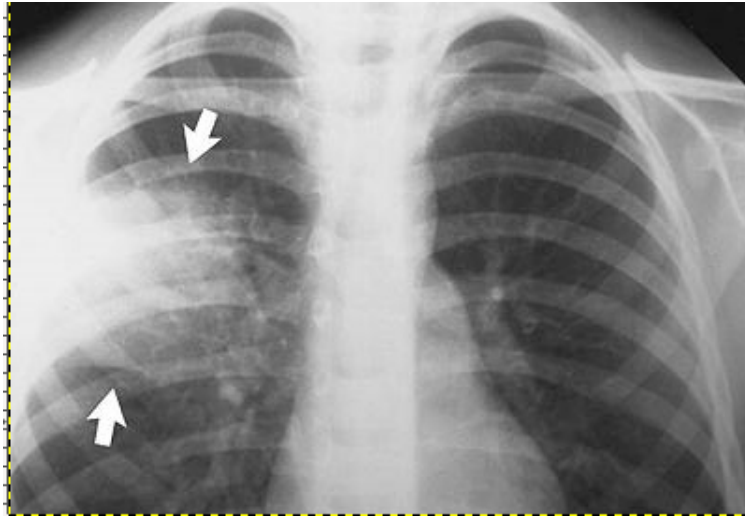


Figure 1.1.1: Chest X-ray

nia.

Lab tests for pneumonia is another method to examine pneumonia. The need for more tests often depends on how severe the symptoms are, age, and overall health of the patient. In general, the sicker, the more tests may need. This is especially true for older adults and infants (Yil et al., 2010). Arterial blood gas test is prescribed for a very ill patients, have severe shortness of breath, or for a condition that increases risk (such as asthma or Chronic obstructive pulmonary disease) mucus test is done (Yil et al., 2010). Tests will include a Gram stain and a sputum culture. And to identify some bacteria that cause pneumonia rapid urine test is used. This can help guide treatment for pneumonia.

1.1.4 Transmission of Pneumonia

Pneumonia can spread through the community in different ways. The bacteria or viruses spread via air-borne droplets from a cough or sneeze. Pneumonia may spread through blood, especially during and shortly after birth. In addition, Parasitic Pneumonia spread if the organisms enter to the body through direct contact with the skin, ingestion, or via an insect vector WHO.

1.1.5 Control of Pneumonia

The cause of Pneumonia have different factor, so no single intervention can effectively prevent, treat, or control pneumonia (Tong, 2013). As such, a combination of main interventions to control pneumonia would include immunization, screening , treatment of the infected individuals and improvements in nutrition and environmental living conditions (e.g. safe drinking water, sanitation, hygiene, low household air pollution) (Tong, 2013).

1.2 Basic Information about Typhoid fever

Typhoid fever is endemic mainly in developing countries that can spread throughout the body, affecting many organs. Without prompt treatment, it can cause serious complications and can be fatal citepwho2008.

1.2.1 Cause of Typhoid fever

Typhoid fever is caused by bacteria called Salmonella typhi (S. typhi) which is a Gram-negative anaerobic rod shaped bacterium that belong to a family of Enterobacteriaceae (Todar, 2011). Figure 1.2.1 show the microscopic picture of S. typhi

1.2.2 Symptom of Typhoid fever

It usually takes 1 to 3 weeks time for patients to develop typhoid symptoms after exposure to the bacteria. The duration of the disease is 3 to 4 weeks depending upon the severity of the disease (mild or severe) with the normal incubation time is 7 to 14 days (Crump et al., 2004). The symptoms are, headaches, constipation or diarrhea, high fever (103 degree F), lethargy, poor appetite, enlarged spleen and liver, rose-colored spots on the chest, chest congestion, abdominal pain, fatigue, chills and generalized pain and weakness citepWh2005. Some conditions with symptoms similar to typhoid fever include Malaria. Therefore Typhoid fever lab Exams and Tests is must to decide that the disease is typhoid fever. Otherwise complications of typhoid occur when a large number of bacteria get into the bloodstream,

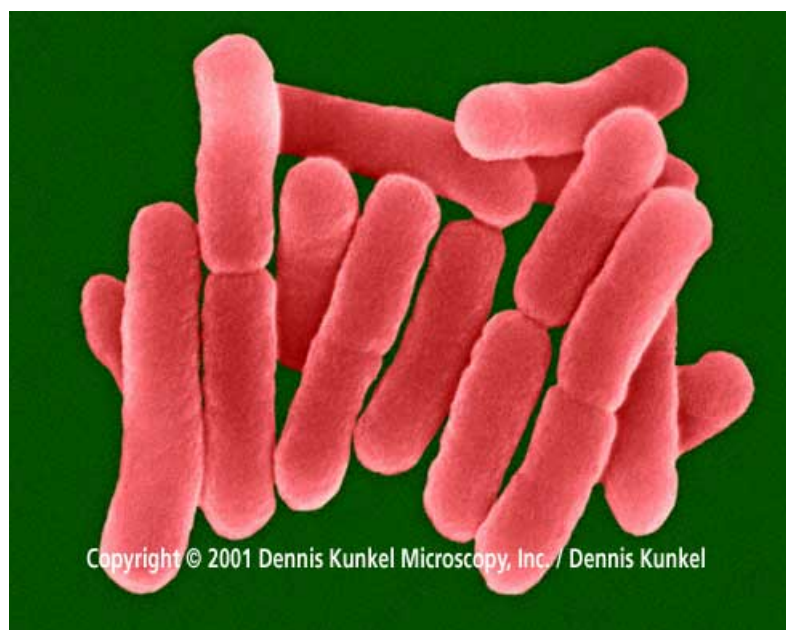


Figure 1.2.1: Salmonella typhi , Source(<http://www.denniskunkel.com/>)

causing bacteremia. They can travel to the lungs, causing pneumonia, or to the lining of the brain (meningitis), the bones (osteomyelitis), the heart valves (endocarditis), the kidneys (glomerulonephritis), the genital or urinary tract, or the muscles. Hepatitis (inflammation of the liver) can also occur.

1.2.3 Diagnosis of Typhoid fever

If a person are suffering from the disease, the complete blood count of the patient will show an increased white blood cell (WBC) count and if blood culture done during the initial phase of the disease (in the first week) shows *S. typhi* bacteria. Another tests is ELISA, which is a recent diagnostic test. ELISA urine test is done to look out for the bacteria causing the disease. Fluorescent antibody study is also a test in which any substances that are specific to the bacterium are looked for. Stool culture is also done to determine the presence of the bacterium in the feces (Christopher et al., 2002).

1.2.4 Transmission of Typhoid fever

Typhoid fever causing bacteria will be in the stool and rarely in the urine of the infected persons. If they don't wash their hands properly they contaminate any drinks or foods they touch. Any individuals who drink or eat the contaminate drinks and food may get the bacteria (Lauria et al., 2009).

After Salmonella typhi bacteria enters to the body it will move down into the digestive system, where they will quickly multiply. Up 5% who get the bacteria become carriers harbouring S.typhi in the gallbladder with out causing any disease symptom . This shows the bacteria start to live in the carrier's and continue to spread through urine and stools for years. It usually takes 1 to 3 weeks time for non carrier patients to develop typhoid symptoms after exposure to the bacteria (Crump et al., 2004).

1.2.5 Control of Typhoid fever

Typhoid fever will be controlled through proper sanitation like washing hands properly after using toilet, mass cleaning of infected human waste from environments and avoiding of eating raw vegetables that have been fertilized by human waste, Provision of a safe water supply.[WHO 2014] In line with treating individuals who develop the symptoms Screening of Carrier's is vital to control Typhoid fever infection, because they release the bacteria with out knowing as they are living with salmonella typhi. Reducing the number of cases in the general population requires the provision of safe drinking water, effective sewage disposal, and hygienic food preparation citepwho2008.

1.3 Some statistics on Pneumonia

In the last few decades, the world has been plagued with outbreaks of several diseases that claimed and continue to claim the lives of millions of people worldwide. Among these disease Pneumonia pandemic has been of concern to many well-meaning nations, organizations and individuals. According to world health organization Pneumonia is a leading infectious

cause of death worldwide . Figure 1.3.1 shows that from 2007 to 2015 the number of under five year children who lost their life due to Pneumonia and estimated that more than 21 millions under five childhoods died due to Pneumonia. [WHO]

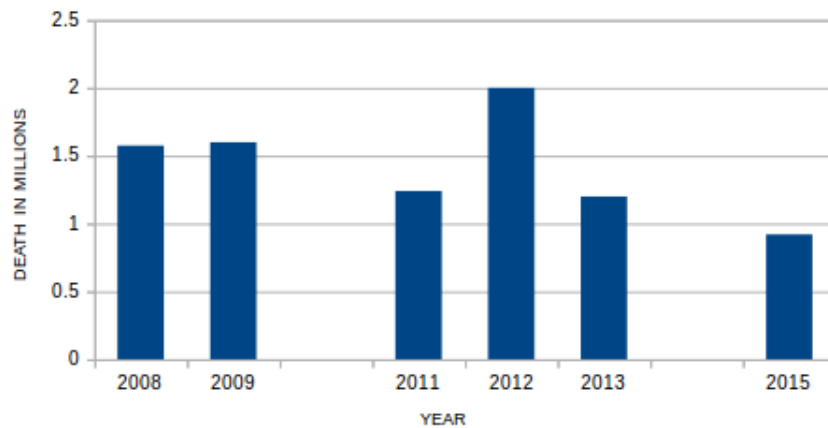


Figure 1.3.1: Under five year death due to Pneumonia

Pneumonia is responsible for 19% of all deaths of children under five years old in 2012. [WHO 2012] April 10th,2013 in Geneva world healthy organization in collaboration with UNICEF developed an action plan named, the Integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea (GAPPD) that used to support the achievement of Millennium Development Goal 6 (MDG 6). The goal of (GAPPD) to see a drop in deaths from pneumonia to fewer than 3 children in 1000 live births, and from diarrhoea to less than 1 in 1000 by 2025.[WHO 2013]

1.4 Some statistics of Typhoid fever

Typhoid fever is one of public health problem in many developing countries . It is estimated that the worldwide incidence of typhoid fever exceeds 50 million cases per year, with more than 600,000 deaths occurring annually, however, the true magnitude is difficult to quantify because the clinical picture is confused with many other febrile illnesses and most typhoid endemic areas lack facilities to confirm the diagnosis (Crump et al., 2004). Figure 1.4.1 below shows Typhoid fever distribution globally.

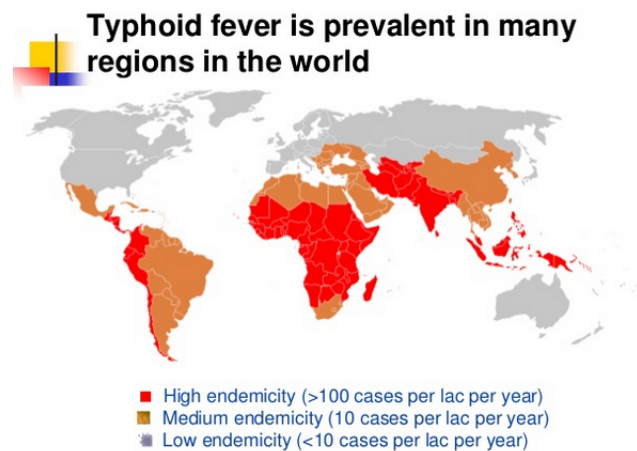


Figure 1.4.1: Typhoid Distribution Globally. Source:(<http://www.slideshare.net/dranwarahmad/typhoid-fever-ppt>)

According to world healthy organization (WHO) data base each year the number of deaths occurring annually greater than 200,000. Figure 1.4.2 shows number of deaths globally from 2000-2016.

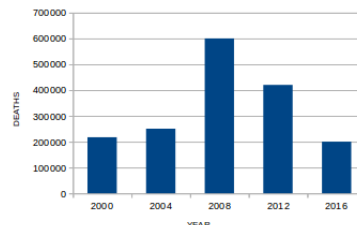


Figure 1.4.2: Typhoid fever deaths globally

1.5 Mathematical Modelling of Pneumonia and Typhoid fever

From the days of Bernoulli, mathematical modelling has played a very significant role in the study of infectious diseases with a major role in increasing our understanding of the dynamics of diseases and providing intervention strategies to mitigate the diseases. One of the earlier models on infectious diseases was that of **Kermack and McKendrick (1927)**. Several models have been proposed to study the effects of some factors on the transmission dynamics of infectious diseases and to provide guidelines as to how the spread can

be controlled. [Smith et al. \(1993\)](#) and [Lipsitch \(1999\)](#) are among the earlier study of the transmission dynamics of Pneumonia only by proposing a model to determine the effects of various factors on the transmission of the disease. [Cvjetanovij et al. \(1971\)](#) is also one of the earlier study on the transmission dynamics of Typhoid fever. This study developed a mathematical model and the proposed model depends up on the endemicity level of Typhoid fever, and the model considered sanitation and vaccination as intervention strategies. Several other models are proposed to to study the dynamics of Pneumonia or Typhoid fever only. [Melegaro et al. \(2004\)](#) proposed and gave a detailed analysis of a dynamical model of Pneumonia by considering susceptible and infected in two groups, children and adults. [Temime et al. \(2004\)](#) also proposed Pneumonia model by considering the population in three age structures. Several other models have been proposed to study dynamics of either Pneumonia only or Typhoid fever only, for instance see studies [Huang et al. \(2008\)](#),[Snedecor et al. \(2009\)](#), [Effelterre et al. \(2010\)](#), [Ong'ala et al. \(2013\)](#), [Adetunde \(2008\)](#),[Mushayabasa \(2011\)](#), [Waleed and Imran \(2015\)](#) to mention a few.

All the above studies have developed mathematical model of pneumonia only or Typhoid dynamics by viewing in different aspects. Some of them considered deterministic model and others stochastic model and subdivided the population in to Susceptible, infective, vaccinated, treated, carrier and recovered. But any of them didn't apply optimal control strategies and also to the best of our knowledge no study have been undertaken co-infection of Pneumonia and Typhoid fever. This is, therefore we are motivated to undertake this study for fulfilling all this gap.

1.6 Research Aim and Objectives

The main aim of this thesis is to study the dynamics of the co-infection of Pneumonia and Typhoid fever with optimal control and cost-effectiveness analysis. In this thesis a study of the optimal strategies of combating the spread of Pneumonia and Typhoid fever is studied. To achieve this, a number of new mathematical models are proposed to describe the dynamics of Pneumonia , Typhoid fever and also their co-infection and incorporate controls aimed at

reducing and/or controlling the spread of the diseases. Qualitative properties of these models in the form of equilibria, conditions of stability, existence of optimal control profiles and the implications of these properties are presented. Threshold quantities, like the basic reproduction number \mathfrak{R}_0 , that informs about the possible eradication or persistence of the infection are also studied.

The thesis addresses a number of mathematical and epidemiological problems, pertaining to the optimal control of Pneumonia, Typhoid fever and their co-infection.

To help achieve the main aim of the thesis, the following objectives were sought:

- i) To study the dynamics of Pneumonia Disease with Optimal Control Cost Effective Strategies.
- ii) To study the dynamics of Typhoid fever Disease with Optimal Control Cost Effective Strategies.
- iii) To study the Co-Dynamics of Pneumonia and Typhoid Fever Diseases with Cost Effective Optimal Control Analysis.

1.7 Organization of the Thesis

The remainder of the thesis is organized as follows. In Chapter 2, some relevant mathematical tools and concepts are presented. Chapter 3 presents a basic deterministic model that describes the dynamics of Pneumonia. This model is comprehensively analyzed both qualitatively and quantitatively. In Chapter 4, a comprehensive model is proposed to study the dynamics of Typhoid fever. Chapter 5 proposes and rigorously analyzes another deterministic model to study the dynamics of Pneumonia and Typhoid fever co-infection. Finally, the main results of the thesis and conclusions drawn there from are presented in Chapter 6. Other relevant components of the thesis that are not in the chapters mentioned above are presented in the Appendices.

Chapter 2

Mathematical Preliminaries

This chapter presents the mathematical principles that underlie the methods and theories used in the thesis. There are currently two streams of methodologies used to study the dynamics of infectious diseases. These are stochastic and non-stochastic methodologies. Among the non-stochastic methodologies is the theory of differential equations, which is by far the most widely used methodology employed in the Mathematical modelling of infectious diseases. This wide application of differential equations is due to the fact that the mathematics of differential equations is well-established and easily implemented using the current state-of-the-art technology. For this reason, the models developed and analyzed in this thesis are differential equation models. A number of differential equation models are proposed in order to describe the spread of Pneumonia and Typhoid fever. These models are qualitatively studied and numerically solved. The best ways of controlling the disease are also sought by constructing optimal control problems involving intervention strategies that are aimed at combating the spread of the diseases with minimal cost. We present in the sequel some basic mathematical preliminaries that are critical in the use of differential equations to model infectious diseases. We give definitions of some basic terms relating to dynamical systems.

Definition 2.0.1. (Perko, 2001) A *dynamical system* is a way of describing the passage in time of all points of a given space \mathcal{S} .

The space \mathcal{S} could be thought of, for example, as the space of the state of some physical system. Dynamical systems arise in almost all fields of learning especially in the sciences

where there is usually an interest in knowing the behavior of a given system at given times in space. Dynamical systems are either *discrete* or *continuous* depending on whether the interest has to do with the state of the system at integer time values or not. A general dynamical system is of the form

$$\phi_t : \mathbb{R}^n \rightarrow \mathbb{R}^n \quad (2.0.1)$$

Definition 2.0.2. A **smooth dynamical system** on \mathbb{R}^n is a continuously differentiable function $\phi : \mathbb{R} \times \mathbb{R}^n \rightarrow \mathbb{R}^n$ where $\phi(t, X) = \phi_t(X)$ satisfies

1. $\phi_0 : \mathbb{R}^n \rightarrow \mathbb{R}^n$ is the identity function: $\phi_0(X_0) = X_0$;
2. The composition $\phi_t \circ \phi_s = \phi_{t+s}$ for each $t, s \in \mathbb{R}$

Most of the dynamical systems in Engineering and Science, and specifically those considered in this thesis, are in the form of differential equations and hence focus is given to the concepts in differential equations.

2.1 Differential Equations

Definition 2.1.1. A differential equation is an equation involving a quantity together with its derivatives with respect to some independent variable(s).

Differential equations are of two types; *ordinary* and *partial* differential equations. An ordinary differential equation is one in which the quantity being described has only one variable on which it depends. A partial differential equation on the other hand, involves a quantity with more than one independent variable. For the most part of this thesis, deterministic models which are ordinary differential equations are dealt with and hence most of the discussions in this section will be focused on this category of differential equations.

Definition 2.1.2. Let x be the state of a dynamical system. Then a generalized deterministic model involving x is given by

$$\frac{dx}{dt} = f(x, t; \lambda) \quad (2.1.1)$$

Where $x \in \mathbb{R}^n$, t represents time, and $\lambda \in \mathbb{R}^m$ represents the parameters upon which the evolution of the system depends. Equation (2.1.1) is called an *Ordinary differential Equation* (ODE). ODEs in which the time variable, t , explicitly appears are said to be *Non-autonomous* while those in which the time variable does not explicitly appear are said to be *Autonomous* ODEs. Most epidemic models including those considered in this thesis are autonomous systems that can be written in the form:

$$\dot{x} = f(x) \tag{2.1.2}$$

where $x = (x_1, x_2, \dots, x_n)$ and $\dot{x} = \frac{dx}{dt}$ represents point-wise time-derivatives of the state variable x . When information about the initial state of the system is provided along with equation (2.1.2) the resulting equation is called an *initial-value problem*, which is given by:

$$\dot{x} = f(x), \text{ with } x(t_0) = x_0 \in \mathbb{R}^n \tag{2.1.3}$$

when data about the initial time state and final time state are given, the differential equation together with these information become a *boundary-value problem*. It should be noted here that the models that are considered in this thesis are compartmental models which involve the rate of change of population sizes of several compartments in a given system. For a given system, with say n compartments, a general dynamical system that describes the evolution of the system is given by:

$$\left. \begin{aligned} \frac{dx_1}{dt} &= f_1(x_1, x_2, \dots, x_n) \\ \frac{dx_2}{dt} &= f_2(x_1, x_2, \dots, x_n) \\ &\vdots \\ \frac{dx_{n-1}}{dt} &= f_{n-1}(x_1, x_2, \dots, x_n) \\ \frac{dx_n}{dt} &= f_n(x_1, x_2, \dots, x_n) \end{aligned} \right\} \tag{2.1.4}$$

Models like (2.1.4) are often compactly represented in the form of (2.1.2) so that $x = (x_1, x_2, \dots, x_n)$ and $f = (f_1, f_2, \dots, f_n)$.

Lemma 2.1.1. (*Hirsch et al., 2004*) Let E be an open subset of \mathbb{R}^n and let $f : E \rightarrow \mathbb{R}^n$. then, if $f \in C^1(E)$, f is locally Lipschitz on E .

Definition 2.1.3. Let $f : E \rightarrow \mathbb{R}^n$ where E is an open subset of \mathbb{R}^n . We say $f \in C^1(E)$ iff the partial derivatives $\frac{\partial f_i}{\partial x_j}$, $i, j = 1, \dots, n$, exist and are continuous on E .

The notation C^k is used to denote the space of all functions with continuous k^{th} – order derivatives.

Definition 2.1.4. (*Perko, 2001*) The function $f : \mathbb{R}^n \rightarrow \mathbb{R}^n$ is *differentiable* at $x_0 \in \mathbb{R}^n$ if there is a linear transformation $Df(x_0) \in \mathcal{L}(\mathbb{R}^n)$ that satisfies

$$\lim_{|h| \rightarrow 0} \frac{|f(x_0 + h) - f(x_0) - Df(x_0)h|}{|h|} = 0$$

The linear transformation $Df(x_0)$ is called the *derivative* of f at x_0

In order to calculate the derivative of a function at a point, the following theorem is quite useful.

Theorem 2.1.2. (*Perko, 2001*) If $f : \mathbb{R}^n \rightarrow \mathbb{R}^n$ is differentiable at x_0 , then the partial derivatives $\frac{\partial f_i}{\partial x_j}$, $i, j = 1, \dots, n$ all exist at x_0 and for all $x \in \mathbb{R}^n$,

$$Df(x_0)x = \sum_{j=1}^n \frac{\partial f}{\partial x_j}(x_0)x_j.$$

Thus, if f is a differentiable function, the derivative is given by the $n \times n$ Jacobian matrix

$$Df = \begin{bmatrix} \frac{\partial f_1}{\partial x_1} & \dots & \frac{\partial f_1}{\partial x_n} \\ \vdots & \ddots & \vdots \\ \frac{\partial f_n}{\partial x_1} & \dots & \frac{\partial f_n}{\partial x_n} \end{bmatrix}.$$

Definition 2.1.5. Suppose V_1 and V_2 are two normed linear spaces with respective norms, $\|\cdot\|_1$ and $\|\cdot\|_2$. Then $f : V_1 \rightarrow V_2$ is continuous at $x_0 \in V_1$ if for all $\varepsilon > 0$, there exists a $\delta > 0$ such that for any $x \in V_1$, if $\|x - x_0\|_1 < \delta$ then $\|f(x) - f(x_0)\|_2 < \varepsilon$

The function f is said to be continuous on the set $E \in V_1$ if it is continuous at every point

in E and when that happens, the notation $f \in C(E)$ is used to mean that f is continuous on E .

Theorem 2.1.3 (Fundamental Existence-Uniqueness theorem (Hirsch et al., 2004)). *Consider the initial value problem (2.1.3). Suppose that f is C^1 . Then first of all, there exists a solutions of this initial value problem and secondly, this is the only such solution. More precisely, there exists an $a > 0$ and a unique solution of (2.1.3) on the interval $[-a, a]$ satisfying the initial condition $x(t_0) = x_0$.*

2.1.1 Equilibrium and Linearization of Autonomous Systems

Definition 2.1.6. Given the autonomous deterministic model (2.1.2), a state \bar{x} is said to be an equilibrium point of the model if $f(\bar{x}) = 0$ (i.e. The function-value at \bar{x} is zero.). Equilibrium points are also called critical points of the model.

For ordinary differential equation models in the form of (2.1.2), the equilibrium points are found by making the left-hand-sides of the equations zero (ie set $\dot{x} = 0$) and solving for the state variable x .

Definition 2.1.7. (Stability in the sense of Lyapunov) An equilibrium point, \bar{x} , of (2.1.2) is said to be locally stable if $\forall \varepsilon > 0, \exists \delta > 0$ such that $\|x_0 - \bar{x}\| < \delta \Rightarrow \|x(t) - \bar{x}\| < \varepsilon$

An equilibrium point which is not locally stable is said to be **Unstable**.

Definition 2.1.8. (Asymptotic Stability) An equilibrium point \bar{x} of the model (2.1.2) is said to be locally asymptotically stable if it is locally stable and furthermore all solutions starting near \bar{x} tend towards \bar{x} as $t \rightarrow \infty$.

That is $\exists \delta > 0$ such that $\|x_0 - \bar{x}\| < \delta \Rightarrow \lim_{t \rightarrow \infty} x(t) = \bar{x}$.

2.1.2 Local Stability Analysis of Equilibrium Points

In mathematical modelling, it is often very important to know the behavior of a dynamical system near an equilibrium point. It is important to know whether or not future evolutions

of the system will remain close to the equilibrium point if initial conditions are close to the equilibrium. To find out about this, the local stability analysis is often carried out. The indirect Lyapunov technique is often employed to determine the local stability of critical points.

Definition 2.1.9. A critical point \bar{x} of a dynamical system is said to be locally stable if all eigenvalues of the Jacobian evaluated at \bar{x} are negative.

Definition 2.1.10. The Jacobian of the dynamical system represented in (2.1.4) is given by:

$$J = Df(x) = \begin{bmatrix} \frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} & \cdots & \frac{\partial f_1}{\partial x_{n-1}} & \frac{\partial f_1}{\partial x_n} \\ \frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x_2} & \cdots & \frac{\partial f_2}{\partial x_{n-1}} & \frac{\partial f_2}{\partial x_n} \\ \vdots & \vdots & \dots & \vdots & \vdots \\ \frac{\partial f_{n-1}}{\partial x_1} & \frac{\partial f_{n-1}}{\partial x_2} & \cdots & \frac{\partial f_{n-1}}{\partial x_{n-1}} & \frac{\partial f_{n-1}}{\partial x_n} \\ \frac{\partial f_n}{\partial x_1} & \frac{\partial f_n}{\partial x_2} & \cdots & \frac{\partial f_n}{\partial x_{n-1}} & \frac{\partial f_n}{\partial x_n} \end{bmatrix} \quad (2.1.5)$$

Definition 2.1.11. An equilibrium point \bar{x} of (2.1.2) is said to be **hyperbolic** if none of the eigenvalues of the Jacobian evaluated at \bar{x} , (ie $Df(\bar{x})$), have a zero real part. The point, \bar{x} , is said to be **non hyperbolic** otherwise.

Definition 2.1.12. Consider the system

$$\begin{aligned} \dot{x} &= f(x), x \in \mathbb{R}^n \\ \dot{y} &= g(y), y \in \mathbb{R}^n \end{aligned} \quad (2.1.6)$$

where f and g are two C^r ($r \geq 1$) functions defined on \mathbb{R}^n . Then the dynamics generated by f and g are said to be C^k ($k \geq r$) conjugate if there exists a C^k diffeomorphism h which takes the orbits of the flow generated by f , $\phi(t, x)$, to the orbits of the flow generated by g , $\psi(t, y)$, preserving orientation and parameterization by time.

Definition 2.1.13. Let \bar{x} denote an equilibrium point of (2.1.2) and let $Df(\bar{x})$ denote the Jacobian evaluated at \bar{x} . Then the system of differential equations given by:

$$\dot{y} = Df(\bar{x})y \quad (2.1.7)$$

is linear in y and is said to be the **linearization** of (2.1.2) near \bar{x} .

Theorem 2.1.4 (Linearization theorem (Hirsch et al., 2004)). ‘Suppose the nonlinear system (2.1.2) has an equilibrium point \bar{x} that is hyperbolic. Then the nonlinear flow is conjugate to the flow of the linearized system in a neighborhood of \bar{x} .

This theorem is also called the Hartman-Grobman theorem and simply says that the local behavior of an hyperbolic equilibrium point of a nonlinear system can be approximated by its linearization.

2.2 Global Stability of Dynamical Systems

The indirect method of Lyapunov which is used to determine the local stability of the equilibrium points has some limitations. Its results apply only in cases where there are infinitesimal perturbations about the equilibrium. No information about the extent of the basin of attraction (which is the domain such that all solutions starting within that domain approach the critical point) is provided. The direct Lyapunov method addresses this problem.

Definition 2.2.1. An equilibrium point \bar{x} is said to be globally asymptotically stable if it is asymptotically stable for all initial condition $x_0 \in \mathbb{R}^n$

Without having to compute the trajectories of the dynamical system (2.1.2), Lyapunov theory can be used to access the global stability of the equilibrium points.

The idea behind Lyapunov direct method is to establish properties of the equilibrium point of the non-linear system by studying how carefully selected scalar functions of the state behave as the system state evolves. It involves constructing a differentiable scalar function $V(x)$ such that:

- a. $V(x)$ is positive definite: $V(0) = 0$; $V(x) > 0$ for all $x \neq 0$ and,
- b. $\nabla V(x) \cdot f(x) < 0$ for all x

where “ \cdot ” designates the dot product, and ∇ designates the gradient vector function.

Definition 2.2.2. (Positive definite functions) a. A continuously differentiable function $V : \mathbb{R}^n \rightarrow \mathbb{R}_+$ is said to be positive definite in a region $U \in \mathbb{R}^n$ that contains the origin if

(i). $V(0) = 0$, and

(ii). $V(x) > 0$,

for $x \in U$, and $x \neq 0$.

b. $V(x)$ is said to be positive semi-definite if $V(x) \geq 0 \forall x \in U$.

c. Conversely, $V(x)$ is said to be negative definite if $V(x) < 0$, and

d. $V(x)$ is said to be negative semi-definite if $V(x) \leq 0$

Theorem 2.2.1. *Let $x_* = 0$ be an equilibrium point of the dynamical system (2.1.2), where $f : U \rightarrow \mathbb{R}^n$ is locally Lipschitz and $U \subset \mathbb{R}^n$ a domain that contains the origin. Let $V : U \rightarrow \mathbb{R}$ be continuously differentiable, positive definite function in U .*

a. If $\dot{V}(x) = \frac{\partial V}{\partial x} \cdot f \leq 0$, then $x_* = 0$ is globally stable.

b. If $\dot{V}(x) = \frac{\partial V}{\partial x} \cdot f < 0$, then $x_* = 0$ is globally asymptotically stable.

Any function V that satisfies the conditions for Lyapunov stability theorem is called **Lyapunov function**. Application of the Lyapunov function theorem is often very difficult because there are no general methods for constructing the Lyapunov functions. However, the following functional forms or their variants can often serve as candidates for Lyapunov functions.

a. Quadratic functions: $V(x) = \sum_{i=1}^n (x_i - x_i^*)^2$.

b. Logarithmic functions: $V(x) = \sum_{i=1}^n \left(x_i - x_i^* - x_i^* \ln \left(\frac{x_i}{x_i^*} \right) \right)$

where $x^* = (x_1^*, x_2^*, \dots, x_n^*)$ is the equilibrium point.

2.3 Bifurcation Analysis

Definition 2.3.1. Bifurcation is (generally) defined as a change in the qualitative behavior of a given dynamical system when an associated parameter is varied. The points of the parameter where the change occurs are called bifurcation points (or bifurcation values).

Definition 2.3.2. Let

$$\dot{x} = f(x, \mu), x \in \mathbb{R}, \mu \in \mathbb{R} \quad (2.3.1)$$

be a one-parameter family of one-dimensional ODEs. An equilibrium solution of (2.3.1) given by $(x, \mu) = (0, 0)$ is said to undergo bifurcation at $\mu = 0$ if the flow for μ near zero and x near zero is not qualitatively the same as the flow near $x = 0$ at $\mu = 0$ (Sharomi, 2010).

The Lyapunov indirect method is often used to study the local stability of disease-free equilibria of epidemic models. This method involves linearizing the model around the disease-free equilibrium and using the eigenvalues of the resultant Jacobian matrix to determine conditions of stability. Doing this for endemic equilibrium states for most models is quite tedious and mathematically intractable. To study the stability of endemic equilibrium points, the center manifold theory (described in (Castillo-Chavez and B., 2004) by Theorem 4.1) is used as an alternative. This theory is reproduced here for convenience.

Theorem 2.3.1. *Theorem 4.1 of (Castillo-Chavez and B., 2004) Consider the following general system of ODEs with a parameter ϕ .*

$$\frac{dx}{dt} = f(x, \phi), f : \mathbb{R}^n \times \mathbb{R} \rightarrow \mathbb{R} \text{ and } f \in \mathbf{C}^2(\mathbb{R}^n \times \mathbb{R}), \quad (2.3.2)$$

where 0 is an equilibrium point of the system (that is, $f(0, \phi) \equiv 0, \forall \phi$) and assume

A1: $A = D_x f(0, 0) = \left(\frac{\partial f_i}{\partial x_j}(0, 0) \right)$ is the linearization matrix of (2.3.2) around the equilibrium point 0 with ϕ evaluated at 0 . Zero is a simple eigenvalue of A and other eigenvalues of A have negative real parts;

A2: Matrix A has a right eigenvector w and a left vector v (each corresponding to the zero eigenvalue).

Let f_k be the k^{th} component of f and

$$a = \sum_{k, i, j=1}^n v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0, 0), \quad (2.3.3)$$

$$b = \sum_{k, i=1}^n v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0, 0). \quad (2.3.4)$$

The local dynamics of the system (2.3.2) around 0 is totally determined by the signs of a and b :

- i. $a > 0, b > 0$. When $\phi < 0$ with $|\phi| \leq 1$, 0 is locally asymptotically stable, and there exists a positive unstable equilibrium; when $0 < \phi \ll 1$, 0 is unstable and there exists a negative and locally asymptotically stable equilibrium;
- ii. $a < 0, b < 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable; when $0 < \phi \ll 1$, 0 is locally asymptotically stable, and there exists a positive unstable equilibrium;
- iii. $a > 0, b < 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable, and there exists a locally asymptotically stable negative equilibrium; when $0 < \phi \ll 1$, 0 is stable, and a positive unstable equilibrium appears;
- iv. $a < 0, b > 0$. When ϕ changes from negative to positive, 0 changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable.

Particularly, if $a > 0$ and $b > 0$, then a backward bifurcation occurs at $\phi = 0$.

This theorem is summarized in Table tab:Bifurcation-types-table (Castillo-Chavez and B., 2004), with some bifurcation diagrams. In the bifurcation diagrams in Table ref tab:Bifurcation-types-table, the vertical axis represents equilibrium points x^* , and the horizontal axis is the parameter ϕ . Solid lines and dashed lines symbolize stable (S) and unstable (U), respectively.

2.3.1 Computation of Bifurcation Co-efficients, a and b

It should be noted here that using the formulas for determining a and b as defined in equations (2.3.3) and (2.3.4) respectively becomes tedious for large systems. In this brief, a simplification of the formulas for a and b is presented to allow for use of softwares like maple and mupad to compute them.

Consider a system of n differential equations of the form:

$$\frac{dx}{dt} = f(x, \phi) \text{ where } x = (x_1, x_2, \dots, x_n) \text{ and } f = (f_1, f_2, \dots, f_n).$$

Let $w = (w_1, w_2, \dots, w_n)^T$ and $v = (v_1, v_2, \dots, v_n)$ be the right and left eigenvectors associated with a simple eigenvalue of the Jacobian (evaluated at $(0, 0)$) of the above system of differential equations and define Then the bifurcation co-efficients, a and b can be computed

using the following formulas:

$$a = v \cdot \begin{pmatrix} w^T H_1 w \\ w^T H_2 w \\ \cdot \\ \cdot \\ \cdot \\ w^T H_n w \end{pmatrix} \quad \text{and} \quad b = v^T M w \quad (2.3.5)$$

2.4 Optimal Control Theory

A major part of the thesis employs concepts in mathematical optimal control theory to study the best methods of combating the spread Pneumonia and Typhoid fever diseases. For this reason, some basic concepts of the theory of optimal control is presented in this section. The simplest optimal control problem is an optimization problem that seeks to maximize/minimize an objective function subject to a dynamical system in the form of equation (ref eq:General-Autonomous-System) together with some initial or boundary conditions. Formally, the simplest optimal control problem is one of the form

$$\left. \begin{array}{l} \text{Maximize } \int_{t_0}^{t_f} g(t, X, u) dt \\ \text{Subject to } \frac{dx}{dt} = f(t, x, u), \quad x(t_0) = x_0, \quad x(t_f) \text{ free} \\ \text{and } u(t) \in \mathcal{U}, \forall t \in [0, t_f] \end{array} \right\} \quad (2.4.1)$$

2.4.1 The Pontryagin's Maximum Principle

The Pontryagin's maximum principle often called the maximum principle is the main tool used to solve optimal control problems. It provide first-order necessary conditions for optimal solution of the problem. The principle provides direction as to how the control u , state variable x and a third variable known as co-state or adjoint variable λ should change over

time through equations of motions for x and λ . The Pontryagin's maximum principle is given in the following theorem.

Theorem 2.4.1. *Let $u(t)$ be a time optimal control and $X(t)$ be the corresponding response of the system. Then there exists a function $\lambda(t) : [0, t_f] \rightarrow \mathbb{R}^n$, such that:*

$$\dot{x} = \frac{\partial H}{\partial \lambda}(x, \lambda, u), x(t_0) = x_0 \quad (\text{State Equation}) \quad (2.4.2)$$

$$\dot{\lambda} = -\frac{\partial H}{\partial x}(x, \lambda, u) \quad (\text{Co-state Equations}) \quad (2.4.3)$$

$$\lambda(t_f) = 0 \quad (\text{Transversality condition}) \quad (2.4.4)$$

$$H(x, \lambda, u) = \max_{u \in A} H(x, \lambda, u) \left\{ \text{or } \frac{\partial H}{\partial u} = 0 \right\} \quad (2.4.5)$$

Where $H = g(t, x, u) + \lambda(t) f(t, x, u)$ is called the **Hamiltonian** of the optimal control problem. Equation (2.4.5) is given in two forms because, when the Hamiltonian is differentiable with respect to u , the condition $\frac{\partial H}{\partial u} = 0$ can often be used to replace $H(x^*, \lambda^*, u^*) = \max_{u \in A} H(x, \lambda, u)$.

2.4.2 Numerical Solution of Optimal Control Problems

Most optimal control problems arising from engineering or biological sciences can not be solved analytically and hence numerical solutions are often sought. Solving optimal control problems in the form of (2.4.1) numerically involves finding piecewise continuous functions $u_i(t)$ that optimize the objective functional. One can resort to total-enumeration methods or linear programming techniques for this purpose, but bearing in mind that any solution of the problem must necessarily satisfy the state and co-state equations as well as the optimality conditions. For most problems, the optimality conditions can often be manipulated to find an explicit expression for the control variable $u(t)$, which can then be substituted into the state (2.4.2) and co-state systems (2.4.3) so that the the two equations then form a two-point boundary value problem. Numerical methods for solving ordinary differential equations and boundary value problems can then be employed to solve the resulting two-point boundary value problem. The numerical scheme employed in this thesis to solve resulting optimal

control problems is the **Forward-Backward Sweep method**. [Lenhart and T. \(2007\)](#) gave a rough outline of this method, which is reproduced here for convenience.

Step 1. Make an initial guess for u over the interval. Store the initial guess as u

Step 2. Using the initial condition $x(t_0) = x_0$ and the stored values for u , solve x forward in time according to its differential equation in the optimality system.

Step 3. Using the transversality condition $\lambda(t_f) = 0$ and the stored values for x and u , solve λ backward in time according to its differential equation in the optimality system.

Step 4. Update the control u by entering the new x and λ values into the characterization.

Step 5. Check convergence. If values of the variables in this iteration and the last iteration are negligibly small, output current values as solutions. If values are not small, return to **Step 2**.

In implementing the above algorithm, the following can be taken note of:

1. For **Step 1**, a simple guess of $u \equiv 0$ can often be used except when division by u occurs in the problem, in which case a different initial guess can be used.

2. Even though many types of convergence criteria exist, it is often sufficient to require $\sum_{i=1}^n |u(i) - u_{old}(i)|$ to be small, where $u(i)$ and $u_{old}(i)$ are the vectors of estimated controls for the current and old iterations respectively. [Lenhart and T. \(2007\)](#) suggested a stricter convergence criterion (that the percentage error $\frac{|u - u_{old}|}{|u|} \leq \delta$ be negligibly small, where δ is the accepted tolerance). This criterion can be manipulated (in order to circumvent issues related to $u \equiv 0$) to get an easily implemented criterion given by

$$\delta \sum_{i=1}^n |u(i)| - \sum_{i=1}^n |u(i) - u_{old}(i)| \geq 0.$$

This requirement can be demanded of all x , λ and u .

2.5 The Basic Reproduction Number, \mathcal{R}_0

The concept of the basic reproduction number is one of the central topics in mathematical modelling of infectious diseases due to its meaning and extreme importance. Hardly can

one find a publication on a mathematical model without mention of this number. It is also called the basic reproduction ratio among other variant forms. It is very important in disease modelling because it gives an indication regarding the future state of the infection. It tells us whether or not the disease will persist or will be eradicated in due course.

Definition 2.5.1. (Diekmann et al., 1990)

The basic reproduction number, denoted \mathfrak{R}_0 , is 'the expected number of secondary cases produced, in a completely susceptible population, by a typical infective individual'

If $\mathfrak{R}_0 < 1$, then it means that on average, an infected individual infects less than one susceptible over the course of its infectious period and the disease can not grow. If however, $\mathfrak{R}_0 > 1$, then an infected individual infects more than one susceptible over the course of its infectious period and the disease will persist. "For the case of a single infected compartment, $\mathfrak{R}_0 > 1$ is simply the product of the infection rate and the mean duration of the infection. However, for more complicated models with several infected compartments this simple heuristic definition of \mathfrak{R}_0 is insufficient" (Driessche et al., 2002). Due to its importance, researchers have sought to find ways of determining \mathfrak{R}_0 and/or its proxies. A review of the current methodologies used to estimate \mathfrak{R}_0 can be found in the work of Heffernan et al. (2005). For the sake of simplicity, a brief description of the method of Driessche et al. (2002) is given. It is this methodology that is employed in this thesis for the calculation of \mathfrak{R}_0 .

2.5.1 Description of the Method of Driessche and Watmough

Consider a compartmental disease transmission model in the form of (2.1.2), where $x = (x_1, \dots, x_n)$ with x_i denoting the number or proportion of individuals in compartment i . Define $\mathcal{F}_i(x)$ as the rate of appearance of new infections in compartment i ; $\mathcal{V}_i^+(x)$ as the rate of transfer of new infectives into compartment i ; $\mathcal{V}_i^-(x)$ as the rate of transfer of infectives out of compartment i and $\mathcal{V}(x) = \mathcal{V}_i^-(x) - \mathcal{V}_i^+(x)$.

Let $X_s = \{x \geq 0 | x_i = 0, i = 1, \dots, m\}$ be the set of all disease free states.

Assuming the following conditions on these functions are true.

A1 If $x \geq 0$ then $\mathcal{F}_i, \mathcal{V}_i^+, \mathcal{V}_i^- \geq 0$ for all $i = 1, \dots, n$.

A2 If $x_i = 0$ then $\mathcal{V}_i^- = 0$. In particular if $x \in X_s$ then $\mathcal{V}_i^- = 0$ for $i = 1, \dots, m$.

A3 $\mathcal{F}_i = 0$ if $i > m$.

A4 If $x \in X_s$ then $\mathcal{F}_i(x) = 0$ and $\mathcal{V}_i^+(x) = 0$ for $i = 1, \dots, m$.

A5 If $\mathcal{F}(x)$ is set to zero then all eigenvalues of $Df(x_0)$ have negative real parts.

Then the Jacobian matrix $Df(x_0)$ can be partitioned as given in the following lemma.

Lemma 2.5.1 (Lemma 1 of (Driessche et al., 2002)). *If x_0 is a DFE of (2.1.2) and $f_i(x)$ satisfies (A1)-(A5), then the derivatives $D\mathcal{F}(x_0)$ and $D\mathcal{V}(x_0)$ are partitioned as follows*

$$D\mathcal{F}(x_0) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix}, D\mathcal{V}(x_0) = \begin{pmatrix} V & 0 \\ J_3 & J_4 \end{pmatrix},$$

where F and V are $m \times m$ matrices defined by

$$F = \left[\frac{\partial \mathcal{F}_i}{\partial x_i}(x_0) \right] \quad \text{and} \quad V = \left[\frac{\partial \mathcal{V}_i}{\partial x_i}(x_0) \right] \quad \text{with} \quad i \leq m, j \leq m.$$

Further, F is non-negative, V is a non-singular M-matrix and all eigenvalues of J_4 have positive real parts.

The following theorem then is used to compute the threshold parameter \mathfrak{R}_0 .

Theorem 2.5.2 (Theorem 2 of (Driessche et al., 2002)). *Consider the disease transmission model given by (2.1.2) with $f(x)$ satisfying conditions (A1)-(A5). If x_0 is a DFE of the model, then x_0 is locally asymptotically stable if $\mathfrak{R}_0 < 1$, but unstable if $\mathfrak{R}_0 > 1$, where \mathfrak{R}_0 is defined by*

$$\mathfrak{R}_0 = \rho(FV^{-1})$$

where $\rho(A)$ denotes the spectral radius of A .

Thus, the threshold quantity \mathfrak{R}_0 plays a major role in determining the qualitative behavior of epidemic models. We note that at $\mathfrak{R}_0 = 1$ the disease-free equilibrium and endemic equilibrium exchange stability. This phenomenon of change of stability, known as *forward bifurcation*, has been observed in several epidemic models ((Kermack and McKendrick, 1927),

(Hethcote and W, 1987),(Castillo-Chavez et al., 1989), (Hethcote, 2000), (Castillo-Chavez and B., 2004)). Figure 2.5.1 is a diagram giving the description of forward bifurcation. When forward bifurcation occurs, then $\mathfrak{R}_0 \leq 1$ is a necessary and sufficient condition for

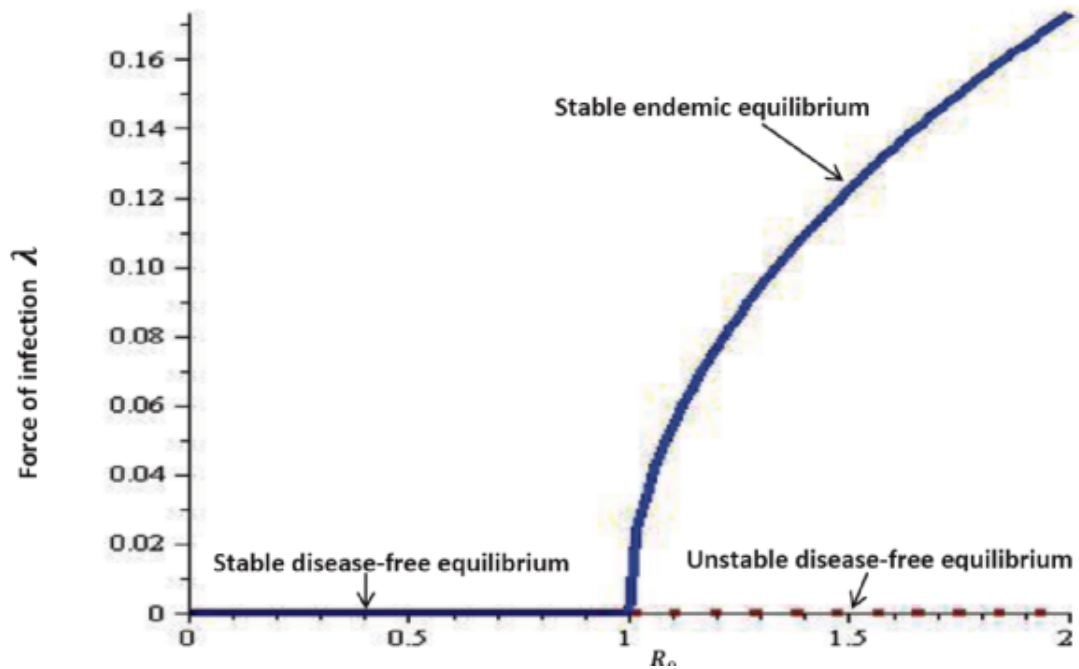


Figure 2.5.1: Forward Bifurcation Diagram.

disease elimination. Another important concept related to the condition $\mathfrak{R}_0 \leq 1$ is that of *backward bifurcation*. This occurs when a stable endemic equilibrium co-exists with a stable disease-free equilibrium. When this happens, then $\mathfrak{R}_0 \leq 1$ only remains a necessary but not sufficient condition for disease elimination and hence disease eradication can not just be achieved by making $\mathfrak{R}_0 < 1$ but the initial population sizes will have to satisfy some conditions. This phenomenon has also been observed in some epidemic models ((Castillo-Chavez et al., 1989), (Dushoff et al., 1998), (Feng et al., 2000), (Elbasha and B., 2006)). A depiction of a backward bifurcation diagram is given in Figure 2.5.2.

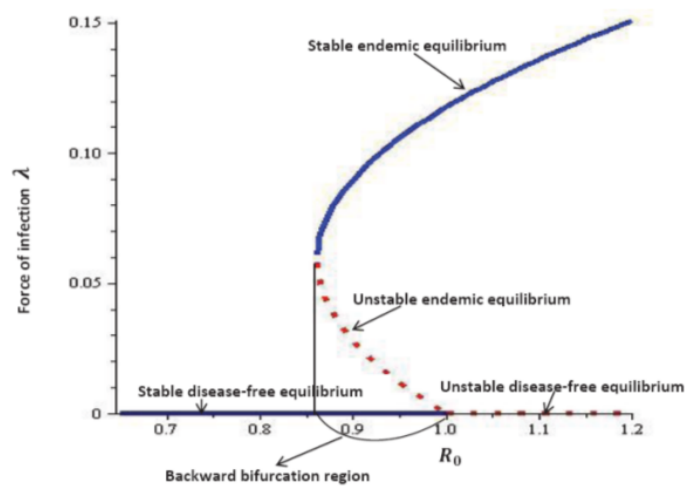


Figure 2.5.2: Backward Bifurcation Diagram Showing the Co-Existence of a Stable Disease Free Equilibrium and Two Branches of Endemic Equilibria.

Chapter 3

Modelling of Pneumonia Disease dynamics

3.1 Introduction

In the report of WHO,2013, "infectious diseases are the leading cause of death in Human beings". According to the fact sheet of WHO,2013 sixteen percent of all deaths each year are from infectious diseases that means over 9.5 million deaths annually attribute to infectious diseases, with most of them in developing countries. From 9.5 million annual death , "Pneumonia and other respiratory infections cause about 2 million child deaths yearly in developing countries" (WHO,2015). If we compare infectious diseases like Malaria, HIV/AIDS, Measles and Pneumonia for under five year children in Africa, pneumonia is the leading cause of deaths (WHO,2015). According to (IHME,2014) every 35 seconds a child dies from pneumonia.

In Ethiopia, pneumonia is one of the leading cause of death. The reported cases shows that, it has been increasing aggregatively in the past 7 years (see figure figure 4.1.1). A lot of Scholars proposed models for understanding of infectious disease dynamics and also for making quantitative predictions of different intervention strategies and their effectiveness, (see, Okosun and Makinde (2011), (2012),(2013) and (2014)). Very few essential research have been done on the dynamics of pneumonia have been done in the last decade. Some of

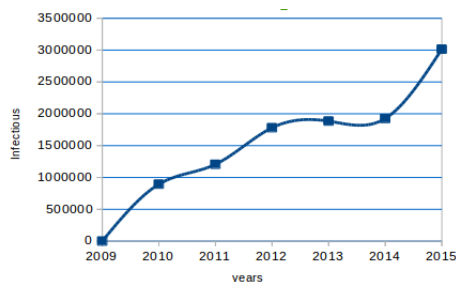


Figure 3.1.1: Reported cases of Pneumonia disease in Ethiopia from 2009 to 2015

them are, Melegaro, *et al.*, 2004, Joseph Emaline, 2012, Ssebuliba, 2013, and Okaka, *et al.*, 2013, proposed a model on pneumonia dynamics. Additionally, Ong'ala *et al.*, 2014 studied and estimated the basic reproductive number as a random variable by first developing and analyzing a deterministic model for transmission patterns of pneumonia.

All the above studies have developed a deterministic as well as stochastic mathematical model of pneumonia dynamics by subdividing the population into sub-classes of Susceptible, infectious, vaccinated, treated, carrier and recovered. But none of them considered optimal control and cost effectiveness strategies and also no study have been undertaken by applying optimal control. This, therefore motivated us to undertake this study to fulfil this gap. To estimate some parameters demographic data was collected from Health Minister of federal democratic republic of Ethiopia.

3.2 Model Description and Formulation

The model divides the total population into five sub-classes according to their disease status. Susceptible (S), vaccinated (V), carrier (C), infected (I) and recovered (R). The model assumes that a fraction of the population has been vaccinated before the disease outbreak at the rate of (p) and ($1 - p$) fraction of population susceptible. (We consider this model due to the reason that, in African particularly in Ethiopian context all new born infants are not taking Pneumococcal conjugate vaccine (PCV). Only those mothers who are aware or who stay around town or city will go to their nearby health center to vaccinate their infants but there are a lot of newborn left without vaccination). The Susceptible class is increased from

vaccinated class in which those individuals who are vaccinated but did not respond to vaccination with waning rate of ϕ and from recovered class in which those individuals who lose their temporary immunity by δ rate. However, individuals from susceptible class move to vaccinated class with vaccination rate of ϑ . The susceptible class is infected either by carrier or symptomatically infected individuals with a force of infection $\lambda = \xi \left(\frac{I(t) + \Upsilon C(t)}{N} \right)$ where, $\xi = k\tau$, k is contact rate, τ is the probability that a contact is effective to cause infection and Υ is transmission coefficient for the carrier. If $\Upsilon > 1$ then, the carriers infect susceptible more likely than infective. If $\Upsilon = 1$, then both carriers and infective have equal chance to infect the susceptible, but if $\Upsilon < 1$ then the infective have good chance to infect susceptible than carriers. The model assumes vaccination is not 100% effective, so vaccinated classes (V) also have a chance of being infectious or carrier with small proportion and the force of infection for the vaccinated class is $\lambda_v = \varepsilon\lambda$, where $0 \leq \varepsilon < 1$ and ε is the proportion of the serotype not covered by the vaccine. Newly infected individuals by the force of infection become either carrier with a probability of ρ to join the carrier class C or move to the infected class I with probability of $1 - \rho$. The carrier class can develop disease symptom or can screen themselves and join the infected class with a rate of χ or recover by gaining natural immunity at β rate. Individuals in the infected class move to recovered compartment at a per capita rate of η by treatment, with treatment efficacy of q proportion of individuals join the recovered class or join the carrier class with $(1 - q)$ proportion by adapting the treatment, or die from the disease at the rate α . In all compartments μ is the natural mortality rate of individuals and also all the parameters are positive.

The above model description can be represented diagrammatically in figure (4.2.1).

The above flow diagram can be written in to a system of five differential equations as follow:

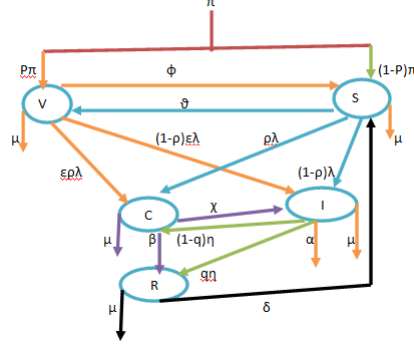


Figure 3.2.1: Flow diagram of the model

$$\left\{ \begin{array}{l} \frac{dS(t)}{dt} = (1-p)\pi + \phi V(t) + \delta R(t) - (\mu + \lambda + \vartheta)S(t), \\ \frac{dV(t)}{dt} = p\pi + \vartheta S(t) - (\mu + \epsilon\lambda + \phi)V(t), \\ \frac{dC(t)}{dt} = \rho\lambda S(t) + \rho\epsilon\lambda V(t) + (1-q)\eta I(t) - (\mu + \beta + \chi)C(t), \\ \frac{dI(t)}{dt} = (1-\rho)\lambda S(t) + (1-\rho)\epsilon\lambda V(t) + \chi C(t) - (\mu + \alpha + \eta)I(t), \\ \frac{dR(t)}{dt} = \beta C(t) + q\eta I(t) - (\mu + \delta)R(t), \end{array} \right. \quad (3.2.1)$$

With initial condition $S(0) = S_0, V(0) = V_0, I(0) = I_0, C(0) = C_0, R(0) = R_0$.

3.3 Model Analysis

3.3.1 Invariant Region

In this section, a region in which solutions of the model system are uniformly bounded is the proper subset $\Omega \subset \mathfrak{R}_+^5$.

The total population at any time t is given by $N = S + V + C + I + R$.

After differentiating both sides of N ,

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dV}{dt} + \frac{dC}{dt} + \frac{dI}{dt} + \frac{dR}{dt}. \quad (3.3.1)$$

Which gives,

$$\frac{dN}{dt} = \pi - \mu N - \alpha I(t). \quad (3.3.2)$$

In the absence of mortality due to pneumonia equation 3.3.2 become,

$$\frac{dN}{dt} \leq \pi - \mu N. \quad (3.3.3)$$

By the separation of variable rule equation 3.3.3 become,

$$\frac{dN}{\pi - \mu N} \leq dt. \quad (3.3.4)$$

Integrating both side of equation 3.3.4 gives,

$$\int \frac{dN}{\pi - \mu N} \leq \int dt. \quad (3.3.5)$$

$\Leftrightarrow \frac{-1}{\mu} \ln(\pi - \mu N) \leq t + c$ which simplifies in to

$$\pi - \mu N \geq A e^{-\mu t}. \quad (3.3.6)$$

where A is constant. By applying the initial condition $N(0) = N_0$ in equation 3.3.7, we get $A = \pi - \mu N_0$ which up on substitution in equation 3.3.7 yields,

$$\pi - \mu N \geq (\pi - \mu N_0) e^{-\mu t}. \quad (3.3.7)$$

Then by rearranging equation ?? we can get,

$$N \leq \frac{\pi}{\mu} - \left[\frac{\pi - \mu N_0}{\mu} \right] e^{-\mu t}. \quad (3.3.8)$$

as $t \rightarrow \infty$ in equation 3.3.8 the population size $N \rightarrow \frac{\pi}{\mu}$ which implies that $0 \leq N \leq \frac{\pi}{\mu}$. Thus the feasible solution set of the system equation of the model enter and remain in the region:

$$\Omega = \{(S, V, C, I, R) \in \mathfrak{R}_+^5 : N \leq \frac{\pi}{\mu}\} \quad (3.3.9)$$

Therefore, the basic model is well posed epidemiologically and mathematically. Hence, it is sufficient to study the dynamics of the basic model in Ω

3.3.2 Positivity of the solutions

In this section We aim at obtaining non-negative solutions when dealing with human populations. Therefore, the next discussion below targets on the conditions under which the model being studied has non-negative solutions. The derivative of a function at a point is one property that unveils the behaviour of that function even if that function is unknown. It is known that if the derivative at a point is positive, then the function is increasing there, if it is negative, then the function is decreasing and if it is zero, then function is constant.

Theorem 3.3.1. *let $\Omega = \{(S, V, C, I, R) \in \mathfrak{R}_+^5 : S_0 > 0, V_0 > 0, C_0 > 0, I_0 > 0, R_0 > 0\}$ then the solution of $\{S, V, C, I, R\}$ are positive for $t \geq 0$.*

Proof: From the system of differential equation 3.2.1 let us taking the first equation

$$\frac{dS}{dt} = (1 - p\psi)\pi + \phi V + \delta R - (\mu + \lambda + \vartheta)S$$

$$\Rightarrow \frac{dS}{dt} \geq -(\mu + \lambda + \vartheta)S$$

$$\Rightarrow \frac{dS}{S} \geq -(\mu + \lambda + \vartheta)d(t)$$

$$\Rightarrow \int \frac{dS}{S} \geq -\int (\mu + \lambda + \vartheta)d(t)$$

$$S(t) \geq S_0 \exp - (\mu + \lambda + \vartheta)t \geq 0.$$

let us take the second equation

$$\frac{dV}{dt} = p\psi\pi + \vartheta S - (\mu + \varepsilon\lambda + \phi)V$$

$$\Rightarrow \frac{dV}{dt} \geq -(\mu + \varepsilon\lambda + \phi)V$$

$$\Rightarrow \frac{dV}{V} \geq -(\mu + \varepsilon\lambda + \phi)d(t)$$

$$\Rightarrow \int \frac{dV}{V} \geq -\int (\mu + \varepsilon\lambda + \phi)d(t)$$

$$V(t) \geq V_0 \exp - (\mu + \varepsilon\lambda + \phi)t \geq 0.$$

let us take the third equation

$$\begin{aligned}
\frac{dC}{dt} &= \rho\lambda S + \rho\varepsilon\lambda V + (1-q)\eta I - (\mu + \beta + \chi)C \\
&\Rightarrow \frac{dC}{dt} \geq -(\mu + \beta + \chi)C \\
&\Rightarrow \frac{dC}{C} \geq -(\mu + \beta + \chi)d(t) \\
&\Rightarrow \int \frac{dC}{C} \geq -\int (\mu + \beta + \chi)d(t) \\
V(t) &\geq C_0 \exp - (\mu + \beta + \chi)t \geq 0.
\end{aligned}$$

let us take the fourth equation

$$\begin{aligned}
\frac{dI}{dt} &= (1-\rho)\lambda S + (1-\rho)\varepsilon\lambda V + \chi C - (\mu + \alpha + \eta)I \\
&\Rightarrow \frac{dI}{dt} \geq -(\mu + \alpha + \eta)I \\
&\Rightarrow \frac{dI}{I} \geq -(\mu + \alpha + \eta)d(t) \\
&\Rightarrow \int \frac{dI}{I} \geq -\int (\mu + \alpha + \eta)d(t) \\
V(t) &\geq I_0 \exp - (\mu + \alpha + \eta)t \geq 0.
\end{aligned}$$

let us take the fifth equation

$$\begin{aligned}
\frac{dR}{dt} &= \beta C + q\eta I - (\mu + \delta)R(t) \\
&\Rightarrow \frac{dR}{dt} \geq -(\mu + \delta)R \\
&\Rightarrow \frac{dR}{R} \geq -(\mu + \delta)d(t) \\
&\Rightarrow \int \frac{dR}{R} \geq -\int (\mu + \delta)d(t) \\
V(t) &\geq R_0 \exp - (\mu + \alpha + (1-q)\eta)t \geq 0.
\end{aligned}$$

This completes the proof of the Theorem.

3.3.3 Disease free equilibrium (DFE)

In this section we obtain the equilibrium point at which the epidemic is eradicated from the population. Letting the right hand side of equation (3.2.1) to zero and letting $C = I = 0$, leads to;

$$(1 - p\Psi)\pi + \phi V_0 - (\mu + \vartheta)S_0 = 0. \quad (3.3.10)$$

$$p\Psi\pi + \vartheta S_0 - (\mu + \phi)V_0 = 0, \quad (3.3.11)$$

then by rearranging equation (3.3.10) and (3.3.11) and after substituting each other, we got,

$$S_0 = \frac{(\mu - P\pi\mu + \phi)\pi}{\mu(\mu + \phi + \vartheta)} = \frac{\pi}{\mu} \mathcal{D},$$

$$\text{where } \mathcal{D} = \frac{\mu - P\pi\mu + \phi}{(\mu + \phi + \vartheta)}.$$

$$V_0 = \frac{(P\pi\mu + \vartheta)\pi}{\mu(\mu + \phi + \vartheta)} = \frac{\pi}{\mu} \mathcal{S}, \text{ where, } \mathcal{S} = \frac{P\pi\mu + \vartheta}{(\mu + \phi + \vartheta)},$$

then the disease free equilibrium point is given by, $E_0 = (\frac{\pi}{\mu} \mathcal{D}, \frac{\pi}{\mu} \mathcal{S}, 0, 0, 0)$.

where, $\mathcal{D} = \frac{\mu - P\pi\mu + \phi}{(\mu + \phi + \vartheta)}$ and $\mathcal{S} = \frac{P\pi\mu + \vartheta}{(\mu + \phi + \vartheta)}$.

3.3.4 The Effective Reproductive Number (R_{eff})

In this section we obtained the threshold parameter that governs the spread of a disease which is called the effective reproduction number is determined. To obtain the effective reproduction number we used the next generation matrix method so that it is the spectral radius of the next generation matrix ([Driessche et al., 2002](#)).

The model equations are re-written starting with newly infective classes:

$$\begin{aligned} \frac{dC(t)}{dt} &= \rho\lambda S(t) + \rho\varepsilon\lambda V(t) + (1-q)\eta I(t) - (\mu + \beta + \chi)C(t), \\ \frac{dI(t)}{dt} &= (1-\rho)\lambda S(t) + (1-\rho)\varepsilon\lambda V(t) + \chi C(t) - (\mu + \alpha + \eta)I(t). \end{aligned}$$

Then by the principle of next generation matrix we can obtained,

$$f = \begin{bmatrix} \rho\lambda S + \rho\varepsilon\lambda V \\ (1-\rho)\lambda S + (1-\rho)\varepsilon\lambda V \end{bmatrix}, \quad (3.3.12)$$

$$v = \begin{bmatrix} (\mu + \beta + \chi)C - (1-q)\eta I \\ (\mu + \alpha + \eta)I - \chi C \end{bmatrix}, \quad (3.3.13)$$

$$(3.3.14)$$

Since $\lambda = aC + bI$,

where $a = k\tau\Upsilon$ is transmission co-efficient for the carrier compartment and

$b = k\tau$ is also the transmission co-efficient for the infective compartment.

The next is obtaining the Jacobian matrix of f and v with respect to C and I at the disease free equilibrium $(S_0, V_0, 0, 0, 0)$.

To simplify our work, we assigned f and v in the following way,

$$f = \begin{bmatrix} f_1 \\ f_2 \end{bmatrix},$$

$$v = \begin{bmatrix} v_1 \\ v_2 \end{bmatrix},$$

where $f_1 = \rho\lambda S + \rho\varepsilon\lambda V$

$$f_2 = (1 - \rho)\lambda S + (1 - \rho)\varepsilon\lambda V$$

$$v_1 = (\mu + \beta + \chi)C - (1 - q)\eta I$$

$$v_2 = (\mu + \alpha + \eta)I - \chi C.$$

The Jacobian matrix of f and v is obtained by F and V respectively.

$$F = \begin{bmatrix} \frac{\partial f_1}{\partial C} & \frac{\partial f_1}{\partial I} \\ \frac{\partial f_2}{\partial C} & \frac{\partial f_2}{\partial I} \end{bmatrix},$$

$$V = \begin{bmatrix} \frac{\partial v_1}{\partial C} & \frac{\partial v_1}{\partial I} \\ \frac{\partial v_2}{\partial C} & \frac{\partial v_2}{\partial I} \end{bmatrix}.$$

The entry members of F is obtained in the following way:

$$\frac{\partial f_1}{\partial C} = \rho a S + \rho \varepsilon a V,$$

$$\frac{\partial f_1}{\partial I} = \rho b S + \rho \varepsilon b V,$$

$$\frac{\partial f_2}{\partial C} = (1 - \rho) a S + (1 - \rho) \varepsilon a V,$$

$$\frac{\partial f_2}{\partial I} = (1 - \rho) b S + (1 - \rho) \varepsilon b V.$$

Similarly the entry members of V is also obtained:

$$\frac{\partial v_1}{\partial C} = \mu + \beta + \chi,$$

$$\frac{\partial v_1}{\partial I} = -(1 - q)\eta,$$

$$\frac{\partial v_2}{\partial C} = -\chi,$$

$$\frac{\partial v_2}{\partial I} = \mu + \alpha + \eta.$$

Then the Jacobian matrix of f and v at the disease free equilibrium are,

$$F = \begin{bmatrix} \rho a(S_0 + \varepsilon V_0) & \rho b(S_0 + \varepsilon V_0) \\ (1 - \rho)a(S_0 + \varepsilon V_0) & (1 - \rho)b(S_0 + \varepsilon V_0) \end{bmatrix},$$

$$V = \begin{bmatrix} \mu + \beta + \chi & -(1 - q)\eta \\ -\chi & \mu + \alpha + \eta \end{bmatrix} \text{ respectively.}$$

It is known that for any two by two matrix say $A = \begin{bmatrix} a & b \\ c & d \end{bmatrix}$, its inverse is obtained by

$$A^{-1} = \frac{1}{ad - bc} \begin{bmatrix} d & -b \\ -c & a \end{bmatrix}.$$

In a similar fashion the inverse of V can be obtained,

$$V^{-1} = \frac{1}{(\mu + \beta + \chi)(\mu + \alpha + \eta) - \chi\eta(1 - q)} \begin{bmatrix} \mu + \alpha + \eta & (1 - q)\eta \\ \chi & \mu + \beta + \chi \end{bmatrix},$$

then the product of F and V^{-1} become,

$$FV^{-1} = \frac{1}{(\mu + \beta + \chi)(\mu + \alpha + \eta) - \chi\eta(1 - q)} \begin{bmatrix} \rho a(\mu + \alpha + \eta)(S_0 + \varepsilon V_0) + \rho b\chi(S_0 + \varepsilon V_0) & \rho a(1 - q)\eta(S_0 + \varepsilon V_0) + \rho b(\mu + \beta + \chi)(S_0 + \varepsilon V_0) \\ (1 - \rho)a(\mu + \alpha + \eta)(S_0 + \varepsilon V_0) + (1 - \rho)\chi(S_0 + \varepsilon V_0) & (1 - \rho)a(1 - q)\eta(S_0 + \varepsilon V_0) + (1 - \rho)b(\mu + \beta + \chi)(S_0 + \varepsilon V_0) \end{bmatrix}.$$

Now we are in the position to obtain the dominant eigenvalue of FV^{-1} .

But to minimize long expression and to simplify our work let us represent the following expressions,

$$a_1 = \frac{\mu + \alpha + \eta}{(\mu + \beta + \chi)(\mu + \alpha + \eta) - \chi\eta(1 - q)}(S_0 + \varepsilon V_0),$$

$$a_2 = \frac{\chi}{(\mu + \beta + \chi)(\mu + \alpha + \eta) - \chi\eta(1 - q)}(S_0 + \varepsilon V_0),$$

$$a_3 = \frac{(1 - q)\eta}{(\mu + \beta + \chi)(\mu + \alpha + \eta) - \chi\eta(1 - q)}(S_0 + \varepsilon V_0),$$

$$a_4 = \frac{(\mu + \beta + \chi)}{(\mu + \beta + \chi)(\mu + \alpha + \eta) - \chi\eta(1 - q)}(S_0 + \varepsilon V_0).$$

Then FV^{-1} re-written as,

$$FV^{-1} = \begin{bmatrix} \rho a a_1 + \rho b a_2 & \rho a a_3 + \rho b a_4 \\ (1 - \rho) a a_1 + (1 - \rho) b a_2 & (1 - \rho) a a_3 + (1 - \rho) b a_4 \end{bmatrix}.$$

The eigenvalue of FV^{-1} can be obtained,

$$\begin{vmatrix} (\rho a a_1 + \rho b a_2) - \lambda & \rho a a_3 + \rho b a_4 \\ (1 - \rho) a a_1 + (1 - \rho) b a_2 & ((1 - \rho) a a_3 + (1 - \rho) b a_4) - \lambda \end{vmatrix} = 0,$$

$$\Rightarrow ((\rho aa_1 + \rho ba_2) - \lambda)((1 - \rho)aa_3 + (1 - \rho)ba_4) - \lambda - ((1 - \rho)aa_1 + (1 - \rho)ba_2)(\rho aa_3 + \rho ba_4) = 0,$$

$$\Rightarrow \lambda^2 - (\rho(aa_1 + ba_2) + (1 - \rho)(aa_3 + ba_4))\lambda - \rho(aa_1 + ba_2)(1 - \rho)(aa_3 + ba_4) - \rho(1 - \rho)(aa_1 + ba_2)(aa_3 + ba_4)$$

,

$$\Rightarrow \lambda^2 - (\rho(aa_1 + ba_2) + (1 - \rho)(aa_3 + ba_4))\lambda - (aa_1 + ba_2)(aa_3 + ba_4)(\rho(1 - \rho) - \rho(1 - \rho)) = 0,$$

$$\Rightarrow \lambda^2 - (\rho(aa_1 + ba_2) + (1 - \rho)(aa_3 + ba_4))\lambda = 0,$$

$$\lambda(\lambda - (\rho(aa_1 + ba_2) + (1 - \rho)(aa_3 + ba_4))) = 0.$$

Then the eigenvalues are,

$$\lambda_1 = 0$$

and

$$\lambda_2 = \rho(aa_1 + ba_2) + (1 - \rho)(aa_3 + ba_4).$$

From λ_1 and λ_2 the dominant eigenvalue is λ_2 . Therefore the effective reproductive number is given by

$$R_{eff} = \rho(aa_1 + ba_2) + (1 - \rho)(aa_3 + ba_4).$$

By back substitution of a_1 , a_2 , a_3 and a_4 the effective reproduction number become:

$$R_{eff} = \left[\frac{\rho(a(\mu + \alpha + \eta) + b\chi)}{(\mu + \beta + \chi)(\mu + \alpha + \eta) - \chi\eta(1 - q)} + \frac{(1 - \rho)(a(1 - q)\eta + b(\mu + \beta + \chi))}{(\mu + \beta + \chi)(\mu + \alpha + \eta) - \chi\eta(1 - q)} \right] (S_0 + \varepsilon V_0),$$

when we also substitute $a = k\tau\Upsilon$ and $b = k\tau$ and $\xi = k\tau$, the effective reproduction number become,

$$R_{eff} = k\tau \left[\frac{\rho(\Upsilon(\mu + \alpha + \eta) + \chi)}{(\mu + \beta + \chi)(\mu + \alpha + \eta) - \chi\eta(1 - q)} + \frac{(1 - \rho)(\Upsilon(1 - q)\eta + (\mu + \beta + \chi))}{(\mu + \beta + \chi)(\mu + \alpha + \eta) - \chi\eta(1 - q)} \right] \left(\frac{\pi}{\mu} \wp + \varepsilon \frac{\pi}{\mu} \mathfrak{J} \right). \quad (3.3.15)$$

3.3.5 Analysis of R_{eff}

The effective reproduction number measures the average number of new infectious generated by a typically infectious individual in a community when some strategies are in place, like vaccination or treatment.

We can re-write the effective number:

$$R_{eff} = k\tau \left[\frac{\rho(\Upsilon(\mu + \alpha + \eta) + \chi)}{(\mu + \beta + \chi)(\mu + \alpha + \eta) - \chi\eta(1 - q)} + \frac{(1 - \rho)(\Upsilon(1 - q)\eta + (\mu + \beta + \chi))}{(\mu + \beta + \chi)(\mu + \alpha + \eta) - \chi\eta(1 - q)} \right] \frac{\pi}{\mu} \wp$$

+

$$k\tau \left[\frac{\rho(\Upsilon(\mu + \alpha + \eta) + \chi)}{(\mu + \beta + \chi)(\mu + \alpha + \eta) - \chi\eta(1 - q)} + \frac{(1 - \rho)(\Upsilon(1 - q)\eta + (\mu + \beta + \chi))}{(\mu + \beta + \chi)(\mu + \alpha + \eta) - \chi\eta(1 - q)} \right] \varepsilon \frac{\pi}{\mu} \mathfrak{S}.$$

Thus

$$R_{eff} = R_s^* \wp + R_v^* \mathfrak{S}$$

where,

$$R_s^* = k\tau \left[\frac{\rho(\Upsilon(\mu + \alpha + \eta) + \chi)}{(\mu + \beta + \chi)(\mu + \alpha + \eta) - \chi\eta(1 - q)} + \frac{(1 - \rho)(\Upsilon(1 - q)\eta + (\mu + \beta + \chi))}{(\mu + \beta + \chi)(\mu + \alpha + \eta) - \chi\eta(1 - q)} \right] \frac{\pi}{\mu}$$

and

$$R_v^* = \varepsilon k\tau \left[\frac{\rho(\Upsilon(\mu + \alpha + \eta) + \chi)}{(\mu + \beta + \chi)(\mu + \alpha + \eta) - \chi\eta(1 - q)} + \frac{(1 - \rho)(\Upsilon(1 - q)\eta + (\mu + \beta + \chi))}{(\mu + \beta + \chi)(\mu + \alpha + \eta) - \chi\eta(1 - q)} \right] \frac{\pi}{\mu}.$$

From this we can see that for the over all disease transmission, there is a contribution from susceptible population (R_s^*) and vaccinated population (R_v^*).

Definition 3.3.1. 1. The threshold parameters R_s^* , is the reproduction number when all individuals are susceptible .

2. The threshold parameters R_v^* , is the reproduction number when all individuals are vaccinated .

We have studied the effect of vaccination on the generation of secondary cases. Now let us see without intervention, that means initially the entire population are susceptible. That means $\varepsilon = 0$, $p = 0$, $\phi = 0$, $\varphi = 0$ and $\pi = 0$.

Then the effective reproductive number is reduced to :

$$R_0 = \left[(1-\rho) \left(b \frac{\mu + \beta + \chi}{(\mu + \beta + \chi)(\mu + \alpha + \eta) - \chi\eta(1-q)} + (1-q)a \frac{\eta}{(\mu + \beta + \chi)(\mu + \alpha + \eta) - \chi\eta(1-q)} \right) + \rho \left(a \frac{\mu + \alpha + \eta}{(\mu + \beta + \chi)(\mu + \alpha + \eta) - \chi\eta(1-q)} + b \frac{\chi}{(\mu + \beta + \chi)(\mu + \alpha + \eta) - \chi\eta(1-q)} \right) \right] \frac{\pi}{\mu}$$

Which is the basic reproductive number, means the average number of secondary infectious caused by a single infective in totally susceptible population.

When a single infective in an entirely susceptible population is introduced, with a probability $1 - \rho$ it becomes a non-carrier, hence makes b effective contacts per unit time. This is multiplied by the average infectious period $\frac{\mu + \beta + \chi}{(\mu + \beta + \chi)(\mu + \alpha + \eta) - \chi\eta(1-q)}$ for non-carrier; this number should be increased by the number of infections caused by this with $(1-q)a \frac{\eta}{(\mu + \beta + \chi)(\mu + \alpha + \eta) - \chi\eta(1-q)}$ proportion. With probability ρ the infective is a carrier, hence makes a effective contacts per unit time during the average period $\frac{\mu + \alpha + \eta}{(\mu + \beta + \chi)(\mu + \alpha + \eta) - \chi\eta(1-q)}$ it remains a carrier. This number should be increased by the number of infectious $b \frac{\chi}{(\mu + \beta + \chi)(\mu + \alpha + \eta) - \chi\eta(1-q)}$. Therefore the expression in the big square bracket in R_0 is the per capita average number of infectious. This number multiplied by the number of susceptibles at the disease-free equilibrium $\frac{\pi}{\mu}$ gives R_0 .

3.3.6 Local stability of disease free equilibrium

Theorem 3.3.2. *The disease free equilibrium point is locally asymptotically stable if $R_{eff} < 1$ and unstable if $R_{eff} > 1$.*

Proof To prove local stability of disease free equilibrium, we obtained the Jacobian matrix of the system (3.2.1) at the disease free equilibrium E_0 :

$$J(S_0, V_0, 0, 0, 0) = \begin{bmatrix} -(\mu + \phi) & \phi & -aS_0 & -bS_0 & \delta \\ \phi & -(\mu + \phi) & -a\varepsilon V_0 & -b\varepsilon V_0 & 0 \\ 0 & 0 & \rho aS_0 + \rho a\varepsilon V_0 - (\mu + \beta + \chi) & \rho bS_0 + \rho b\varepsilon V_0 + (1-q)\eta & 0 \\ 0 & 0 & (1-\rho)aS_0 + (1-\rho)a\varepsilon V_0 + \chi & (1-\rho)bS_0 + (1-\rho)b\varepsilon V_0 - (\mu + \alpha + \eta) & 0 \\ 0 & 0 & \beta & q\eta & -(\mu + \delta) \end{bmatrix}. \quad (3.3.16)$$

To obtain the eigenvalue of (3.3.16),

$$\begin{vmatrix}
-(\mu + \varphi) - \lambda & \phi & -aS_0 & -bS_0 & \delta \\
\phi & -(\mu + \phi) - \lambda & -a\varepsilon V_0 & -b\varepsilon V_0 & 0 \\
0 & 0 & [\rho aS_0 + \rho a\varepsilon V_0 - (\mu + \beta + \chi)] - \lambda & \rho bS_0 + \rho b\varepsilon V_0 + (1 - q)\eta & 0 \\
0 & 0 & (1 - \rho)aS_0 + (1 - \rho)a\varepsilon V_0 + \chi & [(1 - \rho)bS_0 + (1 - \rho)b\varepsilon V_0 - (\mu + \alpha + \eta)] - \lambda & 0 \\
0 & 0 & \beta & q\eta & -(\mu + \delta) - \lambda
\end{vmatrix} = 0$$

$$\Rightarrow -(\mu + \varphi) - \lambda \begin{vmatrix}
-(\mu + \phi) - \lambda & -a\varepsilon V_0 & -b\varepsilon V_0 & 0 \\
0 & [\rho aS_0 + \rho a\varepsilon V_0 - (\mu + \beta + \chi)] - \lambda & \rho bS_0 + \rho b\varepsilon V_0 + (1 - q)\eta & 0 \\
0 & (1 - \rho)aS_0 + (1 - \rho)a\varepsilon V_0 + \chi & [(1 - \rho)bS_0 + (1 - \rho)b\varepsilon V_0 - (\mu + \alpha + \eta)] - \lambda & 0 \\
0 & \beta & q\eta & -(\mu + \delta) - \lambda
\end{vmatrix} -$$

$$\phi \begin{vmatrix}
\phi & -aS_0 & -bS_0 & \delta \\
0 & [\rho aS_0 + \rho a\varepsilon V_0 - (\mu + \beta + \chi)] - \lambda & \rho bS_0 + \rho b\varepsilon V_0 + (1 - q)\eta & 0 \\
0 & (1 - \rho)aS_0 + (1 - \rho)a\varepsilon V_0 + \chi & [(1 - \rho)bS_0 + (1 - \rho)b\varepsilon V_0 - (\mu + \alpha + \eta)] - \lambda & 0 \\
0 & \beta & q\eta & -(\mu + \delta) - \lambda
\end{vmatrix} = 0$$

$$\Rightarrow -(\mu + \varphi) - \lambda [-(\mu + \phi) - \lambda] \begin{vmatrix}
[\rho aS_0 + \rho a\varepsilon V_0 - (\mu + \beta + \chi)] - \lambda & \rho bS_0 + \rho b\varepsilon V_0 + (1 - q)\eta & 0 \\
(1 - \rho)aS_0 + (1 - \rho)a\varepsilon V_0 + \chi & [(1 - \rho)bS_0 + (1 - \rho)b\varepsilon V_0 - (\mu + \alpha + \eta)] - \lambda & 0 \\
\beta & q\eta & -(\mu + \delta) - \lambda
\end{vmatrix} -$$

$$\phi \phi \begin{vmatrix}
[\rho aS_0 + \rho a\varepsilon V_0 - (\mu + \beta + \chi)] - \lambda & \rho bS_0 + \rho b\varepsilon V_0 + (1 - q)\eta & 0 \\
(1 - \rho)aS_0 + (1 - \rho)a\varepsilon V_0 + \chi & [(1 - \rho)bS_0 + (1 - \rho)b\varepsilon V_0 - (\mu + \alpha + \eta)] - \lambda & 0 \\
\beta & q\eta & -(\mu + \delta) - \lambda
\end{vmatrix} = 0$$

$$\Rightarrow -(\mu + \varphi) - \lambda [-(\mu + \phi) - \lambda] - \phi \phi \begin{vmatrix}
[\rho aS_0 + \rho a\varepsilon V_0 - (\mu + \beta + \chi)] - \lambda & \rho bS_0 + \rho b\varepsilon V_0 + (1 - q)\eta & 0 \\
(1 - \rho)aS_0 + (1 - \rho)a\varepsilon V_0 + \chi & [(1 - \rho)bS_0 + (1 - \rho)b\varepsilon V_0 - (\mu + \alpha + \eta)] - \lambda & 0 \\
\beta & q\eta & -(\mu + \delta) - \lambda
\end{vmatrix} = 0$$

$$\Rightarrow -(\mu + \varphi) - \lambda [-(\mu + \phi) - \lambda] - \phi \phi = 0 \tag{3.3.17}$$

or

$$\begin{vmatrix}
[\rho aS_0 + \rho a\varepsilon V_0 - (\mu + \beta + \chi)] - \lambda & \rho bS_0 + \rho b\varepsilon V_0 + (1 - q)\eta & 0 \\
(1 - \rho)aS_0 + (1 - \rho)a\varepsilon V_0 + \chi & [(1 - \rho)bS_0 + (1 - \rho)b\varepsilon V_0 - (\mu + \alpha + \eta)] - \lambda & 0 \\
\beta & q\eta & -(\mu + \delta) - \lambda
\end{vmatrix} = 0, \tag{3.3.18}$$

when we expand equation (3.3.17),

$$\lambda^2 + (2\mu + \phi + \varphi)\lambda + \mu(\mu + \phi + \varphi). \tag{3.3.19}$$

Then by Routh-Hurwitz criteria equation (3.3.19) have strictly negative root.

The determinant of equation (3.3.18) can be obtained,

$$\begin{vmatrix}
\rho a(S_0 + \varepsilon V_0) - (\mu + \beta + \chi) - \lambda & \rho b(S_0 + \varepsilon V_0) + (1 - q)\eta & 0 \\
(1 - \rho)a(S_0 + \varepsilon V_0) + \chi & (1 - \rho)b(S_0 + \varepsilon V_0) - (\mu + \alpha + \eta) - \lambda & 0 \\
\beta & q\eta & -(\mu + \delta) - \lambda
\end{vmatrix} = 0$$

$$\Rightarrow -(\mu + \delta) - \lambda \begin{vmatrix} \rho a(S_0 + \varepsilon V_0) - (\mu + \beta + \chi) - \lambda & \rho b(S_0 + \varepsilon V_0) + (1 - q)\eta \\ (1 - \rho)a(S_0 + \varepsilon V_0) + \chi & (1 - \rho)b(S_0 + \varepsilon V_0) - (\mu + \alpha + \eta) - \lambda \end{vmatrix} = 0,$$

then

$$\lambda_1 = -(\mu + \delta) < 0$$

and

$$(\rho a(S_0 + \varepsilon V_0) - (\mu + \beta + \chi) - \lambda)((1 - \rho)b(S_0 + \varepsilon V_0) - (\mu + \alpha + \eta) - \lambda) - ((1 - \rho)a(S_0 + \varepsilon V_0) + \chi)(\rho b(S_0 + \varepsilon V_0) + (1 - q)\eta) \quad (3.3.20)$$

when we rearrange equation (3.3.20) it become

$$\lambda^2 + a_1\lambda + a_2 = 0,$$

where

$$a_1 = (\mu + \beta + \chi) + (\mu + \alpha + \eta) - (\rho a + (1 - \rho)b)(S_0 + \varepsilon V_0),$$

$$a_2 = -(\rho(a(\mu + \alpha + \eta) + b\chi) + (1 - \rho)(b(\mu + \beta + \chi) + a(1 - q)\eta))(S_0 + \varepsilon V_0) - ((1 - q)\chi\eta - (\mu + \beta + \chi)(\mu + \alpha + \eta))$$

By Routh-Hurwitz criteria,

$$a_1 > 0$$

means that,

$$(\mu + \beta + \chi) + (\mu + \alpha + \eta) > (\rho a + (1 - \rho)b)(S_0 + \varepsilon V_0),$$

and also

$$a_2 > 0$$

means that,

$$-(\rho(a(\mu + \alpha + \eta) + b\chi) + (1 - \rho)(b(\mu + \beta + \chi) + a(1 - q)\eta))(S_0 + \varepsilon V_0) - ((1 - q)\chi\eta - (\mu + \beta + \chi)(\mu + \alpha + \eta))$$

$$\Rightarrow [(\rho(a(\mu + \alpha + \eta) + b\chi) + (1 - \rho)(b(\mu + \beta + \chi) + a(1 - q)\eta))](S_0 + \varepsilon V_0) < (\mu + \beta + \chi)(\mu + \alpha + \eta) - (1 - q)\chi\eta$$

$$\begin{aligned} \Rightarrow \frac{[(\rho(a(\mu + \alpha + \eta) + b\chi) + (1 - \rho)(b(\mu + \beta + \chi) + a(1 - q)\eta))]}{(\mu + \beta + \chi)(\mu + \alpha + \eta) - (1 - q)\chi\eta} (S_0 + \varepsilon V_0) &< 1 \\ \Rightarrow R_{eff} &< 1, \end{aligned}$$

Thus, the disease free equilibrium is locally asymptotically stable if $R_{eff} < 1$.

3.3.7 The endemic equilibrium (EE)

The endemic equilibrium is denoted by E^* and defined as a steady state solutions for the Model (3.2.1). This can occur when there is a persistence of the disease. It can be obtained by equating the system of equation 3.2.1 to zero.

We took the third and the fourth equations of the model 3.2.1 and combined each other then we obtained,

$$C^* = \frac{(1 - \rho)(1 - q)\eta + \rho(\mu + \alpha + \eta)}{(1 - \rho)(\mu + \beta + \chi) + \rho\chi} I^*, \quad (3.3.21)$$

By substituting 4.6.6a in to the fifth equation of the model 3.2.1, we obtained;

$$R^* = \frac{\beta((1 - \rho)(1 - q)\eta + \rho(\mu + \alpha + \eta)) + ((1 - \rho)(\mu + \beta + \chi) + \rho\chi)q\eta}{((1 - \rho)(\mu + \beta + \chi) + \rho\chi)(\mu + \delta)} I^*. \quad (3.3.22)$$

From the second equation of the model 3.2.1, we obtained;

$$V^* = \frac{\rho\Psi\pi + \vartheta S^*}{\mu + \varepsilon\lambda^* + \phi}. \quad (3.3.23)$$

By combining 3.3.23 and the third and fourth equation of the model 3.2.1 we obtained;

$$S^* = \frac{(\mu + \beta + \chi)((1 - \rho)(1 - q)\eta + \rho(\mu + \alpha + \eta)) - (1 - q)\eta((1 - \rho)(\mu + \beta + \chi) + \rho\chi)(\mu + \varepsilon\lambda + \phi)I^*}{(((1 - \rho)(\mu + \beta + \chi) + \rho\chi)(\mu + \delta))\rho\lambda(\mu + \varepsilon\lambda + \phi + \varepsilon\vartheta)}. \quad (3.3.24)$$

From 3.3.22, 3.3.23, 3.3.24 and the first equation of the model (3.2.1) we obtained;

$$I^* = \frac{A_2\lambda^{**}(\lambda^{**2}\varepsilon^2D_2 + \lambda^{**}\mu\varepsilon D_2 + \lambda^{**}\varepsilon D_2 + \lambda^{**}\varepsilon D_2D_6 + \lambda^{**}\varepsilon D_4 + \mu D_2D_6 + \phi D_2D_6 - \lambda^{**}D_2 + D_1D_7 + D_4D_6)}{A_1(\lambda^{**}\varepsilon D_5)D_7 - \delta\lambda^{**3}A_5A_2\varepsilon^2 + \delta\lambda^{**2}D_6A_5A_2\varepsilon + \delta\lambda^{**2}D_5A_5\varepsilon + \delta\lambda^{**}D_6D_5A_5A_2 + A_1(\lambda^{**}\varepsilon + D_5)\lambda^{**}} \quad (3.3.25)$$

where

$$A_1 = (\mu + \beta + \chi)((\mu + \alpha + \eta) - \eta(1 - q)),$$

$$A_2 = \chi\rho + (1 - \rho)(\mu + \beta + \chi),$$

$$A_3 = \rho(\mu + \delta)^2(\chi + (1 - \rho)(\mu + \beta + \chi)),$$

$$A_4 = (\chi\rho + (1 - \rho))(\mu + \delta),$$

$$A_5 = (1 - \rho)\eta(1 - q) + \rho(\mu + \alpha + \eta) + (\chi\rho + (1 - \rho)(\mu + \beta + \chi))q\eta,$$

$$D_1 = \varepsilon p \Psi \pi,$$

$$D_2 = A_3(1 - p \Psi) \pi,$$

$$D_4 = A_3 \phi p \Psi \pi,$$

$$D_5 = \mu + \phi,$$

$$D_6 = \varepsilon \vartheta + \mu + \phi,$$

$$D_7 = A_4 \phi \vartheta - \mu - \vartheta.$$

Hence $E^* = (S^*, V^*, C^*, I^*, R^*)$ is the endemic equilibrium of the model 3.2.1.

Lemma 3.3.3. *For $R_{eff} > 1$ a unique endemic equilibrium point E^* exist and no endemic equilibrium otherwise.*

Proof. For the disease to endemic, $\frac{dC}{dt} > 0$ and $\frac{dI}{dt} > 0$, that is:

$$\begin{aligned} \frac{dC(t)}{dt} &= \rho\lambda S(t) + \rho\varepsilon\lambda V(t) + (1 - q)\eta I(t) - (\mu + \beta + \chi)C(t) > 0, \\ \frac{dI(t)}{dt} &= (1 - \rho)\lambda S(t) + (1 - \rho)\varepsilon\lambda V(t) + \chi C(t) - (\mu + \alpha + \eta)I(t) > 0 \end{aligned} \quad (3.3.26)$$

From the second inequality of (3.3.26),

$$(\mu + \alpha + \eta)I(t) < (1 - \rho)\lambda S(t) + (1 - \rho)\varepsilon\lambda V(t) + \chi C(t)$$

$$\Rightarrow I < \frac{(1 - \rho)\xi \left(\frac{I(t) + \chi C(t)}{N} \right) (S + \varepsilon V) + \chi C}{(\mu + \alpha + \eta)}$$

From the fact $\frac{(S+\varepsilon V)}{N} \leq 1$,

$$I < \frac{(1-\rho)\xi I(t) + (1-\rho)\xi \Upsilon C(t) + \chi C}{(\mu + \alpha + \eta)}. \quad (3.3.27)$$

From the first inequality of (3.3.26),

$$\begin{aligned} (\mu + \beta + \chi)C(t) &< \rho\lambda S(t) + \rho\varepsilon\lambda V(t) + (1-q)\eta I(t) \\ \Rightarrow C &< \frac{\rho\xi\left(\frac{I(t)+\Upsilon C(t)}{N}(S+\varepsilon V) + (1-q)\eta I(t)\right)}{(\mu + \beta + \chi)}. \end{aligned}$$

From the fact $\frac{(S+\varepsilon V)}{N} \leq 1$,

$$C < \frac{\rho\xi I(t) + (1-q)\eta I(t)}{(\mu + \beta + \chi) - \rho\xi\Upsilon}. \quad (3.3.28)$$

By substituting (3.3.28) in to (3.3.27) we can get,

$$I < \frac{(1-\rho)\xi I((\mu + \beta + \chi) - \rho\xi\Upsilon) + (1-\rho)\xi\Upsilon(\rho\xi I + (1-q)\eta I) + \chi(\rho\xi I + (1-q)\eta I)}{(\mu + \alpha + \eta)(\mu + \beta + \chi - \rho\xi\Upsilon)}.$$

Then, by rearranging and cancelling of I in both sides, we can get:

$$\begin{aligned} 1 &< \xi \left[\frac{\rho(\Upsilon(\mu + \alpha + \eta) + \chi)}{(\mu + \beta + \chi)(\mu + \alpha + \eta) - \chi\eta(1-q)} + \frac{(1-\rho)(\Upsilon(1-q)\eta + (\mu + \beta + \chi))}{(\mu + \beta + \chi)(\mu + \alpha + \eta) - \chi\eta(1-q)} \right] \leq \\ \xi \left[\frac{\rho(\Upsilon(\mu + \alpha + \eta) + \chi)}{(\mu + \beta + \chi)(\mu + \alpha + \eta) - \chi\eta(1-q)} + \frac{(1-\rho)(\Upsilon(1-q)\eta + (\mu + \beta + \chi))}{(\mu + \beta + \chi)(\mu + \alpha + \eta) - \chi\eta(1-q)} \right] \left(\frac{\pi}{\mu} \wp + \varepsilon \frac{\pi}{\mu} \mathfrak{S} \right) &= R_{eff} \end{aligned} \quad (3.3.29)$$

$$\Rightarrow 1 < R_{eff}.$$

Thus a unique endemic equilibrium exist when $R_{eff} > 1$. \square

3.3.8 The global stability of the endemic equilibrium

Theorem 3.3.4. *If $R_{eff} > 1$, the endemic equilibrium E^* of the model (3.2.1) is globally asymptotically stable.*

Proof. To prove the global asymptotic stability of the endemic equilibrium we use the method of Lyapunov functions.

Define.

$$L(S^*, V^*, C^*, I^*, R^*) = \left(S - S^* - S^* \ln \frac{S^*}{S} \right) + \left(V - V^* - V^* \ln \frac{V^*}{V} \right) + \left(C - C^* - C^* \ln \frac{C^*}{C} \right) \\ + \left(I - I^* - I^* \ln \frac{I^*}{I} \right) + \left(R - R^* - R^* \ln \frac{R^*}{R} \right).$$

By direct calculating the derivative of L along the solution of (3.2.1) we have;

$$\frac{dL}{dt} = \left(\frac{S - S^*}{S} \right) \frac{dS}{dt} + \left(\frac{V - V^*}{V} \right) \frac{dV}{dt} + \left(\frac{C - C^*}{C} \right) \frac{dC}{dt} + \left(\frac{I - I^*}{I} \right) \frac{dI}{dt} + \left(\frac{R - R^*}{R} \right) \frac{dR}{dt}.$$

$$\frac{dL}{dt} = \left(\frac{S - S^*}{S} \right) [(1 - p\Psi)\pi + \phi V + \delta R - (\mu + \lambda + \vartheta)S] + \left(\frac{V - V^*}{V} \right) [p\Psi\pi + \vartheta S - (\mu + \varepsilon\lambda + \phi)V] \\ + \left(\frac{C - C^*}{C} \right) [\rho\lambda S + \rho\varepsilon\lambda V + (1 - q)\eta I - (\mu + \beta + \chi)C] + \left(\frac{I - I^*}{I} \right) [(1 - \rho)\lambda S \\ + (1 - \rho)\varepsilon\lambda V + \chi C - (\mu + \alpha + \eta)I] + \left(\frac{R - R^*}{R} \right) [\beta C + q\eta I - (\mu + \delta)R].$$

$$\begin{aligned} \frac{dL}{dt} = & \pi + \phi V - \phi V^* + \delta R - \delta R^* - \frac{\pi S^*}{S} - \frac{P\Psi\pi S^*}{S} - \frac{\phi V S^*}{S} + \frac{\phi V^* S^*}{S} - \frac{\delta R S^*}{S} + \frac{\delta R^* S^*}{S} + \chi C - \chi C^* - \frac{(1 - \rho)\lambda S I^*}{I} + \frac{(1 - \rho)\lambda S^* I^*}{I} \\ & - \frac{(1 - \rho)\varepsilon\lambda V I^*}{I} + \frac{(1 - \rho)\varepsilon\lambda V^* I^*}{I} - \frac{\chi C I^*}{I} + \frac{\chi C^* I^*}{I} + (1 - q)\eta I - (1 - q)\eta I^* - \frac{\rho\lambda S C^*}{C} + \frac{\rho\lambda S^* C^*}{C} - \frac{\rho\varepsilon\lambda V C^*}{C} + \frac{\rho\varepsilon\lambda V^* C^*}{C} \\ & - \frac{(1 - q)\eta I C^*}{C} + \frac{(1 - q)\eta I^* C^*}{C} + \beta C - \beta C^* + q\eta I - q\eta I^* - \frac{\beta C R^*}{R} + \frac{\beta C^* R^*}{R} - \frac{q\eta I R^*}{R} + \frac{q\eta I^* R^*}{R} + \phi S - \phi S^* - \frac{P\Psi\pi V^*}{V} - \frac{\phi S V^*}{V} + \frac{\phi S^* V^*}{V} \\ & + \lambda S - \lambda S^* + \varepsilon\lambda V - \varepsilon\lambda V^* - \frac{(V - V^*)^2}{V} [\mu + \varepsilon\lambda + \phi] - \frac{(I - I^*)^2}{I} [\mu + \alpha + \eta] - \frac{(S - S^*)^2}{S} [\mu + \lambda + \varphi] - \frac{(C - C^*)^2}{C} [\mu + \beta + \chi] - \frac{(R - R^*)^2}{R} [\mu + \delta]. \end{aligned} \quad (3.3.30)$$

Thus collecting positive terms together and negative terms together from equation (3.3.31) leads to,

$$\frac{dL}{dt} = Q - K$$

where,

$$Q = \pi + \phi V + \delta R + \frac{\phi V^* S^*}{S} + \frac{\delta R^* S^*}{S} + \chi C + \frac{(1 - \rho)\lambda S^* I^*}{I} + \frac{(1 - \rho)\varepsilon\lambda V^* I^*}{I} + \frac{\chi C^* I^*}{I} + (1 - q)\eta I + \frac{\rho\lambda S^* C^*}{C} + \frac{\rho\varepsilon\lambda V^* C^*}{C} + \frac{(1 - q)\eta I^* C^*}{C} + \beta C + q\eta I + \frac{\beta C^* R^*}{R} + \frac{q\eta I^* R^*}{R} + \phi S + \frac{\phi S^* V^*}{V} + \lambda S + \varepsilon\lambda V \\ K = \phi V^* + \frac{\pi S^*}{S} + \frac{P\Psi\pi S^*}{S} + \frac{\phi V S^*}{S} + \frac{\delta R S^*}{S} + \chi C^* + \frac{(1 - \rho)\lambda S I^*}{I} + \frac{(1 - \rho)\varepsilon\lambda V I^*}{I} + \frac{\chi C I^*}{I} + (1 - q)\eta I^* + \frac{\rho\lambda S C^*}{C} + \frac{\rho\varepsilon\lambda V C^*}{C} + \frac{(1 - q)\eta I C^*}{C} + q\eta I^* + \frac{\beta C R^*}{R} + \frac{q\eta I R^*}{R} + \phi S^* + \frac{P\Psi\pi V^*}{V} + \frac{\phi S V^*}{V} + \lambda S^* + \varepsilon\lambda V^* + \frac{(V - V^*)^2}{V} [\mu + \varepsilon\lambda + \phi] + \frac{(I - I^*)^2}{I} [\mu + \alpha + \eta] + \frac{(S - S^*)^2}{S} [\mu + \lambda + \varphi] + \frac{(C - C^*)^2}{C} [\mu + \beta + \chi] + \frac{(R - R^*)^2}{R} [\mu + \delta].$$

Thus if $Q < K$, then $\frac{dL}{dt} \leq 0$;

Noting that $\frac{dL}{dt} = 0$ if and only if $S = S^*, V = V^*, C = C^*, I = I^*, R = R^*$

Therefore, the largest compact invariant set in $\{(S^*, V^*, C^*, I^*, R^*) \in \Omega : \frac{dL}{dt} = 0\}$ is the singleton

E^* , where E^* is the endemic equilibrium of the system (3.2.1).

By LaSalle's invariant principle (LaSalle, 1976), it implies that E^* is globally asymptotically stable in Ω if $Q < K$. □

3.3.9 Determination of Backward Bifurcation

To explore the possibility of backward or forward bifurcation of the model system (3.2.1) we use the centre manifold theory, explained in chapter 2 section 2.3. This is done by renaming the variables as follows;

Let

$$S = x_1, V = x_2, C = x_3, I = x_4, R = x_5,$$

further by introducing the Vector notation;

$$x = (x_1, x_2, x_3, x_4, x_5)^T.$$

Then the model can be written in the form of:

$$\frac{dx}{dt} = F(x),$$

where

$$F = (f_1, f_2, f_3, f_4, f_5)^T$$

as follows,

$$\left. \begin{aligned} \frac{dx_1}{dt} &= (1 - p\Psi)\pi + \phi x_2 + \delta x_5 - (\mu + \lambda + \vartheta)x_1, \\ \frac{dx_2}{dt} &= p\Psi\pi + \vartheta x_1 - (\mu + \varepsilon\lambda + \phi)x_2, \\ \frac{dx_3}{dt} &= \rho\lambda(x_1 + \varepsilon x_2) + (1 - q)\eta x_4 - (\mu + \beta + \chi)x_3, \\ \frac{dx_4}{dt} &= (1 - \rho)\lambda(x_1 + \varepsilon x_2) + \chi x_3 - (\mu + \alpha + \eta)x_4, \\ \frac{dx_5}{dt} &= \beta x_3 + q\eta x_4 - (\mu + \delta)x_5, \end{aligned} \right\} \quad (3.3.31)$$

where

$$N = x_1 + x_2 + x_3 + x_4 + x_5.$$

Then the Jacobian system at the disease free,

$$J_E = \begin{bmatrix} -(\mu + \phi) & \phi & -\xi\Upsilon\wp & -\xi\wp & \delta \\ \phi & -(\mu + \phi) & -\xi\Upsilon\varepsilon\mathfrak{S} & -\xi\varepsilon\mathfrak{S} & 0 \\ 0 & 0 & \rho\xi\Upsilon(\wp + \varepsilon\mathfrak{S}) - (\mu + \beta + \chi) & \rho\xi(\wp + \varepsilon\mathfrak{S}) + (1 - q)\eta & 0 \\ 0 & 0 & (1 - \rho)\xi\Upsilon(\wp + \varepsilon\mathfrak{S}) + \chi & (1 - \rho)\xi(\wp + \varepsilon\mathfrak{S}) - (\mu + \alpha + \eta) & 0 \\ 0 & 0 & \beta & q\eta & -(\mu + \delta) \end{bmatrix}. \quad (3.3.32)$$

Suppose that $\xi = \xi^*$ is a bifurcation parameter; the system 3.3.32 is linearized at the disease free equilibrium point when $\xi^* = \xi$ with $R_{eff} = 1$, solving for ξ^* for $R_{eff} = 1$ from:-

$$R_{eff} = \xi \left[\frac{\rho(\Upsilon(\mu + \alpha + \eta) + \chi)}{(\mu + \beta + \chi)(\mu + \alpha + \eta) - \chi\eta(1 - q)} + \frac{(1 - \rho)(\Upsilon(1 - q)\eta + (\mu + \beta + \chi))}{(\mu + \beta + \chi)(\mu + \alpha + \eta) - \chi\eta(1 - q)} \right] \left(\frac{\pi}{\mu}\wp + \varepsilon \frac{\pi}{\mu}\mathfrak{S} \right).$$

We obtained,

$$\xi^* = \frac{\mu((\mu + \beta + \chi)(\mu + \alpha + \eta) - \chi\eta(1 - q))}{\pi(\rho(\Upsilon(\mu + \alpha + \eta) + \chi) + (1 - \rho)(\Upsilon(1 - q)\eta + (\mu + \beta + \chi)))(\wp + \varepsilon\mathfrak{S})}.$$

The system 3.3.33 with $\xi = \xi^*$ has a simple zero eigenvalues, hence the centre manifold theory will be used to analyse the dynamics of the system near $\xi = \xi^*$. The Jacobean matrix near $\xi = \xi^*$ has a right eigenvector associated with the zero eigenvalue given by; $w = (w_1, w_2, w_3, w_4, w_5)^T$ from the system;

$$J_E = \begin{bmatrix} -(\mu + \phi) & \phi & -\xi\Upsilon\wp & -\xi\wp & \delta \\ \phi & -(\mu + \phi) & -\xi\Upsilon\varepsilon\mathfrak{S} & -\xi\varepsilon\mathfrak{S} & 0 \\ 0 & 0 & \rho\xi\Upsilon(\wp + \varepsilon\mathfrak{S}) - (\mu + \beta + \chi) & \rho\xi(\wp + \varepsilon\mathfrak{S}) + (1 - q)\eta & 0 \\ 0 & 0 & (1 - \rho)\xi\Upsilon(\wp + \varepsilon\mathfrak{S}) + \chi & (1 - \rho)\xi(\wp + \varepsilon\mathfrak{S}) - (\mu + \alpha + \eta) & 0 \\ 0 & 0 & \beta & q\eta & -(\mu + \delta) \end{bmatrix} \begin{pmatrix} w_1 \\ w_2 \\ w_3 \\ w_4 \\ w_5 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \quad (3.3.33)$$

The system of equation become,

$$\left. \begin{aligned} -(\mu + \phi)w_1 + \phi w_2 - \xi\Upsilon\wp w_3 - \xi\wp w_4 + \delta w_5 &= 0 \\ \phi w_1 - (\mu + \phi)w_2 - \xi\Upsilon\varepsilon\mathfrak{S} w_3 - \xi\varepsilon\mathfrak{S} w_4 &= 0 \\ (\rho\xi\Upsilon(\wp + \varepsilon\mathfrak{S}) - (\mu + \beta + \chi))w_3 + (\rho\xi(\wp + \varepsilon\mathfrak{S}) + (1 - q)\eta)w_4 &= 0 \\ ((1 - \rho)\xi\Upsilon(\wp + \varepsilon\mathfrak{S}) + \chi)w_3 + ((1 - \rho)\xi(\wp + \varepsilon\mathfrak{S}) - (\mu + \alpha + \eta))w_4 &= 0 \\ \beta w_3 + q\eta w_4 - (\mu + \delta)w_5 &= 0 \end{aligned} \right\} \quad (3.3.34)$$

Solving system of equation 3.3.35 we obtained,

$$w_1 = \frac{(\mu + \phi)w_2 + \xi\Upsilon\varepsilon\mathfrak{S}w_3 + \xi\varepsilon\mathfrak{S}w_4}{\vartheta}$$

$$w_2 = w_2 > 0$$

$$w_3 = \frac{((1 - \rho)\xi(\wp + \varepsilon\mathfrak{S}) - (\mu + \alpha + \eta))w_4}{(\mu + \beta + \chi) - \rho\xi\Upsilon(\wp + \varepsilon\mathfrak{S})}$$

$$w_4 = w_4 > 0$$

$$w_5 = \frac{\beta w_3 + q\eta w_4}{(\mu + \delta)}$$

The left eigenvectors of J_E associated with the zero eigenvalue at $\xi^* = \xi$ is given by $v = (v_1, v_2, v_3, v_4, v_5)^T$, from the system 3.3.33.

$$J_E v = \begin{bmatrix} -(\mu + \phi) & \phi & 0 & 0 & 0 \\ \phi & -(\mu + \phi) & 0 & 0 & 0 \\ -\xi\Upsilon\wp & -\xi\Upsilon\varepsilon\mathfrak{S} & \rho\xi\Upsilon(\wp + \varepsilon\mathfrak{S}) - (\mu + \beta + \chi) & (1 - \rho)\xi\Upsilon(\wp + \varepsilon\mathfrak{S}) + \chi & \beta \\ -\xi\wp & -\xi\varepsilon\mathfrak{S} & \rho\xi(\wp + \varepsilon\mathfrak{S}) + (1 - q)\eta & (1 - \rho)\xi(\wp + \varepsilon\mathfrak{S}) - (\mu + \alpha + \eta) & q\eta \\ \delta & 0 & 0 & 0 & -(\mu + \delta) \end{bmatrix} \begin{pmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}. \quad (3.3.35)$$

The system of equation of 3.3.36 become,

$$\left. \begin{aligned} -(\mu + \phi)v_1 + \phi v_2 &= 0 \\ \phi v_1 - (\mu + \phi)v_2 &= 0 \\ -\xi\Upsilon\wp v_1 - \xi\Upsilon\varepsilon\mathfrak{S}v_2 + (\rho\xi\Upsilon(\wp + \varepsilon\mathfrak{S}) - (\mu + \beta + \chi))v_3 + ((1 - \rho)\xi\Upsilon(\wp + \varepsilon\mathfrak{S}) + \chi)v_4 + \beta v_5 &= 0 \\ -\xi\wp v_1 - \xi\varepsilon\mathfrak{S}v_2 + (\rho\xi(\wp + \varepsilon\mathfrak{S}) + (1 - q)\eta)v_3 + ((1 - \rho)\xi(\wp + \varepsilon\mathfrak{S}) - (\mu + \alpha + \eta))v_4 + q\eta v_5 &= 0 \\ \delta v_1 - (\mu + \delta)v_5 &= 0. \end{aligned} \right\} \quad (3.3.36)$$

Solving system of equation 3.3.37 we obtained,

$$v_1 = v_2 = 0,$$

$$v_3 = \frac{((1 - \rho)\xi\Upsilon(\wp + \varepsilon\mathfrak{S}) + \chi)v_4}{(\mu + \beta + \chi) - \rho\xi\Upsilon(\wp + \varepsilon\mathfrak{S})},$$

$$v_4 = v_4 > 0,$$

$$v_5 = 0.$$

To compute a and b we use a formula explained in section 2.3 of chapter 2.

$$a = \sum_{k,j,i=1}^n v_k w_i w_j \frac{\partial^2 f}{\partial x_i \partial x_j}(S_0, V_0, 0, 0, 0), \quad (3.3.37)$$

$$b = \sum_{k,i=1}^n v_k w_i \frac{\partial^2 f}{\partial x_i \partial \xi}, \quad (3.3.38)$$

where

$$\left. \begin{aligned} f_1 &= (1 - p\Psi)\pi + \phi x_2 + \delta x_5 - (\mu + \lambda + \vartheta)x_1, \\ f_2 &= p\Psi\pi + \vartheta x_1 - (\mu + \varepsilon\lambda + \phi)x_2, \\ f_3 &= \rho\lambda(x_1 + \varepsilon x_2) + (1 - q)\eta x_4 - (\mu + \beta + \chi)x_3, \\ f_4 &= (1 - \rho)\lambda(x_1 + \varepsilon x_2) + \chi x_3 - (\mu + \alpha + \eta)x_4, \\ f_5 &= \beta x_3 + q\eta x_4 - (\mu + \delta)x_5. \end{aligned} \right\} \quad (3.3.39)$$

Taking into account system 3.3.40 and considering only the non-zero components of the left eigenvectors v_3 and v_4 , then we obtained,

$$a = (2\xi w_4 v_4) a_0,$$

$$b = \xi w_4 v_4 (\Upsilon r_0 + 1)(\rho(k_0 - 1) + 1)(\wp + \varepsilon\mathfrak{S}),$$

where,

$$a_0 = (\rho(k_0 - 1) + 1)(\Upsilon r_0(w_1 + \varepsilon w_2) + w_1 + \varepsilon w_2),$$

$$k_0 = \frac{((1 - \rho)\xi(\wp + \varepsilon\mathfrak{S}) - (\mu + \alpha + \eta))}{(\mu + \beta + \chi) - \rho\xi\Upsilon(\wp + \varepsilon\mathfrak{S})},$$

$$r_0 = \frac{((1 - \rho)\xi\Upsilon(\wp + \varepsilon\mathfrak{S}) + \chi)}{(\mu + \beta + \chi) - \rho\xi\Upsilon(\wp + \varepsilon\mathfrak{S})}.$$

Since the coefficient b is always positive, it is the sign of the coefficient a and consequently the sign of the quantity a_0 which determines the local dynamics of the disease around the disease-free equilibrium.

Therefore, $a > 0$ depending on whether a_0 is greater or less than 0. Thus we have established the following result.

Theorem 3.3.5. *If $a_0 > 0, a > 0$ then model system (3.2.1) has a backward bifurcation at $R_{eff} = 1$, otherwise, $a < 0$ and a unique endemic equilibrium is locally asymptotically stable for $R_{eff} > 1$ but*

close to 1.

Remark. The appearance of backward bifurcation implies that $R_{eff} < 1$ is not sufficient to control the spread of disease, a stable endemic state may exist even when $R_{eff} < 1$, and R_{eff} must be reduced below the leftmost point on the bifurcation curve for which an endemic equilibrium exists, R_c , sometimes called the minimum transition value. Mathematical speaking, when a backward bifurcation occurs and $R_c < R_{eff} < 1$, there are at least three equilibria, the stable disease-free equilibrium, a larger stable endemic equilibrium, and a smaller unstable endemic equilibrium which acts as a boundary between the basins of attraction for the two stable equilibria. When $R_{eff} > 1$, there exists only one endemic equilibrium.

3.4 Sensitivity Analysis of the Model parameters

we carried out the sensitivity analysis to determine the model robustness to parameter values. This is to help us to identify the parameters that have a high impact on the reproductive number (R_{eff}). In this section we followed the approach of (Chitnis et al., 2006) and also the approach of (Blower and Dowlatabadi, 1994).

Moreover, sensitivity indices allowed us to measure the relative change in a state variable when a parameter changes (Chitnis et al., 2006). The normalized forward sensitivity index of a variable to a parameter is a ratio of the relative change in the variable to the relative change in the parameter. If a variable is a differentiable function of the parameter, the sensitivity index may be alternatively defined using partial derivatives.

Definition 3.4.1. The normalized forward sensitivity index of a variable, u , which depends differentiability on index of a parameter, p is defined as $\Lambda_p^u = \frac{\partial u}{\partial p} \frac{p}{u}$

From an explicit formula for (R_{eff}) in (3.3.10) we derive an analytical expression for the sensitivity of R_{eff} as $\Lambda_p^{R_{eff}} = \frac{\partial R_{eff}}{\partial p} \frac{p}{R_{eff}}$ to each of the parameter involved in (R_{eff}). For example the sensitivity index of R_{eff} with respect to k is $\Lambda_k^{R_{eff}} = \frac{\partial R_{eff}}{\partial k} \frac{k}{R_{eff}} = 1$, other indices $\Lambda_\tau^{R_{eff}}, \Lambda_p^{R_{eff}}, \Lambda_\phi^{R_{eff}}, \Lambda_\vartheta^{R_{eff}}, \Lambda_\varepsilon^{R_{eff}}, \Lambda_\chi^{R_{eff}}, \Lambda_q^{R_{eff}}, \Lambda_\eta^{R_{eff}}, \Lambda_\beta^{R_{eff}}, \Lambda_\tau^{R_{eff}}, \Lambda_\rho^{R_{eff}}, \Lambda_\mu^{R_{eff}}, \Lambda_\alpha^{R_{eff}}$ where obtained and evaluated at, $p = 0.6, \phi = 0.001, \vartheta = 0.9, \varepsilon = 0.4, \chi = 0.00274, q = 0.5, \eta = 0.0238, \beta = 0.0115, k = 6, \tau = 0.89, \rho = 0.338, \mu = 0.002, \alpha = 0.33$ to obtain the following results.

Table 3.4.1: Sensitivity indices table

Parameter symbol	Sensitivity indices
k	+ve
ε	+ve
τ	+ve
ϕ	+ve
χ	+ve
p	-ve
ϑ	-ve
μ	-ve
α	-ve
ρ	-ve
β	-ve
η	-ve
q	-ve

3.4.1 Interpretation of Sensitivity Indices

Table 5.5.1 shows the sensitivity indices of R_{eff} to the parameters for the pneumonia model, evaluated at the baseline parameter values given in Table 5.7.1. The parameters are ordered from most sensitive to least. The most sensitive parameter is the contact rate, and the least sensitive parameter is the progression proportion of the disease. This result implies that, when the parameters k , ε , τ , ϕ and χ are increased keeping other parameters constant they increase the value of R_{eff} thus, they increase the endemicity of the disease as they have positive indices. While the parameters χ , p , ϑ , μ , α , ρ , β , η and q decrease the value of R_{eff} when they are increased while keeping the other parameters constant, implying that they decrease the endemicity of the disease as they have negative indices.

3.5 Extension of the Model into an Optimal Control

In this section, we apply optimal control strategies on the model (3.2.1). This helped us to identify the best intervention strategies that helps to eradicate the disease in the specified time. The optimal control model is an extension pneumonia model by including the following three controls defined as:

- i. u_1 a prevention effort, that protect susceptible from contacting the disease.
- ii. u_2 a treatment effort, to minimize infection by treating infectious.
- iii. u_3 a screening effort, to help carriers to screen themselves.

After incorporating, u_1, u_2 and u_3 in pneumonia model (3.2.1), we obtain the following optimal control model of pneumonia:

$$\begin{cases} \frac{dS}{dt} = (1-p)\pi + \phi V + \delta r - \frac{(1-u_1)\xi(\Upsilon C+I)S}{N} - (\vartheta + \mu)S, \\ \frac{dV}{dt} = p\pi + \vartheta S - \frac{(1-u_1)\xi(\Upsilon C+I)V}{N} - (\mu + \phi)V, \\ \frac{dC}{dt} = \frac{\rho(1-u_1)\xi(\Upsilon C+I)(\epsilon V+S)}{N} + (1-q)(1-u_2)\eta I - (u_3 + \chi)C - (\mu + \beta)C, \\ \frac{dI}{dt} = \frac{(1-\rho)(1-u_1)\xi(\Upsilon C+I)(\epsilon V+S)}{N} + (u_3 + \chi)C - (\eta + u_2)I - (\mu + \alpha)I, \\ \frac{dR}{dt} = \beta C + (u_2 + q\eta)I - (\mu + \delta)R, \end{cases} \quad (3.5.1)$$

To study the optimal levels of the controls the control set U is Lebesgue measurable and it is defined as : $U = \{(u_1(t), u_2(t), u_3(t)) : 0 \leq u_1 < 1, 0 \leq u_2 < 1, 0 \leq u_3 < 1, 0 \leq t \leq T\}$. Our aim is to obtain a control u and S, V, C, I and R that minimize the proposed objective function J and the form of the objective functional is taken in line with literature on epidemic models (Baba and Makinde, 2014), given by:

$$J = \min_{u_1, u_2, u_3} \int_0^{t_f} (b_1 C + b_2 I + \frac{1}{2} \sum_{i=1}^3 w_i u_i^2) dt. \quad (3.5.2)$$

Where b_1, b_2 and w_i are positive. The expression $\frac{1}{2} w_i u_i^2$ represents cost which is associated with the controls u_i . The form is quadratic because we assume that costs are non-linear in its nature. Our aim is to minimize the number of carriers, infectives and costs. Thus, we seek to find an optimal triple controls (u_1^*, u_2^*, u_3^*) such that:

$$J(u_1^*, u_2^*, u_3^*) = \min\{J(u_1, u_2, u_3) / u_i \in U\},$$

where, $U = \{(u_1, u_2, u_3) / \text{each } u_i \text{ is measurable with } 0 \leq u_i < 1 \text{ for } 0 \leq t \leq t_f\}$.

3.5.1 Existence of an optimal control

We note that the existence of an optimal control pair can be proved by using results from (Fleming and Rishel, 1982). It is clear that the system of equations given by (5.6.4) is bounded from above by a linear system. The boundedness of solutions of system (5.6.4) for a finite time interval is used to prove the existence of an optimal control. To use the results on existence, [(Fleming and Rishel, 1982), Theorem 4.1, p68-69] in the special case of the problem (the free terminal point problem)

of optimal control in which the initial time and state and the final time are fixed and there are no conditions on the final state, we must check that the following properties are satisfied.

- (1) The set of controls and corresponding state variables is non-empty.
- (2) The control set U is convex and closed.
- (3) The right hand side of the state system is bounded by a linear function in the state and control.
- (4) The integrand of the objective functional is concave on U .
- (5) The function is bounded below by $a_2 - a_1(|u_1|^2 + |u_2|^2 + |u_3|^2)^{\frac{\alpha}{2}}$ where $a_1, a_2 > 0$ and $\alpha > 1$

An existence result in [(Lukes, 1982), Theorem 9.2.1, p. 182] for the state system (5.6.4) with bounded coefficients is used to give condition 1. The control set U is convex and closed by definition. The right hand side of the state system (5.6.4) satisfies condition 3 as the state solutions are a priori bounded. The integrand in the objective functional, $b_1S + b_2C + b_3I + \frac{1}{2} \sum_{i=1}^3 w_i u_i^2$ is clearly concave on U . Moreover, there are $a_1, a_2 > 0$ and $\alpha > 1$ satisfying

$$b_1C + b_2I + \frac{1}{2} \sum_{i=1}^3 w_i u_i^2 \leq a_2 - a_1(|u_1|^2 + |u_2|^2 + |u_3|^2)^{\frac{\alpha}{2}}$$

because, the state variables are bounded. Finally under assumption 5, there exists an optimal control (u_1, u_2, u_3) that minimizes the objective functional $J(u_1, u_2, u_3)$.

3.5.2 The Hamiltonian and Optimality System

By using the principle of (Pontryagin et al., 1986),” Pontryagins Maximum Principle Pontryagin”, we got the necessary conditions which is satisfied by optimal pair. Therefore, by this principle we obtained a Hamiltonian (H) defined as:

$$H(S, V, C, I, R, t) = L(C, I, u_1, u_2, u_3, t) + \lambda_1 \frac{ds}{dt} + \lambda_2 \frac{dV}{dt} + \lambda_3 \frac{dC}{dt} + \lambda_4 \frac{dI}{dt} + \lambda_5 \frac{dR}{dt},$$

where $L(C, I, u_1, u_2, u_3, t) = b_1C + b_2I + \frac{1}{2} \sum_{i=1}^3 w_i u_i^2$, $\lambda_i, i = 1, 2, 3, 4, 5$ are the adjoint variable functions to be determined suitably by applying Pontryagin’s maximal principle (Pontryagin et al., 1986) and also using (Fleming and Rishel, 1982) for existence of the optimal control pairs.

Theorem 3.5.1. *For an optimal control set u_1, u_2, u_3 that minimizes J over U , there is an adjoint*

variables, $\lambda_1, \dots, \lambda_5$ such that:

$$\left\{ \begin{array}{l} \frac{d\lambda_1}{dt} = - \left(-\frac{(1-u_1)\xi(\Upsilon C+I)}{N} - \vartheta - \mu \right) \lambda_1 - \vartheta \lambda_2 - \frac{\rho(1-u_1)\xi(\Upsilon c+I)\lambda_3}{N} - \frac{(1-\rho)(1-u_1)\xi(\Upsilon C+I)\lambda_4}{N} \\ \frac{d\lambda_2}{dt} = -\phi \lambda_1 - \left(-\frac{(1-u_1)\xi(\Upsilon C+I)}{N} - \mu - \phi \right) \lambda_2 - \frac{\rho(1-u_1)\xi(\Upsilon C+I)\varepsilon\lambda_3}{N} - \frac{(1-\rho)(1-u_1)\xi(\Upsilon C+I)\varepsilon\lambda_4}{N} \\ \frac{d\lambda_3}{dt} = \frac{(1-u_1)\xi\Upsilon S\lambda_1}{N} + \frac{(1-u_1)\xi\Upsilon V\lambda_2}{N} - \left(\frac{\rho(1-u_1)\xi\Upsilon(\varepsilon V+S)}{N} - u_3 - \chi - \mu - \beta \right) \lambda_3 \\ \quad - \left(\frac{(1-\rho)(1-u_1)\xi\Upsilon(\varepsilon V+S)}{N} + u_3 + \chi \right) \lambda_4 - \beta \lambda_5 - b_1 \\ \frac{d\lambda_4}{dt} = \frac{(1-u_1)\xi S\lambda_1}{N} + \frac{(1-u_1)\xi V\lambda_2}{N} - \left(\frac{\rho(1-u_1)\xi(\varepsilon V+S)}{N} + (1-q)(1-u_2)\eta \right) \lambda_3 \\ \quad - \left(\frac{(1-\rho)(1-u_1)\xi(\varepsilon V+S)}{N} - \eta - u_2 - \mu - \alpha \right) \lambda_4 - (\eta q + u_2) \lambda_5 - b_2 \\ \frac{d\lambda_5}{dt} = -\delta \lambda_1 - (-\mu - \delta) \lambda_5 \end{array} \right. \quad (3.5.3)$$

With transversality conditions, $\lambda_i(t_f) = 0, i = 1, \dots, 5$.

Furthermore, we obtain the control set (u_1^*, u_2^*, u_3^*) characterized by

$$\begin{aligned} u_1^*(t) &= \max\{0, \min(1, \Phi_1)\}, & u_3^*(t) &= \max\{0, \min(1, \Phi_3)\}, \\ u_2^*(t) &= \max\{0, \min(1, \Phi_2)\}, \end{aligned}$$

where,

$$\Phi_1 = \frac{\xi(\sigma C+I)(\rho V\varepsilon\lambda_3 - \rho V\varepsilon\lambda_4 + \rho S\lambda_3 - \rho S\lambda_4 + V\varepsilon\lambda_4 - V\lambda_1 + S\lambda_4 - V\lambda_2)}{Nw_1},$$

$$\Phi_2 = -\frac{I(\eta q\lambda_3 - \eta\lambda_3 - \lambda_4 + \lambda_5)}{w_2}, \quad \Phi_3 = \frac{C(\lambda_3 - \lambda_4)}{w_3}.$$

Proof:

The form of the adjoint equation and transversality conditions are standard results from Pontryagin's maximum principle (Pontryagin et al., 1986). We differentiate the Hamiltonian (4.5.3) with respect to states S, V, C, I and R respectively and then the adjoint system can be written as:

$$\begin{aligned} \frac{d\lambda_1(t)}{dt} &= -\frac{dH}{dS} - \left(-\frac{(1-u_1)\xi(\Upsilon C+I)}{N} - \vartheta - \mu \right) \lambda_1 - \vartheta \lambda_2 - \frac{\rho(1-u_1)\xi(\Upsilon C+I)\lambda_3}{N} - \frac{(1-\rho)(1-u_1)\xi(\Upsilon C+I)\lambda_4}{N} \\ \frac{d\lambda_2}{dt} &= -\frac{dH}{dV} = -\phi \lambda_1 - \left(-\frac{(1-u_1)\xi(\Upsilon C+I)}{N} - \mu - \phi \right) \lambda_2 - \frac{\rho(1-u_1)\xi(\Upsilon C+I)\varepsilon\lambda_3}{N} - \frac{(1-\rho)(1-u_1)\xi(\Upsilon C+I)\varepsilon\lambda_4}{N} \\ \frac{d\lambda_3}{dt} &= -\frac{dH}{dC} = \frac{(1-u_1)\xi\Upsilon S\lambda_1}{N} + \frac{(1-u_1)\xi\Upsilon V\lambda_2}{N} - \left(\frac{\rho(1-u_1)\xi\Upsilon(\varepsilon V+S)}{N} - u_3 - \chi - \mu - \beta \right) \lambda_3 \\ &\quad - \left(\frac{(1-\rho)(1-u_1)\xi\Upsilon(\varepsilon V+S)}{N} + u_3 + \chi \right) \lambda_4 - \beta \lambda_5 - b_1 \\ \frac{d\lambda_4}{dt} &= -\frac{dH}{dI} = \frac{(1-u_1)\xi S\lambda_1}{N} + \frac{(1-u_1)\xi V\lambda_2}{N} - \left(\frac{\rho(1-u_1)\xi(\varepsilon V+S)}{N} + (1-q)(1-u_2)\eta \right) \lambda_3 \end{aligned}$$

$$- \left(\frac{(1-\rho)(1-u_1)\xi(\varepsilon v+s)}{N} - \eta - u_2 - \mu - \alpha \right) \lambda_4 - (\eta q + u_2) \lambda_5 - b_2$$

$$\frac{d\lambda_5}{dt} = -\frac{dH}{dR} = -\delta \lambda_1 - (-\mu - \delta) \lambda_5$$

Similarly by following the approach of (Pontryagin et al., 1986), to get the controls, we solved the equation, $\frac{\partial H}{\partial u_i} = 0$ at u_i^* , for $i = 1, 2, 3$ and obtained:

$$u_1^* = \frac{\xi (\Upsilon C + I) (\rho V \varepsilon \lambda_3 - \rho V \varepsilon \lambda_4 + \rho S \lambda_3 - \rho S \lambda_4 + V \varepsilon \lambda_4 - S \lambda_1 + S \lambda_4 - V \lambda_2)}{N w_1},$$

$$u_2^* = -\frac{I(\eta q \lambda_3 - \eta \lambda_3 - \lambda_4 + \lambda_5)}{w_2},$$

$$u_3^* = \frac{C(\lambda_3 - \lambda_4)}{w_3}.$$

When we write by using standard control arguments involving the bounds on the controls, we conclude:

$$u_1^* = \begin{cases} \Phi_1 & \text{if } 0 < \Phi_1 < 1 \\ 0 & \text{if } \Phi_1 \leq 0 \\ 1 & \text{if } \Phi_1 \geq 1. \end{cases} \quad u_3^* = \begin{cases} \Phi_3 & \text{if } 0 < \Phi_3 < 1 \\ 0 & \text{if } \Phi_3 \leq 0 \\ 1 & \text{if } \Phi_3 \geq 1 \end{cases}.$$

In compact notation

$$u_1^*(t) = \max\{0, \min(1, \Phi_1)\},$$

$$u_2^*(t) = \max\{0, \min(1, \Phi_2)\},$$

$$u_3^*(t) = \max\{0, \min(1, \Phi_3)\}.$$

$$\Phi_1 = \frac{\xi (\Upsilon C + I) (\rho V \varepsilon \lambda_3 - \rho V \varepsilon \lambda_4 + \rho S \lambda_3 - \rho S \lambda_4 + V \varepsilon \lambda_4 - S \lambda_1 + S \lambda_4 - V \lambda_2)}{N w_1},$$

$$\Phi_2 = -\frac{I(\eta q \lambda_3 - \eta \lambda_3 - \lambda_4 + \lambda_5)}{w_2},$$

$$\Phi_3 = \frac{C(\lambda_3 - \lambda_4)}{w_3}.$$

The optimality system is formed from the optimal control system (the state system) and the adjoint

variable system by incorporating the characterized control set and initial and transversal condition.

$$\left\{ \begin{array}{l} \frac{dS}{dt} = (1-p)\pi + \phi V + \delta R - \frac{(1-u_1^*)\xi(\Upsilon C+I)S}{N} - (\vartheta + \mu)S, \\ \frac{dV}{dt} = p\pi + \vartheta S - \frac{(1-u_1^*)\xi(\Upsilon C+I)V}{N} - (\mu + \phi)V, \\ \frac{dC}{dt} = \frac{\rho(1-u_1^*)\xi(\Upsilon C+I)(\varepsilon V+S)}{N} + (1-q)(1-u_2^*)\eta I - (u_3^* + \chi)C - (\mu + \beta)C, \\ \frac{dI}{dt} = \frac{(1-\rho)(1-u_1^*)\xi(\Upsilon C+I)(\varepsilon V+S)}{N} + (u_3^* + \chi)C - (\eta + u_2^*)I - (\mu + \alpha)I, \\ \frac{dR}{dt} = \beta C + (u_2^* + q\eta)I - (\mu + \delta)R, \\ \frac{d\lambda_1}{dt} = - \left(-\frac{(1-u_1^*)\xi(\Upsilon C+I)}{N} - \vartheta - \mu \right) \lambda_1 - \vartheta \lambda_2 - \frac{\rho(1-u_1^*)\xi(\Upsilon C+I)\lambda_3}{N} - \frac{(1-\rho)(1-u_1^*)\xi(\Upsilon C+I)\lambda_4}{N}, \\ \frac{d\lambda_2}{dt} = -\phi \lambda_1 - \left(-\frac{(1-u_1^*)\xi(\Upsilon C+I)}{N} - \mu - \phi \right) \lambda_2 - \frac{\rho(1-u_1^*)\xi(\Upsilon C+I)\varepsilon \lambda_3}{N} - \frac{(1-\rho)(1-u_1^*)\xi(\Upsilon C+I)\varepsilon \lambda_4}{N}, \\ \frac{d\lambda_3}{dt} = \frac{(1-u_1^*)\xi \Upsilon S \lambda_1}{N} + \frac{(1-u_1^*)\xi \Upsilon V \lambda_2}{N} - \left(\frac{\rho(1-u_1^*)\xi \Upsilon (\varepsilon V+S)}{N} - u_3^* - \chi - \mu - \beta \right) \lambda_3 \\ \quad - \left(\frac{(1-\rho)(1-u_1^*)\xi \Upsilon (\varepsilon V+S)}{N} + u_3^* + \chi \right) \lambda_4 - \beta \lambda_5 - b_1, \\ \frac{d\lambda_4}{dt} = \frac{(1-u_1^*)\xi S \lambda_1}{N} + \frac{(1-u_1^*)\xi V \lambda_2}{N} - \left(\frac{\rho(1-u_1^*)\xi (\varepsilon V+S)}{N} + (1-q)(1-u_2^*)\eta \right) \lambda_3 \\ \quad - \left(\frac{(1-\rho)(1-u_1^*)\xi (\varepsilon V+S)}{N} - \eta - u_2^* - \mu - \alpha \right) \lambda_4 - (\eta q + u_2) \lambda_5 - b_2, \\ \frac{d\lambda_5}{dt} = -\delta \lambda_1 - (-\mu - \delta) \lambda_5, \end{array} \right.$$

$$\lambda_i(t_f) = 0, \quad i = 1, 2, 3, \quad S(0) = S_0, \quad V(0) = V_0, \quad C(0) = C_0, \quad I(0) = I_0, \quad \text{and} \quad R(0) = R_0.$$

3.5.3 Uniqueness of the Optimality System

Due to the priori boundedness of the state, adjoint functions and the resulting Lipschitz structure of the ODEs, we can obtain the uniqueness of solutions of the optimality system for the small time interval.

Lemma 3.5.2. *The function $u^*(s) = \min(\max(s, a), b)$ is Lipschitz continuous in s , where $a < b$ are fixed positive constants.*

Theorem 3.5.3. *For $t \in [0, t_f]$, the bounded solutions to the optimality system are unique.*

Proof:

Suppose $(S, V, C, I, R, \lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5)$ and $(\bar{S}, \bar{V}, \bar{C}, \bar{I}, \bar{R}, \bar{\lambda}_1, \bar{\lambda}_2, \bar{\lambda}_3, \bar{\lambda}_4, \bar{\lambda}_5)$ are two different solutions of our optimality system.

Let $S = e^{\lambda t}k$, $V = e^{\lambda t}l$, $C = e^{\lambda t}m$, $I = e^{\lambda t}n$, $R = e^{\lambda t}o$, $\lambda_1 = e^{-\lambda t}r$, $\lambda_2 = e^{-\lambda t}w$, $\lambda_3 = e^{-\lambda t}x$, $\lambda_4 = e^{-\lambda t}y$,
 $\lambda_5 = e^{-\lambda t}z$.

Similarly, let

$\bar{S} = e^{\lambda t}\bar{k}$, $\bar{V} = e^{\lambda t}\bar{l}$, $\bar{C} = e^{\lambda t}\bar{m}$, $\bar{I} = e^{\lambda t}\bar{n}$, $\bar{R} = e^{\lambda t}\bar{o}$, $\bar{\lambda}_1 = e^{-\lambda t}\bar{r}$, $\bar{\lambda}_2 = e^{-\lambda t}\bar{w}$, $\bar{\lambda}_3 = e^{-\lambda t}\bar{x}$, $\bar{\lambda}_4 = e^{-\lambda t}\bar{y}$,
 $\bar{\lambda}_5 = e^{-\lambda t}\bar{z}$,

$\lambda > 0$ is to be chosen.

$$u_1^* = \max\{0, \min(1, \Phi_1)\},$$

$$u_2^* = \max\{0, \min(1, \Phi_2)\},$$

$$u_3^* = \max\{0, \min(1, \Phi_3)\},$$

where

$$\Phi_1 = -\tau \frac{(\lambda_1(t)\Psi p + \lambda_2(t)\Psi p - \lambda_1(t))}{w_1},$$

$$\Phi_2 = \eta I \frac{(-\lambda_5(t)q + \lambda_4(t))}{w_2},$$

$$\Phi_3 = \chi C \frac{(\lambda_4(t) - \lambda_3(t))}{w_3}.$$

And

$$\bar{u}_1^* = \max\{0, \min(1, \bar{\Phi}_1)\},$$

$$\bar{u}_2^* = \max\{0, \min(1, \bar{\Phi}_2)\},$$

$$\bar{u}_3^* = \max\{0, \min(1, \bar{\Phi}_3)\},$$

where,

$$\bar{\Phi}_1 = -\tau \frac{(\bar{r}\Psi p + \bar{w}\Psi p - \bar{r})}{w_1},$$

$$\bar{\Phi}_2 = \eta \bar{n} \frac{(-\bar{z}q + \bar{y})}{w_2},$$

$$\bar{\Phi}_3 = \chi \bar{m} \frac{(\bar{y} - \bar{x})}{w_3}.$$

Now we substitute $S = e^{\lambda t} k$ into the first ODE of the optimality system, then we can obtain,

$$\dot{k} + \lambda k = (1 - \max\{0, \min(1, \Phi_1)\})(1 - p\Psi)\pi + \phi l + \delta o - \left(\xi \frac{(\Upsilon m + n)}{N} + \varphi + \mu\right)k.$$

Similarly, due to $V = e^{\lambda t} l$, $C = e^{\lambda t} m$, $I = e^{\lambda t} n$, $R = e^{\lambda t} o$, $\lambda_1 = e^{-\lambda t} r$, $\lambda_2 = e^{-\lambda t} w$, $\lambda_3 = e^{-\lambda t} x$, $\lambda_4 = e^{-\lambda t} y$, $\lambda_5 = e^{-\lambda t} z$,

we can obtain the following equations,

$$\dot{l} + \lambda l = \max\{0, \min(1, \Phi_1)\} p\Psi\pi + \vartheta k - \left(\varepsilon \xi \frac{(\Upsilon m + n)}{N} + \mu + \phi\right)l,$$

$$\dot{m} + \lambda m = \rho \xi \frac{(\Upsilon m + n)}{N} (k + \varepsilon l) + (1 - q)\eta n - \max\{0, \min(1, \Phi_3)\}\chi m - (\mu + \beta)m,$$

$$\dot{n} + \lambda n = (1 - \rho)\xi \frac{(\Upsilon m + n)}{N} (k + \varepsilon l) + \max\{0, \min(1, \Phi_3)\}\chi m - \max\{0, \min(1, \Phi_2)\}\eta n - (\mu + \alpha)n,$$

$$\dot{o} + \lambda o = \beta m + \max\{0, \min(1, \Phi_2)\}q\eta n - (\mu + \delta)o,$$

$$\dot{r} + \lambda r = -r\left(\frac{-\xi(\Upsilon m + n)}{N} - \vartheta - \mu\right) - w\vartheta - x\rho\xi \frac{(m\Upsilon + n)}{N} - y(1 - \rho)\xi \frac{(m\Upsilon + n)}{N},$$

$$\dot{w} + \lambda w = -r\phi - w(-\varepsilon\xi \frac{(m\Upsilon + n)}{N} - \mu - \phi) - x\rho\xi \frac{(m\Upsilon + n)}{N} - y(1 - \rho)\xi \frac{(m\Upsilon + n)\varepsilon}{N},$$

$$\dot{x} + \lambda x = \frac{x\xi\Upsilon k}{N} + \frac{w\varepsilon\xi\Upsilon l}{N} - x\left(\rho\xi \frac{(\varepsilon l + k)}{N} - \max\{0, \min(1, \Phi_3)\}\chi - \mu - \beta\right),$$

$$-y\left((1 - \rho)\xi\Upsilon \frac{(\varepsilon l + k)}{N} + \max\{0, \min(1, \Phi_3)\}\chi\right) - z\beta,$$

$$\dot{y} + \lambda y = \frac{r\xi k}{N} + w\frac{\varepsilon\xi l}{N} - x\left(\rho\sigma \frac{(\varepsilon l + k)}{N} + (1 - q)\eta\right) - y\left((1 - \rho)\xi \frac{(\varepsilon l + k)}{N}\right),$$

$$- \max\{0, \min(1, \Phi_2)\}\eta - \mu - \alpha - z\max\{0, \min(1, \Phi_2)\}q\eta,$$

$$\dot{z} + \lambda z = -r\delta - z(-\mu - \delta),$$

$$\text{where } \dot{k} = \frac{dk}{dt}.$$

The equations for $S, V, C, I, R, \lambda_1, \lambda_2, \lambda_3, \lambda_4$ and λ_5 are subtracted respectively. Then we multiply each equation by appropriate difference of functions and integrate from 0 to t_f . Next, we add all ten integrals equations and will use inequalities to obtain uniqueness. See [Fister et al. \(1998\)](#) for proof of a similar uniqueness result. The uniqueness for a small time interval is usual in "two-point" boundary value problems due to opposite time orientations; the state equations have initial conditions and the adjoint equations have final time conditions. The optimal controls, u_1, u_2 and u_3 are characterized in terms of the unique solution of the optimality system.

3.6 Numerical Simulations

In this section, we perform some numerical experimentation on the basic model (3.2.1) and the resulting optimality system consisting of the state equations (5.6.4) and the adjoint system (5.6.3). We make use of the parameter values given in Table (5.7.1) for the simulation.

An iterative scheme is used to find the optimal solution of the optimality system. Since the state system (3.2.1) have initial conditions and the adjoint systems (5.6.3) have final conditions, we solve the state system using a forward fourth-order Runge-kutta method and solve the adjoint system using a backward fourth-order Runge-Kutta method. The solution iterative scheme involves making a guess of the controls and using that guess to solve the state system. The initial guess of the control together with the solution of the state systems is used to solve the adjoint systems. The controls are then updated using a convex combination of the previous controls and the values obtained using the characterizations . The updated controls are then used to repeat the solution of the state and adjoint systems. This process is repeated until the values in the current iteration are close enough to the previous iteration values (Lenhart and T., 2007).

Using different combinations of the controls, like one control only at a time, two controls at a time and also all controls at a time, that we analyze and compare numerical results from simulations with the following scenarios.

- (i). Using Prevention effort (u_1) of susceptible without treatment ($u_2 = 0$) and with no screening ($u_3 = 0$).
- (ii). Using treatment effort (u_2) without prevention ($u_1 = 0$) and with no screening ($u_3 = 0$).
- (iii). Using screening (u_3) but without prevention ($u_1 = 0$) and no treatment of infectious $u_2 = 0$.
- (iv). Using prevention (u_1) and treatment (u_2) and without screening ($u_3 = 0$).
- (v). Using prevention u_1 and screening(u_3) and without treatment ($u_2 = 0$).
- (vi). Using treatment (u_2) and screening u_3 and without prevention (u_1).
- (vii). Using all the three controls, prevention u_1 treatment of infective (u_2) and screening of carriers u_3 .

We used $b_1 = 300, b_2 = 150, w_1 = 2, w_2 = 2$ and $w_3 = 6$ for simulation of Pneumonia model with

Table 3.6.1: Parameter Values for Pneumonia Model

Parameter symbol	Value	Source
k	0.5	Estimated
ε	0.002	Emile.J,2012
τ	0.89 to 0.99	Jacob.O,2012
ϕ	0.0025	Emile.J,2012
χ	0.001 to 0.01096 per day	Jacob.O,2012
ρ	0.2	Emile.J,2012
ϑ	0.008	Assumed
μ	0.01	Estimated
α	0.057	Estimated
ρ	0.05	Jacob.O,2012
β	0.0115	Jacob.O,2012
η	0.2	Jacob.O,2012
q	0.5 to 1	Jacob.O,2012
Υ	1.2	Assumed
δ	0.1	Emile. J, 2012
Ψ	0.2	Assumed

optimal control and also for cost-effectiveness analysis. Additionally we used $S(0) = 8200, V(0) = 2800, C(0) = 200, I(0) = 210, R(0) = 200$ as initial values.

3.6.1 Control with Prevention only

We simulate the model by Preventive intervention only. From figure (3.6.1) we see that the decrease of infectious and carrier population due to implementation of prevention. This can be attribute the fact that prevention minimizes the rate of joining of individuals in to infective as well as carrier compartments. This implies that, optimized prevention reduces the burden of the infection of pneumonia.

3.6.2 Control with Treatment only

Figure 5.7.1 shows a decrease of infectious population up to 4 month, then after start to go up. Those individuals, who were previously with the disease are being treated and that is why the number of infective population goes down for the first four month. Then, due to lack of prevention newly infected

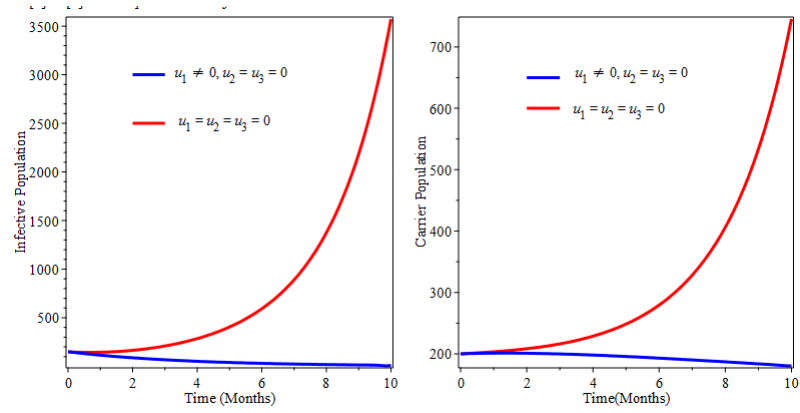


Figure 3.6.1: Simulations of optimal control with prevention only.

individuals start to join the infective as well as the carrier classes. That is why the number of infective start to goes up after four months of going down and the number of carrier also starts to go up after five month.

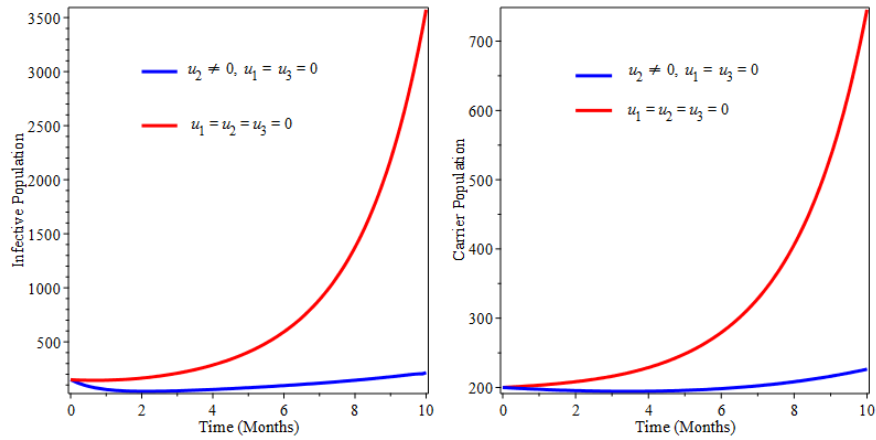


Figure 3.6.2: Simulations optimal control with treatment only.

3.6.3 Control With Screening only

Screening helps carriers to move into the infective classes and start to get treatment. Figure 4.6.3b shows a decrease in carrier population up to five months and then start to increase because due to lack of prevention. Susceptible start to be infected and joins carrier as well as infective classes. As a result of this screening only might not be sufficient to eradicate the burden of the infection of pneumonia.

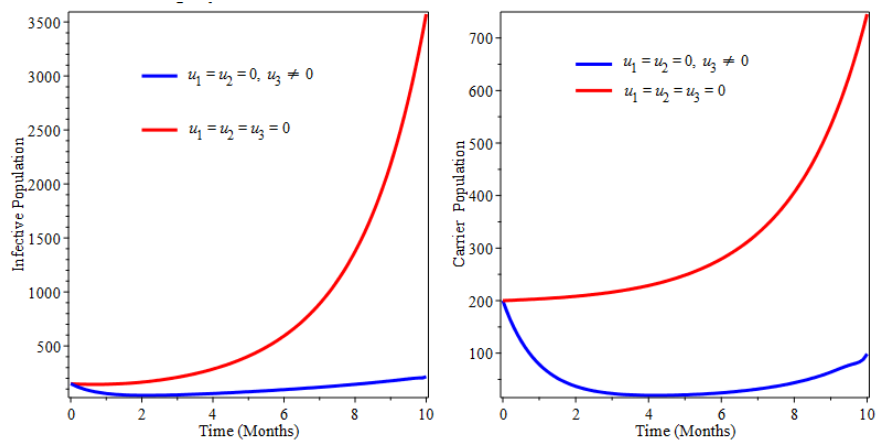


Figure 3.6.3: Simulations of optimal control with Screening only.

3.6.4 Control with Prevention and Treatment

We used prevention and treatment as intervention strategy, and figure (5.7.5) show that, the number of infective and also carriers goes down in the specified time. Therefore, this strategies is effective in eradicating the disease from the community in a specified period of time.

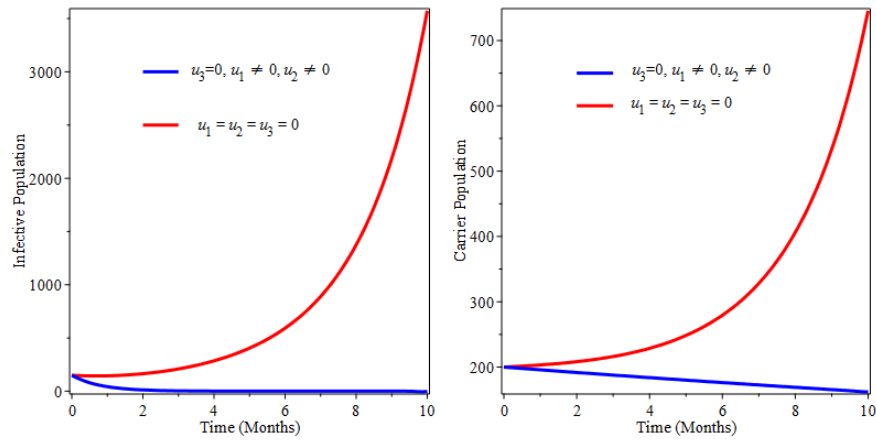


Figure 3.6.4: Simulations optimal control with Prevention and Treatment interventions.

3.6.5 Control with Prevention and Screening

In this strategy we used prevention and screening. The first figure 5.7.5 shows that, the curve for optimal control is above the curve of with out control. Due to the reason that, there is no treatment but individuals from carrier groups are joining infective compartment by screening and also there are a number of infected people in the compartment before prevention with out getting treatment so this situation make the curve to goes up for a time being. After some time the number of infectious goes down because due to prevention strategies new infection is no more coming and also since there is no treatment the number of infective population start to goes down by disease causing death and natural death rates.

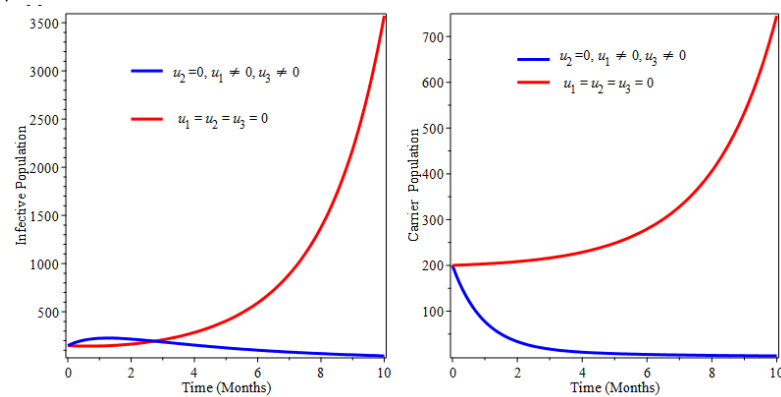


Figure 3.6.5: Simulations of optimal control with prevention and Screening intervention .

3.6.6 Control with Treatment and Screening

We used treatment and screening controls as intervention. From figures ([5.7.7](#)) we observe that optimal control of the combination of treatment and screening helps to bring down the infectious as well as the carrier population which helps to eradicate the disease in the community.

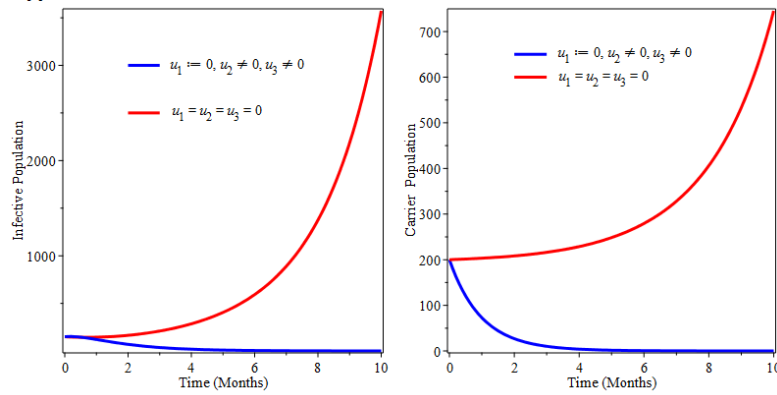


Figure 3.6.6: Simulations of optimal control with treatment and screening intervention.

3.6.7 Control with Prevention, Treatment and Screening

We implement all control the three controls interventions, that helps to minimize the objective function . From figure (3.6.7) we observe that the number of the infectious and carrier populations decrease at the specified time due to the intervention strategies. Therefore, applying this strategy helps to eradicate pneumonia disease in specified period of time.

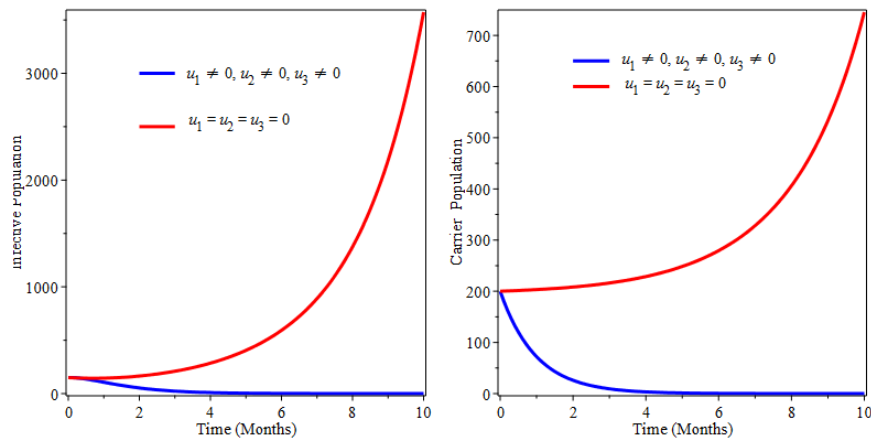


Figure 3.6.7: Simulations of optimal control with Prevention, Treatment and screening interventions.

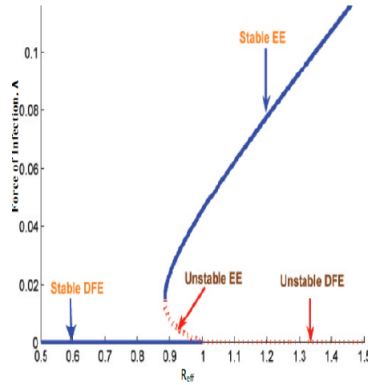


Figure 3.6.8: Backward bifurcation of the force of infection at equilibrium against the effective reproduction number R_{eff}

3.7 Cost-Effectiveness Analysis

Cost-effectiveness analysis used to rank the implemented strategies interims of their cost. Applying one intervention only might to be effective to eradicate the disease from the community. Therefore, we analzed strategies that used more than one intervention method. To achieve, this we used incremental cost-effectiveness ratio (ICER), stated by (Baba and Makinde, 2014);

$$''ICER = \frac{\text{Difference in costs between strategies}}{\text{Difference in health effects between strategies}}''$$

In table (5.8.1) we obtain the total number of infectious averted and total cost for the implemented strategies. The difference between the total infectious individuals without control and the total infectious individuals with control is used to obtain the total number of infectious averted. And also to find the total cost for the implemented strategies we used the cost function, which is $\frac{1}{2}w_1u_1^2$, $\frac{1}{2}w_2u_2^2$ and $\frac{1}{2}w_3u_3^2$ over time. We used the parameter values in table (5.7.1) and to apply ICER technique first we ordered the intervention strategies for pairwise comparison as in table (5.7.1) from A to D with increasing order of effectiveness.

Table 3.7.1: Number of infectious averted and total cost of each strategies

Strategies	Description	Total infectious averted	Total cost (USD)
A	Vaccination and Screening	101,417	5,906.1
B	Treatment and Screening	116,099	5,472.7
C	Prevention and Treatment	117,142	5,292
D	Prevention, Treatment and Screening	119,465	6,948.8

First we compared the cost effectiveness of strategy A and B.

$$ICER(A) = \frac{5,906.1}{101,417} = 0.058,$$

$$ICER(B) = \frac{5,472.7 - 5,906.1}{116,099 - 101,417} = -0.029.$$

From ICER (A) and ICER (B) we can see that strategy B saves 0.029 than strategy A. Therefore, we exclude strategy A, because it is a bit expensive continue to compare strategy B and C.

$$ICER(B) = \frac{5,472.7}{116,099} = 0.047,$$

$$ICER(C) = \frac{5,292 - 5,472.7}{117,142 - 116,099} = -0.0015.$$

Similarly, from ICER (B) and ICER (C) we can see that strategy C saves 0.0015 than strategy B. Therefore, we exclude strategy B, because it is a bit expensive and finally we compared strategy C and D.

$$ICER(C) = \frac{5,292}{117,142} = 0.045,$$

$$ICER(D) = \frac{6,948.8 - 5,292}{119,465 - 117,142} = 0.71.$$

From ICER (C) and ICER (D) we can see that strategy C saves 0.71 than strategy D. Therefore, we exclude strategy D, because it is a bit expensive. Therefore, we conclude that strategy C the cheapest of all compared strategies, that meant it is the most cost-effective for pneumonia disease control interventions strategies.

For further elaboration, figure 5.8.1 shows that applying only one intervention costs the least interims of price but we didnt consider this, due to the reason that a single intervention is not effective to eradicate the disease. And additionally we observe from the figure, applying all the three intervention at once is the most expensive of all the applied intervention strategies.

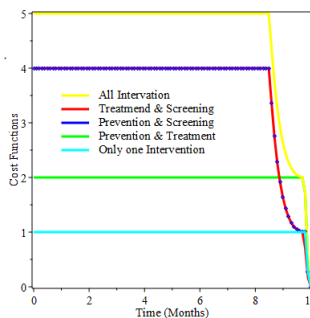


Figure 3.7.1: Cost Function of the intervention strategies for the period of 10 months

3.8 Discussions and Conclusions

In this chapter we described and proposed a pneumonia model, which is deterministic in its nature and also the population is assumed to be variable in size. Several qualitative properties of the model are presented including feasible region, positivity of the solution set, effective reproductive number, equilibria points and their stability. The fact that the DFE is locally asymptotically stable when $R_{eff} < 1$. The possibility of bifurcation of the model is also studied. From the basic model, an optimal control problem is formulated by incorporating three control variables; Prevention, treatment and screening. The Hamiltonian, adjoint variables, characterization of the controls and the optimality system are derived from the optimal control problem and also numerically simulated by considering single control at a time and then combination of two control at a time then lastly by applying all the three control variables. Several combinations of the control variables are compared to determine which combination is most cost effective in the fight against Pneumonia. From the pairwise result of the cost effectiveness analysis, the combination of prevention and treatment of pneumonia is observed to be the best cost effective strategy in terms of cost as well as health benefits. .

Chapter 4

Modelling Typhoid fever Disease dynamics

4.1 Introduction

According to (WHO,2000),”infectious diseases are those disease caused by viruses, bacteria, epi-phytes , parasites such as protozoans or worms that have a potential to spread in to the population easily”. Typhoid fever is one of a common infectious disease in human being, that caused by different species of Salmonella. The most common species of Salmonella that cause Typhoid fever are, *Salmonella paratyphi A, B, C* and *Salmonella paratyphi D* [WHO (2003)]. ” Most of the time Typhoid fever is caused by lack of sanitation in which the disease causing bacteria is transmitted by ingestion of contaminated food or water” WHO,2003. The bacteria is released from the infectious individuals or carriers and then contaminate food or drinking water as a consequence of unsatisfactory hygiene practices. Due to this Typhoid fever is a common disease in developing countries. The data taken from Ethiopia for that past seven years (2009-2015), in figure 4.1.1 indicate that in each year the disease is increasing in alarming rate. Mathematical models have a great benefits for describing the dynamics of infectious disease. Moreover, it plays a significant role in predicting suitable control strategies and analysing and ranking their cost-effectiveness, (for example see, Makinde and Okosun (2011), (2012),(2013) and (2014)). Very essential research results on the transmission dynamics of typhoid have been come out in the last decade, for instance see, Adetunde (2008) , Mushayabasa et al. (2013), Moffat et al.(2014), Steady et al.(2014), Adeboye et al.(2015) ,Andrew et al.(2015),

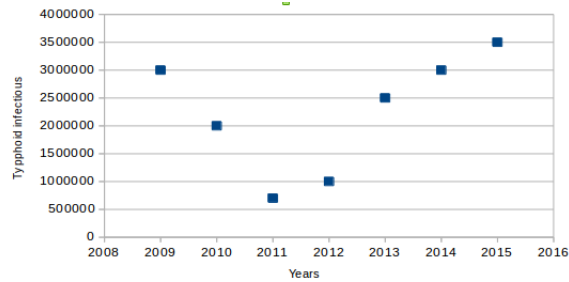


Figure 4.1.1: Reported cases of Typhoid in Ethiopia for the past seven years.

Muhammad et al.(2015) and Okaka et al.(2015) . All of the above studies reveal an important result for Typhoid fever dynamics by considering different countries situation. But we have identified that till now there is no study has been done to investigate the Typhoid fever dynamics with the application of optimal control methods and cost-effectiveness analysis of the applied control strategies.

In view of the above we developed a deterministic mathematical model to investigate the dynamics of Typhoid fever with optimal control strategies and also we investigated the cost-effectiveness of the implemented control strategies .

4.2 Model Description and Formulation

The model considers human population as well as bacteria population (B_c). The human population is divided in to four sub-classes. **Susceptible** (S) includes those individuals who are at risk for developing an infection from Typhoid fever disease. **Infected** (I) this class includes all individuals who are showing the symptom of the disease. **Carrier**(C) includes those individuals who are carrying the disease causing micro-organism but they didn't show disease symptom and they are not aware of as they are with bacteria causing Typhoid fever. **Recovered** (R) includes all individuals that have recovered from the disease and got temporary immunity. The Susceptible class is increased by birth or emigration and also from recovered class by losing temporary immunity with δ rate. Susceptible individuals will got Typhoid causing bacteria when they take foods or waters which is contaminated by Salmonella Bacteria. The force of infection of the model is, $\lambda = \frac{B_c v}{K+B_c}$, where, v is ingestion rate, k is the concentration of Salmonella bacteria in foods or waters and $\frac{B_c}{k+B_c}$ is the probability of individuals in consuming foods or drinks contaminated with Typhoid causing bacteria. After the susceptible got the Typhoid causing bacteria, they have probability of joining carrier with τ rate or being a member

of infective with $1 - \rho$ rate. The infected sub-class is increased from carrier sub-class by θ screening rate. Those individuals in the infected sub-class can get treatment and join recovered sub-class with a rate of β . The recovered sub-class also increase with individuals who came from carrier class by getting natural immunity with a rate of ϕ . In all human sub-classes, μ is the natural death rate of individuals, but in the infective class α is the disease causing death rate. The model assumed the bacteria population in contaminated foods and waters. Where carriers and infective can contribute to increase the number of bacteria population in foods and waters with out proper sanitation with a discharge rate of σ_1 and σ_2 respectively. We consider μ_b is the death rate of Salmonella bacteria and all the described parameters are non-negative.

The above model description is represented using diagrammatically in the figure 4.2.1

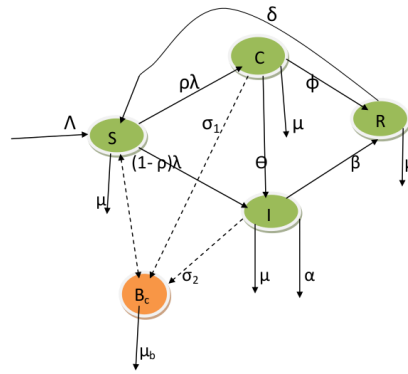


Figure 4.2.1: Flow diagram of the model

The above flow diagrams can be written in to five system of differential equations.

$$\begin{cases} \frac{dS}{dt} = \Lambda + \delta R - (\mu + \lambda)S \\ \frac{dC}{dt} = \rho\lambda S - (\sigma_1 + \theta + \mu + \phi)C \\ \frac{dI}{dt} = (1 - \rho)\lambda S + \theta C - (\sigma_2 + \beta + \mu + \alpha)I \\ \frac{dR}{dt} = \beta I + \phi C - (\mu + \delta)R \\ \frac{dB_c}{dt} = \sigma_1 C + \sigma_2 I - \mu_b B_c \end{cases} \quad (4.2.1)$$

Where, $\lambda = \frac{B_c v}{K + B_c}$, with initial condition $S(0) = S_0$, $I(0) = I_0$, $C(0) = C_0$, $R(0) = R_0$ and $B_c(0) = 0$.

4.3 The Model Analysis

4.3.1 Invariant Region

To obtain the invariant region in which the model solution to be bounded, we consider the total human population (N) and Where, $N = S + C + I + R$.

Then, differentiating N both sides with respect to t leads to;

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dC}{dt} + \frac{dI}{dt} + \frac{dR}{dt}. \quad (4.3.1)$$

By combining equation 4.2.1 and 4.3.1 we obtain can get;

$$\frac{dN}{dt} = \Lambda - \mu N - \alpha I. \quad (4.3.2)$$

In the absence of mortality due to Typhoid fever disease ($\alpha = 0$), equation (4.3.2) become

$$\frac{dN}{dt} \leq \Lambda - \mu N. \quad (4.3.3)$$

Integrating both side of equation (4.3.3),

$$\int \frac{dN}{\Lambda - \mu N} \leq \int dt. \quad (4.3.4)$$

$\Leftrightarrow \frac{-1}{\mu} \ln(\Lambda - \mu N) \leq t + c$ which simplifies in to

$$\Lambda - \mu N \geq A e^{-\mu t} \quad (4.3.5)$$

where A is constant. By applying the initial condition $N(0) = N_0$ in equation (4.3.5), we get $A = \Lambda - \mu N_0$ which up on substitution in equation(4.3.5) yields

$$\Lambda - \mu N \geq (\Lambda - \mu N_0) e^{-\mu t}. \quad (4.3.6)$$

Then by rearranging equation (4.3.6) we can get,

$$N \leq \frac{\Lambda}{\mu} - \left[\frac{\Lambda - \mu N_0}{\mu} \right] e^{-\mu t}. \quad (4.3.7)$$

As $t \rightarrow \infty$ in equation (4.3.7) the population size $N \rightarrow \frac{\Lambda}{\mu}$ which implies that $0 \leq N \leq \frac{\Lambda}{\mu}$. Thus the feasible solution set of the system equation of the model enter and remain in the region:

$$\Omega = \{(S, I, C, R) \in \mathfrak{R}_+^4 : N \leq \frac{\Lambda}{\mu}\} \quad (4.3.8)$$

Therefore, the basic model is well posed epidemiologically and mathematically. Hence, it is sufficient to study the dynamics of the basic model in Ω

4.3.2 Positivity of the solutions

we assumed that the initial condition of the model is non-negative, and now we also showed the solution of the model is also positive.

Theorem 4.3.1. *Let $\Omega = \{(S, C, I, R, B_c) \in \mathfrak{R}_+^5 : S_0 > 0, I_0 > 0, C_0 > 0, R_0 > 0, B_{c_0} > 0\}$ then the solution of $\{S, I, C, R, B_c\}$ are positive for $t \geq 0$.*

Proof:

From the system of differential equation 4.2.1 let us taking the first equation

$$\begin{aligned} \frac{dS}{dt} &= \Lambda + \delta R - (\mu + \lambda)S \\ \Rightarrow \frac{dS(t)}{dt} &\geq -(\mu + \lambda)S(t) \\ \Rightarrow \frac{dS(t)}{S(t)} &\geq -(\mu + \lambda)d(t) \\ \Rightarrow \int \frac{dS(t)}{S(t)} &\geq -\int (\mu + \lambda)d(t). \end{aligned}$$

Then by solving using separation of variable and applying condition

we obtained:

$$S(t) \geq S_0 e^{-(\mu+\lambda)t} \geq 0.$$

And also by taking the first equation of 4.2.1 that is

$$\begin{aligned} \frac{dC}{dt} &= \rho\lambda S - (\sigma_1 + \theta + \mu + \phi)C, \text{ it is true that} \\ \frac{dC}{dt} &\geq -(\sigma_1 + \theta + \mu + \phi)C. \\ \Rightarrow \frac{dC}{C} &\geq -(\sigma_1 + \theta + \mu + \phi)d(t) \\ \Rightarrow \int \frac{dC}{C} &\geq -\int (\sigma_1 + \theta + \mu + \phi)(t). \end{aligned}$$

Then by solving using separation of variable and applying initial

condition gives ;

$$\therefore C(t) \geq C_0 e^{-(\mu+\phi)t} \geq 0.$$

Similarly we took the third equation of 4.2.1 which is;

$$\frac{dI(t)}{dt} = (1 - \rho)\lambda S + \theta C - (\sigma_2 + \beta + \mu + \alpha)I \text{ it is true that}$$

$$\frac{dI}{dt} \geq -(\sigma_2 + \beta + \mu + \alpha)I$$

$$\Rightarrow \frac{dI}{I} \geq -(\sigma_2 + \beta + \mu + \alpha)d(t)$$

$\Rightarrow \int \frac{dI}{I} \geq -\int (\sigma_2 + \beta + \mu + \alpha)d(t)$. Then by solving using separation of variable and applying initial condition gives ;

$$\therefore I(t) \geq I_0 e^{-(\sigma_2 + \beta + \mu + \alpha)t} \geq 0.$$

when we took the fourth equation of 4.2.1 which is,

$$\frac{dR}{dt} = \beta I + \phi C - (\mu + \delta)R,$$

$$\Rightarrow \frac{dR}{dt} \geq -(\mu + \delta)R$$

$$\Rightarrow \frac{dR}{R} \geq -(\mu + \delta)d(t)$$

$$\Rightarrow \int \frac{dR}{R(t)} \geq -\int (\mu + \delta)d(t)$$

$$\therefore R(t) \geq R_0 e^{-(\mu + \delta)t} \geq 0.$$

Finally we took the fifth equation of 4.2.1

$$\frac{dB_c}{dt} = \sigma_1 C + \sigma_2 I - \mu_b B_c$$

$$\Rightarrow \frac{dB_c}{dt} \geq -\mu_b B_c$$

$$\Rightarrow \frac{dB_c}{B_c(t)} \geq -(\mu_b)d(t)$$

$$\Rightarrow \int \frac{dB_c}{B_c} \geq -\int (\mu_b)d(t)$$

$$\therefore B_c \geq B_{c_0} e^{-(\mu_b)t} \geq 0.$$

This completes the proof of the Theorem.

Therefore, the solution of the model is positive.

4.3.3 The disease free equilibrium (DFE)

The disease-free equilibrium is obtained by setting to zero all model variables involving infected and carrier individuals and solving for the non-infected and non-carrier state variables. Therefore, the disease free equilibrium $E_0 = (\frac{\Lambda}{\mu}, 0, 0, 0, 0)$

4.3.4 The Basic Reproductive Number (\mathcal{R}_0)

In this section we obtained the threshold parameter that governs the spread of a disease which is called the basic reproduction number is determined. To obtain the basic reproduction number we used the next generation matrix method so that it is the spectral radius of the next generation matrix (Driessche et al., 2002).

The model equations are re-written starting with newly infective classes:

$$\begin{aligned}\frac{dC}{dt} &= \rho\lambda S - (\sigma_1 + \theta + \mu + \phi)C \\ \frac{dI}{dt} &= (1 - \rho)\lambda S + \theta C - (\sigma_2 + \beta + \mu + \alpha)I \\ \frac{dB_c}{dt} &= \sigma_1 C + \sigma_2 I - \mu_b B_c\end{aligned}$$

Then by the principle of next generation matrix we can obtained

$$f = \begin{bmatrix} \rho \left(\frac{B_c v}{k + B_c} \right) S \\ (1 - \rho) \left(\frac{B_c v}{k + B_c} \right) S \end{bmatrix} \quad (4.3.9)$$

and

$$p = \begin{bmatrix} (\sigma_1 + \theta + \mu + \phi)C \\ (\sigma_2 + \beta + \mu + \alpha)I - \theta C \\ -(\sigma_1 C + \sigma_2 I - \mu_b B_c) \end{bmatrix} \quad (4.3.10)$$

The Jacobian matrix of f and v evaluated at DFE is given by F and P respectively such that;

$$F = \begin{bmatrix} 0 & 0 & \rho \frac{\Delta v}{\mu k} \\ 0 & 0 & (1 - \rho) \frac{\Delta v}{\mu k} \\ 0 & 0 & 0 \end{bmatrix}$$

$$V = \begin{bmatrix} (\sigma_1 + \theta + \mu + \phi) & 0 & 0 \\ -\theta & (\sigma_2 + \beta + \mu + \alpha) & 0 \\ -\delta_1 & -\delta_2 & \mu_b \end{bmatrix}$$

The Inverse of V is obtained and given by;

$$V^{-1} = \begin{bmatrix} \frac{1}{k_1} & 0 & 0 \\ \frac{\theta}{k_1 k_2} & \frac{1}{k_2} & 0 \\ \frac{\theta \sigma_2 + \sigma_1 k_2}{k_1 k_2 \mu_b} & \frac{\sigma_2}{k_2 \mu_b} & \frac{1}{\mu_b} \end{bmatrix}$$

where, $k_1 = (\sigma_1 + \theta + \mu + \phi)$ and $k_2 = (\sigma_2 + \beta + \mu + \alpha)$

Then,

$$FV^{-1} = \begin{bmatrix} \frac{\rho \Lambda v (\theta \sigma_2 + \sigma_1 k_2)}{\mu k k_1 k_2 \mu_b} & \frac{\rho \Lambda v \sigma_2}{\mu k k_2 \mu_b} & \frac{\rho \Lambda v}{v k \mu_b} \\ \frac{(1-\rho) \Lambda v (\theta \sigma_2 + \sigma_1 k_2)}{\mu k k_1 k_2 \mu_b} & \frac{(1-\rho) \Lambda v \sigma_2}{\mu k k_2 \mu_b} & \frac{(1-\rho) \Lambda v}{v k \mu_b} \\ 0 & 0 & 0 \end{bmatrix}$$

The characteristic equation of FV^{-1} is obtained as;

$$\lambda^2 \left(\rho \frac{\Lambda v (\theta \sigma_2 + \sigma_1 k_2)}{\mu k k_1 k_2 \mu_b} + (1-\rho) \frac{\Lambda v \sigma_2}{\mu k k_2 \mu_b} \right) = 0$$

The eigenvalues of FV^{-1} are;

$$\lambda_1 = \lambda_2 = 0$$

$$\lambda_3 = \rho \frac{\Lambda v (\theta \sigma_2 + \sigma_1 k_2)}{\mu k k_1 k_2 \mu_b} + (1-\rho) \frac{\Lambda v \sigma_2}{\mu k k_2 \mu_b}$$

The dominant eigenvalue of FV^{-1} is λ_3 .

Therefore, the basic reproduction number (\mathfrak{R}_0) after substituting k_1 and k_2 is given by

$$\mathfrak{R}_0 = \left[\rho \frac{(\theta \sigma_2 + \sigma_1 (\sigma_2 + \beta + \mu + \alpha))}{(\sigma_1 + \theta + \mu + \phi)} + (1-\rho) \sigma_2 \right] \frac{\Lambda v}{\mu k (\sigma_2 + \beta + \mu + \alpha) \mu_b} \quad (4.3.11)$$

4.3.5 Local stability of disease free equilibrium

Proposition: The disease free equilibrium point is locally asymptotically stable if $\mathfrak{R}_0 < 1$ and unstable if $\mathfrak{R}_0 > 1$

Proof

To proof this theorem first we obtain the Jacobian matrix of the system (4.2.1) at the disease free equilibrium E_0 as follow :

$$J_{E_0} = \begin{bmatrix} -\mu & 0 & 0 & \delta & \frac{v\Lambda}{k\mu} \\ 0 & -(\sigma_1 + \theta + \mu + \phi) & 0 & 0 & \frac{\rho v\Lambda}{\mu k} \\ 0 & \theta & -(\sigma_2 + \beta + \mu + \alpha) & 0 & \frac{(1-\rho)v\Lambda}{\mu k} \\ 0 & \phi & \beta & -(\mu + \delta) & 0 \\ 0 & \sigma_1 & \sigma_2 & 0 & -\mu_b \end{bmatrix} \quad (4.3.12)$$

From the Jacobian matrix of equation (4.3.12) we obtained a characteristic polynomial:

$$(-\lambda - \mu)(-\lambda - (\mu + \delta))(\lambda^3 + L_1\lambda^2 + L_2\lambda + L_3) = 0 \quad (4.3.13)$$

Where, $L_1 = \sigma_2 + \beta + 2\mu + \alpha + \sigma_1 + \phi + \theta + \mu_b$,

$L_2 = \mu_b(\sigma_2 + \beta + 2\mu + \alpha + \sigma_1 + \phi + \theta) + (\sigma_2 + \beta + \mu + \alpha)(\sigma_1 + \mu + \phi + \theta) - (\rho\sigma_1 + (1 - \rho)\sigma_2)\frac{v\Lambda}{\mu k}$,

$L_3 = \mu_b(\sigma_2 + \beta + \mu + \alpha)(\sigma_1 + \mu + \phi + \theta)(1 - \mathfrak{R}_0)$.

From equation 4.3.13 clearly, we see that:

$-\lambda - \mu = 0$, or $-\lambda - (\mu + \delta) = 0$, or $\lambda^3 + L_1\lambda^2 + L_2\lambda + L_3 = 0$.

$\implies \lambda_1 = -\mu < 0, \lambda_2 = -(\mu + \delta) < 0$.

For the last expression, that is,

$$\lambda^3 + L_1\lambda^2 + L_2\lambda + L_3 = 0, \quad (4.3.14)$$

we applied Routh-Hurwitz criteria. By the principle of Routh-Hurwitz criteria, equation 4.3.14 have strictly negative real root if and only if

$$\mathfrak{R}_0 < 1.$$

Therefore, DFE to be locally asymptotically stable if and only if $\mathfrak{R}_0 < 1$.

4.3.6 Global stability of DFE

Theorem 4.3.2. *The disease free equilibrium is globally asymptotically stable in the feasible region Ω if $\mathfrak{R}_0 < 1$.*

Proof: To prove this theorem, we first developed a Lyapunov function, technically.

$$L = \left[\frac{\theta\sigma_2 + \sigma_1 k_2}{k_1} \right] C + \sigma_2 I + k_2 \beta_c$$

Then by differentiating L both sides leads to,

$$\frac{dL}{dt} = \left[\frac{\theta\sigma_2 + \sigma_1 k_2}{k_1} \right] \frac{dC}{dt} + \sigma_2 \frac{dI}{dt} + k_2 \frac{d\beta_c}{dt}. \quad (4.3.15)$$

Combination of equation (4.2.1) and (4.3.15), result,

$$\frac{dL}{dt} = \left[\frac{\theta\sigma_2 + \sigma_1 k_2}{k_1} \right] \rho \lambda S - (\sigma_1 + \theta + \mu + \phi) C + \sigma_2 ((1 - \rho) \lambda S + \theta C - (\sigma_2 + \beta + \mu + \alpha) I) + k_2 (\sigma_1 C + \sigma_2 I - \mu_b B_c). \quad (4.3.16)$$

By collecting like terms of equation (4.3.16),

$$\frac{dL}{dt} = \left[\rho \frac{\theta\sigma_2 + \sigma_1 k_2}{k_1} + (1 - \rho) \sigma_2 \right] \lambda S + (\theta\sigma_2 - \theta\sigma_2 - \sigma_1 k_2) C - \sigma_2 k_2 I + k_2 (\sigma_1 C + \sigma_2 I - \mu_b B_c). \quad (4.3.17)$$

Equation (4.3.17) can be simplified as;

$$\frac{dL}{dt} = \left[\rho \frac{\theta\sigma_2 + \sigma_1 k_2}{k_1} + (1 - \rho) \sigma_2 \right] \lambda S - k_2 \mu_b B_c. \quad (4.3.18)$$

Equation (4.3.18) can be written as interims of \mathfrak{R}_0 ,

$$\frac{dL}{dt} = (\mathfrak{R}_0 \mu_b k_2 \frac{\mu k}{\Lambda \nu}) \lambda S - k_2 \mu_b B_c. \quad (4.3.19)$$

At $S = S_0 = \frac{\Lambda}{\mu}$, equation (4.3.19) become;

$$\frac{dL}{dt} \leq (\mathfrak{R}_0 - 1) k_2 \mu_b B_c. \quad (4.3.20)$$

So $\frac{dL}{dt} \leq 0$ if $\mathfrak{R}_0 \leq 1$. Furthermore,

$$\frac{dL}{dt} = 0 \Leftrightarrow B_c = 0 \text{ which leads to } C = I = 0 \text{ or } \mathfrak{R}_0 = 1.$$

Hence, L is Lyapunov function on Ω and the largest compact invariant set in $\{(S, C, I, R, B_c) \in \Omega, \frac{dL}{dt} = 0\}$ is the singleton $(S_0, 0, 0, 0, 0)$.

Therefore by Lasalles's invariance principle (LaSalle, 1976), every solution to equations of the model (4.2.1) with initial conditions in Ω approaches the disease free equilibrium at t (time) tends to infinity

($t \rightarrow \infty$) whenever $\mathfrak{R}_0 \leq 1$. Hence The disease free equilibrium is globally asymptotically stable.

4.3.7 The endemic equilibrium

The endemic equilibrium is denoted by $E^* = (S^*, C^*, I^*, R^*, B_c^*)$ and it occur when the disease persist in the community. To obtain it we equate all the model equations (4.2.1) to zero. Then we obtain :

$$S^* = \frac{\Lambda(\sigma_2 + \mu + \alpha + \beta)(\sigma_1 + \mu + \theta + \phi)(\mu + \delta)}{(\mu + \lambda^*) - \beta\lambda^*\delta((1 - \rho)(\sigma_1 + \mu + \theta + \phi) + \rho\theta) - \delta\phi\rho\lambda^*(\sigma_2 + \mu + \beta + \alpha)}$$

$$C^* = \frac{\rho\lambda^*\Lambda(\sigma_2 + \mu + \alpha + \beta)(\mu + \delta)}{(\mu + \lambda^*) - \beta\lambda^*\delta((1 - \rho)(\sigma_1 + \mu + \theta + \phi) + \rho\theta) - \delta\phi\rho\lambda^*(\sigma_2 + \mu + \beta + \alpha)}$$

$$I^* = \frac{(\mathfrak{R}_0 k(\sigma_1 + \mu + \theta + \phi)(\sigma_2 + \mu + \beta + \alpha)\mu\mu_b - \sigma_1\rho\Lambda\nu(\sigma_2 + \mu + \beta + \alpha))(\mu + \delta)}{\mu k\sigma_2 + \nu\sigma_2 - \beta\delta\mathfrak{R}_0 k(\sigma_1 + \mu + \theta + \phi)(\sigma_2 + \mu + \beta + \alpha)\mu\mu_b + \beta\delta\sigma_1(\sigma_2 + \mu + \beta + \alpha)\Lambda\nu - \delta\sigma_2\phi\rho\nu(\sigma_2 + \mu + \beta + \alpha)}$$

$$R^* = \frac{\beta I^* + \phi C^*}{\mu + \delta}$$

$$B_c^* = \frac{\lambda^*\Lambda(\mu + \lambda^*)[\sigma_1\rho(\sigma_2 + \mu + \alpha + \beta) + \sigma_2(1 - \rho)(\sigma_1 + \mu + \theta + \phi) + \rho\theta]}{\mu_b[\mu + \lambda^*) - \beta\lambda^*\delta((1 - \rho)(\sigma_1 + \mu + \theta + \phi) + \rho\theta) - \delta\phi\rho\lambda^*(\sigma_2 + \mu + \beta + \alpha)}$$

When we substitute the expression for B_c^* in to the force of infection that is, $\lambda^* = \frac{B_c^*\nu}{k+B_c^*}$ we obtained a characteristic polynomial of force of infection;

$$p(\lambda^*) = D_1\lambda^{*2} + D_2\lambda^* = 0,$$

where $D_1 = 1 + \mathfrak{R}_0(\sigma_2 + \mu + \alpha + \beta)(\sigma_1 + \mu + \theta + \phi)(\mu + \delta)\mu\mu_b k + (\beta\delta((1 - \rho)(\sigma_1 + \mu + \theta + \phi) + \rho\theta) + \delta\phi\rho(\sigma_2 + \mu + \alpha + \beta))$,

$$D_2 = (1 - \mathfrak{R}_0)(\mu + \delta)\mu.$$

Clearly, $D_1 > 0$ and $D_2 \geq 0$. Whenever $\mathfrak{R}_0 < 1$, $\lambda^* = \frac{-D_1}{D_2} \leq 0$. From this, we see that for $\mathfrak{R}_0 < 1$, there is no endemic equilibrium for this model.

Therefore, this condition shows that it is not possible for backward bifurcation in the model if $\mathfrak{R}_0 < 1$.

When we plot I^* over \mathfrak{R}_0 by using the expression for I^* and estimated parameters in table (5.7.1) we got a forward bifurcation figure (4.3.1).

Lemma 4.3.3. *A unique endemic equilibrium point E^* exist and is positive if $\mathfrak{R}_0 > 1$.*

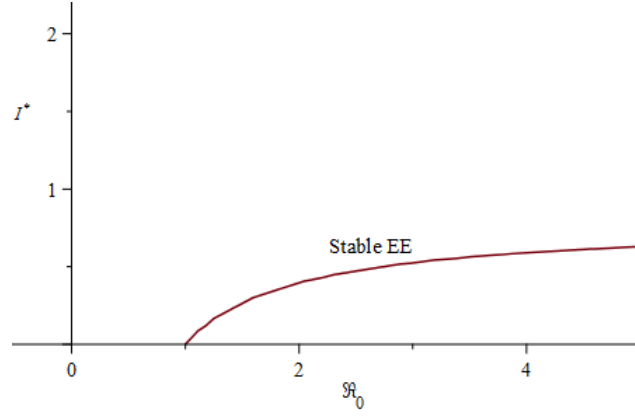


Figure 4.3.1: Forward bifurcation of Typhoid fever model.

The global stability of endemic equilibrium

Theorem 4.3.4. *If $\mathcal{R}_0 > 1$, the endemic equilibrium E^* of the model (3.2.1) is globally asymptotically stable.*

Proof. First we define a Lyapunov function L Such that;

$$L = \left(S - S^* + S^* \ln \frac{S^*}{S} \right) + \left(I - I^* + I^* \ln \frac{I^*}{I} \right) + \left(C - C^* + C^* \ln \frac{C^*}{C} \right) + \left(R - R^* + R^* \ln \frac{R^*}{R} \right) + \left(B_c - B_c^* + B_c^* \ln \frac{B_c^*}{B_c} \right). \quad (4.3.21)$$

The derivative of equation 4.3.21 with respect to t we got;

$$\frac{dL}{dt} = \left(\frac{S - S^*}{S} \right) \frac{dS}{dt} + \left(\frac{I - I^*}{I} \right) \frac{dI}{dt} + \left(\frac{C - C^*}{C} \right) \frac{dC}{dt} + \left(\frac{R - R^*}{R} \right) \frac{dR}{dt} + \left(\frac{B_c - B_c^*}{B_c} \right) \frac{dB_c}{dt}. \quad (4.3.22)$$

By replacing $\frac{dS}{dt}$, $\frac{dC}{dt}$, $\frac{dI}{dt}$, $\frac{dR}{dt}$ and $\frac{dB_c}{dt}$ in equation 4.3.22, from their respective expressions in equation 3.2.1 and then after collecting positive terms together and negative terms also together leads to,

$$\frac{dL}{dt} = H - K.$$

where,

$$H = \Lambda + \delta R + (1 - \rho)\lambda S + \rho\lambda S + \beta I + \theta C + \phi C + Q + \sigma_1 C + \sigma_2 I + \frac{\delta R^* S^*}{S} + \frac{(1 - \rho)\lambda S^* I^*}{I} + \frac{\rho\lambda S^* C^*}{C} +$$

$$\begin{aligned} & \frac{\theta I^* C^*}{I} + \frac{\beta I^* R^*}{R} + \frac{\phi C^* R^*}{R} + \frac{\sigma_1 C^* B_c^*}{B_c} + \frac{\sigma_2 I^* B_c^*}{B_c} \\ K = & \delta R^* + (1 - \rho) \lambda S^* + \rho \lambda S^* + \theta C^* + \beta I^* + \phi C^* + \sigma_1 C^* + \sigma_2 I^* + \frac{\Lambda S^*}{S} + \frac{\delta R S^*}{S} + \frac{(\mu + \lambda)(S - S^*)^2}{S} + \\ & \frac{(1 - \rho) \lambda S I^*}{I} + \frac{(\sigma_2 + \beta + \mu + \alpha)(I - I^*)^2}{I} + \frac{\rho \lambda S C^*}{c} + \frac{\theta I^* C}{I} + \frac{(\sigma_1 + \theta + \mu + \phi)(C - C^*)^2}{C} + \frac{\beta I R^*}{R} + \frac{\theta C R^*}{R} + \frac{(\mu + \delta)(R - R^*)^2}{R} + \frac{Q B_c^*}{B_c} + \\ & \frac{\sigma_1 C B_c^*}{B_c} + \frac{\sigma_2 I B_c^*}{B_c} + \frac{\mu_b (B_c - B_c^*)^2}{B_c} \end{aligned}$$

Thus if $H < K$, then $\frac{dL}{dt} \leq 0$, and $\frac{dL}{dt} = 0$ if and only if $S = S^*, C = C^*, I = I^*, R = R^*, B_c = B_c^*$.

From this, we see that $E^* = (S^*, C^*, I^*, R^*, B_c^*)$ is the largest compact invariant singleton set in $\{(S^*, C^*, I^*, R^*, B_c^*) \in \Omega : \frac{dL}{dt} = 0\}$. Therefore, by the principle of Lasalle, the endemic equilibrium (E^*), is globally asymptotically stable in the invariant region if $H < K$. \square

4.4 Sensitivity Analysis of Model parameters

Since exact values of parameters of epidemic models are not often known, it is proper to examine the robustness of the model to changes in parameter values. This will help to determine parameters that most influence the dynamics of the model. Sensitivity analysis is helpful for experimental design, data assimilation and reduction of complex non-linear models. Values for sensitivity indexes indicate which parameters should be targeted most for interventions purposes. A very high sensitivity index indicates that more care should be taken in the estimation of the associated parameter. The normalized forward sensitivity index is often used to determine the parameters that have higher influence on the basic reproduction number, \mathfrak{R}_0 . Thus, we have $\Delta_v^{\mathfrak{R}_0} = \frac{\partial \mathfrak{R}_0}{\partial v} \frac{v}{\mathfrak{R}_0} = 1$ and since the expressions for the sensitivity indexes of the remaining parameters are quite complex, we evaluate them (using parameter values in Table 5.7.1) and present them in Table ??.

Table 4.4.1: Sensitivity indices table

Parameter symbol	Sensitivity indices
v	1
k	0.999
σ_1	0.26
σ_2	0.03
ρ	0.00506
μ	-1.028
μ_b	-1
α	-0.0592
θ	0.009
β	-0.00017
ϕ	-0.000089

4.4.1 Interpretation of Sensitivity Indices

The sensitivity indices of the basic reproductive number with respect to main parameters are arranged orderly in table (5.5.1). Those parameters that have positive indices (v, k, σ_1, σ_2 and ρ) shows that as they have great impact in expanding the disease in the community if their values are increasing. Due to the reason that the basic reproduction number increases as their values increase, mean that the average number of secondary case infection increases in the community. And also those parameters in which their sensitivity indices are negative ($\mu, \mu_b, \alpha, \theta, \beta$ and ϕ) have an influence of minimizing the burden of the disease in the community is their values increase while the others are left constant. This is also as their values increase, the basic reproduction number decrease, which leads to minimizing the endemicity of the disease in the community.

4.5 Extension of the Model into an Optimal Control

In this section, the basic model of Typhoid fever is generalized by incorporating three control interventions. The controls are prevention (u_1) (sanitation and proper hygiene controls), treatment (u_2) (treating individuals who developed symptoms of the disease) and screening of carriers (u_3 which helps them to get proper treatment if they are aware of their status).

After incorporating the controls in to the basic model of Typhoid fever, we get the following state

equations:

$$\begin{cases} \frac{dS}{dt} = \Lambda + \delta R - (1 - u_1)\lambda S - \mu S \\ \frac{dC}{dt} = (1 - u_1)\rho\lambda S - (\theta + u_3)C - (\sigma_1 + \phi + \mu)C \\ \frac{dI}{dt} = (1 - u_1)(1 - \rho)\lambda S + (1 - u_3)\theta C - (u_2 + \beta)I - (\sigma_2 + \mu + \alpha)I \\ \frac{dR}{dt} = (u_2 + \beta)I + \phi C - (\mu + \delta)R \\ \frac{dB_c}{dt} = \sigma_1 C + \sigma_2 I - \mu_b B_c, \end{cases} \quad (4.5.1)$$

where $\lambda = \frac{B_c v}{k + B_c}$.

To study the optimal levels of the controls the control set U is Lebesgue measurable and it is defined as : The control set (U) defined as: $U = \{(u_1(t), u_2(t), u_3(t)) : 0 \leq u_1 < 1, 0 \leq u_2 < 1, 0 \leq u_3 < 1, 0 \leq t \leq T\}$ is Lebesgue measurable. Our main objective is to obtain the optimal levels of the controls and associated state variables that optimize the objective function. The form of the objective function is taken from (Baba and Makinde, 2014) and given by:

$$J = \min_{u_1, u_2, u_3} \int_0^{t_f} (b_1 I + b_2 c + \frac{1}{2} \sum_{i=1}^3 w_i u_i^2) dt \quad (4.5.2)$$

The coefficients associated with state variables (b_1 and b_2) and with controls (w_i) are positive. Due to the fact that, cost is not linear in its condition we make the cost expression ($\frac{1}{2} w_i u_i^2$) quadratic.

As objective function (5.6.2) shows we aimed to minimize the number of carriers, infectives and costs. That is we want to get an optimal triple (u_1^*, u_2^*, u_3^*) such that:

$J(u_1^*, u_2^*, u_3^*) = \min\{J(u_1, u_2, u_3) / u_i \in U\}$, where $U = \{(u_1, u_2, u_3) / \text{each } u_i \text{ is measurable with } 0 \leq u_i < 1 \text{ for } 0 \leq t \leq t_f\}$ is the set of acceptable controls.

4.5.1 Existence of an optimal control

To show an existence of optimal control it can be used an approach of (Fleming and Rishel, 1982) . We have already justify that the solution of the basic model of Typhoid fever is bounded, so this result can be used to prove the existence of optimal control. For detail proof, [see (Fleming and Rishel, 1982), Theorem 4.1, p68-69].

4.5.2 The Hamiltonian and Optimality System

To obtain the Hamiltonian (H) we follow the approach of (Pontryagin et al., 1986) such that:

$$H = \frac{dJ}{dt} + \lambda_1 \frac{dS}{dt} + \lambda_2 \frac{dC}{dt} + \lambda_3 \frac{dI}{dt} + \lambda_4 \frac{dR}{dt} + \lambda_5 \frac{dB_c}{dt}.$$

That is,

$$H(S, C, I, R, B_c, t) = L(C, I, u_1, u_2, u_3, t) + \lambda_1 \frac{dS}{dt} + \lambda_2 \frac{dC}{dt} + \lambda_3 \frac{dI}{dt} + \lambda_4 \frac{dR}{dt} + \lambda_5 \frac{dB_c}{dt}, \quad (4.5.3)$$

where $L(C, I, u_1, u_2, u_3, t) = b_1 C + b_2 I + \frac{1}{2} \sum_{i=1}^3 w_i u_i^2$,

$\lambda_1, \lambda_2, \lambda_3, \lambda_4$ and λ_5 are the adjoint variable functions. To obtain the adjoint variables we followed the classical result of (Pontryagin et al., 1986).

Theorem 4.5.1. *There exists an optimal control set u_1, u_2, u_3 and corresponding solution, S, C, I, R and B_c , that minimizes $J(u_1, u_2, u_3)$ over U . Furthermore, there exists adjoint functions, $\lambda_1, \dots, \lambda_5$ such that,*

$$\begin{cases} \frac{d\lambda_1}{dt} = -\lambda_1 \left(-\mu - \frac{B_c v (1-u_1)}{k+B_c} \right) - \frac{\lambda_2 (1-\rho)(1-u_1) B_c v}{k+B_c} - \frac{\lambda_3 (1-u_1) \rho v B_c}{k+B_c} \\ \frac{d\lambda_2}{dt} = -b_1 - \lambda_2 (-\theta - u_3) - \lambda_3 (1-u_3) \theta - \lambda_4 \phi - \lambda_5 \sigma_1 \\ \frac{d\lambda_3}{dt} = -b_2 - \lambda_3 (-u_2 - \beta - k_2) - \lambda_4 (u_2 + \beta) - \lambda_5 \sigma_2 \\ \frac{d\lambda_4}{dt} = -\lambda_1 \delta - \lambda_4 (-\mu - \delta) \\ \frac{d\lambda_5}{dt} = -\frac{\lambda_1 B_c v (1-u_1) s}{(k+B_c)^2} - \lambda_2 \left(\frac{(1-u_1) \rho v S}{k+B_c} - \frac{(1-u_1) \rho v B - c S}{(k+B_c)^2} \right) - \lambda_3 \left(\frac{(1-\rho)(1-u_1) v S}{k+B_c} - \frac{(1-\rho)(1-u_1) B_c v S}{(k+B_c)^2} \right) + \lambda_5 \mu_b, \end{cases} \quad (4.5.4)$$

With transversality conditions,

$$\lambda_i(t_f) = 0, i = 1, \dots, 5.$$

and the characterized control set of (u_1^*, u_2^*, u_3^*) is:

$$u_1^*(t) = \max\{0, \min(1, \frac{S(\lambda_2 \rho v B_c - B_c \rho v \lambda_3 + B_c v \lambda_3 - \lambda_1 B_c v)}{(k+B_c) w_1})\},$$

$$u_2^*(t) = \max\{0, \min(1, \frac{I(\lambda_3 - \lambda_4)}{w_2})\},$$

$$u_3^*(t) = \max\left\{0, \min\left(1, \frac{C(\lambda_3\theta + \lambda_2)}{w_3}\right)\right\}.$$

Proof:

To prove this theorem we used the classical result of (Pontryagin et al., 1986). Accordingly, to get the system of adjoint variables we differentiate the Hamiltonian (4.5.3) with respect to each states as follow:

$$\frac{d\lambda_1}{dt} = -\frac{dH}{dS} = -\lambda_1 \left(-\mu - \frac{B_c v(1-u_1)}{k+B_c} \right) - \frac{\lambda_2(1-\rho)(1-u_1)B_c v}{k+B_c} - \frac{\lambda_3(1-u_1)\rho v B_c}{k+B_c},$$

$$\frac{d\lambda_2}{dt} = -\frac{dH}{dI} = -b_1 - \lambda_2(-\theta - u_3) - \lambda_3(1-u_3)\theta - \lambda_4\phi - \lambda_5\sigma_1,$$

$$\begin{aligned} \frac{d\lambda_3}{dt} &= -\frac{dH}{dC} = -b_2 - \lambda_3(-u_2 - \beta - k_2) - \lambda_4(u_2 + \beta) - \lambda_5\sigma_2, \\ \frac{d\lambda_4}{dt} &= -\frac{\lambda_1 B_c v(1-u_1)s}{(k+B_c)^2} - \lambda_2 \left(\frac{(1-u_1)\rho v S}{k+B_c} - \frac{(1-u_1)\rho v B - cS}{(k+B_c)^2} \right) - \lambda_3 \left(\frac{(1-\rho)(1-u_1)vS}{k+B_c} - \frac{(1-\rho)(1-u_1)B_c v S}{(k+B_c)^2} \right) + \lambda_5 \mu_b. \end{aligned}$$

And also for characterization of the optimal control we used the following partial differential equation:

$$\frac{\partial H}{\partial u_i} = 0 \text{ at } u_i = u_i^* \text{ where } i = 1, 2, 3.$$

For $i = 1$

$$\begin{aligned} \frac{\partial H}{\partial u_1} &= 0 \quad \text{at } u_1^*, \\ \Rightarrow u_1^* &= \frac{S(\lambda_2 \rho v B_c - B_c \rho v \lambda_3 + B_c v \lambda_3 - \lambda_1 B_c v)}{(k+B_c)w_1}. \end{aligned}$$

For $i = 2$

$$\begin{aligned} \frac{\partial H}{\partial u_2} &= 0 \quad \text{at } u_2^*, \\ \Rightarrow u_2^* &= \frac{I(\lambda_3 - \lambda_4)}{w_2}. \end{aligned}$$

For $i = 3$

$$\begin{aligned} \frac{\partial H}{\partial u_3} &= 0 \quad \text{at } u_3^*, \\ \Rightarrow u_3^* &= \frac{C(\lambda_3\theta + \lambda_2)}{w_3}. \end{aligned}$$

Since $0 < u_i^* < 1$, we can write in a compact notation:

$$u_1^* = \max\left\{0, \min\left(1, \frac{S(\lambda_2 \rho v B_c - B_c \rho v \lambda_3 + B_c v \lambda_3 - \lambda_1 B_c v)}{(k+B_c)w_1}\right)\right\},$$

$$u_2^* = \max\{0, \min(1, \frac{I(\lambda_3 - \lambda_4)}{w_2})\},$$

$$u_3^* = \max\{0, \min(1, \frac{C(\lambda_3\theta + \lambda_2)}{w_3})\}.$$

4.5.3 The optimality system

It is a system of states (5.6.4) and adjoint (5.6.3) incorporating with the characterization of the optimal control and initial and transversality conditions . Then we have the following optimality system:

$$\left\{ \begin{array}{l} \frac{dS}{dt} = \Lambda + \delta R - (1 - u_1^*)\lambda S - \mu S \\ \frac{dC}{dt} = (1 - u_1^*)\rho\lambda S - (\theta + u_3^*)C - (\sigma_1 + \phi + \mu)C \\ \frac{dI}{dt} = (1 - u_1^*)(1 - \rho)\lambda S + (1 - u_3^*)\theta C - (u_2^* + \beta)I - (\sigma_2 + \mu + \alpha)I \\ \frac{dR}{dt} = (u_2^* + \beta)I + \phi C - (\mu + \delta)R \\ \frac{dB_c}{dt} = Q + \sigma_1 C + \sigma_2 I - \mu_b B_c, \\ \frac{d\lambda_1}{dt} = -\lambda_1 \left(-\mu - \frac{B_c v (1 - u_1^*)}{k + B_c} \right) - \frac{\lambda_2 (1 - \rho)(1 - u_1^*) B_c v}{k + B_c} - \frac{\lambda_3 (1 - u_1^*) \rho v B_c}{k + B_c} \\ \frac{d\lambda_2}{dt} = -b_1 - \lambda_2 (-\theta - u_3^*) - \lambda_3 (1 - u_3^*) \theta - \lambda_4 \phi - \lambda_5 \sigma_1 \\ \frac{d\lambda_3}{dt} = -b_2 - \lambda_3 (-u_2^* - \beta - (\sigma_2 + \mu + \alpha)) - \lambda_4 (u_2^* + \beta) - \lambda_5 \sigma_2 \\ \frac{d\lambda_4}{dt} = -\lambda_1 \delta - \lambda_4 (-\mu - \delta) \\ \frac{d\lambda_5}{dt} = -\frac{\lambda_1 B_c v (1 - u_1^*) S}{(k + B_c)^2} - \lambda_2 \left(\frac{(1 - u_1^*) \rho v S}{k + B_c} - \frac{(1 - u_1^*) \rho v B - c S}{(k + B_c)^2} \right) - \lambda_3 \left(\frac{(1 - \rho)(1 - u_1^*) v S}{k + B_c} - \frac{(1 - \rho)(1 - u_1^*) B_c v S}{(k + B_c)^2} \right) + \lambda_5 \mu_b, \end{array} \right.$$

$$\lambda_i(t_f) = 0, \quad i = 1, 2, 3, 4, 5 \quad S(0) = S_0, \quad I(0) = I_0, \quad C(0) = C_0, \quad R(0) = R_0, \quad B_c(0) = B_{c_0}.$$

4.5.4 Uniqueness of the Optimality System

Since the state and adjoint variables are bounded and also the obtained ordinary differential equations have Lipschitz in their structure, it is possible to show the uniqueness, hence the following theorem.

Theorem 4.5.2. *For $t \in [0, t_f]$, the bounded solutions to the optimality system are unique.*

Proof:

See (Fister et al., 1998) for the proof of this theorem.

4.6 Numerical Simulations

We perform numerical simulation of the optimality system by using the parameter values given in table (5.7.1).

Table 4.6.1: Parameter Values for Typhoid fever Model

Parameter symbol	Parameter description	Value	Source
ν	Salmonella ingestion rate	0.9	Assumed
k	Concentration of Salmonella bacteria in foods and water	50000	Gosh <i>et al</i> ,2006
μ	Human being natural death rate	0.0247	assumed
α	Typhoid induced death rate	0.052	estimated
β	Treatment rate of infectious	0.002	Estimated
σ_1	Discharge rate of Salmonella from carriers	0.9	Gosh <i>et al</i> ,2006
σ_2	Discharge rate of Salmonella from infective	0.8	Assumed
δ	Removal rate from Recovered sub-class to Susceptible sub-class	0.000904	Adetunde,2008
θ	Screening rate of carriers	0.2	Assumed
ϕ	Removal of carriers by natural immunity	0.0003	assumed
ρ	Probability of susceptible joining carrier state	0.3	Assumed
μ_b	Natural/drug induced death rate of bacteria	0.001	Gosh <i>et al</i> ,2006
Λ	Recruitment of human being	100	Assumed

To obtain optimal solution we apply iterative technique. By using an advantage of the initial conditions of the state system we used a forward fourth-order Runge-kutta method to solve it and also due to the final conditions for the adjoint system we used a backward fourth-order Runge-Kutta method to solve it. To solve the state initial guess of controls is used and the solution of the state system and the initial guess helps to solve the adjoint system. Each controls continue to be updated by combining its previous and characterization values. To repeat the solutions the updated controls are used. This situation continues until two consecutive iterations are close enough (Lenhart and Workman, 2007).

To examine the impact of each control on eradication of Typhoid fever disease we used the following strategy:

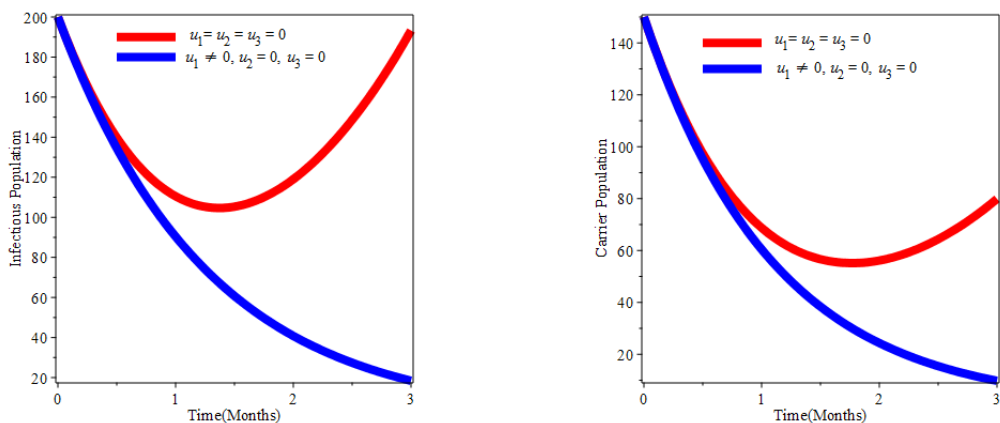
- (i). Applying prevention only (u_1) as intervention,
- (ii). Applying treatment only (u_2) as intervention,
- (iii). Applying screening only (u_3) as intervention,
- (iv). Implementing prevention (u_1) and treatment (u_2) intervention,
- (v). Implementing prevention (u_1) and screening (u_3) intervention,
- (vi). Implementing treatment (u_2) and screening (u_3) intervention,
- (vii). Using all the three controls, prevention effort u_1 treatment effort u_2 and also screening u_3 .

Initial values that we used for Simulation of the optimal control are $S(0) = 1000, C(0) = 150, I(0) =$

$200, R(0) = 300$ and $B_c(0) = 200$ and also coefficients of the state and controls that we used are $b_1 = 25, b_2 = 25, w_1 = 4, w_2 = 3$ and $w_3 = 5$.

4.6.1 Control with Prevention only

We simulated the Optimality system by incorporating prevention intervention only. Figure 4.6.1 a and b shows the decrease of infectious and carrier population in the specified time. We conclude that prevention that include sanitation and other technique is a vital method to reduce Typhoid fever infection. The number of individuals who have been with Typhoid fever disease before implementation of prevention control has gone down due to disease induced and natural deaths. Therefore, applying optimized prevention control can eradicate Typhoid fever disease in the community.



(a) Prevention impact on infectious population (b) Prevention impact on carrier population

Figure 4.6.1: Simulations of Typhoid fever model with prevention control only.

4.6.2 Control with Treatment

We applied treatment only as intervention that is treating individuals who develop disease symptom. From figure 5.7.1 a and b, we understand that the number of infectious and carriers decreased when treatment intervention is applied. The number of infectious and carriers didn't goes to zero over the period of implementation of this intervention strategy. The reason is that due to lack of prevention susceptible individuals still get infected. Therefore, we conclude that, applying optimized treatment only as control intervention decrease the burden of the disease but it can't eradicate Typhoid fever disease in the community.

4.6.3 Control With Screening

As we know screening helps carriers to identify their status as they are leaving with the bacteria or not. Therefore, figure 4.6.3 a and b shows that, the infectious and carrier population goes down by screening effort but their number can't be zero. New infection always there in the community due to the reason that, the disease are not prevented and individuals who develop the symptom of the disease are not getting treatment. Therefore, control with screening only reduce the burden in some extent but it is not helpful to eradicate Typhoid fever disease totally from the community.

4.6.4 Control with Prevention and Treatment

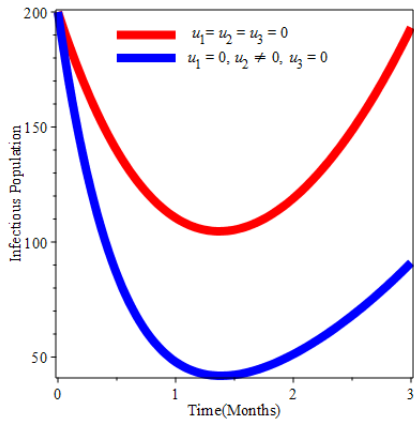
We simulate the model using a combination of prevention and treatment as intervention strategy for control of Typhoid fever disease in the community. Figure 4.6.4 a and b clearly show that the infectious carrier population has gone to zero at the end of the implementation period. Therefore, we conclude that, this strategies is effective in eradicating the disease from the community in a specified period of time.

4.6.5 Control with Prevention and Screening

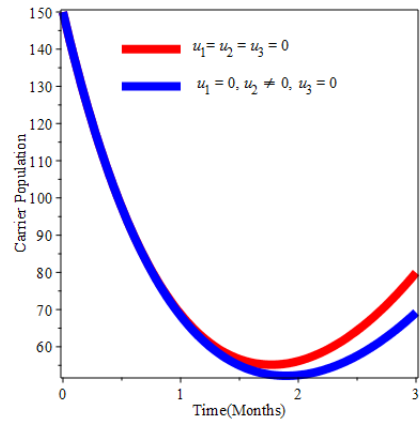
We simulated the model by incorporating optimized prevention and screening as disease control strategy. Figure 4.6.5 a and b shows that the infectious and carrier population goes to zero at the end of the implementation of intervention time. From this we can conclude that, applying prevention and screening can eradicate the disease even if without treating of individuals that have disease symptom. Therefore, applying Optimized Prevention and screening as intervention strategy will eradicate Typhoid fever disease from the community.

4.6.6 Control with Treatment and Screening

In this strategy we applied treatment and screening as intervention to control Typhoid fever disease. Figures 4.6.6 a and b shows that optimized intervention by treating infectious individuals and screening of carriers decrease the number of infectious and carrier populations but didn't goes to zero. Therefore, this strategy is not 100% effective to eradicate the disease in the specified period of time.

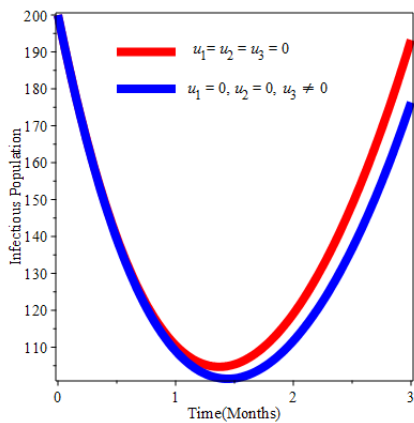


(a) Treatment impact on infectious population

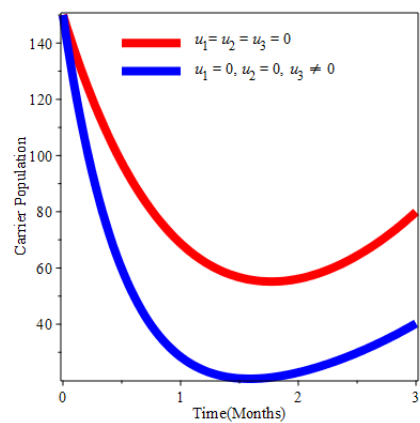


(b) Treatment impact carrier population

Figure 4.6.2: Simulations of Typhoid fever model with treatment control only.

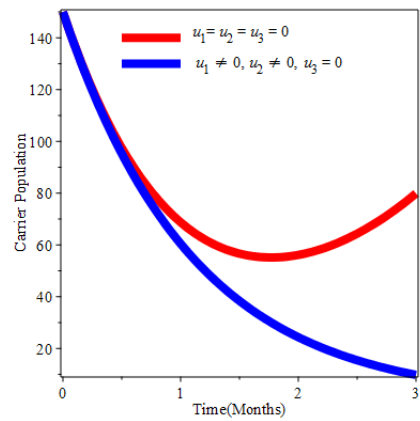
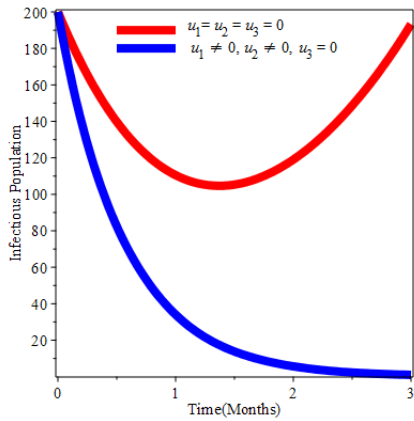


(a) Screening impact on infectious population



(b) Screening only impact on carrier population

Figure 4.6.3: Simulations of Typhoid fever model with screening control only.



(a) Prevention and treatment impact on infectious (b) Prevention and treatment impact on carrier

Figure 4.6.4: Simulations of Typhoid fever model with prevention and treatment controls

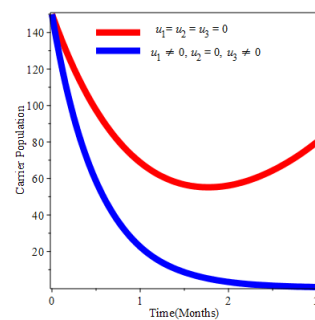
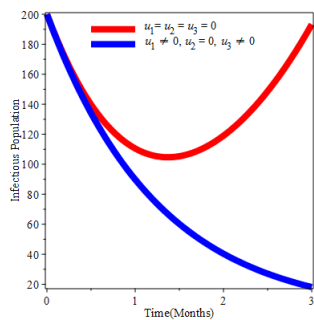
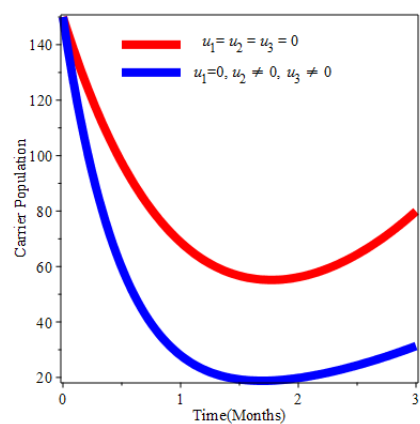
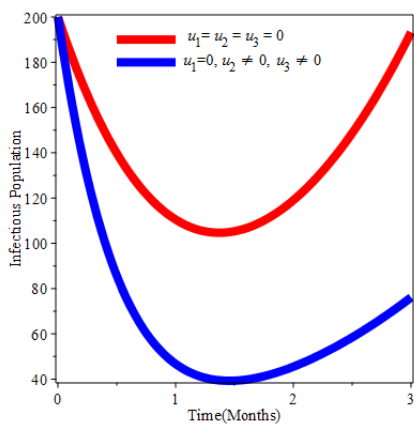


Figure 4.6.5: Simulations of the Typhoid fever model with prevention and screening controls.

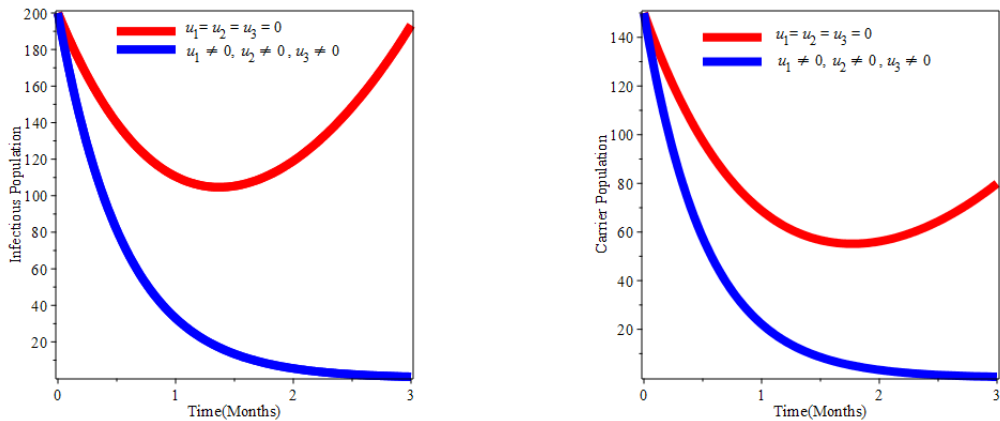


(a) Treatment and screening impact on infectious (b) Treatment and screening impact on carriers

Figure 4.6.6: Simulations of the Typhoid fever model with treatment and screening controls.

4.6.7 Control with Prevention, Treatment and Screening

In this strategy we implemented all the three controls (Prevention, Treatment and Screening) as intervention to eradicate Typhoid fever from the community. Figure 4.6.7 a and b shows that the number of infectious and carriers goes to zero at the end of the implementation period. Moreover, figure 4.6.8 shows that the number of salmonella bacteria population decreased after the implementation of the strategy. Therefore, applying this strategy is effective to eradicate Typhoid fever disease form the community in a specified period of time.



(a) Prevention, treatment and screening impact on infectious (b) Prevention ,treatment and screening impact on carriers

Figure 4.6.7: Simulations of the Typhoid fever model with prevention , treatment and screening controls.

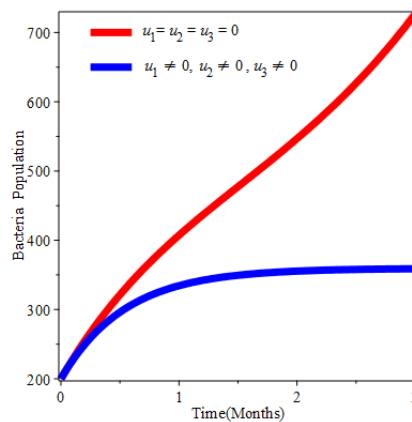


Figure 4.6.8: Simulations of the Typhoid fever model with prevention , treatment and screening controls on Salmonella bacteria populations.

4.7 Cost-Effectiveness Analysis

In this section, we identified a strategy which is cost effective compared to other strategies. To achieve this we used incremental cost-effectiveness ratio (ICER), which is done dividing the difference of costs between two strategies to the difference of the total number of their infectious averted. We estimated the total number of infectious averted for each strategy by subtracting total infectious with control from without control. To get the total cost of each strategy we used their respective cost function ($\frac{1}{2}w_1u_1^2$, $\frac{1}{2}w_2u_2^2$ and $\frac{1}{2}w_3u_3^2$) to calculate over the time of intervention. We didn't consider strategies that implement one intervention only, due to the reason that one intervention only is not guaranteed to eradicate the disease totally from the community. For those strategies which incorporate more than one intervention are ordered below to be compared pairwise.

Strategy A (Prevention and screening).

Strategy B (Treatment and Screening).

Strategy C (Prevention and Treatment).

Strategy D (Prevention, Treatment and Screening).

We used parameter values in table (5.7.1) to estimate the total cost and total infectious averted in table (4.7.1).

Table 4.7.1: Number of infectious averted and total cost of each strategies

Strategies	Description	Total infectious averted	Total cost (USD)
A	Prevention and Screening	11,977	733.07
B	Treatment and Screening	13,805	800
C	Prevention and Treatment	19,699	531.19
D	Prevention, Treatment and Screening	19,987	1104.5

First we compared the cost effectiveness of strategy A and B, $ICER(A) = \frac{733.07}{11,977} = 0.06$,

$$ICER(B) = \frac{733.07 - 800}{11,977 - 13,805} = 0.037$$

This shows that strategy B is cheaper than strategy A by saving 0.037. That means strategy A needs higher money than strategy B. Therefore, we exclude strategy A and continue to compare strategy B and C.

$$ICER(B) = \frac{800}{13,805} = 0.058,$$

$$ICER(C) = \frac{800 - 531.19}{13,805 - 19,699} = -0.039.$$

Similarly this comparison indicate that strategy C is cheaper than strategy B by saving 0.039. There-

fore, strategy B is rejected and continue to compare strategy C with the last strategy which is D.

$$ICER(C) = \frac{573.19}{19,699} = 0.029,$$

$$ICER(D) = \frac{573.19 - 1,104.5}{19,699 - 19,987} = 1.845.$$

Finally this the comparison result reveal strategy C is cheaper than strategy D by saving 0.029.

Therefore, strategy C (combination of Prevention and treatment) is the best strategy interims cost-effectiveness and healthy benefit also from all compared strategies.

Moreover, figure 5.8.1 shows that applying only one intervention strategy the most cheapest than other strategies . But we do not consider this because a single intervention is not effective to eradicate the disease. A combination of prevention and treatment strategy is the cheapest of all other combined intervention strategies . The combination of all the three interventions (Prevention , treatment and screening) is the most expensive strategy compared to other strategies.

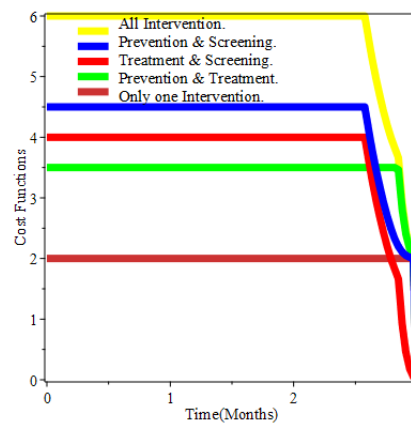


Figure 4.7.1: Cost Function of the intervention strategies for the period of 3 months

4.8 Discussions and Conclusions

In this chapter, a deterministic model for the dynamics of Typhoid fever disease is proposed. The qualitative analysis of the model shows as the solution of the model is bounded and positive. Comprehensive and robust mathematical techniques have been used to analyze the model steady states. It has been established that the model has a disease-free equilibrium which is locally and globally asymptotically stable when the associated reproductive number is less than unity and also it reveals that for $\mathfrak{R}_0 < 1$ there is no possibility of having backward bifurcation. Sensitivity analysis of the reproductive number has been carried out. Results from the sensitivity analysis of the reproductive number suggest that an increase in ν , k , σ_1 and σ_2 has the greatest influence on increasing the magnitude of the associated reproductive number which results in the endemicity of Typhoid fever.

Using Pontryagin's maximum principle, the optimal control problem is formulated and analyzed under the conditions for optimal control of the disease with effective preventive measures (sanitation and proper hygiene controls), treatment regime and screening. Existence conditions for optimal control are established and the optimality system is developed. Seven intervention strategies are proposed to examine each strategy on the eradication of Typhoid. The proposed strategies are investigated numerically and their results are displayed graphically. From the numerical results, we obtained that prevention and the cost put into treatment have a strong impact on the disease control. Effective treatment only without prevention is not the best option in controlling the spread of Typhoid fever. We therefore conclude that adequate control measures which adhere to these control strategies (preventive and treatment) would be a very effective way for fighting the disease and also for cost effectiveness.

Chapter 5

A co-infection model of Pneumonia and Typhoid fever diseases

5.1 Introduction

Pneumonia is the leading cause of serious illness in children and adults throughout the world. The disease is endemic and claims so many lives. Typhoid fever also continues to be an important cause of illness and death in developing countries where safe water supply, environmental sanitation and food hygiene are not optimal. In Africa where pneumonia and Typhoid fever are endemic, it is common for people to be infected by either or both. To mitigate these disease continuous research into the prevention and control of the disease is vital. Mathematical modelling have an important role in describing the dynamics of infectious diseases and also for investigating the optimal use of intervention strategies to control the spread of infectious diseases. For example Okaka,et al (2013) developed a mathematical model for the impact of misdiagnosis and treatment of pneumonia as malaria. Other studies include Steady, et al, (2014) developed a deterministic mathematical model for assessing the transmission dynamics of typhoid fever in malaria endemic settings. The result of the study suggests that a Typhoid fever outbreak in malaria endemic settings may lead to higher population of dually infected individuals displaying clinical symptoms of both infections than the singly infected population displaying clinical symptoms of the diseases. Adeboye, et al,(2015) developed **SIRS** mathematical model that addressed the control of the transmission of Typhoid fever and Malaria simultaneously. The study concluded that the control measures against malaria and typhoid incorporated into the

model had significant impacts on the malaria and typhoid fever by controlling the spread of the two diseases. Okaka, et al, (2015) formulated a mathematical model of malaria- typhoid concurrent and co-infection to establish the effect of misdiagnosing typhoid as malaria and hence treating it with anti-malarias.

Quite a few studies have been undertaken with co-infection of pneumonia with Malaria and also co-infection of Typhoid fever with Malaria. However, all of them did not consider optimal control strategies in their studies. But to the best of our knowledge no work has been done to investigate the Pneumonia- Typhoid co-infection dynamics with the application of optimal control method.

In this Chapter, we take inspiration from the above studies and introduce, an SIR model for Pneumonia- Typhoid fever co-infection with optimal control problem and cost-effectiveness analysis of the optimal intervention strategies are presented.

The main goal of this Chapter is to provide detailed qualitative analysis of Pneumonia- Typhoid fever co-infection model and to propose best strategies that can be employed to effectively control the spread of the two diseases at minimum cost.

The remainder of the Chapter is organized as follows. In section 5.2 , we discuss the formulation of the model in focus whilst sections 5.3, 5.4, and 5.5, deal with qualitative analysis of the basic Pneumonia only model, Typhoid fever only model and the full model respectively. In section 5.6, the main model is extended to form an optimal control problem which is qualitatively analyzed using the Pontryagins Maximum principle. In section ??, numerical experimentation of the resulting optimal control is performed. In Section ?? cost effectiveness analysis is described. Lastly in Section ?? discussion and conclusion of the chapter is presented.

5.2 Model description

The model consider the Typhoid fever causing bacteria (salmonella) population (B) and the human population . The human population is divided in to seven classes, susceptible (S), Pneumonia infectious (I_p), Typhoid infectious (I_t), pneumonia and Typhoid co-infectious (I_{tp}), Pneumonia recovered (R_p), Typhoid recovered (R_t) and Pneumonia - Typhoid co-infectious recovered (R_{tp}).is also considered The recruitment rate susceptible individuals either by birth or immigration is Q and the number of susceptible increases by those individuals that lost their temporary immunity from recovered sub classes of Pneumonia (R_p), Typhoid fever (R_t) and Pneumonia-Typhoid fever co-infected sub class

(R_{tp}) with a rate of δ_1, δ_2 and δ_3 respectively. Any susceptible individuals either can get Pneumonia disease with force of infection $\lambda_1 = \frac{\gamma(I_p + \Upsilon I_{tp})}{N}$ and join Pneumonia infectious sub-class (I_p) or Typhoid fever disease with force of infection $\lambda_2 = \frac{vB}{k+B}$ and join Typhoid fever infectious sub-class (I_t), where Υ is transmission coefficient for the dually infected. If $\Upsilon > 1$ then, dually infected may infect susceptible more likely than pneumonia only infected. If $\Upsilon = 1$, then both dually infected and pneumonia only infective have equal chance to infect the susceptible, but if $\Upsilon < 1$ then pneumonia only infected have good chance to infect susceptible than dually infected. And also γ is infectious rate of Pneumonia, v is the rate of ingestion of Typhoid causing bacteria, k is concentration of bacteria in foods and water. The number of co-infection sub-class is increased from Pneumonia infected group by getting Typhoid fever disease with λ_2 force of infection and also from Typhoid fever infected sub-class by getting Pneumonia disease with λ_1 force of infection. The infectious sub-class of Pneumonia also can get treatment with β_1 rate and move to Pneumonia recovered sub-class R_p or dies due to disease causing death rate of α_1 . Similarly the infected sub-class of Typhoid fever also can get treatment with a rate of β_2 and join Typhoid recovered sub-class or dies from disease causing death with a rate of α_2 . The Pneumonia- Typhoid co-infected sub class can get treatment with a rate of σ and get temporary immunity either from both disease or Pneumonia only or Typhoid only and join the join co-infected recovered sub-class (R_{tp}) with probability of $(1-g)(1-e)$ or Pneumonia recovered sub-class (R_p) with probability of e or Typhoid fever recovered sub-class (R_t) with probability of $g(1-e)$, where $(1-g)(1-e) + g(1-e) + e = 1$. Additionally, individuals in the co-infected sub class also dies either Pneumonia or Typhoid causing death with similar rate of Pneumonia or Typhoid only infected individuals. In all the seven human population sub-classes μ is natural causing death rate. The Typhoid fever causing bacteria (salmonella) population (B) grows in contaminated food or drinks with π rate and also increase its number from the discharge of bacteria from Typhoid fever infected individuals and the co-infected individuals with a rate of σ_1 and σ_2 respectively and also it dies due to Natural/ drug induced death rate of μ_b .

The above description of the model is plotted in figure (5.2.1).

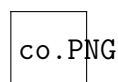


Figure 5.2.1: Flow diagram of the model

From the above flow diagrams we generate the following seven system of differential equation.

$$\left\{ \begin{array}{l} \frac{dS}{dt} = Q + \delta_1 R_p + \delta_2 R_t + \delta_3 R_{tp} - (\lambda_1 + \lambda_2 + \mu)S \\ \frac{dI_p}{dt} = \lambda_1 S - (\lambda_2 + \beta_1 + \alpha_1 + \mu)I_p \\ \frac{dI_t}{dt} = \lambda_2 S - (\lambda_1 + \beta_2 + \alpha_2 + \sigma_1 + \mu)I_t \\ \frac{dI_{tp}}{dt} = \lambda_2 I_p + \lambda_1 I_t - (\sigma + \alpha_1 + \sigma_2 + \alpha_2 + \mu)I_{tp} \\ \frac{dR_p}{dt} = \beta_1 I_p + \sigma e I_{tp} - (\delta_1 + \mu)R_p \\ \frac{dR_t}{dt} = \beta_2 I_t + \sigma g(1 - e)I_{tp} - (\delta_2 + \mu)R_t \\ \frac{dR_{tp}}{dt} = \sigma(1 - g)(1 - e)I_{tp} - (\delta_3 + \mu)R_{tp} \\ \frac{dB}{dt} = pi + \sigma_1 I_t + \sigma_2 I_{tp} - \mu_b B, \end{array} \right. \quad (5.2.1)$$

where, $\lambda_1 = \frac{\gamma(I_p + \gamma I_{tp})}{N}$, $\lambda_2 = \frac{\nu B}{k+B}$ and $S(0) = S_0, I_p(0) = I_{p0}, I_t(0) = I_{t0}, I_{tp}(0) = I_{tp0}, R_p(0) = R_{p0}, R_t(0) = R_{t0}, R_{tp}(0) = R_{tp0}$ and $B(0) = B_0$ are non-negative initial values.

5.3 Pneumonia only model

The Pneumonia only model is obtained from equation (5.2.1) by setting $I_t = I_{tp} = R_t = R_{tp} = B = 0, \delta_2 = \delta_3 = \lambda_2 = 0$. Then we obtain;

$$\left\{ \begin{array}{l} \frac{dS}{dt} = Q + \delta_1 R_p - (\lambda_1^* + \mu)S \\ \frac{dI_p}{dt} = \lambda_1^* S - (\beta_1 + \alpha_1 + \mu)I_p \\ \frac{dR_p}{dt} = \beta_1 I_p - (\delta_1 + \mu)R_p \end{array} \right. \quad (5.3.1)$$

where, $\lambda_1^* = \gamma I_p$

5.3.1 Invariant region

In this section we obtain a region in which the solution of (5.3.1) is bounded. For this model the total population $N_1 = S + I_p + R_p$. Then, after differentiating N_1 with respect to time and substituting the expression for $\frac{dS}{dt}, \frac{dI_p}{dt}$ and $\frac{dR_p}{dt}$ from equation (5.3.1) we obtain;

$$\frac{dN_1}{dt} = Q + \mu N - \alpha_1 I_p. \quad (5.3.2)$$

If there is no death from Pneumonia, equation (5.3.2) become;

$$\frac{dN_1}{dt} \leq Q + \mu N. \quad (5.3.3)$$

After, solving equation (5.3.3) and evaluating it as time tends to infinity, we got;

$$\Omega_1 = \{(S, I_p, R_p) \in \mathfrak{R}_+^3 : 0 \leq N_1 \leq \frac{Q}{\mu}.$$

Therefore, all the solution set of (5.3.1) is bounded in Ω_1 .

5.3.2 Positivity of the solution

In this section we show all solutions of the model (5.3.1) are positive for future time.

Theorem 5.3.1. *If $S_0 > 0, I_{p0} > 0$, and $R_{p0} > 0$ then all the solution set $(S(t), I_p(t)$ and $R_p(t)$ are positive for future time.*

Proof

To prove this theorem first let as define t_1 ,

$$t_1 = \sup\{t > 0 : S(\tau) > 0, I_p(\tau) > 0, R_p(\tau) > 0 \text{ for all } \tau \in [0, t]\}.$$

Since $S_0 \geq 0, I_{p0} \geq 0, R_{p0} \geq 0$, thus $t_1 > 0$. If $t_1 < \infty$, then necessarily S or I_p or R_p is equal to zero at t_1 . From equation (5.2.1), let as take the first equation:

$$\frac{dS}{dt} = Q + \delta_1 R_p - (\lambda_1^* + \mu)S. \quad (5.3.4)$$

Using the variation of constants formula the solution of equation (5.3.4) at t_1 is given by.

$$S(t_1) = S(0) \exp \left[- \int_0^{t_1} (\lambda_1^* + \mu)(s) ds \right] + \int_0^{t_1} (Q + \delta_1 R_p) \exp \left[- \int_s^{t_1} (\lambda_1^* + \mu)(\tau) d\tau \right] ds.$$

Moreover, since all the variables are positive in $[0, t_1]$, then $S(t_1) > 0$.

It can be shown in a similar way that $I_p(t_1) > 0$ and $R_p(t_1) > 0$ which is a contradiction. Hence $t_1 = \infty$.

Therefore, all the solution sets are positive for future time.

5.3.3 Disease free equilibrium

The disease free equilibrium of the model is obtained by letting equation (5.3.1) to zero and evaluating at $I_p = 0$.

Then, we got $E_{0p} = (\frac{Q}{\mu}, 0, 0)$.

5.3.4 Basic reproduction number (\mathfrak{R}_{0p})

To obtain \mathfrak{R}_{0p} we use the next generation matrix method.

$$\text{From } \frac{dI_p}{dt} = \lambda_1^* S - (\beta_1 + \alpha_1 + \mu)I_p,$$

$$f = \gamma I_p S \text{ and } v = (\beta_1 + \alpha_1 + \mu)I_p. \text{ Then,}$$

$$F = \gamma \frac{Q}{\mu} V^{-1} = \frac{\gamma Q}{(\beta_1 + \alpha_1 + \mu)}$$

$$FV^{-1} = \gamma \frac{Q}{\mu} \frac{1}{(\beta_1 + \alpha_1 + \mu)}. \text{ Therefore, the basic reproduction number is given by;}$$

$$\mathfrak{R}_{0p} = \frac{\gamma Q}{\mu(\beta_1 + \alpha_1 + \mu)} \quad (5.3.5)$$

5.3.5 Local stability of disease free equilibrium

Theorem 5.3.2. *The disease free equilibrium point is locally asymptotically stable if $\mathfrak{R}_{0p} < 1$ and unstable if $\mathfrak{R}_{0p} > 1$.*

Poof.

To prove this let us take the right hand side expression of the second equation of 5.3.1;

$x = \lambda_1^* S - (\beta_1 + \alpha_1 + \mu)I_p$. Then the partial derivative of f with respect to I_p at disease free equilibrium is,

$$\frac{\partial x}{\partial I_p} \left(\frac{Q}{\mu}, 0, 0 \right) = \frac{\gamma Q}{\mu} - (\beta_1 + \alpha_1 + \mu)$$

The disease free equilibrium to be stable;

$$\begin{aligned} \frac{\partial f}{\partial I_p} \left(\frac{Q}{\mu}, 0, 0 \right) &= \frac{\gamma Q}{\mu} - (\beta_1 + \alpha_1 + \mu) < 0 \\ \Rightarrow (\beta_1 + \alpha_1 + \mu) \left(\frac{\gamma Q}{\mu(\beta_1 + \alpha_1 + \mu)} - 1 \right) &< 0 \\ \Rightarrow (\beta_1 + \alpha_1 + \mu) (\mathfrak{R}_{0p} - 1) &< 0 \end{aligned}$$

Therefore, the disease free equilibrium is locally asymptotically stable if $\mathfrak{R}_{0p} < 1$ and unstable otherwise.

5.3.6 Global stability of the disease free equilibrium

Theorem 5.3.3. *The disease free equilibrium is globally asymptotically stable if $\mathfrak{R}_{0p} < 1$.*

Proof

To prove the global asymptotic stability of the DFE we use the method of Lyapunov functions.

Systematically, we defined a Lyapunov function L such that;

$$L = \frac{1}{(\beta_1 + \alpha_1 + \mu)} I_p.$$

Then,

$$\begin{aligned} \frac{dL}{dt} &= \frac{1}{(\beta_1 + \alpha_1 + \mu)} \frac{dI_p}{dt} = \frac{1}{(\beta_1 + \alpha_1 + \mu)} (\gamma S I_p - (\beta_1 + \alpha_1 + \mu) I_p) \\ &\Rightarrow \frac{dL}{dt} = \frac{\gamma S I_p}{(\beta_1 + \alpha_1 + \mu)} - I_p \\ &\Rightarrow \frac{dL}{dt} \leq \left(\frac{\gamma Q}{\mu(\beta_1 + \alpha_1 + \mu)} - 1 \right) I_p \\ &\Rightarrow \frac{dL}{dt} \leq (\mathfrak{R}_{0p} - 1) I_p \end{aligned}$$

So $\frac{dL}{dt} \leq 0$ if $\mathfrak{R}_{0p} \leq 1$. Furthermore, $\frac{dL}{dt} = 0$ if $I_p = 0$ or $\mathfrak{R}_{0p} = 1$.

From this we see that, $(S_0, 0, 0)$ is the only singleton in $\{(S, I_p, R_p) \in \Omega_1 : \frac{dL}{dt} = 0\}$.

Therefore by the principle of (LaSalle, 1976), DFE is globally asymptotically stable if $\mathfrak{R}_{0p} \leq 1$.

5.3.7 Endemic equilibrium

The endemic equilibrium is denoted by $E_p^* = (S^*, I_p^*, R_p^*)$ and it occur when the disease persist in the community. To obtain it we equate all the model equations (5.3.1) to zero. Then we obtain :

$$\begin{aligned} S^* &= \frac{Q}{\mu \mathfrak{R}_{0p}} \\ I_p^* &= \frac{Q(\mathfrak{R}_{0p} - 1) + \delta_1 \mathfrak{R}_{0p} R_p}{\mathfrak{R}_{0p}(\beta_1 + \mu + \alpha_1)} \\ R_p^* &= \frac{\beta_1}{\mu + \delta_1} I_p^* \end{aligned}$$

From this we see that for the endemic equilibrium to be exist $\mathfrak{R}_{0p} > 1$.

Lemma 5.3.4. A unique endemic equilibrium point E^* exist and is positive if $\mathfrak{R}_{0p} > 1$.

Using expression for I_p^* in the endemic equilibrium and estimated parameters in table (5.7.1), we plot figure (5.3.1) that shows there is a transcritical bifurcation for pneumonia only model.

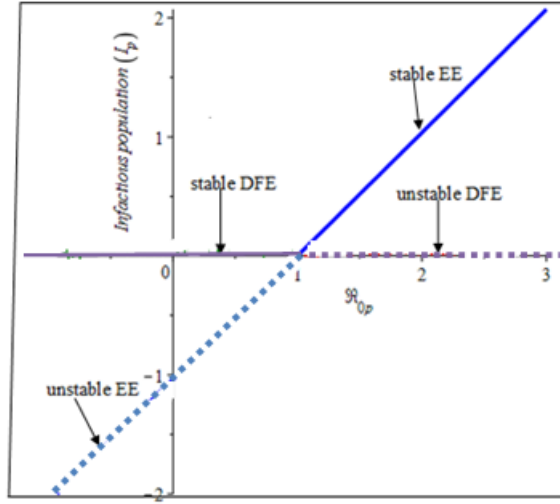


Figure 5.3.1: Transcritical bifurcation.

5.3.8 Global stability of endemic equilibrium

Theorem 5.3.5. If $\mathfrak{R}_{0p} > 1$, the endemic equilibrium E^* of the model (5.3.1) is globally asymptotically stable.

Proof

Systematically we define an appropriate Lyapunov function L Such that;

$$L = \left(S - S^* + S^* \ln \frac{S}{S^*} \right) + \left(I_p - I_p^* + I_p^* \ln \frac{I_p}{I_p^*} \right) + \left(R_p - R_p^* + R_p^* \ln \frac{R_p}{R_p^*} \right). \quad (5.3.6)$$

Then differentiating equation (5.3.6) with respect to t gives,

$$\frac{dL}{dt} = \left(\frac{S - S^*}{S} \right) \frac{dS}{dt} + \left(\frac{I_p - I_p^*}{I_p} \right) \frac{dI_p}{dt} + \left(\frac{R_p - R_p^*}{R_p} \right) \frac{dR_p}{dt}. \quad (5.3.7)$$

After substituting expressions for $\frac{dS}{dt}$, $\frac{dI_p}{dt}$ and $\frac{dR_p}{dt}$ from (5.3.1) in to (5.3.6) and collecting all positive terms together and also negative terms together, we obtain:

$$\frac{dL}{dt} = L_1 - L_2$$

Where, $L_1 = Q + \delta_1 R_p + \lambda_1 S + \beta_1 I_p + \frac{\delta_1 R_p^* S^*}{S} + \frac{\lambda_1 S^* I_p^*}{I_p} + \frac{\beta_1 I_p^* R_p^*}{R_p}$,

$$L_2 = \delta_1 R_p^* + \lambda_1 S^* + \lambda_1 S I_p^* + \frac{Q S^*}{S} + \frac{\delta_1 R_p S^*}{S} + \frac{(\lambda_1 + \mu)(S - S^*)^2}{S} + \frac{\lambda_1 S I_p^*}{I_p} + \frac{(\beta_1 + \alpha_1 + \mu)(I_p - I_p^*)^2}{I_p} + \frac{\beta_1 I_p R_p^*}{R_p} + \frac{(\delta_1 + \mu)(R_p - R_p^*)^2}{R_p}.$$

Thus if $L_1 < L_2$, then $\frac{dL}{dt} \leq 0$, and $\frac{dL}{dt} = 0$ if and only if $S = S^*, I_p = I_p^*, R_p = R_p^*$

From this, we see that $E^* = (S^*, I_p^*, R_p^*)$ is the largest compact invariant singleton set in $\{(S^*, I_p^*, R_p^*) \in \Omega_1 : \frac{dL}{dt} = 0\}$. Therefore, by the principle of (LaSalle, 1976), the endemic equilibrium (E^*), is globally asymptotically stable in the invariant region if $L_1 < L_2$.

5.4 Typhoid fever only model

By letting $I_p = I_{tp} = R_p = R_{tp} = \sigma_2 = 0$ in equation (5.2.1) we obtained Typhoid fever only model.

$$\begin{cases} \frac{dS}{dt} = Q + \delta_2 R_t - (\lambda_2 + \mu)S \\ \frac{dI_t}{dt} = \lambda_2 S - (\beta_2 + \alpha_2 + \sigma_1 + \mu)I_t \\ \frac{dR_t}{dt} = \beta_2 I_t - (\delta_2 + \mu)R_t \\ \frac{dB}{dt} = \pi + \sigma_1 I_t - \mu_b B, \end{cases} \quad (5.4.1)$$

5.4.1 Invariant region

In this section we obtain a region in which the solution of (5.4.1) is bounded. For this model the total human population $N_2 = S + I_t + R_t$. Then, after differentiating N_2 with respect to time and substituting the expression for $\frac{dS}{dt}$, $\frac{dI_t}{dt}$ and $\frac{dR_t}{dt}$ from equation (5.4.1) we obtain;

$$\frac{dN_2}{dt} = Q - \mu N - \alpha_2 I_t - \sigma_1 I_t. \quad (5.4.2)$$

If there is no death from Typhoid fever and Typhoid discharge, equation (5.4.2) become;

$$\frac{dN_2}{dt} \leq Q - \mu N. \quad (5.4.3)$$

After, solving equation (5.4.3) and evaluating it as time tends to infinity, we got;

$$\Omega_2 = \{(S, I_t, R_t, B) \in \mathfrak{R}_+^3 \cup \mathfrak{R}_+ : 0 \leq N_2 \leq \frac{Q}{\mu}\}.$$

Therefore, all the solution set of (5.4.1) is bounded in Ω_2 .

5.4.2 Positivity of the solution

In this section we show all solutions of the model (5.4.1) are positive for future time.

Theorem 5.4.1. *If $S_0 > 0, I_{t_0} > 0, R_{p_0} > 0$ and $B_0 > 0$ then all the solution set $(S(t), I_t(t), R_p(t)$ and $B(t)$ are positive for future time.*

Proof

To prove this theorem first let as define t_1 ,

$$t_1 = \sup\{t > 0 : S(\tau) > 0, I_t(\tau) > 0, R_t(\tau) > 0, B(\tau) > 0 \text{ for all } \tau \in [0, t]\}.$$

Since $S_0 \geq 0, I_{t_0} \geq 0, R_{t_0} \geq 0, B_0 \geq 0$, thus $t_1 > 0$. If $t_1 < \infty$, then necessarily S or I_t or R_t or B is equal to zero at t_1 . From equation (5.4.1), let as take the first equation:

$$\frac{dS}{dt} = Q + \delta_2 R_t - (\lambda_2 + \mu)S \quad (5.4.4)$$

Using the variation of constants formula the solution of equation (5.4.4) at t_1 is given by.

$$S(t_1) = S(0) \exp \left[- \int_0^{t_1} (\lambda_2 + \mu)(s) ds \right] + \int_0^{t_1} (Q + \delta_2 R_t) \exp \left[- \int_s^{t_1} (\lambda_2 + \mu)(\tau) d\tau \right] ds.$$

Moreover, since all the variables are positive in $[0, t_1]$, then $S(t_1) > 0$.

It can be shown in a similar way that $I_t(t_1) > 0, R_t(t_1) > 0$ and $B(t_1)$ which is a contradiction. Hence $t_1 = \infty$. Therefore, all the solution sets are positive for future time.

5.4.3 Disease free equilibrium (DFE)

The disease free equilibrium of the model is obtained by letting equation (5.4.1) to zero and evaluating at $I_t = 0$.

Then, we got $E_{02} = \left(\frac{Q}{\mu}, 0, 0, 0 \right)$.

5.4.4 Basic reproduction number (\mathfrak{R}_{0t})

To obtain \mathfrak{R}_{0t} we used the next generation matrix method.

$$\frac{dI_t}{dt} = \lambda_2 S - (\beta_2 + \alpha_2 + \sigma_1 + \mu)I_t$$

$$\frac{dB}{dt} = \pi + \sigma_1 I_t - \mu_b B$$

By the principle of next generation matrix; $f = \left(\frac{Bv}{k+B} S \right)$ and $c = \begin{pmatrix} (\beta_2 + \alpha_2 + \sigma_1 + \mu)I_t \\ -(\pi + \sigma_1 I_t - \mu_b B) \end{pmatrix}$.

$$F = \begin{pmatrix} 0 & \frac{vQ}{\mu k} \\ 0 & 0 \end{pmatrix} \text{ and } C^{-1} = \begin{pmatrix} \frac{1}{(\beta_2 + \alpha_2 + \sigma_1 + \mu)} & 0 \\ \frac{\sigma_1}{\mu_b(\beta_2 + \alpha_2 + \sigma_1 + \mu)} & \frac{1}{\mu_b} \end{pmatrix}$$

$$FC^{-1} = \begin{pmatrix} \frac{\sigma_1 v Q}{\mu k \mu_b (\beta_2 + \alpha_2 + \sigma_1 + \mu)} & \frac{v Q (\beta_2 + \alpha_2 + \sigma_1 + \mu)}{\mu k} \\ 0 & 0 \end{pmatrix}.$$

The eigenvalues of FC^{-1} are 0 and $\frac{\sigma_1 v Q}{\mu k \mu_b (\beta_2 + \alpha_2 + \sigma_1 + \mu)}$. Since the dominant eigenvalue of FC^{-1} is $\frac{\sigma_1 v Q}{\mu k \mu_b (\beta_2 + \alpha_2 + \sigma_1 + \mu)}$, the basic reproduction of Typhoid only model is given by;

$$\mathfrak{R}_{0t} = \frac{\sigma_1 v Q}{\mu \mu_b (\beta_2 + \alpha_2 + \sigma_1 + \mu)}. \quad (5.4.5)$$

5.4.5 Local stability of disease free equilibrium

Theorem 5.4.2. *The disease free equilibrium point is locally asymptotically stable if $\mathfrak{R}_{0t} < 1$ and unstable if $\mathfrak{R}_{0t} > 1$.*

Poof.

To prove this first we obtain the Jacobian matrix of of 5.4.1 at the disease free equilibrium (E_{02}) such that;

$$J_{E_{02}} = \begin{bmatrix} -\mu & 0 & \delta_2 & \frac{-vQ}{\mu k} \\ 0 & -(\beta_2 + \alpha_2 + \sigma_1 + \mu) & 0 & \frac{vQ}{\mu k} \\ 0 & \beta_2 & -(\delta_2 + \mu) & 0 \\ 0 & \sigma_1 & 0 & -\mu_b \end{bmatrix} \quad (5.4.6)$$

The characteristic polynomial of equation (5.4.6) is:

$$(-\mu - \lambda^*)(-(\mu + \delta_2) - \lambda^*) [\lambda^2 + (\mu_b + \beta_2 + \mu + \alpha_2 + \sigma_1)\lambda^* + \mu_b(\beta_2 + \alpha_2 + \mu + \sigma_1)(1 - \mathfrak{R}_{0t})] = 0 \quad (5.4.7)$$

From equation (5.4.7) it is clear that;

$$-\mu - \lambda^* = 0,$$

$$\Rightarrow \lambda_1^* = -\mu < 0,$$

and

$$-(\mu + \delta_2) - \lambda^* = 0,$$

such that

$$\lambda_2^* = -(\mu + \delta_2) < 0.$$

When we apply we apply Routh-Hurwitz criteria on the polynomial in the closed bracket of equation (5.4.7) to have strictly negative real root if and only if $\mathfrak{R}_{0t} < 1$. Therefore, DFE to be locally asymptotically stable if and only if $\mathfrak{R}_{0t} < 1$.

5.4.6 Global stability of disease free equilibrium

Theorem 5.4.3. *The disease free equilibrium is globally asymptotically stable if $\mathfrak{R}_{0t} < 1$.*

Proof

To prove the global asymptotic stability of the DFE we use the method of Lyapunov functions.

Systematically, we defined a Lyapunov function L such that;

$$L = \frac{\sigma_1}{(\beta_2 + \alpha_2 + \sigma_1 + \mu)} I_t + B.$$

Then,

$$\frac{dL}{dt} = \frac{\sigma_1}{(\beta_2 + \alpha_2 + \sigma_1 + \mu)} \frac{dI_t}{dt} + \frac{dB}{dt}. \quad (5.4.8)$$

After substituting expressions for $\frac{dI_t}{dt}$ and $\frac{dB}{dt}$ from (5.4.1) to equation (5.4.8) and simplifying it, we obtain:

$$\frac{dL}{dt} = \frac{\sigma_1 \lambda_2 S}{(\beta_2 + \alpha_2 + \sigma_1 + \mu)} - \mu_b B = \left(\frac{\sigma_1 \nu S}{(\beta_2 + \alpha_2 + \sigma_1 + \mu)(k + B)} - \mu_b \right) B. \quad (5.4.9)$$

$$\begin{aligned}\Rightarrow \frac{dL}{dt} &\leq \mu_b \left(\frac{\sigma_1 \nu Q}{\mu \mu_b (\beta_2 + \alpha_2 + \sigma_1 + \mu) k} - 1 \right) B \\ &\Rightarrow \frac{dL}{dt} \leq \mu_b (\mathfrak{R}_{0t} - 1) B\end{aligned}$$

So $\frac{dL}{dt} \leq 0$ if $\mathfrak{R}_{0t} \leq 1$. Furthermore, $\frac{dL}{dt} = 0$ if $B = 0$ which mean $I_t = 0$ or $\mathfrak{R}_{0t} = 1$.

From this we see that, $(S_0, 0, 0, 0)$ is the only singleton in $\{(S, I_t, R_t) \in \Omega_2 : \frac{dL}{dt} = 0\}$.

Therefore by the principle of (LaSalle, Jp. (1976)), DFE is globally asymptotically stable if $\mathfrak{R}_{0t} \leq 1$.

5.4.7 Endemic equilibrium

The endemic equilibrium is denoted by $E_t^* = (S^*, I_t^*, R_t^*, B^*)$ and it occur when the disease persist in the community. To obtain it we equate all the model equations (5.4.1) to zero. Then we obtain :

$$\begin{aligned}S^* &= \frac{(\beta_2 + \alpha_2 + \sigma_1 + \mu)}{\lambda_2} I_t^* \\ I_t^* &= \frac{Q\nu(\mathfrak{R}_{0t} - 1)}{\mu \mathfrak{R}_{0t} ((\beta_2 + \alpha_2 + \sigma_1 + \mu)(\delta_2 + \mu) - \delta_2 \beta_2)} \\ R_t^* &= \frac{\beta_2}{\delta_2 + \mu} I_t^* \\ B^* &= \frac{\sigma_1}{\mu_b} I_t^*\end{aligned}$$

From this we see that for the endemic equilibrium to be exist $\mathfrak{R}_{0t} > 1$.

Lemma 5.4.4. *A unique endemic equilibrium point E_t^* exist and is positive if $\mathfrak{R}_{0t} > 1$.*

Using expression for I_t^* in the endemic equilibrium and estimated parameters in table (5.7.1), we plot figure (5.4.1) that shows there is a forward bifurcation for typhoid fever only model.

5.4.8 Global stability of Endemic equilibrium

Theorem 5.4.5. *If $\mathfrak{R}_{0t} > 1$, the endemic equilibrium E_t^* of the model (5.4.1) is globally asymptotically stable.*

Proof

Systematically we define an appropriate Lyapunov function L Such that;

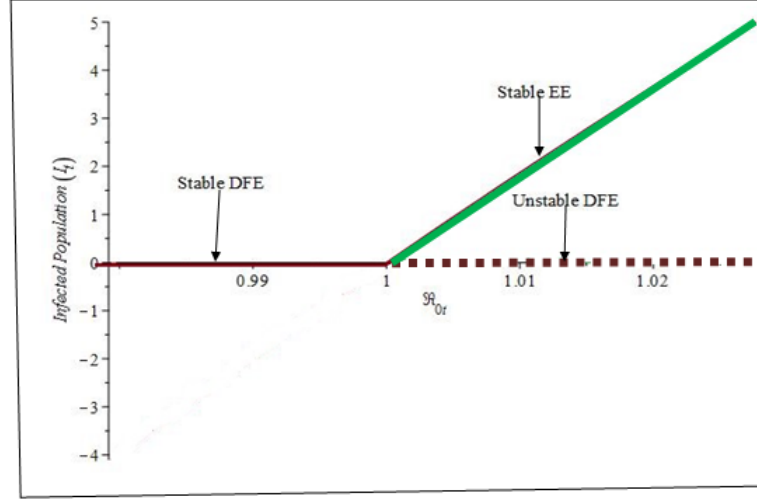


Figure 5.4.1: Forward bifurcation.

$$L = \left(S - S^* + S^* \ln \frac{S^*}{S} \right) + \left(I_t - I_t^* + I_t^* \ln \frac{I_t^*}{I_t} \right) + \left(R_t - R_t^* + R_t^* \ln \frac{R_t^*}{R_t} \right) + \left(B - B^* + B^* \ln \frac{B^*}{B} \right). \quad (5.4.10)$$

Then differentiating equation (5.4.10) with respect to t gives,

$$\frac{dL}{dt} = \left(\frac{S - S^*}{S} \right) \frac{dS}{dt} + \left(\frac{I_t - I_t^*}{I_t} \right) \frac{dI_t}{dt} + \left(\frac{R_t - R_t^*}{R_t} \right) \frac{dR_t}{dt} + \left(\frac{B - B^*}{B} \right) \frac{dB}{dt}. \quad (5.4.11)$$

After substituting expressions for $\frac{dS}{dt}$, $\frac{dI_t}{dt}$, $\frac{dR_t}{dt}$ and $\frac{dB}{dt}$ from (5.4.1) in to (5.4.11) and collecting all positive terms together and also negative terms together, we obtain:

$$\frac{dL}{dt} = M_1 - M_2$$

$$\begin{aligned} \text{Where, } M_1 &= Q + \delta_2 R_t + \lambda_2 S + \beta_2 I_t + \sigma_1 I_t + \frac{\delta_2 R_t^* S^*}{S} + \frac{\lambda_2 S^* I_t^*}{I_t} + \frac{\beta_2 I_t^* R_t^*}{R_t} + \frac{B^* I_t^*}{B}, \\ M_2 &= \delta_1 R_t^* + \lambda_2 S^* + \beta_2 I_t^* + \sigma_1 I_t^* + \frac{\lambda_1 S I_t^*}{I_t} + \frac{Q S^*}{S} + \frac{\delta_2 R_t S^*}{S} \\ &+ \frac{(\lambda_2 + \mu)(S - S^*)^2}{S} + \frac{\lambda_1 S I_t^*}{I_t} + \frac{(\beta_2 + \alpha_2 + \sigma_1 + \mu)(I_t - I_t^*)^2}{I_t} + \frac{\beta_2 I_t R_t^*}{R_t} + \frac{(\delta_2 + \mu)(R_t - R_t^*)^2}{R_t} + \frac{\sigma_1 I_t}{B} + \frac{\mu_b (B - B^*)^2}{B}. \end{aligned}$$

Thus if $M_1 < M_2$, then $\frac{dL}{dt} \leq 0$, and $\frac{dL}{dt} = 0$ if and only if $S = S^*$, $I_t = I_t^*$, $R_t = R_t^*$ and $B = B^*$

From this, we see that $E^* = (S^*, I_t^*, R_t^*, B^*)$ is the largest compact invariant singleton set in $\{(S^*, I_t^*, R_t^*, B^*) \in \Omega_2 : \frac{dL}{dt} = 0\}$. Therefore, by the principle of Lasalle, the endemic equilibrium (E_t^*), is globally asymptotically stable in the invariant region if $M_1 < M_2$.

5.5 Pneumonia- Typhoid fever co-infection model

The model equation of Pneumonia and Typhoid fever co-infection given in equation (5.2.1) is ;

$$\left\{ \begin{array}{l} \frac{dS}{dt} = Q + \delta_1 R_p + \delta_2 R_t + \delta_3 R_{tp} - (\lambda_1 + \lambda_2 + \mu)S \\ \frac{dI_p}{dt} = \lambda_1 S - (\lambda_2 + \beta_1 + \alpha_1 + \mu)I_p \\ \frac{dI_t}{dt} = \lambda_2 S - (\lambda_1 + \beta_2 + \alpha_2 + \sigma_1 + \mu)I_t \\ \frac{dI_{tp}}{dt} = \lambda_2 I_p + \lambda_1 I_t - (\sigma + \alpha_1 + \alpha_2 + \sigma_2 + \mu)I_{tp} \\ \frac{dR_p}{dt} = \beta_1 I_p + \sigma e I_{tp} - (\delta_1 + \mu)R_p \\ \frac{dR_t}{dt} = \beta_2 I_t + \sigma g(1 - e)I_{tp} - (\delta_2 + \mu)R_t \\ \frac{dR_{tp}}{dt} = \sigma(1 - g)(1 - e)I_{tp} - (\delta_3 + \mu)R_{tp} \\ \frac{dB}{dt} = \pi + \sigma_1 I_t + \sigma_2 I_{tp} - \mu_b B, \end{array} \right. \quad (5.5.1)$$

where, $\lambda_1 = \frac{\gamma(I_p + \gamma I_{tp})}{N}$, $\lambda_2 = \frac{\nu B}{k + B}$ and $S(0) = S_0, I_p(0) = I_{p0}, I_t(0) = I_{t0}, I_{tp}(0) = I_{tp0}, R_p(0) = R_{p0}, R_t(0) = R_{t0}, R_{tp}(0) = R_{tp0}$ and $B(0) = B_0$ are non-negative initial values.

5.5.1 Invariant region

In this section we obtain a region in which the solution of (5.6.1) is bounded. For this model the total human population is $N = S + I_p + I_t + I_{tp} + R_p + R_t + R_{tp}$. Then, after differentiating N with respect to time and substituting the expression for $\frac{dS}{dt}, \frac{dI_p}{dt}, \frac{dI_t}{dt}, \frac{dI_{tp}}{dt}, \frac{dR_p}{dt}, \frac{dR_t}{dt}$ and $\frac{dR_{tp}}{dt}$ and from equation (5.6.1) we obtain;

$$\frac{dN}{dt} = Q - \mu N - \alpha_1(I_t + I_{tp}) - \alpha_2(I_t + I_{tp}). \quad (5.5.2)$$

If there is no death from Pneumonia and Typhoid fever, equation (5.5.2) become;

$$\frac{dN}{dt} \leq Q - \mu N. \quad (5.5.3)$$

After, solving equation (5.5.3) and evaluating it as time tends to infinity, we got;

$$\Omega = \{(S, I_p, I_t, I_{tp}, R_p, R_t, R_{tp}) \in \mathfrak{R}^7 : 0 \leq N \leq \frac{Q}{\mu}\}.$$

Therefore, all the solution set of (5.6.1) is bounded in Ω .

5.5.2 Positivity of the solution

In this section we show all the solution of the model (5.6.1) remain positive for future time if their respective initial values are positive.

Theorem 5.5.1. *If $S_0 > 0, I_{p0} > 0, I_{t0} > 0, I_{tp0} > 0, R_{p0} > 0, R_{t0} > 0, R_{tp0} > B_0 > 0$ then all the solution set $(S(t), I_p(t), I_t(t), I_{tp}(t), R_p(t), R_t(t), R_{tp}(t), B(t))$ are positive for future time.*

Proof

To prove this theorem first let as define t_1 ,

$t_1 = \sup\{t > 0 : S(\tau) > 0, I_p(\tau) > 0, I_t(\tau) > 0, I_{tp}(\tau) > 0, R_p(\tau) > 0, R_t(\tau) > 0, R_{tp}(\tau) > 0, \text{ for all } \tau \in [0, t]\}$.

Since $S_0 \geq 0, I_{p0} \geq 0, I_{t0} \geq 0, I_{tp0} \geq 0, R_{p0} \geq 0, R_{t0} \geq 0, R_{tp0} \geq 0, B_0 \geq 0$, thus $t_1 > 0$. If $t_1 < \infty$, then necessarily S or I_p or I_t or I_{tp} or R_p or R_t or R_{tp} or B is equal to zero at t_1 . From equation (5.2.1), let as take the first equation,

$$\frac{dS}{dt} = Q + \delta_1 R_p + \delta_2 R_t + \delta_3 R_{tp} - (\lambda_1 + \lambda_2 + \mu)S. \quad (5.5.4)$$

Using the variation of constants formula the solution of equation (5.5.4) at t_1 is given by.

$$S(t_1) = S(0) \exp \left[- \int_0^{t_1} (\lambda_1 + \lambda_2 + \mu)(s) ds \right] + \int_0^{t_1} (Q + \delta_1 R_p + \delta_2 R_t + \delta_3 R_{tp}) \exp \left[- \int_s^{t_1} (\lambda_1 + \lambda_2 + \mu)(\tau) d\tau \right] ds.$$

Moreover, since all the variables are positive in $[0, t_1]$, then $S(t_1) > 0$.

It can be shown in a similar way that $I_p(t_1) > 0, I_t(t_1) > 0, I_{tp}(t_1) > 0, R_p(t_1) > 0, R_t(t_1) > 0, R_{tp}(t_1) > 0$ and $B(t_1) > 0$ which is a contradiction. Hence $t_1 = \infty$.

Therefore, all the solution sets are positive for future time.

5.5.3 Disease free equilibrium

The disease free equilibrium of equation (5.6.1) is obtained by equating all equations of the model to zero and then letting $I_p = 0, I_t = 0$ and $I_{tp} = 0$. Then we obtain;

$$E_0 = \left(\frac{Q}{\mu}, 0, 0, 0, 0, 0, 0, 0 \right).$$

5.5.4 Basic reproduction number (\mathfrak{R}_0)

By the principle of next generation matrix we consider the following equations from the model.

$$\frac{dI_p}{dt} = \lambda_1 S - (\lambda_2 + \beta_1 + \alpha_1 + \mu)I_p$$

$$\frac{dI_t}{dt} = \lambda_2 S - (\lambda_1 + \beta_2 + \alpha_2 + \sigma_1 + \mu)I_t$$

$$\frac{dI_{tp}}{dt} = \lambda_2 I_p + \lambda_1 I_t - (\sigma + \alpha_1 + \alpha_2 + \sigma_2 + \mu)I_{tp}$$

$$\frac{dB}{dt} = \sigma_1 I_t + \sigma_2 I_{tp} - \mu_b B$$

Then the next generation matrices are given by:

$$F = \begin{pmatrix} \frac{\gamma Q}{\mu} & 0 & \frac{\gamma Q}{\mu} & 0 \\ 0 & 0 & 0 & \frac{vQ}{\mu k} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \quad \&V = \begin{pmatrix} (\beta_1 + \alpha_1 + \mu) & 0 & 0 & 0 \\ 0 & (\beta_2 + \alpha_2 + \sigma_1 + \mu) & 0 & 0 \\ 0 & 0 & (\sigma + \alpha_1 + \alpha_2 + \sigma_2 + \mu) & 0 \\ 0 & -\sigma_1 & -\sigma_2 & \mu_b \end{pmatrix}$$

$$FV^{-1} = \begin{pmatrix} \frac{\gamma Q}{\mu(\beta_1 + \alpha_1 + \mu)} & 0 & \frac{\gamma Q}{\mu(\sigma + \alpha_1 + \alpha_2 + \sigma_2 + \mu)} & 0 \\ 0 & \frac{\sigma_1 v Q}{\mu \mu_b k (\beta_2 + \alpha_2 + \sigma_1 + \mu)} & \frac{\sigma_2 v Q}{\mu \mu_b k (\beta_2 + \alpha_2 + \sigma_1 + \mu)} & \frac{v Q}{\mu \mu_b k} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

Then the eigenvalues of FV^{-1} are;

$$\lambda_1^* = \frac{\gamma Q}{\mu(\beta_1 + \alpha_1 + \mu)} = \mathfrak{R}_{0p}$$

$$\lambda_2^* = \frac{\sigma_1 v Q}{\mu \mu_b k (\beta_2 + \alpha_2 + \sigma_1 + \mu)} = \mathfrak{R}_{0t}$$

$$\lambda_{3,4}^* = 0$$

Since the basic reproduction number is the spectral radius of FV^{-1} , therefore, it is :

$$\mathfrak{R}_0 = \max\{\mathfrak{R}_{0p}, \mathfrak{R}_{0t}\}.$$

5.5.5 Local stability of disease free equilibrium

Theorem 5.5.2. *The disease free equilibrium point is locally asymptotically stable if $\mathfrak{R}_0 < 1$ and unstable if $\mathfrak{R}_0 > 1$.*

Proof.

To prove this we obtain the Jacobian matrix of the model at the disease free equilibrium;

$$J_{E_0} = \begin{bmatrix} -\mu & \frac{-\gamma Q}{\mu} & 0 & \frac{-\gamma Q}{\mu} & \delta_1 & \delta_2 & \delta_3 & \frac{-\nu Q}{\mu k} \\ 0 & \frac{-\gamma Q}{\mu} - (\beta_1 + \alpha_1 + \mu) & 0 & \frac{-\gamma Q}{\mu} & 0 & 0 & 0 & 0 \\ 0 & 0 & -(\beta_2 + \alpha_2 + \sigma_1 + \mu) & 0 & 0 & 0 & 0 & \frac{\nu Q}{\mu k} \\ 0 & 0 & 0 & -(\sigma + \alpha_1 + \alpha_2 + \sigma_2 + \mu) & 0 & 0 & 0 & 0 \\ 0 & \beta_1 & 0 & c_1 & -(\delta_1 + \mu) & 0 & 0 & 0 \\ 0 & 0 & \beta_2 & c_2 & 0 & -(\delta_2 + \mu) & 0 & 0 \\ 0 & 0 & 0 & c_3 & 0 & 0 & -(\delta_3 + \mu) & 0 \\ 0 & 0 & \sigma_1 & \sigma_2 & 0 & 0 & 0 & \mu_b \end{bmatrix} \quad (5.5.5)$$

The characteristic polynomial of equation (5.5.5) is;

$$(-\mu - \lambda^*)(-c_1 - \lambda^*) \left(\left(\frac{\gamma Q}{\mu} - c_3 \right) - \lambda^* \right) (-c_2 - \lambda^*) [(\lambda^*)^3 + k_1(\lambda^*)^2 + (k_2 + k_3(1 - \mathfrak{R}_{0t}))\lambda^* - k_4(1 + \mathfrak{R}_{0t})] = 0 \quad (5.5.6)$$

where,

$$c_1 = \delta_3 + \mu,$$

$$c_2 = \delta_2 + \mu,$$

$$c_3 = \beta_1 + \alpha_1 + \mu,$$

$$k_1 = \beta_2 + 2\alpha_2 + \sigma_1 + 2\mu + \sigma + \alpha_1 + \sigma_2 + \mu_b,$$

$$k_2 = (\sigma + \alpha_1 + \alpha_2 + \sigma_2 + \mu)(\beta_2 + \alpha_2 + \sigma_1 + 2\mu),$$

$$k_3 = \mu_b(\beta_2 + \alpha_2 + \sigma_1 + \mu),$$

$$k_4 = (\mu_b(\beta_2 + \alpha_2 + \sigma_1 + \mu)(\sigma + \alpha_1 + \alpha_2 + \sigma_2 + \mu).$$

From equation (5.5.6) it is clear that;

$$-\mu - \lambda = 0, \Rightarrow \lambda_1^* = -\mu < 0$$

or

$$-c_1 - \lambda = 0, \Rightarrow \lambda_2^* = -c_1 < 0$$

or

$$\left(\frac{-\gamma Q}{\mu} - c_3 \right) - \lambda^* = 0, \Rightarrow \lambda_3^* = c_3(\mathfrak{R}_{0p} - 1), \lambda_3^* < 0 \text{ if } \mathfrak{R}_{0p} < 1$$

or

$$(\lambda^*)^3 + k_1(\lambda^*)^2 + (k_2 + k_3(1 - \mathfrak{R}_{0t}))\lambda^* - k_4(1 + \mathfrak{R}_{0t}) = 0. \quad (5.5.7)$$

When we apply Routh-Hurwitz criteria on equation (5.5.7) it have strictly negative real root if $\mathfrak{R}_{0t} < 1$. Therefore the disease free equilibrium is locally asymptotically stable if $\mathfrak{R}_{0p} < 1$ and $\mathfrak{R}_{0t} < 1$ which means that $\mathfrak{R}_0 < 1$.

5.5.6 Global asymptotic stability of disease free equilibrium

To investigate the global stability of disease free equilibrium we used technique implemented by Castillo- Chavez et al (2002). First the full pneumonia- Typhoid fever model (5.6.1) can be re-written as:

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

Where, X stands for the uninfected population, that is $X = (S, R_p, R_t, R_{tp})$ and Z also stands for the infected population, that is $Z = (I_p, I_t, I_{tp})$. The disease free equilibrium point of the model is denoted by $U = (X^*, 0)$.

The point $U = (X^*, 0)$ to be globally asymptotically stable equilibrium for the model provided that $\mathfrak{R}_0 < 1$ (which is locally asymptotically stable) and the following conditions must be met:

(H₁). For $\frac{dX}{dt} = F(X, 0)$, X^* is globally asymptotically stable.

(H₂). $G(X, Z) = AZ - \tilde{G}(X, Z)$, $\tilde{G}(X, Z) \geq 0$ for $(X, Z) \in \Omega$

If the model (5.6.1) met the above two criteria then the following theorem holds:

Theorem 5.5.3. *The point $U = (X^*, 0)$ is globally asymptotically stable equilibrium provided that $\mathfrak{R}_0 < 1$ and the condition (H₁) and (H₂) are satisfied.*

Proof

From the system (5.6.1) we can get $F(X, Z)$ and $G(X, Z)$;

$$F(X, Z) = \begin{pmatrix} Q + \delta_1 R_p + \delta_2 R_t + \delta_3 R_{tp} - (\lambda_1 + \lambda_2 + \mu)S \\ \beta_1 I_p + \sigma e I_{tp} - (\delta_1 + \mu)R_p \\ \beta_2 I_t + \sigma g(1-e)I_{tp} - (\delta_2 + \mu)R_t \\ \sigma(1-g)(1-e)I_{tp} - (\delta_3 + \mu)R_{tp} \end{pmatrix}$$

$$G(X, Z) = \begin{pmatrix} \lambda_1 S - (\lambda_2 + \beta_1 + \alpha_1 + \mu)I_p \\ \lambda_2 S - (\lambda_1 + \beta_2 + \alpha_2 + \sigma_1 + \mu)I_t \\ \lambda_2 I_p + \lambda_1 I_t - (\sigma + \alpha_1 + \alpha_2 + \sigma_2 + \mu)I_{tp} \end{pmatrix}$$

Consider the reduced system,

$$\left. \frac{dX}{dt} \right|_{Z=0} = \begin{pmatrix} Q - \mu S \\ 0 \\ 0 \\ 0 \end{pmatrix} \quad (5.5.8)$$

From equation (5.5.8), it is obvious that $X^* = (\frac{Q}{\mu}, 0)$ is the global asymptotic point. This can be verified from the solution, namely $S = \frac{Q}{\mu} + (S(0) - \frac{Q}{\mu})e^{-\mu t}$. As $t \rightarrow \infty$, the solution $(S) \rightarrow \frac{Q}{\mu}$, implying that the global convergence of (5.5.8) in Ω .

Let

$$A = \begin{pmatrix} \gamma - (\beta_1 + \alpha_1 + \mu) & 0 & \gamma \\ 0 & -(\beta_2 + \alpha_2 + \sigma_1 + \mu) & 0 \\ 0 & 0 & -(\sigma + \alpha_1 + \alpha_2 + \sigma_2 + \mu) \end{pmatrix}$$

. Then, $G(X, Z)$ can be written as, $G(X, Z) = AZ - \tilde{G}(X, Z)$, where,

$$\tilde{G}(X, Z) = \begin{pmatrix} \tilde{G}_1(X, Z) \\ \tilde{G}_2(X, Z) \\ \tilde{G}_3(X, Z) \end{pmatrix} = \begin{pmatrix} \gamma(I_t + I_{tp})(1 - \frac{S}{N}) + \lambda_2 I_p \\ \lambda_1 I_t \\ -(\lambda_2 I_p + \lambda_1 I_t) \end{pmatrix} \quad (5.5.9)$$

In equation (5.5.9) $\tilde{G}_2(X, Z) < 0$ which leads to $\tilde{G}(X, Z) < 0$, that means the second condition (H_2) is not satisfied, so $U = (X^*, 0)$ may not be globally asymptotically stable when $\mathfrak{R}_0 < 1$.

5.5.7 The endemic equilibrium

The endemic equilibrium is denoted by $E_{tp}^* = (S^*, I_p^*, I_t^*, I_{tp}^*, R_p^*, R_t^*, R_{tp}^*, B^*)$ and it occur when the disease persist in the community. To obtain it we equate all the model equations (5.6.1) to zero. Then we obtain:

$$S^* = \frac{Qc(\lambda_1^* + k_2)(\lambda_2^* + k_1)k_3}{c(\lambda_1^* + \lambda_2^* + \mu)(\lambda_1^* + k_2)(\lambda_2^* + k_1)k_3 - [(\lambda_1^* + k_2)(c_1k_3\lambda_1^* + c_3\lambda_1^*\lambda_2^*) + (\lambda_2^* + k_1)(c_2k_3\lambda_2^* + c_3\lambda_1^*\lambda_2^*)]}$$

$$I_p^* = \frac{\lambda_1^*Qc(\lambda_1^* + k_2)k_3}{c(\lambda_1^* + \lambda_2^* + \mu)(\lambda_1^* + k_2)(\lambda_2^* + k_1)k_3 - [(\lambda_1^* + k_2)(c_1k_3\lambda_1^* + c_3\lambda_1^*\lambda_2^*) + (\lambda_2^* + k_1)(c_2k_3\lambda_2^* + c_3\lambda_1^*\lambda_2^*)]}$$

$$I_t^* = \frac{\lambda_2^*Qc(\lambda_2^* + k_1)k_3}{c(\lambda_1^* + \lambda_2^* + \mu)(\lambda_1^* + k_2)(\lambda_2^* + k_1)k_3 - [(\lambda_1^* + k_2)(c_1k_3\lambda_1^* + c_3\lambda_1^*\lambda_2^*) + (\lambda_2^* + k_1)(c_2k_3\lambda_2^* + c_3\lambda_1^*\lambda_2^*)]}$$

$$I_{tp}^* = \frac{\lambda_1^*\lambda_2^*Qc(\lambda_1^* + k_2)(\lambda_2^* + k_1)}{c(\lambda_1^* + \lambda_2^* + \mu)(\lambda_1^* + k_2)(\lambda_2^* + k_1)k_3 - [(\lambda_1^* + k_2)(c_1k_3\lambda_1^* + c_3\lambda_1^*\lambda_2^*) + (\lambda_2^* + k_1)(c_2k_3\lambda_2^* + c_3\lambda_1^*\lambda_2^*)]}$$

$$R_p^* = \frac{\beta_1 I_p^* + \sigma e I_{tp}^*}{\delta_1 + \mu}$$

$$R_t^* = \frac{\beta_2 I_t^* + \sigma g(1 - e) I_{tp}^*}{\delta_2 + \mu}$$

$$R_{tp}^* = \frac{\sigma(1 - g)(1 - e)}{\delta_3 + \mu} I_{tp}^*$$

$$B^* = \frac{\sigma_1 I_t^* + \sigma_2 I_{tp}^*}{\mu_b}$$

Where,

$$k_1 = \beta_1 + \alpha_1 + \mu$$

$$k_2 = \beta_2 + \alpha_2 + \sigma_1 + \mu$$

$$k_3 = \sigma + \alpha_1 + \alpha_2 + \sigma_2 + \mu$$

$$c = (\delta_1 + \mu)(\delta_2 + \mu)(\delta_3 + \mu)$$

$$c_1 = \delta_1 \beta_1$$

$$c_2 = \delta_2 \beta_2$$

$$c_3 = \delta_1 \sigma e + \delta_2 \sigma g(1 - e) + \delta_3 \sigma(1 - g)(1 - e)$$

5.5.8 Impact of Pneumonia on Typhoid fever infection

To describe impact of Pneumonia on Typhoid fever and vase versa, we express \mathfrak{R}_{0p} interims of \mathfrak{R}_{0t} . Since ,

$$\begin{aligned}\mathfrak{R}_{0t} &= \frac{\sigma_1 v Q}{\mu \mu_b k (\beta_2 + \alpha_2 + \sigma_1 + \mu)} \\ \Rightarrow \mu &= \frac{\sigma_1 v Q}{\mathfrak{R}_{0t} \mu_b k (\beta_2 + \alpha_2 + \sigma_1 + \mu)}.\end{aligned}$$

Then substituting the expression for μ in \mathfrak{R}_{0p} give

$$\mathfrak{R}_{0p} = \frac{\gamma \mathfrak{R}_{0t} \mu_b k (\beta_2 + \alpha_2 + \sigma_1 + \mu)}{\sigma_1 v (\beta_1 + \alpha_1 + \mu)}.$$

To investigate the impact of the two disease each other we did;

$$\frac{\partial \mathfrak{R}_{0p}}{\partial \mathfrak{R}_{0t}} = \frac{\gamma \mu_b k (\beta_2 + \alpha_2 + \sigma_1 + \mu)}{\sigma_1 v (\beta_1 + \alpha_1 + \mu)} > 0. \quad (5.5.10)$$

Equation (5.5.10) shows that Typhoid fever cases increase Pneumonia cases and also similarly Pneumonia cases increase Typhoid fever cases.

To investigate treatment of Pneumonia reduces Typhoid fever diseases;

From

$$\mathfrak{R}_{0p} = \frac{\gamma Q}{\mu (\beta_1 + \alpha_1 + \mu)},$$

we get

$$\mu = \frac{\gamma Q}{\mathfrak{R}_{0p} (\beta_1 + \alpha_1 + \mu)}. \quad (5.5.11)$$

After combination of equation (5.5.11) and \mathfrak{R}_{0t} we obtain,

$$\mathfrak{R}_{0t} = \frac{\sigma_1 v (\mathfrak{R}_{0p} (\beta_1 + \alpha_1 + \mu) + \gamma Q)}{k \mu_b (\beta_1 + \alpha_1 + \mu) (\beta_1 + \alpha_1) (\beta_2 + \alpha_2 + \mu + \sigma_1)} \quad (5.5.12)$$

$$\frac{\partial \mathfrak{R}_{0t}}{\partial \beta_1} = \frac{\sigma_1 v}{k \mu_b (\beta_2 + \alpha_2 + \mu + \sigma_1)} - \frac{[\mathfrak{R}_{0p} (\beta_1^2 + 2\beta_1 (\alpha_1 + \mu) + (\alpha_1 + \mu)^2) + \gamma Q (2\beta_1 + 2\alpha_1 + \mu)]}{(\beta_1 + \alpha_1 + \mu)^2 (\beta_1 + \alpha_1)^2} \quad (5.5.13)$$

Equation (5.5.13) shows $\frac{\partial \mathfrak{R}_{0t}}{\partial \beta_1} < 0$, this mean treatment of Pneumonia (β_1) have an impact in decreasing Typhoid fever infection and similarly can be shown treatment of Typhoid fever (β_2) have an impact in Pneumonia infection cases.

5.5.9 Bifurcation Analysis

We investigated the nature of the bifurcation by using the method introduced in chapter 2, which is based on the use of the center manifold theory. There are two important quantities: the coefficients, say a and b , of the normal form representing the dynamics of the system on the central manifold. These coefficients decide the bifurcation. In particular, if $a < 0$ and $b > 0$, then the bifurcation is forward; if $a > 0$ and $b > 0$, then the bifurcation is backward. Using this approach, the following result may be obtained:

Theorem 5.5.4. *If $\mathfrak{R}_0 < 1$ and*

$$a_0 = \sigma_2 \mu_b \beta_2 - \sigma_1 \frac{v^* Q}{\mu k} (\delta_2 + \mu) > 0 \quad (5.5.14)$$

then system (5.2.1) exhibits a backward bifurcation at $\mathfrak{R}_0 = 1$. If the inequality holds reversed, then the system exhibits a forward bifurcation at $\mathfrak{R}_0 = 1$.

Proof.

First, we consider the transmission rate γ and v as bifurcation parameters so that $\mathfrak{R}_{0p} = 1$ and $\mathfrak{R}_{0t} = 1$ if and only if

$$\gamma = \gamma^* = \frac{\mu(\beta_1 + \alpha_1 + \mu)}{Q}$$

and

$$v = v^* = \frac{k\mu_b(\beta_1 + \alpha_1 + \mu)(\beta_2 + \alpha_2 + \mu + \sigma_1)}{\sigma_1(\mathfrak{R}_{0p}(\beta_1 + \alpha_1 + \mu)(\beta_1 + \alpha_1) + \gamma Q)}$$

Then we make the following change of variables $S = x_1, I_p = x_2, I_t = x_3, I_p = x_4, R_p = x_5, R_t = x_6, R_{tp} = x_7, B = x_8$. In addition, using vector notation $x = (x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8)^T$, the Pneumonia Typhoid model can then be written in the form $\frac{dx}{dt} = F(x)$, with $F = (f_1, f_2, f_3, f_4, f_5, f_6, f_7, f_8)^T$, as

shown below:

$$\begin{cases} \frac{dx_1}{dt} = Q + \delta_1 x_5 + \delta_2 x_6 + \delta_3 x_7 - (\lambda_{1x} + \lambda_{2x} + \mu)x_1 \\ \frac{dx_2}{dt} = \lambda_{1x} x_1 - (\lambda_{2x} + \beta_1 + \alpha_1 + \mu)x_2 \\ \frac{dx_3}{dt} = \lambda_{2x} x_1 - (\lambda_{1x} + \beta_2 + \alpha_2 + \sigma_1 + \mu)x_3 \\ \frac{dx_4}{dt} = \lambda_{2x} x_2 + \lambda_{1x} x_3 - (\sigma + \alpha_1 + \sigma_2 + \alpha_2 + \mu)x_4 \\ \frac{dx_5}{dt} = \beta_1 x_2 + \sigma e x_4 - (\delta_1 + \mu)x_5 \\ \frac{dx_6}{dt} = \beta_2 x_3 + \sigma g(1-e)x_4 - (\delta_2 + \mu)x_6 \\ \frac{dx_7}{dt} = \sigma(1-g)(1-e)x_4 - (\delta_3 + \mu)x_7 \\ \frac{dx_8}{dt} = \pi + \sigma_1 x_3 + \sigma_2 x_4 - \mu_b x_8, \end{cases} \quad (5.5.15)$$

where, $\lambda_{1x} = \gamma(x_2 + \Upsilon x_4)$ and $\lambda_{2x} = \frac{vx_8}{k+x_8}$.

This method involves evaluation of the Jacobian of the system (5.5.15) at the disease free equilibrium (DFE), denoted by J_{E_0} . This becomes

$$J_{E_0} = \begin{bmatrix} -\mu & -J_1 & 0 & -J_2 & \delta_1 & \delta_2 & \delta_3 & -J_3 \\ 0 & -J_4 & 0 & -J_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & -J_5 & 0 & 0 & 0 & 0 & J_6 \\ 0 & 0 & 0 & -J_7 & 0 & 0 & 0 & 0 \\ 0 & \beta_1 & 0 & J_{11} & -J_8 & 0 & 0 & 0 \\ 0 & 0 & \beta_2 & J_9 & 0 & -J_9 & 0 & 0 \\ 0 & 0 & 0 & J_{10} & 0 & 0 & -J_{11} & 0 \\ 0 & 0 & \sigma_1 & \sigma_2 & 0 & 0 & 0 & \mu_b \end{bmatrix} \quad (5.5.16)$$

Where,

$$J_1 = \frac{\gamma Q}{\mu}, J_2 = \frac{\gamma \Upsilon Q}{\mu}, J_3 = \frac{vQ}{\mu k}, J_4 = \frac{\gamma Q}{\mu} + (\beta_1 + \alpha_1 + \mu), J_5 = (\beta_2 + \alpha_2 + \sigma_1 + \mu), J_6 = \frac{vQ}{\mu k},$$

$$J_7 = (\sigma + \alpha_1 + \alpha_2 + \sigma_2 + \mu), J_8 = (\delta_1 + \mu), J_9 = (\delta_2 + \mu), J_{10} = \beta_1 + \alpha_1 + \mu \text{ and } J_{11} = (\delta_3 + \mu). \text{ We}$$

first start by calculating the right eigenvector of $J(E_0)$ denoted respectively by $w = [w_1, w_2, w_3, w_4, w_5, w_6, w_7, w_8]^T$

$$\begin{bmatrix} -\mu & -J_1 & 0 & -J_2 & \delta_1 & \delta_2 & \delta_3 & -J_3 \\ 0 & -J_4 & 0 & -J_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & -J_5 & 0 & 0 & 0 & 0 & J_6 \\ 0 & 0 & 0 & -J_7 & 0 & 0 & 0 & 0 \\ 0 & \beta_1 & 0 & J_{11} & -J_8 & 0 & 0 & 0 \\ 0 & 0 & \beta_2 & J_9 & 0 & -J_9 & 0 & 0 \\ 0 & 0 & 0 & J_{10} & 0 & 0 & -J_{11} & 0 \\ 0 & 0 & \sigma_1 & \sigma_2 & 0 & 0 & 0 & -\mu_b \end{bmatrix} \begin{pmatrix} w_1 \\ w_2 \\ w_3 \\ w_4 \\ w_5 \\ w_6 \\ w_7 \\ w_8 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \quad (5.5.17)$$

Then equation (5.5.17) can be written as;

$$\left\{ \begin{array}{l} -\mu w_1 - J_1 w_2 - J_2 w_4 + \delta_1 w_3 + \delta_2 w_6 + \delta_3 w_7 - J_3 w_8 = 0 \\ -J_4 w_2 - J_2 w_4 = 0 \\ -J_5 w_3 - J_6 w_8 = 0 \\ -J_7 w_4 = 0 \\ \beta_1 w_2 + J_{11} w_4 - J_8 w_5 = 0 \\ \beta_2 w_3 + J_9 w_4 - J_9 w_6 = 0 \\ J_{10} w_4 - J_{11} w_7 = 0 \\ \sigma_1 w_3 + \sigma_2 w_4 - \mu_b w_8 = 0. \end{array} \right. \quad (5.5.18)$$

From equation (5.5.18) we obtain,

$$w_1 = \frac{1}{\mu}(\delta_2 w_6 - J_3 w_8), w_2 = w_4 = w_5 = w_7 = 0, w_3 = w_3 > 0, w_6 = \frac{\beta_2}{J_9} w_3 \text{ and } w_8 = \frac{\sigma_1}{\mu_b} w_3.$$

The left eigenvectors of J_E associated with the zero eigenvalue is given by $v = (v_1, v_2, v_3, v_4, v_5, v_7, v_8)^T$, is calculated as;

$$\begin{bmatrix}
-\mu & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
-J_1 & -J_4 & 0 & 0 & \beta_1 & 0 & 0 & 0 \\
0 & 0 & -J_5 & 0 & 0 & \beta_2 & 0 & \sigma_1 \\
-J_2 & -J_2 & 0 & -J_7 & J_{11} & J_9 & J_{10} & \sigma_2 \\
\delta_1 & 0 & 0 & 0 & -J_8 & 0 & 0 & 0 \\
\delta_2 & 0 & 0 & 0 & 0 & -J_9 & 0 & 0 \\
\delta_3 & 0 & 0 & 0 & 0 & 0 & -J_{11} & 0 \\
-J_3 & 0 & J_6 & 0 & 0 & 0 & 0 & -\mu_b
\end{bmatrix}
\begin{pmatrix}
v_1 \\
v_2 \\
v_3 \\
v_4 \\
v_5 \\
v_6 \\
v_7 \\
v_8
\end{pmatrix}
=
\begin{pmatrix}
0 \\
0 \\
0 \\
0 \\
0 \\
0 \\
0 \\
0
\end{pmatrix}
\quad (5.5.19)$$

Equation (5.5.19) can be written as,

$$\begin{cases}
-\mu v_1 = 0 \\
-J_1 v_1 - J_2 v_2 + \beta_1 v_5 = 0 \\
-J_5 v_3 + \beta_2 v_6 + \sigma_1 v_8 = 0 \\
-J_2 v_1 - J_2 v_2 - J_7 v_4 + J_{11} v_5 + J_9 v_6 + J_{10} v_7 + \sigma_2 v_8 = 0 \\
\delta_1 v_1 - J_8 v_5 = 0 \\
\delta_2 v_1 - J_9 v_6 = 0 \\
\delta_3 v_1 - J_{11} v_7 = 0 \\
-J_3 v_1 + J_6 v_3 - \mu_b v_8 = 0.
\end{cases}
\quad (5.5.20)$$

Solving equation (5.5.20) gives, $v_1 = v_2 = v_5 = v_6 = v_7 = 0$, $v_3 = v_3 > 0$, $v_4 = \frac{\sigma_2}{J_7} v_8$ and $v_8 = \frac{J_5}{\sigma_1} v_3$ where v_3 is calculated to ensure that the eigenvectors satisfy the condition $v \cdot w = 1$.

The coefficients a and b defined in Theorem Appendix B.1, i. e

$$a = \sum_{k,i=1}^n v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j} (S_0, 0, 0, 0, 0, 0, 0, 0), \quad (5.5.21)$$

$$b = \sum_{k,i=1}^n v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial v^*} (S_0, 0, 0, 0, 0, 0, 0, 0), \quad (5.5.22)$$

may be now explicitly computed. Taking into account of system (5.5.15) and considering only the

non-zero components of the left eigenvector v , it follows that:

$$a = v_3 \left(3w_1w_8 \frac{\partial^2 f_3}{\partial x_1 \partial x_8} \right)$$

and

$$b = v_3w_8 \frac{\partial^2 f_3}{\partial x_8 \partial v^*}.$$

where the f_i s denote the right hand side of system (5.5.15). It can be checked that:

$$\frac{\partial^2 f_3}{\partial x_1 \partial x_8} = \frac{v}{k},$$

$$\frac{\partial^2 f_3}{\partial x_8 \partial v^*} = \frac{\Lambda}{\mu k}.$$

It follows:

$$b = \frac{\sigma_1 \Lambda}{\mu \mu_b k} v_3 w_3$$

so that b is always positive, and:

$$a = 3v^* \sigma_1 \left(\frac{a_0}{\mu \mu_b^2 J_9} \right) w_3^2 v_3$$

where a_0 is defined in (5.5.14). Therefore, system (5.2.1) exhibits backward or forward bifurcation at $\mathfrak{R}_0 = 1$ according to the sign of a_0 .

5.5.10 Sensitivity Analysis

We did Sensitivity analysis of some basic parameters of the model. This helped us to identify the parameters that have great influence on the basic reproductive number (\mathfrak{R}_0). We used the techniques outlined in Chitnis *et al.*, (2008). Sensitivity index of \mathfrak{R}_0 with respect to some parameter, say k is given by $\Lambda_k^{\mathfrak{R}_0} = \frac{\partial \mathfrak{R}_0}{\partial k} \frac{k}{\mathfrak{R}_0}$. Since $\mathfrak{R}_0 = \max\{\mathfrak{R}_{0p}, \mathfrak{R}_{0t}\}$, we obtain the sensitivity analysis of \mathfrak{R}_{0p} and \mathfrak{R}_{0t} separately.

$$\Lambda_\gamma^{\mathfrak{R}_{0p}} = \frac{\partial \mathfrak{R}_{0p}}{\partial \gamma} \frac{\gamma}{\mathfrak{R}_{0p}} = \frac{Q}{\mu(\beta_1 + \alpha_1 + \mu)} \frac{\gamma \mu (\beta_1 + \alpha_1 + \mu)}{\gamma Q} = 1 > 0$$

$$\Lambda_{\alpha_1}^{\mathfrak{R}_{0p}} = \frac{\partial \mathfrak{R}_{0p}}{\partial \alpha_1} \frac{\alpha_1}{\mathfrak{R}_{0p}} = -\frac{\alpha_1}{(\beta_1 + \alpha_1 + \mu)} < 0$$

$$\Lambda_{\beta_1}^{\mathfrak{R}_{0p}} = \frac{\partial \mathfrak{R}_{0p}}{\partial \beta_1} \frac{\beta_1}{\mathfrak{R}_{0p}} = -\frac{\beta_1}{(\beta_1 + \alpha_1 + \mu)} < 0$$

$$\Lambda_{\mu}^{\mathfrak{R}_{0p}} = \frac{\partial \mathfrak{R}_{0p}}{\partial \mu} \frac{\mu}{\mathfrak{R}_{0p}} = -\frac{(\beta_1 + \alpha_1 + 2\mu)}{(\beta_1 + \alpha_1 + \mu)} < 0$$

$$\Lambda_v^{\mathfrak{R}_{0r}} = \frac{\partial \mathfrak{R}_{0r}}{\partial v} \frac{v}{\mathfrak{R}_{0r}} = \frac{\sigma_1 Q}{\mu \mu_b (\beta_2 + \alpha_2 + \sigma_1 + \mu)} \frac{v \mu \mu_b (\beta_2 + \alpha_2 + \sigma_1 + \mu)}{\sigma_1 v Q} = 1 > 0$$

$$\Lambda_{\sigma_1}^{\mathfrak{R}_{0r}} = \frac{\partial \mathfrak{R}_{0r}}{\partial \sigma_1} \frac{\sigma_1}{\mathfrak{R}_{0r}} = \frac{(\beta_2 + \alpha_2 + \mu)}{(\beta_2 + \alpha_2 + \sigma_1 + \mu)} > 0$$

$$\Lambda_{\alpha_2}^{\mathfrak{R}_{0r}} = \frac{\partial \mathfrak{R}_{0r}}{\partial \alpha_2} \frac{\alpha_2}{\mathfrak{R}_{0r}} = -\frac{\alpha_2}{(\beta_2 + \alpha_2 + \sigma_1 + \mu)} < 0$$

$$\Lambda_{\beta_2}^{\mathfrak{R}_{0r}} = \frac{\partial \mathfrak{R}_{0r}}{\partial \beta_2} \frac{\beta_2}{\mathfrak{R}_{0r}} = -\frac{\beta_2}{(\beta_2 + \alpha_2 + \sigma_1 + \mu)} < 0$$

$$\Lambda_{\mu_b}^{\mathfrak{R}_{0r}} = \frac{\partial \mathfrak{R}_{0r}}{\partial \mu_b} \frac{\mu_b}{\mathfrak{R}_{0r}} = -\frac{\sigma_1 v Q}{\mu_b^2 \mu (\beta_2 + \alpha_2 + \sigma_1 + \mu)} \frac{\mu_b^2 \mu (\beta_2 + \alpha_2 + \sigma_1 + \mu)}{\sigma_1 v Q} = -1 < 0$$

$$\Lambda_{\mu}^{\mathfrak{R}_{0r}} = \frac{\partial \mathfrak{R}_{0r}}{\partial \mu} \frac{\mu}{\mathfrak{R}_{0r}} = -\frac{(\beta_2 + \alpha_2 + \sigma_1 + 2\mu)}{(\beta_2 + \alpha_2 + \sigma_1 + \mu)} < 0$$

The above sensitivity analysis is summarized in table (5.5.1).

Table 5.5.1: Indices of sensitivity

Symbol	Description	Sensitivity indices
\mathfrak{R}_{0p}	Basic reproduction number of Pneumonia only	
γ	Infectious rate of pneumonia	1
β_1	Treatment rate of Pneumonia	-0.36055
α_1	Pneumonia induced death rate	-0.91942
μ	Natural causing death rate	-1.044
\mathfrak{R}_{0r}	Basic reproduction number of Typhoid fever only	
v	Ingestion rate of Salmonella bacteria	1
σ_1	Discharge rate of salmonella from Typhoid infected individuals	0.011
β_2	Treatment rate of Typhoid fever	-0.0025
α_2	Typhoid fever induced death rate	-0.00642
μ_b	Natural/ drug induced death rate of salmonella	-1
μ	Natural causing death rate	-1.003

In table (5.5.1) Parameters that have positive sensitivity indices, particularly γ and v have great influence in expanding the disease if their values are increased, while the other parameters are unchanged. Due to the reason that, they increase the average number of secondary case infection.

Examining the sensitivity analysis, it is not biologically reasonable to suggest that the human mortality rate (α_1, α_2, μ) be increased in order to control the disease. The other possible sensitive parameters (negative sensitivity indices) that are important for effective control of the disease are treatment rate of pneumonia, treatment rate of typhoid fever and drug /natural induced death rate of salmonella.

Therefore, in section ??, we shall incorporate control measures to determine the optimal strategy for controlling Pneumonia-typhoid fever co-infection.

5.6 Optimal Control

In this section, we extend Pneumonia-Typhoid fever co-infection model (5.6.1) by incorporating five control interventions . This helped us to identify the best intervention strategies that helps to eradicate the disease in the specified time. The control intervention are defined as:

- i. u_1 prevention effort of Pneumonia disease, that protect susceptible from contacting the disease.
- ii. u_2 prevention of typhoid fever disease by keeping proper personal sanitation that protect susceptible from contacting salmonella bacteria.
- iii. u_3 treatment effort of pneumonia infected individuals.
- iv. u_4 treatment effort of typhoid fever infected individuals.
- v. u_5 mass cleaning of environments and ponds to eliminate typhoid causing bacteria.

After incorporating, u_1, u_2, u_3, u_4 and u_5 in pneumonia-Typhoid co-infection model (5.6.1), we obtain the following optimal control model:

$$\left\{ \begin{array}{l} \frac{dS}{dt} = Q + \delta_1 R_p + \delta_2 R_t + \delta_3 R_{tp} - ((1 - u_1)\lambda_1 + (1 - u_2)\lambda_2 + \mu)S \\ \frac{dI_p}{dt} = (1 - u_1)\lambda_1 S - (1 - u_2)\lambda_2 I_p - (\beta_1 + u_3)I_p - (\alpha_1 + \mu)I_p \\ \frac{dI_t}{dt} = (1 - u_2)\lambda_2 S - (1 - u_1)\lambda_1 I_t - t - (\beta_2 + u_4)I_t - (\alpha_2 + \sigma_1 + \mu)I_t \\ \frac{dI_{tp}}{dt} = (1 - u_2)\lambda_2 I_p + (1 - u_1)\lambda_1 I_t - (\sigma + u_3 + u_4)I_{tp} - (\alpha_1 + \alpha_2 + \sigma_2 + \mu)I_{tp} \\ \frac{dR_p}{dt} = (\beta_1 + u_3)I_p + (\sigma e + u_3)I_{tp} - (\delta_1 + \mu)R_p \\ \frac{dR_t}{dt} = (\beta_2 + u_4)I_t + (\sigma g(1 - e) + u_4)I_{tp} - (\delta_2 + \mu)R_t \\ \frac{dR_{tp}}{dt} = (\sigma(1 - g)(1 - e) + u_3 + u_4)I_{tp} - (\delta_3 + \mu)R_{tp} \\ \frac{dB}{dt} = \pi + \sigma_1 I_t + \sigma_2 I_{tp} - (u_5 + \mu_b)B, \end{array} \right. \quad (5.6.1)$$

To study the optimal levels of the controls the control set U is Lebesgue measurable and it is defined as : $U = \{(u_1(t), u_2(t), u_3(t), u_4(t), u_5(t)) : 0 \leq u_1 < 1, 0 \leq u_2 < 1, 0 \leq u_3 < 1, 0 \leq u_4 < 1, 0 \leq u_5 < 1, 0 \leq t \leq T\}$. Our aim is to obtain a control U and $S, I_p, I_t, I_{tp}, R_p, R_t, R_{tp}$ and B that minimize the

proposed J and the form of the objective functional (J) is taken from [16], given by:

$$J = \min_{u_1, u_2, u_3, u_4, u_5} \int_0^{t_f} (b_1 I_p + b_2 I_t + b_3 I_{tp} + \frac{1}{2} \sum_{i=1}^5 w_i u_i^2) dt. \quad (5.6.2)$$

Where b_1, b_2, b_3 and w_i are positive. The expression $\frac{1}{2} w_i u_i^2$ represents cost which is associated with the controls u_i . The form is quadratic because we assume that costs are non-linear in its nature. Our aim is to minimize the number of infectious and costs. Thus, we want to obtain an optimal controls $(u_1^*, u_2^*, u_3^*, u_4^*, u_5^*)$ in which:

$$J(u_1^*, u_2^*, u_3^*, u_4^*, u_5^*) = \min\{J(u_1, u_2, u_3, u_4, u_5) / u_i \in U\},$$

where, $U = \{(u_1, u_2, u_3, u_4, u_5) / \text{each } u_i \text{ is measurable with } 0 \leq u_i < 1 \text{ for } 0 \leq t \leq t_f\}$.

5.6.1 The Hamiltonian and Optimality System

By using the principle of [17], "Pontryagin's Maximum Principle Pontryagin", we obtained a Hamiltonian (H) defined as:

$$H(S, I_p, I_t, I_{tp}, R_p, R_t, R_{tp}, B, t) = L(I_p, I_t, I_{tp}, u_1, u_2, u_3, u_4, u_5, t) + h_1 \frac{ds}{dt} + h_2 \frac{dI_p}{dt} + h_3 \frac{dI_t}{dt} + h_4 \frac{dI_{tp}}{dt} + h_5 \frac{dR_p}{dt} + h_6 \frac{dR_t}{dt} + h_7 \frac{dR_{tp}}{dt} + h_8 \frac{dB}{dt}.$$

Where $L(I_p, I_t, I_{tp}, u_1, u_2, u_3, u_4, u_5, t) = b_1 I_p + b_2 I_t + b_3 I_{tp} + \frac{1}{2} \sum_{i=1}^5 w_i u_i^2$, $h_i, i = 1, 2, 3, 4, 5, 6, 7, 8$ are the adjoint variable functions to be determined suitably by applying Pontryagin's maximal principle [17] and also using [18] for existence of the optimal control pairs.

Theorem 5.6.1. *For an optimal control set u_1, u_2, u_3, u_4, u_5 that minimizes J over U , there is an adjoint*

variables, h_1, \dots, h_8 such that:

$$\left\{ \begin{array}{l} \frac{dh_1}{dt} = -h_1 \left(-\frac{(1-u_2)Bv}{k+B} - \frac{\gamma(I_p + \Upsilon I_{pp})(1-u_1)}{N} - \mu \right) - \frac{h_2 \gamma(I_p + \Upsilon I_{pp})(1-u_1)}{N} - \frac{h_3(1-u_2)Bv}{k+B} \\ \frac{dh_2}{dt} = -b_1 + \frac{h_1 \gamma(1-u_1)S}{N} - h_2 \left(\frac{\gamma(1-u_1)S}{N} - \frac{(1-u_2)Bv}{k+B} - \beta_1 - u_3 - \alpha_1 - \mu \right) + \frac{h_3 \gamma(1-u_1)I_t}{N} \\ \quad - h_4 \left(\frac{(1-u_2)Bv}{k+B} + \frac{\gamma(1-u_1)I_t}{N} \right) - \lambda_5 (\beta_1 + u_3) \\ \frac{dh_3}{dt} = -b_2 - h_3 \left(-\frac{\gamma(I_p + \Upsilon I_{pp})(1-u_1)}{N} - \beta_2 - u_4 - \alpha_2 - \sigma_1 - \mu \right) - \frac{h_4 \gamma(I_p + \Upsilon I_{pp})(1-u_1)}{N} - h_6 (\beta_2 + u_4) - h_8 \sigma_1 \\ \frac{dh_4}{dt} = -b_3 + \frac{h_1 \gamma(1-u_1)S}{N} - \frac{h_2 \gamma(1-u_1)S}{N} + \frac{h_3 \gamma(1-u_1)I_t}{N} - h_4 \left(\frac{\gamma(1-u_1)I_t}{N} - \sigma - u_3 - u_4 - \alpha_1 - \alpha_2 - \sigma_2 - \mu \right) \\ \quad - h_5 (\sigma e + u_3) - h_6 (\sigma (1-e) + u_4) - h_7 (\sigma (1-g) (1-e) + u_3 + u_4) - h_8 \sigma_2 \\ \frac{dh_5}{dt} = -h_1 \delta_1 - h_5 (-\delta_1 - \mu) \\ \frac{dh_6}{dt} = -h_1 \delta_2 - h_6 (-\delta_2 - \mu) \\ \frac{dh_7}{dt} = -h_1 \delta_3 - h_7 (-\delta_3 - \mu) \\ \frac{dh_8}{dt} = -\frac{h_1(1-u_2)BvS}{(k+B)^2} - \frac{h_2(1-u_2)BvI_p}{(k+B)^2} + \frac{h_3(1-u_2)BvS}{(k+B)^2} + \frac{h_4(1-u_2)BvI_p}{(k+B)^2} - h_8 (-u_5 - \mu_b) \end{array} \right. \quad (5.6.3)$$

With transversality conditions, $h_i(t_f) = 0, i = 1, \dots, 8$.

Furthermore, we obtain the control set $(u_1^*, u_2^*, u_3^*, u_4^*, u_5^*)$ characterized by

$$\begin{aligned} u_1^*(t) &= \max\{0, \min(1, \Phi_1)\}, & u_4^*(t) &= \max\{0, \min(1, \Phi_4)\}, \\ u_2^*(t) &= \max\{0, \min(1, \Phi_2)\}, & u_5^*(t) &= \max\{0, \min(1, \Phi_5)\}, \\ u_3^*(t) &= \max\{0, \min(1, \Phi_3)\}, \end{aligned}$$

where,

$$\begin{aligned} \Phi_1 &= -\frac{\gamma(I_p + \Upsilon I_{pp})(Sh_1 - Sh_2 + I_t h_3 - I_t h_4)}{Nw_1} & \Phi_4 &= \frac{(h_4 - h_6 - h_7)I_{pp} + I_t(h_3 - h_6)}{w_4} \\ \Phi_2 &= -\frac{Bv(Sh_1 - Sh_3 + I_p h_2 - I_p h_4)}{(k+B)w_2} & \Phi_5 &= \frac{h_8 B}{w_5} \\ \Phi_3 &= \frac{I_p h_2 - I_p h_5 + h_4 \Upsilon I_{pp} - \Upsilon I_{pp} h_5 - h_7 \Upsilon I_{pp}}{w_3} \end{aligned}$$

Proof:

By using Pontryagin's maximum principle [17] we obtain the following system of adjoint variables: :

$$\frac{dh_1}{dt} = -\frac{dH}{dS} = -h_1 \left(-\frac{(1-u_2)Bv}{k+B} - \frac{\gamma(I_p + \Upsilon I_{pp})(1-u_1)}{N} - \mu \right) - \frac{h_2 \gamma(I_p + \Upsilon I_{pp})(1-u_1)}{N} - \frac{h_3(1-u_2)Bv}{k+B}$$

$$\frac{dh_2}{dt} = -\frac{dH}{dI_p} = -b_1 + \frac{h_1\gamma(1-u_1)S}{N} - h_2 \left(\frac{\gamma(1-u_1)S}{N} - \frac{(1-u_2)Bv}{k+B} - \beta_1 - u_3 - \alpha_1 - \mu \right) + \frac{h_3\gamma(1-u_1)I_t}{N} - h_4 \left(\frac{(1-u_2)Bv}{k+B} + \frac{\gamma(1-u_1)I_t}{N} \right) - h_5(\beta_1 + u_3)$$

$$\frac{dh_3}{dt} = \frac{dH}{dI_t} = -b_2 - h_3 \left(-\frac{\gamma(I_p + \Upsilon I_{tp})(1-u_1)}{N} - \beta_2 - u_4 - \alpha_2 - \sigma_1 - \mu \right) - \frac{h_4\gamma(I_p + \Upsilon I_{tp})(1-u_1)}{N} - h_6(\beta_2 + u_4) - h_8\sigma_1$$

$$\frac{dh_4}{dt} = -\frac{dH}{dI_p} = -b_3 + \frac{h_1\gamma(1-u_1)S}{N} - \frac{h_2\gamma(1-u_1)S}{N} + \frac{h_3\gamma(1-u_1)I_t}{N} - h_4 \left(\frac{\gamma(1-u_1)I_t}{N} - \sigma - u_3 - u_4 - \alpha_1 - \alpha_2 - \sigma_2 - \mu \right) - h_5(\sigma e + u_3) - h_6(\sigma(1-e) + u_4) - h_7(\sigma(1-g)(1-e) + u_3 + u_4) - h_8\sigma_2$$

$$\frac{dh_5}{dt} = -\frac{dH}{dR_p} = -h_1\delta_1 - h_5(-\delta_1 - \mu)$$

$$\frac{dh_6}{dt} = -\frac{dH}{dR_t} = -h_1\delta_2 - h_6(-\delta_2 - \mu)$$

$$\frac{dh_7}{dt} = -\frac{dH}{dR_{tp}} = -h_1\delta_3 - h_7(-\delta_3 - \mu)$$

$$\frac{dh_8}{dt} = -\frac{dH}{dB} = -\frac{h_1(1-u_2)BvS}{(k+B)^2} - \frac{h_2(1-u_2)BvI_p}{(k+B)^2} + \frac{h_3(1-u_2)BvS}{(k+B)^2} + \frac{h_4(1-u_2)BvI_p}{(k+B)^2} - h_8(-u_5 - \mu_b)$$

Similarly by following the approach of [17], to get the controls ,we solved the equation, $\frac{\partial H}{\partial u_i} =$

0 at u_i^* , for $i = 1, \dots, 5$ and obtained:

$$u_1^* = -\frac{\gamma(I_p + \Upsilon I_{tp})(Sh_1 - Sh_2 + I_t h_3 - I_t h_4)}{Nw_1}$$

$$u_2^* = -\frac{Bv(Sh_1 - Sh_3 + \Upsilon I_p h_2 - I_p \lambda_4)}{(k+B)w_2}$$

$$u_3^* = \frac{I_p h_2 - I_p h_5 + h_4 \Upsilon I_{tp} - \Upsilon I_{tp} h_5 - h_7 \Upsilon I_{tp}}{w_3}$$

$$u_4^* = \frac{(h_4 - h_6 - h_7) \Upsilon I_{tp} + I_t (h_3 - h_6)}{w_4}$$

$$u_5^* = \frac{h_8 B}{w_5}$$

When we write by using standard control arguments involving the bounds on the controls, we conclude:

$$u_1^* = \begin{cases} \Phi_1 & \text{if } 0 < \Phi_1 < 1 \\ 0 & \text{if } \Phi_1 \leq 0 \\ 1 & \text{if } \Phi_1 \geq 1. \end{cases} \quad u_2^* = \begin{cases} \Phi_2 & \text{if } 0 < \Phi_2 < 1 \\ 0 & \text{if } \Phi_2 \leq 0 \\ 1 & \text{if } \Phi_2 \geq 1. \end{cases}$$

$$u_3^* = \begin{cases} \Phi_3 & \text{if } 0 < \Phi_3 < 1 \\ 0 & \text{if } \Phi_3 \leq 0 \\ 1 & \text{if } \Phi_3 \geq 1 \end{cases} .$$

$$u_4^* = \begin{cases} \Phi_4 & \text{if } 0 < \Phi_4 < 1 \\ 0 & \text{if } \Phi_4 \leq 0 \\ 1 & \text{if } \Phi_4 \geq 1 \end{cases} .$$

$$u_5^* = \begin{cases} \Phi_5 & \text{if } 0 < \Phi_5 < 1 \\ 0 & \text{if } \Phi_5 \leq 0 \\ 1 & \text{if } \Phi_5 \geq 1 \end{cases} .$$

In compact notation

$$u_1^*(t) = \max\{0, \min(1, \Phi_1)\},$$

$$u_2^*(t) = \max\{0, \min(1, \Phi_2)\},$$

$$u_3^*(t) = \max\{0, \min(1, \Phi_3)\},$$

$$u_4^*(t) = \max\{0, \min(1, \Phi_4)\},$$

$$u_5^*(t) = \max\{0, \min(1, \Phi_5)\}.$$

$$\Phi_1 = -\frac{\gamma(I_p + \Upsilon I_p)(Sh_1 - Sh_2 + I_t h_3 - I_t h_4)}{Nw_1}$$

$$\Phi_2 = -\frac{Bv(Sh_1 - Sh_3 + I_p h_2 - I_p h_4)}{(k+B)w_2}$$

$$\Phi_3 = \frac{I_p h_2 - I_p h_5 + h_4 \Upsilon I_p - \Upsilon I_p h_5 - h_7 \Upsilon I_p}{w_3}$$

$$\Phi_4 = \frac{(h_4 - h_6 - h_7) \Upsilon I_p + I_t (h_3 - h_6)}{w_4}$$

$$\Phi_5 = \frac{h_8 B}{w_5}$$

The optimality system is formed from the optimal control system (the state system) and the adjoint

variable system by incorporating the characterized control set and initial and transversal condition.

$$\left\{ \begin{array}{l}
\frac{dS}{dt} = Q + \delta_1 R_p + \delta_2 R_t + \delta_3 R_{tp} - ((1 - u_1^*)\lambda_1 + (1 - u_2^*)\lambda_2 + \mu)S \\
\frac{dI_p}{dt} = (1 - u_1^*)\lambda_1 S - (1 - u_2^*)\lambda_2 I_p - (\beta_1 + u_3^*)I_p - (\alpha_1 + \mu)I_p \\
\frac{dI_t}{dt} = (1 - u_2^*)\lambda_2 S - (1 - u_1^*)\lambda_1 I_t - t - (\beta_2 + u_4^*)I_t - (\alpha_2 + \sigma_1 + \mu)I_t \\
\frac{dI_{tp}}{dt} = (1 - u_2^*)\lambda_2 I_p + (1 - u_1^*)\lambda_1 I_t - (\sigma + u_3^* + u_4^*)I_{tp} - (\alpha_1 + \alpha_2 + \sigma_2 + \mu)I_{tp} \\
\frac{dR_p}{dt} = (\beta_1 + u_3^*)I_p + (\sigma e + u_3^*)I_{tp} - (\delta_1 + \mu)R_p \\
\frac{dR_t}{dt} = (\beta_2 + u_4^*)I_t + (\sigma g(1 - e) + u_4^*)I_{tp} - (\delta_2 + \mu)R_t \\
\frac{dR_{tp}}{dt} = (\sigma(1 - g)(1 - e) + u_3^* + u_4^*)I_{tp} - (\delta_3 + \mu)R_{tp} \\
\frac{dB}{dt} = \sigma_1 I_t + \sigma_2 I_{tp} - (u_5^* + \mu_b)B \\
\frac{dh_1}{dt} = -h_1 \left(-\frac{(1-u_2)Bv}{k+B} - \frac{\gamma(I_p + \Upsilon I_{tp})(1-u_1)}{N} - \mu \right) - \frac{h_2 \gamma(I_p + \Upsilon I_{tp})(1-u_1)}{N} - \frac{h_3(1-u_2)Bv}{k+B} \\
\frac{dh_2}{dt} = -b_1 + \frac{h_1 \gamma(1-u_1)S}{N} - h_2 \left(\frac{\gamma(1-u_1)S}{N} - \frac{(1-u_2)Bv}{k+B} - \beta_1 - u_3 - \alpha_1 - \mu \right) + \frac{h_3 \gamma(1-u_1)I_t}{N} \\
\quad - h_4 \left(\frac{(1-u_2)Bv}{k+B} + \frac{\gamma(1-u_1)I_t}{N} \right) - \lambda_5 (\beta_1 + u_3) \\
\frac{dh_3}{dt} = -b_2 - h_3 \left(-\frac{\gamma(I_p + \Upsilon I_{tp})(1-u_1)}{N} - \beta_2 - u_4 - \alpha_2 - \sigma_1 - \mu \right) - \frac{h_4 \gamma(I_p + \Upsilon I_{tp})(1-u_1)}{N} - h_6 (\beta_2 + u_4) - h_8 \sigma_1 \\
\frac{dh_4}{dt} = -b_3 + \frac{h_1 \gamma(1-u_1)S}{N} - \frac{h_2 \gamma(1-u_1)S}{N} + \frac{h_3 \gamma(1-u_1)I_t}{N} - h_4 \left(\frac{\gamma(1-u_1)I_t}{N} - \sigma - u_3 - u_4 - \alpha_1 - \alpha_2 - \sigma_2 - \mu \right) \\
\quad - h_5 (\sigma e + u_3) - h_6 (\sigma(1 - e) + u_4) - h_7 (\sigma(1 - g)(1 - e) + u_3 + u_4) - h_8 \sigma_2 \\
\frac{dh_5}{dt} = -h_1 \delta_1 - h_5 (-\delta_1 - \mu) \\
\frac{dh_6}{dt} = -h_1 \delta_2 - h_6 (-\delta_2 - \mu) \\
\frac{dh_7}{dt} = -h_1 \delta_3 - h_7 (-\delta_3 - \mu) \\
\frac{dh_8}{dt} = -\frac{h_1(1-u_2)BvS}{(k+B)^2} - \frac{h_2(1-u_2)BvI_p}{(k+B)^2} + \frac{h_3(1-u_2)BvS}{(k+B)^2} + \frac{h_4(1-u_2)BvI_p}{(k+B)^2} - h_8 (-u_5 - \mu_b)
\end{array} \right. \quad (5.6.4)$$

$$h_i(t_f) = 0, \quad i = 1, 2, 3, \quad S(0) = S_0, \quad V(0) = V_0, \quad C(0) = C_0, \quad I(0) = I_0, \quad \text{and} \quad R(0) = R_0.$$

5.6.2 Uniqueness of the Optimality System

Due to the boundedness of the model (5.6.4) which is considered the state, adjoint functions and also considering Lipschitz structure of the ordinary differential equations. Then it is possible to show the uniqueness of the resulting optimality system by considering small time interval. Hence the

following theorem:

Theorem 5.6.2. *For $t \in [0, t_f]$, the bounded solutions to the optimality system are unique.*

For the proof of the theorem See [19].

5.7 Numerical Simulation

In this section, we performed numerical simulation of the co-infection model (5.6.1) and the resulting optimality system (5.6.4). We make use of the parameter values given in Table (5.7.1) for the simulation.

Table 5.7.1: Parameter Values for Pneumonia Model

Parameter symbol	Value	Source
δ_1	0.002-0.1	[20]
δ_2	0.00904- 0.99	[21]
δ_3	0.01	Assumed
γ	0.001	[20]
ν	0.9	Assumed
k	50.000	[22]
β_1	0.002	Estimated
α_1	0.051	Estimated
β_2	0.002	Estimated
α_2	0.0052	Estimated
σ	0.1	Assumed
g	0.5 - 1	Assumed
e	0.5 -1	[23]
μ	0.00247	[20]
σ_1	0.8	Assumed
σ_2	0.9	Assumed
μ_b	0.0000125	[22]

To simulate the model, which is for obtaining the optimal solution of the resulting optimality system iterative technique is applied. By considering the initial condition of the state system and the final condition of the adjoint systems, we use forward fourth-order Runke-Kutta method to solve the state system and backward fourth-order Runge-Kutta method for solving the state system. The adjoint systems is solved by using the initial guess of the controls incorporating with the obtained solution

for the state system. The controls continues to be updated by combining from the previous result of the controls with the characterization. The solution of the state and adjoint system is repeated by the updated controls. This condition continues repeatedly upto consecutive iteration are close enough each other, [24].

We proposed the following five strategies for numerical simulation of the co-infection model:

- (i). Prevention effort for Pneumonia and treatment effort for Typhoid fever disease ($u_1 \neq 0, u_4 \neq 0, u_2 = u_3 = u_5 = 0$).
- (ii). Using prevention effort for Typhoid fever disease and treatment effort for Pneumonia disease ($(u_2 \neq 0, u_3 \neq 0, u_5 \neq 0, u_1 = 0, u_4 = 0)$).
- (iii). Using treatment effort for both disease ($u_3 \neq 0, u_4 \neq 0, u_1 = u_2 = u_5 = 0$).
- (iv). Using all the intervention efforts ($u_1 \neq 0, u_2 \neq 0, u_3 \neq 0, u_4 \neq 0, u_5 \neq 0$).

We assumed $b_1 = 25, b_2 = 25, b_3 = 25, w_1 = 4, w_2 = 3, w_3 = 5, w_4 = 6$ and $w_5 = 7$ for simulation of the model with optimal control and also for cost-effectiveness analysis. Additionally we used $S(0) = 1000, I_p(0) = 300, I_t(0) = 200, I_{tp}(0) = 150, R_p(0) = 200, R_t(0) = 150, R_{tp}(0) = 150$ and $B(0) = 0$ as initial values

5.7.1 Control with prevention of Pneumonia disease and treatment of Typhoid fever disease

The simulation results from figure (5.7.1) and (5.7.2) shows that a control with prevention of Pneumonia disease and treatment of Typhoid fever disease have a potential of decreasing the co-infectious, Pneumonia infectious and Typhoid fever infectious populations. From this we conclude that applying an optimized controls (prevention of Pneumonia disease and treatment of Typhoid fever disease) can eradicate both diseases from the community in a specified period of time.

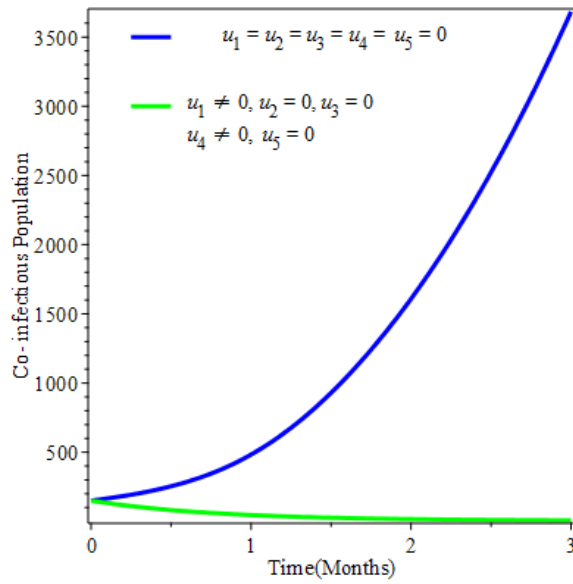


Figure 5.7.1: Simulations optimal control with prevention of Pneumonia disease and treatment of Typhoid fever disease.

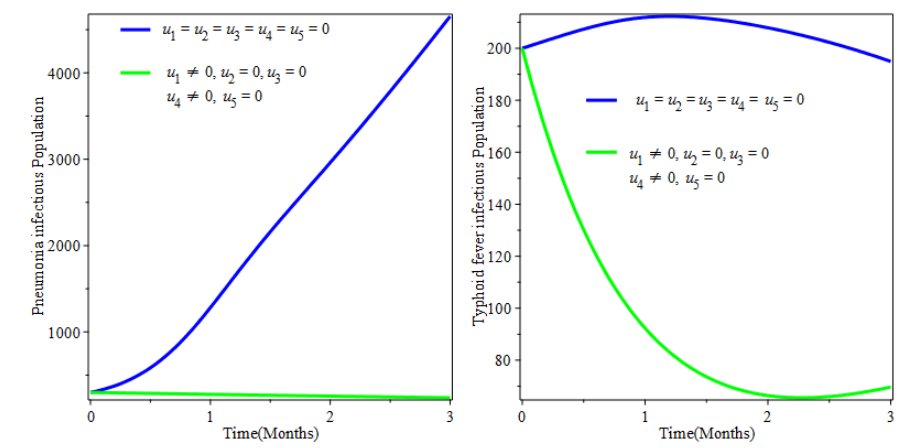


Figure 5.7.2: Simulations optimal control with prevention of Pneumonia disease and treatment of Typhoid fever disease.

5.7.2 Control with prevention effort for Typhoid fever and treatment effort for Pneumonia.

Here we used prevention for Typhoid fever disease and treatment for Pneumonia disease as intervention strategy, and figures (5.7.3) and (5.7.4) shows that, the number of co-infectious, Pneumonia infectious and Typhoid fever infectious population goes down in the specified time. Therefore, this strategies is effective in eradicating the diseases from the community in a specified period of time.

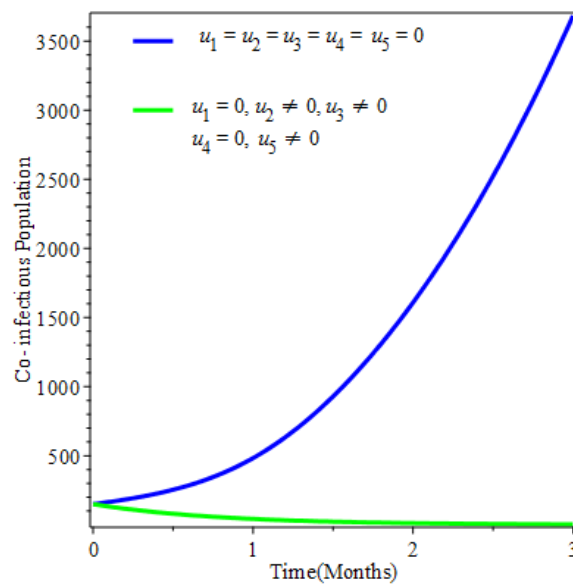


Figure 5.7.3: Simulations optimal control with Prevention of Typhoid fever disease and treatment of Pneumonia disease.

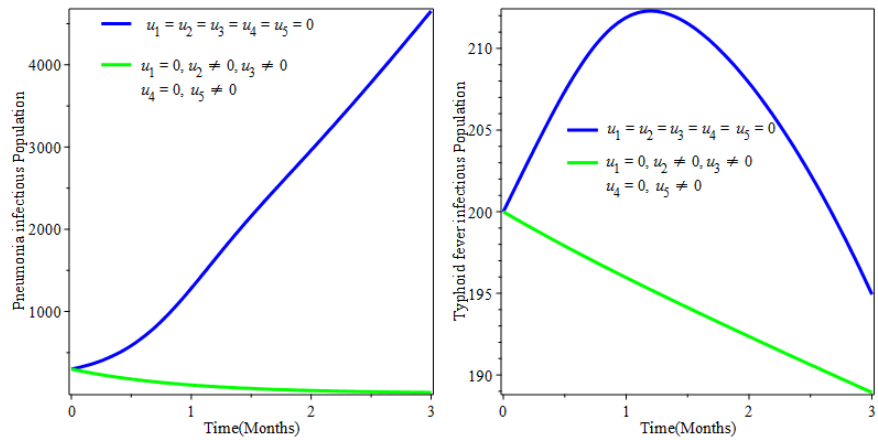


Figure 5.7.4: Simulations optimal control with Prevention of Typhoid fever disease and treatment of Pneumonia disease.

5.7.3 Control with treatment effort only for both disease

In this strategy we used treatment as an intervention for both Pneumonia and Typhoid fever disease. The simulation results in figure 5.7.5 and (5.7.6) shows that the number of co-infectious, Pneumonia infectious and Typhoid fever infectious population goes down in the specified time. Therefore, this strategies is effective in eradicating the diseases from the community in a specified period of time.

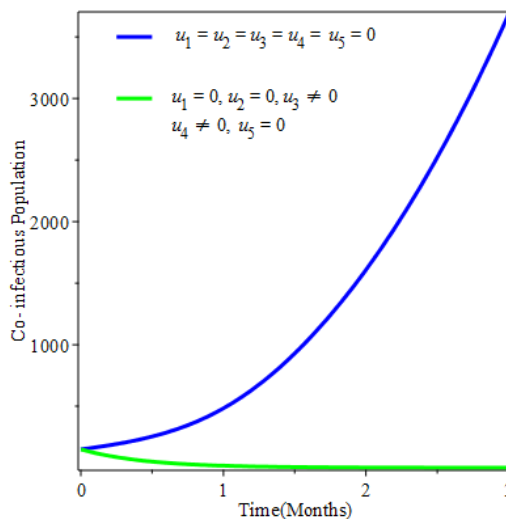


Figure 5.7.5: Simulations of optimal control with treatment of Pneumonia and Typhoid fever disease as intervention .

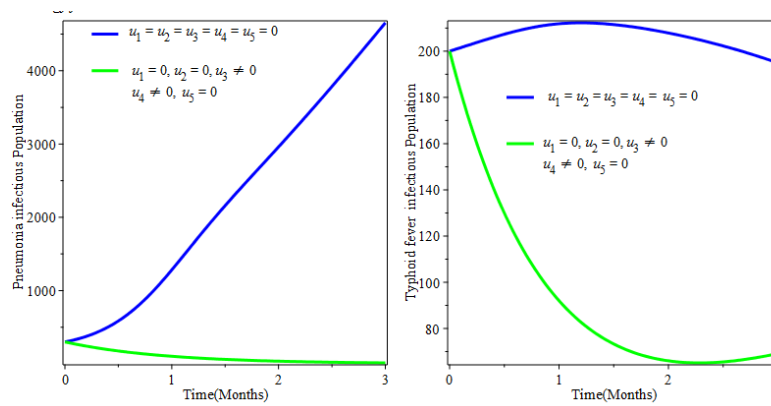


Figure 5.7.6: Simulations of optimal control with treatment of Pneumonia and Typhoid fever disease as intervention .

5.7.4 Control with all intervention efforts

Here we used all interventions efforts (prevention of both disease and treatment of both disease). treatment and screening controls as intervention. From the simulation results in figures (5.7.7) and (5.7.8) we observe that optimal control of the combination of all interventions helps to bring down the co-infectious, Pneumonia infectious as well as the Typhoid fever infectious populations. Therefore, applying this strategy is can eradicate the diseases from the community.

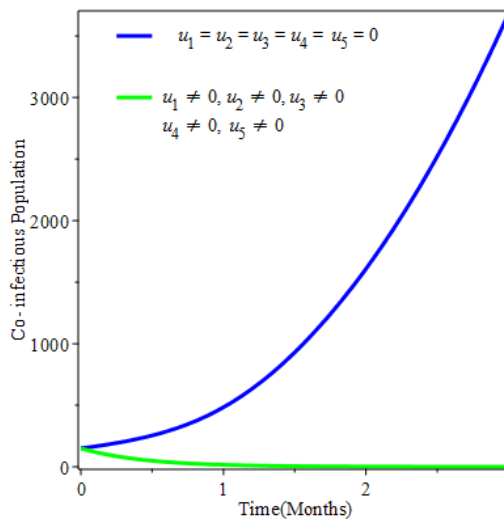


Figure 5.7.7: Simulations of optimal control all interventions.

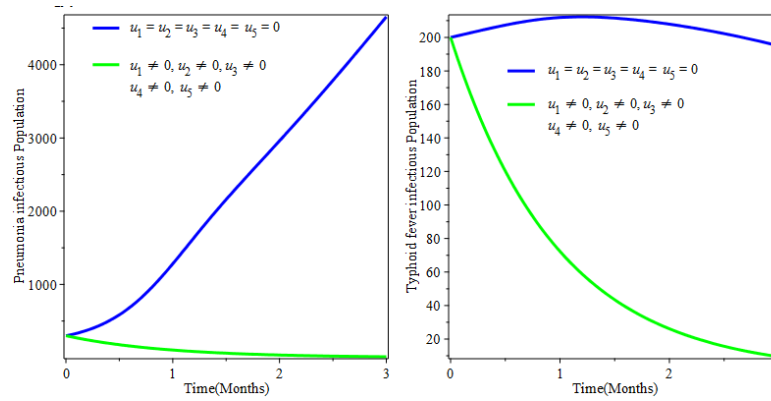


Figure 5.7.8: Simulations of optimal control with all interventions.

5.8 Cost-Effectiveness Analysis

Cost-effectiveness analysis used to rank the implemented strategies interims of their cost. To achieve, this we used incremental cost-effectiveness ratio (ICER), stated by (Baba and Makinde, 2014);

$$ICER = \frac{\text{Difference in costs between strategies}}{\text{Difference in health effects between strategies}}$$

In table (5.8.1) we obtain the total number of co-infectious averted and total cost for the implemented strategies. The total number of co-infectious averted is obtained from the differences of total individuals after and before the implementation of the control strategies. And also to find the total cost for the implemented strategies we used the cost function, which is $\frac{1}{2}w_1u_1^2$, $\frac{1}{2}w_2u_2^2$, $\frac{1}{2}w_3u_3^2$, $\frac{1}{2}w_4u_4^2$ and $\frac{1}{2}w_5u_5^2$ over time. We used the parameter values in table (5.7.1) and to apply ICER technique first we ordered the intervention strategies for pairwise comparison as in table (5.7.1) from A to D with increasing order of effectiveness.

Table 5.8.1: Number of co-infectious averted and total cost of each strategies

Strategies	Description	Averted	Total cost (USD)
1	Pneumonia Prevention and Typhoid fever treatment	370,405	1,354.5
2	Typhoid fever Prevention and Pneumonia treatment	370,792	1,204
3	Control with treatment effort only for both disease	375,659	1,655.5
4	Control with all interventions	375,911	2,709

First we compared the cost effectiveness of strategy A and B.

$$ICER(1) = \frac{1,354.5}{370,405} = 0.003,$$

$$\text{ICER}(2) = \frac{1,354.5 - 1204}{370,405 - 370,792} = -0.389.$$

From ICER (1) and ICER (2) we can see that strategy 2 saves 0.389 than strategy 1. Therefore, we exclude strategy 1, because it is a bit expensive, so we continue to compare strategy 2 and 3.

$$\text{ICER}(2) = \frac{1,204}{370,792} = 0.00325,$$

$$\text{ICER}(3) = \frac{1204 - 1655.5}{370,792 - 355,659} = 0.093.$$

Similarly, from ICER (2) and ICER (3) we can see that strategy 2 saves 0.00325 than strategy 3. Therefore, we exclude strategy 3, because it is a bit expensive and we continue to compare strategy 2 and 4.

$$\text{ICER}(2) = 0.00325$$

$$\text{ICER}(4) = \frac{1204 - 2,709}{370,792 - 375,911} = 0.029$$

Similarly, from ICER (2) and ICER (4) we can see that strategy 2 saves 0.00325 than strategy 4. Therefore, we exclude strategy 4, because it is a bit expensive. Therefore, we conclude that strategy 2 (Typhoid fever prevention and Treatment of Pneumonia) is the cheapest of all compared strategies, that meant it is the most cost-effective for pneumonia-Typhoid fever disease co-infection control interventions strategy but strategy 4 is the most expensive of all the above strategies .

For further elaboration we plotted the cost function of each strategy in figure (5.8.1) and the figure shows that strategy 2 (Pneumonia treatment and Typhoid fever prevention) is the least cost for implementing the intervention and strategy 4 (using all intervention) costs the highest of all strategies for implementation.

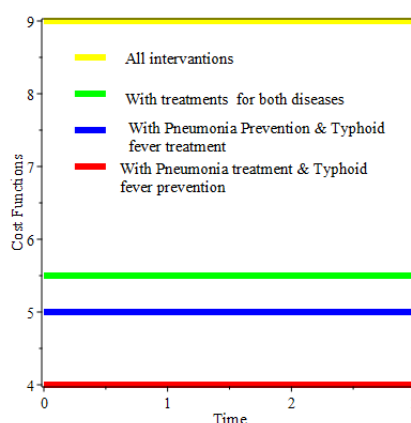


Figure 5.8.1: Cost Function of the intervention strategies

5.9 Discussions and Conclusions

In section 5.2 we briefly described and proposed a pneumonia-Typhoid fever co-infection model, which is deterministic in its nature and also the population is assumed to be variable in size. In section 5.3 we analysed Pneumonia only model by obtaining the feasible region, positivity of the solution set, basic reproductive number, equilibria points and their stability. In section 5.4 also we analysed Typhoid fever only model by obtaining the feasible region, positivity of the solution set, basic reproductive number, equilibria points and their stability. In section 5.5 we analysed the full Pneumonia-Typhoid fever co-infection model by obtaining the feasible region, positivity of the solution set, basic reproductive number which is the maximum of the basic reproductive number of Pneumonia and Typhoid fever only models, equilibria points and their stability are analysed. Moreover, by using Castillo- Chavez *et al.*, (2002) theorem possibility of bifurcation of the model is analyzed. The impact of the two diseases on each other are also investigated and the result indicate that Pneumonia cases increase Typhoid fever cases and also Typhoid fever cases increase Pneumonia cases. Moreover, we explored that treatment of Pneumonia have an impact of reducing Typhoid fever disease and also similarly treatment of Typhoid fever disease have also an impact of reducing Pneumonia disease. Sensitivity analysis of basic parameters and interpretation of the sensitivity index is also done in section 5.5. In section 5.6 the full Pneumonia-Typhoid fever co-infection model is extended, by applying optimal control interventions then the Hamiltonian, the adjoint variables, the characterization of the controls and the optimality system are obtained. In section 5.7 the optimality system is explored numerically by considering different strategies as follows:

- By applying Prevention for Pneumonia and treatment for Typhoid fever disease.
- By applying prevention for Typhoid fever and treatment for Pneumonia disease.
- By applying treatment effort for both disease.
- By applying all control interventions.

In section 5.8 numerically we investigated cost effectiveness analysis to determine, the least and the most expensive strategies by using ICER technique. From the pairwise comparison result we conclude that, applying Prevention effort for Typhoid fever disease and Treatment effort for Pneumonia disease is the best cost effective strategies interims of cost as well as health benefits.

Chapter 6

SUMMARY OF CONTRIBUTIONS AND FUTURE RESEARCH

In this thesis, new deterministic models have been proposed in order to study the dynamics of Pneumonia, Typhoid fever and also their co-infection. These models have been qualitatively analyzed rigorously. The main contribution of the thesis is the proposition of these new mathematical models, their qualitative analysis, and the use of optimal control theory to determine best strategies that can be employed to effectively combat the various infections.

6.1 Summary of Contributions

In chapter 3, a new deterministic model proposed, that describes the dynamics of pneumonia. It is shown that the effective reproduction number of the model is most sensitive to natural death rate (μ), vaccination rate of susceptible ϑ , fraction of vaccinated population before disease outbreak (p), disease induced death rate (α), probability of joining carrier compartment (ρ), recovery rate of carriers (β), treatment rate of infective (η) and treatment efficacy rate (q). It is also shown that the condition $R_{eff} < 1$ is necessary and sufficient for local asymptotic stability of the DFE and the condition $R_{eff} > 1$ is necessary and sufficient for local and global asymptotic stability of the EE. Finally, an optimal control problem is also proposed by incorporating control variables into the model and seeking to minimize an appropriately chosen objective function subject to the modified model. Numerical simulations of the resulting control problem are carried out to determine the effectiveness

of various combinations of the controls. It is revealed from the cost-effectiveness analysis of the employed strategies, the combination of prevention and treatment of pneumonia is most effective in the fight against the disease as well as cost benefit.

In chapter 4 a new deterministic model for typhoid transmission model is proposed. The conditions for existence and stability of equilibrium states characterized in terms of the basic reproduction number are determined. The study showed that there is a disease-free equilibrium which is locally and globally asymptotically stable if $\mathfrak{R}_0 < 1$ and unstable if $\mathfrak{R}_0 > 1$, and the endemic equilibrium which is locally asymptotically stable if $\mathfrak{R}_0 > 1$. It is shown that the basic reproduction number of the model is most sensitive to natural death rate (μ), drug/ natural induced death rate of *salmonella typhi* (μ_b), disease induced death rate (α), screening rate of carriers (θ), recovery rate of carriers naturally (ϕ) and treatment rate (β). The model is modified into an optimal control problem by incorporating control variables (prevention, treatment and screening) into the model and qualitatively analyzed using the Pontryagin's Maximum principle and the existence result of (Fleming and Rishel, 1982). Numerical simulation of the resulting optimal control problem is also carried out, and cost effectiveness analysis showed that the best strategy to fight the typhoid fever is to implement the preventative and treatment control at a time.

In chapter 5, a detailed new deterministic model involving the co-infection of Pneumonia with Typhoid fever is proposed. The model is divided into two basic models, namely; the Pneumonia-only model and the Typhoid fever-only model. These models are rigorously analyzed for qualitative properties. It is observed that the Pneumonia-only, Typhoid fever-only and the full Pneumonia-Typhoid fever models have locally asymptotically stable DFE when their respective basic reproduction numbers are less than unity. The basic reproduction number of the full model is shown to be the greatest of the reproduction numbers of the two sub-models. Bifurcation analysis of the basic sub-models show that the Pneumonia-only does exhibit the feature of transcritical bifurcation and the typhoid fever-only model is however shown to exhibit a forward bifurcation feature. Finally, the Pneumonia-Typhoid fever model is modified into an optimal control problem and analyzed both qualitatively and numerically, and cost effectiveness analysis indicated that the most cost effective strategy that can be used to combat the co-infection is the one that combines preventive control for Typhoid fever and treatment control for Pneumonia.

These results have important public health implications, since they determine the severity and outcome of the epidemic (i.e. clearance or persistence of infection) and provide a framework for the

design of control strategies.

6.1.1 Future Research

The work presented in this thesis can be extended in a lot of respects including the following:

- We note that the models in this thesis are not exhaustive. Incorporating drug resistance compartment could be studied for both Pneumonia and Typhoid fever diseases.
- It should be noted that the models in this thesis all assumed linear incidence and hence each of the models can be extended to include non-linear incidence rates.
- An extension of the models in this thesis to take care of the period between contacting disease causing organisms and development of clinical symptoms will be interesting. In this case, delay differential equation models will be developed.
- Analysing the models based upon immune level dynamics of the diseases.

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