UNIVERSITY OF MINES AND TECHNOLOGY
TARKWA

FACULTY OF ENGINEERING
DEPARTMENT OF MATHEMATICAL SCIENCES

MATHEMATICAL MODELING AND OPTIMAL CONTROL OF THE TRANSMISSION DYNAMICS OF BACTERIAL MENINGITIS POPULATION IN GHANA

BY

MONICA VERONICA CRANKSON

DOCTOR OF PHILOSOPHY IN MATHEMATICS

DECEMBER, 2021

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A THESIS REPORT ENTITLED

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BY

MONICA VERONICA CRANKSON

SUBMITTED IN FULFILLMENT OF THE REQUIREMENT FOR THE AWARD OF THE DEGREE OF DOCTOR OF PHILOSOPHY IN MATHEMATICS

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TARKWA, GHANA

DECEMBER, 2021

DECLARATION

I declare that this thesis is my own work. It is being submitted for the degree of Doctor of Philosophy in the University of Mines and Technology (UMaT), Tarkwa. It has not been submitted for any degree or examination in any other University.

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(Signature of candidate)

..... day of ..... (year) .....

ABSTRACT

This research presents two compartmental models on the transmission dynamics of Bacterial Meningitis, which best describes the scenario in real life. The first model is made up of seven (7) mutually exclusive epidemiological compartments. The quantitative analysis of the model is conducted and the criteria for local and global stabilities of the disease-free equilibrium is established. The simulation results show that getting people vaccinated is crucial to the control of the disease. This leads to the novel two-strain vaccination control model denoted by nine (9) mutually exclusive epidemiological compartments. The model is used to analyze the impact of vaccination and early treatment on the population, especially on the recovered populations. It is ascertained that Bacterial Meningitis will not spread in the population if 25% of the population is immune to the disease. Numerical simulations of the model are carried out by implementing the MATLAB ODE45 algorithm to visualize the effects of the various model parameters on each compartment of the developed model. The two-strain model is then extended to include control by the introduction of five control mechanisms; effective human personal protection (such as wearing face or surgical masks), vaccination for strains 1 and 2, timely and delayed diagnosis treatments of the infection. An optimal control problem is formulated and the existence of its solution is established. The characterization of the controls is performed using the Pontryagin's Maximum Principle. The Forward Backward Sweep (FBS) method is implemented and used to solve the optimal control problem and its corresponding adjoint equations. In order to determine the impact of combination of the control strategies on the different model compartments, numerical simulations of the model are performed using real life data from Ghana Center for Disease Control. It was established that the most efficient and cost-effective control strategy is the strategy involving all the five control variables. This is followed by Strategy C which is only the effective human personal protection (such as face or surgical masks) control, $u_P(t)$. Based on the findings of this research, necessary recommendations are made for the applications of the model to an endemic area.

This thesis is dedicated to

the Most Faithful of all Friends, the Almighty God

for keeping His promise to the end;

and to my lovely parents,

Mr and Mrs Crankson

for their unflinching love and support.

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

BEP ..... Boundary Equilibrium Point

CDC ..... Centre for Disease Control

DFE ..... Disease-Free Equilibrium

EEP ..... Endemic Equilibrium Point

EM ..... Eosinophilic Meningitis

FBS ..... Forward-Backward Sweep

GBS ..... Group B Streptococcus

LTI ..... Linear Time Invariant

OC ..... Optimal Control

OCP ..... Optimal Control Problem

PMP ..... Pontryagin's Maximum Principle

SCIR ..... Susceptible-Carrier-Infected-Recovered

SEIR ..... Susceptible-Exposed-Infected-Recovered

SIR ..... Susceptible-Infected-Removed

SIRC ..... Susceptible-Infected-Removed-Cross Immune

SIRS ..... Susceptible-Infected-Removed-Susceptible

SVCIR ..... Susceptible-Vaccinated-Carrier-Infected-Recovered

SVCITR ..... Susceptible-Vaccinated-Carrier-Infected-Treated-Recovered

SVCIRS ..... Susceptible-Vaccinated-Carrier-Infected-Recovered-Susceptible

WHO ..... World Health Organisation

CHAPTER 1

INTRODUCTION

1.1 Optimization and Optimal Control Problems

Optimization and optimal control pervade mathematics and science as they are the main tools in decision making. Research in these areas is accelerating at a rapid pace due to their numerous applications in various disciplines (Kafash and Alavizadeh, 2020). Optimal control and its applications are found in diverse fields, including aerospace, robotics, engineering, biomedical sciences, economics, finance and management science, and it continues to be an active area of interest in control theory (Chinchuluun *et al.*, 2010).

Optimization is the process in which the best feasible solution for a problem is found. This involves finding an extremum of some functions. In simple mathematical terms, given an analytical function $f \equiv f(x)$, it is required to find the value of x at which the function reaches its maximum or minimum value. A procedure taught towards this solution is to:

1. Differentiate the function with respect to x since the derivative is the instantaneous rate of change of some variable quantity;

2. Set the resulting expression to zero because when a quantity reaches its maximum or minimum value, its instantaneous rate of change at that point is zero; and

3. Solve for x and call the result x_{max} or x_{min} (although such x could also be a point of inflexion).

In solving optimization problems, researchers can also use algorithms that end in a finite number of steps, or iterative methods that converge to a solution (in some specific class of problems), or heuristics that can provide approximate solutions to some problems, although their iterations do not necessarily converge (Snyman, 2005).

Optimization is a very desirable feature in our daily lives. People work and like to use their time in an optimal manner, use resources optimally and so on. In firms and businesses, management takes many technological and managerial decisions at several stages. The ultimate goal of all such decisions is to either minimize the effort required or to maximize the desired benefit. This effort required or benefit desired in any practical situation can be expressed as a function of certain decision variables. The subject of optimization is quite general in the sense that it can be viewed in different ways depending on the approach (algebraic or geometric), the interest (single or multiple), the nature of the signals (deterministic or stochastic) and the stage (single or multiple) used in optimization (Naidu, 2003).

Before one can optimize an objective, a quantitative measure of the performance of the system must be identified. This objective could be profit, time, potential energy, quantity or a combination of quantities that can be represented by a single number. The objective depends on certain characteristics of the system termed as variables. The goal is to find the values of the variables that optimize the objective. These variables are often restricted or constrained in a way (Leitman, 1981).

Optimization problems are categorized as constrained and unconstrained. Constrained optimization problems arise from models in which constraints play an essential role, for example, imposing shape constraints in a design problem. Unconstrained optimization problems on the other hand, arise directly in many practical applications, where an objective function is optimized with no restrictions on these variables (Banga *et al.*, 2003). The presence of constraints creates more challenges while finding the optimum than the unconstrained problems since one needs to find points that satisfy all the constraints. One approach in solving such problem is to reformulate the constrained problem as an unconstrained problem by replacing the constraints with penalization terms and adding to the objective function depending on the number of constraints violated (Olotu, Lawal and Afolabi, 2018). The penalty function to be determined vary from one problem to another, however these penalties should satisfy all the constraints at the end (Nocedal and Wright, 2006).

Some challenges are tackled based on the effect of the constraints on the objective function. For instance, constrained problems with natural constraints on the variables are considered as unconstrained by ignoring the constraints since they do not have influence on the solution or interfere with algorithms. In such cases, the constrained extremum of the problem is the same as the unconstrained extremum, since the constraints do not have any influence on the objective function. For simple optimization problems, it may be possible to determine, before hand, whether or not the constraints have any influence on the minimum point. However, in most of the practical problems, it is extremely difficult to identify such. As such, one has to proceed with the general assumption that the constraints will have some influence on the optimum point. The minimum of a nonlinear programming problem (NLP) will not, in general, be an extreme point of the feasible region and may not even be on the boundary. The problem may even have a local minimum while its corresponding unconstrained problem is not having a local minimum. Also, none of the local minima may correspond to the global minimum of the unconstrained problem. All these characteristics are direct consequences of imposing constraints, hence general algorithms are needed to overcome these kinds of minimization problems (Nocedal and Wright, 2006).

There are many great application problems that can be formulated as continuous optimization problems such as; designing an investment portfolio to maximize expected returns while maintaining an acceptable level of risk, finding the optimal trajectory for an aircraft or a robot arm, controlling a chemical process or a mechanical device to optimize performance or meet standards of robustness and computing the optimal shape of an automobile or aircraft component. Nature optimizes while physical systems tend to a state of minimum energy; the molecules in an isolated chemical system react with one other until the total potential energy of their electrons is minimized. Rays of light follow paths that minimize their travel time (La Torre *et al.*, 2015).

Mathematical control theory is the area of application-oriented mathematics that deals with the basic principles underlying the analysis and design of control systems.

To control an object means to influence its behavior so as to achieve a desired goal. In order to implement this influence, control engineers build devices that incorporate various mathematical techniques (Claudiu, 2006).

Optimal control deals with finding the control and state variables to a dynamical system over a period of time to optimize (i.e., minimize or maximize) a specified performance index while satisfying any constraints on the motion. As such, an Optimal Control Problem (OCP) requires a performance index or a cost functional which is a function of the state and control variables. Its main goal is to find a piecewise continuous control and the associated state variable that optimize a given objective functional (La Torre *et al.*, 2015).

Generally, an optimal control problem is considered as an optimization problem, even though there is a difference in the optimizer. The optimizer in optimal control theory is not just a single value, but a function called the optimal control (Sontag, 1998). In the theory of mathematical optimization, one tries to find maximum or minimum points of functions of real variables and of other functions, whereas with Optimal Control Theory, one tries to find a control law for a given system such that a certain optimality criterion is achieved (Leitman, 1981). Optimal control theory is not only be appreciated for its mathematical formulation of real life problems but also for the long-term research opportunities it has created in many areas of human study. Its application in various disciplines has made it gained the interest of many researchers in recent years. Many real life problems around us can be formulated as optimal control problems.

In general, a constrained dynamic continuous optimal control problem is defined as

$$\text{Minimize } I(x(t), u(t)) = \int_{t_0}^{t_f} f(t, x(t), u(t))dt \tag{1.1}$$

$$\text{Subject to } \dot{x}(t) = h(t, x(t), u(t)) \tag{1.2}$$

$$x(t_0) = x_0, \quad t_0 \leq t \leq t_f \tag{1.3}$$

where $t \in \Re$ represents the independent time variable, t_0 and t_f are the initial and

terminal times respectively, $x(t) \in \Re^n$ is a vector of state variables and $u(t) \in \Re^m$ is a vector of control variables which are going to be optimized, $f : \Re \times \Re^n \times \Re^m \to \Re$ is the functional and $h : \Re \times \Re^n \times \Re^m \to \Re^p$ is a smooth vector field. Both f and h are continuously differentiable functions, that is, $f \in C^2[t_0, t_f]$ and $h \in C^1[t_0, t_f]$. x_0 is the known initial state and the final state $x(t_f)$ could be free (unrestricted) or fixed $(x(t_f) = x_f)$.

Optimal control problems can be difficult to solve, especially those that are not inclined towards programming and numerical methods. Before the arrival of digital computers in the 1950s, only fairly simple or the trivial optimal control problems could be solved. The arrival of the digital computers has enabled the application of optimal control theory and methods to be applied to many complex problems (Becerra, 2004). Despite the advances in software programs, it remains a non-trivial task to utilize a standard package such as MATLAB to solve optimal control problems. One must have sufficient programming skill, as well as a good understanding of the general structure of the solution algorithm and the various solvers required to implement it (Rodrigues, Monteiro and Torres, 2014).

Analytical solutions are generally considered to be "stronger" than numerical ones. The thinking goes that if we can get an analytic solution, it is exact, and then if we need a number at the end of the day, we can just shove numbers into the analytical solution. Therefore, there is always a great interest in discovering methods for analytical solutions. However, even if analytical solutions can be found, one may not be able to compute quickly. As a result, numerical approximations are indispensable, and both approaches contribute holistically to the fields of mathematics and quantitative sciences.

There are two major classes of numerical methods for solving optimal control problems, namely the direct and indirect methods. In a direct method, the state and/or control variables is discretized on a time grid using some form of collocation method. This transforms the problem to a nonlinear optimization problem or nonlinear programming problem (NLP). The resulting nonlinear programming

problem is then solved using various established NLP packages (Bazaraa, Sherali and Shetty, 2006). The complete discretization of the state and control functions eliminates the need to iteratively solve the initial value problem (IVP) although this may lead to a large number of decision variables for the NLP solver (Hull, 2003). Partial parametrization of the control functions is also used in other direct approaches by considering a piecewise constant or higher order polynomial approximations (Banga *et al.*, 2003). In this approach, the inner IVP is solved repeatedly by the outer NLP algorithm while searching for the optimal parameter vector. For the most trivial optimal control problems, a level of programming fluency, in addition to a good understanding of the general structure of the solution strategy and the various solvers are required to implement it (Rodrigues, Monteiro and Torres, 2014).

The indirect method, also known as variational approach, employs the Pontryagin's Minimum Principle to transform the problem into an augmented Hamiltonian system. This leads to a two-point Boundary Value Problem (BVP) which is solved to find the candidate optimal trajectories called extrema. Each of the computed extrema is tested to determine if it is a local minimum, local maximum, or saddle point. Depending on the desired goal, a particular extremum with the least cost functional value is chosen if the goal is to minimize the performance index, or the greatest cost functional value is chosen if the goal is to maximize (Athans and Falb, 2013).

The existence of optimal control for a given problem is of great significance since it does not seem right for one to seek for a solution that does not exist. It is therefore necessary to find out the existence of an optimal control by examining whether a feasible solution can be found or not. For instance, considering the problem of steering a system from a given initial state to a fixed final state in the shortest possible time, one may examine the existence of an optimal control by finding a control that satisfies the physical constraints, which is equivalent to the ability to transfer the system from any initial state to any desired final state in finite time.

1.2 Meningitis

Meningitis, a disease of the Central Nervous System is an acute inflammation of the three protective membranes covering the brain and spinal cord called the meninges (Saez and McCracken, 2003). This inflammation occurs when fluid surrounding the meninges becomes infected. This infection can be caused by different pathogens such as bacteria, virus, fungi and parasites. Injuries, cancer, drugs and other infections can also cause meningitis. Most meningitis infections are attributed to virus, which is the least serious type with the next common causes being bacteria, fungi and parasites (Ginsberg, 2004).

Meningitis affects both men and women equally. The leading organisms causing meningitis vary by age of the patient, time and geographical location (Polkowska *et al.*, 2017). The average age for meningitis is 25 years, but for unclear reasons, Africans seem to develop meningitis more frequently than people of other races (Anon, 2019). The factors that place people at higher risk of contracting meningitis include the following:

1. Age - Adults older than 60 years of age and children younger than 5 years of age. Most cases of viral meningitis occur in children younger than age 5 and Bacterial meningitis is common in those under age 20.

2. Skipping vaccination - Anyone who hasn't completed the recommended childhood or adult vaccination schedule.

3. Compromised immune system - AIDS, alcoholism, use of immunosuppressant drugs and other factors that affect the immune system also makes one susceptible to meningitis. There is an increased risk of one contracting the disease when one's spleen is removed, as such anyone without a spleen should get vaccinated to minimize that risk.

4. Living in an enclosed community setting - People living in close quarters like military barracks, dormitories are at a greater risk of meningococcal meningitis. This is probably because the bacterium spreads by the respiratory route, and this spreads quickly through large groups.

5. Pregnancy - This increases the risk of listeriosis, that is, an infection caused by listeria bacteria, which may also cause meningitis. Listeriosis increases the risk of miscarriage, stillbirth and premature delivery (Anon, 2019).

Figure 1.1 shows the geographic distribution of Meningitis in West African affected Countries.

Figure 1.1 Areas of Africa with frequent Epidemics of Meningitis (Anon, 2020b)

Meningitis has been classified into five main types namely; viral meningitis, fungal meningitis, parasitic meningitis, bacterial meningitis and non-infectious meningitis.

1.2.1 Viral Meningitis

Viral meningitis is the most common cause of meningitis and often goes unreported since most individuals get well without treatment. It is alleged that viral meningitis is largely a benign illness. This is typically the case with the most common virus-causing meningitis, enteroviruses. However, viral meningitis is also associated with severe neurological problems and serious mortality for many of the other virus-causing meningitis especially in children (Chadwick, 2005). Some of these viruses are herpes virus, mumps and measles, flaviviruses, Human immunodeficiency virus (HIV), arboviruses and the influenza virus. Most people are exposed to some of the virus

without developing meningitis (Logan and MacMahon, 2008).

Bacterial and viral meningitis cannot be reliably differentiated in the absence of a lumbar puncture, as such, all suspected cases should be referred to the hospital. Lumbar puncture and analysis of cerebrospinal fluid may be done primarily to exclude bacterial meningitis, but identification of the specific viral cause is itself beneficial. Viral diagnosis informs prognosis, enhances the care of the patient, reduces the use of antibiotics, decreases the length of stay in the hospital, and can help to prevent further spread of infection (Logan and MacMahon, 2008).

1.2.2 Fungal Meningitis

Fungal meningitis is a meningitis that occurs from somewhere in the body to the brain or spinal cord after a fungus has spread. Fungi offer many benefits to humans, however some have the potential of becoming human pathogens. Meningitis can be caused by all the major fungal pathogens since both primary and secondary fungal pathogens can cause central nervous system infections that are life-threatening. People can also get sick if they breathe in fungal spores. To maximize positive results, these infections require immediate and precise diagnosis and carefully chosen management strategies (Raman-Sharma, 2010).

Meningitis from fungi does not spread among individuals but there are numerous risk factors of fungal meningitis, including the use of immunosuppressants (such as after organ transplantation), HIV/AIDS and the loss of immunity associated with aging. However, this is rare in humans with a normal immune system (Honda and Warren, 2009). The symptoms begin gradually with headaches and fever being present for at least a couple of weeks before diagnosis (Sirven and Malamut, 2008).

Cryptococcal meningitis due to cryptococcus neoformans is the most frequent fungal meningitis (Kauffman, Pappas and Patterson, 2013). Multiple studies in Africa suggest cryptococcal meningitis as the most common cause of fungal meningitis, accounting for 20-25 percent of AIDS-related deaths in Africa (Durski *et al.*, 2013). Other common fungal pathogens which can cause fungal meningitis include Coccidioides immitis,

Histoplasma capsulatum, Blastomyces dermatitidis and Candida species. These fungi are minute to see without a microscope (Park *et al.*, 2009).

1.2.3 Parasitic Meningitis

Parasitic meningitis is less common than viral or bacterial meningitis, and is caused by parasites that are found in dirt, faeces, and on some animals and food, like snails, raw fish, poultry, or produce. Parasitic meningitis is not passed from person to person, instead, these parasites infect an animal or hide out on food to contaminate it. If the parasite or parasite eggs are infectious when they are ingested, an infection may occur. Thus, people get infected primarily by eating infected animals or contaminated foods (Graeff-Teixeira, da Silva and Yoshimura, 2009).

Some parasites can cause a rare form of meningitis called eosinophilic meningitis or EM. The three main parasites that cause EM in some infected people are Angiostrongylus cantonensis (neurologic angiostrongyliasis), Baylisascaris procyonis (baylisascariasis; neural larva migrans) and Gnathostoma spinigerum (neurognathostomiasis). As with other meningitis infections, people who develop symptomatic EM from these parasites can have headache, stiff neck, nausea, vomiting, photophobia (eyes being more sensitive to light) and altered mental status (confusion). People with EM caused by Angiostrongylus cantonensis often have tingling or painful feelings in their skin and may have a low-grade fever. All these three parasites sometimes infect the eye(s) and cause severe complications, especially Baylisascaris infection can lead to loss of coordination and muscle control, weakness/paralysis, coma, permanent disability and even death (Anon, 2019).

One very rare type of parasitic meningitis, amebic meningitis, is a life-threatening type of infection. This type is caused when one of several types of ameba enters the body through the nose while one swims in contaminated lakes, rivers, or ponds. The parasite can destroy brain tissue and may eventually cause hallucinations, seizures, and other serious symptoms. The most commonly recognized species is Naegleria fowleri (Gleissner and Chamberlain, 2006).

1.2.4 Non-Infectious Meningitis

Non-infectious meningitis is not an infection, instead, it is a type of meningitis caused by other medical conditions or treatments, such as spread of cancer to the meninges (malignant or neoplastic meningitis) and certain drugs (mainly non-steroidal anti-inflammatory drugs, antibiotics and intravenous immunoglobulins). It may also be caused by several inflammatory conditions such as sarcoidosis, connective tissue disorders and certain forms of vasculitis (inflammatory conditions of the blood vessel wall) (Ginsberg, 2004). Epidermoid cysts and dermoid cysts may cause meningitis by releasing irritant matter into the subarachnoid space. Rarely, migraine may cause meningitis, but this diagnosis is usually only made when other causes have been eliminated (Tebruegge and Curtis, 2008).

1.2.5 Bacterial Meningitis

It is an epidemic prone disease affecting a substantial proportion of the world's population. The bacteria are present worldwide with variable geographic occurrence and incidence. Regional outbreaks can occur at any time, though the Meningitis belt stands at a higher risk. The Meningits belt spans from the Atlantic Ocean to the Red Sea - a semi-arid area of sub-Saharan Africa. There has also been large recorded outbreaks in other sub-Saharan African countries (Anon, 2020a).

The first occurrence of bacterial meningitis in Ghana (then, Gold Coast) was at Cape Coast in 1900. This was found among some East African labourers who were brought to the Gold Coast to support the British campaign against the Ashanti. This outbreak died out rapidly without causing an epidemic in the local population. The next epidemic of bacterial meningitis in the Gold Coast started in 1906 from the north west and spread through the northern territory during the following dry season claiming 8000 lives by 1908. Since then, there has been epidemics every 8-12 years (Kaburi *et al.*, 2017). Ghana experienced the biggest epidemic which recorded 18703 cases and 1356 deaths in 1996/1997 (Woods *et al.*, 2000). The recurrent meningitis outbreaks in the northern part of Ghana namely Northern, North East, Savannah, Upper East and Upper West Regions occur from November to May/June during the dry weather seasons; a season characterized by low humidity, high temperatures and

abundance of dust. The Brong Ahafo, Bono East and upper parts of the Volta region have also recorded sporadic cases (Letsa *et al.*, 2018).

The proximity and inflammation of the protective membranes to the brain and spinal cord can make bacterial meningitis very fatal. It can lead to permanent disability, coma, swelling of the brain and even death if not treated immediately. Therefore, the condition is considered as a medical emergency (Martinez *et al.*, 2013). Case fatality rates which is often between 1 to 2 days after the onset of symptoms may be as high as 50-80% when not treated and about 8-15% when treated. Also, about 10-20% of survivors have serious permanent health problems like epilepsy, hearing impairment or mental retardation. For instance, about sixteen million cases of bacterial meningitis were reported in 2013, leading to 1.6 million lives with disability. In totality, about 10% of all bacterial meningitis results in death (Van de Beek *et al.*, 2016).

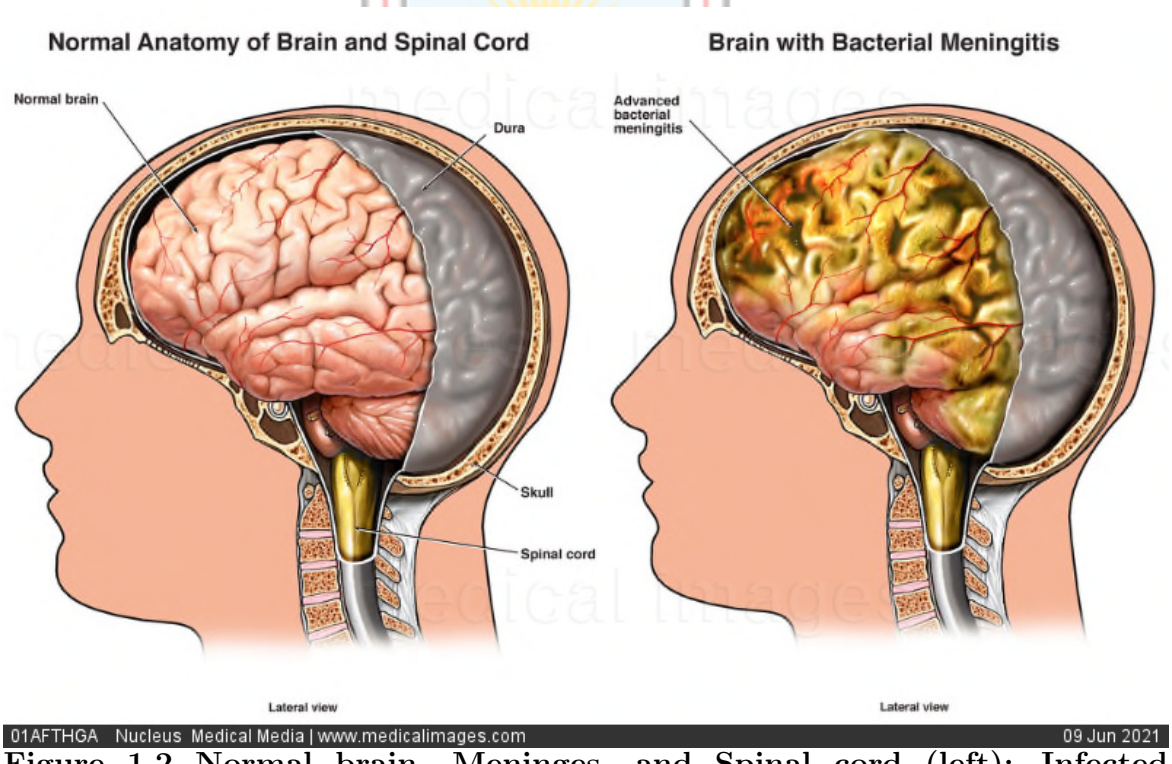


Figure 1.2 Normal brain, Meninges, and Spinal cord (left); Infected and Inflamed brain, Meninges, and Spinal cord due to Bacterial Meningitis(right)

Bacterial meningitis is caused by some strains of bacteria such as Streptococcus pneumoniae (pneumococcus), Neisseria meningitidis (meningococcus), Haemophilus

influenzae (haemophilus), Listeria monocytogenes (listeria). Neisseria meningitidis (Nm), Streptococcus pneumoniae and Haemophilus influenzae type B are the most common bacteria causing over 80% of all cases of bacterial meningitis. Meningitis caused by Haemophilus influenzae type B (Hib) is much less common, now that the Hib vaccine is given to all children as part of routine immunization Anon (2020a).

Streptococcus pneumoniae (Pneumococcus)

Streptococcus pneumoniae is the most common cause of bacterial meningitis in several parts of the world. It often leads to pneumonia. Case Fatality Rates (CFR) for Streptococcus pneumoniae causing Meningitis could be as high as 44%. About 10% of people infected with Streptococcus pneumoniae still die even after receiving effective antibiotics and intensive care (Soeters *et al.*, 2019). There are currently new strains of Streptococcus species emerging. Younger children and older adults are at a higher risk of getting infected with the bacteria.

Neisseria meningitidis (Meningococcus)

This bacteria strain normally spreads through throat droplets and other respiratory fluids such as saliva and phlegm. This causes meningococcal meningitis, also known as Cerebrospinal Meningitis (CSM) which is a highly contagious infection affecting mostly adolescents and young adults. It easily spreads through crowdy settlements such as universities or college dormitories and halls, markets, hospitals and barracks (Van de Beek *et al.*, 2006). Meningococcal meningitis is said to have a high fatality of 50% when not treated and a high frequency of $10-20\%$ of severe long-term sequelae. Early diagnosis and antibiotic treatment is the most important measure to save lives and reduce complications. Neisseria Meningitidis is the main cause of meningitis epidemics in the African meningitis belt and accounts for $80-95\%$ cases of bacterial meningitis admitted in hospitals (Domo *et al.*, 2017).

Haemophilus Influenzae (Haemophilus)

The Hib bacteria is the common cause of meningitis in children. The most striking feature of this bacteria is its age-dependent susceptibility. Hib disease is not common beyond 5 years of age. Generally, Haemophilus Influenzae spreads from one person

to another through human contact or saliva droplets such as sneezing and coughing. The bacteria normally remain in the nose and throat but can sometimes enter the bloodstream and spread, causing serious infection in the individual. In some cases, H. influenzae bacteria can be transmitted by carriers who are not ill themselves (asymptomatic). Persons remain communicable as long as the bacteria is present, which may be for a long time. However, persons become non-communicable after starting appropriate antibiotics medication. People with underlying health conditions are at a higher risk of getting Haemophilus Influenzae infections. The bacteria (Hib) can spread contagiously to cause otitis media and sinusitis. It can also cause invasive disease, predominantly meningitis and pneumonia but also epiglottitis, septic arthritis.

Listeria Monocytogenes (Listeria)

It is food-borne bacteria. Bacterial Meningitis can spread by taking foods containing Listeria bacteria such as sandwich meats, soft cheeses ready to eat foods, unpasteurized dairy products and hot dogs. The bacteria normally affect neonates, pregnant women, the elderly, immunocompromised patients, immunodeficiency syndrome and those receiving immunosuppressive therapy or corticosteroid drugs. It can lead to diseases including sepsis, central nervous system (CNS) infection and endocarditis.

Group B Streptococcus (Group B Strep)

Group B Strep (GBS), also known as Streptococcus Agalactiae, is a Gram-positive encapsulated bacterium possessing an array of virulence factors that render it capable of producing serious disease in susceptible hosts, mostly in new-born babies. The pathogenesis of neonatal GBS infection starts with the asymptomatic colonization of the female genital tract. About 20– 30% of healthy women are infected with GBS on their vaginal or rectal mucosa, and 50– 70% of infants born to these women will become infected with the bacterium. GBS Infections can be classified as Early-onset Disease (EoD) and Late-onset Disease (LoD). Early-onset infections occur within the first seven days of life, but has a median onset of only 6–8 hrs of life, presenting acutely with pneumonia and respiratory failure complicated by bloodstream infection and septicaemia. EoD cases result from ascending infection of the bacterium through the placental membranes to develop infection in utero, or by aspiration of infected

vaginal fluids during the birth process. High risk patients of Early-onset infections are premature and low-birth-weight infants. GBS placental infection is the critical factor triggering premature labour. On the other hand, GBS LoD occurs in infants up to seven (7) months of age, with more indolent symptom progression related to bacteraemia, absence of lung involvement and a high incidence of meningitis (Nizet and Doran, 2013).

Table 1.1 Bacterial Meningitis Associated with Age Group

New Born	**Babies/Children**	**Teens/Young Adults**	**Older Adults**
Group B Strep	S. pneumoniae	N. meningitidis	S. pneumoniae
S. pneumoniae	N. meningitidis	S. pneumoniae	N. meningitidis
Listeria	Group B Strep		Listeria
E. coli	Haemophilus, Hib		Group B Strep

(Anon, 2019)

The average incubation period for bacterial meningitis is four (4) days, but symptoms may develop over several hours after exposure to the bacteria, usually between 2 to 10 days. Early meningitis symptoms may mimic the flu (influenza) but the most common symptoms are fever, headaches and pain of the neck. Other symptoms include confusion or difficulty concentrating, seizures, sleepiness or difficulty walking, vomiting and an inability to tolerate light or loud noises. Young children often exhibit only nonspecific symptoms, such as irritability, drowsiness, or poor feeding. Infants with meningitis may be difficult to comfort, and may even cry harder when held. If a rash is present, it may indicate a particular strain of infection; for instance, meningitis caused by meningococcal bacteria may be accompanied by a characteristic rash (Hodgson *et al.*, 2001).

Most people have a good recovery from bacterial meningitis; however many recover from the acute phase of the disease only to experience some difficulties while trying to get back to their everyday routine (Kaburi *et al.*, 2017). Bacterial meningitis can result in severe health complications such as headaches, decreased appetite, paralysis, irritability, memory problems, stroke, hearing loss, brain damage, kidney failure, seizures and septicemia (body-wide infection and shock). These complications are often permanent. The longer one has the infection without treatment, the greater

the risk of these complications. With prompt treatment, even patients with severe meningitis can have good recovery (Nuoh *et al.*, 2016).

1.2.6 Transmission of Bacterial Meningitis

Bacterial Meningitis was initially transmitted from an animal to a human being but has since become a person to person transmission through infected air droplets, saliva, respiratory secretions and direct contact with contaminated surface. The infection spreads easily when an infected person comes into close proximity or has long term contact with others. Staying in overcrowded housing, attending sports or cultural events, sharing utensils, coughing, sneezing or kissing can contribute to outbreaks (Fordjour and Abdul-Razak, 2020). The bacteria can be carried in the throat and sometimes overwhelms the body's defences allowing the bacteria to spread through the bloodstream to the brain. It is believed that $1 - 10\%$ of the population carries N. meningitidis in their throat at any given time. However, the carriage rate may increase to $10 - 25\%$ in epidemic situations.

1.2.7 Vaccination and Treatment

Bacterial meningitis is preventable due to the availability of effective vaccines against most of the disease causing agents - *S. pneumonia*, *H. influenza* type b and *N. meningitidis* serogroups: A, B, C, W135 and Y. These vaccines are used for prevention, that is routine immunization and in prompt reactive vaccination during outbreaks (McCarthy, Sharyan and Sheikhi Moghaddam, 2018). There is also treatment with antibiotics such as Benzyl penicillin, Ampicillin, Ceftriaxone, Ciprofloxacin, Rifampicin, Gentamicin and Chloramphenicol, but the best way to combat it is to prevent it through vaccination and sound health practices (Trestioreanu *et al.*, 2011). The three types of vaccines available are:

1. Polysaccharide vaccines used during a response to outbreaks, mainly in Africa. They are either bivalent (serogroups A and C), trivalent (A, C and W), or tetravalent (A, C, Y and W) and are not effective before 2 years of age. They offer a 3-year protection but do not induce herd immunity.

2. Conjugate vaccines are used in prevention (routine immunization schedules

and preventive campaigns) and outbreak response. They confer longer-lasting immunity (5 years and more), prevent carriage and induce herd immunity. They can be used at one year of age. Some of the available vaccines are Monovalent C, Monovalent A and Tetravalent (serogroups A, C, Y, W).

3. Protein based vaccine, against N. meningitidis B. It has been introduced into the routine immunization schedule for and used in outbreak response (Anon, 2020a).

Hence, it's imperative for one to get routine vaccinations, know the signs of meningitis, and get medical care right away if one experiences symptoms of this disease. It is also important to see a doctor if you get exposed to an infected person, like a family member or a work colleague. You may need to take medications to prevent the infection. Experts call this prophylaxis. Other preventive measures include respiratory isolation of cases for 24 hours following commencement of treatment and tracing of contacts (Tunkel *et al.*, 2004). It is pertinent to know the particular cause of meningitis to aid in effective treatment.

1.3 Statement of the Problem

Bacterial meningitis is one of the most dangerous infections due to repeated occurence of the infection and the sequelae of delibitating effects among survivors even after treatment. Ghana, which falls within the African meningitis belt, has had recurrent epidemics, particularly in the northern regions. This led to the conduct of a mass preventive immunization campaign in the country in 2012 to address the burden of Group A meningococcus which accounted for an estimated 80-85% of all cases in the country, with epidemics occurring at intervals of 7–14 years. The successful conduct of the mass preventive campaign in the then three northern regions has reduced the meningococcus serogroup A infections. The occurrence of meningitis outbreaks due to Nm serogroups and other bacteria are now of a great concern. The outbreaks due to Streptococcus pneumoniae have also become more noticeable and a public health threat which demands effective preparedness and response strategies (Bekoe, 2017).

From the review of literature, most of the mathematical models developed represent the different types of Bacterial Meningitis such as the Cerebrospinal and Pneumococcal

Meningitis. Other studies have also been carried out on the application of some measures against the spread of the disease. The dynamics of bacterial meningitis in a given population was presented using time-dependent controls, nonlinear deterministic model by Asamoah *et al.* (2018). Their results indicate that effective contact rate and infectious carriers have a great effect in transmitting the disease. The model was extended as an optimal control problem in order to determine the best strategies for the control of the disease. The solution of the optimal control problem showed that the best strategies for controlling bacterial meningitis is the combination of vaccination of susceptible population with other interventions.

The awareness of Bacterial Meningitis as a vaccine preventable disease is commendable, but a number of people may not know that these vaccines are strain-specific. Several previous researchers have used mathematical models to analyze the transmission and control dynamics of bacterial meningitis (Irving *et al.*, 2012; Martcheva and Crispino-O'Connell, 2003; Wiah and Adetunde, 2010; Yusuf and Olayinka, 2019). For the models that consider vaccination, there is a common assumption that the vaccine does not confer immunity to all its recipients and is used as a means of treatment to infected people. However, this assumption has to be lifted as it is nowhere close to the real life situation where the available vaccines confer varying degrees of duration of immunity against the specified strain. Furthermore, these specific vaccines are used for prevention (routine immunization) and in response to outbreaks (prompt reactive vaccination), and not for treatment (Anon, 2018).

Ghana and other countries in the Meningitis belt still record periodic outbreaks despite attempts by researchers to combat the spread of Meningitis. This has necessitated WHO to come up with a roadmap to defeat meningitis by the year 2030 (Anon, 2018). A ten-year evaluation study on meningitis in Ghana, spanning the period 2010–2020 reported about 8328 suspected cases with 845 deaths in the country. For instance, 1164 suspected cases were reported in 2010 with 128 deaths while 2012 has 956 suspected cases with 90 deaths. The Ghana Weekly Epidemiological Reports recorded 1099 suspected cases with 104 deaths in 2017, 988 suspected cases with 71 deaths in 2018 and 891 suspected cases with 23 deaths in 2019 (Anon, 2019).

Even with the availability of drugs and vaccines in the management of meningitis outbreaks, case fatality rates in Ghana remains high ranging between 36-50% (Apanga and Awoonor-Williams, 2016). In 2020, about 506 cases were confirmed with over 50 deaths in the country. This outbreak in the northern part of Ghana was caused mainly by a new strain of bacteria; Neisseria Meningitis Serotype X, which has no vaccine and Steptococcus pneumonia, which has an average case fatality of 40% (Adjorlolo and Egbenya, 2020).

Since the after-effects of meningitis aren't always pleasant, Elmojtaba and Adam (2017) presented a Susceptible-Vaccinated-Carrier-Infected-Recovered-Susceptible (SVCIRS) model to study the dynamics of the meningitis disease. They distinguished between the recovered with disabilities and the recovered without disabilities. Their model suggested that the disease can be controlled if the vaccine uptake rate is high.

As an extension of the available models with a broader focus on Bacterial meningitis, a Treatment compartment is introduced with new model parameters to have a Susceptible-Vaccinated-Carrier-Infected-Treated-Recovered (SVCITR) model. Furthermore, a new two strain mathematical model based on the Susceptible-Vaccinated-Carrier-Infected-Recovered (SVCIR) is also developed with new model parameters and control strategies in order to have a more realistic model which is closer to what is obtainable in the real life situation.

The two-strain model is then formulated as an Optimal Control Problem (OCP) with some time-dependent controls. The OCP formulation and numerical simulation, is very pertinent to comparing the effects of various combination of control strategies on the spread of the disease. Similarly, the characterization of this OCP will aid in the identification of the most effective control strategy against the spread of Bacterial Meningitis. In addition to this, the optimal control solution will also help to indicate the rate at which several controls against the spread of this disease must be applied to an endemic area over a period of time in order to achieve the most efficient result.

1.4 Research Objectives

The objectives of the research are to:

1. develop a mathematical model on the transmission dynamics of Bacterial Meningitis disease with the incorporation of the Treated population.
2. develop a two-strain mathematical model which best describes the transmission dynamics of Bacterial Meningitis disease.
3. estimate models' parameter values from demographic and disease surveillance data.
4. perform sensitivity analysis to assess the contribution of each model parameter on the effective control of the disease.
5. formulate the alarming prevalence of Bacterial Meningitis in Ghana as an optimal control problem and numerically solve the resulting optimality system to determine best strategies to curtail the spread of the disease.
6. conduct a cost effective analysis of the optimal control strategies.

1.5 Methods Used for the Study

The methods employed for the study include:

1. Ordinary Differential Equations
2. Next Generation Matrix Method
3. Pontryagin Maximum Principle
4. Forward Backward Sweep Method
5. Cost-Effective Analysis
    a. Infection Averted Ratio
    b. Average Cost-Effectiveness Ratio
    c. Incremental Cost-Effectiveness Ratio

1.6 Facilities and Resources Used for the Research

The facilities and resources used for the study are:

1. The library.
2. The internet.
3. Personal laptop
4. MATLAB.
5. Maple.

1.7 Organization of the Thesis

The thesis is organized into six chapters:

Chapter 1 is the introductory chapter. It contains the background to the study, statement of problem, objectives of the study, methods used to achieve the objectives, and the facilities that were available for developing and writing the thesis. This chapter also gives the outline of the thesis.

Chapter 2 reviews some important literature on methods for solving optimal control problems and also discusses the results of other researchers relevant to the study. Some earlier important theoretical work and its associated theorems, lemma and proofs are also examined, as well as certain fundamental definitions that are relevant to the study.

Chapter 3 focuses on the formulation of the SVCITR model to study the transmission dynamics of Bacterial meningitis with its stability and sensitivity analysis.

Chapter 4 proposes the two strain model that best describes the transmission of Bacterial meningitis with the local and global stabilities and sensitivity analysis.

Chapter 5 presents the incorporation of control into the model, the formulated optimal control problem and the cost effective analysis.

Chapter 6 gives the summary, findings, conclusions, contributions to science/knowledge, recommendations and suggestions for future research/work.

CHAPTER 2

LITERATURE REVIEW

2.1 Preamble

This chapter introduces detailed mathematical concepts and methods relevant to this study. The definitions and theories are related to dynamical systems associated with the study of mathematical modeling, epidemiology and optimal control theory. Most fundamental laws in science are formulated as differential equations. Complex models involving equations with non-linearity terms often arise in modeling complex problems. Historical development as well as optimal control applied to epidemiology are also considered in this chapter.

2.2 Differential Equation

Definition 2.2.1 *A differential equation (DE) is an equation involving the derivatives of one or more functions (called dependent variables), with respect to one or more independent variables.*

There are basically two types of differential equations, namely; Ordinary Differential Equation (ODE) and Partial Differential Equation (PDE). However, this study is concerned with ODEs.

Definition 2.2.2 *An ordinay differential equation (ODE) is the differential equation that contains only ordinary derivatives of one or more dependent variable(s) with respect to exactly one independent variable.*

Definition 2.2.3 *Let x be a state of a dynamical system. A model which involves x can be written in the form:*

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

where $x \in R^n$, $t \in R$ denotes time, and $\lambda \in R^m$ denotes the parameters upon which changes in the system depend.

Definition 2.2.4 *A non-autonomous ordinary differential equation is an ODE in which the independent variable (usually the time variable) is explicitly stated. Otherwise, if the independent (time) variable is not explicitly stated or defined, the ODE is called an autonomous ordinary differential equation.*

An autonomous system of ODEs can be expressed in the form:

$$\dot{x} = f(t, x) \tag{2.2}$$

where $x = (x_1, x_2, \cdots x_n)$ and $\dot{x} = \frac{dx}{dt}$ is the point-wise time-derivative of the state variable x. In instances where an initial condition to the ODE is given, the ODE is referred to as an Initial Value Problem (IVP) and can be expressed in the form: An autonomous system of ODEs can be expressed in the form:

$$\dot{x} = f(t, x) \qquad x(t_0) = x_0 \in R^n \tag{2.3}$$

We note that the developed model is a deterministic (compartmental) epidemiological model.

Given a system of n compartments. A general dynamical system describing the dynamics of such system can be written in the form

$$\begin{cases} \frac{dx_1}{dt} &= f_1(x_1, x_2, x_3, \cdots, x_n) \\ \frac{dx_2}{dt} &= f_2(x_1, x_2, x_3, \cdots, x_n) \\ \frac{dx_3}{dt} &= f_3(x_1, x_2, x_3, \cdots, x_n) \\ \quad\vdots & \\ \frac{dx_n}{dt} &= f_n(x_1, x_2, x_3, \cdots, x_n) \end{cases} \tag{2.4}$$

This can be expressed in a more simplified form as

$$\frac{dx}{dt} = f(t, x) \tag{2.5}$$

where $x = (x_1, x_2, x_3, \cdots, x_n)$ and $f = (f_1, f_2, f_3, \cdots, f_n)$

2.2.1 Nonlinear Systems

Given an initial value problem of linear systems of ordinary differential equations

$$\dot{x} = A(x), \quad x(0) = x_0 \tag{2.6}$$

where $x \in \mathbb{R}^n$, $A \in \mathbb{R}^{n\times n}$ has a solution through each point $x_0 \in \mathbb{R}^n$, which is $x(t) = e^{At}x_0$. Then, this solution is unique and defined for all $t \in \mathbb{R}$.

A unique solution to a non-linear equation on the other hand exists only under certain conditions. Let's consider a non-linear system of ordinary differential equations given by

$$\dot{x} = f(x) \tag{2.7}$$

and for simplicity, assume that they are autonomous. In general, this equation has a solution if the function f is continuous for all $x \in \mathbb{R}^n$. However, in contrast to the linear problem, a continuity of f is not sufficient to guarantee the uniqueness of the solution of (2.6).

Definition 2.2.5 *Let $f \in C(E)$ where E is an open subset of $\mathbb{R}^n$. Then $x(t)$ is a solution of the differential equation (2.6) on an interval $[a, b]$ if $x(t)$ is differentiable on (a, b) and for all $t \in [a, b]$, $x(t) \in E$ and*

$$\dot{x}(t) = f(x(t))$$

Given $x_0 \in E$, then $x(t)$ is a solution of the initial value problem

$$\dot{x} = f(x), \quad x(t_0) = x_0$$

on an interval $[a, b]$ if $t_0 \in [a, b]$, $x(t_0) = x_0$ and $x(t)$ is a solution of (2.6) on the interval $[a, b]$.

For the existence and uniqueness of the solution, it suffices to show that C^1 functions are locally Lipschitz.

Definition 2.2.6 *Let E be an open subset of $\mathbb{R}^n$. A function $f : E \longrightarrow \mathbb{R}^n$ is said to satisfy a Lipschitz condition on E if there exists a positive constant K such that for*

all $x, y \in E$

$$|f(x) - f(y)| \leq K|x - y|$$

The function f *is said to be locally Lipschitz on* E *if for each point* $x_0 \in E$*, there is an* ϵ *- neighborhood of* x_0*,* $N_\epsilon(x_0) \subset E$ *and a constant* $K_0 > 0$ *such that for all* $x, y \in N_\epsilon(x_0)$

$$|f(x) - f(y)| \leq K_0|x - y|$$

ϵ *- neighhborhood of* x_0 *means an open ball of radius* ϵ *given by*

$$N_\epsilon(x_0) = \{x \in \mathbb{R}^n, |x - x_0| < \epsilon\}.$$

The following lemma points out the conditions in which the function f is said to be locally Lipschitz.

Lemma 2.2.1 *Let* E *be an open subset of* $\mathbb{R}^n$ *and let* $f : E \longrightarrow \mathbb{R}^n$*. If* $f \in C^1(E)$*, then* f *is locally Lipschitz on* E*.*

Proof: Since E is an open subset of $\mathbb{R}^n$, given $x_0 \in E$, there exists an $\varepsilon > 0$ such that $N_\varepsilon(x_0) \subset E$. Let

$$K = \max_{|x| \leq \frac{\varepsilon}{2}} \|D\mathbf{f}(x)\|,$$

be the maximum of the continuous function $D\mathbf{f}(x)$ on the compact set $|x| \leq \frac{\varepsilon}{2}$. Let N_0 denote the $\frac{\varepsilon}{2}$-neighborhood of x_0, $N_{\frac{\varepsilon}{2}}(x_0)$. Then for $x, y \in N_0$, set $u = y - x$. It follows that $x + su \in N_0$ for $0 \leq \delta \leq 1$ since N_0 is a convex set.
Let's define the function $F : [0, 1] \to R^n$ by

$$F(s) = f(x + su).$$

Differentiating by Chain rule,

$$F^{'}(s) = D\mathbf{f}(x + su)u$$

As such,

$$\begin{aligned} f(y) - f(x) &= F(1) - F(0) \\ &= \int_0^1 F^{'}(s)ds = \int_0^1 D\mathbf{f}(x + su)uds \end{aligned}$$

It follows that

$$\begin{aligned} |f(y) - f(x)| &\leq \int_0^1 |D\mathbf{f}(x + su)u|ds \\ &\leq \int_0^1 \|D\mathbf{f}(x + su)\||u|ds \\ &\leq K|u| = K|y - x|. \end{aligned}$$

Hence proved.

The following theorem guarantees the existence and uniqueness of the solution of nonlinear ordinary differential equation.

Theorem 2.2.1 *(The Fundamental Existence - Uniqueness Theorem). Let E be an open subset of $\mathbb{R}^n$ containing x_0 and assume that $f \in C^1(E)$. Then, there exists a positive $a > 0$ such that the initial value problem*

$$\dot{x}(t) = f(x(t)), \quad x(t_0) = x_0 \tag{2.8}$$

has a unique solution $x(t)$ on the time interval $[-a, a]$.

Proof: Since $f \in C^1(E)$, it follows from the lemma that there is an ε- neighborhood $N_\epsilon(x_0) \subset E$ and a constant $K > 0$ such that for all $x, y \subset N_\epsilon(x_0)$,

$$|f(x) - f(y)| \leq K\,|x - y|\,.$$

Let $b = \frac{\varepsilon}{2}$. Then, the continuous function $f(x)$ is bounded on the compact set

$$N_0 = \{x \in \mathbb{R}^n || x - x_0| \leq b\}\,.$$

Let

$$M = \max_{x \in N_0} |f(x)|$$

The Picard's successive approximation $u_k(t)$ is defined by the sequence of function $u_{k+1}(t) = x_0 + \int_0^t f(u_k(s))ds$. Assuming there exists an $a > 0$ such that $u_k(t)$ is defined and continuous on $[-a, a]$ and satisfies

$$\max_{[-a,a]} |u_k(t) - x_0| \leq b, \tag{2.9}$$

then, it follows that $f(u_k(t))$ is defined and continuous on $[-a, a]$ and hence

$$u_{k+1}(t) = x_0 + \int_0^t f(u_k(s))ds$$

is defined and continuous on $[-a, a]$ and satisfies

$$|u_{k+1}(t) - x_0| \leq \int_0^t |f(u_k(s))|ds \leq Ma$$

for all $t \in [-a, a]$. Thus, choosing $0 < a \leq \frac{b}{M}$, it follows by induction that $u_k(t)$ is defined and continuous and satisfies (2.9) for all $t \in [-a, a]$ and $k = 1, 2, 3, ...$
Since for all $t \in [-a, a]$ and $k = 0, 1, 2, 3, \cdots$, $u_k(t) \in N_0$, it follows from the Lipschitz condition satisfied by f that for all $t \in [-a, a]$

$$\begin{aligned} |u_2(t) - u_1(t)| &\leq \int_0^t |f(u_1(s)) - f(u_0(s))|ds \\ &\leq K \int_0^t |u_1(s) - u_0(s)|ds \\ &\leq Ka \max_{[-a,a]} |u_1(t) - u_0(t)| \\ &\leq Kab \end{aligned}$$

Assuming

$$\max_{[-a,a]} |u_j(t) - u_{j-1}(t)| < (Ka)^{j-1}b \tag{2.10}$$

for some integer $j \geq 2$, it follows that for all $t \in [-a, a]$

$$\begin{aligned} |u_{j+1}(t) - u_j(t)| &\leq \int_0^t |f(u_j(s)) - f(u_{j-1}(s))|ds \\ &\leq K \int_0^t |u_j(s) - u_{j-1}(s)|ds \\ &\leq Ka \max_{[-a,a]} |u_j(t) - u_{j-1}(t)| \\ &\leq (Ka)^j b \end{aligned}$$

By induction, it follows that (2.10) holds for $j = 2, 3, \cdots$. Setting $\alpha = Ka$ and

choosing $0 < a < \frac{1}{K}$, we see that for $m > k \geq N$ and $t \in [-a, a]$

$$\begin{aligned} |u_m(t) - u_k(t)| &\leq \sum_{j=k}^{m-1} |(u_{j+1}(t)) - (u_j(t))| \\ &\leq \sum_{j=N}^{\infty} |u_{j+1}(t) - u_j(t)| \\ &\leq \sum_{j=N}^{\infty} \alpha^j b = \frac{\alpha^N}{1-\alpha} b \end{aligned}$$

This last quantity approaches zero as $N \to \infty$. Therefore, for all $\varepsilon > 0$, there exists an N such that $m, k \geq N$ implies that

$$\|u_m - u_k\| = \max_{[-a,a]} |u_m(t) - u_k(t)| < \varepsilon$$

i.e., u_k is a Cauchy sequence of continuous functions in $C([-a, a])$. Taking the limit of both sides of equation defining the successive approximations, we see that the continuous function

$$u(t) = \lim_{k \to \infty} u_k(t) \tag{2.11}$$

satisfies the integral equation

$$u(t) = x_0 + \int_0^t f(u(s))ds \tag{2.12}$$

for all $t \in [-a, a]$. We have used the fact that the integral and the limit can be interchanged since the limit in (2.11) is uniform for all $t \in [-a, a]$. Since $u(t)$ is continuous, $f(u(t))$ is continuous and by the fundamental theorem of calculus, the right-hand side of the integral equation (2.12) is differentiable and

$$u^{'}(t) = f(u(t))$$

for all $t \in [-a, a]$. Furthermore, $u(0) = x_0$ and from (2.9) it follows that $u(t) \in N_\varepsilon(x_0) \subset E$ for all $t \in [-a, a]$. Thus $u(t)$ is a solution of the initial value problem (2.8) on $[-a, a]$.

Let $u(t)$ and $v(t)$ be two solutions of the initial value (2.8) on $[-a, a]$. Then, the continuous function $|u(t) - v(t)|$ achieves its maximum at some point $t_1 \in [-a, a]$.

This follows that

$$\begin{aligned}\|u-v\| &= \max_{[-a,a]} |u(t)-v(t)| \\ &= \left| \int_0^{t_1} f(u(s)) - f(v(s))ds \right| \\ &\leq \int_0^{t_1} |f(u(s)) - f(v(s))|ds \\ &\leq K \int_0^{t_1} |(u(s)) - (v(s))|ds \\ &\leq Ka \max_{[-a,a]} |u(t)-v(t)| \\ &\leq Ka\|u-v\|.\end{aligned}$$

But $Ka < 1$ and this last inequality can only be satisfied if $\|u-v\| = 0$. Hence, $u(t) = v(t)$ on $[-a,a]$. We have shown that the successive approximation converges uniformly to a unique solution of the initial value problem (2.8) on the interval $[-a,a]$ where a is any number satisfying $0 < a < min\left(\frac{b}{M}, \frac{1}{K}\right)$.

Theorem 2.2.2 *Let E be an open subset of $\mathbb{R}^n$ and suppose $f \in C^1(E)$. Then, for each point $x_0 \in E$, there is a maximal open interval (α, β) on which the intial value problem (2.8) exists, $\alpha < t_0 < \beta$ with $\beta < \infty$, then for each compact set $K \subset E$, there is some $t \in (\alpha, \beta)$ such that $\phi(t) \notin K$*

Proof: Suppose that the solution ϕ has maximal interval of existence (α, β) with $\beta < \infty$ and K is a compact subset of E such that $\phi \in K$ for all $t \in (\alpha, \beta)$.
Then, the set $[t_0, \beta] \times K$ is compact. Thus, there is some $M > 0$ such that $|f(t,x)| < M$ for each $(t,x) \in [t_0, \beta] \times K$. Moreover, the function $\phi : [t_0, \beta) \to K$ is continuous.
If $s_1, s_2 \in [t_0, \beta)$ and $s_1 < s_2$ then,

$$|\phi(s_1) - \phi(s_2)| = \left| \int_{s_1}^{s_2} f(t, \phi(t))dt \right| \leq M|s_2 - s_1|$$

2.2.2 Dynamical Systems

Dynamical systems are systems which change in time (in some well defined way). What changes is known as the state of the system. For such systems, the basic problem is to predict the future behaviour. Differential equations are used to represent the (physical or otherwise) law governing the evolution of the system; this

plus the initial conditions should determine uniquely the future evolution of the system.

A dynamical system can be either deterministic or stochastic; discrete or continuous; linear or nonlinear; autonomous or non-autonomous. Dynamical systems are deterministic if there is a unique consequence to every state, or stochastic or random if there is a probability distribution of possible consequences. In this study, a deterministic, continuous, non-linear and autonomous dynamical system is considered. Assuming the temporal behaviour of a system is given as a function $\Phi(x(0), t)$ of the initial state $x(0)$ and time t, and that $x(t)$ satisfies an initial value problem of the form

$$\dot{x}(t) = f(x(t)),\ x \in E,\ x(0) = x_0 \tag{2.13}$$

where, E is an open subset of $\mathbb{R}^n$ and the function $f \in C^1(E \longrightarrow \mathbb{R}^n)$ is a continuously differentiable function. That is, all partial derivatives of f_i with respect to x_j, $\partial f_i/\partial x_j$, with $i, j = 1, \cdots, n$, exist and are continuous. This guarantees the existence of a unique solution $x(t)$ in a time interval $[-a, a]$. (see The Fundamental Existence - Uniqueness Theorem)

Definition 2.2.7 *(Dynamical System) A dynamical system on E is a C^1 - map*

$$\Phi : \mathbb{R} \times E \longrightarrow E \tag{2.14}$$

where E is an open subset of $\mathbb{R}^n$, and if $\Phi_t(t) := \Phi(t, x)$ then Φ_t satisfies

1. *$\Phi_0 = x$ for all $x \in E$ and*
2. *$\Phi_t \circ \Phi_s(x) = \Phi_{t+s}(x)$ for all $s, t \in \mathbb{R}$ and $x \in E$.*

$\Phi(t, x_0)$, for fixed $x_0 \in E$ corresponds to the solution of the initial value problem in (2.13).

The first property in Definition 2.2.7 assures that the initial condition $x(0) = x_0$ is fulfilled. The second property states that the evolution of the system is uniquely determined for every $t \in \mathbb{R}$ if the state, x of the system at any time, t is known. This means that the solution curves in the state space cannot intersect, otherwise the time

evolution of the system would not be unique at the intersection point.

Let's state the following relation between the dynamical system and the initial value problem: If $\Phi(t, x)$ is a dynamical system defined on $E \subseteq \mathbb{R}^n$, then

$$f(x) = \frac{d}{dt}\Phi(t, x)|_{t=0} \tag{2.15}$$

defines a C^1 - vector field on E, and for each $x_0 \in E$, $\Phi(t, x_0)$ solves the initial value problem (2.13). Moreover, a solution of the initial value problem (2.13) exists for every $t \in \mathbb{R}$, meaning for each $x_0 \in E$, the maximal interval of existence of $\Phi(t, x_0)$ is the time interval $I(x_0) = (-\infty, \infty)$. Therefore, each dynamical system is related to a C^1 - vector field f, and the dynamical system describes the solution set of the differential equation defined by this vector field.

Conversely, given a differential equation $\dot{x} = f(x)$, $x \in E$ with $f \in C^1(E)$ and E an open subset of $\mathbb{R}^n$, the solution $\Phi(t, x_0)$ of the initial value problem (2.13) with $x_0 \in E$ will be a dynamical system on E if and only if for all $x_0 \in E$, the maximal interval of existence $I(x_0)$ of $\Phi(t, x_0)$ is $(-\infty, \infty)$. In this case, we say that $\Phi(t, x_0)$ is the dynamical system on E defined by the differential equation $\dot{x} = f(x)$.

2.3 Equilibria and Linearization

An equilibrium point is considered to be a constant solution to a differential equation. It's also referred to as critical point or steady state solution. It is generally computed by equating all the equations of the system to zero and solving for the value(s) of $x \in \mathbb{R}^n$ which satisfies such condition.

We give the standard definitions and theorems required to analyze the stability of an equilibrium point of an autonomous system (Perko, 2001).

Definition 2.3.1 *A point $x^* \in \mathbb{R}^n$ is called an equilibrium point of (2.7), if $f(x^*) = 0$.*

Furthermore, an equilibrium point x^* is called a hyperbolic equilibrium point of (2.7) if none of the eigenvalues of the matrix $D\mathbf{f}(x^*)$ have zero real part.

Consider the linear system

$$\dot{x} = A(x) \tag{2.16}$$

with the matrix $A = D\mathbf{f}(x^*)$. The linear function $Ax = D\mathbf{f}(x^*)x$ is the linear part of x^*.

Definition 2.3.2 *The linear system* (2.16) *with the matrix* $Ax = D\boldsymbol{f}(x^*)x$ *is called the linearization of* (2.7) *at* x^*

Definition 2.3.3 *An equilibrium point of* (2.16) *is called a* ***sink*** *if all the eigenvalues of the matrix* $D\boldsymbol{f}(x^*)$ *have negative real part. If all the eigenvalues of* $D\boldsymbol{f}(x^*)$ *have positive real part, then it is called a* ***source****. Also, it is called a* ***saddle*** *if it is a hyperbolic equilibrium point and* $D\boldsymbol{f}(x^*)$ *has at least one eigenvalue with a positive real part and at least one with negative real part.*

Mathematical modeling and analysis are central to infectious disease epidemiology. Grassly and Fraser (2008) and Martcheva (2015) gave an introduction to the process of disease transmission and its mathematical representation to analyse the emergent dynamics of observed epidemics. The following equilibrium points are pertinent to the study of epidemiological models.

2.3.1 Disease Free Equilibrium

This is the point at which there is no infection in the population. This is obtained by setting all other compartments to zero except the non-disease states. Let $x^* \in \mathbb{R}^n$ be an equilibrium point of equation (2.5), then the Disease Free Equilibrium (DFE) is the point where $x^* = (x_1, 0, 0, \cdots, x_m, 0, \cdots, 0)$ for which all disease states $x_i = 0$ except the disease free states.

2.3.2 Endemic Equilibrium

This is the point at which the disease is considered to persist in the population. Let $x^* \in \mathbb{R}^n$ be an equilibrium point of equation (2.5), then the Endemic Equilibrium (EE) is the point where $x^* = (x_1, x_2, x_3, \cdots, x_n,)$ for which all disease states $x_i > 0$.

2.4 Stability of Equilibria

An equilibrium point x^* is said to be stable if all solutions sufficiently close to x^* stay nearby for all $t \geq 0$. It is asymptotically stable if nearby solutions actually converge to x^* as $t \longrightarrow \infty$. Stability of equilibrium points are basically in two forms namely:

1. Local Stability
2. Global Stability

2.4.1 Local Stability

An equilibrium point of a dynamical system is said to be locally asymptotically stable given that all the trajectories of its solutions at that point converge to such equilibrium point as $t \to \infty$. Thus, every solution that stands close enough to such equilibrium point will eventually converge to it. The local asymptotic stability of the DFE is established by applying the Routh-Hurwitz stability criterion which states that a system of ODEs is locally asymptotically stable at a particular point if all the eigenvalues of its Jacobian matrix are strictly negative or complex with negative real parts at that point. In control system theory, the Routh–Hurwitz stability criterion is a mathematical test which is a necessary and sufficient condition for the stability of a Linear Time Invariant (LTI) control system.

Definition 2.4.1 *Let x^* be an equilibrium point. x^* is said to be locally stable if for all $\epsilon > 0$, there exist a $\delta > 0$, such that $|x(t) - x^*| < \epsilon$ whenever $|x_0 - x^*| < \delta$ for all $t \geq 0$. Furthermore, x^* is locally asymptotically stable if for all $\epsilon > 0$, there exist a $\delta > 0$, such that $\lim_{t \longrightarrow \infty} x(t) = x^*$ whenever $|x_0 - x^*| < \delta$.*

Definition 2.4.2 *Let x^* be an equilibrium point of a dynamical system. x^* is said to be locally stable if each eigenvalue of the Jacobian matrix is negative.*
Consider the system of equation (2.4). *The Jacobian matrix for such system is given*

by

$$J = D\boldsymbol{f}(x) = \begin{pmatrix} \frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} & \frac{\partial f_1}{\partial x_3} & \cdots & \frac{\partial f_1}{\partial x_n} \\ \frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x_2} & \frac{\partial f_2}{\partial x_3} & \cdots & \frac{\partial f_2}{\partial x_n} \\ \frac{\partial f_3}{\partial x_1} & \frac{\partial f_3}{\partial x_2} & \frac{\partial f_3}{\partial x_3} & \cdots & \frac{\partial f_3}{\partial x_n} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ \frac{\partial f_n}{\partial x_1} & \frac{\partial f_n}{\partial x_2} & \frac{\partial f_n}{\partial x_3} & \cdots & \frac{\partial f_n}{\partial x_n} \end{pmatrix} \tag{2.17}$$

Moreover, x^* is said to be hyperbolic, if none of the eigenvalues in (2.17) *at x^* is zero or it is pure imaginary but non-hyperbolic, otherwise.*

2.4.2 Global Stability

The global stability, unlike the local stability, is concerned with the entire system's behaviour in its domain. This is necessary in epidemiological model to ensure predictability of the model as it guarantees the model's independence on the initial size of the population.

Definition 2.4.3 *Let x^* be an equilibrium point of a dynamical system. x^* is said to be globally stable if it is asymptotically stable for any initial condition, $x_0 \in \mathbb{R}^n$.*

The Comparison Theorem and direct Lyapunov function method are often used to establish the global stability of the equilibrium points of a system.

Comparison Theorem

The comparison theorem for the global stability of the DFE can be determined using an approach presented by (Castillo-Chavez, Feng and Huang, 2002). First, the model system is written in the form:

$$\begin{cases} \frac{dX}{dt} = F(X, Y) \\ \frac{dY}{dt} = G(X, Y), \quad G(X, 0) = 0 \end{cases} \tag{2.18}$$

where $X \in \mathbb{R}^n$ denotes the uninfected compartments (non disease states) and $Y \in \mathbb{R}^m$ denotes the infected compartments (disease states) which includes the latent, carrier, infectious, etc.

Theorem 2.4.1 *(Comparison Theorem) The Disease-Free Equilibrium denoted by* $E_0 = (X^*, 0)$ *is said to be globally asymptotically stable (GAS) if the basic reproduction number* $\mathcal{R}_0 < 1$ *and the following two conditions (C1) and (C2) hold:*

C1: For $\frac{dX}{dt} = F(X, 0)$, E_0 *is globally asymptotically stable.*

C2: $G(X, Y) = AY - \hat{G}(X, Y), \quad \hat{G}(X, Y) \geq 0, \quad \forall\ (X, Y) \in \Omega$

where $A = J\left[G(X^*, 0)\right]$ *is an M-matrix (the off diagonal elements of* A *are non-negative),* Ω *is the region where the model is biologically well posed.*

Direct Lyapunov Function

This method established the global stability by analyzing the behaviour of some real-valued functions of the model as the model system changes with time (Martcheva, 2015).

Definition 2.4.4 *Let* $\mathcal{U}$ *be a neighbourhood of* x^* *and* $x \in \mathcal{U}$. *A function* $V : \mathcal{U} \longrightarrow \mathbb{R}$ *is said to be a positive definite function if*

1. $V(x) > 0$ *for all* $x \neq 0$,
2. $V(x) = 0$ *if and only if* $x = 0$,
3. $V(x) \longrightarrow \infty$ *as* $x \longrightarrow \infty$.

Theorem 2.4.2 *(Lyapunov's Direct Method) Let* E *be an open subset of* $\mathbb{R}^n$ *containing* x_0. *Suppose* $f \in C^1(E)$ *and that* $f(x_0) = 0$. *Again, suppose that there exist a real valued function* $V \in C^1(E)$ *satisfying* $V(x_0) = 0$ *and* $V(x) > 0$ *if* $x \neq x_0$. *Then*

1. *if* $\dot{V}(x) \leq 0$ *for all* $x \in E$, x_0 *is stable;*
2. *if* $\dot{V}(x) < 0$ *for all* $x \in E \backslash x_0$, x_0 *is asymptotically stable;*
3. *if* $\dot{V}(x) > 0$ *for all* $x \in E \backslash x_0$, x_0 *is unstable*

Due to the complexity of the models considered, the Comparison theorem is employed in this thesis to establish the global stability.

2.5 Invariance Principle

Epidemiological models generally assess populations, as such, it is necessary to assume that related population sizes can never be negative. Hence, epidemiological models should be considered in (feasible) regions where such property (non-negative) is preserved. Wiggins (2003), for example, gives the following definitions.

Definition 2.5.1 *A point $x_0 \in \mathbb{R}^n$ is called an ω-limit point of $x \in \mathbb{R}^n$, denoted by $\omega(x)$, if there exists a sequence $\{t_i\}$, $t_i \longrightarrow \infty$, such that*

$$\phi(t_i, x) \longrightarrow x_0.$$

Definition 2.5.2 *A point $x_0 \in \mathbb{R}^n$ is called an α-limit point of $x \in \mathbb{R}^n$, denoted by $\alpha(x)$, if there exists a sequence $\{t_i\}$, $t_i \longrightarrow -\infty$, such that*

$$\phi(t_i, x) \longrightarrow x_0.$$

Definition 2.5.3 *The set of all ω-limit points of a flow is called the ω-limit set. Similarly, the set of all α-limit points of a flow is called the α-limit set.*

Definition 2.5.4 *A set M is invariant if and only if for all $x \in M$, $\phi(x,t) \in M$ for all t. A set is positively (negatively) invariant if for all $x \in M$, $\phi(x,t) \in M$ for all $t > 0$ $(t < 0)$.*

Theorem 2.5.1 *(LaSalle Invariance Principle). Let K be a compact subset of the phase space X. Suppose that E is a real-valued smooth function defined on K, whose Lie derivative satisfies $\dot{E}(x) \leq 0$ for all $x \in K$. Let M be the largest invariant set contained in $N := \left\{x \in K \mid \dot{E}(x) = 0\right\}$. Then the $\omega - limit$ of every orbit which remains within K for $t > 0$ is a non-empty subset of M, which implies that such an orbit is asymptotic to M.*

Proof: Let $\gamma := \{\varphi(t, x_0) \mid t > 0\}$ be a forward orbit, contained in the compact set K, and let $\omega - limit$ of γ be non-empty. If $t_n \to +\infty$, then by the compactness of K, there exists a subsequence t_{n_k} such that $x(t_{n_k})$ converges to some $x_0 \in K$.
Now, let $y \in \omega - limit$ of γ then $\varphi(t, y) \in \omega - limit$ of γ, for all $t \in \mathbb{R}$.

Since $y \in \omega - limit$ of γ, there exists a sequence $t_n \to +\infty$ such that $\varphi(t_n, x_0) \to y$. But we have

$$\varphi(t, y) = \varphi(t, \lim_{n\to+\infty} \varphi(t_n, x_0)) = \lim_{n\to+\infty} \varphi(t + t_n, x_0)$$

Setting $s_n := t + t_n$ and observing that $s_n \to +\infty$, we have that $\varphi(t, y) \in \omega - limit$ of γ. Let y_0 be a point of the $\omega - limit$ of γ. Then, there exists a sequence $t_n \to +\infty$ such that $\varphi(t_n, x_0) \to y_0$. Now, let

$$c := E(y_0) = \lim_{n\to+\infty} E\left[\varphi(t_n, x_0)\right].$$

Since $E\left[\varphi(t_n, x_0)\right]$ is a time-nonincreasing function, $\lim_{n\to+\infty} E\left[\varphi(t_n, x_0)\right] = c$ implies $\lim_{t\to+\infty} E\left[\varphi(t_n, x_0)\right] = c$. Therefore, for all y in the $\omega - limit$ of γ, $E(y) = c$ holds. Hence, the $\omega - limit$ is an invariant set contained in a level set of the function E. Thus, the Lie derivative of E must vanish at every point of the $\omega - limit$.
We know that $M \subset K$, which implies that the orbit is asymptotic to the set M. Suppose by contradiction that there exist $\delta > 0$ and a sequence $t_n \to +\infty$ such that $\text{dist}(x(t_n), M) \geq \delta$. The sequence $x(t_n)$ is contained in the compact set K, therefore the set Ω of accumulation points of $x(t_n)$ is a nonempty subset of K. Since $\text{dist}(x(t_n), M) \geq \delta$, we have $\Omega \cap M = \phi$. Hence proved.

2.6 Basic Reproductive Number ($\mathcal{R}_0$)

$\mathcal{R}_0$ is defined as the average number of secondary infections caused by the emergence of an infectious individual into a complete susceptible population. It is obtained by finding the Jacobian at the disease free equilibrium. It's main purpose is to determine the persistence of the disease in the studied population (Yang, 2014). When $\mathcal{R}_0 < 1$, then the infectious individual infects less than one susceptible person over the course of its infectious period and hence, the disease will eventually die out. On the other hand, if $\mathcal{R}_0 > 1$, then the infectious individual infects more than one susceptible person over the course of its infectious period and hence the disease is expected to persist in the population.

The basic reproduction number $\mathcal{R}_0$ has been reviewed extensively with various methods

in its derivation and an overview of the use of $\mathcal{R}_0$ in assessing emerging and re-emerging infectious diseases (Heffernan, Smith and Wahl, 2005). There are mainly two methods used for the analytical derivation of $\mathcal{R}_0$ in compartmental models of disease transmission namely, survival function (Heesterbeek and Dietz, 1996) and next generation matrix method (Van den Driessche and Watmough (2002); Van den Driessche (2017)). The next generation matrix method is used in this thesis since it's the convenient method.

2.6.1 Next Generation Martrix Approach

This operates on the principle that the number of secondary infections produced by a single infected individual can be expressed as the product of the expected duration of the infectious period and the rate secondary infections occur.

Thus, assume that there are n compartments of which m are infected. We define the vector $x_i = (x_1,\ x_2,\ x_3, \cdots, x_n)$ as the number or proportion of individuals in the ith compartment. Let $\mathcal{F}_i(x)$ be the rate of appearance of new infections in compartment i and let $\mathcal{V}_i(x) = \mathcal{V}_i^-(x) - \mathcal{V}_i^+(x)$, where $\mathcal{V}_i^+$ is the rate of transfer of individuals into compartment i by all other means and $\mathcal{V}_i^-$ is the rate of transfer of individuals out of the ith compartment.

$$\dot{x} = f_i(x) = \mathcal{F}_i(x) - \mathcal{V}_i(x) \tag{2.19}$$

Note that $\mathcal{F}_i(x)$ should include only infections that are newly arising, but does not include terms which describe the transfer of infectious individuals from one infected compartment to another. Assuming that $\mathcal{F}_i$ and $\mathcal{V}_i$ satisfy the following axioms outlined by (Van den Driessche and Watmough, 2002). Let $X_s = \{x \geq 0 | x_i = 0, i = 1, ..., m\}$ be the disease free states (non-infected state variables) of the model, where $x = (x_1, ..., x_m)$, $x \geq 0$.

(**A**1) if $x \geq 0$, then $\mathcal{F}_i, \mathcal{V}_i^+, \mathcal{V}_i^- \geq 0$ for $i = 1, ..., m$.

(**A**2) if $x = 0$, then $\mathcal{V}_i^- = 0$. In particular, if $x \in X_s$ then $\mathcal{V}_i^-$ for $i = 1, ..., m$.

(**A**3) $\mathcal{F}_i = 0$ if $i > m$

(**A**4) if $x \in X_s$, then $\mathcal{F}_i(x) = 0$ and $\mathcal{V}_i^+ = 0$ for $i = 1, ..., m$.

(**A**5) if $\mathcal{F}(x)$ is set to zero, then all eigenvalues of $Df(x_0)$ have negative real parts, where $Df(x_0)$ is the Jacobian matrix evaluated at the Disease-free equilibrium (DFE) x_0.

Definition 2.6.1 *(M-Matrix) An $n \times n$ matrix A is an M-matrix if and only if every off-diagonal entry of A is non-positive and the diagonal entries are all positive.*

Lemma 2.6.1 *If x_0 is a Disease-free equilibrium (DFE) of (2.9) and $f_i(x)$ satisfies (**A**1)-(**A**5), then the derivatives $D\mathcal{F}(x0)$ and $D\mathcal{V}(x0)$ are partitioned as*

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

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

$$F = \left[\frac{\partial \mathcal{F}_i}{\partial x_j}(x_0)\right], \quad V = \left[\frac{\partial \mathcal{V}_i}{\partial x_j}(x_0)\right], \quad with \quad 1 \leq i, j \leq m.$$

We note that F is non-negative, V is a non-singular M-matrix and all eigenvalues of J_4 have positive real part.
$G = FV^{-1}$ is called the next generation matrix for the model (2.13) and set

$$\mathcal{R}_0 = \rho(FV^{-1}) \tag{2.20}$$

where ρ is the spectral radius (dominant eigenvalue) of the matrix $G = FV^{-1}$.

Theorem 2.6.1 *Consider the disease transmission model given by (2.13) with $f(x)$ satisfying conditions (A1)-(A5). If x_0 is a DFE of the model, then x_0 is locally asymptotically stable if $\mathcal{R}_0 < 1$, but unstable if $\mathcal{R}_0 > 1$.*

2.7 Sensitivity Analysis

The behaviour of physical and chemical systems is influenced by many parameters that describe the system. The analysis on how a system responds to changes in its parameters is known as **parametric sensitivity** (Varma, Morbidelli and Wu, 2005). When some parameters are slightly varied, while keeping the remaining parameters constant, the response of the system also changes slightly. However, other set of

parameter combinations can cause the system to respond enormously, even if one or more parameters are slightly varied . In this case, it is said that the system behaves in a parametrically sensitive manner (Varma, Morbidelli and Wu, 2005).

Sensitivity Analysis is a method used to determine how different input values affect a particular output value under a set of given assumptions. In other words, it looks into how various sources of uncertainty in a mathematical model contribute to the model's overall uncertainty. It allows for forecasting using both true and historical data. It is a method that helps to predict the outcome of a decision given a number of variables. Sensitivity analysis determines how target variables are influenced based on changes in other variables called the inputs. Hence, it determines how changes in one variable can affect or influence the outcome or the results of a model.

Since the basic reproductive number $\mathcal{R}_0$ is one of the most important variables in mathematical epidemiology, the sensitivity analysis focuses on the influence or contributions of the main model parameters on $\mathcal{R}_0$. It centers on how changes in the value of a particular model parameter can affect $\mathcal{R}_0$ and the extent to which it is being affected. Therefore, sensitivity analysis provides information on the effectiveness of each parameter value to the spread of the disease. It also permits us to gauge the relative change in a variable when a parameter changes. The normalized forward sensitivity index of a variable in relation to a parameter is the proportion of the relative change in the variable to the relative change in the parameter. Suppose, the variable is differentiable with respect to the parameter, then the sensitivity index can be defined using partial derivatives.

Definition 2.7.1 *The normalized forward sensitivity index of $\mathcal{R}_0$, that depends differentiably on a parameter ψ, is defined by*

$$S_{\psi}^{\mathcal{R}_0} = \frac{\partial \mathcal{R}_0}{\partial \psi} \times \frac{\psi}{\mathcal{R}_0} \tag{2.21}$$

In particular, the sensitivity index is a local estimate to establishing an efficient way of reducing $\mathcal{R}_0$.

2.8 Historical Development of Optimal Control

Optimal control is closely related in its origins to the theory of Calculus of Variations (CoV), which deals with finding the maximum or minimum of a functional, since it evolved from variational problems. The first formal results of the calculus of variations can be found in the seventeenth century. Optimal control problems generalize variational problems by separating control and state variables and admitting control constraints. The generalization of the calculus of variations to optimal control theory was strongly motivated by military applications and has since developed rapidly (Rodrigues, Monteiro and Torres, 2014).

Johann Bernoulli posed the Brachistochrone problem in 1696 to other famous contemporary mathematicians like Sir Isaac Newton, Gottfried Wilhelm Leibniz, Jacob Bernoulli, Guillaume Francois Antoine Marquis de L'Hospital and Ehrenfried Walter von Tschirnhaus. Each of these distinguished mathematicians were able to solve the problem with an interesting description of the Brachistochrone problem (Gerdts, 2011).

Some important milestones in the development of optimal control in the 20^{th} century include the formulation of dynamic programming by Richard Bellman in the 1950s, the development of the minimum principle by Lev Pontryagin and co-workers also in the 1950s, and the formulation of the linear quadratic regulator and the Kalman filter by Rudolf Kalman in the 1960s. The Pontryagin Maximum Principle has provided research with suitable conditions for optimization problems with differential equations as constraints (Wilamowski and Irwin, 2011).

The method of optimization for constrained problems with the addition of unknown multipliers became known by the name of its inventor, Lagrange. The Lagrange multiplier rule was introduced for the minimization of a function with equality constraints. Penalty methods were developed based on the Lagrange multiplier rule to eliminate some or all the constraints and add to the objective function with a penalty term which prescribes a high cost to infeasible points (Dong, 2006).

Cauchy made the first application of the steepest descent method to solve unconstrained optimization problems. By middle of the twentieth century, the high-speed digital computers made implementation of the complex optimization procedures possible and stimulated further research on newer methods. There has been remarkable advances which has produced a massive literature on optimization techniques. This advancement has also led to several well defined new areas in optimization theory (Polak, 1973).

In the first few years of optimal control, the indirect method was the preferred method for solving optimal control problems. The calculus of variations is employed in this method to obtain the first-order optimality conditions (Naidu, 2003). The earlier algorithms for optimal control were aimed at unconstrained problems and were derived by using the first and second variation methods of calculus of variations. These methods have been subsequently recognized as gradient, Newton-Raphson, or Gauss-Newton methods in function space (Olotu, 2007).

The modern theory of optimal control had its main developments during the 1950s with the formulation of two main optimization techniques: Dynamic Programming which was introduced by Bellman in 1952 and the Pontryagin's Minimum Principle. The approaches are significantly different but both of them still have applications up to today. The Dynamic Programming makes use of the principle of optimality and it is suitable for solving discrete problems, allowing a significant reduction in the computation of the optimal controls. It is also possible to obtain a continuous approach to the principle of optimality that leads to the solution of a partial differential equation called the Hamilton-Jacobi-Bellman equation.

The major developments in the area of numerical methods of unconstrained optimization was made in the United Kingdom in the 1960s. The development of the simplex method by Dantzig in 1947 for linear programming problems and the annunciation of the principle of optimality in 1957 by Bellman for dynamic programming problems paved the way for development of the methods of constrained

optimization (Horst and Tuy, 2013). The work by Kuhn, Tucker and Neyman (1951) on the necessary and sufficient conditions for the optimal solution of quadratic programming problems laid the foundations for a great deal of research in nonlinear programming. Also, the contributions of Zoutendijk (1960) to nonlinear programming during the early 1960s have been very significant. Although no single technique has been found to be universally applicable for nonlinear programming problems, the work of Fiacco and McCormick (1990) allowed many difficult problems to be solved by using the well-known techniques of unconstrained optimization.

2.9 Optimal Control Problem Formulations

2.9.1 State and Control Variables

The **state variable** (or function) is a set of variables (or functions) $x_1, x_2, \cdots, x_n$ used to describe the condition or mathematical state of the system. The **control variable** (or function) $u_1, u_2, \cdots, u_m$ is an operation that controls the recording, processing, or transmission of data. These two functions drive how the system works to get the desired control. The state variable provides the information which (together with the knowledge of the equations describing the system) enables us to calculate the future behavior from the knowledge of the control variables (or inputs). The relationship between the state x and the control u is the map $u(t) \rightarrow x = x(u)$. Indeed, though this relationship exist, x is just a function of the independent time variable, but in writing $x(u)$, the dependence of x on u is shown.

It is often not possible to determine the values of the state variables directly; instead, only a set of controlled variables which depend in some way on the state variables, is measured. In general, the aim is to make a system perform in some required way by suitably manipulating the inputs, this is being done by some controlling device or a "controller". If the controller operates according to some pre-set pattern without taking account of the output or state, the system is called an **open loop**. However, if there is feedback of information concerning the outputs to the controller, which appropriately modifies its course of action, the system is called **closed loop**.

An open loop control can be basically an "arbitrary" function $u : [t_0, +\infty) \to U$ for which the Initial Value Problem (IVP)

$$\dot{x}(t) = h(t, x(t), u(t)), \qquad x(t_0) = x_0$$

has a well defined solution.
A closed loop control can be identified with a mapping $k : M \to U$ (which may depend on $t \geq t_0$) such that the Initial Value Problem (IVP)

$$\dot{x}(t) = h(t, x(t), k(x(\cdot))), \qquad x(t_0) = x_0$$

has a well defined solution. The mapping $k(\cdot)$ is called **feedback**.
We assume that our system models have the property that, given an initial state and any input, the resulting state and output at some specified later time are uniquely determined.

Constraints are being imposed on the state and control variables which restrict their range of values. For state constrained optimal control problems, the path-wise constraints are imposed on the state trajectories in question. In most cases, the constraints are imposed at the initial and/or terminal point of a fixed interval $[a, b]$. This is known as the endpoint constraints and generally written as

$$(x(a), x(b)) \in E$$

If $x(a) = x_a$ and $x(b) \in \mathbb{R}^n$, then $E = x_a \times \mathbb{R}^n$.
Control constraints are the limitations imposed on the control variables $u(t)$ of an optimal control problem. $u(t)$ takes values from a permissible set of controls U. If $t \in [a, b]$, then the value of the function is $u(t)$.

2.9.2 General Formulations of Optimal Control Problems

The formulation of an optimal control problem requires the following:

1. A mathematical model of the system to be controlled.

2. A specification of the performance index.

3. A specification of all boundary conditions on states and constraints to be satisfied by states and controls.

4. A statement of what variables are free.

The three well known equivalent general formulations of optimal control problems are the Lagrange, Mayer and Bolza formulations.

Optimal Control Problems in Lagrange Form

The objective functional in the problem of Lagrange is in (pure) integral form. The general Lagrange form of an optimal control problem is defined as

$$\text{Minimize } J(x(t), u(t)) = \int_{t_0}^{t_f} f(t, x(t), u(t))dt \tag{2.22}$$

$$\text{Subject to } \dot{x}(t) = h(t, x(t), u(t)) \tag{2.23}$$

$$x(t_0) = x_0, \quad t_0 \leq t \leq t_f \tag{2.24}$$

where f and h are continuously differentiable functions. The control set U is assumed to be a Lebesgue measurable function. Thus, as the control(s) will always be piecewise continuous, the associated states will also be piecewise differentiable (Kirk, 2004).

Definition 2.9.1 *Let $I \subseteq \mathbb{R}$ be an interval (finite or infinite). We say a finite-valued function $u : I \to \mathbb{R}$ is piecewise continuous if it is continuous at each $t \in I$, with the possible exception of at most a finite number of t, and if u is equal to either its left or right limit at every $t \in I$.*

In other words, a piecewise continuous function can have finitely many "jump discontinuities" from one continuous segment to another.

Definition 2.9.2 *Let $x : I \to \mathbb{R}$ be continuous on I and differentiable at all but finitely points of I. Further, suppose that $\dot{x}$ is continuous wherever it is defined. Then, we say x is piecewise differentiable.*

Optimal Control Problems in Mayer Form

In the Mayer form, the functional is not an integral but a function ϕ that depends in general on the dependent variable t and the final point of the t-domain. For time-optimal OCPs, such as in this thesis, the problem of Mayer is often referred to as a problem of optimizing the final time. The objective function is called pay off function and is constrained by a set of differential equations, in general ODE, but differential algebraic equations (DAE) are also encountered. The general Mayer formulation of an optimal control problem is defined as

$$\text{Minimize } J(x(t), u(t)) = \quad \phi(t_f, x(t_f)) \tag{2.25}$$

$$\text{Subject to} \quad \dot{x}(t) = \quad h(t, x(t), u(t)) \tag{2.26}$$

$$x(t_0) = x_0, \quad t_0 \leq t \leq t_f \tag{2.27}$$

where ϕ and h are continuously differentiable functions (Kirk, 2004).

Optimal Control Problems in Bolza Form

The Bolza form of an optimal control problem is a linear combination of the problems of Mayer and Lagrange. This considers a final (terminal) performance index in addition to the integral performance index. The general Bolza formulation is defined as

$$\text{Minimize } J(x(t), u(t)) = \quad \phi(t_f, x(t_f)) + \int_{t_0}^{t_f} f(t, x(t), u(t))dt \tag{2.28}$$

$$\text{Subject to} \quad \dot{x}(t) = \quad h(t, x(t), u(t)) \tag{2.29}$$

$$x(t_0) = x_0, \quad t_0 \leq t \leq t_f \tag{2.30}$$

where f, ϕ and h are continuously differentiable functions (Kirk, 2004).

2.9.3 Equivalence of the Three Formulations

It is clear that the Lagrange and Mayer forms are particular cases of the Bolza form, however the three formulations are said to be equivalent even though the Bolza form looks more general than the other two. This is shown below.

From Bolza to Lagrange

To do this conversion, a new component is added to the vector $x \in \mathbb{R}^n$ such that $x_{n+1}(t) = \phi(t, x(t))$. Substituting it into the Bolza formulation in equations (2.28) to (2.30) gives

$$\text{Minimize } J(x(t), u(t)) = \int_{t_0}^{t_f} f(t, x(t), u(t)) + \dot{x}_{n+1}(t)dt, \quad t \in [t_0, t_f] \tag{2.31}$$

$$\begin{pmatrix} \dot{x}(t) \\ \dot{x}_{n+1}(t) \end{pmatrix} = \begin{pmatrix} h(t, x, u) \\ \frac{d}{dt}\phi(t, x(t)) \end{pmatrix} \tag{2.32}$$

$$\begin{pmatrix} x(t_0) \\ x_{n+1}(t_0) \end{pmatrix} = \begin{pmatrix} x_0 \\ \phi(t_0, x_0) \end{pmatrix} \tag{2.33}$$

which yields a problem of the Lagrange form.

From Lagrange to Mayer

A Lagrange formulation is transformed into a Mayer form by considering a new variable x_{n+1} defined as $\dot{x}_{n+1}(t) = f(t, x(t), u(t))$ with initial condition $x_{n+1}(t_0) = 0$. Putting it into the problem of Lagrange in equations (2.22) to (2.24) gives

$$\text{Minimize } J(x(t), u(t)) = \quad x_{n+1}(t_f) \quad t \in [t_0, t_f] \tag{2.34}$$

$$(\dot{x}(t), \dot{x}_{n+1}(t)) = \quad (h(t, x(t), u(t)), f(t, x(t), u(t))) \tag{2.35}$$

$$(x(t_0), x_{n+1}(t_0)) = \quad (x_0, 0) \tag{2.36}$$

which yields a problem of the Mayer form.

From Mayer to Lagrange

A Mayer form is converted to a Lagrange form by considering a new variable $x_{n+1}(t)$ defined as $\dot{x}_{n+1}(t) = 0$ with the condition that $x_{n+1} = \frac{\phi(t, x(t_f))}{t_f - t_0}$. The Mayer problem

in equations (2.25) to (2.27) becomes

$$\text{Minimize } J(x(t),u(t)) = \int_{t_0}^{t_f} x_{n+1}(t)dt \quad t \in [t_0,t_f] \tag{2.37}$$

$$(\dot{x}(t),\dot{x}_{n+1}(t)) = (h(t,x(t),u(t)),0) \tag{2.38}$$

$$(x(t_0),x_{n+1}(t_0)) = \left(x_0, \frac{\phi(t,x(t_f))}{t_f - t_0}\right) \tag{2.39}$$

which yields a problem of the Lagrange form (Kirk, 2004).

2.9.4 Existence of an Optimal Control - Pontryagin's Maximum Principle

The principal technique for an optimal control problem formulation is to solve a set of necessary condition that an optimal control and it's corresponding state(s) must satisfy. This necessary condition was formulated in 1956 by the Russian mathematician Lev Pontryagin and his students. This principle is used in optimal control theory to find the best possible control in taking a dynamical system from one state to another, especially in the presence of constraints on the state or input controls. Pontryagin's maximum (or minimum) principle, also known as the necessary or optimality condition, is a condition that must be satisfied for a statement to be true. It should be noted, however, that the condition does not validate the statement. Pontryagin introduced the idea of adjoint functions to add the differential equation constraint to the objective functional. Adjoint functions have a similar drive as Lagrange multipliers in multivariate calculus, which adds constraints to the function of several variables to be maximized or minimized.

Consider an optimal control problem of the form

$$\begin{aligned} \text{Maximize } J(x(t),u(t)) &= \int_{t_0}^{t_f} f(t,x(t),u(t))dt \\ \text{Subject to} \quad \dot{x}(t) &= h(t,x(t),u(t)) \\ & \quad x(t_0) = x_0, \quad t_0 \le t \le t_f \end{aligned} \tag{2.40}$$

$x(t_f)$ could be free or restricted

Theorem 2.9.1 *(Pontryagin's Maximum Principle) If $u^*(t)$ and $x^*(t)$ are optimal for problem* (2.40)*, then there exists a piecewise differentiable adjoint variable $\lambda(t)$ such*

that

$$H(t, x^*(t), u(t), \lambda(t)) \leq H(t, x^*(t), u^*(t), \lambda(t)) \tag{2.41}$$

for all controls u at each time t, where H is the Hamiltonian and

$$\dot{\lambda}(t) = -\frac{\partial H(t, x^*(t), u^*(t), \lambda(t))}{\partial x} \tag{2.42}$$

$$\lambda(t_f) = 0 \tag{2.43}$$

Remark 2.9.1 *The last condition $\lambda(t_f) = 0$, called the transversality condition, is only used when the OCP does not have terminal value in the state variable, that is $x(t_f)$ is free.*

This principle was first known as the Pontryagin's maximum principle and proved historically based on maximizing the Hamiltonian. However, it was mostly used for minimization of a performance index, so considered as the minimum principle in this context. The principle converts the problem of finding a control which maximizes the objective functional subject to the state ODE and initial condition to a problem of optimizing the Hamiltonian pointwise. Consequently, with this adjoint equation and Hamiltonian, we have

$$\frac{\partial H}{\partial u} = 0 \tag{2.44}$$

at u^* for each t which is termed as a critical point of the Hamiltonian. This condition is usually called the optimality condition. Therefore, to find the necessary conditions, we do not need to calculate the integral in the objective functional, but only use the Hamiltonian.

Hence, in finding the solution to any optimal control problem, one must:

1. construct the Hamiltonian of the problem;
2. write the adjoint differential equation, transversality boundary condition and the optimality condition in terms of the three unknowns, $x^*(t), u^*(t)$ and $\lambda(t)$;
3. use the optimality equation $\frac{\partial H}{\partial u} = 0$ to solve for $u^*(t)$ in terms of $x^*(t)$ and $\lambda(t)$;
4. solve the two differential equations for $x^*(t)$ and $\lambda(t)$ with the two boundary conditions and

5. use the values or expressions for the optimal state and adjoint from step (3) above to solve for the optimal control.

Remark 2.9.2 *If the Hamiltonian is linear in the control variable u, it can be difficult to calculate u^* from the optimality equation, since $\frac{\partial H}{\partial u}$ would not contain u. Specific ways of solving this kind of problem can be found in Lenhart and Workman (2007).*

2.10 Optimal Control Applied to Epidemiology

Control theory is one of the most interdisciplinary areas of research and has received great practical applications in different areas of study. It has been a discipline where many mathematical ideas and methods are used. Optimal control problems have been reviewed by many researchers and various methods of solution proposed by various authors.

Sargent (2000) presented a review on the different numerical approaches to the solutions of optimal control problems and a brief historical survey of the development of optimal control and calculus of variations. The work of Olotu and Adekunle (2010) examined the Analytic and Numeric Solutions of Discretized Constrained Optimal Control Problem. The associated general Riccati differential equation was solved by numerical-analytical approach using variational iteration method. The results showed that both the analytical and numerical solutions agreed favourably. A geometric convergence ratio profile of a discretized scheme for constrained quadratic control problem was also examined by Olotu and Olorunsola (2008). To pave way for the numerical applications of the developed scheme, the time interval was discretized and the Euler's scheme was used for the differential constraint to obtain a finite approximation. An associated operator was constructed with bilinear form expression. Their scheme was applied to sampled problem which exhibited geometric convergence ratio in the open interval $(0, 1)$.

Ding and Lenhart (2010) presented a work that serves as an introduction to the theory of optimal control applied to systems of discrete time models with an emphasis on disease models. They outlined the steps in solving such optimal control problems

and discussed the necessary conditions. A simple disease example provides detailed methodology in charactering the optimal control through the use of Pontryagin's Maximum Principle. Numerical results were given to illustrate several cases. Similar to this work, is an Introduction to Optimal Control with an Application in Disease Modelling presented by Neilan and Lenhart (2010). In this research, the theory of optimal control applied to systems of ordinary differential equations with emphasis on disease models was considered. A SEIR (Susceptible, Exposed, Infected, Recovered) model with control acting as a rate of vaccination was presented and an optimal control problem was formulated to include an isoperimetric constraint on the vaccine supply. Their numerical results demonstrated how such a constraint alters the optimal vaccination schedule and its possible effect on the population.

Sofia (2014) applied the study of Optimal Control to epidemiological models, giving particular relevance to Dengue which is considered by the World Health Organization as a major concern for public health. Ordinary differential equations were used to develop the models to describe the dynamics underlying the disease, including the interaction between humans and mosquitoes. An analytical study relating to the equilibrium points, stability and basic reproduction number was made. Since the development of a potential vaccine has been a global bet, models based on the simulation of a hypothetical vaccination process in a population were proposed. Optimal Control theory was used to analyze the optimal strategies for using these controls and respective impact on the reduction or eradication of the disease during an outbreak in a population considering a bioeconomic approach. There was a compromise between the realism of epidemiological models and their mathematical tractability in their study.

Gaff and Schaefer (2009) considered variations of standard SIR, SIRS, and SEIR epidemiological models to determine the sensitivity of these models to various parameter values that may not be fully known when the models are used to investigate emerging diseases. Optimal control theory was applied to determine the most effective mitigation strategy to minimize the number of individuals who become infected in the course of an infection while efficiently balancing vaccination and

treatment applied to the models with various cost scenarios. The results from the optimal control simulations suggested that regardless of the particular epidemiological structure and of the comparative cost of mitigation strategies, vaccination, if available, would be a crucial piece of any intervention plan.

An SIR model with variable size population and optimal control problem was formulated with vaccination and treatment as controls by Yusuf and Benyah (2012). Pontryagin's maximum principle was used to characterize the controls and derive the optimality system. Numerical simulations of the resulting optimality system were performed and the results suggested that the optimal combination of vaccination and treatment strategy required to achieve the set objective will depend on the relative cost of each of the control measures. In the case where it is more expensive to vaccinate than to treat, it was proposed that resources should be invested in treating the disease until the disease prevalence begins to fall.

Neilan (2009) considered the use of optimal control theory in population models for the purpose of characterizing strategies of control which minimize an invasive or infected population with the least cost. Three different models and optimal control problems were presented. Each model describes population dynamics via a system of differential equations and includes the effects of one or more control methods. A novel existence result of an optimal control was proven in the case of ordinary differential state equations containing quadratic expressions of the control variable. Their results showed that reduced quantities of vaccine may not be effective in containing disease spread or eliminating the infected population.

A mathematical model of drug therapy for chronic myelogenous leukemia for an individual patient over a fixed time horizon was presented by Nanda, Moore and Lenhart (2007) using ordinary differential equations. Their model describes the interaction between naive T cells, effector T cells and leukemic cancer cells in a hypothetical patient. Two drug therapies, which are a targeted therapy and a broad cytotoxic therapy were incorporated into the model to help find treatment regimens that minimize the cancer cell count and the deleterious effects of the drugs for a given

patient. Analytical and numerical solutions of the model were presented to illustrate the optimal regimens under various assumptions.

An SCIR model for meningococcal meningitis was developed and used to analyze the impact of a vaccination program on the health of the population in epidemic prone countries. The model was solved numerically using Euler's method, and the results showed that to stop the spread of the disease in a highly populated area, the vaccination rate needed to be on the increase (Vereen, 2008). Udofia and Inyama (2012) presented a mathematical model on the transmission dynamics of fowl pox infection in poultry. The interaction between the susceptible and infected birds was considered resulting in a system of ordinary differential equations. The control which represents the effort in applying Chemoprophylaxis control and treatment control in birds with fowl pox was introduced, giving rise to a system of ordinary differential equations with control. The optimal control problem involving the number of birds with latent and active fowl pox infections and the cost of treatment controls were minimized subject to the differential equations. Optimal effort necessary to reduce the transmission rate of fowl pox in the poultry was also determined by analyzing the model using Pontryagin's Maximum Principle and optimality conditions.

Martcheva and Crispino-O'Connell (2003) used an age-structured mathematical model to study the transmission dynamics of meningococcal infection. The conditions that give rise to the stability of the disease-free steady state and the existence of an endemic state were examined. The contribution of the carrier class to the transmission of the disease was established from the numerical simulation. Wiah and Adetunde (2010) investigated the dynamics of cerebrospinal meningitis (CSM) in Jirapa district in the Upper West region of Ghana. Their paper presented the dynamics of cerebrospinal meningitis and suggested ways on how to control the disease. The existence of the solution of the model was established and the stability of equilibria was examined. The numerical simulation showed that early treatment, implementation of cerebrospinal meningitis protocols and cooperation with medical personnel and traditional healers could help control the disease.

Subsequently, Maseno (2011) presented a mathematical model for malaria and meningitis co-infection among children under five years of age. Their analysis showed that the disease-free equilibrium of the model may not be globally asymptotically stable whenever the basic reproduction number is less than unity. The model also had a unique endemic equilibrium which is locally asymptotically stable when the basic reproduction number is less than 1 and unstable when the basic reproduction number is greater than 1. They further deduced that a reduction in malaria infection cases either through protection or prompt effective treatment would reduce the number of new co-infection cases.

The pattern of the transmission dynamics of meningococcal meningitis was investigated using deterministic compartmental models. The results from the numerical simulation of the model showed that seasonal vibration and temporary immunity were due to the irregular epidemics which often occur in the meningitis belt (Irving *et al.*, 2012). The mathematical SIRC epidemic model was considered by Iacoviello and Stasio (2013) with optimal controls over both the susceptible and the infected classes, taking into account the limitations of resources. A suitable cost index was introduced and the optimal control strategy, together with the existence of optimal solution was determined using the Pontryagin's Minimum Principle. Numerical results were presented to analyze the effects of different control strategies.

An age-structured mathematical model of MenA transmission, colonization, and disease in the African meningitis belt was developed and used to explore the impact of various vaccination strategies. The validity of the model was assessed by a comparison of the simulated incidence of invasive MenA and the prevalence of MenA carriage to observed incidence and carriage data. The model was able to reproduce the observed dynamics of MenA epidemics in the African meningitis belt, including seasonal increases in incidence, with large epidemics occurring every eight to twelve years. It was established that the most effective modeled vaccination strategy is to conduct mass vaccination campaigns every 5 years for children aged 1–5 years (Tartof *et al.*, 2013); (Tartof *et al.*, 2017).

Dukić *et al.* (2012) carried out a generalized additive model analysis of meningitis outbreaks in Navrongo, Ghana, which estimated the effects of weather variables such as rain, relative humidity, temperature, and air quality variables including dust and CO emissions, on meningitis incidence in an unbiased way. The models pointed to the relevance of weather and pollution variables, in particular the effects of current month's average maximum temperature, previous month's relative humidity, and previous month's CO emissions due to fires were persistent.

Martinez *et al.* (2013) presented a novel Susceptible, Asymptomatic Infected, Infected with symptoms, Carriers, Recovered and Died mathematical model for the transmission of meningococcal meningitis using cellular automata. Their results established that both the individual and global behaviours of the disease could be determined. This result agreed favourably with the empirical predictions. Blyuss (2016) also used mathematical models to identify crucial factors that determine the meningitis dynamics. Their results suggested temporaral population immunity as a key role and should be considered during disease monitoring and assessment of the efficiency of vaccines deployed.

Mathematical and economic models was used by Christensen *et al.* (2014) to predict the epidemiological and economic impact of vaccination with Bexsero which is designed to protect against Group B meningococcal disease and to help inform vaccine policy in the United Kingdom. Their results suggested that routine infant vaccination could be cost-effective in England under favourable assumptions if the vaccine could be procured at less than 20% of the list price. This was seen to be the most favourable option since it targets majority of the people at risk of disease.

A mathematical model of MenA transmission and disease was created by Karachaliou *et al.* (2015) to investigate the potential impact of a range of immunization strategies. Their age-structured SCIR model incorporated seasonal transmission and a stochastic forcing term that models between year variation in rates of transmission. Their model was used to describe the typical annual incidence of meningitis in the prevaccine era, with irregular epidemics of varying size. Parameter and structural uncertainty

were explored in sensitivity analyses, and their model predicted excellent short-term disease control.

Asamoah *et al.* (2018) presented a mathematical framework of vaccination and treatment on an SCIRS bacterial meningitis model. Their model exhibited a local and global asymptotic stability at the disease-free equilibrium, and a global stability at the endemic equilibrium. Their numerical simulation showed that the optimal (best) way of controlling the transmission of meningitis in Sub-Saharan Africa and the world at large is to encourage the susceptible population to get vaccinated and report any suspected symptoms of meningitis to health practitioners for early detection and immediate care.

A deterministic model for Meningococcal meningitis transmission dynamics with variable total population size was presented by Yusuf (2018). It was shown analytically and numerically that with effective control measures in place, the disease can be eradicated. Their simulation suggested control measures that can reduce the disease transmission rate and immunity waning rate as well as boost the vaccination and treatment rates. This model was used as the constraint equations for the optimal control problem (OCP) formulation to depict the Meningitis epidemic situation in the Meningitis belt in a work presented by Yusuf and Olayinka (2019). The aim of the optimal control problem was to determine the optimal levels of each of the control measures that should be deployed to minimize the incidence and prevalence of the disease together with the cost of control measures within a specified time frame. Pontryagin's Maximum Principle (PMP) was used to derive the optimality system and the resulting optimality system was solved numerically. The simulation results were related to their earlier results.

CHAPTER 3

FORMULATION AND ANALYSIS OF A DETERMINISTIC BACTERIAL MENINGITIS MODEL WITH VACCINATION AND TREATMENT INTERVENTIONS

3.1 Model Description and Formulation

Mathematical modeling is one of the most important tools used in understanding the dynamics of disease transmission. In formulating the model, the total population at time t, denoted by $N(t)$, is divided into seven (7) mutually exclusive epidemiological classes, namely, the Susceptible Class, $S(t)$ Vaccinated Class, $V(t)$ Carrier Class, $C(t)$ Infected Class, $I(t)$ Treated Class, $T(t)$ and two Recovered Classes, $R_1(t)$ and $R_2(t)$. This is given as

$$N(t) = S(t) + V(t) + C(t) + I(t) + T(t) + R_1(t) + R_2(t) \tag{3.1}$$

The Susceptible Class is made up of the individuals who are not yet infected and have also not been vaccinated against the disease. This is generated by the recruitment of individuals at a rate α and by loss of immunity from previous vaccination. The Susceptible class is reduced by natural death, vaccination or by infection through effective contact with infected individuals at the rate

$$\lambda\left(t\right) = \frac{\beta\left[\eta_1 C\left(t\right) + I\left(t\right)\right]}{N\left(t\right)} \tag{3.2}$$

The parameter β is the effective transmission probability per contact and the parameter $\eta_1 \leq 1$ is a modification parameter indicating the infectiousness of the carrier class Agusto and Leite (2019). Thus, the rate of change of the susceptible class is given as

$$\frac{dS}{dt} = \alpha + \omega V - (\lambda + \theta + \mu)S \tag{3.3}$$

The Vaccinated Class are the individuals who have taken the vaccine as a form of

protection from the disease. This population is increased by vaccination of susceptible individuals. Often, individuals develop immunity within two (2) weeks after taking the Meningitis vaccines and are protected for three (3) to five (5) years. Since the vaccines confer varying degrees of immunity to its recipients, the vaccinated individuals may become infected, but at a lower rate than the unvaccinated. The vaccinated class is therefore decreased by been exposed to the disease or by vaccine waning and by natural death. Therefore, the rate of change of the vaccinated class is represented by

$$\frac{dV}{dt} = \theta S - (1-\tau)\lambda V - (\omega + \mu)V \tag{3.4}$$

The Carrier Class is made up of individuals who have the infection but do not show any signs/symptoms even though they are infectious. This class is generated through the effective contact rate λ and decreased as a result of the population becoming symptomatic by the rate σ. This population is also decreased by the treatment rate, κ, natural recovery rate r and by natural death rate μ. As such, the rate of change of the carrier class is expressed as

$$\frac{dC}{dt} = \lambda S + (1-\tau)\lambda V - (\sigma + \kappa + r + \delta + \mu)C \tag{3.5}$$

The Infected Class are individuals with the fully blown infection and showing signs/symptoms. This population is said to have survived the average incubation period of four (4) days. This is also generated through the progression rate of the carrier σ and decreased by the natural recovery rate r, treatment rate κ, diseased induced death rate δ and natural death rate μ. Hence, the differential equation governing the dynamic of the infected class is given by

$$\frac{dI}{dt} = \sigma C - (r + \kappa + \delta + \mu)I \tag{3.6}$$

The Treated Class are the individuals undergoing treatment as a result of an infection. This is generated through the treatment rate κ and decreased by the diseased induced death rate δ, recovery rate γ and natural death rate μ. Thus, the rate of change of

the treated class is described by the diffrential equation

$$\frac{dT}{dt} = \kappa C + \kappa I - (1-\eta_2)\delta T - (1-\wedge)T - (\gamma + \gamma r + \mu)T \tag{3.7}$$

Since the after-effects of bacterial meningitis are not always pleasant, the recovered class is divided into two. The first Recovered class $R_1(t)$ are the individuals who have either undergone treatment and have fully recovered from the infection or have recovered by their own natural immunity. This is generated through the recovery rates and decreased by the complication rate ϵ and natural death rate μ. Therefore, the rate of change of the fully recovered class is expressed as

$$\frac{dR_1}{dt} = rC + rI + \gamma rT - (\epsilon + \mu)R_1 \tag{3.8}$$

The second Recovered class $R_2(t)$ is made up of the individuals who have undergone treatment and have recovered with complications. This population is increased by the recovery rate γ and complication rate $\wedge$, and decreased due to natural death rate μ. Hence, the rate of change of the recovered with complications class is given as

$$\frac{dR_2}{dt} = \gamma T + (1-\wedge)T + \epsilon R_1 - \mu R_2 \tag{3.9}$$

Table 3.1 Description of the Model State Variables

Variables	Description
$S(t)$	Susceptible Population
$V(t)$	Vaccinated Population
$C(t)$	Carrier Population
$I(t)$	Infected Population
$T(t)$	Treated Population
$R_1(t)$	Fully Recovered Population
$R_2(t)$	Recovered with Complications

Table 3.2 Description of Model Parameters

Parameters	Description
α	Recruitment rate into Susceptible population
β	Transmission probability
δ	Disease-induced death
μ	Natural death rate
σ	Progression rate from Carrier to Infected population
γ	Recovery rate
r	Natural recovery rate
θ	Vaccine uptake rate
τ	Vaccine efficacy
ω	Vaccine waning
κ	Treatment rate
$\wedge$	Treatment efficacy
η_1	Modification parameter of infectiousness of the carrier population
η_2	Modification parameter of disease death rate of treated population
ϵ	Complication rate after a period of time

We note that all the model parameters are assumed to be non-negative.

Model Assumptions

1. Every individual in the studied population who has not been infected is susceptible to the disease.
2. A vaccinated individual who loses immunity becomes susceptible with no vaccine protection.
3. The vaccine is only administered to the susceptible population.
4. There is a natural death rate from each compartment.
5. Recovered individuals cannot be re-infected.

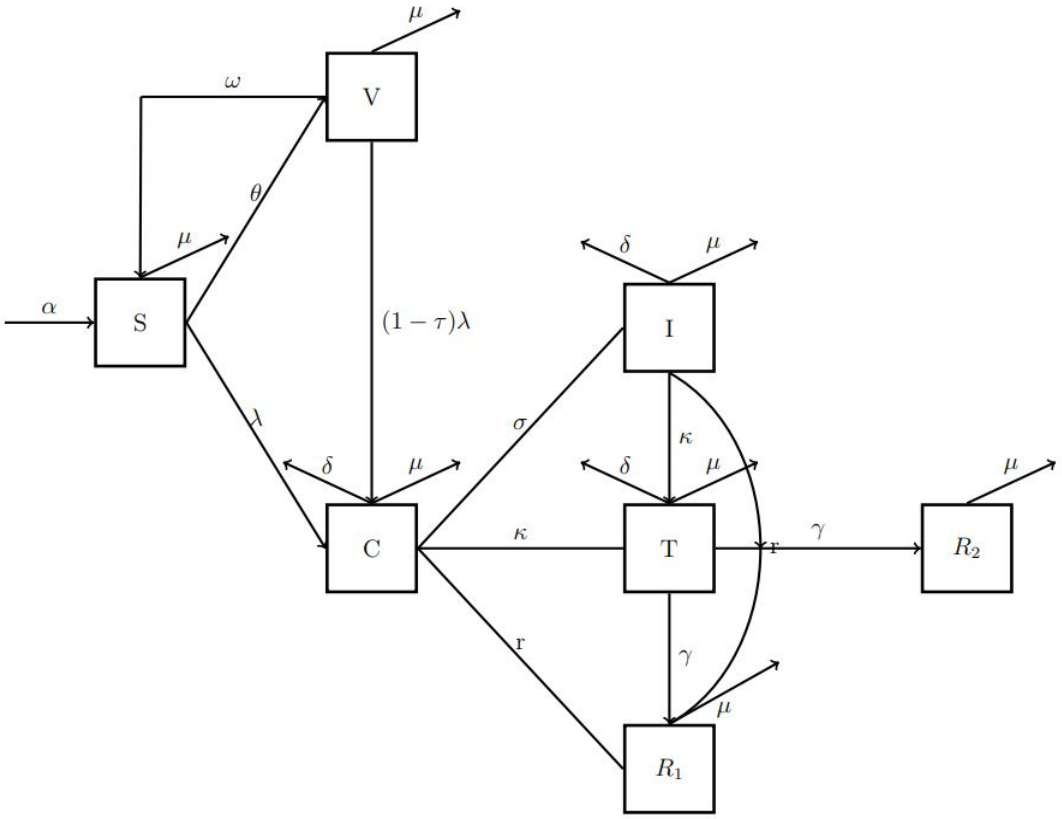


Figure 3.1 Schematic Flow Diagram of the Transmission of Bacterial Meningitis

Model Equations

From the descriptions given in Equations (3.3) to (3.9) and the flow diagram presented in Figure (3.1), the model governing the system of seven mutually exclusive ODEs for bacterial meningitis population dynamics is expressed as

$$\begin{cases} \frac{dS}{dt} &= \alpha + \omega V - (\lambda + \theta + \mu)S \\ \frac{dV}{dt} &= \theta S - (1-\tau)\lambda V - (\omega + \mu)V \\ \frac{dC}{dt} &= \lambda S + (1-\tau)\lambda V - (\sigma + \kappa + r + \delta + \mu)C \\ \frac{dI}{dt} &= \sigma C - (r + \kappa + \delta + \mu)I \\ \frac{dT}{dt} &= \kappa C + \kappa I - (1-\eta_2)\delta T - (1-\wedge)T - (\gamma + \gamma r + \mu)T \\ \frac{dR_1}{dt} &= rC + rI + \gamma r T - (\epsilon + \mu)R_1 \\ \frac{dR_2}{dt} &= \gamma T + (1-\wedge)T + \epsilon R_1 - \mu R_2 \end{cases} \tag{3.10}$$

subject to the initial conditions (ICs):

$$\begin{aligned} S(0) = S_0, \qquad V(0) = V_0, \qquad C(0) = C_0, \qquad I(0) = I_0, \\ T(0) = T_0, \qquad R_1(0) = R_{01}, \qquad R_2(0) = R_{02} \end{aligned} \tag{3.11}$$

3.2 The Model Analyses

3.2.1 The Invariant Region

Definition 3.2.1 *A region within which the solutions to the model are uniformly bounded is defined as* $\Omega \in \Re^7_+$.

The total population is given as

$$N(t) = S(t) + V(t) + C(t) + I(t) + T(t) + R_1(t) + R_2(t) \tag{3.12}$$

Therefore

$$\frac{dN(t)}{dt} = \frac{dS(t)}{dt} + \frac{dV(t)}{dt} + \frac{dC(t)}{dt} + \frac{dI(t)}{dt} + \frac{dT(t)}{dt} + \frac{dR_1(t)}{dt} + \frac{dR_2(t)}{dt} \tag{3.13}$$

Substituting (3.10) into (3.13) yields

$$\frac{dN(t)}{dt} = \alpha - \mu N - \delta C - \delta I - (1 - \eta_2)\delta T \tag{3.14}$$

$$\frac{dN(t)}{dt} \leq \alpha - \mu N(t)$$

Integrating both sides, we have

$$\frac{1}{\mu} \int \frac{\mu}{\alpha - \mu N} dN \leq \int dt$$

which gives

$$-\frac{1}{\mu} In(\alpha - \mu N) \leq t + c$$

where c is the constant of integration.

$$In(\alpha - \mu N) \geq -(\mu t + c)$$

$$(\alpha - \mu N) \geq e^{-(\mu t + c)}$$

$$(\alpha - \mu N) \geq k e^{-\mu t} \tag{3.15}$$

where k is e^c.

Let $N(0) = N_0$. This implies

$$(\alpha - \mu N_0) \geq k \tag{3.16}$$

From Equations (3.15) and (3.16), we get

$$(\alpha - \mu N) \geq (\alpha - \mu N_0) e^{-\mu t}$$

$$\mu N \leq \alpha - (\alpha - \mu N_0) e^{-\mu t}$$

$$N(t) \leq \frac{\alpha}{\mu} - \frac{(\alpha - \mu N_0)}{\mu} e^{-\mu t}$$

$$\Rightarrow N(t) \to \frac{\alpha}{\mu} \text{ as } t \to \infty \tag{3.17}$$

This implies $N(t) \in \left[0, \frac{\alpha}{\mu}\right]$.

Therefore, the feasible set of solution of the model equations enter and remain in the region:

$$\Omega = \{(S, V, C, I, T, R_1, R_2) \in \Re_+^7 : N(t) \leq \frac{\alpha}{\mu}\} \tag{3.18}$$

We note that $\frac{\alpha}{\mu}$ is the upper bound of $N(t)$. However, if $N > \frac{\alpha}{\mu}$ then $N(t)$ will decrease to $\frac{\alpha}{\mu}$ and the solutions $(S, V, C, I, T, R_1, R_2)$ will enter Ω or approach it asymptotically, as such, the region will attract all solutions in $\Re_+^7$. Hence, the model is well posed mathematically and epidemiologically since the region Ω is positively invariant and attracting.

3.2.2 Positivity of the Solution

Theorem 3.2.1 *(The Positivity Theorem) Let* $\Omega = \{(S, V, C, I, T, R_1, R_2) \in \Re_+^7 : S_0 > 0,\ V_0 > 0,\ C_0 > 0,\ I_0 > 0,\ T_0 > 0,\ R_{10} > 0,\ R_{20} > 0\}$*, then the solution of* $(S, V, C, I, T, R_1, R_2)$ *are positive for* $t \geq 0$.

Proof. Considering the first equation of the model

$$\frac{dS}{dt} = \alpha + \omega V - (\lambda + \theta + \mu) S$$

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

$$\int \frac{dS}{S} \geq -\int (\lambda + \theta + \mu)dt$$

$$\ln S(t) \geq -p(t) + c$$

where $p(t) = \int(\lambda + \theta + \mu)dt$ and c is the constant of integration.

$$S(t) \geq e^{(-p(t)+c)}$$

$$S(t) \geq e^{-p(t)} \cdot e^{c}$$

$$S(t) \geq A_1 e^{-p(t)} \tag{3.19}$$

where $A_1 = e^c$. From the theorem, at $t = 0$, $S_0 > 0$ which implies $A_1 = e^c \geq 0$ since $S(0) \geq A_1$. Consequently, $S(t) \geq S_0 e^{-p(t)} \geq 0 \ \forall t \geq 0$.

Similarly, considering the second equation of the model

$$\frac{dV}{dt} = \theta S - (1 - \tau)\lambda V - (\omega + \mu)V$$

$$\frac{dV}{dt} \geq -[(1 - \tau)\lambda + \omega + \mu]V$$

$$\int \frac{dV}{V} \geq -\int [(1 - \tau)\lambda + \omega + \mu]dt$$

$$\ln V(t) \geq -q(t) + c$$

where $q(t) = \int[(1 - \tau)\lambda + \omega + \mu]dt$ and c is the constant of integration.

$$V(t) \geq A_2 e^{-q(t)} \tag{3.20}$$

where $A_2 = e^c$. At $t = 0$, $V_0 > 0$ which implies $A_2 = e^c \geq 0$.
Consequently, $V(t) \geq V_0 e^{-q(t)} \geq 0 \ \forall t \geq 0$.

Applying the same technique to the remaining equations of the system, the third equation yields

$$C(t) \geq C_0 e^{-h_1 t} \geq 0 \qquad \forall t \geq 0 \tag{3.21}$$

where $h_1 = (\sigma + \kappa + r + \delta + \mu) \geq 0$.

The fourth equation yields

$$I(t) \geq I_0 e^{-h_2 t} \geq 0 \qquad \forall t \geq 0 \tag{3.22}$$

where $h_2 = (r + \kappa + \delta + \mu) \geq 0$.

The fifth equation yields

$$T(t) \geq T_0 e^{-h_3 t} \geq 0 \qquad \forall t \geq 0 \tag{3.23}$$

where $h_3 = [(1 - \eta_2)\delta + (1 - \wedge) + \gamma + \gamma r + \mu] \geq 0$.

The sixth equation yields

$$R_1(t) \geq R_{10} e^{-h_4 t} \geq 0 \qquad \forall t \geq 0 \tag{3.24}$$

where $h_4 = (\epsilon + \mu) \geq 0$.

Lastly, the seventh equation yields

$$R_2(t) \geq R_{20} e^{-\mu t} \geq 0 \qquad \forall t \geq 0 \tag{3.25}$$

This completes the proof of the theorem.

3.2.3 Existence of Equilibria

For the developed model, the disease free and endemic equilibrium points are obtained. A Disease Free Equilibrium (DFE) is a state solution to the model in which the studied population remains in the absence of the disease. An Endemic Equilibrium (EE) point of a disease is defined as a positive steady state solution when the disease persists in the studied population.

The Disease Free Equilibrium Point

The DFE of the model is defined as $(S^*(t), V^*(t), 0, 0, 0, 0, 0)$ satisfying $\frac{dS(t)}{dt} = \frac{dV(t)}{dt} = \frac{dC(t)}{dt} = \frac{dI(t)}{dt} = \frac{dT(t)}{dt} = \frac{dR_1(t)}{dt} = \frac{dR_2(t)}{dt} = 0$.

Equating the system of equation in (3.10) to 0 and substituting $C = I = T = R_1 = R_2 = 0$, we obtain the system

$$\begin{cases} \omega V - (\theta + \mu) S = -\alpha \\ \theta S - (\omega + \mu) V = 0 \end{cases} \tag{3.26}$$

Solving the system simultaneously, the DFE is obtained as:

$$\left(\frac{\alpha m_1}{\mu (m_1 + \theta)}, \frac{\alpha \theta}{\mu (m_1 + \theta)}, 0, 0, 0, 0, 0 \right) \tag{3.27}$$

where, $m_1 = \omega + \mu$.

Endemic Equilibrium Point

The EEP of the model is defined as
$(S^*(t), V^*(t), C^*(t), I^*(t), T^*(t), R_1^*(t), R_2^*(t))$ satisfying $\frac{dS(t)}{dt} = \frac{dV(t)}{dt} = \frac{dC(t)}{dt} = \frac{dI(t)}{dt} = \frac{dT(t)}{dt} = \frac{dR_1(t)}{dt} = \frac{dR_2(t)}{dt} = 0$.

This yields the system of equations

$$\begin{cases} \alpha + \omega V - (\lambda + \theta + \mu) S = 0 \\ \theta S - (1 - \tau) \lambda V - (\omega + \mu) V = 0 \\ \lambda S + (1 - \tau) \lambda V - (\sigma + \kappa + r + \delta + \mu) C = 0 \\ \sigma C - (\kappa + r + \delta + \mu) I = 0 \\ \kappa C + \kappa I - (1 - \eta_2) \delta T - (1 - \wedge) T - (\gamma + \gamma r + \mu) T = 0 \\ rC + rI + \gamma r T - (\epsilon + \mu) R_1 = 0 \\ \gamma T + (1 - \wedge) T + \epsilon R_1 - \mu R_2 = 0 \end{cases} \tag{3.28}$$

which results in,

$$S^* = \frac{\alpha [(1 - \tau) \lambda + m_1]}{(1 - \tau) \lambda^2 + g_1 \lambda + g_2} \tag{3.29}$$

$$V^* = \frac{\alpha\,\theta}{(1-\tau)\,\lambda^2 + g_1\lambda + g_2} \tag{3.30}$$

$$C^* = \frac{\alpha\,\lambda\,[(1-\tau)\,(\lambda+\theta) + m_1]}{(\sigma+m_2)\,[(1-\tau)\,\lambda^2 + g_1\lambda + g_2]} \tag{3.31}$$

$$I^* = \frac{\alpha\lambda\sigma\,[(1-\tau)\,(\lambda+\theta) + m_1]}{m_2\,(\sigma+m_2)\,[(1-\tau)\,\lambda^2 + g_1\lambda + g_2]} \tag{3.32}$$

$$T^* = \frac{\kappa\,(C^* + I^*)}{m_3} \tag{3.33}$$

$$R_1^* = \frac{r\,(C^* + I^* + \gamma T^*)}{\epsilon+\mu} \tag{3.34}$$

$$R_2^* = \frac{(\epsilon+\mu)\,(r+1-\Lambda)\,T^* + r\epsilon\,(C^* + I^* + \gamma T^*)}{\mu\,(\epsilon+\mu)} \tag{3.35}$$

where,

$$m_2 = \kappa + r + \delta + \mu, \qquad m_3 = \mu + \gamma\,(r+1) + \delta\,(1-\eta_2) + 1 - \Lambda$$

$$g_1 = (1-\tau)\,(\mu+\theta) + m_1, \qquad g_2 = \mu\,(m_1+\theta)$$

From the force of infection in Equation (3.2),

$$\lambda^* = \frac{\beta\,(\eta_1 C^* + I^*)}{N^*}$$

which can be written as

$$\lambda^* N^* - \beta\,(\eta_1 C^* + I^*) = 0 \tag{3.36}$$

Substituting all the state solutions into Equation (3.36) and simplifying leads to the equation

$$k_1(\lambda^*)^2 + k_2\lambda^* + k_3 = 0 \tag{3.37}$$

where,

$$k_1 = (\sigma+m_2)\,(1-\ \tau)\,[m_3\,(\mu+r+k) - k\delta\,(1-\ \eta_2)]$$

$$k_2 = \mu(1-\tau)m_3m_2^2 + [(m_2-\delta)((1-\tau)\theta+m_1) - \mu(1-\tau)(\beta\eta_1-\sigma)]m_2m_3 + [(m_2-\delta)((1-\tau)\theta+m_1) - \mu\beta(1-\tau)]\sigma m_3 - \delta(\sigma+m_2)(1-\eta_2)((1-\tau)\theta+m_1)\kappa$$

$$\begin{aligned} k_3 &= \mu m_3\left[(\theta+m_1)m_2^2 + (\theta+m_1)\sigma m_2 + \beta(\theta\tau-\theta-m_1)(\eta_1 m_2+\sigma)\right] \\ &= \mu m_3\left[m_2(\theta+m_1)(m_2+\sigma) - \beta((1-\tau)\theta+m_1)(\eta_1 m_2+\sigma)\right] \\ &= \mu m_3 m_2(\theta+m_1)(m_2+\sigma)\left[1 - \frac{\beta((1-\tau)\theta+m_1)(\eta_1 m_2+\sigma)}{m_2(\theta+m_1)(m_2+\sigma)}\right] \\ &= \mu m_2 m_3(\theta+m_1)(\sigma+m_2)(1-\mathcal{R}_0) \end{aligned}$$

3.2.4 The Basic Reproduction Number ($\mathcal{R}_0$)

The basic reproduction number is a fundamental threshold in mathematical study of epidemiology. It helps to forecast the transmission potential of a disease. According to the principle of next generation matrix, the basic reproduction number is the spectral radius of the next generation matrix $\mathcal{F}\mathcal{V}^{-1}$ of the model (3.10). The basic reproduction number associated with (3.10) is given as:

$$\begin{pmatrix} \frac{dC}{dt} \\ \frac{dI}{dt} \end{pmatrix} = f_i - v_i$$

where,

$$f_i = \begin{pmatrix} \frac{\beta(\eta_1 C+I)S}{N} + \frac{(1-\tau)\beta(\eta_1 C+I)V}{N} \\ 0 \end{pmatrix}$$

and

$$v_i = \begin{pmatrix} (\sigma+m_2)C \\ -\sigma C + m_2 I \end{pmatrix}$$

f_i is the rate at which new infections appear in compartment i and v_i represents the movement of individuals into compartment i, with $i \in [1,2]$.

The matrices $\mathcal{F}$ and $\mathcal{V}$ are obtained as follows:

$$\mathcal{F} = \begin{pmatrix} \frac{\partial f_1}{\partial C} & \frac{\partial f_1}{\partial I} \\ \frac{\partial f_2}{\partial C} & \frac{\partial f_2}{\partial I} \end{pmatrix} = \begin{pmatrix} \frac{\beta\eta_1(\theta(1-\tau)+m_1)}{m_1+\theta} & \frac{\beta(\theta(1-\tau)+m_1)}{m_1+\theta} \\ 0 & 0 \end{pmatrix} \tag{3.38}$$

and

$$\mathcal{V} = \begin{pmatrix} \frac{\partial v_1}{\partial C} & \frac{\partial v_1}{\partial I} \\ \frac{\partial v_2}{\partial C} & \frac{\partial v_2}{\partial I} \end{pmatrix} = \begin{pmatrix} \sigma + m_2 & 0 \\ -\sigma & m_2 \end{pmatrix} \tag{3.39}$$

$$\mathcal{V}^{-1} = \begin{pmatrix} \frac{1}{\sigma+m_2} & 0 \\ \frac{\sigma}{m_2(\sigma+m_2)} & \frac{1}{m_2} \end{pmatrix} \tag{3.40}$$

Thus, the next generation matrix:

$$G = \mathcal{F}\mathcal{V}^{-1} = \begin{pmatrix} \frac{(\eta_1 m_2+\sigma)((1-\tau)\theta+m_1)\beta}{m_2(m_1+\theta)(\sigma+m_2)} & \frac{\beta(\theta(1-\tau)+m_1)}{m_2(m_1+\theta)} \\ 0 & 0 \end{pmatrix} \tag{3.41}$$

The eigenvalues of the matrix, G are

$$\begin{pmatrix} 0 \\ \frac{\beta(\eta_1 m_2+\sigma)(\theta(1-\tau)+m_1)}{m_2(m_1+\theta)(\sigma+m_2)} \end{pmatrix}$$

Consequently, the Basic Reproduction Number, which is the spectral radius of G is given as

$$\mathcal{R}_0 = \frac{\beta\left(\eta_1 m_2 + \sigma\right)\left[\left(1-\tau\right)\theta + m_1\right]}{m_2\left(m_1+\theta\right)\left(\sigma+m_2\right)} \tag{3.42}$$

$\mathcal{R}_0$ provides the expected number of newly infected individuals that would arise from introduction of a single case of bacterial meningitis into a completely susceptible population.

3.3 Model Parameter Estimation and Initial Conditions

3.3.1 Initial Conditions

Ghana's demographic data for the year 2017 is adopted for our simulation. Since the disease is endemic in the northern part of Ghana, the total population of the northern part as at 2017 was 4953293 Anon (2020), as such the initial total population, $N(0) = 4953293$. It is known that $10-20\%$ of every population is carrier of Meningitis Anon (2020a), so the average which is 15% is adopted as the case in Ghana. This gives a carrier population of about 742993.95. 10% of the population is assumed to be vaccinated against the disease. In addition, it is assumed that the population in each of the infected and treated class is about one-third of those in carrier class,

which is 247664.65. The two recovered classes is assumed to be zero. Thus, the model variables' initial conditions are: $S(0) = 3219640$, $V(0) = 495329.3$, $C(0) = 742993.95$, $I(0) = T(0) = 247664.65$, $R_1(0) = 0$ and $R_2(0) = 0$.

3.3.2 Model Parameter Values

1. Natural death rate (μ): The average life span in Ghana is 64.17 years, therefore $\mu = \frac{1}{64.17 \times 365} = 4.269 \times 10^{-5}$ per day.

2. Birth or recruitment rate (α): In the absence of the disease, the limiting total human population is assumed to be $\frac{\alpha}{\mu} = 4953293$, so $\alpha = 211$ per day.

3. Disease-induced death rate (δ): The mortality rate due to bacterial meningitis disease in Ghana is $36 - 50\%$. Taking the average to be 43% gives $\delta = 0.43$.

4. Progression rate (σ): The average incubation period is 4 days. Thus, $\sigma = \frac{1}{4} = 0.25$

5. Vaccine waning rate (ω): It takes an average of 4 years for the available vaccines to wane. Therefore, $\omega = \frac{1}{4 \times 365} = 6.8 \times 10^{-4}$ per day

6. Recovery rate (γ): The period of infection of the disease is 1-2 weeks with hospitalization and right treatment, so taking the average, we have 8 days. Therefore, $\gamma_{I1} = \frac{1}{8} = 0.125$.

7. Complication rate (ϵ): Even with appropriate treatment, $10 - 20\%$ of survivors have serious complications or long-term sequelae. Therefore, $\epsilon = \frac{15}{100} = 0.15$

Table 3.3 Model Parameter Values

Parameter	Value	Source
α	211	Estimated
μ	0.000043	Estimated
ω	0.00068	Estimated
β	0.88	Asamoah *et al.* (2018)
γ	0.125	Estimated
r	0.13	Asamoah *et al.* (2018)
η_1	0.75	Assumed
η_2	0.75	Assumed
δ	0.43	Estimated
ϵ	0.15	Estimated
σ	0.25	Estimated
τ	0.85	Elmojtaba and Adam (2017)
κ	0.6 [0,1]	Assumed
θ	0.6 [0,1]	Assumed
$\wedge$	0.6 [0.1-0.9]	Elmojtaba and Adam (2017)

We note that the set of parameter values in Table (3.3) yields a basic reproduction number less than unity ($\mathcal{R}_0 = 0.091$) which implies that with effective vaccination and treatment, this disease which is considered to be endemic could be eradicated.

3.4 Stability Analyses

The equilibrium points of a system can be classified as stable, unstable or asymptotically stable according to the nature of the eigenvalues of the coefficient matrix of the system or the Jacobian matrix of the system (for nonlinear systems) about such equilibrium point.

3.4.1 Local Stability of the Disease-free Equilibrium

Theorem 3.4.1 *The DFE is Locally Asymptotically Stable (LAS) if* $\mathcal{R}_0 < 1$ *and unstable if* $\mathcal{R}_0 > 1$.

Using Theorem 3.4.1, the result in Lemma 3.4.1 follows immediately based on the expressions of $\mathcal{R}_0$.

Lemma 3.4.1 *The DFE of the bacterial meningitis model in* (3.10) *is Locally Asymptotically Stable (LAS) if* $\mathcal{R}_0 < 1$ *and unstable if* $\mathcal{R}_0 > 1$.

Following Definition 2.4.2, the Jacobian matrix, J evaluated at E_0 is given as

$$J = \begin{pmatrix} -(\theta+\mu) & \omega & -\frac{\beta\,\eta_1\,m_1}{m_1+\theta} & -\frac{\beta\,m_1}{m_1+\theta} & 0 & 0 & 0 \\ \theta & -m_1 & -\frac{\beta\,\eta_1\,(1-\tau)\theta}{m_1+\theta} & -\frac{\beta\,(1-\tau)\theta}{m_1+\theta} & 0 & 0 & 0 \\ 0 & 0 & \frac{\beta\,\eta_1\,m_1(1-\tau)\theta}{m_1+\theta} - (\sigma+m_2) & \frac{\beta\,m_1(1-\tau)\theta}{m_1+\theta} & 0 & 0 & 0 \\ 0 & 0 & \sigma & -m_2 & 0 & 0 & 0 \\ 0 & 0 & \kappa & \kappa & -m_3 & 0 & 0 \\ 0 & 0 & r & r & \gamma r & -(\epsilon+\mu) & 0 \\ 0 & 0 & 0 & 0 & \gamma+(1-\wedge) & \epsilon & -\mu \end{pmatrix} \tag{3.43}$$

The eigenvalues of the Jacobian matrix, J are

$$\lambda_{1,2} = -\mu \qquad \lambda_3 = -(m_1+\theta) \qquad \lambda_4 = -(\epsilon+\mu) \qquad \lambda_5 = -m_3$$

and

$$\lambda_{6,7} = -\frac{\beta\,\tau\,\theta\,\eta_1 + (-\beta\,\eta_1+\sigma+2\,m_2)\,(m_1+\theta) - \sqrt{(\beta\,\tau\,\theta\,\eta_1 - (\beta\,\eta_1-\sigma)\,(m_1+\theta))^2 + 4\,(\theta\,(1-\tau)+m_1)\,(m_1+\theta)\,\sigma\,\beta}}{2\,m_1+2\,\theta}$$

Clearly, all the eigenvalues of the Jacobian matrix are strictly negative provided

$$-\frac{\beta\,\tau\,\theta\,\eta_1 + (-\beta\,\eta_1+\sigma+2\,m_2)\,(m_1+\theta) - \sqrt{(\beta\,\tau\,\theta\,\eta_1 - (\beta\,\eta_1-\sigma)\,(m_1+\theta))^2 + 4\,(\theta\,(1-\tau)+m_1)\,(m_1+\theta)\,\sigma\,\beta}}{2\,m_1+2\,\theta} < 0$$

Thus for stability, the negativity condition imposed yields

$$\beta\,\tau\,\theta\,\eta_1 + (-\beta\,\eta_1+\sigma+2\,m_2)\,(m_1+\theta) - \sqrt{(\beta\,\tau\,\theta\,\eta_1 - (\beta\,\eta_1-\sigma)\,(m_1+\theta))^2 + 4\,(\theta\,(1-\tau)+m_1)\,(m_1+\theta)\,\sigma\,\beta} > 0$$

$$[\beta\,\tau\,\theta\,\eta_1 + (-\beta\,\eta_1+\sigma+2\,m_2)\,(m_1+\theta)]^2 > \left[\sqrt{(\beta\,\tau\,\theta\,\eta_1 - (\beta\,\eta_1-\sigma)\,(m_1+\theta))^2 + 4\,(\theta\,(1-\tau)+m_1)\,(b_1+\theta)\,\sigma\,\beta}\right]^2$$

$$[\beta\,\tau\,\theta\,\eta_1 + (-\beta\,\eta_1+\sigma+2\,m_2)\,(m_1+\theta)]^2 > (\beta\,\tau\,\theta\,\eta_1 - (\beta\,\eta_1-\sigma)\,(m_1+\theta))^2 + 4\,(\theta\,(1-\tau)+m_1)\,(b_1+\theta)\,\sigma\,\beta$$

$$(\beta\,\tau\,\theta\,\eta_1 + (-\beta\,\eta_1+\sigma+2\,m_2)\,(m_1+\theta))^2 - (\beta\,\tau\,\theta\,\eta_1 - (\beta\,\eta_1-\sigma)\,(m_1+\theta))^2 - 4\,(\theta\,(1-\tau)+m_1)\,(b_1+\theta)\,\sigma\,\beta > 0$$

$$\left((m_1+\theta)\,{m_2}^2 + ((\beta\,(-1+\tau)\,\eta_1+\sigma)\,\theta - (\beta\,\eta_1-\sigma)\,m_1)\,b_2 + \sigma\,(\theta\,(-1+\tau)-m_1)\,\beta\right)(m_1+\theta) > 0$$

$$\beta\,\theta\,(m_2\eta_1+\sigma)\,(\theta\,\tau-\theta-m_1) + \beta\,m_1\,(m_2\eta_1+\sigma)\,(\theta\,\tau-\theta-m_1) + b_2\,(m_1+\theta)^2\,(\sigma+m_2) > 0$$

$$(\theta\,(-1+\tau)-m_1)\,\theta\,(m_2\eta_1+\sigma)\,\beta + m_1\,(\theta\,(-1+\tau)-m_1)\,(m_2\eta_1+\sigma)\,\beta + m_2\,(m_1+\theta)^2\,(\sigma+m_2) > 0$$

$$\beta\ (m_2\eta_1+\sigma)\,(\theta\,\tau-\theta-m_1)\,(m_1+\theta)+m_2\,(m_1+\theta)^2\,(\sigma+m_2)>0$$

$$m_2\,(m_1+\theta)\,(\sigma+m_2)-\beta\ (m_2\eta_1+\sigma)\,(\theta\ (1-\tau)+m_1)>0$$

$$(m_1+\theta)\,m_2(\sigma+m_2)\left(1-\frac{\beta\ (m_2\eta_1+\sigma)\,(\theta\ (1-\tau)+m_1)}{m_2\,(m_1+\theta)\,(\sigma+m_2)}\right)>0$$

$$(m_1+\theta)\,m_2(\sigma+m_2)\,(1-\mathcal{R}_0)>0 \tag{3.44}$$

Therefore, for Equation (3.44) to be valid, $\mathcal{R}_0$ must be less than 1. Hence the DFE is LAS.

3.4.2 Global Stability of the Disease-free Equilibrium

The global asymptotic stability of the model in (3.10) is investigated by following Castillo-Chavez, Feng and Huang (2002). The model is denoted by:

$$\begin{cases}\frac{dX}{dt}=F(X,Y)\\ \frac{dY}{dt}=G(X,Y)\end{cases} \tag{3.45}$$

where $X=(S,V,R_1,R_2)$ denotes the uninfected population and $Y=(C,I,T)$ denotes the infected population.

Theorem 3.4.2 *The Disease-Free Equilibrium is said to be globally asymptotically stable in* Ω *if* $\mathcal{R}_0<1$ *and the following two conditions hold:*

C1: For $\frac{dX}{dt}=F(X,0)$, E_0 *is globally asymptotically stable.*

C2: $G(X,Y)=J\left[G(X^*,0)\right]Y-\hat{G}(X,Y), \qquad \hat{G}(X,Y)\geq 0, \quad \forall\ (X,Y)\in\Omega$

where $(X^*,0)=E_0=\left(\frac{\alpha m_1}{\mu(m_1+\theta)},\frac{\alpha\theta}{\mu(m_1+\theta)},0,0,0,0,0\right)$, $J\left[G(X^*,0)\right]$ *is the Jacobian of* $G(X,Y)$ *obtained with respect to* $(C,\ I,\ T)$ *and evaluated at* $(X^*,0)$.

Proof.

C1: From the model, it follows that:

$$F(X,0) = \begin{pmatrix} \alpha + \omega V - (\theta + \mu)S \\ \theta S - m_1 V \\ -(\epsilon + \mu)R_1 \\ \epsilon R_1 - \mu R_2 \end{pmatrix} \tag{3.46}$$

From Equation (3.46), it is clear that

$$E_0 = (S, V, C, I, T, R_1, R_2) = \left(\frac{\alpha m_1}{\mu (m_1 + \theta)}, \frac{\alpha \theta}{\mu (m_1 + \theta)}, 0, 0, 0, 0, 0 \right)$$

This can be verified using the method of integrating factors. From Equation (3.46), we have:

$$\frac{dV}{dt} = \theta S - m_1 V \tag{3.47}$$

which can be written in standard from as

$$\frac{dV}{dt} + m_1 V = \theta S \tag{3.48}$$

The integrating factor is given as $I.F. = e^{\int m_1 dt} = e^{m_1 t}$.

Multiplying Equation (3.48) through by the integrating factor yields

$$e^{m_1 t} \left(\frac{dV}{dt} + m_1 V \right) = \theta S e^{m_1 t} \tag{3.49}$$

$$\int \frac{d}{dt} \left(V e^{m_1 t} \right) dt = \theta \int S e^{m_1 t} dt \tag{3.50}$$

Let $I = \int S e^{m_1 t} dt$. Integrating by parts, we have

$$u = S \implies du = S' dt, \quad \text{and} \quad dv = e^{m_1 t} \implies v = \frac{e^{m_1 t}}{m_1}$$

So,

$$I = \frac{S e^{m_1 t}}{m_1} - \frac{1}{m_1} \int S' e^{m_1 t} dt \tag{3.51}$$

$$\implies Ve^{m_1 t} = \theta\left[\frac{Se^{m_1 t}}{m_1} - \frac{1}{m_1}\int S'e^{m_1 t}dt\right] \tag{3.52}$$

$$= \frac{\theta S}{m_1}e^{m_1 t} - \frac{\theta}{m_1}\int S'e^{m_1 t}dt \tag{3.53}$$

Therefore,

$$V = \frac{\theta S}{m_1} - \frac{\theta}{m_1 e^{m_1 t}}\int S'e^{m_1 t}dt \tag{3.54}$$

From Equation (3.54), $V \to \frac{\theta S}{m_1}$ as $t \to \infty$.

Furthermore, from Equation (3.46), we have,

$$\frac{dS}{dt} = \alpha + \omega V - (\theta + \mu)S \tag{3.55}$$

Since $V \to \frac{\theta S}{m_1}$, Equation (3.55) is rewritten as

$$\frac{dS}{dt} = \alpha + \frac{\omega\theta S}{m_1} - (\theta + \mu)S \tag{3.56}$$

$$= \alpha - \frac{\mu\left(m_1 + \theta\right)}{m_1}S \tag{3.57}$$

Therefore, Equation (3.57) can be put in standard form as

$$\frac{dS}{dt} + \frac{\mu\left(m_1 + \theta\right)}{m_1}S = \alpha \tag{3.58}$$

The integrating factor is given as $I.F. = e^{\int \frac{\mu(m_1+\theta)}{m_1}dt} = e^{\frac{\mu(m_1+\theta)}{m_1}t}$.

Multiplying Equation (3.58) through by the integrating factor gives

$$e^{\frac{\mu(m_1+\theta)}{m_1}t}\left(\frac{dS}{dt} + \frac{\mu\left(m_1 + \theta\right)}{m_1}S\right) = \alpha e^{\frac{\mu(m_1+\theta)}{m_1}t} \tag{3.59}$$

$$\int \frac{d}{dt}\left(Se^{\frac{\mu(m_1+\theta)}{m_1}t}\right)dt = \int \alpha e^{\frac{\mu(m_1+\theta)}{m_1}t}dt \tag{3.60}$$

$$Se^{\frac{\mu(m_1+\theta)}{m_1}t} = \frac{\alpha m_1}{\mu(m_1+\theta)}e^{\frac{\mu(m_1+\theta)}{m_1}t} + c \tag{3.61}$$

where c is the constant of integration. Therefore,

$$S = \frac{\alpha m_1}{\mu(m_1+\theta)} + Ce^{-\frac{\mu(m_1+\theta)}{m_1}t} \tag{3.62}$$

From Equation (3.62), $S \to \frac{\alpha m_1}{\mu(m_1+\theta)}$ as $t \to \infty$; and this implies the global convergence of Equation (3.46) in Ω.

C2: $G(X,Y)$ is given as

$$G(X,Y) = \begin{bmatrix} \lambda S + (1-\tau)\lambda V - (\sigma + m_2)C \\ \sigma C - m_2 I \\ \kappa C + \kappa I - m_3 T \end{bmatrix} \tag{3.63}$$

where λ is the force of infection defined in Equation (3.2).
The Jacobian matrix of $G(X,Y)$, $J\left[G(X^*,0)\right]$ is given as

$$\begin{pmatrix} \frac{\beta\,\eta_1\,[S^*+(1-\tau)V^*]}{N^*} - \sigma - m_2 & \frac{\beta\,[S^*+(1-\tau)V^*]}{N^*} & 0 \\ \sigma & -m_2 & 0 \\ \kappa & \kappa & -m_3 \end{pmatrix} \tag{3.64}$$

By the condition in C2 with Equations (3.63) and (3.64), $\hat{G}(X,Y)$ is given by

$$\begin{pmatrix} \frac{\beta(\eta_1 C+I)[(1-\tau)V^*+S^*]}{N^*}\left(1 - \frac{V(1-\tau)+S}{N}\frac{N^*}{(1-\tau)V^*+S^*}\right) \\ 0 \\ 0 \end{pmatrix} \tag{3.65}$$

Since

$$S^* = \frac{\alpha m_1}{\mu(m_1+\theta)}, \qquad V^* = \frac{\alpha\theta}{\mu(m_1+\theta)} \quad \text{and} \quad N^* = \frac{\alpha}{\mu}$$

we have that $S \leq S^*$, and $V \leq V^*$. Thus, it follows that $S \leq N$, and $V \leq N$ in Ω. Therefore, if the total population is at equilibrium level, we have $\left(1 - \frac{V(1-\tau)+S}{N}\frac{N^*}{(1-\tau)V^*+S^*}\right) > 0$; thus, $\hat{G}(X,Y) \geq 0$. Hence it follows from Theorem (3.4.2) that the DFE, $E_0 = (X^*, 0)$ is globally asymptotically stable.

3.5 Sensitivity Analysis

In mathematical modeling of infectious diseases, it is pertinent to ascertain the major parameters of a model that influence the transmission of the disease. Sensitivity

analysis is therefore performed to determine the model's robustness predictions to parameter values.

Definition 3.5.1 *The normalized forward sensitivity index of $\mathcal{R}_0$, that depends differentiably on a parameter ψ, is defined by*

$$S_{\psi}^{\mathcal{R}_0} = \frac{\partial \mathcal{R}_0}{\partial \psi} \times \frac{\psi}{\mathcal{R}_0} \tag{3.66}$$

In particular, the sensitivity index is a local estimate to establishing an efficient way of reducing $\mathcal{R}_0$.

Therefore, all the partially differentiable model parameters with respect to $\mathcal{R}_0$, their values and sensitivity indices are given in Table 3.4.

Table 3.4 Sensitivity Index of Each Model Parameter on $\mathcal{R}_0$

Parameter	Parameter Value	Sensitivity Index
ω	0.00068	$+6.36 \times 10^{-3}$
β	0.88	$+1$
η_1	0.75	$+0.7768$
σ	0.25	$+0.0459$
δ	0.43	-0.3877
μ	0.000043	-3.64×10^{-4}
κ	0.6	-0.5410
τ	0.85	-5.6215
r	0.13	-0.1172
θ	0.6	-6.77×10^{-3}

A positive sensitivity index suggests that the parameter is directly proportional to the value of $\mathcal{R}_0$. Thus, an increase in any of the values of ω, β, η_1 and σ by some percentage will increase the value of $\mathcal{R}_0$, thereby increasing the spread of the disease, and vice versa. However, the parameters with a negative sensitivity index means that these parameters are inversely proportional to the value of $\mathcal{R}_0$. Therefore, when the value of any of these parameters, δ, μ, κ, τ, r, θ is increased while holding all other parameters constant, it will reduce the value of $\mathcal{R}_0$ and, hence, contribute to the eradication of the disease and vice versa. For instance, increasing the modification parameter of the infectiousness of the carrier, η_1 by 10% will lead to a 7.768% increase on $\mathcal{R}_0$ while increasing the treatment rate, κ by 10% will result in a reduction of 5.410% on $\mathcal{R}_0$.

3.6 Numerical Simulation of the Model

The numerical solutions of the model (3.10) is obtained by using MATLAB ODE45 Algorithm with the initial conditions and parameter values staed in Table (3.3).

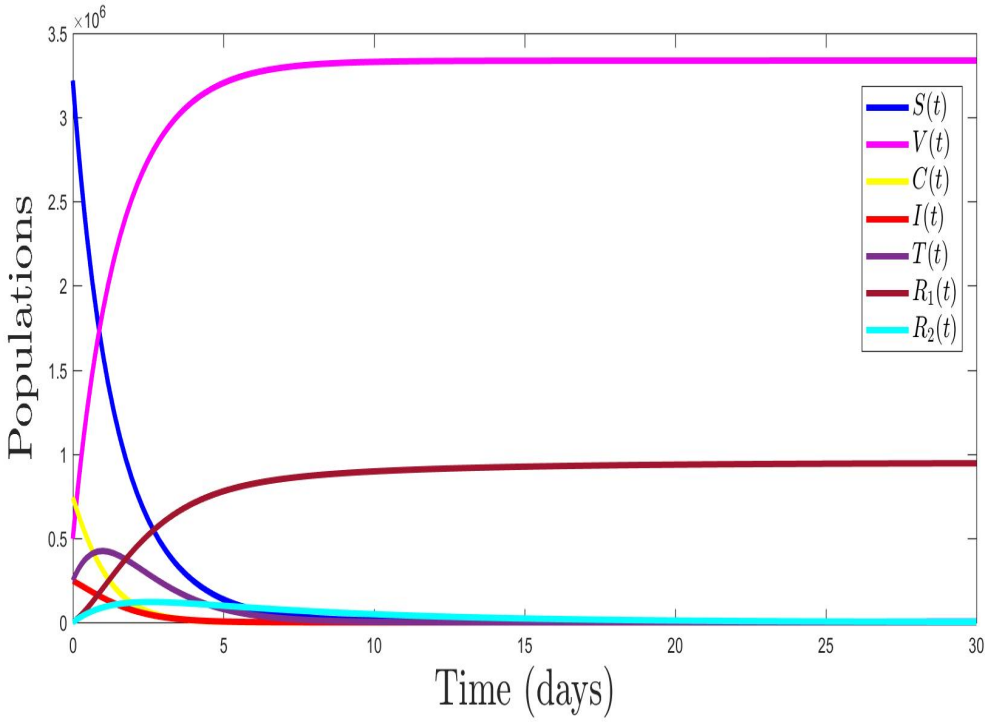


Figure 3.2 Evolution of each subpopulation with Time

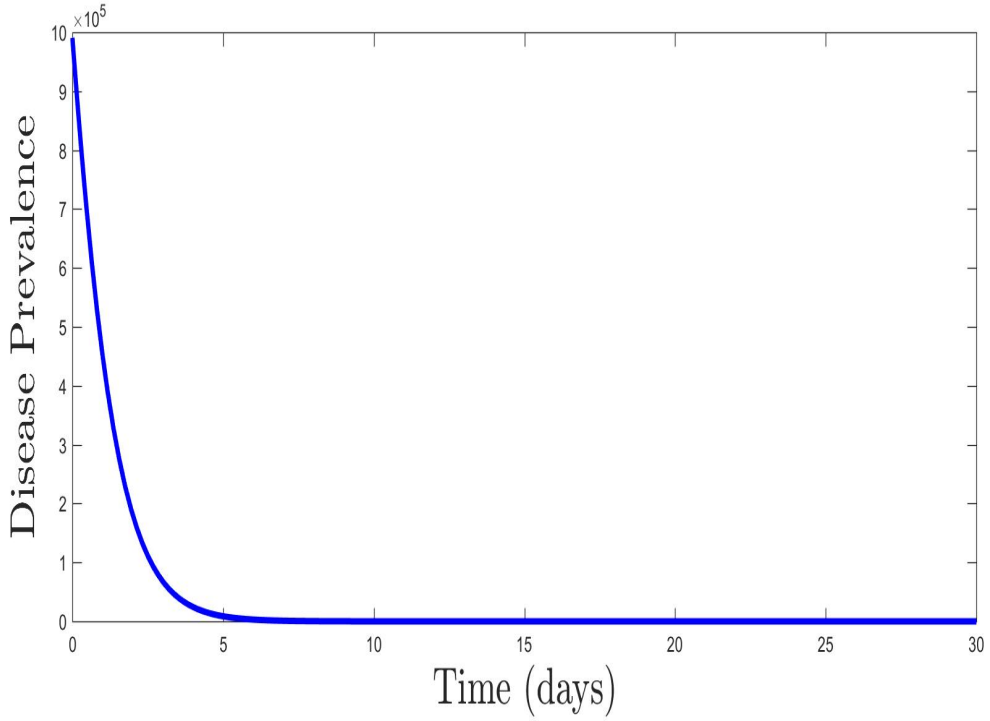
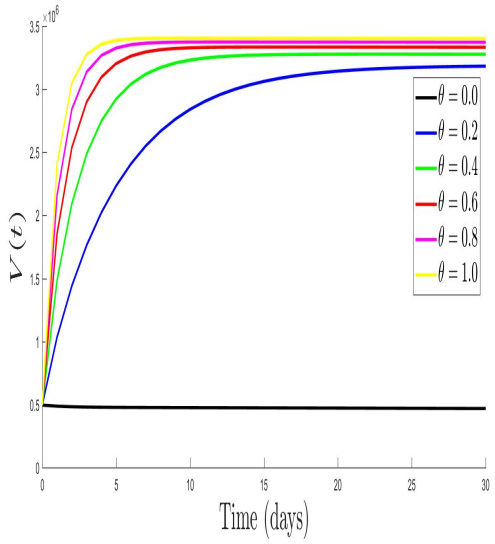
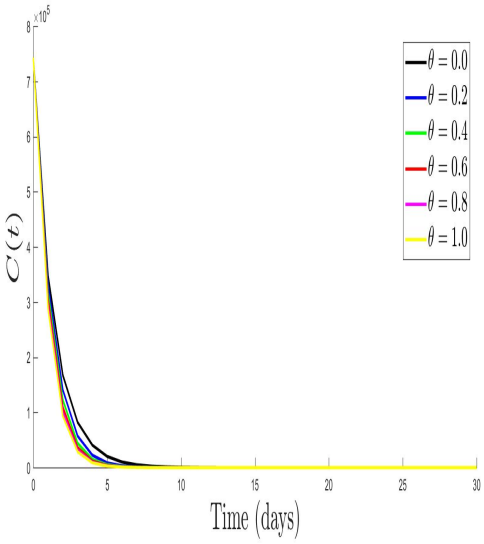


Figure 3.3 Disease Prevalence

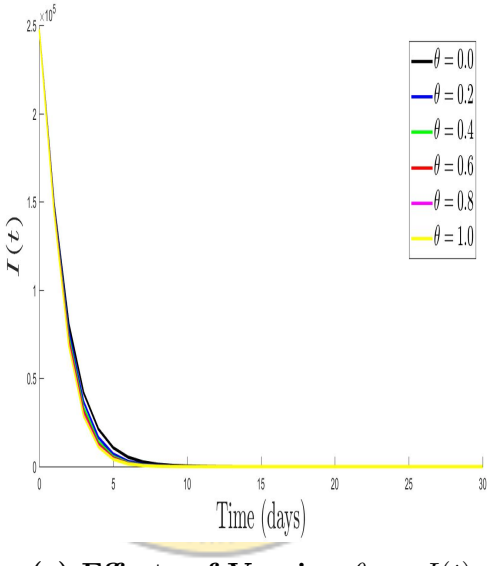
Figure (3.2) gives the numerical simulation of the model compartments in a time span of 30 days. The susceptible population decreases rapidly within the first few days due to getting people vaccinated and the force of infection. However, after these few days, stationarity is achieved due to progression to the other compartments. The vaccinated population on the other hand increases rapidly within the first few days, and this can be attributed to the awareness and sensitivity of the government to get people vaccinated as soon as an infection strikes. The carrier population reduces drastically in size due to the intervention of early treatment given to people who have come into contact with an infected person and the progression of the carriers to the infected class since the period of incubation is very short. The infected population also decreases with time and this can be ascribed to the immediate treatment given to them since the disease is termed as a 'medical emergency'. There is a short increase in the treated class as a result of progression of the carrier and infected but later decreases with time. This decrease is due to the treated population moving to the recovered populations. The two recovered populations increase and remain stable after a period of time. The disease prevalence can be viewed from Figure (3.3) which gives us the number of cases present in the population.



(a) Effects of Varying θ on $V(t)$



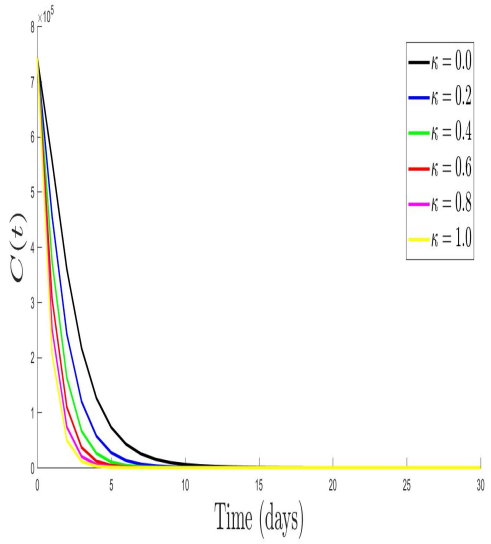
(b) Effects of Varying θ on $C(t)$



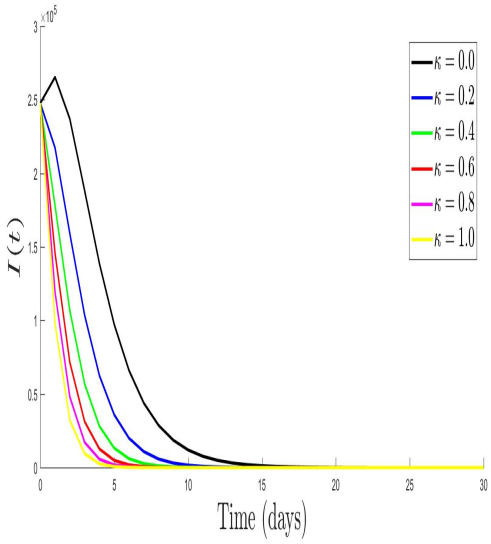
(c) Effects of Varying θ on $I(t)$

Figure 3.4 Effects of Varying θ on $V(t)$, $C(t)$ and $I(t)$ Compartments

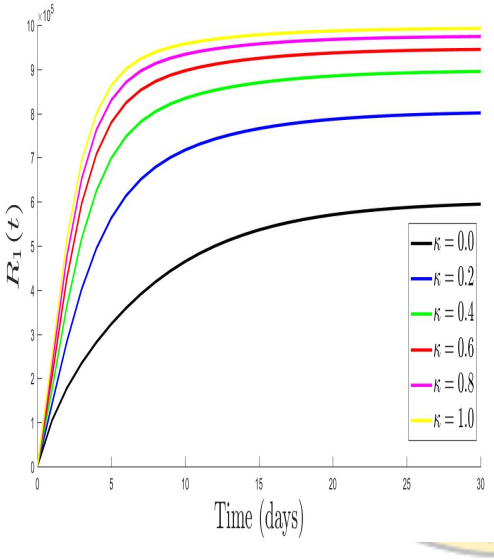
From Figure (3.4), as the vaccine uptake rate increases, the vaccinated population in Figure (3.4(a)) increases and remains stable. There is also a sharp decrease in both the carrier population in Figure (3.4(b)) and infected population in Figure (3.4(c)) even with a small vaccine uptake rate. This shows that infection will be controlled if people continue to receive vaccination.



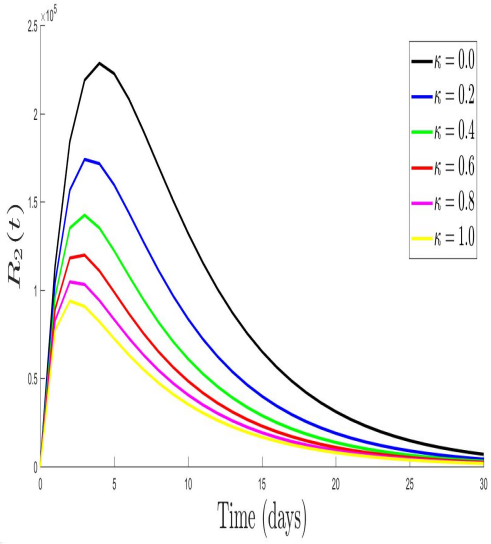
(a) Effects of Varying κ on $C(t)$



(b) Effects of Varying κ on $I(t)$



(c) Effects of Varying κ on $R_1(t)$



(d) Effects of Varying κ on $R_2(t)$

Figure 3.5 Effects of Varying κ on $C(t)$, $I(t)$, $R_1(t)$ and $R_2(t)$ Compartments

Figure (3.5) shows that as the treatment rate increases, there is a rapid decrease in both the carrier population in Figure (3.5(a)) and infected population in figure (3.5(b)). Also, the higher the treatment rate, the more people get fully recovered in Figure (3.5(c)) and the less people recover with complications as seen in Figure (3.5(d)).

CHAPTER 4

FORMULATION AND ANALYSIS OF A TWO-STRAIN DETERMINISTIC BACTERIAL MENINGITIS MODEL

4.1 Two-Strain Model Description and Formulation

In formulating the model, a wide range of parameters were used to incorporate the coexistence of two bacteria meningitis strains, namely the Streptococcus pneumonaie and Neisseria meningitidis. It is evident that the available vaccines are strain-specific, making the risk of contracting an infection from a strain, one has not been vaccinated against, a great concern.

In the proposed model, the total population at time t, denoted by $N(t)$, is divided into nine(9) mutually exclusive epidemiological classes, namely, the Susceptible Class $S(t)$ who can contract both strains 1 and 2, Vaccinated Classes $V_1(t), V_2(t)$, Carrier Classes $C_1(t), C_2(t)$, Infected Classes $I_1(t), I_2(t)$ and two Recovered Classes $R_1(t)$ and $R_2(t)$. This is given as

$$N(t) = S(t) + V_1(t) + V_2(t) + C_1(t) + C_2(t) + I_1(t) + I_2(t) + R_1(t) + R_2(t) \quad (4.1)$$

The Susceptible Class is the population who are not yet infected and have also not taken any of the vaccines against the disease. This is generated by the recruitment of individuals at a rate α and by loss of immunity acquired through previous vaccination ω_1, ω_2. The susceptible population is reduced by infection through effective contact with infected individuals at the rates λ_1 and λ_2, defined by

$$\lambda_1 = \frac{\beta[\eta C_1(t) + I_1(t)]}{N(t)} \quad (4.2)$$

$$\lambda_2 = \frac{\beta[\eta C_2(t) + I_2(t)]}{N(t)} \quad (4.3)$$

where β is the effective transmission probability per contact and $\eta \leq 1$ is a modification

parameter indicating the infectiousness of individuals in the carrier classes. The population is also reduced by natural death rate μ and vaccination θ_1, θ_2. Hence, the rate of change of the susceptible population is described by the differential equation given as

$$\frac{dS}{dt} = \alpha + \omega_1 V_1 + \omega_2 V_2 - (\lambda_1 + \lambda_2 + \theta_1 + \theta_2 + \mu)S \tag{4.4}$$

The Vaccinated Class is divided into two based on the available vaccines for these two strains considered. The Vaccinated population with immunity for strain 1 is the population who have taken the pneumococcal conjugate vaccines as a form of protection from the disease. This population is increased by vaccination of susceptible individuals θ_1. On the average, the pneumococcal conjugate vaccines take two(2) weeks to fully kick in, and are protected for five(5) years. Since this vaccine does not confer immunity to all the strains of bacteria causing meningitis, the vaccinated individuals of strain 1 may become infected by another strain, but at a lower rate than the unvaccinated. This population is decreased by been exposed to the disease or by vaccine waning and natural death. Therefore, the rate of change of the Vaccinated population with immunity for strain 1 is represented as

$$\frac{dV_1}{dt} = \theta_1 S - (1 - \epsilon_1)\lambda_1 V_1 - (\lambda_2 + \omega_1 + \mu)V_1 \tag{4.5}$$

The Vaccinated population with immunity for strain 2 is the population who have taken the meningococcal conjugate vaccines as a form of protection from the disease. This population is increased by vaccination of susceptible individuals to this specific strain θ_2. On the average, the meningococcal conjugate vaccines also take two(2) weeks to fully kick in, and should protect one for three (3) to five(5) years. Since this vaccine does not confer immunity to all the strains of bacteria causing meningitis, the vaccinated individuals of strain 2 may become infected by strain 1 λ_1, but at a lower rate than the unvaccinated. This population is decreased by been exposed to the infection $(1 - \epsilon_1)\lambda_1$ or by vaccine waning ω_2 and natural death μ. Thus, the rate of change of the Vaccinated population with immunity for strain 2 is given as

$$\frac{dV_2}{dt} = \theta_2 S - (1 - \epsilon_2)\lambda_2 V_2 - (\lambda_1 + \omega_2 + \mu)V_2 \tag{4.6}$$

The Carrier Population of strain 1 is made up of the population who have infection from Streptococcus pneumonaie but do not show any signs/symptoms even though they are infectious. This is generated through the effective contact rate λ_1 and decreased as a result of the population becoming symptomatic by the rate σ_1. This population is decreased by the recovery rate γ_{C1} and by natural death rate μ. Consequently, the rate of change of the Carrier Population of strain 1 is expressed as

$$\frac{dC_1}{dt} = \lambda_1(1-\tau_1)S + (1-\epsilon_1)\lambda_1 V_1 - (\sigma_1 + \gamma_{C1} + \mu)C_1 \tag{4.7}$$

The Carrier Population of strain 2 is made up of the population who have infection from Neisseria meningitidis but do not show any signs/symptoms even though they are infectious. This is generated through the effective contact rate λ_2 and decreased as a result of progression to the infected population of strain 2 by the rate σ_2. This population is decreased by the recovery rate γ_{C2} and by natural death rate μ. Therefore, the rate of change of the Carrier Population of strain 2 is described by the differential equation

$$\frac{dC_2}{dt} = \lambda_2(1-\tau_2)S + (1-\epsilon_2)\lambda_2 V_2 - (\sigma_2 + \gamma_{C2} + \mu)C_2 \tag{4.8}$$

The Infected Population of strain 1 is the population with fully blown infection from Streptococcus pneumonaie and show signs/symptoms. This population is said to have survived the average incubation period of one(1) to three(3) days. This is also generated through the effective contact rate λ_1 and progression of the carrier at the rate σ_1. The population is decreased by the recovery rate γ_{I1}, diseased induced death rate δ and natural death rate μ. Hence, the ODE governing the dynamic of the Infected Population of strain 1 is given by

$$\frac{dI_1}{dt} = \sigma_1 C_1 + \lambda_1\tau_1 S + \lambda_1 V_2 - (\gamma_{I1} + \delta + \mu)I_1 \tag{4.9}$$

The Infected Population of strain 2 is the population with fully blown infection from Neisseria meningitidis and exhibit signs/symptoms of the infection. This population is said to have survived the average incubation period of four(4) days. This is also generated through the force of infection λ_2 and progression of the carrier at the rate

σ_2. The population is decreased by the recovery rate γ_{I2}, diseased induced death rate δ and natural death rate μ. It follows that the rate of change of the Infected Population of strain 2 is described by the differential equation given as

$$\frac{dI_2}{dt} = \sigma_2 C_2 + \lambda_2 \tau_2 S + \lambda_2 V_1 - (\gamma_{I2} + \delta + \mu) I_2 \tag{4.10}$$

The first Recovered class $R_1(t)$ is the population who have recovered fully from infection of either strains. This population increases as a result of recovery of the carriers at the rates γ_{C1}, γ_{C2} and the infected at the rates γ_{I1}, γ_{I2}. They are decreased by the complication rate after a period of time $\wedge$ and natural death rate μ. Thus, the rate of change of the Fully Recovered population is expressed as

$$\frac{dR_1}{dt} = \gamma_{C1} C_1 + \gamma_{C2} C_2 + \gamma_{I1} \rho_1 I_1 + \gamma_{I2} \rho_2 I_2 - (\wedge + \mu) R_1 \tag{4.11}$$

The second Recovered class $R_2(t)$ is the population who have recovered from infection of either strains with complications due to the sequelae of delibitating effects among survivors even after recovery. This population is also increased by the recovery rates of the infected populations γ_{I1}, γ_{I2} and the complication rate $\wedge$, and decreased due to natural death rate μ. Hence, the rate of change of the Recovered with Complications population is described by the differential equation given as

$$\frac{dR_2}{dt} = \gamma_{I1}(1 - \rho_1) I_1 + \gamma_{I2}(1 - \rho_2) I_2 + \wedge R_1 - \mu R_2 \tag{4.12}$$

Table 4.1 Description of the Model State Variables

Variables	Description
$S(t)$	Susceptible Population who can contract both strains 1 and 2
$V_1(t)$	Vaccinated Population with Immunity for strain 1
$V_2(t)$	Vaccinated Population with Immunity for strain 2
$C_1(t)$	Carrier Population of strain 1
$C_2(t)$	Carrier Population of strain 2
$I_1(t)$	Infected Population of strain 1
$I_2(t)$	Infected Population of strain 2
$R_1(t)$	Fully Recovered Population from both strains 1 and 2
$R_2(t)$	Recovered with Complications from both strains 1 and 2

Table 4.2 Description of Model Parameters

Parameters	Description
α	Birth or Recruitment rate into Susceptible population
β	Transmission probability
δ	Disease-induced death rate
μ	Natural death rate
σ_1	Rate of Progression from Carrier of strain 1 to Infected population of strain 1
σ_2	Rate of Progression from Carrier of strain 2 to Infected population of strain 2
γ_{C1}	Recovery rate of Carriers of strain 1
γ_{C2}	Recovery rate of Carriers of strain 2
γ_{I1}	Recovery rate of Infected with strain 1
γ_{I2}	Recovery rate of Infected with strain 2
θ_1	Strain 1 Vaccine uptake rate
θ_2	Strain 2 Vaccine uptake rate
ϵ_1	Strain 1 Vaccine efficacy
ϵ_2	Strain 2 Vaccine efficacy
ω_1	Vaccine waning of strain 1
ω_2	Vaccine waning of strain 2
τ_1	Proportion moving to I_1 without first passing through C_1
τ_2	Proportion moving to I_2 without first passing through C_2
$\wedge$	Complication rate after a period of time
ρ_1	Proportion moving to $R_1(t)$ from strain 1 without first passing through $R_2(t)$
ρ_2	Proportion moving to $R_1(t)$ from strain 2 without first passing through $R_2(t)$

We note that all the parameters are assumed to be non-negative.

Model Assumptions

1. Only two strains of Bacterial meningitis are considered in this model.
2. Every individual in the studied population is susceptible to the two strains.
3. Individuals cannot be infected by more than one bacteria strain at the same time.
4. The vaccines are only administered to the susceptible population.
5. A vaccinated individual who loses immunity will return to the susceptible class with no vaccine protection.

6. There is permanent immunity after full recovery.

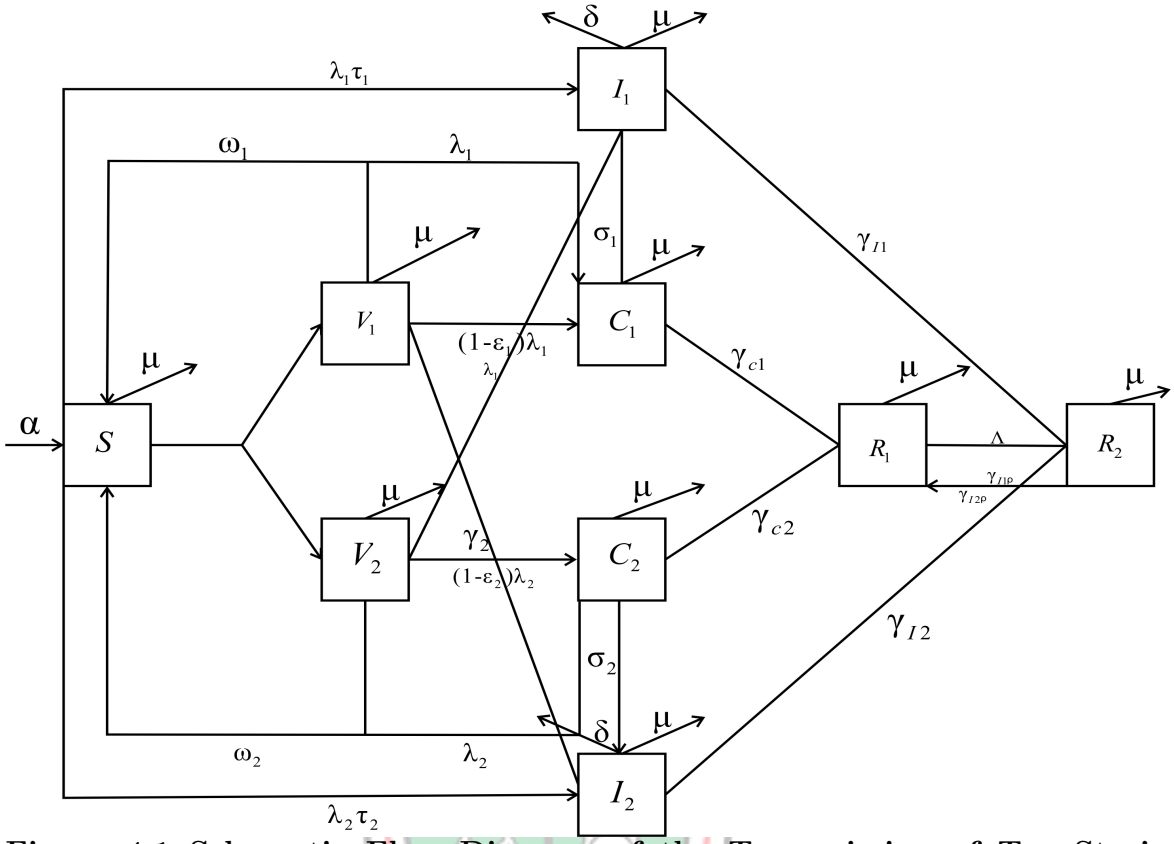


Figure 4.1 Schematic Flow Diagram of the Transmission of Two-Strain Bacterial Meningitis

Model Equations

Following the descriptions given in Equations (4.4) to (4.12) and the flow diagram of the two-strain bacterial meningitis model presented in Figure (4.1), the model governing the system of nine mutually exclusive ODEs for bacterial meningitis population dynamics is expressed as

$$\left.\begin{aligned}
\frac{dS}{dt} &= \alpha + \omega_1 V_1 + \omega_2 V_2 - (\lambda_1 + \lambda_2 + \theta_1 + \theta_2 + \mu)S \\
\frac{dV_1}{dt} &= \theta_1 S - (1-\epsilon_1)\lambda_1 V_1 - (\lambda_2 + \omega_1 + \mu)V_1 \\
\frac{dV_2}{dt} &= \theta_2 S - (1-\epsilon_2)\lambda_2 V_2 - (\lambda_1 + \omega_2 + \mu)V_2 \\
\frac{dC_1}{dt} &= \lambda_1(1-\tau_1)S + (1-\epsilon_1)\lambda_1 V_1 - (\sigma_1 + \gamma_{C1} + \mu)C_1 \\
\frac{dC_2}{dt} &= \lambda_2(1-\tau_2)S + (1-\epsilon_2)\lambda_2 V_2 - (\sigma_2 + \gamma_{C2} + \mu)C_2 \\
\frac{dI_1}{dt} &= \sigma_1 C_1 + \lambda_1\tau_1 S + \lambda_1 V_2 - (\gamma_{I1} + \delta + \mu)I_1 \\
\frac{dI_2}{dt} &= \sigma_2 C_2 + \lambda_2\tau_2 S + \lambda_2 V_1 - (\gamma_{I2} + \delta + \mu)I_2 \\
\frac{dR_1}{dt} &= \gamma_{C1}C_1 + \gamma_{C2}C_2 + \gamma_{I1}\rho_1 I_1 + \gamma_{I2}\rho_2 I_2 - (\wedge + \mu)R_1 \\
\frac{dR_2}{dt} &= \gamma_{I1}(1-\rho_1)I_1 + \gamma_{I2}(1-\rho_2)I_2 + \wedge R_1 - \mu R_2
\end{aligned}\right\} \tag{4.13}$$

subject to the initial conditions (ICs):

$$\begin{aligned}
&S(0) = S_0, \quad V_1(0) = V_{01}, \quad V_2(0) = V_{02}, \quad C_1(0) = C_{01}, \quad C_2(0) = C_{02}, \\
&I_1(0) = I_{01}, \quad I_2(0) = I_{02}, \quad R_1(0) = R_{01}, \quad R_2(0) = R_{02}
\end{aligned} \tag{4.14}$$

4.2 The Model Analyses

4.2.1 The Model's Invariant Region

Definition 4.2.1 *A region within which the solutions to the model are uniformly bounded is defined as* $\Omega \in \Re^9_+$

From the total population in Equation (4.1), we have

$$\frac{dN(t)}{dt} = \frac{dS(t)}{dt} + \frac{dV_1(t)}{dt} + \frac{dV_2(t)}{dt} + \frac{dC_1(t)}{dt} + \frac{dC_2(t)}{dt} + \frac{dI_1(t)}{dt} + \frac{dI_2(t)}{dt} + \frac{dR_1(t)}{dt} + \frac{dR_2(t)}{dt} \tag{4.15}$$

Substituting (4.13) into (4.15) yields

$$\frac{dN(t)}{dt} = \alpha - \mu N - \delta I_1 - \delta I_2 \tag{4.16}$$

$$\frac{dN(t)}{dt} \leq \alpha - \mu N(t) \tag{4.17}$$

Integrating both sides, we have

$$-\frac{1}{\mu}\int \frac{-\mu}{\alpha - \mu N} dN \leq \int dt \tag{4.18}$$

which gives

$$-\frac{1}{\mu}In(\alpha-\mu N)\leq t+c \tag{4.19}$$

where c is the constant of integration.

$$\begin{aligned} In(\alpha-\mu N) &\geq -(\mu t+c) && (4.20)\\ (\alpha-\mu N) &\geq e^{-(\mu t+c)} && (4.21)\\ (\alpha-\mu N) &\geq ke^{-\mu t} && (4.22)\end{aligned}$$

where k is e^c.

Let

$$N(0)=N_0$$

This implies

$$(\alpha-\mu N_0)\geq k \tag{4.23}$$

From (4.22) and (4.23), we get

$$\begin{aligned} (\alpha-\mu N) &\geq (\alpha-\mu N_0)e^{-\mu t} && (4.24)\\ \mu N &\leq \alpha-(\alpha-\mu N_0)e^{-\mu t} && (4.25)\\ N(t) &\leq \frac{\alpha}{\mu}-\frac{(\alpha-\mu N_0)}{\mu}e^{-\mu t} && (4.26)\\ \Rightarrow N(t) &\to \frac{\alpha}{\mu} \text{ as } t\to\infty && (4.27)\end{aligned}$$

This implies $N(t)\in[0,\frac{\alpha}{\mu}]$.

Therefore, the feasible set of solution of the model equations enter and remain in the invariant region:

$$\Omega=\{(S,V_1,V_2,C_1,C_2,I_1,I_2,R_1,R_2)\in\Re_+^9 : N(t)\leq\frac{\alpha}{\mu}\} \tag{4.28}$$

We note that $\frac{\alpha}{\mu}$ is the upper bound of $N(t)$. However, if $N>\frac{\alpha}{\mu}$, then $N(t)$ will decrease to $\frac{\alpha}{\mu}$ and the solutions $(S,V_1,V_2,C_1,C_2,I_1,I_2,R_1,R_2)$ will enter Ω or approach it asymptotically, as such, the region will attract all solutions in $\Re_+^9$. Therefore, the model is well posed mathematically and epidemiologically since the region Ω is positively invariant and attracting. Hence, it is sufficient to study the dynamics of the

model in Ω.

4.2.2 Positivity of the Model's Solution

Theorem 4.2.1 *The Positivity Theorem: Let* $\Omega = \{(S, V_1, V_2, C_1, C_2, I_1, I_2, R_1, R_2) \in \Re_+^9 : S_0 > 0,\ V_{01} > 0,\ V_{02} > 0,\ C_{01} > 0,\ C_{02} > 0,\ I_{01} > 0,\ I_{02} > 0,\ R_{01} > 0,\ R_{02} > 0\}$*, then the solution of* $(S, V_1, V_2, C_1, C_2, I_1, I_2, R_1, R_2)$ *are positive for* $t \geq 0$.

Proof: Considering the first equation of the model

$$\frac{dS}{dt} = \alpha + \omega_1 V_1 + \omega_2 V_2 - (\lambda_1 + \lambda_2 + \theta_1 + \theta_2 + \mu)S \tag{4.29}$$

$$\frac{dS}{dt} \geq -(\lambda_1 + \lambda_2 + \theta_1 + \theta_2 + \mu)S \tag{4.30}$$

$$\int \frac{dS}{S} \geq -\int (\lambda_1 + \lambda_2 + \theta_1 + \theta_2 + \mu)dt \tag{4.31}$$

$$\ln S(t) \geq -f(t) + c \tag{4.32}$$

where $f(t) = \int(\lambda_1 + \lambda_2 + \theta_1 + \theta_2 + \mu)dt$ and c is the constant of integration

$$S(t) \geq e^{(-f(t)+c)} \tag{4.33}$$

$$S(t) \geq e^{-f(t)} \cdot e^{c} \tag{4.34}$$

$$S(t) \geq A_1 e^{-f(t)} \tag{4.35}$$

where $A_1 = e^c$

From the theorem, at $t = 0$, $S_0 > 0$ which implies $A_1 = e^c \geq 0$ since $S(0) \geq A_1$. Consequently, $S(t) \geq S_0 e^{-f(t)} \geq 0 \quad \forall t \geq 0$

Similarly, considering the second equation of the model

$$\frac{dV_1}{dt} = \theta_1 S - (1 - \epsilon_1)\lambda_1 V_1 - (\lambda_2 + \omega_1 + \mu)V_1 \tag{4.36}$$

$$\frac{dV_1}{dt} \geq -[(1 - \epsilon_1)\lambda_1 + \lambda_2 + \omega_1 + \mu]V_1 \tag{4.37}$$

$$\int \frac{dV_1}{V_1} \geq -\int [(1 - \epsilon_1)\lambda_1 + \lambda_2 + \omega_1 + \mu]dt \tag{4.38}$$

$$\ln V_1(t) \geq -g(t) + c \tag{4.39}$$

where $g(t) = \int[(1-\epsilon_1)\lambda_1 + \lambda_2 + \omega_1 + \mu]dt$ and and c is the constant of integration

$$V_1(t) \geq e^{(-g(t)+c)} \tag{4.40}$$

$$V_1(t) \geq e^{-g(t)} \cdot e^c \tag{4.41}$$

$$V_1(t) \geq A_2 e^{-g(t)} \tag{4.42}$$

where $A_2 = e^c$

At $t = 0$, $V_{01} > 0$ which implies $A_2 = e^c \geq 0$.

Consequently, $V_1(t) \geq V_{01}e^{-g(t)} \geq 0 \qquad \forall t \geq 0$

Considering the third equation of the model

$$\frac{dV_2}{dt} = \theta_2 S - (1-\epsilon_2)\lambda_2 V_2 - (\lambda_1 + \omega_2 + \mu)V_2 \tag{4.43}$$

$$\frac{dV_2}{dt} \geq -[(1-\epsilon_2)\lambda_2 + \lambda_1 + \omega_2 + \mu]V_2 \tag{4.44}$$

$$\int \frac{dV_2}{V_2} \geq -\int[(1-\epsilon_2)\lambda_2 + \lambda_1 + \omega_2 + \mu]dt \tag{4.45}$$

$$\ln V_2(t) \geq -h(t) + c \tag{4.46}$$

where $h(t) = \int[(1-\epsilon_2)\lambda_2 + \lambda_1 + \omega_2 + \mu]dt$ and and c is the constant of integration

$$V_2(t) \geq e^{(-h(t)+c)} \tag{4.47}$$

$$V_2(t) \geq e^{-h(t)} \cdot e^c \tag{4.48}$$

$$V_2(t) \geq A_3 e^{-h(t)} \tag{4.49}$$

where $A_3 = e^c$

At $t = 0$, $V_{02} > 0$ which implies $A_3 = e^c \geq 0$.

Consequently, $V_2(t) \geq V_{02}e^{-h(t)} \geq 0 \qquad \forall t \geq 0.$

Considering the fourth equation of the model

$$\begin{aligned}
\frac{dC_1}{dt} &= \lambda_1(1-\tau_1)S + (1-\epsilon_1)\lambda_1 V_1 - (\sigma_1 + \gamma_{C1} + \mu)C_1 && (4.50)\\
\frac{dC_1}{dt} &\geq -(\sigma_1 + \gamma_{C1} + \mu)C_1 && (4.51)\\
\int \frac{dC_1}{C_1} &\geq -\int (\sigma_1 + \gamma_{C1} + \mu)dt && (4.52)\\
\ln C_1(t) &\geq -(\sigma_1 + \gamma_{C1} + \mu)t + c && (4.53)\\
C_1(t) &\geq A_4 e^{-z_1 t} && (4.54)
\end{aligned}$$

where $A_4 = e^c$ and $z_1 = (\sigma_1 + \gamma_{C1} + \mu) \geq 0$

At $t = 0$, $C_{01} > 0$ which implies $A_4 = e^c \geq 0$.

Consequently, $C_1(t) \geq C_{01}e^{-z_1 t} \geq 0 \quad \forall t \geq 0$

In the same way, considering the fifth equation of the model, we have

$$C_2(t) \geq C_{02}e^{-z_2 t} \geq 0 \quad \forall t \geq 0$$

where $z_2 = (\sigma_2 + +\gamma_{C2} + \mu) \geq 0$

and considering the sixth equation of the model, we have

$$I_1(t) \geq I_{01}e^{-z_3 t} \geq 0 \quad \forall t \geq 0$$

where $z_3 = (\gamma_{I1} + \delta + \mu) \geq 0$

Considering the seventh equation of the model, we have

$$I_2(t) \geq I_{02}e^{-z_4 t} \geq 0 \quad \forall t \geq 0$$

where $z_4 = (\gamma_{I2} + \delta + \mu) \geq 0$

and considering the eighth equation of the model, we have

$$R_1(t) \geq R_{01}e^{-z_5 t} \geq 0 \quad \forall t \geq 0$$

where $z_5 = (\wedge + \mu) \geq 0$

Lastly, the ninth equation of the model gives us

$$R_2(t) \geq R_{02}e^{-\mu t} \geq 0 \quad \forall t \geq 0$$

where $\mu \geq 0$ This completes the proof of the theorem.

4.2.3 Existence of Equilibria

For the developed model, four equilibrium points are identified when each of the compartment is at steady state. These are the disease free equilibrium, endemic equilibrium and the boundary equilibrium points. A disease free equilibrium is a state solution to the model in which the studied population remains in the absence of the disease. The disease free equilibrium point is obtained by equating all equations of the model to zero and substituting the values of the state variables $C_1(t)$, $C_2(t)$, $I_1(t)$, $I_2(t)$, $R_1(t)$ and $R_2(t)$ as zero into the model equations. The term "endemic" is used to refer to a disease affecting a number of people simultaneously, so as to show distinct connection with certain localities and is prevalent in that particular area(s) thereof. An endemic equilibrium point of a disease is defined as a positive steady state solution when the disease persists in the studied population. For a two-strain model, the boundary equilibrium points are established which gives the solution when a particular strain persists in the population.

The Disease Free Equilibrium Point

The DFE of the model is defined as $(S^*(t), V_1^*(t), V_2^*(t), 0, 0, 0, 0, 0, 0)$ satisfying $\frac{dS(t)}{dt} = \frac{dV_1(t)}{dt} = \frac{dV_2(t)}{dt} = \frac{dC_1(t)}{dt} = \frac{dC_2(t)}{dt} = \frac{dI_1(t)}{dt} = \frac{dI_2(t)}{dt} = \frac{dR_1(t)}{dt} = \frac{dR_2(t)}{dt} = 0$

Equating the system of equations in (4.13) to 0 and substituting $C_1 = C_2 = I_1 = I_2 = R_1 = R_2 = 0$, we obtain the system of equations

$$\left.\begin{aligned} \omega_1 V_1 + \omega_2 V_2 - (\theta_1 + \theta_2 + \mu)S &= -\alpha \\ \theta_1 S - (\omega_1 + \mu)V_1 &= 0 \\ \theta_2 S - (\omega_2 + \mu)V_2 &= 0 \end{aligned}\right\} \tag{4.55}$$

Solving simultaneously, the DFE is obtained as:

$$E_0 = \left(\frac{(\omega_1 + \mu)(\omega_2 + \mu)\alpha}{\chi\mu}, \frac{(\omega_2 + \mu)\theta_1\alpha}{\chi\mu}, \frac{(\omega_1 + \mu)\theta_2\alpha}{\chi\mu}, 0, 0, 0, 0, 0, 0 \right) \tag{4.56}$$

where

$$\chi = \left(\mu^2 + \mu\,\omega_1 + \mu\,\omega_2 + \mu\,\theta_1 + \mu\,\theta_2 + \omega_1\omega_2 + \omega_1\theta_2 + \omega_2\theta_1\right) \tag{4.57}$$

Endemic Equilibrium Point

The Endemic Equilibrium Point (EEP) of the model is defined as $(S^*(t), V_1^*(t), V_2^*(t), C_1^*(t), C_2^*(t), I_1^*(t), I_2^*(t), R_1^*(t), R_2^*(t))$ satisfying $\frac{dS(t)}{dt} = \frac{dV_1(t)}{dt} = \frac{dV_2(t)}{dt} = \frac{dC_1(t)}{dt} = \frac{dC_2(t)}{dt} = \frac{dI_1(t)}{dt} = \frac{dI_2(t)}{dt} = \frac{dR_1(t)}{dt} = \frac{dR_2(t)}{dt} = 0$.

Boundary Equilibrium Points

Two Boundary Equilibrium Points (BEP) denoted by E_1 and E_2 is defined by

$$E_1 = (S^*(t), V_1^*(t), V_2^*(t), C_1^*(t), 0, I_1^*(t), 0, R_1^*(t), R_2^*(t)) \tag{4.58}$$

where only strain 1 survives, and

$$E_2 = (S^*(t), V_1^*(t), V_2^*(t), 0, C_2^*(t), 0, I_2^*(t), R_1^*(t), R_2^*(t)) \tag{4.59}$$

where only strain 2 survives.

The following system of equations is solved for E_1

$$\left.\begin{aligned}
\alpha + \omega_1 V_1 + \omega_2 V_2 - (\lambda_1 + \theta_1 + \theta_2 + \mu)S &= 0 \\
\theta_1 S - (1 - \epsilon_1)\lambda_1 V_1 - (\omega_1 + \mu)V_1 &= 0 \\
\theta_2 S - (\lambda_1 + \omega_2 + \mu)V_2 &= 0 \\
\lambda_1(1 - \tau_1)S + (1 - \epsilon_1)\lambda_1 V_1 - (\sigma_1 + \gamma_{C1} + \mu)C_1 &= 0 \\
\sigma_1 C_1 + \lambda_1\tau_1 S + \lambda_1 V_2 - (\gamma_{I1} + \delta + \mu)I_1 &= 0 \\
\gamma_{C1} C_1 + \gamma_{I1}\rho_1 I_1 - (\wedge + \mu)R_1 &= 0 \\
\gamma_{I1}(1 - \rho_1)I_1 + \wedge R_1 - \mu R_2 &= 0
\end{aligned}\right\} \tag{4.60}$$

which results in

$$S^* = \frac{(\lambda_1 + b_7)\left[(1-\epsilon_1)\lambda_1 + b_4\right]\alpha}{(1-\epsilon_1)\lambda_1{}^3 + G_2\lambda_1{}^2 + G_1\lambda_1 + \mu\chi} \tag{4.61}$$

$$V_1^* = \frac{\theta_1 S^*}{(1-\epsilon_1)\lambda_1 + b_4} \tag{4.62}$$

$$V_2^* = \frac{\theta_2 S^*}{\lambda_1 + b_7} \tag{4.63}$$

$$C_1^* = \frac{\lambda_1 S^*\left[\theta_1(1-\epsilon_1) + (1-\tau_1)\left((1-\epsilon_1)\lambda_1 + b_4\right)\right]}{a_2\left((1-\epsilon_1)\lambda_1 + b_4\right)} \tag{4.64}$$

$$I_1^* = \frac{\lambda_1\tau_1 S^* + \sigma_1 C_1^* + \lambda_1 V_2^*}{a_1} \tag{4.65}$$

$$R_1^* = \frac{\gamma_{I1}\rho_1 I_1^* + \gamma_{c1} C_1^*}{\wedge + \mu} \tag{4.66}$$

$$R_2^* = \frac{\gamma_{I1}\left[(1-\rho_1)\mu + \wedge\right] I_1^* + \gamma_{C1}\wedge C_1^*}{\mu\ (\wedge + \mu)} \tag{4.67}$$

where

$$a_1 = \gamma_{I1} + \delta + \mu \qquad a_2 = \sigma_1 + \gamma_{C1} + \mu \qquad b_4 = \omega_1 + \mu \qquad b_7 = \omega_2 + \mu$$

$$G_1 = \left[\chi - \omega_1(b_7 + \theta_2)\right](1-\epsilon_1) + \mu\, b_4 - \omega_2\theta_1 + \chi \qquad G_2 = (1-\epsilon_1)(b_7 + \theta_1 + \theta_2 + \mu) + b_4$$

The force of infection in Equation (4.2) becomes

$$\lambda_1^* = \frac{\beta(\eta C_1^* + I_1^*)}{N^*} \tag{4.68}$$

This gives

$$\lambda_1^* N^* - \beta(\eta C_1^* + I_1^*) = 0 \tag{4.69}$$

Substituting the state solutions from Equations (4.61) to (4.67) into Equation (4.69)

yields the following cubic polynomial after some computations

$$K_1\lambda_1^{*3} + K_2\lambda_1^{*2} + K_3\lambda_1^{*} + K_4 = 0 \tag{4.70}$$

where,

$$K_1 = (1-\epsilon_1)\left[(1-\tau_1)\left((\mu+\gamma_{I1})\,\sigma_1 + (\mu+\gamma_{c1})\,a_1\right) + a_2\,(\mu+\gamma_{I1})\,\tau_1\right]$$

$$\begin{aligned} K_2 =& (1-\tau_1)\left[(1-\epsilon_1)\,b_7 + b_4\right]\left[\sigma_1\,(\mu+\gamma_{I1}) + a_1\,(\mu+\gamma_{c1})\right] + a_1\theta_1\,(1-\epsilon_1)\,(\mu+\gamma_{c1}) \\ &+ (1-\epsilon_1)\,(\mu+\gamma_{I1})\left[a_2\,(\tau_1 b_7 + \theta_2) + \sigma_1\theta_1\right] - \beta\,\mu\,(1-\epsilon_1)\,(1-\tau_1)\,(\eta\,a_1 + \sigma_1) \\ &- \mu\,a_2\,(1-\epsilon_1)\,(\beta\,\tau_1 - a_1) + a_2 b_4\tau_1\,(\mu+\gamma_{I1}) \end{aligned}$$

$$\begin{aligned} K_3 =& \, b_7\sigma_1\,(\mu+\gamma_{I1})\left[(1-\tau_1)\,b_4 + (1-\epsilon_1)\,\theta_1\right] + a_1 b_7\left[(1-\tau_1)\,b_4 + (1-\epsilon_1)\,\theta_1\right](\mu+\gamma_{c1}) \\ &+ a_2\,(b_7\tau_1 + \theta_2)\left[b_4\,(\mu+\gamma_{I1}) - \mu\,\beta\,(1-\epsilon_1)\right] + \mu\,a_1a_2\,(1-\epsilon_1)\,(\theta_2 + b_7) + \mu\,a_1a_2\,(\theta_1 + b_4) \\ &- \beta\,\mu\,a_2b_4\tau_1 - \mu\,\beta\,(\eta\,a_1 + \sigma_1)\left((1-\tau_1)\,(1-\epsilon_1)\,b_7 + (1-\tau_1)\,b_4 + (1-\epsilon_1)\,\theta_1\right) \end{aligned}$$

$$\begin{aligned} K_4 =& -\beta\,\mu\,\left(-b_4b_7\,(-1+\tau_1)\,(\eta\,a_1+\sigma_1) + b_7\theta_1\,(1-\epsilon_1)\,(\eta\,a_1+\sigma_1) + b_4\,(b_7\tau_1+\theta_2)\,a_2\right) + \mu\,a_1a_2\chi \\ =& -\beta\,\mu\,\left(-b_7\,(\eta\,a_1+\sigma_1)\,(b_4\tau_1 + \epsilon_1\theta_1 - b_4 - \theta_1) + b_4\,(b_7\tau_1+\theta_2)\,a_2\right) + \mu\,a_1a_2\chi \\ =& -\beta\,\mu\,\left(b_7\,(\eta\,a_1+\sigma_1)\left((1-\tau_1)\,b_4 + (1-\epsilon_1)\,\theta_1\right) + b_4\,(b_7\tau_1+\theta_2)\,a_2\right) + \mu\,a_1a_2\chi \\ =& \mu\,a_1a_2\chi\left(1 - \frac{\beta\,\left(b_7\,(\eta\,a_1+\sigma_1)\left((1-\tau_1)\,b_4 + (1-\epsilon_1)\,\theta_1\right) + b_4\,(b_7\tau_1+\theta_2)\,a_2\right)}{a_1a_2\chi}\right) \\ =& \mu a_1a_2\chi\,(1-\mathcal{R}_{01}) \end{aligned}$$

and $\mathcal{R}_{01}$ is the basic reproduction number relating to strain 1 as defined in Equation (4.89).

For E_2, the following system of equations is solved

$$\left.\begin{aligned}
\alpha+\omega_1V_1+\omega_2V_2-(\lambda_2+\theta_1+\theta_2+\mu)S &= 0\\
\theta_1S-(\lambda_2+\omega_1+\mu)V_1 &= 0\\
\theta_2S-(1-\epsilon_2)\lambda_2V_2-(\omega_2+\mu)V_2 &= 0\\
\lambda_2(1-\tau_2)S+(1-\epsilon_2)\lambda_2V_2-(\sigma_2+\gamma_{C2}+\mu)C_2 &= 0\\
\sigma_2C_2+\lambda_2\tau_2S+\lambda_2V_1-(\gamma_{I2}+\delta+\mu)I_2 &= 0\\
\gamma_{C2}C_2+\gamma_{I2}\rho_2I_2-(\wedge+\mu)R_1 &= 0\\
\gamma_{I2}(1-\rho_2)I_2+\wedge R_1-\mu R_2 &= 0
\end{aligned}\right\} \tag{4.71}$$

which results in

$$S^*=\frac{(\lambda_2+b_4)\left[(1-\epsilon_2)\lambda_2+b_7\right]\alpha}{(1-\epsilon_2)\lambda_2{}^3+G_4\lambda_2{}^2+G_3\lambda_2+\mu\chi} \tag{4.72}$$

$$V_1^*=\frac{\theta_1S^*}{\lambda_2+b_4} \tag{4.73}$$

$$V_2^*=\frac{\theta_2S^*}{(1-\epsilon_2)\lambda_2+b_7} \tag{4.74}$$

$$C_2^*=\frac{\lambda_2S^*\left[\theta_2(1-\epsilon_2)+(1-\tau_2)\left((1-\epsilon_2)\lambda_2+b_7\right)\right]}{a_4\left((1-\epsilon_2)\lambda_2+b_7\right)} \tag{4.75}$$

$$I_2^*=\frac{\lambda_2\tau_2S^*+\sigma_2C_2^*+\lambda_2V_1^*}{a_3} \tag{4.76}$$

$$R_1^*=\frac{\gamma_{I2}\rho_2I_2^*+\gamma_{c2}C_2^*}{\wedge+\mu} \tag{4.77}$$

$$R_2^*=\frac{\gamma_{I2}\left[(1-\rho_2)\mu+\wedge\right]I_2^*+\gamma_{C2}\wedge C_2^*}{\mu\ (\wedge+\mu)} \tag{4.78}$$

where,

$$a_3=\gamma_{I2}+\delta+\mu \qquad a_4=\sigma_2+\gamma_{C2}+\mu$$

$$G_3=\left[\chi-\omega_2(b_4+\theta_1)\right](1-\epsilon_2)+\mu b_7-\omega_1\theta_2+\chi \qquad G_4=(1-\epsilon_2)(b_4+\theta_1+\theta_2+\mu)+b_7$$

The force of infection in Equation (4.3) becomes

$$\lambda_2^* = \frac{\beta(\eta C_2^* + I_2^*)}{N^*} \tag{4.79}$$

This yields

$$\lambda_2^* N^* - \beta(\eta C_2^* + I_2^*) = 0 \tag{4.80}$$

Substituting the state solutions from Equations (4.72) to (4.78) into Equation (4.80) yields the following cubic polynomial after some computations

$$K_5 \lambda_2^{*3} + K_6 \lambda_2^{*2} + K_7 \lambda_2^* + K_8 = 0 \tag{4.81}$$

where,

$$K_5 = (1-\epsilon_2)\left[(1-\tau_2)\left((\mu+\gamma_{I2})\,\sigma_2 + (\mu+\gamma_{c2})\,a_3\right) + a_4\,(\mu+\gamma_{I2})\,\tau_2\right]$$

$$\begin{aligned} K_6 =& (1-\tau_2)\left[(1-\epsilon_2)\,b_4 + b_7\right]\left[\sigma_2\,(\mu+\gamma_{I2}) + a_3\,(\mu+\gamma_{c2})\right] + a_3\theta_2\,(1-\epsilon_2)\,(\mu+\gamma_{c2}) \\ &+ (1-\epsilon_2)\,(\mu+\gamma_{I2})\left[a_4\,(\tau_2 b_4 + \theta_1) + \sigma_2\theta_2\right] - \beta\,\mu\,(1-\epsilon_2)\,(1-\tau_2)\,(\eta\,a_3 + \sigma_1) \\ &- \mu\,a_4\,(1-\epsilon_2)\,(\beta\,\tau_2 - a_3) + a_4 b_7 \tau_2\,(\mu+\gamma_{I2}) \end{aligned}$$

$$\begin{aligned} K_7 =& b_4\sigma_2\,(\mu+\gamma_{I2})\left[(1-\tau_2)\,b_7 + (1-\epsilon_2)\,\theta_2\right] + a_3 b_4\left[(1-\tau_2)\,b_7 + (1-\epsilon_2)\,\theta_2\right](\mu+\gamma_{c2}) \\ &+ a_4\,(b_4\tau_2 + \theta_1)\left[b_7\,(\mu+\gamma_{I2}) - \mu\,\beta\,(1-\epsilon_2)\right] + \mu\,a_3 a_4\,(1-\epsilon_2)\,(\theta_1 + b_4) + \mu\,a_3 a_4\,(\theta_2 + b_7) \\ &- \beta\,\mu\,a_4 b_7 \tau_2 - \mu\,\beta\,(\eta\,a_3 + \sigma_2)\left((1-\tau_2)\,(1-\epsilon_2)\,b_4 + (1-\tau_2)\,b_7 + (1-\epsilon_2)\,\theta_2\right) \end{aligned}$$

$$
\begin{aligned}
K_8 =& -\beta\,\mu\,\left(-b_4 b_7\left(-1+\tau_2\right)\left(\eta\,a_3+\sigma_2\right)+b_7\theta_2\left(1-\epsilon_2\right)\left(\eta\,a_3+\sigma_2\right)+b_7\left(b_4\tau_2+\theta_1\right)a_4\right)+\mu\,a_3a_4\chi\\
=& -\beta\,\mu\,\left(-b_4\left(\eta\,a_3+\sigma_2\right)\left(b_7\tau_2+\epsilon_2\theta_2-b_7-\theta_2\right)+b_7\left(b_4\tau_2+\theta_1\right)a_4\right)+\mu\,a_3a_4\chi\\
=& -\beta\,\mu\,\left(b_4\left(\eta\,a_3+\sigma_2\right)\left(\left(1-\tau_2\right)b_7+\left(1-\epsilon_2\right)\theta_2\right)+b_7\left(b_4\tau_2+\theta_1\right)a_4\right)+\mu\,a_3a_4\chi\\
=&\mu\,a_3a_4\chi\left(1-\frac{\beta\,\left(b_4\left(\eta\,a_3+\sigma_2\right)\left(\left(1-\tau_2\right)b_7+\left(1-\epsilon_2\right)\theta_2\right)+b_7\left(b_4\tau_2+\theta_1\right)a_4\right)}{a_3a_4\chi}\right)\\
=&\mu a_3a_4\chi\left(1-\mathcal{R}_{02}\right)
\end{aligned}
$$

and $\mathcal{R}_{02}$ is the basic reproduction number relating to strain 2 as defined in Equation (4.90).

4.2.4 The Basic Reproduction Number ($\mathcal{R}_0$)

The basic reproduction number is defined as the average number of secondary infections produced by a single case of an infectious individual in a completely susceptible population. The basic reproduction number associated with model (4.13) is derived as follows:

$$
\begin{pmatrix}
\frac{dC_1}{dt}\\
\frac{dI_1}{dt}\\
\frac{dC_2}{dt}\\
\frac{dI_2}{dt}
\end{pmatrix}
= f_i - v_i
$$

where

$$
f_i = \begin{pmatrix}
\lambda_1(1-\tau_1)S + (1-\epsilon_1)\lambda_1 V_1\\
\lambda_1\tau_1 S + \lambda_1 V_2\\
\lambda_2(1-\tau_2)S + (1-\epsilon_2)\lambda_2 V_2\\
\lambda_2\tau_2 S + \lambda_2 V_1
\end{pmatrix} \tag{4.82}
$$

and

$$
v_i = \begin{pmatrix}
(\sigma_1+\gamma_{C1}+\mu)C_1\\
(\gamma_{I1}+\delta+\mu)I_1 - \sigma_1 C_1\\
(\sigma_2+\gamma_{C2}+\mu)C_2\\
(\gamma_{I2}+\delta+\mu)I_2 - \sigma_2 C_2
\end{pmatrix} \tag{4.83}
$$

where f_i is the rate of appearance of new infection(s) in compartment i, v_i represents the rate of transfer of individuals into compartment i, with $i \in [1,4]$.

The matrix $\mathcal{F}$ and $\mathcal{V}$ are obtained as follows:

$$\mathcal{F} = \begin{pmatrix} \frac{\partial f_1}{\partial C_1} & \frac{\partial f_1}{\partial I_1} & \frac{\partial f_1}{\partial C_2} & \frac{\partial f_1}{\partial I_2} \\ \frac{\partial f_2}{\partial C_1} & \frac{\partial f_2}{\partial I_1} & \frac{\partial f_2}{\partial C_2} & \frac{\partial f_2}{\partial I_2} \\ \frac{\partial f_3}{\partial C_1} & \frac{\partial f_3}{\partial I_1} & \frac{\partial f_3}{\partial C_2} & \frac{\partial f_3}{\partial I_2} \\ \frac{\partial f_4}{\partial C_1} & \frac{\partial f_4}{\partial I_1} & \frac{\partial f_4}{\partial C_2} & \frac{\partial f_4}{\partial I_2} \end{pmatrix}$$

$$= \begin{pmatrix} \frac{\eta\,\beta\,b_7[\theta_1(1-\epsilon_1)+(1-\tau_1)b_4]}{\chi} & \frac{\beta\,b_7[\theta_1(1-\epsilon_1)+(1-\tau_1)b_4]}{\chi} & 0 & 0 \\ \frac{\eta\,\beta\,b_4(b_7\tau_1+\theta_2)}{\chi} & \frac{\beta\,b_4(b_7\tau_1+\theta_2)}{\chi} & 0 & 0 \\ 0 & 0 & \frac{\eta\,\beta\,b_4[\theta_2(1-\epsilon_2)+(1-\tau_2)b_7]}{\chi} & \frac{\beta\,b_4[\theta_2(1-\epsilon_2)+(1-\tau_2)b_7]}{\chi} \\ 0 & 0 & \frac{\eta\,\beta\,b_7(b_4\tau_2+\theta_1)}{\chi} & \frac{\beta\,b_7(b_4\tau_2+\theta_1)}{\chi} \end{pmatrix} \tag{4.84}$$

and

$$\mathcal{V} = \begin{pmatrix} \frac{\partial v_1}{\partial C_1} & \frac{\partial v_1}{\partial I_1} & \frac{\partial v_1}{\partial C_2} & \frac{\partial v_1}{\partial I_2} \\ \frac{\partial v_2}{\partial C_1} & \frac{\partial v_2}{\partial I_1} & \frac{\partial v_2}{\partial C_2} & \frac{\partial v_2}{\partial I_2} \\ \frac{\partial v_3}{\partial C_1} & \frac{\partial v_3}{\partial I_1} & \frac{\partial v_3}{\partial C_2} & \frac{\partial v_3}{\partial I_2} \\ \frac{\partial v_4}{\partial C_1} & \frac{\partial v_4}{\partial I_1} & \frac{\partial v_4}{\partial C_2} & \frac{\partial v_4}{\partial I_2} \end{pmatrix}$$

$$= \begin{pmatrix} \sigma_1+\gamma_{C1}+\mu & 0 & 0 & 0 \\ -\sigma_1 & \gamma_{I1}+\delta+\mu & 0 & 0 \\ 0 & 0 & \sigma_2+\gamma_{C2}+\mu & 0 \\ 0 & 0 & -\sigma_2 & \gamma_{I2}+\delta+\mu \end{pmatrix} \tag{4.85}$$

Lastly,

$$\mathcal{V}^{-1} = \begin{pmatrix} \frac{1}{\sigma_1+\gamma_{C1}+\mu} & 0 & 0 & 0 \\ \frac{\sigma_1}{(\sigma_1+\gamma_{C1}+\mu)(\gamma_{I1}+\delta+\mu)} & \frac{1}{\gamma_{I1}+\delta+\mu} & 0 & 0 \\ 0 & 0 & \frac{1}{\sigma_2+\gamma_{C2}+\mu} & 0 \\ 0 & 0 & \frac{\sigma_2}{(\sigma_2+\gamma_{C2}+\mu)(\gamma_{I2}+\delta+\mu)} & \frac{1}{\gamma_{I2}+\delta+\mu} \end{pmatrix} \tag{4.86}$$

Thus, the next generation matrix:

$$G = \mathcal{F}\mathcal{V}^{-1}$$

$$= \begin{pmatrix} \frac{\eta\,\beta\,b_7 b_1(\eta\,a_1+\sigma_1)}{\chi\,a_1 a_2} & \frac{\beta\,b_7 b_1}{\chi\,a_1} & 0 & 0 \\ \frac{\eta\,\beta\,b_4(b_7\tau_1+\theta_2)(\eta\,a_1+\sigma_1)}{\chi\,a_1 a_2} & \frac{\beta\,b_4(b_7\tau_1+\theta_2)}{\chi\,a_1} & 0 & 0 \\ 0 & 0 & \frac{\beta\,b_4 b_2(\eta\,a_3+\sigma_2)}{\chi\,a_3 a_4} & \frac{\beta\,b_4 b_2}{\chi\,a_3} \\ 0 & 0 & \frac{\beta\,b_7(b_4\tau_2+\theta_1)(\eta\,a_3+\sigma_2)}{\chi\,a_3 a_4} & \frac{\beta\,b_7(b_4\tau_2+\theta_1)}{\chi\,a_3} \end{pmatrix} \tag{4.87}$$

where,

$$b_1 = \theta_1(1-\epsilon_1) + (1-\tau_1)b_4 \qquad b_2 = \theta_2(1-\epsilon_2) + (1-\tau_2)b_7$$

The eigenvalues of the matrix, G are

$$= \begin{pmatrix} 0 \\ 0 \\ \frac{\beta\,[b_7(\eta\,a_1+\sigma_1)(b_4(1-\tau_1)+\theta_1(1-\epsilon_1))+a_2 b_4(b_7\tau_1+\theta_2)]}{a_1 a_2 \chi} \\ \frac{\beta\,[b_4(\eta\,a_3+\sigma_2)(b_7(1-\tau_2)+\theta_2(1-\epsilon_2))+a_4 b_7(b_4\tau_2+\theta_1)]}{a_3 a_4 \chi} \end{pmatrix} \tag{4.88}$$

Consequently, the Basic Reproduction Number, which is the spectral radius of G is given as

$$\mathcal{R}_0 = \max\{\mathcal{R}_{01}, \mathcal{R}_{02}\}$$

with

$$\mathcal{R}_{01} = \frac{\beta\,[b_7\,(\eta\,a_1+\sigma_1)\,(b_4\,(1-\tau_1)+\theta_1\,(1-\epsilon_1))+a_2 b_4\,(b_7\tau_1+\theta_2)]}{a_1 a_2 \chi} \tag{4.89}$$

and

$$\mathcal{R}_{02} = \frac{\beta\,[b_4\,(\eta\,a_3+\sigma_2)\,(b_7\,(1-\tau_2)+\theta_2\,(1-\epsilon_2))+a_4 b_7\,(b_4\tau_2+\theta_1)]}{a_3 a_4 \chi} \tag{4.90}$$

representing the basic reproduction numbers relating to strain 1 and 2 respectively.

$\mathcal{R}_{01}$ provides the expected number of newly infected individuals that would arise as a result of introducing a single case of strain 1 into a completely susceptible population. Similarly, $\mathcal{R}_{02}$ yields the expected number of newly infected individuals that would

arise if a single case of strain 2 is introduced into a completely susceptible population.

4.3 Model Parameter Estimation and Initial Conditions

In this study, two strategies are employed in obtaining the parameter values. We first gathered the parameter values from literature and for those parameters not found in the literature, we estimated their values. The bacterial meningitis reported cases from 2017 to 2019 is used (Anon, 2019). Some of the demographic parameters are also estimated from literature. The time unit is assumed to be days.

4.3.1 Initial Conditions

The base year used in our simulations is 2017. Since the disease is endemic in the northern part of Ghana, the total population of the northern part as at 2017 was 4953293 (Anon, 2020), as such the initial total population, $N(0) = 4953293$. Since, the outbreak in that year was due to Neisseria meningitidis strain, the initially infected individuals of strain 2, $I_2(0) = 69$, which is the same as the initial number of infected people reported in data. We assumed $I_1(0) = 153$. From the review of literature, Streptococcus pneumoniae is found in the nose and throat of $20 - 40\%$ of people while Neisseria meningitidis is found in $1 - 10\%$ without causing any symptoms of illness in these people. So taking 140% and 110% of $I_1(0)$ and $I_2(0)$ respectively gives $C_1(0) = 214$ and $C_2(0) = 76$. We assumed $V_1(0) = V_2(0) = R_1(0) = R_2(0) = 0$, so the initial susceptible, $S(0) = N(0) - V_1(0) - V_2(0) - C_1(0) - C_2(0) - I_1(0) - I_2(0) - R_1(0) - R_2(0) = 4952781$.

4.3.2 Parameter Values

(i) Natural death rate (μ): The average life span in Ghana is 64.17 years, therefore $\mu = \frac{1}{64.17 \times 365} = 4.269 \times 10^{-5}$ per day.

(ii) Birth or recruitment rate (α): The limiting total human population in the absence of the disease is assumed to be $\frac{\alpha}{\mu} = 4953293$, so $\alpha = 211$ per day.

(iii) Disease-induced death rate (δ): The mortality rate due to bacterial meningitis disease in Ghana is $36 - 50\%$. Taking the average to be 43% gives $\delta = 0.43$.

(iv) Progression rates (σ_1, σ_2): The average incubation period for Streptococcus pneumonaie is 1-3 days while Neisseria meningitidis is 4 days. Thus, $\sigma_1 = \frac{1}{2} = 0.5$ and $\sigma_2 = \frac{1}{4} = 0.25$

(v) Vaccine waning rates (ω_1, ω_2): It takes 5 years for the pneumococcal conjugate vaccines to wane while that of the meningococcal conjugate vaccines is 3 to 5 years. Therefore, $\omega_1 = \frac{1}{5\times365} = 5.47 \times 10^{-4}$ per day and $\omega_2 = \frac{1}{4\times365} = 6.8 \times 10^{-4}$ per day

(vi) Recovery rates $(\gamma_{C1}, \gamma_{I1})$: The period of infection of the disease is 1-2 weeks with hospitalization and right treatment, so taking the average, we have 8 days. Therefore, $\gamma_{I1} = \frac{1}{8} = 0.125$. For the people exposed to the disease, prophylaxis are administered which have shown to be effective for one to two weeks follow up (Trestioreanu *et al.*, 2011). Therefore, $\gamma_{C1} = \frac{1}{7} = 0.143$.

(vii) Complication rate $(\wedge)$: Even with appropriate treatment, $10 - 20\%$ of survivors have serious complications or long-term sequelae. Therefore, $\wedge = \frac{15}{100} = 0.15$

Table 4.3 Model Parameter Values

Parameters	**Values**	**Source**
α	211	Estimated
μ	0.000043	Estimated
ω_1	0.000547	Estimated
ω_2	0.00068	Estimated
β	0.88	Asamoah *et al.* (2018)
γ_{C1}	0.143	Estimated
γ_{C2}	0.3	Wiah and Adetunde (2010)
γ_{I1}	0.125	Estimated
γ_{I2}	0.1	Wiah and Adetunde (2010)
η	0.75	Assumed
δ	0.43	Estimated
ϵ_1	0.85	Anon (2020b)
ϵ_2	0.90	Anon (2020b)
σ_1	0.5	Estimated
σ_2	0.25	Estimated
τ_1	0.3	Elmojtaba and Adam (2017)
τ_2	0.5	Assumed
θ_1	0.2 [0,1]	Assumed
θ_2	0.5	Wiah and Adetunde (2010)
ρ_1	0.85	Elmojtaba and Adam (2017)
ρ_2	0.9	Assumed
$\wedge$	0.15	Estimated

4.4 Estimated $\mathcal{R}_0$ Value and Herd Immunity

Using the model parameter values given in Table 4.3, the estimated value of $\mathcal{R}_{01}$ is approximately 1.3409 while that of $\mathcal{R}_{02}$ is 0.4853. Therefore,

$$\mathcal{R}_0 = \max\{\mathcal{R}_{01}, \mathcal{R}_{02}\} = \max\{1.3409, 0.4853\} = 1.3409$$

From the biological point of view, this threshold value indicates that Bacterial Meningitis has a higher potential of invading the population if no control effort is implemented to curtail the transmission and spread of the disease. Therefore, it is important to determine the fraction of the population that needs to be immunized in order to cease large outbreaks of Bacterial Meningitis in Ghana. When a large scale of population is immunized against a contagious infectious disease (either by vaccination or recovery from the disease infection), an indirect protection is provided to the remaining scale that is not immune to the disease. This kind of protection is referred to as Herd Immunity (Kwok *et al.*, 2020; Abidemi, Zainuddin and Aziz, 2021). Herd immunity plays a major role in epidemic control including giving a better understanding on how effective a vaccination administration would be without reaching 100% population coverage.

Therefore, the critical level of population immunity, denoted as $\hat{p}$, is calculated with respect to the estimated $\mathcal{R}_0$ value for Ghana Bacterial Meningitis outbreaks as

$$\hat{p} = 1 - \frac{1}{\mathcal{R}_0} = 0.25 \tag{4.91}$$

which implies that Bacterial Meningitis will not spread in the population if 25% of the population is immune to the disease. Hence, successful vaccination of about 25% of the entire population to both strains may lead to eradication of the disease in Ghana.

4.5 Stability Analyses of the Disease-Free Equilibrium

The stability analysis of the Disease-Free Equilibrium (DFE) is carried out in this section. The dimensionless threshold, $\mathcal{R}_{0i}, i = 1, 2$ is used to discuss the local and

global asymptotic stability of the DFE.

4.5.1 Local Asymptotic Stability of the Disease-Free Equilibrium

Theorem 4.5.1 *The DFE is Locally Asymptotically Stable (LAS) if* $\mathcal{R}_0 < 1$ *and unstable if* $\mathcal{R}_0 > 1$.

Using Theorem 4.5.1, the result in Lemma 4.5.1 follows immediately based on the expressions of $\mathcal{R}_{01}, \mathcal{R}_{02}$.

Lemma 4.5.1 *The DFE of the two-strain bacterial meningitis model in* (4.13) *is Locally Asymptotically Stable (LAS) if both* $\mathcal{R}_{01}, \mathcal{R}_{02} < 1$ *and unstable if* $\mathcal{R}_{01}, \mathcal{R}_{02} > 1$.

Following Definition 2.4.2, the Jacobian matrix, J evaluated at E_0 is given as

$$\begin{pmatrix}
-b_3 & \omega_1 & \omega_2 & -\frac{\beta\,\eta\,b_4b_7}{\chi} & -\frac{\beta\,\eta\,b_4b_7}{\chi} & -\frac{\beta\,b_4b_7}{\chi} & -\frac{\beta\,b_4b_7}{\chi} & 0 & 0 \\
\theta_1 & -b_4 & 0 & -\frac{\beta\,\eta\,\theta_1(1-\epsilon_1)b_7}{\chi} & -\frac{\beta\,\eta\,b_7\theta_1}{\chi} & -\frac{\beta\,\theta_1(1-\epsilon_1)b_7}{\chi} & -\frac{\beta\,b_7\theta_1}{\chi} & 0 & 0 \\
\theta_2 & 0 & -b_7 & -\frac{\beta\,\eta\,b_4\theta_2}{\chi} & -\frac{\beta\,\eta\,\theta_2(1-\epsilon_2)b_4}{\chi} & -\frac{\beta\,b_4\theta_2}{\chi} & -\frac{\beta\,\theta_2(1-\epsilon_2)b_4}{\chi} & 0 & 0 \\
0 & 0 & 0 & \frac{\beta\,\eta\,b_1b_7}{\chi} - a_2 & 0 & \frac{\beta\,b_1b_7}{\chi} & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & \frac{\beta\,\eta\,b_2b_4}{\chi} - a_4 & 0 & \frac{\beta\,b_2b_4}{\chi} & 0 & 0 \\
0 & 0 & 0 & \frac{\beta\,\eta\,b_4b_6}{\chi} + \sigma_1 & 0 & \frac{\beta\,b_4b_6}{\chi} - a_1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & \frac{\beta\,\eta\,b_7b_5}{\chi} + \sigma_2 & 0 & \frac{\beta\,b_7b_5}{\chi} - a_3 & 0 & 0 \\
0 & 0 & 0 & \gamma_{C1} & \gamma_{C2} & \gamma_{I1}\rho_1 & \gamma_{I2}\rho_2 & -(\wedge+\mu) & 0 \\
0 & 0 & 0 & 0 & 0 & \gamma_{I1}(1-\rho_1) & \gamma_{I2}(1-\rho_2) & \wedge & -\mu
\end{pmatrix} \tag{4.92}$$

where,

$$b_3 = \theta_1 + \theta_2 + \mu \qquad b_5 = b_4\tau_2 + \theta_1 \qquad b_6 = b_7\tau_1 + \theta_2$$

The eigenvalues of the Jacobian matrix, J are

$$\lambda_{1,2} = -\frac{(a_1 + a_2)\chi - \beta\,\eta\,b_1b_7 - \beta\,b_4b_6 \pm \sqrt{W_1}}{2\chi}$$

$$\lambda_{3,4} = -\frac{(a_3 + a_4)\chi - \beta\,\eta\,b_2b_4 - \beta\,b_5b_7 \pm \sqrt{W_2}}{2\chi}$$

$$\lambda_5 = -\mu \qquad \lambda_6 = -(\wedge + \mu)$$

where,

$$W_1 = \beta^2(\eta\, b_1b_7+b_4b_6)^2+2\chi\beta\,\eta\, b_1b_7(a_1-a_2)-2\chi\beta\, b_4b_6(a_1-a_2)+4\chi\beta\, b_1b_7\sigma_1+\chi^2(a_1-a_2)^2$$

and

$$W_2 = \beta^2(\eta\, b_2b_4+b_5b_7)^2+2\chi\beta\,\eta\, b_2b_4(a_3-a_4)-2\chi\beta\, b_5b_7(a_3-a_4)+4\chi\beta\, b_2b_4\sigma_2+\chi^2(a_3-a_4)^2$$

The remaining three eigenvalues of J are obtained as the roots of the following polynomial:

$$c_1\lambda^3 + c_2\lambda^2 + c_3\lambda + c_4 \tag{4.93}$$

where,

$c_1 = 1$

$c_2 = b_3 + b_4 + b_7$

$c_3 = b_4b_7 + b_3(b_4 + b_7) - \omega_1\theta_1 - \omega_2\theta_2 = \chi + \mu(b_3 + b_4 + \omega_2)$

$c_4 = b_3b_4b_7 - b_4\omega_2\theta_2 - b_7\omega_1\theta_1 = \chi\mu$

Applying the Routh-Hurwitz criteria to the cubic polynomial in Equation (4.93), since all the parameters of the model in (4.13) are positive, it is clear that the condition of stability is established with $c_1 > 0$, $c_2 > 0$, $c_3 > 0$ and $c_4 > 0$.

4.5.2 Global Asymptotic Stability of the Disease-Free Equilibrium

The global asymptotic stability of the model in (4.13) is investigated by following Castillo-Chavez, Feng and Huang (2002). The model is denoted by:

$$\begin{cases} \frac{dX}{dt} = F(X, Y) \\ \frac{dY}{dt} = G(X, Y) \end{cases} \tag{4.94}$$

where $X = (S, V_1, V_2, R_1, R_2)$ denotes the right-hand side of the uninfected population with $C_1 = C_2 = I_1 = I_2 = 0$ and $Y = (C_1, C_2, I_1, I_2)$ denotes the right-hand side of

the infected population.

Theorem 4.5.2 *The Disease-Free Equilibrium is said to be globally asymptotically stable in* Ω *if* $\mathcal{R}_{01}, \mathcal{R}_{02} < 1$ *and the following two conditions hold:*

C1: For $\frac{dX}{dt} = F(X, 0)$, E_0 *is globally asymptotically stable.*

C2: $G(X, Y) = J\left[G(X^*, 0)\right] Y - \hat{G}(X, Y), \qquad \hat{G}(X, Y) \geq 0, \quad \forall\ (X, Y) \in \Omega$

where $(X^*, 0) = E_0 = \left(\frac{\alpha b_4 b_7}{\mu\chi}, \frac{\alpha\theta_1 b_7}{\mu\chi}, \frac{\alpha\theta_2 b_4}{\mu\chi}, 0, 0, 0, 0, 0, 0\right)$, $J\left[G(X^*, 0)\right]$ *is the Jacobian of* $G(X, Y)$ *obtained with respect to* $(C_1,\ C_2,\ I_1,\ I_2)$ *and evaluated at* $(X^*, 0)$.

Proof:

C1: From the model, it follows that:

$$F(X,0) = \begin{pmatrix} \alpha + \omega_1 V_1 + \omega_2 V_2 - (\theta_1 + \theta_2 + \mu)S \\ \theta_1 S - b_4 V_1 \\ \theta_2 S - b_7 V_2 \\ -(\wedge + \mu)R_1 \\ \wedge R_1 - \mu R_2 \end{pmatrix} \tag{4.95}$$

From Equation (4.95), it is clear that

$$E_0 = (S, V_1, V_2, C_1, C_2, I_1, I_2, R_1, R_2) = \left(\frac{\alpha b_4 b_7}{\mu\chi}, \frac{\alpha\theta_1 b_7}{\mu\chi}, \frac{\alpha\theta_2 b_4}{\mu\chi}, 0, 0, 0, 0, 0, 0\right)$$

This can be verified using the method of integrating factors. From Equation (4.95), we have:

$$\frac{dV_1}{dt} = \theta_1 S - b_4 V_1 \tag{4.96}$$

which can be written in standard from as

$$\frac{dV_1}{dt} + b_4 V_1 = \theta_1 S \tag{4.97}$$

The integrating factor is given as $I.F. = e^{\int b_4 dt} = e^{b_4 t}$.

Multiplying Equation (4.97) through by the integrating factor yields

$$e^{b_4 t}\left(\frac{dV_1}{dt} + b_4 V_1\right) = (\theta_1 S)\, e^{b_4 t} \tag{4.98}$$

$$\int \frac{d}{dt}\left(V_1 e^{b_4 t}\right) dt = \theta_1 \int S e^{b_4 t} dt \tag{4.99}$$

Let $I = \int S e^{b_4 t} dt$. Integrating by parts, we have

$$u = S \implies du = S' dt, \quad \text{and} \quad dv = e^{b_4 t} \implies v = \frac{e^{b_4 t}}{b_4}$$

So,

$$I = \frac{S e^{b_4 t}}{b_4} - \frac{1}{b_4}\int S' e^{b_4 t} dt \tag{4.100}$$

$$\implies V_1 e^{b_4 t} = \theta_1 \left[\frac{S e^{b_4 t}}{b_4} - \frac{1}{b_4}\int S' e^{b_4 t} dt\right] \tag{4.101}$$

$$= \frac{\theta_1 S}{b_4} e^{b_4 t} - \frac{\theta_1}{b_4}\int S' e^{b_4 t} dt \tag{4.102}$$

Therefore,

$$V_1 = \frac{\theta_1 S}{b_4} - \frac{\theta_1}{b_4 e^{b_4 t}}\int S' e^{b_4 t} dt \tag{4.103}$$

From Equation (4.103), $V_1 \to \frac{\theta_1 S}{b_4}$ as $t \to \infty$.

Similarly, we can deduce from Equation (4.95) that, $V_2 \to \frac{\theta_2 S}{b_7}$ as $t \to \infty$.

Furthermore, from Equation (4.95), we have,

$$\frac{dS}{dt} = \alpha + \omega_1 V_1 + \omega_2 V_2 - (\theta_1 + \theta_2 + \mu) S \tag{4.104}$$

Since $V_1 \to \frac{\theta_1 S}{b_4}$ and $V_2 \to \frac{\theta_2 S}{b_7}$, Equation (4.104) is rewritten as

$$\begin{aligned}\frac{dS}{dt} =& \alpha + \frac{\omega_1\theta_1 S}{b_4} + \frac{\omega_2\theta_2 S}{b_7} - (\theta_1 + \theta_2 + \mu)S \qquad (4.105)\\ =& \alpha + \left(\frac{\omega_1\theta_1}{b_4} + \frac{\omega_2\theta_2}{b_7} - (\theta_1 + \theta_2 + \mu)\right) S\\ \frac{dS}{dt} =& \alpha - \left(\frac{\mu\chi}{b_4 b_7}\right) S \qquad (4.106)\end{aligned}$$

Therefore, Equation (4.106) can be put in standard form as

$$\frac{dS}{dt} + \frac{\mu\chi}{b_4 b_7} S = \alpha \qquad (4.107)$$

The integrating factor is given as $I.F. = e^{\int \frac{\mu\chi}{b_4 b_7} dt} = e^{\frac{\mu\chi}{b_4 b_7} t}$.

Multiplying Equation (4.107) through by the integrating factor gives

$$e^{\frac{\mu\chi}{b_4 b_7} t}\left(\frac{dS}{dt} + \frac{\mu\chi}{b_4 b_7} S\right) = \alpha e^{\frac{\mu\chi}{b_4 b_7} t} \qquad (4.108)$$

$$\int \frac{d}{dt}\left(S e^{\frac{\mu\chi}{b_4 b_7} t}\right) dt = \int \alpha e^{\frac{\mu\chi}{b_4 b_7} t} dt \qquad (4.109)$$

$$S e^{\frac{\mu\chi}{b_4 b_7} t} = \frac{\alpha b_4 b_7}{\mu\chi} e^{\frac{\mu\chi}{b_4 b_7} t} + c \qquad (4.110)$$

where c is the constant of integration. Therefore,

$$S = \frac{\alpha b_4 b_7}{\mu\chi} + C e^{-\frac{\mu\chi}{b_4 b_7} t} \qquad (4.111)$$

From Equation (4.111), $S \to \frac{\alpha b_4 b_7}{\mu\chi}$ as $t \to \infty$; and this implies the global convergence of Equation (4.95) in Ω.

C2: $G(X, Y)$ is given as

$$G(X,Y) = \begin{bmatrix} \lambda_1(1-\tau_1)S + (1-\epsilon_1)\lambda_1 V_1 - a_2 C_1 \\ \lambda_2(1-\tau_2)S + (1-\epsilon_2)\lambda_2 V_2 - a_4 C_2 \\ \sigma_1 C_1 + \lambda_1\tau_1 S + \lambda_1 V_2 - a_1 I_1 \\ \sigma_2 C_2 + \lambda_2\tau_2 S + \lambda_2 V_1 - a_3 I_2 \end{bmatrix} \qquad (4.112)$$

where $\lambda_1,\ \lambda_2$ are the forces of infection defined in Equations (4.2) and (4.3).

The Jacobian matrix of $G(X,Y)$, $J\left[G(X^*,0)\right]$ is given as

$$\begin{pmatrix} \frac{\beta\eta\left[(1-\epsilon_1)V_1^*+(1-\tau_1)S^*\right]-a_2N^*}{N^*} & 0 & \frac{\beta\left[(1-\epsilon_1)V_1^*+(1-\tau_1)S^*\right]}{N^*} & 0 \\ 0 & \frac{\beta\eta\left[(1-\epsilon_2)V_2^*+(1-\tau_2)S^*\right]-a_4N^*}{N^*} & 0 & \frac{\beta\left[(1-\epsilon_2)V_2^*+(1-\tau_2)S^*\right]}{N^*} \\ \frac{\beta\eta\left(\tau_1S^*+V_2^*\right)+\sigma_1N^*}{N^*} & 0 & \frac{\beta\left(\tau_1S^*+V_2^*\right)-a_1N^*}{N^*} & 0 \\ 0 & \frac{\beta\eta\left(\tau_2S^*+V_1^*\right)+\sigma_2N^*}{N^*} & 0 & \frac{\beta\left(\tau_2S^*+V_1^*\right)-a_3N^*}{N^*} \end{pmatrix} \tag{4.113}$$

By the condition in C2 with Equations (4.112) and (4.113), $\hat{G}(X,Y)$ is given by

$$\begin{pmatrix} \frac{\beta(\eta C_1+I_1)\left[(1-\epsilon_1)V_1^*+(1-\tau_1)S^*\right]}{N^*}\left(1-\frac{(1-\epsilon_1)V_1+(1-\tau_1)S}{N}\frac{N^*}{(1-\epsilon_1)V_1^*+(1-\tau_1)S^*}\right) \\ \frac{\beta(\eta C_2+I_2)\left[(1-\epsilon_2)V_2^*+(1-\tau_2)S^*\right]}{N^*}\left(1-\frac{(1-\epsilon_2)V_2+(1-\tau_2)S}{N}\frac{N^*}{(1-\epsilon_2)V_2^*+(1-\tau_2)S^*}\right) \\ \frac{\beta(\eta C_1+I_1)\left(\tau_1S^*+V_2^*\right)}{N^*}\left(1-\frac{(\tau_1S+V_2)}{N}\frac{N^*}{(\tau_1S^*+V_2^*)}\right) \\ \frac{\beta(\eta C_2+I_2)\left(\tau_2S^*+V_1^*\right)}{N^*}\left(1-\frac{(\tau_2S+V_1)}{N}\frac{N^*}{(\tau_2S^*+V_1^*)}\right) \end{pmatrix} \tag{4.114}$$

Since

$$S^*=\frac{\alpha b_4b_7}{\mu\chi},\quad V_1^*=\frac{\alpha\theta_1b_7}{\mu\chi},\quad V_2^*=\frac{\alpha\theta_2b_4}{\mu\chi}\quad\text{and}\quad N^*=\frac{\alpha}{\mu}$$

we have that $S\leq S^*,\ V_1\leq V_1^*$ and $V_2\leq V_2^*$. Thus, it follows that $S\leq N,\ V_1\leq N$ and $V_2\leq N$ in Ω. Therefore, if the total population is at equilibrium level, we have $\left(1-\frac{(1-\epsilon_1)V_1+(1-\tau_1)S}{N}\frac{N^*}{(1-\epsilon_1)V_1^*+(1-\tau_1)S^*}\right)>0$, $\left(1-\frac{(1-\epsilon_2)V_2+(1-\tau_2)S}{N}\frac{N^*}{(1-\epsilon_2)V_2^*+(1-\tau_2)S^*}\right)>0$, $\left(1-\frac{(\tau_1S+V_2)}{N}\frac{N^*}{(\tau_1S^*+V_2^*)}\right)>0$ and $\left(1-\frac{(\tau_2S+V_1)}{N}\frac{N^*}{(\tau_2S^*+V_1^*)}\right)>0$; thus, $\hat{G}(X,Y)\geq 0$. Hence it follows from Theorem (4.5.2) that the DFE, $E_0=(X^*,0)$ is globally asymptotically stable.

4.6 Sensitivity Analysis

Sensitivity analysis helps in discovering the parameters that have a high impact on the basic reproduction number, thereby providing insight into the parameters to be considered for control strategies. Following Abidemi, Aziz and Ahmad (2020), the standardized forward sensitivity index is employed in carrying out the sensitivity

analysis of model (4.13). The standardized forward sensitivity index of $\mathcal{R}_0$ with respect to a parameter ψ is the proportion of the relative change in ψ. Therefore, Table 4.4 provides all model parameters that are partially differentiable with respect to $\mathcal{R}_{01}$ and $\mathcal{R}_{02}$, their values, and sensitivity indices with respect to each strain.

Table 4.4 Sensitivity Indices (SI) of Each Model Parameter on $\mathcal{R}_{01}$ and $\mathcal{R}_{02}$

Parameters	Values	SI for Strain 1	SI for Strain 2
μ	0.000043	$+1.93 \times 10^{-3}$	-6.28×10^{-3}
ω_1	0.000547	$+0.1362$	-0.4413
ω_2	0.00068	-0.1376	$+0.4507$
β	0.88	$+1$	$+1$
γ_{C1}	0.143	-1.14×10^{-2}	0
γ_{C2}	0.3	0	-0.1775
γ_{I1}	0.125	-0.2200	0
γ_{I2}	0.1	0	-0.1510
η	0.75	$+0.0232$	$+0.1998$
δ	0.43	-0.7567	-0.6492
ϵ_1	0.85	-0.2816	0
ϵ_2	0.90	0	-2.9077
σ_1	0.5	-1.18×10^{-2}	0
σ_2	0.25	0	-2.23×10^{-2}
τ_1	0.3	-1.75×10^{-4}	0
τ_2	0.5	0	-3.52×10^{-4}
θ_1	0.1	-0.1469	$+0.4760$
θ_2	0.5	$+0.1463$	-0.4791

4.6.1 Description of the Sensitivity Indices on $\mathcal{R}_{01}$ and $\mathcal{R}_{02}$

The most sensitive parameter is the transmission probability, β for both strain 1 and 2. Generally, the sensitivity indices for the strain 1 show that, when the parameters μ, ω_1, β, η and θ_2 are increased, keeping constant all other parameters, the value of $\mathcal{R}_{01}$ is increased thereby increasing the endemicity of the disease as they have positive indices. On the other hand, the parameters ω_2, γ_{C1}, γ_{I1}, δ, ϵ_1, σ_1, τ_1 and θ_1 decrease the value of $\mathcal{R}_{01}$ when increased, with all other parameters held constant, resulting in a decrease in the endemicity of the disease as they have negative indices.

Similarly, for strain 2, when the parameters ω_2, β, η and θ_1 are increased, keeping constant all other parameters, the value of $\mathcal{R}_{02}$ is increased resulting in an increase in the endemicity of the disease as they have positive indices. The parameters μ,

ω_1, γ_{C2}, γ_{I2}, δ, ϵ_2, σ_2, τ_2 and θ_2, on the other hand, decrease the value of $\mathcal{R}_{02}$ when increased, with all other parameters held constant, thereby decreasing the endemicity of the disease as they have negative indices.

For example, increasing the vaccine waning rate of strain 1, ω_1 by 10% will lead to a 1.362% increase on $\mathcal{R}_{01}$ while increasing the recovery rate of carriers of strain 2, γ_{C2} by 10% will result in a reduction of 1.775% on $\mathcal{R}_{02}$.

4.7 Numerical Simulations of the Model

The numerical solutions of the model (4.13) is obtained by using MATLAB ODE45 Algorithm for solving non-stiff system of ordinary differential equations with initial conditions and parameter values as stated in Section (4.3). The graphs of each model compartment against time are presented with time ranging from 0 to 30 days.

4.7.1 Susceptible Population

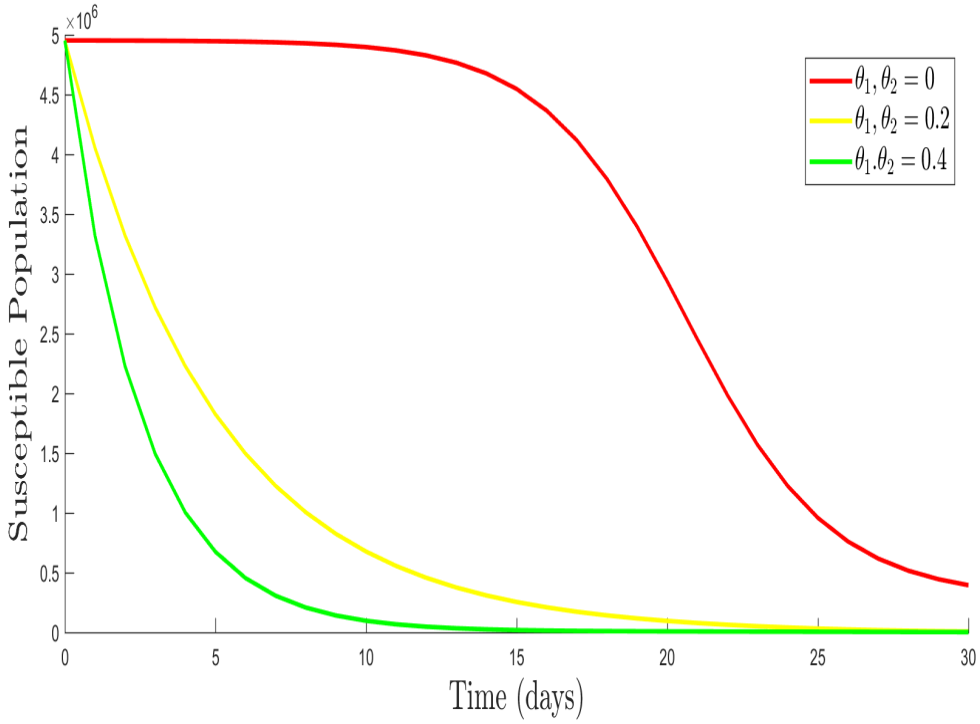
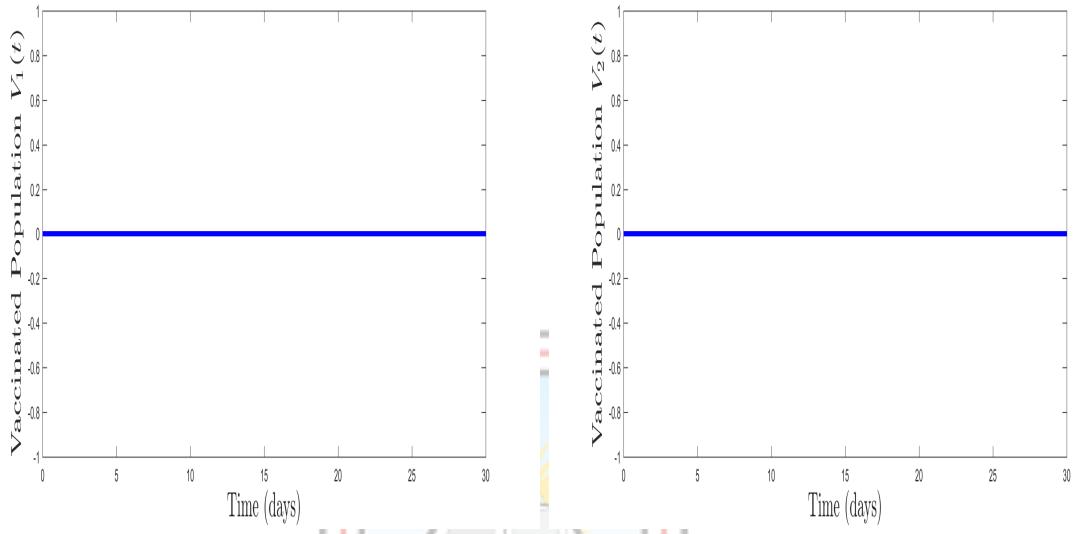


Figure 4.2 Evolution of Susceptible Population varying θ_1, θ_2

Figure 4.2 indicates that the susceptible population decreases after some days due to the forces of infection for strain 1 and 2. It can be observed from this compartment

that, an increase in the vaccine uptake rates for both strains, θ_1, θ_2 leads to a rapid decrease in the population. Hence, awareness of the affected population to get people vaccinated will decrease the susceptible.

4.7.2 Vaccination Populations of Strain 1 and 2



(a) Evolution of $V_1(t)$ **(b) Evolution of $V_2(t)$**

Figure 4.3 Vaccinated Populations of Strain 1 and 2 against Time

Figure 4.3 shows the Vaccinated Population of Strain 1 and 2 at vaccine uptake rates of $\theta_1, \theta_2 = 0$. This presents a steady state solution in the two compartments.

4.7.3 Carrier Population of Strain 1

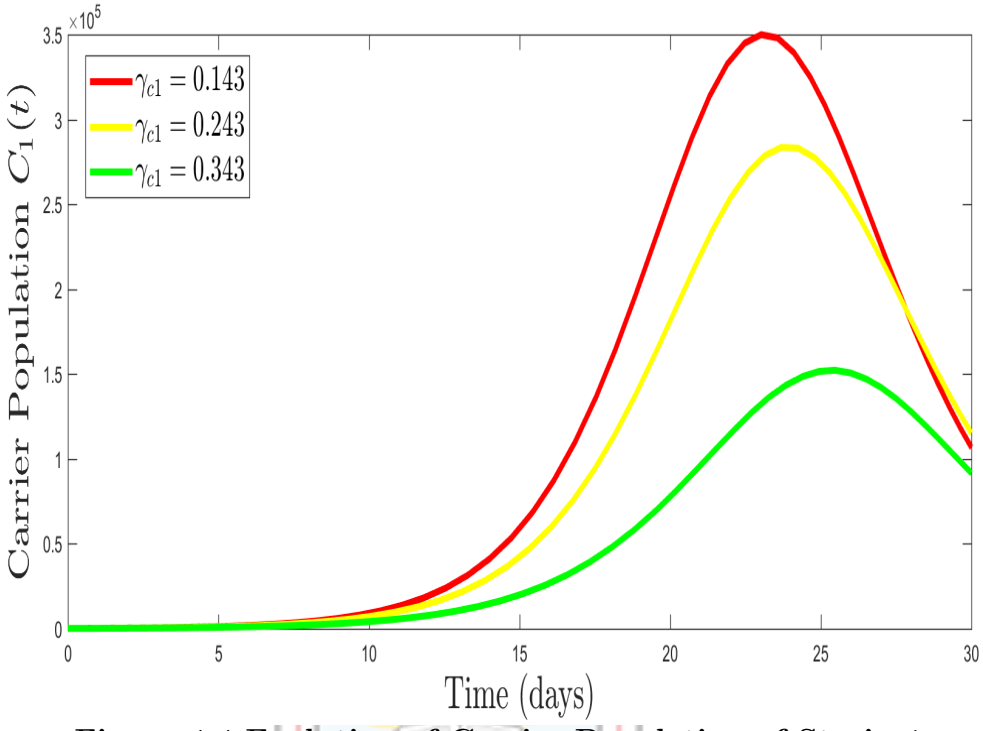


Figure 4.4 Evolution of Carrier Population of Strain 1

In Figure 4.4, the population increased at a faster rate within a duration of 15 days due to the inflow from the susceptible and vaccinated compartments. Thereafter, an equilibrium point is reached and the population begin to decrease due to the progression of the carriers to the infected population since the average incubation period of the strain 1 infection is 2 days. The decrease can also be due to the recovery of the carriers from the infection since an increase in the recovery rate of carriers of strain 1, γ_{C1} leads to a decrease in the population.

4.7.4 Carrier Population of Strain 2

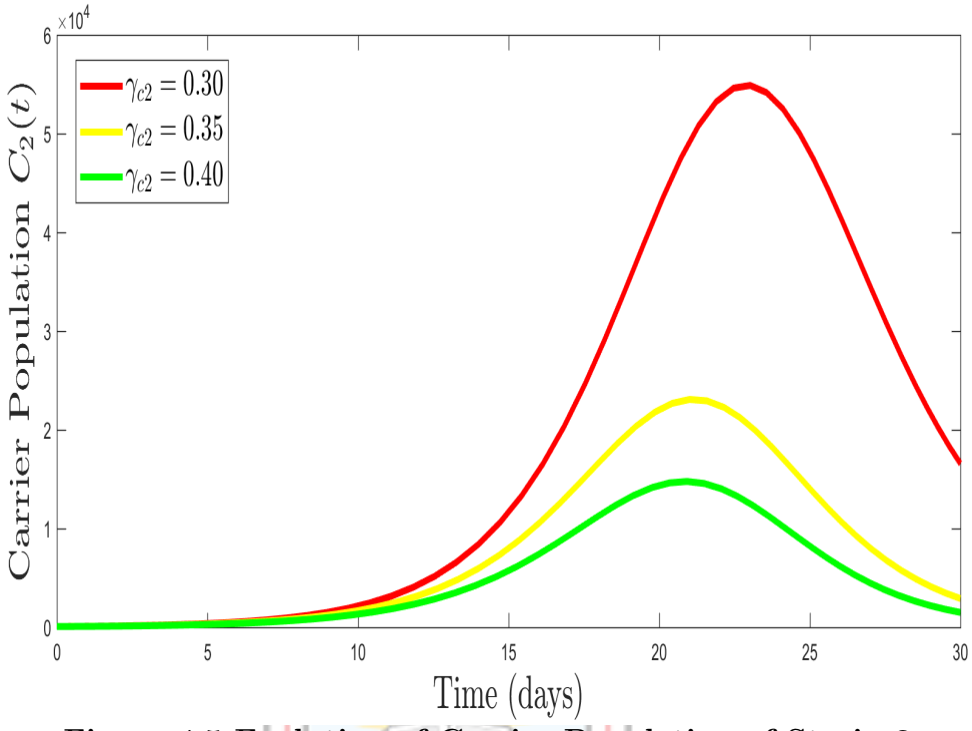


Figure 4.5 Evolution of Carrier Population of Strain 2

Figure 4.5 also shows a rise in the population as a result of movement from the susceptible and vaccinated compartments. The population achieves stationarity momentarily and begin to decrease as the carriers progress to the infected population since the average incubation period of the strain 2 infection is 4 days. The population also decrease due to recovery of the carriers. It can be seen that an increase in the recovery rate of carriers of strain 2, γ_{C2} reduces the population drastically.

4.7.5 Infected Population of Strain 1

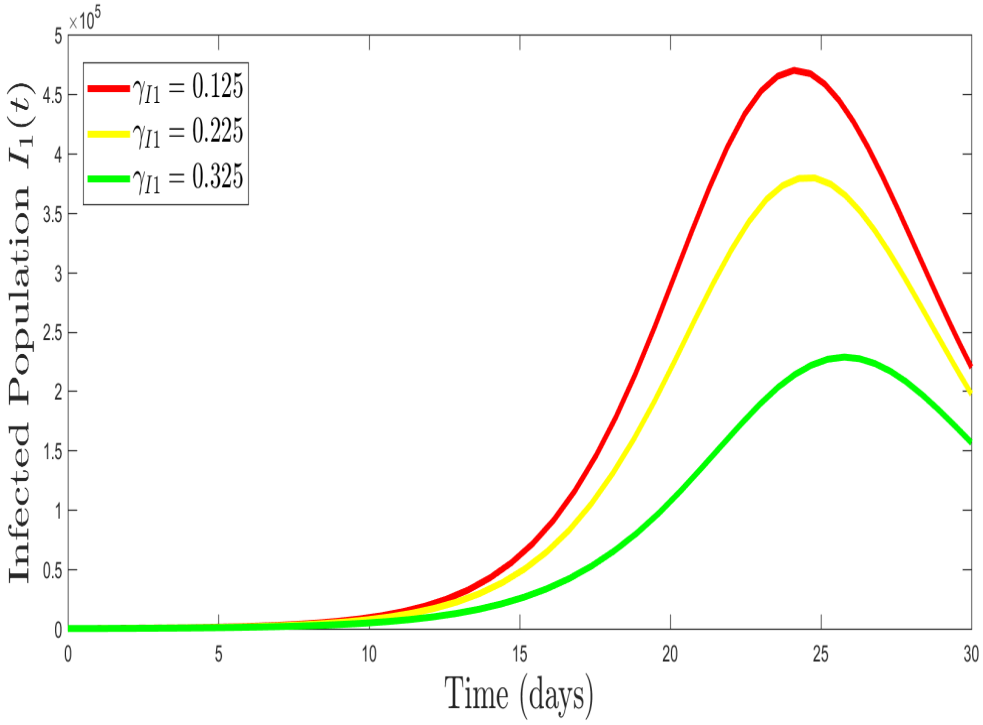


Figure 4.6 Evolution of Infected Population of Strain 1

Figure 4.6 indicates an increase in the population as a result of movement from the susceptible, carrier and vaccinated population with immunity for strain 2. However, the population decreases after this period. This decrease can be ascribed to the availability of treatment for the infected compartment since they are symptomatic and can easily be diagnosed. They also decease due to recovery from the infection and disease-induced death. It can be observed that an increase in the recovery rate of infected with strain 1, γ_{I1} decreases the population.

4.7.6 Infected Population of Strain 2

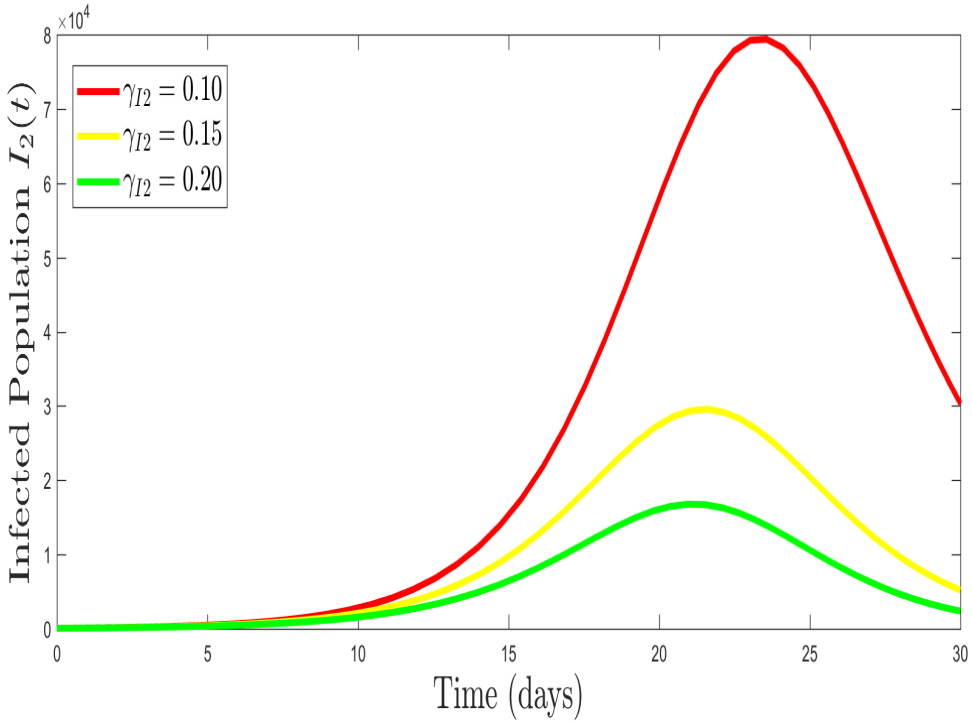


Figure 4.7 Evolution of Infected Population of Strain 2

The population in Figure 4.7 increases due to an inflow from the susceptible, carrier and vaccinated population with immunity for strain 1. The population achieves stationarity momentarily and begins to decrease due to recovery from the infection and disease-induced death. This decrease can also be attributed to the population receiving urgent treatment since the disease is considered as a medical emergency. Also, an increase in the recovery rate of infected with strain 2, γ_{I2} decrease the population rapidly.

4.7.7 Fully Recovered Population from both Strains

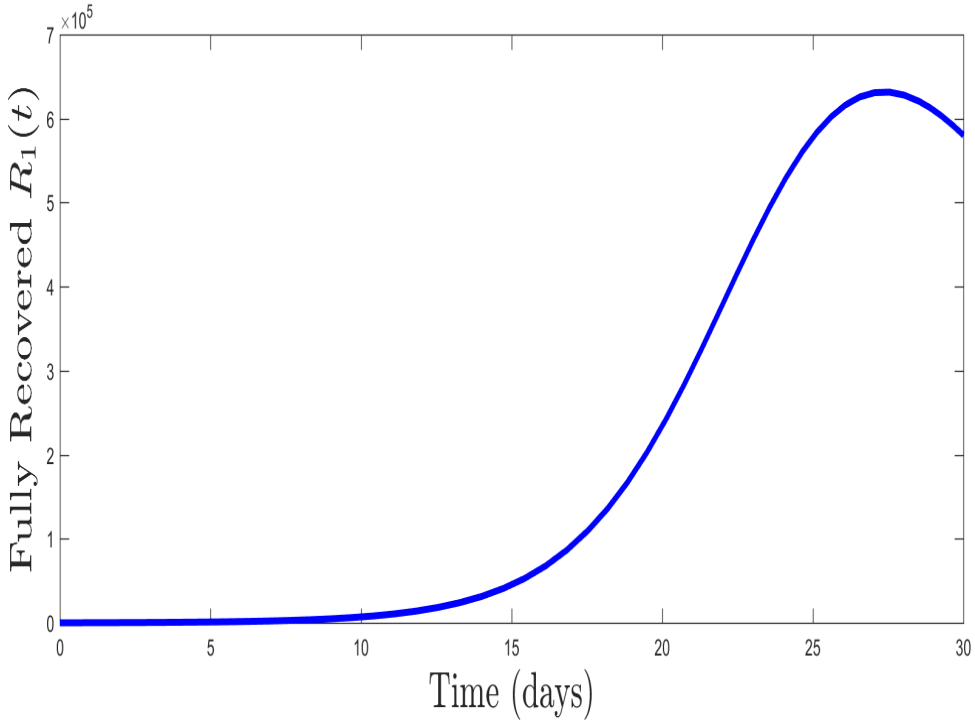


Figure 4.8 Evolution of Fully Recovered Population from both Strains

In Figure 4.8, the fully recovered population maintained a stable state for the first ten (10) days then began to increase afterwards. This is because at the onset of the disease, there was no recovered individual so as they get infected and recover, the population increases. Thereafter, we see a little decrease in the population which can be due to those who recover from the acute phase of the disease only to find that they are experiencing some difficulties/complications.

4.7.8 Recovered with Complications from both Strains

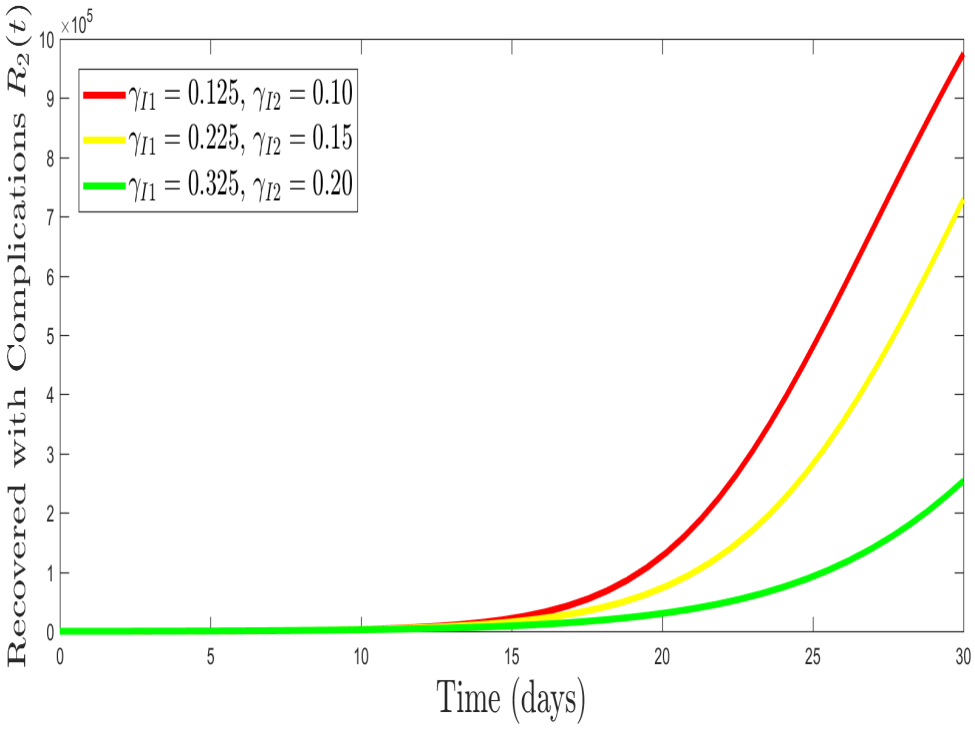
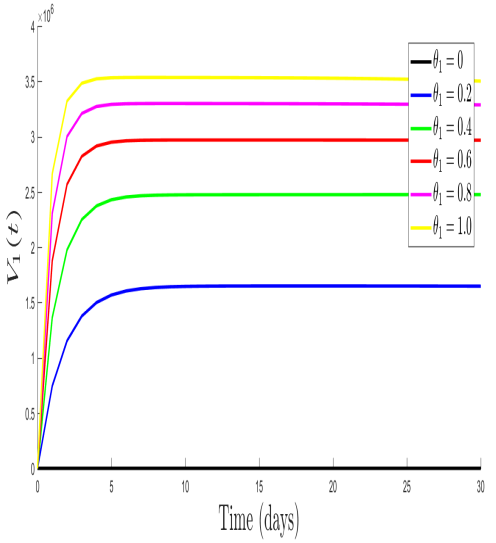


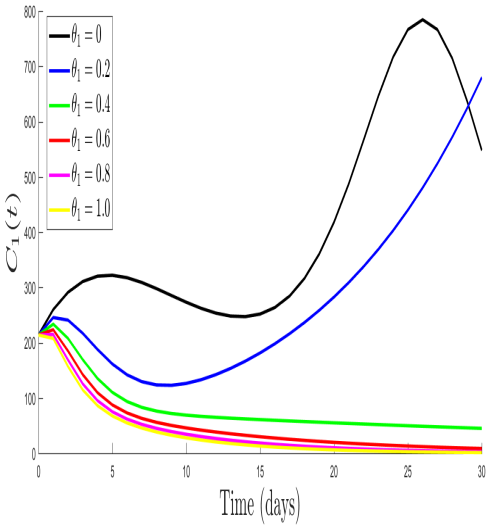
Figure 4.9 Evolution of Recovered with Complications from both Strains

The recovered with complications population in Figure 4.9 also shows a stable state for the first twelve (12) days and a sharp increase as time goes on. It can be observed that an increase in the recovery rates of infected with strain 1 and 2, γ_{I1}, γ_{I2} leads to a decrease in the population.

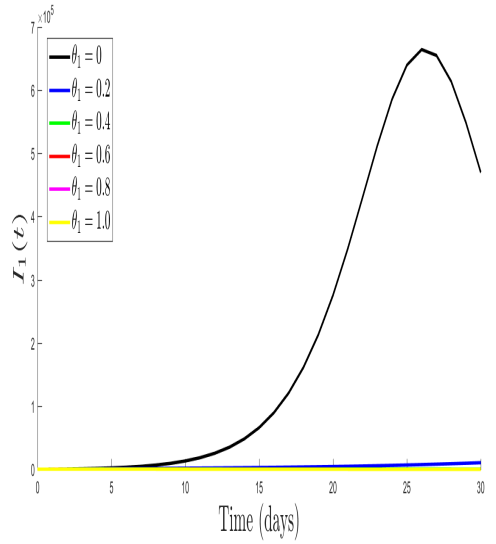
4.7.9 Effects of Varying the Vaccine Uptake Rates θ_1 and θ_2



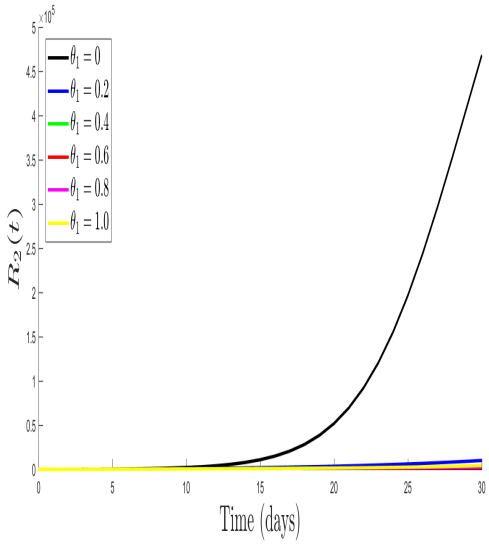
(a) Effects of Varying θ_1 on $V_1(t)$



(b) Effects of Varying θ_1 on $C_1(t)$



(c) Effects of Varying θ_1 on $I_1(t)$

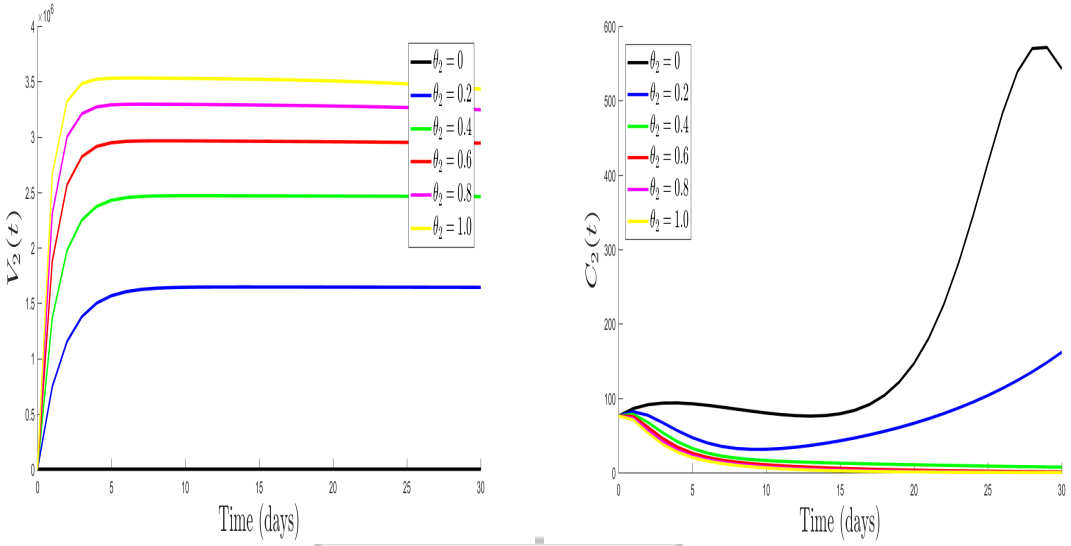


(d) Effects of Varying θ_1 on $R_2(t)$

Figure 4.10 Effects of Varying θ_1 on $V_1(t)$, $C_1(t)$, $I_1(t)$ and $R_2(t)$ Compartments

Varying θ_1 on the Vaccinated Population with immunity for Strain 1 shows a sharp increase in the population within the first 3 days. Morever, a stable state is achieved in the next days as the population becomes immune to the specific strain. On the other hand, varying θ_1 on the Carrier Population of Strain 1 displays a decrease which indicates that getting more people vaccinated will reduce the carriers. Varying θ_1 on the Infected Population of Strain 1 shows a rapid decrease in the population which reveals that the more people take the vaccine, the less the infection. The variation of θ_1 on the Recovered Population with Complications also shows a drastic decrease in

the population. This can be attributed to the immune response of the human body to recognize and fight the bacteria after taking the vaccine.



(a) Effects of Varying θ_2 on $V_2(t)$ **(b) Effects of Varying θ_2 on $C_2(t)$**

(c) Effects of Varying θ_2 on $I_2(t)$ **(d) Effects of Varying θ_2 on $R_2(t)$**

Figure 4.11 Effects of Varying θ_2 on $V_2(t)$, $C_2(t)$, $I_2(t)$ and $R_2(t)$ Compartments

The variation of θ_2 on the Vaccinated Population with immunity for Strain 2 displays a surge in the population within the first three (3) days and achieves stability as the population becomes immune to the specified strain. Varying θ_2 on the Carrier Population of Strain 2 decreases the population as the vaccine uptake rate increases. As θ_2 is varied on the Infected Population of Strain 2, a sharp decrease is also seen which shows the impact of vaccination in curtailing the infection. Varying θ_2 on the Recovered Population with Complications shows a rapid decrease in the population

which means the more we get people vaccinated, the lesser the complications after acute infection.

CHAPTER 5

OPTIMAL CONTROL FORMULATION AND ANALYSIS

5.1 Model Description and Formulation

This section discusses the formulation of the vaccination model (4.13) as optimal control problem. First, the forces of infection, λ_i (for $i = 1, 2$) given in (4.2) and (4.3), are modified as controlled forces of infection as:

$$\begin{aligned} \lambda_1^c &= \frac{(1 - u_P(t))\beta(\eta C_1 + I_1)}{N} \\ \lambda_2^c &= \frac{(1 - u_P(t))\beta(\eta C_2 + I_2)}{N} \end{aligned} \tag{5.1}$$

where the control variable $u_P(t)$ accounts for the effective human personal protection (such as wearing face masks). Also, the vaccination rates θ_1 and θ_2 are considered as time-dependent functions $u_{V1}(t)$ and $u_{V2}(t)$ respectively. Furthermore, two control variables $u_{T1}(t)$ and $u_{T2}(t)$ accounting for the treatment control of timely and delayed diagnosed infected individuals are introduced. Hence, the non-autonomous version of model (4.13) becomes

$$
\begin{aligned}
\frac{dS}{dt} &= \alpha + \omega_1 V_1 + \omega_2 V_2 - (\lambda_1^c + \lambda_2^c + u_{V1}(t) + u_{V2}(t) + \mu)S \\
\frac{dV_1}{dt} &= u_{V1}(t)S - (1-\epsilon_1)\lambda_1^c V_1 - (\lambda_2^c + \omega_1 + \mu)V_1 \\
\frac{dV_2}{dt} &= u_{V2}(t)S - (1-\epsilon_2)\lambda_2^c V_2 - (\lambda_1^c + \omega_2 + \mu)V_2 \\
\frac{dC_1}{dt} &= \lambda_1^c\left[(1-\tau_1)S + (1-\epsilon_1)V_1\right] - (\sigma_1 + \gamma_{c1}(1+u_{T1}(t)) + \mu)C_1 \\
\frac{dC_2}{dt} &= \lambda_2^c\left[(1-\tau_2)S + (1-\epsilon_2)V_2\right] - (\sigma_2 + \gamma_{c2}(1+u_{T1}(t)) + \mu)C_2 \\
\frac{dI_1}{dt} &= \sigma_1 C_1 + \lambda_1^c\left(\tau_1 S + V_2\right) - (\gamma_{I1}(1+u_{T2}(t)) + \delta + \mu)I_1 \\
\frac{dI_2}{dt} &= \sigma_2 C_2 + \lambda_2^c\left(\tau_2 S + V_1\right) - (\gamma_{I2}(1+u_{T2}(t)) + \delta + \mu)I_2 \\
\frac{dR_1}{dt} &= \gamma_{c1}(1+u_{T1}(t))C_1 + \gamma_{c2}(1+u_{T1}(t))C_2 + \rho_1\gamma_{I1}(1+u_{T2}(t))I_1 + \rho_2\gamma_{I2}(1+u_{T2}(t))I_2 - \\
&\quad (\wedge + \mu)R_1 \\
\frac{dR_2}{dt} &= (1-\rho_1)\gamma_{I1}(1+u_{T2}(t))I_1 + (1-\rho_2)\gamma_{I2}(1+u_{T2}(t))I_2 + \wedge R_1 - \mu R_2
\end{aligned}
\tag{5.2}
$$

Extended Model Assumptions

1. Every individual in the studied population uses facial or surgical masks regardless of their status.
2. The carriers are diagnosed and treatment commenced before onset of symptoms.
3. Vaccinated populations are no longer susceptible to the infection.

The goal is to minimize the objective functional given by

$$
J[\,\cdot\,] = \int_0^T \left(A_1(C_1 + I_1) + A_2(C_2 + I_2) + \frac{B_1}{2}u_P^2(t) + \frac{B_2}{2}u_{V1}^2(t) + \frac{B_3}{2}u_{V2}^2(t) + \frac{B_4}{2}u_{T1}^2(t) + \frac{B_5}{2}u_{T2}^2(t) \right) dt \tag{5.3}
$$

constrained by the system (5.2), where T is the final time of control implementation. A_1 and A_2 are the positive relative weights of the carrier and infected populations for strain 1 and 2 respectively. Similarly, B_1, B_2, B_3, B_4 and B_5 are the positive

relative weights for the regularization of the controls $u_P, u_{V1}, u_{V2}, u_{T1}$ and u_{T2} respectively while $\frac{B_i u_j^2}{2}$ represent the cost of controls u_j, for $i = 1, 2, 3, 4, 5$ and $j = P, V1, V2, T1, T2$.

The goal of formulating the objective function is to find an optimal control $(u_P^*, u_{V1}^*, u_{V2}^*, u_{T1}^*, u_{T2}^*)$ such that:

$$F(u_P^*, u_{V1}^*, u_{V2}^*, u_{T1}^*, u_{T2}^*) = \min_U F(u_P, u_{V1}, u_{V2}, u_{T1}, u_{T2})$$

where $U = \{u_i$ is Lebesgue measurable on $[0, T]$ and $u_j \in [0, 1]$ for $j = P, V1, V2, T1, T2\}$, thereby minimizing the weight of the susceptible, carrier and infected population together with the cost of implementing the controls.

5.1.1 Existence of an Optimal Control

In this section, the existence of an optimal control solution for the state system is presented. This involves validating the sufficient conditions that guarantee the existence of a solution to the optimal control problem as stated in the following theorem obtained by Fleming and Rishel (2012). The theorem is stated and proven with respect to the formulated OCP.

Theorem 5.1.1 *Consider the optimal control problem* (5.3) *subject to the state equations* (5.2) *and initial conditions* (4.14). *There exists an optimal control set* $u^* = (u_P^*, u_{V1}^*, u_{V2}^*, u_{T1}^*, u_{T2}^*)$ *with a corresponding solution set* $(S^*, V_1^*, V_2^*, C_1^*, C_2^*, I_1^*, I_2^*, R_1^*, R_2^*)$ *to the control model that minimizes* $F(u_P, u_{V1}, u_{V2}, u_{T1}, u_{T2})$ *over* U *if the following conditions are satisfied:*

C1: The set of solutions to the model equations together with the initial conditions and the corresponding control function in U is non-empty.

C2: The control set U is convex and closed.

C3: The state system can be written as a linear function of the control variables with coefficient dependent on time and state variables.

C4: The Lagrangian

$$L(S(t), V_1(t), V_2(t), C_1(t), C_2(t), I_1(t), I_2(t), R_1(t), R_2(t), u_P(t), u_{V1}(t), u_{V2}(t), u_{T1}(t), u_{T2}(t))$$

of equation (5.3) is convex on U.

C5: There exist constants $\zeta_1, \zeta_2 > 0$ and $\mathcal{V} > 1$ such that; $L(S(t), V_1(t), V_2(t), C_1(t), C_2(t), I_1(t), I_2(t), R_1(t), R_2(t), u_P(t), u_{V1}(t), u_{V2}(t), u_{T1}(t), u_{T2}(t))$ is bounded below by $\zeta_1|(u_P, u_{V1}, u_{V2}, u_{T1}, u_{T2})|^{\mathcal{V}} - \zeta_2$

Proof: In order to verify C1, we use the result obtained by **?**. The model is rewritten in the form;

$$\frac{dZ}{dt} = AZ + F(Z) \tag{5.4}$$

where A=

$$\begin{pmatrix}
-d_6 & \omega_1 & \omega_2 & 0 & 0 & 0 & 0 & 0 & 0 \\
u_{V1} & -b_4 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
u_{V2} & 0 & -b_7 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & -[d_7 + \gamma_{c1} d_1] & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & -[d_8 + \gamma_{c2} d_1] & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & \sigma_1 & 0 & -[\gamma_{I1} d_2 + d_5] & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & \sigma_2 & 0 & -[\gamma_{I2} d_2 + d_5] & 0 & 0 \\
0 & 0 & 0 & \gamma_{c1} d_1 & \gamma_{c2} d_1 & \rho_1 \gamma_{I1} d_2 & \rho_2 \gamma_{I2} d_2 & -(\wedge + \mu) & 0 \\
0 & 0 & 0 & 0 & 0 & \gamma_{I1} d_2 d_3 & \gamma_{I2} d_2 d_4 & \wedge & -\mu
\end{pmatrix}$$

$$F(Z) = \begin{pmatrix} \alpha - (\lambda_1^c + \lambda_2^c)S \\ -[(1-\epsilon_1)\lambda_1^c + \lambda_2^c]V_1 \\ -[(1-\epsilon_2)\lambda_2^c + \lambda_1^c]V_2 \\ \lambda_1^c[(1-\tau_1)S + (1-\epsilon_1)V_1] \\ \lambda_2^c[(1-\tau_2)S + (1-\epsilon_2)V_2] \\ \lambda_1^c(\tau_1 S + V_2) \\ \lambda_2^c(\tau_2 S + V_1) \\ 0 \\ 0 \end{pmatrix}$$

and $Z = (S\ V_1\ V_2\ C_1\ C_2\ I_1\ I_2\ R_1\ R_2)^T$. We note that

$$d_1 = 1 + u_{T1}, \qquad d_2 = 1 + u_{T2}, \qquad d_3 = 1 - \rho_1 \qquad d_4 = 1 - \rho_2$$

$$d_5 = \delta + \mu, \qquad d_6 = u_{V1} + u_{V2} + \mu \qquad d_7 = \sigma_1 + \mu \qquad d_8 = \sigma_2 + \mu$$

It is observed that the system (5.4) is nonlinear with bounded coefficients. Thus setting;

$$G(Z) = A(Z) + F(Z) \tag{5.5}$$

then F(Z) in Equation (5.5) satisfies;

$$\begin{aligned} |F(Z_a) - F(Z_b)| \leq & (p_1|S_a(t) - S_b(t)| + p_2|V_{1a}(t) - V_{1b}(t)| + p_3|V_{2a}(t) - V_{2b}(t)| + \\ & p_4|C_{1a}(t) - C_{1b}(t)| + p_5|C_{2a}(t) - C_{2b}(t)| + p_6|I_{1a}(t) - I_{1b}(t)| + \\ & p_7|I_{2a}(t) - I_{2b}(t)| + p_8|R_{1a}(t) - R_{1b}(t)| + p_9|R_{2a}(t) - R_{2b}(t)| \\ \leq & p(|S_a(t) - S_b(t)| + |V_{1a}(t) - V_{1b}(t)| + |V_{2a}(t) - V_{2b}(t)| + \\ & |C_{1a}(t) - C_{1b}(t)| + |C_{2a}(t) - C_{2b}(t)| + |I_{1a}(t) - I_{1b}(t)| + \\ & |I_{2a}(t) - I_{2b}(t)| + |R_{1a}(t) - R_{1b}(t)| + |R_{2a}(t) - R_{2b}(t)|) \end{aligned} \tag{5.6}$$

This implies that,

$$|G(Z_a) - G(Z_b)| \leq p|Z_a - Z_b| \tag{5.7}$$

where, p $= \max\{p_1, p_2, p_3, p_4, p_5, p_6, p_7, p_8, p_9\} < \infty$ is a positive constant independent of the state variables and $Z = max\{Z_a, Z_b\}$.
Thus, it follows from (5.7) that the function G(Z) is uniformly Lipschitz continuous. From the boundedness of the control variables, it follows that a solution to the model exists. Hence, C1 holds.

The boundedness of the control set U follows directly from the definition of U and since every bounded set is closed, then U is closed. Similarly, the set U is convex since $\{U = u_P, u_{V1}, u_{V2}, u_{T1}, u_{T2} \in [0, 1]\}$, then any line joining any two points within the set will lie entirely within the set (that is the set is connected). Hence C2 holds.

From the system of equations (5.2), it is observed that the state equations depend on the controls $u_P, u_{V1}, u_{V2}, u_{T1}$ *and* u_{T2} linearly, thus C3 is verified.

Furthermore, since the Lagrangian is quadratic in the controls and every quadratic function is convex, then it follows directly that the Lagrangian function of Equation (5.3) is convex. Thus, C4 is verified.

Finally, C5 is verified as follows: The Lagrangian function is defined as;

$$\begin{aligned}
\mathcal{L} =& A_1(C_1 + I_1) + A_2(C_2 + I_2) + \frac{1}{2}\left(B_1u_P^2 + B_2u_{V1}^2 + B_3u_{V2}^2 + B_4u_{T1}^2 + B_5u_{T2}^2\right) \\
\geq& \frac{1}{2}\left(B_1u_P^2 + B_2u_{V1}^2 + B_3u_{V2}^2 + B_4u_{T1}^2 + B_5u_{T2}^2\right) \text{ since } A_1 > 0, A_2 > 0, B_i > 0, i = 1, 2, 3, 4, 5 \\
>& \frac{1}{2}\left(B_1u_P^2 + B_2u_{V1}^2 + B_3u_{V2}^2 + B_4u_{T1}^2 + B_5u_{T2}^2\right) - B_1 \\
\geq& min\left(\frac{1}{2}B_1, \frac{1}{2}B_2, \frac{1}{2}B_3, \frac{1}{2}B_4, \frac{1}{2}B_5\right)\left(u_P^2 + u_{V1}^2 + u_{V2}^2 + u_{T1}^2 + u_{T2}^2\right) - B_1 \\
\geq& B||u_P, u_{V1}, u_{V2}, u_{T1}, u_{T2}||^2 - B_1, \text{where } B = min\left(\frac{1}{2}B_1, \frac{1}{2}B_2, \frac{1}{2}B_3, \frac{1}{2}B_4, \frac{1}{2}B_5\right)
\end{aligned} \tag{5.8}$$

Hence, C5 is satisfied. We therefore conclude that there exists an optimal control $u^* = (u_P^*, u_{V1}^*, u_{V2}^*, u_{T1}^*, u_{T2}^*)$ that minimizes the objective functional F$(u_P, u_{V1}, u_{V2}, u_{T1}, u_{T2})$.

5.1.2 Necessary Condition of the Control

The principal technique for the solution of an optimal control problem is to solve a set of necessary conditions that an OCP and it's corresponding state(s) must satisfy. This necessary condition was developed by Pontryagin and his co-workers in Moscow in the 1950's. Pontryagin introduced the idea of "adjoint" functions to append the state system to the objective functional. This necessary condition, otherwise referred to as optimality condition, can be generated from the Hamiltonian function, $\mathcal{H}$, which is defined, as follows:

$$\mathcal{H} = f(t; x(t); u(t)) + \sum_{j=1}^{n} \lambda_j(t) g_j(t; x(t); u(t))$$

where $g_j(t; x(t); u(t))$ are the state equations.

The Pontryagin's Maximum Principle (PMP) converts the objective functional in Equation (5.3) and the constraints in Equation (5.2) into a problem of point wise minimization of a Hamiltonian, $\mathcal{H}$ with respect to $u_P,\ u_{V1},\ u_{V2},\ u_{T1},\ and\ u_{T2}$. The Hamiltonian, $\mathcal{H}$ is defined as

$$\mathcal{H} = \mathcal{L}(S(t), V_1(t), V_2(t), C_1(t), C_2(t), I_1(t), I_2(t), R_1(t), R_2(t)) + \sum_{i=1}^{9} \lambda_i^T(t) g_i(t, x(t), u(t)) \tag{5.9}$$

where g_i are the right-hand side of the nine(9) state equations in (5.2), λ_i are the co-state or adjoint variables and $\lambda_i(T) = 0, for\ i = \{S(t), V_1(t), V_2(t), C_1(t), C_2(t), I_1(t), I_2(t), R_1(t), R_2(t)\}$. Hence,

$$\begin{aligned}\mathcal{H} =&A_1(C_1+I_1)+A_2(C_2+I_2)+\frac{1}{2}(B_1u_P^2+B_2u_{V1}^2+B_3u_{V2}^2+B_4u_{T1}^2+B_5u_{T2}^2)+\lambda_S\Big[\alpha+\omega_1V_1\\&+\omega_2V_2-(\lambda_1^c+\lambda_2^c+u_{V1}+u_{V2}+\mu)S\Big]+\lambda_{V1}\Big[u_{V1}S-(1-\epsilon_1)\lambda_1^cV_1-(\lambda_2^c+\omega_1+\mu)V_1\Big]+\\&\lambda_{V2}\Big[u_{V2}S-(1-\epsilon_2)\lambda_2^cV_2-(\lambda_1^c+\omega_2+\mu)V_2\Big]+\lambda_{C1}\Big[\lambda_1^c\left[(1-\tau_1)S+(1-\epsilon_1)V_1\right]-\\&(\sigma_1+\gamma_{c1}(1+u_{T1})+\mu)C_1\Big]+\lambda_{C2}\Big[\lambda_2^c[(1-\tau_2)S+(1-\epsilon_2)V_2]-(\sigma_2+\gamma_{c2}(1+u_{T1})+\mu)C_2\Big]\\&+\lambda_{I1}\Big[\sigma_1C_1+\lambda_1^c\left(\tau_1S+V_2\right)-(\gamma_{I1}(1+u_{T2})+\delta+\mu)I_1\Big]+\lambda_{I2}\Big[\sigma_2C_2+\lambda_2^c\left(\tau_2S+V_1\right)-\\&(\gamma_{I2}(1+u_{T2})+\delta+\mu)I_2\Big]+\lambda_{R1}\Big[\gamma_{c1}(1+u_{T1})C_1+\gamma_{c2}(1+u_{T1})C_2+\rho_1\gamma_{I1}(1+u_{T2})I_1+\\&\rho_2\gamma_{I2}(1+u_{T2})I_2-(\wedge+\mu)R_1\Big]+\lambda_{R2}\Big[(1-\rho_1)\gamma_{I1}(1+u_{T2})I_1+(1-\rho_2)\gamma_{I2}(1+u_{T2})I_2+\\&\wedge R_1-\mu R_2\Big]\end{aligned}\tag{5.10}$$

Theorem 5.1.2 *(Pontryagin's Maximum Principle Theorem) If $u^*(t)$ and $x^*(t)$ are optimal for problem (5.3), then there exists a piecewise differentiable adjoint variable $\lambda(t)$ such that*

$$H(t;x^*(t);u(t);\lambda(t))\geq H(t;x^*(t);u^*(t);\lambda(t))$$

and for all control(s) u at each time t, where the Hamiltonian $\mathcal{H}$ is as defined in (5.10), $\lambda_i'(t)=-\frac{\partial H}{\partial x_i}$ (adjoint condition) with $\frac{\partial H}{\partial u}=0$ at $u=u^*$ (optimality condition) and $\lambda_i(T)=0$ (transversality condition).

Proof:

$$\begin{aligned}\frac{\partial\mathcal{H}}{\partial S}=&\lambda_S[-(\lambda_1^c+\lambda_2^c+u_{V1}+u_{V2}+\mu)]+\lambda_{V1}(u_{V1})+\lambda_{V2}(u_{V2})+\lambda_{C1}[\lambda_1^c(1-\tau_1)]+\\&\lambda_{C2}[\lambda_2^c(1-\tau_2)]+\lambda_{I1}(\lambda_1^c\tau_1)+\lambda_{I2}(\lambda_2^c\tau_2)\\=&-\lambda_S(\lambda_1^c+\lambda_2^c+u_{V1}+u_{V2}+\mu)+\lambda_{V1}(u_{V1})+\lambda_{V2}(u_{V2})+\lambda_{C1}(\lambda_1^c)-\lambda_{C1}(\lambda_1^c\tau_1)+\\&\lambda_{C2}(\lambda_2^c)-\lambda_{C2}(\lambda_2^c\tau_2)+\lambda_{I1}(\lambda_1^c\tau_1)+\lambda_{I2}(\lambda_2^c\tau_2)\\=&(\lambda_{V1}-\lambda_S)u_{V1}+(\lambda_{V2}-\lambda_S)u_{V2}+(\lambda_{C1}-\lambda_S)\lambda_1^c+(\lambda_{C2}-\lambda_S)\lambda_2^c+(\lambda_{I1}-\lambda_{C1})\lambda_1^c\tau_1\\&+(\lambda_{I2}-\lambda_{C2})\lambda_2^c\tau_2-\lambda_S\mu\end{aligned}\tag{5.11}$$

$$\begin{aligned}\frac{\partial \mathcal{H}}{\partial V_1} =&\lambda_S w_1 + \lambda_{V1}[-(1-\epsilon_1)\lambda_1^c - (\lambda_2^c + w_1 + \mu)] + \lambda_{C1}[\lambda_1^c(1-\epsilon_1)] + \lambda_{I2}(\lambda_2^c) \\ =&\lambda_S w_1 - \lambda_{V1}[(1-\epsilon_1)\lambda_1^c] - \lambda_{V1}(\lambda_2^c) - \lambda_{V1}(w_1) - \lambda_{V1}(\mu) + \lambda_{C1}[\lambda_1^c(1-\epsilon_1)] + \lambda_{I2}(\lambda_2^c) \\ =&(\lambda_S - \lambda_{V1})w_1 + (\lambda_{I2} - \lambda_{V1})\lambda_2^c + (\lambda_{C1} - \lambda_{V1})[\lambda_1^c(1-\epsilon_1)] - \lambda_{V1}\mu\end{aligned} \tag{5.12}$$

$$\begin{aligned}\frac{\partial \mathcal{H}}{\partial V_2} =&\lambda_S w_2 + \lambda_{V2}[-(1-\epsilon_2)\lambda_2^c - (\lambda_1^c + w_2 + \mu)] + \lambda_{C2}[\lambda_2^c(1-\epsilon_2)] + \lambda_{I1}(\lambda_1^c) \\ =&\lambda_S w_2 - \lambda_{V2}[(1-\epsilon_2)\lambda_2^c] - \lambda_{V2}(\lambda_1^c) - \lambda_{V2}(w_2) - \lambda_{V2}(\mu) + \lambda_{C2}[\lambda_2^c(1-\epsilon_2)] + \lambda_{I1}(\lambda_1^c) \\ =&(\lambda_S - \lambda_{V2})w_2 + (\lambda_{I1} - \lambda_{V2})\lambda_1^c + (\lambda_{C2} - \lambda_{V2})[\lambda_2^c(1-\epsilon_2)] - \lambda_{V2}\mu\end{aligned} \tag{5.13}$$

$$
\begin{aligned}
\frac{\partial \mathcal{H}}{\partial C_1} =& A_1 + \lambda_S\Big[-\Big(\frac{(1-u_P)\beta\eta}{N} - \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big)S\Big] + \lambda_{V1}\Big[-(1-\epsilon_1)V_1\Big(\frac{(1-u_P)\beta\eta}{N} \\
& - \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big)\Big] + \lambda_{V2}\Big[-V_2\Big(\frac{(1-u_P)\beta\eta}{N} - \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big)\Big] + \\
& \lambda_{C1}\Big[\Big(\frac{(1-u_P)\beta\eta}{N} - \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big)\Big((1-\tau_1)S + (1-\epsilon_1)V_1\Big) - (\sigma_1 + \\
& \gamma_{C1}(1+u_{T1}) + \mu)\Big] + \lambda_{I1}\Big[\sigma_1 + (\tau_1 S + V_2)\Big(\frac{(1-u_P)\beta\eta}{N} - \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big)\Big] + \\
& \lambda_{R1}[\gamma_{C1}(1+u_{T1})] \\
=& A_1 - \lambda_S\Big[\frac{(1-u_P)\beta\eta}{N} - \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big]S - \lambda_{V1}\Big[\frac{(1-u_P)\beta\eta}{N} - \\
& \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big](1-\epsilon_1)V_1 - \lambda_{V2}\Big[\frac{(1-u_P)\beta\eta}{N} - \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big]V_2 + \\
& \lambda_{C1}\Big[\frac{(1-u_P)\beta\eta}{N} - \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big]S - \lambda_{C1}\Big[\frac{(1-u_P)\beta\eta}{N} - \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big]\cdot \\
& \tau_1 S + \lambda_{C1}\Big[\frac{(1-u_P)\beta\eta}{N} - \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big](1-\epsilon_1)V_1 - \lambda_{C1}[\sigma_1 + \gamma_{C1}(1+u_{T1}) + \mu] \\
& + \lambda_{I1}(\sigma_1) + \lambda_{I1}\Big[\frac{(1-u_P)\beta\eta}{N} - \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big]\tau_1 S + \lambda_{I1}\Big[\frac{(1-u_P)\beta\eta}{N} - \\
& \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big]V_2 + \lambda_{R1}[\gamma_{C1}(1+u_{T1})] \\
=& A_1 + (\lambda_{C1} - \lambda_S)\Big[\frac{(1-u_P)\beta\eta}{N} - \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big]S + (\lambda_{I1} - \lambda_{C1})\Big[\frac{(1-u_P)\beta\eta}{N} - \\
& \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big]\tau_1 S + (\lambda_{C1} - \lambda_{V1})\Big[\frac{(1-u_P)\beta\eta}{N} - \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big](1-\epsilon_1)V_1 \\
& + (\lambda_{I1} - \lambda_{V2})\Big[\frac{(1-u_P)\beta\eta}{N} - \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big]V_2 + (\lambda_{R1} - \lambda_{C1})\gamma_{C1}(1+u_{T1}) + \\
& (\lambda_{I1} - \lambda_{C1})\sigma_1 - \lambda_{C1}\mu
\end{aligned}
\tag{5.14}
$$

$$
\begin{aligned}
\frac{\partial \mathcal{H}}{\partial C_2} =& A_2 + \lambda_S\Big[-\Big(\frac{(1-u_P)\beta\eta}{N} - \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big)S\Big] - \lambda_{V1}\Big[V_1\Big(\frac{(1-u_P)\beta\eta}{N} - \\
& \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big)\Big] + \lambda_{V2}\Big[-(1-\epsilon_2)V_2\Big(\frac{(1-u_P)\beta\eta}{N} - \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big)\Big] \\
& + \lambda_{C2}\Big[\Big(\frac{(1-u_P)\beta\eta}{N} - \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big)\Big((1-\tau_2)S + (1-\epsilon_2)V_2\Big) - (\sigma_2 + \\
& \gamma_{C2}(1+u_{T1}) + \mu)\Big] + \lambda_{I2}\Big[\sigma_2 + (\tau_2 S + V_1)\Big(\frac{(1-u_P)\beta\eta}{N} - \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big)\Big] + \\
& \lambda_{R1}[\gamma_{C2}(1+u_{T1})] \\
=& A_2 - \lambda_S\Big[\frac{(1-u_P)\beta\eta}{N} - \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big]S - \lambda_{V1}\Big[\frac{(1-u_P)\beta\eta}{N} - \\
& \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big]V_1 - \lambda_{V2}\Big[\frac{(1-u_P)\beta\eta}{N} - \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big](1-\epsilon_2)V_2 + \\
& \lambda_{C2}\Big[\frac{(1-u_P)\beta\eta}{N} - \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big]S - \lambda_{C2}\Big[\frac{(1-u_P)\beta\eta}{N} - \\
& \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big]\tau_2 S + \lambda_{C2}\Big[\frac{(1-u_P)\beta\eta}{N} - \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big](1-\epsilon_2)V_2 - \\
& \lambda_{C2}[\sigma_2 + \gamma_{C2}(1+u_{T1}) + \mu] + \lambda_{I2}(\sigma_2) + \lambda_{I2}\Big[\frac{(1-u_P)\beta\eta}{N} - \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big]\tau_2 S \\
& + \lambda_{I2}\Big[\frac{(1-u_P)\beta\eta}{N} - \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big]V_1 + \lambda_{R1}[\gamma_{C2}(1+u_{T1})] \\
=& A_2 + (\lambda_{C2} - \lambda_S)\Big[\frac{(1-u_P)\beta\eta}{N} - \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big]S + (\lambda_{I2} - \lambda_{C2})\Big[\frac{(1-u_P)\beta\eta}{N} - \\
& \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big]\tau_2 S + (\lambda_{C2} - \lambda_{V2})\Big[\frac{(1-u_P)\beta\eta}{N} - \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big] \cdot \\
& (1-\epsilon_2)V_2 + (\lambda_{I2} - \lambda_{V1})\Big[\frac{(1-u_P)\beta\eta}{N} - \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big]V_1 + \\
& (\lambda_{R1} - \lambda_{C2})\gamma_{C1}(1+u_{T1}) + (\lambda_{I2} - \lambda_{C2})\sigma_2 - \lambda_{C2}\mu
\end{aligned}
\tag{5.15}
$$

$$
\begin{aligned}
\frac{\partial \mathcal{H}}{\partial I_1} =& A_1 + \lambda_S\Big[-\Big(\frac{(1-u_P)\beta}{N} - \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big)S\Big] + \lambda_{V1}\Big[-(1-\epsilon_1)V_1\Big(\frac{(1-u_P)\beta}{N} - \\
& \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big)\Big] + \lambda_{V2}\Big[-V_2\Big(\frac{(1-u_P)\beta}{N} - \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big)\Big] + \\
& \lambda_{C1}\Big[\Big(\frac{(1-u_P)\beta}{N} - \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big)\Big((1-\tau_1)S + (1-\epsilon_1)V_1\Big)\Big] + \lambda_{I1}\Big[(\tau_1 S + V_2) \\
& \Big(\frac{(1-u_P)\beta}{N} - \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big) - (\gamma_{I1}(1+u_{T2}) + \delta + \mu)\Big] + \lambda_{R1}[\rho_1\gamma_{I1}(1+u_{T2})] \\
& + \lambda_{R2}[(1-\rho_1)\gamma_{I1}(1+u_{T2})] \\
=& A_1 - \lambda_S\Big[\Big(\frac{(1-u_P)\beta}{N} - \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big)S\Big] - \lambda_{V1}\Big[\frac{(1-u_P)\beta}{N} - \\
& \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big](1-\epsilon_1)V_1 - \lambda_{V2}\Big[\frac{(1-u_P)\beta}{N} - \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big]V_2 + \\
& \lambda_{C1}\Big[\frac{(1-u_P)\beta}{N} - \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big]S - \lambda_{C1}\Big[\frac{(1-u_P)\beta}{N} - \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big]\cdot \\
& \tau_1 S + \lambda_{C1}\Big[\frac{(1-u_P)\beta}{N} - \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big](1-\epsilon_1)V_1 + \lambda_{I1}\Big[\frac{(1-u_P)\beta}{N} - \\
& \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big]\tau_1 S + \lambda_{I1}\Big[\frac{(1-u_P)\beta}{N} - \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big]V_2 - \lambda_{I1}[\gamma_{I1}\cdot \\
& (1+u_{T2}) + \delta + \mu] + \lambda_{R1}[\rho_1\gamma_{I1}(1+u_{T2})] + \lambda_{R2}[\gamma_{I1}(1+u_{T2})] - \lambda_{R2}[\rho_1\gamma_{I1}(1+u_{T2})] \\
=& A_1 + (\lambda_{C1} - \lambda_S)\Big[\frac{(1-u_P)\beta}{N} - \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big]S + (\lambda_{I1} - \lambda_{C1})\Big[\frac{(1-u_P)\beta}{N} - \\
& \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big]\tau_1 S + (\lambda_{C1} - \lambda_{V1})\Big[\frac{(1-u_P)\beta}{N} - \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big](1-\epsilon_1)V_1 \\
& + (\lambda_{I1} - \lambda_{V2})\Big[\frac{(1-u_P)\beta}{N} - \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big]V_2 + (\lambda_{R2} - \lambda_{I1})\gamma_{I1}(1+u_{T2}) + \\
& (\lambda_{R1} - \lambda_{R2})\rho_1\gamma_{I1}(1+u_{T2}) - \lambda_{I1}(\delta + \mu)
\end{aligned}
\tag{5.16}
$$

$$
\begin{aligned}
\frac{\partial \mathcal{H}}{\partial I_2} =& A_2 + \lambda_S\Big[-\Big(\frac{(1-u_P)\beta}{N} - \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big)S\Big] + \lambda_{V1}\Big[-V_1\Big(\frac{(1-u_P)\beta}{N} - \\
& \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big)\Big] + \lambda_{V2}\Big[-(1-\epsilon_2)V_2\Big(\frac{(1-u_P)\beta}{N} - \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big)\Big] + \\
& \lambda_{C2}\Big[\Big(\frac{(1-u_P)\beta}{N} - \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big)\Big((1-\tau_2)S + (1-\epsilon_2)V_2\Big)\Big] + \lambda_{I2}\Big[(\tau_2 S + V_1) \\
& \Big(\frac{(1-u_P)\beta}{N} - \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big) - (\gamma_{I2}(1+u_{T2}) + \delta + \mu)\Big] + \lambda_{R1}[\rho_2\gamma_{I2}(1+u_{T2})] \\
& + \lambda_{R2}[(1-\rho_2)\gamma_{I2}(1+u_{T2})] \\
=& A_2 - \lambda_S\Big[\frac{(1-u_P)\beta}{N} - \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big]S - \lambda_{V1}\Big[\frac{(1-u_P)\beta}{N} - \\
& \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big]V_1 - \lambda_{V2}\Big[\frac{(1-u_P)\beta}{N} - \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big](1-\epsilon_2)V_2 + \\
& \lambda_{C2}\Big[\frac{(1-u_P)\beta}{N} - \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big]S - \lambda_{C2}\Big[\frac{(1-u_P)\beta}{N} - \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big]\tau_2 S \\
& + \lambda_{C2}\Big[\frac{(1-u_P)\beta}{N} - \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big](1-\epsilon_2)V_2 + \lambda_{I2}\Big[\frac{(1-u_P)\beta}{N} - \\
& \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big]\tau_2 S + \lambda_{I2}\Big[\frac{(1-u_P)\beta}{N} - \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big]V_1 - \\
& \lambda_{I2}[\gamma_{I2}(1+u_{T2})] - \lambda_{I2}(\delta+\mu) + \lambda_{R1}[\rho_2\gamma_{I2}(1+u_{T2})] + \lambda_{R2}[\gamma_{I2}(1+u_{T2})] - \\
& \lambda_{R2}[\rho_2\gamma_{I2}(1+u_{T2})] \\
=& A_2 + (\lambda_{C2} - \lambda_S)\Big[\frac{(1-u_P)\beta}{N} - \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big]S + (\lambda_{I2} - \lambda_{C2})\Big[\frac{(1-u_P)\beta}{N} - \\
& \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big]\tau_2 S + (\lambda_{C2} - \lambda_{V2})\Big[\frac{(1-u_P)\beta}{N} - \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big](1-\epsilon_2)V_2 \\
& + (\lambda_{I2} - \lambda_{V2})\Big[\frac{(1-u_P)\beta}{N} - \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big]V_1 + (\lambda_{R2} - \lambda_{I2})\gamma_{I2}(1+u_{T2}) + \\
& (\lambda_{R1} - \lambda_{R2})\rho_2\gamma_{I2}(1+u_{T2}) - \lambda_{I2}(\delta+\mu)
\end{aligned}
\tag{5.17}
$$

$$
\frac{\partial \mathcal{H}}{\partial R_1} = \lambda_{R1}[-(\wedge + \mu)] + \lambda_{R2}(\wedge) = (\lambda_{R2} - \lambda_{R1}) \wedge -\lambda_{R1}\mu \tag{5.18}
$$

$$
\frac{\partial \mathcal{H}}{\partial R_2} = -\lambda_{R2}\mu \tag{5.19}
$$

The adjoint system/conditions evaluated at the corresponding optimal solutions of the

state equations are derived below:

$$\lambda_S'(t) = -\frac{\partial \mathcal{H}}{\partial S} = (\lambda_S - \lambda_{V1})u_{V1} + (\lambda_S - \lambda_{V2})u_{V2} + (\lambda_S - \lambda_{C1})\lambda_1^c + (\lambda_S - \lambda_{C2})\lambda_2^c + (\lambda_{C1} - \lambda_{I1})\lambda_1^c\tau_1 + (\lambda_{C2} - \lambda_{I2})\lambda_2^c\tau_2 + \lambda_S\mu \tag{5.20}$$

$$\lambda_{V1}'(t) = -\frac{\partial \mathcal{H}}{\partial V_1} = (\lambda_{V1} - \lambda_S)w_1 + (\lambda_{V1} - \lambda_{I2})\lambda_2^c + (\lambda_{V1} - \lambda_{C1})[\lambda_1^c(1-\epsilon_1)] + \lambda_{V1}\mu \tag{5.21}$$

$$\lambda_{V2}'(t) = -\frac{\partial \mathcal{H}}{\partial V_2} = (\lambda_{V2} - \lambda_S)w_2 + (\lambda_{V2} - \lambda_{I1})\lambda_1^c + (\lambda_{V2} - \lambda_{C2})[\lambda_2^c(1-\epsilon_2)] + \lambda_{V2}\mu \tag{5.22}$$

$$\lambda_{C1}'(t) = -\frac{\partial \mathcal{H}}{\partial C_1} = (\lambda_S - \lambda_{C1})\Big[\frac{(1-u_P)\beta\eta}{N} - \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big]S + (\lambda_{C1} - \lambda_{I1})\Big[\frac{(1-u_P)\beta\eta}{N} - \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big]\tau_1 S + (\lambda_{V1} - \lambda_{C1})\Big[\frac{(1-u_P)\beta\eta}{N} - \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big](1-\epsilon_1)V_1 + (\lambda_{V2} - \lambda_{I1})\Big[\frac{(1-u_P)\beta\eta}{N} - \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big]V_2 + (\lambda_{C1} - \lambda_{R1})\gamma_{C1}(1+u_{T1}) + (\lambda_{C1} - \lambda_{I1})\sigma_1 + \lambda_{C1}\mu - A_1 \tag{5.23}$$

$$\lambda_{C2}'(t) = -\frac{\partial \mathcal{H}}{\partial C_2} = (\lambda_S - \lambda_{C2})\Big[\frac{(1-u_P)\beta\eta}{N} - \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big]S + (\lambda_{C2} - \lambda_{I2})\Big[\frac{(1-u_P)\beta\eta}{N} - \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big]\tau_2 S + (\lambda_{V2} - \lambda_{C2})\Big[\frac{(1-u_P)\beta\eta}{N} - \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big](1-\epsilon_2)V_2 + (\lambda_{V1} - \lambda_{I2})\Big[\frac{(1-u_P)\beta\eta}{N} - \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big]V_1 + (\lambda_{C2} - \lambda_{R1})\gamma_{C1}(1+u_{T1}) + (\lambda_{C2} - \lambda_{I2})\sigma_2 + \lambda_{C2}\mu - A_2 \tag{5.24}$$

$$\lambda'_{I1}(t) = -\frac{\partial \mathcal{H}}{\partial I_1} =(\lambda_S - \lambda_{C1})\Big[\frac{(1-u_P)\beta}{N} - \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big]S + (\lambda_{C1} - \lambda_{I1})\Big[\frac{(1-u_P)\beta}{N} - \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big]\tau_1 S + (\lambda_{V1} - \lambda_{C1})\Big[\frac{(1-u_P)\beta}{N} - \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big](1-\epsilon_1)V_1 + (\lambda_{V2} - \lambda_{I1})\Big[\frac{(1-u_P)\beta}{N} - \frac{(1-u_P)\beta(\eta C_1 + I_1)}{N^2}\Big]V_2 + (\lambda_{I1} - \lambda_{R2})\gamma_{I1}(1+u_{T2}) + (\lambda_{R2} - \lambda_{R1})\rho_1\gamma_{I1}(1+u_{T2}) + \lambda_{I1}(\delta+\mu) - A_1 \tag{5.25}$$

$$\lambda'_{I2}(t) = -\frac{\partial \mathcal{H}}{\partial I_2} =(\lambda_S - \lambda_{C2})\Big[\frac{(1-u_P)\beta}{N} - \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big]S + (\lambda_{C2} - \lambda_{I2})\Big[\frac{(1-u_P)\beta}{N} - \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big]\tau_2 S + (\lambda_{V2} - \lambda_{C2})\Big[\frac{(1-u_P)\beta}{N} - \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big](1-\epsilon_2)V_2 + (\lambda_{V2} - \lambda_{I2})\Big[\frac{(1-u_P)\beta}{N} - \frac{(1-u_P)\beta(\eta C_2 + I_2)}{N^2}\Big]V_1 + (\lambda_{I2} - \lambda_{R2})\gamma_{I2}(1+u_{T2}) + (\lambda_{R2} - \lambda_{R1})\rho_2\gamma_{I2}(1+u_{T2}) + \lambda_{I2}(\delta+\mu) - A_2 \tag{5.26}$$

$$\lambda'_{R1}(t) = -\frac{\partial \mathcal{H}}{\partial R_1} = (\lambda_{R1} - \lambda_{R2}) \wedge + \lambda_{R1}\mu \tag{5.27}$$

$$\lambda'_{R2}(t) = -\frac{\partial \mathcal{H}}{\partial R_2} = \lambda_{R2}\mu \tag{5.28}$$

Equations (5.20) to (5.28) are the Adjoint (co-state) equations.

The transversality conditions are given as;

$$\lambda_i(T) = 0, for\ i = \{S, V_1, V_2, C_1, C_2, I_1, I_2, R_1, R_2\} \tag{5.29}$$

5.1.3 Characterization of Optimal Controls

Here, we characterize the optimal controls $(u_P^*, u_{V1}^*, u_{V2}^*, u_{T1}^*, u_{T2}^*)$ which give the optimal levels for the various control measures and the corresponding states $(S^*, V_1^*, V_2^*, C_1^*, C_2^*, I_1^*, I_2^*, R_1^*, R_2^*)$. The optimal solution to the Hamiltonian function is obtained by taking the partial derivatives of $\mathcal{H}$ with respect to the controls,

$u_P, u_{V1}, u_{V2}, u_{T1}$ and u_{T2}. Thus,

$$\begin{aligned}
\frac{\partial \mathcal{H}}{\partial u_P} =& B_1 u_P + \lambda_S\Big[-\Big(\frac{-\beta(\eta C_1 + I_1)}{N} - \frac{\beta(\eta C_2 + I_2)}{N}\Big)S\Big] + \lambda_{V1}\Big[-(1-\epsilon_1)V_1\Big(\frac{-\beta(\eta C_1 + I_1)}{N}\Big) \\
& - V_1\Big(\frac{-\beta(\eta C_2 + I_2)}{N}\Big)\Big] + \lambda_{V2}\Big[-(1-\epsilon_2)V_2\Big(\frac{-\beta(\eta C_2 + I_2)}{N}\Big) - V_2\Big(\frac{-\beta(\eta C_1 + I_1)}{N}\Big)\Big] + \\
& \lambda_{C1}\Big[\frac{-\beta(\eta C_1 + I_1)}{N}\Big((1-\tau_1)S + (1-\epsilon_1)V_1\Big)\Big] + \lambda_{C2}\Big[\frac{-\beta(\eta C_2 + I_2)}{N}\Big((1-\tau_2)S + \\
& (1-\epsilon_2)V_2\Big)\Big] + \lambda_{I1}\Big[\frac{-\beta(\eta C_1 + I_1)}{N}(\tau_1 S + V_2)\Big] + \lambda_{I2}\Big[\frac{-\beta(\eta C_2 + I_2)}{N}(\tau_2 S + V_1)\Big] \\
=& B_1 u_P + \lambda_S\Big[\frac{\beta(\eta C_1 + I_1)}{N} + \frac{\beta(\eta C_2 + I_2)}{N}\Big]S + \lambda_{V1}\Big[\frac{\beta(\eta C_1 + I_1)}{N}\Big](1-\epsilon_1)V_1 + \\
& \lambda_{V1}\Big[\frac{\beta(\eta C_2 + I_2)}{N}\Big]V_1 + \lambda_{V2}\Big[\frac{\beta(\eta C_2 + I_2)}{N}\Big](1-\epsilon_2)V_2 + \lambda_{V2}\Big[\frac{\beta(\eta C_1 + I_1)}{N}\Big]V_2 - \\
& \lambda_{C1}\Big[\frac{\beta(\eta C_1 + I_1)}{N}\Big]S + \lambda_{C1}\Big[\frac{\beta(\eta C_1 + I_1)}{N}\Big]\tau_1 S - \lambda_{C1}\Big[\frac{\beta(\eta C_1 + I_1)}{N}\Big](1-\epsilon_1)V_1 - \\
& \lambda_{C2}\Big[\frac{\beta(\eta C_2 + I_2)}{N}\Big]S + \lambda_{C2}\Big[\frac{\beta(\eta C_2 + I_2)}{N}\Big]\tau_2 S - \lambda_{C2}\Big[\frac{\beta(\eta C_2 + I_2)}{N}\Big](1-\epsilon_2)V_2 - \\
& \lambda_{I1}\Big[\frac{\beta(\eta C_1 + I_1)}{N}\Big]\tau_1 S - \lambda_{I1}\Big[\frac{\beta(\eta C_1 + I_1)}{N}\Big]V_2 - \lambda_{I2}\Big[\frac{\beta(\eta C_2 + I_2)}{N}\Big]\tau_2 S - \\
& \lambda_{I2}\Big[\frac{\beta(\eta C_2 + I_2)}{N}\Big]V_1 \\
=& B_1 u_P + (\lambda_S - \lambda_{C1})\Big[\frac{\beta(\eta C_1 + I_1)}{N}\Big]S + (\lambda_S - \lambda_{C2})\Big[\frac{\beta(\eta C_2 + I_2)}{N}\Big]S + (\lambda_{C1} - \lambda_{I1}) \\
& \Big[\frac{\beta(\eta C_1 + I_1)}{N}\Big]\tau_1 S + (\lambda_{C2} - \lambda_{I2})\Big[\frac{\beta(\eta C_2 + I_2)}{N}\Big]\tau_2 S + (\lambda_{V1} - \lambda_{C1})\Big[\frac{\beta(\eta C_1 + I_1)}{N}\Big] \cdot \\
& (1-\epsilon_1)V_1 + (\lambda_{V1} - \lambda_{I2})\Big[\frac{\beta(\eta C_2 + I_2)}{N}\Big]V_1 + (\lambda_{V2} - \lambda_{C2})\Big[\frac{\beta(\eta C_2 + I_2)}{N}\Big](1-\epsilon_2)V_2 \\
& + (\lambda_{V2} - \lambda_{I1})\Big[\frac{\beta(\eta C_1 + I_1)}{N}\Big]V_2
\end{aligned} \tag{5.30}$$

$$\frac{\partial \mathcal{H}}{\partial u_{V1}} = B_2 u_{V1} + \lambda_S(-S) + \lambda_{V1}(S) = B_2 u_{V1} + (\lambda_{V1} - \lambda_S)S \tag{5.31}$$

$$\frac{\partial \mathcal{H}}{\partial u_{V2}} = B_3 u_{V2} + \lambda_S(-S) + \lambda_{V2}(S) = B_3 u_{V2} + (\lambda_{V2} - \lambda_S)S \tag{5.32}$$

$$\begin{aligned}
\frac{\partial \mathcal{H}}{\partial u_{T1}} =& B_4 u_{T1} + \lambda_{C1}(-\gamma_{c1} C_1) + \lambda_{C2}(-\gamma_{c2} C_2) + \lambda_{R1}(\gamma_{c1} C_1 + \gamma_{c2} C_2) \\
=& B_4 u_{T1} + (\lambda_{R1} - \lambda_{C1})\gamma_{c1} C_1 + (\lambda_{R1} - \lambda_{C2})\gamma_{c2} C_2
\end{aligned} \tag{5.33}$$

$$\begin{aligned}\frac{\partial \mathcal{H}}{\partial u_{T2}} =& B_5 u_{T2} + \lambda_{I1}(-\gamma_{I1} I_1) + \lambda_{I2}(-\gamma_{I2} I_2) + \lambda_{R1}(\rho_1 \gamma_{I1} I_1 + \rho_2 \gamma_{I2} I_2) + \lambda_{R2}[(1-\rho_1)\gamma_{I1} I_1 \\ &+ (1-\rho_2)\gamma_{I2} I_2] \\ =& B_5 u_{T2} + (\lambda_{R2} - \lambda_{I1})\gamma_{I1} I_1 + (\lambda_{R2} - \lambda_{I2})\gamma_{I2} I_2 + (\lambda_{R1} - \lambda_{R2})\rho_1 \gamma_{I1} I_1 + \\ &(\lambda_{R1} - \lambda_{R2})\rho_2 \gamma_{I2} I_2 \end{aligned} \tag{5.34}$$

The optimality condition $\frac{\partial \mathcal{H}}{\partial u} = 0$ is now imposed on equations (5.30) to (5.34) at $u = u^*$. Therefore, the expressions for the control variables, $(u_P^*, u_{V1}^*, u_{V2}^*, u_{T1}^*, u_{T2}^*)$, of the optimal control problem are obtained as follows:

$$u_P^* = \frac{A_P}{B_1} \tag{5.35}$$

where

$$\begin{aligned} A_P =& (\lambda_{C1} - \lambda_S)\Big[\frac{\beta(\eta C_1^* + I_1^*)}{N}\Big] S^* + (\lambda_{C2} - \lambda_S)\Big[\frac{\beta(\eta C_2^* + I_2^*)}{N}\Big] S^* + (\lambda_{I1} - \lambda_{C1}) \cdot \\ &\Big[\frac{\beta(\eta C_1^* + I_1^*)}{N}\Big] \tau_1 S^* + (\lambda_{I2} - \lambda_{C2})\Big[\frac{\beta(\eta C_2^* + I_2^*)}{N}\Big] \tau_2 S^* + (\lambda_{C1} - \lambda_{V1})\Big[\frac{\beta(\eta C_1^* + I_1^*)}{N}\Big] \cdot \\ &(1-\epsilon_1) V_1^* + (\lambda_{I2} - \lambda_{V1})\Big[\frac{\beta(\eta C_2^* + I_2^*)}{N}\Big] V_1^* + (\lambda_{C2} - \lambda_{V2})\Big[\frac{\beta(\eta C_2^* + I_2^*)}{N}\Big](1-\epsilon_2) V_2^* \\ &+ (\lambda_{I1} - \lambda_{V2})\Big[\frac{\beta(\eta C_1^* + I_1^*)}{N}\Big] V_2^* \end{aligned}$$

$$u_{V1}^* = \frac{(\lambda_S - \lambda_{V1}) S^*}{B_2} \tag{5.36}$$

$$u_{V2}^* = \frac{(\lambda_S - \lambda_{V2}) S^*}{B_3} \tag{5.37}$$

$$u_{T1}^* = \frac{(\lambda_{C1} - \lambda_{R1})\gamma_{c1} C_1^* + (\lambda_{C2} - \lambda_{R1})\gamma_{c2} C_2^*}{B_4} \tag{5.38}$$

$$u_{T2}^* = \frac{(\lambda_{I1} - \lambda_{R2})\gamma_{I1} I_1^* + (\lambda_{I2} - \lambda_{R2})\gamma_{I2} I_2^* + (\lambda_{R2} - \lambda_{R1})\rho_1 \gamma_{I1} I_1^* + (\lambda_{R2} - \lambda_{R1})\rho_2 \gamma_{I2} I_2^*}{B_5} \tag{5.39}$$

Imposing the bounds ($0 \leq u_i \leq 1,\ i = P,\ V1,\ V2,\ T1,\ T2$) on the controls gives

$$
\begin{aligned}
u_P^* &= min\left\{max\left(0, \frac{A_P}{B_1}\right), 1\right\} \\
u_{V1}^* &= min\left\{max\left(0, \frac{(\lambda_S - \lambda_{V1})S^*}{B_2}\right), 1\right\} \\
u_{V2}^* &= min\left\{max\left(0, \frac{(\lambda_S - \lambda_{V2})S^*}{B_3}\right), 1\right\} \\
u_{T1}^* &= min\left\{max\left(0, \frac{(\lambda_{C1} - \lambda_{R1})\gamma_{c1}C_1^* + (\lambda_{C2} - \lambda_{R1})\gamma_{c2}C_2^*}{B_4}\right), 1\right\} \\
u_{T2}^* &= min\left\{max\left(0, \frac{(\lambda_{I1} - \lambda_{R2})\gamma_{I1}I_1^* + (\lambda_{I2} - \lambda_{R2})\gamma_{I2}I_2^* + \Phi\rho_1\gamma_{I1}I_1^* + \Phi\rho_2\gamma_{I2}I_2^*}{B_5}\right), 1\right\}
\end{aligned}
\tag{5.40}
$$

where $\Phi = \lambda_{R2} - \lambda_{R1}$

5.2 Numerical Simulations of the Optimal Control

The numerical solutions of the resulting optimality system comprising of the system of the model state equations in Equation (5.2) and the corresponding adjoint Equations in (5.20) to (5.28), with the control variables characterization incorporated in (5.35) to (5.39) are presented. This was implemented using the Forward-Backward Sweep method. The parameter values used for this numerical simulation are given in Table 4.3. All the positive relative weights of the Carrier and Infected populations as well as for the regularization of the controls are given a baseline value of 1.0. Thus, $A_1 = A_2 = B_1 = B_2 = B_3 = B_4 = B_5 = 1.0$. It is noted that the weights in the simulations carried out here are only of theoretical sense to illustrate the control strategies. The analysis is done over a period of 30 days and the graphs and discussions of the results for the various combinations of the five (5) control measures with their corresponding control profiles are also presented. This optimality system is solved with the following initial conditions: $S(0) = 5203562$, $V_1(0) = 60$, $V_2(0) = 100$, $C_1(0) = 43$, $C_2(0) = 22$, $I_1(0) = 31$, $I_2(0) = 20$, $R_1(0) = 0$ and $R_2(0) = 0$.

5.2.1 Optimal Control Effect on Susceptible Population

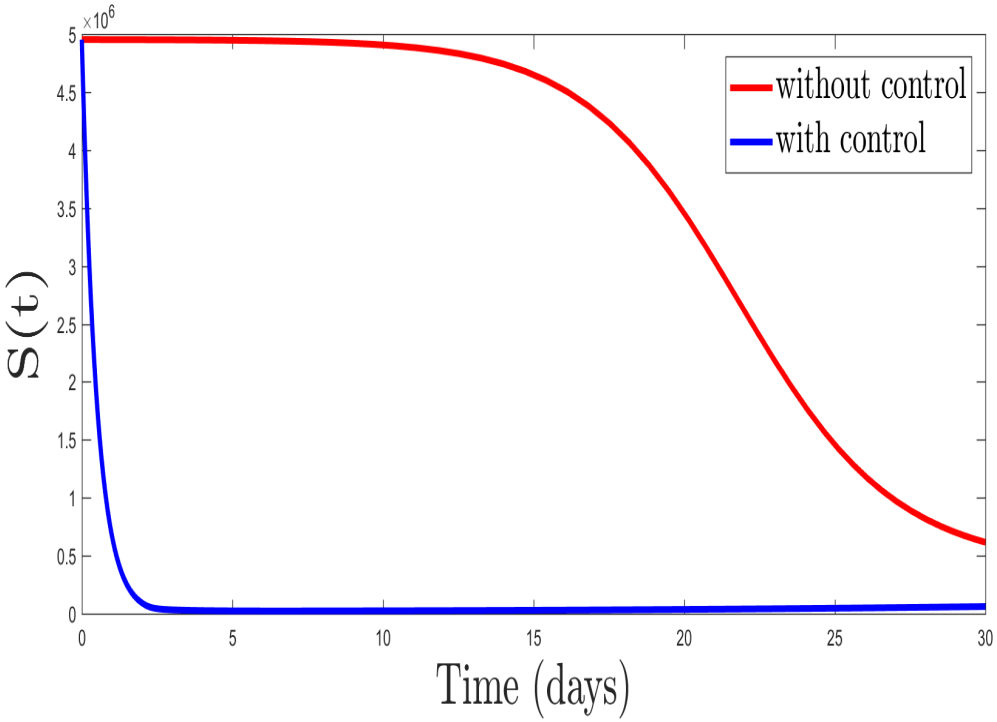


Figure 5.1 Optimal Control Effect on Susceptible Population

Figure 5.1 shows a rapid decrease in the susceptible population within the first few days due to the awareness and intervention to get the affected population vaccinated. Also, the control for the effective human personal protection $u_P(t)$ limit the forces of infection for the susceptible.

5.2.2 Optimal Control Effect on Vaccinated Population with Immunity for Strain 1

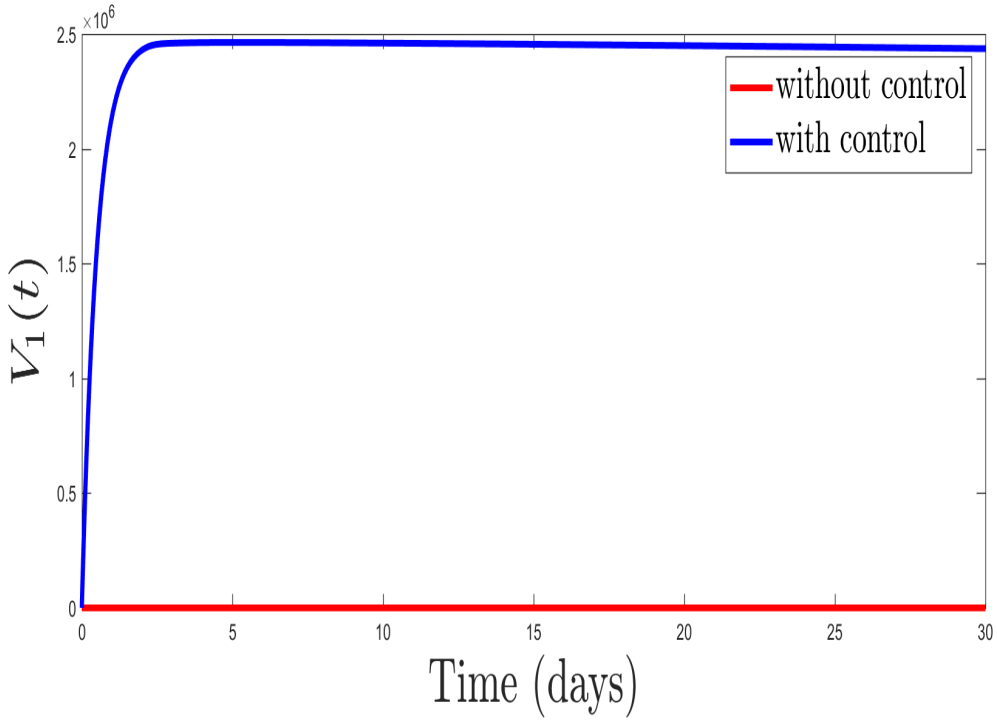


Figure 5.2 Optimal Control Effect on Vaccinated Population of Strain 1

Figure 5.2 displays a strong increase in the population by the intervention of the vaccination control $u_{V1}(t)$. This led to a lot of people in the susceptible population getting vaccinated and moving to the vaccinated compartment. Thereafter, the population is maintained at a stable state due to the balance in the inflow of the susceptible and outflow of individuals within this population as the vaccine wanes. Moreover, this scenario can be achieved by rapidly vaccinating sizeable proportion of the susceptible individuals as soon as new cases of the epidemic to strain 1 are discovered.

5.2.3 Optimal Control Effect on Vaccinated Population with Immunity for Strain 2

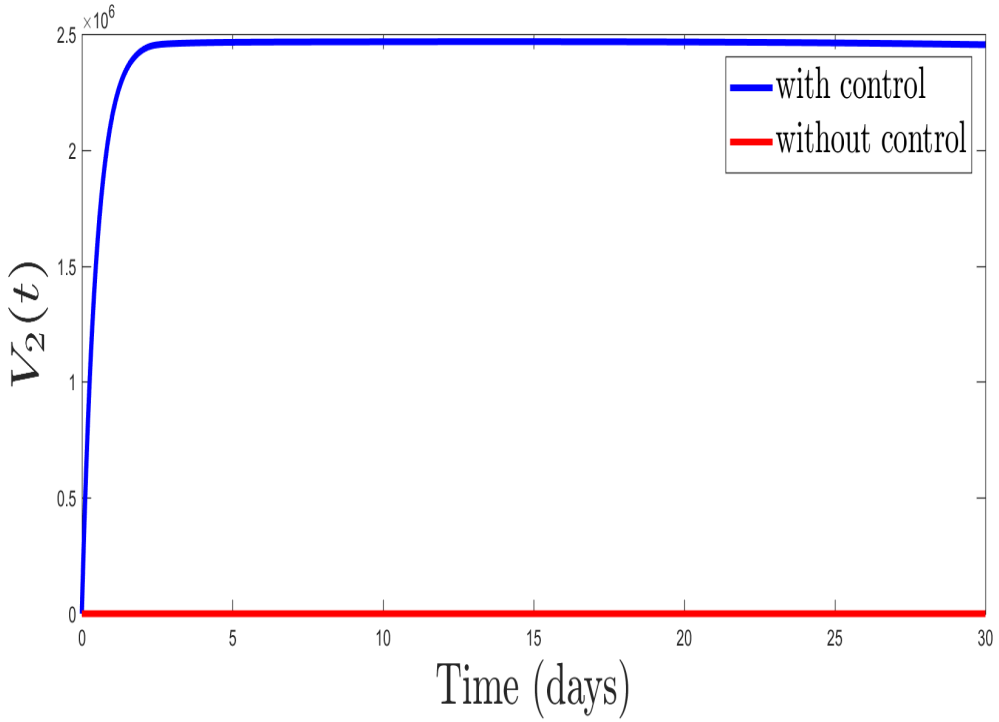


Figure 5.3 Optimal Control Effect on Vaccinated Population of Strain 2

Figure 5.3 also indicates a huge increase in the population by the intervention of the vaccination control $u_{V2}(t)$ as we have more people in the susceptible population taking the vaccine and moving to the vaccinated compartment. The population then remains stable as a result of the balance in the inflow of the susceptible and outflow of individuals within this population as the vaccine wanes. Furthermore, this scenario can be achieved by rapidly vaccinating a good proportion of the susceptible individuals as soon as new cases of the epidemic to strain 2 are discovered.

5.2.4 Optimal Control Effect on Carrier Population of Strain 1

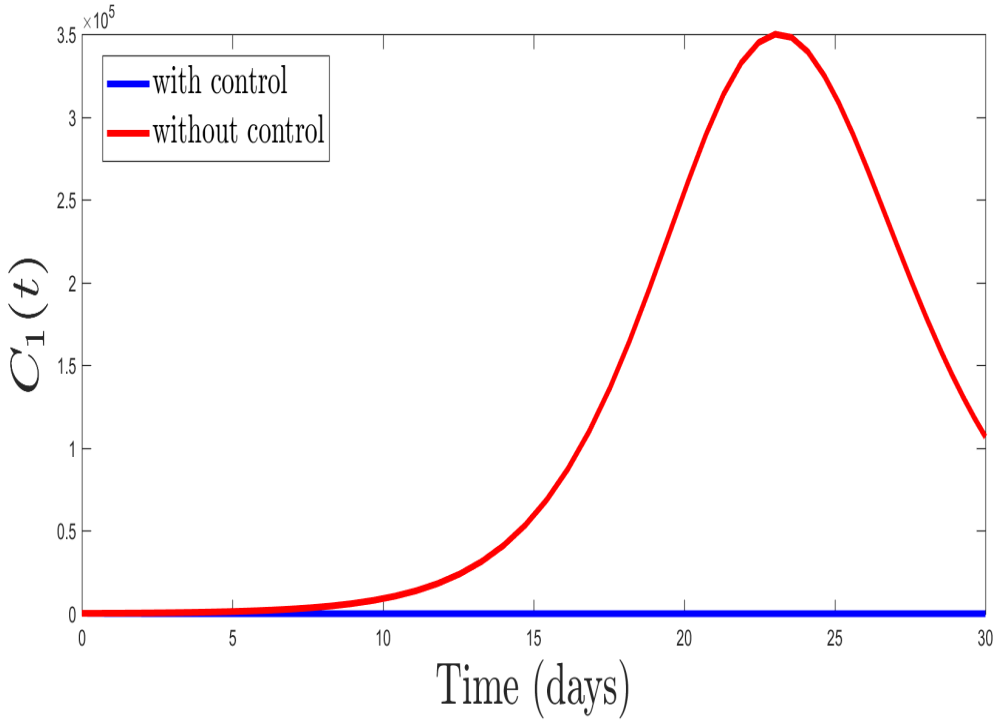


Figure 5.4 Optimal Control Effect on Carrier of Strain 1 Population

In Figure 5.4, the Carrier Population of Strain 1 reduced drastically in size due to the intervention of the treatment control for the timely diagnosed individuals $u_{T1}(t)$. The intervention of the control for effective human personal protection $u_P(t)$ to the susceptible also decreases the infectiousness of individuals.

5.2.5 Optimal Control Effect on Carrier Population of Strain 2

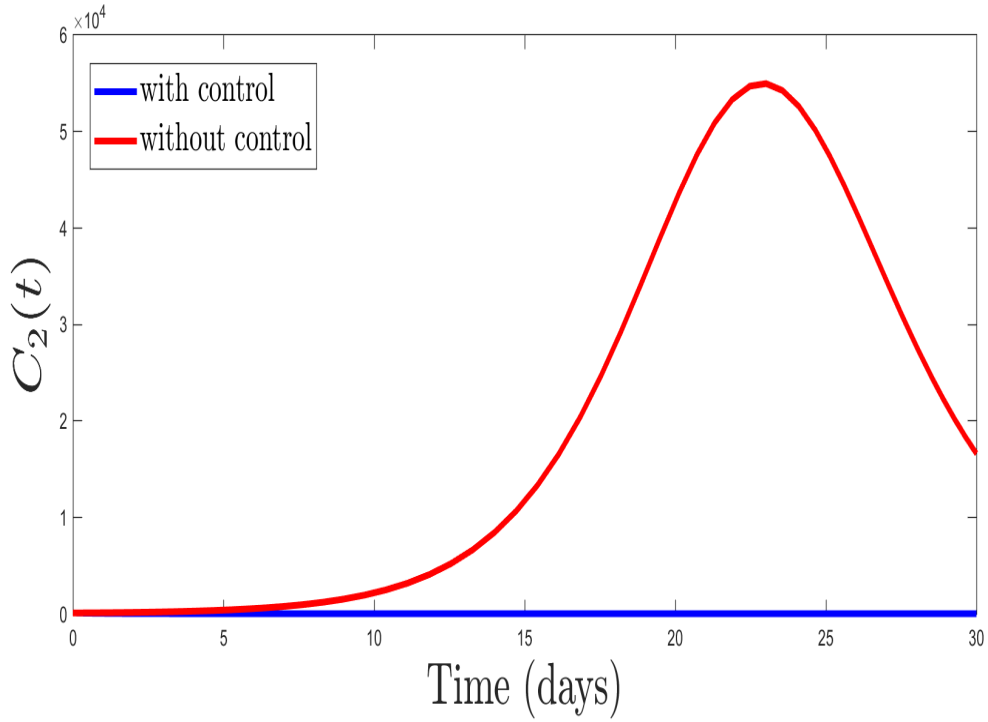


Figure 5.5 Optimal Control Effect on Carrier of Strain 2 Population

Figure 5.5 presents a drastic decrease in the size of the population due to the intervention of the treatment control for the timely diagnosed individuals $u_{T1}(t)$. The decrease can also be attributed to the intervention of the control for effective human personal protection $u_P(t)$ to the susceptible population.

5.2.6 Optimal Control Effect on Infected Population of Strain 1

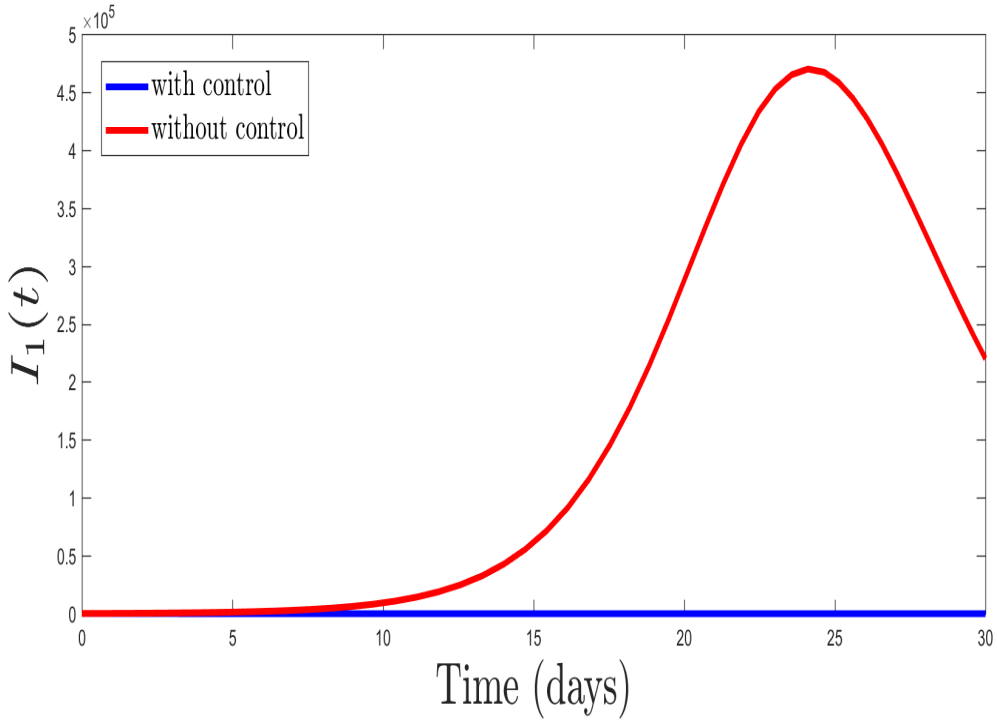


Figure 5.6 Optimal Control Effect on Infected Population of Strain 1

Figure 5.6 also indicates a rapid decrease in the size of the population due to the intervention of the treatment control for the delayed diagnosed individuals $u_{T2}(t)$. This brings a quick recovery to the population, hence their movement to the Recovered population. The effective human personal protection control $u_P(t)$ also decreases the movement of individuals from the susceptible into this population.

5.2.7 Optimal Control Effect on Infected Population of Strain 2

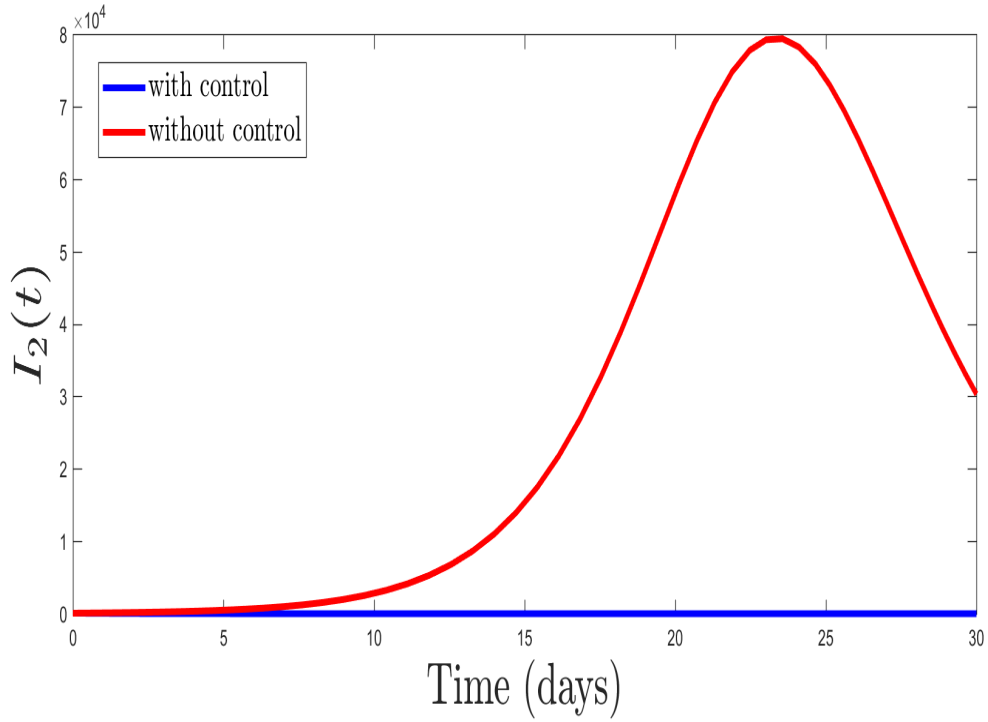


Figure 5.7 Optimal Control Effect on Infected Population of Strain 2

In Figure 5.7, a drastic decrease in the size of the population is observed. This can be attributed to the intervention of the treatment control for the delayed diagnosed individuals $u_{T2}(t)$ which leads to a high recovery rate for this compartment. The population also decrease by the intervention of the effective human personal protection control $u_P(t)$ to the susceptible since it influences the infectiousness of the disease.

5.2.8 Fully Recovered Population from both Strains

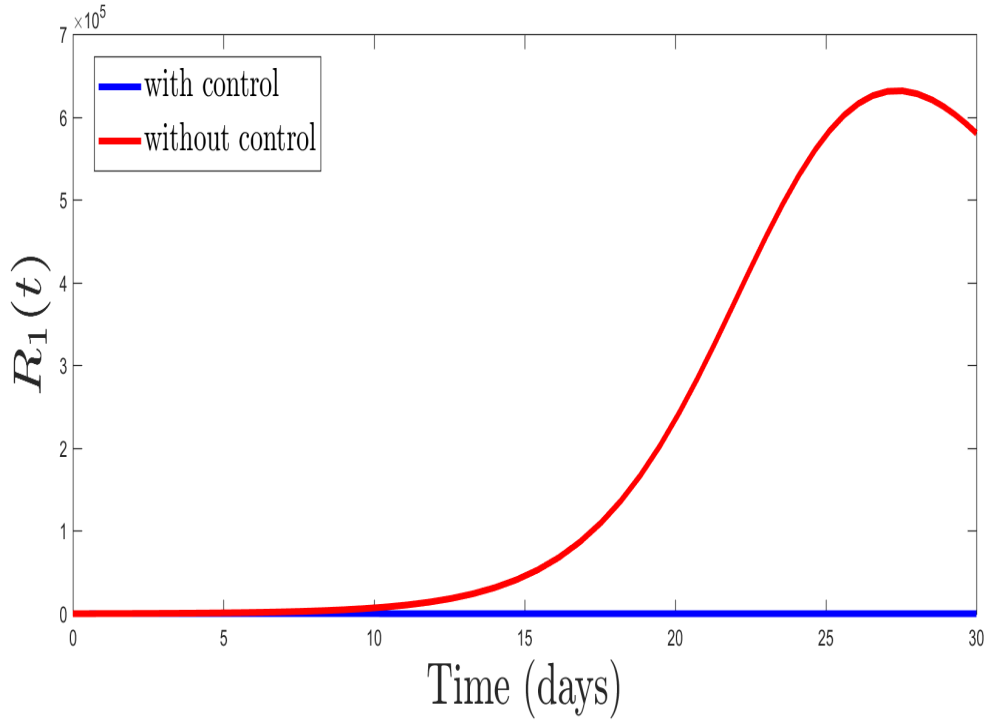


Figure 5.8 Optimal Control Effect on Fully Recovered Population

Figure 5.8 presents a significant decrease in the size of the population. Though we would have expected a rise in this population, the decrease is ascribed to the fact that the intervention of these controls keeps majority of the population in the two vaccinated compartments thereby leading to fewer individuals at the risk of infection. This eventually results in fewer individuals recovering from the infection.

5.2.9 Recovered Population with Complications from both Strains

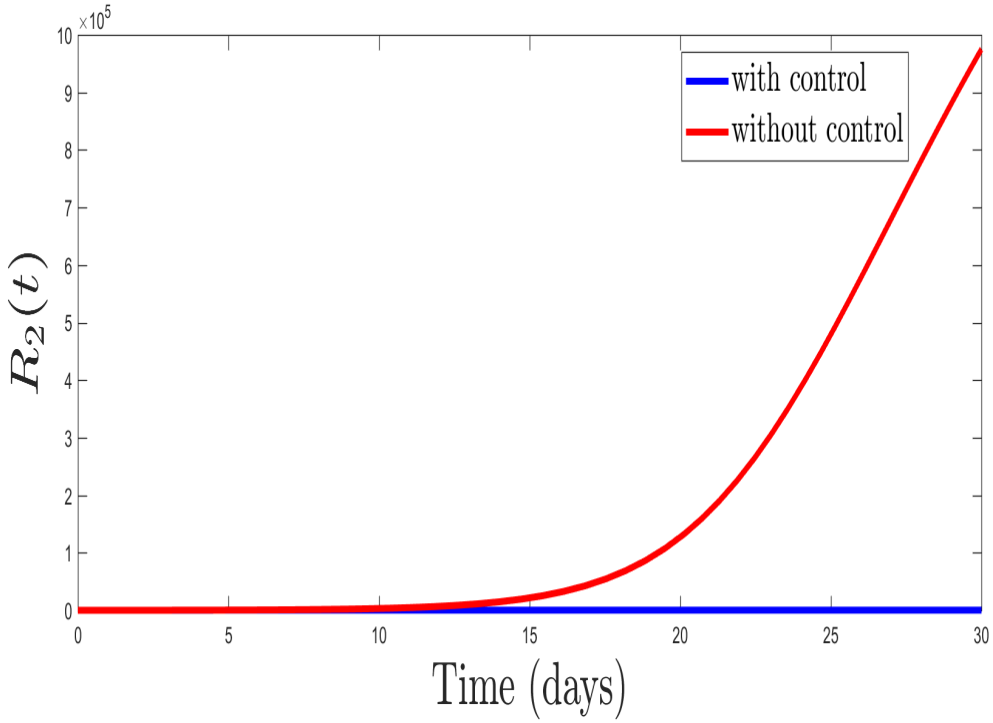


Figure 5.9 Optimal Control Effect on Recovered with Complications

Figure 5.9 indicates a strong decrease in the size of the population due to the intervention of the controls. This shows clearly that with early diagnosis and right treatment we can get a lot of people recovering from the infection with no or less complications.

5.2.10 Simulation Results of the Control Profiles

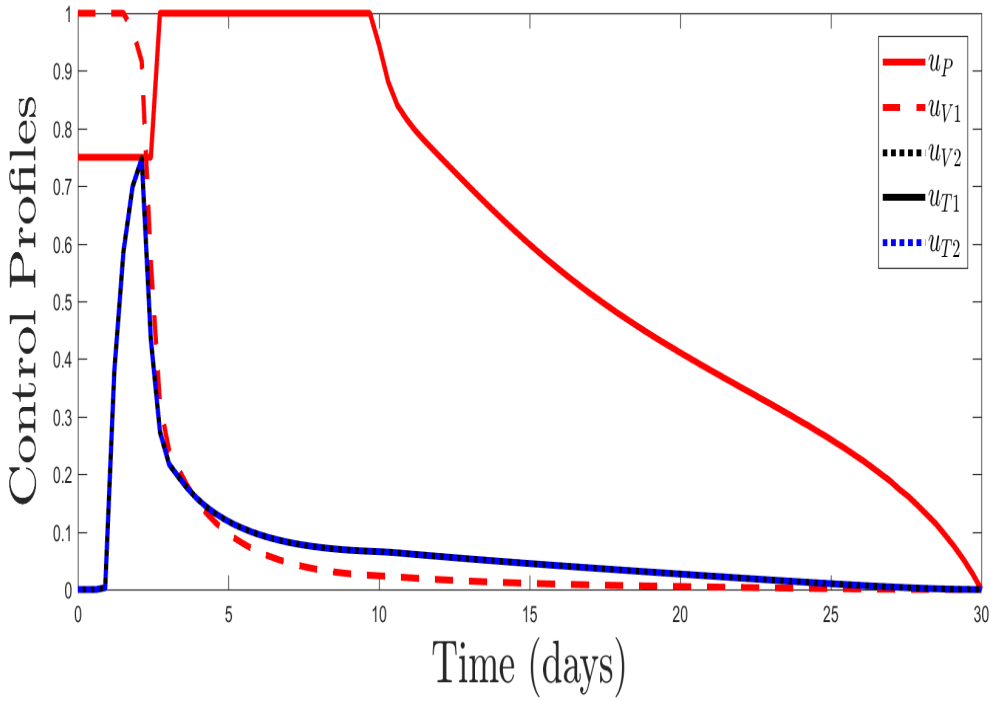


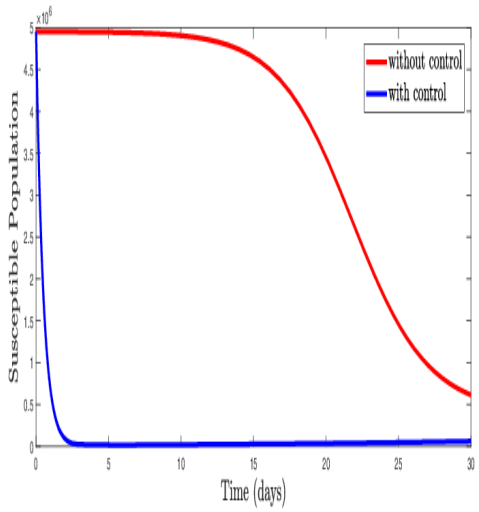
Figure 5.10 Control Profiles

The corresponding simulated time-dependent controls $u_P(t)$, $u_{V1}(t)$, $u_{V2}(t)$, $u_{T1}(t)$, $u_{T2}(t)$ are presented in Figure 5.10. It can be observed that the time-dependent control $u_P(t)$ started at 0.75 and increased to the upper bound, that is $u_P(t) = 1$, for about 10 days before decreasing to the lower bound at the end of the simulation period. The time-dependent control $u_{V1}(t)$ is also seen at the upper bound, that is $u_{V1}(t) = 1$ for about 2 days and decreases to the lower bound till the end of the simulation. Conversely, the remaining time-dependent controls $u_{V2}(t), u_{T1}(t), u_{T2}(t)$ coincide as they all start from the lower bound, that is $u_{V2}(t) = u_{T1}(t) = u_{T2}(t) = 0$ and slowly increase to a maximum of about 0.75 on the third day and gradually decrease to the lower bound with time. These results suggest that to prevent an outbreak, individuals in the community should be vaccinated against strain 1 and continuously wear these facial or surgical masks at the beginning of the season. However, individuals should gradually get vaccinated against the strain 2 and administering of the treatment controls. The results also suggest that an equal effort should be mounted on the three coinciding controls. The results further indicate that to keep the population protected from the disease, all the five controls need to be kept at a relatively high level.

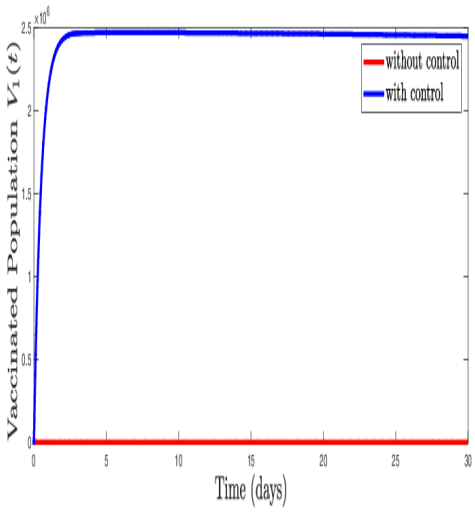
5.3 Optimal Control Intervention Strategies

5.3.1 Strategy A: Optimal Control with Effective Human Protection and Vaccination for both Strains

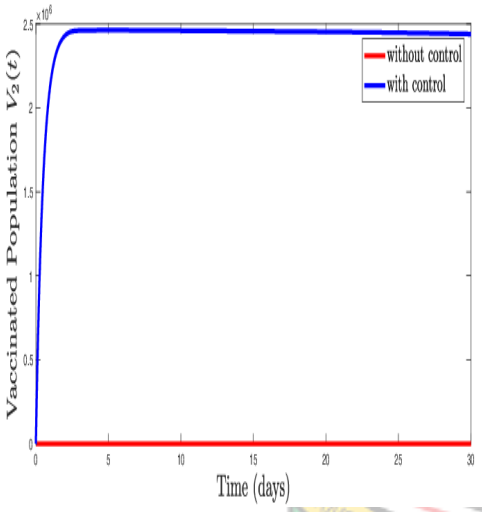
The objective functional is optimized with the effective human protection control, $u_P(t)$ and vaccination controls for both strains, $u_{V1}(t)$ and $u_{V2}(t)$ while setting the other controls: timely and delayed treatment controls, $u_{T1}(t)$ and $u_{T2}(t)$ to zero respectively. The results are presented in Figure (5.11). It can be observed that the Susceptible Population $S(t)$ in Figure 5.11(a) reduced drastically within the first few days while the two Vaccinated Populations $V_1(t)$, $V_2(t)$ in Figures 5.11(b) and 5.11(c) show a strong increase, as a lot of people get vaccinated. This control, even when applied exclusively, leads to a rapid depopulation of the two Carrier Populations $C_1(t)$, $C_2(t)$ in Figures 5.11(d) and 5.11(e) and the two Infected Populations $I_1(t)$, $I_2(t)$ in Figures 5.11(f) and 5.11(g). It is interesting to know that all the four infected classes maintained this decrease throughout the 30 days and this result can also be viewed in Figure 5.11(j). This is realistic because the effective human protection and vaccination of the two strains will reduce the number of infections drastically even without a treatment control since the number of infections will be minimal to curb with available treatment interventions. The two Recovered Populations $R_1(t)$, $R_2(t)$ in Figures 5.11(h) and 5.11(i) also show a drastic decrease since fewer infections will lead to fewer individuals recovering from the infection. The control profiles in Figure 5.11(k), shows that the time-dependent control $u_P(t)$ must be implemented and sustained at its peak for the first 12 days. The time-dependent control $u_{V1}(t)$ should also be at its peak for the first few days while $u_{V2}(t)$ on the other hand must be increased slowly in the first few days and consistently decreasing rate overtime. This combination is seen to reduce the number of infections favourably.



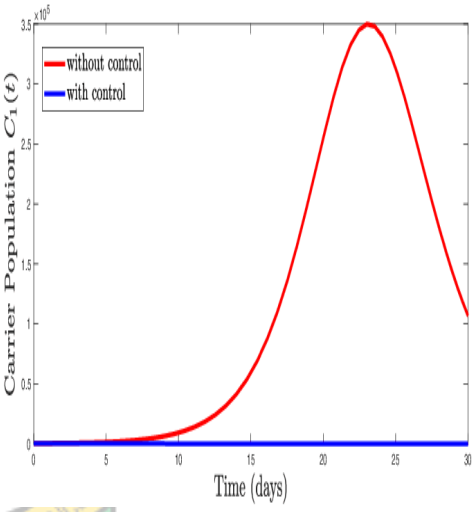
(a) Evolution of $S(t)$



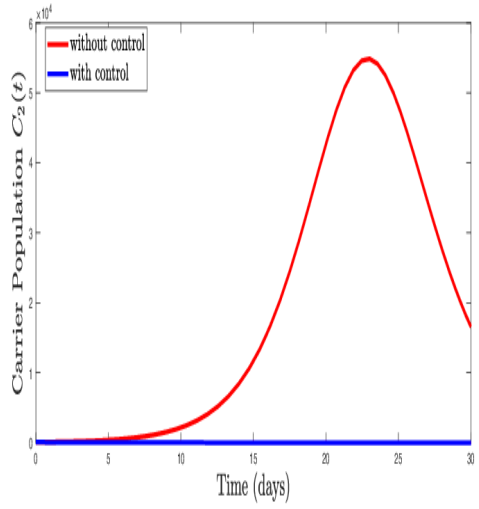
(b) Evolution of $V_1(t)$



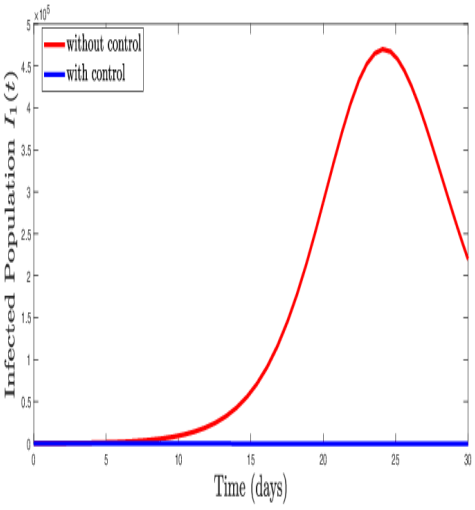
(c) Evolution of $V_2(t)$



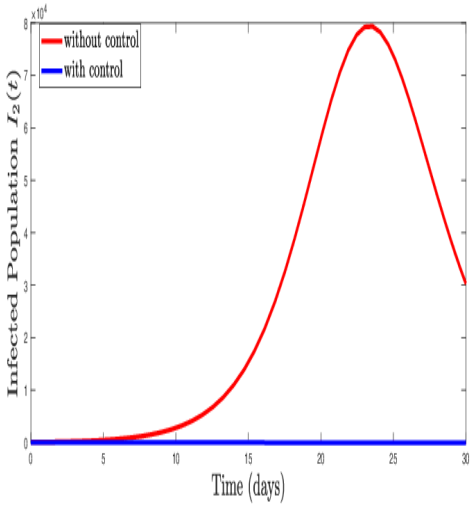
(d) Evolution of $C_1(t)$



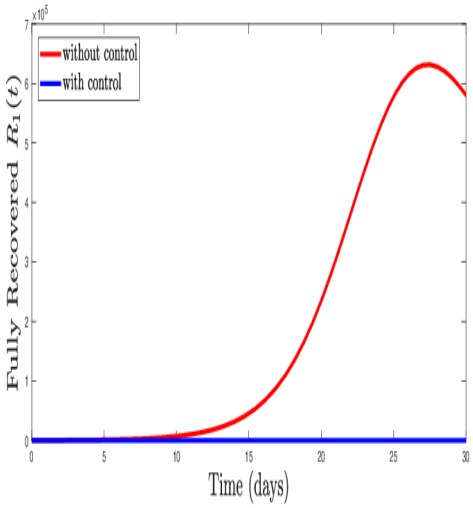
(e) Evolution of $C_2(t)$



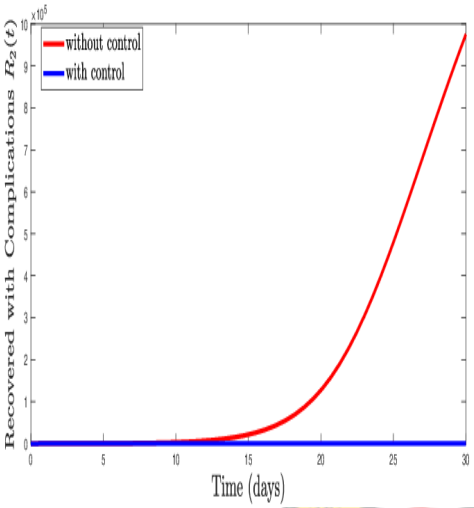
(f) Evolution of $I_1(t)$



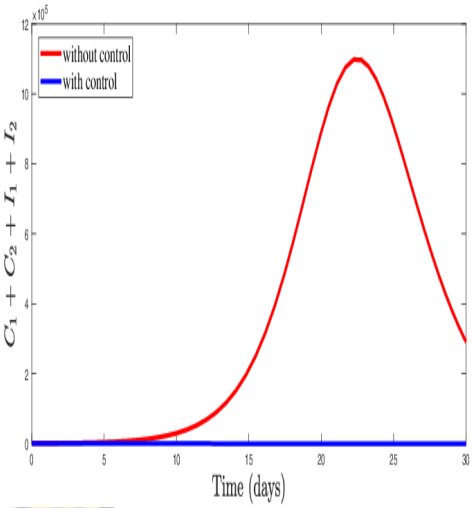
(g) Evolution of $I_2(t)$



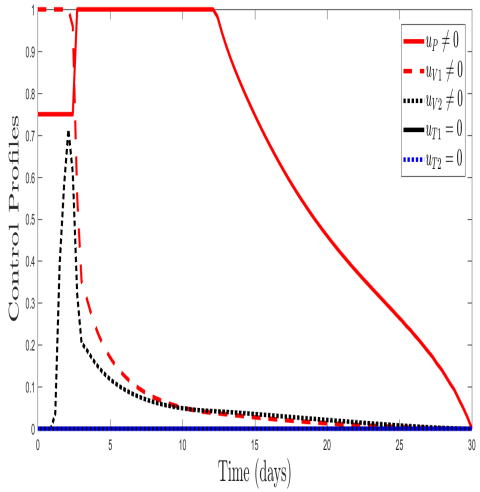
(h) Evolution of $R_1(t)$



(i) Evolution of $R_2(t)$



(j) Disease Prevalence

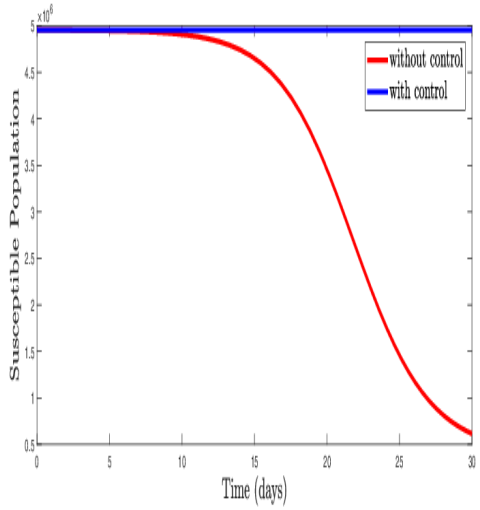


(k) Control Profiles

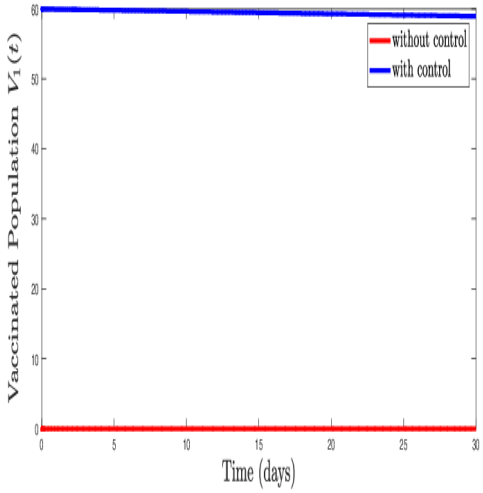
Figure 5.11 Effects of Effective Human Protection and Vaccination for both Strains

5.3.2 Strategy B: Optimal Control with Effective Human Protection and Treatment for Timely and Delayed Diagnosis

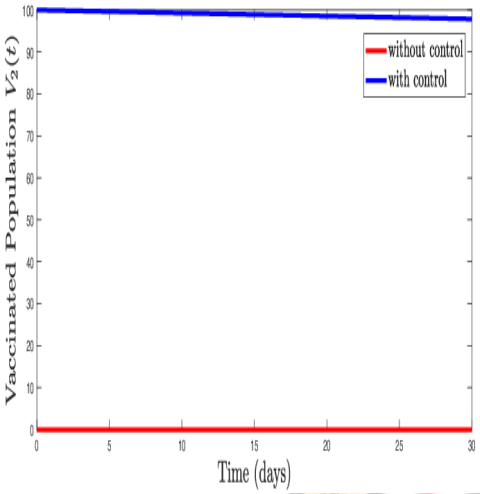
The objective functional is optimized with the effective human protection control, $u_P(t)$, timely treatment control, $u_{T1}(t)$ and delayed treatment control, $u_{T2}(t)$ while setting the other controls: vaccination controls, $u_{V1}(t)$ and $u_{V2}(t)$ to zero respectively. From the results presented in Figure (5.12), it can be observed that majority of the population stayed in the Susceptible Population $S(t)$ in figure 5.12(a) due to the control intervention of surgical or nose masks. The two Vaccinated Populations $V_1(t)$, $V_2(t)$ in Figures 5.12(b) and 5.12(c) exhibit stabilities at their initial conditions but begin to decrease close to the 30^{th} day since there is no vaccination control intervention. This control strategy also decreases the two Carrier Populations $C_1(t)$, $C_2(t)$ in Figures 5.12(d) and 5.12(e) and the two Infected Populations $I_1(t)$, $I_2(t)$ in Figures 5.12(f) and 5.12(g). This shows that the combination of effective human protection and the timely and delayed treatments is efficacious in reducing the number of infections as can be viewed in Figure 5.12(j). The surgical or face masks intervention reduces the spread of the disease while the treatment of the Carrier Population prevents the infection from progressing to the symptomatic stage. The two Recovered Populations $R_1(t)$, $R_2(t)$ in Figures 5.12(h) and 5.12(i) indicate a rapid decrease due to the fewer infections. The control profiles in Figure 5.12(k) show that the two treatment controls, $u_{T1}(t)$, $u_{T2}(t)$ coincide and should be sustained at their peaks together with the effective human protection $u_P(t)$ in the implementation. This suggests that this combination strategy is most effective when sustained maximally for a long period of time. However, this control strategy keeps all the Vaccinated Populations to the lower bound.



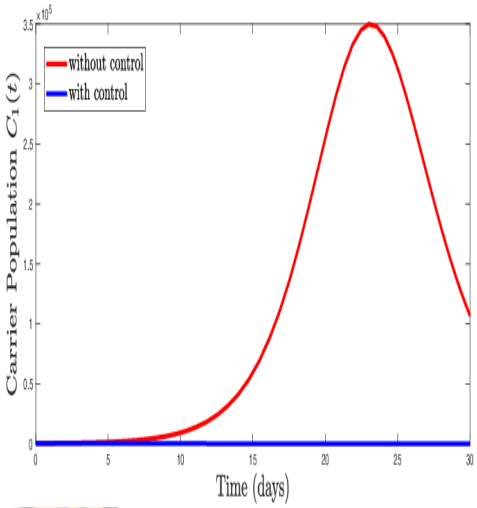
(a) Evolution of $S(t)$



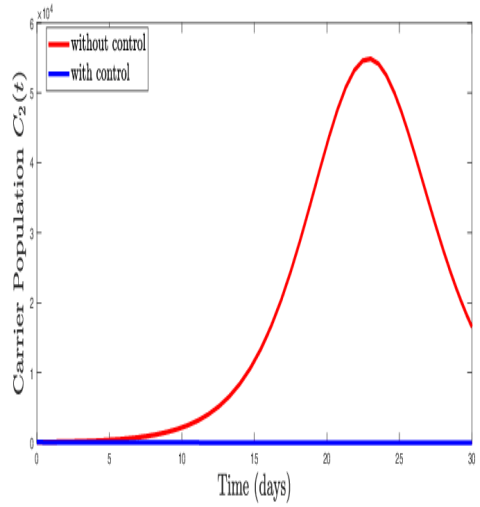
(b) Evolution of $V_1(t)$



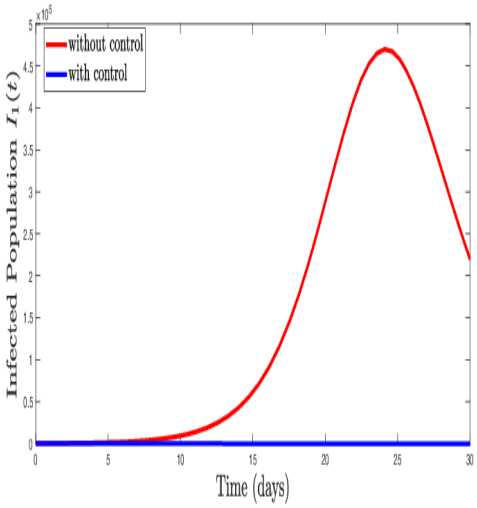
(c) Evolution of $V_2(t)$



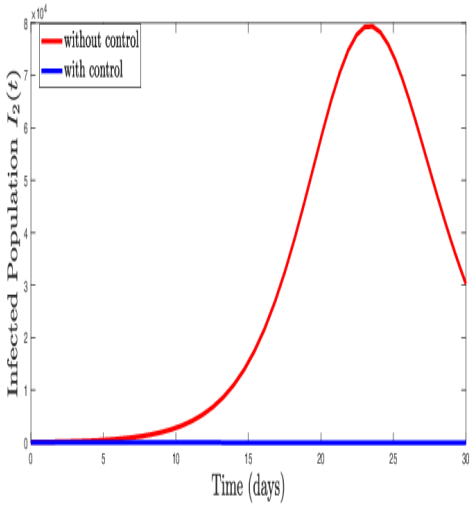
(d) Evolution of $C_1(t)$



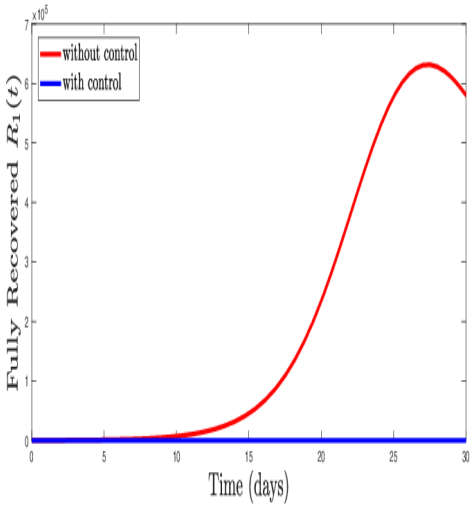
(e) Evolution of $C_2(t)$



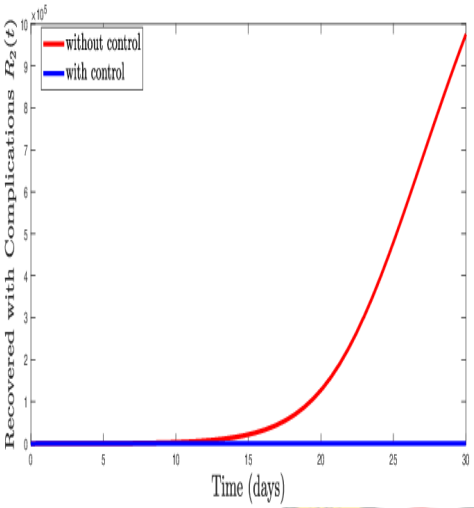
(f) Evolution of $I_1(t)$



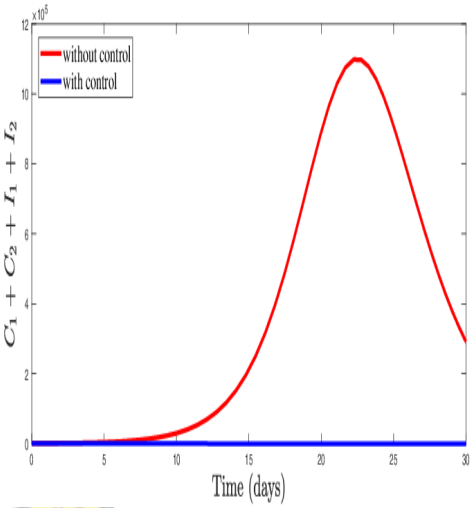
(g) Evolution of $I_2(t)$



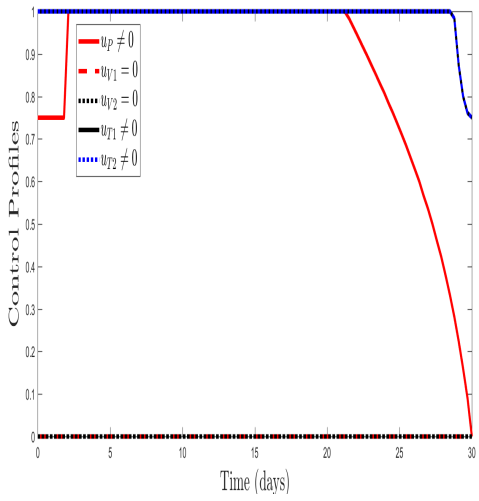
(h) Evolution of $R_1(t)$



(i) Evolution of $R_2(t)$



(j) Disease Prevalence

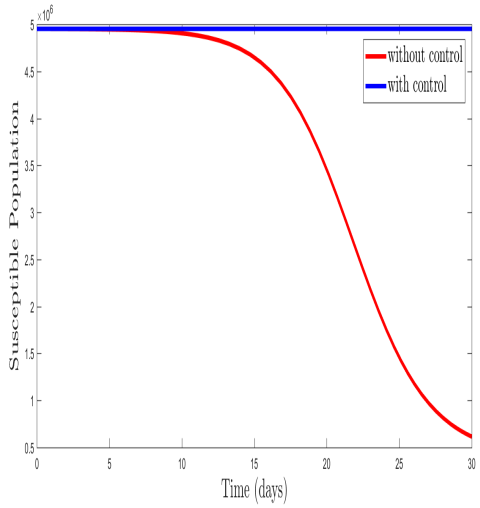


(k) Control Profiles

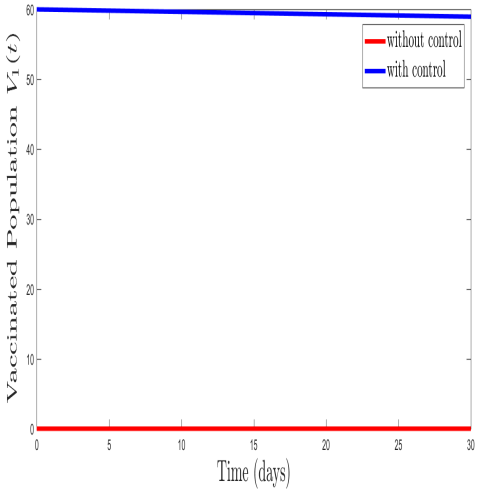
Figure 5.12 Effects of Effective Human Protection and Treatment for Timely and Delayed Diagnosis

5.3.3 Strategy C: Optimal Control with Effective Human Protection

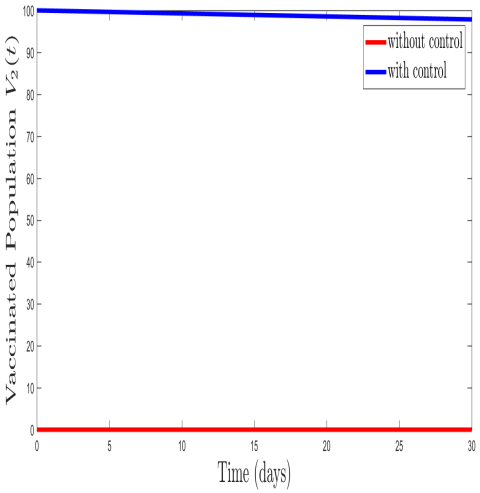
The objective functional is optimized with only effective human protection, $u_P(t)$ while setting the other controls: vaccination controls for both strains, $u_{V1}(t)$ and $u_{V2}(t)$, delayed and timely diagnosis treatment $u_{T1}(t)$ and $u_{T2}(t)$ to zero respectively. As indicated in Figure (5.13), the Susceptible Population $S(t)$ in Figure 5.13(a) remains stable for the whole 30 days due to the effective protection from the use of surgical or nose masks. The Vaccinated Populations of strain 1 and 2, $V_1(t)$, $V_2(t)$ in Figures 5.13(b) and 5.13(c) respectively achieve stability for the whole period considered since people don't get vaccinated. However, there is a tremendous decrease in all the Carrier Populations, $C_1(t)$, $C_2(t)$ and Infected Populations in Figures 5.13(d), 5.13(e), 5.13(f) and 5.13(g) respectively. This could be due to few infections because of the control introduced into the forces of infections. The two Recovered Populations $R_1(t)$, $R_2(t)$ in Figures 5.13(h) and 5.13(i) show a good decrease since fewer infections will lead to fewer people recovering from the disease. The control profiles in Figure 5.13(k), shows that the time-dependent control $u_P(t)$ is implemented and sustained at its peak but begins to decrease to the lower bound after the 25th day. This intervention strategy is seen to reduce the number of infections favourably.



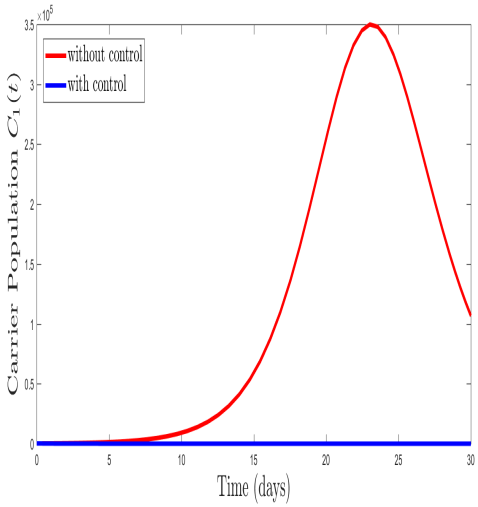
(a) Evolution of $S(t)$



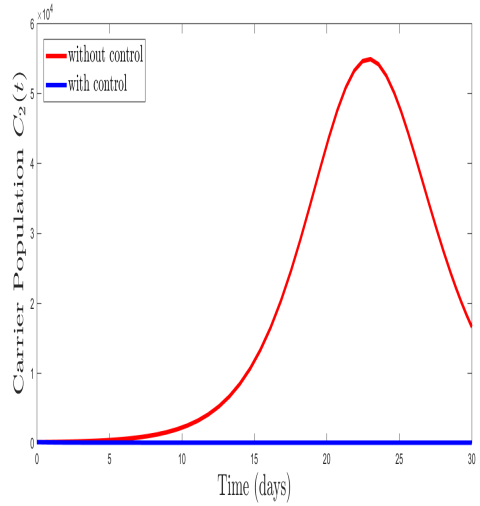
(b) Evolution of $V_1(t)$



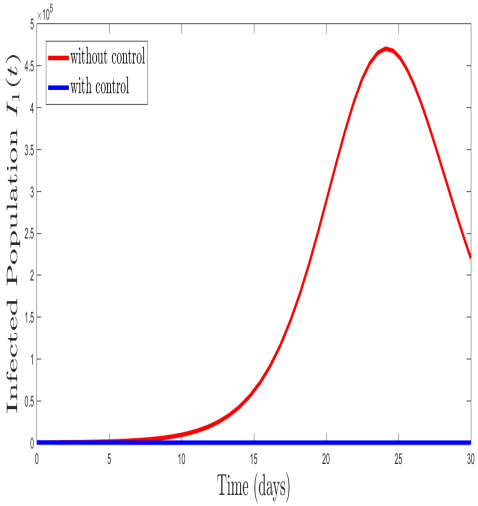
(c) Evolution of $V_2(t)$



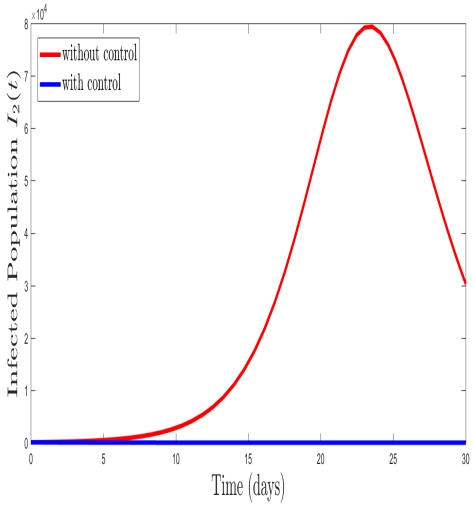
(d) Evolution of $C_1(t)$



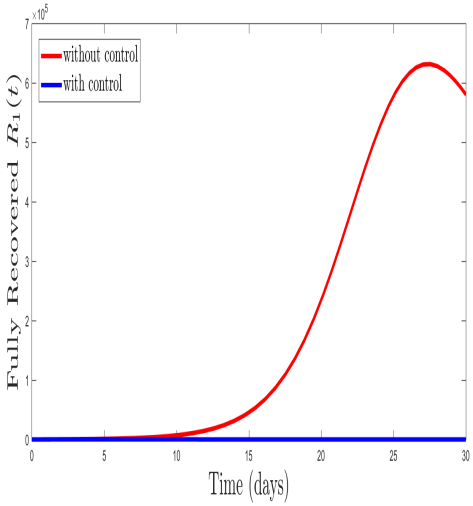
(e) Evolution of $C_2(t)$



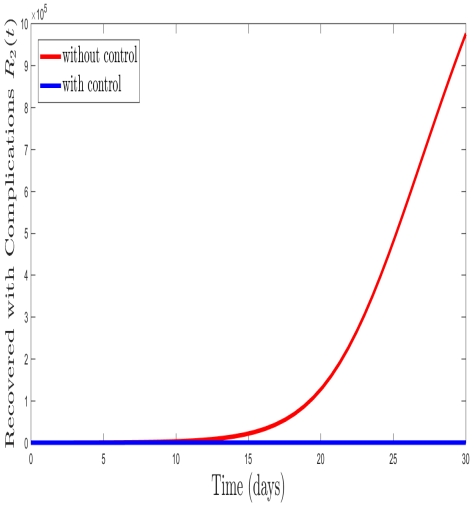
(f) Evolution of $I_1(t)$



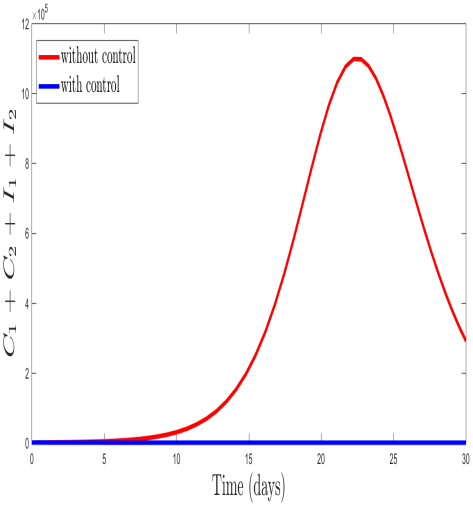
(g) Evolution of $I_2(t)$



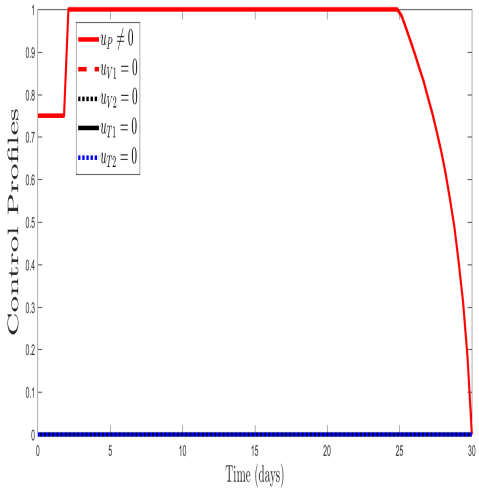
(h) Evolution of $R_1(t)$



(i) Evolution of $R_2(t)$



(j) Disease Prevalence

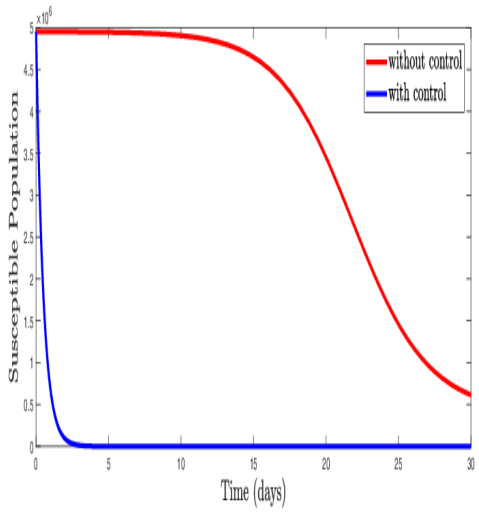


(k) Control Profiles

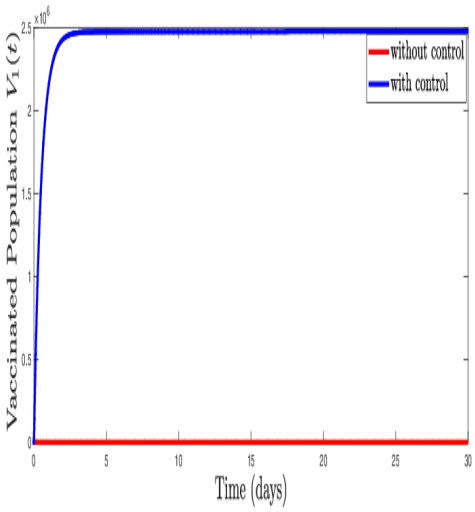
Figure 5.13 Effects of only Effective Human Protection such as face or surgical masks

5.3.4 Strategy D: Optimal Control with Vaccination for both Strains and Treatment for Delayed Diagnosis

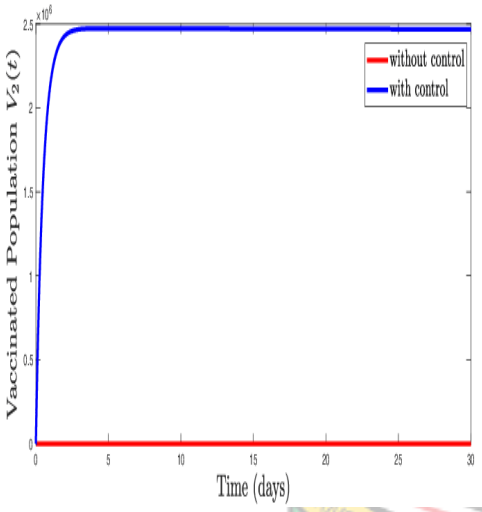
The objective functional is optimized with vaccination controls for both strains, $u_{V1}(t)$ and $u_{V2}(t)$ and delayed treatment control, $u_{T2}(t)$ while setting the other controls: the effective human protection control, $u_P(t)$ and timely treatment control, $u_{T1}(t)$ to zero respectively. From the results presented in Figure (5.14), it can be observed that the Susceptible Population $S(t)$ in Figure 5.14(a) reduced drastically within the first few days while the two Vaccinated Populations $V_1(t)$, $V_2(t)$ in Figures 5.14(b) and 5.14(c) increased and achieved stability due to the intervention of getting people vaccinated. This control intervention leads to a rapid depopulation of the two Carrier Populations $C_1(t)$, $C_2(t)$ in Figures 5.14(d) and 5.14(e) and the two Infected Populations $I_1(t)$, $I_2(t)$ in Figures 5.14(f) and 5.14(g). This contributes to the reduction in the disease prevalence as seen in Figure 5.14(j). This is realistic because the vaccination of the two strains will prevent people from being infected. The treatment control will also lead to a faster rate of recovery from the infection which will reduce the number of secondary infections. The two Recovered Populations $R_1(t)$, $R_2(t)$ in Figures 5.14(h) and 5.14(i) also show a drastic decrease since fewer infections will lead to fewer individuals recovering from the infection. The control profiles in Figure 5.14(k), shows that the time-dependent control $u_{V1}(t)$ must be implemented and sustained at its peak for close to 10 days. The time-dependent controls $u_{V2}(t)$ and $u_{T2}(t)$ coincide and should be increased slowly in the first few days and consistently decreasing rate overtime. This combination is seen to also reduce the number of infections.



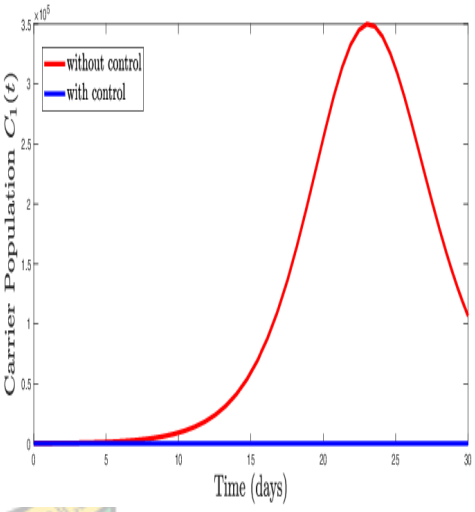
(a) Evolution of $S(t)$



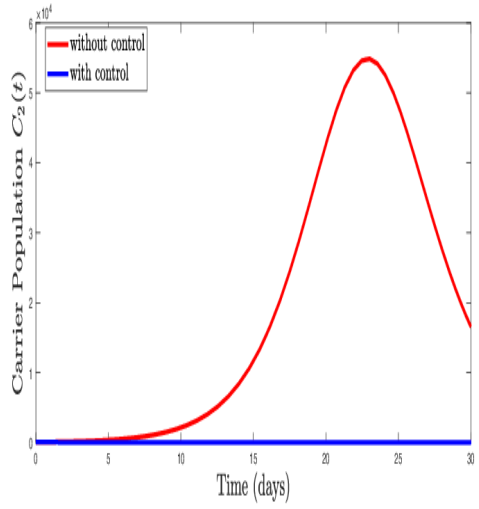
(b) Evolution of $V_1(t)$



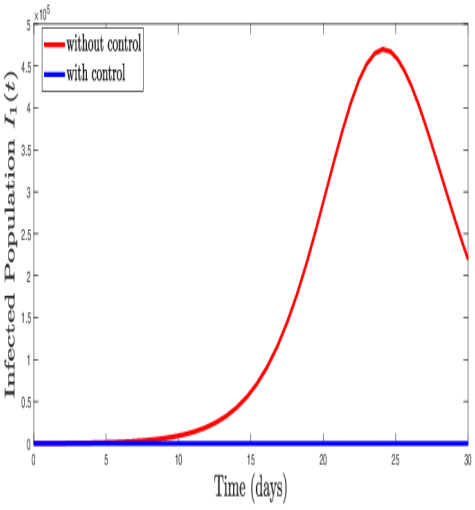
(c) Evolution of $V_2(t)$



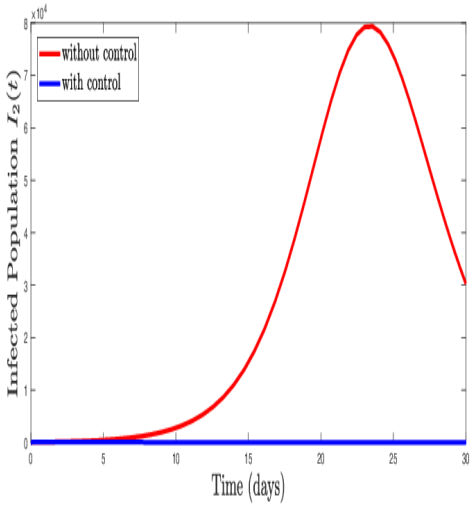
(d) Evolution of $C_1(t)$



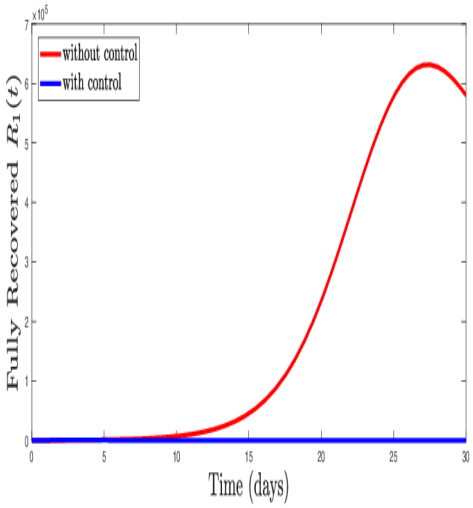
(e) Evolution of $C_2(t)$



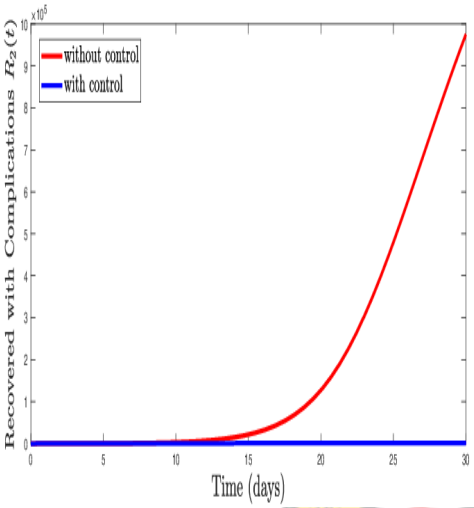
(f) Evolution of $I_1(t)$



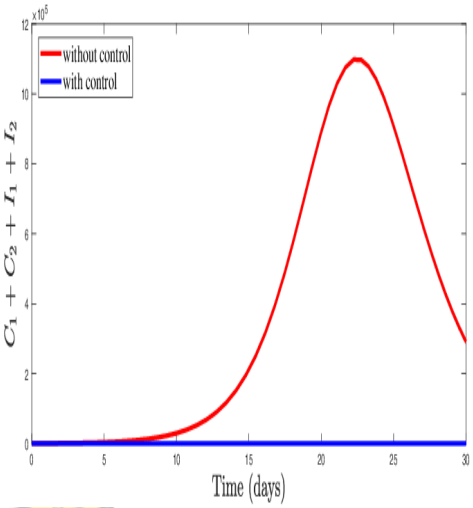
(g) Evolution of $I_2(t)$



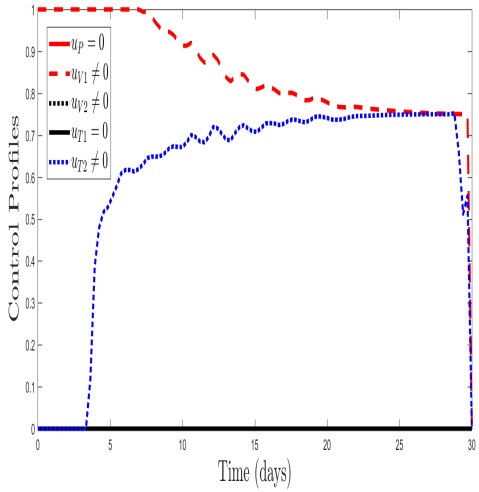
(h) Evolution of $R_1(t)$



(i) Evolution of $R_2(t)$



(j) Disease Prevalence

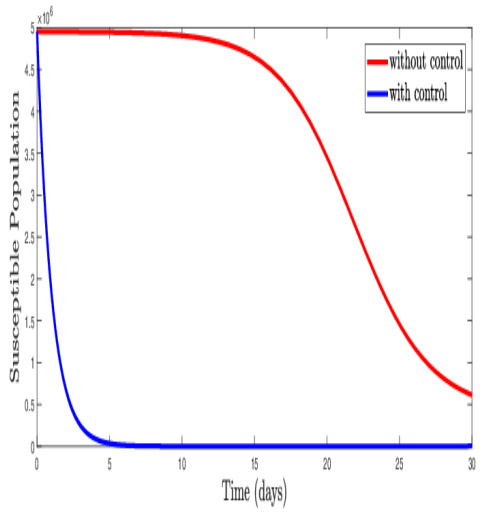


(k) Control Profiles

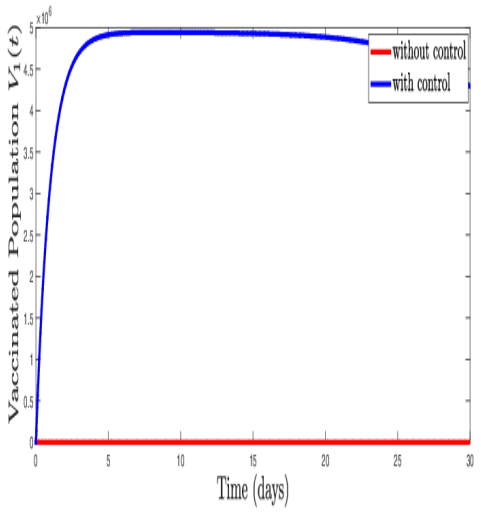
Figure 5.14 Effects of Vaccination for both Strains and Treatment for Delayed Diagnosis

5.3.5 Strategy E: Optimal Control with Vaccination for Strain 1 and Treatment for Timely and Delayed Diagnosis

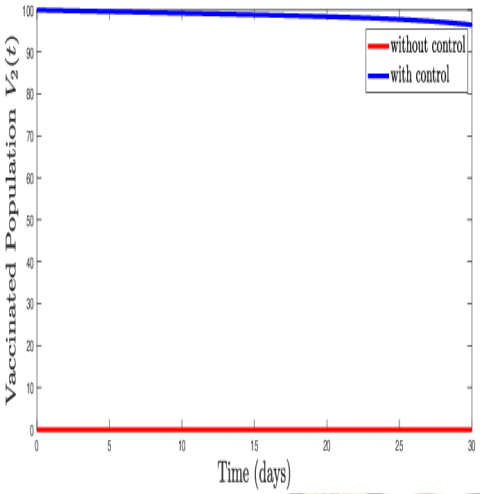
The objective functional is optimized with vaccination control for strain 1, $u_{V1}(t)$ and timely and delayed treatment controls, $u_{T1}(t)$, $u_{T2}(t)$ while setting the other controls: the effective human protection control, $u_P(t)$ and vaccination control for strain 2, $u_{V2}(t)$ to zero respectively. From the results presented in Figure (5.15), it can be observed that the Susceptible Population $S(t)$ in Figure 5.15(a) reduced rapidly within the first few days and achieves some stability afterwards. The Vaccinated Population of strain 1, $V_1(t)$ in Figure 5.15(b) increased drastically and achieved stability due to the intervention of getting people vaccinated but began to decrease close to day 20. This decrease could be attributed to the population getting infected with strain 2. The Vaccinated Population of strain 2, $V_2(t)$ in Figure 5.15(c) achieve stability for the whole period considered due to lack of people getting vaccinated with immunity for strain 2. This control intervention leads to a depopulation of the two Carrier Populations $C_1(t)$, $C_2(t)$ in Figures 5.15(d) and 5.15(e) due to the intervention of the timely diagnosis treatment. The Infected Population of strain 1, $I_1(t)$ in Figure 5.15(f) also reduced drastically while the Infected Population of strain 2, $I_2(t)$ in Figure 5.15(g) indicates an increase in the population. This shows that taking a vaccine against strain 1 infection is not enough to keep you protected from the disease. The behaviour of all the four infected populations can be viewed in Figure 5.15(j) which shows an indication of the disease persisting even with this control intervention. The two Recovered Populations $R_1(t)$, $R_2(t)$ in Figures 5.15(h) and 5.15(i) also show a decrease since the two treatment controls will lead to a faster recovery rate. However, they begin to increase after some time and this could be due to the recovery of more people from the strain 2 infection. The control profiles in Figure 5.15(k), shows that the time-dependent controls $u_{V1}(t)$, $u_{T1}(t)$ and $u_{T2}(t)$ must be implemented and sustained at its peak for the duration considered. However, $u_{V1}(t)$ begins to decrease close to the 30th day. This combination strategy is seen not to be the best as the number of infections begin to increase after some time.



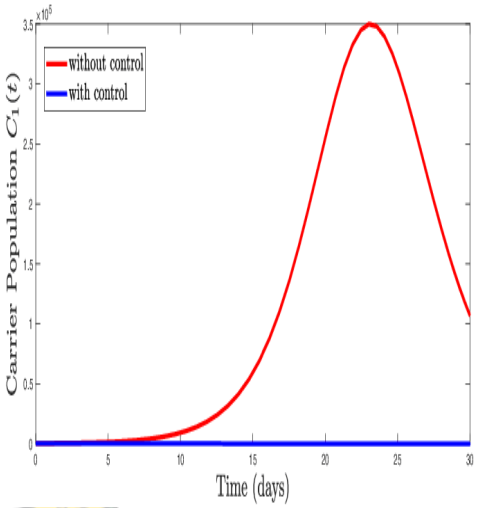
(a) Evolution of $S(t)$



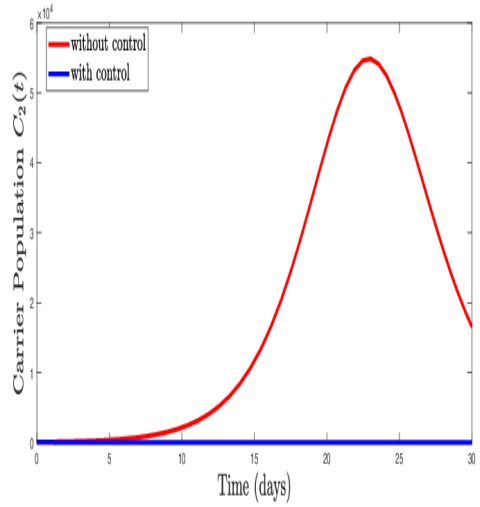
(b) Evolution of $V_1(t)$



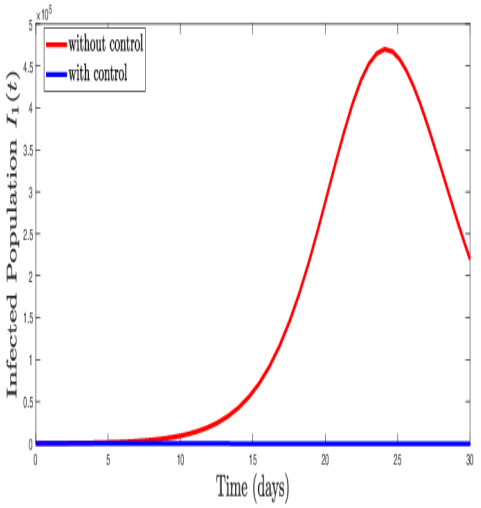
(c) Evolution of $V_2(t)$



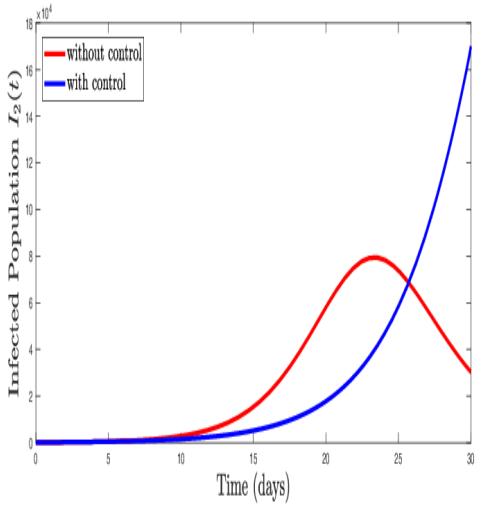
(d) Evolution of $C_1(t)$



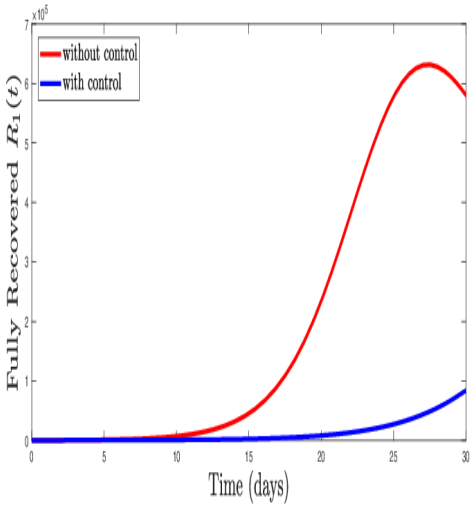
(e) Evolution of $C_2(t)$



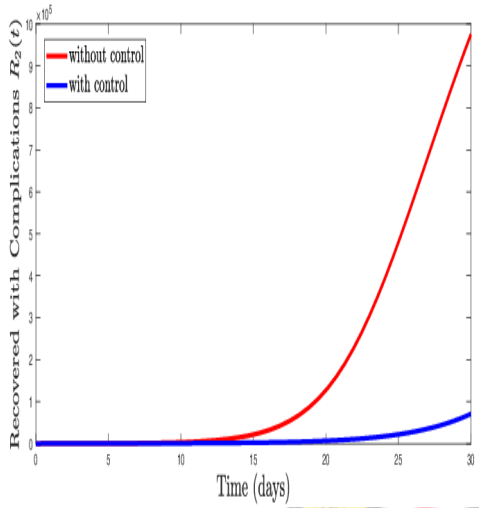
(f) Evolution of $I_1(t)$



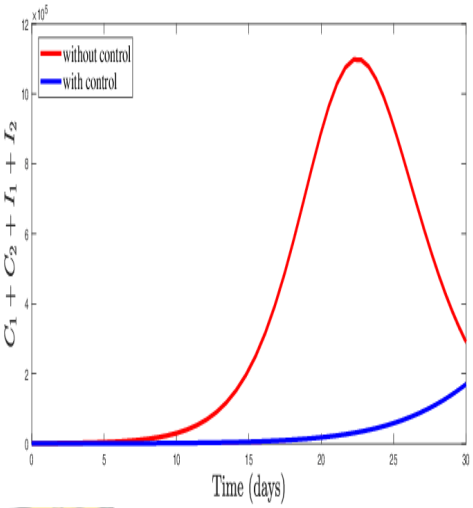
(g) Evolution of $I_2(t)$



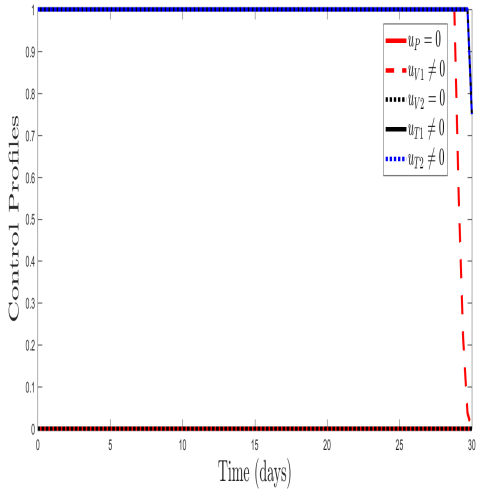
(h) Evolution of $R_1(t)$



(i) Evolution of $R_2(t)$



(j) Disease Prevalence

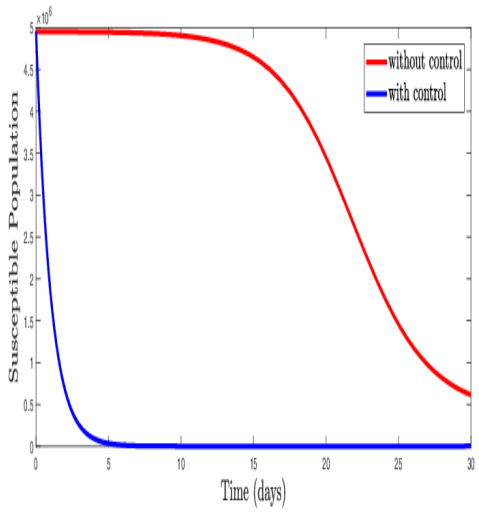


(k) Control Profiles

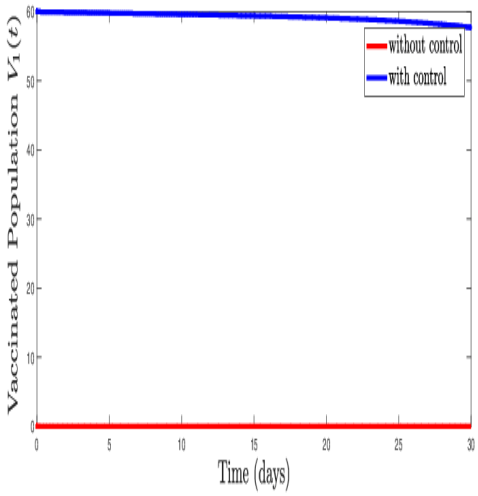
Figure 5.15 Effects of Vaccination for Strain 1 and Treatment for Timely and Delayed Diagnosis

5.3.6 Strategy F: Optimal Control with Vaccination for Strain 2 and Treatment for Timely and Delayed Diagnosis

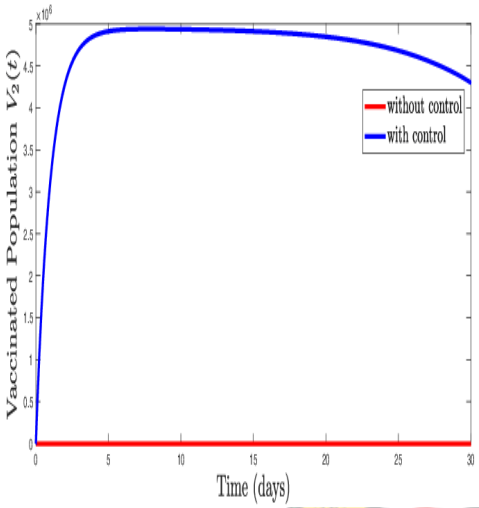
The objective functional is optimized with vaccination control for strain 2, $u_{V2}(t)$ and timely and delayed treatment controls, $u_{T1}(t)$, $u_{T2}(t)$ while setting the other controls: the effective human protection control, $u_P(t)$ and vaccination control for strain 1, $u_{V1}(t)$ to zero respectively. From the results presented in Figure (5.16), it can be observed that the Susceptible Population $S(t)$ in Figure 5.16(a) reduced drastically within the first few days and remains stable. The Vaccinated Population of strain 1, $V_1(t)$ in Figure 5.16(b) achieve stability for the whole period considered due to people not getting vaccinated with immunity for strain 1. The Vaccinated Population of strain 2, $V_2(t)$ in Figure 5.16(c) increased rapidly and achieved stability due to the intervention of people getting vaccinated but began to decrease close to day 20. This decrease could be attributed to the population getting infected with strain 1. The two Carrier Populations $C_1(t)$, $C_2(t)$ in Figures 5.16(d) and 5.16(e) depopulate due to the intervention of the timely diagnosis treatment. The Infected Population of strain 1, $I_1(t)$ in Figure 5.16(f) indicates a reduction for some period of time and an increase afterwards. The Infected Population of strain 2, $I_2(t)$ in Figure 5.16(g) rather shows a drastic decrease in the population. This shows that taking a vaccine against strain 2 infection is not enough to keep you protected from strain 1. The behaviour of all the four infected populations can be viewed in Figure 5.16(j) which shows an indication of the disease prevalence with this control intervention. The two Recovered Populations $R_1(t)$, $R_2(t)$ in Figures 5.16(h) and 5.16(i) show a decrease since the two treatment controls leads to a faster rate of recovery. However, they begin to increase after some time and this could be due to the recovery of more people from the strain 1 infection. The control profiles in Figure 5.16(k), show that the time-dependent controls $u_{V2}(t)$, $u_{T1}(t)$ and $u_{T2}(t)$ must be implemented and sustained at its peak and reduced gradually close to day 30. This combination strategy is also not the best since the number of infections increases after some time.



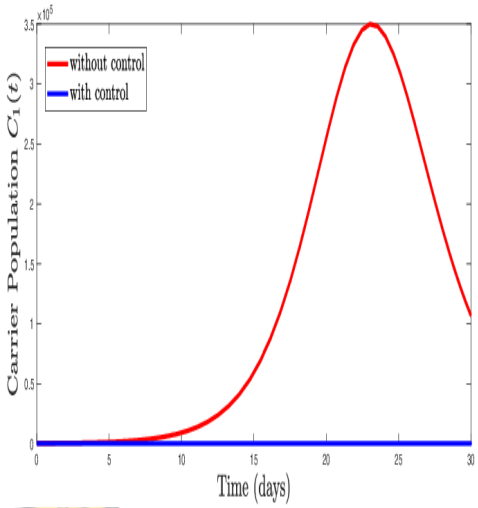
(a) Evolution of $S(t)$



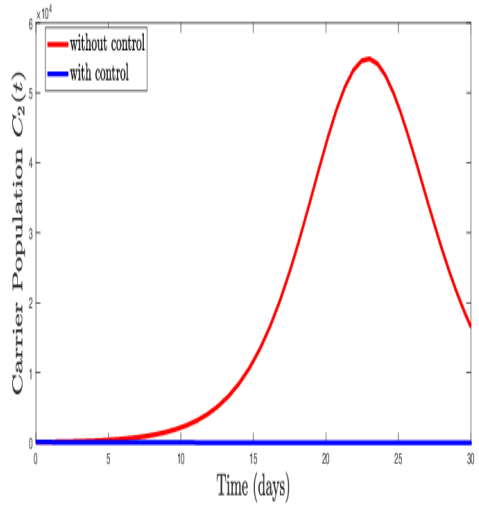
(b) Evolution of $V_1(t)$



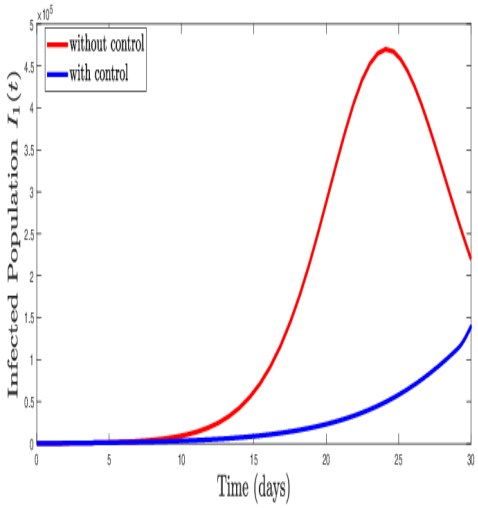
(c) Evolution of $V_2(t)$



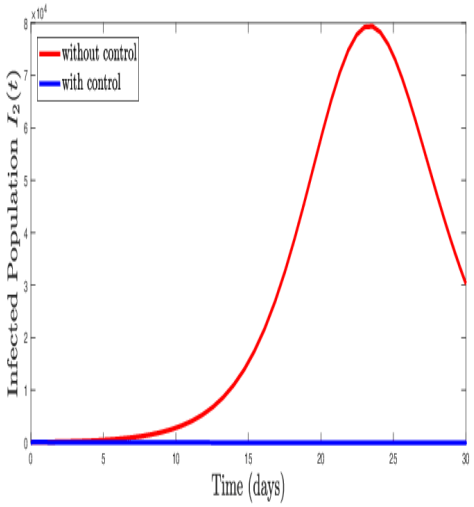
(d) Evolution of $C_1(t)$



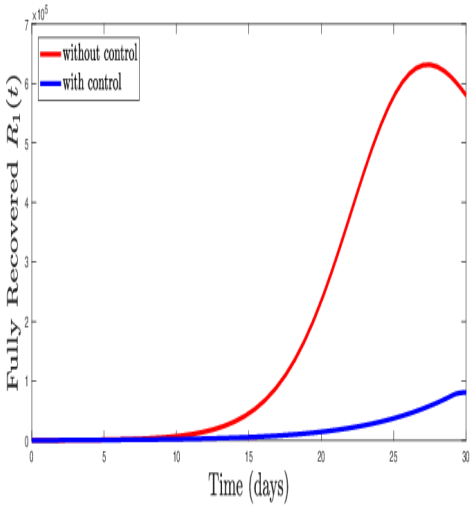
(e) Evolution of $C_2(t)$



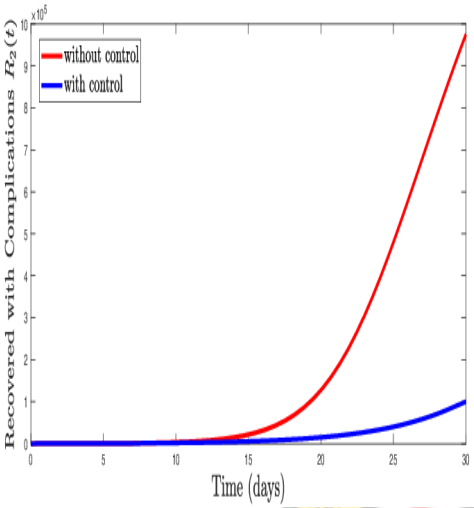
(f) Evolution of $I_1(t)$



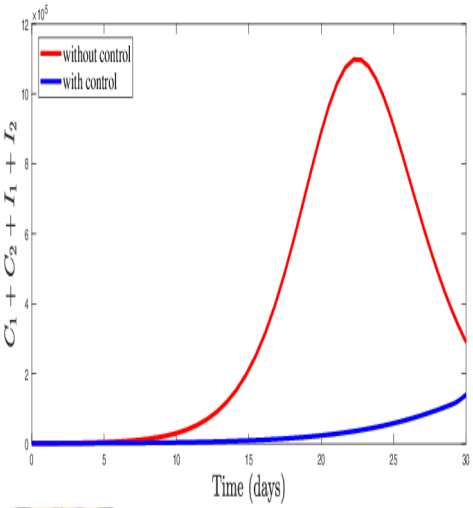
(g) Evolution of $I_2(t)$



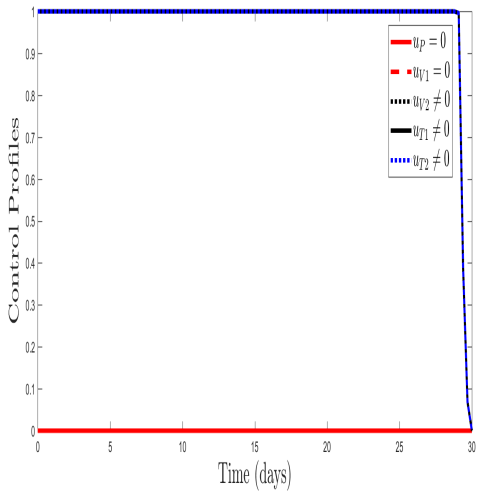
(h) Evolution of $R_1(t)$



(i) Evolution of $R_2(t)$



(j) Disease Prevalence

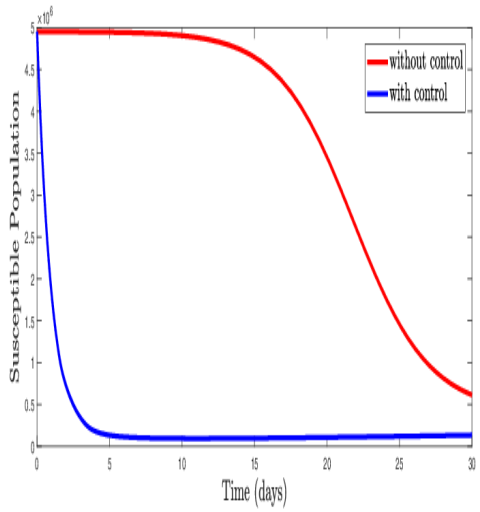


(k) Control Profiles

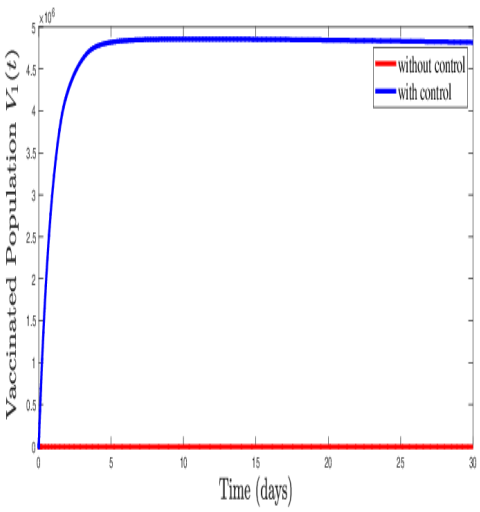
Figure 5.16 Effects of Vaccination for Strain 2 and Treatment for Timely and Delayed Diagnosis

5.3.7 Strategy G: Optimal Control with Effective Human Protection, Vaccination for Strain 1 and Treatment for Timely and Delayed Diagnosis

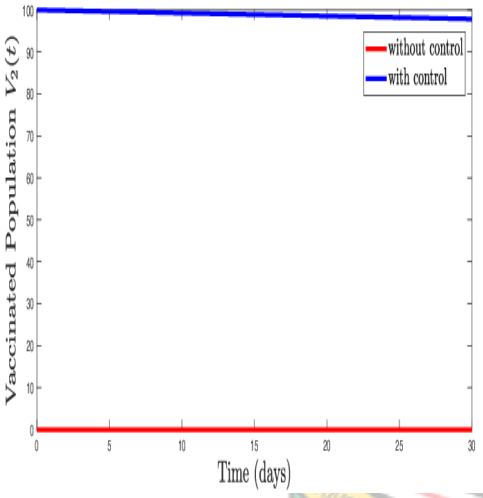
The objective functional is optimized with effective human protection control, $u_P(t)$, vaccination control for strain 1, $u_{V1}(t)$ and timely and delayed treatment controls, $u_{T1}(t)$, $u_{T2}(t)$ while setting the vaccination control for strain 2, $u_{V2}(t)$ to zero. From the results presented in Figure (5.17), it can be observed that the Susceptible Population $S(t)$ in Figure 5.17(a) reduced drastically within the first few days and achieves some stability afterwards. The Vaccinated Population of strain 1, $V_1(t)$ in Figure 5.17(b) increased drastically and achieved stability due to the intervention of people getting vaccinated. The Vaccinated Population of strain 2, $V_2(t)$ in Figure 5.17(c) remains stable for the whole period considered in the absence of the vaccination control for strain 2. This control intervention leads to a depopulation of the two Carrier Populations $C_1(t)$, $C_2(t)$ in Figures 5.17(d) and 5.17(e) due to the introduction of the effective human protection into the forces of infection and the intervention of the timely diagnosis treatment. The Infected Populations of strain 1, $I_1(t)$ in Figure 5.17(f) and strain 2, $I_2(t)$ in Figure 5.17(g) show a tremenduous decrease in the two populations. This shows that the effective human protection and vaccination against strain 1 infection reduce the spread of infections. The disease prevalence in Figure 5.17(j) shows a reduction with this control intervention strategy. The two Recovered Populations $R_1(t)$, $R_2(t)$ in Figures 5.17(h) and 5.17(i) show a decrease due to less infections and intervention of the two treatment controls. The control profiles in Figure 5.17(k), show that the time-dependent controls $u_{T1}(t)$ and $u_{T2}(t)$ coincide and must be implemented and sustained at its peak up to the 25th day. The time-dependent control, $u_P(t)$ must be implemented from 0.75, increased after some few days and sustained at the upper bound till the 25th day where its reduces gradually to its initial point. $u_{V1}(t)$ on the other hand, starts from the upper bound and reduces to the lower bound close to the 15th day. This combination strategy reduces the number of infections favourably.



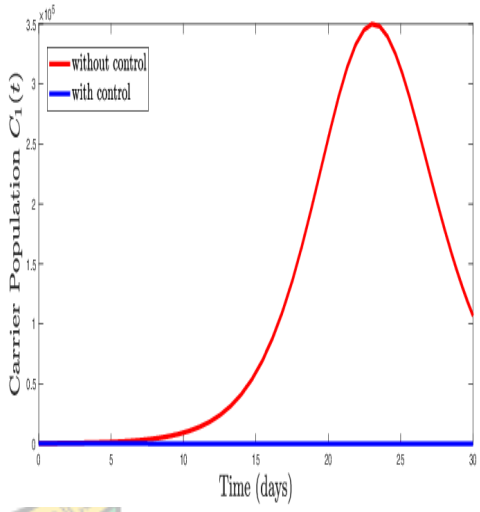
(a) Evolution of $S(t)$



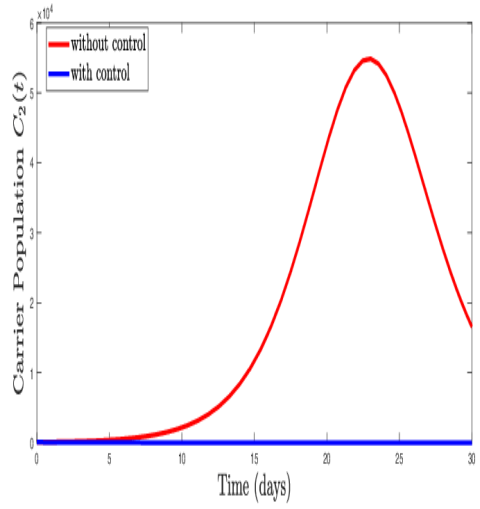
(b) Evolution of $V_1(t)$



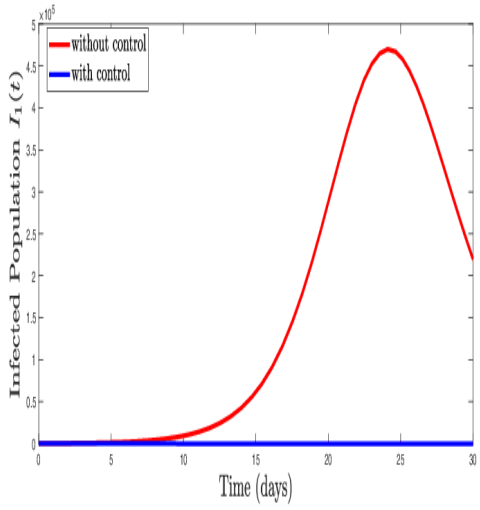
(c) Evolution of $V_2(t)$



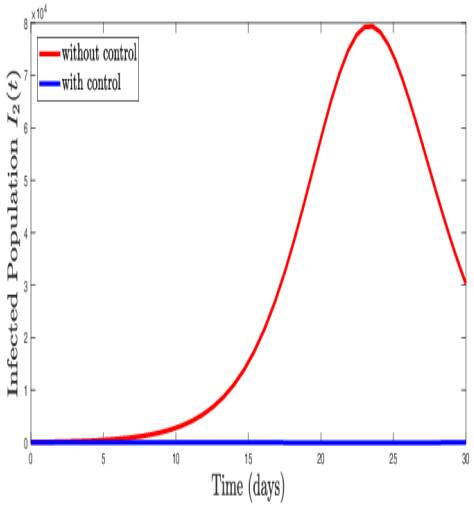
(d) Evolution of $C_1(t)$



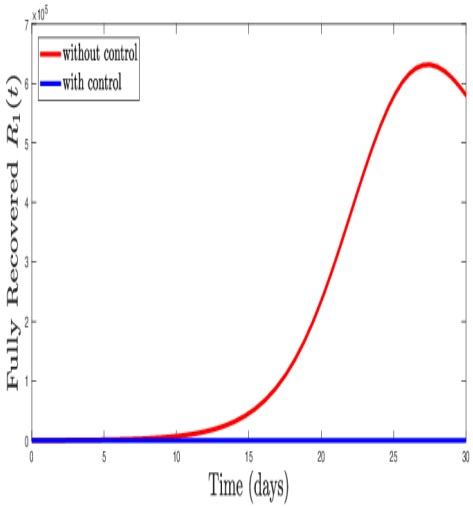
(e) Evolution of $C_2(t)$



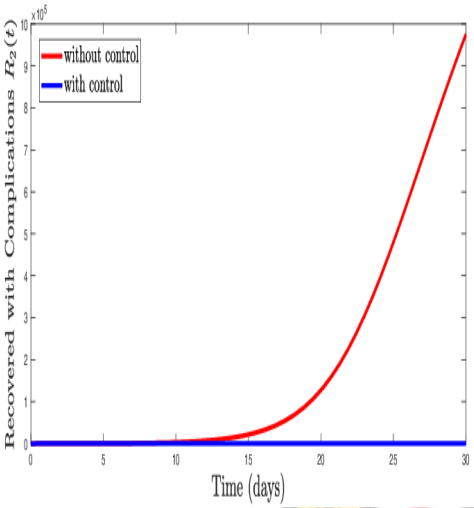
(f) Evolution of $I_1(t)$



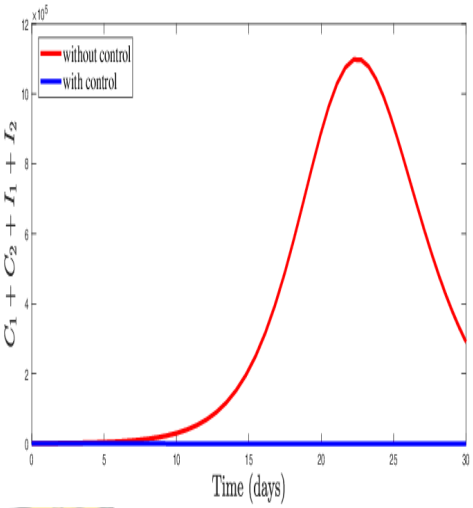
(g) Evolution of $I_2(t)$



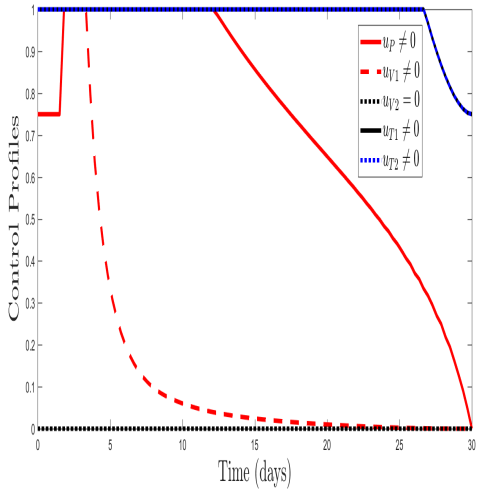
(h) Evolution of $R_1(t)$



(i) Evolution of $R_2(t)$



(j) Disease Prevalence

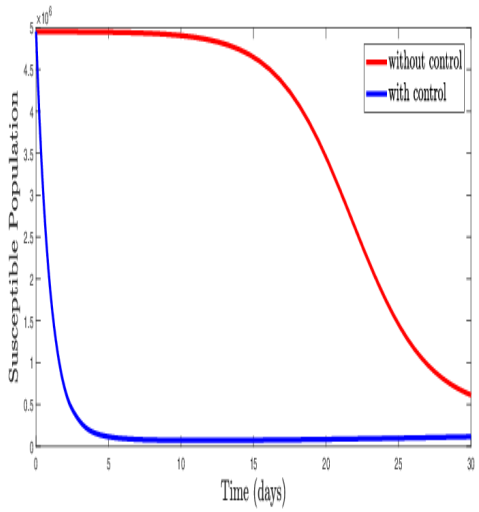


(k) Control Profiles

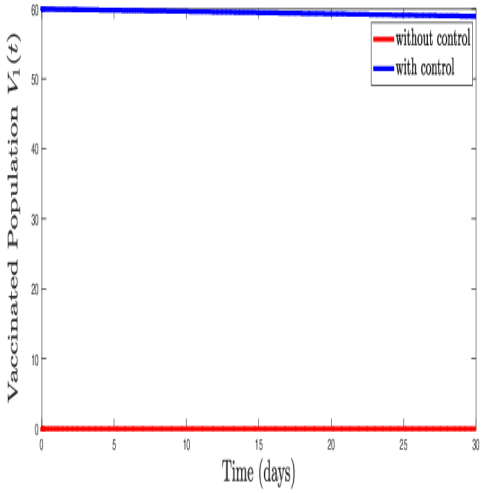
Figure 5.17 Effects of Effective Human Protection, Vaccination for Strain 1 and Treatment for Timely and Delayed Diagnosis

5.3.8 Strategy H: Optimal Control with Effective Human Protection, Vaccination for Strain 2 and Treatment for Timely and Delayed Diagnosis

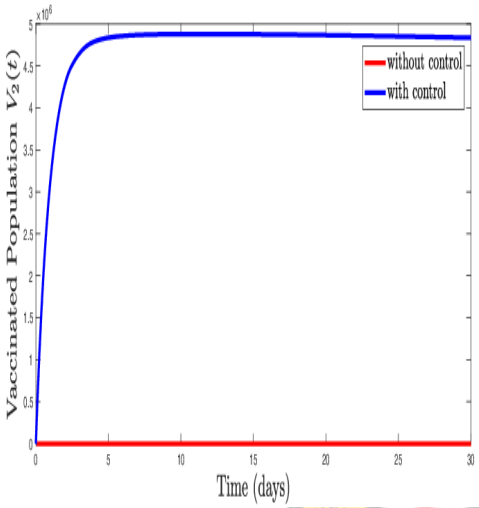
The objective functional is optimized with effective human protection control, $u_P(t)$, vaccination control for strain 2, $u_{V2}(t)$ and timely and delayed treatment controls, $u_{T1}(t)$, $u_{T2}(t)$ while setting the vaccination control for strain 1, $u_{V1}(t)$ to zero. From the results presented in Figure (5.18), it can be observed that the Susceptible Population $S(t)$ in Figure 5.18(a) reduced rapidly within the first few days and remains stable afterwards. The Vaccinated Population of strain 1, $V_1(t)$ in Figure 5.18(b) achieves stability for the whole period considered in the absence of the vaccination control for strain 1. The Vaccinated Population of strain 2, $V_2(t)$ in Figure 5.18(c) increased steadily and achieved stability due to the intervention of people getting vaccinated. This control intervention strategy leads to a depopulation of the two Carrier Populations $C_1(t)$, $C_2(t)$ in Figures 5.18(d) and 5.18(e) due to the introduction of the effective human protection into the forces of infection and the intervention of the timely diagnosis treatment. The Infected Populations of strain 1, $I_1(t)$ in Figure 5.18(f) and strain 2, $I_2(t)$ in Figure 5.18(g) show a drastic decrease in the two populations. This indicates that the effective human protection and vaccination against strain 2 infection reduce the spread of infections. The disease prevalence in Figure 5.18(j) shows a reduction with this control intervention strategy. The two Recovered Populations $R_1(t)$, $R_2(t)$ in Figures 5.18(h) and 5.18(i) show a decrease due to less infections and intervention of the two treatment controls. The control profiles in Figure 5.18(k), show that the time-dependent controls, $u_{V2}(t)$, $u_{T1}(t)$ and $u_{T2}(t)$ coincide and must be implemented and sustained at its peak up to the 5th day and reduced gradually to the lower bound. The time-dependent control, $u_P(t)$ must also be implemented from 0.75, increased after some few days and sustained at the upper bound till the 22nd day where its reduces gradually to the lower bound. This combination strategy reduces the number of infections favourably.



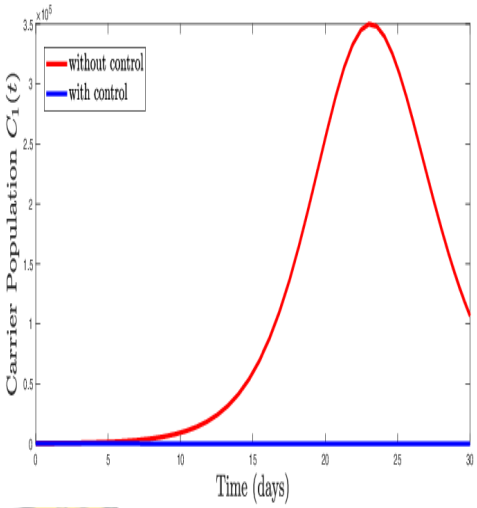
(a) Evolution of $S(t)$



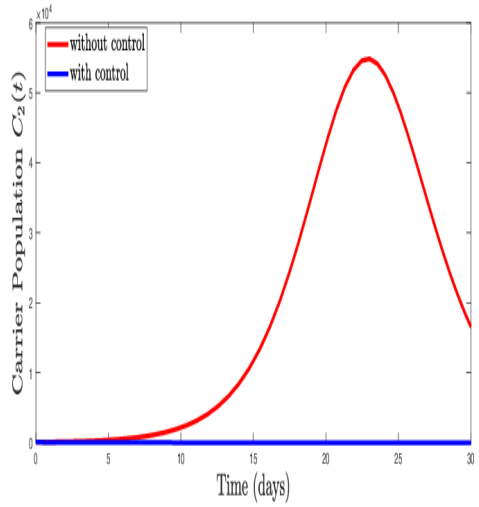
(b) Evolution of $V_1(t)$



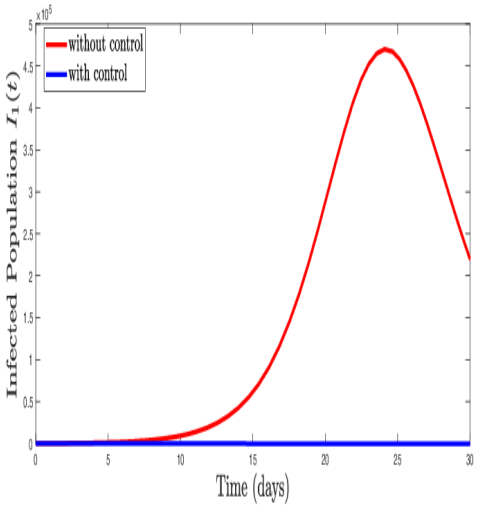
(c) Evolution of $V_2(t)$



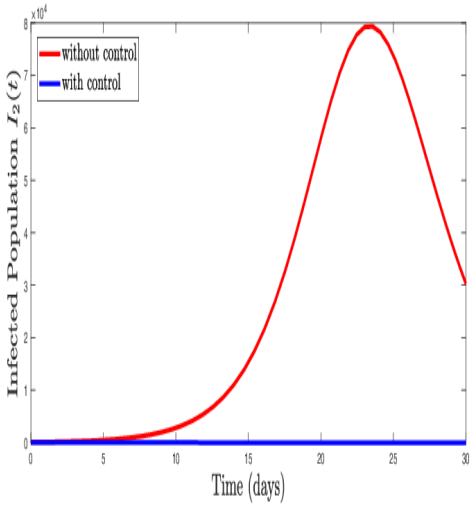
(d) Evolution of $C_1(t)$



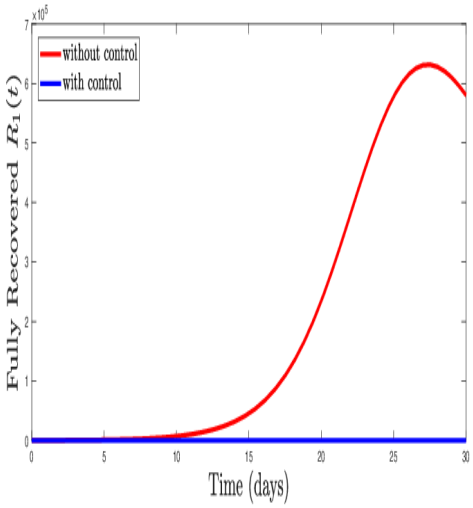
(e) Evolution of $C_2(t)$



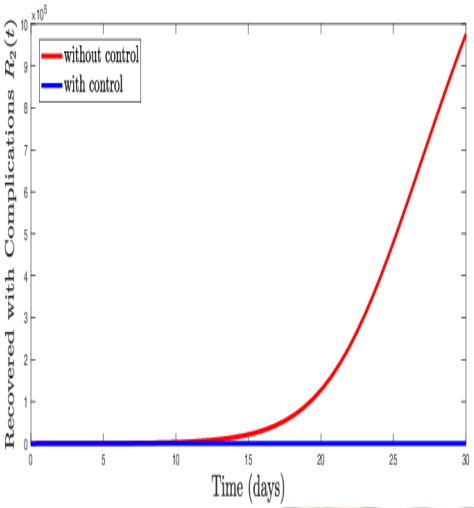
(f) Evolution of $I_1(t)$



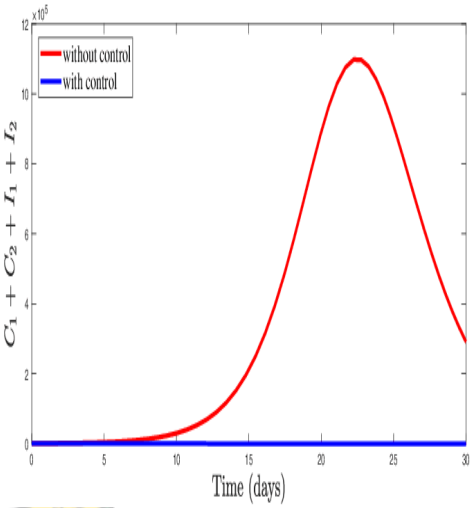
(g) Evolution of $I_2(t)$



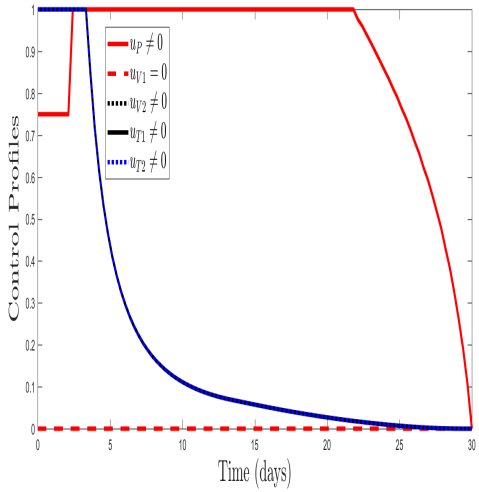
(h) Evolution of $R_1(t)$



(i) Evolution of $R_2(t)$



(j) Disease Prevalence

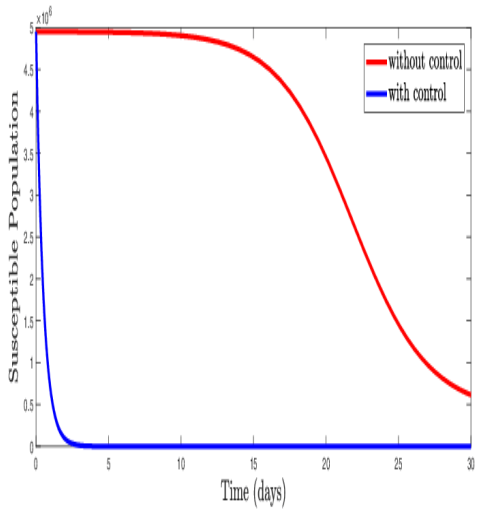


(k) Control Profiles

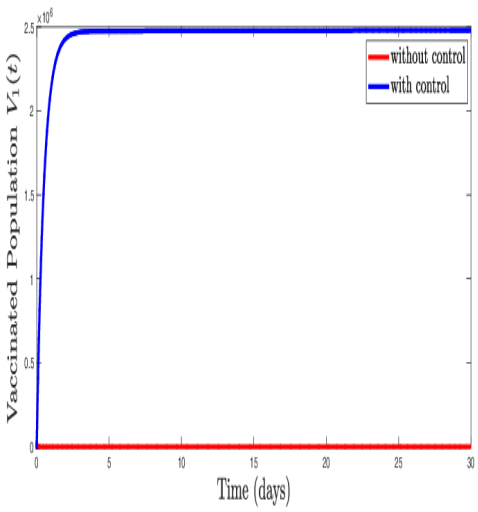
Figure 5.18 Effects of Effective Human Protection, Vaccination for Strain 2 and Treatment for Timely and Delayed Diagnosis

5.3.9 Strategy I: Optimal Control with Vaccination for both Strains and Treatment for Timely and Delayed Diagnosis

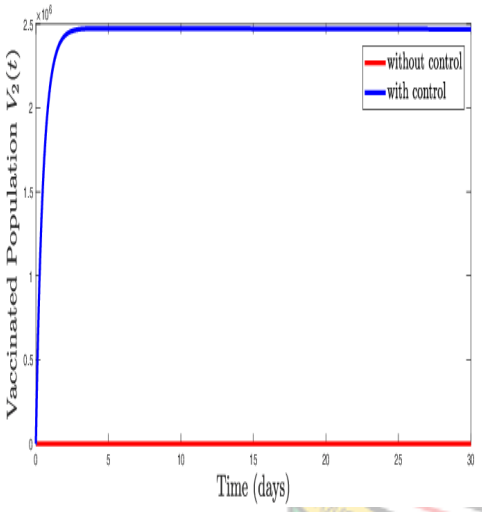
The objective functional is optimized with vaccination control for both strains, $u_{V1}(t)$, $u_{V2}(t)$ and timely and delayed treatment controls, $u_{T1}(t)$, $u_{T2}(t)$ while setting the effective human protection control, $u_P(t)$ to zero. From the results presented in Figure (5.19), it can be observed that the Susceptible Population $S(t)$ in Figure 5.19(a) reduced rapidly within the first few days and achieves stability afterwards. The Vaccinated Populations of strain 1, $V_1(t)$ in Figure 5.19(b) and strain 2, $V_2(t)$ in Figure 5.19(c) increase rapidly and achieve stability due to the intervention of people getting vaccinated for both strains. The two Carrier Populations, $C_1(t)$ and $C_2(t)$ in Figures 5.19(d) and 5.19(e) respectively depict a reduction in the populations due to the intervention of the timely diagnosis treatment and the vaccines. The Infected Populations of strain 1, $I_1(t)$ in Figure 5.19(f) and strain 2, $I_2(t)$ in Figure 5.19(g) present a tremenduous decrease in the two populations. The disease prevalence can be viewed in Figure 5.19(j) which shows that this combination strategy is capable of curtailing the spread of the disease. The two Recovered Populations $R_1(t)$, $R_2(t)$ in Figures 5.19(h) and 5.19(i) show a decrease since the vaccines for the two strains leads to fewer infections, with the two treatment controls also influencing the faster rates of recovery. The control profiles in Figure 5.19(k) show that the time-dependent controls $u_{V2}(t)$, $u_{T1}(t)$ and $u_{T2}(t)$ coincide and must be increased gradually from the lower bound and sustained. $u_{V1}(t)$ on the other hand must be implemented at its peak and decreased slowly after the 4th day to the lower bound.



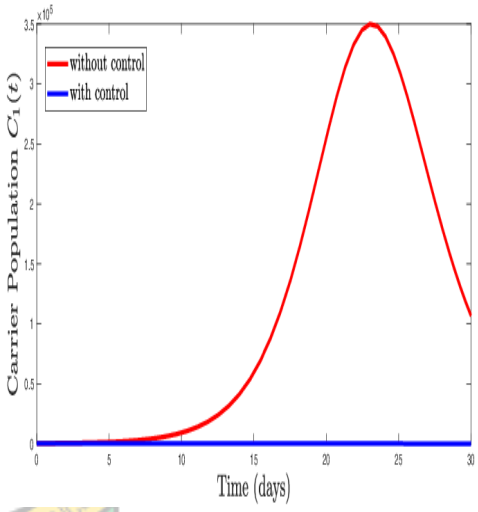
(a) Evolution of $S(t)$



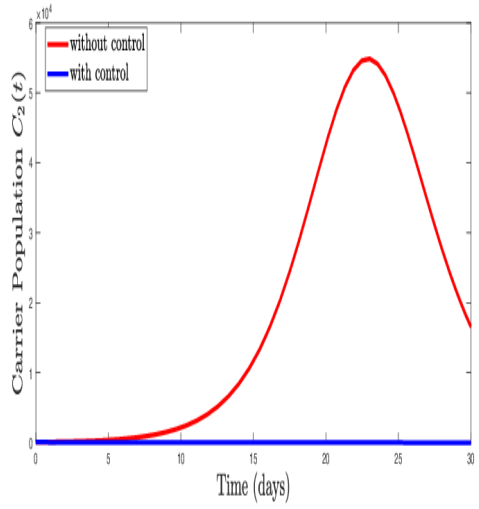
(b) Evolution of $V_1(t)$



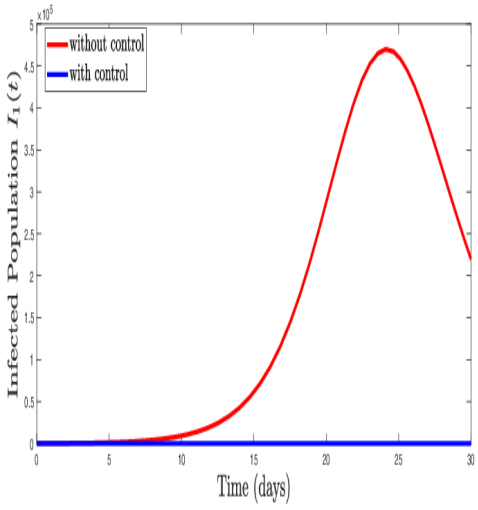
(c) Evolution of $V_2(t)$



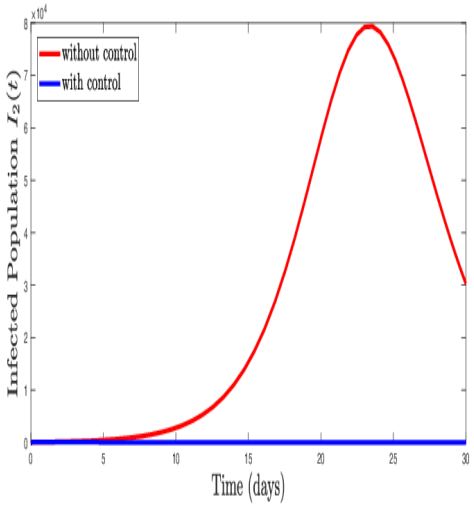
(d) Evolution of $C_1(t)$



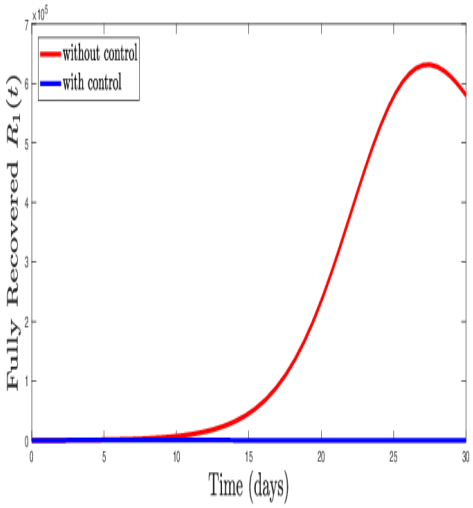
(e) Evolution of $C_2(t)$



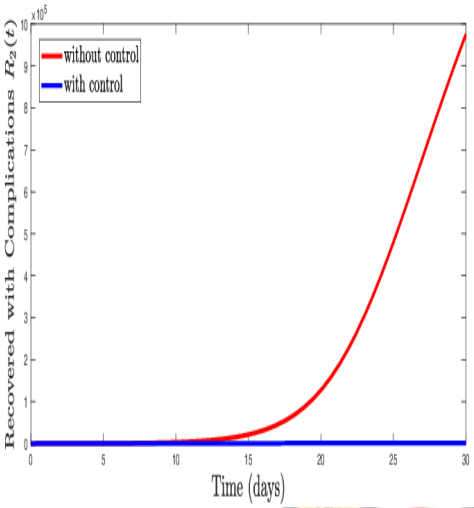
(f) Evolution of $I_1(t)$



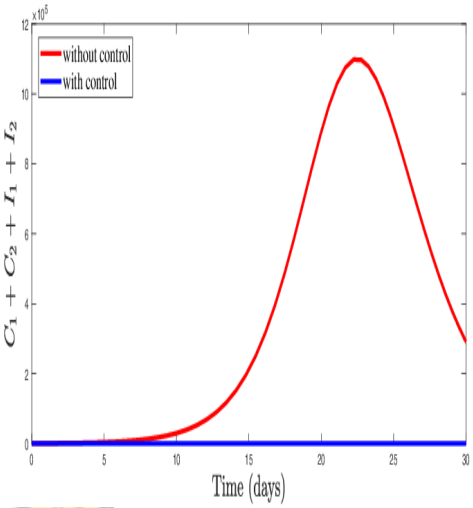
(g) Evolution of $I_2(t)$



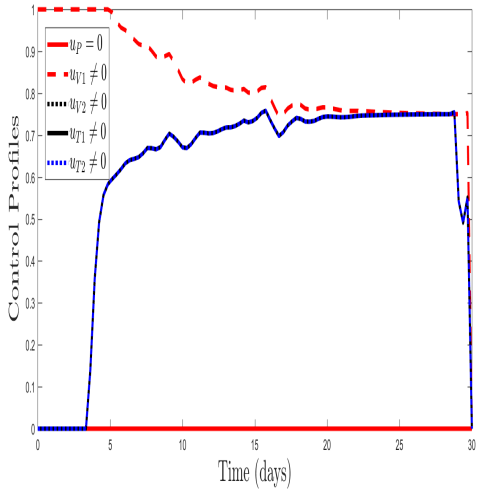
(h) Evolution of $R_1(t)$



(i) Evolution of $R_2(t)$



(j) Disease Prevalence



(k) Control Profiles

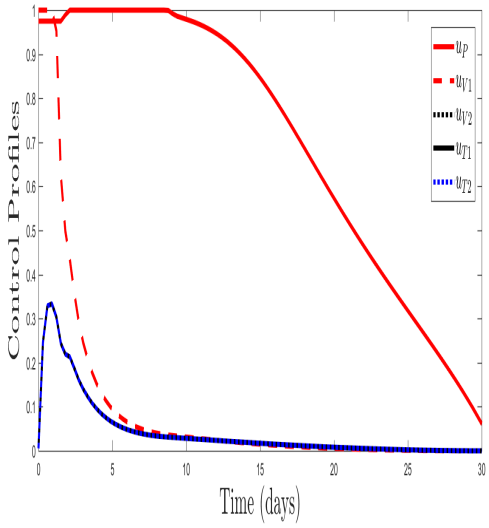
Figure 5.19 Effects of Vaccination for both Strains and Treatment for Timely and Delayed Diagnosis

5.4 Cost-Effectiveness Analysis

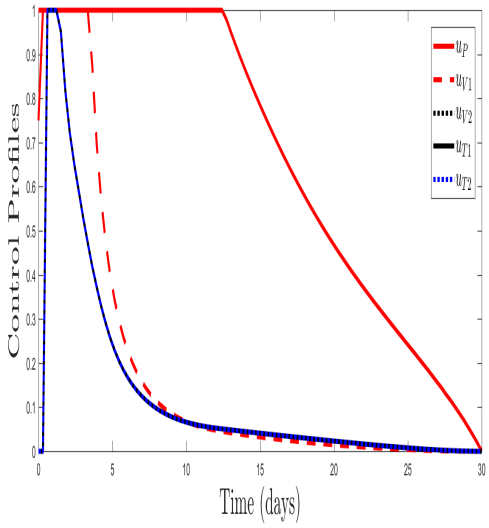
To control and eradicate diseases in a community can be both costly and labor intensive, as such, it is essential to conduct a cost-effectiveness analysis to determine the most cost-effective strategy to use. In this section, a cost-effectiveness analysis is conducted to ascertain the costs associated with the health interventions or strategies which includes the use of effective human personal protection (such as face or surgical masks), vaccination for both strains and timely and delayed diagnosis treatments, and the associated benefits gained from implementing these controls. Following the works of Agusto and ELmojtaba (2017) and Agusto (2013), the cost weights associated with all the five controls are being varied since changes in them give a distinct cost of implementing the control strategies. This is achieved by varying one control at a time keeping all the other controls at the baseline value of 1. The varied weights are 0.10, 1.0, 10.0 and 100 representing very cheap, cheap, expensive and very expensive respectively. The cost-effective analysis is implemented using three different approaches; namely, the Infection Averted Ratio (IAR), the Average Cost-Effectiveness Ratio (ACER) and the Incremental Cost-Effectiveness Ratio (ICER). Ten (10) control strategies consisting of the various combination of time-dependent controls and all the controls are considered for this analysis.

5.4.1 Varying the Weight B_1 associated with Control $u_P(t)$

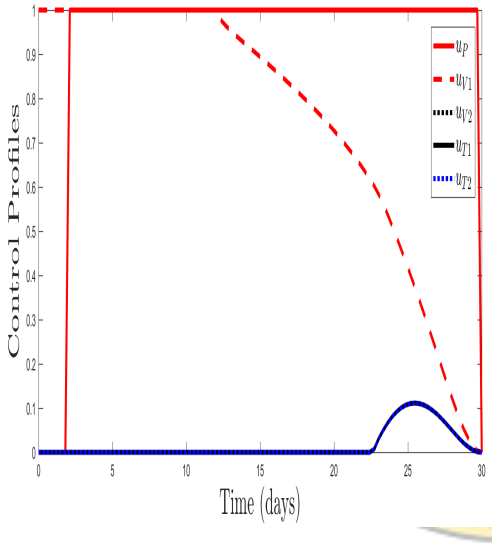
The variation of the weight of the effective personal human protection such as face or surgical masks shows that as the weight B_1 increases from low to high, that is from very cheap to very expensive cost, $u_P(t)$ and $u_{V1}(t)$ increase to the upper bound. $u_{V2}(t)$, $u_{T1}(t)$ and $u_{T2}(t)$ on the other hand increase when B_1 is low and later decrease when B_1 is high, that is very expensive cost. The profile of the control solutions are presented in Figure 5.20. This reciprocal relationship will help to keep the community protected and the infection low and that can be seen in the following state variables in Figure 5.21.



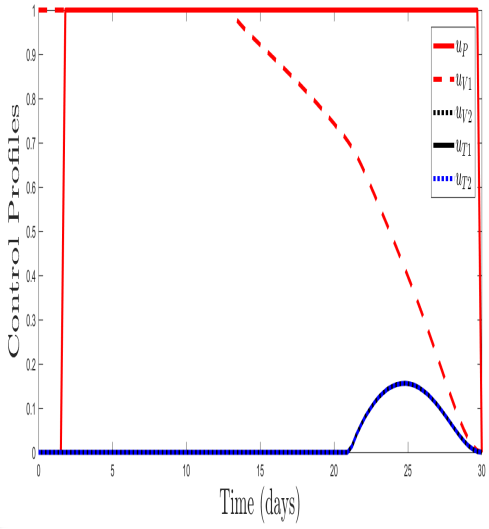
(a) Cost Weight $B_1 = 0.10$



(b) Cost Weight $B_1 = 1.0$

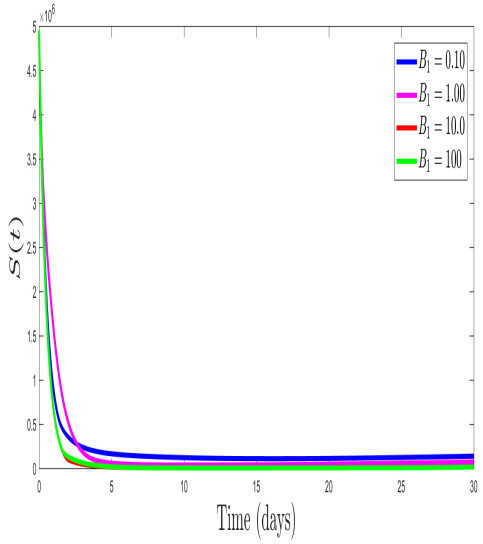


(c) Cost Weight $B_1 = 10.0$

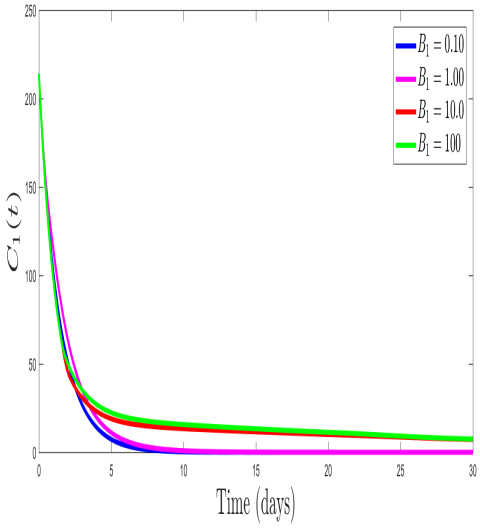


(d) Cost Weight $B_1 = 100$

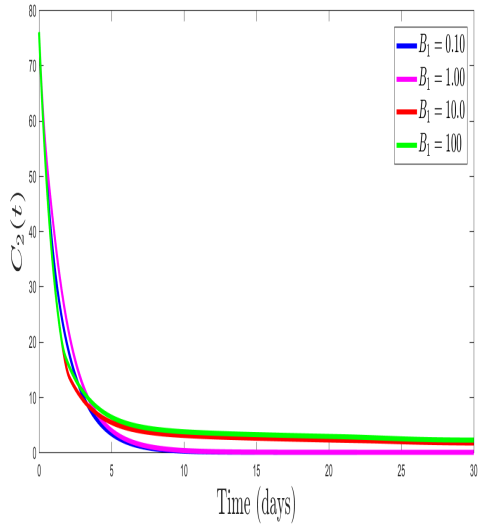
Figure 5.20 Control Profiles using Cost Weights $B_1 = 0.10$, $B_1 = 1.0$, $B_1 = 10.0$ and $B_1 = 100$



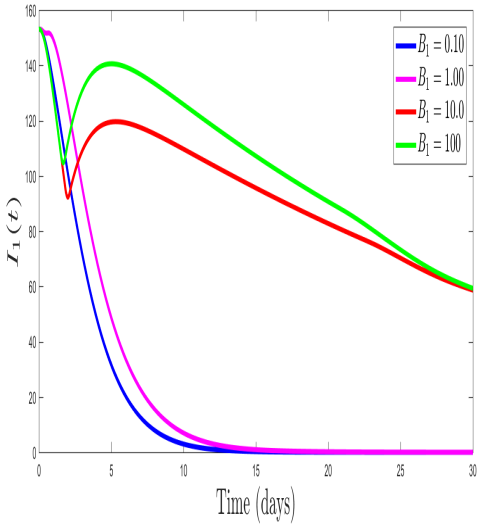
(a) Susceptible varying B_1



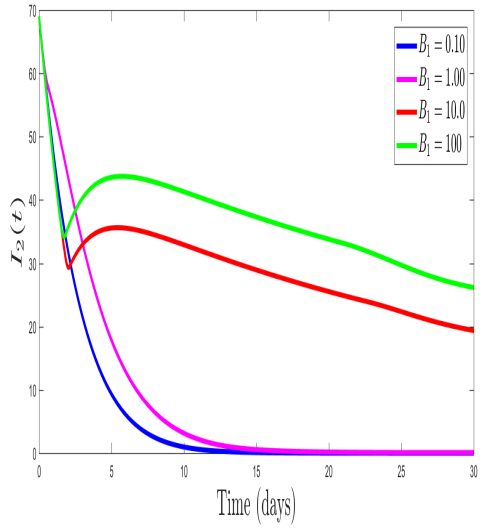
(b) Carrier of Strain 1 varying B_1



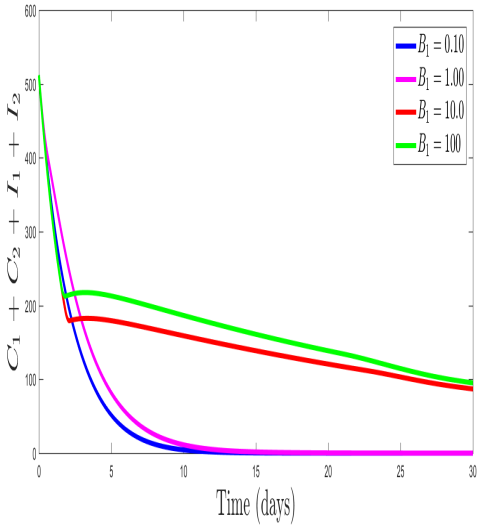
(c) Carrier of Strain 2 varying B_1



(d) Infected of Strain 1 varying B_1



(e) Infected of Strain 2 varying B_1

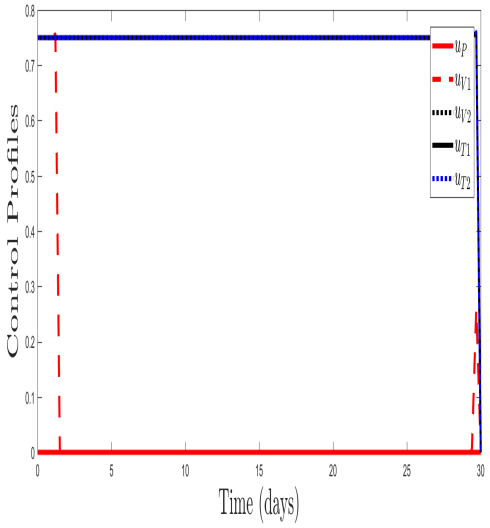


(f) Disease Prevalence varying B_1

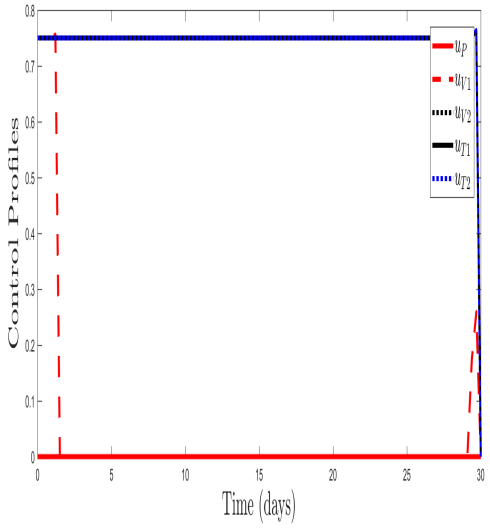
Figure 5.21 Effects of Varying Cost Weights on the Compartments $B_1 = 0.10$, $B_1 = 1.0$, $B_1 = 10.0$ and $B_1 = 100$

5.4.2 Varying the Weight B_2 associated with Control $u_{V1}(t)$

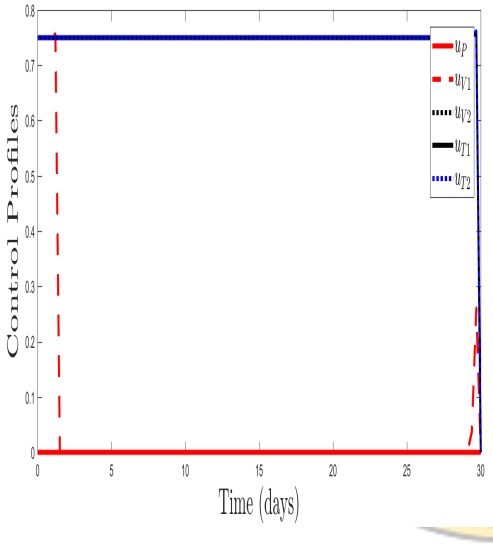
The variation of the weight of the vaccination of strain 1 control keeps $u_P(t)$ to the lower bound as B_2 increases from very cheap to very expensive vaccine. The other controls $u_{V1}(t)$, $u_{V2}(t)$, $u_{T1}(t)$ and $u_{T2}(t)$ initially increase to 0.75 which is close to the upper bound but $u_{V1}(t)$ decrease to the lower bound in about 2 days while the others remain stable at that point but later start to decrease close to day 30. There is a slight increase of $u_{V1}(t)$ on the 29th day but begin to decease again the next day. The control profiles are given in Figure 5.22 and their corresponding state variables in Figure 5.23. It is observed that there is no significant change in the state variables as B_2 is varied. Therefore, this relationship will also help to keep the community protected and the infection low.



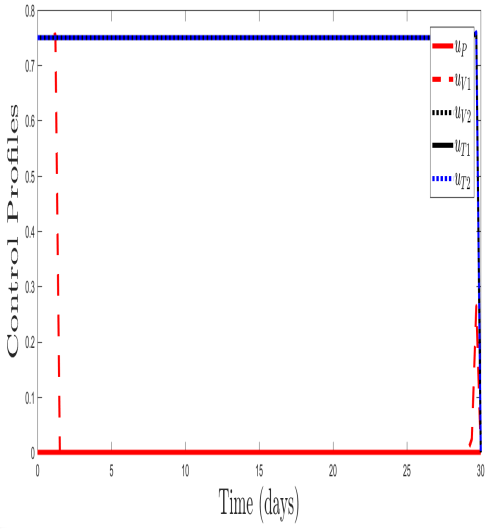
(a) Cost Weight $B_2 = 0.10$



(b) Cost Weight $B_2 = 1.0$

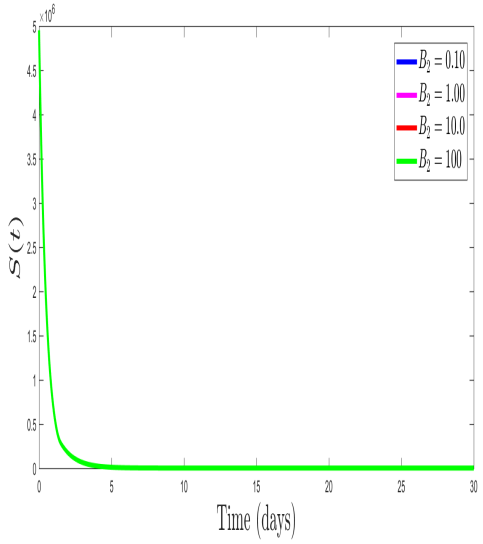


(c) Cost Weight $B_2 = 10.0$

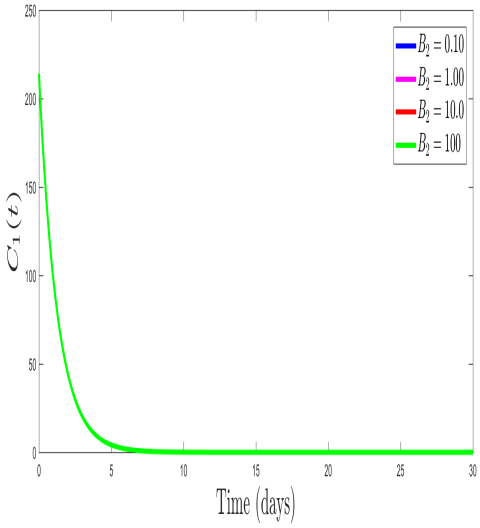


(d) Cost Weight $B_2 = 100$

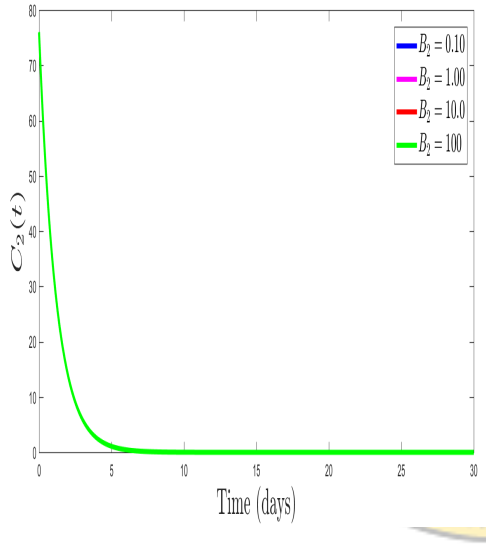
Figure 5.22 Control Profiles using Cost Weights $B_2 = 0.10$, $B_2 = 1.0$, $B_2 = 10.0$ and $B_2 = 100$



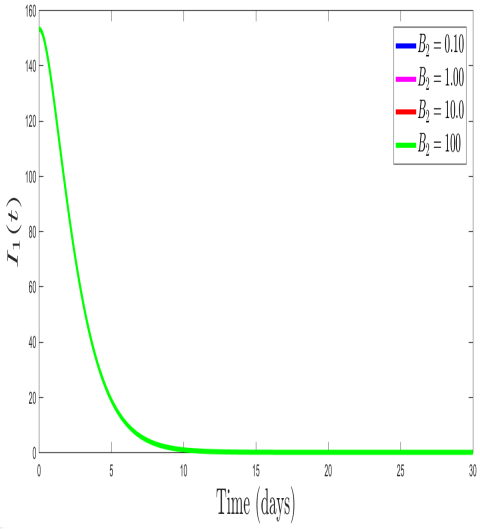
(a) Susceptible varying B_2



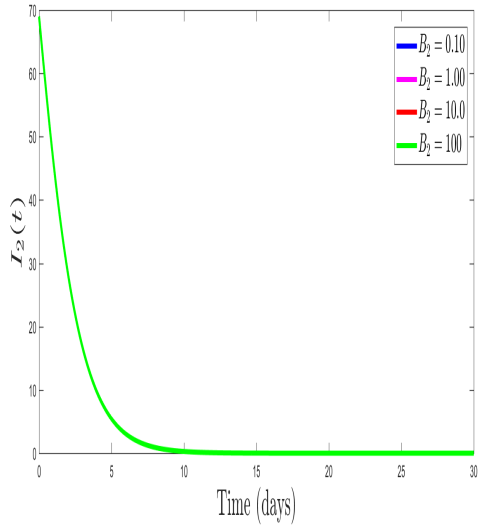
(b) Carrier of Strain 1 varying B_2



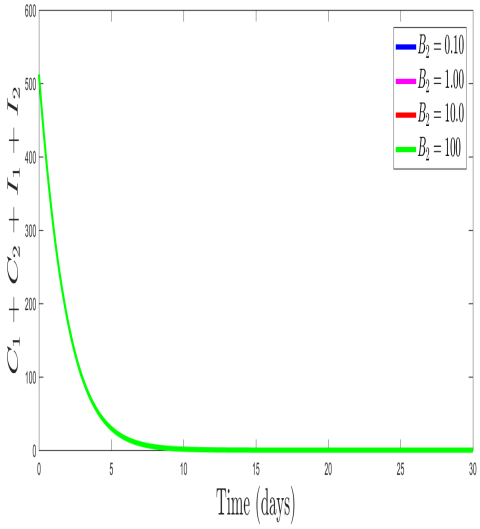
(c) Carrier of Strain 2 varying B_2



(d) Infected of Strain 1 varying B_2



(e) Infected of Strain 2 varying B_2

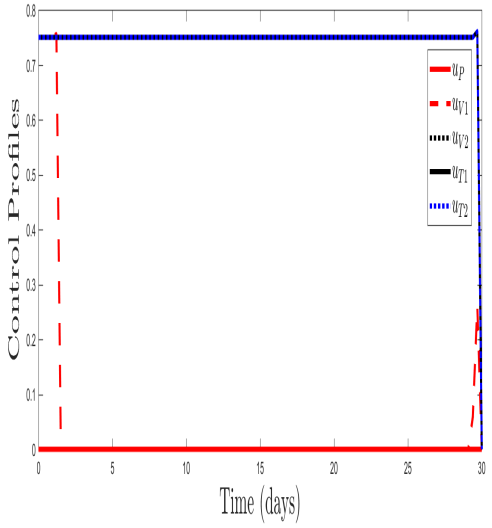


(f) Disease Prevalence varying B_2

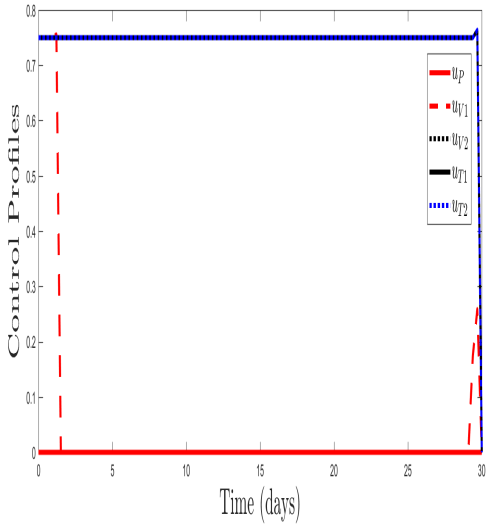
Figure 5.23 Effects of Varying Cost Weights on the Compartments $B_2 = 0.10$, $B_2 = 1.0$, $B_2 = 10.0$ and $B_2 = 100$

5.4.3 Varying the Weight B_3 associated with Control $u_{V2}(t)$

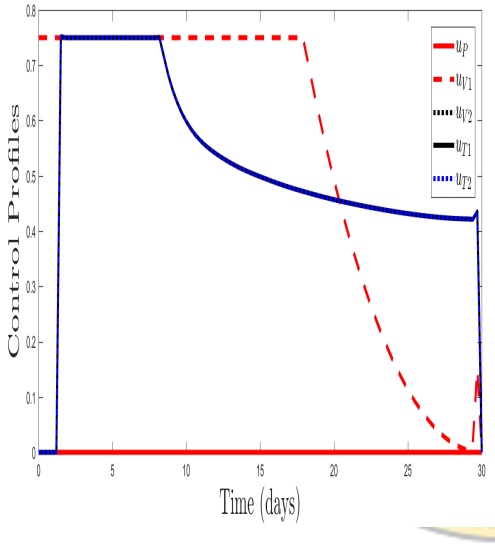
In varying the weight of the vaccination of strain 2 control, it is observed that $u_P(t)$ remains at the lower bound as B_3 increases from very cheap to very expensive vaccine. The other controls $u_{V1}(t)$, $u_{V2}(t)$, $u_{T1}(t)$ and $u_{T2}(t)$ initially increase to 0.75 which is close to the upper bound. $u_{V1}(t)$ begins to decrease to the lower bound in about 2 days when the weight is low (very cheap to cheap). As the weight gets higher (expensive to very expensive), $u_{V1}(t)$ achieves some stability up to the 18th day and begins to decrease again till the 29th day where there is a slight increase. On the other hand, when the weight is low (very cheap to cheap), $u_{V2}(t)$, $u_{T1}(t)$ and $u_{T2}(t)$ achieve stability till close to the 30th day. Thereafter, as the weight gets higher (expensive to very expensive), $u_{V2}(t)$, $u_{T1}(t)$ and $u_{T2}(t)$ begin to increase again to 0.75 and achieve some stability for a while till around the 9th day where they begin to decrease again. The control profiles are given in Figure 5.24 with their corresponding state variables in Figure 5.25. It is observed that the low weights coincide as well as the high weights in Figure 5.25. Therefore, this relationship contributes better to keeping the community protected and the infection low.



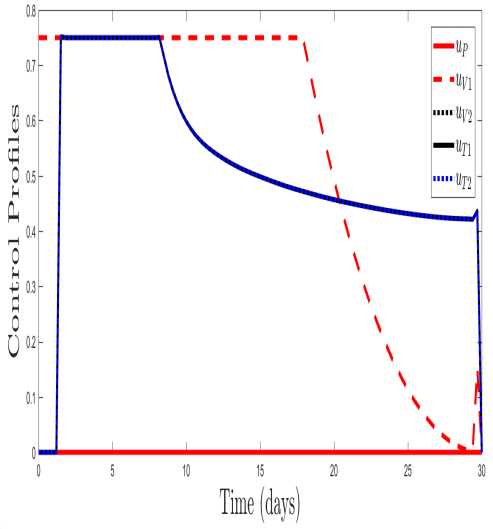
(a) Cost Weight $B_3 = 0.10$



(b) Cost Weight $B_3 = 1.0$

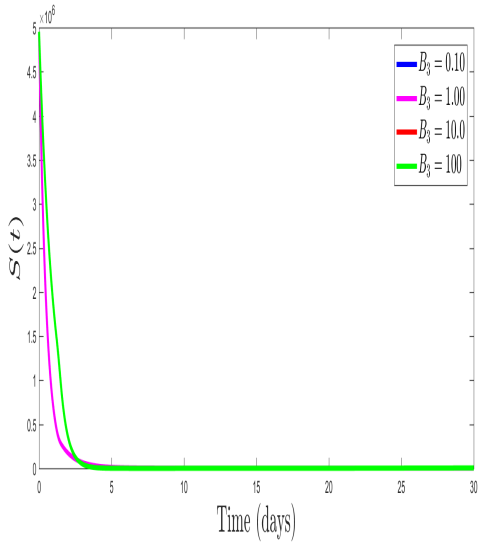


(c) Cost Weight $B_3 = 10.0$

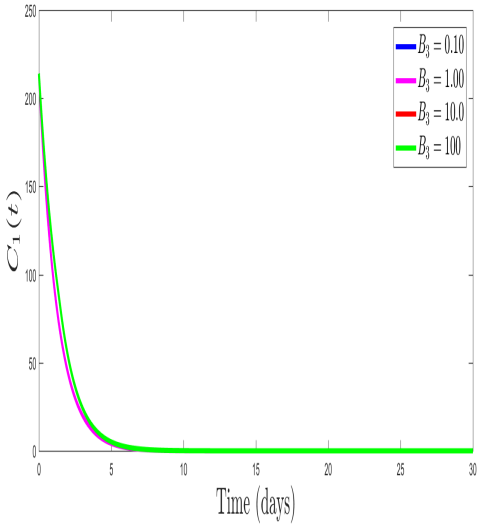


(d) Cost Weight $B_3 = 100$

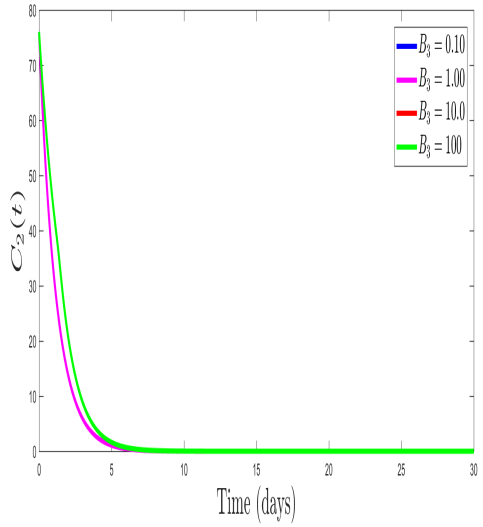
Figure 5.24 Control Profiles using Cost Weights $B_3 = 0.10$, $B_3 = 1.0$, $B_3 = 10.0$ and $B_3 = 100$



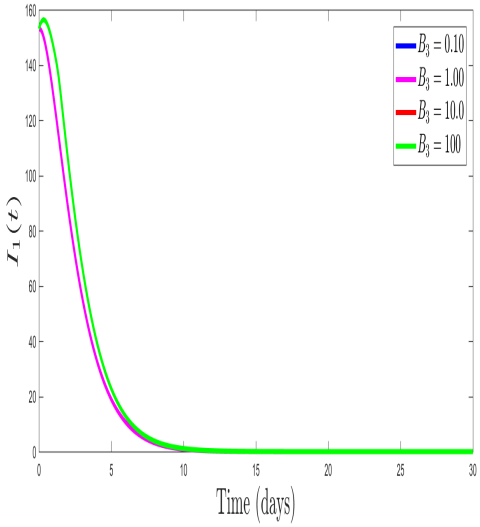
(a) **Susceptible varying** B_3



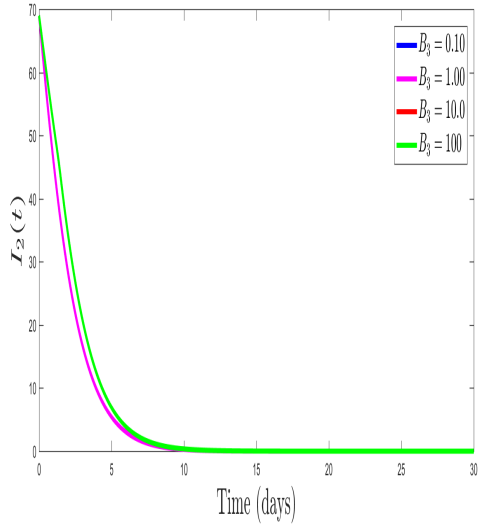
(b) **Carrier of Strain 1 varying** B_3



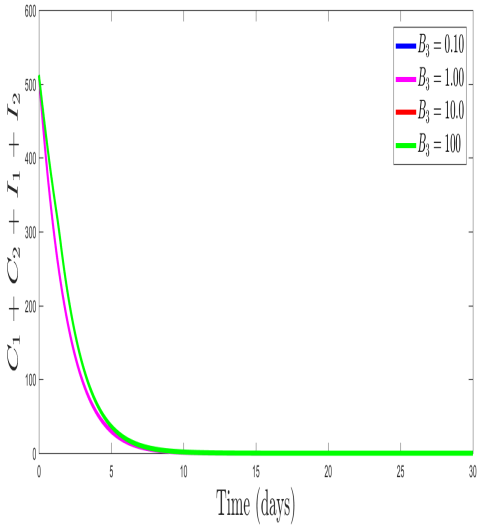
(c) **Carrier of Strain 2 varying** B_3



(d) **Infected of Strain 1 varying** B_3



(e) **Infected of Strain 2 varying** B_3



(f) **Disease Prevalence varying** B_3

Figure 5.25 Effects of Varying Cost Weights on the Compartments $B_3 = 0.10$, $B_3 = 1.0$, $B_3 = 10.0$ **and** $B_3 = 100$

5.4.4 Varying the Weights B_4 and B_5 associated with Controls $u_{T1}(t)$ and $u_{T2}(t)$

It is observed that the variations of the weights of the treatment control for the timely diagnosed individuals, $u_{T1}(t)$ and delayed diagnosed individuals, $u_{T2}(t)$ respectively, depict similar control profiles in Figure 5.22 and state variables solution profiles in Figure 5.23. Hence, the results are not shown here.

5.4.5 Infection Averted Ratio

The Infection Averted Ratio (IAR) is calculated as:

$$\text{IAR} = \frac{\text{Number of Infection Averted}}{\text{Number of Recovered}} \tag{5.41}$$

The number of infection averted above is known as the difference between the total infectious individuals over the simulation period without control and the total infectious individuals with control. The strategy with the highest ratio is the most effective.

The IAR for each intervention strategy is determined using the model parameter values in Table (4.3). Table 5.1 gives the IAR for all the ten strategies implemented. Strategy C which involves the effective human personal protection (such as use of face or surgical masks) $u_P(t)$ is seen to have the highest ratio, hence the most effective. This is followed by Strategy A which involves the combination of effective human personal protection (such as face or surgical masks) and vaccination for strain 1 and 2 ($u_P(t)$, $u_{V1}(t)$, $u_{V2}(t)$). The next effective strategy is the combination of all the five control variables ($u_P(t)$, $u_{V1}(t)$, $u_{V2}(t)$, $u_{T1}(t)$, $u_{T2}(t)$). Strategy F which involves vaccination for strain 2 and timely and delayed diagnosis treatments ($u_{V2}(t)$, $u_{T1}(t)$, $u_{T2}(t)$) is the least effective strategy. This is due to the relatively low number of infection averted and a higher total cost.

Table 5.1 Total Infection Averted, Total Cost and IAR for the Intervention Strategies

Strategies	Total Infection Averted	Total Cost	IAR
Strategy A	20746244	29.5708	1048.2136
Strategy B	20762153	118.2229	626.0071
Strategy C	20760071	26.7725	**1205.3690**
Strategy D	20705052	147.2869	138.5324
Strategy E	15793100	147.7395	3.5832
Strategy F	16883300	145.7215	3.2388
Strategy G	20753770	117.9066	681.5017
Strategy H	20754270	37.5736	686.6363
Strategy I	20716556	195.7430	175.1780
All Controls	20749089	24.4073	852.2937

5.4.6 Average Cost-Effectiveness Ratio

The Average Cost-Effectiveness Ratio (ACER) deals with evaluating a single intervention against the no intervention scenarios. This is calculated as:

$$\text{ACER} = \frac{\text{Total Cost Produced by the Intervention}}{\text{Total Number of Infection Averted}} \tag{5.42}$$

The total cost produced by the intervention is estimated using the cost of controls $\frac{B_i u_j^2}{2}$ from the objective functional in Equation (5.3). The strategy with the least ratio is the most cost-effective.

The ACER for each intervention strategy is presented in Table 5.2. This was determined using the model parameter values in Table 4.3. Based on this approach, the combination of all the five control variables ($u_P(t)$, $u_{V1}(t)$, $u_{V2}(t)$, $u_{T1}(t)$, $u_{T2}(t)$) is the most cost-effective, followed by Strategy C which is the effective human personal protection (such as face or surgical masks) $u_P(t)$. The next cost-effective strategy is Strategy A which involves the combination of effective human personal protection and vaccination for both strains ($u_P(t)$, $u_{V1}(t)$, $u_{V2}(t)$).

Table 5.2 Total Infection Averted, Total Cost and ACER for the Intervention Strategies

Strategies	Total Infection Averted	Total Cost	ACER
Strategy A	20746244	29.5708	1.42×10^{-6}
Strategy B	20762153	118.2229	5.69×10^{-6}
Strategy C	20760071	26.7725	1.29×10^{-6}
Strategy D	20705052	147.2869	7.11×10^{-6}
Strategy E	15793100	147.7395	9.35×10^{-6}
Strategy F	16883300	145.7215	8.63×10^{-6}
Strategy G	20753770	117.9066	5.68×10^{-6}
Strategy H	20754270	37.5736	1.81×10^{-6}
Strategy I	20716556	195.7430	9.45×10^{-6}
All Controls	20749089	24.4073	1.18×10^{-6}

5.4.7 Incremental Cost-Effectiveness Ratio

The Incremental Cost-Effectiveness Ratio (ICER) is the additional cost per additional health outcome computed as:

$$\text{ICER} = \frac{\text{Change in Infection Averted Costs in Strategies } i \text{ and } j}{\text{Change in Total Number of Infection Averted in Strategies } i \text{ and } j} \quad (5.43)$$

This establishes the differences between the various costs and health outcomes of implementing the different intervention strategies of control. The ICER numerator includes (where applicable) the differences in the costs of infection averted or cases prevented, the costs of intervention(s) and the costs of averting productivity losses among others. The denominator on the other hand, is the differences in health outcomes which may include the total number of infections averted or the number of Susceptible cases prevented from entering into the Carrier or Infected populations.

The costs of the various control interventions are assumed to be directly proportional to the number of controls deployed. This assumption is based on the concept that the primary aim of using isolation of infective individuals is to reduce infection. To compare two or more competing intervention strategies incrementally, one intervention is compared with the next-less-effective intervention.

To implement the ICER, the model is simulated for each of the ten intervention

strategies. The results from the simulations are used to rank the control strategies in increasing order of effectiveness based on infection averted. This ranking procedure shows that Strategy E averted the least number of infections, followed by Strategy F, and Strategy B averts the most number of infections as given in Table 5.3.

The ICER is computed as follows:

$$\text{ICER(E)} = \frac{147.7395}{15793100} = 9.35 \times 10^{-6}$$

$$\text{ICER(F)} = \frac{145.7215 - 147.7395}{16883300 - 15793100} = -1.85 \times 10^{-6}$$

$$\text{ICER(D)} = \frac{147.2869 - 145.7215}{20705052 - 16883300} = 4.10 \times 10^{-7}$$

$$\text{ICER(I)} = \frac{195.7430 - 147.2869}{20716556 - 20705052} = 4.21 \times 10^{-3}$$

$$\text{ICER(A)} = \frac{29.5708 - 195.7430}{20746244 - 20716556} = -5.60 \times 10^{-3}$$

$$\text{ICER(All Controls)} = \frac{24.4073 - 29.5708}{20749089 - 20746244} = -1.81 \times 10^{-3}$$

$$\text{ICER(G)} = \frac{117.9066 - 24.4073}{20753770 - 20749089} = 19.97 \times 10^{-3}$$

$$\text{ICER(H)} = \frac{37.5736 - 117.9066}{20754270 - 20753770} = -16.07 \times 10^{-2}$$

$$\text{ICER(C)} = \frac{26.7725 - 37.5736}{20760071 - 20754270} = -1.86 \times 10^{-3}$$

$$\text{ICER(B)} = \frac{118.229 - 26.7725}{20762153 - 20760071} = 43.93 \times 10^{-3}$$

Table 5.3 Incremental Cost-Effectiveness Ratio in Increasing Order of Total Infection Averted

Strategies	Total Infection Averted	Total Cost	ICER
Strategy E	15793100	147.7395	9.35×10^{-6}
Strategy F	16883300	145.7215	-1.85×10^{-6}
Strategy D	20705052	147.2869	4.10×10^{-7}
Strategy I	20716556	195.7430	4.21×10^{-3}
Strategy A	20746244	29.5708	-5.60×10^{-3}
All Controls	20749089	24.4073	-1.81×10^{-3}
Strategy G	20753770	117.9066	19.97×10^{-3}
Strategy H	20754270	37.5736	-16.07×10^{-2}
Strategy C	20760071	26.7725	-1.86×10^{-3}
Strategy B	20762153	118.2229	43.93×10^{-3}

Table 5.3 shows a cost saving of 9.35×10^{-6} for Strategy E over Strategy F in comparing just the two strategies. The lower ICER for Strategy F suggests that Strategy E is strongly dominant over Strategy F. This means that Strategy E is more costly and less effective compared to Strategy F. Therefore, Strategy E is excluded and the ICER for the remaining strategies recomputed.

The ICER for the remaining strategues is recomputed as follows:

$$\text{ICER(F)} = \frac{145.7215}{16883300} = 8.63 \times 10^{-6}$$

$$\text{ICER(D)} = \frac{147.2869 - 145.7215}{20705052 - 16883300} = 4.10 \times 10^{-7}$$

$$\text{ICER(I)} = \frac{195.7430 - 147.2869}{20716556 - 20705052} = 4.21 \times 10^{-3}$$

$$\text{ICER(A)} = \frac{29.5708 - 195.7430}{20746244 - 20716556} = -5.60 \times 10^{-3}$$

$$\text{ICER(All Controls)} = \frac{24.4073 - 29.5708}{20749089 - 20746244} = -1.81 \times 10^{-3}$$

$$\text{ICER(G)} = \frac{117.9066 - 24.4073}{20753770 - 20749089} = 19.97 \times 10^{-3}$$

$$\text{ICER(H)} = \frac{37.5736 - 117.9066}{20754270 - 20753770} = -16.07 \times 10^{-2}$$

$$\text{ICER(C)} = \frac{26.7725 - 37.5736}{20760071 - 20754270} = -1.86 \times 10^{-3}$$

$$\text{ICER(B)} = \frac{118.229 - 26.7725}{20762153 - 20760071} = 43.93 \times 10^{-3}$$

Table 5.4 Incremental Cost-Effectiveness Ratio in Increasing Order of Total Infection Averted Excluding Strategy E

Strategies	Total Infection Averted	Total Cost	ICER
Strategy F	16883300	145.7215	8.63×10^{-6}
Strategy D	20705052	147.2869	4.10×10^{-7}
Strategy I	20716556	195.7430	4.21×10^{-3}
Strategy A	20746244	29.5708	-5.60×10^{-3}
All Controls	20749089	24.4073	-1.81×10^{-3}
Strategy G	20753770	117.9066	19.97×10^{-3}
Strategy H	20754270	37.5736	-16.07×10^{-2}
Strategy C	20760071	26.7725	-1.86×10^{-3}
Strategy B	20762153	118.2229	43.93×10^{-3}

Comparing Strategies F and D in Table 5.4, the lower ICER for Strategy D is an indication that Strategy F is strongly dominant over Strategy D, which means that Strategy F is more costly and less effective compared to Strategy D. Therefore, Strategy F is excluded and the ICER for the remaining strategies is recomputed.

The ICER for the remaining strategues is recomputed as follows:

$$\text{ICER(D)} = \frac{147.2869}{20705052} = 7.11 \times 10^{-6}$$

$$\text{ICER(I)} = \frac{195.7430 - 147.2869}{20716556 - 20705052} = 4.21 \times 10^{-3}$$

$$\text{ICER(A)} = \frac{29.5708 - 195.7430}{20746244 - 20716556} = -5.60 \times 10^{-3}$$

$$\text{ICER(All Controls)} = \frac{24.4073 - 29.5708}{20749089 - 20746244} = -1.81 \times 10^{-3}$$

$$\text{ICER(G)} = \frac{117.9066 - 24.4073}{20753770 - 20749089} = 19.97 \times 10^{-3}$$

$$\text{ICER(H)} = \frac{37.5736 - 117.9066}{20754270 - 20753770} = -16.07 \times 10^{-2}$$

$$\text{ICER(C)} = \frac{26.7725 - 37.5736}{20760071 - 20754270} = -1.86 \times 10^{-3}$$

$$\text{ICER(B)} = \frac{118.229 - 26.7725}{20762153 - 20760071} = 43.93 \times 10^{-3}$$

Table 5.5 Incremental Cost-Effectiveness Ratio in Increasing Order of Total Infection Averted Excluding Strategy E and F

Strategies	Total Infection Averted	Total Cost	ICER
Strategy D	20705052	147.2869	7.11×10^{-6}
Strategy I	20716556	195.7430	4.21×10^{-3}
Strategy A	20746244	29.5708	-5.60×10^{-3}
All Controls	20749089	24.4073	-1.81×10^{-3}
Strategy G	20753770	117.9066	19.97×10^{-3}
Strategy H	20754270	37.5736	-16.07×10^{-2}
Strategy C	20760071	26.7725	-1.86×10^{-3}
Strategy B	20762153	118.2229	43.93×10^{-3}

The comparison of Strategies D and I in Table 5.5 shows that Strategy D has the lower ICER value. This suggests that Strategy I is strongly dominant over Strategy D, thus Strategy I is more costly and less effective compared to Strategy D. Therefore, Strategy I is left out and the ICER for the remaining strategies is recomputed.
The ICER for the remaining strategies is recomputed as follows:

$$\text{ICER(D)} = \frac{147.2869}{20705052} = 7.11 \times 10^{-6}$$

$$\text{ICER(A)} = \frac{29.5708 - 147.2869}{20746244 - 20705052} = -2.86 \times 10^{-3}$$

$$\text{ICER(All Controls)} = \frac{24.4073 - 29.5708}{20749089 - 20746244} = -1.81 \times 10^{-3}$$

$$\text{ICER(G)} = \frac{117.9066 - 24.4073}{20753770 - 20749089} = 19.97 \times 10^{-3}$$

$$\text{ICER(H)} = \frac{37.5736 - 117.9066}{20754270 - 20753770} = -16.07 \times 10^{-2}$$

$$\text{ICER(C)} = \frac{26.7725 - 37.5736}{20760071 - 20754270} = -1.86 \times 10^{-3}$$

$$\text{ICER(B)} = \frac{118.229 - 26.7725}{20762153 - 20760071} = 43.93 \times 10^{-3}$$

Table 5.6 Incremental Cost-Effectiveness Ratio in Increasing Order of Total Infection Averted Excluding Strategy E, F and I

Strategies	Total Infection Averted	Total Cost	ICER
Strategy D	20705052	147.2869	7.11×10^{-6}
Strategy A	20746244	29.5708	-2.86×10^{-3}
All Controls	20749089	24.4073	-1.81×10^{-3}
Strategy G	20753770	117.9066	19.97×10^{-3}
Strategy H	20754270	37.5736	-16.07×10^{-2}
Strategy C	20760071	26.7725	-1.86×10^{-3}
Strategy B	20762153	118.2229	43.93×10^{-3}

Comparing Strategies D and A in Table 5.6, the cost saving of 7.11×10^{-6} is observed for Strategy D over Strategy A. The lower ICER value obtained for Strategy A indicates that Strategy D is strongly dominant over Strategy A. This means Strategy D is more costly and less effective compared to Strategy A, as such, Strategy D is removed and the ICER for the remaining strategies is recomputed.

The ICER for the remaining strategies is recomputed as follows:

$$\text{ICER(A)} = \frac{29.5708}{20746244} = 1.43 \times 10^{-6}$$

$$\text{ICER(All Controls)} = \frac{24.4073 - 29.5708}{20749089 - 20746244} = -1.81 \times 10^{-3}$$

$$\text{ICER(G)} = \frac{117.9066 - 24.4073}{20753770 - 20749089} = 19.97 \times 10^{-3}$$

$$\text{ICER(H)} = \frac{37.5736 - 117.9066}{20754270 - 20753770} = -16.07 \times 10^{-2}$$

$$\text{ICER(C)} = \frac{26.7725 - 37.5736}{20760071 - 20754270} = -1.86 \times 10^{-3}$$

$$\text{ICER(B)} = \frac{118.229 - 26.7725}{20762153 - 20760071} = 43.93 \times 10^{-3}$$

Table 5.7 Incremental Cost-Effectiveness Ratio in Increasing Order of Total Infection Averted Excluding Strategy E, F, I and D

Strategies	Total Infection Averted	Total Cost	ICER
Strategy A	20746244	29.5708	1.43×10^{-6}
All Controls	20749089	24.4073	-1.81×10^{-3}
Strategy G	20753770	117.9066	19.97×10^{-3}
Strategy H	20754270	37.5736	-16.07×10^{-2}
Strategy C	20760071	26.7725	-1.86×10^{-3}
Strategy B	20762153	118.2229	43.93×10^{-3}

The comparison of Strategies A and All Controls in Table 5.7 presents the Strategy involving All Controls to have the lower ICER. This is an indication that Strategy A is strongly dominant over All Controls which means that Strategy A is more costly and less effective compared to All Controls. As a result, Strategy A is excluded and the ICER for the remaining strategies is recomputed.

The ICER for the remaining strategies is recomputed as follows:

$$\text{ICER(All Controls)} = \frac{24.4073}{20749089} = 1.18 \times 10^{-6}$$

$$\text{ICER(G)} = \frac{117.9066 - 24.4073}{20753770 - 20749089} = 19.97 \times 10^{-3}$$

$$\text{ICER(H)} = \frac{37.5736 - 117.9066}{20754270 - 20753770} = -16.07 \times 10^{-2}$$

$$\text{ICER(C)} = \frac{26.7725 - 37.5736}{20760071 - 20754270} = -1.86 \times 10^{-3}$$

$$\text{ICER(B)} = \frac{118.229 - 26.7725}{20762153 - 20760071} = 43.93 \times 10^{-3}$$

Table 5.8 Incremental Cost-Effectiveness Ratio in Increasing Order of Total Infection Averted Excluding Strategy E, F, I, D and A

Strategies	Total Infection Averted	Total Cost	ICER
All Controls	20749089	24.4073	1.18×10^{-6}
Strategy G	20753770	117.9066	19.97×10^{-3}
Strategy H	20754270	37.5736	-16.07×10^{-2}
Strategy C	20760071	26.7725	-1.86×10^{-3}
Strategy B	20762153	118.2229	43.93×10^{-3}

From Table 5.8, All Controls is compared to Strategy G and Strategy G is revealed to have the lower ICER. This suggests that Strategy G is strongly dominant over All Controls which means that Strategy G is more costly and less effective compared to All Controls. Thus, Strategy G is removed and the ICER for the remaining strategies is recomputed.

The ICER for the remaining strategies is recomputed as follows:

$$\text{ICER(All Controls)} = \frac{24.4073}{20749089} = 1.18 \times 10^{-6}$$

$$\text{ICER(H)} = \frac{37.5736 - 24.4073}{20754270 - 20749089} = 2.54 \times 10^{-3}$$

$$\text{ICER(C)} = \frac{26.7725 - 37.5736}{20760071 - 20754270} = -1.86 \times 10^{-3}$$

$$\text{ICER(B)} = \frac{118.229 - 26.7725}{20762153 - 20760071} = 43.93 \times 10^{-3}$$

Table 5.9 Incremental Cost-Effectiveness Ratio in Increasing Order of Total Infection Averted Excluding Strategy E, F, I, D, A and G

Strategies	Total Infection Averted	Total Cost	ICER
All Controls	20749089	24.4073	1.18×10^{-6}
Strategy H	20754270	37.5736	2.54×10^{-3}
Strategy C	20760071	26.7725	-1.86×10^{-3}
Strategy B	20762153	118.2229	43.93×10^{-3}

Comparing the All Controls to Strategy H in Table 5.9, the All Controls is presented to have the lower ICER which suggests that Strategy H is strongly dominant over All Controls. This means that Strategy H is more costly and less effective compared to All Controls. Therefore, it is better to exclude Strategy H and recompute the ICER for the remaining strategies.

The ICER for the remaining strategies is recomputed as follows:

$$\text{ICER(All Controls)} = \frac{24.4073}{20749089} = 1.18 \times 10^{-6}$$

$$\text{ICER(C)} = \frac{26.7725 - 24.4073}{20760071 - 20749089} = 2.15 \times 10^{-4}$$

$$\text{ICER(B)} = \frac{118.229 - 26.7725}{20762153 - 20760071} = 43.93 \times 10^{-3}$$

Table 5.10 Incremental Cost-Effectiveness Ratio in Increasing Order of Total Infection Averted Excluding Strategy E, F, I, D, A, G and H

Strategies	Total Infection Averted	Total Cost	ICER
All Controls	20749089	24.4073	1.18×10^{-6}
Strategy C	20760071	26.7725	2.15×10^{-4}
Strategy B	20762153	118.2229	43.93×10^{-3}

The comparison of All Controls and Strategy C in Table 5.10 presents the Strategy involving All Controls to have the lower ICER. This suggests that Strategy C is strongly dominant over All Controls which means that Strategy C is more costly and less effective compared to All Controls. As a result, Strategy C is excluded and the

ICER for the remaining strategies is recomputed.

The ICER for the remaining strategies is recomputed as follows:

$$\text{ICER(All Controls)} = \frac{24.4073}{20749089} = 1.18 \times 10^{-6}$$

$$\text{ICER(B)} = \frac{118.229 - 24.4073}{20762153 - 20749089} = 7.18 \times 10^{-3}$$

Table 5.11 Incremental Cost-Effectiveness Ratio in Increasing Order of Total Infection Averted Excluding Strategy E, F, I, D, A, G, H and C

Strategies	Total Infection Averted	Total Cost	ICER
All Controls	20749089	24.4073	$\mathbf{1.18 \times 10^{-6}}$
Strategy B	20762153	118.2229	7.18×10^{-3}

From Table 5.11, a comparison between the control strategies left, that is, All Controls and Strategy B presents the All Controls to have the lower ICER. This is an indication that Strategy B is strongly dominant over All Controls which means that Strategy B is more costly and less effective compared to All Controls. As a result, it is better to exclude Strategy B.

Based on all the computed results above, the combination of all the five control variables ($u_P(t)$, $u_{V1}(t)$, $u_{V2}(t)$, $u_{T1}(t)$, $u_{T2}(t)$) is the most cost-effective intervention capable of diminishing the burden of Bacterial meningitis. This is not surprising, as this strategy involves all the key parameters pertaining to curbing the transmission of the disease.

CHAPTER 6

CONCLUSIONS AND RECOMMENDATIONS

6.1 Summary

The application of mathematical models to determine the number of people who could be infected or prevented from being infected under different vaccination campaigns is potentially a cost and life saving tool. Formulating models that can be implemented and easily understood makes the use and results of these models accessible to a wide range of people. This research presents two main deterministic models of a coupled system of ordinary differential equations for the transmission dynamics of Bacterial meningitis disease.

In Chapter 3, The transmission dynamics of bacterial meningitis with a focus on vaccination and effective treatment in curtailing the spread of the disease is presented. The basic reproduction number of the model is computed using the Next Generation matrix. The equilibrium solutions of the model are obtained and used to establish criteria for the model's stability. Using the basic reproduction number, $\mathcal{R}_0$, as a threshold given $\mathcal{R}_0 < 1$, the disease-free equilibrium point is established to be both locally and globally asymptotically stable. The numerical simulations established that the disease can be eradicated with effective and efficient vaccination and treatment since that led the basic reproduction number below unity.

In Chapter 4, a novel deterministic model of a coupled system of nine ordinary differential equations for the transmission dynamics of a two-strain bacterial meningitis disease is presented. The introduction of the vaccination populations of strain 1 and strain 2 accommodates majority of the total human population, thereby relatively curbing the spread of the infections. The positivity analysis of the two-strain model shows that the model is epidemiologically feasible and represents what is obtainable in real life. The mathematical analysis of the model shows that the model has a DFE which is locally and globally asymptotically stable if $\mathcal{R}_{01}, \mathcal{R}_{02} < 1$

and unstable if $\mathcal{R}_{01}, \mathcal{R}_{02} > 1$. The basic reproduction number indicates that with a herd immunity of 25%, the disease could be eradicated over a certain period of time as represented in the numerical simulation results.

The contributions of the model parameters on $\mathcal{R}_0$ using the normalized sensitivity index was examined for the two models. The results indicate that the transmission probability, β is an effective contributor to $\mathcal{R}_0$, as such very essential in the spread and control of the disease. Therefore, control mechanisms that can reduce the transmission probability significantly will most definitely curtail the endemicity of the disease.

In Chapter 5, optimal control theory was used to study the impact of effective human personal protection (such as face or surgical masks), vaccination of strain 1 and 2, and timely and delayed diagnosis treatments as effective control measures against the epidemics. It was established that the application of these time-dependent controls can remarkably reduce the total number of infected (Carrier and Infected) individuals in the population. The variation of the weights B_1, B_2, B_3, B_4 and B_5 corresponding to changes in the costs of implementing the controls $u_P(t)$, $u_{V1}(t)$, $u_{V2}(t)$, $u_{T1}(t)$ and $u_{T2}(t)$ presents an inversely proportional relation between the cost of facial masks used with vaccination of strain 1 and the cost of vaccination of strain 2 with the treatments for timely and delayed diagnosis. Thus, as the cost of facial masks and vaccination of strain 1 increases, the cost of vaccination of strain 2 with the treatments for timely and delayed diagnosis decreases, and vice versa. The lower weights are more cost-effective than the higher weights. When the weights on the costs are low, the five controls avert more infections, but $u_{V2}(t)$, $u_{T1}(t)$ and $u_{T2}(t)$ avert slightly more infections than $u_P(t)$, $u_{V1}(t)$. The most efficient and cost-effective control strategy is the strategy involving all the five control variables. This is followed by Strategy C which is only the effective human personal protection (such as face or surgical masks), $u_P(t)$. However, Strategy F which involves vaccination for strain 2 and timely and delayed diagnosis treatments ($u_{V2}(t)$, $u_{T1}(t)$ and $u_{T2}(t)$) is the least cost-effective strategy. Although Strategy F is not cost-effective, it performs just as well as the other two strategies when the ability to curtail the infection is assessed.

6.2 Findings

The main findings from the study are;

1. Bacterial meningitis is indeed a vaccine preventable disease. This is because as the vaccine uptake rates for both strains increase, the vaccinated populations increase and remain stable, thereby relatively curbing the number of infections.

2. Individuals must commit to take all the available strain vaccines as a form of protection from the disease.

3. Bacterial Meningitis will not spread in the population if at least 25% of the population is immune to the disease.

4. Timely diagnosis with effective treatment plays an important role in reducing the spread of the disease and its delibitating effects after recovery.

5. The transmission of Bacterial meningitis from one person to another can be greatly reduced through the use of facial or surgical masks. This creates a physical barrier against potential contaminants in the immediate environment and prevents secretions from the nose and throat from contaminating the face.

6. The incorporation of the five time-dependent controls: effective human personal protection (such as face or surgical masks), vaccination of strain 1 and 2, and timely and delayed diagnosis treatments reduced the total number of infected (Carrier and Infected) individuals in the population remarkably.

7. The combination of all the five control variables is the most efficient and cost-effective control strategy in curtailing the spread of the disease.

8. The effective human personal-protection such as the use of face or surgical masks is the next efficient and cost-effective control strategy.

6.3 Conclusions

Bacterial meningitis has posed a serious threat to lives and livelihood of people, especially those in the meningitis belt given the potential impact on health systems,

the economy and society as a whole. This study presents two deterministic compartmental models of the disease based on Susceptible-Vaccinated-Carrier-Infected-Treated-Recovered (SVCITR) and Susceptible-Vaccinated-Carrier-Infected-Recovered (SVCIR) respectively. The invariant region, positivity of the solutions and stability of the equilibrium points were examined using quantitative analysis. The basic reproduction number, $\mathcal{R}_0$ was computed using the next generation matrix approach and this was used as a threshold to establish the local and global stabilities of the model. The numerical simulation results of the model demonstrate the effects of the model parameters on each compartment. The results show that getting people vaccinated is crucial to the control of the disease. Furthermore, the sensitivity analysis of $\mathcal{R}_0$ was performed in order to determine the effect of each of the model parameters in controlling the disease. Thus, reducing the values of the parameters with negative sensitivity index will help curtail the spread of the disease.

Optimal Control theory was therefore applied to investigate the optimal strategy for curtailing the spread of the disease using five time-dependent control variables. The numerical simulations show that these control variables avert more infections at low costs. As such, a cost-effective analysis was applied to investigate the most cost-effective strategy from ten different combination of control strategies. The results indicate that the strategy combining all the five control variables is the most cost-effective strategy followed by Strategy C which is the effective human personal-protection. The least cost-effective strategy is Strategy F which is the combination of vaccination for strain 2 and timely and delayed diagnosis treatments.

6.4 Contributions to Science/Knowledge

The main contributions to science/knowledge are:

1. A mathematical model on the transmission dynamics of Bacterial Meningitis disease with the incorporation of the Treated population has been developed

2. A novel two-strain compartmental model for the transmission dynamics of Bacterial Meningitis disease in Ghana has been developed.

3. The alarming prevalence of Bacterial Meningitis in Ghana has been formulated as an optimal control problem.

4. The best strategies to curtail the spread of Bacterial Meningitis disease has been proposed.

5. The most cost-effective strategy to control the spread of Bacterial Meningitis disease has also been determined in this study

6.5 Recommendations

Based on this study, it is recommended that;

1. Epidemiologists use these models to better understand the prevalence, risk factors and relative impact of the various available vaccines in the endemic areas.

2. Health professionals use the optimal control strategies in assessing the vaccine's efficiency once it is administered in a population.

3. Communities with limited resources, especially those in the meningitis belt should consider complementing the use of available vaccines and treatments with the use of facial masks when there is an outbreak.

4. Decision makers should incorporate the findings from this study to provide policy guideline(s) in their quest for cost-effective control strategies whenever there is a bacterial meningitis outbreak.

6.6 Suggestions for Future Work

It is better to have more comprehensive researches done in order to find out additional effective strategies to incorporate in eradicating this disease. Based on this study, it is suggested that future work should consider:

1. Expanding the model to incorporate the age-structure of the population, as well as spatial effects associated with the movement of people and various environmental factors.

2. Investigate the impact of each of the available drugs on the treatment of the infection.

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APPENDIX LATEX ERROR: THERE'S NO LINE HERE TO ENDSEE THE LATEX MANUAL OR LATEX COMPANION FOR EXPLANATION.YOUR COMMAND WAS IGNORED.TYPE I <COMMAND> <RETURN> TO REPLACE IT WITH ANOTHER COMMAND,OR <RETURN> TO CONTINUE WITHOUT IT.

= *

% **Simulation of the Vaccination-Treatment Bacterial Meningitis Model** %

```
function dydt = basicmeningitis1(t,y)
alpha = 211; mu=0.000043; omega=0.00068; gamma=0.125; eta1=0.75; eta2=0.75,
kappa=0.6; epsilon=0.15; tau=0.85; delta=0.43; beta=0.88; theta=0.6; wedge=0.6;
sigma=0.25; r=0.13;
N=y(1)+y(2)+y(3)+y(4)+y(5)+y(6)+y(7);
dydt = zeros(7,1);
dydt(1)=alpha+omega*y(2) -(beta*(eta1*y(3)+y(4))/N+theta + mu)*y(1);
dydt(2)=theta*y(1)- (1-tau)*beta*(eta1*y(3)+y(4))/N*y(2)-(omega + mu)*y(2);
dydt(3)=beta*(eta1*y(3)+y(4))/N*y(1)+ (1-tau)*beta*(eta1*y(3)+y(4))/N*y(2) -
(sigma+kappa+r+delta+ mu)*y(3);
dydt(4)=sigma*y(3)- (kappa+r + delta + mu)*y(4);
dydt(5)=kappa*y(3)+kappa*y(4)-(1-eta2)*delta*y(5)-(1-wedge)*y(5) -
(gamma+gamma*r + mu)*y(5);
dydt(6)=r*y(3)+r*y(4)+gamma*r*y(5) -(epsilon +mu)*y(6);
dydt(7)=gamma*y(5)+(1-wedge)*y(5)+ epsilon*y(6)-mu*y(7);
end
unction [T,Y] = basicmeningitis2()
tspan = [0 30];
y10 = 3219640;
y20 = 495329.3;
y30 = 742993.95;
```

```
y40 = 247664.65;
y50 = 247664.65;
y60 = 0;
y70 = 0;

[T,Y] = ode45(@basicmeningitis1,tspan,[y10 y20 y30 y40 y50 y60 y70]);
figure(1)
plot(T, Y(:,1), 'b', 'LineWidth', 3);
xlabel('Time (days)');
ylabel('S(t)');
figure(2)
plot(T, Y(:,2), 'b', 'LineWidth', 3);
xlabel('Time (days)');
ylabel('V(t)');
figure(3)
plot(T, Y(:,3), 'b', 'LineWidth', 3);
xlabel('Time (days)');
ylabel('C(t)');
figure(4)
plot(T, Y(:,4), 'b', 'LineWidth', 3);
xlabel('Time (days)');
ylabel('I(t)');
figure(5)
plot(T, Y(:,5), 'b', 'LineWidth', 3);
xlabel('Time (days)');
ylabel('T(t)');
figure(6)
plot(T, Y(:,6), 'b', 'LineWidth', 3);
xlabel('Time (days)');
ylabel('R1(t)');
figure(7)
plot(T, Y(:,7), 'b', 'LineWidth', 3);
```

```
xlabel('Time (days)');
ylabel('R2(t)');
figure(8)
plot(T, (Y(:,3)+Y(:,4)),'-b', 'LineWidth', 3);
xlabel('Time (days)');
ylabel('C+I');
```

%% **Simulation of the two-strain Bacterial Meningitis Model** %%

```
function dydt = reformmeningitis1(t,y)
alpha = 211; mu=0.000043; omega1=0.00054; omega2=0.00068; gammac1=0.143;
gammac2=0.3; eta=0.75; gammai1=0.125; gammai2=0.1; epsilon1=0.85;
epsilon2=0.90; tau1=0.3; tau2=0.5; delta=0.43; beta=0.88; theta1=0; theta2=0;
wedge=0.15; rho1=0.85; rho2=0.9; sigma1=0.5; sigma2=0.25;
N=y(1)+y(2)+y(3)+y(4)+y(5)+y(6)+y(7)+y(8)+y(9);
dydt = zeros(9,1);
dydt(1)=alpha+omega1*y(2)+omega2*y(3)-(beta*(eta*y(4)+y(6))/N)*y(1)-
(beta*(eta*y(5)+y(7))/N)*y(1)-(theta1+ theta2+ mu)*y(1);
dydt(2)=theta1*y(1)-(1-epsilon1)*beta*(eta*y(4)+y(6))/N*y(2)-
(beta*(eta*y(5)+y(7))/N)*y(2)-(omega1 + mu)*y(2);
dydt(3)=theta2*y(1)-(1-epsilon2)*beta*(eta*y(5)+y(7))/N*y(3)-
(beta*(eta*y(4)+y(6))/N)*y(3)-(omega2 + mu)*y(3);
dydt(4)=beta*(eta*y(4)+y(6))/N*(1-tau1)*y(1)+(1-epsilon1)*beta*(eta*y(4)+y(6))/N*y(2)
- (sigma1+ gammac1+ mu)*y(4);
dydt(5)=beta*(eta*y(5)+y(7))/N*(1-tau2)*y(1)+(1-epsilon2)*beta*(eta*y(5)+y(7))/N*y(3)
- (sigma2+ gammac2+ mu)*y(5);
dydt(6)=sigma1*y(4)+beta*(eta*y(4)+y(6))/N*tau1*y(1)+beta*(eta*y(4)+y(6))/N*y(3)-
(gammai1 + delta + mu)*y(6);
dydt(7)=sigma2*y(5)+beta*(eta*y(5)+y(7))/N*tau2*y(1)+beta*(eta*y(5)+y(7))/N*y(2)-
(gammai2 + delta + mu)*y(7);
dydt(8)=gammac1*y(4)+gammac2*y(5)+gammai1*rho1*y(6)+gammai2*rho2*y(7)
-(wedge +mu)*y(8);
dydt(9)=gammai1*(1-rho1)*y(6)+gammai2*(1-rho2)*y(7)+wedge*y(8)-mu*y(9);
```

```
end
% function [T,Y] = reformmeningitis2()
tspan = [0 30];
y10 = 4952781;
y20 = 0;
y30 = 0;
y40 = 214;
y50 = 76;
y60 = 153;
y70 = 69;
y80 = 0;
y90 = 0;

[T,Y] = ode45(@reformmeningitis1,tspan,[y10 y20 y30 y40 y50 y60 y70 y80 y90]);
figure(1)
plot(T, Y(:,1), 'b', 'LineWidth', 3);
xlabel('Time (days)');
ylabel('S(t)');
legend('S');
figure(2)
plot(T, Y(:,2), 'b', 'LineWidth', 3);
xlabel('Time (days)');
ylabel('V1(t)');
legend('V1');
figure(3)
plot(T, Y(:,3), 'b', 'LineWidth', 3);
xlabel('Time (days)');
ylabel('V2(t)');
legend('V2');
figure(4)
plot(T, Y(:,4), 'b', 'LineWidth', 3);
xlabel('Time (days)');
```

```
ylabel('C1(t)');
legend('C1');
figure(5)
plot(T, Y(:,5), 'b', 'LineWidth', 3);
xlabel('Time (days)');
ylabel('C2(t)');
legend('C2');
figure(6)
plot(T, Y(:,6), 'b', 'LineWidth', 3);
xlabel('Time (days)');
ylabel('I1(t)');
legend('I1');
figure(7)
plot(T, Y(:,7), 'b', 'LineWidth', 3);
xlabel('Time (days)');
ylabel('I2(t)');
legend('I2');
figure(8)
plot(T, Y(:,8), 'b', 'LineWidth', 3);
xlabel('Time (days)');
ylabel('R1(t)');
legend('R1');
figure(9)
plot(T, Y(:,9), 'b', 'LineWidth', 3);
xlabel('Time (days)');
ylabel('R2(t)');
legend('R2');
figure(10)
plot(T, (Y(:,4)+Y(:,5)+Y(:,6)+Y(:,7)),'-b', 'LineWidth', 3);
xlabel('Time (days)');
ylabel('C1+C2+I1+I2');
Cst=sum(Y(:,4)+Y(:,5)+Y(:,6)+Y(:,7)) % Total Infected %
```

```
disp(Cst)

%% Optimal Control code for the two-strain Bacterial Meningitis Model %%
function Meningitis Optimal Controls ODE45 all in 1
tic;
clear all;
close all;
clc;
format long;
global x0 ptf tf step alpha omega1 omega2 mu epsilon1 epsilon2 tau1 tau2;
global sigma1 sigma2 gammai1 gammai2 delta gammac1 gammac2 rho1 rho2 wedge
global beta eta
global A1 A2 B1 B2 B3 B4 B5;

%% Initial conditions %% x0 = [4952621 60 100 214 76 153 69 0 0];
ptf = [0; 0; 0; 0; 0; 0; 0; 0; 0]; % Initial values for costates %
tf = 30; % Final time %
step = 0.25;

% Parameter values %
alpha = 211;
mu = 0.000043;
omega1 = 0.000547;
omega2 = 0.00068;
gammac1 = 0.143;
gammac2 = 0.3;
gammai1 = 0.125;
gammai2 = 0.1;
epsilon1 = 0.85;
epsilon2 = 0.90;
tau1 = 0.3;
```

```
tau2 = 0.5;
delta = 0.43;
beta = 0.88;
rho1 = 0.85;
rho2 = 0.9;
sigma1 = 0.5;
sigma2 = 0.25;
eta = 0.75;
wedge = 0.15;

% Weight constants %
A1 = 1; A2 = 1; B1 = 1; B2 = 1; B3 = 1; B4 = 1; B5 = 1;
Tu = linspace(0, tf);
t= linspace(0, tf);        % Discretization of time interval
f = @(Tu) (Tu > 0);        % Heaviside function
uP = min(1,max(0,0.5*Tu));        % Initial value for u's
uV1= min(1,max(0,0.5*Tu));
uV2= min(1,max(0,0.5*Tu));
uT1= min(1,max(0,0.5*Tu));
uT2= min(1,max(0,0.5*Tu));

for i=1:100        % Maximum number of iterations
% 1) start with assumed control u's and move forward
options = odeset('AbsTol', 1e-4, 'RelTol', 1e-4);
% [Tx, X] = ode45(@(t,x) stateEq(t, x, uP, uV1, uV2, uT1, uT2, Tu), [0; tf], x0,
options);

% 2) Move backward to get the trajectory costates
x1 = X(:, 1);
x2 = X(:, 2);
x3 = X(:, 3);
x4 = X(:, 4);
```

```
x5 = X(:, 5);
x6 = X(:, 6);
x7 = X(:, 7);
x8 = X(:, 8);
x9 = X(:, 9);
options = odeset('AbsTol', 1e-4, 'RelTol', 1e-4);
% [Tp, P] = ode45(@(t, p) costateEq(t, p, uP, uV1, uV2, uT1, uT2, Tu, x1, x2, x3,
x4, x5, x6, x7, x8, x9, Tx), [tf; 0], ptf, options);
p1 = P(:, 1);
p1 = interp1(Tp, p1, Tx);
p2 = P(:, 2);
p2 = interp1(Tp, p2, Tx);
p3 = P(:, 3);
p3 = interp1(Tp, p3, Tx);
p4 = P(:, 4);
p4 = interp1(Tp, p4, Tx);
p5 = P(:, 5);
p5 = interp1(Tp, p5, Tx);
p6 = P(:, 6);
p6 = interp1(Tp, p6, Tx);
p7 = P(:, 7);
p7 = interp1(Tp, p7, Tx);
p8 = P(:, 8);
p8 = interp1(Tp, p8, Tx);
p9 = P(:, 9);
p9 = interp1(Tp, p9, Tx);

% Calculate deltaH with x's(t) and p's(t)
dH1 = pH1(x1, x2, x3, x4, x5, x6, x7, x8, x9, p1, p2, p3, p4, p5, p6, p7, Tx, uP, Tu);
dH2 = pH2( x1, p1, p2, Tx, uV1, Tu);
dH3 = pH3( x1, p1, p3, Tx, uV2, Tu);
dH4 = pH4(x4, x5, p4, p5, p8, Tx, uT1, Tu);
```

```
dH5 = pH5(x6, x7, p6, p7, p8, p9, Tx, uT2, Tu);
H1norm = dH1'*dH1;
H2norm = dH2'*dH2;
H3norm = dH3'*dH3;
H4norm = dH4'*dH4;
H5norm = dH5'*dH5;

% Calculate the Cost Function
% Weight constants for Strategy 5
A1 = 1; A2 = 1; B1 = 1; B2 = 1; B3 = 1; B4 = 1; B5 = 1;

% Cost function
J = tf*((A1*(x4+x6) +A2*(x5+x7))/length(Tx)+0.5*(B1*(uP*uP')+B2*(uV1*uV1')+
B3*(uV2*uV2')+B4*(uT1*uT1')+B5*(uT2*uT2'))/length(Tu));
obj=J
TCst=0.5*(B1*(uP*uP')+B2*(uV1*uV1')+B3*(uV2*uV2')+B4*(uT1*uT1')+B5*(uT2*uT2'));
% TCst(disp(J1)
% if dH/du < epsilon, exit
%if Hnorm < eps
eps = 1.0e-6;
if (H1norm < eps) && (H2norm < eps) && (H3norm < eps) && (H4norm < eps)
&& (H5norm < eps)
% Display final cost
J
break;
else
% adjust control for next iteration
uPold = uP;
uP = AdjControl1(dH1, Tx, uPold, Tu, step);
uV1old = uV1;
uV1 = AdjControl2(dH2, Tx, uV1old, Tu, step);
uV2old = uV2;
```

```
uV2 = AdjControl3(dH3, Tx, uV2old, Tu, step);
uT1old = uT1;
uT1 = AdjControl4(dH3, Tx, uT1old, Tu, step);
uT2old = uT2;
uT2 = AdjControl5(dH3, Tx, uT2old, Tu, step);
end
end
figure(1)
plot(Tx, X(:, 1), '-b', 'LineWidth', 3);
xlabel('Time (days)');
ylabel('S(t)');
figure(2)
plot(Tx, X(:, 2), '-g', 'LineWidth', 3);
xlabel('Time (days)');
ylabel('V1(t)');
figure(3)
plot(Tx, X(:, 3), '-g', 'LineWidth', 3);
xlabel('Time (days)');
ylabel('V2(t)');
figure(4)
plot(Tx, X(:, 4), '-b', 'LineWidth', 3);
xlabel('Time (days)');
ylabel('C1(t)');
figure(5)
plot(Tx, X(:, 5), '-b', 'LineWidth', 3);
xlabel('Time (days)');
ylabel('C2(t)');
figure(6)
plot(Tx, X(:, 6), '-r', 'LineWidth', 3);
xlabel('Time (days)');
ylabel('I1(t)');
figure(7)
```

```
plot(Tx, X(:, 7), '-r', 'LineWidth', 3);
xlabel('Time (days)');
ylabel('I2(t)');
figure(8)
plot(Tx, X(:, 8), '-g', 'LineWidth', 3);
xlabel('Time (days)');
ylabel('R1(t)');
figure(9)
plot(Tx, X(:, 9), '-r', 'LineWidth', 3);
xlabel('Time (days)');
ylabel('R2(t)');
figure(10)
plot(Tx, (X(:,4)+X(:,5)+X(:,6)+X(:,7)),'-b', 'LineWidth', 3);
xlabel('Time (days)');
ylabel('C1+C2+I1+I2');
Inf=sum(X(:,4)+X(:,5)+X(:,6)+X(:,7));
disp(Inf)
R=sum(X(:,8)+X(:,9));
disp(R)
figure(11)
plot(Tu, uP, '-r', 'LineWidth', 3);
xlabel('Time (days)');
ylabel('uP');
legend('uP');
figure(12)
plot(Tu, uV1, '-r', 'LineWidth', 3);
xlabel('Time (days)');
ylabel('uV1');
figure(13)
plot(Tu, uV2, '-r', 'LineWidth', 3);
xlabel('Time (days)');
ylabel('uV2');
```

```
figure(14)
plot(Tu, uT1, '-r', 'LineWidth', 3);
xlabel('Time (days)');
ylabel('uT1');
figure(15)
plot(Tu, uT2, '-r', 'LineWidth', 3);
xlabel('Time (days)');
ylabel('uT2');
%figure; plot(Tp, P(:, 1));
figure(16)
plot(Tu, uP, '-r', 'LineWidth', 3);
hold on;
plot(Tu, uV1, '–r', 'LineWidth', 3);
hold on;
plot(Tu, uV2, ':k', 'LineWidth', 3);
hold on;
plot(Tu, uT1, '-k', 'LineWidth', 3);
hold on;
plot(Tu, uT2, ':b', 'LineWidth', 3);
hold off;
xlabel('Time (days)');
ylabel('Control Profiles');
h=legend('uP', 'uV1', 'uV2','uT1','uT2');
disp(J);
disp([R,Inf, TCst])

% state equations
function dx = stateEq(t, x, uP, uV1, uV2, uT1, uT2, Tu)
global beta eta epsilon1 epsilon2 alpha omega1 omega2 mu tau1 tau2 sigma1 sigma2;
global gammac1 gammac2 gammai1 gammai2 delta rho1 rho2 wedge;
dx = zeros (9,1);
uP = interp1(Tu, uP, t); % interpolate the controls at time t
```

```
uV1 = interp1(Tu, uV1, t);
uV2 = interp1(Tu, uV2, t);
uT1 = interp1(Tu, uT1, t);
uT2 = interp1(Tu, uT2, t);
N = x(1)+x(2)+x(3)+x(4)+x(5)+x(6)+x(7)+x(8)+x(9);
lambda1 = ((1-uP)*beta*(eta*x(4)+x(6)))/N;
lambda2 = ((1-uP)*beta*(eta*x(5)+x(7)))/N;
pi1 = 1-epsilon1;
pi2 = 1- epsilon2;
dx(1) = alpha + omega1*x(2) + omega2*x(3) - (lambda1 + lambda2 + uV1 + uV2
+ mu)*x(1);
dx(2) = uV1*x(1) - pi1*lambda1*x(2) -(lambda2+omega1+mu)*x(2);
dx(3) = uV2*x(1) - pi2*lambda2*x(3) - (lambda1 + omega2 + mu)*x(3);
dx(4) = lambda1*((1-tau1)*x(1)+pi1*x(2)) - (sigma1 + gammac1*(1+uT1) +
mu)*x(4);
dx(5) = lambda2*((1-tau2)*x(1)+pi2*x(3)) - (sigma2 + gammac2*(1+uT1) +
mu)*x(5);
dx(6) = sigma1*x(4) + lambda1*(tau1*x(1)+x(3)) -
(gammai1*(1+uT2)+delta+mu)*x(6);
dx(7) = sigma2*x(5) + lambda2*(tau2*x(1)+x(2)) -
(gammai2*(1+uT2)+delta+mu)*x(7);
dx(8) = gammac1*(1+uT1)*x(4)+gammac2*(1+uT2)*x(5)+rho1*gammai1*(1+uT2)*x(6)
+rho2*gammai2*(1+uT2)*x(7)-(wedge+mu)*x(8);
dx(9) = (1-rho1)*gammai1*(1+uT2)*x(6)+(1-rho2)*gammai2*(1+uT2)*x(7)+wedge*x(8)-
mu*x(8);

% Costate equations
function dp = costateEq(t, p, uP, uV1, uV2, uT1, uT2, Tu, x1,x2,x3,x4,x5,x6, x7, x8,
x9,xt)
global mu wedge delta gammai1 gammai2 rho1 rho2 beta epsilon1 epsilon2 tau1 tau2;
global A1 A2 % B1 B2 B3 B4 B5;
global sigma1 sigma2 gammac1 eta omega1 omega2 gammac2;
```

```
dp = zeros(9, 1);
% Interpolate the state variables
x1 = interp1(xt, x1, t);
x2 = interp1(xt, x2, t);
x3 = interp1(xt, x3, t);
x4 = interp1(xt, x4, t);
x5 = interp1(xt, x5, t);
x6 = interp1(xt, x6, t);
x7 = interp1(xt, x7, t);
x8 = interp1(xt, x8, t);
x9 = interp1(xt, x9, t);
% Interpolate the control variables
uP = interp1(Tu, uP, t);
uV1 = interp1(Tu, uV1, t);
uV2 = interp1(Tu, uV2, t);
uT1 = interp1(Tu, uT1, t);
uT2 = interp1(Tu, uT2, t);
N = x1+x2+x3+x4+x5+x6+x7+x8+x9;
lambda1 = ((1-uP)*beta*(eta*x4+x6))/N;
lambda2 = ((1-uP)*beta*(eta*x5+x7))/N;
dp(1) = p(1)*mu+(p(1)-p(2)).*uV1+(p(1)-p(3)).*uV2+(p(1)-p(4)).*lambda1+(p(1)-
p(5)).*lambda2+(p(4)-p(6)).*(tau1*lambda1)+(p(5)-p(7)).*(tau2*lambda2);
dp(2) = p(2).*mu+(p(2)-p(1)).*omega1+(p(2)-p(7)).*lambda2+(p(2)-
p(4)).*(lambda1*(1-epsilon1));
dp(3) = p(3).*mu+(p(3)-p(1)).*omega2+(p(3)-p(6)).*lambda1+(p(3)-
p(5)).*(lambda2*(1-epsilon2));
dp(4) = (p(1)-p(4)).*(((1-uP)*beta*eta)./N-lambda1./N)*x1+(p(4)-p(6)).*(((1-
uP)*beta*eta)./N-lambda1./N)*tau1*x1 + (p(2)-p(4)).*(((1-uP)*beta*eta)./N-
lambda1./N)*(1-epsilon1)*x2 + (p(3)-p(6)).*(((1-uP)*beta*eta)./N-
lambda1./N)*x3+(p(4)-p(8)).*gammac1*(1+uT1)+(p(4)-p(6)).*sigma1+p(4).*mu-
A1;
```

```
dp(5) = (p(1)-p(5)).*(((1-uP)*beta*eta)./N-lambda2./N)*x1+(p(5)-p(7)).*(((1-uP)*beta*eta)./N-lambda2./N)*tau2*x1 + (p(3)-p(5)).*(((1-uP)*beta*eta)./N-lambda2./N)*(1-epsilon2)*x3 + (p(2)-p(7)).*(((1-uP)*beta*eta)./N-lambda2./N)*x2+(p(5)-p(8)).*gammac1*(1+uT1)+(p(5)-p(7)).*sigma2+p(5).*mu-A2;
dp(6) = (p(1)-p(4)).*(((1-uP)*beta)./N-lambda1./N)*x1+(p(4)-p(6)).*(((1-uP)*beta)./N-lambda1./N)*tau1*x1 + (p(2)-p(4)).*(((1-uP)*beta)./N-lambda1./N)*(1-epsilon1)*x2 + (p(3)-p(6)).*(((1-uP)*beta)./N-lambda1./N)*x3+(p(6)-p(9)).*gammai1*(1+uT2)+(p(9)-p(8)).*rho1*gammai1*(1+uT2)+p(6).*(mu+delta)-A1;
dp(7) = (p(1)-p(5)).*(((1-uP)*beta)./N-lambda2./N)*x1+(p(5)-p(7)).*(((1-uP)*beta)./N-lambda2./N)*tau2*x1 + (p(3)-p(5)).*(((1-uP)*beta)./N-lambda2./N)*(1-epsilon2)*x3 + (p(3)-p(7)).*(((1-uP)*beta)./N-lambda2./N)*x2+(p(7)-p(9)).*gammai2*(1+uT2)+(p(9)-p(8)).*rho2*gammai2*(1+uT2)+p(7).*(mu+delta)-A2;
dp(8) = (p(8)-p(9)).*wedge + p(8).*mu;
dp(9) = p(9).*mu;

% partial derivative of H with respect to u
function dH1 = pH1(x1, x2, x3, x4, x5, x6, x7, x8, x9, p1, p2, p3, p4, p5, p6, p7, Tx, uP, Tu)
% interpolate the control
global B1 tau1 tau2 epsilon1 epsilon2 beta eta;
uP = interp1(Tu, uP, Tx);
N = x1+x2+x3+x4+x5+x6+x7+x8+x9;
lambda1 = ((1-uP).*beta.*(eta*x4+x6))./N;
lambda2 = ((1-uP).*beta.*(eta*x5+x7))./N;
dH1 = B1*uP-(p4-p1).*(lambda1.*x1)-(p5-p1).*(lambda2.*x1)-(p6-p4).*(lambda1*tau1.*x1) - (p7-p5).*(lambda2*tau2.*x1)-(p4-p2).*(lambda1*(1-epsilon1).*x2) - (p7-p2).*(lambda2.*x2) - (p5-p3).*(lambda2*(1-epsilon2).*x3) - (p6-p3).*(lambda1.*x3);
function dH2 = pH2( x1, p1, p2, Tx, uV1, Tu)
```

```
% interpolate the control
global B2;
uV1 = interp1(Tu, uV1, Tx);
dH2 = B2*uV1 - (p1-p2).*x1;
% partial derivative of H with respect to u2
function dH3 = pH3( x1, p1, p3, Tx, uV2, Tu)
% interpolate the control
global B3;
uV2 = interp1(Tu, uV2, Tx);
dH3 = B3*uV2 - (p1-p3).*x1;
function dH4 = pH4(x4, x5, p4, p5, p8, Tx, uT1, Tu)
% interpolate the control
global gammac1 gammac2 B4;
uT1 = interp1(Tu, uT1, Tx);
dH4 = B4*uT1 - (p4-p8).*gammac1.*x4 - (p5-p8).*gammac2.*x5;
function dH5 = pH5(x6, x7, p6, p7, p8, p9, Tx, uT2, Tu)
% interpolate the control
global gammai1 gammai2 rho1 rho2 B5;
uT2 = interp1(Tu, uT2, Tx);
dH5 = B5*uT2 - (p6-p9).*gammai1.*x6 - (p7-p9).*gammai2.*x7-(p9-
p8).*rho1.*gammai1.*x6-(p9-p8).*rho2.*gammai2.*x7;

% adjust the control
function uPnew = AdjControl1(pH1, Tx, uP, Tu, step)
% interpolate dH/u
pH1 = interp1(Tx, pH1, Tu);
uPnew = min(1,max(0,uP - step*pH1));
function uV1new = AdjControl2(pH2, Tx, uV1, Tu, step)
% interpolate dH/u
pH2 = interp1(Tx, pH2, Tu);
uV1new = min(1,max(0,uV1 - step*pH2));
function uV2new = AdjControl3(pH3, Tx, uV2, Tu, step)
```

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% interpolate dH/u
pH3 = interp1(Tx, pH3, Tu);
uV2new = min(1,max(0,uV2 - step*pH3));
function uT1new = AdjControl4(pH4, Tx, uT1, Tu, step)
% interpolate dH/u
pH4 = interp1(Tx, pH4, Tu);
uT1new = min(1,max(0,uT1 - step*pH4));
function uT2new = AdjControl5(pH5, Tx, uT2, Tu, step)
% interpolate dH/u
pH5 = interp1(Tx, pH5, Tu);
uT2new = min(1,max(0,uT2 - step*pH5));
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Index

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