Epidemiological Modeling of Measles Disease with Optimal Control of Vaccination Strategy

by

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Free World Measles!

No Child Death from Measles!

Abstract

Epidemiological models provide a powerful tool for investigating the dynamics and control of infectious diseases, but quantifying the underlying epidemic structure can be challenging especially for new and under-studied diseases. Measles is a highly infectious disease which has a major impact on child survival, particularly in developing countries. The importance of understanding the epidemiology of this disease is underlined by its ability to change rapidly in the face of increasing immunization coverage with proper cost effectiveness. Much is still to be learned about its epidemiology and the best strategies for administering measles vaccines. However, it is clear that tremendous progress can be made in preventing death and disease from measles with existing knowledge about the disease, and by using the presently available vaccines and applying well-tried methods of treating cases. Since vaccination turned out to be the most effective strategy against childhood disease, developing a framework that would predict an optimal vaccine coverage level needed to control the spread of these diseases is crucial. We consider an optimal control problem subject to an SEIR measles epidemic model with vaccination controls. Our aim is find the best optimal control strategies to make the number of infectious individuals as small as possible and to keep the vaccination ratio of measles as low as possible during a certain vaccination period that will minimize the cost of control. We used Pontryagin's maximum principle to characterize the optimal levels of the controls. The resulting optimality system is solved numerically by forward-backward sweep method. The results show that the optimal vaccination policy differs according to the controlled and uncontrolled individuals and has a very desirable effect upon the population for reducing the number of infected individuals. The effect of vaccination on transmission dynamics of measles is studied. The resulting optimality system also showed that, the use of vaccinating at the highest possible rate to the population as early as possible is essential for controlling an epidemic of the measles disease. Finally, we use our model to simulate the data of measles cases in the Ethiopia from 2004 to 2014 and design a control strategy (optimal vaccination policy) of the country to eliminate the epidemic for the future course with optimal control theory. The results from our simulation are discussed.

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TO GOD BE THE GLORY.

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CHAPTER ONE

1. Epidemiological Models

1.1. General Introduction

Infectious diseases have always been a great concern of human kind since the very beginning of history. In the increasingly interconnected world in which we live, infectious diseases represent a growing threat to global public health. At present, we still have to deal with plagues and diseases. Millions of people die annually from measles, malaria, tuberculosis, AIDS . . . and billions of others are infected. They are still the major causes of mortality in the developing countries [1, 15, 41]

To prevent and to control infectious diseases more effectively, it is important to first fully understand the mechanism of the spread and the transmission dynamics of the diseases, and then provide useful predictions and guidance so that better strategies can be established. Mathematical epidemiology contributes to the understanding of the behavior of infectious diseases, its impacts on possible future predictions about its spreading. Mathematical models are used in comparing, planning, implementing, evaluating and optimizing various detection, prevention and control programs [1, 17, 41].

Epidemiology is the study of health and disease in human population. It is the study of the distribution and determinants of health-related events in specified populations, and the application of this study to control health problems. When talking about an infectious disease, we talk about a communicable disease. It is an illness which arises through transmission of an infectious agent (or its toxic products) from an infected individual to a host [15, 16, 41].

The transmission can happen in a direct or indirect way. The direct transmission of a disease can happen by physical proximity (such as sneezing, coughing, kissing, and sexual contact) or even by a specific parasite that penetrates the host through ingestion or the skin. The indirect transmission involves the vectors that are intermediaries or carriers of the infection [15, 20, 41].

In most of the cases, the direct and indirect transmission of the disease happens between the members that coexist in the host population; this is called the *horizontal transmission*. When the direct transmission occurs from one ascendant to a descendent not yet born, (egg or embryo) it is said that *vertical transmission* happens [20, 41].

Infectious diseases are basically of two types, the first is *acute* (fast infectious) which stay for a short period (days/weeks) e.g. Influenza, Chickenpox, Rubella, Measles etc). The other is *chronic* infectious disease which stay for larger period (month/year) e.g. hepatitis [15].

There are several types of diseases, depending on their *type of transmission mechanism*, some of these are:

Bacteria: which *do not confer immunity* against re-infection and frequently produce harmful toxins to the host. In case of infection, the antibiotics are usually efficient (examples: tuberculosis, meningitis, gonorrhea, syphilis, tetanus);

Viral agents: that *confer immunity* against re-infection; here antibiotics do not produce any effect and usually it is hoped that the immune system of the host responds to an infection by the virus or it will be necessary to take antiviral drugs that retard the multiplication of the virus (examples influenza, chicken pox, measles, rubella, mumps, HIV / AIDS, smallpox);

Vectors: these are usually mosquitoes or ticks and infect by humans and then transmit the disease to other humans (examples: malaria, yellow fever, dengue fever)

1.1.1. Some key terms to describe the infectious disease at the population level

Epidemic: occurrence of an infectious disease clearly in excess of normal expectancy.

Outbreak: an epidemic limited to localized increase in the incidence of a disease.

Endemic: the constant presence/ habitual presence (usual occurrence) of a disease within a given geographical area.

Pandemic: an epidemic occurring over a very wide area, crossing international boundaries and usually affecting a large number of people.

1.1.2. Deterministic and Stochastic Approach to Mathematical Modeling

Mathematical models are a simplified representation of how an infection spreads across a population over time, and generally come in two forms: *stochastic and deterministic models.* If the objective of the study is to model disease propagation in a large population, deterministic model is the most appropriate one. Because, natural and biological discrete events of random occurrence in a small population cannot be explained by deterministic models. Deterministic models split the population into subclasses (compartments), and differential equation (ODE or PDE) with respect to time is formulated for each. The state variables are determined using parameters and initial conditions [20, 26, 41].

Stochastic model include an element of randomness indicative of the real world, which is concerned with mimicking the random or probabilistic event. It is more suitable, for small population size. They provide more insight into an individual-level modeling, taking into consideration small population size where every individual plays an important role in the model. Hence, they are used when known heterogeneities are important as in small or isolated populations. Stochasticity decreases as the number of cases increases [5, 6, 7, 17, 18, 19, 20]. The main focus in this thesis will be the deterministic models, neglecting the others.

1.1.3. Basic Terminology

Most epidemic models are based on dividing the population into a small number of subclasses (compartments). Each containing individuals, that are identical in terms of their status with respect to the disease in question.

Here are some of the main compartments that a model can contain;

Passive immune (M): is composed by newborns that are temporary passively immune due to antibodies transferred by their mothers;

Susceptible (S): is the class of individuals who are susceptible to infection; this can include the passively immune ones who lost their immunity;

Exposed or Latent (E): compartment refers to the individuals that despite being infected, do not exhibit obvious signs of infection and the abundance of the disease may be too low to allow further transmission. Individuals are exposed but not infectious.

Infected (I): in this class, the level of parasite is sufficiently large within the host and there is a potential of transmitting the infection to other susceptible individuals;

Recovered or Resistant (R): includes all individuals who have been infected and have recovered from the disease and are immune for life.

The choice of compartment to include in a model depends on the *characteristics of the particular disease being modeled and the purpose of the model* [1, 15, 20].

Measles epidemic is the cause of millions of death worldwide and a public health problem. It is also one of the most communicable diseases causing infant mortality and morbidity in Ethiopia. Therefore, calling upon all stakeholders for measles prevention and control is appropriate for eradicating the epidemic.

1.2. Epidemiology of Measles

1.2.1. Introduction

Measles is an acute viral infectious disease. References to measles can be found from as early as the 7th century. The disease was described by the Persian physician Rhazes in the 10th century as “more dreaded than smallpox’’ [2, 4,]. It is one of the leading causes of death among people especially young children even though a safe and cost-effective vaccine is available. It is so serious that in the developing world, mothers say, *"Never count your children until after the Measles"* [2, 3, 6].

Measles is one of the most infectious human diseases and can cause serious illness, life-long complications and death. It is highly communicable, with greater than 90% secondary attack rates among susceptible persons. In the absence of measles vaccination, virtually all children will have been infected with measles by the time they are 10 years old. It is still a public health problem in many developing countries, particularly in parts of Africa and Asia. According to the World Health Organization (WHO) [3, 6, 26], more than 20 million people are affected by measles each year with more than 95% of measles deaths occur in countries that have low per capita incomes and weak health infrastructures.

Measles outbreaks can be particularly deadly in countries experiencing or recovering from a natural disaster or conflict. Damage to health infrastructure and health services interrupt routine immunization and overcrowding in residential camps greatly increases the risk of infection. In developing countries with low vaccination coverage, epidemics often occur every two to three years and usually last between two and three months, although their duration varies according to population size, overcrowding and the population's immune status. Outbreaks last longer where family size, and hence the number of household contacts, is large [2, 4, 22].

In the year 2000, the World Health Organization (WHO) [2, 3] estimated that 548,000 children died of measles, this translates to about 1,501 deaths every day or 62 deaths every hour, the majority in developing countries especially with more than half of measles deaths occur in sub-saharan Africa and this burden accounted for 15% of all under-five mortality.

Worldwide; during 2000-2008, global measles mortality declined by 78%, from an estimated 548,000 deaths in 2000 to 158,000 in 2008, and also measles mortality rate declined by 74%, 71% and 75% in the year 2010, 2011 and 2013, respectively making it the fifth most common cause of death in children under five years of age [6, 23, 24, 25, 27]. Due to under-reporting, the true number of measles cases and deaths is estimated to be 10-20 times higher. Measles surveillance data reported an incidence 16.5 measles cases per 100,000 populations in the African Region, WHO-2010 [2, 3, 6].

Therefore, it is necessary to examine the optimal strategies that can be implemented in order to control measles in high burden countries like Ethiopia [22, 23]. High measles-burden countries with limited financial resources are confronted with difficult decisions related to measles control.

1.2.2. Mode of Transmission

Measles is an acute, highly contagious viral disease caused by measles virus *(paramyxovirus).* This highly contagious virus is transmitted primarily by respiratory droplets or airborne spray to mucous membranes in the upper respiratory tract or the conjunctiva. It can be transmitted by direct contact with infected nasal or throat secretions or transmission typically occurs through coughing and sneezing of infected people. The measles virus is sensitive to ultraviolet light, heat and drying. The virus has a short survival time (less than 2 hours) in air or on objects and surfaces.

Humans are the only natural hosts of measles virus. Although monkeys may become infected, transmission among them in the wild does not appear to be a mechanism by which the virus persists in nature. As a result, it can spread rapidly by contact in a susceptible population. Infected people carry the virus in their respiratory tract before they get sick, so they can spread the disease without being aware of it [22].

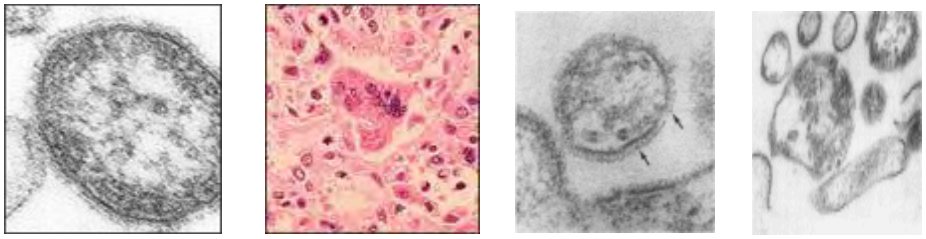


Figure 1.1: Measles Virus under a Microscope. Sources: CDC 2010 [2]

1.2.3. Clinical Features of Measles

Generally measles can be divided into four stages of illness period:

1.2.3.1. Incubation Period and Period of Infectivity

The incubation period is approximately 10–12 days from exposure to the onset of fever and other nonspecific symptoms. It takes aboute 14 days (with a range of 7–18 days), from exposure to the onset of rash/prodrome. Infectivity is greatest four days before rash onset [2].

Measles is highly contagious. Secondary attack rates among susceptible household contacts have been reported to be 75%–90%. Due to the high transmission efficiency of measles, outbreaks have been reported in populations where only 3% to 7% of the individuals were susceptible [2, 3, 22].

1.2.3.2. Prodrome Period

During this period, symptoms appear. They usually begin 12-14 days after exposure. Common symptoms include: fever, fatigue, decreased appetite, red watery eyes, runny nose, cough and with temperature often rising as high as 38°C. Other symptoms may include: vomiting, diarrhea, abdominal pain, sore throat, swollen glands and an enlarged spleen. Koplik's spot is the characteristic symptom of measles. It appears on the inside of the mouth. Koplik's spots are small white areas that may have bluish-colored centers. The prodrome usually lasts 2-4 days (range 1–7 days). However, it can last up to eight days [2, 22].

1.2.3.3. Exanthem (Rash) Period

During this period, a rash develops. The rash usually starts on the face and spreads to the neck, trunk, arms and legs. Often, patients will start to feel better about 48 hours after the rash appears. The rash starts to fade within 3-4 days after it appears. There may be some fine peeling of the skin after the rash fades. Patients are considered highly contagious from 4 days prior till 4 days after the onset of the rash [2, 22].

1.2.3.4. Recovery Period

A cough may last for 1-2 weeks after the measles infection. However, a medical consultation may be necessary to diagnose the exact state of the episode [2, 22].

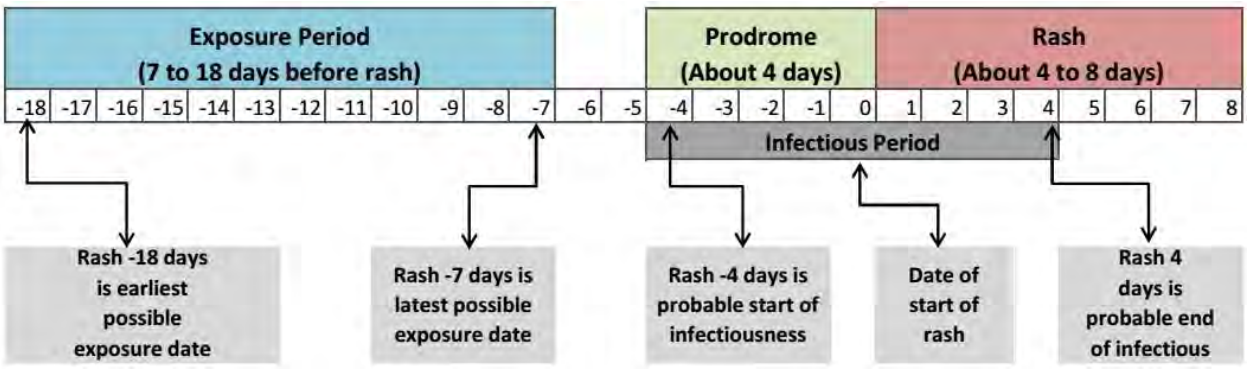
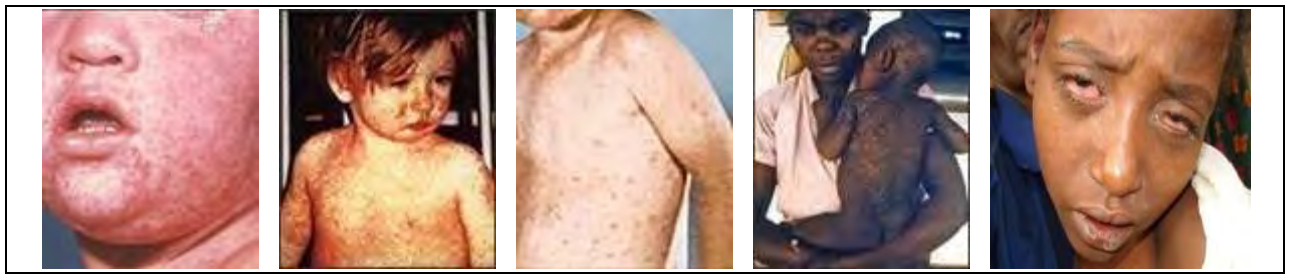


Figure 1.2: The clinical course of measles and its relation to exposure and infectious period for active case finding.



(i) (ii) (iii) (iv) (v)

Figure: 1.3 Photos of Measles and People with Measles. Source: CDC 2010 [4, 22]

The figure depicts that:

(i) Face of boy after three days with measles rash.

(ii) Child with a classic measles rash after four days

(iii) Young boy five to six days into illness with rash and cough.

(iv) Skin sloughing off of a child healing from measles infection.

(v) Eyes of a child with measles.

1.2.4. Prevention

Measles is one of the leading causes of death among young children even though a safe and cost-effective vaccine is available. The best way to reduce the risk of contracting measles is to be immunized with the measles vaccine. This can be given in the form of combined measles, mumps and rubella vaccine commonly referred to as a MMR vaccine.

The measles vaccine has been in use for 50 years. It is safe, effective and inexpensive. While the vaccine is not a 100% guarantee against ever getting the measles, it significantly reduces the risk. In the absence of vaccination, the measles virus would infect almost 100 percent of the population [2, 22, 23, 24, 25, 26, 27].

1.2.5. Measles Vaccination

Implementation of proper and effective vaccination protocol is of primary concern to the epidemiologists and public health decision makers. Vaccination program is usually a government initiative applied on large spatial and temporal scales to reduce the level of complexity of disease [18]. Despite the availability of a safe, heat-stable, effective and inexpensive measles vaccine, and the substantial progress towards measles control, measles remains one of the leading causes of death globally among children [2, 3, 6].

1.2.5.1. Vaccination Schedule and Use

The first dose of MMR (measles, mumps and rubella) vaccine should be given on or after the first birthday. Any dose of measles-containing vaccine (MCV) given before 12 months of age should not be counted as part of a valid dose. Vaccination is generally not given earlier than this because sufficient antimeasles immunoglobulin's (antibodies) are acquired via the placenta from the mother during pregnancy may prevent the vaccine viruses from being effective. Children vaccinated with measles-containing vaccine (MCV) before 12 months of age should be revaccinated with two doses of MMR vaccine. About 15% of vaccinated children fail to develop immunity from the first dose, two doses of the vaccine usually given to children between the ages of four to six are recommended to *ensure immunity* and *prevent outbreaks* [23, 24, 25]. Worldwide; during 2000-2013, measles vaccination prevented an estimated 15.6 million deaths including routine immunization [2, 3, 5].

1.2.6. Complications

Approximately 30% of reported measles cases have one or more complications. Complications of measles are more common among children younger than 5 years of age and adults 20 years of age and older. These include pneumonia, ear and sinus infections, mouth ulcers, persistent diarrhea, Otis, ulceration and blindness, protein energy malnutrition, convulsions and brain damage. Complication rates are increased in persons with immune deficiency disorders, malnutrition, vitamin A deficiency, and inadequate vaccination [2, 3, 22, 62, 65].

1.2.7. The risk factors for Increased Fatality

Unvaccinated young children are at highest risk of measles and its complications, including death. Unvaccinated pregnant women are also at risk. Any non-immune person (who has not been vaccinated or was vaccinated but did not develop immunity) can become infected. Children with vitamin A deficiency, HIV/AIDS, leukemia, and children, who travel to areas where measles is endemic or are in contact with travelers to endemic areas. Malnourished and young children are at higher risk of developing complications and mortality from measles infection [2, 3, 4, 22, 62, 65].

Adverse reactions to vaccination are rare, life-threatening adverse reactions occur in less than one per million vaccinations (<0.0001%). Immunity conferred by vaccination against measles has been shown to persist for at least 20 years and is generally thought to be life-long for most individuals. All persons who do not have the disease or who have not been successfully immunized are *susceptible* [2, 3, 5, 6, 22].

1.2.8. Treatments for Measles

There is no specific medicine that kills the measles virus. Children and adults exposed to measles virus, which have not developed immunity to the disease, can be vaccinated within 3 days after exposure. The vaccine is prescribed for pregnant women and children less than one year. For these categories of people it is often preferred to use immunoglobulin (antibodies), administered within 2 days after exposure to the virus. Treatment aims to ease symptoms until the body's immune system clears the infection. For most cases, rest and simple measures to reduce a fever are all that are needed for a full recovery. Symptoms will usually disappear within 7-10 days.

The following measures are often useful:

- Children should drink as much as possible to prevent dehydration.
- Paracetamol or ibuprofen can be taken to ease fever and aches and pains.
- Antibiotics do not kill the measles virus and so are not normally given.

1.3. Measles in Ethiopia

The population of Ethiopia was estimated to be 87.9 million in 2014; 83% live in rural areas, 12.5% are children <5 years of age, and 90% have access to formal health care services. The country has a surface area of 1.1 million km^2 and is administratively divided into 9 regional states and 2 city administrations. The regional states and city administrations are divided into 103 zones with 736 woredas; the woredas are divided approximately 15, 000 kebeles [48, 49].

In Ethiopia, the National Immunization Programme was established in the 1980s, and currently delivers service through static and outreach sites nationwide. The implementation of the regional measles mortality reduction strategy started in 2002. The current routine immunization schedules recommend a dose of measles vaccination at 9 months of age. The WHO UNICEF coverage estimates for measles vaccination for Ethiopia also indicate an increase from 37 % in 2000 to around 80% in 2010 [22, 62, 65].

Estimated Measles Containing Vaccine first dose (MCV1) coverage in Ethiopia was 56% in 2010 and 57% in 2011; the percentage of districts reporting with almost 80% MCV1 coverage was 45% in 2010 and 43% in 2011. During 2010–2011, annual reported measles incidence decreased from 75 to 42 per 1 million populations. Despite this national progress, some populations remain unprotected. An estimated 1 million children in the country did not receive the first dose of vaccine in 2011. So the case and incidence rate of measles increased from 8,137 to 20,038 and 66 to 167 per million in 2013 and 2014, respectively [2, 3, 22, 62,65].

As Ethiopia has not reached over 90% coverage on the first dose of measles, it is not recommended to start a routine second dose. Therefore the country is using the option of supplementary immunization activities (SIAs) or through routine immunization. When Ethiopia achieves over 90% routine measles vaccination coverage for 3 consecutive years, a second routine dose may be considered as an alternative to periodic campaigns [22].

Table 1.1

The data of measles cases from 2004 to 2014 in Ethiopia

Year	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Case	4,741	2,416	4,820	4,932	3,511	4,735	6,202	3,554	4,878	8,137	15,478

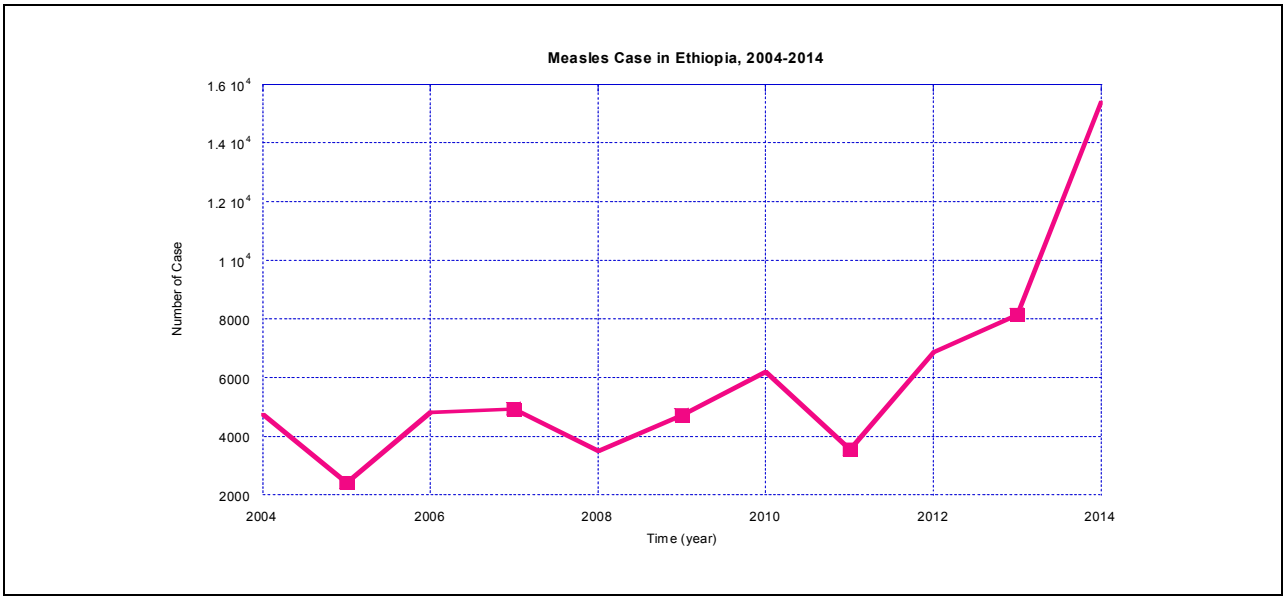


Figure: 1.4 Reported measles cases in the Ethiopia from 2004 to 2014 (CDC 2008, 2012, 2014, 2015 [2, 3, 6, 22, 62,65])

1.4. Optimal Vaccination Strategy

Most infectious diseases could be driven towards eradication, if adequate and timely steps (e.g. vaccination, treatment, educational and enlightenment campaign, etc.) are taken in the course of the epidemic. However, many of these diseases eventually become endemic in our society due to lack of adequate policies and timely interventions to mitigate the spread. Consequently, there is the need for proactive steps towards controlling the spread of infectious diseases, particularly those ones for which both vaccine and cure are available [18, 20, 66].

Optimal Vaccination Strategy: Optimal vaccination requires good management of available resources (money, time, personnel or any other costs considered) *to achieve effective disease control, even without vaccinating the whole population. The* main concern is, "which vaccination policies are optimal?" Optimal in the sense of disease eradication with regard to associated costs.

In order to prevent the disease from becoming endemic, it is necessary to vaccinate a large fraction of susceptible hosts. Despite wide usage of vaccines, some disease like measles still persist somewhere since the vaccination is sometime ineffective and vaccination campaigns are never able to reach everyone. Different vaccination policies have been adopted in different part of the world. In practice, the application of a vaccination policy is limited by factors including cost. Cost may be increased by involving more equipment and personnel. With limited resource, there is need to balance the vaccination rates and the cost. In this section, an optimal vaccination strategy is designed to minimize an objective functional that takes into account both the number of infectious individuals and the cost [66].

The goal of optimal vaccination strategies to measles is to minimize the total number of infectious individuals and the cost associated with vaccination during the vaccination campaign [18, 20, 29, 31].

1.5. Preliminary to Optimal Control Theory

We assume as is often the case, that the budget for the control of the disease is restricted. During one period for vaccination we want to spend at most a reasonable amount of vaccination doses. The aim is to find a vaccination schedule that is as cost effective as possible by *optimization concepts* [15, 37].

We use optimal control to assess the most cost-effective method of introducing the control parameters *(like vaccination, treatment, prevention, isolation...).* Optimal control is a useful mathematical tool which has been used to determine optimal vaccination strategies [15, 31].

The optimal control theory has been used successfully to make decisions involving biological or medical models. This theory is based on the Calculus of variations whose target is to find an optimal functional which is expressed in terms of a system of differential equations. Essentially, a biological or medical model involves a number of variables which are dynamic in nature. For instance measles model may involve the effect of vaccination, treatment, regional features such as economic situations and many others. One would like to find the set of values for these variables which would give optimal positive effects in relation to control of infection diseases [15, 31]..

Using Pontryagin's maximum principle (PMP), which was developed by Pontryagin and his co-workers in the late 1950s,including its extensions and appropriate numerical methods, one can adjust the control in a model to achieve specified goals [15, 31].

The controls are usually functions of time which are coefficients or source terms in the model. Optimal control techniques involve appending adjoint functions to the problem to characterize the optimal control. The optimality system, which characterizes the optimal controls, consists of the differential equations of the original model (state equations) together with the adjoint differential equations. Pontryagin's maximum principle gives the format of the adjoint differential equations and the corresponding terminal boundary conditions. If the original model has four differential equations then the adjoint system has four differential equations also Adjoint functions have a similar purpose as 'Lagrange multipliers' in multivariable calculus (appending constraints to the function of several variables to be maximized or minimized). The adjoint variables bring the state differential equations into the maximization or minimization of the objective functional (goal) [15, 31]. This is dealt with in chapter 4 of this thesis.

1.6. Motivation

Measles is one of the leading causes of preventable death globally among people especially young children even though a safe and cost-effective vaccine is available.

The major problem of measles is that it weakens the immune system and opens the door to secondary health problems, such as pneumonia, blindness, diarrhea, encephalitis etc [2, 3, 6].

There are strong social impact and economic burden of the disease, which in so many ways affects fertility, population growth, saving and investment, premature mortality, and medical costs.

Optimal control theory is another area of mathematics that is used extensively in controlling the spread of infectious diseases (measles) at the lowest economic cost to obtain the optimal vaccination strategy. For such reasons it is important to formulate a transmission dynamics of measles model with optimal control policy to eradicate the measles epidemic and minimize the cost associated for vaccination strategy.

1.7. Statement of the Problems

The spread of measles diseases has always been a concern and poses a threat to public health, as well as the economic and social developments in a developing country. Thus, its prevention and control are very important. Meanwhile, limitation of resource is a main problem in minimizing the incidence rate or outbreak of measles disease which kills millions of child every year.

Most studies of epidemic control of measles focus on increasing the immunization coverage (vaccination coverage) in a population to control the disease, but they do not consider how this parameter affects the strategy over a period of time. Though some of these studies have considered vaccination strategy at different level of immunization approach none of them has studied optimal vaccination strategy by considering measles disease models for countries like Ethiopia. To control this disease a proper allocation of resource to the control parameters by way of optimization is a significant effect in controlling the diseases.

This study is intended to answer the question of *how an optimal vaccination policy* and control strategies *can be put in place such that the cost of the implementation of the intervention is minimized while the disease is controlled within specified period.*

Using these parameters as control variables, the study will determine the possible impact of optimal control method; by adopting a differential mathematical model for the control of measles the epidemic. This is attained by efficiently balancing different vaccination strategies with varies cost scenarios.

1.8. Objective of the Thesis

The general objective of this study is to model the best optimal control strategies, to make the number of infectious individuals as small as possible and to keep the vaccination ratio of measles as low as possible during a certain vaccination period.

1.9. Specific Objective of the Thesis

i. To formulate a non linear ordinary differential equation based model of measles disease showing the impact of optimal control strategy and the system to produce the best outcome.

ii. To verify the effect of vaccination on spread of measles

iii. To compare the best optimal vaccination schedule in mitigating measles disease.

iv. To compare uncontrolled and controlled state strategies on the dynamics of the disease.

v. Perform simulations to illustrate analytical results.

1.10. Significance of the Thesis

The following are the significances of this study:

i. To researchers, it will be a useful reference for any future study for monitoring and controlling strategy for measles disease.

ii. The public health policy maker will be assisted by provision of strategies that can be used to determine the optimal policies for reducing spread of the disease with a minimum cost with control variable.

iii. It will help policy makers in general to have an understanding of how the disease can be controlled through vaccination in order to reduce the incidence rate.

iv. Policy makers choosing whether to eradicate measles need to know about the costs of eradication, control period and its alternatives resource allocation.

1.11. Methodology

i) We employ an optimal control problem with extended SEIR compartmental model as constraints and minimize an objective (cost) function.

ii) Vaccination which is one of the most effective strategies in preventing morbidity and mortality associated with measles diseases is included in this model.

i) We choose an optimal strategy to minimize the total number of infectious individuals and the cost associated with vaccination as control functions.

ii) We derive the optimality system and solve it numerically for our optimal control problem. As stressed in the statement of the problems, measles is among the disease for which our optimal control model is a good approximation.

iii) We will test our theoretical findings by simulating measles vaccination strategies by using epidemiological parameter values on Ethiopian demographic data from this country.

iv) For all numerical solutions presented we use a forward-backward sweep method and

v) The result is executed using MATLAB.

1.12. Thesis Organization

The thesis is organized as follows. In chapter 2, we present the optimal control strategies of measles disease model to be investigated. A precise explanation of our model can be seen in chapter 3, for an SEIR model formulation which includes reproduction number, bifurcation point and qualitative (stability) analysis on the model equilibria. In chapter 4, we introduce optimal control problem subject to SEIR measles model. Pontryagin's Maximum Principle (PMP) is used to characterize the optimal control problem. We characterize the optimal controls, and derive the optimality system. In chapter 5, a simulation of measles vaccination schedules and control strategies in Ethiopia is provided including a discussion of results. Finally, we draw conclusions from this thesis and assess what new insights this work gives to the body of knowledge on optimal control as a recommendations for future work. Chapter 6 is the end of the study.

CHAPTER TWO

2. Literature Review

This chapter reviews the work of other researchers related to the objectives of this thesis. Some of the related works are as follows;

In 2007, Researchers from CDC reported that the global goal to reduce measles deaths by 50% by 2005, compared with 1999 had been achieved. Firstly, Building on this accomplishment, in 2008 the World Health Organization summit on measles endorsed a target of 90% reduction in measles mortality by 2010, compared with 2000. All WHO regions (all except Southeast Asia) have set target dates for measles elimination by 2020 or earlier. Secondly, the establishment of a global measles eradication goal has been extensively discussed by the World Health Assembly and advisory committees to WHO including progress towards regional elimination. The fourth Millennium Development Goal (MDG4) aims to reduce deaths of children by two thirds by 2015 compared with 1990. The proportion of children vaccinated against measles was adopted as an indicator to measure progress towards MDG4. A rebound in measles deaths was considered a substantial threat to achieving this goal. The rapid progress in measles control from 2000 to 2007 was based on implementation of recommended measles mortality reduction strategies, including increasing routine immunization coverage, periodic Supplemental Immunization Activities (SIAs—i.e., mass vaccination campaigns aimed at immunizing 100 percent of a predefined population within several days or weeks) and appropriate management of measles cases. WHO put a strategy by a name “Progress in Global measles control and mortality reduction 2008”. Countries that have fully implemented and sustained these strategies have experienced reductions in measles cases of greater than 90 percent. However, not all countries have managed to do so, and several of the largest recorded outbreaks of the past decade were during 2009–10, WHO measles outbreaks 2011[2, 3, 22, 23, 24, 62, 65]. Previous models have not objectively incorporated measles surveillance data and instead relied on vaccination coverage data as the primary indicator of local disease burden.

Allen [7], stated that an epidemic of rubella occurred on the campus of Texas Tech University in January, February and March of 1989. A vaccination program was initiated as soon as the epidemic was confirmed. Extensive case histories of all confirmed cases were collected by the Lubbock City Health Department and given an exhaustive statistical analysis by a group from the Department of Mathematics at Texas Tech University. The data and statistical analysis were used to formulate stochastic and deterministic models of the measles epidemic based on the standard SEIR model. The analysis and the simulations indicated that in order to prevent measles outbreak on a university campus a high rate of immunity above 98 per cent might be required.

Chen [8], proved that vaccination has a powerful defense against measles. They reappraised measles sero-epidemiological data in Taiwan from 1974 to 2004 having robust age-stratified serological information on exposure and immunity in order to quantitatively characterize measles vaccination programs. They dynamically modeled measles sero-epidemiology to estimate age-dependent intensity of infection associated with the effects of different contact patterns on pre- and post-vaccination. A contact matrix was employed to describe the transmission between and within each age group. They used a deterministic Susceptible–Exposed–Infected–Recovery (SEIR) model to capture subpopulation dynamics. Their study showed that mass regional or nationwide vaccination programs could greatly reduce the potential for a major measles epidemic and have strong direct effects on the potential impact of childhood vaccination. They parameterized a predictive model that should reduce the socio-economic costs of measles surveillance in Taiwan and thereby encourage its continuance, especially for pre-school children.

Roberts and Tobias [9], ‘’A Mathematical model of the dynamics of measles in New Zealand’’ was developed in 1996. The model successfully predicted an epidemic in 1997 and was instrumental in the decision to carry out an intensive MMR (measles-mumps -rubella) immunization campaign in that year. While the epidemic began some months earlier than anticipated, it was rapidly brought under control, and its impact on the population was much reduced. In order to prevent the occurrence of further epidemics in New Zealand, an extended version of the model had since been developed and applied to the critical question of the optimal timing of MMR immunization.

Lloyd [10], illustrated how detailed dynamical properties of a model might depend in an important way on the assumptions made in the formulation of the model. According to his study most mathematical models used to understand the dynamical patterns seen in the incidence of childhood viral diseases, such as measles, employ a simple, but epidemiologically unrealistic, description of the infection and recovery process. The inclusion of more realistic descriptions of the recovery process was shown to cause a significant destabilization of the model. When there was seasonal variation in disease transmission that destabilization leads to the appearance of complex dynamical patterns with much lower levels of seasonality than previously predicted.

Trottier and Philippe [11], also presented a deterministic modeling as applied to the population dynamics of infectious diseases. They used SEIR deterministic model to provide useful insights into the mechanic of many common childhood diseases such as measles. They showed that deterministic models exhibit damped oscillations, showed random variations and predicted the spread of infectious diseases. Their paper provided an introduction to the theory and methods of deterministic modeling and would be followed by two other articles that would show how sensitivity analysis could be helpful for the forecast and control of common infectious diseases at the population scale.

Grais et al. [12], stated that the current World Health Organization recommendations for response during measles epidemics focus on case management rather than outbreak response vaccination (ORV) campaigns, which may occur too late to impact morbidity and mortality and have a high cost per case prevented. They explored the potential impact of an ORV campaign conducted during the 2003–2004 measles epidemic in Niamey, Niger. They measured the impact of this intervention and also the potential impact of alternative strategies. They used a unique geographical, epidemiologic and demographic dataset collected during the epidemic to develop an individual-based simulation model. They estimated that a median of 7.6% (4.9–8.9) of cases was potentially averted as a result of the outbreak response, as a result of vaccination of approximately 57% (84,563 of an estimated 148,600) of children in the target age range (6–59 months), 23 weeks after the epidemic started. They found that intervening early (up to 60 days after the start of the epidemic) and expanding the age range to all children aged 6 months to 15 years may have led to a much larger (up to 90%) reduction in the number of cases in a West African urban setting like Niamey.

A deterministic compartmental mathematical model has been developed by Hethcote in 2000 [16] for the study of the effects of heterogeneous mixing and vaccination distribution on disease transmission in Africa. This study focuses on vaccination against measles in the city of Naimey, Niger, in sub-Saharan Africa. The rapidly growing population consists of a majority group with low transmission rates and a minority group of seasonal urban migrants with higher transmission rates. Demographic and measles epidemiological parameters are estimated from data on Niger. An MSEIR model was applied with 16 age groups for a homogeneously mixing, unvaccinated population in Niger. From measles data, it is estimated that the average period of passive immunity 116 is 6 months, the average latent period $1/\varepsilon$ is 14 days and the average infectious period $1/\gamma$ is 7 days. From data on a 1995 measles outbreak in Niamey, the force of infection is estimated to be the constant 0.762 per year. A computer calculation of the basic reproduction number yields $R_0 = 18.83$.

In New Zealand there has been an outbreak of measles and Pertussis every six and five years respectively by M.G. Roberts 2000 [33]. A model has been used to compare the dynamics of these diseases, and to determine the optimum ages at which children should be vaccinated against them. Whereas measles could be eliminated by giving the second vaccination at five years instead of eleven, it is difficult to devise a practical scheme that would eliminate Pertussis. It is then necessary to consider vaccination schemes in the light of the age-structure of future epidemics as well as their timing.

Anderson and May 1983 [13], considered an age-dependent epidemic model for measles and rubella. The model was age-dependent but assumed homogeneous mixing. They performed simulations and from these estimated the number of measles encephalitis and CRS complications under differing immunization strategies. They approximated the USA strategy by immunizing a given fraction of boys and girls at 1 year of age. Their conclusion is that at low levels of vaccine coverage the UK policy was best to prevent CRS but once the coverage level exceeds 85 per cent the USA policy was best. This gives the reassuring conclusion that at that time the UK policy was best for the UK and the USA policy was optimal for the USA.

Sethi and Staats 1978 [35], analytically solved three different control scenarios using compartment models. They use the concepts of Pontryagin's Maximum Principle to characterize the optimal control solution, using 'bang-bang' controls (*in this scenario, the control is either at*

maximum or minimum, and i.e. the optimal control may only switch between the bounds of the control set /two states). In doing this, they defined the optimal control problems for three different types of intervention in SIR compartment models and provided a useful reference when formulating a model with optimal control. An optimal control problem in a structured population is built. This model contains four connected subgroups, with an SIR model applied to each of them. Optimal control is applied to the model, with quadratic terms for the control functions in the objective functional, and Pontryagin's Maximum Principle is used to characterize the optimal control. Their results support other results found, namely that vaccination is highest at initial time, after which it decreases to very low levels.

Population could be subdivided into a set of distinct classes dependent upon experience with respect to the relevant disease Zaman 2007 [67], They used Susceptible-Infected-Recovered (SIR). In their paper, they described an SIR epidemic model with three components; S, I and R. They described their study of stability analysis theory to find the equilibria for the model. In order to achieve control of the disease, they considered a control problem relative to the SIR model. A percentage of the susceptible populations were vaccinated in that model. They showed that an optimal control exists for the control problem and they used Runge-Kutta fourth order procedure to describe the numerical simulations. They finally described a real example showing the efficiency of that optimal control.

Yan and Zou 2008 [36], applied optimal control to a compartmental model for Severe Acute Respiratory Syndrome (SARS). They consider two different interventions - quarantine and isolation - and search for both an optimal and sub-optimal solution (their sub-optimal solution is found by defining the form of the control function aimed at minimizing the objective functional for that particular form). Their results for the control functions agree with the work discussed above-both the optimal and sub-optimal forms should be introduced at their maximums and decreased over time, which can greatly reduce the number of infected individuals. They also set both control functions as constants in their model and compare the results. In doing this, they found that there are a much greater number of infected individuals under the constant control model, with a much greater cost associated with this model.

Elsa Hansen and Troy Day [37], extended the existing work on the time-optimal control of the basic SIR epidemic model with mass action contact rate. Previous results have focused on minimizing an objective function that is a linear combination of the cost associated with using

control and either the outbreak size or the infectious burden. They instead, provide numerical solutions for the control that minimizes the outbreak size (or infectious burden) under the assumption that there are limited control resources. They provide optimal control policies for an isolation only model, a vaccination only model and a combined isolation–vaccination model (or mixed model). The optimal policies described here contain many interesting features especially when compared to previous analyses. For example, under certain circumstances the optimal isolation only policy is not unique. Furthermore the optimal mixed policy is not simply a combination of the optimal isolation only policy and the optimal vaccination only policy. The results presented here also highlight a number of areas that warrant further study and emphasize that time-optimal control of the basic SIR model is still not fully understood.

Onyango Nelson Owuor 2013 [38], with his paper 'Optimal Vaccination Strategies in an SIR Epidemic Model with Time Scales'-Childhood related diseases such as measles as characterized by short periodic outbreaks lasting about 2 weeks. This means therefore that the timescale at which such diseases operate is much shorter than the time scale of the human population dynamics. He analyzed a compartmental model of the SIR type with periodic coefficients and different time scales for 1) disease dynamics and 2) human population dynamics. Interest is to determine the optimal vaccination strategy for such diseases. In a model with time scales, Singular Perturbation theory is used to determine stability condition for the disease free-state. The stability condition is here referred to as instantaneous stability condition, and implies vaccination is done only when an instantaneous threshold condition is met. We make a comparison of disease control using the instantaneous condition to two other scenarios: one where vaccination is done constantly over time (constant vaccination strategy) and another where vaccination is done when a periodic threshold condition is satisfied. Results show that when time scales of the disease and human population match, he see a difference in the performance of the vaccination strategies and above all, both the two threshold strategies outperform a constant vaccination strategy.

To the best of our knowledge no research work related to the optima vaccination strategies to combat the measles disease has ever been done in Ethiopia.

CHAPTER THREE

3. Model Formulation and Stability Analysis

3.1. Introduction

Epidemiology is essentially a population biology discipline concerned with public health. As such, epidemiology is thus heavily influenced by mathematical theory and model. Mathematical modeling is an interesting tool for understanding epidemiological diseases and for proposing effective strategies to fight them in addition to important tools in analyzing the spread and control of infectious disease. The study of infectious disease by the means of mathematical modeling helps as to understand the behavior of the disease, and the planning of an eradication policy [1, 15, 16, 17, 18, 20, 39, 41].

3.2. Model Formulation

3.2.1 A Model for Measles

The first step in deterministic model (DM) consists in having a complete and realistic picture of the biology of the disease under study (e.g., period of infectivity, latent period, immune status after infection), and to select a parsimonious model (in relation to data available) [22, 26].

The total population size N(t) is divided into four distinct epidemiological subclasses (compartments) of individuals which are susceptible, exposed, infectious, and recovered (with permanent immunity), with sizes denoted by S(t), E(t), I(t), and R(t), respectively where t represents the time.

In the case of measles, as most mothers have been infected, immunoglobulin (IgG) antibodies transferred across the placenta to newborn infants give them *temporary passive immunity* to measles' infection. After the maternal antibodies remains in the body up to nine months, we consider that the infant enters directly in the susceptible class S at birth. So, all the newborns were assumed to be susceptible. When there is an adequate contact of a susceptible with an

infective so that transmission occurs, then the susceptible enters the exposed class E of those in the latent period, who are infected but not yet infectious. After the latent period ends, the individual enters the class I of infectives, those that are infectious in the sense that they are capable of transmitting the infection. When the infectious period ends, the individual enters the recovered class R consisting of those with permanent infection-acquired immunity otherwise they pass away. We exclude *vertical incidence* in our model, which means that the infection rate of newborns by their mothers. Based on the mechanism and characteristics of measles transmission, our model belongs to a deterministic SEIR epidemic model.

3.3. Model Assumptions

1. The population is uniform and mixes homogeneously. The total population size, N(t)=S(t)+E(t)+I(t)+R(t) at any time t>0;
2. The natural birth rate b and death rates μ are assumed to be different rate;
3. The infectious I move from their compartment to R-compartment at a constant rate γ, and latent's (exposed) E move from their compartment to I-compartment at a constant rate ε, so that $1/\gamma$ is the mean infectious period and $1/\varepsilon$ is the mean latent period;
4. Each individual in the population is considered as having an equal probability of contacting the disease with a contact rate β ;
5. An infected individual makes contact and is able to transmit the disease with βN others per unit time, that is, the contact rate is proportional to the total population size;
6. The fraction of contacts by an infected with a susceptible is S/N. Therefore the number of new infections in unit time per infective becomes $(\beta N)(S/N)$. This rate is called an *infection rate*. This gives the rate of new infections or those leaving the susceptible category as $(\beta N)(S/N)I = \beta SI$, which is called an *incidence* of the disease. This type of incidence is called bilinear incidence i.e. proportional to the product of the number of infective individuals and the number of susceptible individuals, we choose the bilinear incidence, because measles highly communicable the size of population has a direct effect to the contact rate of infectious is discussed in [7, 9, 13, 14, 28, 53, 54].
7. The number of infected individuals move from the exposed compartment per unit time is εE at time t

8. The number of recovered individuals move from the infected compartment per unit time is γI at time t;
9. The rate of susceptible, exposed, infected and recovered individual removed from each compartments through natural death and disease induced death are $\mu S,\ \mu E,\ \mu I\ \ \mu R$ and δI respectively;
10. Individuals in the recovered class are assumed to be immune for life;

Table 1.2: Summary of description of variables and parameters for the model

Symbols	Description
S	Susceptibles population (proportion)
E	Exposed individual in the latent period (proportion)
I	Infectives population (proportion)
R	Recovered population (proportion)
β	Contact rate
μ	Average death rate
b	Average birth rate
δ	Disease related death rate
ε	Latency rate
γ	Recovery rate
$1/\varepsilon$	Average Latent period
$1/\gamma$	Average Infectious Period
R_0	Basic Reproduction Number

3.3.1. SEIR Model in Diagram

The dynamics of the disease can be depicted in the following diagram

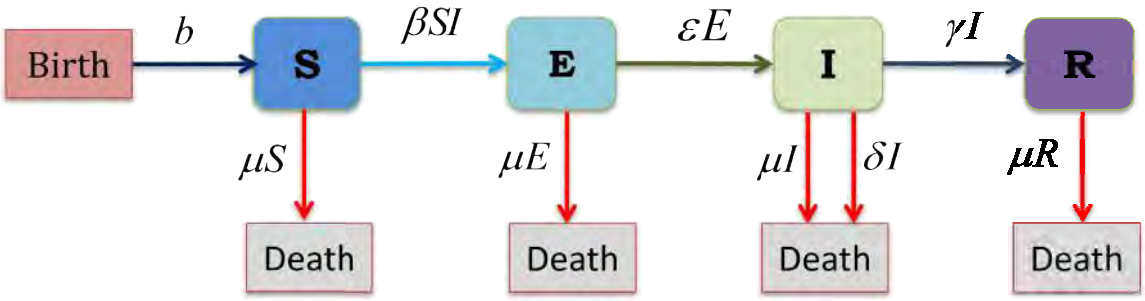


Figure 2 The SEIR schematic model of Measles (flow chart)

The model formulation using the assumptions as is follows.

The inflow of population to the susceptible class is b, by combining assumptions 2,8 and 9 we drive the susceptible populations change per unit of time.

Therefore the rate of susceptible becomes

$$\frac{dS}{dt} = b - \beta SI - \mu S \qquad (1)$$

Beside the number of individuals leave S and enter E, a fraction of exposed E move to infectious group I with a latent rate ε, εE an individual's move from exposed to infectious and some of the exposed group die through natural death rate μ, μS to an individual's move from exposed to death. The rate of exposed becomes

$$\frac{dE}{dt} = \beta SI - \varepsilon E - \mu E \qquad (2)$$

As the number of individuals leave E and enter I, fraction of infected individuals leaves I and enter into the recovered group with latent rate ε and recovery rate γ respectively. This gives rate of infective and recovered as;

$$\frac{dI}{dt} = \varepsilon E - \gamma I - \delta I - \mu I \qquad (3)$$

$$\frac{dR}{dt} = \gamma I - \mu R \qquad (4)$$

The system of differential equation from the assumptions and diagrams for $t \geq 0$ is given in a system/coupled ordinary differential equation form of (5)

Governing Equation of transmission dynamics of measles SEIR model becomes;

$$\begin{cases} \begin{cases} \frac{dS}{dt} = b - \beta SI - \mu S & (5.1) \\ \frac{dE}{dt} = \beta SI - (\varepsilon + \mu)E & (5.2) \\ \frac{dI}{dt} = \varepsilon E - (\gamma + \delta + \mu)I & (5.3) \\ \frac{dR}{dt} = \gamma I - \mu R & (5.4) \end{cases} \\ with \ \ initial \ \ conditions, \\ \begin{cases} S(0) = S_0 \geq 0, \ E(0) = E_0 \geq 0, \\ I(0) = I_0 \geq 0, \ \ R(0) = R_0 \geq 0, \end{cases} \qquad (5.5) \end{cases}$$

The parameters are all *positive constants*. The total population *N*(*t*) can be obtained from

$$N(t) = S(t) + E(t) + I(t) + R(t) \qquad (6)$$

Therefore summing the differential equations (5), leads to the equation

$$\frac{dN}{dt} = b - \delta I - \mu N \qquad (7)$$

Here, it is important to note that in the absence of the disease, equation (7) become $N(t) \to \frac{b}{\mu}$

The population size N(t) declines exponentially to zero if $b < \mu$, may approach zero, remain finite, or grow exponentially to infinity, depending on the infectives I(t), if $b > \mu$. We can still determine whether the disease dies out or not by analyzing the changing tendency of the infective fraction I(t) in the total population, such that the disease persists if the limit $\lim t \to \infty I(t)$ is greater than 0,and dies out if the limit is 0 [1].

Since R does not appear in the first three differential equations, most of the times the last equation is omitted, indeed,

$$R(t) = N(t) - S(t) - E(t) - I(t) \qquad (8)$$

Equation (5) can be written as a standard way

$$\begin{cases} \begin{cases} \dfrac{dS}{dt} = b - \beta SI - \mu S & (9.1) \\ \dfrac{dE}{dt} = \beta SI - (\varepsilon + \mu)E & (9.2) \\ \dfrac{dI}{dt} = \varepsilon E - (\gamma + \delta + \mu)I & (9.3) \\ \dfrac{dN}{dt} = b - \delta I - \mu N & (9.4) \end{cases} \\ with\ \ initial\ \ conditions, \\ \begin{cases} S(0) = S_0 \geq 0,\ E(0) = E_0 \geq 0, \\ I(0) = I_0 \geq 0,\ \ N(0) = N_0 \geq 0, \end{cases} \qquad (9.5) \end{cases}$$

3.4. Positivity of Solutions and the Invariant Region

The basic properties of the equation (9), are *feasible* solutions and *positivity* of solutions. The feasible solution shows the region in which the solution of the equations are *biologically meaningful* and the positivity of the solutions describes the *non-negativity* of the solutions of the equation (9) by [55].

Moreover, under the dynamics described by equations (9), the region

$$\Omega = \left\{ x = (S, E, I, N) \in R_+^4 : S \geq 0, E \geq 0, I \geq 0, S + E + I \leq N \leq \frac{b}{\mu} \right\} \qquad (10)$$

is positively invariant (non-negative solutions).Hence, the system is both mathematically and epidemiologically well-posed (feasible).

Therefore, for initial starting point $x \in R_+^4$; the trajectory lies in Ω. Thus, we can restrict our analysis to the region Ω. In other words, solutions of equation (5) with given non-negative initial data remain positive all the time and are bounded in region Ω above [42, 44, 55].

3.5. Basic Reproductive Number and Equilibria

The analysis of the model includes finding equilibrium points (steady states) of the model, finding the threshold value, basic reproduction number R_0 and investigating the stability of the equilibrium points (disease-free and endemic which will be characterized using the threshold value R_0).

3.5.1. Basic Reproductive Number (R_0)

The basic reproduction ratio of an infectious disease is a pivotal concept in epidemiology. It is a famous result due to Kermack and McKendrick [41]. It is an important measure of transmissibility of the disease.

It represents the expected number of secondary cases produced in a completed susceptible population, by a typical infected individual during its entire period of infectiousness [41, 54, 55].

If $R_0 < 1$ the number of infected individuals will decrease from generation to the next and the disease dies out asymptotically.

However, if $R_0 > 1$ the number of infected individuals will increase from generation to the next with a ratio $R_0 > 1$ and the disease will persist.

The basic reproduction number R_0 can be determined using the method of next-generation matrix as presented in [54, 55].

The next generation matrix is

$$K = FV^{-1} \qquad (12)$$

where F and V are *transmission* and *transition* matrices, respectively, as presented in [54, 55].

The basic reproduction number is the eigenvalue of largest magnitude, or spectral radius of the next generation matrix, that is, the number of all new infectious host types in the next generation.

$$R_0 = \rho(K) = \rho\left(FV^{-1}\right) \qquad (13)$$

where ρ denotes the spectral radius (dominant eigenvalue) of the matrix FV^{-1} [2].

Let $\vec{X}(t)$ be the vector of disease states.

The vector of disease states from the equation (9) is the exposed and infectious compartement, $\vec{X} = \left(E, I\right)^T$. The states can be written as

$$\begin{cases} \dfrac{dE}{dt} = \beta SI - (\varepsilon + \mu)E \\ \dfrac{dI}{dt} = \varepsilon E - (\gamma + \delta + \mu)I \end{cases} \qquad (14)$$

Note that equation (14) is made of two compartments E and I which are disease transmission and transmission. These are used for the determination of R_0.

Then we have matrix $F = \begin{pmatrix} \beta SI \\ 0 \end{pmatrix}$ and $V = \begin{pmatrix} (\varepsilon + \mu)E \\ (\gamma + \delta + \mu)I - \varepsilon E \end{pmatrix}$

We need to differentiate both matrices F and V with respect to I and E to get F and V respectively.

Then we can find the Jacobian for each matrix F and V at no disease (I*=0) equation (9). The equilibrium at no disease for equation (9) is $\left(S^*, E^*, I^*, N^*\right) = \left(b/\mu, 0, 0, b/\mu\right)$.

Linearization using the Jacobian matrix about no disease for equation (14) yields

$$\frac{\vec{X}(t)}{dt} = J\vec{X}(t) \qquad (14.1)$$

From equation (13),

$$JF\left(b/\mu,0,0,b/\mu\right)=\begin{pmatrix}\dfrac{\partial\left(\beta S^{*}I^{*}\right)}{\partial E} & \dfrac{\partial\left(\beta S^{*}I^{*}\right)}{\partial I}\\ \dfrac{\partial\left(0\right)}{\partial E} & \dfrac{\partial\left(0\right)}{\partial I}\end{pmatrix}=\begin{pmatrix}0 & \beta\\ 0 & 0\end{pmatrix} \qquad (14.2)$$

and similarly

$$JV\left(b/\mu,0,0,b/\mu\right)=\begin{pmatrix}\dfrac{\partial\left((\varepsilon+\mu)E^{*}\right)}{\partial E} & \dfrac{\partial\left((\varepsilon+\mu)E^{*}\right)}{\partial I}\\ \dfrac{\partial\left((\gamma+\delta+\mu)I^{*}-\varepsilon E^{*}\right)}{\partial E} & \dfrac{\partial\left((\gamma+\delta+\mu)I^{*}-\varepsilon E^{*}\right)}{\partial I}\end{pmatrix} \qquad (14.3)$$

$$=\begin{pmatrix}\left(\varepsilon+\mu\right) & 0\\ -\varepsilon & \left(\gamma+\delta+\mu\right)\end{pmatrix}$$

Matrix F and V are

$$F=\begin{pmatrix}0 & \beta\\ 0 & 0\end{pmatrix},\ V=\begin{pmatrix}\left(\varepsilon+\mu\right) & 0\\ -\varepsilon & \left(\gamma+\delta+\mu\right)\end{pmatrix} \qquad (14.4)$$

The next generation matrix of equation (9.1)-(9.4) is $K=FV^{-1}$.

Thus, we need to find the spectral radius of FV^{-1}:

$$F=\begin{pmatrix}0 & \beta\\ 0 & 0\end{pmatrix}\quad and\quad V^{-1}=\begin{pmatrix}\dfrac{1}{\left(\varepsilon+\mu\right)} & 0\\ \dfrac{\varepsilon}{\left(\varepsilon+\mu\right)\left(\gamma+\delta+\mu\right)} & \dfrac{1}{\left(\gamma+\delta+\mu\right)}\end{pmatrix} \qquad (14.5)$$

$$FV^{-1}=\begin{pmatrix}\dfrac{\beta\varepsilon}{\left(\varepsilon+\mu\right)\left(\gamma+\delta+\mu\right)} & \dfrac{\beta}{\left(\gamma+\delta+\mu\right)}\\ 0 & 0\end{pmatrix} \qquad (14.6)$$

The basic reproduction number is the eigenvalue of largest magnitude, or spectral radius of the next generation matrix.

The basic reproduction number for the measles model equation (9):

$$R_0 = \frac{\beta\varepsilon}{(\varepsilon+\mu)(\gamma+\delta+\mu)} \qquad (14.7)$$

Interpretation: An exposed individual that survives $\varepsilon/(\varepsilon+\mu)$ becomes infectious and contacts β susceptible individuals during the period of infectivity $1/(\gamma+\delta+\mu)$, which result in a new exposure.

3.6. Stability Analysis of measles SEIR Model

Very often it is almost impossible to find explicitly or implicitly the solutions of a system. A qualitative approach can be considered because make conclusions regardless of whether we know the solutions or not [45]. In this section we discuss the existence of eqiulibria, stability analysis and bifurcation of equation (5) is considered.

Equilibrium: a system at equilibrium does not change over time (plural: equilibria).

In epidemiology we have two types of equilibria points; *disease free-equilibrium and endemic equilibrium*

i. If the equilibrium point has the infectious component equal to zero $(I^*=0)$, this means that the disease has undergone *extinction* is called *disease-free equilibrium (DFE).*

ii. If $I^*>0$ the disease *persist* in the population called *endemic-equilibrium (EE).*

Since the variable *R* does not appear in the first three equations of (5), by recalling equation (9);

$$\begin{cases} \frac{dS}{dt} = b - \beta SI - \mu S & (15.1) \\ \frac{dE}{dt} = \beta SI - (\varepsilon+\mu)E & (15.2) \\ \frac{dI}{dt} = \varepsilon E - (\gamma+\delta+\mu)I & (15.3) \\ \frac{dN}{dt} = b - \delta I - \mu N & (15.4) \end{cases}$$

To find the equilibrium points of equation (15) the right-hand sides of each differential equation are set to zero, leading to the system.

$$\begin{cases} b-\beta S^* I^* -\mu S^* = 0 & (16.1) \\ \beta S I^* -(\varepsilon+\mu)E^* = 0 & (16.2) \\ \varepsilon E^* -(\gamma+\delta+\mu)I^* = 0 & (16.3) \\ b-\delta I^* -\mu N^* = 0 & (16.4) \end{cases}$$

where S*,E*,I* and N* are the equilibria points of equation(15)

Let

$$\beta S^* I^* = \Psi \qquad (17)$$

Substituting (17) into (16) gives,

1. From (16.1) we have $b-\beta S^* I^* -\mu S^* = 0 \Rightarrow b-\Psi-\mu S^* = 0 \Rightarrow S^* = \dfrac{b-\Psi}{\mu}$

2. From (16.2) we have $\beta S I^* -(\varepsilon+\mu)E^* = 0 \Rightarrow \Psi-(\varepsilon+\mu)E^* = 0 \Rightarrow E^* = \dfrac{\Psi}{(\varepsilon+\mu)}$

3. From (16.3) we have $\varepsilon E^* -(\gamma+\delta+\mu)I^* = 0 \Rightarrow \dfrac{\varepsilon\Psi}{(\varepsilon+\mu)} - (\gamma+\delta+\mu)I^* = 0$

$$\Rightarrow I^* = \frac{\varepsilon\Psi}{(\varepsilon+\mu)(\gamma+\delta+\mu)} = \psi\frac{R_0}{\beta}$$

5. From N*, $b-\delta I^* -\mu N^* \Rightarrow b-\delta\left(\psi\dfrac{R_0}{\beta}\right)-\mu N^*$

$$\Rightarrow N^* = \frac{b}{\mu} - \frac{\delta}{\mu}\left(\psi\frac{R_0}{\beta}\right)$$

From 1,2,3,4 we have the following

$$S^* = \frac{b-\Psi}{\mu},\ E^* = \frac{\Psi}{(\varepsilon+\mu)},\ I^* = \frac{\varepsilon\Psi}{(\varepsilon+\mu)(\gamma+\delta+\mu)},\ N^* = \frac{b}{\mu} - \frac{\delta}{\mu}\left(\psi\frac{R_0}{\beta}\right) \qquad (18)$$

Substituting equation (18) into (16) results

From (16.1) $b-\beta S^{*} I^{*}-\mu S^{*}=0$, substituting the value of S* and I*;

$$
\begin{aligned}
&=b-\beta\left(\frac{b-\Psi}{\mu}\right)\left(\psi\frac{R_0}{\beta}\right)-\mu\left(\frac{b-\Psi}{\mu}\right)=0\\
&\Rightarrow b-R_0\left(\frac{b-\Psi}{\mu}\right)\Psi-\mu\left(\frac{b-\Psi}{\mu}\right)\\
&\Rightarrow b-R_0\left(\frac{b-\Psi}{\mu}\right)\Psi-b+\Psi=0\\
&\Rightarrow -R_0\left(\frac{b-\Psi}{\mu}\right)\Psi+\Psi=0\\
&\Rightarrow \Psi\left(-R_0\left(\frac{b-\Psi}{\mu}\right)+1\right)=0
\end{aligned}
$$

$$
\Psi\left(-R_0\left(\frac{b-\Psi}{\mu}\right)+1\right)=0 \qquad (18.1)
$$

By simplifying equation (18.1) we have two roots of Ψ ;

$$
\Psi_0=0 \;\; or \;\; \Psi^{*}=b-\frac{\mu}{R_0} \qquad (19)
$$

substituting equation (19) into (18) gives the following two case:

For $\Psi_0=0$ equations (18) becomes

$$
\begin{aligned}
S_0&=\frac{b-\Psi_0}{\mu}\Rightarrow\frac{b}{\mu}\\
E_0&=\frac{\Psi_0}{(\varepsilon+\mu)}\Rightarrow\frac{0}{(\varepsilon+\mu)}=0\\
I_0&=\frac{\varepsilon\Psi_0}{(\varepsilon+\mu)(\gamma+\delta+\mu)}\Rightarrow\frac{\varepsilon*0}{(\varepsilon+\mu)(\gamma+\delta+\mu)}=0\\
N_0&=\frac{b}{\mu}-\frac{\delta}{\mu}\left(\psi_0\frac{R_0}{\beta}\right)\Rightarrow\frac{b}{\mu}-\frac{\delta}{\mu}\left(0*\frac{R_0}{\beta}\right)=\frac{b}{\mu}
\end{aligned}
\qquad (19.1)
$$

Therefore,

$$\left(S_0, E_0, I_0, N_0\right) = \left(b/\mu, 0, 0, b/\mu,\right) \qquad (20)$$

For $\Psi^* = b - \frac{\mu}{R_0}$ equations (18) becomes

$$S^* = \frac{b - \Psi^*}{\mu} = \left(\frac{b - b - \frac{\mu}{R_0}}{\mu} \right) \Rightarrow \frac{\mu}{\mu R_0} = \frac{1}{R_0}$$

$$E^* = \frac{\Psi^*}{(\varepsilon + \mu)} = \frac{\frac{\mu}{R_0}(R_0 - 1)}{(\varepsilon + \mu)} = \frac{\mu}{R_0}\left(\frac{(R_0 - 1)}{(\varepsilon + \mu)} \right)$$

$$I^* = \frac{\varepsilon \Psi^*}{(\varepsilon + \mu)(\gamma + \delta + \mu)} \Rightarrow \frac{\left(\varepsilon \frac{\mu}{R_0}(R_0 - 1) \right)}{(\varepsilon + \mu)(\gamma + \delta + \mu)}$$

$$= \frac{\mu}{R_0}\left(\frac{\varepsilon}{(\varepsilon + \mu)(\gamma + \delta + \mu)} \right)(R_0 - 1) \qquad (20.1)$$

$$N^* = \frac{b}{\mu} - \frac{\delta}{\mu}\left(\psi * \frac{R_0}{\beta} \right) \Rightarrow \frac{b}{\mu} - \frac{\delta}{\mu}\left(\frac{\mu}{R_0}(R_0 - 1) \right)\left(\frac{R_0}{\beta} \right)$$

$$= \frac{b}{\mu} - \frac{\delta}{\beta}(R_0 - 1)$$

By substituting $\left(\frac{\varepsilon}{(\varepsilon + \mu)(\gamma + \delta + \mu)} \right) = \frac{R_0}{\beta}$ into equation (20.1) the simplification of this equation can be summarized as:

$$\left(S^*, E^*, I^*, N^*\right) = \begin{cases} S^* = \frac{1}{R_0}, \\ E^* = \frac{\mu}{R_0}\left(\frac{(R_0 - 1)}{(\varepsilon + \mu)} \right), \\ I^* = \frac{\mu}{\beta}(R_0 - 1), \\ N^* = \frac{b}{\mu} - \frac{\delta}{\beta}(R_0 - 1) \end{cases} \qquad (20.2)$$

3.6.1. Disease-Free Equilibrium E_0 (DFE)

The disease-free equilibrium point of equation (9) exists if $I^* = 0$, equation (17) $\beta S^* I^* = \Psi$ is zero when $I^* = 0$, then at this point we can determine the disease-free equilibrium. From (19) we develop equation (20) the disease-free equilibrium point of the system (5) , then;

$$E^0 = (S_0, E_0, I_0, N_0) = (b/\mu, 0, 0, b/\mu,) \qquad (21a)$$

3.6.2. Endemic Equilibrium E^* (EE)

We consider the case where there is infection. This true when equation (19) is non zero that is where $\Psi^* = b - \frac{\mu}{R_0}$, which is a unique $(I^* > 1)$, then equation (20.2) shows the endemic equilibrium point of equation (9) [2, 29, 32].

$$E^* = (S^*, E^*, I^*, N^*)$$

where

$$\begin{cases} S^* = \frac{b}{\mu R_0}, \quad E^* = \frac{\mu}{R_0}\left(\frac{(R_0 - 1)}{(\varepsilon + \mu)}\right), \\ I^* = \frac{\mu}{\beta}(R_0 - 1), \quad N^* = \frac{b}{\mu} - \frac{\delta}{\beta}(R_0 - 1) \end{cases} \qquad (21b)$$

Jacobian Matrix:

Given n function $f_1(x_1, x_2, ..., x_n), f_2(x_1, x_2, ..., x_n), ..., f_n(x_1, x_2, ..., x_n)$ describing the n dynamics variables $x_1, x_2, ..., x_n$, the Jacobian matrix J is defined as:

$$J = \begin{pmatrix} \frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} & \cdots & \frac{\partial f_1}{\partial x_n} \\ \frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x_2} & \cdots & \frac{\partial f_2}{\partial x_n} \\ \vdots & \vdots & \ddots & \\ \frac{\partial f_n}{\partial x_1} & \frac{\partial f_n}{\partial x_2} & \cdots & \frac{\partial f_n}{\partial x_n} \end{pmatrix} \qquad (22)$$

3.6.3. Stability of the Equilibria

In this section we define type of stability, linearized system of equation (5) and by analyzing the eigenvalues of the Jacobian matrices of system (5), we get results about the local stability of these equilibria. We discuss type of stability on each equilibria. When we have multiple equilibria for a system, the stability of each must be evaluated separately [45].

Stability:

Equilibrium is *locally stable* if a system near the equilibrium approaches it (locally attracting).

Equilibrium is *globally stable* if a system approaches the equilibrium regardless of its initial position.

Equilibrium is *unstable* if a system near the equilibrium moves away from it (repelling).

Since the variable *R* does not appear in the first three equations of (9), so it is enough to analyze the following reduced system (or we are only interested in the spread of the disease, we only investigate the system consisting of the first three equations)

$$\begin{cases} \dfrac{dS}{dt} = b - \beta SI - \mu S \\ \dfrac{dE}{dt} = \beta SI - (\varepsilon + \mu)E \\ \dfrac{dI}{dt} = \varepsilon E - (\gamma + \delta + \mu)I \end{cases} \qquad (22.1a)$$

The stability is studied by *linearization* of the non-linear system (22.1a) to the Jacobian matrix J at the equilibrium points or steady states of the system and computing the characteristic equation (22.1a), which gives

$$J(S,E,I) = \begin{pmatrix} \dfrac{\partial f_1}{\partial S} & \dfrac{\partial f_1}{\partial E} & \dfrac{\partial f_1}{\partial I} \\ \dfrac{\partial f_2}{\partial S} & \dfrac{\partial f_2}{\partial E} & \dfrac{\partial f_2}{\partial I} \\ \dfrac{\partial f_3}{\partial S} & \dfrac{\partial f_3}{\partial E} & \dfrac{\partial f_3}{\partial I} \end{pmatrix}$$

$$J(S,E,I)=\begin{pmatrix} \frac{\partial(b-\beta SI-\mu S)}{\partial S} & \frac{\partial(b-\beta SI-\mu S)}{\partial E} & \frac{\partial(b-\beta SI-\mu S)}{\partial I} \\ \frac{\partial(\beta SI-(\varepsilon+\mu)E)}{\partial S} & \frac{\partial(\beta SI-(\varepsilon+\mu)E)}{\partial E} & \frac{\partial(\beta SI-(\varepsilon+\mu)E)}{\partial I} \\ \frac{\partial(\varepsilon E-(\gamma+\delta+\mu)I)}{\partial S} & \frac{\partial(\varepsilon E-(\gamma+\delta+\mu)I)}{\partial E} & \frac{\partial(\varepsilon E-(\gamma+\delta+\mu)I)}{\partial I} \end{pmatrix} \qquad (22.1b)$$

Evaluation of equation (22.1b) yields:

$$J(S,E,I)=\begin{pmatrix} -\beta I-\mu & 0 & -\beta S \\ \beta I & -(\varepsilon+\mu) & \beta S \\ 0 & \varepsilon & -(\gamma+\delta+\mu) \end{pmatrix} \qquad (23)$$

3.6.3.1. Stability at disease-free equilibria

In the following section we show that the disease-free equilibrium of the model (9) is globally asymptotically stable if $R_0<1$ and locally asymptotically stable if $R_0>1.$

Evaluating the above Jacobian matrix (23) at the disease-free equilibrium, $E^0=(S_0,E_0,I_0,N_0)=(b/\mu,0,0,b/\mu,)$ gives

$$J_0=J(E^0)=\begin{pmatrix} -\mu & 0 & -\beta \\ 0 & -(\varepsilon+\mu) & \beta \\ 0 & \varepsilon & -(\gamma+\delta+\mu) \end{pmatrix} \qquad (24)$$

where the characteristic polynomial equation is given by

$$P(\lambda)=\det(J_0-\lambda I)=0,\ \textit{where } I \textit{ identity matrix of } 3\times 3 \qquad (24.1)$$

by substituting equation(24) to (24.1), the characteristic polynomial of the Jacobian matrix is

$$(-\lambda-\mu)(-\lambda-(\varepsilon+\mu))(-\lambda-(\gamma+\delta+\mu))=0 \qquad (24.2)$$

Solving the characteristic polynomial (24.2) gives the following three roots

$$\lambda_1 = -\mu < 0, \lambda_2 = -(\varepsilon + \mu) < 0, \lambda_3 = -(\gamma + \delta + \mu) < 0 \qquad (24.3)$$

Since all the eigenvalues are all negative. So we have the following result

Theorem 1: *The disease-free equilibrium* E^0 *is locally asymptotically stable.*

To investigate the global stability of E^0, consider the Lyapunov candidate function $V(S,E,I): R^3 \to R^+$ defined as

$V(S,E,I) = \varepsilon E + (\mu + \delta + \gamma) I, \quad \varepsilon \geq 0$, V be a positive definite function

Differentiating $V(S,E,I)$ with respect to time yields

$$V'(S,E,I) = \varepsilon E' + (\mu + \gamma) I' \qquad (24.4)$$
$$where \quad V' = \frac{dV}{dt}, \; E' = \frac{dE}{dt}, \; I' = \frac{dI}{dt}$$

Simply we want to show that $V'(S,E,I) \leq 0$, if Ω contains no trajectories of the system except the trivial trajectories $S_0 = 0, E_0 = 0, I_0 = 0$ for $t \geq 0$

From equation (24.4) we have

$$\begin{aligned}
\frac{dV}{dt} &= \varepsilon \frac{dE}{dt} + (\mu + \varepsilon) \frac{dI}{dt} = \varepsilon (\beta SI - (\varepsilon + \mu) E) + (\mu + \varepsilon)(\varepsilon E - (\gamma + \delta + \mu) I) \\
&= \varepsilon \beta SI - \varepsilon(\varepsilon + \mu) E + (\varepsilon + \mu) \varepsilon E - (\varepsilon + \mu)(\gamma + \delta + \mu) I \\
&= \varepsilon \beta SI - (\varepsilon + \mu)(\gamma + \delta + \mu) I \\
&= (\varepsilon \beta S^* - (\varepsilon + \mu)(\gamma + \delta + \mu)) I^*, \; in \; DFE \quad S^* = b / \mu, \; I^* = (R_0 - 1)\mu / \beta \\
&\leq \left(\varepsilon \beta \frac{b}{\mu} - (\varepsilon + \mu)(\gamma + \delta + \mu) \right) I^* = (\varepsilon + \mu)(\gamma + \delta + \mu)(R_0 - 1) I \leq 0 \; if \; R_0 < 1.
\end{aligned}$$

$$(\mu + \varepsilon)(\gamma + \mu)(R_0 - 1) I \leq 0 \; if \; R_0 < 1. \qquad (24.5)$$

The maximal compact invariant set in $\left\{ (S,E,I) \in \Omega : \frac{dV}{dt} = 0 \right\}$ is the singleton $\{E^0\}$.

Using Lasalle's invariance principle (Edelstein-Kesher, 2005)[57], we have the following theorem

Theorem 2: *If $R_0 < 1$, the disease-free equilibrium E^0 is globally asymptotically stable and the disease dies out. But if $R_0 > 1$, then E^0 is unstable.*

From theorem 1 since all the eigenvalues are negative, it confirms that the disease-free equilibrium is locally asymptotically stable and from the theorem 2 for $R_0 > 1$ unstable.

3.6.3.2. Stability at endemic equilibria

For global stability of the endemic equilibrium, we used Lyapunov function as discussed in [59].

Evaluating the above Jacobian matrix (23) at the endemic eqiulibrium $E^* = (S^*, E^*, I^*)$.

By susbstituting equation (22) to (23) yields:

$$J^* = J(S^*, E^*, I^*) = \begin{pmatrix} -\beta\left(\frac{\mu}{\beta}(R_0 - 1)\right) - \mu & 0 & -\beta\left(\frac{b}{\mu R_0}\right) \\ \beta\left(\frac{\mu}{\beta}(R_0 - 1)\right) & -(\varepsilon + \mu) & \beta\left(\frac{b}{\mu R_0}\right) \\ 0 & \varepsilon & -(\gamma + \mu) \end{pmatrix} \qquad (25.6)$$

The above system reduced to

$$J^* = \begin{pmatrix} -\mu R_0 & 0 & -\beta\left(\frac{b}{\mu R_0}\right) \\ \mu(R_0 - 1) & -(\varepsilon + \mu) & \beta\left(\frac{b}{\mu R_0}\right) \\ 0 & \varepsilon & -(\gamma + \mu) \end{pmatrix} \qquad (25.7)$$

The characteristic polynomial of Jacobian matrix (23), $J(E^*)$ is given by

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0 \qquad (25.8a)$$

where

$$
\begin{aligned}
a_1 &= 2\mu + \gamma + \varepsilon + \mu R_0 \\
a_2 &= (\mu + \varepsilon + \mu R_0)(\gamma + \delta + \mu)b + \mu R_0(\varepsilon + \mu) \\
a_3 &= \mu(\varepsilon + \mu)(\gamma + \delta + \mu)bR_0 + \varepsilon\beta\mu\frac{(R_0 - 1)}{R_0}
\end{aligned}
\qquad (25.8b)
$$

To determine the sign of the eigenvalues by using Routh−Hurwitz criteria [45], we need to check the condition $a_1 > 0,\ a_2 > 0,\ a_3 > 0$ *and* $a_1 a_2 - a_3 > 0.$

Clearly, $a_1 > 0,$ *and if* $R_0 > 1$ *then* $a_3 > 0.$

$$
\begin{aligned}
a_1 a_2 - a_3 = {} & (2\mu + \delta + \gamma + \varepsilon + \mu R_0)\left[(\mu + \delta + \gamma + \varepsilon + \mu R_0)(\mu + \delta + \gamma) + \mu R_0(\varepsilon + \mu)\right] \\
& + \mu(\varepsilon + \mu)(\mu + \delta + \gamma) - 2\mu(\varepsilon + \mu)(\mu + \delta + \gamma)R_0 > 0
\end{aligned}
$$

$$\therefore a_1 a_2 - a_3 > 0$$

Therefore, by Routh-Hurwitz criteria [45], we conclude that the eigenvalues of $J(E^*)$ are all positive when $R_0 > 1$. So, we have the following result

Theorem 3: *If* $R_0 > 1$*, then the endemic equilibrium* E^* *is unstable .*

Now, we will investigate the global stability of E^*. To do so, we consider the following Lyapunov function [59]

$$
V = \left(S - S^* - S^* \ln\frac{S}{S^*}\right) + \left(E - E^* - E^* \ln\frac{E}{E^*}\right) + \frac{\mu + \varepsilon}{\varepsilon}\left(I - I^* - I^* \ln\frac{I}{I^*}\right) \qquad (25.9)
$$

Differentiating $V(S, E, I)$ with respect to time yields:

$$
\frac{dV}{dt} = \left(1 - \frac{S^*}{S}\right)\frac{dS}{dt} + \left(1 - \frac{E^*}{E}\right)\frac{dE}{dt} + \frac{\mu + \varepsilon}{\varepsilon}\left(1 - \frac{I^*}{I}\right)\frac{dI}{dt} \qquad (25.10)
$$

Substituting the expressions of the derivatives $\frac{dS}{dt}, \frac{dE}{dt}$ and $\frac{dI}{dt}$ in equation (25.10) from equation (9) and using the relation of the endemic equilibrium, we have

$$\begin{cases} b = \beta S^* I^* + \mu S^* & (25.11) \\ \beta S^* I^* = (\varepsilon + \mu) E^* & (25.12) \\ \varepsilon E^* = (\gamma + \delta + \mu) I^* & (25.13) \end{cases}$$

Using the equilibrium condition of system (25.11-25.13) above, equation (25.10) becomes

$$\frac{dV}{dt} = \left(1 - \frac{S^*}{S}\right)\left[-\mu(S - S^*) + \beta S^* I^* - \beta SI\right] + \left(1 - \frac{E^*}{E}\right)\left[\beta SI - (\mu + \varepsilon)E\right] + \frac{\mu + \varepsilon}{\varepsilon}\left(1 - \frac{I^*}{I}\right)\left[\varepsilon E - (\gamma + \mu)I\right]$$

$$\frac{dV}{dt} = -\mu\frac{(S - S^*)^2}{S} + \beta S^* I^* - \beta S^* I^* \frac{S^*}{S} + \beta S^* I \frac{E^*}{E} + (\varepsilon + \mu)E^* - (\varepsilon + \mu)E\frac{I^*}{I} - \frac{\varepsilon + \mu}{\varepsilon}(\gamma + \delta + \mu)I + \frac{\varepsilon + \mu}{\varepsilon}(\gamma + \delta + \mu)I^* \quad (25.14)$$

Note that $\varepsilon E^* = -(\gamma + \mu)I^*$ from (25.13)

This implies that;

$$\beta S^* I - \frac{\varepsilon + \mu}{\varepsilon}(\gamma + \delta + \mu)I = \beta S^* I - (\varepsilon + \mu)E^*\frac{I}{I^*} = \left[\beta S^* I^* - (\varepsilon + \mu)E^*\right]\frac{I}{I^*} = 0$$

So $\frac{dV}{dt} = -\mu\frac{(S - S^*)^2}{S} + 3(\varepsilon + \mu)E^* - \beta S^* I^* \frac{S^*}{S} - \beta SI\frac{E^*}{E} - (\varepsilon + \mu)E\frac{I^*}{I}$

$$\frac{dV}{dt} = -\mu\frac{(S - S^*)^2}{S} + (\varepsilon + \mu)E^*\left(3 - \frac{S^*}{S} - \frac{SE^*I}{S^*EI^*} - \frac{EI^*}{E^*I}\right) \le 0 \quad (25.16)$$

Since the arithmetic mean is greater than or equal to the geometric mean of the quantities

$\frac{S^*}{S}, \frac{SE^*I}{S^*EI^*}, \frac{EI^*}{E^*I}$. *i.e.*, $\frac{S^*}{S} + \frac{SE^*I}{S^*EI^*} + \frac{EI^*}{E^*I} - 3 \ge 0$. Then $\frac{dV}{dt} = 0$ holds only when $S = S^*$ $E = E^*$, $I = I^*$. So the maximal compact invariant set in $\left\{(S, E, I) \in \Omega : \frac{dV}{dt} = 0\right\}$ is the singleton $\{E^*\}$. Using Lasalle's invariance principle [58], we have the following theorem

Theorem 4: *If* $R_0 < 1$*, the endemic equilibrium* E^* *is locally asymptotically stable*

When $R_0 > 1$, the system has two equilibrium points, the disease-free E^0 and endemic equilibrium E^*. Here the disease-free equilibrium is unstable from system equation (25.11-25.13). Then the solution converges to the endemic equilibrium. In other words, the endemic equilibrium point is unstable for $R_0 > 1$.

Table 1.3: Summary for stability of measles model equation (5) (stability depend on R_0)

Equilibrium point	Sign of R_0	Type of stability	Mode of Epidemic
DFE	$R_0 < 1$	globally *asymptotically* stable	No Epidemic
	$R_0 > 1$	*un*stable	Epidemic
EE	$R_0 < 1$	*locally asymptotically* stable	Epidemic
	$R_0 > 1$	*un*stable	Epidemic

3.6.4. Phase plane Diagram

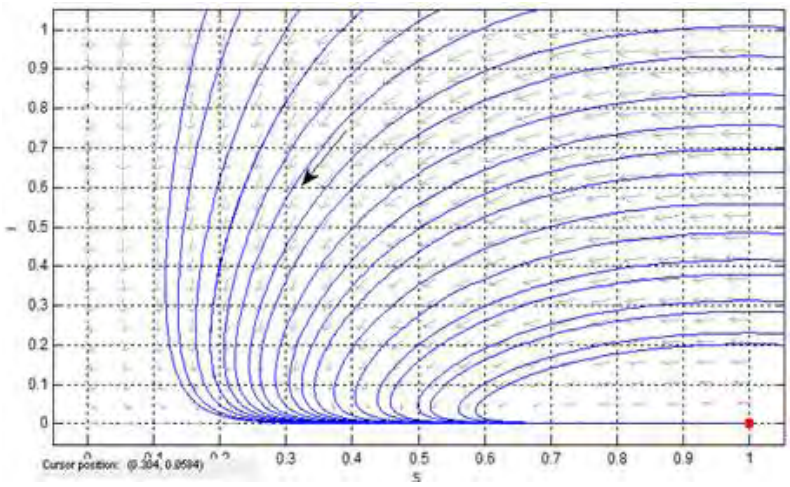


Figure 2.1: Phase plane portrait for the classic SIR endemic model with basic reproduction number $R_0 = 0.5 < 1$ by pplane8.

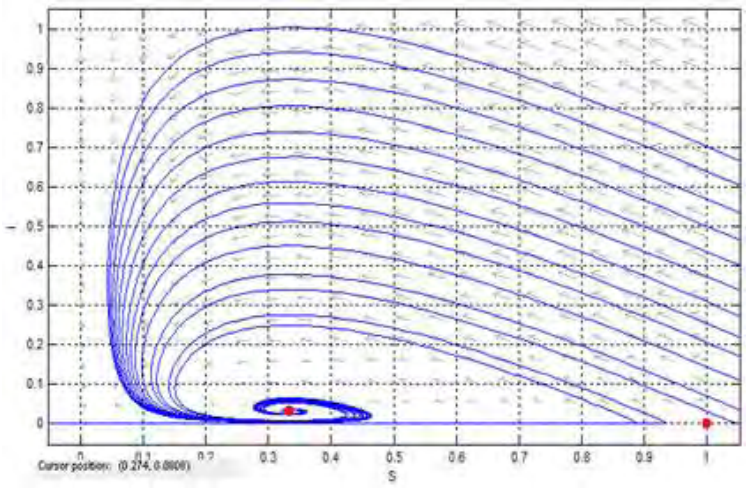


Figure 2.2: Phase plane portrait for the classic SIR epidemic model with basic reproduction number R_0=3, average infectious period $1/\varepsilon$ = 9 days, and average lifetime $1/\mu$ = 26 days. This unrealistically short average lifetime has been chosen so that the endemic equilibrium is clearly above the horizontal axis and the spiraling into the endemic equilibrium can be seen [16].

Figure 2.1 and 2.2 are phase plane portraits for the two possibilities described in the theorems. The theorems above described intuitively in terms of reproduction number R_0, which the threshold quantity. If the reproduction number is less than one $(R_0 < 1)$ then the disease-free equilibrium E^0 is locally asymptotically stable and so that an infective replace itself with less than one new infective , then the disease die out. Moreover, the susceptible eventually approaches one since everyone is susceptible when the disease are disappeared and all of the removed people who are immune have died.

If the reproduction number $(R_0 > 1)$, then the disease-free equilibrium $E*$ is unstable with a repulsive direction into the positive SI quadrant, so the disease can "invade" in the sense that any path starting with a small positive I_0, moves into the positive SI quadrant where the disease persists.

The initial infective I_0 is small, and the initial susceptible S_0 is larger, then S decreases and I first increase to a peak and then decreases just as it would for an epidemic. However, after the

infective has decreases to a low level, the susceptible slowly starts to increase due to the births of new suscpetibles. Thus for this classic SIR endemic model and for many other more complex models equation[16]; the behavior is almost completely dependent on the threshold quantity Ro, which determines not only when the local stability of the disease-free equilibrium switches, but also when the endemic equilibrium enters the feasible region with a positive infective.

3.6.5. Bifurcation point

Bifurcation is a change in the equilibrium points, or in their stability properties, as a parameter is varied. Loosely speaking, a bifurcation is a qualitative change in the dynamics of the system of ODEs as a parameter varies. The phenomenon of bifurcation, i.e., quantitaive change of parameters leading to qualitative change of system properties [16,45].

From the above theorems and tables 1.3, we see that the case $R_0 = 1$ is a critical threshold point where the disease free equilibrium E^0 loses its asymptotic stability and simply becomes (neutrally) stable. Moreover, it becomes unstable immediately $R_0 > 1$ and this will lead to the existence of unstable endemic equilibrium E^*. Then we say that $R_0 = 1$ can literarily be viewed as a transcritical bifurcation point where stability is exchanged between disease-free equilibrium and endemic equilibrium point (or E^0 and E^*) [16, 45].

For the system (9) of measles model the bifurcation of the system depend on reproduction number R_0. For different values R_0 the dynamics can change substantially (see table 1.3). By the data of measles, the reproduction number of measles is 14.6. R_0 is largely influenced by the contact rate of the infectiives, then the reproduction number is largely sensitive to the contact rate of infection and the R_0 also depend on the latent rate of the epidemic by [51, 53, 63, 64].

CHAPTER FOUR

4. Optimal Control Theory

4.1. Introduction

Optimal control theory is another area of mathematics that is used extensively in controlling the spread of infectious diseases. It is a powerful mathematical tool that can be used to make decisions involving complex biological situation. It is often used in the control of the spread of most diseases for which either vaccine or treatment is available. For example, question such as what percentage of the population should be vaccinated as time evolves in a given epidemic model to minimize the number of infected and the cost of implementing the vaccination strategy becomes relevant. The desire outcome will include tradeoffs between two competing factors [31, 50, 52].

The behavior of the underlying dynamical system is described by a *state variable(s).* We assume that there is a way to steer the state by acting upon it with a suitable *control function(s*). The control enters the system of ordinary differential equations and affects the dynamic of the state system. The goal is to adjust the control in order to maximize (or minimize) a give *objective functions,* representing both the goal and cost. The cost may not always represent money but may include side effect, damage caused by control. In this work the goal is the optimal control theory of ordinary differential equations with time fixed.

Optimal control theory is one of the thrusts of this thesis. Basically, given a dynamic system, one can apply a control function to alter the behavior of the system over time. This control function can be constant, or it can also vary with time. In adjusting the control function, the system can be manipulated until some goal for the state of the system is achieved.

In this paper, we will minimize the objective functional, which will result in a balanced minimization of the goal and cost. The control that achieves this balance is called the *optimal control,* and the corresponding state is the *optimal state* [16, 31, 46].

4.2. Optimal Control Problem (OC)

A typical optimal control problem requires *a performance index or cost functional* $\left(J\left[x(t),u(t)\right]\right)$, *a set of state variables* $\left(x(t)\in X\right)$ *and a set of control variables* $\left(u(t)\in U\right)$ in a time $t, t_0 \le t \le t_f$. The main goal consists in finding a piecewise continuous control $u(t)$ and the associated state variable $x(t)$ to minimize a given objective functional.

Basic optimal control Problem in Lagrange formulation**:** An optimal control problem is in the form

$$\max_u J(x(t),u(t)) = \int_{t_0}^{t_f} f\left(t,x(t),u(t)\right)dt$$
$$subject\ to \quad x' = g\left(t,x(t),u(t)\right) \qquad (27)$$
$$x(t_0) = x_0$$

$x(t_f)$ could be free, which means that the value of $x(t_f)$ is unrestricted, or could be fixed, i.e, $x(t_f) = t_f$.

For our purposes, f and g will always be continuously differentiable functions in all three arguments and have first-order partial derivatives with respect to x and t, but not necessarily with respect to u [15, 31, 46].

We assume that the control set U is a measurable function. Thus, as the control(s) will always be piecewise continuous, the associated states will always be piecewise differentiable [15, 31].

We can switch back and forth between maximization and minimization by simply negating the cost functional:

$$\min\left\{J\right\} = -\max\left\{-J\right\}$$

An optimal control problem can be presented in different ways, but equivalent, depending on the purpose or the software to be used.

4.3. Pontryagin's Maximum Principle

The necessary first order conditions to find the optimal control were developed by Pontryagin and his co-workers. This result is considered as one of the most important results of Mathematics in the 20th century. Pontryagin introduced the idea of adjoint functions *to append the differential equation to the objective functional.* Adjoint functions have a similar purpose as Lagrange multipliers in multivariate calculus, which append constraints to the function of several variables to be maximized or minimized.

Hamiltonian - H : For the optimal control problem considered in (27), the function

$$H\left(t,x(t),u(t),\lambda(t)\right) = f\left(t,x(t),u(t)\right) + \lambda(t)g\left(t,x(t),u(t)\right) \qquad (27.1)$$
$$= \text{int}\, grand + adjo\,\text{int}^{*}\, RHS\, of\ DE$$

is called Hamiltonian function and λ is the adjoint variable.

Pontryagin's Maximum Principle-PMP:- If $u^{*}(t)$ and $x^{*}(t)$ are optimal for problem (27), then there exists a piecewise differentiable adjoint variable $\lambda(t)$ such that

$$H\left(t,x^{*}(t),u(t),\lambda(t)\right) \le H\left(t,x^{*}(t),u^{*}(t),\lambda(t)\right) \qquad (27.2)$$

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

$$\lambda'(t) = -\frac{\partial H\left(t,x^{*}(t),u^{*}(t),\lambda(t)\right)}{\partial x} \qquad \left(adjo\,\text{int}\ condition\right) \qquad (27.3)$$

$$\lambda\left(t_f\right) = 0 \qquad \left(transversality\, condition\right) \qquad (27.4)$$

The last condition, $\lambda\left(t_f\right) = 0$, called transversality condition, is only used when the OC problem does not have terminal value in the state variable, i.e., $x\left(t_f\right)$ is free.

This principle convertes the problem of finding a control which maximizes the objective functional subject to the state ODE and initial condition into a problem of optimizing the Hamiltonian pointwise. As consequence, with this adjoint equation and Hamiltonian, we have

$$\frac{\partial H}{\partial u} = 0 \Rightarrow f_u\left(t, x^*, u^*\right) + \lambda g_u\left(t, x^*, u^*\right) = 0 \qquad (27.5)$$

at u^* for each t, namely, the Hamiltonian has a critical point; usually this condition is called *optimality condition.*

The dynamic of the state equation:

$$x' = g\left(t, x, u\right) = \frac{\partial H}{\partial \lambda}, \quad x\left(t_0\right) = x_0 \qquad (27.6)$$

4.4. Optimal control with bounded controls

Many problems require bounds on the control to achieve a realistic solution. Suppose, for instance, that our control is the amount of vaccination or chemicals used in a system. Then, clearly we require this amount to be nonnegative, i.e $u \geq 0$. Often; the control must be bounded above. Perhaps there are physical limitations on the amount of chemicals or environmental regulations which prohibit a certain level of use. We could also have a problem where the control is the percentage of some strength or use. Then $0 \leq u \leq 1$ would be our bounds [15, 31].

Optimal control with bounded control: An optimal control with bounded control can be written in the form

$$\begin{aligned} &\max_u J(x(t), u(t)) = \int_{t_0}^{t_f} f\left(t, x(t), u(t)\right) dt \\ &\quad subject\ to \quad x' = g\left(t, x(t), u(t)\right) \\ &\qquad\qquad\quad x(t_0) = x_0 \\ &\qquad\qquad\quad a \leq u(t) \leq b \end{aligned} \qquad (27.7)$$

where a, b are fixed real constants and a < b.

To solve problems with bounds on the control, it is necessary to develop alternative necessary conditions.

Proposition (Necessary conditions): If $u^*(t)$ and x*(t) are optimal for problem (27.7), then there exists a piecewise differentiable adjoint variable $\lambda(t)$ such that

$$H\left(t, x^*(t), u(t), \lambda(t)\right) \leq H\left(t, x^*(t), u^*(t), \lambda(t)\right) \qquad (27.8)$$

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

$$\lambda'(t) = -\frac{\partial H\left(t, x^*(t), u(*t), \lambda(t)\right)}{\partial x} \quad (adjo\,\text{int}\ condition) \qquad (27.9)$$

$$\lambda\left(t_f\right) = 0 \quad (transversality\ condition) \qquad (27.10)$$

By an adaptation of the PMP, the OC must satisfy *(optimality condition):*

$$u^* = \begin{cases} a & if \ \frac{\partial H}{\partial u} < 0 \\ a < \frac{\partial H}{\partial u} < b & if \ \frac{\partial H}{\partial u} = 0 \\ b & if \ \frac{\partial H}{\partial u} > 0 \end{cases} \quad (Optimality\ Condition) \qquad (27.11)$$

If we have a minimization problem, then u^* is chosen to minimize *H* pointwise. This has the effect of reversing < and > in the first and third lines of optimality condition.

We can also check *concavity conditions* to distinguish between controls that maximize and those minimize the objective functional.

If $\frac{\partial^2 H}{\partial u^2} < 0 \ at \ u^*$ then u^* is the maximization of the problem, while $\frac{\partial^2 H}{\partial u^2} > 0 \ at \ u^*$ goes with minimization [18].

Remark: In some software packages there are no specific characterization for the bounds of the control. In those cases, and when the implementation allows, we can write in a compact way the optimal $\frac{\partial H}{\partial u} = 0$ control obtained without truncation, bounded by a and b

$$u^*(t) = \min\left\{a, \max\left\{b, \frac{\partial H}{\partial u}\right\}\right\} \qquad (27.12)$$

4.5. Steps in formulating optimal system of an optimal control problem

We can view our optimal control problem as having two unknowns, $u*$ and $x*$, at the start. We have introduced an adjoint variable λ, which is similar to a lagrangian multiplier. It attaches the differential equation information onto the maximization of the objective functional. The following is an outline of how this theory can be applied to the simplest problems.

1. Formulate the Hamiltonian for the problem

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

2. Write the adjoint differential equation, transversality boundary condition and optimality condition. Now there are three unknowns, $u*, x*$ and λ.

$$\lambda'=-\frac{\partial H}{\partial x}\Rightarrow\lambda'=-\left(f_x+\lambda g_x\right) \qquad \left(adjo\,\text{int}\ condition\right)$$

$$\lambda\left(t_f\right)=0 \qquad \left(transversality\ condition\right)$$

$$\frac{\partial H}{\partial u}=0\ \ at\,u=u*\Rightarrow f_u\left(t,x,u\right)+\lambda g_u\left(t,x,u\right)=0\ \ \left(optimality\ condition\right)$$

3. Solve for $u*$ in terms of $x*$ and λ.

4. After finding the optimal states and adjoint, solve for the optimal control.

4.6. Relation of maximization principle terms to a classical economics terms

Lastly, the following chart will provide a mapping of the concepts of the maximum principle into a classical economic example from capital theory. The chart is based on the discussion of Robert Dorfman [60] in his-well known article “An Economic Interpretation of Optimal Control Theory’’. In Dorf-man’s discussion, the basic problem is the decision problem of a firm that aims to maximize profits over a time horizon under the capital constraints it faces. In every moment, the firm has a capital stock that needs to be managed. The decisions of the firm (that can vary greatly, from decisions concerning the rate and price of the output to decisions concerning the design of the product) affect the rate at which the size of this capital stock is changing.

Table 1.4: Relation of maximization principle terms to a classical economics terms

Concept in Maximum Principle	Economic Significance
state variable x	amount of capital
control variable u	rate of change of capital
adjoint variable λ	shadow price of capital
$\lambda(t_0), t_0 = 0$	shadow price of a unit of initial capital
$\lambda(t_f)$	shadow price of a unit of terminal capital
function f	current profit
$\lambda(t)g(t,x,u)$	future profit effect of policy u
$g(t,x,u) = x'$	rate of change of capital per unit of time due to the present amount of capital, policy u, and moment
Hamiltonian function H	overall profit prospect: (current profit) +(shadow price) * (change in capital corresponding to policy u)
$x' = \frac{\partial H}{\partial \lambda}$	the way the policy decision affects the rate of change of capital: the change in capital is equal to the contribution of the shadow price to overall profits
$\lambda' = -\frac{\partial H}{\partial x}$	Shadow price depreciates at the rate at which capital contributes to overall profits (*or marginal cost*)
$\lambda(t_f) = 0$	shadow price is driven down to zero at the end of the time interval, i.e. the left-over capital has no economic value to the firm

The marginal cost is an increase in the total of a production run for making one additional unit of an item. The Shadow price associated with a resource tells you how much more profit you would get by increasing the amount of that resource by one unit.

4.7. Our Optimal Control Applied to Measles Model

Generally, the eradication of the disease may be too costly when constant controls are considered as it requires vaccination at higher levels all the time. For eradication to be achievable in a finite time, we need to consider time-dependent controls. We use the optimal control strategies in the form of vaccination to decrease infectious individuals and increase the total number of recovered individuals with minimum investment in disease control.

4.7.1. Formulation-Extended Model with Controls

In this section, an optimal control problem is formulated by incorporating one intervention strategies into our basic model equation (5). The following intervention is incorporated into the basic model;

- $u(t)$ is the control which represents the vaccination ratio of susceptible individuals being vaccinated per unit of time which bounds between 0 and 1.

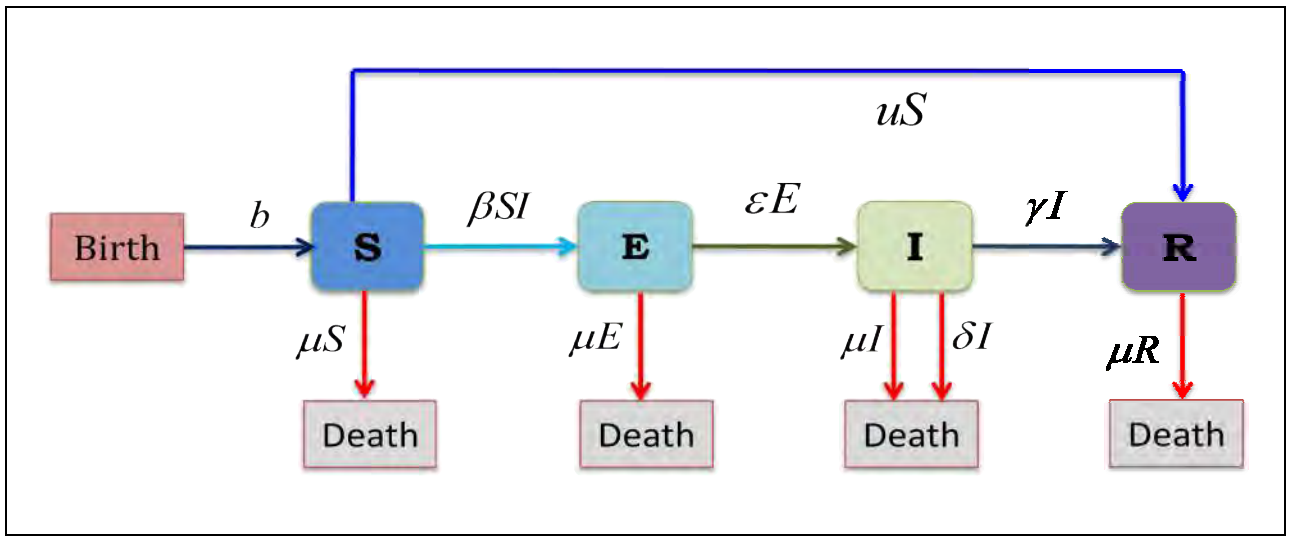


Figure 3: The SEIR schematic model with control u

Here we consider a vaccination campaign over a fixed time period $[0,T]$. The vaccine drives the infected individuals to the recovered class. So, we introduce the control function u and our aim is to set up an optimal control problem related to the SEIR epidemic model (5) which extended as figure 3 above.

The dynamics measles transmission model is governed by the following modified system (state equations):

$$\begin{cases} \dfrac{dS}{dt} = b - \beta SI - \mu S - uS \\ \dfrac{dE}{dt} = \beta SI - (\varepsilon + \mu)E \\ \dfrac{dI}{dt} = \varepsilon E - (\gamma + \delta + \mu)I \\ \dfrac{dR}{dt} = \gamma I - \mu R + uS \end{cases} \qquad (28)$$

$$with\ \ initial\ conditions,$$

$$\begin{cases} S(0) = S_0 \geq 0, \quad E(0) = E_0 \geq 0, \\ I(0) = I_0 \geq 0, \quad R(0) = R_0 \geq 0 \end{cases}$$

Recall equation (9), as R does not appear in the other 3 equations of equation (28). Therefore the state system of differential equations becomes

$$\begin{cases} \dfrac{dS}{dt} = b - \beta SI - \mu S - uS \\ \dfrac{dE}{dt} = \beta SI - (\varepsilon + \mu)E \\ \dfrac{dI}{dt} = \varepsilon E - (\gamma + \delta + \mu)I \\ \dfrac{dN}{dt} = b - \delta I - \mu N \end{cases} \qquad (28.1)$$

$$with\ \ initial\ conditions,$$

$$\begin{cases} S(0) = S_0 \geq 0, \quad E(0) = E_0 \geq 0, \\ I(0) = I_0 \geq 0, \quad N(0) = N_0 \geq 0 \end{cases}$$

The optimal control problem is to minimize the objective (cost) functional J considering the costs of vaccination of susceptible human given by:

$$J(u) = \int_0^T \left(AI + \frac{1}{2} Bu^2 \right) dt \qquad (29a)$$

subject to the differential equations (28.1)

where:

- The control set U is measurable functions and it is defined as:

$$U = \left\{ u(t) \,|\, 0 \le u \le u_{\max} < 1,\ t \in [0, T] \right\} \qquad (29b)$$

- $u_{\max}$ is maximum attainable value for u
- T represents the vaccination period (measles has 2–3-year epidemic cycles)
- The parameter A are balancing cost factors due to the size of infectives and
- B represents the "weight" attached on the cost of vaccination or A and B are weight parameter describing the comparative importance of the two terms (disease burden and cost) in the functional respectively.

For example, a high value of A means that it is more important to reduce the disease burden than to reduce the vaccination costs or a less value of B means that it is more important to reduce the vaccination costs than to reduce the disease burden.

It assumed that the cost of the vaccination is nonlinear and take a quadratic form. The control u is the percentage of the susceptible that is vaccinated per unit time. Thus, u lies between 0 and 1 while $u_{\max}$ will depend on the amount of resources available to implement each of the control measures. If $u = 0$, then no vaccination is done which the model (28.1) is uncontrolled which is equivalent to model equation (9) and $u = 1$ indicates that all susceptible population is vaccinated. The rate of vaccination is assumed to take values in [0, 0.9] instead of [0, 1] to eliminate the case where the entire susceptible population is vaccinated [50, 51, 52].

The vaccination cost could include *the cost of the vaccine, cost of syringes, cost of safety boxes, the vaccine storage cost, other related overheads, etc[47].*

Our target is to minimize the objective functional defined above by decreasing the number of infected individuals and increasing the number of recovered individuals. This is achieved using possible minimal control variables, u or minimizing the cost of the vaccination at each time unit within the implementation period.

The Optimal Control Problem of nonlinear dynamics of SEIN measles epidemic model given by;

$$\begin{aligned}
&\min_u J(u) = \min \int_0^T \left(AI + \frac{1}{2} Bu^2 \right) dt \\
&Subject \quad to: \\
&\begin{cases} \frac{dS}{dt} = b - \beta SI - \mu S - uS \\ \frac{dE}{dt} = \beta SI - (\varepsilon + \mu)E \\ \frac{dI}{dt} = \varepsilon E - (\gamma + \delta + \mu)I \\ \frac{dN}{dt} = b - \delta I - \mu N \end{cases} \qquad (30) \\
&with\ initial\ conditions; \\
&\quad S(0) = S_0 \geq 0,\ E_0 \geq 0,\ I_0 \geq 0,\ N_0 \geq 0 \\
&control\ set\ defined\ as; \\
&\quad U = \left\{ u(t) \,|\, 0 \leq u \leq u_{\max} < 1,\ t \in [0, T] \right\}
\end{aligned}$$

4.7.2. Pontryagin's Maximum Principle (PMP)

From the definition of Hamiltonian which stated in equation (27.1), for the optimal control problem considered in (30), the control u , state variables $S, E, I, and\ N$ with corresponding adjoint functions to be determined suitably $\lambda_1, \lambda_2, \lambda_3\ and\ \lambda_4$. We have the Hamiltonian function:

$$\begin{cases} H(t, S, E, I, N, u, v, \lambda_1, \lambda_2, \lambda_3, \lambda_4) = f(t, S, E, I, N, u, v) + \sum_{i=1}^{4} \lambda_i g_i(t, S, E, I, N, u, v) \\ \qquad \Rightarrow f(t, S, E, I, N, u, v) + \lambda_1 \frac{dS}{dt} + \lambda_2 \frac{dE}{dt} + \lambda_3 \frac{dI}{dt} + \lambda_4 \frac{dN}{dt} \end{cases} \qquad (31)$$

Substituting each of the derivatives in equation (28.1) or (i.e., RHS of equation 28.1) into equation (31) yield:

$$H=\left(AI+\frac{1}{2}Bu^2\right)+\begin{bmatrix}\lambda_1\left(\mu-\beta SI-\mu S-uS\right)+\lambda_2\left(\beta SI-(\varepsilon+\mu)E\right)+\\ \lambda_3\left(\varepsilon E-(\gamma+\delta+\mu)I\right)+\lambda_4\left(b-\delta I-\mu N\right)\end{bmatrix} \qquad (31.1)$$

Next, by applying Pontryagin's maximum principle to the Hamiltonian, we obtain the following results.

Given optimal control u^* and the corresponding solution S^*, E^*, I^* and N^* of equation (30) , there exist adjoint variables $\lambda_1, \lambda_2, \lambda_3$,and λ_4 that satisfy *(adjoint condition)* which is discussed in equation (27.3)[15, 31];

$$\lambda_i^{'}(t)=-\frac{\partial H}{\partial x_i} \qquad (32)$$

Here x_i , *i* = 1, 2, 3, 4 are the state variables *S*, *E*, I and *N*, and g_i are the right hand sides of equation (28.1). We find the adjoint function for each state variable S, E, I and N by differentiating the Hamiltonian in equation (30) with each state variable S, E, I and N.

(i) Adjoint function with respect to S

$$\lambda_1^{'}=-\frac{\partial H}{\partial S}\Rightarrow\lambda_1^{'}=-\left(f_S+\lambda_1 S'\right)$$
$$\lambda_1^{'}=-\left[\left(\lambda_1\left(-\beta I-\mu-u\right)+\lambda_2\left(\beta I\right)\right)\right]$$

$$\lambda_1^{'}=\lambda_1\left(\beta I+\mu+u\right)-\lambda_2\left(\beta I\right) \qquad (32.1)$$

(ii) Adjoint function with respect to E

$$\lambda_2^{'}=-\frac{\partial H}{\partial E}\Rightarrow\lambda_2^{'}=-\left(f_E+\lambda_2 E'\right)$$
$$\lambda_2^{'}=-\left[\lambda_2\left(-(\varepsilon+\mu)\right)+\lambda_3\left(\varepsilon\right)\right]$$

$$\lambda_2^{'}=\lambda_2\left(\varepsilon+\mu\right)-\lambda_3\left(\varepsilon\right) \qquad (32.2)$$

(iii) Adjoint function with respect to I

$$\lambda_3^{'}=-\frac{\partial H}{\partial I}\Rightarrow\lambda_3^{'}=-\left(f_I+\lambda_3 I'\right)$$
$$\lambda_3^{'}=-\left[A+\lambda_1\left(-\beta S\right)+\lambda_2\left(\beta S\right)+\lambda_3\left(-(\gamma+\delta+\mu)\right)+\lambda_4\left(-\delta\right)\right]$$

$$\lambda_3^{'} = -A + \lambda_1(\beta S) - \lambda_2(\beta S) + \lambda_3\left((\gamma + \delta + \mu)\right) + \lambda_4(\delta) \qquad (32.3)$$

(iv) Adjoint function with respect to R

$$\lambda_4^{'} = -\frac{\partial H}{\partial N} \Rightarrow \lambda_4^{'} = -\left(f_N + \lambda_4 N'\right)$$
$$\lambda_4^{'} = -\left[\lambda_4(-\mu)\right]$$

$$\lambda_4^{'} = \lambda_4 \mu \qquad (32.4)$$

From (i)-(iv) the adjoint functions are

$$\begin{cases} \lambda_1^{'} = \lambda_1(\beta I + \mu + u) - \lambda_2(\beta I) \\ \lambda_2^{'} = \lambda_2(\varepsilon + \mu) - \lambda_3(\varepsilon) \\ \lambda_3^{'} = -A + \lambda_1(\beta S) - \lambda_2(\beta S) + \lambda_3(\gamma + \delta + \mu) + \lambda_4(\delta) \\ \lambda_4^{'} = \lambda_4 \mu \end{cases} \qquad (33)$$

with transversality conditions stated in (27.4)

The state variables are not assigned at the final time T so that we have the transversality equations:

$$\lambda_i(T) = 0, \ i = 1,2,3,4 \qquad (34)$$

In order to illustrate the characterization of the optimal control u^*, we consider first the optimality condition.

The optimality condition (differentiating the Hamiltonian H in equation (31.1) with respect to u based on equation (27.5) for each control u^*. We have the following optimality system:

$\frac{\partial H}{\partial u} = 0 \ at \ u = u^* \Rightarrow Bu + \lambda_1(-S), \ at \ u = u^*$ then we get:

$$u^*(t) = (\lambda_1)\frac{S}{B} \qquad (35)$$

taking into account the bounds on u^* and its characterization we obtain;

$$u^*(t) = \begin{cases} 0 & if \ \ \dfrac{\partial H}{\partial u} > 0 \\ (\lambda_1)\dfrac{S}{B} & if \ \ \dfrac{\partial H}{\partial u} = 0 \\ 0.9 & if \ \ \dfrac{\partial H}{\partial u} < 0 \end{cases} \tag{36}$$

so the optimal control u^* can be put as in a compact form:

$$\left| u^* = \max\left(\min\left((\lambda_1)\frac{S}{B}, 0.9 \right), 0 \right) \right. \tag{37}$$

The optimal control and the state are found by solving the following optimality system, which consists of;

i) The state system (28.1),

ii) The adjoint system (33),

iii) Tranversality conditions (34) and

iv) The characterization of the optimal control *u** (37).

Therefore, using the characterization of the optimal control, we have the following optimality system:

$$\begin{cases} S' = b - \beta SI - \mu S - u^* S \\ E' = \beta SI - (\varepsilon + \mu)E \\ I' = \varepsilon E - (\gamma + \delta + \mu)I \\ N' = b - \delta I - \mu N \\ S(0) = S_0 \geq 0,\ E(0) = E_0 \geq 0,\ I(0) = I_0 \geq 0, N(0) = N_0 \geq 0 \\ \lambda_1' = \lambda_1(\beta I + \mu + u^*) - \lambda_2(\beta I) \\ \lambda_2' = \lambda_2(\varepsilon + \mu) - \lambda_3 \varepsilon \\ \lambda_3' = -A + \lambda_1(\beta S) - \lambda_2(\beta S) + \lambda_3(\gamma + \delta + \mu) + \lambda_4 \delta \\ \lambda_4' = \lambda_4 \mu \\ \lambda_i(t_f) = 0,\ i = 1,2,3,4 \end{cases} \tag{38}$$

4.8. Numerical Implementation

There are two major classes of numerical methods for solving OC problems: indirect methods and direct methods. The first ones indirectly solve the problem by converting the optimal control problem to a boundary-value problem, using the Pontryagin's maximum principle-PMP. On the other hand, in a direct method, the optimal solution is found by transcribing an infinite-dimensional optimization problem to a finite-dimensional optimization problem [15, 41, 54, 55].

4.8.1. Indirect methods

In an indirect method, the Pontryagin's maximum principle -PMP is used to determine the first-order optimality conditions of the original optimal control problem. For an indirect method it is necessary to explicitly get the adjoint equations, the control equations and all the transversality conditions, if they exist [15].

4.8.1.1. Backward-forward Sweep Method

This method is described in a recent book by Suzanne Lenhart and Workman [31] and it is known as forward-backward sweep method. The process begins with an initial guess on the control variable. Then, the state equations are simultaneously solved forward in time and the adjoint equations are solved backward in time. The control is updated by inserting the new values of states and adjoints into its characterization, and the process is repeated until convergence occurs [15, 31]. It can be implemented, using the following algorithm:

Considering $\vec{x} = (x_1, ..., x_{N+1})$ and $\vec{\lambda} = (\lambda_1, ..., \lambda_{N+1})$ the vector approximations for the state and the adjoint. The main idea of the algorithm is described as follows:

Step 1. Make an initial guess for $\vec{u}$ over the interval ($\vec{u} \equiv 0$ is almost always sufficient).

Step 2. Using the initial condition $x_1 = x(t_0) = a$ and the values for $\vec{u}$, solve $\vec{x}$ forward in time according to its differential equation in the optimality system;

Step 3. Using the transversality condition $\lambda_{N+1} = \lambda(t_f)$ and the values for $\vec{u}$ and $\vec{x}$, solve $\vec{\lambda}$ backward in time according to its differential equation in the optimality system;

Step 4. Update $\vec{u}$ by entering the new $\vec{x}$ and $\vec{\lambda}$ values into the characterization of the optimal control.

Step 5. Verify convergence: if the variables are sufficiently close to the corresponding in the previous iteration, then output the current values as solutions, else return to Step 2.

We make a few notes about the algorithm. When making the initial guess, $\vec{u} \equiv 0$ is almost always sufficient. For certain problems, where division by u occurs, an alternative initial guess must be used. Occasionally, your initial guess may require adjusting if the algorithm has problems converting. For step 2 and 3, any standard ODE solver can be used. For the purpose of this thesis, a Runge-Kutta 4 routine is used [31].

4.8.1.2. Classical fourth-order Runge-Kutta method (RK)

The most popular Runge-Kutta methods are fourth order. A Runge-Kutta method is a multiple-step method, where the solution at time t_{k+1} is obtained from a defined set of previous values t_{j-k}, . . . , t_k and j is the number of steps.

Given a step size h and an ordinary differential equation $x'(t) = f\left(t, x(t)\right)$, it is possible to make a convenient approximation of $x(t+h)$ given $x(t)$ is

$$x(t+h) = x(t) + \frac{h}{6}\left(k_1 + 2k_2 + 2k_3 + k_4\right) \qquad (39.1)$$

where

$$\begin{aligned} k_1 &= f\left(t, x(t)\right) \\ k_2 &= f\left(t + \frac{1}{2}h, x(t) + \frac{h}{2}k_1\right) \\ k_3 &= f\left(t + \frac{h}{2}, x(t) + \frac{h}{2}k_2\right) \\ k_4 &= f\left(t + h, x(t) + hk_3\right) \end{aligned} \qquad (39.2)$$

CHAPTER FIVE

5. Simulation Results and Discussion

5.1. Introduction

In this section, we solve numerically the optimality system (38) using the forward-backward sweep method developed by Suzanne lenhart and J.T.Workman [31]. In this formulation, there exist initial conditions for the state variables and terminal conditions for the adjoint variables. That is, the optimality system is a two-point boundary value problem, with separated boundary conditions at times t_0 and t_f [51, 52].

The eight ordinary differential equations in (38) comprising the optimality system are numerically solved together with the control characterization which is used to simulate the measles vaccination strategies.

The processes begin with an initial guess on the control variable. Then, the state equations are solved simultaneously forward in time, and next the adjoint equations are simultaneously solved backward in time. The control is updated by inserting the new values of states and adjoints into its characterization, and the process is repeated until convergence occurs. The ODE solver used for the state and adjoint systems is a Runge-Kutta fourth order procedure implemented with MATLAB [15, 31].

The estimation of epidemiological parameters is based on data from Ethiopia Demographic and Health Survey 2015, Central Statistical Agency (CSA), Ethiopian health and nutrition research institute federal democratic republic of Ethiopia - Guideline on Measles Surveillance and Outbreak Management and from other related countries which have related characteristics [22, 48, 49, 61].

Table 1.5: Epidemiological parameters used for the numerical simulations

Parameters	Description	Value	Reference
S_0	Initial Susceptible population	0.5	[22, 50,51]
E_0	Initial Exposed population	0.2	[22, 50,51]
I_0	Initial Infected population	0.2	[22, 50,51]
R_0	Initial Recovered population	0.1	[22, 50,51]
b	Natural birth rate	0.00314 per month	Estimated [22, 48]
μ	Natural death rate	0.00071 per month	Estimated [22, 48]
δ	Disease related death rate	0.01190 per month	Estimated [61]
ε	Latent Rate from E to I	3.0417 per month	Estimated [22, 61]
γ	Recovery Rate from I to R	2.5347 per month	Estimated [22, 41]
β	Contact rate	2.7652 per month	Estimated [61]
B	Weight parameter	0.04-40	[50,51, 52]
A	Weight parameter	1-100	[50,51, 52]
$[0,T]$	Vaccination period	[0,48 month (4 years)]	[2,3,22]
$[0, u]$	Vaccination ratio	$[0, 0.9]$	[22, 50,51, 52]

It is important note that the parameters values above were chosen such that the total population never goes into extinction in the absence of vaccination (i.e. when $u = 0$).

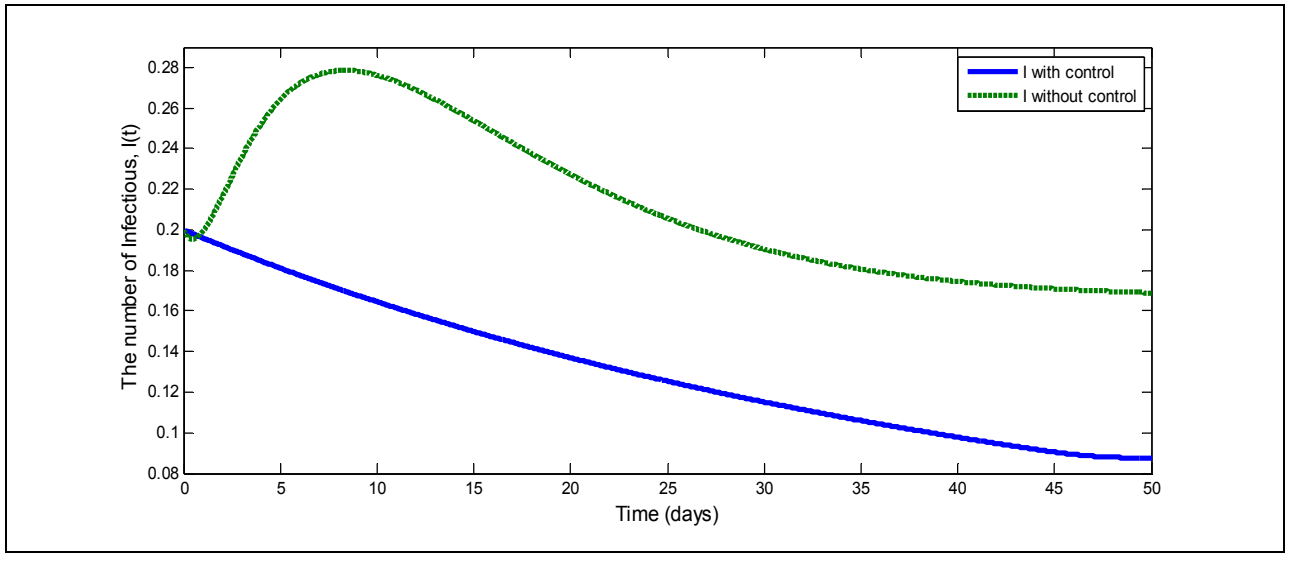


Figure 4: Comparison of infected individuals under an optimal control situation and no control

In figure 4 we show the numerical solution of controlled and uncontrolled infected individuals. From figure 4 we observe that the infectious individuals decrease significantly when control strategies are implemented and both go to stable states at the end of the control period. The results clearly show vaccination given to the susceptible individual significantly reduce the number of infective individuals on the dynamics of the population than unvaccinated population.

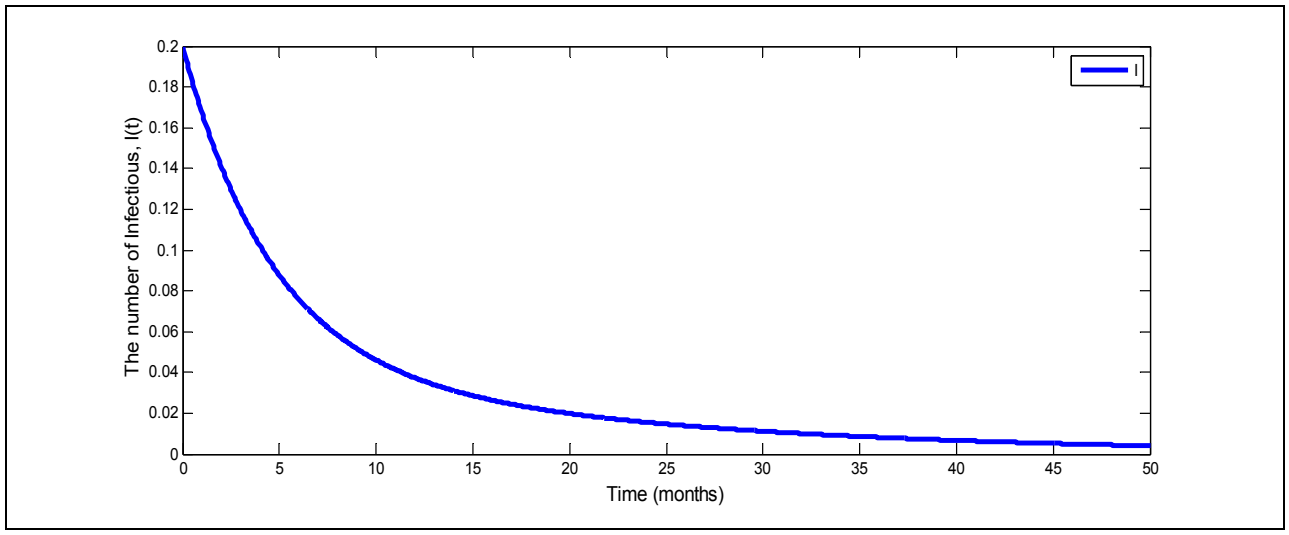


Figure 5: The numerical simulation of the number of infectious individuals I(t) with time (for $u = 0.9$).

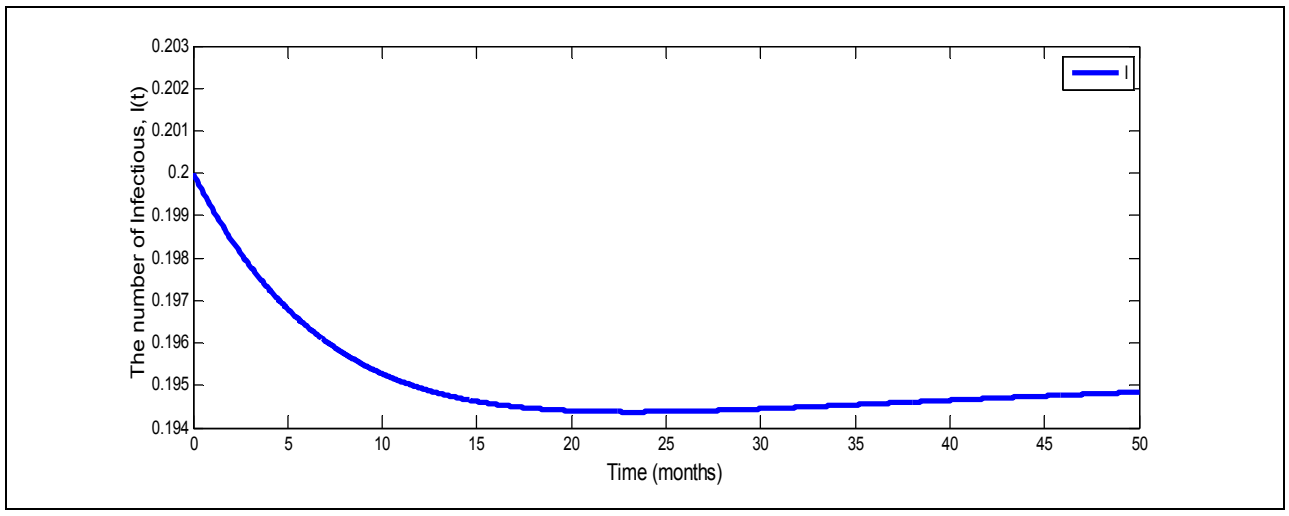


Figure 6: The numerical simulation of the number of infectious individuals I(t) with time (for $u = 0.5$).

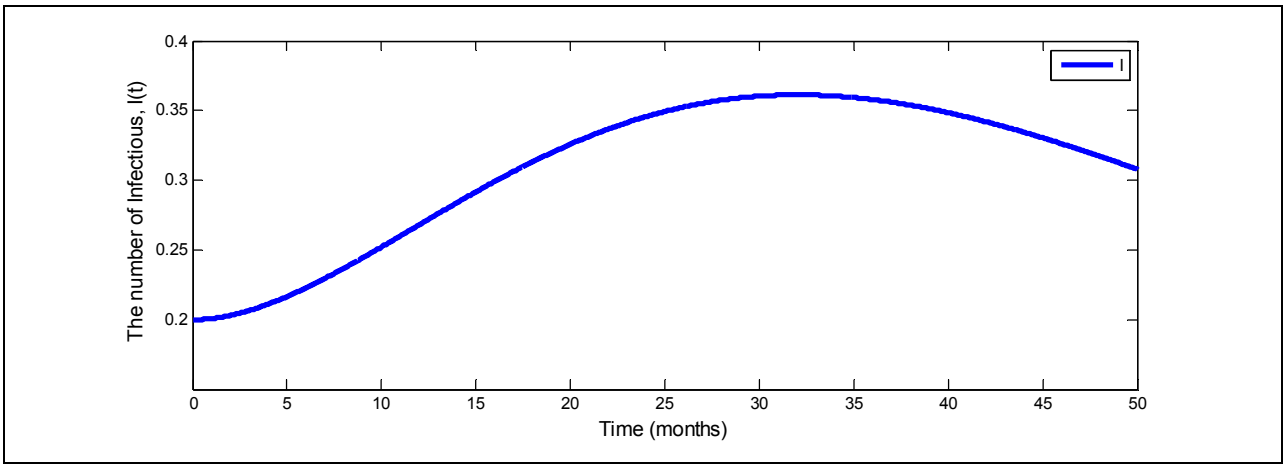


Figure 7: The numerical simulation of the number of infectious individuals I(t) with time (for $u = 0.2$).

Figs. 5, 6 and 7 show, the outcome of the variation of infectious individual at different level of vaccination ratio of susceptible population. The simulation shows that for $u = 0.9$ (when the vaccination ratio is large 90%), controlling the spreading of the disease by 90% vaccination, almost the extinction of measles results in (see figure 5). This also means that the cost associated to this maximum vaccination rate is also high. In figure 6, we see that $u = 0.5$ (a 50% vaccination) also results in reduced control function, but not as high as $u = 0.9$. The figure shows that the number of infectious individual will be in a stable level at the end of the control period, which means that the measles will be become endemic in the population in the long run. The cost associated to this vaccination ratio will be lower than that for $u = 0.9$.

Figure 7 shows what will happen when we are reducing the vaccination rate of susceptible population is reduced to $u = 0.2$. The infectious individuals will increase because the optimal vaccination level is low (see figure 19 and compare with figure 17 and figure 18). Hence, as the disease level increases in the population, the measles outbreak may persist.

Based on our measles model and parameters to control the measles disease effectively, the optimal vaccination ratio of susceptible population should be greater than 0.5 (or >50% vaccination of population). $u > 0.5$ is therefore the minimum critical threshold values of vaccine coverage ratio of measles epidemic. The optimal vaccination policy to be undertaken for controlling the spread of measles with minimum cost is not effective by vaccinating with less than 50% of the susceptible population.

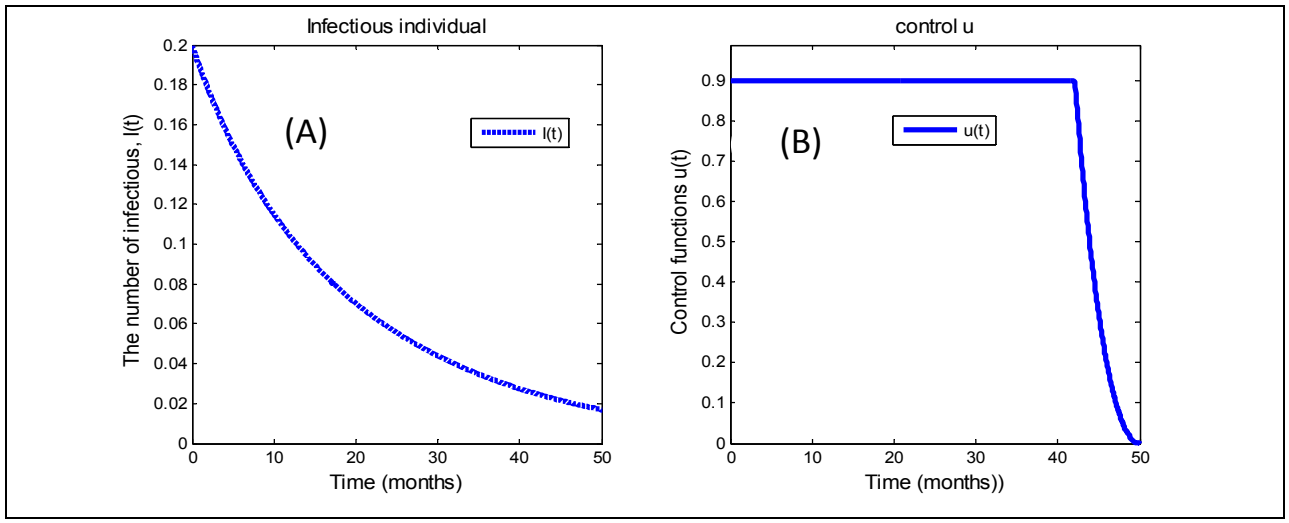


Figure 8: (A) the change of the number of infectious individuals I(t) under optimal control strategy with time and (B) The variation of optimal control function $u(t)$ with time (A=100, $u = 0.9$, $B = 0.04$, $\beta = 2.7652$)

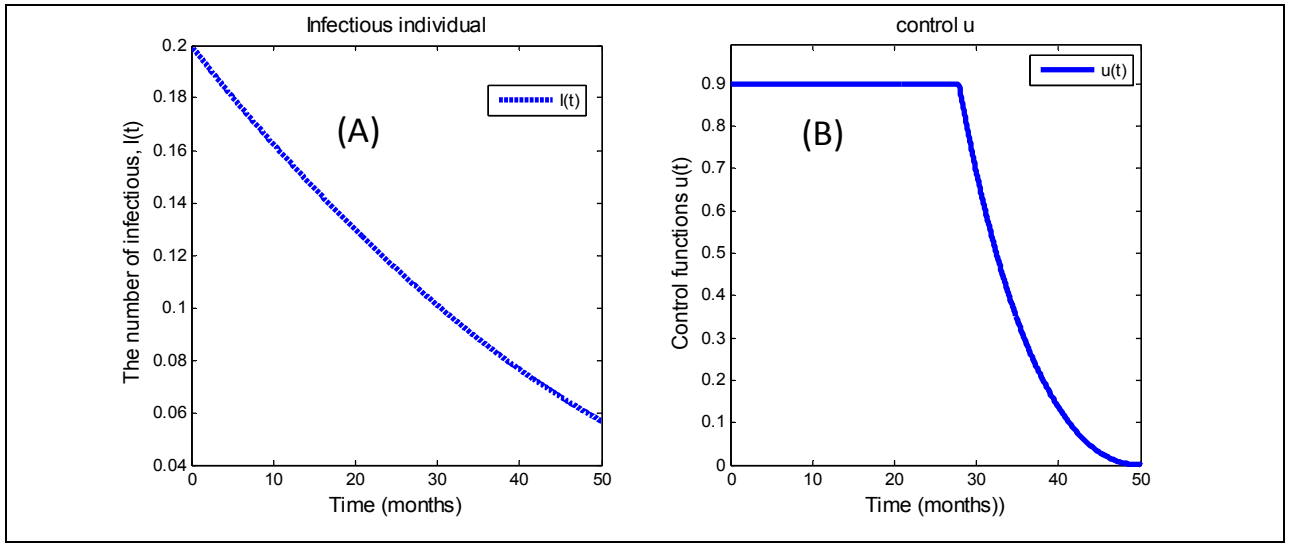


Figure 9: (A) The change of the number of infectious individuals I(t) under optimal control strategy with time and (B) The variation of optimal control function u(t) with time (A=10, $u = 0.9$, $B = 0.04$, $\beta = 2.7652$)

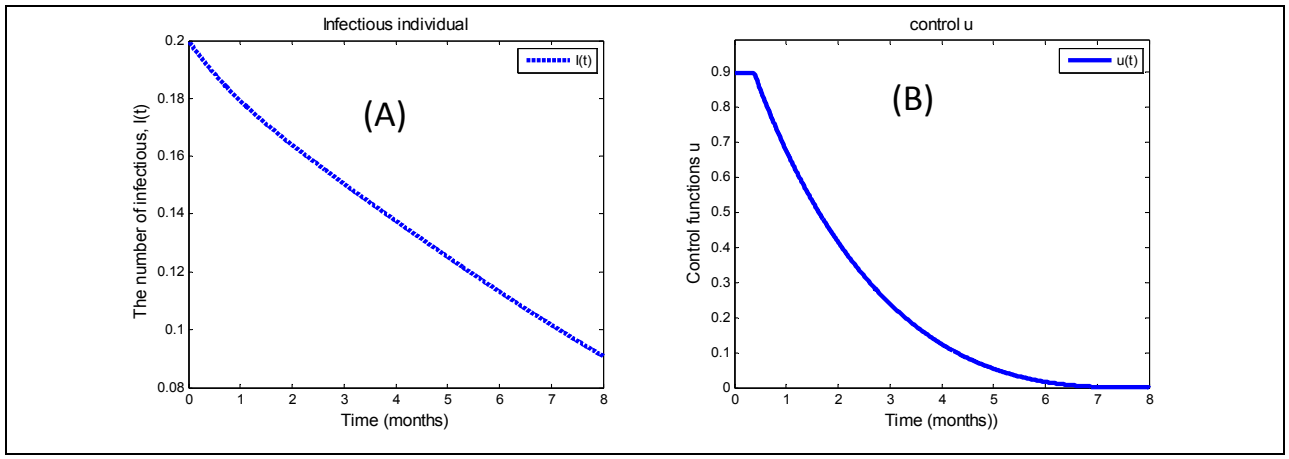


Figure 10: (A) The change of the number of infectious individuals I(t) under optimal control strategy with time and (B) The variation of optimal control function u(t) with time (A=1, $u = 0.9, B = 0.04, \beta = 2.7652$)

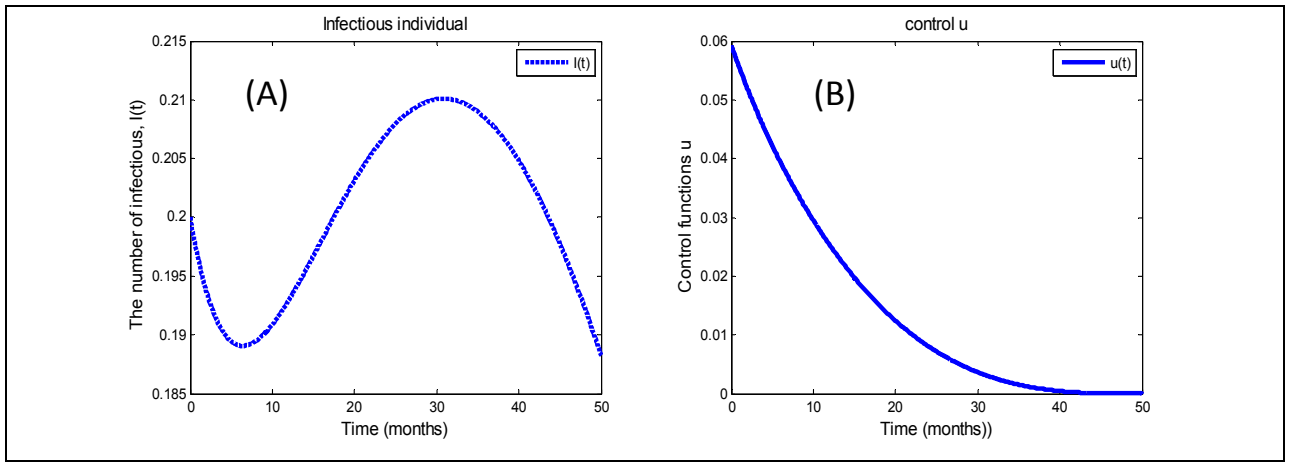


Figure 11: (A) The change of the number of infectious individuals I(t) under optimal control strategy with time and (B) The variation of optimal control function u(t) with time (A=0.1, $u = 0.9, B = 0.04, \beta = 2.7652$)

In figs 8, 9, 10 and 11 we show the changes of the infectious individuals and corresponding optimal vaccination strategy u(t) with time at different A's values. The first thing we observe is that to prevent the spread of measles more effectively; we should adopt a larger vaccination ratio at the beginning of the control period followed by a reduction of vaccination rate. Early detection of measles is therefore more substantial in reducing the infected individuals.

Another observation of this simulation (8-11) is the effect of the weight parameter A on the optimal vaccination policy of the optimal control system. The role played by the weight parameter A in the objective functional is made evident in the figures. This parameter 'measures' the comparative importance of reducing the disease burden than reducing the vaccination costs. When A=0.1 we note that maximum vaccination effort must be provided because the infectious are at the highest level than for case A=1, A=10, A=100. If vaccination is given at a relatively low level, it will produce a major effect on the disease dynamics (compare the infectious time profile for A=10, A=100 with figure 8 and 9 respectively). Note that the control function increases as A values increase with corresponding increment of cost. We conclude that increasing parameter values of A, it becomes more and more important reducing the disease burden than reducing the vaccination costs (compare figs. 16B-19B).

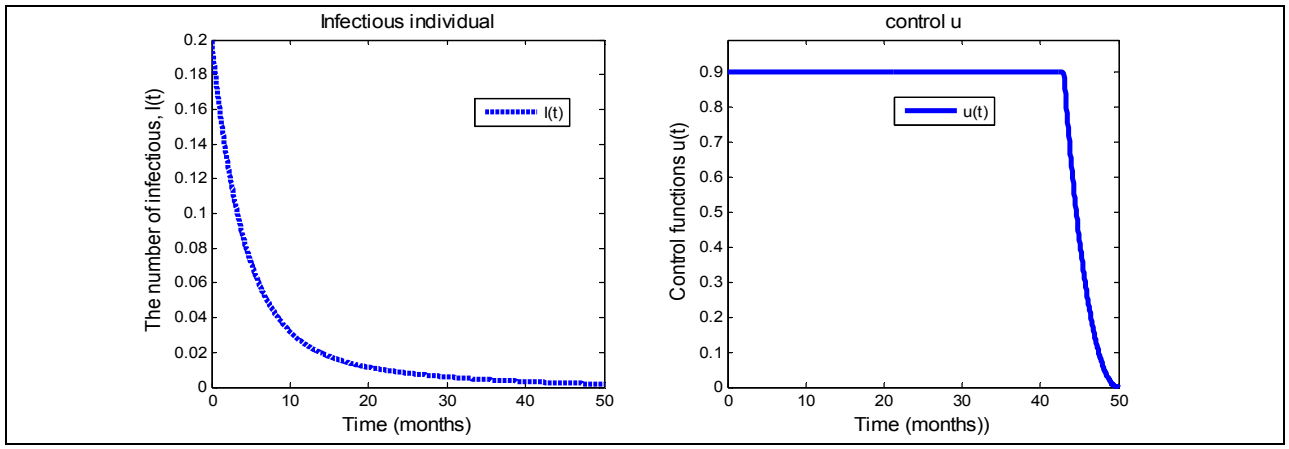


Figure 12: (A) The change of the number of infectious individuals I(t) under optimal control strategy with time and (B) The variation of optimal control function u(t) with time (A=10, B=0.02)

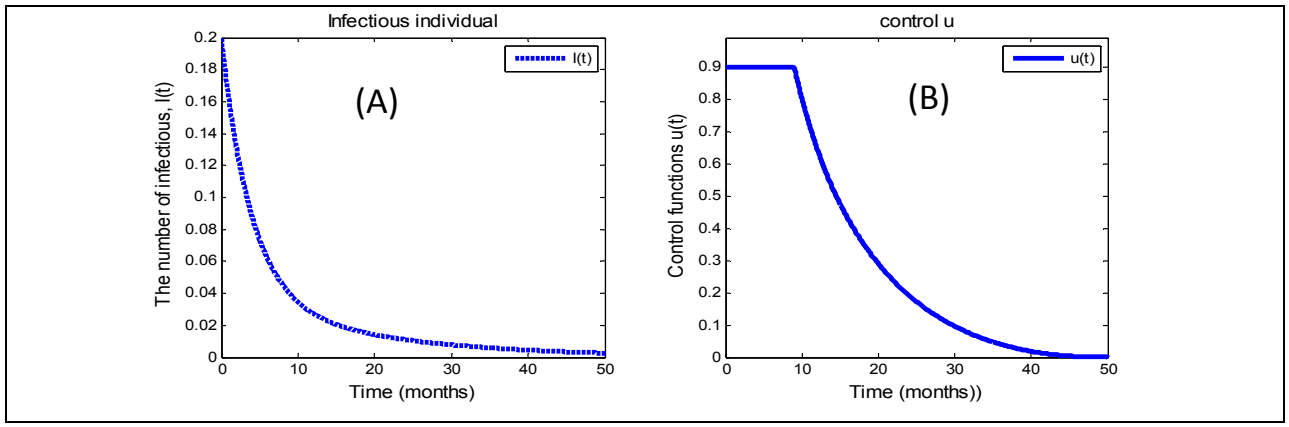


Figure 13: (A) The change of the number of infectious individuals I(t) under optimal control strategy with time and (B) The variation of optimal control function u(t) with time (A=10, B=0.4)

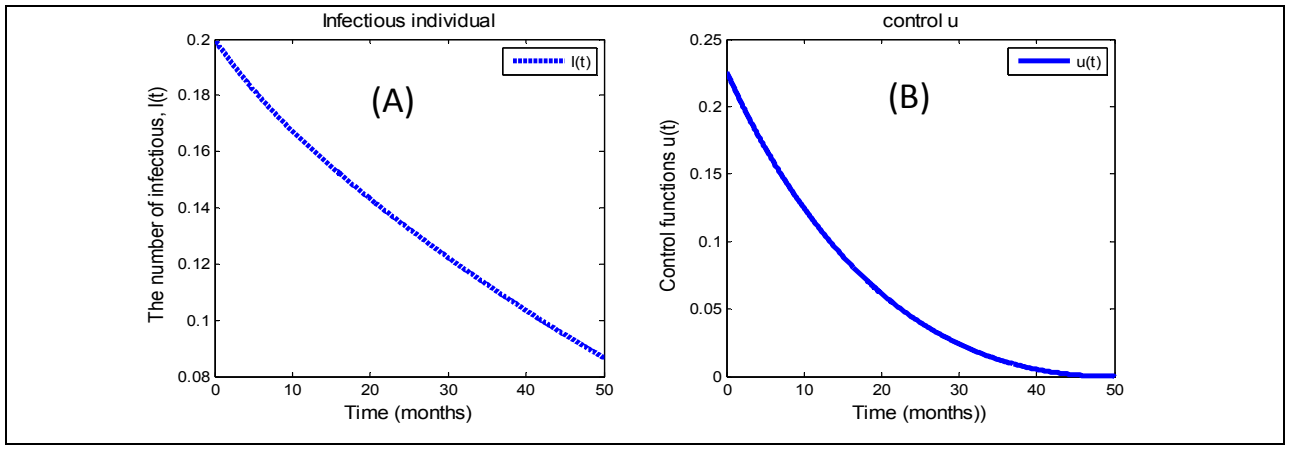


Figure 14: (A) The change of the number of infectious individuals I(t) under optimal control strategy with time and (B) The variation of optimal control function u(t) with time (A=10, B=4)

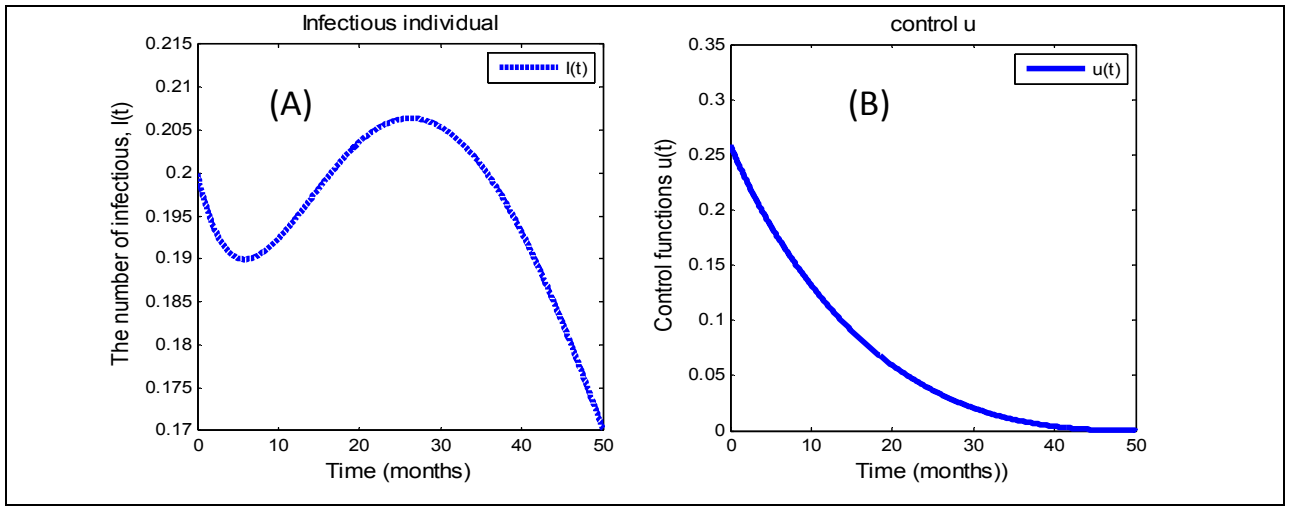


Figure 15: (A) The change of the number of infectious individuals I(t) under optimal control strategy with time and (B) The variation of optimal control function u(t) with time (A=10, B=40)

In figs. 12, 13, 14 and 15 we show the changes of the infectious individuals and corresponding optimal vaccination strategy u(t) with time at different B's values. This parameter 'measures' the comparative importance of reducing the vaccination costs than reducing the disease burden. We observe that for all figures (12-15) as the weight of B increases the control function u(t) decreases and also the corresponding outcome of infectious group increases. Increasing the weight of vaccination for a shorter period cannot reduce the infective group.

Moreover, we observe that for optimality, we mostly use less of the control with the bigger weight and more of the control with the lesser weight. On the other hand, the optimal control attains the maximal value almost all the vaccination period for lower weight of B, which implies a higher cost implementation of control measures (see figs. 16B-19B).

Therefore from the analysis of figs (8-11) and figs. (12-15) if our aim is not only to reduce the number of infectious individuals but also making sure that the cost of implementation of the control measures is low, then the weight constant A should take bigger values and the weight constant B should take lower values.

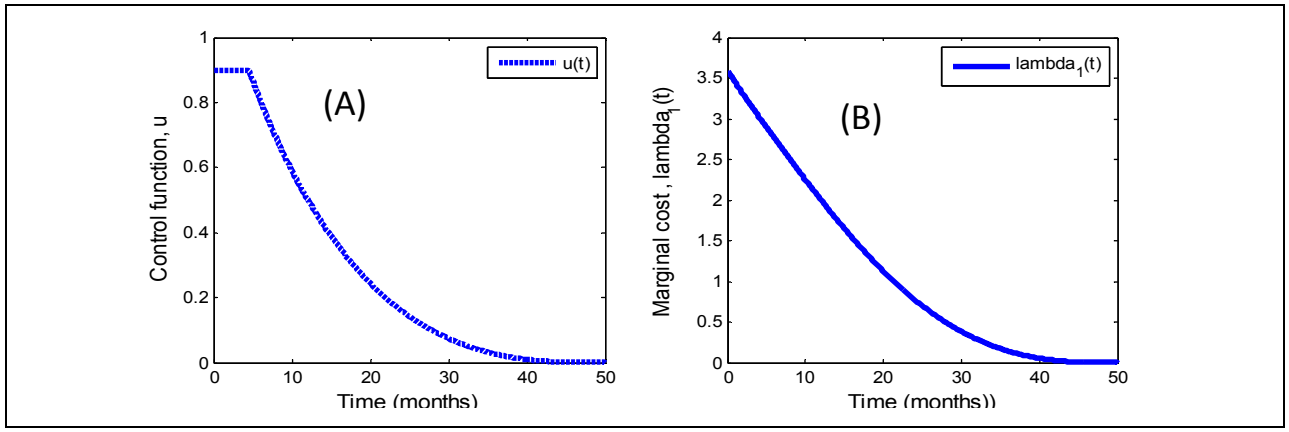


Figure 16: (A) The variation of optimal control function $u(t)$ with time and (B) The marginal cost ($u = 0.9, B = 0.04, \beta = 2.7652$, A=1)

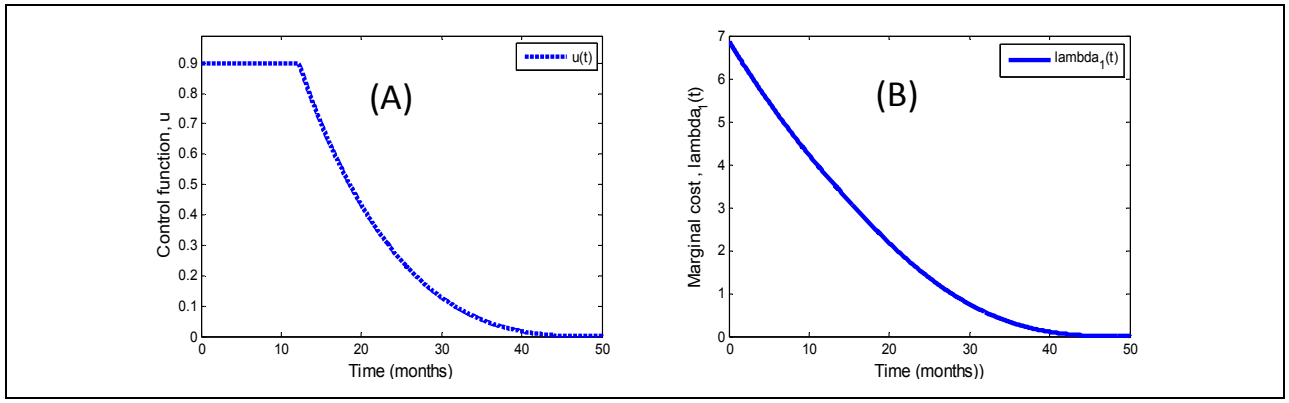


Figure 17: (A) The variation of optimal control function $u(t)$ with time and (B) The marginal cost $\lambda_1(t)$ ($u = 0.9, B = 0.04, \beta = 2.7652$, A=10).

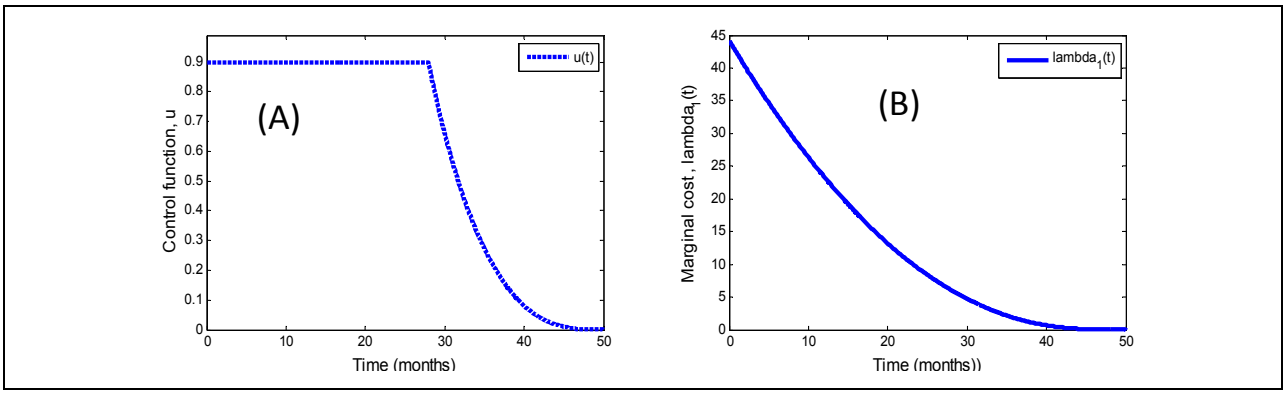


Figure 18: (A) The variation of optimal control function u(t) with time and (B) The marginal cost $\lambda_1(t)$ ($u = 0.9, B = 0.04, \beta = 2.7652$, A=100)

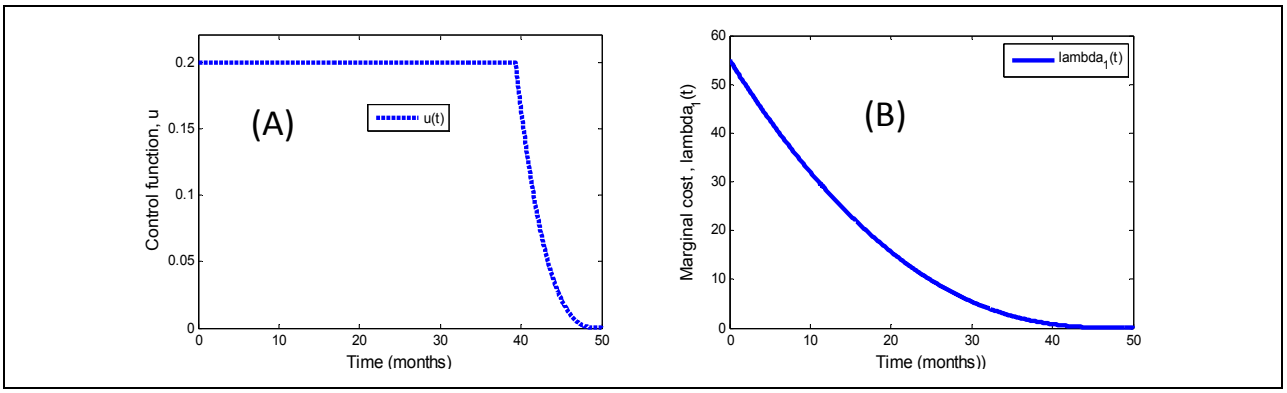


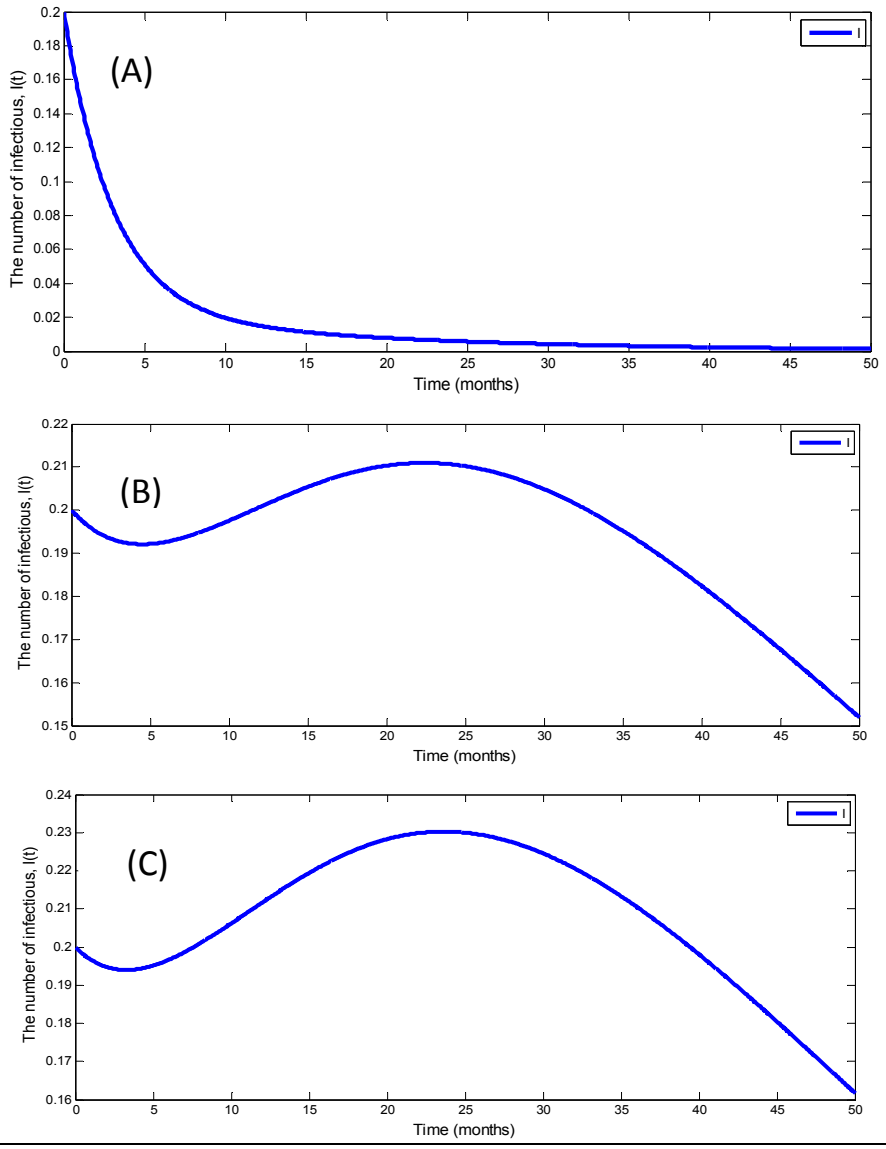
Figure 19: (A) The variation of optimal control function u(t) with time and (B) The marginal cost $\lambda_1(t)$ ($u = 0.2, B = 0.04, \beta = 2.7652$, A=100)

In figure 16 and 17, we show the numerical solutions for the adjoint variables for the case $u = 0.9$, A=1 and A=10. The results indicate that as the weight parameters A increases, the control function $u(t)$ increases as well. This increment leads to the increase of marginal cost of vaccination. This means that to reduce the disease burden more we have to spend more or vaccination at beginning of the control period and gradually decrease the process.

From figs 18 and 19, it can been seen that for a lower a vaccination ratio ($u = 0.2$), the optimal control function is reduced but the corresponding marginal cost is increased in addition to the number of infected individual. However for $u = 0.9$ we observe a higher vaccination ratio for a shorter period and a corresponding reduction in marginal cost. This leads to the conclusion that that vaccination of a susceptible group with a lower vaccination ratio for a long period cannot

reduce infected individuals and results in an overall high marginal cost at the beginning of the control period.

Hence vaccination given to a susceptible group with low rate for a long period cannot reduce the number of infective as well as the cost. This approach rather puts an economic burden without any positive effect in decreasing the measles disease (not economical). The optimal vaccination rate to the susceptible individuals should therefore be higher than this value ($u = 0.2$) to control the disease as well as to minimize the cost of implementation. The optimal control (rate of vaccination) never achieves its maximum value $u = 1$. This is because the reduction in the vaccination at each instant prevents the use of the maximum rate of vaccination.



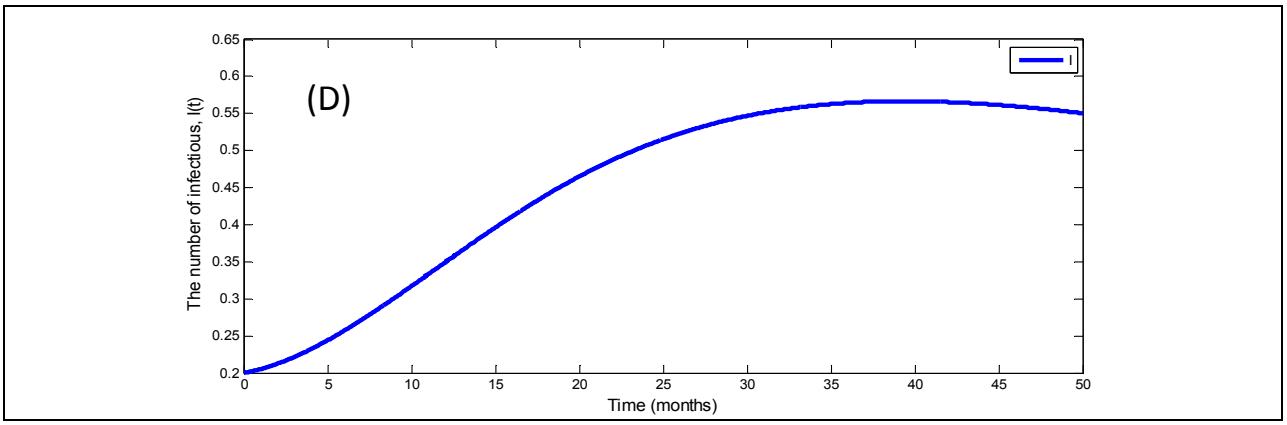


Figure 20 (A, B, C, D): The variation of infectious individual I(t) at different contact rate with time (at $\beta = 0.2, 5, 6\ and\ 10.$) respectively.

From simulation result above, figure 20 (a-d), the measles model indicates that the population of infected individuals increases as the contact rate increases and this happens more sharply at the end of the control period. This rapid increment of the infected individuals may be due to the special characteristic of measles virus which makes it difficult to control especially in countries such as Ethiopia which has a large population and poor sanitation. Vaccination of the whole population is impossible and the rate of the decrease of the infected group is slower than the rate at which the measles virus spread.

This graph also demonstrates that the contact rate has large impact on the spread of the disease through the population. If the contact rate is observed to be high, then the rate of infection of the disease will also be high as would be expected more importantly the result emphasizes that to reduce measles spread, care should be taken to reduce the contact of infected individual from the rest of the population specially those who are vulnerable to the disease virus (children, pregnant women).

The projection of numerical simulation of measles cases in Ethiopia for the next 8 years with optimal vaccination strategy is shown in figures below. Recall the data of measles from Ethiopia (2004-2014):

Year	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Case	4,741	2,416	4,820	4,932	3,511	4,735	6,202	3,554	4,878	8,137	15,478

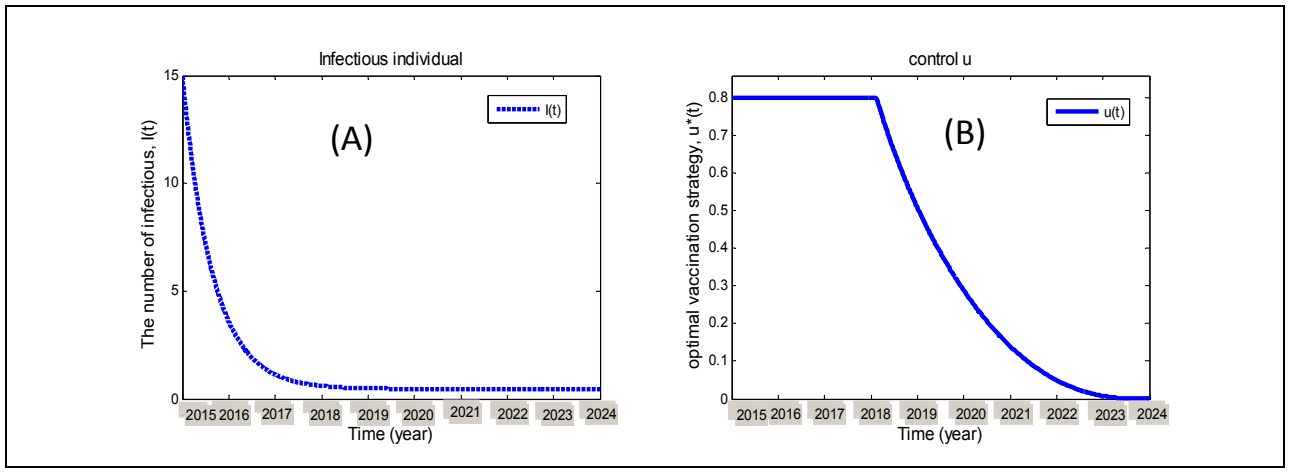


Figure 21: (A) The number of infectious individuals I(t) under optimal vaccination strategy $u*(t)$ with time and (B) The variation of optimal vaccination strategy $u*(t)$ with time

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According to the parameter values obtained from the real measles data in the Ethiopia, we design a vaccination strategy to prevent the outbreak of measles in the Ethiopia. We use the number of cases reported in 2014 as the initial value of measles infected individuals, $I_0 = 15$ (in thousands). In addition, we consider a vaccination period $T = 8$ year and a vaccination ratio $u = 0.8$ or $u = 80\%$ vaccination.

The change of the vaccination coverage ratio $u*(t)$ with time is shown in figure 21(A), and the number of infectious individuals I(t) under the optimal vaccination strategy $u*(t)$ with time is exhibited in figure 21(B). From figure 17, we know that by adopting a vaccination strategy of $u* = 0.8$ for a test prelude of 3 years and optimal vaccination strategy, the spread of the measles disease can be effectively controlled. This must however be viewed with respect to the cost of the projection. The result simulates that vaccination policy of 80% of the susceptible population can effectively control the spread of measles at the end of 3 years (in 2018).

CHAPTER SIX

6. Conclusions and Recommendations

6.1. Conclusions and Remarks

We have presented in this thesis the optimal control of measles disease with two controls measures subject to SEIR epidemiological model. The model control strategies, "vaccination"; is used to demonstrate the optimal control analysis. We established and discussed the conditions for the stability of the model equilibria. Develop an optimal control problem for dynamics of measles model and study the effect of optimal vaccination strategy for driving measles diseases with vaccine towards eradication within a specified period. We sought to determine optimal control strategies that would minimize not only the infected human but also the cost of implementation of the control as well. We used Pontryagin's maximum principle to characterize the controls and derive the optimality system. A state of the art of uncontrolled and controlled mathematical models for measles has been presented. The optimal control problem we presented has an efficient method based on identifying the best intervention; optimal vaccination schedule and control strategies of measles. Finally, in the numerical simulation, we propose an algorithm based on the forward-backward sweep method. The state equations are solved simultaneously forward in time, and next the adjoint equations are simultaneously solved backward in time. The findings are then used to simulate with vaccination period of 3 years (48 months) campaign for measles under several scenarios, by using epidemiological parameter *values estimated based on measles* data from Ethiopian context. The relation between intensive control measures and low cost is clear and expected.

The main findings presented as well as general conclusions are as follows:

The resulting optimality system showed that; a system with optimal control as well as without control dynamics has a very desirable effect upon the population for reducing the number of infected individuals during the control period in properly managed. As the control period increases the number of people saved from measles gradually disease increased.

Based on our measles model and parameters the result of optimal vaccination strategy at different vaccination ratio (u) shown, measles extinction will be possible if the vaccination ratio of susceptible population is greater than or equal to 0.5 $(u \geq 0.5)$, which implies that as the vaccination ratio increases further, then the cases of measles infection will reduce gradually. But if the vaccination ratio is less than this value, measles outbreak may exist in the long run.

In Ethiopia, available data from 2006 to 2014 show that measles is still a health problem. For example in 2014 there is an increment of cases one million children did not take the measles vaccine. Vaccination coverage of measles vaccine is still less than 57%. This is approaching a level where the measles disease will be endemic to the population. The number of infectious individuals will increase through time because the vaccine rate does not exceed the optimal vaccination ratio. Given this level of vaccination coverage, it is possible that the country can experience outbreaks of 2–3 year epidemic cycles. Given this scenario, measles elimination in Ethiopia is not yet achievable.

Based on our model, numerical simulation data of Ethiopia for the next 8 years projection (2015-2024) with optimal vaccination strategy $u^*(t)$ shows the possibility of controlling the spread of measles with optimal vaccination strategy implemented for at least 3 consecutive years of vaccination ratio of greater than or equal to 80% of the susceptible population in the country. However, this optimal vaccination $u^*(t)$ will incur a relatively high cost for the country. But this strategy effectively reduces the disease burden. The policy makers should adopt this optimal vaccination strategy by introducing additional vaccination program from the existing trend. On the other hand, the herd immunity figure of $H = 1 - 1/R_0 = 1 - 1/14.65 = 0.9317$ must be shows that to eradicate measles it requires that roughly 93% of the population must be vaccinated, so measles would require a much higher level of vaccination coverage in addition to a higher cost of implementation. So the country must adopt an optimal vaccination strategy to make this goal possible.

The use of vaccination at the highest possible rate to the population as early as possible is essential for controlling an epidemic of the measles. Moreover, a mass vaccination of population for a short period may not help to accelerate the eradication of measles. When the vaccination cost is relatively low, a gradual increase of the vaccination rate is suggested.

The numerical solution at different contact rate shows that to control the spread of the level of measles disease well in contact must be monitored. This is very important because measles is highly communicable.

Finally, if our aim is to reduce the number of infectious individuals by paying special attention to keep the cost of implementation of the control measures low, then the weight constant A and B should bigger and lower values, respectively. On the other hand, we aim at giving more importance to decreasing of the number of infectious individuals than to the cost of implementation of the control policies we increase the value of A and decrease the weight values of B. *So our goal should based on decreasing disease burden than the cost of implementation the later approach is acceptable because human life has more weight than cost of control measure*. This parameter is very important in managing our minimum resource to be effective and to strike a realistic balance with the disease burden.

6.2. Limitations and Recommendations

In this thesis work, there are some aspects of measles dynamics which were not considered when formulating the mathematical models. The reason was to reduce the complexities which would otherwise arise in the mathematical analysis and in estimation of parameters for the numerical simulations and lead to unnecessary complication of the model.

Modification and extension of the models can address the following points:

Seasonally varying contact rate; most childhood diseases tend to have periodic outbreaks, occasioned by climatic factors and human contact rate patterns, among other factors. The school going childhood age has periodic contact due to school terms as one would expect higher contact rates during school days and lower contact rates during holidays.

Age structure; as the epidemic of measles varies in age structure it is possible to extent the model to the age-structured model and

Appendices

A: ALGORITHM FOR MATLAB CODES FOR OPTIMAL CONTROL PROBLEM

$Algorithm\ 1$

Step 1

for $i = -m,...,0,$ *do*

$S_i = S_0, E_i = E_0, I_i = I_0, R_i = R_0, u_i = 0$

end for

for $i = n,...,n+m,$ *do*

$\lambda_1^i = 0, \quad \lambda_2^i = 0, \lambda_3^i = 0, \lambda_4^i = 0,$

Step 2

$(Forward\ in\ time)$

$S_{i+1} = S_i + h\left[b - \beta S_i I_i - \mu S_i - u_i S_i\right]$

$E_{i+1} = E_i + h\left[\beta S_i I_i - (\varepsilon + \mu) E_i\right]$

$I_{i+1} = I_i + h\left[\varepsilon E_i - (\gamma + \mu + \delta) I_i\right]$

$R_{i+1} = R_i + h\left[\gamma I_i - \mu R_i + u_i S_i\right]$

$(Backward\ in\ time)$

$\lambda_1^{n-i-1} = h\left[\lambda_1^{n-i}\left(\beta I_i + \mu + u_i\right) - \lambda_2^{n-i}\left(\beta I_i\right) - \lambda_4 u_i\right]$

$\lambda_2^{n-i-1} = h\left[\lambda_2^{n-i}\left(\varepsilon + \mu\right) - \varepsilon\lambda_3^{n-i}\right]$

$\lambda_3^{n-i-1} = h\left[-A + \lambda_1^{n-i}\left(\beta S_i\right) - \lambda_2^{n-i}\left(\beta S_i\right) + \lambda_3^{n-i}\left(\left(\gamma + \mu + \delta\right)\right) - \lambda_4^{n-i}\left(\gamma\right)\right]$

$\lambda_4^{n-i-1} = h\left[\lambda_4^{n-i}\mu\right]$

$u^{i+1} = \left(\lambda_1^{n-i}\right)\dfrac{S_{i+1}}{B}$

$u_i = \max\left(\min\left(u^{i+1}, u_{\max}\right), 0\right)$

Step 3

for $i = 1,...,n,$ *do*

write

$S^*\left(t_i\right) = S_i, E^*\left(t_i\right) = E_i, I^*\left(t_i\right) = I_i, R^*\left(t_i\right) = R_i, u^*\left(t_i\right) = u_i$

end for

B: SAMPLE FIGURES

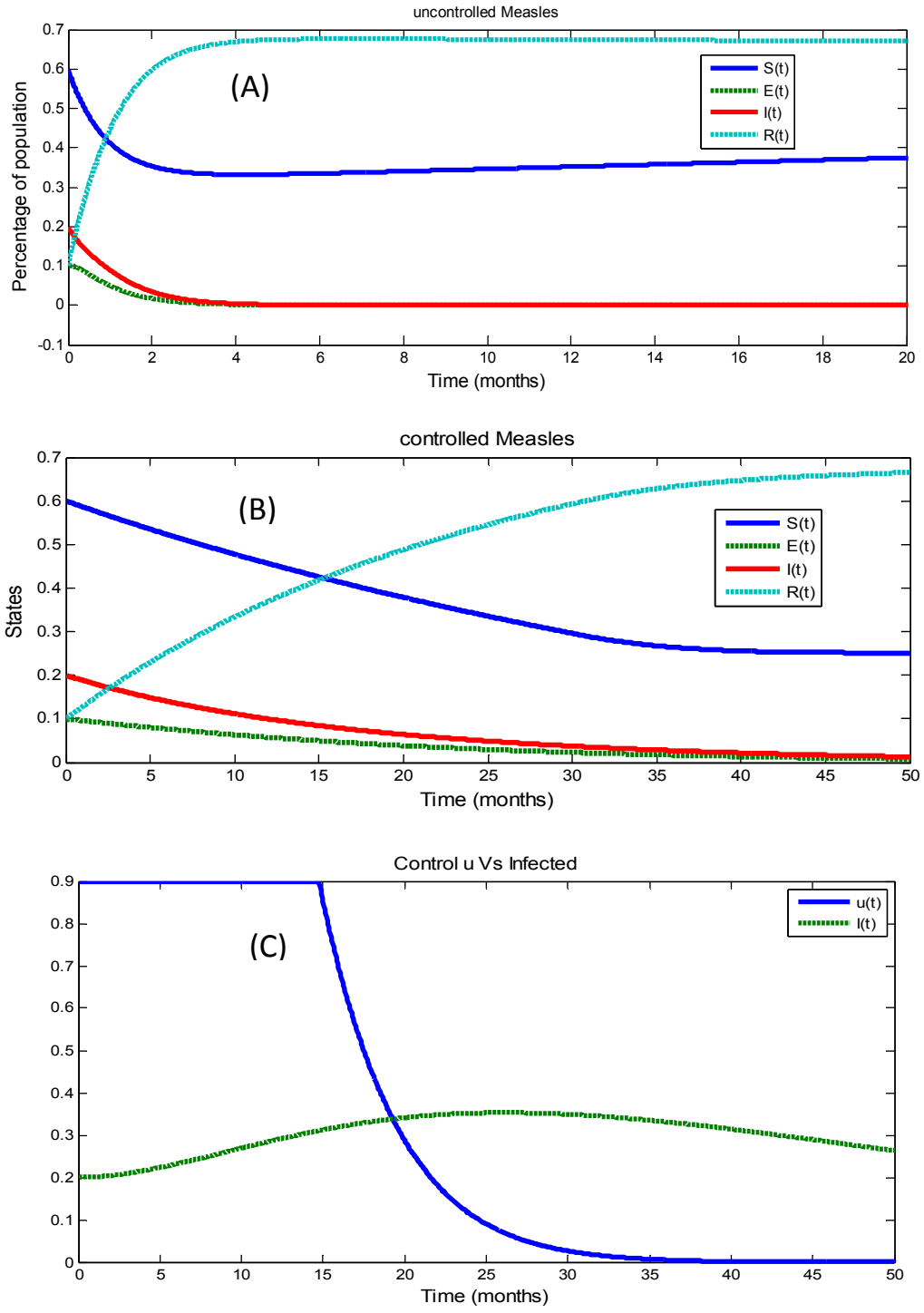

Figure 18: Outcome of the epidemic with uncontrolled, controlled policy and control Vs infected respectively (for A=10, $B = 0.04$, $\beta = 2.7652$).

References

[1] Zhien Ma Xi'an Jiaotong, "Dynamical Modeling and Analysis of Epidemics", China Jia Li University of Alabama in Huntsville, USA (2002).

[2] CDC, Progress in global measles control (http://www.cdc.gov/measles/pubs-mmwr.html)

[3] CDC, Morbidity and Mortality Weekly Report 2008-2015(MMWR) (https://surv.esr.cri.nz/surveillance/WeeklyMeaslesRpt.php)

[4] CDC, Center for Disease Control and prevention (http://www.cdc.gov/measles/about/photos.html)

[5] Wikipedia (http://en.wikipedia.org/wiki/Measles)

[6] WHO/UNICEF, Strengthening Immunization Services through Measles Control, Joint Annual Measles Report 2010

[7] Allen L.J., Lewis T., Martin C. F., Jones M.A., Lo C.K., Stamp M., Mundel G. and Way A.B. Analysis of a Measles Epidemic", Statistic in Medicine, Volume 12, Pages 229-239, Texas Tech University (1993)

[8] Chen S. C, Chang C. F., Jou L. J. and Liao C. M. , "Modeling vaccination programs against measles in Taiwan", Epidemiology and Infection, vol.135, pp.775-786 (2007).

[9] Roberts M. G. and Tobias M. I. Predicting and Preventing Measles Epidemics in New Zealand: Application of a Mathematical Model, Epidemiol infct , volume 124, pages 279-287, New Zealand, Cambridge University press, U. K. (2000)

[10] Lloyd, A. L. "Realistic Distributions of Infectious Periods in Epidemic Models: Changing Patterns of Persistence and Dynamics." Program in Theoretical Biology, Institute for Advanced Study, Einstein Drive, Princeton, New Jersey, 08540, USA (2001).

[11] Trottier H. and Philippe P., "Deterministic Modeling of Infectious Diseases: Theory And Methods", The Internet Journal of Infectious Diseases, Volume 1, Number 2, pages 1528-8366 (2001)

[12] Grais, R.F., Conlan A.J.K.,Ferrari M. J.,Djibo A., Menach A.L.,Bjørnstad O.N. and B.T Grenfell B.T. "Time is of the essence: exploring a measles outbreak response vaccination in Niamey,v154, pp200-254, Niger" (2006).

[13] Anderson, R.M. and May, R.M. Vaccination against rubella and measles: quantitative investigations of different policies, Journal of Hygiene, vol.90, pages 259-325 (1983).

[14] Anderson, R.M. and May, R.M. Age-related changes in the rate of disease transmission: implications for the design of vaccination programs, Journal of Hygiene, vol.94, pages 365-436 (1985).

[15] Helena Sofia Ferreira Rodrigues, Optimal Control and Numerical Optimization Applied to Epidemiological Models, Ph.D. thesis, University of Aveiro (2012).

[16] H. W. Hethcote. The mathematics of infectious diseases. SIAM Journal of Applied Mathematics, vol. 42n, No.4, pp.599–653 (2000).

[17] Lenka Bubniakov. The mathematics of infectious diseases, faculty of mathematics, physics and informatics Comenius University Bratislava, master's thesis (2007).

[18] F. Brauer. Compartmental models in epidemiology. In Mathematical epidemiology, volume 1945 of Lecture Notes in Math., pages 19–79. Springer, Berlin, 2008.

[19] Tracy A. Atkins B.A., "Using Modeling and Simulation to Evaluate Disease Control Measures", University of Central Florida Orlando, Florida, PhD thesis, 1990.

[20] M.J.Keeling and P.Rohani. Modeling infectious diseases in humans and animals. Princeton, NJ: Princeton University Press. xiii, 2008

[21] Kwame Asare Gyasi–Agyei, "Analysis and Modeling of Prevalence of Measles in the Ashanti Region of Ghana", master's thesis, June 2012.

[22] Ethiopian health and nutrition research institute. Guideline on Measles Surveillance and Outbreak Management, January 2012.

[23] WHO/UNICEF, Global Measles and Rubella Strategic Plan 2012- 2020 (2012).

[24] WHO/UNICEF, Measles and Rubella Initiative annual report (2012).

[25] WHO/UNICEF, Status Report on Progress towards Measles and Rubella Elimination SAGA Working Group on Measles and Rubella (22 October 2012).

[26] WHO/UNICEF, Strengthening Immunization Services through Measles Control, Joint Annual Measles Report 2012.

[27] Trottier H. and Philippe P., "Univariate time series analysis of pertussis, mumps measles and rubella: Theory and Methods", The Internet Journal of Infectious Diseases, Volume 3, Number 4, ISSN: 2528-7836, (2006).

[28] Thacker S. B. and Millar J. D. , "Mathematical Modeling and Attempts to Eliminate Measles: A Tribute to the Late Professor George Macdonald", American Journal of Epidemiology, volume 133, issue 6, pp. 517-525, Atlanta (1991)

[29] Nelson Owuor Onyango.The Epidemiology of Childhood Related Diseases: Stability Analysis and Optimal Control, Technische Universität München, masters' thesis (2011).

[30] Victoria Brown, “Modelling Healthcare Provision for an Infectious Disease using Optimal Control”, Department of Mathematical Sciences, PhD thesis, Bath University (2010).

[31] Suzanne Lenhart and John T. Workman. Optimal Control Applied to Biological Models. Chapman and Hall/CRC, first edition, 2007.

[32] Arjada Bardhi, “Two essays on the optimal control of infectious diseases: Examining discrepancies between discrete-time and continuous-time models”, Honors Theses, Bates College, 2012

[33] M.G. ROBERTS, “The elimination of childhood diseases by mass vaccination. Journal of Applied Mathematics & Decision Sciences, 4(2):175-182, New Zealand (2000)

[34] David Greenhalgh, “Age-Structured Models and Optimal Control in Mathematical Epidemiology”: A Survey (2013).

[35] Suresh P. Sethi and Preston W. Staats. Optimal control of some simple deterministic epidemic models. The Journal of the Operational Research Society, 29(2):129-136, 1978.

[36] X. Yan and Y. Zou. Optimal and sub-optimal quarantine and isolation control in SARS epidemics. Mathematical and Computer Modeling, vol.47, pp.235–245, 2008.

[37] Elsa Hansen and Troy Day, Optimal control of epidemics with limited resources, J. Math. Biol. 62: pages 423–451 (2011).

[38] Onyango Nelson Owuor, Müller Johannes, Moindi Stephen Kibet, Optimal Vaccination Strategies in an SIR Epidemic Model with Time Scales, Applied Mathematics, volume 4, pp.1-14, October 2013.

[39] Ankit Agrawal, Global Analysis of an SEIRS Epidemic Model with new Modulated Saturated Incidence, Applied Science Department, Commun. Math. Biol. Neurosci. , vol.2, pp.240-300, India 2014.

[40] Ousmane Moussa Tessa, Mathematical model for control of measles by vaccination, Department of Mathematics and Computer Science, Abdou Moumouni University, Niamey, NIGER, master’s thesis, 2013.

[41] W. O. Kermack and A. G. McKendrick. A contribution to the mathematical theory of epidemics. In Proceedings Royal Society of London (A), volume 115, pp.700-721, 1927.

[42] Amsalework Ayele Ejigu, “Mathematical Modelling of HIV/AIDS Transmission under Treatment Structured, Age of Infection”, Stellenbosch University, Thesis December 2010.

[43] H. S. Rodrigues, M. T. T. Monteiro, D. F. M. Torres, and A. Zinober. Control of dengue disease: a case study in Cape Verde. In J. Vigo Aguiar, editor, Proc. 10th International Conference on Mathematical Methods in Science and Engineering, pages 816–822, 2010.

[44] O.Diekmann, P.Heesterbeek, and M.Roberts, “The construction of next-generation matrices for compartmental epidemic models.” Journal of Royal Society Interface, vol.7, No.47, pp.873–885 (2010).

[45] Alexander Panfilov, Qualitative Analysis of Differential Equations, Theoretical Biology, Utrecht University, Utrecht , February 23, 2010.

[46] Adriana Johnson, Optimal Control of Cell-Cycle-Specific Chemotherapy: An Examination of the Effects of Necrosis, master’s thesis, 2010.

[47] S. Nanda, H. Moore, and S. Lenhart. Optimal control of treatment in a mathematical model of chronic myelogenous leukemia. Math. Biosci., vol.210, No.1, pp.43–156 (2007).

[48] Federal Democratic Republic of Ethiopia, Population Census Commission. Summary statistical report of the 2007 population and housing census, Addis Ababa: Central Statistics Agency, 2008.

[49] Federal Ministry of Health of Ethiopia, Annual report 2014/2015.

[50] Abta Abdelhadi and Laarabi Hassan, Optimal Control Strategy for SEIR with Latent Period and a Saturated Incidence, Applied Mathematics Volume 2013, Article ID 706848, pages 140-195, 22 May 2013.

[51] Abta, Hassan Laarabi, and Hamad Talibi Alaoui, “The Hopf Bifurcation Analysis and Optimal Control of a Delayed SIR Epidemic Model”, International Journal of Analysis Volume 2014, Article ID 940819, pages 111-121, 21 January 2014.

[52] Cristiana J. Silva and Delfim F. M. Torres, Optimization and Control (math.OC); Optimal Control of Tuberculosis, arXiv.org > math > arXiv:1406.3456v1, Cornell University 2010

[53] W. H. Hamer. Epidemic disease in England. The Lancet, 1: pp733-739, 1906.

[54] O. Diekmann, P. Heesterbeek, and M. Roberts. The construction of next-generation matrices for compartmental epidemic models. Journal of Royal Society Interface, vol.7, No.47, pp.873–885, 2010

[55] P. V. D. Driessche and J. Watmough. Reproduction number and sub-threshold endemic equilibria for compartmental models of disease transmission. Mathematical Biosciences, vol.180, pp.29–48, 2002.

[56] P. Simon and J. John. Reproduction numbers and stability of equilibria of SI models for heterogeneous populations. SIAM Journal of Applied Mathematics, vol.52, No.2, pages 541–576, 1992.

[57] L. Edelstein-Keshet, Mathematical models in biology, SIAM 2005

[58] J. Lasalle. The stability of dynamical systems. Philadelphia: SIAM, 1976

[59] P. Simon and J. John. Reproduction numbers and stability of equilibria of SI models for heterogeneous populations. SIAM Journal of Applied Mathematics, vol.52, No.2, pp.541–576,1992

[60] Dorfman, Robert. “An Economic Interpretation of Optimal Control Theory.” American Economic Review, pp.817-831, (December 1969).

[61] Mose Ongau Fred, Johana K. Sigey, Jeconiah A. Okello, James M. Okwoyo & Giterere J.Kang’ethe, “Mathematical Modeling on the Control of Measles by Vaccination”, Vol. 2, No. 3,pp.150-240, (May 2014)

[62] CDC, Progress in global measles control, 2000–2010,MMWR . (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6104a3.htm)

[63] B. Buonomo, D. Lacitignola, “The backward bifurcation of a vaccination model with nonlinear incidence”, Nonlinear Analysis: Modelling and Control, Vol. 16, No. 1, pp.30–46, 25 February 2011

[64] Nicholas Piazza and Hao Wang, “Bifurcation and sensitivity analysis of immunity duration in an epidemic model, International Journal of, Numerical Analysis and Modeling, series B, volume 4, number 2, pp.179-202 (2013)

[65] CDC, Global Measles Mortality, 2000—2008, MMWR (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5847a2.htm)

[66] H.R.Joshi,S.Lenhart, H.Lou and H.Gaff, Optimal Control meths, Contemporary mathematics, volume 410, pp.187-208 (2006)

[67] G. Zaman, Y. Kang, I. Jung. Stability analysis and optimal vaccination of an SIR epidemic model. BioSystems,93, pp.240–249 (2008)