Mathematical modeling of an epidemic under vaccination in two interacting populations

Ibrahim H.I. Ahmed

Supervisor: Prof P.J. Witbooi

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Department of Mathematics and Applied Mathematics,

University of the Western Cape,

South Africa.

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Abstract

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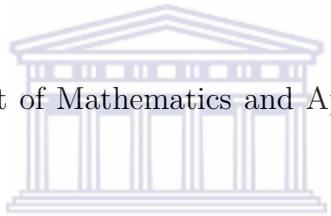
MSc Dissertation, Department of Mathematics and Applied Mathematics, University of the Western Cape.



In this dissertation we present the quantitative response of an epidemic of the so-called SIR-type, in a population consisting of a local component and a migrant component. Each component can be divided into three classes, the susceptible individuals, usually denoted by S, who are uninfected but may contract the disease, infected individuals (I) who are infected and can spread the disease to the susceptible individuals and the class (R) of recovered individuals. If a susceptible individual becomes infected, it moves into the infected class. An infected individual, at recovery, moves to the class R. Firstly we develop a model describing two interacting populations with vaccination. Assuming the vaccination rate in both groups or components are constant, we calculate a threshold parameter and we call it a vaccination reproductive number. This invariant determines whether the disease will die out or becomes endemic on the (in particular, local) population. Then we present the stability analysis of equilibrium points and the effect of vaccination. Our primary finding is that the behaviour of the disease free equilibrium depend on the vaccination rates of the combined population. We show that the disease

free equilibrium is locally asymptotically stable if the vaccination reproductive number is less than one. Also our stability analysis show that the global stability of the disease free equilibrium depends on the basic reproduction number, not the vaccination reproductive number. If the vaccination reproductive number is greater than one, then the disease free equilibrium is unstable and there exists three endemic equilibrium points in our model. Two of these three endemic equilibria are so-called boundary equilibrium points, which means that the infection is only in one group of the population. The third one which we focus on is the general endemic point for the whole system. We derive a threshold condition that determines whether the endemic equilibria is locally asymptotically stable or not. Secondly, by assuming that the rate of vaccination in the migrant population is constant, we apply optimal control theory to find an optimal vaccination strategy in the local population. Our numerical simulation shows the effectiveness of the control strategy. This model is suitable for modeling the real life situation to control many communicable diseases. Models similar to the model used in the main contribution of our dissertation do exist in the literature. In fact, our model can be regarded as being in-between those of [Jia et al., Theoretical Population Biology 73 (2008) 437-448] and [Piccolo and Billings, Mathematical and Computer Modeling 42 (2005) 291-299]. Nevertheless our stability analysis is original, and furthermore we perform an optimal control study whereas the two cited papers do not. The essence of chapter 5 and 6 of this dissertation is being prepared for publication.

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Key words

KEYWORDS

Epidemiology modeling

Local population

Migrant population

Local stability

Global stability

Basic reproduction number

Vaccination

Vaccination reproductive number

Optimal control

Numerical simulation

SIR

Declaration

I declare that *Mathematical modeling of an epidemic under vaccination in two interacting populations* is my own work, that it has not been submitted for any degree or examination in any other university, and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

Ibrahim H.I. Ahmed February, 2011

Signed: .....

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Chapter 1

Introduction

1.1 Introduction

Mathematical modeling of the quantitative evolution of an infectious disease in a population has become an important tool for disease control and eradication if possible. The mathematical model clarifies assumptions, variables and parameters. A basic assumption in epidemic modeling is that the total population is divided into distinct compartments, depending on the effect of the pathogen on the human body. Thus for instance we may have the class of susceptible individuals, usually denoted by S, who are uninfected but may contract the disease. If a susceptible becomes infected, it moves into the infected class, which is denoted by I. An infected individual can spread the disease to the susceptible individuals. Depending on the relevant classes chosen and the possible passage of an individual through the different classes, the different models are described as being of the type SIS, SIR, SEIRS, and MSEIR etc. For more on the different classes, we refer to Hethcote [17] for instance. We shall be mostly concerned with diseases of the type called SIR. Thus we have the classes S and I, and individuals from the class I, may move into the class R of recovered individuals. Individuals in the recovered state are assumed to be immune for life. In [14] of Guo et al. proposes a multi-group SIR model. The multi-group model can be used to investigate infectious diseases with multiple hosts such as West-Nile

virus and other vector borne diseases such as Malaria, See [48] of Tumwiine et al. As a reference on the West-Nile virus see Jang [25]. For more on SIR models, we refer the reader to [52] of Zaman et al., Korobeinikov and Wake [28], Jianwen and Qiuying [23], and to Zhang and Zhang [54].

There are many deterministic continuous-time epidemiology models. The SIS model is a compartmental epidemic model in which the population is divided into two compartments, the susceptible and infected. In this model the individuals pass from the susceptible compartment to the infected compartment and then return to the susceptible class. This type of model is used to describe the dynamics of a disease that does not provide immunity after recovery. The SIRS is similar to the SIS model except that SIRS is suitable for a disease that provides temporary immunity after recovery, but then eventually a recovered individual becomes susceptible again, see [55] by Zhonghua et al. There are other types of diseases such as tuberculosis for which the pathogen requires an incubation period or latent period. Also, recovered individuals become susceptible again. So the model that describes the transmission of this type of disease is SEIRS where E is a latent class, for more on the tuberculosis model, see Bowong [8].

Diseases transmitted by viral agents such as influenza, measles, rubella (German measles), and chicken pox, usually confer immunity against reinfection, while diseases transmitted by bacteria, such as tuberculosis, meningitis, and gonorrhea confer no immunity against reinfection. Other diseases, such as malaria, are transmitted not directly from human to human, but by vectors, which are agents (usually insects) who are infected by humans and who then transmit the disease to humans. The West Nile virus involves two vectors, mosquitoes and birds. For sexually transmitted diseases with heterosexual transmission, each sex acts as a vector and the disease is transmitted back and forth between the sexes, see the book [7] Brauer et al.

In this dissertation, we develop and analyse an SIR epidemiological model to study the transmission dynamics of communicable diseases with vaccination, in two interacting pop-

ulations and to set an optimal control strategy to role out the vaccination on the general SIR model. For the case of SEIR diseases such a study was done in Jia et al., [21]. The basic assumption is that the total population is divided into two subpopulations, local and migrant. Our aim is to understand the transmission dynamics of the diseases and in particular the impact of migrants onto the local subpopulation. Then we formulate a vaccination control strategy, to eradicate the diseases from the two subpopulations, local and migrants. With vaccination, usually it is assumed that a certain percentage of the susceptible population undergoes vaccination. We quantitatively study the effect of vaccination on these subpopulations, and employ optimal control theory to inform the best vaccination strategy.

To better understand the transmission dynamics of a disease in terms of a deterministic SIR model we study the equilibrium points or the steady states of the system, applying different methods of stability analysis. There are usually at least two possible equilibrium states in the model. The disease free equilibrium (DFE) is reached when the disease dies out. Otherwise one or more endemic equilibria may arise where the disease will persist in the population, in a stable state.

The local stability analysis of the equilibrium points is done using the general linearization theorem. We also present some global stability analysis. The Pontryagin maximum principle is used to solve the optimal vaccination problem, and the Runge-Kutta fourth order methods are applied to find the numerical solution to the optimal problem. Our control problem is a generalization of the method used in [52] of Zaman et al.

1.2 Background to research problem.

In this dissertation, we deal with an optimal vaccination strategy in two interacting populations using an SIR epidemic model. We model the dynamics of a disease in two

interacting populations, the local subpopulation and the migrant subpopulation. We try to find the influence of migrant subpopulation on the local subpopulation. Also we search for an optimal vaccination rate that will be most effective to reduce the number of infected individuals. We apply stability analysis theory to understand the equilibrium states of the combined population. Many studies have been done in modeling the transmission dynamics of diseases in two interacting populations. We mention here some of the important articles that are relevant to our theme.

Jia et al., [21], discusses the impact of migrants on the transmission dynamics of tuberculosis in an SEIR model. They propose two models in this regard. Firstly they present an SEIR model without the recruitment of migrants in the infected (incubation period) and infectious classes. In this model they derive a threshold parameter which determines whether the disease will die out or will become endemic in the local populations. In the second model they assume that there is a recruitment of migrants in both the infected (incubation period) and infectious classes. In terms of the second model they find that the only way to eradicate the disease from the local population is by reducing the recruitment of migrants in the infected (incubation) class and infectious classes.

Piccolo and Billings [39] evaluate, in an SIR model, the effect of migrants on the transmission of childhood diseases such as rubella, measles, mumps and pertussis in the city of New York. They assume that the number of unvaccinated individuals among the migrants is a major factor contributing to making the childhood disease become endemic in the specific geographic area of their study. They derive a threshold parameter, which they call the vaccination reproductive number. Depending on the value of this parameter value, either the disease will die out (population free of disease) or will become endemic. This is the most important result from their work, especially the manner in which they analyze the interplay between the two population parts, migrant and local.

Zhou et al., [56] studies the effect of two distinct populations on the short-term incidence

and long-term transmission dynamics of tuberculosis (TB) in Canada. They formulate a discrete time epidemic model for modeling two populations, Canadian born and foreign born in Canada. They focus on the impact of latent TB class of migrants on the incidence of TB in Canada. In the short term study, they derive threshold parameters for both subpopulations, Canadian born and foreign born, to determine whether there will be TB outbreak or not. These parameters depend on the average rate of migrants and the level of importing the latent infection. Their model predicts that TB cases will increase among Canadian born populations and the TB will reemerge in Canada by 2012 if there is no intervention.

The paper of Jia et al., [21], supports the theory that migrants have considerable influence in transmission of most communicable diseases. The theoretical analysis they present contributes to better understanding the transmission of tuberculosis and also to help building more realistic models with control strategy. On the other hand, Piccolo and Billings conclude that the eradication of childhood disease depends on the rate of vaccination on both migrants and locals. They did not indicate the optimal vaccination strategy we should implement to achieve the disease free state. The work of Tumwiine et al., [48], also supports our hypothesis that the migrants population have a great influence in transmission of most communicable diseases. They use a discrete time model whereas in this dissertation we focus on continuous time modeling.

1.3 The two-group vaccination problem.

This study deals with the optimal vaccination strategy on a disease of SIR-type in two interacting populations, local and migrants. A similar combined population is refered to as a *two-group* population in the paper [51] of Yu et al. In this dissertation we use a deterministic continuous time SIR model of an epidemic under vaccination. The main purpose is to find an optimal vaccination strategy on the local subpopulation, aimed at reducing

the number of infected individuals while keeping the vaccination effort sufficiently low. To this end we need to understand the disease transmission mechanism in both subpopulations, and the threshold condition which determines whether the disease will invade the population or die out. In particular, if the disease invades the population we want to know what is the impact of migrants on the locals. Controlling the disease by vaccination prevention strategy we need to determine the optimal vaccination approach to eradicate the disease or to bring the threshold parameter to less than one.

In terms of analyzing the transmission dynamics of the disease, the study only focuses on analysis of two equilibrium solutions of the model. There are one disease free equilibrium and three endemic equilibria. On the disease free equilibria the study investigates the local asymptotic and global asymptotic stability. For the endemic cases we only chose the endemic point which depend on the infectious in both subpopulation, and we analyze the local asymptotic behavior. Also the study applies optimal control theory to find the optimal vaccination strategy for the local subpopulation only. The numerical simulation is run to solve the optimality problem and to compare the result with the model consisting of the two populations without vaccination.

Our basic assumption is that the vaccination rate in the migrant subpopulation is constant. Because the numbers in the migrant population is small, the vaccination rate among migrants can be done at a high percentage. Also we assume that only infected individuals from the migrant subpopulation can transmit the disease to the local susceptible and not vice versa.

Our objectives in this dissertation is as follows. Firstly we want to formulate an SIR epidemic model to study the transmission of disease in populations consisting of two groups, called migrants and locals. Secondly we want to study the quantitative behavior of the model. Thirdly we want to determine the mechanism of disease transmission and to understand which parameter value will lead to persistence of the diseases in the local

populations or die out. After determining the parameter that plays a substantial role in the threshold condition, we set an optimal control strategy to roll out the vaccination. Therefore the main problems addressed in this dissertation can be formulated as follows.

Problem 1.3.1 (SIR model for two-group population): How can we formulate an SIR epidemic model to accommodate two interacting subpopulations?

Problem 1.3.2 (Stability Analysis of Disease Free Equilibrium): Does a disease-free equilibrium of two subpopulations exist for the model in Problem 1.3.1., and what is its stability status?

Problem 1.3.3 (Stability Analysis of Endemic Equilibrium): Can we find the possible endemic equilibria and describe its stability when the disease free equilibria is unstable?

Problem 1.3.4 (An Optimal Vaccination Strategy): Can we apply optimal control theory for the model in Problem 1.3.1, to find an optimal vaccination strategy for the local populations? How can we find numerical solutions?

1.4 Dissertation outline.

The first chapter has an introduction to mathematical role in epidemiology modeling and SIR model. Also it gives an overview to the research problem and the objective of this dissertation.

Chapter two provides a literature review around SIR epidemic models. Firstly it present the evolution of an SIR epidemiology model, by presenting the most important contributions, and some methods of analysis and interpretation. Also it presents and discusses some research work related to incorporating vaccination into epidemiology modeling. The

models that accommodate two interacting populations are discussed. Finally we discuss some papers that present optimal control strategies in epidemic models.

Chapter three provides some mathematical preliminaries that are used throughout the rest of this dissertation. We present some definitions and notation about dynamical systems and stability analysis, and related theories which analyze such systems. Also we present some numerical computation examples for plotting the phase portrait and the trajectories of systems of ordinary differential equations. Theorems and lemmas from optimal control theory that are used in epidemiology modeling are presented.

Chapter four gives in detail an algorithm for calculating the threshold parameter called the basic reproduction number. We present the technique to calculate the basic reproduction number in a simple case and a more complex case by way of an example.

In chapter five we develop and analyze an SIR epidemiological model to study the transmission dynamics of communicable disease with vaccination, in two interacting populations. First we formulate a model with detail of assumption and description of parameters. Secondly we study the stability analysis of the disease free equilibrium and the endemic equilibrium. We derive the threshold condition that we use to prove the local and global stability of the disease free equilibrium and the local stability of the endemic equilibrium.

In chapter six we formulate an optimal control problem relating to the model presented in chapter five. We solve the control problem analytically and we run a numerical simulation to illustrate the behaviour of the solution. For a simple uniform population such a control problem was studied in [52] by Zaman et al. In our presentation we go more general, and we also observe some minor oversights of [52]. This leads to simplification of our problem.

Chapter seven sets out the conclusions and recommendations for further study. In particular we shall touch on work in progress on stochastic models on which we perform

stochastic control theory. The essence of chapter 5 and 6 of this dissertation is being prepared for publication see [5] of Ahmed and Witbooi.

Chapter 2

Literature review

2.1 Introduction

This chapter will briefly review the history of SIR epidemic model together with the method of analysis and epidemiological interpretation. The review will also include the history of vaccination in epidemiology modeling and optimal vaccination strategy in SIR models. The review will further highlight the historical background of using optimal control theory in epidemiology modeling and some background about models describing two interacting population.

2.2 Historical background of an SIR compartmental model

In this section we start of with some of the older work related to SIR epidemic compartmental model. Many of the early developments in the mathematical modeling of communicable diseases are due to public health physicians. The first known result in mathematical epidemiology is a defense of the practice of inoculation against smallpox in 1760 by Daniel Bernoulli, see Dietz and Heesterbeek [11] and Brauer et al., [7].

In 1927 Kermack and McKendrick [30] proposed a basic compartmental model to describe the transmission of a communicable disease. The basic assumptions they made is that

- the total population is of constant size, say N,
- the average infective makes contact, sufficient to transmit infection with βN others per unit time,
- a fraction α of infectives leave the infective class per unit time (or the average time of recovering from the disease is $\frac{1}{\alpha}$).

Figure 2.1 shows the dynamics of diseases in a simple SIR model proposed by Kermack and McKendrick. Their model is described by a set of three ordinary differential equations as follows,

$$\frac{ds}{dt} = -\beta si, \quad \frac{di}{dt} = \beta si - \alpha i, \quad \frac{dr}{dt} = \alpha i$$

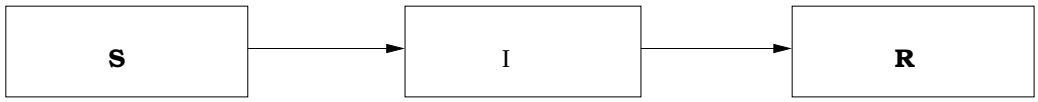


Figure 2.1: Diagram of Kermack and McKendrick SIR model

However Kermack and McKendrick did not consider the demographic effects on the population, assuming that the infective time is short and so they do not consider births and deaths. Also their model assume that all infected members will recover so the total populations size are given by $N = S + I + R$. Nevertheless, the only difference between this old model and the modern basic SIR-model such as that of Hattaf and Yousfi [19] or Zaman et al., [52], is that the new models take into account births and deaths. So the model of Kermack and McKendrick was really a significant advance.

Jianwen and Qiuying [23] presented an SIR epidemic model with age structure, consisting of immature and mature. In their model they studied the global dynamic behavior of the disease free equilibrium and endemic equilibrium, using as a threshold parameter the basic reproduction number σ. They find that the disease free equilibrium is globally asymptotically stable if $\sigma < 1$. On the other hand if the disease free equilibrium is unstable, they proved that there exists an endemic equilibrium and it is globally asymptotically stable if $\sigma > 1$.

Suzanne et al., [37], proposed an SIR epidemic model under the following assumption. The basic assumption is that all offspring are born healthy and thus are considered members of the susceptible class. Also they assumed that the influx of the newborns into the population is proportional to the population size and that the spread of the infection occurs according to the principle of mass action. The mass action law in epidemiology modeling it means that the average number of adequated contacts of persons per unit time increases linearly with the population size, see Hethcote [17]. The global stability of the endemic equilibrium for the model is established in their paper. Also they proved the global stability by constructing a new Lyapunov function for a variety of SIR models in epidemiology.

Khan et al., [29], studied the analytic solution to an SIR epidemic model. They applied a homotopy analysis method for nonlinear differential equations to solve the model analytically. The homotopy analysis method means that the original nonlinear differential equations are replaced by an infinite number of linear subproblems with decoupled linear differential equations. They obtained the explicit series solutions for an SIR model, and a parameter called the convergence control parameter. They use the control parameter to ensure the convergence of the explicit series solution. Also they compare their analytic results with the numerical ones and they found a good comparison.

Awawdeh et al., [3] introduced an SIR model for the spread of nonfatal disease in a population. They studied the accuracy of the Homotopy Analysis Method , for solving this model. Their analytic approximations to the solutions of the epidemic model showed that the Homotopy Analysis Method avoids the difficulties and massive computational work that usually arise from parallel techniques and finite-difference method.

Jiang and Wei [24] proposed a time delayed SIR model with nonlinear incidence rate. By analyzing the distribution of the characteristic values they obtained the existence of Hopf bifurcations at the endemic equilibrium. Also they use the normal form and the center manifold theory to determine the direction of the Hopf bifurcations and the stability of the bifurcating periodic solutions.

Zhang et al., [54] incorporated a constant infectious period in an SIR epidemic model which regard it as time delay. They studied the stability analysis of the disease free equilibrium and endemic equilibrium using Lyapunov functions. Also they derive conditions for global stability of the endemic equilibrium. Their study shows that introduction of distributed delays for non-cyclic infectious disease models do not change local asymptotic behavior of the models; that is, distributed delays can not lead to periodic solutions.

Li et al., [32] presented an SIR epidemic model with nonlinear incidence to simulate the limited resources for the treatment of the patients. They assumed that the rate of treatment is proportional to the number of infectives below the capacity of treatment, and is constant when the number of infectives is greater than the capacity. They showed that the backward bifurcation occur because of the insufficient capacity for treatment. Also they showed that the model has a bistable equilibrium because of limited resource. The basic reproduction number being below one is not enough to eradicate the disease. The level of initial infectious invasion must be lowered to a threshold so that the disease dies out or approaches an endemic equilibrium.

Chinviriyasit and Chinviriyasit [10] modeled the transmission dynamics of whooping cough disease by a spatial SIR reaction-diffusion model. Using linearization and Lyapunov functions they derived sufficient conditions for local and global asymptotic stability respectively. Their main result is that the disease free equilibrium is globally asymptotically stable if the contact rate is small. Also they showed that the dynamics of whooping cough depends on the diffusion rate and the contact rate.

However the SIR model is formulated according to the transmission mechanism of the specific disease. So there are some models considering age structure such as the model presented by Jianwen and Qiuying [23]. They incorporate the demography (immature and mature) in an SIR model. The daily contact rate is the average number of contacts per infective per day. A contact of an infective is an interaction which results in infection of the other individual if he /she is susceptible. Thus the average number of susceptibles infected by an infective per day is βS (β is the contact rate and S is the number of susceptible individuals), and the average number of susceptible infected by the infective class with size NI (N is total population size and I is the number of infective individuals) per day is βNIS. The daily contact rate β is fixed and does not vary seasonally. This type of incidence is called *standard incidence*. For more about standard incidence see Hethcote [16]. Suzanne et al., [37] they assume that the spread of the infection occurs according to the principle of *mass action* instead of the *standard incidence*. According to their assumption the influx of the newborns into the population is proportional to the population size and the force of the infection.

Nevertheless the analytical solution to a nonlinear system of differential equation is difficult if not impossible. Development of methods for analytical solutions is important and its comparison with numerical one will lead to accurate results. There is some recent work in epidemiology modeling such as the work presented by Khan et al., [29], and Awawdeh et al., [3]. They use the approach of Homotopy Analysis Methods for approximating the analytical solutions. But the numerical solution is good for graphically illustrating the

evolution of the model.

In epidemiology modeling, the model formulation depends on the characteristics of the particular disease being modeled and the purpose of the model. For some type of diseases there will be need for considering a time delay, in which delay is a means of modeling incubation of pathogen, see [53] of Zaman et al., for delay model. Model in this type is presented by Zhang et al., [54], Jiang and Wei [24].

The SIR model have become important tools in analyzing the spread and control of infectious diseases. The work presented by Li et al., [32] shows we can use an SIR model to control the limited resources for treatment of the patients.

2.3 Incorporating vaccination in an SIR model

Infectious diseases constitute the leading cause of death in developing countries. For hundreds of years, medical scientists have sought to intervene and prevent infection by inducing immunity through the use of vaccination. Scientists have largely been successful in developing vaccines against a wide array of viruses and bacteria, thereby eliminating many childhood diseases due to infectious diseases. Mathematical modeling of infectious diseases plays a substantial role in determining which vaccination rate and time that should be applied to eradicate the specific diseases.

In this subsection we list some work which incorporate a vaccination strategy into an SIR epidemic models. Since we focus on continuous time models we focus on continuous time vaccination. However we shall point also to the so-called pulse vaccination.

Makinde [35] developed an SIR model that monitors the temporal dynamics of a childhood disease in the presence of preventive vaccination. The vaccination reproductive number for disease control and eradication is derived. The approximation to the solution of the non-linear system of differential equations governing the model, is obtained. This sup-

ports analytical solutions, one of the few cases in the literature. Note that we have earlier refered to analytical solutions in the case of Homotopy Analysis Methods see section (2.2).

Gakkhar and Negi [15] proposed an SIRS epidemic model with impulsive vaccination. Their stability analysis showed that the disease free periodic solution of the impulsive model is globally asymptotically stable if the basic reproduction number is less than one. Also a super critical bifurcation exists if the basic reproduction number is equal to one. Also they prove that if the infection free periodic solution is unstable then the infection free periodic solution is lost and infective begins to oscillate with large amplitude that corresponds to periodic burst of epidemic.

Jiang and Yang [24] studied bifurcation analysis of an SIR epidemic model with birth pulse and pulse vaccination. The numerical results show that the epidemic periodic solution (period-one) bifurcates from the infection-free period solution through a supercritical bifurcation.

d'Onofrio et al., [12] studied the implications of information dependent vaccination, jointly with rational exemption for the dynamics and control of an SIR childhood vaccine preventable infectious diseases. They assumed that a component of the overall vaccination coverage is positively correlated with the available information on the disease. The main result is that if the steady component of vaccination is below the critical elimination threshold, there is no hope to eliminate the disease. A further main consequence of information dependent vaccination is the onset of sustained oscillations. In other words stable oscillations appear when parents, in deciding on whether to vaccinate or not their children, make use of past and not only current information about the disease.

The vaccination strategies discussed in the aforementioned is refered to in the literature as *constant* vaccination. The *pulse vaccination* strategy means repeated application of vaccine over a defined age range. This approach is gaining prominence as a strategy for

elimination of childhood viral infectious such as measles, hepatitis and smallpox, see Meng and Chen [34]. Models with pulse vaccination strategy are also presented by Gakkhar and Negi [15], Jiang and Yang [24], Agur at al., [1], and in [43] Shi et al. In the popular paper [1] of Agur et al., they study a pulse vaccination strategy on a population in which there was a persistence of a measles, with major epidemics roughly every 5 years. Their numerical results show that applying a pulse vaccination strategy every 5 year will prevent the disease. Nevertheless, there was of course a need for more sophisticated pulse vaccination models. One such model can be found in [43] by Shi et al. In [43] they presented an SIR epidemic model to study the effect of impulsive vaccination. They obtained a condition that determines whether the disease will be eradicated or become endemic. In terms of the endemic or persistence situation they introduce an impulsive vaccination strategy, and they find a sufficient condition for the global asymptotic stability for the disease free equilibrium. Also if the impulsive vaccination rate is less than some value, then the disease will become endemic.

2.4 Two interacting populations

Here we present some work related to a two interacting population, or two group models. Piccolo and Billings [39] evaluated, in an SIR model, the effect of migrants on the transmission of childhood diseases in New York. They assumed that the number of unvaccinated individuals among the migrants is a major factor contributing to making the childhood disease become endemic in the specific geographic area of their study. They derived a threshold parameter, which they call the vaccination reproduction number. Depending on the value of this parameter value, either the disease will die out or will become endemic. The model in this dissertation is in some sense related to that of [39], using ideas also from [21], see below.

Jia et al., [21] presented two epidemic models to investigate the impact of immigration

on the transmission dynamics of tuberculosis. For the first model they presented a new analysis on the existence and stability of equilibrium. Their primary finding is that the disease will not die out even though the basic reproductive number of the local subpopulation is less than one given that the basic reproductive number of immigrants is greater than one. They apply the model on the Canadian reported data, and they found that the model suggests that the disease cannot be eradicated in Canada by only reducing the basic reproduction number for the local subpopulation.

Zhou et al., [56] proposed a model of tuberculosis transmission in two demographically distinct populations, Canadian born and foreign born populations, to study the impact of immigration latent tuberculosis cases on the overall tuberculosis incidence rate in the whole population. They derived two basic reproduction numbers for both subgroups. They found that these two basic reproductions with average immigration rate and the level of importing the latent infection, decide whether there will be a tuberculosis epidemic in these subgroups, and determine the levels of such an epidemic if it occurs. Also they used Canadian immigration and tuberculosis incidence case data during 1991-2000 and also validated their model and parameter value using data from 2001-2005. They conclude that the TB infection rate in the Canadian born population is growing slowly and this infection will reach high rates in 2012, and every active TB case will produce more than one new infectious TB case. As a result, TB cases will increase again among the Canadian born population, unless there is intervention.

In a malaria study, Tumwiine et al., [48] introduced an epidemic model for transmission dynamics of malaria in host populations with constant immigration. Their stability analysis found that due to immigration of infective individuals, the model cannot have a disease free equilibrium state and has only the endemic equilibrium point in which the disease persists in the population for long time. Also they derive a basic reproduction number which determines whether the disease can be reduced in the community, when the fraction of infective immigrants approaches a small value.

An important and challenging problem in epidemiological modeling is to describe the presence of more than one disease in a population. So, for instance, Bacaër et al., [6] presented an epidemic model for interaction between HIV and TB. They studied various control measures, namely condom promotion, increased TB detection, TB preventive therapy and antiretroviral therapy on HIV infected individuals.

The work of Piccolo and Billings [39] gives a highlight on modeling two interacting population, in particular the impact of migrant on the transmission of the childhood diseases. Jia et al., [21], extend the idea of Piccolo and Billings [39] to study the dynamics of tuberculosis in two population. This trend leads to improving the modeling of two-groups and deep understanding of the interaction between the groups. Also the model presented by Zhou et al., [56], describes a real situation of tuberculosis evolution in Canada and predict the future of this disease. In addition the most important threats on the tuberculosis is its co-existence with the HIV infection. So the models in [6] presented by Bacaër et al., contribute to a better understanding of the interaction between those two diseases (tuberculosis and HIV). The results from Jia et al., [21] and Zhou et al., [56], will help the researcher to develop a good control strategy for tuberculosis, and the importance of the results [6] of Bacaër et al., is to consider the co-existence when setting any control strategy for tuberculosis.

2.5 Optimal control strategy

This section presents some work related to incorporating the optimal control theory in the disease control strategy. In particular we can mention that the book [31] of Lenhart and Workman is a popular reference for the models of control in epidemiology.

A control strategy with vaccination in a general SIR setting appears in the paper [52] of

Zaman et al. Their stability analysis to the model shows the sufficient condition that determine whether the model is stable or unstable. In the case of the stable model, the level of initial infectious invasion must be lowered to the initial value so the diseases disappear. Secondly they proposed an optimal vaccination strategy to the model, to minimize the number of infected individuals and to maximize the number of recovered individuals. The basic assumption is that a fixed percentage of the susceptible population are vaccinated. The numerical result of the control problem shows that the number of susceptible and infected individuals decrease and the number of recovereds increase.

Vaccination is one method of intervention in epidemiology. There are of course various other methods. Karrakchou et al., [27] presents an optimal control problem on an HIV/AIDS model with chemotherapy treatment. They study the role of chemotherapy treatment in controlling the virus reproduction. Also they prove the existence and uniqueness of the optimal control solution. Their numerical result shows the efficiency of chemotherapy.

Bowong [8] posed the problem of optimal control of the transmission dynamics of tuberculosis. He developed a tuberculosis model with exogenous reinfection and chemoprophylaxis of latently infected individuals, and treatment of the infectious. In the qualitative dynamics analysis of the model, he finds that there exists a backward bifurcation to the model. The stable disease free equilibrium coexist with the endemic equilibrium, when the basic reproduction number is less than a unity. Also he shows that this backward bifurcation is caused by the reinfection of latently infected individuals. Based on this model, he formulates an optimal control problem, to reduce the number of individuals with active tuberculosis, by assuming the chemoprophylaxis as control term. The control result shows that controlling exogenous reinfection using chemoprophylaxis in reducing the number of actively infected individuals with tuberculosis is important.

Again in an SIR setting, in the paper [47] of Tchuenche et al., is presented an influenza

pandemic model with vaccination and treatment. They consider three control variables, the rate at which vaccine wanes, the effectiveness of vaccination, and the effectiveness of the treatment. The objective of their optimal control problem is to maximize the efficacy of vaccination. Also to minimize the cost and the side effects of the drug usage and total number of infected population within a given community subject to emigration. Solution of the control problem shows that a full treatment effort should be given while increasing vaccination at the onset of the outbreak.

Hattaf et al., [19] applied the optimal control theory for the model of a tuberculosis disease with exogenous reinfection. They propose an optimal control problem to reduce the infectious group by the reduction of the contact between infectious and exposed individual. They consider the prevention of exogenous reinfection as control variable. The control solution shows the effectiveness of introducing control that prevents the exogenous reinfection by sensitizing the latent individuals not to have contact with the infectious individuals with active tuberculosis, particularly in an enclosed place.

Following on their previous work, Zaman et al., [53] introduced an optimal technique to an SIR epidemic model with delay, in which to prevent the spread of infected individuals. Considering the treatment of infectious as control variable, they formulate the optimal control problem to minimize the probability that the infected individuals spread and maximize the total number of susceptible and recovered individuals. Their numerical solution to the control system shows that, applying the optimal treatment strategy, is very effective to reduce the spread of infection as well as the total number of infected individuals. Also they apply their optimal treatment strategy to Ebola virus of the Congo, in a specific community. They find that the basic reproduction number from the control system is less than unity so the infection in the community dies out.

Sani and Kroese [41] formulated various mathematical control problems for HIV spread in mobile heterosexual populations, and show how optimal regional control strategies can

be obtained that minimize the national spread of HIV. Their numerical results indicate that the shape of the control functions for different models are qualitatively similar. Also the shape of the control depends on the time horizon, available budget, and the initial number of infectives. Besides HIV/AIDS and TB, another terrible disease in Africa and globally is the vector-borne disease malaria. The forthcoming paper of [36] Okosun et al., studies the optimal control of malaria through the methods of using bednets and using insecticide.

Concluding this chapter we can mention that the models of Piccolo and Billings [39] and of Jia et al., [21], are very similar to the model we present in this dissertation. However, we take the discussion one level further by doing the optimal control.

Chapter 3

Mathematical tools and terminology

3.1 Introduction

This chapter presents some basic mathematical tools and epidemiology concepts. The definitions and theory from dynamical systems related to epidemiology modeling and optimal control concepts that are used throughout this study are presented. For more information we refer to the books of Arrowsmith and Place [2], Mohana [40] and Lenhart and Workman [31].

3.2 Stability analysis and dynamical systems

Consider the following nonlinear system of ordinary differential equation (3.1) and its associated linear system (3.2):

$$\dot{x} = f(x) \tag{3.1}$$

$$\dot{y} = Ay \tag{3.2}$$

with the matrix $A = Df(x_0)$ in a neighborhood of the point x_0 (x_0 is an equilibrium point see definition 3.2.1).

Definition 3.2.1 (See Perko [38]). A point $x_0 \in \mathbb{R}^n$ is called an *equilibrium point* or *critical point* of (3.1) if $f(x_0) = 0$. An equilibrium point x_0 is called a *hyperbolic* equilibrium point of (3.1) if none of the eigenvalues of the matrix $Df(x_0)$ have zero real part. The linear system (3.2) with the matrix $A = Df(x_0)$ is called the linearization of (3.1) at x_0.

Proposition 3.2.2. (see Arrowsmith and Place[2]). *Let A be a real 2×2 matrix, then there is a real, non-singular matrix M such that $J = M^{-1}AM$ is one of the types:*

$$(a) = \begin{vmatrix} \lambda_1 & 0 \\ 0 & \lambda_2 \end{vmatrix}; \quad (b) = \begin{vmatrix} \lambda_0 & 0 \\ 0 & \lambda_0 \end{vmatrix}; \quad (c) = \begin{vmatrix} \lambda_0 & 1 \\ 0 & \lambda_0 \end{vmatrix}; \quad (d) = \begin{vmatrix} \alpha & -\beta \\ \beta & \alpha \end{vmatrix},$$

where $\lambda_0,\ \lambda_1,\ \lambda_2,\ \alpha,\ \beta$. are real numbers. □

Consider a two dimensional linear system, with A being a constant,

$$\dot{x} = Ax. \tag{3.3}$$

The equivalent canonical system to the linear system (3.3) is

$$\dot{y} = Jy. \tag{3.4}$$

Here $J = M^{-1}AM$ is the Jordan form of A and $x = My$.

Definition 3.2.3 (see Arrowsmith and Place [2]) A linear system (3.3) is said to be *simple* if the matrix A is non-singular (determinant of A not equal to zero, and A has non-zero eigenvalues).

Types of equilibrium point for canonical systems 3.2.4. (see Arrowsmith and Place [2]) The canonical system corresponding to a simple linear system is also simple because the eigenvalue of the linear one is the same as the canonical.

- If the eigenvalues of the linear system are real, distinct, then the equilibrium point is a *stable (unstable) node* when all the trajectories are oriented towards (away from) the fixed point.

- If the eigenvalues of the linear system are equal, then the equilibrium point is a *star*.
- If the eigenvalues of the linear system are complex, then the equilibrium point is a *focus or spiral or center*.

Theorem 3.2.4 (Linearization theorem), (see Arrowsmith and Place [2]). *Suppose that the nonlinear system (3.1) have a simple critical point at $x = 0$. Then, in a neighborhood of the origin the phase portraits of the system and its linearization are qualitatively equivalent provided the linearized system is not a center.*

Definition 3.2.5 (See Mohana [40]). Consider the following system of ordinary differential equations (3.4) with the initial condition (3.5),

$$\dot{x} = F(t, x), \tag{3.4}$$

$$x(0) = x_0. \tag{3.5}$$

where $x(t)$ is the vector valued function defined by $x(t) = (x_1(t), ..., x_n(t))$ and $F(t, x) = (F_1(t, x), ..., F_n(t, x))$. Let $x(t, t_0, x_0)$ be a solution to the system (3.4) and (3.5). Then we define the stability of a solution of system (3.4) as follows. A given solution $x(t)$ of the system is *stable* if for each $\epsilon > 0$, there exists a $\delta = \delta(\epsilon) > 0$ such that, for any solution $\bar{x(t)} = x(t, t_0, \bar{x_0})$ for (3.4) and (3.5), the inequality $\|\bar{x_0} - x_0\| \leq \delta$ implies $\|\bar{x}(t) - x(t)\| < \epsilon$ for all $t \geq 0$.

Definition 3.2.6 (See Arrowsmith and Place[2]). The solution of (3.4) and (3.5) is called *asymptotically stable* if it is stable and if there exists a $\delta_0 > 0$ such that $\|\bar{x_0} - x_0\| \leq \delta$ implies $\|\bar{x(t)} - x(t)\| \to 0$ as $t \to \infty$.

Definition 3.2.7 (See Arrowsmith and Place[2]). A solution of (3.4) and (3.5) is said to be *unstable* if it is not stable.

Definition 3.2.8 (See Slotine and Li [44]). The equilibrium point is *globally asymptotically stable* if asymptotic stability holds for all initial states.
The equilibrium point is also said to be asymptotically stable in the large an alternative equivalent term to global asymptotic stability.

Theorem 3.2.9 (See Wiggins [50]). *Let $(x_0, t_0) \in U$. Then there exists a solution of the equation*

$$\dot{x} = f(x, t) \tag{3.6}$$

through the point x_0 at $t = t_0$, denoted $x(t, t_0, x_0)$ with $x(t_0, t_0, x_0) = x_0$, for $|t - t_0|$ sufficiently small. This solution is unique in the sense that any other solution of equation 3.6 through x_0 at $t = t_0$ must be the same as $x(t, t_0, x_0)$ on their common interval of existence. Moreover, $x(t, t_0, x_0)$ is a C^r function of t, t_0 and x_0.

Theorem 3.2.10 (See Wiggins [50]). *The solution $x(t, t_0, x_0)$ can be uniquely extended backward and forward in t up to the boundary of C.*

3.3 A simple epidemic model and phase portrait

Consider the simple SIR epidemic model below (see Hethcote [17]). The phase plane or the direction field is a graphical representation of the solutions of a first-order differential equation. It is achieved without solving the differential equation analytically, and thus it is useful. The representation may be used to qualitatively visualize solutions, or to numerically approximate them. Figure 3.1 (page 27) shows the direction field of the following model,

$$\frac{ds}{dt} = -\beta si, \quad \frac{di}{dt} = \beta Si - \gamma i, \quad \frac{dr}{dt} = \gamma i. \tag{3.7}$$

which is the model of Kermack and McKendrick [30]. Note that the constraint $N = s(t) + i(t) + r(t)$, and with N constraint means that essentially we need only two variables

to describe the system. Moreover, the quantity r never appears on the right hand side. Thus we can work very conveniently with only s and i. The phase diagram displays the points $(s(t), i(t))$ for the same domain of t.

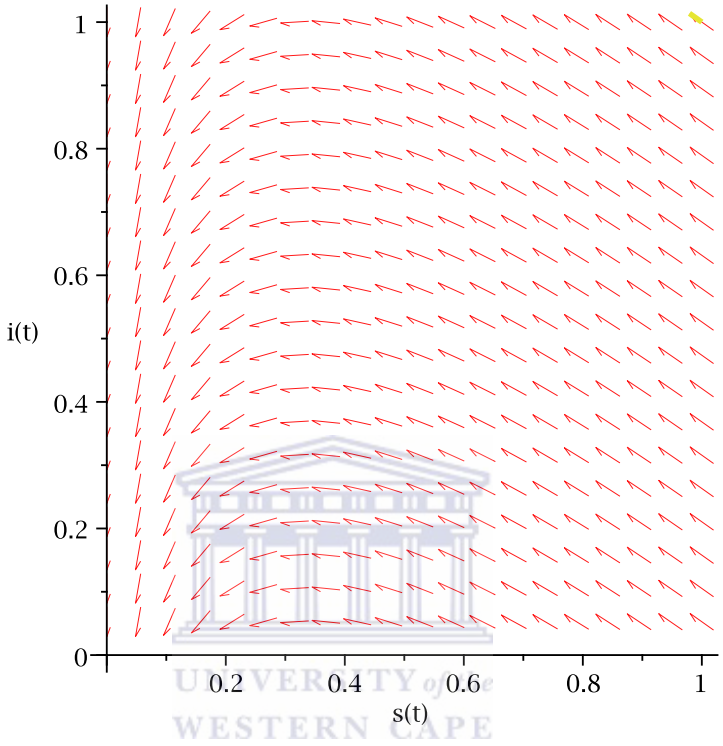


Figure 3.1: Direction field of a simple SIR model

3.4 Numerical solution to the system of differential equation

. Consider the following system of ordinary differential equations.

$$\frac{dx(t)}{dt} = -0.1x(t), \qquad \frac{dy(t)}{dt} = 0.1x(t) - 0.2y(t), \qquad \frac{dz(t)}{dt} = 0.2y(t) \tag{3.8}$$

The initial condition : $x(0) = 1, y(0) = 0$ and $z(0) = 0$.

The numerical solution to the system (3.8) is presented in the Figure 3.2.

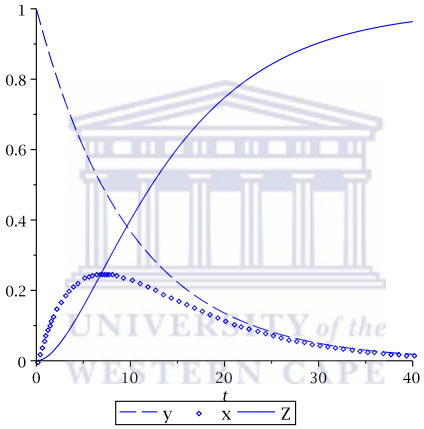


Figure 3.2: Trajectory for a simple SIR model

3.5 Optimal control theory

The following is a popular kind of control problem in epidemiology. Consider the functional

$$J(u) = \int_{t_0}^{t_1} f_0(x(t), u(t), t)dt \tag{3.9}$$

The function $J(u)$ depends on a function u. Our problem is to maximize $J(u)$ subject to the condition:

$$\dot{x}(t) = f(x(t), u(t), t), \tag{3.10}$$

with the initial condition $x(t_0) = x_0$ (3.11)

terminal condition, $(a)x(t_1) = x_1$ or $(b)\ x(t_1) \geq x_1$ or $(c)\ x(t_1)$ free (3.12)

and the control variable restriction $u(t) \in U$, where U is a given subset on the real line.

Theorem 3.5.1 (Pontryagin maximum principle): (see Seierstadt and Sydsaeter [42]). *Let $u^*(t)$ be piecewise continuous function defined on $[t_0, t_1]$ which solves problem (3.9) to (3.12) and let $x^*(t)$ be the associated optimal path. Then there exists a constant p_0 and a continuous and piecewise continuously differentiable function $p(t)$ such that for all $t \in [t_0, t_1]$, we have*

$(p_0, p(t)) \neq 0$.

If $u^*(t)$ maximize $H(x^*(t), u(t), p(t), t)$ for all $u \in U$, that is

$$H(x^*(t), u^*(t), p(t), t) \geq H(x^*(t), u(t), p(t), t),$$

for all $u \in U$ except at the point of discontinuities of $u^*(t)$, then we must have

$$\dot{p}(t) = -\frac{\partial H}{\partial x} \quad \text{where} \quad \frac{\partial H^*}{\partial x} = H_x^{'}(x^*(t), u^*(t), p(t), t).$$

Furthermore, $p_0 = 1$ or $p_0 = 0$. Finally, to each of the terminal conditions $(a), (b), (c)$ in (3.12) there corresponds a transversality condition:

$p(t_1)$ no condition, $p(t_1) \geq 0$, $p(t_1) = 0$ if $x^*(t_1) > x_1$ and $p(t_1) = 0$.

Existence of optimal control 3.5.2 (see Seierstadt and Sydsaeter [42]). Consider the following ordinary differential equation

$$\dot{x} = g(t, x(t), u(t)), \tag{3.13}$$

and suppose the control problem associated with the equation (3.13) is given as follows: Maximize the functional

$$J(u) = \int_{t_0}^{t_1} f(t, x(t), u(t))dt, \tag{3.14}$$

subject to $\dot{x} = g(t, x(t), u(t))$ $x(t_0) = x_0$ and $x(t_1)$ free.

Then the existence theorem for an optimal control is stated as follows.

Theorem 3.5.3 (see Seierstadt and Sydsaeter [42]) *Let the set of controls for problem (3.9) be Lebesgue integrable functions (instead of just piecewise continuous functions) on $t_0 \leq t \leq t_1$ with values in $\mathbb{R}$. Suppose that $f(t, x, u)$ is convex in u, and there exist constants C_4 and $C_1, C_2, C_3 > 0$ and $\beta > 1$ such that*

$$g(t, x, u) = \alpha(t, x) + \beta(t, x)u$$

$$|g(t, x, u)| \leq C_1(1 + |x| + |u|)$$

$$|g(t, x, u) - g(t, xu)| \leq C_2 |x_1 - x| (1 + |u|)$$

$$f(t, x, u) \geq C_3 |u|^{\beta} - C_4$$

for all t with $t_0 \leq t \leq t_1, x, x_1, u$ in R. Then there exists an optimal control u^* maximizing $J(u)$, with $J(u^*)$ finite.

We also note the following very useful lemma.

Lemma 3.5.4 *In Pontryagin Maximum Principle, the constant P_0 is zero if the objective function is convex or concave.*

Chapter 4

The basic reproduction number

4.1 Introduction

To estimate the fate of introducing few number of infected individuals into a completely susceptible population, there is a threshold parameter called the basic reproduction number which is a very useful tool to determine whether the disease will outbreak or not. We define the basic reproduction number as the expected number of secondary cases produced in a completely susceptible population by a typical infective individual and we denote it by the symbol R_0, see Hethcote [17]. This chapter presents a complete algorithm to calculate the basic reproduction number (*See* van den Driessche [49]). We present the algorithm for a simple example in which the basic reproduction number can be calculated directly, and then we also apply it to a more complex case. We give a description of the theory, and we demonstrate it by way of a calculational example 4.2.1, pertaining to an SEIR-model.

4.2 Basic reproduction number for a simple model.

The number of secondary infections produced by a single infected individual can be expressed as the product of the expected duration of the infectious period and the rate at

which secondary infections occur. In the simple model which includes only one infected compartment we can calculate R_0 directly. For complex models we use the so-called next generation matrix approach to compute or to estimate R_0. Here we give an example for a simple SIR epidemic model in which the estimate of R_0 it will be direct.

Example 4.2.1 Consider the SIR compartment epidemic model presented by Hethcote [17].

$$\frac{dS}{dt} = \frac{-\beta IS}{N}, \qquad S(0) = S_0 \leq 0$$

$$\frac{dI}{dt} = \frac{\beta IS}{N} - \gamma I, \qquad I(0) = I_0 \tag{4.1}$$

$$\frac{dR}{dt} = \gamma I.$$

Here $S(t)$ is the number of susceptible at time t and $I(t)$, $R(t)$ is the number of infective and recovered respectively, N is the total population. The subscript β is the average number of adequate contacts between susceptible and infective which is sufficient for transmission and

$$\frac{\beta I}{N}$$

is the average number of contacts with infective per unit time of one susceptible, and

$$\frac{\beta IS}{N}$$

is the number of new cases per unit time. By definition the basic reproduction number is the product of the infection rate and the mean duration of the infection it follows.

$$R_0 = \frac{\beta}{\gamma}. \tag{4.2}$$

4.3 Basic reproduction number for a general compartmental model

If the model contains several infected compartments, for instance, latent period and infection period, then R_0 can not be determined directly from the definition as in section (4.2). In this case we introduce an algorithm to calculate R_0 for a general compartmental epidemic model. Consider the general compartment model in Equation (4.3) below, which models the dynamic of the transmission of a disease in a heterogeneous population in which the individuals can be distinguishable by the stage of the disease, spatial position, and age, but can be grouped into n homogeneous compartments according to stage of disease (susceptible, infected, infectious,...), see van den Driessche [49].

$$\dot{x}_i = f_i(x) = F_i(x) - V_i^-(x) + V_i^+(x), i = 1, ..., n. \tag{4.3}$$

Regarding the system (4.3), let $x = (x_1, ..., x_n)'$ where $x_i \leq 0$ is the number of individuals in each compartment and also we assume that the first m compartments are related to infected individuals, so the $m+1, ..., n$ correspond to those compartments free of disease. Let $X_q = \{x_i \geq 0 \mid x_i = 0 \text{ for } i = 1, ..., m\}$ be the set of disease free states (all compartment with absence of disease). Regarding the system (4.3), let $F_i(x)$ be the rate of appearance of new infections into compartment i, $V_i^-(x)$ be the rate of transfer of individuals out of compartment i and $V_i^+(x)$ the rate of transfer of individuals into compartment i. Also we assume that all these functions are continuous and differentiable at least twice in each variable (x_i) and also they satisfy the following five assumptions.

Assumption one: If $x \geq 0$, then $F_i(x), V_i^-(x), V_i^+(x)$ are all non-negative since each of these functions describe the transition of individuals between compartments.

Assumption two: If $x_i = 0$ then $V_i^-(x) = 0$. If the number of individuals in each compartment is equal to zero then there is no transfer of individuals out of the compartment. In particular if x is the number of individuals in disease state, then the rate of transfer of individual $V_i^-(x)$ will be zero for infected compartments.

Assumption three: $F_i(x) = 0$ if $i > m$. This means that the rate of appearance of new infections into the disease free state is zero. Consider the model in system (4.3) with Assumptions one and two. If $x_i = 0$ then the system 4.3 will become $\dot{x}_i = f_i(x) = F_i + V_i^+ \geq 0$. Hence all the initial variables are nonnegative, and so the system is invariant. From Theorem 3.2.9 and 3.2.10 we conclude that for any nonnegative initial conditions there are unique nonnegative solutions.

Assumption four: If $x \in X_q$, then $F_i(x) = 0$ and $V_i^+(x) = 0$ for $i = 1, ..., m$, this indicates that if the number of individual x is the set of disease free state there will be no transfer out to infected compartment, so in this case we will say that the disease free state is invariant because if the population is free of disease then the population will remain free of disease.

Assumption five: consider the system (4.3) restricted on the set of disease free state X_q, we define the DFE and we subscript it by x_0 to be the local asymptotically stable equilibrium solution to our model restricted to X_q. If $F_i(x) = 0$ all the eigenvalues of the Jacobian matrix $Df(x_0)(x - x_0)$ (which is calculated from system (4.3) around equilibrium point x_0) have negative real part,

$$\dot{x}_i = Df_i(x_0)(x - x_0) = DF(x_0) - DV(x_0). \tag{4.4}$$

where $V(x_0) = V^- - V^+$.

From the standard linearization theorem we know that if all the eigenvalue of the system have negative real part then the equilibrium point is locally asymptotically stable. In what follows we find the derivatives DF_i and DV_i.

Lemma 4.3.1 van den Driessche [49]. *If x_0 is a disease free equilibrium of (4.3) and $f_i(x)$ satisfies (i to v) then the derivatives $DF(x_0)$ and $D\upsilon(X_0)$ are partitioned as*

$$DF(x_0) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix} \qquad D\upsilon(X_0) = \begin{pmatrix} V & 0 \\ J_3 & J_4 \end{pmatrix}$$

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

$$F = \left(\frac{\partial F_i(x_0)}{\partial x_j}\right) \quad V = \left(\frac{\partial V_i(x_0}{\partial x_j}\right)$$

Further, F is nonnegative, V is a nonsingular M-matrix and all eigenvalues of J_4 have positive real parts.

4.4 Calculating the basic reproduction number.

By setting $F_i = 0$ in the system (4.4) we will get the following system,

$$\dot{x}_i = -DV(x_0)(x - x_0) \qquad (4.5).$$

It is obvious that from assumption five and the linearization theorem that the disease free equilibrium in (4.3) is locally asymptotic stable. From the definition of R_0 we want to determine the number of new infections produced by introducing an atypical infection into a completely susceptible population. Let $\Psi_i(0)$ be the number of infected individuals initially in the compartment i, and let $\Psi(t) = (\Psi_1(t), ..., \Psi_m(t))$ denote this initial infected remaining in compartment i after time t. The derivative of Ψ is given by the multiplication of the rate of transfer of individual into and out of the compartment and the $\Psi(t)$ as given in equation (4.6) below.

$$\dot{\Psi}(t) = -V\Psi(t). \tag{4.6}$$

The solution of equation (4.6) is

$$\Psi(t) = \Psi(0)e^{-Vt}.$$

Now integrating $F\Psi(t)$ from zero to infinity yields the expected number of new infections produced by the initially infected individuals.

$$\int_0^\infty F\Psi(t)dt = \int_0^\infty Fe^{-Vt}\Psi(0)dt = F\frac{1}{V}\Psi(0). \tag{4.7}$$

From Lemma 3.1 V is a nonsingular M-matrix and is therefore invertible and all of its eigenvalues have positive real part. So the equation in 4.7 becomes

$$FV^{-1}\Psi(0). \tag{4.8}$$

Now we use the next generation matrix technique to find the definition of R_0 from interpreting the result in 4.8, but first we will give the definition of the next generation matrix. If there are multiple discrete types of infected individuals (Humans and mosquitoes; Humans, dogs, and chickens), then the *next generation matrix* is defined as a square matrix G in which the ij^{th} element g_{ij} of G, is the expected number of secondary infections of type i caused by a single infected individual of type j, and assume that population of type i is entirely susceptible. The next generation matrix also satisfies some properties, it is a non-negative matrix and, as such, it is guaranteed that there will be a single, unique

eigenvalue which is positive, real, and strictly greater than all the others. Consider the the fate of an infected individual introduced into compartment k of a disease free equilibrium. The (j,k) entry of V^{-1} is the average length of time this individual spends in compartment j during its lifetime, assuming that the population remains near the disease free equilibrium except those who are reinfected. The (i,j) entry of F is the rate at which infected individuals in compartment j produce new infections in compartment i. Hence, the (i,k) entry of FV^{-1} is the expected number of new infections in compartment i produced by the infected individual originally introduced into compartment k. So FV^{-1} is the next generation matrix for the model, and then

$$R_0 = \rho(FV^{-1})$$

where ρ is the spectral radius of the matrix.

Example 4.4.1 Consider the SEIR sub model presented by Jia et al [21] as an example of a model with two infected compartments.

$$\frac{dS}{dt} = A - \beta SI - \mu S,$$

$$\frac{dE}{dt} = \beta SI - (k+\mu)E,$$

$$\frac{dI}{dt} = kE - (r+\mu+\mu_I)I,$$

$$\frac{dR}{dt} = rI - \mu R.$$

To compute R_0 we first arrange the system starting with infected compartments as follows.

$$E' = \beta_1 SI - (k_1+\mu)E$$

$$I' = k_1 E - (r_1 + \mu + \mu_{IM})I \tag{4.9}$$

$$S' = \pi - \beta_1 SI - \mu S$$

$$R' = r_1 I - \mu R.$$

Now from the next generation matrix we have $R_0 = \rho(FV^{-1})$, i.e., the spectral radius of (FV^{-1}). So we have to calculate the derivative of F_i and V_i around the equilibrium point $E_0 = (\frac{\pi}{\mu}, 0, 0)$, where $y_i = S, E, I, R$

$$F = \begin{pmatrix} 0 & \beta_1 \pi/\mu \\ 0 & 0 \end{pmatrix}, \quad V = \begin{pmatrix} k_1 + \mu & 0 \\ -k_1 & (r_1 + \mu + \mu_I) \end{pmatrix}$$

$$V^{-1} = \frac{1}{(r_1 + \mu + \mu_I)(k_1 + \mu)} \begin{pmatrix} (r_1 + \mu + \mu_I) & 0 \\ k_1 & (k_1 + \mu) \end{pmatrix}$$

$$= \begin{pmatrix} \frac{1}{k_1+\mu} & 0 \\ \frac{k_1}{(r_1+\mu+\mu_I)(k_1+\mu)} & \frac{1}{(r_1+\mu+\mu_I)} \end{pmatrix}.$$

Now we calculate the product of matrix F with the invers of V,

$$FV^{-1} = \begin{pmatrix} 0 & \beta_1 \frac{\pi}{\mu} \\ 0 & 0 \end{pmatrix} \begin{pmatrix} \frac{1}{k_1+\mu} & 0 \\ \frac{k_1}{(r_1+\mu+\mu_I)(k_1+\mu)} & \frac{1}{(r_1+\mu+\mu_I)} \end{pmatrix} = \begin{pmatrix} \frac{\beta_1 \pi k_1}{\mu(r_1+\mu+\mu_I)} & \frac{\beta_1 \pi}{(r_1+\mu+\mu_I)} \\ 0 & 0 \end{pmatrix}.$$

Then the spectral radius of (FV^{-1}) is

$$\frac{\beta \pi k_1}{\mu(r_1+\mu+\mu_I)(k_1+\mu)}.$$

The basic reproductive number R_0 is given by,

$$R_0 = \frac{\beta_1 \pi}{\mu(r_1+\mu+\mu_{IM})} \frac{k_1}{(k_1+\mu)}.$$

Chapter 5

Vaccination two-group model

5.1 Introduction

This chapter describes a vaccination SIR epidemic model that accommodate two interacting populations sometimes referred to as a two-group model. The transmission dynamics of the disease in a two-group population, migrant and local, is described by means of suitable compartmental SIR model. Then the long term behaviour of the system, such as the disease free equilibria or endemic equilibrium are discussed. The local stability of the disease free equilibria is determined by a threshold parameter, called the *vaccination reproduction number* and the effect of vaccination is also evaluated. Global stability of the disease free equilibria is analyzed by using the basic reproduction number. Finally the local stability of the endemic equilibrium is discussed. As explained below, the ideas come essentially from work of Piccolo and Billings [39], and from the paper [21] of Jia et al. The paper [52] of Zaman et al., is also important. Our model, with dynamics as in (5.2), is an original contribution of this dissertation. Also new is the optimal control problem, which we pursue in chapter 6. The model and the control problem are being prepared for publication, see [5] Ahmed and Witbooi.

5.2 Model formulation

To study the transmission of a disease in two interacting populations, we consider a population which is regarded as consisting of two components, the migrant subpopulation of size N_1 and the local subpopulation of size N_0. Both N_0 and N_1 turns out to be constant. The total population size is $N_T = N_0 + N_1$. This population is subject to a disease which we shall model by way of an SIR model, based on the model proposed in Zaman et al [52]. A similar model as the one we propose here, was presented by Jia et al., [21], but in an SEIR case. We study global stability of the disease free equilibria using the methods of sequences of Thieme et al [46]. We continue the study of the other equilibria by way of the standard linearization argument. Each subpopulation size is constant since the rate of birth is assumed equal to the mortality rate. In addition we assume that the population is uniform and homogeneously mixing. Divide each subpopulation into disjoint classes called the susceptible class (S), the infectious class (I) and the class of the removed (R). Thus there will be three such classes for the local population and also three classes for the migrant population. The sizes of these classes change with time and will be denoted by $S_0(t)$, $I_0(t)$, $R_0(t)$, $S_1(t)$, $I_1(t)$ and $R_1(t)$. Let us agree henceforth to suppress the subscript $(_0)$ for local population, writing simply $S(t)$ instead of $S_0(t)$, etc. The model is described by a system of six differential equations as follows. The schematic diagram depicted in Figure 5.1 illustrates the model and informs the differential equations. We note that the first three equations in 5.1 constitute an SIR model as for instance in [52] of Zaman et al. The last three of the equations become similar to the model in [52] if we take $I_1 = 0$.

$$\frac{dS_1(t)}{dt} = v_1 N_1 - (v_1 + u_1(t))S_1(t) - \beta_1 I_1(t) S_1(t),$$

$$\frac{dI_1(t)}{dt} = \beta_1 I_1(t) S_1(t) - (\gamma_1 + v_1) I_1(t), \tag{5.1a}$$

$$\frac{dR_1(t)}{dt} = \gamma_1 I_1(t) - v_1 r_1(t) + u_1(t) S_1(t),$$

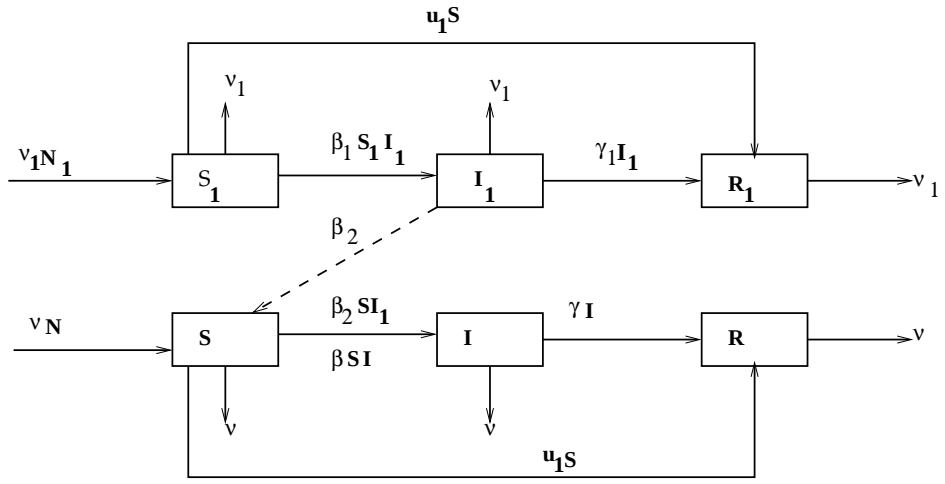


Figure 5.1: The general transfer diagrame for the SIR model with two interacting population

and

$$\frac{dS(t)}{dt} = vN - (v + u(t))S(t) - \beta I(t)S(t)/N - \beta_2 I_1(t)S(t)/N_1,$$

$$\frac{dI(t)}{dt} = \beta I(t)S(t)/N + \beta_2 I_1(t)S(t)/N_1 - (\gamma + v)I(t), \tag{5.1b}$$

$$\frac{dR(t)}{dt} = \gamma I(t) - vR(t) + u(t)S(t).$$

Here v_1 and v are the death rate (equal to the birth rate) in the migrant subpopulation and local subpopulation respectively, u_1 and u are the percentages of susceptible individuals being vaccinated in the respective subpopulations. Individuals enter the recovered compartments either by recovery from the disease at the rate γ_1, γ, or by being vaccinated. Also β_1, β are transmission coefficients (sufficient to transmit the disease) from the susceptible compartment into infectious for the migrant and local subpopulation in the model.

Local individuals get infected through infected migrants at contact rate β_2. The term

$\beta_2 I_1 S$ models the influence of the migrant subpopulation onto the locals as in the paper [21] of Jia et al.

Let us normalize the system (5.1) by using the new variables $s_1 = S_1/N_1, i_1 = I_1/N_1, r_1 = R_1/N_1, s = S/N, i = I/N$ and $r = R/N$. After normalization our model becomes as follows:

$$\begin{aligned}
\frac{ds_1(t)}{dt} &= v_1 - (v_1 + u_1(t))s_1(t) - \beta_1 i_1(t)s_1(t),\\
\frac{di_1(t)}{dt} &= \beta_1 i_1(t)s_1(t) - (\gamma_1 + v_1)i_1(t),\\
\frac{dr_1(t)}{dt} &= \gamma_1 i_1(t) - v_1 r_1(t) + u_1(t)s_1(t),
\end{aligned} \tag{5.2a}$$

and

$$\begin{aligned}
\frac{ds(t)}{dt} &= v - (v + u(t))s(t) - \beta i(t)s(t) - \beta_2 i_1(t)s(t),\\
\frac{di(t)}{dt} &= \beta i(t)s(t) + \beta_2 i_1(t)s(t) - (\gamma + v)i(t),\\
\frac{dr(t)}{dt} &= \gamma i(t) - v r(t) + u(t)S(t).
\end{aligned} \tag{5.2b}$$

5.3 Stability analysis

The stability properties of a dynamical system associated with a model is key to the utility of the model. The long term behavior of the system usually falls into two cases. Either the disease dies out or endemic equilibrium is reached, see Piccolo and Billings [39]. To understand whether the disease will die out or become endemic in the population, we study the equilibrium solution of the system 5.2 by using the threshold parameter called the basic reproduction number. In Proposition 5.2.1 we derive the basic reproduction

number for both subsystems 5.2*a* and 5.1*b* as follows.

Proposition 5.2.1 *If in* 4.2*b we take* $\beta_2 = 0$ *then the two subsystems are mutually independent, and basic reproduction number for the subsystems* 4.2*a and* 4.2*b are given by,*

$$G_1 = \frac{\beta_1}{(\gamma_1 + v_1)} \quad \text{and} \quad G = \frac{\beta}{(\gamma + v)}. \tag{5.3}$$

Here the constants G_1 and G *denotes the basic reproduction number for migrant and local subpopulations respectively.*

Proof. We assume that both subsystems are separated from each other. This means that the term in the local subpopulation system 5.2*b* which models the influence of migrants is set to zero. So both subsystems will reduce to the same SIR model. From the definitions in 4.1 and the example 4.1 the basic reproduction number is the product of the infection rate and the mean duration of infection. From subsystem 5.1*a* the infection transmission rate is β_1 and the mean infection period is $\frac{1}{(\gamma_1+v_1)}$. So $G_1 = \frac{\beta_1}{(\gamma_1+v_1)}$ and since both subsystems are similar, the result for the local subsystem follows likewise.□

The threshold parameter associated with proposition 5.2.1 is obviously not dependent on the vaccination rate. In the following proposition we state an other threshold parameter and we so-call it the *vaccination reproduction number.*

Proposition 5.2.2 *There exists a vaccination reproduction number for each subsystem, given by*

$$K_1 = \frac{\beta_1 v_1}{(v_1 + u_1)(\gamma_1 + v_1)} \quad \text{and} \quad K = \frac{\beta v}{(v + u)(\gamma + v)}. \tag{5.4}$$

Proof. The prove of this proposition follows from the proof of Theorem 5.2.1.1.

In the next subsection we shall use those two threshold conditions above to study whether the disease will die out or not. The proof is a simple exercise and we omit it.

Proposition 5.2.3 *The equilibrium solutions for the system 5.2 are given by the following points*

$$F = (s_{1f}, i_{1f}, r_{1f}, s_f, i_f, r_f), \quad D = (s^*_{1d}, i^*_{1d}, r^*_{1d}, s^*_d, i^*_d, r^*_d),$$
$$X = (s_{1x}, i_{1x}, r_{1x}, s_x, 0, r_x) \quad \text{and } Y = (s_{1y}, 0, r_{1y}, s_y, i_y, r_y) \tag{5.5}$$

where

$$s_{1f} = \frac{v_1}{v_1 + u_1(t)}, \qquad i_{1f} = 0, \qquad r_{1f} = \frac{u_1(t)}{v_1 + u_1(t)},$$

$$s_f = \frac{v}{v + u(t)}, \qquad i_f = 0, \qquad r_f = \frac{u(t)}{v + u(t)}.$$

and

$$s^*_{1d} = \tfrac{(\gamma_1+v_1)}{\beta_1}, \quad i^*_{1d} = \tfrac{v_1-(v_1+u_1)(\gamma_1+v_1)-v_1\beta_1}{\beta_1(\gamma_1+v_1)}, \qquad r^*_{1d} = \frac{\gamma_1\Big(-v_1\beta_1+(v_1+u_1)(\gamma_1+v_1)\Big)}{\beta_1(\gamma_1+v_1)} + \tfrac{u_1(\gamma_1+v)}{\beta_1},$$

$$s^*_d = \tfrac{v(\gamma+v)}{(v\beta+(v+u)-k(\gamma+v))}, \qquad i^*_d = \tfrac{kR}{(\gamma+v)-\beta R}, \qquad r^*_d = \tfrac{\gamma k\beta}{v((\gamma+v)-\beta R)} - \tfrac{uR}{v}. \qquad \square$$

The equilibrium point F is the disease free state and D is the general endemic state. The points X and Y are similar to, what are called the boundary equilibria in the paper [21] of Jia et al. In the sequel we shall do detail analyses on F and D, the two extreme cases. Next subsection give the full stability analysis for the disease free equilibria P_e.

5.4 Local stability of disease free equilibrium

When the disease dies out, the solution approaches a stable disease free equilibria point

$$P_e = (s_{1e}, i_{1e}, r_{1e}, s_e, i_e, r_e).$$

The local asymptotic stability of DFE is determined by the vaccination reproduction number given by Proposition 5.2. In addition we assume in this subsection that $u_1(t)$ and $u(t)$ are constant functions, $u_1(t) \equiv u_1$ and $u(t) \equiv u$.

Let R_u be the maximum of (k_1, k), so the R_u will be referred to as the vaccination reproduction number for the whole system 5.2, and it will be used as threshold parameter to determine the local asymptotical stability for the disease free equilibria. In Theorem 5.5 we state and prove that the DFE is asymptotic stable if $R_u < 1$ and is unstable if $R_u > 1$. We note that if $u = 0$ (the rate of vaccination) then the vaccination reproduction number will be equal to the basic reproduction number in Proposition 5.2.1.

Theorem 5.3.1 *The disease free equilibrium is locally asymptotically stable if $R_u < 1$. If $R_u > 1$ then disease free equilibria is unstable.*

Proof. Let $p_e = (s_{1e}, i_{1e}, r_{1e}, s_e, i_e, r_e)$ be the disease free equilibrium of the system (5.1a and 5.1b). The Jacobian associated with the system (5.2) is,

$$W = \begin{pmatrix} a_1 & 0 & 0 & 0 & 0 & 0 \\ \beta_1 i_1 & b_1 & 0 & 0 & 0 & 0 \\ -u_1(t) & \gamma_1 & -v_1 & 0 & 0 & 0 \\ 0 & \beta_2 s & 0 & a - \beta_2 i_1 & -\beta s & 0 \\ 0 & \beta_2 s & 0 & \beta i + \beta_2 i_1 & c & 0 \\ 0 & 0 & 0 & u(t) & \gamma & -v \end{pmatrix}$$

where

$$a_1 = -v_1 - u_1(t) - \beta_1 i_1, \quad b_1 = \beta_1 s_1 - \gamma_1 - v_1, \quad c = \beta s - \gamma - v.$$

We set out to find the eigenvalues of W. This amounts to solving for λ in the equation,

$$D(\lambda I_6 - W) = 0 \tag{5.7}$$

where I_6 is the 6×6 identity matrix. The equation (5.7) simplifies to $q_1\cdot(\lambda+v_1)\cdot q_2\cdot(\lambda+v) = 0$, where $q_1(\lambda)$ and $q_2(\lambda)$ are the quadratic expressions below:

$$q_1 = (\lambda + v_1 + u_1 + \beta_1 i_1)(\lambda - \beta_1 s_1 + \gamma_1 + v_1) + \beta_1^2 i_1 s_1, \tag{5.8}$$

$$q_2 = (\lambda - \beta s + \gamma + v)(\lambda + v + u(t) + \beta i + \beta_2 i_1) + \beta^2 si + \beta\beta_2 is. \tag{5.9}$$

Now from equation (5.8) we obtain,

$$q_1 = \lambda^2 + A_1\lambda + A_2 \tag{5.10}$$

where A_1 and A_2 are the constants:

$$A_1 = (v_1 + u_1(t) + \beta_1 i_1 - \beta_1 s_1 + \gamma_1 + v_1),$$

$$A_2 = (v_1 + u_1(t) + \beta_1 i_1)(\gamma_1 + v_1 - \beta_1 v_1) + \beta_1^2 i_1 s_1.$$

Substituting the equilibrium values of s_1, i_1, s and i we can simplify:

$$A_1 = v_1 + u_1(t) - \frac{\beta_1 v_1}{v_1 + u_1(t)} + \gamma_1 + v_1, \tag{5.11}$$

$$A_2 = (v_1 + u_1(t))\Big(\gamma_1 + v_1 - \frac{\beta_1 v_1}{v_1 + u_1(t)}\Big). \tag{5.12}$$

From equation (5.8) the roots of q_1 have negative real parts if A_1 and A_2 are both positive. Now we note that A_2 is positive, if and only if

$$\gamma_1 + v_1 - \frac{\beta_1 v_1}{v_1 + u_1} > 0,$$

i.e.

$$R_{0a} = \frac{\beta_1 v_1}{(v_1 + u_1)(v_1 + \gamma_1)} < 1.$$

Then, if $R_{01} < 1$, also $A_1 > 0$. From equation (5.9) we have q_2 as follows,

$$q_2 = \lambda^2 + (v + u + \beta i + \beta_2 i_1 - \beta s + \gamma + v)\lambda + (\gamma + v - \beta s)(v + u + \beta i + \beta_2 i_1) + \beta^2 si + \beta\beta_2 si. \tag{5.13}$$

Now let us define the coefficients B_1 and B_2 as below:

$$B_1 = (v + u + \beta i + \beta_2 i_1 - \beta s + \gamma + v),$$

$$B_2 = (\gamma + v - \beta s)(v + u + \beta i + \beta_2 i_1) + \beta^2 si + \beta\beta_2 si.$$

By applying a similar analysis as for q_1, we find that the roots of equation (5.13) have negative real parts if and only if B_1 and B_2 are both positive, which is equivalent to the condition,

$$R_{0b} = \frac{\beta v}{(v + u)(\gamma + v)} < 1.$$

Therefore the disease free equilibrium is stable if, $R_{0u} < 1$. □

5.5 Global stability of disease free equilibrium

The local asymptotic stability give us the evolution of the system after starting near to the equilibrium point, but if the system is initiated some far away from the equilibrium point then we need the global stability concept to study the evolution of the system. The global stability is closely linked with the numbers,

$$G_1 = \frac{\beta_1}{\gamma_1 + v_1} \text{ and } G = \frac{\beta}{\gamma + v}.$$

As given in proposition 5.2.1, let $R_0 = \max(G_1, G)$ denote the basic reproduction number for the system 5.2. In theorem 5.2.2.2 we shall prove that the DFE is globally asymptotic stable if $R_0 < 1$.

In the proof of the global asymptotic stability theorem we apply a lemma by Thieme [46] which we quote below. Towards the latter, we adopt the following notation.

For a bounded function $f : [0, \infty) \to \mathbb{R}$ we write $f_\infty = \liminf f(t)$, $f^\infty = \limsup f(t)$.

The required lemma by Thieme is now quoted.

Lemma 5.4.2 (Thieme [46]). *Let $f : [0, \infty) \to \mathbb{R}$ be bounded and twice differentiable with bounded second derivative. Let $t_n \to \infty$ and $f(t_n)$ converge to f^∞ or f_∞ for $n \to \infty$. Then $f^{'}(t_n) \to 0,\ n \to \infty$.*

We assume in our model that the different functions do satisfy the conditions of Lemma 5.2.2.1. Of course, in particular we have s_1, i_1, r_1, s, i and r all taking values in the interval [0,1]. We now present the theorem on global asymptotic stability.

Theorem 5.4.3 *The disease free equilibrium is globally asymptotically stable if $G_1 < 1$ and $G < 1$.*

Proof. Consider any solution $\Big(s_1(t), i_1(t), r_1(t), s(t), i(t), r(t)\Big)$ of the system 5.2. We choose a sequence (t_n) such that $(t_n) \to \infty$ and $i_1(t_n) \to i_1^\infty$. We first need to prove that $i_1^\infty = 0$. This will be proved by contradiction. Therefore to the contrary we suppose that $i_1^\infty \neq 0$. By Lemma 5.2.2.1 it follows that $\lim_{n\to\infty} \frac{di_1(t_n)}{dt} = 0$. Then using the second equation in the system 5.2 we get

$$0 = \lim_{n\to\infty} \frac{di_1(t_n)}{dt} \quad = \lim_{n\to\infty} (\beta_1 i_1(t) s_1(t_n) - (\gamma_1 + v_1) i_1(t_n)).$$

Therefore it follows that $\lim_{n\to\infty} s_1(t_n)$ exists, and since $i_1^\infty \neq 0$ we have

$$\lim_{n\to\infty} s_1(t_n) = \frac{\delta_1 + v_1}{\beta_1} = \frac{1}{G_1}.$$

Since by assumption $G_1 < 1$, it follows that

$$\lim s_1 > 1. \tag{5.14}$$

However, $s_1(t) \leq 1$ for all $t \in [0, \infty)$, and so we have a contradiction. Thus we must have $i_1^\infty = 0$. In particular then,

$$i_1^\infty = \lim_{t\to\infty} i_1(t) = 0.$$

From this it also follows that $\lim_{t\to\infty} \frac{di_1(t)}{dt} = 0$. Now consider any sequence (τ_n) such that $\tau_n \to \infty$ and $s_1(\tau_n) \to s_{1\infty}$. Then $i_1(\tau_n) \to 0$, and by Lemma 3.1 we know $\frac{ds_1(\tau_n)}{dt} \to 0$. Therefore

$$s_{1\infty} = \frac{v_1}{v_1 + u_1}.$$

Likewise we can prove that $s_1^\infty = \frac{v_1}{v_1+u_1}$. Therefore in fact $\lim_{t\to\infty} s_1(t)$ exists and

$$\lim_{t\to\infty} s_1(t) = \frac{v_1}{v_1 + u_1}.$$

In view of the identity $s_1 + i_1 + r_1 = 1$ it follows that

$$\lim_{t\to\infty} r_1(t) = \frac{u_1}{v_1 + u_1}.$$

Now we turn to the second half of the system 5.2, the three differential equations pertaining to the local population. Already we have $\lim_{t\to\infty} i_1(t) = 0$. Thus starting with a sequence (t_n), such that $t_n \to \infty$ and $i(t_n) \to i^\infty$, we can repeat the earlier argument and prove that

$$\lim_{t\to\infty} i(t) = 0, \quad \lim_{t\to\infty} s(t) = \frac{v}{v+u}, \quad \text{and} \quad \lim_{t\to\infty} r(t) = \frac{u}{v+u}.$$

□

In theorem 5.2.2.2 if the disease free equilibria is unstable when $R_{0u} > 1$ then there exist other positive or endemic equilibrium and we shall discuss them in the next subsection.

5.6 Local stability of endemic equilibrium

When the disease free equilibrium is unstable, then iandt can readily be checked that the system 5.2 has more than one endemic equilibrium.

We consider the situation under the assumption that $i_1 \neq 0$ and $i \neq 0$. Then the endemic equlibria for the system 5.2 is the point $P_e^* = (s_{1e}^*, i_{1e}^*, r_{1e}^*, s_e^*, i_e^*, r_e^*)$ in 5.5. From theorem 5.2.1.1 if $R_{0u} > 1$ then the DFE $(P_e)$is unstable and there exists positive endemic equilibria P_e^* which mean that the disease will persist.

The following theorem describes the stability conditions of the endemic equilibrium.

Theorem. 5.5.1 *Let $p^* = (s_1^*, i_1^*, r_1^*, s^*, i^*, r^*)$ be the endemic equilibrium for the system 5.2. Then the endemic equilibrium is locally asymptotically stable if $A_1 > 0,\ A_2 > 0,\ B_1 > 0$ and $B_2 > 0$.*

Proof. The Jacobian matrix J of the system at p^*, is as follows,

$$J = \begin{pmatrix} a_1 & -\beta_1 s_1 & 0 & 0 & 0 & 0 \\ \beta_1 i_1 & a_2 & 0 & 0 & 0 & 0 \\ u_1(t) & \gamma_1 & -v_1 & 0 & 0 & 0 \\ 0 & \beta_2 s & 0 & a_3 & -\beta s & 0 \\ 0 & \beta_2 s & 0 & a_4 & a_5 & 0 \\ 0 & 0 & 0 & u(t) & \gamma & -v \end{pmatrix}$$

where and

$a_1 = -(v_1 + u_1) - \beta_1$, $a_2 = \beta_1 s_1 - (\gamma_1 + v_1)$, $a_3 = -(v + u) - \beta i - \beta_2 i_1$, $a_4 = \beta i + \beta_2 i_1$, $a_5 = \beta s - (\gamma + v)$

Now we calculate the eigenvalues of J by solving the following equation for λ,

$$D[\lambda I_6 - J] = 0. \tag{5.15}$$

The equation (5.15) simplifies to $q_1(\lambda+v_1)q_2(\lambda+v) = 0$, where q_1 and q_2 are the quadratic equations below.

$$q_1 = (\lambda + v_1 + u_1 + \beta_1 i_1)(\lambda - \beta_1 s_1 + \gamma_1 + v_1) + \beta_1^2 i_1 s_1, \tag{5.16}$$

and

$$q_2 = (\lambda - \beta s + \gamma + v)(\lambda + v + u(t) + \beta i + \beta_2 i_1) + \beta^2 si + \beta\beta_2 is. \tag{5.17}$$

Now from equation (5.16) we obtain,

$$q_1 = \lambda^2 + A_1\lambda + A_2,$$

with

$$A_1 = (v_1 + u_1(t) + \beta_1 i_1 - \beta_1 s_1 + \gamma_1 + v_1),$$

and

$$A_2 = (v_1 + u_1(t) + \beta_1 i_1)(\gamma_1 + v_1 - \beta_1 v_1) + \beta_1^2 i_1 s_1.$$

At the endemic equilibrium we have,

$$A_1 = v_1 + u_1(t) + \frac{v_1\beta_1 - (v_1 + u_1)(\gamma_1 + v_1)}{(\gamma_1 + v_1)} \tag{5.18}$$

and

$$A_2 = \Big(v_1 + u_1 + \frac{v_1\beta_1 - (v_1 + u_1)(\gamma_1 + v_1)}{(\gamma_1 + v_1)}\Big)(\gamma_1 + v_1 - \beta_1 v_1) + \frac{\beta_1\Big(v_1\beta_1 - (v_1 + u_1)(\gamma_1 + v_1)\Big)}{(\gamma_1 + v_1)}. \tag{5.19}$$

From equation (5.16) the roots of q_1 have negative real parts if A_1 and A_2 are both positive. This will be the case:

$$\text{if} \quad v_1\beta_1 - (v_1 + u_1)(\gamma_1 + v_1) > 0$$

$$\text{i.e. if} \quad \beta_1 v_1 - (v_1 + u_1)(\gamma_1 + v + 1) > 0$$

and

$$(\gamma_1 + v_1 - \beta_1 v_1) > 0.$$

From equation (5.17) we have q_2 as follows,

$$q_2 = \lambda^2 + (v + u + \beta i + \beta_2 i_1 - \beta s + \gamma + v)\lambda + (\gamma + v - \beta s)(v + u + \beta i + \beta_2 i_1) + \beta^2 si + \beta\beta_2 si. \tag{5.20}$$

We can simplify this equation as follows:

$$q_2 = \lambda^2 + B_1\lambda + B_2$$

where

$$B_1 = \ v + u + \frac{\beta(v(\gamma+v))}{v\beta + (v+u) \quad - k(\gamma+v)} + \beta_2 \frac{v_1\beta_1 - (v_1+u_1)(\gamma_1+v_1)}{\beta_1(\gamma_1+v_1)}$$

$$- \frac{\beta v(\gamma+v)}{v\beta + (v+u) - k(\gamma+v)} + \gamma + v$$

and

$$B_2 = \Big(\gamma + v - \frac{\beta v(\gamma+v)}{v\beta + (v+u) - k(\gamma+v)}\Big)\Big(v + u + \frac{\beta kR}{(\gamma+v) - R\beta} + \beta_2 \frac{v_1\beta_1 - (v_1+u_1)(\gamma_1+v_1)}{\beta_1(\gamma_1+v_1)}\Big)$$

$$+ \ (\beta^2 + \beta\beta_2)\Big(\frac{kR}{(\gamma+v) - R\beta}\Big)\Big(\frac{v(\gamma+v)}{v\beta + (v+u) - k(\gamma+v)}\Big).$$

This results from substituting the endemic equilibrium value into equation (5.20).

By a similar analysis as for q_1, we find that the roots of equation (5.20) have negative real parts if B_1 and B_2 are both positive. Therefore the endemic equilibrium is locally asymptotically stable if $A_1 > 0, \quad A_2 > 0, \quad B_1 > 0$ and $B_2 > 0$. □

Directly calculating the system 5.2 we find that there exists other equilibria as follows. If the infection force in the migrant subpopulation is zero, then our model system 5.2 is reduced to a simple SIR model for only local subpopulation under the condition if $i_1(t) = 0$, and it is essentially the same model presented by Zaman et al., [52]. Also if the infectious in the local subpopulation equal to zero then the system 5.2, also will reduce to the basic SIR model with vaccination also under condition $i = 0$.

Chapter 6

Optimal control problem and numerical result

6.1 Introduction

This chapter presents the optimal vaccination strategy on the local population for the model (5.2). The basic assumption in this chapter is that the number of migrants populations is assumed to be small, and then the vaccination can be achieved in high rate. Due to this assumption we consider the percentage of migrants being vaccinated which denoted by u_1 in model (5.2) to be constant. We also consider the control variable to be the percentage of susceptible individuals being vaccinated in the local populations $u(t)$. Our goal is to formulate an optimal control problem with the control variable above to minimize the number of infected individual and maximize the number of recovery in the local population. We solve the optimal problem analytically by using Pontryagin Maximum Principle, see the book [31] Lenhart and Workman. Finally we present numerical results for the optimal system, and also we compare the behavior of the local subpopulation with control and without control. In addition we also present the numerical comparison of migrant subpopulation with vaccination and without vaccination.

6.2 Derivation of optimal control problem

We now pursue the problem of finding an optimal vaccination strategy for the local population. We assume the percentage numbers of the susceptible being vaccinated in the migrant population is constant. We have six state variables s_1, s, i_1, i, r_1, r. We consider the control variable $u(t)$, where $0 \leq u(t) \leq \alpha \leq 1$, to be the percentage of susceptible individuals being vaccinated in the local population per unit of time, and it is restricted with the maximum value α. Our optimal control problem amounts to minimizing the objective function below.

$$J(u) = \int_0^T [ci(t) + qu^2(t)]dt \tag{6.1}$$

Here q is a positive weight parameter associated with the control variable, see Zaman et al., [52], and c is a positive constant that is meant to balance I and u. The integrand in the objective function can be regarded as follows. The first term in the integrand represents the suffering, the lost working hours, the cost of hospitalization etc due to infections. The second term represents the cost of vaccination. A similar objective function is considered in the book of Lenhart and Workman [31] and Zaman et al., [52]. Our problem is then as follows.

Problem 5.1 Minimize $J(u)$ subject to,

$\frac{ds_1}{dt} = v_1 - (v_1 + u_1(t))s_1(t) - \beta_1 i_1(t)s_1(t),$

$\frac{di_1(t)}{dt} = \beta_1 i_1(t)s_1(t) - (\gamma_1 + v_1)i_1(t),$

$\frac{dr_1(t)}{dt} = \gamma_1 i_1(t) - v_1 r_1(t) + u_1(t)s_1(t),$

$$\frac{ds(t)}{dt} = v - (v + u(t))s(t) - \beta i(t)s(t) - \beta_2 i_1(t)s(t),$$

$$\frac{di(t)}{dt} = \beta i(t)s(t) + \beta_2 i_1(t)s(t) - (\gamma + v)i(t) \tag{6.2}$$

$$\frac{dr(t)}{dt} = \gamma i(t) - vr(t) + u(t)s(t).$$

Initial conditions:

$$s_1(0) = s_{10} \geq 0,\ i_1(0) = i_{10} \geq 0,\ r_1(0) = r_{10} \geq 0, s(0) = s_0 \geq 0,\ i(0) = i_0 \geq 0 \tag{6.3}$$

and $r(0) = r_0 \geq 0.$ (6.4)

Terminal conditions,

$$s_1(T), i_1(T), r_1(T), s(T), i(T) \text{ and } r(T) \text{ are free.} \tag{6.5}$$

The control variable is bounded above;

$$0 \leq u(t) \leq \alpha \leq 1. \tag{6.6}$$

The Hamiltonian for this problem is as follows.

$H(t, s_1, i_1, r_1, s, i, r, u, \lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6)$

$$= ci(t) + qu(t)^2 + \lambda_1\Big(v_1 - (v_1 + u_1(t))s_1(t) - \beta_1 i_1(t)s_1(t)\Big)$$

$$+\lambda_2\Big(\beta_1 i_1(t)s_1(t) - (\gamma_1 + v_1)i_1(t)\Big) + \lambda_3\Big(\gamma_1 i_1(t) - v_1 r_1(t) + u_1(t)s_1(t)\Big)$$

$$+\lambda_4\Big(v-(v+u(t))s(t)-\beta i(t)s(t)-\beta_2 i_1(t)s(t)\Big)$$

$$+\lambda_5\Big(\beta i(t)s(t)+\beta_2 i_1(t)s(t)-(\gamma+v)i(t)\Big)+\lambda_6\Big(\gamma i(t)-vr(t)+u(t)s(t)\Big).$$

5.2 Theorem. *Let $s_1^*,\ i_1^*,\ r_1^*,\ s^*,\ i^*,\ r^*$ and $u^*(t)$ be optimal solutions for the optimal control problem (6.1),(6.2), (6.3), (6.4), (6.5) and (6.6). Then the costate variables satisfy the following system of differential equations:*

$$\dot{\lambda}_1(t)=\lambda_1(v_1+u_1)+\beta_1 i_1(t)+\lambda_2\beta_1 i_1(t)+\lambda_3 u_1,$$

$$\dot{\lambda}_2(t)=\lambda_1\beta_1 s_1(t)-\lambda_2\beta_1 s_1(t)+\lambda_2(\delta_1+v_1)-\delta_1\lambda_3+\lambda_4\beta_2 s(t)-\lambda_5\beta_2 s(t),$$

$$\dot{\lambda}_3(t)=v_1\lambda_3,$$

$$\dot{\lambda}_4(t)=\lambda_4(v+u)+\lambda_4\beta i(t)+\lambda_4\beta_2 i_1(t)-\lambda_5\beta i(t)-\lambda_5\beta_2 i_1(t)-\lambda_6 u,$$

$$\dot{\lambda}_5(t)=-1+\lambda_4\beta s(t)-\lambda_5\beta s(t)+\lambda_5(\delta+v)-\lambda_6\delta,$$

$$\dot{\lambda}_6(t)=v\lambda_6.$$

with transversality conditions (or boundary conditions)

$$\lambda_1(T)=0,\lambda_2(T)=0,\lambda_3(T)=0,\lambda_4(T)=0,\lambda_5(T)=0 \text{ and } \lambda_6(T)=0.$$

Furthermore the optimal vaccination strategy $u^*(t)$ is given by,

$$u^*(t)=\min(\max(\lambda_4 s(t)/2q,0),\alpha).$$

Proof. We calculate the partial derivatives of Hamiltonian with respect to the different

state variable s_1, i_1, r_1, s, i, r in order to obtain the time derivatives λ_i of the costate variables. Due to $s_1(T)$, $i_1(T)$, $r_1(T)$, $s(T)$, $i(T)$ and $r(T)$ being free, the following terminal conditions hold.

$$\lambda_1(T) = 0,\ \lambda_2(T) = 0,\ \lambda_3(T) = 0,\ \lambda_4(T) = 0,\ \lambda_5(T) = 0 \text{ and } \lambda_6(T) = 0.$$

We start off by observing that,

$$\dot{\lambda}_3(t) = -\frac{\partial H}{\partial r} = v_1\lambda_3, \text{ and } \lambda_6 = -\frac{\partial H}{\partial r} = v\lambda_6,$$

This implies that λ_3 and λ_6 are of the form

$$\lambda_3 = Ae^{-v_1 t} \text{ and } \lambda_6 = Be^{vt}$$

for some constants A and B respectively. The terminal conditions, $\lambda_3(T) = 0$ and $\lambda_6(T) = 0$, forces A and B to vanish, $A = 0$ and $B = 0$, therefore λ_3 and λ_6 are identically zero, i.e. $\lambda_3 \equiv 0$ and$\lambda_6 \equiv 0$. Now we calculate,

$$\dot{\lambda}_1 = -\frac{\partial H^*}{\partial s_1(t)},\ \dot{\lambda}_2 = -\frac{\partial H^*}{\partial i_1(t)},\ \dot{\lambda}_4 = -\frac{\partial H^*}{\partial s(t)} \text{ and } \dot{\lambda}_5 = -\frac{\partial H^*}{\partial i(t)},$$

and we obtain the equations as asserted in the theorem. The function u^* must optimize H. So we calculate,

$$\frac{\partial H}{\partial u} = 2qu - \lambda_4 s(t).$$

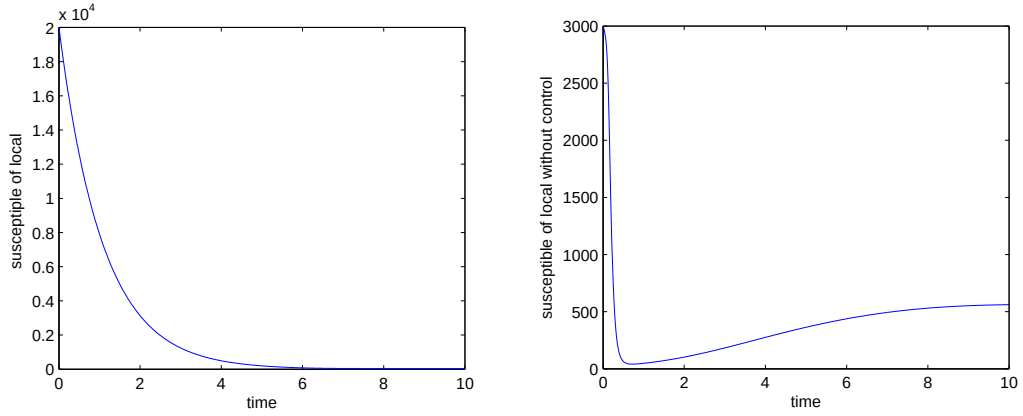
Now if $2qu(t) - \lambda_4 s(t)$ is zero for some value of u in $[0, \alpha]$ then the given value of u is optimal. If for every value of $u \in [0, \alpha]$ we have

$$2qu - \lambda_4 s \geq 0,$$

then we must choose $u = 0$, and if $2qu - \lambda_4 s \leq 0$, then we must choose $u = \delta$. Thus we must have,

$$u^*(t) = \begin{cases} \frac{\lambda_4 S^*}{k} \leq \alpha & \text{if } \lambda_1 \geq 0 \\ 0 \leq u^*(t) \leq \alpha \leq 1 & \text{if } \lambda_1 \leq 0 \end{cases}.$$

Thus we can write $u^*(t) = \min(\max(\frac{\lambda_4 s(t)}{2q}), \alpha)$. □



(a) With control (b) without control

Figure 6.1: The susceptible individuals of local subpopulation

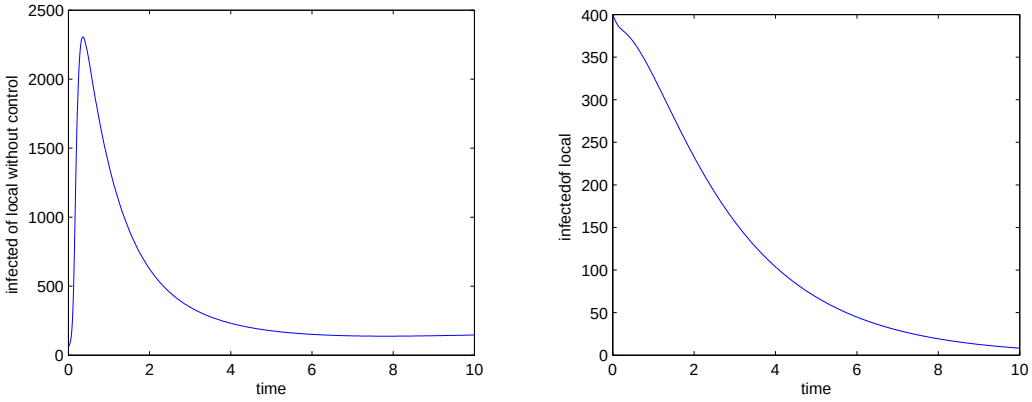
6.3 Numerical simulation

This section presents the result of the optimal control problem in section 6.2 and compares it with the model 5.2 without vaccination.

We solve the optimal control problem in by using fourth order Runge-Kutta methods. Becaese of the terminal condition of the adjoint variable. We first solve the state system by Runge-Kutta forward iteration in time applying the initial guess of the adjoint variable. Then we solve the adjoint system backward in time applying the value of the state variable from the forward solution. For the model without vaccination we solve it using Runge-Kutta forward in time.

The parameter values used in section is similar as in the paper presented by Jia et al., [21], as follows, $s(0) = 20000, i(0) = 400, r(0) = 100, c = 0.0000009, g = 0.08, q = 29, d = 0.0222, \beta_2 = 0.05 * 0.000005, s_1(0) = 3000, i_1(0) = 400, r_1(0) = 100, \mu_1 = 0.0222, \beta_1 = 0.000005, \gamma_1 = 0.058$.

Figure 6.1(a), the number of susceptible individuals with control decreases after five days of vaccination. By day 10, most of the susceptibles will move to the recovered class and vaccination will end. In other hand the number of susceptible individuals in figure 6.1(b) are decreasing at first and then increases. Thus the number of susceptibles is unstable.



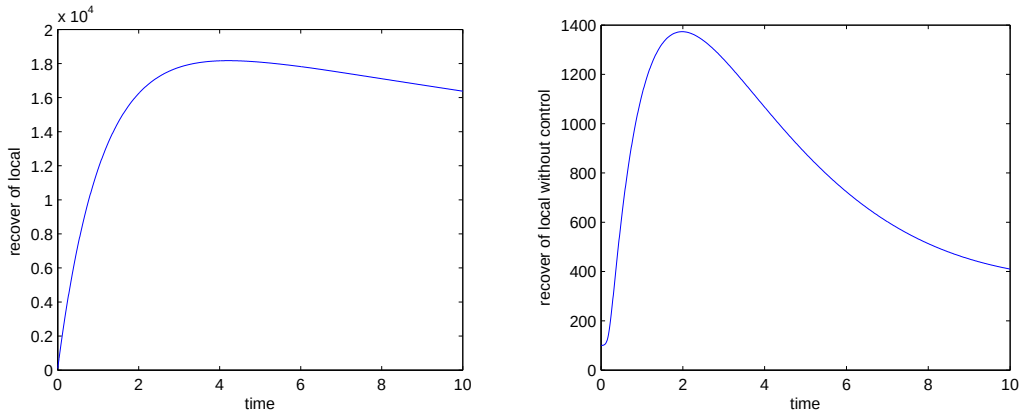
(a) With control (b) without control

Figure 6.2: The infected individuals of local subpopulation

Figure 6.2(a) shows the number of infected individual of local populations with control vaccination. The infected people are decreased sharply after the vaccination. Figure 6.2(b) shows the number of infected individuals in the local population without control. The infected people first increase till it reaches the maximum number. Most of susceptible individuals become infected. In this case the disease will outbreak in the population. Figures 6.2(a) and 6.2(b), shows the efficiency of the optimal vaccination strategy to reduce the number of infected individuals.

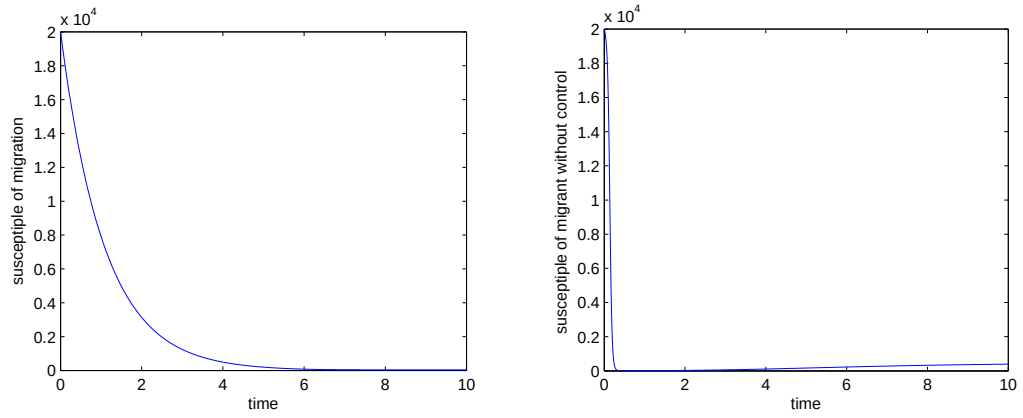
Figures 6.3(a) shows the number of recovered individuals in the local populations with control. The number of recovered population are increasing while the number of susceptible in figure 6.1(a) are decreasing due to vaccination. This proves that the after introducing vaccination most of the susceptible individuals move to the recovered class. In the figure 6.3(b) the recovered individuals without control start increasing then decrease after a few days. That means that most of the susceptible people are moved to the infected class.

Figure 6.4(a) shows the number of susceptible people of migrants populations. By the



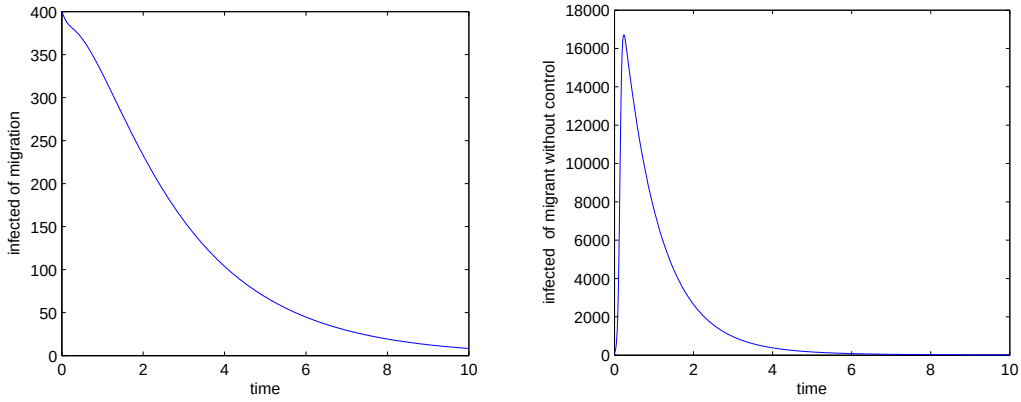
(a) With control (b) without control

Figure 6.3: The recovered individuals of local subpopulation



(a) With control (b) without control

Figure 6.4: The susceptible individuals of migrant subpopulation



(a) With control (b) without control

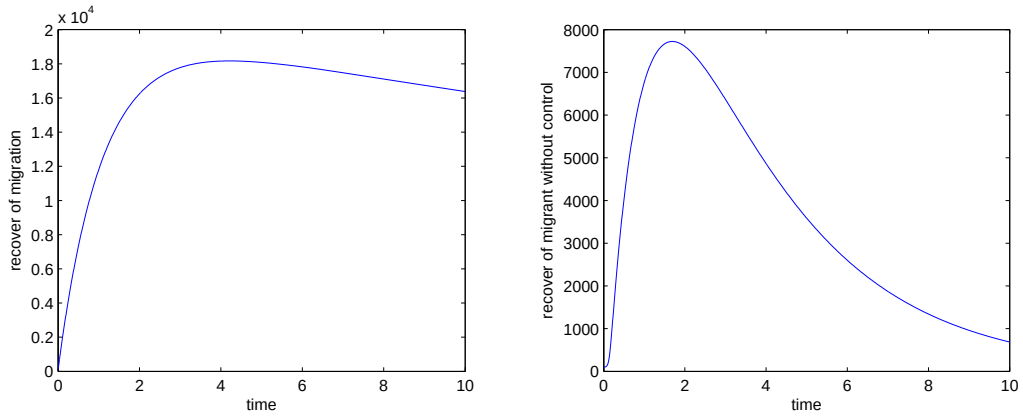
Figure 6.5: The infected individuals of migrant subpopulation

day 7 most of susceptible individuals get recovered due to vaccination and the vaccination will end. The figure 6.4(b) shows the unvaccinated susceptibles of migrants decrease immediately but they move to infected class rather than move to recover as in figure 6.5(b).

Figure 6.5(a) show the infected of migrant population. After introducing vaccination the number of infected individuals decrease sharply, and by day 13 or 15 most of the population are moved to the recovered class. The number of infected individuals of migrants without vaccination increase as shown in figure 6.5(b) . Here also we see the effect of vaccination in the migrant population. After day 15 the infected of migrants with control decrease and the vaccination will end.

Figure 6.6(a) shows the number of susceptible people of migrants populations. By the day 7 most of susceptible individual get recover due to vaccination and the vaccination will end. The figure 6.6(b) show the unvaccinated susceptible of migrant. The susceptible decrease immediately but they move to infected class rather than move to recover as we can see in figure 6.5(b) .

In 6.7, the control u is plotted with associated weight factor q. The associated weight



(a) With control (b) without control

Figure 6.6: The recovered individuals of migrant subpopulation

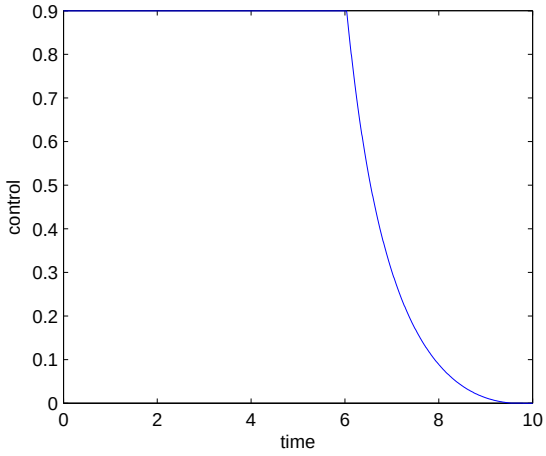


Figure 6.7: Profile of the control variable

factor q plays a significant balancing role. We notice that when q increases, the vaccine is given at the maximal level for a shorter period of time before decreasing in a continuous manner. Mathematically this is due to the fact that the percentage of vaccination given is inversely related to the weight factor q. This says that if the systemic cost of the control to the patient increases, then patients receive the maximal vaccine for a shorter period of time.

Chapter 7

Conclusions

In this dissertation, we developed and analyzed an SIR epidemiological model to study the transmission dynamics of communicable disease with vaccination, in a two-group population and to set an optimal control strategy to roll out the vaccination. In terms of stability analysis to the model, we study the disease free equilibrium and endemic equilibria. In term of the disease free equilibrium our stability analysis show that there exist a threshold condition so-called the vaccination reproduction number determine whether the diseases will invade the population or dies out. Using linearization theory we prove that the disease free equilibrium is locally asymptotically stable if the vaccination reproductive number is less than one. Also we derived another threshold condition, the so-called the basic reproduction number, and we prove that the disease free equilibrium is globally asymptotically stable if the basic reproduction number is lass than one.

When the disease free equilibrium is unstable, there exists three endemic equilibria type. Two of these equilibria are depending on the infected class in each group of the population and these types have been explored in the paper [21] of Jia et al. We only focus on the general one which depends on the rate of infection in the both groups of the population. Our theoretical study of the general endemic equilibrium point shows that the point is locally asymptotically stable.

Based on theoretical analysis of the model we set out an optimal control strategy to roll out the vaccination in the local group of population. Our numerical simulation shows the

efficiency of the control.

The model presented in this dissertation it is very significant in the area of epidemiology modeling. It gives the general framework on modeling two-groups.

Not only is our approach applicable to the deterministic continous time model, but the idea can be extended more generally to stochastic modeling. The latter is important to capture uncertainty in an epidemic model. In the paper [4] of Andersson and Lindenstrand appears a study of an epidemic in a stochastic model. Initally a branching process is employed. Eventually it gets replaced by an approximating Brownian motion. The papers [51] of Yu et al., and [26] of Jaing et al., uses Brownian motions to study stochastic epidemic models. In particular in these papers it is shown how stability behaviour can be analysed in the stochastic models. There is tremendous further scope for using Brownian motions in epidemiological modeling.

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