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Modelling the Dynamics of Drug Sensitive and Multi-Drug Resistant Tuberculosis Undercontol Strategies in Tanzania a

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The Nelson Mandela African Institution of Science and Technology

MODELLING THE DYNAMICS OF DRUG SENSITIVE AND MULTI-DRUG RESISTANT TUBERCULOSIS UNDER CONTROL STRATEGIES IN TANZANIA

Goodluck Mika Mlay

A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Mathematical and Computer Sciences and Engineering of the Nelson Mandela African Institution of Science and Technology

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ABSTRACT

Tuberculosis (TB) is a fatal airborne disease that affects one-third of the world's population and presents high disease burden globally, and resurgence of multi-drug resistant tuberculosis in sub-Saharan Africa raises a concern to assess the impact of spread of drug-resistant strain on global effort of controlling the burden of disease.

The deterministic one-strain tuberculosis model with vaccination and treatment as intervention strategies was considered, first to compute effective reproduction number, R_e and then to investigate the impact of vaccination and treatment on R_e by performing the numerical sensitivity analysis of R_e. The parameters involving vaccination of newborns and treatment of active TB cases were found to have high impact on R_e and as a result a combination of both vaccination and treatment has desirable effect of eradicating TB from community.

To investigate the role of reinfection on transmission dynamics of TB, stability analysis of Disease Free Equilibrium (DFE) and Endemic Equilibrium (EE) were performed. The results show that DFE is locally and globally asymptotically stable whenever $R_e < 1$, there is an existence of backward bifurcation at $R_e = 1$ and by using Lyapunov direct method and LaSalle's invariant principle we show that EE is globally asymptotically stable when $R_e > 1$.

To assess the impact of control measures education campaign and chemoprophylaxis of latently infected individuals on transmission dynamics of TB, the optimal control theory is used and optimal control policy is derived by using Pontryagin's Maximum Principle (PMP). The results show that multiple controls are effective than single control in reducing the number of infected individuals with TB.

To investigate the impact of the exposed immigrants on prevalence and incidence of Multi-drug Resistant Tuberculosis (MDR-TB), the two-strain tuberculosis model with treatment in pres-ence of healthy and exposed immigrants is developed. The results show that the presence of exposed immigrants to community increase prevalence and hence the burden of MDR-TB.

In addition, the increase in treatment rates of separate and combined strains of TB reduce signifi-cantly disease prevalence and alleviate TB infections.

Finally the backward bifurcation theory and local stability of endemic equilibria of MDR-TB model were carried out. We found existence of multiple equilibria and the possibility of backward bifurcation at $R_e = 1$, an indication that reducing R_e below 1 is not a guarantee to eradicate MDR-TB from community.

DECLARATION

I, **GOODLUCK MIKA MLAY**, do hereby declare to the Senate of Nelson Mandela African Institution of Science and Technology that this dissertation is my own original work and that it has neither been submitted nor being concurrently submitted for degree award in any other institution.

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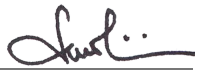
CERTIFICATION

The undersigned certify that have read and found the dissertation acceptable by the Nelson Mandela African Institution of Science and Technology.

Prof. Livingstone S. Luboobi  18-04-2016

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Lastly, I am indebted to express my sincere gratitude to my family. To my guardians for struggling to pay school fees for me to attend secondary education. To my wife Winfrida Mwigilwa, my children Catherine and Robinson and all my siblings. I thank you for endless love, perseverance and moral support when I was in need of it.

God bless you entirely.

DEDICATION

I dedicate this work to my guardians who raised me and to my wife and children.

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LIST OF ABBREVIATION

BCG	**B**acille **C**almette-**G**uérin
CEA	**C**ost **E**ffective **A**nalysis
DFE	**D**isease **F**ree **E**quilibrium
DOTS	**D**irectly **O**bserved **T**reatment **S**hort-course
EDCTP	The **E**uropean and **D**eveloping **C**ountries **C**linical **T**rials **P**artnership
EE	**E**ndemic **E**quilibrium
HBV	**H**epatitis **B** **V**irus
HIV	**H**uman **I**mmunodeficiency **V**irus
MDR-TB	**M**ulti-drug **R**esistant **T**uberculosis
MoHSW	**M**inistry of **H**ealth and **S**ocial Welfare
MTB	**M**ycobacterium **T**uberculosis
MVT	**M**ean **V**alue **T**heorem
NBS	**N**ational **B**ureau of **S**tatistics
NM-AIST	The **N**elson **M**andela **A**frican **I**nstitution of **S**cience and **T**echnology
PMP	**P**ontryagin's **M**aximum **P**rinciple
TB	**T**uberculosis
WHO	**W**orld **H**ealth **O**rganization
XDR-TB	**E**xtensively **D**rug **R**esistant **T**uberculosis
BCG	**B**acille **C**almette-**G**uérin
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XDR-TB	**E**xtensively **D**rug **R**esistant **T**uberculosis

LIST OF NOTATIONS

Symbol	Meaning
$\mathbb{R}$	The field of real numbers
$\mathcal{R}_0$	The basic reproduction number
$\mathbb{R}_+$	The set of non-negative real numbers
$\mathbb{R}^n$	The space of column vectors of size n of real numbers
$\mathbb{R}^n_+$	The positive orthant of $\mathbb{R}^n$ of non-negative real numbers
$(.)^T$	The transpose of the matrix $(.)$
$(.)^{-1}$	The inverse of the matrix $(.)$
$\sum(.)$	summation of $(.)$
$L^1(.,.)$	Lebesgue measurable on $(.,.)$
$\rho(.)$	spectral radius of matrix $(.)$

CHAPTER ONE

General Introduction and Background

Introduction

This chapter describes the general introduction of the study. It mainly focuses on the background information of the study, the rationale of the study, statement of the problem, research objectives, research questions, significance of the study, structure of dissertation and the list of publication and manuscripts.

1.1 Background Information

Tuberculosis (TB) is a bacterial infectious disease caused by bacillus *Mycobacterium tuberculosis* (MTB) with more than one-third of the world human population as its reservoir (Bloom, 1994; Feng et al., 2000; Miller, 1993). The pathogen *Mycobacterium tuberculosis* (MTB) was discovered by German Physicist and Microbiologist Robert Koch in 1882 (Migliori et al., 2007). Before that Tuberculosis was perceived to be inherited disease (Brock, 1999). TB is mainly of two types: pulmonary and extra pulmonary TB. Pulmonary TB affects lungs while extra pulmonary TB affects other sites of human body including bones, joints, lymph nodes, digestive system and skin (Kajunguri, 2009; WHO, 2013). TB is reported in Castillo-Chávez and Song (2004) as epidemic disease spreading in the air when the infectious person with pulmonary TB expel bacteria by coughing, singing, sneezing and speaking.

The symptoms of an active TB are general weakness or tiredness, fever, weight loss, loss of appetite and night sweats. Further symptoms are coughing, coughing up of sputum and/ or blood, shortness of breath and chest pains if the infection in the lung get worse (Nyerere et al., 2014; Okyere, 2007). A small proportion of about 10% of infected individuals with *Mycobacterium tuberculosis* develop TB and become infectious within two years upon infected (Rodrigues, 2009). According to Castillo-Chávez and Song (2004) many individuals infected with TB become latent for the rest of their lives provided that their immune system is not compromised.

The recovered individuals from TB do not acquire the permanent immunity. Some of them they become latent again. Even with treatment interventions, the rates of reinfection TB are higher than those of new TB (Rodrigues, 2009).
There are two ways in which the latently infected individuals can progress to active TB.

i). Reactivation of latent infection: If the immune system is compromised then tubercle bacilli reactivate and cause progression of latent to active TB through what is known as endogenous reactivation (Feng et al., 2000; Kajunguri, 2009; Vynnycky and Fine, 1997).

ii). Reinfection: the latently infected individual can progress to active TB after coming into contact with another individual who is actively infected with TB, the process known as exogenous reinfection (Feng et al., 2000; Kajunguri, 2009; Vynnycky and Fine, 1997).

Despite the availability of treatment, 9 million new cases of TB and about 1.4 million death cases were reported in 2011 worldwide (WHO, 2013). In particular from the same report at most 23000 death cases of TB and 180,000 incidence cases were reported to occur in 2011 in Tanzania.

1.1.1 TB intervention and control strategies

The up to date vaccine Bacille Calmette-Guérin (BCG) is used to protect young infants and children against tuberculosis in some degrees. It wears in time as a result of interaction between vaccine and mycobacterium in the environment especially to the countries located in tropical regions (Gomes et al., 2004; Kajunguri, 2009; Vynnycky and Fine, 1997).
Tuberculosis (TB) is curable with early diagnosis and treatment by using first line drugs which are Isoniazid, Pyrazinamide, Ethambutol and Rifampicin. In addition, the effective treatment is achieved under the strategy, Directly Observed Treatment Short-course (DOTS) instituted by World Health Organization (Kajunguri, 2009; Maliyoni et al., 2012). By using this strategy, a

patient has to take pills in presence of medical professional and willing to show co-operation in regular intake and finishing of TB regimen (Kajunguri, 2009; Maliyoni et al., 2012; WHO, 2012).

However, the current available drugs and TB vaccine BCG (Bacille Calmette Guérin) are proving less and less adequate. BCG vaccine works best to infants and its protective efficacy against pulmonary tuberculosis is highly controversial ranging from 0% to 80% (Brandt et al., 2002; Rodrigues, 2009; WHO, 2013). The BCG vaccine is not safe to a candidate who is HIV-positive (EDCTP, 2012). On the other hand TB drugs take too long to respond to a strain of mycobacterium. For patients with drug-sensitive disease have to use medication for not less than 6 months while those with Multi-drug resistant (MDR-TB) have to consume medication for 20 months (WHO, 2013). This causes toxicity in the bodies of infected individuals, poor compliance to disease and favour relapse of the disease. To avoid these complexities the use of various control strategies such as treatments, vaccination and education campaign altogether to different degrees depending on cost effectiveness of each control are meaningful so as to bring down the level of TB in Tanzania and World at large.

1.1.2 Multi-drug resistant and extensively drug resistant tuberculosis

Multi-drug resistant TB (MDR-TB) is tuberculosis that is resistant to at least isoniazid and rifampicin which are powerful first line drugs for treating drug-sensitive TB (Bhunu and Garira, 2009; Dye and Williams, 2000; Kajunguri, 2009; MoHSW, 2012). Extensively Drug Resistant TB (XDR-TB) is a form of MDR-TB that has an additional resistance to fluoroquinolone and to at least one of injectable second-line drugs (i.e. kanamycin, amikacin and capreomycin) (Kajunguri, 2009; MoHSW, 2012). Individuals acquire MDR-TB or XDR-TB through the following ways.

a). after failing to regularly take and complete a regimen dosage of MDR-TB or XDR-TB.

b). relapse after natural recovery or treatment.

c). coming into contact with individuals having drug-resistant tuberculosis (Maliyoni et al., 2012).

Other factors contributing to drug resistance TB are poor management and control of the disease, low drug quality and wrong prescription of drugs. The burden of MDR-TB is globally increasing and cause a concern for public health sector to curb it (Maliyoni et al., 2012; WHO, 2013). MDR-TB currently has been worrisome globally as it causes many deaths after failing the treatment Dye and Williams (2000). It is reported in MoHSW (2012) that there is an estimate of 450,000 new cases of MDR-TB each year and about 150,000 MDR-TB deaths, among which 25,000 are Extensively Drug resistant TB (XDR-TB) cases.

1.1.3 Multi-drug resistant TB and infective immigrants

The modern transportation systems that enhance human travel over a long distance and rural-urban movements for searching jobs have been major reasons for migration and spread of infectious diseases in the world and Africa in particular (Tumwiine et al., 2010).
The two key disease measures "prevalence" and "incidence" have been used as indicators to determine the impact of the infective immigrants to the existing community.
Multi-drug resistant TB prevalence is the proportion of total population in infectious compartments that includes active MDR-TB cases whether not diagnosed or detected but not successfully treated (Bacaër et al., 2008). On the other hand, Jung et al. (2002) defined MDR-TB incidence rate as the number of new cases of infections in a population per unit time. Thus, incidence shows how fast the disease imposes the risk to the community while prevalence indicates the burden of disease to the community. In other words, we claim that MDR-TB immigrants increase the disease prevalence and hence a burden of disease in terms of allocating resources to

curb it. These resources including buying drugs, building hospitals and clinic centers, employing medical professionals and expenses of providing civic education to public about MDR-TB infections and transmissions.

1.2 Rationale of the Research

Tuberculosis (TB) is a leading fatal infectious disease, causing about 2 million deaths worldwide and 23000 deaths in Tanzania (WHO, 2013). From the population already infected with *Mycobacterium tuberculosis*, roughly a new infection occurs in every second (Maliyoni et al., 2012; WHO, 2013). It mostly kills a working group and causes economic drawbacks to our country Tanzania (WHO, 2013).

Resurgence of multi-drug resistant TB in sub-Saharan Africa and enhancement of transportation systems that increase human travel to long distances and give rise to the possibility of disease spread, have been major public health burden to allocate resources to curb it (Maliyoni et al., 2012; Tumwiine et al., 2010). The clinical symptoms of TB (see Appendix A) have been linked by human perceptions of inheritance, bad eye and witchcraft (Melaku et al., 2013; Venkatraju and Prasad, 2010). These perceptions justify the provision of necessary civic education to the community about TB transmissions and infections and the ways to address them. The more realistic perspective to cut down TB infections is through vaccinating susceptible population, immigrants, new born; improving efficacy of TB and MDR-TB drugs; providing information campaign to public and controlling infections by using control measures which are cost-effective (Maliyoni et al., 2012).

This work calls for suitable use of best combination of treatment, vaccine, education campaign and the use of mathematical techniques to investigate the optimal strategies to bring down the TB infections and transmissions. The results of this research work will sensitize the government to formulate proper intervention programs to combat TB.

1.3 Statement of the Problem

Tuberculosis is the second leading infectious disease whose prevalence and mortality rates are increasing worldwide (WHO, 2013). Regardless of implementation of intervention strategies such as vaccination and treatment, TB has become epidemic and cause economic drawbacks in some societies in the world and Tanzania in particular. Mathematical models to assess the impact of control strategies to the transmission dynamics of susceptible TB and multi-drug resistant TB have been long developed (Castillo-Chávez and Song, 2004; Currie et al., 2003; Dye and Espinal, 2001; Feng et al., 2000; Linas et al., 2011; Mishra and Srivastava, 2014). However, none of these has paid full attention to assess the impact of infected immigrants on prevalence and incidence of MDR-TB. Thus, modeling the impact of intervention strategies vaccination and treatment on transmission dynamics of sensitive TB and impact of infected immigrants on prevalence and incidence of MDR-TB is of great significance for the mathematical understanding of the disease. In this dissertation, we develop and analyze mathematical models of TB involving infected immigrants, vaccination of newborn, treatment of active TB cases as well as searching for optimal strategies to combat TB in Tanzania.

1.4 Research Objectives

1.4.1 General Objective

The main objective of this research was to develop one and two strain tuberculosis models for deriving optimal control policy of tuberculosis in Tanzania.

1.4.2 Specific Objectives

The specific objectives of the study were:

1. To analyze and assess the impact of vaccination and treatment on transmission dynamics of tuberculosis infections.
2. To assess the impacts of reinfection on transmission dynamics of tuberculosis disease.
3. To determine and derive the best control strategies to eradicate TB disease in one-strain tuberculosis model.
4. To assess the impacts of exposed immigrants on prevalence and incidence of MDR-TB.
5. To carry out local stability analysis of endemic equilibria of MDR-TB model in presence of healthy and exposed immigrants.

1.5 Research questions

This research work was guided by the following fundamental questions:

1. Does combination of vaccination and treatment of active TB cases play a role to significantly reduce disease transmissions?
2. What is the impact of reinfection on transmission dynamics of Tuberculosis?
3. (i) Does optimal control strategy for tuberculosis exists?
   (ii) What are the basic properties of control strategies?
4. What is the impact of infected immigrants on MDR-TB prevalence and incidence?

1.6 Significance of the Study

This study is useful to educationalists, public health sectors, researchers, government and society at large.

1. To advise government of Tanzania to invest and finance tuberculosis control programmes such as TB education campaigns for public awareness of the disease and buying drugs of high efficacy to treat active TB cases.

2. To provide awareness to public health sectors of using more than one control mechanism for effective curbing of transmissions and infections of TB.

3. To educate people about the important of early diagnosis and treatment as well as to sensitize parents or guardians to send their children to hospitals to be administered BCG TB vaccine.

4. To researchers, our study will act as a base of further investigations.

5. To educationalists, our study will help them to raise awareness to people about disease transmission and infections through information campaign, educational seminars and media coverage. These efforts will help people to distance themselves from false perceptions and beliefs that TB is inherited and linking the symptoms of TB with witchcraft and a bad eye.

1.7 Structure of the Dissertation

Mathematical models of transmission dynamics of TB and MDR-TB are presented in this dissertation. The structure of dissertation is organized as follows:
Chapter one presents the general introduction, background of the study, statement of the problem, research objectives and research questions.
Chapter two presents the impact of vaccination and treatment on dynamics of one-strain tuberculosis. The findings of the first objective are presented in this chapter.
The role of reinfection on transmission dynamics of one-strain pulmonary tuberculosis is presented in Chapter three. The second objective of the research is achieved in this chapter.

Chapter four presents the optimal control theory of one-strain tuberculosis model with vaccination and treatment as intervention strategies. The third specific objective is achieved in this chapter.

The impacts of exposed immigrants on prevalence and incidence of MDR-TB are presented in Chapter five. The fourth objective is achieved through findings presented in this chapter.

Chapter six presents backward bifurcation theory and local stability of endemic equilibria of two-strain tuberculosis model in presence of healthy and exposed immigrants. The fifth objective is achieved through findings in this chapter.

Chapter seven: This chapter summarizes all findings of this study, concluding the study and suggesting recommendations and future studies as an extension of this work.

1.8 List of Publications and Manuscripts

1.8.1 Published articles

In the course of this study we managed to publish the following papers:

1). Mlay, G. M., Luboobi, L. S., Kuznetsov, D., and Shahada, F. (2014). Dynamics of one-strain pulmonary tuberculosis model with vaccination and treatment. *Communications in Mathematical Biology and Neuroscience*, 2014. Article ID 6.

2). Mlay, G. M., Luboobi, L. S., Kuznetsov, D., and Shahada, F. (2014). The Role of Re-Infection in Modeling the Dynamics of One-Strain Tuberculosis Involving Vaccination and Treatment. *Asian Journal of Mathematics and Applications*, 2014. Article ID ama025.

3). Mlay, G. M., Luboobi, L. S., Kuznetsov, D., and Shahada, F. (2015). Optimal Treatment and Vaccination Control Strategies for the dynamics of Pulmonary Tuberculosis. *International Journal of Advances in Applied Mathematics and Mechanics*. 2(3):196-207.

1.8.2 Manuscripts

The following manuscripts are submitted or ready for submission to journals in course of this study:

1). Mlay, G. M., Luboobi, L. S., Kuznetsov, D., Mpolya, E. A., and Kajunguri, D.(2015). *Modeling dynamics of two-strain tuberculosis with treatment in presence of healthy and exposed immigrants*. Manuscript submitted for publication.

2). Mlay, G. M., Luboobi, L. S., Kuznetsov, D., Mpolya, E. A., and Kajunguri, D.(2015). *Backward bifurcation theory and local stability analysis of endemic equilibria of two-strain model with treatment*. Unpublished Manuscript.

CHAPTER TWO

Dynamics of one-strain Pulmonary tuberculosis model with vaccination and treatment[1]

Abstract: Tuberculosis (TB) is a bacterial infectious disease caused by pathogen *Mycobacterium tuberculosis*. TB inflicts many human deaths and suffering globally and Tanzania in particular due to absence, failure and delayed interventions. A continuous time deterministic model to assess the impact of vaccination and treatment on transmission dynamics of one-strain tuberculosis for the purpose of eliminating TB from community is considered. The model analysis is carried out by computing effective reproduction number R_e used to investigate the impact of vaccination and treatment interventions. Numerical sensitivity analysis of R_e is performed. We find that the parameters for proportion of babies vaccinated at birth and treatment of active TB cases have high impact on R_e. Numerical simulation results show that TB clears from community when $R_e < 1$ and the combination of both vaccination and treatment has desirable effect of curbing TB infections than when one strategy is taken at a time. We recommend that vaccination coverage of newly born babies should be accompanied by treatment of active TB individuals for significant reduction of disease transmission.

2.1 Introduction

Tuberculosis (TB) is bacterial infectious disease caused by pathogen *Mycobacterium tuberculosis* with more than one-third of the world human population as its reservoir (Bloom, 1994; Feng et al., 2000; Miller, 1993). A global annual estimate of 8.6 million people develop Tuberculosis, of which 1.3 million die from disease. It is reported in WHO (2013) that, the burden of disease caused by TB is high in developing world where poor nutrition, congested accommodation and emergency of HIV are manifested. The global estimates of incidence, prevalence

[1]**This chapter is based on the published paper:**
Mlay, G. M., Luboobi, L. S., Kuznetsov, D., and Shahada, F. (2014). Dynamics of one-strain pulmonary tuberculosis model with vaccination and treatment. *Communications in Mathematical Biology and Neuroscience*, 2014. Article ID 6.

and mortality rates per 100,000 population in 2012 were respectively 255, 303 and 26 and Tanzania incidence, prevalence and mortality rates per 100,000 population were 165, 176 and 13 respectively as per WHO (2013). It therefore raises a quest to find desirable means to curtail TB morbidity and mortality rates.

Tuberculosis disease is mainly of two types: pulmonary and extra-pulmonary TB. Pulmonary TB is a common form of TB that affects lung while extra-pulmonary TB affects other parts of body and organs including central nervous system and bone (WHO, 2012). This particular study focuses on pulmonary TB. Tuberculosis is an epidemic disease spreading in the air when the infectious person with pulmonary TB expel bacteria by coughing, singing, sneezing, speaking and so on (Castillo-Chávez and Song, 2004). An individual with active TB has usual symptoms which are general weakness or tiredness, fever, weight loss, loss of appetite and night sweats. Further symptoms are coughing, coughing up of sputum and/ or blood, shortness of breath and chest pains if the infection in the lung get worse (Cohen and Murray, 2004). TB draws back economics of the world and Tanzania in particular as it affects men than women and especially the productive working group (WHO, 2012). A small proportion of about 10% of infected individuals with *Mycobacterium tuberculosis* develop TB and become infectious within two years upon infected (Rodrigues, 2009). Most become latent for the rest of their lives as long as their immune system is not compromised (Castillo-Chávez and Song, 2004). The recovered individuals from TB do not acquire the permanent immunity. Some of them they become latent again. Even with treatment interventions, the rates of reinfection TB are higher than those of new TB (Rodrigues, 2009).

Mathematical modeling of epidemiology of Tuberculosis has recently become the powerful tool to study the dynamics of the disease and impact of various intervention strategies in order to advise public health policy makers to construct suitable intervention programs to combat TB infections. Mishra and Srivastava (2014) formulated a mathematical model of tuberculosis with vaccination. They found that immunizing patients towards infection serves as guideline to a typical active TB control. Abu-Raddad et al. (2009) used an age structured mathematical

model of TB to explore the benefit of vaccine, drug regimen and diagnostics. They find that, the combination of vaccine, drug regimen and diagnosis reduce TB incidence by 71% and neonatal vaccination decreases TB incidence by 39% to 52% by the year 2050. Bhunu et al. (2011) formulated and analyzed one-strain deterministic tuberculosis model that captures the effects of case findings and treatment intervention strategy. They find that case finding accompanied by treatment has high impact on TB dynamics than when each measure is taken separately at a time. Castillo-Chávez and Feng (1997) formulated one-strain and two strain tuberculosis models which involve treatment of drug sensitive and drug-resistant TB. They find that, the lack of compliance with antibiotic treatment cause relapse that leads to resistant TB to drug regimens. This chapter concentrates on formulating a one strain TB model with vaccination and treatment strategies in order to investigate their impact on TB transmission dynamics of population that is purely homogeneous. To add more complex interactions to the dynamics of TB, we subdivide the infectious class into mild and severe groups.

2.2 Model Formulation

Our population model is subdivided into six compartments and is developed from the basic SEIT (Susceptible-Exposed-Infectious-Treated) compartmental model. A compartment of Vaccinated population (V) is added to form SVEIT model. In addition compartment of infectious population (I) is subdivided into two compartments which are severely infected population (I_1) and mildly infected population (I_2). Severely infected population (I_1) progresses faster to treatment group compared to mild infected population (I_2). In this model susceptible population will be recruited at a rate λ. Some susceptible individuals will come into contact with infectious individuals and being infected at a rate of β. A proportion, ρ of babies will be vaccinated at birth while the remaining proportion $(1-\rho)$ will be left out of vaccination to join the susceptible population. Once vaccinated babies loose immunity they become susceptible at per-capita rate θ, whereby $1/\theta$ is the period after which a vaccinated baby looses immunity. The Latently

infected individuals progress to active TB through endogenous reactivation. The proportion $(1-\eta)$ of Latently infected individuals progresses fast to severely infected class, I_1 while the remaining proportion, η progresses slowly to mildly infected class, I_2 at the same per-capita rate ϵ. Under usual circumstances mildly infected individuals take a long time to progress to treatment group, T than severely infected individuals. That is a proportion, ϕ of mildly infected individuals progresses to treatment group, T while the remaining proportion, $1-\phi$ progresses to severely infected class, I_1 at the same per-capita rate ω. The severely infected individuals progress to treatment group at a rate of ν. The treatment group, T is assumed to undergo exogenous re-infection and relapse back to Latent group with infection level, γ. The infectious individuals I_1 and I_2 are assumed to die at disease induced mortality rates of δ_1 and δ_2 respectively while the rest die naturally at a rate of μ. All variables and parameters are assumed to be non-negative. In addition the following assumptions are taken into consideration during the formulation of the model:

a. All individuals are born susceptible.

b. The members of population mix homogeneously.

c. Age, sex, social status, do not affect the probability of being infected.

d. Natural recovery is negligible and hence ignored.

e. Vaccinated population looses immunity and become Susceptible.

f. No more Vaccination can be administered to an individual infected with TB or to someone who previously was vaccinated.

g. Once recovered from Treatment an individual reverts to be Latent and may experience another episode of disease.

h. Once an individual is infected he/she will not recover if no treatment is given.

The description of model formulation in Section 2.2, together with their assumptions lead to compartmental diagram in Figure 2.1. The full description of variables and parameters used to

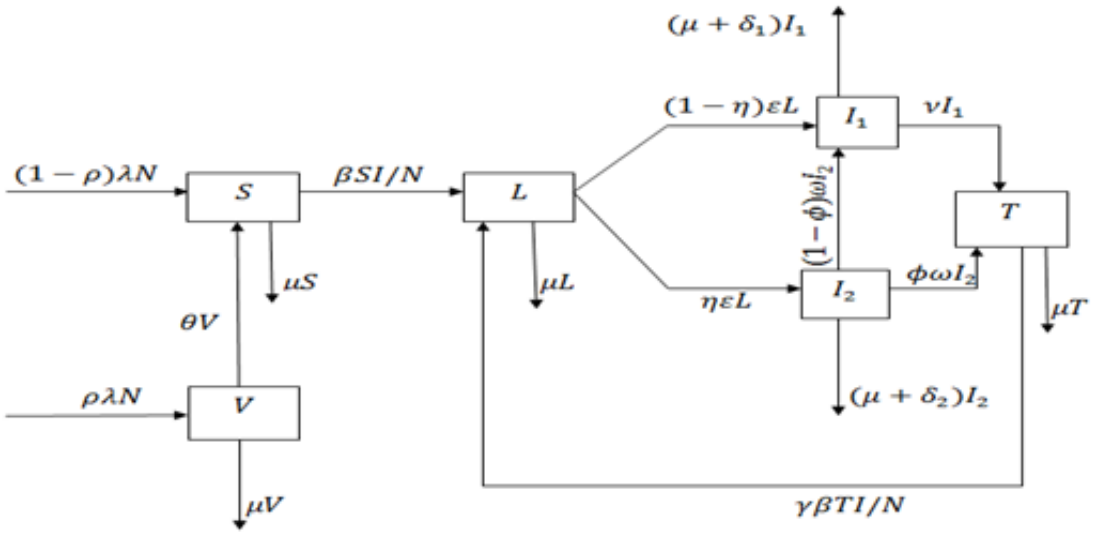

Figure 2.1: Schematic flow diagram showing dynamics of tuberculosis where $I = I_1 + I_2$.

formulate the model are in Table 2.1 and Table 2.2 respectively:

Table 2.1: Description of variables of the model

Variable	Descriptions
$S(t)$	The Susceptible who are at risk of being infected at time t
$L(t)$	The latently infected individuals at time t
$V(t)$	Vaccinated individuals at time t
$I_1(t)$	Individuals who are severely infected with TB at time t
$I_2(t)$	Individuals who are mildly infected with TB at time t
$T(t)$	Individuals Treated against TB at time t

2.2.1 Equations of the Model

Basing on assumptions made and relationship that exists between variables shown in Figure 2.1, the system of six ordinary differential equations that describes the dynamics of tuberculosis in

Table 2.2: Description of Parameters of the model

Parameter	Descriptions
λ	Per capita birth rate.
β	Per capita infection rate.
ρ	Proportional of babies who are being vaccinated at birth.
θ	The rate at which a vaccinated individual looses immunity.
ϵ	The rate of progression from Latent class to both severely and mildly Infected classes.
η	Proportional of Latently infected population progressing to mild infected class.
μ	Per capita natural death rate.
δ_1	Per capita additional death rate of severely infected class.
δ_2	Per capita additional death rate of mildly infected class.
ϕ	Proportional of mildly infected class who are treated.
ω	The transferring rate of mildly infected to both severely infected and treatment classes.
ν	The rate at which a severely infected candidate is transferred to treatment class.
γ	The factor that reduces the level of reinfection.

presence of vaccination and treatment is given by:

$$\frac{dS}{dt} = (1-\rho)\lambda N - \beta S\frac{(I_1+I_2)}{N} - \mu S + \theta V \tag{2.1a}$$

$$\frac{dV}{dt} = \rho\lambda N - (\mu+\theta)V \tag{2.1b}$$

$$\frac{dL}{dt} = \beta S\frac{(I_1+I_2)}{N} + \gamma\beta T\frac{(I_1+I_2)}{N} - (\mu+\epsilon)L \tag{2.1c}$$

$$\frac{dI_1}{dt} = (1-\eta)\epsilon L + (1-\phi)\omega I_2 - (\mu+\delta_1+\nu)I_1 \tag{2.1d}$$

$$\frac{dI_2}{dt} = \eta\epsilon L - (\mu+\omega+\delta_2)I_2 \tag{2.1e}$$

$$\frac{dT}{dt} = \nu I_1 + \phi\omega I_2 - \left(\mu + \gamma\beta\frac{(I_1+I_2)}{N}\right)T \tag{2.1f}$$

$$N = S + V + L + I_1 + I_2 + T. \tag{2.1g}$$

By adding the state equations in (2.1) we end up with rate of change of population,

$$\frac{dN}{dt} = (\lambda-\mu)N - \delta_1 I_1 - \delta_2 I_2. \tag{2.2}$$

2.2.2 Normalization of the Model

The model (2.1) can easily be analyzed after being normalized such that the total population proportion is one. The normalization is done by scaling the population of each compartment by the total population. We transform the actual proportions by setting:

$$s = \frac{S}{N},\ \ v = \frac{V}{N},\ \ l = \frac{L}{N},\ \ i_1 = \frac{I_1}{N},\ \ i_2 = \frac{I_2}{N},\ \ h = \frac{T}{N}. \tag{2.3}$$

whereby $s + v + l + i_1 + i_2 + h = 1$. Substituting (2.3) into (2.2) we end up with

$$\frac{dN}{dt} = (\lambda - \mu - \delta_1 i_1 - \delta_2 i_2)N \tag{2.4}$$

Upon differentiating the proportions in (2.3) with respect to time t and make simplification, leads to the following dimensionless system:

$$\frac{ds}{dt} = (1-\rho)\lambda + \theta v - (\lambda + \beta(i_1 + i_2) - \delta_1 i_1 - \delta_2 i_2)s, \tag{2.5a}$$
$$\frac{dv}{dt} = \rho\lambda - (\lambda + \theta - \delta_1 i_1 - \delta_2 i_2)v, \tag{2.5b}$$
$$\frac{dl}{dt} = \beta s(i_1 + i_2) + \gamma\beta h(i_1 + i_2) - (\lambda + \epsilon - \delta_1 i_1 - \delta_2 i_2)l, \tag{2.5c}$$
$$\frac{di_1}{dt} = (1-\eta)\epsilon l + (1-\phi)\omega i_2 - (\lambda + \delta_1 + \nu - \delta_1 i_1 - \delta_2 i_2)i_1, \tag{2.5d}$$
$$\frac{di_2}{dt} = \eta\epsilon l - (\lambda + \omega + \delta_2 - \delta_1 i_1 - \delta_2 i_2)i_2, \tag{2.5e}$$
$$\frac{dh}{dt} = \nu i_1 + \phi\omega i_2 - (\lambda + \gamma\beta(i_1 + i_2) - \delta_1 i_1 - \delta_2 i_2)\, h \tag{2.5f}$$

subject to condition $s + v + l + i_1 + i_2 + h = 1$. All the feasible solutions of system (2.5) enter the region of biological interest defined by

$$\Omega = \left\{(s, v, l, i_1, i_2, h) \in \mathbb{R}^6_+ : s + v + l + i_1 + i_2 + h = 1\right\}$$

that is positive-invariant. We consider the dynamics of the flow generated by system (2.5) in Ω. In this region, the model (2.5) is considered to be both biologically and mathematically well posed (Hethcote, 2000).

2.3 Analysis of the Model.

The normalized model (2.5) will be analyzed qualitatively so as to get some insights on dynamics of tuberculosis and to get the better understanding of the effects of treatment and vaccination on transmission of TB infections in human population. The threshold that indicates whether the disease can be eliminated from or persist to the community will be determined.

2.3.1 Existence of Disease Free Equilibrium (DFE)

Equilibrium points are found by setting the right hand sides of the model equations (2.5) to zero. That is:

$$\frac{ds}{dt} = \frac{dv}{dt} = \frac{dl}{dt} = \frac{di_1}{dt} = \frac{di_2}{dt} = \frac{dh}{dt} = 0 \tag{2.6}$$

Let the disease free equilibrium point of tuberculosis model (2.5) be, $E_0 = (s^0, v^0, l^0, i_1^0, i_2^0, h^0)$. Supplying information (2.6) into (2.5) and setting $l = i_1 = i_2 = h = 0$ in absence of disease attack we find that

$$s^0 = \frac{\theta + \lambda(1-\rho)}{\lambda + \theta};\ v^0 = \frac{\rho\lambda}{\lambda + \theta} \tag{2.7}$$

Therefore the disease free equilibrium of the model (2.5) exists and is given by:

$$E_0 = (s^0, v^0, l^0, i_1^0, i_2^0, h^0) = \left(\frac{\theta + \lambda(1-\rho)}{\lambda + \theta}, \frac{\rho\lambda}{\lambda + \theta}, 0, 0, 0, 0\right). \tag{2.8}$$

2.3.2 Effective reproduction number,R_e

The effective reproduction number, R_e is defined as the measure of average number of infections caused by a single infectious individual introduced in a community in which intervention strategies (in our case is treatment and vaccination) is administered (Okuonghae and Korobeinikov, 2007; Okuonghae and Aihie, 2008). We derive R_e by using the next generation operator method (Van den Driessche and Watmough, 2002).

If we define $\mathbf{F}$ to be a non-negative $m \times m$ matrix and $\mathbf{V}$ to be a non-singular M-matrix such that

$$\mathbf{F} = \left[\frac{\partial \mathcal{F}_i(E_0)}{\partial x_j}\right] \text{ and } \mathbf{V} = \left[\frac{\partial \mathcal{V}_i(E_0)}{\partial x_j}\right] \text{ with } 1 \leq i, j \leq m,$$

where $\mathcal{F}_i$ is the rate of appearance of new infections in compartment i and $\mathcal{V}_i = \mathcal{V}_i^- - \mathcal{V}_i^+$ in which $\mathcal{V}_i^+$ is the rate of transfer of individual into compartment i by all other means, and $\mathcal{V}_i^-$ is the rate of transfer of individual out of compartment i. The point E_0 is of disease free equilibrium as appeared in (2.8). It follows that the effective reproduction number, R_e of model (2.5) is the spectral radius (dominant eigenvalue) of $\mathbf{FV}^{-1}$ denoted by $R_e = \rho(\mathbf{FV}^{-1})$.

By arranging equations of system (2.5) in such a way that the infectious classes come first we end up with a system of equations represented by

$$x_i' = f_i(x) = \mathcal{F}_i(x) - \mathcal{V}_i(x),\ i = 1, 2, \cdots, n$$

where $\mathcal{V}_i(x) = \mathcal{V}_i^-(x) - \mathcal{V}_i^+(x)$. Each function f_i is continuous and at least twice differentiable in the region defined by Ω. We derive $\mathcal{F}_i$ and $\mathcal{V}_i = \mathcal{V}_i^- - \mathcal{V}_i^+$ respectively to be:

$$\mathcal{F}_i = \begin{bmatrix} \mathcal{F}_1 \\ \mathcal{F}_2 \\ \mathcal{F}_3 \\ \mathcal{F}_4 \\ \mathcal{F}_5 \\ \mathcal{F}_6 \end{bmatrix} = \begin{bmatrix} \beta s(i_1 + i_2) + \gamma\beta h(i_1 + i_2) \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix},$$

and

$$\mathcal{V}_i = \begin{bmatrix} \mathcal{V}_1 \\ \mathcal{V}_2 \\ \mathcal{V}_3 \\ \mathcal{V}_4 \\ \mathcal{V}_5 \\ \mathcal{V}_6 \end{bmatrix} = \begin{bmatrix} (\lambda + \epsilon - \delta_1 i_1 - \delta_2 i_2)l \\ -(1-\eta)\epsilon l - (1-\phi)\omega i_2 + (\lambda + \delta_1 + \nu - \delta_1 i_1 - \delta_2 i_2)i_1 \\ -\eta\epsilon l + (\lambda + \omega + \delta_2 - \delta_1 i_1 - \delta_2 i_2)i_2 \\ -\nu i_1 - \phi\omega i_2 + (\lambda + \gamma\beta(i_1 + i_2) - \delta_1 i_1 - \delta_2 i_2)\, h \\ -(1-\rho)\lambda - \theta v + (\lambda + \beta(i_1 + i_2) - \delta_1 i_1 - \delta_2 i_2)s \\ -\rho\lambda + (\lambda + \theta - \delta_1 i_1 - \delta_2 i_2)v \end{bmatrix}.$$

By considering infected classes only and making use of linearization technique, the Jacobian matrices $\mathbf{F}$ and $\mathbf{V}$ at disease free equilibrium point E_0 are respectively given by:

$$\mathbf{F} = \begin{bmatrix} 0 & \dfrac{\beta(\theta + \lambda(1-\rho))}{\lambda + \theta} & \dfrac{\beta(\theta + \lambda(1-\rho))}{\lambda + \theta} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \text{ and}$$

$$\mathbf{V} = \begin{bmatrix} \lambda + \epsilon & 0 & 0 \\ -(1-\eta)\epsilon & \lambda + \delta_1 + \nu & -(1-\phi)\omega \\ -\eta\epsilon & 0 & \lambda + \omega + \delta_2 \end{bmatrix}.$$

Representing the original parameters by a, b, c, d, e, f and g such that:

$$a = \lambda + \epsilon, b = (1-\eta)\epsilon, c = \lambda + \delta_1 + \nu, d = (1-\phi)\omega, e = \eta\epsilon, f = \lambda + \omega + \delta_2 \text{ and}$$

$$g = \frac{\beta(\theta + \lambda(1-\rho))}{\lambda + \theta},$$

then the inverse of $\mathbf{V}$ and matrix product $\mathbf{FV}^{-1}$ are computed and respectively found to be:

$$\mathbf{V}^{-1} = \begin{bmatrix} \frac{1}{a} & 0 & 0 \\ \frac{bf+ed}{acf} & \frac{1}{c} & \frac{d}{cf} \\ \frac{e}{af} & 0 & \frac{1}{f} \end{bmatrix} \text{ and } \mathbf{FV}^{-1} = \begin{bmatrix} g\left(\frac{bf+ed}{acf} + \frac{e}{af}\right) & \frac{g}{c} & \frac{g(d+c)}{fc} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}.$$

The matrix product $\mathbf{FV}^{-1}$ is upper triangular matrix whose eigenvalues are located at its main diagonal as $0, 0$, and $g\left(\frac{bf+ed}{acf} + \frac{e}{af}\right)$. Thus the effective reproduction number, R_e is:

$$R_e = g\left(\frac{bf+ed}{acf} + \frac{e}{af}\right).$$

Expressing a, b, c, d, e, f and g in terms of original parameters it leads to effective reproduction number:

$$R_e = \frac{\beta(\theta + \lambda(1-\rho))}{(\lambda+\theta)}\left[\frac{(1-\eta)(\lambda+\omega+\delta_2)\epsilon + (1-\phi)\omega\eta\epsilon}{a_1(\lambda+\delta_1+\nu)} + \frac{\eta\epsilon}{a_1}\right]. \tag{2.9}$$

whereby $a_1 = (\lambda+\epsilon)(\lambda+\omega+\delta_2)$.

2.3.3 Local stability of Disease free equilibrium (DFE)

Using Theorem 2 from Van den Driessche and Watmough (2002), the following result is established.

Theorem 2.1. *The disease free equilibrium of model* (2.5)*, given the effective reproduction number,* R_e *is locally asymptotically stable if* $R_e < 1$*, and unstable if* $R_e > 1$.

Proof. It is enough to show that Disease Free equilibrium point of our system (2.5) is stable if and only if trace and determinant of Jacobian matrix at E_0, denoted by $J(E_0)$ are negative and positive respectively. Our Jacobian matrix evaluated at disease free equilibrium point is given by:

$$J(E_0) = \begin{bmatrix} -\lambda & \theta & 0 & -(\beta+\delta_1)c_1 & -(\beta+\delta_2)c_1 & 0 \\ 0 & -(\lambda+\theta) & 0 & \frac{\rho\lambda}{\lambda+\theta}\delta_1 & \frac{\rho\lambda}{\lambda+\theta}\delta_2 & 0 \\ 0 & 0 & -(\lambda+\epsilon) & \beta c_1 & \beta c_1 & 0 \\ 0 & 0 & (1-\eta)\epsilon & -(\lambda+\delta_1+\nu) & (1-\phi)\omega & 0 \\ 0 & 0 & \eta\epsilon & 0 & -(\lambda+\omega+\delta_2) & 0 \\ 0 & 0 & 0 & \nu & \phi\omega & -\lambda \end{bmatrix}.$$

whereby $c_1 = \dfrac{\theta+\lambda(1-\rho)}{\lambda+\theta}$. Trace and determinant of matrix $J(E_0)$ denoted by $\text{Tr}(J(E_0))$ and $\det(J(E_0))$ are respectively given by:

$$\text{Tr}(J(E_0)) = -(6\lambda+\theta+\epsilon+\nu+\omega+\delta_1+\delta_2) < 0$$

and

$$\det(J(E_0)) = -\lambda^2(\lambda+\theta)\begin{vmatrix} (\lambda+\epsilon) & \beta\left(\frac{\theta+\lambda(1-\rho)}{\lambda+\theta}\right) & \beta\left(\frac{\theta+\lambda(1-\rho)}{\lambda+\theta}\right) \\ (1-\eta)\epsilon & -(\lambda+\delta_1+\nu) & (1-\phi)\omega \\ \eta\epsilon & 0 & -(\lambda+\omega+\delta_2) \end{vmatrix}$$

$$= -\lambda^2(\lambda+\theta)\left[\frac{\beta(\theta+\lambda(1-\rho))}{(\lambda+\theta)}\{(1-\eta)(\lambda+\omega+\delta_2)\epsilon + ((1-\phi)\omega+\lambda+\delta_1+\nu)\eta\epsilon\} - (\lambda+\epsilon)(\lambda+\omega+\delta_2)(\lambda+\delta_1+\nu)\right]$$

$$= -A\left[\frac{\beta(\theta+\lambda(1-\rho))}{(\lambda+\theta)}\left\{\frac{(1-\eta)(\lambda+\omega+\delta_2)\epsilon + ((1-\phi)\omega\eta\epsilon}{(\lambda+\epsilon)(\lambda+\omega+\delta_2)(\lambda+\delta_1+\nu)} + \frac{\eta\epsilon}{(\lambda+\epsilon)(\lambda+\omega+\delta_2)}\right\} - 1\right]$$

$$= -A(R_e - 1).$$

where $A = \lambda^2(\lambda+\theta)(\lambda+\epsilon)(\lambda+\delta_1+\nu)(\lambda+\omega+\delta_2) > 0$.
Thus $\det(J(E_0))$ if and only if $R_e < 1$. Since the trace of matrix $J(E_0)$ is negative and its determinant is strictly greater than zero when $R_e < 1$, then disease free equilibrium point E_0 is locally asymptotically stable and completes our proof. □

The results of Theorem 2.1 indicate that TB clears from community if $R_e < 1$. That is when the initial population of model (2.5) is in basin of attraction of disease free equilibrium, E_0.

2.3.4 Analysis of Effective Reproduction number

If we denote the effective reproduction number of model (2.5) by (reproduction number when vaccination and treatment are administered) and combine denominators of equation (2.5) we

end up with:

$$R_e = R_{VT} = \frac{\beta(\theta + \lambda(1-\rho))\left[(1-\eta)(\lambda+\omega+\delta_2)\epsilon + ((1-\phi)\omega + \lambda + \delta_1 + \nu)\eta\epsilon\right]}{(\lambda+\theta)(\lambda+\epsilon)(\lambda+\omega+\delta_2)(\lambda+\delta_1+\nu)} \quad (2.10)$$

We define the threshold R_{VT} as a number of secondary infections when one infectious individual is introduced in a population which is totally susceptible where V is the number of vaccinated newly born babies and T is treatment administered to active TB individuals.

In absence of vaccination and treatment we have

$$\lim_{(\rho,\theta,\phi,\nu)\to(0,0,0,0)} R_{VT} = R_0 = \beta\left[\frac{(1-\eta)(\lambda+\omega+\delta_2)\epsilon + \omega\eta\epsilon}{(\lambda+\epsilon)(\lambda+\omega+\delta_2)(\lambda+\delta_1)} + \frac{\eta\epsilon}{(\lambda+\epsilon)(\lambda+\omega+\delta_2)}\right] \quad (2.11)$$

We define

$$R_{0(severe)} = \beta\left[\frac{(1-\eta)(\lambda+\omega+\delta_2)\epsilon + \omega\eta\epsilon}{(\lambda+\epsilon)(\lambda+\omega+\delta_2)(\lambda+\delta_1)}\right]$$

$$R_{0(mild)} = \frac{\beta\eta\epsilon}{(\lambda+\epsilon)(\lambda+\omega+\delta_2)}. \quad (2.12)$$

where $R_{0(severe)}$ and $R_{0(mild)}$ are basic reproduction numbers for severely and mildly infected classes respectively.

The relation (2.11) simplifies to

$$\lim_{(\rho,\theta,\phi,\nu)\to(0,0,0,0)} R_{VT} = R_0 = \frac{\beta\left[(1-\eta)(\lambda+\omega+\delta_2)\epsilon + (\omega+\lambda+\delta_1)\eta\epsilon\right]}{(\lambda+\epsilon)(\lambda+\omega+\delta_2)(\lambda+\delta_1)} \quad (2.13)$$

which is the basic reproduction number (threshold quantity in absence of intervention strategies). If vaccination alone is administered then, equation (2.10) is written as

$$\lim_{(\phi,\nu)\to(0,0)} R_{VT} = R_V = \frac{\beta(\theta+\lambda(1-\rho))\left[(1-\eta)(\lambda+\omega+\delta_2)\epsilon+(\omega+\lambda+\delta_1)\eta\epsilon\right]}{(\lambda+\theta)(\lambda+\epsilon)(\lambda+\omega+\delta_2)(\lambda+\delta_1)}$$

$$= \frac{\theta+\lambda(1-\rho)}{(\lambda+\theta)}R_0 = K_1 R_0. \tag{2.14}$$

Since $\dfrac{\theta+\lambda(1-\rho)}{(\lambda+\theta)} < 1$ then vaccinating babies at birth with TB vaccine helps reducing initial disease transmission. Differentiating R_V with respect to vaccination rate ρ, we have

$$\frac{\partial R_V}{\partial \rho} = -\frac{\lambda\beta\left[(1-\eta)(\lambda+\omega+\delta_2)\epsilon+(\omega+\lambda+\delta_1)\eta\epsilon\right]}{(\lambda+\theta)(\lambda+\epsilon)(\lambda+\omega+\delta_2)(\lambda+\delta_1)} = -\frac{\lambda}{\lambda+\theta}R_0 < 0. \tag{2.15}$$

The expression in (2.15) reveals that R_V is a decreasing function of ρ and inequality (2.15) confirms that increasing the proportion of vaccinated babies at birth has positive impacts on TB control and increases the efforts to cut out epidemic.

In case only treatment is administered, it follows from equation (2.10) that,

$$\lim_{(\rho,\theta)\to(0,0)} R_{VT} = R_T = \frac{\beta\left[(1-\eta)(\lambda+\omega+\delta_2)\epsilon+((1-\phi)\omega+\lambda+\delta_1+\nu)\eta\epsilon\right]}{(\lambda+\epsilon)(\lambda+\omega+\delta_2)(\lambda+\delta_1+\nu)}. \tag{2.16}$$

Differentiating R_T with respect to proportional of treated mildly infected individuals ϕ we find that

$$\frac{\partial R_T}{\partial \phi} = -\frac{\beta\omega\eta\epsilon}{(\lambda+\epsilon)(\lambda+\omega+\delta_2)(\lambda+\delta_1+\nu)} < 0. \tag{2.17}$$

Thus R_T is a decreasing function of ϕ and it shows that increasing the proportion of treated mildly infected individuals has a positive effect on TB control and increases the efforts to curtail TB spread .

Following an approach employed by Bhunu et al. (2008) and Bhunu et al. (2011), the effective reproduction number R_{VT} can also be established by using the following relation:

$R_{VT} = K_2 R_0$, where by expression for K_2 is given by:

$$K_2 = \frac{(\theta + \lambda(1-\rho))\left[(1-\eta)(\lambda+\omega+\delta_2)\epsilon + (\omega+\lambda+\delta_1)\eta\epsilon\right](\lambda+\delta_1)}{(\lambda+\theta)((1-\eta)(\lambda+\omega+\delta_2)\epsilon + (\omega+\lambda+\delta_1)\eta\epsilon)(\lambda+\delta_1+\nu)} < 1.$$

It follows that,

$$\begin{aligned} K_2 - K_1 &= \frac{(\theta + \lambda(1-\rho))\left[(1-\eta)(\lambda+\omega+\delta_2)\epsilon + (\omega+\lambda+\delta_1)\eta\epsilon\right](\lambda+\delta_1)}{(\lambda+\theta)((1-\eta)(\lambda+\omega+\delta_2)\epsilon + (\omega+\lambda+\delta_1)\eta\epsilon)(\lambda+\delta_1+\nu)} \\ &\quad - \frac{\theta + \lambda(1-\rho)}{\lambda+\theta} \\ &= -\frac{(\theta + \lambda(1-\rho))\left[\phi\omega\eta\epsilon(\lambda+\delta_1) + ((1-\eta)(\lambda+\omega+\delta_2) + \omega\eta)\epsilon\nu\right]}{(\lambda+\theta)((1-\eta)(\lambda+\omega+\delta_2)\epsilon + (\omega+\lambda+\delta_1)\eta\epsilon)(\lambda+\delta_1+\nu)} < 0. \end{aligned}$$

Thus $K_2 - K_1 < 0$. It follows that $R_{VT} - R_V = K_2 R_0 - K_1 R_0 = (K_2 - K_1)R_0$ so that $R_{VT} < R_V$. This implies that the combination of both treatment and vaccination has great impact in reducing disease transmission than to take the two measures one at a time.

Investigating the effect of vaccination in presence of treatment is considered by differentiating R_{VT} with respect to proportional of vaccinated babies at birth ρ as follows:

$$\frac{\partial R_{VT}}{\partial \rho} = -\frac{\beta\lambda\left[(1-\eta)(\lambda+\omega+\delta_2)\epsilon + ((1-\phi)\omega+\lambda+\delta_1+\nu)\eta\epsilon\right]}{(\lambda+\theta)(\lambda+\epsilon)(\lambda+\omega+\delta_2)(\lambda+\delta_1+\nu)} < 0. \tag{2.18}$$

This implies that increasing vaccination coverage of babies at birth has significant impact to the control of TB if accompanied by treatment of active TB.

We have already showed algebraically that $R_{VT} < R_V$. The general relationship that associates the reproduction numbers $R_{VT}, R_T, R_V, R_{0(severe)}, R_{0(mild)}$ and R_0 algebraically is involving. Graphical Illustrations involving these relationships are presented in Nyerere et al. (2014), by using linear relationship that exists between the growth rate of reproduction number with respect to transmission rate β when other parameters remain fixed.

2.3.5 Numerical Sensitivity Analysis of Effective Reproduction number, R_e

In this section numerical sensitivity analysis of effective Reproduction number is performed by using parameters in Table 2.3 whose numerical values are from existing literature as well as estimated to suit this particular intended study to determine the relative importance of each parameter involved in R_e to the transmission of tuberculosis. Sensitivity analysis is used to

Table 2.3: Parameter values for normalized model (2.5).

Parameter	**Value/range**(yr^{-1})	**Source**
λ	0.05	Estimated.
β	2.58	Estimated.
ρ	0.4	Estimated.
θ	0.1	Estimated.
ϵ	0.03	Cohen et al. (2007)
η	0.7 (0.7-0.95)	Okuonghae and Aihie (2008)
μ	0.01923 (0.01-0.04)	Blower et al. (1995)
δ_1	0.3 (0.07-0.365)	Ssematimba et al. (2005)
δ_2	0.2 (0.07-0.365)	Ssematimba et al. (2005)
ϕ	0.6	Estimated.
ω	0.2	Estimated.
ν	0.3	Estimated.
γ	0.2	Estimated.

determine which parameters have high impact on R_e so as to be targeted by intervention strategies (Chitnis et al., 2008; Rodrigues et al., 2013). The approach of Chitnis et al. (2008) is used to calculate the sensitivity indices of to the parameters involved in it so as to determine how best to reduce human mortality and morbidity due to Tuberculosis. The normalized forward sensitivity index is the ratio of relative change of variable to the relative change in parameter. If the variable is a differentiable function of the parameter then the sensitivity index may be defined by using partial derivatives as follows.

Definition 2.2. The normalized forward sensitivity index of variable p that depends on parameter q is defined as

$$\Upsilon_q^p = \frac{\partial p}{\partial q} \times \frac{q}{p}. \tag{2.19}$$

Since we have explicit formula for effective reproduction number R_e in (2.10), it follows that the normalized forward sensitivity indices of R_e with respect to parameters q_i involved in R_e is given by:

$$\Upsilon_{q_i}^{R_e} = \frac{\partial R_e}{\partial q_i} \times \frac{q_i}{R_e} \tag{2.20}$$

For instance the sensitivity indices of R_e with respect to β and ρ are given respectively by: $\Upsilon_{\beta}^{R_e} = \frac{\partial R_e}{\partial \beta} \times \frac{\beta}{R_e} = +1$ and $\Upsilon_{\rho}^{R_e} = \frac{\partial R_e}{\partial \rho} \times \frac{\rho}{R_e} = -0.1538$. By using the same approach the indices $\Upsilon_{\theta}^{R_e}, \Upsilon_{\lambda}^{R_e}, \Upsilon_{\eta}^{R_e}, \Upsilon_{\omega}^{R_e}, \Upsilon_{\delta_1}^{R_e}, \Upsilon_{\epsilon}^{R_e}, \Upsilon_{\phi}^{R_e}, \Upsilon_{\delta_2}^{R_e}$ and $\Upsilon_{\nu}^{R_e}$ are obtained and tabulated accordingly and ordered from highest sensitive to least sensitive parameter as in Table 2.4. (Description of parameters is given in Table 2.2).

Table 2.4: Sensitivity indices evaluated using baseline parameter values in Table 2.3

Parameter	Sensitivity index
β	+1.0000
λ	-0.8382
ϵ	+0.6250
δ_2	-0.3516
η	+0.3034
ω	-0.2649
ρ	-0.1538
ν	-0.1365
δ_1	-0.1365
ϕ	-0.1300
θ	+0.1026

2.3.6 Interpretation of Sensitivity Indices.

From Table 2.4 we find that the parameters β, ϵ, η and θ have positive indices. This means that, increasing (decreasing) one of these parameters while keeping others constant increases (decreases) the value of effective reproduction number, R_e implying the increase (decrease) of endemicity of tuberculosis disease respectively. For instance, $\Upsilon_{\eta}^{R_e} = +0.3034$, implies that increasing proportional of latently infected population, η that is progressing to mild infected

class by 10%, increases the value of R_e by 3.034% and hence increases the endemicity of the disease. In contrast reducing the proportional by 10% decreases the value of R_e by 3.034% and hence lowering the endemicity of the disease. On the other hand the parameters $\lambda, \delta_1, \omega, \rho, \nu, \delta_2$ and ϕ have negative indices, implying that increasing (decreasing) one of these parameters while keeping the rest constant decreases (increases) the value of effective reproduction number, R_e and hence decreases (increases) the endemicity of TB. For example, $\Upsilon_{\rho}^{R_e} = -0.1538$, implies that, increasing the proportional of vaccinated babies ρ by 50% decreases the value of R_e approximately by 7.69% and hence reducing the endemicity of TB. However, decreasing the proportional of vaccinated babies, ρ, by 50% increases the value of R_e by 7.69% and hence increases the endemicity of the disease. In particular, following the magnitudes of sensitive indices, R_e is most positively sensitive to parameters β, ϵ and η. In addition, R_e is most negatively sensitive to parameters $\lambda, \delta_2, \omega$ and ρ. However R_e is moderately negatively sensitive to parameters ν, δ_1 and ϕ followed by the least positive sensitive parameter, θ. In our case the most sensitive and moderate parameters should be careful estimated in order to determine the robustness of model predictions to parameter values and to determine parameters which have high impact on R_e and which should be targeted by intervention strategies (Chitnis et al., 2008).

2.4 Numerical Simulations

In this section numerical simulation of normalized model (2.5) is carried out in order to illustrate the qualitative results by using available parameter values from existing literature as well as estimated ones. Unless otherwise stated parameter values appeared in Table 2.3 will be used during the simulation process.

2.4.1 Impact of vaccination and treatment rates on effective reproduction number R_e

In this section we analyze the effective reproduction number R_e in terms of vaccination rate ρ of newly born babies and treatment rate ν of severely infected individuals. The aim here is to determine by using the threshold R_e whether or not the vaccination and treatment coverage control or eliminate TB from the community.

Figure 2.2 shows the effect of vaccination rate ρ and treatment rate ν of severely infected individuals on effective reproduction number R_e when $\beta = 1.6$. All other parameters are given in Table 2.3. As expected when the vaccination rate ρ is fixed then the effective reproduction number R_e decreases as treatment rate of severely infected individuals ν increases and vice versa. The combination of vaccination coverage and treatment of infectious individuals can reduce the threshold R_e to less than unity. Therefore the best intervention strategy can be vaccination of newly born babies and treatment of severely infected individuals or combination of vaccination and treatment.

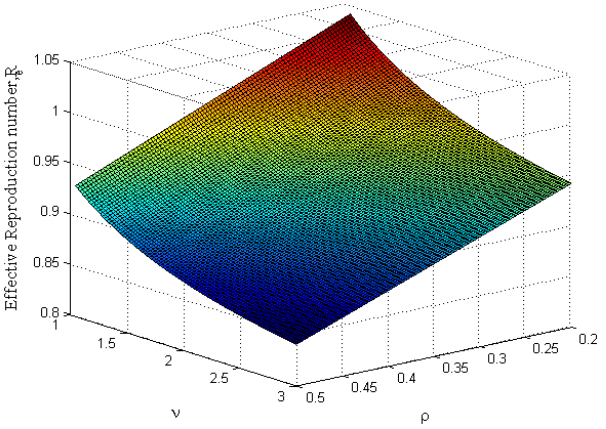

Figure 2.2: Graph of effective reproduction ratio R_e in terms of ρ and ν when $\beta = 1.6$. All other parameters are as in Table 2.3.

2.4.2 Numerical Simulation of model 2.5 when $R_e < 1$

The system (2.5) is solved by using forward Runge-Kutta fourth order scheme and MATLAB software with in-built ordinary differential equation (ode 45) solver used to simulate it to produce time series plot as shown in Figure 2.3. In Figure 2.3 dynamic behaviors of susceptible, vaccinated, latently infected, severely infected, mildly infected and treated classes when effective reproduction number 0.0169 is shown. The plot is produced by using estimated parametric values $\beta = 0.88; \theta = 0.067; \epsilon = 0.00396; \eta = 0.4; \lambda = 0.16; \delta_1 = 0.36; \omega = 0.6; \rho = 0.3; \nu = 0.6; \delta_2 = 0.3$ and $\phi = 0.5$. With initial values $s(0) = 0.55, v(0 = 0.15, l(0) = 0.1, i_1(0) = 0.1, i_2(0) = 0.05$ and $h(0) = 0.05$, the model 2.5 attains the asymptotic stability of disease free equilibrium point, $E_0 = (s^\star, v^\star, l^\star, i_1^\star, i_2^\star, h^\star) = (0.7885, 0.2115, 0, 0, 0, 0)$. In absence of attack, susceptible and vaccinated proportions increase with time to their carrying capacities. At disease free equilibrium point both susceptible and vaccinated they add up to the maximum carrying capacity of population proportions in the community, i.e. $s^\star + v^\star = 1$. On the other hand, latently infected and treated proportions in Figure 2.3 respectively increase with time and decrease to zero with increasing time. In additional infectious groups (severely and mildly infected proportions) decrease and attain disease free equilibrium as time increases. That is in presence of intervention (control strategies) the disease seem to clear from community since the effective reproduction number is $R_e = 0.0169 < 1$. This result supports the theorem of local stability of disease free equilibrium.

2.4.3 Phase portraits illustrating dynamical behavior of population proportions at DFE.

In this section phase portraits to illustrate the dynamics of the model (2.5) at disease free equilibrium point for susceptible class versus latently infected, severely infected, mildly infected, and treated classes are plotted by using estimated parametric values $\beta = 0.88; \theta = 0.067; \epsilon = 0.00396; \eta = 0.4; \lambda = 0.16; \delta_1 = 0.36; \omega = 0.6; \rho = 0.3; \nu = 0.6; \delta_2 = 0.3$ and $\phi = 0.5$.

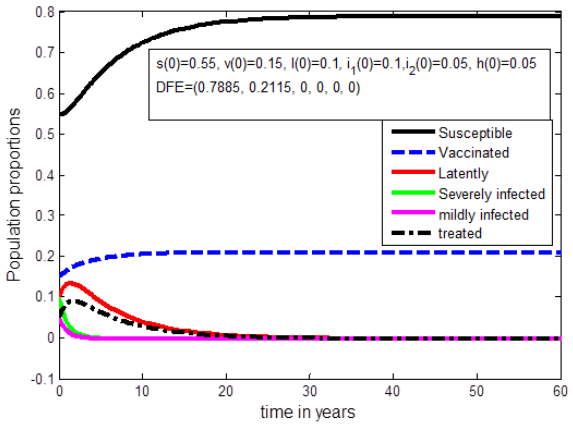

Figure 2.3: Shows the dynamics of susceptible, vaccinated, latently infected, severely infected, mildly infected and treated population proportions in presence of interventions with increasing time.

With different varying initial conditions, each curve of both latently infected and treated population proportions shown in Figure 2.4(a) and Figure 2.4(d) respectively increases for short period of time and finally sharply decrease and stabilize at disease free equilibrium point as time increases. Figure 2.4(b) and Figure 2.4(c) show that the proportions of severely infected and mildly infected decrease as susceptible proportion increases and stabilize at disease free equilibrium point.

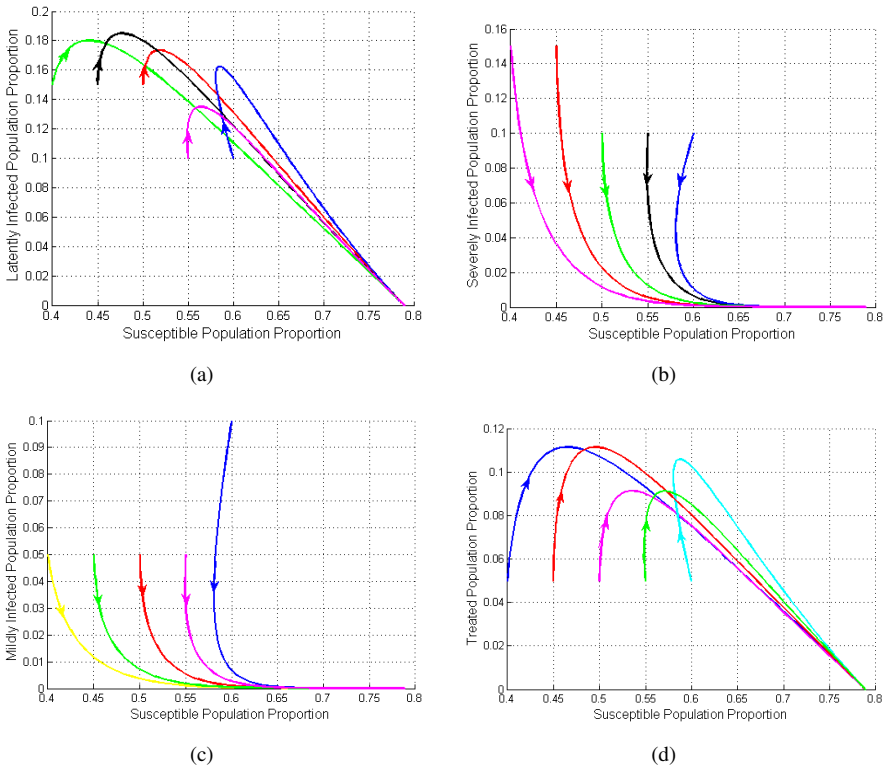

Figure 2.4: Shows Phase plane portraits for dynamics of susceptible population proportion and (a) latently infected (b) severely infected (c) mildly infected (d) treated population proportions showing disease free equilibrium point with varying initial values as time increases.

2.5 Conclusion

In this chapter, a continuous time deterministic model with vaccination and treatment as intervention strategies has been formulated to assess their impacts on transmission dynamics of Tuberculosis Infections. The disease free equilibrium has been proved to be stable when effective reproduction number, $R_e < 1$ and unstable otherwise. The numerical simulation results show that in presence of interventions, both severely and mildly infected population proportions decrease to zero and stabilize at disease free equilibrium as time increases. In addition, the numerical results show that, the combination of both vaccination and treatment reduce threshold R_e to less than unity and have desirable effect of clearing TB from community than when each strategy is taken at a time.

CHAPTER THREE

The Role of Re-Infection in Modeling the Dynamics of One-Strain Tuberculosis Involving Vaccination and Treatment[2]

Abstract: In this chapter, a continuous time deterministic model with vaccination and treatment strategies is formulated to assess the effect of reinfection on the transmission dynamics of Tuberculosis (TB). The involvement of reinfection in our model causes relapse and leads to the possibility of backward bifurcation at critical value of effective reproduction number $R_e = 1$ and hence the existence of multiple equilibria when effective reproduction number $R_e < 1$. This indicates that even by reducing effective reproduction number R_e below one is no longer a sufficient condition to eradicate the disease from community. An additional reduction of effective reproduction number R_e below the saddle-node bifurcation value is required to eradicate disease from community provided that the disease free equilibrium is globally asymptotically stable. Numerical simulation results are presented to validate analytical results. We suggest that reinfection is an important feature of TB and has to be considered when modeling the complex dynamics of TB.

3.1 Introduction

Tuberculosis (TB) is a chronic bacterial infectious disease caused by pathogen *Mycobacterium tuberculosis* with more than one-third of the world human population as its reservoir (Bloom, 1994; Feng et al., 2000; Miller, 1993). A global annual estimate of 8.6 million people develop Tuberculosis, of which 1.3 million die from disease. It is reported in WHO (2013) that, the burden of disease caused by TB is high in developing world where poor nutrition, congested accommodation and emergency of HIV are manifested. The global estimates of incidence,

[2]**This chapter is based on the published paper:**
Mlay, G. M., Luboobi, L. S., Kuznetsov, D., and Shahada, F. (2014). The Role of Re-Infection in Modeling the Dynamics of One-Strain Tuberculosis Involving Vaccination and Treatment. *Asian Journal of Mathematics and Applications*, 2014. Article ID ama025.

prevalence and mortality rates per 100,000 population in 2012 were respectively 255, 303 and 26 and Tanzania incidence, prevalence and mortality rates per 100,000 population were 165, 176 and 13 respectively as per WHO (2013). It therefore raises a quest to find desirable means to curtail TB morbidity and mortality rates.

Tuberculosis disease is mainly of two types: pulmonary and extra-pulmonary TB. Pulmonary TB is a common form of TB that affects lung while extra-pulmonary TB affects other parts of body and organs including central nervous system and bone (WHO, 2012). This particular study focuses on pulmonary TB. Tuberculosis is an epidemic disease spreading in the air when the infectious person with pulmonary TB expel bacteria by coughing, singing, sneezing, speaking and so on (Castillo-Chávez and Song, 2004). An individual with active TB has usual symptoms which are general weakness or tiredness, fever, weight loss, loss of appetite and night sweats. Further symptoms are coughing, coughing up of sputum and/ or blood, shortness of breath and chest pains if the infection in the lung get worse (Cohen and Murray, 2004). TB draws back economics of the world and Tanzania in particular as it affects men than women and especially the productive working group (WHO, 2012). In absence of HIV a small proportion of about 10% of infected individuals with *Mycobacterium tuberculosis* develop TB and becomes infectious within two years upon infected (Rodrigues, 2009). Most become latent for the rest of their lives as long as their immune system is not compromised (Castillo-Chávez and Song, 2004). The recovered individuals from TB do not acquire the permanent immunity. Some of them they become latent again. Even with treatment interventions, the rates of reinfection TB are higher than those of new TB (Rodrigues, 2009). Mathematical modeling of epidemiology of Tuberculosis has recently become the powerful tool to study the complex dynamics of the disease and explore the role of various TB features such as reinfection and reactivation. Feng et al. (2000) formulated mathematical model of TB with exogenous re-infection. The results of their work suggest that exogenous reinfection has drastic effect on qualitative dynamics of TB and it allows the possibility of subcritical bifurcation at critical value of basic reproduction number

$R_0 = 1$. Buonomo and Lacitignola (2011) applied bifurcation method introduced in Castillo-Chávez and Song (2004) based on the use of center manifold theory (Carr, 1981) to derive conditions for existence of either forward or backward bifurcation for vaccination model introduced in Gumel and Moghadas (2003). They clearly explain the role of vaccination, treatment and transmission parameters for the occurrence of forward or backward bifurcation. Okuonghae and Aihie (2008) examined the effect of Direct Observation Therapy Strategy (DOTS) on dynamics of TB against the fraction of active cases detected. They formulated mathematical model that involves the fraction of detected cases undergoing treatment under DOTS and other fraction not detected. The qualitative analysis of this model shows that in presence of exogenous re-infection, reproduction number must be outside the bifurcation range for disease free equilibrium to be asymptotically stable. The parameter for case detection has shown to be important in reducing backward bifurcation range as well as reducing the reproduction number. They further argued that if the critical level for case detection parameter is not reached then TB persist in population and become endemic. Kim et al. (2014) propose mathematical model of TB that includes exogenous reinfection in order to understand the recent increase of TB incidences in Korea. In their study, parameter for case finding effort was found to be significant impacting component on curbing active TB cases. They recommended that for dramatic reduction of TB incidences, the treatment of active TB cases should be accompanied by case finding (taking medication before the actual active TB has clinically diagnosed) effort than to take each measure alone. This chapter concentrates on investigating the role of re-infection on the one strain TB model with vaccination and treatment and its impact on TB transmission dynamics. Bifurcation and stability analysis of equilibrium points are properly investigated.

3.2 Model Formulation

Our population model is subdivided into six compartments and is developed from the basic SEIT (Susceptible-Exposed-Infectious-Treated) compartmental model. A compartment of Vaccinated population (V) is added to form SVEIT model. In addition compartment of infectious population (I) is subdivided into two compartments which are severely infected population (I_1) and mildly infected population (I_2). Severely infected population (I_1) progresses faster to treatment group compared to mild infected population (I_2). In this model susceptible population will be recruited at a rate λ. Some susceptible individuals will come into contact with infectious individuals and being infected at a rate of β. A proportion, ρ of babies will be vaccinated at birth while the remaining proportion $(1-\rho)$ will be left out of vaccination to join the susceptible population. Once vaccinated babies loose immunity they become susceptible at per-capita rate θ, whereby $1/\theta$ is the period after which a vaccinated baby looses immunity. The Latently infected individuals progress to active TB through endogenous reactivation. The proportion $(1-\eta)$ of Latently infected individuals progresses fast to severely infected class, I_1 while the remaining proportion, η progresses slowly to mildly infected class, I_2 at the same per-capita rate ϵ. Under usual circumstances mildly infected individuals take a long time to progress to treatment group, T than severely infected individuals. That is a proportion, ϕ of mildly infected individuals progresses to treatment group, T while the remaining proportion, $1-\phi$ progresses to severely infected class, I_1 at the same per-capita rate ω. The severely infected individuals progress to treatment group at a rate of ν. The treatment group, T is assumed to undergo exogenous re-infection and relapse back to Latent group with infection level, γ. The infectious individuals I_1 and I_2 are assumed to die at disease induced mortality rates of δ_1 and δ_2 respectively while the rest die naturally at a rate of μ. All variables and parameters are assumed to be non-negative. In addition the following assumptions are taken into consideration during the formulation of the model:

i. All individuals are born susceptible.

ii. The members of population mix homogeneously.

iii. Age, sex, social status, do not affect the probability of being infected.

iv. Natural recovery is negligible and hence ignored.

v. Vaccinated population looses immunity and become Susceptible.

vi. No more Vaccination can be administered to an individual infected with TB or to someone who previously was vaccinated.

vii. Once recovered from Treatment an individual reverts to be Latent and may experience another episode of disease.

viii. Once an individual is infected he/she will not recover if no treatment is given.

The above description of model formulation together with the assumptions leads to compartmental diagram in Figure 3.1.The full description of variables and parameters used to formulate the model are in Table 3.1 and Table 3.2 respectively:

Table 3.1: Description of variables of the model

Variable	Descriptions
$S(t)$	The Susceptible who are at risk of being infected at time t
$L(t)$	The latently infected individuals at time t
$V(t)$	Vaccinated individuals at time t
$I_1(t)$	Individuals who are severely infected with TB at time t
$I_2(t)$	Individuals who are mildly infected with TB at time t
$T(t)$	Individuals Treated against TB at time t

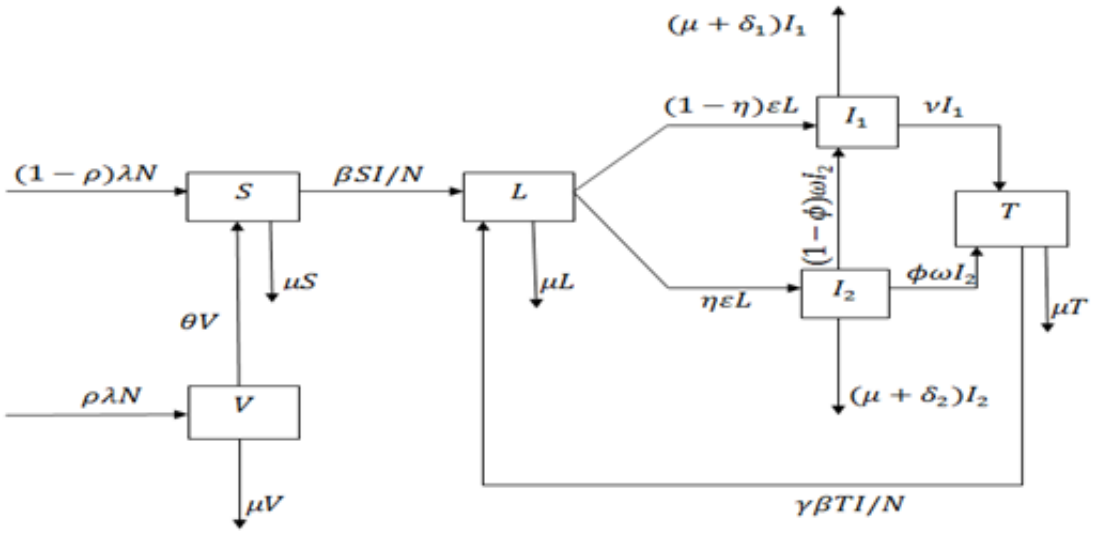

Figure 3.1: Schematic flow diagram showing dynamics of tuberculosis where $I = I_1 + I_2$.

3.2.1 Equations of the Model.

Basing on assumptions made and relationship that exists between variables and parameters shown in Figure 3.1 the system of six ordinary differential equations that describes the dynamics of tuberculosis in presence of vaccination and treatment is given by:

$$\frac{dS}{dt} = (1-\rho)\lambda N - \beta S\frac{(I_1+I_2)}{N} - \mu S + \theta V \tag{3.1a}$$

$$\frac{dV}{dt} = \rho\lambda N - (\mu+\theta)V \tag{3.1b}$$

$$\frac{dL}{dt} = \beta S\frac{(I_1+I_2)}{N} + \gamma\beta T\frac{(I_1+I_2)}{N} - (\mu+\epsilon)L \tag{3.1c}$$

$$\frac{dI_1}{dt} = (1-\eta)\epsilon L + (1-\phi)\omega I_2 - (\mu+\delta_1+\nu)I_1 \tag{3.1d}$$

$$\frac{dI_2}{dt} = \eta\epsilon L - (\mu+\omega+\delta_2)I_2 \tag{3.1e}$$

$$\frac{dT}{dt} = \nu I_1 + \phi\omega I_2 - \left(\mu+\gamma\beta\frac{(I_1+I_2)}{N}\right)T \tag{3.1f}$$

$$N = S + V + L + I_1 + I_2 + T. \tag{3.1g}$$

Table 3.2: Description of Parameters of the model

Parameter	Descriptions
λ	Per capita birth rate.
β	Per capita infection rate.
ρ	Proportional of babies who are being vaccinated at birth.
θ	The rate at which a vaccinated individual looses immunity.
ϵ	The rate of progression from Latent class to both severely and mildly Infected classes.
η	Proportional of Latently infected population progressing to mild infected class.
μ	Per capita natural death rate.
δ_1	Per capita additional death rate of severely infected class.
δ_2	Per capita additional death rate of mildly infected class.
ϕ	Proportional of mildly infected class who are treated.
ω	The transferring rate of mildly infected to both severely infected and treatment classes.
ν	The rate at which a severely infected candidate is transferred to treatment class.
γ	The factor that reduces the level of reinfection.

By adding the state equations in (3.1) we end up with rate of change of population,

$$\frac{dN}{dt} = (\lambda - \mu)N - \delta_1 I_1 - \delta_2 I_2. \tag{3.2}$$

3.2.2 Normalization of the Model.

The model (3.1) can easily be analyzed after being normalized such that the total population proportion is one. The normalization is done by scaling the population of each compartment by the total population. We transform the actual proportions by setting:

$$s = \frac{S}{N}, \;\; v = \frac{V}{N}, \;\; l = \frac{L}{N}, \;\; i_1 = \frac{I_1}{N}, \;\; i_2 = \frac{I_2}{N}, \;\; h = \frac{T}{N}. \tag{3.3}$$

whereby $s + v + l + i_1 + i_2 + h = 1$.

Substituting (3.3) into (3.2) we end up with:

$$\frac{dN}{dt} = (\lambda - \mu - \delta_1 i_1 - \delta_2 i_2)N \tag{3.4}$$

Upon differentiating the proportions in (3.3) with respect to time t and simplifying, leads to the following dimensionless system:

$$\frac{ds}{dt} = (1-\rho)\lambda + \theta v - (\lambda + \beta(i_1 + i_2) - \delta_1 i_1 - \delta_2 i_2)s, \tag{3.5a}$$
$$\frac{dv}{dt} = \rho\lambda - (\lambda + \theta - \delta_1 i_1 - \delta_2 i_2)v, \tag{3.5b}$$
$$\frac{dl}{dt} = \beta s(i_1 + i_2) + \gamma\beta h(i_1 + i_2) - (\lambda + \epsilon - \delta_1 i_1 - \delta_2 i_2)l, \tag{3.5c}$$
$$\frac{di_1}{dt} = (1-\eta)\epsilon l + (1-\phi)\omega i_2 - (\lambda + \delta_1 + \nu - \delta_1 i_1 - \delta_2 i_2)i_1, \tag{3.5d}$$
$$\frac{di_2}{dt} = \eta\epsilon l - (\lambda + \omega + \delta_2 - \delta_1 i_1 - \delta_2 i_2)i_2, \tag{3.5e}$$
$$\frac{dh}{dt} = \nu i_1 + \phi\omega i_2 - (\lambda + \gamma\beta(i_1 + i_2) - \delta_1 i_1 - \delta_2 i_2)\, h \tag{3.5f}$$

subject to condition $s + v + l + i_1 + i_2 + h = 1$. It can be shown that all the feasible solutions of system (3.5) enter the region of biological interest defined by

$$\Omega = \left\{(s, v, l, i_1, i_2, h) \in \mathbb{R}^6_+ : s + v + l + i_1 + i_2 + h = 1\right\}$$

that is positive-invariant. It is enough to consider the dynamics of the flow generated by system (3.5) in Ω. In this region, the model (3.5) is considered to be both biologically and mathematically well posed (Hethcote, 2000).

3.3 Analysis of a Model

We analyze model (3.5) in order to get some insights on dynamics of TB disease and transmission.

3.3.1 Existence and Local Stability of DFE

Let $E_0 = (s^\star, v^\star, l^\star, i_1^\star, i_2^\star, h^\star)$ be a DFE point of model (3.5). We set zero to the right hand side of each equation in (3.5) and assume that in absence of disease attack, $l = i_1 = i_2 = h = 0$ to solve the steady state solution. The disease free equilibrium point is therefore given by : $E_0 = E_0 = (s^\star, v^\star, l^\star, i_1^\star, i_2^\star, h^\star) = \left(\frac{\theta + \lambda(1-\rho)}{\lambda + \theta}, \frac{\rho\lambda}{\lambda + \theta}, 0, 0, 0, 0\right)$. Before we prove for local stability of DFE we define and determine the effective reproduction number, R_e of model (3.5).

Definition 3.3. The effective reproduction number, R_e is defined as the measure of average number of infections caused by a single infectious individual introduced in a community in which intervention strategies (in our case is treatment and vaccination) are administered (Okuonghae and Korobeinikov, 2007).

The effective reproduction number R_e is computed by using next generation operator method (Van den Driessche and Watmough, 2002) and found to be:

$$R_e = \frac{\beta(\theta + \lambda(1-\rho))}{(\lambda + \theta)} \left[\frac{(1-\eta)(\lambda + \omega + \delta_2)\epsilon + (1-\phi)\omega\eta\epsilon}{(\lambda + \epsilon)(\lambda + \omega + \delta_2)(\lambda + \delta_1 + \nu)} + \frac{\eta\epsilon}{(\lambda + \epsilon)(\lambda + \omega + \delta_2)} \right]$$

$$= \frac{\beta(\theta + \lambda(1-\rho))\left[(1-\eta)(\lambda + \omega + \delta_2)\epsilon + ((1-\phi)\omega + \lambda + \delta_1 + \nu)\eta\epsilon\right]}{(\lambda + \theta)(\lambda + \epsilon)(\lambda + \omega + \delta_2)(\lambda + \delta_1 + \nu)} \tag{3.6}$$

Theorem 3.4. *The disease free equilibrium of model* (3.5)*, given the effective reproduction number, R_e is locally asymptotically stable if $R_e < 1$ and unstable if $R_e > 1$.*

Proof. We prove Theorem 3.4 for local stability of DFE by asserting that the trace and determinant of Jacobian matrix at DFE denoted by $J(E_0)$ are strictly negative and positive respectively. Jacobian matrix evaluated at disease free equilibrium point is given by:

$$J(E_0) = \begin{bmatrix} -\lambda & \theta & 0 & -(\beta+\delta_1)c_1 & -(\beta+\delta_2)c_1 & 0 \\ 0 & -(\lambda+\theta) & 0 & \frac{\rho\lambda}{\lambda+\theta}\delta_1 & \frac{\rho\lambda}{\lambda+\theta}\delta_2 & 0 \\ 0 & 0 & -(\lambda+\epsilon) & \beta c_1 & \beta c_1 & 0 \\ 0 & 0 & (1-\eta)\epsilon & -(\lambda+\delta_1+\nu) & (1-\phi)\omega & 0 \\ 0 & 0 & \eta\epsilon & 0 & -(\lambda+\omega+\delta_2) & 0 \\ 0 & 0 & 0 & \nu & \phi\omega & -\lambda \end{bmatrix}.$$

whereby $c_1 = \dfrac{\theta+\lambda(1-\rho)}{\lambda+\theta}$. Trace and determinant of matrix $J(E_0)$ denoted by Tr$(J(E_0))$ and $\det(J(E_0))$ are respectively given by:

$$\text{Tr}(J(E_0)) = -(6\lambda+\theta+\epsilon+\nu+\omega+\delta_1+\delta_2) < 0$$

and

$$\det(J(E_0)) = -\lambda^2(\lambda+\theta)\begin{vmatrix} (\lambda+\epsilon) & \beta\left(\frac{\theta+\lambda(1-\rho)}{\lambda+\theta}\right) & \beta\left(\frac{\theta+\lambda(1-\rho)}{\lambda+\theta}\right) \\ (1-\eta)\epsilon & -(\lambda+\delta_1+\nu) & (1-\phi)\omega \\ \eta\epsilon & 0 & -(\lambda+\omega+\delta_2) \end{vmatrix}$$

$$= -\lambda^2(\lambda+\theta)\left[\frac{\beta(\theta+\lambda(1-\rho))}{(\lambda+\theta)}\{(1-\eta)(\lambda+\omega+\delta_2)\epsilon + ((1-\phi)\omega+\lambda+\delta_1+\nu)\eta\epsilon\} - (\lambda+\epsilon)(\lambda+\omega+\delta_2)(\lambda+\delta_1+\nu)\right]$$

$$= -A\left[\frac{\beta(\theta+\lambda(1-\rho))}{(\lambda+\theta)}\left\{\frac{(1-\eta)(\lambda+\omega+\delta_2)\epsilon + ((1-\phi)\omega\eta\epsilon}{(\lambda+\epsilon)(\lambda+\omega+\delta_2)(\lambda+\delta_1+\nu)} + \frac{\eta\epsilon}{(\lambda+\epsilon)(\lambda+\omega+\delta_2)}\right\} - 1\right]$$

$$= -A(R_e - 1).$$

where $A = \lambda^2(\lambda+\theta)(\lambda+\epsilon)(\lambda+\delta_1+\nu)(\lambda+\omega+\delta_2) > 0$.

We find that Tr$(J(E_0))$ is strictly negative and $\det(J(E_0))$ is strictly positive if and only if $R_e < 1$. We therefore conclude that DFE is locally asymptotically stable. □

3.3.2 Global Analysis of DFE of a model with interventions

We analyze the global stability of disease free equilibrium point of model (3.5) by using an approach presented in Castillo-Chávez et al. (2002). The model (3.5) can be written in the following format:

$$\begin{cases} \frac{dX_n}{dt} &= A(X_n - X_{E_0,n}) + A_1 X_i, \\ \frac{dX_i}{dt} &= A_2 X_i. \end{cases} \tag{3.7}$$

From (3.7), X_n and X_i are vectors of non-transmitting and transmitting compartments respectively. $X_{E_0,n}$ is a vector at disease free equilibrium point E_0 of the same length as X_n. From model (3.5) we define:

$X_n = (s, v, h)^T, X_i = (l, i_1, i_2)^T, X_{E_0,n} = \left(\frac{\theta + \lambda(1-\rho)}{\lambda + \theta}, \frac{\rho\lambda}{\lambda + \theta}, 0\right)$ and

$$X_n - X_{E_0,n} = \begin{bmatrix} s - \dfrac{\theta + \lambda(1-\rho)}{\lambda + \theta} \\ v - \dfrac{\rho\lambda}{\lambda + \theta} \\ h \end{bmatrix}.$$

For global stability of DFE we need to show that matrix A has real negative eigenvalues and A_2 is a Metzler matrix (i.e. the off-diagonal elements of A_2 are non-negative, symbolically denoted by $A_2(x_{ij}) \geq 0, \forall i \neq j$). Using system (3.5), then the first and second equations in (3.7) can be written respectively in expanded form as:

$$\begin{bmatrix} (1-\rho)\lambda + \theta v - (\lambda + \beta(i_1 + i_2) - \delta_1 i_1 - \delta_2 i_2)s \\ \rho\lambda - (\lambda + \theta - \delta_1 i_1 - \delta_2 i_2)v \\ \nu i_1 + \phi\omega i_2 - (\lambda + \gamma\beta(i_1 + i_2) - \delta_1 i_1 - \delta_2 i_2)\, h \end{bmatrix} = A \begin{bmatrix} s - \dfrac{\theta + \lambda(1-\rho)}{\lambda + \theta} \\ v - \dfrac{\rho\lambda}{\lambda + \theta} \\ h \end{bmatrix} + A_1 \begin{bmatrix} l \\ i_1 \\ i_2 \end{bmatrix}$$

and

$$\begin{bmatrix} \beta s(i_1 + i_2) + \gamma\beta h(i_1 + i_2) - (\lambda + \epsilon - \delta_1 i_1 - \delta_2 i_2)l \\ (1-\eta)\epsilon l + (1-\phi)\omega i_2 - (\lambda + \delta_1 + \nu - \delta_1 i_1 - \delta_2 i_2)i_1 \\ \eta\epsilon l - (\lambda + \omega + \delta_2 - \delta_1 i_1 - \delta_2 i_2)i_2 \end{bmatrix} = A_2 \begin{bmatrix} l \\ i_1 \\ i_2 \end{bmatrix}.$$

For compatibility, matrices A, A_1 and A_2 should be of order 3×3. By using non-transmitting elements from Jacobian matrix of system (3.5) and representation in (3.7) we find that:

$$A = \begin{bmatrix} -\lambda & \theta & 0 \\ 0 & -(\lambda + \theta) & 0 \\ 0 & 0 & -\lambda \end{bmatrix}, \; A_1 = \begin{bmatrix} 0 & (-\beta + \delta_1)s & (-\beta + \delta_2)s \\ 0 & \delta_1 v & \delta_2 v \\ 0 & v + h(\delta_1 - \gamma\beta) & \phi\omega + h(\delta_2 - \gamma\beta) \end{bmatrix} \text{ and,}$$

$$A_2 = \begin{bmatrix} -(\lambda+\epsilon) & \beta(s+\gamma h)+\delta_1 l & \beta(s+\gamma h)+\delta_2 l \\ (1-\eta)\epsilon & -(\lambda+\nu+\delta_1(1-i_1)) & (1-\phi)\omega+\delta_2 i_1 \\ \eta\epsilon & \delta_1 i_2 & -(\lambda+\omega+\delta_2(1-i_2)) \end{bmatrix}.$$

We find that A is upper triangular matrix whose eigeinvalues are located on its main diagonal. Therefore eigenvalues of A (i.e. $-\lambda, -(\lambda+\theta)$ and $-\lambda$) are real and negative. In addition A_2 is a Metzler matrix since its off-diagonal elements are non-negative. That is $0 \leq l, i_1, i_2, h < 1$ and both $(1-i_1)$ and $(1-i_2)$ are strictly positive. Therefore DFE for system (3.5) is globally asymptotically stable in region Ω. We have established important theorem:

Theorem 3.5. *The disease-free equilibrium point is globally asymptotically stable in* Ω *if* $R_e < 1$ *and unstable if* $R_e > 1$.

3.3.3 Existence of Endemic Equilibrium Point (EEP) of model with interventions

Let $E_2(s^\star, v^\star, l^\star, i_1^\star, i_2^\star, h^\star)$ be an endemic equilibrium point of model (3.5). The conditions of existence of endemic equilibrium point E_2 are obtained by setting the right hand side of each equation in (3.5) equal to zero and solve model (3.5) in terms of force of infection $f^\star = \beta(i_1+i_2)$ at steady state. Let $k = \lambda - \delta_1 i_1^\star - \delta_2 i_2^\star > 0$, for any pairwise choice of $i_1^\star$ and $i_2^\star$ values at endemic equilibrium. An endemic equilibrium point in terms of force of infection is

given by:

$$\left.\begin{aligned}
s^\star &= \frac{\lambda(\theta + k(1-\rho))}{(f^\star + k)(\theta + k)}, \\
v^\star &= \frac{\rho\lambda}{\theta + k}, \\
l^\star &= \frac{\lambda(\omega + \delta_2 + k)a_3(\gamma f^\star + k)f^\star}{\eta(f^\star + k)(\theta + k)\{a_4(\gamma f^\star + k) - \epsilon\gamma f^\star(\nu a_1 + a_2)\}}, \\
i_1^\star &= \frac{\lambda\epsilon a_3(\gamma f^\star + k)f^\star}{(f^\star + k)(\theta + k)\{a_4(\gamma f^\star + k) - \epsilon\gamma f^\star(\nu a_1 + a_2)\}}, \\
i_2^\star &= \frac{\lambda\eta\epsilon(\theta + k(1-\rho))(\gamma f^\star + k)(\delta_1 + \nu + k)f^\star}{(f^\star + k)(\theta + k)\{a_4(\gamma f^\star + k) - \epsilon\gamma f^\star(\nu a_1 + a_2)\}}, \\
h^\star &= \frac{\lambda\epsilon(\theta + k(1-\rho))(\nu a_1 + a_2)f^\star}{(f^\star + k)(\theta + k)\{a_4(\gamma f^\star + k) - \epsilon\gamma f^\star(\nu a_1 + a_2)\}}.
\end{aligned}\right\} \tag{3.8}$$

In (3.8) we define,

$$\begin{aligned}
a_1 &= (1-\eta)(\omega + \delta_2 + k) + (1-\phi)\omega\eta, \\
a_2 &= \phi\omega\eta(\delta_1 + \nu + k), \\
a_3 &= \{(1-\eta)(\omega + \delta_2 + k) + (1-\phi)\omega\eta\}(\theta + k(1-\rho)), \\
a_4 &= (\epsilon + k)(\omega + \delta_2 + k)(\delta_1 + \nu + k).
\end{aligned}$$

If we substitute representations of $i_1^\star$ and $i_2^\star$ from (3.8) into the force of infection, $f^\star = \beta(i_1 + i_2)$ or $f^\star - \beta(i_1 + i_2) = 0$ we find that:

$$f^\star - \beta\left[\frac{\lambda\epsilon(\theta + k(1-\rho))(\gamma f^\star + k)f^\star[a_1 + \eta(\delta_1 + \nu + k)]}{(f^\star + k)(\theta + k)\{a_4(\gamma f^\star + k) - \epsilon\gamma f^\star(\nu a_1 + a_2)\}}\right] = 0 \tag{3.9}$$

Manipulating and simplifying (3.9) we end up with the following cubic polynomial:

$$f^\star\left(A_1 f^{\star 2} + B_1 f^\star + C_1\right) = 0 \tag{3.10}$$

whereby

$$\begin{aligned} A_1 &= \gamma\left[M-(\nu P+Q)(\theta+k)\right], \\ B_1 &= k\left(M+\gamma\left[M-(\nu P+Q)(\theta+k)\right]\right)-\beta a_5\gamma\left(P+(\delta_1+\nu+k)\eta\epsilon\right), \\ C_1 &= k\left(Mk-\beta a_5\left[P+(\delta_1+\nu+k)\eta\epsilon\right]\right). \end{aligned} \tag{3.11}$$

Furthermore in terms of parameters of model (3.5) we define:

$$M=(\theta+k)(\epsilon+k)(\omega+\delta_2+k)(\delta_1+\nu+k);\ P=(1-\eta)(\omega+\delta_2+k)\epsilon+(1-\phi)\omega\eta\epsilon;$$
$$Q=\phi\omega\eta\epsilon(\delta_1+\nu+k) \text{ and } a_5=\lambda(\theta+k(1-\rho)).$$

We write C_1 in the following format:

$$C_1=(\theta+k)(\epsilon+k)(\omega+\delta_2+k)(\delta_1+\nu+k)k^2(1-R_e). \tag{3.12}$$

From (3.12), $(\theta+k)(\epsilon+k)(\omega+\delta_2+k)(\delta_1+\nu+k)k^2>0$ and R_e is effective reproduction number as indicated in (3.6).

From (3.10), $f^\star=\beta(i_1+i_2)=0$ corresponds to Disease Free Equilibrium (DFE) that we have already discussed while $A_1f^{\star 2}+B_1f^\star+C_1=0$, that can be also be written in the form:

$$f^\star=\frac{-B_1\pm\sqrt{B_1^2-4A_1C_1}}{2A_1}, \tag{3.13}$$

satisfies Endemic Equilibrium. The value of A_1 is strictly positive. Depending on the signs of B_1 and C_1 we have three cases to consider in order to have positive root of force of infection as follows:

Case 1: In absence of re-infection we find that the parameter for level of reinfection, $\gamma=0$. This implies from (3.11) that $A_1=0$. The polynomial $A_1f^{\star 2}+B_1f^\star+C_1=0$ becomes linear, i.e. $B_1f^\star+C_1=0$ or $f^\star=\dfrac{-C_1}{B_1}$. If $B_1>0$ then system (3.5) has stable endemic equilibrium when $C_1<0$. This equilibrium happens when $R_e>1$ as interpreted from (3.12). In this case

backward bifurcation is not possible due to absence of multiple equilibria.

Case 2: Exactly one endemic equilibrium point. From (3.13), suppose $B_1 < 0$ and $C_1 = 0$ or $B_1^2 - 4A_1C_1 = 0$. This means the polynomial has just one positive root and hence the system (3.5) has unique endemic equilibrium.

Case 3: Two endemic equilibria

If $B_1 < 0$, $C_1 > 0$ and $B_1^2 - 4A_1C_1 > 0$, then the polynomial $A_1f^{\star 2} + B_1f^{\star} + C_1 = 0$ has two positive roots. This means that the system (3.5) has two endemic equilibria and hence the possibility of backward bifurcation. These three cases are summarized under the following theorem:

Theorem 3.6. *The number of positive endemic equilibria of Tuberculosis model* (3.5) *is hereunder summarized as follows:*

i. If $C_1 < 0$, $R_e > 1$, then the system has a unique endemic equilibrium.

ii. If $B_1 < 0$ and $C_1 = 0$ or $B_1^2 - 4A_1C_1 = 0$, then the system has exactly one endemic equilibrium.

iii. If $B_1 < 0$, $C_1 > 0$ and $B_1^2 - 4A_1C_1 > 0$, the system has exactly two endemic equilibria.

iv. Otherwise there are no endemic equilibria, i.e. when $A_1C_1 > 0$ and $B_1 > 0$.

From (iii), the critical point of effective reproduction number R_e^c at which a backward bifurcation occurs is computed by setting the discriminant in (3.13) equals to zero. Thus, $B_1^2 - 4A_1C_1 = 0$ implies that

$$B_1^2 - 4A_1(\theta + k)(\epsilon + k)(\omega + \delta_2 + k)(\delta_1 + \nu + k)k^2(1 - R_e^c) = 0$$

$$\text{and } R_e^c = 1 - \frac{B_1^2}{4A_1}(\theta + k)(\epsilon + k)(\omega + \delta_2 + k)(\delta_1 + \nu + k)k^2.$$

Thus backward bifurcation occurs in the range $R_e^c < R_e < 1$. Furthermore, we note from (13) that disease will be endemic if force of infection is strictly positive (i.e. $f^\star > 0$) and both B_1 and A_1C_1 are strictly negative. Thus, $A_1 > 0$ and $A_1(\theta+k)(\epsilon+k)(\omega+\delta_2+k)(\delta_1+\nu+k)k^2(1-R_e) < 0$ if and only if $R_e > 1$. Therefore endemic equilibrium point $E_2(s^\star, v^\star, l^\star, i_1^\star, i_2^\star, h^\star)$ is stable if and only if $R_e > 1$.

3.3.4 Stability of Endemic Equilibrium Point (EEP) of model with intervention

The stability of an endemic equilibrium E_2 of model (3.5) is analyzed by using Centre Manifold theory (Carr, 1981) as described in Theorem 4.1 of Castillo-Chávez and Song (2004). We change the variables of model (5) by setting $s = x_1, v = x_2, l = x_3, i_1 = x_4, i_2 = x_5, h = x_6$ such that $\sum_{i=1}^{6} x_i = 1$. We define vector $X = (x_1, x_2, , x_3, x_4, x_5, x_6)^T$ and $F = (f_1, f_2, , f_3, f_4, f_5, f_6)^T$ in such a way that the model (3.5) is re-written in the form $\frac{dX}{dt} = F$ as follows:

$$\begin{cases} \dot{x_1} = f_1 &= (1-\rho)\lambda + \theta x_2 - (\lambda + \beta(x_4+x_5) - \delta_1 x_4 - \delta_2 x_5)x_1, \\ \dot{x_2} = f_2 &= \rho\lambda - (\lambda + \theta - \delta_1 x_4 - \delta_2 x_5)x_2, \\ \dot{x_3} = f_3 &= \beta x_1(x_4+x_5) + \gamma\beta x_6(x_4+x_5) - (\lambda + \epsilon - \delta_1 x_4 - \delta_2 x_5)x_3, \\ \dot{x_4} = f_4 &= (1-\eta)\epsilon x_3 + (1-\phi)\omega x_5 - (\lambda + \delta_1 + \nu - \delta_1 x_4 - \delta_2 x_5)x_4, \\ \dot{x_5} = f_5 &= \eta\epsilon x_3 - (\lambda + \omega + \delta_2 - \delta_1 x_4 - \delta_2 x_5)x_5, \\ \dot{x_6} = f_6 &= \nu x_4 + \phi\omega x_5 - (\lambda + \gamma\beta(x_4+x_5) - \delta_1 x_4 - \delta_2 x_5)\, x_6. \end{cases} \tag{3.14}$$

The Jacobian matrix $J(E_0)$ of system (3.14) at disease free equilibrium E_0 presented in Section 3.3.1 is given by

$$J(E_0) = \begin{bmatrix} -\lambda & \theta & 0 & (-\beta+\delta_1)r_1 & (-\beta+\delta_2)r_2 & 0 \\ 0 & -(\lambda+\theta) & 0 & \delta_1 r_2 & \delta_2 r_2 & 0 \\ 0 & 0 & -(\lambda+\epsilon) & \beta r_1 & \beta r_1 & 0 \\ 0 & 0 & (1-\eta)\epsilon & -d_1 & (1-\phi)\omega & 0 \\ 0 & 0 & \eta\epsilon & 0 & -d_2 & 0 \\ 0 & 0 & 0 & \nu & \phi\omega & -\lambda \end{bmatrix}. \tag{3.15}$$

From (3.15) we define $d_1 = \lambda+\delta_1+\nu$, $d_2 = \lambda+\omega+\delta_2$, $r_1 = \dfrac{\theta+\lambda(1-\rho)}{\lambda+\theta}$ and $r_2 = \dfrac{\rho\lambda}{\lambda+\theta}$. In particular case when basic reproduction number $R_e = 1$, we choose our bifurcation parameter be β and consider our bifurcation to take place at $\beta = \beta^\star$. Solving β from (3.6) when $R_e = 1$ we find that:

$$\beta = \beta^\star = \frac{(\lambda+\theta)(\lambda+\epsilon)(\lambda+\omega+\delta_2)(\lambda+\delta_1+\nu)}{(\theta+\lambda(1-\rho))\left[m_1+((1-\phi)\omega+\lambda+\delta_1+\nu)\eta\epsilon\right]}, \tag{3.16}$$

and from (3.16) we define, $m_1 = (1-\eta)(\lambda+\omega+\delta_2)\epsilon$. The Jacobian of transformed system (3.14) at $\beta = \beta^\star$ has simple zero eigenvalue that allows us to study the dynamics of the system (3.5) at $\beta = \beta^\star$ using Centre Manifold theory (Carr, 1981). The Jacobian of (3.14) denoted by $J(E_0)$ at $\beta = \beta^\star$ has right eigenvector that corresponds with zero eigenvalue given

by $\mathbf{w} = (w_1, w_2, w_3, w_4, w_5, w_6)^T$, whereby:

$$\begin{cases} w_1 &= \left[\dfrac{m_2 + \beta^\star r_1 \eta\epsilon(\delta_2 r_2\theta + (-\beta^\star + \delta_2)(\lambda+\theta)r_1)}{\lambda(\lambda+\theta)\beta^\star r_1\eta\epsilon}\right] w_5, \\ w_2 &= \left[\dfrac{\delta_1 r_2((\lambda+\epsilon)(\lambda+\omega+\delta_2) - \beta^\star r_1\eta\epsilon) + \delta_2 r_2\beta^\star r_1\eta\epsilon}{(\lambda+\theta)\beta^\star r_1\eta\epsilon}\right] w_5 > 0, \\ w_3 &= \dfrac{(\lambda+\omega+\delta_2)}{\eta\epsilon} w_5 > 0, \\ w_4 &= \left[\dfrac{(\lambda+\epsilon)(\lambda+\omega+\delta_2) - \beta^\star r_1\eta\epsilon}{\beta^\star r_1\eta\epsilon}\right] w_5 > 0, \\ w_5 &= w_5 > 0, \text{ free.} \\ w_6 &= \left[\dfrac{\nu[(\lambda+\epsilon)(\lambda+\omega+\delta_2) - \beta^\star r_1\eta\epsilon] + \phi\omega\beta^\star r_1\eta\epsilon}{\lambda\beta^\star r_1\eta\epsilon}\right] w_5 > 0. \end{cases} \tag{3.17}$$

From (3.17) we define,

$$\begin{aligned} k_1 &= (\lambda+\epsilon)(\lambda+\omega+\delta_2) - \beta^\star r_1\eta\epsilon, \\ m_2 &= (k_1 - \beta^\star r_1\eta\epsilon)(\delta_1 r_2\theta + (-\beta^\star + \delta_1)(\lambda+\theta)r_1), \\ r_1 &= \frac{\theta + \lambda(1-\rho)}{\lambda+\theta}. \end{aligned}$$

By using (3.17) we show that k_1 is strictly positive justifying that the components $w_2, w_4, w_6 > 0$ as follows:

$$\begin{aligned}
k_1 &= (\lambda+\epsilon)(\lambda+\omega+\delta_2) - \beta^\star r_1 \eta\epsilon, \\
&= (\lambda+\epsilon)(\lambda+\omega+\delta_2)\left(1 - \frac{\beta^\star r_1\eta\epsilon}{(\lambda+\epsilon)(\lambda+\omega+\delta_2)}\right), \\
&= (\lambda+\epsilon)(\lambda+\omega+\delta_2)\left(1 - \frac{(\lambda+\theta)(\lambda+\delta_1+\nu)r_1\eta\epsilon}{(\theta+\lambda(1-\rho))\left[m_1+((1-\phi)\omega+\lambda+\delta_1+\nu)\eta\epsilon\right]}\right), \\
&= (\lambda+\epsilon)(\lambda+\omega+\delta_2)\left(1 - \frac{(\lambda+\delta_1+\nu)\eta\epsilon}{m_1+((1-\phi)\omega+\lambda+\delta_1+\nu)\eta\epsilon}\right) > 0.
\end{aligned}$$

whereby, $m_1 = (1-\eta)(\lambda+\omega+\delta_2)\epsilon$. Moreover, the Jacobian matrix $J(E_0)$ at $\beta = \beta^\star$ has left eigenvector $\mathbf{\Psi} = (\Psi_1, \Psi_2, \Psi_3, \Psi_4, \Psi_5, \Psi_6)^T$ associated with zero eigenvalue satisfying the relation $\mathbf{\Psi w} = 1$, whereby:

$$\Psi_1 = \Psi_2 = \Psi_6 = 0,\ \Psi_3 = \frac{(\lambda+\delta_1+\nu)}{\beta^\star r_1}\Psi_4,\ \Psi_4 = \Psi_4 > 0 \text{ and}$$
$$\Psi_5 = \frac{(1-\phi)\omega+\lambda+\delta_1+\nu)}{\lambda+\omega+\delta_2}\Psi_4 > 0. \quad (3.18)$$

We compute the value of a and b that will govern totally the local dynamics of system (3.14) and determine whether it exhibits forward or backward bifurcation by employing Theorem 4.1 of Castillo-Chávez and Song (2004) and as restated in Theorem 3.7.

Theorem 3.7. *Consider the general system of ordinary differential equations* (3.14) *with a parameter β such that $\frac{dx}{dt} = f(x,\beta)$, $f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}$ and $f \in \mathbb{C}^2(\mathbb{R}^n \times \mathbb{R})$, where 0 is an equilibrium point of the system (i.e. $f(0,\beta) \equiv 0, \forall\beta$) and*

1. *$A = D_x f(0,0) = \left(\frac{\partial f_i}{\partial f_j}(0,0)\right)$ is Jacobian (linearization) matrix of the system around the equilibrium 0 with β evaluated at 0,*
2. *Zero is a simple eigenvalue of A and other eigenvalues of A have negative real parts;*
3. *Matrix A has a right eigenvector $\mathbf{w}$ and a left eigenvector $\mathbf{\Psi}$ corresponding to zero eigenvalue.*

Let f_k *be the* k^{th} *component of* f *and* $a = \sum_{k,i,j=1}^{n} \Psi_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0)$ *and* $b = \sum_{k,i=1}^{n} \Psi_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \beta}(0,0)$ *then the local dynamics of the system around the equilibrium point* 0 *is totally determined by the signs of* a *and* b*. In particular, if* $a > 0$ *and* $b > 0$ *then a backward bifurcation occur at* $\beta = 0$*. Signs of* $a > 0$ *and* $b > 0$ *play the vital role in describing the local dynamics of model* (3.14) *around equilibrium point* 0 *as follows:*

a). $a > 0, b > 0$*, when* $\beta < 0$ *with* $|\beta| \ll 1$*,* 0 *is locally asymptotically stable and there exists a positive unstable equilibrium, when* $0 < |\beta| \ll 1$*,* 0 *is unstable and there exists a negative and locally asymptotically stable equilibrium.*

b). $a < 0, b < 0$*, when* $\beta < 0$ *with* $|\beta| \ll 1$*,* 0 *is unstable, when* $0 < |\beta| \ll 1$*,* 0 *is asymptotically stable and there exists a positive unstable equilibrium.*

c). $a > 0, b < 0$*, when* $\beta < 0$ *with* $|\beta| \ll 1$*,* 0 *is unstable and there exists a locally asymptotically stable negative equilibrium, when* $0 < |\beta| \ll 1$*,* 0 *is stable and a positive unstable equilibrium appears.*

d). $a < 0, b > 0$ *when* β *changes from negative to positive,* 0 *changes its stability from stable to unstable. Correspondingly, negative unstable equilibrium becomes positive and locally asymptotically stable.*

Computation of a **and** b.

We compute the value of a and b that will govern totally the local dynamics of system (3.14) and determine the conditions for existence of backward bifurcation following the signs of a and b by employing Theorem 4.1 of Castillo-Chávez and Song (2004) and as implied in Theorem 3.7 of this chapter. Since the components of left eigenvector $\Psi_1 = \Psi_2 = \Psi_6 = 0$ (for $k = 1, 2$ and 6) we compute the values of a and b for only $k = 3, 4, 5$. The only non-zero second order

partial derivatives of (3.14) at DFE when $\beta = \beta^\star$ are:

$$\frac{\partial^2 f_3}{\partial x_1 \partial x_4} = \frac{\partial^2 f_3}{\partial x_1 \partial x_5} = \beta^\star,\ \frac{\partial^2 f_3}{\partial x_4 \partial x_6} = \frac{\partial^2 f_3}{\partial x_5 \partial x_6} = \gamma\beta^\star,\ \frac{\partial^2 f_3}{\partial x_3 \partial x_4} = \frac{\partial^2 f_5}{\partial x_4 \partial x_5} = \delta_1,$$
$$\frac{\partial^2 f_3}{\partial x_3 \partial x_5} = \frac{\partial^2 f_4}{\partial x_4 \partial x_5} = \delta_2,\ \frac{\partial^2 f_4}{\partial x_4^2} = 2\delta_1,\ \frac{\partial^2 f_5}{\partial x_5^2} = 2\delta_2.$$

By using $a = \sum_{k,i,j=1}^{n} \Psi_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0)$ we compute a as follows:

$$\begin{aligned} a &= \Psi_3(w_1 w_4 \beta^\star + w_1 w_5 \beta^\star + w_3 w_4 \delta_1 + w_3 w_5 \delta_2 + w_4 w_6 \gamma\beta^\star + w_5 w_6 \gamma\beta^\star) \\ &\quad + \Psi_3(2w_4^2\delta_1 + w_4 w_5 \delta_2) + \Psi_5(w_4 w_5 \delta_1 + 2w_5^2 \delta_2), \end{aligned} \tag{3.19}$$

$$\begin{aligned} &= \Psi_3 \beta^\star w_1(w_4 + w_5) + w_6 \gamma \Psi_3 \beta^\star (w_4 + w_5) + w_4 \delta_1(\Psi_3 w_3 + 2\Psi_4 w_4 + \Psi_5 w_5) \\ &\quad + w_5 \delta_2(\Psi_3 w_3 + \Psi_4 w_4 + 2\Psi_5 w_5). \end{aligned}$$

On the other hand, the value of b is computed by using the formula, $b = \sum_{k,i=1}^{n} \Psi_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \beta^\star}(0,0)$. The associated non-zero second order partial derivatives of (3.14) at DFE when $\beta = \beta^\star$ and $k = 3, 4, 5$ are:

$$\frac{\partial^2 f_3}{\partial x_4 \partial \beta^\star} = \frac{\partial^2 f_3}{\partial x_5 \partial \beta^\star} = \frac{\theta + \lambda(1-\rho)}{\lambda + \theta}.$$

The value of b is therefore given by:

$$b = \Psi_3 \left(w_4 \frac{\theta + \lambda(1-\rho)}{\lambda + \theta} + w_5 \frac{\theta + \lambda(1-\rho)}{\lambda + \theta} \right) = \Psi_3 \left(\frac{\theta + \lambda(1-\rho)}{\lambda + \theta} \right) (w_4 + w_5) > 0. \tag{3.20}$$

From (3.19), let $\zeta_1 = \Psi_3 \beta^\star w_1(w_4 + w_5)$ and,

$$\zeta_2 = w_6 \gamma \Psi_3 \beta^\star (w_4 + w_5) + w_4 \delta_1(\Psi_3 w_3 + 2\Psi_4 w_4 + \Psi_5 w_5) + w_5 \delta_2(\Psi_3 w_3 + \Psi_4 w_4 + 2\Psi_5 w_5).$$

It follows that the sign of a depends on the value of w_1. If $w_1 > 0$ or $w_1 < 0$ and $\zeta_2 > \zeta_1$ then $a > 0$. We formulate the following theorem.

Theorem 3.8. *If $w_1 > 0$ or $w_1 < 0$ and $\zeta_2 > \zeta_1$, then model* (3.5) *exhibits backward bifurcation at $R_e = 1$. If $\beta < 0$ then there exists unstable positive endemic equilibrium point and correspondingly if $\beta > 0$ then there exists a stable negative endemic equilibrium point. Therefore endemic equilibrium point is locally asymptotically stable if $R_e > 1$ but close to 1.*

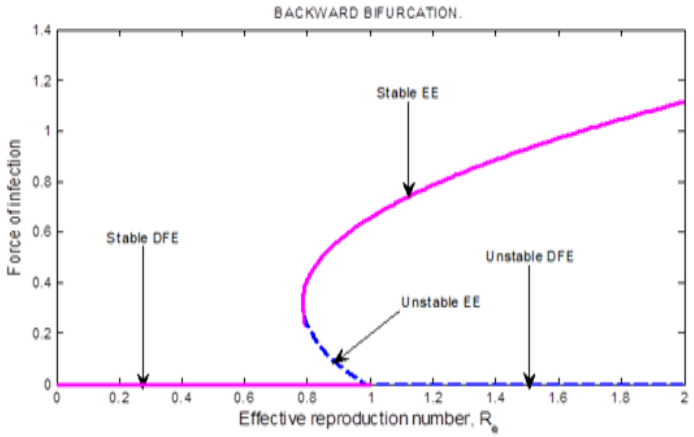

Figure 3.2: Bifurcation diagram showing backward bifurcation with estimated parameters $\beta = 14; \gamma = 1.8; \theta = 0.8; \epsilon = 0.396; \eta = 0.1; \lambda = 0.9; \delta_1 = 0.3; \omega = 0.6; \rho = 0.1, \nu = 0.9, \delta_2 = 0.2; \omega$ and $\phi = 0.1$ for numerical simulation.

Figure 3.2 shows the backward bifurcation of system (3.5) that occurs at threshold parameter $R_e = 1$, due to presence of multiple equilibria and re-infection. DFE stands for Disease Free equilibrium and EE stands for Endemic Equilibrium. In the neighborhood of 1 when $R_e < 1$ then stable DFE coexists with two endemic equilibria: the small unstable EE (with smaller number of TB infectives) and larger stable endemic equilibrium with large number of infectives. This implies that even with classically reducing the threshold parameter to less than unity does not clear TB from community. That is why we say backward bifurcation is an undesirable feature of TB. When $R_e > 1$ then we have two equilibria: unstable DFE and large stable EE. According to Buonomo and Lacitignola (2011) if R_e is nearly below one then disease control

depends on initial sub-populations of the model under consideration. That is reducing $R_e < 1$ below the critical value $R_e^c < 1$ eradicate disease from community given that the disease free equilibrium is globally asymptotically stable.

3.3.5 Global Stability of Endemic Equilibrium Point of a model with intervention.

In this section we prove the global stability of endemic equilibrium point E_2 of system (3.5) by using Lyapunov's direct method. Our Lyapunov function is constructed from suitable choice of logarithmic function. The global properties of endemic equilibrium point are studied by stating and proving the following theorem.

Theorem 3.9. *If $R_e > 1$ then the unique endemic equilibrium E_2 of system* (3.5) *is globally asymptotically stable in the interior of* Ω.

Proof. We use approach of Korobeinikov (2004) as it is used to most complicated compartmental epidemiological models, to construct the Lyapunov function from suitable choice of the following logarithmic function:

$$W = \sum a_i(y_i - y_i^\star \ln(y_i)),$$

where a_i are properly chosen positive constants, y_i is population of compartment i and $y_i^\star$ is the equilibrium level. We define the function $W\colon \{(s, v, l, i_1, i_2, h) \in \Omega\colon s, v, l, i_1, i_2, h > 0\} \to \mathbb{R}$ by:

$$\begin{aligned} W(s, v, l, i_1, i_2, h) = A_1(s - s^\star \ln(s)) + A_2(v - v^\star \ln(v)) + A_3(l - l^\star \ln(l)) \\ + A_4(i_1 - i_1^\star \ln(i_1)) + A_5(i_2 - i_2^\star \ln(i_2)) + A_6(h - h^\star \ln(h)). \end{aligned}$$

The constants $A_1, A_2, \cdots A_6$ are non-negative in Ω and W is Lyapunov function. The function W together with its constants $A_1, A_2, \cdots A_6 > 0$ are chosen in such way that W is continuous and differentiable in a space C^1 and on the interior of Ω, E_2 is global minimum of W on Ω,

and $W(s, v, l, i_1, i_2, h) = 0$. The time derivative of Lyapunov function W computed along the solutions of system (3.5) is:

$$\begin{aligned} W' &= A_1\left(1-\frac{s^\star}{s}\right)\frac{ds}{dt} + A_2\left(1-\frac{v^\star}{v}\right)\frac{dv}{dt} + A_3\left(1-\frac{l^\star}{l}\right)\frac{dl}{dt} + A_4\left(1-\frac{i_1^\star}{i_1}\right)\frac{di_1}{dt} \\ &+A_5\left(1-\frac{i_2^\star}{i_2}\right)\frac{di_2}{dt} + A_6\left(1-\frac{h^\star}{h}\right)\frac{dh}{dt}. \end{aligned} \tag{3.21}$$

At Endemic equilibrium point (EEP) we have:

$$\begin{aligned} (1-\rho)\lambda &= (\lambda + \beta(i_1^\star + i_2^\star) - \delta_1 i_1^\star - \delta_2 i_2^\star)s^\star - \theta v^\star, \\ \rho\lambda &= (\lambda + \theta - \delta_1 i_1^\star - \delta_2 i_2^\star)v^\star, \\ \lambda + \epsilon &= \frac{1}{l^\star}\left(\beta s^\star(i_1^\star + i_2^\star) + \gamma\beta h^\star(i_1^\star + i_2^\star) + (\delta_1 i_1^\star + \delta_2 i_2^\star)l^\star\right), \\ \lambda + \delta_1 + \nu &= \frac{1}{i_1^\star}\left((1-\eta)\epsilon l^\star + (1-\phi)\omega i_2^\star\right) + \delta_1 i_1^\star + \delta_2 i_2^\star, \\ \lambda + \omega + \delta_2 &= \frac{\eta\epsilon l^\star}{i_2^\star} + \delta_1 i_1^\star + \delta_2 i_2^\star, \\ \lambda &= \frac{1}{h^\star}\left(\nu i_1^\star + \phi\omega i_2^\star - (\gamma\beta(i_1^\star + i_2^\star)) + \delta_1 i_1^\star + \delta_2 i_2^\star\right). \end{aligned} \tag{3.22}$$

We re-write W' by using (3.22) as follows:

$$\begin{aligned}
W' &= A_1\left(\frac{s-s^\star}{s}\right)[(\lambda+\beta(i_1^\star+i_2^\star)-\delta_1 i_1^\star-\delta_2 i_2^\star)s^\star-\theta v^\star \\
&\quad +\theta v-(\lambda+\beta(i_1+i_2)-\delta_1 i_1-\delta_2 i_2)s] \\
&\quad +A_2\left(\frac{v-v^\star}{v}\right)[(\lambda+\theta-\delta_1 i_1^\star-\delta_2 i_2^\star)v^\star-(\lambda+\theta-\delta_1 i_1-\delta_2 i_2)v] \\
&\quad +A_3\left(\frac{l-l^\star}{l}\right)\left[\beta s(i_1+i_2)+\gamma\beta h(i_1+i_2)-\frac{1}{l^\star}\{\beta s^\star(i_1^\star+i_2^\star)+\gamma\beta h^\star(i_1^\star+i_2^\star)\right. \\
&\quad \left.+(\delta_1 i_1^\star+\delta_2 i_2^\star)l^\star-(\delta_1 i_1+\delta_2 i_2)l^\star\}\, l\right] \\
&\quad +A_4\left(\frac{i_1-i_1^\star}{i_1}\right)\left[(1-\eta)\epsilon l+(1-\phi)\omega i_2-\frac{1}{i_1^\star}\{(1-\eta)\epsilon l^\star+(1-\phi)\omega i_2^\star\right. \\
&\quad \left.+(\delta_1 i_1^\star+\delta_2 i_2^\star)i_1^\star-(\delta_1 i_1+\delta_2 i_2)i_1^\star\}\, i_1\right] \\
&\quad +A_5\left(\frac{i_2-i_2^\star}{i_2}\right)\left[\eta\epsilon l-\frac{1}{i_2^\star}\{\eta\epsilon l^\star+(\delta_1 i_1^\star+\delta_2 i_2^\star)i_2^\star-(\delta_1 i_1+\delta_2 i_2)i_2^\star\}\, i_2\right] \\
&\quad +A_6\left(\frac{h-h^\star}{h}\right)\left[\nu i_1+\phi\omega i_2-\frac{1}{h^\star}\{\nu i_1^\star+\phi\omega i_2^\star-(\gamma\beta(i_1^\star+i_2^\star)+(\delta_1 i_1^\star+\delta_2 i_2^\star)h^\star\right. \\
&\quad \left.+\gamma\beta(i_1+i_2)h^\star-(\delta_1 i_1+\delta_2 i_2)h^\star\}\, h\right].
\end{aligned} \tag{3.23}$$

Simplification of (3.23) results to:

$$W' = -A_1\lambda\frac{(s-s^\star)^2}{s}-A_2(\lambda+\theta)\frac{(v-v^\star)^2}{v}+P(s,v,l,i_1,i_2,h). \tag{3.24}$$

The function $P(s,v,l,i_1,i_2,h)$ in (3.24) balances the right hand side of (3.23). The function $P(s,v,l,i_1,i_2,h)$ is non-positive following the approaches of McCluskey (2006) and Mukandavire et al. (2009).

That is $P \leq 0$ for every $s,v,l,i_1,i_2,h>0$. Thus $W' \leq 0$ for all $s,v,l,i_1,i_2,h>0$ and zero when $s=s^\star, v=v^\star, l=l^\star=0, i_1=i_1^\star=0, i_2=i_2^\star=0, h=h^\star=0$. Therefore the largest

compact invariant set in Ω such that $W' = 0$ is the singleton $\{E_2\}$ which is Endemic Equilibrium point of model (3.5). LaSalle's invariant principle (LaSalle, 1976) then implies that E_2 is globally asymptotically stable in the interior of the region Ω if $R_e > 1$ and that completes our proof. □

3.4 Numerical simulations and discussions

In this section numerical simulation of normalized model (3.5) is carried out in order to illustrate the qualitative results by using available parameter values from existing literature as well as estimated ones. Unless otherwise stated parameter values appeared in Table 3.3 will be used during the simulation process.

Table 3.3: Parameter values for optimal model (3.5).

Parameter	**Value/range**(yr^{-1})	**Source**
λ	0.05	Estimated.
β	2.58	Estimated.
ρ	0.4	Estimated.
θ	0.1	Estimated.
ϵ	0.03	Cohen et al. (2007)
η	0.7 (0.7-0.95)	Okuonghae and Aihie (2008)
μ	0.01923 (0.01-0.04)	Blower et al. (1995)
δ_1	0.3 (0.07-0.365)	Ssematimba et al. (2005)
δ_2	0.2 (0.07-0.365)	Ssematimba et al. (2005)
ϕ	0.6	Estimated.
ω	0.2	Estimated.
ν	0.3	Estimated.
γ	0.2	Estimated.

3.4.1 Numerical Simulation of a model (3.5) in presence of intervention and TB.

Figure 3.3 shows dynamic behavior of susceptible, vaccinated, latently infected, severely infected, mildly infected and treated classes when $R_e = 1.8519$. The plot is produced by MATLAB by using $\beta = 2.58; \gamma = 0.2; \theta = 0.1; \epsilon = 0.03; \eta = 0.7; \lambda = 0.05; \delta_1 =$

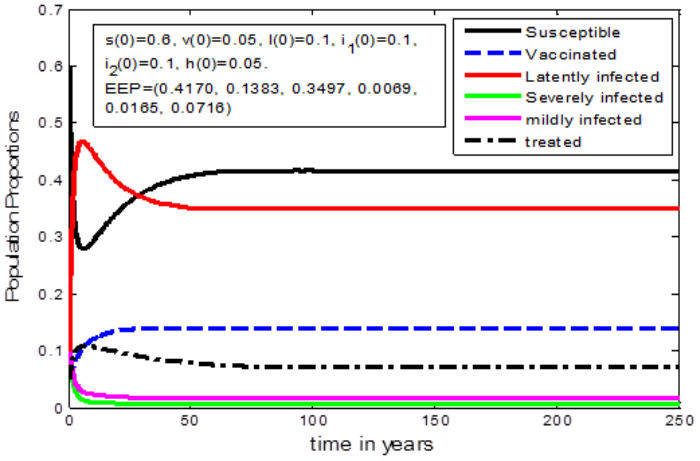

Figure 3.3: Shows the dynamics of susceptible, vaccinated, latently infected, severely infected, mildly infected and treated population proportions in presence of interventions and TB with increasing time.

$0.3; \omega = 0.2; \rho = 0.4; \nu = 0.3; \delta_2 = 0.2$ and $\phi = 0.6$ as estimated parametric values and whose definitions are given in Table 3.2. Starting with initial values $s(0) = 0.60, v(0) = 0.05, l(0) = 0.1, i_1(0) = 0.1, i_2(0) = 0.1$ and $h(0) = 0.05$, the system (3.5) attains the local asymptotic stability of endemic equilibrium point, $E_2 = (s^\star, v^\star, l^\star, i_1^\star, i_2^\star, h^\star) = (0.4170, 0.1383, 0.3497, 0.0069, 0.0165, 0.0716)$. In presence of interventions and TB, susceptible population proportion initially decreases to lower levels and later increases to its carrying capacity with time as shown in Figure 3.3. Vaccinated population proportion initially increases to higher levels and stabilizes as time increases. On the other hand both latently infected and treated population proportions increase to higher levels and gradually decreases to their carrying capacities. However both mildly and severely infected population proportions decreases to their lowest endemic levels. Again even with intervention, disease does not clear from community since effective reproduction number is $R_e = 1.8519 > 1$. Classically this result supports the theorem of local stability of endemic equilibrium.

3.4.2 Phase portraits illustrating dynamical behavior of population proportions at EEP.

In this section phase portraits to illustrate the dynamics of the model (3.5) at endemic equilibrium point for susceptible class versus vaccinated, latently infected, severely infected, mildly infected, and treated classes are plotted by using parameter values indicated in Table 3.3. With different varying initial conditions, each solution curve in Figure 3.4 tends to endemic equilibrium point presented in Section 3.4.1. Therefore we conclude that the system (3.5) is globally stable about endemic equilibrium point E_2 for the parameters displayed in Table 3.3.

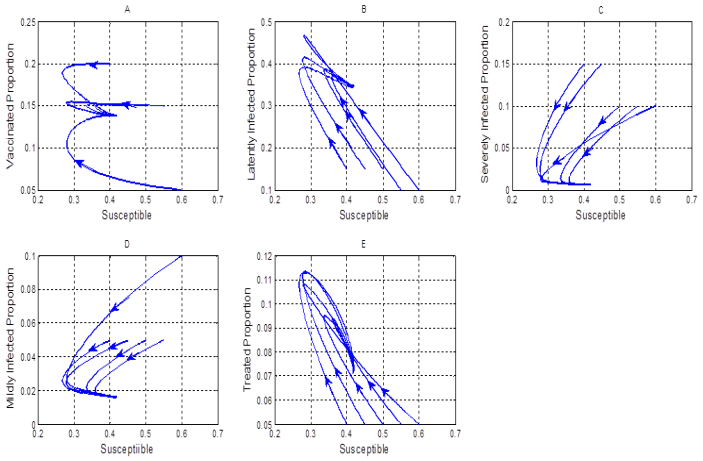

Figure 3.4: Shows Phase plane portraits for dynamics of susceptible population proportion and (A) vaccinated (B) latently infected (C) severely infected (D) mildly infected (E) treated population proportions showing endemic equilibrium point with varying initial values as time increases.

3.5 Conclusion

In this chapter, a continuous time deterministic Tuberculosis model with vaccination and treatment as intervention strategies has been formulated and the role of reinfection on transmission dynamics of TB is critically assessed. In presence of reinfection and multiple equilibria the

backward bifurcation occurs at effective reproduction number $R_e = 1$. In this scenario stable disease free equilibrium coexists with two endemic equilibria: smaller unstable endemic equilibrium (with small number of infected individuals) and larger stable endemic equilibrium (with large number of infected individuals) in the neghbourhood of 1 when $R_e < 1$. This shows that even with classically reducing the threshold R_e below one the disease still persist in the community. We suggest that reinfection is a real TB feature and an important aspect to consider when modeling the complex dynamics of TB.

CHAPTER FOUR

Optimal Treatment and Vaccination Control Strategies for the dynamics of Pulmonary Tuberculosis[3]

Abstract: In this chapter we apply optimal control theory to one-strain tuberculosis model that incorporates vaccination and treatment. In this model the control mechanisms associated with chemoprophylaxis of latently infected with TB and education campaign are incorporated in order to reduce the number of latently and actively infected population with TB through application of Pontryagin's Maximum Principle. Numerical simulations are carried out by using both forward and backward in time fourth order Runge-Kutta schemes. The results show that education campaign control measure alone is more effective in curbing TB transmissions and infections than chemoprophylaxis of latently infected. Furthermore the combination of the two measures has desirable effect of reducing the number of infected individuals with TB than when a single control is used. We suggest that for total eradication of TB from the community, the emphasis of education campaign should be the focal point and chemoprophylaxis of latently infected individuals control strategy has to be paired with treatment of actively infected TB individuals.

4.1 Introduction

Tuberculosis (TB) is a chronic airborne disease caused by pathogen Mycobacterium tuberculosis with more than one-third of the world human population as its reservoir (Bloom, 1994; Feng et al., 2000; Miller, 1993). A global annual estimate of 8.6 million people develop Tuberculosis, of which 1.3 million die from disease. It is reported in WHO (2013) that, the burden

[3]**This chapter is based on the published paper:**
Mlay, G. M., Luboobi, L. S., Kuznetsov, D., and Shahada, F. (2015). Optimal Treatment and Vaccination Control Strategies for the dynamics of Pulmonary Tuberculosis. *International Journal of Advances in Applied Mathematics and Mechanics*,2(3):196-207.

of disease caused by TB is high in developing world where poor nutrition, congested accommodation and emergency of HIV are manifested. The global estimates of incidence, prevalence and mortality rates per 100,000 population in 2012 were respectively 255, 303 and 26 and Tanzania incidence, prevalence and mortality rates per 100,000 population were 165, 176 and 13 respectively as per WHO (2013). It therefore raises a quest to find desirable means to curtail TB morbidity and mortality rates.

Tuberculosis disease is mainly of two types: pulmonary and extra-pulmonary TB. Pulmonary TB is a common form of TB that affects lung while extra-pulmonary TB affects other parts of body and organs including central nervous system and bone (WHO, 2013). This particular study focuses on pulmonary TB. Tuberculosis is a disease that spreads in the air when the infectious person with pulmonary TB expel bacteria by coughing, singing, sneezing, speaking and so on (Castillo-Chávez and Song, 2004). An individual with active TB has usual symptoms which are general weakness or tiredness, fever, weight loss, loss of appetite and night sweats. Further symptoms are coughing, coughing up of sputum and/ or blood, shortness of breath and chest pains if the infection in the lung get worse (Cohen and Murray, 2004). TB draws back economics of the world and Tanzania in particular as it affects men than women and especially the productive working group (WHO, 2013). A small proportion of about 10% of infected individuals with Mycobacterium tuberculosis develop TB and become infectious within two years upon infected (Rodrigues, 2009). Most become latent for the rest of their lives as long as their immune system is not compromised (Castillo-Chávez and Song, 2004). The recovered individuals from TB do not acquire the permanent immunity. Some of them become latently infected again. Even with treatment interventions, the rates of reinfection TB are higher than those of new TB (Rodrigues, 2009). Unlike other diseases, TB has complex dynamics to the extent that even reducing the threshold, effective reproduction number, R_e below one does not guarantee clearance of the disease from the community (Zhou and Sun, 2014). Mathematical modeling of epidemiology of Tuberculosis has recently become the powerful tool to study the dynamics

of the disease and impact of various intervention strategies in order to advise public health policy makers to construct suitable intervention programs to combat TB infections. Agusto (2009) formulated a tuberculosis model that incorporates treatment of infectious and chemoprophylaxis (administration of medication to prevent latently infected individual to progress to active TB) of latently infected individuals. In his modeling, he introduced the controls in treatment, chemoprophylaxis and relapse in order to reduce the number of active TB and latently infected individuals. His study shows that the control programs which follow these strategies can effectively reduce the population that is actively and latently infected with TB. Adekunle et al. (2009) incorporates controls representing chemoprophylaxis and treatment to SEIR model of TB proposed by Bhunu et al. (2008) in order to reduce latently infected as well as actively infected population by using Pontryagin Maximum Principle of optimal control theory. The results of work show that chemoprophylaxis is more effective in controlling disease in population when used alone than applying treatment only. Furthermore, results suggest that the use of both controls concurrently stand out as an effective strategy of reducing the number of infected individuals than to use only one measure at a time. Bowong (2010) introduced the control term to the basic SEI (Susceptible-Exposed-Infectious) model of TB for 'case finding' that represents the effort on chemoprophylaxis parameter on reducing the number of individuals who may become infectious. The results show that the control mechanism boosts up the efforts of chemoprophylaxis in controlling exogenous reinfection an hence reduces the number of actively infected individuals with TB. In this chapter we consider time dependent control mechanisms associated with education campaign and chemoprophylaxis of latently infected individual to one-strain tuberculosis model that incorporates treatment and vaccination as intervention strategies so as to boost their efforts toward reducing the number of latently and actively infected with TB. The optimality system is derived by aid of Pontryagin's Maximum Principle (Pontryagin et al., 1962). Numerical simulation is carried out by using forward and backward in time fourth order Runge-Kutta schemes.

4.2 Optimal Control Model Formulation

In this section we construct a continuous time deterministic one-strain tuberculosis model with control term by modifying the model of Mlay et al. (2014a). The control terms u_1 and u_2 are added as shown in Figure 5.1. The full descriptions of variables and parameters which appear in Figure 5.1 are in Table 4.1 and Table 4.2 respectively.

Table 4.1: Description of variables of the model

Variable	Descriptions
$S(t)$	The Susceptible individuals who are at risk of being infected at time t
$L(t)$	The latently infected individuals at time t
$V(t)$	Vaccinated individuals at time t
$I_1(t)$	Individuals who are severely infected with TB at time t
$I_2(t)$	Individuals who are mildly infected with TB at time t
$T(t)$	Individuals Treated against TB at time t

We aim at introducing control measures which are education campaign and chemoprophylaxis of latently infected individuals to the basic model of Mlay et al. (2014a) to boost the efforts played by intervention strategies (vaccination and treatment) so as to lower TB infections in the community as well as minimizing the cost of administering these controls.

Education campaign denoted by $u_1(t)$ is introduced to the basic model as a control term that will sensitize parents and guardians to vaccinate more babies and hence increasing the proportion of vaccinated babies by $(1 + u_1)\rho$. That is if education campaign is 100% effective then proportion of vaccinated babies will be doubled. Consequently education campaign provides awareness to community on how the disease is transmitted and ways to reduce the probability of being infected. This information in turn reduces the number of susceptible individuals who

Table 4.2: Description of Parameters of the model

Parameter	Descriptions
λ	Per capita birth rate.
β	Per capita infection rate.
ρ	Proportional of babies who are being vaccinated at birth.
θ	The rate at which a vaccinated individual looses immunity.
ϵ	The rate of progression from Latent class to both severely and mildly Infected classes.
η	Proportional of Latently infected population progressing to mild infected class.
μ	Per capita natural death rate.
δ_1	Per capita additional death rate of severely infected class.
δ_2	Per capita additional death rate of mildly infected class.
ϕ	Proportional of mildly infected class who are treated.
ω	The transferring rate mildly infected to both severely infected and treatment classes.
ν	The rate at which a severely infected candidate is transferred to treatment class.
γ	The factor that reduces the level of reinfection.

join the class of latently infected individuals by decreasing the transmission rate to $(1-u_1)\beta$. In addition the education campaign will reduce the number of mildly infected individuals who join severely infected class as a result increases the rate of both infectious classes to treatment and reducing individuals who relapse back to Latent group after treatment. That means if u_1 is a control mechanism indicating the efforts played by education campaign to curtail TB infections and transmissions then $(1-u_1)$ is a failure of the control mechanism.

On the other hand chemoprophylaxis of latently infected individuals denoted by control term u_2 is introduced to the basic model presented in Mlay et al. (2014a) so as to lower active TB cases of latently infected individuals. That is $1-u_2(t)$ is a failure of chemoprophylaxis to prevent the latent infected group from progressing to active TB. Jung et al. (2002) claim that, if $u_2(t)$ is near to 1 then there is low treatment failure of chemoprophylaxis and high implementation cost. The compartmental diagram with control mechanisms, education campaign, $u_1(t)$ and chemoprophylaxis of latently infected individuals with TB, $u_2(t)$ is shown in Figure 4.1.

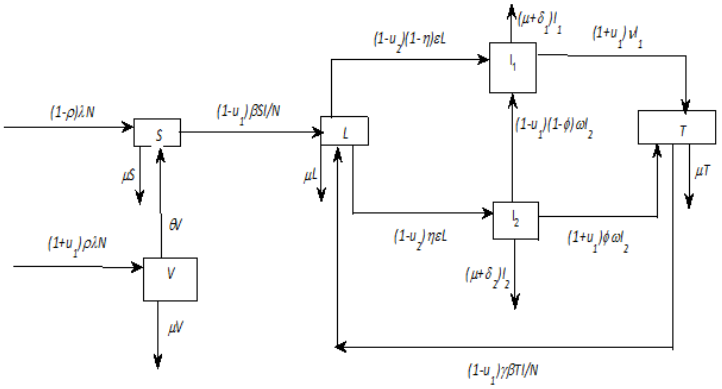

Figure 4.1: Schematic flow diagram showing dynamics of tuberculosis and control mechanisms u_1 and u_2 respectively, whereby $I = I_1 + I_2$.

The state system that is one-strain tuberculosis model with two control variables u_1 and u_2 is obtained from Figure 4.1 as follows:

$$\frac{dS}{dt} = (1-\rho)\lambda N - (1-u_1(t))\beta S\frac{(I_1+I_2)}{N} - \mu S + \theta V, \tag{4.1a}$$

$$\frac{dV}{dt} = (1+u_1(t))\rho\lambda N - (\mu+\theta)V, \tag{4.1b}$$

$$\frac{dL}{dt} = (1-u_1(t))\beta\frac{(I_1+I_2)}{N}(S+\gamma T) - ((1-u_2(t))\epsilon + \mu)L, \tag{4.1c}$$

$$\frac{dI_1}{dt} = (1-u_2(t))(1-\eta)\epsilon L + (1-u_1(t))(1-\phi)\omega I_2 - (\mu+\delta_1+(1+u_1(t))\nu)I_1, \tag{4.1d}$$

$$\frac{dI_2}{dt} = ((1-u_2(t))\eta\epsilon L - ((1-(1-2\phi)u_1(t))\omega + \mu + \delta_2)I_2, \tag{4.1e}$$

$$\frac{dT}{dt} = (1+u_1(t))(\nu I_1 + \phi\omega I_2) - \left(\mu + (1-u_1(t))\gamma\beta\frac{(I_1+I_2)}{N}\right)T. \tag{4.1f}$$

4.2.1 Optimal Control Problem

In model (4.1) we assume that control functions $u_1(t)$ and $u_2(t)$ are Lebesgue integrable functions with $0 < u_1, u_2 < 1$. Our objective functional to be minimized is:

$$J(u_1, u_2) = \int_0^{tf} \left[A_1 L(t) + A_2 I_1(t) + A_3 I_2(t) + \frac{B_1}{2} {u_1}^2 + \frac{B_2}{2} {u_2}^2 \right] dt \tag{4.2}$$

where we want to minimize latent and infectious (severely and mildly infected) groups with drug-sensitive strain TB while keeping the costs of education campaign and chemoprophylaxis of latently infected group low. From equation (4.2), tf is fixed final time, $A_1,\ A_2$ and A_3 are positive weight constants of latently infected, severely infected and mildly infected groups respectively while B_1 and B_2 are positive weight constants which balance the cost factors associated with control mechanisms u_1 and u_2. The cost of each control mechanism is assumed to be non-linear and take quadratic form. That is, $\frac{B_1}{2} {u_1}^2$ is cost of control mechanism associated with educating the public (i.e. education campaign) about vaccinating their newly born children with TB vaccine, symptoms of active TB and the need of sending infectious individuals to hospital while $\frac{B_2}{2} {u_2}^2$ is a cost of control mechanism in latently infected group associated with administering of chemoprophylaxis that prevent them suffer the active TB.
We aim to find control pair,${u_1}^\star$ and ${u_2}^\star$, such that

$$J({u_1}^\star, {u_2}^\star) = \min_{\Gamma} J(u_1, u_2) \tag{4.3}$$

where $\{(u_1, u_2) \in L^1(0, tf) : a_i \leq u_i \leq b_i,\ i = 1, 2\}$ and $a_i, b_i,\ i = 1, 2$ are fixed positive constants.

As basic framework, after formulating model (4.1) and the corresponding objective functional (4.2) the remaining tasks according to Macki and Strauss (1982), Sethi and Thompson (2000)

and Joshi et al. (2006) is to:

(a) prove existence of optimal control,

(b) characterize the optimal control,

(c) prove uniqueness of optimal control,

(d) compute optimal control numerically,

(e) investigate how optimal control depends on various parameters of the model.

4.2.2 Existence of an optimal control

In this section we state and prove the existence of an optimal control. We note that our objective functional in (4.2) has no salvage term (i.e. the value of state at the fixed final time is zero). It falls under category of Mayer optimization problem (Boltyanski, 2001). Therefore by applying the results in Theorem 4.1 of Fleming and Rishel (1975, p. 68-70), Lukes (1982), Lashari et al. (2013) and proof outline presented by Mpeshe et al. (2014) is sufficient enough to prove that an optimal control exists. Before proving an existence of an optimal control, let us state the following theorem:

Theorem 4.10. *Consider an optimal control problem with state equations* (4.1)*. There exists optimal control pair* $({u_1}^\star, {u_2}^\star) \in \Gamma$ *such that*

$$\min_{\Gamma} J(u_1, u_2) = J({u_1}^\star, {u_2}^\star) \tag{4.4}$$

Proof. We begin our proof by following properties of existence of an optimal control presented in Mpeshe et al. (2014). The control set together with corresponding state variables is non-empty by existential results in Lukes (1982, p. 182) [Theorem 9.2.1]. Set of all control variables $(u_1, u_2) \in \Gamma$ is convex by definition. Convexity of objective functional in u_1 and u_2 is satisfied.

Our optimal system is compact (i.e. closed and bounded) as a necessary condition for existence of optimal control. That means state solutions of state system (4.1) are bounded by a linear function. The integrand of objective functional (4.2),$A_1L(t) + A_2I_1(t) + A_3I_2(t) + \frac{B_1}{2}{u_1}^2 + \frac{B_2}{2}{u_2}^2$ is convex on control set Γ. In addition, according to Lashari et al. (2013), there exists a constant $p > 1$ and positive numbers q_1, q_2 such that objective functional is bounded below by $q_1\left(|u_1|^2 + |u_2|^2\right)^{p/2} - q_2$. That is:

$$J(u_1, u_2) \geq q_1\left(|u_1|^2 + |u_2|^2\right)^{p/2} - q_2,$$

because, state variables are bounded, that completes the proof of existence of optimal control following the result in Theorem 4.1 of Fleming and Rishel (1975) [pages 68-70]. □

4.2.3 Characterization of the optimal control

In this section we derive necessary conditions on an optimal control, characterizing optimal control using upper and lower bound technique and formulating optimality system that characterizes the optimal control. The optimal pair should satisfy the necessary conditions that come from Pontryagin Maximum Principle (Pontryagin et al., 1962), and which are also discussed in Mpele et al. (2014). This principle converts state system (4.1), objective functional (4.2) and control set (4.3) into minimal value of Lagrangian of optimal problem. The Lagrangian of the optimal problem is given by:

$$\mathcal{L} = A_1L(t) + A_2I_1(t) + A_3I_2(t) + \frac{B_1}{2}{u_1}^2 + \frac{B_2}{2}{u_2}^2 \tag{4.5}$$

In order to seek for minimum Lagrangian of optimal problem we define the Hamilitonian H for the control problem with respect to u_1 and u_2 as

$$H = A_1 L(t) + A_2 I_1(t) + A_3 I_2(t) + \frac{B_1}{2} {u_1}^2 + \frac{B_2}{2} {u_2}^2 + \sum_{i=1}^{6} \lambda_i f_i \tag{4.6}$$

where f_i is right hand side of the differential equation of ith state variable in system (4.1) and λ_i for $i = 1, 2, \cdots, 6$ is the set of adjoint functions. That means the Hamiltonian consists of integrand of objective functional and the inner product of right hand side of state equations and corresponding adjoint variables $(\lambda_1, \lambda_2, \cdots \lambda_6)$. The expanded form of Hamiltonian H in (4.6) is given by:

$$\begin{aligned}
H = {} & A_1 L(t) + A_2 I_1(t) + A_3 I_2(t) + \frac{B_1}{2} {u_1}^2 + \frac{B_2}{2} {u_2}^2 \\
& + \lambda_1 \left[(1-\rho)\lambda N - (1-u_1(t))\beta S \frac{(I_1 + I_2)}{N} - \mu S + \theta V \right] \\
& + \lambda_2 \left[(1+u_1(t))\rho\lambda N - (\mu + \theta) V \right] \\
& + \lambda_3 \left[(1-u_1(t))\beta \frac{(I_1 + I_2)}{N} (S + \gamma T) - ((1-u_2(t))\epsilon + \mu) L \right] \\
& + \lambda_4 \left[(1-u_2(t))(1-\eta)\epsilon L + (1-u_1(t))(1-\phi)\omega I_2 - (\mu + \delta_1 + (1+u_1(t))\nu) I_1 \right] \\
& + \lambda_5 \left[((1-u_2(t))\eta\epsilon L - ((1-(1-2\phi)u_1(t))\omega + \mu + \delta_2) I_2 \right] \\
& + \lambda_6 \left[(1+u_1(t))(\nu I_1 + \phi\omega I_2) - \left(\mu + (1-u_1(t))\gamma\beta \frac{(I_1 + I_2)}{N} \right) T. \right]
\end{aligned} \tag{4.7}$$

Theorem 4.11. *There exists an optimal control pair* $({u_1}^\star, {u_2}^\star)$ *and the corresponding state solutions* $S^\star, V^\star, L^\star, {I_1}^\star, {I_2}^\star$ *and* $T^\star$*, that minimizes* $J(u_1, u_2)$ *over* Γ*. Furthermore there exists adjoint functions,* $\lambda_1, \lambda_2, \cdots \lambda_6$ *such that*

$$\frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial S}, \frac{d\lambda_2}{dt} = -\frac{\partial H}{\partial V}, \cdots, \frac{d\lambda_6}{dt} = -\frac{\partial H}{\partial T} \text{ adjoint conditions,} \tag{4.8}$$

$$\lambda_1(tf) = \lambda_2(tf) = \cdots = \lambda_6(tf) = 0 \text{ transversality conditions.} \tag{4.9}$$

and $N = S^\star + V^\star + L^\star + {I_1}^\star + {I_2}^\star + T^\star$.

In addition,

$$\frac{\partial H}{\partial u_i} = 0 \text{ at } {u_i}^\star = 0,\ i = 1, 2 \text{ optimality conditions.} \tag{4.10}$$

Proof. The adjoint system is obtained by taking the negative partial derivative of Hamiltonian H with respect to state variables. By using Pontryagin's Maximum Principle the following adjoint system evaluated at optimal control pair and corresponding state variables is hereunder:

$$\begin{aligned}
\frac{d\lambda_1}{dt} &= -\frac{\partial H}{\partial S} = (\lambda_1 - \lambda_3)(1 - {u_1}^\star(t))\beta\frac{{I_1}^\star + {I_2}^\star}{N} + \mu\lambda_1,\\
\frac{d\lambda_2}{dt} &= -\frac{\partial H}{\partial V} = \mu\lambda_2 + \theta(\lambda_2 - \lambda_1),\\
\frac{d\lambda_3}{dt} &= -\frac{\partial H}{\partial L} = -A_1 + \mu\lambda_3 + (1 - {u_2}^\star(t))(\lambda_3 - \lambda_4 + \eta(\lambda_4 - \lambda_5))\epsilon,\\
\frac{d\lambda_4}{dt} &= -\frac{\partial H}{\partial I_1} = -A_2 + \lambda_4(\mu + \delta_1) + (1 - {u_1}^\star(t))\left[\frac{\beta}{N}(S^\star(\lambda_1 - \lambda_3) + \gamma T^\star(\lambda_6 - \lambda_3)\right]\\
&\qquad + (\lambda_4 - \lambda_6)(1 + {u_1}^\star(t))\nu,\\
\frac{d\lambda_5}{dt} &= -\frac{\partial H}{\partial I_2} = -A_3 + \lambda_5(2\phi\omega{u_1}^\star(t) + \mu + \delta_2) - \lambda_6)(1 + {u_1}^\star(t))\phi\omega\\
&\qquad + (1 - {u_1}^\star(t))\left[\frac{\beta}{N}(S^\star(\lambda_1 - \lambda_3) + \gamma T^\star(\lambda_6 - \lambda_3) + (\lambda_5 - \lambda_4(1 - \phi))\omega\right],\\
\frac{d\lambda_6}{dt} &= -\frac{\partial H}{\partial T} = (\lambda_6 - \lambda_3)(1 - {u_1}^\star(t))\gamma\beta\frac{{I_1}^\star + {I_2}^\star}{N} + \mu\lambda_6.\\
N &= S^\star + V^\star + L^\star + {I_1}^\star + {I_2}^\star + T^\star.
\end{aligned} \tag{4.11}$$

The optimal solution of Hamiltonian is obtained by taking partial derivative of H with respect to control

$u_i,\ i = 1, 2$ and set it to zero. That is,

$$\begin{aligned}
\frac{\partial H}{\partial u_1} &= B_1u_1 + \beta\frac{I_1 + I_2}{N}\left[(\lambda_1 - \lambda_3)S + (\lambda_6 - \lambda_3)\gamma T\right] + \lambda_2\rho\lambda N\\
&\quad + \omega I_2\left[(\lambda_6 + \lambda_4 - 2\lambda_5)\phi + (\lambda_5 - \lambda_4)\right] + \nu I_1(\lambda_6 - \lambda_4), &\text{(4.12a)}\\
\frac{\partial H}{\partial u_2} &= B_2u_2 + (\lambda_3 - \lambda_4 + \eta(\lambda_4 - \lambda_5)\epsilon L) &\text{(4.12b)}
\end{aligned}$$

If we set $\dfrac{\partial H}{\partial u_i} = 0$ at ${u_i}^\star$ we find that:

$$u_1{}^\star = \frac{1}{B_1}\left[\beta\frac{I_1+I_2}{N}\{(\lambda_3-\lambda_1)S+(\lambda_3-\lambda_6)\gamma T\}-\lambda_2\rho\lambda N\right.$$
$$\left.+\,\omega I_2\{(2\lambda_5-\lambda_6-\lambda_4)\phi+(\lambda_4-\lambda_5)\}+\nu I_1(\lambda_4-\lambda_6)\right], \tag{4.13a}$$
$$u_2{}^\star = \frac{1}{B_2}\left[\lambda_4-\lambda_3+\eta(\lambda_5-\lambda_4)\epsilon L\right] \tag{4.13b}$$

Characterization of an optimal control is done by using technique involving control bounds $a_i \le u_i \le b_i$ and by setting $S = S^\star, V = V^\star, L = L^\star, I_1 = I_1{}^\star, I_2 = I_2{}^\star$ and $T = T^\star$.
Consider the control bound $a_1 \le u_1 \le b_1$. That means our control u_1 is bounded below by a_1 and above by b_1. Then the characterization of an optimal control $u_1{}^\star$ is given by:

$$u_1{}^\star = \begin{cases} a_1 & \text{if } X \le a_1 \\ X & \text{if } a_1 < X < b_1 \\ b_1 & \text{if } X \ge b_1 \end{cases} \tag{4.14}$$

whereby;

$$X = \frac{1}{B_1}\left[\beta\frac{I_1{}^\star+I_2{}^\star}{N}\{(\lambda_3-\lambda_1)S^\star+(\lambda_3-\lambda_6)\gamma T^\star\}-\lambda_2\rho\lambda N\right.$$
$$\left.+\,\omega I_2{}^\star\{(2\lambda_5-\lambda_6-\lambda_4)\phi+(\lambda_4-\lambda_5)\}+\nu I_1{}^\star(\lambda_4-\lambda_6)\right].$$

In more compact form $u_1{}^\star$ can be written as

$$u_1{}^\star = \min\left\{\max\left\{a_1, \frac{1}{B_1}\left[\beta\frac{I_1{}^\star+I_2{}^\star}{N}\{(\lambda_3-\lambda_1)S^\star+(\lambda_3-\lambda_6)\gamma T^\star\}-\lambda_2\rho\lambda N\right.\right.\right.$$
$$\left.\left.\left.+\,\omega I_2{}^\star\{(2\lambda_5-\lambda_6-\lambda_4)\phi+(\lambda_4-\lambda_5)\}+\nu I_1{}^\star(\lambda_4-\lambda_6)\right]\right\}, b_1\right\} \tag{4.15}$$

Likewise considering the control bound $a_2 \leq u_2 \leq b_2$, the control u_2 is bounded below by a_2 and bounded above by b_2. The characterization of an optimal control ${u_2}^\star$ is given by

$$ {u_2}^\star = \begin{cases} a_2 & \text{if } Y \leq a_2 \\ Y & \text{if } a_2 < X < b_2 \\ b_2 & \text{if } Y \geq b_2 \end{cases} \tag{4.16} $$

where $Y = \dfrac{1}{B_2}\left[\lambda_4 - \lambda_3 + \eta(\lambda_5 - \lambda_4)\epsilon L^\star\right]$. In more compact form ${u_2}^\star$ can be written as

$$ {u_2}^\star = \min\left\{\max\left\{a_2, \frac{1}{B_2}\left[\lambda_4 - \lambda_3 + \eta(\lambda_5 - \lambda_4)\epsilon L^\star\right]\right\}, b_2\right\}. \tag{4.17} $$

□

Our optimality system comprises of the state system (4.1) coupled with adjoint system (4.11) with initial and transversal conditions together with characterization of optimal control.
We note that both $\dfrac{\partial H}{\partial {u_1}^2} = B_1 > 0$ and $\dfrac{\partial H}{\partial {u_2}^2} = B_2 > 0$. That means the second partial derivative of our Hamiltonian H with respect to controls u_1 and u_2 are positive. Therefore the optimal problem is minimum at controls ${u_1}^\star$ and ${u_2}^\star$.

4.2.4 Uniqueness of an optimal control

In this section we prove the uniqueness of an optimal control. According to Joshi et al. (2006), to show the uniqueness of an optimal control is the same as to show the uniqueness of an optimality system. From (4.1) our system with properties of optimality system can be written as:

$$\begin{cases} S' &= p_1(t, S, V, L, I_1, I_2, T) \\ V' &= p_2(t, S, V, L, I_1, I_2, T) \\ L' &= p_3(t, S, V, L, I_1, I_2, T) \\ I_1{}' &= p_4(t, S, V, L, I_1, I_2, T) \\ I_2{}' &= p_5(t, S, V, L, I_1, I_2, T) \\ T' &= p_6(t, S, V, L, I_1, I_2, T) \\ & S(0), V(0), L(0), I_1(0), I_2(0), T(0) \text{ given}, \\ & S(tf), V(tf), L(tf), I_1(tf), I_2(tf), T(tf) \text{ given and } tf \text{ fixed}. \end{cases} \tag{4.18}$$

where $S \in \mathbb{R}^{m_1}, V \in \mathbb{R}^{m_2}, L \in \mathbb{R}^{m_3}, I_1 \in \mathbb{R}^{m_4}, I_2 \in \mathbb{R}^{m_5}, T \in \mathbb{R}^{m_6}$, m_i for $i = 1, 2, \cdots, 6$ is a dimension of vector space $\mathbb{R}^{m_i}$ and

$$p_1 : \mathbb{R} \times \mathbb{R}^{m_1} \times \mathbb{R}^{m_2} \times \mathbb{R}^{m_3} \times \mathbb{R}^{m_4} \times \mathbb{R}^{m_5} \times \mathbb{R}^{m_6} \to \mathbb{R}^{m_1}$$

$$p_2 : \mathbb{R} \times \mathbb{R}^{m_1} \times \mathbb{R}^{m_2} \times \mathbb{R}^{m_3} \times \mathbb{R}^{m_4} \times \mathbb{R}^{m_5} \times \mathbb{R}^{m_6} \to \mathbb{R}^{m_2}$$

$$p_3 : \mathbb{R} \times \mathbb{R}^{m_1} \times \mathbb{R}^{m_2} \times \mathbb{R}^{m_3} \times \mathbb{R}^{m_4} \times \mathbb{R}^{m_5} \times \mathbb{R}^{m_6} \to \mathbb{R}^{m_3}$$

$$p_4 : \mathbb{R} \times \mathbb{R}^{m_1} \times \mathbb{R}^{m_2} \times \mathbb{R}^{m_3} \times \mathbb{R}^{m_4} \times \mathbb{R}^{m_5} \times \mathbb{R}^{m_6} \to \mathbb{R}^{m_4}$$

$$p_5 : \mathbb{R} \times \mathbb{R}^{m_1} \times \mathbb{R}^{m_2} \times \mathbb{R}^{m_3} \times \mathbb{R}^{m_4} \times \mathbb{R}^{m_5} \times \mathbb{R}^{m_6} \to \mathbb{R}^{m_5}$$

$$p_6 : \mathbb{R} \times \mathbb{R}^{m_1} \times \mathbb{R}^{m_2} \times \mathbb{R}^{m_3} \times \mathbb{R}^{m_4} \times \mathbb{R}^{m_5} \times \mathbb{R}^{m_6} \to \mathbb{R}^{m_6}$$

are continuous. Before proving for uniqueness of an optimal control we state the following theorem:

Theorem 4.12. *Assume $p_1, p_2, \cdots p_6$ are bounded and satisfy Lipschitz condition relative to S, V, L, I_1, I_2 and T with constant $A > 0$. Then the solutions of system* (4.18) *are unique if the final time tf is sufficiently small.*

Proof. Suppose (4.18) has two solutions $(S_1(t), V_1(t), L_1(t), I_{1\star}(t), I_{2\star}(t), T_1(t))$ and $(S_2(t), V_2(t), L_2(t), I_{1\star\star}(t), I_{2\star\star}(t), T_2(t))$. Applying Lipschitz condition implied in Maksimov (2013) on p_1 results to:

$$\|S_1(t) - S_2(t)\| \leq \int_0^{t_1} A(\|S_1(r) - S_2(r)\| + \|V_1(r) - V_2(r)\| + \|L_1(r) - L_2(r)\| + \|I_{1\star}(r) - I_{1\star\star}(r)\| + \|I_{2\star}(r) - I_{2\star\star}(r)\| + \|T_1(r) - T_2(r)\|)dr \quad (4.19)$$

A similar inequality holds for solutions $V_1(t)$ and $V_2(t)$ as follows:

$$\|V_1(t) - V_2(t)\| \leq \int_{t_1}^{t_2} A(\|S_1(r) - S_2(r)\| + \|V_1(r) - V_2(r)\| + \|L_1(r) - L_2(r)\| + \|I_{1\star}(r) - I_{1\star\star}(r)\| + \|I_{2\star}(r) - I_{2\star\star}(r)\| + \|T_1(r) - T_2(r)\|)dr \quad (4.20)$$

Lipschitz condition on solutions $L_1(t)$ and $L_2(t)$ implies:

$$\|L_1(t) - L_2(t)\| \leq \int_{t_2}^{t_3} A(\|S_1(r) - S_2(r)\| + \|V_1(r) - V_2(r)\| + \|L_1(r) - L_2(r)\| + \|I_{1\star}(r) - I_{1\star\star}(r)\| + \|I_{2\star}(r) - I_{2\star\star}(r)\| + \|T_1(r) - T_2(r)\|)dr \quad (4.21)$$

Lipschitz condition on solutions $I_{1\star}(t)$ and $I_{1\star\star}(t)$ results to:

$$\|I_{1\star}(t) - I_{1\star\star}(t)\| \leq \int_{t_3}^{t_4} A(\|S_1(r) - S_2(r)\| + \|V_1(r) - V_2(r)\| + \|L_1(r) - L_2(r)\| + \|I_{1\star}(r) - I_{1\star\star}(r)\| + \|I_{2\star}(r) - I_{2\star\star}(r)\| + \|T_1(r) - T_2(r)\|)dr \quad (4.22)$$

Lipschitz condition on solutions $I_{2\star}(t)$ and $I_{2\star\star}(t)$ implies:

$$\|I_{2\star}(t) - I_{2\star\star}(t)\| \leq \int_{t_4}^{t_5} A(\|S_1(r) - S_2(r)\| + \|V_1(r) - V_2(r)\| + \|L_1(r) - L_2(r)\| + \|I_{1\star}(r) - I_{1\star\star}(r)\| + \|I_{2\star}(r) - I_{2\star\star}(r)\| + \|T_1(r) - T_2(r)\|)dr \quad (4.23)$$

Finally Lipschitz condition on solutions $T_1(t)$ and $T_2(t)$, where tf is final time is given by:

$$\|T_1(t) - T_2(t)\| \leq \int_{t_5}^{tf} A(\|S_1(r) - S_2(r)\| + \|V_1(r) - V_2(r)\| + \|L_1(r) - L_2(r)\| + \|I_{1\star}(r) - I_{1\star\star}(r)\| + \|I_{2\star}(r) - I_{2\star\star}(r)\| + \|T_1(r) - T_2(r)\|)dr \quad (4.24)$$

Adding (4.19), (4.20), (4.21), (4.22), (4.23) and (4.24) together yields:

$$\|S_1(t) - S_2(t)\| + \|V_1(t) - V_2(t)\| + \|L_1(t) - L_2(t)\| + \|I_{1\star}(t) - I_{1\star\star}(t)\| + \|I_{2\star}(t) - I_{2\star\star}(t)\| + \|T_1(t) - T_2(t)\| \leq \int_0^{tf} A(\|S_1(r) - S_2(r)\| + \|V_1(r) - V_2(r)\| + \|L_1(r) - L_2(r)\| + \|I_{1\star}(r) - I_{1\star\star}(r)\| + \|I_{2\star}(r) - I_{2\star\star}(r)\| + \|T_1(r) - T_2(r)\|)dr$$

Applying Mean Value Theorem (MVT) for Integrals, there exists a ξ, $0 \leq \xi \leq tf$, such that

$$\|S_1(t) - S_2(t)\| + \|V_1(t) - V_2(t)\| + \|L_1(t) - L_2(t)\| + \|I_{1\star}(t) - I_{1\star\star}(t)\| + \|I_{2\star}(t) - I_{2\star\star}(t)\| + \|T_1(t) - T_2(t)\| \leq A \cdot tf \cdot (\|S_1(\xi) - S_2(\xi)\| + \|V_1(\xi) - V_2(\xi)\| + \|L_1(\xi) - L_2(\xi)\| + \|I_{1\star}(\xi) - I_{1\star\star}(\xi)\| + \|I_{2\star}(\xi) - I_{2\star\star}(\xi)\| + \|T_1(\xi) - T_2(\xi)\|)$$

for all $t \in [0, tf]$. If tf is small enough that $A \cdot tf < 1$ we arrive at a contradiction, completing our proof. □

4.3 Numerical Analysis of Optimal Control Model

In this section we analyze numerically optimal chemoprophylaxis of latently infected population and education campaign strategies of our one-strain tuberculosis model (4.1). We solve the optimality system consisting of twelve ordinary differential equations from state and adjoint equations by using iterative method known as Runge-Kutta scheme.

State system is solved first by using forward in time fourth order Runge-Kutta method with initial conditions $N(0) = 240, S(0) = 144, V(0) = 12, L(0) = 24, I_1(0) = 24, I_2(0) = 24$

and $T(0) = 12$. These initial conditions are estimates implied from Jung et al. (2002) for the purpose of demonstrations. Since the terminal condition of our optimality system is $\lambda_1(tf) = \lambda_2(tf) = \cdots \lambda_6(tf) = 0$, where $tf = 10$ years then the adjoint system is solved by backward fourth order Runge-Kutta scheme by using current iterated solution of state system. The time step during the simulation process will be $h = 0.02$ years. We then update controls by using suitable convex combination of previous controls and the values of characterization of optimal controls ${u_1}^\star$ and ${u_2}^\star$. We repeat this process several times with stopping criteria that the previous solution is very close to the current iterative solution. We assume our controls to be bounded in the interval $[0, 1]$. The weights of objective functional are theoretically chosen to be $A_1 = 0.1, A_2 = A_3 = 1000, B_1 = 1000$ and $B_2 = 500$. The theoretical choice of weights is purposeful for this particular intended study because calculation of real weights is very demanding and need to be acquainted with a lot of information. Parameters used in simulation together with their descriptions are shown in Table 4.3. We investigate the impact of one control at a time and both controls u_1 and u_2 in reducing the infected population with TB.

Table 4.3: Parameter values for optimal model (4.1) of Tuberculosis.

Parameter	**Value/range**(yr^{-1})	**Source**
λ	0.05	Estimated.
β	2.58	Estimated.
ρ	0.4	Estimated.
θ	0.1	Estimated.
ϵ	0.03	Cohen et al. (2007)
η	0.7 (0.7-0.95)	Okuonghae and Aihie (2008)
μ	0.01923 (0.01-0.04)	Blower et al. (1995)
δ_1	0.3 (0.07-0.365)	Ssematimba et al. (2005)
δ_2	0.2 (0.07-0.365)	Ssematimba et al. (2005)
ϕ	0.6	Estimated.
ω	0.2	Estimated.
ν	0.3	Estimated.
γ	0.2	Estimated.

4.3.1 Optimal education campaign strategy

With education campaign strategy, the optimal control u_1 associated with an increase of public awareness of tuberculosis disease and means of eradicating it from community is used to optimize the objective functional (4.2). In this case the optimal control u_2 is set to zero. The panel D of Figure 4.2 shows that the trajectory $u_1(t)$ is at upper bound from $t = 0$ to 4.98 years and gradually decreases to lower bound zero at final time $t = 10$. At this period from $t = 0$ to $t = 4.98$ years, substantial investment in educating the public about tuberculosis disease and means of curbing it is highly needed due to presence of large number of infected individuals in the community. Onwards from $t = 4.98$ to final time $t = 10$, less investment in educating public can be used since the number of infected will be considerably reduced by earlier investment within the period of $t = 0$ to $t = 4.98$ years. Panels A, B and C of Figure 4.2 show that there is significant difference in the number of infected with and without control u_1. This means that effective use of education campaign may be valuable even without use of chemoprophylaxis of latently infected with TB strategy.

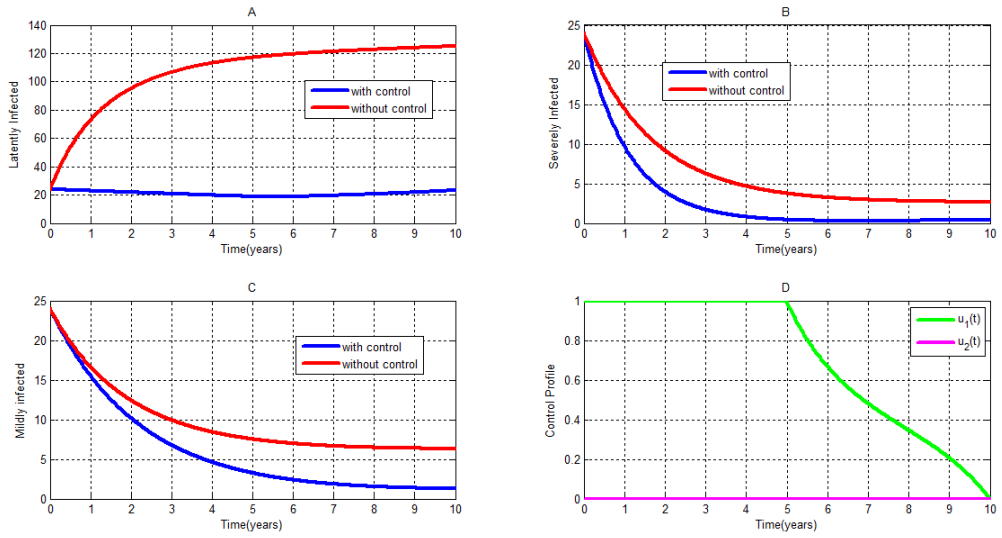

Figure 4.2: Infected with control u_1

4.3.2 Optimal Chemoprophylaxis of Latently Infected with TB strategy

With this strategy, the optimal control u_2 associated with administering of chemoprophylaxis to Latently infected individuals with TB, preventing them to progress to active TB is used to optimize the objective functional J in (4.2) while setting u_1 to zero. The panel D of Figure 4.3 shows that the control u_2 is at upper bound for the period of 9.84 years. According to Jung et al. (2002), if $u_2(t)$ is near to upper bound 1 for a long period of time then there is low treatment failure of chemoprophylaxis and high implementation cost. This means that although it reduces significantly the number of severely and mildly infected individuals as shown in panel B and C respectively with time, it is not alone regarded as effective control to curb TB if not coupled with other controls.

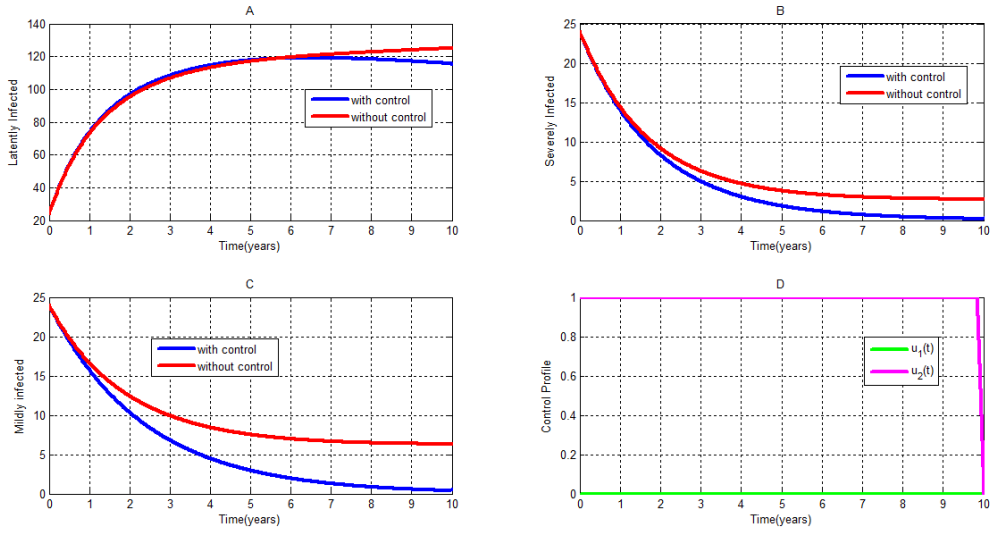

Figure 4.3: Infected with control u_2

4.3.3 Optimal education campaign and Chemoprophylaxis of Latently Infected strategy

With this strategy, both controls u_1 and u_2 are used to optimize the objective functional J in (4.2). The panel D of Figure 4.4 shows that, the control u_1 is at upper bound for a period of 3.66 years before gradually drops to zero at final time while control u_2 is at upper bound for a period of 9.14 years before sharply drops to zero at final time. This is improved trend compared to those in Figure 4.2D and Figure 4.3D respectively. In addition, panels A,B and C of Figure 4.4 show that there is significant difference in the number of infected with and without control. This is similar numerical result as when education campaign strategy is used alone in Section 4.3.1. That is the optimal combination of controls u_1 and u_2 is effective in reducing the number of infected individuals with TB as well as minimizing the cost of implementing them.

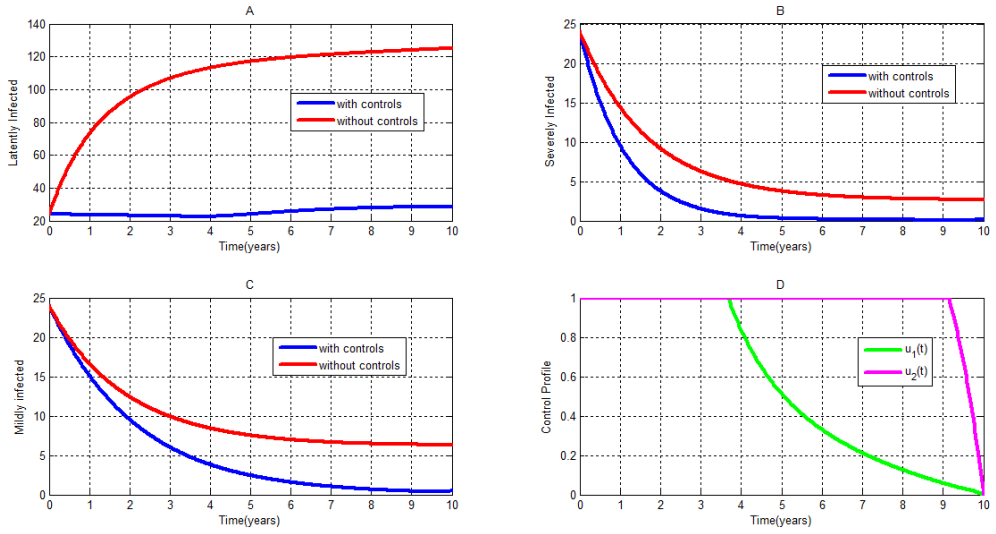

Figure 4.4: Infected with controls u_1 and u_2

4.4 Conclusion

In this chapter we intended to assess the impact of education campaign and chemoprophylaxis of latently infected individuals as control measures in dynamics of TB by using optimal control techniques. The results show that these control measures have enviable effect of reducing the number of infected individuals with TB and the combination of the two controls has desirable effect than when one control is taken at a time. However, results show that the use of education campaign alone has desirable effect of reducing the number of infected individuals from community than when chemoprophylaxis of latently infected is used alone. This is due to the fact that chemoprophylaxis of latently infected individuals is not cost effective. For positive impact, chemoprophylaxis of latently infected strategy has to be coupled with other control measures such as treatment of active TB individuals.

CHAPTER FIVE

Modeling dynamics of two-strain tuberculosis with treatment in presence of healthy and exposed immigrants[4]

Abstract: Multi-drug resistant tuberculosis (MDR-TB) is caused by a pathogen *Mycobacterium tuberculosis* resistant to isoniazid and rifampicin together with or without the rest of other TB drugs. It inflicts many deaths and suffering globally and Tanzania in particular. In the current work we consider a continuous deterministic two-strain TB model in the presence of healthy and exposed immigrants. We assess the impact of treatment on transmission dynamics of multi-drug TB for the purpose of suggesting ways to curb TB from the community. Effective reproduction number, R_e is computed and numerical sensitivity analysis is performed. Sensitivity indices of parameters involving treatment rates of both drug-sensitive and drug-resistant strains are negative as a result of having positive impact on R_e and capable of reducing MDR-TB infections. Numerical simulation results indicate that the presence of exposed immigrants increase disease prevalence as well as disease burden. Moreover, the increase in treatment rates of separate and combined strains of TB have high impact of reducing disease prevalence and alleviate TB infections. We suggest that more efforts such as buying TB drugs and educating the public about early diagnosis and attending treatment have to be taken in order to eradicate multi-drug TB from the community.

5.1 Introduction

Tuberculosis (TB) is a chronic airborne infectious disease caused by a pathogen *Mycobacterium tuberculosis*. TB inflicts many deaths with global annual estimate of 8.6 million people developing the disease and 1.3 million dying from the disease (Mlay et al., 2014a). It is mainly of

[4]**This chapter is based on the submitted paper:**
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two types: pulmonary TB that affects lungs and extra pulmonary TB that affects other organs of the body (Mlay et al., 2014a; WHO, 2012). Our study concentrates on pulmonary tuberculosis. TB presents high burden to developing countries where poor nutrition, congested accommodation and emergency and re-emergency of HIV are manifested. It is globally estimated that incidence, prevalence and mortality rates per 100,000 population are 255, 303 and 26 respectively while Tanzania incidence, prevalence and mortality rates per 100,000 population are 165, 176 and 13 as per WHO (2013). Currently TB is curable with early diagnosis and treatment by using combination of available drugs which are isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin (MoHSW, 2012). The orderly intake of these drugs prevents developing the drug-resistant TB (Collins, 1981).

Multidrug-resistant *Mycobacterium tuberculosis* (MDR-TB) is tuberculosis that is resistant to at least isoniazid (INH) and rifampicin which are most powerful drugs to treat drug-sensitive (drug-susceptible) TB (Bhunu and Garira, 2009; Dye and Williams, 2000; Kajunguri, 2009; MoHSW, 2012). Another form of MDR-TB is Extensively Drug Resistant TB (XDR-TB) that has an additional resistance to fluoroquinolone and to at least one of injectable second-line drugs (i.e. kanamycin, amikacin and capreomycin) (Kajunguri, 2009; MoHSW, 2012). The treatment of MDR-TB resistant to these drugs is expensive, need longer time to cure and are toxic in nature (WHO, 2013). MDR-TB currently has been worrisome globally as it causes many deaths after failing the treatment (Dye and Williams, 2000). It is reported in MoHSW (2012) that there is an estimate of 450,000 new cases of MDR-TB each year and about 150,000 MDR-TB deaths, among which 25,000 are Extensively Drug resistant TB (XDR-TB) cases. Following the Tanzania National Tuberculosis and Leprosy Programme (MoHSW, 2012), Multi-drug resistant TB and extensively drug resistant TB are caused by many reasons including incomplete dosage, irregular intake of medicine and coming into contact with individuals having drug-resistant TB (Maliyoni et al., 2012). Symptoms of MDR-TB are the same as of drug-sensitive (drug-susceptible) TB such as cough for two weeks or more, night sweats, chest and/or back pains, coughing up blood and weight loss (MoHSW, 2012). MDR-TB is

more common to individuals who are previously treated with drug-sensitive TB than those with new TB (MoHSW, 2012). It is therefore argued in Kajunguri (2009); MoHSW (2012) that the prior history of TB treatment of an individual is very important in diagnosing the infection. According to Kajunguri (2009); MoHSW (2012) a patient is at risk to acquire XDR-TB if MDR-TB treatment fails, relapse occurs after MDR-TB treatment and a susceptible individual come into contact with an individual infected with XDR-TB. Mathematical models have been used extensively to address the typical transmission dynamics of multi-drug tuberculosis. Bhunu and Garira (2009) formulated a two strain tuberculosis model with treatment. They further extended the model by incorporating quarantine for multi-drug resistant TB individuals. They concluded that the quarantine of multidrug-resistant TB individuals reduces the reproduction number below one and hence the multi-drug TB epidemic. Kajunguri (2009) presented a mathematical model with interaction between HIV and TB in presence of TB superinfection. On the side of multi-drug TB, he found isoniazid preventive therapy has clear indicative effect of reducing TB prevalence. Maliyoni et al. (2012) presented a deterministic compartmental model to assess the impact of treatment, diagnosis and civic education on importance of completing dosage as control strategies to eradicate completely drug-sensitive TB in Malawi as a result of alleviating MDR-TB transmissions and infections. Castillo-Chávez and Feng (1997) presented a two-strain TB model with treatment of sensitive strain and ignoring the treatment of resistant strain by arguing that it is difficult to treat. In their modelling fast progression after primary infection and exogenous infection of latent individuals were not considered. They concluded that homogeneous mixing plays a big role in tuberculosis transmission. The current work concentrates on formulating two-strain tuberculosis compartmental model with treatment of both strains that describes the transmission dynamics of multi-drug resistance TB in presence of healthy and exposed immigrants. The healthy immigrants join the susceptible class while exposed immigrants who are latently infected with TB join exposed groups of drug-sensitive and drug-resistant classes under given proportions as described in Section 2.2. As a result of entering population, they increase disease prevalence and incidence and consequently the TB

burden. Our work differs from all previous works in that, apart from birth it allows healthy and exposed immigrants as recruits into community which add complexity into transmission dynamics of multi-drug TB. That is, in absence of HIV/AIDS we do not consider the constant recruitment as individuals infected with TB have opportunity to give birth. In addition, it considers endogenous reactivation, exogenous reinfection of latently infected and relapse of both strains. Furthermore, it considers the exogenous reinfection of exposed drug-sensitive individuals with infectious drug-resistant individuals.

This chapter is organized as follows. In Section 5.2, we formulate and describe the model. The qualitative analysis of model and numerical sensitivity analysis of effective reproduction number, R_e are done in Section 5.3. In Section 5.4, we perform numerical simulations to verify qualitative results. Conclusion of our work is presented in Section 5.5.

5.2 Model Formulation

The basic one strain compartmental model, SEIR (Susceptible-Exposed to drug sensitive TB-Infectious with drug sensitive TB- Recovered) presented in Mlay et al. (2014a) and Mlay et al. (2014b) is used to develop a MDR-TB model. We add two more compartments of multi-drug resistant TB to the SEIR model. These are exposed individuals with multi-drug resistant tuberculosis (E_R) and infectious individuals with multi-drug resistant tuberculosis (I_R). We form a new model $SE_sE_RI_sI_RR$ (Susceptible-Exposed to drug sensitive TB-Exposed to multi-drug resistant TB-Infectious with drug sensitive TB-Infectious with multi-drug resistant TB-Recovered). We model new generation of TB cases (both drug sensitive and multi-drug resistant strains) by using standard incidence rate and by assuming that the population is mixing homogeneously. Our model $SE_sE_RI_sI_RR$ explains transmission dynamics of TB multiple strains.

Individuals are recruited to community by birth at per-capita rate of Λ and by immigration of both healthy and infected (exposed) immigrants. The proportion p of total immigrants Π joins

exposed individuals E_s and E_R. The remaining proportion $(1-p)$ are healthy immigrants who join the susceptible class. It is assumed that, the proportion σ of infected immigrants join E_s class while the remaining proportion $(1-\sigma)$ join E_R class. In addition, ability of infectious (sick) immigrants to enter the community is assumed to be negligible and hence ignored. A proportion ρ of susceptible individuals progress to infectious groups I_R and I_s at per-capita transmission rate β via a fast route while the remaining proportion $(1-\rho)$ progress to latent TB at the same per-capita transmission rate of β via a slow route. Infected individuals E_R and E_s progress to active TB (i.e. join I_R and I_s individuals) at per-capita endogenous reactivation rates of γ_1 and γ_2 respectively. It is also assumed that E_R and E_s are exogenously reinfected at per-capita rate of β_1. In addition, the exposed drug sensitive individuals are exogenously reinfected by multi-drug resistant individuals at per-capita transmission rate of β_2 (Gumel and Song, 2008). The proportion ω_1 of drug-sensitive infectious individuals I_s successfully recover at per-capita treatment rate of ϕ_s while the remaining proportion $(1-\omega_1)$ will not complete treatment and as a result develop multi-drug resistant TB and move to E_R class. The proportion ω_2 of infectious muti-drug resistant TB successfully recover at per-capita treatment rate of ϕ_r while the remaining proportion $(1-\omega_2)$ are partially treated and as a result joins the E_R class. TB does not confer permanent immunity and as a result recovered individuals from both strains relapse back to exposed classes of both strains at per-capita reinfection rate of τ. Individuals infectious with Multi-drug resistant TB and drug-sensitive TB die due to natural mortality rate, μ, and at per-capita disease induced mortality rates of α_1 and α_2 respectively while the rest sub-population die at natural mortality rate of μ. All variables and parameters are assumed to be non-negative. In addition the following assumptions were taken into consideration when formulating the model:

i). All individuals are born susceptible.

ii). The members of population mix homogeneously.

iii). Age, sex, social status, do not affect the probability of being infected.

iv). There is possibility of coexistence of both drug-sensitive and multi-drug resistant strains.

v). Ability of infectious immigrants to enter the community is assumed to be negligible and hence ignored.

vi). Recovery is only through treatment (i.e. no natural recovery).

The above description of model formulation together with the assumptions leads to compartmental diagram in Figure 5.1.

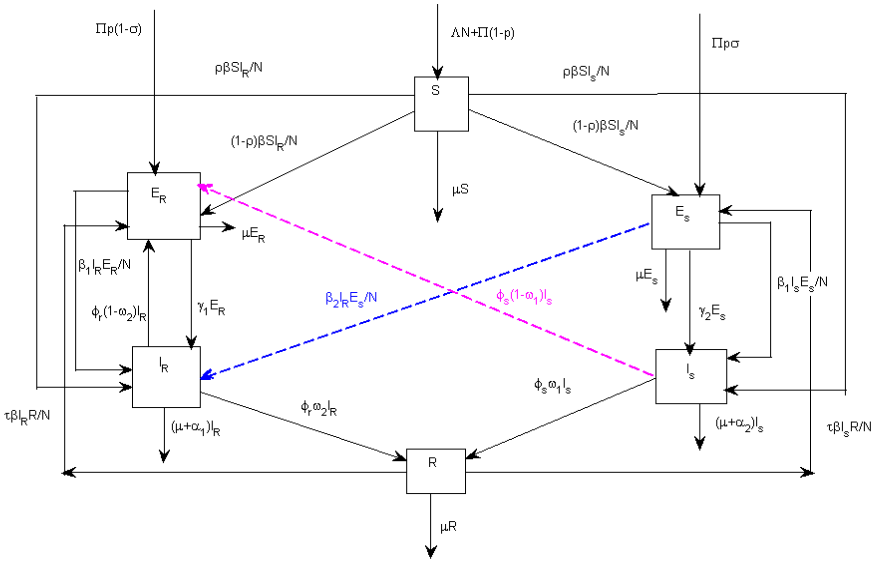


Figure 5.1: Schematic flow diagram showing dynamics of Multi-Drug Resistant tuberculosis.

The full description of variables and parameters used to formulate the model are in Table 3.1 and Table 5.2 respectively.

Table 5.1: Description of variables of the model

Variable	Description
$S(t)$	susceptible individuals at a given time t
$E_s(t)$	Exposed individuals to drug sensitive TB at time t
$E_R(t)$	Exposed individuals to multi-drug resistant TB at time t
$I_s(t)$	Individuals infectious with drug sensitive TB at time t
$I_R(t)$	Individuals infectious with multi-drug resistant TB at time t
$R(t)$	Recovered individuals at time t

Table 5.2: Description of parameters of the model

Parameter	Description
Λ	Per capita birth rate of individuals to community.
Π	Per capita rate of immigrants to community.
p	Proportion of immigrants who joins the exposed classes.
σ	Proportion of infected immigrants with drug sensitive strain.
ρ	Infectious susceptible proportion with both drug sensitive and MDR-TB.
β	Per capita transmission rate from infectious to susceptible individuals.
β_1	Transmission rate associated with exogenous reinfection of both strains.
β_2	Transmission rate associated with exogenous reinfection of multi-drug resistant strain.
γ_1	Per capita endogenous reactivation rate of multi-drug resistant TB individuals.
γ_2	Per capita endogenous reactivation rate of drug-sensitive individuals.
ω_1	A proportion of infectious drug-sensitive individuals that is successful treated.
ϕ_s	Per-capita treatment rate of infectious drug-sensitive individuals.
ω_2	A proportion of infectious multi-drug resistant individuals that is successful treated.
ϕ_r	Per-capita treatment rate of infectious multi-drug resistant individuals.
τ	Per-capita reinfection rate of both strains.
α_1	Per-capita induced mortality rate of infectious multi-drug resistant individuals.
α_2	Per-capita induced mortality rate of infectious drug-sensitive individuals.
μ	Per capita natural death rate.

5.2.1 Equations of the Model

Basing on the assumptions made and relationships existing between variables and parameters shown in Figure 5.1, the following system of ordinary differential equations describe the dynamics of multi-drug resistant tuberculosis:

$$\frac{dS}{dt} = \Lambda N + \Pi(1-p) - \frac{\beta(I_R + I_s)S}{N} - \mu S \tag{5.1a}$$

$$\frac{dE_s}{dt} = \Pi p\sigma + \beta((1-\rho)S + \tau R)\frac{I_s}{N} - \left(\frac{\beta_2 I_R + \beta_1 I_s}{N} + \gamma_2 + \mu\right) E_s \tag{5.1b}$$

$$\frac{dE_R}{dt} = \Pi p(1-\sigma) + \left(\frac{\beta((1-\rho)S + \tau R)}{N} + \phi_r(1-\omega_2)\right) I_R + \phi_s(1-\omega_1)I_s - \left(\frac{\beta_1 I_R}{N} + \gamma_1 + \mu\right) E_R \tag{5.1c}$$

$$\frac{dI_s}{dt} = \rho\frac{\beta I_s S}{N} + \left(\frac{\beta_1 I_s}{N} + \gamma_2\right) E_s - (\phi_s + \mu + \alpha_2)I_s \tag{5.1d}$$

$$\frac{dI_R}{dt} = \rho\frac{\beta I_R S}{N} + \left(\frac{\beta_1 I_R}{N} + \gamma_1\right) E_R + \frac{\beta_2 I_R E_s}{N} - (\phi_r + \mu + \alpha_1)I_R \tag{5.1e}$$

$$\frac{dR}{dt} = \phi_r\omega_2 I_R + \phi_s\omega_1 I_s - \frac{\tau\beta(I_R + I_s)R}{N} - \mu R \tag{5.1f}$$

In (5.1) we define the total population, N as

$$N = S + E_s + E_R + I_s + I_R + R \tag{5.2}$$

By adding the state equations in (5.1) we end up with rate of change of population,

$$\frac{dN}{dt} = \Pi + (\Lambda - \mu)N - \alpha_1 I_R - \alpha_2 I_s \tag{5.3}$$

5.2.2 Normalization of the Model

The model (5.1) can easily be analyzed after being normalized such that the total population proportion is one. The normalization is done by dividing the population of each compartment

by total population. That is we set:

$$s = \frac{S}{N},\ \ e_s = \frac{E_s}{N},\ \ e_R = \frac{E_R}{N},\ \ i_s = \frac{I_s}{N},\ \ i_R = \frac{I_R}{N},\ \ r = \frac{R}{N}. \tag{5.4}$$

where by now $s + e_s + e_R + i_s + i_R + r = 1$. Substituting (5.4) into (5.3) we end up with

$$\frac{dN}{dt} = \Pi + (\Lambda - \mu - \alpha_1 i_R - \alpha_2 i_s)N \tag{5.5}$$

Upon differentiating the proportions in (5.4) with respect to time and making simplification, leads to the following system:

$$\begin{aligned}
\frac{ds}{dt} &= \Lambda + (1-p-s)\frac{\Pi}{N} - (\beta(i_s + i_R) + \Lambda - \alpha_1 i_R - \alpha_2 i_s)s && \text{(5.6a)}\\
\frac{de_s}{dt} &= \frac{\Pi}{N}(p\sigma - e_s) + \beta((1-\rho)s + \tau r)i_s \\
&\quad -(\beta_2 i_R + \beta_1 i_s + \gamma_2 + \Lambda - \alpha_1 i_R - \alpha_2 i_s)e_s && \text{(5.6b)}\\
\frac{de_R}{dt} &= (p(1-\sigma) - e_R)\frac{\Pi}{N} + (\beta((1-\rho)s + \tau r) + \phi_r(1-\omega_2))i_R \\
&\quad +\phi_s(1-\omega_1)i_s - (\beta_1 i_R + \gamma_1 + \Lambda - \alpha_1 i_R - \alpha_2 i_s)e_R && \text{(5.6c)}\\
\frac{di_s}{dt} &= \gamma_2 e_s - \left(\frac{\Pi}{N} + \Lambda + \phi_s + \alpha_2 - \rho\beta s - \beta_1 e_s - \alpha_1 i_R - \alpha_2 i_s\right) i_s && \text{(5.6d)}\\
\frac{di_R}{dt} &= \gamma_1 e_R - \left(\frac{\Pi}{N} + \Lambda + \phi_r + \alpha_1 - \rho\beta s - \beta_1 e_R - \beta_2 e_s - m_3\right) i_R && \text{(5.6e)}\\
\frac{dr}{dt} &= \phi_r\omega_2 i_R + \phi_s\omega_1 i_s - \left(\frac{\Pi}{N} + \Lambda + \tau\beta(i_R + i_s) - \alpha_1 i_R - \alpha_2 i_s\right) r && \text{(5.6f)}\\
\frac{dN}{dt} &= \left(\frac{\Pi}{N} + \Lambda - \mu - \alpha_1 i_R - \alpha_2 i_s\right) N && \text{(5.6g)}
\end{aligned}$$

subject to condition $s + e_s + e_R + i_s + i_R + r = 1$. We define $m_3 = \alpha_1 i_R + \alpha_2 i_s$ in (5.6e). We note that the region of epidemiological interest,

$$\Omega = \{(s, e_s, e_R, i_s, i_R, r) \in \mathbb{R}^6_+ \colon s, e_s, e_R, i_s, i_R, r \geq 0, s + e_s + e_R + i_s + i_R + r = 1\} \tag{5.7}$$

is positively invariant with respect to model system (5.6), where $\mathbb{R}^6_+$ is non-negative cone of $\mathbb{R}^6$ including its lower dimensional faces.

5.3 Analysis of the Model

In this section we analyze model (5.6) in order to get some insights on dynamics of multi-drug resistant TB disease and transmission. The threshold that determines whether the multi-drug TB clears or persists to the community will be computed.

5.3.1 Existence of Disease Free Equilibrium (DFE)

From system (5.6) we notice that all equations depend on the total population, N. Before investigating the existence of disease free equilibrium we set (5.6g) to zero and use the technique employed in Tumwiine et al. (2010) by substituting $\frac{\Pi}{N} = \mu + \alpha_1 i_R + \alpha_2 i_s - \Lambda$ into equations of system (5.6) so as to give the following system

$$\frac{ds}{dt} = \mu + \alpha_1 i_R + \alpha_2 i_s - p(\mu + \alpha_1 i_R + \alpha_2 i_s - \Lambda) - (\mu + \beta(i_s + i_R))s \tag{5.8a}$$

$$\frac{de_s}{dt} = p\sigma(\mu + \alpha_1 i_R + \alpha_2 i_s - \Lambda) + \beta((1-\rho)s + \tau r)i_s - (\mu + \beta_2 i_R + \beta_1 i_s + \gamma_2)e_s \tag{5.8b}$$

$$\frac{de_R}{dt} = p(1-\sigma)(\mu + \alpha_1 i_R + \alpha_2 i_s - \Lambda) + (\beta((1-\rho)s + \tau r) + \phi_r(1-\omega_2))i_R + \phi_s(1-\omega_1)i_s - (\mu + \beta_1 i_R + \gamma_1)e_R \tag{5.8c}$$

$$\frac{di_s}{dt} = \gamma_2 e_s - (\mu + \phi_s + \alpha_2 - \rho\beta s - \beta_1 e_s)i_s \tag{5.8d}$$

$$\frac{di_R}{dt} = \gamma_1 e_R - (\mu + \phi_r + \alpha_1 - \rho\beta s - \beta_1 e_R - \beta_2 e_s)i_R \tag{5.8e}$$

$$\frac{dr}{dt} = \phi_r\omega_2 i_R + \phi_s\omega_1 i_s - (\mu + \tau\beta(i_R + i_s))r \tag{5.8f}$$

subject to condition $s + e_s + e_R + i_s + i_R + r = 1$.

By setting the right hand side of each equation in model system (5.8) to zero, the disease free equilibrium point is found when the proportions of disease groups, $e_s^\star = e_R^\star = i_s^\star = i_R^\star = 0$ and proportion of exposed immigrants $p = 0$. It is established that the disease free equilibrium point in non-negative cone $\mathbb{R}^6$ is $E_0 = (s^\star, e_s^\star, e_R^\star, i_s^\star, i_R^\star, r^\star) = (1, 0, 0, 0, 0, 0)$.

5.3.2 Effective reproduction number

Definition 5.13. The effective reproduction number, R_e is the threshold that indicates the number of infections caused by a single infectious individual introduced in the community in which the intervention strategies are administered (Okuonghae and Korobeinikov, 2007; Okuonghae and Aihie, 2008; Tumwiine et al., 2014).

In our case, R_e is the threshold that determines the behavior of the model (5.6) in the presence of treatment as control strategy. The effective reproduction number is computed by using the Next generation operator method developed by Van den Driessche and Watmough (2002). The effective reproduction number, R_e will help us to determine the local stability of disease free equilibrium, which is locally asymptotic stability when $R_e < 1$ and unstable when $R_e > 1$. The method is demonstrated as follows:
We arrange equations of system (5.8) in such a way that the infectious classes come first and rewrite the resulting system in the form of:

$$x_i' = f_i(x) = \mathcal{F}_i(x) - \mathcal{V}_i(x), i = 1, 2, \cdots, n.$$

where $\mathcal{F}_i$ is the rate of appearance of new infections in compartment i and $\mathcal{V}_i = \mathcal{V}_i^- - \mathcal{V}_i^+$ in which $\mathcal{V}_i^+$ is the rate of transfer of individual into compartment i by all other means, and $\mathcal{V}_i^-$ is the rate of transfer of individual out of compartment i. Each function f_i is continuous and at least twice differentiable in the region defined by Ω. If we consider $\mathbf{F}$ to be a non-negative square matrix, $m \times m$, $\mathbf{V}$ be a non-singular M-matrix and E_0, a disease free equilibrium point such that

$$\mathbf{F} = \left[\frac{\partial \mathcal{F}_i(E_0)}{\partial x_j}\right] \text{ and } \mathbf{V} = \left[\frac{\partial \mathcal{V}_i(E_0)}{\partial x_j}\right] \text{ with } 1 \leq i, j \leq m,$$

then the Jacobian matrices $\mathbf{F}$ and $\mathbf{V}$ at disease free Equilibrium point E_0 following infected classes e_s, i_s, e_R, i_R are respectively given by:

$$\mathbf{F} = \begin{bmatrix} 0 & \beta(1-\rho) & 0 & 0 \\ 0 & \rho\beta & 0 & 0 \\ 0 & 0 & 0 & \beta(1-\rho) \\ 0 & 0 & 0 & \rho\beta \end{bmatrix} = \begin{bmatrix} F_1 & 0 \\ 0 & F_2 \end{bmatrix},$$

$$\mathbf{V} = \begin{bmatrix} \mu+\gamma_2 & 0 & 0 & 0 \\ -\gamma_2 & \mu+\phi_s+\alpha_2 & 0 & 0 \\ 0 & -\phi_s(1-\omega_1) & \mu+\gamma_1 & -\phi_r(1-\omega_2) \\ 0 & 0 & -\gamma_1 & \mu+\phi_r+\alpha_1 \end{bmatrix} = \begin{bmatrix} V_1 & 0 \\ V_3 & V_2 \end{bmatrix}.$$

We define

$$F_1 = \begin{bmatrix} 0 & \beta(1-\rho) \\ 0 & \rho\beta \end{bmatrix} \text{ and } F_2 = \begin{bmatrix} 0 & \beta(1-\rho) \\ 0 & \rho\beta \end{bmatrix} \text{ as well as,}$$

$$V_1 = \begin{bmatrix} \mu+\gamma_2 & 0 \\ -\gamma_2 & \mu+\phi_s+\alpha_2 \end{bmatrix}, \; V_2 = \begin{bmatrix} \mu+\gamma_1 & -\phi_r(1-\omega_2) \\ -\gamma_1 & \mu+\phi_r+\alpha_1 \end{bmatrix} \text{ and}$$

$$V_3 = \begin{bmatrix} 0 & -\phi_s(1-\omega_1) \\ 0 & 0 \end{bmatrix}.$$

We note that V_3 is non-invertible matrix. After long manipulations we obtain the following spectral radii:

$$R_s = \rho(F_1 V_1^{-1}) = \frac{\beta(\gamma_2+\mu\rho)}{(\mu+\gamma_2)(\mu+\phi_s+\alpha_2)}, \tag{5.9}$$

$$R_r = \rho(F_2 V_2^{-1}) = \frac{\beta(\gamma_1+\mu\rho)}{(\mu+\gamma_1)(\mu+\phi_r+\alpha_1)-\phi_r(1-\omega_2)\gamma_1}. \tag{5.10}$$

The effective reproduction number is therefore given by:

$$R_e = \rho(\mathbf{F}\mathbf{V}^{-1}) = \max\{R_s, R_r\}, \tag{5.11}$$

where R_s and R_r are reproduction numbers of drug-sensitive TB only and multi-drug resistant TB only respectively. Thus from Van den Driessche and Watmough (2002) and equations (5.9) and (5.10), the following result holds.

Theorem 5.14. *The disease free equilibrium point, E_0 of a full model* (5.8) *is locally asymptotically stable if $R_e < 1$, that is, if $R_s < 1$ and $R_r < 1$ and unstable if $R_e > 1$, that is, if $R_s > 1$ and $R_r > 1$.*

In absence of treatment, i.e. $\omega_1 = \omega_2 = \phi_s = \phi_r = 0$, equations (5.9) and (5.10) reduce to

$$R_{0s} = \frac{\beta(\gamma_2 + \mu\rho)}{(\mu + \gamma_2)(\mu + \alpha_2)} \text{ and } R_{0r} = \frac{\beta(\gamma_1 + \mu\rho)}{(\mu + \gamma_1)(\mu + \alpha_1)} \tag{5.12}$$

We define R_{0s} and R_{0r} from (5.12) as basic reproduction numbers of drug-sensitive TB only and multi-drug resistant TB only respectively. We deduce that:

$$R_0 = \max\{R_{0s}, R_{0r}\}. \tag{5.13}$$

The threshold R_0 is the basic reproduction number that indicates the initial spread of disease in the community when control strategies are not in place. It indicates the number of secondary infections caused by one infectious candidate who enters a population which is fully susceptible (Hethcote, 2000). The terms in R_e have epidemiological interpretations. Let us interpret terms in R_s and those in R_r will follow in similar way.

The term $\beta\rho$ in R_s is the drug-sensitive rate of infection while the term $\dfrac{\gamma_2}{\mu + \gamma_2}$ is the expected fraction of individuals progressing from E_s class to I_s class. In addition the term $\dfrac{1}{\mu + \phi_s + \alpha_2}$ is the expected time taken for individuals with drug-sensitive TB to spend in infectious class, I_s. The similar interpretation holds for terms in R_r.

Suppose from (5.11), $R_s > R_r$. It follows that the effective reproduction number, R_e is given

by:

$$R_e = R_s = \frac{\beta(\gamma_2 + \mu\rho)}{(\mu + \gamma_2)(\mu + \phi_s + \alpha_2)} \tag{5.14}$$

We now write $R_e = R_s = K_1 R_{0s}$, from which $K_1 = \dfrac{\mu + \alpha_2}{\mu + \phi_s + \alpha_2} < 1$ and R_{0s} is the basic reproduction of drug-sensitive TB presented in (5.12). This means that, the treatment of individuals with drug-sensitive TB reduces the initial disease transmission and epidemic. On the other hand the partial derivative of (5.14) with respect to parameter ϕ_s results to:

$$\frac{\partial R_s}{\partial \phi_s} = \frac{-\beta(\gamma_2 + \mu\rho)}{(\mu + \gamma_2)(\mu + \phi_s + \alpha_2)^2} < 0. \tag{5.15}$$

The inequality expression in (5.15) reveals that R_s is the decreasing function of ϕ_s. It implies that, the increase in treatment rate of individuals with drug-sensitive TB has positive impact on TB control and increase the effort to cut down the epidemic.

In contrast, suppose from (5.11), $R_r > R_s$. The effective reproduction number, R_e of model (5.6) is given by:

$$R_e = R_r = \frac{\beta(\gamma_1 + \mu\rho)}{\mu(\mu + \phi_r + \alpha_1) + \gamma_1(\mu + \phi_r\omega_2 + \alpha_1)}. \tag{5.16}$$

It can be shown from (5.16) that, $R_r = K_2 R_{0r}$, from which we define,

$$K_2 = \frac{(\mu + \gamma_1)(\mu + \alpha_1)}{\mu(\mu + \phi_r + \alpha_1) + \gamma_1(\mu + \phi_r\omega_2 + \alpha_1)},$$

$$= \frac{\mu(\mu + \alpha_1) + \gamma_1(\mu + \alpha_1)}{\mu(\mu + \phi_r + \alpha_1) + \gamma_1(\mu + \phi_r\omega_2 + \alpha_1)} < 1.$$

Thus, successful treatment of multi-drug resistant TB individuals reduces the initial transmission of multi-drug TB and increase the effort to curtail the disease. The partial derivative of R_r with respect to parameter ω_2 results to:

$$\frac{\partial R_r}{\partial \omega_2} = -\frac{\gamma_1\phi_r\beta(\gamma_1 + \mu\rho)}{[\mu(\mu + \phi_r + \alpha_1) + \gamma_1(\mu + \phi_r\omega_2 + \alpha_1)]^2} < 0. \tag{5.17}$$

The inequality in (5.17) indicates that R_r is a decreasing function of ω_2. That is, increasing the proportional of individuals who are successfully treated with multi-drug resistant TB has positive impact on TB control and increase effort of curtailing multi-drug TB infections and transmissions. In addition the partial derivative of R_r with respect to parameter ϕ_r gives:

$$\frac{\partial R_r}{\partial \phi_r} = -\frac{\beta(\gamma_1 + \mu\rho)(\mu + \gamma_1\omega_2)}{[\mu(\mu + \phi_r + \alpha_1) + \gamma_1(\mu + \phi_r\omega_2 + \alpha_1)]^2} < 0. \tag{5.18}$$

It has been shown in (5.18) that R_r is the decreasing function of ϕ_r. Thus, an increase in treatment rate of multi-drug resistant TB individuals has positive impact on curbing multi-drug TB spread and transmissions.

The general relationship between R_s, R_r, R_{0s} and R_{0r} is graphically presented in Nyerere et al. (2014) by using linear relationship that exists between the growth of reproduction number and transmission rate β, while keeping other parameters fixed.

5.3.3 Numerical Sensitivity Analysis of Effective Reproduction number, R_e

We perform numerical sensitivity analysis of effective reproduction number, R_e by using parameters in Table 5.3 whose numerical values are from existing literature as well as estimated for the purpose to suit our intended particular study to determine the impact of each parameter involved in R_e to the transmission of multi-drug TB.

We recall from (5.11) that $R_e = \max(R_s, R_r)$. Computations of R_s and R_r by using values from Table 5.3 result to $R_s = 1.3982$ and $R_r = 1.6898$. Thus $R_r > R_s$ and hence the effective reproduction number, $R_e = R_r$. These values of R_s and R_r suit the coexistence equilibrium. Therefore we are going to explore the relative importance of each parameter involved in R_r to the transmission of multi-drug tuberculosis. Parameters with high impact on R_e and which have to be targeted by intervention strategies are determined by aid of sensitivity analysis of R_e (Chitnis et al., 2008; Rodrigues et al., 2013). In order to determine how best to reduce human mortality and morbidity due to multi-drug TB, the appoach of Chitnis et al. (2008) is used to compute the sensitivity indices of R_e relative to parameters involved in it. The function

Table 5.3: Parameter values for model (5.6)

Parameter	Value (yr^{-1})	Source
Λ	0.03725	Nyerere et al. (2014).
Π	0.06	Estimated.
p	0.04	Estimated.
σ	0.02	Estimated.
ρ	0.2	Blower et al. (1995).
β	1.2	Estimated.
β_1	1.5	Estimated.
β_2	1.7	Estimated.
γ_1	0.05	Cohen et al. (2007).
γ_2	0.03	Cohen et al. (2007).
ω_1	0.8	Dye and Williams (2000); Kajunguri (2009).
ϕ_s	0.3	Maliyoni et al. (2012).
ω_2	0.47	Dye and Williams (2000); Kajunguri (2009).
ϕ_r	0.09	Maliyoni et al. (2012).
τ	0.02	Hattaf et al. (2009)
α_1	0.5	Maliyoni et al. (2012).
α_2	0.3	Maliyoni et al. (2012).
μ	0.01632	NBS (2013)

$R_e = R_r$ is differentiable and hence gives us room to define the sensitivity index in terms of derivatives as follows:

Definition 5.15. The normalized forward sensitivity index of variable R_e that depends on parameter q is defined as

$$\Upsilon_q^{R_e} = \frac{\partial R_e}{\partial q} \times \frac{q}{R_e}. \tag{5.19}$$

Since $R_e = R_r$ is an explicit function, it follows that the sensitivity indices of R_e with respect to parameters q_i involved in $R_e = R_r$ are given by

$$\Upsilon_{q_i}^{R_e} = \frac{\partial R_e}{\partial q_i} \times \frac{q_i}{R_e}. \tag{5.20}$$

For instance sensitivity of parameters β and ω_2 are computed respectively as follows: $\Upsilon_\beta^{R_e} = \frac{\partial R_e}{\partial \beta} \times \frac{\beta}{R_e} = +1$ and $\Upsilon_{\omega_2}^{R_e} = \frac{\partial R_e}{\partial \omega_2} \times \frac{\omega_2}{R_e} = -0.0559$. The rest indices, $\Upsilon_\rho^{R_e}, \Upsilon_{\gamma_1}^{R_e}, \Upsilon_{\phi_r}^{R_e}, \Upsilon_{\alpha_1}^{R_e}, \Upsilon_\mu^{R_e}$ are computed in the same manner and their magnitudes in terms of decreasing sensitivity are tabulated in Table 5.4.

Table 5.4: Sensitivity indices evaluated using baseline parameter values in Table 5.3

Parameter	Sensitivity index
β	+1.0000
α_1	-0.8766
μ	-0.2289
γ_1	+0.2003
ϕ_r	-0.0947
ρ	+0.0613
ω_2	-0.0559

5.3.4 Interpretation of Sensitivity indices

From Table 5.4 we have β, μ and ρ as positive indices. This implies that increasing (decreasing) one of these parameters while the rest are kept fixed, increases (decreases) the value of R_e and hence increases (decreases) the endemicity of multi-drug TB respectively. For instance $\Upsilon_{\rho}^{R_e} = +0.0613$, implies that increasing (decreasing) the proportion of susceptible individuals, ρ to both drug-sensitive and multi-drug resistant TB by 50% increases (decreases) the value of R_e by 3.065 and hence increasing (decreasing) the endemicity of multi-drug TB respectively.
On the other hand, α_1, μ, ϕ_r and ω_2 are parameters with negative indices, implying that increasing (decreasing) one of this parameters while the rest are kept constant, decreases (increases) the value of R_e and respectively decreases (increases) the endemicity of multi-drug TB. For instance $\Upsilon_{\omega_2}^{R_e} = -0.0559$ implies that increasing the proportion of infectious individuals, ω_2, who are successfully treated with multi-drug resistant TB by 50% reduces the value of R_e by 2.799% and hence lowering the endemicity of disease.
The effective reproduction number, R_e is most sensitive to parameters β and α_1. These parameters have to be carefully estimated in order to determine the robustness of model predictions to parameter values purposely to determine the parameters having high impact on R_e and have to be targeted by intervention strategies (Chitnis et al., 2008).

5.4 Numerical Simulations

In this section we simulate the coexistence model (5.8) to verify our qualitative results by using available parameter values from existing literature as well as estimated ones. Unless otherwise stated the parameter values indicated in Table 5.3 will be used in simulation process.

5.4.1 Contour plots for parameters involved in R_e

In this subsection, we investigate the relationship of various parameters and their effect on effective reproduction number, $R_e = R_r$ in the course to determine the dynamics of multi-drug resistant TB. The investigation is done by plotting contours as in Figure 5.2 by using parameters in Table 5.3 and $\beta = 0.7$.

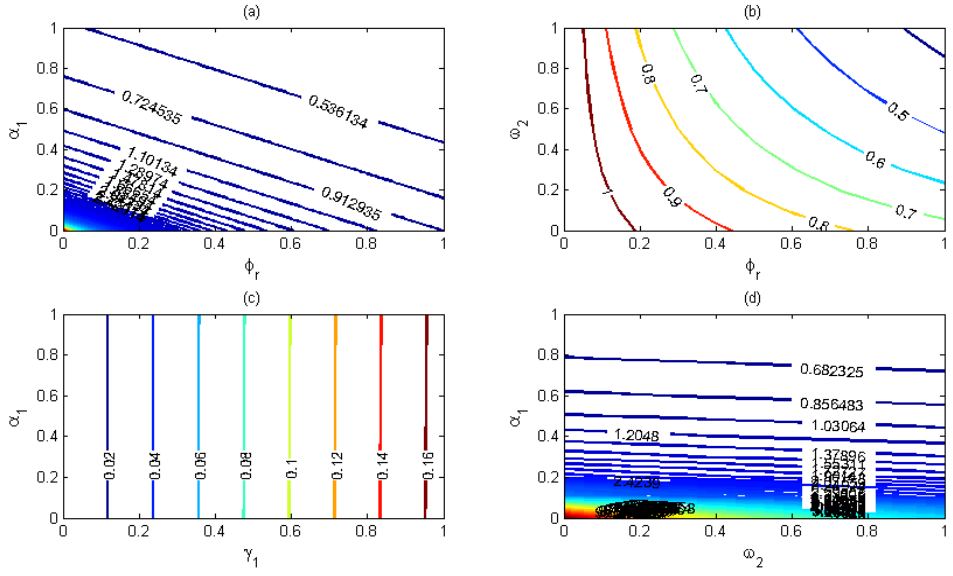


Figure 5.2: Contour plots showing the variation of effective reproduction number, R_e as (a) treatment rate of infectious multi-drug resistant individuals, ϕ_r and induced mortality rate of infectious multi-drug resistant individuals, α_1 vary. (b) ϕ_r and proportion of drug-resistant who are successful treated, ω_2 vary. (c) endogenous reactivation rate for multi-drug resistant individuals, γ_1 and α_1 vary and (d) ω_2 and α_1 vary.

Figure 5.2(a) shows that, the decrease in treatment rate of infectious multi-drug resistant individuals, ϕ_r increases the effective reproduction number and as a consequence increases the

epidemic of multi-drug resistant individuals. In contrast, parameter α_1 has a negative effect on transmission of multi-drug resistant TB, the result that concurs with one discussed in Subsection 5.3.3 and particularly in Table 5.4.

Figure 5.2(b) shows that, the increase in treatment rate, ϕ_r of multi-drug resistant TB individuals reduces the magnitude of effective reproduction number, R_e and has a direct consequence of alleviating the epidemic of multi-drug resistant TB. In addition R_e is more sensitive to ϕ_r than as to parameter ω_2 as it is shown in Table 5.4.

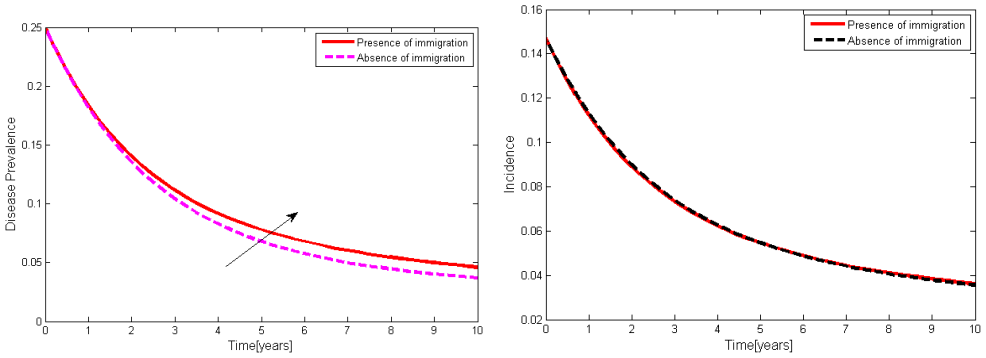
In Figure 5.2(c), endogenous reactivation rate, γ_1 of multi-drug resistant TB individuals has little effect on initial transmission of the disease. In the interval $0 < \gamma_1 < 1$ we find that $0 < R_e < 1$. This means that variation of parameter γ_1 does not impede the possibility of the disease to clear from community. In addition we find that R_e is sensitive to γ_1 than as to α_1.

In Figure 5.2(d) effective reproduction number, R_e is most sensitive to parameter α_1 than as to ω_2. The parameter α_1 has negative effect to the transmission dynamics of multi-drug resistant TB. For instance, the decrease of α_1 increases R_e as a consequence of proliferating the epidemic of multi-drug resistant TB. This result is in line with one discussed in Subsection 5.3.3 as well as shown in Table 5.4.

5.4.2 Impact of immigrants on prevalence and incidence of MDRTB

In this subsection we study the impact of introducing immigrants to community. Disease prevalence is higher in presence of immigrants compared to when immigrants are not allowed in the community as it is shown in Figure 5.3(a). In particular in absence of immigration the disease prevalence reduces from 0.25 to 0.03705, that is approximately 85.18% reduction within a period of ten years compared to reduction of disease prevalence from 0.25 to 0.04609, that is 81.56% reduction in presence of immigration within the same period of time. We find that there is a net increase of TB prevalence to 3.62% in presence of immigrants to the community. This is due to the fact that the exposed immigrants add severity of disease to the existing community. In public health context we may interpret that the presence of immigrants increase the disease burden in terms of allocating resources in building more hospitals and TB clinics, diagnosing

and treating the patients before coming into contact with members in the community. On the other hand the presence of immigrants have a slight impact on incidence of the disease. There is no significant difference on incidence of disease in presence or in absence of immigrants as illustrated in Figure 5.3(b). The reason behind it is, immigrants do not contribute new infections to the community.



(a) (b)

Figure 5.3: Impact of immigrants on disease prevalence and incidence

5.4.3 Disease prevalence on both resistant and sensitive strains

In this subsection we study the relationship between disease prevalence and strains of Multi-drug resistant tuberculosis. In Figure 5.4 we find that the resistant strain has higher disease prevalence compared to sensitive strain. The reason behind it is, sensitive strain receives high treatment rates compared to resistant strain. In fact it is difficult and expensive to treat resistant strain than the sensitive strain.

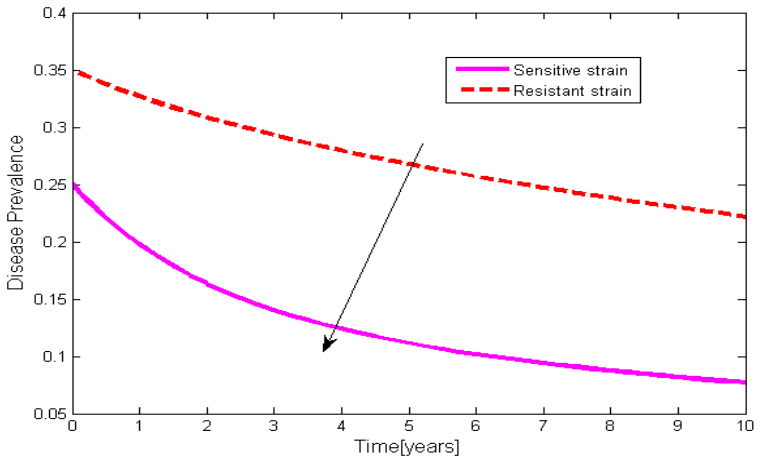


Figure 5.4: Impact of treatment on prevalence of both drug sensitive and multi-drug resistant strains.

5.4.4 Effect of treatment

We study the impact of treatment on transmission dynamics of multi-drug resistant TB by observing how prevalence in population proportion varies with treatment rates of infectious individuals with drug sensitive TB, ϕ_s and those infectious with multi-drug resistant TB, ϕ_r . By increasing the treatment rates of both drug sensitive and multi-drug resistant strains leads to decrease in prevalence within the population proportion.

Figure 5.5 and Figure 5.6 show the variation of disease prevalence with treatment rates of infectious individuals with drug-sensitive TB and those infectious with multi-drug resistant TB respectively. In particular when the treatment rate, ϕ_s for infectious drug-sensitive TB individuals is increased to 0.85 (i.e. 85%) then the TB prevalence reduces from 0.25 to 0.1067, that is approximately 57.32% in the period of ten years as shown in Figure 5.5. However, in the same period of time, increasing treatment rate, ϕ_r of individuals infectious with multi-drug resistant TB to 0.85 (85%) reduces the prevalence from 0.25 to 0.03396, that is approximately 86.42% as shown in Figure 5.6. We claim that increasing treatment rates of multi-drug resistant TB eradicates the disease from community.

In Figure 5.7 the arrow points to the direction of decreasing disease prevalence with increasing treatment rates of both drug-sensitive and multi-drug resistant strains. In particular, when

treatment rates ϕ_s and ϕ_r of both infectious drug-sensitive and multi-drug resistant TB individuals are increased to nearly 1, i.e. $\phi_s = \phi_r = 0.85$, TB prevalence reduces from 0.25 to 0.009606 that counts to 96.16% within a period of ten years. We suggest that, in presence of drug-resistant strain the multi-drug TB can be managed by treating both strains.

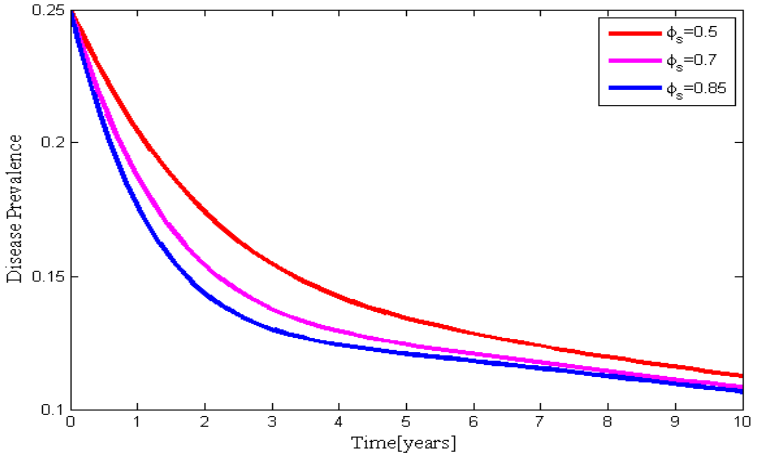


Figure 5.5: Variation of disease prevalence with treatment rates of infectious drug-sensitive individuals.

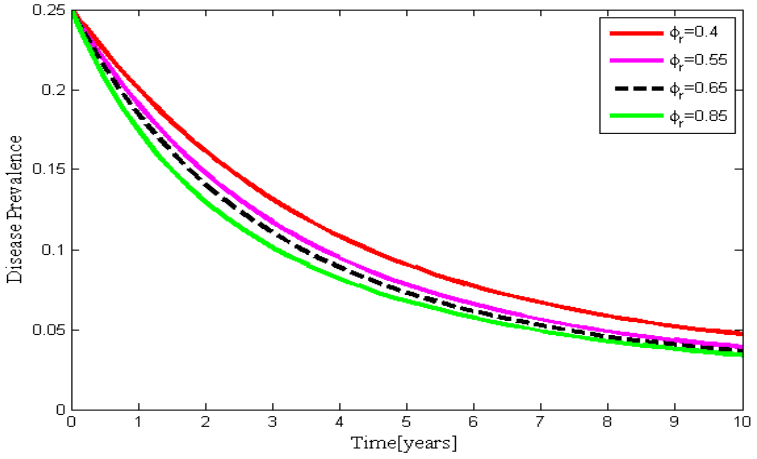


Figure 5.6: Variation of disease prevalence with treatment rates of infectious multi-drug resistant individuals.

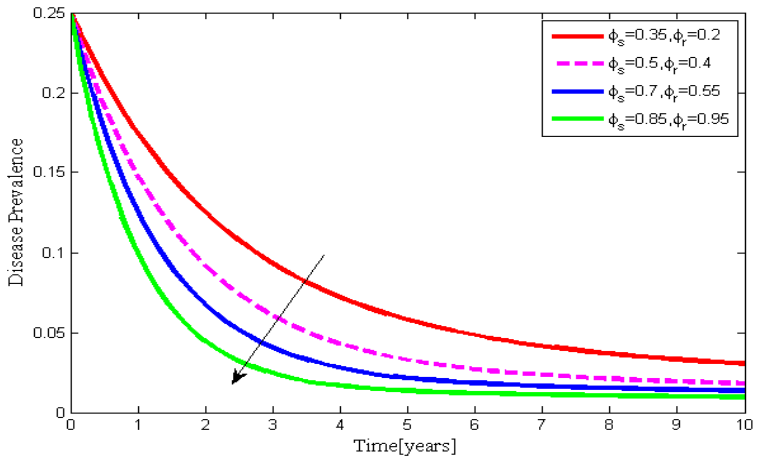


Figure 5.7: Variation of disease prevalence with treatment rates of both infectious drug-sensitive and multi-drug resistant individuals.

5.5 Conclusion

In this chapter, a continuous time deterministic two-strain tuberculosis model with treatment as control strategy in presence of healthy and exposed immigrants has been formulated to assess the impact of treatment on transmission dynamics of multi-drug resistant tuberculosis infections. The threshold, effective reproduction number, R_e that classically indicates the initial spread of the disease has been computed and disease free equilibrium has been proved to be stable when $R_e < 1$ and unstable otherwise. Numerical sensitivity analysis of R_e showed that parameters for treatment of both infectious drug-sensitive and multi-drug resistant TB cases have high impact on R_e as a result of reducing TB infections. Numerical simulation results indicate that in presence of exposed immigrants MDR-TB prevalence increases from 81.56% to 85.18% within a period of ten years as a consequence of increasing disease burden to 3.62%. On the other hand, the presence of exposed immigrants have no significant impact on incidence of MDR-TB as immigrants do not contribute the new cases of disease to community. Furthermore the impact of treatment on prevalence of each and combined strains was assessed. Increasing the treatment rates of both drug-sensitive and multi-drug resistant strains decrease the prevalence of MDR-TB by 96.16%. We suggest that more efforts such as observing immigration rules that emphasizes on screening people who are coming in the country, buying TB

drugs,early detection and treatment of active TB cases, public education campaigns about TB and ways of curbing it are needed to be addressed in order to eradicate multi-drug resistant TB from community.

CHAPTER SIX

Backward bifurcation theory and local stability analysis of endemic equilibria of two-strain model with treatment[5]

Abstract: In this chapter a continuous deterministic two-strain tuberculosis model with treatment of both strains and in presence of healthy and exposed immigrants to assess the impact of treatment as control strategy is considered. The qualitative analysis of local endemic equilibrium of each strain and coexistence of both strains is carried out. The presence of exogenous reinfection to both strains leads to possibility of backward bifurcation for coexistence model at effective reproduction number, $R_e = 1$ and existence of multiple equilibria when $R_e < 1$. In the neighborhood of 1 when $R_e < 1$, disease free equilibrium coexist with large stable endemic equilibrium. This indicates that even by classically reducing R_e below one is no longer a sufficient condition to eliminate the multi-drug resistant tuberculosis from community. An additional reduction of R_e below saddle node bifurcation is required to eliminate the disease given that the disease free equilibrium is globally asymptotically stable. Numerical simulation results are presented to validate analytical results. We suggest the use of control mechanisms such as early diagnosis and civic education to be in line with treatment in order to eradicate multi-drug TB from community.

6.1 Introduction

Tuberculosis (TB) is a chronic bacterial infectious disease caused by a pathogen *Mycobacterium tuberculosis* and affects more than one third of global population (Bloom, 1994; Feng et al., 2000; Miller, 1993). TB is fatal with delayed interventions (Okyere, 2007). It affects lungs (i.e. pulmonary TB) and other sites of body including brain, nervous system, bone, spine and kidney (i.e. extra-pulmonary TB) (WHO, 2012). An annual global estimate of 8.6 million people develop TB among whom 1.3 million die of the disease (WHO, 2013). It is reported

[5]**This chapter is based on the submitted paper:**
Mlay, G. M., Luboobi, L. S., Kuznetsov, D., Mpolya, E. A., and Kajunguri, D.(2015). *Backward bifurcation theory and local stability analysis of endemic equilibria of two-strain model with treatment*. Unpublished Manuscript.

in WHO (2013) that per 100,000 population, the global annual estimates of incidence, prevalence and mortality rates were 255, 303 and 26 respectively while Tanzania incidence, prevalence and mortality rates per 100,000 population in 2002 were 165, 176 and 13 as per WHO (2013). TB is curable with early diagnosis and treatment by using combination of available drugs which are isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin (MoHSW, 2012; WHO, 2013). The proper intake of these drugs prevents development of the multi-drug resistant TB (Collins, 1981).

Multi-drug resistant TB (MDR-TB) is tuberculosis that is resistant to at least isoniazid and rifampicin which are powerful first line drugs for treating drug-sensitive TB (Bhunu and Garira, 2009; Dye and Williams, 2000; Kajunguri, 2009; MoHSW, 2012). The resurgence of multi-drug resistant TB raises public health concern to curb it. An annual global estimate of 0.5 million new cases of MDR-TB were reported in Maliyoni et al. (2012). MDR-TB is expensive but not impossible to treat as long as full compliance to anti-TB drugs is adhered to and a patient is under DOTS(Directly Observed Therapy Strategy) including taking pills in the presence of medical professionals (Maliyoni et al., 2012; Okyere, 2007).

Two-strain Tuberculosis models have been formulated to address the typical transmission dynamics of multi-drug resistant TB. Bhunu and Garira (2009) formulated a two-strain TB model with quarantine to reduce the reproduction number below one and hence reduction of multi-drug resistant TB. Gumel and Song (2008) presented a two-strain TB model with treatment of drug-sensitive strain. They find that disease free equilibrium is locally asymptotically stable when reproduction number is less than one. In addition, their model undergoes backward bifurcation with tri-stability equilibria. Mishra and Srivastava (2014) formulated a multi-drug resistant tuberculosis model of patients with vaccination. They introduced quarantine as a vital role of controlling TB. Castillo-Chávez and Feng (1997) presented a two-strain model with treatment of sensitive strain only by claiming that the resistant strain is difficult to treat. However, their model does not consider the fast progression after primary infection as well as exogenous reinfection of latently infected individuals. Our work concentrates on formulating two-strain TB model with treatment of both strains that describes the dynamics of multi-drug resistant TB. It differs from previous works in that, it allows recruitment of both healthy and exposed

immigrants into the community. In addition, we assume that the recruitment by birth is not constant as individuals with inactive TB in absence of HIV/AIDS take long time to progress to active TB and as a result they have opportunity to give birth. Furthermore our model considers endogenous reactivation, fast progression of primary infection to infectious classes of both strains, exogenous reinfection of latently infected and relapse of both strains. It further considers exogenous reinfection of exposed drug-sensitive individuals with infectious drug resistant individuals.

This chapter is organized as follows. In Section 6.2, we formulate and describe the model. The qualitative and bifurcation analyses of model are done in Section 6.3. In Section 6.4, we perform numerical simulations and discuss the relevance of the results. Conclusion of our work is presented in Section 6.5.

6.2 Model Formulation

The basic one strain compartmental model, SEIR (Susceptible-Exposed to drug sensitive TB-Infectious with drug sensitive TB- Recovered) presented in Mlay et al. (2014a) and Mlay et al. (2014b) is used to develop a MDR-TB model. We add two more compartments of multi-drug resistant TB to the SEIR model. These are exposed individuals with multi-drug resistant tuberculosis (E_R) and infectious individuals with multi-drug resistant tuberculosis (I_R). We form a new model $SE_sE_RI_sI_RR$ (Susceptible-Exposed to drug sensitive TB-Exposed to multi-drug resistant TB-Infectious with drug sensitive TB-Infectious with multi-drug resistant TB-Recovered). We model new generation of TB cases (both drug sensitive and multi-drug resistant strains) by using standard incidence rate and by assuming that the population is mixing homogeneously. Our model $SE_sE_RI_sI_RR$ explains transmission dynamics of TB multiple strains.

Individuals are recruited to community by birth at per-capita rate of Λ and by immigration of both healthy and infected (exposed) immigrants. The proportion p of total immigrants Π joins exposed individuals E_s and E_R. The remaining proportion $(1-p)$ are healthy immigrants who join the susceptible class. It is assumed that, the proportion σ of infected immigrants join E_s

class while the remaining proportion $(1-\sigma)$ join E_R class. In addition, ability of infectious (sick) immigrants to enter the community is assumed to be negligible and hence ignored. A proportion ρ of susceptible individuals progress to infectious groups I_R and I_s at per-capita transmission rate β via a fast route while the remaining proportion $(1-\rho)$ progress to latent TB at the same per-capita transmission rate of β via a slow route. Infected individuals E_R and E_s progress to active TB (i.e. join I_R and I_s individuals) at per-capita endogenous reactivation rates of γ_1 and γ_2 respectively. It is also assumed that E_R and E_s are exogenously reinfected at per-capita rate of β_1. In addition, the exposed drug sensitive individuals are exogenously reinfected by multi-drug resistant individuals at per-capita transmission rate of β_2 (Gumel and Song, 2008). The proportion ω_1 of drug-sensitive infectious individuals I_s successfully recover at per-capita treatment rate of ϕ_s while the remaining proportion $(1-\omega_1)$ will not complete treatment and as a result develop multi-drug resistant TB and move to E_R class. The proportion ω_2 of infectious muti-drug resistant TB successfully recover at per-capita treatment rate of ϕ_r while the remaining proportion $(1-\omega_2)$ are partially treated and as a result joins the E_R class. TB does not confer permanent immunity and as a result recovered individuals from both strains relapse back to exposed classes of both strains at per-capita reinfection rate of τ. Individuals infectious with Multi-drug resistant TB and drug-sensitive TB die due to natural mortality rate, μ, and at per-capita disease induced mortality rates of α_1 and α_2 respectively while the rest sub-population die at natural mortality rate of μ. All variables and parameters are assumed to be non-negative. In addition the following assumptions were taken into consideration when formulating the model:

i). All individuals are born susceptible.

ii). The members of population mix homogeneously.

iii). Age, sex, social status, do not affect the probability of being infected.

iv). There is possibility of coexistence of both drug-sensitive and multi-drug resistant strains.

v). Ability of infectious immigrants to enter the community is assumed to be negligible and hence ignored.

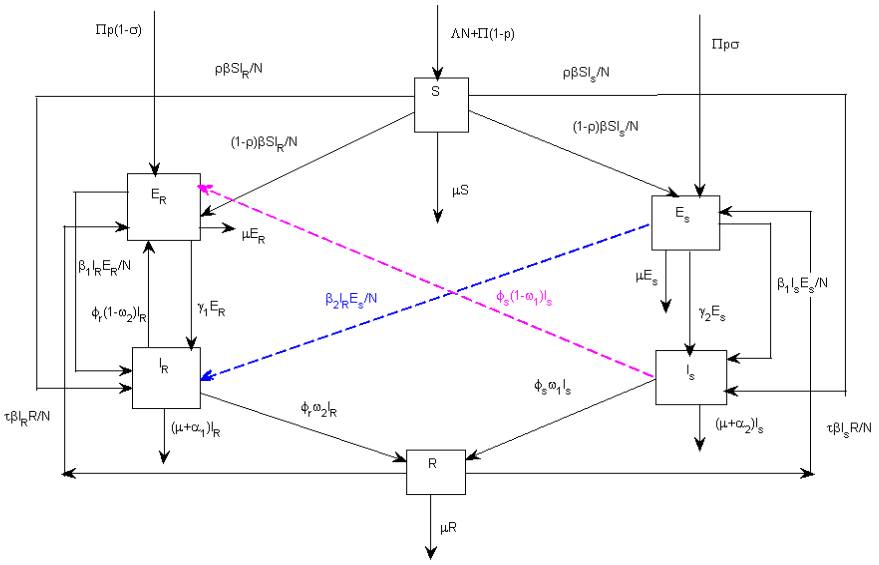


Figure 6.1: Schematic flow diagram showing dynamics of Multi-Drug Resistant tuberculosis.

vi). Recovery is only through treatment (i.e. no natural recovery).

The above description of the dynamics of Multi-drug resistant TB and drug-sensitive TB together with the assumptions leads to compartmental diagram in Figure 6.1.

The full description of variables and parameters used to formulate the model are in Table 6.1 and Table 6.2 respectively.

Table 6.1: Description of variables of the model

Variable	Descriptions
$S(t)$	susceptible individuals at a given time t
$E_s(t)$	Exposed individuals to drug sensitive TB at time t
$E_R(t)$	Exposed individuals to multi-drug resistant TB at time t
$I_s(t)$	Individuals infectious with drug sensitive TB at time t
$I_R(t)$	Individuals infectious with multi-drug resistant TB at time t
$R(t)$	Recovered individuals at time t

Table 6.2: Description of parameters of the model

Parameter	Descriptions
Λ	Per capita birth rate of individuals to community.
Π	Per capita rate of immigrants to community.
p	Proportion of immigrants who joins the exposed classes.
σ	Proportion of infected immigrants with drug sensitive strain.
ρ	Infectious susceptible proportion with both drug sensitive and MDR-TB.
β	Per capita transmission rate from infectious to susceptible individuals.
β_1	Transmission rate associated with exogenous reinfection of both strains.
β_2	Transmission rate associated with exogenous reinfection of multi-drug resistant strain.
γ_1	Per capita endogenous reactivation rate of multi-drug resistant TB individuals.
γ_2	Per capita endogenous reactivation rate of drug-sensitive individuals.
ω_1	A proportion of infectious drug-sensitive individuals that is successful treated.
ϕ_s	Per-capita treatment rate of infectious drug-sensitive individuals.
ω_2	A proportion of infectious multi-drug resistant individuals that is successful treated.
ϕ_r	Per-capita treatment rate of infectious multi-drug resistant individuals.
τ	Per-capita reinfection rate of both strains.
α_1	Per-capita induced mortality rate of infectious multi-drug resistant individuals.
α_2	Per-capita induced mortality rate of infectious drug-sensitive individuals.
μ	Per capita natural death rate.

6.2.1 Equations of the Model

Basing on the assumptions made and relationships existing between variables and parameters shown in Figure 6.1, the following system of ordinary differential equations describe the dynamics of multi-drug resistant tuberculosis:

$$\frac{dS}{dt} = \Lambda N + \Pi(1-p) - \frac{\beta(I_R + I_s)S}{N} - \mu S \tag{6.1a}$$

$$\frac{dE_s}{dt} = \Pi p\sigma + \beta((1-\rho)S + \tau R)\frac{I_s}{N} - \left(\frac{\beta_2 I_R + \beta_1 I_s}{N} + \gamma_2 + \mu\right) E_s \tag{6.1b}$$

$$\frac{dE_R}{dt} = \Pi p(1-\sigma) + \left(\frac{\beta((1-\rho)S + \tau R)}{N} + \phi_r(1-\omega_2)\right) I_R + \phi_s(1-\omega_1)I_s - \left(\frac{\beta_1 I_R}{N} + \gamma_1 + \mu\right) E_R \tag{6.1c}$$

$$\frac{dI_s}{dt} = \rho\frac{\beta I_s S}{N} + \left(\frac{\beta_1 I_s}{N} + \gamma_2\right) E_s - (\phi_s + \mu + \alpha_2)I_s \tag{6.1d}$$

$$\frac{dI_R}{dt} = \rho\frac{\beta I_R S}{N} + \left(\frac{\beta_1 I_R}{N} + \gamma_1\right) E_R + \frac{\beta_2 I_R E_s}{N} - (\phi_r + \mu + \alpha_1)I_R \tag{6.1e}$$

$$\frac{dR}{dt} = \phi_r\omega_2 I_R + \phi_s\omega_1 I_s - \frac{\tau\beta(I_R + I_s)R}{N} - \mu R \tag{6.1f}$$

In (6.1) we define the total population, N as

$$N = S + E_s + E_R + I_s + I_R + R \tag{6.2}$$

By adding the state equations in (6.1) we end up with rate of change of population,

$$\frac{dN}{dt} = \Pi + (\Lambda - \mu)N - \alpha_1 I_R - \alpha_2 I_s \tag{6.3}$$

6.2.2 Normalization of the Model

The model (6.1) can easily be analyzed after being normalized such that the total population proportion is one. The normalization is done by dividing the population of each compartment

by total population. That is we set:

$$s = \frac{S}{N},\ \ e_s = \frac{E_s}{N},\ \ e_R = \frac{E_R}{N},\ \ i_s = \frac{I_s}{N},\ \ i_R = \frac{I_R}{N},\ \ r = \frac{R}{N}. \tag{6.4}$$

where by now $s + e_s + e_R + i_s + i_R + r = 1$. Substituting (5.4) into (6.3) we end up with

$$\frac{dN}{dt} = \Pi + (\Lambda - \mu - \alpha_1 i_R - \alpha_2 i_s)N \tag{6.5}$$

Upon differentiating the proportions in (5.4) with respect to time and making simplification, leads to the following system:

$$\begin{aligned}
\frac{ds}{dt} &= \Lambda + (1-p-s)\frac{\Pi}{N} - (\beta(i_s + i_R) + \Lambda - \alpha_1 i_R - \alpha_2 i_s)s && \text{(6.6a)}\\
\frac{de_s}{dt} &= \frac{\Pi}{N}(p\sigma - e_s) + \beta((1-\rho)s + \tau r)i_s \\
&\quad -(\beta_2 i_R + \beta_1 i_s + \gamma_2 + \Lambda - \alpha_1 i_R - \alpha_2 i_s)e_s && \text{(6.6b)}\\
\frac{de_R}{dt} &= (p(1-\sigma) - e_R)\frac{\Pi}{N} + (\beta((1-\rho)s + \tau r) + \phi_r(1-\omega_2))i_R \\
&\quad +\phi_s(1-\omega_1)i_s - (\beta_1 i_R + \gamma_1 + \Lambda - \alpha_1 i_R - \alpha_2 i_s)e_R && \text{(6.6c)}\\
\frac{di_s}{dt} &= \gamma_2 e_s - \left(\frac{\Pi}{N} + \Lambda + \phi_s + \alpha_2 - \rho\beta s - \beta_1 e_s - \alpha_1 i_R - \alpha_2 i_s\right) i_s && \text{(6.6d)}\\
\frac{di_R}{dt} &= \gamma_1 e_R - \left(\frac{\Pi}{N} + \Lambda + \phi_r + \alpha_1 - \rho\beta s - \beta_1 e_R - \beta_2 e_s - m_4\right) i_R && \text{(6.6e)}\\
\frac{dr}{dt} &= \phi_r\omega_2 i_R + \phi_s\omega_1 i_s - \left(\frac{\Pi}{N} + \Lambda + \tau\beta(i_R + i_s) - \alpha_1 i_R - \alpha_2 i_s\right) r && \text{(6.6f)}\\
\frac{dN}{dt} &= \left(\frac{\Pi}{N} + \Lambda - \mu - \alpha_1 i_R - \alpha_2 i_s\right) N && \text{(6.6g)}
\end{aligned}$$

subject to condition $s + e_s + e_R + i_s + i_R + r = 1$. From (6.6e) we define $m_4 = \alpha_1 i_R + \alpha_2 i_s$. We note that the region of epidemiological interest

$$\Omega = \{(s, e_s, e_R, i_s, i_R, r) \in \mathbb{R}^6_+ : s, e_s, e_R, i_s, i_R, r \geq 0, s + e_s + e_R + i_s + i_R + r = 1\}, \tag{6.7}$$

is positively invariant with respect to model system (6.6), where $\mathbb{R}^6_+$ is non-negative cone of $\mathbb{R}^6$ including its lower dimensional faces.

6.3 Analysis of the Model

In this section we analyze model (6.6) in order to get some insights on dynamics of multi-drug resistant TB disease and transmission.

6.3.1 Existence of Disease Free Equilibrium (DFE)

From system (6.6) we notice that all equations depend on the total population, N. Before investigating the existence of disease free equilibrium we set (6.6g) to zero and use the technique employed in Tumwiine et al. (2010) by substituting $\frac{\Pi}{N} = \mu + \alpha_1 i_R + \alpha_2 i_s - \Lambda$ into equations of system (6.6) so as to give the following system

$$\frac{ds}{dt} = \mu + \alpha_1 i_R + \alpha_2 i_s - p(\mu + \alpha_1 i_R + \alpha_2 i_s - \Lambda) - (\mu + \beta(i_s + i_R))s \tag{6.8a}$$

$$\frac{de_s}{dt} = p\sigma(\mu + \alpha_1 i_R + \alpha_2 i_s - \Lambda) + \beta((1-\rho)s + \tau r)i_s - (\mu + \beta_2 i_R + \beta_1 i_s + \gamma_2)e_s \tag{6.8b}$$

$$\frac{de_R}{dt} = p(1-\sigma)(\mu + \alpha_1 i_R + \alpha_2 i_s - \Lambda) + (\beta((1-\rho)s + \tau r) + \phi_r(1-\omega_2))i_R + \phi_s(1-\omega_1)i_s - (\mu + \beta_1 i_R + \gamma_1)e_R \tag{6.8c}$$

$$\frac{di_s}{dt} = \gamma_2 e_s - (\mu + \phi_s + \alpha_2 - \rho\beta s - \beta_1 e_s)i_s \tag{6.8d}$$

$$\frac{di_R}{dt} = \gamma_1 e_R - (\mu + \phi_r + \alpha_1 - \rho\beta s - \beta_1 e_R - \beta_2 e_s)i_R \tag{6.8e}$$

$$\frac{dr}{dt} = \phi_r \omega_2 i_R + \phi_s \omega_1 i_s - (\mu + \tau\beta(i_R + i_s))r \tag{6.8f}$$

subject to condition $s + e_s + e_R + i_s + i_R + r = 1$.

By setting the right hand side of each equation in model system (6.8) to zero, the disease free equilibrium point is found when the proportions of disease groups, $e_s^\star = e_R^\star = i_s^\star = i_R^\star = 0$ and proportion of exposed immigrants $p = 0$. It is established that the disease free equilibrium point in non-negative cone $\mathbb{R}^6$ is $E_0 = (s^\star, e_s^\star, e_R^\star, i_s^\star, i_R^\star, r^\star) = (1, 0, 0, 0, 0, 0)$.

6.3.2 Effective reproduction number

Definition 6.16. The effective reproduction number, R_e is the threshold that indicates the number of infections caused by a single infectious individual introduced in the community in which the intervention strategies are administered (Okuonghae and Korobeinikov, 2007; Okuonghae and Aihie, 2008; Tumwiine et al., 2014).

In our case, R_e is the threshold that determines the behavior of the model (6.6) in the presence of treatment as control strategy. The effective reproduction number is computed by using Next generation operator method developed by Van den Driessche and Watmough (2002). It is the largest spectral radius of next generation matrix. The effective reproduction number is therefore given by:

$$R_e = \max\{R_s, R_r\}, \tag{6.9}$$

where R_s and R_r are reproduction numbers of drug-sensitive TB only and multi-drug resistant TB only respectively derived to be,

$$R_s = \frac{\beta(\gamma_2 + \mu\rho)}{(\mu + \gamma_2)(\mu + \phi_s + \alpha_2)} \tag{6.10a}$$

$$R_r = \frac{\beta(\gamma_1 + \mu\rho)}{(\mu + \gamma_1)(\mu + \phi_r + \alpha_1) - \phi_r(1 - \omega_2)\gamma_1}. \tag{6.10b}$$

Thus from Van den Driessche and Watmough (2002) and equations (6.10a) and (6.10b), the following result holds.

Theorem 6.17. *The disease free equilibrium point, E_0 of a full model* (6.8) *is locally asymptotically stable if $R_e < 1$, that is, if $R_s < 1$ and $R_r < 1$ and unstable if $R_e > 1$, that is, if $R_s > 1$ and $R_r > 1$.*

6.3.3 Existence of Endemic equilibria

The model sytem (6.8) has three unique endemic equilibrium points. These are two boundary endemic equilibria (drug-sensitive TB only endemic equilibrium, E_{1s} and multi-drug resistant TB only equilibrium, E_{1R}) and coexistence endemic equilibrium, $\hat{E_1}$ (an equilibrium in which both drug-sensitive and multi-drug resistant strains are present).

6.3.4 Drug-sensitive TB only endemic equilibrium

We set $e_R = i_R = 0$ to the system (6.8) in order to reduce it to drug-sensitive TB only model. As a result, we note from (6.8c) that:

$$\Lambda = \mu + \alpha_2 i_s + \frac{1}{p(1-\sigma)}\phi_s(1-\omega_1)i_s. \tag{6.11}$$

We supplying $e_R = i_R = 0$ and representation of Λ from (6.11) to the system (6.8) in order to reduce it to the following drug-sensitive TB only model:

$$\frac{ds}{dt} = \mu + \alpha_2 i_s + \frac{1}{1-\sigma}\phi_s(1-\omega_1)i_s - (\mu + \beta i_s)s \tag{6.12a}$$

$$\frac{de_s}{dt} = -\frac{\sigma}{1-\sigma}\phi_s(1-\omega_1)i_s + \beta((1-\rho)s + \tau r)i_s - (\mu + \beta_1 i_s + \gamma_2)e_s \tag{6.12b}$$

$$\frac{di_s}{dt} = \gamma_2 e_s - (\mu + \phi_s + \alpha_2 - \rho\beta s - \beta_1 e_s)i_s \tag{6.12c}$$

$$\frac{dr}{dt} = \phi_s\omega_1 i_s - (\mu + \tau\beta i_s)r \tag{6.12d}$$

subject to condition $s + e_s + i_s + r = 1$.

We have two forces of infection from (6.12) denoted at steady state as $\lambda_1^\star = \beta i_s^\star$ and $\lambda_2^\star = \beta_1 i_s^\star$ in such a way that $\frac{\lambda_1^\star}{\lambda_2^\star} = \frac{\beta}{\beta_1}$ and $\lambda^\star = \lambda_1^\star = \frac{\beta}{\beta_1}\lambda_2^\star$. The endemic equilibrium point for drug-sensitive TB only model (6.12) in terms of force of force of infection $\lambda^\star$ at steady state is given

by $E_{1s} = (s^\star, e_s^\star, i_s^\star, r^\star, 0, 0)$, where by

$$s^\star = \frac{\mu(h_1\lambda^{\star 3} + h_2\lambda^{\star 2} + h_3\lambda^\star + h_4) + n_1(\mu + \tau\lambda^\star)(a\lambda^{\star 2} + b\lambda^\star + c)\lambda^\star}{(\mu + \lambda^\star)(h_1\lambda^{\star 3} + h_2\lambda^{\star 2} + h_3\lambda^\star + h_4)} \tag{6.13a}$$

$$e_s^\star = \frac{\lambda^\star(k_1\lambda^{\star 3} + k_2\lambda^{\star 2} + k_3\lambda^\star + k_4)}{(\mu + \lambda^\star)(h_1\lambda^{\star 3} + h_2\lambda^{\star 2} + h_3\lambda^\star + h_4)} \tag{6.13b}$$

$$i_s^\star = \frac{(1-\sigma)(\mu + \tau\lambda^\star)(a\lambda^{\star 2} + b\lambda^\star + c)\lambda^\star}{h_1\lambda^{\star 3} + h_2\lambda^{\star 2} + h_3\lambda^\star + h_4} \tag{6.13c}$$

$$r^\star = \frac{\phi_s\omega_1(1-\sigma)(a\lambda^{\star 2} + b\lambda^\star + c)\lambda^\star}{h_1\lambda^{\star 3} + h_2\lambda^{\star 2} + h_3\lambda^\star + h_4}. \tag{6.13d}$$

From (6.13a) we define, $n_1 = (1-\sigma)\alpha_2 + \phi_s(1-\omega)$. We further define from (6.13) that,

$$\begin{aligned}
a &= \beta_1(\mu + \phi_s + \alpha_2),\\
b &= \beta(\mu + \gamma_2)(\mu + \phi_s + \alpha_2) + \beta_1\mu(\mu + \phi_s + \alpha_2 - \beta),\\
c &= \beta\mu[(\mu + \gamma_2)(\mu + \phi_s + \alpha_2) - \beta(\mu\rho + \gamma_2)],\\
&= \beta\mu(\mu + \gamma_2)(\mu + \phi_s + \alpha_2)(1 - R_s).\\
h_1 &= \beta_1\beta\tau(1-\sigma)(\alpha_2 + \phi_s),\\
h_2 &= \beta^2\gamma_2\tau(1-\sigma)(\phi_s + \alpha_2) + \beta_1\beta\mu[(1-\sigma)(\phi_s + \alpha_2) - \phi_s(\omega_1(1-\tau-\sigma) + \sigma\tau)]\\
&\quad + \beta^2\rho\mu\tau[(1-\sigma)\alpha_2 + \phi_s(1-\omega_1)],\\
h_3 &= \beta^2\mu\gamma_2[(1-\sigma)\alpha_2 + \phi_s(1-\omega_1) + \tau\phi_s\omega_1 - \sigma\phi_s(1 + \tau - \omega_1)]\\
&\quad + \beta^2\rho\mu^2((1-\sigma)\alpha_2 + \phi_s(1-\omega_1)) - \beta_1\beta\sigma\phi_s(1-\omega_1)\mu^2,\\
h_4 &= -\beta^2\gamma_2\sigma\phi_s(1-\omega_1)\mu^2,
\end{aligned}$$

and

$$
\begin{aligned}
k_1 &= \beta\tau(\mu+\phi_s+\alpha_2)[(1-\sigma)(\phi_s+\alpha_2(1-\rho))-\rho\phi_s(1-\omega_1)],\\
k_2 &= \mu\beta\tau(\mu+\phi_s+\alpha_2-\beta\rho)[(1-\sigma)(\phi_s+\alpha_2(1-\rho))-\rho\phi_s(1-\omega_1)]\\
&\quad+\beta\mu(\mu+\phi_s+\alpha_2)[(1-\rho)((1-\sigma)\alpha_2+\phi_s(1-\omega_1))+\tau\phi_s\omega_1-\sigma\phi_s(1+\tau-\omega_1)]\\
&\quad+\beta^2\tau\mu\rho(1-\rho)(1-\sigma)[(1-\sigma)\alpha_2+\phi_s(1-\omega_1)],\\
k_3 &= \beta\mu^2[((\mu+\phi_s+\alpha_2)(1-\rho)+\beta\sigma\rho^2)((1-\sigma)\alpha_2+\phi_s(1-\omega_1))\\
&\quad+(\mu+\phi_s+\alpha_2-\beta\rho)(\omega_1-\sigma)\tau\phi_s-\beta\sigma\rho(1-\sigma)\alpha_2],\\
k_4 &= -(\mu+\phi_s+\alpha_2-\beta\rho)(1-\omega_1)\beta\sigma\phi_s\mu^3.
\end{aligned}
$$

From equation (6.13d) and make use of the fact that $\lambda^\star = \beta i_s^\star$ we formulate the relation

$$\lambda^\star = \frac{\beta(1-\sigma)(\mu+\tau\lambda^\star)(a\lambda^{\star 2}+b\lambda^\star+c)\lambda^\star}{h_1\lambda^{\star 3}+h_2\lambda^{\star 2}+h_3\lambda^\star+h_4} \tag{6.14}$$

Simplifying relation (6.14), we obtain the following polynomial:

$$
\begin{aligned}
\lambda^\star[(\beta(1-\sigma)\tau a-h_1)\lambda^{\star 3}+(\beta(1-\sigma)(\mu a+\tau b)-h_2)\lambda^{\star 2}&\\
+(\beta(1-\sigma)\mu b-h_3+\beta(1-\sigma)\tau c)\lambda^\star+\beta(1-\sigma)\mu c]=0.&
\end{aligned}
\tag{6.15}
$$

The relation $\lambda^\star = 0$ from (6.15) satisfies disease free equilibrium for drug-sensitive TB only model that is already discussed, while the polynomial,

$$
\begin{aligned}
(\beta(1-\sigma)\tau a-h_1)\lambda^{\star 3}+(\beta(1-\sigma)(\mu a+\tau b)-h_2)\lambda^{\star 2}&\\
+(\beta(1-\sigma)\mu b-h_3+\beta(1-\sigma)\tau c)\lambda^\star+\beta(1-\sigma)\mu c=0&
\end{aligned}
\tag{6.16}
$$

satisfies the endemic equilibrium, E_{1s} for drug-sensitive TB only model (6.12). Replacing the parameters from model (6.12) and after long algebraic simplifications, the cubic function (6.16) is reduced to:

$$f_1(\lambda^\star) = A_1\lambda^{\star 3}+B_1\lambda^{\star 2}+C_1\lambda^\star+D_1=0. \tag{6.17}$$

We define the coefficients of cubic polynomial (6.17) as follows:

$$A_1 = \beta_1\tau(1-\sigma) > 0. \tag{6.18a}$$

$$\begin{aligned} B_1 = {} & (1-\sigma)[\beta_1\mu + \beta\tau(\mu+\phi_s+\alpha_2+\gamma_2) + \beta_1\tau(\mu+\phi_s+\alpha_2-\beta)] \\ & + \beta_1\phi_s(\sigma\tau + \omega_1(1-\tau-\sigma)) - \beta\rho\tau[(1-\sigma)\alpha_2 + \phi_s(1-\omega_1)]. \end{aligned} \tag{6.18b}$$

$$\begin{aligned} C_1 = {} & (1-\sigma)\mu[\beta(\mu+\phi_s+\alpha_2+\gamma_2) + \beta_1(\mu+\phi_s+\alpha_2-\beta)] \\ & + \beta\gamma_2\phi_s(\sigma\tau + \omega_1(1-\tau-\sigma)) - \beta\rho\mu[(1-\sigma)\alpha_2 + \phi_s(1-\omega_1)] \\ & + \beta_1\sigma\phi_s(1-\omega_1)\mu + \beta(1-\sigma)\tau(\mu+\gamma_2)(\mu+\phi_s+\alpha_2)(1-R_s). \end{aligned} \tag{6.18c}$$

$$D_1 = \beta(1-\sigma)\mu(\mu+\gamma_2)(\mu+\phi_s+\alpha_2)(1-R_s). \tag{6.18d}$$

We write polynomial (6.17) as:

$$f_1(\lambda^\star) = \lambda^\star K(\lambda^\star) + \lambda^\star\beta(1-\sigma)\tau(\mu+\gamma_2)(\mu+\phi_s+\alpha_2)(1-R_s) + D_1. \tag{6.19}$$

From (6.19), we define $K(\lambda^\star) = A_1\lambda^{\star 2} + B_1\lambda^\star + C_0$, from which:

$$\begin{aligned} C_0 = {} & (1-\sigma)\mu[\beta(\mu+\phi_s+\alpha_2+\gamma_2) + \beta_1(\mu+\phi_s+\alpha_2-\beta)] + \beta\gamma_2\phi_s(\sigma\tau + \omega_1(1-\tau-\sigma)) \\ & - \beta\rho\mu[(1-\sigma)\alpha_2 + \phi_s(1-\omega_1)] + \beta_1\sigma\phi_s(1-\omega_1)\mu. \end{aligned} \tag{6.20}$$

We use Descharte's rule of signs to investigate the positive roots of polynomial $f_1(\lambda^\star) = 0$ by regarding the following cases:

(a) Case 1: $C_0 < 0$ and $R_s > 1$. Since A_1 is always positive, i.e. $A_1 > 0$, then regardless of the sign of B_1, the polynomial $f_1(\lambda^\star) = 0$ has at most one positive root due to the fact that $C_1 < 0$ and $D_1 < 0$. That is, $f_1(\lambda^\star) = +A_1\lambda^{\star 3} \pm B_1\lambda^{\star 2} - C_1\lambda^\star - D_1 = 0$ has only one sign change and at most one positive root. Thus the system (6.12) has unique positive endemic equilibrium.

(b) Case 2: $B_1 < 0, C_0 > 0$ and $R_s > 1$. If $B_1^2 - 4A_1C_0 > 0$ then the polynomial $f_1(\lambda^\star) = 0$ has three roots when $\beta_1 > \beta_1^{\star\star}$, where by:

$$\beta_1^{\star\star} = \frac{\beta[((1-\sigma)\alpha_2 + \phi_s(1-\omega_1))\rho\mu - Y]}{\mu[(1-\sigma)(\mu+\phi_s+\alpha_2-\beta) + \sigma\phi_s(1-\omega_1)]},$$

and

$$Y = n_2 + (1-\sigma)\tau(\mu+\gamma_2)(\mu+\phi_s+\alpha_2)(1-R_s).$$

whereby,

$$n_2 = (1-\sigma)(\mu+\phi_s+\alpha_2+\gamma_2)\mu + \gamma_2\phi_s(\sigma\tau + \omega_1(1-\tau-\sigma)).$$

The condition $\beta_1 > \beta_1^{\star\star}$ structures the polynomial (6.17) to be $f_1(\lambda^\star) = +A_1\lambda^{\star 3} - B_1\lambda^{\star 2} + C_1\lambda^\star - D_1 = 0$ and as a result, this polynomial has three sign changes and at most three positive roots. Thus the system (6.12) has three endemic equilibria. In addition when $\beta_1 < \beta_1^{\star\star}$ then the polynomial (6.17) becomes $f_1(\lambda^\star) = +A_1\lambda^{\star 3} - B_1\lambda^{\star 2} - C_1\lambda^\star - D_1 = 0$. This polynomial has one sign change and at most one positive root. Thus the system (6.12) has a unique positive equilibrium.

(c) Case 3: $R_s < 1$. Regardless of whether $B_1 < 0$ and/or $C_1 < 0$ then polynomial $f_1(\lambda^\star) = 0$ has at most two positive roots. In particular if $C_1 < 0$, irrespective of sign of B_1, then $f_1(\lambda^\star) = 0$ has exactly two positive roots as $A_1 > 0$ and $D_1 > 0$. Thus the system (6.12) has two positive endemic equilibria.

With these three cases we formulate the following lemma:

Lemma 6.18. *The number of positive endemic equilibria of drug-sensitive TB only model* (6.12) *are summarized under the following conditions:*

(1). If $C_0 < 0$ with $R_s > 1$, then the system has a unique positive equilibrium.

(2). $C_0 > 0$, $B_1 < 0$ with $R_s > 1$. If $B_1^2 - 4A_1C_0 > 0$ then the system has three endemic equilibria provided that $\beta_1 > \beta_1^{\star\star}$.

(3). $C_0 > 0$, $B_1 < 0$ *with* $R_s > 1$. *If* $B_1^2 - 4A_1C_0 > 0$ *then the system has one endemic equilibrium when* $\beta_1 < \beta_1^{\star\star}$.

(4). $C_0 > 0$, $B_1 < 0$ *with* $R_s < 1$. *If* $B_1^2 - 4A_1C_0 > 0$ *then the system has two endemic equilibria.*

(5). $C_0 > 0$ *with* $R_s < 1$. *If* $B_1^2 - 4A_1C_0 > 0$, *then irrespective of the sign of* B_1 *the system has exactly two endemic equilibria provided that* $C_1 < 0$.

(6). Otherwise there is no endemic equilibria, i.e. $C_0 > 0, B_1 > 0$ *and* $R_s < 1$.

6.3.5 Stability analysis of EEP for drug-sensitive TB only model

The stability of endemic equilibrium for drug-sensitive TB only model is analyzed by using center Manifold theory (Carr, 1981) and as described in Castillo-Chávez and Song (2004). We change the variables of model (6.12) by setting $s = x_1,\ e_s = x_2,\ i_s = x_3$ and $r = x_4$ such that $\sum_{i=1}^{4} x_i = 1$. We define vector $X = (x_1, x_2, x_3, x_4)^T$ and $F = (f_1, f_2, f_3, f_4)^T$ in order to write (6.12) in the format $\frac{dX}{dt} = F$ as follows:

$$\dot{x_1} = f_1 = \mu + \alpha_2 x_3 + \frac{1}{1-\sigma}\phi_s(1-\omega_1)x_3 - (\mu + \beta x_3)x_1 \tag{6.21a}$$

$$\dot{x_2} = f_2 = -\frac{\sigma}{1-\sigma}\phi_s(1-\omega_1)x_3 + \beta((1-\rho)x_1 + \tau x_4)x_3 - (\mu + \beta_1 x_3 + \gamma_2)x_2 \tag{6.21b}$$

$$\dot{x_3} = f_3 = \gamma_2 x_2 - (\mu + \phi_s + \alpha_2 - \rho\beta x_1 - \beta_1 x_2)x_3 \tag{6.21c}$$

$$\dot{x_4} = f_4 = \phi_s\omega_1 x_3 - (\mu + \tau\beta x_3)x_4 \tag{6.21d}$$

The Jacobian (Variation) matrix of system (6.21) at disease free equilibrium, E_0^s is given by:

$$J(E_0^s) = \begin{bmatrix} -\mu & 0 & \alpha_2 + \dfrac{\phi_s(1-\omega_1)}{1-\sigma} - \beta & 0 \\ 0 & -(\mu+\gamma_2) & \dfrac{\sigma\phi_s(1-\omega_1)}{1-\sigma} + \beta(1-\rho) & 0 \\ 0 & \gamma_2 & \rho\beta - (\mu + \phi_s + \alpha_2) & 0 \\ 0 & 0 & \phi_s\omega_1 & -\mu \end{bmatrix}.$$

Let us choose our bifurcation parameter to be β and assume it takes place at $\beta = \beta^\star$ and solve it when reproduction number of drug-sensitive TB only model, $R_s = 1$. Thus,

$$R_s = \frac{\beta(\gamma_2 + \mu\rho)}{(\mu + \gamma_2)(\mu + \phi_s + \alpha_2)} = 1 \Longleftrightarrow \beta = \beta^\star = \frac{(\mu + \gamma_2)(\mu + \phi_s + \alpha_2)}{\gamma_2 + \mu\rho}. \tag{6.22}$$

The Jacobian of transformed system (6.21) has simple zero eigenvalue at $\beta = \beta^\star$. This gives us a way to study dynamics of system (6.12) by using center Manifold theory (Carr, 1981). The Jacobian of system (6.21) denoted by $J(E_0^s)$ at $\beta = \beta^\star$ has right eigenvector $\mathbf{q}$ that corresponds with zero eigenvalue. The components of vector $\mathbf{q} = (q_1, q_2, q_3, q_4)^T$ are computed by using relation $J(E_0^s) \cdot \mathbf{q} = \mathbf{0}$ and result to:

$$q_1 = \frac{1}{\mu}\left[\alpha_2 - \beta^\star + \frac{\phi_s(1-\omega_1)}{1-\sigma}\right] q_3. \tag{6.23a}$$

$$q_2 = \frac{1}{\mu + \gamma_2}\left[\beta^\star(1-\rho) + \frac{\sigma\phi_s(1-\omega_1)}{1-\sigma}\right] q_3. \tag{6.23b}$$

$$q_3 = q_3 > 0, \text{ free.} \tag{6.23c}$$

$$q_4 = \frac{\phi_s\omega_1}{\mu} q_3. \tag{6.23d}$$

It can be shown that the component q_1 of vector $\mathbf{q}$ is negative, i.e. $q_1 < 0$. On the other hand, Jacobian matrix, $J(E_0^s)$ has left eigenvector $\mathbf{v} = (v_1, v_2, v_3, v_4)^T$ at $\beta = \beta^\star$ with zero eigenvalue that satisfies the relation $v \cdot q = 1$. We proceed on computing the components of vector $\mathbf{v}$ by considering $(J(E_0^s))^T \cdot \mathbf{v} = \mathbf{0}$. The components of vector $\mathbf{v} = (v_1, v_2, v_3, v_4)^T$ are therefore given by:

$$v_1 = v_4 = 0, \; v_2 = \frac{\gamma_2}{\mu + \gamma_2} v_3, \; v_3 = v_3 > 0, \text{ free.} \tag{6.24}$$

Computation of values of a and b

The values of a and b are computed in order to govern the local dynamics of transformed system (6.21) and unveil whether the system (6.21) exhibits forward or backward bifurcation by using Theorem 4.1 of Castillo-Chávez and Song (2004) and as re-stated in Theorem 3.4 of Mlay

et al. (2014b, p. 15). Since the components of vector $\mathbf{v}$, $v_1 = v_4 = 0$, we compute values of a for values $k = 2, 3$ only at $\beta = \beta^\star$. The none zero second partial derivatives evaluated at disease free equilibrium of drug-sensitive TB only model and at $\beta = \beta^\star$ are:

$$\frac{\partial^2 f_2}{\partial x_1 \partial x_3} = \beta^\star(1-\rho);\ \frac{\partial^2 f_2}{\partial x_2 \partial x_3} = -\beta_1;\ \frac{\partial^2 f_2}{\partial x_3 \partial x_4} = \beta^\star\tau;\ \frac{\partial^2 f_3}{\partial x_1 \partial x_3} = \rho\beta^\star;\ \frac{\partial^2 f_3}{\partial x_2 \partial x_3} = \beta_1.$$

The value of a is computed by using formula,

$$a = \sum_{k,i,j=1}^{n} v_k q_i q_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0) = \beta^\star q_1 q_3(v_2(1-\rho)+v_3\rho)+\beta_1 q_2 q_3(v_3-v_2)+\beta^\star\tau v_2 q_3 q_4. \quad (6.25)$$

It can be shown from (6.25) that $v_3 - v_2$ is strictly positive as follows:

$$v_3 - v_2 = v_3 - \frac{\gamma_2}{\mu+\gamma_2}v_3 = v_3\left(1 - \frac{\gamma_2}{\mu+\gamma_2}\right) > 0, \text{ since } v_3 > 0 \text{ and } \frac{\gamma_2}{\mu+\gamma_2} < 1.$$

Consequently, we evaluate the value of b by considering only values of $k = 2, 3$, since $v_1 = v_4 = 0$. The associated non-zero second order partial derivative evaluated at $\beta = \beta^\star$ are:

$$\frac{\partial^2 f_2}{\partial x_3 \partial \beta^\star} = 1 - \rho;\ \frac{\partial^2 f_3}{\partial x_3 \partial \beta^\star} = \rho.$$

Thus, the value b is obtained by using the following formula:

$$b = \sum_{k,i=1}^{n} v_k q_i \frac{\partial^2 f_k}{\partial x_i \partial \beta}(0,0) = v_2 q_3(1-\rho) + v_3 q_3 \rho = q_3(v_2(1-\rho) + v_3\rho) > 0. \quad (6.26)$$

If we let $\xi_1 = -\beta^\star q_1 q_3(v_2(1-\rho) + v_3\rho)$ and $\xi_2 = \beta_1 q_2 q_3(v_3 - v_2) + \beta^\star\tau v_2 q_3 q_4$ it follows that $a > 0$ when $\xi_2 > \xi_1$. In addition with the information from (6.26) that $b > 0$ we formulate the following important theorem.

Theorem 6.19. *If $\xi_2 > \xi_1$, $a > 0$, then the model* (6.12) *exhibits backward bifurcation at $R_s = 1$. If $\beta < 0$, then there exists unstable positive equilibrium point and if $\beta > 0$ there exists stable negative equilibrium point. Therefore the endemic equilibrium point of drug-sensitive TB only model is locally asymptotically stable if $R_s > 1$ but close to 1.*

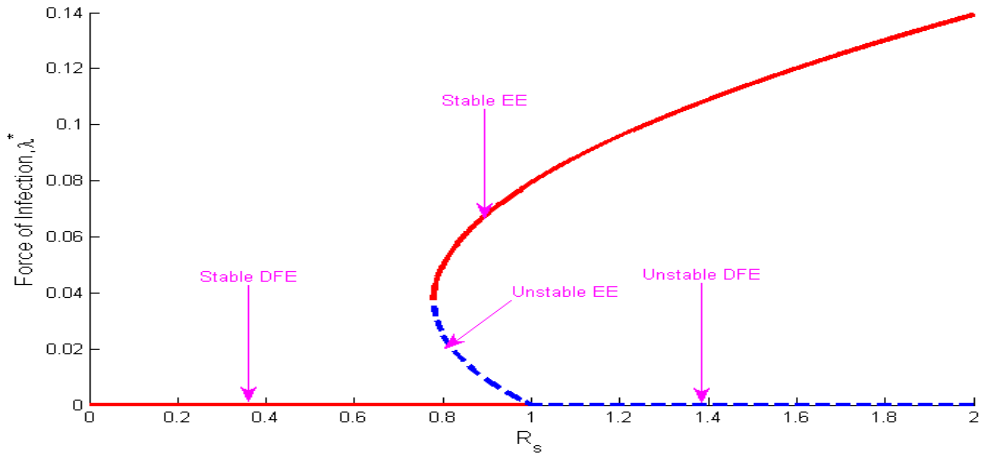


Figure 6.2: Bifurcation diagram showing the backward bifurcation for drug-sensitive TB only model. The bifurcation parameter is drug-sensitive reproduction number, R_s. The solid line indicates stability; the dotted line indicates instability.

Figure 6.2 shows the backward bifurcation for drug-sensitive TB only model (6.12) when force of infection at equilibrium, $\lambda^\star$ is plotted against the reproduction number of drug-sensitive TB, R_s. Backward bifurcation occurs at $R_s = 1$. In the neighborhood of $R_s = 1$ when $R_s < 1$ the disease free equilibrium denoted by DFE coexists with large stable endemic equilibrium, EE. That is even by increasing an effort to reduce the threshold R_s below one is no longer the sufficient condition to eradicate the drug-sensitive TB from the community.

6.3.6 Multi-drug resistant TB only endemic equilibrium

The drug-sensitive TB only model is obtained by setting $e_s = i_s = 0$ in the system (6.8). In addition,we note from (6.8b) that $\Lambda = \mu + \alpha_1 i_R$. These information give rise to the following multi-drug resistant TB only model:

$$\frac{ds}{dt} = \mu + \alpha_1 i_R - (\mu + \beta i_R)s \tag{6.27a}$$

$$\frac{de_R}{dt} = (\beta((1-\rho)s + \tau r) + \phi_r(1-\omega_2))i_R - (\mu + \beta_1 i_R + \gamma_1)e_R \tag{6.27b}$$

$$\frac{di_R}{dt} = \gamma_1 e_R - (\mu + \phi_r + \alpha_1 - \rho\beta s - \beta_1 e_R)i_R \tag{6.27c}$$

$$\frac{dr}{dt} = \phi_r \omega_2 i_R - (\mu + \tau\beta i_R)r. \tag{6.27d}$$

We solve endemic equilibrium, E_{1R} for drug-sensitive TB only model (6.27) in terms of forces of infection, $\lambda_1^\star = \beta i_R^\star$ and $\lambda_2^\star = \beta_1 i_R^\star$ at steady state in such a way that

$$\frac{\lambda_1^\star}{\lambda_2^\star} = \frac{\beta}{\beta_1} \Rightarrow \lambda_1^\star = \frac{\beta}{\beta_1}\lambda_2^\star = \lambda^\star.$$

The non-zero coordinates of endemic equilibrium, $E_{1R} = (s^\star, e_R^\star, i_R^\star, r^\star, 0, 0)$ for multi-drug resistant TB only model (6.27) in terms of force of infection, $\lambda^\star$ are given by

$$s^\star = \frac{\mu(m_4\lambda^{\star 2} + m_5\lambda^\star + m_6) + \alpha_1(\mu + \tau\lambda^\star)(m_1\lambda^{\star 2} + m_2\lambda^\star + m_3)}{(\mu + \lambda^\star)(m_4\lambda^{\star 2} + m_5\lambda^\star + m_6)}, \tag{6.28a}$$

$$e_R^\star = \frac{\lambda^\star(z_1\lambda^{\star 2} + z_2\lambda^\star + z_3)}{(\mu + \lambda^\star)(m_4\lambda^{\star 2} + m_5\lambda^\star + m_6)}, \tag{6.28b}$$

$$i_R^\star = \frac{(\mu + \tau\lambda^\star)(m_1\lambda^{\star 2} + m_2\lambda^\star + m_3)}{\beta(m_4\lambda^{\star 2} + m_5\lambda^\star + m_6)}, \tag{6.28c}$$

$$r^\star = \frac{\phi_r\omega_2(m_1\lambda^{\star 2} + m_2\lambda^\star + m_3)}{\beta(m_4\lambda^{\star 2} + m_5\lambda^\star + m_6)}. \tag{6.28d}$$

From (6.28) we define:

$$\begin{aligned}
m_1 &= \beta_1(\mu + \alpha_1 + \phi_r\omega_2),\\
m_2 &= \beta[\mu(\mu + \phi_r + \alpha_1) + \gamma_1(\mu + \alpha_1 + \phi_r\omega_2)] + \beta_1\mu(\mu + \alpha_1 + \phi_r\omega_2 - \beta),\\
m_3 &= \beta\mu[\mu(\mu + \phi_r + \alpha_1) + \gamma_1(\mu + \alpha_1 + \phi_r\omega_2) - \beta(\gamma_1 + \mu\rho)]\\
&= \beta\mu[\mu(\mu + \phi_r + \alpha_1) + \gamma_1(\mu + \alpha_1 + \phi_r\omega_2)](1 - R_r),\\
m_4 &= \beta_1\tau(\alpha_1 + \phi_r\omega_2),\\
m_5 &= \beta_1\mu(\alpha_1 + \tau\phi_r\omega_2) + \beta\tau[\gamma_1(\alpha_1 + \phi_r\omega_2) + \mu\rho\alpha_1],\\
m_6 &= \beta\mu[\gamma_1(\alpha_1 + \phi_r\omega_2) + \mu\rho\alpha_1],\\
z_1 &= \tau[\phi_r\omega_2(\mu + \phi_r + \alpha_1) + (1 - \omega_2\rho)\alpha_1\phi_r + (1 - \rho)(\mu + \alpha_1)\alpha_1],\\
z_2 &= \mu[q_1 + (\mu + \phi_r + \alpha_1)((1 - \rho)(1 + \tau)\alpha_1 + 2\tau\phi_r\omega_2) - \beta\rho\tau\phi_r\omega_2],\\
z_3 &= \mu^2[\tau\phi_r\omega_2(\mu + \phi_r + \alpha_1 - \beta\rho) + \alpha_1((1 - \rho)(\mu + \alpha_1) + \phi_r(1 - \omega_2\rho))],
\end{aligned}$$

with $q_1 = \phi_r(1-\omega_2)(1+\tau)\rho\alpha_1$. From the relation (6.28c) and make use of the fact that $\lambda^\star = \lambda_1^\star$ and $\lambda_1^\star = \beta i_R^\star$, we come up with the new relation,

$$\lambda^\star = \frac{(\mu + \tau\lambda^\star)(m_1\lambda^{\star 2} + m_2\lambda^\star + m_3)}{(m_4\lambda^{\star 2} + m_5\lambda^\star + m_6)} \tag{6.29}$$

Upon simplifying equation (6.29) we gain the cubic polynomial:

$$(\tau m_1 - m_4)\lambda^{\star 3} + (\tau m_2 - m_5 + \mu m_1)\lambda^{\star 2} + (\mu m_2 - m_6 + \tau m_3)\lambda^\star + \mu m_3 = 0 \tag{6.30}$$

Replacing the actual parameters of the model to equation (6.30) results to polynomial,

$$f(\lambda^\star) = A_2\lambda^{\star 3} + B_2\lambda^{\star 2} + C_2\lambda^\star + D_2 = 0, \tag{6.31}$$

that satisfies multiple equilibria. We define the coefficients of cubic polynomial (6.31) as follows:

$$A_2 = \beta_1\tau > 0. \tag{6.32a}$$

$$B_2 = \beta\tau(\mu + \phi_r + \gamma_1 + (1-\rho)\alpha_1) + \beta_1\tau(\mu + \alpha_1 - \beta) + \beta_1(\mu + \phi_r\omega_2). \tag{6.32b}$$

$$\begin{aligned} C_2 = {} & \mu[\beta(\mu + \phi_r + \gamma_1 + (1-\rho)\alpha_1) + \beta_1(\mu + \alpha_1 + \phi_r\omega_2 - \beta)] \\ & + \tau\beta[\mu(\mu + \phi_r + \alpha_1) + \gamma_1(\mu + \alpha_1 + \phi_r\omega_2)](1 - R_r). \end{aligned} \tag{6.32c}$$

$$D_2 = \beta\mu[\mu(\mu + \phi_r + \alpha_1) + \gamma_1(\mu + \alpha_1 + \phi_r\omega_2)](1 - R_r). \tag{6.32d}$$

We note from (6.32) that A_2 is always positive and $D_2 > 0$ if $R_r < 1$ and $D_2 < 1$ if $R_r > 1$. Before investigating the multiple equilibria of polynomial (6.31), we write it in the format:

$$f(\lambda^\star) = \lambda^\star H(\lambda^\star) + \lambda^\star\tau\beta[\mu(\mu + \phi_r + \alpha_1) + \gamma_1(\mu + \alpha_1 + \phi_r\omega_2)](1 - R_r) + D_2. \tag{6.33}$$

where by $H(\lambda^\star) = A_2\lambda^{\star 2} + B_2\lambda^\star + C_0$ and,

$$C_0 = \mu[\beta(\mu + \phi_r + \gamma_1 + (1-\rho)\alpha_1) + \beta_1(\mu + \alpha_1 + \phi_r\omega_2 - \beta)].$$

Since $A_2 > 0$ we investigate the positive roots of polynomial (6.31) depending on signs of B_2, C_2 and D_2 by using Descharte's rule of signs under the following cases:

(i). Case 1: C_0 and $R_r > 1$. Since A_2 is always positive then the polynomial (6.31) has at most one positive root regardless of the sign of B_2 due to the fact that $C_2 < 0$ and $D_2 < 0$. That is $f(\lambda^\star) = +A_2\lambda^{\star 3} \pm B_2\lambda^{\star 2} - C_2\lambda^\star - D_2 = 0$ has only one sign change. Therefore the system (6.31) has a unique positive endemic equilibrium.

(ii). Case 2: $B_2 < 0$, $C_0 > 0$ and $R_r > 1$. If $B_2^2 - 4A_2C_0 > 0$ then the polynomial (6.31) has three positive roots if $\beta_1 > \beta_1^\star$, where by,

$$\beta_1^\star = \frac{\beta(\mu\rho\alpha_1 - X)}{\mu(\mu + \alpha_1 + \phi_r\omega_2 - \beta)}. \tag{6.34}$$

and

$$X = \mu(\mu + \phi_r + \alpha_1 + \gamma_1) + \tau[\mu(\mu + \phi_r + \alpha_1) + \gamma_1(\mu + \alpha_1 + \phi_r\omega_2)](1 - R_r).$$

That is the polynomial (6.31) becomes $f(\lambda^\star) = +A_2\lambda^{\star 3} - B_2\lambda^{\star 2} + C_2\lambda^\star - D_2 = 0$. This polynomial has three sign changes that implies to have at most three positive roots and possibility of three endemic equilibria. In addition when $\beta_1 < \beta_1^\star$, the polynomial (6.31) becomes $f(\lambda^\star) = +A_2\lambda^{\star 3} - B_2\lambda^{\star 2} - C_2\lambda^\star - D_2 = 0$. This polynomial has one sign change that implies to have at most one positive root.Thus, the system (6.27) has a unique endemic equilibrium.

(iii). Case 3: When $R_r < 1$. Depending on whether $B_2 < 0$ and/or $C_2 < 0$ then the polynomial (6.27) has at most two positive roots, as $A_1 > 0$ and $D_2 > 0$. When $C_0 > 0$ and $B_2^2 - 4A_2C_0 > 0$, with $B_2 < 0$, then there are two positive roots for polynomial (6.31). This implies that the system (6.27) has two endemic equilibria. In particular, if $C_2 < 0$, irrespective of sign of B_2, the system (6.27) has exactly two endemic equilibria. These three cases lead to the following lemma.

Lemma 6.20. *The number of positive endemic equilibria of system* (6.27) *are summarized under the following conditions:*

1). $C_0 < 0$ *with* $R_r > 1$ *then the system has a unique endemic equilibrium.*

2). $B_2 < 0$ *and* $C_0 > 0$ *with* $R_r > 1$. *If* $B_2^2 - 4A_2C_0 > 0$, *then the system has three endemic equilibria when* $\beta_1 > \beta_1^\star$.

3). $B_2 < 0$ *and* $C_0 > 0$ *with* $R_r > 1$. *If* $B_2^2 - 4A_2C_0 > 0$, *then the system has one endemic equilibrium if* $\beta_1 < \beta_1^\star$.

4). $C_0 > 0$, $B_2 < 0$ *and* $R_r < 1$. *If* $B_2^2 - 4A_2C_0 > 0$, *then the system has exactly two endemic equilibria. Irrespective of sign of* B_2, *if* $C_2 < 0$ *then the system has exactly two endemic equilibria.*

5). Otherwise there are no endemic equilibria.

6.3.7 Stability analysis of EEP for multi-drug resistant TB only model

We analyze the stability of endemic equilibrium point for multi-drug resistant TB only model (6.27) by using center Manifold theory (Carr, 1981) and as described in Castillo-Chávez and Song (2004). We have to change the variables of model (6.27) by setting $s = x_1$, $e_R = x_2$, $i_R = x_3$ and $r = x_4$ in such a way that $\sum_{i=1}^{4} x_i = 1$. We define vector $X = (x_1, x_2, x_3, x_4)^T$ and $F = (f_1, f_2, f_3, f_4)^T$ in order to write model (6.27) in the form $\frac{dX}{dt} = F$ as follow:

$$\dot{x_1} = \mu + \alpha_1 x_3 - (\mu + \beta x_3)x_1 \tag{6.35a}$$

$$\dot{x_2} = (\beta((1-\rho)x_1 + \tau x_4) + \phi_r(1-\omega_2))x_3 - (\mu + \beta_1 x_3 + \gamma_1)x_2 \tag{6.35b}$$

$$\dot{x_3} = \gamma_1 x_2 - (\mu + \phi_r + \alpha_1 - \rho\beta x_1 - \beta_1 x_2)x_3 \tag{6.35c}$$

$$\dot{x_4} = \phi_r \omega_2 x_3 - (\mu + \tau\beta x_3)x_4. \tag{6.35d}$$

The Jacobian matrix of transformed system (6.35) at disease free equilibrium, E_0^r denoted by $J(E_0^r)$ is given by:

$$J(E_0^r) = \begin{bmatrix} -\mu & 0 & \alpha_1 - \beta & 0 \\ 0 & -(\mu + \gamma_1) & \beta(1-\rho) + \phi_r(1-\omega_2) & 0 \\ 0 & \gamma_1 & \rho\beta - (\mu + \phi_r + \alpha_1) & 0 \\ 0 & 0 & \phi_r\omega_2 & -\mu \end{bmatrix}. \tag{6.36}$$

In particular case let us choose bifurcation parameter to be β and assume that bifurcation takes place at $\beta = \beta^\star$ and solve it when reproduction number of multi-drug resistant TB only model, $R_r = 1$. We end up with:

$$\beta = \beta^\star = \frac{\mu(\mu + \phi_r + \alpha_1) + \gamma_1(\mu + \alpha_1 + \phi_r\omega_2)}{\gamma_1 + \mu\rho}. \tag{6.37}$$

The Jacobian of transformed system (6.35) has simple zero eigenvalue at $\beta = \beta^\star$ that gives us a way to study dynamics of the system (6.27) by using center Manifold theory (Carr, 1981). Jacobian of system (6.35) denoted by $J(E_0^r)$ at $\beta = \beta^\star$ has right eigenvector, $\mathbf{y} = (y_1, y_2, y_3, y_4)^T$ that corresponds with zero eigenvalue and is computed by using the relation $J(E_0^r) \cdot \mathbf{y} = \mathbf{0}$ and results to the following components:

$$y_1 = \frac{\alpha_1 - \beta^\star}{\mu} y_3. \tag{6.38a}$$

$$y_2 = \frac{\beta^\star(1-\rho) + \phi_r(1-\omega_2)}{\mu + \gamma_1} y_3. \tag{6.38b}$$

$$y_3 = y_3 > 0, \text{ free.} \tag{6.38c}$$

$$y_4 = \frac{\phi_r\omega_2}{\mu} y_3. \tag{6.38d}$$

It can be shown that the component y_1 is strictly negative,i.e. $y_1 < 0$. The rest components of vector $\mathbf{y}$ are strictly positive, i.e. $y_2, y_3, y_4 > 0$. Consequently the Jacobian matrix, $J(E_0^r)$ at $\beta = \beta^\star$ has left eigenvector $\psi = (\psi_1, \psi_2, \psi_3, \psi_4)^T$ associated with zero eigenvalue satisfying relation $\psi \cdot \mathbf{y} = 1$. Now we proceed computing the components of vector ψ by considering

$(J(E_0^r))^T\psi = 0$ and result to:

$$\psi_1 = \psi_4 = 0;\ \psi_2 = \psi_2 > 0,\ \text{free};\ \psi_3 = \frac{\mu+\gamma_1}{\gamma_1}\psi_2. \tag{6.39}$$

Computation of values of a and b

We compute the values of a and b which will govern the local dynamics of transformed system (6.35) and unveil whether the system (6.35) exhibits forward or backward bifurcation by using Theorem 4.1 of Castillo-Chávez and Song (2004) and as re-stated in Theorem 3.4 of Mlay et al. (2014b, p. 15). Since $\psi_1 = \psi_4 = 0$ then we compute a for only values of $k = 2, 3$. The associated non-zero second order partial derivatives at $\beta = \beta^\star$ are:

$$\frac{\partial^2 f_2}{\partial x_1 \partial x_3} = \beta^\star(1-\rho);\ \frac{\partial^2 f_2}{\partial x_2 \partial x_3} = -\beta_1;\ \frac{\partial^2 f_2}{\partial x_3 \partial x_4} = \beta^\star\tau;\ \frac{\partial^2 f_3}{\partial x_1 \partial x_3} = \rho\beta^\star;\ \frac{\partial^2 f_3}{\partial x_2 \partial x_3} = \beta_1.$$

We proceed on computing the value of a as follows:

$$a = \sum_{k,i,j=1}^{n} \psi_k y_i y_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0) = \beta^\star y_1 y_3(\psi_2(1-\rho)+\psi_3\rho) + \beta_1 y_2 y_3(\psi_3-\psi_2) + \beta^\star\tau\psi_2 y_3 y_4. \tag{6.40}$$

Consequently we evaluate b by considering only values of $k = 2, 3$ since $\psi_1 = \psi_4 = 0$. The associated non-zero second order partial derivatives evaluated at $\beta = \beta^\star$ are:

$$\frac{\partial^2 f_2}{\partial x_3 \partial \beta^\star} = 1-\rho;\ \frac{\partial^2 f_3}{\partial x_3 \partial \beta^\star} = \rho.$$

The value of b is computed as follows:

$$b = \sum_{k,i=1}^{n} \psi_k y_i \frac{\partial^2 f_k}{\partial x_i \partial \beta}(0,0) = \psi_2 y_3(1-\rho) + \psi_3 y_3 \rho = y_3(\psi_2(1-\rho)+\psi_3\rho) > 0. \tag{6.41}$$

We show from (6.40), that $\psi_3 - \psi_2$ is strictly positive as follows:

$$\psi_3 - \psi_2 = \frac{\mu+\gamma_1}{\gamma_1}\psi_2 - \psi_2 = \psi_2\left(\frac{\mu+\gamma_1}{\gamma_1} - 1\right) = \frac{\mu}{\gamma_1}\psi_2 > 0.$$

Suppose from (6.40), we denote $\Im_1 = -\beta^\star y_1 y_3(\psi_2(1-\rho)+\psi_3\rho)$ and $\Im_2 = \beta_1 y_2 y_3(\psi_3-\psi_2)+\beta^\star\tau\psi_2 y_3 y_4$. Since $y_1 < 0$ then $a > 0$ if and only if $\Im_1 < \Im_2$. We formulate the following important theorem.

Theorem 6.21. *If $\Im_1 < \Im_2$, $a > 0$, then the model* (6.27) *exhibits backward bifurcation at $R_r = 1$. If $\beta < 0$, then there exists unstable positive equilibrium point and if $\beta > 0$ there exists stable negative equilibrium point. Therefore the endemic equilibrium point of multi-drug resistant TB only model is locally asymptotically stable if $R_r > 1$ but close to 1.*

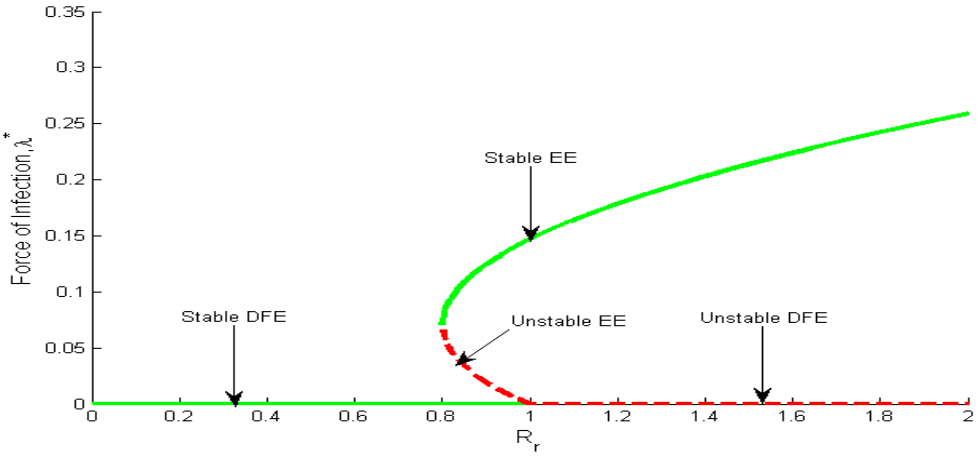


Figure 6.3: Bifurcation diagram showing the backward bifurcation for drug resistant TB only model. The bifurcation parameter is drug resistant reproduction number, R_r. The solid line indicates stability; the dotted line indicates instability.

Figure 6.3 shows the backward bifurcation for multi-drug resistant TB only model (6.27) when force of infection at equilibrium, $\lambda^\star$ is plotted against the reproduction number of multi-drug resistant TB, R_s. Backward bifurcation occurs at $R_r = 1$. In the neighborhood of $R_r = 1$ when $R_r < 1$ the disease free equilibrium denoted by DFE coexists with large stable endemic equilibrium, EE. That is even by increasing an effort to reduce the threshold R_s below one is no longer the sufficient condition to eradicate the multi-drug resistant TB from the community.

6.3.8 Coexistence Endemic Equilibrium

This is an endemic equilibrium that occurs when both drug-sensitive and multi-drug resistant strains are present and in our case we denote it as $E_3 = (s^{\star\star}, e_s^{\star\star}, i_s^{\star\star}, e_R^{\star\star}, i_R^{\star\star}, r^{\star\star})$. We are

impeded to express the coordinates of E_3 in terms of force of infection explicitly due to high volume of algebraic manipulations. We proceed with investigating the conditions for existence and stability of coexistence model (6.8). Our analysis is based on the results of drug-sensitive and multi-drug resistant TB only sub-models.

We have showed in Theorem 6.19 and Theorem 6.21 that both drug-sensitive and multi-drug resistant TB only sub-models exhibit backward bifurcation when center Manifold parameters $a > 0$, $b > 0$ with conditions $\xi_2 > \xi_1$ for drug-sensitive and $\Im_2 > \Im_1$ for multi-drug resistant TB sub-models. As a result the coexistence model (6.8) unveil the same features. Our remaining task is to derive backward bifurcation parameters of both drug-sensitive and multi-drug resistant TB model (6.8). From model (6.8) we make use of changing the variables $s = x_1$, $e_s = x_2$, $i_s = x_3$, $e_R = x_4$, $i_R = x_5$ and $r = x_6$ such that $\sum_{i=1}^{6} x_i = 1$. We denote $X = (x_1, \cdots, x_6)^T$ and $\frac{dX}{dt} = F$ where $F = (f_1, f_2, \cdots, f_6)$ are expressions to the right hand side of (6.8). We now write coexistence model (6.8) as follows:

$$\dot{x_1} = \mu + \alpha_1 x_5 + \alpha_2 x_3 - p(\mu + \alpha_1 x_5 + \alpha_2 x_3 - \Lambda) - (\mu + \beta(x_3 + x_5))x_1 \tag{6.42a}$$

$$\dot{x_2} = p\sigma(\mu + \alpha_1 x_5 + \alpha_2 x_3 - \Lambda) + \beta((1-\rho)x_1 + \tau x_6)x_3 - (\mu + \beta_2 x_5 + \beta_1 x_3 + \gamma_2)x_2 \tag{6.42b}$$

$$\dot{x_3} = \gamma_2 x_2 - (\mu + \phi_s + \alpha_2 - \rho\beta x_1 - \beta_1 x_2)x_3 \tag{6.42c}$$

$$\dot{x_4} = p(1-\sigma)(\mu + \alpha_1 x_5 + \alpha_2 x_3 - \Lambda) + (\beta((1-\rho)x_1 + \tau x_6) + \phi_r(1-\omega_2))x_5 + \phi_s(1-\omega_1)x_3 - (\mu + \beta_1 x_5 + \gamma_1)x_4 \tag{6.42d}$$

$$\dot{x_5} = \gamma_1 x_4 - (\mu + \phi_r + \alpha_1 - \rho\beta x_1 - \beta_1 x_4 - \beta_2 x_2)x_5 \tag{6.42e}$$

$$\dot{x_6} = \phi_r \omega_2 x_5 + \phi_s \omega_1 x_3 - (\mu + \tau\beta(x_5 + x_3))x_6 \tag{6.42f}$$

The Jacobian (variation) matrix at E_0^{rs}, i.e. $J(E_0^{rs})$ is given by:

$$J(E_0^{rs}) = \begin{bmatrix} -\mu & 0 & a_{13} & 0 & a_{15} & 0 \\ 0 & -(\mu+\gamma_2) & a_{23} & 0 & p\sigma\alpha_1 & 0 \\ 0 & \gamma_2 & a_{33} & 0 & 0 & 0 \\ 0 & 0 & a_{43} & -(\mu+\gamma_1) & a_{45} & 0 \\ 0 & 0 & 0 & \gamma_1 & a_{55} & 0 \\ 0 & 0 & \phi_s\omega_1 & 0 & \phi_r\omega_2 & -\mu \end{bmatrix}. \tag{6.43}$$

From (6.43) we further define:

$$\begin{aligned} &a_{13} = \alpha_2 - p\alpha_2 - \beta,\ a_{15} = \alpha_1 - p\alpha_1 - \beta,\ a_{23} = p\sigma\alpha_2 + \beta(1-\rho), \\ &a_{33} = \rho\beta - (\mu + \phi_s + \alpha_2),\ a_{43} = p(1-\sigma)\alpha_2 + \phi_s(1-\omega_1), \\ &a_{45} = p(1-\sigma)\alpha_1 + \beta(1-\rho) + \phi_r(1-\omega_2),\ a_{55} = \rho\beta - (\mu + \phi_r + \alpha_1). \end{aligned}$$

At disease free equilibrium point, E_0^{rs} then the proportional of exposed immigrant, $p = 0$. The variation matrix becomes:

$$J(E_0^{rs}) = \begin{bmatrix} -\mu & 0 & \alpha_2 - \beta & 0 & \alpha_1 - \beta & 0 \\ 0 & -(\mu+\gamma_2) & \beta(1-\rho) & 0 & 0 & 0 \\ 0 & \gamma_2 & a_{33} & 0 & 0 & 0 \\ 0 & 0 & \phi_s(1-\omega_1) & -(\mu+\gamma_1) & a_{45} & 0 \\ 0 & 0 & 0 & \gamma_1 & a_{55} & 0 \\ 0 & 0 & \phi_s\omega_1 & 0 & \phi_r\omega_2 & -\mu \end{bmatrix}. \tag{6.44}$$

From (6.44) we define:

$$a_{33} = \rho\beta - (\mu + \phi_s + \alpha_2),\ a_{45} = \beta(1-\rho) + \phi_r(1-\omega_2),\ a_{55} = \rho\beta - (\mu + \phi_r + \alpha_1).$$

The eigenvalues of Jacobian matrix $J(E_0^{rs})$ can be expressed in terms of effective reproduction number, $R_e = \max\{R_s, R_r\}$, from which R_s is a reproduction number of drug-sensitive and R_r

is a reproduction number of multi-drug resistant strains respectively as shown in Section 6.3.2 and equation (6.9). Regardless of whether $R_s > R_r$ or $R_s < R_r$, if $R_s > 1$ and $R_r > 1$ then coexistence of both drug-sensitive and multi-drug resistant strains are manifested and cause the endemic status. We also compel that if $R_e = \max\{R_s, R_r\}$ then the drug-sensitive TB only model unveil backward bifurcation in a range $R_s^c < R_s < 1$ and multi-drug resistant TB only model exhibits backward bifurcation in a range $R_r^c < R_r < 1$. This implies that the coexistence model exhibits bistability at $R_e = 1$. We therefore formulate the following important theorem.

Theorem 6.22. *The endemic equilibrium point, E_3 for coexistence TB model* (6.8) *is locally asymptotically stable if $R_e > 1$ and unstable otherwise.*

6.4 Numerical Simulations

In this section we carry out numerical simulation of normalized model (6.8) to verify qualitative results by using available parameter values from existing literature as well as estimated ones. Unless otherwise stated parameter values in Table 6.3 will be used during the simulation process.

6.4.1 Numerical Simulation of model (6.12) when $R_s > 1$

In this subsection we investigate the dynamical behaviors of susceptible, infected and recovered population proportion with drug-sensitive TB in presence of intervention and disease. From Figure 6.4 susceptible population proportion decreases to the lowest level and increases to its maximum level and as a result decreases a bit again and attains endemic equilibrium as time increases. On the other hand exposed and recovered population proportion increases in the short period of time and again decreases a bit to attain the endemic equilibrium point as time increases. However, the infectious population proportion with drug-sensitive TB diminish to its lowest level but not zero. This is because the reproduction number of drug-sensitive TB only model in presence of intervention and attack is $R_s = 1.3982 > 1$. This means that the drug-sensitive TB does not clear from the community. This supports the theorem of stability of

Table 6.3: Parameter values for model (6.6)

Parameter	Value (yr^{-1})	Source
Λ	0.03725	Nyerere et al. (2014).
Π	0.06	Estimated.
p	0.04	Estimated.
σ	0.02	Estimated.
ρ	0.2	Blower et al. (1995).
β	1.2	Estimated.
β_1	1.5	Estimated.
β_2	1.7	Estimated.
γ_1	0.05	Cohen et al. (2007).
γ_2	0.03	Cohen et al. (2007).
ω_1	0.8	Dye and Williams (2000); Kajunguri (2009).
ϕ_s	0.3	Maliyoni et al. (2012).
ω_2	0.47	Dye and Williams (2000); Kajunguri (2009).
ϕ_r	0.09	Maliyoni et al. (2012).
τ	0.02	Hattaf et al. (2009)
α_1	0.5	Maliyoni et al. (2012).
α_2	0.3	Maliyoni et al. (2012).
μ	0.01632	NBS (2013)

local endemic equilibrium. The endemic equilibrium point of drug-sensitive TB only model is given by $E_{1s} = (s^\star, e_s^\star, i_s^\star, r^\star) = (0.6296, 0.1348, 0.0154, 0.2202)$.

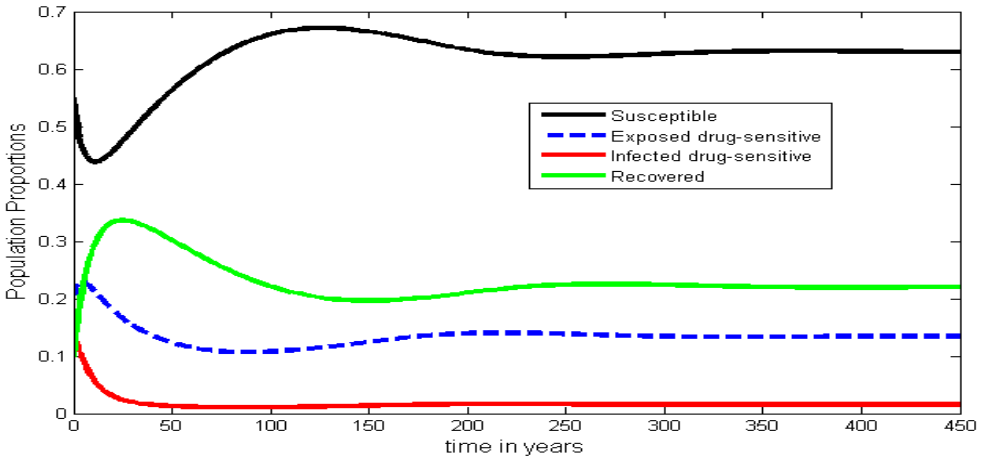


Figure 6.4: Shows dynamics of drug-sensitive TB in presence of intervention and attack with increasing time.

6.4.2 Phase plane portraits of drug-sensitive TB model at EEP

In this subsection we plot phase plane portraits to illustrate the dynamics of model (6.12) at endemic equilibrium point, E_{1s} for drug-sensitive TB only model. The plots for susceptible class versus exposed drug-sensitive, infectious drug-sensitive and recovered classes are produced by using $\beta = 0.35$ and rest of parameter values in Table 6.3. By using different varying initial conditions, each solution curve in Figure 6.5 tends to endemic equilibrium point, E_{1s} discussed in Subsection 6.3.4 and Subsection 6.4.1. We therefore conclude that model (6.12) is globally stable about endemic equilibrium point, E_{1s} for parameter indicated in Table 6.3.

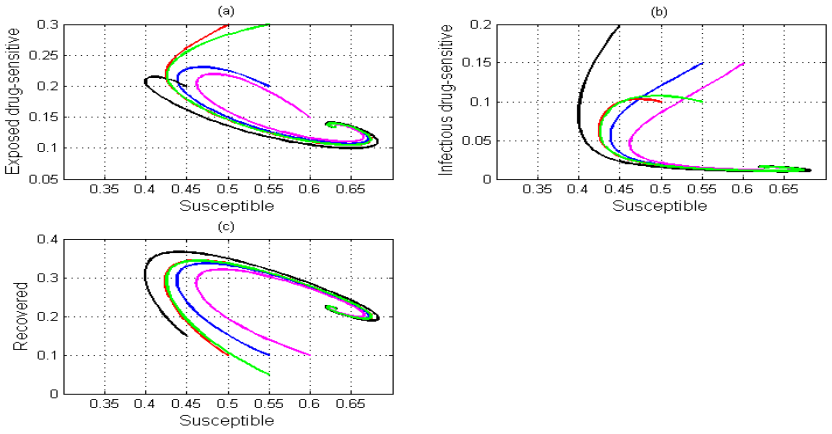


Figure 6.5: Phase plane portrait for dynamics of susceptible population proportion versus (a) exposed drug-sensitive (b) infectious drug-sensitive (c) recovered population proportions showing endemic equilibrium, E_{1s} with varying initial values as time increases.

6.4.3 Numerical Simulation of model (6.27) when $R_r > 1$

In this subsection we investigate the behavior of susceptible, exposed population proportion with multi-drug resistant TB, infectious population proportion with multi-drug resistant TB and recovered population proportion with multi-drug resistant TB. The time series plot is produced by using the parameter values indicated in Table 6.3. As expected in presence of attack susceptible population proportion decreases to its lowest level and increases a bit to attain the endemic equilibrium as time increases as shown in Figure 6.6. On the other hand, exposed population proportion with multi-drug resistant TB increases within a short period of

time and then decreases to attain endemic equilibrium point. In addition, recovered population increases in short period of time and stabilizes as time increases. The only important point to note is that infectious population proportion with multi-drug resistant TB gradually diminish but does not approach zero. This is because the reproduction number of multi-drug resistant TB only model in presence of attack is given by $R_r = 1.6898 > 1$. This supports our theorem of stability of endemic equilibrium of multi-drug resistant TB only model given by $E_{1R} = (s^\star, e_R^\star, i_R^\star, r^\star) = (0.5002, 0.2300, 0.0814, 0.1884)$.

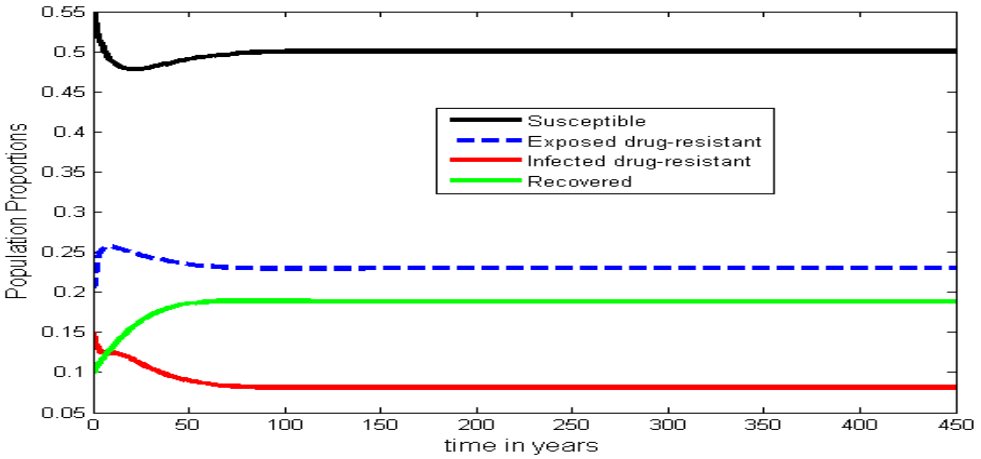


Figure 6.6: Shows dynamics of multi-drug resistant TB in presence of intervention and attack with increasing time.

6.4.4 Phase plane portraits of multi-drug resistant TB model at EEP

In this subsection we plot phase plane portraits to illustrate the dynamics of model (6.27) at endemic equilibrium point, E_{1R} for multi-drug resistant TB only model. The plots for susceptible class versus exposed multi-drug resistant, infectious multi-drug resistant and recovered classes are produced by using $\beta = 0.35$ and rest of parameter values in Table 6.3. By using different varying initial conditions, each solution curve in Figure 6.7 tends to endemic equilibrium point, E_{1R} discussed in Subsection 6.3.6 and Subsection 6.4.3. We therefore conclude that model (6.27) is globally stable about endemic equilibrium point, E_{1R} for parameter indicated in Table 6.3.

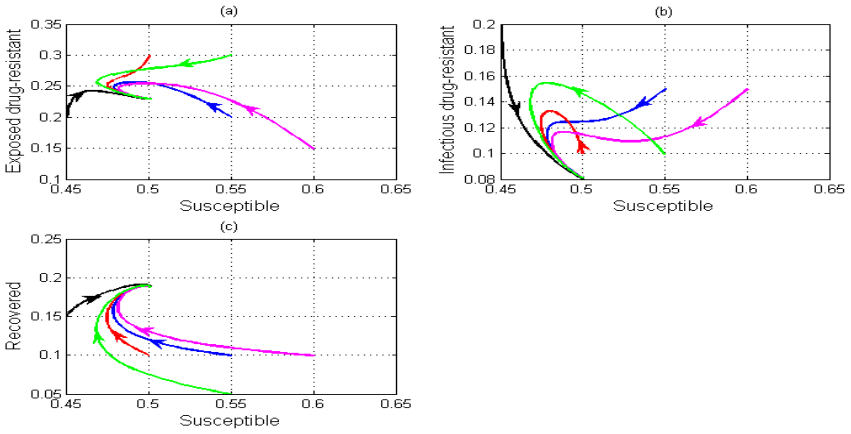


Figure 6.7: Phase plane portrait for dynamics of susceptible population proportion versus (a) exposed multi-drug resistant (b) infectious multi-drug resistant (c) recovered population proportions showing endemic equilibrium, E_{1R} with varying initial values as time increases.

6.5 Conclusion

In this chapter, a continuous deterministic two-strain TB model with treatment in presence of exposed and healthy immigrants has been formulated and the role of treatment as control strategy on transmission dynamics of multi-drug resistant TB is critically assessed. The local stability analysis of endemic equilibria of both drug-sensitive and multi-drug resistant TB sub-models was conducted by using center Manifold theory (Carr, 1981; Castillo-Chávez and Song, 2004). In presence of exogenous reinfection and multiple equilibria the backward bifurcation occurs at drug-sensitive reproduction number, $R_s = 1$ for drug-sensitive sub-model and at multi-drug resistant reproduction number, $R_r = 1$. This indicates that the coexistence model of both strains unveils backward bifurcation at effective reproduction number, $R_e = 1$. In this scenario disease free equilibrium for coexistence model coexist with larger stable endemic equilibrium in the neighborhood of 1 when $R_e < 1$. This shows that even by classically reducing the threshold R_e below one is no longer the sufficient condition to clear multi-drug TB from community. In order to eliminate multi-drug resistant TB we suggest the possibility of using additional control mechanisms in line with treatment control strategy.

CHAPTER SEVEN

General Discussion, Conclusion and Recommendations

7.1 General Discussion

This study aimed at modelling the impacts of vaccination and treatment in the transmission dynamics of one-strain tuberculosis as well as assessing the impact of exposed immigrants on the prevalence and incidence of multi-drug resistant TB (MDR-TB). The general objective of the study was to develop one and two strain tuberculosis models for deriving optimal control policy of tuberculosis in Tanzania.

To achieve the general objective we proposed five specific objectives: to analyze and assess the impact of vaccination and treatment on transmission dynamics of tuberculosis infections; to assess the impacts of reinfection on transmission dynamics of tuberculosis disease; to determine and derive the best control strategies to eradicate TB disease in one-strain tuberculosis model; to assess the impacts of exposed immigrants on prevalence and incidence of MDR-TB; and to carry out local stability analysis of endemic equilibria of MDR-TB model in presence of healthy and exposed immigrants.

The models developed are deterministic with systems of non-linear ordinary differential equations. Several assumptions have been made to make the models biologically realistic. Runge-kutta forward and backward fourth order iterative methods have been used to solve the systems and simulations were carried out by MATLAB with inbuilt tool ODE 45.

To develop the optimal control policy to eradicate TB, the optimal control theory has been used to evaluate different control strategies such as education campaign and chemoprophylaxis of latently infected individuals with TB.

Finally, disease measures, “prevalence” and “incidence” have been used to show the impact the exposed immigrants have in transmission dynamics of MDR-TB.

7.2 Conclusion

The deterministic one-strain tuberculosis model with vaccination and treatment as control strategies together with MDR-TB model with treatment as control strategy in presence of healthy and exposed immigrants are developed and analyzed. To assess the impact of vaccination and treatment on dynamics of one-strain pulmonary tuberculosis model we computed and perform numerical sensitivity analysis of effective reproduction number, R_e. We found that the parameters involving vaccination of newborns and treatment of active TB cases have high impact on R_e and combination of both vaccination and treatment has desirable effect of cutting down TB infections than when one strategy is taken at a time.

To assess the role of reinfection in modelling dynamics of one-strain tuberculosis, the conditions for existence of endemic equilibrium point are obtained in terms of force of infection, $f^\star = \beta(i_1 + i_2)$, where β is a transmission rate, i_1 and i_2 are severe and mild infectious classes. The involvement of reinfection to the model causes relapse and leads to the possibility of backward bifurcation at critical value of effective reproduction number, $R_e = 1$ and hence existence of multiple equilibria when $R_e < 1$. This indicates that even by classically reducing R_e below one is no longer the sufficient condition to eradicate TB from community. An additional reduction of R_e below the saddle-node bifurcation is required for eradication of TB provided that DFE is globally asymptotically stable. In addition DFE and EE were analyzed by using Metzeler matrix and Lyapunov direct method respectively.

The optimal control theory is used to evaluate the impact of control measures of tuberculosis model with vaccination and treatment. These control measures are education campaign and chemoprophylaxis of latently infected individuals with TB. The results show that, education campaign is more effective in curbing TB transmissions and infections than chemoprophylaxis of latently infected individuals with TB and the combination of the two strategies provides enviable effect of reducing TB infections than when one strategy is used at a time. We claimed that the emphasis of education campaign should be of a focal point and chemoprophylaxis of latently infected individuals with TB has to be paired with treatment of active TB cases.

To assess the impact of exposed immigrants on prevalence and incidence of MDR-TB, the

deterministic two strain tuberculosis model with treatment in presence of healthy and exposed immigrants was formulated. The results show that the presence of exposed immigrants increase disease prevalence and hence disease burden. In addition, the increase in treatment rates of separate and combined strains of TB have desirable effect of reducing disease prevalence as a result of alleviating TB infections. We suggested the more efforts of observing immigration rules of screening people before coming in the country, buying TB drugs, early detection and treatment of active TB cases, public education campaigns on the ways of curbing TB are needed to be addressed in order to eradicate TB from the community.

Finally, backward bifurcation theory and local stability analysis of endemic equilibria of two-strain TB model have been carried out by using the center Manifold theory (Carr, 1981). The results show that, the presence of exogenous reinfection to both drug-sensitive and drug-resistance strains leads to the possibility of backward bifurcation for coexistence model at effective reproduction number, $R_e = 1$ and existence of multiple equilibria when $R_e < 1$. Thus, in the neighborhood of one when $R_e < 1$, disease free equilibrium coexist with large stable endemic equilibrium. It indicates that even by classically reducing R_e below one is no longer sufficient condition to eradicate MDR-TB from the community. We suggested additional controls mechanisms in line with treatment control strategy in order to eliminate MDR-TB from community.

Generally mathematical models of TB used in this study are just illustrative and any analysis made was based on assumptions made to build the models. However, the analysis presented in this work will act as a base towards the more complex analysis of dynamics of TB and MDR-TB.

7.3 Recommendations

We make the following recommendations based on the results of our study as follows:

1. To increase awareness of people about transmission dynamics of TB through media coverage, information campaigns using leaflets, meetings and educational seminars that will enhance people's understanding of TB epidemics.

2. Our study presents the impact of exposed immigrants on prevalence and incidence of MDR-TB. Therefore the government of Tanzania has to enforce immigration laws of screening people before coming to the country.

3. To promote TB control programmes such as DOTS and extended them to homes where people reside.

4. To forge out national and international collaborations in running disease control programmes.

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The references (bibliography) information are stored in the file named ”Bibliography.bib”

APPENDICES

Appendix A:The clinical signs of tuberculosis

Figure 7.1: A patient suffering from tuberculosis.
Source: http://www.reuters.com/news/picture/let-sunshine-in-to-fight-tuberculosis-wh?articleId=USTRE52N3XB20090324&slideId=9400028

Appendix B: MATLAB codes for Figures of Chapter one

```
\begin{center}
%\textbf{MATLAB codes for Figure \ref{figure:2}}
\end{center}
\begin{center}
%\textbf{Fig. \ref{figure:2}}
\end{center}
 NU=linspace(1.05,3,100);
RHO=linspace(0.2,0.5,100);
[nu rho]=meshgrid(NU,RHO);
 Re=(beta.*(theta+lambda*(1-rho)).*((1-eta)*...
 (lambda+omega+delta2).*epsilon+...
 ((1-phi).*omega+lambda+delta1+nu).*...
 eta*epsilon))./((lambda+theta).*(lambda+epsilon).*...
 (lambda+omega+delta2).*(lambda+delta1+nu))
figure
surf(nu,rho,Re)
xlabel('\nu');
ylabel('\rho');
zlabel('Effective Reproduction number,R_e');

\begin{center}
\textbf{Fig. \ref{figure:3}}
\end{center}
%function or system file
function f=systems(t,y,rho,lambda,theta,beta,...
delta1,delta2,gamma,epsilon,eta,phi,omega,nu)
s=y(1); v=y(2); l=y(3); i1=y(4); i2=y(5); h=y(6);
```

```
ds=(1-rho)*lambda+theta*v-(lambda+beta*(i1+i2)-...
delta1*i1-delta2*i2)*s;
dv=rho*lambda-(lambda+theta-delta1*i1-
delta2*i2)*v;
dl=beta*s*(i1+i2)+gamma*beta*h*(i1+i2)
-(lambda+epsilon-delta1*i1-delta2*i2)*l;
di1=(1-eta)*epsilon*l+(1-phi)*omega*i2
-(lambda+delta1+nu-delta1*i1-delta2*i2)*i1;
di2=eta*epsilon*l-
(lambda+omega+delta2-delta1*i1-delta2*i2)*i2;
dh=nu*i1+phi*omega*i2-
(lambda+gamma*beta*(i1+i2)-delta1*i1-...
delta2*i2)*h;
f=[ds;dv;dl;di1;di2;dh];
%main file to run on
clear all
close all
clc
c=['k  ';'b--';'r  ';'g  ';'m  ';'k-.'];
%Parameter choosen to reveal DFE
rho=0.3; lambda=0.16; theta=0.067; beta=0.88;
 delta1=0.365;
delta2=0.3;gamma=0.4; epsilon=0.00396;
eta=0.4; phi=0.5;
omega=0.6; nu=0.6;
y0=[0.55 0.15 0.1 0.1 0.05 0.05];
tspan=[0 200];
[t y]=ode45(@systems,tspan,y0,[],rho,lambda,theta,...
beta,delta1,delta2,gamma,epsilon,eta,phi,omega,nu);
```

```
for i=1:6
 plot(t,y(:,i),c(i,:),'Linewidth',3)
 hold on
 end
 xlabel('time in years','FontSize',12)
 ylabel('Population Proportions','FontSize',12)
 legend('Susceptible','Vaccinated','Latently infected',
 'Severely infected','mildly infected','treated')

\begin{center}
\textbf{MATLAB  codes for Figure \ref{figure:4}}
\end{center}
\begin{center}
\textbf{Fig. \ref{figure:4}}
\end{center}

clear all
%close all
clc
c=['k  ';'b--';'r  ';'g  ';'m  ';'k-.'];
%Parameter choosen to reveal DFE
rho=0.3; lambda=0.16; theta=0.067; beta=0.88;
delta1=0.365;
 delta2=0.3;
gamma=0.4; epsilon=0.00396; eta=0.4; phi=0.5;
 omega=0.6;
 nu=0.6;
%  y0=[0.40 0.2 0.15 0.15 0.05 0.05];
% y0=[0.50 0.15 0.15 0.1 0.05 0.05];
% y0=[0.60 0.05 0.1 0.1 0.1 0.05];
```

```
% y0=[0.45 0.15 0.15 0.15 0.05 0.05];
y0=[0.55 0.15 0.1 0.1 0.05 0.05];
tspan=[0 200];
[t y]=ode45(@systems,tspan,y0,[],rho,
lambda,theta,
beta,delta1,delta2,gamma,epsilon,eta,
phi,omega,nu);
hold on
subplot(2,3,1)
plot(y(:,1),y(:,2))
xlabel('Susceptible','FontSize',12)
ylabel('Vaccinated Proportion','FontSize',12)
title('A')
grid on
hold on
subplot(2,3,2)
plot(y(:,1),y(:,3))
xlabel('Susceptible','FontSize',12)
ylabel('Latently Infected Proportion','FontSize',12)
title('B')
grid on
hold on
subplot(2,3,3)
plot(y(:,1),y(:,4))
xlabel('Susceptible','FontSize',12)
ylabel('Severely Infected Proportion','FontSize',12)
title('C')
grid on
hold on
```

```
subplot(2,3,4)
plot(y(:,1),y(:,5))
xlabel('Susceptiible','FontSize',12)
ylabel('Mildly Infected Proportion','FontSize',12)
title('D')
grid on
hold on
subplot(2,3,5)
plot(y(:,1),y(:,6))
xlabel('Susceptible','FontSize',12)
ylabel('Treated Proportion','FontSize',12)
title('E')
grid on
```

Appendix C: MATLAB codes for Figures of Chapter Three

```
\begin{center}
\textbf{MATLAB codes for backward bifurcation
in Figure \ref{fig:2}}
\end{center}
\begin{center}
\textbf{Fig. \ref{fig:2}}
\end{center}
Bifurcation diagram codes % Saved as joto.m file
Re_value=0:0.0001:2;
Root_array=zeros(length(Re_value),2);
%Parameter values used
phi=0.1; lambda=0.9; gamma=1.8; beta=14;
 delta1=0.3; delta2=0.2;
```

```
epsilon=0.396; eta=0.1; omega=0.6;
mu=0.01923; nu=0.9; theta=0.8;
rho=0.1;
hold on
for i=1:1:length(Re_value); Re=Re_value(i);
k=lambda-delta1*iii1-delta2*iii2;
a1=lambda*(theta+k*(1-rho));
a2=gamma*(theta+k); a3=(theta+k)*(epsilon+k);
 a4=(omega+delta2+k);
a5=eta*epsilon; b1=a3*a4; b2=(1-eta)*epsilon;
 b3=(1-phi)*omega;
b4=delta1+nu+k; c1=b1*b2; c2=b3*a5;
c3=b1*b4;d4=c1+c2*a3;
d5=a3*c3; d6=phi*omega; e1=nu*d4*b1+a5*d5*d6;
 e2=b1*d5;
e3=e1*a1; e4=e2*gamma-e1*a2;e5=e2*k;
N=(theta+k)*(epsilon+k)*(omega+delta2+k)*...
(delta1+nu+k);
P=(1-eta)*(omega+delta2+k)*epsilon+(1-phi)...
*omega*eta*epsilon;
Q=phi*omega*eta*epsilon*(delta1+nu+k);
A1=gamma*(N-((nu*P+Q)*(theta+k)));
B1=(k*(N+gamma*(N-(nu*P+Q)*(theta+k)))-...
beta*a1*gamma*(P+(delta1+nu+k)*eta*epsilon));
n=delta1*iii1+delta2*iii2; D=1-(n/lambda);
E=1-(n/(omega+delta2+lambda));
F=1-(n/(delta1+nu+lambda)); G=1-(n/(theta+lambda));
H=1-(n/(epsilon+lambda));
r1=(theta+k)*(epsilon+k)*...
```

```
(omega+delta2+k)*(delta1+nu+k)*k^2;
C1=r1*(1-(Re/(D*E*F*G*H))*...
(1+(lambda*(1-rho)*(D-1))/(theta+...
lambda*(1-rho))*(E+((1-phi)*...
omega*(1-E)+(delta1+nu+lambda)*...
(F-E)*eta*epsilon)/((1-eta)*...
(omega+delta2+lambda)*epsilon)+...
((1-phi)*omega+(delta1+nu+lambda)*eta*epsilon))));
 p=[A1,B1,C1];
r =roots(p); len=length(r);
for t=1:1:len
if (imag(r(t))~=0) || (real(r(t))<0); Root_array(i,t)=0;
else
 Root_array(i,t)=r(t);
end
end
end
f=1;
%while (Root_array(f,1)==0 && Root_array(f,1)==0...
 && Root_array(f,2)==0),
f=f+1; %end
Re_value_Cr=f;
for j=Re_value_Cr:1:length(Re_value)
Root_array(j,:)=sort(Root_array(j,:));
end
f1=Re_value_Cr;
while (Root_array(f1,1)~=0)
 f1=f1+1;
end
```

```
Re_value_Cr2=f1;
Zero_1st=Re_value(1,1:Re_value_Cr2-2);
y_zero=zeros(1,length(Zero_1st));
Unstable=Re_value(1,Re_value_Cr:length(Re_value));
%figure(1)
 plot(Unstable,Root_array(Re_value_Cr:length(Re_value),2),...
 'm','LineWidth',3)
 ylabel('Force of infection','FontSize',12)
 xlabel('Effective reproduction number, R_e','FontSize',12)
 hold off
%figure (2)
plot(Re_value,Root_array(:,1),'b--',Re_value,Root_array(:,2),...
'm','LineWidth',3)
xlabel('Effective reproduction number, R_e','FontSize',12)
ylabel('Force of infection','FontSize',12)
%ylim([0 1.5])

\begin{center}
\textbf{MATLAB  codes for  Figure \ref{fig:3}}
\end{center}
\begin{center}
\textbf{Fig. \ref{fig:3}}
\end{center}
clear all %close all; clc
c=['k  ';'b--';'r  ';'g  ';'m  ';'k-.'];
%Parameters of our choice for Endemic
Equilibrium point (EEP)
phi=0.6; gamma=0.2; rho=0.4; lambda=0.05;
 theta=0.1; beta=2.58;
delta1=0.3; epsilon=0.03; eta=0.7; nu=0.3;
```

```
 omega=0.2;
mu=0.01923; delta2=0.2;
y0=[0.60 0.05 0.1 0.1 0.1 0.05];
tspan=[0 200];
[t y]=ode45(@systems,tspan,y0,[],rho,
lambda,theta,beta,delta1,delta2,...
gamma,epsilon,eta,phi,omega,nu);
 for i=6:6
 plot(t,y(:,i),c(i,:),'Linewidth',3)
  hold on
 end
 xlabel('time in years','FontSize',12)
 ylabel('Population Proportions','FontSize',12)
 legend('Susceptible','Vaccinated',...
 'Latently infected',...
 'Severely infected','mildly infected','treated')

\begin{center}
\textbf{MATLAB  codes for  Figure \ref{fig:4}}
\end{center}
\begin{center}
\textbf{Fig. \ref{fig:4}}
\end{center}
%Using information above and the following codes
hold on
subplot(2,3,1)
plot(y(:,1),y(:,2))
xlabel('Susceptible','FontSize',12)
ylabel('Vaccinated Proportion','FontSize',12)
title('A')
```

```
grid on
hold on
subplot(2,3,2)
plot(y(:,1),y(:,3))
xlabel('Susceptible','FontSize',12)
ylabel('Latently Infected Proportion','FontSize',12)
title('B')
grid on
hold on
subplot(2,3,3)
plot(y(:,1),y(:,4))
xlabel('Susceptible','FontSize',12)
ylabel('Severely Infected Proportion','FontSize',12)
title('C')
grid on
hold on
subplot(2,3,4)
plot(y(:,1),y(:,5))
xlabel('Susceptiible','FontSize',12)
ylabel('Mildly Infected Proportion','FontSize',12)
title('D')
grid on
hold on
subplot(2,3,5)
plot(y(:,1),y(:,6))
xlabel('Susceptible','FontSize',12)
ylabel('Treated Proportion','FontSize',12)
title('E')
grid on
```

Appendix D: MATLAB codes of Figures in Chapter Four

```
\begin{center}
\textbf{MATLAB codes  for Figures \ref{controlu1},
\ref{controlu1} and \ref{controlu1andu2}}
\end{center}
\begin{center}
\textbf{Function File that solves state system}
\end{center}
function ydot = kims2(t,yy,U,Constant)
%this function solves state system with
six differential equations
%  by Mlay, 2014
S=yy(1); % suceptible population
V=yy(2); %vaccinated population
L=yy(3);  % latently infected population
I1=yy(4); %severely infected population
I2=yy(5); % mildly infected population
T_r=yy(6); %Treated population
lambda = Constant(1);beta = Constant(2);
 rho = Constant(3);
theta = Constant(4); epsilon = Constant(5);
 eta = Constant(6);
mu = Constant(7); delta1= Constant(8);
delta2 = Constant(9);phi= Constant(10);
omega = Constant(11); nu= Constant(12);
gamma= Constant(13);
g=S+V+L+I1+I2+T_r;
u1 = U(1); u2=U(2);
```

```
ydot1=(1-rho)*lambda*g-(1-u1)*beta*S*...
((I1+I2)/g)-mu*S+theta*V;
ydot2=(1+u1)*rho*lambda*g-(mu+theta)*V;
ydot3=(1-u1)*beta*((I1+I2)/g)*(S+gamma*T_r)-...
((1-u2)*epsilon+mu)*L;
ydot4=(1-u2)*(1-eta)*epsilon*L+(1-u1)*(1-phi)*...
omega*I2-(mu+delta1+...
(1+u1)*nu)*I1;
ydot5=(1-u2)*eta*epsilon*L-((1-(1-2*phi)*u1)...
*omega+mu+delta2)*I2;
ydot6=(1+u1)*(nu*I1+phi*omega*I2)-(1-u1)*gamma*beta*T_r*...
((I1+I2)/g)-mu*T_r;
ydot  = [ydot1; ydot2; ydot3; ydot4; ydot5; ydot6];

\begin{center}
\textbf{Function File that solves adjoint system}
\end{center}
function ydot = kims2_costate(t,y,U,X,Constant);
%this function solves adjoint system with six equations
%   by Mlay, 2014
 L1=y(1); L2=y(2); L3=y(3); L4=y(4); L5=y(5); L6=y(6);
lambda= Constant(1); beta= Constant(2); rho=Constant(3);
theta= Constant(4); epsilon = Constant(5); eta = Constant(6);
mu = Constant(7); delta1= Constant(8); delta2 = Constant(9);
phi = Constant(10); omega= Constant(11); n= Constant(12);
gamma= Constant(13);
A1=Constant(14); A2= Constant(15); A3= Constant(16);
B1= Constant(17); B2= Constant(18);
%list your suitable parameters
u1 = U(1); u2=U(2);
```

```
S=X(1,:);V = X(2,:);L = X(3,:);I1=X(4,:);
 I2=X(5,:); T_r=X(6,:);
g=S+V+L+I1+I2+T_r;
ydot1=(L1-L3)*(1-u1)*beta*((I1+I2)/g)+mu*L1;
ydot2=mu*L2+theta*(L2-L1);
ydot3=-A1+mu*L3+(1-u2)*(L3-L4+eta*...
(L4-L5))*epsilon;ydot4=-A2+...
L4*(mu+delta1)+(1-u1)*(beta/g*(S*(L1-L3)+...
gamma*T_r*(L6-L3)))+(L4-L6)*(1+u1)*nu;
ydot5=-A3+L5*(2*phi*omega*u1+mu+delta2)-L6*...
(1+u1)*phi*omega+(1-u1)*(beta/g*(S*(L1-L3)+...
gamma*T_r*(L6-L3))+(L5-L4*(1-phi)*omega));
ydot6=(L6-L3)*(1-u1)*gamma*beta*...
((I1+I2)/g)+mu*L6;
ydot=[ydot1; ydot2; ydot3;
 ydot4; ydot5; ydot6];

\begin{center}
\textbf{The main file that calls state and adjoint systems}
\end{center}
clc
clear all
close all
t0 = 0; tf=10; N=500;
time =linspace(t0,tf,N);
% y0  = [72 6 12 12 12 6]; %the estimated initial condition for
% STATE SYSTEM
y0=[144 12 24 24 24 12];
Constant = [0.05 2.58 0.4 0.1 0.03 0.7 0.01923 ...
0.3 0.2 0.6 0.2 0.3 0.2 0.1 1000 1000 1000 500];% Mention all
```

```
lambda= Constant(1); beta= Constant(2); rho=Constant(3);
theta= Constant(4); epsilon = Constant(5); eta = Constant(6);
mu = Constant(7); delta1= Constant(8); delta2 = Constant(9);
phi = Constant(10); omega= Constant(11); n= Constant(12);
gamma= Constant(13);
A1=Constant(14); A2= Constant(15); A3= Constant(16);
B1= Constant(17); B2= Constant(18);
lf  = [0 0 0 0 0 0];
%% TEST SECTION
%  u1 u2
%  U = [0 0];
%  [Tx,X] = ode45(@kims,time,y0,[],U,Constant);
%  u = linspace(0,0,N+1);
%  u1=u'; u2=u';
%  U = [u1 u2];
%  [T, Y]=rk4foward(@kims,t0, tf,N, y0,U,Constant);
%  T=T'; Y=Y';
%  subplot(3,2,1)
%  plot(Tx,X(:,1),'-b');
%  subplot(3,2,2)
%  plot(T,Y(:,1),'--r');
%  subplot(3,2,3)
%  plot(Tx,X(:,2),'-b');
%   subplot(3,2,4)
%  plot(T,Y(:,2),'--r');
%  subplot(3,2,5)
%  plot(Tx,X(:,3),'-b');
%  subplot(3,2,6)
%  plot(T,Y(:,3),'--r');
```

```
%  break
init =y0;
init2 =lf;
h = (tf-t0)/N;
u = linspace(0,0,N+1);
u1=u'; u2=u';
U = [u1 u2];
%% IMPLIMENTATION OF THE ALGORITHM
%Test 1 stoping condition 1
delta = 0.001;
X=init;
i=0; %Initialize iteration counter
mm=size(X);
NumXX =10e10;
Xnew = rand(N+1,mm(2)).*(repmat(X,N+1,1));
DenXnew=norm(Xnew);
while  NumXX/DenXnew>delta
Xold =  Xnew;
oldu = U;
%FORWARD RUNGE KUTTA  FOR STATES
[Tx, X]=rk4foward(@kims2,t0, tf,N, init,U,Constant);
% BACKWARD RUNGEKUTA FOR COSTATES
[Tp, P]=rk4back(@kims2_costate,t0,tf,N,init2,U,X,Constant);
%UPDATE THE CONTROLS
S = X(1,:); V = X(2,:); L = X(3,:); I1=X(4,:); I2=X(5,:);
T_r=X(6,:); L1 = P(1,:); L2 = P(2,:); L3 = P(3,:);
L4 = P(4,:);L5 = P(5,:);L6 = P(6,:);
% Case0:No control,
%  u1 =zeros(1,N+1);
```

```
%  u2 =zeros(1,N+1);
% Case1:u1=0, u2/=0,
%  u1 =zeros(1,N+1);
%  u2 =max(0,min(1,(1/B2)*epsilon.*(L4.*L-L3.*L+eta.*...
(L5.*L-L4.*L))));
% Case2: u1/=0, u2=0,
% g=plus(S,V)+plus(L,I1)+plus(I2,T_r);
% u1 =max(0,min(1,(1/B1).*((I1.*L3.*S)./g-(I1.*L1.*S)./g+...
(I2.*L3.*S)./g-(I2.*L1.*S)./g+...
% gamma.*((I1.*L3.*T_r)./g-(I1.*L6.*T_r)./g+(I2.*L3.*T_r)./g-...
(I2.*L6.*T_r)./g)-rho*lambda.*(g.*L2)+(2*omega*phi.*I2.*L5)-...
omega*phi.*I2.*L6-...
% omega*phi.*I2.*L4+omega.*I2.*L4-...
omega.*I2.*L5+nu*I1.*L4-nu*I1.*L6)));
%  u2 =zeros(1,N+1);
% Case3:u1/=0, u2/=0,
g=plus(S,V)+plus(L,I1)+plus(I2,T_r);
u1 =max(0,min(1,(1/B1).*((I1.*L3.*S)./g-(I1.*L1.*S)./g+...
(I2.*L3.*S)./g-(I2.*L1.*S)./g+...
gamma.*((I1.*L3.*T_r)./g-(I1.*L6.*T_r)./g+(I2.*L3.*T_r)./g-...
(I2.*L6.*T_r)./g)-rho*lambda.*(g.*L2)+(2*omega*phi.*I2.*L5)-...
omega*phi.*I2.*L6-omega*phi.*I2.*L4+omega.*I2.*L4-...
omega.*I2.*L5+nu*I1.*L4-nu*I1.*L6)));
u2 =max(0,min(1,(1/B2)*epsilon.*(L4.*L-L3.*L+eta.*...
(L5.*L-L4.*L))));
Uu=[u1' u2'];
U = 0.5*Uu + 0.5*oldu; % Convex combination of the controls
Xnew =  X';
NumXX =abs(norm(Xnew-Xold));
```

```
DenXnew =norm(Xnew);
i=i+1 %Update iteration counter
end
%% PLOTING
X=X';
Tx =Tx';
XX=X(:,3); YY=X(:,4); VV=X(:,5);
Up = [0 0];
[T,Y] = ode45(@kims2,time,y0,[],Up,Constant);
J =sum((A1*XX(end)+A2*YY(end)+A3*VV(end))+...
((B1/2)*Uu(:,1).*Uu(:,1)+(B2/2)*Uu(:,2).*Uu(:,2))); %Change to
%the suitable objective function
Z=[Tx,X];
%S=[T,Y]
  cd('C:\Users\GOODLUCK\Desktop\Optimalcontrolcode')
  save('case1State', 'Z');
  save('case1Control', 'Uu');
     save('Cost', 'J');
 figure(1)
 subplot(2,2,1)
  plot(Tx,X(:,3),'-b', T, Y(:,3),'--r','LineWidth',3);
 title('A');
legend('u_1\neq 0, u_2\neq 0','u_1=0, u_2=0',2)
xlabel('Time(years)')
grid on
hold on
 ylabel('Latently Infected')
 subplot(2,2,2)
  plot(Tx,X(:,4),'-b',T, Y(:,4),'--r','LineWidth',3);
```

```
 title('B');
legend('u_1\neq 0, u_2\neq 0','u_1=0, u_2=0',2)
xlabel('Time(years)')
 ylabel('Severely Infected')
 grid on
 hold on
 subplot(2,2,3)
plot(Tx,X(:,5),'-b',T, Y(:,5),'--r','LineWidth',3);
 title('C');
legend('u_1\neq 0, u_2\neq 0','u_1=0, u_2=0',2)
xlabel('Time(years)')
 ylabel('Mildly infected')
 grid on
 hold on
 subplot(2,2,4)
 plot(Tx,Uu(:,1),'-g','LineWidth',3); hold on
 plot(Tx,Uu(:,2),'--m','LineWidth',3);
 xlabel('Time(years)')
 ylabel('Control Profile')
 title('D');
 legend('u_1(t)','u_2(t)')
 grid on
 hold off
```

Appendix E: MATLAB codes of Figures in Chapter Five

```
\begin{center}
\textbf{MATLAB  codes  for Figure \ref{Figure:8}}
\end{center}
```

```
clear all
clc
format bank
figure(1)
subplot(2,2,1)
beta=0.7;gamma1=0.05;mu=0.01632;rho=0.2;omega2=0.47;
[phir,alpha1]=meshgrid(0:0.01:1,0:0.01:1);
Rr=(beta.*(gamma1+mu.*rho))./(mu.*(mu+phir+alpha1)+...
gamma1*(mu+phir.*omega2+alpha1));
% %pause
%  Rr=Rr*100
%  %pause
%  Rr=round(Rr)
%  %pause
%  Rr=Rr/100
%  %pause
[C,h]=contour(phir,alpha1,Rr,180,'Linewidth',2);
clabel(C,h)
title('(a)')
xlabel('\phi_{r}','Fontsize',12);
ylabel('\alpha_{1}','Fontsize',12);
hold on
subplot(2,2,2)
beta=0.7;gamma1=0.05;mu=0.01632;rho=0.2;alpha1=0.5;
[phir,omega2]=meshgrid(0:0.1:1,0:0.1:1);
Rr=(beta.*(gamma1+mu.*rho))./(mu.*(mu+phir+alpha1)+...
gamma1*(mu+phir.*omega2+alpha1));
[C,h]=contour(phir,omega2,Rr,'Linewidth',2);
clabel(C,h)
```

```
title('(b)')
xlabel('\phi_{r}','Fontsize',12);
ylabel('\omega_{2}','Fontsize',12);
subplot(2,2,3)
beta=0.7;omega2=0.47;mu=0.01632;rho=0.2;phir=0.09;
[gamma1,alpha1]=meshgrid(0:0.1:1,0:0.1:1);
Rr=(beta.*(gamma1+mu.*rho))./(mu.*(mu+phir+alpha1)+...
gamma1*(mu+phir.*omega2+alpha1));
[C,h]=contour(gamma1,alpha1,Rr,'Linewidth',2);
clabel(C,h)
title('(c)')
xlabel('\gamma_{1}','Fontsize',12);
ylabel('\alpha_{1}','Fontsize',12);
% subplot(2,2,4)
% beta=0.7;gamma1=0.05;mu=0.01632;rho=0.2;phir=0.09;
% [omega2,alpha1]=meshgrid(0:0.1:1,0:0.1:1);
% Rr=(beta.*(gamma1+mu.*rho))./(mu.*(mu+phir+alpha1)+...
gamma1*(mu+phir.*omega2+alpha1));
% [C,h]=contour(omega2,alpha1,Rr,40);
% clabel(C,h)
% title('D')
% xlabel('\omega_{2}','Fontsize',12);
% ylabel('\alpha_{1}','Fontsize',12);
subplot(2,2,4)
beta=0.7;gamma1=0.05;mu=0.01632;rho=0.2;phir=0.09;
[omega2,alpha1]=meshgrid(0:0.1:1,0:0.1:1);
Rr=(beta.*(gamma1+mu.*rho))./(mu.*(mu+phir+alpha1)+...
gamma1*(mu+phir.*omega2+alpha1));
[C,h]=contour(omega2,alpha1,Rr,80,'Linewidth',2);
```

```
clabel(C,h)
title('(d)')
xlabel('\omega_{2}','Fontsize',12);
ylabel('\alpha_{1}','Fontsize',12);

\begin{center}
\textbf{MATLAB codes  for Figure \ref{Figure4a}}
\end{center}
%The same function file as of incidence but the main file
% is different
clear all
close all
tspan=[0 10];
y0=[0.4 0.2 0.15 0.1 0.1 0.05];
% y0=[0.6 0.2 0.05 0.05 0.05 0.05];
[t1,y1]=ode45(@prevalenceimmigrationsystem1,tspan,y0);
[t2,y2]=ode45(@prevalenceimmigrationsystem2,tspan,y0);
%figure(1)
%plot(t,y(:,1),t,y(:,2),t,y(:,3),t,y(:,4))
%legend('S','V','I','A')
%xlabel('Time[year]')
%ylabel('Population')
%hold on
N1=y1(1,1)+y1(1,2)+y1(1,3)+y1(1,4)+y1(1,5)+y1(1,6);
N2=y2(1,1)+y2(1,2)+y2(1,3)+y2(1,4)+y2(1,5)+y2(1,6);
%N3=y3(1,1)+y3(1,2)+y3(1,3)+y3(1,4)+y3(1,5)+y3(1,6);
%figure(1)
%plot(t1,(y1(:,2)+y1(:,3)+y1(:,4)+y1(:,5))/N1,'r',...
t2,(y2(:,2)+y2(:,3)+y2(:,4)+y2(:,5))/N2,'m--' ,'LineWidth',3)
plot(t1,(y1(:,3)+y1(:,5))/N1,'r',...
```

```
t2,(y2(:,3)+y2(:,5))/N2,'m--','Linewidth',3)
legend('Presence of immigration','Absence of immigration')
xlabel('Time[years]','Fontsize',12)
ylabel('Disease Prevalence','Fontsize',12)
hold on

\begin{center}
\textbf{MATLAB  codes  for Figure \ref{Figure4b}}
\end{center}
function f=incidencetwostrainsystem1(t,y)
Lambda=0.03725;
p=0.04; sigma=0.02; rho=0.2; beta=1.2; beta1=1.5; beta2=1.7;
gamma1=0.05; gamma2=0.03; omega1=0.8; omega2=0.47; phis=0.35;
phir=0.2; tau=0.02; alpha1=0.5; alpha2=0.3; mu=0.01632;
s=y(1); es=y(2); is=y(3); eR=y(4); iR=y(5); r=y(6);
ds=mu+alpha1*iR+alpha2*is-p*(mu+alpha1*iR+alpha2*is-Lambda)-...
(mu+beta*(is+iR))*s;
des=p*sigma*(mu+alpha1*iR+alpha2*is-Lambda)+beta*((1-rho)*s...
+tau*r)*is-(mu+beta2*iR+beta1*is+gamma2)*es;
dis=gamma2*es-(mu+phis+alpha2-rho*beta*s-beta1*es)*is;
deR=p*(1-sigma)*(mu+alpha1*iR+alpha2*is-Lambda)+...
(beta*((1-rho)*s+tau*r)+phir*(1-omega2))*iR+phis*(1-omega1)*is-...
(mu+beta1*iR+gamma1)*eR;
diR=gamma1*eR-(mu+phir+alpha1-rho*beta*s-beta1*eR-beta2*es)*iR;
dr=phir*omega2*iR+phis*omega1*is-(mu+tau*beta*iR)*r;
f=[ds;des;dis;deR;diR;dr];
%note that when there is no immigration we replace Pi=p=sigma=0
%The main file when incidence is considered is as follows
clear all
close all
```

```
tspan=[0 10];
y0=[0.35 0.15 0.2 0.1 0.15 0.05];
[t1,y1]=ode45(@incidencetwostrainsystem1,tspan,y0);
[t2,y2]=ode45(@incidencetwostrainsystem2,tspan,y0);
N1=y1(:,1)+y1(:,2)+y1(:,3)+y1(:,4)+y1(:,5)+y1(:,6);
N2=y2(:,1)+y2(:,2)+y2(:,3)+y2(:,4)+y2(:,5)+y2(:,6);
%N3=y3(1,1)+y3(1,2)+y3(1,3)+y3(1,4)+y3(1,5)+y3(1,6);
%figure(1)
beta=1.2;
plot(t1,(beta.*y1(:,1).*(y1(:,3)+y1(:,5))./N1,'r'...
,t2,(beta.*y2(:,1).*(y2(:,3)+y2(:,5))./N2,'k--' ,'LineWidth',3)
legend('Presence of immigration','Absence of immigration')
xlabel('Time[years]','Fontsize',12)
ylabel('Incidence','Fontsize',12)
hold on

\begin{center}
\textbf{MATLAB  codes  for Figure \ref{Figure:5}}
\end{center}
function f=prevalencetwostrainsystem1(t,y)
Lambda=0.03725; p=0.2; sigma=0.02; rho=0.2; beta=0.7;
beta1=0.85; beta2=0.95; gamma1=0.05; gamma2=0.03;
omega1=0.8; omega2=0.47; phis=0.35; phir=0.2; tau=0.02;
alpha1=0.5; alpha2=0.3; mu=0.01632;
s=y(1); es=y(2); is=y(3); eR=y(4); iR=y(5); r=y(6);
ds=mu+alpha1*iR+alpha2*is-p*(mu+alpha1*iR+alpha2*is-Lambda)...
-(mu+beta*(is+iR))*s;
des=p*sigma*(mu+alpha1*iR+alpha2*is-Lambda)+beta*...
((1-rho)*s+tau*r)*is-(mu+beta2*iR+beta1*is+gamma2)*es;
dis=gamma2*es-(mu+phis+alpha2-rho*beta*s-beta1*es)*is;
```

```
deR=p*(1-sigma)*(mu+alpha1*iR+alpha2*is-Lambda)+...
(beta*((1-rho)*s+tau*r)+phir*(1-omega2))*iR+phis*(1-omega1)*is-...
(mu+beta1*iR+gamma1)*eR;
diR=gamma1*eR-(mu+phir+alpha1-rho*beta*s-beta1*eR-beta2*es)*iR;
dr=phir*omega2*iR+phis*omega1*is-(mu+tau*beta*iR)*r;
f=[ds;des;dis;deR;diR;dr];
%The main file
clear all
close all
tspan=[0 10];
 y0=[0.35 0.15 0.1 0.2 0.15 0.05];
[t1,y1]=ode45(@prevalencetwostrainsystem1,tspan,y0);
% [t2,y2]=ode45(@prevalencetwostrainsystem2,tspan,y0);
% [t3,y3]=ode45(@prevalencetwostrainsystem3,tspan,y0);
N1=y1(1,1)+y1(1,2)+y1(1,3)+y1(1,4)+y1(1,5)+y1(1,6);
% N2=y2(1,1)+y2(1,2)+y2(1,3)+y2(1,4)+y2(1,5)+y2(1,6);
% N3=y3(1,1)+y3(1,2)+y3(1,3)+y3(1,4)+y3(1,5)+y3(1,6);
plot(t1,(y1(:,2)+y1(:,3))/N1,'m-',t1,(y1(:,4)+y1(:,5))/N1,...
'r--','LineWidth',3)
legend('Sensitive strain','Resistant strain')
xlabel('Time[years]','Fontsize',12)
ylabel('Disease Prevalence','Fontsize',12)
hold on

\begin{center}
\textbf{MATLAB  codes  for Figure \ref{Figure:1a}}
\end{center}
%The function file is the same as those from above
%scrips, the only
%difference is that we variate values of phis=0.5,...
```

```
% 0.7 and 0.85
%The main file is as follows
clear all
close all
tspan=[0 10];
y0=[0.4 0.2 0.15 0.1 0.1 0.05];
[t1,y1]=ode45(@prevalencecorrectionsensitivesystem1,tspan,y0);
[t2,y2]=ode45(@prevalencecorrectionsensitivesystem2,tspan,y0);
[t3,y3]=ode45(@prevalencecorrectionsensitivesystem3,tspan,y0);
%figure(1)
%plot(t,y(:,1),t,y(:,2),t,y(:,3),t,y(:,4))
N1=y1(1,1)+y1(1,2)+y1(1,3)+y1(1,4)+y1(1,5)+y1(1,6);
N2=y2(1,1)+y2(1,2)+y2(1,3)+y2(1,4)+y2(1,5)+y2(1,6);
N3=y3(1,1)+y3(1,2)+y3(1,3)+y3(1,4)+y3(1,5)+y3(1,6);
plot(t1,(y1(:,3)+y1(:,5))/N1,'r',t2,(y2(:,3)+y2(:,5))/N2,'m',...
 t3,(y3(:,3)+y3(:,5))/N3,'b','LineWidth',3)
legend('\phi_{s}=0.5','\phi_{s}=0.7','\phi_{s}=0.85')
xlabel('Time[years]')
ylabel('Disease Prevalence')
hold on

\begin{center}
\textbf{MATLAB  codes  for Figure \ref{Figure:2}}
\end{center}
%The function file is the same as those from above
% scrips, the only
%difference is that we variate values of phir=0.4,
% 0.55, 0.65 and 0.85
%The main file is as follows
clear all
```

```
close all
tspan=[0 10];
y0=[0.4 0.2 0.15 0.1 0.1 0.05];
[t1,y1]=ode45(@prevalencecorrectionresistantsystem1,tspan,y0);
[t2,y2]=ode45(@prevalencecorrectionresistantsystem2,tspan,y0);
[t3,y3]=ode45(@prevalencecorrectionresistantsystem3,tspan,y0);
[t4,y4]=ode45(@prevalencecorrectionresistantsystem4,tspan,y0);
N1=y1(1,1)+y1(1,2)+y1(1,3)+y1(1,4)+y1(1,5)+y1(1,6);
N2=y2(1,1)+y2(1,2)+y2(1,3)+y2(1,4)+y2(1,5)+y2(1,6);
N3=y3(1,1)+y3(1,2)+y3(1,3)+y3(1,4)+y3(1,5)+y3(1,6);
N4=y4(1,1)+y4(1,2)+y4(1,3)+y4(1,4)+y4(1,5)+y4(1,6);
plot(t1,(y1(:,3)+y1(:,5))/N1,'r',t2,(y2(:,3)+y2(:,5))/N2,...
'm',t3,(y3(:,3)+y3(:,5))/N3,'k--',t4,(y4(:,3)+y4(:,5))/N4,...
'g','LineWidth',3)
legend('\phi_{r}=0.4','\phi_{r}=0.55','\phi_{r}=0.65',...
'\phi_{r}=0.85')
xlabel('Time[years]')
ylabel('Disease Prevalence')
hold on

\begin{center}
\textbf{MATLAB  codes  for Figure \ref{Figure:3}}
\end{center}
%The function file is the same as those from above
% scrips, the only
%difference is that we variate values of phis=0.35,...
%phir=0.2;phis=0.5,
phir=0.4;
phis=0.7,phir=0.55;phis=0.85,phir=0.95.
%The main file is as follows
```

```
clear all
close all
tspan=[0 10];
y0=[0.4 0.2 0.15 0.1 0.1 0.05];
[t1,y1]=ode45(@prevalencetwostrainsystem1,tspan,y0);
[t2,y2]=ode45(@prevalencetwostrainsystem2,tspan,y0);
[t3,y3]=ode45(@prevalencetwostrainsystem3,tspan,y0);
[t4,y4]=ode45(@prevalencetwostrainsystem4,tspan,y0);
N1=y1(1,1)+y1(1,2)+y1(1,3)+y1(1,4)+y1(1,5)+y1(1,6);
N2=y2(1,1)+y2(1,2)+y2(1,3)+y2(1,4)+y2(1,5)+y2(1,6);
N3=y3(1,1)+y3(1,2)+y3(1,3)+y3(1,4)+y3(1,5)+y3(1,6);
N4=y4(1,1)+y4(1,2)+y4(1,3)+y4(1,4)+y4(1,5)+y4(1,6);
plot(t1,(y1(:,3)+y1(:,5))/N1,'r',t2,(y2(:,3)+y2(:,5))/N2,...
'm--',t3,(y3(:,3)+y3(:,5))/N3,t4,(y4(:,3)+y4(:,5))/N4,...
'g','LineWidth',3)
legend('\phi_{s}=0.35,\phi_{r}=0.2','\phi_{s}=0.5,...
\phi_{r}=0.4','\phi_{s}=0.7,\phi_{r}=0.55',...
'\phi_{s}=0.85,\phi_{r}=0.95')
xlabel('Time[years]')
ylabel('Disease Prevalence')
hold on
```

Appendix F: MATLAB codes of Figures in Chapter Six

```
\begin{center}
\textbf{MATLAB codes  for Figure \ref{Figure:4ab}}
\end{center}
%Bifurcation diagram_multi_drug_sensitive TB codes
Re_value=0:0.0001:2;
```

```
Root_array=zeros(length(Re_value),2);
Lambda=0.03725; Pi=0.06; p=0.04; sigma=0.00002;
rho=0.5; beta=0.8; beta1=5.5; beta2=14; gamma1=0.05;
gamma2=0.3; omega1=0.9999; omega2=0.47; phi_s=0.2;
phi_r=0.09; tau=0.3; alpha1=0.5; alpha2=0.0003; mu=0.01632;
hold on
for i=1:1:length(Re_value); Re=Re_value(i);
A1=beta1*tau*(1-sigma);
B1=(1-sigma)*(beta1*mu+beta*tau*(mu+phi_s+alpha2+gamma2)+...
beta1*tau*(mu+phi_s+alpha2-beta))+...
beta1*phi_s*(sigma*tau+omega1*(1-tau-sigma))...
-beta*rho*tau*((1-sigma)*alpha2+phi_s*(1-omega1));
C1=(1-sigma)*mu*(beta*(mu+phi_s+alpha2+gamma2)+...
beta1*(mu+phi_s+alpha2-beta))+beta*gamma2*phi_s*...
(sigma*tau+omega1*(1-tau-sigma))-beta*rho*mu...
*((1-sigma)*...
alpha2+phi_s*(1-omega1))+beta1*sigma*...
phi_s*(1-omega1)*mu+...
beta*(1-sigma)*tau*(mu+gamma2)*...
(mu+phi_s+alpha2)*(1-Re);
D1=beta*(1-sigma)*mu*(mu+gamma2)...
*(mu+phi_s+alpha2)*(1-Re);
 m=[A1,B1,C1,D1];
r =roots(m); len=length(r);
for t=1:1:len
if (imag(r(t))~=0) || (real(r(t))<0);
 Root_array(i,t)=0;
else
Root_array(i,t)=r(t);
```

```
end
end
end
f=1;
while (Root_array(f,1)==0 && Root_array(f,2)==0 &&...
 Root_array(f,3)==0),
f=f+1;
end
Re_value_Cr=f;
for j=Re_value_Cr:1:length(Re_value)
Root_array(j,:)=sort(Root_array(j,:));
end
f1=Re_value_Cr;
while (Root_array(f1,2)~=0)
 f1=f1+1;
end
Re_value_Cr2=f1;
Zero_1st=Re_value(1,1:Re_value_Cr2-1);
y_zero=zeros(1,length(Zero_1st));
Unstable =Re_value(1,Re_value_Cr:length(Re_value));
plot(Zero_1st,y_zero,'r','LineWidth',3)
plot(Unstable, Root_array(Re_value_Cr:length(Re_value),2),
'b--','LineWidth',3)
plot(Unstable,Root_array(Re_value_Cr:length(Re_value),3),
'r','LineWidth',3)
xlabel('R_s','FontSize',12)
ylabel('Force of Infection, \lambda^*','FontSize',12)
hold off

\begin{center}
```

```
\textbf{MATLAB codes  for Figure \ref{Figure:4bb}}
\end{center}
%Bifurcation diagram_multi_drug_sensitive TB codes
Re_value=0:0.0001:2;
Root_array=zeros(length(Re_value),2);
%Parameter values used
Lambda=0.03725; Pi=0.06; p=0.04; sigma=0.02; rho=0.2;
beta=1.2; beta1=1.5; beta2=1.7; gamma1=0.05; gamma2=0.03;
omega1=0.8; omega2=0.47; phi_s=0.3; phi_r=0.09; tau=0.4;
alpha1=0.5; alpha2=0.3; mu=0.01632;
hold on
for i=1:1:length(Re_value); Re=Re_value(i);
 A2=beta1*tau;
 B2=beta*tau*(mu+phi_r+gamma1+(1-rho)...
 *alpha1)+beta1*tau*(mu+alpha1-beta)+...
 beta1*(mu+phi_r*omega2);
 C2=mu*(beta*(mu+phi_r+gamma1+(1-rho)*alpha1)+...
 beta1*(mu+phi_r*omega2+alpha1-beta))+tau*beta*...
(mu*(mu+phi_r+alpha1)
 +gamma1*(mu+phi_r*omega2+alpha1))*(1-Re);
 D2=beta*mu*(mu*(mu+phi_r+alpha1)+gamma1*...
 (mu+phi_r*omega2+alpha1))*(1-Re);
 m=[A2,B2,C2,D2];
r =roots(m); len=length(r);
for t=1:1:len
if (imag(r(t))~=0) || (real(r(t))<0); Root_array(i,t)=0;
else
 Root_array(i,t)=r(t);
end
```

```
end
end

f=1;
while (Root_array(f,1)==0 && Root_array(f,2)==0 &&...
Root_array(f,3)==0),
f=f+1;
end
Re_value_Cr=f;
for j=Re_value_Cr:1:length(Re_value)
Root_array(j,:)=sort(Root_array(j,:));
end
f1=Re_value_Cr;
while (Root_array(f1,2)~=0)
    f1=f1+1;
end
Re_value_Cr2=f1;
Zero_1st=Re_value(1,1:Re_value_Cr2-1);
y_zero=zeros(1,length(Zero_1st));
Unstable =Re_value(1,Re_value_Cr:length(Re_value));
plot(Zero_1st,y_zero,'g','LineWidth',3)
plot(Unstable, Root_array(Re_value_Cr:length(Re_value),2),
'r--','LineWidth',3)
plot(Unstable,Root_array(Re_value_Cr:length(Re_value),3),
'g','LineWidth',3)
xlabel('R_r','FontSize',12)
ylabel('Force of Infection, \lambda^*','FontSize',12)
hold off

\begin{center}
```

```
\textbf{MATLAB  codes  for Figure \ref{Figure:5}}
\end{center}
function f=drugsensitivemodelsystem(t,y,mu,alpha2,sigma,...
phis,omega1,beta,rho,tau,beta1,gamma2)
s=y(1); es=y(2); is=y(3); r=y(4);
ds=mu+alpha2*is+1/(1-sigma)*phis*(1-omega1)*is-...
(mu+beta*is)*s;
des=-sigma/(1-sigma)*phis*(1-omega1)*is+...
beta*((1-rho)*s+tau*r)*is-...
(mu+beta1*is+gamma2)*es;
dis=gamma2*es-(mu+phis+alpha2-rho*beta*s-beta1*es)*is;
dr=phis*omega1*is-(mu+tau*beta*is)*r;
f=[ds;des;dis;dr];
%Here is the main file to run on
clear all
%close all
clc
c=['k  ';'b--';'r  ';'g  '];
%Parameters to unveil EEP
Lambda=0.03725; Pi=0.06; p=0.04; sigma=0.02; rho=0.2;
beta=1.2; beta1=1.5; beta2=1.7; gamma1=0.05; gamma2=0.03;
omega1=0.8; omega2=0.47; phis=0.3; phir=0.09; tau=0.02;
alpha1=0.5; alpha2=0.3; mu=0.01632;
 y0=[0.55 0.2 0.15 0.1];
tspan=[0 450];
[t y]=ode45(@drugsensitivemodelsystem,tspan,y0,[],mu,...
alpha2,sigma,phis,omega1,beta,rho,tau,beta1,gamma2);
for i=1:4
plot(t,y(:,i),c(i,:),'Linewidth',3)
```

```
 hold on
end
xlabel('time in years','FontSize',12)
ylabel('Population Proportions','FontSize',12)
legend('Susceptible','Exposed drug-sensitive',...
'Infected drug-sensitive','Recovered')

\begin{center}
\textbf{MATLAB  codes  for Figure \ref{Figure:5a}}
\end{center}
clear all
%close all
clc
c=['k  ';'b--';'r  ';'g  '];
Lambda=0.03725; Pi=0.06; p=0.04; sigma=0.02; rho=0.2; beta=1.2;
beta1=1.5; beta2=1.7; gamma1=0.05; gamma2=0.03; omega1=0.8;
omega2=0.47; phis=0.3; phir=0.09; tau=0.02; alpha1=0.5;
alpha2=0.3; mu=0.01632;
%   y0=[0.55 0.2 0.15 0.1];
%   y0=[0.50 0.3 0.1 0.1];
%  y0=[0.60 0.15 0.15 0.1];
%  y0=[0.45 0.2 0.2 0.15];
 y0=[0.55 0.3 0.1 0.05];
tspan=[0 450];
[t y]=ode45(@drugsensitivemodelsystem,tspan,y0,[],mu,...
alpha2,sigma,phis,omega1,beta,rho,tau,beta1,gamma2);
figure (1)
subplot(1,3,1)
plot(y(:,1),y(:,2),'g','Linewidth',2)
xlabel('Susceptible','FontSize',12)
```

```
ylabel('Exposed drug-sensitive','FontSize',12)
title('(a)')
grid on
hold on
subplot(1,3,2)
plot(y(:,1),y(:,3),'g','Linewidth',2)
xlabel('Susceptible','FontSize',12)
ylabel('Infectious drug-sensitive','FontSize',12)
title('(b)')
grid on
hold on
subplot(1,3,3)
plot(y(:,1),y(:,4),'g','Linewidth',2)
xlabel('Susceptible','FontSize',12)
ylabel('Recovered','FontSize',12)
title('(c)')
grid on
hold on
```