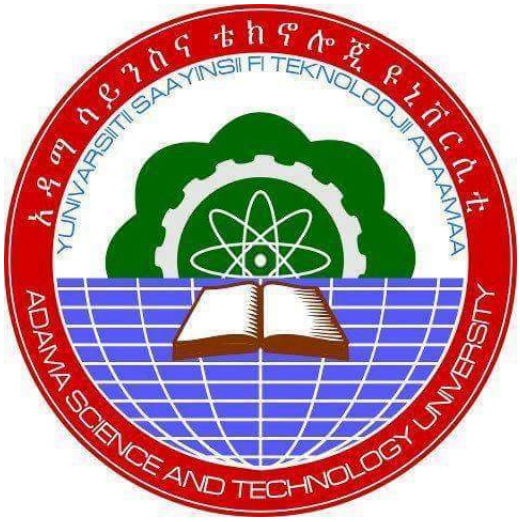
MATHEMATICAL MODEL OF THE TRANSMISSION DYNAMICS OF TUBERCULOSIS WITH OPTIMAL CONTROL STRATEGIES



By

Tokuma Dechesa Hundesa

A Thesis Submitted to Department of Applied Mathematics

School of Applied Natural Science

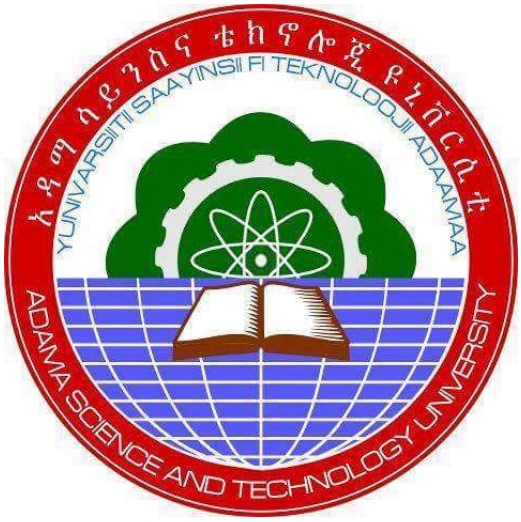
Office of Graduate Studies

Adama Science and Technology University

July, 2020

Adama, Ethiopia

MATHEMATICAL MODEL OF THE TRANSMISSION DYNAMICS OF TUBERCULOSIS WITH OPTIMAL CONTROL STRATEGIES



By

Tokuma Dechesa Hundesa

Advisor : Dr. Legesse Lemecha

A Thesis Submitted to Department of Applied Mathematics

School of Applied Natural Science

Office of Graduate Studies

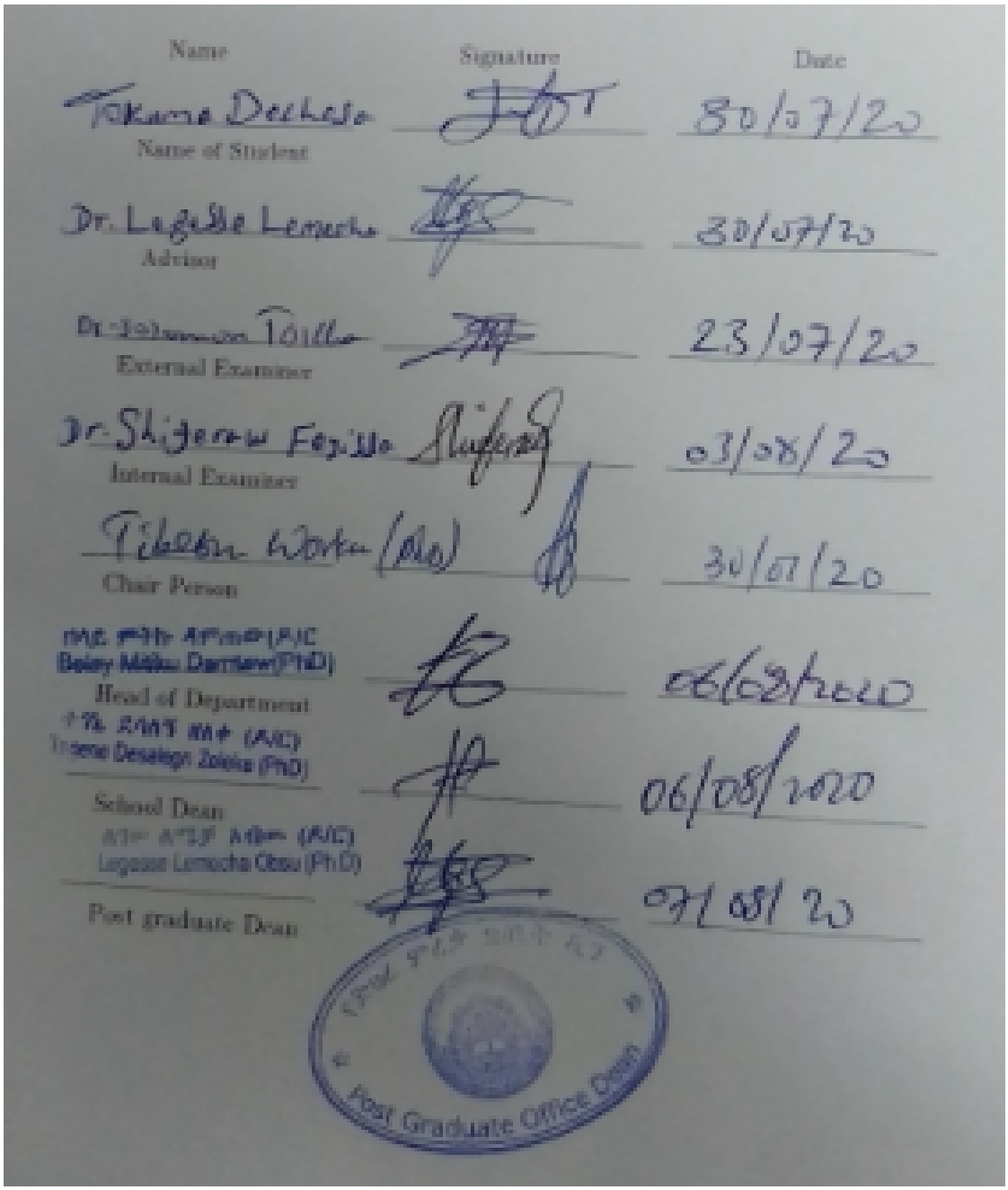
Adama Science and Technology University

July, 2020

Adama, Ethiopia

Approval Page

We, the undersigned, members of the Board of Examiners of the final open defense by Tokuma Dechesa Hundesa have read and evaluated his thesis entitled "Mathematical modeling of the transmission dynamics of tuberculosis with optimal control" and Examined the candidate. This is therefore to certify that the thesis has been accepted in partial fulfillment of the requirement of the degree of Master of Science in Applied Mathematics.



Acknowledgment

First of all, I would like to thank the almighty God for his permission to do my daily activities. Next my special and heart full gratitude and great appreciation goes to my advisor Dr. Legesse Lemecha for his great assistance, contribution, useful suggestion and constructive idea on his excellence advising and limitless effort in encouraging me in my Thesis work by correcting and giving comments as well as devoting his time from starting to its completeness

Table of Contents

Abstract

This thesis focused on a mathematical model of the transmission dynamics of tuberculosis with optimal control to assess the dynamics of tuberculosis infection in East Shewa Zone. The existence and stability of the disease-free and endemic equilibria of the model were performed. Both local and global stability of the disease-free and the endemic equilibrium are determined. Sensitivity indices of R_0 with respect to the model parameters are performed to reveal the transmission dynamics of tuberculosis. Then the optimal control strategy is found by minimizing the number of exposed and infected individual population with tuberculosis taking into account the cost of implementation. The existence of optimal controls is established with the help of Pontryagin's Maximum Principle. The model is then fitted with cumulative cases of infected tuberculosis real data from East Shewa zone Health Office from 2010 to 2019 years. In addition, different simulation cases were comparatively performed to obtain the best control strategies. In general, the numerical simulation results demonstrate good agreement with our analytical results. The simulation results also clearly shown that the epidemic of tuberculosis can be minimized by preventing the failure of treatment in active tuberculosis individuals through continuous supervision and helping patients during treatment period with optimal implementation cost. Furthermore, the optimal control model also predicted that tuberculoses epidemic will be managed for the coming ten years in East Shewa Zone which restively agreeing with world Health Organization strategic goal of ending the global tuberculosis epidemic by 2030.

List of abbreviations

TB	Tuberculosis
R_0	Reproduction number
MTB	Mycotuberculosis bacterium
WHO	World Health Organization
MDR-TB	Multidrug resistant TB
SLITR	Susceptible, exposed, infectious, treatment, recovered
CSA	Central Statistical Agency
PMP	Pontryagin maximum principle
DFE	Disease free equilibrium
E_0	Disease free equilibrium point
EE	Endemic equilibrium
HIV	Human Immunodeficiency Virus
AID	Acquired Immunodeficiency Syndrome
IVP	Initial Value Problems
RK_4	Runge-Kutta order four
ODE	An ordinary differential equations

List of Figures

Chapter 1

Introduction

1.1 Tuberculosis

Tuberculosis(TB) is an infectious disease caused by mycobacterium tuberculosis bacteria(tubercle bacilli)[1]. It was not clear how TB was transmitted until the seminal work of Robert Koch's in 1982. The bacteria lives in the lungs of the infected host. mycobacterium tuberculosis spreads through the air from an infectious person to susceptible person. Persons with active pulmonary or laryngeal tuberculosis generate droplet nuclei that contain Mycobacterium tuberculosis through communication, coughing, singing, shouting, sneezing, or any other forceful expiratory maneuver that shears respiratory secretions from the airways, with coughing being the most efficient at generating infectious aerosols [9, 26].

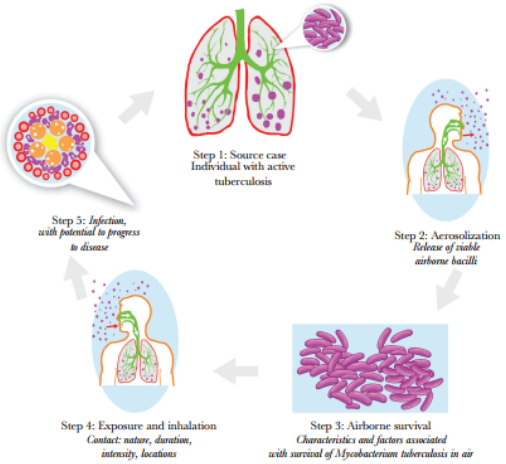


Figure 1.1: sequence of tuberculosis transmission. Source : Aurum Institute [9]

Once infected, the person stays infected for many years, possibly latent infected for life. People with latent TB infection do not fall sick and do not have any symptoms. They are not infectious and can not spread TB to others. TB bacteria become infectious if the immune system cannot stop them from growing. These infections damages the immune system which causes latent TB to develop to infectious tuberculosis. TB is a contagious infection that usually affects the lungs (known as pulmonary TB). It may also invade or attacks other organs including brain, spine, kidneys, central nervous system or lymphatic system (known as extra-pulmonary TB). Extra-pulmonary TB occurs more commonly in people with a weakened immune system and young children [31].

Persons with compromised immune systems, such as people living with HIV, malnutrition, diabetes, and people who use tobacco have a much higher risk of falling ill with

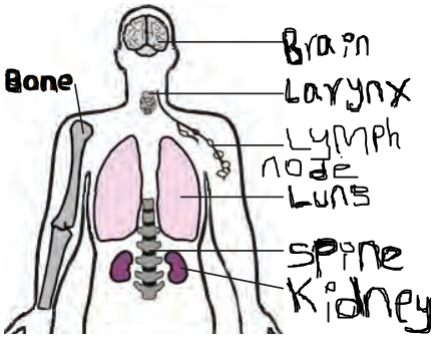


Figure 1.2: Parts of the body that can be affected by TB disease [31]

tuberculosis(TB). Although prevention and treatment of Tuberculosis (TB) continue throughout the world, it does not reduce the incidence of TB cases every year. Many factors can make TB cases continue to increase, including increased air pollution.

Active TB disease is a condition in which the body's immune system is unable to fight off or defend against the mycobacterium tuberculosis bacterium [17]. A person is said to have TB disease or active TB when he or she is infected with mycobacterium tuberculosis and shows signs and symptoms of the disease. The main clinical symptoms of TB infected person are chronic cough, blood-containing sputum(mucus from deep inside the lungs), chest pain, feeling tired all the time or fatigue, night sweats, chills, fever, loss of appetite and weight loss [2].

Tuberculosis occurs in every part of the world and affects all countries as well as all age groups. According to World Health Organization (WHO) Global TB 2017 Report, there was an estimated 10.4 million persons who fell ill with TB in 2016 such that 90% of cases were adults (aged $\geq$ 15 years), 65% were male, 10% were people living with HIV (74% of them in Africa) and about 56% were from five countries: India, Indonesia, China, the Philippines and Pakistan[7]. In the 2016 year, the largest number of new TB cases occurred in the South-East Asia and Western Pacific regions, with 62% of new cases, followed by the African region, with 25% of new cases [23]. Additionally, in 2017, 87% of new TB cases occurred in the 30 high TB burden countries. Eight countries accounted for two thirds of the new TB cases: India, China, Indonesia, Philippines, Pakistan, Nigeria, Bangladesh and South Africa. These countries accounted more than 60% of the whole TB burden in the worldwide [21].

Corresponding to the World Health Organization(WHO) 2018 report, TB is one of the top 10 causes of death and the leading cause from a single infectious agent(above HIV/AIDS) worldwide. Millions of people continue to fall sick with TB each year. In the report and reference cited there in, an estimated 10 million people developed TB and 1.3 million died from the disease(including 300,000 deaths among HIV positive people)[2].

Drug-resistant TB has continued to be a major problem in the effective management and control of TB in a population. In 2016 alone, there were an estimated 600,000 new TB cases with resistance to rifampicin (RR-TB), of which 490,000 had cases of multidrug-resistant TB (MDR-TB)[7]. The World Health Organization (WHO)

estimates that 10.4 million cases of tuberculosis (TB) occurred worldwide in 2017, of which 600,000 were rifampicin (RR) or multidrug-resistant(MDR) TB which defined as Mycobacterium tuberculosis with resistance to at least rifampicin and isoniazid. Multidrug-resistant(MDR) are a common in Sub-Saharan Africans including Ethiopia[15].

Africa is the world's second-largest and second-most having a large population continent. With 1.1 billion people as of 2013, it accounts for about 15% of the world's human population. Global TB incidence is still growing at 1% a year due to the rapid increase in Africa; intense control efforts are helping incidence fall or stabilize in other regions[22]. The unprecedented growth of the tuberculosis epidemic in Africa is attributable to several factors, the most important being the HIV epidemic. Geographically, most TB cases in 2018 were in the WHO regions of Africa is 24%[50]. The challenge in controlling TB in Africa is attributed to poverty, drug-resistant tuberculosis, endemic of the causative agents, and inefficient diagnostic methods, among others[53].

In Ethiopia, tuberculosis (TB) is one of the primary public health problems; HIV/AIDS, poverty, under nutrition, over-crowded living conditions and lack of knowledge about the disease have been known to increase the risk of spreading the bacteria and the risk of developing the disease. Ethiopia is one of the highest TB burden countries in Sub-Saharan African countries[27]. Tuberculosis (TB) is the leading cause of death from an infectious disease in Ethiopia, killing more than 32 thousand people every year(more than 80 people per day), it also has a long-term corrosive impact on the health of Ethiopia's population[25]. According to the WHO report, Ethiopia is one of the 30 high-burden countries, and there were an estimated 172,000 (164 per 100,000 populations) incident cases of TB in 2017. Corresponding to the same report, there were an estimated 25,000 deaths (24 per 100,000) due to TB, excluding HIV related deaths[48]. As in [25], the economic consequences of TB include those due to lost income and productivity during diagnosis and treatment, direct household expenditures for TB care, and the unmeasured disabilities due to permanent lung damage in up to 50% of survivors.

1.2 Mathematical Model

Mathematical model is the application of mathematics to describe real world problems and investigating important questions that arise from it[36]. Mathematical models have a great role in science and engineering fields. Developing a mathematical models is the process that uses mathematics to represent, analyze, make predictions, or otherwise provide insight into the real world phenomena[33]. Mathematical modelling is a means of studying the transmission dynamics of infectious diseases aim to reveal the progression of the disease process and to provide for controlling and decision making. It has played a key role in the formulation of TB control strategies and the establishment of interim goals for intervention programs[27].

1.3 Optimal Control

Optimal control theory is another area of mathematics that is used extensively in controlling the spread of infectious diseases. It is a powerful mathematical tool that can be used to make decisions involving complex biological situation [3]. It is often used in the control of the spread of most diseases for which either vaccine or treatment is available. Optimal control theory has proven to be a successful tool in understanding ways to control the spread of infectious diseases by applying the optimal control intervention strategies. For example, in [4] the authors applied optimal control theory to a set of epidemiological models in their attempt to find the most effective control strategy to minimize the number of individuals who become infected in the course of an epidemic using both treatment and vaccination as control measures. The author in [28] used optimal control theory to minimize the cost of intervention.

Mathematical models with optimal control have played a major role in increasing our understanding of the dynamics of infectious diseases and also to investigate the optimal use of intervention strategies to mitigate the spreads of infectious diseases. It has become a valuable tool in the analysis of infectious disease dynamics and to support the development of control strategies. Optimal control can be used to investigate the optimal use of intervention strategies to reduce the spread of infectious diseases[34].

In 2018, [19] considered the optimal control problem for TB model which incorporates TB prevention and anti-TB treatment efforts as control strategies in order to minimize the number of latent and infectious populations. Recently, in 2019, Rosa and Torres considered fractional optimal control problem to minimize the number of infectious individuals and the cost of control of disease with identification and treatment of the patients. In 2019, the same authors obtained a necessary optimality condition for fractional optimal control problem in both state and control variables[29].

Tuberculosis models have also been modelled and analysed in (Yali Yang et al 2010, Liu et al 2011, Robert et al 2016, Maulana Malik et al 2018, Nkamba et al 2019, Mengistu et al 2019, Sabini et al 2020) to explore the consequences of transmission dynamics of TB at population. In 2018, Ullah et al.[5] considered non linear fractional order model with caputo type derivative in order to investigate the dynamical behavior of TB disease provides a good agreement with real data since 2002-2017 to conclude that the fractional epidemic model is more generalized than the classical model according to them. Also in 2019, behavior change function were introduced into the tuberculosis model and analyzed by the same authors above. The authors also studied the mathematical control analysis of the model in order to reducing the spread of TB in different ways[13, 30].

1.4 Statement of the problem

Tuberculosis (TB) has been considered as major global health threats leading to morbidity and mortality. One in three persons across the world representing 2-3 billion

individuals are known to be infected with mycobacterium tuberculosis (M. tuberculosis) of which 5-15% are likely to develop active TB disease during their lifetime [20]. As reported in various literature, the spread of TB has been a serious concern worldwide. For example see in [1]. In 2016, there were approximately 1.3 million TB deaths among HIV-negative people as well as an additional 300,000 deaths among HIV-positive people.

In addition to the tuberculosis epidemic, drug resistant TB has become a global challenge. Drug-resistant TB has continued to be a major problem in the effective management and control of TB in a population. In 2016 year alone, there were an estimated 600,000 new TB cases with resistance to rifampicin (RR-TB), of which 490,000 had cases of multidrug-resistant TB (MDR-TB)[7]. In 2018, there were about half a million new cases of rifampicin-resistant TB (of which 78% had multidrug-resistant TB)[15]. As indicated in [2], Ethiopia is one of the highest TB burden countries in Sub-Saharan African countries. In Ethiopia, Tuberculosis (TB) is one of the primary public health problems. HIV/AIDS, poverty, under nutrition, over-crowded living conditions and lack of knowledge about the disease have been known to increase the risk of spreading the bacteria and the risk of developing the disease. This country is among the high-burden countries for tuberculosis (TB), TB/HIV, and drug-resistant tuberculosis.

Tuberculosis(TB) becomes a serious public health problem and major causes of deaths in worldwide including Ethiopia. For this reason, many epidemiologists and other scientists invest their effort in understanding the transmission dynamics of tuberculosis and to control its transmission. From interactions with those scientists, mathematicians have developed a significant and effective tool, namely mathematical models of tuberculosis, giving an insight into the dynamics of communicable diseases effectively with the help of these mathematical models and provide useful information to the spread and how to control the communicable diseases. Mathematical modeling of the transmission dynamics of tuberculosis has flourished in 1962 by Waaler et al.[11].

From Waaler models, several models have been developed considering such as compartmental model for the TB disease [6], non-linear mathematical model TB with case detection and treatment [12], effect of vaccination and treatment on the spread of TB [18], effect of diabetes on the spread of TB [32], assess the impact of vaccination and effective contact rate in the spreads of TB [30] and global stability analysis TB infection with incomplete treatment [17]. Ullah et al. [13] also offered recent mathematical model on the transmission dynamics of tuberculosis in 2019. They verified their model with real data from Pakistan. But the authors do not considered optimal control intervention strategies. Hence, in this research we extend the mathematical model proposed in [13] by introducing optimal control function and studied both analytically and numerically with the help of Pontryagin's Maximum Principle. Then we apply our model to study the epidemic of tuberculosis in East Shewa zone Oromia regional state, Ethiopia.

1.5 Objective of the study

1.5.1 General objective

The general objective of this study is to investigate the transmission dynamics of tuberculosis(TB) using mathematical model with optimal control.

1.5.2 Specific objectives

The specific objectives of the study are to:

- Formulate an optimal control which describes the transmission dynamics of tuberculosis (TB).
- Perform parameter estimation.
- Propose an optimal control strategies that are used to minimize the epidemics of tuberculosis(TB).
- Investigate the existence of optimal controls.
- Establish characterization of optimal control.

1.6 Significant of the study

A deep knowledge on the epidemic of TB disease used to design appropriate control and prevention strategies in order to bring a long term solution. Thus, the outcome of this study are helpful to:

- predict the prevalence of TB infectious and to make precautionary measures.
- guide policy makers in making appropriate intervention on how to control and minimize the repercussion effect of TB infection.
- motivate other researchers for further study and mathematical analysis.

1.7 Mathematical Preliminary

In this section, we state some theorems and give the definitions of terminologies that provide the basic mathematical definitions and results, which are crucial for a better understanding for the thesis as an input. Detail about these technical terms can be found in[40]

1.7.1 Routh-Hurwitz criteria

The linear stability of a system of differential equations:

$$\frac{dX}{dt} = AX$$

where, $X = (x_1, x_2, ..., x_n)$ is determined by the roots of the polynomial(characteristic polynomial), A is the jacobian matrix of the linearized system. The solution of the system is obtained by setting $X = x_0 e^{\lambda t}$. Where x_0 is a constant vector to be determined λ is the eigenvalue value of A. The solution $X = x_0 e^{\lambda t}$ (the equilibrium point) is locally stable if all the roots of the characteristic polynomial:

$$P(\lambda) = \lambda^n + a_1\lambda^{n-1} + a_2\lambda^{n-2} + ... + a_{n-1}\lambda + a_n = 0$$

lie in the left hand complex plane that is $Re(\lambda) < 0$ for all roots λ of characteristic polynomial.

Now consider the polynomial

$$\lambda^n + a_1\lambda^{n-1} + a_2\lambda^{n-2} + ... + a_{n-1}\lambda + a_n = 0$$

where all the coefficients $a_1, a_2, ..., a_n$ are real and $a_n \neq 0$. The necessary and sufficient condition for all the roots of the characteristic polynomial equation to have $Re(\lambda <)0$ is the Routh-Hurwitz conditions[39]. These Routh-Hurwitz condition are with $a_n > 0$,

$$D_1 = a_1 > 0$$

$$\det(D_2) = \begin{vmatrix} a_1 & 1 \\ a_3 & a_2 \end{vmatrix} = a_1a_2 - a_3 > 0$$

$$\det(D_3) = \begin{vmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ 0 & 0 & a_3 \end{vmatrix} = a_1a_2a_3 - a_3^2 > 0$$

.

.

.

$$\det(D_n) = \begin{vmatrix} a_1 & a_3 & a_5 & . & . & . & \\ 1 & a_2 & a_4 & . & . & . & \\ 0 & a_1 & a_3 & . & . & . & \\ . & & & & & & \\ . & & & & & & \\ . & & & & & & \\ 0 & 0 & 0 & . & . & . & a_k \end{vmatrix} > 0, \text{for k =1, 2, 3, ... ,n.}$$

1.7.2 Numerical Methods for System of ODEs

Numerical techniques that listed below are summarized from[34]. When a system of ODEs involves equations that can not be solved analytically, numerical methods are used to compute its approximate solution. For example, fourth order Runge Kutta method (RK_4) is widely used for solving initial value problems (IVP) for ordinary differential equation(ODE) which is given by $\dot{x} = \frac{dx}{dt} = f(t, x), x(t_0) = x_0$ on the interval $t_0 \leq t \leq T$, we divide the interval into N small segments of constant length h, which is called the step size given by $h = \frac{T-t_0}{N}$. The numerical methods introduced for a single equation can be easily extended to systems of equations. For example, consider the system of Ordinary differential equation with initial condition.

$$\begin{cases} \frac{dx}{dt} = f(t, x, y), x(t_0) = x_0 \\ \frac{dy}{dt} = g(t, x, y), y(t_0) = y_0 \end{cases} \tag{1.1}$$

We want to obtain a numerical solution on the interval $t_0 \leq t \leq T$. The first step is discretizing the interval by defining the time steps given by

$$t_n = t_0 + nh, n = 0, 1, 2, ..., N$$

where N is the number of steps. Again we use the notation x_n and y_n to denote the approximate values of $x(t_n)$ and $y(t_n)$, respectively. We can summarize the numerical techniques as:
Euler's Method: Given a well-posed initial-value problem (IVP) for the above condition(1.1), Euler's method constructs a sequence of approximation points $(t, x) \approx (t, x(t))$ and $(t, y) \approx (t, y(t))$ to the exact solution of the ordinary differential equation by $t_{n+1} = t_n + h$ in order to obtain

$$\begin{cases} x_{n+1} = x_n + hf(t_n, x_n, y_n), \\ y_{n+1} = y_n + hf(t_n, x_n, y_n). \end{cases} \tag{1.2}$$

Runge-Kutta of Order Four: Given a well-posed initial-value problem (IVP) for the above condition(1.1), the Runge-Kutta method of order four (RK_4) constructs a sequence of approximation points $(t, x) \approx (t, x(t))$ and $(t, y) \approx (t, y(t))$ to the exact

solution of an ODE by $t_{n+1} = t_n + h$ to get the following values of eight slope:

$$\begin{cases} k_{11} = f(t_n, x_n, y_n) \\ k_{21} = f(t_n, x_n, y_n) \\ k_{12} = f(t_n + \frac{h}{2}, x_n + \frac{h}{2}k_{11}, y_n + \frac{h}{2}k_{21}) \\ k_{22} = f(t_n + \frac{h}{2}, x_n + \frac{h}{2}k_{11}, y_n + \frac{h}{2}k_{21}) \\ k_{13} = f(t_n + \frac{h}{2}, x_n + \frac{h}{2}k_{12}, y_n + \frac{h}{2}k_{22}) \\ k_{23} = f(t_n + \frac{h}{2}, x_n + \frac{h}{2}k_{12}, y_n + \frac{h}{2}k_{22}) \\ k_{14} = f(t_n + h, x_n + hk_{13}, y_n + hk_{23}) \\ k_{24} = f(t_n + h, x_n + hk_{13}, y_n + hk_{23}). \end{cases}$$

Then we compute the next approximation using weighted averages of the above slopes,

$$\begin{cases} x_{n+1} = x_n + \frac{h}{6}(k_{11} + 2k_{12} + 2k_{13} + k_{14}) \\ y_{n+1} = y_n + \frac{h}{6}(k_{21} + 2k_{22} + 2k_{23} + k_{24}). \end{cases} \tag{1.3}$$

In such process, the continuous time model is reduced to an approximate discrete time model that is amenable to computer simulation.

1.7.3 Autonomous Linear System

Consider a system of ordinary differential equation which are autonomous.

$$\begin{cases} \frac{dx}{dt} = f(x, y) \\ \frac{dy}{dt} = g(x, y) \end{cases} \tag{1.4}$$

The term autonomous refers to the fact that f and g are not trial function of t .

Local Stability

To determine the behavior near a critical point, we will linearize the non-linear system around the critical point and use our knowledge of linear systems. Let (x_0, y_0) be the equilibrium point of (1.4). If f and g are n-times continuously differentiable functions, then using the Taylor series expansion

$$\begin{aligned} f(x, y) =& f(x_0, y_0) + f_x(x_0, y_0)(x - x_0) + f_y(x_0, y_0)(y - y_0) + \frac{1}{2!}f_{xx}(x_0, y_0)(x - x_0)^2 + \\ & \frac{1}{2!}f_{yy}(x_0, y_0)(y - y_0)^2 + f_{xy}(x_0, y_0)(x - x_0)(y - y_0) + \dots \\ \approx& f(x_0, y_0) + f_x(x_0, y_0)(x - x_0) + f_y(x_0, y_0)(y - y_0) \\ =& f_x(x_0, y_0)(x - x_0) + f_y(x_0, y_0)(y - y_0) \end{aligned}$$

$$\begin{aligned} g(x,y) =& g(x_0,y_0) + g_x(x_0,y_0)(x-x_0) + g_y(x_0,y_0)(y-y_0) + \frac{1}{2!}g_{xx}(x_0,y_0)(x-x_0)^2 + \\ & \frac{1}{2!}g_{yy}(x_0,y_0)(y-y_0)^2 + g_{xy}(x_0,y_0)(x-x_0)(y-y_0) + \dots \\ \approx& g(x_0,y_0) + g_x(x_0,y_0)(x-x_0) + g_y(x_0,y_0)(y-y_0) \\ =& g_x(x_0,y_0)(x-x_0) + g_y(x_0,y_0)(y-y_0) \end{aligned}$$

Then, the linearized form of equation (1.4)can expressed as:

$$\frac{dX}{dt} = AX$$

Where $A = \begin{bmatrix} f_x & f_y \\ g_x & g_y \end{bmatrix}$, $x = \begin{bmatrix} x \\ y \end{bmatrix}$ and A is called the Jacobian matrix.
Let $x = ue^{\lambda t}$ be solution of the system of differential equation

$$\frac{dx}{dt} = Ax$$

where u is a vector to determined. Then

$$\frac{dx}{dt} = u\lambda e^{\lambda t} = \lambda x \Longrightarrow Ax = \lambda x \Longrightarrow x(A - \lambda I) = 0$$

The system will have a non-trival solution if $\det(x(A - \lambda I)) = 0$.
Consider a general autonomous vector field

$$\frac{dx}{dt} = f(x), x \in \mathbb{R}^n \tag{1.5}$$

where $f : \mathbb{R}^n \longrightarrow \mathbb{R}^n$

Definition 1. *(Equilibrium point) A point $x_e \in \mathbb{R}^n$ is an equilibrium point of the system (1.5) if $f(x_e) = 0$*

Definition 2. *(Stability) A point x_e is said to be stable for a given $\varepsilon > 0$, there exists a $\delta = \delta(\varepsilon) > 0$ such that, for any other solution, $y(t)$ of (1.5) satisfying $|x_e(t_0) - y(t_0)| < \delta$ implies $|x_e(t) - y(t)| < \varepsilon$, for $t > t_0$, $t_0 \in \mathbb{R}$*

Definition 3. *A point $x_e(t)$ is said to be locally asymptotically stable if it is Liapunov stable and for any other solution, $y(t)$ of (1.5), there exists a constant $b > 0$ such that if $|x_e(t_0) - y(t_0)| < b$, then $\lim_{t\to\infty}|x_e(t) - y(t)| = 0$ [57].*

Global Stability

A powerful method for analyzing the stability of an equilibrium point is based on the use of Lyapunov functions.

Definition 4. *A function $V: \mathbb{R}^n \to \mathbb{R}$ is said to be positive define if,*

- $V(x) > 0$, *for all* $x \neq 0$,
- $V(x) = 0$ *if and only if* $x = 0$,
- $V(x) \to \infty$ *as* $x \to \infty$

Any function V is called a Lyapunov function, if it satisfies the conditions of positive definite and $\frac{dV}{dt} \leq 0$, $\forall x \in D/\{x_0\}$.

Theorem 1.7.1. *Let* x_0 *be an equilibrium point of the system of (1.5) and consider* $V : D \in \mathbb{R}^n \to \mathbb{R}$ *be continuously differentiable function such that*

- $V(x_0) = 0$
- $V(x) > 0$ $\forall x \in D \subseteq R^n$
- $\dfrac{dV}{dt} < 0$ $\forall x \in D/\{x_0\}$, $\|x\| \to \infty \Longrightarrow V(x) \to \infty$

Then the point x_0 *is globally asymptotically stable.*

Definition 5. *(Invariant Set) A set E is an invariant set with respect to (1.5) if* $x(0) \in E$ *implies* $x(t) \in E$, $\forall t \in \mathbb{R}_+$ *and a set E is positively invariant set with respect to (1.5) if* $x(0) \in E$, *implies* $x(t) \in E$, $\forall t \geq 0$ *[57]*

1.8 Organization of the Thesis

The thesis is organized as follows: Some previous work is reviewed in chapter 2 and in chapter 3, we discussed about Methodology, as well as mathematical procedures. Similarly, in chapter 4, we presented model formulation and fundamental properties of the model. Chapter 5, is devoted to optimal control formulation and its analysis. In chapter 6, the detailed simulation result. Finally, we draw conclusion and reccomendation in chapter 7.

Chapter 2

Literature Review

In this chapter, we review some related literature on the dynamics of tuberculosis and its transmission that are directly related to the objectives of this study. The burden of tuberculosis(TB) is one of the major global health challenges throughout the worldwide. In 2018, as reported in[15] 10 million people fell ill with TB and 1.5 million died from the disease(including 251,000 among people with HIV). Globally, TB incidence is falling about 1% per year. In different time, many researchers develop different mathematical models of infectious disease especially for tuberculosis [14]. Mathematical models for transmission dynamics of tuberculosis are useful in providing better insights into the behavior of the disease. A number of studies have been conducted to emphasize the control of the disease and its dynamic by building different type of mathematical models as system of non-linear differential equations and are increasingly used to study the spread as well as control of infectious diseases [10].

Waaler et al. [11] introduced the first mathematical model of TB by dividing the whole population into three classes like susceptible, latent infected and infectious in 1962. Athithan and Mini Ghosh,[12] refine by using a non-linear mathematical model of tuberculosis with case detection and treatment is proposed and analyzed. Under their consideration the whole population is divided into four compartments such as susceptible, exposed or latent infected , infected and Recovered in order to study the transmission dynamics of the tuberculosis according to them. Based on the immunity level, susceptible individuals move to exposed class or directly to infected class once they come into contact with an infect. In the last few decades, several biologists and mathematicians have developed different epidemic models for the transmission dynamic of TB in different areas around the globe.

A tuberculosis(TB) model with relapse and reinfection is analyzed in [16]. The author review illustrate instances in which mathematical models were used to identify individuals with innate resistance to mycobacterium TB infection, determine the etiologic mechanism of tuberculosis in patients treated with tumor necrosis factor blockers, and predict the risk of relapse and re-infenction in persons undergoing tuberculosis treatment. These examples illustrate the power of various types of mathematical models to increase knowledge and there by inform interventions in the present global tuberculosis epidemic.

Yali Yang et al.[17] proposed two tuberculosis (TB) models with incomplete treatment are investigated. It is assumed that the treated individuals may enter either the latent compartment due to the remainder of Mycobacterium tuberculosis or the infec-

tious compartment due to the treatment failure. The first model is a simple one with treatment failure reflecting the current TB treatment fact in most countries with high tuberculosis incidence. The second model refines the simple one by dividing the latent compartment into slow and fast two kinds of progresses. This improvement can be used to describe the case that the latent TB individuals have been infected with some other chronic diseases (such as HIV and diabetes) which may weaken the immunity of infected individuals and shorten the latent period of TB. Both of the two models assume mass action incidence and exponential distributions of transfers between different compartments. The basic reproduction numbers of the two models are derived and their intuitive epidemiological interpretations are given. The global dynamics of model is proved by using Liapunov functions. At last, some strategies to control the spread of tuberculosis is discussed.

Liu and Zhang et al.[18] proposed a deterministic mathematical model which describes the effect of vaccination and treatment on the spreads of tuberculosis(TB). In their study, the analysis of the dependence of R_0 on the vaccination rate, vaccine efficacy and treatment rate shows that the spread of tuberculosis can be controlled if the vaccine rate or the efficacy rate or the treatment rate reaches a certain threshold. In their study they have shown that the basic reproduction number characterizes the disease transmission dynamics; that means if $R_0 < 1$, there exists only the disease-free equilibrium which is globally asymptotically stable, and if $R_0 > 1$ then there is a disease endemic equilibrium.

Silva and Torres [28] studied the optimal control of systems modeling the dynamics of tuberculosis applying time dependent control functions in the mathematical models, representing strategies for the improvement of the treatment and cure of active infectious and/or latent individuals. According to them the optimal control theory allows then to find the optimal way to implement the strategies, minimizing the number of infectious and/or latent individuals and keeping the cost of implementation as low as possible. They proposed an optimal control problem and solved, by illustrating the procedure and the simulations show an effective reduction in the number of infectious individuals.

Fatmawati and Ahmadin [19] proposed and analysis a mathematical modeling of TB transmission considering logistically growing human population. Their model incorporates TB prevention and ant-TB treatment efforts as control strategies to minimize the number of latent and infectious population. Additionally using pontryagin maximum principle, the optimal control theory is then deduced analytically. The disease free equilibrium is locally asymptotically stable if $R_0 < 1$ and the endemic equilibrium is locally asymptotically stable if $R_0 > 1$. According to them the simulation results of the optimal control indicate that the combination TB prevention and ant-TB treatment give better result in term minimizing the number of latent and infected population.

Rosa and Torres [29] described a caputo fractional order mathematical model for the transmission dynamics of tuberculosis. In their model, the sensitivity analysis has been done, showing the importance of accuracy of parameter values. A fractional optimal control problem is formulated and solved, with the rate of treatment as the control variable. Finally, a cost effectiveness analysis is performed to assess the cost and effectiveness of the control measures during the intervention, showing in which conditions a fractional optimal control problem is useful with respect to classical(integer-order) optimal control. The fractional model ($0 < \alpha < 1$) is recommended when treatment is expensive, it is more effective and not so costly as the classical model.

Parvaneh Esmaili et al.[45] studied a basic tuberculosis model using saturated incidence rate. Incorporated in the model is the therapeutic treatments given to infected individuals. In their model the stability of both the DFE and EE are determined by the threshold quantity according to the authors. Finally, they applied optimal control to their model, in order to show how the use of optimal control strategy will reduce the number of infectious individuals and the result is supported by numerical computations which show that the best strategy in curtailing the epidemics is to carry out the control program and awareness simultaneously.

Egonmwan and Okuonghae [35] proposed a new mathematical model that investigates the impact of diagnosis and treatment of both latent tuberculosis infections and active cases on the transmission dynamics of disease in population. Uncertainty and sensitivity analysis carried out to identify key parameters that have the greatest influence on the transmission dynamics of TB in the population using the reproduction number of the model, incidence of the disease and the total number of infected individuals in the various infective classes as out put responses. The stability of disease free equilibrium and endemic equilibrium is also carried out by using reproduction number. The simulations suggest that, with availability of treatment for both latent and active TB cases, increasing the fraction of latent TB cases that are diagnosed and treated will result in a reduction in the TB burden in the population.

Nkamba et al.[30] introduced the assess impact of vaccination in the spread of TB through a deterministic epidemic model and using the method of global Lyapunov functions, they have established the global stability results of equilibrium points and analyse the stability of epidemic system around the equilibrium (disease free and endemic) as well as the effective contact rate has a high impact in the spread of tuberculosis according to them. Because of this, a great role in the eradication of TB spreading is to reduce influence of effective contact rate.

Ullah et al.[5] studied mathematical model of a non-linear fractional order model in the Caputo sense to explore and simulate the transmission dynamics of TB. Using

the TB confirmed notified cases from the year 2002 to 2017 in Khyber Pakhtunkhwa, Pakistan. They estimated the model parameters and demonstrate that the proposed model provides a good fit to the real data. Initially, they compute the basic reproduction number and the model equilibria. Then, the existence and uniqueness of the model are manifested. Additionally, they explore the local and global stability of the disease free equilibrium point. Finally, the numerical results are obtained in order to verify the analytical results.

Maulana Malik et al.[32] introduced a mathematical model to describe the correlation between tuberculosis and diabetes in order to understand the effect of diabetes on the spread of TB. The idea is by dividing the population between those who have diabetes and who does not have diabetes according to them. From their model, they obtained the Basic Reproduction Number that becomes an indicator where TB can be endemic or not in a population. Through an analysis of the sensitivity of the basic reproduction number and numerical simulations, they were concluded that diabetes has a significant effect on the spread of tuberculosis (TB).

Theresia Shirima Sabini et al.[54], studied a recent deterministic mathematical model of the transmission dynamics of bovine tuberculosis in humans and animals. The basic reproduction number R_0 is computed to determine the behavior of the disease. For DFE and EE, stability analysis of the model coexist when $R_0 = 1$ according to their analysis. Also they performed the sensitivity analysis of their model. Their analysis shows that the rate at which dairy products are produced, the rate of transmission of bovine tuberculosis from animal to animal, and the rates at which human acquires bovine tuberculosis from infectious dairy products and animals drive the transmission of bovine tuberculosis. According to them, the disease decreases as the rate of consumption of dairy products decreases and to control bovine tuberculosis, education campaign, inspection of dairy products, treatment of infected humans, as well as quarantine of infected animals are recommended.

Ullah S. et al.[13], present a recent mathematical model on the dynamics of Tuberculosis (TB) in Khyber Pakhtunkhwa, province of Pakistan. The model is parameterized using TB infected cases reported from the year 2002 to 2017 in Khyber Pakhtunkhwa. The basic reproduction number R_0 for the given period is estimated. Mathematical analysis of the model in terms of stability analysis is derived and discussed in detail. The model at the disease free case is locally as well as globally asymptotically stable when the basic reproduction number $R_0 < 1$. Further, when the basic reproduction number $R_0 > 1$, then the model is stable locally as well as globally in case of endemic. Moreover, the sensitivity analysis of the model parameters are performed and their corresponding graphical results are presented by them. Finally, the numerical results for the sensitive parameters are plotted and their effects are shown on the disease elimination. But nothing has been said about optimal intervention strategies. This will be addressed in the present study.

Chapter 3

Research Methodology

In this chapter we present: study area, source of information, approach of study and mathematical procedures.

3.1 Study area

East Shewa is one of the Zones of Oromia regional state. It is located in the middle of Oromia, connecting the western regions to the eastern ones. This zone is bordered on the south by the west Arsi Zone, on the south west by the Southern Nations, Nationalities and People Regions, on the west by South west Shewa and Oromia Special Zone Surrounding Finfinne, on the North west by North Shewa, on the north by the Amhara Region, on the North east by the Afar Region,and on the south east by Arsi; its western most reach is defined by the course of the Bilate River. The town of Adama was separated from East Shewa and is a special zone now.

Adama city is the second largest city of Oromia region next to Finfine is located in East Shewa. It is located at 8.54°N 39.27°E with an elevation of 1712 meters and 99 km south east of Finfine. The city lies between the base of an escarpment to the west, and the Great Rift Valley to the east. Based on the 2007 census conducted by the Central Statistical Agency of Ethiopia (CSA), Adama city has a total population 220,212 and it has about 7,374.82[49] population density with a busy transportation and the road that connects Finfine to Dire Dawa pass through this city. Additionally, there is also land port of Ethiopia in Mojo and also the new Finfine Djibuti Rail-way runs through East Shewa.

Mojo is also a town in central Ethiopia, named after the near by Modjo River. It located in the East Shewa Zone with elevation between 1788 and 1825 meters above sea level. Based on the Central Statistical Agency in 2007, Mojo has an estimated total population of 29,547 of whom 14,278 were males and 15,269 were females[49]. Additionally, Batu is also another town and separate woreda in central Ethiopia. It is located on the road connecting Finfine to Nairobi in the East Shewa Zone of the Oromia Region of Ethiopia and has an elevation of 1,643 meters above sea level. Finally, as the 2007 national census reported, a total population for Batu of 43,660 of whom 22,956 were men and 20,704 were women[49].

Moreover, Bishoftu is a town and separate woreda of Ethiopia, lying south east of Finfine which is located in the East Shewa Zone of the Oromia Region, and has an elevation of 1,920 metres. According to the Nordic Africa Institute website, other major

businesses in Bishoftu include the Ada Flour and Pasta Factory, the Pasqua Giuseppe PLC, the Salmida Leather Products Manufacturing, Ratson (Women Youth Children Development Programme), and Winrock International Ethiopia. The Bishostu Research Center, founded in 1953, is run by the Ethiopian Institute of Agricultural Research, specializing in agricultural research, which includes acting as the national center for research to improve the yield of teff, lentils, chickpeas, and poultry. Irreechaa celebration and Ethiopian Airlines Flight 302 crashed near the town of this Bishoftu. The 2007 national census reported a total population for Bishoftu of 99,928, of whom 47,860 were men and 52,068 were women[49]. There are also many social institution and Agricultural farms in East Shewa such as Adama Science and Technology University, Oromia State University, Defence University, Industrial Park, non governmental college, Hotels, so on.

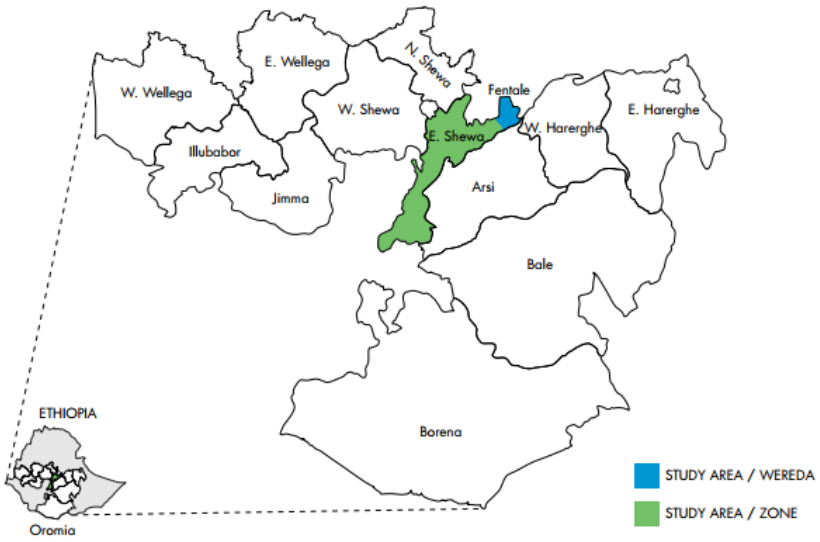


Figure 3.1: Maps of East Shewa zone in Oromia region[56]

Based on the 2007 census conducted by the Central Statistical Agency of Ethiopia(CSA), this Zone has a total population of 1,356,342, of whom 696,350 are men and 659,992 are women; with an area of 8,370.90 square kilo-meters; East Shewa has a population density of 162.03. The government of Ethiopia do not conducted census after 2007 and the existing population data are too old. This forced the researcher to collect estimated data from East Shewa zone for this research. According to East Shewa administrative zone, the current (2019) estimated total population in the zone is about 2,130,372 of which 1, 086,422 are men 1,043,950 are women. According to this estimation 19.9% are urban inhabitant. The living condition in the urban areas are over-crowded and thus we are initiated to study tuberculosis(TB) epidemic in East Shewa zone by collecting secondary data from Adama , Mojo, Batu and Bishoftu Health office.

3.2 Source of information

The applicable source of information for this study are:

- Data comprised a ten year cumulative data of TB infected people in East Shewa Zone: Particularly, Adama city, Mojo, Batu and Bishoftu town
- Other source of information are taken from WHO global report on tuberculosis(TB), books, published journals, and related studies from the Internet are used.

3.3 Descriptions of Mathematical Procedure

To achieve the objective of this research, we employ analytical and numerical method. First we briefly, study the well possedness of the original model both in the mathematical and epidemiological sense. We also perform the qualitative analysis of the model. Local and global stability analysis of the equilibrium points of the model is investigated by using Jacobian matrix and Lyapunov function respectively. Then the sensitivity of reproduction number with respect to model parameters are analyzed. Then we formulate an optimal control which describes the transmission dynamics of tuberculosis (TB) using a system of non-linear ordinary differential equations. The optimal control strategies are found by minimizing the number of infected population taking into account the cost of implementation. The existence of optimal controls and characterization is established using Pontryagin's Maximum Principle. To supplement the analytical solution of the model, we perform a numerical simulation of the model by using the method of Runge-Kutta fourth order. Furthermore, model parameters are fitted with real data collecting from East Shewa using Matlab to predict the prevalence of TB infectious and its optimal control strategies.

Chapter 4

Model Formulation and Analysis

4.1 Model Description

In this section, we present the description of a mathematical model for TB transmission with varying population size in homogeneously mixing population. The population is divided into five epidemiological sub-compartments such as:

S(t) susceptible individuals at any time t,
L(t) number of individuals which is not yet infectious at any time t,
I(t) number of TB active individuals at time t,
T(t) number of treated individuals at any time t,
R(t) Recovered individuals at any time t,
N(t) total population at time t,

where N(t) = S(T)+L(t)+I(t)+L(t)+R(t). Then the flow between the five sub-compartments is shown in the schematic diagram below:

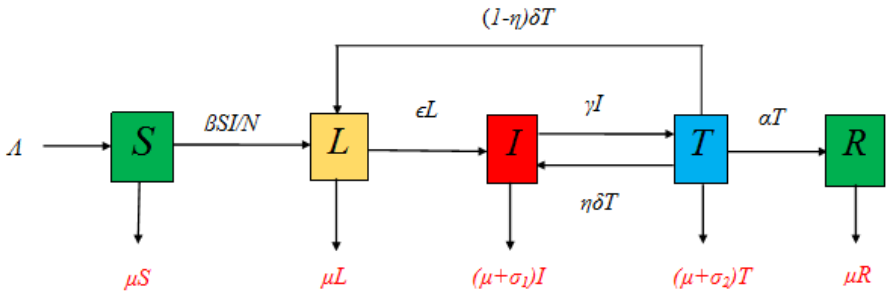


Figure 4.1: schematic diagram of TB model

The five boxes represent the five groups of individuals and the arrows show that the movement between groups, into as well as out of the population.

4.2 Model Formulation

The population is compartmentalized into the proportions of susceptible individuals S(t), exposed L(t), infected individuals I(t), under treatment T(t) and recovered individuals R(t). Thus, the following assumptions were made in the mathematical model:

- A number of susceptible population is increased by the recruitment of individuals into population at a constant rate Λ
- All individuals suffer from natural death, at a constant rate μ.

- Any susceptible class are infected when they come into effective contact with infectious class and the disease transmitted at rate β
- Susceptible (S) class gets infected is proportional to infectious class (I)
- A number of infected class people increases at a rate proportional to both the number of infectious class and the number of susceptible class
- The infectious class and treated class have additional death rate due to the disease with rate constants σ_1 and σ_2 respectively
- The infectious class individuals are treated with a constant rate γ, entering into the treatment class
- The treated individuals enter to either latent class due to the remainder of TB or infective class due to the failure of treatment at a constant rate δ
- The term $(1-\eta)\delta T$, where the parameter η reflects the treatment failure, further by considering $0 \leq \eta \leq 1$; that means, when $\eta = 0$ will mean that all the individuals under treatment become latent and when $\eta = 1$ mean that the failure of treatment and all the treated individuals will still be infectious.
- Treated individuals are recovered at a constant rate α. All parameters and state variables are in the model are assumed to be non-negative.

Table 1: Notations and description of the model parameters

Parameter	Description of the model parameter
Λ	Recruitment rate
β	Disease contact rate
α	Progression rate from compartment T to R
γ	Treatment rate from compartment I to T
μ	Natural death rate
σ_1	Disease related mortality rate of infected individuals
σ_2	Disease related mortality rate in T
δ	Rate at which treated individuals leave the T
η	Treatment failure rate
ϵ	Rate of moving from L to I

The above flow diagram can be written in the five system of non-linear differential equations such as:

$$\begin{cases} \frac{dS}{dt} = \Lambda - \frac{\beta SI}{N} - \mu S, \\ \frac{dL}{dt} = \frac{\beta SI}{N} - (\mu + \epsilon)L + (1-\eta)\delta T, \\ \frac{dI}{dt} = \epsilon L + \eta\delta T - (\mu + \gamma + \sigma_1)I, \\ \frac{dT}{dt} = \gamma I - (\mu + \delta + \sigma_2 + \alpha)T, \\ \frac{dR}{dt} = \alpha T - \mu R. \end{cases} \tag{4.1}$$

with initial condition : $S(0) = S_0 > 0$, $L(0) = L_0 \geq 0$, $I(0) = I_0 \geq 0$, $T(0) = T_0 \geq 0$, and $R(0) = R_0 \geq 0$.

4.3 Model Analysis

In this section, we investigate the invariant region, positivity, disease free-equilibrium, reproduction number, stability and sensitivity of the basic reproduction number.

4.3.1 Invariant Region

In this subsection, we study a region in which the feasible solution of the governing equation for the tuberculosis model is bounded. Summing the system of non-linear ordinary differential equation (4.1) we obtain

$$\frac{d}{dt}(S+L+I+T+R)(t) = \Lambda - \mu(S+L+I+T+R)(t) - \sigma_1 I(t) - \sigma_2 T(t) = \Lambda - \mu N(t) - \sigma_1 I(t) - \sigma_2 T(t)$$

Since σ_1 and σ_2 are non-negative, we have

$$\frac{dN(t)}{dt} = \Lambda - \mu N(t) - \sigma_1 I(t) - \sigma_2 T(t) \leq \Lambda - \mu N(t)$$

$$\dot{N}(t) + \mu N(t) \leq \Lambda$$

By integrating factor,

$$\frac{d}{dt}(N(t)e^{\mu t}) \leq \Lambda e^{\mu t} \tag{4.2}$$

Integrating both sides of the equation (4.2) and simplifying it, then we have

$$N(t) \leq \frac{\Lambda}{\mu} + N(0)e^{-\mu t} \tag{4.3}$$

where N(0) is obtain from initial condition and as $t \longrightarrow \infty$ in equation (4.3), the population size $N(t) \longrightarrow \frac{\Lambda}{\mu}$, which implies that $0 \leq N(t) \leq \frac{\Lambda}{\mu}$. Thus, the feasible region of the system (4.1)is given by the set

$$\Omega = \left\{ (S(t), L(t), I(t), T(t), R(t)) \in \mathbb{R}^5_+ : N(t) \leq \frac{\Lambda}{\mu}, S(t) > 0, L(t) \geq 0, I(t) \geq 0, T(t) \geq 0, R(t) \geq 0 \right\}$$

Hence, the system(4.1) is biologically meaningful and mathematically well-posed with in the domain given by the region Ω.

4.3.2 Boundedness, Existence and Positivity of Solution

In order to show that the model is biologically valid, it is required to prove that the solutions of the system of differential equations(4.1) are bounded, exist and positive for all time.

Lemma 4.3.2.1. *The solutions of the system of model equations (4.1) are bounded. That is , the model state variables S(t), L(t), I(t), T(t) and R(t) are bounded for all time t.*

Proof. Recall that each population size is bounded if and only if the total population size is bounded. Hence, in the present case it is sufficient to prove that the total population size N(t) = S(t)+L(t)+I(t)+T(t)+R(t) is bounded for all time t. It can be begun by showing that all feasible solutions are uniformly bounded in a proper subset $\Omega \subset \mathbb{R}^5_+$, where the feasible region Ω is given by $\Omega = \left\{(S(t), L(t), I(t), T(t), R(t)) \in \mathbb{R}^5_+ : N(t) \leq \frac{\Lambda}{\mu}\right\}$. Now, by summation of all the components of the model(4.1) gives:

$$\frac{dN(t)}{dt} = \Lambda - \mu N(t) - \sigma_1 I(t) - \sigma_2 T(t)$$

It can be expressed without loss of generality, after eliminating the negative term $-\sigma_1 I(t)$ and $-\sigma_2 T(t)$ which is appearing on the right hand side, as an inequality as $\frac{dN(t)}{dt} \leq \Lambda - \mu N(t)$. Equivalently this inequality can be expressed as a linear ordinary differential inequality as $\frac{dN(t)}{dt} + \mu N(t) \leq \Lambda$ giving general solution upon solving as $N(t) \leq \frac{\Lambda}{\mu} + N(0)e^{-\mu t}$, where N(0) obtain from initial condition. Further, it can be observed that $N(t) \longrightarrow \frac{\Lambda}{\mu}$ as $t \longrightarrow \infty$. That is, the total population size N(t) takes off from the value N(0) at the initial time t = 0 and ends up with the bounded value $\frac{\Lambda}{\mu}$ as the time t grows to infinity. Thus it can be concluded that N(t) is bounded as $0 \leq N(t) \leq \frac{\Lambda}{\mu}$. Therefore, $\frac{\Lambda}{\mu}$ is an upper bound of N(t). Hence, feasible solution of the system of model equations (4.1) remains in the region Ω which is positively invariant set. Thus, the system is biologically meaningful and mathematically well posed in the domain Ω. Further, it is sufficient to consider the dynamics of the populations represented by the model system (4.1) in that domain. Therefore, the TB model variables S(t), L(t), I(t), T(t) and R(t) are bounded for all time t. □

Existence and Uniqueness of Solution: The validity and authenticity of any mathematical model depends on whether the given system of equations has a solution, and if the solution is unique. We shall use the Lipchitz condition to verify the existence and uniqueness of solution for the given system of equations. We consider the system of linear equations below:

$$\dot{x} = f(t, x), x(t_0) = x_0 \tag{4.4}$$

Theorem 4.3.1. *(Derrick and Grossman,1976) :*

Let D denote the region $|t - t_0| \leq a$, $|x - x_0| \leq b$, $x = (x_1, x_2, ..., x_n)$, $x_0 = (x_{10}, x_{20}, ..., x_{n0})$ and suppose that $f(t, x)$ satisfies the lipschitz condition

$$|f(t, x_1) - f(t, x_2)| \leq K|x_1 - x_2| \tag{4.5}$$

whenever the pairs (t, x_1) and (t, x_2) belong to D, where K is a positive constant. Then, there is a constant $\delta > 0$ such that there exists a unique continuous vector solution $x(t)$ of the system (4.4) in the interval $|t - t_0| \leq \delta$, where δ is a positive constant. It is important to note that condition (4.5) is satisfied by the requirement that
$\frac{\partial f_i}{\partial x_j}$, i,j = 1,2,...,n are continuous and bounded in D.
This means that we look for a bounded solution of the form $0 < R < \infty$ for exists of unique solution of equation(4.4) in the region D. This is called uniqueness of the solution for the system of equations(4.1).

Lemma 4.3.2.2. *Solutions of the model equations (4.1) together with the initial conditions $S(0) > 0, L(0) \geq 0, I(0) \geq 0, T(0) \geq 0, R(0) \geq 0$ exist in $\mathbb{R}^5_+$; that means the model of state variables S(t), L(t), I(t), T(t) and R(t) exist for all time t and will remain in $\mathbb{R}^5_+$*

Proof. The right hand sides of the system of equations (4.1) can be expressed as follows:
$f_1(S, L, I, T, R) = \Lambda - \frac{\beta SI}{N} - \mu S,$
$f_2(S, L, I, T, R) = \frac{\beta SI}{N} - (\mu + \epsilon)L + (1 - \eta)\delta T,$
$f_3(S, L, I, T, R) = \epsilon L + \eta\delta T - (\mu + \gamma + \sigma_1)I,$
$f_4(S, L, I, T, R) = \gamma I - (\mu + \delta + \sigma_2 + \alpha)T,$
$f_5(S, L, I, T, R) = \alpha T - \mu R.$
According to Derrick and Groosman theorem, let Ω denote the region

$$\Omega = \left\{ (S(t), L(t), I(t), T(t), R(t)) \in \mathbb{R}^5_+ : N(t) \leq \frac{\Lambda}{\mu} \right\}.$$

Then equations (4.1) have a unique solution if $\frac{\partial f_i}{\partial x_j}, i,\ j = 1, 2, 3 \ldots 5$, are continuous and bounded in Ω. Here, using notations $x_1 = S, x_2 = L, x_3 = I, x_4 = T, x_5 = R$, continuity and the boundedness is verified here under the following:
For f_1:
$|\frac{\partial f_1}{\partial S}| = |-(\frac{\beta I}{N} + \mu)| < \infty$, $|\frac{\partial f_1}{\partial L}| = 0 < \infty$, $|\frac{\partial f_1}{\partial I}| = |-(\frac{\beta S}{N})| < \infty$, $|\frac{\partial f_1}{\partial T}| = 0 < \infty$, and $|\frac{\partial f_1}{\partial R}| = 0 < \infty$
For f_2:
$|\frac{\partial f_2}{\partial S}| = |\frac{\beta I}{N}| < \infty$, $|\frac{\partial f_2}{\partial L}| = |-(\mu + \epsilon)| < \infty$, $|\frac{\partial f_2}{\partial I}| = |\frac{\beta S}{N}| < \infty$, $|\frac{\partial f_2}{\partial T}| = |(1 - \eta)\delta| < \infty$ and $|\frac{\partial f_2}{\partial R}| = 0 < \infty$
For f_3:
$|\frac{\partial f_3}{\partial S}| = 0 < \infty$, $|\frac{\partial f_3}{\partial L}| = |\epsilon| < \infty$, $|\frac{\partial f_3}{\partial I}| = |-(\mu + \gamma + \sigma_1)| < \infty$, $|\frac{\partial f_3}{\partial T}| = |\eta\delta| < \infty$, and $|\frac{\partial f_3}{\partial R}| = 0 < \infty$
For f_4:
$|\frac{\partial f_4}{\partial S}| = 0 < \infty$, $|\frac{\partial f_4}{\partial L}| = 0 < \infty$, $|\frac{\partial f_4}{\partial I}| = |\gamma| < \infty$, $|\frac{\partial f_4}{\partial T}| = |-(\mu + \delta + \sigma_2 + \alpha)| < \infty$, and $|\frac{\partial f_4}{\partial R}| = 0 < \infty$
For f_5:
$|\frac{\partial f_5}{\partial S}| = 0 < \infty$, $|\frac{\partial f_5}{\partial L}| = 0 < \infty$, $|\frac{\partial f_5}{\partial I}| = 0 < \infty$, $|\frac{\partial f_5}{\partial T}| = |\alpha| < \infty$, and $|\frac{\partial f_5}{\partial R}| = |-\mu| < \infty$.
Thus, all the partial derivatives $\frac{\partial f_i}{\partial x_j}, i,\ j = 1, 2, \ldots 5$, exist, continuous and bounded in Ω. Hence, by theorem of Lipchitz condition, the model (4.1) has a unique solution.
□

Positivity: It is necessary to prove that all solutions of system with positive initial data remain positive for all time $t \geq 0$ that is for the TB infection model (4.1) to be

epidemiological meaningful and well-posed, we need to prove that all state variables are non-negative for all time $t \geq 0$.

Lemma 4.3.2.3. *If S(0), L(0), I(0), T(0) and R(0) are all non-negative, then the solutions S(t), L(t), I(t), T(t), and R(t) are all positive for* $t \geq 0$.

Proof. From the system of differential equation (4.1), let us take the first equation:

$$\frac{dS(t)}{dt} = \Lambda - \frac{\beta I(t)}{N(t)} S(t) - \mu S(t) \tag{4.6}$$

This equation can be expressed without loss of generality, after eliminating the positive term (Λ), as an inequality as $\frac{dS(t)}{dt} \geq -(\frac{\beta}{N} I(t) + \mu) S(t)$; then using separable method of variables and applying integration, the solution of the foregoing differentially inequality can be obtained as $S(t) \geq S(0) e^{-\mu t - \frac{\beta}{N} \int I(t) dt}$, where S(0) is obtain from initial condition. Since exponential function is always non-negative irrespective of the sign of the exponent, the function $e^{-\mu t - \frac{\beta}{N} \int I(t) dt}$ is a non-negative quantity. Hence, we can concluded that $S(t) \geq 0$.
Positivity of L(t): Similarly, the TB model of second equation for the system (4.1) given by $\frac{dL}{dt} = \frac{\beta SI}{N} - (\mu + \epsilon) L + (1 - \eta) \delta T$ can be expressed without loss of generality, after eliminating the positive term $\frac{\beta SI}{N}$ and $(1 - \eta) \delta T$ as an inequality as $\frac{dL}{dt} \geq -(\mu + \epsilon) L(t)$. Using separable method of variables and on applying integration, the solution of the foregoing differentially inequality can be obtained as $L(t) \geq L(0) e^{-(\mu + \epsilon) t}$, where L(0) is obtain from initial condition. Recall that an exponential function is always non-negative irrespective of the sign of the exponent, i.e, the exponential function $e^{-(\mu + \epsilon) t}$ is a non-negative quantity. Hence, we can concluded that $L(t) \geq 0$. With the similar fashion, we show that the remaining all state variables are non-negative. This proves that the solution of system (4.1) are positive for all $t > 0$. Thus, the model is well-posed both mathematical and epidemiological in Ω
. Positivity of I(t): The model equation (4.1) given by $\frac{dI}{dt} = \epsilon L + \eta \delta T - (\mu + \gamma + \sigma_1) I$ can be expressed without loss of generality, after eliminating the positive term ϵL and $\eta \delta T$ which are appearing on the right hand side, as an inequality as $\frac{dI}{dt} \geq -(\mu + \gamma + \sigma_1) I$. Using separable method of variables and on applying integration, the solution of the foregoing differentially inequality can be obtained as $I(t) \geq I(0) e^{-(\mu + \gamma + \sigma_1) t}$, where I(0) is obtained from initial condition. Recall that an exponential function is always non-negative irrespective of the sign of the exponent, i.e, the exponential function $e^{-(\mu + \gamma + \sigma_1) t}$ is a non-negative quantity. Hence, we can concluded that $I(t) \geq 0$.
Positivity of T(t): The model equation (4.1) given by $\frac{dT}{dt} = \gamma I - (\mu + \delta + \sigma_2 + \alpha) T$ can be expressed without loss of generality, after eliminating the positive term γI which are appearing on the right hand side, as an inequality as $\frac{dT}{dt} \geq -(\mu + \delta + \sigma_2 + \alpha) T$. Using separable method of variables and on applying integration, the solution of the foregoing differentially inequality can be obtained as $T(t) \geq T(0) e^{-(\mu + \delta + \sigma_2 + \alpha) t}$, where T(0) is obtained from initial condition. Recall that an exponential function is always non-negative irrespective of the sign of the exponent, i.e, the exponential function $e^{-(\mu + \delta + \sigma_2 + \alpha) t}$ is a non-negative quantity. Hence, we can concluded that $T(t) \geq 0$.
Positivity of R(t): The model equation (4.1) given by $\frac{dR}{dt} = \alpha T - \mu R$ can be expressed without loss of generality, after eliminating the positive term αT which are appearing on the right hand side, as an inequality as $\frac{dR}{dt} \geq -\mu R$. Using separable method of variables and on applying integration, the solution of the foregoing differentially inequality

can be obtained as $R(t) \geq R(0)e^{-\mu t}$, where R(0) is obtained from initial condition. Recall that an exponential function is always non-negative irrespective of the sign of the exponent, i.e, the exponential function $e^{-\mu t}$ is a non-negative quantity. Hence, we can concluded that $R(t) \geq 0$. Thus, the model variables S(t), L(t), I(t), T(t) and R(t) representing population sizes of various types of cells are positive quantities and will remain in $\mathbb{R}^5_+$ for all time t. □

4.3.3 Disease free Equilibrium Point

Disease free equilibrium points are steady-state solutions where there is no tuberculosis (TB) infection. That is, all the infected classes are zero and the entire population comprise of only susceptible individuals. To find the disease free equilibrium (DFE), we equate the left hand side of model (4.1) equal to zero, evaluating it at $L = 0$ and $I = 0$ and solving for the non-infected state variable. Equating equation (4.1) equal to zero, we have that:

$$\begin{cases} \Lambda - \frac{\beta SI}{N} - \mu S = 0, \ S \neq o \\ \frac{\beta SI}{N} - (\mu + \epsilon)L + (1 - \eta)\delta T = 0, \ L = 0 \\ \epsilon L + \eta\delta T - (\mu + \gamma + \sigma_1)I = 0, \ I = 0 \\ \gamma I - (\mu + \delta + \sigma_2 + \alpha)T = 0, \ T = 0 \\ \alpha T - \mu R = 0, \ R = 0 \end{cases}$$

Solving these equation, the disease free equilibrium is $E_0 = (\frac{\Lambda}{\mu}, 0, 0, 0, 0)$

4.3.4 Basic Reproduction number

The basic reproduction number has the key role in the disease modeling and intuitively from epidemiological point of view, the basic reproduction number, which is denoted by (R_0), is the average number of new cases (infections), that one infected case will generate during its entire infectious lifetime. It is very important in determining whether the global dynamics of the disease can be spread or not. When the value of the basic reproduction number falls less than unity, then the disease will not be spread in the community, whereas, when its values cross the unity, then the disease can be spread in the community i.e., the disease becomes endemic and will produce deaths and sometimes outbreak which is called epidemics. In epidemiology, the epidemic is expected to be eliminated if $R_0 < 1$, and persists if $R_0 > 1$. Therefore, the basic reproduction number is a threshold parameter for a disease and its biological significance is obvious. We use the next generation method given in [38] to compute R_0.
Let us assume that there are n compartments of which the m compartments correspond to infected individuals. In order to compute R_0, it is important to distinguish new infections from all other changes in population.

- $f_i(x)$ be the rate of appearance of new infections in compartment i,
- $\nu_i^+(x)$ be the rate of transfer of individuals into compartment i by all others means
- $\nu_i^-(x)$ be the rate of transfer of individuals out of compartment i.

It is assumed that each function is continuously differentiable at least twice in each variable. The disease transmission model consists of nonnegative initial conditions together with the following system of equations:

$$\frac{dx_i}{dt} = f_i(x) - \nu_i(x),\ i = 1, 2, ..., n \tag{4.7}$$

where $\nu_i(x) = \nu_i^-(x) - \nu_i^+(x)$

The next step is the computation of the square matrices F and V of order $m \times m$, where m is the number of infected class, defined by: $F = [\frac{\partial f_i(x_0)}{\partial x_j}]$ and $V = [\frac{\partial \nu_i(x_0)}{\partial x_j}]$,

where $f(x) = \begin{bmatrix} \frac{\beta SI}{N} \\ 0 \\ 0 \end{bmatrix}$ and $\nu(x) = \begin{bmatrix} k_1 L - (1-\eta)\delta T \\ k_2 I - \epsilon L - \eta\delta T \\ k_3 T - \gamma I \end{bmatrix}$, with $1 \leq i$, $j \leq m$

such that F is non negative, V is non singular matrix and E_0 is the disease free equilibrium point. Now, the jacobian matrices of $f(x)$ and $\nu(x)$ at the disease-free equilibrium E_0 are:

$$Df(E_0) = \begin{pmatrix} 0 & \frac{\beta S_0}{N} & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix},\ and\ D\nu(E_0) = \begin{pmatrix} k_1 & 0 & -(1-\eta)\delta \\ -\epsilon & k_2 & -\eta\delta \\ 0 & -\gamma & k_3 \end{pmatrix}\ respectively.$$

The linearization approach of the system (4.1) associated with matrix F and V at DFE point E_0 is given by

$$F = \begin{pmatrix} 0 & \beta & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix},\ and\ V = \begin{pmatrix} k_1 & 0 & -(1-\eta)\delta \\ -\epsilon & k_2 & -\eta\delta \\ 0 & -\gamma & k_3 \end{pmatrix}\ respectively.$$

where $k_1 = (\mu + \epsilon)$, $k_2 = (\mu + \gamma + \sigma_1)$, $k_3 = (\mu + \delta + \sigma_2 + \alpha)$; then we denote the determinant of V by $det(V) = k_1(k_2k_3 - \eta\delta\gamma) - (1-\eta)\delta\gamma\epsilon$.

$$V^{-1} = \begin{pmatrix} \frac{k_2k_3 - \eta\delta\gamma}{det(V)} & \frac{(1-\eta)\delta\gamma}{det(V)} & \frac{(1-\eta)\delta k_2}{det(V)} \\ \frac{\epsilon k_3}{det(V)} & \frac{k_1k_2}{det(V)} & \frac{(1-\eta)\delta\epsilon + \eta\delta k_1}{det(V)} \\ \frac{\epsilon\gamma}{det(V)} & \frac{k_1\gamma}{det(V)} & \frac{k_1k_2}{det(V)} \end{pmatrix},\ and\ M = FV^{-1} = \begin{pmatrix} \frac{\beta\epsilon k_3}{det(V)} & \frac{\beta k_1k_3}{det(V)} & \frac{\beta\delta(1-\eta) + \eta k_1}{det(V)} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

Since F is non-negative and V is non-singular, then V^{-1} is non-negative and FV^{-1} is non-negative. Hence, the matrix M is called next generation matrix for the model. From this matrix, we determine the value of an eigenvalues of the coefficient matrix M or FV^{-1}. Hence, $\det(FV^{-1}-\lambda I)=\left|FV^{-1}-\lambda I\right|=0$. This implies that

$\begin{vmatrix} \frac{\beta\epsilon k_3}{k_1k_2k_3-\eta\delta\gamma k_1-(1-\eta)\delta\gamma\epsilon}-\lambda & \frac{\beta k_1k_3}{k_1k_2k_3-\eta\delta\gamma k_1-(1-\eta)\delta\gamma\epsilon} & \frac{\beta\delta(1-\eta)+\eta k_1}{k_1k_2k_3-\eta\delta\gamma k_1-(1-\eta)\delta\gamma\epsilon} \\ 0 & 0-\lambda & 0 \\ 0 & 0 & 0-\lambda \end{vmatrix}=0$. From this we obtain

$\left|FV^{-1}-\lambda\right|=\left(\frac{\beta\epsilon k_3}{k_1k_2k_3-\eta\delta\gamma k_1-(1-\eta)\delta\gamma\epsilon}-\lambda\right)\lambda^2=0$. This show that

$\frac{\beta\epsilon k_3}{k_1k_2k_3-\eta\delta\gamma k_1-(1-\eta)\delta\gamma\epsilon}\lambda^2=\lambda^3$

Hence, by cancelling λ^2 on both sides and solving we obtain, $\lambda=\frac{\beta\epsilon k_3}{k_1k_2k_3-\eta\delta\gamma k_1-(1-\eta)\delta\gamma\epsilon}$

Thus, the reproduction number is given by the spectral radius of FV^{-1} that is $R_0=\lambda=\frac{\beta\epsilon k_3}{k_1k_2k_3-\eta\delta\gamma k_1-(1-\eta)\delta\gamma\epsilon}$. Then $\rho(M)$ denotes the spectral radius of a matrix M which is the biggest non-negative eigenvalue of the next generation matrix.

Therefore, $R_0=\frac{\beta\epsilon k_3}{k_1k_2k_3-\eta\delta\gamma k_1-(1-\eta)\delta\gamma\epsilon}$

4.4 Stability analysis of disease free equilibrium

The model (4.1) has a unique disease free equilibrium (DFE), E_0, given by $E_0=(S^0,0,0,0,0)$, where $S^0=\frac{\Lambda}{\mu}$

4.4.1 Local stability of disease free equilibrium

Theorem 4.4.1. *The disease-free equilibrium $E_0=(\frac{\Lambda}{\mu},0,0,0,0)$ of the system (4.1) is locally asymptotically stable if $R_0<1$*

Proof. By considering the linearized system of the governing equation (4.1), we have

$$J(S,L,I,T,R)=\begin{pmatrix} \frac{-\beta I}{N}-\mu & 0 & \frac{-\beta S}{N} & 0 & 0 \\ \frac{\beta I}{N} & -(\mu+\epsilon) & \frac{\beta S}{N} & (1-\eta)\delta & 0 \\ 0 & \epsilon & -(\mu+\gamma+\sigma_1) & \eta\delta & 0 \\ 0 & 0 & \gamma & -(\mu+\delta+\sigma_2+\alpha) & 0 \\ 0 & 0 & 0 & \alpha & -\mu \end{pmatrix}.$$

Therefore, the Jacobian matrix J of model at the disease free equilibrium E_0 reduces to

$$J(E_0)=\begin{pmatrix} -\mu & 0 & -\beta & 0 & 0 \\ 0 & -k_1 & \beta & (1-\eta)\delta & 0 \\ 0 & \epsilon & -k_2 & \eta\delta & 0 \\ 0 & 0 & \gamma & -k_3 & 0 \\ 0 & 0 & 0 & \alpha & -\mu \end{pmatrix} \tag{4.8}$$

where $k_1 = (\mu + \epsilon)$, $k_2 = (\mu + \gamma + \sigma_1)$ and $k_3 = (\mu + \delta + \sigma_2 + \alpha)$.
The eigenvalues of equation (4.8) are the solutions of the characteristics equation

$$|J(E_0) - \lambda I_5| = 0$$

, where I_5 is the identity matrix of order 5. Then we have

$$|J(E_0) - \lambda I_5| = \begin{vmatrix} -\mu - \lambda & 0 & -\beta & 0 & 0 \\ 0 & -k_1 - \lambda & \beta & (1-\eta)\delta & 0 \\ 0 & \epsilon & -k_2 - \lambda & \eta\delta & 0 \\ 0 & 0 & \gamma & -k_3 - \lambda & 0 \\ 0 & 0 & 0 & \alpha & -\mu - \lambda \end{vmatrix} = 0.$$

This implies that

$$|J(E_0) - \lambda I_5| = -(\mu + \lambda) \begin{vmatrix} -k_1 - \lambda & \beta & (1-\eta)\delta & 0 \\ \epsilon & -k_2 - \lambda & \eta\delta & 0 \\ 0 & \gamma & -k_3 - \lambda & 0 \\ 0 & 0 & \alpha & -\mu - \lambda \end{vmatrix}$$

$$= (\mu + \lambda)^2 \begin{vmatrix} -k_1 - \lambda & \beta & (1-\eta)\delta \\ \epsilon & -k_2 - \lambda & \eta\delta \\ 0 & \gamma & -k_3 - \lambda \end{vmatrix} = 0. \tag{4.9}$$

It follows that the characteristic equation computed from equation (4.9) is given by

$$(\mu + \lambda)^2[\lambda^3 + (k_1 + k_2 + k_3)\lambda^2 + (k_1k_2 + k_1k_3 + k_2k_3 - \eta\delta\gamma - \epsilon\beta)\lambda + (k_1k_2k_3 - k_1\eta\delta\gamma - (1-\eta)\delta\gamma\epsilon - \epsilon\beta k_3)] = 0$$

which equivalent to

$$(\mu + \lambda)^2 = 0 \text{ and } \lambda^3 + (k_1 + k_2 + k_3)\lambda^2 + (k_1k_2 + k_1k_3 + k_2k_3 - \eta\delta\gamma - \epsilon\beta)\lambda + (k_1k_2k_3 - k_1\eta\delta\gamma - (1-\eta)\delta\gamma\epsilon - \epsilon\beta k_3) = 0$$

We can write the characteristic equation as $\lambda_1 = \lambda_2 = -\mu$ and $\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0$, where $a_1 = k_1 + k_2 + k_3$,
$a_2 = k_1k_2 + k_1k_3 + k_2k_3 - \eta\delta\gamma - \epsilon\beta$,
$a_3 = k_1k_2k_3 - k_1\eta\delta\gamma - (1-\eta)\delta\gamma\epsilon - \epsilon\beta k_3$.
It can be observed that the first two eigenvalues λ_1 and λ_2 are absolutely negative quantities since the parameter is always positive. Hence, λ_1 and λ_2 are stable. consider the following characteristic equation:

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0 \tag{4.10}$$

Using the Routh-Hurwith criteria [39], it can be observed that all the eigenvalues of the characteristic equation (4.10) have negative real part if $a_1 > 0$, $a_2 > 0$, $a_3 > 0$ and $a_1a_2 - a_3 > 0$. We can see that a_1 is positive becuase of all parameters are positive and their sum is also positive. But in order to say a_2 to be positive, $k_1k_2 + k_1k_3 + k_2k_3 - \eta\delta\gamma - \epsilon\beta$ must be positive. Hence, $a_2 > 0$ if it fulfill that $k_1k_2 + (k_1 + k_2)k_3 > \eta\delta\gamma + \epsilon\beta$. Additionally, $a_1a_2 - a_3 > 0$. This is the same as $a_1a_2 > a_3$. From Routh-Hurwitz criterion, it follows that $a_3 > 0$
$a_3 = k_1k_2k_3 - k_1\eta\delta\gamma - (1-\eta)\delta\gamma\epsilon - \epsilon\beta k_3 > 0$.
From this we get $k_1k_2k_3 - k_1\eta\delta\gamma - (1-\eta)\delta\gamma\epsilon > \epsilon\beta k_3$ and then dividing both sides by $k_1k_2k_3 - k_1\eta\delta\gamma - (1-\eta)\delta\gamma\epsilon$ to get $1 > \frac{\epsilon\beta k_3}{k_1k_2k_3 - k_1\eta\delta\gamma - (1-\eta)\delta\gamma\epsilon}$ which demonstrate that

$1 > R_0$. This implies that $a_3 > 0$ for $R_0 < 1$. Therefore, we can concluded that the disease free equilibrium point of the system(4.1)is locally asymptotically stable if $R_0 < 1$. □

4.4.2 Global stability of disease free equilibrium

Theorem 4.4.2. *The disease free equilibrium of system (4.1) is globally asymptotically stable if* $R_0 < 1$.

Proof. To proof the global stability of the disease-free equilibrium, first we construct a Lyapunov function: $V(S, L, I, T, R) : \mathbb{R}^5_+ \longrightarrow \mathbb{R}^+$ defined as
$V(S, L, I, T, R) = A_1L + A_2I + A_3T$, where A_i, for i = 1, 2, 3, are some positive constants. The Lyapunov function V is continuously differentiable.

- $V(E_0) = 0$
- $V(S, L, I, T, R) > 0$, $\forall (S, L, I, T, R) \in \mathbb{R}^5_+ - \{E_0\}$

Now differentiating V(S,L,I,T,R) with respect to time we obtain $\frac{dV}{dt} = A_1\frac{dL}{dt} + A_2\frac{dI}{dt} + A_3\frac{dT}{dt}$
$= A_1[\frac{\beta SI}{N} - k_1L + (1-\eta)\delta T] + A_2[\epsilon L + \eta\delta T - k_2I] + A_3[\gamma I - k_3T]$
$\leq A_1[\beta I - k_1L + (1-\eta)\delta T] + A_2[\epsilon L + \eta\delta T - k_2I] + A_3[\gamma I - k_3T]$, since $S \leq N$
$=[A_1\beta + A_3\gamma - A_2k_2]I + [A_2\epsilon - A_1k_1]L + [A_1(1-\eta)\delta + A_2\eta\delta - A_3k_3]T$
$\leq A_2k_2\left(\frac{A_1\beta+\gamma A_3}{A_2k_2} - 1\right)I + (A_2\epsilon - k_1A_1)L + ((1-\eta)\delta A_1 + \eta\delta A_2 - k_3A_3)\,T$

Now choosing $A_1 = \frac{\epsilon k_3}{k_1}$, $A_2 = k_3$ and $A_3 = \frac{(1-\eta)\delta\epsilon+\eta\delta k_1}{k_1}$; then we have
$\frac{dV}{dt} = \frac{1}{k_1}(\epsilon\beta k_3 + (1-\eta)\delta\gamma\epsilon + \eta\delta\gamma k_1 - k_1k_2k_3)I$
$\frac{dV}{dt} = \frac{1}{k_1}(\frac{\epsilon\beta k_3}{k_1k_2k_3 - \eta\delta\gamma k_1 - (1-\eta)\delta\gamma\epsilon} - 1)I$. This implies that

$$\frac{dV}{dt} \leq \frac{1}{k_1}(R_0 - 1)I$$

Hence, if $R_0 < 1$, then $\frac{dV}{dt}$ is negative. Therefore, the largest compact invariant set in Ω is the singleton set $(\frac{\Lambda}{\mu}, 0, 0, 0, 0)$. Hence, by LaSalle's invariant principle [40], every solution to equations of model (4.1) with initial conditions in Ω which approaches the disease-free equilibrium point as time t tends to infinity ($t \longrightarrow \infty$) whenever $R_0 < 1$. This implies that the disease-free equilibrium is globally asymptotically stable in Ω. □

4.5 Stability analysis of Endemic Equilibrium

The endemic equilibrium point which denoted by E^* is a steady state solution where the disease persists in the population. For the existence of endemic equilibrium $E^* = (S^*, L^*, I^*, T^*, R^*)$, in the context of this thesis is equivalent to the endemic of tuberculosis in the population and it is obtained by setting rates of changes of variables with respect to time in the model equation (4.1) to zero. Then solving the system of

differential equation simultaneously, we obtain

$$
\begin{aligned}
S^* &= \frac{N^*}{R_0},\\
L^* &= \frac{((\mu+\sigma_1)+\gamma(\mu+\sigma_2\alpha)+\gamma\delta(1-\eta)(R_0-1)}{R_0\{(\mu+\sigma_1)+\gamma(\mu+\sigma_2+\alpha)\delta\gamma(1-\eta)+\epsilon(\gamma+k_3)\}},\\
I^* &= \frac{\epsilon k_3 N^*(R_0-1)}{R_0\{(\mu+\sigma_1)+\gamma(\mu+\sigma_2+\alpha)\delta\gamma(1-\eta)+\epsilon(\gamma+k_3)\}},\\
T^* &= \frac{\epsilon\gamma N^*(R_0-1)}{R_0\{(\mu+\sigma_1)+\gamma(\mu+\sigma_2+\alpha)\delta\gamma(1-\eta)+\epsilon(\gamma+k_3)\}},\\
R^* &= \frac{\alpha T^*}{\mu}.
\end{aligned}
$$

Therefore, system (4.1) has a unique endemic equilibrium whenever $R_0 > 1$.

4.5.1 Local stability of Endemic equilibrium (EE)

Theorem 4.5.1. *The Endemic equilibrium (EE) of system (4.1) at E^* is locally asymptotically stable if $R_0 > 1$.*

Proof. The Jacobian matrix J_{E^*} of the system (4.1) around the EE, E^* is obtained by

$$
J|_{E^*} = \begin{pmatrix}
-\frac{I^*(N^*-S^*)\beta}{N^{*2}} - \mu & \frac{I^*S^*\beta}{N^{*2}} & -\frac{(N^*-I^*)S^*\beta}{N^{*2}} & \frac{I^*S^*\beta}{N^{*2}},\\
\frac{I^*(N^*-S^*)\beta}{N^{*2}} & -\frac{I^*S^*\beta}{N^{*2}} - k_1 & \frac{(N^*-I^*)S^*\beta}{N^{*2}} & \delta(1-\eta) - \frac{I^*S^*\beta}{N^{*2}},\\
0 & \epsilon & -k_2 & \delta\eta,\\
0 & 0 & \gamma & -k_3.
\end{pmatrix} \tag{4.11}
$$

where $E^* = (S^*, L^*, I^*, T^*, R^*)$ is the endemic equilibrium of the system (4.1).
The eigenvalues of equation(4.11) are the solutions of the characteristic equation

$$|J(E^*) - \lambda I| = 0,$$

where I is the identity matrix. Then we have

$$
|J(E^*)-\lambda I| = \begin{vmatrix}
-(\frac{I^*(N^*-S^*)\beta}{N^{*2}} + \mu) - \lambda & \frac{I^*S^*\beta}{N^{*2}} & -\frac{(N^*-I^*)S^*\beta}{N^{*2}} & \frac{I^*S^*\beta}{N^{*2}}\\
\frac{I^*(N^*-S^*)\beta}{N^{*2}} & -(\frac{I^*S^*\beta}{N^{*2}} + k_1) - \lambda & \frac{(N^*-I^*)S^*\beta}{N^{*2}} & \delta(1-\eta) - \frac{I^*S^*\beta}{N^{*2}}\\
0 & \epsilon & -k_2 - \lambda & \delta\eta\\
0 & 0 & \gamma & -k_3 - \lambda
\end{vmatrix} = 0.
$$

The characteristic equation associated to $J|_{E^*}$ is

$$\lambda^4 + b_1\lambda^3 + b_2\lambda^2 + b_3\lambda + b_4 = 0. \tag{4.12}$$

where the coefficients are: $b_1 = k_1 + k_2 + k_3 + \mu + \frac{I^*S^*\beta}{N^{*2}}$
$b_2 = \frac{1}{N^{*2}}\{k_3(\mu N^{*2}+I^*S^*\beta)+QN^{*2}+k_2(\mu N^{*2}+I^*S^*\beta)+k_1((k_2+k_3+\mu)N^{*2}+I^*\beta(N^*-S^*)) + S^*\beta(I^*\mu+(N^*-I^*))\}$
$b_3 = \frac{1}{N^{*2}}\{k_1(k_3(\mu N^{*2}+I^*\beta(N^*-S^*))+QN^{*2}+k_2(\mu N^{*2}+I^*\beta(N^*-S^*)))+k_2(k_3(\mu N^{*2}+I^*S^*\beta) + I^*S^*\mu\beta) + \beta k_3 I^*S^* + I^*S^*\beta(\gamma+\mu\epsilon(1+I^*N^*)) - (\beta\epsilon k_3 S^*I^*N^* + \beta\gamma\delta\eta + \gamma\delta N^{*2}((1-\eta)\epsilon+\mu\eta))\}$

$b_4 = \frac{1}{N^{*2}}\{k_1Q(\mu N^{*2} + \beta I^*(N^* - S^*)) + \beta S^*I^*(k_2k_3 + \epsilon\gamma\mu) - (\beta\mu\epsilon k_3S^*(N^* - I^*) + \mu\gamma(\delta\epsilon(1-\eta)N^{*2} + \beta\delta\eta S^*I^*) + \beta\gamma\delta\epsilon I^*(1-\eta)(N^* - S^*))\}$
where $Q = \{k_3(\mu+\sigma_1) + \gamma(\mu+\sigma_2+\alpha) + \gamma\delta(1-\eta)\}$. Then the eigenvalues of the characteristic polynomial (4.12) will be negative if it fulfill the Routh-Hurwitz conditions that are $b_i > 0$, for $i = 1, 2, 3, 4$ and $b_1b_2b_3 > b_3^2 + b_1^2b_4$. Hence, the EE of the model(4.1) will be locally asymptotically stable if $R_0 > 1$. □

4.5.2 Global stability of endemic equilibrium (EE)

In this subsection, we prove the global asymptotic stability property of the endemic equilibrium(EE) of the model (4.1) at the endemic equilibrium (EE), we have from system (4.1) by using the approach given in [41, 42].

$$\begin{cases} \Lambda = \frac{\beta S^*I^*}{N^*} + \mu S^*, \\ k_1L^* = \frac{\beta S^*I^*}{N^*} + (1-\eta)\delta T^*, \\ k_2I^* = \epsilon L^* + \mu\delta T^*, \\ \gamma I^* = k_3T^*. \end{cases}$$

Theorem 4.5.2. *The unique endemic equilibrium (EE) at E^* of model equation (4.1) is globally asymptotically stable if $R_0 > 1$.*

Proof. To proof the result, we define the following Lyapunov function

$$V(t) = \epsilon\left(S(t) - S^* - S^*\ln(\tfrac{S(t)}{S^*})\right) + \epsilon\left(L(t) - L^* - L^*\ln(\tfrac{L(t)}{L^*})\right) + k_1\left(I(t) - I^* - I^*\ln(\tfrac{I(t)}{I^*})\right) + \tfrac{\delta T^*(k_1\eta+\epsilon(1-\eta))}{\gamma I^*}\left(T(t) - T^* - T^*\ln(\tfrac{T(t)}{T^*})\right)$$
After differentiating V with respect to time gives

$$\frac{dV(t)}{dt} = \epsilon\left[(1-\frac{S^*}{S})\frac{dS}{dt} + (1-\frac{L^*}{L})\frac{dL}{dt}\right] + k_1\left[(1-\frac{I^*}{I})\frac{dI}{dt}\right] + \frac{\delta T^*(k_1\eta+\epsilon(1-\eta))}{\gamma I^*}\left[(1-\frac{T^*}{T})\frac{dT}{dt}\right] \tag{4.13}$$

From direct calculation we have:

$$\begin{cases} \epsilon(1-\frac{S^*}{S})\frac{dS}{dt} = \epsilon(1-\frac{S^*}{S})[\Lambda - \frac{\beta SI}{N} - \mu S] \\ \epsilon(1-\frac{S^*}{S})\frac{dS}{dt} = \epsilon(1-\frac{S^*}{S})[\frac{\beta S^*I^*}{N^*} + \mu S^* - \frac{\beta SI}{N} - \mu S] \\ \epsilon(1-\frac{S^*}{S})\frac{dS}{dt} = \epsilon\mu S^*\left(2 - \frac{S^*}{S} - \frac{S}{S^*}\right) + \frac{\epsilon\beta S^*I^*}{N^*}\left(1 - \frac{S^*}{S} + \frac{IN^*}{I^*N}\right) - \frac{\epsilon\beta SI}{N} \end{cases} \tag{4.14}$$

$$\begin{cases} \epsilon(1-\frac{L^*}{L})\frac{dL}{dT} = \epsilon(1-\frac{L^*}{L})\left[\frac{\beta SI}{N} - k_1L + (1-\eta)\delta T\right] \\ \epsilon(1-\frac{L^*}{L})\frac{dL}{dT} = \frac{\epsilon\beta SI}{N} - \frac{\epsilon\beta SIL^*}{NL} - k_1\epsilon L + k_1\epsilon L^* + (1-\eta)\epsilon\delta T - \frac{(1-\eta)\epsilon\delta TL^*}{L} \\ \epsilon(1-\frac{L^*}{L})\frac{dL}{dT} = \frac{\epsilon\beta SI}{N} - \frac{\epsilon\beta SIL^*}{NL} - k_1\epsilon L + \frac{\epsilon\beta S^*I^*}{N^*} + (1-\eta)\delta\epsilon T^* + (1-\eta)\epsilon\delta T - \frac{(1-\eta)\delta\epsilon TL^*}{L} \end{cases} \tag{4.15}$$

$$\begin{cases} k_1(1-\frac{I^*}{I})\frac{dI}{dt} = k_1(1-\frac{I^*}{I})\left[\epsilon L + \eta\delta T - k_2I\right] = k_1\epsilon L - \frac{k_1\epsilon LI^*}{I} + k_1\eta\delta T - \frac{k_1\eta\delta TI^*}{I} - k_1k_2I + k_1k_2I^* \\ k_1(1-\frac{I^*}{I})\frac{dI}{dt} = k_1\epsilon L - \frac{k_1\epsilon L^*I^*L}{IL^*} + k_1\eta\delta T - \frac{k_1\eta\delta TI^*}{I} + \frac{\epsilon\beta S^*I^*}{N^*} + k_1\eta\delta T^* + \\ \epsilon(1-\eta)\delta T^* - \frac{\epsilon\beta S^*I^*I}{N^*I^*} - \frac{(1-\eta)\epsilon\delta T^*I}{I^*} - \frac{k_1\eta\delta T^*I}{I^*} \\ k_1(1-\frac{I^*}{I})\frac{dI}{dt} = k_1\epsilon L - \frac{\epsilon\beta S^*I^*}{N^*}\frac{LI^*}{L^*I} - (1-\eta)\epsilon\delta T^*\frac{LI^*}{L^*I} + k_1\eta\delta T - k_1\eta\delta T\frac{I^*}{I} + \\ \frac{\epsilon\beta S^*I^*}{N^*} + k_1\eta\delta T^* + \epsilon(1-\eta)\delta T^* - \frac{\epsilon\beta S^*I^*}{N^*}\frac{I}{I^*} - (1-\eta)\epsilon\delta T^*\frac{I}{I^*} - k_1\eta\delta T^*\frac{I}{I^*} \end{cases} \tag{4.16}$$

$$\begin{cases} \frac{\delta T^*(k_1\eta+\epsilon(1-\eta))}{\gamma I^*}[1-\frac{T^*}{T}]\frac{dT}{dt} = \frac{\delta T^*(k_1\eta+\epsilon(1-\eta))}{\gamma I^*}[(1-\frac{T^*}{T})(\gamma I - k_3 T)] = \frac{\delta T^*(k_1\eta+\epsilon(1-\eta))}{I^*}\left(1-\frac{T^*}{T}\right)\left(I-\frac{I^*T}{T^*}\right) \\ \frac{\delta T^*(k_1\eta+\epsilon(1-\eta))}{\gamma I^*}[1-\frac{T^*}{T}]\frac{dT}{dt} = \delta\eta k_1 T^*\frac{I}{I^*} + \delta(1-\eta)\epsilon T^*\frac{I}{I^*} - \delta\eta T^*\frac{IT^*}{I^*T} - \delta(1-\eta)\epsilon T^*\frac{IT^*}{I^*T} - \delta\eta k_1 T + \\ -\delta(1-\eta)\epsilon T + \delta\eta K_1 T^* + \delta(1-\eta)\epsilon T^* \end{cases} \tag{4.17}$$

Using equation(4.14) up to equation(4.17) into equation(4.13), then we obtained the following equation:

$$\frac{dV(t)}{dt} = \epsilon\mu S^*\left(2-\frac{S^*}{S}-\frac{S}{S^*}\right)+\frac{\epsilon\beta S^*I^*}{N^*}\left(3-\frac{S^*}{S}-\frac{I}{I^*}-\frac{LI^*}{L^*I}-\frac{SIL^*N^*}{S^*I^*NL}(1-\frac{LS^*}{L^*S})\right)+ (1-\eta)\epsilon\delta T^*\left(3-\frac{I^*L}{IL^*}-\frac{L^*T}{LT^*}-\frac{T^*I}{TI^*}\right)+\delta\eta k_1 T^*\left(2-\frac{I^*T}{IT^*}-\frac{IT^*}{I^*T}\right) \tag{4.18}$$

Using properties of the arithmetic mean and geometric mean in Equation (4.18) we have

$$\begin{cases} \left(2-\frac{S}{S^*}-\frac{S^*}{S}\right)\leq 0 \\ \left(3-\frac{S^*}{S}-\frac{I}{I^*}-\frac{LI^*}{L^*I}-\frac{SIL^*N^*}{S^*I^*NL}(1-\frac{LS^*}{L^*S})\right)\leq 0 \\ \left(3-\frac{I^*L}{IL^*}-\frac{L^*T}{LT^*}-\frac{T^*I}{TI^*}\right)\leq 0 \\ \left(2-\frac{I^*T}{IT^*}-\frac{IT^*}{I^*T}\right)\leq 0 \end{cases} \tag{4.19}$$

As all the parameters are non-negative, therefore it follows that $\frac{dV(t)}{dt}\leq 0$ when $R_0>1$. Hence, by the LaSalle's Invariance Principle [40], $(S,L,I,T)\rightarrow(S^*,L^*,I^*,T^*)$ as $t\rightarrow\infty$. □

4.6 Sensitivity of the Basic Reproduction Number

We carried out sensitivity analysis in order to determine the relative significance of model parameters on disease transmission. The analysis will enable us to find out parameters that have high impact on the basic reproduction number and which should be targeted by intervention strategies. We perform sensitivity analysis by calculating the sensitivity indices of the basic reproduction number R_0 in order to determine whether tuberculosis(TB) can be spread in the population or not. To carry out this analysis, we use the normalized forward sensitivity index of a variable to a parameter.

Definition 6. *[13] The normalized forward sensitivity index of R_0 depending on the differentiablity on a parameter ψ*

$$S_\psi^{R_0} = \frac{\psi}{R_0}\frac{\partial R_0}{\partial\psi} \tag{4.20}$$

Table 2: The result obtained from the sensitivity analysis of R_0 with respect to model parameters are:

Parameter	Description	Sensitivity
β	Disease contact	+1
α	progression rate from T to R	-0.005485
γ	transmission rate from I to T	-0.134644
δ	rate at which treated individuals leave the T	+0.02167
η	treatment failure rate	+0.00104
ϵ	rate of moving from L to I	+0.03485
μ	natural death rate	-0.008426
σ_1	mortality rate in I	-0.03024
σ_2	mortality rate in T	-0.001788

We calculate the sensitivity indices of the basic reproduction number R_0 with respect to model parameters using above formula given in (4.20) and are tabulated in Table 6.2. These sensitivity indices along with signs are given in Table 2 which provide information that how crucial each parameter is to disease transmission and prevalence. A positive (+) sign in Table 2 indicates that those parameters have great impact on expanding the disease in the community if their values are increasing. Due to the reason that the basic reproduction number increases as their values increase. On the other hand, an index with negative(-) indicates that those parameters have an influence of minimizing the burden of the disease in the community as their values increase and also as their values increase, the basic reproduction number decreases, which leads to minimizing the endemic nature of the disease in the community.

4.7 Bifurcation analysis of the model

The study of changes of the structural stability of a differential equation on varying the parameters by which its right-hand side depends is called bifurcation theory. Bifurcation is a qualitative changes in the behavior of systems, where one or more system parameters are varied. The study of bifurcation is concerned with how the structural and behavioral change occurs when the parameter(s) is changing. The structural change and the transition behavior of a system are the central part of dynamical evolution. The point at which bifurcation occurs is known as the bifurcation point[36].

For the most part, in epidemic models, there are two distinct bifurcations at $R_0 = 1$ forward (supercritical) and backward (subcritical). A forward bifurcation happens when R_0 crosses unity from below; a small positive asymptotically stable equilibrium appears and the disease-free equilibrium losses its stability. On the other hand, a backward bifurcation happens when R_0 is less than unity; a small positive unstable equilibrium appears while the disease-free equilibrium and a larger positive equilibrium are locally asymptotically stable. Epidemiologically, a backward bifurcation "says" that it is not enough to only reduce the basic reproductive number to less than one to eliminate a disease and that when R_0 crosses unity, hysteresis takes place. The existence of backward bifurcation in the developed system (4.1) is explored under the

Centre Manifold theory[52].

4.7.1 Backward bifurcation

We shall use the following theorem in [51], to show that the system (4.1) exhibits backward bifurcation at $R_0 = 1$

Consider the following general system of ordinary differential equations with a parameter β

$$\frac{dx}{dt} = f(x, \beta), f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}^n, f \in C^2(\mathbb{R}^n \times \mathbb{R}) \tag{4.21}$$

Without loss of generality, it is assumed that 0 is an equilibrium point for system (4.21) for all values of the parameter β (that is $f(0, \beta) = 0$) for all β.

Theorem 4.7.1. *assume that*
A1*: $A = D_x f(0,0) = \left(\frac{\partial f_i}{\partial x_j}(0,0)\right)$ is the linearization of system (4.21) around the equilibrium 0 with β evaluated at 0. Zero is a simple eigenvalue of A and all other eigenvalues of A have negative real parts.*
A2*: Matrix A has a non-negative a right eigenvector w and a left eigenvector v corresponding to the zero eigenvalue.*

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

$$\boldsymbol{a} = \sum_{k,i,j=1}^{4} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0), \boldsymbol{b} = \sum_{k,i,=1}^{4} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \beta}(0,0) \tag{4.22}$$

The local dynamic of (4.21) around 0 are totally governed by parameters **a** and **b**.
1) $\mathbf{a} > 0$, $\mathbf{b} > 0$, when $\beta < 0$ with $|\beta| << 1$, 0 is locally asymptotically stable, and there exists a positive unstable equilibrium; when $0 < \beta << 1$, 0 is unstable and there exists a negative and locally asymptotically stable equilibrium.
2) $\mathbf{a} < 0$, $\mathbf{b} < 0$, when $\beta < 0$ with $|\beta| << 1$, 0 is unstable; when $0 < \beta << 1$, 0 is locally asymptotically stable, and there exists a positive unstable equilibrium.
3) $\mathbf{a} > 0$, $\mathbf{b} < 0$, when $\beta < 0$ with $|\beta| << 1$, 0 is unstable, and there exists a locally asymptotically stable negative equilibrium; when $0 < \beta << 1$, 0 is stable, and a positive unstable equilibrium appears.
4) $\mathbf{a} < 0$, $\mathbf{b} > 0$, when β changes from negative to positive, 0 changes its stability from stable to unstable. Correspondingly, a negative unstable equilibrium becomes positive and locally asymptotically stable. To apply the above result, the following simplification and change of variables are made on the system(4.1).
Let $S = x_1$, $L = x_2$, $I = x_3$, $T = x_4$ and $N = x_1 + x_2 + x_3 + x_4$
Moreover, by using vector notation $x = (x_1, x_2, x_3, x_4)^T$, the system can be written in the form
$\frac{dx}{dt} = (f_1, f_2, f_3, f_4)^T$ as follow

$$\begin{cases} \frac{dx_1}{dt} = \Lambda - \frac{\beta}{N}x_1x_3 - \mu x_1 = f_1 \\ \frac{dx_2}{dt} = \frac{\beta}{N}x_1x_3 - (\mu+\epsilon)x_2 + (1-\eta)\delta x_4 = f_2 \\ \frac{dx_3}{dt} = \epsilon x_2 + \eta\delta x_4 - (\mu+\gamma+\sigma_1)x_3 = f_3 \\ \frac{dx_4}{dt} = \gamma x_3 - (\mu+\delta+\sigma_2+\alpha)x_4 = f_4 \end{cases} \tag{4.23}$$

If we choose β as bifurcation parameter, then $R_0 = 1$, we get

$R_0 = \frac{\beta\epsilon k_3}{k_1k_2k_3 - \gamma\delta\eta k_1 - (1-\eta)\gamma\delta\epsilon} = 1$. From this we obtain β as below

$\beta^* = \beta = \frac{k_1k_2k_3 - \gamma\delta\eta k_1 - (1-\eta)\gamma\delta\epsilon}{\epsilon k_3}$

The disease-free equilibrium is $(x_1^*, x_2^*, x_3^*, x_4^*) = (\frac{\Lambda}{\mu}, 0, 0, 0,)$

The linearization matrix of system (4.23) around the disease-free equilibrium when $\beta = \beta^*$ is

$$D_xf = \begin{pmatrix} -\mu & 0 & -\frac{k_1k_2k_3 - \gamma\delta\eta k_1 - (1-\eta)\gamma\delta\epsilon}{\epsilon k_3} & 0 \\ 0 & -k_1 & \frac{k_1k_2k_3 - \gamma\delta\eta k_1 - (1-\eta)\gamma\delta\epsilon}{\epsilon k_3} & (1-\eta)\delta \\ 0 & \epsilon & -k_2 & \eta\delta \\ 0 & 0 & \gamma & -k_3 \end{pmatrix}$$

It is clear that 0 is a simple eigenvalue of D_xf calculated at β^*

The right eigenvector $w = (w_1, w_2, w_3, w_4)^T$, associated with this simple zero eigenvalue can be obtained from $D_xf(E_0, \beta^*).w = 0$. As a result we have

$w_1 = -\frac{(k_1k_2k_3 + \gamma\delta\eta\epsilon - \gamma\delta\epsilon - \gamma\delta\eta k_1)w_3}{\mu\epsilon k_3}$

$w_2 = \frac{(k_2k_3 - \gamma\delta\eta)w_3}{\epsilon k_3} > 0$, $w_3 > 0$ and $w_4 = \frac{\gamma}{k_3}w_3$

Similarly, the left eigenvector $v = (v_1, v_2, v_3, v_4)^T$ corresponding to the simple zero eigenvalue is obtained from $v.D_xf(E_0, \beta^*) = 0$

as $v_1 = 0$, $v_2 > 0$, $v_3 = \frac{k_1}{\epsilon}v_2$ and $v_4 = \frac{\delta(\eta k_1 + \epsilon(1-\eta))}{\epsilon k_3}v_2$

Computation of a : To evaluate **a**, we use the following partial derivatives

$\frac{\partial^2 f_2}{\partial x_3^2} = -\frac{2\beta\mu}{\Lambda}$, $\frac{\partial^2 f_2}{\partial x_2 \partial x_3} = \frac{\partial^2 f_2}{\partial x_3 \partial x_4} = -\frac{\beta\mu}{\Lambda}$, then we get $\mathbf{a} = -\frac{2\beta\mu}{\Lambda}(v_2w_2w_3 + v_2w_3^2 + v_2w_3w_4)$

Computation of b: We find the following partial derivatives to evaluate **b**

$\frac{\partial^2 f_2}{\partial x_3 \partial \beta} = 1$, then we obtain $\mathbf{b} = v_2w_3 > 0$

Since all the terms in the expressions of **b** are positive($\mathbf{b} > 0$), the presence of the bifurcation at $\beta = \beta^*$ depends solely on the sign of **a**. Hence, since the value of **a** is negative, zero changes its stability from stable to unstable.

Chapter 5

TB Model with Optimal Control

In chapter four, we presented a mathematical model for the transmission dynamics of tuberculosis and studied its well-possedness mathematically and epidemiologically without giving intervention mechanism. In this chapter, the intervention mechanism is addressed using the theory of optimal control. Optimal control theory has been applied to various mathematical models for studying the transmission dynamics of TB for example, see in [4, 19, 28, 29] and references cited therein. It deals with the problem of finding a control law for a given system such that a certain optimality criterion is achieved with minimum implementation cost. A control problem includes a cost functional that is a function of state and control variables. An optimal control is a set of differential equations describing the paths of the control variables that minimize the cost function. Our objective is to minimize the number of infectious by reducing treatment failure and the overall cost of the treatment during a fixed time period. For this, we introduce and analyze a control function in the TB model(4.1). After we present the existence of optimal control and characterization, we study the transmission dynamics of TB through numerical simulation.

5.1 Optimal control problem

In this section, we consider an SLITR compartmental model presented in chapter 4 to study the transmission dynamics of TB epidemic. In the model, we introduce one control function $u(\cdot)$ representing the effort that prevents the failure of treatment in active TB individuals I. It corresponds to supervising the patients, helping them to take the TB medications regularly on time and complete the TB treatment. The resulting dynamical control system is given by the following system of nonlinear ordinary differential equations:

$$\begin{cases} \frac{dS}{dt} = \Lambda - \frac{\beta}{N} IS - \mu S, \\ \frac{dL}{dt} = \frac{\beta}{N} IS - (\mu + \epsilon)L + (1-\eta)(1-u)\delta T, \\ \frac{dI}{dt} = \epsilon L + (1-u)\eta\delta T - (\mu + \sigma_1 + \gamma)I, \\ \frac{dT}{dt} = \gamma I - (\mu + \delta + \sigma_2 + \alpha)T, \\ \frac{dR}{dt} = \alpha T - \mu R. \end{cases} \tag{5.1}$$

with initial condition : $S(0) = S_0 > 0$, $L(0) = L_0 \geq 0$, $I(0) = I_0 \geq 0$, $T(0) = T_0 \geq 0$, and $R(0) = R_0 \geq 0$.

The aim is to find the optimal values u^* of the controls u such that the associated state trajectories S^*, L^*, I^*, T^*, R^* are solution of the system (5.1) in the treatment time interval $[0, T]$ with given initial conditions and minimize the objective functional. For this, we consider the objective functiona

$$J(u) = \int_0^T \left(AI(t) + \frac{1}{2} W u^2 \right) dt \longrightarrow \min \tag{5.2}$$

subject to(5.1) with its initial condition where A is relative constant that measures the relative importance of reducing the associated classes on the spread of the disease and the relative weight constants W is a measure of the relative cost of the interventions associated with the control u. Clearly, u depends on the amount of resources available to effectively implement the control measure. The case $u = 0$, implies no control measure is taken and the model equation (5.1) is equivalent to (4.1). On the other hand, $u = 1$ implies a 100% success of intervention which is unrealistic. Thus we assume that $0 \leq u(t) \leq u_{\max} < 1$ for numerical implementation.
In the cost functional, the term $AI(t)$ describe the cost incurred related to TB infectious. Additionally, the function J represents the total cost incurred due to TB infectious and its control strategies. Further, the integrand function $F(S, L, I, T, R, u)$ $= AI(t) + \frac{1}{2} W u^2$ measures the current cost at time t. Lastly, the fixed constant T denotes the terminal treatment time.

The set of admissible control functions is defined by

$$\Omega = \{u(\cdot) \in (Ł^{\infty}(0, T)) : 0 \leq u(t) \leq 1, \forall t \in [0, T]\}. \tag{5.3}$$

Then we consider the optimal control problem of determining $(S^*(\cdot), L^*(\cdot), I^*(\cdot), T^*(\cdot), R^*(\cdot))$, associated with an admissible control $u^* \in \Omega$ on the treatment time interval $[0, T]$, subjected to the state control system (5.1) in $\mathbb{R}^5$ with its initial condition and minimizing the cost functional(5.2). More precisely, the optimal control problem can be defined as

$$J[u^*] = \min_{\Omega} J[u(\cdot)] \tag{5.4}$$

satisfying (5.1) and its initial conditions.

Remark 1. *The optimal control problem is to minimize the objective functional J considering active tuberculosis infections and the costs of treatment of infected individuals. The control functions u is also a bounded Lebesgue measurable function defined on the interval [0, 1].*

5.2 Existence of the optimal control problem

In this subsection, we will investigate the existence of an optimal control of our model(5.1). The boundedness of solutions to system (5.1) for finite time interval is needed to establish the existence of an optimal control and the uniqueness of the optimality system. For model system (5.1) to be epidemiologically meaningful, it is

important to prove that all its state variables are nonnegative for all time. To establish the upper bounds for the solutions, we consider an equation for the total population size N. The rate of change of the total population, obtained by adding all the equations in model (5.1) is given by

$$\frac{dN(t)}{dt} = \Lambda - \mu N(t) - \sigma_1 I(t) - \sigma_2 T(t) - \delta T u \leq \Lambda - \mu N(t)$$

Now, by applying integral factor we obtain $N(t) \leq (N(0) - \frac{\Lambda}{\mu})e^{-\mu t} + \frac{\Lambda}{\mu} \leq \frac{\Lambda}{\mu}$. Thus, N is bounded above by $\frac{\Lambda}{\mu}$. The upper bound for N is also the upper bound for S, L, I, T and R since they are nonnegative from our assumption.

Theorem 5.2.1. *There exist an optimal control u^* and a corresponding solution vector $(S^*, L^*, I^*, T^*, R^*)$ to the state initial value problem (5.1) that minimizes the cost functional $J(u)$ of (5.2) over the set of admissible control Ω.*

Proof. We refer to the conditions in Theorem 4.1 and its corresponding corollary 4.1 in [3]. The requirements there on the set of admissible controls and on the set of end conditions are clearly met here. The following non-trivial requirement from Fleming and Rishel's theorem are listed and verified below:

i. The set of all solutions to system (5.1) with corresponding control functions in Ω is non empty.

ii. The control set is convex and closed.

iii. The integral of the objective functional is convex.

iv. The integrand $F(t, S, L, I, T, R, u)$ in equation(5.2) is convex with respect to control variables and additionally fulfills that $F(S, L, I, T, R, u) \geq f(u)$, where f is continuous and $|u|^{-1} f(u) \to +\infty$ as $|u| \to \infty$.

In order to established condition (i), we refer to Picard-Lindelòf existence theorem[43]. If the solutions of the state equations are a prior bounded and if the state equations are continuous and Lipschitz continuous in the state variables, then there is a unique solution corresponding to every admissible control in the given domain. With the result that, if $g(t, x, u)$ is bounded, continuous, and Lipschitz in the state variable, then there exists a unique solution corresponding to every admissible control Ω. Hence, for any $u \in \Omega$ and the state variables, we have

$$0 \leq N(t) \leq \frac{\Lambda}{\mu} \tag{5.5}$$

and non empty by model assumption. Furthermore, with the bounded established (5.5), it implies that the state system is continuous and bounded. It is possible to show the boundedness of the partial derivative with respect to the state variable, i.e $\frac{\partial g}{\partial x}$, exist and finite, which established the system is Lipschitz with respect to the state variables[43]. This established that the proof of condition (i) is complete.
To proof(ii), consider

$$\Omega = \{u \in \mathbb{R} : |u| \leq 1\}$$

Assume that $u_1, u_2 \in \Omega$ such that $|u_1| \leq 1$ and $|u_2| \leq 1$. Then for any $\alpha \in [0,1]$, $|\alpha u_1 + (1-\alpha)u_2| \leq \alpha|u_1| + (1-\alpha)|u_2| \leq 1$. This implies that the control set Ω is convex and closed.
Next we verify condition (iii), the integral of the cost function is given by

$$F(t, S, L, I, T, R, u) = AI + \frac{1}{2}Wu^2$$

Recall that any affine function is convex and the sum of convex function is also convex [44]. Therefore, F is convex on Ω.
Finally, to verify condition(iv), we note that the integrand $F(t, S, L, I, T, R, u)$ of the objective functional is clearly convex in control. To prove the bound on the $F(t, S, L, I, T, R, u)$ we note that the state system (5.1) is linear in control variable u with coefficients depending on state variables. The integrand of the cost functional $F(t, S, L, I, T, R, u) = AI(t) + \frac{1}{2}Wu^2$ is the sum of convex function and hence convex with respect to control variables. Furthermore,

$$F(t, S, L, I, T, R, u) = AI(t) + \frac{1}{2}Wu^2 \geq \frac{1}{2}Wu^2. \tag{5.6}$$

Let $r = \frac{w}{2} > 0$ and define a continuous function $f(u) = r|u|^2$. Then from equation(5.6) we have $F(S, L, I, T, R, u) \geq f(u)$. Clearly $|u|^{-1}f(u) \to +\infty$ as $|u| \to \infty$. Thus, condition (iv) is achieved. With this we conclude that the existence of an optimal control $(S^*, L^*, I^*, T^*, R^*, u^*)$ that minimizes the cost functional of (5.2) over the set of admissible control Ω. □

The Pontryagin's Maximum Principle (PMP) stated in ([3], theorem 4.1) gives the required necessary optimality condition as given in the following theorem. Note that since we look for minimization, we use Pontryagin's Minimum Principle.

5.3 Characterization of Optimal Control Solutions

Pontryagin's Maximum Principle [46] provides the necessary conditions that an optimal pair must satisfy. According to this principle, for u^* to be optimal with corresponding optimal states S^*, L^*, I^*, T^*, R^*, which minimizes the objective functional(5.2) for a fixed final time T, then there exists a non-trivial absolutely continuous mapping $\lambda : [0, T] \to \mathbb{R}^5, \lambda = (\lambda_1(t), \lambda_2(t), \lambda_3(t), \lambda_4(t), \lambda_5(t))$ called the adjoint vector, such that

1. the Hamiltonian function is defined as

$$\mathcal{H} = AI(t) + \frac{1}{2}Wu^2 + \sum_{i=1}^{5} \lambda_i(t) g_i(t, S, L, I, T, R, u), \tag{5.7}$$

   where g_i stands for the right hands of the constraints (5.1) for $i = 1, 2, 3, 4, 5$.

2. the control system

$$S' = \frac{\partial \mathcal{H}}{\partial \lambda_1}, \quad L' = \frac{\partial \mathcal{H}}{\partial \lambda_2}, \quad I' = \frac{\partial \mathcal{H}}{\partial \lambda_3}, \quad T' = \frac{\partial \mathcal{H}}{\partial \lambda_4}, \quad R' = \frac{\partial \mathcal{H}}{\partial \lambda_5}; \tag{5.8}$$

3. the adjoint system

$$\lambda_1' = -\frac{\partial \mathcal{H}}{\partial S}, \quad \lambda_2' = -\frac{\partial \mathcal{H}}{\partial L}, \quad \lambda_3' = -\frac{\partial \mathcal{H}}{\partial I}, \quad \lambda_4' = -\frac{\partial \mathcal{H}}{\partial T}, \quad \lambda_5' = -\frac{\partial \mathcal{H}}{\partial R}; \tag{5.9}$$

4. and the optimality condition

$$\mathcal{H}(S^*(t), L^*(t), I^*(t), T^*(t), R^*(t), u^*(t), \lambda^*(t)) = \min_{u \in \Omega} \mathcal{H}(S(t), L(t), I(t), T(t), R(t), u(t), \lambda(t)) \tag{5.10}$$

holds for almost all $t \in [0, T]$.

5. Moreover, the transversality condition

$$\lambda_i(T) = 0, \qquad i = 1, \ldots, 5 \tag{5.11}$$

also holds true.

In the following result, we give the characterization of optimal control.

Theorem 5.3.1. *There exists an optimal solution, S^*, L^*, I^*, T^*, R^* and corresponding optimal controls u^* that minimizes $J(u)$ over the set of admissible control Ω. Moreover, there exist an adjoint function $\lambda_i^*(t)$, for i = 1, 2, 3, 4, 5 such that*

$$\begin{cases} \lambda_1' = \lambda_1 \left(\mu + \frac{\beta I}{N}\right) - \frac{\lambda_2 \beta I}{N}, \\ \lambda_2' = \lambda_2 \left(\epsilon + \mu\right) - \lambda_3 \epsilon, \\ \lambda_3' = -A + \frac{\lambda_1 \beta S}{N} - \frac{\lambda_2 \beta S}{N} + \lambda_3 \left(\mu + \sigma_1 + \gamma\right) - \lambda_4 \gamma, \\ \lambda_4' = -\lambda_2 \left(1 - \eta\right)\left(1 - u\right)\delta - \lambda_3 \left(1 - u\right)\eta\,\delta + \lambda_4 \left(\mu + \sigma_2 + \delta + \alpha\right) - \lambda_5 \alpha, \\ \lambda_5' = \lambda_5 \mu. \end{cases} \tag{5.12}$$

with transiversality conditions $\lambda_i^*(T) = 0$, for $i = 1, 2, 3, 4, 5$.
Moreover, the optimal control $u^*(t)$ is given by

$$u^*(t) = \min\left\{\max\left\{0, \frac{T\delta\left(\eta\left(\lambda_3 - \lambda_2\right) + \lambda_2\right)}{W}\right\}, 1\right\} \tag{5.13}$$

Proof. By Corollary 4.1 in Fleming and Rishel [3], the convexity of the integrand (of the objective functional) in (5.2) with respect to u guarantees the existence of an optimal control as proved above. The adjoint equations and transversality conditions can be obtained via the Pontryagin's Maximum Principle such that:

$$\frac{d\lambda_1}{dt} = -\frac{\partial H(t, S, u, \lambda)}{\partial S}, \ \lambda_1(T) = 0,$$

$$\frac{d\lambda_2}{dt} = -\frac{\partial H(t, L, u, \lambda)}{\partial L}, \ \lambda_2(T) = 0,$$

,

$$\frac{d\lambda_3}{dt} = -\frac{\partial H(t, I, u, \lambda)}{\partial I},\ \lambda_3(T) = 0,$$

$$\frac{d\lambda_4}{dt} = -\frac{\partial H(t, T, u, \lambda)}{\partial T},\ \lambda_4(T) = 0,$$

$$\frac{d\lambda_5}{dt} = -\frac{\partial H(t, R, u, \lambda)}{\partial R},\ \lambda_5(T) = 0,$$

Considering the optimality conditions given by $\frac{\partial H}{\partial u} = 0$, the optimal control u^* can be explicitly obtained in terms of state and adjoint variables. That means for the optimality condition, we differentiate the Hamiltonian function with respect to u and equate it to zero by taking into account the boundedness on u. For this reason, we have the following optimality condition:

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

which implies that

$$u^*(t) = \frac{T\delta\ (-\eta\,\lambda_2 + \eta\,\lambda_3 + \lambda_2)}{W}$$

From boundedness on $u^*(t)$ and minimality condition, we have:

$$u^*(t) = \begin{cases} 0, & \text{if } \frac{\partial H}{\partial u} > 0 \\ \frac{T\delta\,(-\eta\,\lambda_2 + \eta\,\lambda_3 + \lambda_2)}{W}, & \text{if } \frac{\partial H}{\partial u} = 0 \\ 1, & \text{if } \frac{\partial H}{\partial u} < 0 \end{cases}$$

Concluding that, the optimal control $u^*(t)$ can be summarized as

$$u^*(t) = \min\left\{\max\left\{0, \frac{T\delta\ (\eta\,(\lambda_3 - \lambda_2) + \lambda_2)}{W}\right\}, 1\right\}$$

This completes the proof of the theorem. □

Chapter 6

Numerical simulation

This chapter present and discusses numerical results for the system(5.1) for different values of parameters given in the model. The simulation process is carried out using Matlab software. We start by defining and estimating the values of parameter used in the model. Then we illustrate the simulation results graphically.

6.1 Parameter Estimations

In this section, we fit the proposed model to cumulative cases of TB infection data and estimate the unknown model parameters. Table 6.1 depicts the cumulative cases of TB infection from 2010 to 2019 extracted from East Shewa Zone, Oromia regional State, Ethiopia. The squared sum of errors (SSE) between model solution and the data can

Table 6.1: Cumulative cases of TB infection from 2010– 2019 (In East Shewa Zone, Oromia Regional State, Ethiopia)

Year	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
TB cases	1820	1869	1721	1585	1262	1455	1516	1348	1171	1524

be computed as

$$SSE(\theta) = arg\min \sum_{i=1}^{n} ||I(t)_i - \bar{I}_i(t)||^2 \tag{6.1}$$

where $||\cdot||$ denotes the Euclidean norm in $\mathbb{R}^n$ and n is the number of available real data points. The expression $\bar{I}_i(t)$ represents the actual cumulative TB infected cases and $I_i(t)$ are the corresponding model solutions at time t_i. In the process of least-squares fitting, we are looking for a value $\bar{\theta}$ of model parameter θ such that the squared sum of errors is the minimum. Clearly, such a problem is nonlinear least-squares problem, since the dependence of a solution $I(t, \theta)$ on the parameter θ is through a highly nonlinear system of differential equations.

In the next section, we study the dynamics of TB through numerical simulations by estimating the values of parameters in the proposed model with appropriate initial conditions with the help of least square technique.

6.2 Simulation results and discussion

Here, we illustrate numerically the solution of the optimal control problem proposed in Section (5.1) and explain the impact of control strategy on the spread Tuberculosis. For this purpose, we use the forward-backward sweep method presented in the book of

Lenhart and Workman [34].

To briefly summarize the procedure, first we solve the control system with an initial guess for the control variables using forward fourth-order Runge-Kutta scheme and transversality conditions. The adjoint system is then solved applying the backward fourth-order Runge-Kutta scheme using the current solution of state variables. Then, the controls are updated by means of convex combination of the previous controls and the values computed in the characterizations process. The updated controls are then utilized to repeat the solution of state and adjoint systems. The iteration continued until a predefined convergence criterion is met.

We assume that initial population of exposed individuals $L(0) = 5,793$. The initial infected population based on collected data $I(0) = 1820$ as given Table 6.1. Initially, we assumed the treated and recovered populations as $T(0) = 150$ and $R(0) = 100$ respectively while the initial susceptible population is given by $S(0) = N(0) - L(0) - I(0) - T(0) - R(0) = 2,122,509$. The natural death rate is computed as $\mu = \frac{1}{66.34}$ per year, where 66.34 years is the average life expectancy in Ethiopia[47]. The total population of East Shewa zone in 2019 was estimated as $N(0) = 2,130,372$[55]. The recruitment rate Λ, is then calculated as $\Lambda = \mu N(0) = 32,112.93333$ per year. The remaining model parameters are estimated using least-square fitting methods which provides a better fit for the model solution to the real data as shown in Figure(6.1) and the corresponding parameters value are depicted in Table 6.2.

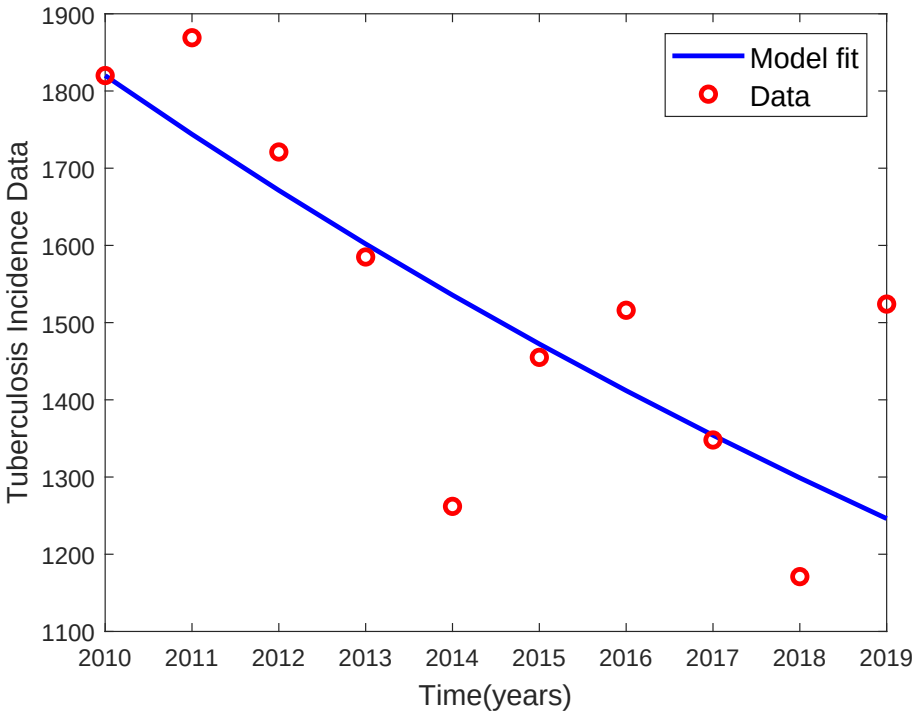


Figure 6.1: SLITR model fit with real data on the number of TB cases in East Shewa Zone

Table 6.2: Values of parameter used in the simulation

Parameter	Description	Value	Reference
$N(0)$	Initial population	2,130,372	[55]
Λ	Recruitment rate	32,112.93333	Estimated
β	Disease contact rate	0.05792	Fitted
α	Progression rate from compartment T to R	0.0276	Fitted
γ	Treatment rate from compartment I to T	0.0125	Fitted
μ	Natural death rate	$\frac{1}{66.34}$	[47]
σ_1	Disease related mortality rate of infected individuals	0.01537	Fitted
σ_2	Disease related mortality rate in T	0.0038	Fitted
δ	Rate at which treated individuals leave the T	0.08373	Fitted
η	Treatment failure rate	0.0105	Fitted
ϵ	Rate of moving from L to I	0.01401	Fitted

The estimation of basic reproduction number for the model is given by

$$R_0 = \frac{\beta\epsilon(\mu+\delta+\sigma_2+\alpha)}{(\mu+\epsilon)(\mu+\gamma+\sigma_1)(\mu+\delta+\sigma_2+\alpha)-\eta\delta\gamma(\mu+\epsilon)-(1-\eta)\delta\gamma\epsilon} = 1.1676 > 1.$$

Since $R_0 > 1$, the prevalence of Tuberculosis will result in an epidemic.

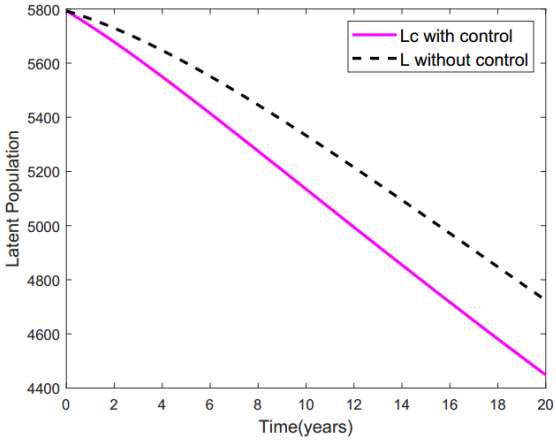
As detailed in [34], first we solve system (5.1) with a guess for the control $u = 0.95$ over the time interval [0, T] using a forward fourth order Runge-Kutta scheme and the transversality conditions $\lambda_i(T) = 0, i = 1, \ldots, 5$. Then, system (5.12) is solved by a backward fourth-order Runge-Kutta scheme using the current iteration solution of (5.1). The control is updated by using a convex combination of the previous control and the values from (5.13). The iteration is terminated when the values of the unknowns at the previous iteration are very close to the ones at the present iteration.

Fist, we compare the number of exposed and infectious population with and without controls. For this, we consider $A = 1.2$, $W = 5$ and the adjoint system with terminal conditions $\lambda_i(T) = 0$, i = 1,...,5, for the final intervention time $T = 20$ years. Further we used the TB real data with initial conditions

$$(S(0), L(0), I(0), T(0), R(0)) = (2122509, 5793, 1820, 150, 100)$$

and the corresponding parameter values are as given in Table6.2. The data, basically covers the epidemic period from 2010 to 2019 as displayed in Table 6.1. The simulation results are displayed in Figure6.2.

TB exposed(latent) populations with and without control.



TB infected populations with and without control.

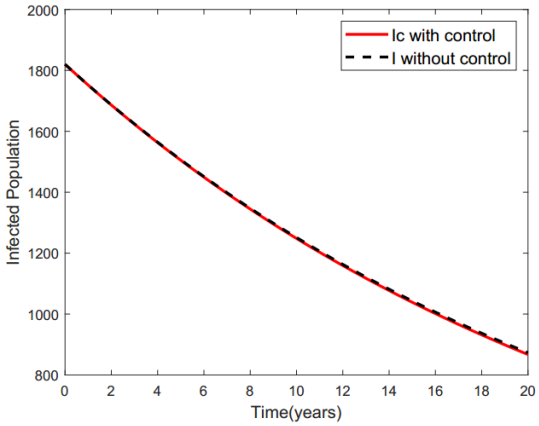


Figure 6.2: Illustrates the impact of control on TB exposed (latent) population and TB infected population based on the real data obtained from East Shewa Zone.

From Figure6.2(a) it is clear that the applied control function u, that is, the effort made to prevent the failure of treatment in active TB infectious individuals I is significantly influenced the exposed (latent) population. That is, supervising the patients, helping them to take the TB medications regularly on time until completing treatment will minimize the exposed population. Comparatively, the impact of control is insignificant in minimizing the TB infected population as illustrated in Figure6.2(b). The corresponding control profile is shown in Figure6.3.

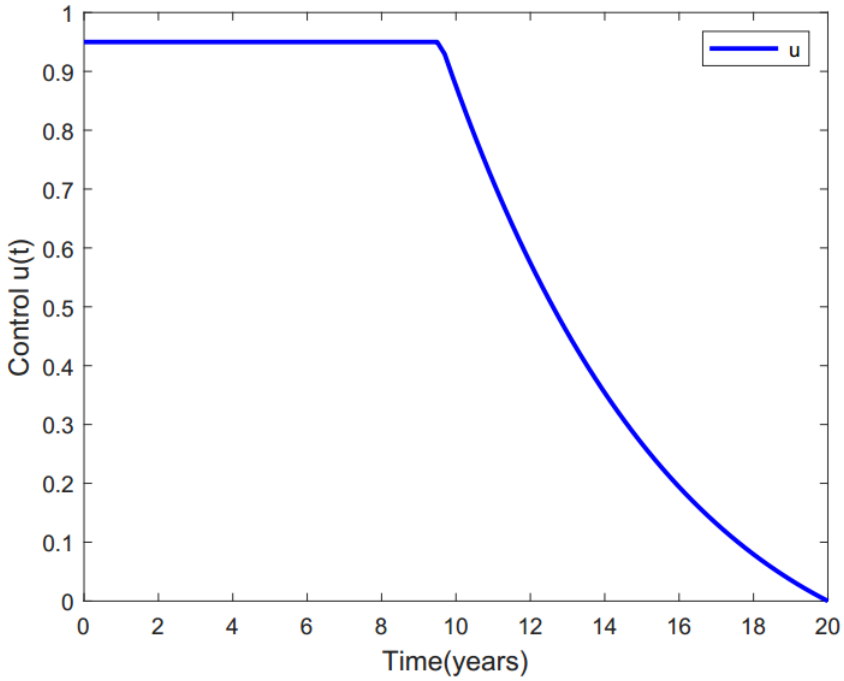
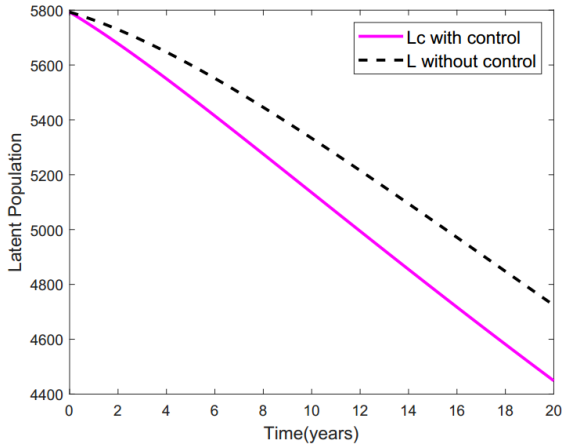


Figure 6.3: Control profile when $A = 1.2$ and $W = 5$

Next we preformed simulation process with the same initial data. In this case, we vary the relative weight constant $W = 35$ which measure the relative cost of intervention associated with the control u fixing $A = 1.2$. As shown in Figure6.4(a), the relative weight cost of intervention associated with control u also influence the exposed population. Also, the relative weight cost of intervention associated with control u has very minimal impact on the infected population as depicted in Figure6.4 (b).

TB exposed(latent) populations with and without control when $W = 35$.



TB infected populations with and without control when $W = 35$.

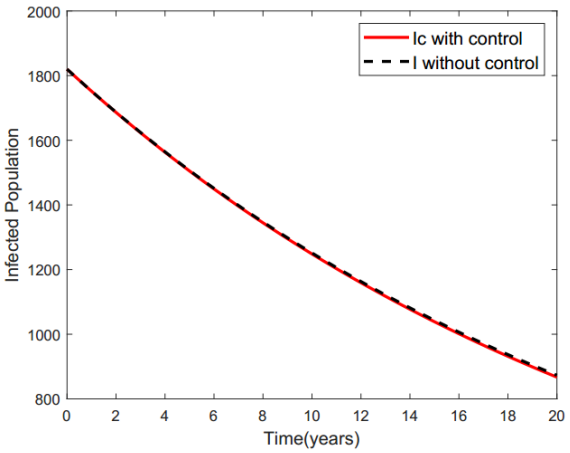


Figure 6.4: Displays the role of relative weighted cost associated with control u on TB exposed (latent) and TB infected population.

Figure 6.5 presents the associated control profile when $A = 1.2$ and $W = 35$. It is evident from this figure that the control function rapidly decrease as we increase relative weighted cost. Lastly, we studied the impact of control function on TB latent and active TB infected population with the same initial data. In this case we considered $A = 0.2$ and $W = 3.5$. The corresponding simulation results are displayed respectively in Figure 6.6 and 6.7

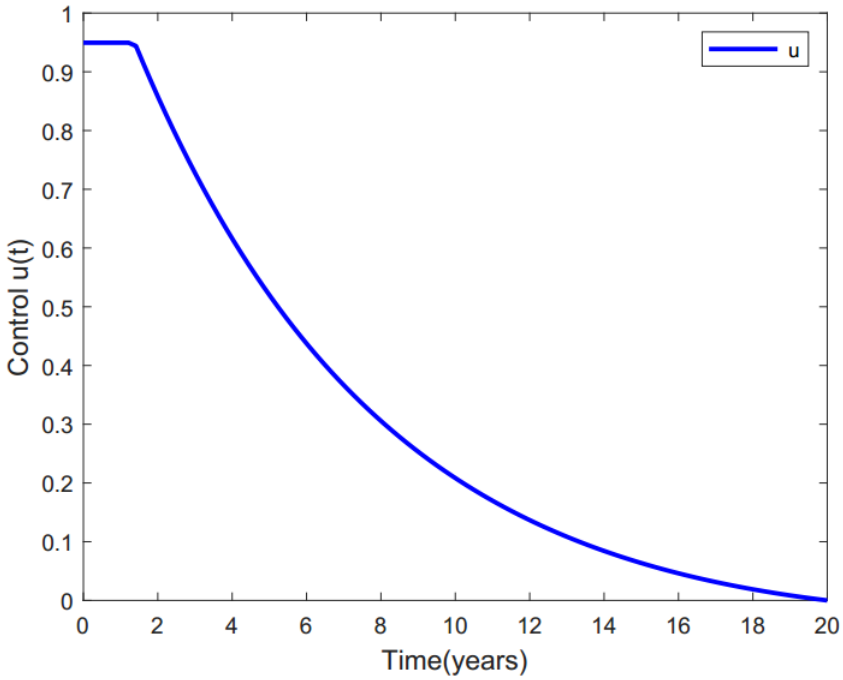
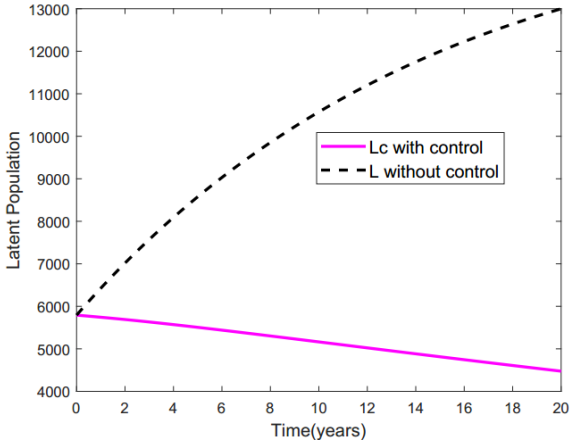


Figure 6.5: Control profile when $A = 1.2$ and $W = 35$

From Figure6.6 one can easily observe that the control function strongly influence both the TB exposed and infected population when $A = 0.2$ and $W = 3.5$. The corresponding control function is displayed in Figure 6.7. From these simulation results, we observe that the epidemic of TB can be effectively minimized by preventing the failure of treatment in active TB infectious individuals through continuous supervision and helping during treatment period with optimal implementation cost. The optimal control model also predicted that Tuberculoses epidemic will be decreased for the coming ten years in East Shewa Zone considering the initial TB infected population equal to 1820. That is by 2030 the epidemic of Tuberculoses will be well control with optimal intervention cost which relatively agree with WHO's[15] strategic goal of ending the global TB epidemic by 2030.

TB exposed populations with and without control when $A = 0.2$ and $W = 3.5$.



TB infected populations with and without control when $A = 0.2$ and $W = 3.5$.

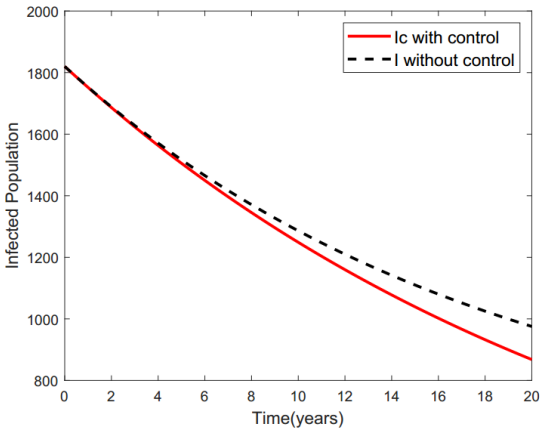


Figure 6.6: The plot shows the impact of relative weighted cost associated with control u and relative constant on TB exposed (latent) and TB infected population.

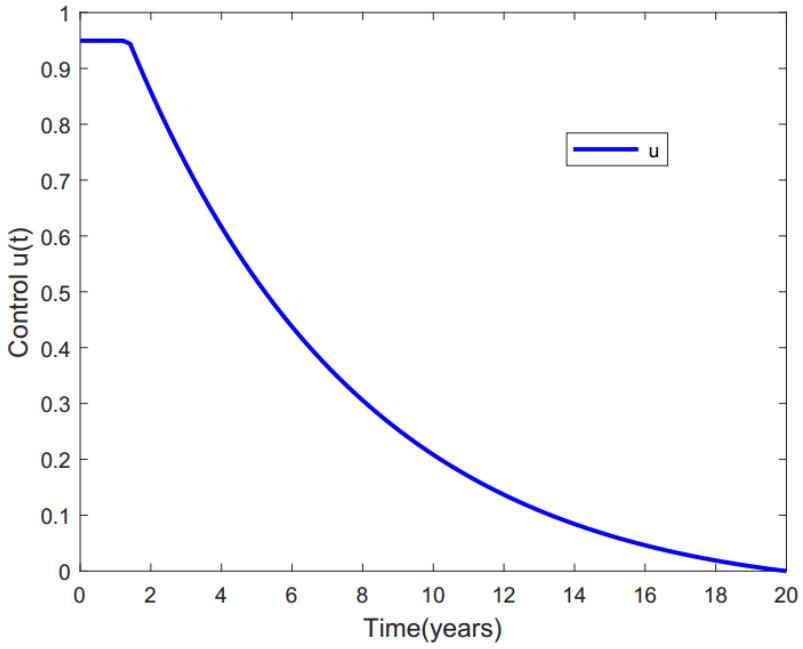


Figure 6.7: Control profile when $A = 0.2$ and $W = 3.5$

Chapter 7

Conclusion and Recommendation

7.1 Conclusion

In this thesis, a mathematical model of the transmission dynamics of tuberculosis (TB) with optimal control was studied by extending the mathematical model introduced in[13] to optimal control model. The well-posedness of the model was established both in the mathematical and epidemiological sense by showing that all solutions of the model are positive and bounded with initial conditions in a certain meaningful set by correcting errors in the original model. The model has two non-negative equilibria, namely, the disease-free and the endemic equilibrium. The existence and stability of the disease-free and endemic equilibria of the model were performed. For the sack of completeness both local and global stability of the disease-free and the endemic equilibrium are determined by a threshold quantity (basic reproduction number R_0). Sensitivity indices of R_0 with respect to the model parameters and bifurcation analysis are performed to reveal the transmission dynamics of tuberculosis.

The optimal control strategy is found by minimizing the number of TB exposed and infected population taking into account the cost of implementation. The existence of optimal controls and characterization is established with the help of Pontryagin's Maximum Principle. The model is then fitted with cumulative cases of infected TB by collecting real data from East Shewa zone Health Office located in Adama city, Mojo, Batu and Bishoftu town from 2010 to 2019 years. Further, different simulation cases were comparatively performed to obtain the best control strategies. In general, the numerical simulation results demonstrate good agreement with our analytical results.

The simulation results also clearly shown that the epidemic of TB can be minimized by preventing the failure of treatment in active TB infectious individuals through continuous supervision and helping patients during treatment period with optimal implementation cost. Furthermore, the optimal control model predicted that Tuberculoses epidemic will be managed for the coming ten years in East Shewa Zone which relatively agree with WHO strategic goal of ending the global TB epidemic by 2030.

7.2 Recommendation

Based on the findings of this study, we recommend to government and concerned stake holders to implement continuous supervision and helping patients during treatment period to prevent failure of treatment in active TB infectious individuals.

Research Fund Acknowledgment

This research project is funded by Adama Science and Technology University under the grant number ASTU/SM-R/016/19, Adama, Ethiopia.

Reference

[1] Castillo-Chavez, Carlos, and Baojun Song. "Dynamical models of tuberculosis and their applications." *Mathematical Biosciences & Engineering* 1.2 (2004): 361.

[2] World Health Organization. "Global tuberculosis report 2018." *Geneva: World Health Organization (2019).*

[3] Fleming, Wendell H., and Raymond W. Rishel. *Deterministic and stochastic optimal control*. Vol. 1. Springer Science & Business Media, 2012.

[4] Gaff, Holly, and Elsa Schaefer. "Optimal control applied to vaccination and treatment strategies for various epidemiological models." *Mathematical Biosciences &Engineering* 6.3 (2009): 469.

[5] Ullah, Saif, Muhammad Altaf Khan, and Muhammad Farooq. "A fractional model for the dynamics of TB virus." *Chaos, Solitons &Fractals*116 (2018): 63-71.

[6] Revelle, Charles S., Walter R. Lynn, and Floyd Feldmann. "Mathematical models for the economic allocation of tuberculosis control activities in developing nations." *American review of respiratory disease* 96.5 (1967): 893-909.

[7] World Health Organization. Global tuberculosis report 2017. World Health Organization, 2017.

[8] World Health Organization. *Investing to overcome the global impact of neglected tropical diseases: third WHO report on neglected tropical diseases* 2015. Vol. 3. World Health Organization, 2015.

[9] Gavin Churchyard, Peter Kim, N. Sarita Shah, Roxana Rustomjee, Neel Gandhi, Overview of Knowledge About Tuberculosis Transmission, *Infectious Diseases society of America*, (2017), 35.

[10] Daniel TM., The history of tuberculosis. Respiratory medicine, 2006, 100(11):1862-1870.

[11] Waaler, Hans, Anton Geser, and Stig Andersen. "The use of mathematical models in the study of the epidemiology of tuberculosis." *American Journal of Public Health & the Nations Health* 52.6 (1962): 1002-1013.

[12] Athithan, S., and Mini Ghosh. "Mathematical modelling of TB with the effects of case detection and treatment." *International Journal of Dynamics & Control* 1.3 (2013): 223-230.

[13] Ullah, Saif, et al. "Modeling and analysis of Tuberculosis (TB) in Khyber Pakhtunkhwa, Pakistan." *Mathematics & Computers in Simulation* 165 (2019): 181-199.

[14] Raviglione, Mario, and Giorgia Sulis. "Tuberculosis 2015: burden, challenges and strategy for control and elimination." *Infectious disease reports* 8.2 (2016).

[15] Annabel, B., D. Anna, and M. Hannah. "Global tuberculosis report 2019." Geneva: World Health Organization (2019).

[16] Wallis, Robert S. "Mathematical models of tuberculosis reactivation and relapse." *Frontiers in Microbiology* 7 (2016): 669.

[17] Yang, Yali, et al. "Global stability of two models with incomplete treatment for tuberculosis." *Chaos, Solitons & Fractals* 43.1-12 (2010): 79-85.

[18] Liu, Junli, and Tailei Zhang. "Global stability for a tuberculosis model." *Mathematical& Computer Modelling* 54.1-2 (2011): 836-845.

[19] Fatmawati, and Ahmadin. "Mathematical modelling of Tuberculosis in a logistically growing human population with optimal control." *World Journal of Modelling & Simulation*, Vol. 14(2018), 90-99.

[20] Agyeman, Akosua Adom, and Richard Ofori-Asenso. "Tuberculosis-an overview." *Journal of Public Health* and Emergency 1.7 (2017).

[21] World Health Organization (WHO). "Media Centre-Visual Impairment and Blindness Fact Sheet No. 282." (2018).

[22] Ricks, Philip M., et al. "Estimating the burden of tuberculosis among foreign-born persons acquired prior to entering the US, 2005?2009." PLoS One 6.11 (2011).

[23] World Health Organization. "Guidelines for treatment of drug-susceptible tuberculosis and patient care." (2017).

[24] World Health Organization. Global diffusion of Health: making universal health coverage achievable: report of the third global survey on Health. World Health Organization, 2017.

[25] Reves, Randall, and Sahil Angelo. "As Ethiopia moves toward tuberculosis elimination, success requires higher investment." *Washington DC: Center for Strategic and International Studies* (2016).

[26] Turner, Richard D., and Graham H. Bothamley. "Cough and the transmission of tuberculosis." *The Journal of infectious diseases* 211.9 (2015): 1367-1372.

[27] Alene, Kefyalew Addis, et al. "Mapping tuberculosis treatment outcomes in Ethiopia." *BMC infectious diseases* 19.1 (2019): 474.

[28] Silva, Cristiana J., and Delfim FM Torres. "Optimal control of tuberculosis: a review." *Dynamics, games and science. Springer, Cham*, 2015. 701-722.

[29] Rosa, Silvério, and Delfim FM Torres. "Optimal control and sensitivity analysis of a fractional order TB model.",1812(2018).

[30] Nkamba, Leontine Nkague, et al. "Mathematical model to assess vaccination and effective contact rate impact in the spread of tuberculosis." *Journal of Biological Dynamics* 13.1 (2019): 26-42.

[31] Kim, Soyoung, A. Aurelio, and Eunok Jung. "Mathematical model and intervention strategies for mitigating tuberculosis in the Philippines." *Journal of Theoretical Biology* 443(2018): 100-112.

[32] Malik, Maulana, Monica Larasati, and Dipo Aldila. "Mathematical modeling and numerical simulation of tuberculosis spread with diabetes effect." *IOP Conf. Series: Journal of Physics: Conf. Series.* Vol. 1108. 2018.

[33] Tahir, Muhammad, Syed Inayat Ali Shah, and Gul Zaman. "Prevention strategy for superinfection mathematical model tuberculosis and HIV associated with AIDS." *Cogent Mathematics & Statistics* 6.1 (2019): 1637166.

[34] Lenhart, Suzanne, and John T. Workman. "Optimal control applied to biological models". *CRC press*, 2007.

[35] Egonmwan, A. O., and D. Okuonghae. "Analysis of a mathematical model for tuberculosis with diagnosis." *Journal of Applied Mathematics and Computing* 59.1-2 (2019): 129-162.

[36] Banerjee, Sandip. Mathematical modeling: models, analysis and applications. *CRC Press*, 2014.

[37] Mitchell, Tarissa, et al. "Immigrant and refugee health: a centers for disease control and prevention perspective on protecting the health and health security of individuals and communities during planned migrations." *Pediatric Clinics* 66.3 (2019): 549-560.

[38] Van den Driessche, Pauline, and James Watmough. "Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission." *Mathematical biosciences* 180.1-2 (2002): 29-48.

[39] Merkin, David R. Introduction to the Theory of Stability. Vol. 24. *Springer Science & Business Media*, 2012.

[40] La Salle, Joseph P. The stability of dynamical systems. *Society for Industrial and Applied Mathematics*, 1976.

[41] Wang, Yi, and Jinde Cao. "Global dynamics of multi-group SEI animal disease models with indirect transmission." *Chaos, Solitons & Fractals* 69 (2014): 81-89.

[42] Wang, Yi, and Jinde Cao. "Global stability of general cholera models with non-linear incidence and removal rates." *Journal of the Franklin Institute* 352.6 (2015): 2464-2485.

[43] Coddington, Earl A., and Norman Levinson. "Theory of ordinary differential equations". *Tata McGraw-Hill Education*, 1955.

[44] Chong, Edwin KP, and Stanislaw H. Zak. An introduction to optimization. *John Wiley & Sons*, 2004.

[45] Baba, Isa Abdullahi, Rabiu Aliyu Abdulkadir, and Parvaneh Esmaili. "Analysis of tuberculosis model with saturated incidence rate and optimal control." *Physica A: Statistical Mechanics and its Applications* 540 (2020): 123-237.

[46] Pontryagin, Lev S., et al. "The mathematical theory of optimal processes, translated by KN Trirogoff." New York (1962).

[47] United nation, Department of Economics and Social affairs population dynamics report, 2019.

[48] Kelemu Mengistu, Ashenafi, and Peter J. Witbooi. "Modeling the Effects of Vaccination and Treatment on Tuberculosis Transmission Dynamics." *Journal of Applied Mathematics* 2019(2019).

[49] Central Statistical Agency of Ethiopia(CSA), 2007.

[50] World Health Organization. "Global tuberculosis report 2018." *Geneva: World Health Organization*(2019).

[51] Castillo-Chavez, Carlos, and Baojun Song. "Dynamical models of tuberculosis and their applications." *Mathematical Biosciences & Engineering* 1.2 (2004): 361.

[52] Carr, Jack. Applications of centre manifold theory. Vol. 35. *Springer Science & Business Media*, 2012.

[53] Adebisi, Yusuff Adebayo, et al. "Burden of tuberculosis and challenges facing its eradication in West Africa." *target* 4.5 (2020).

[54] Shirima Sabini, Theresia, Jacob Ismail Irunde, and Dmitry Kuznetsov. "Modeling the Transmission Dynamics of Bovine Tuberculosis." *International Journal of Mathematics and Mathematical Sciences* 2020 (2020).

[55] East Shewa Administration Zone, 2019.

[56] Rovin, Kimberly, Karen Hardee, and Aklilu Kidanu. "Linking population, fertility, and family planning with adaptation to climate change: perspectives from Ethiopia." *African journal of reproductive health* 17.3 (2013): 15-29.

[57] Wiggins, Stephen. Introduction to applied nonlinear dynamical systems and chaos. Vol. 2. *Springer Science & Business Media*, 2003.