ADAMA SCIENCE AND TECHNOLOGY UNIVERSITY
SCHOOL OF APPLIED NATURAL SCIENCE
APPLIED MATHEMATICS DEPARTMENT

MATHEMATICAL MODEL FOR THE DYNAMICS OF TUBERCULOSIS TRANSMISSION

By
ADEM IBRAHIM
Advisor:
Dr. SHIFERAW FEYISSA

A Thesis Submitted to Applied Mathematics Department School of Applied Natural Science
Presented in partial fulfillment of the requirement for the degree of master's in Applied Mathematics (Specialization in Mathematical Modeling)

Office of Graduate Studies

ADAMA,ETHIOPIA
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Declaration

This thesis is my original work and has not been presented before in application for a higher degree in any other university, and that all sources of the material used for the thesis have been duly acknowledged.

(Advisor)
Signature .....

Adem Ibrahim
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Advisor's Approval Sheet

To:Applied Mathematics program

Subject:Thesis Submission

This is to certify that the thesis entitled "Mathematical model for the dynamics of TB Transmission"submitted in partial fulfillment of the requirements for MSc.degree in Applied Mathematics, and has been carried out by Adem Ibrahim under my supervision. Therefore, I recommend that the student has fulfilled the requirements and hence hereby he can submit the thesis to the department.

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Approval Page

This is to certify that the thesis prepared by Adem Ibrahim, entitled "Mathematical model for the dynamics of TB Transmission"and submitted in partial fulfillment of the requirements for the degree of Master's of Science in Applied Mathematics (Specialization in Mathematical Modeling). As a member of the board of examiners of the MSc.Thesis open defense examination, we certify that we have read and evaluated the thesis prepared by Adem Ibrahim and examined the candidate. We recommended that the thesis be accepted as fulfilling the thesis requirement for the degree of Master's of Science in Applied Mathematics.

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List of Abbreviations

BCG ——————————— Bacille Calmette-Gurin

DFE ——————————— Disease Free Equilibrium.

DOTS ——————————— Directly Observed Therapy Short course

EE ———————————- Endemic Equilibrium.

HIV ——————————— Human immunodeficiency virus

LTBI ———————————- Latent tuberculosis infection

MDG ———————————- Millennium Development Goal

MDR-TB ——————————— Multidrug-resistant tuberculosis

MTB ——————————— Mycobacteriam tuberculosis

R_0 ———————————- Basic reproductive number

SEIR ———————————- Susceptible, exposed, infectious, recovered

SEIS ——————————— Susceptible, exposed, infectious, susceptible

TB ——————————— Tuberculosis

WHO ——————————— World Health Organization

XDR-TB ———————————- Extensively drug-resistant tuberculosis

Abstract

In this study,we modified a mathematical model for the dynamics of tuberculosis transmission using a system of non linear ordinary differential equations. The equilibrium points of the model are investigated and their local stability were determined. The basic reproduction number of the model was obtained using next generation matrix. The disease free equilibrium point is globally asymptotically stable if reproduction number is less than one and the endemic equilibrium point is a globally asymptotically stable if reproduction number is greater than one. The analytic solution were supplemented by the numerical simulation using MATLAB.

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Chapter 1

Introduction

1.1 A mathematical model

A mathematical model is an abstract that uses mathematical language to describe the behavior of a system, designed to aid computations and predictions. Mathematical models are used particularly in the natural sciences and engineering disciplines and also in the social sciences (such as economics, sociology and political science); physicists, engineers, computer scientists, and economists use mathematical models most extensively (Science Daily, 2012).

(Eykhoff ,1974) defined a mathematical model as a representation of the essential aspects of an existing system (or a system to be constructed) which presents knowledge of that system in usable form.

Mathematical model and analysis is central to disease epidemiology. The progress of an epidemic through the population is highly amenable to mathematical model. In particular, the first attempt to model and hence predict or explain patterns dates back over 100 years, although it was the work of (Kermack and McKendrick ,1927) that established the basic foundations of the subject. Once a model that captures the main features of the progression and transmission of a particular disease in a population has been formulated, it can be used to predict the effects of different strategies for disease eradication or control.

1.2 Tuberculosis (TB)

Tuberculosis (TB) is caused by a bacterium called mycobacterium tuberculosis. TB bacteria usually attack the lungs and any part of the body such as the kidney, spine, and brain. If not treated properly, TB disease can be fatal. Latent TB infection can live in the body without making sick. In most people who breath in TB bacteria and become infected, the body is able to fight the bacteria to stop them from growing and TB bacteria become active if the immune system can't stop them from growing .

TB is still a first-class public health challenge and remains the major cause of deaths at the global level, especially in low and middle income countries. Due to its high rate of mortality, this infection is listed in the 10 most causes of deaths in the world. After HIV/AIDS, TB is the second deadliest disease due to a single infectious agent. TB is also known as aerosol transmitted disease because it is mainly spread from an actively TB infected person to a susceptible person through air during coughing, spitting, sneezing, or even talking. This infection is called pulmonary TB and typically affects the human lungs, though it can also invade other body organs. In the case of TB outside the lungs and involving body parts like the bones, spine, central nervous system, and so on, it is known as extra-pulmonary TB.

Most TB patients have a strong immune system and are able to control MTB bacteria, but cannot eliminate it. These infected individuals are not infectious, although they usually test positive. However, it is possible that after an exposed period of years (or decades), these individuals may become symptomatic and infectious. The TB progression for these individuals is comparatively slow. Beside this, some chronic diseases, such as HIV and diabetes can reduce the capacity of the immune system of the infected individuals. TB patients with such chronic diseases are at high risk of developing into active TB, and have a shorter latent period in comparison with those without this disease. TB progression for these individuals to active TB is much faster. It has been observed that a person with HIV infection has 30-50 times more chances to develop active TB than those without HIV (Stevens et al.,2014).
Despite significant advances in TB treatment and control, it is reported by the World

Health Organization (WHO) that one-third of the worlds population is exposed to TB, creating a reservoir for future disease (WHO, 2018). More than 10.4 million new cases were reported worldwide, resulting in 1.4 million TB-induced deaths in 2016. Besides this, about 10.4 million people died from TB disease among patients living with HIV. Most of the deaths due to this infection (over 95%) are reported in the low and middle income countries including India, Pakistan, China, Indonesia, Philippines, Nigeria, South Africa and Ethiopia , where the cost of diagnosis and treatment is high, and not easily accessible. These countries contribute more than 60% of the whole TB burden (WHO , 2018).

Prolonged latency between infection and subsequent disease is characteristic of TB and has important implications for epidemiology. Therefore, from the earliest mathematical models of tuberculosis transmission, latent compartments have been incorporated . Such studies typically model the incidence of active cases as proportional to the number of persons latently infected, and represent the force of infection as a function of the number of persons with active disease, usually assuming frequency-dependent transmission.
Most previously developed models aim to answer specific questions about the likely impact of individual interventions on the burden of TB in a hypothetical population. While models have been developed to estimate the global impact of a bundled intervention such as DOTS, the practical impact of implementation of multi-factorial programmatic strategies at a local or regional level is less frequently modeled. In this study, we aimed to add education about TB on infected class to take TB drugs properly.

1.3 Statement of the problem

Tuberculosis (TB) is a worldwide pandemic disease. TB is a bacterial infection by mycobacterium tuberculosis which most commonly attacks the lungs. It can also affect the circulatory system, bones, joints, central nervous system (causing meningitis), even the skin. 75% of TB cases are lung infections. Tuberculosis is a contagious disease spread through the air. Its communicability is similar to the common cold which

spreads via sputum (phlegm) which is exhaled or sprayed in a sneeze or while speaking. Only persons with active lung infections can spread the disease. It is estimated that 1.6 million people died , one third of the worlds population is infected with TB and a new infection occurred globally every second (WHO , 2015). Tuberculosis has existed for millennial and remains a major global health problem. It causes ill-health for approximately 10 million people each year and is one of the top ten causes of death worldwide (WHO ,2017).

This study is intended to answer the following basic questions:

✓ How to formulate a mathematical model which describes the transmission dynamics of TB ?

✓ what are the basic assumption in developing the mathematical model which describes transmission dynamics of TB ?

✓ what are the interpretations of the solution of the model ?

1.4 Objectives

1.4.1 General objective of the study

The objective of this study is to find the transmission dynamics of TB.

1.4.2 The specific objective of the study

The specific objective of these study are to:

✓ formulate a mathematical model which describes the effect of education on the transmission dynamics of TB.

✓ perform model analysis.

✓ interprate the solution of the model.

1.5 Significance of the study

This study provides a reliable information on how we can use the mathematical modeling to know the dynamics of TB transmission. Our designed model will help health authorities to understand the dynamics of TB and set strategies on the burden of the disease TB transmission.

Methodology

A mathematical model TB transmission will be formulated using a system of ordinary differential equations. Mathematical methods of analysis of differential equations will be applied to derive conditions or threshold parameters that characterize the behavior of disease. The study will involve both qualitative and quantitative analysis of the mathematical model and sensitivity analysis of model parameters for their effects on the outcome of the model results or predictions will be performed.

1.6 Preliminaries

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.

1.6.1 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, 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(λ)< 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(λ)$<$

0 is the Routh-Hurwitz conditions (Kenrad E Nelson, 2013). These Routh-Hurwitz condition are with $a_n > 0$,

$$D_1 = a_1 > 0$$

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

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

$$\vdots$$

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

1.6.2 Derivation of the basic reproductive number

The basic reproductive number, R_0, is the average number of secondary cases produced by one infected individual during the infected individuals entire infectious period when the disease is first introduced (Hyman .J. M et al , 2000). It is used as a predictor for epidemic outbreaks or an estimator of how severe an epidemic outbreak will be. The basic reproductive number is calculated as the dominant eigenvalue of the next generation matrix at the disease-free equilibrium when the entire population is susceptible (Philipps.S et al. , 2011). Factors such as the duration of infectiousness, the infectiousness of an individual and the number of susceptible people with whom the infected individual comes into contact, affect the basic reproduction number.

Suppose that ψ is the probability of infection given a contact between an infected and a susceptible individual, c is the average rate of contacts between infected and susceptible individuals and d is the duration of infectiousness.

Then $R_0 = \psi.c.d.$

A more formal approach to the derivation of the basic reproductive number, R_0 , follows from (Watmough and Van den Driessche ,2008) and (Shuai and Van den Driessche ,2013). To illustrate, let us consider a general compartmental disease transmission model below.

$$\tilde{x} = F(x, y) - V(x, y), \tilde{y} = g(x, y) \tag{1.6.1}$$

where $g = (g_1, ..., g_m)^T, x = (x_1, ..., x_n)^T \in R_m$ represents the populations in disease compartments, $y = (y_1, ..., y_m)^T \in R_m$represents the populations in disease-free compartments.

In addition,

$F = (F_1, ..., F_n)^T$,where F_i represents the rate of new infections in the i^{th} disease compartment and $V = (V_1, ..., V_n)^T$, where V_i represents a net outflow from the i^{th} compartment. The following assumptions are made to ensure the existence of a disease-free equilibrium (DFE) and that the model is well posed.

Assume that $F_i(0, y) = 0, V_i(0, y) = 0, F_i(x, y) \geq 0, V_i(x, y) \leq 0$ when $x_i = 0$ and $\sum_{i=1}^{n} V_i(x, y) \geq 0$ for all $x, y \geq 0, i = 1, ..., n$.

In addition, assume that the disease-free system $y = g(0, y)$ has a unique equilibrium $y = y_0 \geq 0$ that is locally asymptotically stable within the disease-free space. In other words, all solutions with initial conditions of the form (0,y) approach the disease free equilibrium $(0, y_0)$ as $t \longrightarrow \infty$. Let the two $n \times n$ matrices

$$F = \frac{\partial F_i}{\partial x_j}(0, y_0)$$

and

$$V = \frac{\partial V_i}{\partial x_j}(0, y_0)$$

be defined such that $F \geq 0$ and $V^{-1} \geq 0$.

The next generation matrix is then defined as

$$K = FV^{-1} \tag{1.6.2}$$

and the basic reproduction number R_0 is defined as the dominant eigenvalue of K, i.e $R_0 = \rho(FV^{-1})$.

The DFE $P_0 = (0, y_0)$ is said to be locally asymptotically stable if $R_0 = \rho(FV^{-1}) < 1$ and

unstable if $R_0 = (FV^{-1}) > 1$

Autonomous Linear system

Consider a system of Ordinary differential equation which are autonomous

$$\begin{cases} \dfrac{dx}{dt} = f(x,y) \\ \dfrac{dy}{dt} = g(x,y) \end{cases} \tag{1.6.3}$$

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 (1.6.3). If f and g are n-times continuously differentiable functions, then using the Taylor series expansion :

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

$$\begin{aligned} &\approx f(x_0,y_0) + f_x(x_0,y_0)(x-x_0) + f_y(x_0,y_0)(y-y_0) \\ &= f_x(x_0,y_0)(x-x_0) + f_y(x_0,y_0)(y-y_0) \end{aligned}$$

Also,

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

$$\begin{aligned} &\approx g(x_0,y_0) + g_x(x_0,y_0)(x-x_0) + g_y(x_0,y_0)(y-y_0) \\ &= g_x(x_0,y_0)(x-x_0) + g_y(x_0,y_0)(y-y_0) \end{aligned}$$

Then, the linearized form of equation (1.6.3) 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 the 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 $\det(x(A - \lambda I)) = 0$

Global Stability

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

Definition 1. A function V: $R^n \to R$ 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 V is positive definite and $V' \leq 0 \ \forall x \in D/\{x_0\}$.

Theorem 1. Let x_0 be an equilibrium point of the system

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

Let $V : D \in R^n \to R$ be continuously differentiable function such that

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

Then the point x_0 is globally asymptotically stable.

Definition 2. (*Invariant Set*) A set L is an invariant set with respect to (1.6.3) if

$$x(0) \in L \Rightarrow x(t) \in L, \forall t \in \Re_+$$

Definition 3. (*Positively Invariant Set*) A set L is a positively invariant set with respect to (1.6.3) if

$$x(0) \in L \Rightarrow x(t) \in L, \forall t \geq 0$$

1.6.3 Sensitivity analysis

Sensitivity is defined as a way of quantifying how a small change in parameters used in a model affects state variables over time. It is thus important in determining how easily affected the equilibrium is by small changes in parameters.
According to (Shrestha and Lloyd-Smith, 2010), model outputs contain uncertainties from two main sources, which are parameter values used in the model and model structure itself. Sensitivity analysis is done to determine the parameters or changes in the model structure that are most important in determining model outputs. It therefore helps in identifying components of the system that should be targeted for possible disease control measures or interventions or where further information or data need to be collected.

Chapter 2

Literature Review

Chung et al.,(2012) proposed a mathematical model to examine tuberculosis (TB) dynamics and to assess potential infection risk in Taiwan. A well-established mathematical model of TB transmission built on previous models was adopted to study the potential impact of TB transmission. A probabilistic risk model was also developed to estimate site-specific risks of developing disease soon after recent primary infection,exogenous reinfection,or through endogenous reactivation (latently infected TB) among Taiwan regions. Here, they showed that the proportion of endogenous reactivation (53-67%) was larger than that of exogenous reinfection (32-47%). Their simulations showed that as epidemic reaches a steady state, age distribution of cases would finally shift toward older age groups dominated by latently infected TB cases as a result of endogenous reactivation. A comparison of age-weighted TB incidence data with their model simulation output with 95% credible intervals revealed that the predictions were in an apparent agreement with observed data. The median value of overall basic reproduction number (R_o) in eastern Taiwan ranged from 1.65 to 1.72 , where as northern Taiwan had the lowest R_o estimate of 1.50. They found that total TB incidences in eastern Taiwan had 25-27% probabilities of total proportion of infected population exceeding 90% , where as there were 36-66% probabilities having exceeded 20% of total proportion of infected population attributed to latently infected TB. They suggested that their Taiwan-based analysis can be extended to the context of developing countries, where TB remains a substantial cause of elderly morbidity and mortality.

Rui Xu et al.,(2012) investigated an SEIS epidemiological model with a saturation incidence rate and a time representing the latent period of the disease. By means of Lyapunov functional, LaSalle's invariance principle and comparison arguments, it was shown that the global dynamics is completely determined by the basic reproduction number. It is proven that the basic reproduction number is a global threshold parameter in the sense that if it is less than unity, the disease-free equilibrium is globally asymptotically stable and therefore the disease dies out; whereas if it is greater than unity, there is a unique endemic equilibrium which is globally asymptotically stable and thus the disease becomes endemic in the population.

Andam et al.,(2013) proposed a Susceptible - Exposed - Infected - Recovered (SEIR) epidemiological model to investigate the transmission of tuberculosis. The equilibrium points of the model were found and their stability was investigated. By analyzing the model, they found a threshold parameter R_0, the basic reproductive number. It was noted that when R_o <1 the disease will fail to spread and when R_o >1 the disease will persist in the population and become an endemic. The model had two equilibrium namely the disease - free equilibrium and the endemic equilibrium. Using the Routh - Hurwitz stability theorem and computer simulations, it was observed that the number of immunized individuals in the population will increase the level of immunity.

Nidhi Nirwani et al.,(2014) a mathematical model is proposed and analyzed to study the dynamics of tuberculosis based on MSEIR model. They assumed that the rate at which number of latently infected individuals moves to recovery class R and again from recovery class to latent class L is not equal. The possibility of existence of endemic equilibrium state is discussed and examined the basic reproduction number.

Dontwi et al.,(2014) proposed a Susceptible - Exposed - Infected - Recovered (SEIR) epidemiological model is formulated to determine the transmission of tuberculosis. The equilibrium points of the model are found and their stability is investigated. By analyzing the model, a threshold parameter R_0 was found which is the basic reproductive number. It is noted that when $R_0 < 1$ the disease will fail to spread and when

$R_0 > 1$ the disease will persist in the population and become endemic. The model has two nonnegative equilibrium namely the disease free equilibrium and the endemic equilibrium.

Dago et al.,(2015) deterministic mathematical model to have a better insight in the transmission dynamics of TB. The model is shown to have disease-free and endemic equilibrium and their local stabilities are established using the basic reproduction number, R_o. If $R_o < 1$, the infection can be controlled and then eradicated and when $R_o > 1$, the disease will persist.

Ikhimwin et al.,(2016) extended a mathematical model for the transmission dynamics of tuberculosis that examined the impact of certain factors on tuberculosis case detection (Okuonghae , 2011). The extended model now classifies the latently infected individuals by their level of tuberculosis awareness (as was done for the susceptible sub-population) and further expands the number of key factors that can positively affect the tuberculosis case detection rate. The effect of these identified factors on the associated reproduction number of the model is considered. It is shown that the system can undergo the phenomenon of backward bifurcation when the associated reproduction number of the model is less than unity; in a special case, the effect of exogenous re-infection on the backward bifurcation phenomenon is significantly dictated by the level of awareness of the latently infected individuals. Qualitative and quantitative analysis of the model showed the effect of key identified factors on the dynamics of tuberculosis while suggesting a serious concentration on tuberculosis awareness programmes, active case finding strategies and use of active cough identification for identifying likely TB cases and sustaining awareness campaigns over a long period of time.

Lapaan et al.,(2016) proposed a Tuberculosis infection model is formulated and investigated. They showed the existence of disease free equilibrium and endemic equilibrium points. They used La Salle-Lyapunov Invariance Principle to show that if the reproductive number $R_0 < 1$, the disease-free equilibrium of the model is globally

asymptotically stable. Numerical simulations are then performed to illustrate the existence of the disease free equilibrium and the endemic equilibrium point for a given value of R_0. Thus, when $R_0 < 1$, the disease dies out in the population.

In this thesis we will be trying to modify Andam et al.,(2013) model to add education in infected individuals class to take TB drugs properly will become recovered class and recovered class is return to back to susceptible individuals class by using a mathematical model and numerical solution. Therefore, we have to take TB education for the infected individual population .

• We educate for infected person must be receive TB drug properly.

Chapter 3

Model Formulation and Analysis

Model Formulation

The total population at time t, denoted by N(t), is divided into four compartments of susceptible (S(t)) , exposed (E(t)) , infective (I(t)) and the recovered (R(t)). Let Λ be the recruitment rate of individuals into the susceptible class (S). We assume that μ is the natural death rate in all epidemiological classes. Let d be the TB-induced death rates of infected persons (I). Let δ be the rate of recovery due to education to take TB drug properly. The susceptible and infected persons contact with rate of β. Persons move from exposed to infectious compartments with progression rate α. Persons move from infected to recovered compartments with progression rate γ. A persons can die at any stage by natural causes. The recovered individuals persons do enter into the susceptible class again. By considering the above assumptions, the interaction between the four compartments is shown in the schematic diagram in Figure 3.1

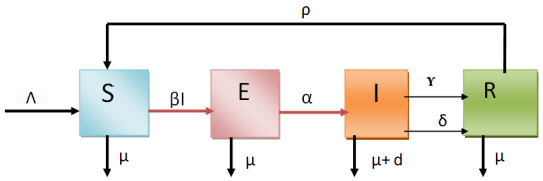

Figure 3.1: Model diagram of the transmission dynamics of TB

Table 3.1: Description of variables

Variables	Interpretation
S(t)	The number of susceptible individual at time t.
E(t)	The number of latently infected individual at time t.
I(t)	The number of infective individuals at time t.
R(t)	The number of recovered individuals at time t.
N(t)	The total population size.

Table 3.2: Parameters of the model

Parameters	Interpretation
Λ	recruitment rate
β	the transmission rate
μ	natural mortality rate
α	the rate at which an individual leaves the latent class by becoming infectious
γ	the rate of recover
δ	the rate of recovery due to education to take TB drug properly
ρ	the rate at which the recovered lose their immunity
d	disease induced death rate

3.1 Model equations

Applying the assumptions above, the total population, N is at full capacity. Also, the individuals are likely to be infected by the infectious individuals in case of contact except those who are immune. Those who are undetected or late detected infectious are the ones contributing to the disease transmission and spread. The rate at which the susceptible class changes is equal to the rate at which infections occur. This occurs when the disease is passed from an infective individual to a susceptible one. The number of susceptible infective contacts is proportional to the product of S(t) and I(t). Hence the rate of change in the susceptible individuals is

$$\frac{dS}{dt} = \Lambda - \beta SI - \mu S + \rho R$$

where βI is rate of infection. The term βI is negative because the number of susceptible individuals decreases. The number of individuals in the exposed class increases since those in the susceptible class becomes exposed to the disease. Let α the rate which an exposed individual becomes infectious. Then the rate of change of the exposed population is given by

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

Let γ be the rate at which an infected individual may recover and δ be the rate at recovery due to education to take TB drug properly. The rate of change of the infective individuals will be

$$\frac{dI}{dt} = \alpha E - (\mu + d + \gamma + \delta)I$$

The rate of change of the recovered is given by

$$\frac{dR}{dt} = (\gamma + \delta)I - (\mu + \rho)R$$

This leads to the following formulations of the $SEIR$ model from the description, assumptions and compartmental diagram and was given as follows;

$$\begin{cases} \frac{dS}{dt} = \Lambda - \beta SI - \mu S + \rho R \\ \frac{dE}{dt} = \beta SI - (\mu + \alpha)E \\ \frac{dI}{dt} = \alpha E - (\mu + d + \gamma + \delta)I \\ \frac{dR}{dt} = (\gamma + \delta)I - (\mu + \rho)R \end{cases} \tag{3.1.1}$$

$$N(t) = S(t) + E(t) + I(t) + R(t)$$

With $S(0) = S_0 > 0, E(0) = E_0 \geq 0, I(0) = I_0 \geq 0, R(0) = R_0 \geq 0$

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dE}{dt} + \frac{dI}{dt} + \frac{dR}{dt} = \Lambda - \mu N - dI$$

Invariant Region

This region will be obtained by considering the following theorem.

Theorem 1

The solutions of the system (3.1.1) are feasible for all $t > 0$ if they enter the invariant region Ω.

proof

Let $\{\Omega = (S, E, I, R) \in \Re_+^4\}$ be any solution of the system (3.1.1) with non-negative initial conditions. From the second equation (3.1.1) in absence of the disease (TB), we have I = 0 , and equation (3.1.1) becomes

$$\frac{dN}{dt} \leq \Lambda - \mu N,$$

$$\frac{dN}{dt} + \mu N \leq \Lambda.$$

Finding the integrating factor,

$$(IF) = e^{\int \mu dt} = e^{\mu t}$$

$$e^{\mu t}N + \mu N e^{\mu t} \leq \Lambda e^{\mu t}$$

$$\frac{d}{dt}(Ne^{\mu t}) \leq \Lambda e^{\mu t}$$

Integrating both sides we get;

$$Ne^{\mu t} \leq \frac{\Lambda}{\mu}e^{\mu t} + c,$$

where c is a constant of integration.

$$N \leq \frac{\Lambda}{\mu} + ce^{-\mu t}.$$

Taking the initial conditions; when t = 0, $N(0) = N_0$.

$$N_0 - \frac{\Lambda}{\mu} \leq c,$$

$$N \leq \frac{\Lambda}{\mu} + (N_0 - \frac{\Lambda}{\mu})e^{-\mu t}.$$

we obtain $0 \leq N \leq \frac{\Lambda}{\mu}$ as $t \longrightarrow \infty$.

Therefore, the feasible solutions set of the model (3.1.1) enters the region

$$\{\Omega = (S, E, I, R) \in \Re_+^4 | S \geq 0, E \geq 0, I \geq 0, R \geq 0, N \leq \frac{\Lambda}{\mu}\}.$$

Thus in this region our model is biologically feasible. Here whenever $N > \frac{\Lambda}{\mu}$, then $\frac{dN}{dt} < 0$,which means the population reduces asymptotically to the carrying capacity and whenever $N \leq \frac{\Lambda}{\mu}$ every solution with initial condition in Ω remains in that region for $t > 0$, so the model is well posed in Ω. Therefore, the region Ω is positively-invariant (i.e. solutions remain positive for all times, t) and the model is well posed and biologically meaningful.□

Positivity of solution

Theorem 2: The solution for the system (3.1.1) is positive for non negative initial conditions.

Proof: Let $t_1 = Sup\{t > 0 : S(0) > 0, E(0) > 0, I(0) > 0 and R(0) > 0\}$.

From the first equation of model (3.1.1), it follows that

$$\frac{dS}{dt} = \Lambda - (\beta I + \mu)S + \rho R$$

$$\frac{dS}{dt} = \Lambda + \rho R - (\beta I + \mu)S$$

which can be rewritten as

$$\frac{d}{dt}[S(t)exp\{\mu t+\int_0^t \beta I(\tau)d\tau\}]=(\Lambda+\rho R)exp\{\mu t+\int_0^t \beta I(\tau)d\tau\}.$$

Thus,

$$S(t_1)exp\{\mu t+\int_0^t \beta I(\tau)d\tau\}-S(0)=\int_0^{t_1}(\Lambda+\rho R)[exp\{\mu y+\int_0^y \beta I(\tau)d\tau\}]dy.$$

So that,

$$S(t_1)=S(0)exp[-\mu t_1-\int_0^t \beta I(\tau)d\tau]+[exp\{-\mu t_1-\int_0^t \beta I(\tau)d\tau\}]\times\int_0^{t_1}(\Lambda+\rho R)[exp\{\mu y+\int_0^y \beta I(\tau)d\tau\}]dy>0.$$

Similarly, it can be shown that $E(0)>0, I(0)>0$ and $R(0)>0$ for all $t>0$.
Thus, all solutions of the system (3.1.1) remain positive for all non-negative initial conditions.

3.2 Model analysis

In this section, we find the disease free-equilibrium, endemic equilibrium, basic reproduction number and stability of the system.

3.2.1 Equilibrium points

Under this, we will find the equilibrium points of the system.

$$\begin{cases}\Lambda-\beta SI-\mu S+\rho R=0\\ \beta SI-(\mu+\alpha)E=0\\ \alpha E-(\mu+d+\gamma+\delta)I=0\\ (\gamma+\delta)I-(\mu+\rho)R=0\end{cases} \tag{3.2.1}$$

Disease-free equilibrium point

At disease-free equilibrium, it is assumed that there is no disease in the system, therefore substituting I= 0 , into the above equations will yield

$$\begin{cases}\Lambda-\beta S(0)-\mu S+\rho R=0\\ \beta S(0)-(\mu+\alpha)E=0\\ \alpha E-(\mu+d+\gamma+\delta)(0)=0\\ (\gamma+\delta)(0)-(\mu+\rho)R=0\end{cases}$$

which reduces to

$$\Lambda - \mu S = 0 \Rightarrow S = \frac{\Lambda}{\mu}, E = 0 \quad and \quad R = 0.$$

Thus, the disease free-equilibrium is

$$(S, E, I, R) = (\frac{\Lambda}{\mu}, 0, 0, 0).$$

Endemic equilibrium point

Endemic equilibrium state indicates that the disease persists in the system. Here, we will be solving four systems of equations to obtain the values of S , E , I and R. However, the endemic equilibrium point will be denoted by (S^*, E^*, I^*, R^*).
From equation (3.2.1),

$$I = \frac{\alpha}{(\mu + d + \gamma + \delta)} E. \tag{3.2.2}$$

Also from equation (3.2.1)

$$S = \frac{(\mu + \alpha)}{\beta I} E. \tag{3.2.3}$$

Substituting equation (3.2.2) into equation (3.2.3) will give us

$$S = \frac{(\mu + \alpha)}{\beta} E \times \frac{(\mu + d + \gamma + \delta)}{\alpha E}$$

$$\Rightarrow S^* = \frac{(\mu + \alpha)(\mu + d + \gamma + \delta)}{\beta \alpha}. \tag{3.2.4}$$

$$\begin{aligned} R &= \frac{(\gamma + \delta)}{(\mu + \rho)} I \\ &= \frac{(\gamma + \delta)\alpha}{(\mu + \rho)(\mu + d + \gamma + \delta)} E \end{aligned} \tag{3.2.5}$$

From equation (3.2.1), $\beta SI = (\mu + \alpha)E$
substituting the above expression into the first equation (3.2.1) will yield

$$\Lambda - (\mu + \alpha)E - \mu S^* + \rho(\frac{(\gamma + \delta)\alpha}{(\mu + \rho)(\mu + d + \gamma + \delta)})E = 0$$

$$(\mu+\alpha)E-\rho\frac{(\gamma+\delta)\alpha}{(\mu+\rho)(\mu+d+\gamma+\delta)}E=\Lambda-\mu S^*$$
$$E((\mu+\alpha)-\frac{\alpha\rho(\gamma+\delta)}{(\mu+\rho)(\mu+d+\gamma+\delta)})=\Lambda-\mu S^*$$
$$E(\frac{(\mu+\alpha)(\mu+\rho)(\mu+d+\gamma+\delta)-\alpha\rho(\gamma+\delta)}{(\mu+\rho)(\mu+d+\gamma+\delta)})=\Lambda-\mu S^*$$
$$E=\frac{(\mu+\rho)(\mu+d+\gamma+\delta)(\Lambda-\mu S^*)}{(\mu+\alpha)(\mu+\rho)(\mu+d+\gamma+\delta)-\alpha\rho(\gamma+\delta)}$$
$$\Rightarrow E^*=\frac{(\mu+\rho)(\mu+d+\gamma+\delta)(\alpha\beta\Lambda-\mu(\mu+\alpha)(\mu+d+\gamma+\delta))}{\alpha\beta((\mu+\alpha)(\mu+\rho)(\mu+d+\gamma+\delta)-\alpha\rho(\gamma+\delta))}. \tag{3.2.6}$$

From equation (3.2.2)

$$\begin{aligned} I &= \frac{\alpha}{(\mu+d+\gamma+\delta)}E^* \\ &= \frac{\alpha}{(\mu+d+\gamma+\delta)}(\frac{(\mu+\rho)(\mu+d+\gamma+\delta)(\alpha\beta\Lambda-\mu(\mu+\alpha)(\mu+d+\gamma+\delta))}{\alpha\beta((\mu+\alpha)(\mu+\rho)(\mu+d+\gamma+\delta)-\alpha\rho(\gamma+\delta))}) \\ &= \frac{(\mu+\rho)(\mu+d+\gamma+\delta)(\alpha\beta\Lambda-\mu(\mu+\alpha)(\mu+d+\gamma+\delta))}{\beta(\mu+d+\gamma+\delta)((\mu+\alpha)(\mu+\rho)(\mu+d+\gamma+\delta)-\alpha\rho(\gamma+\delta))}) \\ \Rightarrow I^* &= \frac{(\mu+\rho)(\alpha\beta\Lambda-\mu(\mu+\alpha)(\mu+d+\gamma+\delta))}{\beta((\mu+\alpha)(\mu+\rho)(\mu+d+\gamma+\delta)-\alpha\rho(\gamma+\delta))}. \end{aligned} \tag{3.2.7}$$

and from equation (3.2.1)

$$\begin{aligned} R &= \frac{(\gamma+\delta)}{(\mu+\rho)}I^* \\ &= \frac{(\gamma+\delta)}{(\mu+\rho)}\frac{(\mu+\rho)(\alpha\beta\Lambda-\mu(\mu+\alpha)(\mu+d+\gamma+\delta))}{\beta((\mu+\alpha)(\mu+\rho)(\mu+d+\gamma+\delta)-\alpha\rho(\gamma+\delta))} \\ \Rightarrow R^* &= \frac{(\gamma+\delta)(\mu+\rho)(\alpha\beta\Lambda-\mu(\mu+\alpha)(\mu+d+\gamma+\delta))}{\beta(\mu+\rho)((\mu+\alpha)(\mu+\rho)(\mu+d+\gamma+\delta)-\alpha\rho(\gamma+\delta))}. \end{aligned} \tag{3.2.8}$$

Therefore, endemic equilibrium Point (S^*, E^*, I^*, R^*) is expressed as follows:

$$\begin{cases} S^* = \frac{(\mu+\alpha)(\mu+d+\gamma+\delta)}{\beta\alpha} \\ E^* = \frac{X[R_0-1]}{\alpha\beta-M} \\ I^* = \frac{\mu[R_0-1]}{\beta-M} \\ R^* = \frac{G\mu[R_0-1]}{H[\beta-M]} \end{cases} \tag{3.2.9}$$

With:

$$X=\mu(\mu+d+\gamma+\delta),\quad M=\frac{\alpha\rho(\gamma+\delta)}{(\mu+\rho)(\mu+\alpha)(\mu+d+\gamma+\delta)},\quad G=\gamma+\delta,\quad H=\mu+\rho$$

Condition of Existence

The system will remain positive provided this condition holds:

$$S^*=\frac{(\mu+\alpha)(\mu+d+\gamma+\delta)}{\beta\alpha}>0.$$

$$E^* = \frac{X[R_0 - 1]}{\alpha\beta - M} > 0$$

$$\Leftrightarrow X[R_0 - 1] > 0$$

$$\Leftrightarrow R_0 - 1 > 0$$

$$\Leftrightarrow R_0 > 1 \quad and \quad \alpha\beta - M > 0.$$

$$I^* = \frac{\mu[R_0 - 1]}{\beta - M} > 0$$

$$\Leftrightarrow \mu[R_0 - 1] > 0$$

$$\Leftrightarrow R_0 - 1 > 0$$

$$\Leftrightarrow R_0 > 1 \quad and \quad \beta - M > 0.$$

and

$$R^* = \frac{G\mu[R_0 - 1]}{H[\beta - M]} > 0$$

$$\Leftrightarrow G\mu[R_0 - 1] > 0$$

$$\Leftrightarrow R_0 - 1 > 0$$

$$\Leftrightarrow R_0 > 1 \quad and \quad H[\beta - M] > 0.$$

The above expression show that the condition of existence. The reproduction number (R_0) will be expressed in next section.

3.2.2 The basic reproduction number (R_0)

The reproduction number R_0 is defined as the average number of secondary cases arising from an average primary case in an entirely susceptible population over the period of infection . The reproduction number is used to predict whether the epidemic will spread or die out. Any epidemiological model has a disease free equilibrium (DFE) at which the population remains in the absence of the disease. According to (Diekmann and Heesterbeek ,2000), we call

$$FV^{-1}$$

the next generation matrix for the model and set the reproduction number,

$$R_0 = FV^{-1}$$

where

$$F = \frac{\partial F_i(x_0)}{\partial x_j}$$

and

$$V = \frac{\partial V_i(x_0)}{\partial x_j}$$

for $i \geq 1$ for the number of compartments, and $1 \leq j \leq m$ for the infected compartments only. F and V are $m \times m$ matrices, where m is the number of infected classes. Let us look at the following system of differential equations.

$$\begin{cases} \frac{dE}{dt} = \beta SI - (\mu + \alpha)E \\ \frac{dI}{dt} = \alpha E - (\mu + d + \gamma + \delta)I \end{cases} \tag{3.2.10}$$

The above system can be represented in matrix form as shown below where F is the Jacobian of the matrix of infection rates and V is the Jacobian of the matrix of transition rates at $(\frac{\Lambda}{\mu}, 0, 0, 0)$ so that

$$F = \begin{bmatrix} 0 & \frac{\beta\Lambda}{\mu} \\ 0 & 0 \end{bmatrix}$$

and

$$V = \begin{bmatrix} (\mu + \alpha) & 0 \\ -\alpha & (\mu + d + \gamma + \delta) \end{bmatrix}$$

$$V^{-1} = \begin{bmatrix} \frac{1}{(\mu+\alpha)} & 0 \\ \frac{\alpha}{(\mu+\alpha)(\mu+d+\gamma+\delta)} & \frac{1}{(\mu+d+\gamma+\delta)} \end{bmatrix}$$

$$FV^{-1} = \begin{bmatrix} 0 & \frac{\beta\Lambda}{\mu} \\ 0 & 0 \end{bmatrix} \begin{bmatrix} \frac{1}{(\mu+\alpha)} & 0 \\ \frac{\alpha}{(\mu+\alpha)(\mu+d+\gamma+\delta)} & \frac{1}{(\mu+d+\gamma+\delta)} \end{bmatrix}$$

We then obtain the spectral radius of FV^{-1}, $\rho(FV^{-1})$ which is defined as the largest eigenvalue of FV^{-1} and the spectral radius for the above system is the basic reproduction number, R_0 , and its expression is given below

$$R_0 = \frac{\alpha\beta\Lambda}{\mu(\mu + \alpha)(\mu + d + \gamma + \delta)} \tag{3.2.11}$$

3.2.3 Local stability analysis

Disease free equilibrium

Theorem 3: The disease-free equilibrium $E_0 = (\frac{\Lambda}{\mu}, 0, 0, 0)$ of the system $(3.1.1)$ is locally asymptotically stable if $R_0 < 1$.

Proof: By considering the linearized system of ordinary differential equation (3.1.1), we have

$$J(S,E,I,R) = \begin{bmatrix} -\beta I - \mu & 0 & -\beta S & \rho \\ \beta I & -(\alpha+\mu) & \beta S & 0 \\ 0 & \alpha & -(\mu+d+\gamma+\delta) & 0 \\ 0 & 0 & (\gamma+\delta) & -(\mu+\rho) \end{bmatrix} \tag{3.2.12}$$

The local stability of the equilibrium may be determined from the Jacobian matrix (3.2.12). This implies that the Jacobian matrix at the disease-free equilibrium is given by

$$J(E_0) = \begin{bmatrix} -\mu & 0 & \frac{-\beta\Lambda}{\mu} & \rho \\ 0 & -(\alpha+\mu) & \frac{\beta\Lambda}{\mu} & 0 \\ 0 & \alpha & -(\mu+d+\gamma+\delta) & 0 \\ 0 & 0 & (\gamma+\delta) & -(\mu+\rho) \end{bmatrix} \tag{3.2.13}$$

The eigenvalues of equation (3.2.13) are the solutions of the characteristic equation

$$|J(E_0) - \lambda I_4| = 0$$

Where I_4 is the identity matrix of order 4. Then we have

$$|J(E_0) - \lambda| = \begin{vmatrix} -\mu-\lambda & 0 & \frac{-\beta\Lambda}{\mu} & \rho \\ 0 & -(\alpha+\mu)-\lambda & \frac{\beta\Lambda}{\mu} & 0 \\ 0 & \alpha & -(\mu+d+\alpha+\delta)-\lambda & 0 \\ 0 & 0 & (\gamma+\delta) & -(\mu+\rho)-\lambda \end{vmatrix} = 0 \tag{3.2.14}$$

solving the equation (3.2.14) gives two eigenvalues of Jacobian matrix are obtained as $\lambda_1 = -\mu, \lambda_2 = -(\mu+\rho)$ and the remaining eigenvalues can be follow that the characteristic equation (3.2.14) is given by

$$\lambda^2 + (2\mu+\alpha+d+\gamma+\delta)\lambda + (\mu+\alpha)(\mu+d+\gamma+\delta) - \frac{\alpha\beta\Lambda}{\mu} = 0$$

We can write the characteristic equation above in the following

$$\lambda^2 + a_1\lambda + a_2 = 0 \tag{3.2.15}$$

Where,

$$a_1 = 2\mu + \alpha + \gamma + d + \delta$$

$$\begin{aligned} a_2 &= (\mu+\alpha)(\mu+d+\gamma+\delta) - \frac{\alpha\beta\Lambda}{\mu} \\ &= (\mu+\alpha)(\mu+d+\gamma+\delta)[1 - \frac{\alpha\beta\Lambda}{\mu(\mu+\alpha)(\mu+d+\gamma+\delta)}] \\ &= (\mu+\alpha)(\mu+d+\gamma+\delta)[1-R_0] \end{aligned}$$

Using the Routh-Hurwitz criterion, it can be seen that all the eigenvalues of the characteristic equation (3.2.15) have negative real part if

$$a_1 > 0, a_2 > 0$$

We can see that a_1 is positive because of this is sum of positive variables, but a_2 to be positive $1 - R_0$ must be positive, which leads to $R_0 < 1$.
Therefore, disease free equilibrium will be locally asymptotically stable if $R_0 < 1$.

Endemic equilibrium point

Theorem 4. The positive equilibrium E^* of the system (3.1.1) is locally asymptotically stable if $R_0 > 1$.

Proof: The local stability of the equilibrium determined from the Jacobian matrix (3.1.1).

$$J(E^*) = \begin{bmatrix} -\beta I^* - \mu & 0 & -\beta S^* & \rho \\ \beta I^* & -(\mu+\alpha) & \beta S^* & 0 \\ 0 & \alpha & -(\mu+d+\gamma+\delta) & 0 \\ 0 & 0 & (\gamma+\delta) & -(\mu+\rho) \end{bmatrix} \tag{3.2.16}$$

where,
$E^* = (S^*, E^*, I^*, R^*)$ is the endemic equilibrium of the system (3.1.1).

The eigenvalues of equation (3.2.16) are the solutions of the characteristic equation

$$|J(E^*) - \lambda I_4| = 0$$

Where I_4 is the identity matrix of order 4. Then we have

$$|J(E^*) - \lambda| = \begin{vmatrix} -(\beta I^* + \mu) - \lambda & 0 & -\beta S^* & \rho \\ \beta I^* & -(\mu + \alpha) - \lambda & \beta S^* & 0 \\ 0 & \alpha & -(\mu + d + \gamma + \delta) - \lambda & 0 \\ 0 & 0 & (\gamma + \delta) & -(\mu + \rho) - \lambda \end{vmatrix} = 0 \tag{3.2.17}$$

Let setting

$$d_1 = (\beta I^* + \mu), d_2 = (\mu + \alpha), d_3 = (\mu + d + \gamma + \delta), d_4 = (\mu + \rho), c_1 = \beta I^*, c_2 = \beta S^*$$

$$|J(E^*) - \lambda| = \begin{vmatrix} d_1 + \lambda & 0 & -c_2 & \rho \\ c_1 & d_2 + \lambda & c_2 & 0 \\ 0 & \alpha & d_3 + \lambda & 0 \\ 0 & 0 & (\gamma + \delta) & d_4 + \lambda \end{vmatrix} = 0 \tag{3.2.18}$$

It follows that the characteristic equation (3.2.18) is given by

$\lambda^4 + (d_1 + d_2 + d_3 + d_4)\lambda^3 + (d_1d_2 + d_1d_3 + d_1d_4 + d_2d_4 + d_3d_4)\lambda^2 + (d_1d_2d_4 + d_1d_3d_4 + d_2d_3c_1)\lambda + d_1d_2d_3d_4 - \alpha(c_2d_1d_4 + c_1c_2d_4 + c_1\rho(\gamma + \delta)) = 0.$

We can write the characteristic equation above as:

$$\lambda^4 + b_1\lambda^3 + b_2\lambda^2 + b_3\lambda + b_4 = 0 \tag{3.2.19}$$

Where,

$$b_1 = d_1 + d_2 + d_3 + d_4$$

$$b_2 = d_1d_2 + d_1d_3 + d_1d_4 + d_2d_4 + d_3d_4$$

$$b_3 = d_1d_2d_4 + d_1d_3d_4 + d_2d_3c_1$$

$$\begin{aligned} b_4 &= d_1d_2d_3d_4 - \alpha(c_2d_1d_4 + c_1c_2d_4 + c_1\rho(\gamma + \delta)) \\ &= d_1d_2d_3d_4 - \alpha c_2d_1d_4 - \alpha(c_1c_2d_4 + \rho c_1(\gamma + \delta)) \\ &= \frac{\mu(d_2d_3d_4 + \alpha\rho(\gamma + \delta))[R_0 - 1]}{Q - 1} \end{aligned} \tag{3.2.20}$$

where,

$$Q = \frac{\alpha\rho(\gamma + \delta)}{\beta d_2d_3d_4} \qquad and \qquad Q > 1$$

For the characteristic polynomial in equation (3.2.19), where $n = 4$, the Routh Hurwitz criteria are,

$$b_1 > 0, b_2 > 0, b_3 > 0, b_4 > 0$$

$$det(H_1) = b_1 > 0$$

$$det(H_2) = \begin{vmatrix} b_1 & 1 \\ b_3 & b_2 \end{vmatrix} = b_1 b_2 - b_3 > 0$$

$$det(H_3) = \begin{vmatrix} b_1 & 1 & 0 \\ b_3 & b_2 & b_1 \\ 0 & 0 & b_3 \end{vmatrix} = b_1 b_2 b_3 - b_3^2 > 0$$

$$det(H_4) = \begin{vmatrix} b_1 & 1 & 0 & 0 \\ b_3 & b_2 & b_1 & 1 \\ 0 & b_4 & b_3 & b_2 \\ 0 & 0 & 0 & b_4 \end{vmatrix} = b_1 b_2 b_3 - b_3^2 - b_4 b_1^2 > 0$$

Using the Routh-Hurwitz criterion, it can be seen that all the eigenvalues of the characteristic equation (3.2.19) have negative real part if

$$b_1 > 0, b_2 > 0, b_3 > 0, b_4 > 0, b_1 b_2 - b_3 > 0, b_1 b_2 b_3 - b_3^2 > 0, b_1 b_2 b_3 - b_3^2 - b_4 b_1^2 > 0 \quad (3.2.21)$$

Obviously we see that b_1,b_2,b_3 and b_4 are positive because they are the sum of positive variables. Since verifying these inequalities will be quite tedious, we make use of the Descartes rule of signs. The Descartes rule of signs can be used to check whether or not the polynomial in equation (3.2.19) has all it zeros having negative real parts. Since, there is no sign change in the sequence of the coefficients (Because all b_i are positive), we say that there is no zero of the polynomial in equation (3.2.19) with a positive real part. Hence, we conclude that all zeros of the characteristic polynomial have negative real parts. Therefore all eigenvalue of the Jacobian of the model in equation (3.1.1) evaluated at the endemic equilibrium have negative real parts whenever $R_0 > 1$.

3.2.4 Global stability analysis

Disease free equilibrium

Theorem 5: The disease-free equilibrium $E_0 = (\frac{\Lambda}{\mu}, 0, 0, 0)$ of the system $(3.1.1)$ is globally asymptotically stable if $R_0 < 1$.

Proof: To proof this theorem, we first develop a Lyapunov function, technically:

$$V(E,I) = \alpha E + (\mu+\alpha)I. \tag{3.2.22}$$

The system of ordinary differential equations given by equation (3.2.10) can be written as:

$$\frac{dV}{dt} = \alpha\frac{dE}{dt} + (\mu+\alpha)\frac{dI}{dt}. \tag{3.2.23}$$

Substituting expression for $\frac{dE}{dt}$ and $\frac{dI}{dt}$ from (3.2.10) to (3.2.23) results in,

$$\begin{aligned}
\frac{dV}{dt} &= \alpha(\beta SI - (\mu+\alpha)E + (\mu+\alpha)(\alpha E - (\mu+d+\gamma+\delta)I) \\
&= \frac{\alpha\beta\Lambda}{\mu}I - \alpha(\mu+\alpha)E + \alpha(\mu+\alpha)E - (\mu+\alpha)(\mu+d+\gamma+\delta)I \\
&= \frac{\alpha\beta\Lambda}{\mu}I - (\mu+\alpha)(\mu+d+\gamma+\delta)I \\
&= (\frac{\alpha\beta\Lambda}{\mu} - (\mu+\alpha)(\mu+d+\gamma+\delta))I. \\
&= (\mu+\alpha)(\mu+d+\gamma+\delta)[R_0-1]I
\end{aligned} \tag{3.2.24}$$

So,

$$\frac{dV}{dt} < 0 \qquad if \quad R_0 < 1$$

Hence, V is Lyapunov function on Ω and the largest compact invariant set in $\{(S,E,I,R) \in \Omega, \frac{dV}{dt} = 0\ \}$ is the singleton $(\frac{\Lambda}{\mu}, 0, 0, 0)$. Therefore, by LaSalles invariance principle (Al-Sheikh SA ,2012), every solution to equations of model (3.1.1) with initial conditions in Ω which approaches the disease-free equilibrium as t (time) tends to infinity $(t \to \infty)$ whenever $R_0 < 1$. Therefore, the disease-free equilibrium is globally asymptotically stable.

Endemic equilibrium point

Theorem 6 The endemic equilibrium given by equation (3.2.10) is globally asymptotically stable if $R_0 > 1$.

Proof

To establish the global stability of the endemic equilibrium , we construct the Lyapunov function $V : \Omega_+ \longrightarrow \Re$ where Ω={(E(t),I(t))/E(t)>0,I(t)>0} as described by (Ullah, Zaman and Islam , 2013) and it is given as

$$V = A[E - E^* \ln(\frac{E}{E^*})] + B[I - I^* \ln(\frac{I}{I^*})] \tag{3.2.25}$$

where A, B are positive constants to be later considered. Taking the derivative of the Lyapunov function V as given in equation (3.2.10) yields

$$\begin{aligned}
\frac{dV}{dt} &= A[\frac{dE}{dt} - E^* \cdot \frac{1}{E}\frac{dE}{dt}] + B[\frac{dI}{dt} - I^* \cdot \frac{1}{I}\frac{dI}{dt}] \\
&= A[(1 - \frac{E^*}{E})\frac{dE}{dt}] + B[(1 - \frac{I^*}{I})\frac{dI}{dt}] \\
&= A[(1 - \frac{E^*}{E})(\beta SI - (\mu + \alpha)E)] + B[(1 - \frac{I^*}{I})(\alpha E - (\mu + d + \gamma + \delta)I)] \\
&= A[(\beta SI - (\mu + \alpha)E - \frac{\beta SIE^*}{E} + (\mu + \alpha)E^*)] + B[(\alpha E - (\mu + d + \gamma + \delta)I) \\
&\quad -\frac{\alpha EI^*}{I} + (\mu + d + \gamma + \delta)I^*] \\
&= A[(E - E^*)(\frac{\beta SI}{E} - (\mu + \alpha))] + B[(I - I^*)(\frac{\alpha E}{I} - (\mu + d + \gamma + \delta))] \\
&= A[(E - E^*)(\mu + \alpha)(\omega_1 R_0 - 1)] + B[(I - I^*)(\mu + d + \gamma + \delta)(\omega_2 R_0 - 1)] \quad (3.2.26)
\end{aligned}$$

where

$$\omega_1 = \frac{(\mu + d + \gamma + \delta)I}{\alpha E}$$

and

$$\omega_2 = \frac{(\mu + \alpha)E}{\beta SI}$$

Choosing $A = B = 1$ equation (3.2.26) becomes

$$\frac{dV}{dt} = (E - E^*)(\mu + \alpha)(\omega_1 R_0 - 1) + (I - I^*)(\mu + d + \gamma + \delta)(\omega_2 R_0 - 1) \quad (3.2.27)$$

Thus from equation (3.2.27)
$\frac{dV}{dt} \leq 0$ if and only if R_0<1 and we have that $\frac{dV}{dt} = 0$ if and only if $E = E^*$ and $I = I^*$. We define the set $\Phi = \{(E^*, I^*) \in \Omega_+ | \frac{dV}{dt} = 0\}$. Therefore the largest compact invariant set is the singleton set Φ which is the endemic equilibrium. By Lasalle Invariance principle Φ is globally asymptotically stable on Ω .

3.3 Sensitivity analysis

Sensitivity analysis for the basic reproduction number R_0 is being investigated to help determine the parameter value that contributes more on the disease transmission. In order to find out, then we utilize the sensitivity index analysis by using partial derivatives when the variable is a differentiable function of the parameter.

Definition 3.3.1 The normalized forward sensitivity index of a variable to a parameter is a ratio of the relative change in the variable to the relative change in the parameter. When a variable is a differentiable function of the parameter, the sensitivity index may be alternatively defined using partial derivatives:

$$\Upsilon_m^{R_0} = (\frac{\partial R_0}{\partial m})(\frac{m}{R_0}) \tag{3.3.1}$$

for m represents all the basic parameters.

From an explicit formula for R_0 in Equation (3.1.1), we derive an analytical expression for the sensitivity of $\Upsilon_m^{R_0} = (\frac{\partial R_0}{\partial m})(\frac{m}{R_0})$ to each of the parameter involved in R_0.
For example, the sensitivity index of R_0 with respect to β is $\Upsilon_\beta^{R_0} = (\frac{\partial R_0}{\partial \beta})(\frac{\beta}{R_0}) = 1$, $\Upsilon_d^{R_0} = -0.00621118$ And with respect to remaining parameters, $\Upsilon_\Lambda^{R_0}$, $\Upsilon_\mu^{R_0}$, $\Upsilon_\alpha^{R_0}$, $\Upsilon_\gamma^{R_0}$, and $\Upsilon_\delta^{R_0}$ are obtained and evaluated at some values of parameters.
Their sensitivity indices were written in table 3.3 in the following.

Table 3.3: Sensitivity indices

Parameter Symbol	sensitivity indices	value
Λ	+ve	+1
β	+ve	+1
α	+ve	+0.166666667
μ	-ve	-0.2581780538
γ	-ve	-0.3105590062
δ	-ve	-0.5590062112
d	-ve	-0.00621118

Interpretation of Sensitivity Indices

The sensitivity indices of the basic reproductive number with respect to main parameters are arranged orderly in table 3.3. Those parameters that have positive indices (Λ, β, α) show that they 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, it means that the average number of secondary cases of infection increases in the community. And also those parameters in which their sensitivity indices are negative (μ, γ, δ, d) have an influence of minimizing the burden of the disease in the community as their values increase while the others

are left constant. And also as their values increase, the basic reproduction number decreases, which leads to minimizing the endemicity of the disease in the community.

Table 3.4: Parameters of the model

Parameters	Interpretation	Estimate (Range)	Source
Λ	recruitment rate	1	[6]
β	the transmission rate	0.388	assumed
μ	natural mortality rate	0.2	assumed
α	the rate at which an individual leaves the latent class by becoming infectious	1	[6]
γ	the rate of recover	0.5	[10]
δ	the rate of recovery due to education to take treatments	0.9	assumed
ρ	the rate at which the recovered lose their immunity	0.4	assumed
d	disease induced death rate	0.01	[10]

3.4 Numerical simulation

In this section, we present a numerical simulations of the model which is carried out using a fourth order Rung-Kutta scheme in Matlab ode45. Consider the parameters as: $\Lambda = 1, \beta = 0.388, \alpha = 1, \mu = 0.2, \gamma = 0.5, \delta = 0.9, \rho = 0.4, d = 0.1$. Then this study give $R_0 < 1$ and if the initial values of susceptible, exposed, infected, recovered population are 0.62, 3.5, 2.5, and 2.0 respectively.

The susceptible population goes to its steady state value while exposed, infected, recovered population approach to zero as time increase as shown in Figure 3.2 . So that the disease free equilibrium is globally asymptotically stable.

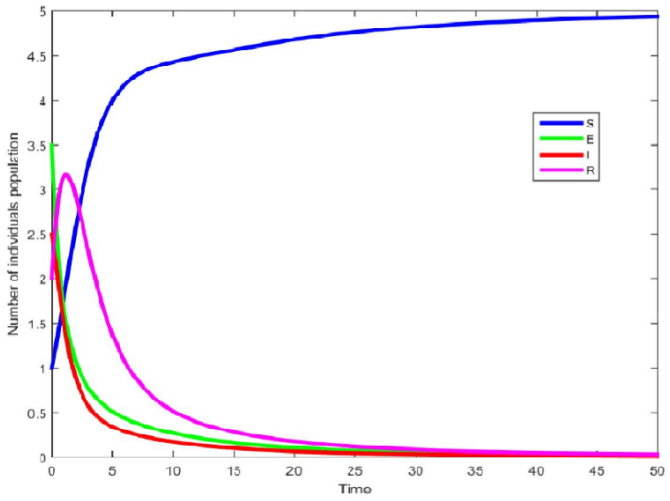

Figure 3.2: The disease free equilibrium is globally asymptotically stable When $R_0 = 0.909804 < 1$.

Again if, we take the parameters of the system as: $\Lambda = 1, \beta = 0.388, \alpha = 1, \mu = 0.2, \gamma = 0.5, \delta = 0.9, \rho = 0.4, d = 0.01$. Then $R_0 = 1.00414 > 1$. if the initial values of susceptible, exposed, infected, recovered population are 0.5, 2, 1, and 1 respectively. Therefore by theorem (5), the endemic equilibrium is a global asymptotically stable as shown in Figure 3.3.

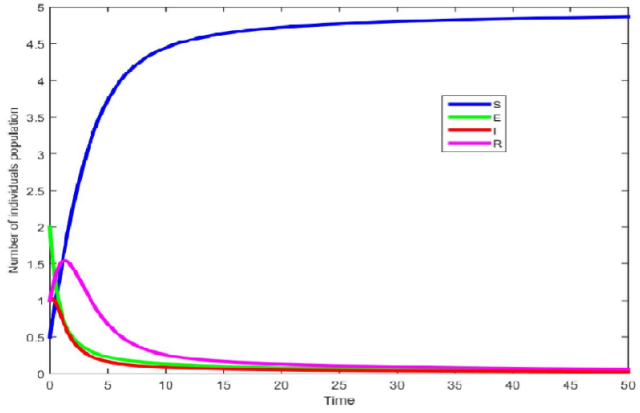

Figure 3.3: The endemic equilibrium is a global asymptotically stable When $R_0 = 1.00414 > 1$.

Figure 3.4: Simulation results of susceptible, exposed, infected and recovered individual population when $R_0 > 1$. Where the parameter $\delta = 0.9$ decreases to 0.001 and $\beta = 0.388$ is increases to 0.988. All the classes exist in the population and approach endemic equilibrium.

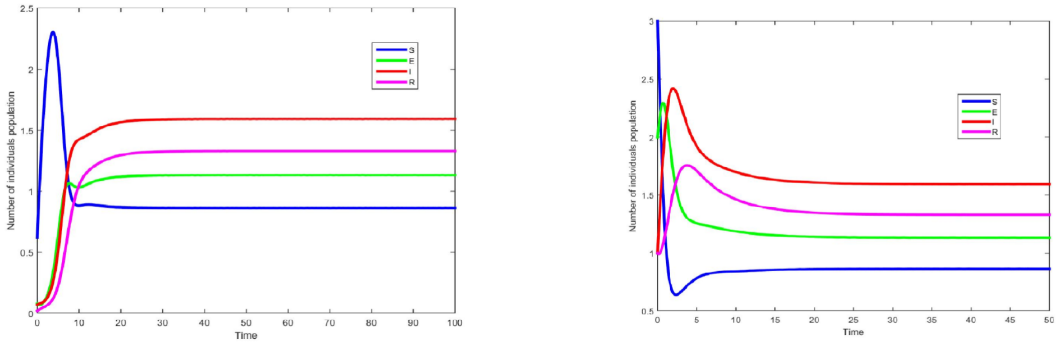

Figure 3.4: If the parameter $\delta = 0.9$ decreases to 0.001 and $\beta = 0.388$ is increases to 0.988

Figure 3.5: Simulation results of susceptible, exposed, infected and recovered individual population when $R_0 > 1$. Where the parameter $\delta = 0.9$ remains and $\beta = 0.388$ is increases to 0.988 . All the classes exist in the population and approach endemic equilibrium.

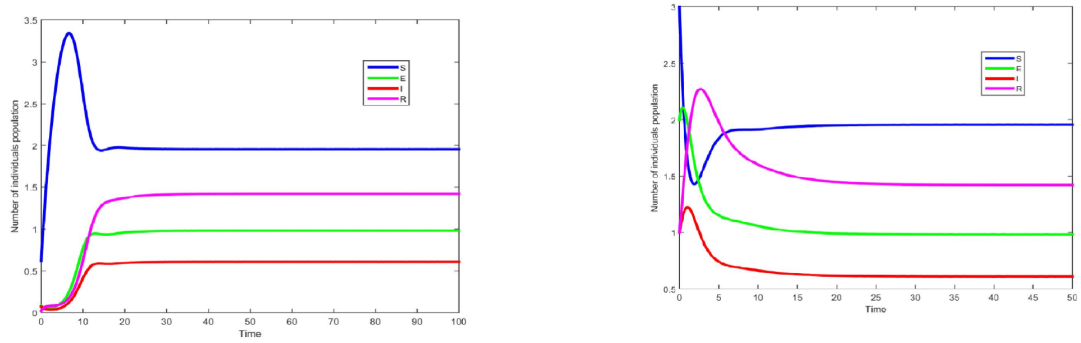

Figure 3.5: When the parameter $\delta = 0.9$ remains and $\beta = 0.388$ is increases to 0.988

Chapter 4

Discussion and Conclusion

4.1 Discussion

In this thesis,we analyzed the transmission dynamics of TB and applied mathematical tools, derived the basic reproduction number and discussed the existence and stability of disease free equilibrium (DFE) and endemic equilibrium (EE). Our analysis shows that if the reproduction number is less than one then the (DFE) is locally asymptotically stable, this implies that only susceptible is present and the other populations reduces to zero, and the disease dies out. For our model have been verified numerically by simulations in figures 2, 3. this show that if β, Λ decreases and α constant then R_0 is also decreases. If the reproduction number is greater than one then (DFE) is unstable, this implies that all the populations are exist. This situation have been verified numerically by simulations in figures 4 and 5 respectively.

Our sensitivity indices of the basic reproductive number with respect to main parameters are arranged orderly in Table 3.3. Those parameters that have positive indices (Λ, β, α) show that they 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, it means that the average number of secondary cases of infection increases in the community. And also those parameters in which their sensitivity indices are negative (μ, γ, δ, d) have an influence of minimizing the burden of the disease in the community as their values increase while the others are left constant. And also as their values increase, the basic reproduction number decreases, which leads to minimizing the endemicity of the disease in the community.

4.2 Conclusion

In this thesis, the individual population presented model SEIR using a deterministic system of ordinary differential equations. This SEIR model is describes the transmission dynamics of TB. The individual population established that the DFE of the models are locally asymptotically stable when the associated reproduction numbers are less than one, this implies that only susceptible is present and the other populations reduces to zero, and the disease dies out. But unstable, when there are greater than one. Also we notice that in order to reduce the basic reproduction number below one, we need to focused on reduction of the burden of TB disease.

Chapter 5

Recommendation

After carefully analyzing the study, we recommend the following in order to help in controlling and eradicating transmission dynamics of tuberculosis:

1. The government should intensify the education on TB in the churches, schools, etc. to sensitize the individuals in the communities of its existence, free access to medical care and treatment duration.

2. More awareness campaigns should be conducted among the sick and the bereaved on the effect of education on their lives especially those infected with TB.

3. Further research work is also recommended in order to help develop other suitable models to help public health professionals to adopt other strategies to control and eradicate the disease. We therefore suggest SEIR model of tuberculosis in a non constant population and a model of tuberculosis in a heterogeneous population using SEIR model for further research work.

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