MODELING THE DYNAMICS OF TUBERCULOSIS IN A COUPLED METAPOPULATION

WESLEY MUTAI

A Thesis Submitted to the Board of Graduate Studies in Partial Fulfillment of the Requirements for the Conferment of the Degree of Master of Science in Applied Mathematics of the University of Kabianga

UNIVERSITY OF KABIANGA

MARCH, 2021

DECLARATION AND APPROVAL

Declaration

This thesis is my original work and has not been presented for the conferment of a degree or for the award of a diploma in this or any other University:

Signature: ..... Date: .....

Wesley Mutai

PGC/AM/0003/16

Approval

This thesis has been submitted for examination with our approval as University Supervisors:

Signature: ..... Date: .....

Dr. Wesley Kirui

Department of Mathematics and Actuarial Science,

South Eastern Kenya University

Signature: ..... Date: .....

Dr. Wilys O. Mukuna

Department of Mathematics and Computer Science,

University of Kabianga

COPYRIGHT

DEDICATION

To my wife Emmy, children Phelgon and Precious. I want to thank you for your love and patience.

ACKNOWLEDGMENTS

First and foremost, I want to thank God for giving me this wonderful opportunity to study at University of Kabianga. Secondly, my sincere thanks and appreciation go to my supervisors; Dr. Wesley Kirui and Dr. Wilys Mukuna for their endless support, encouragement and guidance throughout the research writing period. I want also to thank the Department of Mathematics and Computer Science lecturers as a whole for their unending encouragement throughout .Lastly, I also salute my friends and postgraduate colleagues for sharing their precious time with me. To my family, thank you for being there for me. God bless you all.

ABSTRACT

Tuberculosis (TB) is currently one of the key health test in many developing countries, Kenya included. TB is a curable transmissible ailment caused by Mycobacterium tuberculosis. The formation of the tubercles in tissues of the body like in the lung tissues describes the disease. Interaction with transmissible individuals can make one acquire TB. The behavior of transmissible diseases, its impacts and possible future prediction about its spread has been best understood with the knowledge of mathematical epidemiology. In this study, delay differential equations were formulated for purposes of determining stability of both Disease Free Equilibrium (DFE) and endemic equilibrium(EE) .The delay component was incorporated into Susceptible-Exposed-Infectious-Recovered (SEIR) model. A parameter called the basic reproduction number was computed using next generation matrix approach. Sensitivity analysis was carried out with respect to model parameters. Finally, numerical simulation were done using MATLAB for validation of the analytical results. Parameter values were obtained from secondary data. From the numerical results it was found out that R_0 at DFE was 0.5828 and it was 1.0095 at EE.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND ACRONYMS

TB	Tuberculosis
DDEs	Delay Differential Equations
ODEs	Ordinary Differential Equations
PDEs	Partial Differential Equations
WHO	World Health Organization
DFE	Disease Free Equilibrium
EEP	Endemic Equilibrium Point
MDR-TB	Multi-Drug Resistant Tuberculosis
MATLAB	Mathematics Laboratory
BCG	Bacillus Calmatte Guerine

LIST OF SYMBOLS

S	Susceptible class
I	Infectious class
R	Recovered class
E	Exposed class
L	Latent class
N	Non-infectious class
D	Detected class
T	Treated class
ρ	Spectral radius
t	time
M	Mycobacterium
R_0	Basic Reproductive number

CHAPTER ONE

INTRODUCTION

1.1 Overview

In this chapter, the background information of TB and forms of coupling configurations are discussed. Then definition of delay differential equations is given. This include an example of SEIR model dynamic equations and the next generation matrix for determination of basic reproduction number R_0. Finally, the statement of the problem, objectives, significance and justification of the study are highlighted.

1.2 Background of the Study

Tuberculosis (TB) is caused by a bacterial infection and an ailment of humanbeings and animals whose etiological agent is *Mycobacterium tuberculosis complex* (MTBC); which include four TB causing Mycobacteria: M.cterial infectious ailment of humans and animals initiated by the *bovis*, M.*africanum*, M.*canettiand*, M.*microti*.The formation of tubercles on the lungs and some tissues in the body characterizes the ailment, frequently developing extensively following the primary infection. It is an airborne ailment which is transmitted when individuals with active TB cough, sneeze, speak, sing or spit. *Mycobacterium tuberculosis* is among the causes of death in communities. In the event of incomplete dosage during treatment, the remains of *Mycobacterium tuberculosis* in the human body system in most cases results in bacterium developing resistance to TB antibiotics. This results to multi-drug resistance-TB (MDR-TB).

Mathematical epidemiology has contributed to a more in-depth understanding of

tuberculosis as a transmissible ailment, its effects and possible future forecast about its spread and the mechanisms of its control. The planning, evaluation, prevention and control of TB in a population will be facilitated by model analysis, (Herthcote, 2000). Many populations are structured in space but interconnected by human traveling. A population may be subdivided into separated patches also called subpopulations, each with its dynamics. A group of such a distinctive subpopulation is known as a metapopulation, (Jesse *et al.*, 2008).

Subpopulation interconnections may be random, all-to-all, one-to-many or nearest neighbor connection, (Adu and Rotich, 2007). Metapopulation model for the spread of a disease which is infectious relies on the assumption that the population is homogeneous. This means that all persons in a population have an equal chance of contracting the disease upon interaction with the infected persons. In this research, dynamics of TB in a metapopulation was studied using a coupled subpopulation.

1.2.1 Coupling configurations

Coupling is the arrangement of subpopulations in a way that can affect each other. There are different forms of nearest neighbor coupling. Nearest neighbour coupling is where a subpopulation is connected to their immediate neighbor (Anupi, 2015).The following are the coupling configurations:

(a) Coupling on a line

(b) Coupling on a ring

(c) Coupling on a two-dimensional bravais lattice

(d) One-to-all coupling

(e) All-to-all coupling

(f) Coupling on three-dimension

The above forms of coupling configurations are illustrated in **Figure 1.1** (Anupi, 2015).

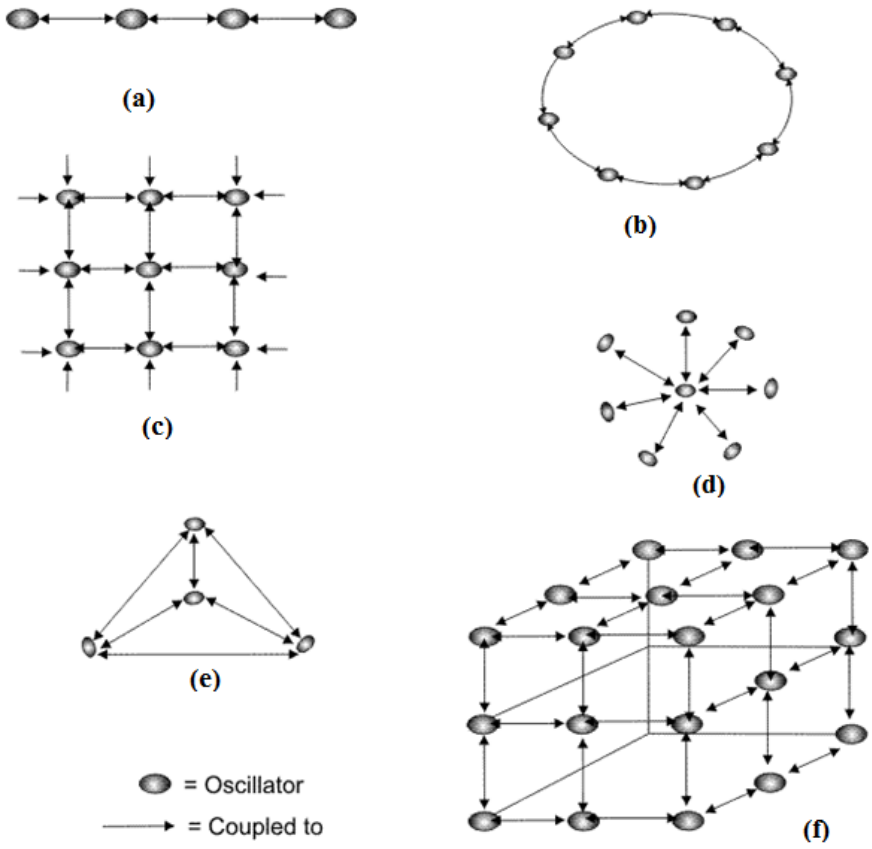

Figure 1.1: *Forms of coupling configurations*

In this study, one-to-all coupling configuration (d)was used to find the relationship between the various subpopulations surrounding the center subpopulation in terms of the spread of a disease.

1.2.2 Delay differential equations

Differential equations also called time delay are equations where the time derivative at the current time depend on the solution and its derivatives at previous time. The

different categories of delay-equations include;

i) Constant DDEs

ii) Variable DDEs

The constant DDE takes the following general form:

$$\dot{x} = f(x(t), x(t-\tau))$$

where the quantities $x \in \mathbb{R}^n$ and $\tau \in \mathbb{R}^n_+$, $\tau > 0$.

DDE with Time-Dependent Delay given below is a variable delay:

$$\dot{u} = f(t; x(t); u(t, \tau(t))), u(t) \in \mathbb{R}^n$$

where delay $\tau(t) \geq 0$ is a given function, (Roussel, 2005).

1.2.3 The SEIR model

The SEIR model is used to envisage the advancement of transmissible ailments in a certain population. Four different compartments of individuals are considered. These are: susceptible (S), exposed (E), infectious (I) and recovered (R). Defenseless or vulnerable individuals are in the category of S compartment, E compartment comprises of the exposed individuals who has the ailment already but are not in a position to transmit. Compartment I involves infected individuals who are capable of spreading the disease. Compartment R comprises the immune recovered individuals. Since immunity is not hereditary, SEIR model assumes that every person is susceptible to the ailment by birth. The ailment is similarly transmitted to the individual by plane occurrence, for example vulnerable persons turn out to be ill once in contact with an infected persons. Direct or

indirect interaction may occur. Direct contact include touching or biting whereas indirect is in form of coughing or sneezing. The transmissible populace may recover fully through immunization or when the person becomes immune, similarly may be removed by dying, (Biswas *et al.*, 2014).

The SEIR compartmental model can thus be formulated.let $S(t), E(t), I(t)$ and $R(t)$ stands for persons in the susceptible, exposed, infectious and recovered class at time t correspondingly. Then, the entire populace at time t is symbolized using:

$$N(t) = S(t) + E(t) + I(t) + R(t) \tag{1.1}$$

Disease transmission in a certain populace can be pronounced, let c represent the rate at which persons exposed becomes infectious, g to be rate in which persons who were infectious recover and a to stand for the rate of death of individuals due to illness. Let b to symbolize rate of natural birth and d to stand for rate of natural death. The number of contacts between susceptible and infectious individuals explains the rate of transmission.

Assume that all vaccinated susceptible individuals become immune due to effective immunization. Let $u(t)$ be vulnerable persons immunized per unit of time. Putting into account these considerations,the dynamical system becomes:

$$\left.\begin{aligned} \tfrac{dS}{dt} &= bN(t) - dS(T) - cS(t)I(t) - u(t)S(t) \\ \tfrac{dE}{dt} &= cS(t)I(t) - (cd)E \\ \tfrac{dI}{dt} &= cE(t)(g + ad)I(t) \\ \tfrac{dR}{dt} &= gI(t) - dR(t) + u(t)S(t) \\ \tfrac{dN}{dt} &= (b - d)N(t) - aI(t) \end{aligned}\right\} \tag{1.2}$$

Using the initial conditions $S(0) = S_0, E(0) = E_0, I(0) = I_0, R(0) = R_0, N(0) = N_0$, It is noted that control measure for such system is u. Supposing $u = 0$, it will imply that vaccination is incorporated and $u = 1$ will imply that susceptible populace was immunized. In a SEIR model, the compartments have transition rates which indicates how the size of each compartment changes with respect to one another.

1.2.4 Next generation matrix

The number of secondary infection cases arising from one infectious case in a population is referred to as Reproduction number denoted by R_0. Determination of R_0 is done using Next generation matrix method by taking into consideration compartmental model of the spread of an infectious disease. The spread of contagious infection through a population is determined by this ratio. For instance, if R_0 for measles in a given population is 15, then this means that we would expect it to spread rapidly since each new case of measles produces 15 new secondary infection cases. Finding the average that is expected from new infections over all the possible infected types is a very useful concept. Next generation matrix is the square matrix G such that ijth element of G, g_ij represent expected number of minor contagions of variety i initiated by a particular disease-ridden individual of category j. Similarly populace of type i is assumed to be entirely susceptible. Spectral radius which is the largest eigenvalue of G gives the basic reproduction number. Desirable properties from a mathematical stand point is found from next generation matrix. Precisely,the matrix is non-negative and as such it is guaranteed that there will be a one,distinct eigenvalue that is positive, real, and larger than all the others. This is the Basic reproduction number R_0.

To clarify, two classes of infected individual shall be considered. The next genera-

tion matrix is thus a 2×2 matrix given as

$$G = \begin{bmatrix} a & b \\ c & d \end{bmatrix} \tag{1.3}$$

Then the eigenvalues of G are:

$$\lambda_{\pm} = \frac{T}{2} \pm \sqrt{\left(\frac{T}{2}\right)^2 - D} \tag{1.4}$$

where $T = a + d$ is the trace of the matrix and $D = ad - bc$ is the determinant of the matrix. For instance if there is a sexually transmitted infection in a heterosexual inhabitants, then f denotes the number of expected infected women and m as the number of expected number of infected men. If the two sexes are in contact with a single infected individual of the opposite sex in a susceptible population, then next generation matrix is given by:

$$G = \begin{bmatrix} 0 & f \\ m & 0 \end{bmatrix} \tag{1.5}$$

R_0 is therefore $\sqrt{fm}$. It is noted that this is thus the geometrical average of the probable number of female and male new secondary infections. When there are more than two distinct kinds of contagious compartments, the eigenvalues are numerically calculated using mathematical software.

The next generation matrix G consists of two component: F and V^{-1} where $F = \left[\frac{\partial F_i(x_0)}{\partial x_j}\right]$ and $V = \left[\frac{\partial V_i(x_0)}{\partial x_j}\right]$.

Such square matrices are for partial derivatives of new infections (F_i) and transfers

amongst diverse compartments (V_i). Distinct classes of infections is found by obtaining the rank of these matrices. Considering a SIR model for two sexes, then next generation matrix shall be 2×2 matrix consisting of two kinds of infection, female and male. x_0 is the DFE state and non-negative matrix is obtained which is not reducible. R_0 is thus the largest eigenvalue of the matrix $G = FV^{-1}$.

1.2.5 SEIR epidemic model

This model is suitable for infection that has a post-infection evolution period in which the exposed individual is not yet infective.The figure below is a flow diagram that was used to derive R_0.

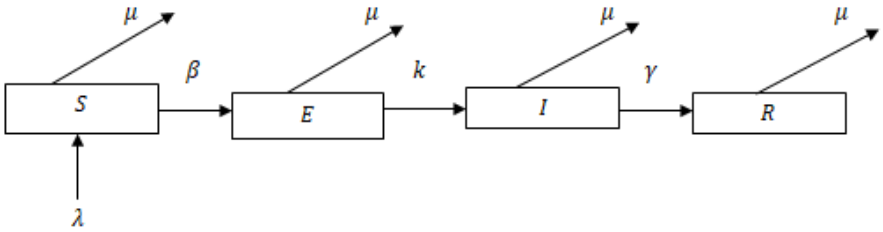

Figure 1.2: *SEIR model flow diagram*

where λ is the "birth rate", β is rate of infection by susceptibles; μ is the death rate rate; k is the transfer rate from exposed to infected, γ is the removal rate.

The SEIR model above will comprise of four ODE's given below:

$$\left.\begin{aligned} \frac{dS}{dt} &= -\beta SI + \lambda - \mu S \\ \frac{dE}{dt} &= \beta SI - (\mu + k)E \\ \frac{dI}{dt} &= kE - (r + \mu)I \\ \frac{dR}{dt} &= \gamma I - \mu R \end{aligned}\right\} \tag{1.6}$$

Determination of next generation matrix for the number of ways for getting new infection and several ways that a person moves between compartments were gotten. To

create new infection between two diseases only one way is involved:

$$F = \begin{bmatrix} \frac{\beta\lambda}{\mu} & 0 \\ 0 & 0 \end{bmatrix} \tag{1.7}$$

Conversely, there are several ways for movement among the conditions:

$$V = \begin{bmatrix} 0 & k+\mu \\ \gamma+\mu & -k \end{bmatrix} \tag{1.8}$$

R_0 is therefore the dominant eigenvalue of the matrix FV^{-1}. Thus;

$$R_0 = \frac{k\beta\lambda}{\mu(k+\mu)(\gamma+\mu)} \tag{1.9}$$

1.3 Statement of the Problem

Despite the numerous research on TB, campaigns,control and the management strategies presently ongoing to accomplish a world free of TB, TB continues to pose a dangerous wellbeing in the world, (Global Tuberculosis Report, 2013). In view of this, there is urgent need to do more research in order to bring the spread and transmission of TB to minimal. The geographical spread of human infectious diseases such as influenza, TB, measles, severe acute respiratory syndrome (SARS), and many other infectious diseases is promoted by human travel which occurs upon interactions of individuals in subpopulations. The objective of disease modelling is to investigate the cause of the disease and understand the mechanisms by which the disease spreads and predict the future course of the disease. Metapopulation provides a framework for modeling disease dynamics for individuals that can be naturally partitioned into spatial subpopulations.The spread

of human diseases in metapopulation is best described by rapid commuter movements of individuals from their home subpopulation to another subpopulation and back again. Here, Coupled lattice-based model is considered where subpopulations are arranged on a grid and coupling is generally to the nearest neighbors only.It was for this reason that the study of the modelling the dynamics of TB in a coupled metapopulation is necessary in order to evaluate the effects on the force of infection among subpopulations.

1.4 General Objective

The general research objective was to formulate a SEIR mathematical model which was used to describe the TB dynamics in a coupled metapopulation.

1.5 Specific Objectives

The specific objectives for this study were:

i. To formulate a delay differential equation model for the spread of TB in a metapopulation.

ii. To determine the disease equilibria and their stabilities.

iii. To carry out sensitivity analysis of the Basic reproduction number R_0 with respect to the model parameters.

iv. To carry out numerical simulations with MATLAB to verify analytic results

1.6 Justification of the Study

The study supports the efforts by the ministry of health to establish and understand the burden of tuberculosis. This will give policy makers and stakeholders a model for mathematical description of the understanding the spread and transmission of TB in order to

make informed policy interventions. The research will also assist mathematicians and research scientists to further come up with appropriate model to help further improve knowledge on TB transmission.

Lastly, the study will provide further information on better methods to hasten the progress towards achieving the millennium development goals (MDGs) for TB eradication.

1.7 Significance of the Study

Infectious diseases like TB are the main cause of sickness and death in many developing countries, Kenya included. The significance of the study is:

1.7.1 Government

The research will assist the government to formulate policies to aid in the control of the spread of TB in the country. This will be done through the ministry of Health in which it will control the spread of TB transmission through some control measures like vaccination and imposing quarantine on infected subpopulation.

1.7.2 Education

This research will help in the development of educational programs geared towards the development of mathematical models of infectious diseases. The schools, universities and other learning institutions will design their curriculum to incorporate infectious diseases in order to create awareness on the impacts of TB infection.

1.8 Scope of the Study

The study focused on formulation of delay SEIR model to describe the dynamics of Tuberculosis in a coupled metapopulation. The study also included the analysis of the model and its simulation to verify analytic results.

1.9 Limitations of the Study

The study limited itself to the subpopulations with nearest neighborhood in describing disease dynamics. The analysis of the model in terms of stability of DFE was restricted to Jacobian matrix.

1.10 Assumptions of the Study

The assumptions of the study was that reducing the duration spent by an individual in an infected subpopulation minimizes infection of Tuberculosis.

CHAPTER TWO

LITERATURE REVIEW

2.1 Introduction

This chapter will provide an overview on the previous related studies which have been done by various scholars. Finally the chapter will give a gap existing on those previous studies and thus the need to carry out research with an aim of bridging the existing gap.

2.2 Review of Related Literature

The rising cases of tuberculosis (TB) in majority of African countries over the past years is majorly contributed to the human immunodeficiency virus and other developing infectious diseases. The mathematical models of transmission of diseases within human populations have assisted in supporting policy makers and epidemiologists in interpretation of epidemiological trends and understanding the dynamics of spread of the disease with efficiency in disease prevention and control. Many years have passed with many scholars coming up with mathematical models for TB. Susceptible-Infectious-Recovered (SIR) models and variants like Susceptible-Exposed-Infectious-Recovery (SEIR) models were introduced in the 1920s and helped to establish the foundations of much of the mathematical epidemiology. In order to efficiently control and prevent infectious diseases like tuberculosis, one needs to be adequately informed about the contrivances for the spread and the diffusion forces of the disease. This will help to predict as well as put strategies to eliminate the disease. The study of dynamics of the disease is an important theoretical method to look into the transmission dynamics

of contagious diseases because they vary over a period of time. The formulation of mathematical model is based on the dynamics of the population, signs and symptoms of disease infection, and the relationship between social and physiological factors. By means of analysis and numerical simulations, mathematical representations can therefore be used as a tool in understanding the spread of infectious epidemic and how to manage or control it. Mathematical models developed for tuberculosis transmission are numerous,some of them are as reviewed in the following:

Feng and Chavez (2001) modeled the analysis and behaviour of a system of ODE's and differentiable-integral equations for the disease transmission dynamics for TB. They showed that the dynamics of the two models are directed by a reproduction ratio, R_0. They considered the scenario if $R_0 > 1$, then the DFE is unstable and there exists a unique positive (endemic) equilibrium. They found out that the qualitative behaviors of the model with randomly dispersed dormant stage are comparable to the ones given by the TB model with an exponentially distributed over latency period . They found out that there is a likelihood of a person getting an active TB infection due to endogenous infections.

Cohen *et al.* (2007) studied a network of TB transmission by modifying the SEIR model in order to ascertain the outcome of non-homogeneous population interactions on the contribution of re-infection over realistic projections. In their model, they simulated the population where each individual was placed at random on a square patch at a constant average density. The results from their study showed disease re-infection was important in populations where the mean disease occurence rate is a force of infection which is unevenly distributed in the population.

Wu *et al.* (2010) developed a model to include age brackets which is made up of eight compartmental classes. They carried out sensitivity investigation to test the effect of various model factors on the patterns in TB warnings as projected by the model. Their results showed that the spread of TB is determined by the infectious rate of active TB cases, vulnerability of persons and the interaction configurations amongst susceptible persons and contagious TB sick individuals.

Tewa *et al.* (2012) in their paper studied the spread of TB through a two patch epidemiological model. They made an assumption that susceptible persons can move between two patches so long as they are not infective persons. They formulated the model by considering a two patch SEI TB. They then analyzed the model by computing the DFE and R_0.They went further and determined the global stability of DFE by showing that DFE has global asymptotic stability when $R_0 < 1$.

Hickson *et al.* (2012) developed a metapopulation model for the drug sensitive TB transmission which was suitable for examining spread between regions of large and small occurrence in Australia and Papua New Guinea .Sensitivity analysis was performed where the results showed that the detection level in Papua New Guinea was the greatest vital factor in relation to increasing quantity with clinical apparent TB for the whole zone. Their model comprised of six compartments; four for the disease itself (SLIN) and two compartments for the interventions (D,T).

Bimal and Jyotika (2013) in their study formulated a model on pulmonary and MDR TB with vaccination. Here, they considered a quarantine class in their epidemic model for MDR TB patients. They observed that quarantine plays an important part in the control of the infection. They formulated susceptible-exposed-infectious-quarantine-recovered-susceptible having a vaccinated class (SEI-QRS-V). The model was used in

describing changing aspects of TB spread in relation to time in human being populace. They showed that if $R_0 < 1$, DFE stability is global in the feasible zone and the disease is wiped out. If $R_0 > 1$, an exceptional endemic balance occurs and has a nearby (local) asymptotic stability.

Trauer *et al.* (2014) presented a mathematical model for simulation of TB spread in high potential endemic zones of Asian-Pacific, where epidemiology does not predominantly motivated by HIV co-infection. They found out that the model could not be calibrated to the estimated incidence rate without allowing for re-infection during latency.At equilibrium, MDR-TB becomes main TB strain . They concluded that the most important determinant of disease rate was early detection and treatment commencement while vaccination rate was less important.

Athithan and Ghosh (2015) in their paper studied a non-linear mathematical model of TB with a case detection and treatment. In the paper, the whole population under consideration was in four compartments; Susceptible, Exposed, Infectious and Recovered (SEIR) model which they used to study transmission dynamics of TB. They computed R_0 and determined the equilibria of the model. Their results showed that an increase in the rate of case detection lead to an increase in the threshold value of R_0. Also, the treatment reduced the equilibrium level of the infective class.

Muhammad *et al.* (2015) presented a paper titled 'mathematical model for vaccinated tuberculosis disease with VEIT model'. In this model, there are four compartments; vaccinated, exposed, infected and treated (VEIT). The paper discussed about formation and analysis of the VEIT model to TB virus infection by exogenous re-infection. They concluded that the model of vaccinated with exogenous re-infection have two equilibria states; DFE and EE. They showed that the eigenvalue of DFE is

always negative so that the system stability is asymptotically stable at DFE.

Chacha (2016) developed a mathematical model that predicted the threat of TB as a contagious airborne infection under stable state and non-unstable state situations. He did this by monitoring the amount of breath out air by contagious persons in a restricted environment. He demonstrated precisely and diagrammatically, the relationship between TB spread possibility and airborne level of infection, average amount of exhaled air taking into consideration TB occurrence and length of contact to contagious persons in a restricted environment. He chose an age structuring model since infection and illness frequency differ in diverse inhabitants on age dependent and host immune aspects. In his study, he found out that TB spread is prevalent in gatherings for instance; schools, public transportation and correctional facilities especially in developing countries.

Houben *et al.* (2016) in their paper developed a TIME impact software tool to support TB policy discussions and integrate capacity building for generating modeling results. The aim of TIME impact in a dynamical compartmental spread model which includes the latency of mycobacterium TB infection resulting from latest re-infection and reactivation.

Adebiyi (2016) in a thesis titled 'mathematical modeling of population dynamics of TB' presented and analyzed a SLIT (susceptible, latent, infectious and treated) model with the inflow of infective. He analyzed the asymptotic behavior,spread and eradication possibility of disease. Sensitivity analysis of R_0 was analysed.The next generation matrix approach and the theorem by Driesch and Watmough (2002) being useful, it was found out that whenever $R_0 < 1$, DFE is locally asymptotically stable and unstable whenever $R_0 > 1$. The simulation results from the thesis indicated to curb TB spread,a

complete control strategic treatment should be administered even with constant inflow of infective immigrants.

Witbooi and Vyabwera (2017) proposed a compartmental model to describe the population dynamics of TB disease in a prison system in South Africa. Their model considered the inflow of susceptible and exposed classes as well as the disease infection into the prison population. The model was used to make quantitative projections of TB prevalence and measure on effects of interventions. In their paper, they presented a deterministic compartmental model using ODE's and determined the global stability of disease free state parameter for eradicating TB.

Fonseca *et al.* (2017) studied experimental model of TB. They discussed the Human based models like the 2D and 3D models. They highlighted the advantages and disadvantages of the available animal and cellular models. They concluded that epidemiological studies assist to determine the progression of a disease and is highly related to host immune status.

Zhao *et al.* (2017) proposed an epidemic disease SEIR model consisting of three age categories: children, the middle-aged, and elderly to look into the role of age on the transmission of TB in Mainland China from 2005 to 2016. They then evaluated the model parameters by the Least Square method and simulated the model parameters. The study demonstrated that diverse age groups have different effects on TB. There were two effective measures that were found to help reach the goals of the WHO End TB Strategy: an increase in the recovery rate and the reduction in the infectious rate of the senior age group.

Enagi *et al.* (2017) modeled the effect of combining Immunization with Latent Tuberculosis treatment in controlling the spread of Tuberculosis. The administration

of Bacillus Calmatte Guerine (BCG) vaccines at birth protects children from early infection of the disease, but the effect of these vaccines expires with time. Their results showed that detection and treatment of Latent Tuberculosis infections using Isoniazid Preventive Therapy prevents the breakdown of Latent Infections into Infectious cases, thus reducing greatly the rate of spread of the disease since only members of the Infectious class can spread the disease to others. The DFE will be stable if effort is intensified in bringing down both the contraction rate and the rate of break down to Infectious Tuberculosis.

Dipo *et al.* (2018) developed a mathematical model of the spread of TB disease involving the age classes in a susceptible compartment under SEIR model. The model had two equilibrium points; DFE and EE. R_0 was constructed using the next generation matrix approach. They found out that TB transmission can be reduced through vaccination and increasing life expectancy. The results from simulation showed also that transmission can also be reduced through vaccine protection period and vaccine efficacy.

2.3 Identification of Knowledge Gap

The above studies did not consider the use of DDEs in the solution to the various equations arising from the models. This study formulated DDEs model for the spread of TB in a coupled metapopulation. The model incorporated the coupling strength in the configuration which is the driving force for the spread of the disease.

CHAPTER THREE

METHODOLOGY

3.1 Introduction

This chapter outlines the methodology used in the thesis. First, the SEIR model for tuberculosis, model assumptions and equations are given. Then the model preliminary analysis, computation of the basic reproduction number equilibrium points and stability analysis are provided. Finally, sensitivity analysis of the basic reproduction number is discussed.

3.2 SEIR Model for Tuberculosis

For the SEIR model, the individuals in the population are divided into four compartments. The susceptible (S) which refers to the healthy individuals that have not yet come into contact with TB bacterium. The exposed (E) are individuals who have come into contact with the disease but are not yet infective or infectious. The infective (I) are those who have become infected with TB and are able to transmit the disease and the recovered (R) are individuals who have recovered from TB. The following is the SEIR diagram The following is a table showing a list of symbols and model parameter

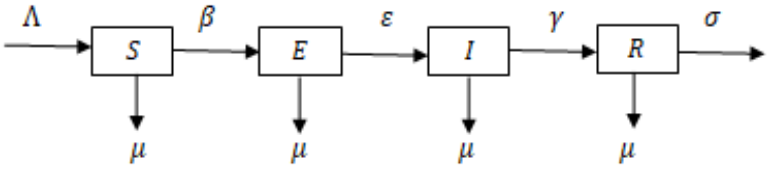

Figure 3.1: *SEIR Model Flow Diagram*

description to be used;

Table 3.1: *Table of parameters and their descriptions*

Parameter	Description
Λ	Recruitment (birth) rate into the susceptible class
μ	Natural death rate coefficient
d	Disease-induced death rate coefficient
β	Probability that susceptible individuals become infected by one infectious individual per contact time
ε	Rate at which the exposed individuals become infectious
γ	Treatment rate for infectious individuals
σ	Recovery rate

3.3 Model Assumptions

The following are the assumptions useful in the derivation of the model:

i) There is uniform interaction of persons in the population which implies that every person who is uninfected has an equal chance of being infected provided he or she comes into contact with the infected individual.

ii) There is disease induced death and death due to natural causes.

iii) Disease transmission takes on a modified frequency dependent form that depends on how much time individuals of each epidemiological class spend in a particular area.

iv) The risk of an infection is a function of the residence time at a local environment.

v) Recruitment rate into the susceptible class is constant at $\Lambda > 0$.

vi) Immigration is not restricted.

vii) Age, sex, social status, race coupled with environmental conditions does not affect the probability of an individual from being infected.

The transition rates from one compartment to another are mathematically expressed as derivatives, hence the model is formulated using delay differential equations. While

developing such models, it is assumed that the population size in a compartment is differentiable with respect to time and that the disease process is deterministic. This means that the changes in population of a compartment can be calculated using only the history used to develop the model.

The TB model is based on SEIR transmission model in one to all coupling configuration. The total population size $N(t)$ at any given time t is given by:

$$N(t) = S(t) + E(t) + I(t) + R(t) \tag{3.1}$$

3.4 Model Equations

Considering the above assumptions and model parameters, the dynamics of TB is modeled by the following system of delay differential equations:

$$\frac{dS_i}{dt} = \Lambda_i - \mu_i S_i - \beta_{ij} \sum_{j=i-1}^{i+1} S_i I_j(t-\tau) - \beta_{ii} S_i I_i(t-\tau) + \sigma R_i \tag{3.2}$$

$$\frac{dS_j}{dt} = \Lambda_j - \mu_j S_j - \beta_{ji} \sum_{i=J-1}^{j+1} S_j I_i(t-\tau) - \beta_{jj} S_j I_j(t-\tau) + \sigma R_j \tag{3.3}$$

$$\frac{dE_i}{dt} = \beta_{ij} \sum_{j=i-1}^{i+1} S_i I_j(t-\tau) - (1-\varepsilon_i) E_i(t-\tau) - E_i(\mu_i + d_i) + \beta_{ii} S_i I_i(t-\tau) \tag{3.4}$$

$$\frac{dE_j}{dt} = \beta_{ji} \sum_{i=j-1}^{j+1} S_j I_i(t-\tau) - (1-\varepsilon_j) E_j(t-\tau) - E_j(\mu_j + d_j) + \beta_{jj} S_j I_j(t-\tau) \tag{3.5}$$

$$\frac{dI_i}{dt} = \varepsilon_i E_i(t-\tau) + (1-\gamma_i) I_i(t-\tau) - I_i(\mu_i + d_i) \tag{3.6}$$

$$\frac{dI_j}{dt} = \varepsilon_j E_j(t-\tau) + (1-\gamma_j) I_j(t-\tau) - I_i(\mu_j + d_j) \tag{3.7}$$

$$\frac{dR_i}{dt} = \gamma_i I_i(t-\tau) - \mu_i R_i - \sigma R_i \tag{3.8}$$

$$\frac{dR_j}{dt} = \gamma_j I_j(t-\tau) - \mu_j R_j - \sigma R_j \tag{3.9}$$

where $\tau > 0$ is the time lag.

3.5 Model Preliminary Analysis

In this section, the preliminary analysis of the model formulated was done. This included; positivity and boundedness of solutions, determination of basic reproduction number, equilibrium points and their stability analysis and finally sensitivity analysis of basic reproduction number.

3.5.1 Positivity and boundedness of solutions

Since the model under consideration represents the population dynamics of living organisms, it is necessary to show that the solutions are always positive and bounded. The compact set is defined by;

$$\Omega = \{S_i, E_i, I_i, R_i \in \mathbb{R}^4 \geq 0, 0 \leq S_i < S_1, 0 \leq E_i < S_2, 0 \leq I_i < S_2, 0 \leq R_i < S_3\}$$

where $S_a > 0, a = 1, 2, 3$.

Proposition 1: The set Ω is positively invariant for model (3.2), (3.4), (3.6) and (3.8).

Proof:

$$\frac{dS_i}{dt} \mid S_{i=0} = \Lambda_i \geq 0 \tag{3.10}$$

$$\frac{dE_i}{dt} \mid E_{i=0} = 0 \Rightarrow \beta_{ij} \sum_{j=i-1}^{i+1} S_i I_j(t-\tau) - \beta_{ii} S_i I_i(t-\tau) \geq 0 \tag{3.11}$$

whenever $S_i, I_i, I_j \geq 0$

$$\frac{dI_i}{dt} \mid I_{i=0} = 0 \Rightarrow \varepsilon_i E_i(t-\tau) \geq 0 \text{ whenever } E_i \geq 0 \tag{3.12}$$

$$\frac{dR_i}{dt} \mid R_{i=0} = 0 = \gamma_j I_j(t-\tau) \geq 0 \tag{3.13}$$

This confirms that $\{S_i(t), E_i(t), I_i(t), R_i(t)\} \in \mathbb{R}^4 \geq 0$ with $\{S_i(0), E_i(0), I_i(0), R_i(0)\} \in \mathbb{R}^4 \geq 0$ Thus $\mathbb{R}^4 \geq 0$ is positively invariant for model (3.2), (3.4), (3.6) and (3.8). For boundedness of solutions, the following are defined;

$$\frac{dS_i}{dt} = \gamma_i \varepsilon_i \left[\Lambda_i - \mu_i S_i\right] \tag{3.14}$$

$$\frac{dE_i}{dt} = -\gamma_i \varepsilon_i \left[E_i(\mu_i + d_i)\right] \tag{3.15}$$

$$\frac{dI_i}{dt} = \gamma_i(1-\varepsilon_i)[I_i(\mu_i + d_i)] \tag{3.16}$$

$$\frac{dR_i}{dt} = -(1-\gamma_i)[(\mu_i - \sigma)R_i] \tag{3.17}$$

Then

$$N_i(t) = S_i(t) + E_i(t) + I_i(t) + R_i(t) \tag{3.18}$$

Let $c =$ min$(\mu_i\gamma_i, \varepsilon_i, \gamma_i\varepsilon_i(\mu_i + d_i), \gamma_i(\mu_i + d_i), (1-\gamma_i)(\mu_i + \sigma))$. Then;

$$\frac{dN(t)}{dt} = \Lambda\gamma_i\varepsilon_i - c(S_i(t) + E_i(t) + I_i(t) + R_i(t))$$

$$\frac{dN(t)}{dt} \geq \omega - cN_i(t); \text{ where } \omega = \Lambda\gamma_i\varepsilon_i$$

$$\frac{dN(t)}{dt} + cN_i(t) \geq \omega$$

$$N(t)e^{ct} \leq \omega e^{ct} - \omega e^{0} + N_0$$

$$N(t) \leq \omega + N_0 e^{-ct} - \omega e^{-ct};\ \text{where } \omega \geq 0.$$

$$\lim_{t \to \infty} N(t) = \omega \tag{3.19}$$

$$\therefore N(t) \text{ is bounded.}$$

3.5.2 Basic reproduction number

In epidemiology, the basic reproductive number (sometimes basic reproduction rate or ratio) of an infection is the number of cases one case generates on the average over the course of its infectious period. This metric is useful because it helps determine whether or not an infectious disease can spread through a population. The basic Reproduction number R_0 is the threshold for many epidemiological models. When $R_0 < 1$, the infection dies out in the long run. One the other hand, if $R_0 > 1$, the infection will be able to spread in a population.

To obtain R_0, the dominant eigenvalue of the next generation matrix is considered. The spectral radius of FV^{-1} (i.e $R_0 = \rho(FV^{-1})$ where ρ is the spectral radius of next generation matrix, where F_i is a matrix representing the rate of new infection entering compartment i and V_i is a matrix representing the rate of transfer into and out of compartment i by other ways.

From the equations (3.2), (3.4), (3.6) and (3.8), the matrices F_i and V_i are given by;

$$F_i = \begin{bmatrix} (1-\varepsilon_i)E_i(t-\tau) \\ (1-\varepsilon_j)E_j(t-\tau) \\ (1-\gamma_i)I_i(t-\tau) \\ (1-\gamma_j)I_j(t-\tau) \end{bmatrix} \tag{3.20}$$

The matrix that represents the rate of transfer into and out of compartment i by any other means at DFE is given by matrix V:

$$V_i = \begin{bmatrix} E_i(\mu_i + d_i) \\ E_j(\mu_j + d_j) \\ I_i(\mu_i + d_i) \\ I_j(\mu_j + d_j) \end{bmatrix} \tag{3.21}$$

The matrices F_i and V_i are then differentiated partially with respect to state variables to obtain 4×4 matrices below;

$$F = \begin{bmatrix} (1-\varepsilon_i)e^{-\lambda\tau} & 0 & 0 & 0 \\ 0 & (1-\varepsilon_j)e^{-\lambda\tau} & 0 & 0 \\ 0 & 0 & (1-\gamma_i)e^{-\lambda\tau} & 0 \\ 0 & 0 & 0 & (1-\gamma_j)e^{-\lambda\tau} \end{bmatrix} \tag{3.22}$$

$$V = \begin{bmatrix} \mu_i + d_i & 0 & 0 & 0 \\ 0 & \mu_j + d_j & 0 & 0 \\ 0 & 0 & \mu_i + d_i & 0 \\ 0 & 0 & 0 & \mu_j + d_j \end{bmatrix} \tag{3.23}$$

The inverse of matrix V is the given by;

$$V = \begin{bmatrix} \frac{1}{\mu_i + d_i} & 0 & 0 & 0 \\ 0 & \frac{1}{\mu_j + d_j} & 0 & 0 \\ 0 & 0 & \frac{1}{\mu_i + d_i} & 0 \\ 0 & 0 & 0 & \frac{1}{\mu_j + d_j} \end{bmatrix} \tag{3.24}$$

The next generation matrix FV^{-1} is given by;

$$FV^{-1} = \begin{bmatrix} \frac{(1-\varepsilon_i)e^{-\lambda\tau}}{\mu_i + d_i} & 0 & 0 & 0 \\ 0 & \frac{(1-\varepsilon_j)e^{-\lambda\tau}}{\mu_j + d_j} & 0 & 0 \\ 0 & 0 & \frac{(1-\gamma_i)e^{-\lambda\tau}}{\mu_i + d_i} & 0 \\ 0 & 0 & 0 & \frac{(1-\gamma_j)e^{-\lambda\tau}}{\mu_j + d_j} \end{bmatrix} \tag{3.25}$$

The eigenvalues of the matrix (3.25) are computed by:

$$|A - I\lambda^*| = 0$$

where $A = FV^{-1}$ and I is a 4×4 identity matrix. This results in the eigenvalues given by:

$$\lambda_1^* = \frac{(1 - \varepsilon_i)e^{-\lambda\tau}}{\mu_i + d_i} \tag{3.26}$$

$$\lambda_2^* = \frac{(1-\varepsilon_j)e^{-\lambda\tau}}{\mu_j + d_j} \tag{3.27}$$

λ_3^* and λ_4^* are obtained from the characteristic equation below;

$$\lambda^{*2} - \lambda^* \left[\left(\frac{(1-\gamma_i)e^{-\lambda\tau}}{\mu_i + d_i} \right) + \frac{(1-\gamma_j)e^{-\lambda\tau}}{\mu_j + d_j} \right] + \left[\left(\frac{(1-\gamma_i)e^{-\lambda\tau}}{\mu_i + d_i} \right) + \frac{(1-\gamma_j)e^{-\lambda\tau}}{\mu_j + d_j} \right]$$

Algebraically;

$$\lambda_3^* = \frac{(1-\gamma_j)e^{-\lambda\tau}}{\mu_j + d_j} \tag{3.28}$$

$$\lambda_4^* = \frac{(1-\gamma_i)e^{-\lambda\tau}}{\mu_i + d_i} \tag{3.29}$$

Thus R_0, which is given by the dominant eigenvalue, is;

$$R_0 = \frac{(1-\gamma_i)e^{-\lambda\tau}}{\mu_i + d_i} \tag{3.30}$$

3.6 Equilibrium Points and Stability Analysis

In epidemiology, there are basically two equilibrium points, namely Disease Free Equilibrium (DFE) where $I = 0$ and Endemic Equilibrium Point (EEP) where $I \neq 0$. DFE occurs in absence of disease while EEP occurs in presence of a disease. The stability of a system is locally studied near fixed points. A system is stable if all the eigenvalues of the system linearized about a fixed point have negative real parts. This condition for stability yields a reproductive ratio denoted by R_0 which will form a stability criterion.

3.6.1 Disease free equilibrium point

Disease Free Equilibrium (DFE) point describes a point when the rate of change is equal to zero. It is evaluated by equating the system of delay differential equations (3.2)-(3.9)

to zero. DFE occurs when the infective class is absent and consequently the recoveries.

3.6.2 Stability of disease free equilibrium

The disease free equilibrium is the state of variable of the model in the absence of disease. Its stability can be tested using the eigenvalues of the Jacobian matrix obtained at DFE, where at this point $R_0 < 1$. To obtain the Jacobian matrix, equations (3.2), (3.4), (3.6) and (3.8) are differentiated with respect to state variables at DFE to get:

$$J_1 = \begin{bmatrix} -\mu_i & 0 & 0 & 0 & -a & -b & 0 & 0 \\ 0 & -\mu_j & 0 & 0 & -c & -d & 0 & 0 \\ 0 & 0 & e & 0 & a & b & 0 & 0 \\ 0 & 0 & 0 & f & c & d & 0 & 0 \\ 0 & 0 & \varepsilon_i e^{-\lambda\tau} & 0 & g & 0 & 0 & 0 \\ 0 & 0 & 0 & \varepsilon_j e^{-\lambda\tau} & 0 & h & 0 & 0 \\ 0 & 0 & 0 & 0 & (1-\gamma_i)e^{-\lambda\tau} & 0 & -\mu_i & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\mu_j \end{bmatrix} \tag{3.31}$$

where

$$a = \beta_{ii} S_i e^{-\lambda\tau}$$

$$b = \beta_{ij} \textstyle\sum_{j=i-1}^{i+1} S_i e^{-\lambda\tau}$$

$$c = \beta_{ji} \textstyle\sum_{i=j-1}^{j+1} S_j e^{-\lambda\tau}$$

$$d = \beta_{jj} S_j e^{-\lambda\tau}$$

$$e = (1-\varepsilon_i)e^{-\lambda\tau} - (\mu_i + d_i)$$

$$f = (1-\varepsilon_j)e^{-\lambda\tau} - (\mu_j + d_j)$$

$$g = (1-\gamma_i)e^{-\lambda\tau} - (\mu_j + d_j)$$

$$h = (1-\gamma_j)e^{-\lambda\tau} - (\mu_j + d_j)$$

The system (3.2)-(3.9) is locally asymptotically stable if all the eigenvalues of linearization matrix (3.31) above are negative. The eigenvalues are:

$$\lambda_1^* = -\mu_i$$

$$\lambda_2^* = -\mu_j$$

$$\lambda_3^* = -\mu_i$$

$$\lambda_4^* = -\mu_j$$

$$\lambda_5^* = (1-\varepsilon_i)e^{-\lambda\tau} - (\mu_i + d_i)$$

$$\lambda_6^* = (1-\varepsilon_j)e^{-\lambda\tau} - (\mu_j + d_j)$$

$$\lambda_{7,8}^* = -(1-\gamma_i)e^{-\lambda\tau} - (\mu_j + d_j) - (1-\gamma_j)e^{-\lambda\tau} - (\mu_j + d_j)$$

$$\pm\sqrt{-(1-\gamma_i)e^{-\lambda\tau} - (\mu_j + d_j)(1-\gamma_j)e^{-\lambda\tau} - (\mu_j + d_j)^2 - 4\left[-(1-\gamma_i)e^{-\lambda\tau} + (\mu_j + d_j)(1-\gamma_j)e^{-\lambda\tau} - (\mu_j + d_j)\right]}$$

which simplifies to:

$$(1-\gamma_i)e^{-\lambda\tau} - (\mu_j + d_j) = 0$$

$$\Rightarrow (1-\gamma_i)e^{-\lambda\tau} = (\mu_j + d_j)$$

$$\Rightarrow \frac{(1-\gamma_i)e^{-\lambda\tau}}{\mu_j + d_j} < 1$$

Thus the DFE is stable whenever;

$$R_0 = \frac{(1-\gamma_i)e^{-\lambda\tau}}{\mu_j + d_j} < 1 \tag{3.32}$$

3.6.3 Endemic equilibrium point

Endemic Equilibrium Point(EEP) E^e is the point whereby the disease is persistent with constant in the population where $I \neq 0$. The analysis of E^e was done at critical points of equations (3.2) - (3.9) which exists when $S_i^* > 0, E_i^* > 0, I_i^* > 0$ and $R_i^* > 0$. Here,

E^e of the ith region is considered thus equations (3.2), (3.4), (3.6) and (3.8) are used since it is assumed E^e of ith region is the same as the jth region.

The corresponding zero solutions is said to be asymptotically stable. The asymptotic stability of the above equations at E^e is established by examining the signs of the linearized equations. Given $E^e = S_i^*, E_i^*, I_i^*$ and R_i^* satisfies;

$$\Lambda_i - \mu_i S_i - \beta_{ij} \sum_{j=i-1}^{i+1} S_i I_j(t-\tau) - \beta_{ii} S_i I_i(t-\tau) = 0 \tag{3.33}$$

$$\beta_{ij} \sum_{j=i-1}^{i+1} S_i I_j(t-\tau) - (1-\varepsilon_i) E_i(t-\tau) - E_i(\mu_i + d_i) + \beta_{ii} S_i I_i(t-\tau) = 0 \tag{3.34}$$

$$\varepsilon_i E_i(t-\tau) + (1-\gamma_i) I_i(t-\tau) - I_i(\mu_i + d_i) = 0 \tag{3.35}$$

$$\gamma_i I_i(t-\tau) - \mu_i R_i - \sigma R_i = 0 \tag{3.36}$$

With algebraic manipulations, the values of $(S_i^*, E_i^*, I_i^*, R_i^*)$ points are obtained as;

$$\left.\begin{aligned} S_i^* &= \tfrac{-(1-\varepsilon_i)(\mu_i+d_i)+(\mu_i+d_i)^2-1+\gamma_i}{\mu_i \varepsilon_i} \\ E_i^* &= \tfrac{\Lambda_i-\mu_i(1+\varepsilon_i)(\mu_i+d_i-1+\gamma_i)+(\mu_i+d_i)^2-(1-\gamma_i)-\varepsilon_i\Lambda_i}{\mu_i\varepsilon_i(1-\varepsilon_i)+1} \\ I_i^* &= \tfrac{\Lambda_i-\mu_i(1+\varepsilon_i)(\mu_i+d_i-1+\gamma_i)+(\mu_i+d_i)^2-(1-\gamma_i)-\varepsilon_i\Lambda_i}{\mu_i\varepsilon_i(1-\gamma_i)+1} \\ R_i^* &= \tfrac{\Lambda_i-\mu_i(1+\varepsilon_i)(\mu_i+d_i-1+\gamma_i)+(\mu_i+d_i)^2-(1+\gamma_i)-\varepsilon_i\Lambda_i}{\mu_i(\mu_i+\sigma)(1-\varepsilon_i)+1} \end{aligned}\right\} \tag{3.37}$$

3.6.4 Stability of endemic equilibrium point

Stability of EEP is guaranteed if all the eigenvalues of the linearization matrix at EEP are negative. The stability analysis at EEP is done by centralizing the equilibrium points

to the origin. Considering equations (3.33), (3.34), (3.35) and (3.36), new variables are introduced as;

$$W_1 = S_i - S_i^* \Rightarrow S_i = W_1 + S_i^*$$

$$W_2 = E_i - E_i^* \Rightarrow E_i = W_2 + E_i^*$$

$$W_3 = I_i - I_i^* \Rightarrow I_i = W_3 + I_i^*$$

$$W_4 = R_i - R_i^* \Rightarrow R_i = W_4 + R_i^*$$

The equations (3.33), (3.34), (3.35) and (3.36), with the new variables becomes;

$$\left.\begin{aligned}
\dot{W}_1 &= \Lambda_i - \mu_i(W_1 + S_i^*) - \beta_{ij}\textstyle\sum_{j=i-1}^{i+1}(W_1 + S_i^*)(I_i^* + W_{3\tau}) \\
&\quad -\beta_{ii}S_i^*(W_1 + S_i^*)(I_i^* + W_{3\tau}) \\
\dot{W}_2 &= \beta_{ij}\textstyle\sum_{j=i-1}^{i+1}(W_1 + S_i^*)(I_i^* - W_{3\tau}) - (1-\varepsilon_i)(W_{2\tau} + E_i^*)(W_{2\tau} + E_i^*)(\mu_i + d_i) \\
&\quad +\beta_{ii}(W_1 + S_i^*)(I_i^* + W_{3\tau}) \\
\dot{W}_3 &= \varepsilon_i(W_{2\tau} + E_i^*) + (1-\gamma_i)(I_i^* + W_{3\tau}) - W_3(\mu_i + d_i) \\
\dot{W}_4 &= \gamma_i(I_i^* + W_{3\tau}) - \mu_i(R_i^* + W_4) - \sigma(R_i^* + W_4)
\end{aligned}\right\} \tag{3.38}$$

A solution of the form $W(t) = W_0 e^{-t}$ and the system (3.38) is linearized about the equilibrium $(W_1, W_2, W_3, W_4) = (S_i^*, E_i^*, I_i^*, R_i^*)$ to obtain $W(t) = A\dot{W}(t)$ where A is a 4×4 matrix. Differentiating system (3.38 partially with respect to state variables, a 4×4 Jacobian matrix, J_2 is obtained and is given as;

$$J_2 = \begin{bmatrix} a & 0 & b & 0 \\ c & d & e & 0 \\ 0 & \varepsilon_i e^{-\lambda\tau} & (1-\gamma_i) - (\mu_i + d_i) & 0 \\ 0 & 0 & \gamma_i e^{-\lambda\tau} & -\mu_i - \sigma \end{bmatrix} \tag{3.39}$$

where

$$a = -\mu_i - \beta_{ij}\sum_{j=i-1}^{i+1}(I_i^* - W_{3\tau}) - \beta_{ii}S_i^*(I_i^* + W_{3\tau})$$

$$b = \beta_{ij}\sum_{j=i-1}^{i+1}(W_1 + S_i^*)e^{-\lambda\tau} + \beta_{ii}W_1e^{-\lambda\tau} + S_i^*e^{-\lambda\tau}$$

$$c = \beta_{ij}\sum_{j=i-1}^{i+1}(I_i^* + W_{3\tau}) + \beta_{ii}S_i^*(I_i^* + W_{3\tau})$$

$$d = (1-\varepsilon_i)(\mu_i + d_i)(W_{2\tau} + W_2e^{-\lambda\tau} + E_\tau^*e^{-\lambda\tau} + E_i^*)$$

$$e = \beta_{ij}\sum_{j=i-1}^{i+1}e^{-\lambda\tau}(S_i^* + W_1) + \beta_{ii}e^{-\lambda\tau}(S_i^* + W_1)$$

Clearly, the eigenvalues are;

$$\left.\begin{aligned} \lambda_1^* &= -\mu_i - \sigma \\ \lambda_2^* &= \gamma_i e^{-\lambda\tau} - (\mu_i + d_i) \\ \lambda_3^* &= -\mu_i - \beta_{ij}\sum_{j=i-1}^{i+1}(I_i^* - W_{3\tau}) - \beta_{ii}S_i^*(I_i^* + W_{3\tau}) \\ \lambda_4^* &= (1-\varepsilon_i)(\mu_i + d_i)(W_{2\tau} + W_2e^{-\lambda\tau} + E_\tau^*e^{-\lambda\tau} + E_i^*) \end{aligned}\right\} \tag{3.40}$$

Here $\lambda_2^* > 0$ since;

$$(\mu_i + d_i) < \gamma_i e^{-\lambda\tau}$$

$$\Rightarrow \frac{\gamma_i e^{-\lambda\tau}}{(\mu_i + d_i)} > 1$$

Thus the EEP is stable whenever;

$$R_0 = \frac{\gamma_i e^{-\lambda\tau}}{(\mu_i + d_i)} > 1 \tag{3.41}$$

It is noted here that the basic reproduction number at EEP is greater than one which implies that the disease persists and is therefore endemic.

3.7 Sensitivity Analysis of Basic Reproduction Number R_0

Sensitivity analysis of basic reproduction number is being investigated to determine the parameter value that contributes more on the disease spread, Adebiyi (2016).In order to find out, sensitivity index analysis is carried out using partial derivatives when the variable is a differentiable function of the parameter. The normalized forward sensitivity index of variable to a parameter is the ratio of the relative change in the variable to the relative change in the parameter (Adebiyi, 2016). When a variable is a differentiable function of the parameter, the sensitivity index may alternatively be defined using partial derivatives as;

$$r_n^{R_0} = \frac{\partial R_0}{\partial n} \times \frac{n}{R_0} \tag{3.42}$$

where;

r is sensitivity index

n is parameter under consideration

R_0 is the basic reproduction number

The derivation of the sensitivity of R_0 to each of the parameters is as shown below:

$$\frac{\partial R_0}{\partial \mu_i} \times \frac{\mu_i}{R_0} = \frac{-\mu_i}{\mu_i + d_i} = -0.7143$$

$$\frac{\partial R_0}{\partial d_i} \times \frac{d_i}{R_0} = \frac{-d_i}{\mu_i + d_i} = -0.2857$$

$$\frac{\partial R_0}{\partial \gamma_i} \times \frac{\gamma_i}{R_0} = \frac{-1}{1 - \gamma_i} = -2.000$$

The sensitivity indices for the parameters in our model are shown in Table 3.2 below.

Table 3.2: *Parameter values and Sensitivity Indices of* R_0

Parameter	Parameter description	Value	Sensitivity index
μ	Natural death rate	0.5	−0.7143
		0.4	−0.6667
		0.3	−0.6000
d	Disease induced rate	0.2	−0.2857
		0.15	−0.2308
		0.1	−0.1667
γ	Treatment rate for infectious class	0.5	−2.000
		0.4	−1.6667
		0.3	−1.4286

Source of parameter values: Biswas *et al.* (2014)

From Table 3.2, it is evident that for all the model parameters, the signs of the sensitivity indexes of R_0 are all negative. This implies that all model parameters under consideration contributed to a decrease in the spread of the TB disease infection. It is also worth noting that γ is more sensitive than the other model parameters since it gives the most negative sensitivity index. Thus γ, the treatment rate for infectious individuals, contributed more to a decrease in TB spread.

3.8 Ethical Considerations

Authorization to carry out research was given by the Board of graduate studies. The data used for simulation was obtained from secondary sources.

CHAPTER FOUR

RESULTS AND DISCUSSIONS

4.1 Introduction

In this chapter, numerical simulations were done using Matlab to verify the analytic results obtained in chapter three. The parameter values were obtained from the literature. Analytic solutions on the previous chapters can be clarified through illustration of analytic results with specific numerical examples. The model equations (3.2)- (3.9) are considered.

4.2 Numerical Simulations and Discussions

Numerical simulations of the models equations are obtained using list of parameters and their estimated values given in Table 4.1.

Table 4.1: *Table of parameters and their Values*

Parameter	**Description**	**Value**
Λ	Recruitment (Birth) rate	0.25
μ	Natural death rate coefficient	0.5
d	Disease-induced death rate	0.2
β	Probability that susceptible becomes infected	0.01
γ	Treatment rate	$0 \leqq \gamma \leq 1$
ε	Rate at which exposed individuals become infectious	0.5
σ	Recover rate	sigma=0.001
S_0	Initial susceptible population	1000
E_0	Initial exposed population	100
I_0	Initial infected population	50
R_0	Initial recovered population	15
N_0	Initial population	1165
τ	Time delay	To be determined

Source: (Biswas *et al.*, 2014)

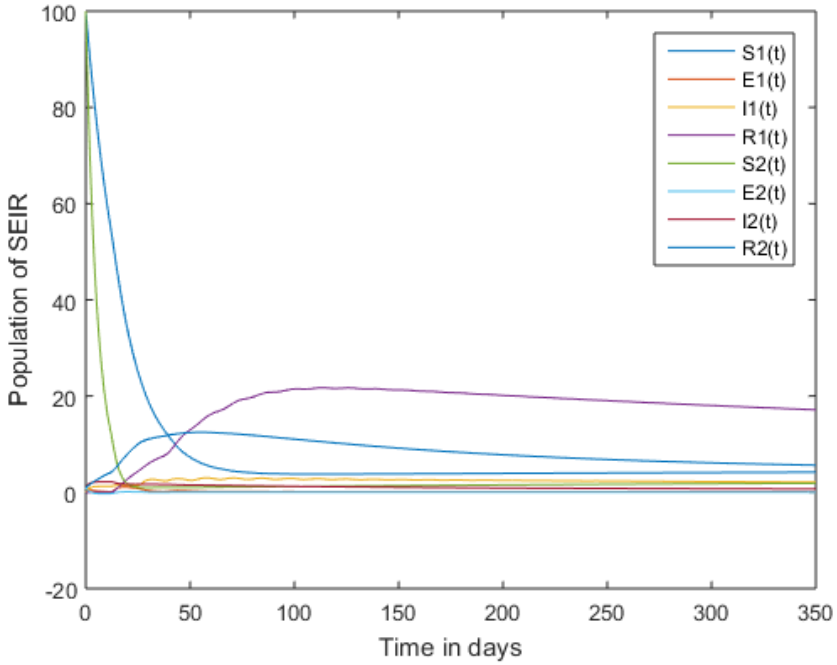

Figure 4.1: *A plot of population of SEIR against Time (in days)*

Figure 4.1 shows the dynamics of populations of various compartments of SEIR against time in days. From the graph, it is clearly seen that the infected individuals are less than the susceptible group.

4.2.1 Analysis of basic reproduction number at DFE

At Disease Free Equilibrium (DFE), $R_0 < 1$ which implies that the disease dies out in the population.Public health interventions aim at reducing and maintaining Ro below 1 which is achieved by reducing average infectious period through treatment, vaccination, isolation or minimizing contact rate between susceptible and infected persons through restriction of movement of infected person in a population. This phenomenon is defined as isolation of patches strategy of controlling disease in a metapopulation, (Anupi, 2015).

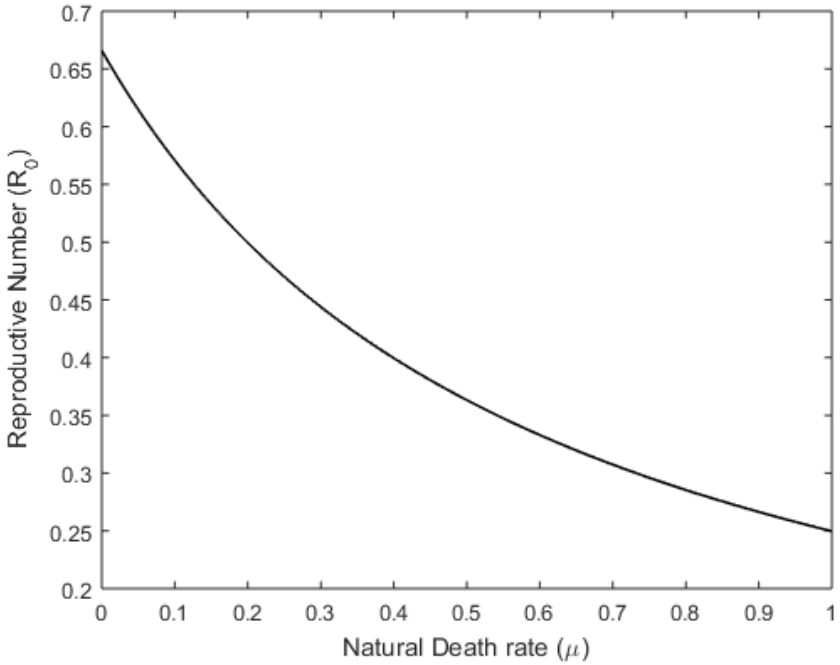

Figure 4.2: *A plot of R_0 at DFE against Natural Death Rate (μ)*

Figure 4.2 shows a plot of reproduction number against the natural death rate. It is evident that R_0 is inversely proportional to the natural death rate.

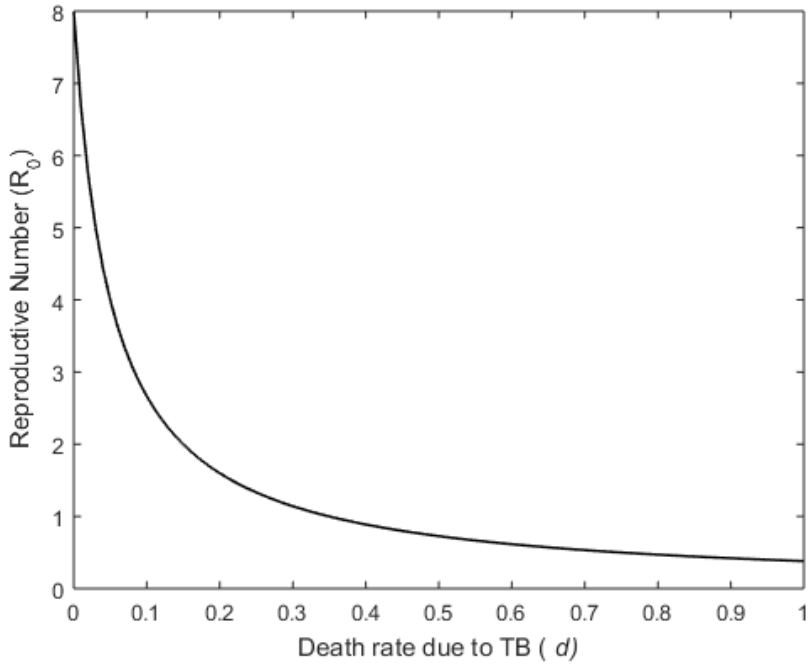

Figure 4.3: *A plot of R_0 at DFE against Death Rate due to TB (d)*

Figure 4.3 shows a plot of reproduction number against the natural death rate. It is

evident that R_0 is inversely proportional to disease-induced death rate (death rate due to TB).

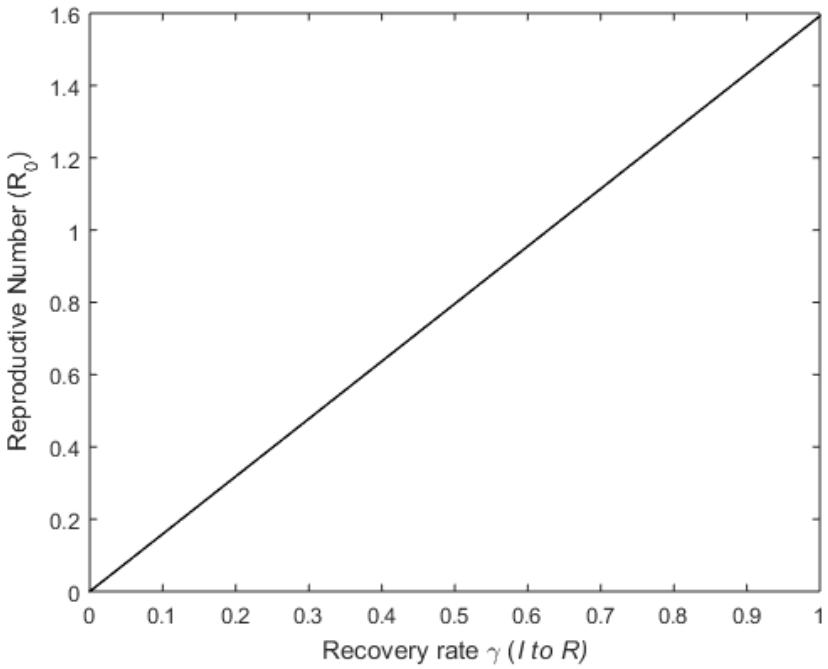

Figure 4.4: *A plot of R_0 at DFE against recovery rate (γ)*

Figure 4.4 shows a plot of reproduction number against the progression rate from I to S (recovery rate). It is evident that R_0 is inversely proportional to recovery rate.

4.2.2 Analysis of basic reproduction number at EEP

At Endemic Equilibrium point (EEP), $R_0 > 1$ which implies that the infection can spread in a population. This is because on average, every infected individual has a higher chance of causing more than one case of infection. This process can only take place as long as there are sufficiently may susceptible individuals available in a population.Once a larger fraction of the population has gone through infection and has become immune, the probability of an infected person meeting a susceptible person decreases and so does the average number of secondary cases. Finally, in order to reduce the spread of infection and subsequently eliminate it, the contact rate between susceptible

and infectious persons must be minimal.

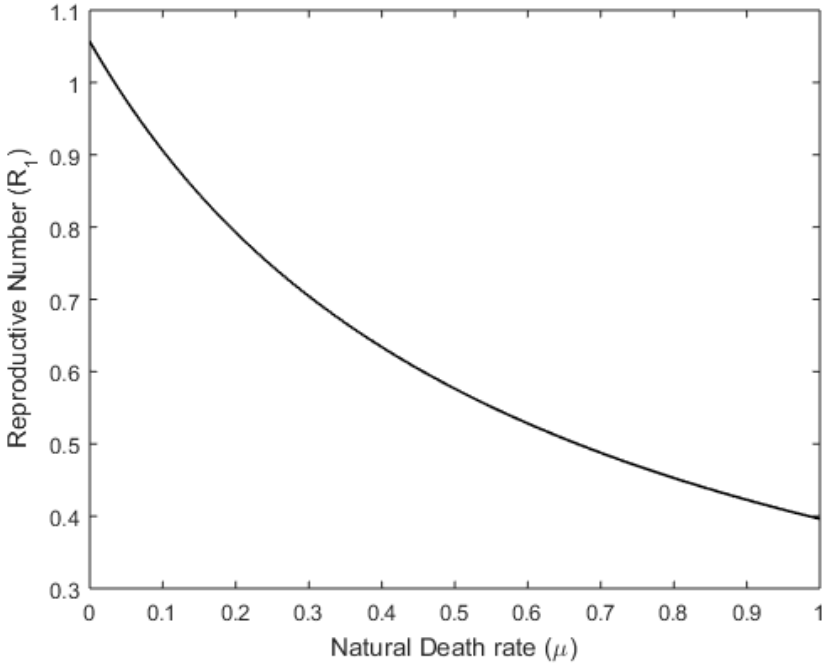

Figure 4.5: *A plot of R_0 at EEP against Natural Death Rate (μ)*

Figure 4.5 shows a plot of reproduction number against the natural death rate. It is evident that R_0 is inversely proportional to the natural death rate indicating that there are more susceptible individuals. Here $R_0 > 1$ when $\mu < 1$, indicating that the epidemic persists.

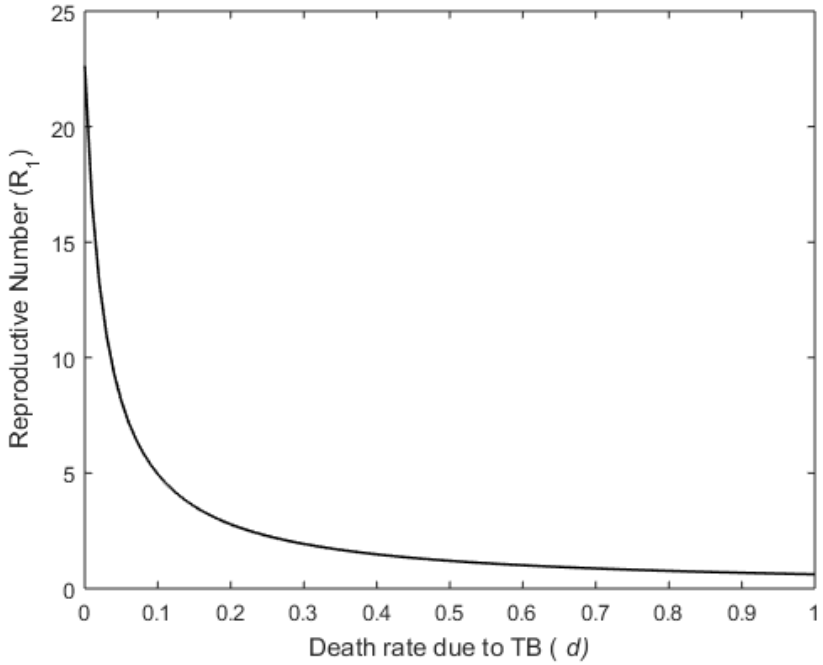

Figure 4.6: *A plot of R_0 at EEP against Death Rate due to TB (d)*

Figure 4.6 shows a plot of reproduction number against the natural death rate. It is evident that R_0 is inversely proportional to disease-induced death rate (death rate due to TB). As death rate due to TB increases, R_0 decreases but it remains greater than unity, that is, $R_0 > 1$.

Interruption of transmission requires that the average age at vaccination should be less than average age of infection. If disease elimination is to be successful, then vaccination must be applied at the youngest possible age.

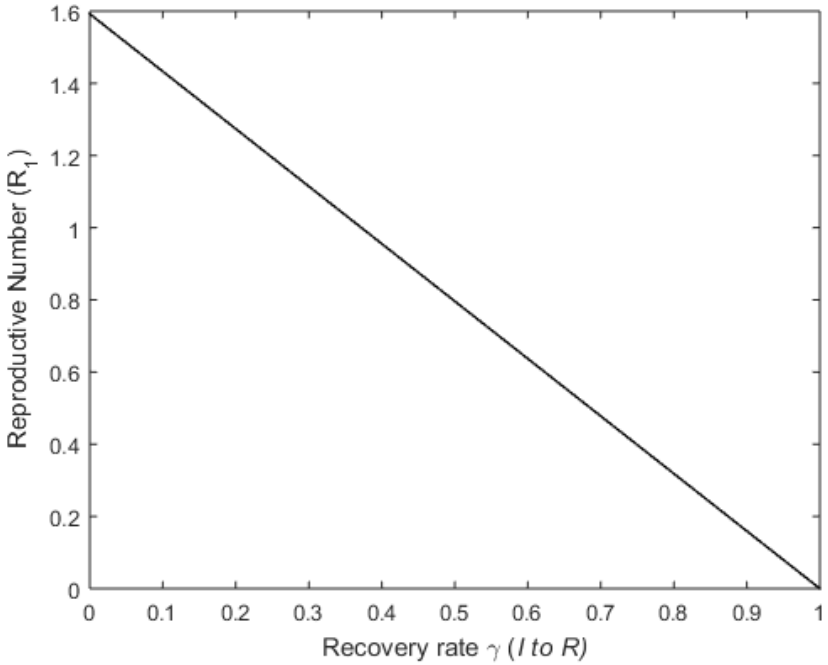

Figure 4.7: *A plot of R_0 at EEP against recovery rate (γ)*

Figure 4.7 shows a plot of reproduction number against the recovery rate (progression rate from I to S). It is evident that R_0 is inversely proportional to recovery rate and $R_0 > 1$ when the recovery rate is less than 0.4.

CHAPTER FIVE

SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

5.1 Introduction

This chapter gives an overview of the thesis on effect of time delay on the spread of TB in a metapopulation, DFE and EEP and their stabilities. Finally, recommendations for further research work are also highlighted.

5.2 Summary

The main objective of the study was to formulate delay differential equation SEIR model for the control of spread of Tuberculosis in a metapopulation. The stability of the model both at DFE and EEP was determined. Numerical simulation was done using MATLAB ODE23 solver to verify the analytic results. Parameter values were obtained from literature.

5.3 Conclusions

We have formulated a delay differential equation of SEIR TB model in a coupled Meta population. DFE was attained when $R_0 < 1$. Numerical simulation of the model was carried out to validate the analytic results. where it was found out that, R_0 was 0.5828 at DFE. Furthermore at EEP, R_0 was found to be 1.0095 hence stability was guaranteed. This ratio plays a vital role in minimizing the spread of tuberculosis.

5.4 Recommendations

The government should increase educational awareness on restriction of travel of people in and out of a subpopulation to avoid the infection. This will minimize the spread of the disease across the sub-populations. To lower transmission and spread of the disease in a metapopulation, there is need to use of preventive measures such as isolation of already infected individuals, campaigns on BCG vaccination of all children under 5 years and seeking medical treatment on infected persons.

5.5 Suggestions for Further Research

This study has not exhausted all about TB dynamics in coupled Metapopulation. The effect of an individual's immune response to TB disease is not included. The model can be extended to include co-infection between TB and HIV in a metapopulation. The carrying capacity of the subpopulation, characteristics of the subpopulations like education levels and economic status are also possible insights for further research work on the dynamics of TB disease in Meta-populations.

REFERENCES

Adebiyi, A. (2016). Mathematical modeling of population dynamics of tuberculosis. *unpublished Master's thesis, University of the Western Cape, South Africa*.

Adu, A. and Rotich, K. (2007). Synchronization, persistence in diffusively coupled lattice oscillators. *Journal of Science*, **12**(1), 41–52.

Anupi, O. (2015). Modeling the dynamics of an epidemic in a metapopulation lattice. *unpublished Masters Thesis, Kisii University, Kenya.*

Athithan, S. and Ghosh, M. (2015). Optimal control of tuberculosis with case detection and treatment. *Journal of modeling and simulation*, **12**(2), 111–122.

Bimal, K. M. and Jyotika, S. (2013). Mathematical model on pulmonary and multidrug-resistant tuberculosis patients with vaccination. *Journal of the Egyptian Mathematical society*, **4**, 311–316.

Biswas, M. H. A., Paiva, L. T. and Pinho, M. (2014). A seir model for the control of infectious diseases with constraints. *Journal of Mathematical Biosciences and Engineering*, **4**(11), 761–784.

Chacha, M. I. (2016). Modeling the transmission of tuberculosis. *Unpublished Masters thesis, , University of Cape Town, South Africa.*

Cohen, T., Colijn, C., Finklea, B. and Murray, M. (2007). Exogenous re-infection and the dynamics of tuberculosis epidemics. *Journal of Royal Society*, **14**(4), 523–531.

Dipo, A., Riyanto, Z. A. and Bustamam, A. (2018). A mathematical model of tb control with vaccination in an age-structured susceptible population. *Journal of physics Conf. Series*.

Driesch, V. and Watmough, J. (2002). Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Journal of Mathematical Biosciences*, **12**, 29–48.

Enagi, A. I., Ibrahim, M. O., Akinwande, N. I., Bawa, M. and Wachin, A. A. (2017). A mathematical model of tuberculosis control incorporating vaccination, latency and infectious treatments. *International Journal of Mathematics and Computer Science*, **12**(2), 97–106.

Feng, Z. and Chavez, C. C. (2001). The role of variable latent periods in mathematical models for tuberculosis. *Journal of dynamics and differential equations*, **41**(1), 3–44.

Fonseca, K. L., Rodrigues, P. N. S., Olsson, I. A. and Saraiva, M. (2017). Experimental study of tuberculosis: from animal models to complex cell systems and organoids. *Journal of PLOS pathogens*, **13**(8).

Global Tuberculosis Report (2013). URL `www.who.int/iris/bitstream/10665/91355/1/9789241564656-eng;Accessedon24thSeptember,2019`.

Herthcote, H. W. (2000). The mathematics of infectious diseases. *Journal of society for industrial and applied mathematics*, **42**(4), 599–653.

Hickson, R. I., Mercer, G. N. and Lokuge, K. M. (2012). A metapopulation model of tuberculosis transmission with a case study from high to low burden areas. *Journal of PLOS ONE*, **7**(4).

Houben, R. M. G., Lalli, M., Sumner, T., M., H., Bonsu, F., Hippner, P., Pillay, Y., Kimerling, M., Ahmedov, S., Pretorius, C. and White, R. G. (2016). Time impact – a new user-friendly tuberculosis model to inform tb policy decisions. *Journal of Biomedical central*, **9**, 56–98.

Jesse, M., Ezano, P., Davis, S. and Hesterbeek, J. (2008). A fully coupled mechanistic model for infectious disease dynamics in a metapopulation movement and epidemic duration. *Journal of theoretical Biology*, **10**, 331–335.

Muhammad, R. T., Lestari, D. and Septiarini, T. W. (2015). Mathematical model for vaccinated tuberculosis disease with veit model. *International Journal of modeling and optimization*, **5**(3), 192–197.

Roussel, M. R. (2005). Delay-differential equations. URL `www.people.uleth.ca/~roussel/nld/delay`.

Tewa, J. J., Bowong, S. and Mewoli, B. (2012). Mathematical analysis of two-patch model for the dynamical transmission of tuberculosis. *Journal of Applied mathematical modeling*, **13**, 2466–2485.

Trauer, J., Denholm, J. and McBryde, E. (2014). Construction of a mathematical model for tuberculosis transmission in highly endemic regions of the asia-pacific. *Journal of theoretical Biology*, **19**, 74–84.

Witbooi, P. and Vyabwera, S. M. (2017). A model of population dynamics of tb in a prison system and application to south africa. *Journal of Biomedical centre*, **10**, 643–697.

Wu, P., Lau, E. H. Y., Cowling, B. J., Chi-Chiu, L., Cheuk-Ming, T. and Leung, G. M. (2010). The transmission dynamics of tuberculosis in a recently developed chinese city. *Journal of PLOS ONE*.

Zhao, Y., Li, M. and Yuan, S. (2017). Analysis of transmission and control of tuberculosis in mainland china, 2005-2016, based on the age-structure mathematical model. *Journal of environmental research and public health*.

APPENDICES

A.1: MATLAB Codes

```
function sol = Mutai

global tau

tau = 8;

sol = dde23(@ddes,tau,[100; 1; 1; 1; 100; 1; 1; 1],[0,150]);

figure(1)

plot(sol.x,sol.y)

legend('S1(t)','E1(t)','I1(t)','R1(t)','S2(t)','E2(t)','I2(t)',

'R2(t)');

xlabel('Time in days');

ylabel('Population of SEIR');

%=========================================

function dydt = ddes(t,v,Z)

global tau

% Parameters:

mu1=0.028;mu2=0.028;d1=0.6;d2=0.6;beta11=0.0043;beta12=0.0043;

beta21=0.0067;beta22=0.0067;epsilon1=0.34; epsilon2=0.34; gamma1=0.3

sigma=0.00001; lambda=0.00001;

% Variable names used in stating the DDEs:

S1 = v(1); E1 = v(2); I1 = v(3); R1 = v(4); S2 = v(5);

E2 = v(6); I2 = v(7); R2 = v(8);
```

```
vlag = Z(:,1); % Z(:,1) corresponds to the lag tau.
dS1dt = Gamma1-mu1*v(1)-beta11*v(1)*vlag(3)-beta12*v(1)*vlag(7)-
beta11*v(1)*vlag(3)+sigma*v(4);
dE1dt = beta11*v(1)*vlag(3)+beta12*v(1)*vlag(7)-
(1-epsilon1)*vlag(2)-v(2)*(mu1+d1)+beta11*v(1)*vlag(3);
dI1dt = epsilon1*vlag(2)+(1-gamma1)*vlag(3)-v(3)*(mu1+d1);
dR1dt = gamma1*vlag(3)-mu1*v(4)-sigma*v(4);
dS2dt = Gamma2-mu2*v(5)-beta21*v(5)*vlag(3)-2*beta22*v(5)*vlag(7)+
sigma*v(8);
dE2dt = beta21*v(5)*vlag(3)-beta22*v(5)*vlag(7)-
(1-epsilon2)*vlag(6)-v(6)*(mu2+d2)+beta22*v(5)*vlag(7);
dI2dt = epsilon2*vlag(6)+(1-gamma2)*vlag(7)-v(7)*(mu2+d2);
dR2dt = gamma2*vlag(7)-mu2*v(8)-sigma*v(8);
dydt = [dS1dt; dE1dt; dI1dt; dR1dt; dS2dt; dE2dt; dI2dt; dR2dt];
%.....................................................
R0=gamma1*(exp(-(lambda*tau))./(mu1+d1);
R1=(1-gamma1)*(exp(-(lambda*tau))./(mu1+d1);
```

Annals of Infectious Disease and Epidemiology

Review Article
Published: 17 Jun, 2020

Modeling the Dynamics of Tuberculosis in a Coupled Metapopulation

Mutai Wesley[1], Kirui Wesley[2] and Mukuna Wilys[1]*

[1]*Department of Mathematics and Computer Science, University of Kabianga, Kenya*

[2]*Department of Mathematics and Actuarial Science, South Eastern Kenya University, Kenya*

Abstract

Tuberculosis (TB) is currently one of the key health tests in many developing countries, Kenya included. TB is a curable transmissible ailment caused by *Mycobacterium tuberculosis*. The formation of the tubercles in tissues of the body like in the lung tissues describes the disease. Interaction with transmissible individuals can make one acquire TB. The behavior of transmissible diseases, its impacts and possible future prediction about its spread has been best understood with the knowledge of mathematical epidemiology. In this study, delay differential equations were formulated for purposes of determining stability of Disease Free Equilibrium (DFE). The delay component was incorporated into Susceptible-Exposed-Infectious-Recovered (SEIR) model. A parameter called the basic reproduction number was computed and numerical simulations were done using MATLAB for validation of the analytical results. Parameter values were obtained from secondary data.

Keywords: TB; Reproduction number; Delay differential equations; Stability; Disease free equilibrium

Introduction

Tuberculosis (TB) is a bacterial infections ailment of humans and animals initiated by the *Mycobacterium Tuberculosis Complex* (MTBC) which include four TB causing Mycobacteria*: M. bovis, M. africanum, M .canetti* and *M .microti.* The formation of tubercles on the lungs and other tissues of the body characterize the ailment, frequently developing extensively after the primary infection. It is an airborne disease which is transmitted when individuals with active TB cough, sneeze, speak, sing or spit. *Mycobacterium tuberculosis* is among the causes of mortality [1-17]. In the case of incomplete treatment, the remains of *mycobacterium tuberculosis* in the human system often results in the bacterium developing resistance to antibiotics. This leads to Multi-Drug Resistance-TB (MDR-TB) [9,18].

Mathematical epidemiology has contributed to a more in-depth appreciative of the activities of tuberculosis as a transmissible ailment, its effects and possible future forecast about its spread and the mechanisms of its control. The planning, evaluation, prevention and control of TB in a population will be facilitated by model analysis [11]. Many populations are structured in space but interconnected by human travelling. A population may be subdivided into separated patches also called subpopulations, each with its dynamics. A group of such a distinctive subpopulation is known as a metapopulation [12]. Subpopulation interconnections may be; random, all-to-all, one-to-many or nearest neighbor connection [2].

Coupling configurations

Coupling is the arrangement of subpopulations in a way that can affect each other. There are different forms of nearest neighbor coupling. Nearest neighbor coupling is where a subpopulation is connected to their immediate neighbor [3]. The following are the coupling configurations: Coupling on a line, Coupling on a ring, Coupling on a two-dimensional Bravais lattice, One-to-all coupling, All-to-all coupling and Coupling on three-dimension.

Review of Related Literature

The increasing rate of Tuberculosis (TB) cases in many countries of Sub-Saharan Africa over the past decade is largely attributed to the Human Immunodeficiency Virus (HIV) and other emerging infections. Mathematical models developed for tuberculosis transmission are numerous; some of

OPEN ACCESS

Correspondence:
Mutai Wesley, Department of Mathematics and Computer Science, University of Kabianga, Kericho, Kenya; E-mail: mutaiwesley13@gmail.com

Received Date: *15 May 2020*
Accepted Date: *11 Jun 2020*
Published Date: *17 Jun 2020*

Citation:
Wesley M, Wesley K, Mukuna AO. Modeling the Dynamics of Tuberculosis in a Coupled Metapopulation. Ann Infect Dis Epidemiol. 2020; 5(2): 1054. ***ISSN: 2475-5664***

them have been reviewed as follows: According to [14] they studied the spread of TB through a two patch epidemiological model. They made an assumption that susceptible individuals can migrate between two patches but not infective individuals. They formulated the model by considering a two patch SEI TB. They then analyzed the model by computing the DFE and R_0. They went further and determined the global stability of DFE by showing that DFE has global asymptotic stability when R_0<1. In [5] they formulated a model on pulmonary and MDR TB with vaccination. Here, they considered a quarantine class in their epidemic model for MDR TB patients. They observed that quarantine plays an important part in the control of the infection. They formulated Susceptible-Exposed-Infectious-Quarantine-Recovered-Susceptible having a Vaccinated class (SEI-QRS-V). The model was used in describing changing aspects of TB spread in relation to time in human being populace. The results showed that the disease R_0, DFE and their stability were determined. They showed that if R_0<1, DFE stability is global in the feasible zone and the disease is wiped out. If R_0>1, an exceptional endemic balance occurs and has a nearby (local) asymptotic stability. According to [4] they studied a non-linear mathematical model of TB with a case detection and treatment. In the paper, the whole population under consideration was in four compartments; Susceptible Exposed Infectious and Recovered (SEIR) model which they used to study transmission dynamics of TB. They computed R_0 and determined the equilibria of the model. Their results showed that an increase in the rate of case detection lead to an increase in the threshold value of R_0. Also, the treatment reduced the equilibrium level of the infective class.

According to [13] they presented a paper titled 'mathematical model for vaccinated tuberculosis disease with VEIT model'. In this model, there are four compartments; Vaccinated Exposed Infected and Treated (VEIT). The paper discussed about formation and analysis of the VEIT model to TB virus infection by exogenous re-infection. They concluded that the model of vaccinated with exogenous re-infection have two equilibria states; DFE and EEP. They showed that the eigenvalue of DFE is always negative so that the system stability is asymptotically stable at DFE.

In [6] a mathematical model that predicted the threat of TB as a contagious airborne infection under stable state and non-unstable state situations was developed. They did this by monitoring the amount of breath out air by contagious persons in a restricted environment. They demonstrated precisely and diagrammatically, the relationship between TB spread possibility and airborne level of infection, average amount of exhaled air taking into consideration TB occurrence and length of contact to contagious persons in a restricted environment. They chose an age structuring model since infection and illness frequency differ in diverse inhabitants on age dependent and host immune aspects. In their study, they found out that TB spread is prevalent in gatherings for instance; schools, public transportation and correctional facilities especially in developing countries. Similarly [1] in his thesis titled 'mathematical modeling of population dynamics of TB' presented and analyzed a SLIT (Susceptible Latent Infectious and Treated) model with the inflow of infective. He analyzed the spread, asymptotic behavior and possible eradication of the disease. He also carried out sensitivity analysis of R_0 to determine the parameter value that contributes more on the disease transmission. He utilized the sensitivity index analysis using partial derivatives when the variable is a differentiable function of the parameter. With the help of next generation matrix and theorem by [15], it was found out that whenever R_0>1, DFE is locally asymptotically stable and unstable whenever R_0>1. The simulation results from the thesis indicated that despite presence of constant inflow of infective immigrants, he proposed a control strategy of complete treatment that can help suppress the spread of TB. According to [16] a compartmental model to describe the population dynamics of TB disease in a prison system in South Africa was developed. Their model considered the inflow of susceptible and exposed classes as well as the disease infection into the prison population. The model was used to make quantitative projections of TB prevalence and measure on effects of interventions. In their paper, they presented a deterministic compartmental model using ODE's and determined the global stability of disease Free State a parameter for eradicating TB. In [8] they modeled the effect of combining Immunization with Latent Tuberculosis treatment in controlling the spread of Tuberculosis. The administration of Bacillus Calmette Guerin (BCG) vaccines at birth protects children from early infection of the disease, but the effect of these vaccines expires with time. Their results showed that detection and treatment of latent tuberculosis infections using Isoniazid Preventive Therapy prevents the breakdown of latent infections into infectious cases, thus reducing greatly the rate of spread of the disease since only members of the infectious class can spread the disease to others. The DFE will be stable if effort is intensified in bringing down both the contraction rate and the rate of break down to infectious tuberculosis. According to [7] they developed a mathematical model of the spread of TB disease involving the age classes in a susceptible compartment under SEIR model. The model had two equilibrium points; DFE and EEP. The R_0 was constructed using the next generation matrix approach. They found out that TB transmission can be reduced through vaccination and increasing life expectancy. The results from simulation showed also that transmission can also be reduced through vaccine protection period and vaccine efficacy. The above studies did not consider the use of Delay Differential Equations (DDE) in the solution to the various equations arising from the models. This study has formulated DDE`s model for the spread of TB in a coupled metapopulation.

Methodology

Introduction

In epidemiology, the basic reproductive number (sometimes basic reproduction rate or ratio) of an infection is the number of cases one case generates on the average over the course of its infectious period. This metric is useful because it helps determine whether or not an infectious disease can spread through a population. The basic Reproduction number R_0 is the threshold for many epidemiological models. When R_0<1, the infection dies out in the long run (i.e. each infected individual produces one average less than one new infected individual). One the other hand, if R_0>1 the infection will be able to spread in a population (i.e. each infected individual produces more than one new infected individual).

To obtain R_0, the dominant eigenvalue of the next generation matrix is considered such that $R_0=\rho(FV^{-1})$ where ρ is the spectral radius of next generation matrix, Matrix F_i represents the rate of new infection entering compartment i and matrix V_i represents the rate of transfer into and out of compartment i by other ways.

Since we are dealing with a large population, a deterministic or compartmental mathematical model is used. In the deterministic model, individuals in the population are assigned to different subgroups or compartments, each representing a specific stage of the epidemic. The Susceptible-Exposed-Infected Removed (SEIR) epidemiological models are utilized to study and analyze the disease, thus the simple SEIR model is used to explain the spread of tuberculosis in a population.

Methods of solution

The stability of the model has been approached from Jacobian matrix method for checking stability of Disease Free Equilibrium (DFE) and numerical simulations have been done using MATLAB to validate the analytic results.

Model equations

The dynamics of TB is modeled by the following system of delay differential equations:

$$\frac{ds_i}{dt} = A_i - \mu_i s_i - \beta_{ij}\sum_{j=i-1}^{i+1} S_i I_j(t-\tau) - \beta_{ii} S_i I_i(t-\tau) \quad (3.1)$$

$$\frac{ds_j}{dt} = A_j - \mu_j sj - \beta_{ij}\sum_{i=j-1}^{j+1} S_j I_i(t-\tau) - \beta_{jj} S_j I_j(t-\tau) \quad (3.2)$$

$$\frac{dE_i}{dt} = \beta_{ij}\sum_{j=i-1}^{i+1} S_i I_j(t-\tau) - (1-\varepsilon_i)E_i(t-\tau) - E_i(\mu_i + d_i)\beta_{ii} S_i I_i(t-\tau) \quad (3.3)$$

$$\frac{dE_j}{dt} = \beta_{ji}\sum_{i=j-1}^{j+1} S_j I_i(t-\tau) + (1-\varepsilon_j)E_j(t-\tau) - E_j(\mu_j + d_j)\beta_{jj} S_j I_j(t-\tau) \quad (3.4)$$

$$\frac{dI_i}{dt} = \varepsilon_i E_i(t-\tau) + (1-\gamma_i)I_i(t-\tau) - I_i(\mu_i + d_i) \quad (3.5)$$

$$\frac{dI_j}{dt} = \varepsilon_j E_j(t-\tau) + (1-\gamma_j)I_j(t-\tau) - I_j(\mu_j + d_j) \quad (3.6)$$

$$\frac{dR_i}{dt} = \gamma_i I_i(t-\tau) - \mu_i R_i - \sigma R_i \quad (3.7)$$

$$\frac{dR_j}{dt} = \gamma_j I_j(t-\tau) - \mu_j R_j - \sigma R_j \quad (3.8)$$

Model preliminary analysis

Positivity and boundedness of solutions: Since the model under consideration represents the population dynamics of living organisms, it is necessary to show that the solutions are always positive and bounded.

We define the compact set

$\{S_i(0), E_i(0), I_i(0), R_i(0)\}\varepsilon\mathbb{R}^4 \geq 0$, $0 \leq E_i < S_2$, $0 \leq I_i < S_2$, $0 \leq R_i < S_3$ where $S_a > 0, a = 1,2,3.$

Proposition 1: The set Ω is positively invariant for model (3.2), (3.4), (3.6) and (3.8).

Proof:

We have $\frac{dS_i}{dt} | S_{i=0} = \Lambda_i \geq 0$ (3.10)

$\frac{dE_i}{dt} | E_{i=0} = 0 = \beta_{ij}\sum_{j=i-1}^{i+1} S_i I_j(t-\tau) - \beta_{ii} S_i I_i(t-\tau) \geq 0$ Whenever $S_i, I_j, I_i \geq 0$ (3.11)

$\frac{dI_i}{dt} | I_{i=0} = 0 = \varepsilon_i E_i(t-\tau) \geq 0$ whenever $E_i \geq 0$ (3.12)

$\frac{dR_i}{dt} | R_{i=0} = 0 = \gamma_i I_i(t-\tau) \geq 0$ (3.13)

This confirms that $\{S_i(t), E_i(t), I_i(t), R_i(t)\}\varepsilon\mathbb{R}^4 \geq 0$ with $\{S_i(0), E_i(0), I_i(0), R_i(0)\}\varepsilon\mathbb{R}^4 \geq 0$

Thus $\mathbb{R}^4 \geq 0$ is positively invariant for model (3.2) - (3.8).

For boundedness we define;

$\frac{dS_i}{dt} = \gamma_i\varepsilon_i[\Lambda_i - u_i S_i]$

$\frac{dS_i}{dt} = \gamma_i\varepsilon_i[E_i(u_i + d_i)]$

$\frac{dI_i}{dt} = \gamma_i(1-\varepsilon_i)[I_i(u_i + d_i)]$

$\frac{dR_i}{dt} = -(1-\gamma_i)[u_i - \sigma]R_i]$

Then

$$N(t) = S_i(t) + E_i(t) + I_i(t) + R_i(t)$$

Let c min $(u_i\gamma_i\varepsilon_i\gamma_i\varepsilon_i(u_i + d_i), \gamma_i(1-\varepsilon_i)(u_i + d_i), (1-\gamma_i)(u_i + \sigma)$

Then

$$\frac{dN(t)}{dt} = \Lambda_i\gamma_i\varepsilon_i - c(s_i(t) + E_i(t) + I_i(t) + R_i(t))$$

$$\frac{dN(t)}{dt} \le \omega - N_i(t)$$

Where $\omega = \Lambda_i\gamma_i\varepsilon_i$

$$\frac{dN(t)}{dt} + cN_i(t) \le \omega$$

$$N(t)e^{ct} \le \omega e^{ct} - \omega e^0 + N_0$$

$$N(t) \le \omega + N_0 e^{-ct} - \omega e^{-ct}$$

Where $\omega \ge 0$. This shows that the solution is bounded.

To obtain R_0, the dominant eigenvalue of the next generation matrix is considered such that $R_0=\rho(FV^{-1})$ where ρ is the spectral radius of next generation matrix, Matrix F_i represents the rate of new infection entering compartment *i* and matrix V_i represents the rate of transfer into and out of compartment *i* by other ways.

From the equations (3.1)-(3.8) the matrices $\boldsymbol{F_i}$ and V_i are given by;

$$F_i = \begin{pmatrix} (1-\varepsilon_i)E_i(t-\tau) \\ (1-\varepsilon_j)E_j(t-\tau) \\ (1-\gamma_i)I_i(t-\tau) \\ (1-\gamma_j)I_j(t-\tau) \end{pmatrix} \tag{3.18}$$

$$V_i = \begin{pmatrix} E_i(\mu_i + d_i) \\ E_j(\mu_j + d_j) \\ I_i(\mu_i + d_i) \\ I_j(\mu_j + d_j) \end{pmatrix} \tag{3.19}$$

We then differentiate matrix F_i and V_i partially with respect to state variables to obtain the below 4 × 4 matrices as;

$$F_i = \begin{bmatrix} (1-\varepsilon_i)e^{-\lambda\tau} & 0 & 0 & 0 \\ 0 & (1-\varepsilon_j)e^{-\lambda\tau} & 0 & 0 \\ 0 & 0 & (1-\gamma_i)e^{-\lambda\tau} & 0 \\ 0 & 0 & 0 & (1-\gamma_j)e^{-\lambda\tau} \end{bmatrix} \tag{3.20}$$

$$V_i = \begin{bmatrix} \mu_i + d_i & 0 & 0 & 0 \\ 0 & \mu_j + d_j & 0 & 0 \\ 0 & 0 & \mu_i + d_i & 0 \\ 0 & 0 & 0 & \mu_j + d_j \end{bmatrix} \tag{3.21}$$

Then, the inverse of V is given by;

$$V^{-1} = \begin{bmatrix} \frac{1}{\mu_i + d_i} & 0 & 0 & 0 \\ 0 & \frac{1}{\mu_j + d_j} & 0 & 0 \\ 0 & 0 & \frac{1}{\mu_i + d_i} & 0 \\ 0 & 0 & 0 & \frac{1}{\mu_j + d_j} \end{bmatrix} \tag{3.22}$$

The next generation matrix FV^{-1} is given by;

$$FV^{-1}=\begin{bmatrix}(1-\varepsilon_i)e^{-\lambda\tau} & 0 & 0 & 0\\ 0 & (1-\varepsilon_j)e^{-\lambda\tau} & 0 & 0\\ 0 & 0 & (1-\gamma_i)e^{-\lambda\tau} & 0\\ 0 & 0 & 0 & (1-\gamma_j)e^{-\lambda\tau}\end{bmatrix}\begin{bmatrix}\frac{1}{\mu_i+d_i} & 0 & 0 & 0\\ 0 & \frac{1}{\mu_j+d_j} & 0 & 0\\ 0 & 0 & \frac{1}{\mu_i+d_i} & 0\\ 0 & 0 & 0 & \frac{1}{\mu_j+d_j}\end{bmatrix} \tag{3.23}$$

Which simplifies to;

$$FV^{-1}=\begin{bmatrix}\frac{(1-\varepsilon_i)e^{-\lambda\tau}}{\mu_i+d_i} & 0 & 0 & 0\\ 0 & \frac{(1-\varepsilon_j)e^{-\lambda\tau}}{\mu_j+d_j} & 0 & 0\\ 0 & 0 & \frac{(1-\gamma_i)e^{-\lambda\tau}}{\mu_i+d_i} & 0\\ 0 & 0 & 0 & \frac{(1-\gamma_j)e^{-\lambda\tau}}{\mu_j+d_j}\end{bmatrix} \tag{3.24}$$

The eigenvalues of the matrix (3.24) are computed by $|A-I\lambda|=0$ given where A is the matrix FV^{-1} and i is 4×4 identity matrix.

$$\lambda_1=\frac{(1-\varepsilon_i)e^{-\lambda\tau}}{\mu_i+d_i}$$

$$\lambda_2=\frac{(1-\varepsilon_j)e^{-\lambda\tau}}{\mu_j+d_j}$$

$\lambda_{3,4}$ is obtained from the characteristic equation below;

$$\lambda^2-\lambda\left(\left(\frac{(1-\gamma_i)e^{-\lambda\tau}}{\mu_i+d_i}\right)+\left(\frac{(1-\gamma_j)e^{-\lambda\tau}}{\mu_j+d_j}\right)\right)+\left(\left(\frac{(1-\gamma_i)e^{-\lambda\tau}}{\mu_i+d_i}\right)+\left(\frac{(1-\gamma_j)e^{-\lambda\tau}}{\mu_j+d_j}\right)\right)=0$$

Algebraically,

$$\lambda_3=\frac{(1-\gamma_j)e^{-\lambda\tau}}{\mu_j+d_j}$$

$$\lambda_4=\frac{(1-\gamma_i)e^{-\lambda\tau}}{\mu_i+d_i}$$

Thus R_0 which is given by the dominant eigenvalue is given as;

$$R_0=\frac{(1-\gamma_i)e^{-\lambda\tau}}{\mu_i+d_i}$$

Equilibrium points and stability analysis

In epidemiology, there are basically two equilibrium points, namely Disease Free Equilibrium (DFE) where *i=0* and Endemic Equilibrium Point (EEP) where $i\neq0$. DFE occurs in absence of disease while EEP occurs in presence of a disease. The stability of a system is locally studied near fixed points. A system is stable if all the eigenvalues of the system linearized about a fixed point have negative real parts. This condition for stability yields a reproductive ratio denoted by R_0 which will form a stability criterion.

Disease free equilibrium: This equilibrium point describes a point when the rate of change is equal to zero. It is evaluated by equating the system of delay differential equation (3.1)-(3.8) to zero. DFE occurs when the infective class is absent and consequently the recoveries.

Stability of Disease Free Equilibrium: The disease free equilibrium is the state of variable of the model in the absence of disease. Its stability can be tested using the eigenvalues of the Jacobian matrix obtained at DFE, where at this point $R_0<1$. To obtain Jacobian matrix we differentiate

equations (3.1)-(3.8) with respect to state variables at DFE to get.

$$FV^{-1}=\begin{bmatrix} -\mu_i & 0 & 0 & 0 & -\beta_{ii}s_i e^{-\lambda\tau} & \beta_{ij}\sum_{i=j-1}^{j+1} s_j e^{-\lambda\tau} & 0 & 0 \\ 0 & -\mu_j & 0 & 0 & -\beta_{ij}\sum_{i=j-1}^{j+1} s_j e^{-\lambda\tau} & -\beta_{ii}s_i e^{-\lambda\tau} & 0 & 0 \\ 0 & 0 & (1-\varepsilon_i e^{-\lambda\tau})-(\mu_i+d_i) & 0 & \beta_{jj}s_j e^{-\lambda\tau} & \beta_{ij}\sum_{j=i-1}^{i+1} s_i e^{-\lambda\tau} & 0 & 0 \\ 0 & 0 & 0 & (1-\varepsilon_j e^{-\lambda\tau})-(\mu_j+d_j) & \beta_{ij}\sum_{i=j-1}^{j+1} s_j e^{-\lambda\tau} & \beta_{jj}s_j e^{-\lambda\tau} & 0 & 0 \\ 0 & 0 & \varepsilon_i e^{-\lambda\tau} & 0 & (1-\gamma_i)e^{-\lambda\tau}-(\mu_i+d_i) & 0 & 0 & 0 \\ 0 & 0 & 0 & \varepsilon_j e^{-\lambda\tau} & 0 & (1-\gamma_j)e^{-\lambda\tau}-(\mu_j+d_j) & 0 & 0 \\ 0 & 0 & 0 & 0 & (1-\gamma_i)e^{-\lambda\tau} & 0 & -\mu_i & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\mu_j \end{bmatrix} \quad (3.25)$$

The system (3.1)-(3.8) is locally asymptotically stable if all the eigenvalues of linearization matrix (3.25) above are negative. The eigenvalues are:

$$\lambda_1=-\mu_i$$

$$\lambda_2=-\mu_j$$

$$\lambda_3=-\mu_i$$

$$\lambda_4=-\mu_j$$

$$\lambda_5=(1-\varepsilon_i)e^{-\lambda\tau}-(\mu_i+d_i)$$

$$\lambda_6=(1-\varepsilon_i)e^{-\lambda\tau}-(\mu_j+d_j)$$

$$\lambda_{7,8}==-(1-\gamma_i)e^{-\tau\lambda}-(\mu_j+d_j)-(1-\gamma_j)e^{-\tau\lambda}-(\mu_j+d_j))\pm\sqrt{-(1-\gamma_i)e^{-\tau\lambda}+(\mu_j+d_j)(1-\gamma_j)e^{-\tau\lambda}-(\mu_j+d_j))^2-4(-(1-\gamma_i)e^{-\tau\lambda}+)(\mu_j+d_j)(1-\gamma_j)e^{-\tau}}$$

Which simplifies to

$$\gamma je^{-t\lambda}-(\mu_j+d_j)<0$$

$$\gamma je^{-t\lambda}<(\mu_j+d_j)$$

$$\frac{\gamma ie^{-\lambda\tau}}{\mu j+dj}<1$$

Thus $R_0=\frac{\gamma ie^{-\lambda\tau}}{\mu j+dj}<1$

When R_0<1, DFE is attained.

Numerical Analysis and Results

This chapter comprises of parameter values obtained from secondary data and graphs obtained using Mat lab (Table 1).

Table 1: Parameters, Definition and Value.

Parameters	Definition	Value
μ	Natural death rate coefficient	0.5
d	Disease-induced death rate	0.2
β	Probability that susceptible becomes infected	0.001
γ	Treatment rate	$0 \le \gamma \le 1$
ε	Rate at which exposed individuals become infectious	0.5
Λ	Recruitment rate	0.005
S_0	Initial susceptible population	1000
I_0	Initial infected population	50
R_0	Initial recovered population	15
N_0	Initial population	1165
E_0	Initial exposed population	100
τ	Time delay	To be determined

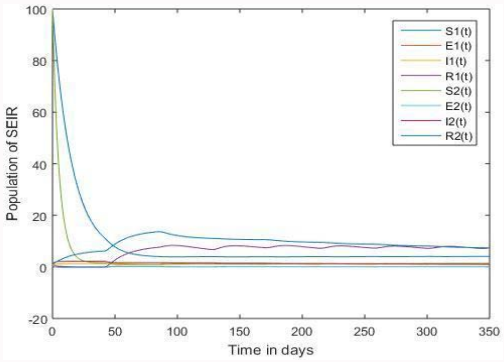

Figure 1: Population of various compartments against time in days. From the graph, it is evident that, initially the infected were at 80, then it drops drastically to below 20 because treatment, time delay and vaccination played a major role in minimizing infection.

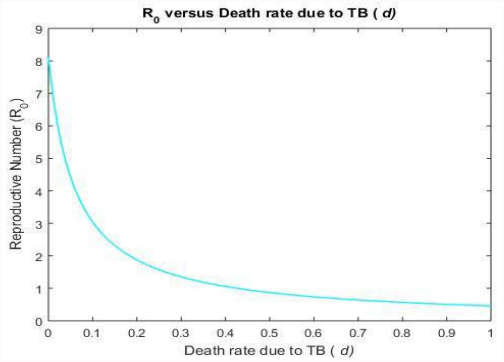

Figure 2: Reproduction number against death rate (d). From the graph it is evident that R_0 is inversely proportional to d.

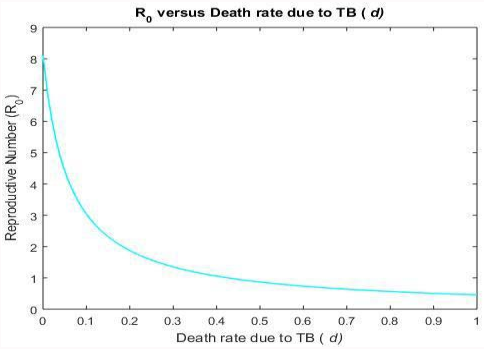

Figure 3: R_0 against progression rate. Form the graph it is evident that R_0 is inversely proportional to progression rate.

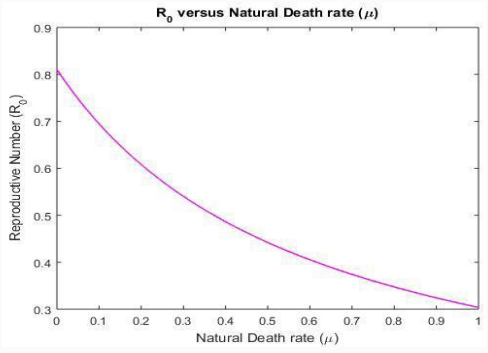

Figure 4: R_0 death rate. From the graph it is evident that R_0 is inversely proportional to death rate, μ.

Conclusion

We have formulated a delay differential equation of SEIR TB model in a coupled Meta population. We obtained a basic reproduction number R_0 which is less than unity. This ratio plays a vital role in minimizing the spread of tuberculosis (Figures 1-4). The spread of contagious diseases remains a test in developing countries. The government should increase educational awareness on restriction of travel of people in and out of a subpopulation to avoid the infection. This will minimize the spread of the disease across the sub-populations. To lower transmission and spread of the disease in a metapopulation, there is need to use of preventive measures such as isolation of already infected individuals, campaigns on BCG vaccination of all children under 5 years and seeking medical treatment on infected persons.

Suggestions for Further Research

This study has not exhausted all about TB dynamics in coupled Metapopulation. The effect of an individual's immune response to TB disease is not included. The model can be extended to include co-infection between TB and HIV in a metapopulation. The carrying capacity of the subpopulation, characteristics of the subpopulations like education levels and economic status are also possible insights for further research work on the dynamics of TB disease in Meta-populations.

References

1. Adebiyi AO. Mathematical modeling of population dynamics of tuberculosis, unpublished Master's Thesis University of the Western Cape. 2016.
2. Adu AMW, Rotich KT. Synchronization, persistence in diffusively coupled lattice oscillators, Sultan Qaboos University. J Sci. 2007;12(1):41-52.
3. Anupi OP. Modeling the dynamics of an epidemic in a metapopulation lattice, unpublished Master's Thesis. 2015.
4. Athithan S, Ghosh M. Optimal control of tuberculosis with case detection and treatment. J Model Simulat. 2015;11(2):111-22.
5. Bimal KM, Jyotika S. Mathematical model on pulmonary and multidrug-resistant tuberculosis patients with vaccination. J Egypt Mathemat Society. 2013;22(2):311-6.
6. Chacha M. Issarow. Modeling the transmission of tuberculosis, unpublished Master's thesis, University of Cape Town. 2016.
7. Dipo A, Riyanto ZA, Bustamam A. A mathematical model of TB control with vaccination in an age-structured susceptible population. J physi Conf Serie. 2018;1108.
8. Enagi AI, Ibrahim MO, Akinwande NI, Bawa M, Wachin AA. A Mathematical model of tuberculosis control incorporating vaccination, latency and infectious treatments (case study of Nigeria). Int J Mathemat Computer Sci. 2017;12(2):97-106.
9. Fonseca KL, Rodrigues PNS, Olsson IA, Saraiva M. Experimental study of tuberculosis: from animal models to complex cell systems and organoids. PLOS Pathog. 2017;13(8):e10006421.
10. Global Tuberculosis Report. 2013.
11. Herthcote HW. The mathematics of infectious diseases. J Society Industrial Applied Mathemat. 2000;42(4):599-653.
12. Jesse M, Ezano P, Davis S, Hesterbeek J. A fully coupled mechanistic model for infectious disease dynamics in a metapopulation movement and epidemic duration. J Theor Biol. 2008;254(2):331-5.
13. Muhammad RT, Lestari D, Septiarini TW. Mathematical model for vaccinated Tuberculosis disease with VEIT model. Int J Model Optimizat. 2015;5(3):192-7.
14. Tewa JJ, Bowong S, Mewoli B. Mathematical analysis of two-patch model for the dynamical transmission of tuberculosis. J Appl Mathemat Model. 2012;36:2466-85.
15. Van den Driesch, Watmough J. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. J Mathemat Biosci. 2002;180(1):29-48.
16. Witbooi P, Vyabwera SM. A model of population dynamics of TB in a prison system and application to South Africa. BMC Res Notes. 2017;10(1):643-97.
17. Wu P, Lau EHY, Cowling BJ, Chi-Chiu L, Cheuk-Ming T, Leung GM. The transmission dynamics of tuberculosis in a recently developed Chinese city. PLOS ONE. 2010;5(5):e10468.
18. Zhao Y, Li M, Yuan S. Analysis of transmission and control of Tuberculosis in mainland China, 2005-2016, based on the age-structure mathematical model. Int J Environ Res Public health. 2017;14(10):1192.