TUBERCULOSIS MODEL: A MATHEMATICAL ANALYSIS

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FACULTY OF SCIENCE
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ABSTRACT

In this thesis, the design and analysis of compartmental deterministic models for the transmission dynamics of infectious disease in a population is studied.

A basic Susceptible-Exposed-Infected-Recovered (SEIR) model for the transmission of infectious disease with immigration of latent and infectious individuals is developed and rigorously analyzed. The model is assumed to have permanent immunity and homogenous mixing. The constant immigration of the infected individuals into the population makes it impossible for the disease to die out which means, there will be no disease-free equilibrium. However, it is shown that there exists an endemic equilibrium which is locally asymptotically stable under certain parameters restriction.

We then extend the 3-compartment Susceptible-Exposed-Infected (SEI) tuberculosis (TB) model with immigration proposed by McCluskey and van den Driessche (MnD) in 2004 into a 4-compartment SEIR model. The treated individuals are moved into the recovered group with slight immunity against the TB. Results show the importance of treatment to the infected and that treatment for the latently infected are more effective in curbing the disease.

In the last model, we analyze the best approach in containing the spread of the disease under different factors. We incorporate the idea of immigration into the TB transmission model with chemoprophylaxis treatment as proposed by Bhunu et al. [3]. The results show that the immigration effects are overwhelmed by the other contributing factors such as the high rate of re-infection, making it insignificant; contradicting with reality. Simply giving treatments also does not give the best result

on a long term basis as the population will eventually die out. Different kinds of intervention are needed to ensure a more successful prevention plan and one way is to reduce the contact rate of the infectious individuals.

ABSTRAK

Tesis ini adalah mengenai reka bentuk dan analisis model kompartmen berketentuan untuk dinamik penularan penyakit berjangkit dalam sesebuah populasi.

Model asas *Rentan-Terdedah-Dijangkiti-Pulih (SEIR)* untuk penularan penyakit berjangkit yang melibatkan imigrasi individual-individual yang terdedah dan terjangkit dibina dan dianalisis secara teliti. Model ini diandaikan mempunyai imuniti kekal dan pergaulan seragam. Imigrasi berterusan individu yang berpenyakit ke dalam populasi menyebabkan mustahil untuk menghapuskan penyakit itu; yakni tidak wujud keseimbangan bebas-penyakit. Walau bagaimanapun di bawah kekangan parameter tertentu, dapat ditunjukkan kewujudan suatu titik keseimbangan yang stabil secara asimptotik tempatan.

Seterusnya, model TB 3-bahagian *Rentan-Terdedah-Dijangkiti* (SEI) dengan imigrasi yang dicadangkan oleh McCluskey and van den Driessche (MnD) pada tahun 2004 dikembangkan kepada model 4-bahagian (SEIR). Individu yang dirawat dipindahkan ke kumpulan yang pulih dengan sedikit imuniti terhadap TB. Hasil kajian menunjukkan betapa pentingnya rawatan kepada individu yang dijangkiti serta keberkesanan rawatan terhadap individu yang terdedah kepada penyakit dalam membendung penularan penyakit.

Model terakhir digunakan untuk menganalisa pendekatan terbaik dalam mengawal penyebaran penyakit di bawah keadaan berbeza. Idea imigrasi digabungkan ke dalam model penularan TB dengan rawatan *chemoprophylaxis* yang diusulkan oleh Bhunu et al. [3]. Hasil kajian menunjukkan bahawa kesan immigrasi tidak begitu penting dibandingkan dengan faktor-faktor penyumbang lain seperti kadar jangkitan semula

yang tinggi; ini bertentangan dengan realiti. Setakat memberi rawatan juga tidak memberi keputusan yang terbaik dalam jangka masa panjang memandangkan seluruh populasi akan mati juga akhirnya. Pelbagai langkah berbeza perlu diambil untuk memastikan pelan pencegahan yang lebih berjaya, dan salah satu daripadanya adalah dengan mengurangkan kadar pertembungan individu yang terjangkit.

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INTRODUCTION

1.1. Introduction

Tuberculosis (TB) is a worldwide pandemic disease. According to World Health Organization (WHO), one-third of the world's population is currently infected by the TB bacillus bacteria. Being a disease of poverty, the vast majority of TB deaths are in the developing world with more than half occurring in Asia [28].

The estimated global incidence rate are falling very slowly from the peak of 141 cases per 100,000 population in 2002 to 128 cases per 100,000 population in 2010. The TB death rate has also fallen by 40% since 1990 and the number of deaths is also declining. Globally, the percentage of people successfully treated reached its highest level at 87% in 2009.

1.2. History of tuberculosis

TB is believed to have been present in humans for thousands of years. Skeletal remains show that prehistoric humans (4000BCE) had TB and tubercular decay has been found in the spines of Egyptian mummies dating from 3000-2400 BCE [14, 25]. It was not identified as a single disease until the 1820s due to the variety of its symptoms. In 1834, Johann Lukas Schonlein gave the disease name 'tuberculosis' [14].

Mycobacterium tuberculosis, the bacteria that caused the tuberculosis was identified by Nobel Laureate Robert Koch in March 1882 and in 1900's, Albert Calmette and Camille Guerin achieved the first genuine success in immunizing against tuberculosis using attenuated bovine-strain tuberculosis called 'BCG' (Bacillus of Calmette and Guerin) [14]. It was not until 1946 with the development of the antibiotic streptomycin

that effective treatment and cure became possible. However, hopes of completely eliminating the disease were dashed following the rise of drug-resistant strains in the 1980s.

1.3. Tuberculosis at a glance

1.3.1. What is tuberculosis?

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* bacteria. It spreads through the air like the common cold. Most TB infections will results as a latent infection where the body is able to fight the bacteria and stopping them from growing. The bacteria thus will become dormant and remain in the body without causing symptoms.

However, when the immune system of a patient with dormant TB is weakened, the TB can become active and cause infection in the lungs or other parts of the body. Only those with active TB can spread the disease. According to WHO, 5-10% of people who are infected with TB will become infectious at some time during their life and if left untreated each person will infect on average 10 to 15 people every year [28].

1.3.2. How does a person get TB?

Tuberculosis is spread through the air from one person to another. The bacteria get into the air when someone who has a tuberculosis lung infection coughs, sneezes, shouts, or spits [5, 28]. People who are nearby can then possibly breathe the bacteria into their lungs and become infected. Even though the disease is airborne, it is believed that TB is not highly infectious and so, occasional contacts with infectious person rarely lead to infection [26]. TB cannot be spread through handshakes, sitting on toilet seats or sharing dishes and utensils with someone who has TB.

1.3.3. Who gets TB?

It is said that, every second, one person in the world is newly infected with TB bacilli [28]. Anyone can catch TB, but people who are particularly at risk include

- those who live in close contact with individuals who have an active TB infection e.g. family members, nurses and doctors,
- those with weak immune system either because of age or health problem e.g. young children or elderly people, alcoholics, intravenous drug users, patient with diabetes, certain cancers and HIV, and
- those who live in environments where the level of existing TB infection is higher than normal e.g. poor and crowded environment, prison inmates, homeless people.

1.3.4. What are the symptoms?

Symptoms of TB disease depend on where in the body the TB bacteria grow. Active TB cases may be pulmonary where it affects the lungs. The early symptoms usually include fatigue or weakness, unexplained weight loss, fever, chills, loss of appetite and night sweats [5, 28]. Since the symptoms are very much similar to a common cold people tend to treat it as one. When the infection in the lung worsens, it may cause chest pain, bad cough that last 3 weeks or longer and coughing up of sputum and/or blood.

There are also cases where the infection spreads beyond the lungs to other parts of the body such as the bones and joints, the digestive system, the bladder and reproductive system and the nervous system. This is known as extra pulmonary TB and the

symptoms will depend upon the organs involved. It is more common in people with weaker immune systems, particularly those with an HIV infection.

1.3.5. Diagnosis of TB

One who came with the symptoms may be suspected with TB based on the patient's medical history, medical conditions and physical exam. There are several different ways to diagnose TB such as analysis of sputum, skin test and chest X-rays.

The skin test is used to identify those who may have been exposed to tuberculosis by injecting a substance called tuberculin under the skin. A positive test shows that the person may have been infected but does not necessarily mean they have active TB. Other tests are done in making a diagnosis of active tuberculosis which includes identifying the causative organism Mycobacterium tuberculosis in the sputum. Sometimes, diagnosis may also be made using the chest X-rays by looking at things such as evidence of active tuberculosis pneumonia, and scarring or hardening in the lungs.

1.3.6. Treatment of TB

Tuberculosis is treated by killing the bacteria using antibiotics. The treatment usually last at least 6 months in duration and sometimes longer up to 24 months. It involves different antibiotics to increase the effectiveness while preventing the bacteria from becoming resistant to the medicines.

The most common medicines used for active tuberculosis are *Isoniazid* (INH), *Rifampin* (RIF), *Ethambutol* and *Pyrazinamide* [5]. People with latent tuberculosis are usually treated using a single antibiotic to prevent them from progressing to active TB disease later in life.

The successful of tuberculosis treatment is largely dependent on the compliance of the patient. One of the main reason that cause the failure of TB treatment is because the patient failed to take the medications as prescribed. In most cases, proper treatment with appropriate antibiotics will cure the TB. Without treatment, tuberculosis can be a lethal infection.

1.4. Problem statement

According to World Health Organization (WHO), the number of people falling ill with TB each year is declining [28]. However, this downward trend is threaten by the increasing number of TB cases in immigrants especially in countries that have substantial levels of immigration from areas with a high prevalence of the disease [16, 21]. The immigrants here are generally the people who are travelling from less to more economically developed geographical areas in search of jobs and better living conditions. As an air-borne infectious disease, it is impossible for any country to isolate itself. In long-term, the best defense against TB is to bring the disease under control worldwide.

1.5. Aim and Objectives

Our aim is to analyze the dynamic of Tuberculosis transmission under different conditions in order to identify key factors which contribute in the spreading of the disease using mathematical model.

The objectives of the study are:

- To see how immigration plays a role in TB spreading,
- To determine how effective the treatment for both latently infected and infectious individuals in controlling the spread of the disease, and

- To deduce an action plan for prevention, control and monitoring of TB from the results obtained.

1.6. Organization of thesis

This thesis is divided into five chapters. Following this introductory Chapter 1, Chapter 2 is the literature review that surveys previous literature and studies relevant to our research. Chapter 3 describes and explains the research methodology used. The sub-topics include the research design, model stability, data collection and data analysis. In Chapter 4 the models and results are presented. The last chapter, Chapter 5, is the conclusion from our results and also suggestions for future research. The bibliography concludes this thesis.

CHAPTER 2

LITERATURE REVIEW

2.1. Introduction

In mathematical modeling, we translate our beliefs about how the world functions into the language of mathematics. A model is a quantified simplification of the complex reality. The construction of a model involves the formulation of a hypothesis about the nature of the relationships that exists between the various relevant factors. Its quality depends on the accuracy of its underlying assumptions.

2.2. History of Mathematical Modelling in Infectious Disease

Mathematical models have become an important tool in analyzing the spread and control of infectious disease. The results from mathematical models can help in determining the plausibility of epidemiologic explanations and predicting the impact of changes on the dynamics of the system. It is important for understanding the population dynamics of the transmission of infectious agents and the potential impact of infectious disease control programs [2].

The very first epidemiological model was formulated by Daniel Bernoulli in 1760 [4] in order to evaluate the impact of variolation on human life expectancy. However, deterministic epidemiology modelling seems to have started in the 20^{th} century when Hamer [13] formulated and analyzed a discrete time model on measles in 1906, followed by Ross [24] with his work on malaria in 1911.

In 1927, Kermack and McKendrick [18] obtained one of the key results in epidemiology by deriving the threshold theorem that predicts the critical fraction of

susceptible in population that must be exceeded in order for an epidemic outbreak to occur. Starting in the middle of the 20th century, mathematical epidemiology showed a rapid growth. The book on mathematical modelling of epidemiological systems that was published by Bailey [3] is said to be an important landmark which, in part, led to the recognition of the importance of modelling in public health decision making [1, 7, 15].

In the epidemiology of tuberculosis, the model approach was first applied by Frost [12]. He predicted in 1937 that with the low and falling rate of transmission of infection in the United States, it was most likely that the disease will eventually be eradicated. His prediction was confirmed by Feldman [10] in 1957 by making further progress in model-making.

Today, variety of models have been formulated, mathematically analyzed and applied to infectious disease.

2.3. The epidemic models

The fundamental process represented in mathematical model of the epidemiology of infectious disease is the transmission of infectious agents.

> Mathematical models characterize transmission in terms of infection rates related to the frequency of contact between individuals and the likelihood of transmission given a contact between a susceptible host and infective host [2].

This process is represented as a series of stages of infection starting with a susceptible host who becomes infected. The infected host will be able to transmit the infection to others when the host becomes infective. The period of time that elapses before an infected host becomes infective is referred as the latent period. The host will then be

removed from the transmission cycle when the host is no longer able to transmit infection. The removal may be caused by death by infection, acquisition of permanent immunity or successful treatment.

Compartments with label such as S, E, I and R are often used to represent the epidemiological classes in a population. The first class is susceptible (S) who can acquire the infection. The second class is exposed (E) who is in the latent period. Next class is infective (I) who can transmit infection to susceptible and lastly the class of recovered (R) who is immune. Acronyms for epidemiology models are often based on the flow patterns between the compartments such as SEI, SIS, SIR, SEIR, SEIS, SEIRS to name a few.

The basic reproduction number is the threshold for many epidemiology models. It is defined as the average number of secondary infections produced when an infected host is introduced into a fully susceptible population [5, 15]. The threshold quantity is used to determine when an infection can invade and persist in a new host population.

In some epidemiological models, the incidence rate (the rate of new infections) is bilinear in the infective fraction I and the susceptible fraction S. Such models usually have an asymptotically stable trivial equilibrium corresponding to the disease-free state, or an asymptotically stable nontrivial equilibrium corresponding to the endemic (i.e. persistent) state depending on the parameter values. However, studies showed that when the restriction to bilinear incidence rates is dropped, the system can have a much wider range of dynamical behaviours.

Liu et al [22] studied the dynamical behaviour of epidemiological models with nonlinear incidence rates. Their studies show that models with nonlinear incidence have a much wider range of dynamical behaviours than do those with bilinear incidence rates. For these models, there is a possibility of multiple attractive basins in phase

space. Because of that, the disease survival depends not only upon the parameters but also upon the initial conditions. There are also cases where periodic solutions may appear by Hopf bifurcation at critical parameter values.

Li and Muldowney [19] studied the SEIR model with nonlinear incidence rates in epidemiology. The purpose of their paper is to prove the global stability of the nontrivial equilibrium for their SEIR model. They proved that any periodic orbit of the system, when it exists, is orbitally asymptotically stable based on a criterion for the asymptotic orbital stability of periodic orbits for general autonomous systems.

Li et al [20] studied the global dynamics of a SEIR model with varying total population size. The model assumes that the local density of the total population is a constant though the total population size may vary with time. They used the homogeneity of the vector field of the model to analyze the derived system of the fractions (s,e,i,r) in determining the behaviour of the population sizes (S,E,I,R) and the total population. The global stability is proved by employing the theory of monotone dynamical systems together with a stability criterion for periodic orbits of multidimensional autonomous systems due to Li and Muldowney [19].

2.4. Review of Tuberculosis Models

Internal and international human migration has increased worldwide in recent years. One of the main factors is because migration was easily done due to improved transportation. Migrants are generally people travelling from less to more economically developed geographical areas in search of jobs and better living conditions. With immigration from areas of high incidence of TB, it is conjectured that this will result in the resurgence of tuberculosis in areas of low incidence. TB cases involved in

immigrants represent a high proportion of the total prevalence rate in many developed countries [16].

In many developed nations, the main countermeasure in order to reduce the risk of TB spreading is by the screening of immigrants upon arrival. Nevertheless, several reports from many developed countries with well-performing screening and treatment systems have shown in the last few years that foreign-born TB patients do not significantly contribute to *M. tuberculosis* transmission to the native population [11, 17].

McCluskey and van den Driessche [23] investigate a SEI TB model with immigration that includes infected (both latent and infectious) individuals [Figure 4.3 (a)]. The model assumed constant recruitment with fixed fraction entering each class. McCluskey and van den Driessche [23] have proved that under certain restrictions on the parameters (including the treatment rates, disease transmission rate and TB induced death rate) the disease will approach a unique endemic level. The immigration of infected results in the disease never dies out and the usual threshold condition found in many epidemic models is not applicable.

Jia et al [16] investigate the impact of immigration on the transmission dynamics of tuberculosis. They too incorporated the recruitment of the latent and infectious immigrants but their model regards the immigrants as a separate subpopulation from the local population. Their theoretical analysis indicated that the disease will persist in the population if there is a prevalence of TB in immigrants. They also showed that the disease never dies out and becomes endemic in host areas. The usual threshold condition does not apply and a unique equilibrium exists for all parameter values. The study suggests that immigrants have a considerable influence on the overall transmission dynamics behaviour of tuberculosis.

Both studies show that when there is an immigration of infected into the population, there will be no disease-free equilibrium. Most study of the model with immigration will focused on the endemic equilibrium and its stability, and sometimes is supported by the numerical simulations. Such is the case with McCluskey and van den Driessche [23] as their paper is focused on the global stability of the model. They first show the existence of a unique endemic equilibrium using Descartes' Rule of Signs. Then they proved its local stability followed by the geometric approach developed in [18] that involves generalizations of Bendixsons' Condition to higher dimensions, to prove its global stability.

Bhunu et al [5] presented a SEIR tuberculosis model which incorporated treatment of infectious individuals and chemoprophylaxis (treatment for the latently infected). The model assumed that the latently infected individuals develop active disease as a result of endogenous re-activation, exogenous re-infection and disease relapse. The study shows that treatment of infectious individuals is more effective in the first years of implementation as it cleared active TB immediately. As a result, chemoprophylaxis will do better in controlling the number of infectious due to reduced progression to active TB.

From these studies, we can conclude that immigration does have an effect on the spread of tuberculosis in such a way that the disease persist in the host population [16, 23]. However, with proper treatments and intervention, the rate of infection from immigrants has little effect to the host population [11, 17]. Further studies are required to determine which factor plays the bigger role in the spreading of tuberculosis in order to maintain the balance and keeping the disease under control. This will be part of our current study.

CHAPTER 3

METHODOLOGY

3.1. Introduction

This thesis involved three mathematical model of tuberculosis. For the first model, we present the analytical part of the model, focusing on the stability of its equilibrium. The second and third model is used to investigate the dynamic of Tuberculosis transmission under different condition. We determined the effect of immigration and treatment and hence deducing an action plan for prevention, control and monitoring of TB.

3.2. Research Design

The research will mainly base its findings through both quantitative and qualitative research methods as this will allow a flexible and iterative approach. Qualitative research method was used as we try to find and build theories that will explain the relationship of one variable with another. Using this method, we are able to interpret our results and relate it with the real world.

3.3. Model Stability

Our first model is a basic SEIR model [Equation 1(a-e), Figure 4.1] where we attempted to study and prove its endemic equilibrium stability. The system was reduced to a sub-system of 3 equations by using the homogeneity characteristic of the system. The equilibrium points are determined and its local stability is proved using the method of first approximation. We showed the Jacobian of the matrix system is stable under certain parameter restrictions, using a Lemma proposed by Li and Muldowney [19]. We have attempted to prove the **global stability** of our model using the geometric

approach as proposed by Li and Muldowney [19]. However, we have not succeeded in applying this particular technique to obtain the global stability.

3.4. Data Collection

When we first started, we intend to use real data for our study. Later we discovered that it is an uphill task to get the permission from the Ministry of Health Malaysia, Department of Immigration Malaysia and also the hospitals that can provide us with the needed data. Thus, the data used in our research was taken from Bhunu et al. [5]. From the literature reviews, it is safe to say that the values are acceptable and commonly used for TB cases in general.

3.5. Data Analysis

3.5.1. Numerical Study

The numerical study is done with the aid of MATLAB. MATLAB is a high-level language and interactive environment for algorithm development, data visualization, data analysis and numeric computation that enables one to perform computationally intensive tasks faster. We solved our model using the built-in-function *ode45* which is an algorithm program based on Runge-Kutta-Fehlberg.

The Runge–Kutta–Fehlberg method (or Fehlberg method) is an algorithm developed by the German mathematician Erwin Fehlberg and is based on the class of Runge–Kutta methods. It is often referred to as an RKF45 method as it uses an $O(h^4)$ method together with an $O(h^5)$ method that uses all of the points of the $O(h^4)$ method. The method's procedure helps to determine if the proper step size h is being used. At each step, two different approximations for the solution are made and compared. If the two answers are in close agreement, the approximation is accepted. If the two answers do not agree

to a specified accuracy, the step size is reduced. If the answers agree to more significant digits than required, the step size is increased.

3.5.2. Variation of Variables and Parameter Values

In order to investigate the dynamics of TB transmission under different condition, we assigned different values of variables and parameters accordingly. The values are varied systematically to find the critical point of the disease spread under each condition if any. Qualitative method was then used to explain and interpret the results and to relate it with the real world.

CHAPTER 4

THE MODELS

4.1. Introduction

In this chapter, we presented 3 models for analysis: one basic model and two extended models. The first model is a basic SEIR model with immigration factor. For the basic model, we are only interested in the analytical part of the model; hence we present the analysis on the stability of the endemic equilibrium.

The second model is an extended model based on TB model with immigration as proposed by McCluskey and van den Driessche [23] and we denote it as MnD model. We extend their SEI model into a SEIR model and analyze its numerical simulation. We then compare the results between the SEI and SEIR model. The purpose of this model is to analyze the effect of immigration and also the effectiveness of the treatment.

The third model is a model where we incorporate the idea of immigration as proposed by McCluskey and van den Driessche [23] into the tuberculosis transmission model with chemoprophylaxis of Bhunu et al. [5]. We use numerical simulations of the model to illustrate the behaviour of the system. This model is used to analyze the best approach in containing the spread of the disease under different factors.

4.2. Basic SEIR Model with Immigration

4.2.1. Model formulation

The SEIR model for the spread of TB disease with immigration is described by the following system of differential equations

$$\frac{dS}{dt} = (1-a-b)\Lambda N - (\lambda + \mu)S \tag{1a}$$

$$\frac{dE}{dt} = a\Lambda N + \lambda S - (k + \mu)E \tag{1b}$$

$$\frac{dI}{dt} = b\Lambda N + kE - (\mu + d + p)I \tag{1c}$$

$$\frac{dR}{dt} = pI - \mu R \tag{1d}$$

with initial condition

$$S(0) = S_0 \geq 0, E(0) = E_0 \geq 0, I(0) = I_0 \geq 0 \text{ and } R(0) = R_0 \geq 0. \tag{1e}$$

Here, the model is divided into four classes: susceptible individuals S, individuals exposed to TB (latently infected) E, infected (infectious) individuals I, and recovered individuals R. New individuals will enter the population at rate ΛN, with fraction $(1-a-b), a, b$ entering the susceptible, exposed and infectious classes respectively. The model flow diagram is shown in Figure 4.1.

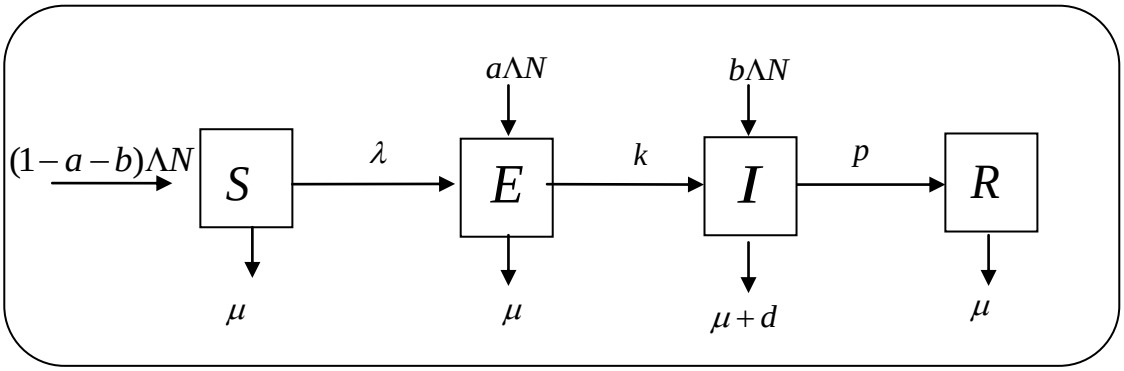

Figure 4.1 Basic SEIR model structure

The constant recruitment of both latently infected and infectious individual into the population will cause the disease to never dies out i.e. there will be no disease-free

equilibrium, and therefore no usual threshold condition. We assume that the local density of the total population is a constant though the total population size

$$N(t) = S(t) + E(t) + I(t) + R(t) \tag{2}$$

may vary with time.

The incidence rate λ is described by the non-linear term

$$\lambda = \beta c I / N, \tag{3}$$

where β is the transmission probability and c is the per capita contact rate. The natural death rate in each class is assumed to be a constant μ and an individual may recover naturally at rate p.We also assume homogeneous mixing and the infectious individuals suffer disease-caused mortality with a constant rate, d. Note that those who recovered, however, will acquire a permanent immunity.

The total population size $N(t)$ can also be determined from the following differential equation

$$\frac{dN}{dt} = (\Lambda - \mu)N - dI, \tag{4}$$

which is derived by adding up all the equations in (1).

Let $s = S/N, e = E/N, i = I/N$ and $r = R/N$ denote the fractions of the classes S, E, I, R, in the population respectively. It is easy to verify that *s, e, i* and *r* satisfy the system of differential equations

$$s' = (1-a-b)\Lambda - \Lambda s + (d - \beta c)is \tag{5a}$$
$$e' = a\Lambda + \beta cis - (k + \Lambda)e + die \tag{5b}$$
$$i' = b\Lambda + ke - (\Lambda + d + p)i + di^2 \tag{5c}$$
$$r' = pi - \Lambda r + dir \tag{5d}$$

subject to restriction $s+e+i+r=1$. Note that the total population size $N(t)$ does not appear in (5). This is a direct result of the homogeneity of the system (1). Observe also that the variable *r* does not appear in the first three equations of (5). This allows us to attack (5) by studying the subsystem

$$s' = (1-a-b)\Lambda - \Lambda s + (d-\beta c)is \quad (6a)$$
$$e' = a\Lambda + \beta cis - (k+\Lambda)e + die \quad (6b)$$
$$i' = b\Lambda + ke - (\Lambda + d + p)i + di^2 \quad (6c)$$

and determining *r* from $r = 1-(s+e+i)$ or

$$r' = pi - \Lambda r + dir \quad (7)$$

We study (6) in the closed set

$$\Gamma = \{(s,e,i) \in \Re_+^3 \mid 0 \le s+e+i \le 1\} \quad (8)$$

where $\Re_+^3$ denotes the non-negative cone of $\Re^3$ including its lower dimension faces. It can be verified that Γ is positively invariant with respect to (6).

We then established that (6) is a competitive system when $\beta c > d$, which is an important property in the study of the global dynamics when the disease persists. We follow the definition and condition of a competitive system given by Li et al [20].

Let $x \mapsto f(x) \in \Re^n$ be a smooth vector field defined for a in an open set $D \subset \Re^n$. The differential equation

$$x' = f(x), \quad x \in D \quad (9)$$

is said to be competitive in *D* if, for some diagonal matrix $H = diag(\varepsilon_1,....,\varepsilon_n)$ where each ε_i is either 1 or -1, $H(\partial f / \partial x)H$ has non-positive off diagonal elements for all $x \in D$. By choosing the matrix H as $H = diag(-1,1,-1)$, one can verify that, when $\beta c > d$, the system (6) is competitive in the convex region Γ with respect to the partial ordering defined by the orthant $\{(s,e,i) \in \Re_+^3 \mid s \le 0, e \ge 0, i \le 0\}$.

4.2.2. The endemic equilibrium

The coordinates of an equilibrium point $P^* = (s^*, e^*, i^*) \in \Gamma$ satisfy

$$(1-a-b)\Lambda - \Lambda s + (d-\beta c)is = 0 \tag{10a}$$
$$a\Lambda + \beta cis - (k+\Lambda)e + die = 0 \tag{10b}$$
$$b\Lambda + ke - (\Lambda + d + p)i + di^2 = 0 \tag{10c}$$

and also $s^* > 0, e^* > 0$ and $i^* > 0$.

Adding the above equations leads to

$$(\Lambda - di^*)(1 - s^* - e^* - i^*) = (p+\Lambda)i^*$$

which gives the following range of i^*.

$$0 < i^* < \min\{1, \frac{\Lambda}{d}\}. \tag{11}$$

s^* and e^* can be uniquely determined from i^* by

$$s^* = \frac{(1-a-b)\Lambda}{\Lambda - (d-\beta c)i^*} \quad \text{and} \quad e^* = \frac{a\Lambda(a\Delta - di^*) + (1-b)\Lambda\beta ci^*}{(\Lambda - di^* + \beta ci^*)(\Lambda + k - di^*)} \tag{12}$$

respectively.

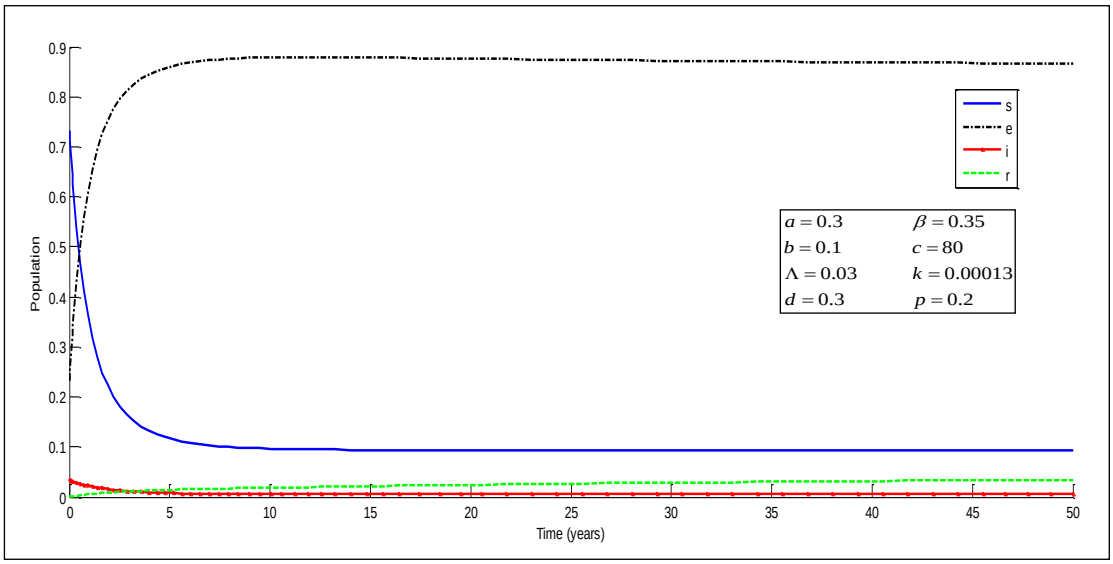

Figure 4.2 A MATLAB plot showing the solutions of system (5) converge to finite limit.

Figure (4.2) shows the numerical solution of system (5) that presents the existence of the globally asymptotically stable endemic equilibrium.

4.2.3. Local asymptotic stability of the endemic equilibrium

The method of first approximation is used to show the asymptotic stability of the equilibrium P^*, by proving that the matrix $J(P^*)$ is stable i.e. all its eigenvalues have negative real part.

The Jacobian matrix of (6) at a point $P = (s, e, i)$ is

$$J(P) = \begin{bmatrix} (d - \beta c)i - \Lambda & 0 & (d - \beta c)s \\ \beta ci & di - (\Lambda + k) & \beta cs + de \\ 0 & k & 2di - (\Lambda + d + p) \end{bmatrix} \tag{13}$$

The following lemma ([Lemma 5.1, Li et al [20]] is used to demonstrate the local stability of P^*.

Lemma. Let A be an $m \times m$ matrix with real entries. For A to be stable, it is necessary and sufficient that

1. The second compound matrix $A^{[2]}$ is stable
2. $(-1)^m \det(A) > 0$

Proof. We have to show that $J(P)$ satisfies both condition given in the Lemma. The second additive compound $J^{[2]}(P)$ of the Jacobian matrix $J(P)$ is given by

$$J^{[2]}(P) = \begin{bmatrix} (2d - \beta c)i - (2\Lambda + k) & \beta cs + de & -(d - \beta c)i \\ k & (3d - \beta c)i - (2\Lambda + d + p) & 0 \\ 0 & \beta ci & 3di - (2\Lambda + d + p + k) \end{bmatrix} \tag{14}$$

For $P^* = (s^*, e^*, i^*)$ and the diagonal matrix $E = diag(i^*, e^*, s^*)$, the matrix $J^{[2]}(P^*)$ is similar to $EJ^{[2]}(P^*)E^{-1}$

$$EJ^{[2]}(P^*)E^{-1}$$
$$= \begin{bmatrix} (2d-\beta c)i^* - (2\Lambda + k) & \frac{\beta c i^* s*}{e^*} + di^* & -(d-\beta c)i^* \\ \frac{e^* k}{i^*} & (3d-\beta c)i^* - (2\Lambda + d + p) & 0 \\ 0 & \frac{\beta c i^* s*}{e^*} & 3di^* - (2\Lambda + d + p + k) \end{bmatrix}$$

The matrix $J^{[2]}(P^*)$ is stable if and only if the $EJ^{[2]}(P^*)E^{-1}$ is stable, for similarity preserves the eigenvalues. Since the diagonal elements of the matrix $EJ^{[2]}(P^*)E^{-1}$ are negative, an easy argument using Gersgorin discs shows that it is stable if it is diagonally dominant in rows.

Set $\gamma = \max\{g_1, g_2, g_3\}$ where

$$\begin{aligned} g_1 &= 2di^* - (2\Lambda + k) + \frac{\beta c i^* s^*}{e^*} \\ g_2 &= \frac{e^* k}{i^*} + (3d - \beta c)i^* - (d + p + 2\Lambda) \\ g_3 &= 3di^* + \frac{\beta c i^* s^*}{e^*} - (d + p + k + 2\Lambda) \end{aligned} \tag{15}$$

Equation (10) can be written as

$$\begin{aligned} \frac{(1-a-b)\Lambda}{s^*} &= \Lambda + (\beta c - d)i^* \\ \frac{\beta c i^* s^*}{e^*} &= \Lambda + k - di^* - \frac{a\Lambda}{e^*} \\ \frac{e^* k}{i^*} &= d + p + \Lambda - di^* - \frac{b\Lambda}{i^*} \end{aligned} \tag{16}$$

Substituting (16) into (15) yields

$$\gamma = \max\{ di^* - \Lambda - \frac{a\Lambda}{e^*},\ 2di^* - \beta ci^* - \Lambda - \frac{b\Lambda}{i^*},\ 2di^* - (d + p + \Lambda) - \frac{a\Lambda}{e^*}\}$$

Then, using (11) and the relation $\beta c > d$, we have $\gamma < 0$ which implies the diagonal dominance as claimed and thus verifies the first condition of the Lemma.

As for the determinant, we have

$$\det(J(P^*)) = \begin{vmatrix} (d-\beta c)i^* - \Lambda & 0 & (d-\beta c)s^* \\ \beta ci^* & di^* - (\Lambda + k) & \beta cs^* + de^* \\ 0 & k & 2di^* - (\Lambda + d + p) \end{vmatrix}$$

$$\begin{aligned}
&= \left[(d-\beta c)i^* - \Lambda\right]\left[(di^* - \Lambda - k)(2di^* - \Lambda - d - p) - k\left(\beta cs^* + de^*\right)\right] + (d-\beta c)s^*\beta ci^* k \\
&= \left[(d-\beta c)i^* - \Lambda\right]\left\{(di^* - \Lambda)\left[(di^* - \Lambda) - (d+p) + di^*\right] - \left[(di^* - \Lambda) - (d+p) + di^*\right]k\right\} \\
&\quad - \left[(d-\beta c)i^* - \Lambda\right]k\left(\beta cs^* + de^*\right) + (d-\beta c)s^*\beta ci^* k \\
&= \left[(d-\beta c)i^* - \Lambda\right]\left\{(di^* - \Lambda)^2 - (di^* - \Lambda)\left[(1-i^*)d + p + k\right] + \left[(1-e^* - i^*)d + p\right]k\right\} \\
&\quad + \Lambda\beta cs^* k \\
&\le 0
\end{aligned}$$

The first term is negative and the numerical result shows that the second term $\Lambda\beta cs^* k$ is overwhelmed by the first term. This verifies the second condition of the Lemma and completes the proof.

4.2.4. Conclusion

The model is a simple SEIR model with immigration with the assumption of permanent immunity. Because of the constant recruitment of infected individuals into the population, the disease never dies out that is, there is no disease free equilibrium. Numerical result [Figure 4.2] shows the existence of a globally asymptotically stable endemic equilibrium under certain parameter restrictions.

4.3. Extending MnD SEI model into SEIR Model

4.3.1. Model formulation

An infected individual may recover naturally at rate p and move on to the recovered class R (though they may carry some live bacilli). The treatment rates for the latently infected and the infectious are assumed to be r_1 and r_2 respectively. The tuberculosis model that was proposed by McCluskey and van den Driessche [23] assumed that the infected individuals will become totally susceptible again after treatment. The model flow diagram for MnD model is as follow:

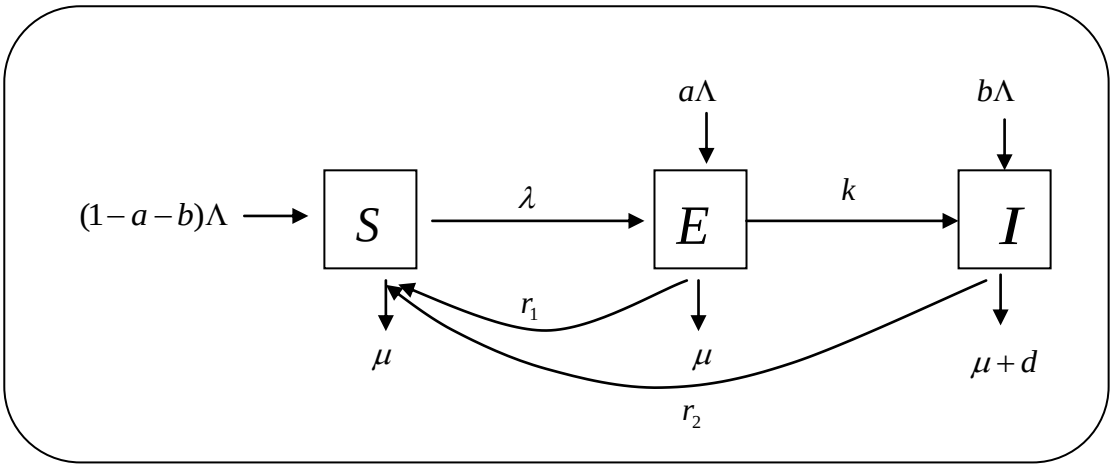

Figure 4.3 (a) The TB model with immigration proposed by McCluskey and van den Driessche

In actuality, recovered individuals are not totally immune to Mtb infection but they do confer some immunity after the primary infection and since there is no absolute cure for TB, they may be re-infected at rate $\delta_2\lambda$ and move into the exposed class again with $\delta_2 \in (0,1)$. For our extended SEIR model, the flow diagram is depicted in Figure 4.3(b) below,

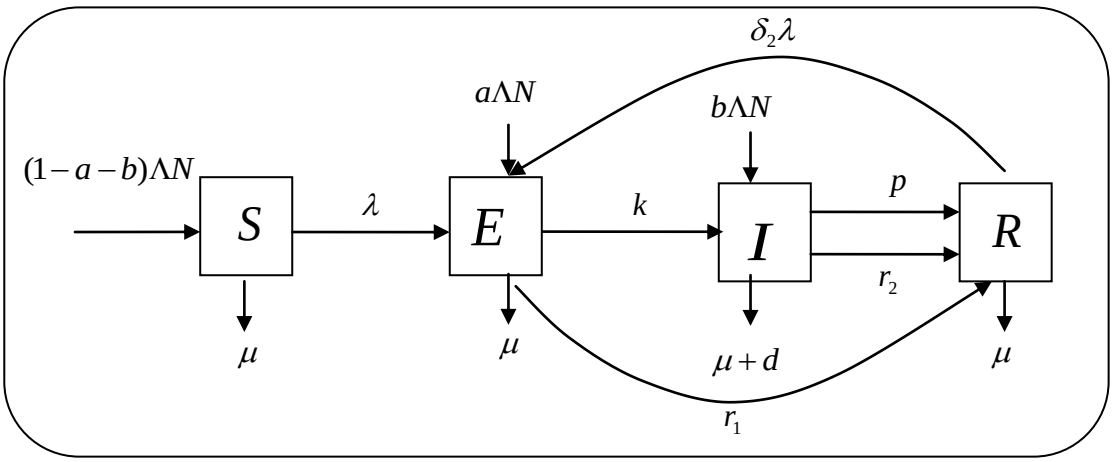

Figure 4.3 (b) Our proposed extended SEIR model structure

The extended model can be described by the following system of differential equations

$$\frac{dS}{dt} = (1-a-b)\Lambda N - (\lambda+\mu)S \tag{17a}$$

$$\frac{dE}{dt} = a\Lambda N + \lambda S - (k+\mu)E - r_1 E + \delta_2 \lambda R \tag{17b}$$

$$\frac{dI}{dt} = b\Lambda N + kE - (\mu + d + p)I - r_2 I \tag{17c}$$

$$\frac{dR}{dt} = r_1 E + r_2 I + pI - (\delta_2\lambda + \mu)R \tag{17d}$$

with initial condition

$$S(0) = S_0 \geq 0, E(0) = E_0 \geq 0, I(0) = I_0 \geq 0 \text{ and } R(0) = R_0 \geq 0. \tag{17e}$$

Based on the biological considerations, model system (17) will be studied in the region,

$$H = \left\{ (S,E,I,R) \in \Re_+^4 : S+E+I+R \leq \frac{\Lambda N}{\mu} \right\},$$

which is positively invariant with respect to system (17).

The phase plane portraits of system (17) are illustrated in Figure 4.4 below:

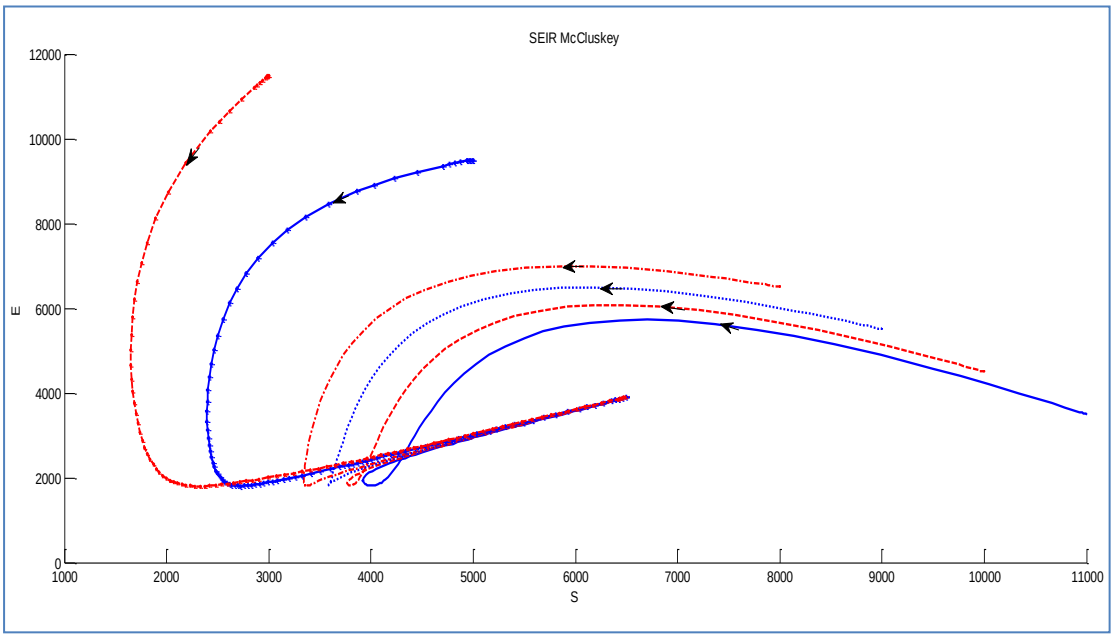

Figure 4.4(a) Susceptibles vs Exposed

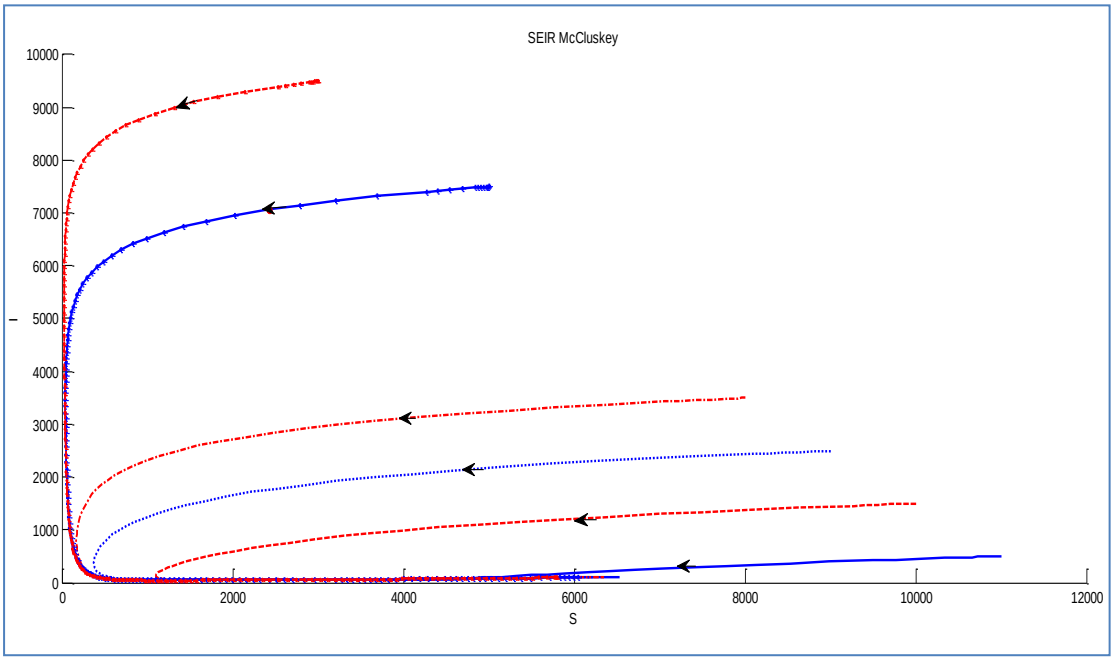

Figure 4.4(b) Susceptibles vs Infectious

Figure 4.4(a,b) Phase plane portraits of system (17) using parameters in Table 4.1

4.3.2. Numerical study

In this section, the numerical simulations for the model systems under different conditions are presented. Note that McCluskey and van den Driessche [23] paper are focused on the global stability of the model. They did not present any numerical solutions of their model. We compare our model and theirs using the parameter values given in Table 4.1 and the initial conditions are taken to be $S(0) = 11{,}000,\ E(0) = 3{,}500,\ I(0) = 500$ and $R(0) = 0.$

Table 4.1 Model parameters and their interpretations

Definition	**Symbol**	**Estimate (Range)**	**Source**
Recruitment rate	Λ	0.03 yr^{-1}	a*
Natural mortality rate	μ	0.01 yr^{-1}	a*
Contact rate	c	80 yr^{-1}	b*
TB induced death rate	d	0.3 yr^{-1}	a*
Probability of being infected	β	0.35 (0.1-0.6) yr^{-1}	a*
Natural rate of progression to active TB	k	0.00013 (0.0001-0.0003) yr^{-1}	a*
Natural recovery rate	p	0.2 (0.15 – 0.25) yr^{-1}	a*
Relapsing rate	q	0.00001 yr^{-1}	b*
Treatment rate for the latently infected	r_1	0.7 yr^{-1}	a*
Treatment rate for the infectives	r_2	0.55 yr^{-1}	b*
Modification parameter	δ_1	0.7 yr^{-1}	b*
Modification parameter	δ_2	0.9 yr^{-1}	b*
Fraction of latently infected immigrants	a	0.3 yr^{-1}	Estimate
Fraction of infectious immigrants	b	0.1 yr^{-1}	Estimate
Probability that the infected will enter the latent stage of the disease	f	0.99 yr^{-1}	b*

The parameters values are taken from Bhunu et al. [5] who also relied on the values taken from Dye and William [8] and Dye et al. [9], aside from their own estimations. In Table 4.1, *a** denotes parameter values and ranges adapted from Dye and William [8], Dye et al. [9] and *b** denotes the parameter values from Bhunu et al. [5].

Figure 4.5 (a, b) shows the trend on the susceptible (S), latently infected (E), infectious (I) and recovered (R) over 50 years time period for both model systems. McCluskey and P. Van den Driessche [23] has shown that their TB model which incorporates immigration of infected individuals at constant rate will results with the disease never dies out i.e. no disease-free equilibrium. In Figure 4.5(a) below, it can be seen that the number of latently infected individuals are increasing gradually over the years. Since the number of infectious individuals remains at relatively small value, the rate of infection is very small and therefore majority of the population remains susceptible. It is also thanks to the high treatment rate that infected individuals can return to being susceptible after being treated.

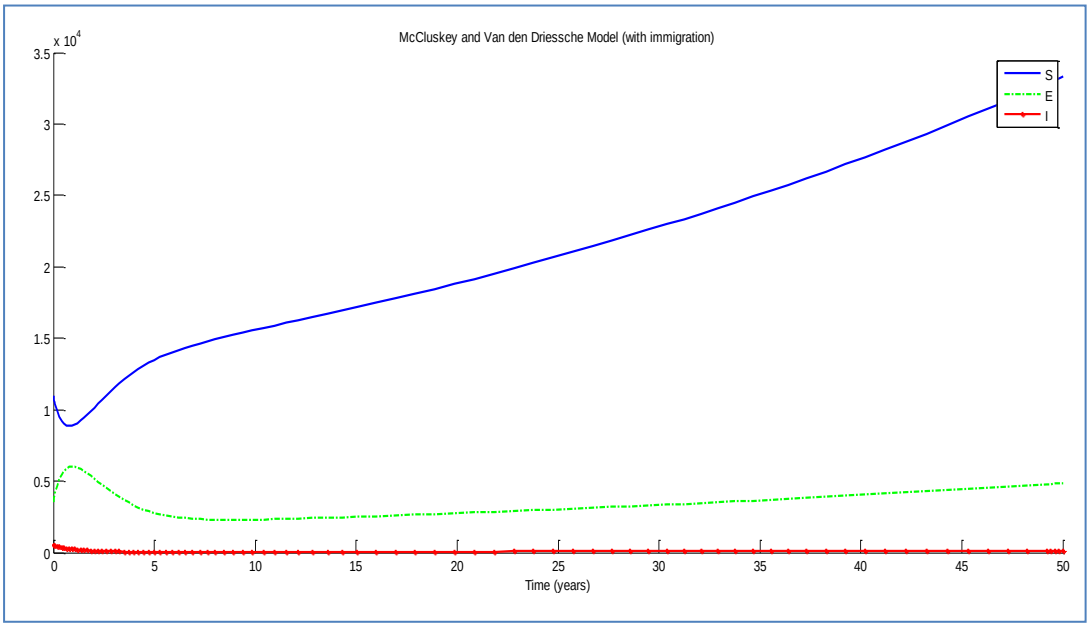

Figure 4.5 (a) A graphical representation showing the trend of all classes for the MnD model

In Figure 4.5(b), the simulation of the proposed SEIR model behaviour is slightly different from MnDs'. The main difference is in the susceptible class behaviour. The number of susceptible decreased steeply before marginally increasing over the years. The population was made up mostly by recovered individuals. Even though they may be re-infected but the rate are relatively very small as it depends on the number of infectious individuals which remains at relatively small number throughout the years.

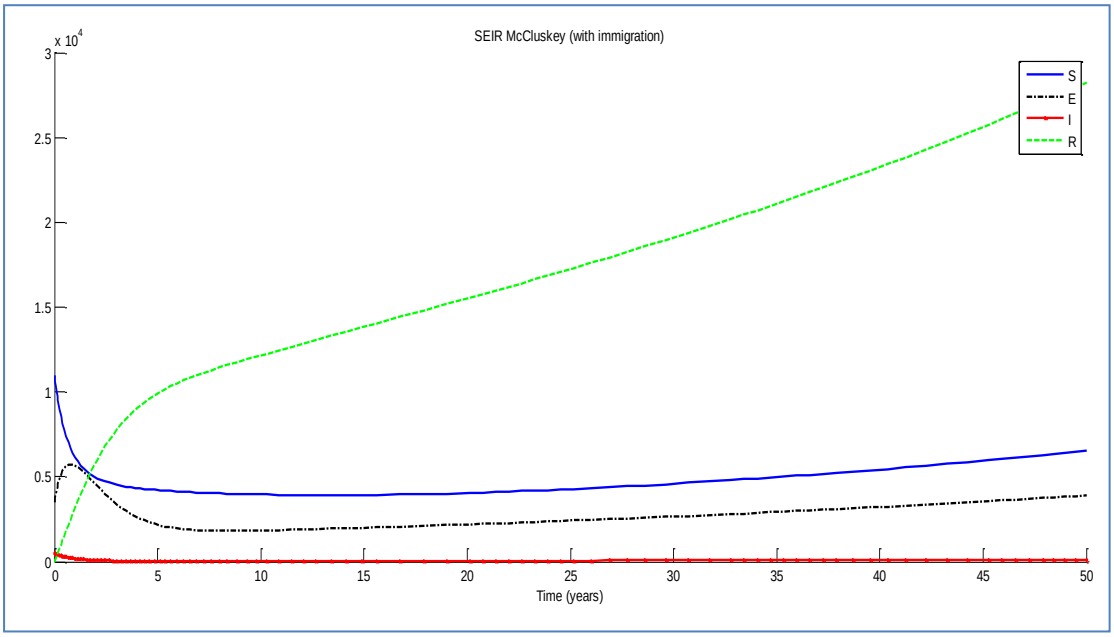

Figure 4.5 (b) A graphical representation showing the trend of all classes for our extended SEIR model

Figure 4.6 (a, b) shows what would happen if we remove the immigration factor. For both model, the disease will dies out in less than 10 years. From figure 4.6(a), the number of susceptible reaches its minimum point during the peak of the disease before steadily increasing, while the disease starts to die out at the same time.

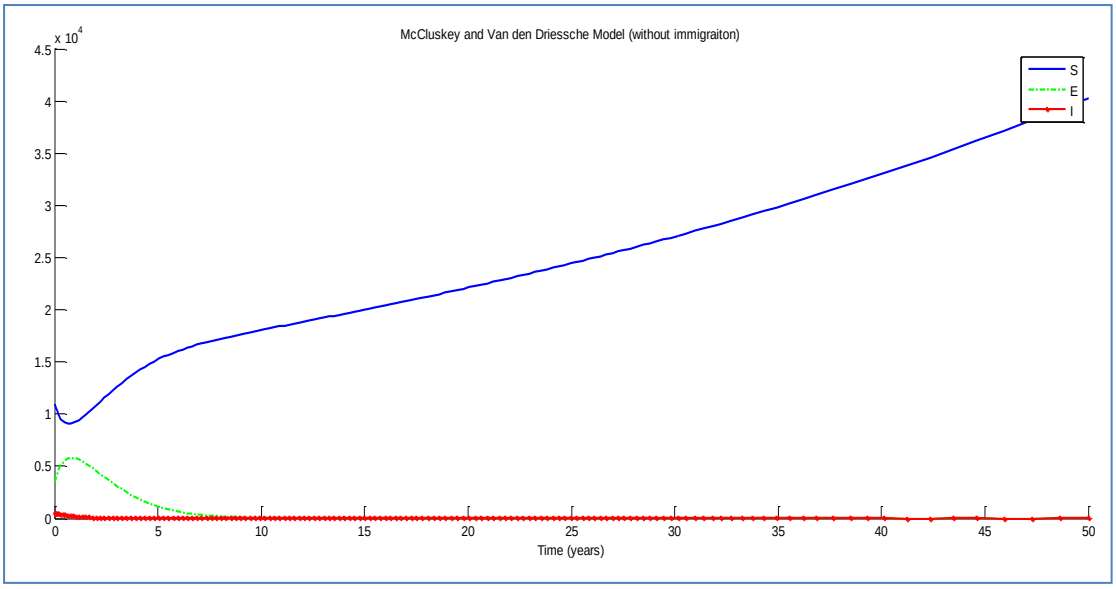

Figure 4.6 (a) MnD model: A graphical simulation when there is no immigration of infected people

However, figure 4.6(b) shows that the first 10 years, the main activities are dominated by the recovered individuals. This can be attributed to the high successful rate of the treatment. After that, the number gradually decreased steadily as the number of infected individuals also decreased.

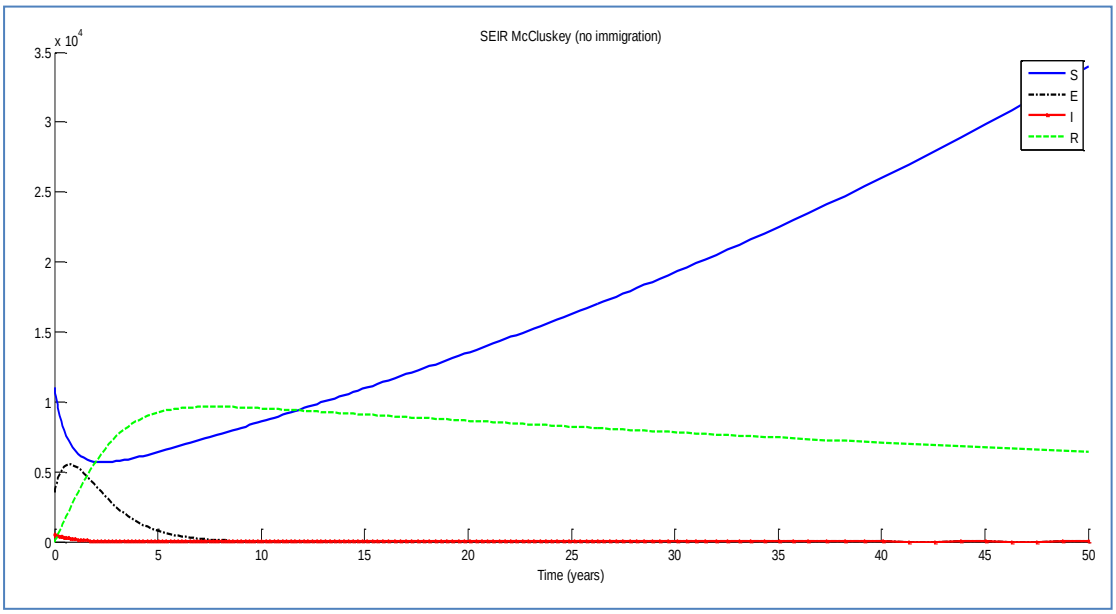

Figure 4.6 (b) SEIR extended model: A graphical simulation when there is no immigration of infected people

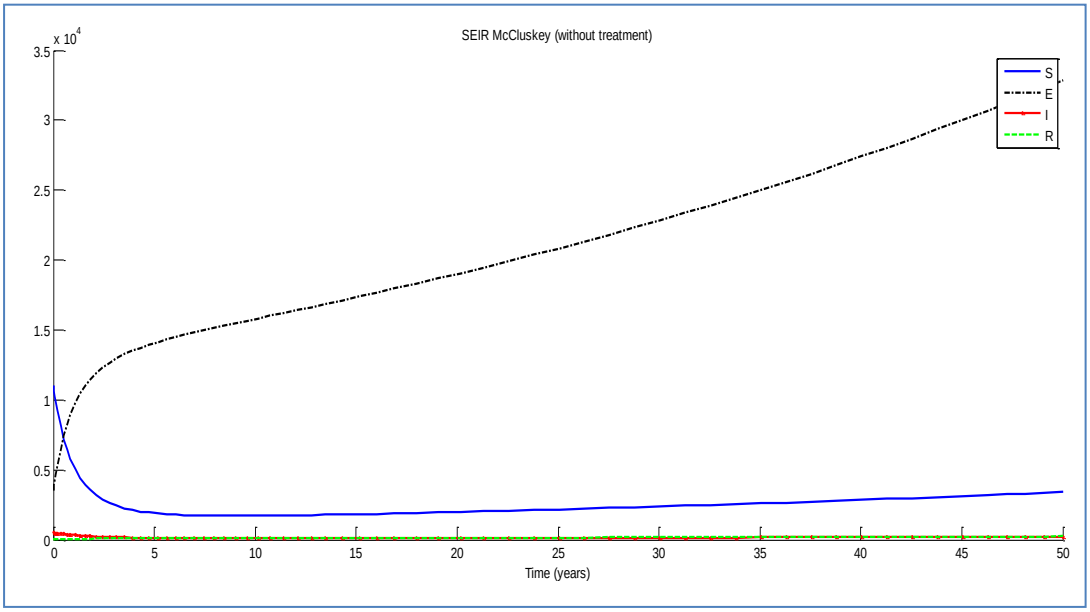

Figure 4.7 Effect of treatment

Figure 4.7 shows how important it is for the infected individuals to receive treatment. If there is no treatment available, almost all the population will be latently infected by the disease. Since the progression rate from latently infected to infectious are very low, the number of infectious are kept at minimum. If given under some condition we cannot treat all the infected people, a better option is to give treatment to those latently infected individuals instead of the infectious ones.

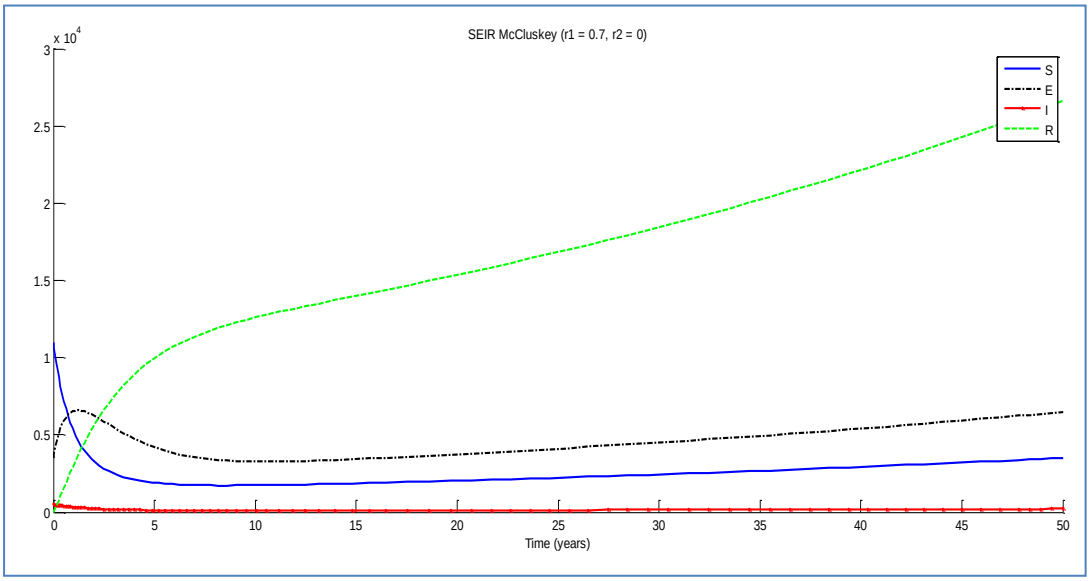

Figure 4.8 (a) Treatment to the latently infected only

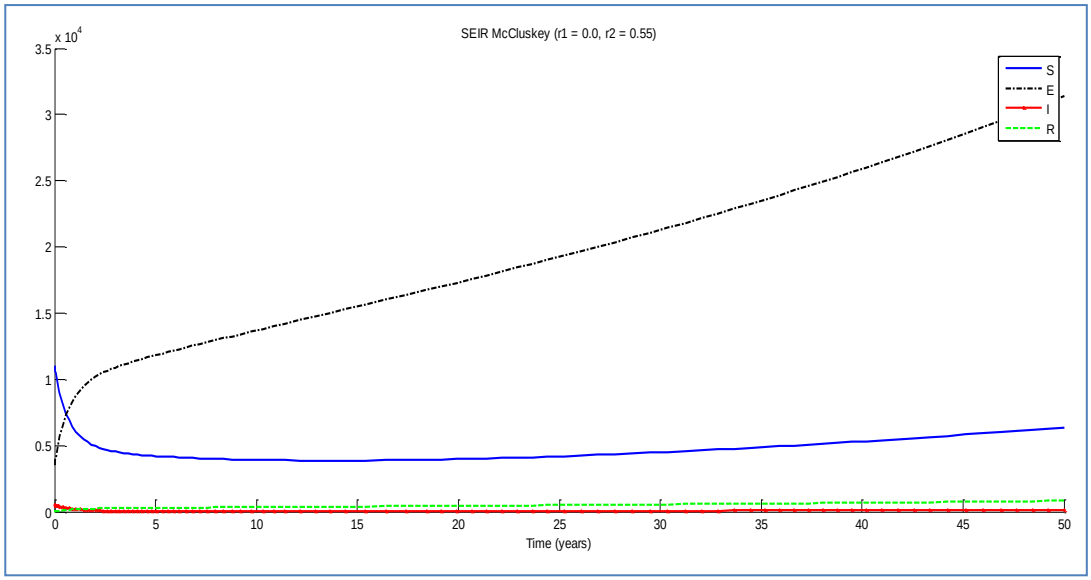

Figure 4.8 (b) Treatment to the infectious only

As shown in Figure 4.8(a) above, treatment to the latently infected are more effective in controlling the disease spreading compared to treatment given only to those infectious (Figure 4.8(b)).

4.3.3. Conclusion

The model is a SEIR model based on the SEI tuberculosis model with immigration proposed by McCluskey and P. van den Driessche [23]. We showed that both their model and ours gave the same conclusion from the result. Here, the immigration of infected individuals plays a very significant role that even with treatment the TB remains endemic. However, even though there is a constant recruitment of infected individuals into the population, the disease spreading can be kept at bay with successful treatment. One of the effective ways to do so is by giving treatment to the latently infected. On the other hand, when there is no immigration of infected, the disease will dies out.

4.4. Extending Bhunu Model

4.4.1. Model formulation

TB is known as a slow disease because of its long and variable latency period. Latently infected individual means that the infecting bacteria are alive in the individuals' body but it is inactive. The individuals will show no symptoms and cannot spread the disease. There are two types of latent period: the short-term latent period where an infected individual takes at least 21 days or 3 to 4 weeks up to 2 years to develop active TB (infectious) and the long-term latent period when it takes longer than 2 years to become infectious.

Most initially infected individuals will enter a long-term latent (exposed) phase and moved from the susceptible class to the exposed class at rate $f\lambda$ in which f is the probability that the infected enters latent stage. They will progress to active TB at rates k for endogenous reactivation and $\delta_1\lambda$ for exogenous re-infection respectively with $\delta_1 \in (0,1)$. Endogenous reactivation refers to secondary tuberculosis that recurs as a result of the activation of a dormant endogenous infection. Causes of the reactivation may include loss of immunity, hormonal changes, or poor nutrition. Exogenous re-infection is caused by organisms that does not normally present in the body but which have gained entrance from the environment. Individuals who have early latent or short-term latent period are treated as infectious $(1-f)$; that is the short latent period is ignored.

Individuals who have recovered from the disease are not totally immune to Mtb infection but they do confer some immunity from their primary infection. Some of those recovered individuals may also have a relapse of the disease back into the infective state at rate q.

These assumptions result in the following system of differential equations:

$$\frac{dS}{dt} = (1-a-b)\Lambda N - (\lambda + \mu)S \tag{18a}$$

$$\frac{dE}{dt} = a\Lambda N + f\lambda S - \delta_1 \lambda E - (k+\mu)E + \delta_2 \lambda R - r_1 E \tag{18b}$$

$$\frac{dI}{dt} = b\Lambda N + (1-f)\lambda S + \delta_1 \lambda E + kE - (\mu + d + p)I + qR - r_2 I \tag{18c}$$

$$\frac{dR}{dt} = pI - \mu R - (q + \delta_2 \lambda)R + r_1 E + r_2 I \tag{18d}$$

with initial condition

$$S(0) = S_0 \geq 0, E(0) = E_0 \geq 0, I(0) = I_0 \geq 0 \text{ and } R(0) = R_0 \geq 0 \tag{18e}$$

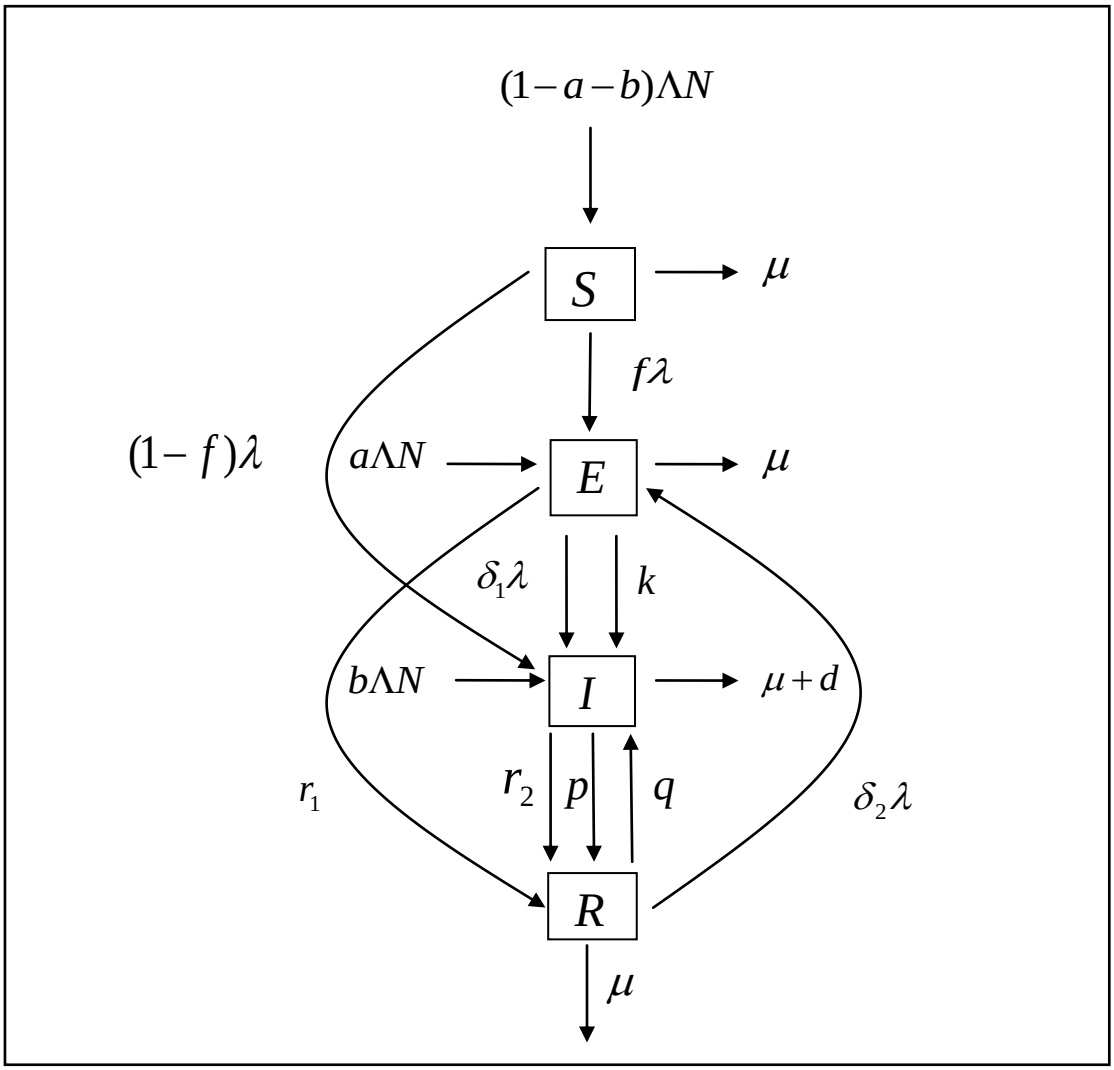

Figure 4.9: Structure of model

The flow diagram of the disease is shown in Figure 4.9 above.

Based on the biological considerations, model system (18) will be studied in the region

$$H = \left\{ (S, E, I, R) \in \Re_+^4 : S + E + I + R \leq \frac{\Lambda N}{\mu} \right\},$$

which is positively invariant with respect to system (18).

The phase plane portraits of system (18) are illustrated in Figure 4.10 below.

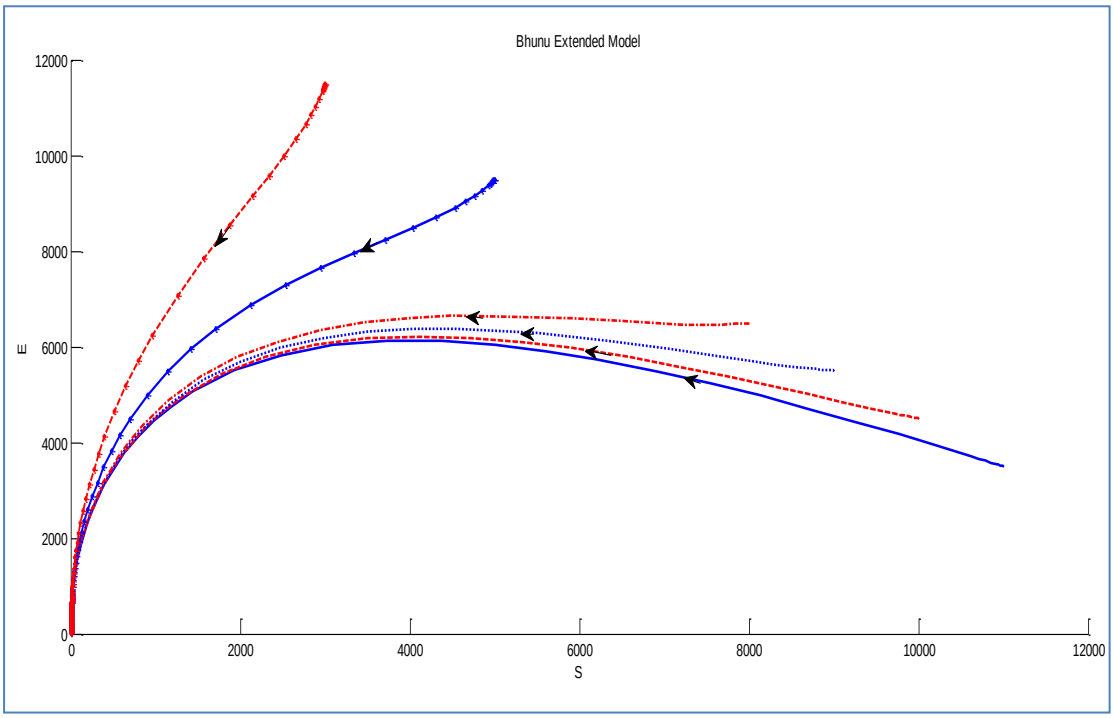

Figure 4.10(a) Susceptible vs Exposed (cont..)

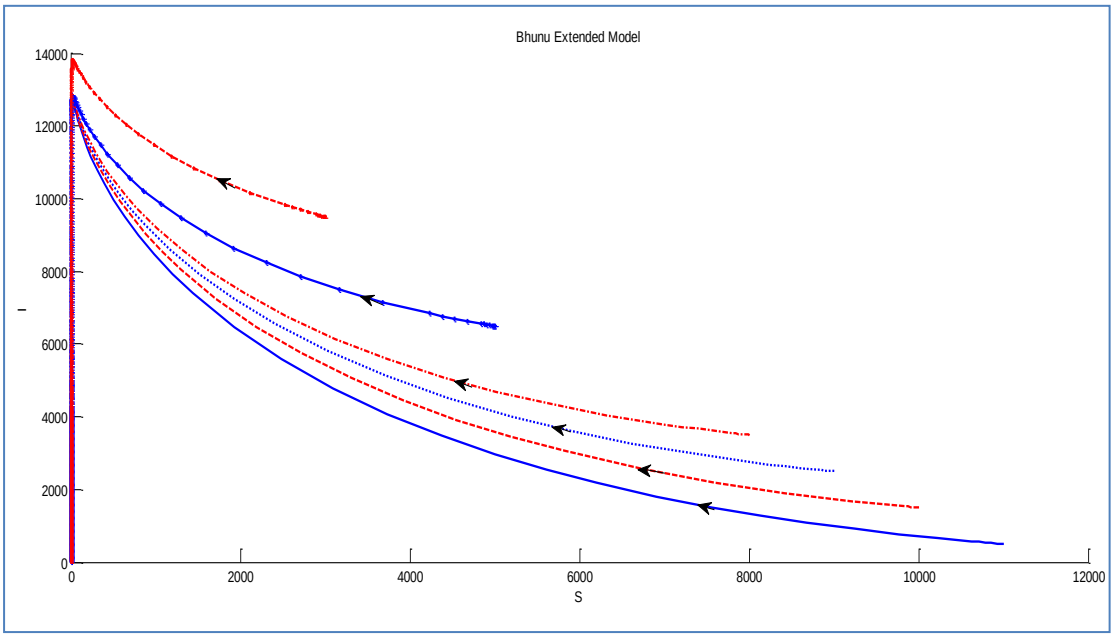

Figure 4.10(b) Susceptible vs Infectious

Figure 4.10(a,b) Phase plane portrait of system (18) using the parameter value in Table 4.1.

4.4.2. Numerical study

In this section, we did numerical simulations for the model system (18) under different conditions. The parameter values that we use are given in Table 4.1 and the initial conditions are chosen to be $S(0) = 11{,}000,\ E(0) = 3{,}500,\ I(0) = 500$ and $R(0) = 0.$

Figure 4.11 is a simulation showing the trend on the susceptible (S), latently infected (E), infectious individuals (I) and the recovered (R) over 20 years time period. The most distinct characteristic is that the number of infected individuals shot up to maximum almost immediately at the beginning before gradually decreasing and eventually dies out. This is because of the high rate of exogenous re-infection for the exposed class. Even though treatment is given to both latently and actively infected individuals, the number of recovered individuals is very small. The results of the treatment can only be seen in the first year of implementation represented by the slight

bump on the graph. This can be explained by the high rate of re-infection and relapse cases for the recovered individuals. Since the disease mortality rate is considerably high, the whole total population eventually will die out in about 20 years time.

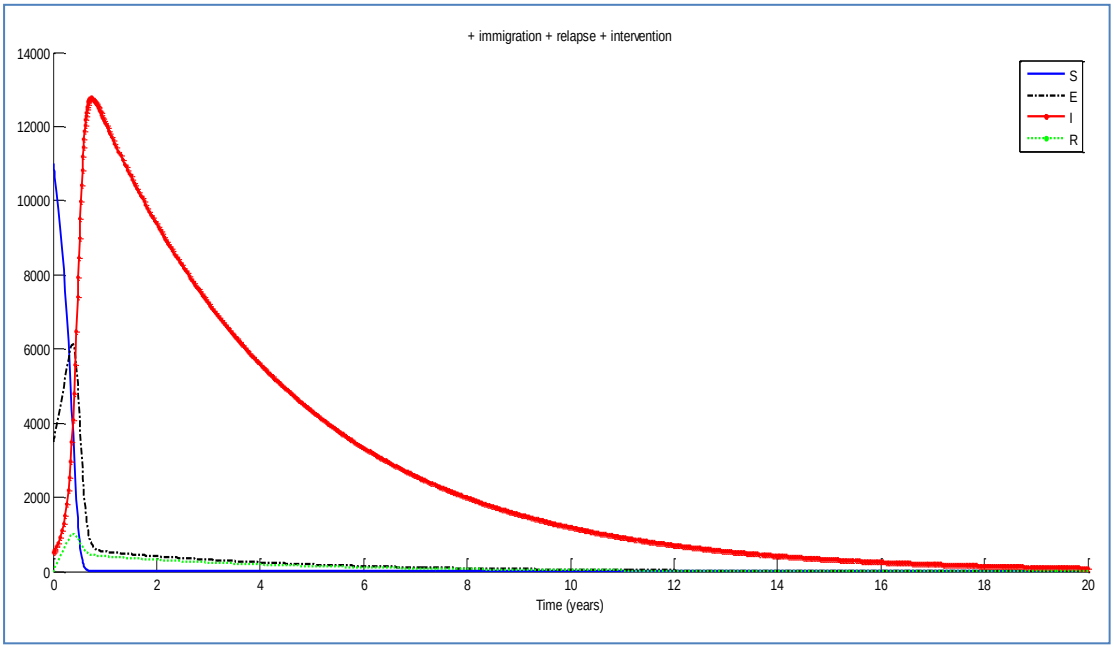

Figure 4.11 A graphical representations showing the trend of all classes for model system (18)

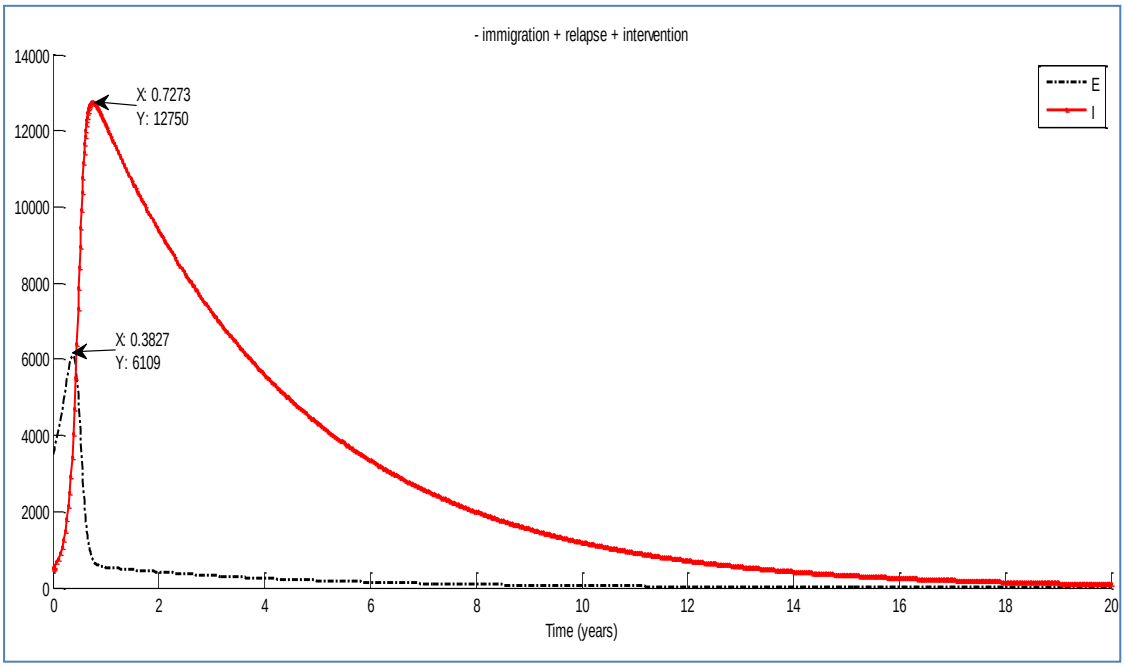

Figure 4.12 (a) Model system with a=b=0: The latently infected and infectious class when there is no immigration of infected individuals

Figure 4.12 (a, b) shows how immigration effects the TB transmission as a whole. Figure 4.12(a) represents the latently and infectious class when there is no immigration of infected individuals into the population. The peak for E class is 6,109 while the peak for I class is 12,750.

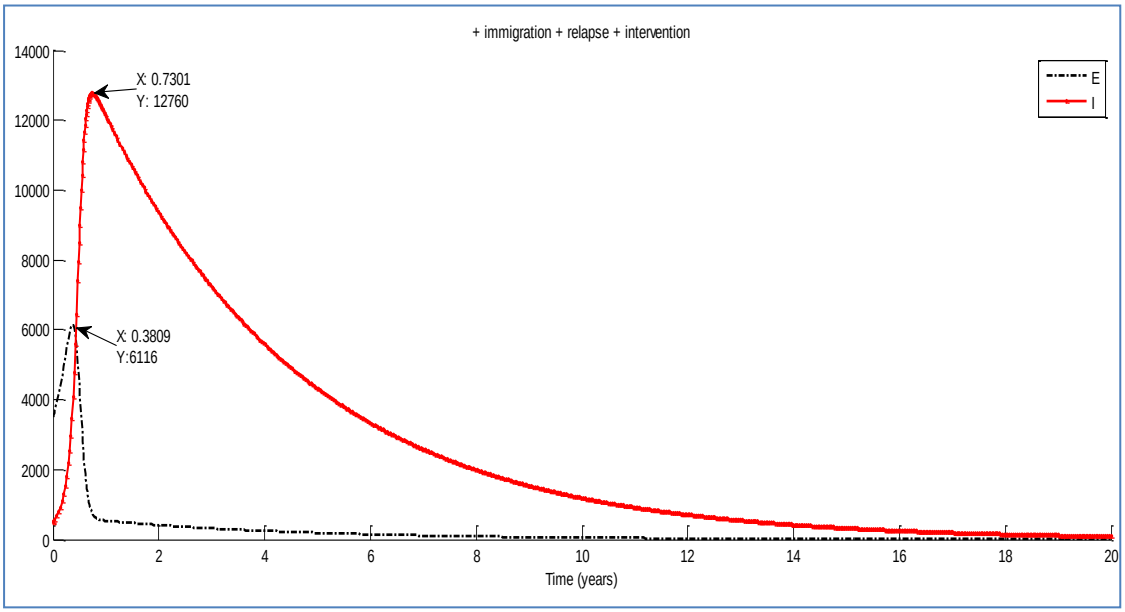

Figure 4.12(b) Model system with a= 0.3, b=0.1: The latently infected and infectious class when there is an immigration of infected individuals

From Figure 4.12(b) we can see that when immigration of infected individuals is taken into consideration, the peak for both classes become slightly higher with E class peaks at 6,116 and I class at 12,760. This change was very small and can be considered insignificant.

Figure 4.13 (a – c) is a graphical representation comparing the trend of all the classes with and without treatment. Whether the treatment is given or not, there is almost no difference to the susceptible class as shown in Figure 4.13(a). This is so because the susceptible class are not dependent on the treatment. Once infected, one will not return to susceptible class even after being treated as there is no permanent cure for TB.

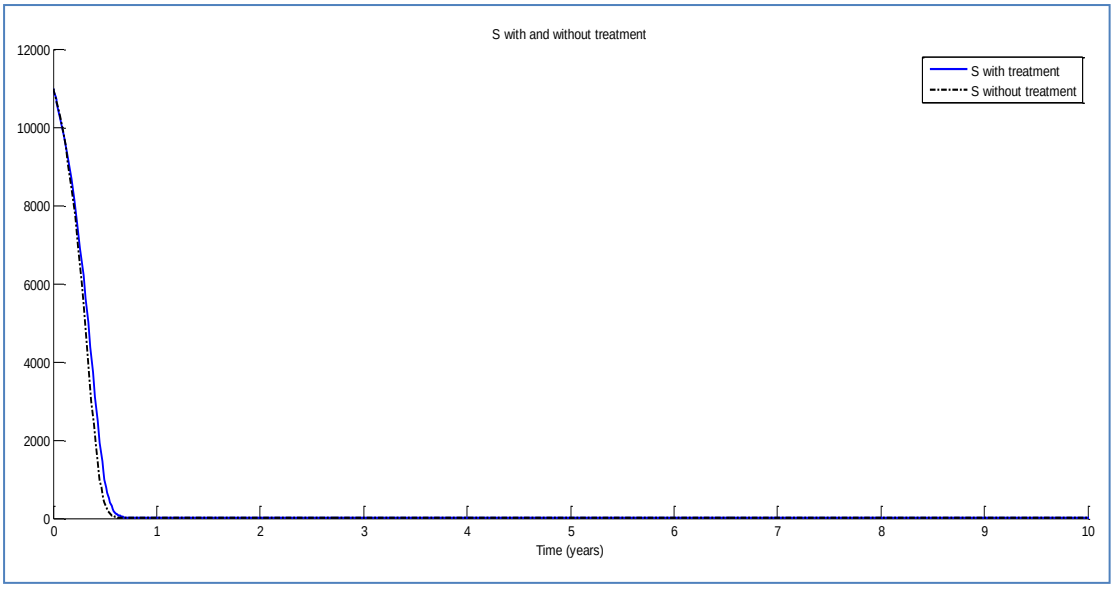

Figure 4.13 (a) The susceptible population with and without treatment

In Figure 4.13(b) we can see how the treatment affects both the latently infected and infectious individuals. Even though there is not much of a difference, the treatment clearly lowered the peak for both classes. Figure 4.13(c) shows a big difference to the recovered population when treatment is given. The graph sky rocketed to its peak before gradually decline as there is a decrease in the number of individuals in the latently infected and infectious classes.

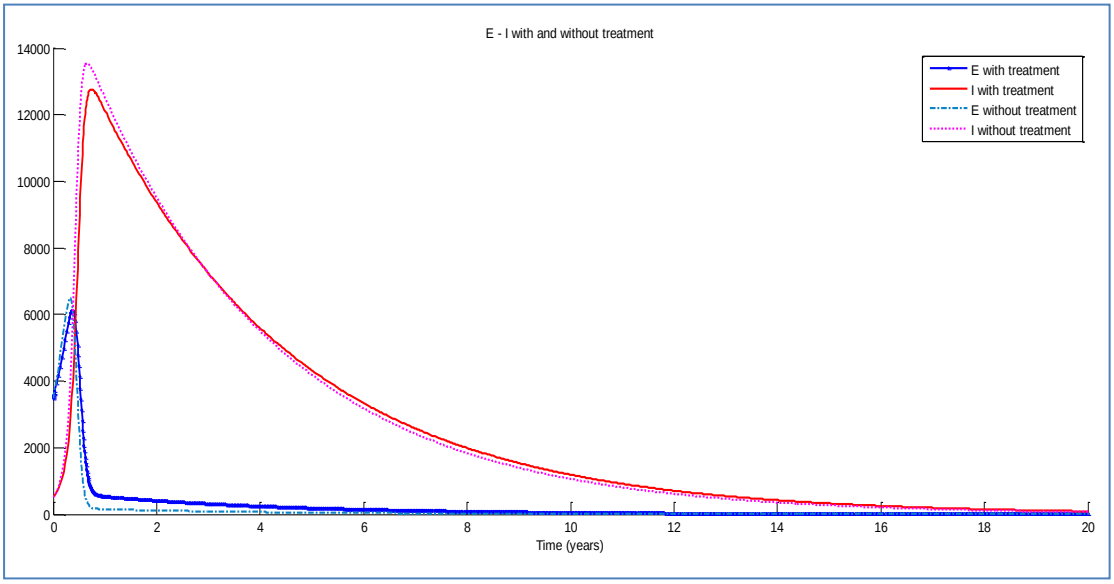

Figure 4.13 (b) The latently infected and the infectious population with and without treatment

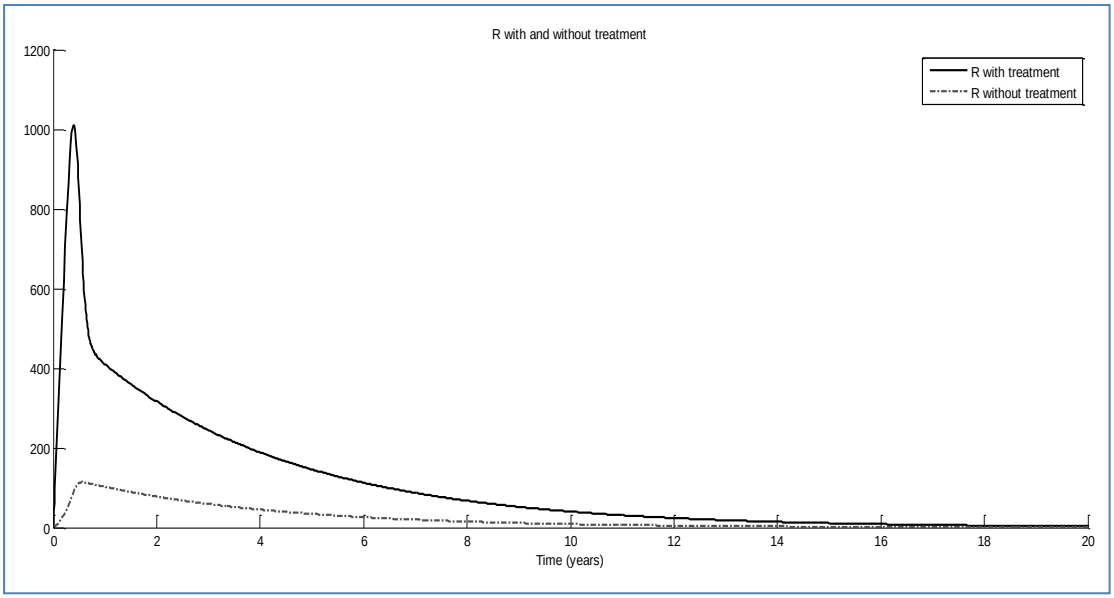

Figure 4.13 (c) The recovered population with and without treatment

From Figure 4.13, we can see that when taking all factors into consideration, even with treatment the whole population will eventually dies out as time passed by. How can we prevent this from happening? Looking at the parameters, the only logical action that we can make is by changing the value of the treatment rates, the fraction of immigrants coming into the population and also the contact rate. Referring to the treatment rate, it is already considerably high and changing it does not contribute any significant improvement. It is the same with the fraction of immigrants. From Figure 4.12(a), (b), it can be concluded that the immigration factor does not have a significant role in affecting the dynamic of TB spreading. Hence, we are left with controlling the contact rate of the TB patients. This action can be translated as reducing the contact rate a person can come in contact with infected individuals.

Figure 4.14 (a, b) shows the trend of each class when being put under different contact rates over the period of 50 years while keeping all other parameters the same.

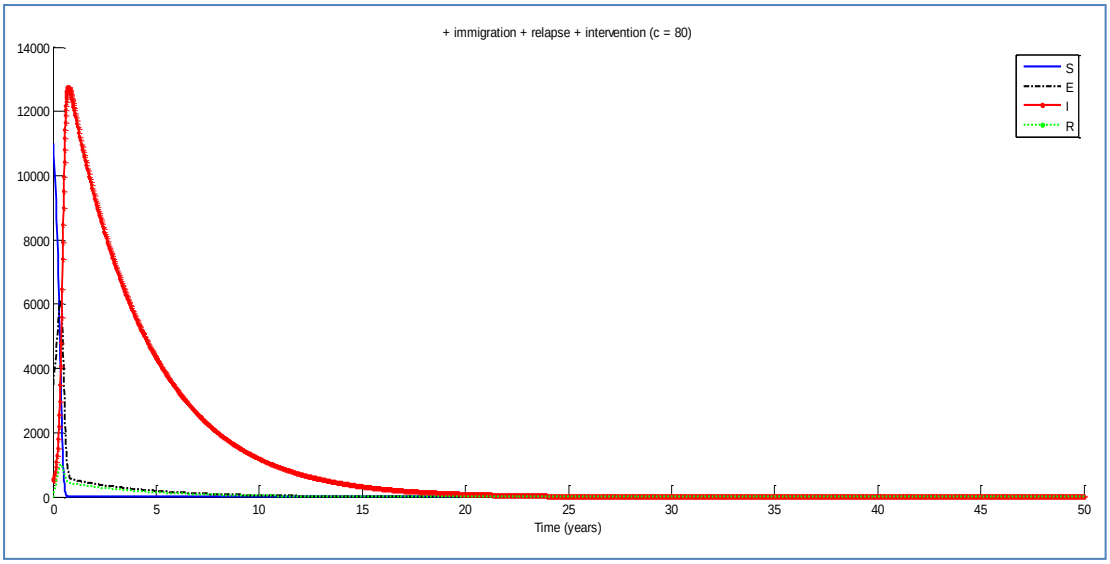

Figure 4.14 (a) Model system with c =80

In Figure 4.14(a) we use the original contact rate c = 80. The total population dies out within 20 years period. By reducing the contact rate to c = 18, it can be seen that the total population after 50 years is not zero (Figure 4.14(b)).

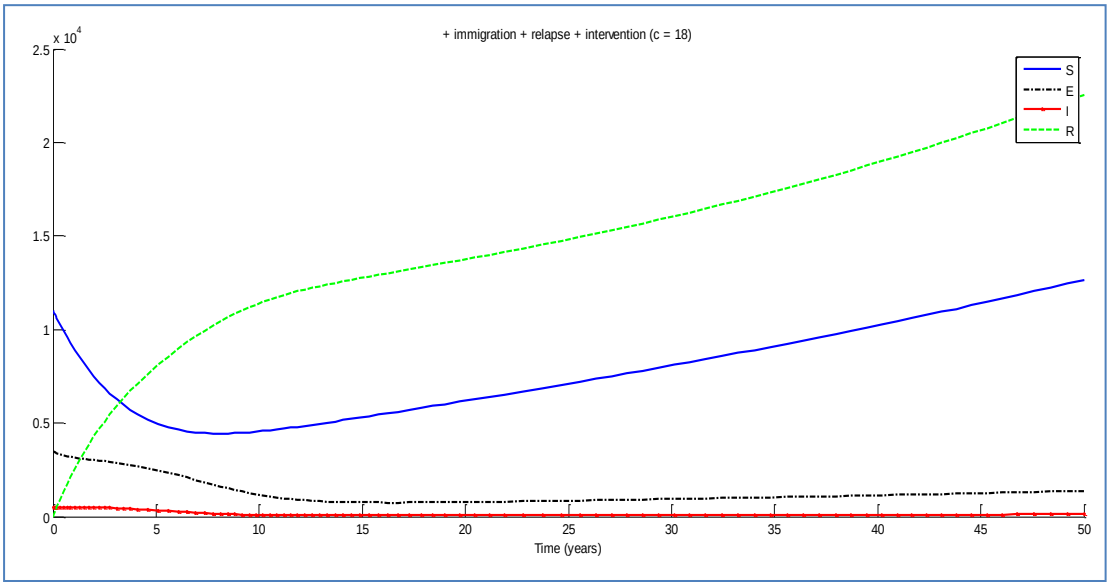

Figure 4.14 (b) Model system with c = 18

The number of recovered individuals keeps increasing over the years. Not only that, we also manage to keep the number of infected at bay. This means that treatment with quarantine proved to be the more efficient method in containing the disease as a whole. Figure 4.15 shows that, with treatment, as long as we reduce the contact rate to less or equal to 18, the total population will live on and we can successfully contained the disease.

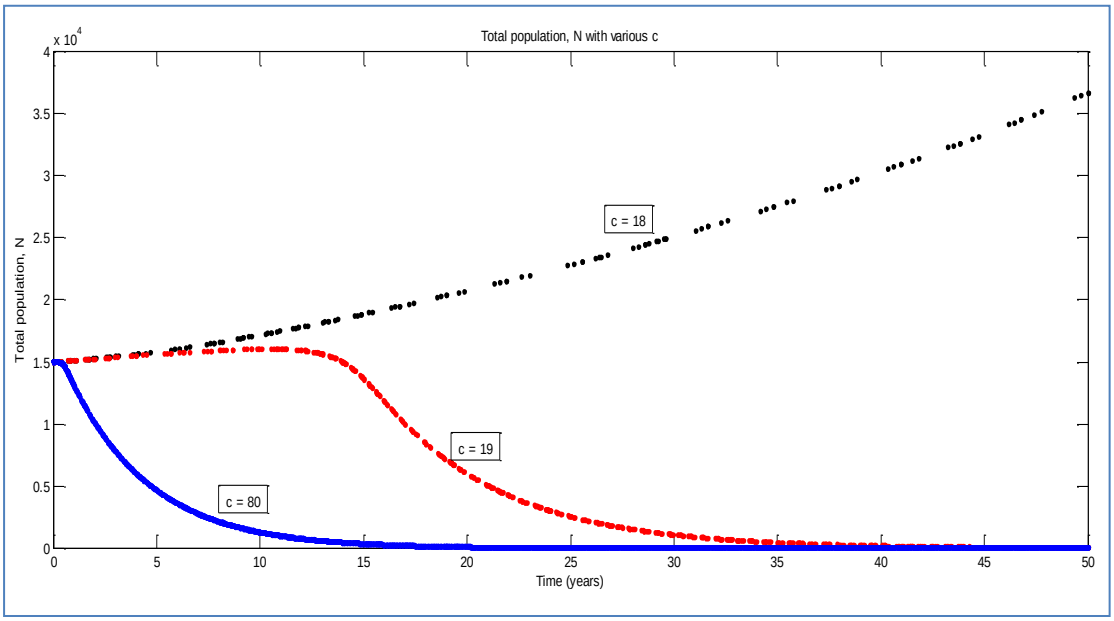

Figure 4.15 Total population with various contact rates, c.

4.4.3. Conclusion

The third model is the extended model where we incorporate the immigration factor into the model proposed by Bhunu et al [5]. Even though in reality immigrants do play a significant role in spreading the TB disease, the results that we obtained proved otherwise. One reason is because since this model takes into consideration too many factors into it, it overwhelms the immigration factor making it less significant. The same thing can be said about the effectiveness of the treatment as a whole. Simply giving the treatments is not the best option in a long term basis as the population will

eventually dies out. Different kinds of intervention are needed to ensure a more successful prevention plan. In this case, we showed that one way to do just that is by reducing the contact rate of the infectious individuals.

CHAPTER 5

CONCLUSION AND FUTURE RESEARCH

5.1. Conclusion

Three mathematical models with immigration have been presented and studied to analyze the dynamic of tuberculosis transmission under different conditions in order to identify key factors which contribute in the spreading of the disease.

We started with a basic SEIR model [Equation 1(a – e), Figure 4.1] with the assumption of permanent immunity and homogenous mixing. Using the model, we analyze the local dynamics. A numerical solution presented in Figure 4.2 shows the existence of a globally asymptotically stable endemic equilibrium under certain parameter restrictions.

Next, we extended a SEI model [Figure 4.3(a)] of McCluskey and van den Driessche [23] into a SEIR model [Equation 17 (a – e), Figure 4.3(b)]. In our model, instead of the complete recovery that goes back to the susceptible population, the treated individuals are moved into the recovered group. The results from both models are compared, and we found that they basically give the same conclusion; that is, immigration of infected individuals plays a very significant role in that the TB never dies out [Figure 4.5]. However, the disease spreading can be kept at bay with effective treatment. Our numerical result [Figure 4.8(a)] also shows that treatment to the latently infected is more effective in keeping the disease under control.

We then incorporate the immigration factor to the model proposed by Bhunu et al [5] to study the effects of immigration under different conditions. This model takes into consideration the relapse, re-infection and re-activation of the disease. From this model

[Equation 18 (a – e)], we found out that the effect of immigration will be overwhelmed by the other factors such as the high rate of re-infection [Figure 4.12]. Simply giving treatments to the infected are definitely not enough since the population will eventually dies out [Figure 4.11]. We showed that by reducing the contact rate of the infectious, the spread of the disease can be controlled [Figure 4.14(b)].

From all the above results, we can conclude that immigration plays a significant role in the dynamic of TB spreading since it has a marked influence to the existence of the disease in the population [Figure 4.6]. However, its effect varies depending on other contributing factors in the area involved. In order to control the spread of the disease, it is very important for the TB patients to receive treatment [Figure 4.7 and 4.13]. Different kinds of intervention are needed to ensure a more successful prevention plan. If the affected area has a low incidence rate, then with proper treatment, the spread of the disease can still be controlled and the immigration of infected will not cause much influence to the population [Figure 4.5(b)]. It is also better to give treatments to the latently infected in order to avoid them becoming infectious and thus keeping the incidence rate at a low level [Figure 4.8]. However, in the area where the prevalence rate is high, the best action plan will be to give treatments to the infected and to quarantine them so that their contact rate with others are reduces and thus lowering the possibility of spreading the disease [Figure 4.14].

5.2. Recommendations for Future Research

We find out that the immigration factors that we used are not accurate enough to represent the complexity of the real world. This may be due to the linear form chosen. It might be a good idea to do a future research with a better approximation of immigration factor using non-linear terms.

Furthermore, if we are to build a model that take into consideration intervention that involves quarantine, it is better to do a sub-model instead of just one gross model to differentiate the quarantine population and the normal population.

APPENDIXES

APPENDIX A

Compound Matrices

An $m \times m$ matrix *A* with real entries will be identified with the linear operator on $\Re^m$ that it represents. Let "$\wedge$" denote the exterior product in $\Re^m$. With respect to the canonical basis in the exterior product space $\wedge^2 \Re^m$, the second additive compound matrix $A^{[2]}$ of *A* represents a linear operator on $\wedge^2 \Re^m$ whose definition on a decomposable element $u_1 \wedge u_2$ is

$$A^{[2]}(u_1 \wedge u_2) = A(u_1) \wedge u_2 + u_1 \wedge A(u_2)$$

Definition over all of $\wedge^2 \Re^m$ is through linear extension. The entries in $A^{[2]}$ are linear relations of those in *A*. Let $A = (a_{ij})$. For any integer $i = 1,...,\binom{m}{2}$, let $(i) = (i_1, i_2)$ be the *i*th member in the lexicographic ordering of integer pairs such that $1 \le i_1 < i_2 \le m$. Then, the entry in the *i*th row and the *j*th column of $Z = A^{[2]}$ is

$$z_{ij} = \begin{cases} a_{i_1 i_1} + a_{i_2 i_2} & f\,(i) = (j) \\ (-1)^{r+s} a_{i_s j_r} & \begin{array}{l} f \text{ exactly one entry } i_s, \text{ of } (i) \text{ does not} \\ \text{occur in } (j) \text{ and } j_r \text{ does not occur in } (i) \end{array} \\ 0 & \text{if } (i) \text{ differs from } (j) \text{ in two or more entries} \end{cases}$$

For any integer $1 \le k \le m$, the *k*th additive compound matrix $A^{[2]}$ of *A* is defined canonically. Pertinent to our purpose is a spectral property of $A^{[2]}$ given in the following proposition. Let $\sigma(A) = \{\lambda_i : i = 1,...,m\}$ be the spectrum of *A*.

Proposition. *The spectrum of* $A^{[2]}, \sigma(A^{[2]}) = \{\lambda_{i1} + \lambda_{i2} : 1 \le i_1 < i_2 \le m\}$.

The second additive compound matrix $A^{[2]}$ of an $m \times m$ matrix $A = (a_{ij})$ is

$$m = 3: \qquad \begin{bmatrix} a_{11} + a_{22} & a_{23} & -a_{13} \\ a_{32} & a_{11} + a_{33} & a_{12} \\ -a_{31} & a_{21} & a_{22} + a_{33} \end{bmatrix},$$

APPENDIX B

The program for MATLAB

```
function dydt = newseir(t,y)
global NewInd Mew f delta1 delta2 k p q d B c a b r1 r2

% clear
% clc

% [t,y] = ode45(@newseir,[0 50],[11000; 3500;500;0]);
% [t,y] = ode45(@newseir,[0 50],[11/15; 7/30;1/30;0]);

% hold on;plot(t,y(:,1),'b',t,y(:,2),'k-.',t,y(:,3),'rx-
',t,y(:,4),'g','LineWidth',2,'MarkerSize',3);legend
('s','e','i','r');xlabel('Time (years)');hold off

NewInd=0.03;
Mew=0.01;
c=80;
f=0.99;
B=0.35;
k=0.00013;

delta1=0.7;
delta2=0.9;
r1=0.7;
r2=0.55;

p=0.2;
q=0.00001;

d=0.3;
a=0.3;
b=0.1;

format long g;


N=y(1)+y(2)+y(3)+y(4);

lambda=(B*c*y(3))/N;

% title('Basic seir in fraction')
% dydt = [(1-a-b)*NewInd-NewInd*y(1)+(d-B*c)*y(1)*y(3);
% a*NewInd+B*c*y(3)*y(1)-(NewInd+k)*y(2)+d*y(3)*y(2);
% b*NewInd+k*y(2)-(NewInd+d+p)*y(3)+d*y(3)*y(3);
% p*y(3)-NewInd*y(4)+d*y(3)*y(4)];

% title('SEIR McCluskey')
% dydt = [(1-a-b)*NewInd*N-(lambda+Mew)*y(1);
% a*NewInd*N+lambda*y(1)-(Mew+k+r1)*y(2)+delta2*lambda*y(4);
% b*NewInd*N+k*y(2)-(Mew+d+p+r2)*y(3);
% r1*y(2)+(p+r2)*y(3)-(Mew+delta2*lambda)*y(4)];
```

```
% title('+ immigration + relapse + intervention')
% dydt = [(1-a-b)*NewInd*N-(lambda+Mew)*y(1);
% a*NewInd*N+f*lambda*y(1)-delta1*lambda*y(2)-
(Mew+k+r1)*y(2)+delta2*lambda*y(4);
% b*NewInd*N+(1-f)*lambda*y(1)+delta1*lambda*y(2)+k*y(2)-
(Mew+d+p+r2)*y(3)+q*y(4);
% r1*y(2)+(p+r2)*y(3)-(Mew+q+delta2*lambda)*y(4)];
```

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