MATHEMATICAL ANALYSIS OF TUBERCULOSIS VACCINE MODELS AND CONTROL STRATEGIES.

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Abstract

The epidemiological study of tuberculosis (TB) has been ongoing for several decades, but the most effective control strategy is yet to be completely understood. The basic reproduction number, $\mathcal{R}_0$, has been found to be plausible indicator for TB control rate. The $\mathcal{R}_0$ value is the average number of secondary TB cases produced by a typical infective individual in a completely susceptible population during its entire infectious period. In this study we develop two SEIR models for TB transmission; one involving treatment of active TB only, with the second incorporating both active TB treatment and post-exposure prophylaxis (PEP) treatment for latent TB. Using the next generation matrix method we obtain $\mathcal{R}_0$. We determine the disease free equilibrium (DFE) point and the endemic equilibrium (EE) point. Global stability conditions of DFE are determined using the Castillo-Chavez theorem. Through model analysis of the reproduction number, $\mathcal{R}_0$, we find that for $\mathcal{R}_0 < 1$, the infection will die out. The value of $\mathcal{R}_0 > 1$ implies that the disease will spread within the population. Through stability analysis, we show that the model exhibits backward bifurcation, a phenomenon allowing multiple stable states for fixed model parameter value. MATLAB **ode45** solver

was used to simulate the model numerically. Using the Latin Hypercube Sampling technique the model is sensitive to treatment and disease transmission parameters, suggesting that to control the disease, more emphasis should be placed on treatment and on reducing TB transmission. For the second model, which incorporated treatment with post-exposure prophylaxis for latently infected individuals, by means of simulations, we found that treatment of latently infected individuals may reduce $\mathcal{R}_0$. Numerical simulations on the latter model also showed that it may be better to introduce a hybrid of active treatment and post-exposure treatment of the latent class. The force of infection was found to reduce when this hybrid control strategy is present. Contour plots and PRCC values highlighted the important parameters that influence the size of the Infective class. The implications of these findings are that TB control measures should emphasise on treatment. Our simplified models assume that there is homogeneous mixing. The model used have not been validated against empirical data.

Declaration

The work described in this dissertation was carried out under the supervision of Prof. P. Sibanda, School of Mathematics, Statistics and Computer Sciences, University of KwaZulu-Natal (PMB), and Prof H Mwambi, School of Mathematics, Statistics and Computer Sciences, University of KwaZulu-Natal (PMB) from January 2010 to November 2013. No portion of the work referred to in this dissertation has been submitted in support of an application for another degree or qualification of this or any other university or institution of learning. The dissertation is my original work except where due reference and credit is given.

Student Signature: .....

Date: .....

Supervisor Signature: .....

Date: .....

Dedication

To God Almighty. To my late father Mr B. P Sithole

Acknowledgement

I thank my supervisors Prof. Sibanda and Prof. Mwambi for their patience, comments, discussions, suggestions and all the guidance through the writing of this dissertation. Thank you to the Sithole family and a special thanks goes to Mr Buzani Mthethwa for the love, support and words of encouragement. My further gratitude go to Sheelagh Halstead and Isaac Wangari for their helpful comments. Thank you to DST/NRF Centre of Excellence in Epidemiological Modelling and Analysis (SACEMA) for study funds.

Chapter 1

Introduction

In this chapter we introduce some tuberculosis history. Central topics about tuberculosis diagnosis, treatment, vaccines and interventions strategies are discussed in this chapter.

Tuberculosis (TB) is an airborne disease caused by the rod-shaped pathogen *Mycobacterium tuberculosis bacillus* (MTB). This pathogen is strictly mammalian and is found in the tissues of an infected host. MTB was found to be the causative agent of tuberculosis by Robert Koch (1843-1910) at the end of the 19th century. This pathogen is suspected to have led to more human deaths than any other microbial pathogen, Palomino et al. [1].

Palaepathology, is the study of diseases from fossils and mummified remains, as inferred from fossil evidence. It is useful in understanding the history of diseases and one may use this understanding to predict its course in the future. Due to characteristic palaepathological lesions, tubercle bacilli has been recognized in ancient remains and was the first disease to be studied by modern bio-molecular methods, Raoult and Drancourt [2]. Molecular methods have been used to demonstrate the presence of tubercle bacillus in ancient remains. By such methods MTB DNA was detected in bone lesions in the spine of a male human skeleton from the Iron Age (400- 230 BC), [3].

Spoligotyping is one of the molecular methods that was used for identification and typing of the MTB complex bacteria. This method was applied to a subculture of the original tuberculosis bacillus isolated by Koch, confirming its species identification as *Mycobacterium bacillus* rather than *Mycobacterium bovis*, Palomino et al. [1]. He then attempted to develop tuberculin, a tuberculosis therapy using sterile filtrate. In August 1890, Koch announced that he had discovered a cure for TB. However, both the tuberculin and its later version proved to be ineffective, although the tuberculin was and is still an effective diagnostic tool, Tan and Berman. [4].

TB today has a widespread distribution and some controversy arises concerning its spread among different population groups due to exploration and colonisation. As mentioned earlier, it has been identified in Iron Age human remains. It was already

common in ancient Egypt and Rome and was known in North America at the time of Columbus. Palomino et al. [1] cite the first epidemic there as being in 1880. Evidently, Africans taken as slaves to North America were free of TB, and contracted it only after contact with Europeans and exposure to the pathogen. However, today TB is prevalent in African countries. Sadly, Africans currently experience a higher mortality and morbidity, even after liberation, Palomino et al. [1].

Until Robert Koch was able to show that the mycobacterium bacillus was the cause of tuberculosis, and that this pathogen was responsible for transmission of the disease among humans, the disease was largely misunderstood. Over the course of history it has been ascribed to immorality, malnutrition or even in the 18th century to vampirism. In the latter case it was believed that a deceased family member had returned from death as a vampire to drain life from surviving family members. TB symptoms were thus considered to be the vampire traits, Palomino et al. [1]. Nevertheless, these theories indicate that people had recognised that the disease frequently spread among family members and was exacerbated by poverty and overcrowding.

Although not yet called TB, the ancient Greeks described a disease with the same symptoms as TB, which they called phthisis. The Greek physician Hippocrates, around 460 BC, identified phthisis as the most fast spreading disease of all time. By the 17th century in Europe, TB reached epidemic proportions and was called “Great White

Plague", Grigg [5]. TB remains one of the greatest killers of mankind, causing as many as 1.3 million deaths and 8.6 million new infections in 2012 only, Global TB report 2013 [6].

1.1 Immunopathology and pathophysiology of tuberculosis

Generally, TB is transmitted by patients with pulmonary TB (i.e TB in the lungs) who cough sputum containing the infectious micro-organisms, Grigg [5]. TB infection introduces MTB into the host body, but the immune system is usually strong enough to keep the bacteria under control in which case the host is latently infected. The immune system responds to MTB by first producing macrophages which surround the tubercle bacilli. However the pathogens can survive and grow within the macrophages, thus evading the host immune system. A further active cell mediated immune response is required to contain and destroy the tubercle bacilli, Raoult and Drancourt[2].

Individuals with latent forms of TB are not clinically ill and cannot transmit the disease. Approximately 90% of TB infected individuals, are able to adequately contain the bacteria and do not progress to active TB during their lifetime. The remaining 10% of latently infected individuals progress to active TB. Individuals with weakened immune systems such as very old or very young, those suffering from malnutrition and other diseases, physical and or mental stress, or other immunosuppressive conditions

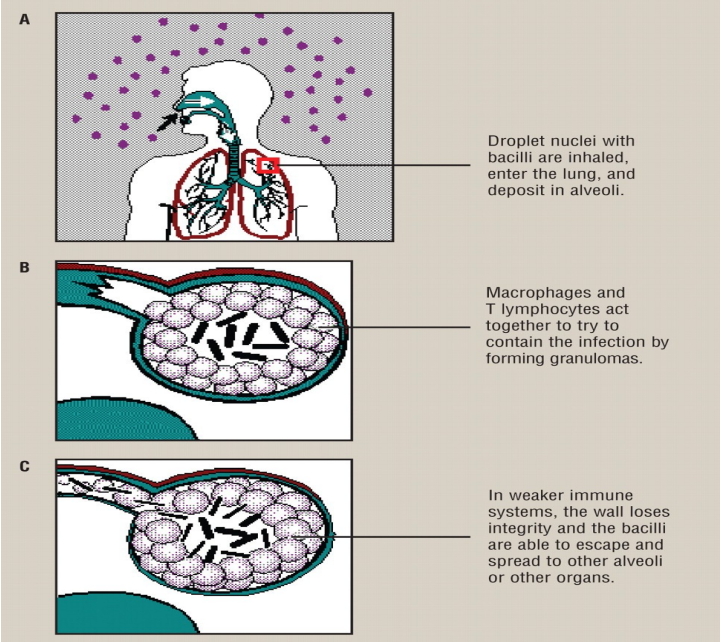

Figure 1.1: Pathophysiology of tuberculosis, (A) Inhalation of bacilli, (B) Containment in a granuloma, (C) Breakdown of the granuloma in less immunocompetent individuals, Source: CDC Report [7]

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are more likely to suffer from the disease. Doherty and Andersen [8] and the CDC Report [7] describe the pathophysiology and the immunopathology of the MTB infection, and discuss in detail how MTB enters the host via a mucosal surface of the lung after inhalation of few droplets from an infectious individual, see Figure 1.1 (A). The droplets are then deposited in the alveolar spaces in the lungs. Ingestion of the bacteria induces a rapid inflammatory response which results in the accumulation of a variety of immune cells and, with time, the formation of granuloma, characterized by a relatively small number of infected phagocytes surrounded by monocytes or macrophages,

Doherty and Andersen [8].

If the infection is successfully contained, the granuloma shrinks and may eventually calcify, see Figure 1.1 (B). If however, the immune response does not successfully control the bacterial replication, the granuloma increase in size and in cellularity. Eventually, cell death in the hypoxic center of the granuloma leads to necrosis, the premature death of living tissues and cells, see Figure 1.1 (C). If the granuloma is close to the surface of the lung, the tissue destruction caused by necrosis can breach the mucosal surface, giving rise to the symptoms of TB, such as a persistent cough with blood in the sputum, fever, night sweats, and weight loss, Doherty and Andersen [8]. At this point the patient is highly infectious, spreading the bacteria by aerosol. In a minority of cases the bacteria spread to other host tissues via lymphatic system and blood, thereby becoming disseminated throughout the body, causing extra-pulmonary TB, e.g miliary or meningitis, Donoghue [9].

1.2 Tuberculosis diagnosis

In many cases, patients infect their surroundings before they are diagnosed, hence early and effective diagnosis should be considered as an important TB control measure. However current testing methodologies are often too slow, and can take up to four weeks to give results, while the tested individual continues to spread the MTB. Mass testing

and treating is recommended for highly exposed individuals (e.g health care workers) and in places most likely to have a TB outbreak such as hospitals, prisons, homeless shelters, workplaces, schools and other areas where people repeatedly congregate. The infection can be detected using diagnostic tools.

The tuberculin skin test (TST) reveals evidence of MTB infection, Feng and Castillo-Chavez [10]. TST is used in populations with low rate of TB infections. Recently, a two-hour *Xpert Mtb/RIF* test was developed by Boehme et al. [11]. This test detects the existence of MTB and resistance to the rifampicin drug within two hours and gives a possibility to go from 'test to treat' rather than 'test and wait'.

Chest radiography X-ray (CXR) can be used to check for lesions and cavities that may suggest TB in the lungs. Visual lobar infiltrates with cavitation in upper and middle lobes of the infected lungs can be seen, Thrupp et al. [12]. These abnormalities may suggest TB, but cannot be used to definitively diagnose TB. Furthermore, results of the X-ray can takes 12 to 24 hours.

Sputum smear microscopy detect acid fast bacilli (AFB) in 24 hours. For a positive sputum smear, the sputum would contain many bacilli that could be observed under a microscope. The test is not specific for TB, because other mycobacteria give the same results giving a false positive, Knechel [13]. Furthermore a false negative sputum

smear is possible, where the sputum may give a positive in a sputum culture.

The sputum culture based method is the 'gold standard' for a definitive diagnosis of TB and can distinguish between tuberculosis non tuberculous mycobacterium. Sputum culture identifies TB in 3-6 weeks when a solid media is used and still takes 4-14 days when high-pressure liquid media chromatography is used, Knechel [13]. Culture methods have the advantage of providing isolates for identification and drug susceptibility testing, Baylan [14].

In summary, the different tests available are suitable in different contexts, depending on speed and required information.

1.3 Tuberculosis vaccines

Not only was TB one of the first diseases for which the causative agent MTB was identified but also one of the first for which a vaccine was developed. The first breakthrough in TB vaccine development was the use of *Mycobacterium bovis* bacillus Calmette-Guerin commonly known as BCG, Doherty and Andersen [8]. This is a neonatal pre-exposure vaccine that is widely used around the globe with about 3 billion people, that is approximately half of the world's population having received it, mostly in areas where TB is endemic, Garba et al. [15].

MTB infection characterized by a black line leads to an increase in the bacterial load, until the relative immune response responsible for reversing this growth develops, Doherty and Andersen [8]. The dotted lines represent the bacterial load in the presence of vaccination. Pre-exposure vaccines, also known as pre-infection vaccines, are given before infection with the pathogen, usually at birth as neonatal vaccines. Pre-exposure vaccination speeds up the development of the immune response, therefore preventing further infections from becoming symptomatic, see Figure 1.2 (A). However, if immunity is not provided, MTB establishes a latent infection which can later reactivate and cause clinical TB.

Post-exposure vaccines are those given to individuals after evidence of infection. Although these vaccines cannot prevent the initial acute infection, their purpose is to strengthen immune surveillance to prevent reactivation of latent infection, see Figure 1.2 (B).

A multiphase vaccine effective both as a pre-exposure and a post-exposure vaccine would be a great achievement in fighting MTB, but so far, there are none available for general use, Garba et al. [15]. In theory multiphase vaccine will not only inhibit the infection from becoming symptomatic but will also prevent later reactivation, see Figure 1.2 (C). An important consequence of preventing reactivation is that the bacterial

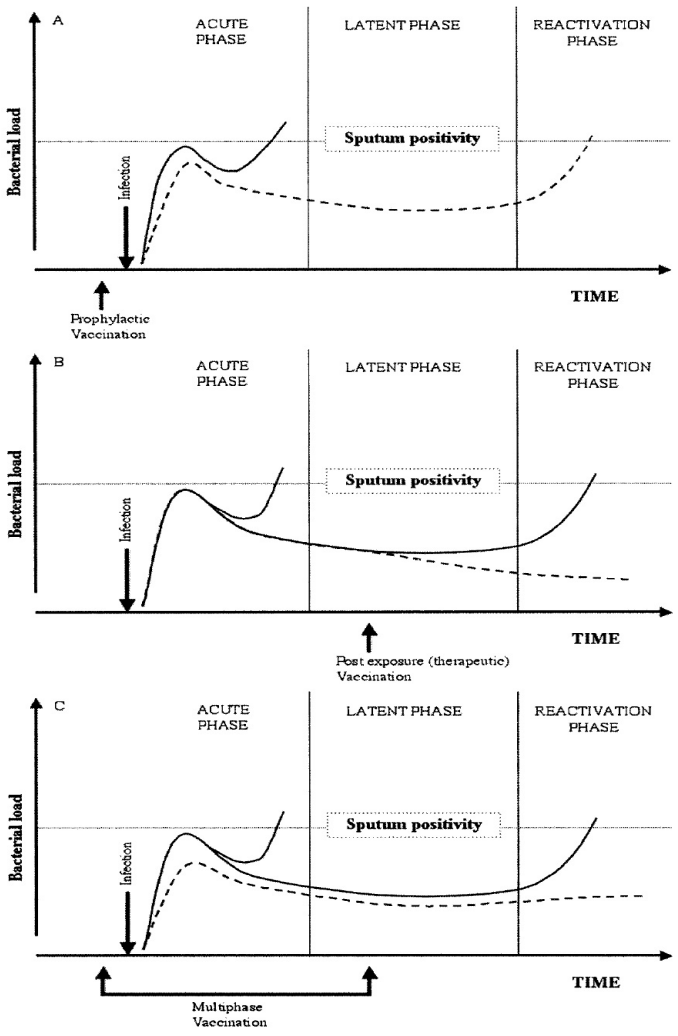

Figure 1.2: The effect of, (A) Pre-exposure vaccination, (B) Postexposure vaccination, and (C) Multiphase vaccination on the bacterial load. Source: Doherty and Andersen. [8].

load be reduced which would prevent the disease and break the cycle of transmission, Doherty and Andersen. [8].

1.4 Antituberculosis drugs and drug resistant tuberculosis

TB is usually treated with a course of four, first line or standard anti-tuberculosis drugs. Failure to properly and consistently use and manage these drugs for the required period can lead to multi-drug resistant TB (MDR-TB) developing. According to [7] MDR-TB is caused by MTB that is resistant to at least two drugs, always involving isoniazid (INH) and rifampicin (RIF). This contrast with polyresistant TB, caused by MTB that is resistant to at least two drugs, but not involving either INH or RIF, not simultaneously, [7].

The first line drugs are cheaper, taken for a shorter duration and have less side effects when compared to the second line drugs used to treat MDR-TB. In the case where there is lack of proper use of the second line drugs, they may become ineffective and an extensively drug resistant tuberculosis (XDR-TB) may develop, [7]. XDR-TB is resistant to both first and second line anti tuberculosis drugs. Therefore, the treatment options are very limited. Consequently adherence to recommended protocols is most important. The four important first line anti-TB drugs are briefly reviewed below.

1.4.1 Isoniazid (INH)

Isoniazid is the most widely used chemotherapeutic agent for the treatment of TB, Ellard et al. [16]. It was first discovered in 1912, and later in 1951 it was found to be effective against TB by weakening the bacilli through inhibiting their mycolic acid or wax coat formation. INH may cause severe liver damage. Liver function tests should be performed periodically and patients should be carefully observed for any symptoms of hepatitis, Ellard et al. [16]. To avoid development of drug resistance, INH is currently never used on its own to treat TB.

1.4.2 Rifampicin (RIF)

In Trevor [17] rifampicin is defined as a bactericidal antibiotic drug of the rifamycin group. RIF is typically used to treat mycobacterium infections, including TB and Hansen's Disease. The powerful effect of RIF is its ability to sterilize and kill tubercle bacilli within pulmonary lesions, van Rie [18]. If it is used alone rifampicin resistance develops quickly during treatment. RIF should thus be used in combination with other antibiotics. Similar to INH, this drug has a disadvantage that it may cause liver damage. Trevor [17] suggested that patients treated with INH and RIF should undergo baseline and frequent liver function tests to detect possible liver damage.

1.4.3 Pyrazinamide (PZA)

Pyrazinamide is a drug used in combination with other medications to treat MTB, Medical Research Council [19]. PZA is an antibiotic that works by stopping the growth of bacteria, and is never used on its own. In 1981 the British Medical Research Council [19], suggested that regimens not containing PZA should continue for nine months or more. Consequently pyrazinamide is used in the first two months of treatment to reduce the duration of treatment required.

1.4.4 Ethambutol (EMB)

Ethambutol is used in the initial phase of TB treatment, primarily to prevent drug resistance to RIF, British Medical Research Council, [19]. EMB is anti-mycobacterial drug bacteriostatic against actively growing TB bacilli, it is used with other anti-TB drugs. It works by obstructing the formation of cell wall. EMB is effective in some extra-pulmonary forms of TB.

1.4.5 Overall tuberculosis treatment

The main two goals of TB treatment is to cure the patient, and minimize transmission of MTB to another person. In this way, successful TB treatment benefits not only the individual patient, but also the whole community. Active TB is treated using combination therapy while latent TB treatment may include only INH. Regimens that use a

single drug usually result in the rapid development of drug resistance and consequent treatment failure. The short course regimen for treating active TB takes six months. Normally if the doses are taken consistently, after six months the patients is considered cured with a relapse rate of 2% to 3%, CDC Morbidity and Mortality Report, [7]. Relapse refers to patients who become or remain culture negative while receiving therapy but at some point after completion either become culture positive or begin to show symptoms of active TB. Patients with TB caused by strains of MTB resistant to at least INH and RIF are at high risk of treatment failure and further acquired drug resistance, CDC Morbidity and Mortality Report, [7]. The summary of the general approach to treatment regimens recommended by CDC Morbidity and Mortality Report, [7] are shown in Figure 1.3. The treatment follows three phases of two months each, the first phase involving a combination of the drugs INH/RIF/EMB/PZA. At the end of each phase, clinical tests on the individual such as chest X ray, sputum smear test or cultures indicate whether INH/RIF treatment should be continued for a further two months, four months or possibly nine months.

1.5 Tuberculosis epidemiology

TB is a major public health problem in developing countries.The worst affected countries are located in sub-Saharan Africa. This regional problem is worsened by the fact that TB remains the main opportunistic disease driving mortality due to HIV, De Cock et al. [20], Dye et al. [21]. Those most at risk include the urban poor, migrants and

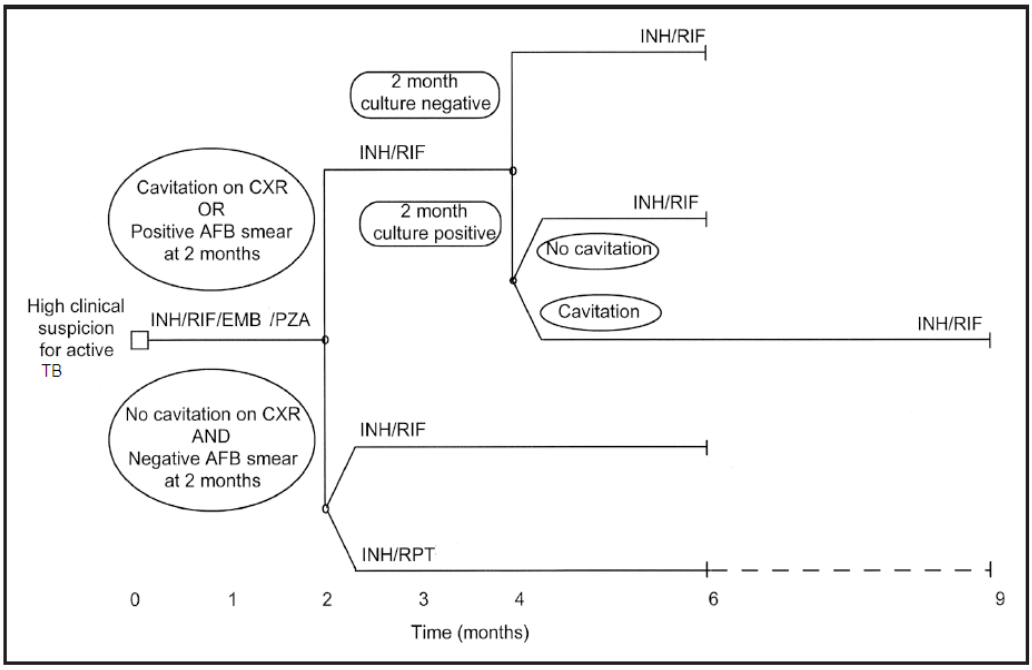

Figure 1.3: Treatment algorithm for active TB. Source:CDC Morbidity and Mortality Report, [7]

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refugees, who are forced to live in overcrowded conditions. South Africa's incidence of tuberculosis (per 100,000 people) is 1003 [6].

WHO Global Tuberculosis Report 2013 [6] show that in 2012, the proportion of TB cases co-infected with HIV was highest in countries in the African Region. About 37% of TB cases were estimated to be co-infected with HIV in this region, which accounted for 75% of TB cases among people living with HIV worldwide. In parts of southern Africa, more than 50% of TB cases were co-infected with HIV [6].

A serious complication of the TB problem in Southern Africa has been the emergence of multi-drug resistant strains of the organism causing the disease. Patients infected with Multi Drug Resistant-TB require prolonged chemotherapy with very expensive medication which will at best cure only half of them. Seven African countries reported starting XDR-TB patients on treatment in 2011 or 2012, most of them in South Africa [6]. Treatment outcomes reported by South Africa reveal the very low likelihood of a favorable outcome in such patients and the high proportion of patients lost to or not evaluated by the health services [6].

1.6 Summary

In Chapter 1, we presented the introduction about TB. We talked about immunopathology of TB infection in the body of an infected host. Information on TB diagnosis, TB vaccines and treatment have been discussed in detail. Even though TB is treatable, challenges such as reinfection and relapse may lead to treatment failure. Antituberculous drugs and standard treatment regimens fail to treat other TB strains such as Multi-drug resistant TB. TB epidemiology and current statistics according to World Health Organization call for more research to be conducted on TB.

Chapter 2

Review of literature on TB models

Some of the literature concerning mathematical models for TB is discussed in this chapter. We discuss different models, the mathematical methods used and the findings. We further compare the models in the literature to the models that will be presented in this dissertation.

2.1 Mathematical models for tuberculosis

Mathematical models can be used to understand, predict and design effective intervention programmes to control TB and other epidemics [10, 22]. Previous work has focused on different aspects of TB epidemiology. For instance there are models for epidemics, control of TB, transmission models, models for treatment and the effect of vaccination.

Mathematical TB studies focused initially on formulating models of untreated TB epidemics. These models were analyzed to predict temporal dynamics of the incidence and prevalence of infection and disease, McCluskey [23, 24]. The models were later extended to accommodate, *inter alia*, treatment, TB vaccines, co-infections and drug resistant strains Blower [22]. Analysis by Ziv et al. [25] also revealed that for any epidemic there are different control strategies, that is specific combinations of vaccination and/or treatment, that would be most effective in controlling TB. Furthermore, from their analysis of an epidemiological model of TB, Murray and Saloman [26] suggested that early active screening and case finding could reduce TB mortality by a quarter to a third.

Methods such as optimal control, uncertainty and sensitivity analysis can be used to gain more insights into an epidemiological model. To illustrate, Agusto [27] showed the optimal positive effects of using both chemoprophylaxis and treatment as control strategies to reduce TB transmission and reduce the population of latently infected and actively infected TB cases. Results were generated by applying the Pontryagins Maximum Principle from optimal control theory. Some models, such as in Porco and Blower [28], ignore exogenous re-infection (that is, re-infection of a latently infected person by another infected individual) in the belief that this type of re-infection occurs often only in heavily exposed and immune-compromised individuals.

The efficacy of different TB control measures was evaluated in 1997 by Gammaitoni and Nucci [29] in a simulation of a deterministic model. These control measures include environmental controls and respiratory protective devices. Environmental controls included ultraviolet germicidal irradiation (UVGI), air filtration and general ventilation to reduce the concentration of MTB droplets in enclosed places. UVGI kill and inactivate micro-organisms already in the air, CDC Report [7] . Respiratory protective devices refer to apparatus such as surgical masks and high-efficiency particulate air (HEPA) masks. In the model by Gammaitoni and Nucci [29], despite all precautions taken, a certain number of people still become infected. This number could be kept low by increasing the disinfection rate and decreasing the period of exposure to the micro-organisms. Consequently, Gammaitonni and Nucci [29] concluded that environmental control alone cannot eliminate the risk of TB transmission during high-risk procedures. These findings suggest that respiratory protective devices, used with air filtration or ultraviolet irradiation, may provide nearly complete protection from TB.

Analysis of transmission models has been conducted for several reasons. For instance, such models could be used to provide new insights into the historical epidemiology of TB, predict epidemic doubling time, predict temporal dynamics of incidence, predict the prevalence of TB infection, determine the effects that TB epidemics may have on the historical decline of other diseases such as leprosy or to estimate the value of the

reproduction number, [15, 23, 24, 30, 31, 32, 33].

Formulating and analyzing TB vaccination models have value in development and administration of vaccines for TB. Vaccination studies by Ziv et al. [25], take into consideration pathogenetic mechanisms by which the vaccine could succeed or fail, namely "take", "degree" and "duration". The term "take" means the protective immunologic response induced by a vaccine to the vaccinated individual. The term "degree" specifies the level of vaccine-induced protection that is assumed to be conferred to those individuals who take the vaccine. Finally, "duration" defines the time frame the vaccine-induced immunity is provided. This can vary from a very short period of time to lifelong immunity, Ziv et al. [25]. It is necessary to identify and quantify these mechanisms for low to moderately effective vaccines. In order to address the challenge of the vast reservoir of latent TB cases that already exists, one would require a new vaccine to have a high efficacy. Efficacy (which could change over time) is usually measured by conducting a clinical trial and measuring the incidence rate in both the vaccinated and the placebo groups. Furthermore, because vaccination of a critical number of individuals in a particular setting can offer protection to the entire population, by efficacy we mean the measure of how much herd immunity the vaccine generates. In this case, herd immunity indicates the immunity generated by a specific proportion of individuals that ultimately protects the entire population Lietman and Blower [34].

The potential public health impact and benefits of mass vaccination campaigns that used either pre-exposure or post-exposure vaccines were compared in mathematical models by Ziv et al. [25]. They formulated a pre-exposure model and a post-exposure model. Both models made use of unvaccinated and vaccinated classes and reflected the pathogenesis and dynamics of the disease. Uncertainty and sensitivity analysis based on Monte Carlo methods were used to analyze the models. Their results suggested that, in terms of reducing new infections, campaigns that used pre-exposure vaccines had substantially greater effectiveness when compared to those that used post-exposure vaccines. Furthermore, according to van den Driessche and Watmough [35], vaccination models should also include treatment rates, because even moderately effective vaccines could have a significant effect on reducing a TB epidemic if they are coupled with moderate to high treatment rates.

Mathematical models focused on prevention and control strategies using simulation approaches, Castillo-Chavez and Song [36]. Most of these models, which incorporate both linear and non-linear terms, are of the SEIR class in which the host population is categorized by their infection status as Susceptible, Exposed (infected but not yet infectious), Infectious and Recovered. Such mathematical modelling provides further insight into transmission dynamics and helps determine the most effective TB control strategies, as advocated by Bowong and Tewa [32].

In 1996 Blower [22] presented two SEIR models for TB; a simple model and a more detailed one. The detailed model had both infectious and non-infectious active TB as well as the recovered class. Most recent models not only pay attention to simulations but also take care of dynamical analysis using modern knowledge of dynamical systems and a variety of mathematical tools, Castillo-Chavez and Song [36]. Model formulations and solution involve a variety of mathematical areas, such as fluid dynamics.

An SEIR model for TB, by Van den Driessche et al. [37], presumes that all susceptible individuals enter the Exposed class, rather than moving directly into the Infective class. However, it is possible that immune-compromised individuals, such as children, the elderly, or the sick are more likely to move into the Infective class soon after contact with the TB disease. This is especially pertinent in Southern African countries with a high incidence of HIV.

In summary, mathematical models for TB transmission need to incorporate more than one control feature. In particular the combination of different control strategies. As a result, in the current study we will consider models that include both vaccination and other treatment strategies.

2.2 Problem statement and the purpose of study

As already shown in the previous chapter, TB remains one of the greatest killers of mankind, causing as many as 1.3 million deaths and 8.6 million new infections in 2012 only, Global TB report 2013 [6]. Thus TB is a burden posing a major treat to the population causing both high morbidity and mortality rates. The burden of TB has influenced the current advance of biomedical sciences, primary public health, and epidemiological research to understand TB dynamics.

As also previously discussed, the current TB epidemic in Southern Africa is exacerbated by the concurrent HIV epidemic. Different treatment regimens are available, but the lack of proper treatment has lead to the emergence of drug resistant TB. TB treatment alone has not proved to be sufficiently effective. However, it was evident from the literature that vaccination and treatment should be considered together as control strategies. Therefore the problem that needs to be addressed is which intervention strategy is the best.

In this study we seek to further the understanding of the dynamics of tuberculosis as influenced by the control strategies of treatment and vaccination. To this end, we first analyse the dynamics of the disease so as to develop, analyse and discuss our own SEIR (mathematical models depicting the dynamics of the disease when different forms of

vaccination and treatment are included. We then analyse the models and the corresponding mathematical equations in biologically feasible regions. The dynamics and behaviour of the model are investigated by means of analysis of the basic reproduction number as well as studying the stability analysis of the equilibrium points. We carry out numerical simulations to evaluate implications of the control strategies in our models. This analysis is done to help us distinguish important parameters from those that are less important. We further interpret these parameters based on the disease dynamics and their implications to the population.

2.3 Outline of the dissertation

This study is divided into six chapters. Each chapter is subdivided into sections and subsections. Chapter 1 gave the background information about TB disease. The chapter included the history of TB, diagnosis, vaccines, treatment. In Chapter 2 we have given a literature review of TB models. In Chapter 3, an SEIR TB model is introduced and discussed in detail. In this model the only control strategy included is treatment of active TB cases. In Chapter 4, an SEIR model extension of the model in Chapter 3 is discussed. The model is different from the first one in that it includes both treatment of active TB cases and prophylactic treatment (post-exposure vaccination) of latent cases as the control strategy. The model incorporates post-exposure vaccination as a control strategy. Analysis and implications of the model are carried out and clearly summarized in the discussion. Numerical simulations are presented in Chapter 5. We

then give an overall discussion of the findings and conclusion in the final chapter.

2.4 Summary

In this chapter we have given a literature review of TB models. We have stated the problem to be addressed in this study and also discussed the purpose of the study. An outline of this document is presented to indicate the format of this dissertation.

Chapter 3

The SEIR TB model

3.1 Introduction

In the previous chapter, we showed that mathematical models played a key role in the formulation of TB control strategies and the establishment of the goals for intervention programs since 1960 where simulations have been carried out using prediction and control strategies, Castillo-Chavez and Song [36]. In particular SEIR models have proved useful. These models classify the host population by their infection status, namely Susceptible, Exposed (infected but not yet infectious), Infectious and Recovered. One of the principal attributes of these models is that the force of infection (the rate at which susceptibles acquire infection) is a function of the number of infectious hosts in the population at any time t and is thus a nonlinear term. Other transitions, such as the recovery of the infectious and the deaths, are modelled as linear terms with

constant coefficients.

In this chapter we present a new SEIR model, which extends the existing SEIR model by Driessche et al. [37], to accommodate some individuals moving directly into the Infective class, and call these individuals 'fast progressors'. The SEIR model by Castillo-Chavez and Feng [38] describes TB dynamics, and considers only one progression rate from Susceptible to Infectious class after infection. While we have been able to adopt most of the features in the Castillo-Chavez and Feng [38] model into our SEIR model, we made some changes. In particular, the present model, as presented in this chapter, has two progression rates; the infectious class is populated by individuals from the latent and from the susceptible classes. Furthermore the present model considers treatment of active TB and no vaccination.

To be consistent in our notation we denote the subpopulation classes as given in Table 3.1. The symbols and definitions of parameters used throughout this study are listed in Table 3.2. Subscripts are used to distinguish between the population classes and parameters. All parameters and variables are assumed to be positive.

Table 3.1: Symbols and description of subpopulations

Symbol	Definition
S	Susceptible population,
E	Exposed population, latently infected but cannot transmit TB,
I	Actively TB infected and infectious TB population,
R	Recovered TB population,
N	Total population.

3.2 Model formulation

We present a transmission model as depicted schematically in Figure 3.1 to describe the transmission dynamics of TB. In our model we divide the host population into four classes; the susceptible (S), i.e those who are at risk of being infected, the exposed or latent (E), i.e those who are exposed to the disease or latently infected who are non-infectious and show no symptoms of the disease, the infected individuals/ infectives (I), those who have active TB and can actively transmit it, and the recovered individuals (R), i.e those who would have recovered from the disease by successful treatment. The total population size, N, is thus given by

$$N = S + E + I + R.$$

The state variables $S,\ E,\ I$ and R are all assumed to be positive as they represent

Table 3.2: Parameters and descriptions

Parameter	Description
Λ	Recruitment rate,
μ	Natural mortality rate,
β	Transmission rate,
δ	Disease induced deaths (ie. TB related deaths),
ρ	Relapse rate,
σ	Treatment rate,
γ	Rate of progression of individuals in E to active TB,
r	Reinfection parameter either endogenous or exogenous,
p	Proportion of individuals in S who develop latent TB after infection.

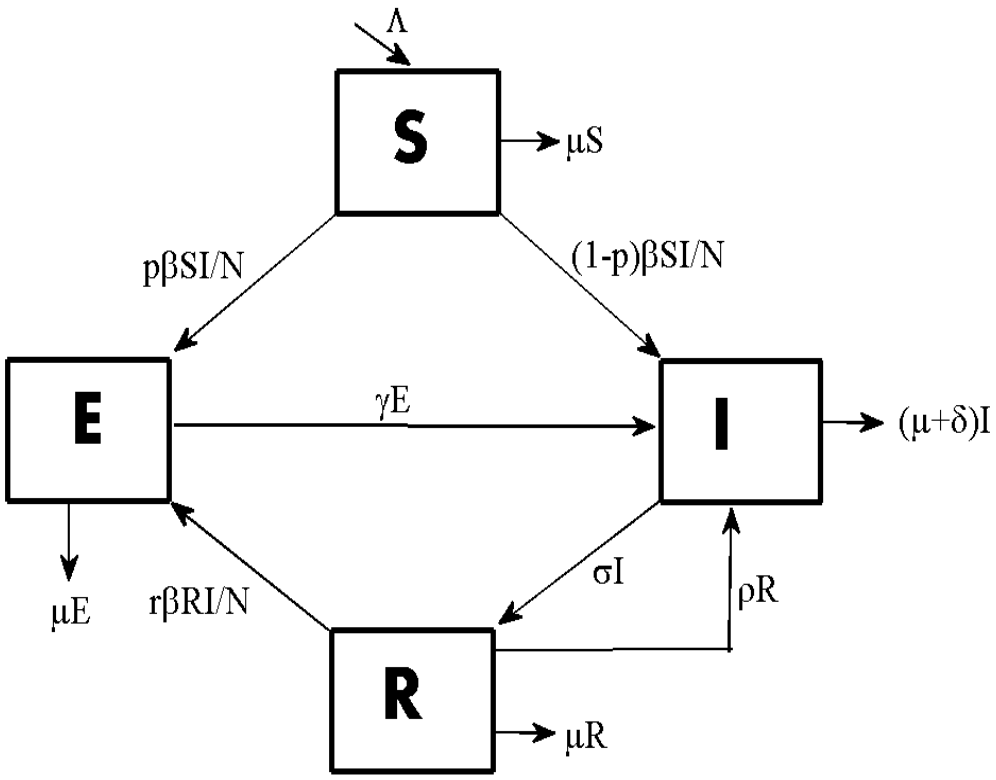


Figure 3.1: Simple SEIR model showing the transmission dynamics of TB.

individual populations. The population is assumed to mix homogeneously, that is every susceptible individual has an equal chance of being infected, and every infective has an equal chance of infecting a susceptible individual. Individuals move from one class/compartment to the other as their status with respect to TB changes with time. We assume that the susceptibles are recruited at a constant rate Λ per year through births and that the recruited individuals are all susceptible. The disease is transmitted at a rate β when a susceptible individual comes into contact with a proportion $\frac{I}{N}$

of infectious individuals. We assume that immediately after infection a proportion p of infected individuals may move to the exposed latent class, or a proportion $(1-p)$ of the infected individuals may develop or progress to active TB. It is assumed that most individuals remain in the exposed latent class for the rest of their lives and never develop active TB. However, those who eventually do develop active TB, either by exogenous or endogenous progression at a rate γ.

Individuals in class I are capable of transmitting the infection with transmission rate β. After successful treatment, infectives move to class R at a rate σ. The active TB class, I is thus populated by individuals from the latent class and individuals who relapse. Recovered individuals can either return to class I by relapse at a rate ρ or can be reinfected and move to E. Their susceptibility to infection when compared to susceptibles is measured by r. In all classes, individuals can die due to other unnatural causes at a rate μ and in addition, those in class I, can also die due to TB at a rate δ. We assume standard incidence. This allows for homogenous mixing such that each individual in the population is equally likely to contact each of the other individuals.

3.3 The model equations

The model depicted in Figure 3.1 is described by the following system of differential equations;

$$\left.\begin{aligned}
\frac{dS}{dt} &= \Lambda - \beta\tfrac{SI}{N} - \mu S, \\
\frac{dE}{dt} &= p\beta\tfrac{SI}{N} + r\beta\tfrac{RI}{N} - (\mu+\gamma)E, \\
\frac{dI}{dt} &= (1-p)\beta\tfrac{SI}{N} + \gamma E + \rho R - (\mu+\sigma+\delta)I, \\
\frac{dR}{dt} &= \sigma I - r\beta\tfrac{RI}{N} - (\mu+\rho)R,
\end{aligned}\right\} \tag{3.1}$$

where the parameters are as defined in Table 3.1. The susceptibles in compartment S and the recovered in compartment R acquire TB infection following contact with an infectious individual in compartment I at a rate,

$$\lambda = \frac{\beta I}{N}. \tag{3.2}$$

The variable λ is known as the force of infection, the rate at which susceptibles acquire infection.

Using (3.2), the system of equations (3.1) can be rewritten as

$$\left.\begin{aligned}
\frac{dS}{dt} &= \Lambda - \lambda S - \mu S, \\
\frac{dE}{dt} &= p\lambda S + r\lambda R - (\mu+\gamma)E, \\
\frac{dI}{dt} &= (1-p)\lambda S + \gamma E + \rho R - (\mu+\sigma+\delta)I, \\
\frac{dR}{dt} &= \sigma I - r\lambda R - (\mu+\rho)R.
\end{aligned}\right\} \tag{3.3}$$

The initial conditions for the above system of equations are given by,

$$S = S_0 \geq 0, \quad E = E_0 \geq 0, \quad I = I_0 \geq 0, \quad R = R_0 \geq 0. \tag{3.4}$$

The model system (3.3) will thus be studied in the biologically feasible region

$$\mathcal{P} = \left\{ (S,\ E,\ I,\ R) \in \mathbb{R}^4_+;\ N \leq \frac{\Lambda}{\mu} \right\}. \tag{3.5}$$

3.4 Positivity and boundedness of solutions

The region $\mathcal{P}$ should be positively invariant with respect to the model system (3.3). It is thus necessary to prove that all the variables $S(t)$, $E(t)$, $I(t)$ and $R(t)$ are non-negative for all time $t \geq 0$ and are bounded in $\mathcal{P}$. We state and prove the following theorem on the positivity and boundedness of the solutions, Castillo-Chavez and Feng [10].

Theorem 1. *Let the state variables be such that, $S(0) \geq 0$, $E(0) \geq 0$, $I(0) \geq 0$ and $R(0) \geq 0$. The solutions S, E, I and R of the model system (3.3) are positive for all $t \geq 0$. The region $\mathcal{P}$ is positively invariant and all the solutions starting in $\mathcal{P}$ enter or stay in $\mathcal{P}$, i.e $\mathcal{P}$ is bounded.*

Proof. Recall that the initial conditions are such that, $S = S_0 \geq 0$, $E = E_0 \geq 0$, $I = I_0 \geq 0$, $R = R_0 \geq 0$.

We prove that P is bounded by contradiction. Assume that there exists a first time, $t_s : S(t_s) = 0,\ S'(t_s) < 0$, and $S(t) \geq 0,\ E(t) \geq 0,\ I(t) \geq 0,\ R(t) \geq 0$, for $0 < t < t_s$. Then, either;

(1) there exists $t_e : E(t_e) = 0,\ E'(t_e) < 0$, and $S(t) \geq 0,\ E(t) \geq 0,\ I(t) \geq 0,\ R(t) \geq 0$,

for $0 < t < t_e$, or

(2) there exists $t_i : I(t_i) = 0,\ I'(t_i) < 0$, and $S(t) \geq 0,\ E(t) \geq 0,\ I(t) \geq 0,\ R(t) \geq 0$, for $0 < t < t_i$, or

(3) there exists $t_r : R(t_r) = 0,\ R'(t_r) < 0$ and $S(t) \geq 0,\ E(t) \geq 0,\ I(t) \geq 0,\ R(t) \geq 0$, for $0 < t < t_r$.

Applying the above conditions to system (3.3) we find that t_s, t_e, t_i and t_r cannot exist. In the first case,

$$S'(t_s) = \Lambda > 0, \tag{3.6}$$

which is a contradiction. Therefore S remains positive for all t. In the second case,

$$E'(t_e) \;=\; p\lambda(t_e)S(t_e) + r\lambda(t_e)R > 0, \tag{3.7}$$

which is a contradiction, and therefore E remains positive. In the third case,

$$I'(t_i) \;=\; (1-p)\lambda(t_i)S(t_i) + \gamma E(t_i) + \rho R(t_i) > 0, \tag{3.8}$$

which is a contradiction, and therefore I remains positive for all time t. In the last case,

$$R'(t_r) \;=\; \sigma I(t_r) > 0, \tag{3.9}$$

which is a contradiction, and therefore R remains positive. Thus in all cases, S, E, I and R remain positive.

To prove that $\mathcal{P}$ is positively invariant with respect to the model system (3.3), we adapt the proof for positive invariance in Safi and Garba [39]. Adding the four equations in (3.3) gives the change in the total population N over time so that,

$$\begin{aligned}
\frac{dN}{dt} &= \frac{d}{dt}(S+E+I+R) \\
&= \Lambda - \lambda S - \mu S + p\lambda S + r\lambda R - (\mu+\gamma)E + (1-p)\lambda S + \gamma E \\
&\quad + \rho R - (\mu+\sigma+\delta)I + \sigma I - r\lambda R - (\mu+\rho)R \\
&= \Lambda - \mu(S+E+I+R) - \delta I \\
N'(t) &= \Lambda - \mu N - \delta I \qquad (3.10)
\end{aligned}$$

Since $N(t) \geq I(t)$, then

$$\Lambda - (\mu+\delta)N(t) \leq N'(t) \leq \Lambda - \mu N(t), \qquad (3.11)$$

which implies that $N'(t)$ is bounded. We consider the upper bound for $N'(t)$ and solve for $N(t)$. We integrate both sides of

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

that is,

$$\int_{N(0)}^{N} \frac{dN}{\Lambda - \mu N} \leq \int_{0}^{t} du.$$

Hence,

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

Therefore

$$N(t) \leq N(0)e^{-\mu t} + \frac{\Lambda}{\mu}(1 - e^{-\mu t}), \tag{3.12}$$

for all $t > 0$. Thus

$$\lim_{t\to\infty} N(t) \leq \frac{\Lambda}{\mu}. \tag{3.13}$$

If $N(0) \leq \frac{\Lambda}{\mu}$, then $\frac{\Lambda}{\mu}$ is the upperbound for N. Alternatively if $N(0) > \frac{\Lambda}{\mu}$ then as $t \to \infty$, $N \to \frac{\Lambda}{\mu}$, that is all solutions starting in the region $\mathcal{P}$ enter or remain in $\mathcal{P}$ for all time. We thus conclude that the region

$$\mathcal{P} = \left\{(S,\ E,\ I,\ R) \in \mathbb{R}^4_+;\ N \leq \frac{\Lambda}{\mu}\right\}. \tag{3.14}$$

is positively invariant for the model system (3.3). □

Solutions of the model (3.3) are therefore considered to be both epidemiologically and mathematically well-posed in $\mathcal{P}$. Hence, it is sufficient to study the dynamics of the model (3.3) in the region $\mathcal{P}$.

3.5 Stability Analysis

3.5.1 Disease free equilibrium (DFE) and its stability

The disease free equilibrium of the model (3.3) is given by,

$$E_{q0} = (S_0,\ E_0,\ I_0,\ R_0) = \left(\frac{\Lambda}{\mu},\ 0,\ 0,\ 0\right). \tag{3.15}$$

The linear stability of E_{q0} is governed by the basic reproduction number $\mathcal{R}_0$, which is determined by using the next generation matrix method, by van den Driessche and Watmough [35].

3.5.2 Basic reproduction number and local stability of DFE

To determine the stability of E_{q0}, we first use the next generation method discussed by van den Driessche and Watmough [35] to determine $\mathcal{R}_0$. $\mathcal{R}_0$ is the number of secondary infections produced by a single infectious individual during his or her entire infectious period, when introduced to a wholly susceptible population. Using this method to compute $\mathcal{R}_0$, it is important to distinguish new infections from all the other changes in the population. For clarity we rearrange the system of equations so that the first m equations correspond to compartments with infection. In this case $m = 2$ out of the total number of $n = 4$ equations.

$$\begin{aligned}
\frac{dE}{dt} &= p\lambda S + r\lambda R - (\mu + \gamma)E, \\
\frac{dI}{dt} &= (1-p)\lambda S + \gamma E + \rho R - (\mu + \sigma + \delta)I, \\
\frac{dR}{dt} &= \sigma I - r\lambda R - (\mu + \rho)R, \\
\frac{dS}{dt} &= \Lambda - \lambda S - \mu S.
\end{aligned}$$

Thus, we let $\mathcal{F}_i$ be the rate of appearance of new infections in compartment i. Furthermore, let $\mathcal{V}_i$ be the rate of transfer of individuals into and out of compartment i.

Thus we represent the new infection matrix $\mathcal{F}$ and the transfer matrix $\mathcal{V}$ by,

$$\mathcal{F} = \begin{pmatrix} p\lambda S \\ \\ (1-p)\lambda S \end{pmatrix}$$

and

$$\mathcal{V} = \begin{pmatrix} (\mu+\gamma)E - r\lambda R \\ \\ (\mu+\sigma+\delta)I - \gamma E - \rho R \end{pmatrix}.$$

The next generation matrix comprises of two parts, matrices F and V^{-1} where both F and V are respectively $m \times m$ matrices for the new infections and for transition terms, defined by;

$$F = \left[\frac{\partial \mathcal{F}_i(x_0)}{\partial x_j}\right] \qquad \text{and} \qquad V = \left[\frac{\partial \mathcal{V}_i(x_0)}{\partial x_j}\right], \tag{3.16}$$

for $1 \leq i,\, j \leq m$. The vector x_0 represents the disease free equilibrium state, and in this case $x_0 = E_{q0}$. For our set of equations we have,

$$F = \begin{pmatrix} 0 & p\beta \\ \\ 0 & (1-p)\beta \end{pmatrix}$$

and

$$V = \begin{pmatrix} \mu+\gamma & 0 \\ \\ -\gamma & \mu+\sigma+\delta \end{pmatrix}.$$

The reproduction number for model (3.3) is the spectral radius ϑ of the next generation matrix FV^{-1}, i.e the dominant eigenvalue of FV^{-1} such that,

$$\mathcal{R}_0 = \vartheta(FV^{-1}),$$

where

$$V^{-1} = \begin{pmatrix} \frac{1}{\gamma+\mu} & 0 \\ \\ \frac{\gamma}{(\gamma+\mu)(\mu+\sigma+\delta)} & \frac{1}{\mu+\sigma+\delta} \end{pmatrix},$$

and

$$FV^{-1} = \begin{pmatrix} \frac{p\beta\gamma}{(\gamma+\mu)(\delta+\mu+\sigma)} & \frac{p\beta}{\delta+\mu+\sigma} \\ \\ \frac{(1-p)\beta\gamma}{(\gamma+\mu)(\delta+\mu+\sigma)} & \frac{(1-p)\beta}{\delta+\mu+\sigma} \end{pmatrix}$$

To find the eigenvalues ω of FV^{-1}, we solve the equation

$$\left|\mathbf{FV}^{-1} - \omega\mathbf{I}\right| = 0.$$

$\mathbf{I}$ is an identity matrix. We obtain two roots $\omega_1 = 0$, and

$$\omega_2 = \frac{\beta(\gamma + \mu(1-p))}{(\gamma+\mu)(\delta+\mu+\sigma)}.$$

Thus, the dominant eigenvalue is ω_2. Hence

$$\mathcal{R}_0 = \frac{\beta(\gamma + \mu(1-p))}{(\gamma+\mu)(\delta+\mu+\sigma)}.$$

$\mathcal{R}_0$ determined this way ensures that the equilibrium point E_{q0} is locally asymptotically stable. The theorem below summarizes the results for the linear stability of the disease free equilibrium point E_{q0}, see van den Driessche and Watmough [35].

Theorem 2. *The disease free-equilibrium is locally asymptotically stable when the basic reproduction number $\mathcal{R}_0 < 1$, and unstable for $\mathcal{R}_0 > 1$.*

The epidemiological meaning of Theorem 2 is that, in general when $\mathcal{R}_0 < 1$, the introduction of a small number of new infectious individuals in the population would not cause large disease outbreaks. Furthermore, since the disease free equilibrium is

locally asymptotically stable the disease will die out. Conversely when $\mathcal{R}_0 > 1$ the disease will invade and persist in the population.

3.5.3 Endemic equilibrium point (EEP) and stability

The system of equations (3.3), has an endemic equilibrium point (EEP) given by,

$$E_{q1} = (S^*,\ E^*,\ I^*,\ R^*).$$

In terms of the force of infection at equilibrium λ^*, the state variables are given by;

$$S^* = \frac{\Lambda}{\lambda^* + \mu}, \qquad R^* = \frac{\sigma I^*}{(r\lambda^* + \mu + \rho)}, \qquad E^* = \frac{\frac{p\lambda^*\Lambda}{\lambda^*+\mu} + \frac{rI^*\lambda^*\sigma}{r\lambda^*+\mu+\rho}}{\gamma + \mu}$$

and I^* is given by the expression,

$$I^* = \frac{(1-p)\lambda^* S^* + \gamma E^* + \rho R^*}{(\mu + \sigma + \delta)}.$$

From (3.3), we solve the equation,

$$\lambda^* N - \beta I^* = 0. \tag{3.17}$$

This gives a polynomial,

$$\lambda^* \Lambda (a_2 \lambda^{*2} + a_1 \lambda^* + a_0) = 0 \tag{3.18}$$

in terms of λ^*, where $\lambda^* \geq 0$. The variables a_2, a_1 and a_0 are given by,

$$\begin{aligned}
a_2 &= r(\gamma + p\delta + \mu + \sigma), \\
a_1 &= (\gamma + p\delta + \mu)(\mu + \rho) + (\gamma + \mu)\sigma + r((\gamma + \mu)(\delta + \mu) - \beta(\gamma + \mu - p\mu) + \mu\sigma), \\
a_0 &= (\gamma + \mu)(\delta + \mu + \sigma) - \beta(\gamma + \mu - \mu\mathrm{p}) \\
&= (\gamma + \mu)(\delta + \mu + \sigma) - \left[\frac{\beta(\gamma + \mu(1-p))}{(\gamma + \mu)(\delta + \mu + \sigma)}\right]
\end{aligned}$$

$$= \quad (\gamma + \mu)(\delta + \mu + \sigma)\left[1 - \mathcal{R}_0\right].$$

All the parameters are assumed to be positive. It follows then that $a_2 > 0$ always. The roots of the polynomial are given by;

$$\lambda^* = 0, \qquad \lambda^*_{1,2} = \frac{-a_1 \pm \sqrt{a_1^2 - 4a_2a_0}}{2a_2}, \tag{3.19}$$

The zero root $\lambda^* = 0$ corresponds to the disease free equilibrium discussed above. So we can see from the expression for a_0 that,

$$a_0 = \begin{cases} > 0 & \text{if } \mathcal{R}_0 < 1 \\ = 0 & \text{if } \mathcal{R}_0 = 1 \\ < 0 & \text{if } \mathcal{R}_0 > 1. \end{cases}$$

We look at the following cases to analyze the stability of the model. We are only interested in the non-negative steady states.

Case 1: $a_0 > 0$ i.e $\mathcal{R}_0 < 1$, and $a_1^2 - 4a_2a_0 \geq 0$

In this case we can either have no positive solutions at all or we can have positive solutions depending on the sign of a_1.

(i) If $a_1 < 0$, then both solutions ${\lambda_1}^*$ and ${\lambda_2}^*$ are positive, i.e two endemic equilibria are obtained.

(ii) If $a_1 > 0$, then both solutions ${\lambda_1}^*$ and ${\lambda_2}^*$ are negative, i.e no endemic equilibrium. If $a_1^2 - 4a_2a_0 = 0$, there is no endemic equilibrium for $a_1 > 0$ and there is only one endemic equilibrium for $a_1 < 0$.

Case 2: $a_0 < 0$ i.e $R_0 > 1$, for $a_1^2 - 4a_2a_0 \geq 0$

In this case we can either have one positive solution of λ^* and negative solutions for either $a_1 > 0$ or $a_1 < 0$. So there is a unique endemic equilibrium.

Case 1(i) implies the possibility of backward bifurcation when the locally asymptotically stable DFE co-exists with the locally asymptotically stable EEP for $\mathcal{R}_0 < 1$. The epidemiological significance of the backward bifurcation is that even though $\mathcal{R}_0 < 1$ is a necessary condition for the disease elimination (or, in this case, for controlling TB), it is no longer a sufficient condition. If the model exhibits a backward bifurcation, the disease may still persist for $\mathcal{R}_0 < 1$. So $\mathcal{R}_0 < 1$, may not necessarily mean that the epidemic dies out. By Garba et al. [15], disease elimination would then depend on the initial size of the state variables S, E, I and R.

The qualitative behavior of an epidemic system with a backward bifurcation differs from that of a system with a forward bifurcation. If there is a forward bifurcation at $\mathcal{R}_0 = 1$ it is not possible for a disease to invade a population if $\mathcal{R}_0 < 1$ because the system will return to the disease-free equilibrium $I = 0$ if some infectives are introduced into the population. On the other hand, if there is a backward bifurcation at $\mathcal{R}_0 = 1$ and enough infectives are introduced into the population to put the initial state of the system above the unstable endemic equilibrium with $\mathcal{R}_0 < 1$, the system will approach the asymptotically stable endemic equilibrium, Brauer [40]. In a case of forward bifurcation, the disease may be controlled by decreasing $\mathcal{R}_0$ to 1, while for backward bifurcations $\mathcal{R}_0 = 1$ may not be sufficient it will therefore be necessary to

bring $\mathcal{R}_0$ well below 1. It is important to identify backward bifurcations to obtain thresholds for the control of disease.

3.6 Parameter sensitivity analysis

3.6.1 Sensitivity analysis of σ and β

In order to implement possible intervention and control strategies successfully it is useful to know which parameters $\mathcal{R}_0$ is most sensitive to. We carry out the sensitivity analysis on the treatment rate σ and on the transmission rate β. We are interested in knowing what effect these parameters have on $\mathcal{R}_0$ as they increase. We first investigate the change in $\mathcal{R}_0$ with respect to σ by computing;

$$\begin{aligned}\frac{\partial \mathcal{R}_0}{\partial \sigma} &= \frac{\partial}{\partial \sigma}\left[\frac{\beta(\gamma+\mu(1-p))}{(\gamma+\mu)(\delta+\mu+\sigma)}\right], \\ &= -\frac{\beta(\gamma+\mu(1-p))}{(\gamma+\mu)(\delta+\mu+\sigma)^2}.\end{aligned}$$

Since $p \in (0,1)$ and all the parameters are assumed to be positive, we therefore have

$$\frac{\partial \mathcal{R}_0}{\partial \sigma} < 0.$$

This implies that the basic reproduction number, $\mathcal{R}_0$, decreases with the increase in the treatment rate σ. In other words a high treatment rate (possibly due to successful treatment) has a positive and desirable effect on $\mathcal{R}_0$. It slows down the number of new infections each infectious individual can produce. This result is consistent with results

from the literature [22, 31] because the treatment rate is increased through interventions, such as more efficient treatment or larger treatment coverage. This leads to each of the infected individuals infecting a smaller number of individuals than before being treated. So this parameter is important and the higher its value, the better. This also has an implication on other control strategies and diagnosis. More accurate diagnosis and testing campaigns lead to more people being treated and a higher treatment rate.

We next investigate the change in $\mathcal{R}_0$ with respect to β by computing;

$$\begin{aligned} \frac{\partial \mathcal{R}_0}{\partial \beta} &= \frac{\partial}{\partial \beta}\left[\frac{\beta(\gamma+\mu(1-p))}{(\gamma+\mu)(\delta+\mu+\sigma)}\right], \\ &= \frac{\gamma+\mu(1-p)}{(\gamma+\mu)(\delta+\mu+\sigma)}. \end{aligned}$$

Again, because $p \in (0,1)$ and all the parameters are assumed to be positive, we have

$$\frac{\partial \mathcal{R}_0}{\partial \beta} > 0.$$

This implies that the reproduction number, $\mathcal{R}_0$, in the population increases with the transmission, β. In other words, if the transmission rate is high, the expected number of new cases produced by an infectious individual is also high. Thus the intervention and control strategies should aim at lowering the transmission rate, β. This can be done through control strategies and interventions that will lead to less transmission, such as less crowding, and taking individual and community precautionary measures.

3.6.2 Effect of the transmission rate β

We investigate the effect and the importance of the transmission parameter on the disease dynamics through simulations, see Table 3.3. This was done by keeping all other parameters fixed but varying the values of β and checking what effect this had on the basic reproduction number, $\mathcal{R}_0$. Recall that the sensitivity analysis showed that

Transmission rate, β	$\mathcal{R}_0$,
0.17866	0.3250
0.27866	0.5070
0.37866	0.6889
0.4866	0.8708
0.52866	0.9618
0.53996	0.9824
0.549680	**1.000**
0.57866	1.0528
0.6789	1.2351
0.766	1.4311

Table 3.3: Transmission rate, β, versus basic reproduction number, $\mathcal{R}_0$, to show linear relationship.

$$\frac{\partial \mathcal{R}_0}{\partial \beta} > 0.$$

This implies that the number of secondary cases $\mathcal{R}_0$ in the population increases with the transmission rate, β. Indeed this is true, as can be shown by results given in Table 3.3 which shows that, $\mathcal{R}_0$ increases with β. The results in Table 3.3 shows that, with other parameters fixed, then $\mathcal{R}_0 < 1$ for values of $\beta < 0.54968$. This can be achieved through carefully selected intervention strategies. Figure 3.2 shows the linear relationship between the reproductive rate and the transmission rate β.

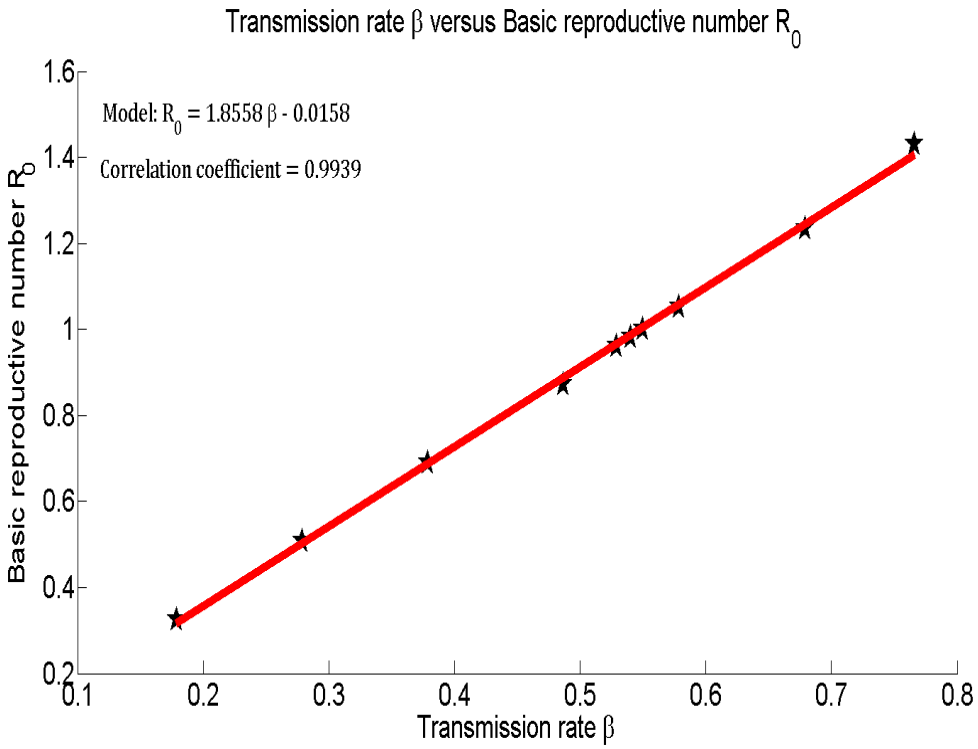


Figure 3.2: Linear relationship between $\mathcal{R}_0$ and β.

3.6.3 Effect of the treatment rate σ

We also investigated the effect and the importance of treatment parameter σ on the disease control. This was done by keeping all the parameters fixed but varying σ to see what effect this has on the basic reproduction number, $\mathcal{R}_0$. The sensitivity analysis

Treatment rate σ	Basic reproduction number $\mathcal{R}_0$
0.3565	1.4446
0.4565	1.1907
0.52866	1.0528
0.5650	**1.000**
0.57866	0.9618
0.6565	0.8810
0.6765	0.8587
0.7765	0.7621
0.8100	0.7344
0.8765	0.6851

Table 3.4: Treatment rate, σ, versus basic reproduction number, $\mathcal{R}_0$, to show linear relationship.

showed that

$$\frac{\partial \mathcal{R}_0}{\partial \sigma} < 0,$$

meaning that, the number of secondary cases $\mathcal{R}_0$ in the population decreases with the transmission σ. Indeed this is true as can be confirmed from Table 3.4. If relevant intervention methods are put in place to keep the treatment rate $\sigma > 0.565$, then disease can be controllable. Figure 3.3 shows the change in $\mathcal{R}_0$ as σ increases.

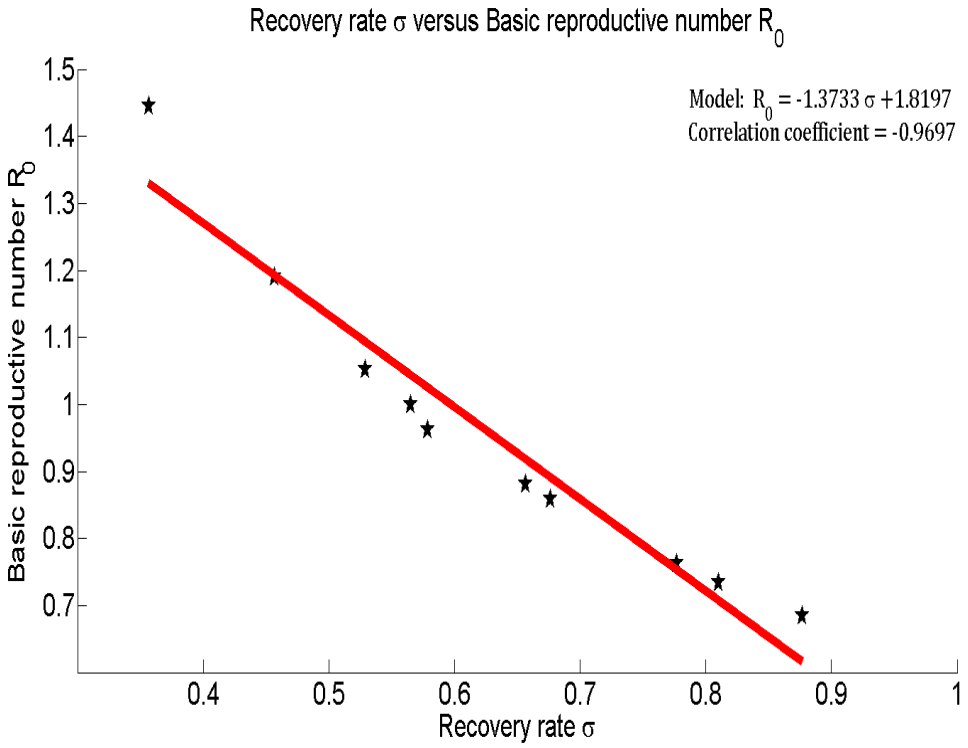


Figure 3.3: Linear relationship between $\mathcal{R}_0$ and β.

3.7 Summary

We have developed and analysed a new SEIR TB model. The model depicts the dynamics and spread of the TB disease in a population. Some assumptions are made

in the design of this model, for instance we assume standard incidence. This means that there is homogenous mixing such that each individual in the population is equally likely to contact each of the other individuals. This model captures information about the disease and gives some insights into the dynamics and spread of the disease. The model analysis highlights the importance of treating active TB cases, while maintaining low transmission rates for the disease.

We provided a proof for positivity and boundedness of the solutions. Stability analysis for both disease free equilibrium and the endemic equilibrium for the SEIR model were found. We calculated the reproduction number using the next generation matrix. We have shown that TB infection rates are lowest when there is high treatment and small transmission rate. For these reasons preventative therapy may be an essential component of TB control. The model presented in this chapter will serve as a base for the model incorporating preventative therapy, which is introduced in the next chapter.

Chapter 4

The SEIR TB model with preventative therapy as a post exposure prophylaxis (PEP) vaccine.

4.1 Introduction

In the previous chapter the simple SEIR model was presented and indicated the need to keep transmission rate low. From the literature review, for instance the recommendation in van den Driessche et al [37]. One way to do this is through preventative therapy of latently infected individuals. When the latently infected individuals receive

post-exposure prophylaxis (PEP) vaccine (which we also call preventative therapy or chemoprophylaxis) their progression to the infectious class is delayed leading to a decrease in the transmission rate. In this chapter we will extend the model from Chapter 3 to include treatment of the latently infected class, E. This type of treatment is called a chemoprophylaxis or preventative therapy and act as a post-exposure prophylaxis (PEP) vaccine.

4.2 Model Formulation

Isoniazid preventative therapy (IPT) for HIV−TB co-infected individuals reduces the reactivation of latent *Mycobacterium tuberculosis* infections and is being evaluated as a potential strategy for improving TB control, Cohen et al. [41]. We present a transmission model, see Figure 4.1, to control the transmission dynamics of TB. In our model as we did in Chapter 3, we divide the host population into four classes of individuals, namely the susceptibles (S), exposed or latent (E), infectious individuals (I), and recovered individuals (R). The R class is also populated by individuals who have received the preventative therapy to treat the latent TB cases. The total population N, is thus given by

$$N = S + E + I + R.$$

The state variables $S,\ E,\ I$ and R are all assumed to be positive, as they represent individual populations and to be biological plausible. The population is also assumed

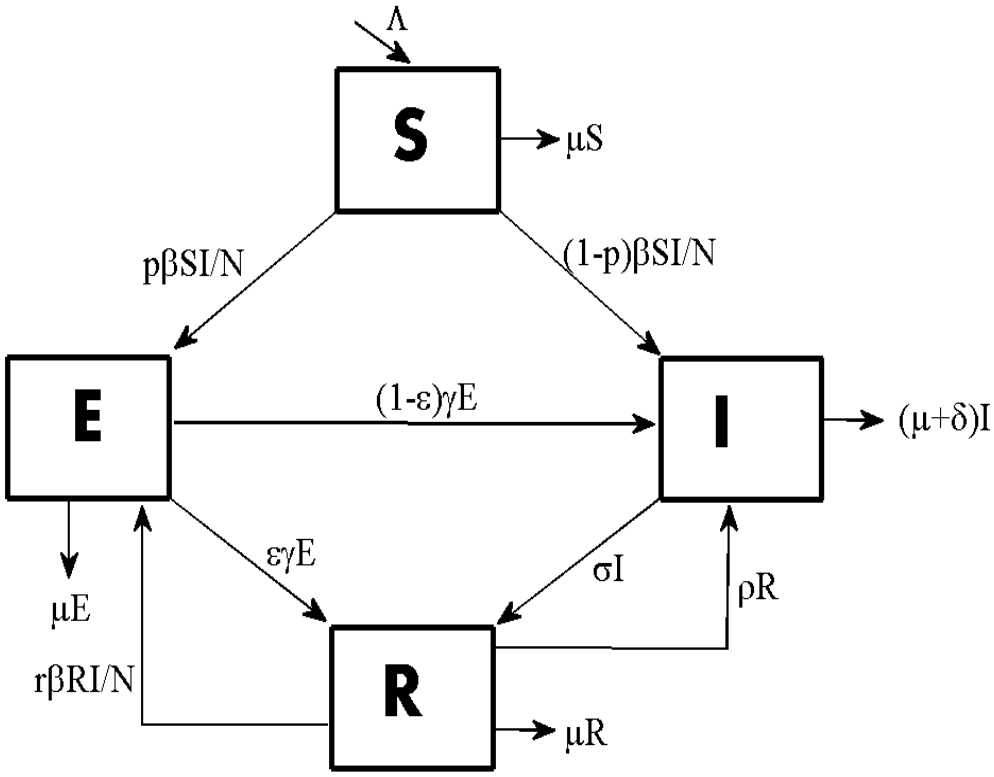


Figure 4.1: Model diagram illustrating the transmission dynamics of TB for a simple SEIR model with the post-exposure vaccination for the of latently infected individuals,E, using a preventative therapy.

to mix homogeneously. Individuals move from one class to the other as their TB status changes with time. The susceptibles are recruited at a constant rate of Λ per year and the recruited individuals are all susceptible. The disease is transmitted at a rate β when a susceptible individual comes into contact with a proportion $\frac{I}{N}$ of infectious individuals. Immediately after infection a proportion p of individuals may move to the

latent class, or a proportion $(1-p)$ of the infected individuals may develop or progress directly to active TB. Most individuals remain in the exposed latent class for the rest of their lives and never develop active TB. However, those who eventually do, develop active TB at a rate γ, γ is the progression rate to active TB. Furthermore we assume effective latent infection post exposure vaccination exists, that is, the individuals in class E can be vaccinated at the rate ϵ. Latent treatment cures an individual, but an individual could still be re-infected. Individuals in class I are capable of transmitting the infection. After successful treatment, infectives move to the R class at a rate σ, σ is the treatment rate of the infectious class. So, the active TB class, I is populated by individuals from the latent class and individuals who relapse. Recovered individuals can either return to class I through relapse at a rate ρ or can be re-infected and move to E. Their susceptibility to infection, when compared to susceptibles, is measured by r. In all classes, individuals can die due to other natural causes besides TB, or unnatural causes, at a rate μ and in addition, those in class I, can also die due to TB at a rate δ. The new system of differential equations is given 4.1. The differential equations that describe the model depicted in Figure 4.1 can be written down as,

$$\left.\begin{aligned}
\frac{dS}{dt} &= \Lambda - \lambda S - \mu S, \\
\frac{dE}{dt} &= p\lambda S + r\lambda R - (\mu+\gamma)E, \\
\frac{dI}{dt} &= (1-p)\lambda S + (1-\epsilon)\gamma E + \rho R - (\mu+\sigma+\delta)I, \\
\frac{dR}{dt} &= \sigma I + \epsilon\gamma E - r\lambda R - (\mu+\rho)R.
\end{aligned}\right\} \tag{4.1}$$

The initial conditions of the above system of equations are given by,

$$S = S_0 \geq 0, \quad E = E_0 \geq 0, \quad I = I_0 \geq 0, \quad R = R_0 \geq 0. \tag{4.2}$$

So, model system (4.1) will be studied in the following biologically feasible region

$$\mathcal{P} = \left\{ (S,\ E,\ I,\ R) \in \mathbb{R}^4_+;\ N \leq \frac{\Lambda}{\mu} \right\}. \tag{4.3}$$

4.3 Proof of positivity and boundedness of solutions

The region $\mathcal{P}$ should be positively invariant with respect to the model system (4.1). It is thus necessary to ensure that all the variables $S(t)$, $E(t)$, $I(t)$ and $R(t)$ are non-negative for all time t, that is solutions of the model system (4.1) with positive initial values remain positive for all time $t \geq 0$ and are bounded in $\mathcal{P}$. We state and prove a theorem on positivity and boundedness of the solutions.

Theorem 3. *Let the state variables be such that, $S(0) \geq 0$, $E(0) \geq 0$, $I(0) \geq 0$ and $R(0) \geq 0$. The solutions S, E, I and R of the model system (4.1) are positive for all $t \geq 0$. The region $\mathcal{P}$ is positively invariant and all the solutions starting in $\mathcal{P}$ enter or stay in $\mathcal{P}$, i.e $\mathcal{P}$ is bounded.*

Proof. Recall that the initial conditions are such that,

$$S = S_0 \geq 0, \quad E = E_0 \geq 0, \quad I = I_0 \geq 0, \quad R = R_0 \geq 0.$$

The proof, as in the case of Theorem(1), is by contradiction. Assume that there exists a first time,

$t_s : S(t_s) = 0,\ S'(t_s) < 0$ and $S(t) \geq 0,\ E(t) \geq 0,\ I(t) \geq 0,\ R(t) \geq 0,$

for $0 < t < t_s$. Then, either;

(1) there exists $t_e : E(t_e) = 0,\ E'(t_e) < 0$ and $S(t) \geq 0,\ E(t) \geq 0,\ I(t) \geq 0,\ R(t) \geq 0,$

for $0 < t < t_e$, or

(2) there exists

$t_i : I(t_i) = 0,\ I'(t_i) < 0$ and $S(t) \geq 0,\ E(t) \geq 0,\ I(t) \geq 0,\ R(t) \geq 0,$

for $0 < t < t_i$, or

(3) there exists

$t_r : R(t_r) = 0,\ R'(t_r) < 0$ and $S(t) \geq 0,\ E(t) \geq 0,\ I(t) \geq 0,\ R(t) \geq 0,$

for $0 < t < t_r$.

In the first case,

$$S'(t_s) = \Lambda > 0, \tag{4.4}$$

which is a contradiction therefore S remains positive. In the second case,

$$E'(t_e) \ = \ p\lambda(t_e)S(t_e) + r\lambda(t_e)R > 0, \tag{4.5}$$

which is a contradiction, therefore E remains positive. In the third case,

$$I'(t_i) \ = \ (1-p)\lambda(t_i)S(t_i) + (1-\epsilon)\gamma E(t_i) + \rho R(t_i) > 0, \tag{4.6}$$

which is a contradiction, therefore I remains positive. In the last case,

$$R'(t_r) \;=\; \sigma I(t_r) + \epsilon\gamma E(t_r) > 0, \tag{4.7}$$

which is a contradiction, therefore R remains positive. Thus, in all cases, S, E, I and R remain positive.

To prove that $\mathcal{P}$ is positively invariant with respect to the model system (4.1), we adapt the proof for positive invariance in [39]. We therefore continue our proof as follows. Adding equations of (4.1) gives the change in the total population N over time so that,

$$\begin{aligned}
\frac{dN}{dt} &= \frac{d}{dt}(S+E+I+R) \\
&= \Lambda - \lambda S - \mu S + p\lambda S + r\lambda R - (\mu+\gamma)E + (1-p)\lambda S + (1-\epsilon)\gamma E \\
&\quad +\rho R - (\mu+\sigma+\delta)I + \sigma I + \epsilon\gamma E - r\lambda R - (\mu+\rho)R \\
&= \Lambda - \mu(S+E+I+R) - \delta I.
\end{aligned}$$

Hence $N'(t) = \Lambda - \mu N - \delta I$. Since $N(t) \geq I(t)$, then

$$\Lambda - (\mu+\delta)N(t) \leq N'(t) \leq \Lambda - \mu N(t) \tag{4.8}$$

implying that $N'(t)$ is bounded. We consider the upper bound of $N'(t)$ and solve for $N(t)$. Following the same discussion as used in Section 3.4 it is easy to show that,

$$N(t) \;\leq\; N(0)e^{-\mu t} + \frac{\Lambda}{\mu}(1-e^{-\mu t}), \qquad \forall t > 0. \tag{4.9}$$

Following the discussion in Section 3.4, it follows that all solutions starting in the region $\mathcal{P}$ enter or stay in $\mathcal{P}$ and that the region

$$\mathcal{P} = \left\{ (S,\ E,\ I,\ R) \in \mathbb{R}^4_+;\ N \leq \frac{\Lambda}{\mu} \right\}. \tag{4.10}$$

is positively invariant for the model system (4.1). This completes the proof for positive invariance and boundedness of the solutions. □

Solutions of the model system (4.1) are therefore considered to be both epidemiologically and mathematically well-posed in $\mathcal{P}$ [15]. Hence, it is sufficient to study the dynamics of the model (4.1) in the region $\mathcal{P}$.

4.4 Stability Analysis

4.4.1 Disease free equilibrium (DFE) and its stability

The disease free equilibrium of the model (4.1) is given by,

$$E_{q0} = (S_0,\ E_0,\ I_0,\ R_0) = \left(\frac{\Lambda}{\mu},\ 0,\ 0,\ 0 \right). \tag{4.11}$$

The linear stability of E_{q0} is governed by the basic reproduction number, $\mathcal{R}_0$, which is determined by using the next generation matrix method, as discussed by van den Driesche and Watmough [35]. The approach is similar to that outlined in Section 3.5 and for clarity we sort the equations so that the first m equations correspond to compartments with infection. In this case $m = 3$ out of a total of $n = 4$ equations.

$$\frac{dE}{dt} = p\lambda S + r\lambda R - (\mu + \gamma)E,$$

$$\begin{aligned}
\frac{dI}{dt} &= (1-p)\lambda S + (1-\epsilon)\gamma E + \rho R - (\mu+\sigma+\delta)I, \\
\frac{dR}{dt} &= \sigma I + \epsilon\gamma E - r\lambda R - (\mu+\rho)R, \\
\frac{dS}{dt} &= \Lambda - \lambda S - \mu S.
\end{aligned}$$

The matrices $\mathcal{F}$ and $\mathcal{V}$ are respectively given by,

$$\mathcal{F} = \begin{pmatrix} p\lambda S + r\lambda R \\ \\ (1-p)\lambda S \end{pmatrix},$$

and

$$\mathcal{V} = \begin{pmatrix} (\mu+\gamma)E \\ \\ (\mu+\sigma+\delta)I - (1-\epsilon)\gamma E - \rho R \end{pmatrix}.$$

The $m \times m$ matrices F and V for the new infections and for transition are defined by equations (3.16) where

$$F = \begin{pmatrix} 0 & p\beta \\ \\ 0 & (1-p)\beta \end{pmatrix},$$

and

$$V = \begin{pmatrix} \mu+\gamma & 0 \\ \\ -(1-\epsilon)\gamma & \mu+\sigma+\delta \end{pmatrix}.$$

The eigenvalues of FV^{-1} are found to be $\omega_1 = 0$ and

$$\omega_2 = \frac{\beta\left(p\gamma(1-\epsilon) + (1-p)(\gamma+\mu)\right)}{(\gamma+\mu)(\mu+\sigma+\delta)}.$$

Since the dominant eigenvalue is ω_2, then

$$\mathcal{R}_0 = \frac{\beta\left(p\gamma(1-\epsilon) + (1-p)(\gamma+\mu)\right)}{(\gamma+\mu)(\mu+\sigma+\delta)}.$$

This ensures that the equilibrium point, E_{q0}, is locally asymptotically stable. The similar results on the linear stability of the disease free equilibrium point, E_{q0}, are summarised in Theorem 2 in Section 3.5.2.

4.4.2 Endemic equilibrium point (EEP) and its stability

The system of equations (4.1), has a endemic equilibrium point(EEP) given by,

$$E_{q1} = (S^*,\ E^*,\ I^*,\ R^*).$$

In terms of the force of infection λ^*, the state variables are given by;

$$\begin{aligned} S^* &= \frac{\Lambda}{\lambda^* + \mu}, \\ E^* &= \frac{rR\lambda^{*2} + p\lambda^*\Lambda + rR\lambda^*\mu}{(\gamma+\mu)(\lambda^*+\mu)}, \\ R^* &= \frac{p\gamma\epsilon\lambda^*\Lambda + I^*(\gamma+\mu)(\lambda^*+\mu)\sigma}{(\lambda^*+\mu)(r\lambda^*(\gamma-\gamma\epsilon+\mu)+(\gamma+\mu)(\mu+\rho))}. \end{aligned}$$

and I^* is given by the following expression,

$$I^* = \frac{(1-p)\lambda^* S^* + (1-\epsilon)\gamma E^* + \rho R^*}{(\mu+\sigma+\delta)}.$$

From (4.1), we obtain the polynomial,

$$\lambda^*\Lambda(a_2\lambda^{*2} + a_1\lambda^* + a_0) = 0, \tag{4.12}$$

The parameters a_2, a_1 and a_0 are given by

$$\begin{aligned} a_2 &= \mu r(\gamma(1-\epsilon)+\mu) + (\ \gamma+\mu)(\mu+\rho) \\ a_1 &= \mu(\gamma - \gamma\epsilon + (\delta+\mu)) + (r\gamma - \gamma\epsilon + \sigma\mu + (\gamma+\mu)(\mu+\sigma+\delta)) \\ a_0 &= -\beta\left[(p\gamma(1-\epsilon) + (1-p)(\gamma+\mu))\right] + (\mu+\gamma)(\mu+\sigma+\delta) \\ &= (\mu+\gamma)(\mu+\sigma+\delta) - \beta\left[(p\gamma(1-\epsilon) + (1-p)(\gamma+\mu))\right] \\ &= (\mu+\gamma)(\mu+\sigma+\delta)\left[1 - \left[\frac{\beta\left(p\gamma(1-\epsilon) + (1-p)(\gamma+\mu)\right)}{(\gamma+\mu)(\mu+\sigma+\delta)}\right]\right] \\ &= (\mu+\gamma)(\mu+\sigma+\delta)\left[1-\mathcal{R}_0\right]. \end{aligned}$$

The roots of (4.12) are given by the earlier equation (3.19) which is found on page where,

$$a_0 = \begin{cases} > 0 & \text{if } \mathcal{R}_0 < 1 \\ < 0 & \text{if } \mathcal{R}_0 > 1. \end{cases}$$

We look at the following cases to analyze the stability. We are only interested in the non-negative steady states.

Case 1: $a_0 > 0$ i.e $\mathcal{R}_0 < 1$, and for $a_1^2 - 4a_2a_0 \geq 0$. In this case we can either have no positive solutions at all or we can have the positive solutions depending on the sign of a_1.

(i) If $a_1 < 0$, then both solutions λ_1 and λ_2 are positive, i.e two endemic equilibria are obtained.

(ii) If $a_1 > 0$, then both solutions λ_1 and λ_2 are negative, i.e no endemic equilibrium exists. If $a_1^2 - 4a_2a_0 = 0$, there is no endemic equilibrium for $a_1 > 0$ and there is only one endemic equilibrium for $a_1 < 0$.

Case 2: $a_0 < 0$ i.e $R_0 > 1$, for $a_1^2 - 4a_2a_0 \geq 0$ and also for $a_1^2 - 4a_2a_0 = 0$. In this case we can either have one positive solution of λ^* and negative solutions, for either $a_1 > 0$ or $a_1 < 0$. So there is a unique endemic equilibrium.

Case 1(i) implies the possibility of backward bifurcation when the locally asymptotically stable DFE co-exist with the locally asymptotically stable EEP for $\mathcal{R}_0 < 1$. The epidemiological significance of the backward bifurcation is that, even though $\mathcal{R}_0 < 1$ is a necessary condition for disease elimination (or, in this case, for controlling TB), it is

no longer a sufficient condition. Because if the model exhibits a backward bifurcation, the disease may still persist for $\mathcal{R}_0 < 1$. So $\mathcal{R}_0 < 1$ may not necessarily mean that the epidemic dies out. By [15] disease elimination would then depend on the initial size of the state variables.

4.5 Sensitivity analysis and parameters

In this section we investigate the sensitivity of $\mathcal{R}_0$ on key disease parameters.

4.5.1 Sensitivity analysis of ϵ, σ and β

We carry out sensitivity analysis on the latent vaccination rate ϵ, recovery rate σ and of the transmission rate β, on $\mathcal{R}_0$. We are interested in exploring further the effect that these parameters have on $\mathcal{R}_0$ as they increase. We first investigate the change in $\mathcal{R}_0$ with respect to ϵ by computing;

$$\begin{aligned}\frac{\partial \mathcal{R}_0}{\partial \epsilon} &= \frac{\partial}{\partial \epsilon}\left[\frac{\beta\left(p\gamma(1-\epsilon)+(1-p)(\gamma+\mu)\right)}{(\gamma+\mu)(\mu+\sigma+\delta)}\right] \\ &= -\frac{\beta\gamma p}{(\gamma+\mu)(\delta+\mu+\sigma)}.\end{aligned}$$

Since $\{p \in (0,1)\}$ and all the parameters are assumed to be positive, we therefore have

$$\frac{\partial \mathcal{R}_0}{\partial \epsilon} < 0.$$

This implies that the reproduction number $\mathcal{R}_0$ in the population decreases with the treatment rate of latently infected individuals ϵ. In other words, a high treatment rate for latently infected individuals has a positive effect on disease intervention and control because it decreases the number of new infections that each infectious individual can produce. This is consistent with literature [22] and expectation, we know that if the recovery rate is increased through interventions, such as more efficient treatment or larger treatment coverage, the number of new infections would decrease. So the parameter ϵ is important and intervention and control strategies should be aimed at increasing it. This also has implication for control strategies such as diagnosis. Increasing diagnosis through early testing as well as increasing the number of treated individuals both depend on the cost-effectiveness since it is only the countries with enough funds that can implement this strategy of identifying and treating latently infected individuals. In other words, the strategy requires first of all testing for latent TB in all people who are known to have been exposed to TB. In practice, people who could have had close contact to TB infected people are family members, neighbors and colleagues at work, schools or churches. More accurate diagnosis and testing campaigns lead to more people being treated, giving a higher recovery rate in addition to reduction of the probability of infectious contacts.

In order to understand the effect of increasing the recovery rate through treatment, we then investigate the change in $\mathcal{R}_0$ with respect to σ by computing;

$$\frac{\partial \mathcal{R}_0}{\partial \sigma} = \frac{\partial}{\partial \sigma}\left[\frac{\beta\left(p\gamma(1-\epsilon)+(1-p)(\gamma+\mu)\right)}{(\gamma+\mu)(\mu+\sigma+\delta)}\right],$$

$$= -\frac{\beta((1-p)(\gamma+\mu)+\gamma p(1-\epsilon))}{(\gamma+\mu)(\delta+\mu+\sigma)^2}.$$

Because $p \in (0,1)$, $\epsilon \in (0,1)$ and all the parameters are assumed to be positive, we therefore have

$$\frac{\partial \mathcal{R}_0}{\partial \sigma} < 0.$$

This implies that the number of secondary cases $\mathcal{R}_0$ in the population will decrease with increasing recovery rate σ. In other words the high treatment rate implied by a higher σ, has a positive effect on $\mathcal{R}_0$ because it decreases the number of new infections that each infectious individual can produce through reducing the time of stay in the infectious class. This result is consistent with literature [31] and is realistic. It implies that increasing the recovery rate through interventions such as more efficient treatment or larger treatment coverage leads to each of the infected individuals infecting a smaller number of individuals than before. Consequently the parameter of post-exposure vaccine, ϵ, is also important and should be kept as high as possible. It also depends on control strategies such as diagnosis. More accurate testing and diagnosis campaigns lead to more people being treated with a higher recovery rate. Thus the impact of σ on $\mathcal{R}_0$ is similar to that of ϵ.

Finally we investigate the change in $\mathcal{R}_0$ with respect to β by computing;

$$\frac{\partial \mathcal{R}_0}{\partial \beta} = \frac{\partial}{\partial \beta}\left[\frac{\beta\left(p\gamma(1-\epsilon)+(1-p)(\gamma+\mu)\right)}{(\gamma+\mu)(\mu+\sigma+\delta)}\right],$$

$$= \frac{(1-p)(\gamma+\mu)+\gamma p(1-\epsilon)}{(\gamma+\mu)(\delta+\mu+\sigma)}.$$

Again, because $p \in (0,1)$, $p \in (0,1)$ and all the parameters are assumed to be positive, in this case, we therefore have

$$\frac{\partial \mathcal{R}_0}{\partial \beta} > 0.$$

This implies that the number of secondary cases $\mathcal{R}_0$ in the population increases with the transmission rate β. Ideally, therefore this parameter should be kept as low as possible.

4.6 Summary

In this chapter we have developed a model with two treatment strategies. The first strategy is to treat active TB the second strategy is to give post-exposure vaccine to latently infected individuals. We prove the positivity and boundedness of the solutions using the same method as in the previous chapter. We found the steady states of the model and analyse their stability. The model exhibits backward bifurcation. We calculated the basic reproduction number. Sensitivity analysis of the reproduction number shows that the reproduction number decrease as σ (active treatment parameter) and ϵ (preventative therapy of post exposure vaccination parameter)increase but increase as β (transmission parameter) increases.

Chapter 5

Numerical simulations

5.1 Introduction

In the previous chapters, two SEIR models were developed; Model 3.1 without prophylaxis and Model 4.1 which included prophylactic treatment. We found that Model 3.1 was sensitive to transmission rate and treatment rate while Model 4.1 was sensitive to treatment rates and transmission rate. In this chapter we carry out numerical simulations on these two models using MATLAB ode solver **ode45**. The parameter values we use for the simulations are reasonable estimates, in line with those in the literature. The chosen values are shown in Table 5.1. In all instances the initial population sizes used were $S(0) = 110000$, $E(0) = 35000$, $I(0) = 5000$, and $R(0) = 0$. These values represent a population where 73% is susceptible, 23% have been exposed to the disease, 3% are infectious, and none has yet recovered.

We then perform uncertainty and sensitivity analysis and consider the population dynamics with the sensitive parameters. We then consider the effect of TB treatment and controls by comparing results for the two models. Finally we look at the force of infection and the contour plots. Force of infection is the rate at which susceptibles acquire infection. Contour plots help us to compare the post-exposure vaccine parameter ϵ to the active TB treatment rate σ with respect to the reproduction number, $\mathcal{R}_0$.

5.2 Numerical simulations

We first investigate the behaviour of our $SEIR$ models by observing the dynamics for the population compartments S, E, I and R. Simulation were carried out on Model 4.1. We first investigate the population dynamics when $\mathcal{R}_0 < 1$ and when $\mathcal{R}_0 > 1$. We wish to determine how each individual population compartment S, E, I and R behaves in each of the cases $\mathcal{R}_0 < 1$ and $\mathcal{R}_0 > 1$. The results are shown graphically in Figures 5.1 and 5.2. It can be seen from Figure 5.1 that when $\mathcal{R}_0 < 1$ all the population classes (except the susceptibles) gradually decrease until they die out as expected. In this case the disease is eventually eradicated. As the infective class decreases (through deaths and recovery), the exposed class also decrease, because there are now less infectious individuals in the population. We note that the recovered class initially increases as the infectives recover until it reaches its peak point. It then drops as there is a decrease

in the number of individuals in all the other classes except for susceptibles. This is the disease free equilibrium point. In other words, as the susceptible population increases the infection dies out.

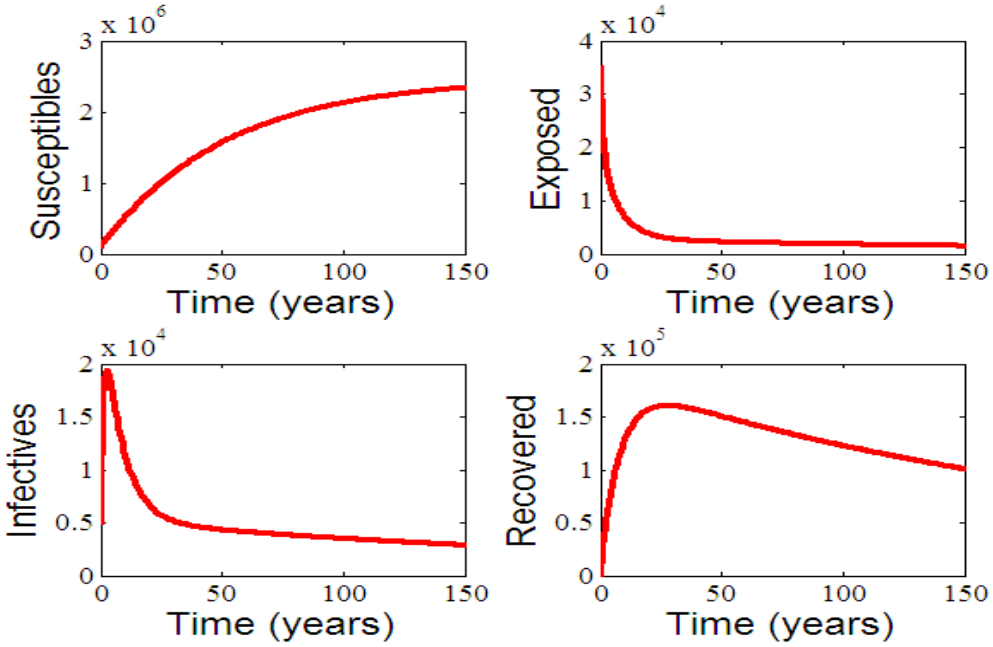


Figure 5.1: Diagram showing change in population dynamics in the four state variables for $\mathcal{R}_0 < 1$. The parameter values are $p = 0.9$, $\mu = 0.0133$, $r = 0.6$, $\Lambda = 1463$, $\rho = 0.02$, $\beta = 0.2581$, $\epsilon = 0.5$ $\gamma = 0.09$, $\delta = 0.003$, $\sigma = 0.4065$, $\mathcal{R}_0$ =0.6127

Figure 5.2 shows that when $\mathcal{R}_0 > 1$, all the population classes increase except for the susceptible class which increases and then decreases slightly to a point where it remains constant. This correspond to an endemic equilibrium point. In this case the disease is persistent and will eventually invade further and further into the population.

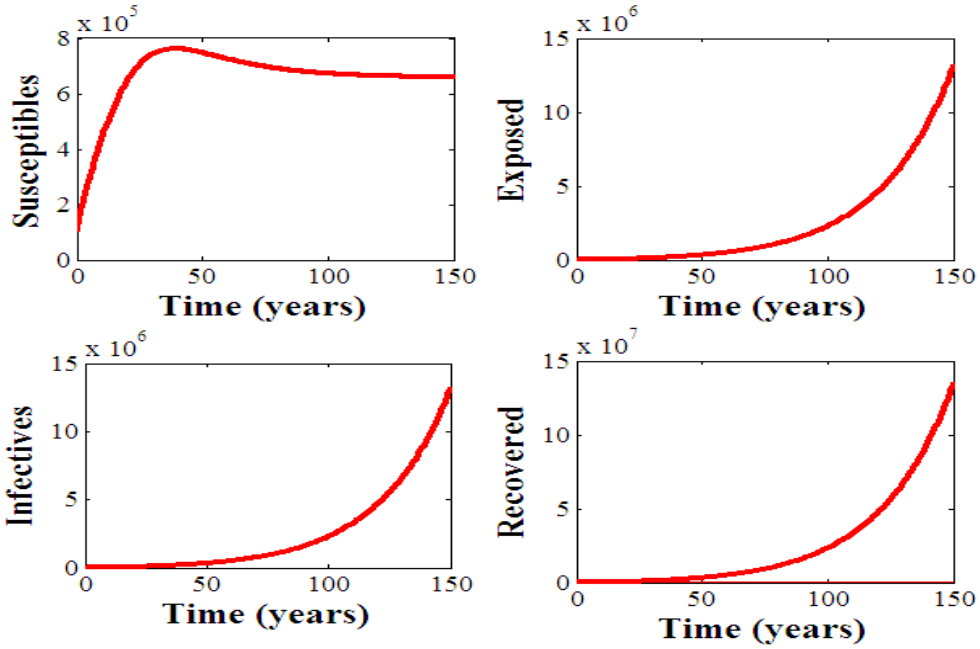


Figure 5.2: Diagram showing the change in population dynamics in the five state variables for $\mathcal{R}_0 > 1$. The parameter values are $p = 0.9$, $\mu = 0.0133$, $r = 0.6$, $\Lambda = 1463$, $\rho = 0.02$, $\beta = 0.6866$, $\epsilon = 0.55$, $\gamma = 0.09$, $\delta = 0.003$, $\sigma = 0.465$, $\mathcal{R}_0$ =1.4654

5.3 Uncertainty and sensitivity analysis.

In most mathematical models some parameters are unknown, not easy to measure, or are known with very little certainty. Techniques such as differential analysis assessed by Shih and Lin [42], response surface methodology used by Rohmer and Bouc [43], Monte-Carlo analysis and variance decomposition methods are used to address the uncertainty and sensitivity analysis of the parameters of interest.

We perform uncertainty and sensitivity analysis in our deterministic models. The output of a deterministic model is entirely determined by the model structure and the input parameters, Marino et.al [44]. It follows that the only uncertainty affecting the output is generated by the input variations. Using uncertainty and sensitivity analysis will allow us to establish which factors affect the model outputs when we decrease or increase certain parameter values. In this way we would know which parameters we should target to achieve a specific goal. For instance, which parameters should we target to decrease the number of individuals in the infectious class?. Information extracted after carrying out this analysis may also be used to draw certain conclusions about a model, thus offsetting the difficulty in carrying out analysis.

5.3.1 Latin Hypercube Sampling (LHS)

We use the strategy of Latin Hypercube Sampling (LHS) to perform the uncertainty analysis and sampling based Partial Rank Correlation Coefficient (PRCC) as an uncertainty analysis index. LHS belongs to the Monte-Carlo class of sampling methods, and allows an unbiased estimate of the average model output, Marino et al. [44]. For each parameter, a probability density function (pdf) is defined and stratified to N equiprobable serial intervals. A single value is then selected randomly from every interval: this is done for every parameter. A particular value from each sampling interval is used only once in the interval. This type of sampling has the advantage of requiring fewer samples than simple random sampling, but achieves the same level of accuracy. In this

way, LHS is efficient and can adequately sample the entire parameter space. Blower and Dowlatabadi [45] introduced LHS into the field of disease modelling by carrying out sensitivity and uncertainty analysis of complex models of disease transmission, and as an example, used an HIV model.

We calculate and PRCC indexes for multiple time points of interest and them plot them against time. We do this to check if, during the model dynamics, the significance of a certain parameter occurs over the entire time interval.

The PRCC is a robust sensitivity measure of the correlation Marino et al. [44]. The PRCC values ranges between -1 and +1. Positive PRCC values indicate positive correlations; correspondingly, negative values indicate negative correlations. Furthermore, values between -0.3 and +0.3 are considered to indicate a weak correlation or even no correlation. Therefore we judge the PRCC values $> +0.6$ or < -0.6 to indicate strong positive and strong negative correlations respectively, with $0.3 < PRCC < 0.6$ or $-0.6 < PRCC < -0.3$ representing positive and negative correlations respectively.

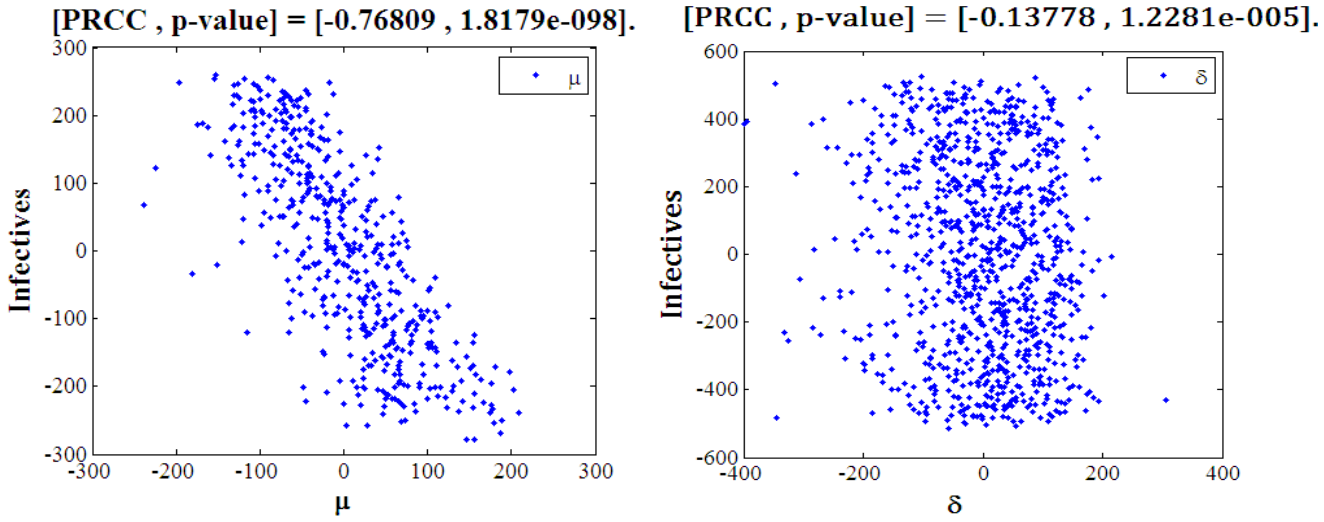
5.3.2 Scatter plots and PRCC indexes.

We used Latin Hypercube Sampling (LHS) to calculate PRCC value, to draw scatter plots and to draw the bar graph. Scatter plots were used in order to decide which parameters are more sensitive in our models and to determine which parameters decrease

or increase with the Infective class size. Values of the parameters are shown in Table 5.1. The scatter plots and the PRCC values on the bar graph were each calculated with a sample size of N = 1000. For each plot, the PRCC values and and p-values are calculated and shown at the top of each scatter plot. Figure 5.8 then shows a bar graph which summarises the PRCC values for each of the parameters, as calculated for days 180 and day 260. We choose these numbers of days because TB treatment usually takes between 6 to 9 months, which is equivalent to 180 to 260 days.

Table 5.1: Model parameter values.

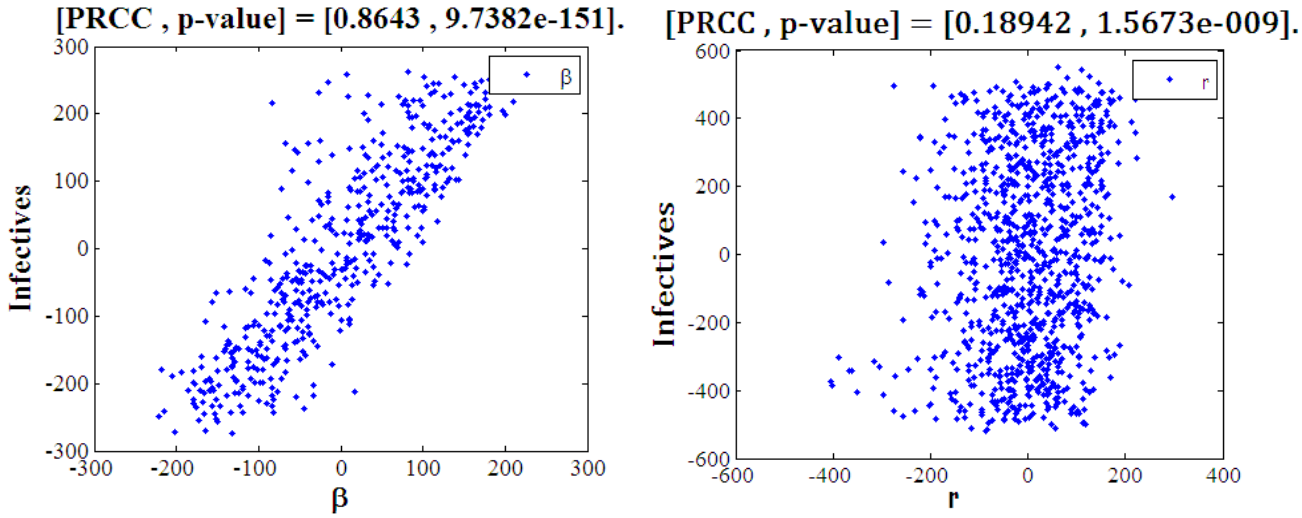
Parameter	Description	Value	Source
Λ	Recruitment rate	1463	Computed,
μ	Natural mortality rate	0.0133	[46],
β	Transmission rate	0.095, (0;1)	Vary,
δ	Disease induced deaths	0.003	[46],
ρ	Relapse rate	0.02	[47],
σ	Recovery or treatment rate	0.05	[46] ,
γ	Rate of progression from E to active TB	0.09	Estimated,
ϵ	Post-exposure prophylaxis efficacy E	0.5	[46],
r	Reinfection parameter	0.6	Estimated,
p	Proportion of individuals from S to E	0.9	[47].



(a) PRCC scatter plot for μ vs I.

(b) PRCC scatter plot for δ vs I.

Figure 5.3: PRCC scatter plots showing effect of parameters μ and δ vs Infectives.

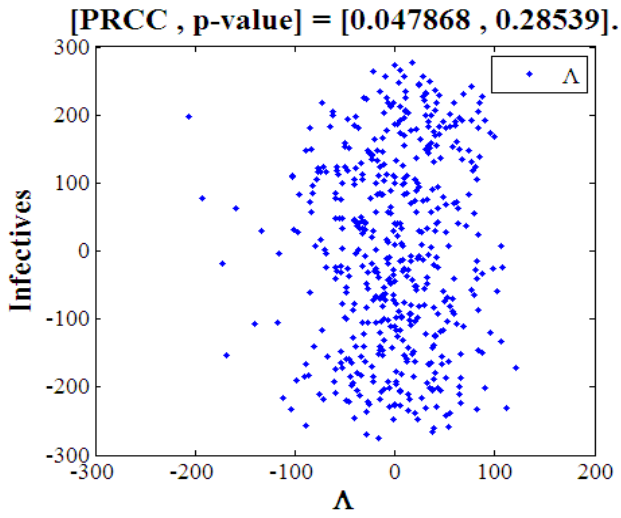


(a) PRCC scatter plot for β vs I.

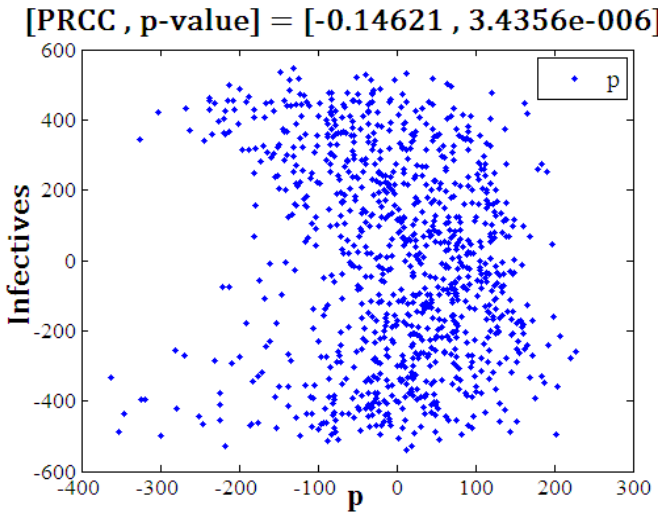
(b) PRCC scatter plot for r vs I.

Figure 5.4: PRCC scatter plots showing effect of parameters β and p vs Infectives.

Figure 5.3 shows the PRCC scatter plot of the natural death rate μ and the PRCC

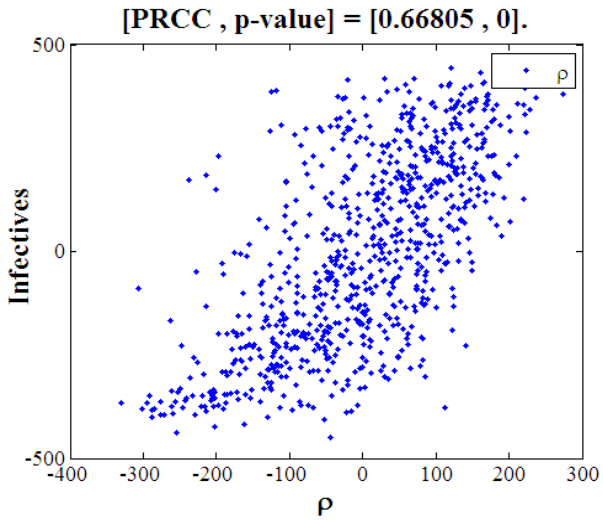


(a) PRCC scatter plot for Λ vs I.

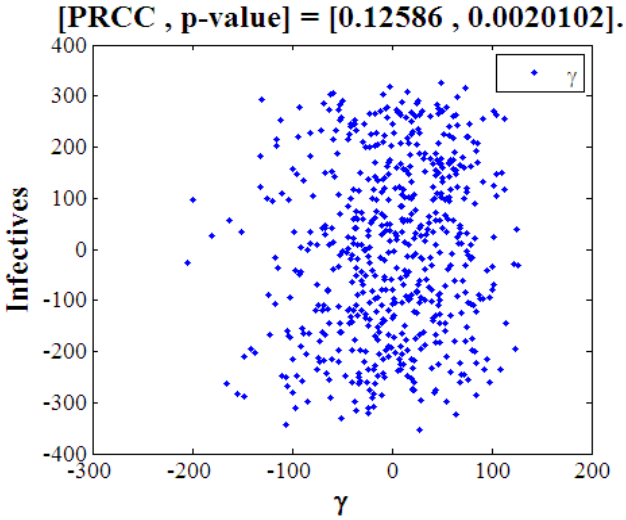


(b) PRCC scatter plot for p vs I.

Figure 5.5: PRCC scatter plots showing effect of parameters Λ and p vs Infectives.

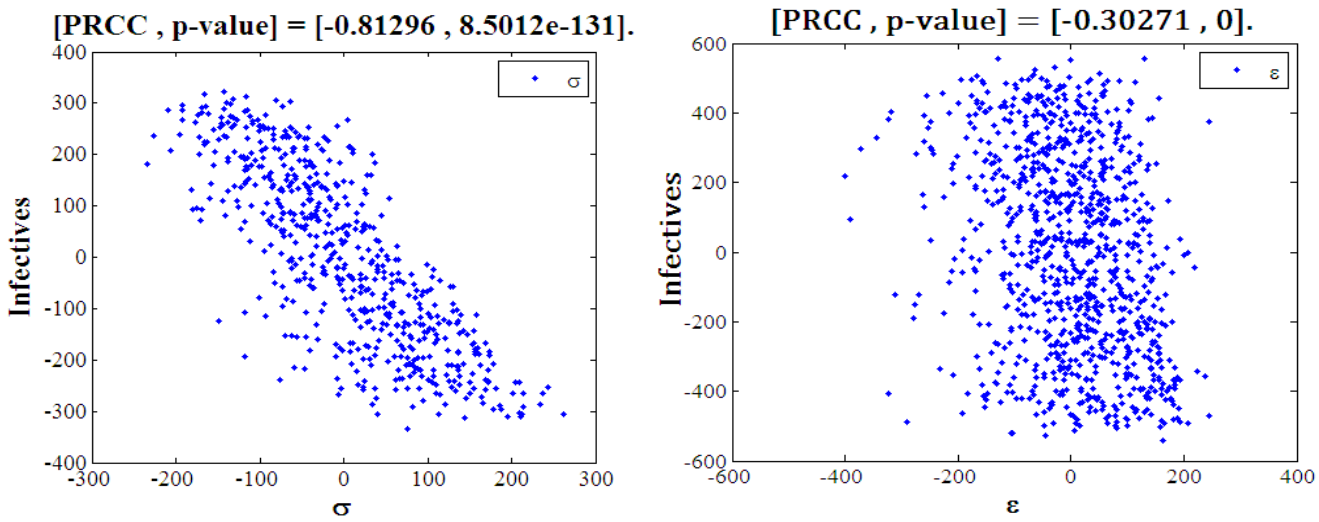


(a) PRCC scatter plot for ρ vs I.



(b) PRCC scatter plot for γ vs I.

Figure 5.6: PRCC scatter plots showing effect of parameters ρ and γ vs Infectives.



(a) PRCC scatter plot for σ vs I.

(b) PRCC scatter plots for ϵ vs I.

Figure 5.7: PRCC scatter plots showing effect of parameters σ and ϵ vs Infectives.

scatter plot of the disease induced death rate δ being compared with the Infective class. As can be seen, both these parameters are negatively correlated with the Infective class. It is expected from the disease dynamics that as death rates decrease, so does the Infective population. Figure 5.4 shows that there is strong positive correlation between β and the Infective class. We also note a positive but very weak correlation between the reinfection rate r and the Infective class. In Figure 5.5, there is a weak positive correlation between Λ, the recruitment rate and the Infective class. There exists a very weak negative correlation between γ and the Infective class. In Figure 5.6, PRCC scatter plots of the relapse rate ρ and the rate of progression from latent to active TB, γ, show a very good positive correlation between ρ and the Infective class, while there exist a positive correlation between γ and the Infective class. We expected

these results because recovered individuals who relapse after treatment directly enter the Infective class and γ represent a direct progression to active TB. Figure 5.7 show PRCC scatter plots for the effect of active treatment parameter σ and the latently infected class treatment parameter ϵ that represent post-exposure vaccination. The two parameters are compared with the Infective class. Both treatment rates are negatively correlated with the Infective class. The negative correlation between σ and Infective class is much more strong than that between ϵ and Infective class.

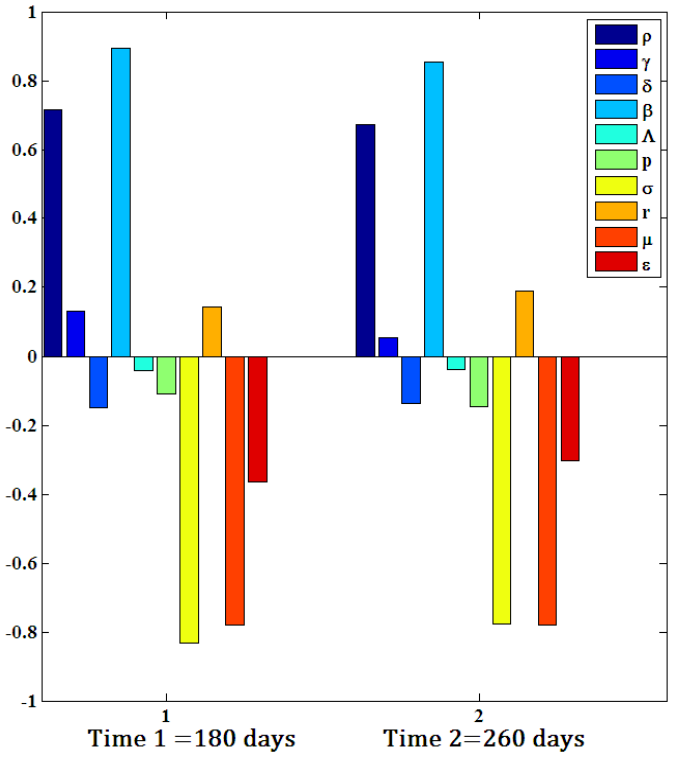


Figure 5.8: Bargraph for the summary of the PRCC values for each parameter.

The bargraph in Figure 5.8 is a summary of the PRCC values for all parameter. We can

have confidence in these PRCC indexes because there is only a minor change between the simulations at day 180 compared to simulations at day 260.

5.4 Population dynamics with sensitive parameters.

If we consider Figure 5.8 it is clear that as the parameters ρ, β, γ and r increase, the Infective class increases as well. From Figure 5.8 it can also be seen that as parameters δ, Λ, μ, p, σ, μ and ϵ increases, the Infective class size decreases. Therefore, the strategy to control TB should focus on decreasing the parameters ρ, β, γ and r, while increasing the parameters δ, Λ, μ, p, σ, μ and ϵ. For some parameters we may not be able to introduce an intervention that will either reduce or decrease them because of other factors influencing those parameters. For instance, Figure 5.8 suggests that increasing the death rate due to other natural causes parameter, μ, will decrease the Infective class size. In reality the parameter μ depends on many variables and it may not be possible to increase it. More deaths do not solve the TB problem.

The PRCC values, scatter plots and the bar graph assist us to know which parameters we should focus on because of their sensitivity. Parameters β and ρ are the most positively correlated with the Infective class while, parameters μ, σ, and ϵ are the most negatively correlated with the Infective class. For this reason the analysis in the following subsections will focus on the parameters β, ρ, σ, and ϵ. We do not include μ

because of the reason mentioned in the previous paragraph.

5.4.1 Variation of parameters β and ρ.

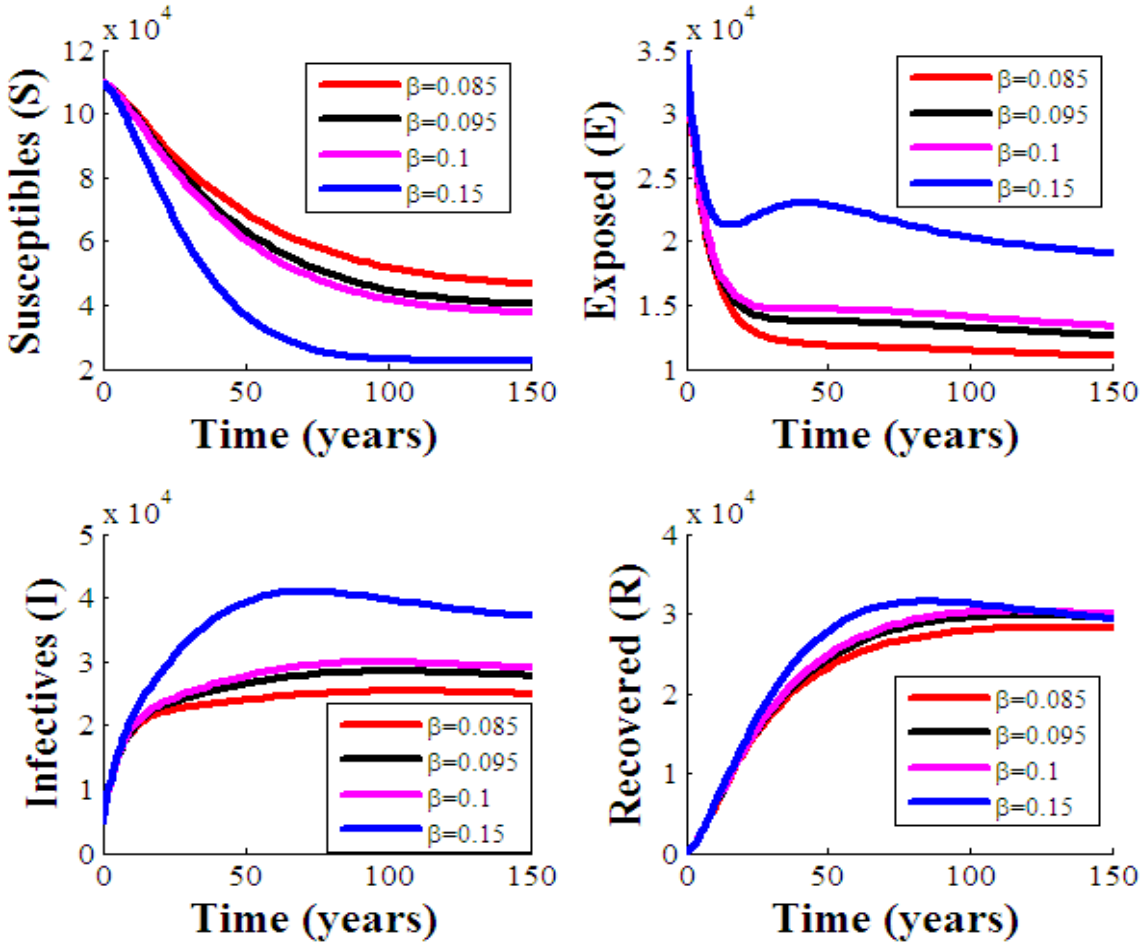


Figure 5.9: Behavior of all populations for various values of transmission parameter β while all other parameters are fixed.

We used MATLAB to plot Figure 5.9 and Figure 5.10 that shows the behaviour of all

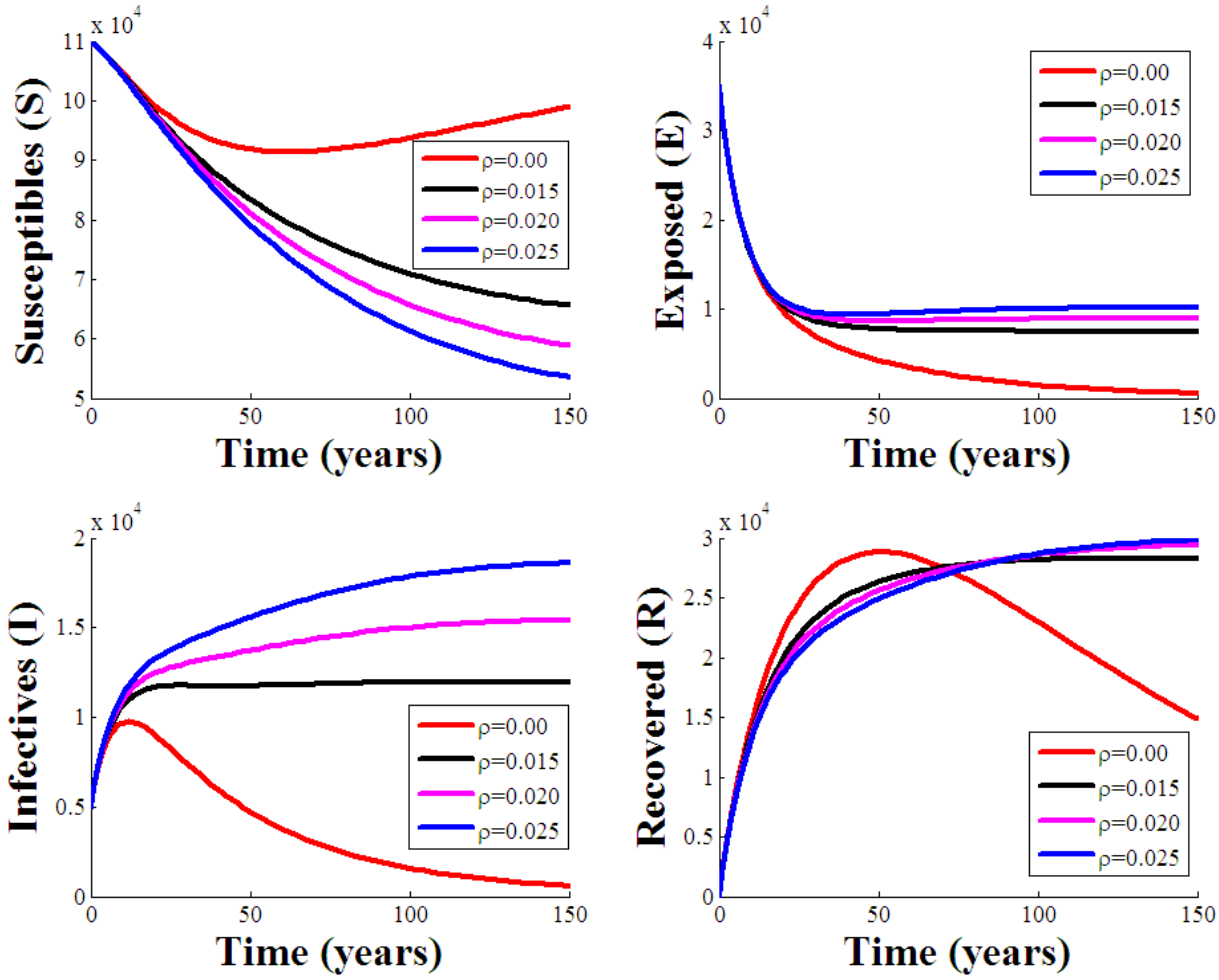


Figure 5.10: Behavior of all populations for various values of transmission parameter ρ while all other parameters are fixed.

the population classes for different values of the transmission rate, β, and the relapse rate, ρ, respectively. The Infective class increases while the Susceptible class decrease as both β and ρ increases. For small transmission rates there are less individuals entering the Exposed class that directly explains the small sizes for the Infected and Recovered classes. For larger values of β, for instance, $\beta = 0.15$ the Susceptibles class

gets smaller in size as individuals get infected and move to the Exposed and Infective classes, see Figure 5.9. The graphs give the sizes of the respective populations over 150 years interval. This does not necessarily model individuals with a 150 years life span.

In a case where TB patients do not complete the treatment doses relapse may occur. A perfect case where there is no relapse, $\rho = 0$ is illustrated with the red line in Figure 5.10. When there is no relapse the treatment is working well, Exposed and Infective classes have a sharp decrease, while the Susceptible class initially decrease then start increasing again after 80 to 100 years. The blue line represent a large value of relapse rate, that leads to an increase in the Infective and Exposed classes.

5.4.2 Variation of parameters σ and ϵ.

As in the previous sub-section, simulations on the control strategies treatment rate, σ, and post-exposure vaccination rate, ϵ, were carried out using MATLAB. However to compare these two strategies in the simulation with different σ values, different ϵ values were also investigated. Figure 5.11 gives the results for different ϵ values, and Figures 5.12 to 5.13 show the results for the different σ values. Figure 5.11 shows the behaviour in all population classes when ϵ is varied, while σ held at zero. It can be seen that no matter how much ϵ increases, the Infective class remains large. Figure 5.12 shows the behaviour in all population classes when σ is varied. As σ increases

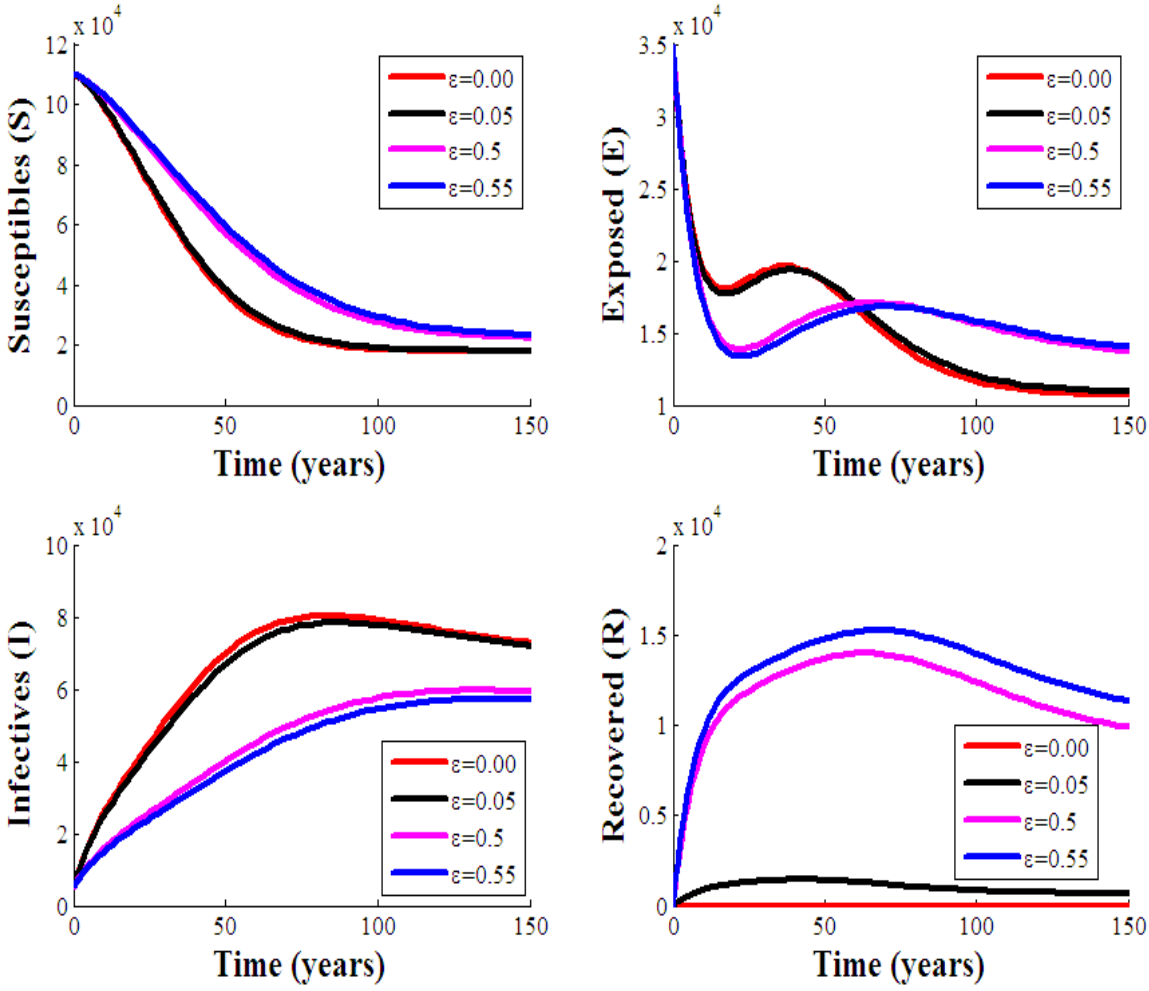


Figure 5.11: Behavior of all populations for various values of transmission parameter ϵ while all other parameters are fixed and $\sigma = 0$.

the Infective class decreases. This contrasts with Figure 5.13 which shows the results when we vary σ in the presence of ϵ. In this last graph it can be seen that the size of the Infective class decreases more significantly than in the previous two cases shown in Figures 5.11 and 5.12.

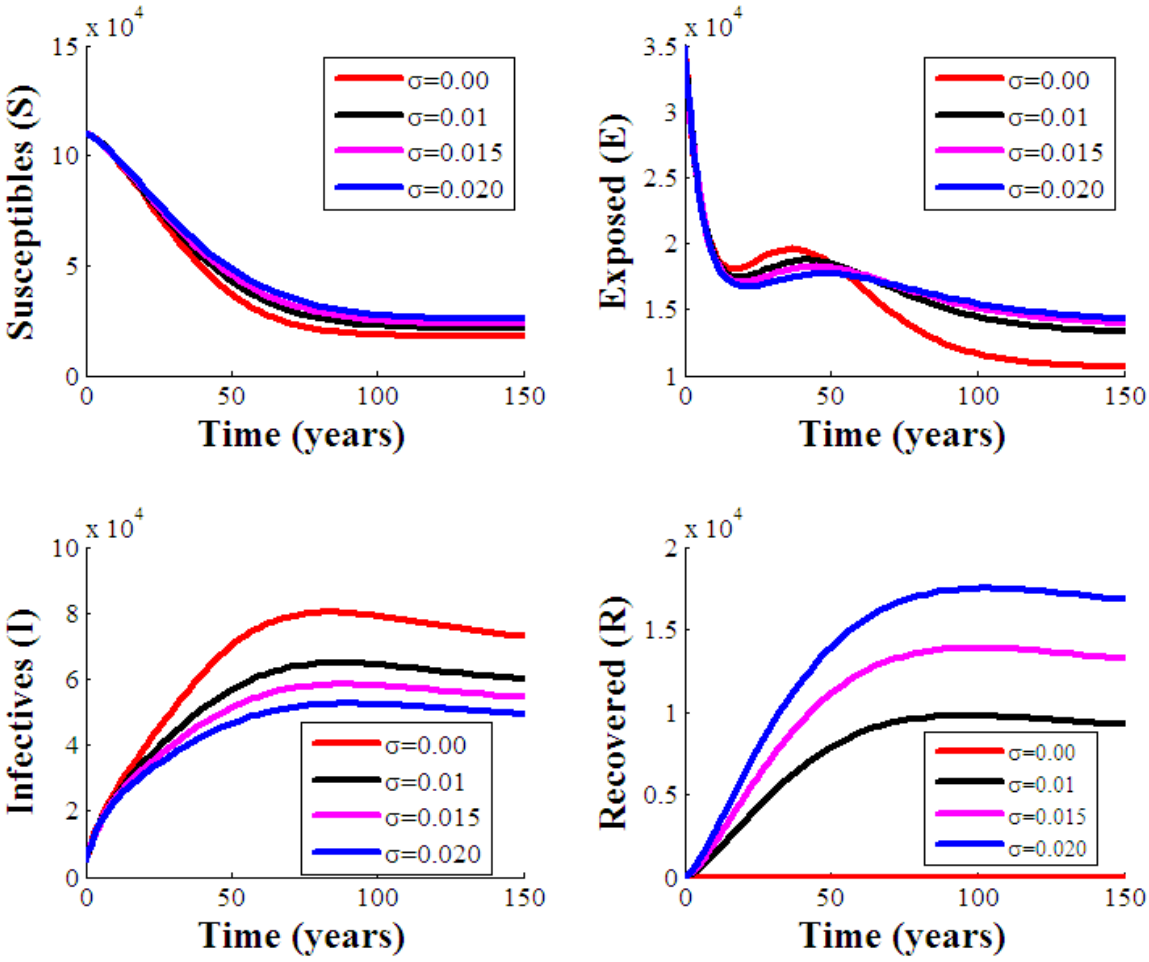


Figure 5.12: Behavior of all populations for various values of transmission parameter σ while all other parameters are fixed and $\epsilon = 0$.

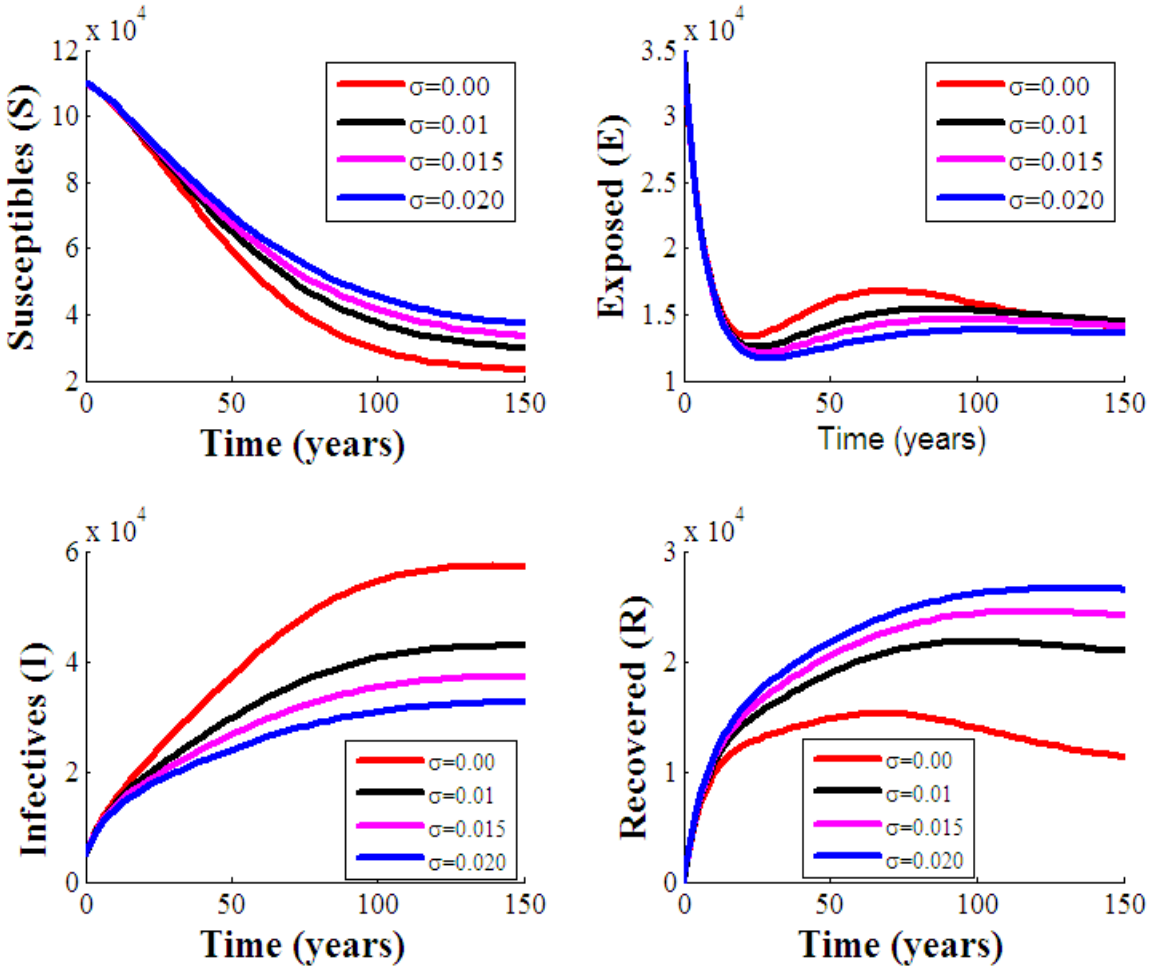


Figure 5.13: Behavior of all populations for various values of transmission parameter σ while all other parameters are fixed and $\epsilon = 0.55$.

5.5 Active TB treatment and post exposure vaccine as TB control strategies.

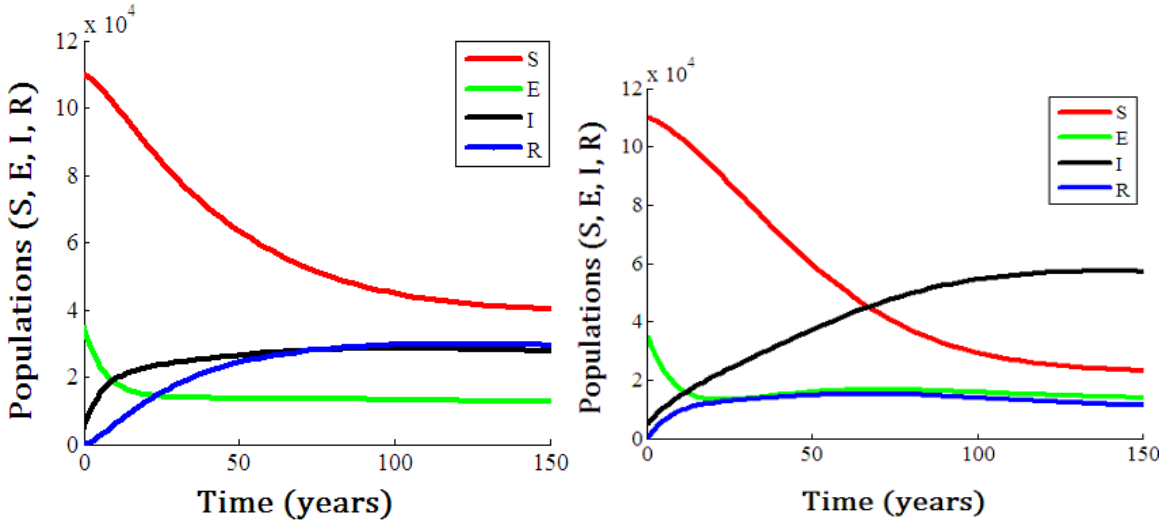
In order to control TB the Infective class should decrease. Two control strategies are now compared. The first treatment strategy considered is illustrated in the first Model

3.1. In this strategy only the active TB Infective class is treated with anti-tuberculosis drugs. The second strategy is depicted in the Model 4.1 where both the active TB treatment and post-exposure prophylaxis are considered.

Post-exposure prophylaxis is used as the preventative treatment for latently infected individuals, and prevent the severity of TB. In other words, it delays the time taken for a latently infected individual to develop active TB. We are interested in determining which of the two strategies is more effective.

5.5.1 Post-exposure prophylaxis therapy only versus active TB treatment only.

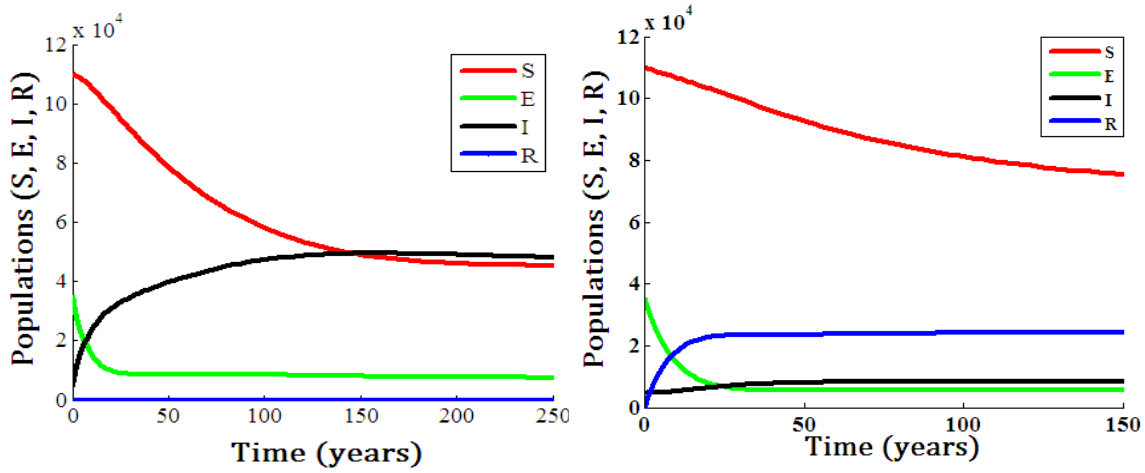
We compare the method of treating only active TB to the method of treating latently infected individuals with preventative therapy. In Part (a) of Figure 5.14 only active TB treatment is considered. In Part (b) of Figure 5.14 only the preventative therapy is considered as a control strategy. In both cases the Susceptible class decreases as individuals get latently infected. The Exposed class decreases as individuals become infected. The Recovered class increases in both cases. The most important observation is the Infected class. For both cases the infected class increases, but when only the preventative therapy is used the Infective class increase much more than that of the case where active TB is treated. Thus treating latent cases is probably a major factor in successful TB management.



(a) Variation of σ with $\epsilon = 0$.

(b) Variation of ϵ, $\sigma = 0$.

Figure 5.14: Variations of σ only and ϵ only. $\sigma = 0$



(a) No treatment, no PEP.

(b) Both active TB treatment and PEP.

Figure 5.15: No treatment versus both active TB treatment and PEP.

5.5.2 No treatment versus treating active TB while providing post exposure vaccination (prophylaxis).

Analysis depicted in Figure 5.15 shows the results when no treatment is present compared with treating both active TB treatment and post-exposure prophylaxis are applied simultaneously. In Part (a) there is no treatment, and the Susceptible class size decreases while the Infective class size increases, until they both become horizontal/stable, showing that after some time there are more infected individuals in the population with the Recovered class remaining at zero. This indicates that TB disease invades the population. In part (b) the effect for hybrid of active TB treatment and post exposure vaccination is shown. The graph indicates that while the Susceptible class drops slightly, while the Infective and Exposed classes remain fairly low. This can be regarded as a favorable result for TB management because it shows the least class sizes for Exposed and Infective classes.

5.6 Force of infection.

The force of infection is rate at which the individuals in the Susceptible class acquire an infection. We investigate this parameter in order to get an idea of how fast the disease spread within the population over a period of time.The graphs in Figure 5.16 indicate that the force of infection increases for all three scenarios, but flattens out

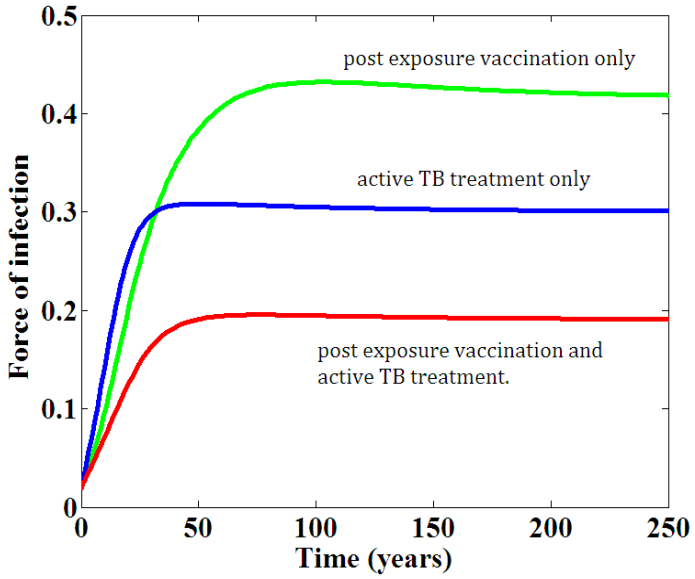


Figure 5.16: Dynamics of the force of infection .

to the lowest value for the hybrid of treatment and post exposure vaccination. This indicates that with both strategies administered simultaneously, the rate at which the disease spreads is considerably reduced.

5.7 Contour plot

In the analysis in Chapter 3 we found that $\mathcal{R}_0 < 1$ implies a possibility for the disease to be controlled, while $\mathcal{R}_0 > 1$ implies that the disease might invade the population. Therefore in order to compare the effect of the two control strategies depicted in model diagram, Figure 4.1 we will use the basic reproduction number,$\mathcal{R}_0$. $\mathcal{R}_0 = 1$ act as an indicator that the disease could be eradicated. A contour plot of $\mathcal{R}_0$ as a function of σ

and ϵ will be carried out using MATLAB. The results are shown in Figure 5.17. This plot provides evidence that active TB treatment is more effective in reducing $\mathcal{R}_0$ when compared to PEP treatment. One would require ϵ greater than σ to achieve the same value of $\mathcal{R}_0$. From Figure 5.17, if we are to control the disease, and have $\mathcal{R}_0$ reduced to 1, we need a high efficacy of PEP treatment $\epsilon = 0.93$. However for the same $\mathcal{R}_0$, we need a rate for active TB treatment to be only σ= 0.38.

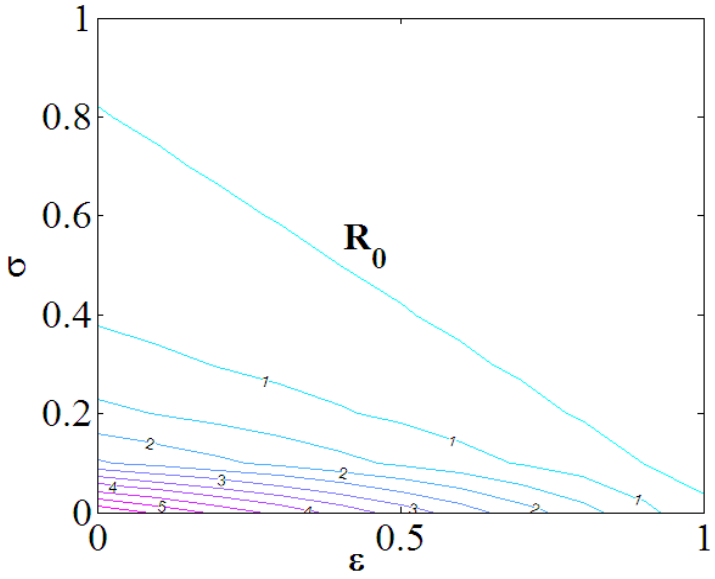


Figure 5.17: The contour plots showing $\mathcal{R}_0$ as a function of σ and ϵ.

Chapter 6

Conclusion

This study was conducted to investigate and analyse the mathematical models on TB treatment and vaccination strategies. In this study we discussed important information about the TB disease in Chapter 1. We gave information about how the disease history, how it is contracted and what it does to the body of the host. A review of literature on mathematical models for TB was done in Chapter 2.

In Chapter3 we extended an SEIR TB model by van den Driessche et al. [37] and presented a new SEIR model. The new model differs from the one in [37] because we have considered the possibility that not all susceptible individuals enter the Exposed class, but some individuals directly enter the Infective class and are called fast progressors. We did this because immune-compromised individuals such as elders, children and sick

are more likely to go to the Infective class soon after contact with the disease. We analysed this model, proved positivity of the solutions and found the equilibrium points. Stability analysis showed that the disease free equilibrium point is both locally and globally asymptotically stable provided that $\mathcal{R}_0 < 1$. This indicated the case where the disease can be controlled. The relationship between $\mathcal{R}_0$ and β was investigated in Chapter 3, using the SEIR model and showed evidence of a very strong positive correlation. A very strong negative correlation between $\mathcal{R}_0$ and σ was found. These results are a good indication that in order to decrease the value of $\mathcal{R}_0$, interventions should target increasing treatment which will then decrease the transmission rate, since an individual on treatment has less chances of infecting other susceptible individuals. The stability analysis results with respect to $\mathcal{R}_0$ of our models is the same as the ones in van den Driessche et al. [37]. The inclusion of vaccination or treatment of exposed individuals in a model with relapse was suggested by van den Driessche et al. in [37]. Our model included this suggestion.

Our study of the literature suggested that post-exposure prophylaxis (PEP) vaccination could be a suitable form of preventative therapy. As a result, in Chapter 4 we further developed our model to include it. The parameter ϵ represents PEP treatment of latently infected individuals, also known as chemoprophylaxis. The model was analysed and $\mathcal{R}_0$ found using the next generation matrix method. The value of $\mathcal{R}_0$ decrease as ϵ increases. The indicates that for TB to be controlled PEP is also one

of the strategies that need to be used. The PEP vaccinations is started immediately after an individual get exposure to a pathogen, MTB, in this case. The PEP vaccination prevent infection by the MTB pathogen to develop into active TB. This then decreases the number of infectious individuals, consequently decreasing the value of $\mathcal{R}_0$.

In order to gain more insights to the dynamics of the models in Chapter 3 and in Chapter 4 we undertook correlation studies and numerical simulations of both models, as reported in Chapter 5. The correlations, simulations and contour plots all gave evidence that the hybrid strategy of active TB treatment and the post-exposure prophylaxis vaccination could eradicate the disease faster than either strategy on its own. Post-exposure prophylaxis vaccination/treatment alone is the least effective control measure because it only delays the rate of progression of the disease in the individual, but does not confer immunity to the treated individual. Treating active TB cases is better, because it not only protects the individual but also the whole community, thus decreasing the transmission rate β, which then directly decreases the reproduction number, $\mathcal{R}_0$. The best results would come from implementing both strategies concurrently. The reality is, however, that in most developing countries, resources and funding are often limited. So it may appear better to focus recourses on only treating active TB cases, especially as some literature show that latent TB diagnosis has limitations. Orainey and Ibrahim [48] show that a well know diagnosis for latent TB, tuberculin skin test (TST) , may be positive in people with prior BCG vaccination

or exposure to non-tuberculous *mycobacteria* and provide a false negative TST results in patients with impaired T-cell function frequently occur. However our results have shown that the hybrid of active TB treatment with post exposure vaccination has a more than additive effect.

In view of these findings, we recommend that both latent and active TB treatment should be implemented at the same time. We urge that resources and technology be acquired for this in order to have the most impact on reducing the TB transmission rate. The transmission rate could be further reduced by protecting an exposed community though post-exposure vaccination, while treating active TB cases, because then infected individuals will be less likely to spread the disease. Nevertheless, other reasonably simple but effective intervention and control strategies should not be neglected. Such measures include less clustering, and taking general precautions to avoid infections, both at individual and community level, as were outlined in Chapters 1 and 2. Taken together, we believe that all the strategies would have a substantial effect on reducing the transmission rate of tuberculosis.

Models are by their nature, a simplification of reality. Nevertheless, a model can be validated if it fits the data. Unfortunately, in this study we did not have TB data by which to validate the model. Consequently we need to evaluate the model in itself. In this regard, if inappropriate assumptions are made, a model may not

reflect the real problem. The two models in this study were simplified by assumptions, which included that of homogeneous mixing within the overall population. However, each individual in the population may not, in fact, have an equal chance of coming into contact with an infectious individual. Furthermore, the models were not age structured; for example, treating TB infected children in a different manner to adult cases. Nevertheless, the findings from these SEIR models are promising. Therefore, future studies could focus on developing a TB model that considers heterogeneous mixing. A model with three control strategies involving pre-exposure vaccination, pos-exposure vaccination and treatment of active TB cases, may also be done in the future work. It is also recommended that empirical data on TB prevalence be used to validate such models.

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