# IMPACT OF EXOGENOUS REINFECTION ON TB INFECTION IN A GENETICALLY SUSCEPTIBLE POPULATION

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Wangari Isaac Mwangi

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Wangari Isaac Mwangi

This dissertation is submitted to the School of Mathematics, Statistics and Computer Science at University of KwaZulu-Natal, Durban, in fulfilment of the requirements for the degree of Master in Science.

As the candidate's supervisor, I have approved this dissertation for submission.

Signed: Dr. F. Chirove .....

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I declare that the contents of this dissertation are original except where due reference has been made. It has not been submitted before for any degree to any other institution.

Wangari Isaac Mwangi

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# Dedication

I dedicate this work to Almighty for His tremendous support and consolation.

To my mother-Wangari, brothers and sisters for their fervent prayers.

# Acknowledgement

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# Abstract

In this study we investigated the impact of exogenous reinfection on genetically resistant and genetically sensitive sub populations. We qualitatively analysed the dynamics of TB by assuming that TB is transmitted in two ways namely homogeneous and heterogeneous modes of transmission. Analytically, we computed the fundamental thresholds used to measure disease persistence; the basic reproduction number $R_0$, and found that the exogenous reinfection parameters do not appear in the basic reproduction number. Hence, basic reproduction number derived in presence of exogenous reinfection does not adequately predict the course of a TB epidemic. We obtained the exogenous reinfection threshold which indicated that exogenous reinfection complicates TB dynamics. Both analytical and simulation results disclosed that when exogenous reinfection is above exogenous reinfection threshold TB dynamics were governed by a backward bifurcation implying TB may continue to invade the population despite basic reproduction number being less than one. We computed critical value of basic reproduction numbers $R_c$ and found that TB can only be eradicated if basic reproduction number is reduced below critical value $R_c$. Furthermore, we incorporated TB therapy in heterogeneous model among individuals with clinically active TB and performed sensitivity and uncertainty analysis using Latin Hypercube Sampling. The sensitivity and uncertainty results showed that transmission rates, reactivation rates and proportion that is genetically resistant greatly influenced outcome variables of our TB model.

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# Chapter 1

# Introduction.

Tuberculosis (TB) is a contagious disease caused by a bacteria called *Mycobacterium tuberculosis* (*M. tuberculosis*). Human beings are the main reservoir of the bacillus. Breathing in of aerosolized droplets harbouring *M. tuberculosis* can result in TB infection [1]. The clinical symptoms of TB include frequent prolonged coughing, chest pain, fever, easy fatigability, night sweating and general weight loss. Before humans understood the entire genome sequence of mycobacteria via Interferon-Gamma Release Assays (IGRAs), diagnosis of individuals with infectious TB depended on chest radiography while diagnosis of dormant TB was done using tuberculin skin test [2].

Factors that aid transmission of the *Mycobacterium tuberculosis* include the concentration, viability, virulence of the mycobacteria residing in the sputum droplet nuclei and duration of time an individual spends near a person whose infection has advanced to active TB [3]. Other factors include overcrowding as seen in public transport, schools and clubs, social-economic status, inaccessibility of health services, malnutrition, success of chemoprophylaxis and therapy determine transmission of the *Mycobacterium tuberculosis*. Furthermore, ineffective TB combating strategies and immigration are likely to impact TB dynamics. Immigration of individuals infected with TB to regions which are susceptible to TB increase TB burden in those regions.

The discovery of *Mycobacterium tuberculosis* bacteria as the causative agent of human tuberculosis (TB) posed a great challenge in medical field in search for a cure and vaccine [4]. Though, there has been advancement and improved technology in medical facilities, TB remains a devastating infection worldwide. Globally, approximately two billion people suffer from TB and one new case of TB is reported every second [5]. Each year about eight to ten million individuals develop infectious TB and two to three millions die from the disease. In Sub-Sahara Afriaaca, South Africa carries the largest burden of infected individuals [6]. In 2009, 407000 TB cases were recorded in South Africa [7]. Worldwide India's contribution to the TB burden is about one-third of all cases, hence it is the country hosting the highest number of individuals infected with TB [6]. The pattern and distribution of TB epidemic across the world has been depicted to be non uniform [8]. For example approximately 80% of the population inhabiting many Asian and African countries is infected as evidenced by tuberculin skin test [8] compared to $5-10\%$ of population that test positive in United states.

Infectious diseases can be categorized as exogenous or endogenous infections [9]. Exogenous infections refer to infections that originate outside the susceptible host while endogenous refer to diseases that occur within an individual due to immune system destabilization. TB infection can occur as result of both exogenous and endogenous infection. The pathogenesis of TB is characterized by the infection either remaining dormant or progressing directly to active TB where clinical symptoms immediately manifest. This depends on host immune response towards the tubercle bacilli. Thus, the exposure to tubercle bacilli does not necessarily result in clinical forms of TB. Studies suggest that about $5-10\%$ of individuals progress directly to active stage after exposure to bacilli [10, 11]. The other population of infected cases develop dormant TB. These individuals may remain latently infected for the rest of their lifetime. However, destabilization of the immune system by the pathogen within the latently infected host triggers reactivation of *M.tuberculosis*. The lifetime risk of a latently infected individual progressing to infectious stage is about $5-10\%$ [12]. Individuals harbouring active TB and are not treated are likely to transmit infection to an average of 10-15 individuals per year [13].

Although, Bacillus Calmette-Guerin (BCG) is the only vaccine so far used in preventing TB, its efficacy is not perfect. Its effectiveness in preventing adult forms of TB has been rated to be relatively poor (roughly 50%) [14]. There is a great variation of BCG efficacy as observed in several places. For instance, in some endemic areas such as Southern India the efficacy is rated at 0% while in the United Kingdom protection is about 75% [15, 16]. This disparity in vaccine efficacy has been attributed to genetically determined immunogenecity of BCG strains, host immune mechanism and individual exposure to environmental mycobacteria [15, 16].

Treatment of TB is affected by the prolonged treatment period of between six to twelve months. Strict adherence to therapy prescriptions has been shown to change about 85% of sputum positive individuals to sputum negative within two months and the individuals becoming uninfectious [17, 18, 19]. Successful completion of TB treatment resulted in about 95% of individuals converting to sputum negative [17, 19]. However, it remains unclear whether individuals who convert from sputum positive to sputum negative revert to dormant state of TB or completely recover from the infection. In developing countries where BCG is commonly administered, only individuals with clinically active TB are treated due to lack of appropriate and efficient medical technology to diagnose latent form of TB. The latent TB is treated using chemoprophylaxis as preventative therapy while the active TB is treated using antibiotics. Due to non compliance to treatment by infected individuals and failure to agree on appropriate TB treatment strategies by health organizations, TB remains a global burden [20, 21, 22]. This has resulted in emergence of multi-drug-resistant (MDR) TB and extensive-drug-resistant (XDR) TB as new strains of TB that are more virulent and persistent. About 77 countries in the world harbour the resistant strains of TB [23].

The biological differences observed among individuals within a family and in different localities of the world suggests that genetic susceptibility plays a crucial role in the persistence of TB. Genetic susceptibility increases the likelihood of some individuals to higher risk of getting TB than others. Thus, nature of some genes determine whether an individual is genetically sensitive or genetically resistant to *M. tuberculosis* [24]. The host genetic make-up has been

shown to determine the outcome of TB infection [24]. Experiments from rabbits and mice have disclosed that individual genetic factors are important in the resistance and susceptibility to mycobacteria.

## 1.1 Problem statement.

In 1980s, TB prevalence was shown to be declining. To date a dramatic increase in prevalence is noted [25]. More investigations on TB dynamics need to be explored to establish the cause of TB resurgence. The contribution of genetic susceptibility of individuals and the effects of exogenous reinfection have been inadequately investigated. One asks a question whether or not exogenous TB reinfection in a population with genetic susceptibility could be a contributing factor to the TB epidemic. Mathematical models have been used successfully to analyse and understand the possible treads exhibited in infectious diseases [26]. Models can be used to contribute to disclosure of limitations that need to be considered when designing controlling strategies within the affected populations. Moreover, data can be used on mathematical models to predict the future treads of the infection.

## 1.2 Aims and objectives.

### 1.2.1 Aim.

The aim of this study is to use mathematical models to investigate and understand the effects of exogenous TB reinfection in a population with genetic susceptibility to TB.

### 1.2.2 Objectives.

The objectives of this study are:

(i) Develop mathematical models with homogeneous TB transmission incorporating exoge-

nous TB re-infection and genetic susceptibility.

(ii) Develop mathematical models with heterogeneous TB transmission incorporating exogenous TB re-infection and genetic susceptibility.

(iii) Analyze mathematical models in (i) and (ii) analytically and carry out numerical simulations using selected data.

(iv) Validate mathematically analyzed results with the TB biology and make projections using the mathematical processes that were derived from the TB biology.

## 1.3 Scope of dissertation.

We have so far provided the introduction of $M.TB$ in this chapter. Chapter 2 incorporates the literature review of TB studies previously done by other researchers. In chapter 3 we shall formulate a compartmental model of TB with homogeneous TB infection and provide a detailed analysis of the model. The model is modified to incorporate heterogeneous transmission of TB infection between the genetically sensitive and genetically resistant sub populations as well as treatment of active TB individuals. In chapter 4 we shall provide numerical simulations of our model. Chapter 5 will contain a detailed discussion of results observations and conclusion.

# Chapter 2

# Literature review and Preliminary concepts.

## Introduction.

In this chapter we review the work conducted by other researchers to capture the general information about TB dynamics. We also outline some major concepts that we will apply in our study.

## 2.1 Literature review.

Murphy et al [1] studied TB dynamics in demographically distinct heterogenous population. In their model they stratified the susceptible population into two sub populations; genetically susceptible and genetically neutral. The objective of the study was to investigate the impact of genetic susceptibility in determining persistence and virulence of TB in India and USA. They hypothesised that HLA-DR2 (Human Leukocyte Antigen) susceptibility allele increased probability of direct progression to active TB, increased reactivation rate from dormant TB to infectious TB and increased the likelihood of transmitting or receiving *M. tuberculosis*. Their

results showed that genetic susceptibility increased prevalence and incidence of TB in the host population. Their study did not incorporate any intervention, exogenous reinfection and natural regression as processes contributing to the dynamics of TB infection. Although there are some studies that consider latently infected individuals to be infectious [27], they assumed individuals at latent stage to be uninfectious.

Another study [28] extend the work in [1] to incorporate treatment in the TB dynamics to investigate the effects of treatment in both low (USA) and high (India) growth populations. They assumed that treatment of latently infected individuals reduces the rate of progression to active TB and upon initiation of therapeutics individuals immediately changed their status from actively infected to the latent state. Their, results suggested that TB cannot be eliminated from high-growth population when treatment of actively infected individuals was maintained at low levels $(30 - 50\%)$, regardless of the proportion which is genetically susceptible. They projected that TB could be eradicated in all demographic and genetic susceptibility settings [28] when therapy was administered at high efficacy of between 50 and 80% levels. They showed that intervention strategies targeted only on one population (either latently infected or actively infected) did not substantively reduce TB prevalence in both low and high growth populations irrespective of the level of genetic susceptibility. Rather a combined strategy would be more effective in combating TB. In their model they did not consider natural regression from active TB to latent stage, exogenous reinfection and heterogeneous infection between latently infected and actively infected individuals of both genetically resistant and genetically susceptible populations.

Singer and Kirschener [29] studied the influence of backward bifurcation in a model of TB with exogenous reinfection. Their study assumed that exogenous reinfection of both latently and infected individuals is possible. However, they argued that it is unclear whether the occurrence of exogenous reinfection is common enough to cause a significant impact on TB infection dynamics in the population. Their model depicted two types of bifurcation; the backward bifurcation and transcritical bifurcation. Backward bifurcation occurred when the basic reproduction number

was less than one and transcritical bifurcation occurred when the basic reproduction number was greater than one. Hence, their model disclosed that it is possible for an epidemic to continue invading the susceptible population despite the basic reproduction number being less than one. Their model predicted that the appearance of backward bifurcation depend on the condition that reinfection rate is higher than the initial infection rate [29]. Numerically they showed that backward bifurcation increases with an increase in the level of exogenous reinfection. They also showed that backward bifurcation is less likely to occur in a community where effective treatment is administered. They suggested that treatment of latently infected individuals reduced the likelihood of developing active TB. Their study did not incorporate natural regression and heterogeneous infection between latently and actively infected individuals.

Study done in [30] excluded exogenous reinfection parameter in their model by making a limiting assumption that exogenous reinfection is likely to occur in places that are highly susceptible to the tubercle bacilli or amongst immunocompromised individuals. However, Feng et al [31] in their model for tuberculosis with exogenous reinfection argued that exogenous reinfection cannot be underestimated in developing countries where high TB incidence rates have been observed (greater than 100 per 100, 000). They proposed that in theoretical studies and models it is hard to exclude reinfection in places where HIV seroprevalence is remarkably high (specifically in Africa) [32]. Moreover, high TB incidence rates (more than 160 per 100,000) have been observed in Central Harlem in U.S.A where HIV seroprevalence is also high [31]. Recently there are several studies that support that exogenous reinfection occur in both low and high incidence populations [33, 34].

According to the experimental studies of air-borne tuberculosis conducted in [35] using guinea pig, their findings did not affirm the hypothesis that re-exposure to tuberculosis is likely to result to infection. Furthermore, they suggested that TB can be wiped out if $R_0$ is decreased below a critical value. Basing their research on major cities such as Mexico city, Rio de Janeiro (Brazil), New york city (United States) and Buenos Aires (Argentina) they argued that public transport, immigration and recent population explosion are drastically changing interaction

within the population. Thus rapid growth of urbanization across the globe is likely to have altered epidemiology of TB within the population. Their research emphasized that TB should no longer be viewed as a disease of the poor but social factors are the one likely to influence TB epidemiology.

Derivation of reinfection threshold has become a key phenomena in mathematical models that study effect of reinfection in disease dynamics. For instance [29, 31] showed that TB endemic will only prevail at certain reinfection threshold levels. A value of reinfection within the interval of zero and one imply that primary infection is likely to occur than reinfection. Some studies hypothesize that primary infection provides partial cross immunity to exogenous reinfection [31]. Values of reinfection within $(1, \infty)$ imply that exogenous reinfection is contributing in progression to active TB. Feng et al [31] suggested that a value of reinfection greater than one is likely to be found amongst HIV-infected individuals whose immune system is compromised. In their research they pointed out that invasion threshold did not depend on reinfection parameter but the reinfection parameter appeared in endemic equilibria.

Gomez et al ascertained in [36] that reinfection threshold does exist as demonstrated in their work [37]. They postulated that level of infection increase by two orders of magnitude and there exist a range within which the impact of mass vaccination is significant. Beyond this range mass vaccination cannot eradicate the infection. This was further emphasized by their simulation results which indicated controllable and uncontrollable zones. From their analysis they suggested that reinfection threshold is not a bifurcation point when the rate at which vaccine is administered is less than one. However, the importance of reinfection threshold cannot be underestimated since it can be used to explicate levels of infection and to evaluate the success of vaccination programmes [37].

## 2.2 Evidence of genetic susceptibility to *M. tuberculosis.*

The large-scale association-based population case studies of candidate genes, family-based linkage studies, analysis of individuals highly susceptible to *M. tuberculosis* and comparison with mouse models showed the genetic components that are involved in determining the susceptibility to mycobacterial pathogens [38]. Individual immune response, specifically MHC (Major Histocompatibility Complex) molecules involved in antigen presentation to immune effector cells play a vital role in determining infection outcome upon exposure to Mycobacteria pathogen. Generally the MHC molecules which occur in two classes (class I and II) perform distinct functions in an immune response to tubercle bacilli. HLA molecules (Human Leukocyte Antigen) are the human MHC molecules. Studies disclosed that, increased susceptibility and resistance to at least 500 infections were linked to HLA antigens, alleles, or haplotypes (set of genes that are typically inherited as a unit) [1, 39]. Several HLA alleles were shown to be major contributors to *M. TB* infection susceptibility [40, 41, 42]. Evidence for this was found in India where HLA-DR2 expression was strongly and consistently associated with development of pulmonary TB and acute multi-bacillary form of TB [1, 41, 43, 44].

Experimental studies done on children who genetically inherited immune defects from a similar origin suggested that the children had an increased susceptibility to tuberculosis. This was confirmed to result from the malfunctioning interferon-gamma secretion [45]. Children with deficient interferon gamma developed miliary tuberculosis after vaccination with BCG. Thus, IFN-$\gamma$R played a role in determining disease progression in the community. The results from population case/control studies conducted with 410 individuals diagnosed positive and 417 control experiments of healthy individuals from Gambia (West Africa) who originated from a similar background depicted that four different types of genes in the population were linked to tuberculosis susceptibility [38, 46].

## 2.3 Preliminary concepts.

**Basic reproduction number**-The basic reproduction number, $R_0$ is defined as the average number of new infections that will occur when one infected individual is introduced into a community where everyone is susceptible to the infection. Models describing dynamics of infectious diseases have a disease free equilibrium point at which the susceptible individual remains when there is no infection. Such models are usually characterized by a critical parameter identified as basic reproduction number. The basic reproduction number is computed using Van den Driessche and Watmough approach [47] where entries of matrix $\mathcal{F}$ represent the rate at which new infections appear while entries of matrix $\mathcal{V}$ represent the net outflow of infected individuals into and out of compartment $i$. $F$ and $V$ represent the Jaccobian matrices of $\mathcal{F}$ and $\mathcal{V}$ evaluated at disease free equilibrium point respectively. Moreover, $F$ is a nonegative matrix while $V$ is a non-singular M-matrix. The model is rewritten as

$$\dot{X}(t) = (F - V)x(t), \tag{2.1}$$

where x(t) is a vector. The matrix $K = FV^{-1}$ is defined as the next generation matrix of a dynamical system (2.1). The dominant or maximum real part of all the eigenvalues of matrix $K$ is referred as the spectral bound or abscissa. Generally the dominant eigenvalue is the basic reproduction number.

**Definition 2.3.1.** Positive definite and negative definite function [48].

Let V be a continuous differentiable function such that $V : \mathbb{R}^n \longrightarrow \mathbb{R}^+$. Then V is said to be a positive definite function in a region $\Omega$ of $\mathbb{R}^n$ that contains the origin if:

- $V(0) = 0$,
- $V(x) > 0$ for $x \in \Omega$ and $x \neq 0$.

Replacing the second condition with $V(x) < 0$ then $V(x)$ is considered as negative definite.

**Definition 2.3.2.** Lyapunouv function [48].

A lyapunouv function $\phi : \mathbb{R}^m \longrightarrow \mathbb{R}$ for the system $\dot{x} = f(x)$ is a continuously differentiable positive definite function $\phi$ in $\Omega$ whose derivative along the trajectories of the system satisfies $\dot{\phi}(x) \leq 0$ in $\Omega$. If a Lyapunouv function exists for a system then $x^*$ is a stable equilibrium point for the system. The equilibrium point of the system is considered to be globally asymptotically stable if the derivative of the function along the trajectories of the autonomous system is negative definite in a positively invariant region.

**Definition 2.3.3.** Descartes Rule of Signs [49].

Considering the nth polynomial

$$f(\lambda) = \lambda^n + b_1\lambda^{n-1} + \cdots + b_n = 0 \tag{2.2}$$

and without loss of generality $b_n > 0$. Letting $M$ be the number of sign changes in the sequence of coefficients $\{b_n, b_{n-1}, \cdots, b_0\}$, and ignoring which are zero. Descartes Rule of Signs states that there are at most $M$ roots of the given polynomial (2.2) which are real and nonnegative. Further, the rule states that there are $M - 2k$, $k \geq 0$ and $k \in \mathbb{Z}^+$ real positive roots. If we let $\omega = -\lambda$ and again applying the Descartes Rule of Signs we obtain $M - 2k$ real negative roots.

**Definition 2.3.4.** Jacobian matrix and auxiliary equation [49].

Given a system of $m$ equations in $m$ variables $y_1, \cdots, y_m$, the system can explicitly be written as

$$x = g(y) \tag{2.3}$$

where $x = (x_1, x_2, \cdots x_m)^T$ and $g(y) = (y_1, y_2, \cdots y_m)^T$. The Jacobian matrix $J$ of the system (2.3) is defined by

$$J(y_1, \ldots, y_m) = \begin{pmatrix} \frac{\partial x_1}{\partial y_1} & \cdots & \frac{\partial x_1}{\partial y_m} \\ \vdots & \ddots & \vdots \\ \frac{\partial x_n}{\partial y_1} & \cdots & \frac{\partial x_n}{\partial y_m} \end{pmatrix}$$

An auxiliary or characteristic equation of the system (2.3) is the equation obtained by setting $det(J - \lambda I) = 0$, where $J$ denote the Jacobian matrix.

**Definition 2.3.5.** Routh-Hurwitz criterion [50].

Supposing we have a characteristic polynomial $P(\lambda) = \lambda^n + c_1\lambda^{n-1} + \cdots + c_{n-1}\lambda + c_n$, where the coefficients $c_i$ are real constants, $i = 1 \cdots n$. The $n$ Hurwitz matrices of the characteristic polynomial are given by

$$H_1 = \begin{pmatrix} c_1 \end{pmatrix}, H_2 = \begin{pmatrix} c_1 & 1 \\ c_3 & c_2 \end{pmatrix}, H_3 = \begin{pmatrix} c_1 & 1 & 0 \\ c_3 & c_2 & c_1 \\ c_5 & c_4 & c_3 \end{pmatrix} \textbf{ and}$$

$$H_n = \begin{pmatrix} c_1 & 1 & 0 & 0 \cdots & 0 \\ c_3 & c_2 & c_1 & 1 \cdots & 0 \\ c_5 & c_4 & c_3 & c_2 \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & 0 \cdots & c_n \end{pmatrix}$$

where $c_j = 0$ if $j > n$. The roots of the characteristic polynomial $P(\lambda)$ are non positive or have non positive real part iff the determinant of all Hurwitz matrices are nonnegative. $det(H_j) > 0$, $j = 1, 2, \cdots n$.

**Example 2.3.6.** Routh Hurwitz criterion.

Routh-Hurwitz Criterion for establishing local Stability of $3 \times 3$ matrices (i.e $n = 3$). The auxiliary polynomial of $3 \times 3$ Jacobian matrix can be algebraically stated in the form $\lambda^3 + c_1\lambda^2 + c_2\lambda + c_3 = 0$. If the conditions $c_1 > 0$, $c_3 > 0$ and $c_1c_2 > c_3$ hold then the dynamic system has a locally stable equilibrium.

**Definition 2.3.7.** Backward bifurcation.

The qualitative change that occur by varying parameters of a dynamical system is defined as bifurcation. In models of infectious diseases, the disease free equilibrium point exist for all

parameters values. The basic reproduction number $R_0$ divides the parameter space into two domains: $R_0 < 1$ and $R_0 > 1$ [51]. In most models the disease free equilibrium point is locally stable if it is globally stable. That is we do not have an endemic equilibrium point when $R_0 < 1$. At $R_0 = 1$ the endemic equilibrium point bifurcates. The bifurcation leading from the uninfected state to an endemic state is defined as forward or supercritical bifurcation [51]. As pointed out in [51] there are certain parameter values at which an endemic equilibrium point occur even though the basic reproduction number is less than unity. Such a bifurcation is described as backward bifurcation. For instance, in [29, 31, 37] backward bifurcation occurred due to presence of exogenous reinfection. Other models which showed the existence of backward bifurcation include: SIS models with saturation recoveries [52], models for drug abuse [53, 54], vector disease models [55] and in [56]. The epidemiological significance of backward bifurcation is that the condition $R_0 < 1$ is not sufficient for an epidemic to stop proliferating within the susceptible community.

**Definition 2.3.8.** Sensitivity analysis.

Sensitivity analysis is a method used to determine how changes in parameter values influence the model output. Many parameters used in mathematical models represent quantities that are difficult to obtain or impossible to measure to a great deal of precision in the real world. Sensitivity analysis is a vital process when building or evaluating a mathematical model. Further, sensitivity analysis can be used to show the parameter values that are reasonable to use when modelling. Latin hypercube sampling (LHS) is one of the methods used to perform sensitivity analysis of parameter values [57].

# Chapter 3

# Tuberculosis model incorporating genetic susceptibility without intervention.

## 3.1 Introduction.

The model formulated in Section 3.2 is an extension of the model in [1], where we introduce exogenous reinfection and natural regression. We first omit the heterogeneous interaction of infected and susceptible individuals as illustrated in [1]. The model also does not include intervention parameters. In study of infectious diseases there are two mechanisms of infection, namely, homogeneous and heterogeneous mode of transmission. For the purpose of tracking both infection processes we first investigate TB dynamics using homogeneous mode of transmission and then combine to check the implication brought about by the combined effects. In the homogeneous model we will include heterogeneous interaction between susceptibles $S_s, S_r$ and actively infected TB individuals $A_r, A_s$ and between TB latently infected $L_s, L_r$ and actively infected TB individuals $A_r, A_s$ respectively. Heterogeneous interaction between latently infected TB individuals and actively infected TB individuals has not been investigated in any other model. Again on the heterogeneous TB model we will incorporate treatment among

individuals with clinically active TB.

## 3.2 Model formulation.

We formulate a tuberculosis model without intervention to investigate the role of exogenous reinfection in a genetically susceptible population on the progression of TB. The mathematical model incorporates two genetically susceptible classes of individuals. The susceptible classes are differentiated from each other by their inherited genetic components depicted by their immune response towards *M. tuberculosis* bacteria. Individuals of the population who are resistant to the *M. tuberculosis* are categorized as genetically resistant $S_r$ while those who are sensitive to *M. tuberculosis* infection are classified as genetically sensitive $S_s$. The transmission of *M. tuberculosis* to susceptible individuals results in those who are latently infected $L(t)$ i.e they are infected but cannot transmit *M. tuberculosis* to other individuals. The transmission can also result directly in individuals with active *M. tuberculosis* $A(t)$. Thus, for genetically resistant population we have three different classes: $S_r(t)$, $L_r(t)$, $A_r(t)$. A similar classification holds for the genetically sensitive individuals i.e $S_s(t)$, $L_s(t)$, $A_s(t)$.

The model framework is given in Figure 3.2.

The model represented by the schematic Figure 3.2 exhibits homogeneous transmission of *M. tuberculosis*. Homogeneous transmission occurs when the infection is transmitted to individuals who possess similar genetic characteristics only. This means a genetically resistant individual with active TB can only transmit TB to a genetically resistant susceptible and genetically resistant latent individuals. Similarly a genetically sensitive individual with active TB can only transmit TB to a genetically sensitive susceptible and/or genetically sensitive latent individual. We use a system of non linear ordinary differential equations to model the dynamics of *M. tuberculosis* within the population. We define the total population as:

$$N(t) = S_r(t) + S_s(t) + L_r(t) + L_s(t) + A_r(t) + A_s(t).$$

We assume that recruitment occurs as a result of constant birth ($b$) and/or immigration at a rate $b$. Let $\tau$ ($0 \leq \tau \leq 1$) represent the proportion of individuals who are genetically resistant

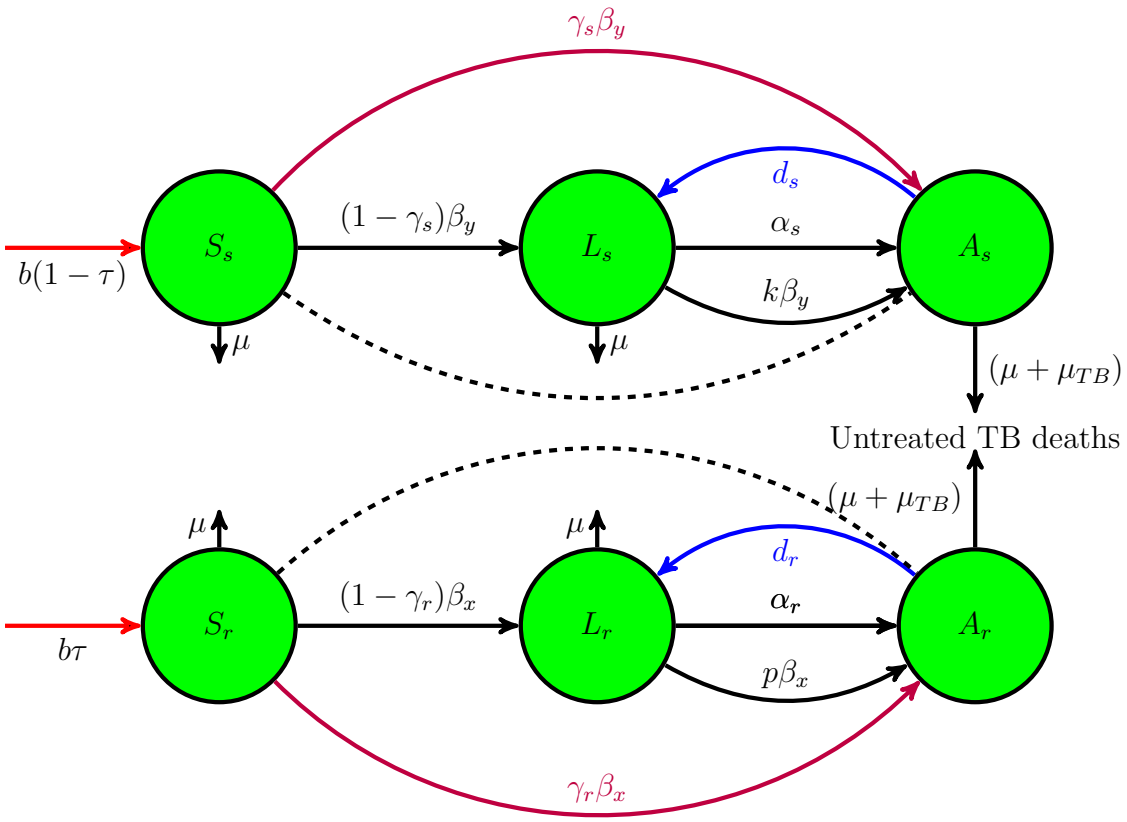



Figure 3.1: A tuberculosis model of genetically resistant individuals ($S_r$, $L_r$, $A_r$) and genetically sensitive individuals ($S_s$, $L_s$, $A_s$). The dotted lines indicate interactions between susceptible and actively infected individuals. The solid arrows indicate movement of individuals after they change their status during the course of infection.

to the *M. tuberculosis* and $1-\tau$ proportion of those who are genetically sensitive. We also assume that the transmission of tuberculosis epidemic occurs as result of sufficient contact due to interaction between individuals of each sub population at rates $\beta_j$ $(j = x, y)$, where $\beta_x$ and $\beta_y$ denote the transmission rates for genetically resistant and genetically sensitive individuals respectively. $\beta_j = \beta c_i$ where $\beta$ is the average number of susceptibles infected by one infectious individual per unit time. $c_i, i \in \{s, r\}$ represent the per-capita contact rates of genetically resistant and genetically sensitive individuals respectively. We consider primary infection where a susceptible individual contracts infection directly from an actively infectious TB individual.

We also consider exogenous reinfection of latently infected individuals by actively infected TB individuals. The genetically resistant and genetically sensitive individuals respond to infection in the following two ways:

(i) They may either be infected with *M. tuberculosis* and their immune system fail to respond, progressing directly to the actively infected class at rates $\gamma_r\beta_x$ (for genetically resistant) and $\gamma_s\beta_y$ (for genetically sensitive).

(ii) The immune system may fight effectively to contain the bacilli but not completely eradicating it, thereby progressing to the latently infected classes at rates $(1-\gamma_r)\beta_x$ (for genetically resistant) and $(1-\gamma_s)\beta_y$ (for genetically sensitive).

Latent TB infection can be reactivated to active TB at rates $\alpha_i$ where $\alpha_i$ represent the probabilities of progression to active TB. Latently infected individuals may develop active TB due to exogenous reinfection at rates $p\beta_x$ and $k\beta_y$ for genetically resistant and genetically sensitive respectively, where $p$ and $k$ represent level of exogenous reinfection. Individuals who are actively infected with TB may naturally recover from the infection (regression) and join the respective latent compartments at rates $d_i$ where $i \in \{r, s\}$. Individuals in all compartments die due to natural causes at rate $\mu$. Some individuals who acquire active TB may die due to illness at rates $\mu_{TB}A_i$, $i \in \{r, s\}$. We make a limiting assumption that death due to illness between the two sub-populations is the same since we are considering average death rate occurring in the susceptible community.The model equations that describe the transmission of *M. tuberculosis* due to genetic susceptibility are given as:

$$\frac{dS_s}{dt} = b(1-\tau) - \lambda_s S_s - \mu S_s, \tag{3.1}$$

$$\frac{dL_s}{dt} = (1-\gamma_s)\lambda_s S_s + d_s A_s - \lambda_s k L_s - (\alpha_s + \mu)L_s, \tag{3.2}$$

$$\frac{dA_s}{dt} = \gamma_s\lambda_s S_s + \lambda_s k L_s + \alpha_s L_s - (d_s + \mu + \mu_{TB})A_s, \tag{3.3}$$

$$\frac{dS_r}{dt} = b\tau - \lambda_r S_r - \mu S_r, \tag{3.4}$$

$$\frac{dL_r}{dt} = (1-\gamma_r)\lambda_r S_r + d_r A_r - \lambda_r p L_r - (\alpha_r + \mu)L_r, \tag{3.5}$$

$$\frac{dA_r}{dt} = \gamma_r\lambda_r S_r + \lambda_r p L_r + \alpha_r L_r - (d_r + \mu + \mu_{TB})A_r. \tag{3.6}$$

Where $\lambda_s = \dfrac{\beta_y A_s}{N}$ and $\lambda_r = \dfrac{\beta_x A_r}{N}$.
We use the standard incidence as a force of infection in our model. $\lambda_s$ is the force of infection for the genetically sensitive sub-population while $\lambda_r$ is the force of infection for genetically resistant sub-population.

## 3.3 Analysis.

### 3.3.1 Feasibility region of the model.

To carry out model analysis we need to establish a biologically feasible region where our model will be biologically meaningful. When there are no genetically sensitive infected individuals and genetically resistant infected individuals in the sub-populations we have $N_s \leq \dfrac{b(1-\tau)}{\mu}$ and $N_r \leq \dfrac{b\tau}{\mu}$ where $N_s$ and $N_r$ denote genetically sensitive and genetically resistant sub-populations respectively. Thus, we investigate the behaviour of our model in $\Omega_0$ where;

$$\Omega_0 = (S_s, S_r, L_s, L_r, A_s, A_r) \in \mathbb{R}^6_+, S_s + L_s + A_s \leq \frac{b(1-\tau)}{\mu},\ S_r + L_r + A_r \leq \frac{b\tau}{\mu}. \tag{3.7}$$

**Theorem 3.3.1.** *The region $\Omega_0$ is positively invariant.*

*Proof.* Considering the fact that $N(t) \leq S_s(t) + S_r(t) + L_s(t) + L_r(t) + A_s(t) + A_r(t)$ satisfy

$$\frac{dN}{dt} = b - \mu N - (A_s + A_r)\mu_{TB} \leq b - \mu N \tag{3.8}$$

The inequality $\frac{dN}{dt} \leq b - \mu N$ generates a first order linear differential equation whose solution yields

$$N(t) = \left(N(0) - \frac{b}{\mu}\right) e^{-\mu t} + \frac{b}{\mu}.$$

As the disease invasion progresses in the sub-populations and time with $N(0) < \frac{b}{\mu}$ tends to infinity we note that the population will reach a carrying capacity $\frac{b}{\mu}$. Consequently, we have

$0 \leq N(t) \leq \dfrac{b}{\mu}$, hence the region $\Omega_0$ is an absorbing set. If $N(0) > \frac{b}{\mu}$ then $\frac{dN}{dt} < 0$, and the population of infected individuals decreases exponentially towards the carrying capacity. Moreover, for $\frac{dN}{dt} > 0$ implies that the population is within the range $0 \leq N \leq \frac{b}{\mu}$. Hence, the total population will increase to approach the maximum value but will not exceed it. We can thus, conclude that solutions stay in $\Omega_0$. Hence, $\Omega_0$ is the positively invariant region. □

### 3.3.2 Disease free equilibrium point.

The equilibrium point which occurs when there are no infected individuals in the susceptible population is defined as the disease free equilibrium point. In our model the disease free equilibrium point is computed by setting the right hand side of the system of differential equations (3.1)-(3.6) to zero and considering that $L_s = L_r = A_s = A_r = 0$. The disease free equilibrium point denoted by $E_0$ is given by,

$$E_0 = \left( \frac{b(1-\tau)}{\mu}, \frac{b\tau}{\mu}, 0, 0, 0, 0 \right). \tag{3.9}$$

### 3.3.3 Basic reproduction number.

One of the most important parameters that explains conditions under which the infection is cleared or persists, is the basic reproduction number denoted as $R_0$. $R_0$ is defined as the expected number of secondary infections that will result when an infected individual is introduced in a completely susceptible population [49]. The basic reproduction number of our TB model would be defined as the rate at which new infections from both genetically sensitive or genetically resistant individuals occur in a disease compartment $i$ after successful interaction with actively infected individuals in compartment $j$. We compute the basic reproduction number using the next generation matrix approach described in [47].

Our model can be written as $\dot{x} = f(x) = \mathcal{F}(x) - \mathcal{V}(x)$ and $\mathcal{V}(x) = \mathcal{V}^-(x) - \mathcal{V}^+(x)$, where $x = (S_s, S_r, L_s, L_r, A_s, A_r)$. $\mathcal{F}(x)$ is matrix for the rate of appearance of new infected individuals in each compartment, $\mathcal{V}^+$ is the rate of transfer of infected individuals into compartment $i$ by all other means and $\mathcal{V}^-$ is the rate of transfer of infected individuals out of compartment $i$ by all

other means. Thus the matrix $\mathcal{V}(x)$ represent the net outflow of individuals from compartment $i$.

The Jaccobian matrix of our dynamic model (3.1)-(3.6) at the disease free equilibrium point can be written as,

$$\dot{x} = (F - V)(x),$$

where $F$ and $V$ are square matrices $(m \times m)$ which have entries given as

$$F = \frac{\partial \mathcal{F}_i(E_0)}{\partial x_j} \text{ and } V = \frac{\partial \mathcal{V}_i(E_0)}{\partial x_j}.$$

Our model has four infective classes $L_s, L_r, A_s$ and $A_r$. From these infective classes we extract matrices $\mathcal{F}(x)$ and $\mathcal{V}(x)$ which are given by

$$\mathcal{F}(x) = \begin{pmatrix} \frac{(1-\gamma_s)\beta_y A_s S_s}{N} \\ \frac{\gamma_s \beta_y A_s S_s}{N} \\ \frac{(1-\gamma_r)\beta_x A_r S_r}{N} \\ \frac{\gamma_r \beta_x A_r S_r}{N} \end{pmatrix},$$

$$\mathcal{V}(x) = \begin{pmatrix} \frac{\beta_y k A_s L_s}{N} + (\alpha_s + \mu)L_s - d_s A_s \\ (d_s + \mu + \mu_{TB})A_s - \alpha_s L_s - \frac{k\beta_y A_s L_s}{N} \\ \frac{\beta_x p A_r L_r}{N} + (\alpha_r + \mu)L_r - d_r A_r \\ (d_r + \mu + \mu_{TB})A_r - \alpha_r L_r - \frac{p\beta_x A_r L_r}{N} \end{pmatrix}.$$

The jacobian matrix of $\mathcal{V}(x)$ evaluated at the disease free equilibrium point $E_0$ denoted by $V$ is given as

$$V = \frac{\partial \mathcal{V}(E_0)}{\partial x_j} = \begin{pmatrix} \alpha_s + \mu & 0 & -d_s & 0 \\ -\alpha_s & 0 & d_s + \mu + \mu_{TB} & 0 \\ 0 & \alpha_r + \mu & 0 & -d_r \\ 0 & -\alpha_r & 0 & d_r + \mu + \mu_{TB} \end{pmatrix}$$

and the jacobian matrix of $\mathcal{F}(x)$ evaluated at the disease free equilibrium point $E_0$ denoted by

$F$ is given as

$$F = \frac{\partial \mathcal{F}(E_0)}{\partial x_j} = \begin{pmatrix} 0 & 0 & \beta_y(1-\gamma_s)(1-\tau) & 0 \\ 0 & 0 & (1-\tau)\gamma_s\beta_y & 0 \\ 0 & 0 & 0 & (1-\gamma_r)\beta_x\tau \\ 0 & 0 & 0 & \gamma_r\beta_x\tau \end{pmatrix}.$$

The inverse matrix for $V$ is

$$V^{-1} = \begin{pmatrix} \frac{1}{D_1(1-\psi_1)} & \frac{d_s}{D_1D_2(1-\psi_1)} & 0 & \\ 0 & 0 & \frac{1}{D_3(1-\psi_2)} & \frac{d_r}{D_3D_4(1-\psi_2)} \\ \frac{\alpha_s}{D_1D_2(1-\psi_1)} & \frac{1}{D_2(1-\psi_1)} & 0 & 0 \\ 0 & 0 & \frac{\alpha_r}{D_3D_4(1-\psi_2)} & \frac{1}{D_3(1-\psi_2)} \end{pmatrix},$$

where $D_1 = \mu + \alpha_s, \quad D_2 = d_s + \mu + \mu_{TB}, \quad D_3 = \mu + \alpha_r, \quad D_4 = d_r + \mu + \mu_{TB}, \quad \psi_1 = \frac{d_s\alpha_s}{D_1D_2} < 1,$ $\psi_2 = \frac{d_r\alpha_r}{D_3D_4} < 1.$

(a) $\psi_1 = \left(\frac{d_s}{D_2}\right)\left(\frac{\alpha_s}{D_1}\right)$ represent movement of infected individuals from latent stage $L_s$ to infectious stage $A_s$,

(b) $\psi_2 = \left(\frac{d_r}{D_4}\right)\left(\frac{\alpha_s}{D_2}\right)$ represent movement of infected individuals from latent compartment $L_r$ to infectious compartment $A_r$,

(c) $\frac{d_s}{D_2} = \frac{d_s}{d_s + \mu + \mu_{TB}}$ represent probability that an individual with clinically active TB in compartment $A_s$ will recover,

(d) $\frac{d_r}{D_4} = \frac{d_r}{d_r + \mu + \mu_{TB}}$ represent that an individual with clinically active TB in compartment $A_r$ will recover,

(e) $\frac{\alpha_s}{D_1} = \frac{\alpha_s}{\mu + \mu_{TB}}$ represent probability that TB latently infected individuals in compartment $L_s$ will progress to active TB $A_s$ through exogenous reinfection,

(f) $\frac{\alpha_r}{D_1} = \frac{\alpha_r}{\mu + \mu_{TB}}$ represent probability that latently infected individuals in compartment $L_r$ will progress to active TB $A_r$ through exogenous reinfection.

The next generation matrix defined by $FV^{-1}$ yields

$$FV^{-1} = \begin{pmatrix} \frac{(1-\tau)(1-\gamma_s)\alpha_s\beta_y}{D_1D_2(1-\psi_1)} & \frac{(1-\tau)(1-\gamma_s)\beta_y}{D_2(1-\psi_1)} & 0 & 0 \\ (1-\tau)\gamma_s\alpha_s\beta_y & (1-\tau)\gamma_s\beta_y & 0 & 0 \\ 0 & 0 & \frac{\tau\gamma_r\alpha_r\beta_x}{D_3D_4(1-\psi_2)} & \frac{\tau\gamma_r\beta_x}{D_3(1-\psi_2)} \end{pmatrix}.$$

The eigenvalues of the matrix $FV^{-1}$ are

$\lambda_1 = \lambda_2 = 0, \quad \lambda_3 = \dfrac{\tau\beta_x[\alpha_r(1-\gamma_r) + D_3\gamma_r]}{D_3D_4(1-\psi_2)}, \quad \lambda_4 = \dfrac{(1-\tau)\beta_y[\alpha_s(1-\gamma_s) + D_1\gamma_s]}{D_1D_2(1-\psi_1)}.$

$\lambda_3$ and $\lambda_4$ are the dominant eigenvalues.

From [49] the basic reproduction number is defined as the spectral radius of the next generation matrix $FV^{-1}$ which is denoted as $\rho(FV^{-1})$.

$$\rho(FV^{-1}) = \max(R_r, R_s) = R_0,$$

where

$$R_r = \lambda_3 = \frac{\tau\beta_x[\alpha_r(1-\gamma_r) + D_3\gamma_r]}{D_3D_4(1-\psi_2)},$$
$$R_s = \lambda_4 = \frac{(1-\tau)\beta_y[\alpha_s(1-\gamma_s) + D_1\gamma_s]}{D_1D_2(1-\psi_1)}.$$

$R_r$ and $R_s$ can be decoupled to yield expressions that can be biologically interpreted.

$$R_r = \underbrace{\frac{\tau\beta_x\alpha_r(1-\gamma_r)}{D_3D_4(1-\psi_2)}}_{N_1} + \underbrace{\frac{\tau\beta_x\gamma_r}{D_4(1-\psi_2)}}_{N_2},$$

$$R_s = \underbrace{\frac{(1-\tau)\beta_y\alpha_s(1-\gamma_s)}{D_1D_2(1-\psi_1)}}_{N_3} + \underbrace{\frac{(1-\tau)\beta_y\gamma_s}{D_2(1-\psi_1)}}_{N_4},$$

where

(i) $N_1$ and $N_3$ represent infections caused by progression from susceptible compartment to infectious compartment via latent compartment of genetically resistant and genetically sensitive individuals respectively,

(ii) $N_2$ and $N_4$ represent infections caused by direct progression to active TB of genetically resistant and genetically sensitive individuals respectively.

(iii) $\frac{1}{D_3D_4(1-\psi_2)}$ is the mean infective period that genetically resistant infected individuals spend in compartments $L_r$ and $A_r$, with $\frac{1}{D_3}$ being duration that infected individuals spend in compartment $L_r$ and $\frac{1}{D_4(1-\psi_2)}$ being duration that genetically resistant infected individuals spend in compartment $A_r$,

(iv) Similarly, $\frac{1}{D_1D_2(1-\psi_1)}$ is the mean infective period that genetically sensitive infected individuals spend in compartments $L_s$ and $A_s$, with $\frac{1}{D_2}$ being duration that infected individuals spend in compartment $L_s$ and $\frac{1}{D_1(1-\psi_1)}$ being duration that genetically sensitive infected individuals spend in compartment $A_s$.

Thus, $R_r$ and $R_s$ are the average numbers of secondary infections that would result when a genetically resistant or genetically sensitive infected individual is introduced in the susceptible population.

**Remark 3.3.1.** Simplification of $R_r$ and $R_s$ yields the following expressions;

$$R_r = \frac{(\alpha_r + \mu\gamma_r)\beta_x\tau}{(\mu+\mu_{TB})\alpha_r + (d_r+\mu_{TB})\mu + \mu^2},$$

$$R_s = \frac{(\alpha_s + \mu\gamma_s)\beta_y(1-\tau)}{(\mu+\mu_{TB})\alpha_s + (d_s+\mu_{TB})\mu + \mu^2},$$

which slightly resemble $R_0$ derived in [1] when only homogeneous transmission of TB is considered.

### 3.3.4 Endemic equilibrium points.

We set the right-hand side of the system of equations (3.1)-(3.6) as follows

$$b(1-\tau) - \frac{\beta_y A_s^* S_s^*}{N^*} - \mu S_s^* = 0, \tag{3.10}$$

$$(1-\gamma_s)\frac{\beta_y A_s^* S_s^*}{N^*} + d_s A_s^* - \frac{\beta_y k A_s^* L_s^*}{N^*} - (\alpha_s + \mu)L_s^* = 0, \tag{3.11}$$

$$\frac{\gamma_s \beta_y A_s^* S_s^*}{N^*} + \frac{\beta_y k A_s^* L_s^*}{N^*} + \alpha_s L_s^* - (d_s + \mu + \mu_{TB})A_s^* = 0, \tag{3.12}$$

$$b\tau - \frac{\beta_x A_x^* S_r^*}{N^*} - \mu S_r^* = 0, \tag{3.13}$$

$$(1-\gamma_r)\frac{\beta_x A_r^* S_r^*}{N^*} + d_r A_r^* - \frac{\beta_x p A_r^* L_r^*}{N^*} - (\alpha_r + \mu)L_r^* = 0, \tag{3.14}$$

$$\frac{\gamma_r \beta_x A_r^* S_r^*}{N^*} + \frac{\beta_x p A_r^* L_r^*}{N^*} + \alpha_s L_r^* - (d_r + \mu + \mu_{TB})A_r^* = 0. \tag{3.15}$$

We use the limiting system where $N^* = \frac{b}{\mu}$ to ensure mathematical tractability. From equations (3.10) and (3.11) we obtain $S_s^*$ and $L_s^*$ as

$$S_s^* = \frac{b^2(1-\tau)}{\mu(\beta_y A_s^* + b)},$$

$$L_s^* = \frac{b^2(1-\gamma_s)A_s^*\beta_y(1-\tau) + b d_s A_s^*(\beta_y A_s^* + b)}{(\beta_y A_s^* + b)[\beta_y k A_s^* \mu + b(\alpha_s + \mu)]}.$$

Substituting both $S_s^*$ and $L_s^*$ in equation (3.12) yields the following expression

$$\begin{aligned} A_s^*[&\mu\beta_y\gamma_s b(1-\tau)(\beta_y\mu k A_s^* b(\alpha_s+\mu)) + \beta_y k\mu(b(1-\tau)(1-\gamma_s)\beta_y\mu A_s^* + d_s\mu(\beta_y A_s^* + b)A_s^*) \\ &+ \alpha_s b^2(1-\tau)(1-\gamma_s)\beta_y\mu + \alpha_s b d_s \mu(\beta_y A_s^* + b) \\ &- (d_s + \mu + \mu_{TB})\mu(\beta_y A_s^* + b)[\beta_y\mu k A_s^* + b(\alpha_s+\mu)]] = 0. \end{aligned} \tag{3.16}$$

We have $A_s^* = 0$ or

$$\begin{aligned}
&\mu\beta_y\gamma_s b(1-\tau)(\beta_y\mu k A_s^* b(\alpha_s+\mu)) + \beta_y k\mu(b(1-\tau)(1-\gamma_s)\beta_y\mu A_s^* + d_s\mu(\beta_y A_s^* + b)A_s^*) \\
&\quad + \alpha_s b^2(1-\tau)(1-\gamma_s)\beta_y\mu + \alpha_s b d_s\mu(\beta_y A_s^* + b) \\
&\quad - (d_s+\mu+\mu_{TB})\mu(\beta_y A_s^* + b)[\beta_y\mu k A_s^* + b(\alpha_s+\mu)] = 0.
\end{aligned} \tag{3.17}$$

$A_s^* = 0$ correspond to the disease free equilibrium while equation (3.17) can be rewritten as

$$f(A_s^*) = X_1 A_s^{*2} + X_2 A_s^* + X_3 = 0, \tag{3.18}$$

where

$$X_1 = k\mu\beta_y^2(\mu+\mu_{TB}) \tag{3.19}$$

$$X_2 = \beta_y\left[bk\mu(\mu+\mu_{TB}) + \frac{bk\mu^2(1-\tau)\beta_y\gamma_s}{\alpha_s} + b[\mu^2 + (\mu+\mu_{TB})\alpha_s + (d_s+\mu_{TB})\mu]\left(1 - \frac{k\mu R_s}{\alpha_s}\right)\right], \tag{3.20}$$

$$X_3 = b^2[\mu^2 + (\mu+\mu_{TB})\alpha_s + (d_s+\mu_{TB})\mu][1-R_s]. \tag{3.21}$$

From equation (3.13) and (3.14) we have

$$S_r^* = \frac{b^2\tau}{\mu(\beta_x A_r^* + b)},$$

$$L_r^* = \frac{b^2(1-\gamma_r)A_r^*\beta_x\tau + b d_r A_r^*(\beta_x A_r^* + b)}{(\beta_y A_r^* + b)[\beta_x p A_r^*\mu + b(\alpha_r+\mu)]}.$$

and substituting $S_r^*$ and $L_r^*$ in equation (3.15) and simplifying yields $A_r^* = 0$ (correspond to the disease free equilibrium) and

$$f(A_r^*) = Y_1 A_r^{*2} + Y_2 A_r^* + Y_3 = 0, \tag{3.22}$$

where

$$Y_1 = p\mu\beta_x^2(\mu+\mu_{TB}), \tag{3.23}$$

$$Y_2 = \beta_x\left[bp\mu(\mu+\mu_{TB}) + \frac{bp\mu^2\tau\beta_x\gamma_r}{\alpha_r} + b[\mu^2 + (\mu+\mu_{TB})\alpha_r + (d_r+\mu_{TB})\mu]\left(1 - \frac{p\mu R_r}{\alpha_r}\right)\right], \tag{3.24}$$

$$Y_3 = b^2[\mu^2 + (\mu+\mu_{TB})\alpha_r + (d_r+\mu_{TB})\mu][1-R_r]. \tag{3.25}$$

The endemic equilibrium points are given as

$$\begin{aligned}
S_s^* =& \frac{b^2(1-\tau)}{\mu(\beta_y A_s^* + b)},\\
L_s^* =& \frac{b^2(1-\gamma_s)A_s^*\beta_y(1-\tau) + bd_s A_s^*(\beta_y A_s^* + b)}{(\beta_y A_s^* + b)[\beta_y k A_s^* \mu + b(\alpha_s + \mu)]},\\
S_r^* =& \frac{b^2\tau}{\mu(\beta_x A_r^* + b)},\\
L_r^* =& \frac{b^2(1-\gamma_r)A_r^*\beta_x\tau + bd_r A_r^*(\beta_x A_r^* + b)}{(\beta_y A_r^* + b)[\beta_x p A_r^* \mu + b(\alpha_r + \mu)]}.
\end{aligned}$$

$A_r^*$ and $A_s^*$ are obtained by solving (3.18) and (3.22).

We continue to investigate the behaviour of the model by computing the exogenous reinfection thresholds as derived in [31].

$$p_0 = \frac{(1+W_r)D_3}{1-X_r} \text{ and } k_0 = \frac{(1+W_s)D_1}{1-X_s}, \tag{3.26}$$

where $D_3 = \dfrac{\alpha_r}{(\alpha_r+\mu)}$, $D_1 = \dfrac{\alpha_s}{\alpha_s+\mu}$, $W_r = \dfrac{\alpha_r}{d_r+\mu+\mu_{TB}}$ and $W_s = \dfrac{\alpha_s}{d_r+\mu+\mu_{TB}}$.

$D_3$ and $D_1$ represent the probability of individuals who survive from the latently infected compartment and move to the infectious stage.
$W_r$ and $W_s$ represent the duration exposed individuals spend in infectious compartment multiplied by the rate at which they leave latently infected compartment.
To compute the critical values of $R_r$ and $R_s$ we rewrite $X_1, X_2, X_3$ and $Y_1, Y_2, Y_3$ as

$$\begin{aligned}
X_1 =& k\mu\beta_y^2(\mu+\mu_{TB}),\\
X_2 =& \Theta_1 + \Pi_1(1-\varphi_1 R_s),\\
X_3 =& b\Pi_1(1-R_s).
\end{aligned}$$

$$\begin{aligned}
Y_1 =& p\mu\beta_x^2(\mu+\mu_{TB}),\\
Y_2 =& \Theta_2 + \Pi_2(1-\varphi_2 R_r),\\
Y_3 =& b\Pi_2(1-R_r).
\end{aligned}$$

where

$$\begin{aligned}
\Theta_1 =&\beta_y \left[ bk\mu(\mu + \mu_{TB}) + \frac{b(1-\tau)k\mu^2\beta_y\gamma_s}{\alpha_s} \right], \\
\Pi_1 =&b\alpha_s d_s \left( \frac{\alpha_s}{d_s D_1 W_s} - 1 \right), \\
\varphi_1 =&\frac{k\mu}{\alpha_s}, \\
\Theta_2 =&\beta_x \left[ bp\mu(\mu + \mu_{TB}) + \frac{b\tau p\mu^2\beta_x\gamma_r}{\alpha_r} \right], \\
\Pi_2 =&b\alpha_r d_r \left( \frac{\alpha_r}{d_r D_3 W_r} - 1 \right), \\
\varphi_2 =&\frac{p\mu}{\alpha_r}.
\end{aligned}$$

The derivation of $\Pi_1$ and $\Pi_2$ is shown in the **Appendix A**. The critical value of the basic reproduction number $R_s$ is obtained by setting the discriminant $\triangle_s$, of the quadratic equation (3.18) to zero.

$$\triangle_s = X_2^2 - 4X_1X_3 = 0,$$

which results in the expression

$$\begin{aligned}
\triangle_s =&\Pi_1^2\varphi_1^2 R_s^2 + [4b\Pi_1 k\mu^2\beta_y^2 + 4b\Pi_1 k\mu\beta_y^2\mu_{TB} - 2\Pi_1^2\varphi_1 \\
&- 2\Theta_1\Pi_1\varphi]R_s + [\Theta_1^2 + 2\Theta_1\Pi_1 + \Pi^2 - 4b\Pi_1 k\mu^2\beta_y^2 - 4b\Pi_1 k\mu\beta_y^2\mu_{TB}] = 0.
\end{aligned} \tag{3.27}$$

Solving (3.27) we obtain the following

$$R_{sc} = \frac{1}{\Pi_1\varphi_1}[\varphi_1(\Theta_1 + \Pi_1) - 2bk\beta_y^2\mu(\mu + \mu_{TB})] + \frac{2\beta_y}{\Pi_1\varphi_1^2}\sqrt{\Gamma_1 + \Gamma_2}, \tag{3.28}$$

where

$$\Gamma_1 = bk\mu\mu_{TB}(2bk\mu^2\beta_y^2 + \Pi_1\varphi_1^2 + bk\mu\beta_y^2\mu_{TB} - \Pi_1\varphi_1), \tag{3.29}$$

$$\Gamma_2 = b\mu(\Pi_1\varphi_1^2 + k^2 b\mu^3\beta_y^2 - \Theta_1 k\mu\varphi_1 - \Pi_1 k\mu\varphi_1 - \Theta_1 k\varphi_1). \tag{3.30}$$

Similarly setting the discriminant $\triangle_r = Y_2^2 - 4Y_1Y_3 = 0$ we can derive $R_{rc}$ as

$$R_{rc} = \frac{1}{\Pi_2\varphi_2}[\varphi_2(\Theta_2 + \Pi_2) - 2bp\beta_x^2\mu(\mu + \mu_{TB})] + \frac{2\beta_x}{\Pi_2\varphi_2^2}\sqrt{\Gamma_3 + \Gamma_4}, \tag{3.31}$$

where

$$\Gamma_3 = bp\mu\mu_{TB}(2bp\mu^2\beta_x^2 + \Pi_2\varphi_2^2 + bp\mu\beta_x^2\mu_{TB} - \Pi_2\varphi_2), \tag{3.32}$$

$$\Gamma_4 = b\mu(\Pi_2\varphi_2^2 + k^2b\mu^3\beta_x^2 - \Theta_1 p\mu\varphi - \Pi_2 p\mu\varphi_2 - \Theta_1 p\varphi_1). \tag{3.33}$$

Thus the critical value of $R_0$ denoted by $R_c$ is given by the maximum of $R_{rc}$ and $R_{sc}$.

$$R_c = \max(R_{rc}, R_{sc}). \tag{3.34}$$

The TB model without any intervention governed by the system of differential equations (3.1)-(3.6) can now be analysed using the following cases:

**Case 3.3.5.** $R_0 > 1 \implies R_r > 1$ and $R_s > 1$. $R_0 > 1$ imply that $X_3$ and $Y_3$ are both negative. Thus the discriminants $\triangle_s > 0$ and $\triangle_r > 0$. This means that each of the expressions (3.18) and (3.22) has a positive root. Thus, our TB model has a unique positive endemic equilibrium when $R_0 > 1$.

**Case 3.3.6.** $R_0 < 1 \quad (R_r < 1$ and $R_s < 1)$ and $p < p_0$, $k < k_0$. From quadratic expressions (3.18) and (3.22) we note that $Y_1, Y_3$ and $X_1, X_3$ are nonnegative. $X_2$ and $Y_2$ are either positive or negative. By the Descartes rule of signs we have two negative roots when $X_2$ and $Y_2$ are both negative and no positive root when they are both nonnegative. Thus, our model system has no positive endemic equilibria.

**Case 3.3.7.** $R_c < R_0 < 1,\ p > p_0$ and $k > k_0$. As derived in (3.28) and (3.31) our model has two nonnegative critical values denoted by $R_{rc}$ and $R_{sc}$.

In case (3.3.7), the model exhibits a backward bifurcation where the disease free equilibrium occur concurrently with the endemic equilibria. The exogenous reinfection parameters do not directly appear in the vital epidemiological threshold $R_0$ but indirectly contribute to the complication in the TB dynamics by inducing a backward bifurcation. This shows that the exogenous reinfection of TB cannot be ignored when assessing the impact of TB infection in a community with TB genetic susceptibility. Exogenous reinfection may result in regeneration of TB infection in the community.

**Remark 3.3.2.** We note that $R_0 > 1$ can also mean that either $R_r > 1$ and $R_s < 1$ or $R_r < 1$ and $R_s > 1$. In this case the progression of TB infection is determined solely either by the genetically sensitive population or by the genetically resistant population. However, disease progression is likely to be favoured when both $R_s$ and $R_r$ are greater than one.

### 3.3.8 Stability of the disease free equilibrium point.

The local stability of the disease free equilibrium point is obtained from the analysis of the jacobian matrix of the infective classes which is given as

$$F - V = \begin{pmatrix} -(\alpha_s + \mu) & 0 & (1-\gamma_s)(1-\tau)\beta_y + d_s & 0 \\ \alpha_s & 0 & \gamma_s(1-\tau)\beta_y - (d_s + \mu + \mu_{TB}) & 0 \\ 0 & -(\alpha_r + \mu) & 0 & (1-\gamma_r)\tau\beta_x + d_r \\ 0 & \alpha_r & 0 & \gamma_r\tau\beta_x - (d_r + \mu + \mu_{TB}) \end{pmatrix}.$$

The criterion for the local stability of the disease free equilibrium point is that the eigenvalues of the jacobian matrix evaluated at $E_0$ must either be negative or have negative real parts. Computing the eigenvalues we obtain the following four real eigenvalues

$$\delta_g = -\frac{1}{2}A_1 \pm \sqrt{\left(\frac{A_1}{2}\right)^2 - \frac{1}{C_1}[1 - R_r]},$$
$$\delta_h = -\frac{1}{2}B_1 \pm \sqrt{\left(\frac{B_1}{2}\right)^2 - \frac{1}{C_1}[1 - R_s]},$$

where

$$A_1 = 2\mu + d_r + \alpha_r + \mu_{TB} - \tau\beta_x\gamma_r,$$
$$B_1 = 2\mu + d_s + \alpha_s + \mu_{TB} - (1-\tau)\beta_y\gamma_s,$$
$$C_1 = (d_i + \mu_{TB})\mu + (\mu + \mu_{TB})\alpha_i + \mu^2.$$

$g, h \in \{1, 2\}$ and $i \in \{s, r\}$.

We note that eigenvalues $\delta_g < 0$ if and only if $R_r < 1$ and $R_{r1} = \dfrac{\tau\beta_x\gamma_r}{d_r + \mu + \mu_{TB}} < 1$.

Similarly $\delta_h < 0$ if $R_s < 1$ and $R_{s1} = \dfrac{(1-\tau)\gamma_s\beta_y}{d_s+\mu+\mu_{TB}} < 1$.

$R_{r1}$ and $R_{s1}$ represent ratios of primary progression rate to duration infected individuals in each sub population spend in infectious stages.

**Lemma 3.3.3.** *Provided the basic reproduction numbers $R_r$, $R_s$ and the ratio of primary progression rate in genetically resistant and genetically sensitive sub population to duration infected individuals spend in each sub population are less than one then the disease free equilibrium point is locally asymptotically stable.*

### 3.3.9 Global stability of the disease free equilibrium point.

To analyse the global stability of the disease free equilibrium point we define a Lyapunouv-Lassalle function as:

$$V = \alpha_s L_s + \alpha_r L_r + (\alpha_s+\mu)A_s + (\alpha_r+\mu)A_r. \tag{3.35}$$

The derivative of the function along the trajectories of our TB model (3.1)-(3.6) is

$$\dot{V} = \alpha_s \dot{L}_s + \alpha_r \dot{L}_r + (\alpha_s+\mu)\dot{A}_s + (\alpha_r+\mu)\dot{A}_r. \tag{3.36}$$

Substituting the expression for $\dot{L}_r$, $\dot{L}_s$, $\dot{A}_r$, and $\dot{A}_s$ yields

$$\begin{aligned}
\dot{V} =& \alpha_s \left[ \frac{(1-\gamma_s)\beta_y A_s S_s \mu}{b} + d_s A_s - \frac{\beta_y k A_s L_s \mu}{b} - (\alpha_s+\mu)L_s \right] \\
&+ \alpha_r \left[ \frac{(1-\gamma_r)\beta_x A_s S_r \mu}{b} + d_r A_r - \frac{\beta_x p A_r L_r \mu}{b} - (\alpha_r+\mu)L_r \right] \\
&+ (\alpha_s+\mu) \left[ \frac{\gamma_s\beta_y A_s S_s \mu}{b} \frac{\beta_y k A_s L_s \mu}{b} + \alpha_s L_s - (d_s+\mu+\mu_{TB})A_s \right] \\
&+ (\alpha_r+\mu) \left[ \frac{\gamma_r\beta_x A_r S_r \mu}{b} + \frac{\beta_x p A_r L_r \mu}{b} + \alpha_r L_r - (d_r+\mu+\mu_{TB})A_r \right].
\end{aligned} \tag{3.37}$$

Expanding and simplifying (3.37) yields

$$\dot{V} = \left[\frac{\mu}{b}(\alpha_s + \mu\gamma_s)\beta_y S_s\right] A_s + \frac{\mu^2}{b}\beta_y k A_s L_s - [\mu d_s + \alpha_s\mu + \alpha_s\mu_{TB} + \mu\mu_{TB} + \mu^2]A_s$$

$$+ \left[\frac{\mu}{b}(\alpha_r + \mu\gamma_r)S_r\right] A_r + \frac{\mu^2}{b}\beta_x p A_r L_r - [\mu\alpha_r + \alpha_r\mu_{TB} + \mu d_r + \mu\mu_{TB} + \mu^2]$$

$$= \frac{R_s A_s}{[\mu^2 + (\mu + \mu_{TB})\alpha_r + (d_r + \mu_{TB})\mu]} + \frac{\mu^2\beta_y k A_s L_s}{bQ_1} - \frac{A_s}{[\mu^2 + (\mu + \mu_{TB})\alpha_r + (d_r + \mu_{TB})\mu]}$$

$$+ \frac{R_r A_r}{[\mu^2 + (\mu + \mu_{TB})\alpha_s + (d_s + \mu_{TB})\mu]} + \frac{\mu^2\beta_x p A_r L_r}{bQ_1} - \frac{A_s}{[\mu^2 + (\mu + \mu_{TB})\alpha_r + (d_r + \mu_{TB})\mu]}$$

$$= \frac{\mu^2(\beta_y k A_s L_s + \beta_x p A_r L_r)}{bQ_1} + \frac{A_s}{[\mu^2 + (\mu + \mu_{TB})\alpha_r + (d_r + \mu_{TB})\mu]}(R_r - 1)$$

$$+ \frac{A_r}{[\mu^2 + (\mu + \mu_{TB})\alpha_s + (d_s + \mu_{TB})\mu]}(R_s - 1) \not\leqslant 0 \text{ for } R_0 \leqslant 1,$$

where $Q_1 = [\mu^2 + (\mu + \mu_{TB})\alpha_s + (d_s + \mu_{TB})\mu]\,[\mu^2 + (\mu + \mu_{TB})\alpha_r + (d_r + \mu_{TB})\mu]$.

**Remark 3.3.4.**

(i) $R_0 \leq 1$ and $k, p > 0$. In the presence of exogenous reinfection $\dot{V} > 0$. Hence, the disease free equilibrium point fails to be globally stable in the Lyapunouv sense.

(ii) $R_0 \leq 1$ and $k = p = 0$. In the absence of exogenous reinfection $\dot{V} \leq 0$ implying that the disease free equilibrium point of TB model is globally stable.

(iii) Remarks (i) and (ii) shows that the presence of exogenous reinfection hampers the eradication of TB infection in the absence of intervention in the sense that the community will never have a permanent disease free situation.

### 3.3.10 Stability analysis of the endemic equilibrium.

To investigate local stability of the system of equations (3.1)-(3.6) we consider the jacobian matrix of the full system of equations (3.1)-(3.6) and evaluate the matrix at the endemic equilibria of case (3.3.5). The resulting matrix has a block triangular form and therefore we can extract two $3 \times 3$ matrices denoted as $J_1$ and $J_2$.

$$J = \left(\begin{array}{c|c} J_1 & 0 \\ \hline 0 & J_2 \end{array}\right).$$

$J_1$ is a Jacobian matrix representing genetically sensitive individuals and $J_2$ is a matrix representing genetically resistant individuals. Since our model exhibit backward bifurcation we have a unique positive endemic equilibria when $R_0 > 1$. Positive endemic equilibria is based on the nonnegativity of $A_s^*$ and $A_r^*$ as observed in the quadratic expressions (3.18) and (3.22). Our $3 \times 3$ Jacobian matrices are

$$J_1 = \begin{pmatrix} -\frac{(\beta_y A_s^* + b\mu)}{b} & 0 & -\frac{\beta_y S_s^* \mu}{b} \\ \frac{(1-\gamma_s)\beta_y A_s^* \mu}{b} & \frac{-(\beta_y k A_s^* \mu + b(\alpha_s + \mu))}{b} & \frac{(1-\gamma_s)\beta_y S_s^* \mu + bd_s - \beta_y k L_s^* \mu}{b} \\ \frac{\gamma_s \beta_y A_s^* \mu}{b} & \frac{[\beta_y k A_s^* \mu + b\alpha_s]}{b} & \frac{(\gamma_s \beta_y S_s^* \mu + \beta_y k L_s^* \mu - b(d_s + \mu + \mu_{TB}))}{b} \end{pmatrix},$$

and

$$J_2 = \begin{pmatrix} -\frac{(\beta_x A_r^* + b\mu)}{b} & 0 & -\frac{\beta_x S_r^* \mu}{b} \\ \frac{(1-\gamma_r)\beta_x A_r^* \mu}{b} & \frac{-(\beta_x p A_r^* \mu + b(\alpha_r + \mu))}{b} & \frac{[(1-\gamma_r)\beta_x S_r^* \mu + bd_r - \beta_x p L_r^* \mu]}{b} \\ \frac{\gamma_r \beta_x A_r^* \mu}{b} & \frac{[\beta_x p A_r^* \mu + b\alpha_r]}{b} & \frac{(\gamma_r \beta_x S_r^* \mu + \beta_x p L_r^* \mu - b(d_r + \mu + \mu_{TB}))}{b} \end{pmatrix}.$$

The symmetry of our TB model allows us to consider any of the Jacobian matrices. Since we cannot obtain closed form of the eigenvalues of $J_1$ and $J_2$ we apply Routh- Hurwitz criterion to investigate local stability. The characteristic polynomial of $J_1$ is given as:

$$P(\lambda) = \lambda^3 + c_1\lambda^2 + c_2\lambda + c_3, \tag{3.38}$$

where

$$
\begin{aligned}
c_1 =& \frac{1}{b}\left[(\beta_y k A_s^* \mu + b(\alpha_s+\mu)) + (\beta_y A_s^* + b\mu) - (\gamma_s \beta_y S_s^* \mu + \beta_y k L_s^* \mu - b(d_s+\mu+\mu_{TB}))\right], \\
c_2 =& \frac{1}{b^2}[(\beta_y k A_s^* \mu + b(\alpha_s+\mu))(\beta_y A_s^* \mu + b\mu) + \gamma_s \beta_y^2 A_s^* \mu^2 \\
& - (\beta_y k A_s^* \mu + b\alpha_s)((1-\gamma_s)\beta_y S_s^* \mu + b d_s - \beta_y k L_s^* \mu) \\
& - (\beta_y k A_s^* \mu + b(\alpha_s+\mu))(\gamma_s \beta_y S_s^* \mu + \beta_y k L_s^* \mu - b(d_s+\mu+\mu_{TB})) \\
& - (\gamma_s \beta_y S_s^* \mu + \beta_y k L_s^* \mu - b(d_s+\mu+\mu_{TB}))(\beta_y A_s^* \mu + b\mu)], \\
c_3 =& \frac{1}{b^3}(\beta_y k A_s^* \mu + b\alpha_s)[(1-\gamma_s)\beta_y^2 A_s^* S_s^* \mu^2 - (\beta_y A_s^* \mu + b\mu)((1-\gamma_s)\beta_y S_s^* \mu + b d_s - \beta_y k L_s^* \mu)] \\
& + \frac{1}{b^3}(\beta_y k A_s^* \mu + b(\alpha_s+\mu))[\gamma_s \beta_y S_s^* \mu + (\beta_y k L_s^* \mu - b(d_s+\mu+\mu_{TB})) \\
& - (\gamma_s \beta_y S_s^* \mu + \beta_y k L_s^* \mu - b(d_s+\mu+\mu_{TB}))(\beta_y A_s^* \mu + b\mu)].
\end{aligned}
$$

$$
c_1 > 0 \Longleftrightarrow (\gamma_s \beta_y S_s^* \mu + \beta_y k L_s^* \mu < b(d_s+\mu+\mu_{TB}),
$$

$$
c_3 > 0 \Longleftrightarrow (\gamma_s \beta_y S_s^* \mu + \beta_y k L_s^* \mu < b(d_s+\mu+\mu_{TB}),
$$

$$
\frac{(1-\gamma_s)\beta_y^2 A_s^* S_s^* \mu^2 + (\beta_y A_s^* \mu + b\mu)\beta_y k L_s^* \mu}{(\beta_y A_s^* \mu + b\mu)((1-\gamma_s)\beta_y S_s^* \mu + b d_s)} > 1.
$$

We now multiply $c_1$ and $c_2$ and express it in the form $\hbar + c_3 > c_3$.

$c_1.c_2 = \hbar + c_3$ where

$$\begin{aligned}
\hbar =& \frac{1}{b^3}(\beta_y k A_s^* \mu + b(\alpha_s + \mu))(\beta_y A_s^* \mu + b\mu)[(\beta_y k A_s^* \mu + b(\alpha_s + \mu)) + (\beta_y A_s^* \mu + b\mu)] \\
& \frac{\gamma_s \beta_y^2 A_s^* \mu^2}{b^2}[(\beta_y A_s^* \mu + b\mu) - (\gamma_s \beta_y S_s^* \mu + \beta_y k L_s^* \mu - b(d_s + \mu + \mu_{TB}))] \\
& - \frac{1}{b^3}(\beta_y k A_s^* \mu + b(\alpha_s + \mu))(\gamma_s \beta_y S_s^* \mu + \beta_y k L_s^* \mu - b(d_s + \mu + \mu_{TB}))[(\beta_y k A_s^* \mu + b(\alpha_s + \mu)) \\
& - (\gamma_s \beta_y S_s^* \mu + \beta_y k L_s^* \mu - b(d_s + \mu + \mu_{TB}))] \\
& - \frac{1}{b^3}(\gamma_s \beta_y S_s^* \mu + \beta_y k L_s^* \mu - b(d_s + \mu + \mu_{TB}))(\beta_y A_s^* \mu + b\mu)[(\beta_y k A_s^* + b(\alpha_s + \mu)) \\
& - (\gamma_s \beta_y S_s^* \mu + \beta_y k L_s^* \mu - b(d_s + \mu + \mu_{TB}))] \\
& - \frac{1}{b^3}(\beta_y A_s^* \mu + b\mu)(\gamma_s \beta_y S_s^* \mu + \beta_y k L_s^* \mu - b(d_s + \mu + \mu_{TB})) \\
& \times [(\beta_y A_s^* \mu + b\mu) + (\beta_y k A_s^* \mu + b(\alpha_s + \mu))] \\
& - \frac{1}{b^3}(\beta_y A_s^* \mu + b\mu)[(\beta_y k A_s^* \mu + b(\alpha_s + \mu)) \\
& \times ((1 - \gamma_s)\beta_y S_s^* \mu + b d_s - \beta_y k L_s^* \mu) + (1 - \gamma_s)\beta_y^2 A_s^* S_s^* \mu^2] \\
& + (\gamma_s \beta_y S_s^* \mu + \beta_y k L_s^* \mu - b(d_s + \mu + \mu_{TB}))[(\beta_y k A_s^* \mu + b\alpha_s)((1 - \gamma_s)\beta_y S_s^* \mu + b d_s - \beta_y k L_s^* \mu)].
\end{aligned}$$

Thus $c_1.c_2 = \hbar + c_3 > c_3$ provided $\hbar > 0$. Now, $\hbar > 0$ provided the following conditions hold:

(i) $\dfrac{(\gamma_s \beta_y S_s^* + \beta_y k L_s^*)}{(d_s + \mu + \mu_{TB})} < 1,$

(ii) $\dfrac{(\beta_y k A_s^* \mu + b(\alpha_s + \mu))\beta_y k L_s^* \mu}{(1 - \gamma_s)\beta_y^2 A_s^* S_s^* \mu + (\beta_y k A_s^* \mu + b(\alpha_s + \mu))((1 - \gamma_s)\beta_y S_s^* + b d_s)} > 1,$

(iii) $\dfrac{(1 - \gamma_s)\beta_y S_s^* \mu + b d_s}{\beta_y k L_s^* \mu} < 1.$

Thus the endemic equilibrium point in case (3.3.5) is locally stable when all the conditions (i)-(iii) are satisfied. We observe that for conditions (i)-(iii) to hold, $R_0 > 1$.

## 3.4 Model incorporating heterogeneous transmission.

In this section we modify the model in Section 3 to include heterogeneous TB transmission. By heterogeneous transmission we mean that TB infection is transmitted to individuals with different genetic characteristics. We introduce contact rates $\beta_w$ and $\beta_z$ as the new transmission parameters that represent interaction between genetically susceptible individuals and actively infected individuals.

$\beta_w$ represent rate of TB transmission between genetically sensitive susceptible individuals and genetically resistant active TB individuals while $\beta_z$ represent adequate transmission between genetically resistant susceptible individuals and genetically sensitive TB active individuals. Thus, the term $\frac{\beta_w S_s A_r}{N} = \lambda_w S_s$ represent the force of infection as a result of interaction between genetically sensitive susceptible individuals in compartment $S_s$ and genetically resistant TB active individuals in compartment $A_r$. Similarly, $\frac{\beta_z S_r A_s}{N} = \lambda_z S_r$ represents the force of infection due to interaction between individuals in compartment $S_r$ and individuals in compartment $A_s$. Individuals infected through the forces of infection $\lambda_w S_s$ and $\lambda_z S_r$ progress either directly to active TB stage or indirectly through the latent TB stages in both genetically sensitive and genetically resistant populations. The terms $\frac{(1-\gamma_s)\beta_w S_s A_r}{N} = (1-\gamma_s)\lambda_w S_r$ and $\frac{(1-\gamma_r)\beta_z S_r A_s}{N} = (1-\gamma_r)\lambda_z S_r$ represent progression to compartments $L_r$ and $L_s$ respectively, due to heterogeneous transmission of TB. The terms $\frac{\gamma_r \beta_w S_s A_r}{N}$ and $\frac{\gamma_s \beta_z S_r S_s}{N}$ represent progression to the active TB compartments $A_r$ and $A_s$ respectively. We also assume that latent infected individuals can be reinfected by both genetically resistant and genetically sensitive actively infected individuals. Hence, we introduce the terms $\frac{k\beta_w A_r L_s}{N} = \lambda_w k L_s$ and $\frac{p\beta_z A_s L_r}{N} = \lambda_z p L_r$ in latently and actively infected compartments. We have $\frac{k\beta_w A_r L_s}{N}$ representing exogenous reinfection due to interaction between genetically resistant TB actively infected individuals and genetically sensitive latently infected TB individuals and $\frac{p\beta_z A_s L_r}{N}$ representing exogenous reinfection occurring due to interaction between genetically sensitive TB active individuals and genetically resistant TB latently infected individuals. The new model framework is represented in Figure 3.2. The new model with heterogeneous transmission is given by

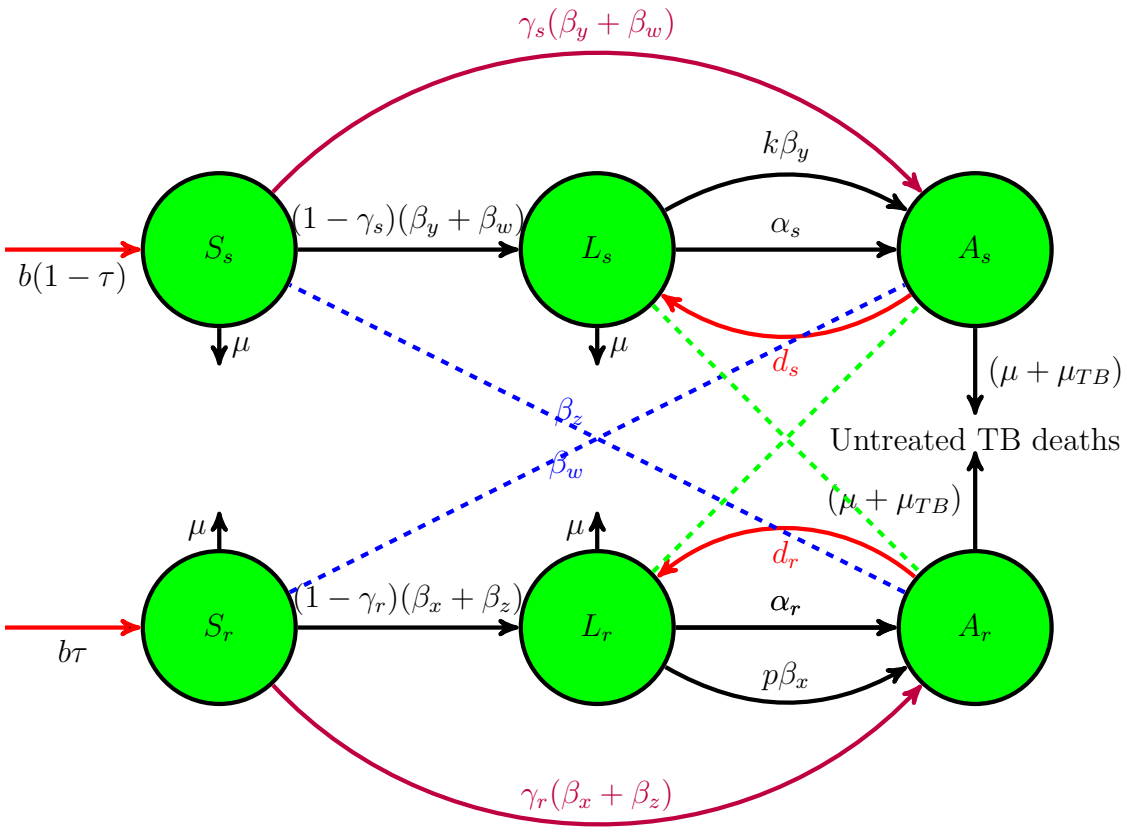



Figure 3.2: Compartmental model of TB with heterogeneous transmission. The dotted lines indicate interaction between individuals of the two sub populations.

$$\frac{dS_s}{dt} = b(1-\tau) - (\lambda_s + \lambda_w)S_s - \mu S_s, \tag{3.39}$$

$$\frac{dL_s}{dt} = (1-\gamma_s)(\lambda_s + \lambda_w)S_s + d_s A_s - (\lambda_s + \lambda_w)kL_s - (\alpha_s + \mu)L_s, \tag{3.40}$$

$$\frac{dA_s}{dt} = (\lambda_s + \lambda_w)\gamma_s S_s + (\lambda_s + \lambda_w)kL_s + \alpha_s L_s - (d_s + \mu + \mu_{TB})A_s, \tag{3.41}$$

$$\frac{dS_r}{dt} = b\tau - (\lambda_r + \lambda_z)S_r - \mu S_r, \tag{3.42}$$

$$\frac{dL_r}{dt} = (1-\gamma_r)(\lambda_r + \lambda_z)S_r + d_r A_r - (\lambda_r + \lambda_z)pL_r - (\alpha_r + \mu)L_r, \tag{3.43}$$

$$\frac{dA_r}{dt} = (\lambda_r + \lambda_z)\gamma_r S_r + (\lambda_r + \lambda_z)pL_r + \alpha_r L_r - (d_r + \mu + \mu_{TB})A_r \tag{3.44}$$

where $\lambda_s = \dfrac{\beta_y A_s}{N}$, $\lambda_r = \dfrac{\beta_x A_r}{N}$, $\lambda_w = \dfrac{\beta_w A_r}{N}$ and $\lambda_z = \dfrac{\beta_z A_s}{N}$.

When there is no infection the disease free equilibrium of the heterogeneous model is given as

$$\bar{E} = \left( \frac{b(1-\tau)}{\mu}, \frac{b\tau}{\mu}, 0, 0, 0, 0 \right).$$

### 3.4.1 Invasion threshold of heterogeneous transmission model.

The method using the next generation matrix fails to compute the reproduction number and thus we resort to the implicit method, a technique used where the next generation matrix fails [28]. We do this by investigating properties of the constant term of the auxiliary polynomial of the Jacobian matrix evaluated at disease free equilibrium point. This technique explores the bifurcation conditions. From the homogeneous transmission we had at least one eigenvalue equal to zero at the bifurcation point. The criteria that there exist one or more zero eigenvalue at bifurcation point gives us insight on how to implicitly determine the basic reproduction number from our model. For a general $n \times n$ matrix, we can obtain the auxiliary polynomial as $\lambda^n + a_1\lambda^{n-1} + \cdots + a_n = 0$. To have at least one eigenvalue equal to zero, the constant term $a_n$ should be equal to zero. Precisely $a_n$ is the determinant of an $n \times n$ matrix. To apply this technique to model (3.39)-(3.44) we obtain the auxiliary polynomial by setting $det(D - \lambda I)$ to zero where $D$ denotes the Jacobian matrix of the system of equations (3.39)-(3.44) evaluated at the disease free equilibrium point. The $det(D) = |D_0|$ is obtained by considering the order of the state variables in $D$ as follows $(S_s, L_s, A_s, S_r, L_r, A_r)$.

$$|D_0| = \begin{vmatrix} -\mu & 0 & -\beta_y(1-\tau) & 0 & 0 & -\beta_w(1-\tau) \\ 0 & -D_1 & (1-\gamma_s)\beta_y(1-\tau) + d_s & 0 & 0 & (1-\gamma_s)\beta_w(1-\tau) \\ 0 & \alpha_s & \gamma_s\beta_y(1-\tau) - D_2 & 0 & 0 & \gamma_s\beta_w(1-\tau) \\ 0 & 0 & -\beta_z\tau & -\mu & 0 & -\beta_x\tau \\ 0 & 0 & (1-\gamma_r)\beta_z\tau & 0 & -D_3 & (1-\gamma_r)\beta_x\tau + d_r \\ 0 & 0 & \gamma_r\beta_z\tau & 0 & \alpha_r & \gamma_r\beta_x\tau - D_4 \end{vmatrix},$$

reduces to

$$
\begin{aligned}
|D_0| = &(1-\tau)\beta_y[\alpha_s(1-\gamma_s)+D_1\gamma_s][D_3D_4(1-\psi_2)] \\
&+\tau\beta_x[\alpha_r(1-\gamma_r)+D_3\gamma_r][D_1D_2(1-\psi_1)] \\
&+(1-\tau)\beta_w[\alpha_s(1-\gamma_s)+D_1\gamma_s]\tau\beta_z[\alpha_r(1-\gamma_r)+D_3\gamma_r] \\
&-(1-\tau)\beta_y[\alpha_s(1-\gamma_s)+D_1\gamma_s]\tau\beta_x[\alpha_r(1-\gamma_r)+D_3\gamma_r] \\
&-[D_1D_2(1-\psi_1)][D_3D_4(1-\psi_2)] = 0.
\end{aligned}
$$

Equating the $det(D)$ to zero and manipulating the expression results in

$$
\begin{aligned}
&\frac{(1-\tau)\beta_y[\alpha_s(1-\gamma_s)+D_1\gamma_s]}{D_1D_2(1-\psi_1)} + \frac{\tau\beta_x[\alpha_r(1-\gamma_r)+D_3\gamma_r]}{D_3D_4(1-\psi_2)} \\
&+\left(\frac{(1-\tau)\beta_w[\alpha_s(1-\gamma_s)+D_1\gamma_s]}{D_1D_2(1-\psi_1)}\right)\left(\frac{\tau\beta_z[\alpha_r(1-\gamma_r)+D_3\gamma_r]}{D_3D_4(1-\psi_2)}\right) \qquad (3.45) \\
&-\left(\frac{(1-\tau)\beta_y[\alpha_s(1-\gamma_s)+D_1\gamma_s]}{D_1D_2(1-\psi_1)}\right)\left(\frac{\tau\beta_x[\alpha_r(1-\gamma_r)+D_3\gamma_r]}{D_3D_4(1-\psi_2)}\right) - 1 = 0.
\end{aligned}
$$

The expression (3.45) can be written as

$$\mathscr{R} = R_s + R_r + R_wR_z - R_sR_r = 1,$$

where

$$R_s = \frac{(1-\tau)\beta_y[\alpha_s(1-\gamma_s)+D_1\gamma_s]}{D_1D_2(1-\psi_1)}, \qquad (3.46)$$

$$R_r = \frac{\tau\beta_x[\alpha_r(1-\gamma_r)+D_3\gamma_r]}{D_3D_4(1-\psi_2)}, \qquad (3.47)$$

$$R_w = \frac{(1-\tau)\beta_w[\alpha_s(1-\gamma_s)+D_1\gamma_s]}{D_1D_2(1-\psi_1)}, \qquad (3.48)$$

$$R_z = \frac{\tau\beta_z[\alpha_r(1-\gamma_r)+D_3\gamma_r]}{D_3D_4(1-\psi_2)}. \qquad (3.49)$$

The expression $R_s + R_r + R_w R_z - R_s R_r$ is equal to one at the bifurcation point. We thus define $\mathscr{R}$ as the basic reproduction number of our heterogeneous transmission model. $R_s$ and $R_r$ are the reproduction numbers for the genetically sensitive and genetically resistant sub populations respectively through the homogeneous mode of transmission. $R_w$ and $R_z$ are the basic reproduction numbers representing the heterogeneous mode of transmission between the genetically sensitive and genetically resistant sub populations. The product $R_w R_z$ define the interaction between both sub populations (that is genetically sensitive and genetically resistant individuals). We showed (see **Appendix B**) that the basic reproduction number for mixing interaction of members of both sub populations is given by the geometric mean of their respective $R_0$. Basically $R_{ht} = \sqrt{R_w R_z}$ is the basic reproduction number of heterogeneous case only. The implication of this expression is that individuals pass through two generations before their present status of infection is established. We subtract the product of $R_s$ and $R_r$ to cancel the effect of intersection between sub populations (homogeneous case) which have already been represented in expressions for $R_s$ and $R_r$.

### 3.4.2 Stability and characteristic equation of the non linear system.

From the analysis of jacobian matrix of our heterogeneous model evaluated at infection free equilibrium we note that we cannot obtain a closed form of eigenvalues due to complexity of the model. We thus explore the constant term of the auxiliary polynomial obtained from our non linear system as described in [58].

**Lemma 3.4.1.** *[58] Given an auxiliary equation* $\lambda^m + l_{m-1}\lambda^{m-1} + \cdots + l_1\lambda + l_0 = 0$, *where all the coefficients are non negative. The following deductions based on the constant term can be made:*

*(i)* $l_0 = 0$, *the root or largest eigenvalue is zero.*

*(ii)* $l_0 > 0$, *all eigenvalues are non positive.*

*(iii)* $l_0 < 0$, *the biggest eigenvalue has a non negative real part.*

The Lemma 3.4.1 apparently suggests that we can determine the stability of our non linear system by investigating the nature of eigenvalues based on the constant term of the auxiliary equation. The jacobian matrix of infective compartments in the order $(L_s, A_s, L_r, A_r)$ is given as.

$$\begin{pmatrix} -(\alpha_s+\mu) & (1-\gamma_s)\beta_y(1-\tau)+d_s & 0 & (1-\gamma_s)\beta_w(1-\tau) \\ \alpha_s & \gamma_s\beta_y(1-\tau)-(d_s+\mu+\mu_{TB}) & 0 & \gamma_s\beta_w(1-\tau) \\ 0 & (1-\gamma_r)\beta_z\tau & -(\alpha_r+\mu) & (1-\gamma_r)\beta_x v_0+d_r \\ 0 & \gamma_r\beta_z\tau & \alpha_r & \gamma_r\beta_x\tau-(d_r+\mu+\mu_{TB}) \end{pmatrix}.$$

The auxiliary equation of the polynomial is given as,

$$\lambda^4 + l_3\lambda^3 + l_2\lambda^2 + l_1\lambda + l_0 = 0, \tag{3.50}$$

where

$$\begin{aligned} l_0 =& Q_1(1-\mathscr{R}), \\ l_1 =& Q_2Q_3[1-R_s] + Q_4Q_5[1-R_r] + \gamma_r\beta_x\tau Q_3R_s \\ &+ \gamma_s\beta_y(1-\tau)Q_5R_r - \gamma_r\beta_x\tau Q_3(1+p^zR_w) - \gamma_s\beta_y(1-\tau)Q_5(1+p^wR_z), \\ l_2 =& Q_3[1-R_s] + Q_5[1-R_r] + Q_2Q_4\left[1-\left(\frac{\gamma_s\beta_y(1-\tau)}{Q_2}+\frac{\gamma_r\beta_x\tau}{Q_4}\right)\right], \\ l_3 =& (\alpha_s+\mu)+(\alpha_r+\mu)-(\gamma_s\beta_y(1-\tau)-(d_s+\mu+\mu_{TB}))-(\gamma_r\beta_x\tau-(d_r+\mu+\mu_{TB})). \end{aligned} \tag{3.51}$$

$Q_1, Q_2, Q_3, Q_4, Q_5, p^z$ and $p^w$ are denoted by the following expressions.

$$\begin{aligned}
Q_1 =&[(\alpha_s + d_s)\mu + (\alpha_s + \mu)\mu_{TB} + \mu^2][(\alpha_r + d_r)\mu + (\alpha_r + \mu)\mu_{TB} + \mu^2],\\
Q_2 =&[(\alpha_r + \mu) + (d_r + \mu + \mu_{TB})],\\
Q_3 =&[(\alpha_s + d_s)\mu + (\alpha_s + \mu)\mu_{TB} + \mu^2],\\
Q_4 =&[(\alpha_s + \mu) + (d_s + \mu + \mu_{TB})],\\
Q_5 =&[(\alpha_r + d_r)\mu + (\alpha_r + \mu)\mu_{TB} + \mu^2],\\
p^z =&\frac{\beta_z}{\beta_x},\\
p^w =&\frac{\beta_w}{\beta_y}.
\end{aligned}$$

As a necessary condition for the lemma 3.4.1 all the coefficients should be positive. Thus,

$$\begin{aligned}
&l_1 > 0, \Leftrightarrow \frac{Q_2Q_3 + Q_4Q_5 + \gamma_r\beta_x\tau Q_3R_s + \gamma_s\beta_y(1-\tau)Q_5R_r}{Q_2Q_3R_s + Q_4Q_5R_r + \gamma_r\beta_x\tau Q_3(1+p^z)R_w + \gamma_s\beta_y(1-\tau)Q_5(1+p^wR_z)} > 1,\\
&l_2 > 0, \Leftrightarrow \left(\frac{\gamma_s\beta_y(1-\tau)}{Q_2} + \frac{\gamma_r\beta_x\tau}{Q_4}\right) < 1,\\
&l_3 > 0, \Leftrightarrow R_{s1} = \frac{\gamma_s\beta_y(1-\tau)}{(d_s + \mu + \mu_{TB})} < 1 \text{ and } R_{r1} = \frac{\gamma_r\beta_x\tau}{(d_r + \mu + \mu_{TB})} < 1.
\end{aligned} \tag{3.52}$$

In all coefficients we have considered $R_s, R_r, R_w$ and $R_z$ to be less than one. Our goal was to investigate the local stability of the disease free equilibrium point based on nature of the constant term of the auxiliary equation. From the auxiliary polynomial we note that $l_0 > 0$ when $\mathscr{R} < 1$. Thus, we can summarize our analysis by the following deduction.

**Lemma 3.4.2.** *If conditions* (3.52) *hold, then the disease free equilibrium point is locally asymptotically stable whenever* $\mathscr{R} < 1$.

## 3.5 TB therapy as intervention.

In Section 3.4 we formulated a model that considered heterogeneous mode of transmission. We extend the model equations (3.39)-(3.44) by assuming that actively infected individuals in each sub population receive TB therapy at rates $\omega_i$, $i \in r, s$. Treatment reduces the number

of individuals with clinically active TB, whereby individuals partially recover and join latently infected compartments. The parameter $\omega_r$ denote the rate at which actively infected individuals ($A_r$) receive TB therapy while $\omega_s$ denote the rate at which actively infected individuals ($A_s$) receive TB therapy. The inclusion of the treatment rate $\omega_r$ on $A_r$ will modify equation (3.44) by an additional term $-\omega_r A_r$ and equation (3.43) by an additional term $+\omega_r A_r$. Similarly, the inclusion of the treatment rate $\omega_s$ on $A_s$ will modify equation (3.41) by an additional term $-\omega_s A_s$ and equation (3.40) by an additional term $+\omega_s A_s$. The new model framework where we replace $d_s$ by $d_s + \omega_s$ and $d_r$ by $d_r + \omega_r$ is in Section 3.4.

The new invasion threshold that depends on TB therapy is given by

$$R(\omega_s, \omega_r) = R_x(\omega_r) + R_y(\omega_s) + R_w(\omega_s)R_z(\omega_r) - R_x(\omega_r)R_y(\omega_s)$$

where

$$R_x(\omega_r) = \frac{\beta_x \tau(\alpha_r + \mu\gamma_r)}{\mu^2 + \mu\omega_r + \mu(d_r + \alpha_r) + \mu_{TB}(\mu + \alpha_r)},$$

$$R_y(\omega_s) = \frac{\beta_y(1-\tau)(\alpha_s + \mu\gamma_s)}{\mu^2 + \mu\omega_s + \mu(d_s + \alpha_s) + \mu_{TB}(\mu + \alpha_s)},$$

$$R_w(\omega_s) = \frac{\beta_w(1-\tau)(\alpha_s + \mu\gamma_s)}{\mu^2 + \mu\omega_s + \mu(d_s + \alpha_s) + \mu_{TB}(\mu + \alpha_s)},$$

$$R_z(\omega_r) = \frac{\beta_z \tau(\alpha_r + \mu\gamma_r)}{\mu^2 + \mu\omega_r + \mu(d_r + \alpha_r) + \mu_{TB}(\mu + \alpha_r)}.$$

We note that when $\tau = 0$ we have $R_x(\omega_r) = R_z(\omega_r) = 0$. This implies that

$$R(\omega_s, \omega_r) = R_y(\omega_s)$$

which is the basic reproduction number for the population with genetically sensitive TB on TB therapy. When $\tau = 1$, we have $R_y(\omega_s) = R_w(\omega_s) = 0$ so that

$$R(\omega_s, \omega_r) = R_x(\omega_r)$$

which is basic reproduction number for sub population with genetically resistant TB on TB therapy.

We observe that

$$\begin{aligned}\frac{\partial R(\omega_s,\omega_r)}{\partial \omega_s} =& \frac{-\mu R_y(\omega_s)}{\mu\omega_s+\mu^2+(d_s+\alpha_s)\mu+(\mu+\alpha_s)\mu_{TB}} - \frac{\mu R_w(\omega_s)R_z(\omega_r)}{\mu\omega_s+\mu^2+(d_s+\alpha_s)\mu+(\mu+\alpha_s)\mu_{TB}} \\ &+ \frac{\mu R_x(\omega_r)R_y(\omega_s)}{\mu\omega_s+\mu^2+(d_s+\alpha_s)\mu+(\mu+\alpha_s)\mu_{TB}}, \\ =& -\left(\frac{R_w(\omega_s)R_z(\omega_r)}{\mu\omega_s+\mu^2+(d_s+\alpha_s)\mu+(\mu+\alpha_s)\mu_{TB}}\right) \\ &-\left(\frac{\mu R_y(\omega_s)}{\mu\omega_s+\mu^2+(d_s+\alpha_s)\mu+(\mu+\alpha_s)\mu_{TB}}\right)(1-R_x(\omega_r)), \\ =& -\Lambda_0-\Lambda_1(1-R_x(\omega_r)),\end{aligned}$$

where

$$\begin{aligned}\Lambda_0 &= \left(\frac{R_w(\omega_s)R_z(\omega_r)}{\mu\omega_s+\mu^2+(d_s+\alpha_s)\mu+(\mu+\alpha_s)\mu_{TB}}\right), \\ \Lambda_1 &= \left(\frac{\mu R_y(\omega_s)}{\mu\omega_s+\mu^2+(d_s+\alpha_s)\mu+(\mu+\alpha_s)\mu_{TB}}\right).\end{aligned}$$

Thus, $\dfrac{\partial R(\omega_s,\omega_r)}{\partial \omega_s} < 0 \iff R_x(\omega_r) \leq 1.$

$$\begin{aligned}\frac{\partial R(\omega_s,\omega_r)}{\partial \omega_r} =& -\left(\frac{\mu R_w(\omega_s)R_z(\omega_r)}{\mu\omega_r+\mu^2+(d_r+\alpha_r)\mu+(\mu+\alpha_r)\mu_{TB}}\right) \\ &-\left(\frac{\mu R_x(\omega_r)}{\mu\omega_r+\mu^2+(d_r+\alpha_r)\mu+(\mu+\alpha_r)\mu_{TB}}\right)(1-R_y(\omega_s)), \\ =& -\Lambda_2-\Lambda_3(1-R_y(\omega_s)).\end{aligned}$$

where

$$\begin{aligned}\Lambda_2 &= \left(\frac{\mu R_w(\omega_s)R_z(\omega_r)}{\mu\omega_r+\mu^2+(d_r+\alpha_r)\mu+(\mu+\alpha_r)\mu_{TB}}\right), \\ \Lambda_3 &= \left(\frac{\mu R_x(\omega_r)}{\mu\omega_r+\mu^2+(d_r+\alpha_r)\mu+(\mu+\alpha_r)\mu_{TB}}\right).\end{aligned}$$

Hence, $\dfrac{\partial R(\omega_s,\omega_r)}{\partial \omega_r} < 0 \iff R_y(\omega_s) \leq 1.$

The partial derivative $\dfrac{\partial R(\omega_s,\omega_r)}{\partial \omega_s}$ suggest that for treatment of genetically sensitive infected individuals to reduce TB proliferation, TB therapy administered on genetically resistant infected

individuals should be effective enough to reduce the basic reproduction number for genetically resistant sub population to a value below one. Similarly, the partial derivative $\frac{\partial R(\omega_s, \omega_r)}{\partial \omega_r}$ suggest that for TB therapy on genetically resistant infected individuals to mitigate TB progression treatment on genetically sensitive infected individuals should be also effective to maintain basic reproduction number for genetically sensitive sub population to a value less than one.

## 3.6 Summary.

In this chapter we formulated three TB models. In the first model we assumed homogeneous interaction amongst susceptible individuals. Our second model was an extension of the first model such that individuals in each sub-population interacted with each other leading to heterogeneous transmission of TB. The third model was an extension of the second model where we incorporated treatment among individuals with active TB. Using the dynamical system that model change of status from one compartment to another we obtained a scenario when there is no infection (disease free equilibrium) and a scenario when the infection persists within the susceptible population (endemic equilibria). The simplicity nature of our first model permitted us to investigate the local and global stability of the disease free equilibrium point (DFE). The qualitative analysis of the DFE point showed that we can only have a locally stable disease free equilibrium if the basic reproduction number is less than unity and the rate of primary progression rate to duration infected individuals spend in each sub-population is less than unity. Study done in [9] reached to a similar conclusion like ours regarding the local stability of the disease free equilibrium point.

We constructed a Lyapunouv La-salle function to analyse the global stability of the disease free equilibrium point and found that the disease free equilibrium point is globally unstable. This was due to the presence of exogenous reinfection parameter. However, in absence of exogenous reinfection the DFE point wound be globally stable. Hence, in a community exogenously reinfected with TB it is impossible to have a TB free community. Interestingly our

Lypunouv La-salle function reached to a similar result as shown in [59] using Carlo-castillo Charvez method to prove the global stability of the disease free equilibrium point of a model that included exogenous reinfection. From the analysis of endemic equilibrium point of our first model we analytically showed that the presence of exogenous reinfection induced backward bifurcation. Epidemiologically it is clearly understood that the classical necessary condition for an epidemic to wane is that the basic reproduction number should be less than unity [47]. However, our model seem not to agree with such a notion since an endemic equilibria occur even when the basic reproduction number is less than unity. Further, analysis of the endemic equilibria showed that TB could only be eradicated if the basic reproduction number is reduced below a certain critical threshold which we denoted us $R_c$. Models such as [9, 28, 29, 31] exhibited backward bifurcation.

In our second model we found that it is impossible to compute the basic reproduction number using the next generation matrix approach. We thus resorted to implicit method where we explored the properties of the constant term of the characteristic polynomial of our dynamical system evaluated at the disease free equilibrium point. We found that $R_0 = 1$ is the bifurcation point. For our third model that incorporated treatment we also found $R_0$ using implicit method. We finalised the chapter by showing that treatment can only have a significant impact within the community if only treatment on both sub-populations is effective enough to mitigate basic reproduction number to a value less than one.

# Chapter 4

# Numerical simulations.

## 4.1 Introduction.

In this chapter we present numerical simulations to enhance the understanding of the predictions of the analytical results since some of the parameter values are not known due to lack of data or because it is difficult to measure and quantify the values. We shall obtain some parameters from literature. Also, we shall estimate some of the parameters and perform some uncertainty and sensitivity analysis. Thus, this chapter will contain sections on parameter estimations, numerical simulations exhibiting various scenarios emanating from our analytical results and uncertainty and sensitivity analysis of the unknown parameters using the latin hypercube sampling.

## 4.2 Parameter estimation.

Generally parameters such as fraction of individuals that directly progress to TB ($\gamma_i$ $i \in \{r, s\}$), reactivation rates ($\alpha_i$ $i \in \{r, s\}$) and transmission rates ($\beta_j$ $j = \{x, y, z, w\}$) can not be precisely approximated. For the purpose of simulation we obtain our initial conditions and parameters from studies on TB dynamics and World Health Organization data released annually [28].

We assume that $\alpha_r \leq \alpha_s$, $\gamma_r \leq \gamma_s$ and $\beta_x \leq \beta_w \leq \beta_z \leq \beta_y$. We adopt transmission rates $\beta_j,\ j = \{x, y, w, z\}$ from the literature in [11, 60, 61] where the $\beta_j' s$ are calculated within a duration of one year that is the average number of secondary infection cases that a single infected individual will produce within one year in a susceptible population. The parameters $\gamma_s, \gamma_r \in [0.05 - 0.1]$ [62] vary due to environmental changes and severity of TB.

The exogenous reinfection parameters $p, k$ satisfy the conditions $p, k > 0$ and can be varied depending on how an individual's immunity system is compromised [31]. The parameter $\tau$ satisfy the condition $0 \leq \tau \leq 1$. We choose $\tau$ to be 0.7. Our initial conditions were entirely based on India population where TB prevalence is relatively high. The initial conditions can be adjusted depending on the case study. The parameter values used have baseline values in Table 4.1.

## 4.3 Simulations.

We first perform sensitivity analysis for basic reproduction numbers $R_s$ and $R_r$ to establish the effects that genetically susceptibility rate ($\tau$) and infection rate $\beta_i\ i \in \{r, s\}$ have on the progression of TB. We perform a similar analysis on the death rate due to TB and the infection rate. We then establish the threshold values $\beta_y^*$ and $\beta_x^*$ of $\beta_y$ and $\beta_x$ respectively at $R_0 = 1$. The expressions for the thresholds are given by equation (4.1).

$$\beta_y^* = \frac{(\mu + \mu_{TB})\alpha_s + (d_s + \mu_{TB})\mu}{(1 - \tau)(\alpha_s + \mu\gamma_s)} \quad \text{and} \quad \beta_x^* = \frac{(\mu + \mu_{TB})\alpha_r + (d_r + \mu_{TB})\mu}{(\tau)(\alpha_r + \mu\gamma_r)} \tag{4.1}$$

Secondly, we shall investigate the effects of exogenous re-infection towards the progression dynamics of TB. We do this by studying the changes in behaviour of the system as we vary the exogenous re-infection rates. Lastly, we shall perform sensitivity analysis on some of the unknown parameters to determine how each of them influences the output variables of the model.

Table 4.1: Table of parameter values.

| **Variables** | **brief description** | **Values** | **references** |
|---|---|---|---|
| $S_s$ | genetically sensitive subpopulation | 298 679 000 | [63, 64] & calculated |
| $S_r$ | genetically resistant subpopulation | 696 918 000 | [63, 64] & calculated |
| $L_s$ | latently infected (sensitive) | 147 552 000 | [63, 64] & calculated |
| $L_r$ | latently infected (resistant) | 344 288 000 | [63, 64] & calculated |
| $A_s$ | infectious individuals (sensitive) | 1 716 000 | [63, 64] & calculated |
| $A_r$ | infectious individuals (resistant) | 735 817 | [63, 64] & calculated |
| **Parameter** | **brief description** | **values** | **references** |
| $\mu$ | natural death | $[0.0133 - 0.04]\ yr^{-1}$ | [61, 65] |
| $\mu_{TB}$ | TB mortality rate | $0.8\ yr^{-}1$ | [66] |
| $\gamma_s$ | direct progression (sensitive) | $[5 - 10]\%$ | [61, 62] |
| $\gamma_r$ | direct progression (resistant) | $[10 - 20]\%$ | approximated |
| $\alpha_r$ | reactivation rate (resistant) | $[0.00167 - 0.0033]\ yr^{-1}$ | [12, 67] |
| $\alpha_s$ | reactivation rate (sensitive) | $[0.0033 - 0.0066]\ yr^{-1}$ | approximated |
| $p$ | reinfection rate (resistant) | [0,1] | approximated |
| $k$ | reinfection rate (sensitive) | [0,1] | approximated |
| $\beta_x$ | new infections $(S_r \bigotimes A_r)$ | $[3, 7]\ yr^{-1}$ | [61, 68] |
| $\beta_y = \xi\beta_x$ | new infections $(S_s \bigotimes A_s)$ | $[7, 11]\ yr^{-1}$ | approximated |
| $\beta_w = \xi_w\beta_x$ | new infections $(S_s \bigotimes A_r)$ | $[5, 9]\ yr^{-1}$ | approximated |
| $\beta_z = \xi_z\beta_x$ | new infections $(S_r \bigotimes A_s)$ | $[5, 9]\ yr^{-1}$ | approximated |
| $b$ | birth rate | $13241000\ yr^{-1}$ | calculated |
| $\tau$ | proportion of genetically resistant | 70% | [43, 44, 69, 70] |
| $d_r$ | natural cure rate (resistant) | $0.086\ yr^{-1}$ | [11] |
| $d_s$ | natural cure rate (sensitive) | $0.021\ yr^{-1}$ | [11] |

$\bigotimes$ denote interactions of individuals between respective compartments.

### 4.3.1 Simulations for sensitivity analysis of $R_0$.

Computing $\beta_y^*$ and $\beta_x^*$ using parameters defined in the Table 4.1 we obtain $\beta_y^* = 6.85$ and $\beta_x^* = 3.5$. From Figures 4.1(a) and 4.1(c), if $\beta_y < \beta_y^*$ then the basic reproduction number $R_s$ is

less than one. Similarly, from figures 4.1(b) and 4.1(d) when $\beta_x < \beta_x^*$, the basic reproduction number $R_r$ is less than one. Thus for values of infection rate less than the infection thresholds the epidemic is likely to die out.

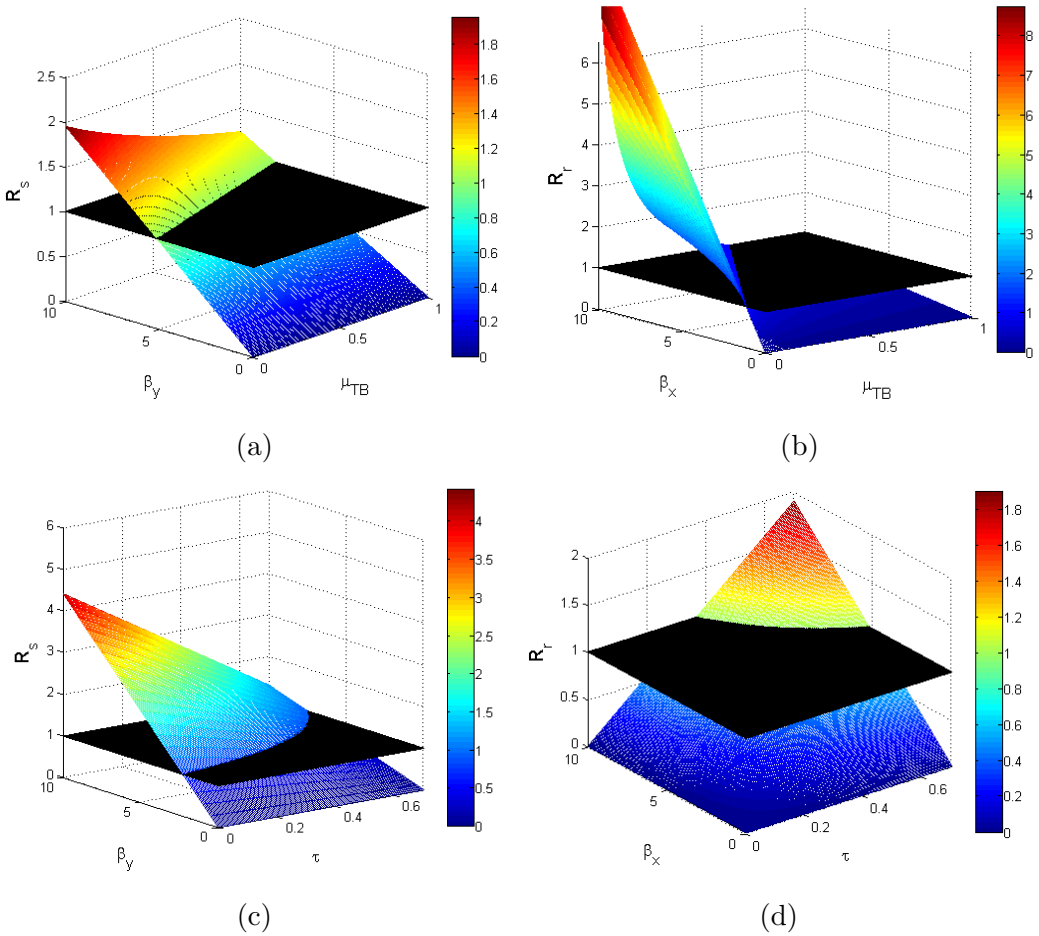



Figure 4.1: Sensitivity analysis for basic reproduction numbers $R_s$ and $R_r$ for model with homogeneous mode of transmission illustrating (a) effect of $(\beta_y, \mu_{TB})$ on $R_s$, (b) effect of $(\beta_x, \mu_{TB})$ on $R_r$, (c) effect of $(\beta_y, \tau)$ on $R_s$ and (c) effect of $(\beta_x, \tau)$ on $R_r$.

Figure 4.1(a) shows that when death rate due to TB is low the basic reproduction number increases linearly with the increase in the rate of infection in the case of genetically sensitive individuals. When both infection rate $\beta_y$ and death due TB are low the basic reproduction number is less than unity. For the case of low infection rate and high death rate due to TB the basic reproduction number for genetically sensitive population remains below one. When

both infection rate and death due to TB are high the basic reproduction number exceeds one. Thus we can argue that the scenarios when we have high infection rate and low death and high infection rate and high death rate are likely to trigger a TB endemic in the population.

For the case of genetically resistant individuals Figure 4.1(b), the basic reproduction number $R_r$ increases exponentially when the death due to TB is low and the infection rate is high. When both infection rate $\beta_x$ and death due to TB $\mu_{TB}$ are low the basic reproduction number is less than one. At low values of $\mu_{TB}$ and high infection rate $\beta_x$, the basic reproduction number is greater than one. When infection rate $\beta_x$ and death due to TB $\mu_{TB}$ are both high the basic reproduction number $R_r$ exceeds one. Finally low infection rate and high death due to TB would imply that the basic reproduction number is less than unity. Thus, the case when we have low $\mu_{TB}$ and high infection rate and the case when we have high infection rate $\beta_x$ and high death rate due to TB $\mu_{TB}$ are the one likely to promote TB progression in the community.

The results from Figures 4.1(a) and 4.1(b) seem to suggest that in a genetically susceptible population TB is more devastating in a huge population compared to a smaller population as indicated by the exponential growth of $R_0$ in the genetically resistant population compared to the genetically sensitive population. This suggests that when there is no intervention, low death rate due to TB implies that infected individuals stay longer as active TB and consequently more susceptible are at higher risk of getting infected. Hence the value of $R_0$ increases. In Figure 4.1(c) when the infection rate $\beta_y$ and proportion that is genetically susceptible $\tau$ are low the basic reproduction number is below one. When infection rate is high and the proportion of genetic susceptibility $\tau$ is low, the basic reproduction number is above one. If both $\beta_y$ and $\tau$ are high then basic reproduction number exceeds one. When the infection rate $\beta_y$ is low and $\tau$ is high the basic reproduction number is less than one. Figure 4.1(d) shows that the reproduction number can only be above unity when both the infection rate $\beta_x$ and proportion of genetic susceptibility $\tau$ are high.

Our results suggest that the infection rates are the key drivers of the increase in the basic

reproduction number compared to the rate at which individuals die due to TB infection and the rate for genetic susceptibility. However, with high infection rates, the increase in deaths due to TB reduces the reproduction numbers even though the reproduction number is maintained above unity.

### 4.3.2 Effects of exogenous reinfection on sub populations.

In this section we investigate the effects of exogenous re-infection on the progression of TB. We consider the case where exogenous reinfection parameters $p$ and $k$ are assumed to be zero. Figure 4.2 shows that the absence of exogenous reinfection does not cause oscillations in the

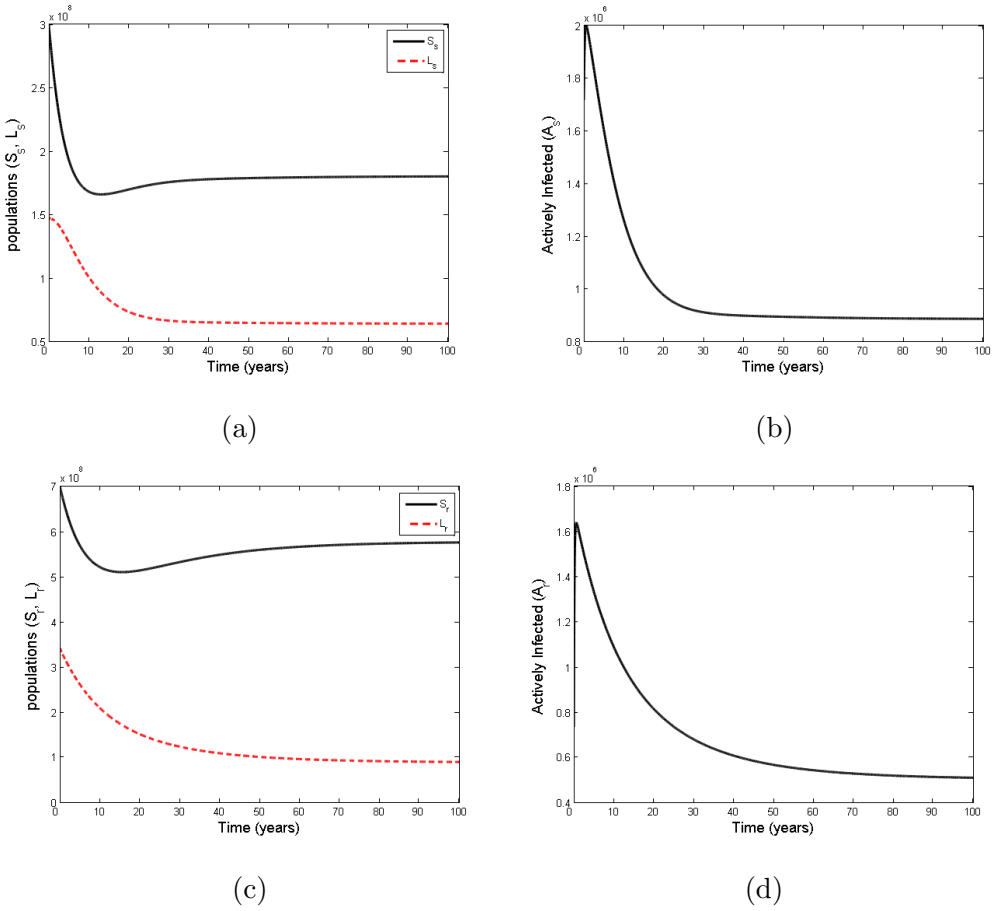



Figure 4.2: Dynamics of genetically sensitive ((*a*) and (*b*)) and genetically resistant ((*c*) and (*d*)) populations in the absence of exogenous reinfection. i.e, $k = p = 0$.

system variables. Thus the system variables approach their endemic states steadily. Figure 4.3 shows the effects of introducing and increasing exogenous reinfection.

The results in Figures 4.3(a) and 4.3(b) shows that an increase in exogenous reinfection decreases both genetically sensitive and genetically resistant susceptible sub-populations. The increase is associated with increase in the actively infected populations (Figures 4.3(c) and 4.3(d)) and a slight increase in the latently infected populations (Figures 4.3(e) and 4.3(f)). An increase in the actively infected populations may imply that the actively infected population increases interaction with susceptibles and pose a high risk of increased population with TB infection.

Using the parameters defined in the Table 4.1 we compute the reinfection thresholds $p_0$ and $k_0$ as derived in Chapter 3, Section 3.3.4. $k_0 = 0.2491$ and $p_0 = 0.1259$. We investigate TB dynamics based on the following hypothetical scenarios:

(i) $p < p_0$, $k > k_0$.

(ii) $p > p_0$, $k < k_0$.

(iii) $p < p_0$, $k > k_0$.

(iv) $p = p_0$, $k = k_0$.

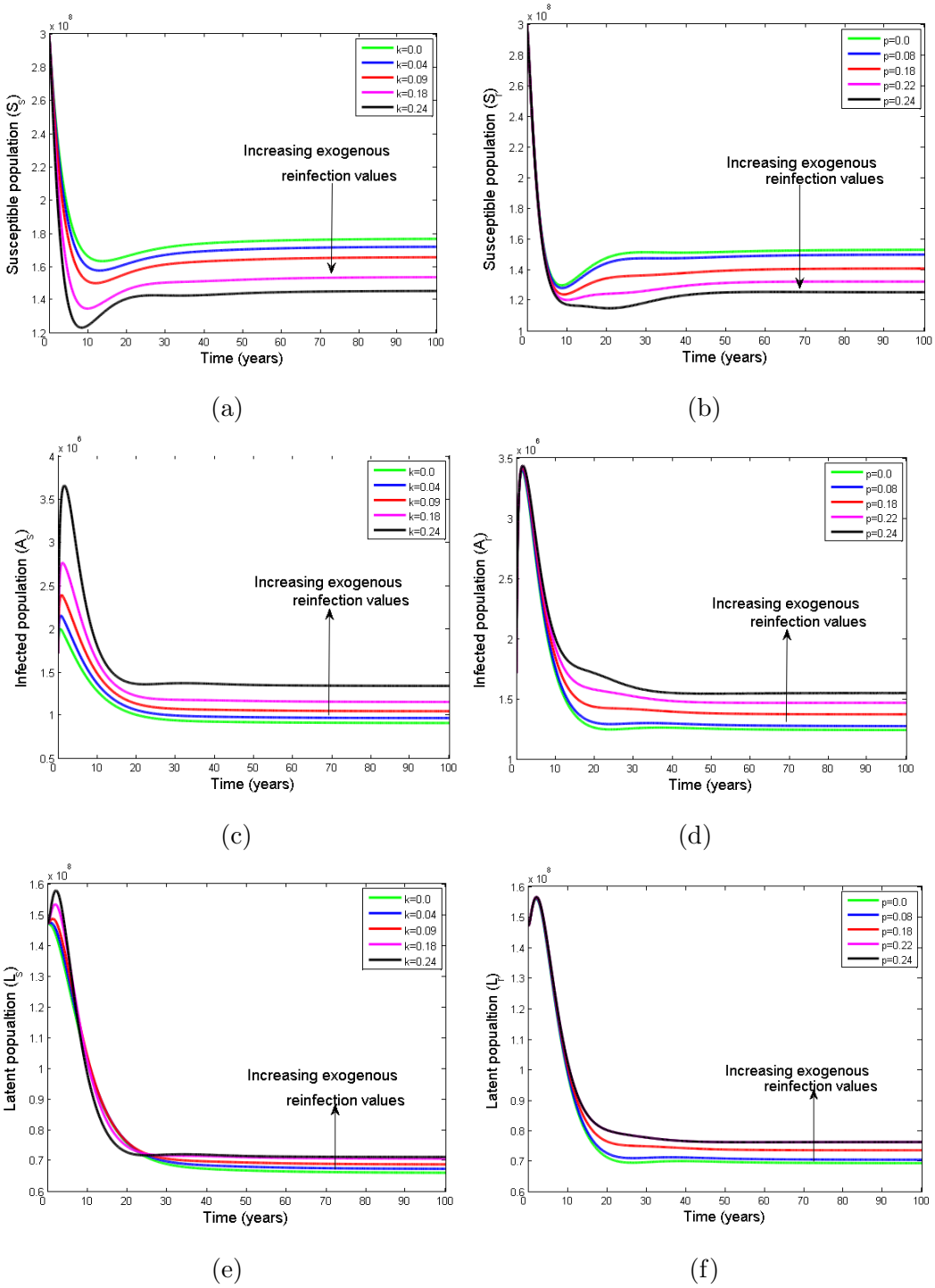



Figure 4.3: Dynamics of genetically sensitive population ((a), (c), (e)) and genetically resistant population ((b), (d) (f)) in the presence of exogenous reinfection.

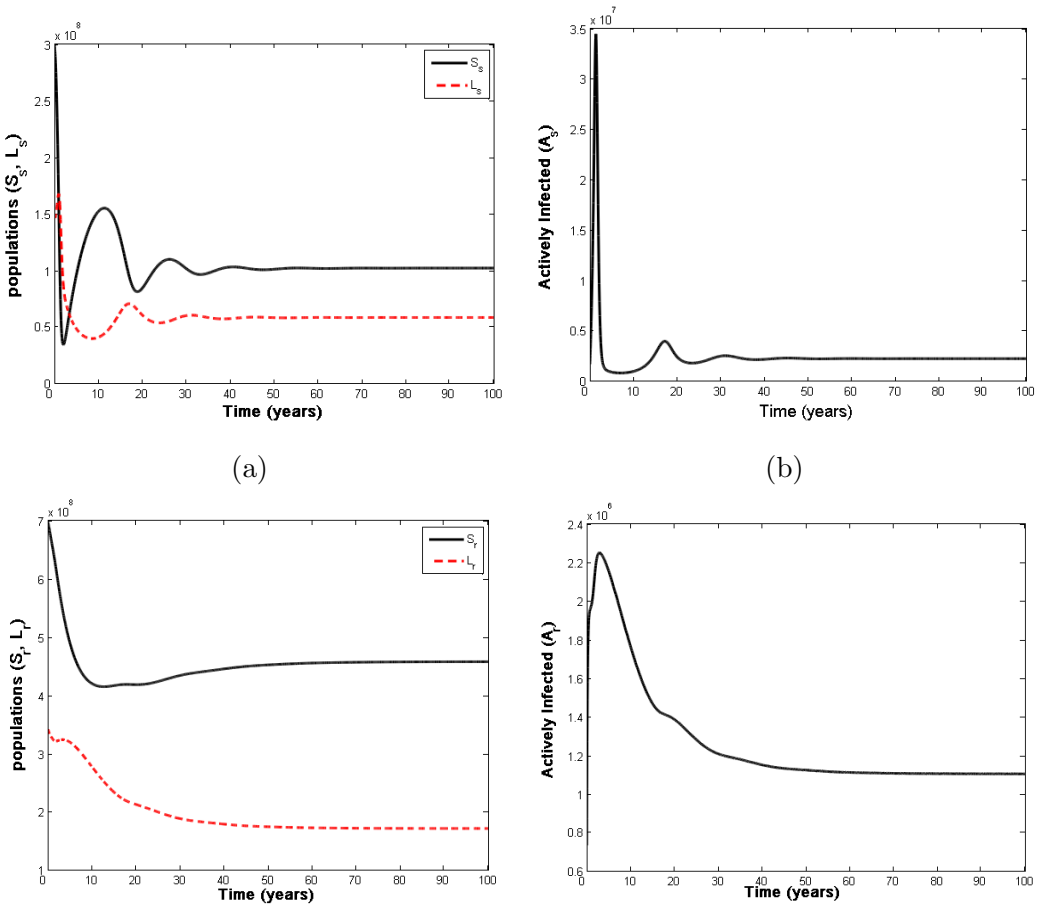



Figure 4.4: Plots of sub populations representing condition (i) where $p = 0.09$ and $k = 0.65$.

Figure 4.4 shows the scenario in hypothesis (i). Figures 4.4(a) and 4.4(b) representing genetically sensitive sub population exhibit damped oscillations before stabilizing at endemic equilibrium points. However, the genetically resistant sub population as shown in Figures 4.4(c) and 4.4(d) does not exhibit oscillations. The results suggest that increasing the exogenous reinfection above the threshold $k_0$ induces some oscillations in state variables. Figures 4.5(a), 4.5(b), 4.5(c) and 4.5(d) do not exhibit oscillations despite $p$ being greater than the reinfection threshold. Thus comparing results for conditions (i) and (ii) we observe that reinfection occurring among genetically sensitive sub population may be more devastating than exogenous reinfection occurring among genetically resistant sub population.

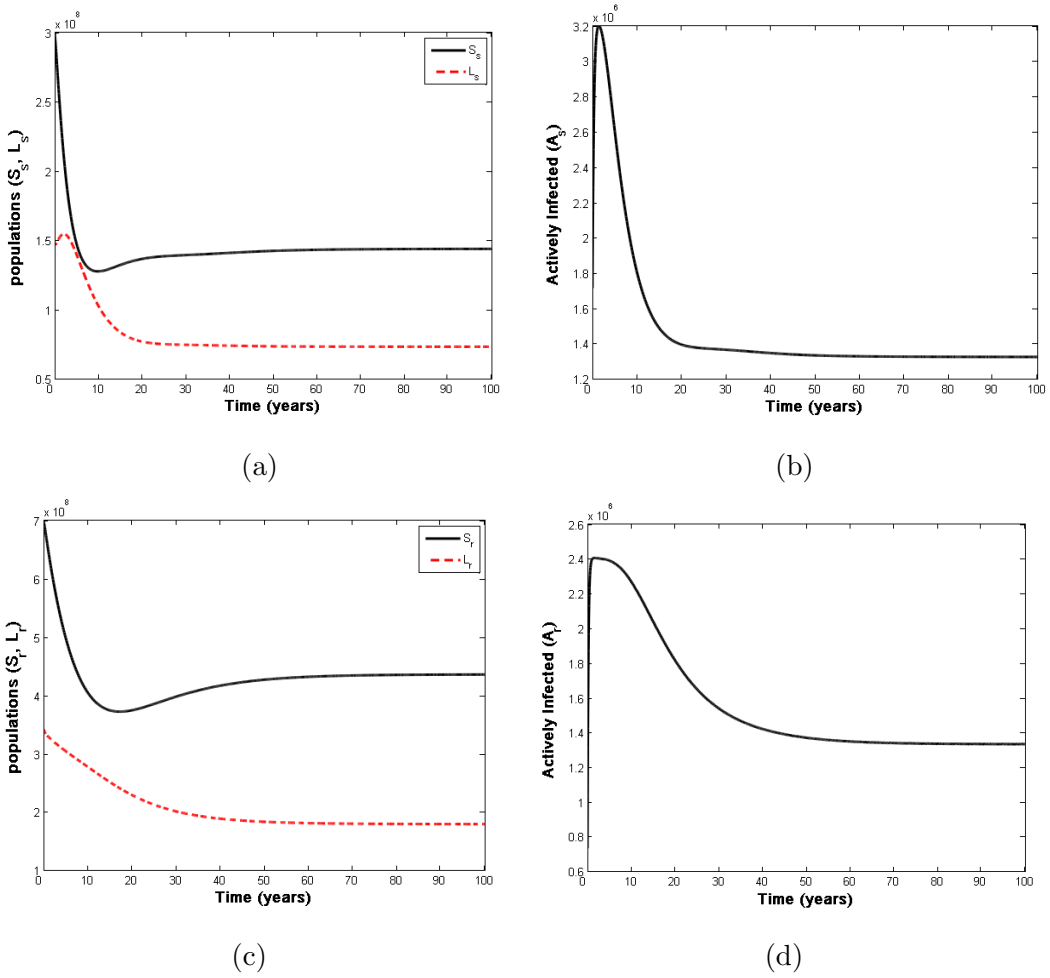



Figure 4.5: Plots of sub populations representing condition (ii) for $k = 0.20$ and $p = 0.18$.

Figure 4.6 which represent condition (iii) where both exogenous reinfections rates are above the exogenous reinfection thresholds. We observe that there are sustained damped oscillations in both sub populations.

Figure 4.7 shows that there are no oscillations in both sub populations. Our results from these four conditions have reaffirmed that exogenous reinfection thresholds exist as ascertained by Gomez et al [37]. In addition, there are limits at which the effects of exogenous reinfection above which it contributes significantly towards TB proliferation. In fact when the exogenous reinfection thresholds are exceeded the dynamics of the model are governed by backward bifurcation as demonstrated in our model analysis. Thus the delay caused by exogenous reinfection does destabilize the typical TB endemic in a TB genetically susceptible population. Biologi-

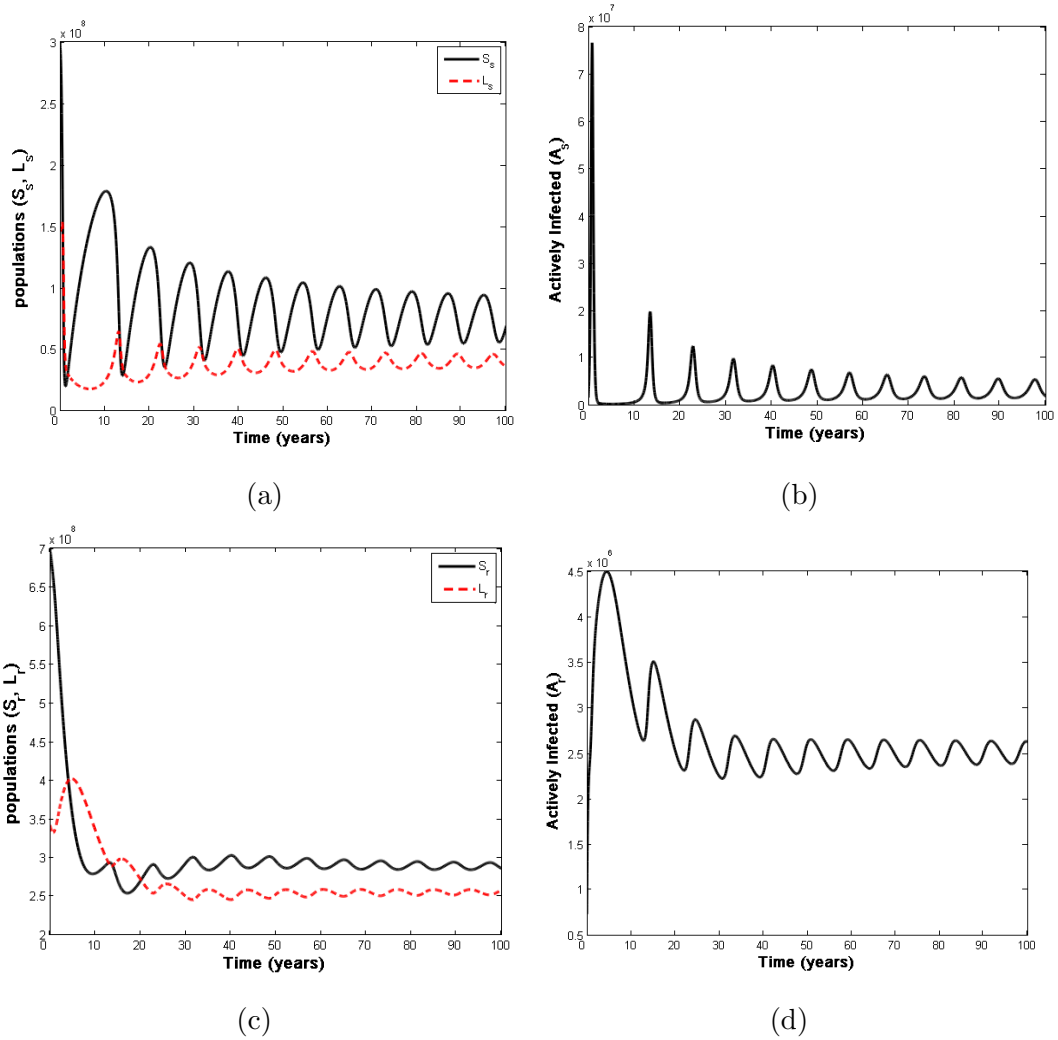



Figure 4.6: Plots of sub populations representing condition (iii) for $p = 0.18$ and $k = 0.985$.

cally, rapid oscillations have implications on the timing of intervention strategies when TB is endemic in that resources may be allocated before there is a surge of TB leading to under planning and under budgeting. Thus, appropriate intervention timing is important in controlling TB epidemic when exogenous reinfection is present in a genetically susceptible population.

### 4.3.3 Bifurcations.

Our TB model revealed the possibility of coexistence of the disease free equilibrium and the endemic equilibrium points. In this section we explore all types of bifurcation likely to be

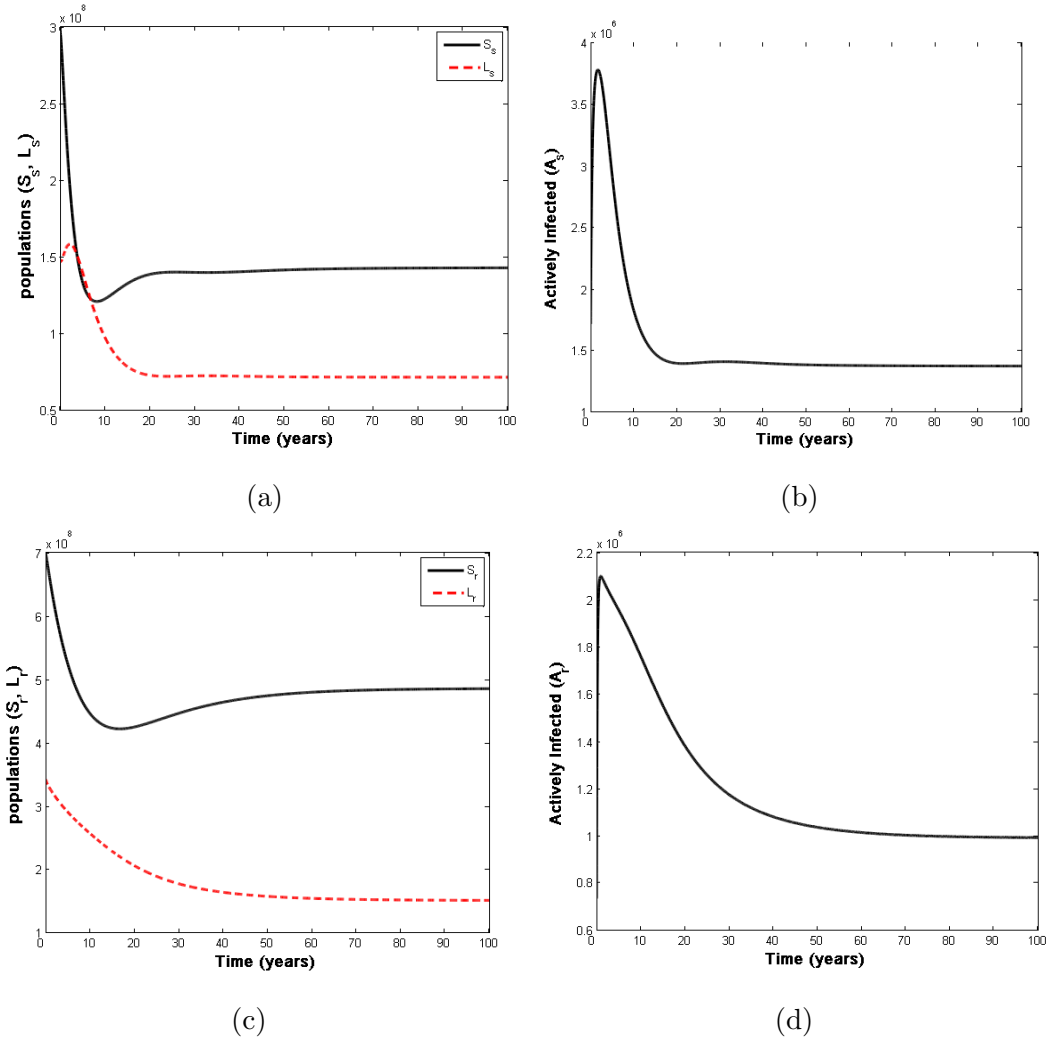



Figure 4.7: Plots of sub populations representing condition (iv) where $p = p_0 = 0.1259$ and $k = k_0 = 0.2491$.

exhibited by our TB model due to change in exogenous reinfection. We will consider two scenarios, i.e when the level of exogenous reinfection is below exogenous reinfection thresholds and when the level of exogenous reinfection is above the reinfection threshold. Using the quadratic expressions (3.18) and (3.22) we plot the steady states of actively infected individuals against the varying basic reproduction numbers for fixed values of exogenous reinfection. Depending on the level of exogenous reinfection our model exhibits the following types of bifurcation.

(i) Transcritical bifurcation.

Figures 4.8(e) and 4.8(f) show the presence of transcritical bifurcation at $R_0 = 1$. For values of exogenous reinfection below exogenous reinfection thresholds ($p \leq p_0$ and $k \leq k_0$) our model has two equilibrium points; the disease free equilibrium point when $R_0 \leq 1$. When $R_0 > 1$ Figures 4.8(e) and 4.8(f) show that we have two steady states; one which correspond to unstable disease free equilibrium point and the other corresponding to a TB endemic scenario.

(ii) Backward bifurcation.

When the level of exogenous reinfection is above exogenous reinfection thresholds our model exhibit backward bifurcation as illustrated by Figures 4.8(a) and 4.8(b). When $R_c < R_0 < 1$ our model exhibit three equilibrium points, namely we have a disease free equilibrium point and two endemic equilibrium points. Furthermore, fixing the exogenous reinfection values we obtained the critical points $R_{sc}$ and $R_{cr}$ of basic reproduction number $R_s$ and $R_r$ respectively. These critical points act as limit point of our basic reproduction number, since below these critical points we have only a stable disease free equilibrium point [29]. Hence, TB can only be eliminated when $R_0 < R_c$. Figures 4.8(c) and 4.8(d) show that backward bifurcation increases with an increase in the level of exogenous reinfection.

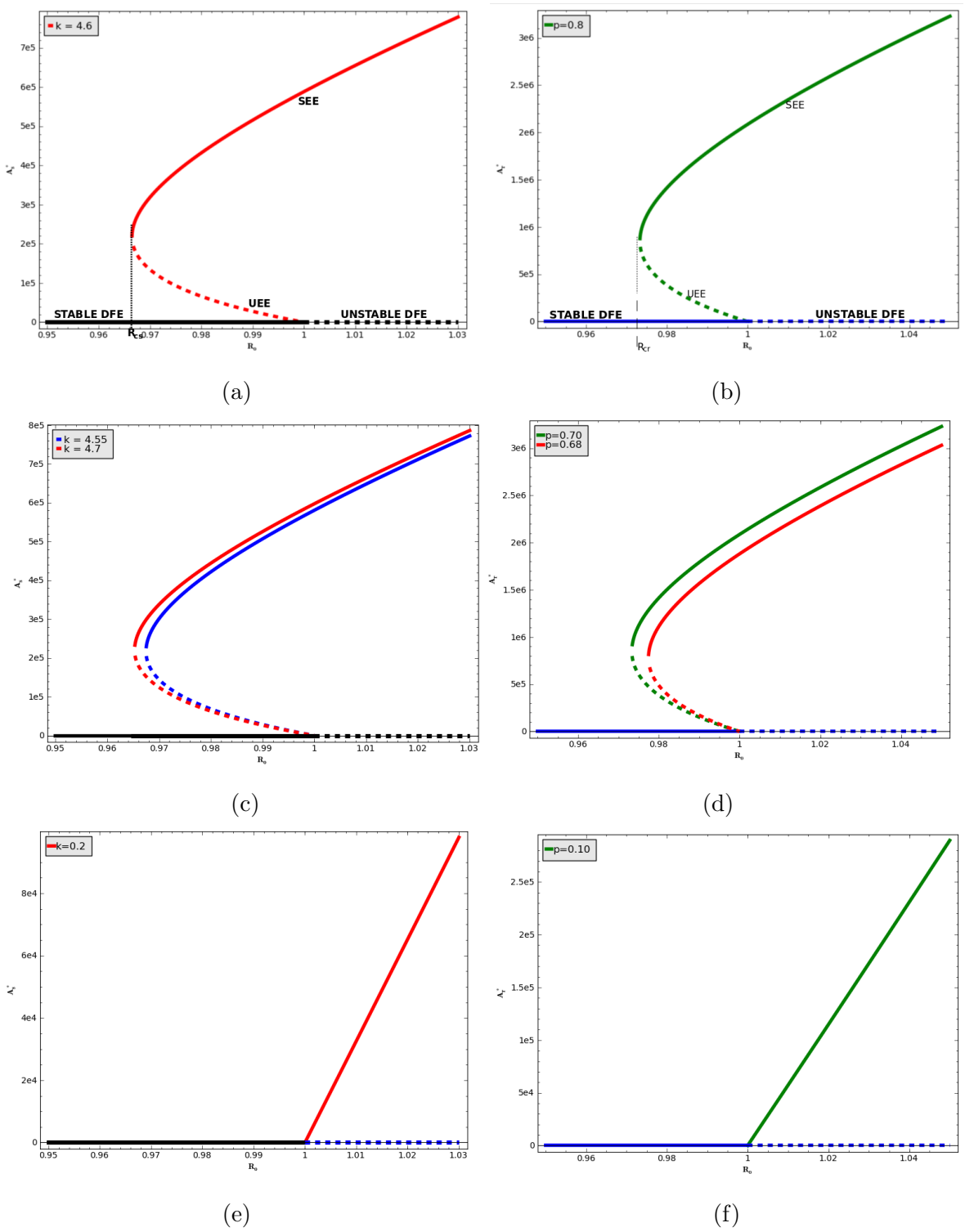



Figure 4.8: The onset of both transcritical and backward bifurcation. SEE denote the stable endemic equilibria and UEE is the unstable endemic equilibria. $R_{cs}$ is the critical value of the basic reproduction number $R_s$ and $R_{cr}$ is the critical value of the basic reproduction number $R_r$.

## 4.4 Uncertainty and sensitivity analysis using latin hypercube sampling technique.

The behaviour of models incorporating high degree of heterogeneity needs to be analysed using numerical methods. The method of uncertainty and sensitivity analysis are important tools that aid in understanding the complexity of models that are characterized with a high degree of uncertainty in approximating the parameter values [71]. Since the values of many parameters used in deterministic models are unknown, their impact in disease transmission can not be underestimated [26, 71]. Uncertainty analysis is mainly used to assess the variability in the outcome variable that occur as a result of uncertainty in estimating the values of the input parameters [72]. Sensitivity analysis can be used together with uncertainty analysis in recognising the input parameters that are vital in contributing to the prediction of the outcome variable. Thus, sensitivity analysis examines how altering the input parameters affect the value of the outcome variable [72]. A dominant parameter has a partial rank correlation coefficient (PRCC) close to one or negative one while parameters with least influence on variable output have rank coefficients close to zero.

The Latin Hypercube Sampling (LHS) is one of the techniques used in exploring the intricate behaviour of mathematical models. The LHS is a stratified Monte Carlo sampling [71, 73] where the uncertainty of every input parameter is considered as a random variable and a probability distribution function is assigned for each parameter. The use of each parameter at a time makes LHS an extremely efficient sampling design. The LHS technique is relevant to our model due to the reasons that: (i) there exists uncertainty in some of the parameters used in the model. (ii) the outcome variables might be non linear functions of the input parameters and (iii) there is a need to analyse the entire parameter space. The qualitative relationship that exist between the input parameter and the output variable is indicated by the sign of the PRCCs [71]. Further the PRCCs can be used to show the degree of monotonicity that occur between the input variable and a specific outcome variable [71, 72].

Table 4.2: Table of range of parameters used in the sensitivity and uncertainty analysis.

| **Parameter** | **min. value** | **max. value** | **parameter** | **min. value** | **max. value** |
|---|---|---|---|---|---|
| $\beta_y$ | 3 | 5 | $\alpha_s$ | 0.001 | 0.005 |
| $\beta_x$ | 1 | 3 | p | 0.01 | 0.18 |
| $\beta_z$ | 2 | 4 | $k$ | 0.01 | 0.25 |
| $\beta_w$ | 2 | 4 | $d_r$ | 0.01 | 0.1 |
| $\tau$ | 0.1 | 0.8 | $d_s$ | 0.01 | 0.05 |
| $\gamma_r$ | 0.001 | 0.0044 | $\mu$ | 0.0129 | 0.04 |
| $\gamma_s$ | 0.05 | 0.25 | $\mu_{TB}$ | 0.25 | 0.95 |
| $\alpha_r$ | 0.001 | 0.0044 | $\omega_r = \omega_s$ | 0.3576 | 3.576 |

**Remark 4.4.1.** The LHS method was used in a case study conducted in [57] to investigate the parameters that contributed in high proportion of multidrug-resistant TB in Papua New Guinea. The sensitivity and uncertainty analysis showed that the rate of progression from dormant TB to clinically active TB was the most influential parameter.

We carry out uncertainty and sensitivity analysis on the heterogeneous transmission TB model using LHS to investigate the effects that the parameters have on the output variables for TB infection. Our sensitivity and uncertainty analysis will involve the following parameters: $\beta_y$, $\beta_x$, $\beta_z$, $\beta_w$, $\alpha_r$, $\alpha_s$, $\gamma_s$, $\gamma_r$, $d_r$, $d_s, \tau$, $\mu$, $\mu_{TB}$, $p$, $k$, $\omega_r$ and $\omega_s$. In our sensitivity analysis we are interested in those parameters that are often unknown but affect TB progression. We shall also limit our analysis to the four infected classes of our model namely: $L_s$, $L_r$, $A_s$ and $A_r$. We run our model 1000 times using varied parameter values as defined in each parameter space. The range of values of our parameters are included in the Table 4.2. We concentrate on interpreting our sensitivity analysis results based on day 20 and day 180 since the incubation period of TB is about two to twelve weeks.

In Figure 4.9(a) the transmission rates $\beta_y$, $\beta_x$, $\beta_w$, and $\beta_z$, fraction that directly progress to

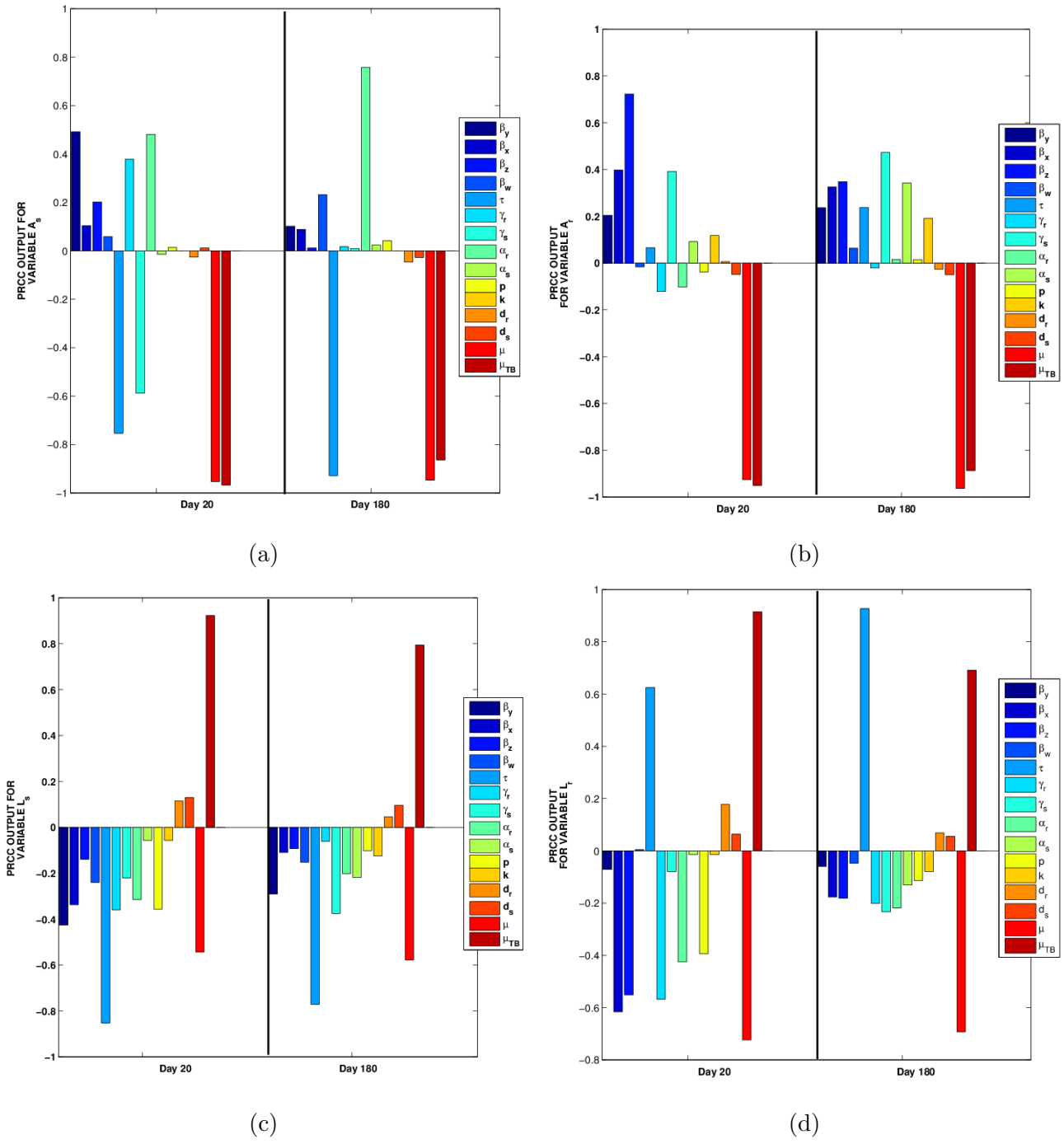



Figure 4.9: Sensitivity and uncertainty results representing heterogeneous model of TB transmission without treatment.

clinically active TB $\gamma_r, \gamma_s$, the level of exogenous reinfection $p$ and reactivation rates $\alpha_r, \alpha_s$ are positively correlated. However, the reactivation rate $\alpha_r$ is strongly positively correlated to variable $A_s$. The results suggests that the increase in these parameters may significantly increase the number of clinically active TB cases. On the other hand the proportion that is genetically susceptible $\tau$, regression rates $d_s, d_r$ and mortality rates $\mu, \mu_{TB}$ are negatively correlated implying that a slight increase of these parameters decrease the genetically sensitive TB active individuals. The parameters $\tau, \mu, \mu_{TB}$ are strongly negatively correlated. Intervention strategies should aim at controlling transmission rates, exogenous reinfection and reactivation parameters so as to reduce TB burden in a genetically susceptible population.

In Figure 4.9(b) the transmission parameters $\beta_y,\ \beta_x,\ \beta_w$ and $\beta_z$, proportion that is genetically resistant $\tau$, fraction that directly progress to active TB $\gamma_s$ and exogenous reinfection parameters $p,\ k$ are positively correlated to variable $A_r$. The reactivation parameter $\alpha_r$ is strongly positively correlated to variable $A_r$. The parameters $d_r,\ d_s, \gamma_r,\ \mu$ and $\mu_{TB}$ are negatively correlated to variable $A_r$. $\mu$ and $\mu_{TB}$ are strongly negatively correlated.

In Figure 4.9(c) the parameters $\beta_y,\ \beta_x,\ \beta_w,\ \beta_z,\ \alpha_r,\ \alpha_s,\ p,\ k,\ \gamma_s,\ \gamma_r$ and $\mu$ are negatively correlated to variable $L_s$. Thus a slight increase in these parameters will further reduce the latent population. However this will have a negative impact on the general population since more active TB cases will result. Hence, intervention strategies should concentrate on reducing the value of these parameters to mitigate TB progression from dormant state to infectious stage. $d_r,\ d_s$ and $\mu_{TB}$ are strongly positively correlated.

In Figure 4.9(d) the parameters $\beta_x,\ \beta_y,\ \beta_w,\ \beta_z,\ \gamma_r,\ \gamma_s,\ \alpha_r,\ \alpha_s,\ p,\ k$ and $\mu$ are negatively correlated while $\tau,\ d_r,\ d_s$ and $\mu_{TB}$ are positively correlated to variable $L_r$. The parameter $\tau$ is strongly positively correlated implying that a slight increase in the parameter significantly influence the outcome of latently infected cases.

### 4.4.1 Effects of treatment on TB.

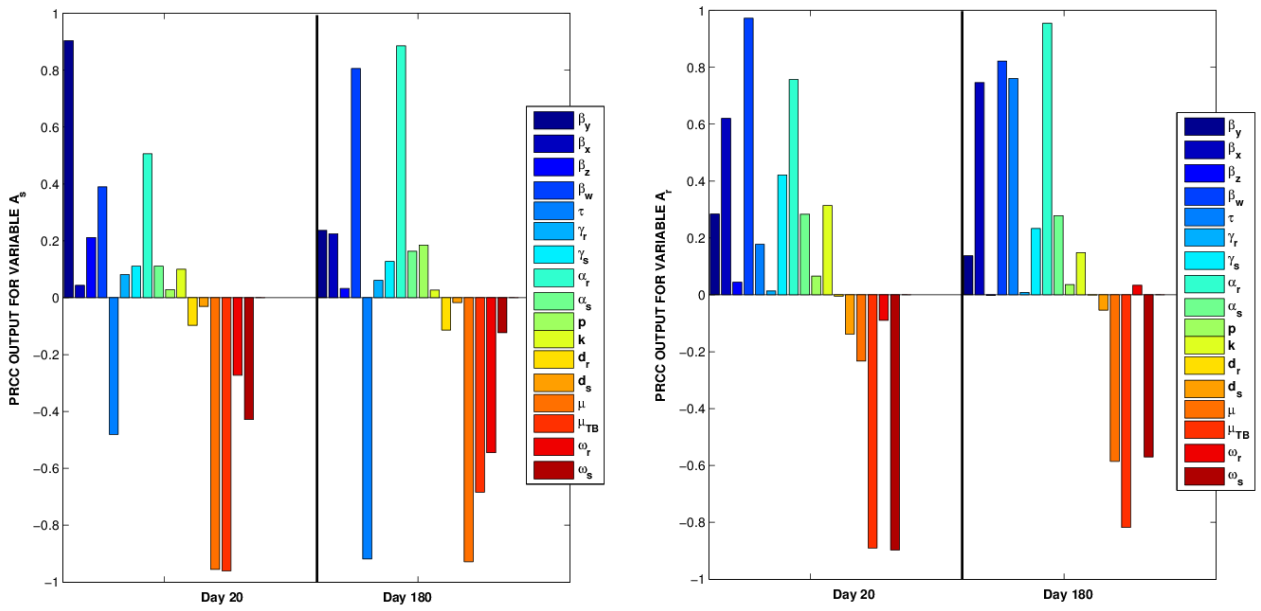
To investigate the effects of treatment on the progression of TB we assume that only individuals with clinically active TB are treated, which is a scenario likely to be found in most developing countries where medical technology is not advanced to diagnose latent state of TB. We also assume that both genetically sensitive and genetically resistant individuals are treated at the same rate, i.e $\omega_r = \omega_s$. From our model with treatment the fraction of infectious individuals receiving TB therapy can be given as $Y_\omega = \dfrac{\omega_i}{d_i + \omega_i + \mu + \mu_{TB}}$ where $i \in \{r, s\}$. This fraction lies between 0 and 100%. For low treatment levels we consider treatment to be within ($30\% \leq Y_\omega \leq 50\%$) while for high treatment level the fraction lies within ($50\% \leq Y_\omega \leq 80\%$) [28] . Using parameter values as defined in the Table 4.1 to compute treatment levels when fraction of treated individuals lies within these two ranges we obtain $0.3576 \leq \omega_s = \omega_r \leq 0.8344$ and $0.8344 \leq \omega_s = \omega_r \leq 3.5970$ as ranges representing low and high therapeutic levels respectively. To perform our sensitivity analysis on our model with treatment we establish the following treatment strategies.

(i) Low treatment level.

(ii) High treatment level.

We investigate the effect of treatment on populations based on day 180 since TB treatment usually takes six to twelve months [28]. Figure 4.10(a) represent a scenario where TB treatment is administered at low level. We observe that the parameters $\beta_y, \beta_x, \beta_w, \beta_z, \gamma_r, \gamma_s, \alpha_r, \alpha_s$, $p$ and $k$ are positively correlated to variable $A_s$. $\beta_w$ and $\alpha_r$ are strongly positively correlated implying that a slight increase in heterogeneous transmission of TB and reactivation rate are likely to trigger a TB epidemic in a genetically sensitive sub population. $\tau, d_r, d_s, \mu, \mu_{TB}, \omega_r$ and $\omega_s$ are negatively correlated to variable $A_s$. The parameters $\tau, \mu$ and $\mu_{TB}$ are strongly negatively correlated to variable $A_s$.

In Figure 4.10(b) we observe that the parameters $\beta_y$, $\beta_x$, $\beta_z$, $\beta_w$, $\tau$, $\gamma_r$, $\gamma_s$, $\alpha_r$, $\alpha_s$, $p$, $k$, and $\omega_r$ are positively correlated while parameters $d_r$, $d_s$, $\mu$, $\mu_{TB}$ and $\omega_s$ are negatively correlated



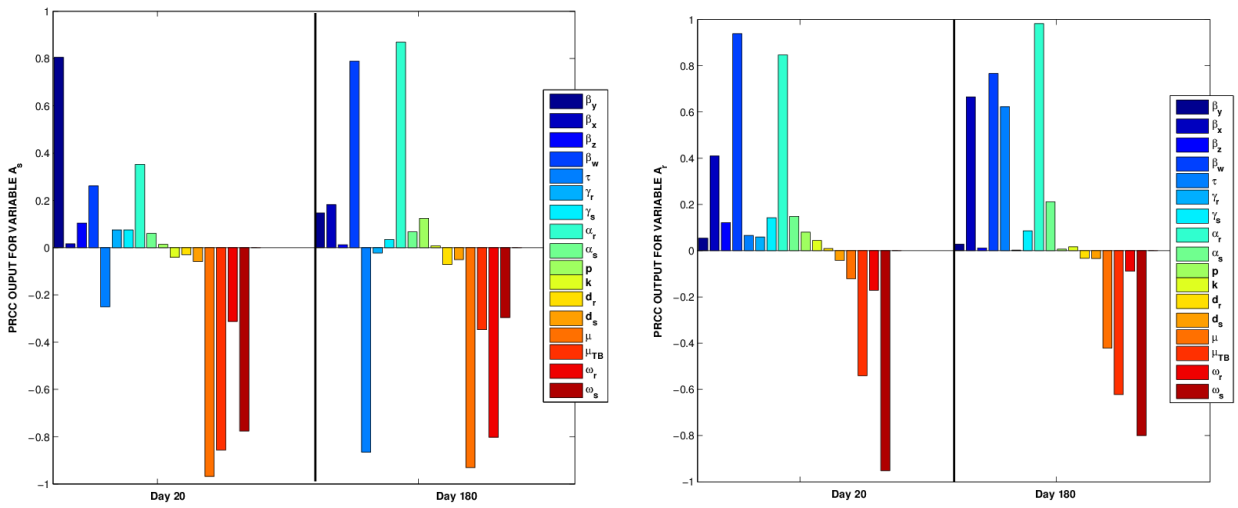

(a) (b)

Figure 4.10: Sensitivity and uncertainty results for actively infected individuals at low treatment level.

to variable $A_r$. The parameters $\beta_x, \beta_w, \tau$ and $\alpha_r$ are strongly positively correlated to variable $A_r$ indicating that a slight increase in these parameters will result to an increase in clinically active TB cases. $\mu, \mu_{TB}$ and $\omega_s$ are strongly negatively correlated to $A_r$. We observe that the parameter $\omega_r$ representing treatment on genetically resistant sub population is initially negatively correlated as depicted on day 20. However, in the long-term the effect of the treatment on the infected population is reversed as evidenced by a positive PRCC on day 180. This may suggest that the population of individuals being treated is very small in comparison to the total population that is suffering from TB. Moreover, it may be due to appearance of drug-resistant strains of *M. tuberculosis* and non compliance of infected individuals to treatment directives [28]. Hence, TB will continue to invade the population irrespective of presence of treatment.

We now consider a scenario where treatment is administered at high levels. We take the levels of treatment to be within the range $0.8344 \leq \omega_r = \omega_s \leq 3.5$. The sensitivity and uncertainty analysis depicting this scenario is illustrated in Figure 4.11. In Figure 4.11(a) the parameters

$\beta_y, \beta_x, \beta_z, \beta_w, \gamma_r, \gamma_s, \alpha_r, \alpha_s$, $p$ and $k$ are positively correlated to variable $A_s$. $\beta_w$ and $\alpha_r$ are strongly positively correlated. An increase in infection rate $\beta_w$ and reactivation rate $\alpha_r$ are likely to cause a TB epidemic in the genetically sensitive sub population. On the other hand the parameters $\tau, \mu, \mu_{TB}, \omega_r$ and $\omega_s$ are negatively correlated. $\tau, \mu$ and $\omega_r$ are strongly negatively correlated. Further, the LHS sensitivity and uncertainty results show that the parameters $\beta_y$, $\beta_x$, $\beta_w$, $\tau$, $\alpha_r$, $\alpha_s$, $d_r$, $\mu$, $\omega_r$ and $\omega_s$ are the significant parameters. Thus a slight alteration of the parameters will greatly influence the outcome of genetically sensitive individuals with active TB. In this scenario it is apparent that treatment of genetically sensitive individuals with active TB reduces TB burden in the population. Also in this scenario we observe that although exogenous reinfection contribute in increasing number of individuals with active TB, in presence of treatment it is not significant.




(a) (b)

Figure 4.11: Sensitivity and uncertainty results for high treatment levels.

In Figure 4.11(b) the parameters $\beta_y$, $\beta_x$, $\beta_z$, $\beta_w$, $\tau$, $\gamma_r$, $\gamma_s$, $\alpha_r$, $\alpha_s$, $p$ and $k$ are positively correlated while $d_r$, $d_s$, $\mu$, $\mu_{TB}$, $\omega_r$, and $\omega_s$ are negatively correlated to variable $A_r$. Amongst these $\beta_x$, $\beta_w$, $\tau$, $\gamma_s$, $\alpha_r$, $\alpha_s$, $\mu$, $\mu_{TB}$, $\omega_r$ and $\omega_s$ are the most significant parameters as evidenced by LHS sensitivity and uncertainty analysis. A slight change in these parameters will significantly affect

the output of variable $A_r$. Also we observe that treating genetically resistant individuals with active TB reduces TB burden in the population as evidenced by a negative PRCC.

# Chapter 5

# Discussion.

In our model we investigated the effect of exogenous reinfection with TB in a genetically susceptible population. We computed the fundamental threshold that governs the severity of an epidemic and found that the exogenous reinfection parameters do not appear in our basic reproduction number. Thus, the basic reproduction number obtained when the population is exogenously reinfected with TB is not a better predictor of the course likely to be taken by TB epidemic. The classical measure of persistence of an epidemic in the susceptible population is the basic reproduction number. When $R_0 \leq 1$ the epidemic ceases while $R_0 > 1$ the infection becomes endemic. For our case we have a scenario where infection persists irrespective of $R_0$ being less than unity. Thus controlling TB in a genetically susceptible population in the presence of exogenous reinfection will not be successful by only forcing $R_0$ to a value less than one. Other factors such as critical value of basic reproduction number, reinfection threshold and backward bifurcation thresholds have to be considered in order to eradicate TB. In fact our mathematical and numerical results suggested that TB can be eliminated when the basic reproduction value is decreased to a value less than $R_c$ i.e $R_0 < R_c < 1$. The gradual transition from transcritical bifurcation to backward bifurcation has vital implications in governing the behaviour of our dynamical system. We do not expect backward bifurcation to occur when exogenous reinfection is less than reinfection threshold. Interestingly, backward bifurcation occur at different values of exogenous reinfection between the two sub-populations.

As suggested by Singer and Kirshner [29] most of the exogenous reinfection values at which backward bifurcation occur are unrealistic and may not be expected in a real epidemic. There is a direct relationship between backward bifurcation and exogenous reinfection. An increases in the level of exogenous reinfection increases backward bifurcation. This scenario show that at high levels of exogenous reinfection TB will continue to invade the susceptible population despite the success of controlling strategies in maintaining basic reproduction number below one. Epidemiologically the knowledge of backward bifurcation may enable public health and policy makers to devise effective treatment strategies.

The appearance of damped oscillations as exhibited by our numerical simulation reaffirmed that exogenous reinfection does destabilize the typical TB endemic. Introduction of intervention when TB has not stabilized will not significantly reduce TB progression. Hence, its crucial for people involved in implementing controlling strategies to understand the qualitative dynamics of TB in a community that has exogenous reinfection with TB. From the sensitivity analysis for basic reproduction number $R_s$ and $R_r$ we observed that the scenarios when we have high infection rate and low death rate $\mu_{TB}$ and high infection rate and the case when we have both infection rate and death due to TB high, are the one likely to cause a TB endemic. However, TB endemic occurring when we have high infection rate and low death rate is more devastating than when we have high infection rate and high death rate. This is due to the fact that infected individuals stay longer in the susceptible population thus infecting more people.

The partial derivatives of the basic reproduction number for heterogeneous transmission model with treatment showed that TB treatment could only reduce TB proliferation if the treatment administered in either genetically sensitive or genetically resistant sub populations is effective enough to reduce the basic reproduction number to a value below one. Thus, treating either genetically sensitive or genetically resistant sub population will not eradicate TB. Epidemiologically, this observation is vital in public heath sectors targeting to combat TB in any given locality, for the sole purpose of overcoming TB progression in that prior visualization of the treatment level likely to reduce TB is important so as to optimize the resources allocated in

controlling strategies.

We investigated the heterogeneous model using Latin Hypercube Sampling by first considering heterogeneous mode of transmission without treatment and later in presence of intervention. From our TB model without treatment, sensitivity and uncertainty analysis results showed that contact rates and reactivation rates greatly influence the outcome of clinically active TB individuals. Thus controlling measures should aim at controlling these parameters in order to mitigate TB progression in the affected population. In our model with treatment we found that low level treatment of genetically resistant individuals may not suppress TB progression in a population. However, the same strategy has better results on genetically sensitive individuals on reduction of the TB burden as evidenced by a negative partial rank correlation coefficient. At high level of TB therapy sensitivity and uncertainty analysis results showed that treatment reduces number of clinically active cases in both genetically sensitive and genetically resistant sub populations. Despite the availability of TB antibiotics and chemoprophylaxis that can eliminate or reduce TB to zero levels, TB has remained a global threat due to ineffective treatment strategies [28]. Theoretically there exist TB treatment levels that can be administered to a given population to eradicate TB. However, these levels are too high to be achieved by many developing countries. For instance, we observed that if 80% of the population that is genetically susceptible is treated then TB is likely to reduce to zero levels. This percentage is too high to be achieved in most developing countries.

Future work may focus on implementing optimal treatment control strategies where both latently and actively infected individuals are treated. Further, factors such as adherence to drug prescriptions, resistance to treatment and effect of nutrition on TB progression should be investigated within the scope of genetic susceptibility.

# Appendix A: Derivation of $\Pi_1$ and $\Pi_2$.

From the quadratic expression (3.18) we have

$$X_1 = k\mu\beta_y^2(\mu + \mu_{TB}),$$

$$X_2 = \beta_y \left[ bk\mu(\mu + \mu_{TB}) + \frac{bk\mu^2(1-\tau)\beta_y\gamma_s}{\alpha_s} + b\underbrace{[\mu^2 + (\mu + \mu_{TB})\alpha_s + (d_s + \mu_{TB})\mu]}_{a}\left(1 - \frac{k\mu R_s}{\alpha_s}\right)\right],$$

$$X_3 = b^2\underbrace{[\mu^2 + (\mu + \mu_{TB})\alpha_s + (d_s + \mu_{TB})\mu]}_{b}[1 - R_s].$$

letting

$$\begin{aligned}(\alpha_s + \mu)(d_s + \mu + \mu_{TB}) =& \alpha_s d_s + \alpha_s\mu + \alpha_s\mu_{TB} + \mu d_s + \mu^2 + \mu\mu_{TB} \\ =& \mu^2 + (\mu + \mu_{TB})\alpha_s + (d_s + \mu_{TB})\mu + \alpha_s d_s. \end{aligned} \tag{1}$$

Subtracting $\alpha_s d_s$ from the equation (1) we have expressions (a) and (b) represented as

$$(\alpha_s + \mu)(d_s + \mu + \mu_{TB}) - \alpha_s d_s = \mu^2 + (\mu + \mu_{TB})\alpha_s + (d_s + \mu_{TB})\mu$$

We have $W_s = \dfrac{\alpha_s}{d_s + \mu + \mu_{TB}}$ and $X_s = \dfrac{\alpha_s}{\alpha_s + \mu}$ which implies that

$$\frac{1}{W_s} = \frac{d_s + \mu + \mu_{TB}}{\alpha_s},$$

$$\frac{1}{X_s} = \frac{\alpha_s + \mu}{\alpha_s}.$$

Thus

$$\begin{aligned}\mu^2 + (\mu + \mu_{TB})\alpha_s + (d_s + \mu_{TB})\mu =& (\alpha_s + \mu)(d_s + \mu + \mu_{TB}) - \alpha_s d_s, \\ =& (\alpha_s + \mu)(d_s + \mu + \mu_{TB})(\frac{\alpha_s^2}{\alpha_s^2}) - \alpha_s d_s, \\ =& \alpha_s^2\left(\frac{\alpha_s + \mu}{\alpha_s}\right)\left(\frac{d_s + \mu + \mu_{TB}}{\alpha_s}\right) - \alpha_s d_s, \\ =& \frac{\alpha_s^2}{X_s W_s} - \alpha_s d_s, \\ =& \alpha_s d_s\left(\frac{\alpha_s^2}{\alpha_s d_s X_s W_s} - 1\right), \\ =& \alpha_s d_s\left(\frac{\alpha_s}{d_s X_s W_s} - 1\right).\end{aligned}$$

Now in $X_2$ and $X_3$ we replace $\mu^2 + (\mu + \mu_{TB})\alpha_s + (d_s + \mu_{TB})\mu$ with $\alpha_s d_s \left(\frac{\alpha_s}{d_s X_s W_s} - 1\right)$. Hence,

$$\begin{aligned}
X_1 =& k\mu\beta_y^2(\mu + \mu_{TB}),\\
X_2 =& \beta_y \left[bk\mu(\mu + \mu_{TB}) + \frac{b(1-\tau)k\mu^2\beta_y\gamma_s}{\alpha_s} + b\alpha_s d_s \left(\frac{\alpha_s}{d_s X_s W_s} - 1\right)(1 - \varphi_1 R_s)\right],\\
X_3 =& b^2\alpha_s d_s \left(\frac{\alpha_s}{d_s X_s W_s} - 1\right).
\end{aligned}$$

We follow a similar procedure to obtain

$$\Pi_2 = b\alpha_r d_r \left(\frac{\alpha_r}{d_r X_r W_r} - 1\right).$$

# Appendix B: Basic reproduction number for heterogeneous mode of transmission only.

We apply van den Driessche approach as described in 3.3 to determine basic reproduction number for heterogeneous mode of transmission. Thus

$$\mathcal{F}(x) = \begin{pmatrix} \frac{(1-\gamma_s)\beta_w A_r S_s}{N} \\ \frac{\beta_w A_r \gamma_s S_s}{N} \\ \frac{(1-\gamma_r)\beta_z A_s S_r}{N} \\ \frac{\beta_z A_s \gamma_r S_r}{N} \end{pmatrix}$$

$$\mathcal{V}(x) = \begin{pmatrix} \frac{\beta_w A_r k L_s}{N} + (\alpha_s + \mu)L_s - d_s A_s \\ (d_s + \mu + \mu_{TB})A_s - \alpha_s L_s - \frac{\beta_w A_r k L_s}{N} \\ \frac{\beta_z A_s p L_r}{N} + (\alpha_r + \mu)L_r - d_r A_r \\ (d_r + \mu + \mu_{TB})A_r - \alpha_r L_r - \frac{\beta_z A_s p L_r}{N} \end{pmatrix}.$$

The partial derivatives of $\mathcal{V}(x)$ and $\mathcal{F}(x)$ evaluated at disease free equilibrium point $\bar{E}$ are given as

$$F = \frac{\partial \mathcal{F}(\bar{E})}{\partial x_i} = \begin{pmatrix} 0 & 0 & 0 & (1-\gamma_s)\beta_w(1-\tau) \\ 0 & 0 & 0 & \beta_w\gamma_s(1-\tau) \\ 0(1-\gamma_r)\beta_z\tau & 0 & 0 & \\ 0 & \beta_z\gamma_r\tau & 0 & 0 \end{pmatrix},$$

$$V = \frac{\partial V(\bar{E})}{\partial x_j} = \begin{pmatrix} (\alpha_s+\mu) & -d_s & 0 & 0 \\ -\alpha_s & (d_s+\mu+\mu_{TB}) & 0 & 0 \\ 0 & 0 & (\alpha_s+\mu) & -d_r \\ 0 & 0 & -\alpha_r & d_r+\mu+\mu_{TB} \end{pmatrix}.$$

The inverse of V is given as

$$V^{-1} = \begin{pmatrix} \frac{d_s+\mu+\mu_{TB}}{\varsigma_1} & \frac{d_s}{\varsigma_1} & 0 & 0 \\ \frac{\alpha_s}{\varsigma_1} & \frac{\mu+\alpha_s}{\varsigma_1} & 0 & 0 \\ 0 & 0 & \frac{d_r+\mu+\mu_{TB}}{\varsigma_2} & \frac{d_r}{\varsigma_2} \\ 0 & 0 & \frac{\alpha_r}{\varsigma_2} & \frac{\alpha_r+\mu}{\varsigma_2} \end{pmatrix}$$

where $\varsigma_1 = \mu^2 + (\alpha_s+d_s)\mu + (\alpha_s+\mu)\mu_{TB}$, $\varsigma_2 = \mu^2 + (\alpha_r+d_r)\mu + (\alpha_r+\mu)\mu_{TB}$.

The next generation matrix $FV^{-1}$ is given as

$$FV^{-1} = \begin{pmatrix} 0 & 0 & \frac{-(1-\tau)(1-\gamma_s)\alpha_r\beta_w}{\varsigma_1} & \frac{-(1-\tau)(1-\gamma_s)(\mu+\alpha_r)\beta_w}{\varsigma_1} \\ 0 & 0 & \frac{(1-\tau)\alpha_r\gamma_s\beta_w}{\varsigma_1} & \frac{(1-\tau)(\mu+\alpha_r)\beta_w\gamma_s}{\varsigma_1} \\ \frac{(1-\gamma_r)\tau\alpha_r\beta_z}{\varsigma_2} & \frac{(1-\gamma_r)\tau(\mu+\alpha_s)\beta_z}{\varsigma_2} & 0 & 0 \\ \frac{\tau\alpha_s\beta_z\gamma_r}{\varsigma_2} & \frac{\tau\gamma_r(\mu+\alpha_s)\beta_z}{\varsigma_2} & 0 & 0 \end{pmatrix}$$

The eigenvalues of $FV^{-1}$ are given as

$$\begin{aligned}
\lambda_1 =& 0,\\
\lambda_2 =& 0,\\
\lambda_3 =& -\sqrt{\left(\frac{\beta_w(1-\tau)(\alpha_s+\mu\gamma_s)}{(\alpha_s+d_s)\mu+(\alpha_s+\mu)\mu+\mu^2}\right)\left(\frac{\beta_z\tau(\alpha_r+\mu\gamma_r)}{(\alpha_r+d_r)\mu+(\alpha_r+\mu)\mu_{TB}+\mu^2}\right)},\\
=& -\sqrt{R_wR_z},\\
\lambda_4 =& \sqrt{\left(\frac{\beta_w(1-\tau)(\alpha_s+\mu\gamma_s)}{(\alpha_s+d_s)\mu+(\alpha_s+\mu)\mu+\mu^2}\right)\left(\frac{\beta_z\tau(\alpha_r+\mu\gamma_r)}{(\alpha_r+d_r)\mu+(\alpha_r+\mu)\mu_{TB}+\mu^2}\right)},\\
=& \sqrt{R_wR_z}.
\end{aligned}$$

The dominant eigenvalue is our basic reproduction number. Thus

$$R_{ht} = \sqrt{R_wR_z}$$

is the basic reproduction number for heterogeneous mode of transmission only.

# Glossary

**Bacillus**- Refer to any of a group of rod-shaped, gram-positive, aerobic or anaerobic bacteria widely found in soil and water.

**Tubercle bacillus** - Refer to a rod-shaped aerobic bacterium (*Mycobacterium tuberculosis*) that causes tuberculosis.

**HLA − DR2**- Is a serological designation for HLA DR alleles that code for $\alpha$ and $\beta$ chains of MHC class II molecules.

**IFN − γR** - The interferon-gamma receptor (IFN-γR) is a receptor which binds interferon-γ, the sole member of interferon type II.

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