MATHEMATICAL MODELS FOR TUBERCULOSIS SPREAD IN HUMANS

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ABSTRACT

We studied two models describing transmission dynamics of tuberculosis (TB) and discussed their implications to human health. The first model is analyzed in the presence of treatment of active TB persons and the screened asymptomatic TB infectives. The second model is analyzed by looking at treatment of drug sensitive TB as well as drug resistant TB individuals. The models are built with a motive to study the dynamical behaviors of the trajectories which has the potential to guide TB control and also to influence policies for decision making. The basic reproduction number for each model is calculated by using the next generation method and conditions for disease elimination/persistence are determined. Numerical simulation results show that for the first model, $R_0 > 1,$ implying that the disease-free equilibrium is unstable. For the second model, however, $R_0 < 1,$ indicating that the disease-free equilibrium is a stable steady state and that in case of an outbreak, the disease will not spread. Simulation results also shows that increasing the rate of treatment significantly reduces the value of the reproductive number. Hence, we concluded through this study that proper screening, early detection and a high treatment rate, leading to a high successful treatment rate can reduce TB spread.

Keywords: TB Model, Disease Free Equilibrium, Basic Reproduction Number, Positivity Analysis.

2010 AMS Mathematics Subject Classification: $92D25,\ 92D30.$

ACRONYMS

TB -Tuberculosis

DOTS - Directly Observed Treatment Short Course

WHO - World Health Organization

SIR - Susceptible-Infected-Recovered

SEIR - Susceptible-Exposed-Infected-Recovered

MDR-TB - Multidrug-resistant tuberculosis

XDR-TB - Extensive drug-resistant tuberculosis

MoHSS - Ministry of Health and Social Services

DFE - Disease Free Equilibrium

LIST OF SYMBOLS

R_0 - Basic Reproductive Number.

S - Susceptible compartment.

E - Exposed to active TB compartment for the model with impact of screening and treatment of latently infected TB individuals.

E_1 - Exposed to active TB compartment for the model with treatment of drug-resistant TB individuals.

E_2 - Exposed to drug resistant TB compartment for the model with treatment of drug-resistant TB individuals.

I_1 - Active TB compartment for both models.

I_2 - Latently infected compartment for the model with impact of screening and treatment of latently infected TB individuals ;

Acquired drug -resistant TB compartment for the model with treatment of drug-resistant TB individuals.

H - Hospitalized compartment for the model with impact of screening and treatment of latently infected TB individuals.

T_1 - Treated compartment for active TB for the model with treatment of drug-resistant TB individuals.

T_2 - Treated compartment for acquired drug-resistant TB for the model with treatment of TB individuals.

μ - Constant natural death rate.

β_1 - Infection parameter due to active TB.

β_2 - Force of infection due to latently infected TB for the model with impact of screening and treatment of latently infected TB individuals;

Force of infection due to transmitted resistant TB for the model with treatment of drug-resistant TB individuals.

α_1 - Rate of exposure to active TB.

α_2 - Rate of exposure to latent TB for the model with impact of screening and treatment of latently infected TB individuals;

Rate of exposure to resistant TB for the model with treatment of drug-resistant TB individuals.

ρ_1 - Treatment rate for active TB.

ρ_2 - Reinfection rate for the model with impact of screening and treatment of latently in fected TB individuals;

Treatment rate for drug- resistant TB for the model with treatment of drug-resistant TB individuals.

γ_1 - Reinfection rate for treated active TB for the model with treatment of drug-resistant TB individuals.

γ_2 - Rate of active TB persons acquiring resistant TB for the model with treatment of drug-resistant TB individuals.

δ_1 - Disease-related death due to active TB for both models.

δ_2 - Disease- related death due to latent TB for the model with impact of screening and treat ment of latently infected TB individuals;

Disease-related death due to drug-resistant TB for the model with treatment of TB

individuals.

σ - Reinfection rate for treated resistant TB individuals for the model with treatment of drug-resistant TB individuals.

σ_1 - Reactivation rate for the model with impact of screening and treatment of latently infected TB individuals.

σ_2 - Treatment rate for latent TB for the model with impact of screening and treatment of latently infected TB individuals.

N - Total population at time t.

Ω_1 - Region in $\mathbb{R}^7_+$ for the model with treatment of drug-resistant TB individuals.

Λ - Replenishing/immigration constant for both models.

T - Matrix transpose.

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DEDICATION

My work is solely dedicated to my dear parents for being the parents any child would wish for. Tate Risto Amakutsi and meme Kristina Uunona, for their unwavering support since my childhood.

DECLARATION

I, Charlotte Amakutsi, declare hereby that this study, MATHEMATICAL MODELS FOR TUBERCULOSIS SPREAD IN HUMANS, is a true reflection of my own research, and that this work, or part thereof has not been submitted for a degree in any other institution of higher learning.

Mrs Charlotte Amakutsi June 2017

CHAPTER 1

INTRODUCTION

1.1 General introduction

Tuberculosis (TB) is an infectious bacterial disease caused by *Mycobacterium bacillus*. It is transmitted through the inhalation of droplets containing the bacillus, which gets into the alveoli and then can spread to other parts of the body [36]. The disease is responsible for many deaths in most parts of the world, specifically among groups with a high prevalence rate of human immune deficiency (HIV) and those living in crowded conditions (see [7, 8, 39]). The most common approach to TB control is to identify and cure the infectious individuals. Effective treatment therefore breaks the cycle of TB transmission.

The disease is worsened by the appearance of the multidrug-resistant strains, which are resistant to at least two of the four drugs in the standard first-line regimen, isoniazid (INH) and rifampicin (RIF) [6]. In some parts of the world, the outbreak of an even more resistant

TB, known as, extensive drug-resistant TB (EDR), has been reported [42]. Although drugs that can cure most tuberculosis patients have been available since the 1950s, TB remains a heavy burden on governments and the World Health Organisation (WHO). Tuberculosis (TB) remains the leading cause of infectious mortality worldwide, after HIV/ AIDS. It is the world's second deadliest communicable disease, according to the World Health Organisation (WHO) 2014 annual TB report [41].

According to the WHO, of the estimated 9.3 million new cases of TB in 2007, sub-Saharan Africa region had the highest estimated incidence rate (363 new cases per 100 000 population per year). The increase of new cases in Africa is attributed mainly to the spread of HIV infections, the collapse of public health programs as well as the emergence of drug-resistant strains of *Mycobacterium tuberculosis* [39]. Lack of adherence to TB medications by patients has not only led to relapses, but to a more serious multi-drug resistant TB (MDR-TB) strain, which has a high rate of treatment failure and longer periods of infectiousness, partly due to time lapse between diagnosis and getting drug-sensitivity test results [6, 8]. It is estimated that globally, 4% of TB patients are infected with the multi-drug resistant TB strain. This strain is complicated and expensive to treat [35]. Furthermore, treatment of multi-drug resistant TB is said to take long and has proved to be less effective [35, 39].

Estimates for high HIV infection rates among TB patients of 2007 exceeded 50% in Botswana, Malawi, South Africa, Zambia and Zimbabwe [12]. In 2013, an estimated 9 million people are said to have developed TB and 1.5 million people reported to have died of TB, 360 000

of whom were HIV positive. A quarter of the estimated 9 million people who developed TB in 2013 are from sub-Saharan Africa [41]. In 2014, 9.6 million incident cases of TB were estimated, of which 1.2 million were new HIV-positive TB cases (12.5% of all TB cases). It is reported that almost three-quarters (74%) of these cases were from Sub-Saharan Africa. It is estimated that 3.3% of new TB cases and 20% of previously treated cases have MDR-TB, of which 9.7% MDR-TB patients have XDR-TB. An estimated 190 000 people have died of MDR-TB in 2014 since only 50% of MDR-TB cases were successfully treated. However, it is reported that by the end of 2014, 43 countries had access to the medicine bedaquiline, a good move to maximise treatment for MBR-TB (see [42]).

In order to fight TB worldwide, the WHO has since 1990 embarked upon the DOTS (Directly Observed Treatment Short course) strategy and enhanced the STOP TB strategy, which combines best practices in the diagnosis and treatment of patients with active TB. According to the WHO's STOP TB partnership targets, at least by the year 2015, TB prevalence and death rates were expected to be reduced by 50% relative to the 1990 levels i.e reducing prevalence to approximately 150 per 100 000 or lower and deaths to approximately 15 per 100 000 per year or lower, including TB cases co-infected with HIV. According to WHO 2015 TB report [42], these Millennium Development Goals (MDGs) have been achieved: TB incidence rate has fallen at an average rate of 1.5% per year since year 2000, TB mortality rate in 2015 was 47% lower than in 1990 (target of 50% reduction was almost met, except in the WHO African and European regions) and TB prevalence rate in 2015 was 42% lower than in 1990. In addition, it is targeted to eliminate TB in the world by 2050, thus the WHO has

now started with the END TB strategy campaign from 2016 - 2035.

Treatments using drugs remain the dominant form of TB control worldwide and thus far, only *Bacillus of Calmette and Guérin* (BCG) vaccination and treatment of active TB have been implemented [39]. According to Castillo-Chavez and Feng [8], the effectiveness of BCG vaccine is disputed, with some field trial results showing protection rates ranging from 70% to 80%, while others showing that the vaccine is completely ineffective for TB prevention.

Mathematical models have proved very crucial in analyzing the causes, dynamics and spreading of TB epidemics. According to Klotz et al. [21], epidemiological modeling of diseases, including tuberculosis, is an established practice. The first mathematical model of tuberculosis was developed by Waaler in 1962, who used ordinary differential equations to forecast tuberculosis infection [39]. In this regard, differential equation models divide the population into compartments, depending on their disease status such as those susceptible to TB, those infected with TB and those who have recovered from TB. Such models rely on the accuracy of parameters, for example, demographic parameters such as birth and death rates, as well as the natural history of infection parameters, such as the infection rate that determines the relative behavior of these groups, transmission rates and recovery or treatment rates.

These differential equation models are extensively being used as a significant tool in epidemiological studies to obtain knowledge and to improve our understanding about a specific disease. Through evaluation of rates, at which individuals flow from one compartment to another under different scenarios, models provide insights into the effects of interventions

that occur as a result of a reduction in a disease transmission. In other words, analysis of these models can help policymakers to make informed decisions with regard to strategies, treatment and quarantine methods [6, 19, 21, 33, 46].

Modeling is necessary for the infectious TB for a number of reasons such as that TB has a complex and poorly understood natural history, the fact that is not easy to conduct interventional research due to the lag between infection and the disease, the behaviour of the susceptible population needs to be studied more, economic challenges in conducting interventions in low and middle income countries; and many unanswered questions about the impact of interventions [46].

Regarding the health burdens of TB, Namibia is no exception. In the 2009 Global TB report, Namibia was ranked at number five in the WHO African region, as one of the 15 countries with the highest estimated incidence rates in 2007 [40].

In 2013, Namibia was ranked fourth in the world in terms of high per capita TB incidence, after Swaziland, Lesotho and South Africa. In the 2008/2009 Ministry of Health and Social Services Annual Report, the Erongo region, along with Khomas, Ohangwena and Kavango, had the highest TB cases in the country, while Walvis Bay and Swakopmund towns hosted the highest number of TB patients [25]. The per capita disease burden, which is the number of cases per population, however, was reported to be the highest in Hardap, Karas and Omaheke regions.

With regard to multi-drug resistant TB (MDR-TB), 137 cases were reported in 2014, of which 6 cases were extensively drug-resistant TB (XDR-TB) (see [26]).

Namibia has since 2010 adopted a Second Medium Term Strategic Plan 2010-2015, to reduce TB prevalence to 50% of 1990 levels by the year, 2015 [25]. Namibia, unfortunately, did not manage to achieve the target on TB notification cases of less than 300 cases per 100 000 population, TB notification cases stood at 589 cases per 100 000 population. Namibia, however, at least managed to achieve the target of reducing the number of people who died from TB to a number less than five, already by the year 2010 [28]. Namibia could not also achieve the target of 87% treatment success rate in all forms of TB by 2015, as the average treatment success rate just stood at 83% [26, 27]. Like the rest of the world, Namibia is committed to TB eradication by 2050. The significance of this study is of added value to the Ministry of Health and Social Services, which can use the findings of this study to complement efforts of the on-going TB eradication programs in the country. For example, policy makers could pass a law that make screening for TB mandatory for patients visiting clinics and hospitals with general fever, weakness and cough.

Several ordinary differential equations (ODEs) models for TB have been formulated and studied [6–8, 21, 23, 36] to understand the transmission dynamics of TB. Nonetheless, TB continues to be a public health problem for sub-Saharan Africa, including Namibia and hence there is need for further research, especially towards understanding the spread of the drug resistant TB strain. TB models are of the Susceptible-Exposed-Infected-Recovered (SEIR) type, in which the population is divided into classes according to their infection status [6].
In this study, we consider two models of the Susceptible-Exposed-Infected-Recovered (SEIR) type, to try to understand the transmission dynamics of tuberculosis, with emphasis on

screening and treatment of all TB patients with active TB, latent TB and drug-resistance TB. The purpose is to use mathematical modeling to find favourable conditions under which the disease can be stopped from spreading further in the population.

The first model in this study is similar to the one used by Klotz et al. [21], but taking into account reactivation and hence the movement of latently infected individuals from the latently infected compartment to the active TB compartment. It is, however, ignoring the immigration of few infected individuals into the exposed compartment. The second model is formulated and based on Figure 3 in Zwerling et al. [46] and this model advocates for the treatment of active TB (drug-sensitive) persons as well as the drug-resistant TB individuals. In the first model, the population is divided into five epidemiological classes: the susceptible, the exposed, active infective, asymptomatic infective (latently infected) and treated, with the number in each class denoted by S,E, I_1, I_2 and H, respectively. The second model has seven groups, which are: the susceptible group (S) , two exposed groups (E_1, E_2), the active TB group (I_1), the acquired drug-resistant group (I_2) and two treated groups, denoted by T_1 and T_2.

The specific aims of this study are to determine the condition under which TB epidemic will cease/occur by carefully analyzing the calculated reproductive number for each model and to determine the effects of treating both the active TB infectives, asymptomatic (latently infected) individuals and drug resistant TB individuals, on the disease dynamics. Screening patients for TB is not mandatory anywhere in the world, although according to Kaur et al. [19], screening and proper counseling have positive impacts in checking HIV and TB spread in human population. It is against this fact that we further study TB disease in the

presence of screening and treatment, with the aim to see if screening for TB disease can be made mandatory for all patients visiting clinics and hospitals with TB related signs and symptoms. Furthermore, drug-resistant TB treatment is too costly and hence the need for effective interventions to prevent further transmission and acquisition of drug-resistance TB.

1.2 Outline of the thesis

This thesis is organized as follows: In Chapter 1, a general introduction to TB modeling is provided. In Chapter 2, a literature review pertaining to TB and mathematical modeling is given, while Chapter 3 deals with the preliminaries, in which some basic definitions are given, the algorithm for deriving the basic reproductive number is provided and the positivity of the systems is discussed. Chapter 4 deals with methodology that constitutes the formulation of the two models. Mathematical analysis and numerical simulations for the two models form subsections of Chapter 4. The discussion and concluding remarks are given in Chapter 5. The thesis then ends with some recommendations, the references and the appendix thereof.

CHAPTER 2

LITERATURE REVIEW

The infectious agent, *Mycobacterium tuberculosis* that causes TB was long discovered in 1882, with the first model for TB published by Waaler et al in 1962 [21, 39]. Several mathematical models have ever since been formulated, to try to understand better the transmission dynamics of TB (See for instance, [6–8, 21, 23, 36]). The emergence of HIV/AIDS and of drug resistant TB strains provide the justification for more modeling of TB infection. The proportion of new TB cases with multi-resistant TB (MDR-TB) reported in 2013 was 3.5% and had not changed in comparison with recent years, according to the WHO [41]. The much higher levels of resistant and poor treatment outcomes are of great concern and hence, a need for the continued fight against the TB disease [41].

Due to lack of clear and low cost tools to diagnose latent TB infection and the uncertainty about the natural history of TB, several assumptions about the disease and the infection have been adopted in models. These assumptions affected the findings of the various models [39]. The basic model for studying disease transmission is the Susceptible-Infected-Recovered

(SIR) model [29,33,34]. In addition, there is also the Susceptible-Exposed-Infected-Recovered (SEIR) model, used to study dynamics of diseases like TB that have an exposed or latent phase. In the SEIR model, the individuals begin in the susceptible (S) class and enter the exposed class, E. Upon being infected, the infection is not active. When the infection become active, individuals enter the infectious (I) class and eventually move to the recovered (R) class [36, 38] upon recovery or death. With any TB model, however, even treated people remain exposed to TB disease. The model assumes that recovery does not grant life-long immunity. In addition, the model assumes mass action, where every individual is equally likely to be in contact with every other individual in the population [29].

In any disease model, the concept of the basic reproduction number (R_0) is very important because it provides threshold conditions that determine whether an infectious disease will spread in a susceptible population when it is introduced into the population or will fail to establish itself. The basic reproduction number is thus defined as the expected number of new cases of infection that can result from a single (typical) infected individual that is introduced in a completely susceptible population.

The concept of a basic reproductive number (R_0) was first introduced by Ross in 1909 and defined in epidemiological modeling as such that if $R_0 < 1$, then the infection will clear from the population, while if $R_0 > 1$, the disease will persist. Thus, R_0 is used as a practical instrument to determine and estimate the amount of effort and prevention measures needed for successful disease eradication campaigns ([14, 16, 18, 38]).

Castillo-Chavez and Feng [8] formulated a series of mathematical models to study the dynamics of TB. They formulated a distributed delay model to study the effect of long and variable periods of latency on the disease dynamics, which showed qualitative behavioural change at a critical value $R_0 = 1$. When $R_0 \leq 1$, a stable disease-free equilibrium existed and for $R_0 > 1$, the disease-free equilibrium became unstable and rather a unique endemic equilibrium existed.

Another model they formulated considered the role of non-adherence to drug taking by TB patients on the development and maintenance of antibiotic resistant TB strain. Like Castillo-Chavez and Feng [8], Bowong et al. [7] also formulated a model with two strains (regular TB and the resistant TB). Both models showed that co-existence was possible but rare when the resistant strain was not the result of antibiotic resistance; but almost certain when the resistant strain was the result of antibiotic resistance.

Blower et al. [5] designed two models, to assess the population level effects of chemoprophylaxis treatment, to prevent latent TB from developing into active TB. Their second model has two TB strains: the drug sensitive and drug resistant. Their model displayed that individuals may acquire resistant TB, either by not taking medicines properly or resistant TB can be directly transmitted to susceptibles. Calculating the reproductive number for their model and using the threshold condition $R_0 < 1$, they computed the maximal acceptable probability of treatment failure. Their research findings were that treatment efficacy, together with high treatment rates should be ensured for effective TB control. In addition, using their model, they estimated the WHO objectives for the year 2000 and showed however, that the targets could not satisfy $R_0 < 1$.

In their paper, Porco and Blower [30] carried out uncertainty and sensitivity analysis of their TB model outcome to quantitatively understand TB transmission dynamics. Uncertainty analysis allowed them to evaluate the variability in the outcomes of the model. Sensitivity analysis results showed that only few of model's input parameters were significant: reactivation parameter, population recruitment rate, fraction of infected persons who develop TB soon after infection and the number of individuals that an index case infects per year.

McCluskey and Van den Driessche [23] formulated two models for TB that included treatment of latent TB (exposed to TB bacteria, but not making one sick) and active infective individuals. Latent infected TB people, though asymptomatic and do not transmit TB, may progress to active TB through either endogenous reactivation or exogenous reinfection. The model that assumed constant recruitment, with a fixed fraction entering each class revealed that immigration of infected individuals resulted in a system having a unique endemic equilibrium and no basic reproduction number. The model showed that even with treatment, TB remained endemic in the population. The other model had a general recruitment term, with all recruitment in the susceptible class only. Disease-free equilibrium (DFE) was found to be globally asymptotically stable when $R_0 \leq 1$ and the disease was expected to die out. These results are similar to those obtained from Bowong et al. [7] model of a one TB strain.

Ziv et al. [44] did a study using mathematical models to predict the potential public health impact of new tuberculosis vaccines in high TB incidence countries. Research findings showed that preexposure vaccines would be almost twice effective as postexposure when it comes to

reducing the number of new infections. They concluded that even when these pre- or post-exposure vaccines are widely distributed and higly effective (50% to 90% efficacy), these vaccines would only reduce the number of TB cases by one third. In the end, they suggested a development of a single vaccine that would serve as both a preexposure as well as a post-exposure vaccine. They also suggested for a development of TB vaccines that would need to provide very long-lasting immunity, even lifelong immunity against TB.

Bowong and Kurths [6] on the other hand, systematically investigated the analysis and parameter estimation of tuberculosis in the modeling framework. The researchers formulated and analyzed a tuberculosis model without seasonality and with seasonality. Their numerical simulation with parameter values from demographic and epidemiological data of Cameroon [6] revealed a decrease in the basic reproduction number as the disease transmission rate decreased. Therefore, full recovery of infectious individuals and a reduction in contacts were found to be an efficient intervention in the fight against TB disease.

In 2008 WHO TB report, South Africa came as a third country in the world with the highest TB burden, after India and China. Together with Swaziland, the two countries were said to have the highest TB notification rates in the world, with about 1% of their population developing TB per year [43]. To help understand why TB control in South Africa was not effective, Middelkoop et al. [24] did a study to determine the force of TB infection in adolescents in high TB and HIV prevalence communities. Results of the study revealed a high force of infection of 3% to 7.3% among adolescents, which increased with age. They ar-

gued that the trend could be due to increased social contact with infectious individuals. They concluded that an effective intervention strategy to control TB epidemic in high TB and HIV prevalence settings, was to reduce the force of infection. They recommended further research be conducted into social interaction patterns at different ages to help better understand the high risk of TB infection in these communities. Given that TB epidemiology has changed since the emergence of HIV due to the fact that HIV infection affects the pathogenesis and transmission of TB, and both TB and HIV are at high levels in Southern Africa, it is of great importance that we also talk of HIV/AIDS when discussing TB.

A simulation model used by Porco et al. [31], to predict the effect of HIV on TB outbreaks revealed that an HIV epidemic can significantly increase the frequency and severity of tuberculosis outbreaks, however, the amplification effect of HIV can be substantially reduced by extremely high TB treatment rates. The authors suggested that the WHO should significantly increase their target treatment levels for TB in countries with high TB and HIV burden. They strongly advocated for controlling TB epidemic in developing countries with severe HIV through chemoprophylaxis treatment and through treatment of HIV infected individuals.

Kaur et al. [19] used a deterministic non-linear mathematical model to determine the effect of screening and treatment on the transmission dynamics of HIV and TB co-infection. Analytical findings and simulation results showed that screening with proper counseling of HIV infectives caused a significant reduction in the progression of HIV to AIDS. Similarly, TB screening resulted in the reduction of TB infection prevalence. They suggested that effective

control measures that put screening with proper counseling into account be taken.

Dye and Williams [13] used a mathematical model for MDR-TB to display that short-course chemotherapy was likely to bring strains resistant to TB drugs, isoniazid and rifampicin, under control, thereby preventing the emergence of MDR-TB. The two authors pointed out that to prevent outbreaks of drug-resistant TB, at least 70% of prevalent, infectious MDR-TB cases should be detected and treated each year, and in addition, at least 80% of these MDR-TB cases should be cured. Research findings clearly pointed out that infections leading to MDR-TB were transmitted from new cases of TB and from treatment failures. They argued that people at high risk of carrying drug-resistant TB, such as the homeless, those in hospitals or prisons should be targetted, as a way of improving case detection and ultimately cure rates.

Chung-Delgado et al. [10] did a study to compare deaths between multidrug-resistant tuberculosis (MDR-TB) and drug-susceptible cases of TB and to determine factors leading to mortality among MDR-TB cases. Results of the study indicated that MDR-TB increased the risk of death during treatment and that a low education level, high number of previous TB episodes, a history of diabetes and HIV infection, are factors that are greatly causing high mortality rates among MDR-TB patients. Studies on MDR-TB by Dye and Williams [13] as well as Kempker et al. [20] also reported low cure rates or poor treatment outcomes, which implied an increased mortality during treatment. Kempker and co-authors found the risk factors associated with poor outcomes among patients with MDR-TB to be: acquired resistance, high baseline drug resistance and sputum smear or culture positivity at 4 months and 6 months. Concerned with the high rates of poor outcomes among MDR-TB patients with

isolates that have acquired resistance in their cohort study, the authors strongly stressed the need for prevention of acquired resistance.

Lack of adherence to TB treatment by patients has adverse effects on treatment outcomes ([**?**, 27, 37, 45]). Zvavamwe and Ehlers [45] carried out a study to assess the efficacy of the community-based DOTS programme in comparison to the standard health facility-based DOTS programme in Namibia and found out that community-based DOTS had better cure rates than health facility-based DOTS. High cure rates achieved through community- based DOTS were also reported in a study by Volmink and Garner [37]. Financial burden, poverty, stigma and discrimination are the factors cited that could prevent patients from going to health-facility to receive their daily medication, hence resulting in the interruption of TB treatment. A study done by Afns and Ji [**?**] also mentioned financial burden, mainly transport money to and from health facilities as well as insufficient knowledge about TB to cause treatment non-compliance.

In another study done in Namibia by Nepolo [27] on the effects of compliance on treatment outcomes, an overall treatment compliance of 89% was reported, lower than the recommended WHO compliance of more than 90%. However, while a high compliance of 97.2% was reported in the initial phase of treatment (the first two months of the six months TB treatment duration), the continuation phase (the last four months of the six months) only recorded 88.1% treatment compliance. Nepolo argued that the low compliance in the continuation phase of treatment could lead to poor treatment outcomes such as prolonged

infections, relapse, high TB mortality and emergence of drug-resistance strains, which could result in high treatment costs. Low compliance in the continuation phase of treatment was also reported in other studies (see for instance, [**?**,2]). Treatment success was reported among 86.1% of patients and overall, the type of area where one resided, was associated with treatment compliance. It was concluded that non-compliance to TB treatment was resulting in poor treatment outcomes and hence there was a need for interventions to address compliance throughout the duration of TB treatment.

The focus of this research will be on the treatment of active TB and screened asymptomatic TB infective individuals as well as on the treatment of drug-sensitive and drug-resistant TB persons. The effects of treatment on the disease dynamics will be investigated for the two models by making use of mathematical modeling.

CHAPTER 3

PRELIMINARIES

This Chapter begins with the definitions of some basic concepts used in dynamical systems such as equilibrium points, asymptotically stable and unstable equilibrium points, disease-free equilibrium, endemic equilibrium and basic reproductive number. Thereafter, we give the algorithm for derivation of the basic reproductive number according to Watmough and Van den Driessche [38]. In addition, we also discuss positivity of non-linear systems, sensitivity analysis and its importance in determining how small changes in parameters affect the equilibrium of dynamic systems.

3.1 Basic definitions

Consider a dynamical system of the form:

$$\dot{X}(t) = f(X(t), t) \quad X(0) = X_0. \tag{3.1}$$

We then give the definitions below from Lungu et al. [22].

Definition 1. *A vector $\bar{X}$ is an equilibrium point for a dynamical system (3.1) if once the state vector is equal to $\bar{X}$, it remains equal to $\bar{X}$ for all future time t. i.e. if $\dot{X}(t) = f(X(t), t)$, then an equilibrium point is a state $\bar{X}$ such that $f(\bar{X}, t) = 0$.*

For the next three definitions, we first consider a spherical region $D(X, \kappa)$ in the state space with center at $\bar{X}$ and radius κ.

Definition 2. *An equilibrium point $\bar{X}$ is stable if there is a $\kappa_0 > 0$ such that for every $\kappa < \kappa_0$, there is r, $0 < r < \kappa$ such that if $X(0)$ is inside the spherical region $D(\bar{X}, r)$, then $X(t)$ is inside $D(\bar{X}, \kappa)$ for all $t > 0$.*

In other words, an equilibrium point is stable if whenever the system state is initiated near that point, the state remains near it, even tending towards the equilibrium point as time increases.

Definition 3. *An equilibrium point $\bar{X}$ is asymptotically stable, if whenever it is stable and in addition, there is a $\bar{\kappa_0} > 0$ such that whenever the state is initiated inside the spherical region $D(\bar{X}, \bar{\kappa_0})$, it tends to $\bar{X}$ as time increases.*

Definition 4. *An equilibrium point $\bar{X}$ is unstable if for some $\kappa_0 > 0$ and any $r > 0$, there is a point in the spherical region $D(\bar{X}, r)$ such that if initiated there, the system state will eventually move outside of $D(\bar{X}, \kappa_0)$.*

Definition 5. *The disease-free equilibrium (DFE) is a state of the dynamic system when there is no disease strain present in the population.*

Definition 6. *The basic reproductive number, R_0, is the expected number of secondary infections produced by an index case in a completely susceptible population.*

Definition 7. *The endemic equilibrium is a state of the dynamic system where the disease is always present in the population without the re-introduction of further new infected individuals and this state is only feasible when $R_0 > 1$.*

3.2 Derivation of the basic reproductive number

The basic reproductive number, R_0, is the average number of secondary cases produced by one infected individual during the infected individual's entire infectious period when the disease is first introduced [18]. It is used as a predictor for epidemic outbreaks or an estimator of how severe an epidemic outbreak will be. The basic reproductive number is calculated as the dominant eigenvalue of the next generation matrix at the disease-free equilibrium when the entire population is susceptible [29].

Factors such as the duration of infectiousness, the infectiousness of an individual and the number of susceptible people with whom the infected individual comes into contact, affect the basic reproduction number.

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

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

A more formal approach to the derivation of the basic reproductive number, R_0 , follows from Watmough and Van den Driessche [38] and Shuai and Van den Driessche [34].

To illustrate, let us consider a general compartmental disease transmission model below.

$$\dot{x} = \mathcal{F}(x, y) - \mathcal{V}(x, y), \qquad \dot{y} = g(x, y), \tag{3.2}$$

where

$g = (g_1, ..., g_m)^T$, $x = (x_1, ..., x_n)^T \in \mathbb{R}^m$ represents the populations in disease compartments, $y = (y_1, ..., y_m)^T \in \mathbb{R}^m$ represents the populations in disease-free compartments.

In addition,

$\mathcal{F} = (\mathcal{F}_1, ..., \mathcal{F}_n)^T$, where $\mathcal{F}_i$ represents the rate of new infections in the ith disease compartment and $\mathcal{V} = (\mathcal{V}_1, ..., \mathcal{V}_n)^T$, where $\mathcal{V}_i$ represents a net outflow from the ith compartment.

The following assumptions are made to ensure the existence of a disease- free equilibrium (DFE) and that the model is well posed.

Assume that $\mathcal{F}_i(0, y) = 0$, $\mathcal{V}_i(0, y) = 0$, $\mathcal{F}_i(x, y) \geq 0$, $\mathcal{V}_i(x, y) \leq 0$ when $x_i = 0$ and

$\sum_{i=1}^{n} \mathcal{V}_i(x,y) \geq 0 \quad$ for all $x, y \geq 0,\ i = 1, ..., n$.

In addition, assume that the disease-free system $\dot{y} = g(0,y)$ has a unique equilibrium $y = y_0 \geq 0$ that is locally asymptotically stable within the disease-free space.

In other words, all solutions with initial conditions of the form $(0,y)$ approach the disease-free equilibrium $(0,y_0)$ as $t \to \infty$.

Let the two $n \times n$ matrices

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

and

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

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

The next generation matrix is then defined as

$$K = FV^{-1},$$

and the basic reproduction number R_0 is defined as the dominant eigenvalue of K, i.e

$$R_0 = \rho(FV^{-1}). \tag{3.3}$$

The DFE $P_0 = (0,y_0)$ is said to be locally asymptotically stable if $R_0 = \rho(FV^{-1}) < 1$ and unstable if $R_0 = \rho(FV^{-1}) > 1$ (See [34, 38]).

3.3 Positivity analysis

The following lemma gives a general condition for positivity of nonlinear dynamic systems [15].

Lemma 1. *The dynamical system (3.1) is positive, if and only if the following condition is satisfied:*

$$\forall X \in \mathbb{R}^n_+ : X_i = 0 \Rightarrow f_i(X) \geq 0. \tag{3.4}$$

3.4 Sensitivity analysis

Sensitivity is defined as a way of quantifying how a small change in parameters used in a model affects state variables over time [4]. It is thus important in determining how easily affected the equilibrium is by small changes in parameters [29].

According to Shrestha and Lloyd-Smith [33], model outputs contain uncertainties from two main sources, which are parameter values used in the model and model structure itself. Sensitivity analysis is done to determine the parameters or changes in the model structure that are most important in determining model outputs. It therefore helps in identifying components of the system that should be targeted for possible disease control measures or interventions or where further information or data need to be collected.

A formal definition of the sensitivity of an outcome, for example, R_0, to the parameter values e.g σ_2 or ρ_1, is given to be mathematically equal to the partial derivative of R_0 with

respect to these parameters.

i.e.

$$\text{sensitive index} = \frac{\partial R_0}{\partial \sigma_2}$$

or

$$\text{sensitive index} = \frac{\partial R_0}{\partial \rho_1}$$

However, for models with more than a few parameters, a more popular approach to sensitivity analysis for epidemic models has been devised and is well-known as the **Latin Hypercube Sampling.** The results from this method are often presented in terms of partial rank correlation coefficients and describe the influence of each parameter on a given model output in a non-parametric manner [4, 33].

In this thesis, we will explore the sensitivity analysis design, in which we fix the values of the $k-1$ parameters and only vary the k th parameter over a specified range. This type of design, only allows for one parameter to be varied at a time [4].

CHAPTER 4

MODELS FORMULATION

In this Chapter, we present the formulations of two TB models and explain with the help of flow diagrams how susceptible individuals, upon being infected with TB, progress through various stages.

4.1 Formulation of the TB model with impact of screening and treatment of latently infected TB individuals

In this Section, we formulate the TB model that incorporates screening and treatment of latently infected TB individuals. In this model, the population is divided into five classes: a class of susceptible individuals, S, a class of individuals exposed to TB, E, a class of individuals actively infected with TB, I_1, a class of individuals latently infected with TB but showing no clinical symptoms of the disease, I_2, and a class of individuals successfully treated for TB, H. The total population in this model is given by $N(t) = S(t) + E(t) +$

$I_1(t) + I_2(t) + H(t)$. Suppose the susceptible population is replenished at a rate given by Λ and is subjected to infections at a rate $\beta_1 I_1$ and $\beta_2 I_2$, representing the force of infection due to infections by individuals with active TB and individuals with latent TB, respectively.

Furthermore, assume that individuals exposed to TB can progress either to the active TB class at a rate α_1 or to the latently infected TB class at a rate α_2. All five classes are subjected to a constant natural death rate μ. However, active TB infectives, I_1, and asymptomatic TB infectives, I_2, are additionally subjected to disease related death at rates δ_1 for those actively infected with TB and δ_2 for those asymptomatically infected with TB. Actively infected individuals are successfully treated and progress to the exposed class at a constant rate ρ_1. Individuals infected with asymptomatic TB become actively infected at a constant rate σ_1. These individuals can also be screened for TB and receive treatment at a constant rate σ_2 and eventually progress to the exposed class at a constant rate ρ_1. Figure 4.1 shows the flow of TB disease in a population.

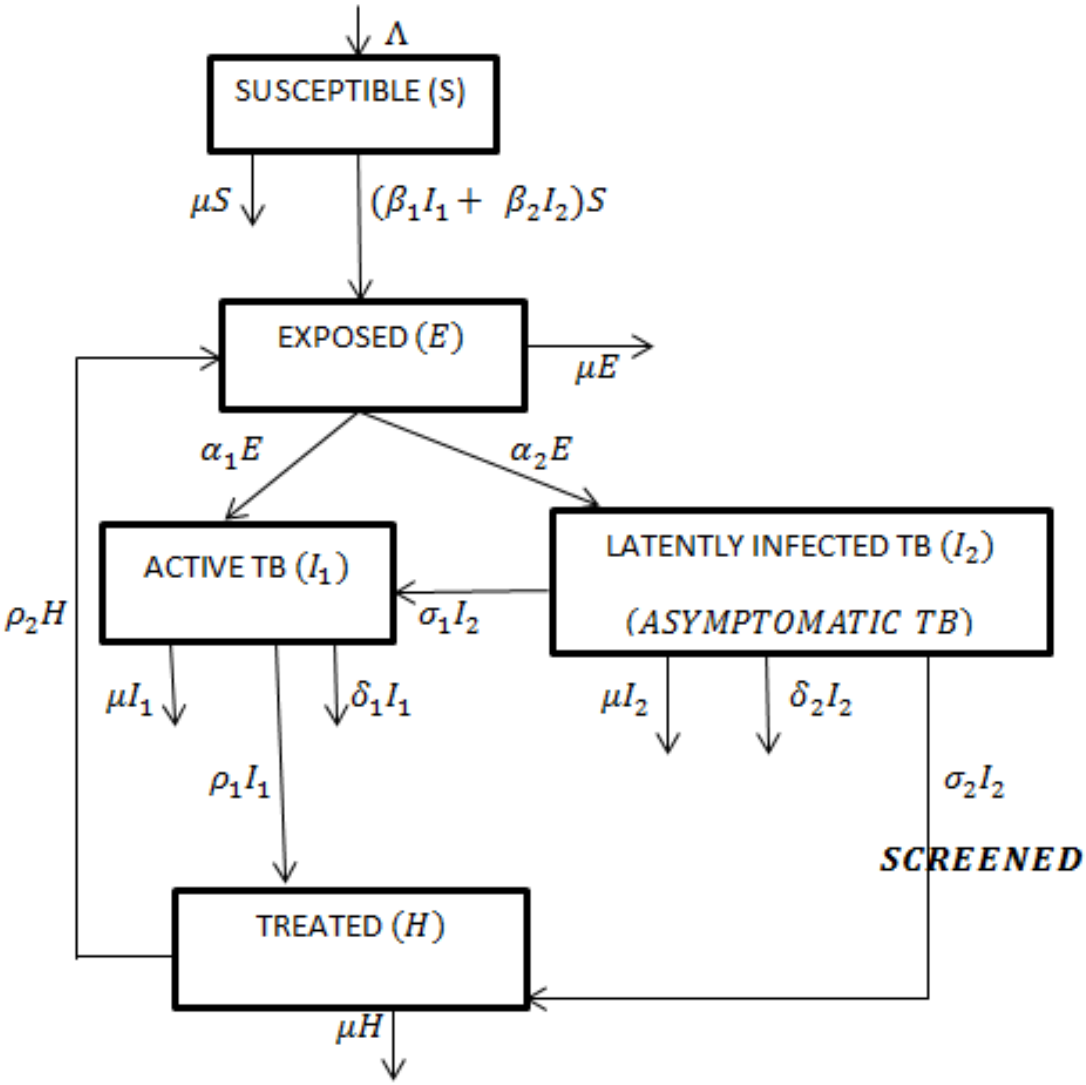


Figure 4.1: Transfer diagram for the TB model with impact of screening and treatment of latently infected individuals ([21])

The information in the transfer diagram in Figure 4.1 gives rise to the following system of nonlinear differential equations.

$$\frac{dS}{dt} = \Lambda - \mu S - (\beta_1 I_1 + \beta_2 I_2)S \tag{4.1}$$

$$\frac{dE}{dt} = (\beta_1 I_1 + \beta_2 I_2)S + \rho_2 H - (\alpha_1 + \alpha_2 + \mu)E \tag{4.2}$$

$$\frac{dI_1}{dt} = \alpha_1 E + \sigma_1 I_2 - (\delta_1 + \rho_1 + \mu)I_1 \tag{4.3}$$

$$\frac{dI_2}{dt} = \alpha_2 E - (\delta_2 + \sigma_1 + \sigma_2 + \mu)I_2 \tag{4.4}$$

$$\frac{dH}{dt} = \rho_1 I_1 + \sigma_2 I_2 - (\mu + \rho_2)H \tag{4.5}$$

The transfer diagram in Figure 4.1 is adapted from Klotz et al. [21]. We ignored immigration of few infected individuals into the exposed group, but took reactivation process into account by having a reactivation parameter, σ_1, which reflects the rate at which latently infected individuals get active TB. Under this scenario, we allow for screening so that latently infected individuals are identified and treated.

4.1.1 Analysis of the TB model with impact of screening and treatment of latently infected TB individuals

In this subsection, we carry out the mathematical analysis, starting by proving that our non-linear system (4.1) — (4.5) is positively invariant. We then discuss the local stability of the disease-free equilibrium for the model. We end the subsection with results from numerical simulation and sensitivity analysis.

Positivity analysis

It is important to show that our model is epidemiologically meaningful by demonstrating that all their state variables are positively invariant for all time.

Lemma 2. *Consider a system of differential equations (4.1) — (4.5).*

If $S(0) \geq 0$, $E(0) \geq 0$, $I_1(0) \geq 0$, $I_2(0) \geq 0$ *and* $H(0) \geq 0$, *then* $S(t) \geq 0$, $E(t) \geq 0$, $I_1(t) \geq 0$, $I_2(t) \geq 0$ *and* $H(t) \geq 0 \ \forall\, t > 0$.

Proof. The solution of equation (4.1) can be written as:

$$S(t) = (S(0) - \frac{\Lambda}{\mu})e^{-\mu t} + \frac{\Lambda}{\mu} - \int_0^t (\beta_1 I_1(\tau) + \beta_2 I_2(\tau))S(\tau)e^{-\mu(t-\tau)}d\tau. \tag{4.6}$$

As $t \to \infty$, this gives

$$S(\infty) = S_\infty = \frac{\Lambda}{\mu} > 0.$$

The remaining equations (4.2) — (4.5) can be written as

$$\begin{bmatrix} \dot{E} \\ \dot{I}_1 \\ \dot{I}_2 \\ \dot{H} \end{bmatrix} = \begin{bmatrix} -(\alpha_1 + \alpha_2 + \mu) & \beta_1 S & \beta_2 S & \rho_2 \\ \alpha_1 & -(\delta_1 + \rho_1 + \mu) & \sigma_1 & 0 \\ \alpha_2 & 0 & -(\delta_2 + \sigma_1 + \sigma_2 + \mu) & 0 \\ 0 & \rho_1 & \sigma_2 & -(\mu + \rho_2) \end{bmatrix} \begin{bmatrix} E \\ I_1 \\ I_2 \\ H \end{bmatrix} \tag{4.7}$$

The matrix

$$M = \begin{bmatrix} -(\alpha_1 + \alpha_2 + \mu) & \beta_1 S & \beta_2 S & \rho_2 \\ \alpha_1 & -(\delta_1 + \rho_1 + \mu) & \sigma_1 & 0 \\ \alpha_2 & 0 & -(\delta_2 + \sigma_1 + \sigma_2 + \mu) & 0 \\ 0 & \rho_1 & \sigma_2 & -(\mu + \rho_2) \end{bmatrix} \tag{4.8}$$

has nonnegative entries off the main diagonal and negative entries on the main diagonal. Hence matrix M is a Metzler matrix. By virtue of that, we conclude that if $E(0) \geq 0$,

$I_1(0) \geq 0, I_2(0) \geq 0$ and $H(0) \geq 0,$ then $E(t) \geq 0, I_1(t) \geq 0, I_2(t) \geq 0$ and $H(t) \geq 0$ $\forall\, t > 0.$ □

Local stability of the disease-free equilibrium

We start this subsection by finding the local stability of the disease-free equilibrium for TB Model with treatment of latently infected TB individuals.

We consider the dynamical system of nonlinear equations (4.1) — (4.5). The disease-free state is found by letting I_1=I_2= 0. In other words, the disease-free equilibrium is determined when the entire population is susceptible [29]. Taking I_1=I_2= 0 in equation (4.1) gives

$$S^* = \frac{\Lambda}{\mu},$$

where S^* is the first component of the disease-free state, when the disease has not yet invaded the population.

Therefore, the disease-free equilibrium state is given by

$$\Gamma_1 = (S^*, E^*, I_1^*, I_2^*, H^*) = (\frac{\Lambda}{\mu}, 0, 0, 0, 0). \tag{4.9}$$

The disease-free equilibrium's stability is discussed in terms of the basic reproduction number, which is given by the spectral radius of the next generation matrix [38].

For this model, the matrix $\mathcal{F}$ representing rates of appearance of new infections in the infected states $E,\ I_1$ and I_2 is given by

$$\mathcal{F} = \begin{bmatrix} (\beta_1 I_1 + \beta_2 I_2)S \\ 0 \\ 0 \end{bmatrix}. \tag{4.10}$$

The matrix $\mathcal{V}$, representing the net outflow of infections from compartments $E,\ I_1$ and I_2, is given by

$$\mathcal{V} = \begin{bmatrix} (\alpha_1 + \alpha_2 + \mu)E - \rho_2 H \\ (\delta_1 + \rho_1 + \mu)I_1 - \alpha_1 E - \sigma_1 I_2 \\ (\delta_2 + \sigma_1 + \sigma_2 + \mu)I_2 - \alpha_2 E \end{bmatrix}. \tag{4.11}$$

The Jacobian of the matrices $\mathcal{F}$ and $\mathcal{V}$ about the disease-free equilibrium, is given by

$$F = \begin{bmatrix} 0 & \frac{\Lambda\beta_1}{\mu} & \frac{\Lambda\beta_2}{\mu} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}, \tag{4.12}$$

and

$$V = \begin{bmatrix} \alpha_1 + \alpha_2 + \mu & 0 & 0 \\ -\alpha_1 & \delta_1 + \rho_1 + \mu & -\sigma_1 \\ -\alpha_2 & 0 & \delta_2 + \sigma_1 + \sigma_2 + \mu \end{bmatrix}. \tag{4.13}$$

The inverse of V is given by:

$$V^{-1} = \begin{bmatrix} \frac{1}{\mu + \alpha_1 + \alpha_2} & 0 & 0 \\ \mathcal{A} & \frac{1}{\mu + \delta_1 + \rho_1} & \mathcal{B} \\ \frac{\alpha_2}{(\mu + \alpha_1 + \alpha_2)(\mu + \delta_2 + \sigma_1 + \sigma_2)} & 0 & \frac{1}{\mu + \delta_2 + \sigma_1 + \sigma_2} \end{bmatrix} \tag{4.14}$$

where,

$$\mathcal{A} = \frac{\alpha_2\sigma_1 + \alpha_1(\mu + \delta_2 + \sigma_1 + \sigma_2)}{(\mu + \delta_1 + \rho_1)(\mu + \delta_2 + \sigma_1 + \sigma_2)(\mu + \alpha_1 + \alpha_2)},$$

and

$$\mathcal{B} = \frac{\sigma_1}{(\mu + \delta_1 + \rho_1)(\mu + \delta_2 + \sigma_1 + \sigma_2)}.$$

The next generation matrix for this model is

$$FV^{-1} = \begin{bmatrix} \mathcal{C} & \frac{\Lambda\beta_1}{\mu(\mu + \delta_1 + \rho_1)} & \frac{\Lambda\beta_2}{\mu(\mu + \delta_2 + \sigma_1 + \sigma_2)} + \frac{\Lambda\beta_1\sigma_1}{\mu(\mu + \delta_1 + \rho_1)(\mu + \delta_2 + \sigma_1 + \sigma_2)} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \quad (4.15)$$

where $\mathcal{C}$ is given by

$$\mathcal{C} = \frac{\Lambda\beta_2\alpha_2}{\mu(\mu + \alpha_1 + \alpha_2)(\mu + \delta_2 + \sigma_1 + \sigma_2)} + \frac{\Lambda\beta_1(\alpha_2\sigma_1 + \alpha_1(\mu + \delta_2 + \sigma_1 + \sigma_2))}{\mu(\mu + \delta_1 + \rho_1)(\mu + \delta_2 + \sigma_1 + \sigma_2)(\mu + \alpha_1 + \alpha_2)}.$$

The eigenvalues of FV^{-1} are

$$\lambda_1 = \mathcal{C} = \frac{\Lambda\beta_2\alpha_2}{\mu(\mu + \alpha_1 + \alpha_2)(\mu + \delta_2 + \sigma_1 + \sigma_2)} + \frac{\Lambda\beta_1(\alpha_2\sigma_1 + \alpha_1(\mu + \delta_2 + \sigma_1 + \sigma_2))}{\mu(\mu + \delta_1 + \rho_1)(\mu + \delta_2 + \sigma_1 + \sigma_2)(\mu + \alpha_1 + \alpha_2)},$$

$$\lambda_2 = 0,$$

and

$$\lambda_3 = 0.$$

The basic reproduction number is thus obtained as the dominant eigenvalue of FV^{-1}, which is:

$$R_0 = \frac{\Lambda\big\{\beta_2\alpha_2(\mu+\delta_1+\rho_1)+\beta_1(\alpha_2\sigma_1+\alpha_1(\mu+\delta_2+\sigma_1+\sigma_2))\big\}}{\mu\big\{(\mu+\delta_1+\rho_1)(\mu+\delta_2+\sigma_1+\sigma_2)(\mu+\alpha_1+\alpha_2)\big\}}. \tag{4.16}$$

Further simplification gives R_0 as a linear combination of R_{0l} and R_{0a} :

$$R_0 = (\frac{\alpha_2}{\mu+\alpha_1+\alpha_2})R_{0l} + (\frac{\alpha_2}{\mu+\alpha_1+\alpha_2})(\frac{\sigma_1}{\mu+\delta_2+\sigma_1+\sigma_2})R_{0a} + (\frac{\alpha_1}{\mu+\alpha_1+\alpha_2})R_{0a} \tag{4.17}$$

where

$$R_{0a} = \frac{\Lambda\beta_1}{\mu(\mu+\delta_1+\rho_1)},$$

is the reproductive number for the active TB group

and

$$R_{0l} = \frac{\Lambda\beta_2}{\mu(\mu+\delta_2+\sigma_1+\sigma_2)},$$

is the reproductive number for the asymptomatic (latently infected) TB infectives.

The coefficients of R_{0l} and R_{0a} indicate the progression status, for example

$$(\frac{\alpha_2}{\mu+\alpha_1+\alpha_2})R_{0l}$$

is the reproductive number for those individuals who developed the latent TB status and remained that way until they were screened. Furthermore

$$(\frac{\alpha_1}{\mu+\alpha_1+\alpha_2})R_{0a}$$

is the reproductive number for those individuals who developed active TB status, remained that way until treated or death. The term

$$(\frac{\alpha_2}{\mu+\alpha_1+\alpha_2})(\frac{\sigma_1}{\mu+\delta_2+\sigma_1+\sigma_2})R_{0a}$$

is the reproductive number for the individuals who progressed through latency TB class before becoming actively infected with TB.

We make an observation that as the treatment rate $\sigma_2 \to \infty$, the first term and second term in R_0 (equation (4.17)) will vanish when

$$\frac{\Lambda\beta_2}{\mu(\mu+\delta_2+\sigma_1+\sigma_2)} \to 0,$$

and when

$$\frac{\sigma_1}{\mu+\delta_2+\sigma_1+\sigma_2} \to 0,$$

leaving only the last term. This shows that screening has a significant impact on the disease dynamics [19]. With proper screening, latently infected TB patients can be detected earlier and be given treatment, thereby reducing the disease spread. This is demonstrated numerically later. The following result can be stated for TB Model 4.1:

Theorem 1. *When $R_0 < 1$, the disease-free equilibrium (4.9) is locally asymptotically stable and unstable when $R_0 > 1$.*

Numerical simulations

Numerical simulations for TB model with impact of screening and treatment of latently infected TB individuals, are done using parameter values given in Table 4.1. Simulation is important for us to confirm or reject the analytical results obtained for the model. For these simulations, we have used MATLAB solver *ode45*.

Parameter values for TB model with impact of screening and treatment of latently infected TB individuals

Table 4.1: Values of parameters used in the TB model with impact of screening and treatment of latently infected TB individuals

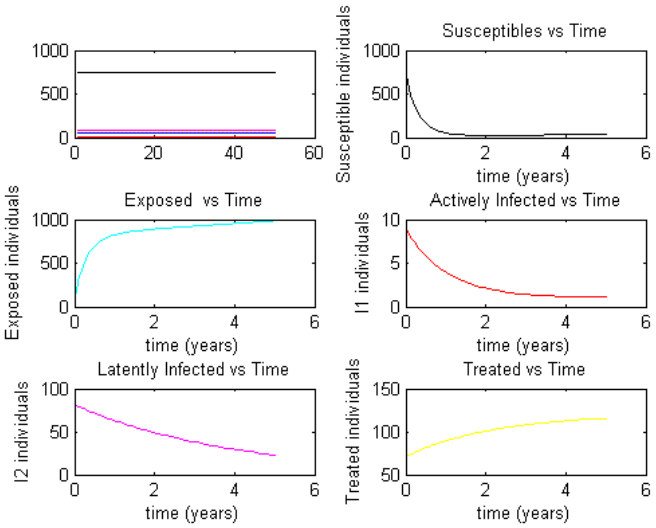
Symbol	Meaning/Description	Value	Source
μ	constant natural death rate	0.01429	[11]
β_1	force of infection due to active TB	$0.00005/yr$	[3]
β_2	force of infection due to latently infected TB	0.042	[17]
α_1	rate at which exposed people get active TB	0.001	(Assumed)
α_2	rate at which exposed people get asymptomatic TB	0.0001	(Assumed)
ρ_1	rate at which active TB people are treated	$0.87/person/yr$	[21]
ρ_2	rate at which treated people become exposed	$0.02/yr$	[9]
δ_1	disease-related death for active TB	$0.0575/yr$	[7]
δ_2	disease-related death for asymptomatic infectives	$0.02/yr$	[32]
σ_1	rate at which asymptomatic TB infectives develop active TB	$0.0005/yr$	[11]
σ_2	rate at which asymptomatic TB people are treated after being screened	$0.22/person/yr$	[21]

Simulation for TB model with impact of screening and treatment of latently infected TB individuals

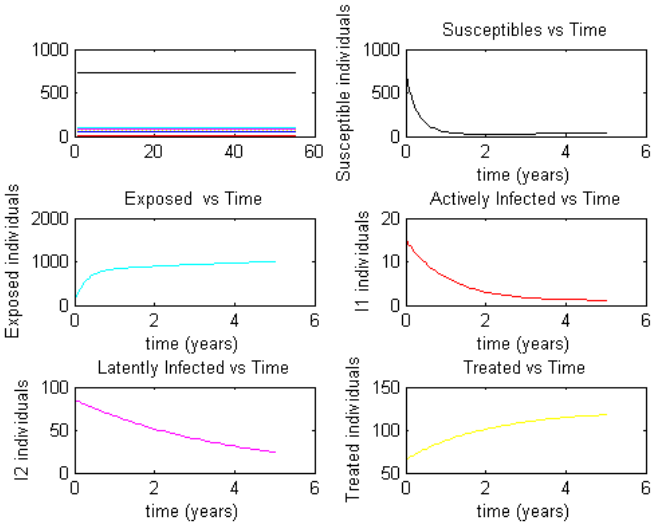
We consider parameter values in Table 4.1 and a 1000 initial population to produce various graphs given in Figure 4.2 and Figure 4.3. Graphical simulation results with varying population sizes for this model are shown in Figure 4.2.

Figure 4.2a is obtained by using the following: $\Lambda = 50$, $S = 749$, $E = 90$, $I_1 = 9$, $I_2 = 81$, and $H = 71$. Reproductive number obtained for this simulation is: $R_0 = 3.7598 > 1$. Figure 4.2b is obtained by using the following: $\Lambda = 55$, $S = 735$, $E = 100$, $I_1 = 15$, $I_2 = 85$, and $H = 65$. Reproductive number obtained for this simulation is: $R_0 = 4.1358 > 1$. Since $R_0 > 1$, this implies that the disease-free equilibrium for this model is an unstable steady state. It is clear that for this TB Model, the disease can only be controlled, but cannot be fully eliminated from the population.

The graphs show that an increase in the number of active TB infective and latently TB infective individuals in the population results in the significant reduction of susceptibles and an increase in the number of exposed individuals. This is so, because recovery from TB does not give long-life immunity, an individual remains exposed to the disease. This results in the large number of treated individuals in the exposed class.



(a)



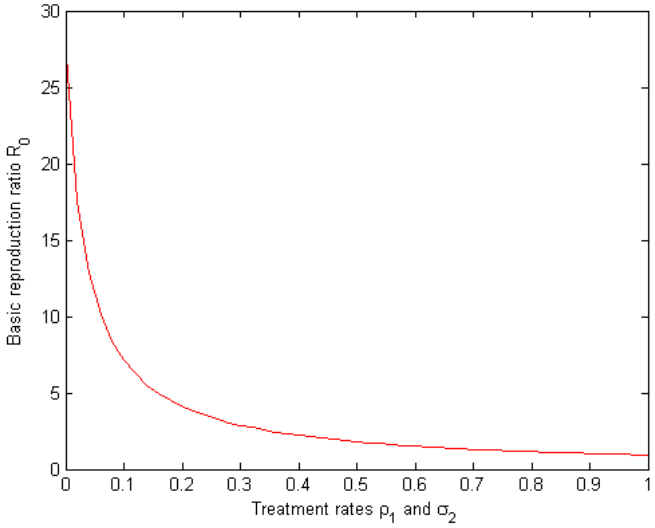
(b)

Figure 4.2: Graphs showing varying population sizes for TB model with impact of screening and treatment of latently infected TB individuals

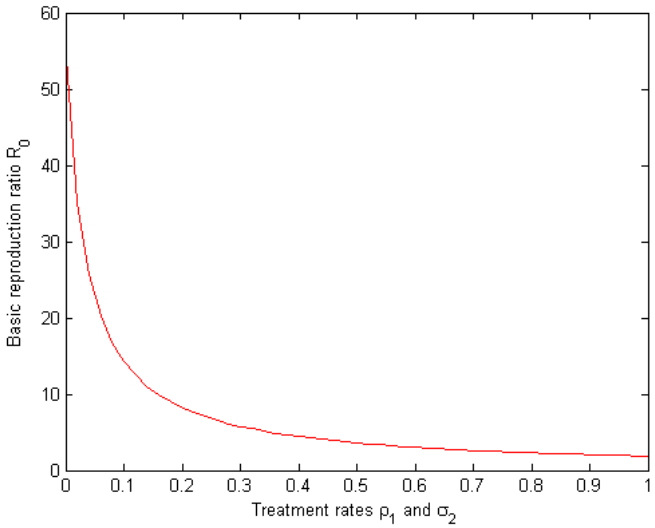
We analyze the effect of both treatment rates ρ_1 and σ_2 on the basic reproductive number, R_0, for TB Model with impact of screening and treatment of latently infected TB individuals. Figure 4.3 shows the effect on R_0.

Figure 4.3a is obtained using parameter values as in Table 4.1 with the replenishing constant $\Lambda = 50$. Figure 4.3b is another graph showing the effect of ρ_1 and σ_2 on the basic reproductive number, when $\Lambda = 100$.

One can clearly see that R_0 decreases when both treatment rates increase.



(a)



(b)

Figure 4.3: Graphs showing the effect of ρ_1 and σ_2 on the basic reproduction number for the model with impact of screening and treatment of latently infected TB individuals

Sensitivity of the reproductive number to changes in parameter values

In this subsection, we use the sensitivity analysis design in which we only vary the value of one parameter, while the values of the other parameters are fixed, in order to see the response of the reproductive number, to changes in certain parameters that constitute the reproductive number, given by equation (4.16). We give the different values of the reproductive numbers in Table 4.2 below, by varying the values of the replenishing constant, Λ, and the natural death rate, μ, which we take to range from $\frac{1}{65\ years}$ to $\frac{1}{70\ years}$. Total population used is $N = 1000$ and the other parameters are kept as in Table 4.1.

Table 4.2: Values of the reproductive number in response to changes in the replenishing constant, Λ and the natural death rate, μ.

(a) Values of R_0 in response to changes in the replenishing constant, Λ.

Λ	20	25	30	35	40	50	55
R_0	1.5039	1.8799	2.2559	2.6318	3.0078	3.7598	4.1358

(b) Values of R_0 in response to changes in the natural death rate, μ, using $\Lambda = 35$.

μ	0.01538 ($\frac{1}{65}$)	0.01515 ($\frac{1}{66}$)	0.01493 ($\frac{1}{67}$)	0.01471 ($\frac{1}{68}$)	0.01449 ($\frac{1}{69}$)	0.01429 ($\frac{1}{70}$)
R_0	2.2739	2.3432	2.4124	2.4847	2.5602	2.6318

We can clearly see from Table 4.2 that the values of the reproductive number for this TB model are bigger than unity. This shows that the disease-free equilibrium for this model, given by equation (4.9) is unstable. We notice here that, increasing the values of Λ and μ result in the increase of the reproductive number, which remains bigger than one.

In this case, the disease will spread in case of an epidemic.

Since the reproductive number of the first model remains bigger than unity, the previous model does not offer much hope regarding the effective treatment of TB that is needed to break the cycle of transmission. In the next section, we formulate a second TB model with treatment of drug sensitive and drug-resistant TB, to see if we can get a reproductive number less than one, which then means that the disease will be contained if an epidemic occurs. Effective treatment is even more important because of this emergence of drug-resistant TB. Once the bacilli become resistant to one or more anti-TB drugs, the infected person can infect others with the same drug-resistant strain, which is more difficult, more expensive to treat, and more likely to be fatal. Hence prevention and effective treatment is needed to stop the spread of drug-resistant TB, a valid reason for formulating and studying a model with treatment of drug-resistant TB.

4.2 Formulation of the TB model with treatment of drug-resistant TB individuals

The second model considers a scenario in which individuals are infected by two TB strains: the wild type strain and the drug resistant strain. In this case, the population is divided into seven classes: a class of susceptible individuals, S, a class of individuals exposed to active TB, E_1, a class of individuals actively infected with TB, I_1, a class of individuals with resistant TB, I_2, a class of individuals successfully treated for sensitive TB, T_1, a class of individuals successfully treated for resistant TB, T_2, and a class of individuals who are exposed to resistant TB, E_2. The total population in this model is thus given by $N(t) = S(t) + E_1(t) + E_2(t) + I_1(t) + I_2(t) + T_1(t) + T_2(t)$.

Suppose the susceptible population is replenished at a rate Λ and is subjected to infections at rates $\beta_1 I_1$ and $\beta_2 I_2$, representing the force of infection arising from infections by individuals with drug sensitive TB and individuals with drug resistant TB, respectively. Suppose further that individuals exposed to active TB progress to the active TB class at a rate α_1 and those exposed to resistant TB progress to the acquired resistant TB class at a rate α_2. Individuals in the active TB class who do not adhere to treatment develop resistant TB and move to the resistant TB class at rate γ_2.

All seven classes are subjected to a constant natural death rate μ. However, active TB infectives, I_1, and resistant TB infectives, I_2, are additionally subjected to disease related death at rates δ_1 for those actively infected with TB and δ_2 for those with resistant TB. Actively

infected individuals are successfully treated at ρ_1 constant rate and progress to the exposed class, E_1, at a constant rate γ_1. In the same manner, individuals infected with resistant TB receive treatment at a constant rate ρ_2 and eventually progress to the exposed class, E_2, at a constant rate σ. The figure below shows the flow of TB disease in a population as narrated above.

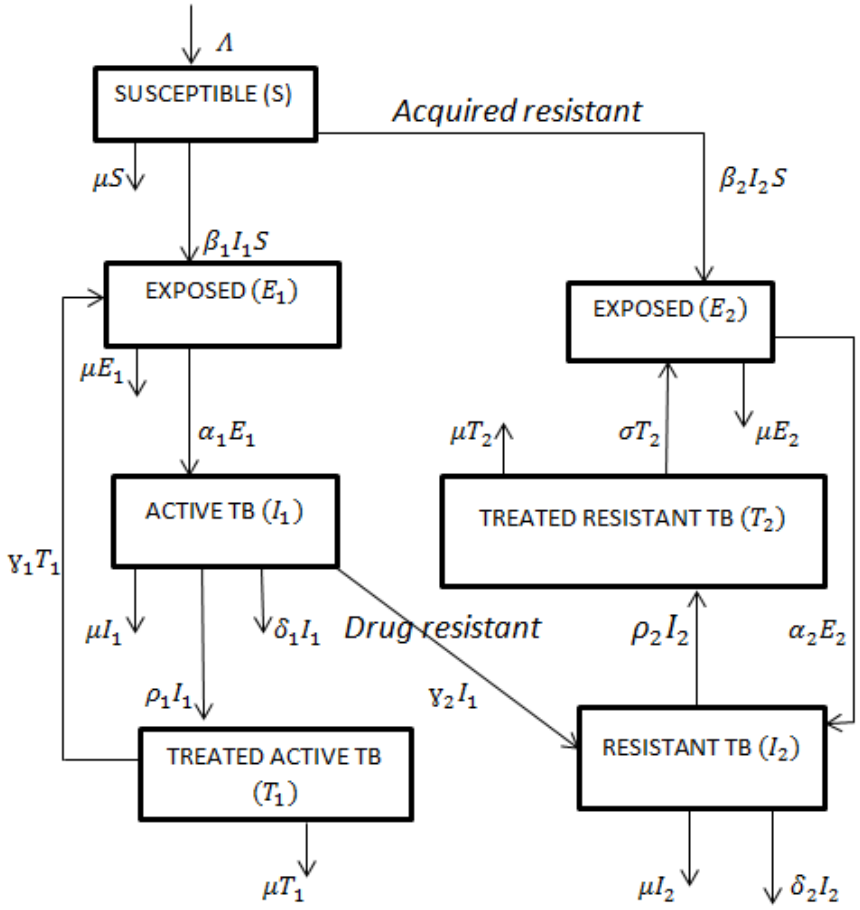


Figure 4.4: Transfer diagram for TB Model that entails treatment of drug-resistant TB individuals ([32, 46])

The transfer diagram in Figure 4.4 is based on figure 3 in Zwerling et al. [46] and figure 1 in Shrestha et al. [32].

The information in the transfer diagram in Figure 4.4 then gives rise to the following system of nonlinear differential equations.

$$\frac{dS}{dt} = \Lambda - \mu S - (\beta_1 I_1 + \beta_2 I_2)S \tag{4.18}$$

$$\frac{dE_1}{dt} = \beta_1 I_1 S + \gamma_1 T_1 - (\alpha_1 + \mu) E_1 \tag{4.19}$$

$$\frac{dI_1}{dt} = \alpha_1 E_1 - (\delta_1 + \rho_1 + \mu) I_1 \tag{4.20}$$

$$\frac{dT_1}{dt} = \rho_1 I_1 - (\gamma_1 + \mu) T_1 \tag{4.21}$$

$$\frac{dI_2}{dt} = \alpha_2 E_2 + \gamma_2 I_1 - (\mu + \rho_2 + \delta_2) I_2 \tag{4.22}$$

$$\frac{dT_2}{dt} = \rho_2 I_2 - (\sigma + \mu) T_2 \tag{4.23}$$

$$\frac{dE_2}{dt} = \beta_2 I_2 S + \sigma T_2 - (\alpha_2 + \mu) E_2 \tag{4.24}$$

4.2.1 Analysis of the TB model with treatment of drug-resistant TB individuals

Like for the TB model with impact of screening and treatment of latently infected TB individuals , we carry out the mathematical analysis for the TB model with treatment of drug-resistant TB individuals . We first start by proving that our nonlinear system of equations (4.18) — (4.24) is positively invariant. We then discuss the local stability of the disease-free equilibrium for the model. We end the subsection with results from numerical simulations and from one-way sensitivity analysis.

Positivity analysis

We show that our model is epidemiologically meaningful by demonstrating that all their state variables are positively invariant for all time i.e $x_i(t) \geq 0$.

Let $S(t) = x_1,\ E_1(t) = x_2,\ I_1(t) = x_3,\ T_1(t) = x_4,\ I_2(t) = x_5,\ T_1(t) = x_6$ and $E_2(t) = x_7$,

so that $x(t) = (x_1(t),\ x_2(t),\ x_3(t),\ x_4(t),\ x_5(t),\ x_6(t),\ x_7(t))$.

Consider the region $\Omega_1 = \{(x_1(t), x_2(t), x_3(t), x_4(t), x_5(t), x_6(t), x_7(t)) \in \mathbb{R}^7_+ \colon N \leq \frac{\Lambda}{\mu}\}$, where N stands for the total population.

It can be shown that all solutions of the system beginning in Ω_1 remain in Ω_1, for all $t \geq 0$. This implies that the regions Ω_1 is therefore positively invariant and attracting, i.e all solutions in $\mathbb{R}^7_+$ eventually enter Ω_1.

We now use the following lemma in Friedman and Lungu [15] to prove the positivity of the

solutions to the differential equations for the dynamic system for this TB model.

Lemma 3. *Consider a system of differential inequalities*

$$\frac{dx_i}{dt} \geq A_i x_i + \sum_{j=1}^{n} B_{ij} x_j + \epsilon \ \ (i = 1, ..., n), \tag{4.25}$$

where

$$B_{ij} \geq 0, \ \epsilon \geq 0.$$

If $x_i(0) \geq \epsilon$ *for* $i = 1, ..., n,$ *then* $x_i(t) \geq 0 \quad \forall\, t > 0$ *and* $1 \leq i \leq n.$

Proof. We may assume that $\epsilon > 0.$ The case $\epsilon = 0$ follows from approximating the system with a sequence $\epsilon = \epsilon_k, \ \epsilon \downarrow 0.$

Suppose $x_i(0) \geq \epsilon > 0,$ for $1 \leq i \leq n,$ does not hold ($n = 5$ for Model 1 and $n = 7$ for Model 2).

Then there exists a smallest number $t_0 > 0$ such that

$$x_i(t) > 0 \ \text{ for } \ 1 \leq i \leq n, \ 0 \leq t < t_0,$$

$$x_i(t_0) = 0 \ \text{ for at least one } \ i, \ \text{i.e } \ i = i0.$$

Then x_{i0} is a decreasing function at $t = t_0$, which means that

$$\frac{dx_{i0}}{dt}(t_0) \leq 0.$$

However, the differential inequality in equation (4.25) for $x_{i0}(t)$ gives

$$\frac{dx_{i0}}{dt}(t_0) \geq \sum_{j=1}^{n} B_{ij} x_j(t_0) + \epsilon \geq \epsilon > 0,$$

which is a contradiction.

Thus from lemma 3, we have that $x_i(0) \geq 0$, which implies that $x_i(t) \geq 0.$ □

Therefore in the region Ω_1, our model is well-posed epidemiologically and mathematically. It is therefore sufficient to study the dynamics of Model 4.4 in Ω_1.

Local stability of the disease-free equilibrium

To find the disease-free state, we let I_1=I_2= 0.

From equation (4.18), we get

$$S^* = \frac{\Lambda}{\mu}.$$

Therefore, the disease-free equilibrium state for this model is given by

$$\Gamma_2 = (S^*, E_1^*, I_1^*, T_1^*, I_2^*, T_2^*, E_2^*) = (\frac{\Lambda}{\mu}, 0, 0, 0, 0, 0, 0). \tag{4.26}$$

For this TB model, the matrix $\mathcal{F}$ representing the rates of appearance of new infections in compartments E_1 , I_1 , E_2 and I_2 is given by

$$\mathcal{F} = \begin{bmatrix} \beta_1 I_1 S \\ 0 \\ \beta_2 I_2 S \\ 0 \end{bmatrix}. \tag{4.27}$$

and $\mathcal{V}$, representing the other transitions is given by

$$\mathcal{V} = \begin{bmatrix} (\alpha_1 + \mu)E_1 - \gamma_1 T_1 \\ (\delta_1 + \rho_1 + \mu)I_1 - \alpha_1 E_1 \\ (\alpha_2 + \mu)E_2 - \sigma T_2 \\ (\mu + \rho_2 + \delta_2)I_2 - \gamma_2 I_1 - \alpha_2 E_2 \end{bmatrix}. \tag{4.28}$$

The Jacobians of $\mathcal{F}$ and $\mathcal{V}$ about the disease-free equilibrium are given by

$$F = \begin{bmatrix} 0 & \frac{\Lambda\beta_1}{\mu} & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{\Lambda\beta_2}{\mu} \\ 0 & 0 & 0 & 0 \end{bmatrix}, \tag{4.29}$$

and

$$V = \begin{bmatrix} \alpha_1 + \mu & 0 & 0 & 0 \\ -\alpha_1 & \delta_1 + \rho_1 + \mu & 0 & 0 \\ 0 & 0 & \alpha_2 + \mu & 0 \\ 0 & -\gamma_2 & -\alpha_2 & \delta_2 + \rho_2 + \mu \end{bmatrix}. \tag{4.30}$$

The inverse of V is given by:

$$V^{-1} = \begin{bmatrix} \frac{1}{\mu + \alpha_1} & 0 & 0 & 0 \\ \mathcal{G} & \frac{1}{\mu + \delta_1 + \rho_1} & 0 & 0 \\ 0 & 0 & \frac{1}{\mu + \alpha_2} & 0 \\ \mathcal{I} & \mathcal{J} & \frac{\alpha_2}{(\mu + \alpha_2)(\mu + \delta_2 + \rho_2)} & \frac{1}{\mu + \delta_2 + \rho_2} \end{bmatrix} \tag{4.31}$$

where $\mathcal{G}, \mathcal{I}$ and $\mathcal{J}$ are given by

$$\mathcal{G} = -\frac{-\mu\alpha_1 - \alpha_1\alpha_2}{(\mu+\alpha_1)(\mu+\alpha_2)(\mu+\delta_1+\rho_1)},$$

$$\mathcal{I} = \frac{\alpha_1\gamma_2}{(\mu+\alpha_1)(\mu+\delta_1+\rho_1)(\mu+\delta_2+\rho_2)},$$

and

$$\mathcal{J} = \frac{\mu^2\gamma_2 + \mu\alpha_1\gamma_2 + \mu\alpha_2\gamma_2 + \alpha_1\alpha_2\gamma_2}{(\mu+\alpha_1)(\mu+\alpha_2)(\mu+\delta_1+\rho_1)(\mu+\delta_2+\rho_2)}.$$

The next generation matrix for this model is

$$FV^{-1} = \begin{bmatrix} \mathcal{K} & \frac{\Lambda\beta_1}{\mu(\mu+\delta_1+\rho_1)} & 0 & 0 \\ 0 & 0 & 0 & 0 \\ \mathcal{L} & \mathcal{M} & \frac{\Lambda\beta_2\alpha_2}{\mu(\mu+\alpha_2)(\mu+\delta_2+\rho_2)} & \frac{\Lambda\beta_2}{\mu(\mu+\delta_2+\rho_2)} \\ 0 & 0 & 0 & 0 \\ \\ \end{bmatrix}, \quad (4.32)$$

where $\mathcal{K}$, $\mathcal{L}$ and $\mathcal{M}$ are given by

$$\mathcal{K} = -\frac{\Lambda\beta_1(-\mu\alpha_1 - \alpha_1\alpha_2)}{\mu(\mu+\alpha_1)(\mu+\alpha_2)(\mu+\delta_1+\rho_1)},$$

$$\mathcal{L} = \frac{\Lambda\alpha_1\beta_2\gamma_2}{\mu(\mu+\alpha_1)(\mu+\delta_1+\rho_1)(\mu+\delta_2+\rho_2)},$$

and

$$\mathcal{M} = \frac{\Lambda\alpha_1(\mu^2\gamma_2 + \mu\alpha_1\gamma_2 + \mu\alpha_2\gamma_2 + \alpha_1\alpha_2\gamma_2)}{\mu(\mu+\alpha_1)(\mu+\alpha_2)(\mu+\delta_1+\rho_1)(\mu+\delta_2+\rho_2)}.$$

The eigenvalues of FV^{-1} are

$$\lambda_1 = \frac{\Lambda\beta_1\alpha_1}{\mu(\mu+\alpha_1)(\mu+\delta_1+\rho_1)},$$

$$\lambda_2 = \frac{\Lambda\beta_2\alpha_2}{\mu(\mu+\alpha_2)(\mu+\delta_2+\rho_2)},$$

$$\lambda_3 = 0,$$

and

$$\lambda_4 = 0.$$

The basic reproduction number is defined as:

$$R_0 = max\{R_{0s}, R_{0r}\} \tag{4.33}$$

where

$$R_{0s} = \frac{\Lambda\beta_1\alpha_1}{\mu(\mu+\alpha_1)(\mu+\delta_1+\rho_1)} = (\frac{\Lambda\beta_1}{\mu})(\frac{\alpha_1}{\mu+\alpha_1})(\frac{1}{\mu+\delta_1+\rho_1}) \tag{4.34}$$

and

$$R_{0r} = \frac{\Lambda\beta_2\alpha_2}{\mu(\mu+\alpha_2)(\mu+\delta_2+\rho_2)} = (\frac{\Lambda\beta_2}{\mu})(\frac{\alpha_2}{\mu+\alpha_2})(\frac{1}{\mu+\delta_2+\rho_2}). \tag{4.35}$$

R_{0s} is the reproductive number representing the average number of secondary infections generated by an infective with drug sensitive strain and R_{0r} is the average number of secondary infections generated by an infective with the drug resistant TB strain.

We make an observation here that as the rate of treatment of drug sensitive TB increases, that is, $\rho_1 \to \infty$, $R_{0s} \to 0$. In this case, treatment could clear drug sensitive TB. Similarly, as the rate of treatment of drug resistant TB increases, that is, $\rho_2 \to \infty$, $R_{0r} \to 0$. In this case, the drug resistant strain could be eradicated, however, no drug has such chemodynamic properties.

We can now state the following results:

Theorem 2. *If* R_0= *max* $\{R_{0s}, R_{0r}\} < 1$, *the disease fails to establish itself and dies out. If* R_0= *max* $\{R_{0s}, R_{0r}\} > 1$, *then either of the following scenarios hold:*

(i) If $R_{0s} > 1$ *and* $R_{0r} < 1$, *drug sensitive TB is endemic and drug resistant TB clears out. (ii) If* $R_{0s} < 1$ *and* $R_{0r} > 1$, *drug sensitive TB clears, while resistant TB is endemic. (iii) If both* R_{0s} *and* R_{0r} *are greater than* 1, *then the two strains become endemic.*

Numerical simulations

Numerical simulations for the TB model with treatment of drug-resistant TB individuals are done using parameter values given in Table 4.3.

Parameter values for the TB model with treatment of drug-resistant TB individuals

Table 4.3: Values of parameters used in the TB model with treatment of drug-resistant TB individuals

Symbol	Meaning/Description	Value	Source
μ	constant natural death rate	0.01429	[11]
β_1	force of infection due to active TB	$0.00005/yr$	[3]
β_2	force of infection due to transmitted resistant TB	0.014	[41]
α_1	rate at which exposed people get active TB	$0.001/yr$	(Assumed)
α_2	rate at which exposed people get resistant TB	0.00001	(Assumed)
ρ_1	rate at which active TB people are treated	$0.87/person/yr$	[21]
ρ_2	rate at which resistant TB people are treated	$0.53/yr$	[42]
δ_1	disease-related death for active TB	$0.0575/yr$	[7]
δ_2	disease-related death for resistant TB infectives	$0.55/yr$	[10]
γ_1	rate at which treated active TB people become exposed	$0.054/yr$	
γ_2	rate at which active TB people acquire resistant TB	0.075	[20]
σ	rate at which resistant TB persons are exposed	0.02	[9]

Simulation for TB model with treatment of drug-resistant TB individuals

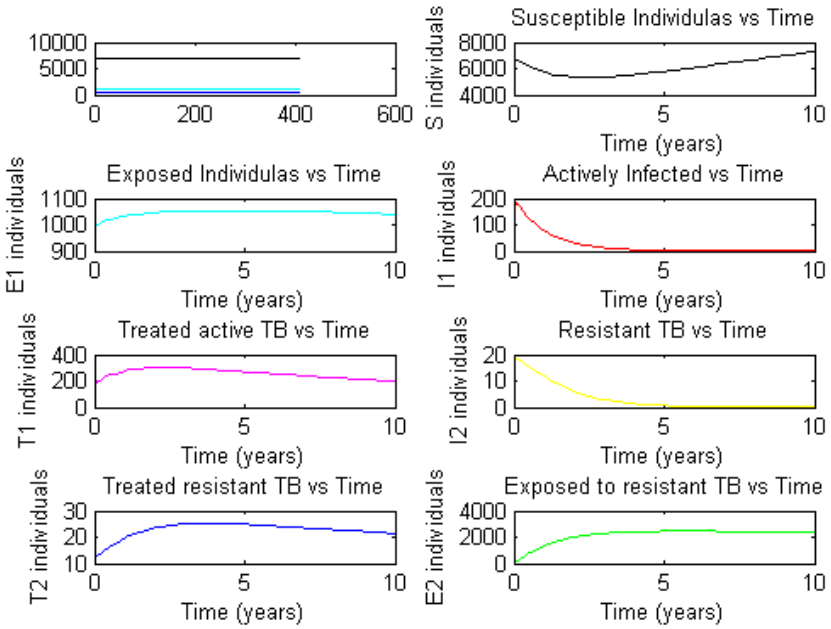
We consider parameter values in Table 4.3 and a total population $N_0 = 8210$ to produce various graphs given in Figure 4.5 and Figure 4.6. Graphical simulation results with varying population sizes for the TB model with treatment of drug-resistant TB individuals are shown in Figure 4.5.

Figure 4.5a is obtained by using the following data: $\Lambda = 410$, $S = 6795$, $E_1 = 995$, $I_1 = 199$, $T_1 = 180$, $I_2 = 19$, $T_2 = 12$ and $E_2 = 10$. Reproductive numbers obtained are: $R_{0s} = 0.0996$ and $R_{0r} = 0.2567$. In this case, R_0= max $\left\{R_{0s}, R_{0r}\right\} = 0.2567 < 1$.

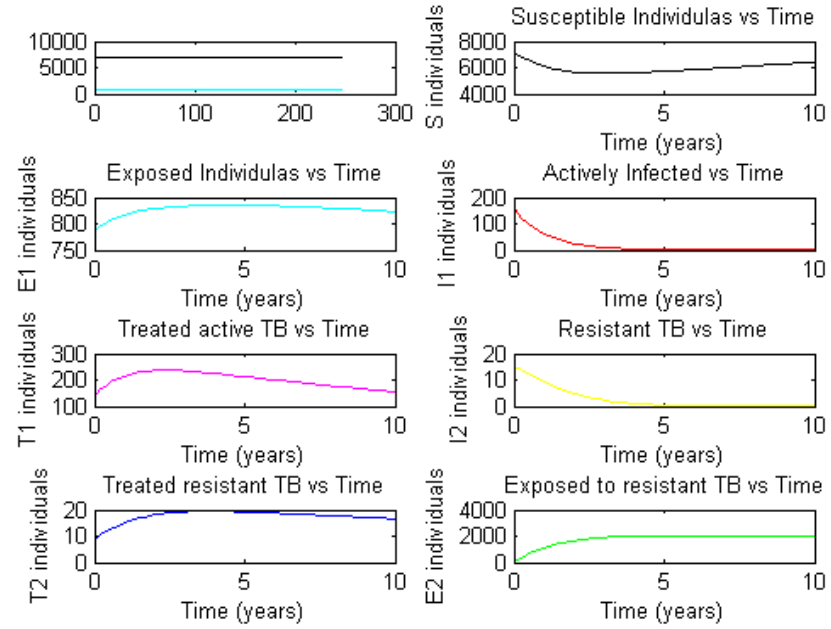
Figure 4.5b is obtained by using the following: $\Lambda = 246$, $S = 7095$, $E_1 = 786$, $I_1 = 157$, $T_1 = 141$, $I_2 = 15$, $T_2 = 9$ and $E_2 = 7$. Reproductive numbers obtained are: $R_{0s} = 0.0598$ and $R_{0r} = 0.1540$.

Hence for Figure 4.5b, R_0= max $\left\{R_{0s}, R_{0r}\right\} = 0.1540 < 1$.

The graphs for this model, however, shows that introducing a significant number of infectives in the population initially causes a decrease in the number of susceptibles, but with time , they increase, possibly due to early detection and successful treatment of drug-sensitive and drug resistant TB individuals. In case of an outbreak, the disease will be contained since $R_0 < 1$.



(a)



(b)

Figure 4.5: Graphs showing varying population sizes for TB model with treatment of drug-resistant TB

Next, we analyze the effect of treatment rate ρ_1 on the basic reproductive number, R_{0s}, as well as the effect of treatment rate ρ_2 on the basic reproductive number, R_{0r}, for this TB Model. These effects are analyzed for when the recruitment rate, Λ, of susceptible is 410 and the other parameters are as in Table 4.3. Figure 4.6 shows the effects of treatment rates ρ_1 and ρ_2 on R_{0s} and R_{0r} respectively.

One can clearly see that R_{0s} decreases when treatment rate ρ_1 is increased. Similarly, R_{0r} decreases when treatment rate ρ_2 is increased.

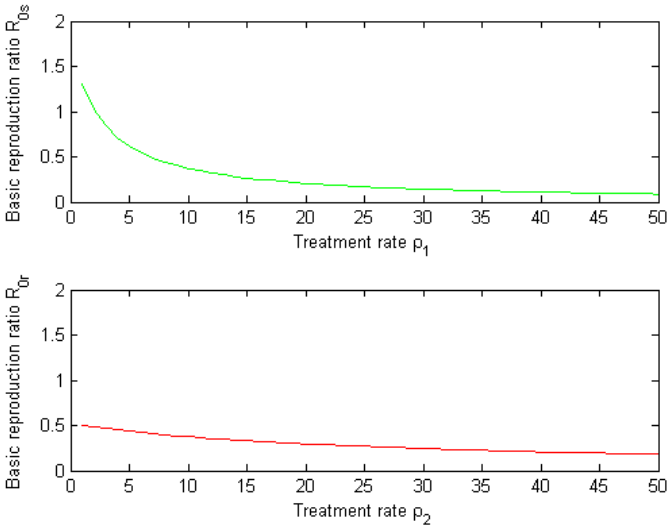


Figure 4.6: Graphs of the basic reproduction numbers R_{0s} and R_{0r} depending on ρ_1 and ρ_2 respectively.

Sensitivity of the reproductive numbers to changes in parameter values

In this subsection, we investigate the sensitivity of the reproductive number, given by equation (4.33). We give the different values of the reproductive numbers, R_{0s} and R_{0r} in

Table 4.4 below, by varying the values of the replenishing constant, Λ, and the natural death rate, μ, which we take to range from $\frac{1}{65\ years}$ to $\frac{1}{70\ years}$. Total population used is $N = 8210$ and the other parameters are kept as in Table 4.3.

Table 4.4: Response of the reproductive numbers to changes in the replenishing constant, Λ and the natural death rate, μ.

(a) Values of R_{0s} and R_{0r} in response to changes in the replenishing constant, Λ.

Λ	165	246	300	410	450	500	600
R_{0s}	0.0401	0.0598	0.0729	0.0996	0.1093	0.1215	0.1458
R_{0r}	0.1033	0.1540	0.1878	0.2567	0.2817	0.3130	0.3756

(b) Values of R_{0s} and R_{0r} in response to changes in the natural death rate, μ, using $\Lambda = 410$.

μ	0.01538	0.01515	0.01493	0.01471	0.01449	0.01429
R_{0s}	0.0863	0.0889	0.0915	0.0941	0.0970	0.0996
R_{0r}	0.2214	0.2282	0.2350	0.2422	0.2496	0.2567

Table 4.4 shows us that the values of the reproductive number for the model with treatment of drug-resistant TB individuals are less than unity. This tells us that the disease-free equilibrium for this model, given by equation 4.26 is stable because $R_0 = \max\left\{R_{0s}, R_{0r}\right\} < 1$. This shows that, in case of an outbreak, the disease will not spread. The value of the reproductive number increases, with an increase in the value of Λ and μ, of course, to a value less than unity.

CHAPTER 5

DISCUSSION AND CONCLUDING REMARKS

In this Chapter, we provide discussions on the two TB models: the model with impact of screening and treatment of latently infected TB individuals and the model with treatment of drug-resistant TB individuals. We end the chapter with the conclusion.

5.1 Discussion of the TB model with impact of screening and treatment of latently infected TB individuals

In this study, TB MODEL 4.1 that looked at the treatment of both active TB persons and latently infected TB infectives is presented and analyzed.

The values of R_0 obtained from simulations are bigger than unity, which implies that the disease-free equilibrium for TB Model 4.1 is unstable. It tells us that even through screening

and treatment interventions, TB disease cannot be fully eliminated from the population, the disease will spread when there is an outbreak. We notice that since R_0 can be expressed as a sum of three terms, the sum of these three terms needs to be less than unity for the disease to fail to establish itself in the population. From simulations, we notice that no matter which parameter one changes, the sum of the three terms fails to be less than 1. This can be explained from the angle that since TB has a latency period, it remains a challenge to the treatment strategists, this then implies that screening should be very accurate to ensure that majority of latently infectives are identified and successfully treated, so that the sum of the three terms can be less than 1. Given this scenario, we point out here that a lot need to be done for a TB-free world dream to be realized in the world by 2050 as per World Health Organization.

However, we also want to put emphasis on the role of the reactivation parameter σ_1 on the basic reproduction number R_0. To ensure that latently infected individuals do not become infectious, there is a need to increase the screening and treatment of individuals in the latently infected compartment. In addition, a greater reduction in the transmission rates β_1 and β_2 also need to be ensured to get $R_0 < 1$ and this can only be achieved through accurate screening and treatment of individuals in the active TB and latently infected compartments. According to Getahun et al. [17], active TB develops in 5% to 15% of individuals with latent infection during their lifetimes. These percentages are said to be higher in persons who are HIV infected, and those from low economic class. Reactivation of latent tuberculosis is said to account for the majority of new cases, mostly in countries with low TB incidence. It is shown through modeling that 8% of persons with latent TB have to be successfully cured

each year, for the global incidence of TB in 2050 to be 14 times as low as the global incidence of 2013, which was estimated to be at a rate of about 1.5 % [41]. Hence the diagnosis and treatment of latent TB infections is very crucial as a way of TB control.

Although the re-infection parameter ρ_2 does not feature in R_0, equation (4.16) and hence does not have a clear effect on the disease dynamics for TB Model with impact of screening and treatment of latently infected TB individuals, we emphasize here that treated active TB and latently infected individuals can become infectious again after successful treatment. Therefore there is a need for major surveillance to ensure that reinfection cases are soon detected and successfully treated to prevent further TB spread.

Figure 4.3 shows the decrease in the value of the reproductive numbers as the treatment values for this TB Model are increased, which shows that TB disease can possibly be reduced through extensive screening and proper treatment.

5.2 Discussion of the TB model with treatment of drug-resistant TB individuals

A TB model that put emphasis on the treatment of both drug sensitive TB and resistant TB individuals is analyzed. Unlike for TB Model with impact of screening and treatment of latently infected TB individuals , the disease-free equilibrium for this model was found to be stable i.e. R_0 = max $\left\{R_{0s}, R_{0r}\right\} < 1$. Figure 4.6 shows the decrease in the value of the reproductive numbers in response to the increment in the treatment values. Thus from simulation, we found out that increasing the number of individuals who receive treatment, help

decrease the spread of TB in the population. It's therefore of utmost important that the treatment parameters ρ_1 and ρ_2 be significantly increased to prevent the disease from spreading. Hence emphasis should be on early detection and successful treatment, which will ensure total elimination and an end to transmission and acquisition of drug-resistance TB in communities.

We, however, observed that, γ_2, the rate at which active TB persons acquire resistant TB, does not feature in the reproductive numbers, R_{0s} and R_{0r}, equations (4.34) and (4.35). This is consistent with the findings of Zwerling et al. [46], that acquisition of resistant TB during treatment is less important than transmission of drug resistant TB when it comes to affecting long-term trajectories of drug resistant TB. This implies then that transmission of resistance TB is more crucial than acquisition of resistant TB during treatment and that TB interventions must focus on reducing the transmission rate and achieving a high drug resistant TB treatment success rate. According to Shrestha et al. [32], a high treatment success rate and a low levels of recent transmission will lead to low future proportions of drug resistant TB. Individuals on TB treatment need therefore to be monitored closely to ensure that they strictly take their medication as prescribed and on time, to prevent drug-resistant cases, which are reported to have high treatment failure and high death rates during treatment, not to mention very long treatment time, high costs and more toxic anti-tuberculosis drug use [10].

5.3 Conclusion

We conclude here that effective treatment breaks the cycle of transmission and to ensure this, both active TB and latently infected TB individuals must be identified and treated in order to reduce the further spread of TB in human population. Furthermore, we emphasize and advocate for proper and effective treatment of patients with resistant TB to ensure the zero re-emergence of multi drug-resistant TB strains. Thus for both models, we suggest that treatment rates for TB be increased, by involving family members and trained health workers to be based in villages, townships and overcrowded places like prisons, military barracks and school hostels etc, to ensure that all TB patients do take and complete their medication courses. This way, we will not only prevent acquisition of resistance TB, but also help reduce TB spread in our communities.

CHAPTER 6

RECOMMENDATIONS

It is recommended that policy makers pass a law that makes screening for TB mandatory for patients visiting clinics and hospitals with general fever, weakness and cough. The screening will help detect patients with infectious asymptomatic TB, so that they can start treatment earlier. This way, asymptomatic TB infectives are stopped from further spreading the disease. We also recommend strengthening the work of community health workers, so that they diligently ensure that TB patients in their communities do religiously take their medications, to prevent resistant TB, which is costly and takes even longer to treat.

We recommend that the Latin Hypercube Sampling-Partial Rank Correlation Coefficient (LHS-PRRC) technique, a more efficient type of sensitivity analysis, be carried out to assess the variability in the outcomes that is due to uncertainty in the input parameters and further identify which input parameters are important in contributing to the variability in the outcome variable.

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CHAPTER 7

APPENDIX

Appendix A

Below are Matlab codes used to obtain population sizes graphs for the TB model with impact of screening and treatment of latently infected TB individuals as shown in Figure 4.2.

```
function CharloteTBmodels
clc, close all
tend=5; %No=1000;
%PoPo=[55 735 100 15 85 65]; %Initial Population Classes level [Lambda S E I1 I2 H]
 PoPo=[50 749 90 9 81 71]
[t, MC]=ode45(@model1,[0 tend],PoPo(2:6),[],[50 0.01429 0.00005 0.042 0.001...
 0.0001 0.87 0.02 0.0575 0.02 0.0005 0.22]);
%Computing Model R0
 Par=[50 0.01429 0.00005 0.042 0.001 0.0001 0.87 0.02 0.0575 0.02 0.0005 0.22];
%[lambda   mu  beta1 beta2 alpha1 alpha2 rho1 rho2 ∆1 ∆2 sigma1 sigma2]
RO=Par(1)*(Par(4)*Par(6)*(Par(2)+Par(9)+Par(7))+Par(3)*(Par(6)*Par(11)...
 +Par(5)*(Par(2)+Par(10)+Par(11)+Par(12))))/(Par(2)*(Par(2)+Par(9)+Par(7))*...
 (Par(2)+Par(10)+Par(11)+Par(12))*(Par(2)+Par(5)+Par(6)))
 %Plotting the graphs % Creating  variables for initial population class levels
Y1=linspace(0,PoPo(1),PoPo(1));Y2=Y1; Y3=Y2; Y4=Y3; Y5=Y4; Y6=Y5; PoP1=1:PoPo(1);
Y1(:)=PoPo(1);Y2(:)=PoPo(2);Y3(:)=PoPo(3); Y4(:)=PoPo(4); Y5(:)=PoPo(5);Y6=PoPo(6);
subplot(3,2,1), plot(PoP1,Y1,'b',PoP1,Y2,'k',PoP1,Y3,'c',PoP1,Y4,'r',PoP1,Y5,'m',PoP1,Y6,'y'),
s1=sprintf('Replenishing constant pi=%d at t=0\n',PoPo(1));
```

```
s2=sprintf('Susceptiple S=%d at t=0\n',PoPo(2));
s3=sprintf('Exposed E=%d at t=0\n',PoPo(3)); s4=sprintf('Actively Infected I1=%d at t=0\n',PoPo(4));
s5=sprintf('Latent I2=%d at t=0\n ',PoPo(5));s6=sprintf('Treated H=%d at t=0\n',PoPo(6));
%legend(s1, s2, s3, s4, s5, s6),axis([0 PoPo(1)+10 0 PoPo(1)+100]);
subplot(3,2,2), plot(t,MC(:,1),'k'), xlabel('time (years)'), ylabel('Susceptible individuals'),title('Susceptibles vs Time
subplot(3,2,3), plot(t,MC(:,2),'c'), xlabel('time (years)'), ylabel('Exposed individuals'),title('Exposed  vs Time')
subplot(3,2,4), plot(t,MC(:,3),'r'), xlabel('time (years)'), ylabel('I1 individuals'),title('Actively Infected vs Time')
subplot(3,2,5), plot(t,MC(:,4),'m'), xlabel('time (years)'), ylabel('I2 individuals'),title('Latently Infected vs Time')
subplot(3,2,6), plot(t,MC(:,5),'y'), xlabel('time (years)'), ylabel('Treated individuals'),title('Treated vs Time')
return
function  Cl=model1(¬,Class,Param)
S=Class(1);E=Class(2);I1=Class(3); I2=Class(4); H=Class(5);
Lambda=Param(1); mu=Param(2); beta1=Param(3); beta2=Param(4);
alpha1=Param(5); alpha2=Param(6);rho1=Param(7); rho2=Param(8);
∆1=Param(9);∆2=Param(10); sigma1=Param(11);sigma2=Param(12);
Cl=zeros(5,1);
Cl(1)=Lambda-mu*S-(beta1*I1+beta2*I2)*S;
Cl(2)=(beta1*I1+beta2*I2)*S+rho2*H-(alpha1+alpha2+mu)*E;
```

```
37 Cl(3)=alpha1*E+sigma1*I2-(Δ1+rho1+mu)*I1;
38 Cl(4)=alpha2*E-(Δ2+sigma1+sigma2+mu)*I2;
39 Cl(5)=rho1*I1+sigma2*I2-(mu+rho2)*H;
40 return
```

Appendix B

Matlab codes used to obtain population sizes graphs for the TB model with treatment of drug-resistant TB individuals as shown in Figure 4.5.

```
function CharlotteTbmodels2
clc, close all
tend=10; N0= 8210;
%Solving the model %Initial Population Classes level [ Lambda S E1 I1 T1 I2 T2 E2]
 PoPo=[246 7095 786 157 141 15 9 7]; %PoPo=[410 6795  995 199 180 19 12 10];
[t, MC]=ode45(@model2,[0 tend],PoPo(2:8),[],[246 0.01429  0.00005  0.014...
 0.001 0.00001 0.87 0.53 0.0575 0.55 0.054 0.075 0.02]);
%Computing Model R0s and R0r  [Lambda mu beta1 beta2 alpha1 alpha2 rho1
%rho2 ∆1 ∆2 gamma1 gamma2 sigma]
Par=[246 0.01429  0.00005  0.014 0.001 0.00001 0.87 0.53 0.0575 0.55 0.054 0.075 0.02];
 RO1=(Par(1)*Par(3)*Par(5))/(Par(2)*(Par(2)+Par(5))*(Par(2)+Par(9)+Par(7)))
 RO2=(Par(1)*Par(4)*Par(6))/(Par(2)*(Par(2)+Par(6))*(Par(2)+Par(10)+Par(8)))
%Plotting the graphs % Creating  variables for initial population class levels
Y1=linspace(0,PoPo(1),PoPo(1));Y2=Y1; Y3=Y2; Y4=Y3; Y5=Y4; Y6=Y5; Y7=Y6; Y8=Y7; PoP1=1:PoPo(1);
Y1(:)=PoPo(1);Y2(:)=PoPo(2);Y3(:)=PoPo(3); Y4(:)=PoPo(4); Y5(:)=PoPo(5);Y6(:)=PoPo(6); Y7(:)=PoPo(7); Y8=PoPo(8);
subplot(4,2,1), plot(PoP1,Y1,'b',PoP1,Y2,'k',PoP1,Y3,'c',PoP1,Y4,'r',PoP1,Y5,'m',PoP1,Y6,'y',PoP1,Y7,'g',PoP1,Y8,'w'),
s1=sprintf('Replenishing constant Lambda=%d at T=0\n',PoPo(1));s2=sprintf('Susceptiple S=%d at t=0\n',PoPo(2));
s3=sprintf('Exposed E1=%d at t=0\n',PoPo(3)); s4=sprintf('Actively Infected I1=%d at t=0\n',PoPo(4));
```

```
s5=sprintf('Treated Active TB T1=%d at t=0\n ',PoPo(5));s6=sprintf('Resistant TB I2=%d at t=0\n',PoPo(6));
s7=sprintf('Treated Resistant TB T2=%d at t=0\n',PoPo(7));s8=sprintf('Exposed E2=%d at t=0\n',PoPo(8));
%legend(s1, s2, s3, s4, s5, s6, s7, s8),axis([0 PoPo(1)+30 0 PoPo(1)+3000]);
subplot(4,2,2), plot(t,MC(:,1),'k'), xlabel('Time (years)'), ylabel('S individuals'),title('Susceptible Individulas vs Tim
subplot(4,2,3), plot(t,MC(:,2),'c'), xlabel('Time (years)'), ylabel('E1 individuals'),title('Exposed Individulas vs Time')
subplot(4,2,4), plot(t,MC(:,3),'r'), xlabel('Time (years)'), ylabel('I1 individuals'),title('Actively Infected vs Time')
subplot(4,2,5), plot(t,MC(:,4),'m'), xlabel('Time (years)'), ylabel('T1 individuals'),title('Treated active TB vs Time')
subplot(4,2,6), plot(t,MC(:,5),'y'), xlabel('Time (years)'), ylabel('I2 individuals'),title('Resistant TB vs Time')
subplot(4,2,7), plot(t,MC(:,6),'b'), xlabel('Time (years)'), ylabel('T2 individuals'),title('Treated resistant TB vs Time'
subplot(4,2,8), plot(t,MC(:,7),'g'), xlabel('Time (years)'), ylabel('E2 individuals'),title('Exposed to resistant TB vs Ti
return
function  Cl=model2(¬,Class,Param)
S=Class(1);E1=Class(2);I1=Class(3); T1=Class(4); I2=Class(5); T2=Class(6);
E2=Class(7); Lambda=Param(1); mu=Param(2); beta1=Param(3);  beta2=Param(4);
alpha1=Param(5);alpha2=Param(6);rho1=Param(7); rho2=Param(8);∆1=Param(9);
∆2=Param(10); gamma1=Param(11); gamma2=Param(12);sigma=Param(13);
Cl=zeros(7,1);
Cl(1)=Lambda-mu*S-(beta1*I1+beta2*I2)*S;
```

```
Cl(2)=beta1*I1*S+gamma1*T1-(alpha1+mu)*E1;
Cl(3)=alpha1*E1-(Δ1+rho1+mu)*I1;
Cl(4)=rho1*I1-(gamma1+mu)*T1;
Cl(5)=alpha2*E2+gamma2*I1-(mu+rho2+Δ2)*I2;
Cl(6)=rho2*I2 -(sigma+mu)*T2;
Cl(7)=beta2*I2*S+sigma*T2-(alpha2+mu)*E2;
return
```

Appendix C

Matlab codes used to obtain the graphs for the effects of treatment rates ρ_1 and σ_2 on the reproductive number for TB model with impact of screening and treatment of latently infected TB individuals as shown in Figure 4.3.

```
function R0Model1(h)
 mu=0.01429; beta1 = 0.00005; beta2=0.042; alpha1=0.001; alpha2=0.0001;
 Δ1=0.0575; Δ2=0.02;  Lambda=100 ; sigma1=0.0005;
 rho1=0:h:1;  sigma2=0:h:1;
R0=zeros(length(rho1),1);
for k=1:length(rho1)
 R0(k)=(Lambda*(alpha2*beta2*(mu+Δ1+rho1(k))...
  + beta1*sigma1*alpha2 + alpha1*beta1*(mu+Δ2+sigma1+sigma2(k))))...
 /(mu*(mu+alpha1+alpha2)*(mu+Δ1+rho1(k))*(mu+Δ2+sigma1+sigma2(k)));

%R0(k)=(Lambda*(alpha2*(beta2*(mu+Δ1+rho1(k))+beta1*sigma1)+alpha1*...
%beta1*(mu+Δ2+sigma1+sigma2(k))))/(mu*(mu+Δ1+rho1(k))*...
 %(mu+Δ2+sigma1+sigma2(k))*(mu+alpha1+alpha2));
 % end
end
R0
plot(rho1,R0,'-r')
xlabel 'Treatment rates \rho_{1} and \sigma_{2}';
ylabel 'Basic reproduction ratio R_{0}'
```

Appendix D

Matlab codes used to obtain the graphs for the effects of treatment rates ρ_1 and ρ_2 on the reproductive numbers for TB model with treatment of drug-resistant TB as shown in Figure 4.6.

```
%%
 beta1 = 0.00005; beta2=0.014; alpha1=0.001; alpha2=0.00001;
 Δ1=0.0575; Δ2=0.55;  mu=0.01429; Lambda=410;
 rho1=0:0.02:1;  rho2=0:0.02:1;
 %sigma=0.005;gamma1=0.12; gamma2=0.1;sigma1=0.005;
 [r,T]=size(rho1);
 [p,t]=size(rho2);
 R0s=zeros(T,r);
 R0r=zeros(t,p);
 for k=1:T
     R0s(k,:)=(Lambda*beta1*alpha1)/(mu*(mu+alpha1)*(mu+Δ1+rho1(k)));
 end

 for j=1:t
     R0r(j,:)=(Lambda*beta2*alpha2)/(mu*(mu+alpha2)*(mu+Δ2+rho2(j)));
 end
R0s
R0r
subplot(2,1,1); plot(R0s,'-g')
xlabel 'Treatment rate \rho_{1}';
```

```
21 ylabel 'Basic reproduction ratio R_{0s}'
22 axis([0 50 0 2])
23 hold on
24 subplot(2,1,2); plot(R0r,'-r')
25 xlabel 'Treatment rate \rho_{2}';
26 ylabel 'Basic reproduction ratio R_{0r}'
27 axis([0 50 0 2])
28 hold off
```