DEPARTMENT OF MATHEMATICS

Modelling The Transmission of Drug Resistant Tuberculosis in Ethiopia

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Contents

Abstract

Tuberculosis is an infectious disease, which is affecting a third of the world's population, that makes Tuberculosis a global health problem. Many countries are trying to eliminate the disease but the emergence of multi-drug resistant strain become a challenge as it is difficult but not impossible to treat despite being too expensive. Now a days mathematical models for infectious disease are important in studying qualitative dynamics of the disease at the population level which can fill in gaps were experiments with the spread of infectious disease in human population are often impossible, unethical or expensive. In this study we formulated a two strain tuberculosis model and discussed some of the dynamical behaviour of the disease . In the model health education will be given to susceptible population to protect them from infection and treatment is offered to infected individuals except for latently infected with drug resistant Tuberculosis. We divided the latent stage for drug sensitive tuberculosis as early stage , for those who are infected latently but stayed not more than 2 years, and long stage, for those who have been infected latently for more than two years, to see the effect of treatment for early latent stage as most of transfer to infectious class occur during the first two years. We used numerical methods to solve the ordinary differential equation and see some of the dynamical behaviour of the disease. Numerical simulation result shows that the interventions can eliminate the sensitive strain, but can only reduce the drug resistant tuberculosis. Treatment for early latent stages have a great role in eliminating the drug sensitive Tuberculosis.

Chapter 1

Introduction

1.1 Tuberculosis

Tuberculosis(TB) is a chronic infectious disease mainly caused by mycobacterium tuberculosis(MTB). The main source of infection is untreated smear-positive pulmonary tuberculosis (PTB) patient discharging the bacilli. It mainly spreads by air borne route when the infectious patient expels droplets containing the bacilli.

Tuberculosis has been known to man kind since ancient times. The organism causing tuberculosis-Mycobacterium tuberculosis existed $15,000$ to $20,000$ years ago [32]. It has been found in relics from ancient Egypt, India and China. In the 18^{th} century in western Europe tuberculosis reached its peak with prevalence as high as 900 deaths per $100,0000$. Poorly ventilated and overcrowded housing, primitive sanitation, malnutrition and other risk factors led to the rise. Even today after the development of advanced screening, diagnostic and treatment methods for the disease, a third of the worlds population has been exposed and is infected with the disease. An estimated 8.8 million incident cases of TB occurred globally in 2010. Asia and Africa possess the largest number of the estimate. In the year approximately 1.4 million people died of TB[27].

Antibiotics were used against tuberculosis for the first time in 1944 after the discovery of Streptomycin [32]. Use of this agent alone led to antibiotic resistance that is still a major problem. Better results followed the development of PAS (para-aminosalicycic acid). PAS was an oral agent unlike Streptomycin. Thereafter more effective drugs like INH (Isoniazed) came in 1950's and treatment with Rifampicin followed. Currently there are fewer than 20 agents activity against mycobacterium.

People usually get TB germs in their bodies only when they spend a long time around some one who is sick with TB. Even then, the body can usually fight off the germs. When a person's immune system is strong, TB germs can't cause a disease. This stage is called latent(sleeping) TB. As long as the immune system stays strong, people with latent TB don't feel sick and they can't spread their TB germs to others. When a person's immune becomes weak they become sick. This stage is called active TB.

1.2 Drug resistant Tuberculosis

Resistance to at least the two major anti-tuberculosis drugs, Isoniazid and rifampicin, has been termed as **Multidrug-Resistant Tuberculosis (MDR-TB)**. Multi-drug resistant tuberculosis is an increasing global problem, with most cases is a result of a mixture of physician error and patient non compliance during treatment of sensitive TB. Although some individuals who have not had previous TB treatment are infected by MDR-TB, but this is not the case for most patients. Recent efforts to fight the drug sensitive Tuberculosis have made considerable progress in different countries but the emergence of this resistant strain make the control efforts difficult.

According to the WHO report 2011, the estimated number of MDR TB to exist in 2010 is $290,000$ (range $220,000 - 400,000$) and reported number of patients enrolled on treatment has increased and reached $46,000$ which is 16% of the cases estimated in the year.

Since drug resistant tuberculosis is expensive to treat, it was a great problem for many countries especially for developing countries as the problem may be vast and increasing and treating such an increasing patients of MDR TB is difficult which makes the emergence of resistant strain is a headache for developing countries.

1.3 Tuberculosis in Ethiopia

According to the global report 2009 by WHO, Ethiopia ranked as $7th$ among the 22 high burden TB countries in the world and is one of three countries in Africa with an estimated incidence of all forms of TB at $378/100,000$ population in 2009. The estimated incidence of smear positive(a form of TB in which TB bacteria are seen when a sputum smear is stained and examined under the microscope) is $163/100,000$ population.

The HIV epidemic has made the TB situation significantly worse by accelerating the progression of TB infection to active TB disease, thus increasing the number of new TB cases. Another challenge to TB control in Ethiopia is emergence of MDR-TB, with 1500 estimated new MDR-TB infections annually. Of these, 1.6% are of new cases and 11.8% are of re-treatment[11, 13].

According to the study conducted in 2011 at St.Peter's TB specialized hospital, Among 376 culture positive for Mycobacterium Tuberculosis 102 were susceptible to all of the four first line anti-TB drugs, Isoniazid(INH), Rifampicin(RIF), Ethambutol(TTB) and streptomycin(STM), and 274 were resistance to at least one Drug-resistance of any. STM(67.3%) was found to be the most common followed by (56.1%) INH, (46.1%)RIF and (43.5%)ETB. Isoniazid + streptomycin combination have highest proportion among the concomitant resistance reported in the year[2]. The prevalence of MDR-TB was found to be high and it is because of re treatment. The trend in drug-resistance against all first line drugs shows a significant increase. This remarkable increase of drug resistance among re-treatment patients supports the idea of inefficient in TB control programs and irregular or improper anti-TB drug in recent years.

According to the Ministry of Health hospital statistics data, tuberculosis is one of the leading cause of morbidity, the fourth cause of hospital admission, and the second cause of hospital death in Ethiopia[3].

1.4 Motivation of the study

In recent years epidemiological modelling of infectious disease transmission has had an increasing influence on the theory and practice of disease management and control.

Mathematical modelling of the spread of infectious disease has become part of epidemiology policy decision making in many countries. Epidemiological modelling studies of diseases have had an impact on public health policy in various countries of the world. Thus modelling approaches have become very important for decision making about infectious disease intervention programs.

Mathematical models have become important tools in analysing the spread and control of infectious diseases. The model formulation process clarifies assumptions, variables, and parameters; moreover models provide conceptual results such as thresholds, basic reproduction numbers, contact numbers, and replacement numbers. Mathematical models and computer simulations are useful experimental tools for building and testing theories, assessing quantitative conjectures, answering specific questions, determining sensitivities to changes in parameter values, and estimating key parameters from data. Understanding the transmission characteristics of infectious diseases in communities, regions and countries can lead to better approaches to decreasing the transmission of these diseases. Mathematical models are used in comparing, planing, implementing, evaluating, and optimizing various detection, prevention, therapy and control programs.

In many sciences it is possible to conduct experiments to obtain information and test hypothesis. Experiments with the spread of infectious diseases in human population

are often impossible, unethical or expensive. Thus mathematical models and computer simulations can be used to perform needed theoretical experiments.

Due to the above facts, this study is motivated to develop a mathematical model for the transmission of tuberculosis including the resistant tuberculosis including some interventions which existed to see their contribution work of controlling the disease. We use data in Ethiopia for numerical simulation results and to capture some of the dynamics.

1.5 Outline of the Thesis

Chapter one deals with the general background about drug susceptible and resistant TB and their global burden. It also provides the situation of Tuberculosis in Ethiopia. In Chapter Two we try to review studies conducted on tuberculosis(with only one strain and two strain) using mathematical modelling. In the third chapter, which contains the main body of the thesis, we present a two strain TB model with different interventions like education, treatment for latently infected drug sensitive individuals as well as treatment for the infectious classes of the two strain. Finally, discussions and conclusions as well as limitations of the work are presented in forth chapter.

Chapter 2

Literature Review

Deterministic models, also known as compartmental models, have been used to explain the dynamics of diseases at population level. These models categorize the population into different sub populations. The SI (SIS) model, for example, has two compartments of susceptible and infectious individuals. The individuals in each compartment follow some kind of transition from one compartment to the other as their state of infection changes. Susceptible individuals are infected upon interaction with individuals who are infectious. The infection is driven by the product of the probability of infection, the number of contacts, the number of susceptible and infected individuals. The product of the number of contacts, probability of infection, and the number of infected individuals is known as the force of infection. It describes the transition from the susceptible class to infected. After being treated, for the SIS models individuals will join the susceptible class again. In such kinds of models unrealistic considerations might have been taken as in some infectious diseases, recovery of an individual provides some immunity.Below we review some of the literatures associated with TB models and their theoretical aspects where the authors contributed.

The first model for the transmission dynamics of TB was built in 1962 by Waaler [12]. He divided the population in to three epidemiological classes: Susceptible, latent and infectious. He used a particular linear function to model infection rates in the imple-

mentation of his model. Using data from a rural area in South India for the period 1950 to 1955 Waaler estimated the parameters of his linear model and predicted that the time trend of TB is unlikely to increase.This linear model did not model the mechanics of transmission.

Brogger developed a model in [24] that improved Waaler's work. He introduced heterogeneity(age) into the model and also changed the method used to calculate infection rates. He formulated infection rate as a combination of linear and non-linear infection terms. In the paper the author aimed to compare different control strategies that included finding and treating more cases and the utilization of vaccination.He used prevalence as an indicator of the effectiveness of control policies.He used data of two WHO/UNICEF projects in Thailand from 1960 to 1963 to estimate the parameters in the model. This model did not formulate clearly the relationship between infection rate and prevalence.

Using Brogger and Waaler's model as a template, ReVelle introduced the first non-linear system of ordinary differential equations that models TB dynamics [4, 5]. He clearly explained infection rate depends linearly on the prevalence using probabilistic approach. In the paper the author's main objective seemed to be associated with the evaluation and implementation of control policies and their cost. He developed an optimization model and used it to select control strategies that could be carried out at minimal cost. ReVelle didn't considered population structure in his model.

Most dynamical models prior to Ferebee's work were motivated by the study of TB in developing nations. But Ferebee set up a discrete model,based up on a set of simple assumptions, to model the dynamics of TB in U.S.A [20]. She used a year as a basic time unit and described her algorithm, method of estimation of relevant parameters, and the number of infected people in the U.S.A. The results showed that the number of new cases would decrease slowly if vaccination were applied to the U.S.A population.This work also gave rough estimate and forecast of TB cases in the U.S.A.

Early mathematical models of TB transmission were developed in such a way that their approach follow a pattern: build a mathematical model for TB transmission; with help from a data set,estimate parameters; find numerical solutions; and predict or make inferences about the relative value of alternative control strategies.There was no qualitative analysis of the models, and the long time behaviour (asymptotic properties) of the models was not studied. In the following sections we shall review some of the recent models and their theoretical results.

People who have latent TB are at high risk of developing active TB and with time passing these individuals face the possibility of progressing to infectious TB,but the likelihood of becoming an active infectious case decreases with the age of infection. Having this condition several researchers developed a dynamical models for TB progression and transmission [21, 22, 23]. The model in [21] partition the population in to susceptible,latent and infectious compartments. The infection rate is divided in to two. i.e proportion that gives rise to immediate active cases(fast progression) and the rest give to latent TB cases with a low risk of progressing to active TB.(slow progression). In the paper sensitivity and uncertainty analysis were carried out and results showed that TB dynamics were quite slow for acceptable parameter ranges.The model requires the parameters that determines the proportion to slow and fast progression is not allowed to change and, the the basic reproduction number R_0(Average number of secondary cases produced by a typical infected (assumed infectious) individual during his/her entire life as infectious (infectious period) when introduced in a population of susceptible.)derived from the model depends linearly on population size. A model that removes this restrictions is done by feng.[31]

Incomplete treatment, wrong therapy, and co-infection with other disease may give rise to new resistant strains of TB. Models that include multiple strains of Tb have been developed. In the next sections we will try to review some of them.

In [6] Castillo-Chavez and Feng present a two strain model, in which the drug resistant strain is not treated, and latent,infections and treated individuals may be re-infected with the drug-resistant strain. Each strain has a different R_0,and there are three equilibrium points(no disease, coexistence of both strains, and only the drug resistant strain). The paper discuss stability of the equilibria and find areas of parameter where coexistence of strains is possible. They reported that coexistence is rare when drug resistance is mainly resulting from transmission but it is certain if the resistant strain is the result of acquisition. Neglecting disease-induced death and making the transmission rate for the two strain equal, they are able to prove that the disease-free equilibrium is globally asymptotically stable if both R_0's are less than 1. This model did not take into account long and variable periods of latency a key feature of TB.

In [23] the authors studied the dynamics by focusing on the threshold R_0 and the development of drug-resistance. By defining X to be the number of drug-resistance cases caused by the failure in treatment of one drug sensitive case the authors use the condition $R_0 < 1$ to compute $r_{max}(X)$ (The maximal acceptable probability of treatment failure). They conclude that the control programs could become perverse(meaning $X > 1$), though this requires a rather high probability of acquisition of drug-resistance due to treatment failure. In countries with high TB burden, they conclude that the efficacy of treatment combined with the effective overall treatment rates must be kept high in order to control TB.

Blower and Gerberding in [22] focus on trajectories in the two strain model and simulate specific control policies numerically in the short term, and using R_0 analysis for long term consequences. In their model, policies leading to the same long-term equilibrium can have different transient approaches to the equilibrium. Furthermore, some transients in their model show a decline in the portion of drug resistant TB over a 10 years period, followed by a slow increase. Using qualitative discussion in terms of TB's inherent fast and slow time scales they argue for vaccination, and warn about consequences of focusing control measures only on drug sensitive TB.

[9]presents a model with explicit fast and slow progression from two latent cases. Drug-resistant TB alone, representing treatment failures as potential transmitters of drug resistant TB. the paper argue that short-course chemotherapy can bring resistant strains under control, preventing drug-resistant TB from emerging. This result depends on the assumption that drug-resistant strains are less transmissible than drug-sensitive strains, but doesn't explicitly represent the dynamics of drug-sensitive strains.

Dye and Williams in [8] used a model that allowed the relative fitness of drug-resistant strains to be as high as 1.($i.e.$ the same as drug-sensitive strains), and concluded that drug-resistant strains could threaten control of TB.They estimate that 70% of drug-resistant cases must be detected and 80% of these must be cured in order to prevent drug-resistant TB outbreaks.

Cohen and Murray in [7] studied models allowing the fitness of drug-resistant strains to be heterogeneous.This model allows that while most mutations will come at a cost to the inadmissibility of the strain, some strains may acquire resistance with minimal negative effect. Thus even in the presence of a good control program, the average fitness of MDR strains will increase as more fit strains are preferentially transmitted.

In [25] Blower and Chou introduce a model that allow the strain may become resistant to increasing number of drugs is sub-optimal treatment regimes are used. They find that individuals with drug resistant disease must be treated to avoid the further emergence of resistance.

And many other models on tuberculosis epidemiology have been conducted and most of them are of general setting and some of them are specific to some countries. The paper in [30] models major factors that control tuberculosis spread in China.The authors divided the TB transmission framework in to two compartments named as detected and undetected.The undetected populations are those individuals who are rural migrants

working in urban areas and are not registered in government register to the TB control programme.They are termed as "floating" population.Because of lack of proper conditions to have medical insurance they are unable to visit the health care institutions. The detected are those individuals who are registered at government register of the TB control programme.Considering this undetected class the authors model the TB transmission in China, calculated R_0 and discussed the stability of different equilibria, sensitivity analysis of some parameters are discussed, they also compare the model with the real data available from ministry of health in China. Firstly they assumed that the spread of TB in the detected class is mainly in due to the number of infections caused by the infected under the class classified as undetected. Based on this assumption they argued that control measures that impact the transmission coefficients are more efficient than changes that affect the endogenous reactivation rate. Improving lifestyle and reducing contact rate of the population may be such measures. Later the authors relax the first assumption and assumed the infection may also come from the class of detected and based on this assumption they reach at a conclusion that there is high chance of infection spreading to a person in the undetected class from the detected one unless infections registered individuals are isolated from general population. Comparing the two models of the two assumptions the paper concluded that for very similar parameters,quite different outcomes are possible so further studies may be necessary to explain the sensitivity of the results to the model.

In the study [17] the authors studied a two strain tuberculosis model with three interventions,diagnosis, treatment and health education. The health education is given to infectious drug sensitive population to make them to complete their treatment properly so that minimize the treatment failure.From the study they concluded that treatment for latently infected and infectious individuals with drug sensitive tuberculosis showed that the drug sensitive tuberculosis can completely eradicated, thus resulting in a reduction of MDR-TB. Treatment for infectious MDR-TB cases alters tuberculosis epidemics because it reduces the spread of MDR-TB strains.The study also showed diagnosis plays an important role in MDR-TB reduction.

Some studies like in [17] formulated a model for dynamics of tuberculosis of TB including health education,but most of them assumed that education is given to people so that they will be educated at a constant rate. This is not the reality, according to study by Kassa and Ouhinou[2011], humans behaviour change by educating about a given disease depends on the prevalence and mortality of the disease and they formulated a behaviour change function as to depend on prevalence.As prevalence of the disease is getting high people's being kin to use every existing self protective measures as well increases.If prevalence is low to some point that people didn't recognize it peoples reaction to the education,which can be measured by the extent people use the protective measures,will be low.We used this concept in out study for the behaviour change that people bring when educated about tuberculosis.

Most of the studies mentioned above studied a two strain model and showed results of their study. Even if treatment failure is the main reason for drug resistant tuberculosis to occur but it can also be transmitted as a primary infection to those who have not priory infection history and to those infected by the sensitive strain. So unlike the other studies in this study we tried to see the role of education to susceptible people in the transmission of the disease that is giving education to susceptible population reduce the prevalence of the resistant strain in addition to the treatment to infectious population of the two strain and latently infected individuals of the sensitive strain.In this study we treated latently infected individuals in to two stages as early latent and long latent to see the role of treatment to early stage, the stage for most of the infected populations progress to active TB with in this stage.

Chapter 3

A two strain Tuberculosis model

3.1 Description of the model

The host population is subdivided in to eight classes :Susceptible(S), who have never exposed to any strain of the Mycobacterium tuberculosis, Educated susceptible(S_E), Susceptible individuals who are educated and are involved in self protective action against the infection. People reaction to protect themselves from the disease depends on the prevalence and mortality of the disease[14]. In areas of high prevalence these educated people always suspect that there may be some one with the TB infection near by so they will try to use any of the protective measures according to the situation. Now the questions how do this educated people protect them selves from the disease or what are the things to do especially with tuberculosis? People may take the following measures if they are educated. When in contact with a patient known or suspected to have active TB disease, place a surgical mask on the patient, if possible, and wear an N95 respirator (or PAPR or SCBA), if one is available. If a respirator is not available, one can use a surgical mask for himself. Not all people with active TB disease are sick enough to spread the disease and not all people who are exposed to TB become infected. Ones risk of becoming infected depends on the length and intensity of the exposure and how symptomatic the sick person is. Brief or distant exposure to TB, or exposure to someone without a cough, rarely leads to infection. It usually takes lengthy contact (i.e., sharing

air space for several hours over a period of several days) with someone with active TB disease for a person to become infected. Therefore,one can keep the length of exposure as brief as possible. Adequate ventilation is also important. If one must transport a patient with known or suspected active TB disease, he/she must keep the windows of his/her vehicle open (if feasible) and set the heating and air-conditioning systems on a non recirculating cycle. And also If a person is using public transportation or in some meeting rooms let the windows open so that the air inside will be ventilated.Generally in what ever the situation educated people always suspect for TB infection so they will not allow things that may expose them for the infection.

Latently infected individuals with multi-drug resistant tuberculosis(E_r),Latently infected individuals with drug sensitive tuberculosis that we divide them in to two stages depending on the duration of time they spent after primary infection: an early stage (E_1)(up two years after primary infection) with high risk of developing active tuberculosis and Later(Long) stage (More than two years after primary infection but not transformed to active TB)of low risk of developing active disease(E_2), Infectious individuals with drug sensitive tuberculosis(I_s), Infectious individuals with multi-drug resistant tuberculosis(I_r), and Recovered individuals(R). Individuals in susceptible class are recruited at a constant rate Π. As these individuals are educated to prevent themselves from the disease, their behaviour changes. Here we use the result in [Kassa and Ouhinou.(2011)],where they used the behaviour change of the people depends on the prevalence of the disease and formulated the behaviour change function,e, as a function of prevalence. So in our model the rate of transfer of susceptible(not educated) individuals to educated class is ηe, in our case e is behaviour change function which depends on the prevalence of both the drug resistant and sensitive strain when the two strains exist in the population.The behaviour change function can be described as $e(m) = \frac{t \times m^n}{m_*^n + m^n}$, where m is prevalence of both drug -resistant and sensitive strains, t is the saturation level of e,and m_* is the prevalence producing half the maximum behavioural change value, n is the hill coefficient that portrays the rate of reaction by the population. η is the rate of dissemination of information about the disease in the population.

The root to infections from either susceptible or susceptible educated classes is fast or slow.These individuals will be infected if they come into effective contact with either active Drug Resistant TB or Drug Sensitive TB cases at a rate of λ_r and λ_s respectively, where the subscript r and s represent the resistant and the sensitive strain respectively. $\lambda_i, (i = r, s)$ is the force of infection and is defined as $\lambda_i = \frac{c\beta_i I_i}{N}$, where β_i is the probability that an individual can be infected by one infectious individual and c is Number of effective contacts a susceptible individuals makes with infectious individuals.

From Susceptible class a proportion of ρ_r and ρ_s progress fast to infectious classes of the resistant strain and the sensitive strain respectively. The remaining $(1 - \rho_r)$ and $(1 - \rho_s)$ progress to infectious class by slow progression through E_r and E_1 respectively. Similarly a proportion of a and b of the educated susceptible individuals will progress fast to infectious classes of the drug resistant and sensitive strain respectively. The remaining will die out without being infected or progress to latent class through slow progression with a proportion of $(1 - a)$ and $(1 - b)$ to E_r and E_1 class respectively.

Individuals in latent classes of both the drug resistant TB strain and the sensitive TB strain progress to infectious (Active TB) classes by either exogenous re-infection or endogenous reactivation. Infected peoples with the sensitive strain from either the susceptible or susceptible but educated class initially progress through the early latent stage (E_1) and can either progress to active tuberculosis by either exogenous re-infection or endogenous reactivation at the rate of $(1 - q_1)(\gamma_s\lambda_s + k_1)$ or progress to long term latent stage at the rate of $(1 - q_1)j$ where $(1 - q_1)$ is a proportion of people not treated in early latent stage. Individuals who are latently infected with TB can get effective treatment during the early latent stage at the rate of σ_1 or during the long term latent TB stage at the rate of σ_2. Now the problem may be detecting or diagnosing all infected individuals early but the Center for disease control and prevention recommend identifying and offering therapy to all close contacts of persons with active TB [16]. During the period of long term TB infection individuals are at low risk of reactivation

to active TB and can slowly progress at the rate of k_3 by endogenous reactivation but we assume same rate of re-infection $\gamma_s\lambda_s$ with that of individuals in E_1 class.Due to exogenous re-infection individuals in E_r class progress to I_r at the rate of $\gamma_r\lambda_r$, where γ_r is the re-infection rate of latently infected individuals with MDR TB strain. Due to endogenous reactivation individuals in E_r progress to I_r at the rate of K_2.

Persons with latent TB infection are considered at high risk of developing active TB during the first 2 years of infection,during which approximately 5% of persons develop active TB [1].Treatment is given to individuals in both latently infected drug sensitive stages, $E_1$and E_2, which is necessary to keep the latent TB infection from developing in to active disease. It reduces short term risk of developing TB disease by approximately 60%. We assume the treatment for individuals in this class reduces their re-activation.

Individuals in I_s and I_r who are diagnosed will start their treatment at the rate of ϕ_s and ϕ_r respectively. From those individuals in I_s class who started treatment a proportion of p will complete the treatment properly as directed by the right health professionals so that cure from the disease and a proportion of $(1-p)$ will not complete treatment so may develop the MDR TB and join to E_r class.Since treatment doesn't provide permanent protection against the disease, individuals who are treated may be infected again if they come to effective contact with active TB case of any of the two strain.To my knowledge there is no research that clearly indicates that treatment for prior active tuberculosis will provide an immunity. But we don't think that people cured of TB and those with no history of infection as well as latently infected are the same.At least they are different by the attitude they have to the disease because those cured know the burden of the disease themselves that is more than hearing.So they keep them selves from second infection than others not yet infected.That is why we treat them in different class.In the study[26] it is indicated that in areas with a high incidence of tuberculosis,exogenous re-infection might also be a cause of the first episode of post primary tuberculosis,since the immunity that develops after primary infection followed by a period of latency cannot be expected to confer more protection against exogenous re-

infection than the immunity that develops after an episode of active disease.We assume that treatment will provide some immunity for the second infection but may be very low.So previously treated individuals will have low rate of infection as compared to not infected as well as non educated. This protection may be from the education that they got during the the treatment process of the previous infection.They know the problem they face during the treatment.Because of this immunity we assume that people may be infected after treatment $h\lambda_r$ and $h\lambda_s$, Where h accounts for the immunity so that join latently infected drug resistant starain class and early latent class respectively.

All individuals in each compartment will die naturally at the rate of μ and individuals in I_s and I_r class will die due to the disease at the rate of d_s and d_r respectively. In the model individuals in S, S_E, E_1, E_2 and I_s can be infected by MDR TB (primary infection) if there is effective contact with individuals in I_r class.

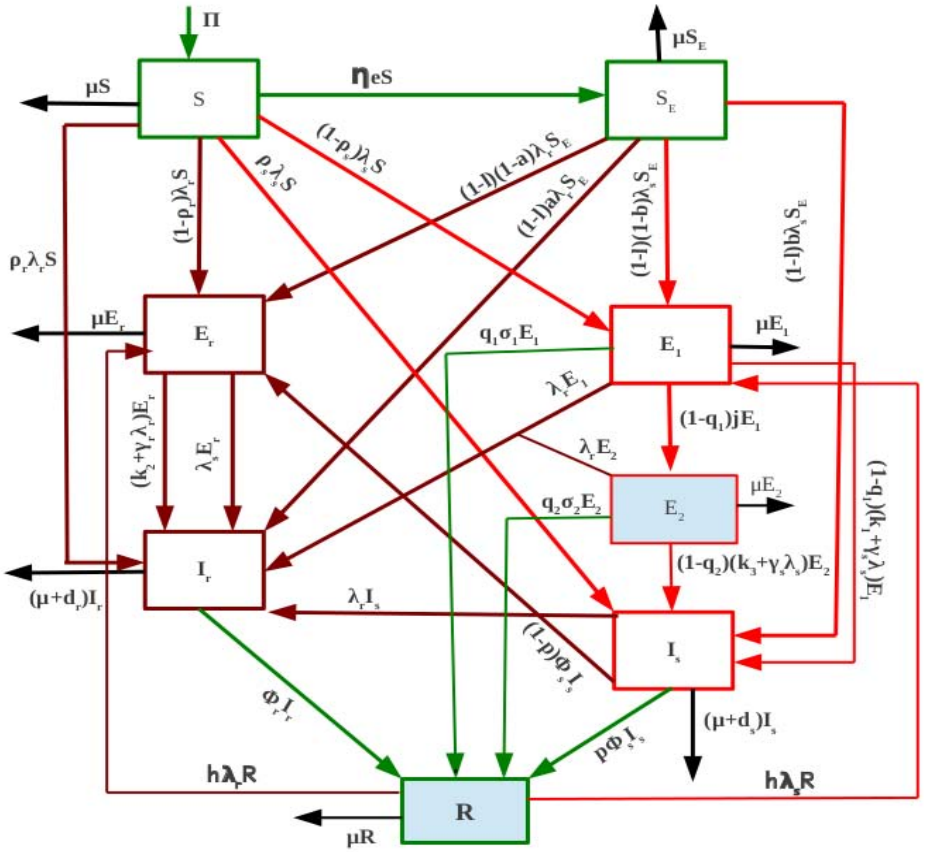


Figure 3.1: Diagram for a two strain tuberculosis transmission model

Table 3.1: Symbols and there description for parameters in the model

No	Symbols	Description
1	S	Susceptible individuals for the disease
2	S_E	Susceptible individuals who are Educated
3	E_r	Latently infected with MDR-TB
4	E_1	Early latently infected with drug sensitive TB
5	E_2	Long latently infected with drug sensitive TB
6	I_r	Infectious individuals with MDR-TB
7	I_s	Infectious individuals with drug sensitive TB
8	R	Recovered Individuals
9	Π	Recruitment rate to susceptible class
10	μ	Natural death rate
11	$\phi_i(i = r, s)$	Treatment rate(r =MDR strain,s =drug sensitive strain)
12	$\lambda_i(i = r, s)$	Force of infection($\lambda_i = \frac{c\beta_i I_i}{N}$)
13	$\beta_i(i = r, s)$	Probability that an individual is infected by one infectious individual
14	c	Number of effective contacts a susceptible individuals makes with infectious individuals per year
15	$d_i(i = r, s)$	Death rate due to the disease
16	p	proportion for those who complete treatment
17	$\gamma_i(i = r, s)$	Re-activation rate
18	$\rho_i(i = r, s)$	Fast progression to infectious
19	$k_j(j = 1, 2, 3)$	Infection rate due to endogenous reactivation
20	e	Behaviour change function depending on the prevalence of both sensitive and MDR strain
21	l	The average effectiveness of existing self-preventive measures.
22	a	Fast progression for educated individuals to MDR infectious class
23	b	Fast progression for educated individuals to drug sensitive infectious class
24	η	Rate of dissemination of information about the disease in the population
24	$q_i(i = 1, 2)$	Proportion of individuals who are treated in early latent and long latent respectively
25	$\sigma_i(i = 1, 2)$	Treatment rate for early latent and long latent respectively
26	h	Acquired immunity due to previous treatment
27	j	Rate that indicates people will join long latent after 2 years

The governing non linear ordinary differential equation for the above dynamics of the disease.

With the above assumptions and relations between different compartments as indicated in Figure (3.1) the dynamics of the two strain model can be ruled by the following non linear ordinary differential equations.

$$\begin{aligned}
\frac{dS}{dt} &= \Pi - \mu S - \eta e S - \lambda_s S - \lambda_r S \\
\frac{dS_E}{dt} &= \eta e S - \mu S_E - (1-l)\lambda_r S_E - (1-l)\lambda_s S_E \\
\frac{dE1}{dt} &= (1-\rho_s)\lambda_s S + (1-l)(1-b)\lambda_s S_E + h\lambda_s R - \lambda_r E_1 \\
&\quad - (1-q_1)(\gamma_s\lambda_s + k_1)E_1 - (q_1\sigma_1 + (1-q_1)j + \mu)E_1 \\
\frac{dE_2}{dt} &= (1-q_1)jE_1 - \lambda_r E_2 - (1-q_2)(k_3 + \gamma_s\lambda_s)E_2 - (q_2\sigma_2 + \mu)E_2 \\
\frac{dI_s}{dt} &= \rho_s\lambda_s S + (1-l)b\lambda_s S_E + (1-q_1)(\gamma_s\lambda_s + k_1)E_1 + \\
&\quad (1-q_2)(\gamma_s\lambda_s + k_3)E_2 - \lambda_r I_s - \phi_s I_s - (\mu + d_s)I_s \\
\frac{dE_r}{dt} &= (1-\rho_r)\lambda_r S + (1-l)(1-a)\lambda_r S_E + (1-p)\phi_s I_s - \lambda_s E_r - \\
&\quad (\gamma_r\lambda_r + k_2)E_r - \mu E_r + h\lambda_r R \\
\frac{dI_r}{dt} &= (\gamma_r\lambda_r + k_2)E_r + \rho_r\lambda_r S + \lambda_r E_1 + \lambda_r E_2 + (1-l)a\lambda_r S_E + \\
&\quad \lambda_r I_s - (\mu + d_r)I_r + \lambda_s E_r - \phi_r I_r \\
\frac{dR}{dt} &= \phi_r I_r + p\phi_s I_s + \sigma_1 E_1 + \sigma_2 E_2 - h\lambda_r R - h\lambda_s R - \mu R
\end{aligned} \tag{3.1}$$

with

$$N(t) = S(t) + S_E(t) + E_1(t) + E_2(t) + I_s(t) + E_r(t) + I_r(t) + R(t),$$

which is the total population at a given time t.

3.2 Positivity and Boundedness of a solution

For the model system (3.1) to be epidemiologically meaningful all solution of the model with positive initial data remain positive for all $t \geq 0$. Below we show the positivity and boundedness of the solution for our system.

Let $S(0) > 0, S_E(0) > 0, E_1(0) > 0, E_2(0) > 0, I_s(0) > 0, E_r(0) > 0, I_r(0) > 0$ and $R(0) >$

0 be given initial data.

Let $t^{'} = sup\{t > 0 : S(t) > 0, S_E(t) > 0, E_1(t) > 0, E_2(t) > 0, I_s(t) > 0, E_r(t) > 0, I_r(t) > 0, R(t) > 0\} \in [0, t]$.

Thus, $t^{'} > 0$.

From the first equation of System (3.1) we have

$$\frac{dS}{dt} = \Pi - \mu S - \eta eS - \lambda_s S - \lambda_r S$$

we can write

$$\frac{dS}{dt} + (\mu + \eta e + \lambda_r + \lambda_s)S = \pi$$

so that

$$S(t^{'})\exp\{\mu t^{'} + \int_0^{t^{'}}(\eta e(u) + \lambda_r(u) + \lambda_s(u))du\} - S(0) = \int_0^{t^{'}} \pi\exp\{\mu w + \int_0^{w}(\eta e(u) + \lambda_r(u) + \lambda_s(u))du\}dw$$

$$\Longrightarrow S(t^{'}) = S(0)D + D\int_0^{t^{'}} \pi\exp\{\mu w + \int_0^{w}(\eta e(u) + \lambda_r(u) + \lambda_s(u))du\}dw > 0$$

Where

$$D = \exp\{\mu t^{'} + \int_0^{t^{'}}(\eta e(u) + \lambda_r(u) + \lambda_s(u))du\} > 0$$

Therefore

$$S(t^{'}) > 0.$$

From the second equation of system (3.1)

$$\frac{dS_E}{dt} = \eta eS - \mu S_E - (1-l)\lambda_r S_E - (1-l)\lambda_s S_E$$

using similar procedure above we reach at

$$S_E(t^{'}) = S_E(0)D_E + D_E\int_0^{t^{'}} \eta e(w)S\mathbf{exp}\{\mu w + \int_0^{w}(1-l)(\lambda_r(u) + \lambda_s(u))du\}dw$$

Where,

$$D_E = \exp\{\mu t^{'} + \int_0^{t^{'}}(1-l)(\lambda_r + \lambda_s(u))du\}$$

Similarly it can be shown that $E_1(t^{'}) > 0, E_2(t^{'}) > 0, I_s(t^{'}) > 0, E_r(t^{'}) > 0, I_r(t^{'}) > 0$ and $R(t^{'}) > 0$

From our assumption for $t^{'}$,we have $t^{'} = \infty$. Because if $t^{'} < \infty$,then one of the state variables should be zero at $t^{'}$ but this is not.
$\Longrightarrow t^{'} = \infty$
Therefore all of the state variables of our model system (3.1) are positive for all $t > 0$ given any positive initial conditions.

Now adding the eight equations in the system (3.1) we get the following

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dS_E}{dt} + \frac{dE_1}{dt} + \frac{dE_2}{dt} + \frac{dI_s}{dt} + \frac{dE_r}{dt} + \frac{dI_r}{dt} + \frac{dR}{dt}$$
$$\Longrightarrow \frac{dN}{dt} = \pi - \mu N - (d_s I_s + d_r I_r) \leq \pi - \mu N$$

From which we can deduce that

$$N(t) = N(0)e^{-\mu t} + \frac{\pi}{\mu}(1 - e^{-\mu t})$$

$$\lim_{t->\infty} N(t) \leq \frac{\pi}{\mu}$$

which implies that the trajectories of model system (3.1) are bounded. In particular

$$N(t) \leq \frac{1}{e^{\mu t}}[\frac{\pi}{\mu}e^{\mu t} + (N(0) - \frac{\pi}{\mu})] \leq \frac{\pi}{\mu} \qquad \textbf{if} \quad N(0) \leq \frac{\pi}{\mu}$$

Thus the set

$$\Omega = \{(S(t), S_E(t), E_1(t), E_2(t), I_s(t), E_r(t), I_r(t), R(t)) \in R_+^8 : N \leq \frac{\pi}{\mu}\}$$

is positively invariant and attractive.The right hand sides of the system (3.1) is smooth, so the system with initial conditions have unique solutions that exists in Ω.Thus the model is mathematically and epidemiologically well posed.

3.3 Local stability of disease free equilibrium

In the absence of infection($i.e \quad E_1 = E_2 = I_s = E_r = I_r = 0$), the system of equation (3.1) has a disease free equilibrium E^0, given by

$$E^0 = (S^0, S_E^0, E_1^0, E_2^0, I_s^0, E_r^0, I_r^0, R^0) = (\frac{\pi}{\mu}, 0, 0, 0, 0, 0, 0, 0)$$

Definition 3.3.1. *The basic reproduction number is the number of secondary infections produced by a single infection introduced in a completely susceptible population.*
The effective reproduction number is the number of secondary infections produced by a single infection introduced in a completely susceptible population when interventions are in place.

Now we use next generation matrix to compute the effective reproduction number, R_e. Which will help us in studying stability of an equilibrium.
From the next generation matrix method we obtain the following matrices.

$$f = \begin{pmatrix} f_{E_1} \\ f_{E_2} \\ f_{I_s} \\ f_{E_r} \\ f_{I_r} \\ f_S \\ f_{S_E} \\ f_R \end{pmatrix} = \begin{pmatrix} (1-\rho_s)\lambda_s S + (1-l)(1-b)\lambda_s S_E + h\lambda_s R \\ 0 \\ \rho_s\lambda_s S + (1-l)b\lambda_s S_E \\ (1-\rho_r)\lambda_r S + (1-l)(1-a)\lambda_r S_E + (1-p)\phi_s T_s + h\lambda_r R \\ \rho_r\lambda_r S + (1-l)a\lambda_r S_E \\ 0 \\ 0 \\ 0 \end{pmatrix} \tag{3.2}$$

$$r = \begin{pmatrix} r_{E_1} \\ r_{E_2} \\ r_{I_s} \\ r_{E_r} \\ r_{I_r} \\ r_S \\ r_{S_E} \\ r_R \end{pmatrix} = \begin{pmatrix} \lambda_r E_1 + (1-q_1)jE_1 + (1-q_1)(\gamma_s\lambda_s + k_1)E_1 + \mu E_1 + q_1\sigma_1 E_1 \\ (1-q_2)(\gamma_s\lambda_s + k_3)E_2 + \lambda_r E_2 + q_2\sigma_2 E_2 + \mu E_2 - (1-q_1)jE_1 \\ \lambda_r I_s + \phi_s I_s + (\mu + d_s)I_s - (1-q_2)(\gamma_s\lambda_s + k_3)E_2 - (1-q_1)(k_1 + \gamma_s\lambda_s)E_1 \\ (\gamma_r\lambda_r + k_2)E_r + \lambda_s E_r + \mu E_r \\ (\phi_r + \mu + d_r)I_r - (\gamma_r\lambda_r + k_2)E_r - \lambda_s E_r - \lambda_r E_1 - \lambda_r I_s - \lambda_r E_2 \\ \lambda_r S + \lambda_s S + \eta e S + \mu S - \pi \\ (1-l)a\lambda_r S_E + (1-l)b\lambda_s S_E + \mu S_E - \eta e S \\ h\lambda_r R + h\lambda_s R + \mu R - p\phi_s I_s - \phi_r I_r - q_1\sigma_1 E_1 - q_2\sigma_2 E_2 \end{pmatrix}$$

Now we find the Jacobian matrix of f and r with respect to E_1, E_2, I_s, E_r, I_r as infected classes evaluated at E^0, the disease free equilibrium. Doing so we get the following:

$$F = \begin{pmatrix} 0 & 0 & (1-\rho_s)c\beta_s & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & c\rho_s\beta_s & 0 & 0 \\ 0 & 0 & 0 & 0 & (1-\rho_r)c\beta_r \\ 0 & 0 & 0 & 0 & c\rho_r\beta_r \end{pmatrix} = \begin{pmatrix} F_1 & 0 \\ 0 & F_2 \end{pmatrix}$$

$$V = \begin{pmatrix} c_1 & 0 & 0 & 0 & 0 \\ -(1-q_1)j & (1-q_2)k_3 + q_2\sigma_2 + \mu & 0 & 0 & 0 \\ -(1-q_1)k_1 & -(1-q_2)k_3 & \phi_s + \mu + d_s & 0 & 0 \\ 0 & 0 & 0 & k_2 + \mu & 0 \\ 0 & 0 & 0 & -k_2 & \phi_{r'} + \mu + d_r \end{pmatrix} = \begin{pmatrix} V_1 & 0 \\ 0 & V_3 \end{pmatrix},$$

where,

$c_1 = (1-q_1)j + (1-q_1)k_1 + \mu + q_1\sigma_1$

Then,

$$R_e = \rho(FV^{-1}),$$

where ρ is the spectral radius of the matrix FV^{-1}. The eigenvalues of FV^{-1} is the eigenvalues of $F_1V_1^{-1}$ and $F_2V_2^{-1}$.

$i.e, \quad R_s = \rho(F_1 V_1^{-1})$

$$\Rightarrow \qquad R_s = \frac{c\beta_s(1-\rho_s)[(1-q_1)(1-q_2)k_3 j + (1-q_1)k_1((1-q_2)k_3 + q_2\sigma_2 + \mu)]}{((1-q_1)j + (1-q_1)k_1 + \mu + q_1\sigma_1)(\phi_s + \mu + d_s)((1-q_2)k_3 + q_2\sigma_2 + \mu)}$$

$$+ \quad \frac{\rho_s c\beta_s}{\phi_s + \mu + d_s}$$

Similarly,

$R_r = \rho(F_2 V_2^{-1})$

$$\Rightarrow \qquad R_r = \frac{c\beta_r(k_2 + \rho_r\mu)}{(k_2+\mu)(\phi_r + \mu + d_r)}$$

Now, the effective reproduction number R_e given by

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

where R_s and R_r are reproduction numbers for drug sensitive TB strain only and MDR-TB strain only respectively.

Theorem 3.1. *The disease free equilibrium E^0 of model system (3.1) is locally asymptotically stable if $R_e < 1$. ,i.e $R_s < 1 \quad and \quad R_r < 1$, and unstable if $R_e > 1, i.e \quad R_s > 1 \quad or \quad R_r > 1$.*

Proof. Let

$$X = (E_1, E_2, I_s, E_r, I_r, S, S_E, R)$$

and

$$f \quad \text{and} \quad r \quad \text{are as defined below,}$$

$f(x)$ is the vector which represents the rate of new infections in the population with $f_i(x)$, the rate of appearance of new infections in compartment i.

$$r(x) = r_i^-(x) - r_i^+(x),$$

where
$r_i^+(x)$ is the rate of transfer of individuals into compartment i,by all other means other than $f_i(x)$
$r_i^-(x)$ represents the rate of transfer of individuals out of compartment i,
where $i = E_1, E_2, I_s, E_r, I_r, S, S_E, R$

Define $X_s = \{x \geq 0 \mid x_i = 0, i = E_1, E_2, I_s, E_r, I_r\}$ Then,we show the following conditions.

A1. Suppose $x \geq 0$, Since each rate represents the transfer of individuals from one compartment to other, we have $f, r^+, r^- \geq 0$.

A2. Suppose $x_i = 0$, then the ith compartment is zero. which implies no transfer out of this ith compartment. Therefore $r_i^-(x) = 0$.

A3. For $i = S, S_E, R$,
Each compartment is uninfected class,which implies no new infectious is introduced to these classes.$i.e f_i = 0, for \quad i = S, S_E, R.$

A4. Suppose $x \in X_s$, then $f_i(x) = 0$ and $r_i^+ = 0$ for $i = E_1, E_2, I_s, E_r, I_r$.
This condition proves invariance of the disease free subspace.

A5. Let the column matrix of (3.2) is set to zero. Then the Jacobian matrix of the system becomes

$$Df(E_0) = \begin{pmatrix} a_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ (1-q_1)j & a_2 & 0 & 0 & 0 & 0 & 0 & 0 \\ (1-q_1)k1 & (1-q_2)k_3 & a_3 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & a_4 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & k2 & a_5 & 0 & 0 & 0 \\ 0 & 0 & -c\beta_s & 0 & -c\beta_r & a_6 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & a_7 & 0 \\ \sigma_3 & \sigma_4 & 0 & 0 & 0 & 0 & 0 & a_8 \end{pmatrix}$$

, where

$$a_1 = -((1-q_1)k1 + (1-q_1)j + \mu)$$

$$a_2 = -((1-q_2)k_3 + q_2\sigma_2 + \mu)$$

$$a_3 = -(\phi_s + \mu + d_s)$$

$$a_4 = -(k2 + \mu)$$

$$a_5 = -(\phi_r + \mu + d_r)$$

$$a_6 = a_7 = a_8 = -\mu$$

are eigenvalues which are all negative, since all the parameters are positive. Therefore by Theorem in [18], the disease free equilibrium, E_0, is locally asymptotically stable when $R_e < 1$ and unstable when $R_e > 1$. □

3.4 Drug sensitive TB only endemic equilibrium

An equilibrium which exists only when drug sensitive strain is present

i.e $E_r = I_r = 0$

The system of equation reduces to:

$$\frac{dS}{dt} = \Pi - \mu S - \eta e S - \lambda_s S$$
$$\frac{dS_E}{dt} = \eta e S - \mu S_E - (1-l)\lambda_s S_E$$

$$\begin{aligned}
\frac{dE1}{dt} &= (1-\rho_s)\lambda_s S + (1-l)(1-b)\lambda_s S_E + h\lambda_s R - \\
&\quad (1-q_1)(\gamma_s\lambda_s + k_1)E_1 - (q_1\sigma_1 + (1-q_1)j + \mu)E_1 \\
\frac{dE_2}{dt} &= (1-q_1)jE_1 - (1-q_2)(k_3+\gamma_s\lambda_s)E_2 - (q_2\sigma_2+\mu)E_2 \\
\frac{dI_s}{dt} &= \rho_s\lambda_s S + (1-l)b\lambda_s S_E + (1-q_2)(\gamma_s\lambda_s+k_3)E_2 + \\
&\quad (1-q_1)(\gamma_s\lambda_s+k_1)E_1 - (\phi_s+\mu+d_s)I_s \\
\frac{dR}{dt} &= p\phi_s I_s + q_1\sigma_1 E_1 + q_2\sigma_2 E_2 - h\lambda_s R - \mu R
\end{aligned} \tag{3.3}$$

with,

$$e(t) = \frac{P_s^n}{P_{s_*}^n + P_s^n} = \frac{\lambda_s^n}{\lambda_{s_0}^n + \lambda_s^n} \quad ,$$

substituting $\lambda_s = c\beta_s P_s$, where $P_s = \frac{I_s}{N}$

The drug sensitive TB only equilibrium in terms of the equilibrium value of the force of infection λ_s^* is given by

$$E^* = (S^*, S_E^*, E_1^*, E_2^*, I_s^*, R^*)$$

Where,

$$S^* = \frac{\pi(\lambda_{s_0}^n + (\lambda_s^*)^n)}{((\lambda_s^*)^{n+1} + \mu(\lambda_s^*)^n + \lambda_{s_0}^n\lambda_s^* + \mu\lambda_{s_0}^n + \eta(\lambda_s^*)^n)}$$

$$S_E^* = \frac{\pi\eta(\lambda_s^*)^n}{(\mu+(1-l)(\lambda_s^*))\left[((\lambda_s^*)^{n+1} + \mu(\lambda_s^*)^n + \lambda_{s_0}^n\lambda_s^* + \mu\lambda_{s_0}^n + \eta(\lambda_s^*)^n)\right]}$$

$$E_1^* = \frac{Z_1(\lambda_s^*)^{n+4} + Z_2(\lambda_s^*)^{n+3} + Z_3(\lambda_s^*)^{n+2} + Z_4(\lambda_s^*)^{n+1} + Z_5(\lambda_s^*)^4 + Z_6(\lambda_s^*)^3 + Z_7(\lambda_s^*)^2 + Z_8\lambda_s^*}{(\mu+(1-l)\lambda_s^*)(\mu((\lambda_{s_o})^n + (\lambda_s^*)^n)) + \lambda_s((\lambda_{s_0})^n + (\lambda_s^*)^n) + \eta(\lambda_s^*)^n)(Q_1(\lambda_s^*)^3 + Q_2(\lambda_s^*)^2 + Q_3\lambda_s^* + Q_4)}$$

$$E_2^* = \frac{Z_9(\lambda_s^*)^{n+3} + Z_{10}(\lambda_s^*)^{n+2} + Z_{11}(\lambda_s^*)^{n+1} + Z_{12}(\lambda_s^*)^3 + Z_{13}(\lambda_s^*)^2 + Z_{14}\lambda_s^*}{(\mu+(1-l)\lambda_s^*)(\mu((\lambda_{s_o})^n + (\lambda_s^*)^n)) + \lambda_s((\lambda_{s_0})^n + (\lambda_s^*)^n) + \eta(\lambda_s^*)^n)(Q_1(\lambda_s^*)^3 + Q_2(\lambda_s^*)^2 + Q_3\lambda_s^* + Q_4)}$$

$$I_s^* = \frac{Z_{15}(\lambda_s^*)^{n+5} + Z_{16}(\lambda_s^*)^{n+4} + Z_{17}(\lambda_s^*)^{n+3} + Z_{18}(\lambda_s^*)^{n+2} + Z_{19}(\lambda_s^*)^{n+1} + Z_{20}(\lambda_s^*)^5 + Z_{21}(\lambda_s^*)^4 + Z_{22}(\lambda_s^*)^3 + Z_{23}(\lambda_s^*)^2 + Z_{24}\lambda_s^*}{(\mu+(1-l)\lambda_s^*)(\mu((\lambda_{s_o})^n + (\lambda_s^*)^n)) + \lambda_s((\lambda_{s_0})^n + (\lambda_s^*)^n) + \eta(\lambda_s^*)^n)(Q_1(\lambda_s^*)^3 + Q_2(\lambda_s^*)^2 + Q_3\lambda_s^* + Q_4)}$$

$$R^* = \frac{Z_{25}(\lambda_s^*)^{n+4} + Z_{26}(\lambda_s^*)^{n+3} + Z_{27}(\lambda_s^*)^{n+2} + Z_{28}(\lambda_s^*)^{n+1} + Z_{29}(\lambda_s^*)^4 + Z_{30}(\lambda_s^*)^3 + Z_{31}(\lambda_s^*)^2 + Z_{32}\lambda_s^*}{(\mu+(1-l)\lambda_s^*)(\mu((\lambda_{s_o})^n + (\lambda_s^*)^n)) + \lambda_s((\lambda_{s_0})^n + (\lambda_s^*)^n) + \eta(\lambda_s^*)^n)(Q_1(\lambda_s^*)^3 + Q_2(\lambda_s^*)^2 + Q_3\lambda_s^* + Q_4)} \tag{3.4}$$

where,

$$
\begin{aligned}
A_1 &= q_1\sigma_1 + (1-q_1)k_1 + (1-q_1)j + \mu \\
A_2 &= (1-q_2)k_3 + q_2\sigma_2 + \mu \\
A_3 &= \phi_s + \mu + d_s \\
A_{12} &= \pi\rho_s\mu + (1-l)b\pi\eta \\
A_7 &= \pi\mu(1-\rho_s) + (1-l)(1-b)\pi\eta \\
A_9 &= \pi\mu(1-\rho_s)(\lambda_{s_0})^n \\
A_8 &= \pi(1-\rho_s)(\lambda_{s_0})^n \\
Z_1 &= (1-q_2)A_3\gamma_s h\pi(1-\rho_s) - (1-q_2)ph\phi_s\gamma_s\pi\rho_s \\
Z_2 &= (1-q_2)A_7A_3\gamma_s h + A_3((1-q_2)\gamma_s\mu + A_2h)\pi(1-\rho_s) - (1-q_2)A_{12}ph\phi_s\gamma_s - A_2ph\phi_s\pi\rho_s \\
Z_3 &= A_7A_3((1-q_2)\gamma_s\mu + A_2h) + A_3A_2\pi(1-\rho_s)\mu - A_{12}A_2ph\phi_s \\
Z_4 &= A_7A_3A_2\mu \\
Z_5 &= (1-q_2)A_8A_3h\gamma_s - (1-q_2)\pi\rho_s\lambda_{s_0}^n ph\phi_s\gamma_s \\
Z_6 &= (1-q_2)A_9A_3h\gamma_s + A_8A_3((1-q_2)\gamma_s\mu + A_2h) - (1-q_2)\pi\rho_s\lambda_{s_0}^n\mu p\phi_s h\gamma_s - A_2ph\phi_s\pi\rho_s\lambda_{s_0}^n \\
Z_7 &= A_9A_3((1-q_2)\gamma_s\mu + A_2h) + A_8A_3A_2\mu - \pi\rho_s\lambda_{s_0}^n\mu A_2ph\phi_s \\
Z_8 &= A_9A_3A_2\mu \\
Z_9 &= A_3(1-q_1)jh\pi(1-\rho_s) - (1-q_1)jph\pi\phi_s\rho_s \\
Z_{10} &= A_3(1-q_1)jhA_7 - A_{12}(1-q_1)jph\phi_s + A_3(1-q_1)j\mu\pi(1-\rho_s) \\
Z_{11} &= (1-q_1)A_3A_7j\mu \\
Z_{12} &= -(1-q_1)\pi\rho_s jph\phi_s\lambda_{s_0}^n + (1-q_1)jA_3hA_8 \\
Z_{13} &= A_3A_9(1-q_1)jh + (1-q_1)A_3A_8j\mu - (1-q_1)jph\phi_s\pi\rho_s\lambda_{s_0}^n\mu \\
Z_{14} &= (1-q_1)A_3A_9j\mu \\
Z_{15} &= (1-q_1)(1-q_2)h\gamma_s^2\pi \\
Z_{16} &= (1-q_1)(1-q_2)A_7h\gamma_s^2 + (1-q_1)(1-q_2)\pi(1-\rho_s)(jh\gamma_s + \mu\gamma_s^2 + \\
&\qquad h\gamma_s k_1) + (1-q1)\pi(1-\rho_s)hA_2\gamma_s + (1-q_1)(1-q_2)A_{12}h\gamma_s^2 + \\
&\qquad \pi\rho_s(q_1(1-q_2)h\sigma_1\gamma_s + (1-q_1)(1-q_2)\mu\gamma_s^2 + \\
&\qquad (1-q_2)hA_1\gamma_s - (1-q_1)hA_2\gamma_s)
\end{aligned}
$$

$$
\begin{aligned}
Z_{17} &= (1-q_1)(1-q_2)A_7(jh\gamma_s + \mu\gamma_s^2 + h\gamma_s k_1) + A_7(1-q1)hA_2\gamma_s + \\
&\quad \pi(1-\rho_s)(1-q_1)(1-q_2)(j\gamma_s\mu + jhk_3 + \mu\gamma_s k_1) + \pi(1-\rho_s)(1-q_1)(\mu A_2\gamma_s + A_2hk_1) + \\
&\quad A_{12}(q_1(1-q_2)\sigma_1 h\gamma_s + (1-q_1)(1-q_2)\mu\gamma_s^2 + (1-q_2)h\gamma_s A_1 + \\
&\quad (1-q_1)hA_2\gamma_s) + \pi\rho_s(q_2(1-q_1)jh\sigma_2 + q_1\sigma_1 hA_2 + (1-q_2)\mu\gamma_s A_1 + \\
&\quad (1-q_1)\mu\gamma_s A_2 + A_1A_2h) \\
Z_{18} &= A_7(1-q_1)(1-q_2)(j\gamma_s\mu + jhk_3 + \mu\gamma_s k_1) + A_7(1-q_1)(\mu A_2\gamma_s + A_2hk_1) + \\
&\quad \pi(1-\rho_s)((1-q_1)(1-q_2)jk_3\mu + (1-q_1)A_2k_1\mu) \\
&\quad + A_{12}(q_2(1-q_1)jh\sigma_2 + q_1\sigma_1 hA_2 + (1-q_2)\mu\gamma_s A_1) + (1-q_1)\mu\gamma_s A_2 + A_1A_2h) - \\
&\quad \pi\rho_s A_2A_1\mu \\
Z_{19} &= A_7((1-q_1)(1-q_2)jk_3\mu + (1-q_1)A_2k_1\mu) + A_{12}A_2A_1\mu \\
Z_{20} &= (1-q_1)(1-q_2)A_8h\gamma_s^2 + (1-q_1)(1-q_2)\pi\rho_s\lambda_{s_0}^n h\gamma_s^2 \\
Z_{21} &= (1-q_1)(1-q_2)A_9h\gamma_s^2 + A_8(1-q_1)(1-q_2)(jh\gamma_s + \mu\gamma_s^2 + h\gamma_s k_1) + \\
&\quad A_8(1-q_1)hA_2\gamma_s + (1-q_1)(1-q_2)h\gamma_s^2\pi\rho_s\lambda_{s_0}^n\mu + \\
&\quad \pi\rho_s\lambda_{s_0}^n(q_1(1-q_1)\sigma_1 h\gamma_s + (1-q_1)(1-q_2)\mu\gamma_s^2 + (1-q_2)h\gamma_s A_1 + (1-q_1)hA_2\gamma_s) \\
Z_{22} &= A_9(1-q1)(1-q2)(jh\gamma_s + \mu\gamma_s^2 + h\gamma_s k_1) + A_9(1-q_1)hA_2\gamma_s + \\
&\quad A_8(1-q_1)(1-q_2)(j\gamma_s\mu + jhk_3 + \mu\gamma_s k_1) + A_8(1-q_1)(\mu A_2\gamma_s + A_2hk_1) + \\
&\quad \pi\rho_s\lambda_{s_0}^n\mu(q_1(1-q_2)\sigma_1 h\gamma_s + (1-q_1)(1-q_2)\mu\gamma_s^2 + \\
&\quad (1-q_2)h\gamma_s A_1 + (1-q_1)hA_2\gamma_s) + \\
&\quad \pi\rho_s\lambda_{s_0}^n(q_2(1-q_1)jh\sigma_2 + q_1\sigma_1 hA_2 + (1-q_2)\mu\gamma_s A_1 + (1-q_1)\mu\gamma_s A_2 + A_1A_2h) \\
Z_{23} &= A_9(1-q_1)(1-q_2)(j\gamma_s\mu + jhk_3 + \mu\gamma_s k_1) + A_9(1-q_1)(\mu A_2\gamma_s + \\
&\quad A_2hk_1) + A_8((1-q_1)(1-q_2)jk_3\mu + (1-q_1)A_2k_1\mu) + \\
&\quad \pi\rho_s\lambda_{s_0}^n\mu(q_2(1-q_1)jh\sigma_2 + q_1\sigma_1 hA_2 + (1-q_2)\mu\gamma_s A_1 + (1-q_1)\mu\gamma_s A_2 - A_1A_2h) + \\
&\quad \pi\rho_s\lambda_{s_0}^n A_2A_1\mu \\
Z_{24} &= A_9((1-q_1)(1-q_2)jk_3\mu + (1-q_1)A_2k_1\mu) + \pi\rho_s\lambda_{s_0}^n\mu A_2A_1\mu \\
Z_{25} &= (1-q_1)(1-q_2)p\phi_s\gamma_s^2\pi(1-\rho_s) - \pi\rho_s p\phi_s\gamma_s^2(1-q_1)(1-q_2) \\
Z_{26} &= -A_7(1-q_1)(1-q_2)p\phi_s\gamma_s^2 - \pi(1-\rho_s)((1-q_1)(1-q_2)jp\phi_s\gamma_s + \\
&\quad (1-q_1)(1-q_2)p\phi_s\gamma_s k_1 + (1-q_1)p\phi_s A_2\gamma_s + q_1(1-q_2)A_3\sigma_1\gamma_s) \\
&\quad - (1-q_1)(1-q_2)A_{12}p\phi_s\gamma_s^2 - \pi\rho_s p\phi_s((1-q_2)\gamma_s A_1 + (1-q_1)A_2\gamma_s) \\
Z_{27} &= -A_7((1-q_1)(1-q_2)jp\phi_s\gamma_s + (1-q_1)(1-q_2)p\phi_s\gamma_s k_1 + (1-q_1)p\phi_s A_2\gamma_s + \\
&\quad q_1(1-q_2)A_3\sigma_1\gamma_s) - \pi(1-\rho_s)((1-q_1)(1-q_2)jp\phi_s k_3 + (1-q_1)q_2j\sigma_2 A_3 + \\
&\quad (1-q_1)p\phi_s A_2k_1 + q_1A_3\sigma_1A_2) - A_{12}p\phi_s((1-q_2)\gamma_s A_1 + (1-q_1)A_2\gamma_s) - \\
&\quad \pi\rho_s p\phi_s A_2A_1
\end{aligned}
$$

$$
\begin{aligned}
Z_{28} &= -A_7((1-q_1)(1-q_2)jp\phi_s k_3 + q_2(1-q_1)j\sigma_2 A_3 + (1-q_1)p\phi_s A_2 k_1 + q_1 A_3\sigma_1 A_2) - \\
&\quad A_{12}p\phi_s A_2 A_1 \\
Z_{29} &= -A_8(1-q_1)(1-q_2)p\phi_s\gamma_s^2 - (1-q_1)(1-q_2)\pi\rho_s\lambda_{s_0}^n p\phi_s\gamma_s^2 \\
Z_{30} &= -A_9(1-q_1)(1-q_2)p\phi_s\gamma_s^2 - A_8(1-q_1)(1-q_2)p\phi_s\gamma_s^2 - \\
&\quad \pi\rho_s\lambda_{s_0}^n\mu(1-q_1)(1-q_2)p\phi_s\gamma_s^2 - \pi\rho_s\lambda_{s_0}^n p\phi_s((1-q_2)\gamma_s A_1 + (1-q_1)A_2\gamma_s) \\
Z_{31} &= -A_9(1-q_1)(1-q_2)p\phi_s\gamma_s^2 - A_8((1-q_1)(1-q_2)jp\phi_s k_3 + \\
&\quad q_2(1-q_1)j\sigma_2 A_3 + (1-q_1)p\phi_s A_2 k_1 + q_1 A_3\sigma_1 A_2) - \pi\rho_s\lambda_{s_0}^n\mu p\phi_s((1-q_2)\gamma_s A_1 + \\
&\quad (1-q_1)A_2\gamma_s) - \pi\rho_s\lambda_{s_0}^n p\phi_s A_2 A_1 \\
Z_{32} &= -A_9((1-q_1)(1-q_2)jp\phi_s k_3 + q_2(1-q_1)j\sigma_2 A_3 + (1-q_1)p\phi_s A_2 k_1 + q_1 A_3\sigma_1 A_2) \\
&\quad - \pi\rho_s\lambda_{s_0}^n\mu p\phi_s A_2 A_1 \\
Q_1 &= (1-q_1)(1-q_2)[A_3 h\gamma_s^2 + ph\phi_s\gamma_s^2] \\
Q_2 &= (1-q_1)(1-q_2)jph\phi_s\gamma_s + A_3((1-q_1)(1-q_2)\mu\gamma_s^2 + (1-q_2)h\gamma_s A_1 + (1-q_1)hA_2\gamma_s) + \\
&\quad ph\phi_s(1-q_1)((1-q_2)\gamma_s k_1 + A_2\gamma_s) + q_1(1-q_2)\sigma_1 A_3 h\gamma_s \\
Q_3 &= (1-q_1)(1-q_2)jp\phi_s hk_3 + A_3((1-q_2)\mu\gamma_s A_1 + (1-q_1)\mu A_2\gamma_s + A_2 A_1 h) + \\
&\quad (1-q_1)q_2 j\sigma_2 A_3 h + (1-q_1)p\phi_s hA_2 k_1 + q_1\sigma_1 A_2 A_3 h \\
Q_4 &= A_3 A_2 A_1\mu
\end{aligned}
$$

and λ_s^* is a positive real root of the following polynomial which we get by substituting E^* in to $\lambda_s^* = \frac{c\beta_s I_s^*}{N}$

$$
\begin{aligned}
&M_1(\lambda_s^*)^{n+6} + M_2(\lambda_s^*)^{n+5} + M_3(\lambda_s^*)^{n+4} + M_4(\lambda_s^*)^{n+3} + M_5(\lambda_s^*)^{n+2} + M_6(\lambda_s^*)^{n+1} + M_7(\lambda_s^*)^6 + \\
&\quad M_8(\lambda_s^*)^5 + M_9(\lambda_s^*)^4 + M_{10}(\lambda_s^*)^3 + M_{11}(\lambda_s^*)^2 + M_{12}\lambda_s^*
\end{aligned} \tag{3.5}
$$

Where,

$$
\begin{aligned}
M_1 &= Z_{15} \\
M_2 &= (1-l)\pi Q_1 + Z_1 + Z_{16} + Z_{25} - c\beta_s Z_{15} \\
M_3 &= (1-l)\pi Q_2 + \pi\mu Q_1 + \pi\eta Q_1 + Z_2 + Z_9 + Z_{17} + Z_{26} - c\beta_s Z_{16} \\
M_4 &= (1-l)\pi Q_3 + \pi\mu Q_2 + \pi\eta Q_2 + Z_3 + Z_{10} + Z_{18} + Z_{27} - c\beta_s Z_{17} \\
M_5 &= (1-l)\pi Q_4 + \pi\mu Q_3 + \pi\eta Q_3 + Z_4 + Z_{11} + Z_{19} + Z_{28} - c\beta_s Z_{18} \\
M_6 &= \pi\mu Q_4 + \pi\eta Q_4 - c\beta_s Z_{19}
\end{aligned}
$$

$$
\begin{aligned}
M_7 &= Z_{20} \\
M_8 &= (1-l)\pi\lambda_{s_0}^n Q_1 + Z_5 + Z_{21} + Z_{29} - c\beta_s Z_{20} \\
M_9 &= (1-l)\pi Q_2\lambda_{s_0}^n + \pi Q_1\mu\lambda_{s_0}^n + Z_6 + Z_{12} + Z_{22} + Z_{30} - c\beta_s Z_{21} \\
M_{10} &= (1-l)\pi Q_3\lambda_{s_0}^n + \pi Q_2\mu\lambda_{s_0}^n + Z_7 + Z_{13} + Z_{22} + Z_{31} - c\beta_s Z_{22} \\
M_{11} &= (1-l)\pi Q_4\lambda_{s_0}^n + \pi Q_3\mu\lambda_{s_0}^n + Z_8 + Z_{24} + Z_{32} - c\beta_s Z_{23} \\
M_{12} &= \pi Q_4\lambda_{s_0}^n\mu - c\beta_s Z_{24}
\end{aligned}
$$

Because of the complicated expression for the equilibrium points and the dynamics at all it is some what complicated to see the behaviour of the dynamics analytically, so we directly go to numerical solutions to capture some of the behaviour of the solutions. We try to see first the behaviour of the dynamics when only the drug sensitive tuberculosis exists in the population with different interventions and also we try to see the role of this interventions in the dynamics. Then we see the dynamics of the model when both the strains circulate in the population. In this section we try to focus on cases more attributable for the spread of the drug resistant strain and the role of the interventions which exist in our model to minimize or stop, if possible, the spread of the resistant strain.

For the numerical simulation purpose we collected some values for the parameters in our model from data of tuberculosis in Ethiopia which are recorded and we get few of them from different articles, some we simply assumed. So may not exactly represent the situation of the disease on ground here in Ethiopia. The parameters used for the simulation purposes are listed in the table (3.2) with their values.

parameter	Values	Source
π	2626762	[29]
μ	0.01769	$\frac{1}{56.19}$
c	10	Assumed
d_s	0.0266	[10]
d_r	0.3	[17]
β_s	0.2	[1]
β_r	0.3	[17]
k_1	0.03	[17]
k_2	0.05	[17]
k_3	0.0002	[16]
ρ_s	0.2	[17]
ρ_r	0.1	[17]
γ_s	0.4	[17]
γ_r	0.02	[17]
ϕ_s	Variable	[0,1]
ϕ_r	Variable	[0,1]
a	0.01	Assumed
b	0.05	Assumed
l	0.6	assumed
j	0.5	Estimated
σ_1	variable	$\in [0, 1]$
σ_2	variable	$\in [0, 1]$
η	0.18	[14]
h	0.99	Assumed
p	0.8	[28]

Table 3.2: Parameters used for the simulation results

In addition to the above parameters we take the following initial population of Ethiopia which corresponds to the year 2011 which we take for $t = 0$(initial time) and for the purpose of the numerical results we partitioned the total population, $84,734,262$, in the following manner. We assume 80% of the population are susceptible. The remaining 20% account for infection and recovered and most infections stay in latency stage. From the data in [28] we have $220,000$ infectious drug sensitive and 500 infectious drug resistant in Ethiopia. We assumed that out of the total adult susceptible population 5% is educated. So with this assumptions we have the following initial data for the simulation purpose.

$P^0 = (S^0, S_E^0, E_1^0, E_2^0, I_s^0, E_r^0, I_r^0, R^0) =$

$$(65887409, 1900000, 6000000, 9500000, 220000, 726353, 500, 500000)$$

3.4.1 The effect of treatment for latent TB On Drug sensitive TB transmission

Individuals with latent Tuberculosis infection are considered at high risk of developing active diseases during the first 2 years of infection, during which approximately 5% of individuals develop active tuberculosis[19]. We guess Therapy for recently infected individuals will help in controlling the disease transmission. For the sake of looking the effect of treatment for recently infected persons, we divided the latent class in to two and for comparison purpose we differentiated the treatment rate of the two classes. As we can see from Figure (3.2), in situations where there is no treatment for latently infected persons the disease may become endemic for $R_s < 1$ and may continue being endemic. Infectious population just raises initially then as time goes it will come to endemic state and stays in the population even if the reproduction number is less than unity. But if we just apply treatment for those latently infected individuals especially for those early infected, the scenario completely changes and the disease dies out as time goes for reproduction number is less than unity. If we ignore treatment for early latently infected but just only for long latent TB cases the disease will continue in the estate of

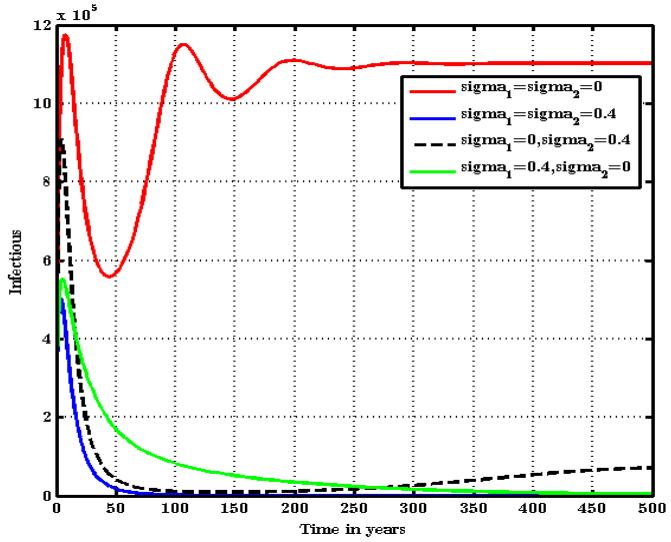


Figure 3.2: Infectious population for drug sensitive Tuberculosis with varying value of treatment for latently infected of the sensitive strain when $R_s < 1$, $\phi_s = 0.4$ and other parameters are as in the table (3.2)

endemicity similar to that of no treatment. If we give treatment for only early latent the disease still dies out. From Figure (3.2) we can also observe that treatment for early latent is a key in eliminating the disease than treatment for long latent TB cases. So from this we understand that besides the treatment given for infectious population it is important to treat early latent TB cases in controlling the disease transmission.

3.4.2 The effect of Health Education in the dynamics of the disease

In this section we try to see the role of educating people in reducing the disease. When we say educating people it mainly depends on the information dissemination rate and the efficacy of the existing self protective measures besides the behaviour change that people bring. Here we try to see the role of health education by varying the information dissemination rate. From Figure (3.3) we can observe that fixing the efficacy of the existing self protective measure and increasing the information dissemination rate we get

a decrease in the prevalence of the disease as time goes. We observed that the prevalence of the disease decreases at the picks and after a while it then come to increase but with a lower rate of increase. We suspect that this behaviour follows from the case that behaviour change of the population depends on the prevalence of the disease. So, as the number of infectious population increases the educated people start from a high pick but because of other interventions the infectious population decrease and may reach to a state that people wouldn't recognize it, in this case the number of educated compartment starts to decrease that is they start to ignore using the existing self protective measures. In this case more people will be infected now the prevalence starts to grow, this will continue to some time then starts to stabilize to some point. This shows even if we educate people with high rate, the education only by itself will not protect them from the disease so education has to be supported with self protective measures with better efficacy and other interventions like treatment must be kept high with quality.

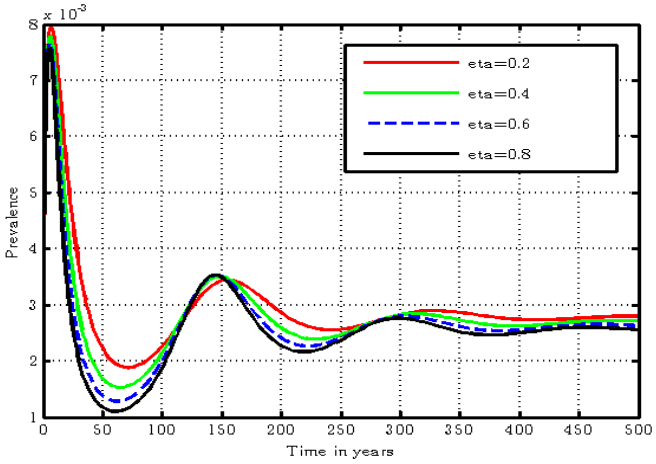
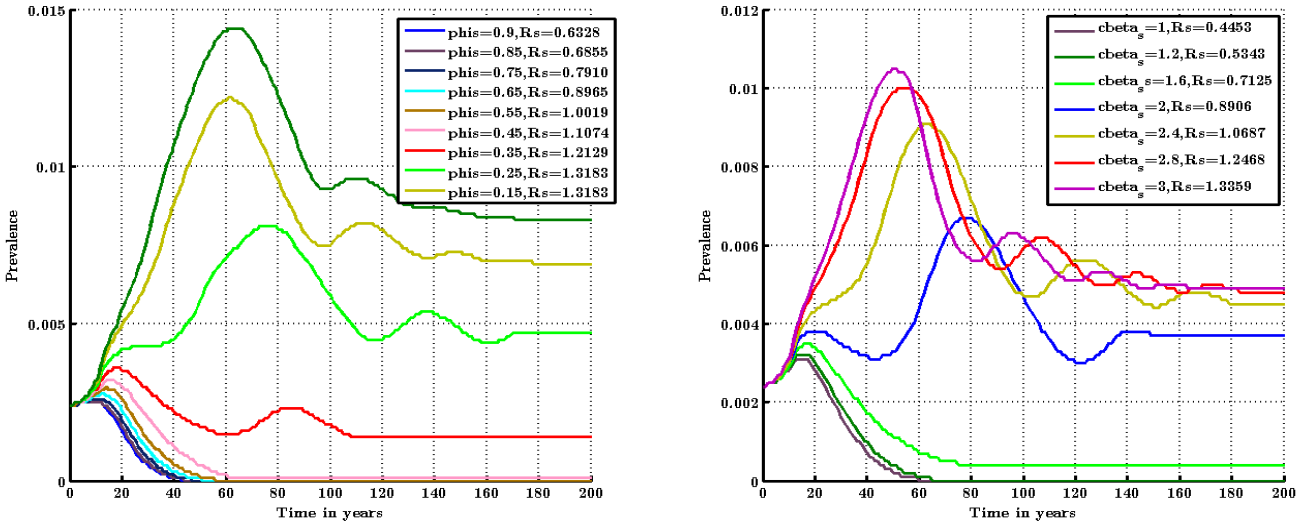


Figure 3.3: Prevalence of drug sensitive Tuberculosis for different values of η when $R_s > 1$.. for parameters are as in the table(3.2)

The reproduction number for the sensitive tuberculosis reacts more to the treatment rate for drug sensitive infectious population,ϕ_s and the transmission rate,$c\beta_s$. This is because of the nature of the disease that TB is transmitted through air so the trans-

mission depends on the way people live or the situation people passing their day to day life. That is, the disease is more transmittable where people are living very close to each other or people who are using public bus frequently have high probability of getting the disease than the one not using such a public transportation in areas where prevalence is high. From Figure (3.4) we can observe that the prevalence changes as the two parameters changes. Figure (3.4(a)) shows as the treatment rate decreases the reproduction number increases correspondingly the prevalence of the drug sensitive tuberculosis increases. But from Figure (3.4(b)) we can observe that as $c\beta_s$ increases the prevalence increases. prevalence of the sensitive strain is more sensitive to treatment rate than the transmission rate. Increasing the treatment rate to greater than 0.65 which will make the reproduction number R_s to less than 0.8965 which in turn makes the prevalence of the disease decrease and the infection can be eliminated. It also needs to make $c\beta_s$ less than 1.2 keeping treatment rate, $\phi_s = 0.4$ for the prevalence to decrease fast to zero. The transmission rate may be decreased by increasing the treatment rate as well as educating more people to protect themselves from the disease. The combination of the two parameters, increasing treatment rate for infectious population of the drug sensitive tuberculosis and decreasing the transmission rate to the above values may bring a good result in eliminating the sensitive tuberculosis.



(a) (b)

Figure 3.4: Sensitivity analysis for the drug Sensitive Tuberculosis only, with respect to (a) ϕ_s (b) $c * \beta_s$ and other parameters are as in the table(3.2)

3.4.3 Bifurcation analysis

In this section discussions about the bifurcation analysis result will depend on numerical simulations. We used the polynomial expression of the force of infection in Equation (3.5) to find the positive roots which correspond to the positive endemic equilibrium of the model and linearised matrix of the system (3.3) which will show us the local behaviour of the solutions of the nonlinear system.

Definition 3.4.1. *A hyperbolic equilibrium point is called stable if all eigenvalues of the linearised matrix evaluated at the fixed point have negative real parts.It is unstable if at least one eigenvalue of the linearised matrix evaluated at the fixed point has a positive real part.*

Because of the complicated expression for the coefficients of the polynomial, it is not easy to explicitly express the roots of the polynomial(3.5). We tried to find all possible positive roots of the polynomial by changing the parameters which are main responsi-

ble for changing the reproduction number, R_s, (which may be assumed as bifurcation parameter). We find an equilibrium point for each of the positive roots and evaluated the Jacobian matrix at this equilibrium points so that we look at the eigenvalues of the Jacobian matrix to show the local stability of the endemic equilibrium.

No	$c\beta_s$ Range	No of Endemic Equilibrium points	Stability Remarks
1	< 1.58	0	The Disease free Equilibrium is stable
2	$1.58 - 1.89$	2	The Disease free and both Endemic Equilibrium points are stable
3	$1.89 - 3.19$	3	One stable and and two unstable endemic equilibrium
4	> 3.19	1	The Disease free equilibrium point is unstable while the Endemic one is stable

Table 3.3: Summary of intervals of the transmission rate for the sensitive strain and the corresponding stabilities of the endemic equilibrium points

Changing $c\beta_s$ and keeping other parameters for the drug sensitive tuberculosis only as in the table (3.2), we have summarized the result from the numerical simulation in the table (3.3)

The case in 2 of table (3.3) where a stable Endemic equilibrium exists with a stable Disease free equilibrium point when the associated reproduction number is less than unity has important implication in disease control. In such cases solutions for this parameters may converge to the endemic equilibrium points which shows the disease may invade even if the reproduction number is less than unity. In such scenarios reduction of reproduction number to less than unity may not be a sufficient condition for a disease to be eliminated. So there will be a threshold value other than one for which the disease can be eliminated if the reproduction number is less than this threshold value. In our case we approximated the new threshold value to be 0.7036 from the numerical simulation result.

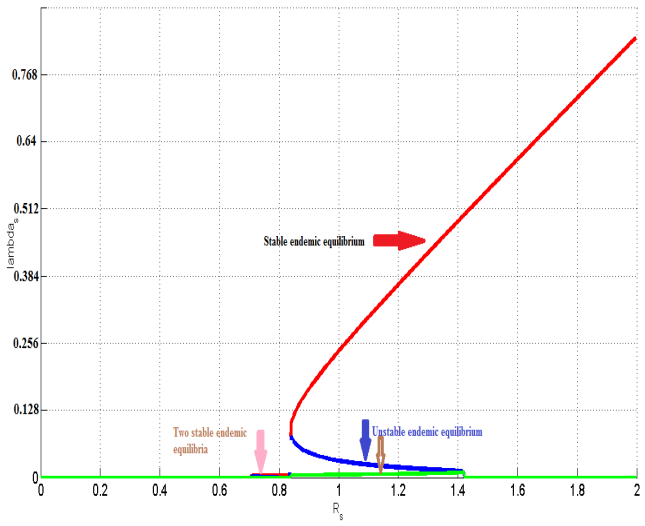


Figure 3.5: Bifurcation diagram for drug sensitive TB only model system (3.3) of force of infection λ_s^* against the drug sensitive TB only reproduction number,R_s, for set of parameters,for drug sensitive TB only,in table (3.2)

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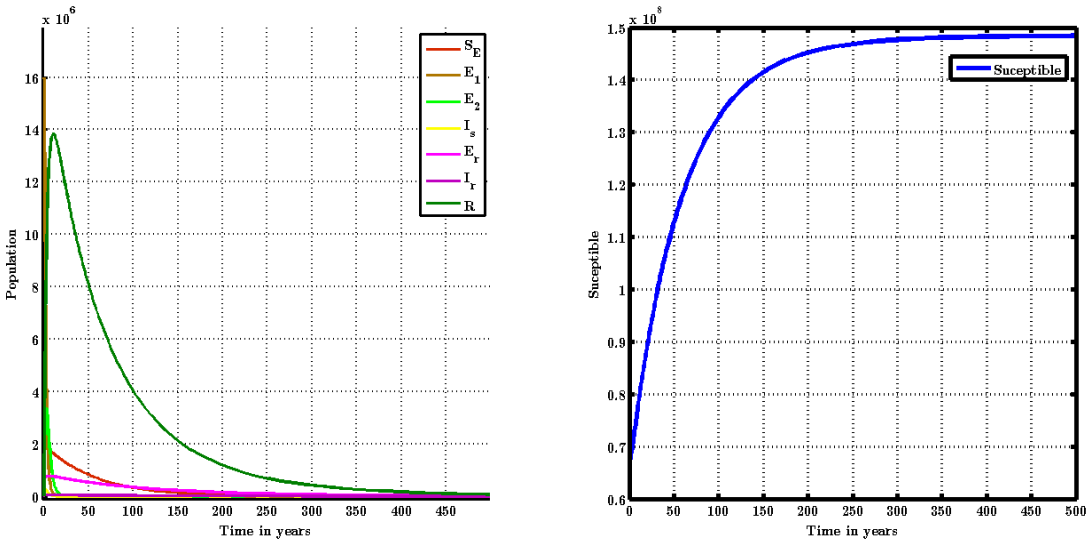
3.5 Dynamical behaviour of the two strain model

We have expressed the endemic equilibrium for the drug sensitive strain only explicitly with respect to the force of infection, λ_s, at the equilibrium point. In this section we try to see the dynamics when the two strain exist in the population. Let the endemic equilibrium when the drug sensitive and Drug resistant strain circulate in the population be denoted by:

$$E = (S, S_E, E_1, E_2, I_s, E_r, I_r, R)$$

It is a routine task to express E in terms of the force of infection explicitly. Because of the complicated dynamics when the two strain circulate in the population we use numerical results to capture some of the long term behaviour of the disease and the effect of the interventions we used on the dynamics of the disease. Here we assumed that the transmission rate of the two strain are equal. The behaviour change function, e,

depends on the prevalence of the two strain which is given by $p = \frac{I_s+I_r}{N}$, where N is the total population and we assumed that people recognize the burden of the disease when the prevalence reaches three percent of the total population so that used $p_0 = 3\%$(the state of prevalence at which people start to recognize the disease and start reaction). From the formula for the reproduction number ,i.e, $R_e = max\{R_s, R_r\}$, the strain with the largest reproduction number invade the population. Figure (3.6) shows the size of the population of all compartments in the model as time goes when the reproduction number for the two strain is less than one.



(a) (b)

Figure 3.6: Graph for the compartments in the model for $R_s < 1$ and $R_r < 1$

As we can observe from this figures except the Susceptible but not educated all other compartments converge to zero and the Susceptible but not educated converge to $\frac{\pi}{\mu}$. Which supports the result in Theorem (3.1) that the disease free equilibrium is locally asymptotically stable when $R_e < 1$..

3.5.1 The role of treatment for the resistant strain

Now a days drug resistant strain is treatable but because of the high cost of the drugs and a patient has to take the drugs for long time ,upto 2 years, with close support from doctors it needs high effort to treat the drug resistant TB. Figure (3.7) shows if we are able to increase the treatment rate for the resistant strain, we get a decrease in the infectious population of the resistant strain. Even if the reproduction number is less than one and the infectious population for drug sensitive strain is getting to zero the drug resistant infectious population takes long time to get to zero or to be eradicated. So it will stay being endemic in the population for long time. This shows the low effectiveness of the interventions to control the resistant strain or interventions existed now are not enough to control the resistant tuberculosis in a short period of time as compared to the sensitive strain. As we increase the treatment rate for the drug resistant strain the reproduction number for the resistant strain decreases so the infectious population for the resistant strain decreases as well.

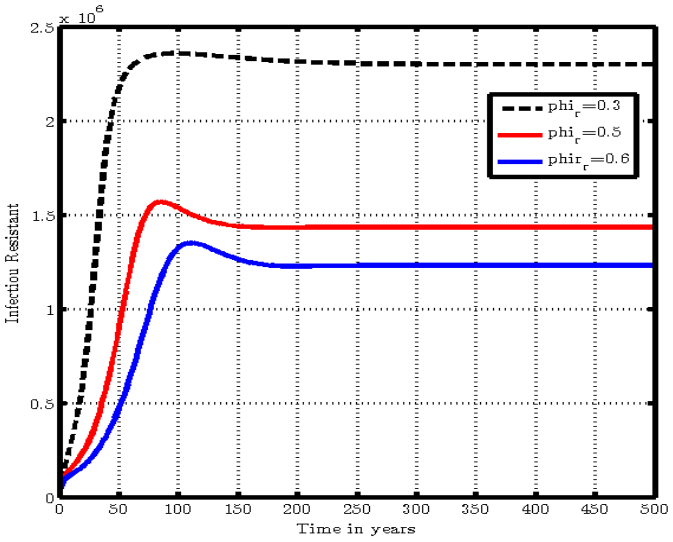


Figure 3.7: Proportion of infectious populations for Drug resistant strain with different treatment rate.

3.5.2 The role of treatment for the Latently infected population on the dynamics of the drug resistant strain

Treatment for latently infected individuals mostly reduces the risk of early transformation to infectious drug sensitive strain through re-activation. It may not prevent them from infection by drug resistant strain. As we see from Figure (3.8) when we increase the treatment rate for latently infected population, it doesn't bring such remarkable change on the drug resistant TB strain like that it brings on the sensitive strain as in Figure (3.2) unless it is supported by an increase in treatment rate for the infectious drug resistant strain as shown in Figure (3.7). This may be because of the treatment for latently infected population doesn't prevent them from an infection by the resistant strain

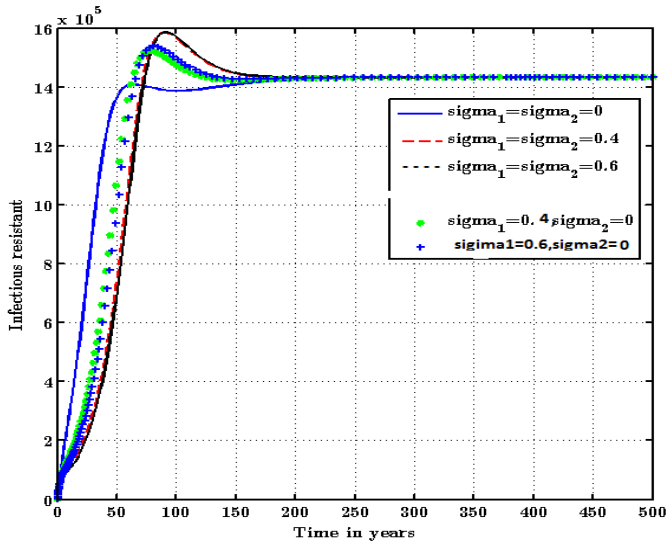


Figure 3.8: Graph which shows the role of treatment for latently infected drug sensitive population on the dynamics of the resistant strain. All other parameters are as in the table(3.2)

3.5.3 The role of Health Education on the dynamics of the drug resistant strain

We try to see the role of education on the drug resistant strain when both the strains circulate in the population with both reproduction numbers are greater than one. Here we choose such situation where the reproduction number is greater than one because of the result that people's behaviour change depends on the prevalence and mortality of the disease. So the role of education is more important when the disease is endemic. Figure (3.9) and (3.10) shows the population of infectious for the drug sensitive and drug resistant strain respectively when $R_s = 1.5225$ and $R_r = 2.3525$. From the graphs one can see that the sensitive strain dies out but the resistant stain becomes endemic. This is because of the strain that have the largest reproduction number will invade the other. As we increase the information dissemination rate fixing the efficiency of the existing self protective measures we observe a decrease in the infectious population of the resistant strain as time goes.

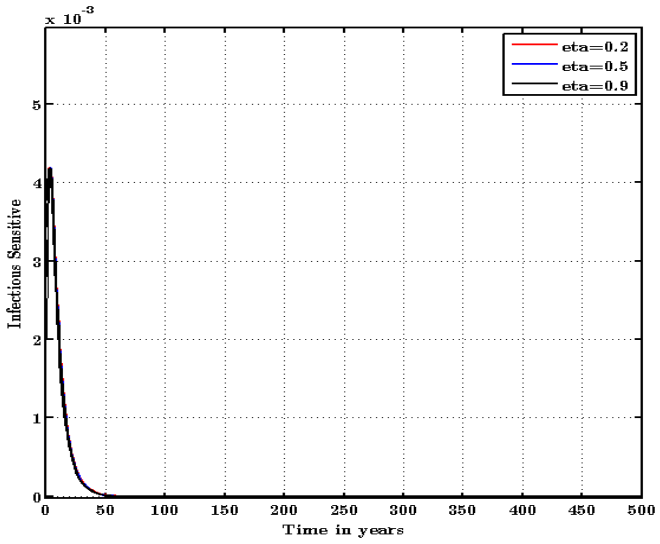


Figure 3.9: Infectious population for sensitive strain with varying value of η. Other parameters are as in the table (3.2)

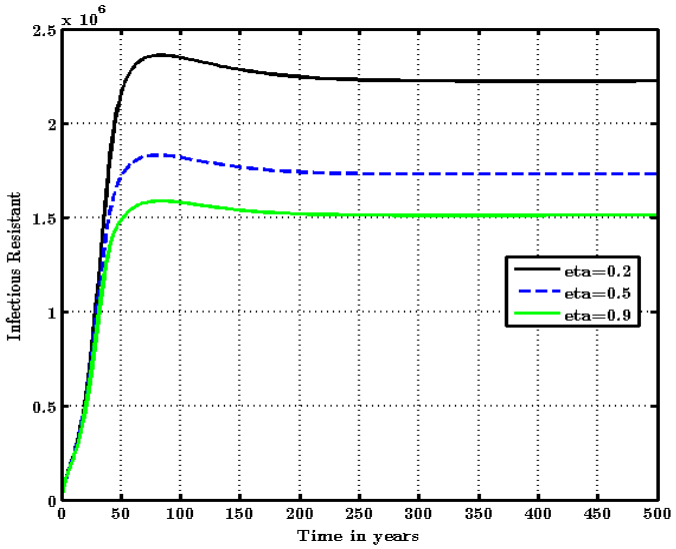


Figure 3.10: The role of education on the transmission of drug resistant tuberculosis. Other parameters are as in the table (3.2)

The increase of information dissemination rate with the increase in the prevalence of the resistant strain increases the educated population. In which case people realize that the disease is invading them and start to use every self protective measures which increases the educated people who are involved in self protective measures. Consequently this decreases the prevalence of the disease(both the strains) as in the Figure (3.11).

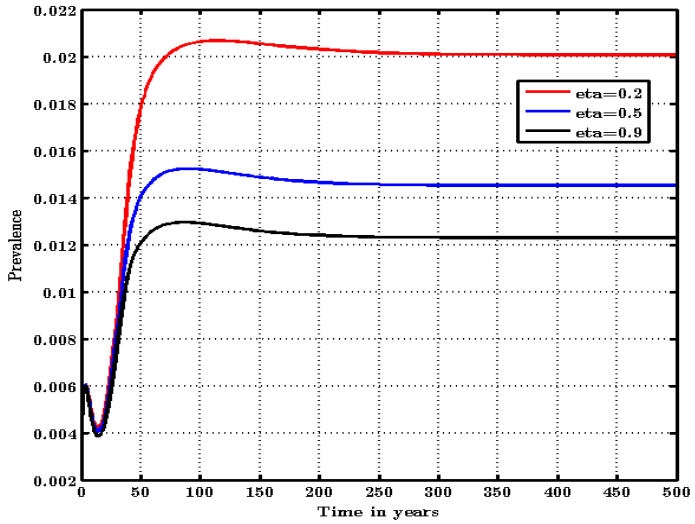


Figure 3.11: Prevalence of the two strain with varying value of η. All other parameters are as in the table (3.2).

By taking the transmission rate of the two strain to be the same we see that as the transmission rate increases the prevalence of the disease increases. Let $c\beta$ be the transmission rate for the two strain, then as $c\beta$ increases the reproduction number for the two strains increases and are less than 1 for $c\beta < 0.9$ then after wards the reproduction number for the drug resistant tuberculosis, R_r, grows to a number which is greater than 1 with the reproduction number for the sensitive strain,R_s, remains less than one until $c\beta$ is greater than 2. From Figure (3.12) we see that the prevalence of the disease, of the two strain, converges to zero until $c\beta$ is 0.6 then it starts to be endemic because of the resistant strain starts to invade even if the susceptible strain diminishes until the transmission rate is greater than 1.6. From the prevalence graph we can see that for a reproduction number for the two strain less than one the prevalence may not always converge to zero for example from figure (3.12) the prevalence for $c\beta = 0.8$ does not converge to zero even if R_r is less than one. Which indicates that only decreasing the value of the reproduction to a number less than one will not be a grant to eradicate a disease. So $c\beta$ must be less than to a umber to which both the reproduction numbers,

for the sensitive strain and the drug resistant strain, less than one and which makes the reproduction number for the two strains less than to some other threshold value other than 1 for which the prevalence converges to zero. Decreasing the transmission rate to which the resistant strain eliminated will completely eliminate the resistant strain.

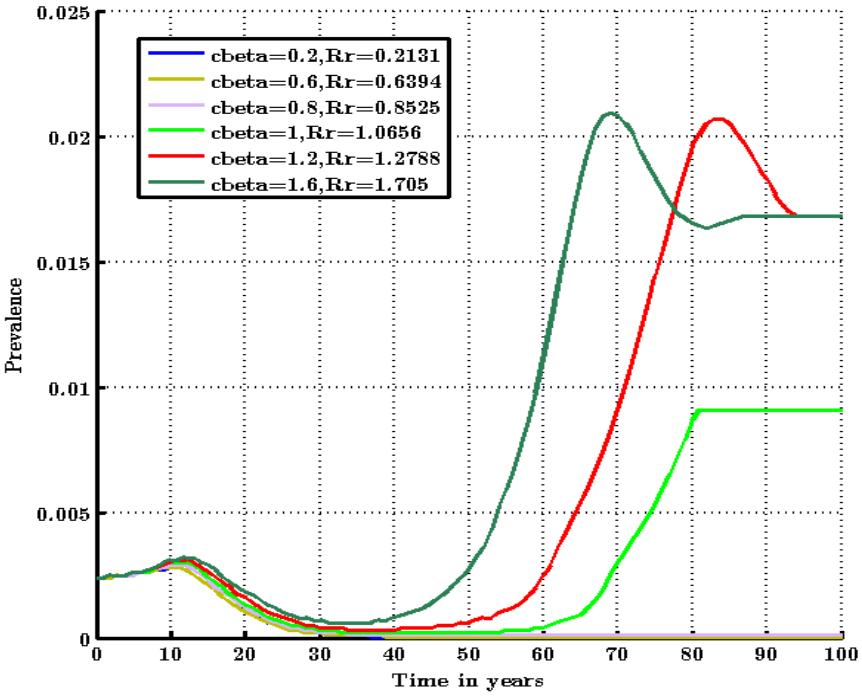


Figure 3.12: Reaction of the prevalence of the two strain to a transmission rate with other parameters as in the table (3.2)

Chapter 4

Discussion and Conclusion

4.1 Discussion and Conclusion

In this thesis we have formulated a two strain tuberculosis model and discussed some of the dynamical behaviour of the drug sensitive and resistant tuberculosis. In the first part of chapter three we have showed well posedness of the nonlinear system of differential equation and also showed that the disease free equilibrium is locally asymptotically stable for $R_e < 1$,($R_s < 1$ and $R_r < 1$. In the second part of the chapter we have discussed the dynamical behaviour of disease when only the drug sensitive tuberculosis exists in the population. From numerical simulation results we discussed the role of different interventions like health education, treatment for latent drug sensitive tuberculosis and for infectious drug sensitive tuberculosis in the overall dynamics of TB. In the last part of the chapter we have seen the long term behaviour of the disease when both strains circulate in the population.

In the drug sensitive TB only model, when only the sensitive tuberculosis circulate in the population, treatment for latently infected individuals especially for early latent has a great role in the eradication of drug sensitive tuberculosis, but care has to be taken that since latently infected with drug sensitive tuberculosis are high in number,treating more latent may contribute more for drug resistant tuberculosis unless the treatment is

completed effectively.

Health education is important in reducing the prevalence of the disease. We considered those educated are engaged in using all existing self protective measures against the disease. Because of the nature of the disease it may be sometimes difficult to apply some of the existing self protective measures, for example one can't wear a mask every day and every where he/she go. But the good thing is the disease needs effective(long and closed) contact with the infectious person to be transmitted to the one not infected so those educated individuals are expected to have no such effective contact with some one diagnosed with TB that may be in family member or coughing, suspecting that he/she may have the disease. If the population of educated compartment increase that decrease the prevalence of the disease because it is educated compartment from which a person can be caught by the disease with lower rate than those not educated. But if the prevalence of the disease decreased to a small number that can't be recognised by the population people may start to ignore the things that they are doing to protect themselves from the disease during prevalence is high in that case the disease may get the chance to be endemic again.

Treatment for infectious drug sensitive tuberculosis is very important in eliminating the sensitive strain. In contrary it may be a case for increment of a drug resistant tuberculosis because failure of treatment is the main cause for the resistant strain so treatment must be supported with effectiveness in the sense of completing the full dose as directed by the doctors.

Backward bifurcation existed for the drug sensitive tuberculosis only model, that is a stable endemic equilibrium existed with stable disease free equilibrium for $R_s < 1$. in which case some solutions of the system may converge to this endemic equilibrium according to the initial condition chosen. Such scenario makes the disease difficult to eliminate by working only on reducing the reproduction number for drug sensitive tuberculosis only, R_s, to less than one, that can only be a necessary condition but not

sufficient to eliminate the disease.

Since there are many parameters in the model it is difficult to fully show which parameters caused such a bifurcation but if we decrease the transmission rate to a number less than 1.58 which makes the reproduction number to less than 0.7036 we may not have such a scenario. But there may be other parameter which may cause such a bifurcation.

We considered a two strain model,when the two strain circulate in the population. We have seen effective treatment can eliminate the drug sensitive tuberculosis which can reduce the MDR TB by reducing treatment failure which is the main cause of the MDR TB. It is better to work on effectiveness of treatment for which WHO recommends DOT(Directly Observed Treatment) strategy in which a patient will take his medicine through close contact of health care professionals which decreases treatment failure because of incomplete treatment. Education plays a great role in reducing the MDR TB as it keeps people not to be caught by the sensitive strain through which most MDR TB cases are produced by failure of treatment, and resistant strain as primary infection.

Because of some of the parameters in our model are simply assumed and taken from different articles the results in the discussions must be validated to specific setting of a country. But generally from numerical simulation result as we concluded above giving treatment for latently infected individuals will bring a great change in the eradication of the sensitive strain especially for early latent. We guess detecting early latent is one of the challenges. And also the number of those infected by latent TB may be large in number treating such a number also a challenge economically for developing countries. Treatment failure may occur during treating latently infected drug sensitive strain, so treating such a great number may led to an increase in the number of drug resistant tuberculosis cases.Care has to be taken with in those limits in the application of treatment.

Decreasing transmission rate transmission rate decrease the prevalence of the disease,which

may be accomplished by educating more people and change their behaviour towards using the existing self protective measures. If we are succeed to change people's behaviour towards using self protective measures as much as possible we can have a change in eradicating the disease. The decrease in transmission rate must be supported by an increase in other interventions like treatment rate.

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Declaration

This thesis is my original work and has not been presented for a degree in any other university and that all sources of information used for the thesis have been fully acknowledged.

Sileshi Sintayehu Signature: _____

This thesis is submitted for examination with my approval as a university advisor.

Dr. Semu Mitiku Signature:_____