Spread and Control of Drug Sensitive and Multi-Drug Resistance Tuberculosis in Ethiopia: A Mathematical Model Analysis

Thesis Submitted to Debre Berhan University for the Award of the Degree of

DOCTOR OF PHILOSOPHY

IN

MATHEMATICAL MODELING

By

SHIMELIS BEKELE ZEREFE, M.Sc

Under the Advisor of

Dr. TEMESGEN TIBEBU MEKONNEN

Associate Professor of Mathematical Modeling

Department of Mathematics

DEBRE BERHAN UNIVERSITY, ETHIOPIA

November, 2020

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DECLARATION

I hereby declare that this thesis entitled **"Spread and Control of Drug Sensitive and Multi-Drug Resistance Tuberculosis in Ethiopia: A Mathematical Model Analysis"** is my own work and that, to the best of my knowledge and belief it contains no material previously published or written by another person or material which has been accepted for the award of any other degree or diploma of the university or other institute of higher learning.

SHIMELIS BEKELE ZEREFE

Debre Berhan University,

Ethiopia

30/11/2020

CERTIFICATE

This is to certify that the thesis entitled **"Spread and Control of Drug Sensitive and Multi-Drug Resistance Tuberculosis in Ethiopia: A Mathematical Model Analysis"** submitted by **Shimelis Bekele Zerefe** twoards the award of the degree of doctor of philosophy in Mathematical Modeling in the department of Mathematics, Debre Berhan University, Debre Berhan, Ethiopia is a genuine record of the work carried out by him under my supervision and guidance.

Dr. Temesgen Tibebu Mekonnen
Associate Professor of Mathematical Modeling
Department of Mathematics, Debre Berhan University
Debre Berhan, Ethiopia
30/11/2020

Dedication

I dedicate this work to the memories of my beloved grand father Zerefe Chinkilo (Late). May his soul rest in Peace.

Acknowledgment

My endless thanks goes to Almighty God for giving me strength and knowledge to accomplish this work. I would like to thank him for his blessing and everything he has done in my life.

I would like to express my sincere thanks to my research Advisor, Dr. Temesgen Tibebu Mekonnen (Associate professor, Mathematics Department, Debre Berhan University) for introducing and supervising me in the field of Mathematical Modelling. I would like to acknowledge his valuable support, guidance, suggestions and encouragement. From him, I learnt a lot, including writing high quality research papers, response to reviewers, to be precise and consistent in every point and so much more.

I would covey may gratitude for Debere Brhan university, Addis Ababa Science and Technology university and Ministry of Science and higher Education for giving me the scholarship. All Mathematics department staffs, special thanks to Mr. Melak Mesfin.

I would like to acknowledge and thank Ministry of health of Ethiopia. Special thanks to Ato. Solomon Kassahun (Monitoring and Evaluation Officer Policy, Planning, Monitoring and Evaluation Directorate Federal Ministry of Health, Ethiopia) for giving me well organized real collected data.

I wish to thank my wife Ms. Seble Argaw, my doughters (Nuhamin Shimelis and Adona Shimelis) and sons (Yohannes Shimelis and Bereket Shimelis)for their patience, understanding, encouragement and support in the process, stay blessed my family.

I would like to thank my colleague students and staff (Mathematics Department, Debre Berhan University) for their support and comments during the process. Words can never be enough to express my feeling, what I can say is that God bless everyone who supported me to accomplish this work.

APPROVAL SHEET

This is to certify that the thesis prepared by **Shimelis Bekele Zerefe** entitled **"Spread and Control of Drug Sensitive and Multi-Drug Resistance Tuberculosis in Ethiopia: A Mathematical Model Analysis"** submitted in fulfillment of the requirement for the degree of doctor of philosophy in mathematical modeling complies with regulation of the University and meets the accepted standards with respect to originality.

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Publications

1. Shimelis Bekele Zerefe and Temesgen Tibebu Mekonnen, Dynamics of a Tuberculosis Model with Vaccination and Dual Treatments: a Mathematical model Analysis, Volume 15, Issue 4 Ser. II (Jul, Aug 2019), PP 47-60 www.iosrjournals.org,IOSR-JM

2. Shimelis Bekele Zerefe, Temesgen Tibebu Mekonnen, Spread and Control of Multidrug Resistance Tuberculosis and Drug-sensitive Tuberculosis in Ethiopia: A Mathematical Model Analysis, American Journal of Applied Mathematics 2020; 8(3): 123-144

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List of Abbreviations

Abbreviation	Description
AFB	Acid-fast bacillus
AIDS	Acquired Immune deficiency syndrome
BCG	Bacilli Calmette-Guérin
CNR	Case Notification Rate
DFE	Disease Free Equilibrium point
DOTS	Direct Observation Treatment Strategies, Short course
DST	Drug Susceptibility Test
DS-TB	Drug Susceptible Tuberculosis
EE	Endemic Equilibrium point
EMB	Ethambutol
EPTB	Extra-Pulmonary Tuberculosis
FMOH	Federal Ministry of Health of Ethiopia
HBC	High Burden Country
HIV	Human immunodeficiency Virus
LTBI	Latent Tuberculosis Infection
MDR-TB	Multi-Drug Resistant Tuberculosis
MTB	Mycobacterium Tuberculosis
NTLCP	National Tuberculosis and Leprosy Control Program
PTB	Pulmonary Tuberculosis
RIF	Rifampicin
RR	Rifampicin Resistant
SNNP	South Nations and Nationality of Peoples
STD	sexually transmitted diseases
TB	Tuberculosis
TST	Tuberculin Skin Test
WHO	World Health Organization
XMDR-TB	Extensively Multi-Drug Resistant Tuberculosis

Abstract

This dissertation investigates the circumstances that can have impact on spreading and controlling tuberculosis disease, first, we studied on the the dynamics of the tuberculosis disease (4.1)-(4.8) with interventions vaccination, chemoprophylaxis and therapeutics treatments of latent and active tuberculosis respectively. The positivity and bounded of the solutions of the dynamical system (4.1)-(4.8) are proved. Stability analysis of disease-free-equilibrium point (DFE) and endemic equilibrium point (EE) were performed. We computed the effective reproduction number; and the computational results showed that DFE is locally and globally asymptotically stable if the effective reproduction number,$R_{eff} < 1$ and unstable if $R_{eff} > 1$. We have proved the local and global stability of EE by using the methods Gershgorin Discs Theorem and Lyapuno function respectively.

We have extended the dynamical system (4.1)-(4.8) to formulate the second nonlinear dynamical system (5.1)-(5.10) by disaggregating the tuberculosis disease in two strains [drug sensitive (DS) and multi drug resistance strains (MDR)] of tuberculosis in Ethiopia context. We proved that the solutions of this two strain tuberculosis dynamical system (5.1)-(5.10) are positive and bounded. We found that the dynamical system (5.1)-(5.10) has disease free and endemic equilibrium points. We proved that the local and global stability of disease free equilibrium point and endemic equilibrium points. We found the effective reproduction number of the dynamical system (5.1)-(5.10) which experience for drug sensitive strain and the effective reproduction number of the dynamical system (5.1)-(5.10) which experience for multi drug resistance strain.

Using standard data collected from different sources we have done numerical simulation on the dynamical system (4.1)-(4.8). we found the numerical value of the effective reproduction number of the dynamical system (4.1)-(4.8) is, $R_{eff} = 0.7 < 1$ which shows that the tuberculosis disease not spreads in the community. The rate of vaccine waning is the most influential parameter to change the effective reproduction number of the dynamical system (4.1)-(4.8).

Using real data collected from different health centers in Ethiopia we performed numerical simulations on the dynamical system (5.1)-(5.10). We found that the numerical

value of the effective reproduction number for the drug sensitive tuberculosis $R_{eff}(DS)$ is 1.03 and the effective reproduction number for the multi-drug resistance tuberculosis $R_{eff}(MDR)$ is 4.78 and the effective reproduction number of the dynamical system (5.1)-(5.10) $max\{1.03, 4.78\} = 4.78$. So that MDR strain is spreads strongly than DS strain. Using sensitive analysis we identified the most influential parameter to change the behavior of the solution of the dynamical system (5.1)-(5.10) and as the result the number of susceptible or vaccinated individuals make effective contacts with an infectious individual is the most influential parameter in the dynamical system (5.1)-(5.10).

Chapter 1

Introduction

1.1 Background on Epidemics

Epidemiology studies the spread of diseases caused by pathogens, such as viruses or bacteria, in populations of hosts, which can be humans, animals, or plants [100]. The goal is to predict the time course of an outbreak of a given disease in a population and the effect of conceivable control measures, such as vaccination, quarantine, treatment, culling, or behavior modification on the severity of the outbreak [90].

The emergence and re-emergence of infectious diseases have become a significant world-wide problem. Proper understanding of transmission mechanisms of diseases caused by existing and new pathogens may facilitate devising prevention tools. Prevention tools against transmissions, including vaccines and drugs, need to be developed at a similar pace to that of the microbes. Implementation and proper use of these sophisticated tools against the microbes is another challenge [5, 45]. Tuberculosis is one of a highly infectious diseases caused by infection with the bacteria mycobacterium tuberculosis and it is an airborne disease and so it is primarily transmitted through the respiratory route [10, 12].

1.1.1 Infectious Disease

An infectious disease is caused by various microbes or pathogen. Most of them are usually microorganisms. Few of them are visible by naked eyes. The most common pathogens are different types of viruses and bacteria. Fungi and Protozoa are also known as pathogens and are responsible for various diseases. Diseases caused by these pathogens are termed as 'infectious' as these pathogens can be easily transmitted from one infected person to another non-infected person. The most common and well-known example of such diseases could be influenza or flu that is caused by some kinds of viruses, TB, HIV, mumps, measles, rubella, smallpox, malaria have also caused millions of infections and deaths [5, 89].

TB usually affects the lungs but it can also affect other parts of the body such as the brain, lymph nodes, kidneys, bones, joints, larynx, intestines or eyes. TB outside the lungs is referred to as extra-pulmonary TB. There are generally two stages of TB infection, one where the bacteria can be spread and can cause illness and one where the bacteria is in a person's body, but is not causing disease and cannot be spread.

People with TB infection have TB bacteria in their bodies but they are not sick because the bacteria are not active. These people do not have symptoms of TB disease and they cannot spread the bacteria to others. However, they may develop TB disease in the future. They are often prescribed treatment to prevent them from developing TB disease.

Tuberculosis can affect anyone. People infected with TB bacteria have a 10% lifetime risk of developing TB disease. However, persons with compromised immune systems, such as people living with HIV, malnutrition or diabetes, or people who use tobacco, have a much higher risk of developing TB disease.

Pathogens

As mentioned above, pathogens are solely responsible for causing an infectious disease. In this sub-section we briefly review some common pathogens that cause diseases. The most common pathogens are: **Bacteria:** Bacteria, single-celled organisms, are well known

microbes that cause various diseases. However, most of the bacteria are harmless and some are even beneficial to human.

Bacteria are useful in producing cheese, yogurt, and chemicals and medicines. They also play some critical role to synthesize food particles in our intestine to produce energy. Insulin that saves millions of diabetic patients is also produced from genetically modified bacteria.

Some bacteria, however, are harmful and life threatening. Gastritis, pneumonia, meningitis, gonorrhea are some examples caused by various bacteria. Most of the bacterial diseases can be treated by antibiotics.

Viruses: Viruses are the most common and harmful microorganisms that cause severe diseases to human and other species. Influenza or flu which probably no one can avoid is caused by viruses. Other examples of viral diseases include chickenpox, herpes, human papillomavirus (HPV), mumps, measles, rubella, viral hepatitis, viral meningitis, and viral pneumonia.

Human Immunodeficiency Virus (HIV) is another deadly virus that spreads mainly through sexual contacts and causes AIDS. Viruses cannot live by themselves, and they need other living cells for their reproduction [75, 98].

Unlike bacterial diseases, viral diseases cannot be treated by antibiotics. Since viruses use host's cells for reproduction, an antiviral drug could be highly toxic and life-threatening for the host. Thus, instead of killing the target cells, antiviral drugs are used to inhibit viral replication processes. Antiviral drugs act to limit the viral loads and helps keep the infected individual healthy until host's immune system controls the infection and eliminates the pathogen [5, 33, 107].

Fungi: Fungi are microorganisms that widely vary in sizes from unicellular, such as yeast, to multicellular, such as mushrooms and toadstools which can easily be seen with naked eyes. Fungi play a critical role in decomposing dead materials which in turn provide nutrients to the land. The lifesaving antibiotic penicillin is also produced from the fungus Penicillium chrysogenum. Some fungi are harmful by causing infections to plants and animals.

Candidiasis, histoplasmosis, mucorycosis, ringworm are common examples of diseases caused by fungi. Vaginal yeast and thrush are fungal diseases that can cause infection to the immune compromised individuals relatively easily [5, 89].

Protozoa: Protozoa are comparatively large single-celled organisms. Some protozoa are useful. For example, in the sewage treatment systems, protozoa are used for decomposing organic matters. Some others are human parasites that cause diseases, such as malaria, toxoplasmosis, cryptosporidiosis, trichomoniasis, leishmaniasis, amoebiasis, amoebic dysentery, and acanthamoeba keratitis. Protozoa can be spread through contaminated food, water or through a vector or carrier like arthropod mosquito. The well-known protozoa species Plasmodium vibax that causes malaria spread through female anopheles mosquitoes. When a female mosquito bites an infected person it receives the parasite plasmodium. The parasite grows and reproduces inside the mosquito. When this mosquito bites another person the parasite can be transmitted through its saliva to that person. Malaria is one of the leading death causing diseases that is responsible for about 700,000 deaths each year worldwide [5, 89]. There are some other pathogens that also cause infectious diseases, e.g parasitic helminths, ectoparasites and prions.

Modes of Transmission

Infectious diseases can spread in various ways and pathogens cause infections by different modes of transmission. Some infections may take place through a direct contact while other may be caused through indirect contacts. Transmission can also be made through carriers or vectors. For examples, malaria, filariasis, west Nile, dengue, chikungunya, and many others spread through mosquitoes. Based on their modes of transmission there are airborne diseases and sexually transmitted diseases, and they have been paid much attention. Many diseases, e.g. TB, influenza, SARS (Severe Acute Respiratory Syndrom), are airborne and can be transmitted through air. The airborne infection spreads from an infected person to an uninfected person through sneeze, cough laugh, singing, talking etc. The microbes that are discharged from an infected person may remain on the dust particles or any other medium. An infection may take place when these microbes are inhaled or reach mucus membrane of an uninfected person through body contact [5].

Hand-shaking also could be a potential way for transmition of infections.

Mycrobacterium tuberculosis is carried in airborne particles, called droplet nuclei, of 1– 5 microns in diameter. Infectious droplet nuclei are generated when persons who have pulmonary or laryngeal TB disease cough, sneeze, shout, or sing. Depending on the environment, these tiny particles can remain suspended in the air for several hours. Transmission occurs when a person inhales droplet nuclei containing M. tuberculosis, and the droplet nuclei traverse the mouth or nasal passages, upper respiratory tract, and bronchi to reach the alveoli of the lungs figure and the dots in the air represent droplet nuclei containing tubercle bacilli 1.1 [5, 96].

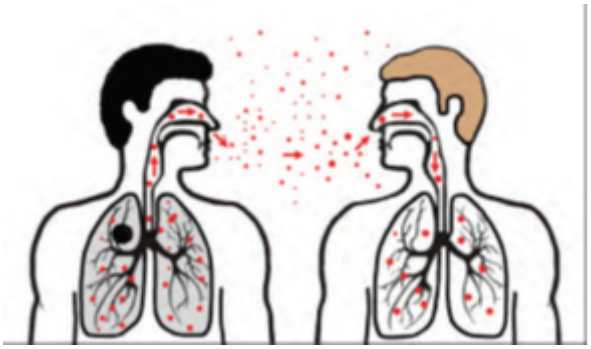

Figure 1.1: ways at which TB spread from person to person through the air.

A significant number of diseases, on the other hand, are Sexually Transmitted Diseases (STD) and they are also transmitted through contaminated blood and semen, breast-feeding, or during childbirth. HIV is one of the most death causing STDs. Other STDs including herpes, syphilis, gonorrhea, chlamydia and trichomonias is also cause significant infection and mortality [5, 75].

Immune System

The human body is equipped with a strong defense system to protect against pathogenic infections. This defense system is designed to protect the host from very simple to sophisticated attacks by the pathogens. Our skin acts as a first defense by drawing a barrier for any harmful entities to get inside. Once this barrier is penetrated, some volunteers from the immune system come forward to act as a secondary defense. A

pathogen has to face several stages of the immune defense before it can cause disease and harm to the host [5, 33].

Our whole immune system is divided into two types innate immune system and adaptive immune system. The innate immune system is comprised of various immune cells, neutrophils, mast cells, natural killer cells, and monocytes, and can attack any suspected foreign intruders with no prior knowledge about the intruders. The innate immune system has a natural ability that can detect almost every invading microbes [5]. This natural response is also referred to as to non-specific defense mechanism as it takes action almost immediately as soon as the pathogens enter into the body.

On the other hand, the adaptive immune system is antigen specific. It is also known as cell mediated immune system and is comprised of B cell and T cell. This immune system is much more complex than the innate immune system. It requires some information about the pathogens in order to attack them efficiently. Such information can be provided by some components from the innate immune system or by somebody within the adaptive immune system. The adaptive immune mechanism also keeps memory of the previous infections or pathogens. This memory is used to prevent any successive infection at the first place before any signal is received from the innate system [5]. Therefore, a pathogen cannot infect a host successfully a second time unless it evolves significantly enough to evade the host's adaptive immune defense.

The combined efforts of innate and adaptive immune systems keep our body safe and healthy. However, in some pathogenic infections, host-pathogen battle may last longer (e.g. HIV infection) or immune defense may fail resulting in a tragic death of the host.

The infections that are cleared off by the innate immune system or by the drug supplement can be repeated. That means the host may be infected again by the same pathogen. Usually, bacterial infections fall into this category. On the other hand, viral infections cannot be cured by drug supplement. The adaptive immune system itself can clear the viral infections and also develop immunity. That is why most viral infections go away on their own in few days without any medication. Since a viral infection boosts immunity successive infection by the same virus seldom occur in the host. The host is now recovered permanently from that pathogenic infection. However, some viral infections such as

herpes, Hepatitis B and C, and HIV can cause latent infection that lasts for a long time.

1.1.2 Disease Prevention and Control

One of the effective ways to control a disease is to reduce contacts. However, in the modern life with increased interactions among individuals, this way is not easy to achieve. In addition to maintaining social distance, alternate prevention measures need to be adopted. Vaccines and drugs are the two widely used prevention tools that can potentially reduce transmissions and control diseases.

Vaccines

A vaccine is used to boost immune system against some specific pathogen. The substance contained in a vaccine has similar physical properties to those of a pathogen. Typically a vaccine can be thought of a fake pathogen that has no ability to reproduce and to cause an infection.

It can be made of a weak or killed pathogen. As vaccines are similar to pathogenic microorganism, they can stimulate the immune system of the host and builds up antibodies against the pathogens to recognize them as foreigners. Thus, whenever such a true microorganism is encountered within a host, the immune system destroys it. This kind of phenomenon is known as immunity. Thus, as long as a vaccine for a disease is available, it is an ideal means of protecting a healthy population from the disease.

Though vaccines are very effective against transmission, typically, there are limits on the amounts, especially in developing countries. Thus, how to distribute the limited vaccines becomes crucial for optimal benefit. Social, economical and ethical issues could be major obstacles in implementation of vaccines [5]. Certain groups of individuals may have higher susceptibility to the infections than others. In influenza, for example, school-going children can be infected more easily and can spread the disease more rapidly than other individuals [5]. Thus to control infections by using vaccines, a proper distribution and implementation strategy is very crucial.

Presently, the only effective vaccine for TB is Bacillus Calmette-Guerin (BCG) which is usually given to infants [73, 79, 82]. This vaccine has a demonstrated efficacy ranging from no protection to 80% protection though a meta-analysis estimated that the overall efficacy of BCG is 50% [73, 110]. Imperfect vaccine efficacy against infection (i.e., vaccine does not offer 100% protection against infection invaccinated individuals)is the main sources of backward bifurcation in vaccination models [2]. The BCG vaccine, which was developed almost 100 years ago and has been shown to prevent severe forms of TB in children, is still widely used [10, 57, 73, 82].

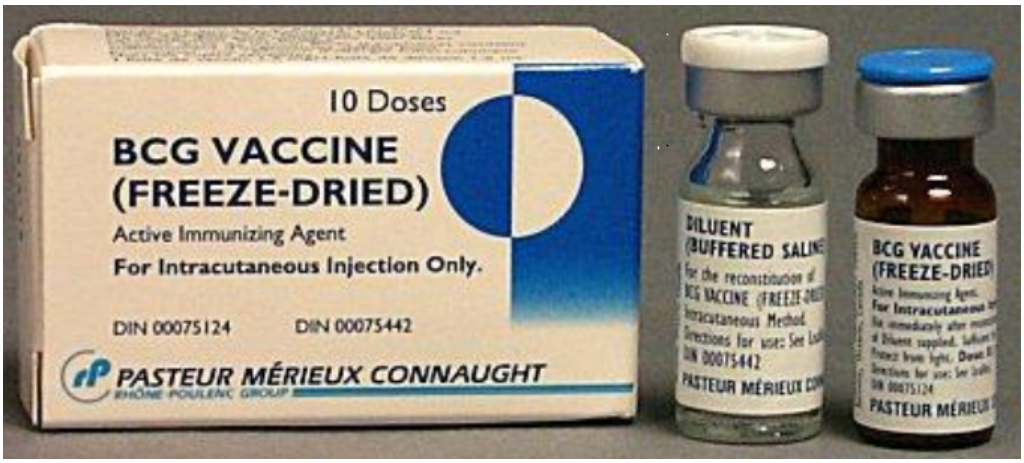

Figure 1.2: BCG Vaccine

However, it is inadequate in preventing pulmonary TB in adults and there is currently no vaccine that is effective in preventing TB disease in adults, either before or after exposure to TB infection.

Drugs

Effective drug treatments of TB were first developed in the 1940s. The currently recommended treatment for cases of drug-susceptible TB is a 6-month regimen of four first-line drugs: isoniazid, rifampicin, ethambutol and pyrazinamide. Treatment for Rifampicin-Resistant TB (RR-TB) and Multi-Drug-Resistant TB (MDR-TB) is longer, and requires more expensive and more toxic drugs (WHO, 2017). Drug Susceptibility Testing (DST) which is available in many countries, and is very important, provides information about which drugs a person is resistant to. TB can usually be cured and more than twenty

drugs have been developed for treating TB. But most of the drugs were developed many years ago. The treatment usually consists of a combination of TB drugs that must be taken for at least six months. But the treatment will only be successful if the drugs are taken exactly as required for the entire length of time [38, 54, 103].

Treatment of tuberculosis (TB) disease is not simple and Drug-Susceptible Tuberculosis (DS-TB) requires a multiple drug regimen taken for at least 6 months. Multi-Drug-Resistant Tuberculosis (MDR-TB) treatment regimens are significantly longer, cause serious side effects and are very expensive [41, 54, 102].

Until early 2016, the treatment regimens recommended by WHO typically lasted for 20 months, and cost about US$ 2000–5000 per person. As a result of new evidence from several countries, WHO issued updated guidance in May 2016. Shortened regimens of 9–12 months are now recommended for patients (other than pregnant women) with pulmonary RR-TB or MDR-TB that is not resistant to second-line drugs. The cost of a shortened drug regimen is about US$ 1000 per person. The latest data reported to WHO show a treatment success rate for MDR-TB of 54%, globally, reflecting high rates of loss to follow-up, unevaluated treatment outcomes and treatment failure. In addition to providing a cure, drugs can also play a significant role in reducing transmission [20, 41, 52].

1.2 The Two-Strain Tuberculosis

In 1882, the Germany, microbiologist Robert Koch discovered the tubercle bacillus, at a time when one of every seven deaths in Europe was caused by TB (WHO) [87]. In the eighteenth century, Western Europe suffered terribly from this disease with a prevalence as high as 900 deaths per 100,000. This was largely due to poor ventilation, overcrowded housing, primitive sanitation, malnutrition among other risk factors that led to the epidemic. Today, this disease ranks as the second leading cause of morbidity and mortality in the world from a single infectious agent, after the human immunodeficiency virus (HIV) [60, 81].

World Health Organization (WHO) declared TB as global epidemic in 1993.The resurgence of tuberculosis in the 1990s and the emergence of drug-resistant tuberculosis in the

first decade of the 21st century increased the importance of epidemiological models for the disease [61, 87].

Tuberculosis (TB) is a preventable and curable disease caused by Mycobacterium Tuberculosis (MTB) that most often affects the lungs. Tuberculosis is a contagious disease that spreads from person to person through the air [22, 84]. When people with pulmonary TB cough, sneeze or spit, they propel the TB germs into the air [80]. If someone has pulmonary disease, which is TB in the lungs, then they may have a bad cough that lasts longer than two weeks. They may also have pain in their chest and they may cough up blood or phlegm from deep inside their lungs. Other symptoms of TB include weakness or fatigue, weight loss, lack of appetite, chills, fever and night sweats [76].

1.2.1 Drug Sensitive Tuberculosis

Tuberculosis is a bacterial disease caused by mycobacterial tuberculosis with an estimated one third of the world population [3, 31], TB remains a major global health problem. In 2012, an estimated 8.6 million people developed TB and 1.3 million died from the disease (including 320,000 deaths among HIV-positive people).

Ethiopia is one of the 22 High-Burden Countries (HBCs) that account for about 80% of the world's TB cases. According to the Global TB report 2013, there were an estimated 230,000 (247 per 100,000 populations) incident cases of TB in Ethiopia in 2012. According to the same report the prevalence of TB was estimated to be 310,000 (224 per 100,000 populations). There were an estimated 16,000 deaths (18 per 100,000) due to TB, excluding HIV related deaths in Ethiopia during the same period [38, 41, 49, 85, 103].

Notified cases of all forms of TB increased significantly in Ethiopia from just over 73,000 in 1999 to a peak of just over 159,000 in 2011, after which there has been an apparent decline in 2012. Notably, rates for extra-pulmonary TB are as high as those for smear positive and smear negative TB. The proportion of pulmonary TB cases detected is only 60-65% while that of extra-pulmonary TB cases is 35-40%. Among the pulmonary TB cases, the number of smear negative cases is more than the smear positive pulmonary TB cases. This is a peculiar picture seen in Ethiopia for over a decade. Moreover, the 2010/11 national TB Prevalence survey showed that smear positive cases accounted for

only 43% of culture positive cases. This indicates the need for more sensitive and specific diagnostics for improving the diagnosis of smear negative TB cases [41, 52, 85, 103].

Human Immunodeficiency Virus (HIV) is a major contributing factor for developing active TB. HIV infected individuals had 3.5-fold higher risk of tuberculosis than HIV negative individuals. Ethiopia is also among high TB/HIV burden countries with over 10% TB/HIV co-infection rate. Among people living with HIV, laboratory diagnosis of TB is more difficult compared to HIV negative, and mortality rates are higher.

A person has drug resistant TB if the TB bacteria that the person is infected with, will not respond to, which means that they are resistant to, at least one of the main TB drugs. Drug susceptible TB is the opposite. If someone is infected with TB bacteria that are fully susceptible, it means that all of the TB drugs will be effective so long as they are taken properly. It still means that several drugs need to be taken together to provide effective TB treatment [10, 43, 59].

1.2.2 Drug-Resistance Tuberculosis

TB is considered drug-resistant (DR) when the organism (mycobacterium tuberculosis) is not killed by anti-TB drugs. And this can be confirmed by a laboratory test called drug susceptibility test (DST) [41, 69].
Four different types of drug resistance:

- **Mono-resistance:** resistance to one anti-tuberculosis drug.
- **Poly-resistance:** resistance to more than one anti-tuberculosis drug, other than both isoniazid and rifampicin.
- **Multi-Drug-Resistance (MDR-TB):** resistance to at least isoniazid and rifampicin.
- **Extensive Drug-Resistance (XDR-TB):** resistance to any fluoroquinolone, and at least one of the three injectable SLDs (capreomycin, kanamycin and Amikacin), in addition to multidrug-resistance.

MDR-TB is the deadlier, harder to diagnose and much more difficult to treat. According to a recent unpublished study in Ethiopia, the proportions of MDR-TB among the nation's new and recurrent TB cases are 2.3% and 17.6% respectively. Ethiopia has also seen patients with cases of extensively drug-resistant TB (XDR-TB), cases due to MDR-TB bacteria that are also resistant to the backup, or the second-line, TB drugs usually used for treating MDR-TB. Compared to MDR-TB diagnosing XDR-TB is even more difficult and treatment outcomes are even worse, leading to higher mortality rates [38, 52, 60, 102].

Ethiopia is one of 27 countries named by WHO as having high burdens of MDR-TB. About 2% of new cases and 18% of the retreatment cases are MDR-TB. Based on WHO estimates in 2014 that about 1,300 MDR-TB occurred among the 120,000 individuals with diagnosed and notified TB cases but, due to inadequate testing, only about 503(39%) of Ethiopia's MDR-TB patients are being actually identified [41, 85].

In 2012, Ethiopia achieved an excellent 83% treatment success rate for the cohort of 271 MDR-TB patients starting on the recommended two-year treatment regimen. However, this impressive accomplishment is over shadowed by the fact that the number of patients treated is only a small proportion of the estimated number of new MDR-TB cases each year. The remaining undetected cases continue to transmit MDR-TB [52, 102, 103].

In Ethiopia the MDR-TB prevalence based on the 2005 nationwide survey was 1.6% and 11.8% among new and retreatment cases, respectively. Rifampicin resistance was lower than 2% in new cases. Annually 2000-2500 MDR-TB cases are estimated to occur among the notified pulmonary TB cases. However in year 2012 for instance, only 212 (10.1%) MDR-TB cases were detected. This indicates majority of the expected MDR-TB cases remain undiagnosed and continue to transmit the disease in the community [41, 102, 103].

With direct U.S. government support, the Ethiopian government has begun rolling out GeneXpert TB test machines designed to rapidly and accurately identify most people with MDR-TB. As of early Oct. 2015, 105 health facilities had access to these machines, but their use and effectiveness is contingent on adequate supplies of electricity and testing materials, and the government of Ethiopia recognizes gaps in implementing the national drug-resistant TB strategies [41, 81].

1.3 Mathematical Models in Infectious Diseases

Mathematical models have been used to study the dynamics of infectious diseases for more than a century. In recent years, applications of mathematics in infectious disease have shown remarkably growing trends. As a result, mathematical modelling is very important tool in analyzing the spread and control of infectious diseases [36, 106] The earliest mathematical modelling can be traced back to the 18th century when Daniel Bernoulli formulated a model for smallpox to estimate the effectiveness of variolation of healthy population with smallpox [5, 59]. However, mathematical models have been growing since the middle of the 20th century after Kermack and McKendrick published their paper on epidemic models in 1927 which contains threshold results that determines whether an epidemic outbreak may occur or not [5, 59].

Rapid diagnostic test, available clinical data and electronic surveillance can facilitate the applications of mathematical models to testing scientific hypotheses and to design practical strategies [5]. The emerging and reemerging diseases have stimulated the interest in mathematical modeling. Models can provide estimates of underlying parameters of a real world problem which are difficult or expensive to obtain through experiment or otherwise.

By estimating transmission rate, reproduction number and other variables and parameters a model can predict whether the associated disease will spread through the population or die out. It can also estimate the impact of a control measure and provide useful guidelines to public health for further efforts required for disease elimination.

1.3.1 Basic Reproduction Number

The basic reproduction ratio (or number) R_0 is one of the most important concepts in epidemic theory and is the most widely used epidemiological measurement of the transmission potential in a given population. The basic reproductive number is defined as the expected number of new infections from one infected individual in a fully susceptible population through the entire duration of the infectious period. The reproduction number is used to predict whether the epidemic will spread or die out.

For a given system, with say n compartments, a general dynamical system $x^{'} = f(x)$ where $x = (x_1, x_2, ..., x_n)$ that describes the evolution of the system is given by:

$$\begin{cases} \frac{dx_1}{dt} = & f_1(x_1, x_2, ..., x_{n-1}, x_n) \\ \frac{dx_2}{dt} = & f_2(x_1, x_2, ..., x_{n-1}, x_n) \\ & \vdots \\ \frac{dx_{n-1}}{dt} = & f_{n-1}(x_1, x_2, ..., x_{n-1}, x_n) \\ \frac{dx_n}{dt} = & f_n(x_1, x_2, ..., x_{n-1}, x_n) \end{cases} \tag{1.1}$$

Rewrite the system (1.1) as $f(x, y) := (F-V)x-F(x, y)+V(x, y)$ where, $x = (x_1, x_2, ..., x_m)^T \in \mathbb{R}^m$ and $y = (y_1, y_2, ..., y_p)^T \in \mathbb{R}^p$ represent the populations in disease compartments and non-disease compartments, respectively; $F = (F_1, F_2, ..., F_m)^T$ and $V = (V_1, V_2, ..., V_m)^T$, where F_i represents the rate of new infections in the i^{th} disease compartment; and V_i represents the transition terms.

According to Diekmann and Heesterbeek [26], we call FV^{-1} the next generation matrix for the model and set the reproduction number,$R_0 = \rho(FV^{-1})$ where $F = \frac{\partial \mathcal{F}_i(x_0)}{\partial x_j}$ and $V = \frac{\partial \mathcal{V}_i(x_0)}{\partial x_j}$ for $i \geq 1$ for the number of compartments, and $1 \leq j \leq m$ for the infected compartments only, where $\mathcal{F}_i$ are the new infections, while the $\mathcal{V}_i$ transfers of infections from one compartment to another, x_0 is the disease-free equilibrium state. $\rho(FV^{-1})$ which is defined as the spectral radius (largest eigenvalue) of a matrix FV^{-1}. F and V are $m \times m$ matrices, where m is the number of infected classes. Consider an infected individual introduced into compartment k of a disease-free population. The (i, j) entry of F is the rate at which an infected individual in compartment j produces new infections in compartment i, and the (j, k) entry of V^{-1} is the average time an infected individual spends in compartment j during its lifetime, assuming that the population remains near the DFE and barring reinfection. Hence, the (i, k) entry of the product FV^{-1} is the expected number of new infections in compartment i produced by the infected individual originally introduced into compartment k.

The basic reproductive number forms a threshold quantity for most models of infectious diseases since for reproductive number is less than unity, the disease-free equilibrium point is locally asymptotically stable while for reproductive number is greater than unity, the disease-free equilibrium point is unstable. In many models, there is a bifurcation at the basic reproductive number is equal to 1.

1.4 Stability Analysis

Mathematical models are becoming more and more complicated when higher degree of nonlinearity is adopted to address real-world problems. Finding an explicit solution of these models is almost impossible. Though numerical simulations can provide good approximating solutions with fixed parameters, general solution may remain unknown. When general solution is hard to achieve, stability analysis can be resorted to get a sense of solution's behavior. In fact, stability analysis can predict the long time behaviour of the model solutions very well.

In general, there are two types of stability analysis, local and global, widely used in the literature. Local stability is concerned with behaviour of the solution of the model near an equilibrium point, while global stability can describe solution behaviour in the whole domain.

1.4.1 Local Stability Analysis of Equilibrium Points

In mathematical modelling, it is often very important to know the behavior of a dynamical system near an equilibrium point [36]. It is important to know whether or not future evolutions of the system will remain close to the equilibrium point if initial conditions are close to the equilibrium.

Definition 1.1. *A equilibrium point $\bar{x}$ of a dynamical system is said to be locally stable if all eigenvalues of the Jacobian evaluated at $\bar{x}$ are negative.*

Definition 1.2. *The Jacobian of the dynamical system represented in (1.1) is given by:*

$$J = \begin{bmatrix} \frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} & \cdots & \frac{\partial f_1}{\partial x_{n-1}} & \frac{\partial f_1}{\partial x_n} \\ \frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x_2} & \cdots & \frac{\partial f_2}{\partial x_{n-1}} & \frac{\partial f_2}{\partial x_n} \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ \frac{\partial f_{n-1}}{\partial x_1} & \frac{\partial f_{n-1}}{\partial x_2} & \cdots & \frac{\partial f_{n-1}}{\partial x_{n-1}} & \frac{\partial f_{n-1}}{\partial x_n} \\ \frac{\partial f_n}{\partial x_1} & \frac{\partial f_n}{\partial x_2} & \cdots & \frac{\partial f_n}{\partial x_{n-1}} & \frac{\partial f_n}{\partial x_n} \end{bmatrix} \tag{1.2}$$

The Routh-Hurwitz Stability Criterion

It was discovered that all coefficients of the characteristic polynomial must have the same sign and non-zero if all the roots are in the left-hand plane. These requirements are necessary but not sufficient. If the above requirements are not met, it is known that the system is unstable. But, if the requirements are met, we still must investigate the system further to determine the stability of the system.

Consider the characteristics equation of a given Jacobian matrix

$$P_n(\lambda) = a_n\lambda^n + a_{n-1}\lambda^{n-1} + a_{n-2}\lambda^{n-2} + ... + a\lambda + a_0$$

To determine whether this system is stable or not, check the following conditions:
Two necessary but not sufficient conditions that all the roots have negatives real parts are:

1. All the polynomial coefficients must be the same sign.
2. All the polynomial coefficients must be nonzero.

The Routh-Hurwitz criterion is a necessary and sufficient criterion for the stability of linear systems. Characteristic equation.

$$a_n\lambda^n + a_{n-1}\lambda^{n-1} + a_{n-2}\lambda^{n-2} + ... + a\lambda + a_0 = 0$$

Routh array:

λ^n	a_n	a_{n-2}	a_{n-4}	$\cdots$
λ^{n-1}	a_{n-1}	a_{n-3}	a_{n-5}	$\cdots$
λ^{n-2}	b_1	b_2	b_3	$\cdots$
λ^{n-3}	c_1	c_2	c_3	$\cdots$
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
λ^1	$\cdots$	$\cdots$	$\cdots$	$\cdots$
λ^0	$\cdots$	$\cdots$	$\cdots$	$\cdots$

where $b_1 = -\frac{1}{a_{n-1}} \begin{vmatrix} a_n & a_{n-2} \\ a_{n-1} & a_{n-3} \end{vmatrix} = \frac{a_{n-1}a_{n-2} - a_n a_{n-3}}{a_{n-1}}$, $b_2 = -\frac{1}{a_{n-1}} \begin{vmatrix} a_{n-2} & a_{n-4} \\ a_{n-1} & a_{n-3} \end{vmatrix}$

$c_1 = -\frac{1}{b_1} \begin{vmatrix} a_{n-1} & a_{n-3} \\ b_2 & b_3 \end{vmatrix}$ and so on.

The necessary condition that all roots have negative real parts is that all the elements of the first column of the array have the same sign. The number of changes of sign equals the number of roots with positive real parts.

Gershgorin Discs Theorem

Let $A = [a_{ij}]$ be a complex $n \times n$ matrix. Define

$$R_i(A) = \Sigma_{j \neq i} |a_{ij}|, \text{ for i,j=1,...,n}$$
$$D_i(A) = \{z \in C | \ |z - a_{ij}| \leq R_i(A)\},$$
$$G(A) = \cup_{i=1}^{n} \{z \in C | \ |z - a_{ij}| \leq R_i(A)\}$$

We call these disks $D_i(A)$ the Gershgorin discs and their union G(A) is called the Gershgorin domain

Theorem 1.1. *(Gershgorin Circle Theorem, 1931) Every eigenvalue of the $n \times n$ complex matrix A lies within at least one of the Gershgorin disks $D_i(A)$.*

Proof. Suppose $Ax = \lambda x$ for $x \neq 0$. Let x_i be the largest component in x with respect to modulus. Then

$$Ax = \lambda x \Sigma_{j=1}^{n} a_{ij} x_j = \lambda x_i$$
$$\Sigma_{j \neq i}^{n} a_{ij} x_j = (\lambda - a_{ii}) x_i$$

Therefore, $|\lambda - a_{ii}| = |\Sigma_{j \neq i}^{n} \frac{a_{ij} x_j}{x_i}| \leq \Sigma_{j \neq i}^{n} |a_{ij}| = R_i$ □

Corollary: Let $A = [a_{ij}]$ be an $n \times n$ complex matrix. If $\Sigma_{j \neq i}^{n} |a_{ij}| < |a_{ii}|$ for all i, then A is invertible.

Theorem 1.2. *(Gershgorin's disc theorem) For any complex $n \times n$ matrix A, all the eigenvalues of A belong to the Gershgorin domain G(A). Furthermore the following properties*

hold: If A is strictly row diagonally dominant, that is $\Sigma_{j=1,j\neq i}^{n}|a_{ij}| < |a_{ii}|$ *for* $i = 1, ..., n$ *then A is invertible.*

i. If A is strictly row diagonally dominant, and if $a_{ii} > 0$ *for* $i = 1, ..., n$*, then every eigenvalue of A has a strictly positive real part.*

ii. If A is strictly row diagonally dominant, and if $a_{ii} < 0$ *for* $i = 1, ..., n$*, then every eigenvalue of A has a strictly negative real part.*

Theorem 1.3. *(Gershgorin's disc theorem) For any complex* $n \times n$ *matrix A, all the eigenvalues of A belong to the Gershgorin domain G(A). Furthermore the following properties hold: If A is strictly column diagonally dominant, that is* $\Sigma_{i=1,j\neq i}^{n}|a_{ij}| < |a_{ii}|$ *for* $i = 1, ..., n$ *then A is invertible.*

i. If A is strictly column diagonally dominant, and if $a_{ii} < 0$ *for* $i = 1, ..., n$*, then every eigenvalue of A has a strictly negative real part.*

ii. If A is strictly column diagonally dominant, and if $a_{ii} > 0$ *for* $i = 1, ..., n$*, then every eigenvalue of A has a strictly positive real part.*

Remark: *Neither strict row diagonal dominance nor strict column diagonal dominance are necessary for inevitability.*

1.4.2 Global Stability of Equilibrium points

The indirect method of Lyapunov which is used to determine the local stability of the equilibrium points has some limitations. Its results apply only in cases where there are infinitesimal perturbations about the equilibrium. The direct Lyapunov method addresses this problem.

Definition 1.3. *An equilibrium point* $\bar{x}$ *is said to be globally asymptotically stable if it is asymptotically stable for all initial condition* $x_0 \in \mathbb{R}^n$

Lyapunov Stability

The method of Lyapunov functions enables the analysis to be extended beyond only a small region near the equilibrium point that is it shows global stability analysis. Let $x = x_0$ be an equilibrium point for $\dot{p} = f(x)$. Let $V : D \to R : D \subset R^n$ be a continuously differentiable function on a neighborhood D of $x = x_0$, such that

$$\textit{(1)}\ V(x_0) = 0$$
$$\textit{(2)}\ V(x) > 0\ \textit{in}\ D - \{x_0\}$$
$$\textit{(3)}\ \dot{V} \leq 0\ \textit{in}\ D - \{x_0\}$$

Then $x = x_0$ is stable. Moreover, if $\dot{V} \leq 0$ in $D - \{x_0\}$ then $x = x_0$ is asymptotically stable.The continuously differentiable function $V(x)$ is called a Lyapunov function.

A Matrix-theoretic Method

A matrix theoretic method is presented to guide the construction of a Lyapunov function. Following [109], set $f(x, y) := (F - V)x - F(x, y) + V(x, y)$ Where, $x = (x_1, x_2, ..., x_n)^T \in \mathbb{R}^n$ and $y = (y_1, y_2, ..., y_m)^T \in \mathbb{R}^m$ represent the populations in disease compartments and non-disease compartments, respectively; $F = (F_1, F_2, ..., F_n)^T$ and $V = (V_1, V_2, ..., V_n)^T$, where F_i represents the rate of new infections in the i^{th} disease compartment; and V_i represents the transition terms, for example, death and recovery in the i^{th} disease compartment. Then for the disease compartments can be written as

$$x^{'} = (F - V)x - f(x, y) \tag{1.3}$$

Let $\omega^T \geq 0$ be the left eigenvector of the nonnegative matrix V^{-1} F corresponding to the eigenvalue $\rho(V^{-1}F) = \rho(V^{-1}F) = R_0$. The following result provides a general method to construct a Lyapunov function for (1.3). Note that this type of Lyapunov function involving the Perron eigenvector has previously been used to study the global dynamics for several specific disease models; see, for example, [109].

Theorem 1.4. *(Perron-Frobenius)*
Let A be an irreducible non-negative $n \times n$ matrix with spectral radius $\rho(A) = r$. Then the following statements hold:

- *r is a positive simple eigenvalue of the matrix A.*
- *A has a left eigenvector ω with eigenvalue r whose components are all positive.*

Theorem 1.5. *Let F, V and $f(x,y)$ be defined above. If $f(x,y) \geq 0$ in $\subset \mathbb{R}^{n+m}, F \geq 0, V^{-1} \geq 0$, and $R_0 \leq 1$, then the function $Q = \omega^T V^{-1} x$ is a Lyapunov function for model (1.3) on Γ.*

Proof. Differentiating Q along solutions of (1.3) gives $Q' = Q'|_{1.1} = \omega^T V^{-1} x' = \omega^T V^{-1}(F - V)x - \omega^T V^{-1} f(x,y) = (R_0 - 1)\omega^T x - \omega^T V^{-1} f(x,y)$ Since $\omega^T \geq 0$, $V^{-1} \geq 0$, and $f(x,y) \geq 0$ in Γ, the last term is non-positive. If $R_0 \geq 1$, then $Q' \leq 0$ in Γ, and thus Q is a Lyapunov function for system (1.3). □

A Graph-theoretic Method

A directed graph (digraph) G consists of a set of vertices and a set of ordered pairs (i,j) of (not necessarily distinct) vertices; each such pair (i,j) is called an arc from its initial vertex i to its terminal vertex j. The in-degree of a vertex i, denoted as $d^-(i)$, is the number of arcs in G whose terminal vertex is i, and the out-degree $d^+(i)$ is the number of arcs whose initial vertex is i. A subdigraph H of G is spanning if H and G have the same vertex sets. A digraph G is weighted if each arc is assigned a positive weight. The weight $w(H)$ of a subdigraph H is the product of the weights on all its arcs.

A (rooted) tree is a subdigraph T of G that is a single connected component and in which the in-degree of one vertex, the root, is zero, but each of the remaining vertices has in-degree 1. A (directed) path P is a subdigraph with distinct vertices labeled $i_1, i_2, ..., i_m$ so that its arcs are of the form (i_k, i_{k+1}) for $k = 1, 2, ..., m-1$; a (directed) cycle C is the subdigraph obtained from such a path P by adding the arc (i_m, i_1).

If $m = 1$, the cycle consisting of a single vertex i_1 and a single arc (i_1, i_1) is called a loop. A unicyclic graph is a subdigraph Q consisting of a collection of disjoint rooted trees whose roots are the vertices of a directed cycle; notice that the in-degree of every vertex of such a graph equals 1.

Given a weighted digraph G with n vertices, define the $n \times n$ weight matrix $A = [a_{ij}]$

with entry $a_{ij} > 0$ equal to the weight of arc (j, i) if it exists and 0 otherwise. We denote such a weighted digraph by (G, A). A digraph G is strongly connected if for any pair of distinct vertices i,j, there exists a directed path from i to j (and also from j to i). A weighted digraph (G, A) is strongly connected if and only if the weight matrix A is irreducible.

To establish global stability properties of the endemic equilibrium, we will use a graph-theoretic method as presented in [109]. A pair (i, j) is called an arc from vertex i to vertex j. Given a weighted digraph G(A) with n vertices, the $n \times n$ weight matrix A is defined with $a_{ij} > 0$ equal to the weight of arc (j, i) if it exists, and $a_{ij} = 0$ otherwise. The Laplacian L of $G(A)$ is defined as

$$l_{ij} = \begin{cases} -a_{ij}, i \neq j, \\ \Sigma_{k \neq i} a_{ik}, i = j \end{cases}$$

Let c_i be the cofactor of l_{ij}. If $G(A)$ is strongly connected, then $c_i > 0$, for all $i = 1, ..., n$. The following combinatorial identities are useful in finding explicit expressions for c_i: If $a_{ij} > 0$ and the out-degree of vertex j satisfies $d^+(j) = 1$, for some i, j, then

$$c_i a_{ij} = \Sigma_{k=1}^{n} c_j a_{ik}$$

If $a_{ij} > 0$ and the in-degree of vertex i satisfies $d^-(i) = 1$, for some i, j, then

$$c_i a_{ij} = \Sigma_{k=1}^{n} c_k a_{ki}$$

Theorem 1.6. *[109] For a given open set $E \subset \mathbb{R}^m$, and a function $f : E \to \mathbb{R}^m$, consider the system*

$$x^{'} = f(x) \tag{1.4}$$

and assume that

i. There exist functions $D_i : E \to \mathbb{R}^m, G_{ij} : E \to \mathbb{R}$ and constants $a_{ij} > 0$ such that $D_i^{'}|_{(1.4)} \leq \Sigma_{j=1}^{n} a_{ij} G_{ij}(x)$ with $x \in E, i = 1, ..., n$

ii. Each directed cycle C of $G(A)$ satisfies $\Sigma_{(s,r) \in S(C)} G_{rs}(x) \leq 0, x \in E$, where $S(C)$ denotes the set of all arcs in C. Then, there exist constants $c_i > 0, i = 1, ..., n$ (as defined above), such that the function $D(x) = \Sigma_{i=1}^{n} c_i D_i(x)$ satisfies $D^{'}|_{(1.4)}(x) \leq 0$, that is, $D(x)$ is a Lyapunov function for (1.4).

1.5 Sensitivity Analysis

Sensitivity analysis is performed to determine the importance of each parameter to the transmission dynamics of TB disease. The analysis helps to measure the relative change in a variable when a parameter changes. Such information is very important to study transmission dynamics of the disease and to optimize control measures of the disease. In order to decide the most influential parameter among the control measures in the present model, we will have taken the estimated values of the parameters.

In conducting the sensitivity analysis, we use methods described by [95]. The normalized forward sensitivity index of a variable to a parameter is the ratio of the relative change in the variable to the relative change in the parameter. Sensitivity indices allow us to measure the relative change in a state variable when a parameter changes. The normalized forward sensitivity index of a variable to a parameter is the ratio of the relative change in the variable to the relative change in the parameter.

When the variable is a differentiable function of the parameter, the sensitivity index may be alternatively defined using partial derivatives.

Definition 1.4. *[95] The normalized forward sensitivity index of a variable, u, that depends differentially on a parameter, p, is defined as:*

$$\Pi_p^u = \frac{\partial u}{\partial p} \times \frac{p}{u} \tag{1.5}$$

In interpreting the sensitivity indices of a variable with respect to a parameter, we first note that keeping all other factors fixed and determine the magnitude of the sensitivity indices. The parameter with higher magnitude is/are more influential. The sign of the sensitivity indices of the variable with respect to the parameters (1.5) show the positive or negative impact of the parameter on the given variable. That is, if the sign of the sensitivity indices, (1.5) is positive then the value of the variable increase whenever the value of the parameter increases and if the sign of the sensitivity indices, (1.5) is negative then the value of the variable decrease whenever the value of the parameter increase.

1.6 Research Problem

Ethiopia is one of the 30 high-TB-burden countries, which together account for 90% of the global TB cases in 2017, Figure 1.3 . Based on WHO estimation for 2014, Ethiopia had 200,000 incidence (new) TB cases in 2014. This number ranks Ethiopia 10^{th} globally and 4^{th} in Africa in terms of absolute TB-burden, after Nigeria, South Africa and the Democratic Republic of Cong. TB kills an estimated 32,000 Ethiopians every year (more than 80 people per day) [2, 49].

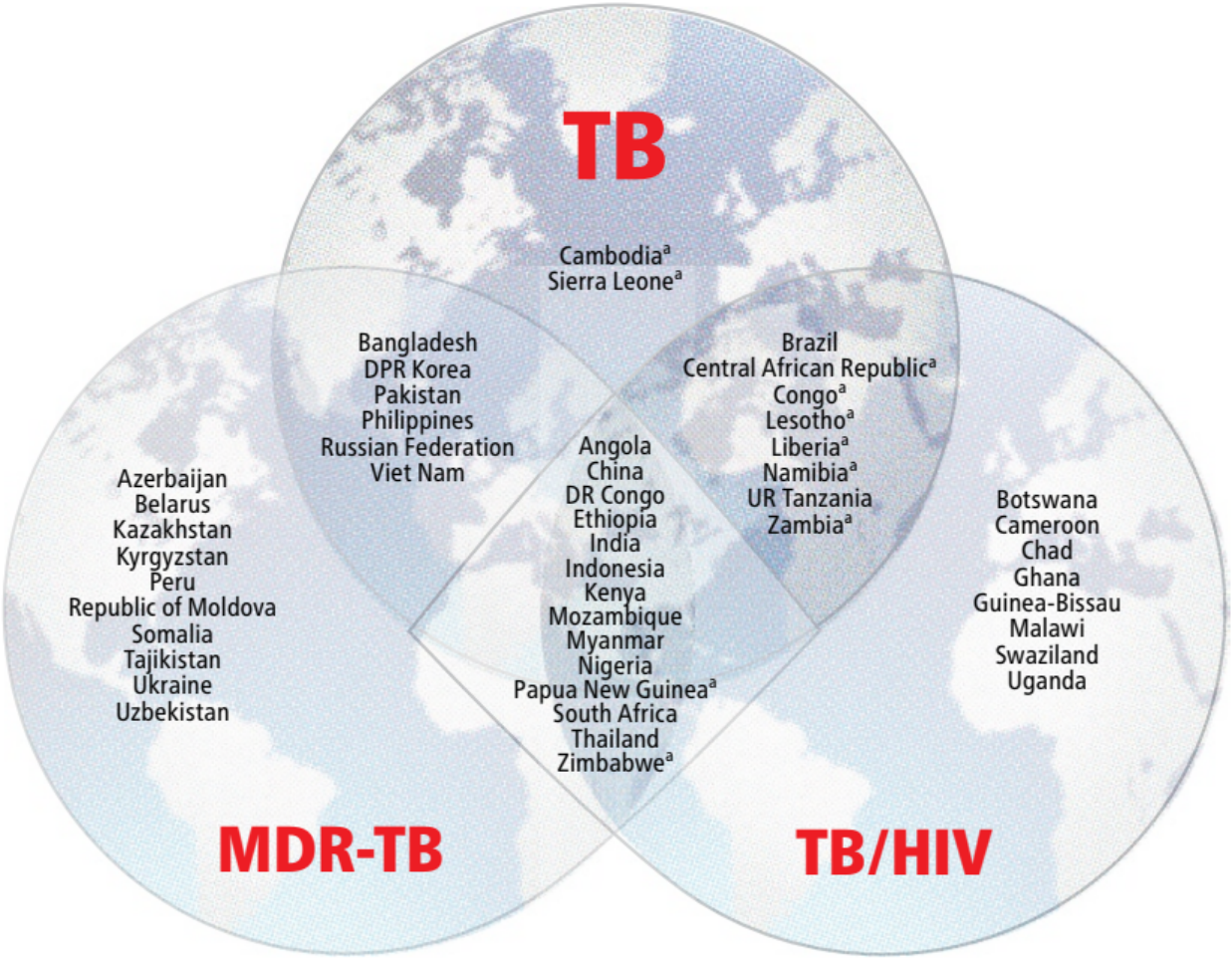

Figure 1.3: List of high TB burden countries [103]

Ethiopia is also ranks 15^{th} among the 30 countries with high burdens of MDR-TB, defined as TB bacteria resistant to the two most first-line TB drugs, isoniazid and rifampin [2, 103].

During the period 1998 to 2015, the concept of an HBC became familiar and widely used

in the context of TB. In 2015, three HBC lists for TB, TB/HIV and MDR-TB were in use. The HBC list for TB (22 countries) had remained unchanged since 2002, and the HBC lists for TB/HIV (41 countries) and MDR-TB (27 countries) had not been updated since 2009 and 2008, respectively.

The 14 countries that are in all three lists are Angola, China, the Democratic Republic of the Congo, Ethiopia, India, Indonesia, Kenya, Mozambique, Myanmar, Nigeria, Papua New Guinea, South Africa, Thailand and Zimbabwe. Then from these data we can observe that the problem is deep rooted in our country Ethiopia (WHO, 2017), figure 1.3 [102, 103].

According to the global report (2017) by WHO, still Ethiopia is one of the 30 high burden TB countries in the world and one of the countries in Africa with an estimated incidence of TB at 177 per 100, 000 population in 2016 and 123 per 100,000 population 2009 EC. Another challenge to TB control in Ethiopia is emergence of MDR-TB, with incidence of MDR TB 5.7 per 100,000 population in 2016 [102, 103]. From the above information we can understand that the spread of TB is one of the challenges faced by public health experts in Ethiopia. In addition, there is no as such fruitful research has done in Ethiopia using Mathematical modeling still know. Thus, we were decided to conduct an epidemiological research on a two-strain tuberculosis with a mathematical model analysis.

Thus, this study is based on deterministic mathematical model with interventions investigations that has raised the following research questions.

(1) Which strains do spread in the society?

(2) Which parameter(s) has(have) higher impact on the spread of either of the two strain tuberculosis disease?

(3) Which parameters are more influential in the control of either of the two strain tuberculosis disease?

1.7 Rationale of the Study

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

Mathematical models have become important tools in analyzing the spread and control of infectious diseases. As, Tuberculosis (TB) is a chronic infectious disease mainly caused by Mycobacterium Tuberculosis(MTB), which is affecting one third of the world's population, that makes Tuberculosis a global health problem. Many countries including Ethiopia are trying to eliminate the disease but the emergence of multi-drug resistant strain also being another challenge as it is difficult but not impossible to treat despite being too expensive. Ethiopia is one of the high burden TB countries, controlling of the spread TB gets a series attention [73].

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 (WHO, 2015)[102].

In Ethiopia the TB CNR (Case Notification Rate) is exist in each regions that ranges from 88 TB cases per 100,000 populations in Somali region to 368 per 100,000 in Dire Dawa (see table 1.2). Addis Ababa, Gambella, and Dire Dawa reported TB Case Notification Rates (CNR) of more than 200/100,000; whereas, Amhara, Oromia, Somali, Benshangul Gumuz and SNNP regions reported a TB CNR of less than the national Average (123 per 100,000). In 2009 EC, a total of 706 RR/MDR-TB cases are diagnosed and enrolled to second line anti TB drug; the treatment success rate of MDR TB reached 71.3%; WHO report (2009 EC) table 1.2 [41].

Table 1.2: Comparison of Baseline and Performance of TB Case Notification Rate, treatment success rate, cure rate by Region in Ethiopia (2009 EC), WHO report:

S/No.	Region	TB case per 100,000	TB treatment success rate (%)	TB Cure Rate(%)	RR/MDR-TB Patients
1	Tigray	129	91	81	100
2	Afar	173	74	54	16
3	Amhara	108	95	91	121
4	Oromia	122	96	91	178
5	Somalia	88	82	53	5
6	Benshangul Gumuz	109	92	83	0
7	SNNPR	118	94	81	92
8	Gambela	242	78	53	2
9	Harari	194	97	96	9
10	Addis Ababa	233	90	85	139
11	Dire Dawa	368	91	90	43
	National	**123**	**94**	**85**	**706**

Due to the above facts, we were motivated to conduct an epidemiological research on the two-strain tuberculosis mathematical model analysis in Ethiopia.

1.8 Objective and outline of the thesis

Main Objective of the Study

The main objective of this study is analyzing the spread and control of drug sensitive and multi-drug resistance tuberculosis in Ethiopia with an epidemiological mathematical model.

The Specific Objective of the Study

(1) To examine whether either of the two strains spread in the society or not.

(2) To recognize the most sensitive parameter(s) in the dynamical system of tuberculosis.

(3) To identify the most influential parameter that changes the numerical values of reproduction number.

(4) To suggest the controlling strategies that help to control TB infection.

Outline of the Thesis

In chapter four of this study we formulated a mathematical model with interventions vaccination, screening and treatment of TB infectious diseases. The positivity and boudedness of the considered model were proved. We used a next generation method to explore the effective reproduction number. We showed the existence of disease free and endemic equilibrium points. We applied the Routh Hiruwtz criteria, the Gorshigorin disc theorem to prove the local stability and Laypunov method to prove the global stability of those equilibrium points.

In chapter five we modified the model in chapter 4 by disaggregating TB bacteria into drug sensitive and multi drug resistance tuberculosis to obtain a new dynamical system with interventions vaccination, screening and treatment. Here, also we used a next generation method to explore the effective reproduction number. We showed the existence of disease free and endemic equilibrium points. The Routh Hiruwtz criteria, Gorshigorin disc theorem and Laypunov method were used to prove the local and/or the global stability of those equilibrium points.

Chapter six describes the numerical simulation of the dynamical system (4.1)-(4.8) in chapter 4 by using standard data collected from different sources. The result shows that the tuberculosis disease not spreads in the community and the rate of vaccine waning is the most influential parameter to change the effective reproduction number of the first dynamical system.

Chapter seven described the numerical simulation of the dynamical system (5.1)-(5.10) in chapter 5 by using real data collected from different health sectors in Ethiopia. The numerical value of the effective reproduction number of the DS-TB is 1.03 and the effective reproduction number of the MDR-TB is 4.78 and the effective reproduction number of the dynamical system $max\{1.03, 4.78\} = 4.78$. So that MDR strain is spreads strongly than DS strain. Using sensitive analysis we identify the most influential parameter to change the behavior of the solution of the considered dynamical system is the number of effective contacts of susceptible or vaccinated individuals make with an infectious individual. Finally, chapter 8 provides the results, conclusion and recommendations of the study.

Chapter 2

Literature Review

Mathematical models can be used to understand, predict and design effective intervention programmes to control TB and other epidemics [50]. Mathematical modeling for the transmission dynamics of TB began in 1962 by Waaler [47, 58, 62, 88, 91]. 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 implementation 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 [47].

Brogger, in [78] that improved Waaler's work, 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 compare different control strategies that included finding and treating more cases and the utilization of vaccination and 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.

Other review on mathematical modeling in TB ReVelle was used Brogger and Waaler's model to introduce the first nonlinear system of ordinary differential equations that models TB dynamics [23]. He clearly explained infection rate depends linearly on the preva-

lence using probabilistic approach. He developed an optimization model and used it to select control strategies that could be carried out at minimal cost.

In [12, 22, 111] the authors suggest that exogenous reinfection has a drastic effect on the qualitative dynamics of TB. In the other studies [12, 35, 67] in controlling and spreading of tuberculosis it is necessary to measure the numerical value of basic reproduction number, R_0, and it should be $R_0 < 1$ to prevent the epidemic. That is decreasing infection rate and increased the recovery rate through intensive treatment, so that the parameters which was influenced in tuberculosis spreading model were the infection rate and the recovery rate parameters. Hence, it would prevent poverty and unproductiveness cases, and gave government policy which was related to control of spreading tuberculosis.

The current standard for first-line drug-susceptibility testing is an automated liquid culture system, which requires 4 to 13 days for results. The treatment of multidrug-resistant tuberculosis is based on expert opinion and requires the creation of combination drug regimens chosen from five hierarchical groups of first-line and second-line drugs (WHO, 2011). Such therapy is associated with a high risk of intolerance and serious toxic effects. Since most of the recommended drugs have serious side effects that render treatment particularly difficult, expert consultation is always advised for the treatment of multidrug-resistant [10, 41, 52].

The study in [12], showed that the incorporation of exogenous reinfection into a two strain TB model allows the possibility of a subcritical bifurcation at the critical value of the basic reproductive number $R_0 = 1$, and hence the existence of multiple endemic equilibria for $R_0 < 1$ and the exogenous reinfection rate larger than a threshold. Thus reducing R_0 to be smaller than one may not be sufficient to eradicate the disease. An additional reduction in reinfection rate may be required. They also assume that the drug-resistant strain play a role in the process of exogenous reinfection for the drug- sensitive strain while the drug- sensitive strain not play a role in the process of exogenous reinfection for the drug-resistant strain. They compute of the basic reproduction number for the drug-sensitive strain and for drug- resistant strain. They showed that if exogenous reinfection forces reach some critical values then a backward bifurcation can happen, creating an endemic equilibrium when $R_0 < 1$.

Carlos Castillo-Chavez and Zhilan Feng, in [17] discussed on a two-strain model for TB and resistant TB with the purpose of determining the role that lack of drug treatment compliance by TB patient plays on the maintenance of antibiotic resistant strain. They consider two trains of TB: the regular TB strain and the resistant TB strain. They considered two latent stages for drug sensitive Tb strain and one latent stage for drug resistance strain. They assumed that the treatment rate for resistant TB individuals is very small and can be neglected.They interpreted the average numbers of secondary infectious cases produced by an ordinary TB strain and one resistant-TB infectious individual during his or her effective infectious period, respectively. They first studied a special version of two-strain model with two competing strains of TB. They found that co-existence is possible but rare while later and noticed that co-existence is almost certain when the second strain is the result of antibiotic resistance. They had showed that relatively drastic changes of qualitative behaviors of the disease dynamics occur when the effect of exogenous reinfection is incorporated into the model. Finally they suggest that the introduction of exogenous reinfection into the basic TB model allows for the possibility of a subcritical bifurcation of endemic equilibrium points at the critical value of the basic reproductive number $R_0 = 1$, and hence the existence of multiple endemic equilibria for $R_0 < 1$.

In [80], the authors propose a mathematical TB model that includes exogenous reinfection in the standard SEIL compartmental model is taken as the base model for the TB transmission dynamics, to gain a better understanding of the recent trend for TB incidence. Their model classifies individuals as the susceptible class (S), the exposed class(E), (or high-risk latent, that is, recently exposed but not yet infectious), the active-TB infectious class (I), and the low risk latent class or treated infected class (L). They suggested that among some key parameters in the model, the case finding effort turned, (e.g., taking the TB medications before occurring active TB) out to be the most significant impacting component on the reduction in the active TB cases. However, they suggest that concentrating on treatment alone or case finding alone will not dramatic affect the reduction in the active TB incidences. Their result shows that taking two or more of the key parameters at the same time will go a long way in reducing the burden of the active TB.

In [5], the researchers modeled the effect of combining Immunization with Latent Tuberculosis treatment in controlling the spread of Tuberculosis.They partitioned the population into five Compartments namely, Immunized M(t), Susceptible S(t), Latently Infected L(t), Infectious I(t) and Recovered R(t) Compartments. They showed that the administration of BCG vaccines at birth protects children from early infection of the disease, but the effect of these vaccines expires with time.

In [57, 67, 70, 71, 74, 97] incorporate the interventions vaccination and treatment and they evaluated the efficacy of TB control measures, other researchers [63, 72] include either of the interventions: isolation, quarantine, vaccine and treatment in order to eliminate TB disease in their models, but they do not consider the waning rate of BCG vaccine and not include vaccination, screening and treatment interventions all together in the dynamics of two strain tuberculosis (drug sensitive and multi-drug resistance tuberculosis).

Most reaserchers apply the local and global stability analysis and sensitivity analysis methods to analyze the properties of their dynamical system. The method of Huwth-Hirtz criteria was applied in most of the studies [16, 35] to show the local stability of disease free equilibrium point and endemic eqiulibrium points. The method of Lyapunov functions is commonly used to establish global stability for mathematical models [9, 19, 21, 28, 35, 46, 67, 66, 77, 93, 99] and Lyapunov functions can construct using graph theoretic method [56, 109].

Even if researches were conducted on a two strain tuberculosis any one of them was not consider the inefficacy of the BCG vaccine & waning of immune and; vaccination, screening and treatment interventions simultaneously to model the dynamics of a two strain tuberculosis. Another scenario that motivated us to conduct this study was that there is no as such significant study done in the Ethiopia context.

Chapter 3

Methodology

3.1 Study Design

In this study we were apply the mixing of quantitative and qualitative research methods to examine the spread and control of two strain tuberculosis. We have developed compartmental models with nonlinear system of ordinary differential equation, and follow a different approach: the next generation operator approach to compute the effective reproduction number and basic reproduction number; Routh – Hurwitz criterion and Gorshigorin disc theorem were applied to proof the local stability of disease free and endemic equilibrium points receptively. We also used the matrix theoretic method and graph theoretic method to construct the Lyapunov function to study the global stability of disease free and endemic equilibrium points respectively. Sensitivity analysis of parameters were done both qualitatively and quantitatively to recognize the impact of each parameters in the spread and control of tuberculosis disease. We have been apply the numerical simulation methods to the associated dynamics to test hypotheses and theory with the real data. This analysis has been presented with illustrations in graphs on the spread and control of the tuberculosis diseases with the interventions: vaccination, screening and treatment of infectious.

3.1.1 Study Population

The study population was comprised both DS-TB and MDR-TB cases who were registered for TB treatment follow up, individuals got a chance of vaccinated, screened individuals in hospitals and the sample health centers of the two Administrative cities and the nine Regional States in Ethiopia in the year 2011 E.C (July, 2018 to June, 2019).

3.1.2 Subject

In order to answer our research question from secondary data sources obtained from selected hospital, health centers and health posts of individuals based on their TB status. We have considered all populations in Ethiopia. Publications and statistical reports from governmental, international, and non-governmental organizations such as the World Health Organization, Federal Office of Public Health have been referred in an attempt to quantify the need for recruitment.

Inclusion and Exclusion Criteria:-

All Tuberculosis patients who developed DS-TB or MDR-TB and were treated, individuals got a chance of vaccinated, screened individuals in the hospital, clinic, health centers in the two administrative cities and the nine regional states was includes in our study. Therefore, all types of TB cases which were treated from July, 2018 to June, 2019 were included but patients individuals who were treated out of the study period and who were transfer from one health center to other health center were excluded.

3.1.3 Data Collection Method

In this study, secondary data was collected from already recorded document in the two administrative cities health bureau and the nine region states health bureau and national TB control program of Ethiopia, during the study period. The data have been include the following information: location of residence, history of previous TB treatment (vacci-

nated, screened and treated before or not), periods of TB treatment, treatment category, site of involvement and so on. We obtained data from the reports of World Health Organization (WHO), Federal Democratic Republic Ethiopia Ministry of Health and related literatures.

We considered that the total population is divided into compartments depending on the epidemiological status of individuals: Vaccinated, Susceptible, Latently infected of DS-TB, Screened DS-TB infected, infectious DS-TB, Latently infected of MDR-TB, Screened MDR-TB infected, MDR-TB infectious and recovered individuals.

The dependent variables are not free from the degree of specialization of physicians; factor which are a much higher risk of developing TB disease like HIV/AIDS status, malnutrition or diabetes, or people who use tobacco and the culture, age, sex, etc of the study.

3.1.4 Measures/ Instruments

We included the following measurments: history of previous TB treatment (vaccinated, screened and treated before or not), periods of TB treatment, treatment category and so on.

3.1.5 Procedure

The procedures we followed are: preparation of proposal, writing the fundamental research frame works, construction of assumptions, clarification of parameters, developing of flow chart and model, formulations of mathematical analysis, incorporating interventions, collecting real data, analyzing the model qualitatively, examining numerical experimentation and reporting the thesis.

3.1.6 Intervention

We formulated Mathematical model for a two-strain TB disease with interventions. The control parameters are prevention of susceptible individual from TB per unit time, screening and treatment of the exposed individuals per unit time and treatment of infectious individuals per unit time and practiced on a year (from July, 2018 to June, 2019).

3.1.7 Sample Size and Data Analysis

For most studies, especially those of human populations, all the people cannot be studied. This may be because the population is too large and therefore impossible to study every person due to time, financial and other resource constraints, or because it cannot be defined uniquely in either time or space. In such situations only a part of the population, a sample, would be studied and the results generalized to cover the whole population.

Ethiopia's population of 107 million lives in its nine regions and its two city administrations of Addis Ababa and Dire Dawa (Ethiopia population 2018 demographic maps graphs). There are further divided into 78 zones, 956 woredas (districts), and finally in to 16, 541 kebeles (neighborhoods). The population is 76% rural, 16% urban and 8% pastoralist. The operation of the system has been decentralized to regional governments and district health offices below them. Each district has a primary hospital with multiple health centers and every health center is administratively linked to five health posts-the lowest tier of Ethiopia's health care system. Each neighborhood has its own health post with two health extension workers (HEWs) who provide a package of up to 16 basic services to rural populations, including TB prevention and treatment follow-up [73].

In 2009 EC, there are a total of 266 Functional Hospitals, 3622 health centers and 16, 660 health posts in Ethiopia. Thus, we were apply a probability sampling method; first of all we were divide target population in to clusters by using the nine regional states and two administrative cities of Ethiopia. These clusters are homogenous among them but may be heterogeneous based on their culture, sex, age.

Since we know our population size and have been a desired confidence level we can use

the Automated Method (or the Manual Calculation Method). So, to perform sample size calculation manually, we need the following values: Population Value (Size of the population from which the sample be selected), Expected Frequency Value and Worst Acceptable Frequency value [48].

Numerical simulations have done using real data from ministry of health, Ethiopia. These numerical analysis have presented with graphs by using soft ware program.

Chapter 4

Analysis on the Dynamics of Tuberculosis Mathematical Model with Interventions

Abstract

In this chapter we considered a nonlinear dynamical system to study the dynamics of tuberculosis with vaccination, chemoprophylaxis and therapeutics treatments of latent and active tuberculosis respectively. The total population is divided in to eight compartments. We found that the dynamical system (4.1)-(4.8) has disease free equilibrium point and endemic equilibrium point. We also found that the effective reproduction number of the considered dynamical system is $R_{eff} = \frac{c\omega_s(\sigma\psi\mu+(\theta+(1-\psi)\mu))}{\theta+\mu}\frac{(1-p)\alpha(\epsilon\gamma\delta+(1-\epsilon)(\gamma+\delta))}{(\alpha+\mu)(\gamma+\mu)(\rho+\mu+d)}$. We proved that the disease free equilibrium point is locally and globally stable if $R_{eff} < 1$ and the endemic equilibrium point is locally stable if $R_{eff} > 1$ and the number of recovered at the endemic equilibrium, $R^* < \frac{\Lambda(d+\mu)}{c\omega\kappa\mu}$. We also proved that the global stability of both disease free and endemic equilibrium points using Liapunov method.

4.1 Introduction

Tuberculosis or TB (short for Tubercles Bacillus) is an air borne and highly infectious disease caused by infection with the bacteria mycobacterium tuberculosis [55]. TB patients are divided into active TB and latent (passive) TB where active TB can transmit disease. According to the World Health Organization, one-third of the world's population is infected, either latently or actively, with tuberculosis [15, 18]. The disease is most commonly transmitted from a person suffering from infectious (active) tuberculosis to other persons by infected droplets created when the person with active TB coughs, sneeze, sing or speak. The infectious bacilli are inhaled as droplets from the atmosphere. In the lung the bacteria are phagocytosed by alveolar macrophages and induce a localized proinflammatory response that leads to the recruitment of mononuclear cells from neighboring blood vessels [28, 51, 70]. Data from a variety of sources suggest that the life time risk of developing clinically evident TB after being infected is approximately 10%, with 90% likelihood of the infection remaining latent. Individuals who have a latent TB infection are neither clinically ill nor capable of transmitting TB [24, 26, 27]. At greater ages, the immunity of persons who have been previously infected may wane, and they may be then at risk of developing active TB as a consequence of either exogenous reinfection (i.e., acquiring a new infection from another infectious individual) or endogenous reactivation of latent bacilli (i.e., re-activation of a pre-existing dormant infection) [18, 55, 68, 70]. The general symptoms of TB disease include feelings of sickness or weakness, weight loss, fever, and night sweats. The symptoms of TB disease of the lungs also include coughing, chest pain, and the coughing up of blood [51, 55, 70]. Diagnosis relies on radiology (commonly chest X- ray), a tuberculin skin test, blood tests, as well as microscopic examination and microbiological culture of bodily fluids (such as sputum) [7, 51, 55].

TB affects all countries and all age groups, but overall the best estimates for 2017 were that 90% of cases were adults (aged $\geq$15 years), 64% were male, 9% were people living with HIV (72% of them in Africa) and two thirds were in eight countries: India (27%), China (9%), Indonesia (8%), the Philippines (6%), Pakistan (5%), Nigeria (4%), Bangladesh (4%) and South Africa (3%). Only 6% of cases were in the WHO European Region and the WHO Region of the Americas, each of which had 3% of cases, there were

under 10 new cases per 100 000 population in most high-income countries, 150–400 in most of the 30 high TB burden countries, and above 500 in a few countries including Mozambique, the Philippines and South Africa [102]. According to the WHO report, Ethiopia is one of the 30 high burden TB countries in the world which together account for 87% of the global TB cases, with an estimated incidence of TB 172,000 individuals in 2017. This number ranks Ethiopia 10th globally and 4th in Africa in terms of absolute TB-burden after Nigeria, South Africa and the Democratic Republic of Congo of estimated incidence TB 418,000, 322,000 262,000 individuals in 2017 [99]. TB kills an estimated 32,000 Ethiopians every year (more than 80 people per day)[73, 105]. In Ethiopia the TB case notification rate is exist in each regions that ranges from 88 TB cases per 100,000 populations in Somali region to 368 per 100,000 in Dire Dawa. Addis Ababa, Gambella, and Dire Dawa reported TB case notification rates of more than 200/100,000; whereas, Amhara, Tigray, Oromia, Somali, Benshangul Gumuz and SNNP regions reported a TB case notification rate of less than the national average (123 per 100,000) in 2017 [44].

Several researchers have continuously researched on how to reduce TB infection using mathematical models by incorporating control measures such as BCG vaccination, education, screening and treatment [9, 67]. Prevention relies on screening programmes and vaccination, usually with Bacillus calmette - Guérin (BCG) vaccine given to infants [7, 18, 55]. The main health-care interventions to prevent new infections of Mycobacterium tuberculosis and their progression to TB disease are treatment of latent TB infection and vaccination of children with the bacille Calmette-Guérin (BCG) vaccine. Meanwhile, for early prevention carried out immunization with BCG vaccine. This vaccine will be effective if given to the baby immediately after birth or at least 2 months after birth (with the note during which the baby is not in contact with active TB patients). TB preventive treatment for a latent TB infection is expanding, but most of those for whom it is strongly recommended are not yet accessing care, whereas coverage of BCG vaccination is high. WHO has strongly recommended treatment for latent TB infection in two priority groups: people living with HIV, and children aged less than 5 years who are household contacts of someone who has bacteriologically confirmed pulmonary TB [102].

A TB vaccine has been available for many decades. The effectiveness BCG vaccine in preventing TB is controversial (Salyers 1994). Results of field trials of the vaccine have differed widely, some indicating protection rates as high as 705% to 80%, others indicating the vaccine was completely ineffective in preventing TB (Salyers 1994) [18]. Some researchers also demonstrated efficacy ranging from no protection to 80% protection though a meta-analysis estimated that the overall efficacy of BCG is 50%, but this conclusion is controversial as the set of trials shows heterogeneity of efficacy (Colditz et al. 1994). Even in populations where BCG appears to be efficacious, there are very few data available on the effect of BCG after fifteen years. [71, 92].

Mainly control of tuberculosis is managed by two types of treatment. The treatment of latent TB is called chemoprophylaxis and treatment of active TB is called therapeutics. Treatment of TB lasts long; therefore control strategies have been developed for compliance to TB treatment. DOTS (Directly Observed Treatment, Short-Course) are a treatment program used for compliance with treatment of drug-sensitive TB. Another control program is DOTS-plus, which is developed for compliance with treatment of drug-resistant TB. A good public health treatment strategy combines different control strategies to control all types of TB infections [9, 15, 32, 55, 77].

Epidemiology is the science of public health. It studies the distribution and determinants of disease status or events in populations, with the aim of controlling public health problems. The study of epidemiology ranges from cluster investigation at the individual level to building mathematical models to simulate disease dynamics at the population level [15].

Mathematical models are important tools in analysing the spread and control of infectious diseases. This started as far back as 1760 when Daniel Bernoulli developed a model for smallpox [21, 51]. Many mathematical models have been developed for many infectious diseases including tuberculosis. Long-term effects of tuberculosis can be examined using epidemiological models. Epidemiological models consist of compartments which represent sets of individuals grouped by disease status. The links between compartments represent transitions from one state of disease to another state. The future of an epidemic can be estimated by finding the basic reproductive number of the model [15].The dynamics of TB are complex due to a combination of various factors of societal order such as social

and environmental factors, malnutrition, heavy alcohol drinking, smoking, HIV, diabetes mellitus [9]. Human Immunodeficiency Virus (HIV) is a major contributing factor for developing active TB. HIV infected individuals had 3.5-fold higher risk of tuberculosis than HIV negative individuals. Ethiopia is also among high TB/HIV burden countries with over 10% TB/HIV co-infection rate. Among people living with HIV, laboratory diagnosis of TB is more difficult compared to HIV negative, and mortality rates are higher [25, 44].

The Lyapunov functions used in this paper to demonstrate the stability of the endemic equilibria are of the same form as those used recently in [9, 19, 21, 28, 46, 66, 67, 77, 93, 99] to determine the global dynamics of their models. Global stability of epidemic models is always mathematically challenging [9]. The difficulty is to choose the coefficients of the Lyapunov function and to prove that its time derivative is non-positive.

In the first section 4.2 this chapter we set the model assumption, draw the flow chart of the model, develop the corresponding dynamical system . In section 4.3 we computed effective reproduction number, analyzed the existence of equilibrium points and proved their local and global stability. At the end in section 4.4 we gave the conclusion for the work.

4.2 The Mathematical Model

We introduce a deterministic tuberculosis model. The total population $N(t)$ is divided in to eight disjoint classes depending on the epidemiological status of individuals: Susceptible $S(t)$, who have never exposed to the Mycobacterium tuberculosis; Vaccinated $V(t)$, individuals who are vaccinated against mycobacterium tuberculosis; we assumed that persons with latent tuberculosis infection are considered at high risk of developing active tuberculosis during the first 2 years of infection, during which approximately 5% of those persons develop active tuberculosis and the likelihood of developing active disease after infection decreases with the age of the infection. Thus, we divide them in to two stages depending on the duration of time they spent after primary infection: An early stage with high risk of developing active tuberculosis $H_r(t)$ (in the first two years after

primary infection) and Later(Long) stage with low risk of developing active disease $L_r(t)$ (More than two years after primary infection but not transformed to active tuberculosis), individuals who screened and treating at early latent stage tuberculosis $T(t)$, Infectious individuals with tuberculosis $I(t)$ that are not yet in treatment, treating infectious $I_T(t)$ and Recovered individuals $R(t)$.

4.2.1 Model Assumptions

We assumed that the Population is closed which means the increase or decrease of population is only caused by birth and death, while the increase and reduction caused by other factors is ignored. That is, there are no immigrants and emigrants. The only way of entry into the population is through new – born babies and the only way of exit is through death from natural causes or death from tuberculosis-related causes. Death caused by factors other than tuberculosis infection is considered a natural death. Population is homogeneous. All newborns are previously uninfected by tuberculosis and therefore join either the vaccinated compartment or the susceptible compartment depending on whether they are vaccinated or not. The immunity conferred on individuals by vaccination expires after some time at a given rate. Infected individuals are divided into two groups: latent infected and active infected. The individual active infected can transmit tuberculosis disease. Latently Infected individuals are divided into two sub groups: early latent infected (high risk to develop active tuberculosis) and long (low risk to develop active tuberculosis) latent infected. All susceptible individuals are equally likely to be infected by infectious individuals in case of contact. Individuals in each compartment have equal natural death rate. Individuals on recovered classes will return to be individuals on infected classes. That the population size in a compartment is differentiable with respect to time and that the epidemic process is deterministic. Vaccine is given to new born populations.
We assumed that individuals are recruited into the population by a constant rate Λ with the proportions ψ of which are vaccinated to protect them against tuberculosis infection and the remaining proportion are susceptible. All susceptible individuals are equally likely to be infected by infectious individuals in case of contact. Furthermore, the vaccine has a waning effect over time (after a time $\frac{1}{\theta}$ vaccinated individuals become susceptible). Susceptible population increases due to the coming in of new births not vaccinated against

the infection and those who were vaccinated but lose their immunity. We assume that vaccinated individuals may infect with the rate of ineffecancy of BCG vaccine $\sigma \in [0, 1]$. When some susceptible and vaccinated individuals come into contact with infectious individuals, they get infected and progress to latently infected classes at a force of infection rate λ and $\sigma\lambda$ respectively where $\lambda = c\omega\frac{I}{N}$ and ω is the probability that an individual is infected by one infectious individual, and c is the percapita contact rate.

The proportion p of class H_r have got a chance of screened and treatment while the remaining proportion $(1-p)$ of the high risk latently tuberculosis infected individuals may not have opportunity for treatment. The proportion ϵ and $(1-\epsilon)$ of individuals of the early latent/exposed individuals for tuberculosis who do not get chance for screened will go to L_r and I respectively at the rate α. Thus, the proportion p, $\epsilon(1-p)$ and $(1-\epsilon)(1-p)$ of individuals in the class H_r is transferred to classes T, L_r and I respectively at a rate α. Individual leaves class L_r at the rate γ in which, the proportion δ goes to class I and; the remaining proportion $(1-\delta)$ recovers naturally and enter to recovered class R. The proportion q of individuals in class I goes for treatment in I_T and the remaining proportion $(1-q)$ enters to class R at the rate ρ. Individuals leave the screened class T and treating class I_T at the rates ϕ, and φ respectively, and go to recovered class, where $\phi > \varphi$.

Individuals in the recovered class are temporarily recovered. Soon they revert back to the latently infected classes H_r after been re-infected by tuberculosis at the rate $\kappa\lambda$, where κ is the reduction in susceptibility due to prior endogenous infection of tuberculosis. We assume that each class conforms to natural death at the rate μ while infectious individuals in I are die due to tuberculosis diseases at the rate d.
Based on the above assumptions we do have the following flow chart: With the above assumptions and relations between different compartments the dynamics of tuberculosis

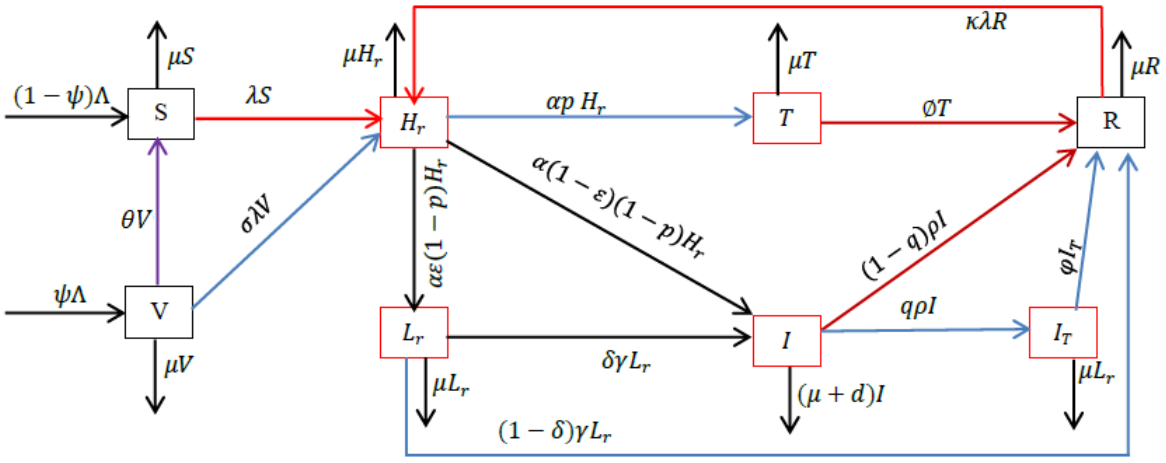

Figure 4.1: Flow chart of dynamical system (4.1)-(4.8) of a tuberculosis model

model can be ruled by the following nonlinear ordinary differential equations.

$$\frac{dV}{dt} = \psi\Lambda - (\sigma\lambda + \theta + \mu)V \tag{4.1}$$

$$\frac{dS}{dt} = (1-\psi)\Lambda + \theta V - (\lambda + \mu)S \tag{4.2}$$

$$\frac{dH_r}{dt} = \lambda(\sigma V + S + \kappa R) - (\alpha + \mu)H_r \tag{4.3}$$

$$\frac{dL_r}{dt} = \epsilon\alpha(1-p)H_r - (\gamma + \mu)L_r \tag{4.4}$$

$$\frac{dT}{dt} = \alpha p H_r - (\phi + \mu)T \tag{4.5}$$

$$\frac{dI}{dt} = \delta\gamma L_r + \alpha(1-\epsilon)(1-p)H_r - (\rho + \mu + d)I \tag{4.6}$$

$$\frac{dI_T}{dt} = q\rho I - (\varphi + \mu)I_T \tag{4.7}$$

$$\frac{dR}{dt} = (1-q)\rho I + \gamma(1-\delta)L_r + \phi T + \varphi I_T - (\kappa\lambda + \mu)R \tag{4.8}$$

With the total population at a given time t is

$$N(t) = S(t) + V(t) + H_r(t) + L_r(t) + I(t) + T(t) + I_T(t) + R(t)$$

Table 4.1: Symbols and their description for state variables and parameters in the dynamical system (4.1)-(4.8)

Symbols	**Description**
S(t)	Susceptible individuals who are at risk of being infected by tuberculosis at time t

V(t)	Vaccinated individuals against tuberculosis at time t.
$H_r(t)$	Early latently(High risk) infected individuals at time t.
$L_r(t)$	Long latently(Low risk) infected individuals at time t.
T(t)	Screened and treating individuals at time t.
I(t)	Individuals who are infectious at time t.
$I_T(t)$	Infectious individuals who start therapy
R	Individuals Recovered against tuberculosis at time t.
Λ	Recruitment of the population
ψ	Proportions new born vaccinated
μ	Natural death rate
σ	The rate of inefficacy of vaccine
θ	The rate of vaccine waning
λ	Force of infection
ω	Probability of acquiring tuberculosis infections one infectious individual
c	Number of effective contacts susceptible individuals makes with infectious individuals per year
α	The rate of progression of individuals from early latently infected
d	Death rate due to the TB disease
p	Proportion of early latently infected individuals who go for treatment
γ	Progression rate from Long latently infected tuberculosis.
δ	The portion of L_r enter in to I
ϵ	Proportion of individuals who do not get chance for screened at H_r and will go to L_r class
ρ	The rate at which individuals leave infectious class
q	Proportion of infectious individuals who go for treatment
ϕ	The rate of chemoprophylaxis treatment of early latent tuberculosis
φ	The rate of therapeutic of treatment active tuberculosis individuals in I_T
κ	Acquired immunity due to previous treatment

4.3 Basic Properties of the Model

4.3.1 Positivity of Solutions of the Dynamical System

For the human population model to be epidemiologically meaningful it should be that all solution of the model with positive initial value remains positive for all time t_0. Therefore, we have been discussed under which the model being studied has non-negative solutions. The derivative of a function at a point is one property that shows the behaviour of that function. It is known that if the derivative at a point is positive, then the function is increasing there, if it is negative, then the function is decreasing and if it is zero, then function is constant. Thus, we show the positivity of the solution for the given dynamical system.

Theorem 4.1. *Let the initial value for the model is* $V(0) > 0, S(0) > 0, H_r(0) > 0, L_r(0) > 0, I(0) > 0, T(0) > 0, I_T(0) > 0$ *and* $R(0) > 0$ *. Then, the solutions* $V(t), S(t), H_r(t), L_r(t), I(t),$
$T(t), I_T(t)$ *and* $R(t)$ *of the dynamical system (4.1)-(4.8) will be remain positive for all time* $t > 0$.

Proof. Let $\bar{t} = sup\{t > 0 : S(t) > 0, V(t) > 0, S(t), H_r(t) > 0, L_r(t) > 0, I(t) > 0, T(t) > 0, I_T(t) > 0$ and $R(t) > 0\} \in [0, t]$ and by considering the eight ordinary differential equations we do have:
From the equation (4.1) we have: $\frac{dV}{dt} = \psi\Lambda - (\sigma\lambda + \theta + \mu)V$
We can be rewrite as: $\frac{dV}{dt} + (\sigma\lambda + \theta + \mu)V = \psi\Lambda$
Multiply both sides by $e^{[\int_0^{\bar{t}}(\theta+\mu+\sigma\lambda(v))dv]} = e^{[\theta\bar{t}+\mu\bar{t}+\int_0^{\bar{t}}\lambda(v)dv]}$

$$\Leftrightarrow \frac{dV}{dt}e^{[\theta\bar{t}+\mu\bar{t}+\int_0^{\bar{t}}\lambda(v)dv]} + (\sigma\lambda(t) + \theta + \mu)V(t)e^{[\theta\bar{t}+\mu\bar{t}+\int_0^{\bar{t}}\lambda(v)dv]} = \psi\Lambda e^{[\theta\bar{t}+\mu\bar{t}+\int_0^{\bar{t}}\lambda(v)dv]}$$

$$\Leftrightarrow \frac{d}{dt}[V(t)e^{[\theta\bar{t}+\mu\bar{t}+\int_0^{\bar{t}}\lambda(v)dv]} - V(0) = \int_0^{\bar{t}}\psi\Lambda e^{[\theta\bar{t}+\mu\bar{t}+\int_0^{\bar{t}}\lambda(v)dv]}dt$$

Therefore, $V(\bar{t})e^{[\theta\bar{t}+\mu\bar{t}+\int_0^{\bar{t}}\lambda(v)dv]} - V(0) = \int_0^{\bar{t}}\psi\Lambda e^{\{\theta\bar{t}+\mu\bar{t}+\int_0^{w}(\lambda(v))dv}\}dt$
Then, $V(\bar{t}) = V(0)M_V + M_V\int_0^{\bar{t}}\psi\Lambda e^{\{\theta\bar{t}+\mu\bar{t}+\int_0^{w}(\lambda(v))dv}\}dw > 0$
Where $M_V = exp - \theta\bar{t} + \mu\bar{t} + \int_0^{\bar{t}}\lambda(v)dv > 0$

From the equation (4.2) we have: $\frac{dS}{dt} = (1-\psi)\Lambda + \theta V - (\lambda + \mu)S$

We can be rewrite as: $\frac{dS}{dt} + (\lambda + \mu)S = (1-\psi)\Lambda + \theta V$

Multiply both sides by $e^{[\int_0^{\bar{t}}(\mu+\lambda(v))dv]} = e^{[\mu t + \int_0^{\bar{t}}\lambda(v)dv]}$

$$\Leftrightarrow \frac{dS}{dt}e^{[\mu t+\int_0^{\bar{t}}\lambda(v)dv]} + (\lambda(t)+\mu)S(t)e^{[\mu t+\int_0^{\bar{t}}\lambda(v)dv]} = [(1-\psi)\Lambda + \theta V]e^{[\mu t+\int_0^{\bar{t}}\lambda(v)dv]}$$

$$\Leftrightarrow \frac{d}{dt}[S(t)e^{\{\mu t+\int_0^{\bar{t}}\lambda(v)dv\}}] - S(0) = \int_0^{\bar{t}}((1-\psi)\Lambda + \theta V(t))e^{\{\mu t+\int_0^{w}(\lambda(v))dv\}dt}$$

Therefore, $S(\bar{t})e^{\{\mu\bar{t}\}+\int_0^{\bar{t}}\lambda(v)dv} - S(0) = \int_0^{\bar{t}}((1-\psi)\Lambda + \theta V(t))e^{\{\mu t+\int_0^{w}(\lambda(v))dv\}}dt$

Then, $S(\bar{t}) = S(0)M_S + M_S\int_0^{\bar{t}}((1-\psi)\Lambda + \theta V(t))e^{\{\mu t+\int_0^{w}(\lambda(v))dv\}}dw > 0$

Where $M_S = e^{-\{\mu t+\int_0^{\bar{t}}\lambda(v)dv\}} > 0$

From the equation (4.3) we have: $\frac{dH_r}{dt} = \lambda(S + \sigma V + \kappa R) - (\alpha + \mu)H_r$

We can be rewrite as: $\frac{dH_r}{dt} + (\alpha + \mu)H_r = \lambda(S + \sigma V + \kappa R)$

Multiply both sides by $e^{[\int_0^{\bar{t}}(\alpha+\mu)dv]} = e^{[\alpha\bar{t}+\mu\bar{t}]}$

$$\Leftrightarrow \frac{dH_r}{dt}e^{[\alpha\bar{t}+\mu\bar{t}]} + (\alpha+\mu)H_re^{[\alpha\bar{t}+\mu\bar{t}]} = \lambda(S+\sigma V+\kappa R)e^{[\alpha\bar{t}+\mu\bar{t}]}$$

$$\Leftrightarrow \frac{d}{dt}H_r(t)e^{[\alpha\bar{t}+\mu\bar{t}]} - H_r(0) = \int_0^{\bar{t}}\lambda(t)(S(t)+\sigma V(t)+\kappa R(t))e^{[\alpha\bar{t}+\mu\bar{t}]}dt$$

Therefore, $H_r(\bar{t})e^{[\alpha\bar{t}+\mu\bar{t}]} - H_r(0) = \int_0^{\bar{t}}\lambda(t)(S(t)+\sigma V(t)+\kappa R(t))e^{[\alpha\bar{t}+\mu\bar{t}]}dt$

Then, $H_r(\bar{t}) = H_r(0)M_H + M_H\int_0^{\bar{t}}\lambda(t)(S(t)+\sigma V(t)+\kappa R(t))e^{[\alpha\bar{t}+\mu\bar{t}]}dw > 0$

Where $M_H = e^{-[\alpha\bar{t}+\mu\bar{t}]} > 0$

From the equation (4.4) we have: $\frac{dL_r}{dt} = \alpha\epsilon(1-p)H_r - (\gamma+\mu)L_r$

We can be rewrite as: $\frac{L_r}{dt} + (\gamma+\mu)L_r = \alpha\epsilon(1-p)H_r$

Multiply both sides by $e^{[\int_0^{\bar{t}}(\gamma+\mu)dv]} = e^{[\gamma\bar{t}+\mu\bar{t}]}$

$$\Leftrightarrow \frac{L_r}{dt}e^{[\gamma\bar{t}+\mu\bar{t}]} + (\gamma+\mu)L_re^{[\gamma\bar{t}+\mu\bar{t}]} = \alpha\epsilon(1-p)H_re^{[}\gamma\bar{t}+\mu\bar{t}]$$

$$\Leftrightarrow \frac{d}{dt}[L_r(t)e^{[\gamma\bar{t}+\mu\bar{t}]}] - L_r(0) = \int_0^{\bar{t}}\alpha\epsilon(1-p)H_re^{[\gamma\bar{t}+\mu\bar{t}]}dt$$

Therefore, $L_r(\bar{t})e^{[\gamma\bar{t}+\mu\bar{t}]} - L_r(0) = \int_0^{\bar{t}}\alpha\epsilon(1-p)H_re^{[\gamma\bar{t}+\mu\bar{t}]}dt$

Then,$L_r(\bar{t}) = L_r(0)M_L + M_L\int_0^{\bar{t}}\alpha\epsilon(1-p)H_re^{[\gamma\bar{t}+\mu\bar{t}]}dw > 0$, Where $M_L = e^{-[\gamma\bar{t}+\mu\bar{t}]} > 0$

From the equation (4.5) we have: $\frac{dT}{dt} = \alpha pH_r - (\phi+\mu)T$

We can be rewrite as: $\frac{dT}{dt} + (\phi+\mu)T = \alpha pH_r$

Multiply both sides by $e^{[\int_0^{\bar{t}}(\phi+\mu)dv]} = e^{[\phi\bar{t}+\mu\bar{t}]}$

$$\Leftrightarrow \frac{dT}{dt}e^{[\phi\bar{t}+\mu\bar{t}]} + (\phi+\mu)Te^{[\phi\bar{t}+\mu\bar{t}]} = \alpha pH_re^{[\phi\bar{t}+\mu\bar{t}]}$$

$$\Leftrightarrow \frac{d}{dt}[T(t)e^{[\phi\bar{t}+\mu\bar{t}]}] - T(0) = \int_0^{\bar{t}}\alpha pH_re^{[\phi\bar{t}+\mu\bar{t}]}dt$$

Therefore, $T(\bar{t})e^{[\phi\bar{t}+\mu\bar{t}]} - T(0) = \int_0^{\bar{t}} \alpha p H_r e^{[\phi\bar{t}+\mu\bar{t}]}dt$

Then, $T(\bar{t}) = T(0)M_T + M_T \int_0^{\bar{t}} \alpha p H_r e^{[\phi\bar{t}+\mu\bar{t}]}dt > 0$, Where $M_T = e^{-[\phi\bar{t}+\mu\bar{t}]} > 0$

From the equation (4.6) we have: $\frac{dI}{dt} = \delta\gamma L_r + \alpha(1-\epsilon)(1-p)H_r - (\rho+\mu+d)I$

We can be rewrite as: $\frac{dI}{dt} + (\rho+\mu+d)I = \delta\gamma L_r + \alpha(1-\epsilon)(1-p)H_r$

Multiply both sides by $e^{[\int_0^{\bar{t}}(\rho+\mu+d)dv]} = e^{[\rho\bar{t}+d\bar{t}+\mu\bar{t}]}$

$$\Leftrightarrow \frac{dI}{dt}e^{[\rho\bar{t}+d\bar{t}+\mu\bar{t}]} + (\rho+\mu+d)Ite^{[\rho\bar{t}+d\bar{t}+\mu\bar{t}]} = [\delta\gamma L_r + \alpha(1-\epsilon)(1-p)H_r]e^{[\rho\bar{t}+d\bar{t}+\mu\bar{t}]}$$

$$\Leftrightarrow \frac{d}{dt}[I(t)e^{[\rho\bar{t}+d\bar{t}+\mu\bar{t}]}] - I(0) = [\delta\gamma L_r + \alpha(1-\epsilon)(1-p)H_r]e^{[\rho\bar{t}+d\bar{t}+\mu\bar{t}]}$$

Therefore, $I(\bar{t})e^{[\rho\bar{t}+d\bar{t}+\mu\bar{t}]} - I(0) = \int_0^{\bar{t}}[\delta\gamma L_r + \alpha(1-\epsilon)(1-p)H_r]e^{[\rho\bar{t}+d\bar{t}+\mu\bar{t}]}dt$

Then, $I(\bar{t}) = I(0)M_I + M_I \int_0^{\bar{t}}[\delta\gamma L_r + \alpha(1-\epsilon)(1-p)H_r]e^{[\rho\bar{t}+d\bar{t}+\mu\bar{t}]}dt > 0$

Where $M_I = e^{-[\rho\bar{t}+d\bar{t}+\mu\bar{t}]} > 0$

From the equation (4.7) we have $\frac{dI_T}{dt} = q\rho I - (\varphi+\mu)I_T$

We can be rewrite as: $\frac{dI_T}{dt} + (\varphi+\mu)I_T = q\rho I$

Multiply both sides by $e^{[\int_0^{\bar{t}}(\varphi+\mu)dv]} = e^{[\varphi\bar{t}+\mu\bar{t}]}$

$$\Leftrightarrow \frac{dI_T}{dt}e^{[}\varphi\bar{t} + \mu\bar{t}] + (\varphi+\mu)I_T e^{[\varphi\bar{t}+\mu\bar{t}]} = q\rho I(t)e^{[\varphi\bar{t}+\mu\bar{t}]}$$

$$\Leftrightarrow \frac{d}{dt}[I_T(t)e^{[\varphi\bar{t}+\mu\bar{t}]}] - I_T(0) = \int_0^{\bar{t}} q\rho I(t)e^{[\varphi\bar{t}+\mu\bar{t}]}dt$$

Therefore, $I_T(\bar{t})e^{[\varphi\bar{t}+\mu\bar{t}]} - I_T(0) = \int_0^{\bar{t}} q\rho I(t)e^{[\varphi\bar{t}+\mu\bar{t}]}dt$

Then, $I_T(\bar{t}) = I_T(0)M_{I_T} + M_{I_T}\int_0^{\bar{t}} q\rho I(t)e^{[\varphi\bar{t}+\mu\bar{t}]}dt > 0$, where $M_{I_T} = e^{-[\varphi\bar{t}+\mu\bar{t}]} > 0$

From the equation (4.8) we have: $\frac{dR}{dt} = \phi T + (1-q)\rho I + \varphi I_T + (1-\delta)\gamma L_r - (\kappa\lambda+\mu)R$

We can be rewrite as: $\frac{dR}{dt} + (\kappa\lambda+\mu)R = \phi T + (1-q)\rho I + \varphi I_T + (1-\delta)\gamma L_r$

Multiply both sides by $e^{[\int_0^{\bar{t}}(\mu+\lambda(v))dv]} = e^{[\mu\bar{t}+\int_0^{\bar{t}}\lambda(v)dv]}$

$$\Leftrightarrow \frac{dR}{dt}e^{[\mu\bar{t}+\int_0^{\bar{t}}\lambda(v)dv]} + (\lambda(t)+\mu)R(t)e^{[\mu\bar{t}+\int_0^{\bar{t}}\lambda(v)dv]}$$

$$= [T + (1-q)\rho I + \varphi I_T + (1-\delta)\gamma L_r]e^{[\mu\bar{t}+\int_0^{\bar{t}}\lambda(v)dv]}$$

$$\Leftrightarrow \frac{d}{dt}[R(t)e^{[\mu\bar{t}+\int_0^{\bar{t}}\lambda(v)dv]} - R(0) = \int_0^{\bar{t}}[T + (1-q)\rho I + \varphi I_T + (1\delta)\gamma L_r]e^{[\mu\bar{t}+\int_0^{\bar{t}}\lambda(v)dv]}dt$$

Therefore, $R(\bar{t})e^{\{[\mu\bar{t}+\int_0^{\bar{t}}\lambda(v)dv]\}} - R(0) = \int_0^{\bar{t}}[T + (1-q)\rho I + \varphi I_T + (1-\delta)\gamma L_r]e^{[\mu\bar{t}+\int_0^{\bar{t}}\lambda(v)dv]}dt$

Then, $R(\bar{t}) = R(0)M_R + M_R\int_0^{\bar{t}}[T + (1-q)\rho I + \varphi I_T + (1-\delta)\gamma L_r]e^{[\mu\bar{t}+\int_0^{\bar{t}}\lambda(v)dv]}dw > 0$

Where $M_R = e^{-[\mu\bar{t}+\int_0^{\bar{t}}\lambda(v)dv]} > 0$

Therefore all of the state variables of our model system (4.1)-(4.8) are positive for all $t > 0$ given any positive initial conditions. □

4.3.2 Boundedness of Solutions of the Dynamical System

Theorem 4.2. *The closed set* $\Omega = \{(V, S, H_r, L_r, T, I, I_T, R) \in \mathbb{R}^8_+ : N \leq \frac{\Lambda}{\mu}\}$ *is positively invariant and attracts all positive solutions of the dynamical system (4.1) – (4.8).*

Proof. Consider the biologically feasible region, Ω and observe that the rate of change of the total population obtained by adding all the equations of the model (4.1)-(4.8) is given by $\frac{dN}{dt} = \Lambda - \mu N - dI \leq \Lambda - \mu N$. It follows that $\frac{dN}{dt} < 0$ whenever $N > \frac{\Lambda}{\mu}$. Furthermore, since $\frac{dN}{dt} = \Lambda - \mu N$; Now using a standard comparison theorem we do have $\int \frac{dN}{(\Lambda - \mu N)} \leq \int dt$. Integrating both sides gives $\Lambda - \mu N \geq Ae^{-\mu t}$, where $A = e^{-c\mu}$ it is a constant. By using initial condition $N(0)$ we do have $\Lambda - \mu N(0) \geq A$ or $N(0) \leq \frac{\Lambda}{\mu} - \frac{A}{\mu} \leq \frac{\Lambda}{\mu}$ and $N(t) \leq N(0)e^{-\mu t} + \frac{\Lambda}{\mu}(1 - e^{-\mu t})$.

Thus $lim_{t\to\infty} N(t) \leq N(0)e^{-\mu t} + \frac{\Lambda}{\mu}(1 - e^{-\mu t})$, which implies that $lim_{t\to\infty} N(t) \leq N(0)e^{-\mu t} - \frac{\Lambda}{\mu}e^{-\mu t} + \frac{\Lambda}{\mu} \leq \frac{\Lambda}{\mu}$ since $N(0) \leq \frac{\Lambda}{\mu}$. Hence as $t \to$ inf the population size $N(t) \to \frac{\Lambda}{\mu}$ which implies that $0 \leq N(t) \leq \frac{\Lambda}{\mu}$.Therefore, all feasible solutions of the dynamical system (4.1) - (4.8) with initial conditions in $\Omega = \{(V, S, H_r, L_r, T, I, I_T, R) \in \mathbb{R}^8_+ : N \leq \frac{\Lambda}{\mu}\}$ do remain in Ω for all $t > 0$. That is, the set Ω is positively invariant and attracting.

From the equation (4.1) we have: $\frac{dV}{dt} = \psi\Lambda - (\sigma\lambda + \theta + \mu)V$
If we add $\sigma\lambda V$ to the right side, we get: $\frac{dV}{dt} \leq \psi\Lambda - (\theta + \mu)V$
Using a standard comparision theorem: $\int \frac{dV}{(\psi\Lambda - (\theta+\mu)}V) \leq \int dt \Leftrightarrow -\frac{1}{(\theta+\mu)} ln(\psi\Lambda - (\theta + \mu)V) \leq t + c$, where c is a constant

$$\Leftrightarrow \psi\Lambda - (\theta + \mu)V \geq Be^{-(\theta+\mu)t}, \text{ where } B = e^{-c(\theta+\mu)} \text{ is a constant}$$
$$\Leftrightarrow V \leq \frac{\psi\Lambda}{(\theta + \mu)} - \frac{B}{(\theta + \mu)}e^{-(\theta+\mu)t}$$

By applying the initial condition $V(0)$:

$$\psi\Lambda - (\theta + \mu)V \geq Be^{-(\theta+\mu)t}, \Leftrightarrow V(0) \leq \frac{\psi\Lambda}{(\theta + \mu)} - \frac{B}{(\theta + mu)} \leq \frac{\psi\Lambda}{(\theta + \mu)},$$

Then from the inequality $\psi\Lambda - (\theta + \mu)V \geq Be^{-(\theta+\mu)t}$, and taking $B = \psi\Lambda - (\theta + \mu)V(0)$ we can get,

$$V(t) \leq \frac{\psi\Lambda}{(\theta+\mu)} - \frac{B}{(\theta+\mu)}e^{-(\theta+\mu)t} \leq \frac{\psi\Lambda}{(\theta+\mu)} - (\frac{\psi\Lambda}{(\theta+mu)} - V(0))e^{-(\theta+\mu)t)}$$

$$V(t) \leq V(0)e^{-(\theta+\mu)t} + \frac{\psi\Lambda}{(\theta+mu)}(1-e^{-(\theta+mu)t})$$

$$V(t) \leq V(0)e^{-(\theta+mu)t} + \frac{\psi\Lambda}{(\theta+mu)}(1-e^{-(\theta+mu)t})$$

$$lim_{t\to\infty}V(t) \leq V(0)e^{-(\theta+mu)t} + \frac{\psi\Lambda}{(\theta+mu)}(1-e^{-(\theta+mu)t})$$

$$lim_{t\to\infty}V(t) \leq (V(0) - \frac{\psi\Lambda}{(\theta+mu)}e^{-(\theta+mu)t} + \frac{\psi\Lambda}{(\theta+mu)}$$

$$\leq \frac{\psi\Lambda}{(\theta+mu)}(Since, V(0) \leq \frac{\psi\Lambda}{(\theta+mu)})$$

From the equation (4.2), we have: $\frac{dS}{dt} = (1-\psi)\Lambda + \theta V - (\lambda+\mu)S$

If we add λS to the right side, we get: $\frac{dS}{dt} \leq (1-\psi)\Lambda + \theta V - \mu S$

Using a standard comparision theorem: $\int \frac{dS}{(1-\psi)\Lambda+\theta V-\mu S} \leq \int dt$

$$\Leftrightarrow -\frac{1}{\mu}ln((1-\psi)\Lambda + \theta V - \mu S) \leq t + c, \ \textit{where c is a constant}$$

$$\Leftrightarrow (1-\psi)\Lambda + \theta V - \mu S \geq Ce^{-\mu t}, \ \textit{where } C = e^{-c\mu t} \textit{ is a constant}$$

$$\Leftrightarrow S \leq \frac{(1-\psi)\lambda + \theta V}{\mu} - \frac{C}{\mu}e^{-\mu t}$$

By applying the initial condition S(0):

$$S(t) \leq \frac{(1-\psi)\Lambda + \theta V}{\mu} - \frac{C}{\mu}e^{-\mu t}, \Leftrightarrow S(0) \leq \frac{(1-\psi)\Lambda + \theta V}{\mu} - \frac{C}{\mu} \leq \frac{(1-\psi)\Lambda + \theta V}{\mu},$$

Then from the inequality $(1-\psi)\Lambda + \theta V - \mu S \geq Ce^{-\mu t}$, and taking $C = (1-\psi)\Lambda + \theta V - \mu S(0)$ we can get,

$$S(t) \leq \frac{(1-\psi)\Lambda + \theta V}{\mu} - \frac{C}{\mu}e^{-\mu t} \leq \frac{(1-\psi)\Lambda + \theta V}{\mu} - \left(\frac{(1-\psi)\Lambda + \theta V}{\mu} - S(0)\right)e^{-\mu t}$$

$$S(t) \leq S(0)e^{-\mu t} + (1-\psi)\Lambda + \theta V(1-e^{-\mu t})$$

$$S(t) \leq S(0)e^{-\mu t} + (1-\psi)\Lambda + \theta V(1-e^{-\mu t})$$

$$lim_{t\to\infty}S(t) \leq S(0)e^{-\mu t} + ((1-\psi)\Lambda + \theta V(1-e^{-\mu t})$$

$$lim_{t\to\infty}S(t) \leq (S(0) - (1-\psi)\Lambda + \theta V e^{-\mu t} + (1-\psi)\Lambda + \theta V \leq (1-\psi)\Lambda + \theta V.$$

Since,$S(0) \leq (1-\psi)\Lambda + \theta V)$

From equation (4.3), we have: $\frac{H_r}{dt} = \lambda(S + \sigma V + \kappa R) - (\alpha + \mu)H_r$

If we add αH_r to the right side, we get: $\frac{dH_r}{dt} \leq \lambda(S + \sigma V + \kappa R) - \mu H_r$

Using a standard comparision theorem: $\int \frac{dH_r}{(S+\sigma V+\kappa R)-\mu H_r} \leq \int dt$

$$\Rightarrow -\frac{1}{\mu} ln((S + \sigma V + \kappa R) - \mu H_r) \leq t + c, \text{ where } c \text{ is a constant.}$$

$$\Rightarrow (S + \sigma V + \kappa R) - \mu H_r \geq De^{-\mu t}, \text{ where } D = e^{-c\mu t} \text{is a constant}$$

$$\Rightarrow H_r \leq \frac{(S + \sigma V + \kappa R)}{\mu} - \frac{D}{\mu} e^{-\mu t}$$

By applying the initial condition $H_r(0)$:

$H_r(t) \leq \frac{(S+\sigma V+\kappa R)}{\mu} - \frac{D}{\mu} e^{-\mu t}$,$\Rightarrow H_r(0) \leq \frac{(S+\sigma V+\kappa R)}{\mu} - \frac{D}{\mu} \leq \frac{(S+\sigma V+\kappa R)}{\mu}$,

Then from the inequality $(S + \sigma V + \kappa R) - \mu H_r \geq De^{-\mu t}$, and taking $D = (S + \sigma V + \kappa R) - \mu H_r(0)$ we can get,

$$H_r(t) \leq \frac{(S + \sigma V + \kappa R)}{\mu} - \frac{D}{\mu} e^{-\mu t} \leq \frac{(S + \sigma V + \kappa R)}{\mu} - \left(\frac{(S + \sigma V + \kappa R)}{\mu} - H_r(0) \right) e^{-\mu t}$$

$$H_r(t) \leq H_r(0)e^{-\mu t} + \frac{(S + \sigma V + \kappa R)}{\mu}(1 - e^{-\mu t})$$

$$H_r(t) \leq H_r(0)e^{-\mu t} + \frac{(S + \sigma V + \kappa R)}{\mu}(1 - e^{-\mu t})$$

$$lim_{t\to\infty} H_r(t) \leq H_r(0)e^{-\mu t} + \frac{(S + \sigma V + \kappa R)}{\mu}(1 - e^{-\mu t})$$

$$lim_{t\to\infty} H_r(t) \leq (H_r(0) - \frac{(S + \sigma V + \kappa R)}{\mu} e^{-\mu t} + \frac{(S + \sigma V + \kappa R)}{\mu} \leq \frac{(S + \sigma V + \kappa R)}{\mu}.$$

(Since, $H_r(0) \leq \frac{(S+\sigma V+\kappa R)}{\mu}$)

From the equation (4.4), we have: $\frac{dL_r}{dt} = \alpha\epsilon(1 - p)H_r - (\gamma + \mu)L_r$

If we add γL_r to the right side, we get: $\frac{dL_r}{dt} \leq \alpha\epsilon(1 - p)H_r - \mu L_r$

By a standard comparision theorem, we get: $\int \frac{dL_r}{\alpha\epsilon(1-p)H_r-\mu L_r} \leq \int dt$

$$\Rightarrow -\frac{1}{\mu} ln(\alpha\epsilon(1 - p)H_r - \mu L_r) \leq t + c, \text{ where } c \text{ is a constant}$$

$$\Rightarrow \alpha\epsilon(1 - p)H_r - \mu L_r \geq Ee^{-\mu t}, \text{ where } E = e^{-c\mu t} \text{is a constant}$$

$$\Rightarrow L_r \leq \frac{\alpha\epsilon(1 - p)H_r}{\mu} - \frac{E}{\mu} e^{-\mu t}$$

By applying the initial condition $L_r(0)$:

$L_r(t) \leq \frac{\alpha\epsilon(1-p)H_r}{\mu} - \frac{E}{\mu} e^{-\mu t}, \Rightarrow L_r(0) \leq \frac{\alpha\epsilon(1-p)H_r}{\mu} - \frac{E}{\mu} \leq \frac{\alpha\epsilon(1-p)H_r}{\mu}$,

Then from the inequality $\alpha\epsilon(1-p)H_r - \mu L_r \geq Ee^{-\mu t}$, and taking $E = \alpha\epsilon(1-p)H_r - \mu L_r(0)$

we can get,

$$L_r(t) \leq \frac{\alpha\epsilon(1-p)H_r}{\mu} - \frac{E}{E}e^{-\mu t} \leq \frac{\alpha\epsilon(1-p)H_r}{\mu} - \left(\frac{\alpha\epsilon(1-p)H_r}{\mu} - L_r(0)\right)e^{-\mu t}$$

$$L_r(t) \leq L_r(0)e^{-\mu t} + \frac{\alpha\epsilon(1-p)H_r}{\mu}(1-e^{-\mu t})$$

$$L_r(t) \leq L_r(0)e^{-\mu t} + \frac{\alpha\epsilon(1-p)H_r}{\mu}(1-e^{-\mu t})$$

$$lim_{t\to\infty}L_r(t) \leq L_r(0)e^{-\mu t} + \frac{\alpha\epsilon(1-p)H_r}{\mu}(1-e^{-\mu t})$$

$$lim_{t\to\infty}L_r(t) \leq L_r(0) - \frac{\alpha\epsilon(1-p)H_r}{\mu}e^{-\mu t} + \frac{\alpha\epsilon(1-p)H_r}{\mu} \leq \frac{\alpha\epsilon(1-p)H_r}{\mu}.$$

Since, $L_r(0) \leq \frac{\alpha\epsilon(1-p)H_r}{\mu}$

From the equation (4.5), we have: $\frac{dT}{dt} = \alpha pH_r - (\phi+\mu)T$

If we add ϕT to the right side, we get: $\frac{dT}{dt} \leq \alpha pH_r - \mu T$

By a standard comparision theorem, we get: $\int \frac{dT}{\alpha pH_r - \mu T} \leq \int dt$

$$\Rightarrow -\frac{1}{\mu}ln(\lambda pH_r - \mu T) \leq t + c, \textit{ where } c \textit{ is a constant}$$

$$\Rightarrow \alpha pH_r - \mu T \geq Fe^{-\mu t}, \textit{where } F = e^{-c\mu t} \textit{is a constant}$$

$$\Rightarrow T \leq \frac{\alpha pH_r}{\mu} - \frac{F}{\mu}e^{-\mu t}$$

By applying the initial condition $T(0)$:

$T(t) \leq \frac{\alpha pH_r}{\mu}e^{-\mu t}, \Rightarrow T(0) \leq \frac{\alpha pH_r}{\mu} - \frac{F}{\mu} \leq \frac{\alpha pH_r}{\mu}$,

Then from the inequality $\alpha pH_r - \mu T \geq Fe^{-\mu t}$, and taking $F = \alpha pH_r - \mu T(0)$ we can get,

$$T(t) \leq \frac{\alpha pH_r}{\mu} - \frac{F}{\mu}e^{-\mu t} \leq \frac{\alpha pH_r}{\mu} - \left(\frac{\alpha pH_r}{\mu} - T(0)\right)e^{-\mu t}$$

$$T(t) \leq T(0)e^{-\mu t} + \frac{\alpha pH_r}{\mu}(1-e^{-\mu t})$$

$$T(t) \leq T(0)e^{-\mu t} + \frac{\alpha pH_r}{\mu}(1-e^{-\mu t})$$

$$lim_{t\to\infty}T(t) \leq T(0)e^{-\mu t} + \frac{\alpha pH_r}{\mu}(1-e^{-\mu t})$$

$$lim_{t\to\infty}T(t) \leq \left(T(0) - \frac{\alpha pH_r}{\mu}\right)e^{-\mu t} + \frac{\alpha pH_r}{\mu} \leq \frac{\alpha pH_r}{\mu}.$$

(Since, $T(0) \leq \frac{\alpha pH_r}{\mu}$)

From the equation (4.6), we have: $\frac{dI}{dt} = \delta\gamma L_r + \alpha(1-\epsilon)(1-p)H_r - (\rho+\mu+d)I$

If we add $(\rho+d)I$ to the right side, we get: $\frac{dI}{dt} \leq \delta\gamma L_r + \alpha(1-\epsilon)(1-p)H_r - \mu I$

By a standard comparision theorem, we get: $\int \frac{dI}{\delta\gamma L_r+\alpha(1-\epsilon)(1-p)H_r-\mu I} \leq \int dt$

$$\Rightarrow -\frac{1}{\mu} ln(\delta\gamma L_r + \alpha(1-\epsilon)(1-p)H_r - \mu I) \leq t + c, \textit{ where } c \textit{ is a constant}$$

$$\Rightarrow \delta\gamma L_r + \alpha(1-\epsilon)(1-p)H_r - \mu I \geq Ge^{-\mu t}, , \textit{ where } G = e^{-c\mu t} \textit{ is a constant}$$

$$\Rightarrow I \leq \frac{\delta\gamma L_r + \alpha(1-\epsilon)(1-p)H_r}{\mu} - \frac{G}{\mu}e^{-\mu t}$$

By applying the initial condition $I(0)$ we have : $I(t) \leq \frac{\delta\gamma L_r+\alpha(1-\epsilon)(1-p)H_r}{\mu} - \frac{G}{\mu}e^{-\mu t}$,

$$\Rightarrow I(0) \leq \frac{\delta\gamma L_r + \alpha(1-\epsilon)(1-p)H_r}{\mu} - \frac{G}{\mu} \leq \frac{\delta\gamma L_r + \alpha(1-\epsilon)(1-p)H_r}{\mu},$$

Then from the inequality $\delta\gamma L_r + \alpha(1-\epsilon)(1-p)H_r - \mu I \geq Ge^{-\mu t}$, and taking $G = \delta\gamma L_r + \alpha(1-\epsilon)(1-p)H_r - \mu I(0)$ we can get,

$$\begin{aligned}
I(t) &\leq \frac{\delta\gamma L_r + \alpha(1-\epsilon)(1-p)H_r}{\mu} - \frac{G}{\mu}e^{-\mu t} \\
&\leq \frac{\delta\gamma L_r + \alpha(1-\epsilon)(1-p)H_r}{\mu} - \left(\frac{\delta\gamma L_r + \alpha(1-\epsilon)(1-p)H_r}{\mu} - I(0)\right)e^{-\mu t} \\
I(t) &\leq I(0)e^{-\mu t} + \frac{\delta\gamma L_r + \alpha(1-\epsilon)(1-p)H_r}{\mu}(1-e^{-\mu t}) \\
I(t) &\leq I(0)e^{-\mu t} + \frac{\delta\gamma L_r + \alpha(1-\epsilon)(1-p)H_r}{\mu}(1-e^{-\mu t}) \\
lim_{t\to\infty} I(t) &\leq I(0)e^{-\mu t} + \frac{\delta\gamma L_r + \alpha(1-\epsilon)(1-p)H_r}{\mu}(1-e^{-\mu t}) \\
lim_{t\to\infty} I(t) &\leq (I(0) - \frac{\delta\gamma L_r + \alpha(1-\epsilon)(1-p)H_r}{\mu}e^{-\mu t} + \frac{\delta\gamma L_r + \alpha(1-\epsilon)(1-p)H_r}{\mu} \\
&\leq \frac{\delta\gamma L_r + \alpha(1-\epsilon)(1-p)H_r}{\mu}.(Since, I(0) \leq \frac{\delta\gamma L_r + \alpha(1-\epsilon)(1-p)H_r}{\mu})
\end{aligned}$$

From the equation (4.7), we have: $\frac{dI_T}{dt} = q\rho I - (\varphi+\mu)I_T$

If we add φI_T to the right side, we get: $\frac{dI_T}{dt} \leq q\rho I - \mu I_T$

By a standard comparision theorem, we get: $\int \frac{dI_T}{q\rho I-\mu I_T} \leq \int dt$

$$\Rightarrow -\frac{1}{\mu} ln(q\rho I - \mu I_T) \leq t + c \textit{ where } c \textit{ is a constant}$$

$$\Rightarrow q\rho I - \mu I_T \geq He^{-\mu t}, \textit{where } H = e^{-c\mu t} \textit{is a constant}$$

$$\Rightarrow I_T \leq \frac{q\rho I}{\mu} - \frac{H}{\mu}e^{-\mu t}$$

By applying the initial condition $I_T(0)$:

$$I_T(t) \leq \frac{q\rho I}{\mu} - \frac{H}{\mu}e^{-\mu t}, \Rightarrow I_T(0) \leq \frac{q\rho I}{\mu} - \frac{H}{\mu} \leq \frac{q\rho I}{\mu}$$

Then from the inequality $q\rho I - \mu I_T \geq He^{-\mu t}$, and taking $H = q\rho I - \mu I_T(0)$ we can get,

$$I_T(t) \leq \frac{q\rho I}{\mu} - \frac{F}{\mu}e^{-\mu t} \leq \frac{q\rho I}{\mu} - \left(\frac{q\rho I}{\mu} - I_T(0)\right)e^{-\mu t}$$

$$I_T(t) \leq I_T(0)e^{-\mu t} + \frac{q\rho I}{\mu}(1 - e^{-\mu t})$$

$$I_T(t) \leq I_T(0)e^{-\mu t} + \frac{q\rho I}{\mu}(1 - e^{-\mu t})$$

$$lim_{t\to\infty} I_T(t) \leq I_T(0)e^{-\mu t} + \frac{q\rho I}{\mu}(1 - e^{-\mu t})$$

$$lim_{t\to\infty} I_T(t) \leq \left(I_T(0) - \frac{q\rho I}{\mu}\right)e^{-\mu t} + \frac{q\rho I}{\mu} \leq \frac{q\rho I}{\mu}.(Since, I_T(0) \leq \frac{q\rho I}{\mu})$$

From the equation (4.8), we have: $\frac{dR}{dt}t = \phi T + (1-q)\rho I + (1-\delta)\gamma L_r - (\kappa\lambda + \mu)R$

If we add $\kappa\lambda R$ to the right side, we get: $\frac{dR}{dt}t \leq \phi T + (1-q)\rho I + (1-\delta)\gamma L_r - \mu R$

By a standard comparision theorem, we get: $\int \frac{dR}{\phi T + (1-q)\rho I + (1-\delta)\gamma L_r - \mu R} \leq \int dt$

$$\Rightarrow -\frac{1}{\mu}ln(\phi T + (1-q)\rho I + (1-\delta)\gamma L_r - \mu R) \leq t + c, \ \textit{where c is a constant}$$

$$\Rightarrow \phi T + (1-q)\rho I + (1-\delta)\gamma L_r - \mu R \geq Ke^{-\mu t}, \textit{where } K = e^{-c\mu t} \textit{ is a constant}$$

$$\Rightarrow R \leq \frac{\phi T + (1-q)\rho I + (1-\delta)\gamma L_r - \mu R}{\mu} - \frac{K}{\mu}e^{-\mu t}$$

By applying the initial condition $R(0)$:

$R(t) \leq \frac{\phi T + (1-q)\rho I + (1-\delta)\gamma L_r - \mu R}{\mu} - \frac{K}{\mu}e^{-\mu t}$

$\Rightarrow R(0) \leq \frac{\phi T + (1-q)\rho I + (1-\delta)\gamma L_r - \mu R}{\mu} - \frac{K}{\mu} \leq \frac{\phi T + (1-q)\rho I + (1-\delta)\gamma L_r - \mu R}{\mu}$,

Then from the inequality $q\phi T + (1-q)\rho I + (1-\delta)\gamma L_r - \mu R \geq Ke^{-\mu t}$, and taking

$K = q\phi T + (1-q)\rho I + (1-\delta)\gamma L_r - \mu R(0)$ we can get,

$$\begin{aligned}
R(t) \leq & \frac{\phi T + (1-q)\rho I + (1-\delta)\gamma L_r - \mu R}{\mu} - \frac{F}{\mu} e^{-\mu t} \\
\leq & \frac{\phi T + (1-q)\rho I + (1-\delta)\gamma L_r - \mu R}{\mu} \\
& - \left(\frac{\phi T + (1-q)\rho I + (1-\delta)\gamma L_r - \mu R}{\mu} - R(0) \right) e^{-\mu t} \\
\leq & R(0)e^{-\mu t} + \frac{\phi T + (1-q)\rho I + (1-\delta)\gamma L_r - \mu R}{\mu}(1 - e^{-\mu t}) \\
\leq & R(0)e^{-\mu t} + \frac{\phi T + (1-q)\rho I + (1-\delta)\gamma L_r - \mu R}{\mu}(1 - e^{-\mu t}) \\
lim_{t\to\infty} R(t) \leq & R(0)e^{-\mu t} + \frac{\phi T + (1-q)\rho I + (1-\delta)\gamma L_r - \mu R}{\mu}(1 - e^{-\mu t}) \\
lim_{t\to\infty} R(t) \leq & \left(R(0) - \frac{\phi T + (1-q)\rho I + (1-\delta)\gamma L_r - \mu R}{\mu} \right) e^{-\mu t} \\
& + \frac{\phi T + (1-q)\rho I + (1-\delta)\gamma L_r - \mu R}{\mu} \\
\leq & \frac{\phi T + (1-q)\rho I + (1-\delta)\gamma L_r - \mu R}{\mu}. \\
& (\textit{Since, } R(0) \leq \frac{\phi T + (1-q)\rho I + (1-\delta)\gamma L_r - \mu R}{\mu})
\end{aligned}$$

Therefore, all feasible solutions of the model (4.1)-(4.8) with initial conditions in $\Omega = \{(V, S, H_r, L_r, T, I, I_T, R) \in \mathbb{R}^8_+ : N \leq \frac{\Lambda}{\mu}\}$ do remain in Ω for all $t > 0$. That is, the set Ω is positively invariant and attracting. □

4.3.3 Existence of Disease Free Equilibrium Point

The disease free equilibrium point of the dynamical system (4.1)−(4.8) is obtained by setting $\frac{dV}{dt} = \frac{dS}{dt} = \frac{dH_r}{dt} = \frac{dL_r}{dt} = \frac{dI}{dt} = \frac{dT}{dt} = \frac{dI_T}{dt} = \frac{dR}{dt} = 0$ and since there is no disease we do have $I = 0$. Let the disease free equilibrium (DFE) of the model (4.1)−(4.8) be denoted as:

$$E^0 = (V^0, S^0, H_r^0, L_r^0, I^0, T^0, I_T^0, R^0)$$

From equation (4.1) of the dynamical system, we have:

$$\frac{dV}{dt} = 0 \Rightarrow \psi\Lambda - (\sigma\lambda + \theta + \mu)V = 0, \Rightarrow V^0 = \frac{\psi\Lambda}{\mu + \theta}.$$

From equation (4.2) of the dynamical system, we have: $\frac{dS}{dt} = 0$

$$\Rightarrow (1-\psi)\Lambda + \theta V - (\lambda+\mu)S = 0,$$
$$\Rightarrow S^0 = \frac{(1-\psi)\Lambda + \theta V^0}{\mu} = \frac{(1-\psi)(\mu+\theta)\Lambda + \theta\psi\Lambda}{\mu(\mu+\theta)} = \frac{(\theta+(1-\psi)\mu)\Lambda}{\mu(\mu+\theta)}.$$

Taking the cases when $I = 0$, the equations $\frac{dH_r}{dt} = \frac{dL_r}{dt} = \frac{dI}{dt} = \frac{dI_T}{dt} = \frac{dT}{dt} = \frac{dR}{dt} = 0$ and if we solve for the rest state variable then we found that $H_r = L_r = T = I_T = R = 0$. Therefore, the disease free equilibrium point of the dynamical system (4.1)−(4.8) is given by:

$$E^0 = (V^0, S^0, H_r^0, L_r^0, T^0, I^0, I_T^0, R^0) = \left(\frac{\psi\Lambda}{(\mu+\theta)}, \frac{(\theta+(1-\psi)\mu)\Lambda}{\mu(\mu+\theta)}, 0, 0, 0, 0, 0, 0\right).$$

4.3.4 Effective Reproduction Number

The reproduction number (basic reproduction number R_0 or effective reproduction number R_{eff}) is defined as the average number of secondary infections caused by typical infected individual during his entire period of infectiousness. This definition is given for the models that represent spread of infection in a population, given an intervention and naturally acquired immunity at that time. We calculate the effective reproduction number R_{eff} by using the next generation operator method on the system (4.1)-(4.8) as described by Van den Driessche and Watmough (2002) as follows. Let

$F_i(x)$ *be the rate of appearance of new infections in compartment i.*

$V_i^+(x)$ *be the rate of transfer of individuals into compartment i by all other means,*

$V_i^-(x)$ *be the rate of transfer of individuals out of the compartment i.*

Then the disease transmission model consists of the system of equations

$$x_i^{'} = f_i(x) = F_i(x) - V_i(x), \text{ where } V_i(x) = V_i^-(x) - V_i^+(x)$$

The effective reproduction number is obtained by taking the largest (dominant) eigenvalue (spectral radius) of the matrix, $FV^{-1} = \{\frac{\partial F_i(E^0)}{\partial x_j}\}\{\frac{\partial V_i(E^0)}{\partial x_j}\}^{-1}$ with $1 \leq i, j \leq n$ where F_i is the rate of appearance of new infection in compartment i, V_i is the transfer of infections from one compartment i to another and E^0 is the disease-free equilibrium point. We rearrange the equations of model system (4.1)-(4.8) with the infected classes,

H_r, L_r and I first, screened and treatment classes, $T(t)$ second, susceptible classes, $S(t)$ third, vaccination class, $V(t)$ fourth, treatment class, $I_T(t)$ fifth and recovered class, $R(t)$ last. Here the infected classes are H_r, L_r and I. Therefore,

$$F_i = \begin{bmatrix} F_1 \\ F_2 \\ F_3 \end{bmatrix} = \begin{bmatrix} \lambda(S + \sigma V + \kappa R) \\ 0 \\ 0 \end{bmatrix}$$

$$F = \left[\frac{\partial F_i(E^0)}{\partial x_j}\right] = \begin{bmatrix} \frac{\partial F_1(E^0)}{\partial H_r} & \frac{\partial F_1(E^0)}{\partial L_r} & \frac{\partial F_1(E^0)}{\partial I} \\ \frac{\partial F_2(E^0)}{\partial H_r} & \frac{\partial F_2(E^0)}{\partial L_r} & \frac{\partial F_2(E^0)}{\partial I} \\ \frac{\partial F_3(E^0)}{\partial H_r} & \frac{\partial F_3(E^0)}{\partial L_r} & \frac{\partial F_3(E^0)}{\partial I} \end{bmatrix} = \begin{bmatrix} 0 & 0 & \frac{c\omega(\sigma V^0 + S^0)}{N^0} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

$$v_i = \begin{bmatrix} v_1 \\ v_2 \\ v_3 \end{bmatrix} = \begin{bmatrix} (\mu + \alpha)H_r \\ -\alpha\epsilon(1-p)H_r + (\mu + \gamma)L_r \\ -\delta\gamma L_r - \alpha(1-\epsilon)(1-p)H_r + (\mu + \rho + d)I \end{bmatrix}$$

$$V = \left[\frac{\partial v_i(E^0)}{\partial x_j}\right] = \begin{bmatrix} \frac{\partial v_1(E^0)}{\partial H_r} & \frac{\partial v_1(E^0)}{\partial L_r} & \frac{\partial v_1(E^0)}{\partial I} \\ \frac{\partial v_2(E^0)}{\partial H_r} & \frac{\partial v_2(E^0)}{\partial L_r} & \frac{\partial v_2(E^0)}{\partial I} \\ \frac{\partial v_3(E^0)}{\partial H_r} & \frac{\partial v_3(E^0)}{\partial L_r} & \frac{\partial v_3(E^0)}{\partial I} \end{bmatrix}$$

$$= \begin{bmatrix} (\alpha + \mu) & 0 & 0 \\ -\alpha\epsilon(1-p) & (\gamma + \mu) & 0 \\ -\alpha(1-\epsilon)(1-p) & -\gamma\delta & (\rho + \mu + d) \end{bmatrix}$$

of the dynamical system (4.1)-(4.8)

Since $detV = (\alpha + \mu)(\gamma + \mu)(\rho + \mu + d) \neq 0$ then V is non-singular. The inverse V^{-1} of the matrix V is given by: $V^{-1} = \frac{1}{detV} V_{adj}$, where V_{adj} is the adjoint matrix of the matrix V. And $V_{adj} = [C_{ij}]^T$ where $C_{ij} = (-1)^{i+j} M_{ij}$ is cofactor of an element v_{ij} of the matrix V and M_{ij} is minor of an element v_{ij} of the matrix V.

We found the adjoint matrix V_{adj} of the matrix V is:

$$V_{adj} = \begin{bmatrix} (\mu + \gamma)(\mu + \rho + d) & 0 & 0 \\ \alpha\epsilon(1-p)(\mu + \rho + d) & (\mu + \alpha)(\mu + \rho + d) & 0 \\ \alpha\epsilon(1-p)\delta\gamma + \alpha(1-\epsilon)(1-p)(\mu + \gamma) & \delta\gamma(\mu + \alpha) & (\mu + \alpha)(\mu + \gamma) \end{bmatrix}$$

Thus,the inverse matrix V^{-1} of the matrix V is given as:

$$V^{-1} = \frac{1}{detV} V_{adj} = \begin{bmatrix} \frac{1}{(\mu+\alpha)} & 0 & 0 \\ \frac{\alpha\epsilon(1-p)}{(\mu+\alpha)(\mu+\gamma)} & \frac{1}{(\mu+\gamma)} & 0 \\ \frac{\alpha\epsilon(1-p)\delta\gamma+\alpha(1-\epsilon)(1-p)(\mu+\gamma)}{(\mu+\alpha)(\mu+\gamma)(\mu+\rho+d)} & \frac{\delta\gamma}{(\mu+\gamma)(\mu+\rho+d)} & \frac{1}{(\mu++d)} \end{bmatrix}$$

We then compute matrix FV^{-1}, defined as the next generation operator (Diekmann, Heesterbeek, & Metz, 1990).

$$FV^{-1} = \begin{bmatrix} 0 & 0 & \frac{c\omega(\sigma V^0+S^0)}{N^0} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} \frac{1}{(\mu+\alpha)} & 0 & 0 \\ \frac{\alpha\epsilon(1-p)}{(\mu+\alpha)(\mu+\gamma)} & \frac{1}{(\mu+\gamma)} & 0 \\ \frac{\alpha\epsilon(1-p)\delta\gamma+\alpha(1-\epsilon)(1-p)(\mu+\gamma)}{(\mu+\alpha)(\mu+\gamma)(\mu+\rho+d)} & \frac{\delta\gamma}{(\mu+\gamma)(\mu+\rho+d)} & \frac{1}{(\mu++d)} \end{bmatrix}$$

$$= \begin{bmatrix} \frac{\alpha\epsilon(1-p)\delta\gamma+\alpha(\gamma+\mu)(1-\epsilon)(1-p)}{(\alpha+\mu)(\gamma+\mu)(\rho+\mu+d)} \frac{c\omega(S^0+\sigma V^0)}{N^0} & \frac{\delta\gamma}{(\gamma+\mu)(\rho+\mu+d)} \frac{c\omega(S^0+\sigma V^0)}{N^0} & \frac{1}{\rho+\mu+d} \frac{c\omega(S^0+\sigma V^0)}{N^0} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

Where, $N^0 = S^0 + V^0 = \frac{\Lambda}{\mu}$.

Therefore, $\lambda_1 = \frac{\alpha\epsilon(1-p)\delta\gamma+\alpha(\gamma+\mu)(1-\epsilon)(1-p)}{(\alpha+\mu)(\gamma+\mu)(\rho+\mu+d)} \frac{c\omega(S^0+\sigma V^0)}{N^0}$, $\lambda_2 = \lambda_3 = 0$ are the eigenvalues of the matrix FV^{-1}. Thus,, the spectral radius of FV^{-1} is, $\lambda_1 = \frac{c\omega(\sigma\psi\mu+(\theta+(1-\psi)\mu))}{(\theta+\mu)} \frac{(1-p)\alpha(\epsilon\gamma\delta+(1-\epsilon)(\gamma+\delta))}{(\alpha+\mu)(\gamma+\mu)(\rho+\mu+d)}$.

Hence, $R_{eff} = \frac{c\omega(\sigma\psi\mu+(\theta+(1-\psi)\mu))}{(\theta+\mu)} \frac{(1-p)\alpha(\epsilon\gamma\delta+(1-\epsilon)(\gamma+\delta))}{(\alpha+\mu)(\gamma+\mu)(\rho+\mu+d)}$ is effective reproduction number for the the dynamical system (4.1)-(4.8).

Local Stability Analysis of the Disease Free Equilibrium Point

Theorem 4.3. *The disease free equilibrium point* $E^0 = \left(\frac{\psi\Lambda}{\mu+\theta}, \frac{(\theta+(1-\psi)\mu)\Lambda}{\mu(\mu+\theta)}, 0, 0, 0, 0, 0, 0\right)$ *of the dynamical system (4.1)−(4.8) is locally asymptotically stable if* $R_{eff} < 1$*; and* E^0 *is unstable otherwise.*

Proof. The Jacobean matrix of the dynamical system (4.1)−(4.8) with respect to $(V, S, H_r, L_r, T, I, I_T, R)$ at any disease free equilibrium point E^0 is

$$J(E^0) = \begin{bmatrix} \frac{\partial f_1(E^0)}{\partial V} & \frac{\partial f_1(E^0)}{\partial S} & \frac{\partial f_1(E^0)}{\partial H_r} & \frac{\partial f_1(E^0)}{\partial L_r} & \frac{\partial f_1(E^0)}{\partial T} & \frac{\partial f_1(E^0)}{\partial I} & \frac{\partial f_1(E^0)}{\partial I_T} & \frac{\partial f_1(E^0)}{\partial R} \\ \frac{\partial f_2(E^0)}{\partial V} & \frac{\partial f_2(E^0)}{\partial S} & \frac{\partial f_2(E^0)}{\partial H_r} & \frac{\partial f_2(E^0)}{\partial L_r} & \frac{\partial f_2(E^0)}{\partial T} & \frac{\partial f_2(E^0)}{\partial I} & \frac{\partial f_2(E^0)}{\partial I_T} & \frac{\partial f_2(E^0)}{\partial R} \\ \frac{\partial f_3(E^0)}{\partial V} & \frac{\partial f_3(E^0)}{\partial S} & \frac{\partial f_3(E^0)}{\partial H_r} & \frac{\partial f_3(E^0)}{\partial L_r} & \frac{\partial f_3(E^0)}{\partial T} & \frac{\partial f_3(E^0)}{\partial I} & \frac{\partial f_3(E^0)}{\partial I_T} & \frac{\partial f_3(E^0)}{\partial R} \\ \frac{\partial f_4(E^0)}{\partial V} & \frac{\partial f_4(E^0)}{\partial S} & \frac{\partial f_4(E^0)}{\partial H_r} & \frac{\partial f_4(E^0)}{\partial L_r} & \frac{\partial f_4(E^0)}{\partial T} & \frac{\partial f_4(E^0)}{\partial I} & \frac{\partial f_4(E^0)}{\partial I_T} & \frac{\partial f_4(E^0)}{\partial R} \\ \frac{\partial f_5(E^0)}{\partial V} & \frac{\partial f_5(E^0)}{\partial S} & \frac{\partial f_5(E^0)}{\partial H_r} & \frac{\partial f_5(E^0)}{\partial L_r} & \frac{\partial f_5(E^0)}{\partial T} & \frac{\partial f_5(E^0)}{\partial I} & \frac{\partial f_5(E^0)}{\partial I_T} & \frac{\partial f_5(E^0)}{\partial R} \\ \frac{\partial f_6(E^0)}{\partial V} & \frac{\partial f_6(E^0)}{\partial S} & \frac{\partial f_6(E^0)}{\partial H_r} & \frac{\partial f_6(E^0)}{\partial L_r} & \frac{\partial f_6(E^0)}{\partial T} & \frac{\partial f_6(E^0)}{\partial I} & \frac{\partial f_6(E^0)}{\partial I_T} & \frac{\partial f_6(E^0)}{\partial R} \\ \frac{\partial f_7(E^0)}{\partial V} & \frac{\partial f_7(E^0)}{\partial S} & \frac{\partial f_7(E^0)}{\partial H_r} & \frac{\partial f_7(E^0)}{\partial L_r} & \frac{\partial f_7(E^0)}{\partial T} & \frac{\partial f_7(E^0)}{\partial I} & \frac{\partial f_7(E^0)}{\partial I_T} & \frac{\partial f_7(E^0)}{\partial R} \\ \frac{\partial f_8(E^0)}{\partial V} & \frac{\partial f_8(E^0)}{\partial S} & \frac{\partial f_8(E^0)}{\partial H_r} & \frac{\partial f_8(E^0)}{\partial L_r} & \frac{\partial f_8(E^0)}{\partial T} & \frac{\partial f_8(E^0)}{\partial I} & \frac{\partial f_8(E^0)}{\partial I_T} & \frac{\partial f_8(E^0)}{\partial R} \end{bmatrix}$$

The Jacobean matrix of the dynamical system (4.1)−(4.8) at the disease free equilibrium point $\left(\frac{\psi\Lambda}{\mu+\theta}, \frac{(\theta+(1-\psi)\mu)\Lambda}{\mu(\mu+\theta)}, 0, 0, 0, 0, 0, 0\right)$ is

$$J(E^0) = \begin{bmatrix} -(\theta+\mu) & 0 & 0 & 0 & 0 & -\sigma c\omega\frac{V^0}{N^0} & 0 & 0 \\ \theta & -\mu & 0 & 0 & 0 & -c\omega\frac{V^0}{N^0} & 0 & 0 \\ 0 & 0 & -(\alpha+\mu) & 0 & 0 & c\omega\frac{(S^0+\sigma V^0))}{N^0} & 0 & 0 \\ 0 & 0 & \alpha\epsilon(1-p) & -(\gamma+\mu) & 0 & 0 & & \\ 0 & 0 & \alpha p & 0 & -(\phi+\mu) & 0 & 0 & 0 \\ 0 & 0 & \alpha(1-\epsilon)(1-p) & \delta\gamma & 0 & -(\rho+\mu+d) & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & q\rho & -(\varphi+\mu) & 0 \\ 0 & 0 & 0 & (1-\delta)\gamma & \phi & (1-q)\rho & \varphi & -\mu \end{bmatrix}$$

The corresponding characteristic equation is obtained by

$$|J(E^0) - \lambda I_8| = \begin{vmatrix} d_1 & 0 & 0 & 0 & 0 & -\sigma c\omega\frac{V^0}{N^0} & 0 & 0 \\ \theta & d_2 & 0 & 0 & 0 & -c\omega\frac{V^0}{N^0} & 0 & 0 \\ 0 & 0 & d_3 & 0 & 0 & c\omega\frac{(S^0+\sigma V^0))}{N^0} & 0 & 0 \\ 0 & 0 & \alpha\epsilon(1-p) & d_4 & 0 & 0 & 0 & 0 \\ 0 & 0 & \alpha p & 0 & d_5 & 0 & 0 & 0 \\ 0 & 0 & \alpha(1-\epsilon)(1-p) & \delta\gamma & 0 & d_6 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & q\rho & d_7 & 0 \\ 0 & 0 & 0 & (1-\delta)\gamma & \phi & (1-q)\rho & \varphi & d_8 \end{vmatrix} = 0$$

where, I_8 is the identity matrix of order eight, $d_1 = -(\theta+\mu) - \lambda, d_2 = -\mu - \lambda, d_3 = -(\alpha+\mu) - \lambda, d_4 = -(\gamma+\mu) - \lambda, d_5 = -(\phi+\mu) - \lambda, d_6 = -(\rho+\mu+d) - \lambda, d_7 = -(\varphi+\mu) - \lambda, d_8 = -\mu - \lambda$

That is,

$$|J(E^0) - \lambda I_8| = d_1 d_2 d_5 d_7 d_8 \begin{vmatrix} d_3 & 0 & c\omega\frac{(S^0+\sigma V^0))}{N^0} \\ \alpha\epsilon(1-p) & d_4 & 0 \\ \alpha(1-\epsilon)(1-p) & \delta\gamma & d_6 \end{vmatrix} = 0$$

Thus, the roots of the characteristic equation are $\lambda_1 = -\mu$ or $\lambda_2 = -\mu$ or $\lambda_3 = -(\theta+\mu)$

or $\lambda_4 = -(\phi + \mu)$ or $\lambda_5 = -(\varphi + \mu)$ or $\lambda^3 + c_1\lambda^2 + c_2\lambda + c_3 = 0$ Where,

$$
\begin{aligned}
c_1 &= 3\mu + \alpha + \gamma + \rho + d, \\
c_2 &= (\alpha+\mu)(\gamma+\mu) + (\alpha+\mu)(\rho+\mu+d) + (\gamma+\mu)(\rho+\mu+d), \\
c_3 &= (\alpha+\mu)(\gamma+\mu)(\rho+\mu+d) - \frac{c\omega(S^0+\sigma V^0)[\delta\gamma\alpha\epsilon(1-p) + \alpha(1-\epsilon)(1-p)(\gamma+\mu)]}{N^0}, \\
&= (\alpha+\mu)(\gamma+\mu)(\rho+\mu+d)\left(1 - \frac{c\omega(S^0+\sigma V^0)[\delta\gamma\alpha\epsilon(1-p) + \alpha(1-\epsilon)(1-p)(\gamma+\mu]}{\alpha+\mu)(\gamma+\mu)(\rho+\mu+d)N^0}\right) \\
&= (\alpha+\mu)(\gamma+\mu)(\rho+\mu+d)[1 - R_{eff}]
\end{aligned}
$$

The Routh-Hurwitz conditions are the necessary and sufficient conditions on the coefficients of the cubic polynomials equations. These conditions ensure that all roots of the polynomials have negative real parts.

The Routh-Hurwitz conditions simplifies to $c_1 > 0, c_2 > 0, c_3 > 0$ and $c_1c_2 > c_3$. That is, the necessary conditions for Routh-Hurwitz $c_3 > 0$ is true if $R_{eff} < 1$. Now justify the sufficient condition for the Routh-Hurwitz criteria: $c_1c_2 - c_3 > 0$, $c_1c_2 - c_3 = (3\mu+\alpha+\gamma+\rho+d)[(\alpha+\mu)(\gamma+\mu)+(\alpha+\mu)(\rho+\mu+d)+(\gamma+\mu)(\rho+\mu+d)] - (\alpha+\mu)(\gamma+\mu)(\rho+\mu+d)[1-R_{eff}]$. Thus, $c_1c_2 - c_3 > 0$ if and only is $R_{eff} < 1$. Therefore all of the eigenvalues of the Jacobean matrix have negative real parts when $R_{eff} < 1$. Thus, the disease free equilibrium E^0, of the dynamical system (4.1)−(4.8) is locally asymptotical stable whenever $R_{eff} < 1$ and unstable otherwise that is unstable if $R_{eff} > 1$. □

Global Stability of Diseases free Equilibrium point

Theorem 4.4. *The diseases free equilibrium point* $E^0 = \left(\frac{\psi\Lambda}{\mu+\theta}, \frac{(\theta+(1-\psi)\mu)\Lambda}{\mu(\mu+\theta)}, 0, 0, 0, 0, 0, 0\right)$ *of the dynamical system (4.1) - (4.8) is globally asymptotically stable in* Ω *if* $R_{eff} < 1$*, and unstable otherwise.*

Proof. We apply a matrix-theoretic method using the Perron eigenvector to prove the global stability of the disease-free equilibrium as in [109]. The dynamical system (4.1)-(4.8), the TB disease compartment of is $x = (H_r, L_r, I)^T \in \mathbb{R}^3$ and non-disease compartment $y \in \mathbb{R}^5$.

That is, $F = \begin{bmatrix} 0 & 0 & c\omega \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$, $V = \begin{bmatrix} (\alpha+\mu) & 0 & 0 \\ -\alpha\epsilon(1-p) & (\gamma+\mu) & 0 \\ -\alpha(1-\epsilon)(1-p) & -\gamma\delta & (\rho+\mu+d) \end{bmatrix}$ and
$x^{'} = (F-V)x - f(x,y)$

Where, the non-negative matrix F, of the new TB infection terms, and the matrix V, of the transition terms of TB and $f(x,y) = (0,0,0)^T$

Since $detV = (\alpha+\mu)(\gamma+\mu)(\rho+\mu+d) \neq 0$, the matrix V is invertible. Therefore,

$$V^{-1} = \begin{bmatrix} \frac{1}{\alpha+\mu} & 0 & 0 \\ \frac{\alpha\epsilon(1-p)}{(\alpha+\mu)(\gamma+\mu)} & \frac{1}{\gamma+\mu} & 0 \\ \frac{\alpha\epsilon(1-p)\gamma\delta+\alpha(1-\epsilon)(1-p)(\gamma+\mu)}{(\alpha+\mu)(\gamma+\mu)\rho+\mu+d} & \frac{\gamma\delta}{(\gamma+\mu)} & \frac{1}{(\rho+\mu+d)} \end{bmatrix}$$

Thus, the product of the matricies V^{-1} and F is:

$$V^{-1}F = \begin{bmatrix} \frac{1}{\alpha+\mu} & 0 & 0 \\ \frac{\alpha\epsilon(1-p)}{(\alpha+\mu)(\gamma+\mu)} & \frac{1}{\gamma+\mu} & 0 \\ \frac{\alpha\epsilon(1-p)\gamma\delta+\alpha(1-\epsilon)(1-p)(\gamma+\mu)}{(\alpha+\mu)(\gamma+\mu)\rho+\mu+d} & \frac{\gamma\delta}{(\gamma+\mu)} & \frac{1}{(\rho+\mu+d)} \end{bmatrix} \begin{bmatrix} 0 & 0 & c\omega \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

$$= c\omega \begin{bmatrix} 0 & 0 & \frac{1}{\alpha+\mu} \\ 0 & 0 & \frac{\alpha\epsilon(1-p)}{(\alpha+\mu)(\gamma+\mu)} \\ 0 & 0 & \frac{\alpha\epsilon(1-p)\gamma\delta+\alpha(1-\epsilon)(1-p)(\gamma+\mu)}{(\alpha+\mu)(\gamma+\mu)(\rho+\mu+d)} \end{bmatrix}$$

Hence, $\lambda_1 = \lambda_2 = 0$ and $\lambda_3 = \frac{\alpha\epsilon(1-p)\gamma\delta+\alpha(1-\epsilon)(1-p)(\gamma+\mu)}{(\alpha+\mu)(\gamma+\mu)(\rho+\mu+d)}$, are eigenvalues of $V^{-1}F$. Let,
$\varpi^T = (u_1, u_2, u_3)$ be the left eigenvector of $V^{-1}F$ corresponding to $\lambda_3 = \frac{\alpha\epsilon(1-p)\gamma\delta+\alpha(1-\epsilon)(1-p)(\gamma+\mu)}{(\alpha+\mu)(\gamma+\mu)(\rho+\mu+d)}$

Thus,

$$\varpi^T V^{-1}F = c\omega(u_1,u_2,u_3) \begin{bmatrix} -\frac{\alpha\epsilon(1-p)\gamma\delta+\alpha(1-\epsilon)(1-p)(\gamma+\mu)}{(\alpha+\mu)(\gamma+\mu)(\rho+\mu+d)} & 0 & \frac{1}{\alpha+\mu} \\ 0 & -\frac{\alpha\epsilon(1-p)\gamma\delta+\alpha(1-\epsilon)(1-p)(\gamma+\mu)}{(\gamma+\mu)(\gamma+\mu)(\rho+\mu+d)} & \frac{\alpha\epsilon(1-p)}{(\alpha+\mu)(\gamma+\mu)} \\ 0 & 0 & 0 \end{bmatrix}$$

That is, $\varpi^T = (0,0,1)$ is the left eigenvector of $V^{-1}F$ corresponding to the eigenvalue $\lambda_3 = \frac{\alpha\epsilon(1-p)\gamma\delta+\alpha(1-\epsilon)(1-p)(\gamma+\mu)}{(\alpha+\mu)(\gamma+\mu)(\rho+\mu+d)}$.

Lets' define a function $W(H_r, L_r, I)$ as:

$$W = \varpi^T V^{-1}x = \frac{\alpha\epsilon(1-p)\gamma\delta+\alpha(1-\epsilon)(1-p)(\gamma+\mu)}{(\gamma+\mu)(\gamma+\mu)(\rho+\mu+d)}H_r + \frac{\gamma\eta}{\gamma+\mu}L_r + \frac{1}{(\rho+\mu+d)}I$$

The derivative of W with respect to time:

$$\begin{aligned}
W^{'} &= \varpi^T V^{-1} x^{'},\ \textit{Since } x^{'} = (F-V)x - f(x,y) \\
&= \varpi^T V^{-1}[(F-V)x - f(x,y)] \\
&= \varpi^T[(V^{-1}F - V^{-1}V)x - V^{-1}f(x,y)] \\
&= c\omega(0,0,1)\begin{bmatrix} -1 & 0 & \frac{1}{\alpha+\mu} \\ 0 & -1 & \frac{\alpha\epsilon(1-p)}{(\alpha+\mu)(\gamma+\mu)} \\ 0 & 0 & \frac{\alpha\epsilon(1-p)\gamma\delta+\alpha(1-\epsilon)(1-p)(\gamma+\mu)}{(\alpha+\mu)(\gamma+\mu)(\rho_s+\mu+d_s)} - 1 \end{bmatrix} x - \varpi^T V^{-1} f(x,y)] \\
&= (R_{eff}-1)x - V^{-1}f(x,y) \\
&= (R_{eff}-1)x - \varpi^T V^{-1} f(x,y)
\end{aligned}$$

Since $\varpi^T > 0$, $V^{-1} > 0$ and $f(x,y) = 0, W^{'} < 0$, if $R_{eff} < 1$.

Hence, $W^{'} < 0$, if $R_{eff} < 1$. And $W^{'} = 0$, at the disease free equilibrium point E^0. By LaSalle's invariant principle, every solution to the model equations (4.1)−(4.8) with initial conditions in Ω tends to E^0 as $t \to \infty$. Hence, since the region Ω is positively-invariant, the disease free equilibrium point, E^0 is globally asymptotically stable in Ω if $R_{eff} < 1$. □

4.3.5 The Endemic Equilibrium Point

The endemic equilibrium point in terms of the equilibrium value of the force of infection λ^* is given as:

$$E^* = (V^*, S^*, H_r^*, L_r^*, T^*, I^*, I_T^*, R^*)$$

From equation (4.1) of the dynamical system (4.1)−(4.8):

$$\frac{dV}{dt} = \psi\Lambda - (\sigma\lambda + \theta + \mu)V = 0 \ \textit{implies}\ V^* = \frac{\psi\Lambda}{(\sigma\lambda^* + \theta + \mu)}$$

From equation (4.2) of the dynamical system (4.1)−(4.8):

$$\begin{aligned}
\frac{dS}{dt} = (1-\psi)\Lambda + \theta V - (\lambda+\mu)S = 0 \Rightarrow S^* &= \frac{(1-\psi)\Lambda + \theta V^*}{(\lambda^*+\mu)} \\
&= \frac{\Lambda(1-\psi)\sigma(\lambda^*) + \theta + (1-\psi)\mu]}{(\lambda^*+\mu)[\sigma\lambda^* + \theta + \mu]} \\
&= \frac{\Lambda(1-\psi)\sigma\lambda^* + \theta + (1-\psi)\mu]}{(\lambda^*+\mu)[\sigma\lambda^* + \theta + \mu]}
\end{aligned}$$

From equation (4.3) of the dynamical system (4.1)−(4.8):

$$\frac{dH_r}{dt} = \lambda S + \sigma\lambda V + \kappa\lambda R - (\alpha+\mu)H_r = 0 \Rightarrow H_r^* = \frac{\lambda^*(S^* + \sigma V^* + \kappa R^*)}{(\alpha+\mu)}$$

From equation (4.4) of the dynamical system (4.1)−(4.8):

$$\frac{dL_r}{dt} = \alpha\epsilon(1-p)H_r - (\gamma+\mu)L_r = 0 \Rightarrow L_r^* = \frac{\alpha\epsilon(1-p)H_r^*}{(\gamma+\mu)}$$

From equation (4.5) of the dynamical system (4.1)−(4.8):

$$\begin{aligned}
\frac{dI}{dt} =& \delta\gamma L_r + \alpha(1-\epsilon)(1-p)H_r - (\rho+\mu+d)I = 0 \\
\Rightarrow I^* =& \frac{\delta\gamma L_r^* + \alpha(1-\epsilon)(1-p)H_r^*}{(\rho+\mu+d)} \\
\Rightarrow I^* =& \frac{(\delta\gamma\alpha\epsilon(1-p) + \alpha(\gamma+\mu)(1-\epsilon)(1-p))}{(\gamma+\mu)(\rho+\mu+d)} H_r^* \\
\Rightarrow H_r^* =& \frac{(\gamma+\mu)(\rho+\mu+d)}{\delta\gamma\alpha\epsilon(1-p) + \alpha(\gamma+\mu)(1-\epsilon)(1-p)} I^* and \\
\Rightarrow L_r^* =& \frac{\alpha\epsilon(1-p)H_r^*}{(\gamma+\mu)} = \frac{\alpha\epsilon(1-p)(\rho+\mu+d)}{(\delta\gamma\alpha\epsilon(1-p) + \alpha(\gamma+\mu)(1-\epsilon)(1-p))} I^*
\end{aligned}$$

From equation (4.6) of the dynamical system (4.1)−(4.8):

$$\begin{aligned}
\frac{dT}{dt} =& \alpha p H_r - (\phi+\mu)T = 0 \Rightarrow T^* = \frac{\alpha p H_r^*}{(\phi+\mu)} \\
\Rightarrow T^* =& \frac{\alpha p(\gamma+\mu)(\rho+\mu+d)}{(\phi+\mu)[\delta\gamma\alpha\epsilon(1-p) + \alpha(\gamma+\mu)(1-\epsilon)(1-p)]} I^*
\end{aligned}$$

From equation (4.7) of the dynamical system (4.1)−(4.8):

$$\frac{dI_T}{dt} = q\rho I - (\varphi+\mu)I_T = 0 \Rightarrow I_T^* = \frac{q\rho I^*}{(\varphi+\mu)}$$

From equation (4.8) of the dynamical system (4.1)−(4.8):

$$\begin{aligned}
\frac{dR}{dt} =& (1-q)\rho I + \gamma(1-\delta)L_r + \phi T + -(\kappa\lambda+\mu)R = 0 \\
R^* =& \frac{(1-q)\rho I^* + \gamma(1-\delta)L_r^* + \phi T^*}{(\kappa\lambda^*+\mu)} = \frac{(1-q)\rho I^* + \gamma(1-\delta)L_r^* + \phi T^*}{(\kappa\lambda^*+\mu)} \\
=& \frac{1}{(\kappa\lambda^*+\mu)} \frac{(1-q)\rho + \gamma(1-\delta)\alpha\delta(1-p)(\rho+\mu+d)}{[\gamma\delta\alpha\epsilon(1-p) + \alpha(\gamma+\mu)(1-\epsilon)(1-p)]} \\
&+ \frac{1}{(\kappa\lambda^*+\mu)} \frac{\phi\alpha p(\gamma+\mu)(\rho+\mu+d)}{(\phi+\mu)[\gamma\delta\alpha\epsilon(1-p) + \alpha(\gamma+\mu)(1-\epsilon)(1-p)]} I^*
\end{aligned}$$

Hence, the endemic equilibrium point is:

$$E^* = (V^*, S^*, H_r^*, L_r^*, I^*, T^*, I_T^*, R^*)$$

where $V^* = \frac{\psi\Lambda}{\sigma\lambda^*+\theta+\mu}$, $S^* = \frac{\Lambda(1-\psi)\sigma\lambda^*+\theta+(1-\psi)\mu]}{(\lambda^*+\mu)(\sigma\lambda^*+\theta+\mu)}$, $H_r^* = \frac{(\gamma+\mu)(\rho+\mu+d)}{\gamma\delta\alpha\epsilon(1-p)+\alpha(\gamma+\mu)(1-\epsilon)(1-p))} I^*$
$L_r^* = \frac{\alpha\epsilon(1-p)(\rho+\mu+d)}{\gamma\delta\alpha\epsilon(1-p)+\alpha(\gamma+\mu)(1-\epsilon)(1-p)} I^*$, $T^* = \frac{\alpha p(\gamma+\mu)(\rho+\mu+d)}{(\phi+\mu)[\gamma\delta\alpha\epsilon(1-p)+\alpha(\gamma+\mu)(1-\epsilon)(1-p)]} I^*$, $I_T^* = \frac{q\rho I^*}{(\varphi+\mu)}$
$R^* = \frac{1}{\kappa\lambda^*+\mu} \times \{(1-q)\rho + \frac{\gamma(1-\delta)\alpha\epsilon(1-p)(\rho+\mu+d)}{[\gamma\delta\alpha\epsilon(1-p)+\alpha(\gamma+\mu)(1-\epsilon)(1-p)]} + \frac{\phi\alpha p(\gamma+\mu)(\rho+\mu+d)}{(\phi+\mu)[\gamma\delta\alpha\epsilon(1-p)+\alpha(\gamma+\mu)(1-\epsilon)(1-p)]}\} I^*$

Existence of endemic equilibrium point

As the endemic equilibrium point E^* given in terms λ^* the existence of the equilibrium value of the force of infection λ^* shows the existence of E^*. So, we are going to set the conditions that λ^* exists.

$$\lambda^* = \frac{c\omega\mu}{\Lambda} I^*$$

where $N^*(t)$ is replaced by its limiting value, $N^* = \frac{\Lambda}{\mu}$

$$\lambda^* = \frac{c\omega\mu}{\Lambda} I^* \Rightarrow \lambda^* = \frac{c\omega\mu}{\Lambda} \frac{\gamma\delta\alpha\epsilon(1-p) + \alpha(\gamma+\mu)(1-\epsilon)(1-p)}{(\gamma+\mu)(\rho+\mu+d)} H_r^*$$
$$\Rightarrow \lambda^* = a_1 R_{eff}\lambda^* \frac{[(1-\psi)\sigma\lambda^* + \theta + (1-\psi)\mu]}{(\lambda^*+\mu)(\sigma\lambda^*+\theta+\mu) + \frac{\sigma\psi}{(\sigma\lambda^*+\theta+\mu)}} + a_1 a_2 R_{eff}\lambda^{*2}$$

Where, $a_1 = \frac{\mu(\theta+\mu)}{\Lambda+(\theta+(1-\phi)\mu)}$, and

$$a_2 = \frac{\kappa\Lambda}{c\omega\mu}\left\{\frac{\rho+\gamma(1-\delta)\alpha\epsilon(1-p)(\rho+\mu+d)}{[\gamma\delta\alpha\epsilon(1-p)+\alpha(\gamma+\mu)(1-\epsilon)(1-p)]} + \frac{\phi\alpha p(\gamma+\mu)(\rho+\mu+d)}{(\phi+\mu)[\gamma\delta\alpha\epsilon(1-p)+\alpha(\gamma+\mu)(1-\epsilon)(1-p)]}\right\}$$

$$\Rightarrow \sigma a_1 a_2 R_{eff}(\lambda^*)^4 + [(\sigma\mu+\theta+\mu)a_1 a_2 R_{eff} - \sigma](\lambda^*)^3$$
$$+ [\mu(\theta+\mu)a_1 a_2 + \sigma a_1]R_{eff} - (\sigma\mu+\theta+\mu)(\lambda^*)^2$$
$$+ a_1 R_{eff}[\theta + (1-\psi)\mu - \sigma\psi\mu] - \mu(\theta+\mu)\lambda^* = 0$$

$$\Rightarrow B_1(\lambda^*)^4 + B_2(\lambda^*)^3 + B_3(\lambda^*)^2 + B_4\lambda^* = 0 \tag{4.9}$$

where $B_1 = \sigma a_1 a_2 R_{eff} > 0$, $B_2 = (\sigma\mu+\theta+\mu)a_1 a_2 R_{eff} - \sigma$

$B_3 = [\mu(\theta+\mu)a_1 a_2 + \sigma a_1]R_{eff} - (\sigma\mu+\theta+\mu)$, $B_4 = a_1 R_{eff}[\theta + (1-\psi)\mu - \sigma\psi\mu] - \mu(\theta+\mu)$

The solutions for the quartic polynomial (4.9) are $\lambda^* = 0$ and $B_1(\lambda^*)^3 + B_2(\lambda^*)^2 + B_3\lambda^* + B_4 = 0$. The case $\lambda^* = 0$ corresponds to no TB disease and $B_1(\lambda^*)^3 + B_2(\lambda^*)^2 + B_3\lambda^* + B_4 = 0$ corresponds to the existence of at most three endemic equilibrium points.

Theorem 4.5. *In the equation of polynomial,* $B_1(\lambda^*)^3 + B_2(\lambda^*)^2 + B_3\lambda^* + B_4 = 0$, *the relation between roots and coefficients are given by:*

1) $\frac{B_2}{B_1} = -$*(sum of all roots)*

2) $\frac{B_3}{B_1}$ = *sum of products of roots taken two at a time*

3) $\frac{B_4}{B_1} = -$ *(products of roots taken three at a time)*

Remark:

The TB model system (4.1)−(4.8) has:

1) one positive endemic equilibrium if $B_2 < 0$, and $B_3 = B_4 = 0$. That is if $R_{eff} < \frac{\sigma}{(\sigma\mu+\theta+\mu)a_1a_2}$, one positive endemic equilibrium. And the root will be, $r_1 = -\frac{B_2}{B_1}$.

2) two positive endemic equilibrium if $B_2 < 0, B_3 > 0$ and $B_4 = 0$. That is, if $\frac{(\sigma\mu+\theta+\mu)}{(\mu(\theta+\mu)a_1a_2+\sigma a_1)} < R_{eff} < \frac{\sigma}{(\sigma\mu+\theta+\mu)a_1a_2}$ two positive endemic equilibrium. $r_1 + r_2 = -\frac{B_2}{B_1}$ and $r_1r_2 = \frac{B_3}{B_1}$.

   Therefore $r_1(-r_1 - \frac{B_2}{B_1}) = \frac{B_3}{B_1} \Rightarrow r_1^2 + r_1\frac{B_2}{B_1} + \frac{B_3}{B_1} = 0$

   $\Rightarrow r_1 = \frac{-B_2 \pm \sqrt{B_2^2 - 4B_1B_3}}{2B_1}$.

   Then has two roots if $B_2 < 0$ and $B_2^2 - 4B_1B_3 > 0$. $R_{eff} < \frac{\sigma}{(\sigma\mu+\theta+\mu)a_1a_2}$ and

   $[(\sigma\mu + \theta + \mu)a_1a_2R_{eff} - \sigma]^2 > 4[\mu(\theta + \mu)a_1a_2 + \sigma a_1]Reff - (\sigma\mu + \theta + \mu)$

3) three positive endemic equilibrium if the coefficients $B_2 < 0, B_3 > 0$ and $B_4 < 0$ with the relation to the three roots $r_1+r_2+r_3 = -B_2/B_1$, $r_1r_2+r_1r_3+r_2r_3 = B_3/B_1$ and $r_1r_2r_3 = -B_4/B_1$

   That is, if $\frac{(\sigma\mu+\theta+\mu)}{\mu(\theta+\mu)a_1a_2+\sigma a_1} < R_{eff} < \frac{\sigma}{(\sigma\mu+\theta+\mu)a_1a_2}$ and $R_{eff} < \frac{\mu(\theta+\mu)}{a_1[\theta+(1-\psi)\mu-\sigma\psi\mu]}$.

4) no positive endemic equilibrium otherwise.

Theorem 4.6. *The model (4.1)−(4.8) has unique endemic equilibrium if* $B_2 < 0$ *and* $B_3 = B_4 = 0$. *That is, the model (4.1)−(4.8) has unique endemic equilibrium* $\lambda^* = m^* = -B_2/B_1$.

Proof. Since $B_3 = B_4 = 0$, from quartic polynomial 4.9, $B_1(\lambda^*)^4 + B_2(\lambda^*)^3 + B_3(\lambda^*)^2 + B_4\lambda^* = 0$ we have $(\lambda^*)^3(B_1\lambda^* + B_2) = 0$. Then the only positive endemic equilibrium is, $\lambda^* = -B_2/B_1$ since $B_1 > 0$ and $B_2 < 0$. The model (4.1)−(4.8) has unique endemic equilibrium if $B_2 < 0$ and $B_3 = B_4 = 0$. □

Theorem 4.7. *The dynamical system (4.1)−(4.8) has unique endemic equilibrium if* $R_{eff} < \frac{\sigma}{(\sigma\mu+\theta+\mu)a_1a_2}$ *and* $B_2 = B_3 = 0$. *That is, the model (4.1)−(4.8) has unique endemic equilibrium when* $\lambda^* = m^* = -B_2/B_1 = \frac{\sigma-(\sigma\mu+\theta+\mu)a_1a_2R_{eff}}{\sigma a_1a_2R_{eff}}$

Proof. The model (4.1)−(4.8) has unique endemic equilibrium if $B_2 < 0$ and $B_3 = B_4 = 0$. That is, $B_2 < 0 \Rightarrow R_{eff} < \frac{\sigma}{(\sigma\mu+\theta+\mu)a_1a_2}$. And hence, at the unique endemic equilibrium point, $\lambda^* = m^* = -B_2/B_1 = \frac{\sigma-(\sigma\mu+\theta+\mu)a_1a_2R_{eff}}{\sigma a_1a_2R_{eff}}$ Where, $m^* = \frac{\sigma-(\sigma\mu+\theta+\mu)a_1a_2R_{eff}}{\sigma a_1a_2R_{eff}}$. □

Local Stability of the Endemic Equilibrium Point

Theorem 4.8. *The endemic equilibrium* E^* *of the dynamical system (4.1)− (4.8) is locally asymptotically stable if* $R_{eff} > 1$ *and* $R^* < \frac{\Lambda(d+\mu)}{c\omega\kappa\mu}$

Proof. E^* exists and is unique if $R_{eff} > 1$. The components of the unique endemic equilibrium E^* can then be obtained by substituting the unique value of $\lambda^* = m^*$ in to (4.1)-(4.8). Then the endemic equilibrium, $E^* = (V^*, S^*, H_r^*, L_r^*, I^*, T^*, I_T^*, R^*)$, where

$$
\begin{aligned}
V^* =& \frac{\psi\Lambda}{(\sigma m^* + \theta + \mu)}, S^* = \frac{\Lambda(1-\psi)\sigma m^* + (\theta + (1-\psi)\mu]}{(m^* + \mu)(\sigma m^* + \theta + \mu)}, \\
H_r^* =& \frac{\Lambda m^*(\gamma+\mu)(\rho+\mu+d)}{(c\omega\mu(\gamma\delta\alpha\epsilon(1-p) + \alpha(\gamma+\mu)(1-\epsilon)(1-p))}, \\
L_r^* =& \frac{\Lambda m^*\alpha\epsilon(1-p)(\rho+\mu+d)}{c\omega\mu(\gamma\delta\alpha\epsilon(1-p) + \alpha(\gamma+\mu)(1-\epsilon)(1-p))}, I^* = \frac{\Lambda m^*}{c\omega\mu}, \\
T^* =& \frac{\Lambda m^*\alpha p(\gamma+\mu)(\rho+\mu+d)}{c\omega\mu(\phi+\mu)[\gamma\delta\alpha\epsilon(1-p) + \alpha(\gamma+\mu)(1-\epsilon)(1-p)]}, (I_T)^* = \frac{q\rho I^*}{(\varphi+\mu)} \\
R^* =& \frac{\Lambda m^*}{\mu(c\omega\kappa m^* + \Lambda)}\rho + \frac{\gamma(1-\eta)\alpha\epsilon(1-p)(\rho+\mu+d)}{[\gamma\delta\alpha\epsilon(1-p) + \alpha(\gamma+\mu)(1-\epsilon)(1-p)]} \\
&+ \frac{\Lambda m^*}{\mu(c\omega\kappa m^* + \Lambda)} \frac{\phi\alpha p(\gamma+\mu)(\rho+\mu+d)}{(\phi+\varphi\mu)[\gamma\delta\alpha\epsilon(1-p) + \alpha(\gamma+\mu)(1-\epsilon)(1-p)]} \\
m^* =& \frac{\sigma - (\sigma\mu+\theta+\mu)a_1a_2R_{eff}}{\sigma a_1a_2R_{eff}}
\end{aligned}
$$

The Jacobean matrix of the dynamical system (4.1)-(4.8) at the endemic equilibrium

point E^* is given by:

$$J(E^*) = \begin{bmatrix} g_1 & 0 & 0 & 0 & b_1 & 0 & 0 & 0 \\ \theta & g_2 & 0 & 0 & b_2 & 0 & 0 & 0 \\ \sigma m^* & m^* & g_3 & 0 & z & 0 & 0 & \kappa m^* \\ 0 & 0 & \alpha\epsilon(1-p) & g_4 & 0 & 0 & 0 & 0 \\ 0 & 0 & \alpha(1-\epsilon)(1-p) & \delta\gamma & g_5 & 0 & 0 & 0 \\ 0 & 0 & \alpha p & 0 & 0 & g_6 & 0 & 0 \\ 0 & 0 & 0 & 0 & q\rho & 0 & g_7 & 0 \\ 0 & 0 & 0 & \gamma(1-\delta) & \rho & \phi & \varphi & g_8 \end{bmatrix} \tag{4.10}$$

Where, $m^* = \frac{\sigma-(\sigma\mu+\theta+\mu)a_1a_2R_{eff}}{\sigma a_1 a_2 R_{eff}}$, $g_1 = -(\sigma m^* + \theta + \mu)$, $g_2 = -(m^* + \mu)$,$g_3 = -(\alpha + \mu)$, $g_4 = -(\gamma+\mu)$,$g_5 = -(\rho+\mu+d)$,$g_6 = -(\phi+\mu)$,$g_7 = -(\varphi+\mu)$,$g_8 = -(\kappa m^*+\mu)$,$b_1 = \frac{\sigma c\omega V^*}{N^*}$, $b_2 = \frac{c\omega V^*}{N^*}$, $z = \frac{c\omega\mu}{\Lambda}(S^* + \sigma V^* + \kappa R^*)$

The characteristic equation of $J(E^*)$ denoted by $|J(E^*) - \lambda I| = 0$, and given by:

$$\begin{vmatrix} g_1-\lambda & 0 & 0 & 0 & b_1 & 0 & 0 & 0 \\ \theta & g_2-\lambda & 0 & 0 & b_2 & 0 & 0 & 0 \\ \sigma m^* & m^* & g_3-\lambda & 0 & z & 0 & 0 & \kappa m^* \\ 0 & 0 & \alpha\epsilon(1-p) & g_4-\lambda & 0 & 0 & 0 & 0 \\ 0 & 0 & \alpha(1-\epsilon)(1-p) & \delta\gamma & g_5-\lambda & 0 & 0 & 0 \\ 0 & 0 & \alpha p & 0 & 0 & g_6-\lambda & 0 & 0 \\ 0 & 0 & 0 & 0 & q\rho & 0 & g_7-\lambda & 0 \\ 0 & 0 & 0 & \gamma(1-\delta) & \rho & \phi & \varphi & g_8-\lambda \end{vmatrix} = 0 \tag{4.11}$$

Now we apply the Gershgorin circle theorem to determine the sign of the eigenvalues of the characteristic equation $|J(E^*) - \lambda I| = 0$.

From the first column of the Jacobian matrix $J(E^*)$,(4.10)

$$|g_1| = (\sigma m^* + \theta + \mu) \ and \ \Sigma_{i=1,i\neq1}^{8} c_{i1} = \theta + \sigma m^*$$
$$\Rightarrow |g_1| > \Sigma_{i=1,i\neq1}^{8} c_{i1}$$

From the second column of the Jacobian matrix $J(E^*)$,(4.10)

$$|g_2| = (m^* + \mu), \ and \ \Sigma_{i=1,i\neq2}^{8} c_{i2} = m^* \Rightarrow |g_2| > \Sigma_{i=1,i\neq2}^{8} c_{i2}$$

From the third column of the Jacobian matrix $J(E^*)$, (4.10)

$$|g_3| = (\alpha + \mu),\ and\ \Sigma_{i=1,i\neq 3}^{8} c_{i3} = \alpha\epsilon(1-p) + \alpha(1-\epsilon)(1-p) + \alpha p = \alpha$$
$$\Rightarrow |g_3| > \Sigma_{i=1,i\neq 3}^{8} c_{i3}$$

From the fourth column of the Jacobian matrix $J(E^*)$, (4.10)

$$|g_4| = (\gamma + \mu),\ and\ \Sigma_{i=1,i\neq 4}^{8} c_{i4} = \delta\gamma + \gamma(1-\delta) = \gamma \Rightarrow |g_4| > \Sigma_{i=1,i\neq 4}^{8} c_{i4}$$

From the fifth column of the Jacobian matrix $J(E^*)$,(4.10)

$$|g_5| = \rho + \mu + d\ and\ \Sigma_{i=1,i\neq 5}^{8} c_{i5} = b_1 + b_2 + z + \rho = \frac{c\omega}{N^*}\kappa R^* + \rho$$

If we let $N^* = \frac{\Lambda}{\mu}$, then $\Sigma_{i=1,i\neq 5}^{8} c_{i5} = \frac{c\omega\mu\kappa}{\Lambda} R^* + \rho$. $\Rightarrow |g_5| > \Sigma_{i=1,i\neq 5}^{7} c_{i5}$ if $R^* < \frac{\Lambda(d+\mu)}{c\omega\mu\kappa}$.

From the sixth column of the Jacobian matrix $J(E^*)$,(4.10)

$$|g_6| = (\phi + \mu)\ and\ \Sigma_{i=1,i\neq 6}^{8} c_{i6} = \phi \Rightarrow |g_6| > \Sigma_{i=1,i\neq 6}^{8} c_{i6}$$

From the sixth column of the Jacobian matrix $J(E^*)$, (4.10)

$$|g_7| = (\varphi + \mu)\ and\ \Sigma_{i=1,i\neq 7}^{8} c_{i7} = \varphi \Rightarrow |g_7| > \Sigma_{i=1,i\neq 7}^{8} c_{i7}$$

From the seventh column of the Jacobian matrix $J(E^*)$, (4.10)

$$|g_8| = (\kappa m^* + \mu)\ and\ \Sigma_{i=1,i\neq 8}^{8} c_{i8} = \kappa m^* \Rightarrow |g_8| > \Sigma_{i=1,i\neq 8}^{8} c_{i8}$$

Therefore, $|g_5| > \Sigma_{i=1,i\neq 5}^{8} c_{i5}$ if $R^* < \frac{\Lambda(d+\mu)}{c\omega\mu\kappa}$ and for the remaining column of the Jacobian matrix $J(E^*)$, $|g_i| > \Sigma_{i=1,i\neq j}^{8} c_{ij}$ for $j = \{1,\ldots,8\} - \{5\}$. Therefore, $|c_{ii}| > \Sigma_{i=1,i\neq j}^{8} c_{ij}$, for $j = 1,\ldots,8$, for the matrix $J(E^*)$,(4.10) if $R^* < \frac{\Lambda(d+\mu)}{c\omega\mu\kappa}$. That is, the matrix $J(E^*)$ is a strictly column diagonally dominant matrix if $R^* < \frac{\Lambda(d+\mu)}{c\omega\mu\kappa}$. And also all diagonal elements of $J(E^*)$ are negative. Therefore, using the Gershgorin circle theorem, the radius of the disc less than the magnitude of corresponding element if $R^* < \frac{\Lambda(d+\mu)}{c\omega\kappa\mu}$. We can show that all eigenvalues of $J(E^*)$ has negative real part if $R_{eff} > 1$ and $R^* < \frac{\Lambda(d+\mu)}{c\omega\kappa\mu}$. Hence, the endemic equilibrium point E^* is locally asymptotically stable if $R_{eff} > 1$ and $R^* < \frac{\Lambda(d+\mu)}{c\omega\kappa\mu}$. □

Global Stability of Endemic Equilibrium Point

Theorem 4.9. *The endemic equilibrium E^* of Model (4.1)-(4.8) is globally asymptotically stable if $R_{eff} > 1$, $\frac{V}{V^*}$, $\frac{S}{S^*}$, $\frac{R}{R^*} \leq 1$ and $\frac{H_r}{H_r^*} \leq \frac{I}{I^*}$.*

Proof. We use a graph-theoretic method as in [109] to construct a Lyapunov function. We define functions:

$$D_1 = V - V^* - V^* ln\frac{V}{V^*} \ , \ D_2 = S - S^* - S^* ln\frac{S}{S^*} \ , \ D_3 = H_r - H_r^* - H_r^* ln\frac{H_r}{H_r^*},$$
$$D_4 = L_r - L_r^* - L_r^* ln\frac{L_r}{L_r^*} \ , \ D_5 = I - I^* - I^* ln\frac{I}{I^*}, D_6 = T - T^* - T^* ln\frac{T}{T^*},$$
$$D_7 = I_T - I_T^* - I_T^* ln\frac{I_T}{I_T^*} \ , \ D_8 = R - R^* - R^* ln\frac{R}{R^*}$$

Differentiating the functions D_i for $i = 1, ..., 8$ with respect to time, and use the values at the endemic equilibrium point E^* that:

$$\psi\Lambda = (\sigma\lambda^* + \theta + \mu)V^*, \qquad (1-\psi)\Lambda = -\theta V^* + (\lambda^* + \mu)S^*,$$
$$(\alpha + \mu) = \frac{\lambda^*(S^* + \sigma V^* + \kappa R^*)}{H_r^*}, \qquad (\gamma + \mu) = \frac{\alpha\epsilon(1-p)H_r^*}{L_r^*},$$
$$(\rho + \mu + d) = \frac{\delta\gamma L_r^*}{I^*} + \frac{\alpha(1-\epsilon)(1-p)H_r^*}{I^*}, \quad (\phi + \mu) = \frac{\alpha p H_r^*}{T^*},$$
$$(\varphi + \mu) = \frac{q\rho}{I_T^*}I^*, \qquad \mu = \frac{\rho I^*}{R^*} + \frac{\gamma(1-\delta)L_r^*}{R^*} + \frac{\phi T^*}{R^*} + \frac{\varphi(I_T)^*}{R^*} - \kappa\lambda^*$$

And using the inequality $1 - x + lnx \leq 0$, for all $x > 0$ and the values at the endemic equilibrium point E^* that:

$$\begin{aligned}
D_1' =& (1 - \frac{V^*}{V})V' = (1 - \frac{V^*}{V})(\psi\Lambda - (\sigma\lambda + \theta + \mu)V) \\
=& -(\theta + \mu)\frac{(V - V^*)^2}{V} + \frac{c\sigma\omega}{N^*}V^*\left(I^* - \frac{IV}{V^*} + I - \frac{V^*}{V}\right) \\
=& -(\theta + \mu)\frac{(V - V^*)^2}{V} + \frac{c\sigma\omega}{N^*}V^*I^*\left(1 - \frac{IV}{I^*V^*} - \frac{V^*}{V} + \frac{I}{I^*}\right) \\
\leq& \frac{c\sigma\omega}{N^*}V^*I^*\left(1 - \frac{IV}{I^*V^*} - \frac{V^*}{V} + \frac{I}{I^*}\right) \leq \frac{c\sigma\omega}{N^*}V^*I^*\left(-ln\frac{IV}{I^*V^*} - \frac{V^*}{V} + \frac{I}{I^*}\right) \\
\leq& \sigma\lambda^*V^*\left(-ln\frac{I}{I^*} + ln\frac{V^*}{V} - \frac{V^*}{V} + \frac{I}{I^*}\right) = a_{15}G_{15}
\end{aligned}$$

$$
\begin{aligned}
D_2^{'} =& \left(1-\frac{S^*}{S}\right) S^{'} = \left(1-\frac{S^*}{S}\right)((1-\psi)\Lambda + \theta V - (\lambda+\mu)S) \\
=&(1-\frac{S^*}{S})(-\theta V^* + (\lambda^*+\theta)S^* + \theta V - (\lambda+\mu)S) \\
=&-\mu\frac{(S-S^*)^2}{S} + \theta V^*\left(\frac{S^*}{S} - 1 - \frac{VS^*}{V^*S} + \frac{V}{V^*}\right) + \frac{c\omega}{N^*}S^*I^*\left(1 - \frac{IS}{I^*S^*} - \frac{S^*}{S} + \frac{I}{I^*}\right) \\
\leq&\theta V^*\left(\frac{S^*}{S} - 2 - ln\frac{VS^*}{V^*S} + \frac{V}{V^*}\right) + S^*\lambda^*\left(-ln\frac{I}{I^*} + ln\frac{S^*}{S} - \frac{S^*}{S} + \frac{I}{I^*}\right) \\
=&: a_{21}G_{21} + a_{25}G_{25}
\end{aligned}
$$

$$
\begin{aligned}
D_3^{'} =& \left(1-\frac{H_r^*}{H_r}\right) H_r^{'} = \left(1-\frac{H_r^*}{H_r}\right)(\lambda S + \sigma\lambda V + \kappa\lambda R - (\alpha+\mu)H_r) \\
=& \left(1-\frac{H_r^*}{H_r}\right)(\lambda S + \sigma\lambda V + \kappa\lambda R + \lambda^*\left(-\frac{S^*}{H_r^*} - \sigma\frac{V^*}{H_r^*} - \kappa\frac{R^*}{H_r^*})H_r\right) \\
\leq&\lambda^*S^*\left(\frac{IS}{I^*S^*} - \frac{I}{I^*} - ln\frac{S}{S*}\right) + \sigma V^*\lambda^*\left(\frac{IV}{I^*S^*} - ln\frac{V}{V^*}\right) + \kappa R^*\lambda^*\left(\frac{IR}{I^*R^*} - \frac{I}{I^*} - ln\frac{R}{R^*}\right) \\
&+ (S^* + \sigma V^* + \kappa R^*)\lambda^*\left(\frac{I}{I^*} - \frac{H_r}{H_r^*} + ln\frac{H_r}{H_r^*} - ln\frac{I}{I^*}\right) \\
=&: a_{32}G_{32} + a_{31}G_{31} + a_{38}G_{38} + a_{35}G_{35}
\end{aligned}
$$

$$
\begin{aligned}
D_4^{'} =& \left(1-\frac{L_r^*}{L_r}\right) L_r^{'} = \left(1-\frac{L_r^*}{L_r}\right)(\alpha\epsilon(1-p)H_r - (\gamma+\mu)L_r) \\
=&\alpha\epsilon(1-p)H_r^*\left(1-\frac{L_r^*}{L_r}\right)\left(\frac{H_r^*}{H_r} - \frac{L_r^*}{L_r}\right) = \alpha\epsilon(1-p)H_r^*\left(1 - \frac{L_r^*}{L_r} + \frac{H_r^*}{H_r} - \frac{H_r^*}{H_r}\frac{L_r^*}{L_r}\right) \\
\leq&\alpha\epsilon(1-p)H_r^*\left(-\frac{L_r^*}{L_r} - ln\frac{L_r^*}{L_r}\frac{H_r^*}{H_r} + \frac{H_r^*}{H_r}\right) \\
\leq&\alpha\epsilon(1-p)H_r^*\left(-\frac{L_r}{L_r^*} + ln\frac{L_r}{L_r^*} - ln\frac{H_r}{H_r^*} + \frac{H_r}{H_r^*}\right) = a_{43}G_{43}
\end{aligned}
$$

$$
\begin{aligned}
D_5^{'} =& \left(1-\frac{I^*}{I}\right) I^{'} = (1-\frac{I^*}{I})(\delta\gamma L_r + \alpha(1-\epsilon)(1-p)H_r - (\rho+\mu+d)I) \\
=& \left(1-\frac{I^*}{I}\right)(\delta\gamma L_r + \alpha(1-\epsilon)(1-p)H_r - (\delta\gamma L_r^* + \alpha(1-\epsilon)(1-p)H_r^*)\frac{I}{I^*} \\
=&\delta\gamma L_r^*\left(1 - \frac{I}{I^*} - \frac{I}{I_r^*}\frac{L_r}{L_r^*} + \frac{L_r}{L_r^*}\right) + \alpha(1-\epsilon)(1-p)H_r^*\left(1 - \frac{I_s}{I_s^*} - \frac{I}{I^*}\frac{H_r}{H_r^*} + \frac{H_r}{H_r^*}\right) \\
\leq&\delta\gamma L_r^*\left(-\frac{I}{I^*} - ln\frac{I}{I^*}\frac{L_r}{L_r^*} + \frac{L_r}{L_r^*}\right) + \alpha(1-\epsilon)(1-p)H_r^*\left(-\frac{I}{I^*} - ln\frac{I}{I^*}\frac{H_r}{H_r^*} + \frac{H_r}{H_r^*}\right) \\
\leq&\delta\gamma L_r*\left(-\frac{I}{I^*} + ln\frac{I}{I^*} - ln\frac{L_r}{L_r^*} + \frac{L_r}{L_r^*}\right) + \alpha(1-\epsilon)(1-p)H_r^*\left(-\frac{I}{I^*} + ln\frac{I}{I^*} - ln\frac{H_r}{H_r} + \frac{H_r}{H_r}\right) \\
=&: a_{54}G_{54} + a_{53}G_{53}
\end{aligned}
$$

$$
\begin{aligned}
D_6^{'} =& \left(1-\frac{T^*}{T}\right)T^{'} = \left(1-\frac{T^*}{T}\right)(\alpha p H_r - (\phi+\mu)T) = (\phi+\mu)T^*\left(1-\frac{T^*}{T}\right)\left(\frac{H_r}{H_r^*}-\frac{T^*}{T}\right)\\
=&(\phi+\mu)T^*\left(\frac{H_r}{H_r^*}-\frac{T}{T^*}-\frac{T^*}{T}\frac{H_r}{H_r^*}+1\right) \leq (\phi+\mu)T^*(\frac{H_r}{H_r^*}-\frac{T}{T^*}-ln\frac{T^*}{T}\frac{H_r}{H_r^*})\\
\leq&(\phi+\mu)T^*(\frac{H_r}{H_r^*}-ln\frac{H_r}{H_r^*}-\frac{T}{T^*}+ln\frac{T}{T^*}) =: a_{63}G_{63}
\end{aligned}
$$

$$
\begin{aligned}
D_7^{'} =& \left(1-\frac{I_T^*}{I_T}\right)I_T^{'} = \left(1-\frac{I_T^*}{I_T}\right)(q\rho I - (\varphi+\mu)I_T) = (\varphi+\mu)I_T^*\left(1-\frac{I_T^*}{I_T}\right)\left(\frac{I}{I^*}-\frac{I_T^*}{I_T}\right)\\
=&(\varphi+\mu)T^*\left(\frac{I}{I^*}-\frac{I_T}{I_T^*}-\frac{I_T^*}{I_T}\frac{I}{I^*}+1\right) \leq (\varphi+\mu)I_T^*(\frac{I}{I^*}-\frac{I_T}{I_T^*}-ln\frac{I_T^*}{I_T}\frac{I}{I^*})\\
\leq&(\phi+\mu)T^*(\frac{I}{I^*}-ln\frac{I}{I^*}-\frac{T}{T^*}+ln\frac{T}{T^*}) =: a_{75}G_{75}
\end{aligned}
$$

$$
\begin{aligned}
D_8^{'} =& \left(1-\frac{R^*}{R}\right)R^{'} = (1-\frac{R^*}{R}(\gamma(1-\delta)L_r+\phi T+\varphi I_T-(\kappa\lambda+\mu)R)\\
=&\left(1-\frac{R^*}{R}\right)(\gamma(1-\delta)L_r+\phi T+\varphi I_T-\kappa\lambda R-\left(\rho I^*+\gamma(1-\delta)\frac{L_r^*}{R^*}+\phi\frac{T^*}{R^*}+\varphi\frac{I_T^*}{R^*}-\kappa\lambda^*)R\right)\\
=&\rho I^*\left(\frac{I}{I^*}-ln\frac{I}{I^*}+ln\frac{R}{R^*}-\frac{R}{R^*}\right)+\gamma(1-\delta)L_r^*\left(1-\frac{R}{R*}-\frac{L_r}{L_r^*}\frac{R^*}{R}+\frac{L_r}{L_r^*}\right)\\
&+\phi T^*\left(1-\frac{R}{R^*}+\varphi I_T^*(1-\frac{R}{R^*}-\frac{T}{T^*}\frac{R^*}{R}+\frac{T}{T^*}\right)+\kappa I^*R^*\left(\frac{R}{R^*}-1-\frac{R}{R^*}\frac{I}{I^*}+\frac{I}{I^*}\right)\\
\leq&\rho I^*\left(\frac{I}{I^*}-ln\frac{I}{I^*}+ln\frac{R}{R*}-\frac{R}{R*}\right)+\gamma\left(1-\delta)L_r^*(-\frac{R}{R*}-ln\frac{L_r}{L_r^*}\frac{R}{R*}+\frac{L_r}{L_r^*}\right)\\
&+\phi T^*\left(-\frac{R}{R*}-ln\frac{T}{T^*}\frac{R^*}{R}+\frac{T}{T^*}\right)+\varphi I_T^*\left(-\frac{R}{R*}-ln\frac{I_T}{I_T^*}\frac{R^*}{R}+\frac{I_T}{I_T^*}\right)\\
&+\kappa I^*R^*\left(\frac{R}{R*}-2-ln\frac{R}{R*}\frac{I}{I^*}+\frac{I}{I^*}\right)\\
\leq&\rho I^*\left(\frac{I}{I^*}-ln\frac{I}{I^*}+ln\frac{R}{R^*}-\frac{R}{R^*}\right)+\gamma(1-\delta)L_r^*\left(-\frac{R}{R^*}+ln\frac{R}{R^*}-ln\frac{L_r}{L_r^*}+\frac{L_r}{L_r^*}\right)\\
&+\phi T^*\left(-\frac{R}{R^*}+ln\frac{R}{R^*}-ln\frac{T}{T^*}+\frac{T}{T^*}\right)+\varphi I_T^*\left(-\frac{R}{R^*}+ln\frac{R}{R^*}-ln\frac{I_T}{I_T^*}+\frac{I_T}{I_T^*}\right)\\
&+\kappa I^*R^*\left(\frac{R}{R^*}-2-ln\frac{R}{R^*}\frac{I}{I^*}+\frac{I}{I^*}\right)\\
=&: a_{84}G_{84}+a_{86}G_{86}+a_{87}G_{87}+a_{85a}G_{85a}+a_{85b}G_{85b}
\end{aligned}
$$

Where, $a_{15}=a_{31}=\sigma V^*\lambda^*$, $a_{21}=\theta$,$a_{25}=a_{32}=S^*\lambda^*$, $a_{38}=\kappa R^*\lambda^*$, $a_{35}=(S^*+\sigma V^*+\kappa R^*)\lambda^*$, $a_{43}=\alpha\epsilon(1-p)H_r^*$, $a_{54}=\gamma\delta L_r^*$, $a_{53}=\alpha(1-\epsilon)(1-p)H_r^*$, $a_{63}=(\phi+\mu)T^*$, $a_{75}=(\varphi+\mu)I_T^*$, $a_{84}=\rho I^*$, $a_{86}=\gamma(1-\delta)L_r^*$, $a_{87}=\varphi IT$, $a_{85a}=\phi T^*$, $a_{85b}=\kappa I^*R^*$ and all other $a_{ij}=0$

With the constants a_{ij} above and the matrix $A=[a_{ij}]$ for $i,j=1,...,8,5a,5b$, we construct the directed graph $G(A)$ as Figure 4.2 below.

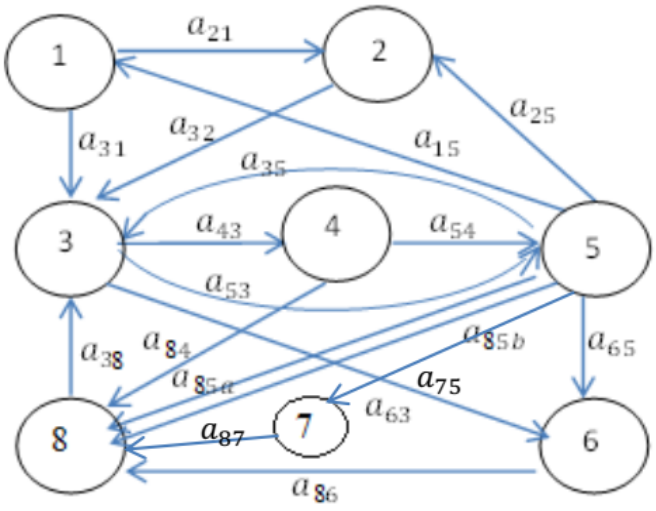

Figure 4.2: The digraph G(A) for dynamical system (4.1)-(4.8).

The associated weighted digraph G(A) (figure 4.2)has eight vertices. Along the cycles in figure 4.2:

$G_{35} + G_{53} = \left(\frac{I}{I^*} - \frac{H_r}{H_r^*} + ln\frac{H_r}{H_r^*} - ln\frac{I}{I^*}\right) + \left(-\frac{I}{I^*} + ln\frac{I}{I^*} - \frac{H_r}{H_r^*} + \frac{H_r}{H_r^*}\right) = 0$ and

$G_{35} + G_{43} + G_{54} = \left(\frac{I}{I^*} - \frac{H_r}{H_r^*} + ln\frac{H_r}{H_r^*} - ln\frac{I}{I^*}\right) + \left(-\frac{L_r}{L_r^*} + ln\frac{L_r}{L_r^*} - ln\frac{H_r}{H_r^*} + \frac{H_r}{H_r^*}\right)$

$+ \left(-\frac{I_r}{I_r^*} + ln\frac{I_r}{I_r^*} - ln\frac{L_r}{L_r^*} + \frac{L_r}{L_r^*}\right) = 0.$

And the other cycles $\sum G_{ij} \leq 0$ in figure 4.2, if $\frac{V}{V^*}$, $\frac{S}{S^*}$, $\frac{R}{R^*} \leq 1$ and $\frac{H_r}{H_r^*} \leq \frac{I}{I^*}$. By Proposition 1.3 of [109], there exists $c_i > 0, i = 1, \ldots, 8$ such that $D = \Sigma_{i=1}^{8} c_i D_i$ is a Lyapunov function for the dynamical system (4.1)-(4.8). The relations between c_i's can be derived from Theorems 3.3 and 3.4 of [109] such that:

$a_{32} > 0$ and $d^+(2) = 1$ implies $c_3 a_{32} = \Sigma_{k=1}^{8} c_2 a_{2k}$

$$\Rightarrow c_3 a_{32} = c_2(a_{21} + a_{25}) \Rightarrow c_3 = c_2 \frac{a_{21} + a_{25}}{a_{32}}.$$

$a_{15} > 0$ and $d^-(1) = 1$ implies $c_1 a_{15} = \Sigma_{k=1}^{8} c_k a_{k1}$

$$\Rightarrow c_1 a_{15} = c_2 a_{21} + c_3 a_{31} \Rightarrow c_1 = c_2 \frac{a_{21}a_{32} + a_{31}(a_{21} + a_{25})}{(a_{32}a_{15})}$$

$a_{43} > 0$ and $d^-(4) = 1$ implies $c_4 a_{43} = \Sigma_{k=1}^{8} c_k a_{k4}$

$$\Rightarrow c_4 a_{43} = c_5 a_{54} \Rightarrow c_4 = c_5 \frac{a_{54}}{a_{43}}$$

$a_{38} > 0$ and $d^+(8) = 1$ implies $c_3 a_{38} = \Sigma_{k=1}^{8} c_8 a_{8k}$

$$\Rightarrow c_3 a_{38} = c_8(a_{84} + a_{85a} + a_{85b} + a_{86}) \Rightarrow c_8 = c_3 \frac{a_{38}}{(a_{84} + a_{85a} + a_{85b} + a_{86})}$$

$$\Rightarrow c_8 = c_2 \frac{a_{38}(a_{21} + a_{25})}{a_{32}(a_{84} + a_{85a} + a_{85b} + a_{86})}$$

$a_{86} > 0$ and $d^+(6) = 1$ implies $c_8 a_{86} = \Sigma_{k=1}^{8} c_6 a_{6k}$

$$\Rightarrow c_8 a_{86} = c_6(a_{65} + a_{63}) \Rightarrow c_6 = c_8 \frac{a_{76}}{(a_{65} + a_{63})}$$

$$\Rightarrow c_6 = c_2 \frac{a_{86} a_{38}(a_{21} + a_{25})}{a_{32}(a_{65} + a_{63})(a_{84} + a_{85a} + a_{85b} + a_{86})}$$

$a_{87} > 0$ and $d^+(7) = 1$ implies $c_8 a_{87} = \Sigma_{k=1}^{8} c_7 a_{7k}$

$$\Rightarrow c_8 a_{87} = c_7 a_{75} \Rightarrow c_7 = c_8 \frac{a_{87}}{a_{75}}$$

$$\Rightarrow c_7 = c_2 \frac{a_{87} a_{38}(a_{21} + a_{25})}{a_{75} a_{32}(a_{84} + a_{85a} + a_{85b} + a_{86})}$$

Therefore, $D = c_1 D_1 + c_2 D_2 + c_3 D_3 + c_4 D_4 + c_5 D_5 + c_6 D_6 + c_7 D_7 + c_8 D_8$ is a Lyapunov function for the dynamical system (4.1)$-$ (4.8). Therefore, E^* is globally asymptotically stable in the interior of Ω when $R_{eff} > 1$, $\frac{V}{V^*}$, $\frac{S}{S^*}$, $\frac{R}{R^*} \leq 1$ and $\frac{H_r}{H_r^*} \leq \frac{I}{I^*}$. □

4.4 Conclusion

This chapter presents a deterministic model for the dynamics of tuberculosis Mathematical model with interventions: vaccination, chemoprophylaxis and therapeutics treatments. The total population is divided in to eight compartments. We found that the effective reproduction number of the dynamical system (4.1)-(4.8) is $R_{eff} = c\omega \left(\frac{\sigma\psi\mu + (1-\psi)\mu + \theta}{\mu + \theta}\right) \frac{\alpha\epsilon(1-p)\delta\gamma + \alpha(1-\epsilon)(1-p)(\mu+\gamma)}{(\mu+\alpha)(\mu+\gamma)(\mu+\rho+d)}$. We have recognized the existence of the disease free equilibrium point and endemic equilibrium point of the dynamical system. We proved that the disease free equilibrium point is locally asymptotically stable if $R_{eff} < 1$ and globally asymptotically stable if the effective reproduction number $R_{eff} < 1$. We also proved the local stability of the endemic equilibrium point and also its global stability using a Liapunov function.

Chapter 5

Spread and Control of Drug Sensitive and Multi-Drug Resistance Tuberculosis in Ethiopia

Abstract

In this chapter we formulated a nonlinear dynamical system to study the dynamics of a two-strain tuberculosis epidemic in Ethiopia (5.1)-(5.10). We proved that the solution of the dynamical system (5.1)-(5.10) is positive and bounded. We found that the dynamical system (5.1)-(5.10) has disease free and endemic equilibrium points. We proved that the local and global stability of disease free equilibrium point and endemic equilibrium point. We found the effective reproduction number of the dynamical system. Also, the effective reproduction number of the dynamical system (5.1)-(5.10) which experience drug sensitive strain and the effective reproduction number of the dynamical system (5.1)-(5.10) which experience multi drug resistance strain.

5.1 Introduction

Tuberculosis is among the most ancient diseases. German Microbiologist Robert Koch discovered the causative organism Mycobacterium tuberculosis on 24^{th} March 1882. World

Health Organization (WHO) declared tuberculosis as global epidemic in 1993 [12, 14]. The lifetime risk of TB reactivation for a person with documented Latent Tuberculosis Infection (LTBI) is estimated to be 5%-10%, with the majority developing TB disease within the first five years after initial infection the risk of developing TB disease following infection depends on several factors [12, 22]. There is a huge TB-latent human; this increased its average probability of re-activation due to the emergence and growth HIV and TB drug-resistant strains [12]. One of the biggest health challenges facing the world is tied in to the dramatic increases in the levels of drug resistance TB, particular in hospital settings [12, 29]. In 2016, the World Health Organization (WHO) reports roughly 9.4 million new cases (incidence) per year, an active-TB prevalence of 14 million, and 1.6 to 1.9 million deaths per year, a number that includes 400,000 deaths coming from HIV positive individuals each year. Most active-TB cases are concentrated in South East Asia, African and Western Pacific regions [12, 39]. In Ethiopia there were in average of 177 TB cases per 100,000 TB in 2016 [8, 39, 40, 42].

The emergence and re-emergence of infectious diseases have become a significant worldwide problem. Proper understanding of transmission mechanisms of diseases caused by existing and new pathogens may facilitate devising prevention tools. Prevention tools against transmissions, including vaccines and drugs, need to be developed at a similar pace to that of the microbes. Implementation and proper use of these sophisticated tools against the microbes is another challenge [13]. Tuberculosis is one of a highly infectious diseases caused by infection with the bacteria mycobacterium tuberculosis and it is an airborne disease and so it is primarily transmitted through the respiratory route [30, 29].

Currently, WHO recommends that, the countries use three major categories of health interventions for TB prevention: treatment of LTBI; prevention of transmission of Mycobacterium tuberculosis through infection control; and vaccination of children with the Bacille Calmette-Guérin (BCG) vaccine. In 2016, 154 countries reported providing BCG vaccination as a standard part of these rogrammes, of which 111 reported coverage above 90% [39]. Results of field trials of the BCG vaccine have differed widely, some indicating protection rates as high as 70% to 80%, others indicating the vaccine was completely ineffective in preventing TB [104].

Drug Susceptibility Testing (DST) is very important to provide information about which

drugs a person is resistant. Treatment of tuberculosis disease is not simple and Drug-Susceptible Tuberculosis (DS-TB) requires a multiple drug regimen taken for at least six months. But the treatment will only be successful if the drugs are taken exactly as required for the entire length of time [39]. The currently recommended treatment for cases of drug-susceptible TB must be faithfully carried out over 6-9 months regimen of four first-line drugs: isoniazid, rifampicin, ethambutol and pyrazinamide and is a source of concern due the fact that a number of TB-active individuals do not complete treatment giving rise to the emergence of drug resistance TB strains [12, 39]. Treatment for Rifampicin-Resistant TB (RR-TB) and multidrug-resistant tuberculosis (MDR-TB) is longer, and requires more expensive and more toxic drugs [4, 39].

Multi-Drug-Resistant (MDR) tuberculosis is a form of tuberculosis caused by bacteria that do not respond to, at least, isoniazid and rifampicin, which are the two most powerful, standard anti-tuberculosis drugs [11, 22, 104]. According to the World Health Organization (WHO) global TB report in 2017, it is estimated that there will be 490,000 new cases of multi-drug resistant tuberculosis (MDR-TB) in 2016, in addition, 110,000 new patients who resistant to rifampicin meet the treatment conditions of multi drug resistance tuberculosis [39, 52]. A combination of poor compliance and poor medical supervision or when the anti-TB drugs are mismanaged (incomplete course of treatment) or misused (wrong dose or time length to complete the drugs) can result multi-drug resistance. However some acquire Multi-Drug Resistant Tuberculosis (MDR-TB) by being infected with a multi-drug resistant strain. MDR-TB is transmitted in the same way as the normal drug sensitive strain [22, 52, 65]. Drug-resistant TB has a higher mortality rate, among them, multi-drug resistant tuberculosis (MDR-TB) is more prominent, and has become another new serious problem [52]. Multi-Drug-Resistant Tuberculosis (MDR-TB) treatment regimens are significantly longer, cause serious side effects and are very expensive. The latest data reported to WHO show a treatment success rate for Multi-Drug Resistant Tuberculosis (MDR-TB) of 54%, globally, reflecting high rates of loss to follow-up, unevaluated treatment outcomes and treatment failure [39, 65] and TB treatment outcomes in Ethiopia have been assessed only in small and fragmented observational studies [86].

In this chapter we present a non-linear mathematical model to study the transmission

dynamics and control of tuberculosis in Ethiopia which describes the infectious disease of two strains tuberculosis. The interventions: vaccination, screening and treatments are incorporated in our model. The structure of the chapter is described as follows: In section 5.2 we introduce the model assumption, flow chart of the model, develop the corresponding dynamical system and calculate effective reproduction number. In section 5.3 we investigate the positivity and boundedness of the solution for the dynamical system (5.1)-(5.10). Moreove, we showed that the existence of disease free equilibrium point and its local and global stability. In section 5.4 the existence of endemic equilibrium points (the drug-sensitive only equilibrium point, the drug-resistance only equilibrium point and the endemic equilibrium that both strains are co-exist) are analyzed and proved their local and global stability. Finally, in section 5.5 we gave the conclusion for the work.

5.2 Model Assumptions and Formulation

In this section, we introduce a deterministic TB model by disaggregating the mycobacterium tuberculosis in to two strains (DS-TB, MDR-TB). The total population $N(t)$ is divided in to ten disjoint classes depending on the epidemiological status of individuals such as: Susceptible S(t), who have never exposed to any strain of the Mycobacterium tuberculosis, Vaccinated $V(t)$, who have taken BCG vaccine against mycobacterium tuberculosis, an early stage infected with high risk of developing active drug sensitive tuberculosis $H_s(t)$ and Later(Long) stage infected with low risk of developing active drug sensitive tuberculosis $L_s(t)$, Infectious individuals with drug sensitive tuberculosis $I_s(t)$, Latently infected individuals with multi-drug resistant tuberculosis $E(t)$, Infectious individuals with multi-drug resistant tuberculosis $I_r(t)$, Screened Early latently infected with drug sensitive tuberculosis $T_s(t)$, Screened latently infected with multi-drug resistant tuberculosis $T_r(t)$ and Recovered individuals $R(t)$.

Assume that individuals are recruited into the population by a constant rate Λ with the proportions ψ of which are vaccinated to protect them against tuberculosis infection. Furthermore, that the vaccine has a waning effect over time (after a time $\frac{1}{\theta}$ vaccinated individuals become susceptible again) and reduces due to expiration of duration of vaccine efficacy. We assume that vaccinated individuals may infect with the rate of inefficacy of

vaccine $\sigma \in [0, 1]$. Susceptible population increases due to the coming in of new births not vaccinated against the infection and those who were vaccinated but lose their immunity. When some susceptible & vaccinated individuals come into contact with infectious individuals, they get infected and progress to latently infected classes of drug susceptible and multi-drug resistant tuberculosis at a force of infection rates λ_s & $\sigma\lambda_s$, and λ_r & $\sigma\lambda_r$ respectively where $\lambda_i = c\omega_i \frac{I_i}{N}$, where $i = s, r$ and ω_i is the probability that an individual is infected by one infectious individual, and c is the number of effective contacts.

Individuals leave the high risk latently drug sensitive TB class at the rate α of which the proportion p have a chance be screened and the remaining proportion enters to long latent with drug sensitive TB or develop active TB . The proportion ϵ and $(1 - \epsilon)$ of individuals of the early latent/exposed individuals for drug sensitive tuberculosis who do not get chance for screened will go to L_s and I respectively at the rate α. Thus, the proportion p, $\epsilon(1 - p)$ and $(1 - \epsilon)(1 - p)$ of individuals in the class H_s are transferred to classes T_s, L_s and I_s respectively at a rate α. Individual leaves class L_s at the rate γ in which, the proportion η goes to class I_s and; the remaining proportion $(1 - \eta)$ recovers naturally and enter to recovered class R.

Individuals in H_s and, L_s can also be infected by MDR-TB (primary infection) if there is effective contact with individuals in I_r class. Individuals leave I_s class at the rates ρ_s that the proportion q of individuals in infectious classes of drug susceptible tuberculosis progress to the recovered class while the remaining $(1 - q)$ proportion of individuals with active drug sensitive TB may develop MDR-TB because of improper treatment .

The proportion ν of the latently infected multi-drug resistant tuberculosis are screened for treatment and the remaining proportion developed active drug resistant tuberculosis and leaves E class at the rate of δ. Individual in I_r class recovers at the rate ρ_r and goes to R class. Individuals leave the screened classes T_s and T_r at the rates ϕ, and φ respectively, and go to recovered class.

Due to the nature of the disease, the infection will only kill individuals whose TB progresses to the infectious stage. Moreover, individuals in the recovered class are temporarily recovered. Soon they revert back to the latently infected classes H_s and E , after been re-infected by either drug sensitive or multi-drug resistant strain at the rate $\kappa\lambda_s$

and $\kappa\lambda_r$ respectively, where κ is the reduction in susceptibility due to prior endogenous infection of tuberculosis. We assume that each class conforms to natural death at the rate μ while infectious individuals in I_s and I_r are die due to TB diseases at the rate d_s and d_r respectively. State variables and parameters in the dynamical system listed in the following table.

Table 5.1: Symbols and their description for state variables and parameters in the dynamical system (5.1)-(5.10)

Symbol	**Description**
V	Vaccinated individuals against tuberculosis disease.
S	Susceptible individuals for the disease
H_s	Early latently infected with drug sensitive tuberculosis
L_s	Long latently infected with drug sensitive tuberculosis
I_s	Infectious individuals with drug sensitive tuberculosis
T_s	Screened Early latently infected with drug sensitive tuberculosis
E	Latently infected with multi-drug resistant tuberculosis
I_r	Infectious individuals with multi-drug resistant tuberculosis
T_r	Screened Latently infected with multi-drug resistant tuberculosis
R	Recovered Individuals
Λ	Recruitment of population
ψ	Proportions new born vaccinated
μ	Natural death rate
σ	The rate of inefficacy of vaccine individuals
θ	The rate of vaccine waning
$\lambda_i, i = s, r$	Force of infection (s =DS strain, r =MDR strain)
$\omega_i, i = s, r$	Probability of acquiring TB infections per contact with one infectious individual(s =DS strain, r =MDR strain)
c	Number of effective contacts susceptible or vaccinated individuals makes with infectious individuals.

α	The rate of progression of individuals from early latently infected with DS-TB.
$d_i, i = s, r$	Death rate due to the disease (s = DS strain, r =MDR strain)
p	Proportion of latently infected DS-TB at early stage for treatment
ϵ	Proportion of individuals who do not get chance for screened at H_s and will go to L_s class.
ϕ	Rate of individuals move from T_s to R
q	Proportion of infectious individuals with DS-TB who enters to recovered class.
γ	Progression rate from Long latently infected with DS-TB strain.
δ	Progression rate from latency MDR-TB.
φ	Rate of individuals move from T_r to R
η	The portion of L_s enter in to I_s
ν	The portion of E enter in to I_r
$\rho_i, i = s, r$	The recovery rate infectious individuals (s =DS strain, r =MDR strain).
κ	Acquired immunity due to previous treatment.

Based on the above assumptions we do have the following flow chart:

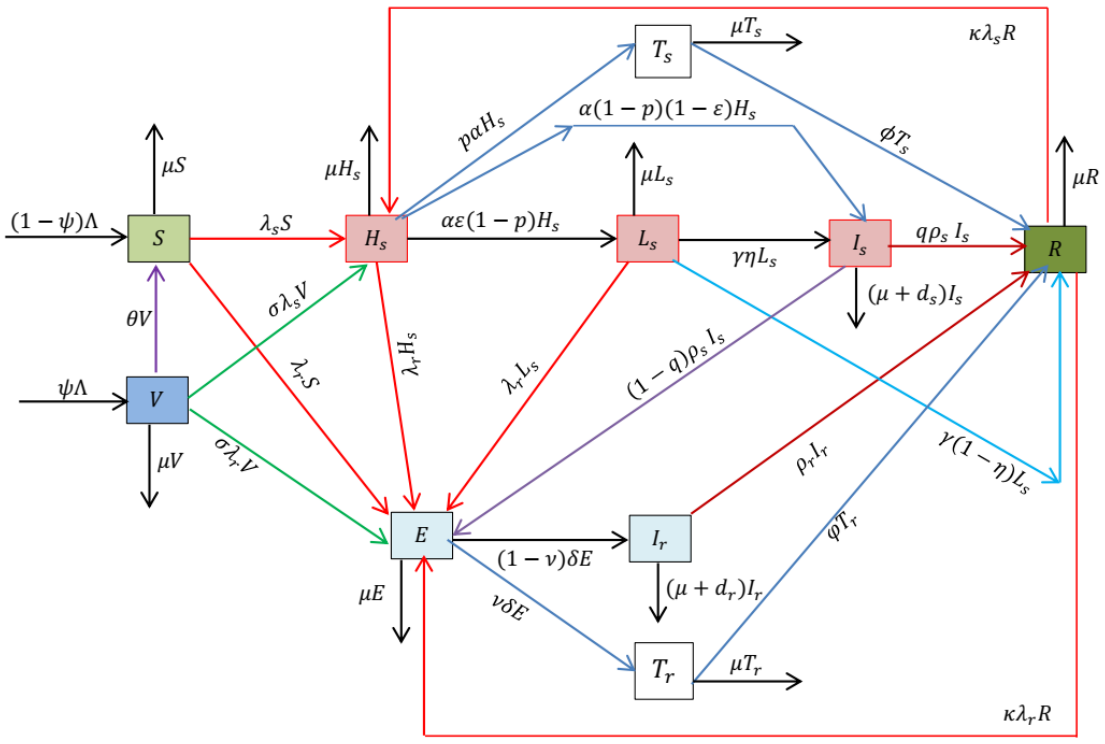

Figure 5.1: Flow Chart of the Dynamical System (5.1)-(5.10)of a two strain tuberculosis

The corresponding dynamical system of the above flow chart is

$$\frac{dV}{dt} = \psi\Lambda - (\sigma(\lambda_s + \lambda_r) + \theta + \mu)V \tag{5.1}$$
$$\frac{dS}{dt} = (1-\psi)\Lambda + \theta V - (\lambda_s + \lambda_r + \mu)S \tag{5.2}$$
$$\frac{dH_s}{dt} = \lambda_s(\sigma V + S + \kappa R) - (\alpha + \lambda_r + \mu)H_s \tag{5.3}$$
$$\frac{dL_s}{dt} = \epsilon\alpha(1-p)H_s - (\gamma + \lambda_r + \mu)L_s \tag{5.4}$$
$$\frac{dI_s}{dt} = \eta\gamma L_s + \alpha(1-\epsilon)(1-p)H_s - (\rho_s + \mu + d_s)I_s \tag{5.5}$$
$$\frac{dT_s}{dt} = \alpha p H_s - (\phi + \mu)T_s \tag{5.6}$$
$$\frac{dE}{dt} = \lambda_r(S + H_s + L_s + \sigma V + \kappa R) + (1-q)\rho_s I_s - (\delta + \mu)E \tag{5.7}$$
$$\frac{dI_r}{dt} = (1-\nu)\delta E - (\rho_r + \mu + d_r)I_r \tag{5.8}$$
$$\frac{dT_r}{dt} = \nu\delta E - (\varphi + \mu)T_r \tag{5.9}$$
$$\frac{dR}{dt} = q\rho_s I_s + \rho_r I_r + \gamma(1-\eta)L_s + \phi T_s + \varphi T_r - (\kappa(\lambda_s + \lambda_r) + \mu)R \tag{5.10}$$

With the total population at a given time t is

$$N(t) = S(t) + V(t) + H_s(t) + L_s(t) + T_s(t) + I_s(t) + E(t) + T_r(t) + I_r(t) + R(t)$$

5.3 Basic Properties of the Model

5.3.1 Positivity of Solutions of the Dynamical System

Theorem 5.1. *Let the initial data for the model (5.1)−(5.10) be* $V(0) > 0, S(0) > 0, H_s(0) > 0, L_s(0) > 0,\ I_s(0) > 0, T_s(0) > 0, E(0) > 0, I_r(0) > 0, T_r(0) > 0$ *and* $R(0) > 0$ *. Then, the solutions* $V(t), S(t), H_s(t), L_s(t), I_s(t), T_s(t), E(t), I_r(t), T_r(t)$ *and* $R(t)$ *of the model (5.1)−(5.10) will be remain positive for all time* $t > 0$.

Proof. Let $\bar{t} = sup\{t > 0 : V(0) > 0, S(0) > 0, H_s(0) > 0, L_s(0) > 0, I_s(0) > 0, T_s(0) > 0, E(0) > 0,\ I_r(0) > 0, T_r(0) > 0$ and $R(0) > 0 t \in [0, t]\}$.

From the equation (5.1) of the system (5.1)−(5.10): $\frac{dV}{dt} = \psi\Lambda - (\sigma(\lambda_s + \lambda_r) + \theta + \mu)V$
We can be rewrite as: $\frac{dV}{dt} + (\sigma(\lambda_s + \lambda_r) + \theta + \mu)V = \psi\Lambda$

Multiply both sides by $e^{\left[\theta t+\mu t+\int_0^{\bar{t}}\sigma(\lambda_s+\lambda_r)(\tau)d\tau\right]}$

$$\Leftrightarrow \frac{dV}{dt}e^{\left[\theta t+\mu t+\int_0^{\bar{t}}\sigma(\lambda_s+\lambda_r)(\tau)d\tau\right]}+\left(\sigma\left(\lambda_s+\lambda_r\right)(t)+\theta+\mu\right)V(t)\,e^{\left[\theta t+\mu t+\int_0^{\bar{t}}\lambda(v)dv\right]}$$

$$=\psi\Lambda e^{\left[\theta t+\mu t+\int_0^{\bar{t}}\sigma(\lambda_s+\lambda_r)(\tau)d\tau\right]}$$

$$\Leftrightarrow \frac{d}{dt}\left[V(t)\,e^{\left[\theta t+\mu t+\int_0^{\bar{t}}\sigma(\lambda_s+\lambda_r)(\tau)d\tau\right]}\right]-V(0)$$

$$=\int_0^{\bar{t}}\psi\Lambda e^{\left[\theta t+\mu t+\int_0^{w}\sigma(\lambda_s+\lambda_r)(\tau)d\tau\right]}dt$$

$$\Leftrightarrow V\left(\bar{t}\right)e^{\left\{\mu\bar{t}+\theta\bar{t}+\int_0^{\bar{t}}\sigma(\lambda_s+\lambda_r)(\tau)d\tau\right\}}-V(0)=\int_0^{\bar{t}}\psi\Lambda e^{\left\{\mu t+\theta t+\int_0^{w}\sigma(\lambda_s+\lambda_r)(\tau)d\tau\right\}}dt$$

$$\Leftrightarrow V\left(\bar{t}\right)=V(0)\,Q_1+Q_1\int_0^{\bar{t}}\psi\Lambda e^{\left\{\mu t+\theta t+\int_0^{w}(\sigma(\lambda_s+\lambda_r)(\tau))d\tau\right\}}dt>0$$

$$where\ \ Q_1=e^{-\left\{\mu t+\theta t+\int_0^{\bar{t}}\sigma(\lambda_s+\lambda_r)(\tau)d\tau\right\}}>0$$

From the equation (5.2) of the system (5.1)−(5.10): $\frac{ds}{dt}=(1-\psi)\,\Lambda+\theta V-(\lambda_s+\lambda_r+\mu)\,S$
We can be rewrite as: $\frac{ds}{dt}+(\lambda_s+\lambda_r+\mu)\,S\ =(1-\psi)\,\Lambda+\theta V$
Multiply both sides by $e^{\left[\mu t+\int_0^{\bar{t}}(\lambda_s+\lambda_r)(\tau))d\tau\right]}$

$$\Leftrightarrow \frac{dS}{dt}e^{\left[\mu t+\int_0^{\bar{t}}(\lambda_s+\lambda_r)(\tau))d\tau\right]}+\left(\left(\lambda_s+\lambda_r\right)(t)+\mu\right)S(t)\,e^{\left[\mu t+\int_0^{\bar{t}}(\lambda_s+\lambda_r)(\tau))d\tau\right]}$$

$$=\left[(1-\psi)\,\Lambda+\theta V\ \right]e^{\left[\mu t+\int_0^{\bar{t}}(\lambda_s+\lambda_r)(\tau))d\tau\right]}$$

$$\Leftrightarrow \frac{d}{dt}\left[S(t)\,e^{\left[\mu t+\int_0^{\bar{t}}(\lambda_s+\lambda_r)(\tau))d\tau\right]}\right]-S(0)$$

$$=\int_0^{\bar{t}}\left((1-\psi)\,\Lambda+\theta V(t)\right)e^{\left[\mu t+\int_0^{\bar{w}}(\lambda_s+\lambda_r)(\tau))d\tau\right]}dt$$

$$\Leftrightarrow S\left(\bar{t}\right)e^{\left[\mu t+\int_0^{\bar{t}}(\lambda_s+\lambda_r)(\tau))d\tau\right]}-S\left(0\right)=\int_0^{\bar{t}}\left(\left(1-\psi\right)\Lambda+\theta V\left(t\right)\right)e^{\left[\mu t+\int_0^{\bar{w}}(\lambda_s+\lambda_r)(\tau))d\tau\right]}dt$$

$$\Leftrightarrow S\left(\bar{t}\right)=S\left(0\right)Q_2+Q_2\int_0^{\bar{t}}\left(\left(1-\psi\right)\Lambda+\theta V\left(t\right)\right)e^{\left[\mu t+\int_0^{\bar{w}}(\lambda_s+\lambda_r)(\tau))d\tau\right]}dt>0$$

$$where\ \ Q_2=e^{-\left[\mu t+\int_0^{\bar{t}}(\lambda_s+\lambda_r)(\tau))d\tau\right]}>0$$

From the equation (5.3) of the system (5.1)−(5.10): $\frac{dH_s}{dt}=\lambda_sS+\sigma\lambda_sV+\kappa\lambda_sR-\left(\alpha+\lambda_r+\mu\right)H_s$

We can be rewrite as: $\frac{dH_s}{dt}+\left(\alpha+\lambda_r+\mu\right)H_s=\lambda_sS+\sigma\lambda_sV+\kappa\lambda_sR$

Multiply both sides by $e^{\left[\alpha\bar{t}+\mu\bar{t}+\int_0^{\bar{t}}\lambda_r(\tau)d\tau\right]}$

$$\Leftrightarrow\frac{dH_s}{dt}e^{\left[\alpha\bar{t}+\mu\bar{t}+\int_0^{\bar{t}}\lambda_r(\tau)d\tau\right]}+\left(\alpha+\lambda_r+\mu\right)H_se^{\left[\alpha\bar{t}+\mu\bar{t}+\int_0^{\bar{t}}\lambda_r(\tau)d\tau\right]}$$

$$=\left(\lambda_sS+\sigma\lambda_sV+\kappa\lambda_sR\right)e^{\left[\alpha\bar{t}+\mu\bar{t}+\int_0^{\bar{t}}\lambda_r(\tau)d\tau\right]}$$

$$\Leftrightarrow\frac{d}{dt}\left[H_s\left(t\right)e^{\left[\alpha\bar{t}+\mu\bar{t}+\int_0^{\bar{t}}\lambda_r(\tau)d\tau\right]}\right]-H_s\left(0\right)$$

$$=\int_0^{\bar{t}}\left(\lambda_sS+\sigma\lambda_sV+\kappa\lambda_sR\right)e^{\left[\alpha\bar{t}+\mu\bar{t}+\int_0^{\bar{t}}\lambda_r(\tau)d\tau\right]}\,dt$$

$$\Leftrightarrow H_s\left(\bar{t}\right)\left[\alpha\bar{t}+\mu\bar{t}+\int_0^{\bar{t}}\lambda_r\left(\tau\right)d\tau\right]-H_s\left(0\right)$$

$$=\int_0^{\bar{t}}\left(\lambda_sS\left(t\right)+\sigma\lambda_sV\left(t\right)+\kappa\lambda_sR\left(t\right)\right)\left[\alpha\bar{t}+\mu\bar{t}+\int_0^{\bar{t}}\lambda_r\left(\tau\right)d\tau\right]dt$$

$$\Leftrightarrow H_s\left(t\right)=H_s\left(0\right)Q_3+Q_3\int_0^{\bar{t}}\left[\left(\lambda_sS\left(t\right)+\sigma\lambda_sV\left(t\right)+\kappa\lambda_sR\left(t\right)\right)\left(\alpha\bar{t}+\mu\bar{t}+\int_0^{\bar{t}}\lambda_r\left(\tau\right)d\tau\right)\right]dt>0$$

$$where\ \ Q_3=e^{-\left[\alpha\bar{t}+\mu\bar{t}+\int_0^{\bar{t}}\lambda_r(\tau)d\tau\right]}>0$$

From the equation (5.4) of the system (5.1)−(5.10): $\frac{dL_s}{dt}=\alpha\varepsilon\left(1-p\right)H_s-\left(\lambda_r+\gamma+\mu\right)L_s$

We can be rewrite as: $\frac{dL_s}{dt}+\left(\lambda_r+\gamma+\mu\right)L_s=\alpha\varepsilon\left(1-p\right)H_s$

Multiply both sides by $= e^{\left[\gamma\bar{t}+\mu\bar{t}+\int_0^{\bar{t}}\lambda_r(\tau)d\tau\right]}$

$$\Leftrightarrow \frac{dL_s}{dt}e^{\left[\gamma\bar{t}+\mu\bar{t}+\int_0^{\bar{t}}\lambda_r(\tau)d\tau\right]}+\left(\lambda_r+\gamma+\mu\right)L_s e^{\left[\gamma\bar{t}+\mu\bar{t}+\int_0^{\bar{t}}\lambda_r(\tau)d\tau\right]}$$

$$=\alpha\varepsilon\left(1-p\right)H_s e^{\left[\gamma\bar{t}+\mu\bar{t}+\int_0^{\bar{t}}\lambda_r(\tau)d\tau\right]}$$

$$\Leftrightarrow \frac{d}{dt}\left[L_s\left(t\right)e^{\left[\gamma\bar{t}+\mu\bar{t}+\int_0^{\bar{t}}\lambda_r(\tau)d\tau\right]}\right]-L_s\left(0\right)$$

$$=\int_0^{\bar{t}}\alpha\varepsilon\left(1-p\right)H_s e^{\left[\gamma\bar{t}+\mu\bar{t}+\int_0^{\bar{t}}\lambda_r(\tau)d\tau\right]}\,dt$$

$$\Leftrightarrow L_s\left(\bar{t}\right)e^{\left[\gamma\bar{t}+\mu\bar{t}+\int_0^{\bar{t}}\lambda_r(\tau)d\tau\right]}-L_s\left(0\right)=\int_0^{\bar{t}}\alpha\varepsilon\left(1-p\right)H_s e^{\left[\gamma\bar{t}+\mu\bar{t}+\int_0^{\bar{t}}\lambda_r(\tau)d\tau\right]}\,dt$$

$$\Leftrightarrow L_s\left(t\right)=L_s\left(0\right)Q_4+Q_4\int_0^{\bar{t}}\alpha\varepsilon\left(1-p\right)H_s e^{\left[\gamma\bar{t}+\mu\bar{t}+\int_0^{\bar{t}}\lambda_r(\tau)d\tau\right]}dt>0$$

$$where\;\; Q_4=e^{-\left[\gamma\bar{t}+\mu\bar{t}+\int_0^{\bar{t}}\lambda_r(\tau)d\tau\right]}>0$$

From the equation (5.5) of the system (5.1)−(5.10): $\frac{dI_s}{dt}=\gamma\eta L_s+\alpha\left(1-\varepsilon\right)\left(1-p\right)H_s-\left(\rho_s+\mu+d_s\right)I_s$

We can be rewrite as: $\frac{dI_s}{dt}+\left(\rho_s+\mu+d_s\right)I_s=\gamma\eta L_s+\alpha\left(1-\varepsilon\right)\left(1-p\right)H_s+\alpha\left(1-\varepsilon\right)\left(1-p\right)H_s$

Multiply both sides by $e^{[\rho_s\bar{t}+d_s\bar{t}+\mu\bar{t}]}$

$$\Leftrightarrow \frac{dI_s}{dt}e^{[\rho_s\bar{t}+d_s\bar{t}+\mu\bar{t}]}+\left(\rho+\mu+d\right)Ie^{[\rho_s\bar{t}+d_s\bar{t}+\mu\bar{t}]}$$

$$=\left[\gamma\eta L_s+\alpha\left(1-\varepsilon\right)\left(1-p\right)H_s\right]e^{[\rho_s\bar{t}+d_s\bar{t}+\mu\bar{t}]}$$

$$\Leftrightarrow \frac{d}{dt}\left[I_s\left(t\right)e^{[\rho_s\bar{t}+d_s\bar{t}+\mu\bar{t}]}\right]-I_s\left(0\right)=\left[\gamma\eta L_s+\alpha\left(1-\varepsilon\right)\left(1-p\right)H_s\right]e^{[\rho_s\bar{t}+d_s\bar{t}+\mu\bar{t}]}$$

$$\Leftrightarrow I_s\left(\bar{t}\right)e^{[\rho_s\bar{t}+d_s\bar{t}+\mu\bar{t}]}-I_s\left(0\right)=\int_0^{\bar{t}}\left[\gamma\eta L_s+\alpha\left(1-\varepsilon\right)\left(1-p\right)H_s\right]e^{[\rho\bar{t}+d_s\bar{t}+\mu\bar{t}]}\,dt$$

$$\Leftrightarrow I_s\left(t\right)=I_s\left(0\right)Q_5+Q_5\int_0^{\bar{t}}\left[\gamma\eta L_s+\alpha\left(1-\varepsilon\right)\left(1-p\right)H_s\right]e^{[\rho_s\bar{t}+d_s\bar{t}+\mu\bar{t}]}\,dt>0$$

$$where\;\; Q_5=e^{-[\rho_s\bar{t}+d_s\bar{t}+\mu\bar{t}]}>0$$

From the equation (5.6) of the system (5.1)−(5.10): $\frac{dT_s}{dt} = \alpha p H_s - (\phi + \mu) T_s$

We can be rewrite as:$\frac{dT_s}{dt} + (\phi + \mu) T_s = \alpha p H_s$

Multiply both sides by $e^{[\phi \bar{t} + \mu \bar{t}]}$

$$\Leftrightarrow \frac{dT_s}{dt} e^{[\phi \bar{t} + \mu \bar{t}]} + (\phi + \mu) T_s e^{[\phi \bar{t} + \mu \bar{t}]} = \alpha p \ H_s e^{[\phi \bar{t} + \mu \bar{t}]}$$

$$\Leftrightarrow \frac{d}{dt} \left[T_s (t) e^{[\phi \bar{t} + \mu \bar{t}]} \right] - T_s (0) = \int_0^{\bar{t}} \alpha p \ H_s e^{[\phi \bar{t} + \mu \bar{t}]} \, dt$$

$$\Leftrightarrow T_s \left(\bar{t} \right) e^{[\phi \bar{t} + \mu \bar{t}]} - T_s (0) = \int_0^{\bar{t}} \alpha p \ H_s e^{[\phi \bar{t} + \mu \bar{t}]} \, dt$$

$$\Leftrightarrow T_s \left(\bar{t} \right) = T_s (0) Q_6 + Q_6 \int_0^{\bar{t}} \alpha p \ H_s e^{[\phi \bar{t} + \mu \bar{t}]} \, dt > 0 \ \ where \ \ Q_6 = e^{-[\phi \bar{t} + \mu \bar{t}]} > 0$$

From the equation (5.7) of the system (5.1)−(5.10):

$$\frac{dE}{dt} = \lambda_r (S + H_s + L_s + \sigma V + \kappa R) - (\delta + \mu) E$$

We can be rewrite as: $\frac{dE}{dt} + (\delta + \mu) E = \lambda_r (S + H_s + L_s + \sigma V + \kappa R) + (1 - q) \rho_s I_s$

Multiply both sides by $e^{[\delta \bar{t} + \mu \bar{t}]}$

$$\Leftrightarrow \frac{dE}{dt} e^{[\delta \bar{t} + \mu \bar{t}]} + (\delta + \mu) E e^{[\delta \bar{t} + \mu \bar{t}]} = \lambda_r (S + H_s + L_s + \sigma V + \kappa R) e^{[\delta \bar{t} + \mu \bar{t}]}$$

$$\Leftrightarrow \frac{d}{dt} \left[E (t) e^{[\delta \bar{t} + \mu \bar{t}]} \right] - E (0)$$

$$= \int_0^{\bar{t}} \left[\lambda_r (S + H_s + L_s + \sigma V + \kappa R) + (1 - q) \rho_s I_s \right] e^{[\delta \bar{t} + \mu \bar{t}]} \, dt$$

$$\Leftrightarrow E \left(\bar{t} \right) e^{[\delta \bar{t} + \mu \bar{t}]} - E (0)$$

$$= \int_0^{\bar{t}} \left[\lambda_r (t) (S + H_s + L_s + \sigma V + \kappa R) + (1 - q) \rho_s I_s \right] e^{[\delta \bar{t} + \mu \bar{t}]} \, dt$$

$$\Leftrightarrow E \left(\bar{t} \right) = E (0) Q_7 + Q_7 \int_0^{\bar{t}} \left[\lambda_r (t) (S + H_s + L_s + \sigma V + \kappa R) + (1 - q) \rho_s I_s \right] exp \left[\varphi \bar{t} + \mu \bar{t} \right] \, dt > 0$$

$$where \ \ Q_7 = e^{-[\delta \bar{t} + \mu \bar{t}]} > 0$$

From the equation (5.8) of the system (5.1)−(5.10): $\frac{dI_r}{dt} = (1 - \nu) \delta E \ - (\rho_r + \mu + d_r) I_r$

We can be rewrite as: $\frac{dI_r}{dt} + (\rho_r + \mu + d_r) I_r = (1 - \nu) \delta E$

Multiply both sides by $e^{[\rho_r \bar{t}+\mu\bar{t}+d_r\bar{t}]}$

$$\Leftrightarrow \frac{dI_r}{dt} e^{\left[\mu t+\int_0^{\bar{t}} \lambda(v)dv\right]} + (\lambda(t)+\mu) I_r(t) e^{[\rho_r \bar{t}+\mu\bar{t}+d_r\bar{t}]}$$

$$= [(1-\nu)\delta E\,] e^{[\rho_r \bar{t}+\mu\bar{t}+d_r\bar{t}]}$$

$$\Leftrightarrow \frac{d}{dt}\left[I_r(t) e^{[\rho_r \bar{t}+\mu\bar{t}+d_r\bar{t}]}\right] - I_r(0) = \int_0^{\bar{t}} [(1-\nu)\delta E\,] e^{\left[\mu t+\int_0^{\bar{t}} \lambda(v)dv\right]} dt$$

$$\Leftrightarrow I_r\left(\bar{t}\right) e^{[\rho_r \bar{t}+\mu\bar{t}+d_r\bar{t}]} - I_r(0) = \int_0^{\bar{t}} [(1-\nu)\delta E\,] e^{[\rho_r \bar{t}+\mu\bar{t}+d_r\bar{t}]} dt$$

$$\Leftrightarrow I_r\left(\bar{t}\right) = I_r(0) Q_8 + Q_8 \int_0^{\bar{t}} [(1-\nu)\delta E\,] e^{[\rho_r \bar{t}+\mu\bar{t}+d_r\bar{t}]} dt > 0$$

$$where \;\; Q_8 = e^{-[\rho_r \bar{t}+\mu\bar{t}+d_r\bar{t}]} > 0$$

From the equation (5.9) of the system (5.1)−(5.10): $\frac{dT_r}{dt} = \nu\delta E - (\varphi+\mu) T_r$

We can be rewrite as: $\frac{dT_r}{dt} + (\varphi+\mu) T_r = \nu\delta E$

Multiply both sides by $e^{(\varphi\bar{t}+\mu\bar{t})}$

$$\Leftrightarrow \frac{dT_r}{dt} e^{(\varphi\bar{t}+\mu\bar{t})} + (\lambda(t)+\mu) T_r(t) e^{\left[\mu t+\int_0^{\bar{t}} \lambda(v)dv\right]} = [\nu\delta E\,] e^{[\varphi\bar{t}+\mu\bar{t}]}$$

$$\frac{d}{dt}\left[T_r(t) e^{[\varphi\bar{t}+\mu\bar{t}]}\right] - T_r(0) = \int_0^{\bar{t}} [\nu\delta E\,] exp\left(\varphi\bar{t}+\mu\bar{t}\right)$$

$$\Leftrightarrow T_r\left(\bar{t}\right) e^{[\varphi\bar{t}+\mu\bar{t}]} - T_r(0) = \int_0^{\bar{t}} [\nu\delta E\,] e^{[\varphi\bar{t}+\mu\bar{t}]}$$

$$\Leftrightarrow T_r\left(\bar{t}\right) = T_r(0) Q_9 + Q_9 \int_0^{\bar{t}} [\nu\delta E] e^{[\varphi\bar{t}+\mu\bar{t}]} > 0$$

$$where \;\; Q_9 = e^{-[\varphi\bar{t}+\mu\bar{t}]} > 0$$

From the equation (5.10) of the system (5.1)−(5.10):

$$\frac{dR}{dt} = q\rho_s I_s + \rho_r I_r + \gamma(1-\eta) L_s + \phi T_s + \varphi T_r - (\kappa(\lambda_s+\lambda_r)+\mu) R$$

We can be rewrite as:

$$\frac{dR}{dt} + (\kappa(\lambda_s+\lambda_r)+\mu) R = q\rho_s I_s + \rho_r I_r + \gamma(1-\eta) L_s + \phi T_s + \varphi T_r$$

Multiply both sides by $e^{\left[\mu t+\kappa\int_0^{\bar{t}}(\lambda_s+\lambda_r)(\tau)d\tau\right]}$

$$\Leftrightarrow \frac{dR}{dt}e^{\left[\mu t+\kappa\int_0^{\bar{t}}(\lambda_s+\lambda_r)(\tau)d\tau\right]}+\left(\kappa\left(\lambda_s+\lambda_r\right)+\mu\right)R\left(t\right)e^{\left[\mu t+\kappa\int_0^{\bar{t}}(\lambda_s+\lambda_r)(\tau)d\tau\right]}$$

$$=\left[q\rho_s I_s+\rho_r I_r+\gamma\left(1-\eta\right)L_s+\phi T_s+\varphi T_r\ \right]e^{\left[\mu t+\kappa\int_0^{\bar{t}}(\lambda_s+\lambda_r)(\tau)d\tau\right]}$$

$$\Leftrightarrow \frac{d}{dt}\left[R\left(t\right)e^{\left[\mu t+\kappa\int_0^{\bar{t}}(\lambda_s+\lambda_r)(\tau)d\tau\right]}\right]-R\left(0\right)$$

$$=\int_0^{\bar{t}}\left[q\rho_s I_s+\rho_r I_r+\gamma\left(1-\eta\right)L_s+\phi T_s+\varphi T_r\ \right]e^{\left[\mu t+\kappa\int_0^{\bar{t}}(\lambda_s+\lambda_r)(\tau)d\tau\right]}dt$$

$$\Leftrightarrow R\left(\bar{t}\right)e^{\left[\mu\bar{t}+\kappa\int_0^{\bar{t}}(\lambda_s+\lambda_r)(\tau)d\tau\right]}-R\left(0\right)$$

$$=\int_0^{\bar{t}}\left[q\rho_s I_s+\rho_r I_r+\gamma\left(1-\eta\right)L_s+\phi T_s+\varphi T_r\ \right]e^{\left[\mu t+\kappa\int_0^{\bar{t}}(\lambda_s+\lambda_r)(\tau)d\tau\right]}dt$$

$$\Leftrightarrow R\left(\bar{t}\right)=R\left(0\right)Q_{10}+Q_{10}\int_0^{\bar{t}}\left[q\rho_s I_s+\rho_r I_r+\gamma\left(1-\eta\right)L_s+\phi T_s+\varphi T_r\ \right]$$

$$e^{\left[\mu t+\kappa\int_0^{\bar{t}}(\lambda_s+\lambda_r)(\tau)d\tau\right]}dt>0$$

$$where\ \ Q_{10}=e^{-\left[\mu t+\kappa\int_0^{\bar{t}}(\lambda_s+\lambda_r)(\tau)d\tau\right]}>0$$

Therefore all of the state variables of our model system (5.1)−(5.10) are positive for all $t>0$ given any positive initial conditions. □

5.3.2 Boundedness of Solutions of the Dynamical System

Theorem 5.2. *The dynamical system (5.1)−(5.10) is positively invariant in the closed invariant set* $\Omega=\{(V,S,H_s,L_s,I_s,T_s,E,I_r,T_r,R)\in R_+^{10}:N\leq\frac{\Lambda}{\mu}\}$.

Proof. Consider the biologically feasible region, Ω and observe that the rate of change of the total population obtained by adding all the equations (5.1)−(5.10) of the model.

$\frac{dN}{dt} = \Lambda - \mu N - (d_s I_s + d_r I_r)$. For $N > \frac{\Lambda}{\mu}$. we do have $\frac{dN}{dt} \leq 0$. Furthermore using a standard comparison theorem $\frac{dN}{dt} \leq \Lambda - \mu N$ it follows that $\int \frac{dN}{\Lambda - \mu N} \leq \int dt \Longrightarrow -ln(\Lambda - \mu N) \leq \mu(t + c)$ where c is a constant $\Longleftrightarrow -\mu N \geq Ae^{-\mu t}$, where $A = e^{-c\mu}$ is a constant. And then applying the initial condition $N(0)$ we do have $\Lambda - \mu N(0) \geq A$ that is $N(0) \leq \frac{\Lambda}{\mu}$. Then from the inequality $\Lambda - \mu N \geq Ae^{-\mu t}$ and taking $A = \Lambda - \mu N(0)$, we get $N(t) \leq \frac{\Lambda}{\mu} - \frac{A}{\mu} e^{-\mu t} \leq \frac{\Lambda}{\mu - N(0)} e^{-\mu t}$. For time $t > 0$ we do have $\lim_{\to\infty} N(t) \leq N(0)e^{(} - \mu t) - \frac{\Lambda}{\mu} e^{-\mu t} + \frac{\Lambda}{\mu} \leq \frac{\Lambda}{\mu}$ (Since, $N(0) \leq \frac{\Lambda}{\mu}$. Hence if $N(0) \leq \frac{\Lambda}{\mu}$, as $t \to \infty$ the population size $N(t) \to \frac{\Lambda}{\mu}$ which implies that $0 \leq N(t) \leq \frac{\Lambda}{\mu}$.

From the equation (5.1) of the system (5.1)−(5.10): $\frac{dV}{dt} = \psi\Lambda - (\sigma(\lambda_s + \lambda_r) + \theta + \mu) V$

If we add $(\sigma(\lambda_s + \lambda_r)V$ to the right side, we get: $\frac{dV}{dt} \leq \psi\Lambda - (\theta + \mu) V$

Using a standard comparision theorem:

$$\int \frac{dV}{\psi\Lambda - (\theta + \mu) V} \leq \int dt \Rightarrow -\frac{1}{(\theta + \mu)} \ln(\psi\Lambda - (\theta + \mu) V) \leq t + c \text{ where } c \text{ is a constant}$$

$$\Rightarrow \psi\Lambda - (\theta + \mu) V \geq \mathrm{B}e^{-(\theta+\mu)t} \text{ where } B = e^{-c(\theta+\mu)} \text{is a constant}$$

$$\Rightarrow V \leq \frac{\psi\Lambda}{(\theta + \mu)} - \frac{\mathrm{B}}{(\theta + \mu)} e^{-(\theta+\mu)t}$$

By applying the initial condition V(0):

$$\psi\Lambda - (\theta + \mu) V \geq \mathrm{B}e^{-(\theta+\mu)t} \Rightarrow \mathrm{V}(0) \leq \frac{\psi\Lambda}{(\theta + \mu)} - \frac{\mathrm{B}}{(\theta + \mu)} \leq \frac{\psi\Lambda}{(\theta + \mu)}$$

Then from the inequality $\psi\Lambda - (\theta + \mu) V \geq \mathrm{B}e^{-(\theta+\mu)t}$, and taking $\mathrm{B} = \psi\Lambda - (\theta + \mu) V(0)$ we can get,

$$V(t) \leq \frac{\psi\Lambda}{(\theta + \mu)} - \frac{\mathrm{B}}{(\theta + \mu)} e^{-(\theta+\mu)t} \leq \frac{\psi\Lambda}{(\theta + \mu)} - \left(\frac{\psi\Lambda}{(\theta + \mu)} - \mathrm{V}(0)\right) e^{-(\theta+\mu)t}$$

$$V(t) \leq V(0) e^{-(\theta+\mu)t} + \frac{\psi\Lambda}{(\theta + \mu)} \left(1 - e^{-(\theta+\mu)t}\right)$$

$$V(t) \leq V(0) e^{-(\mu+\theta)t} + \frac{\psi\Lambda}{\mu + \theta} \left(1 - e^{-(\mu+\theta)t}\right)$$

$$\lim_{t\to\infty} V(t) \leq V(0) e^{-(\mu+\theta)t} + \frac{\psi\Lambda}{\mu + \theta} \left(1 - e^{-(\theta+\mu)t}\right)$$

$$\lim_{t\to\infty} V(t) \leq \left(V(0) - \frac{\psi\Lambda}{\mu + \theta}\right) e^{-(\mu+\theta)t} + \frac{\psi\Lambda}{\mu + \theta} \leq \frac{\psi\Lambda}{\mu + \theta} \text{ Since, } V(0) \leq \frac{\psi\Lambda}{(\theta + \mu)}$$

From the equation (5.2) of the system (5.1)−(5.10): $\frac{ds}{dt} = (1 - \psi)\Lambda + \theta V - (\lambda_s + \lambda_r + \mu) S$

If we add $(\lambda_s + \lambda_r) S$ to the right side, we get: $\frac{dS}{dt} \leq (1 - \psi)\Lambda + \theta V - \mu S$

Using a standard comparision theorem:

$$\int \frac{dS}{(1-\psi)\Lambda+\theta V-\mu S} \leq \int dt \Rightarrow -\frac{1}{\mu}\ln\left((1-\psi)\Lambda+\theta V-\mu S\right) \leq t+c \quad \textit{where where } c \textit{ is a constant}$$

$$\Rightarrow \ (1-\psi)\Lambda+\theta V-\mu S \geq \mathrm{C}e^{-\mu t} \ \textit{where } C = e^{-c\mu t} \textit{is a constant}$$

$$\Rightarrow \ S \leq \frac{(1-\psi)\Lambda+\theta V}{\mu} - \frac{\mathrm{C}}{\mu}e^{-\mu t}$$

By applying the initial condition S(0):

$$S(t) \leq \frac{(1-\psi)\Lambda+\theta V}{\mu} - \frac{\mathrm{C}}{\mu}e^{-\mu t} \Rightarrow \mathrm{S}(0) \leq \frac{(1-\psi)\Lambda+\theta V}{\mu} - \frac{\mathrm{C}}{\mu} \leq \frac{(1-\psi)\Lambda+\theta V}{\mu}$$

Then from the inequality $(1-\psi)\Lambda+\theta V-\mu S \geq \mathrm{C}e^{-\mu t}$, and taking $\mathrm{C} = (1-\psi)\Lambda+\theta V-\mu S(0)$ we can get,

$$S(t) \leq \frac{(1-\psi)\Lambda+\theta V}{\mu} - \frac{\mathrm{C}}{\mu}e^{-\mu t} \leq \frac{(1-\psi)\Lambda+\theta V}{\mu} - \left(\frac{(1-\psi)\Lambda+\theta V}{\mu} - \mathrm{S}(0)\right)e^{-\mu t}$$

$$S(t) \leq S(0)e^{-\mu t} + \frac{(1-\psi)\Lambda+\theta V}{\mu}\left(1-e^{-\mu t}\right)$$

$$S(t) \leq S(0)e^{-\mu t} + \frac{(1-\psi)\Lambda+\theta V}{\mu}\left(1-e^{-\mu t}\right)$$

$$\lim_{t\to\infty} S(t) \leq S(0)e^{-\mu t} + \frac{(1-\psi)\Lambda+\theta V}{\mu}\left(1-e^{-\mu t}\right)$$

$$\lim_{t\to\infty} S(t) \leq \left(S(0) - \frac{(1-\psi)\Lambda+\theta V}{\mu}\right)e^{-\mu t} + \frac{(1-\psi)\Lambda+\theta V}{\mu} \leq \frac{(1-\psi)\Lambda+\theta V}{\mu}$$

$$\textit{Since,} \ \ S(0) \leq \frac{(1-\psi)\Lambda+\theta V}{\mu}$$

From the equation (5.3) of the system (5.1)−(5.10): $\frac{dH_s}{dt} = \lambda_s S + \sigma\lambda_s V + \kappa\lambda_s R - (\alpha+\lambda_r+\mu)H_s$

If we add $(\alpha+\lambda_r)H_s$ to the right side, we get: $\frac{dH_s}{dt} \leq \lambda(S+\sigma V+\kappa R) - \mu H_s$

Using a standard comparision theorem:

$$\int \frac{dH_s}{(S+\sigma V+\kappa R)-\mu H_s} \leq \int dt$$

$$\Rightarrow -\frac{1}{\mu}\ln\left((S+\sigma V+\kappa R)-\mu H_s\right) \leq t+c \quad \textit{where } c \textit{ is a constant}$$

$$\Rightarrow \ (S+\sigma V+\kappa R)-\mu H_s \geq \mathrm{D}e^{-\mu t} \ \textit{where } D = e^{-c\mu t} \textit{is a constant}$$

$$\Rightarrow \ H_s \leq \frac{(S+\sigma V+\kappa R)}{\mu} - \frac{\mathrm{D}}{\mu}e^{-\mu t}$$

By applying the initial condition $H_s(0)$:

$$H_s(t) \leq \frac{(S+\sigma V+\kappa R)}{\mu} - \frac{\mathrm{D}}{\mu}e^{-\mu t} \Rightarrow H_s(0) \leq \frac{(S+\sigma V+\kappa R)}{\mu} - \frac{\mathrm{D}}{\mu} \leq \frac{(S+\sigma V+\kappa R)}{\mu}$$

Then from the inequality $(S+\sigma V+\kappa R)-\mu H_s \geq \mathrm{D}e^{-\mu t}$ and taking $\mathrm{D}=(S+\sigma V+\kappa R)-\mu H_s(0)$ we can get,

$$H_s(t) \leq \frac{(S+\sigma V+\kappa R)}{\mu} - \frac{\mathrm{D}}{\mu}e^{-\mu t} \leq \frac{(S+\sigma V+\kappa R)}{\mu} - \left(\frac{(S+\sigma V+\kappa R)}{\mu} - H_s(0)\right)e^{-\mu t}$$

$$H_s(t) \leq H_s(0)\,e^{-\mu t} + \frac{(S+\sigma V+\kappa R)}{\mu}\left(1-e^{-\mu t}\right)$$

$$\lim_{t\to\infty} H_s(t) \leq H_s(0)\,e^{-\mu t} + \frac{(S+\sigma V+\kappa R)}{\mu}\left(1-e^{-\mu t}\right)$$

$$\lim_{t\to\infty} H_s(t) \leq \left(H_s(0) - \frac{(S+\sigma V+\kappa R)}{\mu}\right)e^{-\mu t} + \frac{(S+\sigma V+\kappa R)}{\mu} \leq \frac{(S+\sigma V+\kappa R)}{\mu}$$

$$\textit{Since, } \; H_s(0) \leq \frac{(S+\sigma V+\kappa R)}{\mu}$$

From the equation (5.4) of the system (5.1)−(5.10): $\frac{dL_s}{dt} = \alpha\varepsilon(1-p)H_s - (\lambda_r+\gamma+\mu)L_s$

If we add $(\lambda_r+\gamma)L_s$ to the right side, we get: $\frac{dL_s}{dt} \leq \alpha\varepsilon(1-p)H_s - \mu L_s$

Using a standard comparision theorem:

$$\int \frac{dL_s}{\alpha\varepsilon(1-p)H_s - \mu L_s} \leq \int dt$$

$$\Rightarrow -\frac{1}{\mu}\ln\left(\alpha\varepsilon(1-p)H_s - \mu L_s\right) \leq t + c \quad \textit{where } c \textit{ is a constant}$$

$$\Rightarrow \; \alpha\varepsilon(1-p)H_s - \mu L_s \geq \mathrm{E}e^{-\mu t} \textit{ where } E = e^{-c\mu t} \textit{is a constant}$$

$$\Rightarrow L_s \leq \frac{\alpha\varepsilon(1-p)H_s}{\mu} - \frac{\mathrm{E}}{\mu}e^{-\mu t}$$

By applying the initial condition $L_s(0)$:

$$L_s(t) \leq \frac{\alpha\varepsilon(1-p)s}{\mu} - \frac{\mathrm{E}}{\mu}e^{-\mu t} \Rightarrow L_s(0) \leq \frac{\alpha\varepsilon(1-p)H_s}{\mu} - \frac{\mathrm{E}}{\mu} \leq \frac{\alpha\varepsilon(1-p)H_s}{\mu}$$

Then from the inequality $\alpha\varepsilon(1-p)H_s - \mu L_s \geq \mathrm{E}e^{-\mu t}$ and taking $\mathrm{E}=\alpha\varepsilon(1-p)H_s - \mu L_s(0)$ we can get,

$$L_s(t) \leq \frac{\alpha\varepsilon(1-p)H_s}{\mu} - \frac{\mathrm{E}}{\mu}e^{-\mu t} \leq \frac{\alpha\varepsilon(1-p)H_s}{\mu} - \left(\frac{\alpha\varepsilon(1-p)H_s}{\mu} - L_s(0)\right)e^{-\mu t}$$

$$L_s(t) \leq L_s(0)\,e^{-\mu t} + \frac{\alpha\varepsilon(1-p)H_s}{\mu}\left(1-e^{-\mu t}\right)$$

$$L_s(t) \leq L_s(0)\,e^{-\mu t} + \frac{\alpha\varepsilon(1-p)H_s}{\mu}\left(1-e^{-\mu t}\right)$$

$$\lim_{t\to\infty} L_s(t) \leq L_s(0)\,e^{-\mu t} + \frac{\alpha\varepsilon(1-p)H_s}{\mu}\left(1-e^{-\mu t}\right)$$

$$\lim_{t\to\infty} L_s(t) \leq \left(L_s(0) - \frac{\alpha\varepsilon(1-p)H_s}{\mu}\right)e^{-\mu t} + \frac{\alpha\varepsilon(1-p)H_s}{\mu} \leq \frac{\alpha\varepsilon(1-p)H_s}{\mu}$$

$$\textit{where } L_s(0) \leq \frac{\alpha\varepsilon(1-p)H_s}{\mu}$$

From the equation (5.5) of the system (5.1)−(5.10): $\frac{dT_s}{dt} = \alpha p\ H_s - (\phi + \mu)\, T_s$

If we add ϕT_s to the right side, we get: $\frac{dT_s}{dt} \leq \alpha p H_s - \mu T_s$

Using a standard comparision theorem:

$$\int \frac{dT_s}{\alpha p H_s - \mu T_s} \leq \int dt \Rightarrow -\frac{1}{\mu} \ln\left(\alpha p H_s - \mu T_s\ \right) \leq t + c \quad \textit{where } c \textit{ is a constant}$$

$$\Rightarrow\ \alpha p H_s - \mu T_s\ \geq \mathrm{F} e^{-\mu t} \textit{ where } F = e^{-c\mu t} \textit{ is a constant}$$

$$\Rightarrow T_s \leq \frac{\alpha p H_r}{\mu} - \frac{\mathrm{F}}{\mu} e^{-\mu t}$$

By applying the initial condition $T_s(0)$:

$$T_s\left(t\right) \leq \frac{\alpha p H_s}{\mu} - \frac{F}{\mu} e^{-\mu t} \Rightarrow T_s\left(0\right) \leq \frac{\alpha p H_s}{\mu} - \frac{\mathrm{F}}{\mu} \leq \frac{\alpha p H_s}{\mu}$$

Then from the inequality $\alpha p H_s - \mu T_s \quad \geq \mathrm{F} e^{-\mu t}$ and taking $\mathrm{F} = \alpha p H_s - \mu T\left(0\right)$ we can get,

$$T\left(t\right) \leq \frac{\alpha p H_s}{\mu} - \frac{\mathrm{F}}{\mu} e^{-\mu t} \leq \frac{\alpha p H_s}{\mu} - \left(\frac{\alpha p H_s}{\mu} - T_s\left(0\right)\right) e^{-\mu t}$$

$$T_s\left(t\right) \leq T_s\left(0\right) e^{-\mu t} + \frac{\alpha p H_s}{\mu}\left(1 - e^{-\mu t}\right)$$

$$T_s\left(t\right) \leq T_s\left(0\right) e^{-\mu t} + \frac{\alpha p H_s}{\mu}\left(1 - e^{-\mu t}\right)$$

$$\lim_{t \to \infty} T_s\left(t\right) \leq T_s\left(0\right) e^{-\mu t} + \frac{\alpha p H_s}{\mu}\left(1 - e^{-\mu t}\right)$$

$$\lim_{t \to \infty} T_s\left(t\right) \leq \left(T_s\left(0\right) - \frac{\alpha p H_s}{\mu}\right) e^{-\mu t} + \frac{\alpha p H_s}{\mu} \leq \frac{\alpha p H_s}{\mu} \ \textit{since}\ \ T\left(0\right) \leq \frac{\alpha p H_s}{\mu}$$

From the equation (5.6) of the system (5.1)−(5.10): $\frac{dI_s}{dt} = \gamma \eta L_s + \alpha\left(1 - \varepsilon\right)\left(1 - p\right) H_s - \left(\rho_s + \mu + d_s\right) I_s$

If we add $\left(\rho_s + d_s\right) I_s$ to the right side, we get: $\frac{dI_s}{dt} \leq \gamma \eta L_s + \alpha\left(1 - \varepsilon\right)\left(1 - p\right) H_s - \mu I$

Using a standard comparision theorem:

$$\int \frac{dI_s}{\gamma \eta L_s + \alpha\left(1 - \varepsilon\right)\left(1 - p\right) H_s - \mu I} \leq \int dt$$

$$\Rightarrow -\frac{1}{\mu} \ln\left(\gamma \eta L_s + \alpha\left(1 - \varepsilon\right)\left(1 - p\right) H_s - \mu I_s\ \right) \leq t + c \textit{where } c \textit{ is a constant}$$

$$\Rightarrow \gamma \eta L_s + \alpha\left(1 - \varepsilon\right)\left(1 - p\right) H_s - \mu I_s \geq \mathrm{G} e^{-\mu t} \textit{where } G = e^{-c\mu t} \textit{is a constant}$$

$$\Rightarrow I_s\ \leq \frac{\gamma \eta L_s + \alpha\left(1 - \varepsilon\right)\left(1 - p\right) H_s}{\mu} - \frac{\mathrm{G}}{\mu} e^{-\mu t}$$

By applying the initial condition $I_s(0)$:

$$I_s\ \left(t\right) \leq \frac{\gamma \eta L_s + \alpha\left(1 - \varepsilon\right)\left(1 - p\right) H_s}{\mu} - \frac{G}{\mu} e^{-\mu t}$$

$$\Rightarrow I_s\left(0\right) \leq \frac{\gamma \eta L_s + \alpha\left(1 - \varepsilon\right)\left(1 - p\right) H_s}{\mu} - \frac{\mathrm{G}}{\mu} \leq \frac{\gamma \eta L_s + \alpha\left(1 - \varepsilon\right)\left(1 - p\right) H_s}{\mu}$$

Then from the inequality $\gamma\eta L_s + \alpha(1-\varepsilon)(1-p)H_s - \mu I_s \geq \mathrm{G}e^{-\mu t}$ and taking $\mathrm{G} = \delta\gamma L_s + \alpha(1-\varepsilon)(1-p)H_s - \mu I_s\ (0)$ we can get,

$$
\begin{aligned}
I_s\ (t) &\leq \frac{\gamma\eta L_s + \alpha(1-\varepsilon)(1-p)H_s}{\mu} - \frac{\mathrm{G}}{\mu}e^{-\mu t} \\
&\leq \frac{\gamma\eta L_s + \alpha(1-\varepsilon)(1-p)H_s}{\mu} - \left(\frac{\gamma\eta L_s + \alpha(1-\varepsilon)(1-p)H_s}{\mu} - I_s\ (0)\right)e^{-\mu t} \\
I_s\ (t) &\leq I_s\ (0)\, e^{-\mu t} + \frac{\gamma\eta L_s + \alpha(1-\varepsilon)(1-p)H_s}{\mu}\left(1 - e^{-\mu t}\right) \\
I_s\ (t) &\leq I_s\ (0)\, e^{-\mu t} + \frac{\gamma\eta L_s + \alpha(1-\varepsilon)(1-p)H_s}{\mu}\left(1 - e^{-\mu t}\right) \\
\lim_{t\to\infty} I_s\ (t) &\leq I_s\ (0)\, e^{-\mu t} + \frac{\gamma\eta L_s + \alpha(1-\varepsilon)(1-p)H_s}{\mu}\left(1 - e^{-\mu t}\right) \\
\lim_{t\to\infty} I_s\ (t) &\leq \left(I_s\ (0) - \frac{\gamma\eta L_s + \alpha(1-\varepsilon)(1-p)H_r}{\mu}\right)e^{-\mu t} + \frac{\gamma\eta L_s + \alpha(1-\varepsilon)(1-p)H_r}{\mu} \\
&\leq \frac{\gamma\eta L_s + \alpha(1-\varepsilon)(1-p)H_s}{\mu}\ \textit{since}\ I_s\ (0) \leq \frac{\gamma\eta L_s + \alpha(1-\varepsilon)(1-p)H_s}{\mu}
\end{aligned}
$$

From the equation (5.7) of the system (5.1)−(5.10): $\frac{dE}{dt} = \lambda_r(S + H_s + L_s + \sigma V + \kappa R) + (1-q)\rho_s I_s - (\delta+\mu)E$

If we add δE to the right side, we get: $\frac{dE}{dt} \leq \lambda_r(S + H_s + L_s + \sigma V + \kappa R) + (1-q)\rho_s I_s - \mu E$

Using a standard comparision theorem:

$$
\begin{aligned}
&\int \frac{dE}{\lambda_r(S + H_s + L_s + \sigma V + \kappa R) + (1-q)\rho_s I_s - \mu E} \leq \int dt \\
&\Rightarrow -\frac{1}{\mu}\ln\left(\lambda_r(S + H_s + L_s + \sigma V + \kappa R) + (1-q)\rho_s I_s - \mu E\ \right) \leq t + c \textit{where } c \textit{ is a constant} \\
&\Rightarrow \lambda_r(S + H_s + L_s + \sigma V + \kappa R) + (1-q)\rho_s I_s - \mu E \geq \mathrm{H}e^{-\mu t}\ \textit{where } H = e^{-c\mu t} \textit{is a constant} \\
&\Rightarrow E\ \leq \frac{\lambda_r(S + H_s + L_s + \sigma V + \kappa R) + (1-q)\rho_s I_s}{\mu} - \frac{H}{\mu}e^{-\mu t}
\end{aligned}
$$

By applying the initial condition $E(0)$:

$$
\begin{aligned}
E\ (t) &\leq \frac{\lambda_r(S + H_s + L_s + \sigma V + \kappa R) + (1-q)\rho_s I_s}{\mu} - \frac{H}{\mu}e^{-\mu t} \\
\Rightarrow E(0) &\leq \frac{\lambda_r(S + H_s + L_s + \sigma V + \kappa R) + (1-q)\rho_s I_s}{\mu} - \frac{\mathrm{H}}{\mu} \\
&\leq \frac{\lambda_r(S + H_s + L_s + \sigma V + \kappa R) + (1-q)\rho_s I_s}{\mu}
\end{aligned}
$$

Then from the inequality $\lambda_r(S + H_s + L_s + \sigma V + \kappa R) + (1-q)\rho_s I_s - \mu E \geq \mathrm{H}e^{-\mu t}$ and

taking $\mathrm{H} = \lambda_r \left(S + H_s + L_s + \sigma V + \kappa R\right) + \left(1 - q\right) \rho_s I_s - \mu E\ (0)$ we have:

$$
\begin{aligned}
E\ (t) \leq & \frac{\lambda_r \left(S + H_s + L_s + \sigma V + \kappa R\right) + \left(1 - q\right) \rho_s I_s}{\mu} - \frac{\mathrm{H}}{\mu} e^{-\mu t} \\
\leq & \frac{\lambda_r \left(S + H_s + L_s + \sigma V + \kappa R\right) + \left(1 - q\right) \rho_s I_s}{\mu} \\
& - \left(\frac{\lambda_r \left(S + H_s + L_s + \sigma V + \kappa R\right) + \left(1 - q\right) \rho_s I_s}{\mu} - E\ (0) \right) e^{-\mu t} \\
E\ (t) \leq & E\ (0)\, e^{-\mu t} + \frac{\lambda_r \left(S + H_s + L_s + \sigma V + \kappa R\right) + \left(1 - q\right) \rho_s I_s}{\mu} \left(1 - e^{-\mu t}\right) \\
\lim_{t \to \infty} E\ (t) \leq & E\ (0)\, e^{-\mu t} + \frac{\lambda_r \left(S + H_s + L_s + \sigma V + \kappa R\right) + \left(1 - q\right) \rho_s I_s}{\mu} \left(1 - e^{-\mu t}\right) \\
\lim_{t \to \infty} E\ (t) \leq & \left(E\ (0) - \frac{\lambda_r \left(S + H_s + L_s + \sigma V + \kappa R\right) + \left(1 - q\right) \rho_s I_s}{\mu} \right) e^{-\mu t} \\
& + \frac{\lambda_r \left(S + H_s + L_s + \sigma V + \kappa R\right) + \left(1 - q\right) \rho_s I_s}{\mu} \\
& \leq \frac{\lambda_r \left(S + H_s + L_s + \sigma V + \kappa R\right) + \left(1 - q\right) \rho_s I_s}{\mu} \\
& \textit{since } E\ (0) \leq \frac{\lambda_r \left(S + H_s + L_s + \sigma V + \kappa R\right) + \left(1 - q\right) \rho_s I_s}{\mu}
\end{aligned}
$$

From the equation (5.8) of the system (5.1)−(5.10): $\frac{dI_r}{dt} = \left(1 - \nu\right) \delta E\ - \left(\rho_r + \mu + d_r\right) I_r$

If we add $\left(\rho_r + d_r\right) I_r$ to the right side, we get: $\frac{dI_r}{dt} \leq \left(1 - \nu\right) \delta E\ - \mu I_r$

Using a standard comparision theorem:

$$
\begin{aligned}
& \int \frac{dI_r}{\left(1 - \nu\right) \delta E\ - \mu I_r} \leq \int dt \\
& \Rightarrow -\frac{1}{\mu} \ln \left(\left(1 - \nu\right) \delta E\ - \mu I_r\ \right) \leq t + c \textit{ where } c \textit{ is a constant} \\
& \Rightarrow 1 - \nu) \delta E\ - \mu I_r\ \geq \mathrm{J} e^{-\mu t} \textit{ where } J = e^{-c\mu t} \textit{is a constant} \\
& \Rightarrow I_r\ \leq \frac{\left(1 - \nu\right) \delta E\ - \mu I_r}{\mu} - \frac{\mathrm{J}}{\mu} e^{-\mu t}
\end{aligned}
$$

By applying the initial condition $I_r(0)$:

$$
I_r\ (t) \leq \frac{\left(1 - \nu\right) \delta E\ - \mu I_r}{\mu} - \frac{J}{\mu} e^{-\mu t}\ \Rightarrow I_r\left(0\right) \leq \frac{\left(1 - \nu\right) \delta E\ - \mu I_r}{\mu} - \frac{\mathrm{J}}{\mu} \leq \frac{\left(1 - \nu\right) \delta E\ - \mu I_r}{\mu}
$$

Then from the inequality $\left(1 - \nu\right) \delta E\ - \mu I_r\ \geq \mathrm{J} e^{-\mu t}$ and taking $\mathrm{J} = \left(1 - \nu\right) \delta E\ - \mu I_r\left(0\right)$

we can get,

$$I_r\ (t) \leq \frac{(1-\nu)\,\delta E}{\mu} - \frac{\mathrm{J}}{\mu}e^{-\mu t} \leq \frac{(1-\nu)\,\delta E}{\mu} - \left(\frac{(1-\nu)\,\delta E}{\mu} - I_r\ (0)\right)e^{-\mu t}$$

$$I_r\ (t) \leq I_r\ (0)\,e^{-\mu t} + \frac{(1-\nu)\,\delta E}{\mu}\left(1-e^{-\mu t}\right)$$

$$\lim_{t\to\infty} I_r\ (t) \leq I_r\ (0)\,e^{-\mu t} + \frac{(1-\nu)\,\delta E}{\mu}\left(1-e^{-\mu t}\right)$$

$$\lim_{t\to\infty} I_r\ (t) \leq \left(I_r\ (0) - \frac{(1-\nu)\,\delta E}{\mu}\right)e^{-\mu t} + \frac{(1-\nu)\,\delta E}{\mu} \leq \frac{(1-\nu)\,\delta E}{\mu}$$

since $I_r\ (0) \leq \dfrac{(1-\nu)\,\delta E}{\mu}$

From the equation (5.9) of the system (5.1)−(5.10): $\frac{dT_r}{dt} = \nu\delta E - (\varphi+\mu)\,T_r$

If we add φT_r to the right side, we get: $\frac{dT_r}{dt} \leq \nu\delta E - \mu T_r$

Using a standard comparision theorem:

$$\int \frac{dT_r}{\nu\delta E - \mu T_r} \leq \int dt$$

$$\Rightarrow -\frac{1}{\mu}\ln\left(\nu\delta E - \mu T_r\right) \leq t + c \text{ where } c \text{ is a constant}$$

$$\Rightarrow \nu\delta E - \mu T_r \geq \mathrm{K}e^{-\mu t} \text{ where } K = e^{-c\mu t} \text{ is a constant}$$

$$\Rightarrow T_r\ \leq \frac{\nu\delta E}{\mu} - \frac{\mathrm{K}}{\mu}e^{-\mu t}$$

By applying the initial condition $T_r(0)$:

$$T_r\ (t) \leq \frac{\nu\delta E}{\mu} - \frac{H}{\mu}e^{-\mu t}\ \Rightarrow T_r\,(0) \leq \frac{\nu\delta E}{\mu} - \frac{\mathrm{K}}{\mu} \leq \frac{\nu\delta E}{\mu}$$

Then from the inequality $\nu\delta E - \mu T_r\ \geq \mathrm{K}e^{-\mu t}$ and taking $\mathrm{K} = \nu\delta E - \mu T_r\ (0)$ we can get,

$$T_r\ (t) \leq \frac{\nu\delta E}{\mu} - \frac{\mathrm{K}}{\mu}e^{-\mu t} \leq \frac{\nu\delta E}{\mu} - \left(\frac{\nu\delta E}{\mu} - T_r\ (0)\right)e^{-\mu t}$$

$$T_r\ (t) \leq T_r\ (0)\,e^{-\mu t} + \frac{\nu\delta E}{\mu}\left(1-e^{-\mu t}\right)$$

$$\lim_{t\to\infty} T_r\ (t) \leq T_r\ (0)\,e^{-\mu t} + \frac{\nu\delta E}{\mu}\left(1-e^{-\mu t}\right)$$

$$\lim_{t\to\infty} T_r\ (t) \leq \left(T_r\ (0) - \frac{\nu\delta E}{\mu}\right)e^{-\mu t} + \frac{\nu\delta E}{\mu} \leq \frac{\nu\delta E}{\mu}$$

$$\textit{since } T_r\ (0) \leq \frac{\nu\delta E}{\mu}$$

From the equation (5.10) of the system (5.1)−(5.10):

$$\frac{dR}{dt} = q\rho_s I_s + \rho_r I_r + \gamma\,(1-\eta)\,L_s + \phi T_s + \varphi T_r - (\kappa\,(\lambda_s+\lambda_r)+\mu)\,R$$

If we add $\kappa(\lambda_s+\lambda_r)R$ to the right side, we get:

$$\frac{dR}{dt} \le q\rho_s I_s + \rho_r I_r + \gamma(1-\eta)L_s + \phi T_s + \varphi T_r - \mu R$$

Using a standard comparision theorem:

$$\int \frac{dR}{q\rho_s I_s + \rho_r I_r + \gamma(1-\eta)L_s + \phi T_s + \varphi T_r - \mu R} \le \int dt$$

$$-\frac{1}{\mu}\ln\left(q\rho_s I_s + \rho_r I_r + \gamma(1-\eta)L_s + \phi T_s + \varphi T_r - \mu R\right) \le t + c \quad \textit{where } c \textit{ is a constant}$$

$$\Rightarrow q\rho_s I_s + \rho_r I_r + \gamma(1-\eta)L_s + \phi T_s + \varphi T_r - \mu R \ge \mathrm{L}e^{-\mu t} \textit{ where } L = e^{-c\mu t} \textit{ is a constant}$$

$$\Rightarrow R \le \frac{q\rho_s I_s + \rho_r I_r + \gamma(1-\eta)L_s + \phi T_s + \varphi T_r - \mu R}{\mu} - \frac{\mathrm{L}}{\mu}e^{-\mu t}$$

By applying the initial condition $R(0)$:

$$\begin{aligned} R(t) &\le \frac{q\rho_s I_s + \rho_r I_r + \gamma(1-\eta)L_s + \phi T_s + \varphi T_r - \mu R}{\mu} - \frac{\mathrm{L}}{\mu}e^{-\mu t} \\ \Rightarrow R(0) &\le \frac{q\rho_s I_s + \rho_r I_r + \gamma(1-\eta)L_s + \phi T_s + \varphi T_r - \mu R}{\mu} - \frac{\mathrm{L}}{\mu} \\ &\le \frac{q\rho_s I_s + \rho_r I_r + \gamma(1-\eta)L_s + \phi T_s + \varphi T_r - \mu R}{\mu} \end{aligned}$$

Then from the inequality $q\rho_s I_s + \rho_r I_r + \gamma(1-\eta)L_s + \phi T_s + \varphi T_r - \mu R \ge \mathrm{L}e^{-\mu t}$ and taking $\mathrm{L} = q\rho_s I_s + \rho_r I_r + \gamma(1-\eta)L_s + \phi T_s + \varphi T_r - \mu R - \mu R\ (0)$, we can get:

$$\begin{aligned} R(t) &\le \frac{q\rho_s I_s + \rho_r I_r + \gamma(1-\eta)L_s + \phi T_s + \varphi T_r - \mu R}{\mu} - \frac{\mathrm{F}}{\mu}e^{-\mu t} \\ &\le \frac{q\rho_s I_s + \rho_r I_r + \gamma(1-\eta)L_s + \phi T_s + \varphi T_r - \mu R}{\mu} \\ &\quad - \left(\frac{q\rho_s I_s + \rho_r I_r + \gamma(1-\eta)L_s + \phi T_s + \varphi T_r - \mu R}{\mu} - R(0)\right)e^{-\mu t} \\ R(t) &\le R(0)e^{-\mu t} + \frac{q\rho_s I_s + \rho_r I_r + \gamma(1-\eta)L_s + \phi T_s + \varphi T_r - \mu R}{\mu}\left(1 - e^{-\mu t}\right) \\ \lim_{t\to\infty} R(t) &\le R(0)e^{-\mu t} + \frac{q\rho_s I_s + \rho_r I_r + \gamma(1-\eta)L_s + \phi T_s + \varphi T_r - \mu R}{\mu}\left(1 - e^{-\mu t}\right) \\ \lim_{t\to\infty} R(t) &\le \left(R(0) - \frac{q\rho_s I_s + \rho_r I_r + \gamma(1-\eta)L_s + \phi T_s + \varphi T_r - \mu R}{\mu}\right)e^{-\mu t} \\ &\quad + \frac{q\rho_s I_s + \rho_r I_r + \gamma(1-\eta)L_s + \phi T_s + \varphi T_r - \mu R}{\mu} \\ &\le \frac{q\rho_s I_s + \rho_r I_r + \gamma(1-\eta)L_s + \phi T_s + \varphi T_r - \mu R}{\mu} \\ &\quad \textit{since } R(0) \le \frac{q\rho_s I_s + \rho_r I_r + \gamma(1-\eta)L_s + \phi T_s + \varphi T_r - \mu R}{\mu} \end{aligned}$$

Therefore all feasible solutions of the dynamical system with initial conditions in $\Omega = \{(V, S, H_s, L_s, I_s, T_s, E, I_r, T_r, R) \in \mathbb{R}^{10}_+ : N \leq \frac{\Lambda}{\mu}\}$ do remain in Ω for all $t > 0$. That is the set Ω is positively invariant. □

5.3.3 Existence of Disease Free Equilibrium Point

The disease free equilibrium point of the dynamical system (5.1)−(5.10) is obtained by setting $\frac{dV}{dt} = \frac{dS}{dt} = \frac{dH_s}{dt} = \frac{dL_s}{dt} = \frac{dI_t}{dt} = \frac{dT_s}{dt} = \frac{dE}{dt} = \frac{dI_r}{dt} = \frac{dT_r}{dt} = \frac{dR}{dt} = 0$ and since there is no disease we do have $I_s = I_r = 0$.

Let the disease free equilibrium (DFE) of the model (5.1)−(5.10) be denoted as:

$$E^0 = (V^0, S^0, H_s^0, L_s^0, I_s^0, T_s^0, E^0, I_r^0, T_r^0, R^0)$$

From equation (5.1) of the dynamical system, we have:

$$\frac{dV}{dt} = 0 \Rightarrow \psi\Lambda - (\sigma(\lambda_s + \lambda_r) + \theta + \mu)V = 0, \Rightarrow V^0 = \frac{\psi\Lambda}{\mu + \theta}$$

From equation (5.2) of the dynamical system, we have:

$$\begin{aligned}\frac{dS}{dt} = 0 \Rightarrow (1-\psi)\Lambda + \theta V - (\lambda_s + \lambda_r + \mu)S = 0,\\ \Rightarrow S^0 = \frac{(1-\psi)\Lambda + \theta V^0}{\mu} = \frac{(1-\psi)(\mu+\theta)\Lambda + \theta\psi\Lambda}{\mu(\mu+\theta} = \frac{(\theta + (1-\psi)\mu)\Lambda}{\mu(\mu+\theta)}\end{aligned}$$

Taking the cases when $I_s = I_r = 0$, the equations $\frac{dH_s}{dt} = \frac{dL_s}{dt} = \frac{dI_s}{dt} = \frac{dE}{dt} = \frac{dI_r}{dt} = \frac{dT_s}{dt} = \frac{dT_r}{dt} = \frac{dR}{dt} = 0$ and if we solve for the rest state variable then we find that $H_s = L_s = T_s = E = T_r = R = 0$. Therefore, the disease free equilibrium point E^0 of the dynamical system (5.1)−(5.10) is given by:

$$E^0 = \left(V^0, S^0, H_s^0, L_s^0, I_s^0, T_s^0, E^0, I_r^0, T_r^0, R^0\right) = \left(\frac{\psi\Lambda}{(\mu+\theta)}, \frac{(\theta + (1-\psi)\mu)\Lambda}{\mu(\mu+\theta)}, 0, 0, 0, 0, 0, 0, 0, 0\right).$$

5.3.4 The Effective Reproduction Number R_{eff} and Basic Reproduction Number R_0,

The average number of secondary infections caused by typical infected individual during his entire period of infectiousness the dynamical system is obtained by taking the largest

(dominant) eigenvalue (spectral radius) of the matrix FV^{-1}:

$$FV^{-1} = \left[\frac{\partial F_i(E^0)}{\partial x_j}\right]\left[\frac{\partial V_i(E^0)}{\partial x_j}\right]^{-1} \quad with\ 1 \leq i, j \leq n$$

where F_i is the rate of appearance of new infection in compartment i, V_i is the transfer of infections from one compartment i to another and E^0 is the disease-free equilibrium point. We rearrange the equations of model system (5.1)−(5.10) with the infected classes H_s, L_s, I_s, E and I_r first, susceptible class $S(t)$ second, vaccination class, $V(t)$ third, and recovered class, $R(t)$ last. Making use of the next generation operator method, we compute the effective reproduction number R_{eff}. The non-negative matrix F, of the new infection terms, and the matrix V, of the transition terms associated with the model system (5.1)−(5.10)are given respectively by:

$$F_i = \begin{bmatrix} \lambda_s\left(S + \sigma V + \kappa R\right) \\ 0 \\ 0 \\ \lambda_r\left(S + H_s + L_s + \sigma V + \kappa R\right) \\ 0 \end{bmatrix} \quad and$$

$$V_i = \begin{bmatrix} (\alpha + \lambda_r + \mu)H_s \\ -\alpha\epsilon(1-p)H_s + (\lambda_r + \gamma + \mu)L_s \\ -\gamma\eta L_s - \alpha(1-\epsilon)(1-p)H_s + (\rho_s + \mu + d_s)I_s \\ -(1-q)\rho_s I_s + (\delta + \mu)E \\ -(1-\nu)\delta E + (\rho_r + \mu + d_r)I_r \end{bmatrix}$$

Now we find the Jacobean matrix of F_i and v_i with respect to H_s, L_s, I_s, E and I_r as infected classes evaluated at the disease free equilibrium E^0. Doing so we get the following:

$$F = \begin{bmatrix} 0 & 0 & c\omega_s\frac{(S^0+\sigma V^0)}{N^0} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & c\omega_r\frac{(S^0+\sigma V^0)}{N^0} \end{bmatrix} \quad and$$

$$V = \begin{bmatrix} (\alpha+\mu) & 0 & 0 & 0 & 0 \\ -\alpha\epsilon(1-p) & (\gamma+\mu) & 0 & 0 & 0 \\ -\alpha(1-\epsilon)(1-p) & -\gamma\eta & (\rho_s+\mu+d_s) & 0 & 0 \\ 0 & 0 & -(1-q)\rho_s & (\delta+\mu) & 0 \\ 0 & 0 & 0 & -(1-\nu)\delta) & (\rho_r+\mu+d_r) \end{bmatrix}$$

Since $detV = (\alpha+\mu)(\gamma+\mu)(\rho_s+\mu+d_s)(\delta+\mu)(\rho_r+\mu+d_r) \neq 0$ and then V is non-singular. The inverse V^{-1} of the matrix V is given by: $V^{-1} = \frac{1}{detV}V_{adj}$ where V_{adj} is the adjoint matrix of the matrix V. And $V_{adj} = [C_{ij}]^T$ where $C_{ij} = (-1)^{(i+j)}M_{ij}$ is cofactor of an element v_{ij} of the matrix V and M_{ij} is minor of an element v_{ij} of the matrix V.

$$V_{adj} = \begin{bmatrix} c_{11} & c_{21} & c_{31} & c_{41} & c_{51} \\ c_{12} & c_{22} & c_{32} & c_{42} & c_{52} \\ c_{13} & c_{23} & c_{33} & c_{43} & c_{53} \\ c_{14} & c_{24} & c_{34} & c_{44} & c_{54} \\ c_{15} & c_{25} & c_{35} & c_{45} & c_{55} \end{bmatrix}, \quad where$$

$$c_{21} = c_{31} = c_{32} = c_{41} = c_{42} = c_{43} = c_{51} = c_{52} = c_{53} = c_{54} = 0,$$

$$c_{11} = (\gamma+\mu)(\rho_s+\mu+d_s)(\delta+\mu)(\rho_r+\mu+d_r),$$

$$c_{12} = \alpha\epsilon(1-p)(\rho_s+\mu+d_s)(\delta+\mu)(\rho_r+\mu+d_r),$$

$$c_{22} = (\alpha+\mu)(\rho_s+\mu+d_s)(\delta+\mu)(\rho_r+\mu+d_r),$$

$$c_{13} = (\rho_r+\mu+d_r)(\delta+\mu)(\alpha\epsilon(1-p)\gamma\eta + \alpha(\gamma+\mu)(1-\epsilon)(1-p)),$$

$$c_{23} = (\rho_r+\mu+d_r)\delta+\mu)\gamma\eta(\alpha+\mu),$$

$$c_{33} = (\alpha+\mu)(\gamma+\mu)(\delta+\mu)(\rho_r+\mu+d_r),$$

$$c_{14} = (\rho_r+\mu+d_r)(1-q)\rho_s[\gamma\eta\alpha\epsilon(1-p) + \alpha(1-\epsilon)(1-p)(\gamma+\mu)],$$

$$c_{24} = (\rho_r+\mu+d_r)(1-q)\rho_s\gamma\eta(\alpha+\mu),$$

$$c_{34} = (\alpha+\mu)(\gamma+\mu)(1-q)\rho_s(\rho_r+\mu+d_r),$$
$$c_{44} = (\alpha+\mu)(\gamma+\mu)(\rho_s+\mu+d_s)(\rho_r+\mu+d_r),$$
$$c_{15} = (1-\nu)\delta(1-q)\rho_s[\gamma\eta\alpha\epsilon(1-p)+\alpha(1-\epsilon)(1-p)(\gamma+\mu)],$$
$$c_{25} = \gamma\eta(\alpha+\mu)(\delta+\mu)(1-q)\rho_s,$$
$$c_{35} = (\alpha+\mu)(\gamma+\mu)(1-\nu)\delta(1-q)\rho_s,$$
$$c_{45} = (\alpha+\mu)(\gamma+\mu)(\rho_s+\mu+d_s)(1-\nu)\delta, \ and$$
$$c_{55} = (\alpha+\mu)(\gamma+\mu)(\rho_s+\mu+d_s)(\delta+\mu)$$

we compute V^{-1} as follows:

$$V^{-1} = \frac{1}{detV}V_{adj} = \frac{1}{detV}\begin{bmatrix} c_{11} & c_{21} & c_{31} & c_{41} & c_{51} \\ c_{12} & c_{22} & c_{32} & c_{42} & c_{52} \\ c_{13} & c_{23} & c_{33} & c_{43} & c_{53} \\ c_{14} & c_{24} & c_{34} & c_{44} & c_{54} \\ c_{15} & c_{25} & c_{35} & c_{45} & c_{55} \end{bmatrix} = \begin{bmatrix} v_{11} & v_{21} & v_{31} & v_{41} & v_{51} \\ v_{12} & v_{22} & v_{32} & v_{42} & v_{52} \\ v_{13} & v_{23} & v_{33} & v_{43} & v_{53} \\ v_{14} & v_{24} & v_{34} & v_{44} & v_{54} \\ v_{15} & v_{25} & v_{35} & v_{45} & v_{55} \end{bmatrix}, \text{ where}$$

$$v_{21} = v_{24} = v_{31} = v_{32} = v_{41} = v_{42} = v_{43} = v_{51} = v_{52} = v_{53} = v_{54} = 0,$$
$$v_{11} = \frac{1}{\alpha+\mu}, v_{12} = \frac{\alpha\epsilon(1-p)}{(\alpha+\mu)(\gamma+\mu)}, v_{13} = \frac{\alpha\epsilon(1-p)\gamma\eta+\alpha(\gamma+\mu)(1-\epsilon)(1-p)}{(\alpha+\mu)(\gamma+\mu)(\rho_s+\mu+d_s)}, v_{22} = \frac{1}{\gamma+\mu},$$
$$v_{23} = \frac{\gamma\eta}{(\gamma+\mu)(\rho_s+\mu+d_s)}, v_{14} = \frac{(1-q)\rho_s\alpha\epsilon(1-p)\gamma\eta+\alpha(\gamma+\mu)(1-\epsilon)(1-p)]}{(\alpha+\mu)(\gamma+\mu)(\rho_s+\mu+d_r)(\delta+\mu)(\rho_s+\mu+d_r)},$$
$$v_{34} = \frac{)(1-q)\rho_s}{(\gamma+\mu)(\rho_s+\mu+d_r)(\rho_s+\mu+d_r)}, v_{15} = \frac{(1-q)\rho_s\alpha\epsilon(1-p)\gamma\eta+\alpha(\gamma+\mu)(1-\epsilon)(1-p)]}{(\alpha+\mu)(\gamma+\mu)(\rho_s+\mu+d_s)(\rho_r+\mu+d_r)},$$

$$v_{25} = \frac{\gamma\eta(1-q)\rho_s}{(\gamma+\mu)(\rho_s+\mu+d_s)(\rho_r+\mu+d_r)}, v_{35} = \frac{(1-\nu)\delta(1-q)\rho_s}{(\delta+\mu)(\rho_s+\mu+d_s)(\rho_r+\mu+d_r)}, v_{44} = \frac{1}{\delta+\mu},$$
$$v_{45} = \frac{(1-\nu)\delta}{(\delta+\mu)(\rho_r+\mu+d_r)}, v_{33} = \frac{1}{\rho_s+\mu+d_s}, v_{55} = \frac{1}{\rho_r+\mu+d_r},$$

We compute the effective reproduction number R_{eff} using next generation operator method. In the dynamical system (5.1)−(5.10) the rate of appearance of new infections F and the transfer rate of individuals V at the disease free equilibrium point,

$E^0 = (V^0, S^0, H_s^0, L_s^0, I_s^0, T_s^0, E^0, I_r^0, T_r^0, , R^0) = \left(\frac{\psi\Lambda}{\mu+\theta}, \frac{(\theta+(1-\psi)\mu)\Lambda}{\mu(\mu+\theta)}, 0, 0, 0, 0, 0, 0, 0, 0\right)$ is

$$FV^{-1} = \begin{bmatrix} 0 & 0 & \frac{c\omega_s(S^0+\sigma V^0)}{N^0} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{c\omega_r(S^0+\sigma V^0)}{N^0} \end{bmatrix} \begin{bmatrix} v_{11} & 0 & 0 & 0 & 0 \\ v_{12} & v_{22} & 0 & 0 & 0 \\ v_{13} & v_{23} & v_{33} & 0 & 0 \\ v_{14} & 0 & v_{34} & v_{44} & v_{54} \\ v_{15} & v_{25} & v_{35} & v_{45} & v_{25} \end{bmatrix}$$

$$= \begin{bmatrix} m_1 & m_2 & m_3 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ m_4 & m_5 & m_6 & m_7 & m_8 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

Where, $N^0 = S^0+V^0 = \frac{\Lambda}{\mu}$,$m_1 = v_{13}c\frac{\omega_s(S^0+\sigma V^0)}{N^0}$, $m_2 = v_{23}c\frac{\omega_s(S^0+\sigma V^0)}{N^0}$, $m_3 = v_{33}c\frac{\omega_s(S^0+\sigma V^0)}{N^0}$, $m_4 = v_{15}c\frac{\omega_r(S^0+\sigma V^0)}{N^0}$, $m_5 = v_{25}c\frac{\omega_r(S^0+\sigma V^0)}{N^0}$, $m_6 = v_{35}c\frac{\omega_r(S^0+\sigma V^0)}{N^0}$, $m_7 = v_{45}c\frac{\omega_r(S^0+\sigma V^0)}{N^0}$ and $m_8 = v_{55}c\frac{\omega_r(S^0+\sigma V^0)}{N^0}$.

The spectral radius (largest eigenvalue) of FV^{-1} is the required effective reproduction number obtained by $R_{eff} = \max\{R_{eff}(DS), R_{eff}(MDR)\}$ Where,

$$R_{eff}(\text{DS}) = \frac{c\omega_s(\sigma\psi\mu + (\theta + (1-\psi)\mu))}{\theta+\mu} \times \frac{(1-p)\alpha(\epsilon\gamma\eta + (1-\epsilon)(\gamma+\eta))}{(\alpha+\mu)(\gamma+\mu)(\rho_s+\mu+d_s)},$$

$$R_{eff}(\text{MDR}) = \frac{c\omega_r(\sigma\psi\mu + (\theta + (1-\psi)\mu))}{(\theta+\mu)} \times \frac{(1-\nu)\delta}{(\delta+\mu)(\rho_r+\mu+d_r)}$$

Basic Reproduction Number

If there is no intervention that is ($\psi = p = \nu = 0$) then the dynamical system (5.1)−(5.10) should become:

$$\frac{dV}{dt} = -(\sigma(\lambda_s + \lambda_r) + \theta + \mu)V \tag{5.11}$$
$$\frac{dS}{dt} = \Lambda + \theta V - (\lambda_s + \lambda_r + \mu)S \tag{5.12}$$
$$\frac{dH_s}{dt} = \lambda_s(\sigma V + S + \kappa R) - (\alpha + \lambda_r + \mu)H_s \tag{5.13}$$
$$\frac{dL_s}{dt} = \epsilon\alpha H_s - (\gamma + \lambda_r + \mu)L_s \tag{5.14}$$
$$\frac{dI_s}{dt} = \eta\gamma L_s + \alpha(1-\epsilon)H_s - (\rho_s + \mu + d_s)I_s \tag{5.15}$$
$$\frac{dT_s}{dt} = -(\phi + \mu)T_s \tag{5.16}$$
$$\frac{dE}{dt} = \lambda_r(S + H_s + L_s + \sigma V + \kappa R) + (1-q)\rho_s I_s - (\delta + \mu)E \tag{5.17}$$
$$\frac{dI_r}{dt} = \delta E - (\rho_r + \mu + d_r)I_r \tag{5.18}$$
$$\frac{dT_r}{dt} = -(\varphi + \mu)T_r \tag{5.19}$$
$$\frac{dR}{dt} = q\rho_s I_s + \rho_r I_r + \gamma(1-\eta)L_s + \phi T_s + \varphi T_r - (\kappa(\lambda_s + \lambda_r) + \mu)R \tag{5.20}$$

with the total population at a given time t:

$$N(t) = V(t) + S(t) + H_s(t) + L_s(t) + I_s(t) + T_s(t) + E(t) + I_r(t) + T_r(t) + R(t)$$

The disease free equilibrium point of the dynamical system (5.11)−(5.20)will be:

$$E^0 = \left(0, \frac{\Lambda}{\mu}, 0, 0, 0, 0, 0, 0, 0, 0\right)$$

The non-negative matrix F, of the new infection terms, and the matrix V, of the transition terms associated with the model system (5.11)−(5.20) are given respectively by:

$$F = \begin{bmatrix} 0 & 0 & c\omega_s & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & c\omega_r \end{bmatrix} \; and$$

$$V = \begin{bmatrix} (\alpha+\mu) & 0 & 0 & 0 & 0 \\ -\alpha\epsilon & (\gamma+\mu) & 0 & 0 & 0 \\ -\alpha(1-\epsilon) & -\gamma\eta & (\rho_s+\mu+d_s) & 0 & 0 \\ 0 & 0 & -(1-q)\rho_s & (\delta+\mu) & 0 \\ 0 & 0 & 0 & -\delta & (\rho_r+\mu+d_r) \end{bmatrix}$$

Since $detV = (\alpha+\mu)(\gamma+\mu)(\rho_s+\mu+d_s)(\delta+\mu)(\rho_r+\mu+d_r) \neq 0$ and then V is non-singular. The inverse V^{-1} of the matrix V is given by: $V^{-1} = \frac{1}{detV}V_{adj}$ where V_{adj} is the adjoint matrix of the matrix V.

$$FV^{-1} = \begin{bmatrix} m_1 & m_2 & m_3 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ m_4 & m_5 & m_6 & m_7 & m_8 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

Where, $N^0 = S^0 = \frac{\Lambda}{\mu}$,$m_1 = v_{13}c\omega_s$, $m_2 = v_{23}c\omega_s$, $m_3 = v_{33}c\omega_s$, $m_4 = v_{15}c\omega_r$, $m_5 = v_{25}c\omega_r$, $m_6 = v_{35}c\omega_r$, $m_7 = v_{45}c\omega_r$ and $m_8 = v_{55}c\omega_r$.

Then the basic reproduction number R_0 is computed when $(\psi = p = \nu = 0)$, then the basic reproduction number R_0 of the model system (5.11)$-$(5.20) is:

$$R_0 = \max\{R_0(DS), R_0(MDR)\}$$

$$Where\ R_0(\text{DS}) = c\omega_s \frac{\alpha(\epsilon\gamma\eta + (1-\epsilon)(\gamma+\eta))}{(\alpha+\mu)(\gamma+\mu)(\rho_s+\mu+d_s)}\ and\ R_0(\text{MDR}) = c\omega_r \frac{\delta}{(\delta+\mu)(\rho_r+\mu+d_r)}$$

We can also compute the effective reproduction number of drug sensitive TB and drug resistance TB dynamical system: From the system of differential equations (5.1)-(5.6) and (5.10); and the reproduction number of drug sensitive TB and from the system of

differential equations (5.1)-(5.2) and (5.7)-(5.10) we calculate the reproduction number of drug sensitive TB.

$F_1 = \begin{bmatrix} 0 & 0 & c\omega_s \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$ of the system of differential equations (5.1)−(5.6)and (5.10) and

$F_2 = \begin{bmatrix} 0 & 0 \\ 0 & c\omega_r \end{bmatrix}$ of the system of differential equations (5.1),(5.2)and (5.7)−(5.10).

$V_1 = \begin{bmatrix} (\alpha+\mu) & 0 & 0 \\ -\alpha\epsilon(1-p) & (\gamma+\mu) & 0 \\ -\alpha(1-\epsilon)(1-p) & -\gamma\eta & (\rho_s+\mu+d_s) \end{bmatrix}$ of the system of differential equations (5.1)−(5.6)and (5.10) and

$V_2 = \begin{bmatrix} (\delta+\mu) & 0 \\ -\delta(1-\nu) & (\rho_r+\mu+d_r) \end{bmatrix}$ of the system of differential equations (5.1),(5.2) and (5.7)−(5.10).

Since $detV_1 = (\alpha+\mu)(\gamma+\mu)(\rho_s+\mu+d_s) \neq 0$ and $detV_2 = (\delta+\mu)(\rho_r+\mu+d_r) \neq 0$ then V_1 and V_2 is non-singular.

$$F_1V_1^{-1} = \begin{bmatrix} m_1 & m_2 & m_3 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \; and \; F_2V_2^{-1} = \begin{bmatrix} m_7 & m_8 \\ 0 & 0 \end{bmatrix}$$

Then, the spectral radius of $F_1V_1^{-1}$ is:

$$R_{eff}(\text{DS}) = \frac{c\omega_s(\sigma\psi\mu + (\theta + (1-\psi)\mu))}{\theta+\mu} \times \frac{(1-p)\alpha(\epsilon\gamma\eta + (1-\epsilon)(\gamma+\eta))}{(\alpha+\mu)(\gamma+\mu)(\rho_s+\mu+d_s)}$$

And the spectral radius (largest eigenvalue) of $F_2V_2^{-1}$ is:

$$R_{eff}(\text{MDR}) = \frac{c\omega_r(\sigma\psi\mu + (\theta + (1-\psi)\mu))}{(\theta+\mu)} \times \frac{(1-\nu)\delta}{(\delta+\mu)(\rho_r+\mu+d_r)}$$

Hence, $R_{eff}(\text{DS})$ and $R_{eff}(\text{MDR})$ are effective reproduction numbers for the TB drug sensitive strain and for the drug-resistant TB strain, respectively.

Local Stability Analysis of the Disease Free Equilibrium Point

Theorem 5.3. *The disease free equilibrium point* $\left(\frac{\psi\Lambda}{\mu+\theta}, \frac{(\theta+(1-\psi)\mu)\Lambda}{\mu(\mu+\theta)}, 0, 0, 0, 0, 0, 0, 0, 0\right)$ *of the dynamical system (5.1)−(5.10) is locally asymptotically stable if* $R_{eff}(DS) < 1$ *and* $R_{eff}(MDR) < 1$*; and* E^0 *is unstable otherwise.*

Proof. The Jacobean matrix of the dynamical system (5.1)−(5.10) with respect to $(V, S, H_s, L_s, I_s, T_s, E, I_r, T_r, R)$at the disease free equilibrium point E^0 is

$$J(E^0) = \begin{bmatrix} \frac{\partial f_1(E^0)}{\partial V} & \frac{\partial f_1(E^0)}{\partial S} & \frac{\partial f_1(E^0)}{\partial H_s} & \frac{\partial f_1(E^0)}{\partial L_s} & \frac{\partial f_1(E^0)}{\partial I_s} & \frac{\partial f_1(E^0)}{\partial T_s} & \frac{\partial f_1(E^0)}{\partial E} & \frac{\partial f_1(E^0)}{\partial I_r} & \frac{\partial f_1(E^0)}{\partial T_r} & \frac{\partial f_1(E^0)}{\partial R} \\ \frac{\partial f_2(E^0)}{\partial V} & \frac{\partial f_2(E^0)}{\partial S} & \frac{\partial f_2(E^0)}{\partial H_s} & \frac{\partial f_2(E^0)}{\partial L_s} & \frac{\partial f_2(E^0)}{\partial I_s} & \frac{\partial f_2(E^0)}{\partial T_s} & \frac{\partial f_2(E^0)}{\partial E} & \frac{\partial f_2(E^0)}{\partial I_r} & \frac{\partial f_2(E^0)}{\partial T_r} & \frac{\partial f_2(E^0)}{\partial R} \\ \frac{\partial f_3(E^0)}{\partial V} & \frac{\partial f_3(E^0)}{\partial S} & \frac{\partial f_3(E^0)}{\partial H_s} & \frac{\partial f_3(E^0)}{\partial L_s} & \frac{\partial f_3(E^0)}{\partial I_s} & \frac{\partial f_3(E^0)}{\partial T_s} & \frac{\partial f_3(E^0)}{\partial E} & \frac{\partial f_3(E^0)}{\partial I_r} & \frac{\partial f_3(E^0)}{\partial T_r} & \frac{\partial f_3(E^0)}{\partial R} \\ \frac{\partial f_4(E^0)}{\partial V} & \frac{\partial f_4(E^0)}{\partial S} & \frac{\partial f_4(E^0)}{\partial H_s} & \frac{\partial f_4(E^0)}{\partial L_s} & \frac{\partial f_4(E^0)}{\partial I_s} & \frac{\partial f_4(E^0)}{\partial T_s} & \frac{\partial f_4(E^0)}{\partial E} & \frac{\partial f_4(E^0)}{\partial I_r} & \frac{\partial f_4(E^0)}{\partial T_r} & \frac{\partial f_4(E^0)}{\partial R} \\ \frac{\partial f_5(E^0)}{\partial V} & \frac{\partial f_5(E^0)}{\partial S} & \frac{\partial f_5(E^0)}{\partial H_s} & \frac{\partial f_5(E^0)}{\partial L_s} & \frac{\partial f_5(E^0)}{\partial I_s} & \frac{\partial f_5(E^0)}{\partial T_s} & \frac{\partial f_5(E^0)}{\partial E} & \frac{\partial f_5(E^0)}{\partial I_r} & \frac{\partial f_5(E^0)}{\partial T_r} & \frac{\partial f_5(E^0)}{\partial R} \\ \frac{\partial f_6(E^0)}{\partial V} & \frac{\partial f_6(E^0)}{\partial S} & \frac{\partial f_6(E^0)}{\partial H_s} & \frac{\partial f_6(E^0)}{\partial L_s} & \frac{\partial f_6(E^0)}{\partial I_s} & \frac{\partial f_6(E^0)}{\partial T_s} & \frac{\partial f_6(E^0)}{\partial E} & \frac{\partial f_6(E^0)}{\partial I_r} & \frac{\partial f_6(E^0)}{\partial T_r} & \frac{\partial f_6(E^0)}{\partial R} \\ \frac{\partial f_7(E^0)}{\partial V} & \frac{\partial f_7(E^0)}{\partial S} & \frac{\partial f_7(E^0)}{\partial H_s} & \frac{\partial f_7(E^0)}{\partial L_s} & \frac{\partial f_7(E^0)}{\partial I_s} & \frac{\partial f_7(E^0)}{\partial T_s} & \frac{\partial f_7(E^0)}{\partial E} & \frac{\partial f_7(E^0)}{\partial I_r} & \frac{\partial f_7(E^0)}{\partial T_r} & \frac{\partial f_7(E^0)}{\partial R} \\ \frac{\partial f_8(E^0)}{\partial V} & \frac{\partial f_8(E^0)}{\partial S} & \frac{\partial f_8(E^0)}{\partial H_s} & \frac{\partial f_8(E^0)}{\partial L_s} & \frac{\partial f_8(E^0)}{\partial I_s} & \frac{\partial f_8(E^0)}{\partial T_s} & \frac{\partial f_8(E^0)}{\partial E} & \frac{\partial f_8(E^0)}{\partial I_r} & \frac{\partial f_8(E^0)}{\partial T_r} & \frac{\partial f_8(E^0)}{\partial R} \\ \frac{\partial f_9(E^0)}{\partial V} & \frac{\partial f_9(E^0)}{\partial S} & \frac{\partial f_9(E^0)}{\partial H_s} & \frac{\partial f_9(E^0)}{\partial L_s} & \frac{\partial f_9(E^0)}{\partial I_s} & \frac{\partial f_9(E^0)}{\partial T_s} & \frac{\partial f_9(E^0)}{\partial E} & \frac{\partial f_9(E^0)}{\partial I_r} & \frac{\partial f_9(E^0)}{\partial T_r} & \frac{\partial f_9(E^0)}{\partial R} \\ \frac{\partial f_{10}(E^0)}{\partial V} & \frac{\partial f_{10}(E^0)}{\partial S} & \frac{\partial f_{10}(E^0)}{\partial H_s} & \frac{\partial f_{10}(E^0)}{\partial L_s} & \frac{\partial f_{10}(E^0)}{\partial I_s} & \frac{\partial f_{10}(E^0)}{\partial T_s} & \frac{\partial f_{10}(E^0)}{\partial E} & \frac{\partial f_{10}(E^0)}{\partial I_r} & \frac{\partial f_{10}(E^0)}{\partial T_r} & \frac{\partial f_{10}(E^0)}{\partial R} \end{bmatrix}$$

The Jacobean matrix of the dynamical system (5.1)−(5.10)at disease free equilibrium point $\left(\frac{\psi\Lambda}{\mu+\theta}, \frac{(\theta+(1-\psi)\mu)\Lambda}{\mu(\mu+\theta)}, 0, 0, 0, 0, 0, 0, 0, 0\right)$ is

$$J(E^0) = \begin{bmatrix} a_1 & 0 & 0 & 0 & a_2 & 0 & 0 & a_3 & 0 & 0 \\ \theta & -\mu & 0 & 0 & a_4 & 0 & 0 & a_5 & 0 & 0 \\ 0 & 0 & a_6 & 0 & a_7 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & a_8 & a_9 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & a_{10} & \eta\gamma & a_{11} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & p\alpha & 0 & 0 & a_{12} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & a_{13} & 0 & a_{14} & a_{15} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & a_{16} & a_{17} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \nu\delta & 0 & a_{18} & 0 \\ 0 & 0 & 0 & a_{19} & q\rho_s & \phi & 0 & \rho_r & \varphi & -\mu \end{bmatrix}$$

Where $a_1 = -(\theta+\mu), a_2 = -\sigma c\omega_s \frac{V^0}{N^0}, a_3 = -\sigma c\omega_r \frac{V^0}{N^0}, a_4 = c\omega_s \frac{S^0}{N^0}, a_5 = -c\omega_r \frac{S^0}{N^0},$
$a_6 = -(\alpha+\mu), a_7 = c\omega_s \frac{(S^0+\sigma V^0)}{N^0}, a_8 = \alpha\epsilon(1-p), a_9 = -(\gamma+\mu), a_{10} = \alpha(1-\epsilon)(1-p),$
$a_{11} = -(\rho_s+\mu+d_s), a_{12} = -(\phi+\mu), a_{13} = (1-q)\rho_s, a_{14} = -(\delta+\mu), a_{15} = c\omega_r \frac{(S^0+\sigma V^0)}{N^0},$
$a_{16} = (1-\nu)\delta, a_{17} = -(\rho_r+\mu+d_r), a_{18} = -(\varphi+\mu), a_{19} = \gamma(1-\eta)$
The corresponding characteristic equation is obtained by

$$\begin{vmatrix} a_1-\lambda & 0 & 0 & 0 & a_2 & 0 & 0 & a_3 & 0 & 0 \\ \theta & -\mu-\lambda & 0 & 0 & a_4 & 0 & 0 & a_5 & 0 & 0 \\ 0 & 0 & a_6-\lambda & 0 & a_7 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & a_8 & a_9-\lambda & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & a_{10} & \eta\gamma & a_{11}-\lambda & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & p\alpha & 0 & 0 & a_{12}-\lambda & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & a_{13} & 0 & a_{14}-\lambda & a_{15} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & a_{16} & a_{17}-\lambda & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \nu\delta & 0 & a_{18}-\lambda & 0 \\ 0 & 0 & 0 & a_{19} & q\rho_s & \phi & 0 & \rho_r & \varphi & -\mu-\lambda \end{vmatrix} = 0$$

Or $(\lambda+\mu)^2(a_{12}-\lambda)(a_{18}-\lambda)[\lambda^2+(a_{14}+a_{17})\lambda+a_{14}a_{17}-a_{15}a_{16}][-\lambda^3+(a_6+a_9+a_{11})]\lambda^2-$
$(a_6a_9+a_6a_{11}+a_9a_{11}+a_7a_{10})\lambda+a_6a_9a_{11}+\gamma\eta a_7a_8-a_7a_{10}a_9] = 0$

Thus, the roots of the characteristic equation are $\lambda_1 = -\mu$, $\lambda_2 = -\mu$, $\lambda_3 = -(\theta+\mu)$,
$\lambda_4 = -(\phi+\mu)$, $\lambda_5 = -(\varphi+\mu)$, $\lambda^2-(a_{14}+a_{17})\lambda+a_{14}a_{17}-a_{15}a_{16} = 0$
or $\lambda^3-(a_6+a_9+a_{11})\lambda^2+(a_6a_9+a_6a_{11}+a_9a_{11}+a_7a_{10})\lambda+a_6a_9a_{11}-\gamma\eta a_7a_8+a_7a_{10}a_9 = 0$
$\Rightarrow \lambda^2+b_1\lambda+b_2 = 0$ and $\lambda^3+c_1\lambda^2+c_2\lambda+c_3 = 0$
Where,

$$\begin{aligned} b_1 =& -(a_{14}+a_{17}) = \delta+\mu+\rho_r+\mu+d_r \\ b_2 =& a_{14}a_{17}-a_{15}a_{16} = (\delta+\mu)(\rho_r+\mu+d_r)-c\omega_r\frac{(S^0+\sigma V^0)}{N^0}(1-\nu)\delta \\ =& (\delta+\mu)(\rho_r+\mu+d_r)(1-R_{eff}(MDR)) \\ c_1 =& -(a_6+a_9+a_{11}) = 3\mu+\alpha+\gamma+\rho_s+d_s, \\ c_2 =& (a_6a_9+a_6a_{11}+a_9a_{11}+a_7a_{10}) \\ =& (\alpha+\mu)(\gamma+\mu)+(\alpha+\mu)(\rho_s+\mu+d_s)+(\gamma+\mu)(\rho_s+\mu+d_s), \end{aligned}$$

$$
\begin{aligned}
c_3 =& a_6a_9a_{11} - \gamma\eta a_7a_8 + a_7a_{10}a_9 \\
=& (\alpha+\mu)(\gamma+\mu)(\rho_s+\mu+d_s) - \frac{(c\omega_s(S^0+\sigma V^0)[\gamma\eta\alpha\epsilon(1-p)+\alpha(1-\epsilon)(1-p)(\gamma+\mu)])}{N^0}, \\
=& (\alpha+\mu)(\gamma+\mu)(\rho_s+\mu+d_s) - (c\omega_s\frac{[\gamma\eta\alpha\epsilon(1-p)+\alpha(1-\epsilon)(1-p)(\gamma+\mu](S^0+\sigma V^0)}{N^0} \\
=& (\alpha+\mu)(\gamma+\mu)(\rho_s+\mu+d_s)[1-R_{eff}(DS)]
\end{aligned}
$$

The Routh-Hurwitz conditions are the necessary and sufficient conditions on the coefficients of the quadratic and cubic polynomials equations. These conditions ensure that all roots of the polynomials have negative real parts.

The Routh-Hurwitz conditions simplifies to $b_1 > 0, b_2 > 0, c_1 > 0, c_2 > 0, c_3 > 0$ and $c_1c_2 > c_3$. That is, the necessary conditions for Routh-Hurwitz $b_2 > 0$ and $c_3 > 0$ is true if $R_{eff}(MDR) < 1$ and $R_{eff}(DS) < 1$ respectively. Now justify the sufficient condition for the Routh-Hurwitz criteria: $c_1c_2-c_3 > 0$, $c_1c_2-c_3 = (3\mu+\alpha+\gamma+\rho_s+d_s)[(\alpha+\mu)(\gamma+\mu)+(\alpha+\mu)(\rho_s+\mu+d_s)+(\gamma+\mu)(\rho_s+\mu+d_s)]-(\alpha+\mu)(\gamma+\mu)(\rho_s+\mu+d_s)[1-R_{eff}(DS)]$. Thus, $c_1c_2 - c_3 > 0$ if and only is R_{eff} (DS)< 1. Therefore all of the eigenvalues of the Jacobean matrix have negative real parts when $R_{eff}(DS) < 1$ and $R_{eff}(MDR) < 1$. Thus, the disease free equilibrium E^0, of the dynamical system (5.1)−(5.10) is locally asymptotical stable whenever R_{eff} (DS)< 1 and $R_{eff}(MDR) < 1$ and unstable otherwise that is unstable if $R_{eff} > 1$. □

Global Stability of Diseases free Equilibrium point

Theorem 5.4. *The diseases free equilibrium point* $\left(\frac{\psi\Lambda}{\mu+\theta}, \frac{(\theta+(1-\psi)\mu)\Lambda}{\mu(\mu+\theta)}, 0, 0, 0, 0, 0, 0, 0, 0\right)$ *of the dynamical system (5.1)−(5.10) is globally asymptotically stable in* Ω *if* R_{eff} *(DS)*< 1 *and* R_{eff} *(MDR)*< 1*, and unstable otherwise.*

Proof. We apply a matrix-theoretic method using the Perron eigenvector to prove the global stability of the disease-free equilibrium as in [109]. The dynamical system (5.1)−(5.10), the drug sensitive TB disease compartment of is $x_1 = (H_s, L_s, I_s)^T \in \mathbb{R}^3$ and non-disease (drug sensitive TB) compartment $y_1 \in \mathbb{R}^7$.

That is, $F_1 = \begin{bmatrix} 0 & 0 & c\omega_s \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$, $V_1 = \begin{bmatrix} (\alpha+\mu) & 0 & 0 \\ -\alpha\epsilon(1-p) & (\gamma+\mu) & 0 \\ -\alpha(1-\epsilon)(1-p) & -\gamma\eta & (\rho_s+\mu+d_s) \end{bmatrix}$ and

$x_1^{'} = (F_1 - V_1)x_1 - f_1(x_1, y_1)$

Where, the non-negative matrix F_1, of the new drug sensitive TB infection terms, and the matrix V_1, of the transition terms of drug sensitive TB and $f_1(x_1, y_1) = (\lambda_r H_s, \lambda_r L_s, 0)^T$

$$V_1^{-1}F_1 = c\omega_s \begin{bmatrix} 0 & 0 & \frac{1}{\alpha+\mu} \\ 0 & 0 & \frac{\alpha\epsilon(1-p)}{(\alpha+\mu)(\gamma+\mu)} \\ 0 & 0 & \frac{\alpha\epsilon(1-p)\gamma\eta+\alpha(1-\epsilon)(1-p)(\gamma+\mu)}{(\alpha+\mu)(\gamma+\mu)(\rho_s+\mu+d_s)} \end{bmatrix}$$

Since $detV_1 = (\alpha+\mu)(\gamma+\mu)(\rho_s+\mu+d_s) \neq 0$, the matrix V_1 is invertible. And the inverse of V_1 and $V_1^{-1}F_1$ are:

$$V_1^{-1} = \begin{bmatrix} \frac{1}{\alpha+\mu} & 0 & 0 \\ \frac{\alpha\epsilon(1-p)}{(\alpha+\mu)(\gamma+\mu)} & \frac{1}{\gamma+\mu} & 0 \\ \frac{\alpha\epsilon(1-p)\gamma\eta+\alpha(1-\epsilon)(1-p)(\gamma+\mu)}{(\alpha+\mu)(\gamma+\mu)\rho_s+\mu+d_s} & \frac{\gamma\eta}{(\gamma+\mu)} & \frac{1}{(\rho_s+\mu+d_s)} \end{bmatrix}$$

$$V_1^{-1}F_1 = \begin{bmatrix} \frac{1}{\alpha+\mu} & 0 & 0 \\ \frac{\alpha\epsilon(1-p)}{(\alpha+\mu)(\gamma+\mu)} & \frac{1}{\gamma+\mu} & 0 \\ \frac{\alpha\epsilon(1-p)\gamma\eta+\alpha(1-\epsilon)(1-p)(\gamma+\mu)}{(\alpha+\mu)(\gamma+\mu)\rho_s+\mu+d_s} & \frac{\gamma\eta}{(\gamma+\mu)} & \frac{1}{(\rho_s+\mu+d_s)} \end{bmatrix} \begin{bmatrix} 0 & 0 & c\omega_s \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

$$= c\omega_s \begin{bmatrix} 0 & 0 & \frac{1}{\alpha+\mu} \\ 0 & 0 & \frac{\alpha\epsilon(1-p)}{(\alpha+\mu)(\gamma+\mu)} \\ 0 & 0 & \frac{\alpha\epsilon(1-p)\gamma\eta+\alpha(1-\epsilon)(1-p)(\gamma+\mu)}{(\alpha+\mu)(\gamma+\mu)(\rho_s+\mu+d_s)} \end{bmatrix}$$

Hence, $\lambda_{11} = \lambda_{12} = 0$ and $\lambda_{13} = \frac{\alpha\epsilon(1-p)\gamma\eta+\alpha(1-\epsilon)(1-p)(\gamma+\mu)}{(\alpha+\mu)(\gamma+\mu)(\rho_s+\mu+d_s)}$, are eigenvalues of $V_1^{-1}F_1$.

Let, $\omega_1^T = (u_1, u_2, u_3)$ be the left eigenvector of $V_1^{-1}F_1$ corresponding to $\lambda_{13} = \frac{\alpha\epsilon(1-p)\gamma\eta+\alpha(1-\epsilon)(1-p)(\gamma+\mu)}{(\alpha+\mu)(\gamma+\mu)(\rho_s+\mu+d_s)}$

Thus, $\omega_1^T V_1^{-1}F_1 = c\omega_s(u_1, u_2, u_3) \begin{bmatrix} -\frac{\alpha\epsilon(1-p)\gamma\eta+\alpha(1-\epsilon)(1-p)(\gamma+\mu)}{(\alpha+\mu)(\gamma+\mu)(\rho_s+\mu+d_s)} & 0 & \frac{1}{\alpha+\mu} \\ 0 & -\frac{\alpha\epsilon(1-p)\gamma\eta+\alpha(1-\epsilon)(1-p)(\gamma+\mu)}{(\alpha+\mu)(\gamma+\mu)(\rho_s+\mu+d_s)} & \frac{\alpha\epsilon(1-p)}{(\alpha+\mu)(\gamma+\mu)} \\ 0 & 0 & 0 \end{bmatrix}$

i.e, $\omega_1^T = (0, 0, 1)$ is the left eigenvector of $V_1^{-1}F_1$ corresponding to the eigenvalue $\lambda_{13} = \frac{\alpha\epsilon(1-p)\gamma\eta+\alpha(1-\epsilon)(1-p)(\gamma+\mu)}{(\alpha+\mu)(\gamma+\mu)(\rho_s+\mu+d_s)}$.

Lets' define a function $W_1(H_s, L_s, I_s)$ as:

$$W_1 = \omega_1^T V_1^{-1} x_1 = \frac{\alpha\epsilon(1-p)\gamma\eta + \alpha(1-\epsilon)(1-p)(\gamma+\mu)}{(\alpha+\mu)(\gamma+\mu)(\rho_s+\mu+d_s)} H_s + \frac{\gamma\eta}{\gamma+\mu} L_s + \frac{1}{(\rho_s+\mu+d_s)} I_s$$

The derivative of W_1 with respect to time:

$$\begin{aligned}
W_1^{'} =& \omega_1^T V_1^{-1} x_1^{'}, \ \textit{Since, } x_1^{'} = (F_1 - V_1)x_1 - f_1(x_1, y_1) \\
=& \omega_1^T V_1^{-1}[(F_1 - V_1)x_1 - f_1(x_1, y_1)] \\
=& \omega_1^T [(V_1^{-1} F_1 - V_1^{-1} V_1)x_1 - V_1^{-1} f_1(x_1, y_1)] \\
=& c\omega_s(0,0,1) \begin{bmatrix} -1 & 0 & \frac{1}{\alpha+\mu} \\ 0 & -1 & \frac{\alpha\epsilon(1-p)}{(\alpha+\mu)(\gamma+\mu)} \\ 0 & 0 & \frac{\alpha\epsilon(1-p)\gamma\eta + \alpha(1-\epsilon)(1-p)(\gamma+\mu)}{(\alpha+\mu)(\gamma+\mu)(\rho_s+\mu+d_s)} - 1 \end{bmatrix} x_1 - \omega_1^T V_1^{-1} f_1(x_1, y_1)] \\
=& [(R_{eff}(DS) - 1)x_1 - V_1^{-1} f_1(x_1, y_1)] \\
=& (R_{eff}(DS) - 1)x_1 - \omega_1^T V_1^{-1} f_1(x_1, y_1)
\end{aligned}$$

Since $\omega_1^T > 0$, $V_1^{-1} > 0$ and $f_1(x_1, y_1) \geq 0, W_1^{'} < 0$, if $R_{eff}(DS) < 1$.

The multi drug resistance TB disease compartment of the dynamical system (5.1)−(5.10) is $x_2 = (E, I_r)^T \in \mathbb{R}^2$ and non-disease (multi drug resistance TB) compartment $y_2 \in \mathbb{R}^8$.

$$x_2^{'} = (F_2 - V_2)x_2 - f_2(x_2, y_2)$$

Where, the non-negative matrix F_2, of the new multi drug resistance TB infection terms, and the matrix V_2, of the transition terms of multi drug resistance TB.

$$F_2 = \begin{bmatrix} 0 & 0 \\ 0 & c\omega_s \end{bmatrix} \text{ and } V_2 = \begin{bmatrix} (\delta+\mu) & 0 \\ -\delta(1-\nu) & (\rho_r+\mu+d_r) \end{bmatrix}$$

and $f_2(x_2, y_2) = (0, 0)^T$

Since, $detV_2 = (\delta+\mu)(\rho_r+\mu+d_r) \neq 0$, the matrix V_2 is invertible.

Therefore, $V_2^{-1} = \begin{bmatrix} \frac{1}{(\delta+\mu)} & 0 \\ \frac{\delta(1-\nu)}{(\delta+\mu)(\rho_r+\mu+d_r)} & \frac{1}{(\rho_r+\mu+d_r)} \end{bmatrix}$

Where, the non-negative matrix F_2, of the new multi drug resistance TB infection terms, and the matrix V_2, of the transition terms of multi drug resistance TB and $f_2(x_2, y_2) =$

$(0,0)^T$. Therefore,$V_2^{-1}F_2 = \begin{bmatrix} \frac{1}{\delta+\mu} & 0 \\ \frac{\delta(1-\nu)}{(\delta+\nu)(\rho_r+\mu+d_r)} & \frac{1}{(\rho_r+\mu+d_r)} \end{bmatrix} \begin{bmatrix} 0 & 0 \\ 0 & c\omega_r \end{bmatrix} = \begin{bmatrix} 0 & \delta+\mu \\ 0 & \frac{\delta(1-\nu)}{(\delta+\nu)(\rho_r+\mu+d_r)} \end{bmatrix}$

Hence, $\lambda_{21} = 0$ and $\lambda_{22} = \frac{\delta(1-\nu)}{(\delta+\nu)(\rho_r+\mu+d_r)}$ are eigenvalues of $V_2^{-1}F_2$. Let, $\omega_2^T = (z_1, z_2)$ be the left eigenvector of $V_2^{-1}F_2$ corresponding to the eigenvalue $\lambda_{22} = \frac{\delta(1-\nu)}{(\delta+\nu)(\rho_r+\mu+d_r)}$

Therefore, $\omega_2^T = (0,1)$ left eigenvector of $V_2^{-1}F_2$ corresponding to $\lambda_{22} = \frac{\delta(1-\nu)}{(\delta+\nu)(\rho_r+\mu+d_r)}$.

Lets' define a function $W_2(E, I_r)$ as:

$$\begin{aligned} W_2 =& \omega_2^T V_2^{-1} x_2 = (0,1) \begin{bmatrix} \frac{1}{\delta+\mu} & 0 \\ \frac{\delta(1-\nu)}{(\delta+\nu)(\rho_r+\mu+d_r)} & \frac{1}{(\rho_r+\mu+d_r)} \end{bmatrix} (E, I_r,)^T \\ =& \frac{\delta(1-\nu)}{(\delta+\nu)(\rho_r+\mu+d_r)} E + \frac{1}{(\rho_r+\mu+d_r)} I_r \end{aligned}$$

The derivative W_2 with respect to time:

$$\begin{aligned} W_2^{'} =& \omega_2^T V_2^{-1} x_2^{'}, \ \textit{Since, } x_2^{'} = (F_2 - V_2)x_2 - f_2(x_2, y_2) \\ =& \omega_2^T V_2^{-1}[(F_2 - V_2)x_2)] \\ =& \omega_2^T [(V_2^{-1}F_2 - V_2^{-1}V_2)x_2] \\ =& (0,1)\{ \begin{bmatrix} 0 & \delta+\mu \\ 0 & \frac{\delta(1-\nu)}{(\delta+\nu)(\rho_r+\mu+d_r)} \end{bmatrix} - I \} x_2 \\ =& (R_{eff}(MDR) - 1)x_2 \end{aligned}$$

and Since $\omega_2^T > 0$, then $W_2^{'} < 0$, if $R_{eff}(MDR) < 1$.

Now we can define a Lyapunov function $W(H_s, L_s, I_s, E, I_r)$ for the system (5.1)−(5.10) as:

$$W(H_s, L_s, I_s, E, I_r) = A_1 H_s + A_2 L_s + A_3 I_s + A_4 E + A_5 I_r$$

where,
$A_1 = \frac{\alpha\epsilon(1-p)\gamma\eta + \alpha(1-\epsilon)(1-p)(\gamma+\mu)}{(\gamma+\mu)(\gamma+\mu)(\rho_s+\mu+d_s)}$, $A_2 = \frac{\gamma\eta}{\gamma+\mu}$, $A_3 = \frac{1}{(\rho_s+\mu+d_s)}$, $A_4 = \frac{\delta(1-\nu)}{(\delta+\nu)(\rho_r+\mu+d_r)}$, $A_5 = \frac{1}{(\rho_r+\mu+d_r)}$.

Differentiate W with respect to time, we have

$$\begin{aligned}
W^{'} =&\frac{(\alpha\epsilon(1-p)\gamma\eta+\alpha(1-\epsilon)(1-p)(\gamma+\mu))}{(\alpha+\mu)(\gamma+\mu)(\rho_s+\mu+d_s)}H_s^{'}+\frac{\gamma\eta}{\gamma+\mu}L_s^{'}+\frac{1}{(\rho_s+\mu+d_s)}I_s^{'}\\
&+\frac{\delta(1-\nu)}{(\delta+\mu)(\rho_s+\mu+d_r)}E^{'}+\frac{1}{\rho_r+\mu+d_r}I_r^{'}\\
=&\frac{(\alpha\epsilon(1-p)\gamma\eta+\alpha(1-\epsilon)(1-p)(\gamma+\mu))}{(\alpha+\mu)(\gamma+\mu)(\rho_s+\mu+d_s)}H_s^{'}+\frac{\gamma\eta}{\gamma+\mu}L_s^{'}+\frac{1}{(\rho_s+\mu+d_s)}I_s^{'}\\
&+\frac{\delta(1-\nu)}{(\delta+\mu)(\rho_s+\mu+d_r)}E^{'}+\frac{1}{\rho_r+\mu+d_r}I_r^{'}+(R_{eff}(MDR)-1)I_r
\end{aligned}$$

Substituting the derivatives and simplify:

$$\begin{aligned}
W^{'} =&(R_{eff}(DS)-1)I_s-(0,0,1)\begin{bmatrix}\frac{1}{\alpha+\mu} & 0 & 0\\ \frac{\alpha\epsilon(1-p)}{(\alpha+\mu)(\gamma+\mu)} & \frac{1}{\gamma+\mu} & 0\\ \frac{\alpha\epsilon(1-p)\gamma\eta+\alpha(1-\epsilon)(1-p)(\gamma+\mu)}{(\alpha+\mu)(\gamma+\mu)\rho_s+\mu+d_s} & \frac{\gamma\eta}{(\gamma+\mu)} & \frac{1}{(\rho_s+\mu+d_s)}\end{bmatrix}(\lambda_r H_s,\lambda_r L_s,0)^T\\
&+(R_{eff}(MDR)-1)I_r\\
W^{'} =&(R_{eff}(DS)-1)I_s+(R_{eff}(MDR)-1)\,I_r\\
&-\lambda_r\left(\frac{\alpha\epsilon(1-p)\gamma\eta+\alpha(1-\epsilon)(1-p)(\gamma+\mu)}{(\alpha+\mu)(\gamma+\mu)(\rho_s+\mu+d_s)}H_s+\frac{\gamma\eta}{\gamma+\mu}L_s\right)
\end{aligned}$$

Hence, $W^{'}<0$, if $R_{eff}(DS)<1$ and $R_{eff}(MDR)<1$. And $W^{'}=0$, at the disease free equilibrium point E^0.

By LaSalle's invariant principle, every solution to the model equations (5.1)−(5.10) with initial conditions in Ω tends to E^0 as $t\to\infty$. Hence, since the region Ω is positively-invariant, the disease free equilibrium point, E^0 is globally asymptotically stable in Ω if $R_{eff}<1$. □

5.4 Existence of Endemic Equilibrium Point

There are three possible endemic equilibria for the dynamical system (5.1)−(5.10): two boundary equilibria E_1 (when only the drug sensitive TB-strain is present) and E_2 (when only the multi drug resistant TB-strain is present), and E_3 (when both strains exist).

5.4.1 The Drug Sensitive TB-strain only Equilibrium

This is obtained by setting $\lambda_r = 0$ and $q = 1$ (that treatment of active drug sensitive TB is 100% effective) in the dynamical system (5.1)−(5.10). The drug sensitive TB only equilibrium in terms of the equilibrium value of the force of infection λ_s^* is given as:

$$E_1 = (V^*, S^*, H_s^*, L_s^*, I_s^*, T_s^*, 0, 0, 0, R^*)$$

From equation (5.1) of the dynamical system (5.1)−(5.10):

$$\frac{dV}{dt} = \psi\Lambda - (\sigma(\lambda_s + \lambda_r) + \theta + \mu)V = 0 \Rightarrow V^* = \frac{\psi\Lambda}{(\sigma\lambda_s^* + \theta + \mu)}$$

From equation (5.2) of the dynamical system (5.1)−(5.10):

$$\begin{aligned}
\frac{dS}{dt} &= (1-\psi)\Lambda + \theta V - (\lambda_s + \lambda_r + \mu)S = 0 \\
\Rightarrow S^* &= \frac{(1-\psi)\Lambda + \theta V^*}{(\lambda_s^* + \lambda_r^* + \mu)} = \frac{\Lambda(1-\psi)\sigma(\lambda_s^* + \lambda_r^*) + \theta + (1-\psi)\mu]}{(\lambda_s^* + \lambda_r^* + \mu)[\sigma(\lambda_s^* + \lambda_r^*) + \theta + \mu]} \\
&= \frac{\Lambda(1-\psi)\sigma\lambda_s^* + \theta + (1-\psi)\mu]}{(\lambda_s^* + \mu)[\sigma(\lambda_s^* + \theta + \mu]}
\end{aligned}$$

From equation (5.3) of the dynamical system (5.1)−(5.10):

$$\frac{dH_s}{dt} = \lambda_s S + \sigma\lambda_s V + \kappa\lambda_s R - (\alpha + \lambda_r + \mu)H_s = 0 \Rightarrow H_s^* = \frac{\lambda_s^*(S^* + \sigma V^* + \kappa R^*)}{(\alpha + \mu)}$$

From equation (5.4) of the dynamical system (5.1)−(5.10):

$$\frac{dL_s}{dt} = \alpha\epsilon(1-p)H_s - (\lambda_r + \gamma + \mu)L_s = 0 \Rightarrow L_s^* = \frac{\alpha\epsilon(1-p)H_s^*}{(\gamma + \mu)}$$

From equation (5.5) of the dynamical system (5.1)−(5.10):

$$\begin{aligned}
\frac{dI_s}{dt} &= \gamma\eta L_s + \alpha(1-\epsilon)(1-p)H_s - (\rho_s + \mu + d_s)I_s = 0 \\
\Rightarrow I_s^* &= \frac{\gamma\eta L_s^* + \alpha(1-\epsilon)(1-p)H_s^*}{(\rho_s + \mu + d_s)} \\
\Rightarrow I_s^* &= \frac{(\gamma\eta\alpha\epsilon(1-p) + \alpha(\gamma+\mu)(1-\epsilon)(1-p))}{(\gamma+\mu)(\rho_s + \mu + d_s)}H_s^* \\
\Rightarrow H_s^* &= \frac{(\gamma+\mu)(\rho_s + \mu + d_s)}{\gamma\eta\alpha\epsilon(1-p) + \alpha(\gamma+\mu)(1-\epsilon)(1-p)}I_s^* and \\
\Rightarrow L_s^* &= \frac{\alpha\epsilon(1-p)H_s^*}{(\gamma+\mu)} = \frac{\alpha\epsilon(1-p)(\rho_s + \mu + d_s)}{(\gamma\eta\alpha\epsilon(1-p) + \alpha(\gamma+\mu)(1-\epsilon)(1-p))}I_s^*
\end{aligned}$$

From equation (5.6) of the dynamical system (5.1)−(5.10):

$$\begin{aligned}
\frac{dT_s}{dt} &= \alpha p H_s - (\phi + \mu)T_s = 0 \Rightarrow T_s^* = \frac{\alpha p H_s^*}{(\phi + \mu)} \\
\Rightarrow T_s^* &= \frac{\alpha p(\gamma+\mu)(\rho_s + \mu + d_s)}{(\phi+\mu)[\gamma\eta\alpha\epsilon(1-p) + \alpha(\gamma+\mu)(1-\epsilon)(1-p)]}I_s^*
\end{aligned}$$

From equation (5.7) of the dynamical system (5.1)−(5.10):

$$\frac{dE}{dt} = \lambda_r(S + H_s + L_s + \sigma V + \kappa R) + (1-q)\rho_s I_s - (\delta+\mu)E = 0$$
$$\Rightarrow E^* = \frac{\lambda_r^*(S^* + H_s^* + L_s^* + \sigma V^* + \kappa R^*) + (1-q)\rho_s I_s^*}{(\delta+\mu)} = 0, (since,\ q = 1\ and\ I_r = 0)$$

From equation (5.8) of the dynamical system (5.1)−(5.10):

$$\frac{dI_r}{dt} = (1-\nu)\delta E - (\rho_r + \mu + d_r)I_r = 0 \Rightarrow I_r^* = 0$$

From equation (5.9) of the dynamical system (5.1)−(5.10):

$$\frac{dT_r}{dt} = \nu\delta E - (\varphi+\mu)T_r = 0 \Rightarrow T_r^* = \frac{\nu\delta E^*}{(\varphi+\mu)} = 0$$

From equation (5.10) of the dynamical system (5.1)−(5.10):

$$\begin{aligned}
\frac{dR}{dt} =& q\rho_s I_s + \rho_r I_r + \gamma(1-\eta)L_s + \phi T_s + \varphi T_r - (\kappa(\lambda_s+\lambda_r)+\mu)R = 0\\
R^* =& \frac{\rho_s I_s^* + \rho_r I_r^* + \gamma(1-\eta)L_s^* + \phi T_s^* + \varphi T_r^*}{(\kappa(\lambda_s^*+\lambda_r^*)+\mu)} = \frac{\rho_s I_s^* + \gamma(1-\eta)L_s^* + \phi T_s^*}{(\kappa\lambda_s^*+\mu)}\\
=& \frac{1}{(\kappa\lambda_s^*+\mu)}\frac{\rho_s + \gamma(1-\eta)\alpha\eta(1-p)(\rho_s+\mu+d_s)}{[\gamma\eta\alpha\epsilon(1-p) + \alpha(\gamma+\mu)(1-\epsilon)(1-p)]}\\
&+ \frac{1}{(\kappa\lambda_s^*+\mu)}\frac{\phi\alpha p(\gamma+\mu)(\rho_s+\mu+d_s)}{(\phi+\mu)[\gamma\eta\alpha\epsilon(1-p) + \alpha(\gamma+\mu)(1-\epsilon)(1-p)]}I_s^*
\end{aligned}$$

Hence, the drug sensitive TB-strain only equilibrium point:

$$E_1 = (V^*, S^*, H_s^*, L_s^*, I_s^*, T_s^*, 0, 0, 0, R^*)$$

where $V^* = \frac{\psi\Lambda}{\sigma\lambda_s^*+\theta+\mu}$, $S^* = \frac{\Lambda(1-\psi)\sigma\lambda_s^*+\theta+(1-\psi)\mu]}{(\lambda_s^*+\mu)(\sigma\lambda_s^*+\theta+\mu)}$, $H_s^* = \frac{(\gamma+\mu)(\rho_s+\mu+d_s)}{\gamma\eta\alpha\epsilon(1-p)+\alpha(\gamma+\mu)(1-\epsilon)(1-p))}I_s^*$
$L_s^* = \frac{\alpha\epsilon(1-p)(\rho_s+\mu+d_s)}{\gamma\eta\alpha\epsilon(1-p)+\alpha(\gamma+\mu)(1-\epsilon)(1-p)}I_s^*$, $T_s^* = \frac{\alpha p(\gamma+\mu)(\rho_s+\mu+d_s)}{(\phi+\mu)[\gamma\eta\alpha\epsilon(1-p)+\alpha(\gamma+\mu)(1-\epsilon)(1-p)]}I_s^*$,
$R^* = \frac{1}{\kappa\lambda_s^*+\mu} \times \{\rho_s + \frac{\gamma(1-\eta)\alpha\epsilon(1-p)(\rho_s+\mu+d_s)}{[\gamma\eta\alpha\epsilon(1-p)+\alpha(\gamma+\mu)(1-\epsilon)(1-p)]} + \frac{\phi\alpha p(\gamma+\mu)(\rho_s+\mu+d_s)}{(\phi+\mu)[\gamma\eta\alpha\epsilon(1-p)+\alpha(\gamma+\mu)(1-\epsilon)(1-p)]}\}I_s^*$

Existence of drug sensitive TB-strain only equilibrium

As the drug sensitive TB-strain only equilibrium E_1 given in terms λ_s the existence of the equilibrium value of the force of infection λ_s shows the existence of E_1. Therefore, we are going to put the conditions that λ_s exists.

$$\lambda_s^* = \frac{c\omega_s\mu}{\Lambda}I_s^*$$

where $N^*(t)$ is replaced by its limiting value, $N^* = \frac{\Lambda}{\mu}$

$$\Rightarrow \lambda_s^* = \frac{c\omega_s\mu}{\Lambda}\frac{\gamma\eta\alpha\epsilon(1-p)+\alpha(\gamma+\mu)(1-\epsilon)(1-p)}{(\gamma+\mu)(\rho_s+\mu+d_s)}H_s^*$$

$$\Rightarrow \lambda_s^* = a_1 R_{eff}(DS)\lambda_s^* \frac{[(1-\psi)\sigma\lambda_s^*+\theta+(1-\psi)\mu]}{(\lambda_s^*+\mu)(\sigma\lambda_s^*+\theta+\mu)+\frac{\sigma\psi}{(\sigma\lambda_s^*+\theta+\mu)}} + a_1 a_2 R_{eff}(DS)\lambda_s^{*2}$$

Where, $a_1 = \frac{\mu(\theta+\mu)}{\Lambda+(\theta+(1-\phi)\mu)}$,

$$a_2 = \frac{\kappa\Lambda}{c\omega_s\mu}\{\frac{\rho_s+\gamma(1-\eta)\alpha\epsilon(1-p)(\rho_s+\mu+d_s)}{[\gamma\eta\alpha\epsilon(1-p)+\alpha(\gamma+\mu)(1-\epsilon)(1-p)]} + \frac{\phi\alpha p(\gamma+\mu)(\rho_s+\mu+d_s)}{(\phi+\mu)[\gamma\eta\alpha\epsilon(1-p)+\alpha(\gamma+\mu)(1-\epsilon)(1-p)]}\}$$

$$\Rightarrow \sigma a_1 a_2 R_{eff}(DS)(\lambda_s^*)^4 + [(\sigma\mu+\theta+\mu)a_1 a_2 R_{eff}(DS) - \sigma](\lambda_s^*)^3$$
$$+ [\mu(\theta+\mu)a_1 a_2 + \sigma a_1]R_{eff}(DS) - (\sigma\mu+\theta+\mu)(\lambda_s^*)^2$$
$$+ a_1 R_{eff}(DS)[\theta+(1-\psi)\mu-\sigma\psi\mu] - \mu(\theta+\mu)\lambda_s^* = 0$$

$$\Rightarrow B_1(\lambda_s^*)^4 + B_2(\lambda_s^*)^3 + B_3(\lambda_s^*)^2 + B_4\lambda_s^* = 0 \tag{5.21}$$

Where, $B_1 = \sigma a_1 a_2 R_{eff}(DS) > 0$

$$B_2 = (\sigma\mu+\theta+\mu)a_1 a_2 R_{eff}(DS) - \sigma$$

$$B_3 = [\mu(\theta+\mu)a_1 a_2 + \sigma a_1]R_{eff}(DS) - (\sigma\mu+\theta+\mu)$$

$$B_4 = a_1 R_{eff}(DS)[\theta+(1-\psi)\mu-\sigma\psi\mu] - \mu(\theta+\mu)$$

The solutions for the quartic polynomial (5.21) are $\lambda_s^* = 0$ and $B_1(\lambda_s^*)^3 + B_2(\lambda_s^*)^2 + B_3\lambda_s^* + B_4 = 0$. The case $\lambda_s^* = 0$ corresponds to no drug sensitive TB and $B_1(\lambda_s^*)^3 + B_2(\lambda_s^*)^2 + B_3\lambda_s^* + B_4 = 0$ corresponds to the existence of at most three drug sensitive TB only endemic equilibrium points.

Theorem 5.5. *In the equation of polynomial,* $B_1(\lambda_s^*)^3 + B_2(\lambda_s^*)^2 + B_3\lambda_s^* + B_4 = 0$*, the relation between roots and coefficients are given by:*

1) $\frac{B_2}{B_1} = -$*(sum of all roots)*

2) $\frac{B_3}{B_1} =$ *sum of products of roots taken two at a time*

3) $\frac{B_4}{B_1} = -$ *(products of roots taken three at a time)*

Remark:

The TB model system (5.1)−(5.10) has:

1) one positive drug sensitive TB only endemic equilibrium if $B_2 < 0$, and $B_3 = B_4 = 0$. That is if $R_{eff}(DS) < \frac{\sigma}{(\sigma\mu+\theta+\mu)a_1a_2}$, one positive drug sensitive TB only endemic equilibrium. And the root will be, $r_1 = -\frac{B_2}{B_1}$.

2) two positive drug sensitive TB only endemic equilibrium if $B_2 < 0, B_3 > 0$ and $B_4 = 0$. That is, if $\frac{(\sigma\mu+\theta+\mu)}{(\mu(\theta+\mu)a_1a_2+\sigma a_1)} < R_{eff}(DS) < \frac{\sigma}{(\sigma\mu+\theta+\mu)a_1a_2}$ two positive drug sensitive TB only endemic equilibrium. $r_1 + r_2 = -\frac{B_2}{B_1}$ and $r_1r_2 = \frac{B_3}{B_1}$.
Therefore $r_1(-r_1 - \frac{B_2}{B_1}) = \frac{B_3}{B_1} \Rightarrow r_1^2 + r_1\frac{B_2}{B_1} + \frac{B_3}{B_1} = 0 \Rightarrow r_1 = \frac{-B_2 \pm \sqrt{B_2^2 - 4B_1B_3}}{2B_1}$.
Then has two roots if $B_2 < 0$ and $B_2^2 - 4B_1B_3 > 0$. $R_{eff}(DS) < \frac{\sigma}{(\sigma\mu+\theta+\mu)a_1a_2}$ and
$[(\sigma\mu+\theta+\mu)a_1a_2R_{eff}(DS)-\sigma]^2 > 4[\mu(\theta+\mu)a_1a_2 + \sigma a_1]Reff(DS) - (\sigma\mu+\theta+\mu)$

3) three positive drug sensitive TB only endemic equilibrium if the coefficients $B_2 < 0, B_3 > 0$ and $B_4 < 0$ with the relation to the three roots:
$r_1 + r_2 + r_3 = -B_2/B_1$, $r_1r_2 + r_1r_3 + r_2r_3 = B_3/B_1$ and $r_1r_2r_3 = -B_4/B_1$
That is, if $\frac{(\sigma\mu+\theta+\mu)}{\mu(\theta+\mu)a_1a_2+\sigma a_1} < R_{eff}(DS) < \frac{\sigma}{(\sigma\mu+\theta+\mu)a_1a_2}$ and $R_{eff}(DS) < \frac{\mu(\theta+\mu)}{a_1[\theta+(1-\psi)\mu-\sigma\psi\mu]}$.

4) no positive drug sensitive TB only endemic equilibrium otherwise.

Theorem 5.6. *The model (5.1)−(5.10) has unique drug sensitive TB only endemic equilibrium if $B_2 <0$ and $B_3 = B_4 = 0$. That is, the model (5.1)−(5.10) has unique drug sensitive TB only endemic equilibrium $\lambda_s^* = m^* = -B_2/B_1$.*

Proof. Since $B_3 = B_4 = 0$, from quadric polynomial $B_1(\lambda_s^*)^4 + B_2(\lambda_s^*)^3 + B_3(\lambda_s^*)^2 + B_4\lambda_s^* = 0$ we have $(\lambda_s^*)^3(B_1\lambda_s^* + B_2) = 0$. Then the only positive drug sensitive TB only endemic equilibrium is, $\lambda_s^* = -B_2/B_1$ since $B_1 > 0$ and $B_2 < 0$. The model (5.1)−(5.10) has unique drug sensitive TB only endemic equilibrium if $B_2 < 0$ and $B_3 = B_4 = 0$. □

Theorem 5.7. *The dynamical system (5.1)−(5.10) has unique drug sensitive TB only endemic equilibrium if $R_{eff}(DS) < \frac{\sigma}{(\sigma\mu+\theta+\mu)a_1a_2}$ and $B_2 = B_3 = 0$. That is, the model (5.1)−(5.10) has unique endemic equilibrium when $\lambda_s^* = m^* = -B_2/B_1 = \frac{\sigma-(\sigma\mu+\theta+\mu)a_1a_2R_{eff}(DS)}{\sigma a_1a_2R_{eff}(DS)}$*

Proof. The model (5.1)-(5.10) has unique endemic equilibrium if $B_2 < 0$ and $B_3 = B_4 = 0$. That is, $B_2 < 0 \Rightarrow R_{eff}(DS) < \frac{\sigma}{(\sigma\mu+\theta+\mu)a_1a_2}$. And hence, at the unique endemic equilibrium point, $\lambda_s^* = m^* = -B_2/B_1 = \frac{\sigma-(\sigma\mu+\theta+\mu)a_1a_2R_{eff}(DS)}{\sigma a_1a_2R_{eff}(DS)}$ Where, $m^* = \frac{\sigma-(\sigma\mu+\theta+\mu)a_1a_2R_{eff}(DS)}{\sigma a_1a_2R_{eff}(DS)}$. □

Local stability of drug sensitive TB-strain only equilibrium point

Theorem 5.8. *The drug sensitive TB only equilibrium E_1 of the dynamical system (5.1)−(5.6), (5.10) when $q = 1$ is locally asymptotically stable if R_{eff} (DS)$> 1 > R_{eff}$ (MDR) and $R^* < \frac{\Lambda(d_s+\mu)}{c\omega_s\kappa\mu}$*

Proof. In this case, $E = I_r^* = T_r^* = 0$ in system (5.1)−(5.10), that is,
E_1 exists and is unique if $R_{eff}(DS) > 1$ and E_1 to exist alone if the resistant strain does not exist (i.e., $R_{eff}(MDR) < 1$). The components of the unique endemic equilibrium E_1 can then be obtained by substituting the unique value of $\lambda_s^* = m^*$ in to the dynamical system (5.1)−(5.6), (5.10). Then drug sensitive TB only equilibrium, $E_1 = (V^*, S^*, H_s^*, L_s^*, I_s^*, T_s^*, 0, 0, 0, R^*)$, where

$$
\begin{aligned}
V^* =& \frac{\psi\Lambda}{(\sigma m^* + \theta + \mu)}, S^* = \frac{\Lambda(1-\psi)\sigma m^* + (\theta + (1-\psi)\mu]}{(m^* + \mu)(\sigma m^* + \theta + \mu)},\\
H_s^* =& \frac{\Lambda m^*(\gamma+\mu)(\rho_s + \mu + d_s)}{(c\omega_s\mu(\gamma\eta\alpha\epsilon(1-p) + \alpha(\gamma+\mu)(1-\epsilon)(1-p))}\\
L_s^* =& \frac{\Lambda m^*\alpha\epsilon(1-p)(\rho_s+\mu+d_s)}{c\omega_s\mu(\gamma\eta\alpha\epsilon(1-p) + \alpha(\gamma+\mu)(1-\epsilon)(1-p))}, I_s^* = \frac{\Lambda m^*}{c\omega_s\mu},\\
T_s^* =& \frac{\Lambda m^*\alpha p(\gamma+\mu)(\rho_s+\mu+d_s)}{c\omega_s\mu(\phi+\mu)[\gamma\eta\alpha\epsilon(1-p) + \alpha(\gamma+\mu)(1-\epsilon)(1-p)]}\\
R^* =& \frac{\Lambda m^*}{\mu(c\omega_s\kappa m^* + \Lambda)}\{\rho_s + \frac{\gamma(1-\eta)\alpha\epsilon(1-p)(\rho_s+\mu+d_s)}{[\gamma\eta\alpha\epsilon(1-p) + \alpha(\gamma+\mu)(1-\epsilon)(1-p)]}\}\\
&+ \frac{\Lambda m^*}{\mu(c\omega_s\kappa m^* + \Lambda)}\frac{\phi\alpha p(\gamma+\mu)(\rho_s+\mu+d_s)}{(\phi+\mu)[\gamma\eta\alpha\epsilon(1-p) + \alpha(\gamma+\mu)(1-\epsilon)(1-p)]}\\
m^* =& \frac{\sigma - (\sigma\mu + \theta + \mu)a_1a_2R_{eff}(DS)}{\sigma a_1a_2R_{eff}(DS)}
\end{aligned}
$$

The Jacobean matrix of the dynamical system (5.1)−(5.6), (5.10) at equilibrium E_1 is given by:

$$
J(E_1) = \begin{bmatrix}
g_1 & 0 & 0 & 0 & b_1 & 0 & 0\\
\theta & g_2 & 0 & 0 & b_2 & 0 & 0\\
\sigma m^* & m^* & g_3 & 0 & z & 0 & \kappa m^*\\
0 & 0 & \alpha\epsilon(1-p) & g_4 & 0 & 0 & 0\\
0 & 0 & \alpha(1-\epsilon)(1-p) & \gamma\eta & g_5 & 0 & 0\\
0 & 0 & \alpha p & 0 & 0 & g_6 & 0\\
0 & 0 & 0 & \gamma(1-\eta) & \rho_s & \phi & g_7
\end{bmatrix}
$$

Where, $m^* = \frac{\sigma-(\sigma\mu+\theta+\mu)a_1a_2R_{eff}(DS)}{\sigma a_1a_2R_{eff}(DS)}$, $g_1 = -(\sigma m^*+\theta+\mu)$, $g_2 = -(m^*+\mu)$,$g_3 = -(\alpha+\mu)$, $g_4 = -(\gamma+\mu)$,$g_5 = -(\rho_s+\mu+d_s)$,$g_6 = -(\phi+\mu)$,$g_7 = -(\kappa m^*+\mu)$,$b_1 = \frac{\sigma c\omega_s V^*}{N^*}$,$b_2 = \frac{c\omega_s V^*}{N^*}$, $z = \frac{c\omega_s\mu}{\Lambda}(S^* + \sigma V^* + \kappa R^*)$

The characteristic equation of $J(E_1)$ denoted by $|J(E_1) - \lambda I| = 0$, and given by:

$$\begin{vmatrix} g_1-\lambda & 0 & 0 & 0 & b_1 & 0 & 0 \\ \theta & g_2-\lambda & 0 & 0 & b_2 & 0 & 0 \\ \sigma m^* & m^* & g_3-\lambda & 0 & z & 0 & \kappa m^* \\ 0 & 0 & \alpha\epsilon(1-p) & g_4-\lambda & 0 & 0 & 0 \\ 0 & 0 & \alpha(1-\epsilon)(1-p) & \gamma\eta & g_5-\lambda & 0 & 0 \\ 0 & 0 & \alpha p & 0 & 0 & g_6-\lambda & 0 \\ 0 & 0 & 0 & \gamma(1-\eta) & \rho_s & \phi & g_7-\lambda \end{vmatrix} = 0$$

Now we apply the Gershgorin circle theorem to determine the sign of the eigenvalues of the characteristic equation $|J(E_1) - \lambda I| = 0$.

From the first column of the Jacobian matrix $J(E_1)$ the dynamical system (5.1)−(5.6), (5.10),

$$|g_1| = (\sigma m^* + \theta + \mu) \ and \ \Sigma_{i=1,i\neq1}^{7} c_{i1} = \theta + \sigma m^*$$
$$\Rightarrow |g_1| > \Sigma_{i=1,i\neq1}^{7} c_{i1}$$

From the second column of the Jacobian matrix $J(E_1)$ of the dynamical system (5.1)−(5.6), (5.10),

$$|g_2| = (m^* + \mu), \ and \ \Sigma_{i=1,i\neq2}^{7} c_{i2} = m^* \Rightarrow |g_2| > \Sigma_{i=1,i\neq2}^{7} c_{i2}$$

From the third column of the Jacobian matrix $J(E_1)$ of the dynamical system (5.1)−(5.6), (5.10),

$$|g_3| = (\alpha + \mu), \ and \ \Sigma_{i=1,i\neq3}^{7} c_{i3} = \alpha\epsilon(1-p) + \alpha(1-\epsilon)(1-p) + \alpha p = \alpha$$
$$\Rightarrow |g_3| > \Sigma_{i=1,i\neq3}^{7} c_{i3}$$

From the fourth column of the Jacobian matrix $J(E_1)$ of the dynamical system (5.1)−(5.6), (5.10),

$$|g_4| = (\gamma + \mu), \ and \ \Sigma_{i=1,i\neq4}^{7} c_{i4} = \gamma\eta + \gamma(1-\eta) = \gamma \Rightarrow |g_4| > \Sigma_{i=1,i\neq4}^{7} c_{i4}$$

From the fifth column of the Jacobian matrix $J(E_1)$ of the dynamical system (5.1)−(5.6), (5.10),

$$|g_5| = \rho_s + \mu + d_s \ and \ \Sigma_{i=1,i\neq 5}^{7} c_{i5} = b_1 + b_2 + z + \rho_s = \frac{c\omega_s}{N^*}\kappa R^* + \rho_s$$

If we let $N^* = \frac{\Lambda}{\mu}$, then $\Sigma_{i=1,i\neq 5}^{7} c_{i5} = \frac{c\omega_s\mu\kappa}{\Lambda}R^* + \rho_s$. $\Rightarrow |g_5| > \Sigma_{i=1,i\neq 5}^{7} c_{i5}$ if $R^* < \frac{\Lambda(d_s+\mu)}{c\omega_s\mu\kappa}$.

From the sixth column of the Jacobian matrix $J(E_1)$,

$$|g_6| = (\phi + \mu) \ and \ \Sigma_{i=1,i\neq 6}^{7} c_{i6} = \phi \Rightarrow |g_6| > \Sigma_{i=1,i\neq 6}^{7} c_{i6}$$

From the seventh column of the Jacobian matrix $J(E_1)$,

$$|g_7| = (\kappa m^* + \mu) \ and \ \Sigma_{i=1,i\neq 7}^{7} c_{i7} = \kappa m^* \Rightarrow |g_7| > \Sigma_{i=1,i\neq 7}^{7} c_{i7}$$

Therefore, $|g_5| > \Sigma_{i=1,i\neq 5}^{7} c_{i5}$ if $R^* < \frac{\Lambda(d_s+\mu)}{c\omega_s\mu\kappa}$ and for the remaining column of the Jacobian matrix $J(E_1)$, $|g_i| > \Sigma_{i=1,i\neq j}^{7} c_{ij}$ for $j = \{1,\ldots,7\} - \{5\}$. Therefore, if $|c_{ii}| > \Sigma_{i=1,i\neq j}^{7} c_{ij}$, for $j = 1,\ldots,7$, for the matrix $J(E_1)$,

Hence, the matrix $J(E_1)$ is a strictly column diagonally dominant matrix if $R^* < \frac{\Lambda(d_s+\mu)}{c\omega_s\mu\kappa}$. And also all diagonal elements of $J(E_1)$ are negative. Therefore, using the Gershgorin circle theorem, the radius of the disc less than the magnitude of corresponding element if $R^* < \frac{\Lambda(d_s+\mu)}{c\omega_s\kappa\mu}$ We can show that all eigenvalues of $J(E_1)$ has negative real part if R_{eff}(DS)$> 1 > R_{eff}$(MDR) and $R^* < \frac{\Lambda(d_s+\mu}{c\omega_s\kappa\mu}$ Hence, the drug resistance TB only equilibrium E_1 is locally asymptotically stable if R_{eff} (DS)$> 1 > R_{eff}$(MDR) and $R^* < \frac{\Lambda(d_s+\mu}{c\omega_s\kappa\mu}$. □

Global Stability of Drug Sensitive TB only Endemic Equilibrium Point

Theorem 5.9. *The drug sensitive TB only equilibrium E_1 of Model (5.1)-(5.6), (5.10) is globally asymptotically stable if $q = 1, R_{eff}$ (DS)$> 1 > R_{eff}$ (MDR), $\frac{V}{V^*}$, $\frac{S}{S^*}$, $\frac{R}{R^*} \leq 1$ and $\frac{H_s}{H_s^*} \leq \frac{I_s}{I_s^*}$.*

Proof. We use a graph-theoretic method as in [109] to construct a Lyapunov function.

We define functions:

$$D_1 = V - V^* - V^* ln\frac{V}{V^*}, D_2 = S - S^* - S^* ln\frac{S}{S^*}, D_3 = H_s - H_s^* - H_s^* ln\frac{H_s}{H_s^*},$$
$$D_4 = L_s - L_s^* - L_s^* ln\frac{L_s}{L_s^*}, D_5 = T_s - T_s^* - T_s^* ln\frac{T_s}{T_s^*}, D_6 = I_s - I_s^* - I_s^* ln\frac{I_s}{I_s^*},$$
$$D_7 = R - R^* - R^* ln\frac{R}{R^*}$$

Differentiating the functions D_i for $i = 1, ..., 7$ with respect to time,, and use the values at the endemic equilibrium point E_1 that:

$$\psi\Lambda = (\sigma\lambda_s^* + \theta + \mu)V^*, \qquad (1-\psi)\Lambda = -\theta V^* + (\lambda_s^* + \mu)S^*,$$
$$(\alpha + \mu) = \frac{\lambda_s^*(S^* + \sigma V^* + \kappa R^*)}{H_s^*}, \qquad (\gamma + \mu) = \frac{\alpha\epsilon(1-p)H_s^*}{L_s^*},$$
$$(\rho_s + \mu + d_s) = \frac{\gamma\eta L_s^*}{I_s^*} + \frac{\alpha(1-\epsilon)(1-p)H_s^*}{I_s^*}, \qquad (\phi + \mu) = \frac{\alpha p H_s^*}{T_s^*},$$
$$\mu = \frac{\rho_s I_s^*}{R^*} + \frac{\gamma(1-\eta)L_s^*}{R^*} + \frac{\phi T_s^*}{R^*} - \kappa\lambda_s^*$$

And using the inequality $1 - x + lnx \leq 0$, for all $x > 0$ and the values at the endemic equilibrium point E_1 that:

$$\begin{aligned}
D_1^{'} =& \left(1 - \frac{V^*}{V}\right)V^{'} = \left(1 - \frac{V^*}{V}\right)(\psi\Lambda - (\sigma\lambda_s + \theta + \mu)V) \\
=& -(\theta + \mu)\frac{(V - V^*)^2}{V} + \frac{c\mu\omega_s}{N^*}V^*\left(I_s^* - \frac{I_s V}{V^*} + I_s - \frac{I_s^* V^*}{V}\right) \\
=& -(\theta + \mu)\frac{(V - V^*)^2}{V} + \frac{c\sigma\omega_s}{N^*}V^* I_s^*\left(1 - \frac{I_s V}{I_s^* V^*} - \frac{V^*}{V} + \frac{I_s}{I_s^*}\right) \\
\leq& \frac{c\sigma\omega_s}{N^*}V^* I_s^*\left(1 - \frac{I_s V}{I_s^* V^*} - \frac{V^*}{V} + \frac{I_s}{I_s^*}\right) \leq \frac{c\sigma\omega_s}{N^*}V^* I_s^*\left(-ln\frac{I_s V}{I_s^* V^*} - \frac{V^*}{V} + \frac{I_s}{I_s^*}\right) \\
\leq& \sigma\lambda_s^* V^*\left(-ln\frac{I_s}{I_s^*} + ln\frac{V^*}{V} - \frac{V^*}{V} + \frac{I_s}{I_s^*}\right) = a_{15}G_{15}
\end{aligned}$$

$$\begin{aligned}
D_2^{'} =& \left(1 - \frac{S^*}{S}\right)S^{'} = \left(1 - \frac{S^*}{S}\right)((1-\psi)\Lambda + \theta V - (\lambda_s + \mu)S) \\
=& \left(1 - \frac{S^*}{S}\right)(-\theta V^* + (\lambda_s^* + \theta)S^* + \theta V - (\lambda_s + \mu)S) \\
=& -\mu\frac{(S - S^*)^2}{S} + \theta V^*\left(\frac{S^*}{S} - 1 - \frac{V S^*}{V^* S} + \frac{V}{V^*}\right) + \frac{c\omega_s}{N^*}S^* I_s^*\left(1 - \frac{I_s S}{I_s^* S^*} - \frac{S^*}{S} + \frac{I_s}{I_s^*}\right) \\
\leq& \theta V^*\left(\frac{S^*}{S} - 2 - ln\frac{V S^*}{V^* S} + \frac{V}{V^*}\right) + S^*\lambda_s^*\left(-ln\frac{I_s}{I_s^*} + ln\frac{S^*}{S} - \frac{S^*}{S} + \frac{I_s}{I_s^*}\right) \\
=& : a_{21}G_{21} + a_{25}G_{25}
\end{aligned}$$

$$
\begin{aligned}
D_3^{'} &= \left(1-\frac{H_s^*}{H_s}\right) H_s^{'} = \left(1-\frac{H_s^*}{H_s}\right) \lambda_s S + \sigma\lambda_s V + \kappa\lambda_s R - (\alpha+\mu)H_s) \\
&= \left(1-\frac{H_s^*}{H_s}\right) (\lambda_s S + \sigma\lambda_s V + \kappa\lambda_s R + \lambda_s^* \left(-\frac{S^*}{H_s^*} - \sigma\frac{V^*}{H_s^*} - \kappa\frac{R^*}{H_s^*}\right) H_s \\
&\leq \lambda_s^* S^* \left(\frac{I_s S}{I_s^* S^*} - \frac{I_s}{I_s^*} - ln\frac{S}{S*}\right) + \sigma V^* \lambda_s^* \left(\frac{I_s V}{I_s^* S_*} - ln\frac{V}{V^*}\right) + \kappa R^* \lambda_s^* \left(\frac{I_s R}{I_s^* R^*} - \frac{I_s}{I_s^*} - ln\frac{R}{R^*}\right) \\
&\quad + (S^* + \sigma V^* + \kappa R^*)\lambda_s^* \left(\frac{I_s}{I_s^*} - \frac{H_s}{H_s^*} + ln\frac{H_s}{H_s^*} - ln\frac{I_s}{I_s^*}\right) \\
&=: a_{32}G_{32} + a_{31}G_{31} + a_{37}G_{37} + a_{35}G_{35}
\end{aligned}
$$

$$
\begin{aligned}
D_4^{'} &= \left(1-\frac{L_s^*}{L_s}\right) L_s^{'} = \left(1-\frac{L_s^*}{L_s}\right) (\alpha\epsilon(1-p)H_s - (\gamma+\mu)L_s) \\
&= \alpha\epsilon(1-p)H_s^* \left(1-\frac{L_s^*}{L_s}\right) \left(\frac{H_s^*}{H_s} - \frac{L_s^*}{L_s}\right) = \alpha\epsilon(1-p)H_s^* \left(1 - \frac{L_s^*}{L_s} + \frac{H_s^*}{H_s} - \frac{H_s^*}{H_s}\frac{L_s^*}{L_s}\right) \\
&\leq \alpha\epsilon(1-p)H_s^* \left(-\frac{L_s^*}{L_s} - ln\frac{L_s^*}{L_s}\frac{H_s^*}{H_s} + \frac{H_s^*}{H_s}\right) \\
&\leq \alpha\epsilon(1-p)H_s^* \left(-\frac{L_s}{L_s^*} + ln\frac{L_s}{L_s^*} - ln\frac{H_s}{H_s^*} + \frac{H_s}{H_s^*}\right) = a_{43}G_{43}
\end{aligned}
$$

$$
\begin{aligned}
D_5^{'} &= \left(1-\frac{I_s^*}{I_s}\right) I_s^{'} = \left(1-\frac{I_s^*}{I_s}\right) (\gamma\eta L_s + \alpha(1-\epsilon)(1-p)H_s - (\rho_s+\mu+d_s)I_s) \\
&= \left(1-\frac{I_s^*}{I_s}\right) (\gamma\eta L_s + \alpha(1-\epsilon)(1-p)H_s - (\gamma\eta L_s^* + \alpha(1-\epsilon)(1-p)H_s^*)\frac{I_s}{I_s^*} \\
&= \gamma\eta L_s^* \left(1 - \frac{I_s}{I_s^*} - \frac{I_s}{I_s^*}\frac{L_s}{L_s^*} + \frac{L_s}{L_s^*}\right) + \alpha(1-\epsilon)(1-p)H_s^* \left(1 - \frac{I_s}{I_s^*} - \frac{I_s}{I_s^*}\frac{H_s}{H_s^*} + \frac{H_s}{H_s^*}\right) \\
&\leq \gamma\eta L_s^* \left(-\frac{I_s}{I_s^*} - ln\frac{I_s}{I_s^*}\frac{L_s}{L_s^*} + \frac{L_s}{L_s^*}\right) + \alpha(1-\epsilon)(1-p)H_s^* \left(-\frac{I_s}{I_s^*} - ln\frac{I_s}{I_s^*}\frac{H_s}{H_s^*} + \frac{H_s}{H_s^*}\right) \\
&\leq \gamma\eta L_s * \left(\frac{I_s}{I_s^*} + ln\frac{I_s}{I_s^*} - ln\frac{L_s}{L_s^*} + \frac{L_s}{L_s^*}\right) + \alpha(1-\epsilon)(1-p)H_s^* \left(-\frac{I_s}{I_s^*} + ln\frac{I_s}{I_s^*} - ln\frac{H_s}{H_s^*} + \frac{H_s}{H_s^*}\right) \\
&=: a_{54}G_{54} + a_{53}G_{53}
\end{aligned}
$$

$$
\begin{aligned}
D_6^{'} &= \left(1-\frac{T_s^*}{T_s}\right) T_s^{'} = \left(1-\frac{T_s^*}{T_s}\right) (\alpha p H_s - (\phi+\mu)T_s) \\
&= (\phi+\mu)T_s^* \left(1-\frac{T_s^*}{T_s}\right) \left(\frac{H_s}{H_s^*} - \frac{T_s^*}{T_s}\right) = (\phi+\mu)T_s^* \left(\frac{H_s}{H_s^*} - \frac{T_s}{T_s^*} - \frac{T_s^*}{T_s}\frac{H_s}{H_s^*} + 1\right) \\
&\leq (\phi+\mu)T_s^* \left(\frac{H_s}{H_s^*} - \frac{T_s}{T_s^*} - ln\frac{T_s^*}{T_s}\frac{H_s}{H_s^*}\right) \leq (\phi+\mu)T_s^* \left(\frac{H_s}{H_s^*} - ln\frac{H_s}{H_s^*} - \frac{T_s}{T_s^*} + ln\frac{T_s}{T_s^*}\right) =: a_{63}G_{63}
\end{aligned}
$$

$$
\begin{aligned}
D_7' &= \left(1-\frac{R^*}{R}\right)R' = \left(1-\frac{R^*}{R}\right)(\gamma(1-\eta)L_s + \phi T_s - (\kappa\lambda_s+\mu)R) \\
&= \left(1-\frac{R^*}{R}\right)(\gamma(1-\eta)L_s + \phi T_s - \kappa\lambda_s R - (\rho_s I_s^* + \gamma(1-\eta)\frac{L_s^*}{R^*} + \phi\frac{T_s^*}{R^*} - \kappa\lambda_s^*)R) \\
&= \rho_s I_s^*\left(\frac{I_s}{I_s^*} - ln\frac{I_s}{I_s^*} + ln\frac{R}{R^*} - \frac{R}{R^*}\right) + \gamma(1-\eta)L_s^*\left(1 - \frac{R}{R*} - \frac{L_s}{L_s^*}\frac{R^*}{R} + \frac{L_s}{L_s^*}\right) \\
&\quad + \phi T_s^*\left(1 - \frac{R}{R^*} - \frac{T_s}{T_s^*}\frac{R^*}{R} + \frac{T_s}{T_s^*}\right) + \kappa I_s^* R^*\left(\frac{R}{R^*} - 1 - \frac{R}{R^*}\frac{I_s}{I_s^*} + \frac{I_s}{I_s^*}\right) \\
&\leq \rho_s I_s^*\left(\frac{I_s}{I_s^*} - ln\frac{I_s}{I_s^*} + ln\frac{R}{R*} - \frac{R}{R*}\right) + \gamma(1-\eta)L_s^*\left(-\frac{R}{R*} - ln\frac{L_s}{L_s^*}\frac{R}{R*} + \frac{L_s}{L_s^*}\right) \\
&\quad + \phi T_s^*\left(-\frac{R}{R*} - ln\frac{T_s}{T_s^*}\frac{R^*}{R} + \frac{T_s}{T_s^*}\right) + \kappa I_s^* R^*\left(\frac{R}{R*} - 2 - ln\frac{R}{R*}\frac{I_s}{I_s^*} + \frac{I_s}{I_s^*}\right) \\
&\leq \rho_s I_s^*\left(\frac{I_s}{I_s^*} - ln\frac{I_s}{I_s^*} + ln\frac{R}{R^*} - \frac{R}{R^*}\right) + \gamma(1-\eta)L_s^*\left(-\frac{R}{R^*} + ln\frac{R}{R^*} - ln\frac{L_s}{L_s^*} + \frac{L_s}{L_s^*}\right) \\
&\quad + \phi T_s^*\left(-\frac{R}{R^*} + ln\frac{R}{R^*} - ln\frac{T_s}{T_s^*} + \frac{T_s}{T_s^*}\right) + \kappa I_s^* R^*\left(\frac{R}{R^*} - 2 - ln\frac{R}{R^*}\frac{I_s}{I_s^*} + \frac{I_s}{I_s^*}\right) \\
&=: a_{74}G_{74} + a_{76}G_{76} + a_{75a}G_{75a} + a_{75b}G_{75b}
\end{aligned}
$$

Where, $a_{15} = a_{31} = \sigma V^*\lambda_s^*$, $a_{21} = \theta$,$a_{25} = a_{32} = S^*\lambda_s^*$, $a_{37} = \kappa R^*\lambda_s^*$, $a_{35} = (S^* + \sigma V^* + \kappa R^*)\lambda_s^*$, $a_{43} = \alpha\epsilon(1-p)H_s^*$, $a_{54} = \gamma\eta L_s^*$,$a_{53} = \alpha(1-\epsilon)(1-p)H_s^*$, $a_{63} = (\phi+\mu)T_s^*$, $a_{74} = \rho_s I_s^*$, $a_{76} = \gamma(1-\eta)L_s^*$, $a_{75a} = \phi T_s^*$, $a_{75b} = \kappa\lambda_s^* R^*$ and all other $a_{ij} = 0$

With the constants a_{ij} above and $A = [a_{ij}]$ *for* $i, j = 1, ..., 7, 5a, 5b$, we construct the directed graph $G(A)$ as Figure 5.2.

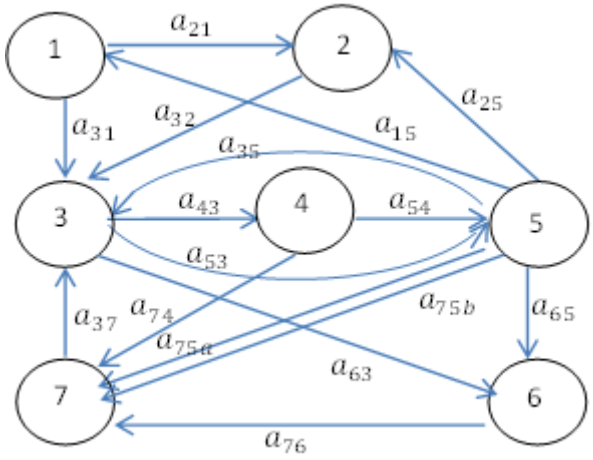

Figure 5.2: The digraph G(A) for dynamical system (5.1)-(5.6),(5.10).

The associated weighted digraph G(A) (figure 5.2) has seven vertices. Along the cycles

in figure 5.2:
$G_{35}+G_{53}=\frac{I_s}{I_s^*}-\frac{H_s}{H_s^*}+ln\frac{H_s}{H_s^*}-ln\frac{I_s}{I_s^*})+(-\frac{I_s}{I_s^*}+ln\frac{I_s}{I_s^*}-\frac{H_S}{H_s^*}+\frac{H_s}{H_s^*})=0$ and
$G_{35}+G_{43}+G_{54}=(\frac{I_s}{I_s^*}-\frac{H_s}{H_s^*}+ln\frac{H_s}{H_s^*}-ln\frac{I_s}{I_s^*})+(-\frac{L_s}{L_s^*}+ln\frac{L_s}{L_s^*}-ln\frac{H_s}{H_s^*}+\frac{H_s}{H_s^*})+(-\frac{I_s}{I_s^*}+ln\frac{I_s}{I_s^*}-ln\frac{L_s}{L_s^*}+\frac{L_s}{L_s^*})=0.$
And for the other cycles in figure 5.2, $\sum G_{ij}\leq 0$, if $\frac{V}{V^*}$, $\frac{S}{S^*}$, $\frac{R}{R^*}\leq 1$ and $\frac{H_s}{H_s^*}\leq\frac{I_s}{I_s^*}$. By Proposition 1.3 of [109], there exists $c_i>0, i=1,\ldots,7$ such that $D=\Sigma_{i=1}^7 c_i D_i$ is a Lyapunov function for equations (5.1)-(5.6),(5.10). The relations between c_i's can be derived from Theorems 3.3 and 3.4 of [109] such that:

$a_{32}>0$ and $d^+(2)=1$ implies $c_3a_{32}=\Sigma_{k=1}^7 c_2a_{2k}$

$$\Rightarrow c_3a_{32}=c_2(a_{21}+a_{25})\Rightarrow c_3=c_2\frac{a_{21}+a_{25}}{a_{32}}$$

$a_{15}>0$ and $d^-(1)=1$ implies $c_1a_{15}=\Sigma_{k=1}^7 c_ka_{k1}$

$$\Rightarrow c_1a_{15}=c_2a_{21}+c_3a_{31}\Rightarrow c_1=c_2\frac{(a_{21}a_{32}+a_{31}(a_{21}+a_{25}))}{(a_{32}a_{15})}$$

$a_{43}>0$ and $d^-(4)=1$ implies $c_4a_{43}=\Sigma_{k=1}^7 c_ka_{k4}$

$$\Rightarrow c_4a_{43}=c_5a_{54}\Rightarrow c_4=c_5\frac{a_{54}}{a_{43}}$$

$a_{37}>0$ and $d^+(7)=1$ implies $c_3a_{37}=\Sigma_{k=1}^7 c_7a_{7k}$

$$\begin{aligned}\Rightarrow & c_3a_{37}=c_7(a_{74}+a_{75a}+a_{75b}+a_{76})\\ \Rightarrow & c_7=c_3\frac{a_{37}}{(a_{74}+a_{75a}+a_{75b}+a_{76})}\\ \Rightarrow & c_7=c_2\frac{a_{37}(a_{21}+a_{25})}{(a_{32}(a_{74}+a_{75a}+a_{75b}+a_{76}))}\end{aligned}$$

$a_{76}>0$ and $d^+(6)=1$ implies $c_7a_{76}=\Sigma_{k=1}^7 c_6a_{6k}\Rightarrow c_7a_{76}=c_6(a_{65}+a_{63})$

$$\Rightarrow c_6=c_7\frac{a_{76}}{(a_{65}+a_{63})}\Rightarrow c_6=c_2\frac{(a_{76}a_{37}(a_{21}+a_{25}))}{(a_{32}(a_{65}+a_{63})(a_{74}+a_{75a}+a_{75b}+a_{76}))}$$

Therefore, $D=c_1D_1+c_2D_2+c_3D_3+c_4D_4+c_5D_5+c_6D_6+c_7D_7$ is a Lyapunov function for (5.1)$-$ (5.6), (5.10). Therefore, E_2 is globally asymptotically stable in the interior of Ω when R_{eff} (DS)$>1>R_{eff}$ (MDR) . □

5.4.2 The Multi-Drug Resistant TB Strain only Equilibrium Point

This equilibrium solution is obtained by setting $\lambda_s = 0$ in equations (5.1)−(5.10) of the model. The multi-drug resistant TB expressed only in terms of the equilibrium value of the force of infection λ_r^* is given by:

$$E_2 = (V^*, S^*, 0, 0, 0, 0, E^*, I_r^*, T_r^*, R^*)$$

From equation (5.1) the dynamical system (5.1)−(5.10):

$$\frac{dV}{dt} = \psi\Lambda - (\sigma(\lambda_s + \lambda_r) + \theta + \mu)V = 0 \Rightarrow V^* = \frac{\psi\Lambda}{(\sigma\lambda_r^* + \theta + \mu)}$$

From equation (5.2) the dynamical system (5.1)−(5.10):

$$\begin{aligned} \frac{dS}{dt} &= (1-\psi)\Lambda + \theta V - (\lambda_s + \lambda_r + \mu)S = 0 \\ \Rightarrow S^* &= \frac{(1-\psi)\Lambda + \theta V^*}{(\lambda_s^* + \lambda_r^* + \mu)} = \frac{\Lambda[(1-\psi)\sigma\lambda_r^* + \theta + (1-\psi)\mu]}{(\lambda_r^* + \mu)[\sigma\lambda_r^* + \theta + \mu]} \end{aligned}$$

Since $\lambda_s = 0$, from equation (5.3), (5.4), (5.5), and (5.6)of the dynamical system (5.1)−(5.10), we have: $H_s^* = L_s^* = I_s^* = T_s^* = 0$

From equation (5.7) the dynamical system (5.1)−(5.10):

$$\begin{aligned} \frac{dE}{dt} =& \lambda_r(S + H_s + L_s + \sigma V + \kappa R) + (1-q)\rho_s I_s - (\lambda + \mu)E = 0 \\ \Rightarrow E^* =& \frac{\lambda_r^*(S^* + H_s^* + L_s^* + \sigma V^* + \kappa R^*) + (1-q)\rho_s I_s}{(\delta + \mu)} = \frac{\lambda_r^*(S^* + \sigma V^* + \kappa R^*)}{(\delta + \mu)} \\ =& \frac{\lambda_r^*}{(\delta + \mu)} \frac{\Lambda(1-\psi)\sigma\lambda_r^* + \theta + (1-\psi)\mu}{(\lambda_r^* + \mu)[\sigma\lambda_r^* + \theta + \mu]} + \frac{\sigma\psi\Lambda}{(\sigma\lambda_r^* + \theta + \mu)} \\ &+ \kappa I_r^* \frac{\rho_r(\varphi + \mu)(1-\nu)\delta + \varphi\nu\delta(\rho_r + \mu + d_r)}{(\kappa\lambda_r^* + \mu)(\varepsilon + \mu)(1-\nu)\delta)} \end{aligned}$$

From equation (5.8) the dynamical system (5.1)−(5.10):

$$\begin{aligned} \frac{dI_r}{dt} &= (1-\nu)\delta E - (\rho_r + \mu + d_r)I_r = 0 \\ \Rightarrow I_r^* &= \frac{(1-\nu)\delta}{(\rho_r + \mu + d_r)} E^* \Rightarrow E^* = \frac{(\rho_r + \mu + d_r)}{(1-\nu)\delta} I_r^* \end{aligned}$$

From equation (5.9) the dynamical system (5.1)−(5.10):

$$\frac{dT_s}{dt} = \nu\delta E - (\varphi + \mu T_r = 0 \Rightarrow T_r^* = \frac{\nu\delta E^*}{(\varphi + \mu)} = \frac{\nu\delta(\rho_r + \mu + d_r)}{(\varphi + \mu)(1-\nu)\delta} I_r^*$$

From equation (5.10) the dynamical system (5.1)−(5.10):

$$\begin{aligned}\frac{dR}{dt} &= q\rho_s I_s + \rho_r I_r + \gamma(1-\eta)L_s + \phi T_s + \varphi T_r - (\kappa(\lambda_s+\lambda_r)+\mu)R = 0\\ R^* &= \frac{(\rho_s I_s^* + \rho_r I_r^* + \gamma(1-\eta)L_s^* + \phi T_s^* + \varphi T_r^*)}{((\kappa(\lambda_s^*+\lambda_r^*)+\mu))}\\ &= \frac{(\rho_r I_r^* + \varphi T_r^*)}{(\kappa\lambda_r^*+\mu)} = \frac{\rho_r(\varphi+\mu)(1-\nu)\delta + \varphi\nu\delta(\rho_r+\mu+d_r)}{(\kappa\lambda_r^*+\mu)(\varphi+\mu)(1-\nu)\delta} I_r^*\end{aligned}$$

Therefore, the multi-drug resistant TB-strain only equilibrium is given as:
$E_2 = (V^*, S^*, 0, 0, 0, 0, E^*, I_r^*, T_r^*, R^*)$ where,

$$\begin{aligned}V^* &= \frac{\psi\Lambda}{\sigma\lambda_r^*+\theta+\mu}, S^* = \frac{\Lambda[(1-\psi)\sigma\lambda_r^*+\theta+(1-\psi)\mu]}{(\lambda_r^*+\mu)[\sigma\lambda_r^*+\theta+\mu]}, E^* = \frac{(\rho_r+\mu+d_r)}{(1-\nu)\delta} I_r^*,\\ T_r^* &= \frac{\nu\delta(\rho_r+\nu+d_r)}{(\varphi+\mu)(1-\nu)\delta} I_r^*, R^* = \frac{\rho_r(\varphi+\mu)(1-\nu)\delta + \varphi\nu\delta(\rho_r+\mu+d_r)}{(\kappa\lambda_r^*+\mu)(\varphi+\mu)(1-\nu)\delta}\end{aligned}$$

Existence of multi-drug resistance TB-strain only equilibrium

As the multi drug resistance TB-strain only equilibrium E_2 given in terms λ_r the existence of the equilibrium value of the force of infection λ_r shows the existence of E_2. Therefore, we are going to put the conditions that λ_r exists.
At multi-drug resistance TB-strain only equilibrium we have:

$$\lambda_r^* = \frac{c\omega_r\mu}{\Lambda} I_r^*$$

where $N^*(t)$ is replaced by its limiting value, $N^* = \frac{\Lambda}{\mu}$

$$\begin{aligned}\Rightarrow \lambda_r^* &= \frac{c\omega_r\mu(1-\nu)\delta}{\Lambda(\rho_r+\mu+d_r)} E^*\\ &= \frac{\mu(\theta)+mu}{\Lambda(\sigma\psi\mu+(\theta+(1-\psi)\mu))} \frac{(\sigma\psi\mu+(\theta+(1-\psi)\mu))}{(\theta+\mu)} \frac{c\omega_r(1-\nu)\delta}{(\delta+\mu)(\rho_r+\mu+d_r)} \lambda_r^*(S^*+\sigma V^*+\kappa R^*)\\ \Rightarrow \lambda_r^* &= \frac{\mu(\theta+\mu)}{(\Lambda+(\theta+(1-\psi)\mu)))} R_{eff}(MDR)\lambda_r^*(S^*+\sigma V^*+\kappa R^*)\\ \Rightarrow \lambda_r^* &= e_1 R_{eff}(MDR)\lambda_r^*\{\frac{((1-\psi)\sigma\lambda_r^*+\theta+(1-\psi)\mu+\sigma\psi(\lambda_r^*+\mu))}{(\lambda_r^*+\mu)[\sigma\lambda_r^*+\theta+\mu]} + e_2\frac{\lambda_r^*}{(\kappa\lambda_r^*+\mu)}\}\end{aligned}$$

Where, $e_1 = \frac{\mu(\theta+\mu)}{[\sigma\psi\mu+(\theta+(1-\psi)\mu)]}, e_2 = \frac{([\rho_r(\varphi+\mu)(1-\nu)\delta+\varphi\nu\delta(\rho_r+\mu+d_r)])}{(c\omega_r\mu(\varphi+\mu)(1-\nu)\delta)}$

$$\Rightarrow \lambda_r^* = e_1 R_{eff}(MDR)\lambda_r^* \{\frac{(\sigma\lambda_r^* + \theta + (1-\psi)\mu + \sigma\psi\mu)}{(\lambda_r^* + \mu)[\sigma\lambda_r^* + \theta + \mu]} + e_2 \frac{\lambda_r^*}{(\kappa\lambda_r^* + \mu)}\}$$

$$\Rightarrow \lambda_r^*(\lambda_r^* + \mu)(\sigma\lambda_r^* + e_4)(\kappa\lambda_r^* + \mu)$$

$$= e_1 R_{eff}\lambda_r^*(\sigma\lambda_r^* + e_3)(\kappa\lambda_r^* + \mu) + e_2\lambda_r^*(\lambda_r^* + \mu)(\sigma\lambda_r * + e_4)$$

where, $e_3 = \theta + (1-\psi)\mu + \sigma\psi\mu, e_4 = \theta + \mu$

$$\Rightarrow \sigma\kappa(\lambda_r^*)^4 + \{\mu\sigma\kappa + \kappa\theta + \mu\kappa + \mu\sigma\}(\lambda_r^*)^3 + \mu[e_4 + \kappa e_4 + \mu\sigma](\lambda_r^*)^2 + \mu^2 e_4\lambda_r^*$$

$$= e_1 R_{eff}(MDR)\{e_2\sigma(\lambda_r^*)^4 + [e_2(\mu\sigma + e_4) + \sigma\kappa](\lambda_r^*)^3 + [e_2 e_4\mu + (e_3\kappa + \mu\sigma)](\lambda_r^*)^2 + e_3\mu\lambda_r^*\}$$

$$\Rightarrow \{\sigma\kappa - R_{eff}(MDR)e_1e_2\sigma\}(\lambda_r^*)^4 + \{\mu\sigma\kappa + \kappa\theta + \mu\kappa + \mu\sigma\}(\lambda_r^*)^3 + \{\mu[e_4 + \kappa e_4 + \mu\sigma]$$

$$- R_{eff}(MDR)e_1[e_2e_4\mu + (e_3\kappa + \mu\sigma)]\}(\lambda_r^*)^2 + \{\mu^2 e_4 - R_{eff}(MDR)e_1e_3\mu\}\lambda_r^* = 0$$

$$\Rightarrow D_1(\lambda_r^*)^4 + D_2(\lambda_r^*)^3 + D_3(\lambda_r^*)^2 + D_4\lambda_r^* = 0 \tag{5.22}$$

Where,

$$D_1 = \sigma\kappa - R_{eff}(MDR)e_1e_2\sigma$$

$$D_2 = \mu\sigma\kappa + \kappa\theta + \mu\kappa + \mu\sigma - R_{eff}(MDR)e_1[e_2(\mu\sigma + e_4) + \sigma\kappa]$$

$$D_3 = \mu[e_4 + \kappa e_4 + \mu\sigma] - R_{eff}(MDR)e_1[e_2e_4\mu + (e_3\kappa + \mu\sigma)]$$

$$D_4 = \mu^2 e_4 - R_{eff}(MDR)e_1e_3\mu$$

The solutions for the quartic polynomial (5.22) are $\lambda_r^* = 0$ and $D_1(\lambda_r^*)^3 + D_2(\lambda_r^*)^2 + D_3\lambda_r^* + D_4 = 0$. The case $\lambda_r^* = 0$ corresponds to no multi drug resistance TB and $D_1(\lambda_r^*)^3 + D_2(\lambda_r^*)^2 + D_3\lambda_r^* + D_4 = 0$ corresponds to the existence of at most three multi-drug resistance TB only endemic equilibrium points.

Remark:
The TB model system (5.1)−(5.10) has:

a) one positive multi-drug resistance TB only endemic equilibrium if $D_2/D_1 < 0$, and $D_3 = D_4 = 0$.

b) two positive multi-drug resistance TB only endemic equilibrium if $D_2/D_1 < 0$, $D_3/D_1 > 0$ and $D_4 = 0$.

c) three positive multi-drug resistance TB only endemic equilibrium if $D_2/D_1 < 0$, $D_3/D_1 > 0$ and $D_4/D_1 < 0$.

d) no positive multi-drug resistance TB only endemic equilibrium otherwise.

Theorem 5.10. *The model (5.1)-(5.10) has unique multi-drug resistance TB only endemic equilibrium if $D_2/D_1 < 0$ and $D_3 = D_4 = 0$. That is, the model (5.1)-(5.10) has unique drug resistance TB only endemic equilibrium $\lambda_r^* = n^* = -D_2/D_1$.*

Proof. Since $D_3 = D_4 = 0$, from quadric polynomial (5.22), $D_1{\lambda_r}^{*4} + D_2{\lambda_r}^{*3} + D_3{\lambda_r}^{*2} + D_4{\lambda_r}^* = 0$ we have ${\lambda_r}^{*3}(D_1{\lambda_r}^* + D_2) = 0$. Then the only positive multi-drug resistance TB only endemic equilibrium is $\lambda_r^* = -D_2/D_1$. The model (5.1)-(5.10) has unique multi-drug resistance TB only endemic equilibrium if $D_2/D_1 < 0$ and $D_3 = D_4 = 0$. That is $\frac{D_2}{D_1} < \frac{\mu\sigma\kappa+\kappa\theta+\mu\kappa+\mu\sigma-R_{eff}(MDR)e_1[e_2(\mu\sigma+e_4)+\sigma\kappa]}{\sigma\kappa-R_2e_1e_2\sigma} < 0$. This implies that, if $\frac{\mu\sigma\kappa+\kappa\theta+\mu\kappa+\mu\sigma}{e_1[e_2(\mu\sigma+e_4)+\sigma\kappa]} < \frac{\kappa}{e_1e_2}$ then $\frac{\mu\sigma\kappa+\kappa\theta+\mu\kappa+\mu\sigma}{e_1[e_2(\mu\sigma+e_4)+\sigma\kappa]} < R_{eff}(MDR) < \frac{\kappa}{e_1e_2}$ or if $\frac{\mu\sigma\kappa+\kappa\theta+\mu\kappa+\mu\sigma}{e_1[e_2(\mu\sigma+e_4)+\sigma\kappa]} > \frac{\kappa}{e_1e_2}$ then $\frac{\mu\sigma\kappa+\kappa\theta+\mu\kappa+\mu\sigma}{e_1[e_2(\mu\sigma+e_4)+\sigma\kappa]} > R_{eff}(MDR) > \frac{\kappa}{e_1e_2}$ □

Remark:

If $0 < q < 1$ treatment of multi-drug sensitive is not 100% efficient due to non-compliance, then there are two possible endemic equilibria for system (5.1)-(5.10), namely, E_2 (only the multi-drug resistance equilibrium), and the interior equilibrium point E_3 (when both strains exist). But there is no multi-drug sensitive only equilibrium E_1 for the dynamical system (5.1)-(5.10) and the multi-drug resistant TB-strain only equilibrium E_2 in the case $0 < q < 1$ is identical in the case $q = 1$.

Local stability of the Multi-Drug Resistant TB Strain only Equilibrium Point

Theorem 5.11. *The multi-drug resistance TB only equilibrium point E_2 of Model (5.1), (5.2), (5.7)-(5.10) is locally asymptotically stable if R_{eff} (DS) $< 1 < R_{eff}$ (MDR) and $R^* < \frac{\Lambda(\mu+d_r)}{c\omega_r\kappa\mu}$*

Proof. The Jacobean matrix of the dynamical system (5.1), (5.2), (5.7)-(5.10) at equilib-

rium E_2 is given by:

$$J(E_2) = \begin{bmatrix} f_1 & 0 & 0 & a_1 & 0 & 0 \\ \theta & f_2 & 0 & a_2 & 0 & 0 \\ \sigma n^* & n^* & f_3 & y & 0 & \kappa n^* \\ 0 & 0 & (1-\nu)\delta & f_4 & & 0 \quad 0 \\ 0 & 0 & \nu\delta & 0 & g_5 & 0 \\ 0 & 0 & 0 & \rho_r & \varphi & g_6 \end{bmatrix}$$

Where,

$$n^* = \frac{\sigma\mu(1+\kappa) + \kappa(\theta+\mu) - R_{eff}(MDR)e_1\kappa((\sigma\mu+\theta+\mu)+\sigma)}{\sigma\kappa(R_{eff}(MDR)e_1e_2 - 1)}, e_1 = \frac{\mu(\theta+\mu)}{[\sigma\psi\mu + (\theta+(1-\psi)\mu)]}$$

$$e_2 = \frac{[\rho_r(\varphi+\mu)(1-\nu)\delta + \varphi\nu\delta(\rho_r+\mu+d_r)]}{c\omega_r\mu(\varphi+\mu)(1-\nu)\delta}, f_1 = -(\sigma n^* + \theta + \mu), f_2 = -(n^* + \mu),$$

$$f_3 = -(\delta+\mu), f_4 = -(\rho_r+\mu+d_r), f_5 = -(\varphi+\mu), f_6 = -(\kappa n^* + \mu), a_1 = -\frac{\sigma c\omega_r V^*}{N^*}$$

$$a_2 = -\frac{c\omega_r S^*}{N^*}, y = -\frac{c\omega_r\mu}{\Lambda}(S^* + \sigma V^* + \kappa R^*)$$

The characteristic equation of the matrix $J(E_2)$ is given by $|J(E_2) - \lambda I| = 0$:

$$\begin{vmatrix} f_1-\lambda & 0 & 0 & a_1 & 0 & 0 \\ \theta & f_2-\lambda & 0 & a_2 & 0 & 0 \\ \sigma n^* & n^* & f_3-\lambda & y & 0 & \kappa n^* \\ 0 & 0 & (1-\nu)\delta & f_4-\lambda & & 0 \quad 0 \\ 0 & 0 & \nu\delta & 0 & g_5-\lambda & 0 \\ 0 & 0 & 0 & \rho_r & \varphi & g_6-\lambda \end{vmatrix} = 0$$

Now we apply the Gershgorin circle theorem,[83] to determine the sign of the eigenvalues of the characteristic equation $|J(E_2) - \lambda I| = 0$. From the first column of the Jacobian matrix $J(E_2)$ the dynamical system (5.1), (5.2), (5.7)-(5.10),

$$|f_1| = (\sigma n^* + \theta + \mu) \text{ and } \Sigma_{i=1,i\neq1}^6 c_{i1} = \theta + \sigma n^*$$
$$\Rightarrow |f_1| > \Sigma_{i=1,i\neq1}^6 c_{i1}$$

From the second column of the Jacobian matrix $J(E_2)$ of the dynamical system (5.1), (5.2), (5.7)-(5.10),

$$|f_2| = (n^* + \mu), \text{ and } \Sigma_{i=1,i\neq2}^6 c_{i2} = n^* \Rightarrow |f_2| > \Sigma_{i=1,i\neq2}^6 c_{i2}$$

From the third column of the Jacobian matrix $J(E_2)$ of the dynamical system (5.1), (5.2), (5.7)-(5.10),

$$|f_3| = (\delta + \mu), \ and \ \Sigma_{i=1,i\neq 3}^{6} c_{i3} = \delta(1-\nu) + \delta(1-\nu) = \delta$$
$$\Rightarrow |f_3| > \Sigma_{i=1,i\neq 3}^{6} c_{i3}$$

From the fourth column of the Jacobian matrix $J(E_2)$ of the dynamical system (5.1), (5.2), (5.7)-(5.10),

$$|f_4| = \rho_r + \mu + d_r and \ \Sigma_{i=1,i\neq 4}^{6} c_{i4} = a_1 + a_2 + y + \rho_r = \frac{c\omega_r}{N^*}\kappa R^* + \rho_r$$

If we let $N^* = \frac{\Lambda}{\mu}$, then $\Sigma_{i=1,i\neq 4}^{6} c_{i4} = \frac{c\omega_r \mu\kappa}{\Lambda} R^* + \rho_r$. $\Rightarrow |f_4| > \Sigma_{i=1,i\neq 4}^{6} c_{i4}$ if $R^* < \frac{\Lambda(d_r+\mu)}{c\omega_r\mu\kappa}$.

From the fifth column of the Jacobian matrix $J(E_2)$ of the dynamical system (5.1), (5.2), (5.7)-(5.10),

$$|f_5| = (\varphi + \mu) and \ \Sigma_{i=1,i\neq 5}^{6} c_{i5} = \varphi \Rightarrow |g_5| > \Sigma_{i=1,i\neq 5}^{6} c_{i5}$$

From the sixth column of the Jacobian matrix $J(E_2)$ of the dynamical system (5.1), (5.2), (5.7)-(5.10),

$$|f_6| = (\kappa N^* + \mu) and \ \Sigma_{i=1,i\neq 6}^{6} c_{i6} = \kappa N^* \Rightarrow |f_6| > \Sigma_{i=1,i\neq 6}^{6} c_{i6}$$

The matrix $J(E_2)$ is a strictly column diagonally dominant matrix and also all diagonal elements of $J(E_2)$ are negative, if $R^* < \frac{\Lambda(\mu+d_r)}{c\omega_r\kappa\mu}$. Hence, all eigenvalues of $J(E_2)$ has negative real part if $R_{eff}(DS) < 1 < R_{eff}(MDR)$ and $R^* < \frac{\Lambda(\mu+d_r)}{c\omega_r\kappa\mu}$.Therefore, the multi-drug resistance TB only equilibrium E_2 is locally asymptotically stable if $R_{eff}(DS) < 1 < R_{eff}(MDR)$ and $R^* < \frac{\Lambda(\mu+d_r)}{c\omega_r\kappa\mu}$. □

Global Stability of Multi Drug Resistant TB only Endemic Equilibrium Point

Theorem 5.12. *The multi-drug resistance TB only equilibrium E_2 of Model (5.1), (5.2), (5.7)-(5.10) is globally asymptotically stable if $R_{eff}(DS) < 1 < R_{eff}(MDR)$ and $\frac{V}{V^*}, \frac{S}{S^*}, \frac{R}{R^*} \leq 1$ and $\frac{E}{E^*} \leq \frac{I_r}{I_r^*}$.*

Proof. We use a graph-theoretic method as in [109] to construct a lyapunov function.

We define functions: $Q_1 = V - V^* - V^* ln\frac{V}{V^*}$, $Q_2 = S - S^* - S^* ln\frac{S}{S^*}$, $Q_3 = E - E^* - E^* ln\frac{E}{E^*}$, $Q_4 = T_r - T_r^* - T_r^* ln\frac{T_r}{T_r^*}$, $Q_5 = I_r - I_r^* - I_r^* ln\frac{I_r}{I_r^*}$, $Q_6 = R - R^* - R^* ln\frac{R}{R^*}$ Where $E_2 = (V^*, S^*, E^*, T_r^*, I_r^*, R^*)$ is the multi-drug resistant TB only endemic equilibrium.

Differentiating the functions $Q_i for i = 1, ..., 6$ with respect to time we have :

$$Q_1{}' = \left(1 - \frac{V^*}{V}\right)\dot{V}, Q_2{}' = \left(1 - \frac{S^*}{S}\right)\dot{S}, Q_3{}' = \left(1 - \frac{E^*}{E}\right)\dot{E},$$
$$Q_4{}' = \left(1 - \frac{{I_r}^*}{I_r}\right) I_r \, Q_5{}' = \left(1 - \frac{{T_r}^*}{T_r}\right) T_r \; and \; Q_6{}' = \left(1 - \frac{R^*}{R}\right)\dot{R}$$

Substituting their respective derivatives we get:

$$Q_1{}' = \left(1 - \frac{V^*}{V}\right)\{\psi\Lambda - (\sigma\lambda_s + \theta + \mu)\, V \,\}$$
$$Q_2{}' = \left(1 - \frac{S^*}{S}\right)\{(1-\psi)\,\Lambda + \theta V - (\lambda_s + \mu)\, S\}$$
$$Q_3{}' = \left(1 - \frac{E^*}{E}\right)\{\lambda_r\,(S + \sigma V + \kappa R) - (\delta + \mu)\, E \,\}$$
$$Q_4{}' = \left(1 - \frac{{I_r}^*}{I_r}\right)\{(1-\nu)\,\delta E \; - (\rho_r + \mu + d_r)\, I_r\}$$
$$Q_5{}' = \left(1 - \frac{{T_r}^*}{T_r}\right)\{\nu\delta E - (\varphi + \mu)\, T_r\}$$
$$Q_6{}' = \left(1 - \frac{R^*}{R}\right)\{\rho_r I_r + \varphi T_r - (\kappa\lambda_r + \mu)\, R\}$$

At the endemic equilibrium point E_2 we have:

$$\psi\Lambda = (\sigma {\lambda_r}^* + \theta + \mu)\, V^*, (1-\psi)\,\Lambda = -\theta V^* \; + ({\lambda_r}^* + \mu)\, S^*$$
$$(\delta + \mu) = \frac{{\lambda_r}^*\,(S^* \; + \sigma V^* \; + \kappa R^*)}{E^*}, (\rho_r + \mu + d_r) = (1-\nu)\,\delta\frac{E^*}{{I_r}^*}$$
$$(\varphi + \mu) = \nu\delta\frac{E^*}{{T_r}^*} and \;\; \mu = \rho_r\frac{{I_r}^*}{R^*} + \varphi\frac{{T_r}^*}{R^*} - \kappa {\lambda_r}^*$$

Using the inequality, $1 - x + lnx \leq 0$ for all $x > 0$ at the endemic equilibrium point E_2 we get:

$$Q_1^{'} \leq \sigma V^* \lambda_r^* \left(\frac{I_r}{I_r^*} - ln\frac{V^*}{V} - \frac{I_r V}{I_r^* V^*}\right) =: b_{14} Q_{14}$$
$$Q_2^{'} \leq \theta V^* \left(-2 - ln\frac{V}{V^*} - ln\frac{S}{S^*} + \frac{S^*}{S} + \frac{V}{V^*}\right) =: b_{21} Q_{21}$$

$$
\begin{aligned}
Q_3^{'} \leq & \lambda_r^*(S^* + \sigma V^* + \kappa R^*)\left(\frac{I_r}{I_r^*} - \frac{E}{E^*} - ln\frac{I_r}{I_r^*} + ln\frac{E}{E^*}\right) + \lambda_r^* S^*\left(\frac{I_r S}{I_r^8 S^*} - \frac{I_r}{I_r^*} - ln\frac{S}{S^*}\right) \\
& + \sigma\lambda_r^*\left(\frac{I_r V}{I_r^* V^*} - \frac{I_r}{I_r^*} - ln\frac{V}{V^*}\right) + \kappa\lambda_r^* R^*\left(\frac{I_r R}{I_r^* R^*} - \frac{I_r}{I_r^*} - ln\frac{R}{R^*}\right) \\
& =: b_{34}Q_{34} + b_{31}Q_{31} + b_{32}Q_{32} + b_{36}Q_{36} \\
Q_4^{'} \leq & (1-\nu)\delta E^*\left(\frac{E}{E^*} - \frac{I_r}{I_r^*} - ln\frac{E}{E^*} + ln\frac{I_r}{I_r^*}\right) =: b_{43}Q_{43} \\
Q_5^{'} \leq & \nu\delta E^*\left(\frac{E}{E^*} - \frac{T_r}{T_r^*} - ln\frac{E}{E^*} + ln\frac{T_r}{T_r^*}\right) =: b_{53}Q_{53} \\
Q_6^{'} \leq & \rho_r I_r^*\left(\frac{I_r}{I_r^*} - ln\frac{I_r}{I_r^*} + ln\frac{R}{R^*} - \frac{R}{R^*}\right) + \varphi T_r^*\left(\frac{T_r}{T_r^*} - ln\frac{T_r}{T_r^*} + ln\frac{R}{R^*} - \frac{R}{R^*}\right) \\
& + \kappa\lambda_r^* R^*\left(-ln\frac{R}{R^*} - ln\frac{I_r}{I_r^*} - 2 + \frac{R}{R^*} + \frac{I_r}{I_r^*}\right) =: b_{64a}Q_{64a} + b_{64a}Q_{64a} + b_{65}Q_{65}
\end{aligned}
$$

Where, $b_{14} = b_{32} = \sigma\lambda_r^* V^*$, $b_{21} = \theta V^*$, $b_31 = \lambda_r^* S^*$, $b_{34} = \lambda_r^*(S^* + \sigma V^* + \kappa R^*)$, $b_{36} = \kappa\lambda_r^* R^*$, $b_{43} = (1-\nu)\delta E^*$, $b_{53} = \nu\delta E^*$, $b_{64a} = \rho_r I_r^*$, $b_{64b} = \kappa\lambda_r R^*$, $b_{65} = \varphi T_r^*$, and all other $b_{ij} = 0$.

With the constants b_{ij} above and $B = [b_{ij}]$ for $i, j = 1, ..., 6, 5a, 5b$, we construct the directed graph $G(B)$ as Figure 5.3.

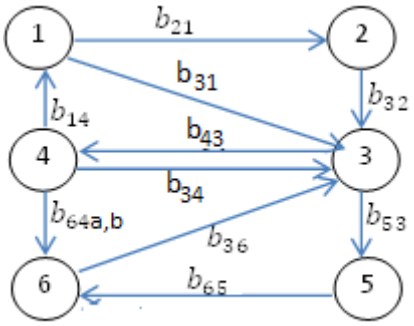

Figure 5.3: The digraph G(B) for dynamical system (5.1),(5.2),(5.7)-(5.10).

The associated weighted digraph $G(B)$ (figure 5.3) has six vertices. Along the cycle in figure 5.3, $G_{34} + G_{43} = (\frac{I_r}{I_r^*} - \frac{E}{E^*} - ln\frac{I_r}{I_r^*} + ln\frac{E}{E^*}) + (\frac{E}{E^*} - \frac{I_r}{I_r^*} - ln\frac{E}{E^*} + ln\frac{I_r}{I_r^*}) = 0$ and for the other cycles in figure 5.3, $\Sigma G_{ij} \leq 0$, if $\frac{V}{V^*}, \frac{S}{S^*}, \frac{R}{R^*} \leq 1$ and $\frac{E}{E^*} \leq \frac{I_r}{I_r^*}$. By Proposition 1.3 of [109], there exists $c_i > 0$, $i = 1, \ldots, 6$ such that $Q = \Sigma_{i=1}^6 c_i Q_i$ is a Lyapunov function for equations (5.1),(5.2),(5.7)-(5.10). The relations between c_i's can be derived from Theorems 3.3 and 3.4 of [109] such that:

$b_{21} > 0$ and $d^+(1) = 1$ implies $c_2 b_{21} = \Sigma_{k=1}^{6} c_1 b_{1k}$

$$\Rightarrow c_2 b_{21} = c_1 b_{14} \Rightarrow c_2 = c_1 \frac{b_{14}}{b_{21}}.$$

$b_{32} > 0$ and $d^+(2) = 1$ implies $c_3 b_{32} = \Sigma_{k=1}^{6} c_2 b_{2k} \Rightarrow c_3 b_{32} = c_2 b_{21}$

$$\Rightarrow c_3 = c_2 \frac{b_{21}}{b_{32}} = c_1 \frac{b_{14}}{b_{32}}.$$

$b_{36} > 0$ and $d^+6) = 1$ implies $c_3 b_{36} = \Sigma_{k=1}^{6} c_6 b_{6k}$

$$\Rightarrow c_5 b_{36} = c_6(b_{64a} + b_{64b} + b_{65}) \Rightarrow c_6 = c_5 \frac{b_{36}}{(b_{64a} + b_{64b} + b_{65})}$$
$$\Rightarrow c_6 = c_1 \frac{b_{14}}{b_{32}} \frac{(b_{34} + b_{31} + b_{32} + b_{36})}{b_{53}} \frac{b_{36}}{(b_{64a} + b_{64b} + b_{65})}$$

$b_{53} > 0$ and $d^-(5) = 1$ implies $c_5 b_{43} = \Sigma_{k=1}^{6} c_k b_{k5}$

$$\Rightarrow c_5 b_{53} = c_6 b_{65} \Rightarrow c_5 = c_6 \frac{(b_{65}}{b_{53}}$$
$$\Rightarrow c_5 = c_1 \frac{b_{14}}{b_{32}} \frac{(b_{34} + b_{31} + b_{32} + b_{36})}{b_{53}} \frac{b_{36}}{(b_{64a} + b_{64b} + b_{65})} \frac{b_{65}}{b_{53}}$$

$b_{43} > 0$ and $d^-(4) = 1$ implies $c_4 b_{43} = \Sigma_{k=1}^{6} c_k b_{k4}$

$$\Rightarrow c_4 b_{43} = c_1 b_{14} + c_3 b_{34} + c_6(b_{64a} + b_{64b})$$
$$\Rightarrow c_4 b_{43} = c_1 b_{14} + c_1 \frac{b_{14} b_{34}}{b_{32}} + c_1 \frac{b_{14}}{b_{32}} \frac{(b_{34} + b_{31} + b_{32} + b_{36})}{b_{53}} \frac{b_{36}(b_{64a} + b_{64b}}{(b_{64a} + b_{64b} + b_{65})}$$
$$\Rightarrow c_4 = c_1 \frac{1}{b_{43}} (b_{14} + \frac{b_{14} b_{34}}{b_{32}} + \frac{b_{14} b_{36} b_{64} (b_{34} + b_{31} + b_{32} + b_{36})}{b_{32} b_{53} (b_{64a} + b_{64b} + b_{65})})$$

Therefore, $Q = c_1 Q_1 + c_2 Q_2 + c_3 Q_3 + c_4 Q_4 + c_5 Q_5 + c_6 Q_6$ is a Lyapunov function for (5.1), (5.2), (5.7)–(5.10). Therefore, E_2 is globally asymptotically stable in the interior of Ω when$R_{eff}(MDR) > 1$. □

5.4.3 The Endemic Equilibrium where both TB strains co-exist

The endemic equilibrium where both TB strains co-exist is given as:

$$E_3 = (V^*, S^*, H_s^*, L_s^*, I_s^*, T_s^*, E^*, I_r^*, T_r^*, R^*)$$

From equation (5.1) of the dynamical system (5.1)−(5.10):

$$\frac{dV}{dt} = \psi\Lambda - (\sigma(\lambda_s + \lambda_r) + \theta + \mu)V = 0 \Rightarrow V^* = \frac{\psi\Lambda}{(\sigma(\lambda_s^* + \lambda_r^*) + \theta + \mu)}$$

From equation (5.2) of the dynamical system (5.1)−(5.10):

$$\begin{aligned}\frac{dS}{dt} =&(1-\psi)\Lambda+\theta V-(\lambda_s+\lambda_r+\mu)S=0\\ \Rightarrow S^* =&\frac{(1-\psi)\Lambda+\theta V^*}{(\lambda_s^*+\lambda_r^*+\mu)}=\frac{\Lambda[(1-\psi)\sigma(\lambda_s^*+\lambda_r^*)+\theta+(1-\psi)\mu]}{(\lambda_s^*+\lambda_r^*+\mu)[\sigma(\lambda_s^*+\lambda_r^*)+\theta+\mu]}\end{aligned}$$

From equation (5.3) of the dynamical system (5.1)−(5.10):

$$\frac{dH_s}{dt}=\lambda_s S+\sigma\lambda_s V+\kappa\lambda_s R-(\alpha+\lambda_r+\mu)H_s=0\Rightarrow H_s^*=\frac{\lambda_s^*(S^*+\sigma V^*+\kappa R^*)}{(\alpha+\lambda_r^*+\mu)}$$

From equation (5.4) of the dynamical system (5.1)−(5.10):

$$\frac{dL_s}{dt}=\alpha\epsilon(1-p)H_s-(\lambda_r+\gamma+\mu)L_s=0$$

$$\Rightarrow L_s^*=\frac{\alpha\epsilon(1-p)H_s^*}{(\lambda_r^*+\gamma+\mu)}=\frac{\alpha\epsilon(1-p)(\lambda_r^*+\gamma+\mu)(\rho_s+\mu+d_s)}{(\gamma\eta\alpha\epsilon(1-p)+(\lambda_r^*+\gamma+\mu)\alpha(1-\epsilon)(1-p))I_s^*}$$

From equation (5.5) of the dynamical system (5.1)−(5.10):

$$\frac{dI_s}{dt}=\gamma\eta L_s+\alpha(1-\epsilon)(1-p)H_s-(\rho_s+\mu+d_s)I_s=0$$

$$\Rightarrow I_s^*=\frac{(\gamma\eta L_s^*+\alpha(1-\epsilon)(1-p)H_s^*)}{(\rho_s+\mu+d_s}=\frac{(\gamma\eta\alpha\epsilon(1-p)+(\lambda_r^*+\gamma+\mu)\alpha(1-\epsilon)(1-p))}{(\lambda_r^*+\gamma+\mu)(\rho_s+\mu+d_s)}H_s^*$$

$$\Rightarrow H_s^*=\frac{(\lambda_r^*+\gamma+\mu)(\rho_s+\mu+d_s)}{(\gamma\eta\alpha\epsilon(1-p)+(\lambda_r^*+\gamma+\mu)\alpha(1-\epsilon)(1-p))}I_s^*$$

From equation (5.6) of the dynamical system (5.1)−(5.10):

$$\frac{dT_s}{dt}=\alpha pH_s-(\phi+\mu)T_s=0$$

$$\Rightarrow T_s^*=\frac{\alpha pH_s^*}{(\phi+\mu)}=\frac{\alpha p(\lambda_r^*+\gamma+\mu)(\rho_s+\mu+d_s)}{(\phi+\mu)[\gamma\eta\alpha\epsilon(1-p)+(\lambda_r^*+\gamma+\mu)\alpha(1-\epsilon)(1-p)]}I_s^*$$

From equation (5.7) of the dynamical system (5.1)−(5.10):

$$\frac{dE}{dt}=\lambda_r(S+H_s+L_s+\sigma V+\kappa R)+(1-q)\rho_s I_s-(\delta+\mu)E=0$$

$$\Rightarrow E^*=\frac{\lambda_r^*(S^*+H_s^*+L_s^*+\sigma V^*+\kappa R^*)+(1-q)\rho_s I_s^*}{(\delta+\mu)}$$

From equation (5.8) of the dynamical system (5.1)−(5.10):

$$\frac{dI_r}{dt}=(1-\nu)\delta E-(\rho_r+\mu+d_r)I_r=0$$

$$\Rightarrow I_r^*=\frac{(1-\nu)\delta E^*}{(\rho_r+\mu+d_r)}\Rightarrow E^*=\frac{(\rho_r+\mu+d_r)I_r^*}{(1-\nu)\delta}$$

From equation (5.9) of the dynamical system (5.1)−(5.10):

$$\frac{dT_r}{dt} = \nu\delta E - (\varphi+\mu)T_r = 0 \Rightarrow T_r^* = \frac{\nu\delta E^*}{(\varphi+\mu)} = \frac{\nu(\rho_r+\mu+d_r)I_r^*}{(\varphi+\mu)(1-\nu)}$$

From equation (5.10) of the dynamical system (5.1)−(5.10):

$$\begin{aligned}
\frac{dR}{dt} =& q\rho_s I_s + \rho_r I_r + \gamma(1-\eta)L_s + \phi T_s + \varphi T_r - (\kappa(\lambda_s+\lambda_r)+\mu)R = 0\\
\Rightarrow R^* =& \frac{(\rho_s I_s^* + \rho_r I_r^* + \gamma(1-\eta)L_s^* + \phi T_s^* + \varphi T_r^*)}{(\kappa(\lambda_s^*+\lambda_r^*)+\mu)}\\
\Rightarrow R^* =& \frac{1}{(\kappa(\lambda_s^*+\lambda_r^*)+\mu)}(\rho_s + \frac{\gamma(1-\eta)\alpha\epsilon(1-p)(\rho_s+\mu+d_s)(\lambda_r^*+\gamma+\mu)}{\gamma\eta\alpha\epsilon(1-p)+(\lambda_r^*\gamma+\mu)\alpha(1-\epsilon)(1-p)}\\
&+ \frac{\phi\alpha p(\rho_s+\mu+d_s)(\lambda_r^*+\gamma+\mu)}{(\phi+\mu)[\gamma\eta\alpha\epsilon(1-p)+(\lambda_r^*+\gamma+\mu)\alpha(1-\epsilon)(1-p)]})I_s^*\\
&+ \frac{1}{(\kappa(\lambda_s^*+\lambda_r^*)+\mu)}(\rho_r + \frac{\varphi\nu\delta[(\rho_r+\mu+d_r)]}{(\varphi+\mu)(1-\nu)\delta})I_r^*
\end{aligned}$$

Thus, the endemic equilibrium where both TB strains co-exist is given as:

$$E_3 = (V^*, S^*, H_s^*, L_s^*, I_s^*, T_s^*, E^*, I_r^*, T_r^*, R^*)$$

Where

$$\begin{aligned}
V^* =& \frac{\psi\Lambda}{\sigma(\lambda_s^*+\lambda_r^*)+\theta+\mu}, S^* = \frac{\Lambda[(1-\psi)\sigma(\lambda_s^*+\lambda_r^*)+\theta+(1-\psi)\mu]}{(\lambda_s^*+\lambda_r^*+\mu)[\sigma(\lambda_s^*+\lambda_r^*)+\theta+\mu]},\\
H_s^* =& \frac{(\lambda_r^*+\gamma+\mu)(\rho_s+\mu+d_s)}{\gamma\eta\alpha\epsilon(1-p)+(\rho_r^*+\gamma+\mu)\alpha(1-\epsilon)(1-p)}I_s^*,\\
L_s^* =& \frac{\alpha\epsilon(1-p)(\lambda_r^*+\gamma+\mu)(\rho_s+\mu+d_s)}{\gamma\eta\alpha\epsilon(1-p)+(\lambda_r^*+\gamma+\mu)\alpha(1-\epsilon)(1-p)}I_s^*\\
T_s^* =& \frac{\alpha p(\lambda_r^*+\gamma+\mu)(\rho_s+\mu+d_s)}{(\phi+\mu)[\gamma\eta\alpha\epsilon(1-p)+(\lambda_r^*+\gamma+\mu)\alpha(1-\epsilon)(1-p)]}\\
E^* =& \frac{\lambda_r^*(S^*+H_s^*+L_s^*+\sigma V^*+\kappa R^*)+(1-q)\rho_s I_s^*}{(\delta+\mu)}, T_r^* = \frac{\nu\delta(\rho_r+\mu+d_r)I_r^*]}{(\varphi+\mu)(1-\nu)\delta}\\
R^* =& \frac{1}{(\kappa(\lambda_s^*+\lambda_r^*)+\mu)}(\rho_s + \frac{\gamma(1-\eta)\alpha\epsilon(1-p)(\rho_s+\mu+d_s)(\lambda_r^*+\gamma+\mu)}{\gamma\eta\alpha\epsilon(1-p)+(\lambda_r^*\gamma+\mu)\alpha(1-\epsilon)(1-p)}\\
&+ \frac{\phi\alpha p(\rho_s+\mu+d_s)(\lambda_r^*+\gamma+\mu)}{(\phi+\mu)[\gamma\eta\alpha\epsilon(1-p)+(\lambda_r^*+\gamma+\mu)\alpha(1-\epsilon)(1-p)]})I_s^*\\
&+ \frac{1}{(\kappa(\lambda_s^*+\lambda_r^*)+\mu)}(\rho_r + \frac{\varphi\nu\delta[(\rho_r+\mu+d_r)]}{(\varphi+\mu)(1-\nu)\delta})I_r^*
\end{aligned}$$

Local Stability of the endemic equilibrium where both TB strains co-exist

Theorem 5.13. *The equilibrium point where both TB strains co-exist E_3 of the dynamical system (5.1)−(5.10) is locally asymptotically stable if $R_{eff}(DS) > 1, R_{eff}(MDR) > 1$ and $R^* < \min\{\frac{\Lambda(d_s+\mu)}{c\omega_s\kappa\mu}, \frac{\Lambda(\mu+d_r)}{c\omega_r\kappa\mu}\}$.*

Proof. The Jacobian matrix of the dynamical system (5.1)−(5.10) at endemic equilibrium where both TB strains co-exist E_3 is given by:

$$J(E_3) = \begin{bmatrix} d_1 & 0 & 0 & 0 & e_1 & 0 & 0 & h_1 & 0 & 0 \\ \theta & d_2 & 0 & 0 & e_2 & 0 & 0 & h_2 & 0 & 0 \\ \sigma\lambda_s^* & \lambda_s^* & d_3 & 0 & e_3 & 0 & 0 & h_3 & 0 & \kappa\lambda_s^* \\ 0 & 0 & e_4 & d_4 & 0 & 0 & 0 & h_4 & 0 & 0 \\ 0 & 0 & e_5 & \eta\gamma & d_5 & & 0 & 0 & 0 & 0 \\ 0 & 0 & p\alpha & 0 & 0 & d_6 & 0 & 0 & 0 & 0 \\ \sigma\lambda_r^* & \lambda_r^* & \lambda_r^* & \lambda_r^* & e_6 & 0 & d_7 & h_5 & 0 & \kappa\lambda_r^* \\ 0 & 0 & 0 & 0 & 0 & 0 & e_7 & d_8 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \nu\delta & 0 & d_9 & 0 \\ 0 & 0 & 0 & e_8 & q\rho_s & \phi & 0 & \rho_r & \varphi & d_{10} \end{bmatrix}$$

Where, $d_1 = -(\sigma(\lambda_s^* + \lambda_r^*) + \theta + \mu)$, $d_2 = -(\lambda_s^* + \lambda_r^* + \mu)$, $d_3 = -(\lambda_r^* + \alpha + \mu)$,
$d_4 = -(\lambda_r^* + \gamma + \mu)$, $d_5 = -(\rho_s + \mu + d_s)$, $d_6 = -(\phi + \mu)$, $d_7 = -(\delta + \mu)$,
$d_8 = -(\rho_r + \mu + d_r)$, $d_9 = -(\varphi + \mu)$, $d_{10} = -(\kappa(\lambda_s^* + \lambda_r^*) + \mu)$, $e_1 = -\frac{\sigma c\omega_s V^*}{N^*}$, $e_2 = -\frac{c\omega_s S^*}{N^*}$,
$e_3 = \frac{c\omega_s}{N^*}(\sigma V^* + S^* + \kappa R^*)$, $e_4 = \alpha\epsilon(1-p)$, $e_5 = \alpha(1-\epsilon)(1-p)$, $e_6 = (1-q)\rho_s$, $e_7 = (1-\nu)\delta$,
$h_1 = -\frac{\sigma c\omega_r V^*}{N^*}$, $h_2 = -\frac{c\omega_r S^*}{N^*}$, $h_3 = -\frac{c\omega_r H_s^*}{N^*}$, $h_4 = -\frac{c\omega_r L_s^*}{N^*}$, $h_5 = \frac{c\omega_r}{N^*}(\sigma V^* + S^* + \kappa R^*)$,

The characteristic equation will be:

$$\begin{vmatrix} s_1 & 0 & 0 & 0 & e_1 & 0 & 0 & h_1 & 0 & 0 \\ \theta & s_2 & 0 & 0 & e_2 & 0 & 0 & h_2 & 0 & 0 \\ \sigma\lambda_s^* & \lambda_s^* & s_3 & 0 & e_3 & 0 & 0 & h_3 & 0 & \kappa\lambda_s^* \\ 0 & 0 & e_4 & s_4 & 0 & 0 & 0 & h_4 & 0 & 0 \\ 0 & 0 & e_5 & \eta\gamma & s_5 & & 0 & 0 & 0 & 0 \\ 0 & 0 & p\alpha & 0 & 0 & s_6 & 0 & 0 & 0 & 0 \\ \sigma\lambda_r^* & \lambda_r^* & \lambda_r^* & \lambda_r^* & e_6 & 0 & s_7 & h_5 & 0 & \kappa\lambda_r^* \\ 0 & 0 & 0 & 0 & 0 & 0 & e_5 & s_8 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \nu\delta & 0 & s_9 & 0 \\ 0 & 0 & 0 & e_8 & q\rho_s & \phi & 0 & \rho_r & \varphi & s_{10} \end{vmatrix} = 0$$

where, $s_1 = d_1 - \lambda$, $s_2 = d_2 - \lambda$, $s_3 = d_3 - \lambda$, $s_4 = d_4 - \lambda$, $s_5 = d_5 - \lambda$, $s_6 = d_6 - \lambda$, $s_7 = d_7 - \lambda$, $s_8 = d_8 - \lambda$, $s_9 = d_9 - \lambda$, $s_{10} = d_{10} - \lambda$.

Now we apply the Gershgorin circle theorem,[83] to determine the sign of the eigenvalues

of the characteristic equation $|J(E_3) - \lambda I| = 0$.

From the fifth column of the Jacobean matrix $J(E_3)$, $|d_5| = \rho_s + \mu + d_s$ and $\Sigma_{i=1,i\neq 5}^{10} c_{i5} = e_1+e_2+e_3+(1-q)\rho_s+q\rho_s = \frac{c\omega_s}{N^*}\kappa R^*+\rho_s$. If we use $N^* = \frac{\Lambda}{\mu}$, then $\Sigma_{i=1,i\neq 5}^{10} c_{i5} = \frac{c\omega_s\mu\kappa}{\Lambda}R^*+\rho_s$. Therefore, $|d_5| > \Sigma_{i=1,i\neq 5}^{10} c_{i5}$ if $R^* < \frac{\Lambda(\mu+d_s)}{c\omega_s\mu\kappa}$.

From the eighth column of the Jacobian matrix $J(E_3)$:

$|d_8| = \rho_r+\mu+d_r$ and $\Sigma_{i=1,i\neq 5}^{10} c_{i8} = h_1+h_2+h_3+h_4+h_5+\rho_r = \frac{c\omega_r}{N^*}\kappa R^*+\rho_r$. If we take N^* at its limit value, $N^* = \frac{\Lambda}{\mu}$, then $\Sigma_{i=1,i\neq 8}^{10} c_{i8} = \frac{c\omega_s\mu\kappa}{\Lambda}R^* + \rho_r$. Therefore, $|d_8| > \Sigma_{i=1,i\neq 8}^{10} c_{i8}$ if $R^* < \frac{\Lambda(\mu+d_r)}{c\omega\mu\kappa}$.

For the remaining column of the Jacobian matrix $J(E_3)$:

$$|d_i| > \Sigma_{i=1,i\neq j}^{10} c_{ij} \text{ for } j = \{1,\ldots,10\} - \{5,8\}$$

Implies, the radius of the disc is $R_i = \Sigma_{i=1,j\neq i}^{10} c_{ij} < |c_{ii}|$ for $i,j = \{1,\ldots,10\}$ if $R^* < \min\{\frac{\Lambda(d_s+\mu)}{c\omega_s\kappa\mu}, \frac{\Lambda(\mu+d_r)}{c\omega_r\kappa\mu}\}$. Therefore, the matrix $J(E_3)$ is a strictly column diagonally dominant matrix. And also all diagonal elements of $J(E_3)$ are negative. Hence, all eigenvalues of $J(E_3)$ has negative real part if $R_{eff}(DS) > 1, R_{eff}(MDR) > 1$ and $R^* < \min\{\frac{\Lambda(d_s+\mu)}{c\omega_s\kappa\mu}, \frac{\Lambda(\mu+d_r)}{c\omega_r\kappa\mu}\}$. Therefore, the interior equilibrium E_3 is locally asymptotically stable if $R_{eff}(DS) > 1, R_{eff}(MDR) > 1$ and $R^* < \min\{\frac{\Lambda(d_s+\mu)}{c\omega_s\kappa\mu}, \frac{\Lambda(\mu+d_r)}{c\omega_r\kappa\mu}\}$. □

Global stability the endemic equilibrium where both TB strains co-exist

Theorem 5.14. *The the endemic equilibrium where both TB strains co-exist E_3 of the system (5.1)–(5.10) is globally asymptotically stable if $R_{eff}(DS) > 1, R_{eff}(MDR) > 1$, $\frac{V}{V^*}$, $\frac{S}{S^*}$, $\frac{R}{R^*} \leq 1$, $\frac{H_s}{H_s^*} \leq \frac{I_s}{I_s^*}$ and $\frac{E}{E^*} \leq \frac{I_r}{I_r^*}$.*

Proof. We use a graph-theoretic method as in [109] to construct a lyapunov function.

Define the functions:

$B_1 = V - V^* - V^* ln\frac{V}{V^*}$, $B_2 = S - S^* - S^* ln\frac{S}{S^*}$, $B_3 = H_s - H_s^* - H_s^* ln\frac{H_s}{H_s^*}$, $B_4 = L_s - L_s^* - L_s^* ln\frac{L_s}{L_s^*}$ $B_5 = I_s - I_s^* - I_s^* ln\frac{I_s}{I_s^*}$, $B_6 = T_s - T_s^* - T_s^* ln\frac{T_s}{T_s^*}$, $B_7 = E - E^* - E^* ln\frac{E}{E^*}$ $B_8 = T_r - T_r^* - T_r^* ln\frac{T_r}{T_r^*}$, $B_9 = I_r 0 - I_r^* - I_r^* ln\frac{I_r}{I_r^*}$, $B_{10} = R - R^* - R^* ln\frac{R}{R^*}$ Where $E_3 = (V^*, S^*, H_s^*, L_s^*, T_s^*, I_s^*, E^*, T_r^*, I_r^*, R^*)$ is the endemic equilibrium where both TB strains co-exist.

Differentiating the function B_i, $i = 1,\ldots,10$ with respect to time,

$$B_1^{'} = (1 - \frac{V^*}{V})V^{'} \ , \qquad B_2^{'} = (1 - \frac{S^*}{S})S^{'}, \qquad B_3^{'} = (1 - \frac{H_s^*}{H_s})H_s^{'},$$

$$B_4^{'} = (1 - \frac{L_s^*}{L_s})L_s^{'}, \qquad B_5^{'} = (1 - \frac{I_s^*}{I_s})I_s^{'}, \qquad B_6^{'} = (1 - \frac{T_s^*}{T_s})T_s^{'},$$

$$B_7^{'} = (1 - \frac{E^*}{E})E^{'}, \qquad B_8^{'} = (1 - \frac{I_r^*}{I_r})I_r^{'}, \qquad B_9^{'} = (1 - \frac{T_r^*}{T_r})T_r^{'},$$

and $$B_{10}^{'} = (1 - \frac{r^*}{R})R^{'}$$

Substituting their derivatives we have:

$$B_1^{'} = \left(1 - \frac{V^*}{V}\right)\{\psi\Lambda - (\sigma(\lambda_s + \lambda_r) + \theta + \mu)V\}$$
$$B_2^{'} = \left(1 - \frac{S^*}{S}\right)\{(1 - \psi)\Lambda + \theta V - (\lambda_s + \lambda_r + \mu)S\}$$
$$B_3^{'} = \left(1 - \frac{H_s^*}{H_s}\right)\{\lambda_s(S + \sigma V + \kappa R) - (\alpha + \mu + \lambda_r)H_s\}$$
$$B_4^{'} = \left(1 - \frac{L_s^*}{L_s}\right)\{\alpha\epsilon(1 - p)H_s - (\gamma + \mu + \lambda_r)L_s\}$$
$$B_5^{'} = \left(1 - \frac{I_s^*}{I_s}\right)\{\gamma\eta L_s + \alpha(1 - \epsilon)(1 - p)H_s - (\rho_s + \mu + d_s)I_s\}$$
$$B_6^{'} = \left(1 - \frac{T_s^*}{T_s}\right)\{\alpha p H_s - (\phi + \mu)T_s\}$$
$$B_7^{'} = \left(1 - \frac{E^*}{E}\right)\{\lambda_r(S + H_s + L_s + \sigma V + \kappa R) + (1 - q)\rho_s I_s - (\delta + \mu)E\}$$
$$B_8^{'} = \left(1 - \frac{I_r^*}{I_r}\right)\{(1 - \nu)\delta E - (\rho_r + \mu + d_r)I_r\}$$
$$B_9^{'} = \left(1 - \frac{T_r^*}{T_r}\right)\{\nu \deg E - (\varphi + \mu)T_r\}$$
$$B_{10}^{'} = \left(1 - \frac{r^*}{R}\right)\{q\rho_s I_s + \rho_r I_r + \gamma(1 - \eta)L_s + \phi T_s + \varphi T_r - (\kappa(\lambda_s + \lambda_r) + \mu)R\}$$

At the endemic equilibrium point E_3 we have:

$$\psi\Lambda = (\sigma(\lambda_s^* + \lambda_r^*) + \theta + \mu)V^*, \qquad (1 - \phi)\Lambda = -\theta V^* + (\lambda_s^* + \lambda_r^* + \mu)S^*$$
$$(\alpha + \mu) = \frac{\lambda_s^*(S^* + \sigma V^* + \kappa R^*)}{H_s^*} - \lambda_r^*, \qquad (\gamma + \mu) = \frac{\alpha\epsilon(1 - p)H_s^*}{L_s^*} - \lambda_r^*$$
$$(\rho_s + \mu + d_s) = \gamma\eta\frac{L_s^*}{I_s^*} + \alpha(1 - \epsilon)(1 - p)\frac{H_s^*}{I_s^*}, \quad (\phi + \mu) = \alpha p\frac{H_s^*}{T_s^*},$$
$$(\rho_r + \mu + d_r) = (1 - \nu)\delta\frac{E^*}{I_r^*}, \qquad (\varphi + \mu) = \nu\delta\frac{E^*}{T_r^*}$$
$$(\delta + \mu) = \frac{\lambda_r^*(S^* + H_s^* + L_s^* + \sigma V^* + \kappa R^*)}{E^*} + (1 - q)\rho_s\frac{I_s^*}{E^*} \ and$$
$$\mu = q\rho_s\frac{I_s^*}{R^*} + \gamma(1 - \eta)\frac{L_s^*}{R^*} + \phi\frac{T_s^*}{R^*} - \kappa\lambda_s^* + \rho_r\frac{I_r^*}{R^*} + \phi\frac{T_r^*}{R^*} - \kappa\lambda_r^*$$

Using the inequality $1 - x + lnx \leq 0$, for all $x > 0$ and the endemic equilibrium point E_3

we have:

$$
\begin{aligned}
B_1^{'} =& \left(1-\frac{V^*}{V}\right)\{(\sigma(\lambda_s^*+\lambda_r^*)+\theta+\mu)V^*-(\theta(\lambda_s+\lambda_r)+\theta+\mu)V\} \\
=& -(\theta+\mu)\frac{(V-V^*)^2}{V}+\frac{c\sigma\omega_s}{N^*}V^*I_s^*\left(1-\frac{I_sV}{I_s^*V^*}-\frac{V^*}{V}+\frac{I_s}{I_s^*}\right) \\
&+\frac{c\sigma\omega_r}{N^*}V^*I_r^*\left(1-\frac{I_rV}{I_r^*V^*}-\frac{V^*}{V}+\frac{I_r}{I_r^*}\right) \\
\leq& \frac{c\sigma\omega_s}{N^*}V^*I_s^*\left(1-\frac{I_sV}{I_s^*V^*}-\frac{V^*}{V}+\frac{I_s}{I_s^*}\right)+\frac{c\sigma\omega_r}{N^*}V^*I_r^*\left(1-\frac{I_rV}{I_r^*V^*}-\frac{V^*}{V}+\frac{I_r}{I_r^*}\right) \\
\leq& \frac{c\sigma\omega_s}{N^*}V^*I_s^*\left(1-\frac{I_sV}{I_s^*V^*}-\frac{V^*}{V}+\frac{I_s}{I_s^*}\right)+\frac{c\sigma\omega_r}{N^*}V^*I_r^*\left(1-\frac{I_rV}{I_r^*V^*}-\frac{V^*}{V}+\frac{I_r}{I_r^*}\right) \\
\leq& \sigma V^*\lambda_s^*\left(-ln\frac{I_s}{I_s^*}+ln\frac{V^*}{V}-\frac{V^*}{V}+\frac{I_s}{I_s^*}\right)+\sigma V^*\lambda_r^*\left(\frac{I_r}{I_r^*}-ln\frac{V^*}{V}-\frac{I_rV}{I_r^*V^*}\right) \\
=& : a_{15}G_{15}+a_{18}G_{18}
\end{aligned}
$$

$$
\begin{aligned}
B_2^{'} =& \left(1-\frac{S^*}{S}\right)\{-\theta V^*+(\lambda_s^*+\lambda_r^*+\mu)S^*+\theta V-(\lambda_s+\lambda_r+\mu)S\} \\
=& -\mu\frac{(S-S^*)^2}{S}+\theta V^*\left(\frac{S^*}{S}-1-\frac{VS^*}{V^*S}+\frac{V}{V^*}\right)+\frac{c\sigma\omega_s}{N^*}S^*I_s^*\left(I_s^*-\frac{I_sS}{S^*}-\frac{S^*I_s^*}{S}+I_s\right) \\
&+\frac{c\sigma\omega_r}{N^*}S^*I_r^*\left(I_r^*-\frac{I_rS}{S^*}-\frac{S^*I_r^*}{S}+I_r\right) \\
\leq& \theta V^*\left(\frac{S^*}{S}-2-ln\frac{VS^*}{V^*S}+\frac{V}{V^*}\right)+\frac{c\sigma\omega_s}{N^*}S^*I_s^*\left(1-\frac{I_sS}{S^*I_s^*}-\frac{S^*}{S}+\frac{I_s}{I_s^*}\right) \\
&+\frac{c\sigma\omega_r}{N^*}S^*I_r^*\left(1-\frac{I_rS}{S^*I_r^*}-\frac{S^*}{S}+\frac{I_r}{I_r^*}\right) \\
\leq& \theta V^*(\frac{S^*}{S}-2-ln\frac{VS^*}{V^*S}+\frac{V}{V^*})+S^*\lambda_s^*\left(-ln\frac{I_s}{I_s^*}+ln\frac{S^*}{S}-\frac{S^*}{S}+\frac{I_s}{I_s^*}\right) \\
&+S^*\lambda_r^*\left(-ln\frac{I_r}{I_r^*}+ln\frac{S^*}{S}-\frac{S^*}{S}+\frac{I_r}{I_r^*}\right) \\
=& a_{21}G_{21}+a_{25}G_{25}+a_{28}G_{28}
\end{aligned}
$$

$$
\begin{aligned}
B_3^{'} =& \left(1-\frac{H_s^*}{H_S}\right)\{\lambda_s(S+\sigma V+\kappa R)-\lambda_rH_s-\lambda_s^*(S^*+\sigma V^*+\kappa R^*)\frac{H_s}{H_s^*}+\lambda_r^*H_s\} \\
=& \lambda_s^*S^*H_s^*\left(1-\frac{Hs^*}{H_s}\right)\left(\frac{\lambda_sS}{\lambda_s^*S^*}-\frac{H_s}{H_s^*}\right)+\sigma V^*\lambda_s^*H_s^*\left(1-\frac{H_s^*}{H_s}(\frac{\lambda_sV}{V^*\lambda_s^*}-\frac{H_s}{H_s^*}\right) \\
&+\kappa R^*\lambda_s^*H_s^*\left(1-\frac{H_s^*}{H_s}\right)\left(\frac{\lambda_sR}{R^*\lambda_s^*}-\frac{H_s}{H_s^*}\right)+\lambda_r^*H_s^*\left(\frac{H_s}{H_s^*}-1\right)\{1-\frac{\lambda_r}{\lambda_r^*}\} \\
\leq& \lambda_s^*S^*\left(\frac{\lambda_sS}{\lambda_s^*S^*}-\frac{H_s}{H_s^*}-ln\frac{\lambda_sS}{\lambda_s^*S^*}\frac{H_s^*}{H_s}\right)+\sigma V^*\lambda_s^*\left(\frac{\lambda_sV}{V^*\lambda_s^*}-\frac{H_s}{H_s^*}-ln\frac{\lambda_sV}{V^*\lambda_s^*}\frac{H_s^*}{H_s}\right) \\
&+\kappa R^*\lambda_s^*\left(\frac{\lambda_sR}{R^*\lambda_s^*}-\frac{H_s}{H_s^*}-ln\frac{\lambda_sR}{R^*\lambda_s^*}\frac{H_s^*}{H_s}\right)+\lambda_r^*H_s^*\left(\frac{H_s}{H_s^*}-1-\frac{H_s}{H_s^*}\frac{\lambda_r}{\lambda_r^*}+\frac{\lambda_r}{\lambda_r^*}\right)
\end{aligned}
$$

$$
\begin{aligned}
=&\lambda_s^* S^* \left(\frac{I_s S}{I_s^* S^*} - \frac{I_s}{I_s^*} - ln\frac{S}{S^*}\right) + \sigma V^* \lambda_s^* \left(\frac{I_s V}{V^* I_s^*} - \frac{I_s}{I_s^*} - ln\frac{V}{V^*}\right) + \kappa R^* \lambda_s^* \left(\frac{I_s R}{R^* I_s^*} - \frac{I_s}{I_s^*} - ln\frac{R}{R^*}\right) \\
&+ \lambda_s^* S^* \left(\frac{I_s}{I_s^*} - \frac{H_s}{H_s^*} + ln\frac{H_s}{H_s^*} - ln\frac{I_s}{I_s^*}\right) + \sigma V^* \lambda_s^* \left(\frac{I_s}{I_s^*} - \frac{H_s}{H_s^*} + ln\frac{H_s}{H_s^*} - ln\frac{I_s}{I_s^*}\right) \\
&+ \kappa R^* \lambda_s^* \left(\frac{I_s}{I_s^*} - \frac{H_s}{H_s^*} + ln\frac{H_s}{H_s^*} - ln\frac{I_s}{I_s^*}\right) + \lambda_r^* H_s^* \left(\frac{H_s}{H_s^*} - 1 - \frac{H_s}{H_s^*}\frac{\lambda_r}{\lambda_r^*} + \frac{\lambda_r}{\lambda_r^*}\right) \\
\leq&\lambda_s^* S^* \left(\frac{I_s S}{I_s^* S^*} - \frac{I_s}{I_s^*} - ln\frac{S}{S^*}\right) + \sigma V^* \lambda_s^* \left(\frac{I_s V}{I_s^* V^8} - \frac{I_s}{I_s^*} - ln\frac{V}{V^*}\right) + \kappa R^* \lambda_s^* \left(\frac{I_s R}{I_s^* R^*} - \frac{I_s}{I_s^*} - ln\frac{R}{R}\right) \\
&+ (S^* + \sigma V^* + \kappa R^*) \lambda_s^* \left(\frac{I_s}{I_s^*} - \frac{H_s}{H_s^*} + ln\frac{H_s}{H_s^*} - ln\frac{I_s}{I_s^*}\right) + \lambda_s^* H_s^* \left(\frac{H_s}{H_s^*} - 1 - \frac{H_s \lambda_r}{H_s^* \lambda_r^*}\right) \\
=&: a_{32}G_{32} + a_{31}G_{31} + a_{310}G_{310} + a_{35}G_{35} + a_{38}G_{38}
\end{aligned}
$$

$$
\begin{aligned}
B_4' =& \left(1 - \frac{L_s^*}{L_s}\right) \{\alpha\epsilon(1-p)H_s - \lambda_r L_s - \alpha\epsilon(1-p)H_s^* \frac{L_s}{L_s^*} + \lambda_r^* L_s\} \\
=&\alpha\epsilon(1-p)\left(1 - \frac{L_s^*}{L_s}\right)\left(H_s - \frac{H_s^*}{L_s^*}L_s\right) + \lambda_r^* L_s^* \left(\frac{L_s}{L_s^*} - 1\right)\{1 - \frac{\lambda_r}{\lambda_r^*} \\
=&\alpha\epsilon(1-p)H_s^*\left(1 - \frac{L_s}{L_s^*} - \frac{L_s^*}{L_s}\frac{H_s}{H_s^*} + \frac{H_s}{H_s^*}\right) + \lambda_r^* L_s^* \left(\frac{L_s}{L_s^*} - 1 - \frac{L_s}{L_s^*}\frac{\lambda_r}{\lambda_r^*} + \frac{\lambda_r}{\lambda_r^*}\right) \\
\leq&\alpha\epsilon(1-p)H_s^*\left(-\frac{L_s}{L_s^*} - ln\frac{L_s^*}{L_s}\frac{H_s}{H_s^*} + \frac{H_s}{H_s^*}\right) + \lambda_r^* L_s^* \left(\frac{L_s}{L_s^*} - 2 - ln\frac{L_s}{L_s^*}\frac{\lambda_r}{\lambda_r^*} + \frac{\lambda_r}{\lambda_r^*}\right) \\
\leq&\alpha\epsilon(1-p)H_s^*\left(-\frac{L_s}{L_s^*} + ln\frac{L_s}{L_s^*} - ln\frac{H_s}{H_s^*} + \frac{H_s}{H_s^*}\right) \lambda_r^* L_s^* \left(ln\frac{L_s}{L_s^*} - 2 - ln\frac{L_s\lambda_r}{L_s^*\lambda_r^*} + \frac{\lambda_r}{\lambda_r^*}\right) \\
=&: a_{43}G_{43} + a_{48}G_{48}
\end{aligned}
$$

$$
\begin{aligned}
B_5' =& (1 - \frac{I_s^*}{I_s})\gamma\eta L_s + \alpha(1-\epsilon)(1-p)H_s - [\gamma\eta L_s^* + \alpha(1-\epsilon)(1-p)H_s^*]ln\frac{I_s}{I_s^*} \\
=& \gamma\eta L_s^*(1 - \frac{I_s}{I_s^*} - \frac{I_s^*}{I_s}\frac{L_s}{L_s^*} + \frac{L_s}{L_s^*}) + \alpha(1-\epsilon)(1-p)H_s^*(1 - \frac{I_s}{I_s^*} - \frac{I_s^*}{I_s}\frac{H_s}{H_s^*} + \frac{H_s}{H_s^*}) \\
\leq& \gamma\eta L_s^*(-\frac{I_s}{I_s^*} - ln\frac{I_s^*}{I_s}\frac{L_s}{L_s^*} + \frac{L_s}{L_s^*}) + \alpha(1-\epsilon)(1-p)H_s^*(-\frac{I_s}{I_s^*} - ln\frac{I_s^*}{I_s}\frac{H_s}{H_s^*} + \frac{H_s}{H_s^*}) \\
\leq& \gamma\eta L_s^*(-\frac{I_s}{I_s^*} + ln\frac{I_s}{I_s^*} - ln\frac{L_s}{L_s^*} + \frac{L_s}{L_s^*}) + \alpha(1-\epsilon)(1-p)H_s^*(-\frac{I_s}{I_s^*} + ln\frac{I_s}{I_s^*} - ln\frac{H_s}{H_s^*} + \frac{H_s}{H_s^*}) \\
=&: a_{54}G_{54} + a_{53}G_{53}
\end{aligned}
$$

$$
\begin{aligned}
B_6' =& \left(1 - \frac{T_s^*}{T_s}\right)\{\alpha p H_s - \alpha p H_s^* \frac{T_s}{T_s^*}\} = (\phi + \mu)T_s^*\left(1 - \frac{T_s^*}{T_s}\right)\left(\frac{H_s}{H_s^*} - \frac{T_s}{T_s^*}\right) \\
=&(\phi + \mu)T_s^*\left(\frac{H_s}{H_s^*} - \frac{T_s}{T_s^*} - \frac{T_s^*}{T_s}\frac{H_s}{H_s^*} + 1\right) \leq (\phi + \mu)T_s^*\left(\frac{H_s}{H_s^*} - ln\frac{H_s}{H_s^*} - \frac{T_s}{T_s^*} + ln\frac{T_s}{T_s^*}\right) \\
=&: a_{63}G_{63}
\end{aligned}
$$

$$
\begin{aligned}
B_7' =&(1-\frac{E^*}{E})(\lambda_r(S+H_s+L_s+\sigma V+\kappa R)+(1-q)\rho_s I_s\\
&-\lambda_r^*(S^*+H_s^*+L_s^*+\sigma V^*+\kappa R^*)\frac{E^*}{E}-(1-q)\rho_s I_s^*\frac{E^*}{E})\\
=&\lambda_r^* S^*(\frac{I_r S}{I_r^* S^*}-\frac{E}{E^*}+1-\frac{E^*}{E}\frac{I_r S}{I_r^* S^*})+\sigma\lambda_r^* V^*(\frac{I_r V}{I_r^* V^*}-\frac{E}{E^*}+1-\frac{I_r V}{I_r^* V^*}\frac{E^*}{E}\\
&+\lambda_r^* H_s^*(\frac{I_r H_s}{I_r^* H_s^*}-\frac{E}{E^*}+1-\frac{E^*}{E}\frac{I_r H_s}{I_r^* H_s^*})+\lambda_r^* L_s^*(\frac{I_r L_s}{I_r^* L_s^*}-\frac{E}{E^*}-ln\frac{E^*}{E}\frac{I_r L_s}{I_r^* L_s^*})\\
&+\kappa\lambda_r^* R^*(\frac{I_r R}{I_r^* R^*}-\frac{E}{E^*}-1-\frac{I_r R}{I_r^* R^*}\frac{E^*}{E})+(1-q)\rho_s I_s^*(\frac{I_s}{I_s^*}-\frac{E}{E^*}-\frac{I_s}{I_s^*}\frac{E^*}{E}+1)\\
\leq&\lambda_r^* S^*(\frac{I_r S}{I_r^* S^*}-\frac{E}{E^*}-ln\frac{E^*}{E}\frac{I_r S}{I_r^* S^*})+\sigma\lambda_r^* V^*(\frac{I_r V}{I_r^* V^*}-\frac{E}{E^*}-ln\frac{I_r V}{I_r^* V^*}\frac{E^*}{E})\\
&+\kappa\lambda_r^* R^*(\frac{I_r R}{I_r^* R^*}-\frac{E}{E^*}-ln\frac{I_r R}{I_r^* R^*}\frac{E^*}{E})+\lambda_r^* H_s^*(\frac{I_r H_s}{I_r^* H_s^*}-\frac{E}{E^*}-ln\frac{E^*}{E}\frac{I_r H_s}{I_r^* H_s^*})\\
&+\lambda_r^* L_s^*(\frac{I_r L_s}{I_r^* L_s^*}-\frac{E}{E^*}-ln\frac{E^*}{E}\frac{I_r L_s}{I_r^* Ls^*})+(1-q)\rho_s I_s^*(\frac{I_s}{I_s^*}-\frac{E}{E^*}-ln\frac{I_s}{I_s^*}\frac{E^*}{E})
\end{aligned}
$$

$$
\begin{aligned}
=&\lambda_r^* S^*(\frac{I_r S}{I_r^* S^*}-\frac{I_r}{I_r^*}+\frac{I_r}{I_r^*}-\frac{E}{E^*}-lnS/S^*-ln\frac{I_r}{I_r^*}+ln\frac{E}{E^*})\\
&+\sigma\lambda_r^* V^*(\frac{I_r V}{I_r^* V^*}-\frac{I_r}{I_r^*}+\frac{I_r}{I_r^*}-\frac{E}{E^*}-ln\frac{V}{V^*}-ln\frac{I_r}{I_r^*}+ln\frac{E}{E^*})\\
&+\kappa\lambda_r^* R^*(\frac{I_r R}{I_r^* R^*}-\frac{I_r}{I_r^*}+\frac{I_r}{I_r^*}-\frac{E}{E^*}-ln\frac{R}{R^*}-ln\frac{I_r}{I_r^*}+ln\frac{E}{E^*})\\
&+\lambda_r^* H_s^*(\frac{I_r H_s}{I_r^* H_s^*}-\frac{I_r}{I_r^*}+\frac{I_r}{I_r^*}-\frac{E}{E^*}-ln\frac{I_r H_s}{I_r^* H_s^*}+ln\frac{E}{E^*})\\
&+\lambda_r^* L_s^*(\frac{I_r L_s}{I_r^* L_s^*}-\frac{I_r}{I_r^*}+\frac{I_r}{I_r^*}-\frac{E}{E^*}-ln\frac{I_r L_s}{I_r^* Ls^*}+ln\frac{E}{E^*})\\
&+(1-q)\rho_s I_s^*(\frac{I_s}{I_s^*}-\frac{E}{E^*}-ln\frac{I_s}{I_s^*}+ln\frac{E}{E^*})\\
\leq&\lambda_r^*(S^*+\sigma V^*+\kappa R^*+H_s^*+L_s^*)(\frac{I_r}{I_r^*}-\frac{E}{E^*}-ln\frac{I_r}{I_r^*}+ln\frac{E}{E^*})\\
&+\lambda_r^* S^*(\frac{I_r S}{I_r^* S^*})-\frac{I_r}{I_r^*}-ln\frac{S}{S^*})+\sigma\lambda_r^* V^*(\frac{I_r V}{I_r^* V^*}-\frac{I_r}{I_r^*}-lnV/V^*)\\
&+\kappa\lambda_r^* R^*(\frac{I_r R}{I_r^* R^*}-\frac{I_r}{I_r^*}-ln\frac{R}{R^*})+\lambda_r^* H_s^*(\frac{I_r H_s}{I_r^* H_s^*})-\frac{I_r}{I_r^*}-ln\frac{H_s}{H_s^*})\\
&+\lambda_r^* L_s^*(\frac{I_r L_s}{I_{r*} L_s^*}-\frac{I_r}{I_r^*}-ln\frac{L_s}{L_s^*})+(1-q)\rho_s I_s^*(\frac{I_s}{I_s^*}-\frac{E}{E^*}-ln\frac{I_s}{I_s^*}+ln\frac{E}{E^*})\\
=:&\, a_{78}G_{78}+a_{72}G_{72}+a_{71}G_{71}+a_{73}G_{73}+a_{74}G_{74}+a_{710}G_{710}+a_{75}G_{75}
\end{aligned}
$$

$$
\begin{aligned}
B_8^{'} =&(1-\frac{I_r^*}{I_r})((1-\nu)\delta E-[(1-\nu)\delta E^*]\frac{I_r}{I_r^*})=(1-\nu)\delta E^*(1-\frac{I_r^*}{I_r})(\frac{E}{E^*}-\frac{I_r}{I_r^*})\\
=&(1-\nu)\delta E^*(1+\frac{E}{E^*}-\frac{I_r}{I_r^*}-\frac{I_r^*}{I_r}\frac{E}{E^*})\leq(1-\nu)\delta E^*(\frac{E}{E^*}-\frac{I_r}{I_r^*}-ln\frac{I_r^*}{I_r}\frac{E}{E^*})\\
=&(1-\nu)\delta E^*(\frac{E}{E^*}-\frac{I_r}{I_r^*}-ln\frac{E}{E^*}+ln\frac{I_r}{I_r^*})=:a_{87}G_{87}
\end{aligned}
$$

$$
\begin{aligned}
B_9^{'} =&(1-\frac{T_s^*}{T_s})(\nu\delta E-\nu\delta E^*\frac{T_r}{T_r^*})=\nu\delta E^*(\frac{E}{E^*}-\frac{T_r}{T_r^*}-1-\frac{T_s^*}{T_s}\frac{E}{E^*})\\
=&\nu\delta E^*(\frac{E}{E^*}-\frac{T_r}{T_r^*}-ln\frac{T_s^*}{T_s}\frac{E}{E^*})\leq\nu\delta E^*(\frac{E}{E^*}-\frac{T_r}{T_r^*}-ln\frac{E}{E^*}+ln\frac{T_r}{T_r^*})=:a_{97}G_{97}
\end{aligned}
$$

$$
\begin{aligned}
B_{10}^{'} =&(1-\frac{R^*}{R})\{q\rho_sI_s+\rho_rI_r+\gamma(1-\eta)L_s+\phi T_s+\varphi T_r-\kappa(\lambda_s+\lambda_r)R\\
&-q\rho_sI_s^*+\gamma(1-\eta)L_s^*+\phi T_s^*-\kappa\lambda_s^*R^*+\rho_rI_r^*+\varphi T_r^*-\kappa\lambda_r^*R^*)\frac{R}{R^*}\}\\
=&\rho_sI_s^*(\frac{I_s}{I_s^*}+1-\frac{I_s}{I_s^*}\frac{R^*}{R}-\frac{R}{R^*})+\gamma(1-\eta)L_s^*(1-\frac{R}{R^*}-\frac{L_s}{L_s^*}\frac{R^*}{R}+\frac{L_s}{L_s^*})\\
&+\phi T_s^*(1-\frac{R}{R^*}-\frac{T_s}{T_s^*}\frac{R^*}{R}+\frac{T_s}{T_s^*})+\kappa\lambda_s^*R^*(\frac{R}{R^*}-1-\frac{I_s}{I_s^*}\frac{R}{R^*}+\frac{I_s}{I_s^*})\\
&+\rho_rI_r^*(\frac{I_r}{I_r^*}-\frac{R^*}{R}\frac{I_r}{I_r^*}-\frac{R}{R^*}+1)+\varphi T_r^*(\frac{T_r}{T_r^*}-\frac{R^*}{R}\frac{T_r}{T_r^*}-\frac{R}{R^*}+1)\\
&+\kappa\lambda_r^*R^*(\frac{RI_r}{R^*I_r^*})+1-\frac{R}{R^*}-\frac{I_r}{I_r^*})\\
\leq&\rho_sI_s^*(\frac{I_s}{I_s^*}-ln\frac{I_s}{I_s^*}+ln\frac{R}{R^*}-\frac{R}{R^*})+\gamma(1-\eta)L_s^*(-\frac{R}{R^*}-ln\frac{L_s}{L_s^*}\frac{R^*}{R}+\frac{L_s}{L_s^*})\\
&+\phi T_s^*(-\frac{R}{R^*}-ln\frac{T_s}{T_s^*}\frac{R^*}{R}+\frac{T_s}{T_s^*})+\varphi T_r^*(\frac{T_r}{T_r^*}-ln\frac{R}{R^*}\frac{T_r}{T_r^*}-\frac{R}{R^*})\\
&+\kappa\lambda_s^*R^*(\frac{R}{R^*}-2-ln\frac{R}{R^*}\frac{I_s}{I_s^*}+\frac{I_s}{I_s^*})+\rho_rI_r^*(\frac{I_r}{I_r^*}-ln\frac{R}{R^*}\frac{I_r}{I_r^*}-\frac{R}{R^*})\\
&+\kappa\lambda_r^*R^*(\frac{RI_r}{R^*I_r^*}-1+\frac{R}{R^*}+\frac{I_r}{I_r^*})\\
=&\rho_sI_s^*(\frac{I_s}{I_s^*}-ln\frac{I_s}{I_s^*}+ln\frac{I_s}{I_s^*}-\frac{R}{R})+\gamma(1-\eta)L_s^*(-\frac{R}{R}+ln\frac{R}{R}-ln\frac{L_s}{L_s^*}+\frac{L_s}{L_s^*})\\
&+\phi T_s^*(-\frac{R}{R}+ln\frac{R}{R}-ln\frac{T_s}{T_s^*}+\frac{T_s}{T_s^*})+\kappa\lambda_s^*R^*(\frac{R}{R}-2-ln\frac{R}{R}+\frac{I_s}{I_s^*})\\
&+\rho_r^*I_r^*(\frac{I_r}{I_r^*}-ln\frac{I_r}{I_r^*}+ln\frac{R}{R}-\frac{R}{R})+\varphi T_r^*\left(\frac{T_r}{T_r^*}-ln\frac{T_r}{T_r^*}+ln\frac{R}{R}-\frac{R}{R}\right)\\
&+\kappa\lambda_r^*R^*\left(-ln\frac{R}{R}-ln\frac{I_r}{I_r^*}-2+\frac{R}{R}+\frac{I_r}{I_r^*}\right)\\
=&:a_{105a}G_{105a}+a_{104}G_{104}+a_{106}G_{106}+a_{105b}G_{105b}+a_{108a}G_{108a}+a_{109}G_{109}+a_{108b}G_{108b}
\end{aligned}
$$

Where, $a_{15}=a_{31}=\sigma V^*\lambda_s^*$, $a_{18}=a_{71}=\sigma V^*\lambda_r^*$, $a_{21}=\theta V^*$, $a_{25}=a_{32}=S^*\lambda_s^*$, $a_{28}=a_{72}=S^*\lambda_r^*$,

$a_{310} = \kappa R^* \lambda_s^*$, $a_{35} = (S^* + \sigma V^* + \kappa R^*)\lambda_s^*$, $a_{38} = a_{73} = \lambda_r^* H_s^*$, $a_{43} = \alpha\epsilon(1-p)H_s^*$,
$a_{48} = a_{74} = \lambda_r^* L_s^*$, $a_{54} = \gamma\eta L_s^*$, $a_{53} = \alpha(1-\epsilon)(1-p)H_s^*$, $a_{63} = (\phi + \mu)T_s^*$, $a_{710} = \kappa\lambda_r^* R^*$,
$a_{75} = (1-q)\rho_s I_s^*$, $a_{87} = (1-\nu)\delta E^*$, $a_{97} = \nu\delta E^*$, $a_{105}a = \rho_s I_s^*$, $a_1 04 = \gamma(1-\eta)L_s^*$,
$a_{106} = \phi T_s^*$,
$a_{105b} = \kappa\lambda_s^* R^*$, $a_{108a} = \rho_r I_r^*$, $a_{109} = \varphi T_r^*$, $a_{108b} = \kappa\lambda_r^* R^*$ and all other $a_{ij} = 0$.

The corresponding digraph G(A) (figure 5.4) for $A = [a_{ij}]$, $i, j = 1, ..., 10, 5a, 5b, 8a, 8b$, is given below:

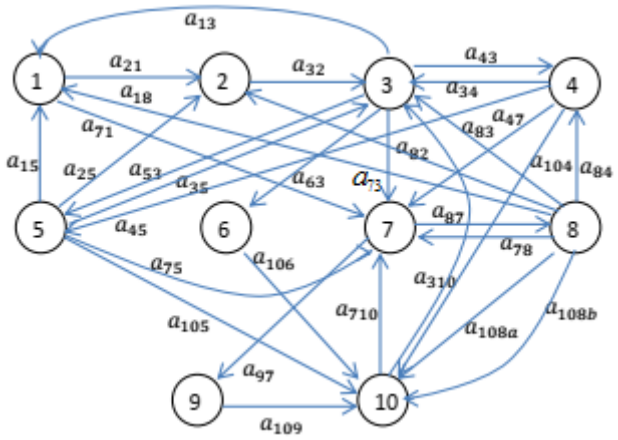

Figure 5.4: The digraph G(A) for the dynamical system (5.1)-(5.10)

Along the cycle of the associated weighted digraph G(A) of figure 5.4:
$G_{35} + G_{53} = \frac{I_s}{I_s^*} - \frac{H_s}{H_s^*} + ln\frac{H_s}{H_s^*} - ln\frac{I_s}{I_s^*}) + (-\frac{I_s}{I_s^*} + ln\frac{I_s}{I_s^*} - \frac{H_S}{H_s^*} + \frac{H_s}{H_s^*}) = 0$,
$G_{35} + G_{43} + G_{54} = (\frac{I_s}{I_s^*} - \frac{H_s}{H_s^*} + ln\frac{H_s}{H_s^*} - ln\frac{I_s}{I_s^*}) + (-\frac{L_s}{L_s^*} + ln\frac{L_s}{L_s^*} - ln\frac{H_s}{H_s^*} + \frac{H_s}{H_s^*}) + (-\frac{I_s}{I_s^*} + ln\frac{I_s}{I_s^*} - ln\frac{L_s}{L_s^*} + \frac{L_s}{L_s^*}) = 0$,
$G_{78} + G_{87} = (\frac{I_r}{I_r^*} - \frac{E}{E^*} - ln\frac{I_r}{I_r^*} + ln\frac{E}{E^*}) + (\frac{E}{E^*} - \frac{I_r}{I_r^*} - ln\frac{E}{E^*} + ln\frac{I_r}{I_r^*}) = 0$, $G_{34} + G_{43} = 0$ and for the other cycles in figure 5.4, $\Sigma G_{ij} \leq 0$ if $\frac{V}{V^*}$, $\frac{S}{S^*}$, $\frac{R}{R^*} \leq 1$, $\frac{H_s}{H_s^*} \leq \frac{I_s}{I_s^*}$ and $\frac{E}{E^*} \leq \frac{I_r}{I_r^*}$.

By Proposition 1.3 of [109], there exists $c_i > 0, i = 1, \ldots, 10$ such that $B = \Sigma_{i=1}^{10} c_i B_i$ is a Lyapunov function for equations (5.1)−(5.10). The relations between c_i's can be derived from Theorems 3.3 and 3.4 of [109] such that:
$a_{97} > 0, d^+(7) = 1$ implies $c_9 a_{97} = \Sigma_{k=1}^{10} c_7 a_{9k}$

$$\Rightarrow c_9 a_{97} = c_7 a_{97} \Rightarrow c_9 = c_7$$

$a_{106} > 0, d^+(6) = 1$ implies $c_{10}a_{106} = \Sigma_{=1}^{10} c_6 a_{10k}$

$$\Rightarrow c_{10}a_{106} = c_6(a_{105a} + a_{104} + a_{106} + a_{105b} + a_{108a} + a_{109} + a_{108b})$$
$$\Rightarrow c_{10} = c_6\frac{(a_{105a} + a_{104} + a_{106} + a_{105b} + a_{108a} + a_{109} + a_{108b})}{a_{106}}$$

$a_{87} > 0, d^-(8) = 1$ implies $c_8 a_{87} = \Sigma_{k=1}^{10} c_k a_{k8}$

$$\Rightarrow c_8 a_{87} = c_1 a_{18} + c_2 a_{28} + c_3 a_{38} + c_4 a_{48} + c_7 a_{78} + c_{10}(a_{108a} + a_{108b})$$
$$\Rightarrow c_8 = \frac{c_1 a_{18} + c_2 a_{28} + c_3 a_{38} + c_4 a_{48} + c_7 a_{78} + c_{10}(a_{108a} + a_{108b})}{a_{87}}$$

Therefore, $B = c_1B_1 + c_2B_2 + c_3B_3 + c_4B_4 + c_5B_5 + c_6B_6 + c_7B_7 + c_8B_8 + c_9B_9 + c_{10}B_{10}$ is a Lyapunov function for (5.1)−(5.10). Therefore, E_3 is globally asymptotically stable in the interior of Ω when $R_{eff}(DS) > 1$ and $R_{eff}(MDR) > 1$. □

5.5 Conclusion

In this study we have presented and analyzed the two strain TB model with interventions: vaccination of newly born babies, screening of latently infected and treatments of infectious individuals for both strains of tuberculosis (drug sensitive and multi-drug resistance tuberculosis). We found that $R_{eff}(DS) = \frac{c\omega_s(\sigma\psi\mu+(\theta+(1-\psi)\mu))}{(\theta+\mu)}\frac{(1-p)\alpha(\epsilon\gamma\eta+(1-\epsilon)(\gamma+\eta))}{(\alpha+\mu)(\gamma+\mu)(\rho_s+\mu+d_s)}$ and $R_{eff}(MDR) = \frac{c\omega_r(\sigma\psi\mu+(\theta+(1-\psi)\mu))}{(\theta+\mu)}\frac{(1-\nu)\delta}{(\delta+\mu)(\rho_r+\mu+d_r)}$ the effective reproduction numbers of drug sensitive and multi-drug resistance tuberculosis respectively. And, thus $R_{eff} = \max R_{eff}(DS), R_{eff}(MDR)$ is the effective reproduction number of the system (5.1)-(5.10). We have discussed on the existence of disease free equilibrium point, endemic equilibrium (drug-sensitive TB only endemic equilibrium, drug-resistance TB only endemic equilibrium and endemic equilibrium when both strains exist) points and presented the conditions that the local and global stability of those equilibrium points.

Chapter 6

Numerical Simulation and Sensitivity Analysis for Analysis on the Dynamics of Tuberculosis Mathematical Model with Interventions

Abstract

This chapter present the numerical simulation for the nonlinear dynamical system (4.1)−(4.8). Using standard data collected from different sources we found the numerical value of the effective reproduction number is $R_{eff} = 0.7 < 1$ which shows that the tuberculosis disease not spreads in the community. We have done also sensitivity analysis to identify the most influential parameter that affects the effective reproduction number and we found rate of vaccine waning θ is the most influential parameter to change the effective reproduction number.

6.1 Introduction

In this chapter, we perform some numerical experimentation on the tuberculosis model (4.1)-(4.8) to verifying some of the analytical results. This is done by using a set of parameter values whose sources are mainly from related literatures, WHO and Federal Democratic Republic of Ethiopia Ministry of Health reports as well as estimation in order to have more realistic simulation results. In section 6.2 numerical simulations of the results are done by using data reported by WHO and related literature. In sections 6.3 and 6.4 the sensitivity analysis and discussion were done respectively to provided an explanation of the results . Finally, in section 6.5 we gave conclusions based on our finding of this work.

6.2 Numerical Simulations

The Table-6.1 below presents the values and their respective sources of the parameters of the model (4.1)-(4.8).

Table 6.1: Parameter estimation for parametrs in the dynamical system (4.1)-(4.8)

Descriptions	**Symbols**	**Value**	**Source**
Recruitment of the population	Λ	3845257	[102]
Proportions new born vaccinated	ψ	0.9	[102]
Natural death rate	μ	0.0077	[66]
The rate of inefficacy of vaccine individuals	σ	0.2	[67, 102]
The rate of BCG vaccine waning	θ	0.0667	Estimated
Probability of acquiring TB infections per contact with one active TB	ω	0.5	[67]
Number of effective contacts susceptible or vaccinated individuals makes with infectious individuals per year.	c	2	Estimated
The rate of progression of individuals from early latently infected with TB.	α	0.03	[67]

Death rate due to the TB disease	d	0.00025	[102]
Proportion of H_r move to T	p	0.2	Estimated
The portion of L_r enter in to I	δ	0.1	Estimated
Progression rate from L_r	γ	0.03	[67]
Proportion of individuals who do not get chance for screened at H_r and will go to L_r class.	ϵ	0.5	Estimated
The recovery rate infectious individuals	ρ	0.3	[67]
Proportion of infectious individuals who enters to R	q	0.94	[102]
Rate of individuals move from T to R	ϕ	2	Estimated
Rate of individuals move from I_T to R	φ	1.33	Estimated
Acquired immunity due to previous treatment.	κ	0.99	Estimated

6.2.1 Numerical Simulation for the Effective Reproduction Number

The effective reproduction number R_{eff} of the model system (4.1)-(4.8) is:

$$R_{eff} = c\omega \left(\frac{\sigma\psi\mu + (1-\psi)\,\mu + \theta}{\mu + \theta} \right) \frac{\alpha\varepsilon\,(1-p)\,\delta\gamma + \alpha\,(1-\varepsilon)\,(1-p)\,(\mu+\gamma)}{(\mu+\alpha)\,(\mu+\gamma)\,(\mu+\rho+d)}$$

Thus, the numerical value of effective reproduction number, $R_{eff} = 0.70 < 1$. Now we are going to illustrate and discussed on the relation between effective reproduction number and the parameters as follows:

Let us consider the parameter contact rate c as a variable and keeping all other parameters constant and written the effective reproduction number as a function of c, $R_{eff}(c) = 0.510027891273821c$

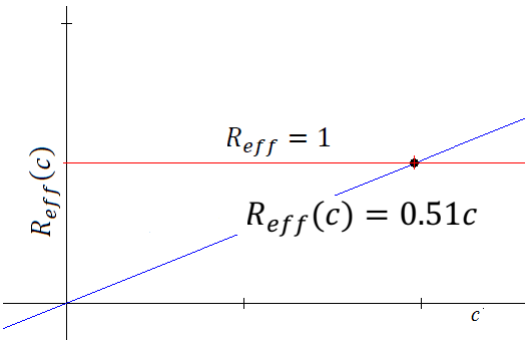

Figure 6.1: Graph of the effective reproduction number R_{eff} vrs the effective contact rate , c

In the graph figure 6.1 the lines $R_{eff}(c) = 0.51c$ and $R_{eff} = 1$ intersect at $c = 1.96$. Thus, $R_{eff} < 1$ when the contact rate, $c < 1.96$ and $R_{eff} > 1$ when $c > 1.96$ implies the TB disease spreads in the community when $c > 1.96$.

Consider the parameter probability of transmission ω as a variable and keeping all other parameters constant, then the effective reproduction number can be written as a function of ω: $R_{eff}(\omega) = 2.04\omega$.

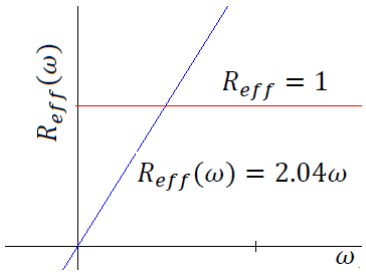

Figure 6.2: Graph of the effective reproduction number R_{eff} vrs probability of acquiring TB ω

In the figure 6.2 the lines $R_{eff}(\omega) = 2.04\omega$ and $R_{eff} = 1$ intersect at $\omega = 0.49$, then $R_{eff} < 1$ when $\omega < 0.49$ and $R_{eff} > 1$ when $0.49 < \omega$.

Consider the rate of progression of individuals from early latently infected with TB, α as a variable and keeping all other parameters as constant, the effective reproduction number can be written as a function of α: $R_{eff}(\alpha) = \frac{1.13\alpha}{\alpha+0.02}$

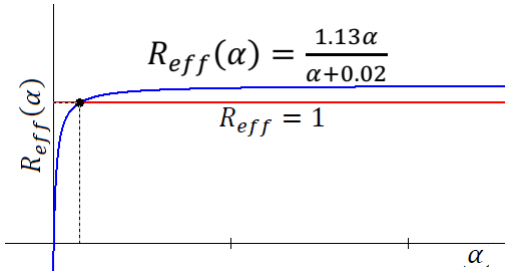

Figure 6.3: Graph of the effective reproduction number R_{eff} vrs rate of progression from H_r, α

In figure 6.3 above the curve $R_{eff}(\alpha) = \frac{1.13\alpha}{\alpha+0.02}$ and the line $R_{eff} = 1$ intersect at $\alpha = 0.14$, then $R_{eff} < 1$ when $\alpha < 0.14$ and $R_{eff} > 1$ when $\alpha > 0.14$

Consider the progression rate from L_r, γ as a variable and keeping all other parameters as constant, the effective reproduction number can be written as a function of γ: $R_{eff}(\gamma) = \frac{0.01\gamma+0.0002}{0.002\gamma+0.0005}$

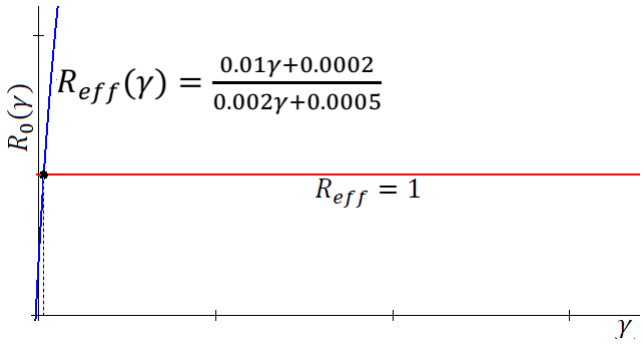

Figure 6.4: Graph of the effective reproduction number R_{eff} vrs progression rate from L_s, γ

In figure 6.4 the curve $R_0(\gamma) = \frac{0.01\gamma+0.0002}{0.002\gamma+0.0005}$ and the line $R_{eff} = 1$ intersect at $\gamma = 0.03$, then $R_{eff} < 1$ when $\gamma < 0.03$ and $R_{eff} > 1$ when $\gamma > 0.03$.

Consider the rate of inefficacy of vaccine individuals, σ as a variable and keeping all other parameters as constant, the effective reproduction number can be written as a function of σ: $R_{eff}(\sigma) = 0.19\sigma + 2.01$

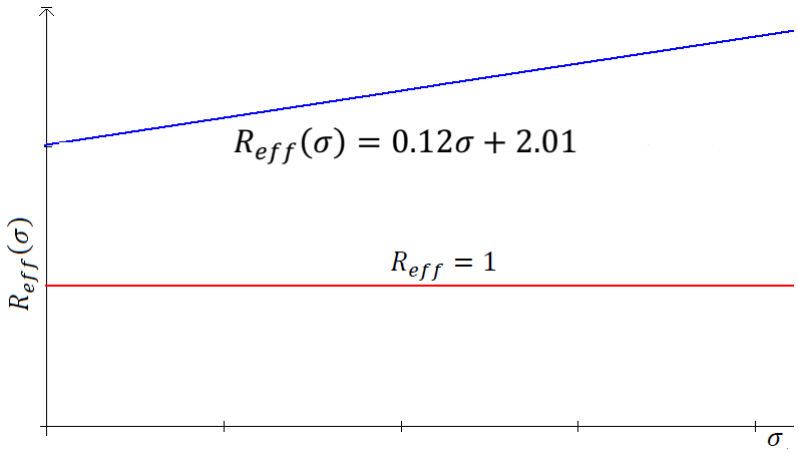

Figure 6.5: Graph of the effective reproduction number R_{eff} vrs infficacy rate of BCG vaccinve σ

In figure 6.5 the curve $R_{eff}(\sigma) = 0.19\sigma + 2.01$ and the line $R_{eff} = 1$ do not intersect and $R_{eff} > 1$ for every value of σ.

Consider the rate of BCG vaccine waning, θ as a variable and keeping all other parameters as constant, the effective reproduction number can be written as a function of θ: $R_{eff}(\theta) = 1.21\frac{0.005+\theta}{0.02+\theta}$

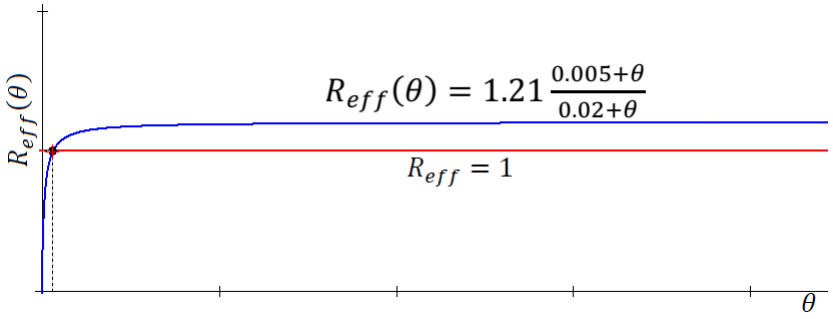

Figure 6.6: Graph of the effective reproduction number R_{eff} vrs vaccine wanning rate θ

In figure 6.6 the curve $R_{eff}(\theta) = 1.21\frac{0.005+\theta}{0.02+\theta}$ and the line $R_{eff} = 1$ intersect at $\theta = 0.06$, then $R_{eff} < 1$ when $\theta < 0.06$ and $R_{eff} > 1$ when $\theta > 0.06$

Consider the proportions new born vaccinated, ψ as a variable and keeping all other parameters as constant, the effective reproduction number can be written as a function of ψ: $R_{eff}(\psi) = -0.21\psi + 1.20718341374269$

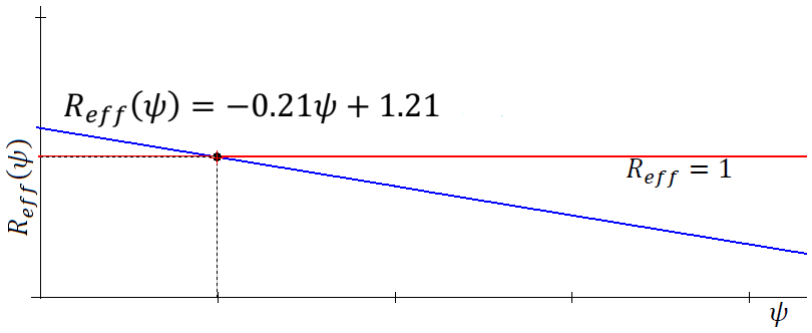

Figure 6.7: Graph of the effective reproduction number R_{eff} vrs proportion of vaccinated newly born babies ψ

In figure 6.7 the curve $R_{eff}(\psi) = -0.21\psi + 1.21$ and the line $R_{eff} = 1$ intersect at $\psi = 0.99$, then $R_{eff} < 1$ when $\psi > 0.99$ and $R_{eff} > 1$ when $\psi < 0.99$

Consider the proportion of H_r move to T, p as a variable and keeping all other parameters as constant, the effective reproduction number can be written as a function of p: $R_{eff}(p) = (1-p)0.87$

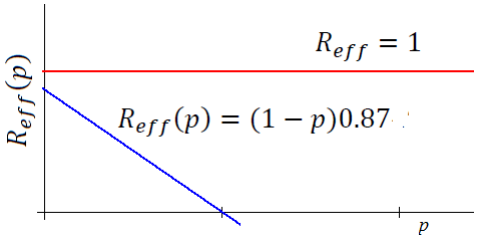

Figure 6.8: Graph of the effective reproduction number R_{eff} vrs proportion of H_s move to T_s, p

In figure 6.8 the curve $R_{eff}(p) = (1-p)0.87$ and the line $R_{eff} = 1$ have no intersection in the first quadrant however $R_{eff} < 1$ for all $p \in [0, 1]$

Take the proportion of individuals who do not get chance for screened at H_r and will go to L_r class, ϵ as a variable and keeping all other parameters as constant, the effective reproduction number can be written as a function of ϵ: $R_{eff}(\epsilon) = -1.24\epsilon + 1.34$.

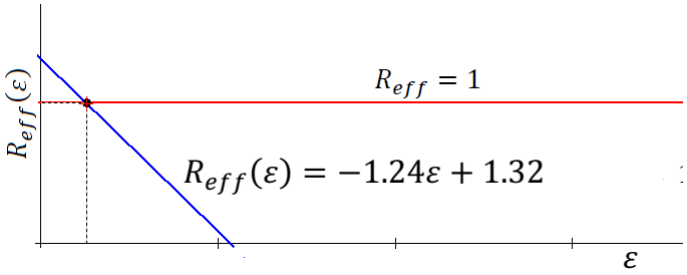

Figure 6.9: Graph of the effective reproduction number R_{eff} vrs proportion of H_r will go to L_r, ϵ

In figure 6.9 the lines $R_{eff}(\epsilon) = -1.24\epsilon + 1.32$ and $R_{eff} = 1$ intersect at $\epsilon = 0.26$, then $R_{eff} < 1$ when $\epsilon > 0.26$ and $R_{eff} > 1$ when $\epsilon < 0.26$.

Consider the portion of L_r enter in to I, δ as a variable and keeping all other parameters as constant, the effective reproduction number can be written as a function of δ: $R_{eff}(\delta) = 0.41\delta + 0.66$,

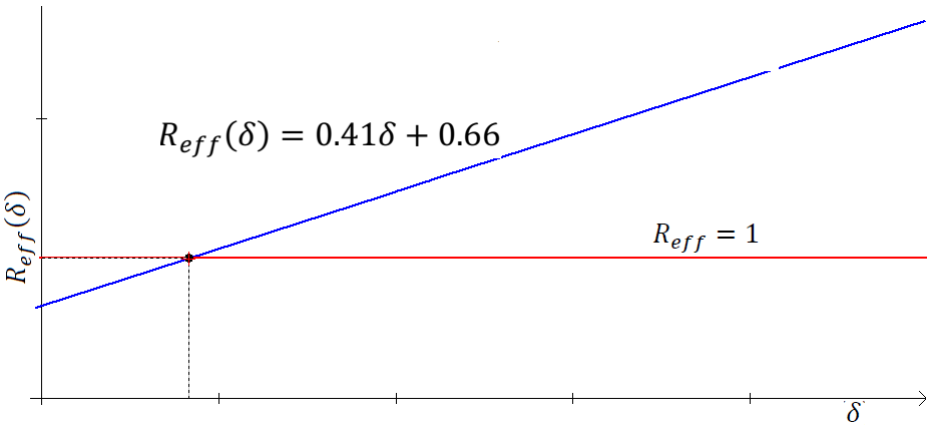

Figure 6.10: Graph of the effective reproduction number R_{eff} vrs portion of L_r enter in to I, δ

In figure 6.10 the lines $R_{eff}(\delta) = 0.41\delta + 0.66$ and $R_{eff} = 1$ intersect at $\delta = 0.83$. Then $R_{eff} < 1$ when $\delta < 0.83$ and $R_{eff} > 1$ when $\delta > 0.83$.

Consider the death rate due to the TB disease, d as a variable and keeping all other parameters as constant, then the effective reproduction number can be written as a function of d: $R_0\,(d) = \frac{2.23}{d+0.09}$

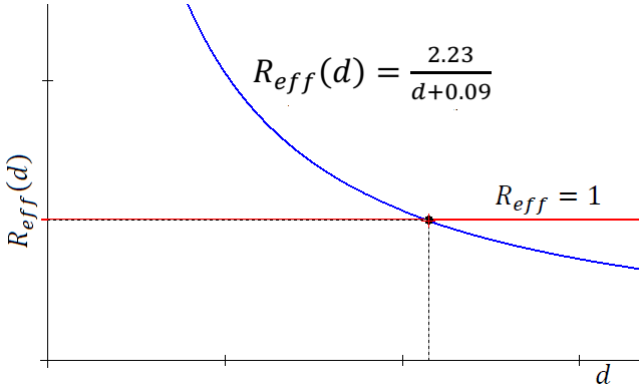

Figure 6.11: Graph of the effective reproduction number R_{eff} vrs induced death rate, d

In figure 6.11 the curve $R_0\,(d) = \frac{2.23}{d+0.09}$ and the line $R_{eff} = 1$ intersect at $d = 2.14$, then $R_{eff} < 1$ when $d > 2.14$ and $R_{eff} > 1$ when $d < 2.14$.

Consider the recovery rate infectious individuals, ρ as a variable and keeping all other parameters as constant, then the effective reproduction number can be written as a function of ρ: $R_{eff}\,(\rho) = \frac{2.23}{\rho+0.02}$

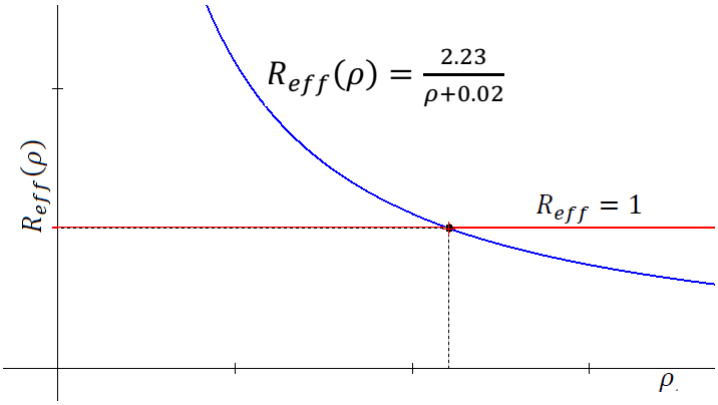

Figure 6.12: Graph of the effective reproduction number R_{eff} vrs recovery rate of I, ρ

In figure 6.12 the curve $R_{eff}\,(\rho) = \frac{2.23}{\rho+0.02}$ and the line $R_{eff} = 1$ intersect at $\rho = 2.21$, then $R_{eff} < 1$ when $\rho > 2.21$ and $R_{eff} > 1$ when $\rho < 2.21$.

6.3 Sensitivity Analysis

We perform sensitivity analyses on a mathematical model of TB transmission to determine the relative importance of model parameters to disease transmission and control. We apply the normalized forward sensitivity index of R_{eff} to a parameter is the ratio of the relative change in the variable to the relative change in the parameter [66]. In interpreting the sensitivity indices of R_{eff} with respect to a parameter, we first note that keeping all other factors fixed and determine the magnitude of the sensitivity indices. The parameter with higher magnitude is/are more influential. The sign of the sensitivity indices of R_{eff} with respect to the parameters show the positive or negative impact of the parameter onR_{eff}. That is if the sign of the sensitivity indices is positive then the value of R_{eff} increase whenever the value of the parameter increases and if the sign of the sensitivity indices is negative then the value of R_{eff} decrease whenever the value of the parameter increase [66, 67].

As we have an explicit formula for R_{eff}, we derive an analytical expression for the sensitivity of R_{eff},

$$R_{eff} = c\omega \left(\frac{\sigma\psi\mu + (1-\psi)\,\mu + \theta}{\mu + \theta} \right) \frac{\alpha\epsilon\,(1-p)\,\delta\gamma + \alpha\,(1-\epsilon)\,(1-p)\,(\mu+\gamma)}{(\mu+\alpha)\,(\mu+\gamma)\,(\mu+\rho+d)}$$

to each of the parameters of the dynamical system (4.1)-(4.8) as, $\Pi_x{}^{R_{eff}} = \frac{\partial R_{eff}}{\partial x} \times \frac{x}{R_{eff}}$ where x is the parameter of the dynamical system (4.1)-(4.8)which involves in R_{eff}. We evaluate the nonzero sensitivity indices ofR_{eff} with respect to the parameters as follows: Sensitivity index of R_{eff} with respect to the parameters c is given as:

$$\Pi_c{}^{R_{eff}} = \frac{\partial R_{eff}}{\partial c} \times \frac{c}{R_{eff}} = 1$$

Sensitivity index of R_{eff} with respect to the parameters ω is given as:

$$\Pi_\omega{}^{R_{eff}} = \frac{\partial R_{eff}}{\partial \omega} \times \frac{\omega}{R_{eff}} = 1$$

Sensitivity index of R_{eff} with respect to the proportion of vaccinated new born, ψ is given as:

$$\Pi_\psi{}^{R_{eff}} = \frac{\partial R_{eff}}{\partial \psi} \times \frac{\psi}{R_{eff}} = \frac{(\sigma-1)\,\psi\mu}{\sigma\psi\mu + (1-\psi)\,\mu + \theta}$$

Sensitivity index of R_{eff} with respect to the rate of inefficacy of BCG vaccine σ is given as:

$$\Pi_{\sigma}^{R_{eff}} = \frac{\partial R_{eff}}{\partial \sigma} \times \frac{\sigma}{R_{eff}} = \frac{\sigma\psi\mu}{\sigma\psi\mu + (1-\psi)\mu + \theta}$$

Sensitivity index of R_{eff} with respect to the rate of BCG vaccine waning θ is given as:

$$\Pi_{\theta}^{R_{eff}} = \frac{\partial R_0}{\partial \theta} \times \frac{\theta}{R_{eff}} = \frac{(1-\sigma)\psi\mu}{(\mu+\theta)(\sigma\psi\mu + (1-\psi)\mu + \theta)}$$

Sensitivity index of R_{eff} with respect to the rate of individuals leave from H_r, α is given as:

$$\Pi_{\alpha}^{R_{eff}} = \frac{\partial R_{eff}}{\partial \alpha} \times \frac{\alpha}{R_{eff}} = \frac{\mu}{(\mu+\alpha)}$$

Sensitivity index of R_{eff} with respect to the rate of individuals leave from L_r class γ is given as:

$$\Pi_{\gamma}^{R_{eff}} = \frac{\partial R_{eff}}{\partial \gamma} \times \frac{\gamma}{R_{eff}} = \frac{\gamma\left[\alpha\epsilon(1-p)\delta + \alpha(1-\epsilon)(1-p)\right]}{\alpha\epsilon(1-p)\delta\gamma + \alpha(1-\epsilon)(1-p)(\mu+\gamma)} - \frac{\gamma}{(\mu+\gamma)}$$

Sensitivity index of R_{eff} with respect to the proportion of H_r, who go for treatment, p is given as:

$$\Pi_{p}^{R_{eff}} = \frac{\partial R_{eff}}{\partial \mathrm{p}} \times \frac{p}{R_{eff}} = -\frac{p\left[\alpha\epsilon\delta\gamma + \alpha(1-\epsilon)(\mu+\gamma)\right]}{\alpha\epsilon(1-p)\delta\gamma + \alpha(1-\epsilon)(1-p)(\mu+\gamma)}$$

Sensitivity index of R_{eff} with respect to the Proportion of individuals who do not get chance for screened at H_r who will go to L_r class, ϵ is given as:

$$\Pi_{\epsilon}^{R_{eff}} = \frac{\partial R_{eff}}{\partial \epsilon} \times \frac{\epsilon}{R_{eff}} = \frac{\alpha(1-p)\epsilon\left[\delta\gamma - (\mu+\gamma)\right]}{\alpha\epsilon(1-p)\delta\gamma + \alpha(1-\epsilon)(1-p)(\mu+\gamma)}$$

Sensitivity index of R_{eff} with respect to the rate at which individuals leave infectious class I, ρ is given as:

$$\Pi_{\rho}^{R_{eff}} = \frac{\partial R_{eff}}{\partial \rho} \times \frac{\rho}{R_{eff}} = -\frac{\rho}{(\mu+\rho+d)}$$

Sensitivity index of R_{eff} with respect to the portion of L_r enter in to I, δ

$$\Pi_{\delta}^{R_{eff}} = \frac{\partial R_{eff}}{\partial \delta} \times \frac{\delta}{R_{eff}} = \frac{\delta\alpha\epsilon(1-p)\gamma}{\alpha\epsilon(1-p)\delta\gamma + \alpha(1-\epsilon)(1-p)(\mu+\gamma)}$$

Sensitivity index of R_{eff} with respect to the induced death rate, d

$$\Pi_{d}^{R_{eff}} = \frac{\partial R_{eff}}{\partial d} \times \frac{d}{R_{eff}} = -\frac{d}{(\mu+\rho+d)}$$

Sensitivity index of R_{eff} with respect to the natural death rate, μ

$$\Pi_{\mu}^{R_{eff}} = \frac{\partial R_{eff}}{\partial \mu} \times \frac{\mu}{R_{eff}}$$

$$= \frac{\mu\left(1+(\sigma-1)\psi\right)}{\left(1+(\sigma-1)\psi\right)\mu+\theta} + \frac{\mu(1-\epsilon)}{(1-\epsilon)\mu+\epsilon\delta\gamma+(1-\epsilon)\gamma} - \frac{\mu}{\mu+\theta} - \frac{\mu}{\mu+\gamma} - \frac{\mu}{\mu+d+\rho}$$

Using the data in table 6.1 the resulting sensitivity indices of R_{eff} to the parameters are shown in table 6.2 with the order from most sensitive to the least:

Table 6.2: The numerical values of the sensitivity indices of R_{eff} with respect to each of the parameter which involve in R_{eff}

Parameters	The sensitivity index of R_{eff} to the parameters
θ	+2.16
γ	+1.26
c	+1
ω	+1
α	+0.38
δ	+0.0585
σ	+0.046
d	-0.00075
μ	-0.134
ψ	-0.184
ϵ	-0.883
ρ	-0.942
p	-1.25

6.4 Discussion

In this section we discussed on the numerical results of dynamics of tuberculosis disease (4.1)-(4.8). And we have been evaluate the effect of each parameter on effective reproduction number,

$$R_{eff} = c\omega\left(\frac{\sigma\psi\mu+(1-\psi)\mu+\theta}{\mu+\theta}\right)\frac{\alpha\epsilon(1-p)\delta\gamma+\alpha(1-\epsilon)(1-p)(\mu+\gamma)}{(\mu+\alpha)(\mu+\gamma)(\mu+\rho+d)}$$

. Consequently, Figure 6.1 shows that if the contact rate, $c < 1.96$ then the effective reproduction number,$R_{eff} < 1$ and then the disease is not spread in the community if $c > 1.96$ then $R_{eff} > 1$ implies the TB disease spreads in the community when $c > 1.96$. Figure 6.2 shows that the effective reproduction number,$R_{eff} < 1$ when the probability of acquiring TB infections per contact with one active TB, $\omega < 0.49$ and $R_{eff} > 1$ when $0.49 < \omega < 1$. Implies that the TB disease spreads in the community when $0.49 < \omega < 1$ and not spread in the community if $\omega < 0.49$ From figure 6.3 we observe that the effective reproduction number, $R_{eff} < 1$ if the rate of progression of individuals from early latently infected with TB, $\alpha < 0.0.14$ and $R_{eff} > 1$ if $\alpha > 0.14$. Thus disease spreads in the community when $\alpha > 0.14$ and not spread in the community if $\alpha < 0.14$. Figure 6.4 shows that the TB disease do not spread in the society when the Progression rate from long latently infected class, $\gamma < 0.03$ and spread in the society when $\gamma > 0.03$. From figure 6.5 and 6.10 we can notice that $R_{eff} > 1$ for all values of the rate of inefficacy of vaccine individuals, σ and the portion of long latent infected develop active TB, δ respectively. Therefore the disease spread in the society for all value of σ and δ. Figure 6.6 shows that the TB disease spread in the society if the rate of BCG vaccine waning, $\theta > 0.06$ and not spread in the society if $\theta < 0.06$. In figure 6.6, $R_{eff} < 1$ if $\theta > 0.99$ and $R_{eff} > 1$ if $\theta < 0.99$ implies that the disease do not spread in the society when $\theta > 0.99$ and disease spread in the society when $\theta < 0.99$. Figure 6.8 shows that $R_{eff} < 1$ for all values of the proportion of screened early infected, $p \in [0, 1]$ and then the disease spread in the community for all values of p. Figure 6.9 shows that the disease do not spread in the society when the proportion of individuals who do not get chance for screened at early latent stage $\epsilon > 0.26$ and the disease spread in the society when $\epsilon < 0.26$. Through figure 6.11 and figure 6.12 illustrates that the disease do not spread in the society when the death rate due to the TB disease, $d > 2.14$ and the recovery rate infectious individuals, $\rho > 2.21$ respectively and spread in the society when $d < 2.14$ and $\rho < 2.21$ respectively.

The parameters such as number of effective contacts of susceptible or vaccinated individuals makes with infectious individuals per year c, probability of TB disease transmission from infectious person to another person ω, the rate of inefficacy of BCG vaccine σ, the rate of BCG vaccine waning θ, the rate of individuals leave from early latently infected class α, the rate of individuals leave from long latently infected class have positive con-

tributions for the transmission of TB, implies that, when those parameters are increased keeping other parameters constant they increase the value of the effective reproduction number, R_{eff}. While the parameters such as the proportion of vaccinated new born individuals ψ, the proportion of early latently infected individuals who go for treatment p, the rate at which individuals leave infectious class will help to decrease the value of the effective reproduction number, R_{eff} as they increase. The most sensitive parameter in the spread and control of tuberculosis disease is the waning rate of BCG vaccine, θ, followed by the progression rate from long latently infected tuberculosis to active TB, γ and the proportion p of early stage latently infected individuals who have got the chance for screened and treatment (table 6.2).

6.5 Conclusion

This chapter presented the numerical simulation for the dynamical system (4.1)−(4.8). Using standard data collected from different sources we found the numerical value of the effective reproduction number is $R_{eff} = 0.7$ which shows that the tuberculosis disease not spreads in the community. We have done the numerical simulation of the dynamical system. The waning rate of Bacilli Calmette-Guérin (BCG) vaccine, θ, followed by the progression rate from long latently infected to active tuberculosis, γ and the proportion p of early stage latently infected individuals who go for treatment are the most influential parameters to change the effective reproduction number of the model (4.1)-(4.8). The result shows that vaccination alone cannot eliminate tuberculosis disease from a population, but can slow the rate of transmission from long stage latently infected; and increasing the portion screened and treating of early stage latently infected.

Chapter 7

Parameter Estimation, Numerical Simulation and Sensitivity Analysis for Spread and Control of Drug Sensitive and Multi-Drug Resistance Tuberculosis in Ethiopia

Abstract

In this chapter we presented the numerical simulation for the nonlinear dynamical system of two-strain Tuberculosis epidemic in Ethiopia (5.1)−(5.10). Using real data collected from different health centers from Ethiopia we found that the numerical value of the effective reproduction number of the drug sensitive tuberculosis is $R_{eff}(DS) = 1.03$ and the effective reproduction number of the drug resistance tuberculosis is $R_{eff}(MDR) = 4.78$.These numerical values indicate that both strains of tuberculosis persist in the community with interventions. Numerical simulation is also done to illustrate the influence of different parameters on the effective reproduction number. Using sensitive analysis we identify the most influential parameter to change the behavior of the solution of the considered dynamical system is the number of effective contacts of susceptible or vacci-

nated individuals make with an infectious individual c, with the sensitivity index of both $R_{eff}(DS)$ and $R_{eff}(MDR)$ are equal to 1.

7.1 Introduction

We performed some numerical experimentation on the tuberculosis model (5.1)−(5.10). This is done by using a set of parameter values whose sources are mainly from Federal Democratic Republic of Ethiopia Ministry of Health (EMH), Ethiopia Demographics Profile (EDP), world health organization (WHO) reports and other related literatures as well as estimation in order to have more realistic simulation results. In section 7.2 parameters are estimated by using data reported by the Ministry of Health of Ethiopia. In section 7.3 numerical simulations are done. In section 7.4 sensitivity analysis of investigated. Finally,in sections 7.5 and 7.6 we discussed and provide an explanation on the finding of this work.

7.2 Parameter Estimation

We take initial condition from the data of Ministry of Health of Ethiopia [43]: $V(0) = 9436405$, $I_s(0) = 42139$,$T_s(0) = 83546$, $E(0) = 8098$, $I_r(0) = 774$, $T_r(0) = 528$ and $R(0) = 3597$. We assumed that more than half of the population (62%) belongs to susceptible class S(0)=62355690 and that a big percentage about 33% is infected with TB in latent stage that is $H_s(0) = 2 \times (417729 \ per \ year) = 835,458$ and $L_s(0) = 32,164,542$,. This is justified from the fact that "about one third of the world's population has latent TB", as it is indicated from the webpage of the World Health Organization (WHO, 2017).

In the Ethiopian demography profile the birth rate of Ethiopian population is 36.5 per 1000 population and the total population is 105,350,020. Therefore we can calculate the recruitment of the population as:

$$\Lambda = birth \ rate \times total \ population = \frac{(36.5 \times 105,350,020)}{1000} = 3845275$$

In Ethiopia the BCG vaccine programs has implemented and so that according to the

Ethiopian Ministry of Health in a year there are 1887281 newly born babies have taken BCG vaccine.

Therefore, we can estimate the proportion of newly born BCG vaccinated babies in Ethiopia as:

$$\psi = \frac{number\ of\ newly\ born\ vaccinated\ babies}{Total\ number\ of\ newly\ born\ babies} = 1887281/3845275 = 0.49$$

According to Ethiopia demography profile, in Ethiopia there are 7.7 deaths per 1000 population. Hence the natural death rate of the population in Ethiopia is estimated as:

$$\mu = \frac{number\ of\ death}{number\ of\ total\ population} = 7.7/1000 = 0.0077$$

As the world health organization report the maximum efficacy of BCG vaccine is 80%, this implies that there is a 20% inefficacy rate of the BCG vaccine. That is the rate of inefficacy of BCG vaccine is estimated as:

$$\sigma = 1 - \ proportion\ of\ maximum\ efficacy\ of\ BCG\ vaccine = 1 - 0.8 = 0.2$$

From the world health organization report the BCG vaccine efficacy reduces in time and loses completely its efficacy after 15 years. Therefore we can calculate the rate of BCG vaccine waning rate per year as:

$$\theta = 1/(mean\ life\ time\ of\ BCG\ vaccine) = \frac{1}{15 years} = 0.067 per\ year$$

Probability of acquiring TB infections per contact with a drug sensitive strain infectious individual:

$$\omega_s = \frac{number\ of\ newly\ infected\ individuals\ from\ a\ DS\text{-}TB\ infectious}{total\ number\ of\ people\ who\ contact\ a\ DS\text{-}TB\ infectious} = 0.2$$

Probability of acquiring MDR-TB infections per contact with an infectious individual:

$$\omega_r = \frac{number\ of\ newly\ infected\ from\ an\ MDR\text{-}TB\ infectious}{total\ number\ of\ people\ who\ contact\ with\ an\ MDR\text{-}TB\ infectious} = 0.3$$

Number of effective contacts susceptible or vaccinated individuals makes with infectious individuals per year: c= the average number of susceptible or vaccinated individuals makes contacts with an infectious individuals per year = 11

Death rate due to the drug sensitive TB disease:

$$d_s = \frac{the\ number\ of\ people\ die\ due\ to\ DS\text{-}TB\ disease}{total\ number\ of\ petient\ with\ DS\text{-}TB\ disease} = 0.00025$$

Death rate due to the multi-drug resistance TB disease:

$$d_r = \frac{the\ number\ of\ people\ die\ due\ to\ MDR\text{-}TB\ disease}{total\ number\ of\ petient\ with\ MDR\text{-}TB\ disease} = 0.105$$

From the real data of Ethiopia Ministry of health on tuberculosis we can also estimate the following parameters:

Rate of individuals move from T_s to R:

$$\phi = \frac{1}{mean\ infection\ period\ early\ latently\ infected\ DS\text{-}TB} = 0.94$$

Rate of individuals move from T_r to R:

$$\varphi = \frac{1}{mean\ infection\ period\ of\ latently\ infected\ MDR\text{-}TB} = 0.88$$

Rate of recovery of active drug sensitive tuberculosis:

$$\rho_s = \frac{1}{mean\ infectous\ period\ of\ active\ DS\text{-}TB} = 0.83$$

Rate of recovery of active multi-drug resistance tuberculosis:

$$\rho_r = \frac{1}{mean\ infectous\ period\ of\ active\ MDR\text{-}TB} = 0.498$$

Progression rate from early latency drug sensitive tuberculosis:

$$\alpha = \frac{1}{average\ early\ latent\ period\ of\ DS\text{-}TB} = 1/(2year) = 0.5per\ year$$

Progression rate from latency multi-drug resistant tuberculosis:

$$\delta = \frac{1}{average\ life\ time\ latently\ infected\ MDR\text{-}TB} = 0.55per\ year$$

Proportion of individuals who do not get chance for screened at H_s and will go to L_s class:

$$\epsilon = \frac{number\ of\ individuals\ who\ move\ from\ H_s\ to\ L_s}{total\ number\ individuals\ who\ do\ not\ get\ chance\ for\ screened\ at\ H_s} = 0.9$$

Proportion of latently infected DS-TB at early stage for treatment:

$$p = \frac{number\ of\ screend\ at\ H_s\ and\ move\ to\ T_s}{total\ number\ individuals\ at\ H_s} = \frac{83546}{417729} = 0.2$$

The proportion of latently infected with MDR-TB who got a chance of screen and treatment:

$$\nu = \frac{number\ of\ individuals\ who\ screened\ latent\ MDR\text{-}TB}{total\ number\ latently\ infected\ with\ MDR\text{-}TB} = 0.065$$

The portion of L_s enter in to I_s:

$$\eta = \frac{number\ of\ individuals\ L_s who\ develope\ active\ DS\text{-}TB}{total\ number\ long\ latently\ infected\ with\ DS\text{-}TB} = 0.5$$

Proportion of infectious individuals with DS-TB who enters to recovered class.

$$q = \frac{number\ of\ cured\ individuals\ active\ DS\text{-}TB}{total\ number\ active\ DS\text{-}TB} = 0.18$$

Progression rate from Long latently infected with drug sensitive TB.

$$\gamma = \frac{1}{mean\ infected\ period\ for\ long\ latent\ DS\text{-}TB} = 0.1 per\ year$$

Acquired immunity due to previous treatment:

$$\kappa = \frac{number\ of\ reinfected\ cases}{total\ number\ of\ recovered\ individuals} = 0.06$$

Table 7.1: Parameter estimation for parametrs in the dynamical system (5.1)-(5.10)

Descriptions	**Symbols**	**Value**	**Source**
Recruitment of the population	Λ	3845257	[37]
Proportions new born vaccinated	ψ	0.49	[37, 43]
Natural death rate	μ	0.0077	[37]
The rate of inefficacy of BCG vaccine individuals	σ	0.2	[103]
The rate of vaccine BCG waning	θ	0.0667	[103]
Probability of acquiring TB infections per contact with one active DS-TB	ω_s	0.2	[13]
Probability of acquiring TB infections per contact with one active MDR-TB	ω_r	0.3	[64]
Number of effective contacts susceptible or vaccinated individuals makes with infectious individuals per year.	c	11	[108]
The rate of progression of individuals from early latently infected with DS-TB.	α	0.5	[103]
Death rate due to the DS-TB strain disease	d_s	0.00025	[1, 108]
Death rate due to the MDR-TB strain disease	d_r	0.105	[1, 94]

Proportion of H_s move to T_s	p	0.2	[43]
The portion of L_s enter in to I_s	η	0.5	[103]
Progression rate from L_s	γ	0.1	[103]
Progression rate from latency MDR-TB.	δ	0.55	[43]
Proportion of individuals who do not get chance for screened at H_s and will go to L_s class.	ϵ	0.9	[103]
The recovery rate infectious individuals DS-TB strain,	ρ_s	0.83	[43]
The recovery rate infectious individuals MDR-TB strain.	ρ_r	0.498	[1, 94]
Proportion of infectious individuals with DS-TB who enters to R.	q	0.18	[43]
The portion of E who screened for treatment	ν	0.065	[43]
Rate of individuals move from T_s to R	ϕ	0.94	[43]
Rate of individuals move from T_r to R	φ	0.88	[43]
Acquired immunity due to previous treatment.	κ	0.06	[30]

7.3 Numerical Simulation for the Dynamics

The numerical value of $R_{eff}(Ds) = 1.03$, $R_{eff}(MDR) = 4.78$ and then $R_{eff} = max\{1.03, 4.78\} = 4.78$. Consequently, both strain of tuberculosis spread in the community. Figures 7.1 and 7.2 show the behavior of solution curves of the infected variables in the period of 10 years.

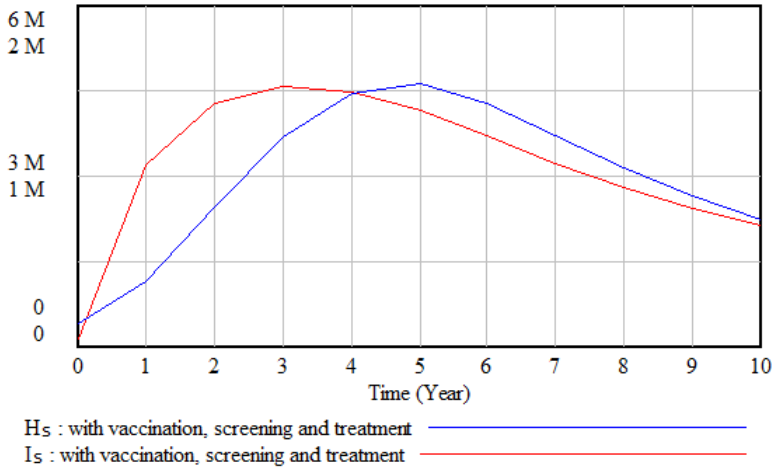

Figure 7.1: Variations of latent DS-TB, DS-TB infectious

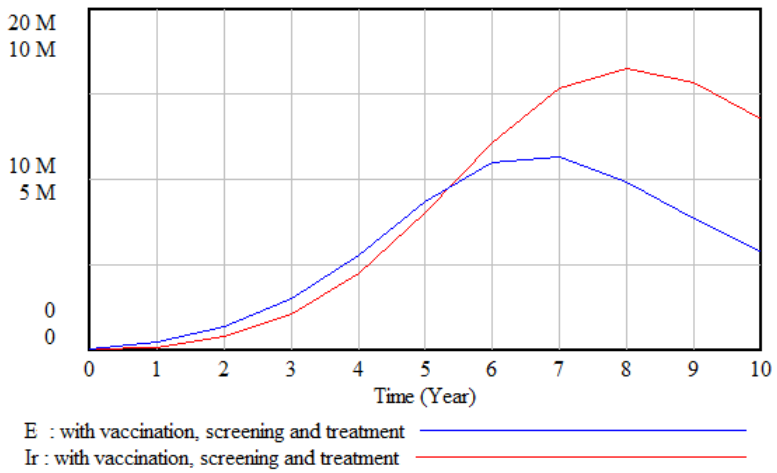

Figure 7.2: Variations of latent MDR-TB and MDR-TB infectious

We discussed on the relation between effective reproduction number and the parameters involved in it. Now we consider the parameters that involve in both $R_{eff}(DS)$ and $R_{eff}(MDR)$ and discuss on their impact on the transmission of DS-TB and/or MDR-TB strains. Here five parameters are involve in common for both effective reproduction numbers $R_{eff}(DS)$ and $R_{eff}(MDR)$. Let us consider the parameter, the number of effective contacts c as a variable and keeping all other parameters constant and written the effective reproduction numbers as a function of c, $R_{eff}(DS)(c) = 0.09c$ and $R_{eff}(MDR)(c) = 0.43c$. Consider the rate of inefficacy of vaccine individuals σ as a variable and keeping all other parameters as constant, the effective reproduction numbers can be written as a function of σ: $R_{eff}(DS)(\sigma) = 0.06\sigma + 1.02$ and $R_{eff}(MDR)(\sigma) = 0.25\sigma + 4.74$.

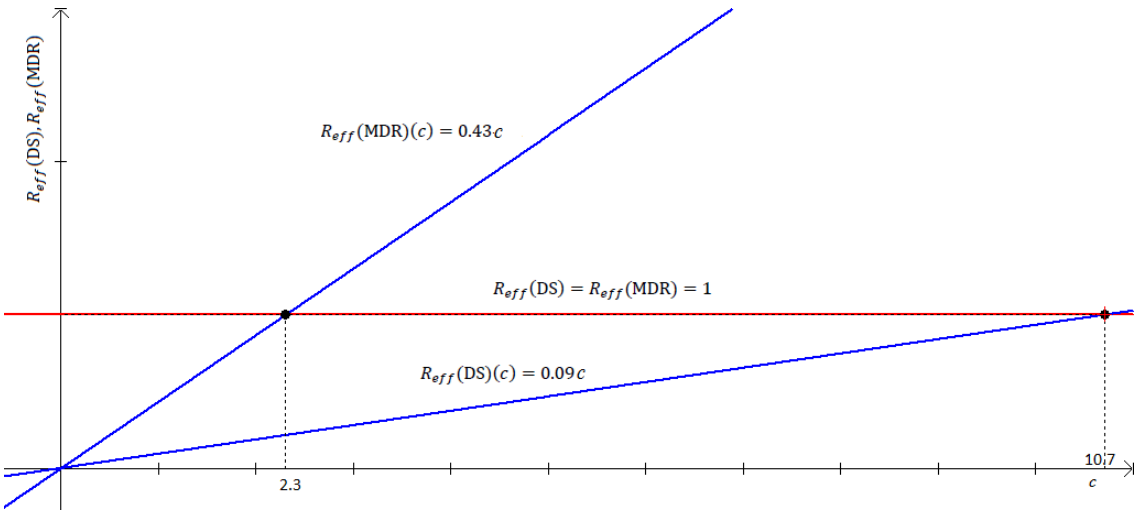

Figure 7.3: Graph of the effective reproduction numbers $R_{eff}(DS)$ and $R_{eff}(MDR)$ vrs effective contact rate , c

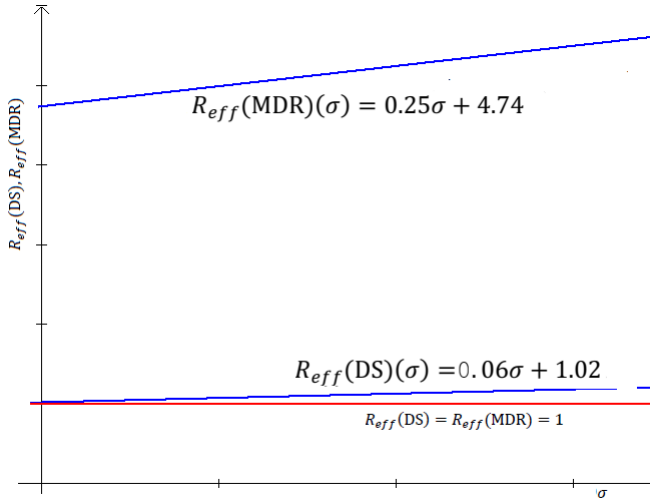

Figure 7.4: Graph of the effective reproduction numbers $R_{eff}(DS)$ and $R_{eff}(MDR)$ vrs infficacy rate of BCG vaccinve, σ

In the figure 7.3 the lines $R_{eff}(DS)(c) = 0.09c$ and $R_{eff}(MDR)(c) = 0.43c$ intersect with $R_{eff}(MDR) = R_{eff}(DS) = 1$ intersect at the values of $c = 10.7$ and $c = 2.3$ respectively. Thus, $R_{eff}(DS) < 1$ when the contact rate, $c < 10.7$ and $R_{eff}(DS) > 1$ when $c > 10.7$. For the value of $2.3 < c < 10.7$ only MDR-TB spread in the society. Whereas $R_{eff}(MDR) < 1$ when the number of effective contacts, $c < 2.3$ and $R_{eff}(MDR) > 1$ when $c > 2.3$. This implies the TB disease spreads in the community when $c > 2.3$ and eliminate if $c < 2.3$. Figure 7.4 shows that both $R_eff(DS)(\sigma)$ and $R_{eff}(MDR)(\sigma)$ are

above $R_{eff}(DS) = R_{eff}(MDR) = 1$, thus for every values of σ the both strains of the TB disease spread in the society. Of course the transmission of MDR-TB is higher than DS-TB.

Consider the rate of vaccine waning θ as a variable and keeping all other parameters as constant, the effective reproduction numbers can be written as a function of θ: $R_{eff}(DS)(\theta) = \frac{(0.005+1.07\theta)}{(\theta+0.0077)}$ and $R_{eff}(MDR)(\theta) = \frac{4.9824(\theta+0.0047)}{(\theta+0.0077)}$. Consider the proportions new born vaccinated ψ as a variable and keeping all other parameters as constant, the reproduction number can be written as a function of ψ: $R_{eff}(DS)(\psi) = 1.07 - 0.09\psi$ and $R_{eff}(MDR)(\psi) = 4.99 - 0.42\psi$.

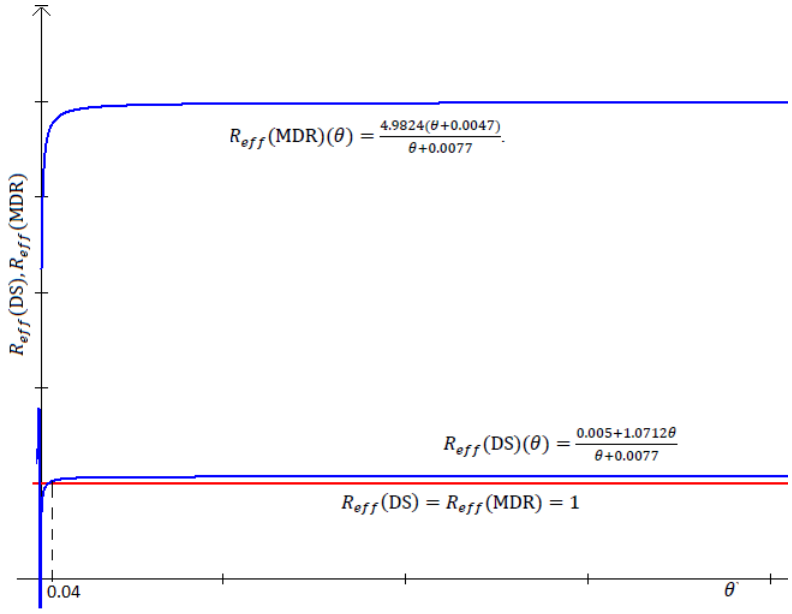

Figure 7.5: Graph of the effective reproduction numbers $R_{eff}(DS)$ and $R_{eff}(MDR)$ vrs vaccine wanning rate, θ

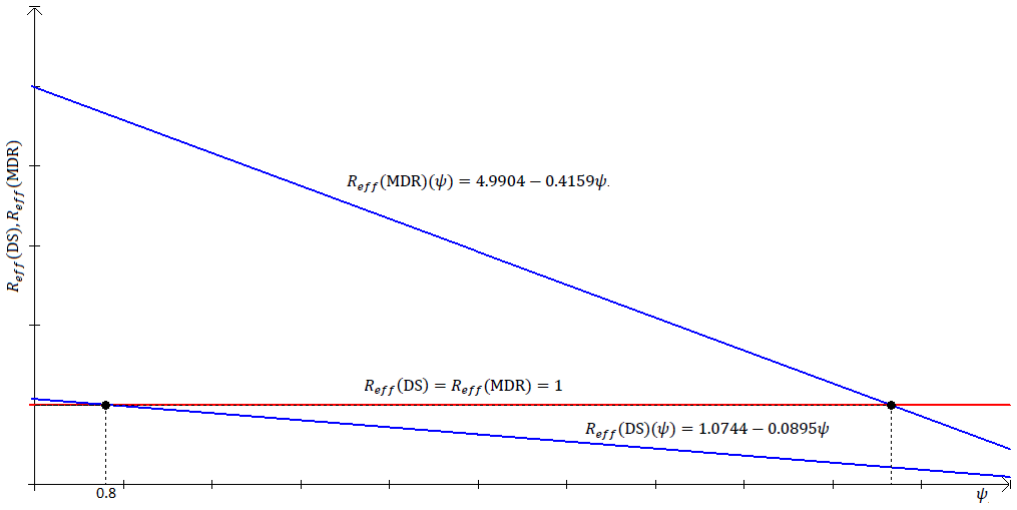

Figure 7.6: Graph of the effective reproduction numbers $R_{eff}(DS)$ and $R_{eff}(MDR)$ vrs proportion of vaccinated newly born babies, ψ

In figure 7.5 the curve: $R_{eff}(DS)(\theta) = \frac{(0.005+1.07\theta)}{(\theta+0.0077)}$ and the line $R_{eff}(DS) = 1$ intersect at $\theta = 0.038$, then $R_{eff}(DS) < 1$ when $\theta < 0.04$ and $R_{eff}(DS) > 1$ when $\theta > 0.04$. But the curve θ: $R_{eff}(MDR)(\theta) = \frac{(0.005+1.07\theta)}{(\theta+0.0077)}$ is above $R_{eff}(MDR) = 1$. This implies the MDR-TB spreads in the community for every value of θ. And for the value of $\theta < 0.04$ the DS-TB does not spread in the society. In figure 7.6 the curve $R_{eff}(DS)(\psi)$ and the line $R_{eff}(DS) = 1$ intersect at $\psi = 0.8$, then $R_{eff}(DS) < 1$ when $\psi > 0.8$ and $R_{eff}(DS) > 1$ when $\psi < 0.8$. And $R_{eff}(MDR) > 1$ for all values of ψ. This shows that the MDR-TB exist always, but DS-TB spreads for $\psi < 0.8$.

Taking the natural death rate μ as a variable and keeping all other parameters as constant, the effective reproduction numbers can be written as a function of μ:
$R_{eff}(DS)(\mu) = \frac{(0.12\mu+0.01)}{(0.0667+\mu)(0.5+\mu)(0.1+\mu)(\mu+0.83)}$ and $R_{eff}(MDR)(\mu) = 3.04\frac{(0.61\mu+0.0667)}{(0.0667+\mu)(0.60+\mu)}$

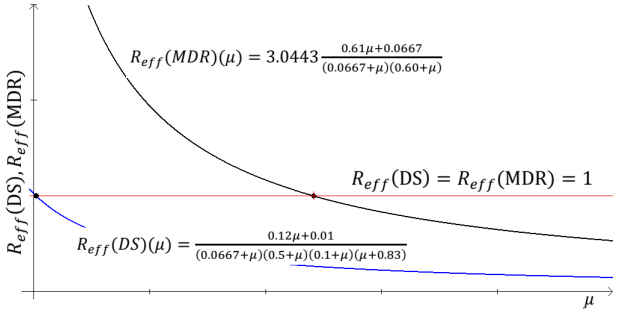

Figure 7.7: Graph of the effective reproduction numbers $R_{eff}(DS)$ and $R_{eff}(MDR)$ vrs natural death rate, μ

In figure 7.7 the curve $R_{eff}(DS)\frac{(0.12\mu+0.01)}{(0.0667+\mu)(0.5+\mu)(0.1+\mu)(\mu+0.83)}$ and the line $R_{eff}(DS)(\mu) = 1$ intersect at $\mu = 0.01$, then $R_{eff}(DS)$ <1 when $\mu > 0.01$ and $R_{eff}(DS) > 1$ when $\mu < 0.01$. And $R_{eff}(MDR) > 1$ for all values of $\mu < 1.3$. This shows that the MDR-TB exists, but not DS-TB spreads for $0.01 < \mu < 1.3$.

Now we consider the parameters that involve in $R_{eff}(DS)$ only and discuss on their impact on the transmission of DS-TB.

Consider the Proportion of latently infected drug sensitive TB at early stage for treatment p as a variable and keeping all other parameters as constant, the effective reproduction number can be written as a function of p: $R_{eff}(DS)(p) = 1.29(1-p)$. Again, consider the recovery rate infectious individuals DS-TB strain disease ρ_s as a variable and keeping all other parameters as constant, then the effective reproduction number can be written as a function of ρ_s: $R_{eff}(DS)(\rho_s) = \frac{0.85}{(\rho_s+0.01)}$

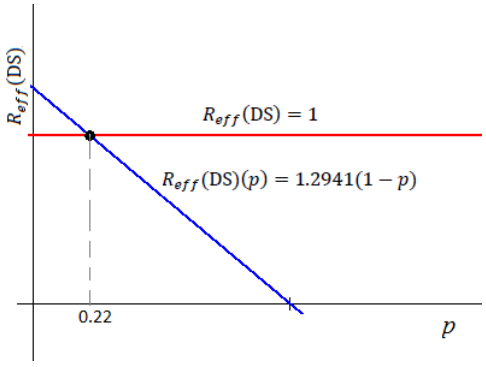

Figure 7.8: Graph of the effective reproduction number $R_{eff}(DS)$ vrs proportion of H_s move to T_s, p

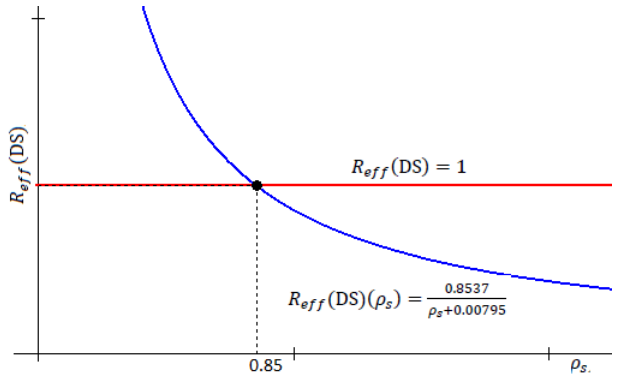

Figure 7.9: Graph of the effective reproduction number $R_{eff}(DS)$ vrs recovery rate of I_s, ρ_s

In figure 7.8 the curve $R_{eff}(DS)(p) = 1.29(1-p)$ and the line $R_{eff}(DS) = 1$ intersect at $p = 0.22$, $R_{eff}(DS) < 1$ when $p > 0.22$ and $R_{eff}(DS) > 1$ when $p < 0.22$. In figure 7.9 the curve $R_{eff}(DS)(\rho_s) = \frac{0.85}{(\rho_s+0.01)}$ and the line $R_{eff}(DS) = 1$ intersect at $\rho_s = 0.85$, $R_{eff}(DS) < 1$ when $\rho_s > 0.85$ and $R_{eff}(DS) > 1$ when $\rho_s < 0.85$.

Taking the portion of L_s enter in to I_s, η as a variable and keeping all other parameters as constant, the effective reproduction number can be written as a function of η: $R_{eff}(DS)(\eta) = \frac{(0.005+1.0712\eta)}{(\eta+0.0077)}$

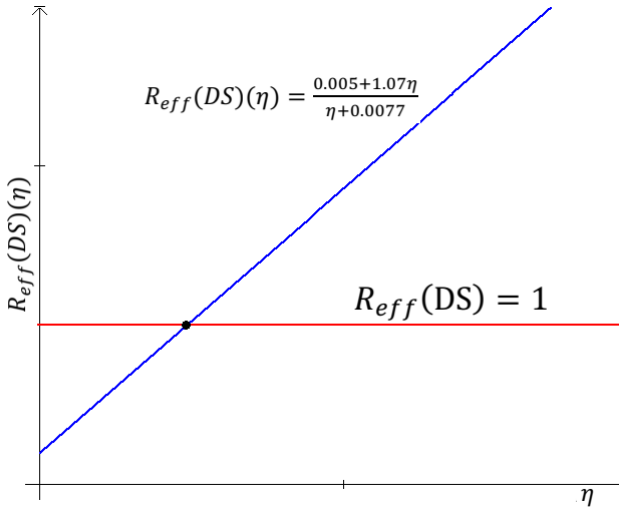

Figure 7.10: Graph of the effective reproduction number $R_{eff}(DS)$ vrs portion of L_s enter in to I_s, η

In figure 7.10 the curve $R_{eff}(DS)(\eta) = \frac{(0.005+1.0712\eta)}{(\eta+0.0077)}$ and the line $R_{eff} = 1$ intersect at

$\eta = 0.48$, $R_{eff}(DS) < 1$ when $\eta < 0.48$ and $R_{eff} > 1$ when $\eta > 0.48$.

The effective reproduction number $R_{eff}(DS)$ can also be given as a function of the induced death rate due to the DS-TB disease d_s: $R_{eff}(DS)(d_s) = \frac{0.85}{(d_s+0.84)}$

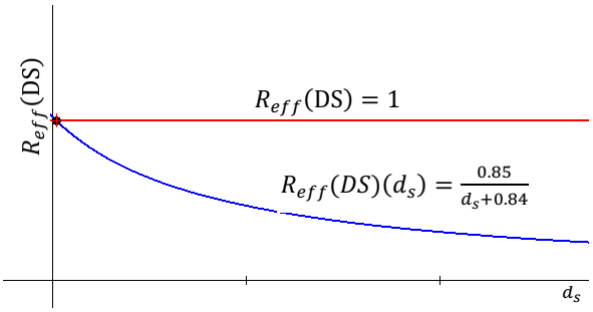

Figure 7.11: Graph of the effective reproduction number $R_{eff}(DS)$ vrs induced death rate of I_s, d_s

In figure 7.11 the curve $R_{eff}(DS)(d_s) = \frac{0.85}{(d_s+0.84)}$ and the line $R_{eff}(DS) = 1$ intersect at $d_s = 0.02$, $R_{eff}(DS) < 1$ when $d_s > 0.023$ and $R_{eff}(DS) > 1$ when $d_s < 0.02$.

The effective reproduction number $R_{eff}(MDR)$ can also be given as a function of the recovery rate infectious MDR-TB individuals ρ_r: keeping all other parameters as constant, $R_{eff}(MDR)(\rho_r) = \frac{2.92}{\rho_r+0.11}$. And the effective reproduction number $R_{eff}(MDR)$ can also be given as a function of the portion of E enter in to I_r, ν: keeping all other parameters as constant, $R_{eff}(MDR) = 5.12(1-\nu)$.

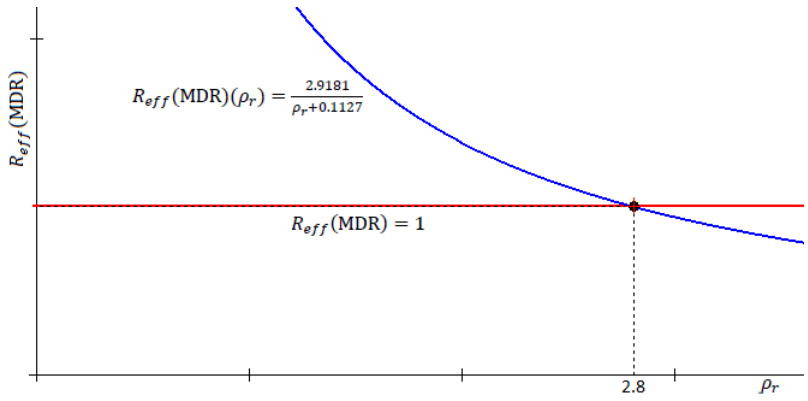

Figure 7.12: Graph of the effective reproduction number $R_{eff}(MDR)$ vrs recovery rate of I_r, ρ_r

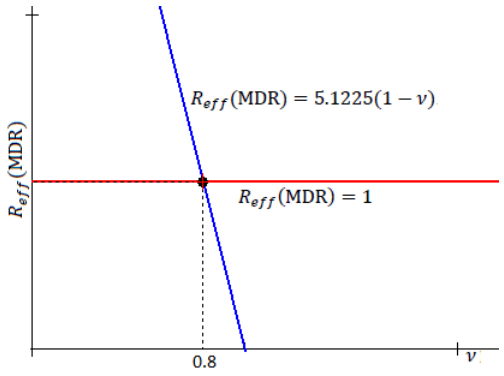

Figure 7.13: Graph of the effective reproduction number $R_{eff}(MDR)$ vrs portion of E who screened, ν

In figure 7.12 the curve $R_{eff}(MDR)(\rho_r) = \frac{2.92}{\rho_r + 0.11}$ and the line $R_{eff}(MDR) = 1$ intersect at $\rho_r = 2.8$, $R_{eff}(MDR) < 1$ when $\rho_r > 2.8$ and $R_{eff}(MDR) > 1$ when $\rho_r < 2.8$. In figure 7.13 the curve $R_eff(MDR)(\nu) = 5.12(1-\mu)$ and the line $R_{eff}(MDR) = 1$ intersect at $\nu = 0.8$, $R_{eff}(MDR) < 1$ when $\nu > 0.8$ and $R_{eff}(MDR) > 1$ when $\nu < 0.8$.

The effective reproduction number $R_{eff}(MDR)$ can also be given as a function of the death rate due to the MDR-TB disease d_r: keeping all other parameters as constant, $R_{eff}(MDR)(d_r) = \frac{2.92}{(0.51 + d_r)}$.

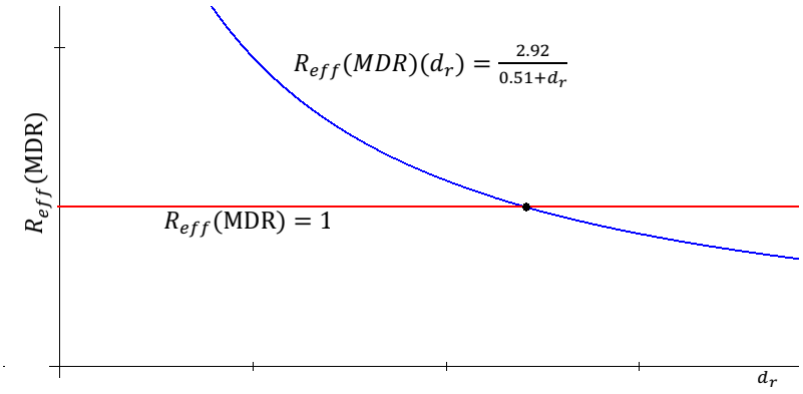

Figure 7.14: Graph of the reproduction number $R_{eff}(MDR)$ vrs induced death rate I_r, d_r

In figure 7.14 the curve $R_{eff}(MDR)(d_r) = \frac{2.92}{(0.51 + d_r)}$ and the line $R_{eff}(MDR) = 1$ intersect at $d_r = 2.4$, $R_{eff}(MDR) < 1$ when $d_r > 2.4$ and $R_{eff}(MDR) > 1$ when $d_r < 2.4$.

7.4 Sensitivity Analysis

We apply the normalized forward sensitivity index of the effective reproduction number R_{eff} to a parameter [66] to analysis the impact of parameters in the spread and control of TB. That is the ratio of the relative change in the effective reproduction numbers to the relative change in the parameter .

If $R_{eff}(DS) > R_{eff}(MDR)$, then we have:

$$R_{eff} = \max\{R_{eff}(DS), R_{eff}(MDR)\} = R_{eff}(DS) = c\omega_s \frac{(\theta+(1-\psi)\mu)+\mu\sigma\psi}{(\mu+\theta)} \frac{(\alpha\epsilon(1-p)\gamma\eta+\alpha(\gamma+\mu)(1-\epsilon)(1-p))}{(\alpha+\mu)(\gamma+\mu)(\rho_s+\mu+d_(s))}$$

Therefore, we evaluate the nonzero sensitivity indices of $R_{eff}(DS)$ with respect to the parameters as follows:

Sensitivity index of $R_{eff}(DS)$ with respect to the parameters c is given as:

$$\begin{aligned}
\Pi_c^{R_{eff}(DS)} &= \frac{\partial R_{eff}(DS)}{\partial c} \times \frac{c}{R_{eff}(DS)} \\
&= \omega_s \left(\frac{(\theta + (1-\psi)\mu) + \mu\sigma\psi}{(\mu+\theta)} \right) \left\{ \begin{array}{l} \frac{\alpha\varepsilon(1-p)\gamma\eta}{(\alpha+\mu)\times(\gamma+\mu)\ \times(\rho_s+\mu+d_s)} + \\ \frac{\alpha(\gamma+\mu)(1-\varepsilon)(1-p)}{(\alpha+\mu)\times(\gamma+\mu)\ \times(\rho_s+\mu+d_s)} \end{array} \right\} \times \\
&\left(\frac{c}{c\omega_s \left(\frac{(\theta+(1-\psi)\mu)\Lambda+\mu\sigma\psi\Lambda}{\mu(\mu+\theta)} \right) \frac{(\alpha\varepsilon(1-p)\gamma\eta+\alpha(\gamma+\mu)(1-\varepsilon)(1-p))}{(\alpha+\mu)\times(\gamma+\mu)\ \times(\rho_s+\mu+d_s)}} \right) = 1
\end{aligned}$$

Sensitivity index of $R_{eff}(DS)$ with respect to the parameters ω_s is:

$$\begin{aligned}
\Pi_{\omega_s}^{R_{eff}(DS)} =& \frac{\partial R_0}{\partial \omega_s} \times \frac{\omega_s}{R_0} \\
=& c \left(\frac{(\theta + (1-\psi)\mu) + \mu\sigma\psi}{(\mu+\theta)} \right) \left\{ \begin{array}{l} \frac{\alpha\varepsilon(1-p)\gamma\eta}{(\alpha+\mu)\times(\gamma+\mu)\ \times(\rho_s+\mu+d_s)} + \\ \frac{\alpha(\gamma+\mu)(1-\varepsilon)(1-p)}{(\alpha+\mu)\times(\gamma+\mu)\ \times(\rho_s+\mu+d_s)} \end{array} \right\} \\
&\times \left(\frac{\omega_s}{c\omega_s \left(\frac{(\theta+(1-\psi)\mu)+\mu\sigma\psi}{(\mu+\theta)} \right) \frac{(\alpha\varepsilon(1-p)\gamma\eta+\alpha(\gamma+\mu)(1-\varepsilon)(1-p))}{(\alpha+\mu)\times(\gamma+\mu)\ \times(\rho_s+\mu+d_s)}} \right) = 1
\end{aligned}$$

Sensitivity index of $R_{eff}(DS)$ with respect to the proportion of vaccinated new born, ψ is given as:

$$\Pi_{\psi}^{R_{eff}(DS)} = \frac{(\mu\psi(\sigma-1))}{(\theta+\mu+\mu\psi(\sigma-1))} < 0 \ \textit{Since}\ \sigma - 1 < 0 \ \textit{and}\ \theta + \mu + \mu\psi(\sigma-1) > 0$$

Hence, ψ has negative impact on the transmission of drug sensitive tuberculosis. Therefore, increasing ψ decreases $R_{eff}(DS)$.

Sensitivity index of $R_{eff}(DS)$ with respect to the rate of inefficacy of BCG vaccine σ is given as:

$$\Pi_{\sigma}^{R_{eff}(DS)} = \frac{\partial R_{eff}(DS)}{\partial \sigma} \times \frac{\sigma}{R_{eff}(DS)} = \frac{\psi\sigma\mu}{\theta + \mu + \psi\mu(\sigma - 1)} > 0$$

positive effect on the transmission of drug sensitive tuberculosis. Therefore, if σ increasing, then $R_{eff}(DS)$ increases.

Sensitivity index of $R_{eff}(DS)$ with respect to the rate of BCG vaccine waning θ is given as:

$$\Pi_{\theta}^{R_{eff}(DS)} = \frac{\partial R_{eff}(DS)}{\partial \theta} \times \frac{\theta}{R_{eff}(DS)} = \quad \frac{\psi\mu\theta\,(1-\sigma)}{(\mu+\theta)\,[\theta + \mu + \mu\psi\,(\sigma - 1)]} > 0$$

implies θ has positive contribution for the transmission of drug sensitive tuberculosis. Therefore, increasing θ increases the effective reproduction number $R_{eff}(DS)$.

Sensitivity index of $R_{eff}(DS)$ with respect to the rate of individuals leave from H_s, α is given as:

$$\Pi_{\alpha}^{R_{eff}(DS)} = \frac{\partial R_{eff}(DS)}{\partial \alpha} \times \frac{\alpha}{R_{eff}(DS)} = \frac{\mu}{\alpha + \mu} > 0$$

implies α has positive contribution for the transmission of drug sensitive tuberculosis. Therefore, increasing α forces to increase the effective reproduction number $R_{eff}(DS)$.

Sensitivity index of $R_{eff}(DS)$ with respect to the rate of individuals leave from L_s class γ is given as:

$$\Pi_{\gamma}^{R_{eff}(DS)} = \frac{\partial R_{eff}(DS)}{\partial \gamma} \times \frac{\gamma}{R_{eff}(DS)} = \left\{ \frac{(\varepsilon\eta + (1-\varepsilon))\,\gamma}{(\varepsilon\gamma\eta + (\gamma+\mu)\,(1-\varepsilon))} - \frac{\gamma}{(\gamma+\mu)} \right\} > 0$$

This implies that γ has positive effect on the transmission of tuberculosis. Thus, increasing γ leads to increase $R_{eff}(DS)$.

Sensitivity index of $R_{eff}(DS)$ with respect to the proportion of H_s, who go for treatment, p is given as:

$$\Pi_{p}^{R_{eff}(DS)} = \frac{\partial R_{eff}(DS)}{\partial \mathrm{p}} \times \frac{p}{R_{eff}(DS)} = -\frac{p}{1-p} < 0$$

implies p has negative contribution for the transmission of tuberculosis. Hence, increasing p causes to decrease the effective reproduction number $R_{eff}(DS)$.

Sensitivity index of $R_{eff}(DS)$ with respect to the proportion of individuals who do not get chance for screened at H_s who will go to L_s class, ϵ is given as:

$$\Pi_{\epsilon}^{R_{eff}(DS)} = \frac{\partial R_{eff}(DS)}{\partial \epsilon} \times \frac{\epsilon}{R_{eff}(DS)} = \frac{\epsilon(1-p)(\gamma\eta - (\gamma+\mu))}{(\epsilon(1-p)\gamma\eta + (\gamma+\mu)(1-\epsilon)(1-p))} < 0$$

implies that ϵ has negative contribution for the transmission of tuberculosis. Thus, increasing ϵ leads to decrease $R_{eff}(DS)$.

Sensitivity index of $R_{eff}(DS)$ with respect to the rate at which individuals leave infectious class I_s, ρ_s is given as:

$$\Pi_{\rho_s}^{R_{eff}(DS)} = \frac{\partial R_{eff}(DS)}{\partial \rho_s} \times \frac{\rho_s}{R_{eff}(DS)} = -\frac{\rho_s}{\rho_s + \mu + d_s} < 0$$

this implies ρ_s has negative contribution for the transmission of tuberculosis. Thus increasing ρ_s forces to decrease $R_{eff}(DS)$.

Sensitivity index of $R_{eff}(DS)$ with respect to the portion of L_s enter in to I_s, η is given as:

$$\Pi_{\eta}^{R_{eff}(DS)} = \frac{\partial R_{eff}(DS)}{\partial \eta} \times \frac{\eta}{R_{eff}(Ds)} = \frac{\eta\gamma\epsilon}{(\epsilon\gamma\eta + (\gamma+\mu)(1-\epsilon))} > 0$$

implies η has positive contribution for the transmission of tuberculosis. Then increasing η leads to increase $R_{eff}(DS)$.

Sensitivity index of $R_{eff}(DS)$ with respect to the induced death rate of infectious individuals by drug sensitive TB, d_s is given as:

$$\Pi_{d_s}^{R_0} = \frac{\partial R_0}{\partial d_s} \times \frac{d_s}{R_0} = -\frac{d_s}{(\rho_s + \mu + d_s)} < 0$$

his implies d_s has negative contribution for the transmission of tuberculosis. Thus, increasing d_s forces to decrease $R_{eff}(DS)$.

For the parameters of which the sensitivity index of $R_{eff}(DS)$ has positive sign the effective reproduction number increase as those parameters increase and vise verse, while for those parameters of which sensitivity index of $R_{eff}(DS)$ has negative sign then the effective reproduction number increase as the parameters decrease and vise versa. Thus we have shown that the parameters like number of effective contacts of susceptible individuals makes with infectious individuals per year, probability of drug susceptible tuberculosis

transmission from infectious person to another person, the rate of inefficacy of BCG vaccine, the rate of BCG vaccine waning, the rate of individuals leave from early latently infected class with drug susceptible tuberculosis, the rate of individuals leave from long latently infected class with drug susceptible tuberculosis have positive contributions for the transmission of TB, implies that, when those parameters are increased keeping other parameters constant they increase the value of $R_{eff}(DS)$. Thus, they increase the endemicity of the drug susceptible tuberculosis as they have positive indices. While the parameters:- the proportion of vaccinated new born individuals, the proportion of early latently infected of drug susceptible tuberculosis individuals who go for treatment, the rate at which individuals leave infectious class of drug sensitive tuberculosis will help to control the spread of the disease that is, when they are increased keeping all the other parameters constant decrease the value of $R_{eff}(DS)$.

If $R_{eff}(MDR) > R_{eff}(DS)$, then we have $R_{eff} = \max\{R_{eff}(DS), R_{eff}(MDR)\} = R_{eff}(MDR) = \frac{(\sigma\psi\mu+(\theta+(1-\psi)\mu)}{(\mu+\theta)}\frac{c\omega_r(1-\nu)\delta}{(\delta+\mu)(\rho_r+\mu+d_r)}$. Therefore, we evaluated the nonzero sensitivity indices of $R_{eff}(MDR)$ with respect to the parameters as follows:

Sensitivity index of $R_{eff}(MDR)$ with respect to the parameters c is given as:

$$\Pi_c^{R_{eff}(MDR)} = \frac{\partial R_{eff}(MDR)}{\partial c} \times \frac{c}{R_{eff}(MDR)} = 1$$

Sensitivity index of $R_{eff}(MDR)$ with respect to the parameters ω_r is:

$$\Pi_{\omega_r}^{R_{eff}(MDR)} = \frac{\partial R_{eff}(MDR)}{\partial \omega_r} \times \frac{\omega_r}{R_{eff}(MDR)} = 1$$

Sensitivity index of $R_{eff}(MDR)$ with respect to the proportion of vaccinated new born, ψ is given as:

$$\Pi_{\psi}^{R_{eff}(MDR)} = \frac{\partial R_{eff}(MDR)}{\partial \psi} \times \frac{\psi}{R_{eff}(MDR)} = \frac{\mu\psi(\sigma-1)}{\theta+(1-\psi)\mu+\mu\sigma\psi} < 0$$

Hence, ψ has negative impact on the transmission of drug resistance tuberculosis. Therefore, increasing ψ decreases $R_{eff}(MDR)$.

Sensitivity index of $R_{eff}(MDR)$ with respect to the rate of inefficacy of BCG vaccine σ is given as:

$$\Pi_{\sigma}^{R_{eff}(MDR)} = \frac{\partial R_{eff}(MDR)}{\partial \sigma} \times \frac{\sigma}{R_{eff}(MDR)} = \frac{\mu\sigma\psi}{\theta+(1-\psi)\mu+\sigma\psi} > 0$$

implies σ has positive effect on the transmission of drug resistant tuberculosis. Therefore, if σ increasing, then $R_{eff}(MDR)$ increases.

Sensitivity index of $R_{eff}(MDR)$ with respect to the rate of BCG vaccine waning θ is given as:

$$\Pi_{\theta}^{R_{eff}(MDR)} = \frac{\partial R_{eff}(MDR)}{\partial \theta} \times \frac{\theta}{R_{eff}(MDR)} = \frac{\theta\psi\mu}{(\theta+\mu)(\theta+(1-\psi)\mu)+\mu\sigma\psi} > 0$$

mplies θ has positive contribution for the transmission of multi-drug resistance tuberculosis. Therefore, increasing θ increases $R_{eff}(MDR)$.

Sensitivity index of $R_{eff}(MDR)$ with respect to the rate of progression of individuals from latency multi-drug resistant tuberculosis δ , is given as:

$$\Pi_{\delta}^{R_{eff}(MDR)} = \frac{\partial R_{eff}(MDR)}{\partial \delta} \times \frac{\delta}{R_{eff}(MDR)} = \frac{\mu}{(\delta+\mu)} > 0$$

implies δ has positive contribution for the transmission of multi-drug resistance tuberculosis. Therefore, increasing δ increases $R_{eff}(MDR)$.

Sensitivity index of $R_{eff}(MDR)$ with respect to the rate of portion of E enter in to I_r, ν is given as:

$$\Pi_{\nu}^{R_{eff}(MDR)} = \frac{\partial R_{eff}(MDR)}{\partial \nu} \times \frac{\nu}{R_{eff}(MDR)} = -\frac{\nu}{(1-\nu)} < 0$$

implies ν has negative contribution for the transmission of multi-drug resistance tuberculosis. Therefore, increasing ν decreases $R_{eff}(MDR)$.

Sensitivity index of $R_{eff}(MDR)$ with respect to the rate of recovery rate infectious individuals MDR strain ρ_r is given as:

$$\Pi_{\rho_r}^{R_{eff}(MDR)} = \frac{\partial R_{eff}(MDR)}{\partial \rho_r} \times \frac{\rho_r}{R_{eff}(MDR)} = -\frac{\rho_r}{\rho_r+\mu+d_r} < 0$$

implies ρ_r has negative contribution for the transmission of multi-drug resistance tuberculosis. Therefore, increasing ρ_r decreases $R_{eff}(MDR)$.

Sensitivity index of $R_{eff}(MDR)$ with respect to the death rate due to the MDR -TB disease d_r is given as:

$$\Pi_{d_r}^{R_{eff}(MDR)} = \frac{\partial R_{eff}(MDR)}{\partial d_r} \times \frac{d_r}{R_{eff}(MDR)} = -\frac{d_r}{\rho_r+\mu+d_r} < 0$$

implies d_r has negative contribution for the transmission of multi-drug resistance tuberculosis. Therefore, increasing d_r decreases $R_{eff}(MDR)$.

Using the data in table 7.1 the resulting sensitivity indices of $R_{eff}(DS)$ and $R_{eff}(MDR)$ to the different parameters which involve in the effective reproduction numbers $R_{eff}(DS)$ and $R_{eff}(MDR)$ respectively are shown in table 7.2 with the order from most sensitive to the least:

Table 7.2: Numerical values of the sensitivity indices of $R_{eff}(MDR)$ and $R_{eff}(MDR)$ with respect to each parameter involved in $R_{eff}(MDR)$ and $R_{eff}(MDR)$ respectively

Parameters	Sensitivity index of $R_{eff}(DS)$	Parameters	Sensitivity index of $R_{eff}(MDR)$
c	+1	c	+1
ω_s	+1	ω_s	+1
ρ_s	-0.99	ρ_r	-0.82
ϵ	-0.93	d_r	-0.17
η	+0.81	ν	-0.07
p	-0.25	ψ	-0.042
ψ	-0.11	θ	+0.038
γ	+0.058	δ	+0.014
θ	+0.038	σ	+0.011
α	+0.015		
σ	+0.011		
d_s	-0.0003		

7.5 Discussion

In this work we considered non-linear dynamical system (5.1)-(5.10) to study the dynamics of a two strain Tuberculosis disease. The effective reproduction number is: $R_{eff} = c\frac{(\sigma\phi\mu+(\theta+(1-\phi)\mu)}{(\theta+\mu)} \max\{\frac{(\omega_s(\alpha\epsilon(1-p)\gamma\eta+\alpha(\gamma+\mu)(1-\epsilon)(1-p)))}{((\alpha+\mu)(\gamma+\mu)(\rho_s+\mu+d_s))}, \frac{(\omega_r(1-\nu)\delta)}{((\delta+\mu)(\rho_r+\mu+d_r))}\}$. Then the numerical value of $R_{eff} = max\{1.03, 4.78\} = 4.78$. In the figure 7.3, the effective reproduction number of DS-TB, $R_{eff}(DS) < 1$ when the number of contact of susceptible individuals with an infectious, $c < 10.7$ and $R_{eff}(DS) > 1$ when $c > 10.7$. Moreover, the

effective reproduction number of MDR-TB, $R_{eff}(MDR) < 1$ when number of contact of susceptible individuals with an infectious, $c < 2.3$ and $R_{eff}(MDR) > 1$ when $c > 2.3$. Thus the only MDR TB spreads in the society when the value of $2.3 < c < 10$; both strains spread in the society if $c > 10.7$ and both strains do not spread in the society if $c < 2.3$. Figure 7.4 shows that the effective reproduction number for both DS-TB and MDR-TB strains ($R_{eff}(DS) > 1$ and $R_{eff}(MDR) > 1$) are greater than one for every values of the rate of inefficacy of vaccine individuals, σ, therefore both strains of the TB disease spread in the society what ever the value of σ is. Of course the transmision of MDR-TB is higher than DS-TB.

Figure 7.5 shows that $R_{eff}(DS) < 1$ when the rate of vaccine waning, $\theta < 0.038$ and $R_{eff}(DS) > 1$ when $\theta > 0.038$. But $R_{eff}(MDR) > 1$ for all values of θ. This implies that the MDR-TB spreads in the community for every value of θ. And for the value of $\theta < 0.038$ the DS-TB does not spread in the society. That is, if $\theta < 0.038$ the only MDR-TB spreads in the community and boths DS-TB and MDR-TB spreads in the community when $\theta > 0.038$. From figure 7.6 we observe that $R_{eff}(DS) < 1$ when proportions new born vaccinated per the total newly born babies, $\psi > 0.8$ and $R_{eff}(DS) > 1$ when $\psi < 0.8$ while, $R_{eff}(MDR) > 1$ for all values of ψ. This shows that the MDR-TB spreads in the society for all values of ψ, but DS-TB spreads for $\psi < 0.8$. Implies both strain spreads in the community if $\psi < 0.8$ and only MDR-TB spreads in the community if $\psi > 0.8$. This indicates that giving BCG vaccine has no significant impact in the control of MDR-TB; however we can reduce DS-TB by BCG vaccine.

From the sensitivity index of effective reproduction numbers (Table-7.2) we observe that the parameters contact rate c, the rate of inefficacy of vaccine individuals σ, the rate of vaccine waning θ, the probability of transmission ω_s and ω_r, the rate of progression of individuals from early latently infected with DS-TB α, the progression rate from Long latent DS-TB strain γ, the portion of L_s enter in to I_s, η and the progression rate from latent MDR-TB δ have positive contribution in the transmission of TB disease. While, the proportions new born vaccinated ψ, natural death rate μ, the proportion of individuals who do not get chance for screened at H_s and will go to L_s class ϵ, the proportion of latent MDR-TB at early stage for treatment p, the recovery rates infectious individuals ω_s and ω_r, the induced death rates d_s and d_r; and of the portion of E enter in to I_r, ν

have negative impact on the transmission of TB disease.

From table 7.2, the parameter of which the sensitivity index of $R_{eff}(DS)$ or $R_{eff}(MDR)$ has positive sign the effective reproduction number increase as these parameter increase and vise verse, while for those parameters of which sensitivity index of $R_{eff}(DS)$ and $R_{eff}(MDR)$ have negative sign then the effective reproduction number increase as the parameters decrease and vise versa. The number of effective contact of susceptible or vaccinated individual with an infectious individual of both strains c, the probability of transmission followed by the recovery rates infectious individuals are the most influential parameters in the spread and control of tuberculosis disease, this is because of that magnitude of the sensitivity indices the effective reproduction $R_{eff}(DS)$ with respect to the effective contact rate and the treatment rate ρ_s of the DS-TB infectious individuals; and the sensitivity indices the effective reproduction $R_{eff}(MDR)$ with respect to the effective contact rate and the treatment rate ρ_r of the MDR-TB infectious individuals ρ_r are maximum compared to others. For all of those reasons, reducing the number of effective contact and increasing recovery rate have great role to control tuberculosis disease.

7.6 Conclusion

In this chapter we have presented and analyzed the numerical simulation on the two strain TB model with interventions: vaccination of newly born babies, screening of latently infected and treatments of infectious individuals for both strains of tuberculosis (DS-TB and MDR-TB)(5.1)-(5.10). We estimate the value of parameters which involve the dynamical system (5.1)-(5.10). We evaluated the numerical value of the reproduction numbers. Consequently, $R_{eff}(DS) = 1.03$ and $R_{eff}(MDR) = 4.78$, which show that the disease of both strain tuberculosis spread in the community and MDR-TB spreads vastly in the society. The sensitivity analysis shows that the number of effective contact of susceptible or vaccinated individual with an infectious individual of both strains is the most influential parameter to change the reproduction number respectively.

Chapter 8

Results, Conclusions and Recommendations

8.1 Results

In this study, we have presented and analyzed mathematical model for the dynamics of two strain Tuberculosis disease in Ethiopia. The objective of this study was analyzing an epidemiological mathematical model for the spread and control of a two-strain tuberculosis model in Ethiopia. Under this section the summary of the results based on the different chapters of the dissertation is discussed as below.

In Chapter Four, we considered a mathematical model with the effects of screening, treatment and vaccination interventions on the dynamics of tuberculosis disease, the model was formulated with the aim of assessing the impact of screening, treatment and vaccination on the disease. The positivity and boundedness of solution of the dynamical system (4.1)-(4.8) were investigated. Existence and stability of the equilibrium points were studied. we applied Routh – Hurwitz criterion method and Laypunove function to proof the local and global stability DFE. As the result, the disease free equilibrium point was is locally asymptotically stable and globally stable for $R_{eff} < 1$. Existence of the endemic equilibrium point was also investigated and proved its local and global stability. Thus, the endemic equilibrium point is local and global stability under a certain

condition.

In Chapter Five, we formulated a mathematical model (5.1)-(5.10) for tuberculosis disease by disaggregating in two strains that is, drug sensitive and drug resistant tuberculosis. Using the next generation matrix method, we computed the effective reproduction numbers. We have discussed on the existence of disease free equilibrium point, endemic equilibrium (drug-sensitive TB only endemic equilibrium, drug-resistance TB only endemic equilibrium and endemic equilibrium when both strains exist) points and presented the conditions that the local and global stability of those equilibrium points.

In Chapter Six, we have used standard data to make numerical experimentation on the dynamical system (4.1)-(4.8) formulated in chapter four. We got that the numerical value of the effective reproduction number, $R_{eff} = 0.7$, which shows that globally tuberculosis speed slowly. The waning rate of Bacilli Calmette-Guérin (BCG) vaccine, followed by the progression rate from long latently infected tuberculosis to active TB have a great role to change the effective reproduction number. The result shows that vaccination alone cannot eliminate tuberculosis disease from a population, but also other interventions are needed.

In Chapter Seven, we have used real data collected from health sectors in Ethiopia to undergo numerical experimentation on the dynamical system (5.1)-(5.10) formulated in chapter five. We evaluated the numerical value of the effective reproduction numbers $R_{eff}(DS) = 1.03$ and $R_{eff}(MDR) = 4.78$, which show that both strain tuberculosis disease spread in the community and MDR-TB spreads vastly in the society. Sensitivity analysis was performed on different parameters with the effective reproduction numbers, R_{eff} to understand how sensitive the model is to the different parameter values and its structure dynamics using the normalized forward sensitivity index. The sensitivity analysis shows that the number of effective contact of susceptible or vaccinated individual with an infectious individual of both strains is the most influential parameter to change the reproduction number respectively.

8.2 Conclusions

The main objective of this research was to formulate and analyze mathematical models for the dynamics of a two strain tuberculosis disease. Three interventions were incorporated in the dynamical system that are, vaccination, screening and treatment. In this work;

1) We developed a mathematical model of the two-strain of tuberculosis.

2) We computed the effective reproduction numbers.

3) We investigated the existence of disease free and endemic equilibrium points and proved both local and global stability of equilibrium points.

4) We investigated the impact of each parameters of the model on spread and control of tuberculosis.

A non-linear dynamical system (4.1)-(4.8) with vaccination, screening and treatment was formulated for the tuberculosis disease and takes place investigations on the basic properties of the model and its solution. We computed the effective reproduction number. We examined the existence of both disease free and endemic equilibrium points of the corresponding dynamical system and proved their local and global stability.

We extend the dynamical system (4.1)-(4.8) by disaggregating the tuberculosis disease in to two strain (drug sensitive and multi-drug resistance) tuberculosis, set our assumptions and formulate a non-linear dynamical system for two strain tuberculosis with interventions vaccination, screening and treatment (5.1)-(5.10). We computed the effective reproduction numbers for drug sensitive tuberculosis ($R_{eff}(DS)$), the effective reproduction numbers for multi-drug resistance tuberculosis ($R_{eff}(MDR)$) and the effective reproduction numbers for the considered dynamical system (5.1)-(5.10), $R_{eff} = max\{R_{eff}(DS), R_{eff}(MDR)\}$. In addition, We analyzed the existence and stability of equilibrium points of the dynamical system (5.1)-(5.10).

To examine whether the TB disease spread in the society or not we calculated the numerical value for effective reproduction number ($R_{eff} = 0.7$) of the dynamical system (4.1)-(4.8) and the result shows that globally TB disease does not spread in the society.

The waning rate of Bacilli Calmette-Guérin (BCG) vaccine, followed by the progression rate from long latently infected tuberculosis to active have a great role to change the effective reproduction number.

We evaluated the numerical value of the effective reproduction numbers of the dynamical system (5.1)-(5.10). Consequently, $R_{eff}(DS) = 1.03$ and $R_{eff}(MDR) = 4.78$, which show that the disease of both strain tuberculosis spread in the community and MDR-TB spreads vastly in the society. As the result numerical values of $(R_{eff}(DS))$ and $(R_{eff}(MDR))$ are both greater than one; and so that both strain spread in the community of Ethiopia of course MDR-TB transmits in the society more strongly than DS-TB. The sensitivity analysis shows that the number of effective contact of susceptible or vaccinated individual with an infectious individual of both strains is the most influential parameter to change the effective reproduction numbers respectively in the Ethiopian context.

8.3 Recommendations

In this study we found that the numerical value of the effective reproduction number of the drug sensitive and multi drug resistant tuberculosis dynamical system $(5.1)-(5.10)$ are $R_{eff}(DS) = 1.03$ and $R_{eff}(MDR) = 4.78$ respectively. Those are greater than unity and from this we observe that both drug sensitive and multi drug resistant tuberculosis disease spread in the community. To control the spread of the disease we have to be sure that the numerical value of effective reproduction numbers are less than unity. For this, we identified the following control parameters.

The first control parameter is the rate of the proportion of newly born BCG vaccinated babies ψ. $\psi = \frac{\textit{the number of newly born vaccinated babies}}{\textit{the total number of newly born babies}} = 0.49$, where the number of newly born vaccinated babies is 1887281 and the total number of newly born babies is 3845275. The intersection point of $R_{eff}(DS) = 1$ and the effective reproduction number of drug sensitive tuberculosis as a function of the rate of proportion of newly born BCG vaccinated babies $R_{eff}(DS)(\psi)$ is $(\psi, R_{eff}(DS)) = (0.8, 1)$. Therefore, for effective reproduction drug sensitive strain to be less than unity, the control parameter ψ should be greater than 0.8. But from the real data we obtained that $\psi = \frac{1887281}{3845275} = 0.49$. Hence, this value

should approach 0.8 by fixing the total number of newly born babies on 3845275 and increasing the number of newly born vaccinated babies from 1887281 to 3076220.

The second control parameter is the rate of the proportion of screened latent drug sensitive tuberculosis infected at early stage for treatment p. $p = \frac{\textit{the number of screened early latent DS-TB infected}}{\textit{the total number of early latent DS-TB infected}} = 0.2$, where the number of screened early latent DS-TB infected is 83546 and the total number of early latently infected DS-TB is 417729. The intersection point of $R_{eff}(DS) = 1$ and the effective reproduction number of drug sensitive tuberculosis as a function of the proportion of screened latent drug sensitive tuberculosis infected at early stage $R_{eff}(DS)(p)$ is $(p, R_{eff}(DS)) = (0.22, 1)$. Therefore, for effective reproduction number of drug sensitive strain to be less than unity, the control parameter p should be greater than 0.22. But from the real data we obtained that $p = \frac{83546}{417729} = 0.2$. Hence, this value should approach 0.22 by fixing the total number of early latently infected DS-TB on 417729 and increasing the number of screened early latent DS-TB infected from 83,546 to 91,900.

The third control parameter is the rate of the proportion of screened latently infected MDR-TB for treatment ν. $\nu = \frac{\textit{the number of screened latent MDR-TB infected}}{\textit{the total number of latent MDR-TB infected}} = 0.065$, where the number of screened latently MDR-TB infected is 528 and the total number of latently infected MDR-TB is 8098. The intersection point of $R_{eff}(MDR) = 1$ and the effective reproduction number of multi drug resistant tuberculosis as a function of the proportion of screened latently infected MDR-TB, $R_{eff}(MDR)(\nu)$ is $(\nu, R_{eff}(MDR)) = (0.8, 1)$. Therefore, for effective reproduction number of multi drug resistant strain to be less than unity, the control parameter ν should be greater than 0.8. But from the real data we obtained that $\nu = \frac{528}{8098} = 0.065$. Hence, this value should approach 0.8 by fixing the total number of latently infected MDR-TB on 8098 and increasing the number of screened latently MDR-TB infected from 528 to 6478.

The fourth control parameter is the recovery rate of active DS-TB ρ_s.
$\rho_s = \frac{1}{\textit{the mean infection period of active DS-TB}} = 0.83$, where the mean infection period of active DS-TB is 1.2 years. The intersection point of $R_{eff}(DS) = 1$ and the effective reproduction number of drug sensitive tuberculosis as a function of the recovery rate of active DS-TB, $R_{eff}(DS)(\rho_s)$ is $(\rho_s, R_{eff}(DS)) = (0.85, 1)$. Therefore, for effective reproduction number of drug sensitive strain to be less than unity, the control parameter ρ_s should be greater

than 0.85. But from the real data we obtained that $\rho_s = \frac{1}{1.2\ years} = 0.83$. Hence, this value should approach 0.85 by decreasing the mean infection period of active DS-TB from 1.2 years to 1.18 years.

The fifth control parameter is the recovery rate of active MDR-TB ρ_r.
$\rho_r = \frac{1}{the\ mean\ infection\ period\ of\ active\ MDR\text{-}TB} = 0.498$, where the mean infection period of active MDR-TB is 2.01 years. The intersection point of $R_{eff}(MDR) = 1$ and the effective reproduction number of multi drug resistant tuberculosis as a function of the recovery rate of active MDR-TB, $R_{eff}(MDR)(\rho_r)$ is $(\rho_r, R_{eff}(MDR)) = (2.8, 1)$. Therefore, for effective reproduction number of multi drug resistant strain to be less than unity, the control parameter ρ_r should be greater than 2.8. But from the real data we obtained that $\rho_r = \frac{1}{2.01\ years} = 0.498$. Hence, this value should approach 2.8 by decreasing the mean infection period of active MDR-TB from 2.01 years to 0.4 years.

The sixth control parameter is the rate of the average number of susceptible or vaccinated individuals contact with an infectious individual c. The intersection point of $R_{eff}(DS) = 1$ and the effective reproduction number of drug sensitive tuberculosis as a function of c, $R_{eff}(DS)(c)$ is $(c, R_{eff}(DS)) = (10.7, 1)$ and the intersection point of $R_{eff}(MDR) = 1$ and the effective reproduction number of multi drug resistant tuberculosis as a function of c, $R_{eff}(MDR)(c)$ is $(c, R_{eff}(MDR)) = (2.3, 1)$. Therefore, for effective reproduction number of drug sensitive strain to be less than unity, the control parameter c should be less than 10.7 and; for effective reproduction number of multi drug resistant strain to be less than unity, the control parameter c should be less than 2.3. But from the real data we obtained that $c = 11$. Hence, to control the disease this value should decrease from 11 to 2.

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