A MATHEMATICAL MODEL OF TUBERCULOSIS DYNAMICS

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CERTIFICATION

This is to certify that this seminar work on **"A MATHEMATICAL MODEL OF TUBERCULOSIS DYNAMICS"** was carried out by **EZEUGO PEARL UZOAMAKA** with the registration number **20181090055** in partial fulfillment for the requirement of the award of Bachelor of Technology (B.Tech) Degree in Mathematics.

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DEDICATION

I dedicate this project to Jehovah God, who has been my source of strength and whose grace has helped me scale through. I also dedicate this work to my parents, friends, aunts, uncles and grand parents.

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ABSTRACT

Tuberculosis (TB) remains a global health challenge, necessitating the exploration of effective control strategies. This study employs mathematical modeling techniques to investigate TB transmission dynamics and control measures. The introduction provides an overview of TB as a major public health concern, outlining its epidemiology, transmission dynamics, and the need for effective control measures. A comprehensive literature review examines previous research on TB transmission dynamics, highlighting the role of mathematical modeling in understanding disease spread and informing control strategies. The SLITR model, a compartmental model, is introduced as a tool for understanding TB transmission dynamics. The model's differential equations and parameters are derived, laying the foundation for subsequent analyses. An in-depth analysis of TB transmission dynamics is conducted using the SLITR model. This study explores the impact of key parameters, such as the transmission rate and treatment rate, on disease progression and control. The study concludes by summarizing key findings, including the significance of treatment rate in controlling TB transmission, the role of the basic reproduction number in disease stability, and recommendations for future research and public health interventions.

Contents

Chapter 1

INTRODUCTION

1.1 Background of Study

An ancient scourge is tuberculosis (TB). It has afflicted humanity for all of recorded human history and prehistory. It has shown similar behavior to other infectious diseases, with periods of high epidemic activity followed by periods of decline, however its temporal variability defies conventional theories of epidemic cycles, (Frith 2014). More people may have died from Mycobacterium TB than from any other microbiological infection. According to WHO, a total of 1.3 million people died from Tuberculosis in 2022 Worldwide, Tuberculosis is the second leading infectious killer after COVID-19. The genus Mycobacterium may have evolved more than 150 million years ago, according to certain theories.The current global range of Mycobacterium ulcerans exhibits distinct environmental needs, resulting in significant separation between its endemic locations. Paleopathological evidence reaches back to 8000 BCE, and evidence of bone tuberculosis has been discovered in Egyptian mummies from 2400 BCE and Neolithic era artifacts from 5800 BCE (Frith, 2014).

Over the centuries, TB has had many names, including psithisis pulmonaris,white plague, and consumption (Prabhu and Singh, 2019). The name consumption came from the fact that the infection seems to "consume" the patient. Dutch scientist, Sylvius de la Boe, provided the first pathological and anatomical descriptions of the disease in 1679 by identifying tubercles as a consistent and characteristic pathologic manifestation in the lungs of patients with Tuberculosis. His reports were later pub-

lished in Opera Medica, describing how the disease usually affected the lungs, but later progressed to cavitary lesions and abscesses. He was the first to cite an association between phthisis and a disease of the lymph nodes of the neck, termed Scrofula (Prabhu and Singh, 2019). On March 24, we remember the day in 1882 that shocked the scientific world when Dr. Robert Koch revealed to a small group of scientists at the University of Berlin's Institute of Hygiene that he had found the TB bacillus, the source of tuberculosis. "At this memorable session, Koch appeared before the public with an announcement which marked a turning-point in the story of a virulent human infectious disease," said Paul Ehrlich, Koch's colleague. Koch used several of his microscope slides and other pieces of data to persuasively describe the aetiology of TB in basic, straightforward terms." One in seven persons died from tuberculosis (TB) at the time of Koch's statement in Berlin, when the disease was rampaging over Europe and the Americas (Ryan,1992).

In terms of cases of TB, Nigeria is ranked third, behind only China and India. An estimated 245,000 Nigerians lose their lives to tuberculosis (TB) each year, and an additional 590,000 cases are reported; about 140,000 of these cases are HIV-positive. In Nigeria, tuberculosis (TB) causes almost 10% of all fatalities. Despite the availability of modern therapies, the illness claims the lives of around thirty individuals per hour (WHO, 2022). About one-third of the world's population is estimated to be afflicted with tuberculosis (TB), according to the World Health Organization (WHO) classification of the disease in 1993. Although Africa is home to 13 of the 15 nations with the highest incidence rates of tuberculosis, These days, five Asian nations—Bangladesh, India, Indonesia, Pakistan, and the Philippines—account for more over half of all new cases. This has caused a change in the focus of public health initiatives to the Southeast Asian Region (SEAR), since 42% of Disability-Adjusted Life Years (DALY) lost there are due to infectious illnesses. DALY is a worldwide metric used to compare the total burden of disease, defined as the number of years lost as a result of illness, disability, or premature death. The slogan for year 2023 and 2024 for the world TB day is "Yes,We Can End TB" UNICEF is one of the organizations spearheading other global campaigns. Its programs

aim to enhance child survival, growth, and development, water sanitation and hygiene, and vaccination accessibility. In addition, groups like "Americares" strive to offer humanitarian relief and medical assistance in the event of environmental calamities like the monsoon. Even with the assistance of government programs and non-governmental organizations (NGOs) in the healthcare and humanitarian sectors, much more has to be done to enhance access to healthcare and support communities who are disadvantaged and vulnerable.

The TB germs transfer from person to person through the air. Bacteria that cause tuberculosis (TB) can enter the air when a person who has the illness of the lungs or throat coughs, talks, or sings. People in the vicinity might inhale these germs and acquire an infection. TB can only be passed from mother to child if the mother has cough, or is not on any medication. But this usually happens in rare cases. TB can be cured with the right treatment, but people who are treated can still contact the disease again. This time they are more likely to develop multi drug resistance and may die from the disease.
The TB germs can enter the lungs of an individual and start to develop there when they are breathed in. They can then travel through the blood to the kidney, spine, and brain, among other organs. It is possible for TB illness to spread to the throat or lungs. This implies that other people may come into contact with the germs. Other bodily organs, including the kidney or spine, are often not contagious when it comes to tuberculosis.

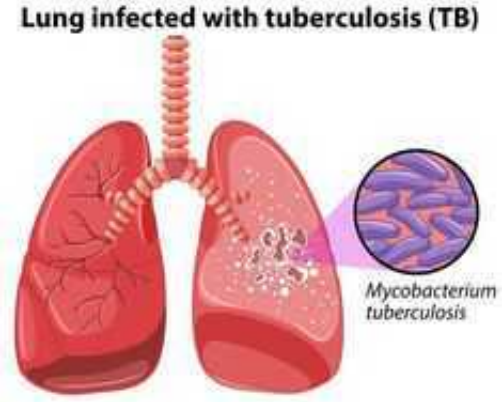
• Types of Tuberculosis
Latent TB Infection (LTBI): latent tuberculosis infection (LTBI) is when a person is infected with Mycobacterium tuberculosis, but does not have active tuberculosis (TB). Active tuberculosis can be contagious while latent tuberculosis is not, and it is therefore not possible to get TB from someone with latent tuberculosis. The bacteria would live in your body without making you sick, TB bacteria can remain inactive in the body for a lifetime without causing the disease. If you have a weak immune system then the bacteria would multiply and cause TB disease. They usually have

a skin test or blood test result indicating TB infection, Certain conditions can increase a person's risk for tuberculosis disease: Diabetes (high blood sugar), weakened immune system (for example, HIV or AIDS), being malnourished, tobacco use e.t.c.

• **TB Disease:** TB bacteria become active if the immune system can't stop them from growing. When TB bacteria are active (multiplying in your body), this is called TB disease. People with TB disease are sickly. They may also be able to spread the bacteria to people they spend time with every day.

Common symptoms of TB includes; prolonged cough, (sometimes with blood), chest pain, weakness, fatigue, weight loss, fever, night sweats e.t.c. Symptoms in children varies unlike adults. From 1-12-year-old children may have a fever that won't go away and weight loss while age below 0-12 months may have symptoms like being unusually fussy, Vomiting, Poor feeding, Bulging soft spot on the head, Poor reflexes. Tuberculosis also affects the Kidneys, Liver, Fluid surrounding the brain and spinal cord, Heart muscles, Genitals, Lymph nodes, Bones and joints, Skin, Walls of blood vessels, Voice box, also called larynx.

According to CDC(Centre for Disease Control) 2023, the TB skin test is performed by injecting a small amount of fluid (called tuberculin) into the skin on the lower part of the arm. A person given the tuberculin skin



test must return within 48 to 72 hours to have a trained health care worker look for a reaction on the arm. The result depends on how your body reacts to the injection. Other tests are: Blood Test, Sputum test, X-ray, Urine Test, Breath test.

Common drugs used for treatment of TB includes; Isoniazid, Rifampin (Rimactane), Rifabutin (Mycobutin), Rifapentine (Priftin), Pyrazinamide, Ethambutol (Myambutol).
Most of these drugs need to be taken for 4-6 months without stop for it to be effective. Tuberculosis that doesn't respond to standard drugs is called drug- resistant TB and requires more toxic treatment with different medicines.
TB can be prevented by; wearing a mask, ventilating rooms by opening windows, covering their mouth and nose when coughing or sneezing

The only available vaccine for tuberculosis is BCG, otherwise known as Bacille Calmette-Guerin.. The vaccination is given solely to newborns who are very susceptible to TB immediately after birth. The BCG vaccination triggers an immunological response that helps shield young children and newborns from severe TB. Only in nations where TB is highly prevalent is the vaccination utilized due to the infection risk and inconsistent protection it provides (von Reyn CF, Vuola JM, 2002). BCG should not be administered to HIV-infected individuals (Nuttall and Eley 2011). The vaccine is not 100% effective since a child when grown can still contact TB after 15years. TB vaccine does not work on adults.

Drug resistance develops when TB medications are prescribed incorrectly by medical professionals, when the treatments are of low quality, or when patients discontinue therapy too soon. The two most effective first-line TB medications, isoniazid and rifampicin, do not affect germs that cause multidrug-resistant tuberculosis (MDR-TB). Second-line medications can be used to treat and cure MDR-TB. Second-line therapy options, however, need the use of costly, toxic, and lengthy medications. If MDR-TB is suspected, begin therapy based on an empirical basis prior to the availability of culture data; If feasible, obtain testing for molecular drug

susceptibility. Adjust the first regimen as needed in light of the susceptibility findings. Avoid adding any more drugs to a regimen that isn't working. Give at least four medications for the continuation phase of therapy and at least five for the intense phase. The medications are as follows: A fluoroquinolone: levofloxacin or moxifloxacin preferred, Bedaquiline, Linezolid, Clofazimine (available only through Investigational New Drug application through the FDA), Cycloserine, An aminoglycoside: streptomycin or amikacin preferred, Ethambutol, Pyrazinamide, Delamanid, Ethionamide, Para- aminosalicylic acid. Sometimes surgical procedures like Lobectomy, and Pneumonectomy are recommended for patients with poor reaction after medical treatment. (WHO 2019)

1.2 Statement of Problem

The WHO estimates that 1.3 million people died from tuberculosis in 2022. Multi-drug resistant tuberculosis (MDR-TB) continues to be a health security risk and a public health emergency. In 2022, only roughly 2 out of 5 patients with drug-resistant tuberculosis received therapy. Globally, drug resistance poses a serious challenge to tuberculosis care and prevention. It prolongs the treatment process and makes it more difficult, sometimes leading to worse patient outcomes. In the long run, the best way is to have more accurate diagnosis and treatment for drug resistant patients more accessible.

1.3 Aim & Objectives

The project aims to develop a mathematical model to better understand the dynamics of TB transmission and to evaluate the impact of interventions aimed at controlling the spread of the disease.
The objectives of the study are:

- Formulate a mathematical model
- Gather information on the transmission dynamics of TB within a specified population.

- To infer from the data acquired an action plan for tuberculosis prevention,
- To determine how effective the treatment for both latently infected and infectious individuals in controlling the spread of the disease

1.4 Justification of Study

Mathematical models enable the prediction of future trends in TB incidence, prevalence, and drug resistance patterns, By developing a comprehensive model for TB dynamics, researchers contribute to the global effort to combat TB and achieve targets related to ending the TB epidemic by 2030. This aligns with broader public health objectives and international commitments to improve health outcomes and reduce health inequalities worldwide. It would also help in assessing the impact of interventions such as case detection, treatment initiation, contact tracing, vaccination campaigns, and infection control measures.

1.5 Scope of Study

In this study, we would only be focusing on Tuberculosis and Multidrug resistant TB. The data would be gotten from WHO and other health care agencies.

1.6 Limitations

TB transmission dynamics are influenced by a variety of factors, including biological factors (e.g., strain diversity, drug resistance), social determinants (e.g., poverty, access to healthcare), and environmental factors (e.g., air quality, population density). Capturing the full complexity of TB dynamics in a mathematical model may be challenging and may require additional data and model refinements. Adopting model-based advice into practice and policy may provide political, economical, and logistical obstacles. Collaboration between researchers, policymakers, healthcare professionals, and impacted communities is necessary for the effective translation of model findings into practicable public health initiatives.

Chapter 2

LITERATURE REVIEW

Mathematics is a very precise and concise language with well defined rules for manipulation that helps us to formulate ideas. In mathematical modelling it involves the use of mathematics to describe a real world problem which would enable us to better understand and discover new ways to solve the problem. There are different stages, steps and classification in mathematical modelling. One classification that we would be dealing with is deterministic models which involves the use of known data. Mathematical modelling is a useful way in analyzing the epidemiology of a disease. In 17601, Bernoulli created the first mathematical model of infectious disease transmission to assess the effects of variolation, a rudimentary smallpox vaccine, on life-tables utilized in actuarial calculations. (White, 2016) Mathematical models of infectious disease transmission are increasingly being used to guide public health policy. Examples include: planning control strategies for tuberculosis (TB), human immunodeficiency virus (HIV) and sexually transmitted infections (STIs).

Nadhirah Abdul Halim(2013): He built three mathematical models to determine the transmission dynamics of infectious disease in a population. The first model is a basic SEIR() which focused on stabilizing rhe eqilibrum with immigration. Using the system's homogeneity feature, the system was broken down into a subsystem consisting of three equations. This approach was used to establish the equilibrium points and demonstrate the local stability of the first estimate. He demonstrated the stability of the matrix system's Jacobian under specific parameter constraints. while the

second and third is used to investigate the dynamic of Tuberculosis transmission under different condition. He determined the effect of immigration and treatment and hence deduced an action plan for prevention, control and monitoring of TB. His conclusion was that immigration plays a significant role in the dynamic of TB spreading since it has a marked influence to the existence of the disease in the population. He also suggested that In order to prevent the latently infected from spreading and lowering the incidence rate, it was preferable to treat them. Nonetheless, in areas with high prevalence rates, treating sick individuals and placing them in quarantine will be the best course of action as it will minimize their interaction with others and, thus, the risk of the disease spreading.

Waleed M. Sweileh (2022): He aimed to analyze global research activity on mathematical modeling of transmission and control of several infectious diseases with a known history of serious outbreaks. He concluded high-income nations dominated the sector and demonstrated inadequate cross-border collaboration in research with low- and middle-income nations. middle-class and lower-class through training and cooperation with active institutions and writers, countries need to increase their level of competence in this subject. In order to comprehend and stop the transmission of infectious illnesses depending on the circumstances present in each nation, health authorities must also finance and spend in gaining knowledge and experience in this area.

Dauda M.K, Magaji A.S, Okolo P.N, Bulus J., Shehu U.S. (2020): Data from the Tuberculosis Medical Centre in Kaduna were analyzed to develop the transmission dynamics of tuberculosis infection in the city using the SEIR compartmental model. The fundamental reproduction number was calculated using the model's disease-free equilibrium (DFE) condition. The findings of the stability study for the endemic equilibrium state (EEs) and the disease-free equilibrium state (DFEs) indicate that the DFEs is asymptotically stable both locally and globally. According to the numerical stability study, unless effective control measures like a regular and extended vaccination program are implemented, TB infection would continue to be endemic (persist) in Kaduna city.

Zhao, Jing Liu, Zhiyang Zhao, Mengmeng Zhai, Hao Ren, Xuchun Wang, Yiting Li, Yu Cui, Yuchao Qiao, Jiahui Ren, Limin Chen and Lixia Qiu. BMC Infectious Diseases (2023): This paper aim was to build an EMDARMA-LSTM hybrid model based on the idea of decomposition before integration, and use the existing incidence data of tuberculosis to predict the incidence trend of this infectious disease in the next year, and achieve good results. The conclusion was that the EMD-ARMA-LSTM combination model can improve prediction accuracy better than other models, and can provide a theoretical basis for predicting the epidemic trend of pulmonary tuberculosis and formulating prevention and control policies. The prediction performance of the decomposition-based single model is better than that of the undecomposed single model, and the prediction performance of the combined model using the advantages of different models is better than that of the decomposition-based single model. Not only can the model be used to forecast infectious diseases like TB, but it can also be expanded to include data sets for hand, foot, and mouth disease and influenza. Thus, this work has some relevance in the field of epidemiology, where it may help relevant departments develop pertinent preventive and control measures in addition to drawing people's attention to infectious illnesses by predicting their future prevalence.

Andrawus J., Eguda F.Y, Maiwa S.I, Dibal I.M, Urum T.G, Anka G.H, (2020): This paper built a new mathematical model for a tuberculosis transmission dynamics incorporating first and second line treatment. To better understand the dynamics of the illness, a mathematical model of TB transmission dynamics combining first and second line therapy was developed and examined in this article. It was demonstrated that when the RC is less than one, the DFE is locally asymptotically stable, and when the RC is more than one, the EEP is similarly locally asymptotically stable. Based on numerical modeling, treating infectious individuals can significantly lower the number of patients requiring second-line treatment in a community, which in turn lowers the burden of tuberculosis (TB) in that community.

Alsdurf (2021): In high-burden areas, Alsdurf and associates created a mathematical model to evaluate the effects of latent TB infection screening and preventative medication. Their work emphasizes how crucial it is to include intervention coverage levels and population-specific epidemiological data in model forecasts in order to support policy choices.

Vignesh Gopalakrishnan(2024): In this study, they set out to investigate the use of the pre-trained model DINO (DETR with Improved De-Noising Anchor Boxes for End-to-End Object Detection) for tuberculosis localization using the TBX11K data set. Their objectives were to evaluate the model's performance, point out its advantages and disadvantages, and open the door for further developments in medical picture analysis. In summary, this experimentation represents a major advancement toward more precise and effective methods for TB diagnosis and localization. Notwithstanding ongoing difficulties, the DINO pretrained model provides a solid basis for further study because to its skill at feature extraction and capacity for self-supervised learning.

Zizhen Zhang, Weishi Zhang, Kottakkaran Sooppy Nisar, Nadia Gul, Anwar Zeb, Vijayakumar V., (2023): They aimed to explore transmission dynamics of tuberculosis, so a tuberculosis transmission model with vaccination and time delay was developed. They analyzed positivity and boundedness as well as local stability of tuberculosis-free equilibrium in respect of the time delay due to latent period of tuberculosis. In this paper, a tuberculosis transmission model with vaccination and time delay is proposed by taking into account the time delay due to the latent period of tuberculosis into the model formulated by Ojo R.A. Compared with the tuberculosis transmission model by Ojo, the proposed model with time delay is more general. According to computation, we obtain that the tuberculosis disease dies out from the model when the basic reproduction number R0¡1. And the model has a tuberculosis disease-free equilibrium D_0 when $R_0 < 1$ and a unique tuberculosis disease-existence equilibrium D when $R_0 > 1$.

Rita Makabayi-Mugabe1, Joseph Musaazi, Stella Zawedde-Muyanja, Enock Kizito, Hellen Namwanje, Philip Aleu, Danielle Charlet, Debora B. Freitas

Lopez, Haley Brightman, Stavia Turyahabwe and Abel Nkolo. Makabayi-Mugabe et al. BMC Health Services Research (2022), The introduction of community-based directly observed treatment (CB-DOT) for patients with multi-drug resistant tuberculosis (MDR-TB) has become possible with the development of all-oral regimens. Their goal was to ascertain patient preferences for several aspects of a community-based strategy for MDR-TB care in Uganda. The conclusion they discovered that individuals with multidrug-resistant tuberculosis (MDR-TB) favored receiving treatment from a community health worker (CHW) or an expert client who lives in the area, as well as receiving travel vouchers to facilitate monthly follow-up visits to the clinic. Expert clients and CHWs were seen as informed, experienced, sympathetic, and capable of providing patients with the right advice and direction on how to manage side effects. Additionally, they were thought to be able to keep things private while providing care. Family members were perceived as not having enough understanding of MDR-TB, and patients doubted their capacity to provide the necessary assistance. They did not include children and other risk populations, like pregnant women so their preferences are not represented in this findings. Future studies could include children and other vulnerable populations so that their views are taken into consideration.

Akinsola O.J, Yusuf O.B, Ige O.M and Okonji P.E, (2018), The study was designed to develop suitable cure models that can predict time to sputum conversion among MDR-TB patients. In summary, the majority of patients with multi-drug resistant tuberculosis achieved sputum conversion within 13 weeks of beginning therapy, despite a high risk of drug resistance in the examined group. It is simple to identify factors that are adversely related to culture conversion at two months, either prior to diagnosis or early in the course of MDR-TB treatment. By recognizing them early on and giving them intensive treatment, this may contribute to better patient care. Combination cure models enable simultaneous modeling of the treated fraction and the remaining uncured persons with incidence and latency components, respectively. The main benefit of the mixture model, particularly for researchers studying medicine, is in its straightforward interpretations, which provide the survival function expression together with

the fraction of treated and non-cured people.

From these various studies, we can see that there are various models that can be built to stop the spread of tuberculosis. Mathematical modeling is useful in informing TB control strategies and actions, as recent research have shown. Researchers are better able to comprehend the intricate dynamics of tuberculosis transmission and pinpoint practical methods for lowering the burden of tuberculosis in high-risk environments by incorporating epidemiological data and intervention tactics into mathematical models.

Chapter 3

METHODOLOGY

In mathematical modeling, differential equations are useful tools that provide a systematic framework for explaining the dynamics of infectious illnesses such as tuberculosis (TB). This chapter explores the use of differential equations to simulate the dynamics of tuberculosis transmission and assess the effects of alternative treatments.
We construct a compartmental model to capture the progression of TB within a population. The model divides the population into several compartments:

3.1 Next generation operator method and the basic reproduction number

The next generation operator method (Van den Driessche & Watmough, 2002) is used to establish the local asymptotic stability (LAS) of the disease-free equilibrium (DFE) of a disease transmission model. Suppose the given disease transmission model, with non-negative initial conditions, can be written in terms of the following system:

$$\dot{x}_i = f(x) = \mathcal{F}_i(x) - \mathcal{V}_i(x), i = 1, \ldots, n \tag{3.1}$$

where $\mathcal{V}_i = \mathcal{V}_i^- - \mathcal{V}_i^+$and the functions satisfy Axioms (B1)-(B5) below.
The function $\mathcal{F}_i(x)$ represents the rate of appearance of new infections in compartment i.
The function $\mathcal{V}_i^+(x)$ represents the rate of transfer of individuals into com-

partment i, $\mathcal{V}_i^-(x)$ represents the rate of transfer of individuals out of compartment i.
Furthermore, the number of individuals in each compartment is given by $x = (x_1, \ldots, x_n)^t, x_i \geq 0$, and $X_s = \{x \geq 0 \mid x_i = 0, i = 1, \ldots, m\}$ is defined as the disease-free states (non-infected variables of the model).

B1 If $x \geq 0$, then $\mathcal{F}_i, \mathcal{V}_i^-, \mathcal{F}_i^+ \geq 0$ for $i = 1, \ldots, m$;

B2 if $x_i = 0$, then $\mathcal{V}_i^- = 0$. In particular, if $x \in X_s$ then $\mathcal{V}_i^- = 0$ for $i = 1, \ldots, m$;

B3 $\mathcal{F}_i = 0$ if $i > m$;

B4 if $x \in X_s$ then $\mathcal{F}_i(x) = 0$ and $\mathcal{V}_i^+ = 0$ for $i = 1, \ldots, m$;

B5 if $F(x)$ is set to zero, then all eigenvalues of $Df(x_0)$ have negative real parts

Lemma 3.1. (Van den Driessche 83 Watmough, 2002).
If $\bar{x}$ is a DFE of (3.1) and $\mathcal{F}_i(x)$ satisfy (B1)-(B5), then the derivatives $D\mathcal{F}(\bar{x})$ and $D\mathcal{V}(\bar{x})$ are partitioned as

$$D\mathcal{F}(\bar{x}) = \begin{bmatrix} F & 0 \\ 0 & 0 \end{bmatrix}, \quad D\mathcal{V}(\bar{x}) = \begin{bmatrix} V & 0 \\ J_3 & J_4 \end{bmatrix}$$

where F and V are the $m \times m$ matrices defined by

$$F = \frac{\partial \mathcal{F}_i}{\partial x_j}(\bar{x}), \quad V = \frac{\partial \mathcal{V}_i}{\partial x_j}(\bar{x}), \quad \text{with} \quad 1 \leq i, j \leq m$$

Further, F is a non-negative matrix, V is a non-singular M-matrix and J_3, J_4 are matrices associated with the transition terms of the model, and all eigenvalues of J_4 have positive real parts.

Theorem 3.1. (Van den Driessche & Watmough, 2002).
Consider the disease transmission model given by (1.5) with $f(x)$ satisfying Axioms (B1)-(B5). If $\bar{x}$ is a DFE of the model, then $\bar{x}$ is locally asymptotically stable (LAS) if $\mathcal{R}_0 = \rho\left(FV^{-1}\right) < 1$ (where ρ is spectral radius), but unstable if $\mathcal{R}_0 > 1$.

Theorem 3.2. (Wiggins (2003)).
Suppose all the eigenvalues of $Df(\bar{x})$ have negative real parts. Then the

equilibrium solution $x = \bar{x}$ of the system (??) is locally asymptotically stable, and unstable if at least one of the eigenvalues has positive real part. The following theorem is used to establish the presence of the backward bifurcation phenomenon for the models considered in this dissertation.

Theorem 3.3. (Castillo-Chavez & Song, 2004).
Consider the following system of ordinary differential equations with a parameter ϕ

$$\frac{dx}{dt} = f(x, \phi), \quad f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R} \text{ and } f \in C^2\left(\mathbb{R}^n \times \mathbb{R}\right) \tag{3.2}$$

where 0 is an equilibrium point of the system (that is, $f(0, \phi) \equiv 0$ for all ϕ) and assume
A1: $A = D_x f(0,0) = \left(\frac{\partial f_i}{\partial x_j}(0,0)\right)$ is the linearization matrix of the system (1.6) around the equilibrium 0 with ϕ evaluated at 0 .
Zero is a simple eigenvalue of A and other eigenvalues of A have negative real parts;
A2: Matrix A has a right eigenvector w and a left eigenvector v (each corresponding to the zero eigenvalue).
Let f_k be the kth component of f and

$$a = \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0),$$
$$b = \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0)$$

The local dynamics of the system around 0 is totally determined by the sign of a and b.

- $a > 0, b > 0$. When $\phi < 0$ with $|\phi| \ll 1, 0$ is locally asymptotically stable and there exists a positive unstable equilibrium; when $0 \leq \phi \ll 1, 0$ is unstable and there exists a negative, locally asymptotically stable equilibrium;

- $a < 0, b < 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable; when $0 < \phi \ll 1$, 0 is locally asymptotically stable equilibrium, and there exists

a positive unstable equilibrium;

- $a > 0, b < 0$. When $\phi < 0$ with $|\phi| \ll 1, 0$ is unstable and there exists a locally asymptotically stable negative equilibrium; when $0 \leq \phi \ll 1, 0$ is stable and a positive unstable equilibrium appears;

- $a < 0, b > 0$. When ϕ changes from negative to positive, 0 changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable. Particularly, if $a > 0$ and $b > 0$, then a backward bifurcation occurs at $\phi = 0$.

Theorem 3.4. (Descartes Rule of Signs, (Wang, 2004)).
Let $p(x) = a_0 x^{b_0} + a_1 x^{b_1} + \cdots + a_n x^{b_n}$ denote a polynomial with non-zero real coefficients a_i, where the b_i are integers satisfying $0 \leq b_0 < b_1 < b_2 < \cdots < b_n$. Then the number of positive real zeros of $p(x)$ (counted with multiplicities) is either equal to the number of variations in sign in the sequence $a_0, \ldots, a_n$ of the coefficients or less than that by an even whole number. The number of negative zeros of $p(x)$ (counted with multiplicities) is either equal to the number of variations in sign in the sequence of the coefficients of $p(-x)$ or less than that by an even whole number.

3.2 Lyapunov Function Theory

Establishing the global properties of a dynamical system is generally not trivial and the direct Lyapunov method (Dushoff, Huang & Castillo-Chavez, 1998) is one of the most powerful methods. The method requires the construction of an auxiliary function with certain properties, that is a Lyapunov function.

Definition 3.1. Consider the following system

$$\dot{x} = f(x), \quad x \in \mathbb{R}^n \tag{3.3}$$

Let, $\bar{x}$ be an equilibrium solution of (1.7) and let $V : U \to \mathbb{R}$ be a c^1 function defined on some neighborhood U of $\bar{x}$ such that

- V is positive-definite,

- $\dot{V}(x) \leq 0$ in $U \backslash \{\bar{x}\}$.

Any function, V, that satisfies the Conditions (i) and (ii) above is called a Lyapunov function.

Theorem 3.5. (La Salle's Invariance Principle (La Salle, 1976)).
Consider the following system (3.3). Let,

$$S = \{x \in \bar{U} : \dot{V} = 0\} \tag{3.4}$$

and M be the largest invariant set of (3.3) in S. If V is a Lyapunov function on U and $\gamma^+(x_0)$ is a bounded orbit of (3.3) which lies in S, then the ω - limit of set $\gamma^+(x_0)$ belongs to M; that is, $x(t, x_0) \to M$ as $t \to \infty$

Corollary 3.1.
If $V(x) \to \infty$ as $|x| \to \infty$ and $\dot{V} \leq 0$ on $\mathbb{R}^n$, then every. solution of (1.7) is bounded and approaches the largest invariant set M of 3.3 in the set where $\dot{V} = 0$.
In particular, if $M = \{0\}$, then the solution $x = 0$ is globally-asymptotically stable (GAS)

3.2.1 Construction of Lyapunov functions to prove the GAS of the disease free equilibrium (DFE)

.
Suppose that there are $n > 0$ disease compartments and $m > 0$ non-disease compartments.
Then a general compartmental disease transmission model can be written as

$$\dot{x} = \mathcal{F}(x, y) - \mathcal{V}(x, y), \quad \dot{y} = g(x, y) \tag{3.5}$$

with
$g = (g_1, g_2, \ldots, g_m)^T \in \mathbb{R}^m, x = (x_1, x_2, \ldots, x_n)^T \in \mathbb{R}^n$ and $y = (y_1, y_2, \ldots, y_m)^T \in \mathbb{R}^m$ represents the populations in disease compartments and non-disease compartments respectively;

$\mathcal{F} = (\mathcal{F}_1, \mathcal{F}_2, \ldots, \mathcal{F}_n)^T$ and $\mathcal{V} = (\mathcal{V}_1, \mathcal{V}_2, \ldots, \mathcal{V}_n)^T$,
where
$\mathcal{F}_i$ represents the rate of appearance of new infections in the ith disease compartment, $\mathcal{V}_i$ represents the transitions in and out of the ith disease compartment, for example, death, recovery, etc. Following Van den Driessche and Watmough (2002), define two $n \times n$ matrices

$$F = \frac{\partial \mathcal{F}_i}{\partial x_j}(\bar{x}), \quad V = \frac{\partial \mathcal{V}_i}{\partial x_j}(\bar{x}), \quad \text{with} \quad 1 \leq i, j \leq m \tag{3.6}$$

it is assumed that $F \geq 0$ and $V \geq 0$. Set

$$f(x, y) = (F - V)x - \mathcal{F}(x, y) + \mathcal{V}(x, y) \tag{3.7}$$

Then (3.5) for the disease compartments can be written as

$$\dot{x} = (F - V)(x) - f(x, y) \tag{3.8}$$

Let $\omega^T \geq 0$ be the left eigenvector of the non-negative matrix $V^{-1}F$ corresponding to the eigenvalue $\mathcal{R}_0$.
The following result provides a general method to construct a Lyapunov function to prove the GAS of DFE of the system (3.5).

Theorem 3.6. (Shuai & Van den Driessche, 2013).
Let F, V and $f(x, y)$ be defined as in (3.6) and (3.7), respectively.
If $f(x, y) \geq 0$ in $\Gamma \subset \mathbb{R}_+^{n+m}, F \geq 0, V^{-1} \geq 0$ and $\mathcal{R}_0 \leq 1$,
then the function $Q = \omega^T V^{-1} x$ is a Lyapunov function for model (3.5) on Γ

3.2.2 Construction of Lyapunov functions to prove the GAS of the endemic equilibrium point (EEP)

The non-linear Lyapunov functions used for studying the global properties of the endemic equilibria are of the Goh-Volterra type (Goh, 1976):

$$L_1(x_1, x_2, \ldots, x_n) = \sum_{i=1}^{n} c_i \left(x_i - x_i^{**} - x_i^{**} \ln \frac{x_i}{x_i^{**}} \right) \tag{3.9}$$

where x_i are the state variables, c_i are the coefficients to be determined and $x_i{}^*$ are the state variables at the endemic steady state.
Other types of Lyapunov functions that can be used include the quadratic Lyapunov functions (Vargas-De-Leon, 2011):

$$W_2\left(y_1, y_2, \ldots, y_n\right) = \sum_{i=1}^{n} \frac{c_i}{2}\left(y_i - y_i^{**}\right)^2 \tag{3.10}$$

and composite-Volterra type (Vargas-De-Leon, 2011):

$$W_3\left(y_1, y_2, \ldots, y_n\right) = c\left[\sum_{i=1}^{n}\left(y_i - y_i^{**}\right) - \sum_{i=1}^{n} \ln \frac{\sum_{i=1}^{n} y_i}{\sum_{i-1}^{n} y_i^{**}}\right] \tag{3.11}$$

3.3 Runge-Kutta method

Let us consider an initial value problem

$$\frac{dy}{dt} = f(t, y(t)) \tag{3.12}$$

$$y(t) = \left(y_1(t), y_2(t), \ldots, y_n(t)\right)^T. \quad f \in [a, b] \times \mathbb{R}^n \to \mathbb{R}^n$$

with an initial condition

$$y(0) = y_0 \tag{3.13}$$

We are interested in a numerical approximation of the continuously differentiable solution $y(t)$ of the IVP (3.12)-(3.13) over the interval $t \in [a, b]$. To this aim, we subdivide the interval $[a, b]$ into M subintervals and select the mesh points t_j.

$$t_j = a + jh, \quad j = 0, 1, \ldots, M, \quad h = \frac{b-a}{M} \tag{3.14}$$

The value h is called a step size. The family of explicit Runge-Kutta (RK) methods of the mth stage is given by Stoer and Bulirsch (1993).

$$y\left(t_{n+1}\right)=y_{n+1}=y_n+h\sum_{i=1}^{m}c_ik_i \tag{1.19}$$

where

$$\begin{aligned}
k_1 &= f\left(t_n,y_n\right),\\
k_2 &= f\left(t_n+\alpha_2 h,y_n+h\beta_{21}k_1\left(t_n,y_n\right)\right),\\
k_3 &= f\left(t_n+\alpha_3 h,y_n+h\left(\beta_{31}k_1\left(t_n,y_n\right)+\beta_{32}k_2\left(t_n,y_n\right)\right)\right)\\
&\;\;\vdots\\
k_m &= f\left(t_n+\alpha_m h,y_n+h\sum_{j=1}^{m-1}\beta_{mj}k_j\right).
\end{aligned}$$

To specify a particular method, we need to provide the integer m (the number of stages), and the coefficients α_i (for $i=1,2,\ldots,m$), β_{ij} (for $1\leq j<i\leq m$), and c_i(for $i=1,2,\ldots,m$).
The classical RK method or RK4 method, which corresponds to the case $m=4$ is the one used by the MATLAB ODE solver, which numerically solves the systems of nonlinear equations in the current study.
In general, the accuracy of can be improved by

- reducing the time step h,
- using the method with the higher convergency order

The equations of the models are solved numerically using the the MATLAB ODE45 solver which is based on the fourth order Runge-Kutta method. The stability of the method is well established in May and Noye (1984).

VARIABLES	DESCRIPTION
$S(t)$	Susceptible: Individuals susceptible to TB infection
$L(t)$	Latent: Individuals infected with TB but not yet infectious
$I(t)$	Infectious: Individuals actively infectious and capable of transmitting TB
$T(t)$	Treatment: Individuals undergoing TB treatment
$R(t)$	Recovered: Individuals who have recovered from TB are no longer infectious

Table 3.1: Description of Variables in the TB Model

PARAMETERS	DESCRIPTION
β	Transmission rate
π	Recruitment rate
λ	Standard incidence force of infection
ρ	Progression rate from exposed to active TB
τ	Treatment rate
γ	Recovery rate
μ	Natural Death rate
N	Total Population size

Table 3.2: Parameters of the TB Model

$$\frac{dS}{dt} = \pi - \lambda S - \mu S$$

$$\frac{dL}{dt} = \lambda S - \rho L - \mu L$$

$$\frac{dI}{dt} = \rho L - \tau I - \mu I$$

$$\frac{dT}{dt} = \tau I - \gamma T - \mu T$$

$$\frac{dR}{dt} = \gamma T - \mu R$$

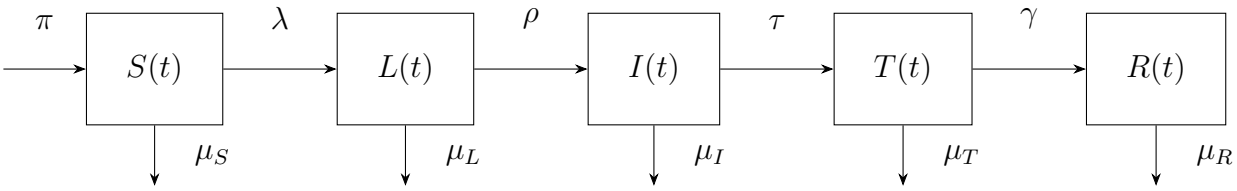


Figure 3.1: Compartmental Model for Tuberculosis

where $\lambda = \frac{\beta I}{N}$

$N(t) = S(t) + L(t) + I(t) + T(t) + R(t)$

Chapter 4

RESULTS AND DISCUSSION

In epidemiological modeling, the understanding of how an infectious disease propagates through a population is crucial for developing effective control strategies. The SLITR model, a compartmental model, provides a framework for examining the dynamics of an infectious disease with distinct states: Susceptible (S), Latent (L), Infectious (I), Treated (T), and Recovered (R). This model helps in understanding not only the progression of the disease through these stages but also the impact of interventions such as treatment and preventive measures.

4.1 Key Features of the Model

The SLITR model incorporates several key parameters that influence disease dynamics:

- **Transmission rate (β)**: Represents how effectively the disease can spread from infectious individuals to susceptible ones.
- **Progression rates (ρ, τ)**: Indicate the speed at which individuals move from latent to infectious states and from infectious to treated states, respectively.
- **Recovery and mortality rates (γ, μ)**: These parameters are crucial for understanding the removal processes either through recovery or death.

4.2 Disease-Free Equilibrium (DFE)

The concept of Disease-Free Equilibrium is pivotal in epidemiological modeling as it represents a state where the disease is absent from the population. In the SLITR model, reaching the DFE implies that the disease has been eradicated, with no active or latent infections present in the system. Mathematically, this is indicated by the absence of individuals in the infectious, latent, and treated compartments, leading to a stable state where all individuals are either susceptible or recovered.

4.2.1 Importance of Basic Reproduction Number (R0)

The Basic Reproduction Number, R_0, is a critical threshold that signifies the average number of secondary infections produced by a single infectious individual in a fully susceptible population. If R_0 is less than 1, the disease is expected to die out; if R_0 is greater than 1, the disease can spread through the population. Calculating R_0 from the SLITR model helps in assessing the potential for disease outbreak and persistence, guiding public health interventions aimed at reducing transmission.

4.3 Mathematical Representation of the SLITR Model

The differential equations representing the SLITR model are as follows:

$$\begin{aligned}
\frac{dS}{dt} &= \pi - \lambda S - \mu S, \\
\frac{dL}{dt} &= \lambda S - \rho L - \mu L, \\
\frac{dI}{dt} &= \rho L - \tau I - \mu I, \\
\frac{dT}{dt} &= \tau I - \gamma T - \mu T, \\
\frac{dR}{dt} &= \gamma T - \mu R, \quad \text{where } \lambda = \frac{\beta I}{N}.
\end{aligned}$$

4.4 Analysis of Disease-Free Equilibrium (DFE)

Given no disease in the population, we analyze the system under the assumption that the infected classes are zero. From the equation for susceptible individuals:

$$\pi - \mu S = 0 \implies S = \frac{\pi}{\mu}.$$

For the latent and infectious compartments, since there is no introduction of new infections:

$$L = 0,$$
$$I = 0.$$

Similarly, for treated and recovered individuals:

$$T = 0,$$
$$R = 0.$$

Therefore, the Disease-Free Equilibrium (DFE) is given by:

$$DFE = (S^*, L^*, I^*, T^*, R^*) = \left(\frac{\pi}{\mu}, 0, 0, 0, 0\right).$$

4.4.1 Basic Reproduction Number using Next Generation Matrix Method

At D.F.E, since $I = 0$, the matrix F for new infections is as follows:

$$F = \begin{bmatrix} 0 & \beta N^* S^* & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix},$$
$$N^* = S^* + L^* + I^* + T^* + R^* = \frac{\pi}{\mu}.$$

Recall from section (4.3)

$$\frac{ds}{dt} = \pi - \lambda s - \mu s \tag{1}$$
$$\frac{dL}{dt} = \lambda s - \rho L - \mu L \tag{2}$$
$$\frac{dI}{dt} = \lambda L - \tau I - \mu I \tag{3}$$
$$\frac{dT}{dt} = \tau I - \varepsilon T - \mu T \tag{4}$$
$$\frac{dR}{dt} = \gamma T - \mu R \quad where \quad \lambda = \frac{\beta I}{N} \tag{5}$$

4.5 DFE (Disease free equilibrium)

When there's no disease in the population, we set infected class to zero from eqn(1), we set $\frac{\beta SI}{N} = \mu S = 0$

$$\pi - 0 - \mu S = 0$$
$$\pi - \mu s = 0$$
$$\mu S = \pi$$
$$S = \frac{\pi}{\mu} -$$

from eq (2) $\lambda S = 0$

$$0 - \rho L - \mu L = 0$$
$$L(-\rho - \mu) = 0$$
$$L = 0$$

from eq (3) everything is zero.

$$I = O$$

from eqn (4) $\tau I = 0$

$$0 - \gamma\tau - \mu T = 0$$
$$T(-\gamma - \mu) = 0$$
$$T = 0.$$

from eq (5)

$$\gamma T - \mu R = 0$$

Since $T = 0; \quad \mu R = 0$

$$R = 0.$$

Since death can't be zero

$$\begin{aligned} \therefore \quad DFE = E^0 &= (S^*, L^*, I^*, T, R^*) \\ &= \left(\frac{\pi}{\mu}, 0, 0, 0, 0\right) \end{aligned}$$

Basic Reproduction number using next generation method.

$$\begin{aligned} L\dot{F}_1 &= \lambda S = \frac{\beta SI}{N} \\ IF_2 &= 0 \\ \tau F_3 &= 0 \\ F &= \begin{pmatrix} \frac{\partial\left(\frac{\beta SI}{N}\right)}{\partial L} & \frac{\partial\left(\frac{\beta SI}{N}\right)}{\partial I} & \frac{\partial\left(\frac{\beta SI}{N}\right)}{\partial T} \\ \frac{\partial(0)}{\partial L} & \frac{\partial(0)}{\partial I} & \frac{\partial(0)}{\partial T} \\ \frac{\partial(0)}{\partial L} & \frac{\partial(0)}{\partial I} & \frac{\partial(0)}{\partial T} \end{pmatrix} \end{aligned}$$

$$F = \begin{pmatrix} \frac{-\beta S^* I^*}{N^{*2}} & \frac{N^{*2}\beta S - \beta S^* I^*}{N^{*2}} & \frac{-\beta S^* I^*}{N^{*2}} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

at D.F.E $I = 0$

$$\begin{aligned} F &= \begin{bmatrix} 0 & N^*\beta S^* & 0 \\ 0 & N^{*2} & 0 \\ 0 & 0 & 0 \end{bmatrix} \\ N^* &= S^* + L^* + I^* + T^* + R^* \\ N^* &= \frac{\pi}{\mu} + 0 + 0 + 0 + 0 \\ N^* &= \frac{\pi}{\mu} \end{aligned}$$

$N^* = S^*$

Hence we have,

$$F = \begin{bmatrix} 0 & \frac{S^*\beta S^*}{S^{*2}} & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

$$F = \begin{bmatrix} 0 & \beta & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

$$V_1 = \rho L + \mu L$$

$$V_2 = -\rho L + \tau I + \mu I$$

$$V_3 = -\tau I + \gamma T + \mu T$$

$$V = \begin{pmatrix} \frac{\partial(+\rho L+\mu L)}{\partial L} & \frac{\partial(+\rho L+\mu L)}{\partial I} & \frac{\partial(+\rho L+\mu L)}{\partial T} \\ \frac{\partial(-\rho L+\tau I+\mu I)}{\partial L} & \frac{\partial(-\rho L+\tau I+\mu I)}{\partial I} & \frac{\partial(-\rho L+\tau I+\mu D}{\partial T} \\ \frac{\partial(-\tau I+LT+\mu T)}{\partial L} & \frac{\partial(-\tau I+\gamma T+\mu T)}{\partial I} & \frac{\partial(-\tau I+\gamma T+\mu T)}{\partial T} \end{pmatrix}$$

$$V = \begin{pmatrix} \rho+\mu & 0 & 0 \\ -\rho & \tau+\mu & 0 \\ 0 & -\tau & \gamma+\mu \end{pmatrix}$$

$$|v| = \rho + \mu \begin{vmatrix} \tau+\mu & 0 \\ -\tau & \gamma+\mu \end{vmatrix}$$

$$|v| = (\rho+\mu)[(\tau+\mu)(\tau+\mu)]$$

$$|v| = (-\rho+\mu)(\tau+\mu)(\gamma+\mu)$$

$$\operatorname{Adj} V = \begin{pmatrix} V_{11} & V_{12} & V_{13} \\ V_{21} & V_{22} & V_{23} \\ V_{31} & V_{32} & V_{33} \end{pmatrix}^{\top}$$

$$V_{11} = \begin{vmatrix} \tau+\mu & 0 \\ -\tau & \gamma+\mu \end{vmatrix} = (\tau+\mu)(\gamma+\mu)$$

$$V_{12} = \begin{vmatrix} -\rho & 0 \\ 0 & \gamma+\mu \end{vmatrix} = -\rho(\gamma+\mu)$$

$$V_{13} = \begin{vmatrix} -\rho & \tau+\mu \\ 0 & -\tau \end{vmatrix} = \rho\tau$$

$$V_{21} = \begin{vmatrix} 0 & 0 \\ -\tau & \gamma+\mu \end{vmatrix} = 0$$

$$V_{22} = \begin{vmatrix} +\rho+\mu & 0 \\ 0 & \gamma+\mu \end{vmatrix} = (+\rho+\mu)(\gamma+\mu)$$

$$V_{23} = \begin{vmatrix} +\rho+\mu & 0 \\ 0 & -\tau \end{vmatrix} = -\tau(+\rho+\mu)$$

$$V_{31} = \begin{vmatrix} 0 & 0 \\ \tau+\mu & 0 \end{vmatrix} = 0$$

$$V_{32} = \begin{vmatrix} +\rho+\mu & 0 \\ -\rho & 0 \end{vmatrix} = 0$$

$$V_{33} = \begin{vmatrix} 7\rho+\mu & 0 \\ -\rho & \tau+\mu \end{vmatrix} = (+\rho+\mu)(\tau+\mu)$$

$$\text{Cofactor } V = \begin{bmatrix} (\tau+\mu)(\gamma+\mu) & -\rho(\gamma+\mu) & \rho\tau \\ 0 & (+\rho+\mu)(\gamma+\mu) & -\tau(+\rho+\mu) \\ 0 & 0 & (+\rho+\mu)(\tau+\mu) \end{bmatrix}$$

$$\text{Adj}\, V = \text{ cofactor } T$$

$$\begin{bmatrix} +-+ \\ -+- \\ +-+ \end{bmatrix} \times \begin{bmatrix} (\tau+\mu)(\gamma+\mu) & 0 & 0 \\ -\rho(\tau+\mu) & (+\rho+\mu)(\tau+\mu) & 0 \\ \rho\tau & -\tau(u\rho+\mu) & (+\rho+\mu)(\tau+\mu) \end{bmatrix}$$

$$AdjV = \begin{bmatrix} (\tau+\mu) & 0 & 0 \\ \rho(\gamma+\mu) & (\rho+\mu)(\gamma+\mu) & 0 \\ \rho\tau & -\tau(\rho+\mu) & (\rho+\mu)(\tau+\mu) \end{bmatrix}$$

$$V^{-1} = \frac{AdjV}{IV}$$

$$V' = \begin{bmatrix} \frac{1}{(\rho+\mu)} & 0 & 0 \\ \frac{\rho}{(\beta\rho+\mu)(\tau+\mu)} & \frac{1}{(\tau+\mu)} & 0 \\ \frac{\rho\dot{\tau}}{(\tau\rho+\mu)(\tau+\mu)(\chi+\mu)} & \frac{\tau}{(\tau+\mu)(\tau+\mu)} & \frac{1}{(\tau+\mu)} \end{bmatrix}$$

$$\left|Fv^{-1} - \lambda I\right| = 0$$

$$\begin{bmatrix} \begin{bmatrix} \frac{\beta\rho}{(\rho+\mu)(\tau+\mu)} & \frac{\beta}{\tau+\mu} & 0 \end{bmatrix} \\ 0 \quad 0 \quad 0 \\ 0 \quad 0 \quad 0 \end{bmatrix} - \begin{bmatrix} \lambda & 0 & 0 \\ 0 & \lambda & 0 \\ 0 & \lambda & 0 \\ 0 & 1 & \end{bmatrix}$$

$$= \begin{vmatrix} \frac{\beta\rho}{(\rho+\mu\rho)(\tau+\mu)} - \lambda & \frac{\beta}{\tau+\mu} & 0 \\ 0 & \lambda & 0 \\ 0 & 0 & -\lambda \end{vmatrix}$$

$$= \frac{\beta\rho}{(\rho+\mu)(\tau+\mu)} - \lambda \begin{vmatrix} -\lambda & 0 \\ 0 & -\lambda \end{vmatrix}$$

$$= \frac{\beta\rho}{(\rho+\mu)(\tau+\mu)} - \lambda\left[\lambda^2\right] = 0$$

$$\lambda_1 = 0, \lambda_2 = 0, \quad \lambda_3 = \frac{\beta\rho}{(-\rho+\mu)(\tau+\mu)}$$

$$R_0 = p\left(FV^{-1}\right) = \frac{\beta\rho}{(+\rho+\mu)(\tau+\mu)}$$

4.6 EEP (Endemic equilibrium point)

We equate all equation to zero and express them in terms of λ from eq (1)

$$\begin{aligned}
&\pi - \lambda s - \mu S = 0 \\
&S(\lambda + \mu) = \pi \\
&S = \frac{\pi}{\lambda + \mu}
\end{aligned}$$

from eq(2)

$$\begin{aligned}
&\lambda S - \rho L - \mu L = 0 \\
&L(\rho + \mu) = \lambda S \\
&L = \frac{\lambda\left(\frac{\pi}{\lambda+\mu}\right)}{\rho + \mu} = \frac{\lambda\pi}{\lambda + \mu} \div \rho + \mu \\
&L = \frac{\lambda\pi}{(\lambda + \mu)(\rho + \mu)}
\end{aligned}$$

from eq(3)

$$\begin{aligned}
&\rho L - \tau I - \mu I = 0 \\
&I(\tau + \mu) = \rho L \\
&I = \frac{\rho\left(\frac{\lambda\pi}{(\lambda+\mu)(\rho+\mu)}\right)}{(\tau + \mu)} = \frac{\lambda\rho\pi}{(\lambda + \mu)(\rho + \mu)} \div \tau + \mu \\
&I = \frac{\lambda\rho\pi}{(\lambda+\mu)(\rho+\mu)(\tau+\mu)}
\end{aligned}$$

from eqn(4)

$$\begin{aligned}
&\tau I - \gamma T - \mu T = 0 \\
&T(\gamma + \mu) = \tau I \\
&T = \frac{\lambda\rho\tau\pi}{(\lambda + \mu)(\rho + \mu)(\tau + \mu)(\tau + \mu)}
\end{aligned}$$

from eq (3)

$$VT - \mu R = 0$$
$$\mu R = \gamma T$$
$$R = \gamma \left(\frac{\lambda\rho\tau\pi}{(\lambda+\mu)(\rho+\mu)(\tau+\mu)(\gamma+\mu)} \right) \div \mu$$
$$R = \frac{\lambda\rho\tau\gamma\pi}{\mu(\lambda+\mu)(\rho+\mu)(\tau+\mu)(\gamma+\mu)}$$

$$N = S + L + I + I + R$$

$$N = \frac{\pi+\mu}{\lambda+\mu} + \frac{\lambda\pi}{(\lambda+\mu)(\rho+\mu)} + \frac{\lambda\rho\pi}{(\lambda+\mu)(\rho+\mu)(\tau+\mu)}$$

$$+\frac{\lambda\rho\tau\pi}{(\lambda+\mu)(\rho+\mu)(\tau+\mu)(\gamma+\mu)} + \frac{\lambda\rho\tau\pi}{\mu(\lambda+\mu)(\rho+\mu)(\tau+\mu)(\gamma+\mu)}$$

$$\frac{\beta\lambda\rho\pi}{(\lambda+\mu)(\rho+\mu)(\tau+\mu)} \times \frac{\mu(\lambda+\mu)(\rho+\mu)(\tau+\mu)(\gamma+\mu)}{nvm}$$

$$\lambda = \frac{\beta\lambda\rho\pi\mu(\gamma+\mu)}{num}$$

$$\lambda.num. - \beta\lambda\rho\pi\mu(\gamma+\mu) = 0$$

$$\lambda \left[\begin{array}{l} \mu\pi(\rho+\mu)(\tau+\mu)(\gamma+\mu) + \lambda\pi\mu(\tau+\mu)(\gamma+\mu) + \\ \lambda\rho\pi\mu(\tau+\mu) + \lambda\rho\tau\pi\mu + \lambda\rho\tau\gamma\pi - \beta\lambda\rho\pi\mu(\tau+\mu) \end{array} \right] = 0$$

$\lambda\mu\pi(\rho+\mu)(\tau+\mu)(\gamma+\mu)+\lambda^2\pi\mu(\tau+\mu)(\gamma+\mu)+ \lambda^2\rho\pi\mu(\tau+\mu)+\lambda^2\rho\tau\pi\mu+ \lambda^2\rho\tau\gamma\pi - \beta\lambda\rho\pi\mu(\gamma+\mu) = 0$

$\lambda^2[\pi\mu(\tau+\mu)(\gamma+\mu) + \rho\pi\mu(\gamma+\mu) + \rho\tau\pi\mu + \rho\tau\tau\pi]$

$$+\lambda[\mu\pi(\rho+\mu)(\tau+\mu)(\gamma+\mu) - \beta\rho\pi\mu(\gamma+\mu)] = 0$$

multiply through by.

$$\frac{1}{\pi\mu(\rho+\mu)(\tau+\mu)(\tau+\mu)}$$

.

$$\frac{\lambda^2\pi\mu(\tau+\mu)(c+\mu)}{\pi\mu(\rho+\mu)(\tau+\mu)(\tau+\mu)}+\frac{\lambda^2\rho\pi\mu(\tau+\mu)}{\pi\mu(\rho+\mu)(\tau+\mu)(\tau+\mu)}$$

$$\frac{+\lambda^2\rho\tau\pi\mu}{\pi\mu(\rho+\mu)(\tau+\mu)((+\mu)}+\frac{\lambda^2\rho\tau\gamma\pi}{\pi\mu(\rho+\mu)(\tau+\mu)(\gamma+\mu)}$$

$$+\frac{\lambda\mu\pi(\rho+\mu)(\tau+\mu)(\tau+\mu)}{\pi\mu(\rho+\mu)(\tau+\mu)(\gamma+\mu)}-\frac{\lambda\beta\rho\pi\mu(\tau+\mu)}{\pi\mu(\rho+\mu)(\tau+\mu)(\tau+\mu)}=0$$

$$=\frac{\lambda^2}{(\rho+\mu)}+\frac{\lambda^2}{(\rho+\mu)(\tau+\mu)}+\frac{\lambda^2\rho\tau}{(\rho+\mu)(\tau+\mu)(\gamma+\mu)}$$
$$+\frac{\lambda^2 g\tau\tau}{\mu(\rho+\mu)(\tau+\mu)(\tau+\mu)}+\frac{\lambda(\rho+\mu)}{(\rho+\mu)}-\frac{\lambda\beta\rho}{(\rho+\mu)(\tau+\mu)}=0$$

$$+\lambda\left[1-R_0\right]=0$$

According to Descartes's rule of signs

$$\lambda^2[a+b+c+d]+\lambda\left[1-R_0\right]=0$$

we will have one sign charge from +ve to -ve, one positive root, one endemic equation is unique if $R_0>1$

Lemma. The number of +ve endemic equilitria of model is summarized as follows:

1. If $R_0>1$, the system has one unique endemic positive root and so
2. If $R_0<1$, the system has no endemic equation

4.7 SLITR MODEL SIMULATION FOR TUBERCULOSIS (TB)

Simulations of the model were carried out using Python Data on the number of TB and the parameter values used are presented in Table below, initial values used in the simulation models are data population in US while the parameters used are estimated values of the infection.

Parameter	Values
β	0.12
τ	0.6
ρ	0.129
τ	0.76
τ	0.9
μ	0.012

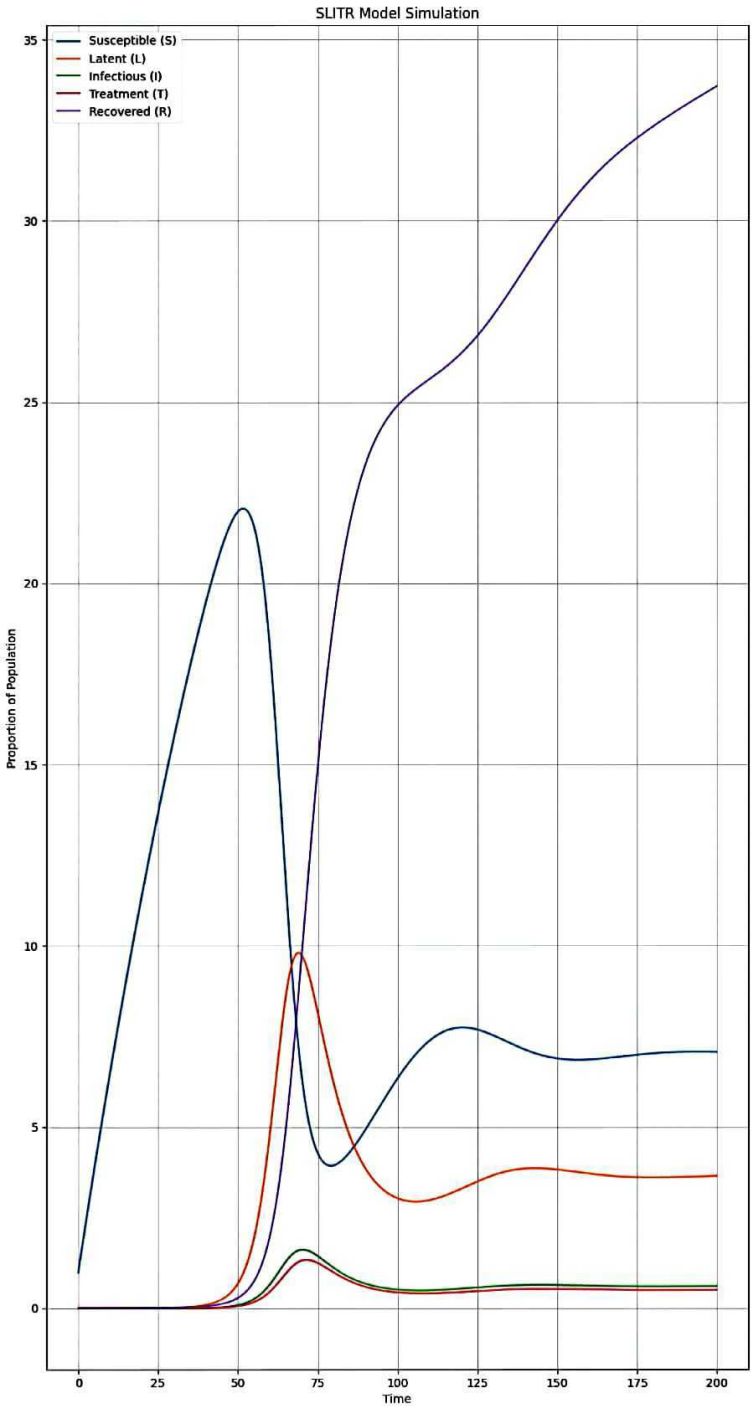


Figure 4.1: SLITR model

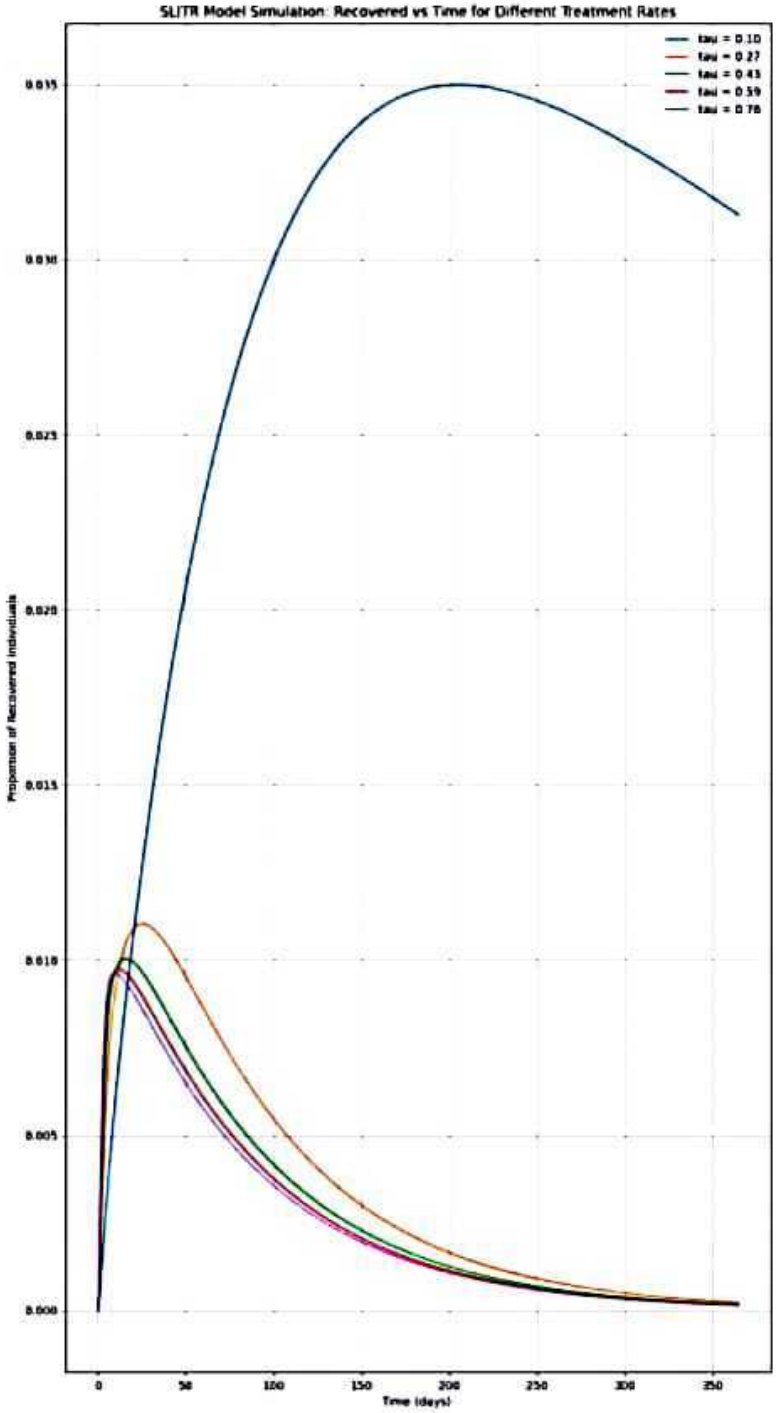


Figure 4.2: Recovered against time as treatment rate varies from 0.10 to 0.76

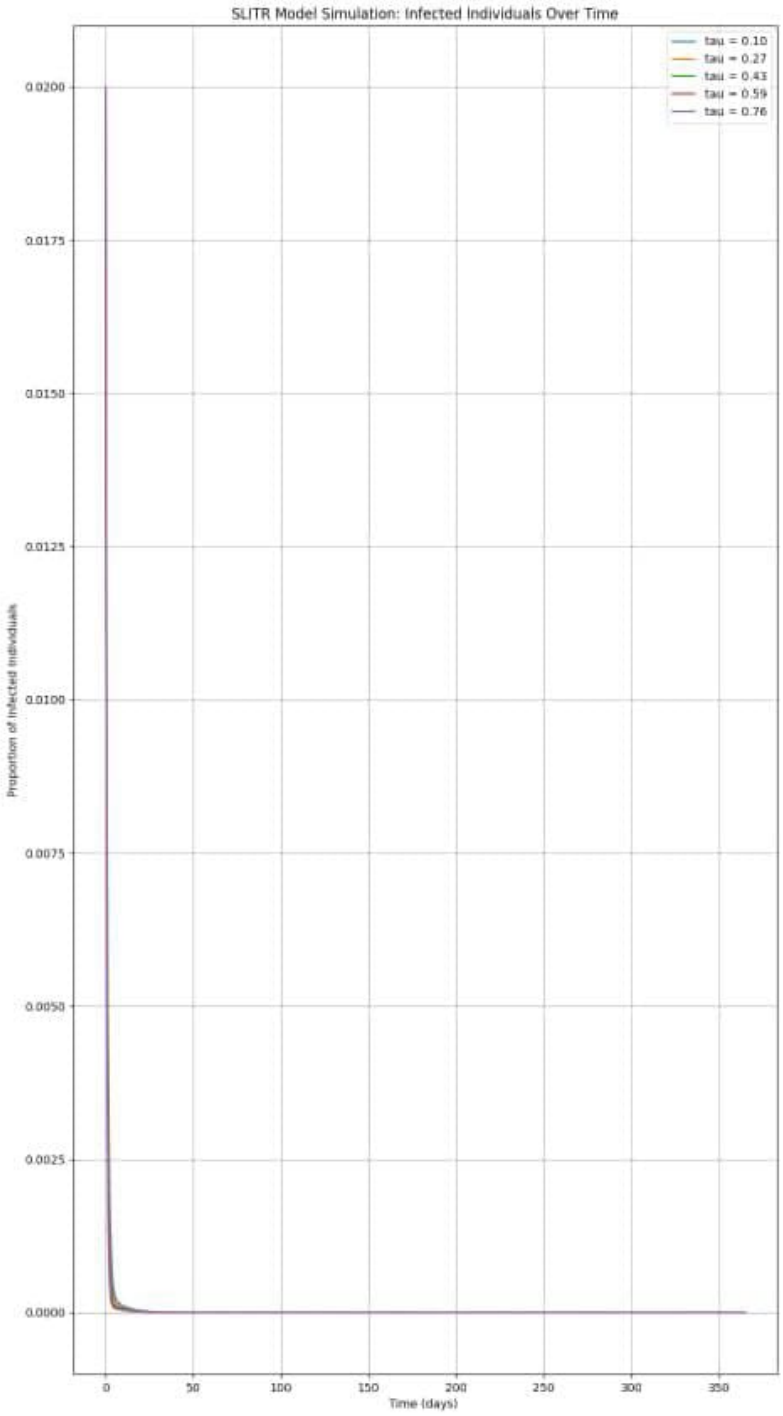


Figure 4.3: Infected against time as treatment rate varies

Chapter 5

SUMMARY AND CONCLUSION

5.1 Summary

This study utilized the SLITR model to explore the dynamics of tuberculosis (TB) transmission and control within a population. By converting key biological behaviors into a system of differential equations, we simulated various scenarios to understand how changes in parameters like the treatment rate τ affect disease progression and control.

Our simulations revealed that the treatment rate significantly influences the dynamics of the disease, with higher rates leading to quicker reductions in the infectious population and faster movement towards disease elimination. The analysis of the endemic equilibrium point (EEP) underscored the critical role of the basic reproduction number, R0, in determining the stability of the disease within the population. Specifically, when $R0 > 1$, TB persists in the population, but effective control strategies can push R0 below 1, leading to disease elimination.

However, the study's findings are subject to the limitations of the model's assumptions, such as homogeneous mixing and constant parameter values. Future research could expand on this by incorporating varying population dynamics, resistance mechanisms, and spatial factors, which could provide more nuanced insights into TB management and control strategies.

5.2 Conclusion Reached

In conclusion, this work highlights the utility of mathematical modeling in understanding infectious disease dynamics and assists in the formulation of effective public health interventions for TB control. Further research in more complex scenarios is recommended to enhance the robustness and applicability of the findings.

5.3 Recommendation

Based on the findings of this study, the following recommendations are proposed for public health policymakers and practitioners:

- **Enhanced Treatment Access:** Increase efforts to improve access to TB treatment, particularly in high-burden regions. This includes investing in healthcare infrastructure, training healthcare workers, and providing financial support to patients to ensure compliance with treatment regimens.
- **Targeted Intervention Strategies:** Develop targeted intervention strategies that take into account the local epidemiological context and specific population dynamics. Tailoring interventions to the needs of different demographic groups and geographic regions can optimize resource allocation and improve outcomes.
- **Community Engagement and Education:** Implement community-based education and awareness programs to reduce stigma associated with TB, promote early detection, and encourage treatment adherence. Engaging with community leaders and leveraging existing networks can enhance the reach and effectiveness of these initiatives.
- **Integration of TB Services:** Integrate TB services with other healthcare programs, such as HIV/AIDS care and maternal health services, to provide comprehensive care and address co-morbidities. This approach can streamline service delivery and improve patient outcomes.

- **Research and Surveillance:** Invest in research and surveillance activities to monitor TB trends, identify emerging challenges, and evaluate the effectiveness of interventions. Longitudinal studies and epidemiological surveys can provide valuable data for evidence-based decision-making.
- **Bifurcation Analysis:** Conduct bifurcation analysis to explore the qualitative changes in the dynamics of TB transmission under varying parameters. Understanding the bifurcation behavior can provide insights into the stability and complexity of the disease system, informing the development of more effective control strategies.

5.4 Suggestions for Further Studies

Building on the insights gained from this study, the following areas are recommended for further research:

- **Dynamic Modeling of Drug Resistance:** Investigate the dynamics of drug-resistant TB strains within the population and assess the impact of different treatment strategies on the emergence and spread of resistance. Incorporating factors such as treatment adherence, diagnostic capabilities, and drug availability can provide valuable insights into the evolution of resistance.
- **Spatial Modeling and Geographic Variability:** Explore the spatial dynamics of TB transmission by developing spatially explicit models that account for geographic variability in disease prevalence, healthcare access, and population movement. Analyzing spatial patterns can inform targeted intervention strategies and resource allocation.
- **Economic Analysis of TB Control Programs:** Conduct economic evaluations of TB control programs to assess their cost-effectiveness and identify areas for optimization. Cost-benefit analyses can help policymakers allocate resources efficiently and prioritize interventions that offer the greatest public health impact.
- **Impact of Socioeconomic Factors:** Investigate the influence of socioeconomic factors, such as poverty, education level, and housing

conditions, on TB transmission and treatment outcomes. Understanding the social determinants of health can inform the development of more equitable and effective intervention strategies.

- **Integration of Digital Health Technologies:** Explore the potential of digital health technologies, such as mobile applications for symptom monitoring and telemedicine for remote consultations, in improving TB diagnosis, treatment adherence, and surveillance. Integrating these technologies into existing healthcare systems can enhance patient care and disease control efforts.

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APPENDIX

```
import numpy as np
import matplotlib.pyplot as plt
from scipy.integrate import solve_ivp

# Function to define the SLITR model
def SLITR_model(t, y, pi, beta, rho, tau, gamma, mu, N):
    S, L, I, T, R = y
    lambda_ = beta * I / N
    dS_dt = pi - lambda_ * S - mu * S
    dL_dt = lambda_ * S - (rho + mu) * L
    dI_dt = rho * L - (tau + mu) * I
    dT_dt = tau * I - (gamma + mu) * T
    dR_dt = gamma * T - mu * R
    return [dS_dt, dL_dt, dI_dt, dT_dt, dR_dt]

# Initial conditions
S0 = 0.99   # Initial proportion of susceptible individuals
L0 = 0.01   # Initial proportion of latent individuals
I0 = 0.0    # Initial proportion of infectious individuals
T0 = 0.0    # Initial proportion of individuals in treatment
R0 = 0.0    # Initial proportion of recovered individuals
N = 1.0     # Total population (normalized to 1 for simplicity)
y0 = [S0, L0, I0, T0, R0]

# Parameters
pi = 0.6  # Recruitment rate
beta = 0.12 # Transmission rate
rho = 0.129   # Progression rate from latent to infectious
tau = 0.76  # Treatment rate
gamma = 0.9# Recovery rate
mu = 0.012 # Natural death rate

# Time vector
t_start = 0
t_end = 365
t_step = 0.1
t = np.arange(t_start, t_end, t_step)

# Solve the SLITR model
solution = solve_ivp(SLITR_model, [t_start, t_end], y0, args=(pi,
   beta, rho, tau, gamma, mu, N), t_eval=t)

# Plot the results
plt.figure(figsize=(12, 8))
```

```
plt.plot(solution.t, solution.y[0], label='Susceptible (S)')
plt.plot(solution.t, solution.y[1], label='Latent (L)')
plt.plot(solution.t, solution.y[2], label='Infectious (I)')
plt.plot(solution.t, solution.y[3], label='Treatment (T)')
plt.plot(solution.t, solution.y[4], label='Recovered (R)')
plt.xlabel('Time')
plt.ylabel('Proportion of Population')
plt.title('SLITR Model Simulation')
plt.legend()
plt.grid(True)
plt.show()
```

Listing 5.1: SLITR Model in Python

```python
import numpy as np
import matplotlib.pyplot as plt
from scipy.integrate import solve_ivp

# SLITR model differential equations
def SLITR_model(t, y, pi, beta, rho, tau, gamma, mu):
    S, L, I, T, R = y
    N = S + L + I + T + R
    lam = beta * I / N
    dS_dt = pi - lam * S - mu * S
    dL_dt = lam * S - (rho + mu) * L
    dI_dt = rho * L - (tau + mu) * I
    dT_dt = tau * I - (gamma + mu) * T
    dR_dt = gamma * T - mu * R
    return [dS_dt, dL_dt, dI_dt, dT_dt, dR_dt]

# Initial conditions
S0 = 0.99  # Initial proportion of susceptible individuals
L0 = 0.0   # Initial proportion of latent individuals
I0 = 0.01  # Initial proportion of infectious individuals
T0 = 0.0   # Initial proportion of individuals under treatment
R0 = 0.0   # Initial proportion of recovered individuals
y0 = [S0, L0, I0, T0, R0]

# Parameters
pi = 0.6   # Recruitment rate
beta = 0.12  # Transmission rate
rho = 0.129   # Progression rate from exposed to active TB
gamma = 0.9 # Recovery rate
mu = 0.012  # Natural death rate

# Time vector
t_start = 0
t_end = 365
t_step = 0.1
t = np.arange(t_start, t_end, t_step)

# Range of tau values
tau_values = np.linspace(0.1, 0.76, 5)

# Plotting the results
plt.figure(figsize=(12, 8))

for tau in tau_values:
    solution = solve_ivp(SLITR_model, [t_start, t_end], y0, args=(
```

```
        pi, beta, rho, tau, gamma, mu), t_eval=t)
    plt.plot(solution.t, solution.y[4], label=f'tau = {tau:.2f}')

plt.xlabel('Time (days) ')
plt.ylabel('Proportion of Recovered Individuals')
plt.title('SLITR Model Simulation: Recovered vs Time for Different
    Treatment Rates')
plt.legend()
plt.grid(True)
plt.show()
```

Listing 5.2: SLITR Model in Python

```python
import numpy as np
import matplotlib.pyplot as plt
from scipy.integrate import solve_ivp

# Define the SLITR model differential equations
def SLITR_model(t, y, pi, beta, rho, tau, gamma, mew):
    S, L, I, T, R = y
    N = S + L + I + T + R
    lambda_infection = beta * I / N
    dS_dt = pi - lambda_infection * S - mew * S
    dL_dt = lambda_infection * S - (rho + mew) * L
    dI_dt = rho * L - (tau + gamma + mew) * I
    dT_dt = tau * I - mew * T
    dR_dt = gamma * I - mew * R
    return [dS_dt, dL_dt, dI_dt, dT_dt, dR_dt]

# Initial conditions
S0 = 0.99  # Initial proportion of susceptible individuals
L0 = 0.0   # Initial proportion of latent individuals
I0 = 0.02  # Initial proportion of infectious individuals
T0 = 0.0   # Initial proportion of individuals in treatment
R0 = 0.0   # Initial proportion of recovered individuals
y0 = [S0, L0, I0, T0, R0]

# Parameters
pi = 0.6   # Recruitment rate
beta = 0.12 # Transmission rate
rho = 0.129  # Progression rate from latent to infectious
gamma = 0.9 # Recovery rate
mew = 0.012 # Natural death rate

# Time vector
t_start = 0
t_end = 365
t_step = 0.1
t = np.arange(t_start, t_end, t_step)

# Varying treatment rate tau
tau_values = np.linspace(0.1, 0.76, 5)

plt.figure(figsize=(12, 8))

for tau in tau_values:
    # Solve the SLITR model
    solution = solve_ivp(SLITR_model, [t_start, t_end], y0, args=(
```

```
        pi, beta, rho, tau, gamma, mew), t_eval=t)

    # Plot infected individuals over time
    plt.plot(solution.t, solution.y[2], label=f'tau = {tau:.2f}')

plt.xlabel('Time (days) ')
plt.ylabel('Proportion of Infected Individuals')
plt.title('SLITR Model Simulation: Infected Individuals Over Time'
    )
plt.legend()
plt.grid(True)
plt.show()
```

Listing 5.3: SLITR Model in Python