Mathematical modeling of TB disease dynamics in a crowded population.

Sibaliwe Maku Vyambwera

A thesis submitted in partial fulfilment of the requirement for the degree of Doctor of Philosophy in the Department of Mathematics and Applied Mathematics at the Faculty of Natural Sciences, University of the Western Cape.

Supervisor: Prof Peter Witbooi

March 13, 2020

Keywords

crowded environment
prison TB model
inflow of infecteds
removal rate
stochastic TB model
almost sure exponential stability
two-group TB model
sentenced convict
remand
awaiting trial
cross effect
multi-drug resistant TB
basic reproduction number
disease-free equilibrium
endemic equilibrium
local and global stability of disease free
Lyapunov function
Optimal control

Abstract

Mathematical modeling of TB disease dynamics in a crowded population.

Sibaliwe Maku Vyambwera

PhD Dissertation, Department of Mathematics and Applied Mathematics, Faculty of Natural Sciences, University of the Western Cape.

Tuberculosis is a bacterial infection which is a major cause of death worldwide. TB is a curable disease, however the bacterium can become resistant to the first line treatment against the disease. This leads to a disease called drug resistant TB that is difficult and expensive to treat. It is well-known that TB disease thrives in communities in overcrowded environments with poor ventilation, weak nutrition, inadequate or inaccessible medical care, etc, such as in some prisons or some refugee camps. In particular, the World Health Organization discovered that a number of prisoners come from socio-economic disadvantaged population where the burden of TB disease may be already high and access to medical care may be limited. In this dissertation we propose compartmental models of systems of differential equations to describe the population dynamics of TB disease under conditions of crowding. Such models can be used to make quantitative projections of TB prevalence and to measure the effect of interventions. Indeed we apply these models to specific regions and for specific purposes. The models are more widely applicable, however in this dissertation we calibrate and apply the models to prison populations.

The basic model in this dissertation is a minor modification of the model in the paper [Buonomo, B and Lacitignola, D. Analysis of a tuberculosis model with a case study in Uganda, *Biological Dynamics* **4**, (2010) $571 - 593$]. The models are more widely applicable, however in this dissertation we calibrate and apply the models to prison populations. Our models allow for the inflow of susceptible, exposed and TB-infectives into the population. Removal of individuals out of the prison population can be either by death or by being released from prison, as compared to a general population in which removal is only by death. The first of our original contributions in this thesis is a new deterministic model for TB dynamics in a prison. Secondly we impose stochastic perturbations on the same model. We prove existence and uniqueness of positive solutions of a stochastic model. We introduce an invariant generalizing the basic reproduction number and we analyse the stability of the disease free equilibrium. Our main theorem in this regard implies that the stochastic perturbation enhances stability of the disease free equilibrium of the underlying deterministic model.

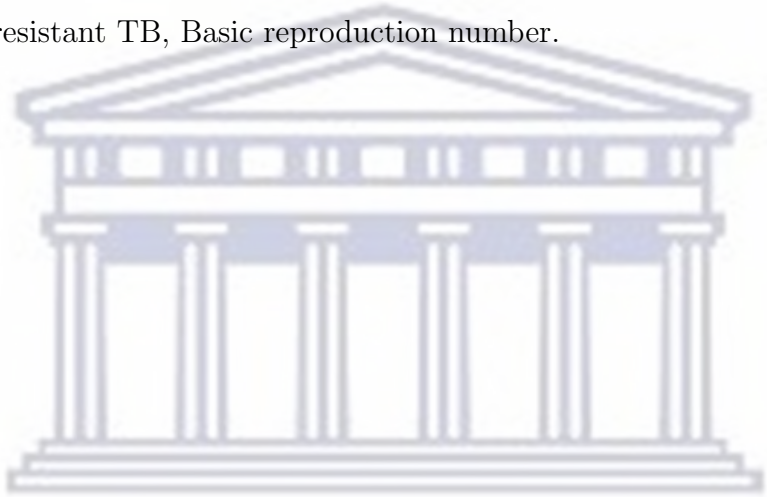
Thirdly, we consider a two-group TB model, to cover the case of the prison population consisting of two sub-populations which are sentenced detainees and the awaiting-trial (remand) inmates. Like in the previous cases we study the global stability of the disease free equilibrium by using a Lyapunov function and present some simulation results. The two-group gives better accuracy when relevant, compared to the original model.

Multi-drug resistant tuberculosis is caused by individuals who are unable to adhere to the treatment or incorrect use of treatment or incomplete treatment. As a fourth contribution we present a multi-strain TB model to understand the transmission dynamics of drug sensitive TB in a crowded environment such as prison. This model and all of the aforegoing models are calibrated to a South African prison population.

As our final contribution we apply optimal control on the first model, in order to deter-

mine a mathematically optimal rollout of screening and treatment in the fight against TB. In particular, we illustrate the results by way of application to a prison system in DRC. Throughout our study we pay special attention to the possibilities for extinction of the disease, which mathematically means stability of the DFE. Also we supply numerical simulations and illustrations.

Keywords: Prison TB model, inflow of infecteds, removal rate, stochastic TB model, almost sure exponential stability, two-group model, sentenced convict, remand, awaiting trial, multi-drug resistant TB, Basic reproduction number.



Declaration

I declare that a *Mathematical modeling of TB disease dynamics in a crowded population* is my own work, that it has not been submitted for any degree or examination in any other university, and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

Sibaliwe Maku Vyambwera

Signed: .....

Acknowledgements

All praise, adoration and glory to my Lord Jesus Christ for His richest grace and mercy for the accomplishment of this dissertation.

I would like to express my deepest appreciation to my supervisor, Prof. Peter Witbooi, for his tremendous support, help and guidance throughout my dissertation. Your advice on both research as well as on my career have been invaluable.

My sincere thanks to the University of the Western Cape for their financial support through Lecturer stewardship. Many thanks to all my colleagues at the department of Mathematics and Applied Mathematics.

I owe thanks to a very special person, my husband, Mr Mbusa Vyambwera for his continued and unfailing love, support and understanding during my pursuit of Ph.D degree that made the completion of thesis possible. You were always around, at times I thought that it is impossible to continue, you helped me to keep things in perspective. I greatly value his contribution and deeply appreciate his belief in me.

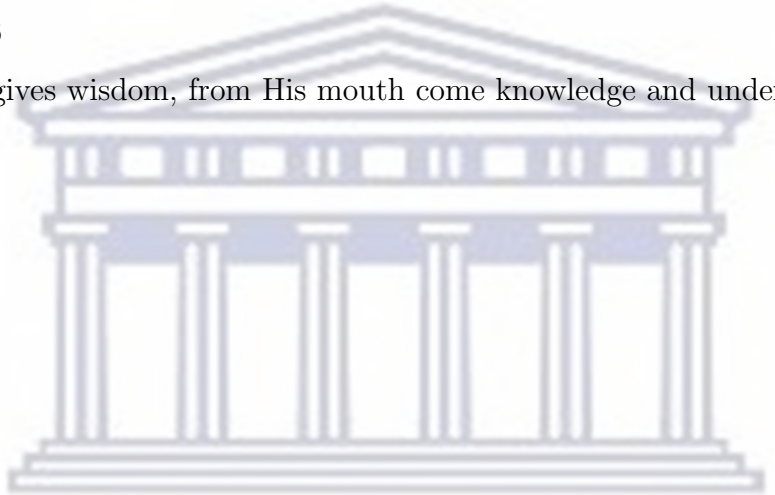
I appreciate my children, Mumbere (Wasi), Lwanzo, Dorothea and Asifiwe for abiding my ignorance and the patience they showed during my thesis writing. Words would never say how grateful I am to all of you. I consider myself the luckiest in the world to have such a lovely and caring family, standing beside me with their love and unconditional support.

I sincerely thank my parents, Mr Dumisani Maku and Mrs Babalwa Maku for their prayers, love and emotional support throughout my life.

I would like express my gratitude to Pastor Amos F. Okocha, Pastor Adeyemi A. Adedotun and their wife's from Solid Rock Ministries in Brackenfell Cape town South Africa, for their supportive prayers.

Proverbs 2:6

For the Lord gives wisdom, from His mouth come knowledge and understanding.



Dedication

This thesis is dedicated to my family the Vyambwera's and to my parents Mr and Mrs Maku.

Contents

List of Acronyms

ART, antiretroviral

a.s, almost surely

DCS, Department of Correctional Services

DFE, Disease Free Equilibrium

EEP, Endemic Equilibrium Point

HIV, Human Immunodeficiency Virus

i.i.d., independent and identically distributed

LTBI, Latent Tuberculosis Infection

MDR-TB, Multi-Drug Resistant Tuberculosis

ODE, ordinary differential equation

SDE, Stochastic Differential Equation

SIR, Susceptible-Infective-Recovered

SEIR, Susceptible-Exposed-Infective-Recovered

MTB, Mycobacterium Tuberculosis

TB, Tuberculosis

WHO, Word Health Organization

XDR-TB, Extensively Drug Resistant Tuberculosis

List of Notations

σ, perturbation parameter

Q, a martingale measure equivalent to the market measure

$\mathbb{P}$, a probability measure, usually the market measure

$(\Omega, \mathcal{F}, \mathbb{P})$, Probability triple

$\{\mathcal{F}_n\}_{n\geq 0}, \{\mathcal{F}_t\}_{t\geq 0}$, Filtration

W, Brownian motion or Wiener process

List of Tables

List of Figures

List of Publications

The following papers are published:

1. P.Witbooi and S. Maku Vyambwera, A model of population dynamics of TB in prison system and application to South Africa, BMC Research Notes, vol. 10, no. 1, article no. 643, 2017.

2. S. Maku Vyambwera and P. Witbooi, A stochastic TB model on a crowded environment, Journal of Applied Mathematics, 2018, 1-8 pages.

Chapter 1

Introduction

Infectious diseases have been a great concern of human being for ages. Millions of people die every year from tuberculosis, AIDS, malaria, etc, and millions of others are infected. Infectious disease is an illness which arises through transmission of an harmful pathogen from an infected individual or vector to a new host. The transmission can either be direct (transfer of an infectious agent from the infected individual directly to the new host i.e. sexual intercourse, biting etc.) or indirect (transfer of an infectious agent through a vector or by contaminated objects such as water, food, air etc.) [75]. Our research will focus on one infectious disease, which is tuberculosis. Tuberculosis (TB) is an infectious disease caused by bacillus *Mycobacterium tuberculosis (MTB)* that most often affects the lungs (pulmonary TB) and can affect other parts as well such as brain, kidneys, spine etc, which is called (extra-pulmonary TB). Infectious droplet nuclei spreads through air when people who are infected with pulmonary TB cough, sneeze or spit. The tiny particle can remain suspended in the air for several hours in the darkness, but direct sunlight rapidly destroys the infectious droplet nuclei. Allowing air and sunshine into the rooms where tuberculosis patients live can reduce the risk of infection for those who are living in contact with them. People who are at very high risk of inhaling infectious particles are those who are living or sleeping near a patient with TB disease.

Tuberculosis is still claimed to be the second leading cause of death worldwide after the human immunodeficiency virus (HIV). It has been reported that for instance in 2015 10.4 million people fell ill with TB and 1.8 million died from TB disease [76]. Among these deaths, it has been stated that 95 percent of TB deaths occur in low and middle income countries [75]. Researchers have found that TB is the leading killer of HIV-positive individuals. In 2015 about 400 000 individuals died of HIV associated TB and there were an estimated 1.1 million new cases of TB amongst individuals who were HIV-positive. It has been found that between 2000 and 2015 an estimated 49 million people infected with TB have been saved [75]. Furthermore, about 80 percent of TB cases occurred in 22 countries and some of these countries were experiencing a major decline while the other countries were improving in there numbers during 2015 [76]. According to the World Health Organization, 480 000 individuals developed MDR-TB in the world in 2015 and more than half of these cases were from India, China and the Russian Federation [76].

1.1 Tuberculosis background

Tuberculosis is an ancient disease that has killed millions of people in different parts of the world. There were many names given to this disease that killed so many people. It was known as white plague or consumption, as it consumed and left people weak and emaciated. It was also believed that tuberculosis is an inherited disease. There was no cure for this dreaded disease and scientific evidence on how TB was transmitted was also lacking. Robert Koch became interested in the research on TB during his time as the government advisor of the imperial Department of Health in Berlin in 1880. Koch was convinced that the disease was caused by a bacterium and was infections and tested his four assumptions using guinea pigs. In 1882 after a long search, Robert Koch the German physician and microbiologist discovered the pathogen that causes consumption, *Mycobacterium tuberculosis* [22]. Koch's investigations made the bacillus visible. Later, he succeeded in growing the bacteria in pure culture. Following this he inoculated the bacteria in animal which became infected and reproduce the disease. The discovery of the

Mycobacterium that causes tuberculosis and the proof that it was an infectious disease has lead to massive medical TB campaigns and advertisements on how to prevent TB. Unfortunately, TB disease has created fear and stigma. Those who were infected with TB suffered and were treated as outcast. Till today there are still some remnant of fear and shame when TB is spoken about in our communities. It is important to educate people about TB.

1.2 Tuberculosis Biology

The disease TB is caused by *Mycobacterium Tuberculosis*. Once a person has inhaled these droplet nuclei containing tubercle bacilli, they will travel down through the trachea and enter the lungs and then penetrate into the alveoli sacs. Once in the alveoli sacs the tubercle bacilli begins to multiply in the alveoli. The immune system of the body starts working and microphages begin to surround the tubercle bacilli. The cells form a barrier shell called granuloma that keeps the bacilli contained and under control. The TB tubercle remains in the lungs but the body is protected from the disease by the granuloma. In eight to ten weeks the person is most likely to be tested positive for latent TB infection. If the immune system is unable to keep the tubercle under control the shell breaks down and tubercle bacilli escape and multiply. The person becomes sick with TB disease and maybe infectious. The process can occur in different areas in the body such as lungs kidneys, brain or bone which will be called Extra Pulmonary Tuberculosis. When the TB escapes from the granuloma and begins destroying the lungs, it is called Pulmonary Tuberculosis.

1.3 Stages of Tuberculosis

The progression of TB can be separated into two categories namely, Latent Tuberculosis Infection (LTBI) and Tuberculosis disease (Infectious stage). We will describe the dissimilarities of these two stages of TB.

1.3.1 Latent Tuberculosis Infection (LTBI)

Individuals with LTBI have *Mycobacterium tuberculosis* in their bodies but do not have TB disease and are unable to spread the infection to other people. This stage is usually called early infection. It occurs when the first host comes into contact with TB bacteria and if the immune system is strong enough it will fight off the TB bacteria. If the immune system is unable to reject the TB bacteria, the individuals will now fall under latent stage. The individuals at this stage may remain asymptomatic for months or over their entire lives. By identifying such individuals with LTBI will help to accomplish the goal of TB control and can also prevent infected people from developing TB diseases.

1.3.2 TB disease (Infectious Stage)

This is the stage when TB bacteria overcomes the defences of the immune system and begin to multiply, resulting in the progression from latent TB infection to TB disease. Some individuals develop TB disease soon after infection while others develop TB disease later when the immune system becomes weak. Individuals with TB disease are considered to be infectious and can spread TB bacteria to others. The general symptoms of TB disease are weight loss, loss of appetite, night sweats, fever, fatigue and chills. Tuberculosis at this stage can also travel from the lungs to the other parts of the body by passing through the bloodstream. However, only those with Pulmonary (lung) disease can be infectious. If TB disease is suspected, persons should be referred for a complete medical evaluation. If the results are positive then the patient will immediately be under treatment, if left untreated during this stage, the patient might die.

1.4 Symptoms and Diagnosis

Most common symptoms of active lung TB are coughs with sputum or blood at times, chest pains, fatigue, unintentional weight loss, fever and night sweats which may last three or more weeks. Several countries still depend on a long used method called sputum smear

microscopy to diagnose TB. This is where trained laboratory technicians gaze at sputum samples under a microscope to see if TB bacteria exist in the sputum. Unfortunately, the microscope can only identify half the number of TB cases and is unable to identify multi-drug resistant TB. A positive TB skin test and TB blood test can only inform us that a person has been infected with TB bacteria. It is unable to tell us whether a person has LTBI or has progressed to TB disease. Tests like chest X-ray and sample of sputum are able to identify the TB disease. In 2010, the World Health Organization (WHO) permitted the X-pert MTB/RIF for use in TB endemic countries [77]. The use of this machine has expanded significantly as it can detect simultaneously active TB and resistance to rifampicin, the most important TB medicine. The diagnosis is fast and efficient as compared to the microscope test. Diagnosis can be made within two hours and the test is now recommended by WHO as the initial diagnostic test in all individuals with signs and symptoms of TB.

1.5 Treatment of Tuberculosis

Tuberculosis is a treatable and curable disease. It is very important to treat people who are infected with tuberculosis. If left untreated such a person may become sick and this may lead to life threatening situations. Tuberculosis may develop resistance if treatment is not administered properly. In fact, if patients stop taking the treatment before time, they may become sick again and in worst scenarios the TB bacteria that is still alive may become resistant to the treatment, which is referred to as multi-drug resistant tuberculosis (MDR-TB). Multi-Drug resistant is a form of TB caused by bacteria that is unable respond to ioniazid, rifampicin, ethambutol and pyrazinamide which are the four most powerful first-line anti-TB drug. Multi-Drug resistant TB is difficult to treat especially in the old age. A two strain mathematical model has been investigated by Castillo-Chavez and Feng [18], where treatment of multi-drug resistant individuals has been omitted as it is difficult to treat. Once again HIV/AIDS individuals are at great risk of developing multi-drug resistant TB. World Health Organization has reported about 450 000 incident cases of

MDR-TB and 170 000 deaths in the world in 2015 [76]. We also have another disease that comes after MDR-TB which is called Extensively drug resistant (XDR-TB). XDR-TB occurs when resistance to second line drugs develops on top of MDR-TB.

1.6 Other factors that cause TB transmission

There are several factors that cause TB transmission. So for example, people who are in close contact with infectious individuals are at high risk of being infected. These may be family or friends with infectious TB disease. TB infection may be caused by immigrations i.e., people from parts of the world may have high rates of TB. Concentration camps arise mostly from displacement of people due to political conflicts in developing countries and are at high risk of becoming infected with tuberculosis due to close contact with infectious individuals. People with weak immune system such as babies, young children, HIV infected individuals, etc, are at great risk of getting infected with TB. People who work or reside in facilities or institutions that house people who are at high risk for TB such as hospitals, homeless shelters, correctional facilities, nursing homes, and residential homes for those with HIV.

1.7 Problem Identification

In this dissertation, our main focus is to formulate mathematical TB models that would assist in analysing the dynamics of TB in a crowded environment such as prisons, mines and concentration camps. Mathematical models can assist in projecting how infectious diseases progress over time and will assist to inform public health interventions. We want to do this by introducing the notion of compartmental models under certain assumption representing health status such as susceptible, exposed, infectious and treated. These mathematical models will use some assumptions and will also be used to find parameter values for various crowded environments. We will use the parameters to compute the effects of possible interventions, like treatment.

1.8 Outline of the thesis

The thesis has been organised in the following manner:
Chapter 1 of this study provides us with the biological background of tuberculosis and the objective of this study. A literature review on different tuberculosis models has been discussed in Chapter 2. The modelling of TB depends on specific special consideration such as living conditions, treatment, co-infection with other diseases, MDR-TB, XDR-TB, vaccination and so on. Similar models have been proposed in the papers [54], [1], [11], [8] and [52]. In [54], the authors presented a number of models which are modified to capture different type of tuberculosis infection such as different treatment strategies, drug resistance and co-infection of TB with other diseases. In Chapter 3, we present the relevant mathematical tools that will be applied in Chapter 4, 5, 6 and 7.

In Chapter 4, we propose a compartmental model that considers the dynamics of TB disease in a prison system. The model will allow the inflow of susceptible, exposed and the infectious individuals into the prison population. This model is a minor modification of the model in [14], and forms the kernel around which the other models are formulated. The essence of Chapter 4 is in how the model is calibrated for the South African prison system. In Chapter 5, we further impose a stochastic perturbation into the deterministic model in Chapter 4 and further analyse further the dynamics of tuberculosis. We present the analytical results by means of simulations.

A two-group TB model that considers the dynamics of TB in the sentenced and remand population has been presented in Chapter 6. A two strain TB model to understand the transmission dynamics of drug sensitive TB and multi-drug resistant TB in a crowded environment such as a prison has been studied in Chapter 7.

In Chapter 8, we follow up a model in Chapter 4 by considering an optimal intervention strategies on TB epidemiology in a dense population. We perform this in a Congo prison system where control measures are not stable. Our aim is to minimize the proportion of active TB disease individuals while minimizing the cost. All simulations presented in this thesis were performed using MATLAB. This work will contribute in informing public health policy. It can help the authorities to get a better understanding of the dynamic transmission of active TB. It will allow them to provide a new policies to reduce the risk of transmission.

Chapter 2

Literature review

Tuberculosis is one of the world's deadliest diseases as one quarter of the world's population has latent TB. Most people are infected by a TB bacteria but do not suffer TB disease and are unable to transmit the disease. In 2018, 10 million people worldwide were infected with TB disease and 1.5 million died due to TB related disease including 251000 among people with HIV. Mathematical models are very useful in understanding the behaviour and impact of infections disease and to make future predictions about the spread of the disease. There are three steps that need to be taken into consideration when dealing with mathematical modelling of biological systems. The first step is to formulate a mathematical model that represents accurately the biological process that is being investigated. Secondly, one must apply the mathematical techniques as to be able to understand the behaviour of the model. Lastly, the proper interpretation of the results of the model to determine whether the biological results are obtained is also important.

Differential equations have been applied to many types of biological systems ranging through population, epidemics and physiological systems [4]. Our research will focus on epidemic models which describes the process subsequent to occurrence of a disease which infects an often substantial proportion of a population, possible causing many deaths over a short period of time before vanishing. The word *endemic* refers to a state of the disease that persist within the population for a sustained and possibly indefinite period of time,

usually only infecting a relatively small proportion of the population [2]. However, when an epidemic occurs on a scale which crosses international boundaries, this usually affects a large number of people, and is referred to as a *pandemic*. Kermack and McKendrick revealed that if the density of susceptible individuals exceeds a critical threshold then an epidemic is likely to occur. Nonetheless an epidemic is unable to be activated if below the critical threshold. Kermack and McKendrick [36] established in 1927 an "SIR" mathematical model that considers the transmission of infectious diseases. A model in which the exposed class is omitted is usually called the Susceptible-Infective-Recovered (SIR). This kind of a mathematical model has been applied in the paper of Kermack and McKendrick [36]. However, if the disease has an exposed class, such a model is refereed to as an Susceptible-Exposed-Infective-Recovered (SEIR), such a model has been presented in Ozcaglar et al. [54] for instance. The models are based on different mathematical systems such as system of ordinary differential equations, simulation models and Markov Chain Monte Carlo methods. The study in [54] provides a review of an earlier study on modeling of different aspects of tuberculosis dynamics. Various authors have incorporated different infection aspects such as age dependency, treatment, drug resistance, control strategies, HIV/TB co-infection, reinfection, public health campaigns e.t.c., [57, 18, 14, 8, 52, 51].

TB treatment saved 58 million lives globally between 2000 and 2018, with a drop of 38% in TB deaths [77]. The formulation of the model clarifies assumptions, variables and parameters. These models provide conceptual results such as thresholds, basic reproduction numbers, contact numbers, and replacement numbers. Similar work has been done in the paper of Moualeu et al. [51], where a deterministic model for the transmission dynamics of TB in Sub-Saharan Africa has been presented. The main objective of the model is to determine the role of TB diagnosis, treatment, lack of information about the epidemiological status of some people, and the role of traditional medicine and natural recovery on the dynamics of TB. It was observed in [51] that parameters representing the proportion of individuals having access to medical facilities have a large impact on the dynamics of the disease. An increase in these parameter value over time can significantly reduce the

disease burden in the population.

World Health Organization has declared that tuberculosis is the leading killer of HIV positive people, i.e., patience who are infected with HIV are at risk of developing active TB. It was also reported in 2018 that there were 477000 cases of TB among people living with HIV [77]. A six compartmental model with interaction between HIV and TB epidemics has been investigated in [8]. The authors proposed and analysed sensitivity of the steady states with respect to changes in parameter values. Most of the control measures studied had an obvious positive impact in controlling the HIV or TB epidemics, i.e, in the case for condom use, increased TB detection and providing treatment. The situation for antiretroviral (ART) is more complicated, although the future for the prevalence of HIV is uncertain, it seems that a generalized access to ART would lead to a significant decrease of the TB notification rate. It is difficult to guess if the observations drawn from the model with parameters adapted to the particular South African township are still valid for less crowded areas with high HIV prevalence [8]. Nonetheless, reliable data on both HIV and TB are still rare.

In 2018, World Health Organization has declared an estimate of 1.1 million children who become ill with TB and 251000 children died of TB including children with HIV associated TB [77]. There was an increase of 100000 children as compared to 2017 results and also 19000 increase of children who died of HIV associated with TB. Nyabadza and Winkler [52] considered a compartmental model of TB that is age dependent and whose parameters are set as a function of age. The authors emphasized that the TB dynamics in adults is different from the one that is in children and are largely dependent on age. Nyabadza and Winkler [52] collected data from the City of Cape town in health department and applied a simple reliable TB model. The model was then fitted to the TB incident data from City of Cape town. It was surprising for the authors to find that in Cape town metropole, the higher the incident rate of TB disease are an indicative of co-infection with HIV and has lead to higher sexual active population. All the age groups projections reflect a significant

increase in active TB disease incidence. However, the projected incidence rates for individuals in the $0-4$ year, $25-34$ year, $35-44$ year and $45-54$ year age groups reflect the most prominent increases in incidence rates over time. The authors identified that it is important to note that the incidence increases as age decreases [52]. They also found that there was a direct relationship between mortality as a results of TB and infection rate i.e. the higher the transmission of TB the higher the number of disease-induced deaths. The authors concluded that HIV individuals are at high risk of getting infected with TB disease and the authors will focus on the extra-pulmonary TB cases that are linked to HIV.

It is also important to note that TB is easily transmitted to children whose immune systems are weak. A study from China [70] has further developed the role of age structure on the transmission of TB. An SEIR epidemic model with age groupings involving three categories which are children, the middle aged, and senior has been proposed to investigate the role of age on the transmission of Tuberculosis. By means of the Least Square method, the authors [70] evaluated the parameters and simulated the model, the model approved well with the annual reported TB data in China. The results confirmed that considering the age grouping was sensible to describe the transmission and to improve the control strategies of targeting therapy for TB in China.

A mathematical TB model that takes into account of undiagnosed and lost sight infectious with the aim of controlling TB propagation through these classes has been presented in [51]. The authors introduced an optimal time dependent prevention policies that considers the execution cost. Furthermore, educational diagnosis campaign and chemoprophylaxis of latently infected individuals has been introduced using Stop TB strategy. The authors have also taken into account the actual data on TB in Cameroon and the rate of success of treatment. Their results showed that the application of education and diagnose campaign with chemoprophylaxis reduce the TB burden.

An epidemiological model of TB with infectivity in latent period and imperfect treatment

has been introduced in [61]. Wang et al. introduced a new model of TB where individuals in the latent period has a weaker infection. They further assume that both the latent and infective period can receive a successful and unsuccessful treatment. The authors introduced an extension of the ordinary differential equations (ODE's) model where the infective stage is classified as age-since infection (i.e. the time spent in the infective stage). They finalized their research by proving that the disease free equilibrium is globally asymptotic stable if $R_0 < 1$ and the endemic equilibrium is locally asymptotically stable if the basic reproduction number R_0 is greater than one. Numerical simulation were presented to show the results.

It was observed that the spread of the disease will flourish in overcrowded places such as camps, mine and prisons. Our research will focus on the dynamics of TB disease in crowded environment specifically prisons. In Robertson et al. [31], a mathematical model was developed to explore the interactions between incarceration conditions and TB control measures. It was noted that according to the regulations of South Africa, an inmate is supposed to have a space of $3,34\text{m}^2$ in a communal cell but due to overcrowding they only have $1,4\text{m}^2$ for 23 hours a day [31]. The transmission probability within a prison cell has been estimated by using Wells-Riley equation and probability analysis. It was observed that the levels of overcrowding in a communal cell and poor TB case finding will result in a higher TB transmission risk. Overcrowding conditions for the awaiting trial prisoners are highly favourable for the spread of TB diseases. Finally, the authors [31] concluded that by improving passive case finding, modest ventilation increase or decrease lock-up time would lower the impact of the disease transmission.

Buonomo and Lacitignola [14], proposed a model that dealt with the TB population dynamics in concentration camps with a case study in Uganda. The case study has been taken from a paper of Ssematimba et al. [57] which is about internally displaced people's camps in Uganda. In the study, population density on the dynamics of tuberculosis has been investigated as it determines the level of respiratory contact in a community and

this level directly determines the infection rate of airborne diseases like tuberculosis. It was also noticed that displaced individuals are at a greater risk of becoming infected with TB disease due to close contact with the infectious individuals.

Some models focus only on the patient groups and infection types and eliminate the immigration and emigration. These models will assume that the population is closed and no immigrants are accommodated. Such models will not be able capture the physical dynamics of tuberculosis in open populations with high density of immigrants. A model by Jia et al. accounted for the impact of immigration by SEIR models for both immigrant and local sub-population, and establish that immigrants have an important influence on the internal dynamics of tuberculosis in a population [30]. The model with Canadian born and foreign born sub-populations by Zhou et al. shows that increasing the mixing of two sub-populations increases the TB infection rate of Canadian born individuals [69]. More models have to include immigration in the population-level studies to capture the real dynamics of tuberculosis.

A delayed differential equation model with influence of temporary migration on the transmission of infectious disease in a migrant's home village has been studied in the paper of Wang and Wang [62]. In general, temporary migrant workers were considered as the major driving force for the rising incidence of infectious disease in cities. Hence, it was not discovered that temporary migration may have a huge impact on the spread of disease in migrants home villages. In [62], it assumed that a proportion of these returning workers acquire infection when they were away from their home village. Furthermore, these temporary infectious migrant were assumed that they are unable to migrate but stay at home for treatment. As a results of economic pressure or not knowing their status some of these infectious individuals were still migrating to urban areas, this has led to re-emerging of disease that were under control in the urban areas. It was noticed that a single control strategy which is to reduce the migration time period has a little effect on reducing the disease endemic level. This reduction will also have a huge effect in the economy of China.

The authors established that the local government should encourage returning migrant workers to undertake medical examination and offer help for quarantine process. In fact, it has come to our attention that a similar trend is also transpire ring in prison system and our research will focus in this regard.

An individual may develop multi-drug resistant tuberculosis (MDR-TB) due to incomplete treatment or by acquiring infection from a person with MDR-TB. In 2018, 484000 individuals developed TB that was resistant to rifampicin (RR-TB), the first-line drug. There were 187000 MDR/RR-TB cases that were detected and 156000 of these started treatment with a second-line regimen [77]. A mathematical model of tuberculosis with drug resistance effect has been studied in Ronoh et al. [56]. An ordinary $SEIRS$ model has been extended as to include MDR-TB.

Controlling infectious disease has been a progressing difficult matter in recent years. Vaccination is an important strategy for eliminating infectious diseases as it enables the vaccinated individuals to acquire a permanent or temporary immunity. Individuals who are temporary immune may loose their immunity over a period of time [71]. The asymptotic behavior of a stochastic SIS epidemic model with vaccination has been analysed in [71]. A susceptible-exposed-infectious-quarantine-recovered-susceptible with vaccination compartment model(SEIQRS-V) that considers the spread of tuberculosis disease in human population for both pulmonary and drug resistant has been established. In [47], two new classes which are vaccination class and quarantine class have been introduced into the model, where the quarantine class is a class for multi-drug resistant patients and the vaccination class is the class that deals with vaccinating the infants which is assumed as a susceptible population. By using Runge-Kutta method of order 4 with real parametric values, the figures have shown stability towards the disease free equilibrium. The results of Mishra and Srivastava [47] have shown that by separating the multi-drug resistant TB patients fast recovery has been archived and it almost tend to end the spread of infection. Finally by vaccinating the population in a group immunizes them towards the infection.

A mathematical study of a TB model with treatment interruption and two latent periods has been studied in the paper of Liu and Wang [43]. Individuals in active TB cases are treated and once the treatment is interrupted there is no further treatment. However, if treatment interruptions occurs frequently, this may lead to MDR-TB cases. The numerical results claim that the treatment of active cases reduces the progression of TB epidemic cases and helps to control the spread of TB while treatment interruptions may have negative, positive or no effect on combating TB epidemic. A continuous model that considers the optimal control strategy for the transmission dynamics of TB has been formulated. The optimal control has shown a great reduction of active TB individuals by controlling exogenous reinfection using chemoprophylaxis.

The models mentioned so far are deterministic and they do not consider the stochastic disturbance of environment which in fact exist. One of the greatest significant differences between the deterministic and stochastic epidemic models is their asymptotic dynamics. It is noticed that stochastic solutions converge to the disease-free equilibrium even though the equivalent deterministic solution converges to endemic equilibrium [5]. In [44], the authors showed that the deterministic model admits a unique endemic equilibrium which is globally asymptotically stable if its basic reproduction number is greater than one. An $SIRS$ epidemic model with media coverage and environmental fluctuations to describe disease transmission has been proposed in [60]. The spread of infectious disease is influenced by the level of environmental fluctuations. Wang et al. [60] concluded by illustrating simulations that if the magnitude of the intensity of noise is large the extinction of disease in the stochastic model occurs whether the basic reproduction number greater or less than one. On the other hand if the magnitude of the intensity of noise is small the results showed that the disease may persist if the basic reproduction number is greater than one. Similar work has been done in [44, 65, 41, 17]

An SEIRS epidemic model with stochastic perturbation on transmission from susceptible class to the latent and infectious has been considered in the paper of Witbooi [65]. It was

proved that the system permits a disease free equilibrium which is almost surely exponentially stable whenever the basic reproduction number of the underlying deterministic model is below unity and even slightly beyond under given conditions. It was observed that under higher perturbation the infectious trajectories for the deterministic model does not seem to converge while that of the stochastic model converges to zero. Finally, the results were clearly shown by means of simulations and observing the behaviour of the infections class trajectories.

An analysis of the deterministic and stochastic $SIRS$ epidermic models with non-linear incidence has been modelled in the paper of Liu and Chen [41]. The authors started off by considering first the deterministic $SIRS$ model and established criteria for the existence, uniqueness and global asymptotic stability of a disease free equilibrium and an endemic equilibrium by means of Lyapunov functions. Furthermore, perturbations of white noise was introduced into the deterministic model. The authors proved the global positivity of solutions and conditions are found for extinction of the disease by large white noise. Similar focus is also found in the following papers [42, 66, 65]. It was noticed that the results were totally different from the deterministic model in which the disease persisted.

The dynamics of an $SIRS$ epidemic model with a ratio-dependent incidence rate has been studied in [17] using the theory of stochastic differential equations. The study presents some relevant properties of the deterministic model, including boundedness, dissipation, persistence, and the stability of disease-free and endemic points. It also proves the existence of global solutions, stochastic boundedness, permanence for the stochastic models.

In the paper of Lahrouz et al. [38] they have formulated an SIRS epidemic model with saturated incidence rate and disease-inflicted mortality. In the same paper, the authors have further looked at the stochastic version. The global existence and positivity of the solution of the stochastic system has been established. Under suitable conditions on the intensity of the white noise perturbation, the global stability in probability and p^{th} mo-

ment of the system has also been proved. A Stochastic model of infections disease for heterogeneous populations has been proposed in [49]. The authors considered the dynamics of infectious disease in heterogeneous populations from temporal-spatial surveillance data. The model is evaluated using both simulated data and the real data from the 2009 H1N1 epidemic in Hong Kong and achieves acceptable prediction accuracy.

Chapter 3

Mathematical tools

In this chapter, we introduce some mathematical tools that will be used in the rest of the dissertation. There are important phases that needs to be followed in order to study biological system, such as formulation, analysis and interpretation. In order to apply a mathematical model, the underlying mathematical theory, tools, and techniques must be carefully applied and understood thoroughly. We use differential equations as they are applied when there is a continuous change in the states such as continuous reproduction and death.

3.1 Basics on ODE's in epidemic model

It is necessary to know whether or not we have a unique solution to a first order differential equation (ODE) initial value problem such as,

$$\dot{x}\,(t) = F(x,t),\ x(0) = x_0,$$

where $F(x)$ is bounded in a neighborhood of the point x_0.

Definition 3.1.1. (see Birkhoff and Rota [12]) A vector-valued function $X(x,t)$ satisfies the Lipschitz condition in a region $\mathbb{U}$ of (x,t)-space if and only if, for some

constant L,

$$|X(x,t) - X(y,t)| \leq L\,|x-y| \text{ if } (x,t) \text{ and } (y,t) \in \mathbb{U}.$$

Theorem 3.1.2. Let E be an open subset containing x_0 and assume that $F \subseteq C^1(E)$. Then, there exist an $a > 0$ such that the initial value problem

$$\dot{x} = f(x); \quad x(0) = x_0$$

has a unique solution $x(t)$ on the interval $[-a, a]$ [12].

3.2 Invariant Region

A set M is an *invariant set* with respect to a system of ordinary differential equation

$$\dot{x} = f(x)$$

if $x(0) \in M \Rightarrow x(t) \in M$, for all $t \in \mathbb{R}$.
A set M is a *positively invariant set* with respect to $\dot{x} = f(x)$ if $x(0) \in M \Rightarrow x(t) \in M$, for all $t \geq 0$.

3.3 Equilibria and Linearization

Definition 3.3.1. Given a system of differential equation

$$\dot{x} = f(t),$$

an equilibrium or steady stable x^* of this system is a point in the state space for which

$$X(t) = x^*$$

is a solution for $f(t) = 0$, for all t. For more detail see Allen [4].

Definition 3.3.2. (see Allen [4]).

(a) An equilibrium solution x of $\dot{X}= F(X)$ is said to be *locally stable* if for each $\epsilon > 0$ there exist a $\delta > 0$ with the property that every solution $X(t)$ of $\dot{X}= F(X)$ with initial condition $X(t_0) = X_0$ and

$$\|X_0 - x\|_2 < \delta,$$

satisfies the condition that

$$\|X_t - x\|_2 < \epsilon$$

for all $t \geq t_0$. If the equilibrium is not locally stable it is said to be *unstable*.

(b) An equilibrium solution x is said to be *locally asymptotically* stable if it is locally stable and if there exist $\gamma > 0$ such that

$\|X_0 - x\|_2 < \gamma$ implies $\lim_{t\to\infty} \|X(t) - x\|_2 = 0$.

Let (U^*, V^*) be a steady state of

$$\dot{U}= f(U,V), \qquad \dot{V}= g(U,V), \tag{3.1}$$

so that $f(U^*, V^*) = g(U^*, V^*) = 0$. Let $u = U - U^*$ and $v = V - V^*$. We assume that we may neglect higher order terms if u and v are sufficiently small, and we obtain the approximate (linearized) equations

$$\dot{u}= f_u(U^*, V^*)u + f_v(U^*, V^*)v, \tag{3.2}$$

$$\dot{v}= g_u(U^*, V^*)u + g_v(U^*, V^*)v, \tag{3.3}$$

or, defining the Jacobian matrix $J(U, V)$ in the usual way,

$$\dot{w}= J^*w, \tag{3.4}$$

where w is the column vector (u, v), and a star denotes the evaluation at the steady state. The behavior of the system near (U^*, V^*) depends on the eigenvalues of the matrix $J^* = J(U^*, V^*)$. It can be shown that the neglect of higher order terms is valid, and the

non-linear system behaves like a linear system near the steady state, as long as neither of the eigenvalues of J^* has zero real part.

Making the definitions $\beta = \text{tr}J^*$, $\gamma = \det J^*$, $\delta = \text{disc}J^*$, where $\text{tr}J^*$ is the trace of the Jacobian matrix J^*, $\det J^*$ is the determinant of the Jacobian matrix J^* and $\text{disc}J^*$ is the discriminant of the Jacobian matrix J^*. The eigenvalue equation is $\lambda^2 - \beta\lambda + \gamma = 0$, and we may determine the character of the steady state from the signs of these, see Britton [13]. We quote the theorem.

Theorem 3.3.3. *(Steady states and eigenvalues)* **see Britton [13]**,

- *If $\gamma < 0$, the (trivial) steady state of the second order system is at (3.4) is a saddle point. Both eigenvalues are real one positive and one negative.*
- *If $\gamma > 0$, $\delta > 0$, $\beta < 0$, it is a stable node. Both eigenvalues are real and negative.*
- *If $\gamma > 0$, $\delta > 0$, $\beta > 0$, it is an unstable node. Both eigenvalues are real and positive.*
- *If $\gamma > 0$, $\delta < 0$, $\beta < 0$, it is a stable focus. The eigenvalues are complex conjugate, with negative real part.*
- *If $\gamma > 0$, $\delta < 0$, $\beta > 0$, it is an unstable focus. The eigenvalues are complex conjugates, with positive real part.*
- *If $\gamma > 0$, $\delta < 0$, $\beta = 0$, it is a center. The eigenvalues are complex conjugates, and purely imaginary.*

Theorem 3.3.4. Linearization Theorem [13]. *Let us suppose that the non-linear system*

$$\dot{y} = Y(y) \tag{3.5}$$

has a simple fixed point at $y = 0$. Then, in a neighborhood of the origin, the phase portraits of the system and its linearization are qualitatively equivalent provided the linearized system is not at center.

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

Lemma 3.3.5. see Van Den Driessche and Watmough [59]. *Suppose that x_0 is a disease free equilibrium of a system*

$$\dot{x}_i = f_i(x) = F_i(x) - V_i(x), \quad i = 1, \ldots, n,$$

where $V_i = V_i^- - V_i^+$ and $f_i(x)$ satisfy the following conditions from (B1)-(B5):

$(B1)$ if $x \geq 0$, then $F_i(x), V_i^+(x), V_i^-(x) \geq 0$ for $i = 1, \ldots, n$, since each of these functions describe the transition of individuals between compartments.

$(B2)$ If $x_i = 0$, then $V_i^-(x) = 0$. In particular, if $x \in X_s$ then $V_i^- = 0$ for $i = 1, \ldots, m$. If the number of individuals in each compartment is equal to zero then there is no transfer of individuals out of the compartment.

$(B3)$ $F_i = 0$ if $i > m$. This means that the rate of appearance of new infections into the disease free state is zero.

$(B4)$ If $x \in X_s$ then $F_i(x) = 0$ and $V_i^+(x) = 0$ for $i = 1, \ldots, m$, this indicates that if the number of individual x is the set of disease free state there will be no transfer out to infected compartment. In this case we will say that the disease free state is invariant because if the population is free of disease then the population will remain free of disease.

$(B5)$ If $F(x) = 0$, then all eigenvalues have negative real parts.

Thus the derivatives $DF(x_0)$ and of $DV(x_0)$ are partitioned as

$$DF(x_0) = \begin{pmatrix} F & 0 \\ & \\ 0 & 0 \end{pmatrix}, \; DV(x_0) = \begin{pmatrix} V & 0 \\ & \\ J_3 & J_4 \end{pmatrix},$$

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

$$F = \left(\frac{\partial F_i}{\partial x_j}(x_0) \right), \text{ and } V = \left(\frac{\partial V_i}{\partial x_j}(x_0) \right) \text{ with } 1 \leq i, j \leq m.$$

Further, F is non-negative, then V is a nonsingular M-matrix and all eigenvalues of J_4 have positive real part.

3.4 Background of Epidemiology of Tuberculosis

In this section, we will now give a brief introduction to epidemiological modelling of tuberculosis.

3.4.1 Compartmental Classes

Epidemiological models are presented in the form of compartments i.e., the stages of TB determine groupes of individual the given disease status. In population biology, they mostly use the following common abbreviations:

S: Susceptible, individuals who are not infected.

E: Exposed, individuals who are infected but unable to transmit the disease.

I: Infected, individuals who are infected and infectious.

R: Recovery, individuals who are successfully treated.

Various models use different approaches in constructing the epidemiological models, some compartments may be included or excluded. Some models have more compartments, according to the hypothesis of the model.

We now consider an SIR model that has been studied by Kermack and McKendrik (1927)

[36, 4]. The total population size is assume to be constant, N and is subdivided into three groups such as susceptible (S), infected (I) and immune or removed (R) individuals at time t. The probability of a birth equals the probability of death which is given by the parameter b. The parameter β is the contact number i.e., the average number of successful contacts made by one infected individual during his or her infectious time. Hence, βS is the proportion of contacts made by one infected individual that results in an infection of a susceptible individual and βSI is the total number of contacts made by infected class that results in infection. The probability of recovery is represented by γ_1 and the ratio $\frac{1}{\gamma_1}$ is the average length of the infectious period when there are no deaths. The length of infections period may reduce due to death and is represented by $\frac{1}{\mu_1+\gamma_1}$. We now present the SIR epidemic model as follows:

$$\begin{aligned} \dot{S} &= bK - \beta SI - \mu_1 S, \\ \dot{I} &= \beta SI - (\mu_1 + \gamma_1)I, \\ \dot{R} &= \gamma_1 I - \mu_1 R. \end{aligned} \tag{3.6}$$

Since the probability of birth is the same as death we therefore have $b = \mu_1$. The initial condition $S(0) + I(0) + R(0) = N$ where $S(0), I(0), R(0) > 0$.

3.4.2 Equilibria

One of the variable R in system (3.4) is extraneous and can be eliminated and obtain the equilibria by setting the time derivatives in the equations to be equal to zero. The equilibrium point at $S = N$ and $I = 0$ represents a disease free equilibrium. The endemic equilibrium point simplifies to:

$$S^* = \frac{(\mu_1 + \gamma_1)}{\beta}, \qquad I^* = \frac{\mu_1\Big[\beta K - (\mu_1 + \gamma_1)\Big]}{\beta(\mu_1 + \gamma_1)}.$$

3.4.3 The basic reproduction number

The basic reproduction number is sometimes referred to as a ratio. It is one of the most useful threshold parameters or invariants, which characterize mathematical properties concerning infectious disease models [14], [59]. The basic reproduction number is widely used in mathematical epidemiology models. The analysis of the model includes finding equilibrium points (steady states) of the model, finding the basic reproduction number R_0 and investigating the stability of the equilibrium points (disease free equilibrium (DFE) and endemic equilibrium point (EEP)) which will be characterized using the invariant R_0. The stability of these equilibria change at the bifurcation point which occurs when $R_0 = 1$, which will be discussed later. Consequently, the point $R_0 = 1$ describes an important threshold for understanding the transmission dynamics of infectious diseases. The basic reproduction number has a biological interpretation.

Definition 3.4.3.1 The Basic Reproduction Number or Basic Reproduction Ratio is defined as the average number of secondary infections that are produced when one infected individual is introduced into a group of susceptible individuals. For more information see Allen [4, 6, 59].

It is implicitly assumed that the infected outsider is in the host population for the entire infectious period and mixes with the host population in exactly the same way that a population native would mix. The basic reproduction number R_0 turns out to be the threshold quantity that determines whether a disease can invade a population. If $R_0 < 1$, then on average an infected individual produces less than one new infected individual over the course of its infectious period, and the infection is unable grow. Conversely, if $R_0 > 1$ then each infected individual produces, on average, more than one new infection, and the disease can invade the population [4]. Therefore, it is important that all heath control measures or strategies of a disease should lower R_0 to less than unity.

We notice that since the model has one infected compartment, then we can obtain R_0 by following the definition, the rate of transmission multiply by the infection period. The parameter β is the rate of transmission and the infectious period is

$$\frac{1}{\mu_1 + \gamma_1}.$$

Therefore, the basic reproduction number is given by

$$R_0 = \frac{\beta K}{\mu_1 + \gamma_1}.$$

However, for more complicated models with several infected compartments the definition of R_0 is insufficient to calculate R_0. The basic reproduction number R_0 can be determined using the method of next-generation matrix as presented in Van den Driessche and Watmough [59]. In cases where we have more than one infected compartment we will then use the next generation matrix to find the basic reproduction number.

3.4.4 The next generation matrix

The next generation method introduced by Van den Driessche and Watmough [59], is a general method of finding R_0 in a case where we have more than one infected compartment. Suppose we have n disease compartments and m non-disease compartments, and let $x \in \mathbb{R}^n$ and $y \in \mathbb{R}^m$ be sub-populations in each of these compartments. We denote the rate of secondary infection increase of the i^{th} disease compartment by F_i and V_i the rate disease progression, death and recovery decrease the i^{th} compartment. Thus we have the following compartmental model:

$$\begin{aligned} \frac{dx_i}{dt} &= F_i(x,y) - V_i(x,y), \qquad i = 1, ..., n, \\ \frac{dy_i}{dt} &= g_j(x,y), \qquad j = 1, ..., m. \end{aligned}$$

The calculation of the basic reproduction number is based on linearization of the ordinary differential equation (ODE) model about a disease free equilibrium, while the following assumption ensure the existence of the equilibrium and well-posedness of the model.

- Assume $F_i(0, y) = 0$ and $V_i(0, y) = 0$ for all $y \geq 0$ and $i = 1, ..., n$. All new infections are secondary infections arising from infected host, there is no immigration of individuals into the disease compartments.

- Assume $F_i(0, y) \geq 0$ for all non-negative x and y and $i = 1, ..., n$. The function F represents new infections and can not be negative.

- Assume $V_i(0, y) \leq 0$ whenever $x_i = 0, i = 1, ..., n$. Each component, V_i represents a net outflow from compartment i and must be negative (inflow only) whenever the compartment is empty.

- Assume $\sum_{i=1}^{n} V_i(x, y) \geq 0$ for all non-negative x and y. This sum represents the total outflow from all infected compartments. Terms in the model leading to increase in $\sum_{i=1}^{n} x_i$ are assumed to represent secondary infections and therefore belong in F.

- Assume the disease free system $\frac{dy}{dt} = g(0, y)$ has a unique equilibrium that is asymptotically stable. That is, all solution with initial conditions of the form $(0, y)$ approach a point $(0, y_0)$ as $t \to \infty$. This point is referred to as the disease free equilibrium.

Now assuming that F_i and V_i meet the above conditions, we can form the next generation matrix FV^{-1} from matrices of partial derivatives of F_i and V_i. Now we have

$$F = \Big[\frac{\partial F_i(x_0)}{\partial x_j}\Big]$$

and

$$V = \Big[\frac{\partial V_i(x_0)}{\partial x_j}\Big],$$

where i, $j = 1, ..., m$ and where x_0 is the disease free equilibrium. The entries of FV^{-1} give the rate at which infected individuals in x_j produce new infections in x_i, times the average length of time an individual spends in a single visit to compartment j. R_0 is given by the spectral radius (dominant eigenvalue) of the matrix FV^{-1}.

If the basic reproduction number is less than unity i.e., $R_0 < 1$ then the disease-free equilibrium is locally asymptotically stable, which implies that the disease will die out in the population. On the other hand, if the reproduction number is greater than unity, then the endemic equilibrium is locally asymptotically stable. The technique used to determine the stability of the equilibrium points for complex models will be shown in the following Chapters.

3.5 Lyapunov function and stability

It is important to investigate the global behaviour of epidemiological dynamics of mathematical models for a multidimensional differential equation system. Lyapunov method and LaSalle's Invariance Principle are the most successful methods for proving the global stability of a model. There is no unique method to construct or find a Lyapunov function which proves the stability of an equilibrium. A suitable Lyapunov function needs to be constructed so that its derivative along solutions of the system is negative definite [40]. Let

$$\mathbb{R}^n_+ = \{x = (x_1, x_2, ..., x_n) : x_i > 0, i = 1, 2, ..., n\}$$

is often feasible and positively invariant. We now construct a Lypunov function as follows:

$$V = \sum_{i=1}^{n} a_i \Big(x_i - x_i^* - x_i^* \ln \frac{x_i}{x_i^*} \Big), \tag{3.7}$$

where $a_i > 0$ $(i = 1, 2, ..., n)$ is positive definite in $\mathbb{R}^n_+$. We now choose the suitable coefficients of a_i in (3.7) and anaylse the derivative $\dot{V}$ such that the derivative is a negative definite. This method may work well for simple epidemic models as it is relatively easy to get the constants a_i.

Lemma 3.5.1. (see Guanrong [26]) Lyapunov barrier.

Let $V : N \to \mathbb{R}$, be continuously differentiable, where $N \subset \mathbb{R}^m$, is a non-empty open

and bounded set, with $\dot{V(x)} \leq 0$ for all $x \in N$, and let $m = \min_{x \in \delta N} V(x)$. Then, for any $u_0 \in N$ such that $V(u_0) < m$, the set $C(u_0) = \{u \in N : V(u) \leq V(u_0)\}$ has the property that $\Gamma^+(u_0) \subseteq C \subseteq N$.

Definition 3.5.2. ([26] (Sign) Definite functions)

A function $F : N \to \mathbb{R}$ is positive definite at $u^* \in N$ if

(i)$F(u^*) = 0$,

(ii)$F(u) > 0$ for all $u \in N$ with $u \neq u^*$. F is negative definite if $-F$ is positive definite.

Definition 3.5.3. ([26] Lyapunov function).

A continuous differentiable function $V : N \to \mathbb{R}$, where $N \subseteq R^m$, is a Lyapunov function for $\dot{u} = f(u)$ at $u^* \in N$ if

(i) $V(u)$ is positive definite at u^*, and

(ii) $\dot{V}(u) \leq 0$ for all $u \in N$. If in addition, $\dot{V}(u)$ is negative definite at u^*, then V is a strict Lyapunov function.

Theorem 3.5.4. ([26] Lyapunov first stability theorem (Lyapunov stability condition))

Suppose that u^* is a fixed point of $\dot{u} = f(x)$. Suppose for some open set $N \subseteq \mathbb{R}^m$, containing u^* there exist $V : N \to \mathbb{R}$, such that V is a Lyapunov at u^*. Then u^* is Lyapunov stable.

Theorem 3.5.5. ([26], Lyapunov's second stability theorem (Lyapunov asymptotic stability condition)).

Suppose there exist a Lyapunov function and let u^* be a fixed point of $\dot{u} = f(u)$ and suppose that for some open set $N \subset \mathbb{R}^m$, containing u^*, there exists $V : N \to \mathbb{R}$, such that V is strict Lyapunov at u^*. Then u^* is asymptotically stable.

Then the zero solution is asymptotically stable and such function V is called a strong

Lyapunov function for the system. In this dissertation we will use the Lyapunov function to investigate the existence and uniqueness of global positive solutions of stochastic models. The method of Lyapunov functions is commonly used to establish global stability results for biological models, see [60, 30, 42] for instance.

3.6 Optimal control method

Optimal control theory has been used as a very powerful mathematical tool to make decisions involving complex biological situations and it has been derived from the calculus of variations. Optimal control techniques are of great use in developing optimal strategies to control various kinds of diseases. For more information, consult the book of Lenhart and Workman [39]. It has been used, for instance, in finding the percentage of the population that should be vaccinated as time evolves in a given epidemic model to minimize the number of infected and the cost of implementing the vaccination strategy.
The behavior of a dynamic system is described by the state variable(s). We assume that there is a way to control the state variable(s) x, by acting upon it with a suitable control. We noticed that the dynamic system (state x) depends on the control u. The goal is to adjust the control u in order to minimize or maximize a given objective functional, $J(u(t), x(t), t)$, that attains the desired goal, and the required costs to achieving it. The optimal control is obtained when the desired goal is achieved with the least cost. The functional depends on the control and the state variables. There are a number of different methods for calculating the optimal control for a specific model. Pontryagin Maximum Principle for example allows the calculation of the optimal control for an ordinary differential equations model system with given constraints. See the book of Lenhart and Workman [39].

The following are characteristics that an optimal control problem may exhibit

- Controllability: ability to use controls to steer a system from one position to another.

- Observability: deducing system information from control input and observe output.
- Stabilization: implementing controls to force stability.

The principal technique for the optimal control problem is to solve a set of necessary conditions, that an optimal control and corresponding state must satisfy. It is important to understand the logical difference between necessary conditions and the sufficient conditions of solution sets.

Let us consider the optimal control problem of the form below.

Determine

$$\min_u \left\{ \phi(t_f, x(t_f)) + \int_0^{t_f} g_0(t, x(t), u(t))dt \right\}$$

where

$$f(x(t)) = [x_1(t), x_2(t), ..., x_{n_s}(t)]^T \in \mathbb{R}^{\mathbf{n}}$$

is the state vector and

$$u(t) = [u_1(t), u_2(t), u_3(t), ..., u_{n_c}(t)]^T \in \mathbb{R}^{\mathbf{m}}$$

is the control vector.

The state and the control variables are governed by the dynamics described by a set of first order differential equations:

$$\frac{dx}{dt} = f(t, x(t), u(t)) \qquad x_0 = x(0), 0 \leq t \leq t_f. \tag{3.8}$$

The functions:

$$f(h_0) : T \times \mathbb{R}^n \times \mathbb{R}^m \to \mathbb{R}^n$$

$$f(g_0) : T \times \mathbb{R}^n \times \mathbb{R}^m \to \mathbb{R}^n$$

are continuously differentiable with respect to each component of x and u, and piecewise continuous with respect to t.

3.7 Pontryagin's Maximum Principle

The Pontryagin's Maximum Principle converts the maximization or minimization of the objective functional J, coupled with the state variable into pointwise maximizing or minimizing of the Hamiltonian with respect to the control. The Hamiltonian $H(t, x, u, \lambda)$ is a function of four variables. Time t is the underlying variable for each of x, u and λ is a function of t, called the adjoint variable.

Theorem 3.7.1. [39] If $u^*(t)$ and $x^*(t)$ are optimal for problem (3.8), then there exists a piecewise differential adjoint variable $\lambda(t)$ such that

$$H(t, x^*(t), u(t), \lambda(t)) \leq H(t, x^*(t), u^*(t), \lambda(t))$$

for all controls u at each time t, where the Hamiltonian H is

$$H = f(t, x(t), u(t)) + \lambda(t) g(t, x(t), u(t))$$

and

$$\frac{\lambda(t)}{dt} = -\frac{\partial H(t, x^*(t), u^*(t), \lambda(t))}{\partial x},$$

$$\lambda(t_f) = 0.$$

Necessary conditions: If $u^*(t)$ and $x^*(t)$ are optimal, then the following conditions hold:

$$\frac{\lambda(t)}{dt} = -\frac{\partial H(t, x^*(t), u^*(t), \lambda(t))}{\partial x}, \tag{3.9}$$

$$\lambda(t_f) = 0, \tag{3.10}$$

$$\frac{\partial H(t, x^*(t), u^*(t), \lambda(t))}{\partial u} = 0. \tag{3.11}$$

Sufficient conditions: If $u^*(t)$, $x^*(t)$ and $\lambda(t_f)$ satisfy conditions (3.9), (3.10), and (3.11), then $u^*(t)$ and $x^*(t)$ are optimal.

3.8 Stochastic process

A stochastic process is a collection of random variables indexed by time t or known as a probability distribution over a space of paths. The concept of stochastic process is very important in both mathematical theory and its applications in science, engineering economics, etc. It is used to model large numbers of various phenomena where the quantity of interest varies discretely or continuously through time in a non-predictable fashion.

Definition 3.8.1. Let T be a subset of $[0, \infty)$. A family of random variable $\{X_t\}_{t\in T}$ is said to be a discrete-time variable process, and when $T = [0, \infty)$, it is called a continuous-time process.

Definition 3.8.2. Let Ω be a non-empty set. Let T be a fixed positive number, and assume that for each $t\in[0, T]$ there is a σ-algebra $\mathcal{F}_t$. Assume further that $\mathcal{F}_s \subset \mathcal{F}_t$ and $\mathcal{F} = \bigcup_{t\leq 0} \mathcal{F}_t$ for all $0 \leq s < t < \infty$. Then the collection of $\{\mathcal{F}_t\}$ of σ-algebras a *filtration* and the $(\Omega, \mathcal{F}, \mathbb{P}, \mathcal{F}_t)$ is called a filtered probability space.

We consider $\mathcal{F}_t$ as the set of information available at time t or $\{\mathcal{F}_t\}_{t>0}$ which is describing the flow of information over time, where we suppose that we do not lose information as time passes.

Definition 3.8.3. A real-valued stochastic process is an indexed family of real-valued functions, $\{X_t\}_{t\geq 0}$. We say that $\{X_t\}_{t\geq 0}$ is *adapted* to the filtration $\{\mathcal{F}_t)\}_{t\geq 0}$ if X_s is $\mathcal{F}_t$-measurable for each $t \leq s$, see [23, p29] for more information.

A probability triple $(\Omega, \mathcal{F}, \mathbb{P})$, where Ω is some set called the sample space, $\mathcal{F}$ is a collection of subsets of Ω, and $\mathbb{P}$ is the probability of each event $A \in \mathcal{F}$. The collection $\mathcal{F}$ is a σ-field, that is, $\Omega \in \mathcal{F}$ and $\mathcal{F}$ is closed under the operations of countable union and taking complements. The probability $\mathbb{P}$ must satisfy the usual axiom of probability [23, p29].

- $0 \leq \mathbb{P}[A] \leq 1,$ for all $A \in \mathcal{F}$,
- $\mathbb{P}[\Omega] = 1$,
- $\mathbb{P}[A \cup B] = \mathbb{P}[A] + \mathbb{P}[B]$ for any disjoint $A, B \in \mathcal{F}$,
- If $A_n \in \mathcal{F}$ for all $n \in \mathbb{N}$ and $A_1 \subseteq A_2 \subseteq ...$, then $\mathbb{P}[A_n] \uparrow \mathbb{P}[\bigcup_n A_n]$ as $n \uparrow \infty$.

3.8.1 Markov Chain

Markov Chain is the stochastic process whose effect of the past on the future is summarized only by the current state, rather than the whole history.

Definition 3.8.1.1. The stochastic process $\{X_n\}_{n\geq 0}$ with its natural filtration, $\{\mathcal{F}_n\}_{n\geq 0}$ is a discrete time *Markov process* if

$$\mathbb{P}\left[X_{n+1} \in B | \mathcal{F}_n\right] = \mathbb{P}\left[X_{n+1} \in B | X_n\right], \tag{3.12}$$

for all $B \in \mathcal{F}$. This means that the probability that $X_{n+1} \in B$ given that we know the whole history of the process up to time n is the same as the probability that $X_{n+1} \in B$ given only the value of X_n [23].

3.8.2 Martingale

A martingale is known to be a model of a fair game. It is a stochastic process in which the conditional expectation of the next value at time T, given the current and preceding values at time t, is the current value at time t.

Definition 3.8.2.1. A stochastic process $\{X_n\}_{n\geq 0}$ is called a *martingale* with respect to filtration $\{\mathcal{F}\}_n$ if

- For each n, X_n is an $\mathcal{F}_n$-measurable variable with $\mathbb{E}\left[|X_n|\right] < \infty$.
- If $m < n$, then

$$\mathbb{E}\left[X_n | \mathcal{F}_m\right] = X_m. \tag{3.13}$$

Definition 3.8.2.2. A $(\mathbb{P}, \{\mathcal{F}\}_{t\geq 0})$-martingale $\{M_t\}_{t\geq 0}$ is said to be square-integrable if

$$\mathbb{E}\left[|M_t|^2\right] < \infty,$$

for each $t > 0$.

The theorem states that a random variable that is measurable with respect to the filtration generated by Brownian motion can be written in terms of an Ito integral with respect to its Brownian motion. Mathematically this can be expressed as follows:

Theorem 3.8.2.3. (Martingale representation theorem) Let $\{\mathcal{F}_t\}_{t\geq 0}$ denote the natural filtration of the $\mathbb{P}$-Brownian motion $\{W_t\}_{t\geq 0}$. Let $\{M_t\}_{t\geq 0}$ be a square-integrable $(\mathbb{P}, \{\mathcal{F}\}_{t\geq 0})$-martingale. Then there exist an $\{\mathcal{F}\}_{t\geq 0}$-predictable process $\{\theta\}_{t\geq 0}$ such that with $\mathbb{P}$-probability one,

$$M_t = M_0 + \int_0^t \theta_s dW_s. \tag{3.14}$$

3.8.3 Stopping time

A random variable τ is a stopping time for a stochastic process if it is a rule for stopping this process such that the decision to stop at, say time t can be taken only on the basis of the information available at time t. Mathematically we say:

Definition 3.8.3.1. A random variable $\tau : \Omega\ [0, \infty]$ (it may take the value ∞) is called an *$\mathcal{F}_t$-stopping time (or stopping time)* if $\{\omega\ :\ \tau(\omega) \leq t\} \in \mathcal{F}_t$ for any $t \geq 0$. The stopping time is said to be finite if $\mathbb{P}(\tau{=}\infty) = 0$.

Remark 3.8.3.2. If $\tau(\Omega) = k$ (constant), then τ is a stopping time. If τ is a stopping time with respect to filtration $(\mathcal{F}_t)_{t\in\mathbb{R}_+}$ generated by the stochastic process $(X_t)_{t\in\mathbb{R}_+}, t \in \mathbb{R}_+$, then τ is called a stopping time of the process.

Definition 3.8.3.3. (see Etheridge [23]). Suppose that X is an $\mathcal{F}-$measurable random variable with $\mathbb{E}[|X|] < \infty$. Suppose that $\mathcal{G} \subseteq \mathcal{F}$ is a σ-field, then the *conditional expectation* of X is given by $\mathcal{G}$, written as $\mathbb{E}[X|\mathcal{G}]$, is a $\mathcal{G}$-measurable random variable with the property that for any $A \in \mathcal{G}$,

$$\mathbb{E}[[X|\mathcal{G}]; A] \triangleq \int_A \mathbb{E}[X|\mathcal{G}]\, d\mathbb{P} = \int_A X d\mathbb{P} \triangleq \mathbb{E}[X; A].$$

The conditional expectation exists, but is only unique up to the addition of a random variable that is zero with probability one a.s.

3.8.4 Brownian motion

Brownian motion refers to the ceaseless, irregular random motion of small particles immersed in a liquid or gas, as observed by R. Brown in 1827. The phenomenon can be explained by the perpetual collisions of the particles with the molecules of the surrounding medium. Suppose $W(t)$ is the displacement from the origin at a time t of a small particle. The displacement of particle over the time interval t_1 to t_2 is long compared to the time between impacts. The central limit theorem can be applied to the sum of a large number of these disturbances so that it can be assumed $W(t_2) - W(t_1)$ has a normal density. The density of the particle's displacement depends on the length of the time interval and not on the time of observation. Therefore, the probability density of the displacement from time t_1 to t_2 is the same as from time $t_1 + t$ to time $t_2 + t$ [5].

The stochastic process associated with the Brownian motion is called the Brownian process or the Wiener process. The concept has found application in a wide range of fields. So for instance, Brownian motion has become one of the fundamental building blocks of modern quantitative finance. Indeed, the basic continuous time model for financial asset prices assumes that the log-return of a given financial asset follow a Brownian motion with drift. There are also interesting applications of Brownian motion to epidemiology. For more information the reader may consult Mao and Etheridge, [46, 23].

Definition 3.8.4.1. (see Allen [5]). A stochastic process $\{W(t) : t \in [0, \infty)\}$ is a $\mathbb{P}-$*Brownian motion or a* $\mathbb{P}$*-Wiener process* if $W(t)$ depends continuously on t, $W(t) \in (-\infty, \infty)$, and the following three conditions hold:

(*i*) For $0 \leq t_1 < t_2 < \infty$, $W(t_2) - W(t_1)$ is normally distributed with mean zero and variance $t_2 - t_1$, that is, $W(t_2) - W(t_1) \sim N(0, t_2 - t_1)$.

(*ii*) For $0 \leq t_0 < t_1 < t_2 < \infty$, the increments $W(t_1) - W(t_0)$ and $W(t_2) - W(t_1)$ are independent.

(*iii*) $\text{Prob}\{W(0) = 0\} = 1$.

Note that the conditions in Definition 3.8.4.1 implies that the Wiener process has stationary and independent increments. For intervals $0 \leq t_0 < t_1 < t_2 < ... < t_{n-1} < t_n$, the n random variable $W(t_1) - W(t_0), W(t_2) - W(t_1), ..., W(t_n) - W(t_{n-1})$ are independent. Also, the increments $W(t_1 + \Delta t) - W(t_1)$ and $W(t_2 + \Delta t) - W(t_2)$ are stationary, meaning that they have the same normal density, $N(0, \Delta t)$, for any $t_1, t_2 \in [0, \infty)$ and $\Delta t > 0$. To simplify notation, define $\Delta t_i = t_{i+1} - t_i$ and $\Delta W(t_i) = W(t_{i+1}) - W(t_i)$.

Theorem 3.8.4.2. [5] (Strong law of large numbers)
Let $X_1, X_2, ..., X_n, ...$, be a sequence of independent and identically distributed (i.i.d.) random variables with finite mean, $|\mu| < \infty$, and positive standard deviation, $0 < \sigma < \infty$. Then the mean $\bar{X} \equiv \bar{X}(n)$ satisfies

$$\lim_{n \to \infty} E(\left|\bar{X}(n) - \mu\right|^2) = 0 \tag{3.15}$$

and

$$\text{Prob}\left\{\lim_{n \to \infty} \left|\bar{X}(n) - \mu\right| = 0\right\} = 1. \tag{3.16}$$

The convergence in (3.16) is known as *mean square convergence* and the convergence in (3.17) is known as *convergence with probability one or as convergence almost surely (a.s.).* The probability in (3.17) is often expressed as

$$\lim_{n \to \infty} \bar{X}(n) = \mu \tag{3.17}$$

with probability one. Notice that the mean square convergence for the random sample $\bar{X}(n)$ is equivalent to convergence of the variance to zero,

$$E(\left|\bar{X}(n) - \mu\right|^2) = Var(\bar{X}(n)) = \frac{\sigma_2}{n} \to 0 \tag{3.18}$$

as $n \to \infty$.

Theorem 3.8.4.3. [5] (Quadratic variation) For a partition $\Pi = \{t_0, t_1, ..., t_j\}$ of an interval $[0, T]$, let $|\Pi| = \max_i(t_{i+1} - t_i)$. A Brownian motion W_t satisfies the following equation with probability 1:

$$\lim_{|\Pi \to 0|} \sum (W_{t_{i+1}} - W_{t_i})^2 = T.$$

3.9 Stochastic Integration

There are a variety of ways to define a stochastic integral. The two most well-known definitions of a stochastic integral are Itô and Stratonovich. The name Itô refers to the Japanese mathematician Kiyoshi Itô (1915-2008) who developed much of the basic theory and Ruslan Stratonovish defined the alternative Itô stochastic integral. In our dissertation we shall use the Itô definition which is most frequently used in biological examples.

The following Theorem shows that the expectation on an Itô stochastic integral is zero and the expectation of the square of the integral is the integral of the expectation of the integrand squared.

Theorem 3.9.1. Suppose $f(t)$ is a random function satisfying

$$\int_a^b \mathbb{E}(f^2(t))dt < \infty.$$

Then

(i) $\mathbb{E}\left[\int_a^b f(t)dW(t)\right] = 0$ and

(ii) $\mathbb{E}\left[\left(\int_a^b f(t)dW(t)\right)^2\right] = \int_a^b \mathbb{E}(f^2(t))dt.$

Property (ii) in Theorem 3.9.1 is known as *Itô isometry property* [5]. Properties (i) and (ii) are straight forward to verify for constant function $f(t) = c$:

$$\mathbb{E}\left[\int_a^b cdW(t)\right] = c\mathbb{E}[W(b) - W(a)] = 0$$

because $W(b) - W(a) \sim N(0, b-a)$.

$$\mathbb{E}\left[\left(\int_a^b cdW(t)\right)^2\right] = c^2\mathbb{E}[(W(b) - W(a))^2] = c^2(b-a)$$

because $\mathbb{E}[(W(b) - W(a))^2] = \text{Var}(W(b) - W(a)) = b - a$.

Definition 3.9.2. [5] An *Itô process or stochastic integral* is a stochastic process on $(\Omega, \mathcal{F}, \mathbb{P})$ adopted to $\mathcal{F}_t$ which can be written in the form:

$$X_t = X_0 + \int_0^t a(X_t, t)ds + \int_0^t b(X_t)dB_s, \tag{3.19}$$

where $a(X_t, t)$ is a drift form, $b(X_t, t)$ is the diffusion for and B_s is a standard Wiener process.

A short notation can be written as follows:

$$dX_t = a(X_t, t)dt + b(X_t, t)dB_t. \tag{3.20}$$

We will now introduce the most important Lemma called the Itô Lemma.

Lemma 3.9.3. (Itô Lemma) Suppose $F(X_t, t)$ is a twice differentiable on t and also that X_t follows the Itô process

$$dX_t = \alpha(X_t, t)dt + \sigma(X_t, t)dB_t, \quad t \geq 0$$

where B_t is a Wiener process and α and σ are functions of X_t and t respectively. The variable X_t has a drift rate of α and a variance rate of σ^2. Then Itô Lemma follows the process

$$dF_t = \left(\frac{\partial F}{\partial X_t}\alpha + \frac{\partial F}{\partial t} + \frac{1}{2}\frac{\partial^2 F}{\partial X_t^2}\sigma_t^2\right)dt + \frac{\partial F}{\partial X_t}\sigma dB_t.$$

Thus, we see that the space of Itô processes is closed under twice-continuously differentiable transformations.

3.10 The multi-dimensional Itô's formula

Let $x(t)$ be a d-dimensional *Itô's process* on $t \geq 0$ with the stochastic differential [46], i.e., a stochastic process of the form

$$dx(t) = f(t)dt + g(t)dB(t),$$

where $f \in L^1(\mathbb{R}_+; \mathbb{R}^d)$ and $g \in L^2(\mathbb{R}_+; \mathbb{R}^{d\times m})$. Then any $V(x(t), t)$ is again an Ito's process with the stochastic differential given by

$$\begin{aligned} dV(x(t),t) &= \left[V_t(x(t),t) + V_x(x(t),t)f(t) + \frac{1}{2}\text{trace}(g^T(t)V_{xx}(x(t),t)g(t))\right] \\ &+ V_x(x(t),t)g(t)dB(t). \qquad a.s. \end{aligned}$$

Note that

$$dtdt = 0, dB(t_i)dt = 0, dB_i dB_i = dt, dB_i dB_j = 0 \text{ if } i \neq j. \tag{3.21}$$

3.11 Stability in probability theory

Consider the general n-dimensional stochastic system

$$dx(t) = f(t, x(t))dt + g(t, x(t))dB(t) \tag{3.22}$$

on $t \geq 0$ with initial value $x(0) = x_0$. The solution is denoted by $x(t, x_0)$. Assume that $f(t, 0) = g(t, 0) = 0$ for all $t \geq 0$, so the origin point is an equilibrium of (2.8) The equilibrium $x = 0$ of the system (2.8) is said to be:

(i) Stable in probability if for all $\epsilon > 0$,

$$\lim_{x_0 \to 0} P\left(\sup_{t \geq 0} |x(t, x_0)| \geq \epsilon\right) = 0;$$

(iv) Almost surely exponentially stable if for all $x_0 \in \mathbb{R}^n$

$$\lim_{x_0 \to 0} \sup \frac{1}{t} \ln |x(t, x_0)| < 0 \quad a.s.;$$

We refer the reader to a paper of Lahrouz et al., [38].

3.12 Differential Operator

We define the differential operator L associated with the following equation:

$$dx(t) = f(x(t), t)dt + g(x(t), t)dB(t) \qquad t \geq t_0,$$

by

$$L = \frac{\partial f(x(t), t)}{\partial t} + \sum_{i=1}^{d} f(x, t) \frac{\partial}{\partial x_i} + \frac{1}{2} \sum_{i,j=1}^{d} \left[g(x, t) g^T(x, t)\right]_{i,j} \frac{\partial^2}{\partial x_i \partial x_j}.$$

If L acts on a function of $V \in C^{2,1}(S_h \times \mathbb{R}_+; \mathbb{R}_+)$, then

$$LV = V_t(x, t) + V_x(x, t) + \frac{1}{2} \text{trace}\left[g^T(x, t) V_{xx}(x, t) g(x, t)\right],$$

where $V_t = \frac{\partial V}{\partial t}$, $V_x = \left(\frac{\partial V}{\partial x_1}, ..., \frac{\partial V}{\partial x_d}\right)$, $V_{xx} = \left(\frac{\partial^2 V}{\partial x_i \partial x_j}\right)_{d \times d}$. For more information the reader may consult the book of Mao, [46].

Chapter 4

A model of population dynamics of TB in a prison system and application to South Africa

---

A modification of the material in this chapter has been published in [1*a*].

Authors: Peter Witbooi and Sibaliwe Maku Vyambwera.

4.1 Abstract

Background: Tuberculosis continues to spread in South African prisons in particular, as prisons are over-capacitated and have poor ventilation. The awaiting trial detainees are not screened on admission and are at high risk of getting infected with TB.

Results: We propose a compartmental model to describe the population dynamics of TB disease in prisons. Our model considers the inflow of susceptible, exposed and TB infectives into the prison population. Removal of individuals out of the prison population can be either by death or by being released from prison, as compared to a general population in which removal is only by death. We describe conditions, including non-inflow of infectives into the prison, which will ensure that TB can be eradicated from the prison

population. The model is calibrated for the South African prison system by using data in existing literature. The model can be used to make quantitative projections of TB prevalence and to measure the effect of interventions. Illustrative simulations in this regard are presented. The model can be used for other prison populations too, if data is available to calculate the model parameters.

Conclusion: Various simulations generated with our model serve to illustrate how it can be utilized in making future projections of the levels of prevalence of TB, and to quantify the effect of interventions such as screening, treatment or reduction of transmission parameter values through improved living conditions for inmates. This makes it particularly useful as there are various targets set by the World Health Organization and by governments, for reduction of TB prevalence and ultimately its eradication. Towards eradication of TB from a prison system, the theorem on global stability of the disease-free state is a useful indicator.
Keywords: Prison TB model, Inflow of infecteds, Removal rate.

[1*a*] P.J. Witbooi and S. Maku Vyambwera. A model of population dynamics of TB in a prison system and application to South Africa. *BMC Res Notes* **10:643**, (2017) $1 - 8$.

4.2 Introduction

The World Health Organization (WHO) has recently launched the End TB Strategy program with the aim to reduce the number of deaths due to tuberculosis and the TB incidence rate by 95% and 90% in 2030, respectively. Their focus will be the most vulnerable who are infected by TB such as the poor, refugees, HIV-infected people and prisoners. The three main pillars of the program are: integrated patient centered TB care and prevention, bold policies and supportive systems and intensified research and innovation [75].

Prisons have been recognized internationally as institutions with very high tuberculosis

burden as compared to a general population [74]. South African prisons are well known as being overcrowded. In 2015, 61 of the 90 centres in South Africa were inspected and it was found that their occupancy were more than 100% [86, p52]. The National Strategic Plan $2012 - 2016$ [91, 92] of the Department of Health is aimed at reduction of TB infection. It has prioritized TB screening in prison and mines in view of overcrowding in these premises. The pipeline report for 2013 [92] points out factors that aggravates TB transmission. The transmission of TB in a prison is driven by the amount of air shared between inmates, the number of inmates per cell, the length of the lock-up time, how much fresh airflow is used and the presence of infectious inmates in the same enclosure with susceptible inmates. Awaiting trial inmates are being kept in a very intensely crowded environment. So for instance, one could have as many as 86 inmates in a facility which was designed for 20, sharing a single toilet [93]. The Department of Correctional Services admits that overcrowding is a major problem in prisons. In Robertson et al. [31] a mathematical model is developed to explore the incarceration conditions and TB control measures. In this paper we model the population dynamics of the TB disease in a prison population with special emphasis on the South African prison system. The focus in [31] is on the effective contact rate, which in this Chapter is denoted by c_1. In this work we quantify the broader effect of c_1 on the prevalence of the TB infection. In the literature already, the paper [50] considers a mathematical model for assessing the population dynamics of HIV and HCV coexistence within correctional facilities.

The current Chapter presents a deterministic compartmental model ordinary differential equations. A prison model must consider the inflow of infected people into the system. The removal rate in the case of a prison population is completely different from the case of a general population. For a prison population, individuals are removed not only through death, but also by being released. We give detail on the general method of calculating the removal rates from the system. We make specific calculations in the South African context, and we determine other parameters and input data for the model. Our Theorem 4.4.1. determines threshold conditions that will ensure the eradication of TB disease from

the prison. Finally, we illustrate the utility of the model and of the theorem through simulations.

4.3 The model

We introduce a deterministic compartmental model which is based on the papers of Buonomo and Lacitignola [14] and Ssematimba et al. [57], the latter two papers being on tuberculosis in concentration camps. This type of very dense population necessarily has a very high contact rate between the individuals, in particular healthy susceptible people are in very close and frequent contact with people having infectious active TB. Due to the similarities between concentration camps and prisons such as overcrowding, the amount of air shared between the individuals etc., we consider this model, modified to accommodate inflow of infected, to be applicable to prison populations.

The prison population consists of sentenced prisoners together with awaiting trial detainees, and the size of the population at time t is denoted by $N(t)$. We divide the population into four compartments namely, susceptible individuals $S(t)$, individuals with active TB who are not infectious, $E(t)$, individuals infected with active TB who are infectious $I(t)$, and the class of individuals under treatment $T(t)$ (and often these variables will be written without stressing the dependence on the time variable (t)). Due to the classes used, the model is referred to as being of $SEIT$ type. We modify the model of Buonomo and Lacitignola [14] by allowing for the inflow of exposed individuals and infectious individuals into the prison population.

It is important to note that in general populations, removal of individuals out of the system is only by death. In this model, removal is by death or by discharge from prison, and the discharge is the dominant factor. This rate of removal is denoted by μ. In the classes S, E and T the probability of an individual being removed from the class is denoted by μ, and will be referred to as the *removal rate*. For the class I, mortality due to TB-disease

amplifies the removal rate by an additional increment d, which will be referred to as the disease-induced mortality rate. The total inflow into the population is assumed to be at a rate A_0. We find it useful to express A_0 in the form $A_0 = \mu A$ for some constant positive number A and with μ being the removal rate. The number A will be seen to be the upper limit of $N(t)$. We assume that there are non-negative numbers f_S, f_E and f_I such that the inflow into the classes of (respectively) susceptible, exposed and infectious happen at the rates $f_S\mu A, f_E\mu A$ and $f_I\mu A$, respectively.

Susceptible individuals get infected with active TB at a rate c_1SI, where c_1 is the effective contact rate between the infectious and susceptible individuals. Individuals in the exposed class $E(t)$ become infectious at a rate c_3EI and progress to the infectious class $I(t)$ at rate kE , where c_3 is the effective contact rate between the exposed and infectious individuals. Successfully treated individuals who were infectious move to exposed class at a rate c_2TI. Exposed and infectious individuals move into treatment class $T(t)$ at a rate r_1E and r_2I respectively.

$$\begin{aligned}
\dot{S} &= f_S\mu A - c_1SI - \mu S, \\
\dot{E} &= f_E\mu A + c_1SI + c_2TI - c_3EI - (\mu + r_1 + k)E, \\
\dot{I} &= f_I\mu A + kE - (\mu + r_2 + d)I + c_3EI, \\
\dot{T} &= r_1E + r_2I - c_2TI - \mu T. \qquad (4.1)
\end{aligned}$$

If $f_E + f_I + f_S = 1$, then our model system (4.1) does not have a disease free equilibrium due to the fact that there is an inflow of infectives into the prison population. Thus it is clear that TB in prison cannot be eliminated as long as the wider population has individuals with active TB that go to prison.

Proposition 4.3.1 *Suppose that we have a solution*

$$X(t) = (S(t), E(t), I(t), T(t))$$

of model system (4.1) over an interval $t \in [0, \tau)$ *with* $S(0) + E(0) + I(0) + T(0) < A$ *and*

that $X(t) \in \mathbb{R}^4_{++}$ *for all* $0 \leq t \leq \tau$, *a.s., then,* $S(t) + E(t) + I(t) + T(t) \leq A$.

Proof. Given any solution in $X(t)$ satisfying the conditions of Proposition 4.3.1, then we have the total population in system (4.1) obeying the following Ordinary differential equation:

$$\begin{aligned} \frac{d(N-A)}{dt} &= -\mu(N-A) - dI \\ &\leq -\mu(N-A) \text{ a.s.} \end{aligned}$$

Therefore, similarly as in [65], for instance, $N(0) < A$ implies that $N(t) < A$ for all $t \in [0, \tau)$. □

We first study the model without the inflow of infectives. If $f_E = 0$ and $f_I = 0$ then the model given by the system (4.1) has a unique feasible disease free equilibrium given by

$$P_0 = (S_0, E_0, I_0, T_0) = (A, 0, 0, 0).$$

For a specific prison facility in a larger system, the conditions $f_E = 0$ and $f_I = 0$, can be achieved by admitting only susceptible inmates, while those carrying active TB are housed in facilities elsewhere. More generally, the condition is met if the ambient population is infection-free.

The *basic reproduction number*, denoted by R_0, of a disease in a population is defined as the average number of secondary infections that are produced when one infected individual is introduced into a group of susceptible individuals. For more information see the books [6] of Anderson and May or [4] of Allen. For the model of [14], R_0 is given by the formula:

$$R_0 = \frac{kc_1 A}{\mu_1 \mu_2},$$

with $\mu_1 = \mu + r_1 + k$ and $\mu_2 = \mu + r_2 + d$.

The basic reproduction number is a good indicator as to whether or not a disease will stay endemic in a population. If $R_0 > 1$ then each infectious individual produces, on average,

more than one new infection, and the disease will persist in the population. If $R_0 < 1$, then on average an infected individual produces less than one new infected individual over the course of its infectious period, and it is more difficult for the infection to grow. In order to ensure that such a disease vanishes from the population, it may be necessary to impose conditions stronger than $R_0 < 1$. This problem is addressed in Theorem 4.4.1. below.

4.4 Global stability for disease equilibrium

If the disease free equilibrium is *globally asymptotically stable*, it means that starting from any given state, in the long run the disease will vanish from the population. We now investigate the global stability of the disease free equilibrium of system (4.1) (subject to no inflow of infected) by using the Lyapunov function approach and we introduce the following invariant. Let

$$c_* = \max\left\{c_1,\ c_2,\ c_3\left(\frac{\mu_1}{k} - 1\right)\right\},$$

and let

$$R_* = \frac{kc_*A}{\mu_1\mu_2}.$$

Theorem 4.4.1. *In model (4.1) let us consider the special case, $f_E = 0 = f_I$. If $R_* < 1$, then the disease free equilibrium P_0 is globally asymptotically stable.*

Proof. Starting with the condition $R_* < 1$ we can choose numbers ϵ_1 such that the following conditions are satisfied:

$$\left(\frac{k}{\mu_1} + \epsilon_1\right) c_*A - \mu_2 < 0, \tag{4.2}$$

and let $a_3 = \frac{k}{\mu_1} + \epsilon_1$. Now choose $a_2 > 0$ such as to satisfy the following two inequalities:

$$a_3c_*A - \mu_2 + a_2r_2 < 0 \quad \text{and} \quad a_2r_1 - \epsilon_1\mu_1 < 0. \tag{4.3}$$

Next we choose a_1 sufficiently small such that

$$a_1 c_1 A + a_3 c_* A - \mu_2 + a_2 r_2 < 0.$$

We now define a function $V(S, E, I, T)$ as follows,

$$V = a_1(A - S) + a_2 T + a_3 E + I \tag{4.4}$$

Then it can routinely be shown that the function $V(S, E, I, T)$ is Lyapunov at the disease-free equilibrium point P_0, and therefore P_0 is globally asymptotically stable. □

Thus, if the system does not satisfy the condition $R_* < 1$ for global stability, then as far as possible the authorities must intervene and make changes that will alter the values of the parameters so as to achieve this condition.

4.5 Calibrating the model

As can be seen from the disease-free equilibrium, the number A turns out to be the maximum value of the varying population size $N(t)$. For the case of the South African prison system, from the report [86] we deduce the value

$$A = 160\ 000.$$

In a disease model on general populations, the removal rate is calculated as the inverse of the life expectancy [8, 18, 51]. In 2015, life expectancy in South Africa was given as 67 years (y), [89], so the mortality rate for the general population would be $\frac{1}{67}\text{y}^{-1}$. In a prison model however, removal of individuals from the prison population entails both removal through death and removal by release from prison (assuming that the rate of escaping from prison is negligible). We proceed with determining this parameter. Henceforth, we assume *time* to be measured in *years*, y.

4.5.1 Numerical values for the removal rates.

The removal rate μ and the additional removal rate d due to TB are calculated as below. Firstly we note that since we are working with probabilities, we can express μ as follows:

$$\mu = \mu_p + \mu_m - \mu_m\mu_p,$$

where μ_p is the rate of release from prison and μ_m is the mortality rate in the prison, excluding death specifically as a result of TB. In this prison model we assume that $\mu_p > \mu_m$ as the release rate is the dominant factor. Deaths due to TB constitute a separate parameter.

Release from prison: For calculating μ_p we used data from the public health paper [33]. The time served by prisoners is given in a frequency table which is convenient for calculating the average time served by inmates. We consider the awaiting trial detainees to stay for a nominal average period of 6 weeks, and the sentenced prisoners to serve on average 75% of their sentence time. The value μ_p calculated in this way is

$$\mu_p = 0.1789391 \text{ (year}^{-1}\text{)}.$$

Mortality: In the classes S, E and T the probability of an individual being removed from the class due to death (except death as a result of TB) is denoted by μ_m. For the class I, mortality due to TB-disease amplifies the removal rate by an additional increment d, which will be referred to as the disease-induced mortality rate. An estimate of μ_m can be obtained as follows. Consider a period of length τ, over which the average value of the sum of the class sizes S, E, and T is denoted by Q. If the total number of deaths in these three classes during this period is D, then a value for μ_m can be estimated by the formula

$$\mu_m = \frac{D}{\tau Q}.$$

The constant d can be estimated as follows. Consider a period of length τ_1. If the total number of mortalities in the I-class during this period is D_1, then we estimate a value for

d by the formula

$$\mu_m + d = \frac{D_1}{\tau_1 I}, \quad \text{i.e.,} \quad d = \frac{D_1}{\tau_1 I} - \mu_m \ .$$

For the years $2012 - 2015$ the mortality rate is estimated using results from:

(i) [86, Figure 7 on p42] for the numbers of inmates in total in S.A. prisons,

(ii) [86, Figure 16 on p85] for the number of unnatural deaths,

(iii) [86, Figure 20 on p91] for the number of natural deaths, and

(iv) [90], the latter being particularly helpful in establishing an upper limit (20% of A) for the value of $S(t)$.

The report [86] does not give the details of deaths in prison due to TB. In [86, Table 22 p71] TB comes up as the most prominent cause of natural death in prisons. Let us denote the rate of deaths due to TB by μ_{TB}. According to the report in [88] we can take $\mu_{TB} = \frac{11}{80}\mu_m$ so that we can calculate $d = \mu_{TB}(1 - \mu)$.

Our calculations yield the following values:

$$\mu_m = 0.003628, \quad \mu_{TB} = 0.02292, \quad \text{and} \quad \mu = 0.18192 \ (\text{year}^{-1}).$$

Now note that d is the additional rate of removal due to TB. Thus

$$d = \mu_{TB}(1 - \mu) = 0.01876 \ (\text{year}^{-1}).$$

4.5.2 The parameters c_i

The formula [14, formula (17)] in the paper of Buonomo and Lacitignola stresses the fact that the force of infection is proportional to the population density. This means that when moving from a free population to a concentration camp, the force of infection will multiply by a significant factor, and in a prison population it will be another factor higher. Using data for the year 2015 obtained from [90] and life expectancy from [89], a simple

calculation shows that a lower bound for the effective contact rate (let us denote it by c_0) for TB in South Africa (the entire population) yields (a lower bound)

$$c_0 = \frac{(55-44) \text{ million}}{67 \times 390000 \times (44 \text{ million})} = 1.5308 \times 10^{-7} \text{year}^{-1}.$$

When applying this to a sub-population, this parameter should be scaled up, inversely to the change in population size. Furthermore, in the prison system we expect a value a few factors higher. In order not to present a situation worse than reality, for the prison system we use a figure $c_1 = 1.5c_0 \times \frac{P}{A}$ where P is the population size of South Africa in the year 2015. Thus we obtain a value

$$c_1 = 0.00007893 \text{ year}^{-1}.$$

For the coefficient c_3 in comparison with the coefficient k (evaluated in "Other parameters" section 4.5.3.), since c_3 is multiplied by E we allow a nominal value

$$c_3 = k/(2A).$$

The treatment time is usually 6 months, see [24] for instance. This means that the rate of departure from the T-class per year is $2T$. In the model the flow out of the T-class into the E-class is assumed to be proportional to TI. For this reason we choose a value of c_2 at

$$c_2 = 2(10/A),$$

such that when I reaches a reasonably high value such as around $I = 0.1A$, then the average time spent in class T is approximately 6 months.

4.5.3 Other parameters

The progression rate from the exposed and infectious classes to treatment class are, $r_1 = 0.30$ and $r_2 = 0.5$ respectively [14]. Using data for the year 2015 obtained from [90], for the transfer rate k in South Africa (the entire population) from E to I we obtain a value 450 000/[0.8(55 million)]. The value used in [14] (i.e., 0.1) is a factor 10 times higher than

this rough calculation. For our purpose we use the value

$$k = 0.05 \ .$$

In a prison system where high quality screening is performed, the parameters $f_S, f_E,$ and f_I can be determined fairly accurately. In the absence of such facilities, the best estimates for these parameters are derived from the proportions, in the bigger population, of susceptible, latent and infectious. Thus we have the following:

$$f_S = 0.2, \ f_E = 0.74, \ \text{and} \ f_I = 0.06.$$

4.5.4 Initial conditions for simulation

We require initial conditions in order to run simulations that can be useful for projection of numbers in the future. According to the annual report of the Department of Correctional Services [72] we know the numbers of infectious TB patients and those under treatment. Thus we know $I(t_{15})$ and $T(t_{15})$, t_{15} denoting the time 31 March 2015. We also have a value for $N(t_{15}) = 159\ 563$. In order to find a reasonable split of the number

$$N(t_{15}) - [I(t_{15}) + T(t_{15})]$$

between $S(t_{15})$ and $E(t_{15})$, since $S+E+I+T = N,$ we recall from [90] that approximately only 20% of the South African population are susceptible, i.e., has never been infected with the TB bacterium. These observations lead to the following initial condition:

$$S(t_{15}) = 32000, \quad E(t_{15}) = 107000, \quad I(t_{15}) = 3500, \quad T(t_{15}) = 17100 \ .$$

4.6 Simulations

Through simulations we utilize the model to investigate the effect of interventions, by making future projections of the levels of TB prevalence in a prison system. We test the various scenarios, including the case of no inflow of infected individuals. Model system (4.1) has been evaluated for global stability in Theorem 4.4.1., which has assured us that

if the condition of the theorem is satisfied, then starting from any point in our model system (4.1), the disease will ultimately vanish from the prison population. We will also illustrate this result by means of simulation.

4.7 Results and discussion

We presented and motivated a model for the population dynamics of TB in a prison system. Parameter values for the South African prison population have been calculated from data in the open literature and these are summarized in Table 4.1 and Table 4.2. Theorem 4.4.1., guarantees the ultimate eradication of TB for a prison system. Sample simulations have been run, to be discussed below.

4.7.1 No inflow of infectives

We first provide an analysis of our model system without the inflow of the infectives, i.e., when $f_E = 0$ and $f_I = 0$. In this case we use the parameters from Table 4.1, while varying the values of the parameters c_i not listed in Table 4.1. The reason for varying these parameters is to be able to obtain different values of R_* to illustrate Theorem 4.4.1. Figure 4.1 (Case 1) shows the trend of all classes over 15 years with $c_1 = 0.00008$ and we compute $R_* = 1.72$. The graphs indicate that the disease will persist in the prison population.

Figure 4.2 (Case 2) shows variation of susceptible, exposed, infected and treated classes over 15 years, with $c_1 = 0.00004$ and in this case we obtain $R_* = 0.86$. Under these conditions, the theorem assures us that the TB disease will vanish.

In Figure 4.3, we show the infectious classes I of both Case 1 and Case 2 for comparison, and we stretch the time horizon to 60 years. For Case 2 the graph gives an indication of how fast the infectious class falls to zero. In order to make it vanish faster, further intervention is necessary to reduce the value of R_*.

Table 4.1: Model parameters and initial conditions

Parameter	Numerical value	Source
μ	0.18192	[33], [86]
d	0.01876	[88], [86]
r_1	0.30	[14]
r_2	0.50	[14]
k	0.05	[90], [14]
A	1600000	[86]
$S_{t_{15}}$	32000	[86]
$E_{t_{15}}$	107000	[86]
$I_{t_{15}}$	3500	[86]
$T_{t_{15}}$	17100	[86]

Table 4.2: Inflow and contact rates

Parameter	Numerical value	Source
c_1	0.00007893	[90]
c_2	$20/A$	[24]
c_3	$k/(2A)$	Estimated
f_S, f_E, f_I	$0.2, 0.74, 0.06$, respectively	[86]

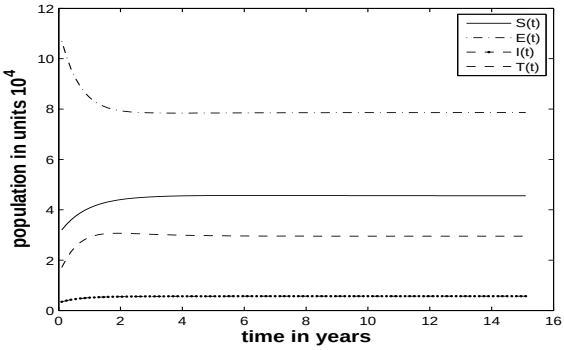


Figure 4.1: Prison population in different classes without the inflow of infectives and $R_* = 1.72$.

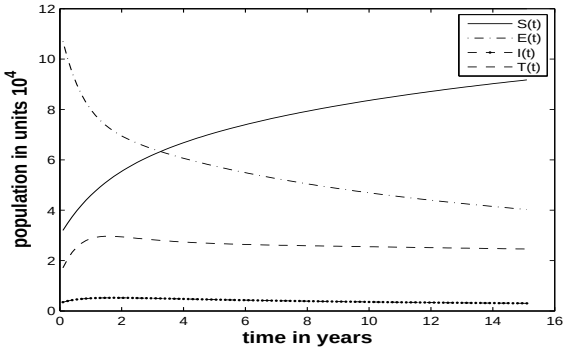


Figure 4.2: Infective class without the inflow of infectives for two cases $R_* = 1.72$, $R_* = 0.86$.

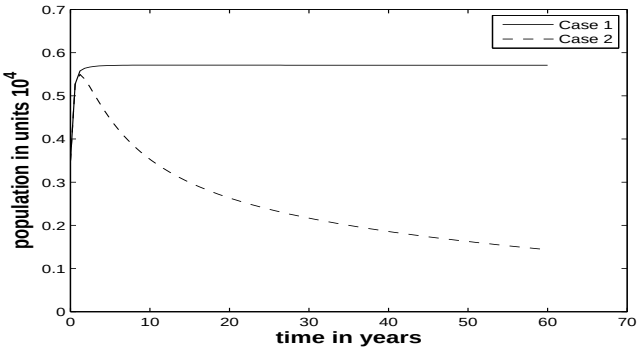


Figure 4.3: The prison population in different classes without the inflow of infectives and $R_* = 0.86$.

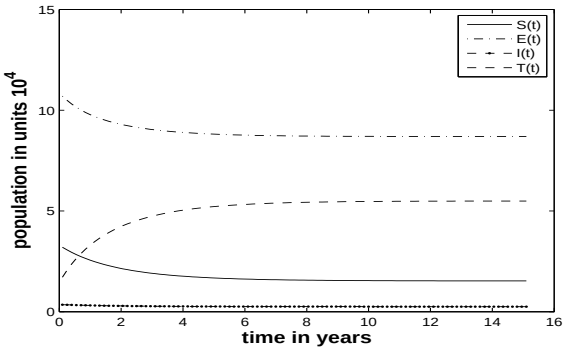


Figure 4.4: The different classes with the inflow of infectives at $f_E = 0.74$ and $f_I = 0.06$ (Case A).

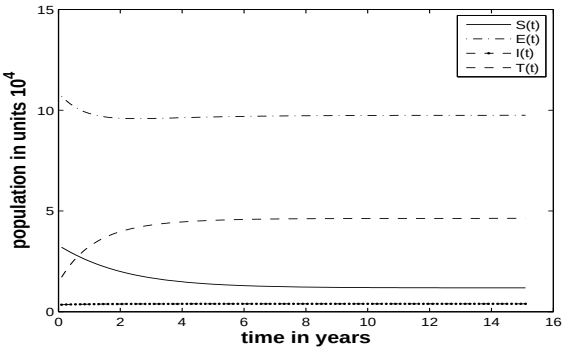


Figure 4.5: The different classes with reduced inflow of infectives $f_E = 0.77$, $f_I = 0.03$ (Case B).

4.7.2 General case

In this section, we will consider the general case, i.e., the model with the inflow of the infective into the prison population. We use the parameters from Table 4.1 and Table 4.2. We consider two scenarios for comparison. We first consider the case (call it case A) with $f_E = 0.64$ and $f_I = 0.06$. The curves are depicted in Figure 4.4 In Figure 4.5 (Case B) we use the inflow parameters at the values $f_E = 0.77$ and $f_I = 0.03$. The comparison shows the effect of reduction of inflow of infectious individuals. In order to better compare visually, the I-classes of Case A and Case B are drawn on the same system of axes in Figure 4.6. We see a remarkable drop in the I numbers when the inflow of infecteds is halved.

These graphs demonstrate the extent to which this model can be utilized when planning to roll out an intervention strategy.

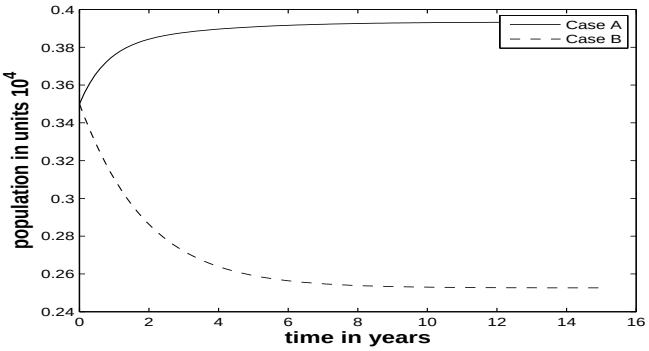


Figure 4.6: Comparison of Infective classes with $f_I = 0.06$ (Case A) and $f_I = 0.03$ (Case B).

4.8 Conclusion

We started by applying an existing population model of TB to a specific crowded environment (concentration camps). This model was adjusted to apply to prisons or prison systems. In this compartmental model we allowed for inflow of infectives into classes other than just the susceptible class. In fact, such inflow has to be accommodated in the model if there is TB infection in the ambient population. On the removal side it is important to note that release from prison is the main component, complemented by removal through death. We have described conditions (for mathematical stability of the disease free state of the system) that will cause the TB infection to vanish from the prison population. It was observed that if there is no inflow of infected individuals in a specific prison site or system then the disease will vanish from the prison provided that the numerical value of the invariant R_* is below unity.

For the case of the South African prison system, most of the crucial parameters of the model were calculated using data from public domain prison data. Other parameters, including initial conditions for computations, were obtained from data in various published literature, together with interpolation methods. As illustrated in the previous section,

the model can be utilized in making future projections of the levels of prevalence of TB, and to quantify the effect of interventions such as screening, treatment or reduction of transmission parameter values through improved living conditions for the inmates.

Chapter 5

A Stochastic TB Model for a Crowded Environment

A modification of the material in this chapter has been published in [1*b*].

Authors: Sibaliwe Maku Vyambwera and Peter Witbooi.

5.1 Abstract

We propose a stochastic compartmental model for the population dynamics of tuberculosis. The model is applicable to crowded environments such as for people in high density camps or in prisons. We start off with a known ordinary differential equation model, and we impose stochastic perturbation. We prove the existence and uniqueness of positive solutions of the stochastic model. We introduce an invariant generalizing the basic reproduction number and prove the stability of the disease free equilibrium when it is below unity or slightly higher than unity and the perturbation is small. Our main theorem implies that the stochastic perturbation enhances stability of the disease free equilibrium of the underlying deterministic model. Finally, we perform some simulations to illustrate the analytical findings and the utility of the model.

[1*b*] S. Maku Vyambwera and P. Witbooi, A stochastic TB model on a crowded environment, Journal of Applied Mathematics, 2018, 1-8 pages.

5.2 Introduction

Tuberculosis (TB) continues to be a major global health problem that is responsible for 1.5 millions deaths worldwide each year [76]. TB is most prevalent in communities with socio-economical problems but are not confined to such. The authors in [14, 57] associate TB infection with poverty and underdevelopment of some countries. It has been observed globally that one of the major factors driving TB infection is overcrowding. TB mostly occurs in poorest countries that are not developed and particularly where a population is overcrowded and in countries that are influenced by war. Conflict is the most common cause of large population displacement, which often results in relocation to temporary settlements such as camps. Factors including malnutrition and overcrowding in camp settings further increase the exposure to TB infection in these populations. Following up on a paper of Ssematimba et al. [57] regarding internally displaced people's camps in Uganda, Buonomo and Lacitignola [14] proposed a model that considers the dynamics of TB in concentration camps with a case study in Uganda. Another type of crowded environment which provides favourable conditions for TB to flourish, is prisons and more so if the prison is full beyond its capacity. There are more than 10 million inmates in prisons all over the world. The United States of America is in the top rank with about 2.2 million inmates while South Africa is in rank 11 [73]. South African prisons has approximately 160000 inmates in custody, of which 120000 are sentenced individuals while the rest are awaiting trial. This means that a large number of inmates are kept in remand population and some of them might not be found guilty at the end of the process, after having been exposed to high risk of TB infection.

Mathematical models have been used to model TB by considering the size of the area and how size and density affects the extent to which TB can invade a certain population

[18, 57, 7, 14, 8]. Quite obviously, considering the manner in which TB is aerially transmitted from one person to another, the prison situation provides favourable conditions for TB to flourish. TB is an infectious disease caused by bacillus Mycobacterium tuberculosis that most often affects the lungs (pulmonary TB) and can affect other parts as well such as brain, kidneys and spine (extrapulmonary TB) [75, 25]. The TB infection can take place when an infected individual releases some droplet nuclei which can remain airborne in any indoor area for up to four hours. The tubercle bacillus can persist in a dark area for several hours but it is exceptionally sensitive to sunshine. The risk of infection increases as the length of prison stay increases and the sentenced offenders are more likely to get TB infection as compared to the awaiting trial inmates.

Against this background Chapter 4 offers a model for the population dynamics of TB in a prison or prison system. In particular, it computes the parameters relevant to South Africa for the given model, using publicly available data. The current Chapter considers a stochastic form of the model in Chapter 4. It is well understood that stochastic differential equations (sde) attempts to reflect the effect of random disturbances in or on a system. A second reason for studying sde models is that it is good to know that a given model carries some resilience against small disturbances. In this case we consider the transmission parameters to be stochastically perturbed, similarly as in [65]. Stochastic perturbation has been studied by Yang and Mao [66], they considered a multi-group SEIR epidemic model. In most cases, it has been observed in [64, 66] that by introducing a stochastic perturbation into an unstable disease-free equilibrium model system of ordinary differential equation may lead to a system being stable in sde. Stochastic differential equation models for various diseases have been studied and similar work has been done in [65, 63, 66, 42, 38].

Our dissertation focuses on the analysis of TB in prisons as prisons have been recognized as institutions with very high TB burden as compared to a general population [74]. For a deterministic model of similar type, in Chapter 4, we computed parameter values pertain-

ing to South Africa. For the stochastic model in this Chapter the focus is on mathematical analysis. In Section 5.3, the model is introduced, based on the paper of Buonomo and Lacitignola [14]. The existence and uniqueness of the solution to the stochastic models is investigated by using the Lyapunov method in Section 5.4. Stability of the disease free equilibrium for stochastic models is shown in Section 5.5. We show our results by means of numerical simulations and conclude in Section 5.6.

5.3 The model

We introduce a stochastic compartmental model which is based on the deterministic model in the paper of Buonomo and Lacitignola [14]. We divide the population, which is of size $N(t)$ at time t, into four compartments namely, the class $S(t)$ of susceptible individuals $S(t)$, the class $E(t)$ of individuals infected with TB but who are not infectious, the class $I(t)$ of individuals infected with active TB who are infectious and the class $T(t)$ of individuals under treatment.

It is important to note that in general populations, removal of individuals out of the system is only by death. In this model, as in Chapter 4, the removal is by death or by discharge from prison, and the discharge is the dominant factor. This rate of removal is denoted by μ. The disease induced mortality rate is denoted by δ. Individuals are recruited into the susceptible class $S(t)$ at a constant rate μA. Susceptible individuals get infected with active TB at a rate c_1SI, where c_1 is the effective contact rate between the infectious and susceptible individuals. Individuals leave the exposed class $E(t)$ for infectious class $I(t)$ at rate kE. Exposed individuals who are infectious, move to the infectious class $I(t)$ at a rate c_3EI, where c_3 is the effective contact rate between the exposed and infectious individuals. Successfully treated individuals who were infectious move to exposed class at a rate c_2TI, where c_2 which is the effective contact rate between the treated and infectious individuals. Exposed and infectious individuals moves into class $T(t)$ at the rate r_1 and r_2, respectively.

Let us assume $(\Omega, \mathcal{F}, \{\mathcal{F}_t\}_{t\geq t_0}, \mathbb{P})$ to be a complete probability space with a filtration $\{\mathcal{F}_t\}_{t\geq t_0}$ which is right continuous. Let $W_i(t)$ $(i = 1, 2)$ be two mutually independent Brownian motions. Let $\sigma \geq 0$ be the intensity of the perturbation, which shall serve as the intensity of the perturbation. We also fix two other positive numbers p and q with $p + q = 1$, that will balance the perturbation. The stochastic perturbations are similar to those in the model of [65].

Model system 5.1:

$$\begin{aligned}
dS &= [f_S\mu A - c_1SI - \mu S]\,dt - \sigma(pESdW_1(t) + qISdW_2(t)),\\
dE &= [f_E\mu A + c_1SI + c_2TI - c_3EI - (\mu + r_1 + k)E]\,dt + \sigma pESdW_1(t),\\
dI &= [f_I\mu A + kE - (\mu + r_2 + \delta)I + c_3EI]\,dt + \sigma qISdW_2(t),\\
dT &= [r_1E + r_2I - c_2TI - \mu T]\,dt.
\end{aligned} \tag{5.1}$$

It is noticed that if $f_E + f_I + f_S = 1$ then system (5.1) does not have a disease free equilibrium. We will first investigate the model without the inflow of infected individuals, i.e., when $f_E = f_I = 0$. In this case the disease free state

$$E_0 = (S_0, E_0, I_0, T_0) = (A, 0, 0, 0)$$

is an equilibrium point. The underlying deterministic model of (5.1) is the model given by the same system of equations in the special case $\sigma = 0$, i.e., without stochastic perturbation as in (4.1). The underlying deterministic model coincides with the model of Buonomo and Lacitignola [14]. The basic reproduction number of the underlying deterministic model has already been computed in paper [14], and is given by the following formula:

$$R_0 = \frac{kc_1A}{\mu_1\mu_2}, \tag{5.2}$$

where $\mu_1 = \mu + r_1 + k$ and $\mu_2 = \mu + r_2 + \delta$.

We now present the following set:

$$\Delta_A = \left\{ x \in \mathbb{R}^4 : x_1, x_2, x_3, x_4 > 0 \quad x_1 + x_2 + x_3 + x_4 \leq A \right\}. \tag{5.3}$$

Remark 5.3.1 For the rest of this Chapter we will assume that the sample paths are restricted to Ω_0, which is defined as follows:

$$\Omega_0 = \{ w \in \Omega | \, (S(t, w(t)), E(t, w(t)), I(t, w(t)), T(t, w(t))) \in \Delta_A \text{ for all } t \geq 0 \}.$$

Lemma 5.3.2 [64] For $k \in \mathbb{N}$, let $X(t) = (X_1(t), X_2(t), ..., X_k(t))$ be a bounded $\mathbb{R}^k$-valued function and let $(t_{0,n})$ be any increasing unbounded sequence of positive real numbers. Then there is family of sequences $(t_{l,n})$ such that for each $l \in 1, 2, ..., k$, $(t_{l,n})$ is a subsequence of $(t_{l-1,n})$ and the sequence $X_l(t_{l,n})$ converges to a chosen limit point of the sequence $X_l(t_{l-1,n})$.

5.4 Existence and uniqueness of positive global solutions

Proposition 5.4.1 *Suppose that we have a solution*

$$X(t) = (S(t), E(t), I(t), T(t))$$

of the system (5.1) over an interval $t \in [0, \tau)$ with $S(0) + E(0) + I(0) + T(0) < A$ and with $X(t) \in \mathbb{R}^4_{++}$ for all $0 \leq t \leq \tau$, a.s., then $S(t) + E(t) + I(t) + T(t) \leq A$.

Proof. Given any solution $X(t)$ satisfying the conditions of Proposition 5.4.1, then we have the total population in system (5.1) obeying the following ordinary differential equation:

$$\begin{aligned} \frac{d(N - A)}{dt} &= -\mu(N - A) - \delta I \\ &\leq -\mu(N - A) \text{ a.s.} \end{aligned}$$

Therefore, similarly as in [65] for instance, $N(0) < A$ implies that $N(t) < A$ for all $t \in [0, \tau)$. □

In this section, we investigate the existence and uniqueness of global positive solutions of stochastic models by using the Lyapunov method. This method is popularly applied for such problems, see [60, 30] for instance.

Theorem 5.4.2. *There is a unique solution $(S(t), E(t), I(t), T(t)) \in \mathbb{R}^4_+$ to the system (5.1) on $t \geq 0$ for any given initial value $(S(0), E(0), I(0), T(0)) \in \mathbb{R}^4_+$, and the solution will remain in $\mathbb{R}^4_+$ with probability one, namely $(S(t), E(t), I(t), T(t)) \in \mathbb{R}^4_+$ for all $t \geq 0$ almost surely.*

Sketch of proof. Since the coefficients in (5.1) satisfy the Lipschitz condition locally, for any given initial value $(S(0), E(0), I(0), T(0))$, there is a unique local solution $(S(t), E(t), I(t), T(t))$ on $t \in [0, \tau_{\text{en}})$, where τ_{en} is the explosion time. Our aim is to show that this solution is global and positive almost surely, i.e., $\tau_{\text{en}} = \infty$ a.s.
Let $r_0 > 0$ such that $S(0), E(0), I(0), T(0) > r_0$. For each integer $r \leq r_0$, we define the stopping times

$$\tau_r = \inf \{t \in [0, \tau_{en}] : S(t) \leq r \text{ or } E(t) \leq r \text{ or } I(t) \leq r \text{ or } T(t) \leq r\}.$$

Let

$$\tau = \lim_{r \to 0} \tau_r = \inf \{t \in [0, \tau_{en}) : S(t) \leq 0 \text{ or } E(t) \leq 0 \text{ or } I(t) \leq 0 \text{ or } T(t) \leq 0\}.$$

For this purpose we introduce a function V as follows:

$$V = \ln \frac{A}{S} + \ln \frac{A}{E} + \ln \frac{A}{I} + \ln \frac{A}{T}. \tag{5.4}$$

We note that by Proposition 5.4.1, each of the terms

$$\ln\frac{A}{S}, \ln\frac{A}{E}, \ln\frac{A}{I}, \ln\frac{A}{T}$$

are positive, and

$$\lim_{u\to 0^+}\frac{A}{u} = +\infty.$$

By Itô's formula, for all $t \geq 0,\ s \in\ [0, t\wedge\tau_r]$, we have

$$\begin{aligned} dV(X(s)) &= -\frac{1}{S(s)}\Big(f_S\mu A - c_1S(s)I(s) - \mu S(s) + \frac{(\sigma pE(s))^2}{2} + \frac{(\sigma qI(s))^2}{2}\Big)ds \\ &- \frac{1}{E(s)}\Big(f_E\mu A + c_1S(s)I(s) + c_2T(s)I(s) - c_3E(s)I(s) - (\mu + r_1 + k)E(s) \\ &+ \frac{(\sigma pS(s))^2}{2}\Big)ds \\ &- \frac{1}{I(s)}\Big(f_I\mu A + kE(s) - (\mu + r_2 + \delta)I(s) + c_3E(s)I(s) + \frac{(\sigma qS(s))^2}{2}\Big)ds \\ &- \frac{1}{T(s)}\Big(r_1E(s) + r_2I(s) - c_2T(s)I(s) - \mu T(s))\Big)ds \\ &+ \sigma p(E(s) - S(s))dW_1(s) + \sigma q(I(s) - S(s))dW_2(s). \end{aligned}$$

After eliminating some negative terms we have the following inequality:

$$dV(X(s)) \leq M_1ds + dM_2(s), \tag{5.5}$$

where

$$M_1 = 4\mu + r_1 + r_2 + k + d + I(c_1 + c_2) + c_3(E + I) + \frac{\sigma^2}{2}(p^2E^2 + q^2I^2) + \frac{1}{2}(\sigma(p + q)S)^2$$

and

$$dM_2(s) = \sigma p(E - S)dW_1(s) + \sigma q(I - S)dW_2(s).$$

Taking the integral in (5.5) from 0 to $t\wedge\tau_{r0}$, we have:

$$\int_0^{t\wedge\tau_r} dV(X(s)) \ \leq\ \int_0^{t\wedge\tau_r} M_1ds + \int_0^{t\wedge\tau_r} dM_2(s).$$

By taking expectations, the latter inequality yields:

$$\mathbb{E}[V(S(t\wedge\tau_r),E(t\wedge\tau_r),I(t\wedge\tau_r),T(t\wedge\tau_r))]\leq V(X(0))+M_1t. \tag{5.6}$$

Now we note that

$$\begin{aligned}\mathbb{E}V[S(t\wedge\tau_r),E(t\wedge\tau_r),I(t\wedge\tau_r),T(t\wedge\tau_r)] &= \mathbb{E}[\Psi_{(\tau_r\leq t)}V(S(t\wedge\tau_r),E(t\wedge\tau_r),I(t\wedge\tau_r),T(t\wedge\tau_r))]\\ &+ \mathbb{E}[\Psi_{(\tau_r>t)}V(S(t\wedge\tau_r),E(t\wedge\tau_r),I(t\wedge\tau_r),T(t\wedge\tau_r))]\\ &\geq \mathbb{E}[\Psi_{(\tau_r\leq t)}V(S(\tau_r),E(\tau_r),I(\tau_r),T(\tau_r))],\end{aligned}$$

where $\Psi_{(.)}$ is the indicator function. If $\tau_r<\infty$, then there are some components of $S(\tau_r),E(\tau_r),I(\tau_r),T(\tau_r)$ equal to r, therefore $(S(\tau_r),E(\tau_r),I(\tau_r),T(\tau_r))\geq\ln(\frac{A}{r})$.
Thus we have

$$\mathbb{E}[V(S(t\wedge\tau_r),E(t\wedge\tau_r),I(t\wedge\tau_r),T(t\wedge\tau_r))]\geq\ln\Big(\frac{A}{r}\Big)\mathbb{P}(\tau_r\leq t).$$

Combining (5.5) and (5.6) gives, for all $t\geq 0$,

$$\mathbb{P}(\tau\leq t)\leq\frac{V(X(0))+M_1t}{\ln\Big(\frac{A}{r}\Big)}$$

Letting $r\to 0$, we obtain, for all $t\geq 0$, $\mathbb{P}(\tau\leq t)=0$. Hence $\mathbb{P}(\tau=\infty)=1$. As $\tau_{en}=\tau=\infty$ a.s. Therefore, the solution of model (5.1) will not explode at a finite time with probability one. This completes the proof. □

5.5 Stability of disease free equilibrium

Let us choose a positive number a_3 and two non-negative numbers a_1 and a_2. Specific values will be assigned to these numbers in different analyses.
Let us assume that

$$a_3\geq\frac{k}{\mu_1}. \tag{5.7}$$

Now we define a stochastic process $Z(X(t))$

$$Z(X(t)) = a_1(A - S(t)) + a_2T(t) + a_3E(t) + I(t) \tag{5.8}$$

and a process

$$V(X(t)) = \ln Z(X(t)). \tag{5.9}$$

For $w \in \Omega_0$, we note that $Z(X(t)) > 0$ and therefore $V(X(t))$ is defined for all $w \in \Omega_0$. For convenience, we introduce the variables:

$$Q_Z = \frac{A-S}{Z},\ T_Z = \frac{T}{Z},\ E_Z = \frac{E}{Z},\ I_Z = \frac{I}{Z}$$

and for a stochastic process $x(t)$ we shall write

$$\langle x \rangle_s = \frac{1}{s}\int_0^s x(u)du.$$

5.5.1 On the Lypunov exponent of Z

The Lyapunov exponent of a quantity $q(t)$, $t \geq 0$ is defined as

$$\limsup_{t\to\infty} \frac{1}{t} \ln q(t).$$

The infinitesimal generator $\mathcal{L}$ of the system (5.1) (see Øksendal [53]) will play an important role in the sequel. Now we can calculate $\mathcal{L}V$ and express it as a function of $X(t)$. From Lemma 5.3.2 it follows that for each $w \in \Omega_0$ there is an increasing sequence (t_n^w) with the following properties (but we shall suppress the w and write (t_n)):
For every $w \in \Omega$,

$$\lim_{n\to\infty} \langle \mathcal{L}V(X) \rangle_{t_n} = \limsup_{t\to\infty} \langle \mathcal{L}V(X) \rangle_t \tag{5.10}$$

and the limits below, which shall be denoted by q, τ, j, i and define below do exist:

$$q = \lim_{n\to\infty} \langle Q_Z \rangle_{t_n},\ \tau = \lim_{n\to\infty} \langle T_Z \rangle_{t_n},\ j = \lim_{n\to\infty} \langle E_Z \rangle_{t_n},\ i = \lim_{n\to\infty} \langle I_Z \rangle_{t_n}. \tag{5.11}$$

We write

$$\Lambda = \limsup_{t\to\infty} \langle \mathcal{L}V(X) \rangle_t$$

Let

$$c_* = \max\left\{c_1,\ c_2,\ c_3\left(\frac{\mu}{k} - 1\right)\right\}.$$

We can write

$$\int_0^t dV = \int_0^t \mathcal{L}V dt + M(t) \tag{5.12}$$

where

$$M(t) = \int_0^t \frac{1}{Z}\sigma p(E-S)dW_1 + \int_0^t \frac{1}{Z}\sigma q(I-S)dW_2$$

and we note that by the strong law of large numbers [38],

$$\lim_{n\to\infty} \frac{1}{t}M(t) = 0 \ \ a.s.$$

Therefore

$$\begin{aligned}\limsup_{t\to\infty} \frac{1}{t}V(X(t)) &= \limsup_{t\to\infty} \frac{1}{t}\int_0^t \mathcal{L}V(X(s))ds\ a.s. \\ &= \lim_{n\to\infty} \frac{1}{t_n}\int_0^{t_n} \mathcal{L}V(X(s))ds\ a.s. \end{aligned} \tag{5.13}$$

Now we expand $\mathcal{L}V$:

$$\begin{aligned}\mathcal{L}V &= \frac{-a_1}{Z}[\mu A - c_1 SI - \mu S] - \frac{a_1^2\sigma^2}{2Z^2}(p^2E^2S^2 + q^2I^2S^2) + \frac{a_2}{Z}[r_1E + r_2I - c_2TI - \mu T] \\ &+ \frac{a_3}{Z}[c_1SI + c_2TI - c_3EI - (\mu + r_1 + k)E] - \frac{a_3^2}{2Z^2}\sigma^2(p^2E^2S^2) \\ &+ \frac{1}{Z}[kE - (\mu + r_2 + \delta)I + c_3EI] - \frac{1}{2Z^2}(\sigma^2q^2I^2S^2) - a_1a_3(\sigma pES)^2 - a_1(\sigma qIS)^2.\end{aligned}$$

With regard to the calculation of $\mathcal{L}V$ we note the following:

$$\begin{aligned}a_3I_Z\{c_1S + c_2T - c_3E\} + c_3I_ZE &= a_3I_Z\left\{c_1S + c_2T + c_3(\frac{1}{a_3} - 1)E\right\} \\ &\leq a_3I_Zc_*(S + T + E) \\ &\leq a_3I_Zc_*A.\end{aligned}$$

Therefore,

$$\begin{aligned}\mathcal{L}V &\leq a_3I_Zc_*A - I_Z(\mu_2 - a_2r_2) + E_Z(a_2r_1 - a_3\mu_1 + k) - a_2\mu T_Z \\ &+ I_Z(a_1c_1S - a_2c_2T) - a_1\mu Q + B,\end{aligned}$$

where

$$\begin{aligned} B &= -\frac{(a_1\sigma)^2}{2}\left[(pE_ZS)^2+(qI_ZS)^2\right]-\frac{a_3^2}{2}\left[(\sigma pE_ZS)^2\right] \\ &- \frac{1}{2}\left[(\sigma qI_ZS)^2\right]-a_1a_3(\sigma pE_ZS)^2-a_1(\sigma qI_ZS)^2. \end{aligned}$$

This yields the inequality:

$$\mathcal{L}V \leq I_Z((a_1c_1+a_3c_*)A-\mu_2+a_2r_2)+E_Z(k-a_3\mu_1+a_2r_1)-a_2\mu_2T_Z-a_1\mu Q_Z+B. \quad (5.14)$$

In the expression for B, if we ignore the multiples of a_1 (they are negative), then we obtain an inequality:

$$B \leq -\frac{(\sigma S)^2}{2}\left\{(pa_3E_Z)^2+(qI_Z)^2\right\}.$$

5.5.2 Stability theorems

We now introduce another invariant R_σ, which enables us to formulate stability theorems for the stochastic model (5.1). As a corollary of the main theorem we can deduce a global stability theorem for disease free equilibrium. Let

$$R_\sigma = \frac{kc_*A}{\mu_1\mu_2}.$$

In the model of Buonomo and Lacitignola [14], we have backward bifurcation at $R_0 = 1$. Therefore, the condition $R_0 < 1$ does not imply global stability of the underlying deterministic model. As a corollary to the main theorem, Theorem 5.5.2.2, will follow that for the model in [14] the disease free equilibrium is globally asymptotically stable when $R_\sigma < 1$. In preparation for our main theorem we introduce a function $h(x)$ as follows:

$$h(x) = \frac{p^2(1-x)^2+q^2x^2}{x}; \quad x>0.$$

Then

$$\lim_{x\to\infty} h(x) = \infty \text{ and if } q \neq 0, \text{ then } \lim_{x\to 0^+} h(x) = \infty. \quad (5.15)$$

Also we note that:

$$h^{'}(x) = \frac{1}{x^2}[-p^2 + x^2].$$

Therefore $h^{'}(x) = 0 \quad \Leftrightarrow \quad x = p$ and we know that $p \leq 1$. Since h has only one critical value on the interval $(0, \infty)$, in view of (5.15) it follows that the critical point is an absolute minimum of h on the interval $(0, \infty)$.

Therefore the minimum value $h_{\min}$ of h over $[0, 1]$ is:

$$\begin{aligned} h_{\min} &= \frac{p^2(1-p) + q^2 p}{p} \\ &= p(1-p) + (1-p^2) \\ &= (1-p)(p+1+p) \\ &= (1-p)(1+2p). \end{aligned}$$

Proposition 5.5.2.1. *If*

$$R_\sigma - \frac{(\sigma A)^2 h_{\min}}{2\mu_2} < 1, \tag{5.16}$$

then (I, E) *converges exponentially to zero almost surely.*

Proof. We introduce the function V of equation (5.9), with $a_1 = a_2 = 0$. Now note that (5.16) is equivalent to

$$\frac{kc_*A}{\mu_1} - \frac{(\sigma A)^2 h_{\min}}{2} - \mu_2 < 0. \tag{5.17}$$

We choose a number $\epsilon > 0$ sufficiently small such that

$$\frac{k+\epsilon}{\mu_1} c_* A - \mu_2 - \frac{(\sigma A)^2}{2}\ h_{\min} < 0.$$

Now we choose

$$a_3 = \frac{k+\epsilon}{\mu_1}.$$

From the inequality (5.14) it follows that

$$\mathcal{L}V \ \leq \ [a_3 c_* A - \mu_2] I_Z + [k - a_3\mu_1] E_Z - B_1,$$

where

$$B_1 = \frac{(\sigma A)^2}{2}\left\{p^2(a_3 E_Z)^2 + (qI_Z)^2\right\}.$$

Note that we can express B_1 as follows:

$$B_1 = \frac{(\sigma A)^2}{2}\left\{p^2(1-I_Z)^2 + (qI_Z)^2\right\} = \frac{(\sigma A)^2}{2} I_Z h(I_Z). \tag{5.18}$$

Therefore, we have

$$B_1 \geq \frac{(\sigma A)^2}{2} I_Z h_{\min},$$

and consequently,

$$\mathcal{L}V \leq [a_3 c_* A - \mu_2 - \frac{(\sigma A)^2}{2} h_{\min}]I_Z + [k - a_3\mu_1]E_Z.$$

Therefore

$$\Lambda \leq [a_3 c_* A - \mu_2 - \frac{(\sigma A)^2}{2} h_{\min}]i + \epsilon j$$

where i and j are defined in (5.11). Since i and j cannot both be zero, it follows that $\Lambda < 0$.

This completes the proof. □

Theorem 5.5.2.2. (a) *If (E(t), I(t)) almost surely converges exponentially to 0, then*:

$$\lim_{t\to\infty} S(t) = A \text{ (a.s.)} \quad \text{and} \quad \lim_{t\to\infty} T(t) = 0 \text{ (a.s.)}.$$

(b) *If*

$$R_\sigma - \frac{(\sigma A)^2 h_{\min}}{2\mu_2} < 1,$$

then disease free equilibrium is almost surely exponential stable.

Proof. (a) Suppose on the contrary that we have :

$$\lim_{t\to\infty}(A - S(t)) + T(t) > 0 \text{ (a.s.)}.$$

Let Z be the same as in (5.8), with $a_1 = a_2 = a_3 = 1$. Since $(E(t), I(t))$ almost surely converges exponentially to 0 while

$$\lim_{t\to\infty}(A - S(t)) + T(t) > 0 \text{ (a.s.)},$$

it follows that $j = 0$ and $i = 0$ (a.s.). Thus from the inequality (5.14) it follows that

$$\Lambda \leq -\mu_2 T_Z - \mu Q_Z \text{ (a.s.)}.$$

Therefore $\Lambda < 0$. This implies that Z converges to 0, and thus

$$\lim_{t\to\infty}(A - S(t)) + T(t) = 0 \text{ (a.s.)},$$

which is a contradiction. This completes the proof of (a).

(b) This follows from Proposition 5.5.2.1. and Theorem 5.5.2.2.(a). □

5.6 Numerical Simulation

The simulations presented here illustrate the analytical results of our model in (5.1). The parameter values have already been calculated in the paper Chapter 4, by using real data, mostly from [86, 88, 90]. We will now use those parameter values, listed in Table 4.1 and Table 4.2 in Chapter 4, and vary the value of c_1 and σ in order for us to be able to find different values of R_0 and R_σ. We first consider a model without the inflow of infective cases and then with the inflow of infective cases.

We give some numerical simulations to show different dynamic outcomes of the deterministic model and its stochastic version. We illustrate by means of simulations, the possible disease eradication in the absence of the inflow of infectives. This will be shown in Figure 4.1, 4.2 and 4.3. Over these three cases we vary the value of c_1 and σ so as to obtain different values of R_0 and R_σ.

In Figure 5.1, we present a case in which we take $c_1 = 0.000065$, $\sigma = 0.04$ and then we obtain $R_0 = 1.3917$ and $R_\sigma = 1.1653$. This situation does not satisfy the conditions of Theorem 5.5.2.2.(a), and indeed the I-class does not appear to converge to zero. This means that the disease will persist in our prison population.

In Figure 5.2, we notice that when the perturbation is sufficiently big, then the disease will possibly be eliminated for a stochastic model even if for the deterministic model it does not seem be the case. We have chosen $c_1 = 0.000062$, $\sigma = 0.05$ and then we calculate $R_0 = 1.3275$ and $R_\sigma = 0.9737$.

Figure 5.1: $R_0 = 1.3917, R_\sigma = 1.1653$, and $c_1 = 0.000065$, $\sigma = 0.04$.

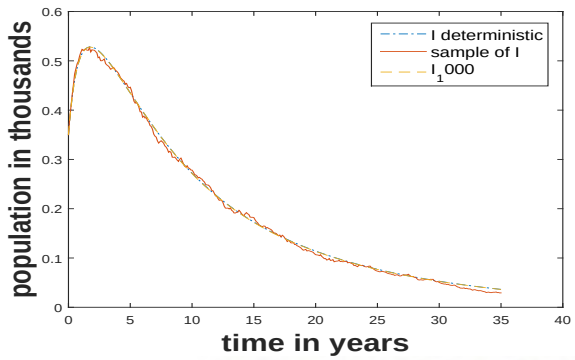
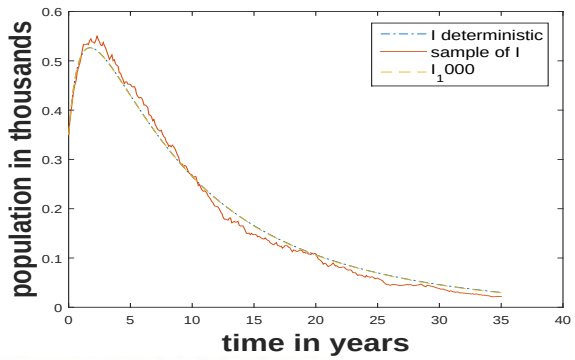


Figure 5.2: $R_0 = 1.3275, R_\sigma = 0.9737$, and $c_1 = 0.000062$, $\sigma = 0.05$.



In Figure 5.3, a choice of $c_1 = 0.000054$ and $\sigma = 0.04$, yields $R_0 = 1.1562$, and $R_\sigma = 0.9298$. This choice of parameters satisfies the conditions in Theorem 5.5.2.2.(a), and surely the infectious class seem to converge to zero.

We now study model (5.1) with the inflow of infectives and present a sample computation. We choose $c_1 = 0.00007893$ as in Table 1 and $\sigma = 0.04$. Then the values of R_0 and R_σ can be calculated as $R_0 = 1.6900, R_\sigma = 1.4635$. In Figure 5.4, it is observed that when the basic reproduction number for the underlying deterministic model is above unity, then the disease will persist into our prison system. It is also seen that the inflow of infectives

Figure 5.3: $R_0 = 1.1562$, $R_\sigma = 0.9298$, and $c_1 = 0.000054$, $\sigma = 0.04$.

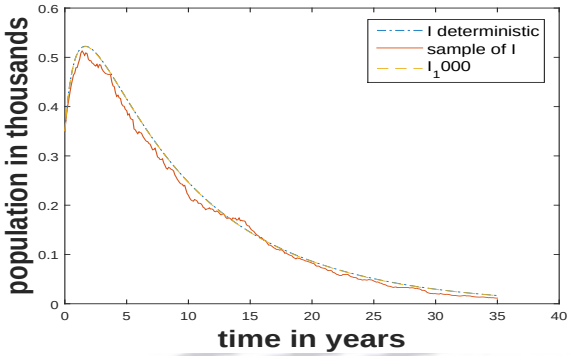
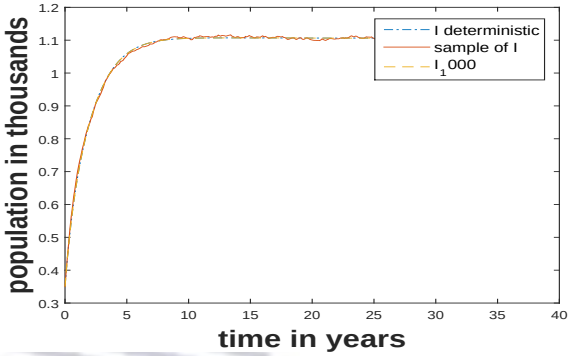


Figure 5.4: $R_0 = 1.6900, R_\sigma = 1.4635$, and $c_1 = 0.00007893$, $\sigma = 0.04$ with $f_S = 0.2$, $f_E = 0.74$, $f_I = 0.06$.



cases play a part in influencing the number of TB infected cases in the prison system.

5.7 Conclusion

A stochastic $SEIT$ model was presented and analysed to assess the impact of active TB on a crowded environment, specifically in prisons. We started off by verifying that there is a unique global positive solution for the system of stochastic differential equation in (5.1). It was noted that whenever the basic reproduction number is significantly greater than unity then the disease will persist in the prison population through our simulations in Figure 5.1 and Figure 5.2. It has also been observed for a stochastic model that when the perturbation is sufficiently big then the disease tends to vanish and this can be seen in Figure 5.2. It is more important to study smaller perturbation. It has been observed that whenever $R_\sigma < 1$, then I and E almost surely converge exponentially to zero in step with Theorem 5.5.2.2.(a), in the absence of the inflow of infective. These results can also be seen in Figure 5.3. By introducing the inflow of infectives cases into the prison system, TB remains endemic, as can be seen in Figure 5.4. By screening the inflow on admission and providing for them a separate accommodation, TB infection in a prison system can be greatly reduced.

Chapter 6

A two-group model for population dynamics of TB in a crowded environment

6.1 Abstract

We introduce a two-group epidemic model of tuberculosis that considers the dynamics of TB in a prison system. The total population of inmates are considered as consisting of two-groups: the sentenced inmates and those inmates who are awaiting trial and does not serve a sentence as yet. The two threshold parameters for local stability are computed and analysed. We also discuss the global stability of the disease free equilibrium by using a Lyapunov function. We apply the model to South African reported data on tuberculosis and observe a good agreement between the model prediction and the data. Numerical results are presented to illustrate analytical results. The two-group model gives better accuracy than the model in Chapter 4.

Keywords: Two-group TB model, Inflow of infecteds, Removal rate, Sentenced inmates, Remand inmates, Cross-effect.

6.2 Introduction

Infectious diseases contribute substantially to the global burden of disease and are major public health issues worldwide. Overcrowding still continues to be a major problem in South African correctional centres which provides ideal conditions for the rapid spread of contagious diseases such as TB in particular. Following up on the annual report of the Judicial Inspectorate for Correctional Services and Chapter 4 and 5 (regarding the increase of inmates), on 31 March 2018, correctional services had about 164 000 inmates in 243 correctional facilities [94]. The prison population has drastically increased during the 2017/2018 financial year as compared to the previous 10 year period, regardless of the effort of the criminal justice sector to reduce the population to manageable levels. The remand detainees consisted of about 46000 and the sentenced offenders had 118 000 out of 118 723 bed capacity including simple foam mattresses and not raised beds.

According to the Department of Correctional Services (DCS) report, the region with the highest number of remand detainees were Western Cape followed by Gauteng. These overcapacitated correctional centres create difficulties for South Africa to guarantee conditions of detention that are consisted with human dignity. Overcrowding compromises the inmates access to physical exercise, accommodation, nutrition, educational programs and medical treatment [87, 82]. Moreover, correctional centres vary from unit to unit and this depends on the sentenced and remand population. For example, the remand sections were found to have terrible health conditions and broken infrastructure as compared to those occupied by sentenced offenders [81, 82]. Sentenced inmates are aware that they will spend time in these units and they take more care when using the facilities. Health conditions for sentenced offenders and remand detainees housed in a single cell were found to be much better as compared to a communal cell. Following from Chapter 4, regarding the dynamics of TB in crowded environments such as South African prison, it has been discovered that the spread of TB tends to flourish in crowded places such as prison. The compartmental model in Chapter 4 considers the inflow of susceptible, exposed and

TB infectives into the prison system. As compared to a general population in which the removal is only by death, the model (4.1) has considered two ways of removal which is by death or by discharge from prison, and the discharge is the dominant factor. The model computes the parameters relevant to South African data. Other papers that have contributed to this line of work are [14, 57, 7]. In-particular, Buonomo and Lacitignola considered the dynamics of TB in concentration camps with a case study in Uganda.

The department of correctional services continues to provide health care services such as nutrition, hygiene, pharmaceutical services and primary health care in the prison population. In 2013, 4675 inmates out of 6233 were treated and 1709 inmates out of 2057 were treated in 2014 [80]. The support from Department of Health and partners such as National Strategic Plan improved the reduction of infecteds. It was clearly observed that there has been a significant decrease of inmates infected with TB from 2013 to 2016. In 2015 the department of correctional services managed to treat 1239 out of 1485 inmates infected with TB, and 1034 inmates of 1250 in 2016 [82]. The offenders who were released before completing their treatment were also under supervision which was provided by DCS. Moualeu et al. [51] produced a paper of modeling of TB and they put a huge effect on parameter identification based on the data in Cameroon. It was observed that an increase in the proportion of individuals having access to medical facilities has a large impact of reducing the disease burden over time.

According to legislation for Correctional Service, inmates on admission must all be medically assessed before collaborating with the prison population, but due to shortage of medical staff especially after hours, this was not always possible. The inmates usually spend their first night in a communal cell and will be ordered to consult the nurse within 24 hours after admission. TB is a chronic disease caused by the bacillus *Mycobacterium tuberculosis* and spreads from person to person through air [75]. A paper of Jia et. al [29] considered the impact of immigration on the epidemiology of tuberculosis by using mathematical models. The authors present a theoretical framework to investigate how

infectious individual among immigrants can lead to outbreaks of TB in host areas. They performed a qualitative investigation of the long term transmission dynamic behaviour of TB in host with large number of immigrants. Quite obviously, it was noticed that the disease cannot be eradicated even though the basic reproduction number is less than unity due to the immigrants.

In this Chapter, we propose a two-group deterministic compartmental model TB model that considers the dynamics of TB in a prison system. Our model divides the prison population into two-groups which are sentenced individuals and remand individuals. Both models allow the inflow of infectives. This division of the prison system will enable us to more accurately monitor the dynamics of the TB disease of each group. In our model we assume that there is interaction between susceptible individuals and infectious individuals. The infectious individuals do not migrate from one sub-population to the other due to medical reasons. We will compute the parameters of the model by using South African data as in Chapter 4. Because it is a two-group system we split the parameters accordingly. Furthermore, we use mathematical analysis such as Lyapunov function combined with simulations to investigate the behaviour of the model.

6.3 The model

In order for us to investigate the dynamics of TB in a prison population, we divide the total prison population (N) into sentenced sub-population (N_s) and the awaiting (remand) sub-population (N_a). We further subdivide the sentenced sub-population into compartments such as susceptible class (S), exposed class (E), infectious class (I), treatment class (T) and the awaiting sub-population as susceptible class (U), exposed class (L), infectious class (J) and treatment class (H). Susceptible individuals are recruited into the sentenced and awaiting sub-population at a constant rate ρA and μB, respectively. We assume that there is inflow of susceptible, exposed and infected individuals will appear into the susceptible class, exposed class and the infected class at a rate

$f_S\rho A, f_E\rho A, f_I\rho A$ and $f_U\mu B, f_L\mu B, f_J\mu B$, respectively into the sentenced and the remand sub-population. We assume that $f_S + f_E + f_I = 1$ and $f_U + f_L + f_J = 1$. People under TB treatment are considered to be unfit to commit crime. We assume that there is no inflow of infectives into the treatment class for any of the sub-population groups. The model is described by eight ordinary differential equation as follows:

$$\begin{aligned}
\dot{S} &= f_S\rho A - \alpha S(I + \varphi J) - \rho S, \\
\dot{E} &= f_E\rho A + \alpha S(I + \varphi J) - \zeta E(I + \varphi J) - (\rho + k)E + gT, \\
\dot{I} &= f_I\rho A + \zeta E(I + \varphi J) + kE - (\rho + \delta + p)I, \\
\dot{T} &= pI - (\rho + g)T, \\
\dot{U} &= f_U\mu B - \beta U(J + \psi I) - \mu U, \\
\dot{L} &= f_L\mu B + \beta U(J + \psi I) - \xi L(J + \psi I) - (\mu + \iota)L + hH, \\
\dot{J} &= f_J\mu B + \xi L(J + \psi I) + \iota L - (\mu + \gamma + q)J, \\
\dot{H} &= qJ - (\mu + h)H. \qquad (6.1)
\end{aligned}$$

It is important to note that in general populations, removal of individuals out of the system is only by death. In this model, as in model (4.1), removal is by death or by discharge from prison. These rates of removal are denoted by ρ and μ, respectively. The rate at which individuals die due to TB disease is denoted by δ and γ in each sub-population, respectively. Susceptible individuals who are in the sentenced and awaiting sub-population acquire TB infection at a rate $\alpha S(I + \varphi J)$ and $\beta U(J + \psi I)$ and move into the exposed classes E and L, respectively. Parameters α and β are the transmission coefficients from susceptible classes to the exposed class, respectively. The cross-effect between the sentenced and awaiting individuals is represented by φ and ψ, respectively. Exposed individuals leave the exposed class (E) and (L) for infectious class (I) and (J) at a rate kE and ιJ, respectively. Exposed individuals who become infectious in the sentenced and awaiting sub-population move to the infectious class at a rate $\zeta E(I + \varphi J)$ and $\xi L(J + \psi I)$, where ζ and ξ represent the transmission coefficient from exposed class to the infectious class, respectively. Infectious individuals receive treatment and move to

the treatment class at a rate pI and qJ, where p and q are treatment rates, respectively. Successfully treated individuals move to exposed class at a rate gT and hH, respectively.

The total population for sentenced and awaiting sub-population is given by

$$N_s(t) = S(t) + E(t) + I(t) + T(t)$$

and

$$N_a(t) = U(t) + L(t) + J(t) + H(t),$$

respectively.

It is important to prove that all the state variables of system (6.1) are non-negative for all time. From model system (6.1), we get

$$\frac{dN_s}{dt} = \rho(A - N_s) - \delta I, \tag{6.2}$$

$$\frac{dN_a}{dt} = \mu(B - N_a) - \gamma J, \tag{6.3}$$

respectively. Thus we have $\frac{dN_s}{dt} < 0$ for $N_s > A$ and $\frac{dN_a}{dt} < 0$ for $N_a > B$. We consider all solutions of system (6.1) in the following positively invariant subset $\Lambda \in \mathbb{R}^8$:

$$\Lambda = \Lambda_s + \Lambda_a,$$

where

$$\begin{aligned} \Lambda_s &= \{(S, E, I, T) \mid S, E, I, T \in [0, \infty), S + E + I + T \leq A\}, \\ \Lambda_a &= \{(U, L, J, H) \mid U, L, J, H \in [0, \infty), U + L + J + H \leq B\}. \end{aligned}$$

We first analyse the model without the inflow of infecteds, i.e., when

$$f_E = f_I = f_L = f_J = 0, \text{ and } f_S = f_U = 1,$$

and a disease free equilibrium does exist. Model system (6.1) has a disease free equilibrium

$$\begin{aligned} P_0^* &= (S_0, E_0, I_0, T_0, U_0, L_0, J_0, H_0) \\ &= (P_{s0}^*, P_{a0}^*), \end{aligned}$$

where $P^*_{s0} = (A, 0, 0, 0)$ and $P^*_{a0} = (B, 0, 0, 0)$. Convergence to P^*_0 means that the disease will die out in the prison system. Similary with the convergence to P^*_{s0} which is the sentenced subgroup and P^*_{a0} the awaiting trial individuals.

The basic reproduction number, R_0 of model system (6.1), is computed by using the next generation matrix approach which has been developed by Van den Driessche and Watmough [59]. By using the notation in [59], the matrices F and V, for new infection term and the remaining transfer terms, respectively, are given by:

$$F = \begin{pmatrix} 0 & \alpha_1 A & 0 & 0 & \alpha_1 \varphi A & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \beta_1 \psi B & 0 & \beta_1 B & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

and

$$V=\begin{pmatrix} \rho+k & 0 & -g & 0 & 0 & 0 \\ -k & \rho+\delta+p & 0 & 0 & 0 & 0 \\ 0 & -p & \rho+g & 0 & 0 & 0 \\ 0 & 0 & 0 & \mu+\iota & 0 & -h \\ 0 & 0 & 0 & -\iota & \mu+\gamma+q & 0 \\ 0 & 0 & 0 & 0 & -q & \mu+h \end{pmatrix}.$$

Thus we have:

$$FV^{-1}=\begin{pmatrix} \frac{k\alpha A(\rho+g)}{gk(\rho+\delta)+\rho\rho_0\rho_1} & \frac{\alpha A(\rho+g)(\rho+k)}{gk(\rho+\delta)+\rho\rho_0\rho_1} & \frac{k\alpha gA}{gk(\rho+\delta)+\rho\rho_0\rho_1} & \frac{\alpha\iota\psi A(\mu+h)}{h\iota(\mu+\gamma)+\mu\mu_0\mu_1} & \frac{\alpha\psi A(\mu+h)(\mu+\iota)}{h\iota(\mu+\gamma)+\mu\mu_0\mu_1} & \frac{\alpha\iota\psi hA(\rho+g)}{h\iota(\mu+\gamma)+\mu\mu_0\mu_1} \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{\beta\psi kB(\rho+g)}{gk(\rho+\delta)+\rho\rho_0\rho_1} & \frac{\beta\psi B(\rho+g)(\rho+k)}{gk(\rho+\delta)+\rho\rho_0\rho_1} & \frac{\beta\psi gkB}{gk(\rho+\delta)+\rho\rho_0\rho_1} & \frac{\beta\iota B(\mu+h)}{h\iota(\mu+\gamma)+\mu\mu_0\mu_1} & \frac{\beta B(\mu+h)(\mu+\iota)}{h\iota(\mu+\gamma)+\mu\mu_0\mu_1} & \frac{\beta\iota hB}{h\iota(\mu+\gamma)+\mu\mu_0\mu_1} \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

where $\rho_0=(\rho+\delta+p)$, $\rho_1=(\rho+k+g)$, $\mu_0=(\mu+\gamma+q)$ and $\mu_1=(\mu+\iota+h)$.

The basic reproduction number, R_0, is defined as the spectral radius of the next gen-

eration matrix [4, 6]. In this case R_0 has two positive eigenvalues corresponding to the reproduction numbers for each subpopulation. Therefore, the basic reproduction number for system (6.1) is the maximum of the two and in this case is given by:

$$R_0 = \max\{R_{s0}, R_{a0}\}, \tag{6.4}$$

where

$$R_{s0} = \frac{k\alpha A(\rho + g)}{\rho\rho_0\rho_1 + gk(\rho + \delta)}, \tag{6.5}$$

and

$$R_{a0} = \frac{\beta\iota B(\mu + h)}{\mu\mu_0\mu_1 + h\iota(\mu + \gamma)}. \tag{6.6}$$

The parameter gives a threshold condition, that the disease will eradicate in our prison system if $R_0 \leq 1$ and if $R_0 > 1$ then the disease will persist into the prison system. The parameters, R_{s0} and R_{a0} represent the basic reproduction numbers of the sentenced sub-population and the remand sub-population, respectively. The numbers R_{s0} and R_{a0} are also defined as the average number of secondary infections that are produced when one infectious individual is introduced into a group of susceptible individuals. For more information see the book of Anderson and May [6] or Allen [4].

6.4 Global stability of disease free equilibrium

We now investigate the global stability of a disease free equilibrium of system (6.1) by using the Lyapunov function approach. To conduct the analytical analysis of global stability of disease free equilibrium, we assume that there is no inflow of infecteds i.e., $f_E = f_I = f_L = f_J = 0$. We introduce the following invariants of model (6.1), which will serve to describe global asymptotic stability of P_0^*.

Let

$$\alpha_0 = \max\left\{\alpha, \frac{\rho\zeta}{k}\right\} \quad \text{and} \quad \beta_0 = \max\left\{\beta, \frac{\mu\xi}{\iota}\right\}. \tag{6.7}$$

We introduce the following two numbers:

$$R_{g1} = \frac{k(\rho+g)(\alpha_0 A + \beta_0 \psi B)}{\rho(\rho+\delta+p)(\rho+k+g)+gk(\rho+\delta)},$$

and

$$R_{g2} = \frac{\iota(\mu+h)(\varphi\alpha_0 A + \beta_0 B)}{\mu(\mu+\gamma+q)(\mu+\iota+h)+h\iota(\mu+\gamma)}.$$

Note that

$$\begin{aligned}\rho_0(\rho+k)(\rho+g)-pkg &= \rho\rho_0\rho_1+gk(\rho+\delta),\\ \mu_0(\mu+\iota)(\mu+h)-q\iota h &= \mu\mu_0\mu_1+h\iota(\mu+\gamma).\end{aligned}$$

Theorem 6.4.1. Consider the case when there is no inflow of infected cases in system (6.1), i.e., $f_E = f_I = 0 = f_L = f_J$. Suppose that $R_{g1} < 1,$ and $R_{g2} < 1$. Then the disease free equilibrium is globally asymptotically stable.

Proof. The condition $R_{g1} < 1$ implies that:

$$k(\rho+g)(\alpha_0 A+\beta_0\psi B)-gk(\rho+\delta)-\rho\rho_0\rho_1<0$$
$$k(\rho+g)(\alpha_0 A+\beta_0\psi B)+pkg-\rho_0(\rho+k)(\rho+g)<0$$

It is possible to find, consecutively, $a_0 > 0$, $\epsilon_1 >$ and $\epsilon_2 > 0$ such that:

$$[a_0+k(\rho+g)][\alpha_0 A+\beta_0\psi B]+p(kg+\epsilon_1)-\rho_0[(\rho+k)(\rho+g)-\epsilon_2]<0. \tag{6.8}$$

Let a_0 be as above, and let

$$\begin{aligned}a_1 &= k(\rho+g),\\ a_2 &= (\rho+k)(\rho+g)-\epsilon_2>0,\\ a_3 &= kg+\epsilon_1.\end{aligned}$$

Likewise, the condition $R_{g2} < 1$ implies that:

$$\iota(\mu+h)(\varphi\alpha_0 A+\beta_0 B)-h\iota(\mu+\gamma)-\mu\mu_0\mu_1<0,$$
$$\iota(\mu+h)(\varphi\alpha_0 A+\beta_0 B)+q\iota h-\mu_0(\mu+\iota)(\mu+h)<0.$$

It is also possible to find, consecutively, $b_0 > 0$, $\epsilon_3 >$ and $\epsilon_4 > 0$ such that:

$$[b_0 + \iota(\mu + h)][\varphi\alpha_0 A + \beta_0 B] + q(\iota h + \epsilon_3 - \mu_0[(\mu + \iota)(\mu + h) - \epsilon_4] < 0. \tag{6.9}$$

Let b_0 be as above. Now we introduce numbers b_i as follows:

$$\begin{aligned} b_1 &= \iota(\mu + h), \\ b_2 &= (\mu + \iota)(\mu + h) - \epsilon_4 > 0, \\ b_3 &= \iota h + \epsilon_3. \end{aligned}$$

We define the following function V, which we shall prove to be a Lyapunov function to guarantee the global asymptotically stable:

$$V = a_0(A - S) + a_1 E + a_2 I + a_3 T + b_0(B - U) + b_1 L + b_2 J + b_3 H.$$

We calculate the time derivative:

$$\begin{aligned} \dot{V} &= -a_0[\rho(A - S) + \alpha S(I + \varphi J)] \\ &\quad +a_1[\alpha S(I + \varphi J) - \zeta E(I + \varphi J) - (\rho + k)E + gT] \\ &\quad +a_2[\zeta E(I + \varphi J) + kE - \rho_0 I] + a_3[\rho A + pI - (\rho + g)T] \\ &\quad -b_0[\mu(B - U) + \beta U(J + \psi I)] \\ &\quad +b_1[\beta U(J + \psi I) - \xi L(J + \psi I) - (\mu + \iota)L + hH] \\ &\quad +b_2[\xi L(J + \psi I) + \iota L - (\mu + \gamma + q)J] + b_3[\mu B + qJ - (\mu + h)H], \\ &= -a_0\rho(A - S) + E[a_2 k - a_1(\rho + k)] \\ &\quad +I[\alpha S(a_0 + a_1) + \zeta E(a_2 - a_1) + \beta\psi U(b_0 + b_1) + \xi\psi L(b_2 - b_1) \\ &\quad +a_3 p - a_2\rho_0] + T[a_1 g - a_3(\rho + g)] \\ &\quad -b_0\mu(B - U) + L[b_2\iota - b_1(\mu + \iota)] \\ &\quad +J[\beta U(b_0 + b_1) + \xi L(b_2 - b_1) + \alpha\varphi S(a_0 + a_1) + \zeta\varphi E(a_2 - a_1) \\ &\quad +b_3 q - b_2\mu_0] + H[b_1 h - b_3(\mu + h)]. \end{aligned} \tag{6.10}$$

Therefore, we now have the following inequality from (6.11):

$$\dot{V} \leq -a_0\rho(A - S) + E[a_2 k - a_1(\rho + k)]$$

$$+I[\alpha_0 A(a_0+a_1)+\beta_0\psi B(b_0+b_1)+a_3p-a_2\rho_0]$$
$$+T[a_1g-a_3(\rho+g)]-b_0\mu(B-U)+L[b_2\iota-b_1(\mu+\iota)]$$
$$+J[\beta_0 B(b_0+b_1)+\alpha_0\varphi A(a_0+a_1)+b_3q-b_2\mu_0]+H[b_1h-b_3(\mu+h)].$$

We obtain $\dot{V}$ as

$$\dot{V} \leq -a_0\rho(A-S)+p_EE+p_II+p_TT+p_LL+p_JJ+p_HH, \tag{6.11}$$

where the coefficients are

$$\begin{aligned}
p_E &= a_2k-a_1(\rho+k),\\
p_I &= \alpha_0A(a_0-a_1)+\beta_0\psi B(b_0+b_1)+a_3p-a_2\rho_0,\\
p_T &= a_1g-a_3(\rho+g),\\
p_L &= b_2\iota-b_1(\mu+\iota),\\
p_J &= \beta_0B(b_0+b_1)+\alpha_0\varphi A(a_0+a_1)+b_3q-b_2\mu_0\\
p_H &= b_1h-b_3(\mu+h).
\end{aligned}$$

We now check that these coefficients are negative,

$$p_E = a_2k-a_1(\rho+k)=k(\rho+k)(\rho+g)-\epsilon_2k-k(\rho+k)(\rho+g)=-\epsilon_2k,$$

Likewise,

$$p_L=-\epsilon_4\iota<0.$$

We now have

$$p_T = a_1g-a_3(\rho+g)=kg(\rho+g)-(kg+\epsilon_1)(\rho+g)=-\epsilon_1(\rho+g)<0,$$

and similarly,

$$p_H=-\epsilon_3(\mu+h)<0. \tag{6.12}$$

We now check

$$\begin{aligned}
p_I &= \alpha_0A(a_0-a_1)+\beta_0\psi B(b_0+b_1)+a_3p-a_2\rho_0,\\
&= \alpha_0A[a_0-k(\rho+g)]+\beta_0\psi B[b_0+\iota(\mu+h)]+p(kg+\epsilon_1)-\rho_0(\rho+k)(\rho+g)-\epsilon_2\rho_0.
\end{aligned}$$

Therefore, by condition (6.9), $p_I < 0$.

Likewise,

$$\begin{aligned} p_J &= \beta_0 B[b_0 + \iota(\mu + h)] + \alpha_0 \varphi A[a_0 + k(\rho + g)] + q(\iota h + \epsilon_3) - \mu_0(\mu + \iota)(\mu + h)\epsilon_4 \mu_0 \\ &\leq 0. \end{aligned}$$

This proves that $V(A - S, E, I, T, U, L, J, H) < 0$, is negative definite and therefore, P_0^* is globally asymptotically stable. □

Theorem 6.4.1 asserts that TB can be eradicated in a prison system of the type of this model if there is no inflow of infected individuals, and

$$R_g = \min\{R_{ga}, R_{gs}\}$$

can be kept below unity.

6.5 Numerical values

We assume that the average period spent by remand individuals in custody is six weeks and that gives us a value of μ_p as

$$\mu_p = \frac{1}{6} \text{ week}^{-1} = \frac{52}{6} \text{ year}^{-1} = 8.6667 \text{ year}^{-1}.$$

Similarly as in Chapter 4, we calculate an estimate for the removal rates μ and ρ using Table 1. We further assume that on average, a sentenced inmate completes 75% of sentenced time. Then we obtain the release rate

$$\rho_p = 0.1249 \text{ year}^{-1}.$$

In Chapter 4, we calculated a value for the general mortality rate excluding deaths due to TB. This numerical value will be taken as the common value of μ_m and ρ_m. Thus we can calculate the values of μ and ρ as:

$$\begin{aligned} \mu &= \mu_p + \mu_m - \mu_m \mu_p = 8.6389 \text{ year}^{-1} \\ \rho &= \rho_p + \rho_m - \rho_m \rho_p = 0.1281 \text{ year}^{-1} \end{aligned}$$

Since the remand inmates do not stay in prison long, we can estimate the disease mortality for this group as being the same as in the outside population. We assume the value $\gamma = 0.3$ as in the reference [11].

For sentenced inmates the disease induced mortality rate is assumed to be such as to yield the same expected number of deaths due to TB as in the model of Chapter 4. Thus we take

$$\delta = 0.01876 \times \frac{N}{N_s} = 0.02616 \text{ year}^{-1}.$$

The rest of the parameters are evaluated along the same lines as in Chapter 4.

6.5.1 Effective Contact rates

The contact rates for sentenced and awaiting individuals are computed by using a lower bound for the effective rates c_0 as in Chapter 4, given by:

$$\alpha = 7.1351 \times 10^{-5} \text{ year}^{-1}$$

and

$$\beta = 1.8303 \times 10^{-4} \text{ year}^{-1},$$

respectively. The transmission coefficients between the exposed class and the infectious class are given by

$$\zeta = \frac{k}{2N_s} \quad \text{and} \quad \xi = \frac{\iota}{2N_a},$$

respectively, as in Chapter 4.

6.5.2 Other parameters

For sentenced individuals the progression rate from the exposed class to the infectious class is the same as in Chapter 4, which is $k = 0.05$. As for remand inmates, we assume ι

to be the same as the general population $\iota = 0.1$ [14].

Sentenced inmates receive treatment at the rate $p = 0.5$ and the remand inmates at $q = 0.3$, from Chapter 4. Sentenced inmates recover and progress to the exposed class after a successful treatment at a rate of $g = 2(10/N_s)$ and remand inmates at $h = 2(10/N_a)$, as in Chapter 4.

The inflow of infectives are computed by splitting the parameter values obtained in Chapter 4:

$$f_S = 0.14, f_U = 0.06, f_E = 0.53, f_L = 0.21, f_I = 0.04, \text{ and } f_J = 0.02.$$

The initial values are obtained by splitting the values of the initial values of the one-group model in Chapter 4. The remand population constitutes a fraction $\frac{2}{7}$ of the prison population and splitting these parameters would lead to:

$$S = 23500,\ E = 78800,\ I = 2300,\ T = 13000,$$
$$U = 9300,\ L = 31000,\ J = 900, \text{ and } H = 5200.$$

Table 6.1: Model parameters

Parameter	Estimated value	Source
μ	8.6389 year^{-1}	Estimated from Chapter 4, data from [86, 33]
ρ	0.1249 year^{-1}	Estimated from Chapter 4, data from [86, 33]
γ	0.3 year^{-1}	Estimated from Chapter 4
δ	0.02616 year^{-1}	Estimated from Chapter 4, data from [88, 86]
p	0.50 year^{-1}	[14]
q	0.30 year^{-1}	[14]
k	0.05 year^{-1}	[14, 90]
ι	0.1 year^{-1}	[14]
h	$20/N_s$	[14, 90]
g	$20/N_a$	[14, 90]
ζ	$k/2N_s$	Estimated from Chapter 4
ξ	$\iota/2N_a$	Estimated from Chapter 4

6.6 Numerical Simulations

A two-group model system (6.1) is simulated by using South African real data and these parameter values are presented in Table 6.1, Table 6.2 and Table 6.3.

6.6.1 Simulations without the inflow of infective

We proceed by using parameters in Table 6.1 and Table 6.3 to analyse the simulation results in the absence of the inflow of infectives. The trajectory plot of the two-group model system (6.1) are presented in Figure 6.1 when $R_{g1} < 1$ and $R_{g2} < 1$. In order for us to obtain different values of R_{g1} and R_{g2}, we vary the values of $\alpha = 0.0000142$ and $\beta = 0.00002260$. We observed that the trajectories of the two-group model (6.1) converges to disease free equilibrium. Therefore the disease will disappear in both sub-population groups as Theorem 6.4.1 says. A slight increase in the contact rate α and β leads to

Table 6.2: Contact rates parameters and inflow of infectives

Parameter	Estimated value	Source
α	0.000071351 year^{-1}	Estimated from Chapter 4, see also [90]
β	0.00018303 year^{-1}	Estimated from Chapter 4, see also [90]
f_S, f_E, f_I	$0.14, 0.53, 0.04$	[86]
f_U, f_L, f_J	$0.06, 0.21, 0.02$	[86]

convergence of disease free equilibrium in the sentenced sub-population while the remand population is experiencing endemicity. This is due to inmates that are not screened for TB immediately on admission in the remand population while inmates in the sentenced population are screened and put under treatment. The simulation results can be seen in Figure 6.2 with $R_{g1} = 0.997$ and $R_{g2} = 1.11$.

In the absence of treatment i.e., when $p = q = 0$, Figure 6.3 reveals that the disease will persist in both sub-population with $R_{g1} = 3.27$ and $R_{g2} = 1.71$. Therefore, the sentenced sub-population will be at high risk of disease infection as they spend more time in prison than the remand population. It is noticed that the conditions will aggravate if there is increase in contact rates in Figure 6.4.

In the absence of cross-effect between the two sub-populations and an increase in the contact rates, the disease in the prison system will be eradicated due to the treatment that is administered. This can be seen in Figure 6.5 with $R_{g1} = 0.920$ and $R_{g2} = 0.968$. Quite obviously, in the absence of treatment and cross-effect the disease becomes persistent and the inmates will be at high risk of getting infected. TB transmission is driven exclusively by the systematic and prolonged exposure of susceptible to infectious individuals and this can be seen in Figure 6.6 with $R_{g1} = 3.12$ and $R_{g2} = 1.66$. Hence, sentenced inmates are considered to be in an active sub-population and are at risk of TB infection due to close

Table 6.3: Initial conditions

Parameter	Estimated value	Source
N	164000	[94]
N_s	118000	[94]
N_a	46000	[94]
S	23500	Estimated from Chapter 4, data from [94]
E	78800	Estimated from Chapter 4, data from [94]
I	2300	Estimated from Chapter 4, data from [94]
T	13000	Estimated from Chapter 4, data from [94]
U	9300	Estimated from Chapter 4, data from [94]
L	31000	Estimated from Chapter 4, data from [94]
J	900	Estimated from Chapter 4, data from [94]
H	5200	Estimated from Chapter 4, data from [94]

and frequent contacts with infectious inmates.

Figure 6.1: $\alpha = 0.0000142$, $\beta = 0.00002260$ and $R_{g1} = 0.963, R_{g2} = 0.997$.

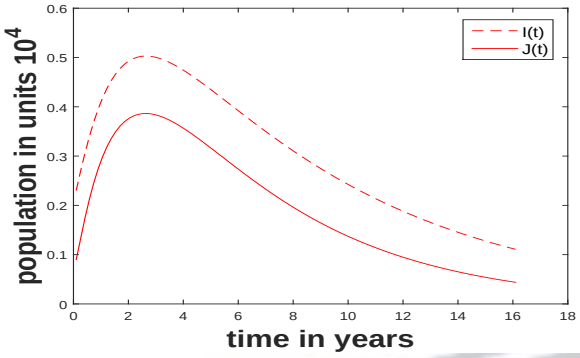


Figure 6.2: $\alpha = 0.0000146$, $\beta = 0.0000255$, and $R_{g1} = 0.997$, $R_{g2} = 1.11$.

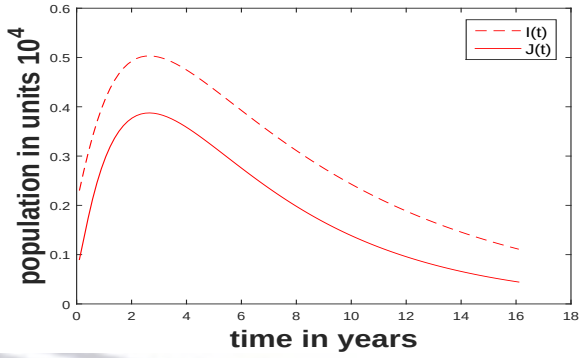


Figure 6.3: $\alpha = 0.0000142$, $\beta = 0.00002260$, $q = 0$, $p = 0$ and $R_{g1} = 3.27$, $R_{g2} = 1.71$.

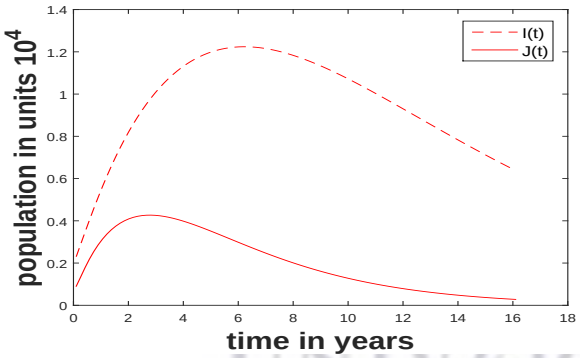
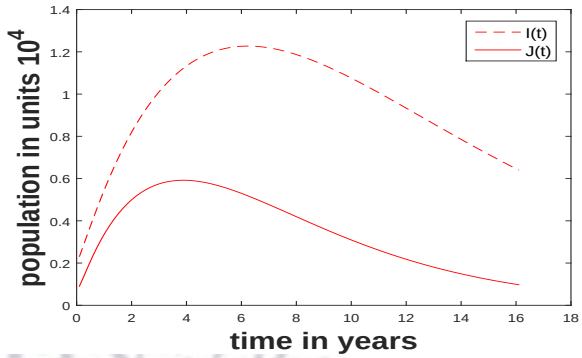


Figure 6.4: $\alpha = 0.0000146$, $\beta = 0.0000255$, $q = 0, p = 0$ and $R_{g1} = 3.39, R_{g2} = 1.91$.



6.6.2 Simulations with the inflow of infective

We now introduce the inflow of infectives in Figure 6.7 and use the contact rates in Table 6.2. The results show that the two-group model system (6.1) always has an endemic equilibrium and is globally asymptotically stable, which indicates that the disease will persist in the presence of the inflow of infectives. A further simulation that illustrates the dynamics of the infections classes I and J when there is an inflow of infectives and a reduction in contact rates has been presented in Figure 6.7.

Figure 6.8, reveals that the disease will still persist in both population groups even though $R_{g1} < 1$ and $R_{g2} < 1$. In figure 6.9, it is noticed that even though the contact rate has been reduced, the infectious class of sentenced inmates is increasing drastically in the absence

Figure 6.5: $\alpha = 0.0000146, \beta = 0.0000255, \varphi = 0, \psi = 0$ and $R_{g1} = 0.920$, $R_{g2} = 0.968$.

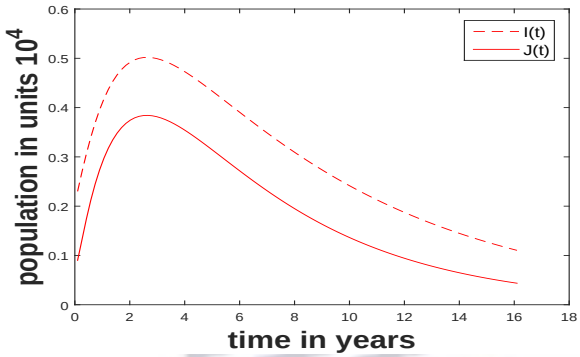


Figure 6.6: $\alpha = 0.0000146$, $\beta = 0.0000255, \varphi = 0, \psi = 0$ $q = 0$, $q = 0$ and $R_{g1} = 3.12, R_{g2} = 1.66$.

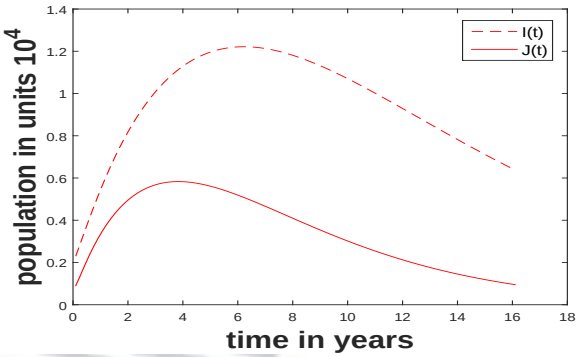


Figure 6.7: $\alpha = 0.000071351$, $\beta = 0.00018303$ and $R_{g1} = 4.55, R_{g2} = 4.89$.

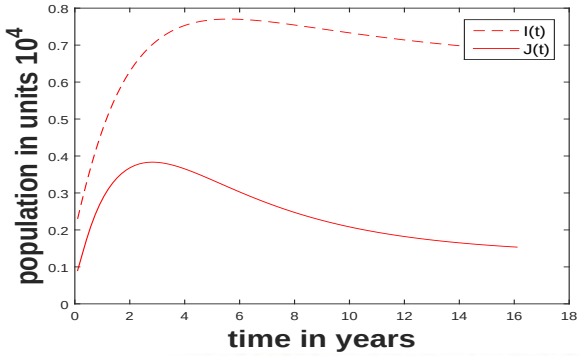
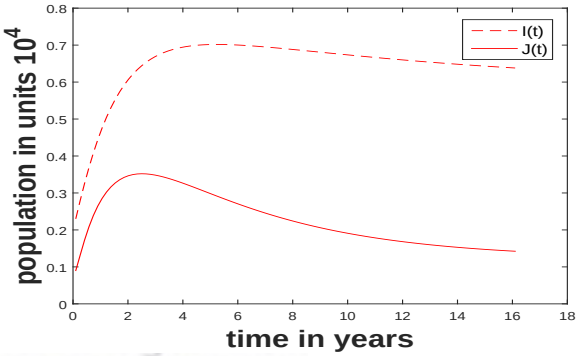


Figure 6.8: $\alpha = 0.0000146$, $\beta = 0.000340$ and $R_{g1} = 0.893, R_{g2} = 0.908$.



of treatment with $R_{g1} = 3.03$ and $R_{g2} = 1.28$ in the remand population. The situation will worsen if we use the contact rates in Table 6.2 with the absence of treatment, this can be seen in Figure 6.10. The inflow of infectives makes it impossible for the prison system to converge towards disease free equilibrium.

Figure 6.9: $\alpha = 0.0000146$, $\beta = 0.000340$, $q = 0$, $p = 0$ and $R_{g1} = 3.03, R_{g2} = 1.28$.

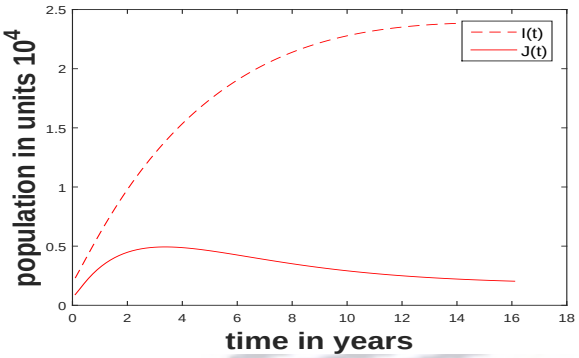
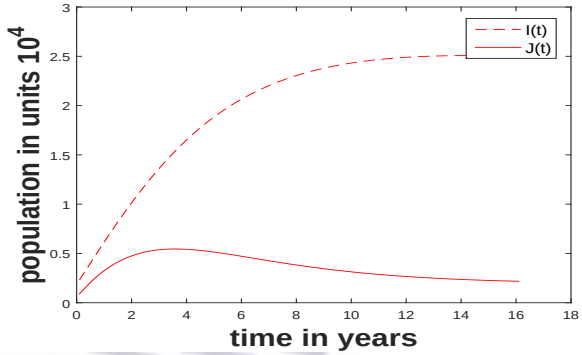


Figure 6.10: $\alpha = 0.000071351$, $\beta = 0.00018303$, $q = 0$, $p = 0$ and $R_{g1} = 15.50, R_{g2} = 6.89$.



6.7 Conclusion

In this chapter, we introduced a two-group model to monitor the disease in a prison system. We divided the total prison population into sentenced population and remand population. The theoretical analysis Theorem 6.4.1 together with simulation results confirm that subject to certain conditions, the disease free equilibrium is globally asymptotically stable. Our simulation results have shown that when we have inflow of infecteds, then the disease cannot be eradicated even though the basic reproduction number R_0 is less than unity. Finally, more consideration should be given to monitor the inflow of infecteds so as to reduce the number of infectious individuals in order to eradicate the disease in the prison population. This can be done by screening the inmates on admission and also by providing a comprehensive curative and preventive services for latent cases and active cases.

Chapter 7

Modeling drug-resistant TB population dynamics in a crowded environment

7.1 abstract

We present a two strain TB model to understand the transmission dynamics of drug-sensitive TB and multi-drug resistant TB in a crowded environment such as prison. The model allows for the inflow of infective into the susceptible class, exposed class for drug-sensitive, infectious class for drug-sensitive and the exposed class for multi-drug resistant patients. The basic reproduction R_0 which measures the average number of new infectious generated by a distinctive infectious individual in a prison population has been premeditated. We also prove the global stability of the disease free equilibrium by using a Lyapunov function. Finally, we present the analytical results by means of simulations.

7.2 Introduction

Multi-drug resistant TB is a form of TB caused by bacteria that cannot be controlled with the first-line anti-TB drugs which are Isoniazid and Rifampicin. The World Health Organization declared that an estimate of 558000 new cases of multi-drug resistant tuberculosis occurred globally and 230000 people died from the disease in 2017 [76]. Nevertheless, the number of these multi-drug resistant cases grew in 2017 by 12% as compared to 2016 with an estimated 490000 people who developed MDR-TB. In addition, 110000 people with rifampicin-resistant TB were newly eligible for MDR-TB treatment in 2016. Multi-drug resistant TB remains a public health crisis and health security threat worldwide. However, MDR-TB is treatable and curable by using the second line drugs and the treatment may take up to two years. Only 55% of MDR-TB patients were successfully treated worldwide in 2017.

There were 54 million lives that were saved through diagnosis and treatment between 2000 and 2017 and these individuals were infected with drug-sensitive TB or with multi-drug resistant TB [77]. MDR-TB may be acquired in different forms such as through incorrect treatment or through infection by an infectious MDR-TB patient [77]. Yang et al. [71], studied the global stability of two models with incomplete treatment for tuberculosis. The authors assumed that treated individuals may progress either to a latent compartment due to the remnant of *Mycobacterium tuberculosis* or infectious class due to treatment failure. It was discovered that increasing the treatment rate has a positive effect on TB control and also increasing the protection of susceptible individuals with chronic disease against TB infection is also helpful for controlling the spread of TB. China and India have been identified with the largest number of MDR-TB cases, and South Africa is in the top seven of the countries with highest burden of TB disease [75]. A study in mathematical modelling on pulmonary and multi-drug resistant tuberculosis patients with vaccination has been proposed in the paper of Mishra and Srivastava [47]. The authors noticed that there was a speedy recovery and almost tend to end the spread of TB infection as the

quarantine was used as control over MDR-TB patients. Vaccination has also played a great role in immunizing the population towards TB infection. A study of mathematical models with MDR-TB has been proposed, in the papers [55, 18, 28, 58, 11].

Multi-drug resistant TB is difficult to treat and the treatment is expensive as compared to the normal TB treatment. An optimal control problem for tuberculosis and MDR-TB transmission has been considered in the paper of Hafidh et al [27]. The model involves three control variables which are BCG vaccination, treatment with first-line and treatment with second line anti-TB drug. The aim of the problem is to minimize the number of infected individuals and also to minimize the cost of the control that is given. Pontryagin's Minimum Principle has been use to derive the optimal control. The authors observed that the optimal control strategy gives better results in minimizing the total number of infected individuals.

In South Africa, an estimated 322000 people became ill with TB in 2017 and 78000 people died from TB. Tuberculosis thrives in places where people lack access to proper TB treatment, live with inadequate ventilation and where there is poor sanitation and nutrition. In particular, prisons are an excellent example for thriving MDR-TB infection. In this study we will focus on the transmission dynamics of drug sensitive TB and multi-drug resistant TB with treatment. Drug sensitive TB and multi-drug resistant TB is a treatable and curable disease, without treatment adherence the disease might spread, and improper treatment may give rise to MDR-TB.

7.3 The model

The total prison population $N(t)$ is subdivided into seven classes according to their disease status which are susceptible individuals (S), individuals exposed to drug-sensitive TB only (E), infectious individuals with drug-sensitive TB (I), individuals who are treated against drug-sensitive TB (T), individuals who are exposed to multi-drug resistant TB and are

now latently infected (L), infectious individuals with MDR-TB (J) and ultra treated individuals for MDR-TB patients (U). The model allows the inflow into the classes of susceptible (S), exposed to drug sensitive TB, infectious individuals with drug-sensitive TB (I), exposed to multi-drug resistant TB (L), at the rates $f_S\mu A$, $f_E\mu A$, $f_I\mu A$ and $f_L\mu A$. We assume that $f_S + f_E + f_I + f_L = 1$ and that there is no inflow into the treatment class (T) of drug-sensitive, infectious class (J) and ultra treated class (U) with MDR-TB patients as they are very sick and probably admitted to hospital. Susceptible individuals recruited into the susceptible class $S(t)$ at a constant rate A. Our compartmental model is presented as follows:

$$\begin{aligned}
\dot{S} &= f_S\mu A - c\beta_0 SI - c\beta_1 SJ - \mu S,\\
\dot{E} &= f_E\mu A + c\beta_0 SI - c\beta_2 EJ - c\beta_4 EI - (\mu + k_1 + r_1)E + \iota_1 T,\\
\dot{I} &= f_I\mu A + k_1 E - (\mu + d_1 + r_2)I - c\beta_3 IJ + c\beta_4 EI,\\
\dot{T} &= r_1 E + r_2 I - (\mu + \iota_1 + \iota_2)T,\\
\dot{L} &= f_L\mu A + \iota_2 T + \iota_3 U - (\mu + k_2 + r_3)L + cJ(\beta_1 S + \beta_2 E + \beta_3 I),\\
\dot{J} &= k_2 L - (\mu + d_2 + r_4)J,\\
\dot{U} &= r_3 L + r_4 J - (\mu + d_3 + \iota_3)U.
\end{aligned} \tag{7.1}$$

Susceptible individuals get infected with tubercle bacillus if they come into contact with drug sensitive TB and MDR-TB individual, at a rate $c\beta_0 SI$ and $c\beta_1 SJ$, respectively. The parameter β_0 is the probability that susceptible individuals become infected by one drug sensitive TB infectious individual and c is the per capita contact rate. Individuals in E class progress to active TB class I at the rate $c\beta_4 EI$, where β_4 is the probability that exposed individuals become infected by one drug-sensitive TB infectious individual. The individuals in the exposed class for drug-sensitive TB and drug resistant TB leave for infectious class at the rates $k_1 E$ and $k_2 L$, respectively. The individuals in J class with drug-resistant TB can infect S, E and I individuals at a rate $cJ(\beta_1 S + \beta_2 E + \beta_3 I)$, where β_1, β_2 and β_3 are the probabilities that S, E and I individuals become infected by

one drug resistant TB infectious individual, respectively. Individuals in E, I, L and J classes moves into the treatment class at a rate r_1, r_2, r_3, and r_4, respectively. Successfully treated individuals for drug sensitive TB and MDR-TB move to the E and L class at a rate $\iota_1 T$ and $\iota_3 U$, respectively. Individuals who did not complete their treatment develop MDR-TB and move to the L class at a rate ιT. The parameters d_1, d_2 and d_3 are the disease-induced death rate coefficients for individuals in I, J and U, respectively and the individuals in the respective subgroups die naturally at a rate μ.

The model system (7.1) signifies a human population, hence all related parameters and state variable are assumed to be nonnegative for all $t > 0$. Let $N(t)$ represent the size of the prison total population at time t.
Hence,

$$N(t) = S(t) + E(t) + I(t) + T(t) + L(t) + J(t) + U(t).$$

By adding the equations in model (7.1), we get

$$\frac{dN}{dt} = \mu(A - N) - (d_1 I + d_2 J + d_3 U).$$

It is clear that if $N > A$ and $\frac{dN}{dt} < 0$. Therefore, all the solutions of system (7.1) with non-negative initial values in the space $\mathbb{R}^7_+$ exists and are bounded for all $t \geq 0$. It can easily be shown that the set

$$\Gamma = \left\{(S, I, T, L, J, U) \in \mathbb{R}^7_+ \mid S \leq N \leq A\right\}$$

is positively invariant and attracts all nonnegative solutions of model system (7.1). Hence, we will only consider solutions in model (7.1) with initial values in Γ.
In the absence of infection (i.e., $E = I = L = J = 0$), model system (7.1) possesses the disease free equilibrium given by

$$E_0 = (S(0), E(0), I(0), T(0), L(0), J(0), U(0)) = \left(\frac{A}{\mu}, 0, 0, 0, 0, 0, 0\right).$$

The basic reproduction number, R_0, is defined as the anticipated number of secondary cases produced by a single infection in a completely susceptible population. This is a

threshold quantity that predicts a disease outbreak and helps to evaluate control strategies in a population. Therefore, if $R_0 < 1$, then the infected individual produces less than one new infected individual over the course of its infections period, and the infection cannot invade the population. On the other hand if $R_0 > 1$, then the infected individual produces on average more than one infection, and the disease can invade the population. Following the next generation matrix method applied in Van Den Driessche [59] to compute R_0, we define F and V from system (7.1) as:

$$F = \begin{pmatrix} c\beta_0 SI - c\beta_1 EJ \\ -\beta_3 IJ + c\beta_4 EI \\ cJ(\beta_1 S + \beta_2 E + \beta_3 I) \\ 0 \end{pmatrix} \quad \text{and} \quad V = \begin{pmatrix} (\mu + k_1 + r_1)E - \iota T \\ (\mu + d_1 + r_2)I - k_1 E \\ (\mu + k_2 + r_3)L - \iota_2 T - \iota_3 U \\ (\mu + d_2 + r_4)J - k_2 L \end{pmatrix}.$$

We now obtain the partial derivatives of F and V with respect to E, I, T, L, J and U at the disease free equilibrium point E_0

$$F = \begin{pmatrix} 0 & c\beta_0 \frac{A}{\mu} & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & c\beta_1 \frac{A}{\mu} \\ 0 & 0 & 0 & 0 \end{pmatrix} \quad \text{and}$$

$$D(V) = \begin{pmatrix} \mu + k_1 + r_1 & 0 & 0 & 0 \\ k_1 & \mu + d_1 + r_2 & 0 & 0 \\ 0 & 0 & \mu + k_2 + r_3 & 0 \\ 0 & 0 & -k_2 & \mu + d_2 + r_4 \end{pmatrix}.$$

The basic reproduction number is given by $R_0 = \rho(FV^{-1})$, where ρ represents the spectral radius or the dominant eigenvalue of the matrix FV^{-1} which is given by:

$$R_0 = \max\{R_{0s}, R_{0r}\}, \tag{7.2}$$

where

$$R_{0s} = \frac{c\beta_0 k_1 A}{\mu(\mu + k_1 + r_1)(\mu + d_1 + r_2)},$$
$$R_{0r} = \frac{c\beta_1 k_2 A}{\mu(\mu + k_2 + r_3)(\mu + d_2 + r_4)}.$$

Thus, R_{0s} and R_{0r} represent the reproduction numbers for drug-sensitive TB and MDR-TB, respectively.

7.4 Global Stability

We find it convenient to introduce the following constants:

$$\begin{aligned} \mu_1 &= \mu + k_1 + r_1, \quad \mu_4 = \mu + k_2 + r_3, \\ \mu_2 &= \mu + d_1 + r_2, \quad \mu_5 = \mu + d_2 + r_4, \\ \mu_3 &= \mu + \iota_1 + \iota_2, \quad \mu_6 = \mu + d_3 + \iota_3. \end{aligned}$$

In the proof of the global stability theorem we shall use a Lyapunov function V. Towards constructing this function we shall require several constraints. We proceed now by iden-

tifying these numbers, and this is based on inspection of the time derivative of V.

Let

$$\begin{aligned} a_1 &= \frac{r_2k_1\mu_1 + r_1\mu\mu_1\mu_2}{r_2k_1 + r_1\mu_2}, \quad a_2 = \frac{k_1\mu_1\mu_2(1-\mu)}{r_2k_1 + r_1\mu_2}, \\ z_0 &= \frac{1}{\iota_2}(a_2\mu_3 - \iota_1k_1), \qquad z_1 = \frac{1}{\mu_5\mu_6}(\iota_3r_4z_0 + \mu\mu_4\mu_5\mu_6), \\ b_2 &= \frac{z_0\iota_3}{\mu_6}. \end{aligned} \tag{7.3}$$

Now we introduce two positive constants β_s and β_r on the assumption that $z_0 \neq 0$

$$\begin{aligned} \beta_s &= \max\Big\{\beta_0, (\frac{a_1}{k_1} - 1)\beta_4\Big\}, \\ \beta_r &= \max\Big\{\beta_1, (1 - \frac{k_1}{z_0})\beta_2, (1 - \frac{a_1}{z_0}\beta_3)\Big\}. \end{aligned}$$

We specify two invariants that describe a threshold for global asymptotic stability of E_0^*, the disease-free equilibrium,

$$R_{gs} = \frac{c\beta_sk_1A}{\mu\mu_1\mu_2}, \quad R_{gr} = \frac{c\beta_rk_2A}{\mu\mu_4\mu_5}.$$

The following condition will be necessary in the global stability theorem

$$a_2\mu_3 > \iota_1k_1. \tag{7.4}$$

The condition (7.4) implies that $z_0 > 0$ and in particular that $a_2 > 0$.

Theorem 7.4.1 *Suppose that condition (7.4) hold. If $R_{gs} < 1$ and $R_{gr} < 1$, then the disease-free equilibrium is globally asymptotically stable.*

Proof. Let

$$\epsilon = \min\{\frac{1 - R_{gr}}{2\mu_5}, z_1, \frac{\mu_4z_0}{k_2}\Big\}.$$

By condition (7.4) we have $z_0 > 0$. Since also we assume $1 - R_{gr} > 0$, it follows that $\epsilon > 0$.

Now we choose $b_1 = z_1 - \epsilon$ and $b_0 = z_0 - \frac{k_2\epsilon}{2\mu_4}$. Then b_0 and b_1 are positive numbers.

The condition $R_{gs} < 1$ implies an inequality

$$c\beta_s k_1 A - \mu\mu_1\mu_2 < 0.$$

Then there exists $\alpha > 0$, and we can insist on

$$\alpha < \min\Big\{\frac{\iota_2\epsilon}{\iota_1}, \frac{k_2\epsilon}{2\mu_4}\Big\},$$

such that

$$c\beta_s(2\alpha + k_1)A - \mu\mu_1\mu_2 < 0$$

We now proceed to define a function $V(x)$, which we shall prove as being a Lyapunov function. The function is as follows:

$$V = \alpha(A - S) + a_0E + a_1I + a_2T + b_0L + b_1J + b_2U,$$

where $\alpha, a_1, a_3, b_0, b_1$ and b_3 are as above and $a_0 = \alpha + k_1$. We note that

$$\alpha + b_0 \leq z_0.$$

Now

$$\begin{aligned}
\dot{V} &= -\alpha[\mu(A - S) + c\beta_0 SI + c\beta_1 SJ] + a_0[c\beta_0 SI - c\beta_2 EJ - c\beta_4 EI - \mu_1 E + \iota_1 T] \\
&\quad + a_1[k_1 E - \mu_2 I - c\beta_3 IJ + c\beta_4 EI] + a_2[r_1 E + r_2 I - \mu_3 T] \\
&\quad + b_0[\iota_2 T + \iota_3 U - \mu_4 L + cJ(\beta_1 S + \beta_2 E + \beta_3 I)] \\
&\quad + b_1[k_2 L - \mu_5 J] + b_2[r_3 L + r_4 J - \mu_6 U] \\
&= -\alpha\mu(A - S) + E[a_1 k_1 + a_2 r_1 - a_0\mu_1] \\
&\quad + I[\alpha c\beta_0 S + c\beta E(a_1 - a_0) + a_2 r_2 - a_1\mu_2 + a_0 c\beta_0 S] \\
&\quad + T[b_0\iota_2 + a_0\iota_1 - a_2\mu_3] + L[b_1 k_2 + b_2 r_3 - b_0\mu_4] \\
&\quad + J[c\beta_1 S(\alpha + b_0) + b_0 c\beta_2 E - a_0 c\beta_2 E + c\beta_3 I(b_0 - a_1) + b_2 r_4 - b_1\mu_5] \\
&\quad + U[b_0\iota_3 - b_2\mu_6].
\end{aligned}$$

Now

$$\dot{V} \leq -\alpha\mu(A-S) + C_E E + C_I I + C_T T + C_L L + C_J J + C_U U,$$

where the coefficients $C_i,\ i = E, T, L, U, I, J$ respectively, are as follows:

$$\begin{aligned}
C_E &= a_1 k_1 + a_2 r_1 - a_0 \mu_1, \\
C_T &= b_0 \iota_2 + a_0 \iota_1 - a_2 \mu_3, \\
C_L &= b_1 k_2 + b_2 r_3 - b_0 \mu_4, \\
C_U &= b_0 \iota_3 - b_2 \mu_6, \\
C_I &= c\beta_s A(\alpha + a_0) + a_2 r_2 - a_1 \mu_2, \\
C_J &= c\beta_r A(\alpha + b_0) + b_2 r_4 - b_1 \mu_5.
\end{aligned}$$

We check that these coefficients are negative. A routine calculation gives

$$a_2 r_2 - a_1 \mu_2 = \mu\mu_1\mu_2 \quad \text{and} \quad b_2 r_4 - b_1 \mu_5 = \mu\mu_4\mu_5.$$

Therefore,

$$\begin{aligned}
C_I &= c\beta_s A(\alpha + a_0) + a_2 r_2 - a_1 \mu_2 \\
&= c\beta_s A(2\alpha + k_1) - \mu\mu_1\mu_2. \qquad (7.5)
\end{aligned}$$

Since $R_{gs} < 1$, we have $C_I < 0$. Similarly $C_J < 0$, for

$$\begin{aligned}
C_J &= c\beta_r A(\alpha + b_0) + b_2 r_4 - b_1 \mu_5 \\
&= c\beta_r A(\alpha + b_0) - \mu\mu_4\mu_5. \qquad (7.6)
\end{aligned}$$

Thus $\dot{V} < 0$. This concludes that proof. □

Therefore, in the absence of inflow of the infected individuals and with

$$R_g = \min\{R_{gs}, R_{gr}\}$$

less than unity, Theorem (7.4.1) affirms that TB in crowded environments can be eliminated.

7.5 Numerical value

We consider a certain area in South Africa that is experiencing high prevalence MDR-TB with a population size of

$$A = 160000.$$

Removal rate in a general population is only by death and this parameter is excluding deaths due to TB. In 2019, the life expectancy in South Africa has decreased to 63 years [84]. Therefore, the natural mortality rate μ in a case of general population is simply calculated by taking the inverse of life expectancy,

$$\mu = \frac{1}{63} \text{ year}^{-1}.$$

7.5.1 Disease induced death rate and recovery rate

According to World Health Organization [77], 56% of MDR cases were treated successfully. If we take treatment duration on the average as 9 months then

$$d_3 = \frac{0.44}{0.75} \text{ year}^{-1}.$$

After successful treatment the individuals recover and move the latency class L at a rate

$$\iota_3 = \frac{0.56}{0.75} \text{ year}^{-1}.$$

As for d_2, it must be bigger than d_3. We propose to have:

$$d_2 = 1.5\ d_3.$$

Due to some individuals defaulting on treatment or interruption of TB treatment, the individuals in class T will then progress to latent class L at a rate ι_2. The parameter ι_2 depends on the region. From [100] we are led to have a default rate of 18%, so we pick:

$$\iota_2 = \frac{0.18}{0.5} \text{ year}^{-1}.$$

The disease induced death rate for drug sensitive TB is given by $d_1 = 0.02256$ (from Chapter 4) and we assume that individuals recover faster, at $\iota_1 = 0.99$.

We will use the contact rate calculated in Chapter 4 for South African which is given by

$$c = 7.893\times10^{-5} \text{ year}^{-1}.$$

We assume that the transmission parameters are

$$\beta_2 = \beta_3 = \beta_4 = 0.00004,$$

from Chapter 4 and the parameter values for are estimated,

$$\beta_0 = \beta_1 = 0.0000014.$$

7.5.2 Progression rate and treatment rate

The progression rate for drug sensitive from E class to I class for a general population has already been computed in Chapter 4 by using South African data. We will also assume that the same progression rate for drug-resistant from L class to J class which are

$$k_1 = k_2 = 0.1 \text{ year}^{-1},$$

respectively.

Progression rate from E and I class to the treatment class T for drug sensitive TB are given by

$$r_1 = 0.3 \text{ year}^{-1} \text{ and } r_2 = 0.5 \text{ year}^{-1},$$

respectively. By taking 9 months as treatment duration [101], we adopt the same parameter values for drug sensitive TB patients in the latency class (L) and infectious class (J)

$$r_3 = 0.3 \text{ year}^{-1} \text{ and } r_4 = 0.5 \text{ year}^{-1},$$

respectively.

7.5.3 Initial conditions and inflow of infectives

From Chapter 4, 20% of the South African population are susceptible. The paper of Cox et al. [21], reported 21% of patients infected with MDR-TB and 48% were on treatment. By using the initial conditions in Chapter 4 and these explanations, we are led to the following initial conditions:

$$S = 20000, E = 44095, I = 1731, T = 5720, L = 22715, J = 459, U = 5280.$$

The inflow of infective are split as in Chapter 6 as follows:

$$f_S = 0.2, f_E = 0.53, f_I = 0.06, f_L = 0.21.$$

7.6 Simulations

We now present our analytical results by means of simulations. We start off by considering model system (7.1) without the inflow of infectives i.e., when $f_E = f_I = f_L = 0$. We then examine a situation where the inflow of infectives occur.

7.6.1 No inflow of infectives

We use the parameter values listed in Table 7.1. and we vary the value of the parameter c which is not listed in Table 7.1. Figure 7.1 shows a variation between exposed class E and L, infectious class I and J of the drug sensitive TB and drug resistant TB. We now show the dissimilarity between the exposed classes and infectious classes of drug sensitive TB and drug resistant TB. Figure 7.1 admits for an endemic population i.e., the disease will persevere in the population as $R_{gs} = 1.58$ and $R_{gr} = 1.3$ when $c = 0.00004$ and $\beta_1 = 0.000003$. In Figure 7.2, it is noticed that $R_{gs} = 0.985$ and $R_{gr} = 0.38$ when $c = 0.000025$ which means that the disease will not persist in the population and Theorem 7.4.1 is satisfied.

Table 7.1: Model parameters and initial conditions

Parameter	Numerical value	Source
μ	0.01587	[84]
β_0	0.0000014	Estimated
β_1	0.0000014	Estimated
$\beta_2 = \beta_3 = \beta_4$	0.000042	Estimated
d_1	0.02616	Estimated in Chapter 4, data from [88, 86]
d_2	0.8800	Estimated
d_3	0.5887	[77]
ι_1	0.89	Estimated from Chapter 4
ι_2	0.3600	[100]
ι_3	0.7467	[77]
$r_1 = r_3$	0.30	[14]
$r_2 = r_4$	0.50	[14]
$k_1 = k_2$	0.05 to 0.1	Estimated in Chapter 4
A	100000	Estimated
S	20000	[90]
E	44095	[86, 21]
I	1731	[86, 21]
T	5720	[86, 21]
L	22715	[86, 21]
J	459	[86, 21]
U	5280	[86, 21]

Table 7.2: Inflow and contact rates

Parameter	Numerical value	Source
c	0.00007893	[90]
f_S, f_E, f_I, f_L	$0.2, 0.53, 0.06, 0.21$, respectively	[86]

Figure 7.1: $c = 0.00004, \beta_1 = 0.000003$ and $R_{gs} = 1.58, R_{gr} = 1.3$.

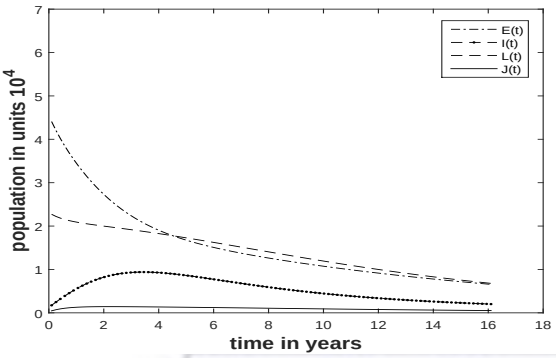
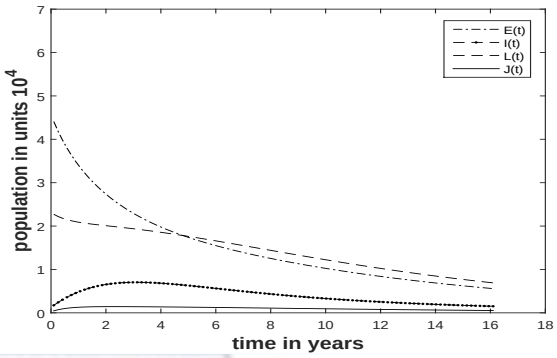


Figure 7.2: $c = 0.000025$ and $R_{gs} = 0.985, R_{gr} = 0.38$.



By extracting the infectious classes and increase the time to 40 years, it is seen clearly that the infectious classes I and J converges to disease free equilibrium and this can be seen in Figure 7.3. with $R_{gs} = 0.985$ and $R_{gr} = 0.814$ when $c = 0.000025$ and $\beta_1 = 0.000003$. Therefore, in the long run the disease will be eradicated. Figure 7.4. shows the infectious class for drug sensitive TB with endemicity while the infectious class for drug resistant TB shows disease free equilibrium with $R_{gs} = 1.58$ and $R_{gr} = 0.61$ when $c = 0.000022$.

We further notice that if there are no individuals who default in treatment then the drug resistant class J converges faster to the disease free equilibrium while drug sensitive TB class I remain endemic. This can be seen in Figure 7.5 with $R_{gs} = 0.985, R_{gr} = 0.814$ when $c = 0.000025, \beta_1 = 0.000003$. When there is an increase in the default rate $\iota_2 = 0.6$, we notice in Figure 7.6 a faster convergence in I class while J class becomes slow.

Figure 7.3: $c = 0.000025, \beta_1 = 0.000003$ and $R_{gs} = 0.985, R_{gr} = 0.814$.

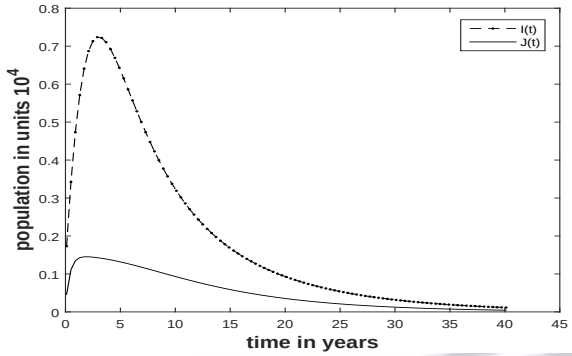


Figure 7.4: $c = 0.00004$ and $R_{gs} = 1.58, R_{gr} = 0.61$.

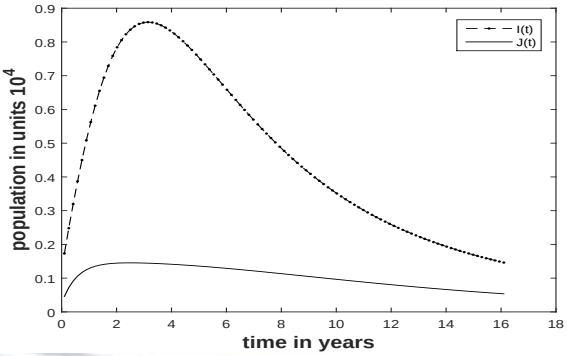


Figure 7.5: $c = 0.000025, \iota_2 = 0$ and $R_{gs} = 0.985, R_{gr} = 0.38$.

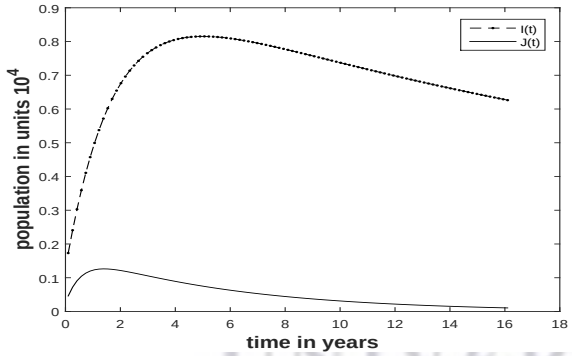
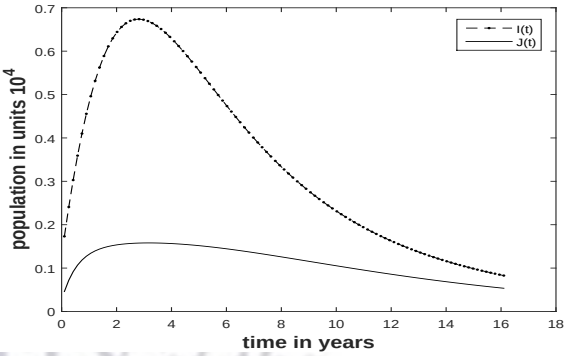


Figure 7.6: $c = 0.000025, \iota_2 = 0.6$ and $R_{gs} = 0.985, R_{gr} = 0.38$.



7.6.2 Inflow of infectives

We now study model system (7.1) by introducing the inflow of infectives i.e., when $f_E + f_I + f_L > 0$ and use the parameter values presented in Table 7.2. Figure 7.7. presents a scenario of model system (7.1) with the inflow of infective i.e., when $f_E = 0.53, f_I = 0.06, f_L = 0.21$. The results show that the disease will persist in the population due to the inflow of infectives. Thus we have $R_{gs} = 1.58$ and $R_{gr} = 1.3$ when $c = 0.00004$ and $\beta_1 = 0.000003$. The infectious class J of Figure 7.7 converges as there is no inflow of infectives into that class. We also note that even though the basic reproduction number is less than unity ($R_{gs} = 0.985, R_{gr} = 0.38$) in Figure 7.8, the disease will still persist due to the inflow of infectives.

Figure 7.7: $c = 0.00004, \beta_1 = 0.000003$ and $R_{gs} = 1.58, R_{gr} = 1.3$.

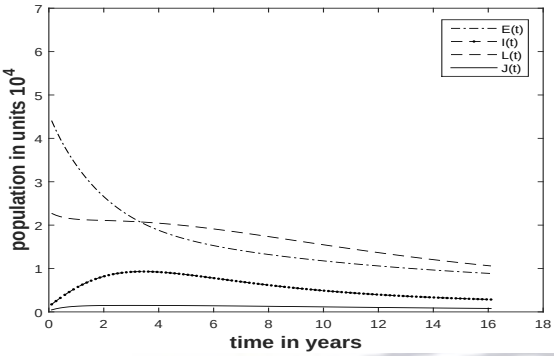
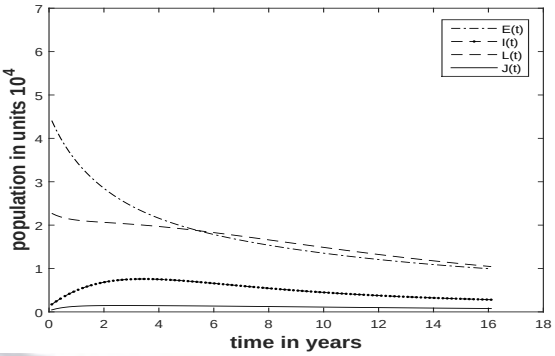


Figure 7.8: $c = 0.000025$ and $R_{gs} = 0.985, R_{gr} = 0.38$.



We extract the infectious classes I and J from Figure 7.8 and the population remains endemic even though the reproduction numbers are less the unity. In Figure 7.11 and Figure

Figure 7.9: $c = 0.00004, \beta_1 = 0.000003$ and $R_{gs} = 1.58, R_{gr} = 1.4$.

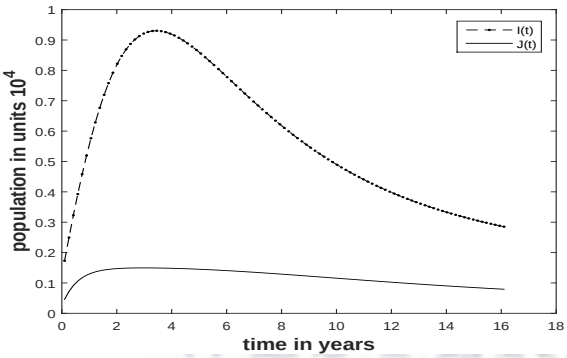
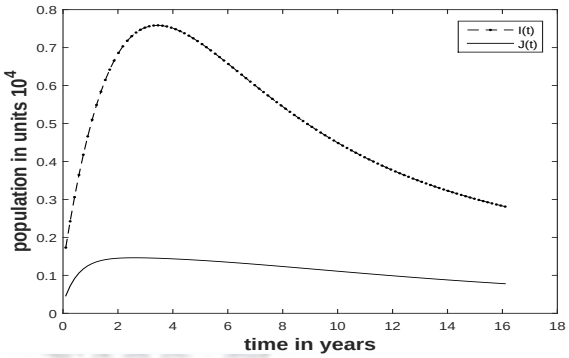


Figure 7.10: $c = 0.000025$ and $R_{gs} = 0.985, R_{gr} = 0.38$.



7.12 the disease persist with $R_{gs} = 3.11$ and $R_{gr} = 1.2$ when $c = 0.00007893$. It is also noticed that even after 40 years the disease will still persist in the population, especially with the infectious class I due to the inflow of infected individuals. In our simulations it is crystal clear that the inflow of infectives make it impossible for a population to stay endemic, unless proper controls such as treatment, screening, quarantine for MDR-TB patients, etc., are in use.

In Figure 7.13, the I class remains endemic in the absence of treatment defaulters with $R_{gs} = 1.97, R_{gr} = 0.76$ while the J class converges to disease free equilibrium. Both

Figure 7.11: $c = 0.00007893$ and $R_{gs} = 3.11, R_{gr} = 1.2$.

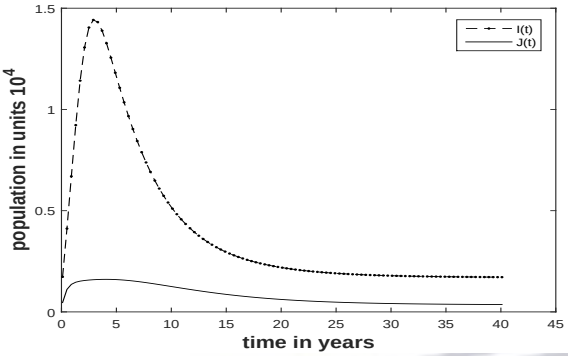


Figure 7.12: $c = 0.00007893$ and $R_{gs} = 3.11, R_{gr} = 1.2$.

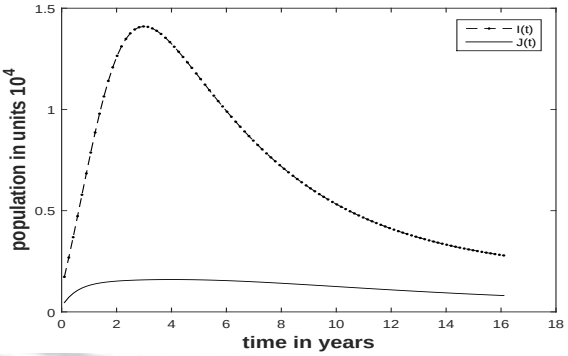


Figure 7.13: $c = 0.00005, \iota_2 = 0$ and $R_{gs} = 1.97, R_{gr} = 0.76$.

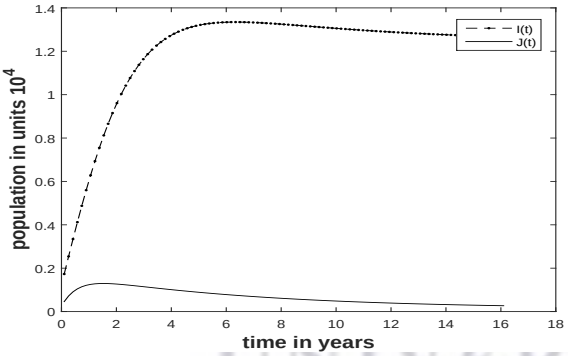
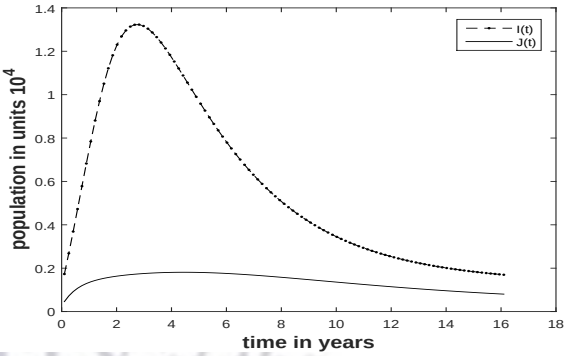


Figure 7.14: $c = 0.00007893, \iota_2 = 0.6$ and $R_{gs} = 3.11, R_{gr} = 1.2$.



strains in Figure 7.14 remain endemic in the presence of treatment defaulters $\iota_2 = 0.6$.

7.7 Conclusion

Default on TB treatment is well documented, and defaulters comprise a significant proportion of those on treatment. So for instance studies have observed a default rate of 7% in the Free State province of RSA [37] and 14% in Karachi, Pakistan [20]. Statistics such as these are the motivation for the study in this chapter. The consequences of defaulting on TB treatment in a prison are just so much more serious (since those at risk are in prison not of their own choice).

We introduced a (new) multi-strain model that considers the dynamics of drug sensitive TB and drug resistant TB in a crowded environment. The model allows for the inflow of infectives not only into the susceptible class, but also into the exposed class and infectious classes for drug sensitive TB, and into the latent class of drug-resistant TB sub-population. The global stability of the disease free equilibrium has been proved by using a Lyapunov function and Figure 7.2 confirmed the outcome of Theorem 7.4.1. We noticed that if there is no default in treatment, then the J class converges faster to the disease free equilibrium while the I class becomes endemic. MDR-TB is mostly controlled by treatment and quarantine, as can be seen in Figures 7.8, 7.11 and 7.13 as the inflow of the infectives in the J class were not considered. The model is very useful in making future projections and for testing the effects of interventions. Future work in this regard could consider optimal intervention strategies, especially for eradicating MDR-TB from prisons or other crowded populations.

Chapter 8

Optimal intervention strategies on TB epidemiology in a dense population

8.1 Abstract

Following up on the model system in Chapter 4, prison system in South Africa are well controlled in terms of managing TB disease. This can be seen from the department of correctional service annual report from the year 2015 to 2017 [80, 83] as the number of infected inmates are reducing. International agencies recomends a minimum space of 5.4 m^2 of floor space per prisoner while South African prisons stipulated a minimum allocation of 3.34 m^2 floor area in a communal cell [31]. The Democratic Republic of the Congo (DRC) assigned a floor space of 0.22 m^2 per prisoner in a communal cell [35]. We now study model system (4.1) and consider a crowded environment where control measures are mostly inactive or sometimes distracted. We use optimal control problem so as to minimise infectious active TB individuals while the cost of treatment is minimized. We further calibrate the model by using Democratic republic of the Congo prison data. Finally, we present our results numerically.

8.2 Introduction

In 2017, 2.5 million people fell ill with tuberculosis in the African region, accounting for a quarter of new tuberculosis cases worldwide [78]. An estimated 417000 people died from TB disease in the African region with 1.3 million deaths globally. Democratic Republic of the Congo (DRC) situated in Central Africa has an estimated population of 86.79 million people and a high burden country for tuberculosis, TB/HIV and multi-drug resistant TB. World Health Organization reported an estimate 262000 new cases of TB in Congo and 56500 TB related deaths that occurred in 2017 [79]. Overcrowding is still the main factor that flourishes tuberculosis in prison system. The Makala Central prison which was build to house a maximum of 1500 inmates has now detained over 8000 prisoners, which has crossed worrisome to the inmates as the minimum size is 5.4 m^2 per prisoner internationally [31, 16, 95]. Overcrowding in prisons has caused serious threat to life and health conditions of the prisoners such as malnutrition, lack of sunshine, inadequate access to care, etc., worldwide. The department of human rights reported about inadequate supplies of food, little access to water and poor ventilation which results in extreme heat.

Limited access to high quality TB diagnosis can cause poor TB screening, inaccuracy of diagnosis. In 2014 X-pert MTB/RIF were introduced in Kasai Oriental Province for the use in Mbuji-Mayi Central Prison. This has caused an improvement in the fight against TB and MDR-TB, especially for the Mbuji-Mayi Central prison as they provided results of active TB cases for the first time in the prisons records in Congo DRC [35]. By the end of 2014 laboratory confirmed TB in 31 out of 57 sputum specimen from prisoners with convincing symptoms of TB.

8.3 Model

In Chapter 4, a model that describes the dynamics of Tuberculosis in South African prisons has been studied. We now continue in this Chapter by using the same model for crowded

prison situations in the DRC. Our model is applicable in any crowded environment. We add to the original model system (4.1) in Chapter 4 two control function, $r_3(t)$ and $r_4(t)$. The control r_3 represents a fraction of distinctive TB exposed individuals that is identified and the treatment begins to be implemented so as to reduce individuals that maybe infectious. The control r_4 represents a fraction of distinctive TB Infectious individuals that is identified and treated so as to reduce infectious individuals.

$$\begin{aligned}
\dot{S} &= f_S\mu A - c_1SI - \mu S,\\
\dot{E} &= f_E\mu A + c_1SI + c_2TI - c_3EI - (\mu + r_3(t) + k)E,\\
\dot{I} &= f_I\mu A + kE - (\mu + r_4(t) + d)I + c_3EI,\\
\dot{T} &= r_3(t)E + r_4(t)I - c_2TI - \mu T.
\end{aligned} \tag{8.1}$$

Optimal control is a powerful tool in mathematics which can be used to assist in making decisions in this current situation. In some countries economic situations, political conflicts which creates displacement of people makes it difficult to implement TB control measures. In such environments, especially due to economic situations the main notion is to minimise the active infected individuals with the lowest cost possible. Our objective function to be minimized is given by:

$$J(r_3, r_4) = \int_0^T [I(t) + g_1(W_1r_3^2(t) + W_2r_4^2(t))]dt \tag{8.2}$$

where we want to minimise the infectious active TB individuals while the cost of treatment is kept minimised as well. The weight factors (positive constants) W_1 and W_2 represent a patients level of acceptance of treatment. The constant g_1 is the measure of the relative cost of the intervention related to the controls r_3 and r_4. We pursue to find an optimal control pair r_3^* and r_4^* such that

$$J(r_3^*, r_4^*) = \min_{\Omega} J(r_3, r_4) \tag{8.3}$$

where

$$\Omega = \{(r_3, r_4) \in L^1(0, T) | 0 \leq r_i \leq 1, i = 3,\ 4\}. \tag{8.4}$$

An optimal pair must satisfy necessary conditions that comes from Pontryagin's Principle. The principle takes (8.1), (8.2) and (8.3) into a problem of minimizing pointwise a Hamiltonian H which is given by:

$$\begin{aligned} H &= H(S(t), E(t), I(t), T(t), \lambda(t), r_3(t), r_4(t)) \\ &= I(t) + g_1(W_1 r_3^2(t) + W_2 r_4^2) + \lambda_1(f_S \mu A - c_1 SI - \mu S) \\ &\quad + \lambda_2(f_E \mu A + c_1 SI + c_2 TI - c_3 EI - (\mu + r_3(t) + k)E) \\ &\quad + \lambda_3(f_I \mu A + kE - (\mu + r_4(t) + d)I + c_3 EI) \\ &\quad + \lambda_4(r_3(t)E + r_4(t)I - c_2 TI - \mu T), \end{aligned} \tag{8.5}$$

where $\lambda(t) = (\lambda_1(t), \lambda_2(t), \lambda_3(t), \lambda_4(t))$ is the adjoint vector. According to the Pontryagin's Maximum Principle defined in the mathematical tools, if $(r_3^*, r_4^*) \in \Omega$ is optimal for the problem in (8.1), (8.3) with initial $S(0), E(0), I(0), T(0)$ and fixed final time T, then there exist a non-trivial absolutely continuous mapping $\lambda : [0, T] \to \mathbb{R}^5,\ \lambda(t) = (\lambda_1(t), \lambda_2(t), \lambda_3(t), \lambda_4(t))$, such that

$$\dot{S} = \frac{\partial H}{\partial \lambda_1},\quad \dot{E} = \frac{\partial H}{\partial \lambda_2},\quad \dot{I} = \frac{\partial H}{\partial \lambda_3},\quad \dot{T} = \frac{\partial H}{\partial \lambda_4}$$

and

$$\dot{\lambda_1} = -\frac{\partial H}{\partial S},\quad \dot{\lambda_2} = -\frac{\partial H}{\partial E},\quad \dot{\lambda_3} = -\frac{\partial H}{\partial I},\quad \dot{\lambda_4} = -\frac{\partial H}{\partial T}.$$

The minimization condition

$$\begin{aligned} &H(S^*(t), E^*(t), I^*(t), T^*(t), \lambda^*(t), r_5^*(t), r_6^*(t)) \\ &= \min_{0 \le r_5, r_6 \le 1} H(S^*(t), E^*(t), I^*(t), T^*(t), \lambda^*(t), r_3(t), r_4(t)) \end{aligned} \tag{8.6}$$

holds almost everywhere on $0, T$. Furthermore, the transversality conditions $\lambda_i(T) = 0,\ i = 1, 2, ..., 5$ hold.

Theorem 8.1. *There exists an optimal control pair r_3^*, r_4^* and corresponding, $S^*, E^*, I^*,$ and T^*, that minimizes $J(u_1, u_2)$ over Ω. Moreover, there exists adjoint functions $(\lambda_1^*(t), \lambda_2^*(t), \lambda_3^*(t), \lambda_4^*(t))$,*

such that

$$\begin{aligned}
\dot{\lambda_1} &= \lambda_1(c_1 I + \mu) - \lambda_2 c_1 I \\
\dot{\lambda_2} &= \lambda_2[c_3 I + (\mu + r_3(t) + k)] - \lambda_3(k + c_3 I) - \lambda_4 r_3(t) \\
\dot{\lambda_3} &= \lambda_1 c_1 S - 1 - \lambda_2(c_1 S + c_2 T - c_3 E) + \lambda_3(\mu + r_4(t) + d - c_3 E) \\
&\quad -\lambda_4(r_4(t) - c_2 T) \\
\dot{\lambda_4} &= -\lambda_2 c_2 I + \lambda_4(c_2 I + \mu)
\end{aligned} \tag{8.7}$$

with transversality conditions

$$\lambda_i(T) = 0, i = 1, ..., 4 \tag{8.8}$$

and

$$N = S^* + E^* + I^* + T^*$$

The following characterization holds

$$r_3^*(t) = \min\Big\{ \max\Big\{0\ , \frac{(\lambda_2^* - \lambda_4^*)E^*}{2g_1 W_1}\Big\},\ 1\Big\} \tag{8.9}$$

and

$$r_4^*(t) = \min\Big\{ \max\Big\{0\ , \frac{(\lambda_3^* - \lambda_4^*)I^*}{2g_1 W_1}\Big\},\ 1\Big\} \tag{8.10}$$

Proof. We now apply the Pontryagin Maximum Principle and get

$$\begin{aligned}
&\frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial S},\ \lambda_1(T) = 0, \frac{d\lambda_2}{dt} = -\frac{\partial H}{\partial E},\ \lambda_2(T) = 0, \\
&\frac{d\lambda_3}{dt} = -\frac{\partial H}{\partial I},\ \lambda_3(T) = 0, \frac{d\lambda_4}{dt} = -\frac{\partial H}{\partial T},\ \lambda_4(T) = 0,
\end{aligned} \tag{8.11}$$

evaluated at the optimal control pair and corresponding states, which results in the stated adjoint system (8.7) and (8.8).

Furthermore, we now consider the optimality conditions,

$$\frac{\partial H}{\partial r_3} = 0, \quad \frac{\partial H}{\partial r_4} = 0 \tag{8.12}$$

and solve for r_3^*, r_4^*, subject to the constraints, the characterization (8.9) and (8.10) can be derived.

The characterization of r_3^* can be shown as follows:

$$\frac{\partial H}{\partial r_3} = 2g_1 W_1 r_3 + (\lambda_4 - \lambda_2)E = 0 \tag{8.13}$$

at r_3^* on the set $\{t|0 < r_3^*(t) < 0\}$
From the set r_3^* can be obtained as follows:

$$r_3^*(t) = \frac{(\lambda_2^* - \lambda_4^*)E^*}{2g_1 W_1}.$$

Therefore, taking into account the bounds on r_3^* leads us to obtain the characterization of r_3^* in (8.9) and (8.10). □

8.4 Numerical values

The total prison population of the Democratic Republic of the Congo including the remand population is given by

$$A = 20550,$$

with 5550 sentenced inmates and 15000 remand inmates in 120 institutions [96].

8.4.1 Numerical Value for disease induced death rate

In order for us to compute the disease induced death rate in Congo DRC prison system. Let μ_{TB} be denoted by the rate of deaths due to TB as in Chapter 4. In [97, 99], 103 deaths due to lack of appropriate care out of 223 were reported during visits to holding cells and prisons in Congo DRC. The article does not specify the number of deaths due to TB, it only reports that TB aggravated the already overcrowded prison system leading to 20% increase in deaths in the previous year. More than 95% of deaths are caused by TB in low and middle income countries [34]. In Africa, TB flourishes especially in prison systems and Congo DRC is one of the countries most affected as the annual incidence reached 325 cases per 100000 population with 116894 new TB cases [34]. Therefore, our calculation will be as follows:

$$\mu_{TB} = \frac{98}{223}\mu_m = 0.16422,$$

where $\mu_m = 0.003628$ as in Chapter 4. Hence,

$$d = \mu_{TB}(1 - \mu) = 0.13434,$$

where $\mu = 0.18192$ year^{-1} as in Chapter 4.

8.4.2 Initial conditions for simulation

We now calculate the initial condition so as to predict the future conditions our our model system (8.1). In Kayomo et al. [35], it was reported that among 918 inmates in the prison population 29 TB cases were already taking treatment. An additional of 475 were likely TB case patients and TB infection was confirmed positive in 170 of the inmates. This will lead us to estimate the infection TB inmates in this way

$$I = 0.19\ A = 3905.$$

It also follows that the number of inmates who are under treatment in prison population is estimated as

$$T = 0.032\ A = 658.$$

According to World Health Organization, Congo DRC shares 80% of the worldwide TB burden [3]. Thus

$$S = 4110 \quad \text{and} \quad E = 11877.$$

8.4.3 Parameters of c_i

Using data acquired in [98, 79] to calculate the effective contact rate for TB in Congo DRC (the entire population) as in Chapter 4 denoted by c_4

$$c_4 = \frac{(84 - 64) \text{ million}}{62 \times 262000 \times 64 \text{ million}} = 3.9534{\times}10^{-7} \text{ year}^{-1}.$$

As in Chapter 4 we now calculate c_1, c_2 and c_3 in this way

$$c_1 = c_0 \times \frac{P_1}{A} = 0.001616 \text{ year}^{-1}, \quad c_3 = \frac{k}{2A}, \quad c_2 = 2(10/A),$$

where P_1 is the 2018 population size of Congo DRC. The rest of the parameters will be adopted from Chapter 4 and are presented in Table 8.1 and 8.2.

8.5 Simulations

We first study our model without the inflow of infectives so as to examine for possible eradication of the disease. Figure 8.1 reveals that the prison system is unable to eradicate the disease due to high contact rate which is $c_1 = 0.0008$ and leads to $R_* = 1.89$. In Figure 8.1, we notice that when $c_1 = 0.0004$ leads to $R_* = 0.947$. We also notice that when it is 6.5 years the number of Exposed and susceptible individuals becomes equal and leading to a higher increase in number of susceptible inmates. Following up on Chapter 4 in Figure 4.2, we notice that there is a faster convergence in the exposed class as compared to Figure 8.2.

We now analyze model system (8.1) by using the parameter values in Table 8.1 and vary the parameter value of $c = 0.0003$. We notice that in Figure 8.4, the numerical results

Table 8.1: Model parameters and initial conditions

Parameter	Numerical value	Source
μ	0.18192	[33], [86]
d	0.13434	[97, 99, 34], [86]
r_1	0.30	[14]
r_2	0.50	[14]
k	0.05	[90], [14]
A	20550	[96]
$S_{t_{15}}$	4110	[35]
$E_{t_{15}}$	11877	[35]
$I_{t_{15}}$	3905	[35]
$T_{t_{15}}$	658	[35]

Table 8.2: Inflow and contact rates

Parameter	Numerical value	Source
c_1	0.001616	[98, 79]
c_2	$20/A$	[24]
c_3	$k/(2A)$	Estimated
f_S, f_E, f_I	$0.2, 0.74, 0.06$, respectively	[86]

shows the number susceptible individuals decreasing due the absence of control and this leads to higher number of infected individuals. Figure 8.5, represents the population of infected individuals with out optimal control treatment and it is noticed that the population is sharply increasing which means that the disease will persist and the population will become endemic.

Figure 8.1: Prison population in different classes without the inflow of infectives and $R_* = 1.89$.

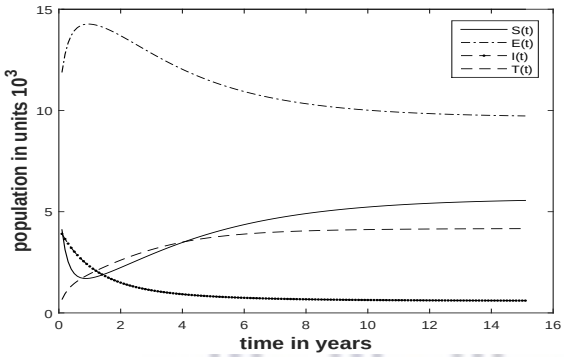
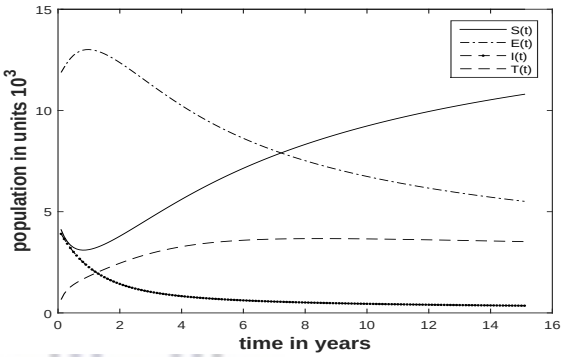


Figure 8.2: Prison population in different classes without the inflow of infectives and $R_* = 0.947$.



The infectious classes of Figures 8.1 and 8.2 are presented in Figure 8.3 and a faster convergence over a period of 60 years is seen when $R_* = 0.947$.

In Figure 8.6, it is noticed that the infected individuals converges to a disease free equilibrium due to the optimal control treatment. This means that the disease will not persist in the Congo DRC prison population. The treated population in Figure 8.7 decreases due the absence of optimal control treatment. Therefore, the population will not experience any endemicity.

We also notice in Figure 8.8 that in the absence of optimal control treatment, the prison system of Congo DRC becomes endemic when $c_1 = 0.001616$ from Table 8.2 this is also due to the inflow of the infectives. By reducing the contact rate to $c_1 = 0.0000001$ in Figure 8.9, the susceptible individuals increases drastically even if there is inflow of infectives and this will lead to a decrease in the infectious class.

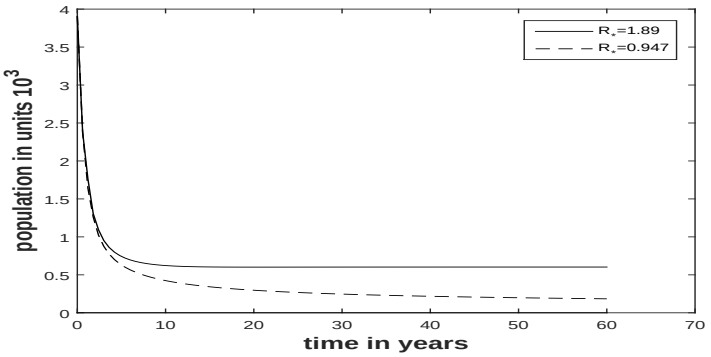


Figure 8.3: Infective class without the inflow of infectives for two cases $R_* = 1.89$, $R_* = 0.947$.

Figure 8.4: Susceptible population without control.

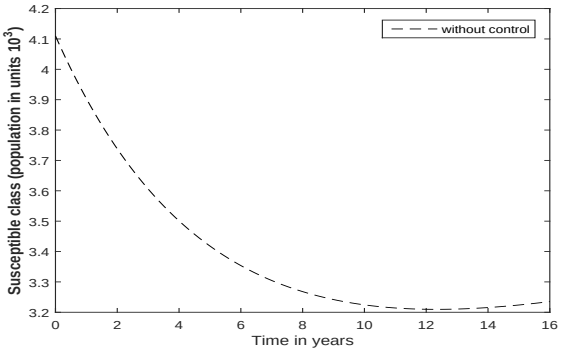
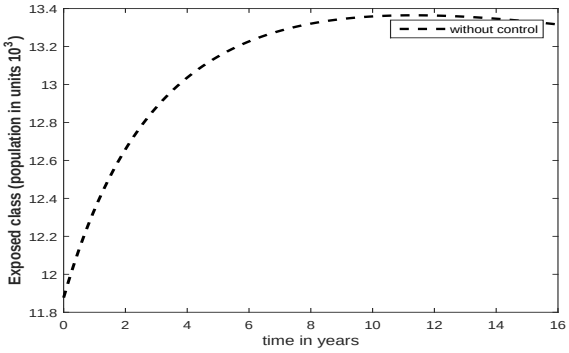


Figure 8.5: Exposed population without control.



8.6 Conclusion

In this Chapter, we applied optimal control theory by considering its applicability to real life situations such as crowded environment for instance. We considered a prison population in Congo DRC where control programs are not always adhered. The parameter values that align with Congo DRC prisons have been calculated and further simulated in the above Figures. Numerical results indicate in the absence of control strategies the is population experiencing edemicity while in the presence of control eradication of disease is noticed. The greatness of intervention can be peaceful along the time, in other models this is not the case. Control programs that follow these strategies can effectively reduce

Figure 8.6: Infectious population with control.

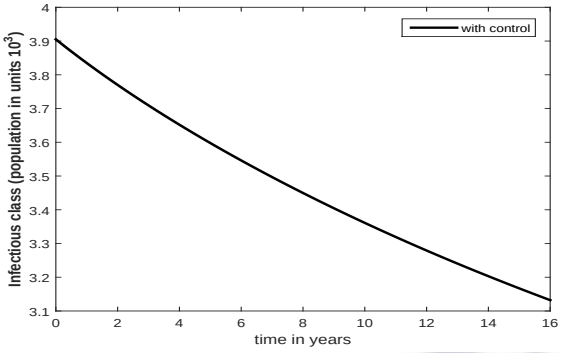


Figure 8.7: Treated population with control.

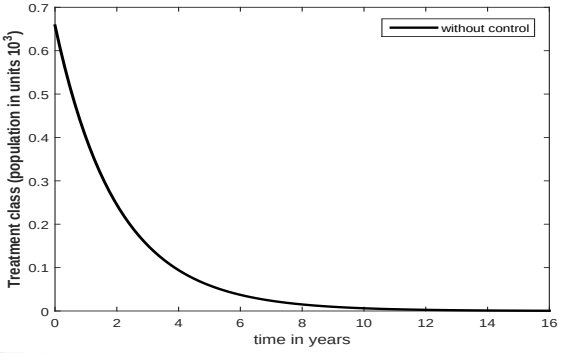


Figure 8.8: Infectious population with control.

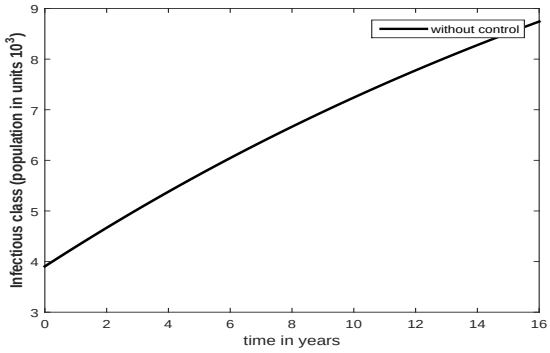
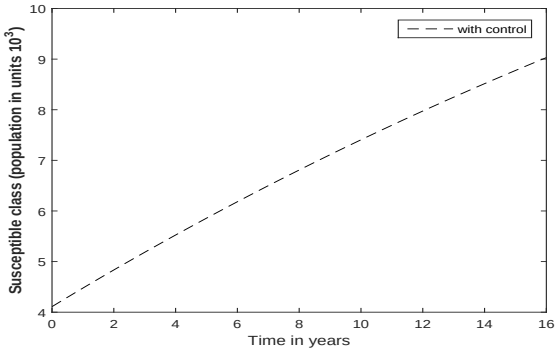


Figure 8.9: Susceptible population with control.



the number of infectious TB cases as seen in Figure 8.6. while minimizing treatment cost.

Chapter 9

Conclusion

The main objective of this thesis was to develop a model that can be applied in a crowded environment. We chose a prison system as one of the crowded environment in South Africa. We noticed that a prison population has its own population within the general population. A disease models in a general population the removal rate is calculated as the inverse of the life expectancy. The life expectancy has decreased from 67 years in the year 2015 to 63 years in 2019 and this is due to infectious diseases and chronic diseases [89, 84, 68]. Therefore, the mortality rate of a general population fluctuate over time.

The model in Chapter 4 has been taken from a paper of Buonomo and in this Lacitignola [14] and Ssematimba et al. [57], these two papers considered tuberculosis in a crowded environment. This model was adjusted to apply to prison systems and the compartmental model allowed for inflow of infectives into classes other than just the susceptible class. We noticed that the removal rate in a prison system is not the same as in general population is by death only. Removal rate is by being released from prison and by death, these parameters were calibrated accordingly. It was observed that if at a specific prison site or system there is no inflow of infected individuals, then the disease will vanish from the prison provided that the numerical value of the invariant R_* is below unity. For the case of the South African prison system, most of the crucial parameters of the model were calculated using data from public domain prison data. Other parameters, including ini-

tial conditions for computations, were obtained from data in various published literature, together with interpolation methods.

In chapter 5, we introduced stochastic perturbation into the model in chapter 4 and further apply it into a prison system. We proved that there is a unique global positive solution for the system of stochastic differential equation in (5.1). It was noted that whenever the basic reproduction number is significantly greater than unity then the disease will persist in the prison population through our simulations in Chapter 5. It has also been observed for a stochastic model that when the perturbation is sufficiently big then the disease tends to vanish and this can be seen in Figure 4.2. It is more important to study smaller perturbation. It has been observed that whenever $R_\sigma < 1$, then I and E almost surely converge exponentially to zero in step with Theorem 4.2.2.(a), in the absence of the inflow of infective.

A two-group model that considers the sentenced and remand population has been studied in Chapter 6. This has assisted us in monitoring the dynamics of TB disease between the two sub-populations. The model also allows the inflow of infectives into the inflow of susceptible, exposed and infected individuals will appear into the susceptible class, exposed class and the infected class. Hence, we assume that there is no inflows of infectives into the treatment class for both sub-population groups, they are unfit to commit crime as they are under treatment. The threshold parameter have been analysed by using the next generation matrix. We also prove the behaviour of global stability of the disease free equilibrium by using the Lyapunov function.

A two strain model that considers the dynamics of drug sensitive TB and drug resistant TB in a crowded environment has been proposed in Chapter 5. The model allowed the inflow of infectives into the susceptible class, exposed class, infectious class of drug sensitive respectively, and into the latent class of drug resistant class. The global stability of the disease free equilibrium by using the Lyapunov function has been proved and the

outcome Theorem 7.4.1 has been confirmed through simulations. The model is very useful in making future projections. We noticed that if there is no default in treatment, the J class converges faster to the disease free equilibrium while the I class becomes endemic. MDR-TB is mostly controlled by treatment and quarantine, as the inflow of the infectives in the J class were not proposed.

Following up from Chapter 4, we used model 4.1 in the Congo DRC prison where control measures are not always implemented. Optimal control theory is a powerful mathematical tool that can be used to reduce active infectious individuals while controlling the cost of the treatment. We notice in Chapter 8 that by implementing the optimal control treatment the disease can be eradicated.

By introducing the inflow of infectives cases into the prison system, TB remains endemic, as can be seen in the above Chapters. By screening the inflow on admission and providing for them a separate accommodation, TB infection in a prison system can be greatly reduced. South Africa prison are using these control and we have seen the results from the annual report for correctional services. The fight against the spread of TB diseases in DCS facilities has improved significantly. In 2014, the number of inmates who were cured were 4675 out of 6233 and in the year of 2018, 636 out of 728 inmates were successfully treated [80, 83].

Inmates have the right to receive health care, including preventive measures, equivalent to the care available in South African communities. Inmates with pulmonary TB must be admitted in the health facility and isolated for two weeks and hospitalisation must be considered for severe extra pulmonary disease.

Bibliography

[1] Adetunde I.A. The Mathematical models of the dynamic behavior of tuberculosis disease in the Upper East Region of the Northern part of Ghana: A case study of Bawku. *Academic journals Inc.* **1(1)** (2009), 15 – 30.

[2] R. M. Anderson and R. M. May. Population biology of infectious diseases. Report of the dahlem workshop, berlin, 14-19 March 1982. In population biology of infectious diseases. Report of the Dahlem workshop, Berlin, 14 - 19 March 1982. Berlin, German Federal Republic; Springer-Verlag, 1982.

[3] Loukia Aketi, Zacharie Kashongwe, Christian Kinsiona, Serge Bisuta Fueza, Jack Kokolomami, Grace Bolie, Paul Lumbala, and Joseph Shiku Diayisu. Childhood Tuberculosis in a Sub-Saharan Tertiary Facility: Epidemiology and Factors Associated with Treatment Outcome. *PLoS ONE*, DOI:10.1371/journal.pone.0153914 April 21, 2016.

[4] Allen L.J.S. *An introduction to Mathematical Biology*, Prentice Hall, USA (2007).

[5] Allen L.J.S. *An introduction to Stochastic Process with Applications to Biology,* Chapman and Hall, CRC (2010).

[6] R.M. Anderson and R.M. May, *Infectious Diseases of Humans: Dynamics and Control*, Oxford University, London/New York, 1991.

[7] J.P. Aparicio, A.F. Capurro and C. Castillo-Chavez. Transmission and Dynamics of Tuberculosis on Generalized Households. *J. theor. Biol.* **206**, (2000) 327 – 341.

[8] N. Bacaer, R. Ouifki, C. Pretorius, R. Wood, B. Williams. Modelling the joint epidemics of TB and HIV in a South African township. *J. Math. Biol.* **57** (2008) 557 – 593.

[9] C.P. Bhunu. Mathematical analysis of a three-strain tuberculosis transmission model. *Applied Mathematical Modelling* **35** (2011) 4647 – 4660.

[10] C. P. Bhunu and W. Garira. A Two Strain Tuberculosis Transmission Model with Therapy and Quarantine. *Mathematical Modelling and Analysis* **14** (2009) 291 – 312.

[11] C.P. Bhunu, S Mushayabasa, G. Magombedze and L.I. Roeger. Tuberculosis transmission model with case detection and treatment. *J. Appl. Math. and Informatics* **29** (2011) 529 – 546.

[12] G. Birkhoff and R.G. Carlo. *Ordinary Differential Equations*, John Wiley and Sons Inc., New York, (1989).

[13] N.F. Britton. *Essential Mathematical Biology.* University of Bath, Claverton Down, Bath BA27AY, UK (2003).

[14] B. Buonomo and D. Lacitignola. Analysis of a tuberculosis model with a case study in Uganda, *Biological Dynamics* **4**, (2010) 571 – 593.

[15] V. Capasso and D. Bakstein. *An Introduction to Continuous-Time Stochastic process.*

[16] Canada: Immigration and Refugee Board of Canada, Democratic Republic of the Congo: Prison conditions in Kinshasa, including the treament of prisoners (2015 June 2017), 28 June 2017, COD105817.FE, available at: https://www.refworld.org/docid/59843b394.html [accessed 16 November 2019]

[17] Y. Cai, X. Wang, W. Wang, and M. Zhao. Stochastic Dynamics of an SIRS Epidemic Model with Ratio-Dependent Incidence Rate. *Abstract and Applied Analysis* vol. 2013, Article ID 172631, 11 pages.

[18] C. Castillo-Chavez and Z. Feng. To treat or not to treat: the case of tuberculosis *J. Math. Biol.* **35** (1997) 629 – 656.

[19] J.R. Chasnov. *Introduction to Differential Equations.* The Hong Kong University of Science and Technology, Department of mathematics 2009-2012.

[20] N. Chida, Z. Ansari, H. Hussain, M. Jaswal, S. Symes, A.J. Khan, et al. (2015) Determinants of Default from Tuberculosis Treatment among Patients with Drug-Susceptible Tuberculosis in Karachi, Pakistan: A Mixed Methods Study. PLoS ONE 10(11):e0142384. doi:10.1371/journal.pone.0142384.

[21] H. Cox, L. Dickson-Hall, W. Jassat, M. Moshabela, K. Kielmann, A. Grant, M. Nicoli, J. Black, K. Mlisana, L. Vanleeuw and M. Loveday. Drug-resistant tuberculosis in South Africa: history, progress and opportunities for achieving universal access to diagnosis and effective treatment.

[22] T.M. Daniel. The history of tuberculosis. *Respiratory Medicine* **100**, (2006) 1862 – 1870.

[23] Etheridge A. *A Course in Financial Calculus.* Cambridge University Press, New Jersey (2002).

[24] J.V. Ershova, L.J. Podewils, L.E. Bronner, H.G. Stockwell, S. Dlamini and L.D. Mametja. Evaluation of adherence to national treatment guidelines among tuberculosis patients in three provinces of South Africa. *S. Afr. Med. J.* **104(5)** (2014), 362C8.

[25] Z. Feng, C. Castillo-Chavez and A. Capurro. A model for tuberculosis with exogeneous reinfection. *Theor. Pop. Biol.* **57**, (2000) 235 – 247.

[26] C. Guanrong. *Stability of nonlinear system.* Encyclopedia of RF and Microwave Engineering, Wiley, New York, (2004), 4881 – 4896.

[27] E. P. Hafidh, N. Aulida, B. D. Handari, and D. Aldila. Optimal Control Problem for Tuberculosis and Multidrug Resistant Tuberculosis Transmission Mode. *AIP Conference Proceedings*, **2023** 020223 (2018).

[28] E. Ibargen-Mondragn and L. Esteva. On the interactions of sensitive and resistant Mycobacterium tuberculosis to antibiotics. *Mathematical Biosciences* **246** (2013) 84−93.

[29] Z.W. Jia, G.Y. Tang, Z. Jin, C. Dye, S.J. Vlas, X.W. Li, D. Feng, L.Q. Fang, W.J. Zhao and W.C. Cao. Modeling the impact of immigration on the epidemiology of tuberculosis. *Theoretical Population Biology,* **73** (2008), 437 − 448.

[30] D. Jiang, J. Yu, C. Ji. and N. Shi. Asymptotic behavior of global positive solution to a stochastic SIR model. *Mathematical and Computer Modelling* **54** (2011) 221 − 232.

[31] S. Johnstone-Robertson, S.D. Lawn, A. Welte, L. Bekker and R. Wood. Tuberculosis in a South African prison: a transmission modelling analysis, *SAMJ* **101, No.11**, (2011) 809 − 813.

[32] D.W. Jordan and P. Smith. *Nonlinear Ordinary Differential Equations.* Oxford University Press, Walton Street, Oxford OX26DP, (1987).

[33] R. Jules-Macquet. *The State of South African Prisons*, Edition One. NICRO Public Education Series, Pretoria, (2014).

[34] G.M. Kalonji, G. De Connick, L.O. Ngongo, D.K. Nsaka, T. Kabengele, F.T. Kandolo, F. Ilunga-Ilunga, A. Adelin and D. Giet. Prevalence of tuberculosis and associated risk factors in the Central Prison of MbujiMayi, Democratic Republic of Congo. *Tropical Medicine and Health*, (2016) 44 : 30.

[35] M.K. Kayomo, E. Hasker, Mu. Aloni, L. Nkuku, M. Kazadi, T. Kabengele, D. Muteteke, F. Kapita, A. Lufulwabo, Y.D. Mukadi, J. Muyembe-Tamfum, M. Ieven,

B.C. de Jong and M. Boelaert. Outbreak of Tuberculosis and Multidrug-Resistant Tuberculosis, Mbuji-Mayi Central Prison, Democratic Republic of the Congo. *Emerging Infectious Diseases*, **24** (2018), 2029 − 2035.

[36] W.O. Kermack and A.G. McKendrick. Contributions to the Mathematical Theory of Epidemics - I.*Proceedings of the Royal Society,* **115**, (1927) 700 − 721.

[37] G. Kigozi , C. Heunis, P. Chikobvu, S. Botha and D. van Rensburg. Factors influencing treatment default among tuberculosis patients in a high burden province of South Africa. *International Journal of Infectious Diseases*, 54 (2017) 95-102.

[38] A. Lahrouz, L. Omari, D. Kiouach. Global analysis of a deterministic and stochastic nonlinear SIRS epidemic mode, *Nonlinear Analysis: Modelling and Control,* **16** (2011) 59 − 76.

[39] S. Lenhart, J. Workman. *Optimal control applied to Biological Models. Mathematical and Computational Biology Series.* Chapman and Hall/CRC, London, UK (2007).

[40] J. Li, Y. Xiao, F. Zhang, and Y. Yang. An algebraic approach to proving the global stability of a class of epidemic models. *Real Eorld Application,* **12**, (2012) 2006−2016.

[41] Q. Liu and Q. Chen. Analysis of the deterministic and stochastic SIRS epidemic models with nonlinear incidence. *Phys. A* **428**, (2015) 140 − 153.

[42] Z. Liu. Dynamics of positive solutions to SIR and SEIR epidemic models with saturated incidence rates. *Real World Applications* **14**, (2013) 1286 − 1299.

[43] L. Liu and Y. Wang . A mathematical model study of a TB model with treatment interruptions and two latent periods. *Computational and Mathematical Methods in Medicine,* (2014), 15*pp.*

[44] W. Liu. SIRS epidemic model incorporating media coverage with random perturbation. *Abstract and Applied Analysis*, vol. 2013, Article ID 792308, 9 pages, 2013.

[45] M. Maliyoni, P. M. M. Mwamtobe, S. D. Hove-Musekwa, and J. M. Tchuenche. Modelling the Role of Diagnosis, Treatment, and Health Education on Multidrug-Resistant Tuberculosis Dynamics. *Biomathematics* **2012**, 20 pages.

[46] Mao X. *Stochastic Differential Equations and Applications,* Horwood, Chichester, 1997.

[47] B.K. Mishra and J. Srivastava. Mathematical model on pulmonary and multidrug resistant tuberculosis patients with vaccination. *Journal of the Egyptian mathematical Society* **22** (2014) 311 − 316.

[48] D.P. Moualeu, M Weiser, R. Ehrig, P. Deuflhard. Optimal control for a tuberculosis model with undetected cases in Camerron. *ZIB-Report* 2013.

[49] R. Ming, J. Liu, W.K.W. Cheung and X. Wan. Stochastic modelling of infectious diseases for heterogeneous populations. *Infectious Diseases of Poverty*, (2016) 5 : 107.

[50] S. Mushayabasa, C.P. Bhunu and G.G.R. Stewart. A mathematical model for assessing the impact of intravenous drug misuse on the dynamics of HIV and HCV within correctional institutions. *ISRN Biomath.* (2012), 2012 : 17.

[51] D.P. Moualeu, S. Roblitz, R. Ehrig and P. Deuflahard. Parameter Identification for a Tuberculosis Model in Cameroon. *ZIB-Report* 2013 13.

[52] F. Nyabadza and D. Winkler. A simulation age-specific tuberculosis model for the Cape Town metropole. *South African Journal of Science*, **109** (2013) 1 − 7.

[53] B. Øksendal. *Stochastic Differential Equations. An Introduction with Applications* Springer-Verlag Heidelberg New York, USA (2000).

[54] C. Ozcaglar, A. Shabbeer, S.L. Vandeberg, B. Yener and K.P. Bennett. Epidemiological models of mycobacterium tuberculosis complex infections. *mathematical Biosciences*, **236** (2012) 77 − 96.

[55] P. Rodrigues, M. Gabriela, M. Gomes and C. Rebelo. Drug resistance in tuberculosis–a reinfection model. *Theoretical Population Biology,* **71** (2007) 196 − 212.

[56] M. Ronoh, R. Jaroudi, P. Fotso, V. Kamdoum, N. Matendechere, J. Wairimu, R. Auma and J. Lugoye. A Mathematical Model of Tuberculosis with Drug Resistance Effects. *Applied Mathematics*, **7**, (2016), 1303 − 1316.

[57] A. Ssematimba, J.Y.T. Mugisha and L.S. Luboobi. Mathematical models for the dynamics of Tuberculosis in density-dependent population: The case of internally displaced people's camps (IDPCs) in Uganda, *Journal of mathematics and statistics*, **3** (2005) 217 − 224.

[58] J.M. Trauer, J.T. Denholm and E.S. McBryde. Construction of a mathematical model for tuberculosis transmission in highly endemic regions of the Asia-pacific. *Journal of Theoretical Biology* **358** (2014) 74 − 84.

[59] P. Van Den Driessche and J. Watmough. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission, *Math. Biosci.*, **180** (2002) 29 − 48.

[60] L. Wang, H. Huang, A. Xu and W. Wang. Stochastic Extinction in an SIRS Epidemic Model Incorporating Media Coverage. *Abstract and Applied Analysis*, (2013) 1 − 8.

[61] J. Wang, S. Gao, X. Li. A TB model with infectivity in latent period and imperfect treatment.*Discrete Dyn. Nat. Soc.* (2012) 19.

[62] L. Wang and X. Wang. Influence of temporary migration on the transmission of infectious diseases in amigrants1 home village. *Journal of Theoretical Biology* **300**, (2012) 100 − 109.

[63] P.J. Witbooi. Stability of an SEIR epidemic model with independent stochastic perturbations. *Physica A* **392**, (2013) 4928 − 4936.

[64] P.J. Witbooi, G. Muller and G.J Van Schalkwyk. Vaccination control in a stochastic SVIR epidemic model. *Comput. Math. Methods Med.* (2015) $1-9$.

[65] P.J. Witbooi. An SEIRS epidemic model with stochastic transmission. *Adv. Difference Equ.*, bf 109 (2017) 16pp.

[66] Q. Yanga and X. Mao. Extinction and recurrence of multi-group SEIR epidemic models with stochastic perturbations. *Nonlinear Anal. Real World Appl.* **14,** (2013) $1434-1456$.

[67] Ya. Zhao and D. Jiang. The Behavior of an SVIR Epidemic Model with Stochastic Perturbation. *Abstr. appl. Anal.* (2014) 7 pages.

[68] M. Zhou, H. Wang, X. Zeng, P. Yin, J. Zhu, W. Chen, X. Li, L. Wang, L. Wang, Y. Liu, J. Liu, M. Zhang, J. Qi, S. Yu, A. Afshin, Em. Gakidou, S. Glenn, V.S. Krish, M.K. Miller-Petrie, W.C. Mountjoy-Venning, E.C. Mullany, S.B. Redford, H. Liu, M. Naghavi, S.I. Hay, L. Wang, C.J.L. Murray and X. Liang. Mortality, morbidity, and risk factors in China and its provinces, 199012017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet* **394** (2019) $1145-1158$.

[69] Y. Zhou, K. Khan, Z. Feng, and J Wu. Projection of tuberculosis incidence with increasing immigration trends. *Journal of Theoretical Biology,* **254** (2008), $215-228$

[70] Y.U. Zhao, L.I. Mingtao and S. Yuan. Analysis of transmission and control op Tuberculosis in Mainland China, $2005-2016$, based on the age-structure mathematical model. *Environmental Research and Public Health,* **14** (2017), 1192.

[71] Y. Zhao, Q. Zhang, and D. Jiang. The asymptotic behavior of a stochastic SIS epidemic model with vaccination. *Advances in Difference Equations*, (2015), 2015 : 328.

[72] http://www.dcs.gov.za/Publications/Annual/Reports/DCS/Annual/Report/2014-2015.pdf (downloaded July 2016).

[73] May 2017, http://www.prisonstudies.org/highest-to-lowest/prison-population-total?field-region-taxonomy-tid=All.

[74] www.prisonstudies.org/country/southafrica. Accessed 31 April 2016.

[75] http://www.who.int/topics/tuberculosis/en/.

[76] http://www.who.int/mediacentre/factsheets/fs104/en/.

[77] https://www.who.int/tb/publications/factsheet-global.pdf?ua=1. 31 October 2019.

[78] https://www.who.int/tb/publications/global-report/gtbr2018-main-text-28Feb2019.pdf

[79] http://worldpopulationreview.com/countries/dr-congo-population/.

[80] http://www.dcs.gov.za/wp-content/uploads/2016/08/DCS-Annual-Report-2014-2015.pdf

[81] http://www.dcs.gov.za/wp-content/uploads/2016/08/DCS-Annual-Report-2015-2016.pdf

[82] http://www.dcs.gov.za/wp-content/uploads/2017/12/DCS-AR-2016-2017.pdf

[83] http://www.dcs.gov.za/wp-content/uploads/2018/10/DCS-AR-2017-18-WEB.pdf Accessed 13 November 2019.

[84] http://www.statssa.gov.za/publications/P0302/P03022019.pdf Accessed 11 November 2019.

[85] https://www.statssa.gov.za/publications/P0302/P03022017.pdf Accessed 11 November 2019.

[86] http://www.dcs.gov.za/wp-content/uploads/2016/08/DCS-Annual-Report-2014-2015.pdf Accessed 02 October 2019.

[87] http://judicialinsp.dcs.gov.za/Annualreports/JICS Annual Report 2015-2016 as at 4 October 2016 v 12.pdf

[88] http://www.dailymaverick.co.za/article/2013-07-01-the-losing-battle-against-tb-in-prisons/ Accessed June 2016.

[89] Statistics South Africa, Statistical release P0302: Mid-year population estimates 2015, Pretoria, July 2015.

[90] https://www.tbfacts.org/tb-statistics-south-africa/. Accessed July 2016.

[91] https://www.health-e.org.za/wp-content/uploads/2015/10/Departmentof-Health-Annual-Report-201415.pdf. Accessed 12 July 2016.

[92] http://www.spotlightnsp.co.za/download/NSP/Review/7/Web.pdf.Accessed June 2016.

[93] http://businesstech.co.za/news/lifestyle/114266/inside-south-africasmost-dangerous-prison/. Accessed June 2016.

[94] http://pmg-assets.s3-website-eu-west-1.amazonaws.com/JICS_Annual_Report-1718_Final.pdf. Accessed 13 December 2018.

[95] https://rm.coe.int/16806cc449.

[96] https://www.prison-insider.com/countryprofile/prisonscongo-en. Accessed 17 November 2019.

[97] https://reliefweb.int/sites/reliefweb.int/files/resources/UNJHRO%20-%20Report%20on%20death%20in%20detention%20-%20March%202013%20-%20ENGLISH%20TRANSLATION.pdf Accessed 17 November 2019.

[98] https://www.worldometers.info/world-population/democratic-republic-of-the-congo-population/. Accessed 17 November 2019.

[99] https://www.state.gov/wp-content/uploads/2019/03/Democratic-Republic-of-the-Congo-2018.pdf Accessed 20 November 2019.

[100] https://www.spotlightnsp.co.za/2014/05/18/defaulting-on-treatment-where-are-we/ Accessed 21 November 2019.

[101] https://www.ncbi.nlm.nih.gov/books/NBK138752/. Accessed 17 November 2019.