MODIFIED DETERMINISTIC MODELLING FOR TUBERCULOSIS INFECTION

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MODIFIED DETERMINISTIC MODELLING FOR TUBERCULOSIS INFECTION

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LIST OF ABBREVIATIONS

AIDS	Acquired Immunodeficiency Syndrome
BCG	Bacillus Calmette-Guérin
BP	Transcritical Bifurcation
DFE	Disease-Free Equilibrium
EE	Endemic Equilibrium
EEP	Endemic Equilibrium Point
GAS	Globally Asymptotically Stable
HB	Hopf Bifurcation
HIV	Human Immunodeficiency Virus
LAS	Locally Asymptotically Stable
MDR-TB	Multidrug-Resistant Tuberculosis
ODE	Ordinary Differential Equation
SEIR	Susceptible-Exposed-Infective-Recovered
SEIRE	Susceptible-Exposed-Infective-Recovered-Exposed
SI	Sensitivity Index
SLC	Stable Limit Cycle
SVEIRE	Susceptible-Vacinated-Exposed-Infective-Recovered-Exposed
TB	Tuberculosis
USLC	Unstable Limit Cycle

WHO	World Health Organization
XDR-TB	Extensively Drug-Resistant Tuberculosis

LIST OF SYMBOLS

Roman Letters

A	HIV-infected individuals with AIDS symptoms
A_{TB}	HIV-infected with AIDS symptoms coinfected with TB
b	birth rate
c	saturation form of treatment
c_1	contact rate
E	exposed individuals
f	fast progression rate
g	progression rate to the early exposed stage
H	HIV-infected individuals
H_{TB}	infected individuals coinfected with TB
I	infected individuals
I_m	identity matrix
j	probability of treatment failure
l	natural TB recovery rate
m	half saturation constant of infection
M	infected individuals undergoing ARV's (antiretroviral, that is the treatment of HIV/AIDS and TB)
N	total population

p	exogenous re-infection rate
P_A	pre-AIDS stage
P_{ATB}	pre-AIDS stage with TB
q	relapsed rate
R	recovered individuals
R_0	basic reproduction number
R_C	effective reproduction number with saturated treatment
R_{ph}	effective reproduction number with public health education and hospital treatment
R_V	effective reproduction number with an imperfect vaccine
S	susceptible individuals
T_f	final time
T^0	disease-free equilibrium
T^*	endemic equilibrium
u_1	efforts to reduces endogenous reaction
u_2	treatment of exposed individuals that has been identified
u_3	approved drugs for TB
v_1	effort of preventing susceptible individuals from TB exposure
v_2	latent case finding interventions
v_3	case holding control
v_4	active case finding control

z	reduction in infection due individual in the hospital

Greek Letters

Λ	recruitment rate
α	chemoprophylaxis treatment
β	transmission rate
β_1	transmission rate without media alert
β_2	transmission rate with media alert among the susceptible individuals
β_3	transmission rate with media alert among the exposed individuals
γ	recovery rate
γ_1	recovery rate from I_1 to I_2
γ_2	recovery rate from I_2 to I_1
γ_3	ineffective therapy rate
δ	disease induced death rate
δ_1	disease induced death rate for I_1
δ_2	disease induced death rate for I_2
ε	saturated incidence rate
η	individuals vaccinated at the steady state
η_1	progression rate from I_1 to I_2
η_2	progression rate from I_2 to I_1

θ	rate at which vaccine wanes
κ	progression rate from E to I
κ_1	progression rate from I_1 to I_2
κ_2	progression rate I_2 to I_1
λ	force of infection rate
μ	natural death rate
μ_D	death rate as a result of AIDS
μ_{DTB}	death rate as a result of coinfection
ν	reduction in infection risk due to awareness rate
ξ	rate at which susceptible individuals are vaccinated
ϖ	impact of delaying the treatment of infected individuals
σ	modification parameter for re-infection
$\varsigma_1 - \varsigma_{12}$	co-infection rate
ϕ	rate at which educated susceptible become susceptible again
ψ	information dissemination (awareness rate)
ω	reduction in risk of infection due to vaccination rate
ω_1	successful treatment rate
ω_2	unsuccessful treatment rate

PEMODELAN BERKETENTUAN TERUBAHSUAI BAGI JANGKITAN BATUK KERING

ABSTRAK

Batuk kering, disebabkan oleh *Mycobacterium tuberculosis*, ialah salah satu penyakit berjangkit yang menyerang paru-paru manusia dan menyebabkan 10 juta jangkitan baru di seluruh dunia, dengan rata-rata 1.2 juta kematian. Pemodelan matematik telah digunakan untuk memahami corak penularan jangkitan serta mengenalpasti kawalan yang sesuai dalam mencegah penularan. Melalui pemodelan matematik juga, dinamik sesuatu jangkitan dapat diramal dengan lebih berkesan. Ini seterusnya membawa kepada tujuan utama tesis ini yang mana empat model jangkitan batuk kering berketentuan berpetak diperkenalkan. Model yang dibangunkan ini mengambil kira faktor-faktor penularan jangkitan batuk kering, seperti pendidikan kesihatan masyarakat dan rawatan di hospital, vaksin yang tidak sempurna, pemulihan tepu (rawatan) serta kawalan optimum. Ketaknegatifan dan keterbatasan penyelesaian akan dianalisis untuk setiap model yang diperkenalkan. Kaedah matriks generasi-hadapan digunakan untuk menentukan kuantiti ambang yang dikenali sebagai nombor reproduksi asas, R_0 untuk setiap model. Analisis manifold berpusat digunakan untuk memperoleh ambang percabangan transkritikal Hopf ke belakang secara tepat. Keseimbangan unik endemik terbukti stabil secara asimptot sejagat menggunakan teori fungsi Lyapunov untuk setiap model. Model asas menunjukkan bahawa keseimbangan bebas penyakit adalah stabil secara asimptot sejagat jika $R_0 < 1$. Analisis kestabilan menunjukkan percabangan normal (ke depan) atau dikenali sebagai percabangan transkritikal terhasil apabila $R_0 = 1$. Dalam model kedua, pendidikan kesihatan awam dan rawatan hospital diga-

bungkan ke dalam model asas. Analisis yang sama dijalankan, dan model ini memperlihatkan fenomena percabangan ke belakang yang menunjukkan kewujudan bersama kestabilan keseimbangan bebas penyakit dan keseimbangan endemik. Kesan epidemiologi yang didapati daripada hasil dapatan ini ialah $R_{ph} < 1$ tidak lagi mencukupi bagi mengawal penularan batuk kering secara efektif dalam populasi. Simulasi berangka menunjukkan bahawa pendidikan kesihatan awam dan rawatan di hospital mempunyai pengaruh besar dalam mengurangkan beban penyebaran batuk kering. Model ketiga mempertimbangkan dinamik jangkitan batuk kering yang menggabungkan vaksin yang tidak sempurna dan faktor-faktor eksogenus lain seperti jangkitan semula pada individu yang dirawat dan jangkitan semula eksogenus. Cerapan model yang didapati menunjukkan pencabangan ke belakang, walaupun $R_V < 1$. Keputusan ini mendedahkan bahawa vaksin batuk kering tak sempurna boleh secara efektif mengurangkan penyebaran penyakit dalam populasi walaupun terdapat peningkatan dalam keberkesanan dan liputan kesan am. Secara spesifiknya ia menunjukkan keberkesanan vaksin pada sebilangan kecil manusia pada keadaan mantap dapat mengurangkan beban penyakit. Dalam model keempat, pemulihan tepu tak linear (rawatan) dipertimbangkan. Syarat-syarat kestabilan keseimbangan tempatan dan kewujudan pencabangan ke belakang serta pencabangan Hopf ditetapkan. Keputusan menunjukkan bahawa gabungan pemulihan tepu tak linear (rawatan) ke dalam model akan menyebabkan dinamik yang kompleks. Akhirnya, teori kawalan optimum diaplikasikan pada model asas menggunakan Prinsip Maksimum Pontryagins untuk mengkaji strategi optimum bagi mengawal dan menghilangkan jangkitan batuk kering. Keputusan mencadangkan bahawa strategi-strategi kawalan sangat bermanfaat dalam mengurangkan beban penularan jangkitan batuk kering di dalam sesuatu populasi.

MODIFIED DETERMINISTIC MODELLING FOR TUBERCULOSIS INFECTION

ABSTRACT

Tuberculosis (TB), caused by the *Mycobacterium tuberculosis*, is one of the contagious disease that mainly attacks human lungs and caused 10.6 million new infection globally, with an average of 1.6 million people dying. In general, mathematical modelling can serve to understand the transmission pattern and identify suitable controls in preventing the infections. Through mathematical modelling as well, the dynamics of an infection can be predicted more effectively. This in turn leads to the main purpose of this thesis where four compartmental deterministic models for tuberculosis infection is proposed. The developed models addressed the important factors related to the transmission of tuberculosis infection, such as public health education and hospital treatment, an imperfect vaccine, nonlinear saturated recovery (treatment) and optimal control. The non-negativity and boundedness of the solutions are analysed for each presented model. The next generation matrix is employed to determine the threshold value known as basic reproduction number, R_0, for each model. The center manifold analysis are used to derive an exact transcritical and backward bifurcation threshold. The unique endemic equilibrium is shown to be globally asymptotically stable using a suitable Lyapunov function theory for each model, respectively. Numerical experiments are also are conducted to illustrate the analytical results. The basic model reveals that the disease-free equilibrium is globally-asymptotically stable whenever $R_0 < 1$. The stability analysis demonstrates that a normal (i.e., forward) bifurcation known as transcritical bifurcation emerges at $R_0 = 1$. In the second model, we incorporate public

health education and hospital treatment into the basic model. Similar analysis was performed, the model exhibits the phenomenon of backward bifurcation, where the stable disease-free equilibrium co-exists with a stable endemic equilibrium. The epidemiological consequence of this result are that the $R_{ph} < 1$ is no longer sufficient, although necessary, for effectively controlling the spread of TB in a population. Numerical simulation indicates that public health education and hospital treatment have a significant effect on reducing the prevalence of TB burden. The third model considers dynamics of the TB infection that incorporated an imperfect vaccine and other exogenous factors such as re-infection among the treated individuals and exogenous re-infection. The proposed model is observed to show a backward bifurcation, even when $R_V < 1$. The results reveal that an imperfect tuberculosis vaccine can effectively reduce the spread of infectious diseases within the population, although an increase in the effectiveness and coverage increases the general effect. It is specifically shown that the effective vaccination of very few people at steady state decreases the disease burden. In the fourth model, nonlinear saturated recovery (treatment) model is considered. The conditions for the local stability of equilibria and the existence of backward bifurcation and Hopf bifurcation are established. The results showed that the incorporation of the nonlinear saturated recover into TB models lead to rich dynamics. Finally, optimal control theory is applied on the basic model using the Pontryagins' Maximum Principle to investigate optimal strategies for controlling and eliminating TB. The results suggest that the control strategy is advantageous in reducing the burdens of TB transmission in the population.

CHAPTER 1

INTRODUCTION

1.1 Background

Tuberculosis (TB) is one of the hazardous infectious diseases that has become a significant widespread phenomenon, claiming more lives more than any other contagious disease every day according to (World Health Organization, 2022). Approximately 1/3 of the total population has a TB infection, resulting in millions of deaths and new cases annually (World Health Organization, 2022). The report corroborates that TB is one of the tops ten causes of mortality globally of both human and animal populations (World Health Organization, 2019; Ullah et al., 2019; Sudre et al., 1992; Dolin et al., 1994; Castillo-Chavez and Song, 2004). In 2021, for instance, 10.6 million individuals developed TB, and more than 1.6 million died from it, including 187000 HIV-positive persons (Kabunga et al., 2020; World Health Organization, 2022). Typically, the signs may not be instantaneous when an individual contracts the disease. Thus the individual remains asymptomatic for a long time or is latently infected for life (Adebiyi, 2016). Young adult may get infected by TB when they are most active (World Health Organization, 2021). Generally, the TB-related deaths often happen in the middle-income countries, for example, India, which leads the count, followed by Indonesia, China, Philippines, Pakistan, Nigeria, Bangladesh, and South Africa. Such countries accounted for over 87% of the entire TB trouble in the world. As a result, it is vital to implement techniques and methods that make it simple to understand how this disease spreads and predict its progression.

TB is a communicable disease caused by *Mycobacterium tuberculosis* affecting mostly the lungs (Jaramillo, 1999; Daniel et al., 1994). However, it can also attack different organs including the brain, kidney, spine, central nervous system, or the lymphatic system (World Health Organization, 2022; Ullah et al., 2019; Khan et al., 2019; Khajanchi et al., 2018; Zhang et al., 2015). It is important to note that the active lung TB disease typically begins with a cough, with sputum or blood on occasion, chest pains, fatigue, unexpected weight reduction, fever, and night sweats, which may last at least three or more weeks at times. It has been reported by Bar (1922) that a pregnant woman who is infected may infect the foetus in some situations. Only individual who have active TB can spread the disease. The latently infected individuals do not spread the bacteria (World Health Organization, 2022; Kabunga et al., 2020). Transmission starts with one individual then onto the next relies upon the number of infected and expelled drops, the period of contaminated risk exposure, the virulence of the *Mycobacterium tuberculosis*, and the activity of environmental ventilation (World Health Organization, 2020; Daniel et al., 1994; Kabunga et al., 2020).

1.2 History of TB

From the beginning of time, the sickness of TB has differently known as consumption, phthisis, and the great white plague. It is widely accepted that the causative agent, *Mycobacterium tuberculosis* began from other, more primitive organisms of the identical bacteria genus. In 2014, consequences of another DNA investigation of a tuberculosis genome recreated from in southern Peru suggest that human tuberculosis is under 6,000 years of age. Regardless of whether scientists theorize that people initially obtained it in Africa around 5,000 years ago (Zimmer, 2014), there is evidence

that the foremost TB infection happened about 9,000 years before then (Hershkovitz et al., 2008). The infection spread more along trading routes, including to domestic animals, such as dairy animals and goats in Africa. It has believed that seals and ocean lions on African seashores became infected and spread it over the Atlantic to South America (Zimmer, 2014).

1.2.1 Re-infection TB, Recurrent TB and Endogenous Reactivation

Re-infection TB, also known exogenous re-infection, is a TB episode caused by getting re-infected with a new TB strain from another infectious person (Feng et al., 2000; Chiang and Riley, 2005). Recurrent TB is branded as the incidence of a repeat episode of TB after the successful treatment of the first infection (Kar and Mondal, 2012; Wangari et al., 2016). Notably, there are two systems by which recurrent TB can happen: (i) relapse with the previously responsible strain or (ii) exogenous re-infection from a new exposure (Chaisson and Churchyard, 2010; Luzze et al., 2013; Guerra-Assunção et al., 2015). Remember that re-infection of the individuals who have latent state TB is not viewed as recurrent TB (Wangari, 2017).

The differences between these two terms is that with re-infection TB, a person does not require recovery from the initial episode, whereas for recurrent TB a person must have been cured of the first incidence of TB. Endogenous reactivation is described as reactivating an initial latent infection (Styblo and Enarson, 1991; Bloom, 1994). Endogenous reactivation happens among latently infected individuals in the context of TB (Feng et al., 2000).

1.2.2 Biology of TB

TB is a disease, fundamentally in the lungs (pneumonia), generally caused by bacteria known as *Mycobacterium tuberculosis*. TB is primarily transmitted from person to person by inhaling contaminated air during close contact. The life cycle of this bacterial is introduced in Figure 1.1. The infection can stay inactive (dormant) for quite a

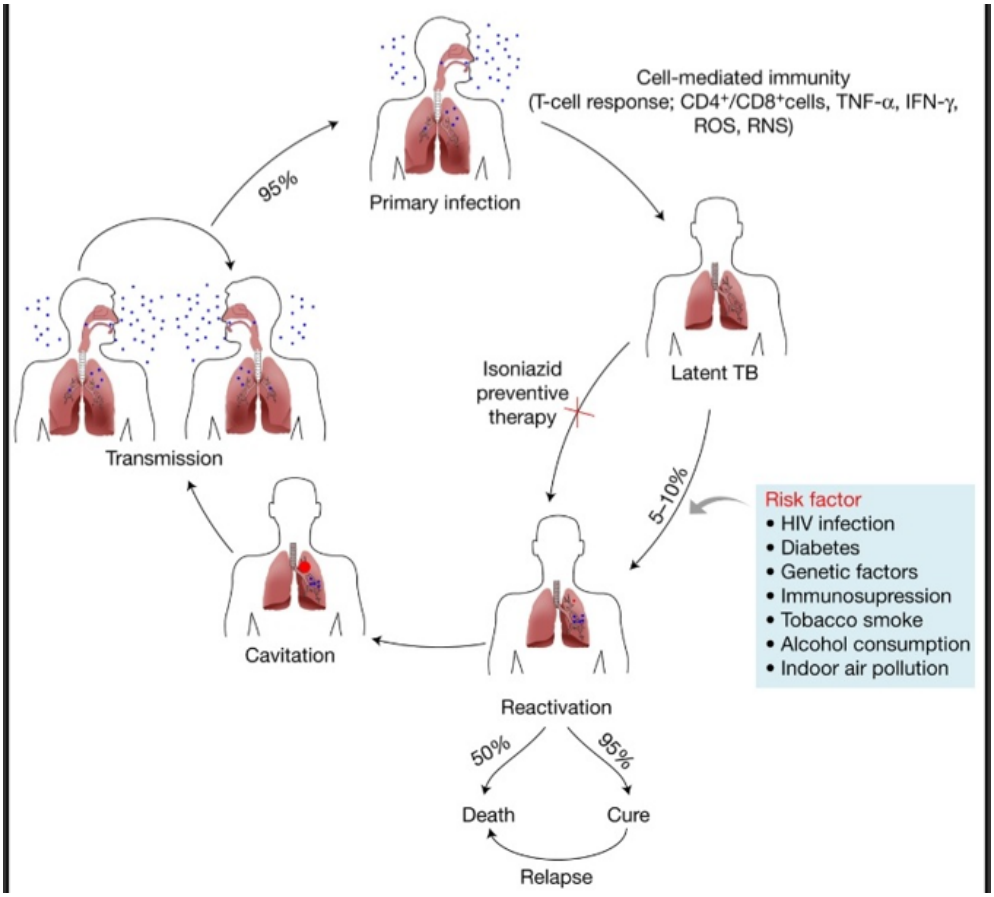

Figure 1.1: Life cycle of *Mycobacterium tuberculosis*. Demonstrations from Kumar et al. (2011).

long time without causing side effects or spreading to others. When a patient immune system is dormant debilitated, the TB can end up active (reactivate) and cause infection within the lungs or other parts of the body. We can contact TB through close contact, alcohol and medication misuse, certain illnesses (such as diabetes, cancer, HIV), and

occupations (healthcare workers). The most widely recognized symptoms and signs of TB are coughs, fatigue, weight loss, fever, and night sweat. The diagnosis of TB includes skin tests, chest X-rays, Polymerase Chain Reaction (PCR) tests to detect the genetic material of the causative bacteria, and sputum analysis (smear and culture) (World Health Organization, 2022).

1.2.3 Treatment of TB

TB is a treatable and curable illness. It is fundamental to treat individuals who are contagious with TB. Whenever left untreated, a particular individual may become ill, which may prompt life-threatening circumstances. If treatment is not administered correctly, TB can develop resistance. Indeed, suppose patients quit taking medicine before time. In that case, they may become infected once more, and the TB bacteria that are still alive may become resistant to the treatment, known as multi-drug resistant tuberculosis (MDR-TB) in the worst cases (World Health Organization, 2019). A MDR-TB is a type of TB caused by bacteria that can not react to the four most effective first-line anti-TB drugs, namely, isoniazid, rifampicin, ethambutol, and pyrazinamide. A MDR-TB is hard to treat, particularly in old age.

Castillo-Chavez and Feng (1997) have investigated a two strains mathematical model, where treatment of multi-drug resistant individuals has been excluded as it is hard to treat. Furthermore, individuals with HIV/AIDS are at great danger of developing MDR-TB. In 2015, the World Health Organization estimated about 450,000 MDR-TB and 170,000 deaths worldwide (World Health Organization and others, 2011). There is also another sickness that comes after MDR-TB, which is called extensively

drug-resistant (XDR-TB). The XDR-TB happens when resistance from second-line drugs develops on top of MDR-TB. Most instances of XDR-TB happening are in developing countries (World Health Organization and others, 2011). Numerous individual in developing countries do not take a physical test due to the significant expense (World Health Organization, 2001, 1988). Subsequently, some exposed people can not be detected. The key to TB control is to comply with and successfully complete a treatment plan (Wares et al., 2003; Cheng et al., 1997; Fox, 1958). Nonadherence to treatment has been referred to as a significant obstruction to the control of TB, and it assumes a huge part in the association with high transmission rate, morbidity, and cost of TB (Cramm et al., 2010; Munro et al., 2007).

Commonly, there are three types of medical interventions for treating TB, which are treating latently infected TB individuals to avert endogenous reactivation, treating active TB patients, and vaccination to reduce TB epidemics (Gomes et al., 2007). Previous studies assert that vaccinating susceptible individuals can effectively control the spread (Liu et al., 2008; Anderson and May, 1992). Vaccination can be denoted in mathematical compartmental models as an exchange between susceptible individuals and the recovered compartment (Buonomo and Lacitignola, 2011). Some vaccinations prevent infection but the vaccinated individual can still spread the infection (Buonomo and Della Marca, 2019). Bacille Calmette-Guerin (BCG) is the primary effective TB vaccine commonly administered (Andersen and Doherty, 2005), with above 50% efficiency against lung infections and over 80% types of TB in children. Considerably, adults are more prone to spreading TB than children (Nadolinskaia et al., 2020). Regrettably, BCG has not effectively protect adults against TB. As such, there is a need

for new vaccines that target both children and adult population (Fine et al., 1999).

1.3 Modelling of TB

There is an increase in TB modelling research in recent decades. Mathematical modeling enlightens policymakers on the probable population-level effect and cost-effectiveness related to executing new diagnostic tests. Notably, models consider numerous settings, populations, and diagnostic algorithms to ensure that the right diagnostic approach is chosen for the right setting. This implies that models aid the understanding of population characteristics that will lead to different approaches and impact. To identify approaches to control the infectious diseases in the population, several investigation have been carried out in mathematics (Kabunga et al., 2020; Ndondo et al., 2021; Ullah et al., 2019; Xiang et al., 2016). Mathematical model are designed and applied in study of epidemiological phenomena, as well as to explain the ecological problems (Martcheva, 2015). Mathematical epidemiology is now well-established in the academic literature, and mathematical modelling is contributing significantly to both mathematics and public health (Martcheva, 2015; Hethcote, 2000, 1994; Vynnycky and White, 2010; Keeling and Rohani, 2011). One of the fundamental goals of these mathematical models is to see how a certain disease spreads in the population, so that in the future the disease can be eradicated. In other words, mathematical model attempt to respond to the question of how to control infection in the population (prevention and monitoring) (Martcheva, 2015; Vynnycky and White, 2010; Kabunga et al., 2020).

Mathematical modeling has recently received a lot of interest in both epidemiol-

ogy and ecology. Mathematical modeling can aid in the explanation of real-world systems and the investigating the impact of various components (Martcheva, 2015; Keeling and Rohani, 2011). This thesis focuses on the use of mathematical modeling to investigate TB infections and how they spread in populations using various control strategies. Models can be categorised in a variety of ways such as linear and nonlinear, static/dynamic, discrete/continuous, deterministic/stochastic (Martcheva, 2015; Keeling and Rohani, 2011). In this thesis, we will focus on deterministic models.
A deterministic model is one in which every set of variable states is uniquely determined by the parameters in the model and the initial state of the variables (Martcheva, 2015).

1.4 Motivation

In recent years, many researchers have focused mostly on epidemiology of TB transmission based on susceptible, infected and recovered SIR and susceptible, exposed, infected and recovered SEIR models with the aim to slow down the transmission. Additionally, researchers have also collected enormous amounts of information about the disease, and how it is transferred, and individuals affected with it (Adebiyi, 2016; Kar and Mondal, 2012; McCluskey and van den Driessche, 2004; Rohaeti et al., 2015; Blower et al., 1995; Fatimaa and Mishra, 2020). Comparing with previous results, our study take into the account, the aspects of re-infections, exogenous re-infections, public health education, vaccination, saturated treatment and optimal control. The present study sought to complement and broaden the previously mentioned studies. To the author's knowledge, there are still lack of studies that focus on the dynamics of the TB infection by incorporating different dynamical features as

introduced in this thesis, public health education together with hospital treatment and saturated treatment. Considering the abovementioned, we are motivated to construct and qualitatively investigate a new enhancement thus more comprehensive deterministic model using ordinary differential equation, to better understand the global burden and control of TB in the population.

1.5 Problem Statement

Despite numerous efforts and control strategies at present set up aimed at achieving a TB-free world (World Health Organization, 2019), TB keeps on causing a major public health issue worldwide. It is projected that one-fourth of the population is infected with *Mycobacterium tuberculosis*. Perhaps 5-15 percent of these individuals will develop active tuberculosis. According to a WHO report, every year, 10 million individuals become sick and 1.5 million individuals die from TB, making it the world's leading infectious killer. Therefore, tackling TB and assessing control measures to minimize and eradicate TB is critically important. For the last two decades, several researches have been conducted on TB particularly. Still more research is needed to minimize the burden of TB to a minimal level. As a result, it is essential to formulate a mathematical model to investigate the dynamics of tuberculosis as well as the effects of different types of control strategies in terms of dynamical behaviour. This study will also examine into how public health education and hospital treatment, as well as an imperfect vaccine, saturated treatment, and optimal control, can help to decrease the TB burden faster.

1.6 Research Questions

The thesis aims to address some of the key mathematical and epidemiological questions:

1. How many equilibria does the basic TB model exhibit? Furthermore, under what conditions are the obtained equilibrium points locally and globally asymptotically stable? And which type of bifurcation will the system experience?

2. What is the role of public health education and hospital treatment to eliminate tuberculosis or at least reducing its prevalence? And how can we determine the most influence parameters in the dynamical behaviour?

3. What is the impact of an imperfect vaccine on the transmission dynamics of tuberculosis disease?

4. What is the dynamical behaviour of the basic model with the mass action and saturated recovery (treatment)? Will the use of mass action and saturated treatment have any impact on the theoretical outcome obtained in such a scenario?

5. What is the impact of personal protection, chemoprophylaxis, and treatment strategies to eradicate TB disease?

1.7 Research Aim and Objectives

The main aim of this thesis was to design and analyse a various deterministic model of transmission dynamics of TB infection. To succeed the aim of this research, the following objectives will be achieved, these include:

1. to develop a basic SEIRE TB model and qualitatively analyze it. The basic SEIRE model monitors the dynamic of susceptible (S), Exposed (E), Infectious (I), and Recovered (R) individuals.

2. to extend the basic SEIRE TB model to study the role of public health education and hospital treatment. Similar analysis will be carried out as in the case of the basic TB model. To perform sensitivity analysis to identify the most influential parameter in the dynamical behavior of the TB model

3. to construct a TB model with mass action that incorporated an imperfect vaccine and other exogenous factors such as re-infection among the treated individuals and exogenous re-infection. Some of the properties to be consider include, the model equilibrium points and the phenomenon of backward bifurcation;

4. to develop TB model with nonlinear saturated recovery (treatment). The local and global stabilities of disease-free equilibrium points as well as co-existing equilibrium points will be investigated;

5. to formulate optimal control strategies for TB model based on personal protection and chemoprophylaxis of exposed individuals and treatment of infected individuals using the basic model.

1.8 Methodology

This thesis focuses on the development of of deterministic models of TB infection that is based on systems of ordinary differential equations. These mathematical models improve on the previous studies' model for TB infection. In addition, the models are then analysed by using a standard qualitative methods given below:

- Model formulation, where the population is broken down into epidemiological classes.
- The boundedness and non-negativity of the solutions of TB models are investigated by using the standard comparison theorem and positivity property.
- The basic reproduction number of TB models is calculated by employing the next-generation matrix approach.
- The existence conditions of both disease-free and endemic equilibrium points of the TB models are obtained.
- The theory of stability analysis is used to explain the qualitative study of the proposed model.
- The global stability of the equilibrium points of TB models is studied by constructing suitable Lyapunov functions.
- The proof of the existence of backward bifurcation and transcritical bifurcation is determined by employing the center manifold theorem.
- A Hopf bifurcation of TB models is illustrated by taking the saturated recovery and some other TB parameters as bifurcation parameters.
- The theoretical results of TB models are demonstrated numerically by using MATLAB-R2020b, MAPLE and XPPAUT.

1.9 Scope of the Research

This thesis covers the deterministic models of TB infection based on ordinary differential equations incorporating various control strategies. In this thesis all individuals

with TB infection have to go through the latent period. The theoretical analysis and numerical simulations are conducted to ensure the quality of the proposed models.

1.10 Limitation of the Research

This study has a limitations. Validation process of the model is in fact, a crucial part of the whole model development process. Once the model development phases are completed, model validation occurs. This thesis does not consider model validation due to the lack of access to real data of TB.

1.11 Significant of the Study

The ideas and findings provided in this thesis will be helpful to relevant authorities in assessing the effect of different control strategies for minimizing the prevalence of the global burden of TB. The results on the different control strategies in TB dynamics will also be necessary for raising awareness among decision-makers to ensure that the national health network is prepared and equipped to prevent, limit or eradicate TB. This study will however, serve as a foundation for future studies into the transmission dynamics of TB and other related infectious diereses.

1.12 Thesis Organization

The organisation of this thesis is shown in Figure 1.2. Chapter 1 presented the biological history of TB, statement of the problem, the research questions, the significant of study, the aim of this study as well as research methodology. Chapter 2 is dedicated to the related literature review on various TB models. In Chapter 3, the appropriate

mathematical tools to be used in Chapters 4–8 are derived. From Chapters 4 to 8, the details of the five objectives concerned in this thesis are discussed. In Chapter 4 we presented the basic model of TB with standard incidence rate. The basic reproduction number was computed and analyzed. The existence of bifurcations is considered and the result on the stability of the disease-free equilibrium (DFE) and endemic equilibrium (EE) are investigated. The stability of the endemic equilibrium was explored using the centre manifold theorem. Global stability using Lyapunov function are also presented. In Chapter 5, we incorporated the public health education and hospital treatment of TB in to the basic model. Sensitivity analysis are also investigated. In Chapter 6, we incorporated an imperfect vaccine in to dynamics of TB and other exogenous factors such as re-infection among the treated individuals and exogenous re-infection using bilinear incidence rate. Both the theoretically and numerically findings are presented in Chapter 6. The saturated recovery (treatment) function was introduced into the dynamics of TB infection in Chapter 7. The conditions for the local stability of equilibria and the existence of backward bifurcation and Hopf bifurcation are established. The influences of varying the saturated recovery (treatment) function are also demonstrated. In Chapter 8, we introduced chemoprophylaxis treatment into the first model studied in Chapter 1. We considered an optimal control techniques. We aimed at minimizing the population of those exposed and infected with TB disease while minimizing costs. The overall concluding remarks, as well as suggestions for future works, are offered in Chapter 9.

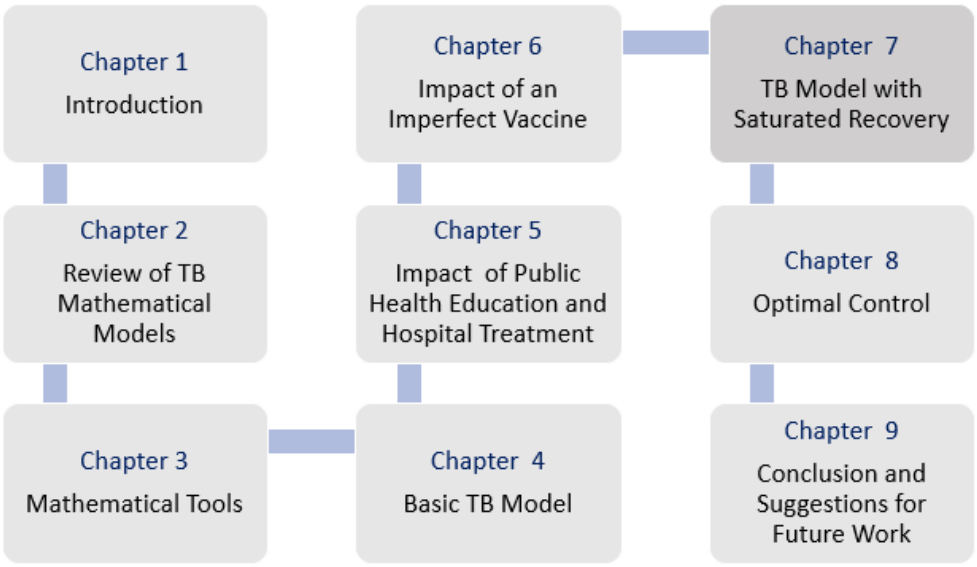

Figure 1.2: Flowchart of the thesis.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

Tuberculosis is one of the most contagious disease, affecting one-quarter of the global population. A lot of people are infected with TB bacteria but do not develop the disease or spread it. In 2021, 10.6 million individuals were infected with TB infection and 1.6 million died from TB-related infections, including 187000 people with HIV (World Health Organization, 2022). Mathematical models are extremely helpful in understanding the control and effect of infectious diseases and making potential forecasts about the spread. There are three stages to be understood while working with mathematical modeling of biological systems. The initial stage is to form a mathematical model that correctly describes the biological process being studied. Then, one should apply mathematical techniques in order to understand the model's behaviour. Finally, the appropriate translation of the results of the model is needed to decide whether the biological results obtained is significant. Differential equations have been applied to many types of biological systems ranging through population, epidemics and physiological systems (Allen, 2007b).

There are three different states of the disease, which are endemic, epidemic, and pandemic Grennan (2019). Endemic refers to a disease that is constantly present in a given location or population. The number of the affected individuals is generally low, and it does not significantly increase or decrease overtime but it is always there.

Examples are chickenpox which affect children at a regular predictable rate, dengue in tropical and subtropical regions, and malaria which is permanently present in many part of Africa. Epidemic is a widespread occurrence of an infectious disease in a community at a particular time. Examples include Zika virus infection, starting in Brazil in 2014 and spreading to most of Latin America and the Caribbean; the 2014–2016 Ebola outbreak in West Africa, which was large enough to be considered an epidemic, and yellow fever. Pandemic refers to an epidemic that has spread over several countries or continents, usually affecting a large number of people. Examples are HIV/AIDS which claimed the lives of more than 36 million since 1981 and with over 30 million cases, and COVID-19 pandemic which was declared by the WHO as a global outbreak. TB is considered as endemic. The focal point of this thesis will be on the endemic.

2.2 Foundation of Mathematical Modelling of Infectious Diseases

The foundation of mathematical modelling of infectious diseases is typically made through one for the main epidemic models introduced by Kermack and McKendrick (1927), notable as the SIR epidemic model. In epidemiology, mathematical modeling continues to play a key contribution in gaining a better understanding of the underlying mechanism both for spread of emerging and re-emerging infectious disease, as well as recommending a powerful control measures (Sharomi, 2010). Despite the fact that TB is a major public health concern, substantial progress has been made in terms of employing mathematical modeling and analysis to obtain understanding into its transmission patterns (Kabunga et al., 2020; Kim et al., 2018; Egonmwan and Okuonghae, 2019a; Kar and Mondal, 2012; Wangari, 2017).

Kermack and McKendrick (1927) developed an SIR mathematical model that addresses infectious disease transmission. It comprises the susceptible (S), infected (I) and recovered (R) compartments. The original SIR model constructed by Kermack and McKendrick (1927) was based on the idea that people may be divided into one of three groups: those who are susceptible to infection, those who are infected and hence infectious, and those who have recovered and therefore immune. The SIR model is the foundation of mathematical epidemiology. Figure 2.1 depicts the model in Kermack and McKendrick (1927) and it is represented by the following system of ODEs:

$$\begin{aligned} \frac{dS}{dt} &= -\frac{\beta SI}{N}, \\ \frac{dI}{dt} &= \frac{\beta SI}{N} - \gamma I, \\ \frac{dR}{dt} &= \gamma I, \end{aligned} \tag{2.1}$$

where N denotes the total population, S, I and R represents the susceptible, infected

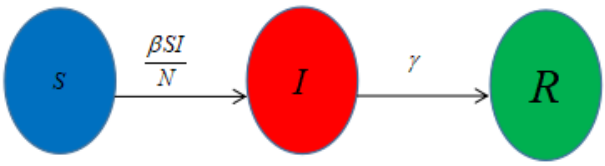

Figure 2.1: Schematic diagram of SIR model (Kermack and McKendrick, 1927).

and recovered individuals, respectively. The parameters β, and γ are the transmission and recovery rates, respectively. The SIR model equations (2.1) have been modified to include vital and convincing biological and epidemiological characteristics including vulnerability and latent or exposed people who do not yet exhibit disease symptoms

(Wangari, 2017). Simple SIR models are often unable to capture such possibilities. Some modified SIR models includes susceptible, infected and susceptible individuals (SIS), susceptible, infected, recovered and susceptible individuals (SIRS), susceptible, exposed, infected and recovered individuals (SEIR), susceptible, exposed, infected, recovered and susceptible individuals (SEIRS), susceptible, exposed, infected, recovered and exposed individuals (SEIRE) and susceptible, exposed, infected, recovered and infected individuals (SEIRI), respectively, are the most popular abbreviations for models. The modified SIR models will be considered in further detail in Section 3.

2.3 Epidemic Models and Control Strategies

Mathematical models describe how to control diseases in great detail. They are powerful techniques for evaluating the potential influence of various control intervention strategies (Garba, 2008). The critical threshold known as the basic reproductive number, R_0, refers to the number of new infections created by a single infected person introduced into a completely susceptible population over the duration of disease is the main parameters in these models. Models give an orderly method of designing and representing significant aspects in epidemiology and control by investigating their impacts. One of the most significant control strategies to reduce the spread of disease is the assessment of public health measures. Clearly, the main goal of public health interventions is to reduce R_0, below unity to make infectious prevention possible (Garba, 2008; Wangari, 2017). This gives a criterion towards enhancing control strategies including vaccination, which lowers the susceptibility of the population and quarantine/isolation, which brings down the occurrence of disease.

2.4 Review of Tuberculosis Infection Models and Their Results

Deterministic models comprising ODEs are used to explain and monitor TB transmission. These models help in understanding the processes involved in the dynamics of TB infection. The parameters presented in this chapter are given in Table 2.1

The first TB infection model was built by Waaler et al. (1962). The population was classified into susceptible (S), exposed (E) and infected (I) compartments. They evaluated parameters inside the model for South India, and concluded that the future trend of TB was unlikely to grow. The transmission mechanism was ignored from their model. The model constructed by Waaler et al. (1962), Blower et al. (1995), Wangari (2017) and Kar and Mondal (2012) is given by

$$\begin{aligned} \frac{dS}{dt} &= \Lambda - \beta SI - \mu S, \\ \frac{dE}{dt} &= (1-f)\beta SI - (\mu+\kappa)E, \\ \frac{dI}{dt} &= f\beta SI + \kappa E - (\mu+\delta+\gamma)I. \end{aligned} \tag{2.2}$$

Here, Λ denotes the recruitment rate, β denotes the transmission rate, μ is the rate of natural death, f is the proportion of those who get TB fast (that is the proportion of new cases that are classified as infectious), γ is the recovery rate, δ is the death rate due to TB, and κ is the progression rate from E to I.

Blower et al. (1995), Kar and Mondal (2012) and Wangari (2017) used the same assumptions that infected individuals who recover from the disease can move to the recovered class. Therefore, they included the recovered compartment (R). The model

Table 2.1: Description of parameters used in Chapter 2.

State Variables	Description
Λ	Recruitment rate
N	Total population
β	Transmission rate
β_1	Transmission rate without media alert
β_2	Transmission rate with media alert among the susceptible individuals
β_3	Transmission rate with media alert among the exposed individuals
μ	Natural death rate
κ	Progression rate from E to I
m	Half saturation constant of infection
α	Progression from E to R due chemoprophylaxis treatment
γ	Recovery rate
γ_3	Ineffective therapy rate
θ	Rate at which vaccine wanes
c	Saturation form of treatment
c_1	Contact rate
ϖ	Impact of delaying the treatment of infected individuals
ξ	Rate at which susceptible individuals are vaccinated
g	Progression rate to the early exposed stage
φ	Progression rate from E_2 to I
j	Probability of treatment failure
ω	Reduction in risk of infection due to vaccination rate
ω_1	Successful treatment rate
ω_2	Unsuccessful treatment rate
ε	Saturated incidence rate
g	Rate of progression to the early exposed stage
p	Exogenous re-infection
f	Fast progression rate
q	Relapsed rate
b	Birth rate
ψ	Information dissemination (awareness rate)
ϕ	Rate at which educated susceptible become susceptible again
ν	Reduction in infection as a result of awareness rate
l	Natural TB recovery rate
σ	Modification parameter for re-infection
v_1	Effort of preventing susceptible individuals from TB exposure
v_2	Latent case finding interventions
v_3	Case holding control
v_4	Active case finding control
δ	TB induced death rate
μ_{DTB}	Death rate as a result of coinfection
μ_D	Death rate as a result of AIDS

developed by Blower et al. (1995) is given by

$$\frac{dS}{dt} = \Lambda - \beta SI - \mu S,$$

$$\frac{dE}{dt} = (1-f)\beta SI - (\mu + \kappa)E,$$

$$\frac{dI}{dt} = f\beta SI + \kappa E - (\mu + \delta + \gamma)I, \tag{2.3}$$

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

2.4.1 TB Treatment Models

Between 2000 and 2021, TB treatments saved the lives of 74 million people globally, resulting in a 20 percent reduction in TB mortality (World Health Organization, 2021). Using a deterministic approach, Rohaeti et al. (2015) developed and analysed SIR TB dynamics in West Java, Indonesia. Their model assessed the impact of TB treatment. They investigated the case in which $R_0 > 1$, in which the disease-free equilibrium is unstable and a positive (endemic) equilibrium emerges. Their findings also revealed that the most relevant parameters in the spread of TB are γ and β. They demonstrated that in Bogor, the spread of TB can be controlled by increasing the recovery rate γ and reducing the transmission rate, β. The Rohaeti et al. (2015) model

are as follows:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \beta SI - \mu S, \\
\frac{dI}{dt} &= \beta SI - (\mu + \delta + \gamma)I, \\
\frac{dR}{dt} &= \gamma I - \mu R.
\end{aligned} \tag{2.4}$$

Fatimaa and Mishra (2020) formulated a mathematical model of TB with an early treatment for latent patients, α, and treatment of infectives, γ, as strategies in reducing the TB transmission. They studied the following deterministic model of TB:

$$\begin{aligned}
\frac{dS}{dt} &= bN - \frac{\beta SI}{N} + \sigma R - \mu S, \\
\frac{dE}{dt} &= \frac{\beta SI}{N} - (\kappa + \alpha + \mu)E, \\
\frac{dI}{dt} &= \kappa E - (\mu + \delta + l + \gamma)I, \\
\frac{dR}{dt} &= \alpha E + (l + \gamma)I - (\sigma + \mu)R,
\end{aligned} \tag{2.5}$$

where the parameters b represent birth rate, κ is the progression rate from E to I, α is the chemoprophylaxis treatment (treatment for those that have been exposed), respectively, the parameters l, and σ are natural TB recovery, and re-infection, respectively. The local stability of equilibrium points was investigated. They found that α and γ lower the effective reproduction number to less than one. It indicates that early treatment of TB patients is more beneficial in reducing the spread of TB burden. However, they did not proved the conditions that guarantee the existence, uniqueness and bound-

edness of solution of the TB model (2.5). The criteria for the existence of bifurcation analysis and the global stability of any equilibrium point were also not investigated in their work.

A deterministic model for the TB infection that combines chemoprophylaxis as treatment of exposed and treatment of infected individuals was formulated and analyzed by Bhunu et al. (2008). Results showed that treatment of is most successful in the first years of introduction as it clears active TB quickly. After that, chemoprophylaxis will do its best to control the number of infectious diseases due to reduced progression to active TB. Bhunu et al. (2008) presented the following compartmental model of TB infection:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \frac{\beta c_1 SI}{N} - \mu S, \\
\frac{dE}{dt} &= \frac{f\beta c_1 SI}{N} - \frac{p\beta c_1 EI}{N} - (\kappa + \alpha + \mu) E + \frac{\sigma\beta c_1 RI}{N}, \\
\frac{dI}{dt} &= \frac{(1-f)\beta c_1 SI}{N} + \frac{p\beta c_1 EI}{N} + \kappa E - (\mu + \delta + l + \gamma) I + qR, \\
\frac{dR}{dt} &= \alpha E + (l+\gamma) I - (q+\mu) R - \frac{\sigma\beta c_1 RI}{N},
\end{aligned} \tag{2.6}$$

where c_1 corresponds to the contact rate, q represents the relapsed rate and p is the exogenous re-infection.