Mathematical Modeling and the Dynamical Analysis of HIV/TB Interaction

by

Julius Unuabona Slim Ehiemua

A Thesis submitted to the Faculty of Graduate Studies of the University of Manitoba
in partial fulfillment of the requirements for the award of the degree of

MASTER OF SCIENCE

Department of Mathematics,
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Abstract

The thesis is based on the design and analysis of a series of realistic deterministic models for the transmission dynamics of Human Immunodeficiency Virus (HIV) and Tuberculosis (TB) in a population. In addition to the enormous public health and socio-economic burden each of these diseases inflicts globally, the synergistic relationship between the diseases (where one disease accelerates progression of the other) has equally devastating effects. First of all, a basic model for the transmission dynamics of the two diseases, incorporating the essential epidemiological and biological features of the two diseases, is designed. Appropriate dynamical systems theories and methodologies, such as stability/bifurcation theory, center manifold theory, comparison theory, Lyapunov function theory and Lasalle Invariance principle, are used to analyze the qualitative dynamics of the model. The TB component of the model was shown to undergo backward bifurcation, where a stable disease-free equilibrium co-exists with a endemic equilibrium when the associated reproduction threshold is less than unity, due to the exogenous re-infection property of TB disease. The HIV component of the basic model has a globally stable disease-free equilibrium when its reproduction number is less than unity.

The model is then extended to include an imperfect HIV vaccine and the directly observed treatment, short-course (DOTS) for TB. Some of the main public health contributions of the thesis include the following.

(i) an imperfect HIV vaccine, with modest efficacy, can lead to the elimination of HIV from the community if the coverage rate is high enough.

(ii) TB transmission by latently-infected individuals play a vital role in the spread of TB.

(iii) TB can be effectively controlled using DOTS with large enough coverage if latent transmission and duration in the latent class are minimized.

(iv) a backward bifurcation in TB modelling was caused by exogenous re-infection, whilst that in HIV in the presence of a vaccine arises due to the imperfect nature of the vaccine.

(v) the treatment of people with active TB in the mixed HIV/TB class, with large enough coverage, can eliminate the mixed HIV/TB infection in the community.

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Dedication

To my beloved brother, Henry Omoighe (Ehiemua), who is not lost.
See you later, Henry ...

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Glossary of Abreviations

Abbreviation	Meaning
AIDS	Acquired Immune-Deficiency Syndrome
ARV	Anti-Retroviral Drugs
DFE	Disease-Free Equilibrium
DOTS	Directly Observed Treatment Short-course
EEP	Endemic Equilibrium Point
GAS	Globally Asymptotically Stable
HAART	Highly-active Anti-Retroviral Therapy
HIV	Human Immuno-deficiency Virus
LAS	Locally Asymptotically Stable
Mtb	Mycobacterium tuberculosis
PLWHA	People Living With HIV/AIDS
TB	Tuberculosis
WHO	World Health Organization
SIR	Susceptible, Infected, Recovered Model

Chapter 1

Introduction

The central theme of this thesis is the use of mathematical theories and methodologies to understand the transmission dynamics of two diseases of major public health significance, namely the human immunodeficiency virus (HIV) and mycobacterium tuberculosis (TB). Before giving details of the mathematical formulations and analyses, it is necessary to provide background information of each of the two diseases, as below.

1.1 HIV/AIDS

HIV, the causative agent of the acquired immune deficiency syndrome (AIDS), was first recognized in the 1980s. Since then, the pandemic continues to pose unprecedented threat to global health and human development. An estimated 34-46 million people are currently living with HIV/AIDS and more than 20 million people have died from AIDS during the last 20 years. AIDS is now the leading cause of death in sub-Saharan Africa and the fourth-leading cause of death globally. The pandemic has cut life expectancy significantly in many countries in sub-Saharan Africa. For example, life expectancy in Botswana decreased from 65 years in 1985-1990 to 40 years in 2000-2005 [60]. Although the pandemic seems to have stabilized in Africa, HIV is now threatening other major global centres such as China, India and Russia [8, 16, 20]. The global and regional trends of HIV/AIDS is depicted in Figures 1.1 and 1.2.

Global summary of the AIDS epidemic December 2006

Number of people living with HIV in 2006		
	Total	**39.5 million (34.1–47.1 million)**
	Adults	37.2 million (32.1–44.5 million)
	Women	17.7 million (15.1–20.9 million)
	Children under 15 years	2.3 million (1.7–3.5 million)
People newly infected with HIV in 2006		
	Total	**4.3 million (3.6–6.6 million)**
	Adults	3.8 million (3.2–5.7 million)
	Children under 15 years	530 000 (410 000–660 000)
AIDS deaths in 2006	**Total**	**2.9 million (2.5–3.5 million)**
	Adults	2.6 million (2.2–3.0 million)
	Children under 15 years	380 000 (290 000–500 000)

Figure 1.1: The ranges around the estimates in this table define the boundaries within which the actual numbers lie, based on the best available information [33].

Regional HIV and AIDS statistics and features, 2004 and 2006

	Adults and children living with HIV	Adults and children newly infected with HIV	Adult (15–49) prevalence (%)	Adult and child deaths due to AIDS
Sub-Saharan Africa				
2006	24.7 million [21.8–27.7 million]	2.8 million [2.4–3.2 million]	5.9% [5.2%–6.7%]	2.1 million [1.8–2.4 million]
2004	23.6 million [20.9–26.4 million]	2.6 million [2.2–2.9 million]	6.0% [5.3%–6.8%]	1.9 million [1.7–2.3 million]
Middle East and North Africa				
2006	460 000 [270 000–760 000]	68 000 [41 000–220 000]	0.2% [0.1%–0.3%]	36 000 [20 000–60 000]
2004	400 000 [230 000–650 000]	59 000 [34 000–170 000]	0.2% [0.1%–0.3%]	33 000 [18 000–55 000]
South and South-East Asia				
2006	7.8 million [5.2–12.0 million]	860 000 [550 000–2.3 million]	0.6% [0.4%–1.0%]	590 000 [390 000–850 000]
2004	7.2 million [4.8–11.2 million]	770 000 [480 000–2.1 million]	0.6% [0.4%–1.0%]	510 000 [330 000–740 000]
East Asia				
2006	750 000 [460 000–1.2 million]	100 000 [56 000–300 000]	0.1% [<0.2%]	43 000 [26 000–64 000]
2004	620 000 [380 000–1.0 million]	90 000 [50 000–270 000]	0.1% [<0.2%]	33 000 [20 000–49 000]
Oceania				
2006	81 000 [50 000–170 000]	7100 [3400–54 000]	0.4% [0.2%–0.9%]	4000 [2300–6600]
2004	72 000 [44 000–150 000]	8000 [3900–61 000]	0.3% [0.2%–0.8%]	2900 [1600–4600]
Latin America				
2006	1.7 million [1.3–2.5 million]	140 000 [100 000–410 000]	0.5% [0.4%–1.2%]	65 000 [51 000–84 000]
2004	1.5 million [1.2–2.2 million]	130 000 [100 000–320 000]	0.5% [0.4%–0.7%]	53 000 [41 000–69 000]
Caribbean				
2006	250 000 [190 000–320 000]	27 000 [20 000–41 000]	1.2% [0.9%–1.7%]	19 000 [14 000–25 000]
2004	240 000 [180 000–300 000]	25 000 [19 000–35 000]	1.1% [0.9%–1.5%]	21 000 [15 000–28 000]
Eastern Europe and Central Asia				
2006	1.7 million [1.2–2.6 million]	270 000 [170 000–820 000]	0.9% [0.6%–1.4%]	84 000 [58 000–120 000]
2004	1.4 million [950 000–2.1 million]	160 000 [110 000–470 000]	0.7% [0.5%–1.1%]	48 000 [34 000–66 000]
Western and Central Europe				
2006	740 000 [580 000–970 000]	22 000 [18 000–33 000]	0.3% [0.2%–0.4%]	12 000 [<15,000]
2004	700 000 [550 000–920 000]	22 000 [18 000–33 000]	0.3% [0.2%–0.4%]	12 000 [<15 000]
North America				
2006	1.4 million [880 000–2.2 million]	43 000 [34 000–65 000]	0.8% [0.6%–1.1%]	18 000 [11 000–26 000]
2004	1.2 million [710 000–1.9 million]	43 000 [34 000–65 000]	0.7% [0.4%–1.0%]	18 000 [11 000–26 000]
TOTAL				
2006	39.5 million [34.1–47.1 million]	4.3 million [3.6–6.6 million]	1.0% [0.9%–1.2%]	2.9 million [2.5–3.5 million]
2004	36.9 million [31.9–43.8 million]	3.9 million [3.3–5.8 million]	1.0% [0.8%–1.2%]	2.7 million [2.3–3.2 million]

Figure 1.2: Regional HIV and AIDS statistics and features, 2004 and 2006 [33].

1.1.1 Socio-economic and public health impact of HIV

In addition to being a major public health problem, HIV/AIDS has far reaching consequences to all social and economic sectors of society. It exacerbates poverty, reduces educational opportunities, devastates the workforce, creates large numbers of orphans, and exerts tremendous pressure on already limited health and social services. For example, HIV/AIDS has cut annual growth rates in Africa by 2−4% per year [15]. The annual economic loss of slower economic growth as a result of HIV/AIDS-related death or disability in 50 countries (USA, Russia, 5 in Asia, 8 in Latin America, and 35 in sub-Saharan Africa) during 1992−2000 is estimated at $25 billion [20].

1.1.2 Replication cycle

HIV infects and replicates primarily in *$CD4^+$ T cells*. An infected individual typically passes through several infection stages, being highly infectious during the pre-antibody phase (primary infection stage; characterized by high viremia with over 10 million viral copies per *ml*), maintaining low infectivity during the asymptomatic phase (secondary infection stage), and becoming highly infectious as (s)he progresses toward AIDS (AIDS stage) [16, 18, 26, 32, 37, 39, 45]. Figure 1.3 depicts the typical course of HIV disease *in vivo*.

Studies of HIV RNA in infected individuals show that viral levels vary widely between individuals, where individuals with higher viral loads during the chronic phase tend to develop AIDS more rapidly [41]. Another crucial related fact is that RNA levels are correlated with infectiousness [22, 49]. Thus, infected individuals in the primary and AIDS stages are more infectious than those in the asymptomatic stage (because of their high viral load).

1.1.3 Control strategies of HIV in a population

HIV is controlled in two main ways, therapeutically and preventively. The therapeutic component is primary based on the use of antiretroviral drugs (ARVs). Since their introduction in the early 1990s [45, 46], ARVs, particularly the highly active antiretroviral therapies (HAART), have had dramatic impact in curtailing the burden (morbidity and mortality) of the HIV pandemic in many countries where these drugs are accessible [44]. The use of such life-saving drugs, over long periods of time, reduces the viral loads in HIV-infected individuals to non-detectable levels (typically characterized by HIV RNA of less than 50 copies/ml) [34]. In addition to making these individuals less infectious (owing to the positive correlation between viral load and HIV transmission [22, 23]), HAART extends the life, and the quality of life, of infected individuals [45]. Unfortunately, however, these drugs are still not widely available in

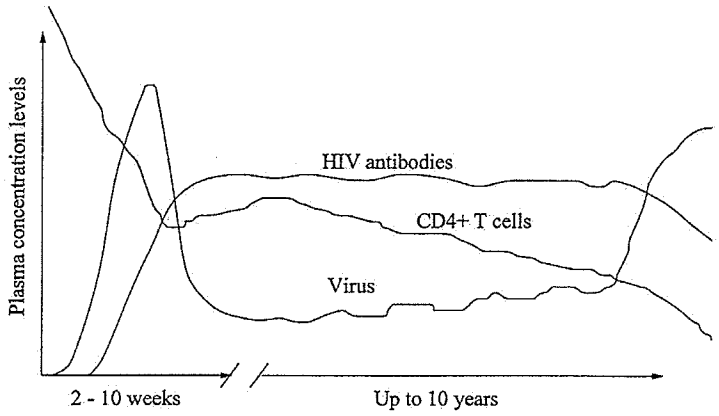

Figure 1.3: The time course of HIV infection in a typical infected adult [45].

many resource-poor nations of the world. Further, their widespread use is associated with the emergence and transmission of drug resistance strains, as well as numerous side effects and toxicities.

Preventive strategies against HIV include the use of condoms, education about safer sex practices, counseling, screening blood products, discouraging needle sharing etc. Although these efforts have helped halt the spread of HIV to some extent in some resource-poor nations, it is generally believed that the "best" way to curtail the AIDS pandemic is via the use of an effective vaccine [12, 17]. However, it is unlikely that a highly effective vaccine will be available soon. Instead, the current expectation is that

the most likely vaccine that will be developed in the foreseeable future may have lower efficacy in protecting against infection and/or result in a shorter duration of protection in successfully immunized people than most traditional vaccines.

1.2 Mycobacterium Tuberculosis

TB, an infectious disease caused by the bacterium *Mycobacterium tuberculosis*, affects at least 2 billion people (one-third of the world's population) and is the second greatest contributor of adult mortality amongst infectious diseases, causing approximately 2 million deaths a year worldwide [55, 56, 61]. The recent World Health Organization (WHO) report on global TB control [61] shows that although the number of TB cases was stable or falling in 5 of 6 WHO regions in 2004, the number of cases in Africa continues to grow (where the TB epidemic is still driven by the spread of HIV). Overall, more than 80% of all TB patients live in 22 countries mostly in sub-Saharan Africa and Asia. In the United States, about 10 to 15 million people have latent TB.

1.2.1 Transmission mechanism

TB is an airborne-transmitted disease. The causative agent of TB transmission is *Tubercle bacillus*, which reside in the lungs of infectious individuals. The *baccili* spread in the air when infectious individuals sneeze, cough, speak or sing. A susceptible individual may become infected with TB if he or she inhales bacilli from the air. The particles containing *Mycobacterium tuberculosis* are so small that normal air currents not only keep them airborne but also transport them throughout rooms or buildings [59]. Individuals who regularly share space with those with active TB (the infectious stage of the disease) have a higher risk of becoming infected than those who do not. Bacilli become established in the alveoli of the lungs from where they spread throughout the body. Initially infected individuals typically undergo a long and varied period of latency before the onset of active disease.

1.2.2 Control strategies of TB in a population

The high burden of TB infections in regions within Asia, Africa and some parts of Europe (notably the Russia federation and other eastern European nations) necessitated a global effort, spear-headed by WHO, for the effective control of the TB epidemic worldwide. This resulted in a number of global initiatives such as the "Stop TB Partnership", "International Standards of Tuberculosis Care and the Patient's Charter" and "Global Plan to Stop TB". The key components of these initiatives are to achieve the Millennium Development Goal (of halting, and beginning to reverse the incidence

of TB by 2015), providing access to quality TB diagnosis and treatment (based on the use of antibiotics) for all and, subsequently, saving millions of lives.

Control strategies to curtail the spread of tuberculosis are generally classified as the directly observed treatment, short-course (abbreviated as DOTS) methods. The five elements of DOTS are: political commitment with increased and sustained financing; case detection through quality-assured bacteriology; standardized treatment, with supervision and patient support; an effective drug supply and management system; and monitoring and evaluation system, and impact measurement according to a publication on the subject by the World Health Organization's website. The new six-point strategy, developed by WHO over a two-year period, builds on the successes of DOTS while also addressing the key challenges facing TB control in providing access to TB treatment and care, including TB/HIV and MDR-TB patients.

1.3 Public Health and Socio-Economic Impact of HIV/TB Interaction

It is believed that about 90% of individuals without the HIV infection who are infected with TB do not develop active TB (the TB disease); while at the same time, HIV is the most powerful risk factor for the progression of the TB disease from latency to its active stage. Statistically, while an HIV positive individual infected with TB has a 50% lifetime risk of developing TB, another individual who is HIV negative when effectively exposed to TB has only a 10% risk of developing TB [43]. It has also been observed that when CD4+ T cells count decrease in HIV-1 infected persons, the risk of tuberculosis is increased either from primary infection or from reactivation of latent Mtb infection [42]. The socio-economic and public health implication of the coexistence of both diseases in any given population, particularly among resource-poor nations, is enormous. HIV patients in the AIDS stage die more quickly on having being additionally infected with tuberculosis.

1.3.1 Control strategies against HIV/TB co-infection in a population

HIV is the main reason for failure to meet Tuberculosis (TB) control targets in high HIV settings. TB is a major cause of death among people living with HIV/AIDS. Sub-Saharan Africa bears the brunt of the HIV fuelled TB epidemic. The rapidly increasing HIV epidemic in other parts of the world could also increase the number of HIV-related TB cases. In order to control TB in high HIV settings, the DOTS strategy should be complemented with additional collaborative TB/HIV activities.

These collaborative TB/HIV activities have the objectives of creating the mechanism of collaboration between TB and HIV/AIDS programmes, reducing the burden of TB among People Living with HIV/AIDS (PLWHA) and reducing the burden of HIV among TB patients [62].

1.4 Justification and Objectives

The enormous global impact of the HIV/TB co-infection demands rigorous qualitative studies to gain insight into the transmission dynamics of these diseases in a population and to evaluate their control strategies. Furthermore, relatively little has been done in the study of disease dynamics in a population that is infested with both HIV and TB.

The main objectives of this study is to use mathematical theories and techniques to address important questions associated with HIV/TB interaction in a population, such as the following:

(i) What are the qualitative and quantitative community-wide impacts associated with the use of control strategies such as the DOTS treatment (for TB) and an imperfect HIV-vaccine for HIV?

(ii) What is the epidemiological impact of the transmission of TB by those with latent TB and those with HIV/TB co-infection?

(iii) What types of bifurcations does the HIV/TB transmission system exhibits?

(iv) What are the epidemiological thresholds (and conditions) that govern the persistence or elimination of each of the two diseases and their co-infection?

1.5 Thesis Outline

The thesis begins with an introductory chapter (Chapter 1) describing the socio-economic and public health impact of the two diseases. The main mathematical concepts used in the thesis are briefly described in Chapter 2. In Chapter 3, a basic deterministic model for HIV-TB interaction in a population is presented. The HIV-only and TB-only sub-models of the basic model are rigorously analyzed in Chapters 4 and 5, respectively. The full model is analyzed in Chapter 6. The model is extended to include the use of imperfect HIV vaccine and treatment for TB in Chapter 7. Concluding remarks are provided in Chapter 8.

Chapter 2

Mathematical and Epidemiological Preliminaries

The mathematical models to be considered in this thesis will take the form of deterministic and compartmental systems of nonlinear ordinary differential equations (ODEs). The models will be analyzed at steady state using appropriate dynamical systems theories, tools and methodologies. Such analyzes would enable the determination of important epidemiological thresholds that govern the persistence or elimination of the disease being modelled.

In this chapter, some of the key mathematical theories and methodologies used in this thesis will be introduced. Further, the associated epidemiological concepts will be introduced.

2.1 Mathematical Preliminaries

Consider the following system of n first order, nonlinear differential equations (where a dot represents differentiation with respect to time, t)

$$\dot{x} = f(x, t; \mu); \quad x \in U \subset \mathbb{R}^n; t \in \mathbb{R}, \mu \in V \subset \mathbb{R}^p, p, n \in \mathbb{Z}_+ \text{and } 0 \leq p \leq n. \tag{2.1}$$

Definition 2.1 *Given a function $x = x(t)$, an ordinary differential equation (ODE) is an equation $F(t, x, x', x'', \cdots, x^{(k)}) = 0$, where x' denotes the first derivative of x with respect to t, x'', the second derivative with respect to t, and in general, $x'^{(k)}$ the k-th derivative of x with respect to t provided each derivative in the function F has a degree of 1. k is called the degree of the ODE F.*

In view of Definition 2.1 above, the system (2.1) is an ODE system where the parameter μ is a constant and the notation x' is used interchangeably with $\dot{x}$.

A geometric interpretation of the above ODE system in (2.1) is as a vector field, so we will interchangeably refer to system (2.1) as a vector field.

Definition 2.2 *A solution of (2.1) is any vector or n-tuple* $x = \hat{x} = (x_1, x_2, \cdots, x_n)$ *such that*

$$[\dot{x} - f(x, t; \mu)]|_{x=\hat{x}} = 0.$$

Definition 2.3 *A system of the form (2.1) is said to be autonomous if the function* f *does not explicitly depend on* t*, that is, if* $f = f(x)$*. If* f *in (2.1) explicitly depend on* t*, then system (2.1) is a non-autonomous system.*

Thus, if (2.1) is an autonomous system, then, we can write

$$\dot{x} = f(x), \quad x \in \mathbb{R}^n. \tag{2.2}$$

Definition 2.4 *If the ODE* $F(t, x, x', x'', \cdots, x^{(k)}) = 0$ *in Definition 2.1 can be rewritten in the form*

$$\sum_{i=0}^{k} a_i(t) x^{(i)} = q(t), \tag{2.3}$$

where $q(t)$ *and each* $a_i(t)$ *are functions of time* t*, then* $F(t, x, x', x'', \cdots, x^{(k)}) = 0$ *is said to be a* ***linear ODE****, otherwise, it is called a* ***non-linear ODE****.*

Remark: In this thesis, we shall only consider nonlinear autonomous ODE systems.

Definition 2.5 *An equilibrium* $\bar{x}(t)$ *is said to be stable if there exists some numbers* $\delta, \epsilon, t_0, t > 0$ *where* $\delta, \epsilon, t_0, t \in \mathbb{R}$*,* $\delta = \delta(\epsilon)$*,* $t > t_0$ *such that if* $y(t)$ *is a solution of (2.2) satisfying* $|\bar{x}(t_0) - y(t_0)| < \delta$*, then* $|\bar{x}(t) - y(t)| < \epsilon$*.*

Definition 2.6 *An equilibrium* $\bar{x}(t)$ *is said to be asymptotically stable if all solutions* $y(t)$ *of (2.2) in* $|\bar{x}(t) - y(t)| < r_0$*,* $r_0 \in \mathbb{R}$ *converge to* $\bar{x}(t)$ *as* $t \to \infty$*. That is,* $\bar{x}(t)$ *is asymptotically stable if (i) it is stable, and (ii) there exists a constant* $r_0 > 0$ *such that if* $|\bar{x}(t) - y(t)| < r_0$ *then* $\lim_{t \to \infty} |\bar{x}(t) - y(t)| = 0$*. If all solutions* $y(t)$ *of (2.2) asymptotically converge to the equilibrium point* $\bar{x}(t)$ *of (2.2) only for initial conditions* $y_0(t)$ *close to* $\bar{x}(t)$*, then the equilibrium point* $\bar{x}(t)$ *is said to be* ***locally asymptotically stable*** *(LAS). If on the other hand, all solutions* $y(t)$ *of (2.2) asymptotically converge to* $\bar{x}(t)$ *for all initial conditions* $y_0(t)$ *in the feasible region of system (2.2), then the point* $\bar{x}(t)$ *is said to be* ***globally asymptotically stable*** *(GAS).*

Local asymptotic stability means that not only do initial conditions close to the "origin of equilibrium" (that is, the equilibrium point $\bar{x}(t)$) stay close to the origin (stable),

they also approach the origin asymptotically (the limit condition on the state). Therefore, "asymptotic stability" is a stronger condition than plain "stability" (given in Definition 2.5) because it requires that trajectories satisfy more restrictive conditions. Furthermore, the condition of global asymptotic stability imposes yet more restrictive conditions than those on local asymptotic stability, on trajectories of all points in system (2.2).

Some systems may have solutions that are different from the usual solutions computed by basic methods (such as equilibria). These solutions do affect the stability of the model's equilibria, and are called closed orbits, because of the effect they have on the shape of the phase plane diagrams obtained from the analysis of the models. One of such closed orbits is called periodic orbits, as defined below.

Definition 2.7 *Let $\dot{x} = f(x)$, $x \in \mathbb{R}^n$ be a vector field. $x(t)$ is called a periodic solution if $x(t+T) = x(t)$, for all $t > T > 0$.*

2.1.1 Limit sets

Definition 2.8 *Let X denote the set of points such that if $x \in X$, there is a neighborhood U of x so that $g(U) \cap U = \emptyset$, ($\emptyset$ being the empty set) for all non-trivial $g \in G$ (G a group of homeomorphisms of a space onto itself). A point y is a* limit-point *if there is a $z \in X$ and there is a sequence $\{g_m\}$ of distinct elements of G with $g_m(z) \to y$. The set of limit-points is the limit-set.*

In the study of dynamical systems, a limit set represents the state of a dynamical system after an infinite amount of time, in other words, at steady state. Limit sets are used to study the long term characteristics of dynamical systems. Examples of limit sets include equilibrium points and periodic orbits.

Definition 2.9 *A point $x_0 \in \mathbb{R}^n$ is said to be an ω-limit point of $x \in \mathbb{R}^n$, denoted by $\omega(x)$, if there exists a sequence $\{t_i\}$, $t_i \to \infty$ such that $\phi(t_i, x) \to x_0$.*

Definition 2.10 *A point $x_0 \in \mathbb{R}^n$ is said to be an α-limit point of $x \in \mathbb{R}^n$, denoted by $\alpha(x)$, if there exists a sequence $\{t_i\}$, $t_i \to -\infty$ such that $\phi(t_i, x) \to x_0$.*

Definition 2.11 *The set of all ω-limit points of a flow is called the ω-limit set, and the set of all α-limit points of a flow is called the α-limit set [63].*

Definition 2.12 *Let $S \subset \mathbb{R}^n$ be a set. Then S is said to be invariant under the vector field $\dot{x} = f(x)$ if for any $x_0 \in \mathbb{R}^n$, we have $x(t, 0, x_0) \in S$ for all $t \in \mathbb{R}$.*

Definition 2.13 *If $t \geq 0$ in Definition 2.12, then S is said to be a positively invariant set.*

2.1.2 Methods for local asymptotic stability of equilibria

Two standard methods used to investigate the local asymptotic stability of equilibria in this thesis are the *method of linearization* and the *next generation operator method* (which is a special case of the method of linearization). These are briefly described below.

Method of linearization

Using our previous notation, the equilibrium solution of the system

$$\dot{x}(t) = f(x(t)) \tag{2.4}$$

is given by $\bar{x}(t)$. For the analysis of local stability of the equilibrium, we study the effect of a small perturbation $\epsilon(t)$ on the equilibrium point $\bar{x}(t)$ as follows. With this perturbation, $\epsilon(t)$, of the system about the equilibrium point $\bar{x}(t)$, the instantaneous value $x(t)$ of the system becomes $x(t) = \bar{x}(t) + \epsilon(t)$, which on differentiation, yields $\dot{x}(t) = \dot{\bar{x}}(t) + \dot{\epsilon}(t)$. Hence, (2.4) becomes

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

which, on applying Taylor series approximation, yields

$$\dot{\bar{x}}(t) + \dot{\epsilon}(t) = f(\bar{x}(t)) + Df(\bar{x}(t))\epsilon(t) + O(|\epsilon(t)|^2), \tag{2.5}$$

where Df is the derivative of f with respect to t, and $|\cdot|$ is the norm of $\mathbb{R}^n$. Since $\dot{\bar{x}}(t) = f(\bar{x}(t))$, (2.5) simplifies to

$$\dot{\epsilon}(t) = Df(\bar{x}(t))\epsilon(t) + O(|\epsilon(t)|^2). \tag{2.6}$$

By ignoring the $O(|\epsilon(t)|^2)$ terms which comprises of higher order powers of $\epsilon(t)$, we are left with only linear terms in $\epsilon(t)$ (the resulting system is where the method gets its name) and (2.6) becomes $\dot{\epsilon}(t) = Df(\bar{x}(t))\epsilon(t)$. Further, since at equilibrium $\bar{x}(t) = \bar{x}$, we have

$$\dot{\epsilon}(t) = Df(\bar{x})\epsilon(t) \tag{2.7}$$

which yields the general solution

$$\epsilon(t) = \epsilon(0)exp[Df(\bar{x})t], \quad \epsilon(0) > 0 \tag{2.8}$$

where, $\epsilon(0) = exp(k)$ with k being a constant of integration. Clearly, the perturbation (deviation from equilibrium point, $\bar{x}(t)$) is $\epsilon(t)$ and if $\lim_{t\to\infty} \epsilon(t) = 0$, then $x(t) = \bar{x}(t)$ and the equilibrium point $\bar{x}$ is stable. Furthermore, from (2.8), we see that $\lim_{t\to\infty} \epsilon(t) = 0$ is

only possible if $Df(\bar{x}) < 0$, establishing the following result.

Theorem 2.1 *If the eigenvalues of $Df(\bar{x})$ all have negative real parts, then the equilibrium solution $\bar{x}$ of the vector $\dot{x} = f(x)$ is asymptotically stable.*

This method is quite laborious (even not feasible at times) to apply for large dynamic systems, such as some of the ones considered in this thesis. An alternative method which is quite robust for large systems, is presented below.

Example 2.1 *Consider the following system [57].*

$$\dot{x} = -x + x^3, \quad \dot{y} = -2y \tag{2.9}$$

The point $(x = 0, y = 0)$ is one of the three equilibrium points of the system (2.9). We use the method of linearization above to investigate the asymptotic stability of $(0, 0)$ as follows. Setting $f_1 = -x + x^3$ and $f_2 = -2y$, so that $f = (f_1, f_2)^T$ and the Jacobian, $Df(x, y) = J(x, y)$ of (2.9) is given by

$$J(x,y) = \begin{pmatrix} \frac{\partial f_1}{\partial x} & \frac{\partial f_1}{\partial y} \\ \\ \frac{\partial f_2}{\partial x} & \frac{\partial f_2}{\partial y} \end{pmatrix} = \begin{pmatrix} -1 + 3x^2 & 0 \\ 0 & -2 \end{pmatrix}.$$

Thus, $J(0,0) = \begin{pmatrix} -1 & 0 \\ 0 & -2 \end{pmatrix}$, with eigenvalues satisfying the characteristic polynomial $(\lambda + 1)(\lambda + 2) = 0$, so that $\lambda_1 = -1$ and $\lambda_2 = -2$. Since $\lambda_1 < 0$ and $\lambda_2 < 0$, then the equilibrium point (0,0) is asymptotically stable.

The next generation operator method

The next generation method (developed by Diekmann and Hesterbeek [14] and refined for epidemiological models by van den Driessche and Watmough [58]) is used to analyze the local asymptotic stability of the disease-free or a boundary equilibrium. Epidemiological models of Kermack-Mckendrick type, subdivides the total population (N) into a number of mutually-exclusive compartments, with each representing a disease state or type. Suppose a disease transmission model (with nonnegative initial conditions) can be written in terms of the following system:

$$\dot{x}_i = f(x_i) = F_i(x) - V_i(x), i = 1, \cdots, n \tag{2.10}$$

where, $V_i = V_i^- - V_i^+$, the function f and other quantities are as described below and satisfy the given as follows. Let $X_s = \{x \geq 0 | x_i = 0, i = 1, 2, \cdots, m\}$ be the number

of disease-free (non-infectious) states of the model, where, x_i is the number individuals in compartment i, and the vector $x = (x_1, \cdots, x_n)^t$, $x_i \geq 0$ represents the distribution of the individuals within the population. Thus, $N = x_1 + x_2, \cdots, x_n$. The following conditions hold in the population.

(A1) if $x_i \geq 0$, then $F_i, V_i^+, V_i^- \geq 0$ for $i = 1, 2, \cdots, m$.

(A2) if $x_i = 0$, then $V_i^- = 0$ and in particular, if$x_i \in X_s$, then $V_i^- = 0$ for $i = 1, 2, \cdots, m$.

(A3) $F_i = 0$ if $i > m$.

(A4) if $x \in X_s$, then $F_i(x) = 0$ and $V_i^+(x) = 0$ for $i = 1, 2, \cdots, m$.

(A5) if $F(x) = 0$, then all eigenvalues of the matrix $Df(x_0)$ have negative real parts.

Here, $F_i(x)$ represents the rate of appearance of new infections into compartment i, $V_i^+(x)$ represents the rate of transfer of individuals into compartment i by all other means, and $V_i^-(x)$ is the rate of transfer of individuals out of compartment i. It is assumed that these functions are at least twice continuously differentiable in each variable [58]

Definition 2.14 ***(M-Matrix).*** *Any matrix A, that can be written as*

$$A = sI - B,\ s > 0,\ B \geq 0$$

with $s \in \mathbb{R}$ and B a matrix, for which $s \geq \rho(B)$, the spectral radius of B, is called an M-matrix [4].

Definition 2.15 *A nonnegative matrix A is a matrix where all the elements are equal to or greater than zero. That is, if $A = (a_{ij})$, then $\forall_{ij}\ a_{ij} \geq 0$.*

Lemma 2.1 (van den Driessche and Watmough [58]) *If $\bar{x}$ is a DFE of (2.10) satisfying the axioms (A1) through (A5), then the derivatives $F(\bar{x})$ and $DV(\bar{x})$ are partitioned as*

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

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

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

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

Theorem 2.2 (van den Driessche and Watmough [58]) *Consider the disease transmission model given by (2.10) with $f(x)$ satisfying axioms (A1) through (A5). If $\bar{x}$ is a DFE of the model, then $\bar{x}$ is LAS if $\mathcal{R}_0 = \rho(FV^{-1}) < 1$ (where, ρ is spectral radius), and unstable if $\mathcal{R}_0 > 1$.*

2.1.3 Methods for global stability of equilibria

In this section, we shall discuss some standard methods for analyzing the global asymptotic stability of a dynamical system of the type (2.1). These include the use of the Comparison Theorem, Lyapunov functions and the LaSalle's Invariance principle, as well as the use of Dulac's criterion. These techniques are used in the thesis to prove global asymptotic stability of equilibria.

Comparison Theorem

Definition 2.16 *A function f is of type $\mathbb{K}$ in $\mathbb{D}$ if for each i and all t, $f_i(t,a) \leq f_i(t,b)$ for any two points a and b in $\mathbb{D}$ satisfying $a \leq b$ and $a_i = b_i$.*

Theorem 2.3 Comparison Theorem. *Let f be a continuous on $\mathbb{R} \times \mathbb{D}$ and of type $\mathbb{K}$ where $\mathbb{D}$ is an open subset of $\mathbb{R}^n$. Let $x(t)$ be a solution of $\dot{x} = f(t,x)$ defined on $[a,b]$. If $z(t)$ is a continuous function on $[a,b]$ satisfying $\dot{z} \leq f(t,z)$ on (a,b) with $z(a) \leq x(a)$, then $z(t) \leq x(t)$ for all $t \in [a,b]$. If $y(t)$ is continuous on $[a,b]$ satisfying $\dot{y} \geq f(t,y)$ on (a,b) with $y(a) \geq x(a)$, then $y(t) \geq x(t)$ for all $t \in [a,b]$.*

Lyapunov Functions

Lyapunov functions are a class of functions that can be used to prove the stability of equilibrium points in dynamical systems. They are energy-like functions that decrease along trajectories. The existence of a Lyapunov function in a given neighborhood precludes the existence of closed orbits in the neighborhood [57].

Definition 2.17 *A continuously differentiable real-valued function, f, is said to be positive definite on a neighborhood, D, centered at the origin if $f(0) = 0$, and $f(x) > 0$ for all other $x \in D$. That is, $f(0) = 0$, $f(x) > 0 \ \forall \ x$ such that $0 < |x| < \infty$, and $\lim_{x \to \infty} f(x) \to \infty$.*

We now present a formal definition of a Lyapunov function and state the theorem that states how the Lyapunov function can be used to investigate stability.

Definition 2.18 *A scalar function $V(x) : \mathbb{R}^n \rightarrow \mathbb{R}$ is said to be a candidate Lyapunov function if it is locally positive definite (that is, if $\mathbb{U}$ is a neighborhood of $x = 0$ such $V(0) = 0$ and $V(x) > 0$ $\forall x \in \mathbb{U}$.*

We used the phrase "candidate" in Definition 2.18 above because the function $V(x)$ is only pronounced to be a Lyapunov function if it is used successfully to prove stability as in the following theorem [31, 63].

Theorem 2.4 [47] *Let E be an open subset of $\mathbb{R}^n$ containing x_0. Suppose that $f \in C^1(E)$ and that $f(x_0) = 0$. Suppose further that there exists a function $V \in C^1(E)$ satisfying $V(x_0) = 0$ and $V(x) > 0$ if $x \neq x_0$. Then,*

(a) if $V(x) \leq 0$ for all $x \in E$, x_0 is stable

(b) if $V(x) < 0$ for all $x \in E \sim \{x_0\}$, x_0 is asymptotically stable

(c) if $V(x) > 0$ for all $x \in E \sim \{x_0\}$, x_0 is unstable

A function $V : \mathbb{R}^n \rightarrow \mathbb{R}$ that satisfies Theorem 2.4 is called a Lyapunov fucntion.

LaSalle's Invariance Principle

In proving global stability in this thesis, Theorem 2.4 is combined with the LaSalle's Invariance Principle, described below.

Definition 2.19 *Let $V : \mathbb{R}^n \rightarrow \mathbb{R}$ be a function such that $V(x) \rightarrow \infty$ as $\|x\| \rightarrow \infty$, then V is said to be radially unbounded.*

Theorem 2.5 LaSalle's Invariance Principle. *Let $\dot{x} = f(x)$ be a vector field with equilibrium point $\bar{x}$ and suppose there is a positive definite, continuously differentiable, and radially unbounded function $V : \mathbb{R}^n \rightarrow \mathbb{R}$, such that*

$$\frac{\partial V}{\partial x}(x - \bar{x})f(\bar{x}) \leq W(x) \leq 0, \quad \forall x \in \mathbb{R}^n. \tag{2.11}$$

Then, $\bar{x}$ is globally stable and the solution $x(t)$ converges to the largest invariant set S contained in $E = \{x \in \mathbb{R}^n : W(x) = 0\}$[24].

We now state as a variation of the above theorem which is attributed to Krasowskii and Lasalle.

Theorem 2.6 (Krasowskii-Lasalle Invariance principle) *Let Ω be a positively invariant set of $\dot{x} = f(x)$. Let $V : \Omega \to \mathbb{R}_{\geq 0}$ be a continuously differentiable function $V(x)$ such that $\dot{V}(x) \leq 0$, $\forall x \in \Omega$. Let $E = \{x \in \Omega : \dot{V}(x) = 0\}$, and let M be the largest invariant set contained in E. Then, every bounded solution $x(t)$ starting in Ω converges to M as $t \to \infty$.*

The following is a useful corollary to Theorem 2.6 above.

Corollary 2.1 (Global Asymptotic Stability) *Let $x = 0$ be the only equilibrium of the system $\dot{x} = f(x)$. Let $V : \mathbb{R}^n \to \mathbb{R}_{\geq 0}$, be a continuously differentiable, positive definite, radially unbounded function V (x) such that $V(x)$ such that $\dot{V}(x) \leq 0$, $\forall x \in \mathbb{R}^n$. Let $E = \{x \in \mathbb{R}^n : \dot{V}(x) = 0\}$, and suppose that no solution other than $x(t) \equiv 0$ can stay forever in E. Then, the origin is globally asymptotically stable.*

Example 2.2 *Consider the following system* [47].

$$\begin{aligned} \dot{x}_1 &= -2x_2 + x_2x_3 - x_1^3 \\ \dot{x}_2 &= x_1 - x_1x_3 - x_2^3 \\ \dot{x}_3 &= x_1x_2 - x_3^3 \end{aligned} \tag{2.12}$$

Let $x = (x_1, x_2, x_3)^T$ and define $V(x) = x_1^2 + 2x_2^2 + x_3^2$. The system (2.12) has an equilibrium $x = (0, 0, 0)^T \equiv 0$. Clearly, $V(0) = 0$, and $V(x) > 0$ $\forall x = (x_1, x_2, x_3) \neq 0$. Further,

$$\dot{V}(x) = \frac{d}{dt}(x_1^2 + 2x_2^2 + x_3^2) = 2x_1\dot{x}_1 + 4x_2\dot{x}_2 + 2x_3\dot{x}_3 = -2(x_1^4 + 2x_2^4 + x_3^4)$$

Thus, $\dot{V}(x) < 0$ $\forall x \in \mathbb{R}^3_+$. Hence, $V(x)$ is a Lyapunov function. Furthermore, it follows, by combining Theorem 2.4 with Corollary 2.1, that the equilibrium point $x = (0, 0, 0)$ is GAS.

Remark. One setback with the use of Lyapunov functions is that there is no known generalized method for formulating them and so they are generally not easy to find.

Dulac's Criterion

For planar systems, the Dulac's Criterion is used to exclude periodic orbits from the steady-state of all solutions to the system $\dot{x} = f(x)$. We shall however be using the Dulac's Criterion along with the Poincaré-Bendixson theorem which suggests the existence of periodic orbits or equilibrium points as the steady-state of the solutions to the system $\dot{x} = f(x)$. We first state the theorems as follows.

Theorem 2.7 (Poincaré-Bendixson [13]). *Let $\omega(a)$ be a non-empty ω-limit set of the vector field $\dot{x} = f(x)$ in $\mathbb{R}^2$, where $f \in C^1$. If $\omega(a)$ is a bounded subset of $\mathbb{R}^2$ and $\omega(a)$ contains no equilibrium points, then $\omega(a)$ is a periodic orbit.*

A more convenient form of the above theorem is the following Corollary.

Corollary 2.2 (Poincaré-Bendixson [13]). *Let K be a positive invariant subset of the vector field $\dot{x} = f(x)$ in $\mathbb{R}^2$, where $f \in C^1$. If K is a closed and bounded set, then K contains either a periodic orbit or an equilibrium point.*

Theorem 2.8 (Dulac's Criterion). *If $\mathcal{D} \subseteq \mathbb{R}^2$ is a simply connected open set and $div(Bf) = \frac{\partial}{\partial x_1}(Bf_1) + \frac{\partial}{\partial x_2}(Bf_2) > 0$ (< 0) for all $x \in D$ where B is a C^1 function, then the vector field $\dot{x} = f(x)$ where $f \in C^1$ has no periodic orbit which is contained in D. The function $B(x_1, x_2)$ is called a Dulac function for the vector field in the set D.*

Note that the notation "> 0 (< 0)" implies that $div(B)$ is either positive (> 0) throughout the region $\mathcal{D}$ or it is negative (< 0) throughout $\mathcal{D}$ (that is, the sign of $div(B)$ should not change within region $\mathcal{D}$). It should also be noted that the investigation of global stability here, relies on the fact that, by the Poincaré-Bendixson theorem, all solutions of the system $\dot{(x)} = f(x)$ converge, at steady-state to either equilibrium points or closed orbits and that if we use the Dulac's criterion to eliminate closed orbits as steady-state options, then it follows that the equilibrium point is the only possibility to which all solutions converge, and hence it must be a globally stable point.

Example 2.3 *Consider the following system* [38].

$$\dot{x} = y + x^3, \quad \dot{y} = x + y + y^3 \tag{2.13}$$

We investigate the existence of periodic cycles as follows. Any function $B = B(x, y)$ involving only positive powers of x and y would do. In [38], *$B = 1$ was used, however, we shall use $B = xy$ in this example as follows. With $f_1 = y + x^3$, $f_2 = x + y + y^3$, $f = f_1 + f_2$, $x_1 = x$ and $x_2 = y$. Then,*

$$\begin{aligned} div(Bf) &= \frac{\partial(Bf_1)}{\partial x_1} + \frac{\partial(Bf_2)}{\partial x_2} \\ &= y + 4yx^3 + x^2 + 2xy + 4xy^3. \end{aligned}$$

From this example, we see that $div(Bf) > 0$ for all $(x, y) \in \mathbb{R}^2_+$. Thus, by Theorem 2.8, there are no periodic orbits in the planar region. Hence, the equilibrium point $(x = 0, y = 0)$ is globally stable.

2.2 Epidemiological Preliminaries

Dating back to the 20th century, deterministic epidemiological models have been successfully used to study the transmission dynamics and control of infectious diseases. Records of early works include the use od a discrete-time model by Hamer in the study of the recurrence of the measles epidemic in 1906 [25], the development of differential equation models by Ross in the study of the incidence and control of malaria in 1911 [50] and the works by Kermack and McKendrick in the end of the 1920s [3, 35, 40] in the study of epidemic models and the computation of a threshold, now known as the basic reproduction number of a disease [28].

To date, the vast majority of mathematical models for infectious diseases are formulated based on the frameworks in the aforementioned studies. In this approach, the various stages of a disease (or the different types of diseases to be considered in a study) are split into mutually exclusive compartments, each compartment representing a state variable, and the number of compartments in the modeling would correspond to the number disease-states in the population. A typical compartmental model is referred to as the classical SIR model which is effective in modeling the dynamics of the spread of a single disease in a population; the state variables S, I, and R representing the number of susceptible, the number of infected and the number of recovered individuals respectively in the population. The total size of the population, usually denoted by the variable N, would equal the sum of individuals in each compartment, which in the SIR model would yield $N+S+I+R$. It is customary to reflect the fact that these numbers change with time, by appending the notation (t) to each variable. Hence, for the SIR model, the population size at a given time, t, would be written as $N(t) = S(t) + I(t) + R(t)$.

2.2.1 Deterministic versus Stochastic Model Formulation

A deterministic system is a system in which no randomness is involved in the development of future states of the system. Deterministic models thus produce the same output for a given starting condition.

On the other hand, a stochastic model is a tool for estimating probability distributions of potential outcomes by allowing for random variation in one or more inputs over time. The random variation is usually based on fluctuations observed in historical data for a selected period using standard time-series techniques. Distributions of potential outcomes are derived from a large number of simulations (stochastic projections) which reflect the random variation in the input(s). Stochastic models are more suitable (over deterministic ones) in a number of situations, such as when:

(i) systems of interest may be subject to external forcing that cannot be defined except in probabilistic terms. Then, the behaviour of the system, insofar as we

are able to describe it, must be thought of as stochastic;

(ii) the system may have a large number of interacting components that we cannot describe individually and in detail. Thus, instead we view the statistical conglomeration of all the components and their interactions as a stochastic model;

(iii) the initial state of the system is frequently poorly known. In such a case there is an ensemble of possible initial states whose time-dependent behaviour one might choose to follow. Instead of following any one ensemble member it is preferable to look at the entire ensemble in a collective, or, better, a stochastic framework;

(iv) the time frame of the process being modelled is short (so that the effect of randomness and uncertainties cannot be ignored);

(v) or the sample size of the population being investigated is small.

The choice between deterministic- or stochastic-based modelling is often not an easy one. This is compounded by the fact that real life systems and processes usually comprise of components, some of which are best represented by random variables while others are purely deterministic in nature. Rather than obtaining outputs that are always the same for the same set of inputs, the outputs of stochastic processes have elements that are based on probability value(s). Thus, the outputs are obtained as averages over given spans.

Since this thesis addresses the dynamics of two diseases (HIV and TB) that have relatively large time-scales (HIV replication may span decades; and, similarly, TB dynamics in infected individuals may last decades) and affect large number of of people, we shall use deterministic formulations throughout this thesis.

2.2.2 Incidence functions

In formulating the model for his study of the recurrence of the measles epidemic, Hamer (see [25]) assumed that the number of new cases of infection per unit time depends on the product of the densities of the susceptibles and the infectives [28]. This assumption formed a general framework for the development of mathematical models in studying the dynamics of infectious diseases. The number of new cases of infection per unit time is known as a disease *incidence* or the *incidence function* for a disease and it is a measure of the spreadability or the *infective force* of a disease. We now develop from first principles the two types of incidence functions broadly used in epidemiological studies.

Consider an SIR model in which the number of susceptibles, infectives, and recovered individuals are denoted by $S(t)$, $I(t)$ and $R(t)$, respectively. Let $\beta(t)$ be the average

number of adequate contacts (that is, contacts sufficient for disease transmission) of a susceptible individual with others in the population per unit time, t. Then the total number of contacts that a susceptible individual can make with infected individuals is $\beta(t)I$, yielding an average of $\frac{\beta(t)I}{N}$ effective contact per unit time, that one susceptible person might make with the entire population. This is equivalent to an average number of effective contacts equal to $\frac{\beta(t)IS}{N}$ for the S susceptible people in the population. Alternatively, the number of new cases due to the $S(t)$ class is given by λS where, $\lambda = \frac{\beta(t)I}{N}$ is the force of infection of the disease. Now, if $\beta(t)$ is constant, then λS is referred to as *standard incidence* function [1, 2, 28], and the number of new cases of infection is given by incidence method is given by $\frac{\beta IS}{N}$. However, if $\beta(t)$ is dependent on the population size, N, then $\beta(t) = \beta N$, and λS is referred to as *mass action incidence* function [27, 28, 29], yielding the number of new cases of infection given by βIS.

A relevant question to ask is which of these two incidence functions is suited for modelling human diseases. Data [1, p.157][2, p.306] suggests that the standard incidence formulation is more realistic for human diseases than the simple mass action method [30]. Consequently, the models in this thesis will adopt a standard incidence formulation. It should be mentioned that models with standard incidence formulations are, generally, more difficult to analyze than those with the simple mass action incidence formulation (This is because of the occurrence of the total population term, N, in the denominator of the term, $\frac{\beta(t)IS}{N}$, for the number of new cases of infected individuals when the standard incidence formulation is used; adding more nonlinearity to the system).

2.2.3 Reproduction number

As mentioned above, a good analysis of an epidemiological model should produce results that are useful to health care practitioners and governments for the prevention and control of endemic or pandemic diseases. These results are usually associated with some epidemiological thresholds, which represent critical values beyond which the disease spread would be out of control, and thus are benchmarks for characterizing the dynamics of diseases. One of such epidemiological thresholds is the *basic reproduction number* [14, 21, 28, 58], denoted by $\mathcal{R}_0$, which is defined as the the average number of secondary cases generated by a single case of an infected individual that is placed in a population that consists of individuals that are completely susceptible to the disease. Thus, the disease persists if $\mathcal{R}_0 > 1$, and dies out if $\mathcal{R}_0 < 1$. Thus, the point $\mathcal{R}_0 = 1$ represents a point of transition from a stable *disease-free equilibrium* (for which $\mathcal{R}_0 < 1$), to an *endemic equilibrium* (for which $\mathcal{R}_0 > 1$). That is, $\mathcal{R}_0 = 1$ is a *forward*

bifurcation threshold. However, in some disease-models, the phenomenon of *backward bifurcation* (see, for instance, [10, 16, 51, 55, 58]), occurs where a stable disease-free equilibrium co-exists with a stable endemic equilibrium when $\mathcal{R}_0 < 1$.

2.2.4 Global stability and backward bifurcation

As we shall see later in this thesis, every equilibrium point that is stable is associated with a condition (for stability) that is often described in terms of the basic reproduction number of the model. Bifurcation refers to a change in the states of equilibrium (that is, a change from one type of equilibrium to another). epidemiologically, bifurcation occurs when there is a change from disease-free to endemic equilibria (vice-versa), and the change occurs at a bifurcation point. The change in equilibria can either be forward or backward. these two terms shall be formally encountered and mathematically described in later chapters. As we shall also see, global stability is affected ny backward bifurcation. Thus, one method with which we shall be establishing global stability is to investigate the existence or nonexistence of backward bifurcation. One robust method for doing this uses the Center Manifold Theory [9] which is discussed in Section 6.3.

2.2.5 Local versus global stability

The discussion in the last section gives some insight into what global stability is. On the other hand, local stability can be inferred from Definition 2.6 given early above. The implication of the definition is that only initial conditions that are sufficiently close to the equilibrium point converge to the equilibrium point, and that we do not have any guarantee that initial points that are not close will converge to the equilibrium point in question. Global stability is more extensive and would require that any initial condition (chosen in the feasible region of the model) converge to the equilibrium point.

Chapter 3

Formulation of Basic HIV/TB Model

3.1 Model Formulation

In order to gain insights into the transmission dynamics of the two diseases in a community, a basic model which incorporates many of the essential epidemiological and biological features of each of the two diseases is designed below. The basic model will be of a form of a deterministic system of non-linear differential equations. In line with the conditions outlined in Section 2.2.1 for stochastic modelling, we outline similar assumptions that were made to justify the choice of deterministic modelling framework as follows.

(i) the model is assumed to be characterized by constant flows of individuals into the system and between the disease compartments;

(ii) the population size considered are relatively large;

(iii) all the mathematical analysis to be carried out are at steady state. Thus, for such a long time, it is plausible to assume that the associated stochastic properties can be well represented by their deterministic equivalents;

(iv) considering large scale stochastic systems fall beyond the scope of this thesis.

The total population at time t, denoted by $N(t)$, is sub-divided into six mutually-exclusive compartments (classes), namely: individuals susceptible to both diseases ($S(t)$), individuals infected with HIV only but show no clinical symptoms of AIDS ($I(t)$), individuals infected with HIV only displaying clinical symptoms of AIDS($A(t)$), individuals exposed to tuberculosis ($L(t)$), individuals with active TB only ($T(t)$), and individuals dually-infected with both HIV and TB only ($M(t)$) so that $N(t) = S(t) + I(t) + A(t) + L(t) + T(t) + M(t)$. For mathematical convenience, it is assumed

that individuals in the $M(t)$ and $L(t)$ classes do not transmit infection to others. These assumptions will be relaxed in the extended model in Chapter 7. Individuals in all classes suffer natural death at a rate μ.

Individuals are recruited into the sexually-active population at a rate Π, and these individuals are assumed to be susceptible. Susceptible individuals acquire HIV infection, following contact with HIV-infected individuals in the I or A class, at a rate $\lambda_h = \dfrac{\beta_h(I+\eta_h A)}{N}$, where β_h is the associated effective contact rate, N is the total population, and η_h is a modification parameter that models the relative infectiousness of individuals in the AIDS class, A, in relation to those in the I class. In other words, since individuals with AIDS have higher viral load (and there is positive correlation between viral load and infectiousness [49]), it is assumed that individuals with AIDS are more infectious than those in the I class.

Similarly, susceptible individuals acquire TB infection following contact with individuals in the active TB class at a rate $\lambda_t = \dfrac{\beta_t T}{N}$, where β_t is the associated effective contact rate. Individuals in the I class acquire TB infection (and move to the mixed HIV/TB class) at a rate $\theta_h \lambda_t$, where the modification parameter $\theta_h > 1$ accounts for the assumed increase in susceptibility to TB infection among those infected with HIV [52]. Similarly, individuals at the AIDS stage of HIV infection acquire TB infection at an increased rate $\theta_h \eta_h \lambda_t$, where the parameter $\eta_h > 1$ accounts for the fact that individuals with AIDS are more likely to get TB infection that those in the I class (owing to the higher viral load and diminished immune response of AIDS people in comparison to those in the I class). Individuals in the I class develop AIDS symptoms at a rate σ_h; and those in the AIDS class suffer an additional HIV-related mortality at a rate δ_a.

Individuals in the latent class of TB infection acquire HIV infection (and move to the mixed infection class) at a rate λ_h. Latent individuals are re-infected (exogenously) with TB, following contact with individuals with active TB, at a rate $r\lambda_t$, where $r > 0$ is the exogenous re-infection parameter. Individuals in the L class develop active TB (via endogenous reactivation) at a rate σ_t.

The population of active TB individuals (T) is increased following the exogenous reinfection and endogenous reactivation of latent TB individuals. People with active TB acquire HIV infection at the rate λ_h, and suffer a TB-induced mortality at a rate δ_t. Similarly, individuals in the mixed HIV/TB class die at a rate δ_m.

Putting all these together, the basic HIV/TB model is given by the following deterministic system of differential equations. (A flow diagram of the model is depicted in Figure 3.1, and the associated parameters and variables are described in Table 6.1).

$$\begin{aligned}
\frac{dS}{dt} &= \Pi - \lambda_h S - \lambda_t S - \mu S, \\
\frac{dI}{dt} &= \lambda_h S - \theta_h \lambda_t I - \sigma_h I - \mu I, \\
\frac{dA}{dt} &= \sigma_h I - \theta_h \eta_h \lambda_t A - \mu A - \delta_a A, \\
\frac{dL}{dt} &= \lambda_t S - \lambda_h L - r\lambda_t L - \sigma_t L - \mu L, \\
\frac{dT}{dt} &= r\lambda_t L + \sigma_t L - \lambda_h T - \mu T - \delta_t T, \\
\frac{dM}{dt} &= \theta_h \lambda_t I + \theta_h \eta_h \lambda_t A + \lambda_h L + \lambda_h T - \mu M - \delta_m M,
\end{aligned} \tag{3.1}$$

where, $\lambda_h = \dfrac{\beta_h(I + \eta_h A)}{N}$, $\lambda_t = \dfrac{\beta_t T}{N}$ and $N = S + I + A + L + T + M$.

It should be mentioned that the HIV components of the model (3.1) is in line with some of the published models for HIV epidemiology (see for instance [16, 21, 26, 32, 39, 48, 51, 52, 53, 54]). Similarly, the TB component of the basic model (3.1) follows the general formulation in earlier studies, such as [5, 6, 7, 10, 11, 19, 52, 55].

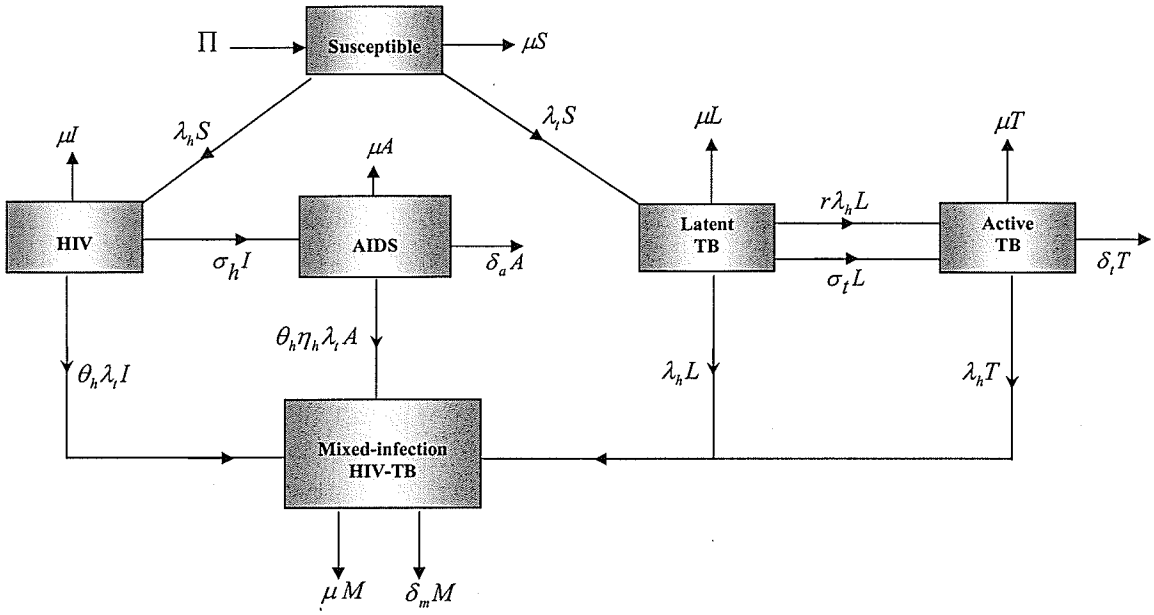

Figure 3.1: Flow diagram of the basic HIV-TB model (3.1).

The model (3.1) is among the very few models designed for the HIV/TB co-infection in the literature ([43, 52]).

In the following section, the basic dynamical features of model (3.1) will be investigated.

3.2 Invariant Region

Solutions to (3.1) are defined in the biologically-feasible region given by

$$\mathcal{D} = \{(S, I, A, L, T, M) \in \mathbb{R}^6_+; \ S + I + A + L + T + M \leq \Pi/\mu\}. \tag{3.2}$$

The region $\mathcal{D}$ will be shown to be positively-invariant and attracting as follows. Adding all the equations in (3.1) gives

$$\frac{dN}{dt} = \Pi - \mu N - \delta_a A - \delta_t T - \delta_m M. \tag{3.3}$$

Since the right hand side of (3.3) is bounded by $\Pi - \mu N$ (that is, $\frac{dN(t)}{dt} \leq \Pi - \mu N$), a standard comparison theorem can be used to show that $N(t) \leq N(0)e^{\mu t} + \frac{\Pi}{\mu}(1 - e^{-\mu t})$.

Consequently, $N(t) \leq \frac{\Pi}{\mu}$ for $N(0) \leq \frac{\Pi}{\mu}$. Additionally, whenever $N(t) > \frac{\Pi}{\mu}$, then $dN(t)/dt < 0$. Hence, every solution of the model (3.1) that originates in $\mathcal{D}$ remains in $\mathcal{D}$ as $t \to \infty$ (so that the ω-limit sets of (3.1) are contained in $\mathcal{D}$ and $\mathcal{D}$ attracts all solutions in $\mathbb{R}^6_+$). Thus, $\mathcal{D}$ is positively-invariant and attracting. It is therefore sufficient to analyze the dynamics of the flow associated with (3.1) in $\mathcal{D}$ and that the system (3.1) is (mathematically and epidemiologically) well-posed in $\mathcal{D}$ [28].

In the subsequent chapters, we shall first analyze the qualitative dynamics of the associated sub-models, namely: the HIV-only sub-model and the TB-only sub-model. The main motivation for this is that by so doing, we will progressively build understanding of the qualitative dynamics of the interaction between HIV and TB.

Chapter 4

Analysis of the HIV-only Sub-Model

The HIV-only sub-model is obtained by setting all the TB-related variables and parameters in (3.1) to zero (that is, set $L(t) = T(t) = \beta_t = 0$), is given by the following system of differential equations.

$$\begin{aligned} \frac{dS}{dt} &= \Pi - \lambda_h S - \mu S, \\ \frac{dI}{dt} &= \lambda_h S - \sigma_h I - \mu I, \\ \frac{dA}{dt} &= \sigma_h I - \mu A - \delta_a A, \end{aligned} \tag{4.1}$$

where, now, $N = S + I + A$ (with the other variables and parameters of this sub-model as defined in Table 6.1). The dynamics of (4.1) will be considered in the following region

$$\mathcal{D}_h = \{(S(t), I(t), A(t)) \in \mathbb{R}^3_+; S(t) + I(t) + A(t) \leq \Pi/\mu\}. \tag{4.2}$$

Using the approach in Section 3.2, it can be shown that the region $\mathcal{D}_h$ is positively-invariant.

4.1 Stability of the DFE

In this section, we shall obtain an expression for the DFE of the sub-model (4.1), define the basic reproduction number for the sub-model, and analyze the local and global stability of the DFE.

4.1.1 Local stability of the disease-free equilibrium

The HIV-only sub-model has a DFE, obtained by setting $\lambda_h = \dfrac{\beta_h(I+\eta_h A)}{N} = 0$ in (4.1), given by

$$\mathcal{E}_{0h} = (S^*, I^*, A^*) = (\Pi/\mu, 0, 0). \tag{4.3}$$

Using the *next generation operator method* [58] on the HIV-only sub-model (4.1), the non-negative matrix, F, of new infections in each compartment, and the M-matrix, V, of the transfer rates of individuals between compartments, are respectively, given by

$$F = \begin{pmatrix} \dfrac{\beta_h S^*}{N^*} & \dfrac{\beta_h \eta_h S^*}{N^*} \\ 0 & 0 \end{pmatrix} \quad \text{and} \quad V = \begin{pmatrix} \sigma_h + \mu & 0 \\ -\sigma_h & \delta_a + \mu \end{pmatrix}. \tag{4.4}$$

Since F and V are computed at the DFE, it follows that $N^* = S^*$. Thus,

$$F = \begin{pmatrix} \beta_h & \beta_h \eta_h \\ 0 & 0 \end{pmatrix}. \tag{4.5}$$

The *basic reproduction number* of infection, denoted by $\mathcal{R}_h$, is given by $\mathcal{R}_h = \rho(FV^{-1})$, where ρ is the spectral radius (or dominant eigenvalue) of the matrix FV^{-1}. Since,

$$FV^{-1} = \frac{1}{(\sigma_h+\mu)(\delta_a+\mu)} \begin{bmatrix} \beta_h(\delta_a+\mu+\sigma_h\eta_h) & \beta_h\eta_h(\sigma_h+\mu) \\ 0 & 0 \end{bmatrix},$$

it follows that,

$$\mathcal{R}_h = \rho(FV^{-1}) = \frac{\beta_h(\delta_a+\mu+\eta_h\sigma_h)}{(\sigma_h+\mu)(\delta_a+\mu)}. \tag{4.6}$$

Thus, using Theorem 2 of [58], we have established the following result.

Theorem 4.1 *The DFE of the HIV-only sub-model (4.1) is locally asymptotically stable (LAS) if $\mathcal{R}_h < 1$, and unstable if $\mathcal{R}_h > 1$.*

Definition 4.1 *The threshold quantity, $\mathcal{R}_h$, is the basic reproduction number for HIV-infection. It measures the average number of secondary cases generated by a single HIV case in a completely susceptible population.*

Theorem 4.1 shows that HIV can be eliminated from the community if $\mathcal{R}_h < 1$ provided the initial number of infectives is small enough (that is, if the initial number of infectives is in the basin of attraction of the DFE). In order for such elimination to be independent of the initial conditions, a global stability result is needed. This is provided below.

4.1.2 Global stability of the DFE

We state the following theorem for the global stability of the DFE (4.3) of the sub-model (4.1).

Theorem 4.2 *The DFE of the HIV-only sub-model (4.1) is globally asymptotically stable (GAS) in $\mathcal{D}_h$, if $\mathcal{R}_h \leq 1$.*

Proof
Consider the following Lyapunov function:

$$\mathcal{P} = (\mu + \delta_a + \eta_h\sigma_h)I + \eta_h(\sigma_h + \mu)A, \tag{4.7}$$

with Lyapunov derivative

$$\begin{aligned}
\dot{\mathcal{P}} &= (\mu + \delta_a + \eta_h\sigma_h)\dot{I} + \eta_h(\sigma_h + \mu)\dot{A} \\
&= (\mu + \delta_a + \eta_h\sigma_h)\left(\frac{\beta_h IS}{N} + \frac{\beta_h\eta_h AS}{N} - \sigma_h I - \mu I\right) \\
&\quad +\eta_h(\sigma_h + \mu)(\sigma_h I - \delta_a A - \mu A) \\
&= \left\{(\mu + \delta_a + \eta_h\sigma_h)\left[\frac{\beta_h S}{N} - (\sigma_h + \mu)\right] + \sigma_h\eta_h(\sigma_h + \mu)\right\} I \\
&\quad + \left[(\mu + \delta_a + \eta_h\sigma_h)\frac{\beta_h\eta_h S}{N} - \eta_h(\sigma_h + \mu)(\delta_a + \mu)\right] A \\
&\leq \{(\mu + \delta_a + \eta_h\sigma_h)[\beta_h - (\sigma_h + \mu)] + \sigma_h\eta_h(\sigma_h + \mu)\} I \\
&\quad + [\beta_h\eta_h(\mu + \delta_a + \eta_h\sigma_h) - \eta_h(\sigma_h + \mu)(\delta_a + \mu)] A \quad (\text{since } S \leq N) \\
&= [\beta_h(\mu + \delta_a + \eta_h\sigma_h) - (\sigma_h + \mu)(\delta_a + \mu)] I \\
&\quad +\eta_h [\beta_h(\mu + \delta_a + \eta_h\sigma_h) - (\sigma_h + \mu)(\delta_a + \mu)] A \\
&= (\sigma_h + \mu)(\delta_a + \mu)(\mathcal{R}_h - 1)(I + \eta_h A) \\
&\leq 0 \quad (\text{if } \mathcal{R}_h \leq 1).
\end{aligned}$$

Since all the model parameters are non-negative, it follows that $\dot{\mathcal{P}} \leq 0$ for $\mathcal{R}_h \leq 1$ with $\dot{\mathcal{P}} = 0$ only if $I = A = 0$ (note that equality holds only if $S = N = \Pi/\mu$, which

corresponds to the DFE, $\mathcal{E}_0$). Hence, $\mathcal{P}$ is a Lyapunov function on $\mathcal{D}_h$. Furthermore, $\mathcal{E}_0$ is the single compact invariant set in $\mathcal{D}_h$. Consequently, by LaSalle's Invariance Principle [24], every solution to the equations of the HIV-only sub-model (4.1), with initial conditions in $\mathcal{D}_h$, approaches $\mathcal{E}_{0h}$ as $t \to \infty$. □

The epidemiological implication of Theorem 4.2 is that HIV will be eliminated from the community if $\mathcal{R}_h \leq 1$ regardless of the initial sizes of the model variables.

4.2 Existence and Stability of Endemic Equilibria

In the above, we considered the DFE of the sub-model (4.1) and analyzed it for its local and global asymptotic stability. Another type of equilibrium that system (4.1) can have is an endemic equilibrium, where the disease is present in the population. We now obtain conditions for the existence of these types of equilibria and also carry out their stability analysis.

4.2.1 Existence of endemic equilibria

Let $\mathcal{E}_{1h} = (S^{**}, I^{**}, A^{**})$ represents any arbitrary endemic equilibrium of the HIV-only sub-model (4.1) (that is, an equilibrium point where at least one of the components I^{**} and A^{**} is non-zero). Solving for the variables in (4.1) and simplifying gives the following components of $\mathcal{E}_{1h}$

$$\begin{aligned} S^{**} &= \frac{\Pi(\sigma_h + \delta_a + \mu)}{(\delta_a + \mu)(\sigma_h + \mu)(\mathcal{R}_h - 1) + \mu(\sigma_h + \delta_a + \mu)}, \\ I^{**} &= \frac{(\delta_a + \mu)(\mathcal{R}_h - 1)S^{**}}{(\sigma_h + \delta_a + \mu)}, \\ A^{**} &= \frac{\sigma_h(\mathcal{R}_h - 1)S^{**}}{(\sigma_h + \delta_a + \mu)}. \end{aligned} \tag{4.8}$$

Consequently, the sub-model (4.1) has a unique endemic equilibrium which exists (that is, it is biologically meaning) only if $\mathcal{R}_h > 1$. This result is summarized below.

Lemma 4.1 *The HIV-only sub-model (4.1) has a unique endemic equilibrium point (EEP), denoted by $\mathcal{E}_{1h}$, whenever $\mathcal{R}_h > 1$.*

The local stability of $\mathcal{E}_{1h}$ is now explored.

4.2.2 Local stability of the endemic equilibrium

Let

$$\lambda_h^{**} = \frac{\beta_h(I^{**} + \eta_h A^{**})}{N^{**}}. \tag{4.9}$$

Then, it follows, using (4.8), that

$$\lambda_h^{**} = \frac{(\sigma_h + \mu)(\delta_a + \mu)}{\sigma_h + \delta_a + \mu}(\mathcal{R}_h - 1). \tag{4.10}$$

Further,

$$N^{**} = S^{**} + I^{**} + A^{**} = \mathcal{R}_h S^{**}. \tag{4.11}$$

The stability of $\mathcal{E}_{1h}$ will be determined by linearizing the system (4.1) around $\mathcal{E}_{1h}$ as follows. The Jacobian, J, of (4.1), evaluated at $\mathcal{E}_{1h}$, is given by

$$J(\mathcal{E}_{1h}) = \begin{pmatrix} j_{11} - \mu & j_{12} & j_{13} \\ j_{21} & j_{22} - (\sigma + \mu) & j_{23} \\ 0 & \sigma_h & -(\delta + \mu) \end{pmatrix} \tag{4.12}$$

where,

$$\begin{aligned} j_{11} = -j_{21} &= \frac{\beta_h(I^{**} + \eta_h A^{**})}{N^{**}} - \frac{\beta_h(I^{**} + \eta_h A^{**})S^{**}}{N^{**^2}}, \\ j_{12} = -j_{22} &= -\frac{\beta_h S^{**}}{N^{**}} + \frac{\beta_h(I^{**} + \eta_h A^{**})S^{**}}{N^{**^2}}, \\ j_{13} = -j_{23} &= -\frac{\beta_h \eta_h S^{**}}{N^{**}} + \frac{\beta_h(I^{**} + \eta_h A^{**})S^{**}}{N^{**^2}}. \end{aligned} \tag{4.13}$$

Using (4.9) and (4.11), the quantities in (4.13) can be re-written as

$$\begin{aligned} j_{11} = -j_{21} &= \lambda_h^{**}\left(1 - \frac{1}{\mathcal{R}_h}\right), \\ j_{12} = -j_{22} &= -\frac{\beta_h}{\mathcal{R}_h} + \frac{\lambda_h^{**}}{\mathcal{R}_h}, \\ j_{13} = -j_{23} &= -\frac{\beta_h \eta_h}{\mathcal{R}_h} + \frac{\lambda_h^{**}}{\mathcal{R}_h}. \end{aligned} \tag{4.14}$$

Substituting (4.14) in (4.12), it follows that the eigenvalues of $J(\mathcal{E}_{1h})$ satisfy the following characteristic polynomial:

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0, \tag{4.15}$$

where,

$$\begin{aligned} a_1 &= \lambda_h^{**} + 2\mu + \delta_h + \frac{\sigma_h\eta_h(\sigma_h+\mu)}{\delta_h+\mu+\sigma_h\eta_h}, \\ a_2 &= (\delta_h+\mu)(\mu+\lambda_h^{**}) + (\sigma_h+\mu)\left(\lambda_h^{**} + \frac{\mu\sigma_h\eta_h}{\delta_h+\mu+\sigma_h\eta_h}\right), \\ a_3 &= \frac{\lambda_h^{**}\left\{\mu\sigma_h + (\delta_h+\mu)[\mu\mathcal{R}_h + \sigma_h(\mathcal{R}_h-1)]\right\}}{\mathcal{R}_h}. \end{aligned} \tag{4.16}$$

It should be noted that whenever $\mathcal{R}_h > 1$, the components I^{**}, A^{**} and λ_h^{**} are all positive (see (4.8) and (4.10)). Thus, each of the coefficients a_1, a_2 and a_3 in (4.16) is positive provided $\mathcal{R}_h > 1$. Furthermore,

$$\begin{aligned} a_1a_2 - a_3 &= \left[\lambda_h^{**} + 2\mu + \delta_h + \frac{\sigma_h\eta_h(\sigma_h+\mu)}{\delta_h+\mu+\sigma_h\eta_h}\right] \\ &\times \left[(\delta_h+\mu)(\mu+\lambda_h^{**}) + (\sigma_h+\mu)\left(\lambda_h^{**} + \frac{\mu\sigma_h\eta_h}{\delta_h+\mu+\sigma_h\eta_h}\right)\right] \\ &- \frac{\lambda_h^{**}\left\{\mu\sigma_h + (\delta_h+\mu)[\mu\mathcal{R}_h + \sigma_h(\mathcal{R}_h-1)]\right\}}{\mathcal{R}_h} \\ &= \left[\lambda_h^{**} + 2\mu + \delta_h + \frac{\sigma_h\eta_h(\sigma_h+\mu)}{\delta_h+\mu+\sigma_h\eta_h}\right] \\ &\times \left[(\delta_h+\mu)(\mu+\lambda_h^{**}) + (\sigma_h+\mu)\left(\lambda_h^{**} + \frac{\mu\sigma_h\eta_h}{\delta_h+\mu+\sigma_h\eta_h}\right)\right] \\ &+ \frac{\lambda_h^{**}\sigma_h(\delta_h+\mu)}{\mathcal{R}_h} - \frac{\lambda_h^{**}\mu\sigma_h}{\mathcal{R}_h} - \lambda_h^{**}(\delta_h+\mu)(\mu+\sigma_h) \\ &= \left[\lambda_h^{**} + 2\mu + \delta_h + \frac{\sigma_h\eta_h(\sigma_h+\mu)}{\delta_h+\mu+\sigma_h\eta_h}\right] \\ &\times \left[(\delta_h+\mu)(\mu+\lambda_h^{**}) + \lambda_h^{**}(\sigma_h+\mu) + \frac{\mu\sigma_h\eta_h(\sigma_h+\mu)}{\delta_h+\mu+\sigma_h\eta_h}\right] \\ &+ \frac{\lambda_h^{**}\sigma_h\delta_h}{\mathcal{R}_h} - \lambda_h^{**}(\delta_h+\mu)(\mu+\sigma_h) \end{aligned}$$

$$
\begin{aligned}
&= \left[\lambda_h^{**} + \mu + \frac{\sigma_h\eta_h(\sigma_h+\mu)}{\delta_h+\mu+\sigma_h\eta_h}\right] \\
&\times \left[(\delta_h+\mu)(\mu+\lambda_h^{**}) + \lambda_h^{**}(\sigma_h+\mu) + \frac{\mu\sigma_h\eta_h(\sigma_h+\mu)}{\delta_h+\mu+\sigma_h\eta_h}\right] \\
&+ (\mu+\delta_h)\left[(\delta_h+\mu)(\mu+\lambda_h^{**}) + \lambda_h^{**}(\sigma_h+\mu) + \frac{\mu\sigma_h\eta_h(\sigma_h+\mu)}{\delta_h+\mu+\sigma_h\eta_h}\right] \\
&+ \frac{\lambda_h^{**}\sigma_h\delta_h}{\mathcal{R}_h} - \lambda_h^{**}(\delta_h+\mu)(\mu+\sigma_h) \\
&= \left[\lambda_h^{**} + \mu + \frac{\sigma_h\eta_h(\sigma_h+\mu)}{\delta_h+\mu+\sigma_h\eta_h}\right] \\
&\times \left[(\delta_h+\mu)(\mu+\lambda_h^{**}) + \lambda_h^{**}(\sigma_h+\mu) + \frac{\mu\sigma_h\eta_h(\sigma_h+\mu)}{\delta_h+\mu+\sigma_h\eta_h}\right] \\
&+ (\mu+\delta_h)\left[(\delta_h+\mu)(\mu+\lambda_h^{**}) + \frac{\mu\sigma_h\eta_h(\sigma_h+\mu)}{\delta_h+\mu+\sigma_h\eta_h}\right] + \frac{\lambda_h^{**}\sigma_h\delta_h}{\mathcal{R}_h} \\
&> 0 \quad \text{for } \lambda_h^{**} > 0 \ \text{(i.e., } \mathcal{R}_h > 1\text{)}.
\end{aligned}
$$

Thus, $a_1a_2 - a_3 > 0$ whenever $\mathcal{R}_h > 1$. Therefore, it follows from the Routh-Hurwitz criterion that the eigenvalues of the matrix $J(\mathcal{E}_{1h})$ all have negative real parts, establishing the following result.

Theorem 4.3 *The endemic equilibrium of the HIV-only sub-model (4.1) is LAS whenever $\mathcal{R}_h > 1$, and unstable otherwise.*

It is not easy to prove the global stability of the endemic equilibrium of the HIV-only sub-model (4.1). Here, we provide a global stability proof for a special case for which $\delta_a = 0$. Setting $\delta_a = 0$ in (4.1) gives

$$
\begin{aligned}
\frac{dS}{dt} &= \Pi - \lambda_h S - \mu S, \\
\frac{dI}{dt} &= \lambda_h S - \sigma_h I - \mu I, \\
\frac{dA}{dt} &= \sigma_h I - \mu A.
\end{aligned} \tag{4.17}
$$

For the reduced HIV-only sub-model (4.17), it is easy to see that $\frac{dN}{dt} = \Pi - \mu N$. Like in the case of the HIV-only sub-model (4.1), model (4.17) has a unique endemic equilibrium given by (4.8) with $\delta_a = 0$. We claim the following result.

Theorem 4.4 *The endemic equilibrium of the reduced model (4.17) is GAS in* $\mathcal{D}_h \backslash \mathcal{D}_0$, *with* $\mathcal{D}_0 = \{(S, I, A) \in \mathcal{D}_h : \ I = A = 0\}$ *whenever* $\mathcal{R}_h|_{\delta_a=0} > 1$.

Proof

Note, first of all, that the equilibrium $\mathcal{E}_{1h}$ of (4.1) is LAS whenever $\mathcal{R}_h > 1$. Thus, the unique EEP of (4.17) is also LAS whenever $\mathcal{R}_h|_{\delta_a=0} > 1$. Since $\frac{dN}{dt} = \Pi - \mu N$, it follows that $N \to \Pi/\mu$ as $t \to \infty$. Consequently, using $S = N - I - A = \Pi/\mu - I - A$, and substituting for λ_h, (4.17) reduces to the following two-dimensional limiting system.

$$\begin{aligned} \frac{dI}{dt} &= \frac{\beta_h(I + \eta_h A)}{\Pi/\mu}(\Pi/\mu - I - A) - (\sigma_h + \mu)I, \\ \frac{dA}{dt} &= \sigma_h I - \mu A. \end{aligned} \tag{4.18}$$

Using Dulac's Criterion [47] with multiplier $1/IA$, it follows that

$$\begin{aligned} &\frac{\partial}{\partial I}\left[\frac{\beta_h(I + \eta_h A)}{IA\Pi/\mu}(\Pi/\mu - I - A) - \frac{(\sigma_h + \mu)}{A}\right] + \frac{\partial}{\partial A}\left(\frac{\sigma_h}{A} - \frac{\mu}{I}\right) \\ &= -\left[\frac{\beta_h \mu}{\Pi} + \frac{\beta_h \eta_h \mu}{\Pi I^2}\left(1 - \frac{A}{\Pi/\mu}\right) + \frac{\sigma_h}{A^2}\right] \\ &< 0 \qquad \text{since } \Pi/\mu = N > A \text{ in } \mathcal{D}_h. \end{aligned} \tag{4.19}$$

Thus, by Dulac's Criterion, there are no periodic orbits in the region $\mathcal{D}_h \backslash \mathcal{D}_0$. It follows, by Poincaré-Bendixson theorem, that all solutions of the limiting system (4.18) starting in the region $\mathcal{D}_h \backslash \mathcal{D}_0$ with $I > 0$ and $I + A < N = \Pi/\mu$ approaches (I^{**}, A^{**}) as $t \to \infty$. Since the EEP of (4.17) is LAS whenever $\mathcal{R}_h|_{\delta_a=0} > 1$ (see Theorem 4.3), the absence of periodic orbits in $\mathcal{D}_h \backslash \mathcal{D}_0$ shows that the EEP of (4.17) is GAS in $\mathcal{D}_h \backslash \mathcal{D}_0$ whenever $\mathcal{R}_h|_{\delta_a=0} > 1$. □

4.3 Numerical Simulations

Numerical simulations of the HIV-only sub-model (4.1) are carried out, using the set of parameter values tabulated in Table 4.1, to illustrate some of the theoretical results obtained in this chapter. It should be emphasized that these parameters in Table 4.1 (and the rest of the thesis) are chosen primarily to illustrate the theoretical results; and some of the estimated values used may not be very realistic epidemiologically. With the set of parameter values in Table 4.1, $\mathcal{R}_h = 0.6420 < 1$ (so that by Theorem 4.2, the DFE is GAS). The time-series of total infected individuals at time t, $I(t)+A(t)$ using various initial conditions is depicted in Figure 4.1. It illustrates that the DFE is GAS. On the other hand, when the model parameters are changed such that $\mathcal{R}_h = 8.7032 > 1$, the infected components converge to some non-negative values, signifying the persistence of HIV in this case (see Figure 4.2).

4.4 Summary

In this chapter, a three-dimensional compartmental model for HIV transmission is considered. The model has two equilibria, namely a DFE and a unique endemic equilibrium, which exists whenever a certain epidemiological threshold, known as the basic *reproduction number*, $\mathcal{R}_h$, exceeds unity (that is, $\mathcal{R}_h > 1$). It is also shown, using the theory of Lyapunov function and LaSalle Invariance Principle, that the DFE is globally-asymptotically stable whenever $\mathcal{R}_h \leq 1$. Furthermore, it is shown that the unique endemic equilibrium is locally asymptotically stable whenever it exists. The epidemiological implications of these results is that HIV can be eliminated from the community if $\mathcal{R}_h \leq 1$, and will persist if $\mathcal{R}_h > 1$. A limiting case, where the HIV-induced mortality parameter δ_a is set to zero, is also considered. By using a suitable Dulac function and Poincaré-Bendixson theorem, this limiting system is shown to have a globally asymptotically stable endemic equilibrium whenever $\mathcal{R}_h|_{\delta_a=0} > 1$.

Table 4.1: Parameter values for the HIV-only sub-model (4.1)

Parameter	Nominal Value $(year)^{-1}$	Reference
Π	5000	[48]
β_h	0.3	assumed
σ_h	0.5	assumed
η_h	1.2	assumed
δ_a	5.3	assumed
μ	1/50	assumed

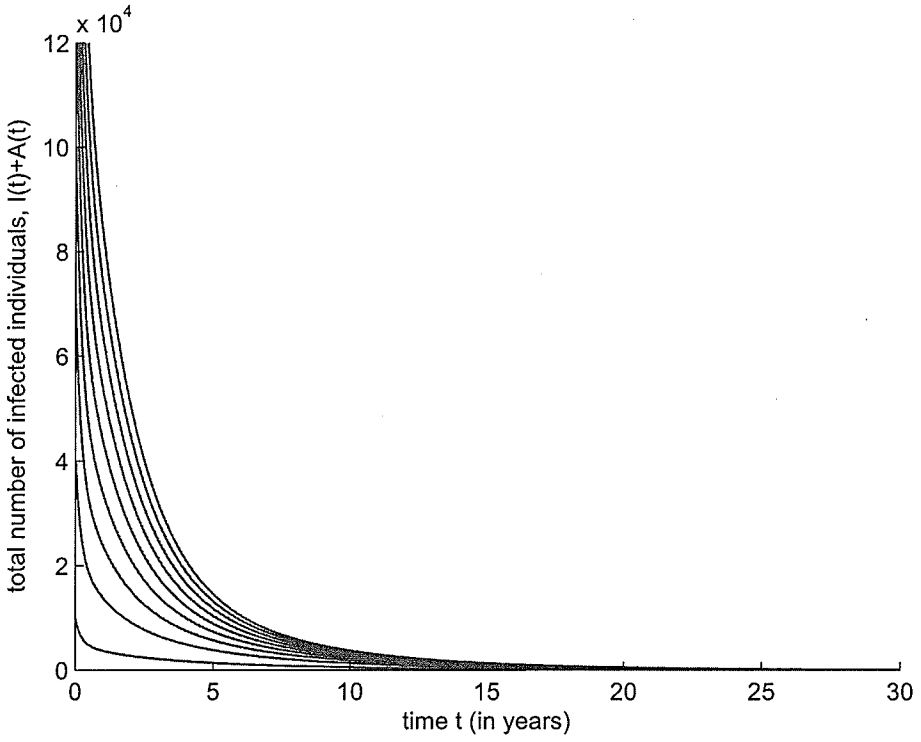

Figure 4.1: Total infectives as a function of time for different initial conditions for the HIV-only sub-model (4.1), using the parameters in Table 4.1 (so that $\mathcal{R}_h = 0.6420 < 1$).

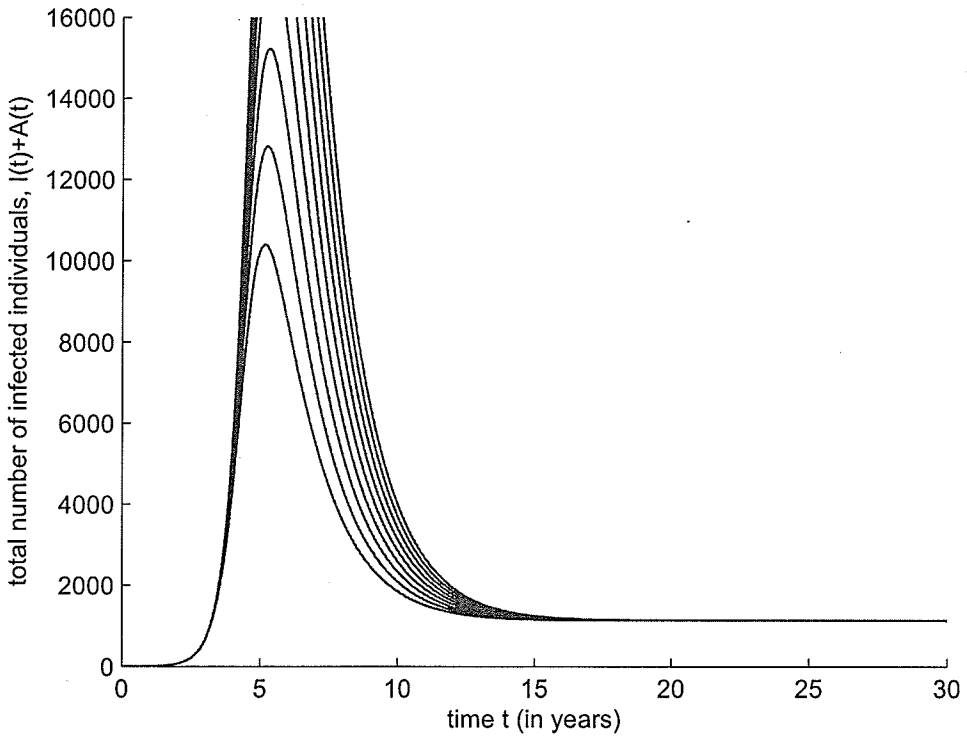

Figure 4.2: Total infectives as a function of time for different initial conditions for the HIV-only sub-model (4.1), using the parameters $\Pi = 500$, $\beta_h = 1.3$, $\eta_h = 7.2$, $\sigma_h = 0.6$, $\delta_a = 1.3$ and $\mu = 1/30$ (giving $\mathcal{R}_h = 8.7032 > 1$).

Chapter 5

Analysis of the TB-only Sub-model

The TB-only sub-model, obtained by setting all the HIV-related variables in (3.1) to zero (that is, $I(t) = A(t) = M(t) = 0$), is given by

$$\begin{aligned} \frac{dS}{dt} &= \Pi - \lambda_t S - \mu S, \\ \frac{dL}{dt} &= \lambda_t S - r\lambda_t L - \sigma_t L - \mu L, \\ \frac{dT}{dt} &= r\lambda_t L + \sigma_t L - \delta_t T - \mu T, \end{aligned} \tag{5.1}$$

where, now, $N = S + L + T$. The solutions of (5.1) are defined in the feasible domain given by

$$\mathcal{D}_t = \{(S(t), L(t), T(t)) \in \mathbb{R}^3 : S(t) + L(t) + T(t) \leq \Pi/\mu\}. \tag{5.2}$$

As in Chapter 3, it can be shown that the region $\mathcal{D}_t$ is positively-invariant.

5.1 Local Stability of DFE

The DFE of the TB-only sub-model (5.1) is given by

$$\mathcal{E}_{0t} = (S^*, L^*, T^*) = (\Pi/\mu, 0, 0). \tag{5.3}$$

For the system (5.1), the associated next generation matrices are given by

$$F = \begin{pmatrix} 0 & \beta_t \\ 0 & 0 \end{pmatrix} \quad \text{and} \quad V = \begin{pmatrix} \sigma_t + \mu & 0 \\ -\sigma_t & \delta_t + \mu \end{pmatrix}.$$

so that, $\mathcal{R}_t = \rho(FV^{-1})$ is given by

$$\mathcal{R}_t = \frac{\beta_t \sigma_t}{(\sigma_t + \mu)(\delta_t + \mu)}. \tag{5.4}$$

Thus, using Theorem 2 of [58], we have established the following result.

Theorem 5.1 *The DFE of the TB-only sub-model (5.1) is LAS if $\mathcal{R}_t < 1$ and unstable if $\mathcal{R}_t > 1$.*

Definition 5.1 *The threshold, $\mathcal{R}_t$, is the basic reproduction number for TB-infection. It measures the average number of secondary cases generated by a single TB case in a completely susceptible population.*

Theorem 5.1 shows that TB can be eliminated from the community if $\mathcal{R}_t < 1$ provided the initial number of TB cases is small enough (that is, if the initial number of TB cases is in the basin of attraction of $\mathcal{E}_{0t}$). A stronger (global) stability result will be given for a special case of the TB-only sub-model (5.1) in Section 5.4.

The existence of endemic equilibria for the TB-only system (5.1) is explained next.

5.2 Existence and Stability of Endemic Equilibria

Let $\mathcal{E}_{1t} = (S^{**}, I_h^{**}, A^{**})$ be an arbitrary endemic equilibrium of the TB-only sub-model (5.1). Let

$$\lambda_t^{**} = \frac{\beta_t T^{**}}{N^{**}} \quad \text{with} \quad N^{**} = S^{**} + L^{**} + T^{**}. \tag{5.5}$$

Using λ_t^{**} in (5.1), it follows that the variables S, L, and T at steady state, take the form:

$$\begin{aligned} S^{**} &= \frac{\Pi}{\lambda_t^{**} + \mu}, \\ L^{**} &= \frac{\lambda_t^{**} S^{**}}{r\lambda_t^{**} + \sigma_t + \mu}, \\ T^{**} &= \frac{\lambda_t^{**}(r\lambda_t^{**} + \sigma_t) S^{**}}{(\delta_t + \mu)(r\lambda_t^{**} + \sigma_t + \mu)}. \end{aligned} \tag{5.6}$$

Substituting (5.6) in (5.5), noting that $N^{**} = S^{**} + L^{**} + T^{**}$ and after some simplifications, gives the following quadratic equation in λ_t^{**}:

$$a\lambda_t^{**2} + b\lambda_t^{**} + c = 0, \tag{5.7}$$

where,

$$\begin{aligned} a &= r, \\ b &= (r+1)(\delta_t+\mu)+\sigma_t-r\beta_t, \\ c &= (\sigma_t+\mu)(\delta_t+\mu)(1-\mathcal{R}_t). \end{aligned} \tag{5.8}$$

Thus, we have established the following results.

Theorem 5.2 *The TB-only sub-model in (5.1)*

(i) has a unique endemic equilibrium when $c < 0$,

(ii) has a unique endemic equilibrium whenever $b < 0$ *and either* $c = 0$ *or* $b^2 - 4ac = 0$,

(iii) has two endemic equilibria whenever $b < 0$ *and* $c > 0$,

(iv) has no endemic equilibrium, otherwise - that is, whenever $b > 0$ *and* $c > 0$

Unlike the HIV-only sub-model, the above theorem shows that the TB-only sub-model can have multiple endemic equilibria when $c > 0$ ($\mathcal{R}_t > 1$) and $b < 0$. This is often a signature for the phenomenon of backward bifurcation, where a stable endemic equilibrium coexists with a stable disease-free equilibrium ($\mathcal{E}_{0t}$).

The epidemiological implication of this phenomenon is that the classical requirement of having the associated reproduction number $\mathcal{R}_t$ to be less than unity is, although necessary, now no longer sufficient for the effective control (or elimination) of the disease in the community. In such a case, the elimination of the disease will depend on the initial size of the sub-population of the model.

This possibility of backward bifurcation in (5.1) is now explored below.

5.3 Backward Bifurcation in the TB-only Sub-model.

Using the third equation in (5.8) to substitute for c in (5.7) yields the quadratic equation,

$$a(\lambda_t^{**})^2 + b\lambda_t^{**} + (\sigma_t+\mu)(\delta_t+\mu)(1-\mathcal{R}_t) = 0, \tag{5.9}$$

and solving for $\mathcal{R}_t$, we have,

$$\mathcal{R}_t = \frac{1}{(\sigma_t+\mu)(\delta_t+\mu)}[a\lambda_t^{**2} + b\lambda_t^{**} + (\sigma_t+\mu)(\delta_t+\mu)]. \tag{5.10}$$

Since $a = r > 0$, it follows from (5.10), that $\mathcal{R}_t$ has a *minimum value* at the point when $\lambda_t^{**} = -b/2a = -b/2r$ (this point corresponds to the condition $b^2 - 4ac = 0$, which is obtained by substituting $\lambda_t^{**} = -b/2a$ into (5.7)). This minimum value of $\mathcal{R}_t$

in (5.10), denoted by $\mathcal{R}_t^*$, and also referred to as the *threshold* or *critical* value of $\mathcal{R}_t$, is given by (entails setting $\lambda_t^{**} = -b/2a$ in (5.10))

$$\mathcal{R}_t^* = 1 - \frac{b^2}{4a(\sigma_t + \mu)(\delta_t + \mu)}. \tag{5.11}$$

For co-existence of both the disease-free and endemic equilibrium at a backward bifurcation, it is necessary that $\mathcal{R}_t^* < \mathcal{R}_t < 1$, resulting in the following theorem.

Theorem 5.3 *The TB-only sub-model in (5.1) undergoes a backward bifurcation whenever item (iii) of Theorem 5.2 holds and* $0 < \mathcal{R}_t^* < \mathcal{R}_t < 1$.

This backward bifurcation phenomenon is illustrated, using a suitable set of parameter values, in Figures 5.1 and 5.2.

The backward bifurcation in (5.1) arises because the re-infection parameter r is non-zero. If $r = 0$, it is clear that the coefficient a of (5.7) is zero, and the quadratic reduces to a linear function with at most one solution (hence, no two endemic equilibria can exist in this case, thereby excluding the possibility of backward bifurcation). To further demonstrate this fact, it is shown below that the TB-only sub-model (5.1) with $r = 0$, has a globally stable DFE (hence, completely ruling out backward bifurcation in this special case).

5.4 Global Stability of the DFE for the Case $r = 0$.

We claim the following.

Theorem 5.4 *The DFE of the TB-only sub-model (5.1) with* $r = 0$ *is GAS in* $\mathcal{D}_t$ *iff* $\mathcal{R}_t < 1$.

Proof

The proof is based on using a comparison theorem ([21, 36, 52]). With $r = 0$, the TB-only sub-model (5.1) reduces to:

$$\begin{aligned} \frac{dS}{dt} &= \Pi - \lambda_t S - \mu S, \\ \frac{dL}{dt} &= \lambda_t S - \sigma_t L - \mu L, \\ \frac{dT}{dt} &= \sigma_t L - \delta_t T - \mu T. \end{aligned} \tag{5.12}$$

It can be shown that the invariant region $\mathcal{D}_t$ (given in (5.2)) is the feasible region for the reduced system (5.12). Furthermore, it is clear that the special case (5.12) has the same disease-free equilibrium, $\mathcal{E}_{0t} = (\Pi/\mu, 0, 0)$, as the sub-model (5.1). The equations for L and T can be written in terms of the next generation matrices F and V in Section 5.1 to obtain,

$$\begin{pmatrix} \frac{dL(t)}{dt} \\ \\ \frac{dT(t)}{dt} \end{pmatrix} = (F - V) \begin{pmatrix} L(t) \\ \\ T(t) \end{pmatrix} - \left(1 - \frac{S}{N}\right) \begin{pmatrix} 0 & \beta_t \\ \\ 0 & 0 \end{pmatrix} \begin{pmatrix} L(t) \\ \\ T(t) \end{pmatrix}. \tag{5.13}$$

Since $S \leq N$, for all $t \geq 0$ in the feasible region $\mathcal{D}_t$ for system (5.12), equation (5.13) can be expressed by the following inequality:

$$\begin{pmatrix} \frac{dL(t)}{dt} \\ \\ \frac{dT(t)}{dt} \end{pmatrix} \leq (F - V) \begin{pmatrix} L(t) \\ \\ T(t) \end{pmatrix}. \tag{5.14}$$

Using the fact that the eigenvalues of the matrix $F-V$ all have negative reals parts (see local stability result in Theorem 5.1, where $\rho(FV^{-1}) < 1$ if $\mathcal{R}_t < 1$, which is equivalent to the matrix $F-V$ having eigenvalues with negative real parts when $\mathcal{R}_t < 1$), it follows that the linearized differential inequality system (5.14) is stable whenever $\mathcal{R}_t < 1$. Consequently [4], $(L(t), T(t)) \to (0, 0)$ as $t \to \infty$. It follows, by using a comparison theorem that $(L(t), T(t)) \to (0, 0)$ as $t \to \infty$ (see [36], p.31). Thus, substituting $(L(t) = 0 = T(t)$ in (5.12), we have that in system (5.12), $S(t) \to S^* = \Pi/\mu$ as $t \to \infty$ whenever $\mathcal{R}_t < 1$. This means that in (5.12), which is the special case of (5.1) when $r = 0$, $(S(t), L(t), T(t)) \to (S^*, 0, 0) = (\Pi, 0, 0)$ as $t \to \infty$ for $\mathcal{R}_t < 1$, so that $\mathcal{E}_{0t}$ is GAS in $\mathcal{D}_t$ if $\mathcal{R}_t < 1$, as stated in Theorem 5.4. □

Thus, the backward bifurcation phenomenon in the TB-only model can be removed if the exogenous reinfection parameter, r, is set to zero. In other words, this analysis confirms that exogenous reinfection is responsible for the backward bifurcation in the TB dynamics.

5.4.1 Stability of the endemic equilibrium for the case $r = 0$.

We now illustrate the above theorem for the special case when $r = 0$. Clearly, when $r = 0$, the Jacobian of the system (5.12) will have eigenvalues that satisfy

$$b_0\lambda^3 + b_1\lambda^2 + b_2\lambda + b_3 = 0,$$

where, the coefficients b_0, b_1, b_2, and b_3 are given by:

$$\begin{aligned}
b_0 &= 1, \\
b_1 &= \lambda_t^{**} + \xi_t + \rho_t + \mu, \\
b_2 &= (\rho_t + \xi_t)\lambda_t^{**} + \mu\rho_t + \xi_t\rho_t + \mu\xi_t - \frac{\rho_t\sigma_t\beta_t\xi_t}{(\xi_t + \sigma_t)\lambda_t^{**} + \xi_t\rho_t}, \\
b_3 &= \xi_t\rho_t\lambda_t^{**} + \mu\xi_t\rho_t + \frac{\mu\sigma_t\xi_t\rho_t\lambda_t^{**}}{(\xi_t + \sigma_t)\lambda_t^{**} + \xi_t\rho_t} - \frac{\rho_t\sigma_t\xi_t(\xi_t + \mu\beta_t)}{(\xi_t + \sigma_t)\lambda_t^{**} + \xi_t\rho_t}.
\end{aligned} \tag{5.15}$$

Using $r = 0$ in (5.8), and substituting the results in (5.7) yields

$$\lambda_t^{**} = \frac{\xi_t\rho_t(\mathcal{R}_t - 1)}{\xi_t + \sigma_t}. \tag{5.16}$$

Furthermore, substituting (5.16) in (5.15), and after some manipulations, yields

$$\begin{aligned}
b_0 &= 1, \\
b_1 &= \frac{\xi_t\rho_t(\mathcal{R}_t - 1)}{\xi_t + \sigma_t} + \xi_t + \rho_t + \mu, \\
b_2 &= \mu(\sigma_t + \xi_t) + \frac{2\xi_t\rho_t^2(\mathcal{R}_t - 1)}{\xi_t + \sigma_t}, \\
b_3 &= \frac{\xi_t\rho_t(\mathcal{R}_t - 1)}{(\xi_t + \sigma_t)}\left[\mu\left(\xi_t + \frac{\sigma_t}{\mathcal{R}_t}\right) + \sigma_t\xi_t\left(1 - \frac{1}{\mathcal{R}_t}\right)\right].
\end{aligned} \tag{5.17}$$

Clearly, the coefficients, b_0, b_1, b_2, and b_3, are all positive whenever $\mathcal{R}_t > 1$. Furthermore,

$$
\begin{aligned}
b_1b_2 - b_3 &= \left[\frac{\xi_t\rho_t(\mathcal{R}_t-1)}{\xi_t+\sigma_t} + \xi_t + \rho_t + \mu\right]\left[\mu(\sigma_t+\xi_t) + \frac{2\xi_t\rho_t^2(\mathcal{R}_t-1)}{\xi_t+\sigma_t}\right] \\
&\quad -\frac{\xi_t\rho_t(\mathcal{R}_t-1)}{(\xi_t+\sigma_t)}\left[\mu\left(\xi_t+\frac{\sigma_t}{\mathcal{R}_t}\right) + \sigma_t\xi_t\left(1-\frac{1}{\mathcal{R}_t}\right)\right] \\
&= \frac{\xi_t\rho_t(\mathcal{R}_t-1)}{\xi_t+\sigma_t}[\mu(\sigma_t+\xi_t)] + \frac{2\xi_t^2\rho_t^3(\mathcal{R}_t-1)^2}{(\xi_t+\sigma_t)^2} + \frac{\xi_t^2\sigma_t\rho_t(\mathcal{R}_t-1)}{\mathcal{R}_t(\xi_t+\sigma_t)} \\
&\quad + (\xi_t+\rho_t+\mu)\left[\mu(\sigma_t+\xi_t) + \frac{2\xi_t\rho_t^2(\mathcal{R}_t-1)}{\xi_t+\sigma_t}\right] \\
&\quad -\frac{\xi_t\rho_t(\mathcal{R}_t-1)}{(\xi_t+\sigma_t)}\left[\mu\left(\xi_t+\frac{\sigma_t}{\mathcal{R}_t}\right) + \sigma_t\xi_t\right] \\
&= \frac{\xi_t\rho_t(\mathcal{R}_t-1)}{\xi_t+\sigma_t}\left[\mu\sigma_t\left(1-\frac{1}{\mathcal{R}_t}\right)\right] + \frac{2\xi_t^2\rho_t^3(\mathcal{R}_t-1)^2}{(\xi_t+\sigma_t)^2} + \frac{\xi_t^2\sigma_t\rho_t(\mathcal{R}_t-1)}{\mathcal{R}_t(\xi_t+\sigma_t)} \\
&\quad +\mu(\xi_t+\rho_t+\mu)(\sigma_t+\xi_t) + \frac{\xi_t\rho_t(\mathcal{R}_t-1)}{\xi_t+\sigma_t}[2\rho_t(\xi_t+\rho_t+\mu) - \sigma_t\xi_t] \\
&= \frac{\xi_t\rho_t(\mathcal{R}_t-1)}{\xi_t+\sigma_t}\left[\mu\sigma_t\left(1-\frac{1}{\mathcal{R}_t}\right)\right] + \frac{2\xi_t^2\rho_t^3(\mathcal{R}_t-1)^2}{(\xi_t+\sigma_t)^2} + \frac{\xi_t^2\sigma_t\rho_t(\mathcal{R}_t-1)}{\mathcal{R}_t(\xi_t+\sigma_t)} \\
&\quad +\mu(\xi_t+\rho_t+\mu)(\sigma_t+\xi_t) + \frac{\xi_t\rho_t(\mathcal{R}_t-1)(\rho_t+\mu)(2\rho_t+\xi_t)}{\xi_t+\sigma_t} \\
&> 0 \text{ for } \mathcal{R}_t > 1.
\end{aligned}
\tag{5.18}
$$

Thus, by Routh Hurwitz criterion, the eigenvalues of the Jacobian of the TB-only system (5.1) with $r = 0$, all have negative real parts. Hence, the endemic equilibrium of the system is LAS provided $\mathcal{R}_t > 1$.

5.5 Numerical Simulations

Numerical simulations of the TB-only sub-model (5.1) are carried out, using appropriate sets of parameter values to illustrate some of the theoretical results obtained in this chapter.

Figures 5.1, and 5.2 demonstrate the existence of backward bifurcation in the TB-only sub-model in a region where the critical and basic reproduction numbers are $\mathcal{R}_t^* = 0.8449 < 1$ and $\mathcal{R}_t = 0.8559 < 1$, respectively.

For the set of parameter values in Table 5.1, $\mathcal{R}_t = 0.2164 < 1$ (so that by Theorem 5.1, the DFE is LAS). The time-series plots depicted in Figure 5.3, of the total TB-infected individuals at time t, $L(t) + T(t)$, show convergence of solution profiles to the DFE.

When the model parameters are changed such that $\mathcal{R}_t = 12.2918 > 1$, the infected components converge to some non-negative values, signifying the persistence of TB in this case (see Figure 5.4).

Table 5.1: Parameter values for the TB-only sub-model (5.1)

Parameter	**Nominal Value** $(year)^{-1}$	**Reference**
Π	$50,000$	[52]
β_t	0.08	assumed
σ_t	0.333	[10]
r	0.23	assumed
δ_t	0.06	assumed
μ	0.18	assumed

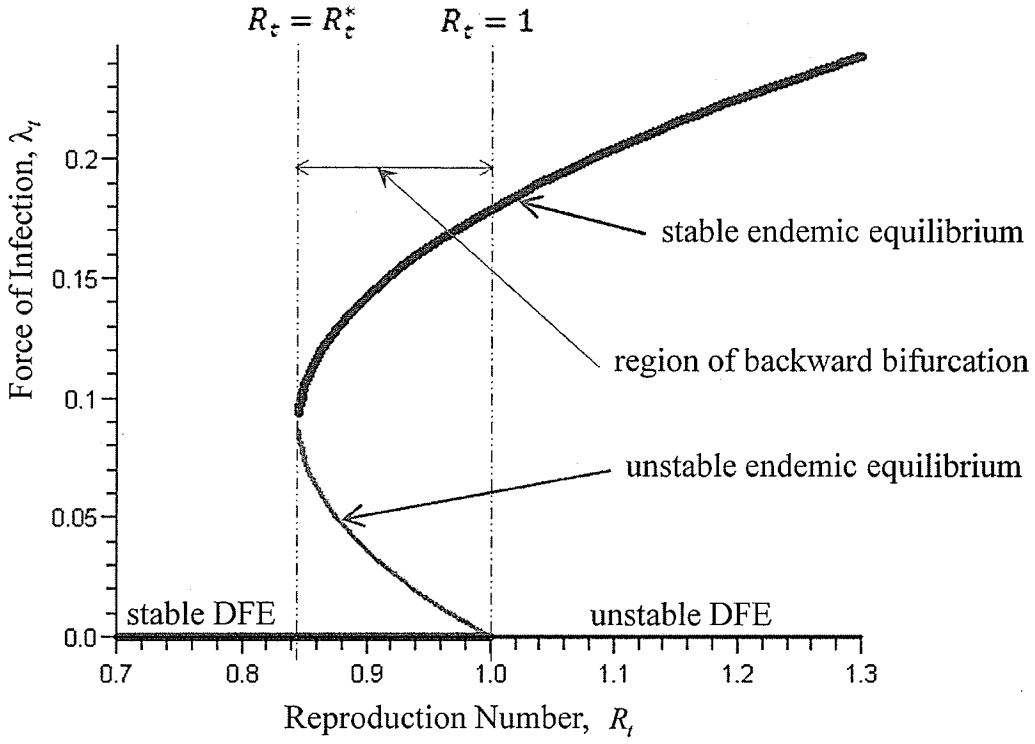

Figure 5.1: Backward bifurcation diagram for the TB-only sub-model (5.1). Parameter values used are: $\Pi = 5000$, $\beta_t = 0.8$, $r = 0.25$, $\sigma_t = 1/72$, $\delta_t = 0.011995$ and $\mu = 0.101$ (giving $\mathcal{R}_t^* = 0.8449 < 1$, $\mathcal{R}_t = 0.8559 < 1$, so that $\mathcal{R}_t^* < \mathcal{R}_t < 1$).

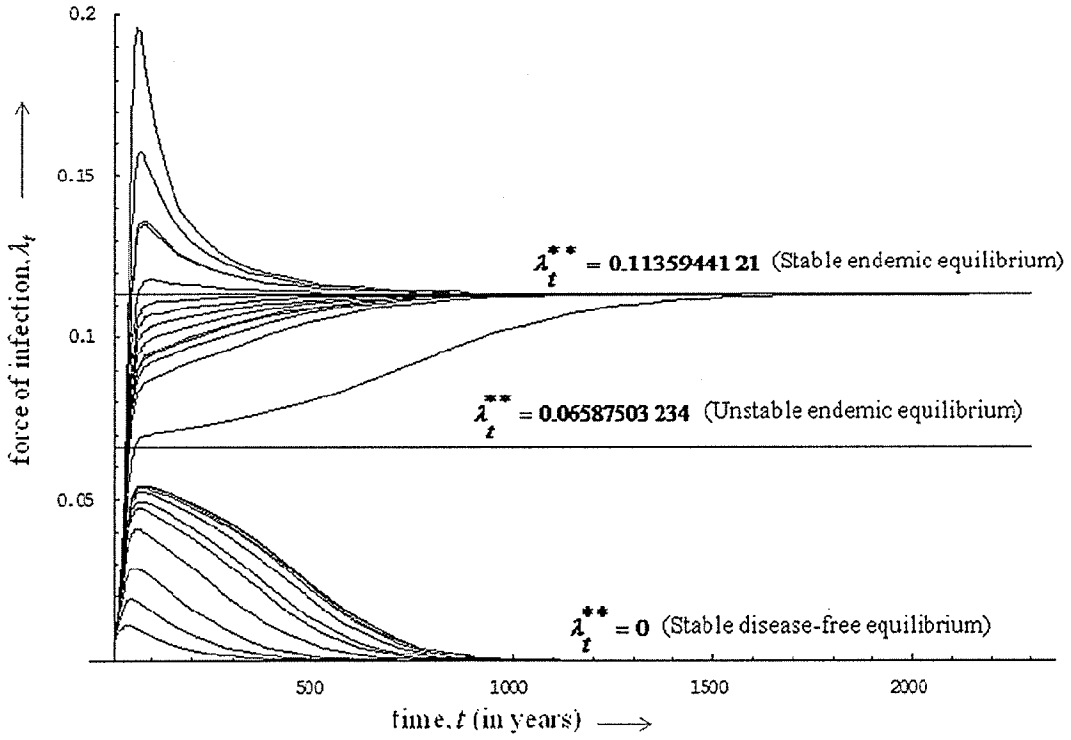

Figure 5.2: Time series showing backward bifurcation in the TB-only sub-model (5.1) using $\Pi = 5000$, $\beta_t = 0.8$, $r = 0.25$, $\sigma_t = 1/72$, $\delta_t = 0.011995$ and $\mu = 0.101$ (giving $\mathcal{R}_t^* = 0.8449 < 1$, $\mathcal{R}_t = 0.8559 < 1$ and $\mathcal{R}_t^* < \mathcal{R}_t < 1$).

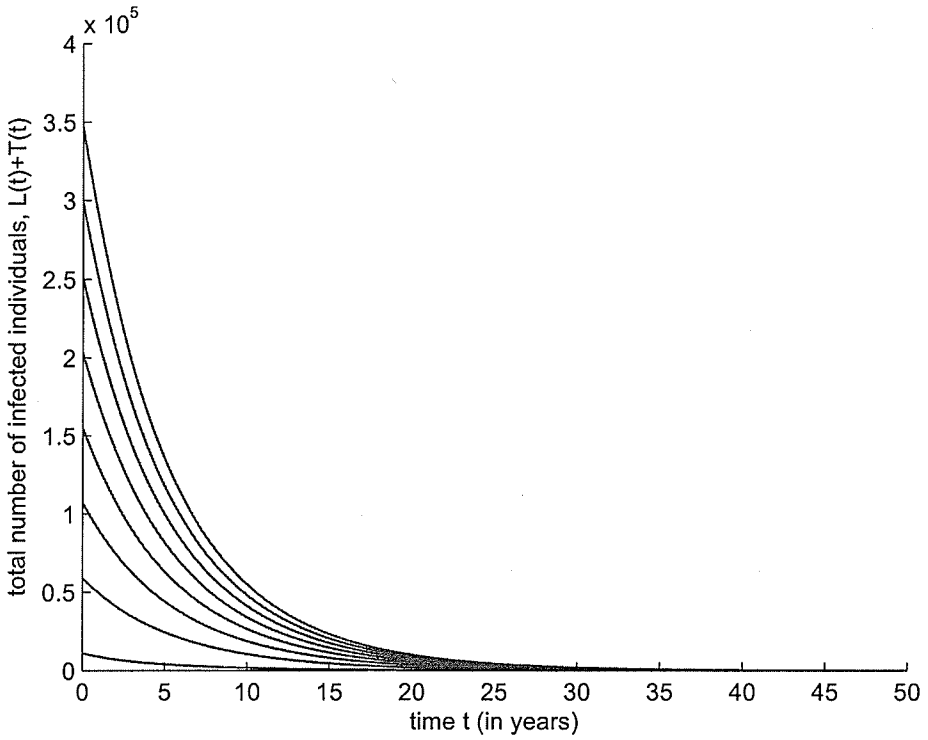

Figure 5.3: Time series of the TB-only sub-model (5.1) showing convergence to the DFE, $\mathcal{E}_{0t}$. Parameters used are $\Pi = 50000$, $\beta_t = 0.08$, $r = 0.23$, $\sigma_t = 0.333$, $\delta_t = 0.06$ and $\mu = 0.18$ (so that $\mathcal{R}_t = 0.2164 < 1$).

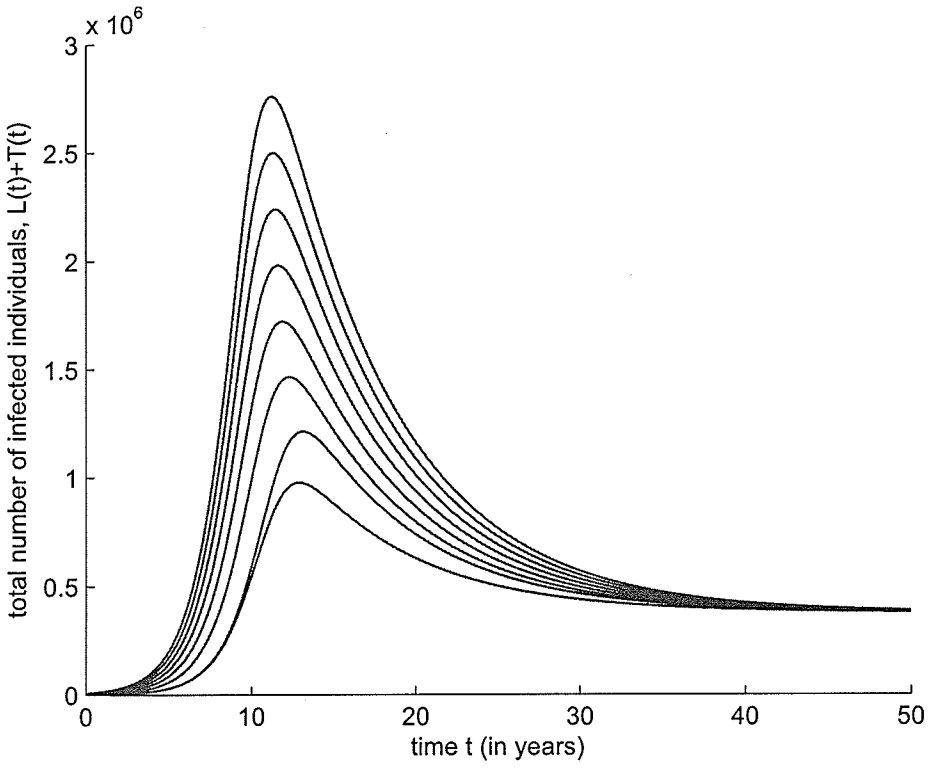

Figure 5.4: Time series of the TB-only sub-model (5.1) showing convergence to the endemic equilibrium, $\mathcal{E}_{1t}$. Parameters used are $\Pi = 50000$, $\beta_t = 1.85$, $r = 0.43$, $\sigma_t = 0.533$, $\delta_t = 0.1$ and $\mu = 0.04$ (giving $\mathcal{R}_t = 12.2918 > 1$).

Chapter 6

Analysis of the Full HIV-TB Model

Having analyzed the two sub-models in Chapters 4 and 5, the dynamics of the full HIV-TB model (3.1) is now considered. It should be recalled that the model (3.1) consists of the following system of differential equations.

$$\begin{aligned}
\frac{dS}{dt} &= \Pi - \lambda_h S - \lambda_t S - \mu S, \\
\frac{dI}{dt} &= \lambda_h S - \theta_h \lambda_t I - \sigma_h I - \mu I, \\
\frac{dA}{dt} &= \sigma_h I - \theta_h \eta_h \lambda_t A - \delta_a A - \mu A, \\
\frac{dL}{dt} &= \lambda_t S - \lambda_h L - r\lambda_t L - \sigma_t L - \mu L, \\
\frac{dT}{dt} &= r\lambda_t L + \sigma_t L - \lambda_h T - \delta_t T - \mu T, \\
\frac{dM}{dt} &= \theta_h \lambda_t I + \theta_h \eta_h \lambda_t A + \lambda_h L + \lambda_h T - \delta_m M - \mu M,
\end{aligned} \tag{6.1}$$

where,

$$\lambda_h = \frac{\beta_h(I + \eta_h A)}{N}, \quad \lambda_t = \frac{\beta_t T}{N} \quad \text{and} \quad N = S + I + A + L + T + M.$$

Recall that for this model, all solutions to (6.1) are defined in the positively invariant biologically-feasible region, $\mathcal{D}$, given in (3.2) by

$$\mathcal{D} = \{\mathcal{E} \in \mathbb{R}^6_+; \ S(t) + I(t) + A(t) + L(t) + T(t) + M(t) \leq \Pi/\mu\}, \tag{6.2}$$

where, $\mathcal{E} = (S(t), I(t), A(t), L(t), T(t), M(t))$.

6.1 Equilibria of the Full HIV-TB Model

Let $\mathcal{E} = (S^*, I^*, A^*, L^*, T^*, M^*)$ represents any arbitrary equilibrium of the full HIV-TB model (6.1). It follows then that, by solving in (6.1) at steady state, the components of $\mathcal{E}$ are:

$$\begin{aligned}
S^* &= \frac{\Pi}{\lambda_h^* + \lambda_t^* + \mu}, \\
I^* &= \frac{\lambda_h^* S^*}{\theta_h \lambda_t^* + \rho_h}, \\
A^* &= \frac{\sigma_h \lambda_h^* S^*}{(\theta_h \lambda_t^* + \rho_h)(\theta_h \eta_h \lambda_t^* + \xi_a)}, \\
L^* &= \frac{\lambda_t^* S^*}{\lambda_h^* + r\lambda_t^* + \rho_t}, \\
T^* &= \frac{\lambda_t^* (r\lambda_h^* + \sigma_t) S^*}{(\lambda_h^* + \xi_t)(\lambda_h^* + r\lambda_t^* + \rho_t)}, \\
M^* &= \frac{\theta_h \lambda_t^* (I^* + \eta_h A^*) + \lambda_h^* (L^* + T^*)}{\xi_m}.
\end{aligned} \tag{6.3}$$

Clearly, (6.3) gives rise to, at least, four types of equilibria namely:

(i) a disease-free equilibrium (corresponding to the case: $\lambda_h^* = \lambda_t^* = 0$),

(ii) an HIV-only boundary equilibrium (corresponding to the case: $\lambda_h^* \neq 0$, $\lambda_t^* = 0$),

(iii) a TB-only boundary equilibrium (corresponding to the case: $\lambda_h^* = 0$, $\lambda_t^* \neq 0$),

(iv) and an endemic equilibrium (corresponding to the case: λ_h^*, $\lambda_t^* \neq 0$).

In this chapter, the focus will be on the analysis of the dynamics of the DFE (that is, (6.3) with $\lambda_h^* = \lambda_t^* = 0$). In particular, to determine whether or not the model (6.1) undergoes the phenomenon of backward bifurcation at the DFE. The DFE of model (6.1) is given by

$$\mathcal{E}_0 = (S^*, I^*, A^*, L^*, T^*, M^*) = (\Pi/\mu, 0, 0, 0, 0, 0). \tag{6.4}$$

6.2 Stability Analysis of the DFE.

The associated next generation matrices (F and V) are:

$$F = \begin{pmatrix} \frac{\beta_h S^*}{N^*} & \frac{\beta_h \eta_h S^*}{N^*} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{\beta_t S^*}{N^*} & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}, V = \begin{pmatrix} \sigma_h + \mu & 0 & 0 & 0 & 0 \\ -\sigma_h & \delta_a + \mu & 0 & 0 & 0 \\ 0 & 0 & \sigma_t + \mu & 0 & 0 \\ 0 & 0 & -\sigma_t & \delta_t + \mu & 0 \\ 0 & 0 & 0 & 0 & \delta_m + \mu \end{pmatrix},$$

The matrix FV^{-1} has two non-zero eigenvalues $\mathcal{R}_h$ and $\mathcal{R}_t$ (where $\mathcal{R}_h$ and $\mathcal{R}_t$ are as defined in (4.6) and (5.4) respectively). Thus,

$$\rho(FV^{-1}) = \max\{\mathcal{R}_h, \mathcal{R}_t\}.$$

Now, let

$$\mathcal{R}_{HT} = \rho(FV^{-1}) = \max\{\mathcal{R}_h, \mathcal{R}_t\}.$$

Thus, we have established the following result.

Theorem 6.1 *The DFE of the full HIV/TB model (6.1) is LAS iff $\mathcal{R}_{HT} < 1$, and unstable if $\mathcal{R}_{HT} > 1$.*

The quantity $\mathcal{R}_{HT}$ is the basic reproduction number of the full model (6.1). Simulations were carried out for $\mathcal{R}_{HT} < 1$ (Figure 5.3) showing convergence to the DFE.

Theorem 6.1 shows that HIV can be eliminated from the community if $\mathcal{R}_{HT} < 1$, provided the initial number of infectives is small enough (that is, if the initial number of infectives is in the basin of attraction of the DFE).

Since the TB-only sub-model (5.1) in Chapter 5 exhibits backward bifurcation, it is instructive to determine whether or not the full HIV-TB model (6.1) undergoes backward bifurcation as well. This is investigated below.

6.3 Existence of Backward Bifurcation

Owing to the relative large size of the system (6.1), it is laborious to explore the possibility of backward bifurcation in (6.1) using the method in Section 5.2. Consequently, we will adopt a method that is based on the use of the Center Manifold Theory [10, 52, 58]. The method entails reducing model (6.1) into a transformed system whose Jacobian has a zero-eigenvalue, and then applying a theorem, by Castillo-Chavez and

Song [10] (see also [52, 58]), to explore the possibility of backward bifurcation. First, the theorem in [10] is reproduced below for convenience.

Theorem 6.2 [10]. *Consider the following general system of ordinary differential equations with a parameter ϕ*

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

where 0 is an equilibrium point of the system (that is, $f(0, \phi) \equiv 0$ for all ϕ) and

1. $A = D_x f(0,0) = \left(\frac{\partial f_i}{\partial x_j}(0,0)\right)$ *is the linearization matrix of the system around the equilibrium 0 with ϕ evaluated at 0;*
2. *Zero is a simple eigenvalue of A and other eigenvalues of A have negative real parts;*
3. *Matrix A has a right eigenvectors w, and a left eigenvector v corresponding to the zero eigenvalue.*

Let f_k be the k^{th} component of f and

$$a = \sum_{i,j,k=1}^{n} \left(v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}\bigg|_{(0,0)} \right)$$

$$b = \sum_{i,k=1}^{n} \left(v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}\bigg|_{(0,0)} \right)$$

then, the local dynamics of the system around the equilibrium point 0 is totally determined by the signs of a, and b. Particularly, if $a > 0$, and $b > 0$, then backward bifurcation occurs at $\phi = 0$.

We now proceed to analyze the possible existence of backward bifurcation in the model (6.1). In order to apply Theorem 6.2, we first define the following change of variables: $S = x_1, I = x_2, A = x_3, L = x_4, T = x_5$, and $M = x_6$, so that (6.1) is transformed into the following system of equations.

$$
\begin{aligned}
\frac{dx_1}{dt} &= \Pi - \left[\frac{\beta_h(x_2+\eta_h x_3)}{N} + \frac{\beta_t x_5}{N} + \mu\right] x_1 &&= f_1,\\
\frac{dx_2}{dt} &= \frac{\beta_h(x_2+\eta_h x_3)x_1}{N} - \left(\frac{\theta_h\beta_t x_5}{N} + \sigma_h + \mu\right) x_2 &&= f_2,\\
\frac{dx_3}{dt} &= \sigma_h x_2 - \left(\frac{\theta_h\eta_h\beta_t x_5}{N} + \delta_a + \mu\right) x_3 &&= f_3,\\
\frac{dx_4}{dt} &= \frac{\beta_t x_5 x_1}{N} - \left[\frac{\beta_h(x_2+\eta_h x_3)}{N} + \frac{r\beta_t x_5}{N} + \sigma_t + \mu\right] x_4 &&= f_4,\\
\frac{dx_5}{dt} &= \left(\frac{r\beta_t x_5}{N} + \sigma_t\right) x_4 - \left[\frac{\beta_h(x_2+\eta_h x_3)}{N} + \delta_t + \mu\right] x_5 &&= f_5,\\
\frac{dx_6}{dt} &= \frac{(x_2+\eta_h x_3)[\theta_h\beta_t x_5 + \beta_h(x_4+x_5)]}{N} - (\delta_m+\mu)x_6 &&= f_6
\end{aligned}
\tag{6.5}
$$

where, $N = x_1 + x_2 + x_3 + x_4 + x_5 + x_6$, and the DFE is $\mathcal{X}_0 = (\Pi/\mu, 0, 0, 0, 0, 0)$. The corresponding Jacobian, $J(\mathcal{X}_0)$, is given by

$$
J(\mathcal{X}_0) = \begin{pmatrix}
-\mu & -\beta_h & -\beta_h\eta_h & 0 & -\beta_t & 0\\
0 & \beta_h - \sigma_h - \mu & \beta_h\eta_h & 0 & 0 & 0\\
0 & \sigma_h & -\delta_a - \mu & 0 & 0 & 0\\
0 & 0 & 0 & -\sigma_t - \mu & \beta_t & 0\\
0 & 0 & 0 & \sigma_t & -\delta_t - \mu & 0\\
0 & 0 & 0 & 0 & 0 & -\delta_m - \mu
\end{pmatrix}, \tag{6.6}
$$

from which it can be shown that $\mathcal{X}_0$ is stable if $\mathcal{R}_{HT} = \max\{\mathcal{R}_h, \mathcal{R}_t\} < 1$. We need to consider situations under which $J(\mathcal{X}_0)$ will have a zero eigenvalue (to apply the center manifold theory). It can be shown that $\mathcal{R}_{HT} = 1$ will yield a zero (simple) eigenvalue for $J(\mathcal{X}_0)$. Since $\mathcal{R}_{HT} = \max\{\mathcal{R}_h, \mathcal{R}_t\}$, it follows that there are two possibilities under which $\mathcal{R}_{HT} = 1$ will occur; namely when $\mathcal{R}_h = 1$ or $\mathcal{R}_t = 1$. Here, we consider just one of these cases, namely $\mathcal{R}_t = 1$ (note that $\mathcal{R}_t$ is given in (5.4)).

Consider the case $\mathcal{R}_{HT} = 1 = \mathcal{R}_t > \mathcal{R}_h$ (bifurcation point). Define a bifurcation parameter, β^*, obtained by solving for β_t from $\mathcal{R}_t = 1$ as follows. With $\mathcal{R}_t = 1$, (5.4) becomes

$$
1 = \frac{\beta^*\sigma_t}{(\delta_t+\mu)(\sigma_t+\mu)} \quad \Rightarrow \quad \beta^* = \frac{(\delta_t+\mu)(\sigma_t+\mu)}{\sigma_t}. \tag{6.7}
$$

Here, and in the rest of the thesis, we shall denote the Jacobian, $J(\mathcal{X}_0)$, at the bifurcation point β^*, by J_{β^*}. Thus,

$$J_{\beta^*} = \begin{pmatrix} -\mu & -\beta_h & -\beta_h\eta_h & 0 & -\beta^* & 0 \\ 0 & \beta_h - \sigma_h - \mu & \beta_h\eta_h & 0 & 0 & 0 \\ 0 & \sigma_h & -\delta_a - \mu & 0 & 0 & 0 \\ 0 & 0 & 0 & -\sigma_t - \mu & \beta^* & 0 \\ 0 & 0 & 0 & \sigma_t & -\delta_t - \mu & 0 \\ 0 & 0 & 0 & 0 & 0 & -\delta_m - \mu \end{pmatrix} \tag{6.8}$$

The next step is to compute, as shown below, the eigenvectors of J_{β^*} associated with the simple eigenvalue, 0.

Eigenvectors of J_{β^*}

Let the left and right eigenvectors of J_{β^*}, associated with the eigenvalue 0, be denoted by $v = (v_1, v_2, v_3, v_4, v_5, v_6)$ and $w = (w_1, w_2, w_3, w_4, w_5, w_6)^T$, respectively. Then, since $\mathcal{R}_t = 1$, we can show that simple is an eigenvalue of J_{β^*}, and thus we can, respectively, write

$$\begin{aligned} vJ_{\beta^*} &= \mathcal{O}^T, \\ J_{\beta^*}w &= \mathcal{O}, \end{aligned} \tag{6.9}$$

where, $\mathcal{O}$ is a 6×1 zero-column vector. The associated non-zero left and right eigenvectors of the Jacobian, J_{β^*}, (corresponding to the zero eigenvalue) in (6.8) can be expressed as

$$\begin{aligned} v &= \left[0, \frac{(\delta_a + \mu)v_3}{\beta_h\eta_h}, v_3, \frac{\sigma_t v_5}{\sigma_t + \mu}, v_5, 0\right], \\ w &= \left\{\frac{-1}{\mu}\left[\frac{\beta_h(\delta_a + \mu + \sigma_h\eta_h)w_3}{\sigma_h} + \beta^* w_5\right], \frac{(\delta_a + \mu)w_3}{\sigma_h}, w_3, \frac{\beta^* w_5}{\sigma_t + \mu}, w_5, 0\right\}^T. \end{aligned} \tag{6.10}$$

Next, we compute the quantities a and b for the system (6.5) from the expressions

$$\begin{aligned} a &= \sum_{i,j,k=1}^{6} \left(v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}\bigg|_{\mathcal{X}_0} \right), \\ b &= \sum_{i,k=1}^{6} \left(v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \beta^*}\bigg|_{\mathcal{X}_0} \right). \end{aligned} \tag{6.11}$$

Computation of a

By taking the summation in (6.11), it follows that

$$\begin{aligned} a &= \frac{(\delta_a+\mu)v_3}{\beta_h\eta_h}\sum_{i,j=2}^{5}\left(w_iw_j\frac{\partial^2 f_2}{\partial x_i\partial x_j}\bigg|_{\mathcal{X}_0}\right)+v_3\sum_{i,j=2}^{5}\left(w_iw_j\frac{\partial^2 f_3}{\partial x_i\partial x_j}\bigg|_{\mathcal{X}_0}\right) \\ &+\frac{\sigma_t v_5}{\sigma_t+\mu}\sum_{i,j=2}^{5}\left(w_iw_j\frac{\partial^2 f_4}{\partial x_i\partial x_j}\bigg|_{\mathcal{X}_0}\right)+v_5\sum_{i,j=2}^{5}\left(w_iw_j\frac{\partial^2 f_5}{\partial x_i\partial x_j}\bigg|_{\mathcal{X}_0}\right). \end{aligned} \tag{6.12}$$

Next, we use (6.10) and the right hand sides of (6.5) to evaluate each of the summations in (6.12), yielding

$$\begin{aligned} \sum_{i,j=2}^{5}\left(w_iw_j\frac{\partial^2 f_2}{\partial x_i\partial x_j}\bigg|_{\mathcal{X}_0}\right) &= -P_2^{(t)}, \\ \sum_{i,j=2}^{5}\left(w_iw_j\frac{\partial^2 f_3}{\partial x_i\partial x_j}\bigg|_{\mathcal{X}_0}\right) &= -\frac{2w_3w_5\theta_h\eta_h\beta^*\mu}{\Pi}, \\ \sum_{i,j=2}^{5}\left(w_iw_j\frac{\partial^2 f_4}{\partial x_i\partial x_j}\bigg|_{\mathcal{X}_0}\right) &= \frac{2\mu\beta^{*2}rw_5^2}{\Pi(\sigma_t+\mu)}-P_4^{(t)}, \\ \sum_{i,j=2}^{5}\left(w_iw_j\frac{\partial^2 f_5}{\partial x_i\partial x_j}\bigg|_{\mathcal{X}_0}\right) &= \frac{2r\mu\beta^{*2}w_5^2}{\Pi(\sigma_t+\mu)}-P_5^{(t)}, \end{aligned} \tag{6.13}$$

where,

$$\begin{aligned} P_2^{(t)} &= \frac{2\beta_h\mu(\delta_a+\mu)^2w_3^2}{\Pi\sigma_h^2}+\frac{2\beta_h\mu(1+\eta_h)(\delta_a+\mu)w_3^2}{\Pi\sigma_h}+\frac{2\mu\beta_h\beta^*(\delta_a+\mu)w_3w_5}{\Pi\sigma_h(\sigma_t+\mu)} \\ &+\frac{2\mu(\delta_a+\mu)(\beta_h+\beta^*)w_3w_5}{\Pi\sigma_h}+\frac{2\mu\beta_h\eta_hw_3^2}{\Pi}+\frac{2\mu\beta_h\eta_h\beta^*w_3w_5}{\Pi(\sigma_t+\mu)}+\frac{2\mu\beta_h\eta_hw_3w_5}{\Pi}, \end{aligned} \tag{6.14}$$

$$P_4^{(t)} = \frac{2\beta_h\mu\beta^*(\delta_a+\mu)w_3w_5}{\Pi\sigma_h(\sigma_t+\mu)} + \frac{2\beta^*\mu(\delta_a+\mu)w_3w_5}{\Pi\sigma_h} + \frac{2\beta_h\eta_h\mu\beta^*w_3w_5}{\Pi(\sigma_t+\mu)} + \frac{2\mu\beta^*w_3w_5}{\Pi} + \frac{2\mu\beta^{*2}w_5^2}{\Pi(\sigma_t+\mu)}, \tag{6.15}$$

and,

$$P_5^{(t)} = \frac{2\beta_h\mu(\delta_a+\mu)w_3w_5}{\Pi\sigma_h} + \frac{2\mu\beta_h\eta_hw_3w_5}{\Pi}. \tag{6.16}$$

Thus, using (6.13), (6.14), (6.15) and (6.16) in (6.13) in (6.12) gives

$$a = \frac{2r\mu\beta^{*2}v_5w_5^2}{\Pi(\sigma_t+\mu)} - \frac{2r\mu\beta^{*2}\sigma_tv_5w_5^2}{\Pi(\sigma_t+\mu)^2} - \left[\frac{(\delta_a+\mu)v_3P_2^{(t)}}{\beta_h\eta_h} + \frac{2v_3w_3w_5\theta_h\eta_h\beta^*\mu}{\Pi} + \frac{\sigma_tv_5P_4^{(t)}}{\sigma_t+\mu} + v_5P_5^{(t)}\right],$$

which simplifies to,

$$a = \frac{2r\mu^2\beta^{*2}v_5w_5^2}{\Pi(\sigma_t+\mu)^2} - \left[\frac{(\delta_a+\mu)v_3P_2^{(t)}}{\beta_h\eta_h} + \frac{2v_3w_3w_5\theta_h\eta_h\beta^*\mu}{\Pi} + \frac{\sigma_tv_5P_4^{(t)}}{\sigma_t+\mu} + v_5P_5^{(t)}\right]. \tag{6.17}$$

Now, let

$$C_t = \frac{2\mu^2\beta^{*2}v_5w_5^2}{\Pi(\sigma_t+\mu)^2}, \tag{6.18}$$

and,

$$G_t = \left[\frac{(\delta_a+\mu)v_3P_2^{(t)}}{\beta_h\eta_h} + \frac{2v_3w_3w_5\theta_h\eta_h\beta^*\mu}{\Pi} + \frac{\sigma_tv_5P_4^{(t)}}{\sigma_t+\mu} + v_5P_5^{(t)}\right].$$

Hence, the expression for a in (6.17) becomes

$$a = rC_t - G_t. \tag{6.19}$$

Computation of b

Using (6.10) to eliminate the zero- contributions of the summation of the second equa-

tion in (6.11), we have

$$
\begin{aligned}
b &= \frac{(\delta_a+\mu)v_3}{\beta_h\eta_h}\sum_{i=2}^{5}\left(w_i\frac{\partial^2 f_2}{\partial x_i\partial\beta^*}\Big|_{\mathcal{X}_0}\right)+v_3\sum_{i=2}^{5}\left(w_i\frac{\partial^2 f_3}{\partial x_i\partial\beta^*}\Big|_{\mathcal{X}_0}\right)\\
&+\frac{\sigma_t v_5}{\sigma_t+\mu}\sum_{i=2}^{5}\left(w_i\frac{\partial^2 f_4}{\partial x_i\partial\beta^*}\Big|_{\mathcal{X}_0}\right)+v_5\sum_{i=2}^{5}\left(w_i\frac{\partial^2 f_5}{\partial x_i\partial\beta^*}\Big|_{\mathcal{X}_0}\right).
\end{aligned}
\tag{6.20}
$$

Because the parameter β^* in (6.20) is given by $\beta^* = \beta_t$, we have that each of the summations in (6.20) with $\beta^* = \beta_t$, yields

$$
\begin{aligned}
\sum_{i=2}^{5}\left(w_i\frac{\partial^2 f_2}{\partial x_i\partial\beta^*}\Big|_{\mathcal{X}_0}\right) &= 0, \quad \sum_{i=2}^{5}\left(w_i\frac{\partial^2 f_3}{\partial x_i\partial\beta^*}\Big|_{\mathcal{X}_0}\right) = 0,\\
\sum_{i=2}^{5}\left(w_i\frac{\partial^2 f_4}{\partial x_i\partial\beta^*}\Big|_{\mathcal{X}_0}\right) &= w_5, \quad \sum_{i=2}^{5}\left(w_i\frac{\partial^2 f_5}{\partial x_i\partial\beta^*}\Big|_{\mathcal{X}_0}\right) = 0, ,
\end{aligned}
$$

and, hence, (6.20) reduces to

$$
b = \frac{\sigma_t v_5 w_5}{\sigma_t+\mu} > 0. \tag{6.21}
$$

Since b above is automatically positive, it follows from (6.19) that $a > 0$ if $rC_t > G_t$. Thus, by Theorem 6.2 above [10], the model (6.1) will undergo backward bifurcation if $r > \dfrac{G_t}{C_t}$ (i.e., if both $a > 0$ and $b > 0$). This result is summarized below.

Theorem 6.3 *The full HIV-TB model (6.1) undergoes a backward bifurcation when* $\mathcal{R}_h < \mathcal{R}_t = 1 = \mathcal{R}_{HT}$ *and* $r > \dfrac{G_t}{C_t}$.

This phenomenon is illustrated in the S, L and T components of the HIV-TB model (6.1) in Figures 6.1, 6.2, and 6.3, respectively, using the following parameters: $\Pi = 1$, $\beta_h = 0.5$, $\sigma_h = 0.8$, $\sigma_t = 0.2$, $r = 60$, $\eta_h = 0.4$, $\delta_a = 0.5$, $\delta_t = 0.1$, $\delta_m = 0.1$, $\theta_h = 0.03$, $\theta_t = 0.2$, $\mu = 0.14$, and $v_3 = v_5 = w_3 = w_5 = 1$ (so that, $\mathcal{R}_h = 0.7979 < \mathcal{R}_t = 1$, and $r = 60 > 21.345 = C_t/G_t$).

Now, since the terms C_t and G_t in (6.18) are positive, we observe that the condition $a > 0$ in (6.19) cannot hold if $r = 0$. Thus, the phenomenon of backward bifurcation in model (6.1) can be removed if $r = 0$. In fact, the DFE of (6.1) can be shown to be globally asymptotically stable when $r = 0$ as shown below.

6.4 GAS of the DFE for System (6.1) with $r = 0$.

We claim the following result.

Theorem 6.4 *The DFE of the HIV-TB model (6.1) with $r = 0$ is GAS in $\mathcal{D}$ iff $\mathcal{R}_{HT} \leq 1$.*

Proof
Let $K_1 = \sigma_h + \mu$, $K_2 = \delta_a + \mu$, $K_3 = \sigma_t + \mu$, $K_4 = \delta_t + \mu$, and $K_5 = \delta_m + \mu$. It then follows from (4.6) and (5.4) that

$$\begin{aligned} \beta_h(K_2 + \eta_h\sigma_h) - K_1K_2 &= K_1K_2(\mathcal{R}_h - 1), \\ \beta_t\sigma_t - K_3K_4 &= K_3K_4(\mathcal{R}_t - 1). \end{aligned} \tag{6.22}$$

Let $r = 0$ in (6.1). Consider the Lyapunov function:

$$\mathcal{P} = \left(\frac{K_2 + \eta_h\sigma_h}{K_1\eta_h}\right) I + A + \frac{\sigma_t}{K_3}L + T, \tag{6.23}$$

with Lyapunov derivative

$$\begin{aligned} \dot{\mathcal{P}} &= \left(\frac{K_2 + \eta_h\sigma_h}{K_1\eta_h}\right)\dot{I} + \dot{A} + \frac{\sigma_t}{K_3}\dot{L} + \dot{T} \\ &= \left(\frac{K_2 + \eta_h\sigma_h}{K_1\eta_h}\right)\left[\frac{\beta_h(I + \eta_h\sigma_h A)S}{N} - \theta_h\lambda_t I - K_1 I\right] + (\sigma_h I - \theta_h\eta_h\lambda_t A - K_2 A) \\ &\quad + \frac{\sigma_t}{K_3}\left(\frac{\beta_t TS}{N} - \lambda_h L - K_3 L\right) + (\sigma_t L - \lambda_h T - K_4 T) \\ &= \left[\frac{\beta_h(K_2 + \eta_h\sigma_h)S}{K_1\eta_h N} + \sigma_h - \frac{K_1(K_2 + \eta_h\sigma_h)}{K_1\eta_h}\right] I - \frac{\theta_h(K_2 + \eta_h\sigma_h)\lambda_t I}{K_1\eta_h} \\ &\quad + \left[\frac{\beta_h\eta_h\sigma_h(K_2 + \eta_h\sigma_h)S}{K_1\eta_h N} - K_2\right] A - \theta_h\eta_h\lambda_t A - \frac{\sigma_t\lambda_h L}{K_3} \\ &\quad + \left(\frac{\beta_t\sigma_t S}{K_3 N} - K_4\right) T - \lambda_h T \end{aligned}$$

$$= \left\{\left[\frac{\beta_h(K_2+\eta_h\sigma_h)}{K_1\eta_h}\right]\frac{S}{N} - \frac{K_1K_2}{K_1\eta_h}\right\} I - \frac{\theta_h(K_2+\eta_h\sigma_h)\lambda_t I}{K_1\eta_h}$$

$$+ \left\{\left[\frac{\beta_h\sigma_h(K_2+\eta_h\sigma_h)}{K_1}\right]\frac{S}{N} - \frac{K_1K_2}{K_1}\right\} A - \theta_h\eta_h\lambda_t A - \frac{\sigma_t\lambda_h L}{K_3}$$

$$+ \left[\left(\frac{\beta_t\sigma_t}{K_3}\right)\frac{S}{N} - \frac{K_3K_4}{K_3}\right] T - \lambda_h T.$$

Using the fact that $S(t) \leq N(t)$ for all $t > 0$, we have

$$\begin{aligned}
\dot{\mathcal{P}} &\leq \left[\frac{\beta_h(K_2+\eta_h\sigma_h)}{K_1\eta_h} - \frac{K_1K_2}{K_1\eta_h}\right] I - \frac{\theta_h(K_2+\eta_h\sigma_h)\lambda_t I}{K_1\eta_h} \\
&\quad + \left[\frac{\beta_h\sigma_h(K_2+\eta_h\sigma_h)}{K_1} - \frac{K_1K_2}{K_1}\right] A - \theta_h\eta_h\lambda_t A - \frac{\sigma_t\lambda_h L}{K_3} \\
&\quad + \left(\frac{\beta_t\sigma_t}{K_3} - \frac{K_3K_4}{K_3}\right) T - \lambda_h T \\
&= \frac{K_2}{\eta_h}(\mathcal{R}_h - 1)(I + \eta_h A) + K_4(\mathcal{R}_t - 1)T \\
&\quad - \left\{\theta_h\lambda_t\left[\frac{(K_2+\eta_h\sigma_h)I}{K_1\eta_h} + \eta_h A\right] + \lambda_h\left(\frac{\sigma_t L}{K_3} + T\right)\right\} \\
&\leq 0 \quad \text{if } \mathcal{R}_{HT} \leq 1.
\end{aligned}$$

The proof is completed using the same argument as in the proof of Theorem 4.2. □

Since the model (6.1) with $r = 0$ has a globally stable DFE, it is clear that the system (6.1) cannot undergo backward bifurcation when $r = 0$. This result is summarized below.

Lemma 6.1 *The HIV-TB model (6.1) with $r = 0$ does not undergo backward bifurcation.*

Thus, like the TB-only model (5.1), the full HIV/TB model (6.1) loses its backward bifurcation phenomenon whenever $r = 0$.

6.5 Summary

In summary, it is shown that the full HIV-TB model (6.1)
(i) has a locally stable DFE when $\mathcal{R}_{HT} < 1$; the DFE is GAS if $r = 0$ and $\mathcal{R}_{HT} < 1$.
(ii) undergoes the phenomenon of backward bifurcation at $\mathcal{R}_{HT} = 1$ and that the backward bifurcation is removed when $r = 0$.

Simulations were carried out as depicted in Figures 6.1 6.2, 6.3, 6.4, and 6.5 (using the parameters specified in each plot). Figures 6.1, 6.2 and 6.3 illustrates the phenomenon of backward bifurcation (for $r \neq 0$), while Figure 6.4 illustrate the occurrence of forward bifurcation for the case $r = 0$. Figure 6.5 depicts the solution profiles of the state variables of the model for the case $\mathcal{R}_{HT} < 1$.

Table 6.1: Variables and parameters for the full HIV/TB model (6.1)

Variable/ Parameter	**Description**
$S(t)$	number of susceptible individuals at time t
$I(t)$	number of chronic (asymptomatic HIV-infected individuals at time t
$A(t)$	number of individuals at the AIDS stage of the HIV infection, at time t
$L(t)$	number of individuals with latent TB at time t
$T(t)$	number of individuals with active TB at time t
$M(t)$	number of individuals with mixed infection at time t
$N(t)$	total population size at time t
Π	recruitment rate into the population
β_h, β_t	effective contact rates for HIV and TB, respectively
σ_h, σ_t	progression rates for HIV and TB, respectively
η_h	modification factor for infection from individuals with AIDS
r	rate of exogenous re-infection for latent TB individuals
δ_a, δ_t	mortality rates for HIV and TB, respectively
μ	natural death rate
θ_h	modification parameter for increase in TB susceptibility for individuals infected with HIV.

Table 6.2: Parameter values for the full HIV/TB model (6.1)

Parameter	**Nominal Value** $(year)^{-1}$
Π	$50,000$
β_h	0.012
β_t	0.016
η_h	1.2
r	0.5
σ_h	0.5
σ_t	0.09
δ_a	0.003
δ_t	0.01
δ_m	0.04
μ	0.18

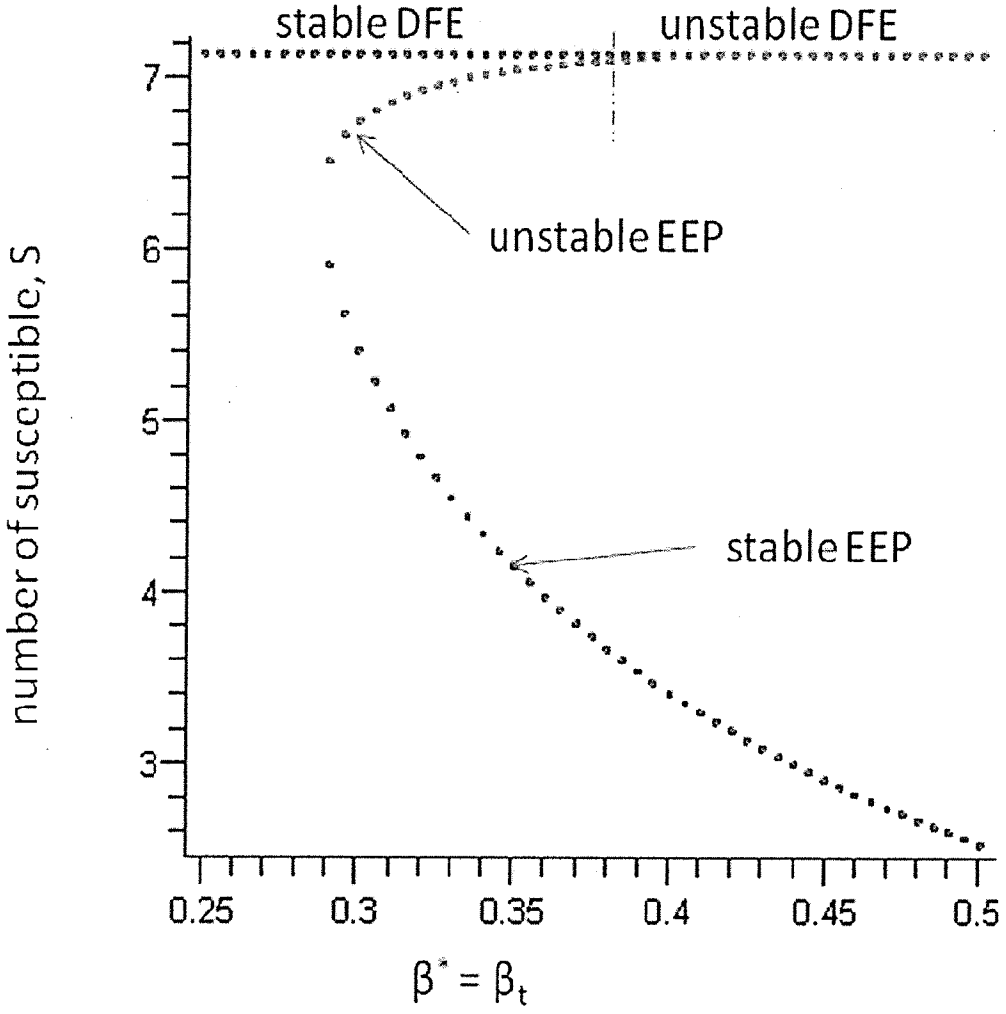

Figure 6.1: Backward bifurcation for the susceptible class, $S(t)$, in the full model (6.1) using $\Pi = 1$, $\beta_h = 0.5$, $\sigma_h = 0.8$, $\sigma_t = 0.2$, $r = 60$, $\eta_h = 0.4$, $\delta_a = 0.5$, $\delta_t = 0.1$, $\delta_m = 0.1$, $\theta_h = 0.03$ and $\mu = 0.14$. Here, $0.7979 = \mathcal{R}_h < \mathcal{R}_t = 1$.

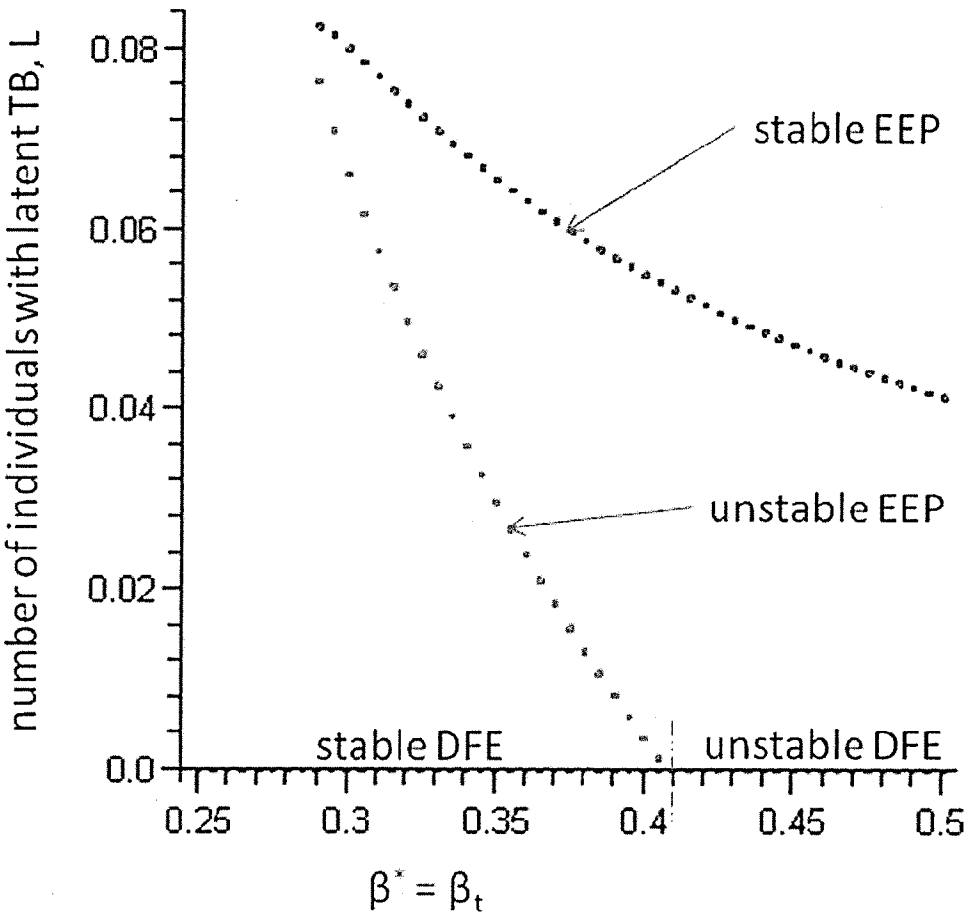

Figure 6.2: Backward bifurcation for the latent TB class, $L(t)$, in the full model (6.1) using $\Pi = 1$, $\beta_h = 0.5$, $\sigma_h = 0.8$, $\sigma_t = 0.2$, $r = 60$, $\eta_h = 0.4$, $\delta_a = 0.5$, $\delta_t = 0.1$, $\delta_m = 0.1$, $\theta_h = 0.03$ and $\mu = 0.14$. Here, $0.7979 = \mathcal{R}_h < \mathcal{R}_t = 1$.

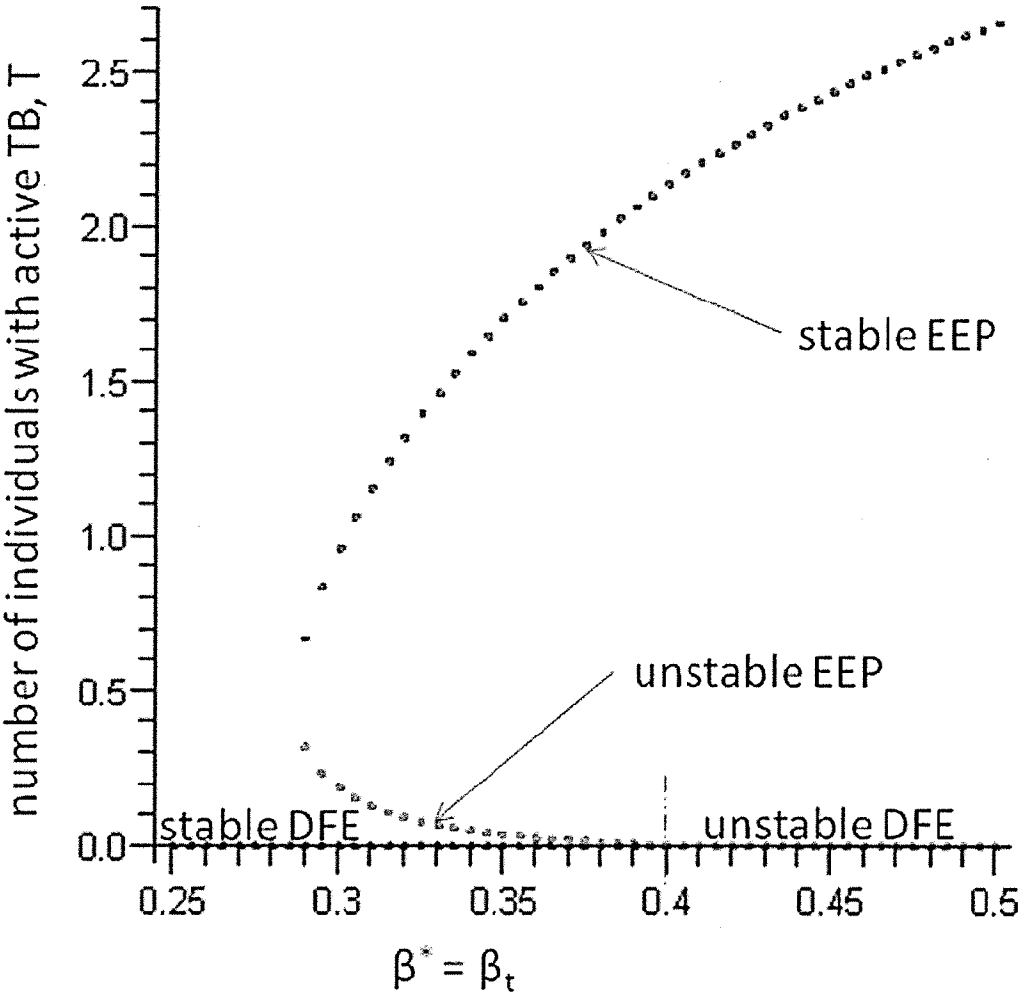

Figure 6.3: Backward bifurcation for the active TB class, $T(t)$, in the full model (6.1) using $\Pi = 1$, $\beta_h = 0.5$, $\sigma_h = 0.8$, $\sigma_t = 0.2$, $r = 60$, $\eta_h = 0.4$, $\delta_a = 0.5$, $\delta_t = 0.1$, $\delta_m = 0.1$, $\theta_h = 0.03$ and $\mu = 0.14$. Here, $0.7979 = \mathcal{R}_h < \mathcal{R}_t = 1$.

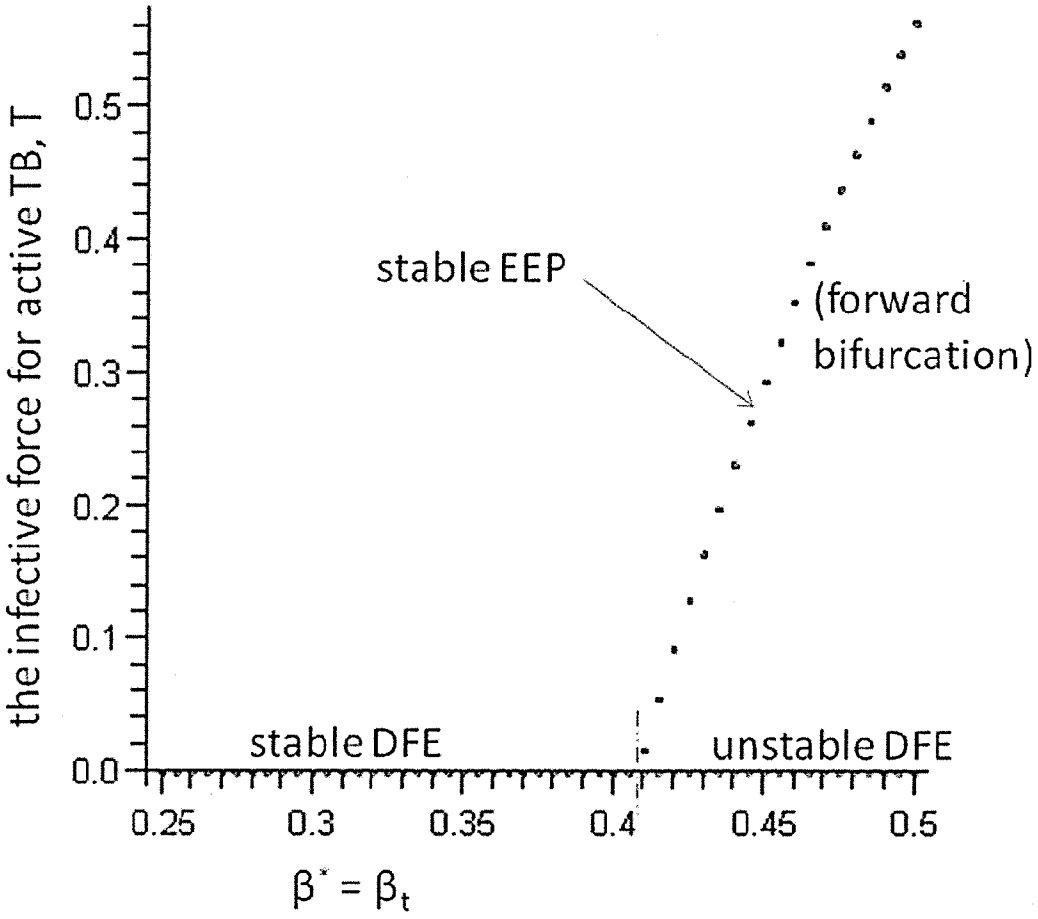

Figure 6.4: Removal of backward bifurcation in the active TB class, $T(t)$, in the full model (6.1) using $\Pi = 1$, $\beta_h = 0.5$, $\sigma_h = 0.8$, $\sigma_t = 0.2$, $r = 0$, $\eta_h = 0.4$, $\delta_a = 0.5$, $\delta_t = 0.1$, $\delta_m = 0.1$, $\theta_h = 0.03$ and $\mu = 0.14$. Here, $0.7979 = \mathcal{R}_h < \mathcal{R}_t = 1$. The figure shows the dynamics of the active TB component when $r = 0$.

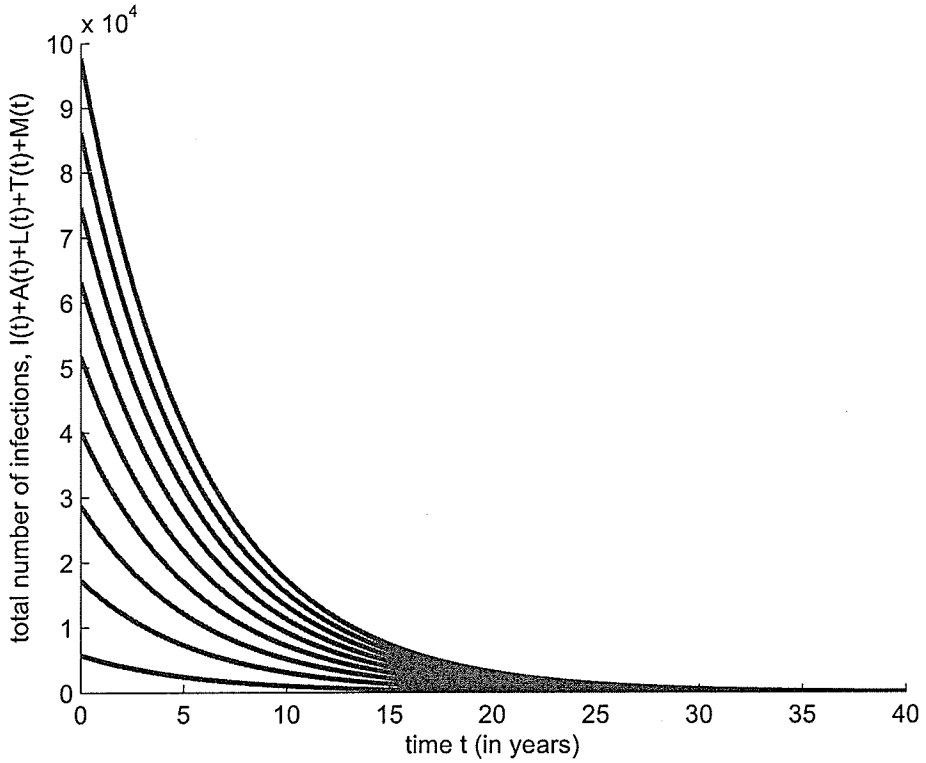

Figure 6.5: Time series of the TB-only sub-model (6.1) showing convergence to the DFE, $\mathcal{E}_0$, using the parameters in Table 5.1 (so that $\mathcal{R}_h = 0.0755 < 1$, $\mathcal{R}_t = 0.0281$ and $\mathcal{R}_{HT} = \max\{\mathcal{R}_h, \mathcal{R}_t\} = 0.0755 < 1$).

Chapter 7

Extended HIV/TB Model

In Chapter 3, we introduced and formulated a basic HIV-TB model (3.1) that we progressively analyzed in Chapters 4, 5, and 6. An important simplification that was applied in the formulation was that individuals that were dually-infected (class $M(t)$) were not transmitting any of the two diseases. This assumption is, however, an over-simplification, since, clearly, individuals dually-infected can pass either of the two diseases to susceptible individuals.

In this Chapter, the non-transmitting simplification is removed. It is now assumed that those in the $M(t)$ class can transmit either HIV or TB to individuals in the $S(t)$ class. Further, although there is no definitive evidence in the support or against it, the extended model also assumes that dually-infected individuals can pass both diseases to a susceptible individual. Individuals in the $M(t)$ class make effective contact with susceptible individuals at a rate $\lambda_m = \dfrac{\beta_m M}{N}$, where β_m is the associated effective contact rate. Of the effective contacts that are made with the susceptible class, q_h, q_t, and $q_m = (1 - q_h - q_t)$, are the fractions that become infected with HIV, TB and the dual HIV/TB infections, respectively.

Another extension applied is that those with latent TB can also transmit TB infection. Consequently, in order to model the relative infectiousness of individuals in the active TB class (T), in relation to those in the latent TB class (L), we introduce a modification parameter, κ, with $0 < \kappa < 1$; so that $\lambda_t = \dfrac{\beta_t(\kappa L + T)}{N}$.

In Chapter 1, various control strategies have been presented for the two diseases, notably the use of the DOTS therapy for TB and ARVs for HIV. In this chapter, the impact of some of these strategies in reducing the burden of the two diseases (as well as that of the mixed infection class) will be investigated. This is the main objective of this chapter, and is achieved by extending model (3.1) to incorporate additional components. This entails introducing new compartments of active TB individuals who are treated with DOTS (W) at a rate τ_t, individuals with the mixed infection treated

of TB (Y) at a rate τ_m and individuals in the W class in whom treatment fails (U). The failure rate of treatment is denoted by α. Individuals in the Y class progress to AIDS at a rate σ_y, and those in whom treatment fails suffer disease-induced death at a rate δ_u.

Finally, the model is further extended to include an imperfect HIV vaccine, by incorporating a class, V, of vaccinated individuals. Susceptible individuals are vaccinated against HIV at a rate ζ. These individuals acquire HIV infection at a reduced rate $(1-\epsilon)\lambda_h$, where $0 < \epsilon < 1$ is the vaccine efficacy. Vaccinated individuals acquire TB infection at a rate λ_t, and mixed infection at a rate $(1-\epsilon)\lambda_m$. The vaccine wanes at a rate ω. In other words, while the vaccine is expected to offer some direct benefits against HIV infection, the vaccine offers no such benefits against TB infection.

Putting all these together, the extended HIV-TB model (which incorporates treatment for both HIV and TB as well as imperfect HIV vaccine) is given by

$$
\begin{aligned}
\frac{dS}{dt} &= \Pi + \omega V - \lambda_h S - \lambda_t S - \lambda_m S - \zeta S - \mu S, \\
\frac{dV}{dt} &= \zeta S - \omega V - (1-\epsilon)\lambda_h V - \lambda_t V - (1-\epsilon)\lambda_m V - \mu V, \\
\frac{dI}{dt} &= \lambda_h S + q_h \lambda_m S + (1-\epsilon)\lambda_h V + q_h(1-\epsilon)\lambda_m V - \theta_h \lambda_t I - \sigma_h I - \mu I, \\
\frac{dA}{dt} &= \sigma_h I + \sigma_y Y - \theta_h \lambda_t A - \mu A - \delta_a A, \\
\frac{dL}{dt} &= \lambda_t S + q_t \lambda_m S + \lambda_t V + q_t(1-\epsilon)\lambda_m V - \lambda_h L - r\lambda_z L - \sigma_t L - \mu L, \\
\frac{dT}{dt} &= r\lambda_z L + \sigma_t L - \lambda_h T - \tau_t T - \mu T - \delta_t T, \\
\frac{dM}{dt} &= q_m \lambda_m S + \theta_h \lambda_t I + \theta_h \lambda_t A + \lambda_h L + \lambda_h T + q_m(1-\epsilon)\lambda_m V - \tau_m M \\
&\quad -\mu M - \delta_m M, \\
\frac{dW}{dt} &= \tau_t T - \alpha W - \mu W, \\
\frac{dY}{dt} &= \tau_m M - \sigma_y Y - \mu Y, \\
\frac{dU}{dt} &= \alpha W - \mu U - \delta_u U.
\end{aligned}
\tag{7.1}
$$

In (7.1), $\lambda_h = \dfrac{\beta_h(I+\eta_h A)}{N}$, $\lambda_t = \dfrac{\beta_t(\kappa_t L + T)}{N}$, $\lambda_m = \dfrac{\beta_m M}{N}$, $\lambda_z = \dfrac{\beta_t T}{N}$, $q_m = 1 - q_h - q_t$, $0 < \omega, \zeta, \epsilon, q_h, q_t, q_m < 1$ and $N = S + V + I + A + L + T + M + W + Y + U$.

The flow diagram of the model is depicted in Figure 7.1 and the associated variables and parameters of the model are described in Table 7.1.

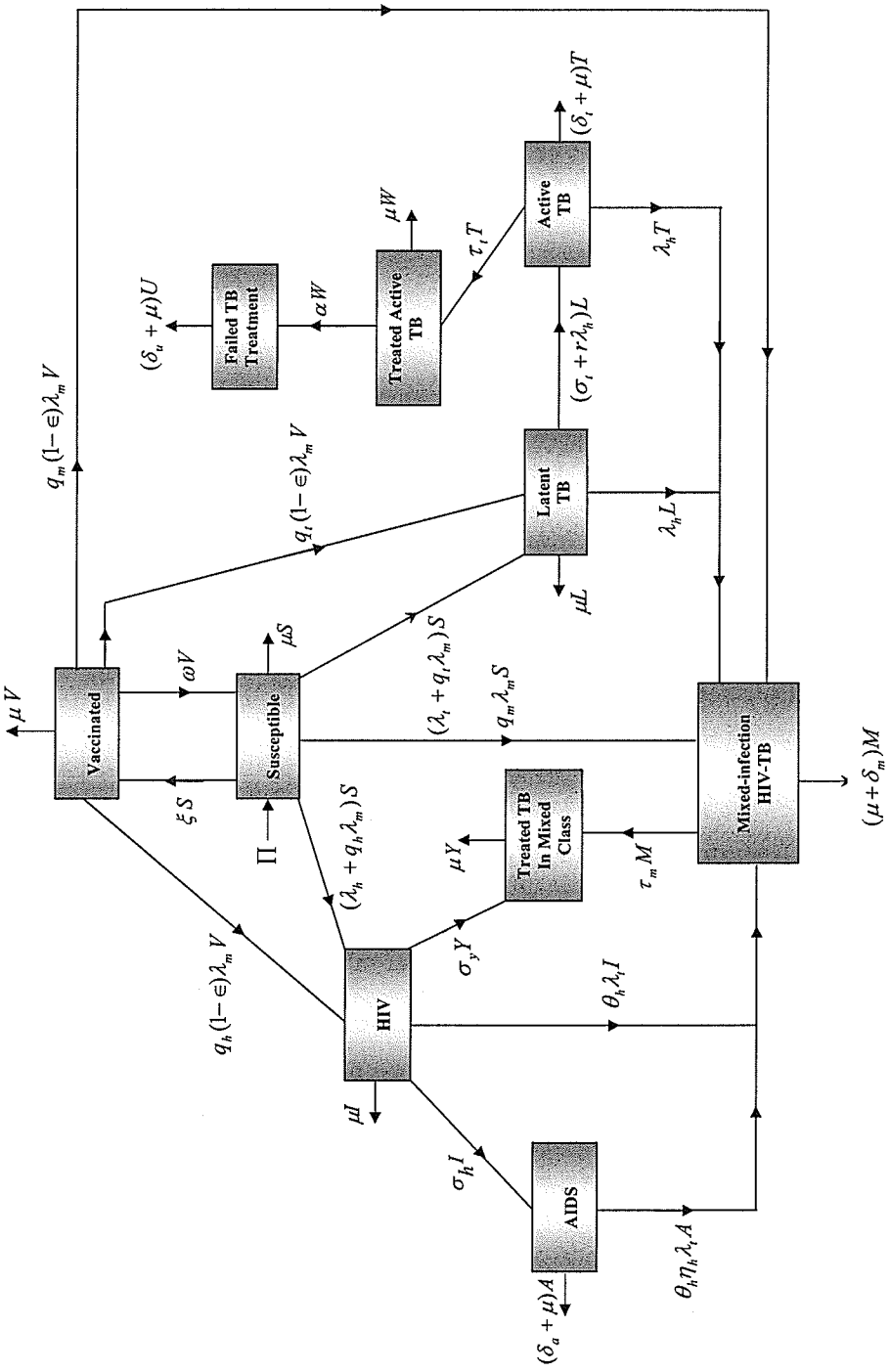

Figure 7.1: Flow diagram of the extended HIV-TB model (7.1)

Table 7.1: Variables and parameters for the extended model (7.1)

Variable/ Parameter	Description
$S(t)$	number of susceptible individuals at time t
$V(t)$	number of susceptible individuals that are vaccinated at time t
$I(t)$	number of chronic (asymptomatic HIV-infected individuals at time t
$A(t)$	number of individuals at the AIDS stage of the HIV infection, at time t
$L(t)$	number of individuals with latent TB at time t
$T(t)$	number of individuals with active TB at time t
$M(t)$	number of individuals with mixed infection at time t
$W(t)$	number of individuals from the T class that are administered with active TB treatment at time t
$Y(t)$	number of individuals from the M class that are administered with active TB treatment at time t
$U(t)$	number of individuals from the W class with failed TB treatment at time t
$N(t)$	total population size at time t
Π	recruitment rate into the population
ζ	vaccination rate of susceptible individuals
ω	waning rate of vaccine
ϵ	effectiveness of vaccine
θ_h	modification parameter
$\beta_h, \beta_t, \beta_m$	effective contact rates of HIV, TB and mixed infection respectively
σ_h, σ_y	progression rates of HIV
σ_t	progression rate of TB
η_h	modification factor for infectiousness of AIDS
κ	modification factor for infectiousness of latent TB
r	rate of exogenous re-infection for latent TB individuals
$\delta_a, \delta_t, \delta_m, \delta_u$	mortality rates of HIV, TB, mixed infection and failed treatment classes, respectively
τ_m, τ_t	treatments rates of active TB in the M and T classes respectively
α	failure rate of treatment in the W class
μ	natural death-rate in the community
q_h, q_t, q_m	fractions of new cases of HIV, TB and mixed infections that respectively result from the effective contact between individuals with mixed infection and susceptible individuals

In addition to being among the few models for HIV-TB interaction in a population, to the author's knowledge, model (7.1) is among the very first (if not the first) HIV-TB model to have incorporated the following features in an HIV-TB framework.

(a) TB transmission by latently-infected individuals;

(b) Vaccination for HIV in an HIV-TB co-infection model;

(c) Transmission of HIV-TB co-infection to a susceptible individual.

The objective of this chapter is to assess the following in the context of the transmission dynamics of HIV and TB in a community:

(i) the impact of the transmission dynamics of TB by individuals with latent TB;

(ii) the impact of transmission of HIV, TB and the HIV-TB co-infection by individuals infected with both diseases (that is, those with the HIV-TV co-infection);

(iii) the impact of DOTS treatment and an imperfect HIV vaccine.

7.1 Basic Properties

Solutions to (7.1) are defined in the biologically-feasible region given by

$$\Gamma = \{\mathcal{E} \in \mathbb{R}^{10}_{+}; S(t)+V(t)+I(t)+A(t)+L(t)+T(t)+M(t)+W(t)+Y(t)+U(t) \leq \Pi/\mu\},$$

where,

$$\mathcal{E} = (S(t), V(t), I(t), A(t), L(t), T(t), M(t), W(t), Y(t), U(t)).$$

It can be shown, as in Section 3.2, that the region Γ is positively-invariant. Hence, the system (7.1) is (mathematically and epidemiologically) well-posed in Γ.

In the sections that follow, we shall consider three sub-models of the extended model (7.1), namely: the HIV-only sub-model with vaccination, the TB-only sub-model with treatment, and the mixed-only sub-model with vaccination.

7.2 HIV-only Sub-model with Vaccination

This sub-model is obtained by setting the variables $L = T = M = W = Y = U = 0$ in (7.1), resulting in the following.

$$\begin{aligned}
\frac{dS}{dt} &= \Pi + \omega V - \lambda_h S - \zeta S - \mu S, \\
\frac{dV}{dt} &= \zeta S - \omega V - (1-\epsilon)\lambda_h V - \mu V, \\
\frac{dI}{dt} &= \lambda_h S + (1-\epsilon)\lambda_h V - \sigma_h I - \mu I, \\
\frac{dA}{dt} &= \sigma_h I - \mu A - \delta_a A,
\end{aligned} \tag{7.2}$$

with $N = S + V + I + A$ and $\lambda_h = \dfrac{\beta_h(I + \eta_h A)}{N}$. The DFE of the sub-model (7.2) is given by

$$\mathcal{E}^{(v)}_{h,0} = (S^*, V^*, 0, 0) = \left[\frac{\Pi(\omega+\mu)}{\mu(\zeta+\omega+\mu)}, \frac{\Pi\zeta}{\mu(\zeta+\omega+\mu)}, 0, 0\right]. \tag{7.3}$$

For system (7.2), the next generation matrices, F and P, are given by

$$F = \begin{pmatrix} g_\epsilon & \eta_h g_\epsilon \\ 0 & 0 \end{pmatrix} \text{ and } P = \begin{pmatrix} \sigma_h + \mu & 0 \\ -\sigma_h & \delta_a + \mu \end{pmatrix}, \tag{7.4}$$

where,

$$g_\epsilon = \frac{\beta_h[\omega + \mu + \zeta(1-\epsilon)]}{\omega + \mu + \zeta}, \tag{7.5}$$

so that,

$$\mathcal{R}^{(v)}_h = \rho(FP^{-1}) = \frac{\beta_h[\omega + \mu + \zeta(1-\epsilon)](\delta_a + \mu + \eta_h\sigma_h)}{(\omega+\mu+\zeta)(\sigma_h+\mu)(\delta_a+\mu)}. \tag{7.6}$$

Thus, the following result is established.

Theorem 7.1 *The DFE of the HIV-only sub-model (7.2) with vaccination is LAS if* $\mathcal{R}^{(v)}_h < 1$, *and unstable otherwise.*

Definition 7.1 *The threshold quantity* $\mathcal{R}^{(v)}_h$, *is the basic reproduction number for the HIV-only sub-model (7.2) with vaccination. It measures the average number of secondary cases generated by a single HIV-infected individual in a population where a*

fraction of the susceptible individuals is vaccinated.

Observe that in the absence of vaccination ($V = \zeta = \omega = 0$), the quantity $\mathcal{R}_h^{(v)}$ reduces to $\mathcal{R}_h$ (given in (4.6)). Furthermore, it is easy to see that

$$\mathcal{R}_h^{(v)} = \frac{[\omega + \mu + \zeta(1-\epsilon)]}{(\omega + \mu + \zeta)}\mathcal{R}_h \leq \mathcal{R}_h. \tag{7.7}$$

Thus, introducing vaccination to the HIV-only sub-model (4.1) reduces the associated basic reproduction number, $\mathcal{R}_h$ (since $\epsilon \leq 1$). That is, the vaccination program will always have beneficial public health impact.

The possibility of backward bifurcation in the sub-model (7.2) is now explored.

7.2.1 Backward bifurcation in HIV-only sub-model

Let $\mathcal{E}_{h,1}^{(v)} = (S^{**}, V^{**}, I^{**}, A^{**})$ denotes an arbitrary endemic equilibrium in the model (7.2). Then, solving (7.2) for the variables V^{**}, I^{**}, and A^{**} (in terms of S^{**}) at $\mathcal{E}_{h,1}^{(v)}$ yields

$$\begin{aligned} V^{**} &= \frac{\zeta S^{**}}{\omega + \mu + \lambda_h^{**}(1-\epsilon)}, \\ I^{**} &= \frac{\lambda_h^{**} S^{**}[\omega + \mu + (1-\epsilon)(\lambda_h^{**} + \zeta)]}{(\sigma_h + \mu)[\omega + \mu + \lambda_h^{**}(1-\epsilon)]}, \\ A^{**} &= \frac{\sigma_h \lambda_h^{**} S^{**}[\omega + \mu + (1-\epsilon)(\lambda_h^{**} + \zeta)]}{(\delta_a + \mu)(\sigma_h + \mu)[\omega + \mu + \lambda_h^{**}(1-\epsilon)]}. \end{aligned} \tag{7.8}$$

Using (7.8) and noting that $N^{**} = S^{**} + V^{**} + I^{**} + A^{**}$, it follows that

$$\frac{N^{**}}{S^{**}} = \frac{\lambda_h^{**}(\delta_a + \mu + \sigma_h)[\omega + \mu + (1-\epsilon)(\lambda_h^{**} + \zeta)] + (\delta_a + \mu)(\sigma_h + \mu)[\omega + \mu + \zeta + \lambda_h^{**}(1-\epsilon)]}{(\delta_a + \mu)(\sigma_h + \mu)[\omega + \mu + \lambda_h^{**}(1-\epsilon)]}. \tag{7.9}$$

Further substituting (7.8) and (7.9) in $\lambda_h^{**} = \dfrac{\beta_h(I^{**} + \eta_h A^{**})}{N^{**}}$, and simplifying, gives

$$\begin{aligned} &\lambda_h^{**}(\delta_a + \mu + \sigma_h)[\omega + \mu + (1-\epsilon)(\lambda_h^{**} + \zeta)] + (\delta_a + \mu)(\sigma_h + \mu)[\omega + \mu + \zeta + \lambda_h^{**}(1-\epsilon)] \\ &= \beta_h(\delta_a + \mu + \eta_h \sigma_h)[\omega + \mu + (1-\epsilon)(\lambda_h^{**} + \zeta)], \end{aligned} \tag{7.10}$$

which can be re-written as,

$$a_0 \lambda^{**2}_h + a_1 \lambda_h^{**} + a_2 = 0,$$

where,

$$\begin{aligned} a_0 &= (\delta_a+\mu+\sigma_h)(1-\epsilon), \\ a_1 &= (\delta_a+\mu+\sigma_h)[\omega+\mu+\zeta(1-\epsilon)]+(\delta_a+\mu)(\sigma_h+\mu)(1-\epsilon)\left(1-\mathcal{R}_h\right), \\ a_2 &= (\delta_a+\mu)(\sigma_h+\mu)(\omega+\mu+\zeta)\left(1-\mathcal{R}_h^{(v)}\right). \end{aligned} \tag{7.11}$$

Since $a_0 > 0$, it follows that the threshold reproduction number, $\mathcal{R}_h^{(v,**)}(< \mathcal{R}_h^{(v)} < 1)$, is obtained from the condition $a_1^2 - 4a_0a_2 = 0$, and given by

$$\mathcal{R}_h^{(v,**)} = 1 - \frac{a_1^2}{4a_0(\delta_a+\mu)(\sigma_h+\mu)(\omega+\mu+\zeta)}. \tag{7.12}$$

Thus, the HIV-only sub-model (7.2) undergoes a backward bifurcation whenever $0 < \mathcal{R}_h^{(v,**)} < \mathcal{R}_h^{(v)} < 1$.

Hence, unlike the HIV-only sub-model (4.1) (without vaccination), the HIV-only sub-model with vaccination (7.2) exhibits backward bifurcation. Further, it is easy to see that this phenomenon can be removed by setting $\epsilon = 1$. The Lyapunov function in Section 4.1.2 (that is, $\mathcal{P} = [(\delta_a+\eta_h\sigma_h)I+\eta_h(\sigma_h+\mu)A)$ can be used to prove the global asymptotic stability of the DFE, $\mathcal{E}_{h,0}^{(v)}$, of system (7.2) with $\epsilon = 1$. Thus, the imperfect nature of the HIV vaccine ($\epsilon < 1$) is responsible for the backward bifurcation property of the HIV-only sub-model (7.2) with vaccination.

7.3 The TB-only Sub-model With Treatment

The TB-only sub-model with treatment is obtained by setting $V = I = A = M = \lambda_h = \lambda_m = Y = \zeta = 0$ in (7.1), giving

$$\begin{aligned} \frac{dS}{dt} &= \Pi - \lambda_t S - \mu S, \\ \frac{dL}{dt} &= \lambda_t S - r\lambda_z L - \sigma_t L - \mu L, \\ \frac{dT}{dt} &= r\lambda_z L + \sigma_t L - \tau_t T - \mu T - \delta_t T, \\ \frac{dW}{dt} &= \tau_t T - \alpha W - \mu W, \\ \frac{dU}{dt} &= \alpha W - \mu U - \delta_u U, \end{aligned} \tag{7.13}$$

where, $\lambda_t = \dfrac{\beta_t(\kappa L + T)}{N}$, $\lambda_z = \dfrac{\beta_t T}{N}$, and $N = S + L + T + W + U$. The DFE, $\mathcal{E}_{t,0}^{(t)} = (S^*, L^*, T^*, W^*, U^*)$, for model (7.13) is given by $\mathcal{E}_{t,0}^{(t)} = (\Pi/\mu, 0, 0, 0, 0)$. Here, the non-negative matrix F and the M-matrix, P, for model (7.13) are:

$$F = \begin{pmatrix} \beta_t\kappa & \beta_t & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \text{ and } P = \begin{pmatrix} \sigma_t + \mu & 0 & 0 & 0 \\ -\sigma_t & \tau_t + \delta_t + \mu & 0 & 0 \\ 0 & -\tau_t & \alpha + \mu & 0 \\ 0 & 0 & -\alpha & \delta_u + \mu \end{pmatrix}, \tag{7.14}$$

so that the associated effective reproduction number, $\mathcal{R}_t^{(t)}$, for the TB-only sub-model (7.13) is given by

$$\mathcal{R}_t^{(t)} = \rho(FP^{-1}) = \frac{\beta_t[\kappa(\tau_t + \delta_t + \mu) + \sigma_t]}{(\sigma_t + \mu)(\tau_t + \delta_t + \mu)}. \tag{7.15}$$

Thus, the following result is established.

Theorem 7.2 *The DFE, $\mathcal{E}_{t,0}^{(t)}$, of the TB-only sub-model (7.13) with treatment is LAS if $\mathcal{R}_t^{(t)} < 1$, and unstable otherwise.*

Definition 7.2 *The threshold quantity $\mathcal{R}_t^{(t)}$, is the basic reproduction number for the sub-model (7.13) with TB-treatment. It measures the effective number of secondary cases of TB-infection generated by a single individual that is infected with TB in a population where a fraction of those infected with active TB are given TB treatment.*

It is worth noting that in the absence of TB treatment, and if members of the L class are non-transmitting ($\kappa = \tau_t = W = U = 0$), the reproduction number $\mathcal{R}_t^{(t)}$ becomes equal to $\mathcal{R}_t$ (from (5.4)) since the sub-model (7.13) reduces to the model (5.1).

7.3.1 Backward bifurcation in TB-only sub-model

Here, too, in order to use the Center Manifold theory (see Section 6.3), we define $S = x_1, L = x_2, T = x_3, W = x_4$, and $U = x_5$, so that (7.13) is transformed into the

following system of equations.

$$\begin{aligned}
\dot{x_1} &= \Pi - \lambda_t x_1 - \mu x_1 &&= f_1,\\
\dot{x_2} &= \lambda_t x_1 - r\lambda_z x_2 - \sigma_t x_2 - \mu x_2 &&= f_2,\\
\dot{x_3} &= r\lambda_z x_2 + \sigma_t x_2 - \tau_t x_3 - \delta_t x_3 - \mu x_3 &&= f_3,\\
\dot{x_4} &= \tau_t x_3 - \alpha x_4 - \mu x_4 &&= f_4,\\
\dot{x_5} &= \alpha x_4 - \delta_u x_5 - \mu x_5 &&= f_5,
\end{aligned} \tag{7.16}$$

where, $N = x_1 + x_2 + x_3 + x_4 + x_5$, $\lambda_z = \dfrac{\beta_t x_3}{N}$, $\lambda_t = \dfrac{\beta_t(\kappa x_3 + x_4)}{N}$. The reduced system (7.16) has a DFE given by $\mathcal{X}_0 = (\Pi/\mu, 0, 0, 0, 0)$. Solving for β_t from $\mathcal{R}_t^{(v)} = 1$ gives $\beta^* = \beta_t = \dfrac{(\sigma_t + \mu)(\tau_t + \delta_t + \mu)}{\sigma_t + \kappa(\tau_t + \delta_t + \mu)}$. Thus, evaluating the Jacobian, $J(\mathcal{X}_0)$, at β^* gives

$$J_{\beta^*} = \begin{pmatrix}
-\mu & -\kappa\beta^* & -\beta^* & 0 & 0\\
0 & \kappa\beta^* - \sigma_t - \mu & \beta^* & 0 & 0\\
0 & \sigma_t & -\tau_t - \delta_t - \mu & 0 & 0\\
0 & 0 & \tau_t & -\alpha - \mu & 0\\
0 & 0 & 0 & \alpha & -\delta_u - \mu
\end{pmatrix}. \tag{7.17}$$

The associated left and right eigenvectors of J_{β^*} (corresponding to the zero eigenvalue) are given by,

$$\begin{aligned}
v &= \left(0, \frac{Q_1 v_3}{\beta^*}, v_3, 0, 0\right),\\
w &= \left[\frac{-\beta_t Q_2(\kappa Q_1 + \sigma_t)w_5}{\alpha\mu\sigma_t\tau_t}, \frac{Q_1 Q_2 w_5}{\alpha\tau_t\sigma_t}, \frac{Q_2 w_5}{\alpha\tau_t}, \frac{(\delta_u + \mu)w_5}{\alpha}, w_5\right]^T,
\end{aligned} \tag{7.18}$$

where, $Q_1 = (\tau_t + \delta_t + \mu)$, and $Q_2 = (\alpha + \mu)(\delta_u + \mu)$.

Next, we compute

$$a = \sum_{i,j,k=1}^{5} \left(v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}\bigg|_{\mathcal{X}_0} \right) \text{ and } b = \sum_{i,k=1}^{5} \left(v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \beta^*}\bigg|_{\mathcal{X}_0} \right). \tag{7.19}$$

It can be shown that

$$\begin{aligned} a &= \frac{Q_1 v_3}{\beta^*} \sum_{i,j=1}^{5} \left(w_i w_j \frac{\partial^2 f_2}{\partial x_i \partial x_j}\bigg|_{\chi_0} \right) + v_3 \sum_{i,j=1}^{5} \left(w_i w_j \frac{\partial^2 f_3}{\partial x_i \partial x_j}\bigg|_{\chi_0} \right), \\ &\text{and} \\ b &= \frac{Q_1 v_3}{\beta^*} \sum_{i=1}^{5} \left(w_i \frac{\partial^2 f_2}{\partial x_i \partial \beta^*}\bigg|_{\chi_0} \right) + v_3 \sum_{i=1}^{5} \left(w_i \frac{\partial^2 f_3}{\partial x_i \partial \beta^*}\bigg|_{\chi_0} \right). \end{aligned} \tag{7.20}$$

Using (7.16) and (7.18) in(7.20) gives

$$\begin{aligned} a &= -\frac{2Q_1 Q_2 \mu v_3 w_5^2}{\alpha^2 \tau_t^2 \sigma_t^2 \Pi} \left[\begin{array}{l} Q_1 Q_2 (Q_1\kappa + \sigma_t\kappa + \sigma_t + \sigma_t r) + Q_2 \sigma_t^2 \\ \tau_t \sigma_t (\delta_a + \mu + \alpha)(Q_1\kappa + \sigma_t) - Q_2 \sigma_t r \beta^* \end{array} \right], \\ &\text{and} \\ b &= \frac{Q_1 Q_2 v_3 w_5 (Q_1\kappa + \sigma_t)}{\beta_t \alpha \tau_t \sigma_t}. \end{aligned} \tag{7.21}$$

The expression for a in (7.21) can be rewritten as

$$a = C_t^{(t)} \beta^* - G_t^{(t)},$$

where,

$$C_t^{(t)} = \frac{2 v_3 Q_1 Q_2 w_5^2 \mu Q_2 \sigma_t r}{\alpha^2 \tau_t^2 \sigma_t^2 \Pi}, \tag{7.22}$$

and,

$$G_t^{(t)} = \frac{2 v_3 Q_1 Q_2 w_5^2 \mu}{\alpha^2 \tau_t^2 \sigma_t^2 \Pi} \left[\begin{array}{l} Q_1 Q_2 (Q_1\kappa + \sigma_t\kappa + \sigma_t + \sigma_t r) \\ + Q_2 \sigma_t^2 + \tau_t \sigma_t (\delta_a + \mu + \alpha)(Q_1\kappa + \sigma_t) \end{array} \right].$$

Thus, we have established the following result.

Theorem 7.3 *The TB-only sub-modelwith treatment, (7.13), undergoes a backward bifurcation when* $\mathcal{R}_t^{(t)} = 1$ *and* $\beta^* > \dfrac{G_t^{(t)}}{C_t^{(t)}}$.

In the following section, we shall show that the exogenous re-infection parameter, r, governs the existence of backward bifurcation in the system (7.13) .

7.3.2 Endemic equilibrium when $r = 0$

Let $\mathcal{E}_{t,1}^{(t)}|_{r=0}$ denote an arbitrary endemic equilibrium of the system (7.13) when $r = 0$. By setting $\frac{dL}{dt} = \frac{dT}{dt} = \frac{dW}{dt} = \frac{dU}{dt} = r = 0$ in the last four equations of (7.13), $\lambda_t^{**} = \frac{\beta_t(\kappa L^{**} + T^{**})}{N^{**}}$, and solving for the variables L^{**}, T^{**}, W^{**}, and U^{**}, we have

$$\begin{aligned} L^{**} &= \frac{\lambda_t^{**} S^{**}}{\sigma_t + \mu}, \\ T^{**} &= \frac{\sigma_t \lambda_t^{**} S^{**}}{(\sigma_t + \mu)(\tau_t + \delta_t + \mu)}, \\ W^{**} &= \frac{\tau_t \sigma_t \lambda_t^{**} S^{**}}{(\alpha + \mu)(\sigma_t + \mu)(\tau_t + \delta_t + \mu)}, \\ U^{**} &= \frac{\alpha \tau_t \sigma_t \lambda_t^{**} S^{**}}{(\delta_u + \mu)(\alpha + \mu)(\sigma_t + \mu)(\tau_t + \delta_t + \mu)}. \end{aligned} \tag{7.23}$$

By substituting (7.23) in $N^{**} = S^{**} + L^{**} + T^{**} + W^{**} + U^{**}$, it follows that

$$\frac{N^{**}}{S^{**}} = \frac{\left[\begin{array}{l}(\alpha+\mu)(\delta_u+\mu)(\tau_t+\delta_t+\sigma_t) \\ +(\mu^2+\tau_t\sigma_t)(\delta_u+\mu+\alpha)+\mu\delta_u\alpha\end{array}\right]\lambda_t^{**} + \left[\begin{array}{l}(\alpha+\mu)(\sigma_t+\mu) \\ \times(\delta_u+\mu)(\tau_t+\delta_t+\mu)\end{array}\right]}{(\delta_u+\mu)(\alpha+\mu)(\sigma_t+\mu)(\tau_t+\delta_t+\mu)}. \tag{7.24}$$

Next, using (7.23) and (7.24) in $\lambda_t^{**} = \frac{\beta_t(\kappa L^{**} + T^{**})}{N^{**}}$, and simplifying, gives the following linear equation

$$b_0 \lambda_t^{**} + b_1 = 0, \tag{7.25}$$

where,

$$\begin{aligned} b_0 &= (\alpha+\mu)(\delta_u+\mu)(\tau_t+\delta_t+\sigma_t) + (\mu^2+\tau_t\sigma_t)(\delta_u+\mu+\alpha) + \mu\delta_u\alpha \\ b_1 &= -(\alpha+\mu)(\delta_u+\mu)\{\beta_t[\kappa(\mu+\tau_t+\delta_t)+\sigma_t] - (\mu+\tau_t+\delta_t)(\sigma_t+\mu)\} \\ &= -(\alpha+\mu)(\delta_u+\mu)(\mu+\tau_t+\delta_t)(\sigma_t+\mu)\left(\mathcal{R}_t^{(t)} - 1\right). \end{aligned} \tag{7.26}$$

Thus, from (7.26), $\lambda_t^{**} = -\frac{b_1}{b_0}$. Hence, $\lambda_t^{**} < 0$ if $\mathcal{R}_t^{(t)} < 1$; so that the sub-model (7.13) has no positive (endemic) equilibrium when $\mathcal{R}_t^{(t)} < 1$. Clearly, the absence of two endemic equilibria when $\mathcal{R}_t^{(t)} < 1$ suggests that backward bifurcation is not feasible in the sub-model (7.13) when $r = 0$. A global stability proof for the DFE of the sub-model

(7.13) is now given for the case $r = 0$.

7.3.3 Global stability of DFE of model (7.13) for $r = 0$

We claim the following.

Theorem 7.4 *The DFE of the sub-model (7.13) with $r = 0$ is GAS in Γ iff $\mathcal{R}_t^{(t)} < 1$, and unstable when $\mathcal{R}_t^{(t)} > 1$.*

Proof
With $r = 0$, the model (7.13) reduces to

$$\begin{aligned}
\frac{dS}{dt} &= \Pi - \lambda_t S - \mu S, \\
\frac{dL}{dt} &= \lambda_t S - \sigma_t L - \mu L, \\
\frac{dT}{dt} &= \sigma_t L - \tau_t T - \mu T - \delta_t T, \\
\frac{dW}{dt} &= \tau_t T - \alpha W - \mu W, \\
\frac{dU}{dt} &= \alpha W - \mu U - \delta_u U.
\end{aligned} \tag{7.27}$$

The last four equations of (7.27) can be expressed, in terms of the next generation matrices F and P for the sub-model (7.27), as below.

$$\begin{pmatrix} \frac{dL(t)}{dt} \\ \frac{dT(t)}{dt} \\ \frac{dW(t)}{dt} \\ \frac{dU(t)}{dt} \end{pmatrix} = (F - P) \begin{pmatrix} L(t) \\ T(t) \\ W(t) \\ U(t) \end{pmatrix} - \left(1 - \frac{S}{N}\right) \begin{pmatrix} \beta_t\kappa & \beta_t & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \begin{pmatrix} L(t) \\ T(t) \\ W(t) \\ U(t) \end{pmatrix}.$$

so that (since $S(t) \leq N(t)$ for all $t \geq 0$)

$$\begin{pmatrix} \frac{dL(t)}{dt} \\ \frac{dT(t)}{dt} \\ \frac{dW(t)}{dt} \\ \frac{dU(t)}{dt} \end{pmatrix} \leq (F-P) \begin{pmatrix} L(t) \\ T(t) \\ W(t) \\ U(t) \end{pmatrix}. \tag{7.28}$$

The proof is completed using the same argument as in the proof of Theorem 5.4. □

7.4 Mixed-only Sub-model With Vaccination

This model is obtained by setting $I = A = L = T = \lambda_h = \lambda_t = \lambda_z = \sigma_y = \tau_t = \tau_m = W = U = 0$ and $q_m = 1$ in (7.1), giving

$$\begin{aligned} \frac{dS}{dt} &= \Pi + \omega V - \lambda_m S - \zeta S - \mu S, \\ \frac{dV}{dt} &= \zeta S - \omega V - (1-\epsilon)\lambda_m V - \mu V, \\ \frac{dM}{dt} &= \lambda_m S + (1-\epsilon)\lambda_m V - \mu M - \delta_m M, \end{aligned} \tag{7.29}$$

where,

$$\lambda_m = \frac{\beta_m M}{N} \text{ and } N = S + V + M. \tag{7.30}$$

The DFE of the model (7.29) is given by $\mathcal{E}^{(v)}_{m,0} = (S^*, V^*, 0)$, where $S^* = \dfrac{(\omega+\mu)\Pi}{\mu(\zeta+\omega+\mu)}$ and $V^* = \dfrac{\zeta\Pi}{\mu(\zeta+\omega+\mu)}$. Here, the associated reproduction number is given by

$$\widetilde{\mathcal{R}}^{(v)}_m = \frac{\beta_m[\omega+\mu+\zeta(1-\epsilon)]}{(\delta_m+\mu)(\omega+\mu+\zeta)}. \tag{7.31}$$

It is worth mentioning here that the mixed-only sub-model (7.29) above with vaccination exhibits similar dynamics to that of the HIV-only sub-model (7.2) with vaccina-

tion. That is, it can be shown that the system (7.29) exhibits backward bifurcation (for $\epsilon \neq 1$), and that the sub-model (7.29) has a DFE that is GAS whenever $\epsilon = 1$. Furthermore, the basic reproduction number (in the absence of vaccination) of model (7.29), denoted by $\mathcal{R}_m$, is given by

$$\mathcal{R}_m = \frac{\beta_m}{(\delta_m + \mu)}. \tag{7.32}$$

Thus, using (7.31) and (7.32) gives

$$\widetilde{\mathcal{R}}_m^{(v)} = \frac{[\omega + \mu + \zeta(1-\epsilon)]}{(\omega + \mu + \zeta)}\mathcal{R}_m \leq \mathcal{R}_m. \tag{7.33}$$

Up till now, we have considered sub-models of the extended model (7.1). In so doing, we separately obtained three basic reproductive numbers: $\mathcal{R}_h^{(v)}$, $\mathcal{R}_t^{(t)}$, and $\widetilde{\mathcal{R}}_m^{(v)}$. These numbers will be shown to constitute important epidemiological thresholds for the extended model (7.1). However, the last, ($\widetilde{\mathcal{R}}_m^{(v)}$), of these three will be shown to assume a more general form that was obtained for the mixed-only sub-model (7.29) above. In the sections that follow below, we shall see how these three thresholds feature in the extended model (7.1).

7.5 Analysis of the Full Extended Model

The extended model (7.1) has a DFE given by

$$\begin{aligned} \mathcal{E}_0^{(v)} &= [S^*, V^*, I^*, A^*, L^*, T^*, M^*, W^*, Y^*, U^*] \\ &= \left[\frac{(\omega+\mu)\Pi}{\mu(\zeta+\omega+\mu)}, \frac{\zeta\Pi}{\mu(\zeta+\omega+\mu)}, 0, 0, 0, 0, 0, 0, 0, 0\right]. \end{aligned} \tag{7.34}$$

In the sections that follow, we shall focus on a series of analyses: the stability analysis of the DFE, $\mathcal{E}_0^{(v)}$, to obtain the thresholds that characterize the dynamics of the extended model (7.1). This is followed by the analyses of the limiting values of these thresholds to obtain suprema and infima for this model. We conclude the chapter with a summary after a bifurcation analysis for the conditions of backward bifurcation and the global stability of the DFE.

7.5.1 Local stability of the DFE

The next generation matrices associated with the model (7.1) are

$$F = \begin{pmatrix} \beta_h g_\epsilon & \eta_h \beta_h g_\epsilon & 0 & 0 & q_m \beta_m G & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \kappa\beta_t & \beta_t & q_t \beta_m g_\epsilon & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & q_m \beta_m g_\epsilon & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

and,

$$P = \begin{pmatrix} \sigma_h + \mu & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -\sigma_h & \delta_a + \mu & 0 & 0 & 0 & 0 & -\sigma_y & 0 \\ 0 & 0 & \sigma_t + \mu & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\sigma_t & \tau_t + \delta_t + \mu & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \tau_m + \delta_m + \mu & 0 & 0 & 0 \\ 0 & 0 & 0 & \tau_t & 0 & \alpha + \mu & 0 & 0 \\ 0 & 0 & 0 & 0 & \tau_m & 0 & \sigma_y + \mu & 0 \\ 0 & 0 & 0 & 0 & 0 & \alpha & 0 & \delta_u + \mu \end{pmatrix},$$

where, $g_\epsilon = \dfrac{\omega + \mu + \zeta(1-\epsilon)}{\omega + \mu + \zeta}$. It follows that

$$\mathcal{R}_{HT}^{(vt)} = \rho(FP^{-1}) = \max\{\mathcal{R}_h^{(v)}, \mathcal{R}_t^{(t)}, \mathcal{R}_m^{(v)}\}, \tag{7.35}$$

with,

$$\begin{aligned}
\mathcal{R}_h^{(v)} &= \frac{\beta_h[\omega+\mu+\zeta(1-\epsilon)](\delta_a+\mu+\eta_h\sigma_h)}{(\omega+\mu+\zeta)(\sigma_h+\mu)(\delta_a+\mu)}, \\
\mathcal{R}_t^{(t)} &= \frac{\beta_t[\kappa(\tau_t+\delta_t+\mu)+\sigma_t]}{(\sigma_t+\mu)(\tau_t+\delta_t+\mu)}, \\
\mathcal{R}_m^{(v)} &= \frac{q_m\beta_m[\omega+\mu+\zeta(1-\epsilon)]}{(\omega+\mu+\zeta)(\tau_m+\delta_m+\mu)}.
\end{aligned} \tag{7.36}$$

Thus, we have established the following result.

Theorem 7.5 *The DFE of the extended HIV-TB model (7.1) is LAS if* $\mathcal{R}_{HT}^{(vt)} < 1$, *and unstable if* $\mathcal{R}_{HT}^{(vt)} > 1$.

Definition 7.3 *The threshold quantity* $\mathcal{R}_{HT}^{(vt)}$, *is the basic reproduction number for the extended model (7.1) with HIV-vaccination, and TB-treatment. It measures the average number of secondary cases generated by a single individual that is infected with either HIV, or TB in a completely susceptible population where a fraction of the susceptible is vaccinated against HIV, and a fraction of those infected with active TB is treated.*

Observe that we can rewrite $\mathcal{R}_m^{(v)}$ in (7.36) in terms of $\widetilde{\mathcal{R}}_m^{(v)}$ (from (7.31)) as follows.

$$\begin{aligned}
\mathcal{R}_m^{(v)} &= \frac{q_m\beta_m[\omega+\mu+\zeta(1-\epsilon)]}{(\omega+\mu+\zeta)(\tau_m+\delta_m+\mu)}, \\
&= \frac{q_m}{(1+\frac{\tau_m}{\delta_m+\mu})}\frac{\beta_m[\omega+\mu+\zeta(1-\epsilon)]}{(\omega+\mu+\zeta)(\delta_m+\mu)}.
\end{aligned}$$

Hence,

$$\mathcal{R}_m^{(v)} = \frac{q_m}{\left(1+\frac{\tau_m}{\delta_m+\mu}\right)}\widetilde{\mathcal{R}}_m^{(v)} \leq \widetilde{\mathcal{R}}_m^{(v)} \text{ (since } q_m \leq 1). \tag{7.37}$$

Further, combining (7.33) with (7.37) yields

$$\mathcal{R}_m^{(v)} \leq \widetilde{\mathcal{R}}_m^{(v)} \leq \mathcal{R}_m. \tag{7.38}$$

Thus, it follows from (7.33) and (7.38) that the use of an imperfect HIV vaccine reduces the average number of secondary infections due to HIV and the HIV/TB mixed infection.

7.5.2 Threshold analysis

(i) Effect of vaccine coverage on HIV-infection

Taking the limit of $\mathcal{R}_h^{(v)}$ in (7.36) as the vaccine coverage rate, ζ, tends to infinity gives

$$\begin{aligned}
\lim_{\zeta\to\infty}\mathcal{R}_h^{(v)} &= \lim_{\zeta\to\infty}\frac{\beta_h[\omega+\mu+\zeta(1-\epsilon)](\delta_a+\mu+\eta_h\sigma_h)}{(\omega+\mu+\zeta)(\sigma_h+\mu)(\delta_a+\mu)}\\
&= \lim_{\zeta\to\infty}\frac{[\omega+\mu+\zeta(1-\epsilon)]\mathcal{R}_h}{(\omega+\mu+\zeta)}\\
&= \lim_{\zeta\to\infty}\frac{\left[\dfrac{\omega+\mu}{\zeta}+(1-\epsilon)\right]\mathcal{R}_h}{\left(\dfrac{\omega+\mu}{\zeta}+1\right)}\\
&= (1-\epsilon)\mathcal{R}_h \;\leq\; \mathcal{R}_h,
\end{aligned} \tag{7.39}$$

where, the basic reproduction number, $\mathcal{R}_h$, of HIV is given in (4.6). Thus, epidemiologically, we see that the use of an imperfect vaccine, with large enough coverage ($\zeta\to\infty$), reduces the basic reproduction number of HIV. In fact, if $\epsilon = 1$, $\lim_{\zeta\to\infty}\mathcal{R}_h^{(v)} = 0$. That is, if the vaccine is 100% effective, then HIV will be eliminated from the community.

(ii) Effect of latent transmission and treatment on TB-infection

Denote $\mathcal{R}_t^{(t)}\Big|_{\kappa=0}$ and $\mathcal{R}_t^{(t)}\Big|_{\tau_t=0}$ as the basic reproduction numbers of the model (7.1) in the absence of transmission by latent TB individuals ($\kappa = 0$), and in the absence of treatment for active TB in the TB-only class ($\tau_t = 0$), respectively. Then (7.15) can be re-written as

$$\mathcal{R}_t^{(t)}\Big|_{\kappa=0} = \frac{\beta_t\sigma_t}{(\sigma_t+\mu)(\tau_t+\delta_t+\mu)} = \frac{\mathcal{R}_t}{\left(1+\dfrac{\tau_t}{\delta_t+\mu}\right)} \leq \mathcal{R}_t. \tag{7.40}$$

Further,

$$\mathcal{R}_t^{(t)}\Big|_{\tau_t=0} = \frac{\beta_t[\kappa(\delta_t+\mu)+\sigma_t]}{(\sigma_t+\mu)(\delta_t+\mu)} = \left[1+\frac{\kappa(\delta_t+\mu)}{\sigma_t}\right]\mathcal{R}_t \geq \mathcal{R}_t. \tag{7.41}$$

In (7.40) and (7.41), $\mathcal{R}_t$ is the reproduction number of the TB-only component of model (3.1). In other words, $\mathcal{R}_t$ is a reproduction number of system (7.1) in the absence of treatment for individuals with active TB. Thus, equations (7.40) and (7.41) show that the number of new cases of TB infection in the model (7.1) is reduced (below $\mathcal{R}_t$) when latent TB individuals are not transmitting; and the number of new cases of TB infection

increases (beyond $\mathcal{R}_t$) in the absence of treatment of active TB individuals in the T class, respectively. The absence of transmission by latently-infected individuals and the presence of treatment for active TB reduces the reproduction number $\left(\mathcal{R}_t^{(t)}\Big|_{\kappa=0} \leq \mathcal{R}_t\right)$, hence offering beneficial public health impact.

By rewriting the expression for $\mathcal{R}_t^{(t)}$ in (7.15) and $\mathcal{R}_t^{(t)}\Big|_{\tau_t=0}$ in (7.41) as

$$\begin{aligned} \mathcal{R}_t^{(t)}\Big|_{\tau_t=0} &= \frac{\beta_t}{(\sigma_t+\mu)}\left[\kappa+\frac{\sigma_t}{(\delta_t+\mu)}\right], \\ &\text{and} \\ \mathcal{R}_t^{(t)} &= \frac{\beta_t}{(\sigma_t+\mu)}\left[\kappa+\frac{\sigma_t}{(\tau_t+\delta_t+\mu)}\right], \end{aligned} \tag{7.42}$$

it follows that,

$$\mathcal{R}_t^{(t)}\Big|_{\kappa=0} \leq \mathcal{R}_t^{(t)} \leq \mathcal{R}_t^{(t)}\Big|_{\tau_t=0}. \tag{7.43}$$

The public health implication of the inequality (7.43) is that the use of TB treatment reduces the basic reproduction number (as expected) and, hence, reduces the new cases of TB infection in the community. Further, it can be seen that

$$\begin{aligned} \lim_{\tau_t\to\infty}\mathcal{R}_t^{(t)} &= \lim_{\tau_t\to\infty}\frac{\beta_t[\kappa(\tau_t+\delta_t+\mu)+\sigma_t]}{(\sigma_t+\mu)(\tau_t+\delta_t+\mu)} \\ &= \lim_{\tau_t\to\infty}\frac{\beta_t\left[\kappa\left(1+\dfrac{\delta_t+\mu}{\tau_t}\right)+\dfrac{\sigma_t}{\tau_t}\right]}{(\sigma_t+\mu)\left(1+\dfrac{\delta_t+\mu}{\tau_t}\right)} \\ &= \frac{\beta_t\kappa}{\sigma_t+\mu}. \end{aligned} \tag{7.44}$$

Thus, the asymptotic dynamics of TB is dependent on the number of new infections generated by the latently-infected individuals (at the rate $\beta_t\kappa$) and the duration in the latently-infected class $\left(\dfrac{1}{\sigma_t+\mu}\right)$. Therefore, the task of effectively controlling the spread of TB infection in the model (7.1) (that is, making $\mathcal{R}_t^{(t)} < 1$) is enhanced by reducing the number of infections generated by latently-infected individuals or, having shorter durations in the L class . The latter may sound counter-intuitive, but it is logical since it essentially means we ensure that people move from the L class too the T class, where effective treatment is available at a faster rate.

(iii) Effect of vaccination coverage on mixed-infection

Finally, from the expression for $\mathcal{R}_m^{(v)}$ in (7.36), we have

$$\begin{aligned} \lim_{\zeta\to\infty} \mathcal{R}_m^{(v)} &= \lim_{\zeta\to\infty} \frac{q_m\beta_m[\omega+\mu+\zeta(1-\epsilon)]}{(\omega+\mu+\zeta)(\tau_m+\delta_m+\mu)} \\ &= \frac{q_m\beta_m(1-\epsilon)}{(\tau_m+\delta_m+\mu)}. \end{aligned} \tag{7.45}$$

which, with (7.32), yields

$$\lim_{\zeta\to\infty} \mathcal{R}_m^{(v)} \leq q_m(1-\epsilon)\mathcal{R}_m. \tag{7.46}$$

Thus, the use of an imperfect vaccine with large enough coverage ($\zeta \to \infty$), reduces the basic reproduction number of the mixed-infection. Furthermore, it is easy to see that

$$\lim_{\tau_m\to\infty} \mathcal{R}_m^{(v)} = \lim_{\tau_m\to\infty} \frac{q_m\beta_m[\omega+\mu+\zeta(1-\epsilon)]}{(\omega+\mu+\zeta)(\tau_m+\delta_m+\mu)} = 0. \tag{7.47}$$

Hence, the treatment of people with active TB in the mixed class, with large coverage ($\tau_m \to \infty$), will eliminate the HIV/TB mixed infection from the community. This is a very important result of this research; and achieving this will be a big public health breakthrough, as curtailing TB infection in sufferers of HIV/AIDS has a enormous impact on reducing the disease-related mortality of both diseases.

7.5.3 Backward bifurcation in the extended model (7.1)

As before, let $S = x_1, V = x_2, I = x_3, A = x_4, L = x_5, T = x_6, M = x_7, W = x_8, Y = x_9$, and $U = x_{10}$, so that the system (7.1) is transformed into the following system of equations.

$$
\begin{aligned}
\dot{x_1} &= \Pi + \omega x_2 - \lambda_h x_1 - \lambda_t x_1 - \lambda_m x_1 - \zeta x_1 - \mu x_1 &&= f_1,\\
\dot{x_2} &= \zeta x_1 - \omega x_2 - (1-\epsilon)\lambda_h x_2 - \lambda_t x_2 - (1-\epsilon)\lambda_m x_2 - \mu x_2 &&= f_2,\\
\dot{x_3} &= \lambda_h x_1 + q_h \lambda_m x_1 + (1-\epsilon)\lambda_h x_2 + q_h(1-\epsilon)\lambda_m x_2 - \theta_h \lambda_t x_3 &&\\
&\quad -\sigma_h x_3 - \mu x_3 &&= f_3,\\
\dot{x_4} &= \sigma_h x_3 + \sigma_y x_9 - \theta_h \lambda_t x_4 - \delta_a x_4 - \mu x_4 &&= f_4,\\
\dot{x_5} &= \lambda_t x_1 + q_t \lambda_m x_1 + \lambda_t x_2 + q_t(1-\epsilon)\lambda_m x_2 - \lambda_h x_5 - r\lambda_z x_5 &&\\
&\quad -\sigma_t x_5 - \mu x_5 &&= f_5, \qquad (7.48)\\
\dot{x_6} &= r\lambda_z x_5 + \sigma_t x_5 - \lambda_h x_6 - \tau_t x_6 - \delta_t x_6 - \mu x_6 &&= f_6,\\
\dot{x_7} &= q_m \lambda_m x_1 + \theta_h \lambda_t x_3 + \theta_h \lambda_t x_4 + \lambda_h x_5 + \lambda_h x_6 &&\\
&\quad + q_m(1-\epsilon)\lambda_m x_2 - \tau_m x_7 - \delta_m x_7 - \mu x_7 &&= f_7,\\
\dot{x_8} &= \tau_t x_6 - \alpha x_8 - \mu x_8 &&= f_8,\\
\dot{x_9} &= \tau_m x_8 - \sigma_y x_9 - \mu x_9 &&= f_9,\\
\dot{x_{10}} &= \alpha x_8 - \delta_u x_{10} - \mu x_{10} &&= f_{10},
\end{aligned}
$$

where, $N = x_1 + x_2 + x_3 + x_4 + x_5 + x_6 + x_7 + x_8 + x_9 + x_{10}$, $\lambda_h = \dfrac{\beta_h(x_3 + \eta_h x_4)}{N}$ $\lambda_t = \dfrac{\beta_t(\kappa x_3 + x_4)}{N}$ and $\lambda_z = \dfrac{\beta_t x_6}{N}$. The DFE of (7.48) is

$$
\mathcal{X}_0 = \left[\frac{(\omega+\mu)\Pi}{\mu(\zeta+\omega+\mu)}, \frac{\zeta\Pi}{\mu(\zeta+\omega+\mu)}, 0, 0, 0, 0, 0, 0, 0, 0\right].
$$

The corresponding Jacobian, $J(\mathcal{X}_0)$, is given by

$$
J(\mathcal{X}_0) = \begin{pmatrix}
-c_0 & \omega & -c_1 & -c_1\eta_h & -c_2\kappa & -c_2 & -c_3 & 0 & 0 & 0\\
\zeta & -c_4 & -c_5 & -c_5\eta_h & -c_6\kappa & -c_6 & -c_7 & 0 & 0 & 0\\
0 & 0 & c_8 - c_9 & c_8\eta_h & 0 & 0 & q_h d_0 & 0 & 0 & 0\\
0 & 0 & \sigma_h & -d_1 & 0 & 0 & 0 & 0 & \sigma_y & 0\\
0 & 0 & 0 & 0 & d_2 - d_3 & \beta_t & q_t d_0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & \sigma_t & -d_4 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & q_m d_0 - d_5 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & \tau_t & 0 & -d_6 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -d_7 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -d_8
\end{pmatrix}, \qquad (7.49)
$$

where,

$$\mathcal{K}_1 = \frac{(\omega+\mu)}{(\zeta+\omega+\mu)},\ \mathcal{K}_2 = \frac{\zeta(1-\epsilon)}{(\zeta+\omega+\mu)},\ \mathcal{K}_3 = \frac{\omega+\mu+\zeta(1-\epsilon)}{(\zeta+\omega+\mu)},$$

$$c_0 = \zeta+\mu,\ c_1 = \beta_h\mathcal{K}_1,\ c_2 = \beta_t\mathcal{K}_1,\ c_3 = \beta_m\mathcal{K}_1,\ c_4 = \omega+\mu,$$

$$c_5 = \beta_h\mathcal{K}_2,\ c_6 = \frac{\beta_t\mathcal{K}_2}{1-\epsilon},\ c_7 = \beta_m\mathcal{K}_2,\ c_8 = \beta_h\mathcal{K}_3,\ c_9 = \sigma_h+\mu, \tag{7.50}$$

$$d_0 = \beta_m\mathcal{K}_3,\ d_1 = \delta_a+\mu,\ d_2 = \kappa\beta_t,\ d_3 = \sigma_t+\mu,\ d_4 = \tau_t+\delta_t+\mu,$$

$$d_5 = \tau_m+\delta_m+\mu,\ d_6 = \alpha+\mu,\ d_7 = \sigma_y+\mu,\ d_8 = \delta_u+\mu.$$

The stability threshold for the transformed system (7.48) is $\mathcal{R}_{HT}^{(vt)}$. Since, from (7.35), it was given that $\mathcal{R}_{HT}^{(vt)} = \max\{\mathcal{R}_h^{(v)}, \mathcal{R}_t^{(t)}, \mathcal{R}_m^{(v)}\}$, it follows that there are three possible stability factors: $\mathcal{R}_h^{(v)}$, $\mathcal{R}_t^{(t)}$, $\mathcal{R}_m^{(v)}$, respectively given in (7.36). Correspondingly, the three possible bifurcation parameters β_h^*, β_t^*, and β_m^* are respectively obtained from (7.36) by setting $\mathcal{R}_h^{(v)} = 1$, $\mathcal{R}_t^{(t)} = 1$, $\mathcal{R}_m^{(v)} = 1$, $\beta_h = \beta_h^*$, $\beta_t = \beta_t^*$, $\beta_m = \beta_m^*$ and solving for β_h^*, β_t^*, and β_m^* in the resulting equations. Here, the case $\mathcal{R}_h^{(v)} = 1$ is considered. Solving for β_h from $\mathcal{R}_h^{(v)} = 1$ gives

$$\beta_h = \beta^* = \frac{(\omega+\mu+\zeta)(\sigma_h+\mu)(\delta_a+\mu)}{[\omega+\mu+\zeta(1-\epsilon)](\delta_a+\mu+\eta_h\sigma_h)},$$

so that $J(\mathcal{X}_0)$ at β^* becomes

$$J_{\beta^*} = \begin{pmatrix}
-c_0 & \omega & -c_1^* & -c_1\eta_h & -c_2\kappa & -c_2 & -c_3 & 0 & 0 & 0 \\
\zeta & -c_4 & -c_5 & -c_5^*\eta_h & -c_6\kappa & -c_6 & -c_7 & 0 & 0 & 0 \\
0 & 0 & c_8^*-c_9 & c_8\eta_h & 0 & 0 & q_hd_0 & 0 & 0 & 0 \\
0 & 0 & \sigma_h & -d_1 & 0 & 0 & 0 & 0 & \sigma_y & 0 \\
0 & 0 & 0 & 0 & d_2-d_3 & \beta_t & q_td_0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & \sigma_t & -d_4 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & q_md_0-d_5 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & \tau_t & 0 & -d_6 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -d_7 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -d_8
\end{pmatrix}, \tag{7.51}$$

where, $c_1^* = \beta^*\mathcal{K}_1$, $c_5^* = \beta^*\mathcal{K}_2$ and $c_8^* = \beta^*\mathcal{K}_3$. It follows that the non-zero left and right eigenvectors, v and w, (corresponding to the zero eigenvalues of J_{β^*}) are respectively

given by

$$v = \left(\frac{c_4 v_2}{\omega}, v_2, e_1 v_2 + e_2 v_9, \frac{d_7 v_9}{\sigma_y}, e_3 v_2 + \frac{d_4 v_6}{\beta_t}, v_6, 0, 0, v_9, 0\right)$$

and

$$w = \left(\frac{c_4 e_4 + \omega e_5}{c_0 c_4 - \zeta\omega}, \frac{\zeta e_4 + c_0 e_5}{c_0 c_4 - \zeta\omega}, \frac{d_1 w_4}{\sigma_h}, w_4, \frac{d_4 d_6 w_8}{\sigma_t \tau_t}, \frac{d_6 w_8}{\tau_t}, 0, w_8, 0, 0\right)^T,$$

where,

$$\begin{aligned}
e_1 &= \frac{\eta_h(c_1^* c_4 + c_5\omega)}{c_8^*\omega\eta_h}, \\
e_2 &= \frac{d_1 d_7}{c_8^*\sigma_y\eta_h}, \\
e_3 &= \frac{(c_2 c_4 + c_6\omega)}{\omega\beta_t}, \\
e_4 &= \frac{c_1^*(d_1 + \eta_h\sigma_h)w_4}{\sigma_h} + \frac{d_6 c_2(d_4\kappa + \sigma_t)w_8}{\sigma_t\tau_t},
\end{aligned} \tag{7.52}$$

and

$$e_5 = \frac{c_5^*(d_1 + \eta_h\sigma_h)w_4}{\sigma_h} + \frac{d_6 c_6(d_4\kappa + \sigma_t)w_8}{\sigma_t\tau_t}.$$

For system (7.48), the following parameters must be computed.

$$\begin{aligned}
a &= \sum_{i,j,k=1}^{10}\left(v_k w_i w_j \left.\frac{\partial^2 f_k}{\partial x_i \partial x_j}\right|_{\chi_0}\right), \\
b &= \sum_{i,k=1}^{10}\left(v_k w_i \left.\frac{\partial^2 f_k}{\partial x_i \partial \beta^*}\right|_{\chi_0}\right).
\end{aligned} \tag{7.53}$$

Using $v_7 = v_9 = v_{10} = w_9 = w_{10} = 0$ in the expressions for the eigenvector v and w above, together with $\beta^* = \beta_h$ and (7.48) in (7.53) gives

$$\begin{aligned}
a &= C_h^{(v)}\beta^* - G_h^{(v)}, \\
b &= \frac{(\sigma_y + \mu)(\delta_a + \mu)(\delta_a + \mu + \eta_h\sigma_h)w_4 v_9}{\sigma_h\eta_h\sigma_y\beta^*},
\end{aligned} \tag{7.54}$$

where,

$$C_h^{(v)} = \frac{\left[\begin{array}{l} 2\mu v_6 w_4 w_8(\alpha+\mu)(\delta_a+\mu+\eta_h\sigma_h)\times \\ (\mu^2+2\tau_t\mu+2\delta_t\mu+2\tau_t\delta_t+\delta_t^2+\tau_t^2+\beta_t\sigma_t) \end{array}\right]}{\Pi\sigma_t\tau_t\sigma_h\beta_t}. \tag{7.55}$$

The expression for $G_h^{(v)}$ is too lengthy and not reported here. It follows from (7.54) and (7.55) , b and $C_h^{(v)}$ are positive, and it can also be shown that $G_h^{(v)}$ is positive. Thus, if $a > 0$ in (7.54), then by Theorem 6.2, the following result is established.

Theorem 7.6 *The extended HIV-TB model (7.1) undergoes a backward bifurcation when* $\mathcal{R}_h^{(v)} = 1$ *and* $\beta^* > \dfrac{G_h^{(v)}}{C_h^{(v)}}$.

7.6 Summary

In this chapter, the basic HIV-TB model (3.1) is extended to incorporate treatment for TB in two different classes, as well as the use of a potential imperfect HIV vaccine.

Rigorous analysis of the model revealed the following.

(i) The HIV-only sub-model with vaccination undergoes a vaccine-induced backward bifurcation. Furthermore, the introduction of vaccination into the HIV-only sub-model (7.2) causes a reduction in the basic reproduction number of the HIV-only model in (4.1) demonstrating the public health impact of such an intervention.

(ii) The TB-only model undergoes backward bifurcation, resulting from the exogenous re-infection property of TB disease; the full extended model (7.1) also undergoes backward bifurcation.

(iii) A large enough coverage of the use of an imperfect vaccine ($\zeta \to \infty$) against HIV-infection reduces the number of new cases of HIV or mixed infections.

(iv) The absence of TB transmission by latently-infected individuals reduces the reproduction number for TB (in the absence of treatment and infection by latently-infected individuals).

(v) The reproduction number $\mathcal{R}_t^{(t)}$ is bounded by $\mathcal{R}_t^{(t)}\Big|_{\kappa=0} \leq \mathcal{R}_t^{(t)} \leq \mathcal{R}_t^{(t)}\Big|_{\tau_t=0}$.

(vi) Mixed infection (that is, the class M) can be eliminated from a community infested with HIV and TB infections, by ensuring a large enough coverage ($\tau_m \to \infty$) of the DOTS therapy treatment for individuals with mixed infections involving active TB.

Chapter 8

Contributions and Future Work

8.1 Contributions

The main contributions of the thesis can be described under the following categories.

(A) Model Formulation

(i) A reasonably realistic model for the interaction between HIV and TB is designed, and gradually refined to include control strategies (vaccine for HIV and DOTS for TB). Further, this is the very first HIV-TB model that incorporates:

(a) TB transmission by latently-infected individuals;

(b) Vaccination for HIV in an HIV-TB co-infection model;

(c) Transmission of HIV-TB co-infection to a susceptible individual.

(ii) This study is amongst the very few studies that offer rigorous analysis of HIV/TB interaction in a population.

(B) Mathematical Analysis

(i) The study uses a number of dynamical systems tools and methodologies to analyze the associated models (which are relatively large in comparison to the many models of single diseases in the literature). These include standard linearization, next generation operator method, comparison theorem, center manifold theory, Lyaponuv function theory, Lasalle Invariance principle, etc.

(ii) Global stability results are provided for the DFE of a number of models; and LAS results are given for endemic equilibria of many of the associated models (which are generally relatively large).

(iii) The center manifold theory is used to establish backward bifurcation in TB models (with exogenous re-infection) and HIV models with vaccination.

(C) Public Health

The study provides some important insights into the transmission mechanisms and control of the two diseases, including the following:

(i) An imperfect vaccine (of modest efficacy) with large enough coverage can lead to the elimination of HIV.

(ii) The presence of exogenous re-infection induces backward bifurcation in the TB models.

(iii) The presence of backward bifurcation in HIV models with imperfect vaccine.

(iv) TB transmission by latently-infected individuals plays significant role in TB transmission dynamics.

(v) Effective treatment for TB can lead to its effective control if transmission by latent individuals is minimized, or if the duration in the latent class is short.

(vi) Mortality rate among TB and HIV sufferers can be lowered by effectively treating active TB with large enough coverage, with the effect that mixed infection is eliminated in the community.

8.2 Future Work

There are two major areas of possible future work, namely model refinement and mathematical analysis. Specifically,

(i) the model can be refined to include multiple strains of TB and HIV, as well as to include pediatric TB and HIV as separate compartment in the model;

(ii) and most of the mathematical analyses in this thesis was restricted to establishing local and global asymptotic stabilities of disease-free equilibria; and the local asymptotic stability of endemic equilibria. The work can be extended to explore ways to investigate the global dynamics of the associated boundary equilibria.

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