MATHEMATICAL MODEL OF THE CO-DYNAMICS OF DIABETES AND TUBERCULOSIS

BY

AGWU, CHUKWUEMEKA OBUJI (B.SC., M.SC)

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CERTIFICATION

This is to certify that this work "**MATHEMATICAL MODEL FOR THE CO-DYNAMICS OF DIABETES AND TUBERCULOSIS**" was carried out by Agwu Chukwuemeka Obuji (2016404408), in partial fulfillment for the award of **Doctor of Philosophy Ph.D** in Mathematics in the Department of Mathematics of the Federal University of Technology, Owerri.

Prof. S. C. Inyama		17/10/2023
(Principal Supervisor)	Signature	Date
Dr. Mrs J. U Chukwuchekwa	Chukwuchekwa	17/10/2023
(Co-Supervisor)	Signature	Date
Dr. G. A. Okeke		20/12/2023
(Co-Supervisor)	Signature	Date
Dr. Mrs J. U Chukwuchekwa	Chukwuchekwa	17/10/2023
(Head of Department)	Signature	Date
Prof. Mrs. C. E. Ogukwe		17/10/2023.
(Dean, SOPS)	Signature	Date
Prof. B. O. Esonu	----------	----------
(Dean, Postgraduate School)	Signature	Date
Prof G. C. E Mbah		17/10/23
(External Examiner)	Signature	Date

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ABSTRACT

In this work, a mathematical model for the co-dynamics of diabetes and tuberculosis co-infection was developed and analyzed. The positivity and boundedness of the solution of the developed model was also proved. Local stability of the model as well as global stability of the model were verified. Furthermore, bifurcation analysis of the model was carried out. The Pontryagin's Maximum Principle was used to establish the necessary conditions for the existence of optimal control. Cost effectiveness analysis was carried out on the strategies and it was observed that the control strategy which combines applying prevention effort against development of diabetes by encouraging healthy lifestyle and prevention effort against development of TB by encouraging personal hygiene is the least expensive strategy as it significantly impacted the most in reducing the disease burden in the population with the best cost-effective result.

Keywords: Mathematical models, Co-dynamics, Co-infection, Diabetes, Tuberculosis,Global stability, Bifurcation analysis, Pontryagin maximum principle, Optimal control, Population.

Chapter 1

INTRODUCTION

1.1 Background of study

Tuberculosis is an infectious disease which is caused by Mycobacterium tuberculosis (MTB). According to a record from World Health Organization, tuberculosis is one of the leading cause of death worldwide with South-East Asia, Africa and Western Pacific as the most heavily affected region in 2014, accounting for 30%, 28% and 19% of all tuberculosis cases respectively (WHO, 2015). Irrespective of the fact that Tuberculosis (TB) is preventable and also curable, it remains a significant contributor to the mortality and morbidity in the world (Yang et al.,2015; Zhu et al.,2017). Every year about 10 million people fall ill with tuberculosis (TB). Although it is a disease that can be prevented and treated,TB kills 1.5 million people every year, making it the world?s leading cause of death as an infectious disease (WHO, 2021). According to the 2011 World Health Organization (WHO) report on TB, TB is the leading cause of death among people living with HIV and a major cause of antiretroviral resistance (WHO, 2021). Although only a few people (about five to ten percent) infected with tuberculosis develop the active TB in their lifetime (Zhu et al., 2017), estimates indicate that tuberculosis has infected more than thirty percent of the world's population, with prevalence highest in Africa and Asia (WHO, 2016). Although there have been a lot of effective therapy, Tuberculosis remain a major infectious

disease globally, causing around 1.5 million death in 2014 only (WHO. 2015).After treatment for TB, individuals who do not completely clear all Mycobacterium tuberculosis bacteria can evolve into a state called latent tuberculosis In this latent state, they have a 5% to 15% risk of their lifetime to develop active TB in the future (Restrepo and Schlesinger, 2014). Major Tuberculosis control measures is centered on the timely identification and treatment of individuals with the infectious disease. This measure aims to reduce the spread of tuberculosis.

Tuberculosis transmission occurs almost exclusively from person to person and a prerequisite is having contact with a source case. More than 80% of new TB cases result from exposure to sputum smear positive case, even though smear negative / culture positive cases can be responsible for up to 17% of new diagnoses (Zumla, 2013). Irrespective of the huge success of this strategy in tuberculosis control, the persistence of tuberculosis in many parts of the world suggests the need to expand control efforts to identify and address the individual and social determinants of the disease. It is estimated that between the year 2000 and 2020, about one billion people will be newly infected, 200 million will become sick, 35 million will die from Tuberculosis worldwide if Tuberculosis control is not further enhanced(WHO, 2010). Nearly 80% of both incident cases and death will be in twenty two "high burden" countries, mostly located in sub-sahara Africa and South-East Asia where the problem is exacerbated by high rate of co-infection with HIV (WHO, 2010). Although most countries with high burden of Tuberculosis have adopted and widely implemented the World Health Organization's Stop TB Strategy, the rate of decline have been slower than expected (WHO, 2010, Dye and Williams,2010); Possible explanations include patient and health system delays in diagnosis and treatment, and the rise of risk factors which includes co-infection with HIV, air pollution, alcohol abuse, crowding, diabetes, malnutrition and tobacco smoking(Lonnroth et al. 2010).

Diabetes is a non communicable disease that can impair host immunity and lead to increased susceptibility to various infectious diseases including Tuberculosis (Martinez and Kornfeld, 2014). It occurs when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin produced. A rise in blood sugar called hyperglycemia is a common effect of uncontrolled diabetes and can progress over time to seriously damage many of the body system, especially the nerves and blood vessels which often leads to unhealed wounds, amputation, blindness and other related problems. Diabetes is classified into two types, the first is called Type 1 diabetes mellitus (Type 1 DM) which is known as insulin dependent, juvenile or childhood-onset, and is characterized by a deficient insulin and requires daily administration of insulin. The possible cause of Type 1 diabetes is not known and it is not preventable with current knowledge. The following are some of the symptoms of Type 1 diabetes, fatigue, weight loss, vision change, constant hunger, thirst (polydipsia), excessive urine (polyuria), etc. The second type of diabetes is called Type 2 diabetes, which is known as non-insulin dependent or adult on-set. This type of diabetes occurs when the body is unable to effectively make use of insulin. Symptoms of Type 2 diabetes are similar to that of Type 1 diabetes but are often less marked, as a result the disease may be diagnosed several years after onset, when complication have already set in. Type 2 diabetes comprises of 90% of people living with diabetes around the world and is largely as a result of excess body weight and physical inactivity. Also aging, change in life style, socioeconomic factors and population growth have led to an increased prevalence of diabetes, especially type 2 diabetes. The total number of people living with diabetes worldwide is predicted to rise from 285 million in 2010, accounting for 3.5 million deaths and projected to 439 million in 2030 (Ruslami et al.,2010, Harries et al., 2011, IDF, 2009). Over 70% of patients with diabetes live in low income and developing countries (Dooley and

Chaisson, 2009). Diabetes accounts for the deaths of 5.1 million people globally in 2013. This is similar in number to combined deaths from the major infectious diseases including Acquired Immunodeficiency Syndrome(AIDS), malaria and Tuberculosis (WHO, 2010). Countries with highest burden of diabetes are China, USA, Russia, and India. Many other countries that have large number of diabetes cases include Brazil, Several European countries and African countries (Nigeria, South Africa and East African States)and many of these are countries with high burden of Tuberculosis(IDF,2014).

Codynamics of Tuberculosis and Diabetes

Effect of Tuberculosis on Diabetes: Glucose intolerance has been reported among 16.5% to 49% of patients with active tuberculosis. In one study, 56.6% of cases with glucose intolerance at the time of diagnosis had normal glucose level after treatment of the infectious disease, a phenomena called "transient hyperglycemia (Singh et al.,1984, Jawad et al., 1995).Therefore the control of hyperglycemia is more difficult during active phase of tuberculosis and many patients requires insulin for control of hyperglycemia (Pimazoni, 2009). Although a definite cause of hyperglycemia associated with tuberculosis had not been identified, some probable mechanisms have been suggested(Young et al., 2009). Inflammation caused by cytokines such as IL6 and TNFa in response to tuberculosis infection may cause an increase in insulin resistance and decreased insulin production, there by leading to hyperglycemia (Pickup, 2004)

Effect of Diabetes on Tuberculosis: According to Deshmukh (1984),It is estimated that the risk of getting infected with tuberculosis as a result of diabetes is 25% . At individual level, Acquired Immunodeficiency Syndrome (AIDS) is a more potent risk factor for tuberculosis in comparison to diabetes, but due to the high frequency of diabetes when compared to AIDS, its effect on tuberculosis is equal or even greater than AIDS. In countries with high burden of

HIV infection, the effect of diabetes on tuberculosis may be masked by HIV(Restrepo, 2007). Some reports has it that ethnicity may influence the effect of diabetes on tuberculosis and that the influence is greater among Hispanic and non-North American populations(Pablos-Mendez et al., 1997, Jeon and Murray, 2008). Other report has it that a higher frequency of tuberculosis among patients with diabetes may be related to more frequent contact with health care settings and that transmission of disease is more probable in these settings. Adjustment of contact history however, did not reduce the strength of the association (Alisjahbana et al., 2006).

Effect of Diabetes on Latent Tuberculosis infection: Diabetes is known for its immune suppression. The pathophysiology of tuberculosis is complex. Getting infected with the disease is primarily dependent on exogenous factors. However, reactivation of the disease depends largely on the influence of immune sufficiency (Pablos-Mendez et al., 1997). In spite the frequent studies on the relationship between diabetes and active tuberculosis, the effect of diabetes on latent tuberculosis has been less investigated. The few existing reports about the high prevalence of latent tuberculosis infection among diabetics have been co-founded by an absence of control groups (Mansilla et al. 1995, Vega et al., 1996).In other studies, the prevalence of TB infection was not affected by the presence of diabetes (Webb et al., 2009; Hernandez et al., 1992; Brock et al., 2006), or its effects was removed after adjusting for other variables (Chang-Yeung et al., 2006). Therefore, it appears that diabetic patients are not at greater risk for infection with latent tuberculosis.

Effect of Diabetes on Active Tuberculosis: The frequency of diabetes among active cases of tuberculosis was 5.6%, 7.3% and 14.8% in studies from India, Turkey and Indonesia, respectively. In 35% to 61% of these patients, diabetes was diagnosed for the first time after detection of tuberculosis (Deshmukh et al., 1984; Alisjahbana et al., 2007; Tatar et al. 2009).

Furthermore, impaired glucose tolerance is common (Mugusi et al., 1990). Some suggested that reversible glucose intolerance is not specific for tuberculosis and may occur in the setting of any infection such as pneumonia (Basoglu et al., 1999) but many studies have confirmed a special correlation between diabetes and active tuberculosis. In 10 case control studies, the pooled odds ratio of tuberculosis among diabetes cases was 2.2 (ranged from 1.16 to 7.81)and in 4 cohort studies pooled relative risk was 2.52 (95% Cl:1.53 to 4.03) (Ottmani et al., 2010; WHO , 2010). The degree of this effect can be influenced by factors such as age and ethnicity. The relation between diabetes and tuberculosis is more prominent in younger people (Jeon and Murray, 2008). Some other reports has it that patients with Type 1 diabetes are more susceptible than those that have Type 2 diabetes. This higher susceptibility may be related to a longer duration of disease or could be due to the fact that control of hyperglycemia is more difficult among type 1 (Ruslami et al., 2010; Olmos et al., 1989). Additionally, the risk of tuberculosis is higher among patients who are using insulin (Dobler et al. 2012), particularly, those who need higher doses of insulin (Jeon et al. 2010; Boucot et al. 1952). Poor glycemic control has been significantly associated with the occurrence of tuberculosis (Leung et al. 2008). In population with higher incidence of tuberculosis, diabetes is a more important risk factor (Jeon and Murray 2008). Diabetes accounts for a small proportion of TB cases in settings such as Australia with a low incidence of tuberculosis (Dobler et al., 2012). This number was 14.8% in India and 25% in a Mexican setting (Young et al., 2009). Therefore, population attributed risk for tuberculosis from diabetes is dependent upon diabetes prevalence.

1.2 Problem Statement

The burden of diabetes is on the increase worldwide,same with that of Tuberculosis. The association between Diabetes and Tuberculosis is the next challenge for global control of tuberculosis and increased understanding of the co-dynamics of the two diseases is important for proper planning and collaboration to reduce the dual burden of diabetes and tuberculosis. Despite the increasing threat posed by the emerging relationship between the two, to the best of our knowledge, no mathematical model has been holistically formulated to study the co-dynamics of the two diseases and their optimal control.

1.3 Aim and Objectives of The Study

The general aim of this thesis is to develop a deterministic mathematical model for the co-dynamics of diabetes and tuberculosis which will provide a robust epidemiological and a better medical insight on their co-dynamics and as well on their management.

The specific objectives of this study are;

i. to demonstrate some basic properties of the model (that is, positivity and boundedness of the solutions of the developed models).

ii. to determine the existence of the equilibrium points of the model (disease-free equilibrium).

iii. to investigate the local and global asymptotic stability of these equilibrium points.

iv. to carry out an optimal control analysis on the model that will help eradicate the burden posed by the co-dynamics of the two diseases and carry out numerical simulations of the model, using relevant data.

1.4 Justification of study

The association between diabetes and tuberculosis is currently supported by a growing body of literature (Dye, 2006, Joan and Murry, 2008, Restrepo et a.,2011). According to a recent meta-analysis conducted by Restrepo et al (2011), diabetes patients have three times the risk of contracting tuberculosis than non-diabetes and studies report the fraction of tuberculosis cases attributable to diabetes to be between 15% and 25%. This is supported by the fact that diabetes is generally diagnosed before tuberculosis develops. A possible cause of increased prevalence of tuberculosis among diabetic patiences could be attributed to lowered immunity of the diabetic patients (McMahen and Bistrian, 1995, Koziel and koziel, 1995). As a result of the increasing rate of mortality due to this co-dynamics, there is need to develop a mathematical model that will adequately analyze the co-dynamics to give a better public health strategic solution.

1.5 Scope of Study

The Scope of this study is limited to establishment of a deterministic model for the co-dynamics of diabetes and tuberculosis, establishment of the basic properties of the developed model, solving for its equilibrium points, investigating the local and global asymptotic stability of the model and optimal control analysis of the model, carrying out numerical simulation of the model and cost-effectiveness analysis of the proposed control strategies.

1.6 Definition of terms

Definition 1.1. *A mathematical model is a representation of a real-world system or process using mathematical structures and relationships. It is a set of equations, formulas, or algorithms that describe the behavior or characteristics of the system under study. .*

Definition 1.2. *An autonomous system of ordinary differential equation is a system of ordinary differential equations which does not depend explicitly on the independent variable. Where time is the independent variable, this system is called a time-invariant system.*

Consider the system

$$\dot{x} = f(x); \quad x \in \mathbb{R}^n \tag{1.1}$$

Definition 1.3. *$x = \bar{x} \in R^n$ is an equilibrium solution of system (1.1) if $f(\bar{x}) = 0$. An equilibrium solution is a constant solution. It is obtained by setting the derivative to zero and solving for the dependent variable.*

Definition 1.4. *The disease-free equilibrium (DFE) is defined as the equilibrium point at which no disease is present in the population.*

Definition 1.5. *An ordinary differential equation (ODE) is a differential equation containing one or more functions of one independent variable and its derivatives. This is at variance with a partial differential equation which contains one or more functions of more than one independent variable and their derivatives.*

Definition 1.6. *Susceptible individuals: are members of a population who can be potentially infected by a disease when in contact with an infectious agent.*

Definition 1.7. *Exposed or Latent individuals: are individuals who are infected with a disease but are not infectious (cannot transmit to another).*

Definition 1.8. *Infectious individuals: are individuals who have acquired the disease (already infected) and can infect others with the disease.*

Definition 1.9. *Incidence rate: of a disease is a measure of the number of new cases of the disease occurring per susceptible population within a given time period. It is the rate of appearance of newly diagnosed cases of a disease over a specified period of time (maybe a week, month or year). It gives information about the risk of contracting the disease.*

Definition 1.10. *Prevalence: refers to the total number of individuals in a population who have a particular disease at a specific period of time, usually expressed as a percentage of the population. It indicates how widespread a disease is.*

Definition 1.11. *Bifurcation is defined as a sudden change in the qualitative behaviour or topological structure of a given dynamical system. This usually occurs when an associated parameter is varied.*

Definition 1.12. *The basic reproduction number denoted by R_0, is the average number of secondary infections generated by the introduction of one infectious individual into a completely susceptible (uninfected) population. It indicates how contagious an infectious disease is and hence a key parameter in determining if the disease will persist in that population.*

Chapter 2

LITERATURE REVIEW

In this chapter we review the published work of other researchers relative to the objectives of this work.

2.1 Conceptual Literature

Most literatures dealing with diabetes mainly concentrated on glucose and insulin dynamics (Derouich and Boutayeb, 2002, Bellazzi et al., 2001, Parker et al., 2001), the epidemiology of the disease (Stains et al., 1993, Paterson et al., 1993, Boutayeb and Kerfati, 1993) and economic cost and risk models (Bagust et al., 2002, Richard et al., 2001, O'Brien et al., 2003).

Parvaneh et al (2013), in their work on diabetes mellitus and tuberculosis facts and controversies, did a bidirectional study on the association between diabetes and tuberculosis, and found out that the link between diabetes and tuberculosis is more prominent in developing countries where TB burden is endemic and the burden of diabetes is increasing. They then suggested a model similar to that of HIV-Tuberculosis program for prevention, screening and treatment of both diseases can be the best approach to solving the challenges posed by diabetes and

tuberculosis. Susan (2014), in her work on worldwide increase in diabetes: Implications for tuberculosis control, discussed the current knowledge of the impact of diabetes globally on the epidemiology of tuberculosis with particular emphasis on tuberculosis control, including the drug resistance MDR-TB. Yogarabindranath, et al, (2017) in their research on the epidemiology of latent tuberculosis infection among patients with and without diabetes mellitus, conducted an observational study to compare the prevalence and risk factors associated with LTBI factors in Malaysian adults with and without diabetes. To achieve this, they recruited four hundred and four patients with diabetes and 359 patients without diabetes at a regional primary care clinic as participant in their case-control study. The tuberculin sensitive test (TST) was performed. The presence of LTBI was defined by a TST value of 10 mm in diabetic patients and 10 mm in the non-diabetic individuals and the researchers used a logistic regression model to identify variables associated with LTBI, the obtained result showed that there was no significant difference between the diabetic patients and the non-diabetic individuals as the LTBI prevalence among patients with diabetes was 28.5% whereas the prevalence of LTBI among non-diabetic in individuals was 29.2%. But when a critical cut-off of 8 mm was used, the adjusted odds ratio of LTBI in diabetes patients was 1.88 (95% confidence interval: 1.22-2.82). Also smoking was observed to be an independent risk factor for LTBI regardless of diabetes status of the individual. HbA1c Levels or anthropometric measurements were not associated with LTBI in diabetic patients. In another study on diabetes mellitus and latent tuberculosis infection: A systematic review and metaanalysis by Meng-Rui and Ya-Ping (2017), the researchers included observational studies that applied either the tuberculin skin test or the interferon gamma release assay for diagnosis of LTBI which provided adjusted effect estimate for the association between diabetes and LTBI. In their thirteen studies (1 cohort study and 12 cross-sectional studies) which

involved 38263 participants. The cohort study showed an increased but non-significant risk of LTBI among diabetics (risk ratio, 4.40;95% confidence interval [CL], 0.50-38.55) and for the cross-sectional studies the pooled odds ratio from the random effects model was 1.18 (95% CL, 1.06-1.30). They concluded that diabetes was associated with a small but statistically significant risk of LTBI. Damiano et al (2016) in their work, Tuberculosis and diabetes: Current state and future perspectives, outlined the association between tuberculosis and diabetes, focusing on epidemiology, physiopathology, clinical aspect, diagnosis and treatment, and evaluated future perspectives, with particular attention to developing countries. They concluded that tuberculosis and diabetes are clear example of correlation between communicable and non-communicable diseases, with a growing worldwide trend, especially in the context of poverty, poor sanitation, nutritional deficiencies, hypovitaminosis, etc

2.2 Related Literature

Several mathematical models have been developed to understand the co-dynamics of two or more diseases(Omame and Okuonghae, 2021, Egeonu et al 2021,Omame et al., 2021). Mtisi and Jean (2009) developed and rigorously analyzed a mathematical model for the co-dynamics of tuberculosis and malaria. They simulated the model to investigate the co−existence of the two diseases when the associated reproduction numbers of the two diseases are greater than unity and equally carried out sensitivity analysis on the main parameters that drive the dynamics of the diseases. Mukandavire et al. (2009) formulated and analyzed a co-infection model for HIV and Malaria. They showed that the reduction in sexual activity of individuals with malaria symptoms decreases the number of new cases of HIV and the mixed HIV−malaria infection. Mushayabasa et al. (2011) designed a mathematical model to explore the co-interaction of gon-

orrhea and HIV in the presence of antiretroviral therapy and gonorrhea treatment. They showed that gonorrhoea only treatment strategy is highly significant in reducing the co-infection new cases. Sharomi et al., (2008) considered a mathematical model for the transmission dynamics of HIV/TB coinfection when there is treatment. They observed that the HIV-only treatment strategy could reduce mixed infection cases than the TB-only treatment strategy. Roeger et al.(2009) modelled TB and HIV co-infection. They observed that high progression rates from HIV to AIDS may increase the prevalence of HIV. Also, Naresh and Tripathi (2005) studied the dynamics of HIV and TB coinfection. They showed that if the HIV infection is minimized at an early stage through the use of drugs, the progression to AIDS stage could be significantly reduced. The dynamics of HIV/AIDS and TB in the presence of treatment was studied by Bhunu et al. (2009). They reported that AIDS-only treatment strategy could bring down the number of latent individuals moving to active TB stage, and that treatment of latent and active TB cases could equally reduce movement to AIDS stage by individuals infected with HIV. In another paper, Hussaini et al (2016) developed a mathematical model for the transmission dynamics of HIV and Anthroponetic Visceral Leishmaniasis (AVL) coinfection in a population. They showed that the two diseases co-exist, with AVL dominating HIV whenever the reproduction number of each disease is greater than unity. More recently, Nwankwo and Okuonghae (2018) studied the transmission dynamics of HIV Syphilis co-infection when there is treatment for Syphilis. They showed that high treatment rates for primary syphilis (in both singly and dually infected individuals) will result in a significant decrease in the incidence of co-infection of the two diseases in the population. Agusto and Adekunle (2014) developed and analyzed an optimal control model for the co-infection of HIV/AIDS and two strains of tuberculosis. They reported that the most effective control strategy in the fight against HIV/AIDS-TB co-infection

is one that combines the prevention of treatment failure in drug-sensitive tuberculosis infectious individuals and the treatment of individuals with drug-resistant tuberculosis. Niazi and Kalra (2012), in their work titled Diabetes and Tuberculosis: A review of the role of optimal glycemic control, observed that the drugs used to treat tuberculosis (especially rifampicin and isoniazid) interact with oral anti-diabetic drugs and may lead to suboptimal glycemic control. Similarly some of the newer oral anti-diabetic drugs may interact with anti-tuberculosis drugs and lower their efficacy. They therefore concluded that diabetes and tuberculosis interact with each other at multiple levels, each exacerbating the other and that management of patients with concomitant tuberculosis and diabetes differs from that of either disease alone

2.3 Specific Literature

Very few mathematical models have been developed for the co-dynamics of diabetes and tuberculosis. Buotayeb et al (2004) developed a mathematical model for the dynamic population of diabetes and its complications, although they considered the linear and non-linear cases only diabetic patients, due to the complex nature of the non-linear model only results of the linear model were given. Their results showed that high incidence rate of diabetes will lead to high burden of complications and low incidence rate of diabetes will lead to lower burden of complications. Moualen, et al(2012) in their work developed a model for the transmission dynamics of tuberculosis and its impact on diabetes, due to the complex nature of the model dynamics, they could not analyze the complete model, but rather they succeeded in finding the reproduction number for tuberculosis dynamics.Their results suggested that there is a need for increased attention to intervention strategies such as the chemoprophylaxis of tuberculosis latent individuals

and treatment of active TB in people with diabetes. Motivated by the suggestion of Parvaneh, et al (2013), that there is need to develop a model for TB and diabetes co-dynamics that is similar to that of HIV-TB co-infection, the works of Boutayeb, et al (2004) and Moualen, et al(2012) . The present endeavour is to extend the works of Boutayeb, et al (2004) and Moualen, et al(2012) by;

- Developing a comprehensive model for the co-dynamics of diabetes and tuberculosis that incorporates the total human population (both diabetics and non diabetics, tuberculosis infected and non infected population).
- Analysing the complex structured model to give a better public health strategic solution that will drastically lower the burden of the co-dynamics of diabetes and tuberculosis .

These we will be able to achieve by;

- Including compartment for latent tuberculosis infected individuals who have diabetes with complication.
- Including compartment for active tuberculosis infected individuals who have diabetes with complication.
- Including death rates due to complications
- Assessing the impact of tuberculosis treatment on the control of the co-dynamics of diabetes and tuberculosis using optimal control analysis.

These, to the best of our knowledge, have not been done by any previous researcher.

Chapter 3

METHODOLOGY

In this chapter we introduce some of the key mathematical theories and methodologies relevant to this work.

Definition 3.1 Consider the system

$$\dot{x} = f(x); \quad x \in \mathbb{R}^n \tag{3.1}$$

$$\dot{y} = g(y); \quad y \in \mathbb{R}^n, \tag{3.2}$$

where f and g are two $C^r \;\; r \geq 1$ ODEs defined on $\mathbb{R}^n$. The dynamics generated by the vector field f and g of (3.1) and (3.2) are said to be locally C^k conjugate $k \leq \;\; r$ if there exist a C^k diffeomorphism h which takes the orbits of the flow generated by $f \;\; \phi(x,t)$, to the orbits of the flow generated by g, $\nu(t,y)$, preserving orientation and parameterization by time.

Theorem 3.1. *(Hartman and Grobman (Wiggins, 1983)). Consider a $C^r \;\; r \geq 1$ vector field f and the system*

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

With domain of f an open subset of $\mathbb{R}^n$. Suppose also that (3.2) has equilibrium solutions which are hyperbolic. Consider the associated linear ODE system

$$\dot{\xi} = Df(\bar{x})\, x, \quad \xi \in \mathbb{R}^n \tag{3.4}$$

then the flow generated by (3.3) is C^0 conjugate to the flow generated by the linearized system (3.4) in a neighborhood of the equilibrium point.

This theorem guarantees that an orbit structure near a hyperbolic equilibrium solution is topologically-equivalent to the orbit structure given by the associated linearized dynamical system.

3.1 Stability of the Disease Free Equilibrium Point(DFE)

Stability analysis of equilibrium points in a dynamical system is a critical aspect of understanding and predicting system behavior. It involves examining how the system responds to small disturbances and is essential in fields where the dynamics of systems play a significant role.
The stability of an equilibrium point in a dynamical system refers to the behavior of the system in the vicinity of that point when it experiences small perturbations. An equilibrium point is a state where the system's variables remain constant over time. Stability analysis helps determine whether, following a disturbance, the system will return to the equilibrium point (stable), move away indefinitely (unstable), or remain in the perturbed state (neutral or marginally stable).
Understanding the stability of equilibrium points is crucial in various scientific and engineering fields, including physics, biology, economics, and control systems engineering. It helps predict

the long-term behavior of a system and is fundamental for control system design, optimization, and decision-making.

There are two primary types of stability associated with equilibrium points:

(1) Local Stability: Local stability focuses on the behavior of the system in the immediate vicinity of an equilibrium point. It is analyzed by linearizing the system's equations around the equilibrium point, creating a linear approximation. The stability is determined by examining the eigenvalues of the linearized system. If all eigenvalues have negative real parts, the equilibrium point is locally stable. If at least one eigenvalue has a positive real part, the equilibrium point is locally unstable.

(2) Global Stability: Global stability considers the behavior of the system across its entire state space. It assesses whether the equilibrium point is a global attractor, meaning that trajectories from any initial condition in the state space converge to the equilibrium point. Global stability analysis often involves Lyapunov functions, which are scalar functions that provide a measure of how "far" the system is from the equilibrium point. If a Lyapunov function exists that is decreasing over time and reaches a minimum at the equilibrium point, the system is globally stable.

3.1.1 The Next Generation Operator Method

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

$$\bar{x}_i = f(x) = \mathscr{F}_(x) - \mathscr{V}_i(x), \quad i = 1 \cdots, n$$

Where $v_i = \mathscr{V}_i^- - \mathscr{V}_i^+$ and the functions satisfy axioms (M1)-(M5) below:

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

M1 If $x \geq 0$, then $\mathscr{F}_i, \mathscr{V}_i^-, \mathscr{F}_i^+ \geq 0$ for $i = 1, ..., m$;

M2 if $x_i = 0$, then $\mathscr{V}_i^- = 0$. In particular, if $x \in X_s$ then $\mathscr{V}_i^- = 0$ for $i = 1, ..., m$;

M3 $\mathscr{F}_i = 0$ if $i > m$;

M4 if $x \in X_s$ then $\mathscr{F}_i(x) = 0$ and $\mathscr{V}_i^+ = 0$ for $i = 1, ..., m$;

M5 if $F(x)$ is set to zero, then all eigenvalues of $Df(x_0)$ have negative real parts

Lemma 3.1.1. *(van den Driessche and Watmough, 2002). If $\bar{x}$ is a DFE of (3.1) and (3.2) and $\mathscr{F}_i(x)$ satisfy (M1)-(M5), then the derivatives $D\mathscr{F}(\bar{x})$ and $D\mathscr{V}(\bar{x})$ are partitioned as*

$$D\mathscr{F}(\bar{x}) = \begin{bmatrix} F & 0 \\ 0 & 0 \end{bmatrix}, \quad D\mathscr{V}(\bar{x}) = \begin{bmatrix} V & 0 \\ J_3 & J_4 \end{bmatrix} \tag{3.5}$$

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

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

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

Theorem 3.2. *(van den Driessche and Watmough, 2002). Consider the disease transmission model given by (3.1) and (3.2) with $f(x)$ satisfying Axioms (M1)-(M5). If $\bar{x}$ is a DFE of the model, then $\bar{x}$ is locally asymptotically stable (LAS) if $\mathscr{R}_0 = \rho(FV^{-1}) < 1$ (where ρ is spectral radius), but unstable if $\mathscr{R}_0 > 1$.*

3.1.2 Method of Evaluation of Global Asymptotic Stability of The DFE

We will use the approach developed in Castillo Chavez et al(2002) to investigate the global asymptotic stability of the DFE of the system (3.1). Here two conditions are listed such that if met will guarantee the GAS of the DFE.

Firstly, system (3.1) must be written in the form:

$$\begin{aligned} \frac{dX}{dt} &= P(X,Z) \\ \frac{dZ}{dt} &= Q(X,Z), Q(X,0) = 0 \end{aligned} \tag{3.7}$$

where $X \in R^m$ denotes (its components) the number of uninfected individuals and $Z \in R^n$ denotes (its components) the number of infected individuals. $U_0 = (X^*, 0)$ denotes the disease-free equilibrium of this system 3.2. The conditions $(W1)$ and $(W2)$ below must be satisfied in order to guarantee local asymptotic stability:

$(W1)$: For $\frac{dV}{dt} = P(X,0), X^*$is globally asymptotically stable (GAS),

$(W2)$: $Q(X,Z) = BZ - \hat{Q}(X,Z)X, Q(X,Z) \geq 0$ for $(X,Z) \in \Omega$,

where $B = D_Z Q(X^*, 0)$ is an M-matrix (the off-diagonal elements of B are nonnegative) and Ω

is the region where the model makes biological sense. If system (3.1) satisfies the above two conditions then the following theorem holds:

Theorem 3.3. *For the system (3.1), the fixed point $U_0 = (X^*, 0)$ is a globally asymptotic stable (GAS) equilibrium of the system (3.1) provided that $R_0 < 1$ LAS and assumptions $(W1)$ and $(W2)$ are met.*

3.2 Bifurcation Analysis

Bifurcation analysis is a powerful tool in mathematical modeling that unveils the richness and complexity of a system's behavior as parameters are varied. Understanding bifurcations is essential for making predictions, designing control strategies, and gaining insights into the intricate dynamics of complex systems.

Bifurcation is a phenomenon in dynamical systems theory where the qualitative behavior of the system undergoes a qualitative change as a parameter is varied. In other words, as a system's parameters are modified, the system transitions from one type of behavior to another. This can involve the creation or destruction of equilibrium points, periodic orbits, or other invariant sets, leading to a significant alteration in the system's dynamics.

The importance of bifurcation in a mathematical model equation lies in its ability to reveal the complex and often unexpected behaviors that a system can exhibit. Bifurcation analysis helps researchers and scientists understand how a system responds to changes in its parameters and provides insights into the stability, periodicity, and bifurcation structure of the system.

The following are the importance of bifurcation in mathematical modeling:

1 Diversity of Behaviors: Bifurcation analysis helps uncover verious possible behavious of a system. Depending on the values of the parameters, a system can exhibit stable

equilibrium points, periodic oscillations, chaotic behavior, or other dynamic patterns.

2 Identification of Critical Points: Bifurcation points often correspond to critical values of parameters where significant changes occur in the system's behavior. Identifying these points is crucial for understanding the system's overall dynamics and stability.

3 Parameter Sensitivity: Bifurcation analysis helps identify regions in parameter space where the system is particularly sensitive to changes. Understanding these sensitive regions is essential for robust system design and control.

4 Prediction of Transitions: Bifurcation analysis allows researchers to predict and understand transitions between different dynamic regimes. This is particularly valuable for anticipating sudden and drastic changes in the system's behavior as parameters are varied.

5 Model Validation: Bifurcation analysis provides a means to validate mathematical models. By comparing model predictions with observed bifurcation patterns in real-world systems, researchers can refine and improve their models to better represent the actual dynamics.

6 Understanding Complexity: Bifurcation phenomena contribute to our understanding of the inherent complexity of dynamic systems. The ability to predict and control bifurcations is essential for managing complex systems in various scientific, engineering,

and biological applications.

7 Control and Optimization: In fields like control theory and optimization, bifurcation analysis aids in designing control strategies or optimizing parameters to achieve desired system behavior while avoiding undesirable bifurcations.

Backward and forward bifurcation are specific types of bifurcation phenomena observed in dynamical systems when parameters are varied. These phenomena are characterized by changes in the stability and structure of equilibrium points, and they play a significant role in understanding the behavior of complex systems.

Forward bifurcation occurs when an equilibrium point undergoes a qualitative change in its stability as a parameter is increased. In this case, a stable equilibrium point becomes unstable or a new stable equilibrium point is created as the parameter crosses a critical value. Forward bifurcation is often associated with the creation of limit cycles or other periodic behaviors. This type of bifurcation is crucial in studying the emergence of oscillatory or periodic solutions in a system as a parameter is changed.

Backward bifurcation, on the other hand, occurs when the stability of an equilibrium point changes as a parameter is decreased. In backward bifurcation, a stable equilibrium point becomes unstable or a new stable equilibrium is created as the parameter decreases below a critical value. This type of bifurcation is often associated with the coexistence of multiple stable equilibrium points. Backward bifurcation is particularly important in the context of infectious

disease models. It can lead to the persistence of an infectious disease even when the transmission rate is below a certain threshold.

The following are importance of backward bifurcation in a dynamical system:

1 Epidemiology: In epidemiological models, backward bifurcation is crucial in understanding the persistence of infectious diseases, especially in scenarios where the transmission rate is reduced but the disease persists due to the coexistence of multiple equilibria.

2 Climate Modeling: Bifurcation phenomena, including both forward and backward bifurcation, are important in climate modeling. Changes in climatic parameters can lead to bifurcations in climate systems, influencing long-term climate patterns.

3 Control and Optimization: Understanding forward and backward bifurcations is essential in control theory and optimization. These phenomena can guide the design of control strategies to avoid undesired states or to achieve specific objectives in a system.

4 Ecology: Bifurcation analysis is vital in ecological modeling. It helps explain shifts in ecosystems, such as the sudden emergence or disappearance of species, in response to changing environmental conditions.

5 Engineering Systems: In engineering, particularly in control systems, bifurcation analysis aids in designing systems that exhibit desired behaviors while avoiding unwanted states.

The following theorem is used to establish the presence of backward bifurcation phenomenon for the models considered in the dissertation.

Theorem 3.4. *(Castillo-chavez & Song 2004).*

Consider the following system of ordinary differential equations with a parameter ϕ:

$$\frac{dx}{dt} = f(x,\phi), \quad f : \mathbb{R}^n \times \mathbb{R} \text{ and } f \in C^2(\mathbb{R}^n \times \mathbb{R}) \tag{3.8}$$

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

A1: $\Lambda = D_x f(0,0) = \left(\frac{df_i}{dx_j(0,0)}\right)$ *is the linearization matrix of the system* (3.8) *around the equilibrium 0 with evaluated at 0. Zero is a simple eigenvalue of A and other eigenvalues of A negative real part;*

A2: Matrix A has a right eigenvector w and a left eigenvector v (each corresponding to the zero eigenvalue).

Let f_k be the kth component of f and

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

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

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

- *$a < 0, b < 0$ when $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable; when $0 < \phi \ll 1$, asymptotically stable equilibrium, and there exist a positive unstable equilibrium;*

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

- *$a < 0, b > 0$ When ϕ changes from negative to positive, 0 changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable.*

  Particularly, if $a > 0, b > 0$ then a backward bifurcation occurs at $\phi = 0$

3.3 Optimal Control

Optimal control theory allows us to understand and make decisions regarding complex biological events by adjusting a control variable. It is a standard approach used to find a set of control strategies that will optimize the outcome of a physical system. Typically we have a deterministic mathematical model consisting of state variable(s) which describe the behavior of the underlying dynamical system that will be controlled. We can change the behavior of the state variable(s) by adjusting the control function(s). An additional component to an optimal control problem is a set of variable constraints that properly define the components of the model. Following the approach used by Lenhart et al(2010). Given a piecewise continuous control function $u(t)$, there exists an associated continuous and piecewise differentiable state variable $x(t)$ defined on some finite time interval $[t_0, t_1]$ that solves, $x'(t) = g(t, x(t), u(t))$, with the initial condition $x(t_0) = x_0$. The goal is to find an optimal control $u^*(t)$ that either maximizes or

minimizes the objective functional J(u). In the case of a minimization problem,

$$J(u^*) = \min J(u)$$

where

$$J(u) = \int_{t_0}^{t_1} f(t, x(t), u(t))dt$$

Here, f and g are continuously differentiable functions of their arguments. The objective functional depends on both the state and control variables and will balance judiciously the desired goal with the required cost to reach it. The principle technique for this optimal control problem is to solve a set of necessary conditions that an optimal control and corresponding state must satisfy. These first order necessary conditions are given by Pontryagin's Maximum Principle.

Theorem 3.5. *(Pontryagin's Maximum Principle:). If $u^*(t)$ and $x^*(t)$ are optimal for*

$$\max_u \int_{t_0}^{t_1} f(t, x(t), u(t))dt$$

subject to

$$x'(t) = g(t, x(t), u(t))$$

$$x(t_0) = x_0, x(t_1)$$

then there exist a piecewise differentiable adjoint variable $\lambda(t)$ such that

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

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

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

and

$$\lambda'(t) = -\frac{\partial H(t, x^*(t), u^*(t), \lambda(t))}{\partial x}$$

$$\lambda(t_1) = 0$$

The final time condition on the adjoint variable is called the transversality condition. This principle outlined in Theorem 3.5 changes the problem of finding the control that maximizes the objective functional subject to the state ordinary differential equation(s) and initial condition(s) to the problem of optimizing the Hamiltonian pointwise. By maximizing the Hamiltonian H with respect to $u(t)$ at $u^*(t)$ we obtain the following necessary conditions:

$$\begin{aligned} \frac{\partial H}{\partial u} = 0 &\implies f_u + \lambda g_u = 0 \\ \lambda' = -\frac{\partial H}{\partial u} &\implies \lambda' = -(f_x + g_x) \\ \lambda(t_1) = 0 & \end{aligned}$$

These are referred to as the optimality condition, adjoint equation, and transversality condition respectively. In addition, in a maximization problem, for each $t \in (t_0, t_1)$

$$\frac{\partial^2 H}{\partial u^2} \leq 0 \text{ at } u^*(t)$$

must hold from concavity. To obtain a genuine solution in optimal control, many of the real world optimal control problems require bounds on the controls in which case Pontryagin's

Maximum Principle still holds. In order to solve optimal problems as mentioned above with control bounds, we have $a \leq u(t) \leq b$ where a and b are fixed real constants and $a < b$.

3.4 Numerical Analysis/Simulation

Numerical analysis plays a vital role in scientific and engineering disciplines, providing practical tools for solving mathematical problems in situations where analytical methods are not feasible. It has wide-ranging applications in areas such as physics, engineering, finance, computer science, and more.

Simulation in numerical analysis refers to the process of using a computer to model the behavior of a system, process, or phenomenon through the implementation of numerical methods and algorithms. This approach is particularly useful when it is impractical or impossible to analyze a system analytically or experimentally. Simulation involves representing the essential features of a system mathematically, using numerical techniques to solve the corresponding equations, and then observing the system's behavior over time or under various conditions.

Numerical analysis and simulation are crucial tools when dealing with model equations, especially in situations where analytical solutions are challenging or impossible to obtain. The need for numerical analysis and simulation arises from the complexity and nonlinearity of many real-world problems. These methods provide practical tools for exploring, analyzing, and understanding systems described by model equations, offering insights that would be challenging or impossible to obtain through analytical means alone.

For numerical simulation of our model, we will use fourth-order Runge-Kutta method in mathlab.

3.5 Model formulation

In this proposed model, we assumed that human population is classified based on their diabetic status and tuberculosis status. We also assumed random mixing of the population, and that non-diabetic individual is potentially diabetic.

The model sub-divides the human population into the following classes: Susceptible individuals to both diabetes and tuberculosis, $(S(t))$, individuals with diabetes without complication susceptible to tuberculosis $(S_D(t))$, latently tuberculosis infected individuals who are potentially diabetics $(L(t))$, infectious individuals who are potentially diabetics $(I(t))$, individuals that recovered from tuberculosis who are potentially diabetics $(R_T(t))$, individuals with diabetes without complication but are latently infected $(L_D(t))$, individual with diabetes without complication but with active tuberculosis $(I_D(t))$, individuals that recovered from tuberculosis but has diabetes without complication $(R_D(t))$, individuals with diabetes with complication who are latently infected with tuberculosis $(L_C(t))$ and individuals with diabetes with complication but with active tuberculosis $(I_C(t))$.

Hence the total human population at time, t, denoted by $N(t)$ is given by

$$N(t) = S(t) + S_D(t) + L(t) + I(t) + R_T(t) + L_D(t) + I_D(t) + R_D(t) + L_C(t) + I_C(t) \tag{3.9}$$

3.5.1 Model Assumptions

- We assumed that transmission of tuberculosis occur due to adequate contact between susceptible individuals and infectious individuals and that susceptible individuals are first latently infected as a result of contact with actively and latently infected individuals at the

rate λ given by

$$\lambda = \beta \frac{(I + \eta_1 I_D + \eta_2 I_C)}{N} \tag{3.10}$$

where $\eta_2 > \eta_1 > 1$, η_1 and η_2 are modification parameters and β is the effective contact rate of diabetics and non-diabetics infectious individuals that is sufficient to transmit infection to diabetes and non-diabetics susceptible individuals, $\eta_2 > \eta_1$ implies that the infection rate for infectious individuals with complication is greater than that of individuals without complication.

- That individuals who recover from tuberculosis infection can be reinfected and reactivation can also take place as a result of immune suppression due to diabetes, incomplete medication, etc.

- That individuals will first develop latent tuberculosis before developing active tuberculosis.

- The individuals that are diabetic can easily contact tuberculosis because of the suppressed immunity;

- The co-infection is such that the individual will first becom diabetic before contaction tuberculosis.

Table 3.1: Description of variables and parameters in the model equation

Variable	**Interpretation**
S	Susceptible individuals to both diabetes and tuberculosis
S_D	individuals with diabetes without complication susceptible to tuberculosis
L	Individuals with latent tuberculosis who are potential diabetic
I	Individuals with active tuberculosis who are potential diabetic
R_T	Tuberculosis recovered individuals who are potential diabetic
L_D	Individuals who have diabetes without complication but have latent tuberculosis
I_D	Individuals with active tuberculosis who have diabetes without complication
R_D	Individuals who have recovered for tuberculosis but have diabetes without complication
L_C	Individuals who have diabetes with complication but have latent tuberculosis
I_C	Individuals with active tuberculosis who have diabetes with complication
Parameter	**Interpretation**
Λ	Recruitment level
μ	Natural death rate
λ	Force of infection
β	TB Contact rate between infectious and uninfected individuals
α_1	Rate of acquiring diabetes without complication
α_2	Rate of acquiring diabetes with complication
τ_1	Modification parameter for increased rate of acquiring diabetes without complication due to active tuberculosis
τ_2	Modification parameter for increased rate of acquiring diabetes with complication due to active tuberculosis
ψ_1	Modification parameter for rate of acquiring diabetes by individuals who recovered from active tuberculosis
θ	Modification parameter for increased infection rate due to diabetes without complication
ξ_1	Re−infection rate for individuals who recovered from tuberculosis
ξ_2	Re−infection rate for individual who recovered from tuberculosis but have diabetes without complication
k_1	Re−activation rate for latent tuberculosis individuals who are potential diabetics
k_2	Re−activation rate for laent tuberculosis individuals who have diabetes without complication
k_3	Re−activation rate for laent tuberculosis individuals who have diabetes with complication
σ_1	Exogenous re−infection rate for latent tuberculosis infected individuals who are potential diabetics
σ_2	Exogenous re−infection rate for latent tuberculosis infected individuals who have diabetes without complication
σ_3	Exogenous re−infection rate for latent tuberculosis infected individuals who have diabetes with complication
r_1	Recovery rate for active tuberculosis individuals without diabetes

r_2	Recovery rate for active tuberculosis individuals who have diabetes without complication
r_3	Recovery rate for active tuberculosis individuals who have diabetes with complication
d_1	Death rate due to active tuberculosis for individuals without diabetes
d_2	Death rate due to active tuberculosis for individuals with diabetes without complication
d_3	Death rate due to active tuberculosis for individuals with diabetes with complication
δ_1	Death rate due to complication for L_C compartment
δ_2	Death rate due to complication for I_C compartment

3.5.2 Description of Model Equation

The population of the susceptible class to both diseases is generated at the recruitment level Λ of those that are neither diabetic nor infected with tuberculosis through birth or immigration. The population is decreased by the rate λ at which some of them becomes infected with tuberculosis, it is also reduced by the rate α_1 at which they develop diabetes without complication, it is further reduced by natural death at the rate μ. Thus we have,

$$\frac{dS}{dt} = \Lambda - (\lambda + \alpha_1 + \mu)S \tag{3.11}$$

The population of the class of individuals who are diabetic without complication but are susceptible to tuberculosis (S_D) is generated when non diabetic individuals develop diabetes without complication (at the rate α_1), it is decreased by tuberculosis infection as a result of contact with the infectious individuals at the rate $\theta\lambda$ where θ is the modification parameter. This population is further decreased by natural death. Thus we have,

$$\frac{dS_D}{dt} = \alpha_1 S - \theta\lambda S_D - \mu S_D \tag{3.12}$$

The population of latently infected individual who are potential diabetic (L) is generated by the infection of non-diabetic individuals (at the rate λ), it is increased by the population of

individuals who recovered from tuberculosis infection but got re-infected as a result of contact with infectious individuals (at the rate $\xi_1\lambda$). The population is decreased by reactivation of the latent tuberculosis (at the rate k_1) this reactivation occurs as a result of incomplete treatment, old age, physical inactivity, obesity or lack of exercise and suppressed immunity, it is also decreased through exogenous re-infection of the previously infected individuals(at the rate $\sigma_1\lambda$). The population is further decreased by natural death. Thus we have,

$$\frac{dL}{dt} = \lambda(S+\xi_1 R_T) - (k_1+\sigma_1\lambda)L - \mu L \tag{3.13}$$

The population of the infectious individuals who are potential diabetics (I) is generated by the reactivation of latent tuberculosis infection as a result of supressed immunity (at the rate k_1); it is also increased through exogenous re-infection of latent infected individuals (at the rate $\sigma_1\lambda$). The population is decreased at the rate $\tau_1\alpha_1$ at which individuals acquired diabetes as a result of glucose intolerance due to tuberculosis medication, old age, physical inactivity, obesity or lack of exercise; they are also decreased as a result of recovery from tuberculosis (at the rate r_1). The population is further decreased as a result of death due to the disease (at the rate d_1) and through natural death. Thus we have

$$\frac{dI}{dt} = (k_1+\sigma_1\lambda)L - \tau_1\alpha_1 I - (r_1+d_1+\mu)I \tag{3.14}$$

The population of the tuberculosis recovered class who are potential diabetics (R_T) is increased by the recovery of individual in the $I-$class (at the rate r_1). It is reduced by reinfection as a result of effective contact with infected individual (at the rate $\xi_1\lambda$) and it is further reduced by

development of diabetes (at the rate $\psi_1\alpha_1$) and natural death. Thus we have

$$\frac{dR_T}{dt} = r_1 I - \lambda\xi_1 R_T - \psi_1\alpha_1 R_T - \mu R_T \tag{3.15}$$

The population of individuals who have diabetes without complication but are latently infected with tuberculosis (L_D) is increased when individuals in the S_D- class become infected with tuberculosis (at the rate $\theta\lambda$), they are further increased by re-infection of previously recovered from the TB infection but have diabetes without complication (at the rate $\lambda\xi_2$). The population is decreases by reactivation of the TB infection on individuals who have previously recovered from TB but are diabetic without complication (at the rate k_2). It is further decreased by exogenous re-infection of the previously infected individuals in the L_D- class (at the rate $\sigma_2\lambda$). It is further decreased when individuals acquire diabetes with complication or develop complication due to diabetes (at the rate α_2), and through natural death. Therefore we have

$$\frac{dL_D}{dt} = \lambda(\theta S_D + \xi_2 R_D) - (k_2 + \sigma_2\lambda)L_D - \alpha_2 L_D - \mu L_D \tag{3.16}$$

The population of individuals who have diabetes without complication but with active tuberculosis is increased by reactivation of tuberculosis of individuals in L_D- class (at the rate k_2), it is further increased by exogenous re-infection of previously infected individuals (at the rate $\sigma_2\lambda$). The population is also increased when individuals in I- class develop diabetes without complication (at the rate $\tau_1\alpha_1$). The population is reduced as a result of development of diabetes with complication (at the rate $\tau_2\alpha_2$). It is also decreased as a result of recovery from tuberculosis (at

the rate r_2), death due to the disease (at the rate d_2) and natural death. Therefore we have

$$\frac{dI_D}{dt} = (k_2 + \sigma_2\lambda)L_D + \tau_1\alpha_1 I - \tau_2\alpha_2 I_D - (r_2 + d_2 + \mu)I_D \tag{3.17}$$

The population of individuals who recovered from tuberculosis but have diabetes without complication $(R_D(t))$, is generated when individuals with active tuberculosis who have diabetes without complication recover from the TB disease (at the rate r_2). It is further increased when individuals who recovered from tuberculosis develop diabetes without complication (at the rate $\psi_1\alpha_1$), it is also increased when individuals who have active tuberculosis but with diabetes with complication recover from tuberculosis (at the rate r_3). The population is decreased when individuals in the class got re-infected (at the rate $\lambda\xi_2$) and through natural death. Thus we have

$$\frac{dR_D}{dt} = r_2 I_D + \psi_1\alpha_1 R_T + r_3 I_C - \lambda\xi_2 R_D - \mu R_D \tag{3.18}$$

The population of individuals who are latently infected with tuberculosis but have diabetes with complication $(L_C(t))$, is increased when latently infected individuals who have diabetes without complication develop complication, it is also reduced by reactivation and exogenous reinfection (at the rate k_3 and $\sigma_3\lambda$ respectively), it is further decreased by death due to complication (at the rate δ_1) and through natural death.

$$\frac{dL_C}{dt} = \alpha_2 L_D - (k_3 + \sigma_3\lambda)L_C - (\delta_1 + \mu)L_C \tag{3.19}$$

Finally, the population of actively infectious individuals who have diabetes with complication $(I_C(t))$, is generated by reactivation and exogenous re-infection of latently infected individuals

who have diabetes with complication (at the rate k_3 and $\sigma_3\lambda$ respectively), it is further increased when infectious individuals who have diabetes develop complication (at the rate $\tau_2\alpha_2$). This population is decreased by recovery of tuberculosis (at the rate r_3), death due to tuberculosis (at the rate d_3), death due to complication (at the rate δ_2) and natural death. Thus we have

$$\frac{dI_C}{dt} = (k_3+\sigma_3\lambda)L_C + \tau_2\alpha_2 I_D - (r_3+d_3+\delta_2+\mu)I_C \tag{3.20}$$

Based on the above formulations and assumptions, the co-infection model for the co-dynamics of diabetics and tuberculosis given by the following differential equations:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - (\lambda+\alpha_1+\mu)S \\
\frac{dS_D}{dt} &= \alpha_1 S - \theta\lambda S_D - \mu S_D \\
\frac{dL}{dt} &= \lambda(S+\xi_1 R_T) - (k_1+\sigma_1\lambda)L - \mu L \\
\frac{dI}{dt} &= (k_1+\sigma_1\lambda)L - \tau_1\alpha_1 I - (r_1+d_1+\mu)I \\
\frac{dR_T}{dt} &= r_1 I - \lambda\xi_1 R_T - \psi_1\alpha_1 R_T - \mu R_T \\
\frac{dL_D}{dt} &= \lambda(\theta S_D + \xi_2 R_D) - (k_2+\sigma_2\lambda)L_D - \alpha_2 L_D - \mu L_D \\
\frac{dI_D}{dt} &= (k_2+\sigma_2\lambda)L_D + \tau_1\alpha_1 I - \tau_2\alpha_2 I_D - (r_2+d_2+\mu)I_D \\
\frac{dR_D}{dt} &= r_2 I_D + \psi_1\alpha_1 R_T + r_3 I_C - \lambda\xi_2 R_D - \mu R_D \\
\frac{dL_C}{dt} &= \alpha_2 L_D - (k_3+\sigma_3\lambda)L_C - (\delta_1+\mu)L_C \\
\frac{dI_C}{dt} &= (k_3+\sigma_3\lambda)L_C + \tau_2\alpha_2 I_D - (r_3+d_3+\delta_2+\mu)I_C
\end{aligned} \tag{3.21}$$

with the corressponding initial conditions

$$S(0) \geq 0, S_D(0) \geq 0, L(0) \geq 0, I(0) \geq 0, R_T(0) \geq 0, L_D(0) \geq 0, I_D(0) \geq 0, R_D(0) \geq 0, L_C(0) \geq 0, I_C(0) \geq 0. \quad (3.22)$$

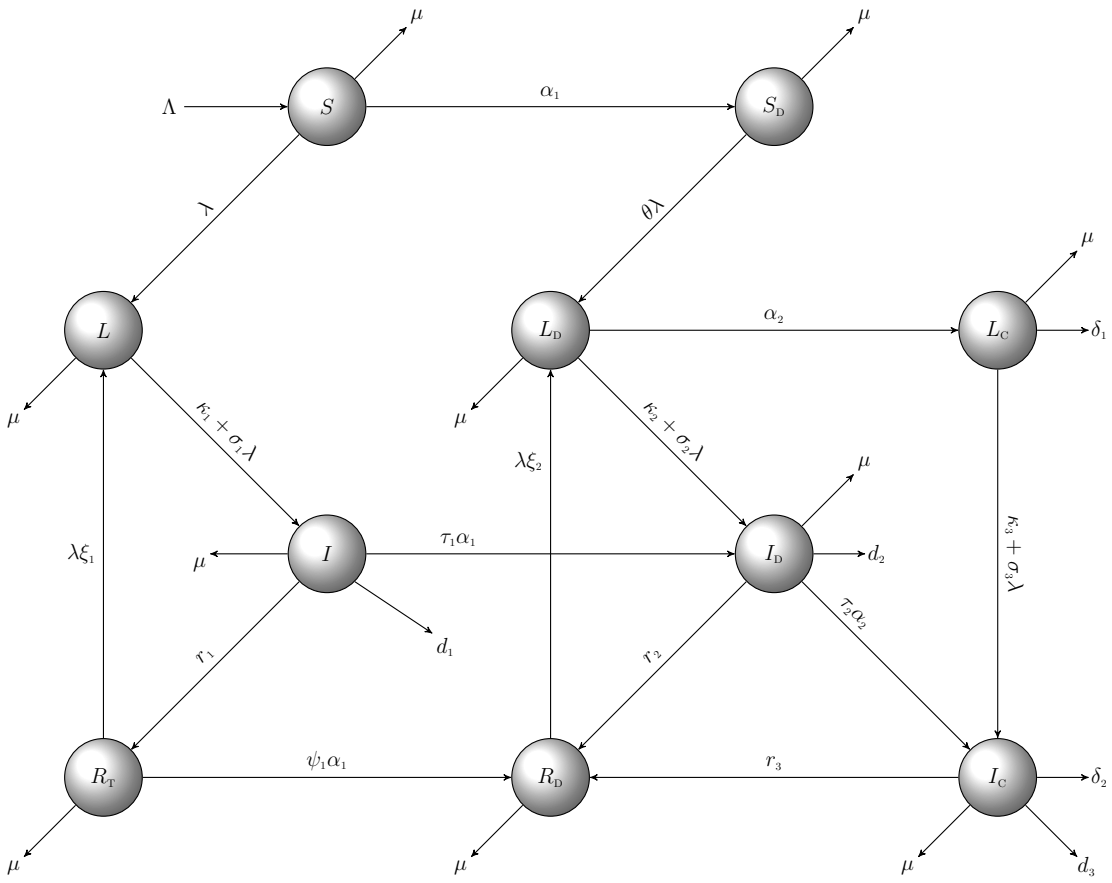


Figure 3.1: Diagram of the model

Chapter 4

RESULTS AND DISCUSSION

In this chapter, we will be analyzing our formulated model and as well discuss the results obtained.

4.1 Basic Properties of The Model

Our aim is to obtain from our analyses results that will be applicable to real life situations. Therefore it is important to show that our model is epidemiologically and mathematically well-posed. This we will prove by ascertaining that all state variables will remain positive for all time t and will also be enclosed within a defined feasible region.

4.1.1 Positivity of Solution

For the model (3.21) to be epidemiologically meaningful, it is appropriate to show that all its state variables are non-negative over time.

Theorem 4.1. *For the model* (3.21) *,let the initial data be* $S > 0, S_D > 0, L > 0, I > 0, R_T > 0, L_D > 0, I_D > 0, R_D > 0, L_C > 0, I_C > 0$. *Then the solutions* $(S, S_D, L, I, R_T, L_D, I_D, R_D, L_C, I_C)$

of the model are positive for all time $t > 0$.

Proof. Let

$t_1 = \sup\{t > 0 : S > 0, S_D > 0, L > 0, I > 0, R_T > 0, L_D > 0, I_D > 0, R_D > 0, L_C > 0, I_C > 0\}$.

Taking the first equation of the model (3.21)

$$\frac{dS}{dt} = \Lambda - (\lambda + \alpha_1 + \mu)S$$

re-writing it in the form

$$\frac{d}{dt}\left\{S(t)\exp\left[\int_0^t \lambda(u)du + \alpha_1 t + \mu t\right]\right\} = \Lambda\exp\left[\int_0^t \lambda(u)du + \alpha_1 t + \mu t\right],$$

so that

$$\left\{S(t_1)\exp\left[\int_0^{t_1} \lambda(u)du + \alpha_1 t_1 + \mu t_1\right]\right\} - S(0) = \Lambda\int_0^{t_1}\exp\left[\int_0^x \lambda(u)du + \alpha_1 x + \mu x\right]dx,$$

hence

$$S(t_1) = S(0)\exp\left[-\int_0^{t_1} \lambda(u)du - \alpha_1 t_1 - \mu t_1\right] + \exp\left[-\int_0^{t_1} \lambda(u)du - \alpha_1 t_1 - \mu t_1\right]$$
$$\times \Lambda\int_0^{t_1}\exp\left[\int_0^x \lambda(u)du + \alpha_1 x + \mu x\right]dx > 0.$$

Following an argument similar as above, we can prove that:

$S_D > 0, L > 0, I > 0, R_T > 0, L_D > 0, I_D > 0, R_D > 0, L_C > 0, I_C > 0$.

□

4.1.2 Invariant Region

The model (3.21) will be analyzed in a biologically feasible region as follows.

$$\mathscr{D} = \left\{ (S, S_D, L, I, R_T, L_D, I_D, R_D, L_C, I_C) \in \mathfrak{R}_+^{10} : N \leq \frac{\Lambda}{\mu} \right\}. \tag{4.1}$$

where $N = S + S_D + L + I + R_T + L_D + I_D + R_D + L_C + I_C$ To establish the positive invariance of $\mathscr{D}$.

Add all the equations of system (3.21) gives

$$\frac{dN}{dt} = \Lambda - \mu N(t) - [d_1 I + d_2 I_D + \delta_1 L_C + (d_3 + \delta_2) I_C]. \tag{4.2}$$

which gives

$$\Lambda - (\mu N(t) - [d_1 I + d_2 I_D + \delta_1 L_C + (d_3 + \delta_2) I_C]) \leq \frac{dN}{dt} < \Lambda - \mu N, \tag{4.3}$$

From Comparison theorem by Lakshmikantham et al (1989) we have that, $N(t) \leq \frac{\Lambda}{\mu}$ if $N(0) \leq \frac{\Lambda}{\mu}$.

Hence, the region $\mathscr{D}$ is positively invariant. Therefore, it is sufficient to consider the dynamics of the flow generated by the system (3.21) in $\mathscr{D}$. Thus, within this region, the model (3.21) is said to be epidemiologically and mathematically well-posed. which means that, every solution of the model (3.21) with initial conditions in $\mathscr{D}$ will remain in $\mathscr{D}$ for all time $t \geq 0$. This result is summarized as follows;

Lemma 4.1.1. *For the system* (3.21)*, the region* $\mathscr{D} \subset \mathfrak{R}_+^{10}$ *is positively-invariant with initial conditions in* $\mathfrak{R}_+^{10}$.

4.1.3 Disease-Free Equilibrium

The system (3.21) has a disease-free equilibrium (DFE) obtained by setting the left hand side of the system (3.21) and the infected classes to zero and solve for the state variable. thus the DFE exists and is given by

$$D_0 = (S^*, S_D^*, L^*, I^*, R_T^*, L_D^*, I_D^*, R_D^*, L_D^*, I_C^*) = (S^*, S_D^*, 0, 0, 0, 0, 0, 0, 0, 0) \tag{4.4}$$

where $S^* = \frac{\Lambda}{\mu+\alpha_1}$ and

$$S_D* = \frac{\alpha_1 S^*}{\mu} = \frac{\alpha_1 \Lambda}{\mu(\mu+\alpha_1)}$$

4.2 Analysis of the Model

4.2.1 Local Stability of the Disease-Free Equilibrum(DFE)

The local asymptotic stability of the DFE of the system (3.21) will be obtained by applying the Next Generation Operator Method on the system (3.21) .Using the same notation as used in Vanden Driessche(2002) , the matrix f_i (of new infections) is given by

$$f = \begin{bmatrix} \lambda S \\ 0 \\ \theta \lambda S_D \\ 0 \\ 0 \\ 0 \end{bmatrix} \tag{4.5}$$

evaluation of f_i at the DFE we have the matrix

$$F = \begin{bmatrix} 0 & \frac{\beta S^*}{N^*} & 0 & \frac{\eta \beta S^*}{N^*} & 0 & \frac{\eta_2 \beta S^*}{N^*} \\ 0 & 0 & 0 & 0 & 0 & \\ 0 & \frac{\theta \beta^* S_D^*}{N^*} & 0 & \frac{\theta \eta_1 \beta S_D^*}{N^*} & 0 & \frac{\theta \eta_2 \beta S_D^*}{N^*} \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix} \tag{4.6}$$

the matrix $v_i = v_i^- - v_i^+$(of transfer individuals between compactments) is given by

$$v_i^- = \begin{bmatrix} (k_1 + \sigma_1 \lambda + \mu)L \\ (\tau_1 \alpha_1 + r_1 + d_1 + \mu)I \\ (k_2 + \sigma_2 \lambda + \alpha_2 + \mu)L_D \\ (\tau_2 \alpha_2 + r_2 + d_2 + \mu)I_D \\ (k_3 + \sigma_3 \lambda + \delta_1 + \mu)L_C \\ (r_3 + d_3 + \delta_2 + \mu)I_C \end{bmatrix} \tag{4.7}$$

$$v_i^+ = \begin{bmatrix} \lambda\xi_1 R_T \\ (k_1+\sigma_1\lambda)L \\ \lambda\xi_2 R_D \\ (k_2+\sigma_2\lambda)L_D + \tau_1\alpha_1 I \\ \alpha_2 L_D \\ (k_3+\sigma_3\lambda)L_C + \tau_2\alpha_2 I_D \end{bmatrix} \tag{4.8}$$

$$v_i = \begin{bmatrix} (k_1+\sigma_1\lambda+\mu)L - \lambda\xi_1 R_T \\ (\tau_1\alpha_1 + r_1 + d_1 + \mu)I - (k_1+\sigma_1\lambda)L \\ (k_2+\sigma_2\lambda+\alpha_2+\mu)L_D - \lambda\xi_2 R_D \\ (\tau_2\alpha_2 + r_2 + d_2 + \mu)I_D - (k_2+\sigma_2\lambda)L_D - \tau_1\alpha_1 I \\ (k_3+\sigma_3\lambda+\delta_1+\mu)L_C - \alpha_2 L_D \\ (r_3 + d_3 + \delta_2 + \mu)I_C - (k_3+\sigma_3\lambda)L_C - \tau_2\alpha_2 I_D \end{bmatrix} \tag{4.9}$$

evaluation of v_i at the DFE we have the matrix

$$V = \begin{bmatrix} G_1 & 0 & 0 & 0 & 0 & 0 \\ -k & G_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & G_3 & 0 & 0 & 0 \\ 0 & -\tau_1\alpha_1 & -k_2 & G_4 & 0 & 0 \\ 0 & 0 & -\alpha_2 & 0 & G_5 & 0 \\ 0 & 0 & 0 & -\tau_2\alpha_2 & k_3 & G_6 \end{bmatrix} \tag{4.10}$$

By van dan Driessche and watmough (2002), the basic reproduction number of the system (3.21) is

$$R_0 = \rho FV^{-1}$$
$$= \frac{\beta(G_1G_2S_D^*\theta[G_4 4k_3\alpha_2\eta_2 + G_5k_2(G_6\eta_1 + \alpha_2\eta_2\tau_2)] + S^*G_3G_5k_1[G_4G_6 + \alpha_1\tau_1(G_4G_6 + \alpha_1\tau_1(G_6\eta_1 + \alpha_2\eta_2\tau_2)])}{G_1G_2G_3G_4G_5G_6N^*} \tag{4.11}$$

$$R_0 = \frac{\beta\Phi}{G_1G_2G_3G_4G_5G_6N^*} \tag{4.12}$$

where

$$\Phi = (G_1G_2S_D^*\theta[G_4k_3\alpha_1\eta_2 + G_5k_2(G_6\eta_1 + \alpha_2\eta_2\tau_2)] + S^*G_3G_5k_1[G_4G_6 + \alpha_1\tau_1(G_4G_6 + \alpha_1\tau_1(G_6\eta_1 + \alpha_2\eta_2\tau_2)]) \tag{4.13}$$

and

$$\left.\begin{aligned} G_1 &= k_1 + \mu \\ G_2 &= \tau_1\alpha_1 + r_1 + d_1 + \mu \\ G_3 &= k_2 + \alpha_2 + \mu(k_2 + \alpha_2 + \mu) \\ G_4 &= \tau_2\alpha_2 + r_2 + d_2 + \mu \\ G_5 &= k_3 + \delta_1 + \mu \\ G_6 &= r_3 + d_3 + \delta_2 + \mu \end{aligned}\right\} \tag{4.14}$$

and

$$N^* = \frac{\Lambda}{\mu} \tag{4.15}$$

Hence, the following result;

Lemma 4.2.1. *The DFE of the system* (3.21) *is locally asymptotically stable (LAS) when ever* $R_0 \leq 1$ *and unstable if* $R_0 \geq 1$.

4.2.2 Global Asymptotic Stability of the DFE

Using the approach developed in Castillo Chavez et al(2002) to investigate the global asymptotic stability of the DFE of the system (3.1).

Theorem 4.2. *For the system* (3.21)*, the fixed point* $U_0 = (X^*, 0)$ *is a globally asymptotic stable (GAS) equilibrium point of the system* (3.21) *provided that* $R_0 < 1$ *(LAS) and assumptions* $(W1)$ *and* $(W2)$ *are met.*

Proof. Recall that the two conditions are

$(W1)$: For $\frac{dX}{dt} = P(X,0), X^*$is globally asymptotically stable (GAS),

$(W2)$: $Q(X,Z) = BZ - \hat{Q}(X,Z)X, Q(X,Z) \geq 0$ for $(X,Z) \in \Omega$,

where $B = D_Z Q(X^*, 0)$ is an M-matrix (the off-diagonal elements of B is nonnegative) and Ω is the region where the model makes biological sense. For the system (3.21) we have that

$$\frac{dX}{dt} = P(X,Z) = \begin{bmatrix} \Lambda - (\alpha_1 + \lambda + \mu)S \\ \alpha_1 S - \theta\lambda S_D - \mu S_D \\ r_1 I - \lambda\xi_1 R_T - \varphi_1\alpha_1 R_T - \mu R_T \\ r_2 I_D + \varphi_1\alpha_1 R_T - \lambda\xi_2 R_D + r_3 I_C - \mu R_D \end{bmatrix} \tag{4.16}$$

and

$$\frac{dX}{dt} = P(X,0) = \begin{bmatrix} \Lambda - (\alpha_1 + \mu)S \\ \alpha_1 S - \mu S_D \\ 0 \\ 0 \end{bmatrix} \tag{4.17}$$

This implies that

$$X^* = (\frac{\Lambda}{\alpha_1 + \mu}, \frac{\alpha_1\Lambda}{\mu(\mu + \alpha_1)}, 0, 0, 0, 0, 0, 0, 0, 0) \tag{4.18}$$

is the global asymptotic point.

Also

$$\frac{dZ}{dt} = Q(X,Z) = \begin{bmatrix} \lambda(S+\xi_1 R_T) - (k_1+\sigma_1\lambda)L - \mu L \\ (k_1+\sigma_1\lambda)L - (\tau_1\alpha_1 + r_1 + d_1 + \mu)I \\ \lambda(\theta S_D + \xi_2 R_D) - \sigma_2\lambda L_D - (k_2+\alpha_2+\mu)L_D \\ (K_2+\sigma_2\lambda)L_D + \tau_1\alpha_1 I - \tau_2\alpha_2 I_D - (r_2+d_2+\mu)I_D \\ \alpha_2 L_D - (k_3+\sigma_3\lambda)L_C - (\delta_1+\mu)L_C \\ (K_3+\sigma_3\lambda)L_C + \tau_2\alpha_2 I_D - (r_3+d_3+\delta_2+\mu)I_C \end{bmatrix} \tag{4.19}$$

and

$$B = D_Z Q(X^*,0) = \begin{bmatrix} -(k_1+\mu) & \frac{\beta\mu}{\mu+\alpha_1} & 0 & \frac{\beta\eta_1\mu}{\mu+\alpha_1} & 0 & \frac{\beta\eta_2\mu}{\mu+\alpha_1} \\ k_1 & -G_2 & 0 & 0 & 0 & 0 \\ 0 & \frac{\beta\theta\alpha_1}{\mu+\alpha_1} & -G_3 & \frac{\beta\eta_1\theta\alpha_1}{\mu+\alpha_1} & 0 & \frac{\beta\eta_2\theta\alpha_1}{\mu+\alpha_1} \\ 0 & \tau_1\alpha_1 & K_2 & -G_4 & 0 & 0 \\ 0 & 0 & \alpha_2 & 0 & -G_5 & 0 \\ 0 & 0 & 0 & \tau_2\alpha_2 & k_3 & -G_6 \end{bmatrix} \tag{4.20}$$

Hence,

$$BZ = \begin{bmatrix} -(k_1+\mu)L + \frac{\beta\mu I}{\mu+\alpha_1} + \frac{\beta\eta_1\mu I_D}{\mu+\alpha_1} + \frac{\beta\eta_2\mu I_C}{\mu+\alpha_1} \\ k_1 1L - G_2 I \\ \frac{\beta\theta\alpha_1 I}{\mu+\alpha_1} - G_3 L_D + \frac{\beta\eta_1\theta\alpha_1 I_D}{\mu+\alpha_1} + \frac{\beta\eta_2\theta\alpha_1 I_C}{\mu+\alpha_1} \\ \tau_1\alpha_1 I - k_2 L_D - G_4 I_D \\ \alpha_2 L_D - G_5 L_C \\ \tau_2\alpha_2 I_D + k_3 L_C - G_6 I_C \end{bmatrix} \tag{4.21}$$

where

$$G_1 = k_1+\mu, \quad G_2 = \tau_1\alpha_1 + r_1 + d_1 + \mu, \quad G_3 = k_2+\alpha_2+\mu, \quad G_4 = \tau_2\alpha_2 + r_2 + d_2 + \mu,$$

$$G_5 = k_3 + \delta_1 + \mu, \quad G_6 = r_3 + d_3 + \delta_2 + \mu$$

then

$$Q(X,Z) = BZ - \hat{Q}(X,Z) \tag{4.22}$$

where

$$\hat{Q} = AZ - Q(X,Z) = \begin{bmatrix} -\xi_1\lambda R_T - \sigma_1\lambda L + \beta I\left(\frac{S^*}{N^*} - \frac{S}{N}\right) + \beta\eta_1 I_D\left(\frac{\theta S_D^*}{N^*} - \frac{S}{N}\right) + \beta\eta_2 I_C\left(\frac{\theta S_D^*}{N^*} - \frac{S}{N}\right) \\ -\sigma_1\lambda L \\ -\xi_2\lambda R_D - \sigma_2\lambda L_D + \beta I\left(\frac{S_D^*}{N^*} - \frac{S}{N}\right) + \beta\eta_1 I_D\left(\frac{\theta S_D^*}{N^*} - \frac{S}{N}\right) + \beta\eta_2 I_C\left(\frac{\theta S_D^*}{N^*} - \frac{S}{N}\right) \\ -\sigma_2\lambda L_D \\ \sigma_3\lambda L_C \\ -\sigma_3\lambda L_C \end{bmatrix} \tag{4.23}$$

□

It can be seen that component 1 and 3 may be negative, while component 2, 4 and 6 are negative.

This means that $\hat{Q}(X,Z)$ is not positive semi-definite. The implication is that condition $(W2)$ in not satisfied. Consequently the disease free equilibrium U_0, is not globally asymptotically stable when $R_0 \leq 1$. Clearly, we see that setting

$$\xi_1 = \xi_2 = \sigma_1 = \sigma_2 = \sigma_3 = 0 \tag{4.24}$$

we have that $\hat{Q}(X,Z) \geq 0$

Hence, re-infection and exogenous re-infection rate induces the phenomenon of backward bifurcation.

4.2.3 Backward bifurcation analysis of the model without controls

In this section, we explore the type of bifurcation the model (3.21) may undergo, using the Centre Manifold Theory developed by Castillo-Chavez and Song (2004)

Theorem 4.3. *Given that the coefficient $a > 0$, (defined below), when $\mathscr{R}_0 < 1$*

$$\begin{aligned}
a = {} & \nu_3\left(-\frac{2\beta x_1^* n_1}{N^{*2}}(\omega_4+\eta_1\omega_7+\eta_2\omega_{10})+\frac{2\beta}{N^*}(\omega_4+\eta_1\omega_7+\eta_2\omega_{10})(\omega_1-\sigma_1\omega_3+\xi\omega_5)\right)\\
& +\left(\frac{2\beta\sigma_1\omega_3\nu_4}{N^*}(\omega_4+\eta_1\omega_7+\eta_2\omega_{10})\right)\\
& +\nu_6\left(-\frac{2\beta\theta x_2^* n_1}{N^{*2}}(\omega_4+\eta_1\omega_7+\eta_2\omega_{10})-\frac{2\beta}{N^*}(\omega_4+\eta_1\omega_7+\eta_2\omega_{10})(\sigma_2\omega_6-\xi_2\omega_8)\right)\\
& +\left(\frac{2\nu_7\omega_6\beta\sigma_2}{N^*}(\omega_4+\eta_1\omega_7+\eta_2\omega_{10})\right)+\left(\frac{2(\nu_{10}-\nu_9)\omega_9\beta\sigma_2}{N^*}(\omega_4+\eta_1\omega_7+\eta_2\omega_{10})\right)
\end{aligned}$$

then model (3.21) *will exhibit the property of backward bifurcation at $\mathscr{R}_0 = 1$.Also, when $a < 0$, then the system* (3.21) *will exhibit a forward bifurcation at $\mathscr{R}_0 = 1$.*

Proof

Suppose

$$\xi_e = (S^{**}, S_{\text{D}}^{**}, L^{**}, I^{**}, R_{\text{T}}^{**}, L_{\text{D}}^{**}, I_{\text{D}}^{**}, R_{\text{D}}^{**}, L_{\text{C}}^{**}, I_{\text{C}}^{**}) \tag{4.25}$$

is an arbitrary endemic equilibrium.

Let

$$S = x_1, S_{\text{D}} = x_2, L = x_3, I = x_4, R_{\text{T}} = x_5, L_{\text{D}} = x_6, I_{\text{D}} = x_7, R_{\text{D}} = x_8, L_{\text{C}} = x_9, I_{\text{C}} = x_{10} \tag{4.26}$$

with,

$$
\begin{aligned}
\frac{dx_1}{dt} &= \Lambda - (\lambda + \alpha_1 + \mu)x_1 \\
\frac{dx_2}{dt} &= \alpha_1 x_1 - \theta\lambda x_2 - \mu x_2 \\
\frac{dx_3}{dt} &= \lambda(x_1 + \xi_1 x_5) - (k_1 + \sigma_1\lambda)x_3 - \mu x_3 \\
\frac{dx_4}{dt} &= (k_1 + \alpha_1\lambda)x_3 - \tau_1\alpha_1 x_4 - (r_1 + d_1 + \mu)x_4 \\
\frac{dx_5}{dt} &= r_1 x_4 - \lambda\xi_1 x_5 - \psi_1\alpha_1 x_5 - \mu x_5 \\
\frac{dx_6}{dt} &= \lambda(\theta x_2 + \xi_2 x_8) - (k_2 + \alpha_2\lambda)x_6 - \alpha_2 x_6 - \mu x_6 \\
\frac{dx_7}{dt} &= (k_2 + \alpha_2\lambda)x_6 + \tau_1\alpha_1 x_4 - \tau_2\alpha_2 x_7 - (r_2 + d_2 + \mu)x_7 \\
\frac{dx_8}{dt} &= r_2 x_7 + \psi_1\alpha_1 x_5 + r_3 x_{10} - \lambda\xi_2 x_8 - \mu x_8 \\
\frac{dx_9}{dt} &= \alpha_2 x_6 - (k_3 + \alpha_3\lambda)x_9 - (\delta_1 + \mu)x_9 \\
\frac{dx_{10}}{dt} &= (k_3 + \alpha_3\lambda)x_9 + \tau_2\alpha_2 x_7 - (r_3 + d_3 + \delta_2 + \mu)x_{10}
\end{aligned}
\tag{4.27}
$$

with:

$$
\lambda = \beta\frac{(x_4 + \eta_1 x_7 + \eta_2 x_{10})}{\sum_{i=1}^{10} x_i} \tag{4.28}
$$

$$J(\xi_0) = \begin{pmatrix} -(\alpha_1+\mu_H) & 0 & 0 & -\frac{x_1^*\beta}{N^*} & 0 & 0 & -\frac{x_1^*\beta\eta_1}{N^*} & 0 & 0 & -\frac{x_1^*\beta\eta_2}{N^*} \\ \alpha_1 & -\mu & 0 & -\frac{x_2^*\beta\theta}{N^*} & 0 & 0 & -\frac{x_2^*\beta\theta\eta_1}{N^*} & 0 & 0 & -\frac{x_2^*\beta\theta\eta_2}{N^*} \\ 0 & 0 & -G_1 & \frac{x_1^*\beta}{N^*} & 0 & 0 & \frac{x_1^*\beta\eta_1}{N^*} & 0 & 0 & \frac{x_1^*\beta\eta_2}{N^*} \\ 0 & 0 & k_1 & -G_2 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & r_1 & -(\psi_1\alpha_1+\mu) & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{x_2^*\beta\theta}{N^*} & 0 & -G_3 & \frac{x_2^*\beta\theta\eta_1}{N^*} & 0 & 0 & \frac{x_2^*\beta\theta}{N^*} \\ 0 & 0 & 0 & \tau_1\alpha_1 & 0 & 0 & -G_4 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \psi_1\alpha_1 & 0 & r_2 & -\mu & 0 & r_3 \\ 0 & 0 & 0 & 0 & 0 & \alpha_2 & 0 & 0 & -G_5 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \tau_2\alpha_2 & 0 & k_3 & -G_6 \end{pmatrix} \tag{4.29}$$

with,

$$\begin{aligned} &G_1 = k_1+\mu, \quad G_2 = \tau_1\alpha_1+r_1+d_1+\mu, \quad G_3 = k_2+\alpha_2+\mu, \quad G_4 = \tau_2\alpha_2+r_2+d_2+\mu \\ &G_5 = k_3+\delta_1+\mu \quad G_6 = r_3+d_3+\delta_2+\mu \end{aligned} \tag{4.30}$$

Consider the case when $\mathscr{R}_0 = 1$. Assume, further, that β is chosen as a bifurcation parameter. Solving for $\beta = \beta^*$ from $\mathscr{R}_0 = 1$ gives

$$\beta^* = \beta^* = \frac{G_1G_2G_3G_4G_5G_6N^*}{\Phi} \tag{4.31}$$

Evaluating the Jacobian of the system (4.27) at the DFE, $J(\xi_0)$, and using the approach in Castillo-Chavez and Song (2004), we have right eigenvector given by

$$\mathbf{w} = [\omega_1, \omega_2, \omega_3, \omega_4, \omega_5, \omega_6, \omega_7, \omega_8, \omega_9, \omega_{10}]^T$$

where,

$$\omega_1 = -\frac{\beta G_4 N^* x_1^* + \eta_1 \beta \tau_1 \alpha_1}{G_4 N^*}\omega_4 - \frac{\eta_2 \beta x_1^*}{N^*}\omega_{10} \quad \omega_2 = \frac{\alpha_1 \omega_1}{\mu} - \frac{G_4 \beta \theta x_2^* + \beta \theta \eta_1 \tau_1 \alpha_1 x_2^*}{\mu G_4 N^*}\omega_4 - \frac{\theta \eta_2 \beta x_2}{\mu N^*}\omega_{10}$$

$$\omega_3 = \frac{G_4 \beta x_1^* + \eta_1 \beta \tau_1 \alpha_1 x_1^*}{G_1 G_4 N^*}\omega_4 + \frac{\eta_2 \beta x_1^*}{G_1 N^*}\omega_{10}, \quad \omega_4 = \omega_4 > 0, \quad \omega_5 = \frac{r_1}{\psi_1 \alpha_1 + \mu}\omega_4$$

$$\omega_6 = \frac{G_4 \beta \theta x_2^* + \beta \theta \eta_1 \tau_1 \alpha_1 x_2^*}{G_3 G_4 N^*}\omega_4 + \frac{\eta_2 \beta \theta x_2^*}{G_3 N^*}\omega_{10}, \quad \omega_7 = \frac{\tau_1 \alpha_1}{G_4}\omega_4, \quad \omega_8 = \left(\frac{\psi_1 \alpha_1 r_1}{\mu(\psi_1 \alpha_1 + \mu)} + \frac{r_2 \tau_1 \alpha_1}{\mu}\right)\omega_4$$

$$\omega_9 = \frac{\alpha_2}{G_5}\omega_6, \quad \omega_{10} = \omega_{10} > 0 \tag{4.32}$$

The components of the left eigenvector of $J(\xi_0)|_{\beta_S = \beta_S^*}$, $\mathbf{v} = (\nu_1, \nu_2, ..., \nu_{11})$, satisfying $\mathbf{v}.\mathbf{w} = 1$ are

$$\nu_3 = \frac{\nu_4 k_1}{G_1}, \quad \nu_4 = \nu_4 > 0, \quad \nu_6 = \frac{\nu_9 \alpha_2}{G_3}, \quad \nu_7 = \frac{\nu_3 x_1^* \beta \eta_1}{G_4 N^*} + \frac{\nu_6 \theta \beta \eta_1 x_2^*}{G_4 N^*} + \frac{\nu_{10} \tau_2 \alpha_2}{G_4}, \nu_9 = \frac{\nu_{10} k_3}{G_5}, \quad \nu_{10} = \nu_{10} > 0$$

$$\nu_1 = \nu_2 = \nu_5 = \nu_8 = 0. \tag{4.33}$$

The bifurcation coefficients are given by:

$$a = \sum_{k,i,j=1}^{n} \nu_k \omega_i \omega_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0) \quad \text{and} \quad b = \sum_{k,i=1}^{n} \nu_k \omega_i \frac{\partial^2 f_k}{\partial x_i \partial \beta_S^*}(0,0),$$

are computed to be

$$
\begin{aligned}
a = \nu_3 &\left(-\frac{2\beta x_1^* n_1}{N^{*2}}(\omega_4 + \eta_1\omega_7 + \eta_2\omega_{10}) + \frac{2\beta}{N^*}(\omega_4 + \eta_1\omega_7 + \eta_2\omega_{10})(\omega_1 - \sigma_1\omega_3 + \xi\omega_5) \right) \\
&+ \left(\frac{2\beta\sigma_1\omega_3\nu_4}{N^*}(\omega_4 + \eta_1\omega_7 + \eta_2\omega_{10}) \right) \\
&+ \nu_6 \left(-\frac{2\beta\theta x_2^* n_1}{N^{*2}}(\omega_4 + \eta_1\omega_7 + \eta_2\omega_{10}) - \frac{2\beta}{N^*}(\omega_4 + \eta_1\omega_7 + \eta_2\omega_{10})(\sigma_2\omega_6 - \xi_2\omega_8) \right) \\
&+ \left(\frac{2\nu_7\omega_6\beta\sigma_2}{N^*}(\omega_4 + \eta_1\omega_7 + \eta_2\omega_{10}) \right) + \left(\frac{2(\nu_{10} - \nu_9)\omega_9\beta\sigma_2}{N^*}(\omega_4 + \eta_1\omega_7 + \eta_2\omega_{10}) \right)
\end{aligned} \tag{4.34}
$$

with

$$
n_1 = \omega_1 + \omega_2 + \omega_3 + \omega_4 + \omega_5 + \omega_6 + \omega_7 + \omega_8 + \omega_9 + \omega_{10} \tag{4.35}
$$

and

$$
b = \sum_{k,i=1}^{20} \nu_k\omega_i \frac{\partial^2 f_k}{\partial x_i \partial \beta^*}(0,0) = \nu_3 \left(\frac{2\beta x_1^*}{N^*}(\omega_4 + \eta_1\omega_7 + \eta_2\omega_{10}) \right) + \left(\frac{2\beta\theta}{N^*}(\omega_4 + \eta_1\omega_7 + \eta_2\omega_{10}) \right) > 0 \tag{4.36}
$$

It follows from Castillo-Chavez and Song (2004) that the model (3.21) will exhibit a backward bifurcation if the coefficient, a, above is positive.

4.2.4 Analysis Of The Optimal Control Model

Consider the following control parameters;

i. u_1 - prevention effort against development of diabetes by encouraging healthy lifestyle.

ii. u_2 - prevention effort against development of complication due to diabetes by regular medical check-up and keeping proper personal sanitation to avoid contracting tuberculosis.

iii. u_3 - TB treatment effort for TB infectious but non-diabetic individuals.

iv. u_4 - TB Treatment effort for TB infectious persons that have diabetes without complication.

v. u_5 - TB Treatment effort TB infectious persons that have diabetes with complication.

vi. u_6 - Prevention measures against activation of TB .

After incorporating u_1, u_2, u_3, u_4, u_5 and u_6 in the system (3.21), we obtain the following optional control model:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - (\alpha_1[1-u_1] + [1-u_6]\lambda + \mu)S \\
\frac{dS_D}{dt} &= \alpha_1[1-u_1]S - [1-u_6]\theta\lambda S_D + \mu S_D \\
\frac{dL}{dt} &= [1-u_6]\lambda(S + \xi_1 R_T) - (k_1 + \sigma_1[1-u_6]\lambda)L - \mu L \\
\frac{dI}{dt} &= (k_1 + \sigma_1[1-u_6]\lambda)L - \tau_1\alpha_1[1-u_1]I - (u_3 + d_1 + \mu)I \\
\frac{dR_T}{dt} &= u_3 I - [1-u_6]\lambda\xi_1 R_T - \psi_1\alpha_1[1-u_1]R_T - \mu R_T \\
\frac{dL_D}{dt} &= [1-u_6]\lambda(\theta S_D + \xi_2 R_D) - (k_2 + \sigma_2[1-u_6]\lambda)L_D - [1-u_2]L_D - \mu L_D \\
\frac{dI_D}{dt} &= (k_2 + \sigma_2[1-u_6]\lambda)L_D + \tau_1\alpha_1[1-u_1]I - \tau_2\alpha_2[1-u_2]I_D - (u_4 + d_2 + \mu)I_D \\
\frac{dR_D}{dt} &= u_4 I_D + \psi_1\alpha_1[1-u_1]R_T - [1-u_6]\lambda\xi_2 R_D + u_5 I_C - \mu R_D \\
\frac{dL_C}{dt} &= \alpha_2[1-u_2]L_D - (k_3 + \sigma_3[1-u_6]\lambda)L_C - (\delta_1 + \mu)L_C \\
\frac{dI_C}{dt} &= (k_3 + \sigma_3[1-u_6]\lambda)L_C + \tau_2\alpha_2[1-u_2]I_D - (u_5 + d_3 + \delta_2 + \mu)I_C
\end{aligned} \tag{4.37}$$

therefore, to study the optimal control levels of the control parameter, we define a Lebesgue measurable control set

$$U = \Big\{ (u_1(t), u_2(t), u_3(t), u_4(t), u_5(t), u_6(t)) : \\ 0 \leq u_1 \leq 1, 0 \leq u_2 \leq 1, 0 \leq u_3 \leq 1, 0 \leq u_4 \leq 1, 0 \leq u_5 \leq 1, 0 \leq u_6 \leq 1, 0 \leq t \leq T \Big\} \tag{4.38}$$

Our aim is to obtain a control set U and I, I_D and I_C that minimize the proposed J. The proposed objective functional (J) is given by:

$$J(\min u_1, u_2, u_3, u_4, u_5, u_6) = \int_0^{tf} (p_1 I + p_2 I_D + p_3 I_C + \frac{1}{2} \sum_{i=1}^{6} w_i u_i^2) dt \tag{4.39}$$

where t_f is the final time of control implementation, p_1, p_2 and p_3 are positive weight constants of the infections human population, w_i is the weight constants of the optimal controls u_i, for $i = 1...6$.

the expression $\frac{1}{2} w_i u_i^2$ is quadratic because we assume that costs are non-linear in its nature.

Therefore, our aim is to minimize the number of infectious individuals and costs. Thus want to obtain optimal control $(u_1^*, u_2^*, u_3^*, u_4^*, u_5^*, u_6^*)$

in which:

$$J(u_1^*, u_2^*, u_3^*, u_4^*, u_5^*, u_6^*) = \min(J(u_i) : u_i \in U, i = 1...6) \tag{4.40}$$

where $U = u_i(t) : 0 \leq u_i(t) \leq 1, 0 \leq t \leq t_f$ is Lebesgue measurable non empty set for the controls.

By using Pontryagin's Maximum principle (Pontryagin, 1986) we obtained a Hamiltonia(H) defined as:

$$\begin{aligned} H(S,S_D,L,I,R_T,L_D,I_D,R_D,L_C,I_C) &= L(I,I_D,I_C,u_1,u_2,u_3,u_4,u_5,u_6,t) \\ &+ h_1\frac{dS}{dt} + h_2\frac{dS_D}{dt} + h_3\frac{dL}{dt} + h_4\frac{dI}{dt} + h_5\frac{dR_T}{dt} \\ &+ h_6\frac{dL_D}{dt} + h_7\frac{dI_D}{dt} + h_8\frac{dR_D}{dt} + h_9\frac{dL_C}{dt} + h_{10}\frac{dI_C}{dt} \end{aligned} \tag{4.41}$$

Where

$$L(I,I_D,I_C,u_1,u_2,u_3,u_4,u_5,u_6,t) = p_I I + p_2 I_D + p_3 I_C + \frac{1}{2}\sum_{i=1}^{6} w_i u_i^2 \tag{4.42}$$

$h_i, i = 1...10$, are the adjoint variable function to be determined suitably by applying pontryagin's maximum principle and also following the work of Fleming(1982), we obtain the existence of the optimal control pairs.

Theorem 4.4. *For an optimal control set*

u_1,u_2,u_3,u_4,u_5,u_6 *that minimizes J and U, there is an adjoint variable,* $h_1,...h_{10}$ *such that:*

$$\begin{aligned} \frac{dh_1}{dt} &= h_1\mu - (1-u_1)(h_2-h_1) - \beta(1-u_6)\frac{I+\eta_1 I_D+\eta_2 I_C}{N}(h_3-h_1) \\ &+ \beta(1-u_6)\frac{(I+\eta_1 I_D+\eta_2 I_C)}{N^2}[S(h_3-h_1) + S_D\theta(h_6-h_2) + L\sigma_1(h_4-h_3) \\ &+ L_D\sigma_2(h_7-h_6) + L_C\sigma_3(h_{10}-h_9) + R_D\xi_2(h_6-h_8) + R_T\xi_1(h_3-h_5)] \end{aligned} \tag{4.43}$$

$$\frac{dh_2}{dt} = h_2\mu - \frac{\beta(1-u_6)(I+\eta_1 I_D+\eta_2 I_C)(h_6-h_2)\theta}{N} + \frac{\beta(1-u_6)(I+\eta_1 I_D+\eta_2 I_C)}{N^2}[S(h_3-h_1)$$

$$+S_D\theta(h_6-h_2)+L\sigma_1(h_4-h_3)+L_D\sigma_2(h_7-h_6)+L_C\sigma_3(h_{10}-h_9)+R_D\xi_2(h_6-h_8)$$

$$+R_T\xi_1(h_3-h_5)]$$

$$\frac{dh_3}{dt} = h_3\mu - k_1(h_4-h_3) - \frac{\beta(1-u_6)(I+\eta_1 I_D+\eta_2 I_C)\theta_1(h_4-h_3)}{N} +$$

$$\frac{\beta(1-u_6)(I+\eta_1 I_D+\eta_2 I_C)}{N^2}[S(h_3-h_1)+S_D\theta(h_6-h_2)+L\sigma_1(h_4-h_3)+$$

$$L_D\sigma_2(h_7-h_6)+L_C\sigma_3(h_{10}-h_9)+R_D\xi_2(h_6-h_8)+R_T\xi_1(h_3-h_5)]$$

$$\frac{dh_4}{dt} = -p_1-\tau_1(1-u_1)(h_7-h_4)+h_4(d_1+\mu)-u_3(h_5-h_4)-\beta(1-u_6)[\frac{1}{N}-$$

$$\frac{(I+\eta_1 I_D+\eta_2 I_C)}{N^2}][S(h_3-h_1)+S_D\theta(h_6-h_2)+L\sigma_1(h_4-h_3)+$$

$$L_D\sigma_2(h_7-h_6)+L_C\sigma_3(h_{10}-h_9)+R_D\xi_2(h_6-h_8)+R_T\xi_1(h_3-h_5)]$$

$$\frac{dh_5}{dt} = -\psi_1(1-u_1)(h_8-h_5)+h_5\mu+\frac{\beta(1-u_6)(I+\eta_1 I_D+\eta_2 I_C)\xi_1(h_5-h_3)}{N}+$$

$$\frac{\beta(1-u_6)(I+\eta_1 I_D+\eta_2 I_C)}{N^2}[S(h_3-h_1)+S_D\theta(h_6-h_2)+$$

$$L\sigma_1(h_4-h_3)+L_D\sigma_2(h_7-h_6)+L_C\sigma_3(h_{10}-h_9)+R_D\xi_2(h_6-h_8)+R_T\xi_1(h_3-h_5)]$$

$$\frac{dh_6}{dt} = -k_2(h_7-h_6)-(1-u_2)(h_9-h_6)+h_6\mu-\frac{\beta(1-u_6)(I+\eta_1 I_D+\eta_2 I_C)\sigma_2(h_7-h_6)}{N}$$

$$+\frac{\beta(1-u_6)(I+\eta_1 I_D+\eta_2 I_C)}{N^2}[S(h_3-h_1)+S_D\theta(h_6-h_2)+L\sigma_1(h_4-h_3)+L_D\sigma_2(h_7-h_6)+$$

$$L_C\sigma_3(h_{10}-h_9)+R_D\xi_2(h_6-h_8)+R_T\xi_1(h_3-h_5)]$$

$$\frac{dh_7}{dt} = -p_2-\tau_2(1-u_2)(h_{10}-h_7)-u_4(h_8-h_7)+h_7(d_2+\mu)-\beta(1-u_6)[\frac{\eta_1}{N}$$

$$-\frac{(I+\eta_1 I_D+\eta_2 I_C)}{N^2}][S(h_3-h_1)+S_D\theta(h_6-h_2)+$$

$$L\sigma_1(h_4-h_3)+L_D\sigma_2(h_7-h_6)+L_C\sigma_3(h_{10}-h_9)+R_D\xi_2(h_6-h_8)+R_T\xi_1(h_3-h_5)]$$

$$\frac{dh_8}{dt} = h_8\mu+\frac{\beta(1-u_6)(I+\eta_1 I_D+\eta_2 I_C)\xi_2(h_8-h_6)}{N}+\frac{\beta(1-u_6)(I+\eta_1 I_D+\eta_2 I_C)}{N^2}[S(h_3-h_1)$$

$$+S_D\theta(h_6-h_2)+L\sigma_1(h_4-h_3)+L_D\sigma_2(h_7-h_6)+L_C\sigma_3(h_{10}-h_9)+R_D\xi_2(h_6-h_8)$$

$$+R_T\xi_1(h_3-h_5)]$$

$$\frac{dh_9}{dt} = -k_3(h_{10}-h_9) + h_9(\delta_1+\mu) - \frac{\beta(1-u_6)(I+\eta_1 I_D+\eta_2 I_C)\sigma_3(h_{10}-h_9)}{N}$$
$$+ \frac{\beta(1-U_6)(I+\eta_1 I_D+\eta_2 I_C)}{N^2}[S(h_3-h_1)+S_D\theta(h_6-h_2)+L\sigma_1(h_4-h_3)+L_D\sigma_2(h_7-h_6)$$
$$+L_C\sigma_3(h_{10}-h_9)+R_D\xi_2(h_6-h_8)+R_T\xi_1(h_3-h_5)]$$
$$\frac{dh_{10}}{dt} = -p_3 - u_5(h_8-h_{10}) + h_{10}(d_3+\delta_3+\mu) - \beta(1-u_6)[\frac{\eta_2}{N} - \frac{(I+\eta_1 I_D+\eta_2 I_C)}{N^2}][S(h_3-h_1)$$
$$+S_D\theta(h_6-h_2)$$
$$+L\sigma_1(h_4-h_3)+L_D\sigma_2(h_7-h_6)+L_C\sigma_3(h_{10}-h_9)+R_D\xi_2(h_6-h_8)+R_T\xi_1(h_3-h_5)]$$

With transversality conditions, $h_i(t_f)=0, i=1,...,10$. Furthermore, we obtain the control set $(u_1^*,u_2^*,u_3^*,u_4^*,u_5^*,u_6^*)$ characterized by

$$\begin{aligned}
u_1^*(t) &= max\left\{0, min\left\{1, \frac{S(h_2-h_1)+\tau_1 I(h_7-h_4)+\psi_1 R_T(h_8-h_5)}{w_1}\right\}\right\}\\
u_2^*(t) &= max\left\{0, min\left\{1, \frac{L_D(h_9-h_6)+\tau_2 I_D(h_{10}-h_7)}{w_2}\right\}\right\}\\
u_3^*(t) &= max\left\{0, min\left\{1, \frac{I(h_4-h_5)}{w_3}\right\}\right\}\\
u_4^*(t) &= max\left\{0, min\left\{1, \frac{I_D(h_7-h_8)}{w_4}\right\}\right\}\\
u_5^*(t) &= max\left\{0, min\left\{1, \frac{I_C(h_{10}-h_8)}{w_5}\right\}\right\}\\
u_6^*(t) &= max\{0, min\{1, \gamma_6\}\}
\end{aligned} \tag{4.44}$$

where,

$$\gamma_6 = \frac{\beta(I+\eta_1 I_D+\eta_2 I_C)[\Phi+L_C\sigma_3(h_{10}-h_9)+R_D\xi_2(h_6-h_8)+R_T\xi_1(h_3-h_5)]}{w_6} \tag{4.45}$$

with

$$\Phi = S(h_3 - h_1) + S_D\theta(h_6 - h_2) + L\sigma_1(h_4 - h_3) + L_D\sigma_2(h_7 - h_6) \tag{4.46}$$

Proof. By using Pontryagin maximum principle we obtain the following system of adjoint variables:

$$\begin{aligned}
&\frac{dh_1}{dt} = -\frac{dH}{dS}, \quad \frac{dh_2}{dt} = -\frac{dH}{dS_D} \quad \frac{dh_3}{dt} = -\frac{dH}{dL} \quad \frac{dh_4}{dt} = -\frac{dH}{dI} \quad \frac{dh_5}{dt} = -\frac{dH}{dR_T} \quad \frac{dh_6}{dt} = -\frac{dH}{dL_D} \\
&\frac{dh_7}{dt} = -\frac{dH}{dI_D} \quad \frac{dh_8}{dt} = -\frac{dH}{dR_D} \quad \frac{dh_9}{dt} = -\frac{dH}{dL_C} \quad \frac{dh_{10}}{dt} = -\frac{dH}{dI_C}
\end{aligned} \tag{4.47}$$

Similarly to get the controls, we solved the equation (4.43), $\frac{dH}{du_i} = 0$, at u_i^* , for i = 1,...,6 and obtained:

$$\begin{aligned}
u_1^* &= \frac{S(h_2 - h_1) + \tau_1 I(h_7 - h_4) + \psi_1 R_T(h_8 - h_5)}{w_1} \\
u_2^* &= \frac{L_D(h_9 - h_6) + \tau_2 I_D(h_{10} - h_7)}{w_2} \\
u_3^* &= \frac{I(h_4 - h_5)}{w_3} \\
u_4^* &= \frac{I_D(h_7 - h_8)}{w_4} \\
u_5^* &= \frac{I_C(h_{10} - h_8)}{w_5} \\
u_6^* &= \frac{\beta(I + \eta_1 I_D + \eta_2 I_C)[\Phi + L_C\sigma_3(h_{10} - h_9) + R_D\xi_2(h_6 - h_8) + R_T\xi_1(h_3 - h_5)]}{w_6}
\end{aligned} \tag{4.48}$$

with

$$\Phi = S(h_3 - h_1) + S_D\theta(h_6 - h_2) + L\sigma_1(h_4 - h_3) + L_D\sigma_2(h_7 - h_6) \tag{4.49}$$

we write by using standard control arguments involving the bounds on the controls, and conclude:

$$u_1^* = \begin{cases} \gamma_1, & if \quad 0 \leq \gamma_1 \leq 1 \\ 0, & if \quad \gamma_1 \leq 0 \\ 1, & if \quad \gamma_1 \geq 1 \end{cases}$$

$$u_2^* = \begin{cases} \gamma_2, & if \quad 0 \leq \gamma_2 \leq 1 \\ 0, & if \quad \gamma_2 \leq 0 \\ 1, & if \quad \gamma_2 \geq 1 \end{cases}$$

$$u_3^* = \begin{cases} \gamma_3, & if \quad 0 \leq \gamma_3 \leq 1 \\ 0, & if \quad \gamma_3 \leq 0 \\ 1, & if \quad \gamma_3 \geq 1 \end{cases}$$

$$u_4^* = \begin{cases} \gamma_4, & if \quad 0 \leq \gamma_4 \leq 1 \\ 0, & if \quad \gamma_4 \leq 0 \\ 1, & if \quad \gamma_4 \geq 1 \end{cases}$$

$$u_5^* = \begin{cases} \gamma_5, & if \quad 0 \leq \gamma_5 \leq 1 \\ 0, & if \quad \gamma_5 \leq 0 \\ 1, & if \quad \gamma_5 \geq 1 \end{cases}$$

$$u_6^* = \begin{cases} \gamma_6, & if \quad 0 \leq \gamma_6 \leq 1 \\ 0, & if \quad \gamma_6 \leq 0 \\ 1, & if \quad \gamma_6 \geq 1 \end{cases}$$

In compact notation we have:

$$
\begin{aligned}
u_1^*(t) &= max\{0, max(1,\gamma_1)\},\\
u_2^*(t) &= max\{0, max(1,\gamma_2)\},\\
u_3^*(t) &= max\{0, max(1,\gamma_3)\},\\
u_4^*(t) &= max\{0, max(1,\gamma_4)\},\\
u_5^*(t) &= max\{0, max(1,\gamma_5)\},\\
u_6^*(t) &= max\{0, max(1,\gamma_6)\},\\
\gamma_1 &= \frac{S(h_2-h_1)+\tau_1 I(h_7-h_4)+\psi_1 R_T(h_8-h_5)}{w_1}\\
\gamma_2 &= \frac{L_D(h_9-h_6)+\tau_2 I_D(h_{10}-h_7)}{w_2}\\
\gamma_3 &= \frac{I(h_4-h_5)}{w_3}\\
\gamma_4 &= \frac{I_D(h_7-h_8)}{w_4}\\
\gamma_5 &= \frac{I_C(h_{10}-h_8)}{w_5}\\
\gamma_6 &= \frac{\beta(I+\eta_1 I_D+\eta_2 I_C)[\Phi+L_C\sigma_3(h_{10}-h_9)+R_D\xi_2(h_6-h_8)+R_T\xi_1(h_3-h_5)]}{w_6}
\end{aligned}
\tag{4.50}
$$

with

$$
\Phi = S(h_3-h_1)+S_D\theta(h_6-h_2)+L\sigma_1(h_4-h_3)+L_D\sigma_2(h_7-h_6) \tag{4.51}
$$

□

4.2.5 Numerical Simulations

Numerical simulation of the model (3.21) and the resulting optimality system (4.43) was carried out. The values of the paramerters in Table 4.1 was used for the simulation. For us to achieve this simulation, we use forward and backward fourth-order Runke-Kutta method to solve the state system. The adjoint systems is solved by using the initial guess of the controls incorporating with the obtained solution for the state system. (Lenhart(2007)).

The following nine control strategies were implemented and used for numerical simulation of the co-infection model (3.21) on order to bring down the burden of the diseases on the population:

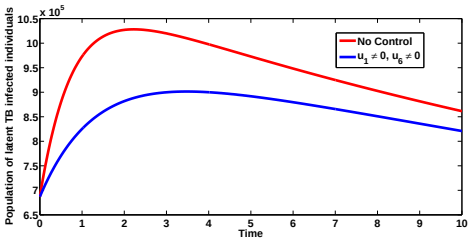
4.2.5.1 Strategy A: Prevention Effort Against Development Of Diabetes $(u_1 \neq 0)$ And Prevention Measures Against Development of TB $(u_6 \neq 0)$

Simulation result of the optimal control system when strategy A (prevention effort against development of diabetes $(u_1 \neq 0)$ and Prevention measures against activation of TB $(u_6 \neq 0)$) is implemented. Figure 4.1 shows that the total number of individuals latently and actively infected with diabetes and tuberculosis were significantly reduced, as 40,500 new latent TB infected individuals were averted while 8,423 new active TB infected individuals were prevented.

For individuals co-infected with latent TB and diabetes without complication as well as individuals co-infected with active TB and diabetes without complication(Figure 4.2) Specifically, this strategy averts 181,040 new cases of co-infection with latent TB / diabetes without complication and prevented 9349 new cases of active TB / diabetes without complication after a period of 10 years. The graph of this control strategy given in Figure 4.2 shows that by implementing this control strategy $(u_1 \neq 0, u_6 \neq 0)$ the infected population raised steadily to its

Table 4.1: Parameters in the model equation and their value

Parameter	**Value per year**	**Reference**
Λ	667685	Moualen et al., 2012
μ	0.01876	Moualen et al., 2012
β	1.8	Moualen et al., 2012
α_1	0.009	Moualen et al., 2012
α_2	0.01	Moualen etal., 2012
τ_1	1.01	Moualen et al., 2012
τ_2	1.05	Moualen et al., 2012
ψ	1.01	Assumed
θ	1.01	Assumed
ξ_1	0.0986	Moualen et al., 2012
ξ_2	0.1	Moualen et al., 2012
k_1	0.00013	Dye et al., 2000
k_2	2*k_1	Moualen et al., 2012
k_3	2*k_2	Estimated
σ_1	1.02	Assumed
σ_2	1.01*σ_1	Assumed
σ_3	1.01*σ_2	Assumed
r_1	0.7372	Moualen et al., 2012
r_2	0.7372	Moualen et al., 2012
r_3	0.7372	Moualen et al., 2012
d_1	0.275	Moualen et al., 2012
d_2	1.25*d_1	Moualen et al., 2012
d_3	1.25*d_2	Estimated
δ_1	0.005	Assumed
δ_2	0.1*δ_1	Assumed



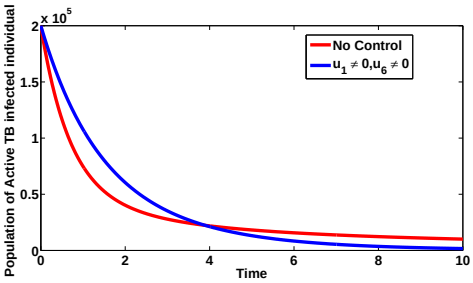
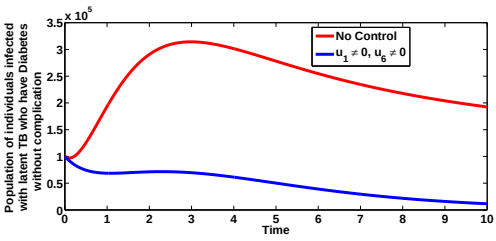


Figure 4.1: Plots of the total number of latently and actively-infected individuals when strategy A is implemented ($u_1 \neq 0, u_6 \neq 0$). Here, $\beta = 0.2001$. All other parameters as in Table 4.1



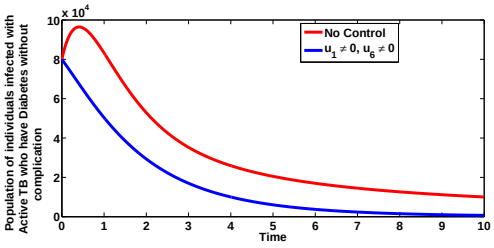


Figure 4.2: Plots of the total number of individuals co-infected with latent TB and diabetes without complication and individuals co-infected with active TB and diabetes without complication when strategy A is implemented ($u_1 \neq 0, u_6 \neq 0$). Here, $\beta = 0.2001$. All other parameters as in Table 4.1

peak in about 3 years, and then dropped to 181,040 co-infected individuals with latent TB and diabetes without complication in about 10 years.

For individuals co-infected with latent TB and diabetes with complication as well as individuals co-infected with active TB and diabetes with complication(Figure 4.3) Specifically, this strategy averts 1,566,100 new cases of co-infection of latent TB / diabetes with complication and prevented 89,886 new cases of active TB / diabetes with complication after a period of 10 years. The graph of this control strategy given in Figure 4.3 shows that by implementing this control strategy $(u_1 \neq 0, u_6 \neq 0)$ the infected population raised steadily to its peak in about 2 years, and then dropped to 9874 actively co-infected individuals from 91,970 co-infected individuals with active TB and diabetes with complication in about 10 years.

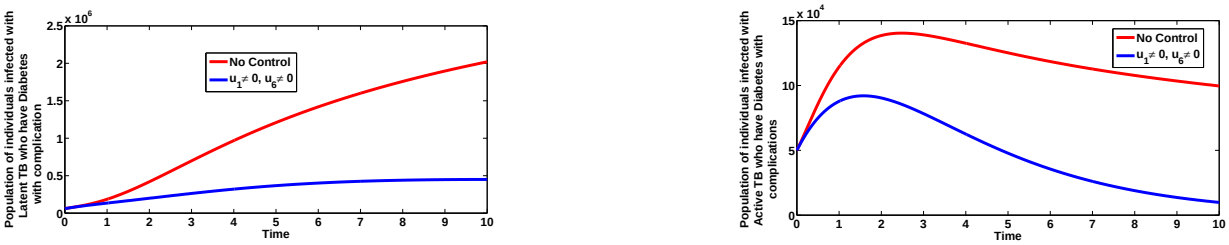


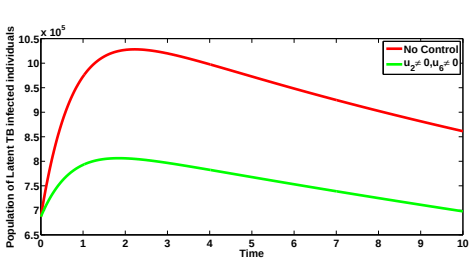
Figure 4.3: Plots of the total number of individuals co-infected with latent TB and diabetes with complication and individuals co-infected with active TB and diabetes with complication when strategy A is implemented ($u_1 \neq 0, u_6 \neq 0$). Here, $\beta = 0.2001$. All other parameters as in Table 4.1

4.2.6 Strategy B: Prevention Effort Against Development of Complications Due To Diabetes $(u_2 \neq 0)$ and Prevention Measures Against Development Of TB $(u_6 \neq 0)$

For strategy B (prevention effort against development of complications due to diabetes $(u_2 \neq 0)$ and Prevention measures against activation of TB $(u_6 \neq 0)$) . Figure 4.4 . shows that the total number of individuals latently and actively infected with diabetes and tuberculosis was significantly reduced, as 168,300 new latent TB infected individuals were averted while 9,659 new active TB infected individuals were prevented.

For individuals co-infected with latent TB and diabetes without complication as well as individuals co-infected with active TB and diabetes without complication,as shown in Figure 4.5 this strategy averts 161,700 new cases of co-infection of latent TB/diabetes without complication and it prevented 9,096 new cases of active TB / diabetes without complication after a period of 10 years. The graph of this control strategy given in Figure 4.5 shows that by implementing this control strategy $(u_2 \neq 0, u_6 \neq 0)$ the infected population raised steadily to its peak in about 2 years, and then dropped to 31,260 individuals from 110,700 co-infected individuals with latent TB and diabetes without complication in about 10 years.

For individuals co-infected with latent TB and diabetes with complication as well as individuals co-infected with active TB and diabetes with complication as shown in Figure 4.6 this



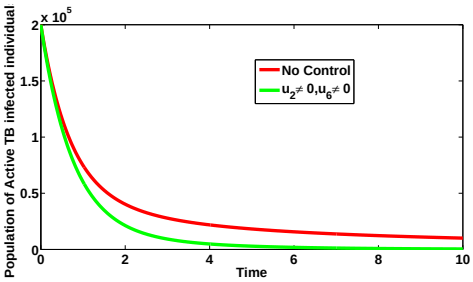
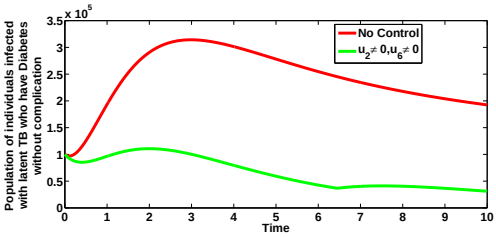


Figure 4.4: Plots of the total number of latently and actively-infected individuals when strategy B is implemented ($u_2 \neq 0, u_6 \neq 0$). Here, $\beta = 0.2001$. All other parameters as in Table 4.1



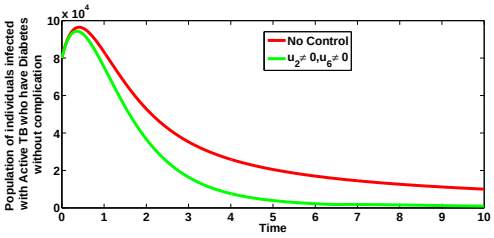
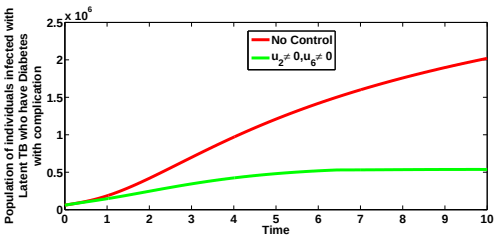


Figure 4.5: Plots of the total number of individuals co-infected with latent TB and diabetes without complication and individuals co-infected with active TB and diabetes without complication when strategy B is implemented ($u_2 \neq 0, u_6 \neq 0$). Here, $\beta = 0.2001$. All other parameters as in Table 4.1

strategy averts 1,481,000 new cases of co-infection of latent TB / diabetes with complication and prevented 90,783 new cases of active TB / diabetes with complication after a period of 10 years. The graph of this control strategy given in Figure 4.6 shows that by implementing this control strategy ($u_2 \neq 0, u_6 \neq 0$) the infected population raised steadily to its peak in about 2 years, and then dropped to 8907 active TB co-infected individuals from 118,500 co-infected individuals with active TB and diabetes with complication in about 10 years.



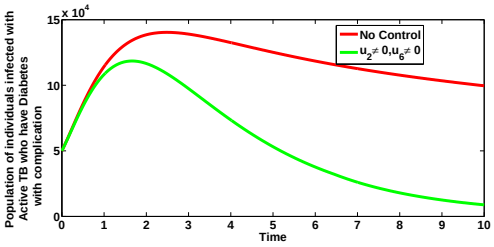


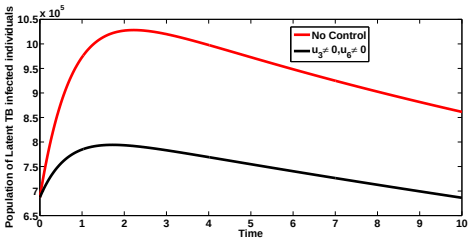
Figure 4.6: Plots of the total number of individuals co-infected with latent TB and diabetes with complication and individuals co-infected with active TB and diabetes with complication when strategy B is implemented ($u_2 \neq 0, u_6 \neq 0$). Here, $\beta = 0.2001$. All other parameters as in Table 4.1

4.2.7 Strategy C: TB Treatment Effort For Non-Diabetic Patients $(u_3 \neq 0)$ And Prevention Measures Against Development Of TB $(u_6 \neq 0)$

For strategy C (TB treatment effort for TB infectious but non-diabetic individuals $(u_3 \neq 0)$ and Prevention measures against activation of TB $(u_6 \neq 0)$) . Figure 4.7 shows that when this intervention strategy is implemented, the total number of individuals latently and actively infected with diabetes and tuberculosis significant decreases, as 175,500 new latent TB infected individuals were averted while 9,817 new active TB infected individuals were prevented.

For individuals co-infected with latent TB and diabetes without complication as well as individuals co-infected with active TB and diabetes without complication,as shown in Figure 4.8 this strategy averts 185,489 new cases of co-infection of latent TB/diabetes without complication and it prevented 9,808 new cases of active TB / diabetes without complication after a period of 10 years. The graph of for this control strategy given in Figure 4.8 shows that by implementing this control strategy $(u_3 \neq 0, u_6 \neq 0)$ the infected population raised steadily to its peak in less than 2 years, and then dropped to 7,511 individuals from 95,480 co-infected individuals with latent TB and diabetes without complication in about 10 years.

For individuals co-infected with latent TB and diabetes with complication as well as individuals co-infected with active TB and diabetes with complication as shown in Figure 4.9 this strategy averts 1,549,400 new cases of co-infection of latent TB / diabetes with complication and prevented 93,275 new cases of active TB / diabetes with complication after a period of 10 years. The graph of this control strategy given in Figure 10 shows that by implementing this control strategy $(u_3 \neq 0, u_6 \neq 0)$ the infected population raised steadily to its peak in less than 2 years, and then dropped to 6415 active TB co-infected individuals from 108,100 co-infected individuals with active TB and diabetes with complication in about 10 years.



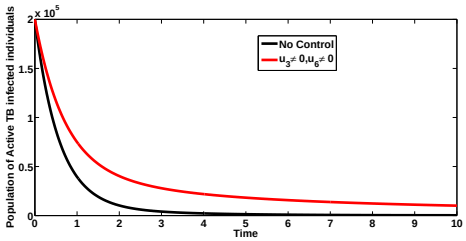
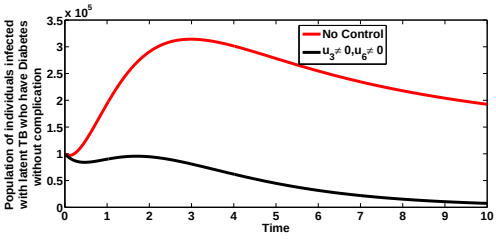


Figure 4.7: Plots of the total number of latently and actively-infected individuals when strategy C is implemented ($u_3 \neq 0, u_6 \neq 0$). Here, $\beta = 0.2001$. All other parameters as in Table 4.1



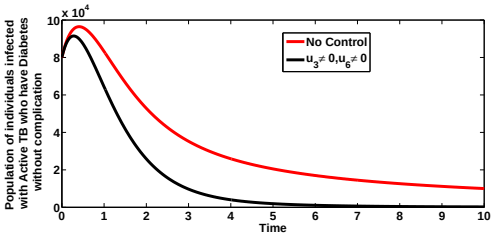
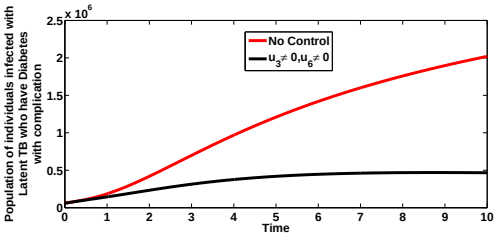


Figure 4.8: Plots of the total number of individuals co-infected with latent TB and diabetes without complication and individuals co-infected with active TB and diabetes without complication when strategy C is implemented($u_3 \neq 0, u_6 \neq 0$). Here, $\beta = 0.2001$. All other parameters as in Table 4.1



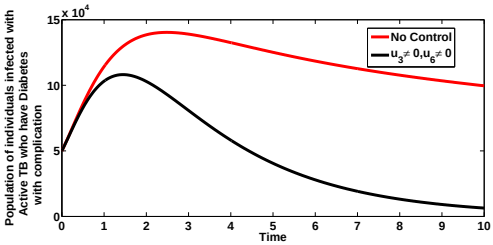


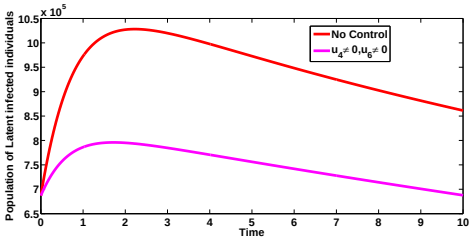
Figure 4.9: Plots of the total number of individuals co-infected with latent TB and diabetes with complication and individuals co-infected with active TB and diabetes with complication when strategy C is implemented ($u_3 \neq 0, u_6 \neq 0$). Here, $\beta = 0.2001$. All other parameters as in Table 4.1

4.2.8 Strategy D: TB Treatment Effort For Diabetic-TB Patients Without Complications ($u_4 \neq 0$) And Prevention Measures Against Development Of TB ($u_6 \neq 0$)

For strategy D (TB treatment effort for diabetic-TB patients without complications ($u_4 \neq 0$) and Prevention measures against activation of TB ($u_6 \neq 0$)) Figure 4.10 shows that when this intervention strategy is implemented, the total number of individuals latently and actively infected with diabetes and tuberculosis significant decreases, as 173,500 new latent TB infected individuals were averted while 9,787 new active TB infected individuals were prevented.

For individuals co-infected with latent TB and diabetes without complication as well as individuals co-infected with active TB and diabetes without complication,as shown in Figure 4.11 this strategy averts 185,579 new cases of co-infection of latent TB/diabetes without complication and it prevented 9,802 new cases of active TB / diabetes without complication after a period of 10 years. The graph of this control strategy given in Figure 4.11 shows that by implementing this control strategy ($u_4 \neq 0, u_6 \neq 0$) the infected population raised steadily to its peak in less than 2 years, and then dropped to 7221 individuals from 96,360 co-infected individuals with latent TB and diabetes without complication in about 10 years.

For individuals co-infected with latent TB and diabetes with complication as well as individuals co-infected with active TB and diabetes with complication as shown in Figure 4.12 this strategy averts 1,554,000 new cases of co-infection of latent TB / diabetes with complication and prevented 93,576 new cases of active TB / diabetes with complication after a period of 10 years. The graph of this control strategy given in Figure 4.12 shows that by implementing this control strategy ($u_4 \neq 0, u_6 \neq 0$) the infected population raised steadily to its peak in less than 2 years, and then dropped to 6113 active TB co-infected individuals from 101,300 co-infected individuals with active TB and diabetes with complication in about 10 years.



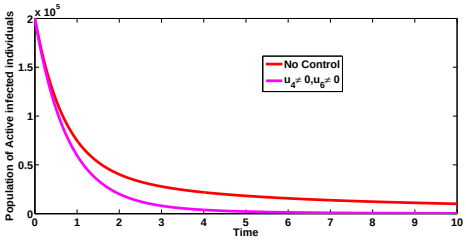
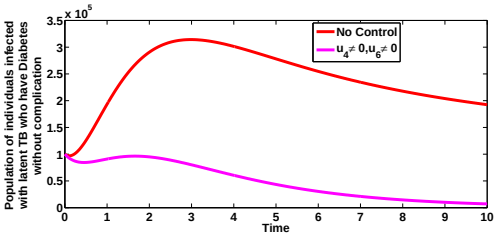


Figure 4.10: Plots of the total number of latently and actively-infected individuals when strategy D is implemented ($u_4 \neq 0, u_6 \neq 0$). Here, $\beta = 0.2001$. All other parameters as in Table 4.1



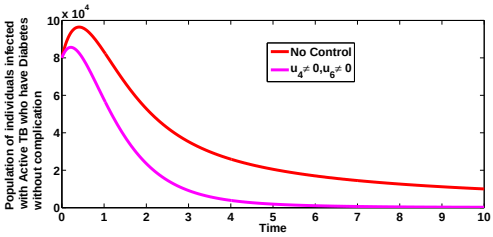
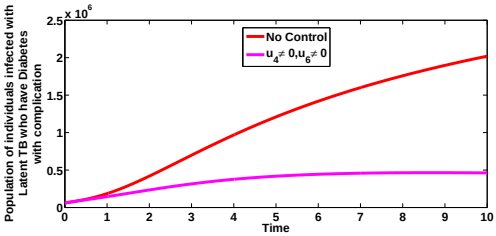


Figure 4.11: Plots of the total number of individuals co-infected with latent TB and diabetes without complication and individuals co-infected with active TB and diabetes without complication when strategy D is implemented ($u_4 \neq 0, u_6 \neq 0$). Here, $\beta = 0.2001$. All other parameters as in Table 4.1



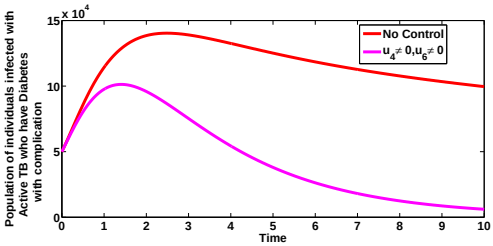


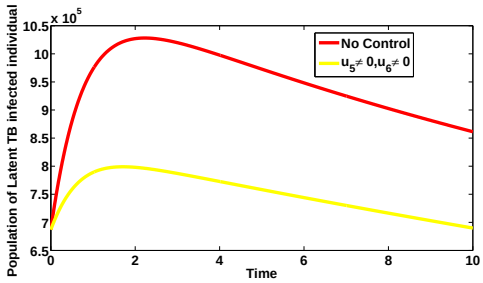
Figure 4.12: Plots of the total number of individuals co-infected with latent TB and diabetes with complication and individuals co-infected with active TB and diabetes with complication when strategy D is implemented ($u_4 \neq 0, u_6 \neq 0$). Here, $\beta = 0.2001$. All other parameters as in Table 4.1

4.2.9 Strategy E: TB Treatment Effort For Diabetic TB Patients With Complications($u_5 \neq 0$) And Prevention Measure Against Development Of TB ($u_6 \neq 0$)

For strategy E (TB treatment effort for diabetic TB patients with complications($u_5 \neq 0$) and Prevention measures against activation of TB ($u_6 \neq 0$)) . Figure 4.13 shows that when this intervention strategy is implemented, the total number of individuals latently and actively infected with diabetes and tuberculosis significant decreases, as 171,500 new latent TB infected individuals were averted while 9,983 new active TB infected individuals were prevented.

For individuals co-infected with latent TB and diabetes without complication as well as individuals co-infected with active TB and diabetes without complication,as shown in Figure 4.14 this strategy averts 190,882 new cases of co-infection of latent TB/diabetes without complication and it prevented 9,915 new cases of active TB / diabetes without complication after a period of 10 years. The graph of this control strategy given in Figure 4.14 shows that by implementing this control strategy ($u_5 \neq 0, u_6 \neq 0$) the infected population raised steadily to its peak in less than 2 years, and then dropped to 1618 individuals from 97,950 co-infected individuals with latent TB and diabetes without complication in about 10 years.

For individuals co-infected with latent TB and diabetes with complication as well as individuals co-infected with active TB and diabetes with complication as shown in Figure 4.15 this strategy averts 1,629,100 new cases of co-infection of latent TB / diabetes with complication and prevented 98,900 new cases of active TB / diabetes with complication after a period of 10 years. The graph of this control strategy given in Figure 4.15 shows that by implementing this control strategy ($u_4 \neq 0, u_6 \neq 0$) the infected population raised steadily to its peak in less than 2 years, and then dropped to 720 active TB co-infected individuals from 83,410 co-infected



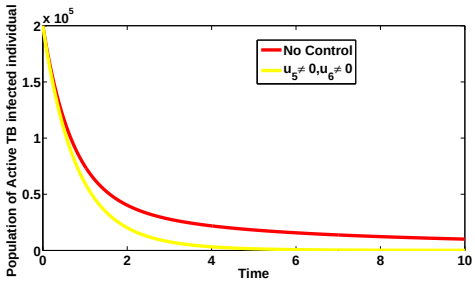
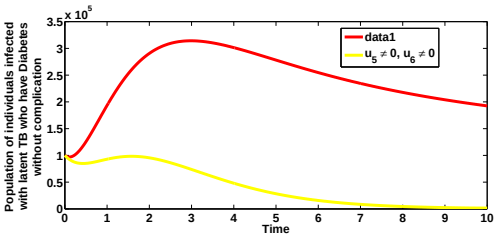


Figure 4.13: Plots of the total number of latently and actively-infected individuals when strategy E is implemented ($u_5 \neq 0, u_6 \neq 0$). Here, $\beta = 0.2001$. All other parameters as in Table 4.1



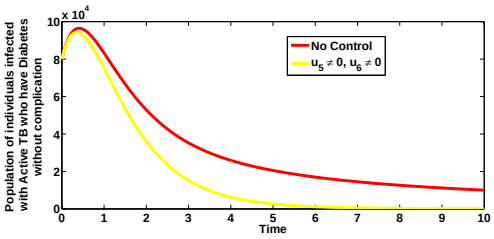
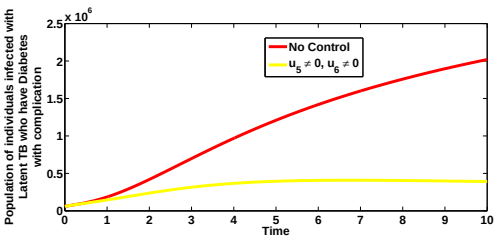


Figure 4.14: Plots of the total number of individuals co-infected with latent TB and diabetes without complication and individuals co-infected with active TB and diabetes without complication when strategy E is implemented ($u_5 \neq 0, u_6 \neq 0$). Here, $\beta = 0.2001$. All other parameters as in Table 4.1

individuals with active TB and diabetes with complication in about 10 years.

4.2.10 Strategy F:Prevention Effort Against Development Of Complications Due To Diabetes $(u_2 \neq 0)$ and TB Treatment Effort For Non-Diabetic Patients $(u_3 \neq 0)$

For strategy F (prevention effort against development of complications due to diabetes $(u_2 \neq 0)$ and TB treatment effort for TB infectious but non-diabetic individuals $(u_3 \neq 0)$) . Figure



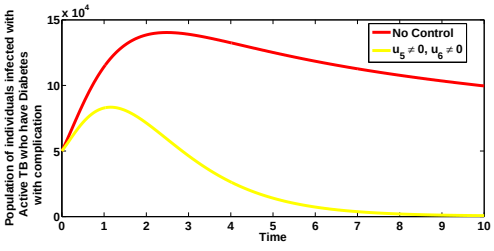
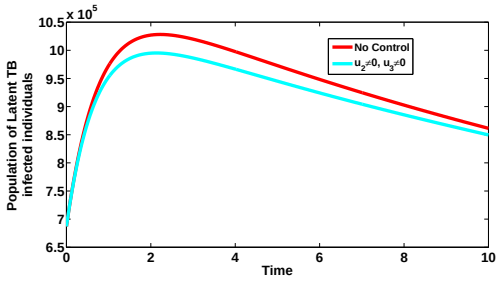


Figure 4.15: Plots of the total number of individuals co-infected with latent TB and diabetes with complication and individuals co-infected with active TB and diabetes with complication when strategy E is implemented ($u_5 \neq 0, u_6 \neq 0$). Here, $\beta = 0.2001$. All other parameters as in Table 4.1

4.16 shows that when this intervention strategy is implemented, the total number of individuals latently and actively infected with diabetes and tuberculosis significant decreases, as 11,900 new latent TB infected individuals were averted while 7,142 new active TB infected individuals were prevented.

For individuals co-infected with latent TB and diabetes without complication as well as individuals co-infected with active TB and diabetes without complication,as shown in Figure 4.17 this strategy averts 41,400 new cases of co-infection of latent TB/diabetes without complication and it prevented 5,062 new cases of active TB / diabetes without complication after a period of 10 years. The graph of this control strategy given in Figure 4.17 shows that by implementing this control strategy $(u_2 \neq 0, u_3 \neq 0)$ the infected population raised steadily to its peak in about 2 years, and then dropped to 151,500 individuals from 247,700 co-infected individuals with latent TB and diabetes without complication in about 10 years.

For individuals co-infected with latent TB and diabetes with complication as well as individuals co-infected with active TB and diabetes with complication as shown in Figure 4.18 this strategy averts 667,000 new cases of co-infection of latent TB / diabetes with complication and prevented 64,620 new cases of active TB / diabetes with complication after a period of 10 years. The graph of this control strategy given in Figure 4.18 shows that by implementing this control strategy $(u_2 \neq 0, u_3 \neq 0)$ the infected population raised steadily to its peak in less than 2 years, and then dropped to 35,490 active TB co-infected individuals from 120,000 co-infected individuals with active TB and diabetes with complication in about 10 years.



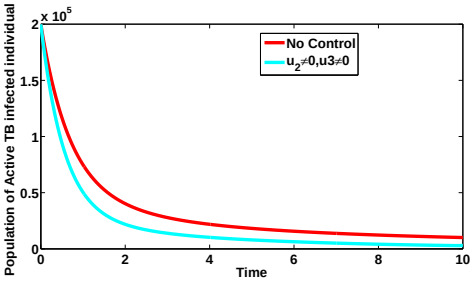
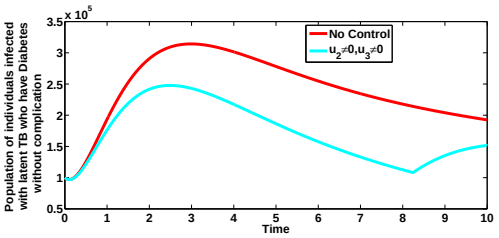


Figure 4.16: Plots of the total number of latently and actively-infected individuals when strategy F is implemented ($u_2 \neq 0, u_3 \neq 0$). Here, $\beta = 0.2001$. All other parameters as in Table 4.1



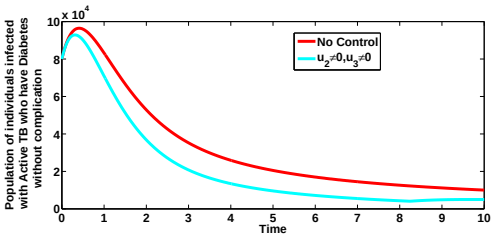
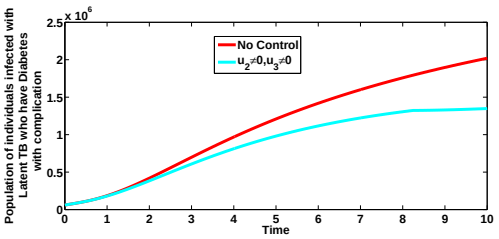


Figure 4.17: Plots of the total number of individuals co-infected with latent TB and diabetes without complication and individuals co-infected with active TB and diabetes without complication when strategy F is implemented ($u_2 \neq 0, u_3 \neq 0$). Here, $\beta = 0.2001$. All other parameters as in Table 4.1



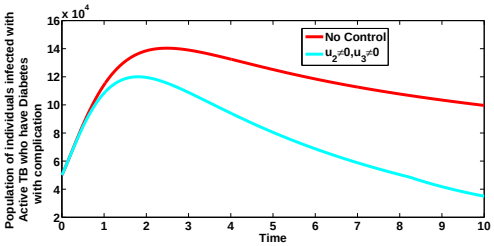


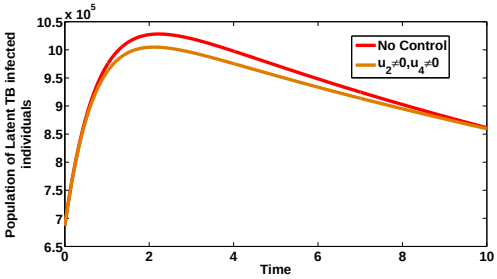
Figure 4.18: Plots of the total number of individuals co-infected with latent TB and diabetes with complication and individuals co-infected with active TB and diabetes with complication when strategy F is implemented ($u_2 \neq 0, u_3 \neq 0$). Here, $\beta = 0.2001$. All other parameters as in Table 4.1

4.2.11 Strategy G:Prevention Effort Against Development Of Complications Due To Diabetes $(u_2 \neq 0)$ And TB Treatment Effort For Individuals Who Have Diabetes Without Complication $(u_4 \neq 0)$

For strategy G (prevention effort against development of complications due to diabetes $(u_2 \neq 0)$ and TB Treatment effort for TB infectious persons that have diabetes without complication $(u_4 \neq 0)$) . Figure 4.19 shows that when this intervention strategy is implemented, the total number of individuals latently and actively infected with diabetes and tuberculosis significant decreases, as 1,700 new latent TB infected individuals were averted while 7,090 new active TB infected individuals were prevented.

For individuals co-infected with latent TB and diabetes without complication as well as individuals co-infected with active TB and diabetes without complication,as shown in Figure 4.20 this strategy averts 11,400 new cases of co-infection of latent TB/diabetes without complication and it prevented 5,933 new cases of active TB / diabetes without complication after a period of 10 years. The graph of this control strategy given in Figure 4.20 shows that by implementing this control strategy $(u_2 \neq 0, u_4 \neq 0)$ the infected population raised steadily to its peak in about 3 years, and then dropped to 192,500 individuals from 314,200 co-infected individuals with latent TB and diabetes without complication in about 10 years.

For individuals co-infected with latent TB and diabetes with complication as well as individuals co-infected with active TB and diabetes with complication as shown in Figure 4.21 this strategy averts 827,000 new cases of co-infection of latent TB / diabetes with complication and prevented 75,480 new cases of active TB / diabetes with complication after a period of 10 years. The graph of this control strategy given in Figure 4.21 shows that by implementing this control strategy $(u_2 \neq 0, u_4 \neq 0)$ the infected population raised steadily to its peak in about 2



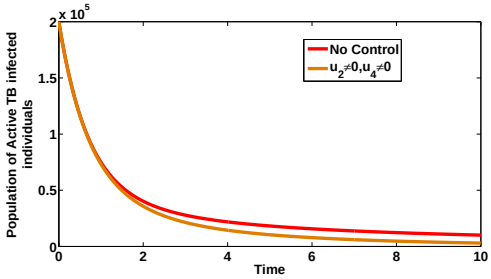
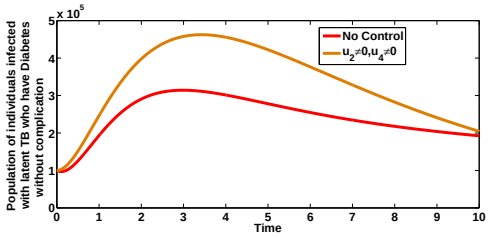


Figure 4.19: Plots of the total number of latently and actively-infected individuals when strategy G is implemented ($u_2 \neq 0, u_4 \neq 0$). Here, $\beta = 0.2001$. All other parameters as in Table 4.1



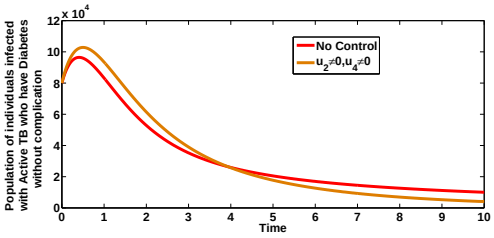
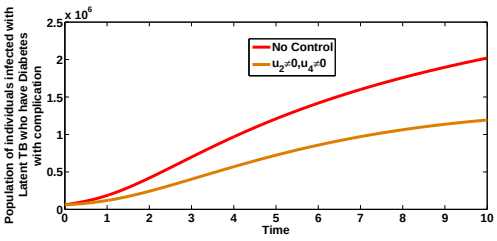


Figure 4.20: Plots of the total number of individuals co-infected with latent TB and diabetes without complication and individuals co-infected with active TB and diabetes without complication when strategy G is implemented ($u_2 \neq 0, u_4 \neq 0$). Here, $\beta = 0.2001$. All other parameters as in Table 4.1

years, and then dropped to 24,110 active TB co-infected individuals from 74,110 co-infected

individuals with active TB and diabetes with complication in about 10 years.



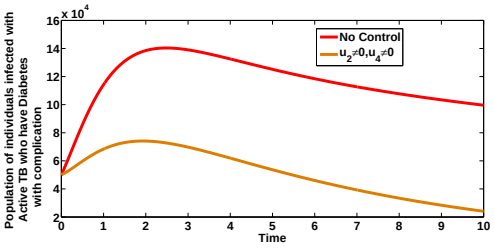


Figure 4.21: Plots of the total number of individuals co-infected with latent TB and diabetes with complication and individuals co-infected with active TB and diabetes with complication when strategy G is implemented ($u_2 \neq 0, u_4 \neq 0$). Here, $\beta = 0.2001$. All other parameters as in Table 4.1

4.2.12 Strategy H:Prevention Effort Against Development Of Complications Due To Diabetes $(u_2 \neq 0)$ And TB Treatment Effort For Individuals Who Have Diabetes With Complication $(u_5 \neq 0)$

For strategy H (prevention effort against development of complications due to diabetes $(u_2 \neq 0)$ and TB Treatment effort TB infectious persons that have diabetes with complication $(u_5 \neq 0)$) . Figure 4.22 shows that when this intervention strategy is implemented, the total number of individuals latently and actively infected with diabetes and tuberculosis significant decreases, as -7.000 new latent TB infected individuals were averted while 9,240 new active TB infected individuals were prevented.

For individuals co-infected with latent TB and diabetes without complication as well as individuals co-infected with active TB and diabetes without complication,as shown in Figure 4.23 this strategy averts 168,140 new cases of co-infection of latent TB/diabetes without complication and it prevented 8,855 new cases of active TB / diabetes without complication after a period of 10 years. The graph of this control strategy given in Figure 4.23 shows that by implementing this control strategy $(u_2 \neq 0, u_5 \neq 0)$ the infected population raised steadily to its peak in about 2 years, and then dropped to 4,417 individuals from its peak of 219,700 co-infected individuals with latent TB and diabetes without complication in about 10 years.

For individuals co-infected with latent TB and diabetes with complication as well as individuals co-infected with active TB and diabetes with complication as shown in Figure 4.24 this strategy averts 944,000 new cases of co-infection of latent TB / diabetes with complication and prevented 95,273 new cases of active TB / diabetes with complication after a period of 10 years. The graph of this control strategy given in Figure 4.24 shows that by implementing this control strategy $(u_2 \neq 0, u_5 \neq 0)$ the infected population raised steadily to its peak in less than

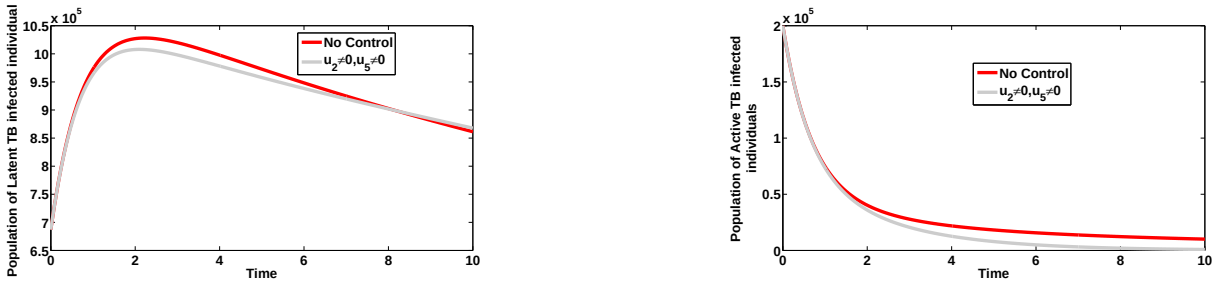


Figure 4.22: Plots of the total number of latently and actively-infected individuals when strategy H is implemented ($u_2 \neq 0, u_5 \neq 0$). Here, $\beta = 0.2001$. All other parameters as in Table 4.1

Figure 4.23: Plots of the total number of individuals co-infected with latent TB and diabetes without complication and individuals co-infected with active TB and diabetes without complication when strategy H is implemented ($u_2 \neq 0, u_5 \neq 0$). Here, $\beta = 0.2001$. All other parameters as in Table 4.1

2 years, and then dropped to 4,417 active TB co-infected individuals from 90,920 co-infected

individuals with active TB and diabetes with complication in about 10 years.

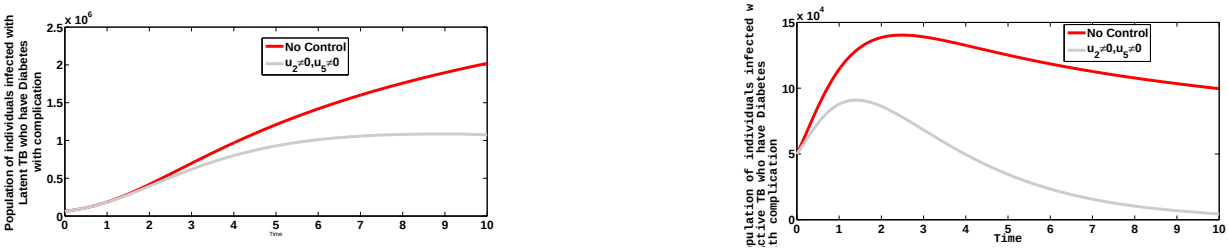


Figure 4.24: Plots of the total number of individuals co-infected with latent TB and diabetes with complication and individuals co-infected with active TB and diabetes with complication when strategy H is implemented ($u_2 \neq 0, u_5 \neq 0$). Here, $\beta = 0.2001$. All other parameters as in Table 4.1

4.2.13 Strategy I: TB Treatment Effort For Non-Diabetic Individuals $(u_3 \neq 0)$,TB Treatment Effort For Individuals Who Have Diabetes Without Complication $(u_4 \neq 0)$ And TB Treatment Effort For Individuals Who Have Diabetes With Complication $(u_5 \neq 0)$

For strategy I (TB treatment effort for non-diabetic individuals $(u_3 \neq 0)$,TB Treatment effort for TB infectious persons that have diabetes without complication $(u_4 \neq 0)$ and TB Treatment effort TB infectious persons that have diabetes with complication $(u_5 \neq 0)$) . Figure 4.25 shows that when this intervention strategy is implemented, the total number of individuals latently and actively infected with diabetes and tuberculosis significant decreases, as 39,300 new latent TB infected individuals were averted while 10,814 new active TB infected individuals were prevented.

For individuals co-infected with latent TB and diabetes without complication as well as individuals co-infected with active TB and diabetes without complication,as shown in Figure 4.26 this strategy averts 189,330 new cases of co-infection of latent TB/diabetes without complication and it prevented 9,887 new cases of active TB / diabetes without complication after a period of 10 years. The graph of this control strategy given in Figure 4.26 shows that by implementing this control strategy $(u_3 \neq 0, u_4/neq0, u_5 \neq 0)$ the infected population raised steadily to its peak in less than 2 years, and then dropped to 3470 individuals from its peak of 171,400 co-infected individuals with latent TB and diabetes without complication in about 10 years.

For individuals co-infected with latent TB and diabetes with complication as well as individuals co-infected with active TB and diabetes with complication as shown in Figure 4.27 this strategy averts 1,407,000 new cases of co-infection of latent TB / diabetes with complication and prevented 98,849 new cases of active TB / diabetes with complication after a period of

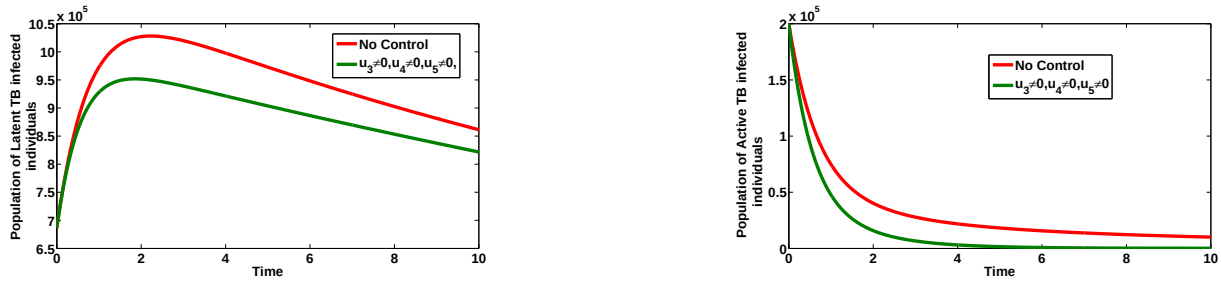


Figure 4.25: Plots of the total number of latently and actively-infected individuals when strategy I is implemented ($u_3 \neq 0, u_4 \neq 0, u_5 \neq 0$). Here, $\beta = 0.2001$. All other parameters as in Table 4.1

Figure 4.26: Plots of the total number of individuals co-infected with latent TB and diabetes without complication and individuals co-infected with active TB and diabetes without complication when strategy I is implemented ($u_3 \neq 0, u_4 \neq 0, u_5 \neq 0$). Here, $\beta = 0.2001$. All other parameters as in Table 4.1

10 years. The graph of this control strategy given in Figure 4.27 shows that by implementing this control strategy ($u_3 \neq 0, u_4/neq0, u_5 \neq 0$) the infected population raised steadily to its peak in less than 2 years, and then dropped to 146 active TB co-infected individuals from 85,110 co-infected individuals with active TB and diabetes with complication in about 10 years.

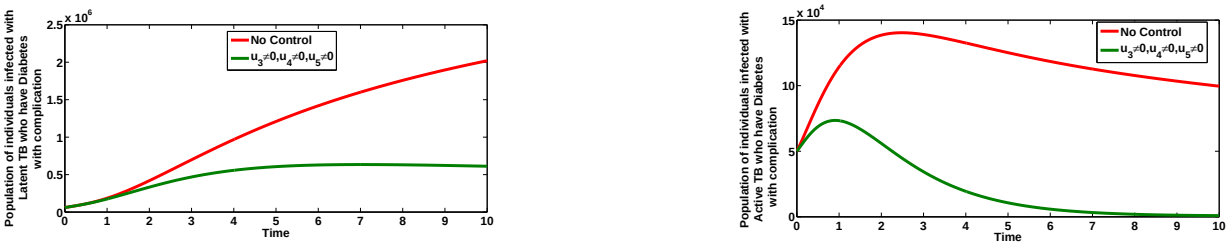


Figure 4.27: Plots of the total number of individuals co-infected with latent TB and diabetes with complication and individuals co-infected with active TB and diabetes with complication when strategy I is implemented ($u_3 \neq 0, u_4 \neq 0, u_5 \neq 0$). Here, $\beta = 0.2001$. All other parameters as in Table 4.1

4.2.14 Cost-Effectiveness Analysis

In this section, we seek to determine the most cost-effective intervention strategy in combating TB and diabetes co-infection. To achieve this, two methods are employed: the average cost-effectiveness ratio (ACER) and the incremental cost-effectiveness ratio (ICER). The cost-effectiveness analysis is used to evaluate the health interventions related benefits so as to justify the costs of the strategies (Tilahun et al(2017)). This is obtained by comparing the differences among the health outcomes and costs of those interventions. ACER deals with a single intervention strategy and weighing the intervention against its baseline option. It is the ratio of the total cost of the intervention to the total number of infection averted by the intervention. The formula is given thus:

$$\text{ACER} = \frac{\text{Total cost produced by intervention}}{\text{Total number of infection averted}}.$$

Likewise, ICER is concerned with the comparison of the differences between the costs and health outcomes of two alternative intervention strategies competing for the same resources. It is the ratio of the change in costs of two alternative strategies to the change in the total number of infection averted by the two strategies. The ICER formula is given by:

$$\text{ICER} = \frac{\text{Difference in costs between strategies}}{\text{Difference in health effects between strategies}}.$$

We calculated the total number of cases averted and the total cost of the strategies applied and presented it in Table 4.2. The total number of cases prevented is obtained by calculating the total number of individuals when controls are implemented and the total number when control is not administered. In a similar manner, we apply the cost functions

$\frac{1}{2}w_1u_1^2, \frac{1}{2}w_2u_2^2, \frac{1}{2}w_3u_3^2, \frac{1}{2}w_4u_4^2, \frac{1}{2}w_5u_5^2, \frac{1}{2}w_6u_6^2$, over time, to compute the total cost for the various strategies that were carried out. We assume the weight constants $w_1 = 500, w_2 = 550, w_3 = 650, w_4 = 700, w_5 = 700, w_6 = 400$. We also assumed here that;

- the cost of implementing TB treatment control for no -diabetic individuals is much higher compared to the cost of implementing the preventive controls which are mainly non-pharmaceutical.

- the cost of implementing TB treatment control for diabetic individuals is much higher than the cost of implementing the preventive control measures for (which are mainly non pharmaceutical) for the same class of individuals.

- the cost of implementing TB treatment control for non-diabetic individuals is much lesser than the cost of implementing TB treament control for diabetic individuals.

- the cost of implementing TB treatment control for diabetic individuals with complication is much higher that the cost of implementing TB treatment control for diabetic individuals without complication.

using the formular for ACER, we compute the ACER for the control strategies as shown in Table 4.2

Table 4.2: Increasing Order Of The Total Infection Averted Due To The Control Strategies

Strategy	**Total infection averted**	**Total cost**	**ACER**	**ICER**
Strategy F	797,124	1200	0.0015054	0.0015054
Strategy G	928,633	1250	0.0013460	0.0003802
Strategy H	1,218,508	1,450	0.0011900	0.0069000
Strategy I	1,755,180	2,250	0.0012819	0.0014907
Strategy A	1,895,298	900	0.0004748	-0.0008127
Strategy B	1,920,538	950	0.0004965	0.0019810
Strategy C	2,023,289	1,050	0.0005189	0.0011720
Strategy D	2,026,245	1,100	0.0005428	0.0015273
Strategy E	2,110,280	1,300	0.0006160	0.0018606

Also , using ICER method we now compare the cost effectiveness of strategy F(prevention effort against development of complication due to diabetes by regular medical checkup and keeping proper personal hygiene to avoid contracting tuberculosis($u_2 \neq 0$) and TB treatment effort for non diabetic individuals($u_3 \neq 0$)) and strategy G (prevention effort against development of complication due to diabetes by regular medical checkup and keeping proper personal hygiene to avoid contracting tuberculosis($u_2 \neq 0$) and TB Treatment effort for TB infectious persons that have diabetes without complication($u_4 \neq 0$)).

$$\text{ICER (F)} = \frac{1200}{797,124} = 0.0015254$$

$$\text{ICER (G)} = \frac{1200 - 1250}{797,124 - 928,633} = 0.0003802$$

From the computation of ICER (F) and ICER (G), we observe that ICER (F) is greater than ICER (G), which implies that strategy G ia more cost effective and less expensive compared to strategy F. therefore strategy F is removed from subsequent ICER computation. The result can be seen in Table 4.3

Again, we compare the cost effectiveness of strategy G (prevention effort against develop-

Table 4.3: Increasing Order Of The Total Infection Averted Due To The Control Strategies F and G

Strategy	**Total infection averted**	**Total cost**	ACER	ICER
F:	797,124	1,200	0.0015054	0.0015054
G:	928,633	1,250	0.0013460	0.0003802

ment of complication due to diabetes by regular medical checkup and keeping proper personal hygiene to avoid contracting tuberculosis($u_2 \neq 0$) and TB Treatment effort for TB infectious persons that have diabetes without complication($u_4 \neq 0$)) and strategy H (prevention effort a-gainst development of complication due to diabetes by regular medical checkup and keeping proper personal hygiene to avoid contracting tuberculosis($u_2 \neq 0$) and TB Treatment effort TB infectious persons that have diabetes with complication($u_5 \neq 0$)).

$$\text{ICER (G)} = \frac{1250}{928,633} = 0.0013461$$

$$\text{ICER (H)} = \frac{1250 - 1450}{928,633 - 1,218,508} = 0.0006900$$

From the computation of ICER (G) and ICER (H),we observe that ICER (G) is greater than ICER (H), showing that strategy G is more expensive and less cost effective than strategy H. hence strategy G is removerd from subsequent ICER computation. Table 4.4 shows the comparation of the cost effectivness of Stategy F, strategy G and strategy H.

Table 4.4: Increasing Order Of The Total Infection Averted Due To The Control Strategies F,G and H

Strategy	**Total infection averted**	**Total cost**	ACER	ICER
F:	797,124	1,200	0.0015054	0.0015054
G:	928,633	1,250	0.0013460	0.0003802
H:	1,218,508	1,450	0.0011900	0.0006900

Next, we compare the cost effectiveness of Strategy H (prevention effort against development of complication due to diabetes by regular medical checkup and keeping proper personal hygiene to avoid contracting tuberculosis($u_2 \neq 0$) and TB Treatment effort TB infectious persons that have diabetes with complication($u_5 \neq 0$)) and strategy I (TB treatment effort for non-diabetes individuals ($u_3 \neq 0$), TB Treatment effort for TB infectious persons that have diabetes without complication($u_4 \neq 0$) and TB Treatment effort TB infectious persons that have diabetes with complication($u_5 \neq 0$)).

$$\text{ICER (H)} = \frac{1450}{1,218,508} = 0.0011900$$
$$\text{ICER (I)} = \frac{1450 - 2250}{1,218,508 - 1,755,180} = 0.0014907$$

From the computation of ICER (H) and ICER (I), we have that ICER (I) is greater than ICER (H), showing that strategy H is less expensive and more cost effective than strategy I. Hence strategy I is removed from subsequent ICER computation.

we now compare the cost effectiveness of strategy H and strategy A (prevention effort against development of diabetes by encouraging healthy lifestyle ($u_1 \neq 0$) and prevention effort against development of TB by encouraging personal hygiene).

$$\text{ICER (H)} = 0.0011900$$
$$\text{ICER (A)} = \frac{1450 - 900}{1,218,508 - 1,895,298} = -0.0008127$$

observe that from the computation of ICER (H) and ICER (A), ICER (H) is greater than ICER (A), showing that strategy A is less expensive and more cost effective than strategy H.

Hence Strategy H is removed from subsequent ICER computation.

we again compare the cost effectiveness of strategy A (prevention effort against development of diabetes by encouraging healthy lifestyle ($u_1 \neq 0$) and prevention effort against development of TB by encouraging personal hygiene ($u_6 \neq 0$)) and strategy B (prevention effort against development of complication due to diabetes by regular medical checkup and keeping proper personal hygiene to avoid contracting tuberculosis($u_2 \neq 0$) and prevention effort against development of TB by encouraging personal hygiene ($u_6 \neq 0$)).

$$\text{ICER (A)} = \frac{900}{1,895,298} = 0.0004748$$
$$\text{ICER (B)} = \frac{900-950}{1,895,298-1,920,538} = 0.0019810$$

observe that from the computation of ICER (A) and ICER (B), ICER (B) is greater than ICER (A), showing that strategy A is less expensive and more cost effective than strategy B. Hence Strategy B is removed from subsequent ICER computation.

We again compare the cost effectiveness of strategy A (prevention effort against development of diabetes by encouraging healthy lifestyle ($u_1 \neq 0$) and prevention effort against development of TB by encouraging personal hygiene ($u_6 \neq 0$)) and strategy C (TB treatment effort for non-diabetes individuals ($u_3 \neq 0$ and prevention effort against development of TB by encouraging personal hygiene ($u_6 \neq 0$)).

$$\text{ICER (A)} = 0.0004748$$
$$\text{ICER (C)} = \frac{900-1050}{1,895,298-2,023,289} = 0.0011720$$

observe that from the computation of ICER (A) and ICER (C), ICER (C) is greater than ICER (A), showing that strategy A is again less expensive and more cost effective than strategy C. Hence Strategy C is removed from subsequent ICER computation.

We again compare the cost effectiveness of strategy A (prevention effort against development of diabetes by encouraging healthy lifestyle ($u_1 \neq 0$) and prevention effort against development of TB by encouraging personal hygiene ($u_6 \neq 0$)) and strategy D (TB Treatment effort for TB infectious persons that have diabetes without complication($u_4 \neq 0$) and prevention effort against development of TB by encouraging personal hygiene ($u_6 \neq 0$)).

$$\text{ICER (A)} = 0.0004748$$

$$\text{ICER (D)} = \frac{900 - 1100}{1,895,298 - 2,026,245} = 0.0015273$$

Again from the computation of ICER (A) and ICER (D), ICER (D) is greater than ICER (A), showing that strategy A is again less expensive and more cost effective than strategy D. Hence Strategy D is removed from subsequent ICER computation.

Finally, We compare the cost effectiveness of strategy A (prevention effort against development of diabetes by encouraging healthy lifestyle ($u_1 \neq 0$) and prevention effort against development of TB by encouraging personal hygiene ($u_6 \neq 0$)) and strategy E (TB Treatment effort TB infectious persons that have diabetes with complication($u_5 \neq 0$) and prevention effort against development of TB by encouraging personal hygiene ($u_6 \neq 0$)).

$$\text{ICER (A)} = 0.0004748$$

$$\text{ICER (E)} = \frac{900 - 1300}{1,895,298 - 2,110,280} = 0.0018606$$

Again from the computation of ICER (A) and ICER (E), ICER (E) is greater than ICER (A), showing that strategy A is less expensive and more cost effective than strategy E. Hence Strategy A has the least ICER and is the most cost effective of all the control strategies for the prevention of the co-infection of TB and diabetes. This also conform with the results obtained from the ACER method in Table 4.2, that strategy A is the most cost effective strategy.

Chapter 5

CONCLUSION AND RECOMMENDATION

5.1 Conclusion

In this work, we formulated and analyzed a mathematical model for the dynamics of TB infection in order to assess the impact of Diabetes on the dynamics of their co-infection. We analyzed the model by obtaining the feasible region, positivity of the solution set, basic reproductive number which is the maximum of the basic reproductive number of the co-infection model, equilibria points and their stability are analyzed.By using theorem (4.3) we investigated bifurcation of the model to explore the possibility of backward bifurcation.The model was shown to undergo the phenomenon of backward bifurcation when the bifurcation coefficient a is less than one. we extended the full co-infection model by applying optimal control interventions and we obtained the Hamiltonian, the adjoint variables , the characterization of the controls and the optimality system.we simulate the optimality system by considering different strategies as follows:

i. Strategy A - prevention effort against development of diabetes $(u_1 \neq 0)$ and prevention effort against development of TB $(u_6 \neq 0)$

ii. Strategy B - prevention effort against development of complication due to diabetes ($u_2 \neq 0$) and Prevention measures against activation of TB ($u_6 \neq 0$)

iii. Strategy C - TB treatment effort for TB infectious but non-diabetic individuals ($u_3 \neq 0$) and Prevention measures against activation of TB ($u_6 \neq 0$)

iv. Stategy D - TB treatment effort for diabetic TB patients without complications ($u_4 \neq 0$) and Prevention measures against activation of TB ($u_6 \neq 0$)

v. Strategy E - TB treatment effort for diabetic TB patients with complications($u_5 \neq 0$) and Prevention measures against activation of TB ($u_6 \neq 0$)

vi. Strategy F - :prevention effort against development of complications due to diabetes ($u_2 \neq 0$) and TB treatment effort for TB infectious but non-diabetic individuals ($u_3 \neq 0$) .

vii Strategy G -prevention effort against development of complications due to diabetes ($u_2 \neq 0$) and TB Treatment effort for TB infectious persons that have diabetes without complication ($u_4 \neq 0$)

viii. Strategy H -prevention effort against development of complications due to diabetes ($u_2 \neq 0$) and TB Treatment effort TB infectious persons that have diabetes with complication ($u_5 \neq 0$)

ix. Strategy I - TB treatment effort for non-diabetic individuals ($u_3 \neq 0$) ,TB Treatment effort for TB infectious persons that have diabetes without complication ($u_4 \neq 0$) and TB Treatment effort TB infectious persons that have diabetes with complication ($u_5 \neq 0$)

The model was simulated using data relevant to the dynamics of the diseases in Lagos, Nigeria, making predictions for the attainment of peak periods in the presence or absence of comorbidi-

ty. Numerically we investigated cost effectiveness analysis to determine, the least and the most expensive strategies by using ACER and ICER technique. From the comparison result we conclude that, Strategy A, which is applying prevention effort against development of diabetes by encouraging healthy lifestyle and prevention effort against development of TB by encouraging personal hygiene is the best cost effective strategy with health benefits as it was able to significantly avert 40,500 new cases of latent TB and 8,423 new cases of active TB. Furthermore for individuals co-infected with latent TB and diabetes without complication, the strategy averted 181,040 cases and prevented 9,349 new cases of active TB and diabetes without complication co-infection. Also for individuals co-infected with latent TB and diabetes with complication, it averted 1,566,100 new cases while it prevented 89,886 new cases of active TB and diabetes with complication co-infection.

5.2 Recommendation

It is evident from this study that the co-dynamics of diabetes and tuberculosis disease has a very profound impact on the dynamic transmission of tuberculosis and hence its controllability. Having done quite an exhaustive but not all-encompassing job in this research, for the diseases to be drastically controlled, we therefore recommend as follows:

i. Individual should endeavour to live a healthy lifestyle by eating adequate diet and exercising regularly in order not to become diabetic.

ii. Prevention effort should be made against development of tuberculosis by encouraging constant hygiene practice.

iii. Individuals who are diabetic should ensure that they do not develop complication due to diabetes by ensuring that they take their medication seriously and exercise regularly.

iv. Tuberculosis treatment effort and protection against tuberculosis infection should be made for diabetic individuals who have developed complication as this will help lower their death rate due to the co-dynamics of TB and diabetes.

5.3 Contribution to Knowledge

In this work, we improved on the existing works of Boutayeb et al (2004) and Moualen et al (2012) by formulating a model which holistically understudied the dynamics of diabetes and tuberculosis co-infection and adequately analyzed the co-dynamics in order to give a better public health strategic solution to the menace caused by the co-infection of diabetes and tuberculosis when compared to the work of Buotayeb et al (2004) and Moualen et al (2012). We were able to;

1. Formulate a comprehensive model for the co-dynamics of diabetes and tuberculosis that incorporates the total human population (both diabetic and non diabetic, tuberculosis infected and non-infected population).

2. Analyze the complex structured model to give a better public health strategic solution that will drastically lower the burden of the co-dynamics of diabetes and tuberculosis .

These we were able to do by;

i. Incorporating compartment for latent tuberculosis infected individuals who have diabetes with complication.

ii Incorporating compartment for active tuberculosis infected individuals who have diabetes with complication.

iii. Incorporating death rates due to complications

iv. Investigating the local and global stability of developed model

v. Assessing the impact of tuberculosis and diabetes treatment and prevention on the control of the co-dynamics of diabetes and tuberculosis using optimal control analysis.

5.4 Area Of Further Study

In this work, we have done some extensive analyses of the co-dynamics of the diabetes and tuberculosis. This is can be extended as a lot more studies can be done in this area. We aim to carry out further studies in the following area:

i. Study of the co-dynamics of multi-drug resistant TB and diabetes.

ii. Study of the dynamics of two-strain TB co-infection with diabetes.

iii. Analysis of Stochastic version of the TB-Diabetes co-infection model.

iv. More studies could also be devoted to other mathematical (fractional, agent based model, within/intra-host) and epidemiological dynamics of this co-interaction.

LIST OF PUBLICATION

1. Agwu C. O, Omame A.,Inyama S. I.,(2023) Analysis of Mathematical Model of Diabetes and Tuberculosis Co-infection. Int.J.Appl.Comput.Math.Vol 9:36/https://doi.org/10.1007/s40819-023-01515-5.

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