Mathematical models for the study of adherence to tuberculosis treatment taking into account the effects of HIV/AIDS and diabetes

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With love to all the people who have been with
me and those who cannot be with me today.

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Veni, vidi, vici.
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Resumo

Erick Manuel Delgado Moya. **Modelos matemáticos para o estudo da aderência ao tratamento da tuberculose levando em conta os efeitos do HIV/AIDS e diabetes**. Tese (Doutorado). Instituto de Matemática e Estatística, Universidade de São Paulo, São Paulo, 2021.

Neste trabalho, propomos um novo modelo matemático para o estudo da eficácia do tratamento da tuberculose, tendo em conta as subpopulações vulneráveis, o HIV/AIDS e doentes diabéticos. O nosso modelo estuda os diferentes tipos de resistência ao tratamento, multirresistente (MDR-TB) e extensivamente resistente aos fármacos (XDR-TB). Utilizamos duas técnicas de modelagem, equações diferenciais ordinárias (EDO) e derivadas de ordem fracional (EDF) no sentido de Caputo. As principais características matemáticas e epidemiológicas do modelo são investigadas. Foi obtido o número básico de reprodução ($\mathfrak{R}_0$) nas diferentes subpopulações (diabéticos, HIV/AIDS, e aqueles que não sofrem destas doenças). Apresentamos resultados que nos permitem saber como o número básico de reprodução é afetado quando variamos os parâmetros de resistência e recuperação conjuntamente. Realizamos uma análise de sensibilidade dos parâmetros associados à tuberculose. Demonstramos a persistência da tuberculose numa subpopulação num caso particular, mostrando a necessidade de aplicar uma estratégia de controle. Formulamos e estudamos um problema de controle ótimo com o objetivo de reduzir a resistência ao tratamento da tuberculose. Os controles se concentram na reinfecção/reactivação, MDR-TB e XDR-TB diferenciados em subpopulações. Para formular estes problemas, utilizamos os modelos ODE e FDE. A fim de estudar o nosso modelo, realizamos simulações computacionais. Entre os resultados obtidos, temos que o maior número de casos de infectados foram os TB sensíveis, e os casos de MDR-TB ultrapassam os casos de XDR-TB, exceto na subpopulação de diabéticos, que tem um crescimento de casos de XDR-TB que ultrapassa os outros compartimentos de todas as subpopulações. Mostramos a necessidade de prestar uma atenção diferenciada a estas subpopulações vulneráveis devido ao comportamento de casos resistentes. Em relação ao estudo de controle, obtivemos que a estratégia mais eficaz é quando ativamos todos os controles e começamos com um controle elevado. Com esta estratégia, reduzimos significativamente o número de casos resistentes e impedimos o crescimento de casos ao longo do tempo. Este trabalho ajuda as políticas de saúde sobre como agir nesta doença e estas ideias podem ser aplicadas a outras epidemias de transmissão respiratória.

Palavras-chave: Modelo. Tuberculose. HIV/AIDS. Diabetes. Controle ótimo. Derivadas fracionárias no sentido de Caputo.

Abstract

Erick Manuel Delgado Moya. **Mathematical models for the study of adherence to tuberculosis treatment taking into account the effects of HIV/AIDS and diabetes**. Thesis (Doctorate). Institute of Mathematics and Statistics, University of São Paulo, São Paulo, 2021.

In this work, we propose a new mathematical model for the study of the effectiveness of TB treatment taking into account the vulnerable subpopulations, HIV/AIDS and diabetic patients. Our model studies the different types of treatment resistance, multidrug-resistant (MDR-TB) and extensively drug-resistant (XDR-TB). We use two modeling techniques, ordinary differential equations (ODE) and fractional-order derivatives equations (FDE) in the Caputo sense. The main mathematical and epidemiological properties of the model are investigated. The basic reproduction number ($\mathfrak{R}_0$) in the different subpopulations (diabetics, HIV/AIDS, and those who do not suffer from these diseases) was studied. We present results that allow us to know how the basic reproductive number is affected when we vary the parameters of resistance and recovery together. We performed a sensitivity analysis of the parameters associated with TB. We proved the persistence of tuberculosis in a subpopulation showing the need to apply a control strategy. We formulated and studied an optimal control problem with the objective of reducing resistance to tuberculosis treatment. The controls are focused on reinfection/reactivation, MDR-TB and XDR-TB differentiated into subpopulations. We use the models with ODE and FDE in the formulation of the control problems. In order to study our models, we performed computational simulations. Among the results obtained, we have that drug-sensitive TB reported a greater number of cases with respect to MDR-TB and XDR-TB cases, and MDR-TB cases surpass XDR-TB cases, except in the diabetes subpopulation, which has a growth of XDR-TB cases that surpasses the other compartments of resistant of all the subpopulations. We show the need to pay differentiated attention to these vulnerable subpopulations due to the behavior of resistant cases. Regarding the control study, we obtained that the most effective strategy is to activate all controls and start with a high control. With this strategy we reduced the number of resistant cases significantly and prevented the growth of cases. This work helps health policies on how to act in this disease and these ideas can be applied to other epidemics of respiratory transmission.

Keywords: Model. Tuberculosis. HIV/AIDS. Diabetes. Optimal control. Fractional derivatives in the Caputo sense.

List of Abbreviations

ODE	Ordinary differential equations
FDE	Fractional derivative equations
TB	Tuberculosis
PECE	Predict-Evaluate-Correct-Evaluate method
MDR-TB	Multidrug-resistant TB
XDR-TB	Extensively drug resistant TB
HIV	Human immunodeficiency virus
AIDS	Acquired Immunodeficiency Syndrome
FOCP	Fractional-order optimal control problem

List of Symbols

$\frac{d}{dt}$	Ordinary derivative
H	Hamiltonian
$\mathfrak{R}_0$	Basic reproduction number
$\frac{d^n}{dt^n}$	Ordinary derivative of order n
$\int$	Riemann integral
$\mathbb{X}$	Random variable
$E[\mathbb{X}]$	Expected values of $\mathbb{X}$
$\lim f$	Limit of a function f
${}_a\mathbb{I}_t^\alpha$	Left-sided Riemann-Liouville fractional integral
${}_t\mathbb{I}_b^\alpha$	Right-sided Riemann-Liouville fractional integral
${}_a\mathbf{D}_t^\alpha$	Left-sided Riemann-Liouville fractional derivatives
${}_t\mathbf{D}_b^\alpha$	Right-sided Riemann–Liouville fractional derivatives
${}_a^c\mathbb{D}_t^\alpha$	Left-sided fractional derivatives in the Caputo sense
${}_t^c\mathbb{D}_b^\alpha$	Right-sided fractional derivatives in the Caputo sense
$Beta(\cdot,\cdot)$	Beta distribution
$B(\cdot)$	Beta function
$\Gamma(\cdot)$	Gamma function
AC^n	Set of functions with order derivative $n-1$ absolutely continuous
$\mathbb{R}$	Set of real numbers
$\mathbb{R}^+$	Set of all positive real numbers
$[\alpha]$	Part entire of α

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Chapter 1

Introduction

Background Information

Tuberculosis (TB) is one of the top 10 causes of death worldwide. TB is a chronic bacterial infectious disease contemporary caused by *Mycobacterium TB*. The bacteria get released in the air by a carrier with active TB through coughing, sneezing or talking. The largest number of TB patients are asymptomatic, in this case, it is named as latent TB and does not constitute a risk of transmission. An important feature of this disease is that all the TB people aren't equally infectious [43, 80].

TB treatments are mainly based on the use of antibiotics and we have two lines of treatment. Among the drugs included in the first-line of treatment are rifampicin (RIF), isoniazid (INH), pyrazinamide (PZA), ethambutol (EMB), and streptomycin (SM). The amikacin (AMK), kanamycin (KAN), capreomycin (CAP), cycloserine (CS)/Terizidone (LEV), ofloxacin (OFX), moxifloxacin (MOX), levofloxacin, Ethionamide (ETH)/ prothionamide (PTH), p-aminosalicylic acid (PAS) are in the second-line of treatment [91].

Multidrug-resistant tuberculosis (MDR-TB) is caused by resistance to at least isoniazid and rifampicin, the main drugs used to treat tuberculosis. The extensively drug-resistant TB (XDR-TB) is a type of MDR-TB that is resistant to isoniazid and rifampicin, in addition to any fluoroquinolose (ofloxacin, levoflaxin, moxifloxacim, and ciprofloxacin) and at least one of three injectable second-line drug (amikacin, kanamycin, capreomycin) [1, 91, 53].

A total of 1.5 million people died of TB in 2020 including 214,000 people with HIV. Tuberculosis is the 13th leading cause of death in the world. An estimated 10 million people fell ill with TB worldwide in 2020. An estimated 66 million lives were saved through TB diagnosis and treatment between 2000 and 2020. Only one in three people with drug-resistant TB accessed treatment in 2020 [95]. Tuberculosis transmission and multidrug-resistant tuberculosis have a strong impact on the population and are a current problems for the countries health systems.

Reinfection or reactivation is linked to the immune status of the patient and takes into account the behavior of the prevalence of the disease; in the case of HIV, the higher the prevalence, the higher the incidence of TB. Several studies have now shown that multiple genotypes can be detected by sampling both respiratory and extrapulmonary sites in seropositive individuals, illustrating the presence of migration routes within and between

organs. Reactivation of TB may occur if the patient's immune system is weakened and cannot contain the latent bacteria. The bacteria then become active; they overload the immune system and cause the person to become ill with tuberculosis [75].

The impact that HIV has on the pathogenesis of TB is evident. HIV infection has an important role in increasing the likelihood of developing TB disease infection and increases the risk of reactivation of TB (post-primary TB). The risk of transitioning from latent to active TB is estimated to be 12 to 20 times higher in people living with HIV. The risk of death in TB-HIV/AIDS co-infected persons is twice that of HIV-infected persons without TB. The lifetime risk of progression from latent to active tuberculosis in HIV-positive individuals is estimated at 5-10% [109].

Diabetes represents an important risk factor for respiratory diseases. It increases the TB risk from 1.5 to 7.8 times and the TB risk relative among patients with diabetes is 3.11 [87, 9, 63, 80]. The tuberculosis treatment regimen for diabetics is the same as for the general population, but diabetes can affect the efficacy of first-line TB drugs, particularly the use of rifampicin [87, 24, 80]. TB can develop impaired glucose intolerance (IGT) in patients. After successful completion of TB treatment, IGT normalizes, but it remains an important risk factor for the future development of diabetes [17, 21, 80].

The metabolic factors related to HIV, and antiretroviral therapy, may increase the incidence of diabetes over time. Anti-HIV drugs can contribute to the risk of diabetes. These include the older reverse transcriptase inhibitors (zidovudine, stavudine and didanosine) and protease inhibitors (indinavir, and lopinavir). The possibility that weight gain may increase the risk of developing diabetes is being studied. Some current treatments, such as integrase inhibitors (dolutegravir and bictegravir, raltegravir, and elvitegravir), have been associated with weight gain, although the reasons remain unclear [32].

1.0.1 Objectives

The aim of this work topresent a new mathematical model to study the resistance to TB treatment taking into account the influence of HIV/AIDS and diabetes and to present and solve the optimal control problem to reduce resistance to TB treatment. The specific objectives are:

- To present the mathematical model of TB treatment resistance with HIV/AIDS and diabetes.
- To use different modeling techniques, in particular ordinary differential equations and fractional differential equations.
- To study the basic reproduction number and the influence of parameters associated with resistance and recovery on it.
- To study the stability of the infection-free equilibrium points, the relationship with the basic reproduction number, and the existence of endemic equilibrium points.
- To present, study and solve the optimal control problem of treatment resistance and reinfection/reactivation of tuberculosis.
- To perform computational simulations to validate the model with the different techniques and optimal control problems.

1.0.2 Thesis Organization and Innovative Results

In the following section, we presented the theoretical results used in the work.

In the second chapter, we presented a state of art on the modeling of epidemics mainly tuberculosis and its relationships with HIV/AIDS and diabetes. A new mathematical model with ordinary differential equations focused on the resistance to the treatment of tuberculosis that relates tuberculosis, HIV/AIDS and diabetes and taking into account two types of resistance is presented. We found the basic reproduction number of the general model and by subpopulations. We studied the influence of resistance and recovery parameters on the basic reproduction numbers and obtained theoretical results that allow us to characterize different scenarios. We characterized the infection-free equilibrium points and their local and global stability related to the basic reproduction numbers. We investigated the sensitivity index of the parameters on the basic reproduction number and performed computational simulations to verify the theoretical results and studied the resistance compartments. The model and the main results were published and are as reference [80].

From the third to the fifth chapter, at the beginning a state of art was performed to introduce the different modeling techniques and the applications to tuberculosis mainly.

In the third chapter, we incorporated controls on resistance and reinfection/reactivation. As the controlled system is the model presented in the second chapter, it allows us to apply differentiated control to the different subpopulations and to take into account the different costs of control implementation. This is an important factor because reinfection/reactivation behavior, treatment resistance, and costs are not the same in different subpopulations. We performed computational simulations with different control strategies and studied two possibilities to start the control process.

In the fourth chapter, taking advantage of the use of fractional-order derivatives, we studied the model using fractional derivatives in the Caputo sense. We studied the basic properties of the model and the basic reproduction number using fractional-order derivative theory. We performed computational simulations for different fractional-orders, in order to validate the model and study the influence of the use of fractional-order derivatives in the Caputo sense. This work was published and is found as reference [54].

In the fifth chapter, we used the model of the fourth chapter to incorporate the controls and studied the optimal control problem. We presented a theoretical study of the control problem using the optimal control theory with fractional-order derivatives and performed computational simulations for different fractional-orders.

In the sixth chapter, we presented the final conclusions of the thesis.

1.1 Theorical Background

1.1.1 Basic Reproduction Number ($\mathfrak{R}_0$)

The basic reproduction number, $\mathfrak{R}_0$ is among the most important quantities in infectious disease epidemiology. It plays a fundamental role in the study of mathematical models of emerging infectious diseases in outbreak situations and provides information for the design of control strategies. In a population composed only of susceptible individuals, the average number of infections caused by an infected individual is defined as $\mathfrak{R}_0$.

The $\mathfrak{R}_0$ is mathematically characterized considering the transmission of the infection as a demographic process, in which the production of offspring is considered as causing a new infection through transmission. Thus, in consecutive generations of infected individuals, we can consider the infection process. Consecutive generations increasing in size indicate a growing population, and the growth factor per generation indicates the growth potential. This growth factor is the mathematical characterization of $\mathfrak{R}_0$. Then, we have that, if $0 < \mathfrak{R}_0 < 1$ the infection will die out in the long run and if $\mathfrak{R}_0 > 1$ the infection will be able to spread in a population [45]. The higher the $\mathfrak{R}_0$ the more difficult it will be to control the epidemic. The $\mathfrak{R}_0$ can be affected by several factors, such as the duration of infectivity of the affected patients, the infectivity of the organism and the degree of contact between the susceptible and infected populations. To find the $\mathfrak{R}_0$ in systems modeling epidemic behavior defined with ODE, we start with the equations that describe the production of new infections and the changes of state among infected individuals, which is called the infected subsystem. We first linearize the infected subsystem over the infection-free steady state. Linearization shows that $\mathfrak{R}_0$ characterizes the initial spread potential of an infected in a fully susceptible population and we assume that the change in the susceptible population is negligible during the first virus outbreak. In the next subsections, we show the relationship between $\mathfrak{R}_0$ and the local and global asymptotic stability at the infection-free equilibrium point [45].

The relationship between $\mathfrak{R}_0$ and local stability in disease-free point

The basic reproduction number depends on how we define the infected and uninfected compartments, and not only on the structure of the model. We define the number of individuals in the compartments as $x = (x_1, ..., x_n)$, where $x_i \geq 0, i = 1, ..., n$. Then, we order the compartments such that the first m ($m < n$) compartments correspond to infected individuals. Let X_s be the set of all disease-free states, that is

$$X_s = \{x \geq 0 | \quad x_i = 0, i = 1, ..., m\}.$$

$T_i(x)$ is the rate of new infections in compartment i, $\Sigma_i^+(x)$ the rate of transfer of individuals into compartment i by other means, and $\Sigma_i^-(x)$ the rate of transfer out of compartment i. We assume that all functions are continuously differentiable at least twice in each variable. The disease transmission model is defined as:

$$\dot{x_i} = T_i(x) - \Sigma_i(x) = f_i(x), \quad i = 1, ..., n, \tag{1.1}$$

with non-negative initial conditions, where $\Sigma_i = \Sigma_i^- - \Sigma_i^+$ and the following assumptions are satisfied:

(P1) If $x \geq 0$, then $T_i, \Sigma_i^-, \Sigma_i^+ \geq 0$ for $i = 1, ..., m$ (each function represents a directed transfer of individuals, and are non-negative).

(P2) if $x_i = 0$ then $\Sigma_i^-(x) = 0$ (if a compartment is empty, there is no transfer of individuals out of the compartment by any means).

(P3) $T_i = 0$ if $i > m$, (the incidence of infection for uninfected compartments is null).

(P4) If $x \in X_s$ then $T_i(x) = 0$ and $\Sigma_i^+(x) = 0$ for $i = 1, ..., m$ (there is no inmigration of

infectives, density independent).

(P5) Consider a population near the disease-free equilibrium point x_0. If, we introduce some infected individuals it does not lead to an epidemic, i.e. the population remains close to x_0, then according to the linearized system the population will return to x_0.

$$\dot{x} = Df(x_0)(x - x_0), \tag{1.2}$$

where $Df(x_0)$ is the Jacobian matrix, $\left[\frac{\partial f_i}{\partial x_j}\right]_{(i,j)}$ evaluated at the x_0. We have that some derivatives are one-sided, since x_0 is on the boundary of the domain. We focus our study to systems in which x_0 is stable in the absence of a new infection. That is, If $T(x)$ is set to zero, then all eigenvalues of $Df(x_0)$ have negative real parts.

The following lemma shows us a way to partition $Df(x_0)$ by the above conditions.

Lemma 1.1.1. *If x_0 is the equilibrium disease-free point of system (1.1) and $f_i(x)$ satisfies (P1)-(P5), then the derivatives $DT(x_0)$ and $D\Sigma(x_0)$ can be decomposed as*

$$DT(x_0) = \begin{bmatrix} \mathbf{T} & 0 \\ 0 & 0 \end{bmatrix},$$

$$D\Sigma(x_0) = \begin{bmatrix} \Sigma & 0 \\ J_3 & J_4 \end{bmatrix},$$

where $\mathbf{T}$ and Σ are the $m \times m$ matrices defined by $\mathbf{T} = \left[\frac{\partial T_i}{\partial x_j}(x_0)\right]$, $\Sigma = \left[\frac{\partial \Sigma_i}{\partial x_j}(x_0)\right]$ with $1 \leq i, j \leq m$. Further, $\mathbf{T}$ is non-negative, Σ is a non-singular M-matrix[1] and all eigenvalues of J_4 have positive real part.

The (j,k) entry of Σ^{-1} is the average length of time this individual spends in compartment j during his lifetime, we assumed that the population remains close to disease-free equilibrium and without reinfection. The (i,j) entry of $\mathbf{T}$ is the rate where individuals in j produce new infections in i. Then, the input (i,k) in $\mathbf{T}\Sigma^{-1}$ is the expected number of new infections in compartment i produced by the infected individual introduced in compartment k. We define $\mathbf{T}\Sigma^{-1}$ as the next-generation matrix for the model and

$$\mathfrak{R}_0 = \rho(\mathbf{T}\Sigma^{-1}),$$

where $\rho(-\mathbf{T}\Sigma^{-1})$ denotes the spectral radius of a matrix $\mathbf{T}\Sigma^{-1}$.

The following lemmas are part of the proof of the Theorem (1.1.4). For more details of Lemmas (1.1.2)-(1.1.3) and Theorem (1.1.4) and its proofs, the readers could consult to [51].

Lemma 1.1.2. *Let H be a non-singular M-matrix and suppose B and BH^{-1} have the Z sign pattern[2]. Then B is a non-singular M-matrix if and only if BH^{-1} is a non-singular M−matrix.*

---

[1] If B is non-negative matrix, and $r > \rho(B)$ where $\rho(B)$ is the spectral ratio of B, then $A = rI_m - B$ is non-singular M- matrix where I_m is the identity matrix. If $r = \rho(B)$, then A is a singular M-matrix [51].

[2] A matrix $B = [b_{ij}]$ has the Z sign pattern if $b_{ij} \leq 0$ for all $i \neq j$.

Lemma 1.1.3. *Let H be a non-singular $M-$matrix and suppose $K \geq 0$. Then,*

i. $(H - K)$ is non-singular $M-$matrix if and only if $(H - K)H^{-1}$ is a non-singular $M-$matrix.

ii. $(H - K)$ is singular $M-$matrix if and only if $(H - K)H^{-1}$ is a singular $M-$matrix.

If all the eigenvalues of matrix $Df(x_0)$ have negative real parts then x_0 is locally asymptotically stable and unstable if any eigenvalue of $Df(x_0)$ has positive real part. Using the Lemma (1.1.1), we can decompose the eigenvalues into two sets, the $\mathbf{T} - \Sigma$ eigenvalues and those of $-J_4$ which all have negative real part. Therefore, the stability of the infection-free point depends on the $\mathbf{T} - \Sigma$ eigenvalues. The following theorem shows the relationship between the $\mathfrak{R}_0$ and the local stability in x_0.

Theorem 1.1.4. *Consider the disease transmission model given by (1.1) and $f(x)$ satisfies (P1)-(P5). If x_0 is the equilibrium disease-free point of the model, then x_0 is locally asymptotically stable (l.a.s) if $\mathfrak{R}_0 < 1$, but unstable if $\mathfrak{R}_0 > 1$ with $\mathfrak{R}_0 = \rho(\mathbf{T}\Sigma^{-1})$.*

Proof. The (P1)-(P5) conditions are used in the Lemmas (1.1.2) and (1.1.3) that are applied in the proof.

Let $J_1 = \mathbf{T} - \Sigma$. As Σ is non-singular M-matrix and $\mathbf{T}$ is non-negative, $-J_1 = \Sigma - \mathbf{T}$, has the Z sign pattern. Thus,

$$s(J_1) < 0 \Leftrightarrow -J_1 \text{ is a non-singular matrix,}$$

where $s(J_1)$ denotes the maximum real part of all the eigenvalues of the matrix J_1. Since $\mathbf{T}\Sigma^{-1}$ is non-negative, $-J_1\Sigma^{-1} = I - \mathbf{T}\Sigma^{-1}$ also has the Z sign pattern. For the application of Lemma (1.1.2) with $H = \Sigma$ and $B = -J_1 = \Sigma - \mathbf{T}$, we have

$$-J_1 \text{ is a non-singular M-matrix} \Longleftrightarrow I - \mathbf{T}\Sigma^{-1} \text{ is a non-singular M-matrix.}$$

Finally, since $\mathbf{T}\Sigma^{-1}$ is non-negative, all eigenvalues of $\mathbf{T}\Sigma^{-1}$ have magnitude less than or equal to $\rho(\mathbf{T}\Sigma^{-1})$. Then,

$$I - \mathbf{T}\Sigma^{-1} \text{ is a non-singular M-matrix,} \Longleftrightarrow \rho(\mathbf{T}\Sigma^{-1}) < 1.$$

Hence,

$$s(J_1) < 0 \quad \Leftrightarrow \quad \mathfrak{R}_0 < 1.$$

Analogously, we have that

$$\begin{aligned} s(J_1) = 0 &\Longleftrightarrow -J_1 \text{ is a singular M-matrix,} \\ &\Longleftrightarrow I - \mathbf{T}\Sigma^{-1} \text{ is a singular M-matrix, for Lemma (1.1.3) with } H = \Sigma \text{ and } K = \mathbf{T} \\ &\Longleftrightarrow \rho(\mathbf{T}\Sigma^{-1}) = 1. \end{aligned}$$

The rest of the equivalences are obtained as in the non-singular case. Therefore, $s(J_1) = 0$ if and only if $\mathfrak{R}_0 = 1$. Then, we have that $s(J_1) > 0$ if and only if $\mathfrak{R}_0 > 1$. □

Global Stability for the Disease-Free Equilibrium

In this subsection, we list two conditions that if met, also guarantee the global asymptotic stability of the disease-free point. First, we write the system as:

$$\begin{aligned} \frac{dx}{dt} &= F(x, I), \\ \frac{dI}{dt} &= G(x, I), \qquad\qquad G(x, 0) = 0, \end{aligned} \tag{1.3}$$

where $x \in \mathbb{R}^{n-m}$ denotes the number of uninfected individuals (components) and $I \in \mathbb{R}^m$ denotes the number of infected individuals including latent, infectious, etc (components). $X_0 = (x^*, 0)$ denotes the disease-free equilibrium point. The conditions (H_1) and (H_2) below must be satisfied to guarantee local asymptotic stability.

- (H_1): For $\dfrac{dx}{dt} = F(x, 0), \quad x^*$ is globally asymptotically stable (g.a.s) in Ω,
- (H_2): $G(x, I) = AI - G^*(x, I)$, $G^*(x, I) \geq 0$ for $(x, I) \in \Omega$,

where $A = D_I G(x^*, 0)$ is an M-matrix (Jacobian of G with the off-diagonal elements nonnegative) and Ω is the invariant biologically feasible region of the system.

If the system (1.3) satisfies the above two conditions, then we have the following theorem:

Theorem 1.1.5. *The fixed point $X_0 = (x^*, 0)$ is a globally asymptotic stable (g.a.s) equilibrium point of the system provided that $\mathfrak{R}_0 < 1$ (l.a.s) and that assumptions (H_1) and (H_2) are satisfied.*

This theorem, its proof and examples of its application can be found in [38].

Proof. Let $I_0 = I(0)$, we have that $I(t) \geq 0$ if $I_0 > 0$ and that e^{At} is a positive semigroup (since A is an M- matrix). Hence, using the variation-of-constants formula, we have

$$0 \leq I(t) = e^{At} I_0 - \int_0^t e^{A(t-s)} G^*(x(s), I(s)) ds \leq e^{At} I_0. \tag{1.4}$$

Since A is an M-matrix, A has a dominant eigenvalues $m(A)$ with $m(A) < 0$ for $\mathfrak{R}_0 < 1$. Thus,

$$\lim_{t\to\infty} \|e^{At}\| = 0 \quad \Longrightarrow \quad \lim_{t\to\infty} I(t) = 0. \tag{1.5}$$

Note that x^* is a g.a.s equilibrium of $\dfrac{dx}{dt} = F(x, 0)$, a limiting system of $\dfrac{dx}{dt} = F(x(t), I(t))$.
Thus,

$$\lim_{t\to\infty} x(t) = x^*. \tag{1.6}$$

□

1.1.2 Fractional-Order Derivative

In this subsection, we present definitions and results that show the advantages of using fractional-order derivatives in epidemiological models. The main bibliographic reference used to present the results is [29].

Definition 1.1.1. *(Fractional integral of Riemann-Liouville, [116, 29]) Let $\alpha \in \mathbb{R}^+$, $b > 0$ and $f \in \mathbb{L}^p([0,b] \to \mathbb{R}^m)$, with $1 \leq p \leq \infty$. The fractional integral of Riemann-Liouville, for $t \in [0,b]$, of order α, is given by*

$$\mathbb{I}_t^\alpha f(t) = \frac{1}{\Gamma(\alpha)} \int_0^t (t-s)^{\alpha-1} f(s) ds,$$

where $\Gamma(\cdot)$ is the Gamma function and when $\alpha \in \mathbb{N}$, we have $\Gamma(\alpha) = \alpha!$
We define $AC^n[0,b]$ as the set of functions with order derivative $n-1$ absolutely continuous in $[0,b]$ [47].

Definition 1.1.2. *(Fractional derivative of Riemann-Liouville, [116, 29]) Let $\alpha \in \mathbb{R}^+$, $b > 0$, $f \in AC^n[0,b]$, and $n = [\alpha]$ (part entire of α). The fractional derivative of Riemann-Liouville of order α, is given by*

$$\mathbf{D}_t^\alpha f(t) = \mathbf{D}_t^n \mathbb{I}_t^{n-\alpha} f(t) = \frac{d^n}{dt^n} \left(\frac{1}{\Gamma(n-\alpha)} \int_0^t (t-s)^{n-\alpha-1} f(s) ds \right). \tag{1.7}$$

Definition 1.1.3. *(Fractional derivative in the Caputo sense, [116, 29]) Let $\alpha \in \mathbb{R}^+$, $b > 0$ and $f \in AC^n[0,b]$. For $t \in [0,b]$, the fractional derivative in the Caputo sense of order α is given by*

$$^c\mathbb{D}_t^\alpha f(t) = \mathbf{D}_t^\alpha (f(t) - f(0)). \tag{1.8}$$

For $\alpha \in (0,1)$, we have that

$$^c\mathbb{D}_t^\alpha f(t) = \mathbb{I}_t^{1-\alpha} \dot{f}(t), \tag{1.9}$$

where $\dot{f}(t)$ represent of the first derivative of f.

Other definition of the fractional derivative in the Caputo sense is:

Definition 1.1.4. *(See [99, 54]) For $\alpha > 0$, with $n-1 < \alpha < n$, $n \in \mathbb{N}$, the fractional derivative in the sense of Caputo is defined as*

$$^c\mathbb{D}_t^\alpha f(t) = \frac{d^\alpha f(t)}{dt^\alpha} := \frac{1}{\Gamma(n-\alpha)} \int_0^t (t-s)^{n-\alpha-1} f^n(s) ds.$$

Now, we present definitions and statistical results that we will use.

Definition 1.1.5. *(Beta distribution (Beta$(\cdot,\cdot)$), [99, 29]) A random variable[3], $\mathbb{X}$, follows the*

[3] A random variable is a variable whose value is unknown or a function that assigns values to each of an experiment's outcomes [52].

Beta distribution if its probability density function is given by

$$f_{\mathbb{X}}(x) = f_{\mathbb{X}}(x; p, q) = \frac{1}{B(p,q)} x^{p-1}(1-x)^{q-1}\mathbf{I}_{(0,1)}(x), \tag{1.10}$$

where $p, q > 0$, $\mathbf{I}_{(0,1)}$ is the indicator function of interval $(0,1)$ and $B(\cdot)$ is the beta function.

Remark 1.1.6. *When $p = q = 1$, the Beta distribution becomes the uniform distribution over the range $(0,1)$.*

Definition 1.1.6. *(See [99, 29]) Let $\mathbb{X}$ be a continuous random variable with the probability density function $f_{\mathbb{X}}(\cdot)$. The expectation or expected value of $\mathbb{X}$ is given by*

$$E[\mathbb{X}] = \int_{-\infty}^{\infty} x f_{\mathbb{X}}(x) dx. \tag{1.11}$$

Proposition 1.1.7. *(See [99, 29]) Let $g : \mathbb{R} \to \mathbb{R}$ and $\mathbb{X}$ be a continuous random variable with the probability density function $f_{\mathbb{X}}(\cdot)$. The expectation or expected value of $g(\mathbb{X})$ is given by*

$$E[g(\mathbb{X})] = \int_{-\infty}^{\infty} g(x) f_{\mathbb{X}}(x) dx. \tag{1.12}$$

Let's mention important properties of fractional derivatives in the Caputo sense.

Lemma 1.1.8. *Let $n-1 < \alpha < n$, $n \in \mathbb{N}$, $\alpha \in \mathbb{R}^+$ and $f(t)$ be such that ${}^c\mathbb{D}_t^\alpha f(t)$ exists. Then,*

- $\lim_{\alpha \to n} {}^c\mathbb{D}_t^\alpha f(t) = f^{(n)}(t)$,
- $\lim_{\alpha \to n-1} {}^c\mathbb{D}_t^\alpha f(t) = f^{(n-1)}(t) - f^{(n-1)}(0)$,

where $f^{(n)}$ and $f^{(n-1)}$ are the classical integer derivatives of f of order n and $n-1$ respectively.

Lemma 1.1.9. *(Linearly) Let $n-1 < \alpha < n$, $n \in \mathbb{N}$, $\lambda \in \mathbb{C}$ and the function $f(t)$ and $g(t)$ be such that both ${}^c\mathbb{D}_t^\alpha f(t)$ and ${}^c\mathbb{D}_t^\alpha g(t)$ exist. The Caputo fractional derivative is a linear operator, i.e:*

$${}^c\mathbb{D}_t^\alpha(\lambda f(t) + g(t)) = \lambda\, {}^c\mathbb{D}_t^\alpha f(t) + {}^c\mathbb{D}_t^\alpha g(t).$$

Lemma 1.1.10. *(Non-commutative) Let $n-1 < \alpha < n$ and $n, m \in \mathbb{N}$ and $f(t)$ be such that ${}^c\mathbb{D}_t^\alpha f(t)$ exists. Then,*

$${}^c\mathbb{D}_t^\alpha \mathbf{D}^m f(t) = {}^c\mathbb{D}_t^{\alpha+m} f(t) \neq \mathbf{D}^m({}^c\mathbb{D}_t^\alpha f(t)).$$

Memory Effect

The fractional calculus is a great tool that can be employed to describe real-life phenomena with so-called memory effect. One way to introduce the memory effect into a mathematical model is to change the order of the derivative so that it is non-integer [47, 29].

Let f be a real function defined in $[0,t]$, $t_1, t_2 \in [0,t]$ are such that $0 < t_1 < t_2$, and

$F = (\mathbb{I}^\alpha f)(t_2) - (\mathbb{I}^\alpha f)(t_1)$, for $\alpha \in \mathbb{R}^+$. If $\alpha \neq 1$ it can be seen that the value of F depends on the entire range of f over $[0, t_2]$, whereas F depends only on the range of f over $[t_1, t_2]$. Now, if $\alpha = 1$ [29]:

$$\begin{aligned} F &= (\mathbb{I}^\alpha f)(t_2) - (\mathbb{I}^\alpha f)(t_1) \\ &= \frac{1}{\Gamma(\alpha)}\left[\int_0^{t_2} (t_2 - s)^{\alpha-1} f(s)ds - \int_0^{t_1} (t_1 - s)^{\alpha-1} f(s)ds\right] \\ &= \frac{1}{\Gamma(\alpha)}\left[\int_{t_1}^{t_2} (t_2 - s)^{\alpha-1} f(s)ds + \int_0^{t_1} [(t_2 - s)^{\alpha-1} - (t_1 - s)^{\alpha-1}] f(s)ds\right]. \end{aligned}$$

Note that if $\alpha = 1$, the second integral is eliminated and we obtain:

$$F = \int_{t_1}^{t_2} f(s)ds.$$

Now, we study the memory effect in derivatives and integrals of fractional-order based on the expected values of a random variable. The following proposition characterizes three fractional operators that depend on expected values of a random variable ($E[\mathbb{X}]$).

Proposition 1.1.11. *Let $\alpha \in \mathbb{R}^+$ and $f \in AC[0, b]$. Under these conditions, we have*

$$\mathbb{I}_t^\alpha f(t) = \frac{t^\alpha}{\Gamma(\alpha + 1)} E[f(tU)]; \tag{1.13}$$

$$\mathbf{D}_t^\alpha f(t) = \frac{t^{-\alpha}}{\Gamma(1 - \alpha)} E[f(tW)] + \frac{t^{1-\alpha}}{\Gamma(3 - \alpha)} E[\dot{f}(tV)], \quad \text{if} \quad 0 < \alpha < 1; \tag{1.14}$$

$${}^c\mathbb{D}_t^\alpha f(t) = \frac{t^{1-\alpha}}{\Gamma(2 - \alpha)} E[\dot{f}(tW)], \quad \text{if} \quad 0 < \alpha < 1, \tag{1.15}$$

where U, V and W are random variables with $U \sim Beta(1, \alpha)$, $V \sim Beta(2, 1 - \alpha)$ and $W \sim Beta(1, 1 - \alpha)$.

The previous proposition is presented and proved in [29]. Let's present the proof of (1.15).

Proof. For $\alpha \in (0, 1)$, we have that

$$\begin{aligned} {}^c\mathbb{D}_t^\alpha f(t) &= \mathbb{I}_t^{1-\alpha} \dot{f}(t) \\ &= \frac{1}{\Gamma(1 - \alpha)} \int_0^1 (t - s)^{-\alpha} \dot{f}(s)ds \\ &= \frac{1}{\Gamma(1 - \alpha)} \int_0^t t^{-\alpha} \left(1 - \frac{s}{t}\right)^{-\alpha} \dot{f}(s)ds \\ &= \frac{1}{\Gamma(1 - \alpha)} \int_0^1 t^{1-\alpha} (1 - u)^{-\alpha} \dot{f}(tu)du \\ &= \frac{t^{1-\alpha}}{\Gamma(1 - \alpha)} B(1, 1 - \alpha) \int_0^1 \frac{(1 - u)^{(1-\alpha)-1}}{B(1, 1 - \alpha)} \dot{f}(tu)du \end{aligned}$$

$$= \frac{t^{1-\alpha}}{(1-\alpha)\Gamma(1-\alpha)} \int_0^1 \frac{(1-w)^{(1-\alpha)-1}}{B(1,1-\alpha)} \dot{f}(tw)dw$$
$$= \frac{t^{1-\alpha}}{\Gamma(2-\alpha)} E[\dot{f}(tW)],$$

where $W \sim Beta(1, 1-\alpha)$. Thus, we obtain (1.15). □

Remark 1.1.12. *We can rewrite Caputo's derivative as follows [29]:*

$$^c\mathbb{D}_t^\alpha f(t) = \frac{t^{-\alpha}}{\Gamma(1-\alpha)} E[f(tW) - f(0)] + \frac{t^{1-\alpha}}{\Gamma(3-\alpha)} E[\dot{f}(tV)]. \tag{1.16}$$

The Hysteresis Phenomenon

When the current state of a system is influenced by its historical past, that system is said to be influenced by the phenomenon of hysteresis. This is a typical kernel used to define integral and fractional differential operators, such as the Caputo derivative. Fractional operators can be interpreted from the statistical approach, through the mathematical expectation, where the past history of the system follows a *Beta* distribution. As the α parameter is between 0 and 1, recent times are more influential than past times in this distribution [19, 29].

We can use fractional operator (1.13)-(1.15) to interpret the hysteresis effect. More precisely, the rate of variation of the Caputo derivative is given explicitly by the weighted average of all past derivatives as we can see in Formula (1.13). The other operators have similar explanations [29].

As U has distribution $B(1, \alpha)$, the random variable $S = tU$ has the values in the interval $(0, t)$. Thus, from (1.13), $\mathbb{I}_t^\alpha f(t)$ coincides with $\frac{t\alpha}{\Gamma(\alpha+1)} E[f(S)]$, $0 \leq s \leq t$. The $\mathbb{I}_t^\alpha f(t)$ is affected by all previous values in t because the expected value $E[f(S)]$ is affected as well. Given that $E[f(S)]$ is in (1.14) and (1.15), we may deduce that $\mathbf{D}_t^\alpha f(t)$ and $^c\mathbb{D}_t^\alpha f(t)$ also have memory effect. With the formulas (1.13)-(1.15), we arrive at the following interpretations [29]:

- The fractional integral $\mathbb{I}_t^\alpha f(t)$ is proportional to the weighted average of $f(s)$, considering all prior values s of t, distributed by a *Beta* distribution;
- $\mathbf{D}_t^\alpha f(t)$ is the sum of two amounts proportional to the weighted average of $f(s)$;
- $^c\mathbb{D}_t^\alpha f(t)$ is proportional to the weighted average of the classic derivative $\dot{f}(s)$, considering all prior values $s < t$, distributed by a *Beta* distribution;
- if $\alpha = 1$, then $U \sim B(1, 1)$, U has uniform distribution such that $\mathbb{I}_t^\alpha = tE[f(tU)] = \int_0^t f(s)ds$. Therefore, $\mathbf{D}_t^\alpha f(t) = \frac{d}{dt}\mathbb{I}_t^0 f(t) = \frac{d}{dt} f(t) = \dot{f}(t)$ and $^c\mathbb{D}_t^\alpha[f(t) - f(0)] = \frac{d}{dt}\mathbb{I}_t^0[f(t) - f(0)] = \frac{d}{dt}[f(t) - f(0)] = \dot{f}(t)$. Consequently, when $\alpha = 1$ the fractional and integer calculus coincide.

The authors of [29] show the influence of *Beta* distribution on fractional operators, in particular on the Riemann-Liouville and Caputo fractional operators.

Numerical Method

The algorithm used in this work to numerically solve nonlinear differential equations of fractional-order can be found in [48, 49, 50]. The algorithm has the structure of a PECE (Predict-Evaluate-Correct-Evaluate) method and combines a fractional-order algorithm with a classical method. The approach chosen is Adams-Bashforth-Moulton for both integrators. The key to deriving the method in the fractional variant is to use the trapezoidal quadrature product formula. This algorithm is independent of the $\alpha-$parameter and behaves very similar to the classical Adams-Bashforth-Moulton method. The stability properties do not change in the fractional version compared to the classical algorithm.

Optimal Control Problem with FDE

The following definitions are used to formulate and study the fractional-order optimal control problem (FOCP).

We assume that $\alpha \in \mathbb{R}^+$, $b > 0$, $f \in AC^n[a,b]$, and $n = [\alpha]$. We define the left-sided and right-sided fractional integral Riemann-Louville for $f : \mathbb{R}^+ \longrightarrow \mathbb{R}$, $\alpha > 0$ are:

$$ {}_a\mathbb{I}_t^\alpha f(t) := \frac{1}{\Gamma(\alpha)} \int_a^t \frac{f(s)ds}{(t-s)^{1-\alpha}}, \qquad \text{(Left)} \tag{1.17} $$

$$ {}_t\mathbb{I}_b^\alpha f(t) := \frac{1}{\Gamma(\alpha)} \int_t^b \frac{f(s)ds}{(s-t)^{1-\alpha}}. \qquad \text{(Right)} \tag{1.18} $$

Note: Let's define $\mathbb{I}_t^\alpha f(t) = {}_0\mathbb{I}_t^\alpha f(t)$.

The left-sided and right-sided Riemann–Liouville fractional derivatives are define as [33, 66]:

$$ {}_a\mathbf{D}_t^\alpha f(t) = \frac{d^n}{dt^n}\left(\frac{1}{\Gamma(n-\alpha)} \int_a^t (t-s)^{n-\alpha-1} f(s)ds \right), \qquad \text{(Left)} \tag{1.19} $$

$$ {}_t\mathbf{D}_b^\alpha f(t) = \frac{d^n}{dt^n}\left(\frac{(-1)^n}{\Gamma(n-\alpha)} \int_t^b (s-t)^{n-\alpha-1} f(s)ds \right). \qquad \text{(Right)} \tag{1.20} $$

Note: Let's denote $\mathbf{D}_t^\alpha f(t) = {}_0\mathbf{D}_t^\alpha f(t)$.

The left-sided and right-sided fractional derivatives proposed by Caputo are given by [33, 66]:

$$ {}_a^c\mathbb{D}_t^\alpha f(t) = \frac{1}{\Gamma(n-\alpha)} \int_a^t (t-s)^{n-1-\alpha} f^n(s)ds, \qquad \text{(Left)} \tag{1.21} $$

$$ {}_t^c\mathbb{D}_b^\alpha f(t) = \frac{(-1)^n}{\Gamma(n-\alpha)} \int_t^b (s-t)^{n-1-\alpha} f^n(s)ds. \qquad \text{(Right)} \tag{1.22} $$

Note: Let's define ${}^c\mathbb{D}_t^\alpha f(t) = {}_0^c\mathbb{D}_t^\alpha f(t)$.

The Riemann-Liouville and Caputo derivatives are related by the following formulas

[66]:

$$ {}_{a}\mathbf{D}_{t}^{\alpha}\, f(t) = {}_{a}^{c}\mathbb{D}_{t}^{\alpha}\, f(t) + \sum_{k=0}^{n-1} \frac{f^{(k)}(a)}{\Gamma(k+1-\alpha)}(t-a)^{k-\alpha}, \tag{1.23} $$

$$ {}_{t}\mathbf{D}_{b}^{\alpha}\, f(t) = {}_{t}^{c}\mathbb{D}_{b}^{\alpha}\, f(t) + \sum_{k=0}^{n-1} \frac{f^{(k)}(b)}{\Gamma(k+1-\alpha)}(t-b)^{k-\alpha}. \tag{1.24} $$

Now, we will present a general formulation of the fractional-order optimal control problem (FOCP) and obtain the necessary conditions for the optimality of the FOCP. Finding the optimal control $u(t)$ that minimizes the functional J is defined as:

$$ J(u) = \int_{0}^{b} f(t, x, u)dt, \tag{1.25} $$

subject to the model with control

$$ {}^{c}\mathbb{D}_{t}^{\alpha}\, x(t) = g(t, x, u), \tag{1.26} $$

with initial condition

$$ x(0) = x_I, \tag{1.27} $$

where $x(t)$ and $u(t)$ are the state and control variables, f and g are differential functions and $0 < \alpha \leq 1$.

Theorem 1.1.13. *If $f(x, u)$ is a minimizer of (1.25) satisfying the constraint (1.26) and the boundary condition (1.27), then there exists a function $\lambda \in \mathbb{C}^1[0, b]$ such that the triplet (x, u, λ) satisfies:*

1. *the state and co-state systems*

$$ {}^{c}\mathbb{D}_{t}^{\alpha}\, x(t) = \frac{\partial H}{\partial \lambda}(t, x(t), u(t), \lambda(t)), \tag{1.28} $$

$$ {}_{t}^{c}\mathbb{D}_{b}^{\alpha}\, \lambda(t) = \frac{\partial H}{\partial x}(t, x(t), u(t), \lambda(t)), \tag{1.29} $$

2. *the stationary condition*

$$ \frac{\partial H}{\partial u}(t, x(t), u(t), \lambda(t)) = 0, \tag{1.30} $$

3. *and the transversality condition*

$$ {}_{t}\mathbb{I}_{b}^{1-\alpha}\, \lambda\big|_{t=b} = \lambda(b) = 0, \tag{1.31} $$

where the Hamiltonian H is defined by

$$ H(t, x, u, \lambda) = f(t, x, u) + \lambda \cdot g(t, x, u). \tag{1.32} $$

The theorem and its proof are in [66].

Lemma 1.1.14 (See [66]). *The following equations are equivalent:*

$$ {}_t^c\mathbb{D}_b^\alpha \lambda(t) = \frac{\partial H}{\partial x}(t, x(t), u(t), \lambda(t)), \tag{1.33} $$

$$ {}^c\mathbb{D}_t^\alpha \lambda(b-t) = \frac{\partial H}{\partial x}(b-t, x(b-t), u(b-t), \lambda(b-t)), \tag{1.34} $$

where $\alpha \in (0, 1]$.

The proof of Lemma (1.1.14) is found in [66] and we can find applications of this lemma in [66, 14].

Chapter 2

A Mathematical Model for the Study of Effectiveness in Therapy in Tuberculosis

2.1 Introduction

In recent years, the use of mathematical models with different techniques to predict the behavior of epidemics has been increasing [18, 93, 94]. For example, Farman et al. [18] used evolutionary computational techniques and the Padé approach to study a nonlinear model of Hepatitis B. A. Omame et al. [93] introduced and analyzed a model of human papillomavirus (HPV) and *Chlamydia trachomatis* co-infection, and studied different control strategies to eliminate HPV and *Chlamydia trachomatis* co-infection. Omame and Okuonghae [94] proposed a co-infection model for oncogenic HPV and tuberculosis with an optimal control analysis and proved that the combination of HPV prevention and tuberculosis treatment has a positive impact on the reduction of oncogenic HPV and co-infection [80].

In recent decades, the number of mathematical papers on the impact of tuberculosis on society has been growing [25, 58, 90, 91, 92, 123, 118, 77, 76, 16, 88, 12]. For example, Okuonghae and Ikhimwin [91] developed a mathematical model for the tuberculosis transmission dynamics classifying latently infected individuals by their level of knowledge of tuberculosis. Zhang and Feng [123] performed a global analysis of a dynamic model for the propagation of tuberculosis with isolation and incomplete treatment. Nkamba et al. [16] formulated a mathematical model to study the impact of vaccination on tuberculosis transmission and proved that vaccination is not sufficient to control tuberculosis in the population. Trauer et al. [118] introduced a mathematical model to simulate the transmission of tuberculosis in the highly endemic regions of Asia-Pacific. Egonmwan and Okuonghae [88] proposed a mathematical model that investigates the impact of diagnosis and treatment on latent and active cases of TB transmission in a population. Guzzetta et al. [12] proposed a computational model that takes into account the age structure and individual sociodemographic basis (IBM) for the dynamics of tuberculosis infection in an epidemic situation [80].

Tuberculosis is the most frequent opportunistic infection and the leading cause of death among persons living with HIV/AIDS, and studies on TB-HIV/AIDS co-infection have been increasing in recent decades. For example, Long et al. [74] introduced two variants of a co-epidemic model (TB-HIV/AIDS) and showed the effects of each epidemic on transmission. Azeez et al. [3] developed a mathematical model for the TB-HIV/AIDS co-infection to predict the propagation of these diseases in different scenarios. Bhunu et al. [30] proposed a mathematical model of HIV/AIDS and tuberculosis co-infection that takes into account antiretroviral therapy and treatment of different forms of tuberculosis, and showed that antiretroviral therapy has a strong influence on the reduction of tuberculosis cases. Naresh et al. [83] proposed a nonlinear mathematical model to study the impact of tuberculosis on the propagation of HIV infection. Gakkhar and Chavda [84] introduced a mathematical model for TB-HIV/AIDS co-infection and showed that an increase in the rate of progression from latent to active TB in coinfected people can increase the prevalence of TB. Kumar et al. [68] formulated a mathematical model for the dynamics of TB-HIV/AIDS co-infection taking into account the HIV treatment in active tuberculosis and co-infection cases. Tanvi et al. [114] explored a model of HIV/AIDS and TB co-infection with detection and treatment of both diseases, designed an optimal control problem, and showed the importance of rapid detection of cases of both diseases and treatment to reduce co-infection [80].

The study of the relationship between diabetes and tuberculosis has intensified in recent years. For example, Coll et al. [42] introduced and studied a prevalence model for diabetes. Ferjouchia et al. [13] presented a mathematical model describing the whole blood glucose-insulin system and the objective is to propose a therapeutic scheme for diabetes patients. Moualeu et al. [78] proposed a deterministic model to determine the impact of diabetes on tuberculosis transmission and demonstrated the importance of chemoprophylaxis for individuals with latent tuberculosis and treatment of diabetics with active tuberculosis. Girard et al. [10] presented a study on the impact of migration on tuberculosis transmission in the growing diabetes pandemic and showed that improved access to health care for diabetic patients could decrease the impact of diabetes on tuberculosis among migrants [80].

The aim of this chapter is to propose a new mathematical model to study resistance to tuberculosis treatment considering the impact of HIV/AIDS and diabetes. We studied the mathematical and epidemiological properties of the model. The local and global stability conditions of the disease-free equilibrium points are deduced. Some simulations are presented to illustrate the behavior of the model. The innovative aspect of our work is that it simultaneously models tuberculosis, HIV/AIDS, and diabetes, focusing on the efficacy of tuberculosis treatment.

2.2 Model Formulation

The model has 18 compartments and the population is stratified into those who do not suffer from HIV/AIDS neither diabetes (index T), those HIV/AIDS positive (index H), and diabetic individuals (index D). We defined three subpopulations, TB-Only, TB-HIV/AIDS, and TB-Diabetes. The compartments of the model are TB uninfected (S_T, S_H and S_D), latent individuals (E_T, E_H and E_D), drug-sensitive TB individuals (I_{T_1}, I_{H_1} and I_{D_1}), MDR-TB individuals (I_{T_2}, I_{H_2} and I_{D_2}), XDR-TB individuals (I_{T_3}, I_{H_3} and I_{D_3}) and TB recovered (R_T, R_H

and R_D). We have excluded cases starting with both diseases (HIV/AIDS and diabetes) [80].

The equations of uninfected individuals are:

$$\begin{aligned}
\frac{dS_T}{dt} &= M_T - (\mu + \alpha_H + \alpha_D + \lambda)S_T, \\
\frac{dS_H}{dt} &= M_H + \alpha_H(S_T + S_D) - (\alpha_{HD} + \mu + \mu_H + \omega_H\lambda)S_H, \\
\frac{dS_D}{dt} &= M_D + \alpha_{HD}S_H + \alpha_D S_T - (\alpha_H + \mu + \omega_D\lambda + \mu_D)S_D.
\end{aligned} \tag{2.1}$$

The M_T, M_H and M_D are recruitment rates for the different subpopulations. We assume that the application of antiretroviral therapy begins from the detection of an HIV+ individual and we define the rate of acquiring diabetes by use of antiretroviral treatment as α_{HD} and it is assumed equal if is acquired for another cause. The rate of an individual acquiring HIV is α_H. The rate of developing diabetes is α_D [80]. By definition $\alpha_{HD} \neq \alpha_D$.

The TB-infection rate is defined as

$$\lambda = \alpha^* \frac{I_{T_1} + I_{T_2} + I_{T_3} + \epsilon_H(I_{H_1} + I_{H_2} + I_{H_3}) + \epsilon_D(I_{D_1} + I_{D_2} + I_{D_3})}{N},$$

where α^* is the effective contact rate and N is the total population ($N = S_T + S_H + S_D + E_T + E_H + E_D + I_{T_1} + I_{T_2} + I_{H_1} + I_{H_2} + I_{D_1} + I_{D_2} + I_{T_3} + I_{H_3} + I_{D_3} + R_T + R_H + R_D$). The parameters ϵ_j, $j = H, D$ are modifications parameters, associated with TB infectivity in HIV-positive and diabetic patients. The natural death rate μ is the same from any compartment. Diabetics not infected with tuberculosis , S_D, and HIV positive patients not infected with tuberculosis S_H, are infected with TB at a rate $\omega_H\lambda$, $\omega_D\lambda$, where $\omega_H, \omega_D > 1$, and are associated with TB transmissibility of HIV-positive and diabetic patient respectively. The μ_H is the death rate by HIV/AIDS and μ_D is the death rate by diabetes [80].

The dynamics of the latent individuals, are given by:

$$\begin{aligned}
\frac{dE_T}{dt} &= \lambda(S_T + \beta_1^{'}R_T) - (\alpha_H + \alpha_D + \mu + \eta)E_T, \\
\frac{dE_H}{dt} &= \omega_H\lambda(S_H + \beta_1^{'}R_H) + \alpha_H(E_T + E_D) - (\epsilon_H^*\eta + \mu + \mu_H + \alpha_{HD})E_H, \\
\frac{dE_D}{dt} &= \omega_D\lambda(S_D + \beta_1^{'}R_D) + \alpha_{HD}E_H + \alpha_D E_T - (\alpha_H + \epsilon_D^*\eta + \mu + \mu_D)E_D.
\end{aligned} \tag{2.2}$$

The latent state will be entered by those who come into contact with TB and those who recover (partial immunity). We define ϵ_j^*, $j = H, D$ as the parameters modification associated with resistance to tuberculosis treatment in HIV/AIDS and diabetics. We assume that TB-recovered R_i, $i = T, D, H$ acquire partial immunity so that from the recovered compartment enter the latent compartment with a parameter associated with reinfection/reactivation TB, $\beta_1^{'}$ with $\beta_1^{'} \leq 1$ [80].

The drug-sensitive TB and MDR-TB, are represented by the following equations:

$$\begin{aligned}
\frac{dI_{T_1}}{dt} &= (1-\beta^*)\eta E_T - (l_T + t_H\alpha_H + t_D\alpha_D + \mu + d_T + \eta_{11})I_{T_1},\\
\frac{dI_{T_2}}{dt} &= (1-p_T)\beta^*\eta E_T + l_T I_{T_1} - (t_H\alpha_H + t_D\alpha_D + m_T + \mu + t_T^{'}d_T + \eta_{14})I_{T_2},\\
\frac{dI_{H_1}}{dt} &= t_H\alpha_H(I_{T_1} + I_{D_1}) + (1-\beta^*)\epsilon_H^*\eta E_H - (l_H + \mu + \mu_H + d_{TH} + \eta_{12} + t_{HD}\alpha_{HD})I_{H_1},\\
\frac{dI_{H_2}}{dt} &= t_H\alpha_H(I_{T_2} + I_{D_2}) + (1-p_H)\beta^*\epsilon_H^*\eta E_H + l_H I_{H_1} - (m_H + \mu + \mu_H + t_H^{'}d_{TH} + \eta_{15} + t_{HD}\alpha_{HD})I_{H_2},\\
\frac{dI_{D_1}}{dt} &= t_D\alpha_D I_{T_1} + t_{HD}\alpha_{HD}I_{H_1} + (1-\beta^*)\epsilon_D^*\eta E_D - (l_D + t_H\alpha_H + \mu + d_{TD} + \eta_{13} + \mu_D)I_{D_1},\\
\frac{dI_{D_2}}{dt} &= t_D\alpha_D I_{T_2} + t_{HD}\alpha_{HD}I_{H_2} + (1-p_D)\epsilon_D^*\beta^*\eta E_D + l_D I_{D_1} - (m_D + t_H\alpha_H + \mu + t_D^{'}d_{TD} + \eta_{16} + \mu_D)I_{D_2}.
\end{aligned} \tag{2.3}$$

The η is the natural rate of progression of tuberculosis. The β^* is the proportion of active TB cases that are resistant. From the latent state, the person will move to three possible compartments of infected, drug-sensitive TB, MDR-TB, or XDR-TB in a first infection. The t_H and t_D are modification parameters associated with diabetes or HIV infection from the compartments of active TB infection. We define d_T, as TB death rate, d_{TH} is the death rate by co-infection TB and HIV/AIDS and d_{TD} is the death rate by combination TB and diabetes. We assume that $d_{TD} \geq d_T$ and $d_{TH} \geq d_T$. The $t_T^{'}$, $t_H^{'}$ and $t_D^{'}$ represent modification parameters associated with death by TB, death by combination TB-HIV/AIDS and by combination TB-Diabetes after being MDR-TB. The l_T, l_H and l_D rates are the cases that will be MDR-TB (first resistance). The expressions $(1-p_T)\eta$, $(1-p_H)\epsilon_H^*\eta$ and $(1-p_D)\epsilon_D^*\eta$ are the cases that in a first infection are going to be MDR-TB and $p_T\eta$, $p_H\epsilon_H^*\eta$ and $p_D\epsilon_D^*\eta$ are the cases that will be XDR-TB in a first infection. The t_{HD} is the parameter modification associated with the combination of treatment for TB and antiretroviral therapy and the possibility of developing diabetes. The η_{11}, η_{12} and η_{13} are the recovery rate after being drug-sensitive TB and m_T, m_H and m_D are the recovery rate after being MDR-TB. We assume that $\eta_{1l} > m_l$ for $l = 1, 2, 3$ [80].

The XDR-TB and recovered dynamic, is interpreted by the following equations:

$$\begin{aligned}
\frac{dI_{T_3}}{dt} &= p_T\beta^*\eta E_T + \eta_{14}I_{T_2} - (\eta_{11}^* + t_H\alpha_H + t_D\alpha_D + \mu + t_T^*d_T)I_{T_3},\\
\frac{dI_{H_3}}{dt} &= p_H\beta^*\epsilon_H^*\eta E_H + \eta_{15}I_{H_2} + t_H\alpha_H(I_{T_3} + I_{D_3}) - (\eta_{12}^* + t_{HD}\alpha_{HD} + \mu + \mu_H + t_H^*d_{TH})I_{H_3},\\
\frac{dI_{D_3}}{dt} &= p_D\beta^*\epsilon_D^*\eta E_D + \eta_{16}I_{D_2} + t_{HD}\alpha_{HD}I_{H_3} + t_D\alpha_D I_{T_3} - (t_H\alpha_H + \eta_{13}^* + \mu + \mu_D + t_D^*d_{TD})I_{D_3},\\
\frac{dR_T}{dt} &= m_T I_{T_2} + \eta_{11}I_{T_1} + \eta_{11}^*I_{T_3} - (\alpha_H + \alpha_D + \mu + \beta_1^{'}\lambda)R_T,\\
\frac{dR_H}{dt} &= m_H I_{H_2} + \eta_{12}I_{H_1} + \eta_{12}^*I_{H_3} + \alpha_H(R_T + R_D) - (\alpha_{HD} + \mu + \mu_H + \beta_1^{'}\omega_H\lambda)R_H,\\
\frac{dR_D}{dt} &= m_D I_{D_2} + \eta_{13}I_{D_1} + \eta_{13}^*I_{D_3} + \alpha_D R_T + \alpha_{HD}R_H - (\alpha_H + \mu + \mu_D + \beta_1^{'}\omega_D\lambda)R_D.
\end{aligned} \tag{2.4}$$

The η_{11}^*, η_{12}^* and η_{13}^* are the recovery rate after being XDR-TB. Due to the characteristics of tuberculosis, let us assume that $\eta_{1l} > \eta_{1l}^*$ and $m_l > \eta_{1l}^*$ for $l = 1, 2, 3$. The t_T^*, t_H^* and t_D^* are modification parameters associated with death by TB, co-infection TB-HIV/AIDS and combination TB-Diabetes after being XDR-TB respectively [80]. The parameters definition is in Table (2.1).

Parameter	Description
M_T, M_H, M_D	Recruitment rates
α^*	Effective contact rates for TB infection
α_D	Acquiring diabetes rate
α_H	Acquiring HIV rate
α_{HD}	Diabetes development rate by use of HIV therapy
$\omega_H, \omega_D, \epsilon_H, \epsilon_D$	Modification parameters
μ	Natural mortality rate
η	Natural rate of progression to active TB
$t_H, t_D, t_{HD}, t_T^*, t_H^*, t_D^*$	Modification parameters
$t_T^{'}, t_H^{'}, t_D^{'}$	Modification parameters
$\epsilon_H^*, \epsilon_D^*, \beta_1^{'}$	Modification parameters
l_T, l_H, l_D	Resistant TB development rates
d_T	TB induced death rate
d_{TH}	TB-HIV induced death rate
d_{TD}	TB-Diabetes induced death rate
μ_H, μ_D	Death rate of HIV/AIDS and diabetes respectively.
m_T, m_H, m_D	TB recovery rates for MDR-TB
β^*	Proportion of active TB cases that are resistant.
$\eta_{11}, \eta_{12}, \eta_{13}$	TB recovery rates of drug-sensitive TB infected
$\eta_{14}, \eta_{15}, \eta_{16}$	Resistant (XDR-TB) TB development rates after being MDR-TB
$\eta_{11}^*, \eta_{12}^*, \eta_{13}^*$	TB recovery rates of XDR-TB
p_T, p_H, p_D	Rates related to developing XDR-TB resistance

Table 2.1: *Description of parameters of the model (2.5).*

To summarize, the effectiveness of the TB treatment with the presence of HIV/AIDS and diabetes is modeled with the following system of differential equations:

$$\begin{aligned}
\frac{dS_T}{dt} &= M_T - (\mu + \alpha_H + \alpha_D + \lambda)S_T, \\
\frac{dS_H}{dt} &= M_H + \alpha_H(S_T + S_D) - (\alpha_{HD} + \mu + \mu_H + \omega_H\lambda)S_H, \\
\frac{dS_D}{dt} &= M_D + \alpha_{HD}S_H + \alpha_D S_T - (\alpha_H + \mu + \omega_D\lambda + \mu_D)S_D, \\
\frac{dE_T}{dt} &= \lambda(S_T + \beta_1^{'}R_T) - (\alpha_H + \alpha_D + \mu + \eta)E_T, \\
\frac{dE_H}{dt} &= \omega_H\lambda(S_H + \beta_1^{'}R_H) + \alpha_H(E_T + E_D) - (\epsilon_H^*\eta + \mu + \mu_H + \alpha_{HD})E_H,
\end{aligned}$$

$$
\begin{aligned}
\frac{dE_D}{dt} &= \omega_D\lambda(S_D + \beta_1^{'}R_D) + \alpha_{HD}E_H + \alpha_D E_T - (\alpha_H + \epsilon_D^*\eta + \mu + \mu_D)E_D,\\
\frac{dI_{T_1}}{dt} &= (1-\beta^*)\eta E_T - (l_T + t_H\alpha_H + t_D\alpha_D + \mu + d_T + \eta_{11})I_{T_1},\\
\frac{dI_{T_2}}{dt} &= (1-p_T)\beta^*\eta E_T + l_T I_{T_1} - (t_H\alpha_H + t_D\alpha_D + m_T + \mu + t_T^{'}d_T + \eta_{14})I_{T_2},\\
\frac{dI_{H_1}}{dt} &= t_H\alpha_H(I_{T_1} + I_{D_1}) + (1-\beta^*)\epsilon_H^*\eta E_H - (l_H + \mu + \mu_H + d_{TH} + \eta_{12} + t_{HD}\alpha_{HD})I_{H_1},\\
\frac{dI_{H_2}}{dt} &= t_H\alpha_H(I_{T_2} + I_{D_2}) + (1-p_H)\beta^*\epsilon_H^*\eta E_H + l_H I_{H_1} - (m_H + \mu + \mu_H + t_H^{'}d_{TH} + \eta_{15} + t_{HD}\alpha_{HD})I_{H_2},\\
\frac{dI_{D_1}}{dt} &= t_D\alpha_D I_{T_1} + t_{HD}\alpha_{HD}I_{H_1} + (1-\beta^*)\epsilon_D^*\eta E_D - (l_D + t_H\alpha_H + \mu + d_{TD} + \eta_{13} + \mu_D)I_{D_1},\\
\frac{dI_{D_2}}{dt} &= t_D\alpha_D I_{T_2} + t_{HD}\alpha_{HD}I_{H_2} + (1-p_D)\epsilon_D^*\beta^*\eta E_D + l_D I_{D_1} - (m_D + t_H\alpha_H + \mu + t_D^{'}d_{TD} + \eta_{16} + \mu_D)I_{D_2},\\
\frac{dI_{T_3}}{dt} &= p_T\beta^*\eta E_T + \eta_{14}I_{T_2} - (\eta_{11}^* + t_H\alpha_H + t_D\alpha_D + \mu + t_T^*d_T)I_{T_3},\\
\frac{dI_{H_3}}{dt} &= p_H\beta^*\epsilon_H^*\eta E_H + \eta_{15}I_{H_2} + t_H\alpha_H(I_{T_3} + I_{D_3}) - (\eta_{12}^* + t_{HD}\alpha_{HD} + \mu + \mu_H + t_H^*d_{TH})I_{H_3},\\
\frac{dI_{D_3}}{dt} &= p_D\beta^*\epsilon_D^*\eta E_D + \eta_{16}I_{D_2} + t_{HD}\alpha_{HD}I_{H_3} + t_D\alpha_D I_{T_3} - (t_H\alpha_H + \eta_{13}^* + \mu + \mu_D + t_D^*d_{TD})I_{D_3},\\
\frac{dR_T}{dt} &= m_T I_{T_2} + \eta_{11}I_{T_1} + \eta_{11}^*I_{T_3} - (\alpha_H + \alpha_D + \mu + \beta_1^{'}\lambda)R_T,\\
\frac{dR_H}{dt} &= m_H I_{H_2} + \eta_{12}I_{H_1} + \eta_{12}^*I_{H_3} + \alpha_H(R_T + R_D) - (\alpha_{HD} + \mu + \mu_H + \beta_1^{'}\omega_H\lambda)R_H,\\
\frac{dR_D}{dt} &= m_D I_{D_2} + \eta_{13}I_{D_1} + \eta_{13}^*I_{D_3} + \alpha_D R_T + \alpha_{HD}R_H - (\alpha_H + \mu + \mu_D + \beta_1^{'}\omega_D\lambda)R_D,
\end{aligned}
\tag{2.5}
$$

with initial conditions:
$S_T(0) > 0$, $S_H(0) > 0$, $S_D(0) > 0$, $E_T(0) > 0$, $E_H(0) > 0$, $E_D(0) > 0$, $I_{T_1}(0) > 0$, $I_{T_2}(0) > 0$, $I_{H_1}(0) > 0$, $I_{H_2}(0) > 0$, $I_{D_1}(0) > 0$, $I_{D_2}(0) > 0$, $I_{T_3}(0) > 0$, $I_{H_3}(0) > 0$, $I_{D_3}(0) > 0$, $R_T(0) > 0$, $R_H(0) > 0$ and $R_D(0) > 0$.

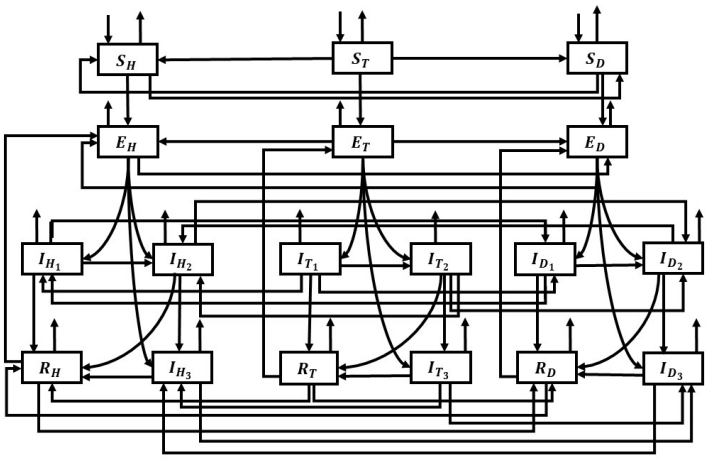


Figure 2.1: *Diagram of model (2.5).*

Model Properties

In this subsection, we show the existence, positivity, and boundedness of solutions and find the biologically feasible region. The proof of the following results can be found in [80].

Theorem 2.2.1. *Let the initial data for the model (2.5) be* $S_i(0) > 0, E_i(0) > 0, I_{i_1}(0) > 0, I_{i_2}(0) > 0, I_{i_3}(0) > 0, R_i(0) > 0, i = T, H, D$. *Then, the solutions* $(S_i(t), E_i(t), I_{i_1}(t), I_{i_2}(t), I_{i_3}(t), R_i(t)), i = T, H, D$ *of the model (2.5), with positive initial data, will remain positive for all time* $t > 0$. *Furthermore,*

$$\limsup_{t\to\infty} N(t) \leq \frac{M_T + M_H + M_D}{\mu}. \tag{2.6}$$

Proof. Let us remark that the first equation of the system (2.5),

$$\frac{dS_T}{dt} = M_T - (\mu + \alpha_H + \alpha_D + \lambda)S_T,$$

can be rewritten as,

$$\frac{d}{dt}\left[S_T(t)\exp\left\{(\mu+\alpha_H+\alpha_D)t+\int_0^t \lambda(\tau)d\tau\right\}\right] = M_T\exp\left\{(\mu+\alpha_H+\alpha_D)t+\int_0^t \lambda(\tau)d\tau\right\}. \tag{2.7}$$

Hence, fot $t_1 > 0$,

$$S_T(t_1)\exp\left\{(\mu+\alpha_H+\alpha_D)t_1+\int_0^{t_1} \lambda(\tau)d\tau\right\}-S_T(0) = \int_0^{t_1} M_T\left[\exp\left\{(\mu+\alpha_H+\alpha_D)y+\int_0^y \lambda(\tau)d\tau\right\}\right]dy. \tag{2.8}$$

So that,

$$\begin{aligned} S_T(t_1) =& S_T(0)\exp\left\{-(\mu+\alpha_H+\alpha_D)t_1 - \int_0^{t_1}\lambda(\tau)d\tau\right\} + \exp\left\{-(\mu+\alpha_H+\alpha_D)t_1 - \int_0^{t_1}\lambda(\tau)d\tau\right\} \\ &\times \int_0^{t_1} M_T\left[\exp\left\{(\mu+\alpha_H+\alpha_D)y + \int_0^y \lambda(\tau)d\tau\right\}\right]dy > 0. \end{aligned} \tag{2.9}$$

Analogously, a similar result can be shown for $S_H(t), S_D(t), E_i(t), I_{i_1}(t), I_{i_2}(t), I_{i_3}(t), R_i(t), i = T, H, D$, for $t > 0$. Thus, all solutions of the model (2.5) remain positive for non-negative initial conditions [80].
Since the total population is the sum of all the compartments, we have that

$$\frac{dN}{dt} = M_T+M_H+M_D-\mu N-\mu_H(S_H+E_H+I_{H_1}+I_{H_2}+I_{H_3}+R_H)-\mu_D(S_D+E_D+I_{D_1}+I_{D_2}+I_{D_3}+R_D)-$$

$$\left(d_T(I_{T_1}+t_T^{'}I_{T_2}+t_T^{*}I_{T_3})+d_{TH}(I_{H_1}+t_H^{'}I_{H_2}+t_H^{*}I_{H_3})+d_{TD}(I_{D_1}+t_D^{'}I_{D_2}+t_D^{*}I_{D_3})\right).$$

Then,

$$M_T + M_H + M_D - (\mu + \mu_H + \mu_D + d_T + d_{TH} + d_{TD})N \leq \frac{dN}{dt} \leq M_T + M_H + M_D - \mu N,$$

which give,

$$\frac{M_T + M_H + M_D}{\mu + \mu_H + \mu_D + d_T + d_{TH} + d_{TD}} \leq \liminf_{t\to\infty} N(t) \leq \limsup_{t\to\infty} N(t) \leq \frac{M_T + M_H + M_D}{\mu}. \quad (2.10)$$

So, we have that:

$$\limsup_{t\to\infty} N(t) \leq \frac{M_T + M_H + M_D}{\mu}.$$

□

The biologically feasible region is where all variables are non-negative and the solutions of the system (2.5) remain positive with non-negative initial conditions.

Lemma 2.2.2. *The closed set*

$$D = \left\{ (S_i, E_i, I_{i_1}, I_{i_2}, I_{i_3}, R_i) \in \mathbb{R}^{18}_+, i = T, H, D \,:\, N(t) \leq \frac{M_T + M_H + M_D}{\mu} \right\},$$

is positively invariant and attracts all positive solutions of the model (2.5).

Proof. The derivative of N (total population) is the sum of the derivative of all compartments:

$$\frac{dN}{dt} = M_T + M_H + M_D - \mu N - \mu_H(S_H + E_H + I_{H_1} + I_{H_2} + I_{H_3} + R_H) - \mu_D(S_D + E_D + I_{D_1} + I_{D_2} + I_{D_3} + R_D) -$$

$$\left(d_T(I_{T_1} + t_T' I_{T_2} + t_T^* I_{T_3}) + d_{TH}(I_{H_1} + t_H' I_{H_2} + t_H^* I_{H_3}) + d_{TD}(I_{D_1} + t_D' I_{D_2} + t_D^* I_{D_3})\right).$$

Since $\frac{dN}{dt} \leq M_T + M_H + M_D - \mu N$, it follows that $\frac{dN}{dt} \leq 0$, if $N(t) \geq \frac{M_T + M_H + M_D}{\mu}$. Hence, a standard comparison Theorem [69] can be used to show that $N(t) \leq N(0)\exp\{-\mu t\} + \frac{M_T + M_H + M_D}{\mu}\left(1 - \exp\{-\mu t\}\right)$. In particular, if $N(0) \leq \frac{M_T + M_H + M_D}{\mu}$, then $N(t) \leq \frac{M_T + M_H + M_D}{\mu}$ for all $t > 0$. Hence, the domain D is positively invariant. Furthermore, if $N(0) > \frac{M_T + M_H + M_D}{\mu}$, then either the solution enters the domain D in finite time or $N(t)$ approaches $\frac{M_T + M_H + M_D}{\mu}$ asymptotically as $t \to \infty$. Hence, the domain D attracts all solutions in $\mathbb{R}^{18}_+$ [80]. □

The set D is the biologically feasible region of model (2.5). The model (2.5) is mathematically and epidemiologically well posed in D.

Theorem 2.2.3. *The solutions of model system (2.5) with non-negative initial conditions exists for all times.*

Proof. The right-hand side of the system (2.5) is locally Lipschitz continuous, and this proves the local existence of the solution. Global existence of the solution follows from bounds known a priory [80]. □

2.3 Basic Reproduction Number Study

In this section, the basic reproduction number, $\mathfrak{R}_0$, is computed using the next-generation matrix method [45, 51, 44]. We calculated the basic number of reproduction in the different subpopulations to study the transmission of tuberculosis in them.

TB-Only Submodel

We have the TB-Only submodel when $S_H = S_D = E_H = E_D = I_{H_1} = I_{H_2} = I_{D_1} = I_{D_2} = I_{H_3} = I_{D_3} = R_H = R_D = 0$, which is given by

$$\begin{aligned}
\frac{dS_T}{dt} &= M_T - (\mu + \alpha_H + \alpha_D + \lambda_T)S_T,\\
\frac{dE_T}{dt} &= \lambda_T(S_T + \beta_1^{'}R_T) - (\alpha_H + \alpha_D + \eta + \mu)E_T,\\
\frac{dI_{T_1}}{dt} &= (1-\beta^*)\eta E_T - (l_T + t_H\alpha_H + t_D\alpha_D + \mu + d_T + \eta_{11})I_{T_1},\\
\frac{dI_{T_2}}{dt} &= (1-p_T)\beta^*\eta E_T + l_T I_{T_1} - (m_T + \mu + t_T^{'}d_T + \eta_{14} + t_H\alpha_H + t_D\alpha_D)I_{T_2},\\
\frac{dI_{T_3}}{dt} &= \beta^* p_T\eta E_T + \eta_{14}I_{T_2} - (\eta_{11}^* + \mu + t_T^*d_T + t_H\alpha_H + t_D\alpha_D)I_{T_3},\\
\frac{dR_T}{dt} &= m_T I_{T_2} + \eta_{11}I_{T_1} + \eta_{11}^*I_{T_3} - (\mu + \beta_1^{'}\lambda_T + \alpha_H + \alpha_D)R_T,
\end{aligned} \tag{2.11}$$

with initial conditions:

$$S_T(0) > 0,\ E_T(0) > 0,\ I_{T_1}(0) > 0,\ I_{T_2}(0) > 0,\ I_{T_3}(0) > 0 \text{ and } R_T(0) > 0.$$

The TB-infection rate for this submodel is defined as

$$\lambda_T = \alpha^*\frac{I_{T_1} + I_{T_2} + I_{T_3}}{N_T},$$

and the total population is given by

$$N_T = S_T + E_T + I_{T_1} + I_{T_2} + I_{T_3} + R_T.$$

Due to biological constraints, the system (2.11) is studied in the following region:

$$D_1 = \left\{(S_T, E_T, I_{T_1}, I_{T_2}, I_{T_3}, R_T) \in \mathbb{R}_+^6 \ :\ N_T(t) \leq \frac{M_T}{\mu}\right\}.$$

We can show for this submodel (2.11) that the solutions, $(S_T(t), E_T(t), I_{T_1}(t), I_{T_2}(t), I_{T_3}(t), R_T(t))$ are bounded and positively invariant in D_1 (biologically feasible region).

Disease-Free Equilibrium Point

The disease-free equilibrium point of model (2.11) is given by $\epsilon_0^T = \left(S_0^T, 0, 0, 0, 0, 0\right)$, where $S_0^T = \dfrac{M_T}{\mu + \alpha_H + \alpha_D}$.

The matrices for the new infection terms, F_T and the other terms, V_T for system (2.11) are given by:

$$F_T = \begin{bmatrix} 0 & \dfrac{M_T\alpha^*}{N_T(\alpha_H+\alpha_D+\mu)} & \dfrac{M_T\alpha^*}{N_T(\alpha_H+\alpha_D+\mu)} & \dfrac{M_T\alpha^*}{N_T(\alpha_H+\alpha_D+\mu)} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix},$$

$$V_T = \begin{bmatrix} k_{11} & 0 & 0 & 0 \\ -(1-\beta^*)\eta & k_{12} & 0 & 0 \\ -(1-p_T)\beta^*\eta & -l_T & k_{13} & 0 \\ -p_T\beta^*\eta & 0 & -\eta_{14} & k_{14} \end{bmatrix},$$

where $k_{11} = \alpha_H + \alpha_D + \eta + \mu$, $k_{12} = l_T + t_H\alpha_H + t_D\alpha_D + \mu + d_T + \eta_{11}$, $k_{13} = \mu + t_T^{'}d_T + \eta_{14} + m_T + t_H\alpha_H + t_D\alpha_D$ and $k_{14} = \mu + t_T^*d_T + \eta_{11}^* + t_H\alpha_H + t_D\alpha_D$.

The basic reproduction number obtained is

$$\mathfrak{R}_0^T = \rho(F_TV_T^{-1}) = \frac{\alpha^*M_T\eta\Big((1-\beta^*)(k_{13}k_{14} + l_T(k_{14}+\eta_{14})) + (1-p_T)\beta^*k_{12}(k_{14}+\eta_{14}) + \beta^*p_Tk_{12}k_{13}\Big)}{N_T(\alpha_H+\alpha_D+\mu)k_{11}k_{12}k_{13}k_{14}}, \tag{2.12}$$

where $\rho(F_TV_T^{-1})$ indicate the spectral radius of $F_TV_T^{-1}$. We have the following lemma [80]:

Lemma 2.3.1. *The disease-free equilibrium point ϵ_0^T is locally asymptotically stable when $\mathfrak{R}_0^T < 1$ and unstable when $\mathfrak{R}_0^T > 1$.*

Proof. The Jacobian matrix of the submodel (2.11) at ϵ_0^T is

$$J(\epsilon_0^T) = \begin{bmatrix} -(\mu+\alpha_H+\alpha_D) & 0 & \dfrac{-M_T\alpha^*}{N_T(\mu+\alpha_H+\alpha_D)} & \dfrac{-M_T\alpha^*}{N_T(\mu+\alpha_H+\alpha_D)} & \dfrac{-M_T\alpha^*}{N_T(\mu+\alpha_H+\alpha_D)} & 0 \\ 0 & -k_{11} & \dfrac{M_T\alpha^*}{N_T(\mu+\alpha_H+\alpha_D)} & \dfrac{M_T\alpha^*}{N_T(\mu+\alpha_H+\alpha_D)} & \dfrac{M_T\alpha^*}{N_T(\mu+\alpha_H+\alpha_D)} & 0 \\ 0 & (1-\beta^*)\eta & -k_{12} & 0 & 0 & 0 \\ 0 & (1-p_T)\beta^*\eta & l_T & -k_{13} & 0 & 0 \\ 0 & p_T\beta^*\eta & 0 & \eta_{14} & -k_{14} & 0 \\ 0 & 0 & \eta_{11} & m_T & \eta_{11}^* & -(\mu+\alpha_H+\alpha_D) \end{bmatrix},$$

Trace$[J(\epsilon_0^T)]$=$-2(\alpha_H+\alpha_D+\mu) - k_{11} - k_{12} - k_{13} - k_{14} < 0$,
and its determinant is
Det$[J(\epsilon_0^T)]$= $-(\alpha_H+\alpha_D+\mu)^2\Big(\frac{M_T\alpha^*\eta}{(\alpha_H+\alpha_D+\mu)}\big((1-\beta^*)(k_{13}k_{14}+l_T(k_{14}+\eta_{14})) + (1-p_T)\beta^*k_{12}(k_{14}+\eta_{14}) + \beta^*p_Tk_{12}k_{13}\big) - k_{11}k_{12}k_{13}k_{14}\Big) > 0$.

If,

$$\frac{(\alpha_H+\alpha_D+\mu)\alpha^* M_T\eta\big((1-\beta^*)(k_{13}k_{14}+l_T(k_{14}+\eta_{14}))+(1-p_T)\beta^* k_{12}(k_{14}+\eta_{14})+\beta^* p_T k_{12}k_{13}\big)}{N_T} <$$

$(\alpha_H+\alpha_D+\mu)^2 k_{11}k_{12}k_{13}k_{14}$, then

$$\frac{M_T\alpha^*\eta\big((1-\beta^*)(k_{13}k_{14}+l_T(k_{14}+\eta_{14}))+(1-p_T)\beta^* k_{12}(k_{14}+\eta_{14})+\beta^* p_T k_{12}k_{13}\big)}{N_T(\alpha_H+\alpha_D+\mu)k_{11}k_{12}k_{13}k_{14}} < 1.$$

Thus $\mathfrak{R}_0^T < 1$, which means that the solution of Det$[J(\epsilon_0^T) - \lambda I]$=0 ($I$ is the Identity matrix) have negative real parts, implying that ϵ_0^T is locally asymptotically stable whenever $\mathfrak{R}_0^T < 1$ and unstable if $\mathfrak{R}_0^T > 1$. □

Now, we list two conditions that if met, also guarantee the global asymptotic stability of the disease-free equilibrium point. Following [38], we rewrite the model (2.11) as

$$\begin{aligned}\frac{dS}{dt} &= F(S,I),\\ \frac{dI}{dt} &= G(S,I), \quad G(S,0)=0,\end{aligned} \tag{2.13}$$

where $S \in \mathbb{R}_+^2$ is the vector whose components are the number of uninfected and recovered individuals (S_T, R_T) and $I \in \mathbb{R}_+^4$ denotes the number of infected individuals including the latent and the infectious $(E_T, I_{T_1}, I_{T_2}, I_{T_3})$.

The disease-free equilibrium is now denoted by $E_0^T = (S_0^{T_*}, 0)$ where $S_0^{T_*} = (S_0^T, 0)$, $S_0^T = \left(\frac{M_T}{\mu+\alpha_H+\alpha_D}, 0\right)$.

The conditions that must be fulfilled to guarantee the global asymptotic stability of E_0^T are,

$$\begin{aligned}(H_1):&\quad \text{For}\quad \frac{dS}{dt} = F(S,0), \quad S_0^{T_*} \quad \text{is globally asymptotically stable,}\\ (H_2):&\quad G(S,I) = AI - G^*(S,I), \quad G^*(S,I)\geq 0, \quad \text{for} \quad (S,I)\in D_1,\end{aligned}$$

where $A = D_I G(S_0^{T_*}, 0)$ ($D_I G(S_0^{T_*}, 0)$ is the Jacobian of G at $(S_0^{T_*}, 0)$) and D_1 is the region where the model makes biological sense (biologically feasible region).

If model (2.11) satisfies the conditions (H_1) and (H_2), then the following result holds [80].

Lemma 2.3.2. *The fixed point E_0^T is a globally asymptotically stable equilibrium of model (2.11) provided that $\mathfrak{R}_0^T < 1$ and that the conditions (H_1) and (H_2) are satisfied.*

Proof. Let

$$F(S,0) = \begin{pmatrix} M_T - (\mu + \alpha_H + \alpha_D)S_T \\ 0 \end{pmatrix}.$$

As $F(S,0)$ is a linear equation, we have that $S_0^{T_*}$ is globally stable, hence H_1 is satisfied. Let's

$$A = D_I G(S_T^*, 0) = \begin{pmatrix} -k_{11} & \alpha^* & \alpha^* & \alpha^* \\ (1-\beta^*)\eta & -k_{12} & 0 & 0 \\ (1-p_T)\beta^*\eta & l_T & -k_{13} & 0 \\ p_T\beta^*\eta & 0 & \eta_{14} & -k_{14} \end{pmatrix},$$

$$I = \left(E_T, \quad I_{T_1}, \quad I_{T_2}, \quad I_{T_3}\right),$$

$$G^*(S,I) = AI^T - G(S,I),$$

$$G^*(S,I) = \begin{pmatrix} G_1^*(S,I) \\ G_2^*(S,I) \\ G_3^*(S,I) \\ G_4^*(S,I) \end{pmatrix} = \begin{pmatrix} \alpha^*(I_{T_1} + I_{T_2} + I_{T_3})\left(1 - \dfrac{S_T + \beta_1' R_T}{N_T}\right) \\ 0 \\ 0 \\ 0 \end{pmatrix}.$$

Since $S_T + \beta_1' R_T$ is always less than or equal to N_T, $\dfrac{S_T + \beta_1' R_T}{N_T} \leq 1$. Thus, $G^*(S,I) \geq 0$ for all $(S,I) \in D_1$ and E_0^T is a globally asymptotically stable. □

The proof of the local and global stability at the infection-free equilibrium point can be found in [80].

Using the threshold quantity, $\mathfrak{R}_0^T$, in (2.12), we want to study the impact of resistance to tuberculosis treatment on the dynamics of the disease in a population and find conditions that characterize these effects. Parameters l_T and η_{14} associated with MDR-TB and XDR-TB are between 0 and 1 by definition. Now, we are going to study the possible combinations in the behavior of these parameters based on the limits. We have

$$\lim_{\substack{l_T \to 0 \\ \eta_{14} \to 0}} \mathfrak{R}_0^T = \frac{\alpha^* M_T \eta\left((1-\beta^*)k_{13}^0 k_{14} + (1-p_T)\beta^* k_{12}^0 k_{14} + \beta^* p_T k_{12}^0 k_{13}^0\right)}{N_T(\alpha_H + \alpha_D + \mu)k_{11}k_{12}^0 k_{13}^0 k_{14}}, \tag{2.14}$$

where k_{12}^0 is k_{12} for $l_T = 0$ and k_{13}^0 is k_{13} for $\eta_{14} = 0$. Then, in practice $l_T \to 0$ and $\eta_{14} \to 0$ means zero resistance, i.e. elimination of resistance to tuberculosis treatment. If the limit (2.14) is greater than unity, then when $l_T \to 0$ and $\eta_{14} \to 0$ it has a negative impact on TB transmission control. That is, if

$$\frac{\alpha^* \eta M_T}{N_T(\alpha_H + \alpha_D + \mu)} > \frac{k_{11}k_{12}^0 k_{13}^0 k_{14}}{(1-\beta^*)k_{13}^0 k_{14} + (1-p_T)\beta^* k_{12}^0 k_{14} + \beta^* p_T k_{12}^0 k_{13}^0}. \tag{2.15}$$

Now, we study the case when $l_T \to 1$ and $\eta_{14} \to 0$. We have

$$\lim_{\substack{l_T \to 1 \\ \eta_{14} \to 0}} \mathfrak{R}_0^T = \frac{\alpha^* M_T \eta\left((1-\beta^*)(k_{13}^0 k_{14} + k_{14}) + (1-p_T)\beta^* k_{12}^1 k_{14} + \beta^* p_T k_{12}^1 k_{13}^0\right)}{N_T(\alpha_H + \alpha_D + \mu)k_{11}k_{12}^1 k_{13}^0 k_{14}}, \tag{2.16}$$

where k_{12}^1 is k_{12} for $l_T = 1$. Then, if the limit (2.16) is greater than unity, then when $l_T \to 1$ and $\eta_{14} \to 0$ it means a negative impact on TB transmission control. That is, when

$$\frac{\alpha^* M_T}{N_T(\alpha_H + \alpha_D + \mu)} > \frac{k_{11}k_{12}^1 k_{13}^0 k_{14}}{(1-\beta^*)(k_{13}^0 k_{14} + k_{14}) + (1-p_T)\beta^* k_{12}^1 k_{14} + \beta^* p_T k_{12}^1 k_{13}^0}. \tag{2.17}$$

In the case of $l_T \to 0$ and $\eta_{14} \to 1$, follows that

$$\lim_{\substack{l_T \to 0 \\ \eta_{14} \to 1}} \mathfrak{R}_0^T = \frac{\alpha^* M_T \eta\big((1-\beta^*)k_{14}k_{13}^1 + (1-p_T)\beta^* k_{12}^0(k_{14}+1) + k_{12}^0 k_{13}^1 \beta^* p_T\big)}{N_T(\alpha_H + \alpha_D + \mu)k_{11}k_{12}^0 k_{13}^1 k_{14}}, \tag{2.18}$$

where k_{13}^1 is k_{13} for $\eta_{14} = 1$ and $k_{13}^1 = k_{13}^0 + 1$. If the limit (2.18) is greater than unity, then when $l_T \to 0$ and $\eta_{14} \to 1$ it has a negative impact on TB transmission control. That is, if:

$$\frac{\alpha^* M_T}{N_T(\alpha_H + \alpha_D + \mu)} > \frac{k_{11}k_{12}^0 k_{13}^1 k_{14}}{(1-\beta^*)k_{14}k_{13}^1 + (1-p_T)\beta^* k_{12}^0(k_{14}+1) + k_{12}^0 k_{13}^1 \beta^* p_T}. \tag{2.19}$$

For $l_T \to 1$ and $\eta_{14} \to 1$, we have

$$\lim_{\substack{l_T \to 1 \\ \eta_{14} \to 1}} \mathfrak{R}_0^T = \frac{\alpha^* M_T \eta\big((1-\beta^*)(k_{14}k_{13}^1 + (k_{14}+1)) + (1-p_T)\beta^* k_{12}^1(k_{14}+1) + k_{12}^1 k_{13}^1 \beta^* p_T\big)}{N_T(\alpha_H + \alpha_D + \mu)k_{11}k_{12}^1 k_{13}^1 k_{14}}. \tag{2.20}$$

If the limit (2.20) is greater than unity, then when $l_T \to 1$ and $\eta_{14} \to 1$ it has a negative impact on TB transmission control. That is, when

$$\frac{\alpha^* M_T}{N_T(\alpha_H + \alpha_D + \mu)} > \frac{k_{11}k_{12}^1 k_{13}^1 k_{14}}{(1-\beta^*)(k_{14}k_{13}^1 + (k_{14}+1)) + (1-p_T)\beta^* k_{12}^{'}(k_{14}+1) + k_{12}^1 k_{13}^1 \beta^* p_T}. \tag{2.21}$$

Let us define the following expressions:

$$\Delta_T = \frac{\alpha^* M_T}{N_T(\alpha_H + \alpha_D + \mu)}, \tag{2.22}$$

$$\Delta_{T_1} = \frac{k_{11}k_{12}^0 k_{13}^0 k_{14}}{(1-\beta^*)k_{13}^0 k_{14} + (1-p_T)\beta^* k_{12}^0 k_{14} + \beta^* p_T k_{12}^0 k_{13}^0}, \tag{2.23}$$

$$\Delta_{T_2} = \frac{k_{11}k_{12}^1 k_{13}^0 k_{14}}{(1-\beta^*)(k_{13}^0 k_{14} + k_{14}) + (1-p_T)\beta^* k_{12}^1 k_{14} + \beta^* p_T k_{12}^1 k_{13}^0}, \tag{2.24}$$

$$\Delta_{T_3} = \frac{k_{11}k_{12}^0 k_{13}^1 k_{14}}{(1-\beta^*)k_{14}k_{13}^1 + (1-p_T)\beta^* k_{12}^0(k_{14}+1) + k_{12}^0 k_{13}^1 \beta^* p_T}, \tag{2.25}$$

$$\Delta_{T_4} = \frac{k_{11}k_{12}^1 k_{13}^1 k_{14}}{(1-\beta^*)(k_{14}k_{13}^1 + (k_{14}+1)) + (1-p_T)\beta^* k_{12}^{'}(k_{14}+1) + k_{12}^1 k_{13}^1 \beta^* p_T}. \tag{2.26}$$

We have the following lemma:

Lemma 2.3.3. *1. The impact when $l_T \to 0$ and $\eta_{14} \to 0$ is positive in reducing TB transmission in this subpopulation only if $\Delta_T < \Delta_{T_1}$, no impact if $\Delta_T = \Delta_{T_1}$ and a negative impact if $\Delta_T > \Delta_{T_1}$.*

2. *The impact when* $l_T \to 1$ *and* $\eta_{14} \to 0$ *is positive in reducing TB transmission in this subpopulation only if* $\Delta_T < \Delta_{T_2}$*, no impact if* $\Delta_T = \Delta_{T_2}$ *and a negative impact if* $\Delta_T > \Delta_{T_2}$.

3. *The impact when* $l_T \to 0$ *and* $\eta_{14} \to 1$ *is positive in reducing TB transmission in this subpopulation only if* $\Delta_T < \Delta_{T_3}$*, no impact if* $\Delta_T = \Delta_{T_3}$ *and a negative impact if* $\Delta_T > \Delta_{T_3}$.

4. *The impact when* $l_T \to 1$ *and* $\eta_{14} \to 1$ *is positive in reducing TB transmission in this subpopulation only if* $\Delta_T < \Delta_{T_4}$*, no impact if* $\Delta_T = \Delta_{T_4}$ *and a negative impact if* $\Delta_T > \Delta_{T_4}$.

Now, we study the relationship between resistance and recovery parameters. The treatment aims to avoid resistance and for patients to recover. First, we analyze the relationship between the MDR-TB parameter (l_T) and the recovery parameter (η_{11}), because we want to avoid MDR-TB so it is necessary that the patient recovers before having this resistance. We have the following limits:

$$\lim_{\substack{l_T\to 0\\ \eta_{11}\to 1}} \mathfrak{R}_0^T = \frac{\alpha^* M_T \eta\Big((1-\beta^*)k_{13}k_{14} + (1-p_T)\beta^* k_{12}^{01}(k_{14}+\eta_{14}) + p_T\beta^* k_{12}^{01}k_{13}\Big)}{N_T(\alpha_H+\alpha_D+\mu)k_{11}k_{12}^{01}k_{13}k_{14}}, \tag{2.27}$$

where k_{12}^{01} represents k_{12} when $l_T \to 0$ and $\eta_{11} \to 1$.

$$\lim_{\substack{l_T\to 1\\ \eta_{11}\to 0}} \mathfrak{R}_0^T = \frac{\alpha^* M_T \eta\Big((1-\beta^*)(k_{13}k_{14} + (k_{14}+\eta_{14})) + (1-p_T)\beta^* k_{12}^{10}(k_{14}+\eta_{14}) + p_T\beta^* k_{12}^{10}k_{13}\Big)}{N_T(\alpha_H+\alpha_D+\mu)k_{11}k_{12}^{10}k_{13}k_{14}}, \tag{2.28}$$

where k_{12}^{10} represents k_{12} when $l_T \to 1$ and $\eta_{11} \to 0$.

$$\lim_{\substack{l_T\to 1\\ \eta_{11}\to 1}} \mathfrak{R}_0^T = \frac{\alpha^* M_T \eta\Big((1-\beta^*)(k_{13}k_{14} + (k_{14}+\eta_{14})) + (1-p_T)\beta^* k_{12}^{11}(k_{14}+\eta_{14}) + p_T\beta^* k_{12}^{11}k_{13}\Big)}{N_T(\alpha_H+\alpha_D+\mu)k_{11}k_{12}^{11}k_{13}k_{14}}, \tag{2.29}$$

where k_{12}^{11} represents k_{12} when $l_T \to 1$ and $\eta_{11} \to 1$.

$$\lim_{\substack{l_T\to 0\\ \eta_{11}\to 0}} \mathfrak{R}_0^T = \frac{\alpha^* M_T \eta\Big((1-\beta^*)k_{13}k_{14} + (1-p_T)\beta^* k_{12}^{00}(k_{14}+\eta_{14}) + p_T\beta^* k_{12}^{00}k_{13}\Big)}{N_T(\alpha_H+\alpha_D+\mu)k_{11}k_{12}^{00}k_{13}k_{14}}, \tag{2.30}$$

where k_{12}^{00} represents k_{12} when $l_T \to 0$ and $\eta_{11} \to 0$.

Let us denote:

$$\Delta_{T_5} = \frac{k_{11}k_{12}^{00}k_{13}k_{14}}{(1-\beta^*)k_{13}k_{14} + (1-p_T)\beta^* k_{12}^{00}(k_{14}+\eta_{14}) + p_T\beta^* k_{12}^{00}k_{13}}, \tag{2.31}$$

$$\Delta_{T_6} = \frac{k_{11}k_{12}^{01}k_{13}k_{14}}{(1-\beta^*)k_{13}k_{14} + (1-p_T)\beta^* k_{12}^{01}(k_{14}+\eta_{14}) + p_T\beta^* k_{12}^{01}k_{13}}, \tag{2.32}$$

$$\Delta_{T_7} = \frac{k_{11}k_{12}^{10}k_{13}k_{14}}{(1-\beta^*)(k_{13}k_{14} + (k_{14}+\eta_{14})) + (1-p_T)\beta^* k_{12}^{10}(k_{14}+\eta_{14}) + p_T\beta^* k_{12}^{10}k_{13}}, \tag{2.33}$$

$$\Delta_{T_8} = \frac{k_{11}k_{12}^{11}k_{13}k_{14}}{(1-\beta^*)(k_{13}k_{14}+(k_{14}+\eta_{14}))+(1-p_T)\beta^*k_{12}^{11}(k_{14}+\eta_{14})+p_T\beta^*k_{12}^{11}k_{13}}. \tag{2.34}$$

We have the following lemma:

Lemma 2.3.4. *1. The impact when $l_T \to 0$ and $\eta_{11} \to 0$ is positive in reducing TB transmission in this subpopulation only if $\Delta_T < \Delta_{T_5}$, no impact if $\Delta_T = \Delta_{T_5}$ and a negative impact if $\Delta_T > \Delta_{T_5}$.*

2. The impact when $l_T \to 0$ and $\eta_{11} \to 1$ is positive in reducing TB transmission in this subpopulation only if $\Delta_T < \Delta_{T_6}$, no impact if $\Delta_T = \Delta_{T_6}$ and a negative impact if $\Delta_T > \Delta_{T_6}$.

3. The impact when $l_T \to 1$ and $\eta_{11} \to 0$ is positive in reducing TB transmission in this subpopulation only if $\Delta_T < \Delta_{T_7}$, no impact if $\Delta_T = \Delta_{T_7}$ and a negative impact if $\Delta_T > \Delta_{T_7}$.

4. The impact when $l_T \to 1$ and $\eta_{11} \to 1$ is positive in reducing TB transmission in this subpopulation only if $\Delta_T < \Delta_{T_8}$, no impact if $\Delta_T = \Delta_{T_8}$ and a negative impact if $\Delta_T > \Delta_{T_8}$.

Now, we examine the relationship between the XDR-TB parameter (η_{14}) and recovery after reporting as XDR-TB (m_T). The aim, in this case, is to have a patient recover before reporting as XDR-TB. We show the relationships between these parameters with respect to $\mathfrak{R}_0^T$. We have

$$\lim_{\substack{\eta_{14}\to 0\\ m_T\to 1}} \mathfrak{R}_0^T = \frac{\alpha^* M_T \eta\big((1-\beta^*)(k_{13}^{01}k_{14}+l_Tk_{14})+(1-p_T)\beta^*k_{12}k_{14}+p_T\beta^*k_{12}k_{13}^{01}\big)}{N_T(\alpha_H+\alpha_D+\mu)k_{11}k_{12}k_{13}^{01}k_{14}}, \tag{2.35}$$

where k_{13}^{01} represents k_{13} when $\eta_{14} \to 0$ and $m_T \to 1$.

$$\lim_{\substack{\eta_{14}\to 1\\ m_T\to 0}} \mathfrak{R}_0^T = \frac{\alpha^* M_T \eta\big((1-\beta^*)(k_{13}^{10}k_{14}+l_T(k_{14}+1))+(1-p_T)\beta^*k_{12}(k_{14}+1)+p_T\beta^*k_{12}k_{13}^{10}\big)}{N_T(\alpha_H+\alpha_D+\mu)k_{11}k_{12}k_{13}^{10}k_{14}}, \tag{2.36}$$

where k_{13}^{10} represents k_{13} when $\eta_{14} \to 1$ and $m_T \to 0$.

$$\lim_{\substack{\eta_{14}\to 1\\ m_T\to 1}} \mathfrak{R}_0^T = \frac{\alpha^* M_T \eta\big((1-\beta^*)(k_{13}^{11}k_{14}+l_T(k_{14}+1))+(1-p_T)\beta^*k_{12}(k_{14}+1)+p_T\beta^*k_{12}k_{13}^{11}\big)}{N_T(\alpha_H+\alpha_D+\mu)k_{11}k_{12}k_{13}^{11}k_{14}}, \tag{2.37}$$

where k_{13}^{11} represents k_{13} when $\eta_{14} \to 1$ and $m_T \to 1$.

$$\lim_{\substack{\eta_{14}\to 0\\ m_T\to 0}} \mathfrak{R}_0^T = \frac{\alpha^* M_T \eta\big((1-\beta^*)(k_{13}^{00}k_{14}+l_Tk_{14})+(1-p_T)\beta^*k_{12}k_{14}+p_T\beta^*k_{12}k_{13}^{00}\big)}{N_T(\alpha_H+\alpha_D+\mu)k_{11}k_{12}k_{13}^{00}k_{14}}, \tag{2.38}$$

where k_{13}^{00} represents k_{13} when $\eta_{14} \to 0$ and $m_T \to 0$.

Let us consider the following expressions:

$$\Delta_{T_9} = \frac{k_{11}k_{12}k_{13}^{00}k_{14}}{(1-\beta^*)(k_{13}^{11}k_{14}+l_Tk_{14})+(1-p_T)\beta^*k_{12}(k_{14}+1)+p_T\beta^*k_{12}k_{13}^{00}}, \tag{2.39}$$

$$\Delta_{T_{10}} = \frac{k_{11}k_{12}k_{13}^{01}k_{14}}{(1-\beta^*)(k_{13}^{01}k_{14}+l_Tk_{14})+(1-p_T)\beta^*k_{12}k_{14}+p_T\beta^*k_{12}k_{13}^{01}}, \tag{2.40}$$

$$\Delta_{T_{11}} = \frac{k_{11}k_{12}k_{13}^{10}k_{14}}{(1-\beta^*)(k_{13}^{10}k_{14}+l_T(k_{14}+1))+(1-p_T)\beta^*k_{12}(k_{14}+1)+p_T\beta^*k_{12}k_{13}^{10}}, \tag{2.41}$$

$$\Delta_{T_{12}} = \frac{k_{11}k_{12}k_{13}^{11}k_{14}}{(1-\beta^*)(k_{13}^{11}k_{14}+l_T(k_{14}+1))+(1-p_T)\beta^*k_{12}(k_{14}+1)+p_T\beta^*k_{12}k_{13}^{11}}. \tag{2.42}$$

We obtain the following lemma:

Lemma 2.3.5. *1. The impact when $\eta_{14} \to 0$ and $m_T \to 0$ is positive in reducing TB transmission in this subpopulation only if $\Delta_T < \Delta_{T_9}$, no impact if $\Delta_T = \Delta_{T_9}$ and a negative impact if $\Delta_T > \Delta_{T_9}$.*

2. *The impact when $\eta_{14} \to 0$ and $m_T \to 1$ is positive in reducing TB transmission in this subpopulation only if $\Delta_T < \Delta_{T_{10}}$, no impact if $\Delta_T = \Delta_{T_{10}}$ and a negative impact if $\Delta_T > \Delta_{T_{10}}$.*

3. *The impact when $\eta_{14} \to 1$ and $m_T \to 0$ is positive in reducing TB transmission in this subpopulation only if $\Delta_T < \Delta_{T_{11}}$, no impact if $\Delta_T = \Delta_{T_{11}}$ and a negative impact if $\Delta_T > \Delta_{T_{11}}$.*

4. *The impact when $\eta_{14} \to 1$ and $m_T \to 1$ is positive in reducing TB transmission in this subpopulation only if $\Delta_T < \Delta_{T_{12}}$, no impact if $\Delta_T = \Delta_{T_{12}}$ and a negative impact if $\Delta_T > \Delta_{T_{12}}$.*

Studying the resistance parameters (l_T, η_{14}) in conjunction with the recovery parameters (η_{11}, m_T). We present two cases, (1) when the resistance parameters tend to unity and the recovery parameters tend to zero, (2) the opposite case:

$$\lim_{\substack{l_T\to 1\\ \eta_{14}\to 1\\ \eta_{11}\to 0\\ m_T\to 0}} \mathfrak{R}_0^T = \frac{\alpha^*M_T\eta\left((1-\beta^*)(k_{13}^{10}k_{14}+(k_{14}+1))+(1-p_T)\beta^*k_{12}^{10}(k_{14}+1)+p_T\beta^*k_{12}^{10}k_{13}^{10}\right)}{N_T(\alpha_H+\alpha_D+\mu)k_{11}k_{12}^{10}k_{13}^{10}k_{14}}, \tag{2.43}$$

$$\lim_{\substack{l_T\to 0\\ \eta_{14}\to 0\\ \eta_{11}\to 1\\ m_T\to 1}} \mathfrak{R}_0^T = \frac{\alpha^*M_T\eta\left((1-\beta^*)k_{13}^{01}k_{14}+(1-p_T)\beta^*k_{12}^{01}k_{14}+p_T\beta^*k_{12}^{01}k_{13}^{01}\right)}{N_T(\alpha_H+\alpha_D+\mu)k_{11}k_{12}^{01}k_{13}^{01}k_{14}}, \tag{2.44}$$

and if we define

$$\Delta_{T_{13}} = \frac{k_{11}k_{12}^{10}k_{13}^{10}k_{14}}{(1-\beta^*)(k_{13}^{10}k_{14}+(k_{14}+1))+(1-p_T)\beta^*k_{12}^{10}(k_{14}+1)+p_T\beta^*k_{12}^{10}k_{13}^{10}}, \tag{2.45}$$

$$\Delta_{T_{14}} = \frac{k_{11}k_{12}^{01}k_{13}^{01}k_{14}}{(1-\beta^*)k_{13}^{01}k_{14}+(1-p_T)\beta^*k_{12}^{01}k_{14}+p_T\beta^*k_{12}^{01}k_{13}^{01}}, \tag{2.46}$$

we obtain the following lemma:

Lemma 2.3.6. *1. The impact of the resistance parameters when they tend to unity ($l_T, \eta_{14} \to 1$) with respect to the recovery parameters when they tend to zero ($\eta_{11}, m_T \to 0$) is positive in reducing tuberculosis transmission in this subpopulation only if $\Delta_T < \Delta_{T_{13}}$, no impact if $\Delta_T = \Delta_{T_{13}}$ and a negative impact if $\Delta_T > \Delta_{T_{13}}$.*

2. The impact of the recovery parameters recovery parameters when they tend to unity ($\eta_{11}, m_T \to 1$) with respect to the recovery parameters when they tend to zero ($l_T, \eta_{14} \to 0$) is positive in reducing tuberculosis transmission in this subpopulation only if $\Delta_T < \Delta_{T_{14}}$, no impact if $\Delta_T = \Delta_{T_{14}}$ and a negative impact if $\Delta_T > \Delta_{T_{14}}$.

Endemic Equilibrium Point

To find the endemic equilibrium point of TB-Only submodel (2.11), we solve the following system of equations,

$$\begin{pmatrix} -(\mu+\alpha_H+\alpha_D+\lambda_T) & 0 & 0 & 0 & 0 & 0 \\ \lambda_T & -k_{11} & 0 & 0 & 0 & \beta_1^{'}\lambda_T \\ 0 & (1-\beta^*)\eta & -k_{12} & 0 & 0 & 0 \\ 0 & (1-p_T)\beta^*\eta & l_T & -k_{13} & 0 & 0 \\ 0 & p_T\beta^*\eta & 0 & \eta_{14} & -k_{14} & 0 \\ 0 & 0 & \eta_{11} & m_T & \eta_{11}^* & -(\mu+\beta_1^{'}\lambda_T+\alpha_H+\alpha_D) \end{pmatrix} \begin{pmatrix} S_T^* \\ E_T^* \\ I_{T_1}^* \\ I_{T_2}^* \\ I_{T_3}^* \\ R_T^* \end{pmatrix} = \begin{pmatrix} -M_T \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}.$$

Then, the endemic equilibrium point is $\epsilon_*^T = (S_T^*, E_T^*, I_{T_1}^*, I_{T_2}^*, I_{T_3}^*, R_T^*)$, where:

$$\begin{aligned}
S_T^* &= \frac{M_T}{\lambda_T^*+\alpha_H+\alpha_D+\mu}, \quad E_T^* = \frac{M_T\lambda_T^*k_{12}k_{13}k_{14}(\alpha_H+\alpha_D+\beta_1^{'}\lambda_T^*+\mu)}{A_1}, \\
I_{T_1}^* &= \frac{M_T(1-\beta^*)\eta\lambda_T^*k_{13}k_{14}(\alpha_H+\alpha_D+\beta_1^{'}\lambda_T^*+\mu)}{A_1}, \\
I_{T_2}^* &= \frac{M_T\lambda_T^*(\alpha_H+\alpha_D+\beta_1^{'}\lambda_T^*+\mu)(k_{12}k_{14}\beta^*\eta(1-p_T)+k_{14}l_T(1-\beta^*)\eta)}{A_1}, \\
I_{T_3}^* &= \frac{M_T\lambda_T^*(\alpha_H+\alpha_D+\beta_1^{'}\lambda_T^*+\mu)(l_T\eta_{14}(1-\beta^*)\eta+k_{12}\beta^*\eta\eta_{14}(1-p_T)+k_{12}k_{13}\beta^*\eta p_T)}{A_1}, \\
R_T^* &= \frac{M_T\lambda_T^*((1-\beta^*)\eta(k_{13}k_{14}\eta_{11}+l_T(k_{14}m_T+\eta_{11}^*\eta_{14})+(1-p_T)k_{12}\beta^*\eta(k_{14}m_T+\eta_{11}^*\eta_{14})}{A_1} \\
&\frac{+k_{12}k_{13}\eta\eta_{11}^*\beta^*p_T)}{A_1},
\end{aligned} \tag{2.47}$$

and $A_1 = (\alpha_H+\alpha_D+\mu+\lambda_T^*)(\alpha_H+\alpha_D+\mu+\beta_1^*\lambda_T^*)k_{11}k_{12}k_{13}k_{14} - (\alpha_H+\alpha_D+\mu+\lambda_T^*)\beta_1^{'}\lambda_T^*((1-p_T)k_{12}\beta^*\eta(k_{14}m_T+\eta_{11}^*\eta_{14})+(1-\beta^*)\eta(k_{13}k_{14}\eta_{11}+l_T(k_{14}m_T+\eta_{11}^*\eta_{14})+k_{12}k_{13}\beta^*\eta\eta_{11}^*p_T)$.

Substituting equations (2.47) into the TB-infection rate for this submodel $\left(\lambda_T = \alpha^*\frac{I_{T_1}+I_{T_2}+I_{T_3}}{N_T}\right)$, we have that

$$\lambda_T^* = \frac{\alpha^*M_T\lambda_T^*(\alpha_H+\alpha_D+\beta_1^{'}\lambda_T^*+\mu)\big((1-\beta^*)\eta(k_{13}k_{14}+l_T(k_{14}+\eta_{14})+(1-p_T)k_{12}\beta^*\eta(k_{14}+\eta_{14})+k_{12}k_{13}\beta^*\eta p_T\big)}{N_TA_1},$$

which reduces to

$$\lambda_T^*\left(\frac{\alpha^*M_T\lambda_T^*(\alpha_H+\alpha_D+\beta_1^{'}\lambda_T^*+\mu)\big((1-\beta^*)\eta(k_{13}k_{14}+l_T(k_{14}+\eta_{14})+(1-p_T)k_{12}\beta^*\eta(k_{14}+\eta_{14})+k_{12}k_{13}\beta^*\eta p_T\big)}{N_TA_1}\right.$$

$$- \frac{(\alpha_H + \alpha_D + \mu + \lambda_T^*)(\alpha_H + \alpha_D + \mu + \beta_1^* \lambda_T^*)\big(k_{11}k_{12}k_{13}k_{14} + \beta_1' \lambda_T^*((1-p_T)k_{12}\beta^*\eta(k_{14}M_T\eta_{11}^*\eta_{14})\big)}{A_1}$$
$$+ \frac{(\alpha_H + \alpha_D + \mu + \lambda_T^*)(\alpha_H + \alpha_D + \mu + \beta_1^* \lambda_T^*)\big((1-\beta^*)\eta(k_{13}k_{14}\eta_{11} + l_T(k_{14}m_T + \eta_{11}^*\eta_{14}) + k_{12}k_{13}\beta^*\eta\eta_{11}^* p_T\big)}{A_1}\Bigg) = 0,$$

where $\lambda_T^* = 0$ corresponds to the disease-free equilibrium and $\lambda_T^* \neq 0$ means the existence of endemic equilibrium. For a disease to spread, the force of infection (λ_T^*) should be positive.

So for λ_T^* to be positive, we need the following inequality to be satisfied.

$$\frac{\alpha^* M_T(\alpha_H + \alpha_D + \mu)((1-\beta^*)\eta(k_{13}k_{14} + l_T(k_{14} + \eta_{14}) + (1-p_T)k_{12}\beta^*\eta(k_{14} + \eta_{14}) + k_{12}k_{13}\beta^*\eta p_T)}{N_T} -$$
$$(\alpha_H + \alpha_D + \mu)^2 k_{11}k_{12}k_{13}k_{14} > 0,$$

and

$$\frac{\alpha^* M_T((1-\beta^*)\eta(k_{13}k_{14} + l_T(k_{14} + \eta_{14}) + (1-p_T)k_{12}\beta^*\eta(k_{14} + \eta_{14}) + k_{12}k_{13}\beta^*\eta p_T)}{N_T(\alpha_H + \alpha_D + \mu)k_{11}k_{12}k_{13}k_{14}} > 1,$$

which implies that $\mathfrak{R}_0^T > 1$.
Then, we have the following lemma:

Lemma 2.3.7. *The TB-Only submodel (2.11) has a unique endemic equilibrium point ϵ_*^T, whenever $\mathfrak{R}_0^T > 1$.*

TB-HIV/AIDS Submodel

The submodel that relates TB to HIV/AIDS is when $S_D = S_T = E_D = E_T = I_{D_1} = I_{D_2} = I_{T_1} = I_{T_2} = I_{T_3} = R_T = I_{D_3} = R_D = 0$ and is given by

$$\begin{aligned}
\frac{dS_H}{dt} &= M_H - (\alpha_{HD} + \mu + \mu_H + \omega_H\lambda_H)S_H,\\
\frac{dE_H}{dt} &= \omega_H\lambda_H(S_H + \beta_1' R_H) - (\epsilon_H^*\eta + \mu + \mu_H + \alpha_{HD})E_H,\\
\frac{dI_{H_1}}{dt} &= (1-\beta^*)\epsilon_H^*\eta E_H - (l_H + \mu + \mu_H + d_{TH} + \eta_{12} + t_{HD}\alpha_{HD})I_{H_1},\\
\frac{dI_{H_2}}{dt} &= (1-p_H)\beta^*\epsilon_H^*\eta E_H + l_H I_{H_1} - (m_H + \mu + \mu_H + t_H' d_{TH} + \eta_{15} + t_{HD}\alpha_{HD})I_{H_2},\\
\frac{dI_{H_3}}{dt} &= p_H\beta^*\epsilon_H^*\eta E_H + \eta_{15}I_{H_2} - (\eta_{12}^* + \mu + \mu_H + t_H^* d_{TH} + t_{HD}\alpha_{HD})I_{H_3},\\
\frac{dR_H}{dt} &= m_H I_{H_2} + \eta_{12}I_{H_1} + \eta_{12}^* I_{H_3} - (\mu + \mu_H + \beta_1'\omega_H\lambda_H + \alpha_{HD})R_H,
\end{aligned} \tag{2.48}$$

with non-negative initial conditions and

$$\lambda_H = \alpha^* \frac{\epsilon_H(I_{H_1} + I_{H_2} + I_{H_3})}{N_H},$$

where $N_H = S_H + E_H + I_{H_1} + I_{H_2} + I_{H_3} + R_H$.

Considering biological constraints, the system (2.48) will be studied in the following region:

$$D_2 = \left\{ (S_H, E_H, I_{H_1}, I_{H_2}, I_{H_3}, R_H) \in \mathbb{R}^6_+ \ : \ N_H(t) \leq \frac{M_H}{\mu} \right\}.$$

It can be easily shown that the solutions $(S_H(t), E_H, I_{H_1}(t), I_{H_2}(t), I_{H_3}(t), R_H(t))$ of the system are bounded and positively invariant.

The disease-free equilibrium point, ϵ_0^H, is given by $\epsilon_0^H = \left(S_0^H, 0, 0, 0, 0, 0 \right)$, where $S_0^H = \dfrac{M_H}{\alpha_{HD} + \mu + \mu_H}$.

The matrices for the new infection terms, F_H and the other terms, V_H are given respectively, by:

$$F_H = \begin{bmatrix} 0 & \dfrac{M_H \alpha^* \omega_H \epsilon_H}{\alpha_{HD} + \mu + \mu_H} & \dfrac{M_H \alpha^* \omega_H \epsilon_H}{\alpha_{HD} + \mu + \mu_H} & \dfrac{M_H \alpha^* \omega_H \epsilon_H}{\alpha_{HD} + \mu + \mu_H} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix},$$

$$V_H = \begin{bmatrix} k_{21} & 0 & 0 & 0 \\ -(1-\beta^*)\epsilon_H^* \eta & k_{22} & 0 & 0 \\ -(1-p_H)\beta^* \epsilon_H^* \eta & -l_H & k_{23} & 0 \\ -\beta^* p_H \epsilon_H^* \eta & 0 & -\eta_{15} & k_{24} \end{bmatrix},$$

where $k_{21} = \alpha_{HD} + \epsilon_H^* \eta + \mu + \mu_H$, $k_{22} = l_H + \mu + \mu_H + d_{TH} + \eta_{12} + t_{HD}\alpha_{HD}$, $k_{23} = \mu + \mu_H + t_H^{'} d_{TH} + \eta_{15} + m_H + t_{HD}\alpha_{HD}$ and $k_{24} = \mu + \mu_H + t_H^* d_{TH} + \eta_{12}^* + t_{HD}\alpha_{HD}$. In this way, the basic reproduction number is given by

$$\mathfrak{R}_0^H = \rho(F_H V_H^{-1}) = \frac{\alpha^* \epsilon_H \omega_H M_H \epsilon_H^* \eta \big((1-\beta^*)(k_{23}k_{24} + l_H(k_{24} + \eta_{15})) + (1-p_H)\beta^* k_{22}(k_{24} + \eta_{15}) + \beta^* p_H k_{22} k_{23} \big)}{N_H(\alpha_{HD} + \mu + \mu_H) k_{21} k_{22} k_{23} k_{24}}. \tag{2.49}$$

We define (H_1) and (H_2) as in the submodel (2.11) and using the same idea from the demonstration, we get the following lemmas:

Lemma 2.3.8. *The disease-free equilibrium ϵ_0^H is asymptotically stable when $\mathfrak{R}_0^H < 1$ and is unstable whenever $\mathfrak{R}_0^H > 1$.*

Lemma 2.3.9. *The fixed point $E_0^H = (S_0^{H_*}, 0, 0, 0, 0)$ where $S_0^{H_*} = \left(\dfrac{M_H}{\mu + \alpha_{HD} + \mu_H}, 0 \right)$ is a globally asymptotically stable equilibrium of submodel (TB-HIV/AIDS) if $\mathfrak{R}_0^H < 1$ and the assumption (H_1) and (H_2) are satisfied.*

We make a procedure analogous to the model (2.11) for l_H and η_{15} (MDR-TB and XDR-TB parameters for TB-HIV/AIDS submodel) and we obtain the limit:

$$\lim_{\substack{l_H\to 0\\ \eta_{15}\to 0}} \mathfrak{R}_0^H = \frac{\alpha^* M_H \omega_H \epsilon_H \epsilon_H^* \eta\left((1-\beta^*)k_{23}^0 k_{24} + (1-p_H)\beta^* k_{22}^0 k_{24} + \beta^* p_H k_{22}^0 k_{23}^0\right)}{N_H(\mu_H + \alpha_{HD} + \mu)k_{21}k_{22}^0 k_{23}^0 k_{24}}, \tag{2.50}$$

where k_{22}^0 is k_{22} for $l_H = 0$ and k_{23}^0 is k_{23} for $\eta_{15} = 0$. Then, in practice $l_H \to 0$ and $\eta_{15} \to 0$ means zero resistance, i.e. elimination of resistance to tuberculosis treatment in this subpopulation. If the limit (2.50) is greater than unity, then when $l_H, \eta_{15} \to 0$, it has a negative impact on TB transmission control. That is, when

$$\frac{\alpha^* \omega_H \epsilon_H \epsilon_H^* \eta M_H}{N_H(\alpha_{HD} + \mu_H + \mu)} > \frac{k_{21}k_{22}^0 k_{23}^0 k_{24}}{(1-\beta^*)k_{23}^0 k_{24} + (1-p_H)\beta^* k_{22}^0 k_{24} + \beta^* p_H k_{22}^0 k_{23}^0}. \tag{2.51}$$

Now, we study the case when $l_H \to 1$ and $\eta_{15} \to 0$. We get the limit

$$\lim_{\substack{l_H\to 1\\ \eta_{15}\to 0}} \mathfrak{R}_0^H = \frac{\alpha^* \omega_H \epsilon_H \epsilon_H^* M_H \eta\left((1-\beta^*)(k_{23}^0 k_{24} + k_{24}) + (1-p_H)\beta^* k_{22}^1 k_{24} + \beta^* p_H k_{22}^1 k_{23}^0\right)}{N_H(\alpha_{HD} + \mu_H + \mu)k_{21}k_{22}^1 k_{23}^0 k_{24}}, \tag{2.52}$$

where k_{22}^1 is k_{22} for $l_H = 1$. Then if the limit (2.52) is greater than unity, then when $l_H \to 1$ and $\eta_{15} \to 0$ it has a negative impact on TB transmission control. That is, whereas

$$\frac{\alpha^* \omega_H \epsilon_H \epsilon_H^* M_H}{N_H(\alpha_{HD} + \mu_H + \mu)} > \frac{k_{21}k_{22}^1 k_{23}^0 k_{24}}{(1-\beta^*)(k_{23}^0 k_{24} + k_{24}) + (1-p_H)\beta^* k_{22}^1 k_{24} + \beta^* p_H k_{22}^1 k_{23}^0}. \tag{2.53}$$

In the case when $l_H \to 0$ and $\eta_{15} \to 1$. We have

$$\lim_{\substack{l_H\to 0\\ \eta_{15}\to 1}} \mathfrak{R}_0^H = \frac{\alpha^* \omega_H \epsilon_H \epsilon_H^* M_H \eta\left((1-\beta^*)k_{24}k_{23}^1 + (1-p_H)\beta^* k_{22}^0(k_{24}+1) + k_{22}^0 k_{23}^1 \beta^* p_H\right)}{N_H(\alpha_{HD} + \mu_H + \mu)k_{21}k_{22}^0 k_{23}^1 k_{24}} > 0, \tag{2.54}$$

where k_{23}^1 is k_{23} for $\eta_{15} = 1$ and $k_{23}^1 = k_{23}^0 + 1$. If the limit (2.54) is greater than unity, then $l_H \to 0$ and $\eta_{15} \to 1$ means a negative impact on TB transmission control. That is, if we have

$$\frac{\alpha^* \omega_H \epsilon_H \epsilon_H^* M_H}{N_H(\alpha_{HD} + \mu_H + \mu)} > \frac{k_{21}k_{22}^0 k_{23}^1 k_{24}}{(1-\beta^*)k_{24}k_{23}^1 + (1-p_H)\beta^* k_{22}^0(k_{24}+1) + k_{22}^0 k_{23}^1 \beta^* p_H}. \tag{2.55}$$

For $l_H \to 1$ and $\eta_{15} \to 1$, we have

$$\lim_{\substack{l_H\to 1\\ \eta_{15}\to 1}} \mathfrak{R}_0^H = \frac{\alpha^* M_H \omega_H \epsilon_H \epsilon_H^* \eta\left((1-\beta^*)(k_{24}k_{23}^1 + (k_{24}+1)) + (1-p_H)\beta^* k_{22}^1(k_{24}+1) + k_{22}^1 k_{23}^1 \beta^* p_H\right)}{N_H(\alpha_{HD} + \mu_H + \mu)k_{21}k_{22}^1 k_{23}^1 k_{24}}. \tag{2.56}$$

If the limit (2.56) is greater than unity, then when $l_H \to 1$ and $\eta_{15} \to 1$ has a negative impact on TB transmission control, if

$$\frac{\alpha^*\omega_H\epsilon_H\epsilon_H^*M_H}{N_H(\alpha_{HD}+\mu_H+\mu)} > \frac{k_{21}k_{22}^1k_{23}^1k_{24}}{(1-\beta^*)(k_{24}k_{23}^1+(k_{24}+1))+(1-p_H)\beta^*k_{22}^1(k_{24}+1)+k_{22}^1k_{23}^1\beta^*p_H}. \tag{2.57}$$

We consider the following expressions:

$$\Delta_H = \frac{\alpha^*\omega_H\epsilon_H\epsilon_H^*M_H}{N_H(\alpha_{HD}+\mu_H+\mu)}, \tag{2.58}$$

$$\Delta_{H_1} = \frac{k_{21}k_{22}^0k_{23}^0k_{24}}{(1-\beta^*)k_{23}^0k_{24}+(1-p_H)\beta^*k_{22}^0k_{24}+\beta^*p_Hk_{22}^0k_{23}^0}, \tag{2.59}$$

$$\Delta_{H_2} = \frac{k_{21}k_{22}^1k_{23}^0k_{24}}{(1-\beta^*)(k_{23}^0k_{24}+k_{24})+(1-p_H)\beta^*k_{22}^1k_{24}+\beta^*p_Hk_{22}^1k_{23}^0}, \tag{2.60}$$

$$\Delta_{H_3} = \frac{k_{21}k_{22}^0k_{23}^1k_{24}}{(1-\beta^*)k_{24}k_{23}^1+(1-p_H)\beta^*k_{22}^0(k_{24}+1)+k_{22}^0k_{23}^1\beta^*p_H}, \tag{2.61}$$

$$\Delta_{H_4} = \frac{k_{21}k_{22}^1k_{23}^1k_{24}}{(1-\beta^*)(k_{24}k_{23}^1+(k_{24}+1))+(1-p_H)\beta^*k_{22}^1(k_{24}+1)+k_{22}^1k_{23}^1\beta^*p_H}. \tag{2.62}$$

Then, we obtain the following lemma:

Lemma 2.3.10. *1. The impact when $l_H \to 0$ and $\eta_{15} \to 0$ is positive in reducing TB transmission in this subpopulation only if $\Delta_H < \Delta_{H_1}$, no impact if $\Delta_H = \Delta_{H_1}$ and a negative impact if $\Delta_H > \Delta_{H_1}$.*

2. *The impact when $l_T \to 1$ and $\eta_{15} \to 0$ is positive in reducing TB transmission in this subpopulation only if $\Delta_H < \Delta_{H_2}$, no impact if $\Delta_H = \Delta_{H_2}$ and a negative impact if $\Delta_H > \Delta_{H_2}$.*

3. *The impact when $l_H \to 0$ and $\eta_{15} \to 1$ is positive in reducing TB transmission in this subpopulation only if $\Delta_H < \Delta_{H_3}$, no impact if $\Delta_H = \Delta_{H_3}$ and a negative impact if $\Delta_H > \Delta_{H_3}$.*

4. *The impact when $l_H \to 1$ and $\eta_{15} \to 1$ is positive in reducing TB transmission in this subpopulation only if $\Delta_H < \Delta_{H_4}$, no impact if $\Delta_H = \Delta_{H_4}$ and a negative impact if $\Delta_H > \Delta_{H_4}$.*

We apply the same procedure as for the previous submodel to study the relationships for l_H and η_{12}. We have the following limits:

$$\lim_{\substack{l_H\to 0\\ \eta_{12}\to 1}} \mathfrak{R}_0^H = \frac{\alpha^*\omega_H\epsilon_H\epsilon_H^*M_H\eta\big((1-\beta^*)k_{23}k_{24}+(1-p_H)\beta^*k_{22}^{01}(k_{24}+\eta_{15})+p_H\beta^*k_{22}^{01}k_{23}\big)}{N_H(\alpha_{HD}+\mu_H+\mu)k_{21}k_{22}^{01}k_{23}k_{24}}, \tag{2.63}$$

where k_{22}^{01} represents k_{22} when $l_H \to 0$ and $\eta_{12} \to 1$.

$$\lim_{\substack{l_H\to 1\\ \eta_{12}\to 0}} \mathfrak{R}_0^H = \frac{\alpha^*\omega_H\epsilon_H\epsilon_H^*M_H\eta\big((1-\beta^*)(k_{23}k_{24}+(k_{24}+\eta_{15}))+(1-p_H)\beta^*k_{22}^{10}(k_{24}+\eta_{15})+p_H\beta^*k_{22}^{10}k_{23}\big)}{N_H(\alpha_{HD}+\mu_H+\mu)k_{21}k_{22}^{10}k_{23}k_{24}}, \tag{2.64}$$

where k_{22}^{10} represents k_{22} when $l_H \to 1$ and $\eta_{12} \to 0$.

$$\lim_{\substack{l_H \to 1 \\ \eta_{12} \to 1}} \mathfrak{R}_0^H = \frac{\alpha^* \omega_H \epsilon_H \epsilon_H^* M_H \eta \Big((1-\beta^*)(k_{23}k_{24} + (k_{24}+\eta_{15})) + (1-p_H)\beta^* k_{22}^{11}(k_{24}+\eta_{15}) + p_H \beta^* k_{22}^{11} k_{23} \Big)}{N_H(\alpha_{HD} + \mu_H + \mu) k_{21} k_{22}^{11} k_{23} k_{24}}, \tag{2.65}$$

where k_{22}^{11} represents k_{22} when $l_H \to 1$ and $\eta_{12} \to 1$.

$$\lim_{\substack{l_H \to 0 \\ \eta_{12} \to 0}} \mathfrak{R}_0^H = \frac{\alpha^* \omega_H \epsilon_H \epsilon_H^* M_H \eta \Big((1-\beta^*) k_{23}k_{24} + (1-p_H)\beta^* k_{22}^{00}(k_{24}+\eta_{15}) + p_H \beta^* k_{22}^{00} k_{23} \Big)}{N_H(\alpha_{HD} + \mu_H + \mu) k_{21} k_{22}^{00} k_{23} k_{24}}, \tag{2.66}$$

where k_{22}^{00} represents k_{22} when $l_H \to 0$ and $\eta_{12} \to 0$.

Let us define the following expressions:

$$\Delta_{H_5} = \frac{k_{21} k_{22}^{00} k_{23} k_{24}}{(1-\beta^*) k_{23}k_{24} + (1-p_H)\beta^* k_{22}^{00}(k_{24}+\eta_{15}) + p_H \beta^* k_{22}^{00} k_{23}}, \tag{2.67}$$

$$\Delta_{H_6} = \frac{k_{21} k_{22}^{01} k_{23} k_{24}}{(1-\beta^*) k_{23}k_{24} + (1-p_H)\beta^* k_{22}^{01}(k_{24}+\eta_{15}) + p_H \beta^* k_{22}^{01} k_{23}}, \tag{2.68}$$

$$\Delta_{H_7} = \frac{k_{21} k_{22}^{10} k_{23} k_{24}}{(1-\beta^*)(k_{23}k_{24} + (k_{24}+\eta_{15})) + (1-p_H)\beta^* k_{22}^{10}(k_{24}+\eta_{15}) + p_H \beta^* k_{22}^{10} k_{23}}, \tag{2.69}$$

$$\Delta_{H_8} = \frac{k_{21} k_{22}^{11} k_{23} k_{24}}{(1-\beta^*)(k_{23}k_{24} + (k_{24}+\eta_{15})) + (1-p_H)\beta^* k_{22}^{11}(k_{24}+\eta_{15}) + p_H \beta^* k_{22}^{11} k_{23}}. \tag{2.70}$$

We obtain the following lemma:

Lemma 2.3.11. *1. The impact when $l_H \to 0$ and $\eta_{12} \to 0$ is positive in reducing TB transmission in TB-HIV/AIDS subpopulation only if $\Delta_H < \Delta_{H_5}$, no impact if $\Delta_H = \Delta_{H_5}$ and a negative impact if $\Delta_H > \Delta_{H_5}$.*

2. The impact when $l_H \to 0$ and $\eta_{12} \to 1$ is positive in reducing TB transmission in TB-HIV/AIDS subpopulation only if $\Delta_H < \Delta_{H_6}$, no impact if $\Delta_H = \Delta_{H_6}$ and a negative impact if $\Delta_H > \Delta_{H_6}$.

3. The impact when $l_H \to 1$ and $\eta_{12} \to 0$ is positive in reducing TB transmission in TB-HIV/AIDS subpopulation only if $\Delta_H < \Delta_{H_7}$, no impact if $\Delta_H = \Delta_{H_7}$ and a negative impact if $\Delta_H > \Delta_{H_7}$.

4. The impact when $l_H \to 1$ and $\eta_{12} \to 1$ is positive in reducing TB transmission in TB-HIV/AIDS subpopulation only if $\Delta_H < \Delta_{H_8}$, no impact if $\Delta_H = \Delta_{H_8}$ and a negative impact if $\Delta_H > \Delta_{H_8}$.

Now, we study the relationships between the parameters associated with XDR-TB (η_{15}) and recovery after MDR-TB (m_H). We have the following limits:

$$\lim_{\substack{\eta_{15} \to 0 \\ m_H \to 1}} \mathfrak{R}_0^H = \frac{\alpha^* M_H \omega_H \epsilon_H^* \epsilon_H \eta \Big((1-\beta^*)(k_{23}^{01} k_{24} + l_H k_{24}) + (1-p_H)\beta^* k_{22} k_{24} + p_H \beta^* k_{22} k_{23}^{01} \Big)}{N_H(\alpha_{HD} + \mu_H + \mu) k_{21} k_{22} k_{23}^{01} k_{24}}, \tag{2.71}$$

where k_{23}^{01} represents k_{23} when $\eta_{15} \to 0$ and $m_H \to 1$.

$$\lim_{\substack{\eta_{15}\to 1\\ m_H\to 0}} \mathfrak{R}_0^H = \frac{\alpha^* M_H \omega_H \epsilon_H^* \epsilon_H \eta\big((1-\beta^*)(k_{23}^{10}k_{24} + l_H(k_{24}+1)) + (1-p_H)\beta^* k_{22}(k_{24}+1) + p_H\beta^* k_{22}k_{23}^{10}\big)}{N_H(\alpha_{HD}+\mu_H+\mu)k_{21}k_{22}k_{23}^{10}k_{24}}, \tag{2.72}$$

where k_{23}^{10} represents k_{23} when $\eta_{15} \to 1$ and $m_H \to 0$.

$$\lim_{\substack{\eta_{15}\to 1\\ m_H\to 1}} \mathfrak{R}_0^H = \frac{\alpha^* M_H \omega_H \epsilon_H^* \epsilon_H \eta\big((1-\beta^*)(k_{23}^{11}k_{24} + l_H(k_{24}+1)) + (1-p_H)\beta^* k_{22}(k_{24}+1) + p_H\beta^* k_{22}k_{23}^{11}\big)}{N_H(\alpha_{HD}+\mu_H+\mu)k_{11}k_{22}k_{23}^{11}k_{24}}, \tag{2.73}$$

where k_{23}^{11} represents k_{23} when $\eta_{15} \to 1$ and $m_H \to 1$.

$$\lim_{\substack{\eta_{15}\to 0\\ m_H\to 0}} \mathfrak{R}_0^H = \frac{\alpha^* M_H \omega_H \epsilon_H^* \epsilon_H \eta\big((1-\beta^*)(k_{23}^{00}k_{24} + l_H k_{24}) + (1-p_H)\beta^* k_{22}k_{24} + p_H\beta^* k_{22}k_{23}^{00}\big)}{N_H(\alpha_{HD}+\mu_H+\mu)k_{11}k_{22}k_{23}^{00}k_{24}}, \tag{2.74}$$

where k_{23}^{00} represents k_{23} when $\eta_{15} \to 0$ and $m_H \to 0$.

We define the following expressions:

$$\Delta_{H_9} = \frac{k_{21}k_{22}k_{23}^{00}k_{24}}{(1-\beta^*)(k_{23}^{11}k_{24} + l_H k_{24}) + (1-p_H)\beta^* k_{22}k_{24} + p_H\beta^* k_{22}k_{23}^{00}}, \tag{2.75}$$

$$\Delta_{H_{10}} = \frac{k_{21}k_{22}k_{23}^{01}k_{24}}{(1-\beta^*)(k_{23}^{01}k_{24} + l_H k_{24}) + (1-p_H)\beta^* k_{22}k_{24} + p_H\beta^* k_{22}k_{23}^{01}}, \tag{2.76}$$

$$\Delta_{H_{11}} = \frac{k_{21}k_{22}k_{23}^{10}k_{24}}{(1-\beta^*)(k_{23}^{10}k_{24} + l_H(k_{24}+1)) + (1-p_H)\beta^* k_{22}(k_{24}+1) + p_H\beta^* k_{22}k_{23}^{10}}, \tag{2.77}$$

$$\Delta_{H_{12}} = \frac{k_{21}k_{22}k_{23}^{11}k_{24}}{(1-\beta^*)(k_{23}^{11}k_{24} + l_H(k_{24}+1)) + (1-p_H)\beta^* k_{22}(k_{24}+1) + p_H\beta^* k_{22}k_{23}^{11}}. \tag{2.78}$$

Then, we have the following lemma:

Lemma 2.3.12. *1. The impact when $\eta_{15} \to 0$ and $m_H \to 0$ is positive in reducing TB transmission in TB-HIV/AIDS subpopulation only if $\Delta_H < \Delta_{H_9}$, no impact if $\Delta_H = \Delta_{H_9}$ and a negative impact if $\Delta_H > \Delta_{H_9}$.*

2. The impact when $\eta_{15} \to 0$ and $m_H \to 1$ is positive in reducing TB transmission in TB-HIV/AIDS subpopulation only if $\Delta_H < \Delta_{H_{10}}$, no impact if $\Delta_H = \Delta_{H_{10}}$ and a negative impact if $\Delta_H > \Delta_{H_{10}}$.

3. The impact when $\eta_{15} \to 1$ and $m_H \to 0$ is positive in reducing TB transmission in TB-HIV/AIDS subpopulation only if $\Delta_H < \Delta_{H_{11}}$, no impact if $\Delta_H = \Delta_{H_{11}}$ and a negative impact if $\Delta_H > \Delta_{H_{11}}$.

4. The impact when $\eta_{15} \to 1$ and $m_H \to 1$ is positive in reducing TB transmission in TB-HIV/AIDS subpopulation only if $\Delta_H < \Delta_{H_{12}}$, no impact if $\Delta_H = \Delta_{H_{12}}$ and a negative impact if $\Delta_H > \Delta_{H_{12}}$.

We studied the relationships between resistance (l_D, η_{16}) and recovered (η_{12}, m_H) parameters. We have that:

$$\lim_{\substack{l_H\to 1\\ \eta_{15}\to 1\\ \eta_{12}\to 0\\ m_H\to 0}} \mathfrak{R}_0^H = \frac{\alpha^* M_H \omega_H \epsilon_H^* \epsilon_H \eta\big((1-\beta^*)(k_{23}^{10}k_{24}+(k_{24}+1))+(1-p_H)\beta^* k_{22}^{10}(k_{24}+1)+p_H\beta^* k_{22}^{10}k_{23}^{10}\big)}{N_H(\alpha_{HD}+\mu_H+\mu)k_{21}k_{22}^{10}k_{23}^{10}k_{24}}, \tag{2.79}$$

$$\lim_{\substack{l_H\to 0\\ \eta_{15}\to 0\\ \eta_{12}\to 1\\ m_H\to 1}} \mathfrak{R}_0^H = \frac{\alpha^* M_H \omega_H \epsilon_H^* \epsilon_H \eta\big((1-\beta^*)k_{23}^{01}k_{24}+(1-p_H)\beta^* k_{22}^{01}k_{24}+p_H\beta^* k_{22}^{01}k_{23}^{01}\big)}{N_H(\alpha_{HD}+\mu_H+\mu)k_{21}k_{22}^{01}k_{23}^{01}k_{24}}. \tag{2.80}$$

We define the following expressions:

$$\Delta_{H_{13}} = \frac{k_{21}k_{22}^{10}k_{23}^{10}k_{24}}{(1-\beta^*)(k_{23}^{10}k_{24}+(k_{24}+1))+(1-p_H)\beta^* k_{22}^{10}(k_{24}+1)+p_H\beta^* k_{22}^{10}k_{23}^{10}}, \tag{2.81}$$

$$\Delta_{H_{14}} = \frac{k_{21}k_{22}^{01}k_{23}^{01}k_{24}}{(1-\beta^*)k_{23}^{01}k_{24}+(1-p_H)\beta^* k_{22}^{01}k_{24}+p_H\beta^* k_{22}^{01}k_{23}^{01}}. \tag{2.82}$$

We obtain the following lemma:

Lemma 2.3.13. *1. The impact of the resistance parameters when they tend to unity $(l_H, \eta_{15} \to 1)$ with respect to the recovery parameters when they tend to zero $(\eta_{12}, m_H \to 0)$ is positive in reducing tuberculosis transmission in TB-HIV/AIDS subpopulation only if $\Delta_H < \Delta_{H_{13}}$, no impact if $\Delta_H = \Delta_{H_{13}}$ and a negative impact if $\Delta_H > \Delta_{H_{13}}$.*

2. The impact of the recovery parameters recovery parameters when they tend to unity $(\eta_{12}, m_H \to 1)$ with respect to the recovery parameters when they tend to zero $(l_H, \eta_{15} \to 0)$ is positive in reducing tuberculosis transmission in TB-HIV/AIDS subpopulation only if $\Delta_H < \Delta_{H_{14}}$, no impact if $\Delta_H = \Delta_{H_{14}}$ and a negative impact if $\Delta_H > \Delta_{H_{14}}$.

Endemic Equilibrium Point

To find the endemic equilibrium point, the subsystem (2.48) is transformed into the following system of equations:

$$\begin{pmatrix} -(\mu+\mu_H+\alpha_{HD}+\lambda_H) & 0 & 0 & 0 & 0 & 0\\ \omega_H\lambda_H & -k_{21} & 0 & 0 & 0 & \beta_1'\omega_H\lambda_H\\ 0 & (1-\beta^*)\epsilon_H^*\eta & -k_{22} & 0 & 0 & 0\\ 0 & (1-p_H)\epsilon_H^*\beta^*\eta & l_H & -k_{23} & 0 & 0\\ 0 & p_H\beta^*\epsilon_H^*\eta & 0 & \eta_{15} & -k_{24} & 0\\ 0 & 0 & \eta_{12} & m_H & \eta_{12}^* & -(\mu+\mu_H+\beta_1'\omega_H\lambda_H+\alpha_{HD}) \end{pmatrix} \begin{pmatrix} S_H^*\\ E_H^*\\ I_{H_1}^*\\ I_{H_2}^*\\ I_{H_3}^*\\ R_H^* \end{pmatrix} = \begin{pmatrix} -M_H\\ 0\\ 0\\ 0\\ 0\\ 0 \end{pmatrix}.$$

Then, the endemic quilibrium point is $\epsilon_*^H = (S_H^*, E_H^*, I_{H_1}^*, I_{H_2}^*, I_{H_3}^*, R_H^*)$, where:

$$
\begin{aligned}
S_H^* &= \frac{M_H}{\omega_H\lambda_H^* + \alpha_{HD} + \mu + \mu_H}, \quad E_H^* = \frac{M_H\omega_H\lambda_H^* k_{22}k_{23}k_{24}(\alpha_{HD} + \omega_H\beta_1^{'}\lambda_H^* + \mu + \mu_H)}{A_2},\\
I_{H_1}^* &= \frac{M_H(1-\beta^*)\epsilon_H^*\eta\omega_H\lambda_H^* k_{23}k_{24}(\alpha_{HD} + \omega_H\beta_1^{'}\lambda_H^* + \mu + \mu_H)}{A_2},\\
I_{H_2}^* &= \frac{M_H\omega_H\lambda_H^*(\alpha_{HD} + \omega_H\beta_1^{'}\lambda_H^* + \mu + \mu_H)(k_{22}k_{24}\epsilon_H^*\beta^*\eta(1-p_H) + k_{24}l_H(1-\beta^*)\epsilon_H^*\eta)}{A_2},\\
I_{H_3}^* &= \frac{M_H\omega_H\lambda_H^*(\alpha_{HD} + \omega_H\beta_1^{'}\lambda_H^* + \mu + \mu_H)(l_H\eta_{15}(1-\beta^*)\epsilon_H^*\eta + k_{12}\beta^*\epsilon_H^*\eta\eta_{15}(1-p_H) + k_{22}k_{23}\beta^*\epsilon_H^*\eta p_H)}{A_2},\\
R_H^* &= \frac{M_H\omega_H\lambda_H^*((1-\beta^*)\epsilon_H^*\eta)(k_{23}k_{24}\eta_{12} + l_T(k_{24}m_H + \eta_{12}^*\eta_{15}) + (1-p_H)k_{22}\beta^*\epsilon_H^*\eta(k_{24}m_H + \eta_{12}^*\eta_{15})}{A_2}\\
&\frac{+k_{22}k_{23}\beta^*\epsilon_H^*\eta\eta_{12}^* p_H)}{A_2},
\end{aligned}
\tag{2.83}
$$

and $A_2 = (\alpha_{HD} + \mu + \mu_H + \omega_H\lambda_H^*)(\alpha_{HD} + \mu + \mu_H + \omega_H\beta_1^*\lambda_H^*)k_{21}k_{22}k_{23}k_{24} - (\alpha_{HD} + \mu + \omega_H\lambda_H^*)\beta_1^{'}\omega_H\lambda_H^*((1-p_H)k_{22}\beta^*\epsilon_H^*\eta(k_{24}m_H + \eta_{12}^*\eta_{15}) + (1-\beta^*)\epsilon_H^*\eta(k_{23}k_{24}\eta_{12} + l_H(k_{24}m_H + \eta_{12}^*\eta_{12}) + k_{22}k_{23}\beta^*\epsilon_H^*\eta\eta_{12}^* p_H)$.

Proceeding analogously to the TB-Only submodel (2.11), we obtain the following theorem:

Theorem 2.3.14. *The TB-HIV/AIDS submodel (2.48) has a unique endemic equilibrium point ϵ_*^H, whenever $\mathfrak{R}_0^H > 1$.*

TB-Diabetes Submodel

The submodel that relates TB to diabetes is obtained when $S_H = S_T = E_H = E_T = I_{H_1} = I_{H_2} = I_{T_1} = I_{T_2} = I_{H_3} = R_H = I_{T_3} = R_T = 0$ and is given by the system:

$$
\begin{aligned}
\frac{dS_D}{dt} &= M_D - (\alpha_H + \mu + \mu_D + \omega_D\lambda_D)S_D,\\
\frac{dE_D}{dt} &= \omega_D\lambda_D(S_D + \beta_1^{'}R_D) - (\eta + \mu + \mu_D + \alpha_H)E_D,\\
\frac{dI_{D_1}}{dt} &= (1-\beta^*)\epsilon_D^*\eta E_D - (l_D + t_H\alpha_H + \mu + \mu_D + d_{TD} + \eta_{13})I_{D_1},\\
\frac{dI_{D_2}}{dt} &= (1-p_D)\epsilon_D^*\beta^*\eta E_D + l_D I_{D_1} - (t_H\alpha_H + m_D + \mu + \mu_D + t_D^{'}d_{TD} + \eta_{16})I_{D_2},\\
\frac{dI_{D_3}}{dt} &= p_D\beta^*\epsilon_D^*\eta E_D + \eta_{16}I_{D_2} - (\eta_{13}^* + t_H\alpha_H + \mu + \mu_D + t_D^*d_{TD})I_{D_3},\\
\frac{dR_D}{dt} &= m_D I_{D_2} + \eta_{13}I_{D_1} + \eta_{13}^* I_{D_3} - (\alpha_H + \mu + \mu_D + \beta_1^{'}\omega_D\lambda_D)R_D,
\end{aligned}
\tag{2.84}
$$

with non-negative initial conditions and

$$
\lambda_D = \alpha^*\frac{\epsilon_D(I_{D_1} + I_{D_2} + I_{D_3})}{N_D},
$$

where $N_D = S_D + E_D + I_{D_1} + I_{D_2} + I_{D_3} + R_D$.

The system (2.84) will be studied in the following region biologically feasible:

$$D_3 = \left\{ (S_D, E_D, I_{D_1}, I_{D_2}, I_{D_3}, R_D) \in \mathbb{R}^6_+ \,:\, N_D(t) \leq \frac{M_D}{\mu} \right\}.$$

It can be easily shown that solutions $(S_D(t), I_{D_1}(t), I_{D_2}(t), I_{D_3}(t), R_D(t))$ of the system are bounded and positively invariant.

The disease-free equilibrium point, ϵ_0^D, is given by $\epsilon_0^D = \left(S_0^D, 0, 0, 0, 0, 0\right)$, where $S_0^D = \dfrac{M_D}{\mu + \mu_D + \alpha_H}$.

The matrices for the new infection terms, F_D and the other terms, V_D are given by:

$$F_D = \begin{bmatrix} 0 & \dfrac{M_D\alpha^*\omega_D\epsilon_D}{\alpha_H+\mu+\mu_D} & \dfrac{M_D\alpha^*\omega_D\epsilon_D}{\alpha_H+\mu+\mu_D} & \dfrac{M_D\alpha^*\omega_D\epsilon_D}{\alpha_H+\mu+\mu_D} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix},$$

$$V_D = \begin{bmatrix} k_{31} & 0 & 0 & 0 \\ -(1-\beta^*)\epsilon_D^*\eta & k_{32} & 0 & 0 \\ -(1-p_D)\epsilon_D^*\beta^*\eta & -l_D & k_{33} & 0 \\ -p_D\epsilon_D^*\beta^*\eta & 0 & -\eta_{16} & k_{34} \end{bmatrix},$$

where $k_{31} = \alpha_H + \epsilon_D^*\eta + \mu + \mu_D$, $k_{32} = l_D + \mu + d_{TD} + \eta_{13} + t_H\alpha_H + \mu_D$, $k_{33} = \mu + t_D^{'}d_{TD} + \eta_{16} + m_D + t_H\alpha_H + \mu_D$, and $k_{34} = \mu + \mu_D + t_D^*d_{TD} + \eta_{13}^* + t_H\alpha_H$.

The basic reproduction number is given by

$$\mathfrak{R}_0^D = \rho(F_H V_H^{-1}) = \frac{\alpha^*\epsilon_D\omega_D M_D\left((1-\beta^*)\epsilon_D^*\eta(k_{33}k_{34} + l_D(k_{34}+\eta_{16})) + (1-p_D)\epsilon_D^*\beta^*\eta k_{32}(k_{34}+\eta_{16}) + k_{32}k_{33}\epsilon_D^*\beta^*\eta p_D\right)}{N_D(\alpha_H+\mu+\mu_D)k_{31}k_{32}k_{33}k_{34}}. \tag{2.85}$$

We define (H_1) and (H_2) as in the previous submodels (2.11) and (2.48) and using the same idea from the demonstration, we have the following lemmas:

Lemma 2.3.15. *The disease-free equilibrium ϵ_0^D is asymptotically stable when $\mathfrak{R}_0^D < 1$ and is unstable whenever $\mathfrak{R}_0^D > 1$.*

Lemma 2.3.16. *The fixed point $E_0^D = (S_0^{D_*}, 0, 0, 0, 0)$ where $S_0^{D_*} = \left(\dfrac{M_D}{\mu + \alpha_H + \mu_D}, 0\right)$ is a globally asymptotically stable equilibrium of submodel (TB-Diabetes) if $\mathfrak{R}_0^D < 1$ and the assumption (H_1) and (H_2) are satisfied.*

We make a procedure analogous to the previous submodels for l_D and η_{16} (MDR-TB and XDR-TB parameters for TB-Diabetes submodel) and we obtain the following limits:

$$\lim_{\substack{l_D\to 0 \\ \eta_{16}\to 0}} \mathfrak{R}_0^D = \frac{\alpha^* M_D\omega_D\epsilon_D\epsilon_D^*\eta\left((1-\beta^*)k_{33}^0k_{34} + (1-p_D)\beta^*k_{32}^0k_{34} + \beta^*p_Dk_{32}^0k_{33}^0\right)}{N_D(\mu_D+\alpha_H+\mu)k_{31}k_{32}^0k_{33}^0k_{34}}, \tag{2.86}$$

where k_{32}^0 is k_{32} for $l_D = 0$ and k_{33}^0 is k_{33} for $\eta_{16} = 0$. Then, in practice $l_D \to 0$ and $\eta_{16} \to 0$ imply zero resistance, i.e. elimination of resistance to tuberculosis treatment. If the limit (2.86) are greater than unity, then when $l_D, \eta_{16} \to 0$ has a negative impact on TB transmission control. That is, if we have

$$\frac{\alpha^*\omega_D\epsilon_D\epsilon_D^*\eta M_D}{N_D(\alpha_h+\mu_D+\mu)} > \frac{k_{31}k_{32}^0k_{33}^0k_{34}}{(1-\beta^*)k_{33}^0k_{34}+(1-p_D)\beta^*k_{32}^0k_{34}+\beta^*p_Dk_{32}^0k_{33}^0}. \tag{2.87}$$

Now, we study the case when $l_D \to 1$ and $\eta_{16} \to 0$. Then, we have that

$$\lim_{\substack{l_D\to 1\\ \eta_{16}\to 0}} \mathfrak{R}_0^D = \frac{\alpha^*\omega_D\epsilon_D\epsilon_D^*M_D\eta\big((1-\beta^*)(k_{33}^0k_{34}+k_{34})+(1-p_D)\beta^*k_{32}^1k_{34}+\beta^*p_Dk_{32}^1k_{33}^0\big)}{N_D(\alpha_H+\mu_D+\mu)k_{31}k_{32}^1k_{33}^0k_{34}}, \tag{2.88}$$

where k_{32}^1 is k_{32} for $l_D = 1$. Then, if the limit (2.88) are greater than unity, then when $l_D \to 1$ and $\eta_{16} \to 0$ has a negative impact on TB transmission control. That is, if we have

$$\frac{\alpha^*\omega_D\epsilon_D\epsilon_D^*M_D}{N_D(\alpha_H+\mu_D+\mu)} > \frac{k_{31}k_{32}^1k_{33}^0k_{34}}{(1-\beta^*)(k_{33}^0k_{34}+k_{34})+(1-p_D)\beta^*k_{32}^1k_{34}+\beta^*p_Dk_{32}^1k_{33}^0}. \tag{2.89}$$

In the case when $l_D \to 0$ and $\eta_{16} \to 1$. We have

$$\lim_{\substack{l_D\to 0\\ \eta_{16}\to 1}} \mathfrak{R}_0^D = \frac{\alpha^*\omega_D\epsilon_D\epsilon_D^*M_D\eta\big((1-\beta^*)k_{34}k_{33}^1+(1-p_D)\beta^*k_{32}^0(k_{34}+1)+k_{32}^0k_{33}^1\beta^*p_D\big)}{N_D(\alpha_H+\mu_D+\mu)k_{31}k_{32}^0k_{33}^1k_{34}}, \tag{2.90}$$

where k_{33}^1 is k_{33} for $\eta_{16} = 1$ and $k_{33}^1 = k_{33}^0 + 1$. If the limit (2.90) are greater than unity, then when $l_D \to 0$ and $\eta_{16} \to 1$ has a negative impact on TB transmission control. That is, if we have

$$\frac{\alpha^*\omega_D\epsilon_D\epsilon_D^*M_D}{N_D(\alpha_H+\mu_D+\mu)} > \frac{k_{31}k_{32}^0k_{33}^1k_{34}}{(1-\beta^*)k_{34}k_{33}^1+(1-p_D)\beta^*k_{32}^0(k_{34}+1)+k_{32}^0k_{33}^1\beta^*p_D}. \tag{2.91}$$

For $l_D \to 1$ and $\eta_{16} \to 1$. We have that

$$\lim_{\substack{l_D\to 1\\ \eta_{16}\to 1}} \mathfrak{R}_0^D = \frac{\alpha^*M_D\omega_D\epsilon_D\epsilon_D^*\eta\big((1-\beta^*)(k_{34}k_{33}^1+(k_{34}+1))+(1-p_D)\beta^*k_{32}^1(k_{34}+1)+k_{32}^1k_{33}^1\beta^*p_D\big)}{N_D(\alpha_H+\mu_D+\mu)k_{31}k_{32}^1k_{33}^1k_{34}}. \tag{2.92}$$

If the limit (2.92) are greater than unity, then when $l_D \to 1$ and $\eta_{16} \to 1$ has a negative impact on TB transmission control. That is, if we have

$$\frac{\alpha^*\omega_D\epsilon_D\epsilon_D^*M_D}{N_D(\alpha_H+\mu_D+\mu)} > \frac{k_{31}k_{32}^1k_{33}^1k_{34}}{(1-\beta^*)(k_{34}k_{33}^1+(k_{34}+1))(1-p_D)\beta^*k_{32}^1(k_{34}+1)+k_{32}^1k_{33}^1\beta^*p_D}. \tag{2.93}$$

Let us consider the following expressions:

$$\Delta_D = \frac{\alpha^* \omega_D \epsilon_D \epsilon_D^* M_D}{N_D(\alpha_D + \mu_D + \mu)}, \tag{2.94}$$

$$\Delta_{D_1} = \frac{k_{21}k_{22}^0 k_{23}^0 k_{24}}{(1-\beta^*)k_{33}^0 k_{34} + (1-p_D)\beta^* k_{32}^0 k_{34} + \beta^* p_D k_{32}^0 k_{33}^0}, \tag{2.95}$$

$$\Delta_{D_2} = \frac{k_{31}k_{32}^1 k_{33}^0 k_{34}}{(1-\beta^*)(k_{33}^0 k_{34} + k_{34}) + (1-p_D)\beta^* k_{32}^1 k_{34} + \beta^* p_D k_{32}^1 k_{33}^0}, \tag{2.96}$$

$$\Delta_{D_3} = \frac{k_{31}k_{32}^0 k_{33}^1 k_{34}}{(1-\beta^*)k_{34}k_{33}^1 + (1-p_D)\beta^* k_{32}^0 (k_{34}+1) + k_{32}^0 k_{33}^1 \beta^* p_D}, \tag{2.97}$$

$$\Delta_{D_4} = \frac{k_{31}k_{32}^1 k_{33}^1 k_{34}}{(1-\beta^*)(k_{34}k_{33}^1 + (k_{34}+1))(1-p_D)\beta^* k_{32}^1 (k_{34}+1) + k_{32}^1 k_{33}^1 \beta^* p_D}. \tag{2.98}$$

We have the following lemma:

Lemma 2.3.17. *1. The impact when $l_D \to 0$ and $\eta_{16} \to 0$ is positive in reducing TB transmission in this subpopulation only if $\Delta_D < \Delta_{D_1}$, no impact if $\Delta_H = \Delta_{D_1}$ and a negative impact if $\Delta_H > \Delta_{D_1}$.*

2. *The impact when $l_H \to 1$ and $\eta_{16} \to 0$ is positive in reducing TB transmission in this subpopulation only if $\Delta_D < \Delta_{D_2}$, no impact if $\Delta_D = \Delta_{D_2}$ and a negative impact if $\Delta_D > \Delta_{D_2}$.*

3. *The impact wheN $l_D \to 0$ and $\eta_{16} \to 1$ is positive in reducing TB transmission in this subpopulation only if $\Delta_D < \Delta_{D_3}$, no impact if $\Delta_D = \Delta_{D_3}$ and a negative impact if $\Delta_D > \Delta_{D_3}$.*

4. *The impact when $l_D \to 1$ and $\eta_{16} \to 1$ is positive in reducing TB transmission in this subpopulation only if $\Delta_D < \Delta_{D_4}$, no impact if $\Delta_D = \Delta_{D_4}$ and a negative impact if $\Delta_D > \Delta_{D_4}$.*

We will study the relationship between resistance and recovery parameters. First, we start with the relationship between l_D and η_{13}. We obtain the following limits:

$$\lim_{\substack{l_D \to 0 \\ \eta_{13} \to 1}} \mathfrak{R}_0^D = \frac{\alpha^* \omega_D \epsilon_D \epsilon_D^* M_D \eta \left((1-\beta^*)k_{33}k_{34} + (1-p_D)\beta^* k_{32}^{01}(k_{34}+\eta_{16}) + p_D \beta^* k_{32}^{01} k_{33}\right)}{N_D(\alpha_H + \mu_D + \mu)k_{31}k_{32}^{01}k_{33}k_{34}}, \tag{2.99}$$

where k_{32}^{01} represents k_{32} when $l_D \to 0$ and $\eta_{13} \to 1$.

$$\lim_{\substack{l_D \to 1 \\ \eta_{13} \to 0}} \mathfrak{R}_0^D = \frac{\alpha^* \omega_D \epsilon_D \epsilon_D^* M_D \eta \left((1-\beta^*)(k_{33}k_{34} + (k_{34}+\eta_{16})) + (1-p_D)\beta^* k_{32}^{10}(k_{34}+\eta_{16}) + p_D \beta^* k_{32}^{10} k_{33}\right)}{N_D(\alpha_D + \mu_D + \mu)k_{31}k_{32}^{10}k_{33}k_{34}}, \tag{2.100}$$

where k_{32}^{10} represents k_{32} when $l_D \to 1$ and $\eta_{13} \to 0$.

$$\lim_{\substack{l_D \to 1 \\ \eta_{13} \to 1}} \mathfrak{R}_0^D = \frac{\alpha^* \omega_D \epsilon_D \epsilon_D^* M_D \eta \left((1-\beta^*)(k_{33}k_{34} + (k_{34}+\eta_{16})) + (1-p_D)\beta^* k_{32}^{11}(k_{34}+\eta_{16}) + p_D \beta^* k_{32}^{11} k_{33}\right)}{N_D(\alpha_H + \mu_D + \mu)k_{31}k_{32}^{11}k_{33}k_{34}}, \tag{2.101}$$

where k_{32}^{11} represents k_{32} when $l_D \to 1$ and $\eta_{13} \to 1$.

$$\lim_{\substack{l_D \to 0 \\ \eta_{13} \to 0}} \mathfrak{R}_0^D = \frac{\alpha^* \omega_D \epsilon_D \epsilon_D^* M_D \eta \Big((1-\beta^*) k_{33} k_{34} + (1-p_D) \beta^* k_{32}^{00} (k_{34} + \eta_{16}) + p_D \beta^* k_{32}^{31} k_{33} \Big)}{N_D (\alpha_H + \mu_D + \mu) k_{31} k_{32}^{00} k_{33} k_{34}}, \tag{2.102}$$

where k_{32}^{00} represents k_{32} when $l_D \to 0$ and $\eta_{13} \to 0$.

Let us consider the following expressions:

$$\Delta_{D_5} = \frac{k_{31} k_{32}^{00} k_{33} k_{34}}{(1-\beta^*) k_{33} k_{34} + (1-p_D) \beta^* k_{32}^{00} k_{34} + p_D \beta^* k_{32}^{00} k_{33}}, \tag{2.103}$$

$$\Delta_{D_6} = \frac{k_{31} k_{32}^{01} k_{33} k_{34}}{(1-\beta^*) k_{33} k_{34} + (1-p_D) \beta^* k_{32}^{01} (k_{34} + \eta_{16}) + p_D \beta^* k_{32}^{01} k_{33}}, \tag{2.104}$$

$$\Delta_{D_7} = \frac{k_{31} k_{32}^{10} k_{33} k_{34}}{(1-\beta^*)(k_{33} k_{34} + (k_{34} + \eta_{16})) + (1-p_D) \beta^* k_{32}^{10} (k_{34} + \eta_{16}) + p_D \beta^* k_{32}^{10} k_{33}}, \tag{2.105}$$

$$\Delta_{D_8} = \frac{k_{31} k_{32}^{11} k_{33} k_{34}}{(1-\beta^*)(k_{33} k_{34} + (k_{34} + \eta_{16})) + (1-p_D) \beta^* k_{32}^{11} (k_{34} + \eta_{16} + p_D \beta^* k_{32}^{11} k_{33}}. \tag{2.106}$$

We have the following lemma:

Lemma 2.3.18. *1. The impact when $l_D \to 0$ and $\eta_{13} \to 0$ is positive in reducing TB transmission in TB-Diabetes subpopulation only if $\Delta_D < \Delta_{D_5}$, no impact if $\Delta_D = \Delta_{D_5}$ and a negative impact if $\Delta_D > \Delta_{D_5}$.*

2. The impact when $l_D \to 0$ and $\eta_{13} \to 1$ is positive in reducing TB transmission in TB-Diabetes subpopulation only if $\Delta_D < \Delta_{D_6}$, no impact if $\Delta_D = \Delta_{D_6}$ and a negative impact if $\Delta_D > \Delta_{D_6}$.

3. The impact when $l_D \to 1$ and $\eta_{13} \to 0$ is positive in reducing TB transmission in TB-Diabetes subpopulation only if $\Delta_D < \Delta_{D_7}$, no impact if $\Delta_D = \Delta_{D_7}$ and a negative impact if $\Delta_D > \Delta_{D_7}$.

4. The impact when $l_D \to 1$ and $\eta_{13} \to 1$ is positive in reducing TB transmission in TB-Diabetes subpopulation only if $\Delta_D < \Delta_{D_8}$, no impact if $\Delta_D = \Delta_{D_8}$ and a negative impact if $\Delta_D > \Delta_{D_8}$.

Now, we study the relationship between the XDR-TB parameter (η_{16}) and recovery (m_D). We have the following limits:

$$\lim_{\substack{\eta_{16} \to 0 \\ m_D \to 1}} \mathfrak{R}_0^D = \frac{\alpha^* M_D \omega_D \epsilon_D^* \epsilon_D \eta \Big((1-\beta^*)(k_{33}^{01} k_{34} + l_D k_{34}) + (1-p_D) \beta^* k_{32} k_{34} + p_D \beta^* k_{32} k_{33}^{01} \Big)}{N_D (\alpha_H + \mu_D + \mu) k_{31} k_{32} k_{33}^{01} k_{34}}, \tag{2.107}$$

where k_{33}^{01} represents k_{33} when $\eta_{16} \to 0$ and $m_D \to 1$.

$$\lim_{\substack{\eta_{16} \to 1 \\ m_D \to 0}} \mathfrak{R}_0^D = \frac{\alpha^* M_D \omega_D \epsilon_D^* \epsilon_D \eta \Big((1-\beta^*)(k_{33}^{10} k_{34} + l_D (k_{34} + 1)) + (1-p_D) \beta^* k_{32} (k_{34} + 1) + p_D \beta^* k_{32} k_{33}^{10} \Big)}{N_D (\alpha_H + \mu_D + \mu) k_{31} k_{32} k_{33}^{10} k_{34}}, \tag{2.108}$$

where k_{33}^{10} represents k_{33} when $\eta_{16} \to 1$ and $m_D \to 0$.

$$\lim_{\substack{\eta_{15}\to 1\\ m_D\to 1}} \mathfrak{R}_0^D = \frac{\alpha^* M_D \omega_D \epsilon_D^* \epsilon_D \eta\Big((1-\beta^*)(k_{33}^{11}k_{34} + l_D(k_{34}+1)) + (1-p_D)\beta^* k_{32}(k_{34}+1) + p_D\beta^* k_{32}k_{33}^{11}\Big)}{N_D(\alpha_H + \mu_D + \mu)k_{31}k_{32}k_{33}^{11}k_{34}}, \tag{2.109}$$

where k_{33}^{11} represents k_{33} when $\eta_{16} \to 1$ and $m_D \to 1$.

$$\lim_{\substack{\eta_{15}\to 0\\ m_D\to 0}} \mathfrak{R}_0^D = \frac{\alpha^* M_D \omega_D \epsilon_D^* \epsilon_D \eta\Big((1-\beta^*)k_{33}^{00}k_{34} + (1-p_D)\beta^* k_{32}k_{34} + p_D\beta^* k_{32}k_{33}^{00}\Big)}{N_D(\alpha_H + \mu_D + \mu)k_{31}k_{32}k_{33}^{00}k_{34}}, \tag{2.110}$$

where k_{33}^{00} represents k_{33} when $\eta_{16} \to 0$ and $m_D \to 0$.

Let us define the following expressions:

$$\Delta_{D_9} = \frac{k_{31}k_{32}k_{33}^{00}k_{34}}{(1-\beta^*)k_{33}^{00}k_{34} + (1-p_D)\beta^* k_{32}k_{34} + p_D\beta^* k_{32}k_{33}^{00}}, \tag{2.111}$$

$$\Delta_{D_{10}} = \frac{k_{31}k_{32}k_{33}^{01}k_{34}}{(1-\beta^*)(k_{33}^{01}k_{34} + l_D k_{34}) + (1-p_D)\beta^* k_{32}k_{34} + p_D\beta^* k_{32}k_{33}^{01}}, \tag{2.112}$$

$$\Delta_{D_{11}} = \frac{k_{31}k_{32}k_{33}^{10}k_{34}}{(1-\beta^*)(k_{33}^{10}k_{34} + l_D(k_{34}+1)) + (1-p_D)\beta^* k_{32}(k_{34}+1) + p_D\beta^* k_{32}k_{33}^{10}}, \tag{2.113}$$

$$\Delta_{D_{12}} = \frac{k_{31}k_{32}k_{33}^{11}k_{34}}{(1-\beta^*)(k_{33}^{11}k_{34} + l_D(k_{34}+1)) + (1-p_D)\beta^* k_{32}(k_{34}+1) + p_D\beta^* k_{32}k_{33}^{11}}. \tag{2.114}$$

We obtain the following lemma:

Lemma 2.3.19. *1. The impact when $\eta_{16} \to 0$ and $m_D \to 0$ is positive in reducing TB transmission in TB-Diabetes subpopulation only if $\Delta_D < \Delta_{D_9}$, no impact if $\Delta_D = \Delta_{D_9}$ and a negative impact if $\Delta_D > \Delta_{D_9}$.*

2. The impact when $\eta_{16} \to 0$ and $m_D \to 1$ is positive in reducing TB transmission in TB-Diabetes subpopulation only if $\Delta_D < \Delta_{D_{10}}$, no impact if $\Delta_D = \Delta_{D_{10}}$ and a negative impact if $\Delta_D > \Delta_{D_{10}}$.

3. The impact when $\eta_{16} \to 1$ and $m_D \to 0$ is positive in reducing TB transmission in TB-Diabetes subpopulation only if $\Delta_D < \Delta_{D_{11}}$, no impact if $\Delta_D = \Delta_{D_{11}}$ and a negative impact if $\Delta_D > \Delta_{D_{11}}$.

4. The impact when $\eta_{16} \to 1$ and $m_D \to$ is positive in reducing TB transmission in TB-Diabetes subpopulation only if $\Delta_D < \Delta_{D_{12}}$, no impact if $\Delta_D = \Delta_{D_{12}}$ and a negative impact if $\Delta_D > \Delta_{D_{12}}$.

Studying the resistance parameters (l_D, η_{16}) respect to the recovery parameters (η_{13}, m_D). We have:

$$\lim_{\substack{l_D\to 1\\ \eta_{16}\to 1\\ \eta_{13}\to 0\\ m_D\to 0}} \mathfrak{R}_0^D = \frac{\alpha^* M_D \omega_D \epsilon_D^* \epsilon_D \eta\Big((1-\beta^*)(k_{33}^{10}k_{34} + (k_{34}+1)) + (1-p_D)\beta^* k_{32}^{10}(k_{34}+1) + p_D\beta^* k_{32}^{10}k_{33}^{10}\Big)}{N_D(\alpha_H + \mu_D + \mu)k_{31}k_{32}^{10}k_{33}^{10}k_{34}}, \tag{2.115}$$

$$\lim_{\substack{l_D\to 0\\ \eta_{16}\to 0\\ \eta_{13}\to 1\\ m_D\to 1}} \mathfrak{R}_0^D = \frac{\alpha^* M_D \omega_D \epsilon_D^* \epsilon_D \eta\big((1-\beta^*)k_{33}^{01}k_{34} + (1-p_D)\beta^* k_{32}^{01}k_{34} + p_D\beta^* k_{32}^{01}k_{33}^{01}\big)}{N_D(\alpha_H+\mu_D+\mu)k_{31}k_{32}^{01}k_{33}^{01}k_{34}}. \tag{2.116}$$

Let us consider:

$$\Delta_{D_{13}} = \frac{k_{31}k_{32}^{10}k_{33}^{10}k_{34}}{(1-\beta^*)(k_{33}^{10}k_{34}+(k_{34}+1)) + (1-p_D)\beta^* k_{32}^{10}(k_{34}+1) + p_D\beta^* k_{32}^{10}k_{33}^{10}}, \tag{2.117}$$

$$\Delta_{D_{14}} = \frac{k_{31}k_{32}^{01}k_{33}^{01}k_{34}}{(1-\beta^*)k_{33}^{01}k_{34} + (1-p_D)\beta^* k_{32}^{01}k_{34} + p_D\beta^* k_{32}^{01}k_{33}^{01}}. \tag{2.118}$$

We obtain the following lemma:

Lemma 2.3.20. *1. The impact of the resistance parameters when $l_D, \eta_{16} \to 1$ with respect to the recovery parameters when $\eta_{13}, m_D \to 0$ is positive in reducing tuberculosis transmission in TB-Diabetes subpopulation only if $\Delta_D < \Delta_{D_{13}}$, no impact if $\Delta_D = \Delta_{D_{13}}$ and a negative impact if $\Delta_D > \Delta_{D_{13}}$.*

2. The impact of the recovery parameters recovery parameters when they tend to unity ($\eta_{13}, m_D \to 1$) with respect to the recovery parameters when they tend to zero ($l_D, \eta_{16} \to 0$) is positive in reducing tuberculosis transmission in TB-Diabetes subpopulation only if $\Delta_D < \Delta_{D_{14}}$, no impact if $\Delta_D = \Delta_{D_{14}}$ and a negative impact if $\Delta_D > \Delta_{D_{14}}$.

Endemic Equilibrium Point

To find the endemic equilibrium point the subsystem (2.84) is transformed into the following system of equations:

$$\begin{pmatrix} -(\mu+\mu_H+\alpha_H+\lambda_D) & 0 & 0 & 0 & 0 & 0 \\ \lambda_D & -k_{31} & 0 & 0 & 0 & \beta_1'\omega_D\lambda_D \\ 0 & (1-\beta^*)\epsilon_D^*\eta & -k_{32} & 0 & 0 & 0 \\ 0 & (1-p_D)\epsilon_D^*\beta^*\eta & l_D & -k_{33} & 0 & 0 \\ 0 & p_D\beta^*\epsilon_D^*\eta & 0 & \eta_{16} & -k_{34} & 0 \\ 0 & 0 & \eta_{13} & m_D & \eta_{13}^* & -(\mu+\mu_D+\beta_1'\omega_D\lambda_D+\alpha_H) \end{pmatrix} \begin{pmatrix} S_D^* \\ E_D^* \\ I_{D_1}^* \\ I_{D_2}^* \\ I_{D_3}^* \\ R_D^* \end{pmatrix} = \begin{pmatrix} -M_D \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}.$$

Then, the endemic quilibrium point is $\epsilon_*^D = (S_D^*, E_D^*, I_{D_1}^*, I_{D_2}^*, I_{D_3}^*, R_D^*)$, where:

$$S_D^* = \frac{M_D}{\omega_D\lambda_D^* + \alpha_H + \mu + \mu_D}, \quad E_D^* = \frac{M_D\omega_D\lambda_D^* k_{32}k_{33}k_{34}(\alpha_H + \omega_D\beta_1'\lambda_D^* + \mu + \mu_D)}{A_3},$$

$$I_{D_1}^* = \frac{M_D(1-\beta^*)\epsilon_D^*\eta\omega_D\lambda_D^* k_{33}k_{34}(\alpha_H + \omega_D\beta_1'\lambda_D^* + \mu + \mu_D)}{A_3},$$

$$I_{D_2}^* = \frac{M_D\omega_D\lambda_D^*(\alpha_H + \omega_D\beta_1'\lambda_D^* + \mu + \mu_D)(k_{32}k_{34}\epsilon_D^*\beta^*\eta(1-p_D) + k_{34}l_D(1-\beta^*)\epsilon_D^*\eta)}{A_3},$$

$$I_{D_3}^* = \frac{M_D\omega_D\lambda_D^*(\alpha_H + \omega_D\beta_1'\lambda_D^* + \mu + \mu_D)(l_D\eta_{16}(1-\beta^*)\epsilon_D^*\eta + k_{32}\beta^*\epsilon_D^*\eta\eta_{16}(1-p_D) + k_{32}k_{33}\beta^*\epsilon_D^*\eta p_D)}{A_3},$$

$$R_D^* = \frac{M_D\omega_D\lambda_D^*((1-\beta^*)\epsilon_D^*\eta)(k_{33}k_{34}\eta_{13} + l_D(k_{34}m_D + \eta_{13}^*\eta_{16}) + (1-p_D)k_{32}\beta^*\epsilon_D^*\eta(k_{34}m_D + \eta_{13}^*\eta_{16})}{A_3}$$

$$\frac{+k_{32}k_{33}\beta^*\epsilon_D^*\eta\eta_{13}^* p_D)}{A_3}, \tag{2.119}$$

and $A_3 = (\alpha_H+\mu+\mu_D+\omega_D\lambda_D^*)(\alpha_H+\mu+\mu_D+\omega_D\beta_1^*\lambda_D^*)k_{31}k_{32}k_{33}k_{34}-(\alpha_H+\mu+\omega_D\lambda_D^*)\beta_1'\omega_D\lambda_D^*((1-p_D)k_{32}\beta^*\epsilon_D^*\eta(k_{34}m_D+\eta_{13}^*\eta_{16})+(1-\beta^*)\epsilon_D^*\eta(k_{33}k_{34}\eta_{13}+l_D(k_{34}m_D+\eta_{13}^*\eta_{13})+k_{32}k_{33}\epsilon_D^*\beta^*\eta\eta_{13}^*p_D)$.

Analogous to the procedure applied to the previous submodel (2.11), we can obtain the following theorem:

Theorem 2.3.21. *The Diabetes-TB submodel (2.84) has a unique endemic equilibrium point ϵ_*^D, whenever $\mathfrak{R}_0^D > 1$.*

Persistence

In previous sections, we worked with α^* (effective contact rate) as a constant for a given situation. In many situations, we can see it as depending on the situation/region and it takes different values. In general, α^* relates to the level of contagion/propagation of the disease. Now, to study persistence we will consider α^* as dependent on N_D (total population) and a particular case $t_H = 1$.

Firstly, we will normalize the model with respect to N_D. Then, $x_1 = \dfrac{S_D}{N_D}$, $x_2 = \dfrac{E_D}{N_D}$, $x_3 = \dfrac{I_{D_1}}{N_D}$, $x_4 = \dfrac{I_{D_2}}{N_D}$, $x_5 = \dfrac{I_{D_3}}{N_D}$, $x_6 = \dfrac{R_D}{N_D}$ and express (2.84) in these terms, as followed:

$$
\begin{aligned}
N_D &= S_D + E_D + I_{D_1} + I_{D_2} + I_{D_3} + R_D,\\
\frac{dN_D}{dt} &= M_D - (\mu + \mu_D + \alpha_H)N_D - d_{TD}(x_3 + t_D' x_4 + t_D^* x_5)N_D,\\
\frac{dx_1}{dt} &= \frac{M_D}{N_D}(1 - x_1) - \omega_D\epsilon_D\alpha^*(x_3 + x_4 + x_5)x_1 + d_{TD}(x_3 + t_D' x_4 + t_D^* x_5)x_1,\\
\frac{dx_2}{dt} &= \omega_D\epsilon_D\alpha^*(x_3 + x_4 + x_5)(x_1 + \beta_1' x_6) - \left(\frac{M_D}{N_D} - \epsilon_D^*\eta\right)x_2 + d_{TD}(x_3 + t_D' x_4 + t_D^* x_5)x_2,\\
\frac{dx_3}{dt} &= (1 - \beta^*)\epsilon_D^* - \left(l_D + \eta_{13} + \frac{M_D}{N_D}\right)x_4 + d_{TD}(x_3 + t_D' x_4 + t_D^* x_5 - 1)x_3,\\
\frac{dx_4}{dt} &= (1 - p_D)\beta^*\epsilon_D^* - \left(m_D + \eta_{16} + \frac{M_D}{N_D}\right)x_4 + d_{TD}(x_3 + t_D' x_4 + t_D^* x_5 - t_D')x_4,\\
\frac{dx_5}{dt} &= p_D\beta^*\epsilon_D^* - \left(\eta_{13}^* + \frac{M_D}{N_D}\right)x_4 + d_{TD}(x_3 + t_D' x_4 + t_D^* x_5 - t_D^*)x_5,\\
\frac{dx_6}{dt} &= m_D x_4 + \eta_{13}x_3 + \eta_{13}^* x_5 - \omega_D\epsilon_D\alpha^*(N_D)(x_3 + x_4 + x_5)x_6 - \frac{M_D}{N_D}x_6 + d_{TD}(x_3 + t_D' x_4 + t_D^* x_5)x_6.
\end{aligned}
\tag{2.120}
$$

We have that $x_1 + x_2 + x_3 + x_4 + x_5 + x_6 = 1$. The manifold $x_1 + x_2 + x_3 + x_4 + x_5 + x_6 = 1$, $x_1, x_2, x_3, x_4, x_5, x_6 \geq 0$, is forward invariant, under solution flow of system (2.120), which has a global solution that satisfies (2.84). Now, let's find the conditions under which the disease and host subpopulation will persist.

Theorem 2.3.22. *Let $\alpha^*(0) = 0$, $N(0) > 0$. Then, the population is uniformly persistent, that is,*

$$\liminf_{t\to\infty} N(t) \geq \epsilon, \tag{2.121}$$

where $\epsilon > 0$ does not depend on the initial data.

Proof. We have to demonstrate that the set

$$X_1 = \left\{ N = 0, x_i \geq 0, i = 1, ..., 6, \sum_{i=1}^{6} x_i = 1 \right\},$$

is uniform strong repeller for

$$X_2 = \left\{ N > 0, x_i \geq 0, i = 1, ..., 6, \sum_{i=1}^{6} x_i = 1 \right\}.$$

The following results are presented and proved in [30, 117, 107] and are used to demostrate the conditions of persistence.

Theorem 2.3.23. *Let $\mathbb{X}$ be a locally compact metric space with metric d. Let $\mathbb{X}$ be the disjoint union of two sets X_1 and X_2 such that X_2 is compact. Let ϕ be a continuous semiflow on X_1. Then X_2 is a uniform strong repeller for X_1.*

Theorem 2.3.24. *Let D be a bounded interval in $\mathbb{R}$ and $g : (t_0, \infty) \times D \to \mathbb{R}$ be bounded and uniformly continuous. Further, let $x : (t_0, \infty) \to D$ be a solution of $\dot{x} = g(t, x)$, which is defined on the whole interval (t_0, ∞). Then there exist sequences $s_n, t_n \to \infty$ such that*

$$\lim_{n\to\infty} g(s_n, x_\infty) = 0 = \lim_{n\to\infty} g(t_n, x^\infty). \tag{2.122}$$

Lemma 2.3.25. *If the assumptions of Theorem (2.3.24) are satisfied, then*

1. $$\lim_{t\to\inf} \inf g(t, x_\infty) \geq 0 \geq \lim_{t\to\infty} \sup g(t, x_\infty), \tag{2.123}$$

2. $$\lim_{t\to\inf} \inf g(t, x^\infty) \geq 0 \geq \lim_{t\to\infty} \sup g(t, x^\infty). \tag{2.124}$$

We have that the assumptions of Theorem (2.3.23) are satisfed, it suffices to show that X_2 is a uniform weak repulsive for X_1. We define

$$r = x_2 + x_3 + x_4 + x_5 + x_6. \tag{2.125}$$

Then,

$$r^{'} = \omega_D \epsilon_D \alpha^*(N_D)(x_3 + x_4 + x_5)x_1 - \frac{M_D}{N_D} r + d_{TD}((r-1)(x_3 + t_D^{'} x_4 + t_D^* x_5)). \tag{2.126}$$

Using that $x_1, x_2, x_3, x_4, x_5, x_6 \leq 1$, we have

$$\frac{M_D}{N_D^\infty} + d_{TD}(1 - r^\infty)(1 + t_D^{'} + t_D^*) \leq 3\omega_D \epsilon_D \alpha^*(N_D) \tag{2.127}$$

$$\Longrightarrow \alpha^*(N_D) \geq \frac{M_D}{3\omega_D \epsilon_D N_D^\infty} + \frac{d_{TD}(1 - r^\infty)(1 + t_D^{'} + t_D^*)}{3\omega_D \epsilon_D}. \tag{2.128}$$

From the equation of N_D in (2.120), we obtain

$$\liminf_{t\to\infty} \frac{1}{N_D}\frac{dN_D}{dt} \geq \frac{M_D}{N_D^\infty} - (\mu + d_{TD}(x_3^\infty + t_D^{'} x_4^\infty + t_D^* x_5^\infty)) \geq \frac{M_D}{N_D^\infty} + (\mu + d_{TD}(1 + t_D^{'} + t_D^*)r^\infty). \quad (2.129)$$

As N_D increase exponentially,

$$\frac{M_D}{N_D^\infty} \leq \mu + d_{TD}(1 + t_D^{'} + t_D^*)r^\infty, \quad (2.130)$$

that is

$$\frac{1}{d_{TD}(1 + t_D^{'} + t_D^*)}\left(\frac{M_D}{N_D^\infty} - \mu\right) \leq r^\infty. \quad (2.131)$$

Combining (2.128) and (2.131), we have

$$\alpha^*(N_D^\infty) \geq \frac{1}{3\omega_D\epsilon_D}\left(\left(\frac{M_D}{N_D^\infty} - \mu\right)\left(\frac{M_D}{3\omega_D\epsilon_D N_D^\infty(1 + t_D^{'} + t_D^*)} - 1\right) + d_{TD}(1 + t_D^{'} + t_D^*)\right). \quad (2.132)$$

As $\alpha^*(0) = 0$ and $\alpha^*(N_D)$ is continuous at 0, $N_D^\infty \geq \epsilon > 0$ whit ϵ not depending on the initial data. From (2.132), we see that we can relax $\alpha^*(0) = 0$ and require that:

$$\alpha^*(0) < \frac{1}{3\omega_D\epsilon_D}\left(\left(\frac{M_D}{N_D^\infty} - \mu\right)\left(\frac{M_D}{3\omega_D\epsilon_D N_D^\infty(1 + t_D^{'} + t_D^*)} - 1\right) + d_{TD}(1 + t_D^{'} + t_D^*)\right). \quad (2.133)$$

This conclude the proof. □

With this result, we proved the persistence of tuberculosis in this subpopulation. Therefore, it is necessary to apply control strategies to reduce and eradicate the disease in the community.

Full Model Study

The model (2.5) has a disease-free equilibrium, given by

$$\epsilon_0^G = (S_0^T, S_0^H, S_0^D, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0).$$

We computed the basic reproduction number as in the previous submodels by next-generation matrix method. The dominant eigenvalues of the next-generation matrix are $\mathfrak{R}_0^T$, $\mathfrak{R}_0^H$ and $\mathfrak{R}_0^D$. Therefore, the basic reproduction number of the model (2.5) is

$$\mathfrak{R}_0 = \max\{\mathfrak{R}_0^T, \mathfrak{R}_0^H, \mathfrak{R}_0^D\}.$$

Using the analytical results of the TB-Only, TB-HIV/AIDS and TB-Diabetes submodels, we have conditions for which the MDR-TB and XDR-TB parameters have a positive impact on the reduction of TB transmission for the full model [80].

Global Stability

Now, we list two conditions that if satisfied, also guarantee the global asymptotic stability of the disease-free equilibrium point. Following [38], we can rewrite the model (2.5) as

$$\begin{aligned} \frac{dS}{dt} &= F(S,I), \\ \frac{dI}{dt} &= G(S,I), \quad G(S,0)=0, \end{aligned} \tag{2.134}$$

where $S \in \mathbb{R}^6_+$ is the vector whose components are the number of uninfected and recovered and $I \in \mathbb{R}^{12}_+$ denotes the number of infected individuals including the latent and the infectious (the other variables of the model (2.5)).

The disease-free equilibrium is now denoted by $E^G_0 = (S^*_0, 0)$, $S^*_0 = (S_0, 0, 0, 0)$, $S_0 = (S^T_0, S^H_0, S^D_0)$ where $S^T_0 = \dfrac{M_T}{\mu + \alpha_H + \alpha_D}$, $S^H_0 = \dfrac{M_H}{\mu + \mu_H + \alpha_{HD}}$ and $S^D_0 = \dfrac{M_D}{\mu + \mu_D + \alpha_H}$.

The conditions (H_1) and (H_2) below must be satisfied to guarantee the global asymptotic stability of E^G_0.

$$\begin{aligned} &(H_1): \quad \text{For} \quad \frac{dS}{dt} = F(S,0), \quad S^*_0 \quad \text{is globally asymptotically stable,} \\ &(H_2): \quad G(S,I) = AI - G^*(S,I), \quad G^*(S,I) \geq 0, \quad \text{for} \quad (S,I) \in \Omega, \end{aligned}$$

where $A = D_I G(S^*_0, 0)$ ($D_I G(S^*_0, 0)$ is the Jacobian of G at $(S^*_0, 0)$) is a M-matrix (the off-diagonal elements of A are non-negative) and Ω is the biologically feasible region.

We have de following theorem:

Theorem 2.3.26. *The fixed point E^G_0 is a globally asymptotically stable equilibrium of model (2.5) provided that $\mathfrak{R}_0 < 1$ and that the conditions (H_1) and (H_2) are satisfied.*

Proof. Let

$$F(S,0) = \begin{pmatrix} M_T - (\mu + \alpha_H + \alpha_D)S_T \\ M_H - (\mu + \mu_H + \alpha_{HD})S_H \\ M_D - (\mu + \mu_D + \alpha_H)S_D \\ 0 \\ 0 \\ 0 \end{pmatrix}.$$

As $F(S,0)$ is a linear equation, we obtain that S^*_0 is globally asymptotic stable, thus H_1 is satisfied.
Let's, $\mathbf{A} = [\mathbf{A_1} \mid \mathbf{A_2}]$, where

$$\mathbf{A_1} = \begin{pmatrix} -k_{11} & 0 & 0 & \alpha^* & \alpha^* & \alpha^*\epsilon_H \\ \alpha_H & -k_{21} & \alpha_H & \omega_H\alpha^* & \omega_H\alpha^* & \omega_H\alpha^*\epsilon_H \\ \alpha_D & \alpha_{HD} & -k_{31} & \omega_D\alpha^* & \omega_D\alpha^* & \omega_D\alpha^*\epsilon_H \\ (1-\beta^*)\eta & 0 & 0 & -k_{12} & 0 & 0 \\ (1-p_T)\beta^*\eta & 0 & 0 & l_T & -k_{13} & 0 \\ 0 & (1-\beta^*)\epsilon_H^*\eta & 0 & t_H\alpha_H & 0 & -k_{22} \\ 0 & (1-p_H)\beta^*\epsilon_H^*\eta & 0 & 0 & t_H\alpha_H & l_H \\ 0 & 0 & (1-\beta^*)\epsilon_D^*\eta & t_D\alpha_D & 0 & t_{HD}\alpha_{HD} \\ 0 & 0 & (1-p_D)\beta^*\epsilon_D^*\eta & 0 & t_D\alpha_D & 0 \\ p_T\beta^*\eta & 0 & 0 & 0 & \eta_{14} & 0 \\ 0 & p_H\epsilon_H^*\beta^*\eta & 0 & 0 & 0 & 0 \\ 0 & 0 & p_D\epsilon_D^*\beta^*\eta & 0 & 0 & 0 \end{pmatrix},$$

$$\mathbf{A_2} = \begin{pmatrix} \alpha^*\epsilon_H & \alpha^*\epsilon_D & \alpha^*\epsilon_D & \alpha^* & \alpha^*\epsilon_H & \alpha^*\epsilon_D \\ \omega_H\alpha^*\epsilon_H & \omega_H\alpha^*\epsilon_D & \omega_H\alpha^*\epsilon_D & \omega_H\alpha^* & \omega_H\alpha^*\epsilon_H & \omega_H\alpha^*\epsilon_D \\ \omega_D\alpha^*\epsilon_H & \omega_D\alpha^*\epsilon_D & \omega_D\alpha^*\epsilon_D & \omega_D\alpha^* & \omega_D\alpha^*\epsilon_H & \omega_D\alpha^*\epsilon_D \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & t_H\alpha_H & 0 & 0 & 0 & 0 \\ -k_{23} & 0 & t_H\alpha_H & 0 & 0 & 0 \\ 0 & -k_{32} & 0 & 0 & 0 & 0 \\ t_{HD}\alpha_{HD} & l_D & -k_{33} & 0 & 0 & 0 \\ 0 & 0 & 0 & -k_{14} & 0 & 0 \\ \eta_{15} & 0 & 0 & t_H\alpha_H & -k_{24} & t_H\alpha_H \\ 0 & 0 & \eta_{16} & t_D\alpha_D & t_{HD}\alpha_{HD} & -k_{34} \end{pmatrix},$$

$$\mathbf{I} = \begin{pmatrix} E_T, & E_H, & E_D, & I_{T_1}, & I_{T_2}, & I_{H_1}, & I_{H_2}, & I_{D_1}, & I_{D_2}, & I_{T_3}, & I_{H_3}, & I_{D_3} \end{pmatrix},$$

$$G^*(S,I) = AI^T - G(S,I),$$

$$G^*(S,I) = \begin{pmatrix} G_1^*(S,I) \\ G_2^*(S,I) \\ G_3^*(S,I) \\ G_4^*(S,I) \\ G_5^*(S,I) \\ G_6^*(S,I) \\ G_7^*(S,I) \\ G_8^*(S,I) \\ G_9^*(S,I) \\ G_{10}^*(S,I) \\ G_{11}^*(S,I) \\ G_{12}^*(S,I) \end{pmatrix} = \begin{pmatrix} \alpha^*\left(I_{T_1} + I_{T_2} + I_{T_3} + \epsilon_H(I_{H_1} + I_{H_2} + I_{H_3}) + \epsilon_D(I_{D_1} + I_{D_2} + I_{D_3})\right)\left(1 - \dfrac{S_T + \beta_1' R_T}{N}\right) \\ \omega_H\alpha^*\left(I_{T_1} + I_{T_2} + I_{T_3} + \epsilon_H(I_{H_1} + I_{H_2} + I_{H_3}) + \epsilon_D(I_{D_1} + I_{D_2} + I_{D_3})\right)\left(1 - \dfrac{S_H + \beta_1' R_H}{N}\right) \\ \omega_D\alpha^*\left(I_{T_1} + I_{T_2} + I_{T_3} + \epsilon_H(I_{H_1} + I_{H_2} + I_{H_3}) + \epsilon_D(I_{D_1} + I_{D_2} + I_{D_3})\right)\left(1 - \dfrac{S_D + \beta_1' R_D}{N}\right) \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}.$$

Since $S_T + \beta_1' R_T$, $S_H + \beta_1' R_H$ and $S_D + \beta_1' R_D$ are always less than or equal to N, $\dfrac{S_T + \beta_1' R_T}{N} \leq 1$, $\dfrac{S_H + \beta_1' R_H}{N} \leq 1$ and $\dfrac{S_D + \beta_1' R_D}{N} \leq 1$. Thus, $G^*(S,I) \geq 0$ for all $(S,I) \in D$, the E_0^G is a globally

asymptotically stable. □

Analogous proofs of this theorem can be found in the bibliographic references [97, 98].

After analyzing the basic reproduction number, the infection-free equilibrium points, and the endemic equilibrium points, we have the following conclusions:

- if $\mathfrak{R}_0 = \max\{\mathfrak{R}_0^T, \mathfrak{R}_0^H, \mathfrak{R}_0^D\} < 1$, then $\epsilon_0^T, \epsilon_0^H, \epsilon_0^D$ exist and are globally asymptotically stable (Lemmas (2.3.2), (2.3.9) and (2.3.16)) and ϵ_0^G is globally asymptotically stable (Theorem (2.3.26)).
- if $\mathfrak{R}_0 = \max\{\mathfrak{R}_0^T, \mathfrak{R}_0^H, \mathfrak{R}_0^D\} > 1$, and we suppose that $\mathfrak{R}_0 = \mathfrak{R}_0^T$ then ϵ_0^G is unstable and we will study 3 possible cases:
  1. $\mathfrak{R}_0 = \mathfrak{R}_0^T$ and $\mathfrak{R}_0^H, \mathfrak{R}_0^D < 1$, then ϵ_0^T is unstable (Lemma (2.3.1)), $\epsilon_0^H, \epsilon_0^D$ are globally asymptotically stable (Lemmas (2.3.9) and (2.3.16)) and exists ϵ_*^T (Lemma (2.3.7)).
  2. $\mathfrak{R}_0 = \mathfrak{R}_0^T$ and $\mathfrak{R}_0^H > 1, \mathfrak{R}_0^D < 1$, then ϵ_0^T and ϵ_0^H are unstable (Lemmas (2.3.1) and (2.3.8)), ϵ_0^D is globally asymptotically stable (Lemma (2.3.16)) and exist ϵ_*^T and ϵ_*^H (Lemmas (2.3.7) and (2.3.14)).
  3. $\mathfrak{R}_0 = \mathfrak{R}_0^T$ and $\mathfrak{R}_0^H, \mathfrak{R}_0^D > 1$, then $\epsilon_0^T, \epsilon_0^H\ \epsilon_0^D$ are unstable (Lemmas (2.3.1), (2.3.8) and (2.3.15) and exist ϵ_*^T, ϵ_*^H and ϵ_*^D (Lemmas (2.3.7), (2.3.14) and (2.3.21)).

2.4 Sensitive Analysis

In this section, we study the impact of the parameters on the threshold quantity, $\mathfrak{R}_0$. The sensitivity analysis of the basic reproduction number determines the relative importance of the parameters present in the basic reproduction number, such as the parameters of transmission, resistance, recovery, among others. The sensitivity index can be defined using the partial derivatives, provided that the variable be differentiable with respect to the parameter under study. Sensitivity analysis also helps to identify the transcendence of the parameter values in the predictions using the model [86, 40, 122].

Definition 2.4.1. *([122]) The normalized forward sensitivity index of a variable, v, that depends differentiability on a parameter p is defined as:*

$$\Upsilon_p^v := \frac{\partial v}{\partial p} \times \frac{p}{v}. \tag{2.135}$$

We can characterize the sensitivity index as follows:

- A positive value of the sensitivity index implies that an increase in the parameter value causes an increase in the basic reproduction number.
- A negative value of the sensitivity index implies that an increase of the parameter value causes a decrease of the basic reproduction number.

We will study the sensitivity index specifically for parameters associated with TB transmission, resistance, and recovery. We obtain the following expressions:

$$\mathrm{Y}_{M_T}^{\mathfrak{R}_0} = \begin{cases} +1, & \text{if} \quad \mathfrak{R}_0 = \mathfrak{R}_0^T, \\ 0, & \text{Otherwise.} \end{cases}$$

Sensitivity index expressions for β^*, α^* and η are:

$$\mathrm{Y}_{\beta^*}^{\mathfrak{R}_0} = \begin{cases} \dfrac{\beta^*(-k_{13}k_{14} - l_T(k_{14}+\eta_{14}) + (1-p_T)k_{12}(k_{14}+\eta_{14}) + k_{12}k_{13}p_T)}{(1-\beta^*)(k_{13}k_{14} + l_T(k_{14}+\eta_{14})) + (1-p_T)\beta^* k_{12}(k_{14}+\eta_{14}) + k_{12}k_{13}\beta^* p_T}, & \text{if} \quad \mathfrak{R}_0 = \mathfrak{R}_0^T, \\ \dfrac{\beta^*(-k_{23}k_{24} - l_H(k_{24}+\eta_{15}) + (1-p_H)k_{22}(k_{24}+\eta_{15}) + k_{22}k_{23}p_H)}{(1-\beta^*)(k_{23}k_{24} + l_H(k_{24}+\eta_{15})) + (1-p_H)\beta^* k_{22}(k_{24}+\eta_{15}) + k_{22}k_{23}\beta^* p_H}, & \text{if} \quad \mathfrak{R}_0 = \mathfrak{R}_0^H, \\ \dfrac{\beta^*(-k_{33}k_{34} - l_D(k_{34}+\eta_{16}) + (1-p_D)k_{32}(k_{34}+\eta_{16}) + k_{32}k_{33}p_D)}{(1-\beta^*)(k_{33}k_{34} + l_D(k_{34}+\eta_{16})) + (1-p_D)\beta^* k_{32}(k_{34}+\eta_{16}) + k_{32}k_{33}\beta^* p_D}, & \text{if} \quad \mathfrak{R}_0 = \mathfrak{R}_0^D. \end{cases}$$

$$\mathrm{Y}_{\alpha^*}^{\mathfrak{R}_0} = \mathrm{Y}_{\eta}^{\mathfrak{R}_0} = +1.$$

Sensitivity index expressions for parameters associated with resistance are:

$$\mathrm{Y}_{l_T}^{\mathfrak{R}_0} = \begin{cases} \dfrac{l_T\big((1-\beta^*)(k_{14}((1-t_T^{'})d_T + (\eta_{11}-M_T) + \eta_{14}(1-t_T^*)d_T + (\eta_{11}-\eta_{11}^*))\big)}{k_{12}\big((1-\beta^*)(k_{13}k_{14} + l_T(k_{14}+\eta_{14})) + (1-p_T)\beta^* k_{12}(k_{14}+\eta_{14}) + k_{12}k_{13}\beta^* p_T\big)}, & \text{if} \quad \mathfrak{R}_0 = \mathfrak{R}_0^T, \\ 0, & \text{Otherwise.} \end{cases}$$

$$\mathrm{Y}_{l_H}^{\mathfrak{R}_0} = \begin{cases} \dfrac{l_H\big((1-\beta^*)(k_{24}((1-t_H^{'})d_{TH} + (\eta_{12}-M_H) + \eta_{15}(1-t_H^*)d_{TH} + (\eta_{12}-\eta_{12}^*))\big)}{k_{22}\big((1-\beta^*)(k_{23}k_{24} + l_H(k_{24}+\eta_{15})) + (1-p_H)\beta^* k_{22}(k_{24}+\eta_{15}) + k_{22}k_{23}\beta^* p_H\big)}, & \text{if} \quad \mathfrak{R}_0 = \mathfrak{R}_0^H, \\ 0, & \text{Otherwise.} \end{cases}$$

$$\mathrm{Y}_{l_D}^{\mathfrak{R}_0} = \begin{cases} \dfrac{l_D\big((1-\beta^*)(k_{34}((1-t_D^{'})d_{TD} + (\eta_{13}-M_D) + \eta_{16}(1-t_D^*)d_{TD} + (\eta_{13}-\eta_{13}^*))\big)}{k_{32}\big((1-\beta^*)(k_{33}k_{34} + l_D(k_{34}+\eta_{16})) + (1-p_D)\beta^* k_{32}(k_{34}+\eta_{16}) + k_{32}k_{33}\beta^* p_D\big)}, & \text{if} \quad \mathfrak{R}_0 = \mathfrak{R}_0^D, \\ 0, & \text{Otherwise.} \end{cases}$$

$$\mathrm{Y}_{\eta_{14}}^{\mathfrak{R}_0} = \begin{cases} \dfrac{\eta_{14}\big(((1-\beta^*) + k_{12}\beta^*(1-p_T))((t_T^{'}-t_T^*)d_T + (M_T-\eta_{11}^*))\big)}{k_{13}\big((1-\beta^*)(k_{13}k_{14} + l_T(k_{14}+\eta_{14})) + (1-p_T)\beta^* k_{12}(k_{14}+\eta_{14}) + k_{12}k_{13}\beta^* p_T\big)}, & \text{if} \quad \mathfrak{R}_0 = \mathfrak{R}_0^T, \\ 0, & \text{Otherwise.} \end{cases}$$

$$\mathrm{Y}_{\eta_{15}}^{\mathfrak{R}_0} = \begin{cases} \dfrac{\eta_{15}\big(((1-\beta^*) + k_{22}\beta^*(1-p_H))((t_H^{'}-t_H^*)d_{TH} + (m_H-\eta_{12}^*))\big)}{k_{23}\big((1-\beta^*)(k_{23}k_{24} + l_H(k_{24}+\eta_{15})) + (1-p_H)\beta^* k_{22}(k_{24}+\eta_{15}) + k_{22}k_{23}\beta^* p_H\big)}, & \text{if} \quad \mathfrak{R}_0 = \mathfrak{R}_0^H, \\ 0, & \text{Otherwise.} \end{cases}$$

$$\mathrm{Y}_{\eta_{16}}^{\mathfrak{R}_0} = \begin{cases} \dfrac{\eta_{16}\big(((1-\beta^*) + k_{32}\beta^*(1-p_D))((t_D^{'}-t_D^*)d_{TD} + (M_D-\eta_{13}^*))\big)}{k_{33}\big((1-\beta^*)(k_{33}k_{34} + l_D(k_{34}+\eta_{16})) + (1-p_D)\beta^* k_{32}(k_{34}+\eta_{16}) + k_{32}k_{33}\beta^* p_D\big)}, & \text{if} \quad \mathfrak{R}_0 = \mathfrak{R}_0^D, \\ 0, & \text{Otherwise.} \end{cases}$$

Sensitivity index expressions for parameters associated with recovery are:

$$\mathrm{Y}_{\eta_{11}}^{\mathfrak{R}_0} = \begin{cases} -\dfrac{\eta_{11}\big((1-\beta^*)(k_{13}k_{14} + l_T(k_{14}+\eta_{14})\big)}{k_{12}\big((1-\beta^*)(k_{13}k_{14} + l_T(k_{14}+\eta_{14})) + (1-p_T)\beta^* k_{12}(k_{14}+\eta_{14}) + k_{12}k_{13}\beta^* p_T\big)}, & \text{if} \quad \mathfrak{R}_0 = \mathfrak{R}_0^T, \\ 0, & \text{Otherwise.} \end{cases}$$

$$\Upsilon^{\mathfrak{R}_0}_{\eta_{12}} = \begin{cases} -\dfrac{\eta_{12}\big((1-\beta^*)(k_{23}k_{24}+l_H(k_{24}+\eta_{15})\big)}{k_{22}\big((1-\beta^*)(k_{23}k_{24}+l_H(k_{24}+\eta_{15}))+(1-p_H)\beta^*k_{22}(k_{24}+\eta_{15})+k_{22}k_{23}\beta^*p_H\big)}, & \text{if} \quad \mathfrak{R}_0=\mathfrak{R}_0^H, \\ 0, & \text{Otherwise.} \end{cases}$$

$$\Upsilon^{\mathfrak{R}_0}_{\eta_{13}} = \begin{cases} -\dfrac{\eta_{13}\big((1-\beta^*)(k_{33}k_{34}+l_D(k_{34}+\eta_{16})\big)}{k_{32}\big((1-\beta^*)(k_{33}k_{34}+l_D(k_{34}+\eta_{16}))+(1-p_D)\beta^*k_{32}(k_{34}+\eta_{16})+k_{32}k_{33}\beta^*p_D\big)}, & \text{if} \quad \mathfrak{R}_0=\mathfrak{R}_0^D, \\ 0, & \text{Otherwise.} \end{cases}$$

$$\Upsilon^{\mathfrak{R}_0}_{m_T} = \begin{cases} -\dfrac{m_T\big((1-\beta^*)l_T(k_{14}+\eta_{14}+(1-p_T)\beta^*k_{12}(k_{14}+\eta_{14})\big)}{k_{13}\big((1-\beta^*)(k_{13}k_{14}+l_T(k_{14}+\eta_{14}))+(1-p_T)\beta^*k_{12}(k_{14}+\eta_{14})+k_{12}k_{13}\beta^*p_T\big)}, & \text{if} \quad \mathfrak{R}_0=\mathfrak{R}_0^T, \\ 0, & \text{Otherwise.} \end{cases}$$

$$\Upsilon^{\mathfrak{R}_0}_{m_H} = \begin{cases} -\dfrac{m_H\big((1-\beta^*)l_H(k_{24}+\eta_{15}+(1-p_H)\beta^*k_{22}(k_{24}+\eta_{15})\big)}{k_{23}\big((1-\beta^*)(k_{23}k_{24}+l_H(k_{24}+\eta_{15}))+(1-p_H)\beta^*k_{22}(k_{24}+\eta_{15})+k_{22}k_{23}\beta^*p_H\big)}, & \text{if} \quad \mathfrak{R}_0=\mathfrak{R}_0^H. \\ 0, & \text{Otherwise.} \end{cases}$$

$$\Upsilon^{\mathfrak{R}_0}_{m_D} = \begin{cases} -\dfrac{m_D\big((1-\beta^*)l_D(k_{34}+\eta_{16}+(1-p_D)\beta^*k_{32}(k_{34}+\eta_{16})\big)}{k_{33}\big((1-\beta^*)(k_{33}k_{34}+l_D(k_{34}+\eta_{16}))+(1-p_D)\beta^*k_{32}(k_{34}+\eta_{16})+k_{32}k_{33}\beta^*p_D\big)}, & \text{if} \quad \mathfrak{R}_0=\mathfrak{R}_0^H, \\ 0, & \text{Otherwise.} \end{cases}$$

$$\Upsilon^{\mathfrak{R}_0}_{\eta^*_{11}} = \begin{cases} -\dfrac{\eta^*_{11}\big(\eta_{14}(l_T(1-\beta^*)+(1-p_T)k_{12}\beta^*)+k_{12}k_{13}\beta^*p_T\big)}{k_{13}\big((1-\beta^*)(k_{13}k_{14}+l_T(k_{14}+\eta_{14}))+(1-p_T)\beta^*k_{12}(k_{14}+\eta_{14})+k_{12}k_{13}\beta^*p_T\big)}, & \text{if} \quad \mathfrak{R}_0=\mathfrak{R}_0^T, \\ 0, & \text{Otherwise.} \end{cases}$$

$$\Upsilon^{\mathfrak{R}_0}_{\eta^*_{12}} = \begin{cases} -\dfrac{\eta^*_{12}\big(\eta_{15}(l_H(1-\beta^*)+(1-p_H)k_{22}\beta^*)+k_{22}k_{23}\beta^*p_H\big)}{k_{23}\big((1-\beta^*)(k_{23}k_{24}+l_H(k_{24}+\eta_{15}))+(1-p_H)\beta^*k_{22}(k_{24}+\eta_{15})+k_{22}k_{23}\beta^*p_H\big)}, & \text{if} \quad \mathfrak{R}_0=\mathfrak{R}_0^H, \\ 0, & \text{Otherwise.} \end{cases}$$

$$\Upsilon^{\mathfrak{R}_0}_{\eta^*_{13}} = \begin{cases} -\dfrac{\eta^*_{13}\big(\eta_{16}(l_D(1-\beta^*)+(1-p_D)k_{32}\beta^*)+k_{32}k_{33}\beta^*p_D\big)}{k_{33}\big((1-\beta^*)(k_{33}k_{34}+l_D(k_{34}+\eta_{16}))+(1-p_D)\beta^*k_{32}(k_{34}+\eta_{16})+k_{32}k_{33}\beta^*p_D\big)}, & \text{if} \quad \mathfrak{R}_0=\mathfrak{R}_0^D, \\ 0, & \text{Otherwise.} \end{cases}$$

Using the conditions of the parameters in our study, we have that:

- The sensitivity index of parameters M_T, α^* and η are positive or null this means that a growth in these parameters leads to a growth in the basic reproduction number.
- The sensitivity index of parameters associated with recovery ($m_T, m_H, m_D, \eta_{1l}, \eta^*_{1l}, l = 1, 2, 3$) are negative or null, which implies that an increase in these parameters leads to a decrease in the basic reproduction number.
- The sensitivity index of the other parameters studied depends on the scenario where the model is applied.

We can characterize the sensitivity index of $\mathfrak{R}_0$ with respect to β^* with the following

lemma:

Lemma 2.4.1. *The sensitivity index of the basic reproduction number with respect to the β^* parameter is greater than zero if:*

$$\frac{((1-p_T)k_{12}-l_T)(k_{14}+\eta_{14})}{k_{13}(k_{14}-k_{12}p_T)} > 1, \quad for \quad \mathfrak{R}_0 = \mathfrak{R}_0^T, \tag{2.136}$$

$$\frac{((1-p_H)k_{22}-l_H)(k_{24}+\eta_{15})}{k_{23}(k_{24}-k_{22}p_H)} > 1, \quad for \quad \mathfrak{R}_0 = \mathfrak{R}_0^H, \tag{2.137}$$

$$\frac{((1-p_D)k_{32}-l_D)(k_{34}+\eta_{16})}{k_{33}(k_{34}-k_{32}p_D)} > 1, \quad for \quad \mathfrak{R}_0 = \mathfrak{R}_0^D. \tag{2.138}$$

2.5 Numerical Results

For the numerical simulations, we use a set of parameters extracted from [35, 78, 122, 107, 36, 37, 64, 61, 5, 41] with illustrative purposes and to support the analytical results, see Tables (2.2)-(2.3) and we use the fourth-order Runge–Kutta numerical scheme coded in MATLAB programming language. The initial conditions for the TB-Only and TB-Diabetes subpopulations are taken from [35], and the values for the subpopulation of TB-HIV/AIDS are assumed and do not represent a specific demographic area, but fall within the range of actual achievable data, see Table (2.2). The parameter values and initial conditions assumed were discussed and validated by specialists. Numerical simulations of Model (2.5) for another scenario can be found in the work referenced as [80].

Variable	Value	Variable	Value	Variable	Value
$S_T(0)$	8741400	$S_H(0)$	111000	$S_D(0)$	200000
$E_T(0)$	565600	$E_H(0)$	5000	$E_D(0)$	8500
$I_{T_1}(0)$	20000	$I_{H_1}(0)$	1400	$I_{D_1}(0)$	1800
$I_{T_2}(0)$	1300	$I_{H_2}(0)$	400	$I_{D_2}(0)$	550
$I_{T_3}(0)$	700	$I_{H_3}(0)$	210	$I_{D_3}(0)$	250
$R_T(0)$	8800	$R_H(0)$	500	$R_D(0)$	300

Table 2.2: *Numerical values for the initial conditions of model (2.5).*

Parameter	Value	Reference
M_T, M_H, M_D	667685, 10000, 50000	[78, 35], Assumed, Assumed
α^*	9.5	[35, 78, 122]
α_H, α_D	0.0075, 0.009	Assumed, [78, 35]
ω_H, ω_D	1.22, 1.10	[78, 35, 107]
α_{HD}	0.00173	[36]
ϵ_H, ϵ_D	1.3, 1.1	Assumed, [78, 35]
μ, μ_H, μ_D	$1/53.5, 0.045, 0.03$	[78, 35, 107], Assumed
η, β^*	0.05, 0.04	[78, 35, 107, 37, 64]
d_T, d_{TH}, d_{TD}	$0.0275, 0.033, 1.5 * d_T$	[78, 35, 107]
$\epsilon_H^*, \epsilon_D^*$	1.3, 1.1	[107], Assumed
$t_T^{'}, t_H^{'}, t_D^{'}$	1, 1.01, 1	Assumed
t_T^*, t_H^*, t_D^*	1.01, 1.02, 1.01	Assumed
$\beta_1^{'}$	0.9	[107]
l_T, l_H, l_D	0.0018, 0.0022, 0.0048	[122, 61, 5, 41], Assumed
m_T, m_H, m_D	0.6266,0.45,0.4054	[78, 35], Assumed
$\eta_{14}, \eta_{15}, \eta_{16}$	0.013, 0.022, 0.026	[122, 61, 5, 41], Assumed
$\eta_{11}, \eta_{12}, \eta_{13}$	0.7372, 0.55, 0.7372	[78, 35], Assumed
p_T, p_H, p_D	0.00225,0.0035,0.0041	[122, 37, 64], Assumed
$\eta_{11}^*, \eta_{12}^*, \eta_{13}^*$	0.4006,0.255,0.3317	[78, 35], Assumed
t_H, t_D, t_{HD}	1.01, 1.01, 1.01	Assumed

Table 2.3: *Numerical values for the parameters of model (2.5).*

The values of the basic reproduction numbers for the values of the Table (2.3) are $\mathfrak{R}_0^T = 1.3156$, $\mathfrak{R}_0^H = 0.1182$ and $\mathfrak{R}_0^D = 0.2101$, then $\mathfrak{R}_0 = \max\{R_0^T, R_0^H, R_0^D\} = 1.3156 > 1$.

We study the behavior of $\mathfrak{R}_0$ with respect to the effective contact rate (α^*) and the parameters associated with MDR-TB and XDR-TB. For the variation of α^*, we have that the $\mathfrak{R}_0^D$ is in the interval $[0.0995, 0.3317]$, $\mathfrak{R}_0^T$ is in $[0.6232, 2.0773]$ and $\mathfrak{R}_0^H$ is in $[0.0560, 0.1866]$. We can observe that the basic reproduction number for TB-HIV/AIDS and TB-Diabetes subpopulations is less than unity. This implies a decrease in the number of contagions if there is a reduction in the effective contact rate, see Figure (2.2). For the TB-Only subpopulation, $\mathfrak{R}_0^T$ takes values greater and less than unity, this means that for certain values of α^* the infection will be able to start spreading in this subpopulations, and for others there will be a decline in the number of cases.

In Figure (2.3), we analyze the response of $\mathfrak{R}_0$ when the parameters that represent MDR-TB and XDR-TB are varying. For Figure (2.3a), we vary l_T, l_H and l_D to study what happens with the basic reproduction number with respect to these parameters that represent the MDR-TB. The $\mathfrak{R}_0^D \in [0.2095, 0.2217]$, $\mathfrak{R}_0^T \in [1.3153, 1.3311]$ and $\mathfrak{R}_0^H \in [0.1181, 0.1205]$. In Figure (2.3b), we varied η_{14}, η_{15} and η_{16} (parameters associated with the XDR-TB) and we obtain that $\mathfrak{R}_0^D \in [0.2099, 0.2103]$, $\mathfrak{R}_0^T \in [1.3151, 1.3177]$ and $\mathfrak{R}_0^H \in [0.1181, 0.1184]$.

In both cases, the $\mathfrak{R}_0$ of the TB-Only subpopulation remains greater than unity, demonstrating that growth in the parameters associated with MDR-TB and XDR-TB negatively affects this community and in the TB-HIV/AIDS and TB-Diabetes subpopulations, the opposite occurs. The greatest difficulty of control is found in the TB-Only subpopulation. However, to control the epidemic it is necessary to control it in all subpopulations.

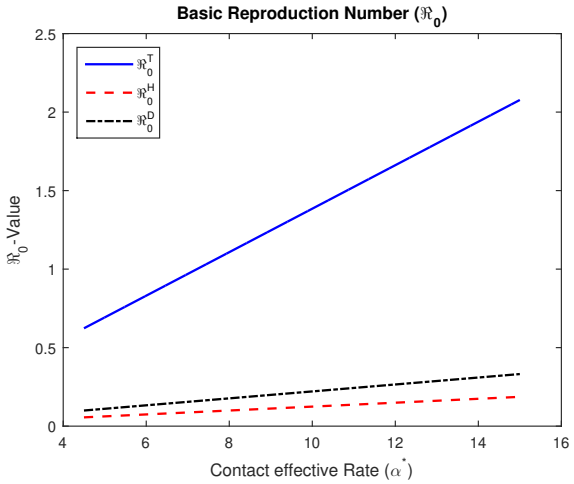
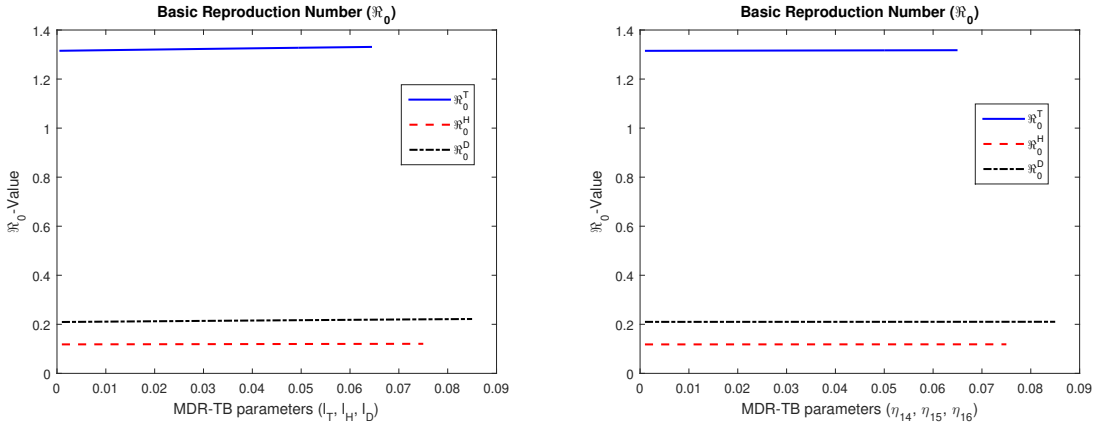


Figure 2.2: *Behavior of $\mathfrak{R}_0$ with respect to effective contact rate, α^*, for the different subpopulations and $\alpha^* \in [4.5, 15]$.*



(a) **(b)**

Figure 2.3: *(a) Graphical behavior of $\mathfrak{R}_0$ with respect to the variation of the MDR-TB parameters (l_T, l_H, l_D), for $l_T \in [0.0005, 0.065]$, $l_H \in [0.001, 0.075]$ and $l_D \in [0.001, 0.0855]$. (b) Graphical behavior of $\mathfrak{R}_0$ with respect to the variation of the XDR-TB parameters $(\eta_{14}, \eta_{15}, \eta_{16})$ for $\eta_{14} \in [0.001, 0.065]$, $\eta_{15} \in [0.001, 0.075]$ and $\eta_{16} \in [0.001, 0.085]$.*

The following Table (2.4) presents the application of the Lemmas (2.3.3)-(2.3.6) to the scenario under study:

Value	Values	Inequalities	Results
$\Delta_T = 0.0894$	$\Delta_{T_1} = 0.0680$ $\Delta_{T_2} = 0.0627$ $\Delta_{T_3} = 0.0671$ $\Delta_{T_4} = 0.0533$	$\Delta_T > \Delta_{T_1}$ $\Delta_T > \Delta_{T_2}$ $\Delta_T > \Delta_{T_3}$ $\Delta_T > \Delta_{T_4}$	Using the result (2.3.3), we have that any variation of l_T and η_{14} negatively affects $\mathfrak{R}_0^T$.
$\Delta_T = 0.0894$	$\Delta_{T_5} = 0.0056$ $\Delta_{T_6} = 0.0889$ $\Delta_{T_7} = 0.0375$ $\Delta_{T_8} = 0.0710$	$\Delta_T > \Delta_{T_5}$ $\Delta_T > \Delta_{T_6}$ $\Delta_T > \Delta_{T_7}$ $\Delta_T > \Delta_{T_8}$	For the variations of l_T and η_{11} using the Lemma (2.3.4), we have that any variation negatively affects $\mathfrak{R}_0^T$.
$\Delta_T = 0.0894$	$\Delta_{T_9} = 0.0459$ $\Delta_{T_{10}} = 0.0691$ $\Delta_{T_{11}} = 0.0647$ $\Delta_{T_{12}} = 0.0678$	$\Delta_T > \Delta_{T_9}$ $\Delta_T > \Delta_{T_{10}}$ $\Delta_T > \Delta_{T_{11}}$ $\Delta_T > \Delta_{T_{12}}$	Analogously, variations of η_{14} and m_T using Lemma (2.3.5) negatively affect $\mathfrak{R}_0^T$.
$\Delta_T = 0.0894$	$\Delta_{T_{13}} = 0.0231$ $\Delta_{T_{14}} = 0.0909$	$\Delta_T > \Delta_{T_{13}}$ $\Delta_T < \Delta_{T_{14}}$	For l_T, η_{14} tending to unity and η_{11}, m_T tending to zero, the $\mathfrak{R}_0^T$ is negatively affected and in the opposite case it is not affected, using Lemma (2.3.6).

Table 2.4: *Study of the* $\mathfrak{R}_0^T$.

Figures (2.4a) and (2.4b) show the behavior of $\mathfrak{R}_0^T$ when we vary l_T and η_{14}. We can see that in this case, any variation of these parameters affects negatively the $\mathfrak{R}_0^T$ since the $\mathfrak{R}_0^T > 1$.

Figures (2.4c) and (2.4d) show the behavior of $\mathfrak{R}_0^T$ when we vary l_T and η_{11}. In this case, it is always greater than unity and presents the highest value of the whole study when l_T and η_{11} tend to zero. We recommend paying attention to the joint behavior of these parameters and their relationship with other parameters.

Figures (2.4e) and (2.4f) show the variation of the parameters η_{14} and m_T in $\mathfrak{R}_0^T$. The $\mathfrak{R}_0^T$ is always greater than unity, so it is evident that the epidemic in the submodel will persist.

We show that variations of the resistance and recovery parameters (in pairs) in this scenario negatively affect $\mathfrak{R}_0^T$ and in these cases $\mathfrak{R}_0^T$ is always greater than unity.

The following Table (2.5) shows the application of the Lemmas (2.3.10)-(2.3.13) to the scenario under study.

Value	Values	Inequalities	Results
$\Delta_H = 0.0076$	$\Delta_{H_1} = 0.0025$ $\Delta_{H_2} = 0.0178$ $\Delta_{H_3} = 0.0201$ $\Delta_{H_4} = 0.1745$	$\Delta_H > \Delta_{H_1}$ $\Delta_H < \Delta_{H_2}$ $\Delta_T < \Delta_{H_3}$ $\Delta_H < \Delta_{H_4}$	The variations of the parameters l_H and η_{15} result (2.3.10) do not negatively affect $\mathfrak{R}_0^H$ using the except when l_H and η_{15} tend to zero.
$\Delta_H = 0.0076$	$\Delta_{H_5} = 3.9350e-04$ $\Delta_{H_6} = 0.0047$ $\Delta_{H_7} = 0.0128$ $\Delta_{H_8} = 0.0251$	$\Delta_H > \Delta_{H_5}$ $\Delta_H > \Delta_{H_6}$ $\Delta_H < \Delta_{H_7}$ $\Delta_H < \Delta_{H_8}$	For the variations of l_H and η_{12} tending to zero and l_H tending to zero and η_{12} tending to unity negatively affect $\mathfrak{R}_0^H$ and other cases not affect $\mathfrak{R}_0^H$, using the Lemma (2.3.11).
$\Delta_H = 0.0076$	$\Delta_{H_9} = 1.0036e-04$ $\Delta_{H_{10}} = 0.0098$ $\Delta_{H_{11}} = 0.0105$ $\Delta_{H_{12}} = 0.0366$	$\Delta_H > \Delta_{H_9}$ $\Delta_H < \Delta_{H_{10}}$ $\Delta_H < \Delta_{H_{11}}$ $\Delta_H < \Delta_{H_{12}}$	The variations of η_{15} and m_H tending to zero affect $\mathfrak{R}_0^H$ and the other cases do not affect it negatively, using the Lemma (2.3.12).
$\Delta_H = 0.0076$	$\Delta_{H_{13}} = 0.0746$ $\Delta_{H_{14}} = 0.0168$	$\Delta_H < \Delta_{H_{13}}$ $\Delta_H < \Delta_{H_{14}}$	For l_H, η_{15} tending to zero and η_{12}, m_H tending to unity and the opposite case it is not affected the $\mathfrak{R}_0^H$ using (2.3.13).

Table 2.5: *Study of the* $\mathfrak{R}_0^H$.

For the variation of the parameters in their respective intervals, the $\mathfrak{R}_0^H$ is always less than unity, see Figures (2.5a)-(2.5f).

When we vary l_H and η_{12}, the worst results are obtained when they are tending to zero and when l_H tends to zero and η_{12} tends to unity, see Figures (2.5c) and (2.5d). We can verify the theoretical result presented in Lemma (2.3.11) applied to this scenario.

Figures (2.5e) and (2.5f) show the variation of η_{15} and m_H in $\mathfrak{R}_0^H$, in this case, we see that the negative influence is observed when the parameters tend to zero (theoretical result verified) but also the highest values are reached when η_{15} tends to zero and m_H tends to unity. We observed that the difference between Δ_H and $\Delta_{H_{10}}$ is smaller with respect to the combinations of the parameters that do not have a negative influence. We recommend to pay attention to this case because the system can be influenced by other parameters.

The following Table (2.6) shows the theoretical results (2.3.17)-(2.3.20) applied to this scenario.

Value	Values	Inequalities	Results
$\Delta_D = 0.0174$	$\Delta_{D_1} = 0.0039$ $\Delta_{D_2} = 0.0257$ $\Delta_{D_3} = 0.0359$ $\Delta_{D_4} = 0.2499$	$\Delta_D > \Delta_{D_1}$ $\Delta_D < \Delta_{D_2}$ $\Delta_D < \Delta_{D_3}$ $\Delta_D < \Delta_{D_4}$	The variation of l_D and η_{16} tend to zero negatively affects $\mathfrak{R}_0^D$ and the other cases does not affect, using the Lemma (2.3.17).
$\Delta_D = 0.0174$	$\Delta_{D_5} = 4.6227e-04$ $\Delta_{D_6} = 0.0059$ $\Delta_{D_7} = 0.0167$ $\Delta_{D_8} = 0.0329$	$\Delta_D > \Delta_{D_5}$ $\Delta_D > \Delta_{D_6}$ $\Delta_D > \Delta_{D_7}$ $\Delta_D < \Delta_{D_8}$	When l_D and η_{13} tend to unity it does not negatively affects $\mathfrak{R}_0^D$ and the other cases affect negatively to $\mathfrak{R}_0^D$, using the Lemma (2.3.18).
$\Delta_D = 0.0174$	$\Delta_{D_9} = 1.8483e-04$ $\Delta_{D_{10}} = 0.0185$ $\Delta_{D_{11}} = 0.0200$ $\Delta_{D_{12}} = 0.0695$	$\Delta_D > \Delta_{D_9}$ $\Delta_D < \Delta_{D_{10}}$ $\Delta_D < \Delta_{D_{11}}$ $\Delta_D < \Delta_{D_{12}}$	For η_{16} and m_D tending to zero, negatively affected to $\mathfrak{R}_0^D$ and in the other cases, it is not affected, using Lemma (2.3.19).
$\Delta_D = 0.0174$	$\Delta_{D_{13}} = 0.0981$ $\Delta_{D_{14}} = 0.0243$	$\Delta_D < \Delta_{D_{13}}$ $\Delta_D < \Delta_{D_{14}}$	For l_D and η_{16} tending to zero and η_{13} and m_D tending to unity and l_D and η_{16} tending to unity and η_{13}, m_D tending to zero, using (2.3.20) the $\mathfrak{R}_0^D$ is not affected.

Table 2.6: *Study of the* $\mathfrak{R}_0^D$.

The variation of the parameters l_D and η_{16}, the $\mathfrak{R}_0^D$ is always less than unity, see Figures (2.6a) and (2.6b).

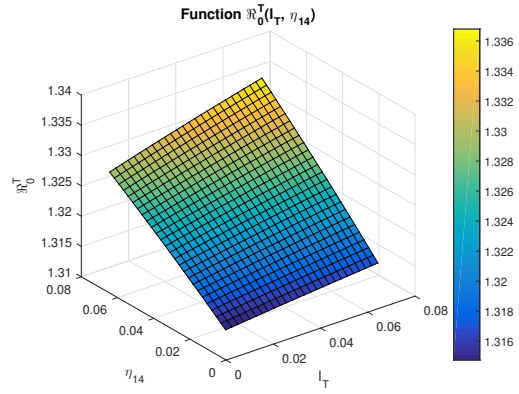
For the variation of l_D and η_{13}, we have that $\mathfrak{R}_0^D$ takes values greater and less than unity. When l_D and η_{16} tend to zero, the highest value of $\mathfrak{R}_0^D$ are achieved ($\Delta_D > \Delta_{D_5}$) and when l_D tends to zero and η_{16} tends to unity ($\Delta_D > \Delta_{D_6}$), verifying the theoretical results presented in the Table 2.6. When η_{13} tends to unity and η_{16} tends to zero, we find values for which $\mathfrak{R}_0^D$ is greater and less than unity so we must take into account the relationship with other parameters. We recommend to apply control strategies to the behavior of these parameters, see Figures (2.6c) and (2.6d).

When we vary η_{16} and m_D together, the $\mathfrak{R}_0^D$ always remains less than unity. The worst results are reached when η_{15} and m_D are tending to zero which is when these parameters according to the theoretical results ($\Delta_D > \Delta_{D_9}$) affect negatively $\mathfrak{R}_0$, see Figures (2.6e) and (2.6f).

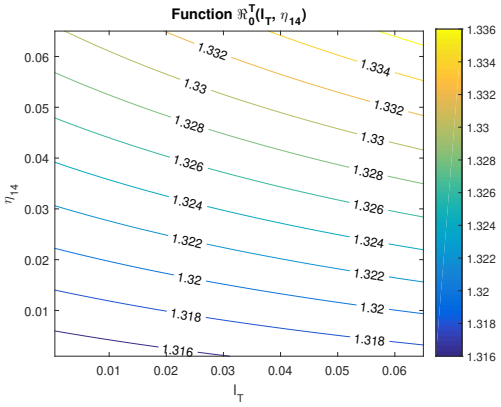
In the two-by-two variations in the different basic reproduction numbers the highest values were obtained for $\mathfrak{R}_0^T$ corresponding to the TB-Only submodel, as the general model has the basic reproduction number defined as $\mathfrak{R}_0 = \max\{\mathfrak{R}_0^T, \mathfrak{R}_0^H, \mathfrak{R}_0^D\}$ then, we can extend

the results to the general model (2.5).

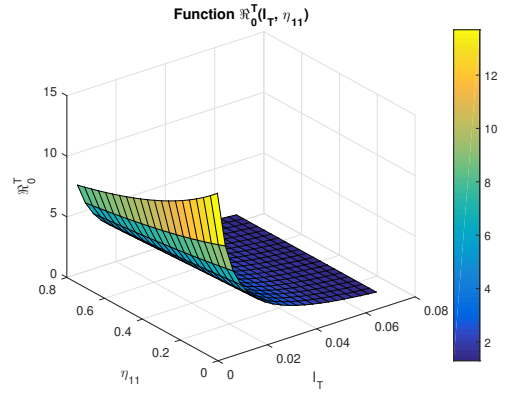
These results allow us to know how the variations of these parameters (resistance and recovery) affect the transmission of tuberculosis in the different submodels and general model, using the basic reproduction numbers.



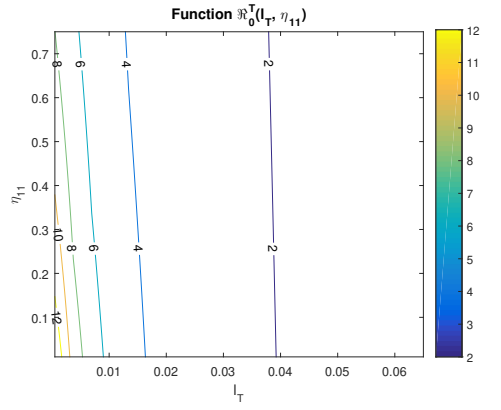
(a) *Graphic representation of* $\mathfrak{R}_0^T(l_T, \eta_{14})$



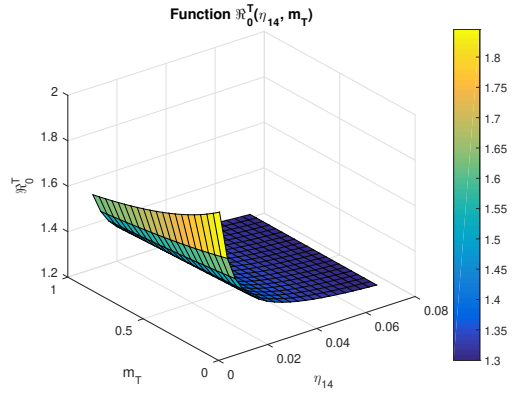
(b) *Contour lines* $\mathfrak{R}_0^T(l_T, \eta 14)$



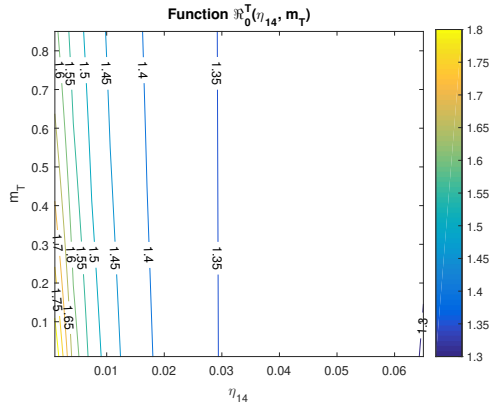
(c) *Graphic representation of* $\mathfrak{R}_0^T(l_T, \eta 11)$



(d) *Contour lines* $\mathfrak{R}_0^T(l_T, \eta_{11})$

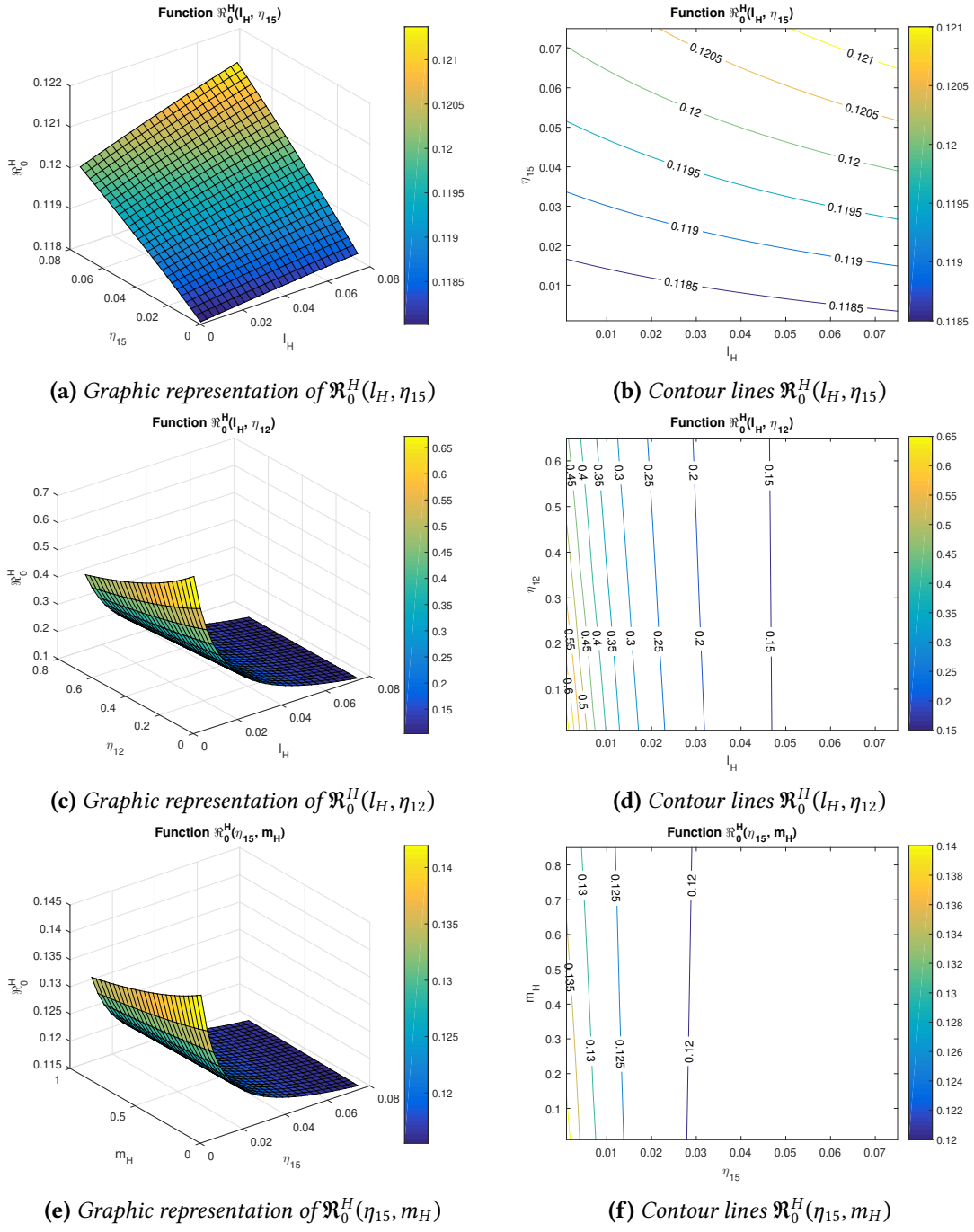


(e) *Graphic representation of* $\mathfrak{R}_0^T(\eta_{14}, m_T)$



(f) *Contour lines* $\mathfrak{R}_0^T(\eta_{14}, m_T)$

Figure 2.4: *Variations of the resistance and recovery parameters in* $\mathfrak{R}_0^T$*, for* $l_T \in [0.0005, 0.065]$, $\eta_{14} \in [0.001, 0.065]$, $\eta_{11} \in [0.01, 0.75]$ *and* $m_T \in [0.01, 0.85]$.



(a) *Graphic representation of* $\mathfrak{R}_0^H(l_H, \eta_{15})$

(b) *Contour lines* $\mathfrak{R}_0^H(l_H, \eta_{15})$

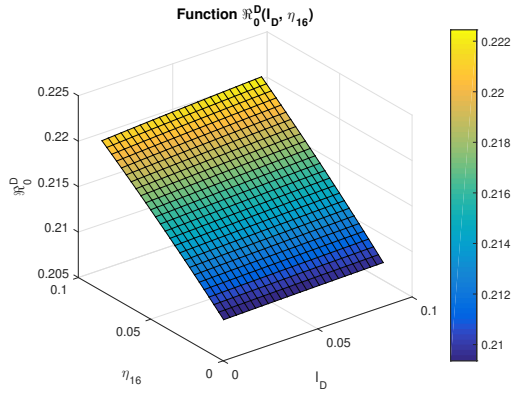
(c) *Graphic representation of* $\mathfrak{R}_0^H(l_H, \eta_{12})$

(d) *Contour lines* $\mathfrak{R}_0^H(l_H, \eta_{12})$

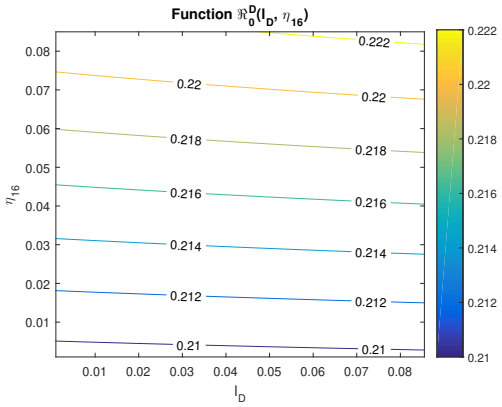
(e) *Graphic representation of* $\mathfrak{R}_0^H(\eta_{15}, m_H)$

(f) *Contour lines* $\mathfrak{R}_0^H(\eta_{15}, m_H)$

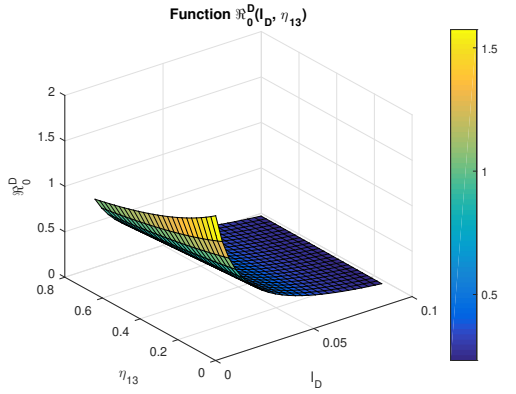
Figure 2.5: *Variations of the resistance and recovery parameters in* $\mathfrak{R}_0^H$*, for* $l_H \in [0.001, 0.075]$, $\eta_{15} \in [0.001, 0.075]$, $\eta_{12} \in [0.01, 0.65]$ *and* $m_H \in [0.01, 0.85]$.



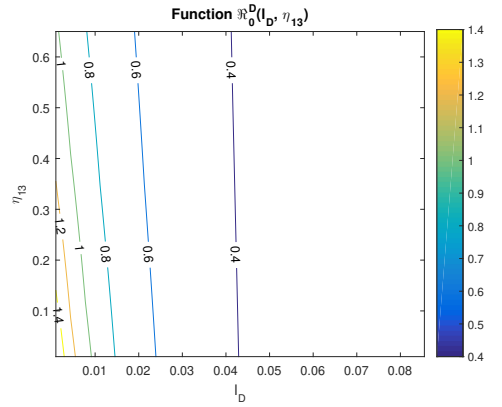
(a) *Graphic representation of* $\mathfrak{R}_0^H(l_D, \eta_{16})$



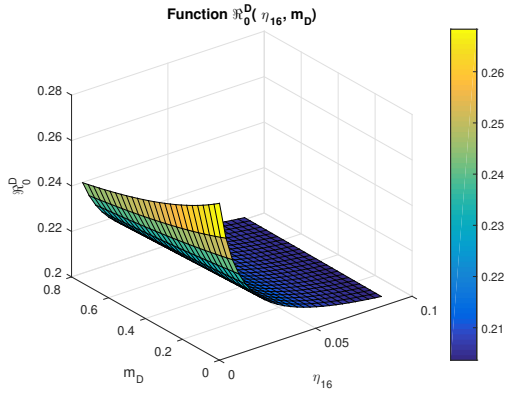
(b) *Contour lines* $\mathfrak{R}_0^H(l_D, \eta_{16})$



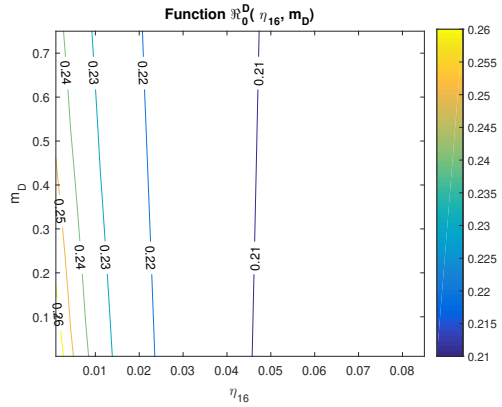
(c) *Graphic representation of* $\mathfrak{R}_0^H(l_D, \eta_{13})$



(d) *Contour lines* $\mathfrak{R}_0^H(l_D, \eta_{13})$



(e) *Graphic representation of* $\mathfrak{R}_0^H(\eta_{16}, m_D)$



(f) *Contour lines* $\mathfrak{R}_0^H(\eta_{16}, m_D)$

Figure 2.6: *Variations of the resistance and recovery parameters in* $\mathfrak{R}_0^D$*, for* $l_D \in [0.001, 0.0855]$*,* $\eta_{16} \in [0.001, 0.085]$*,* $\eta_{13} \in [0.01, 0.65]$ *and* $m_D \in [0.01, 0.75]$.

The Table (2.7) shows the sensitivity index of the parameters with respect to the basic reproduction number. They are calculated knowing that for the values of the simulations the $\mathfrak{R}_0 = \mathfrak{R}_0^T$. The inequality (2.136) is $1.3156 > 1$ so we have that β^* has a positive sensitivity index and the increase in its value causes an increase in the basic reproduction number.

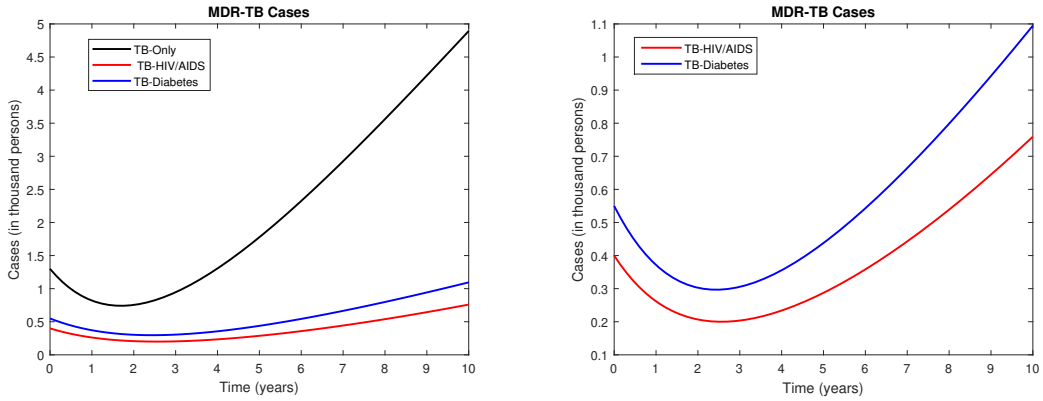
Parameter	Value
M_T	$+1$
α^*	$+1$
η	$+1$
β^*	$+0.0068$
l_T	$+0.0029$
η_{14}	$+0.0123$
η_{11}	-0.8664
m_T	-0.0378
η_{11}^*	$-7.4598e-4$

Table 2.7: *Sensitivity index of the parameters in the scenario under study.*

Now, we will present the behavior of the resistant and recovered, comparing the subpopulations for 10 years.

In the study of MDR-TB cases, we found that the highest number of cases was reported by the TB-Only subpopulation followed by the TB-Diabetes subpopulation, see Figures (2.7a) and (2.7b). This shows that diabetics are more prone to this type of resistance compared to HIV/AIDS. Here, we can mention the influence of antiretroviral treatment and medical follow-up on HIV-positive people because TB represents an opportunistic disease in this subpopulation.

An important fact is that when we compare the TB-Only and TB-HIV/AIDS subpopu-



(a) *Comparison of MDR-TB cases between subpopulations, time 10 years.*

(b) *Comparison of MDR-TB cases between HIV/AIDS and diabetes subpopulations, time 10 years.*

Figure 2.7: *Behavior of MDR-TB cases over time.*

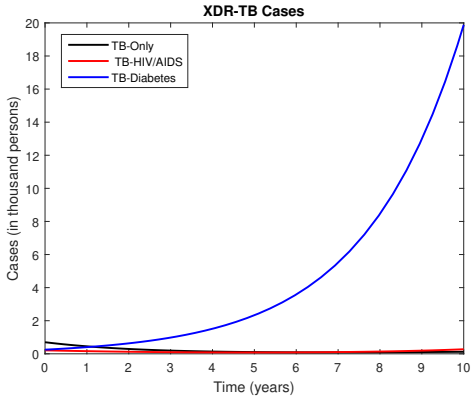
lations, despite the fact that TB-HIV/AIDS presented the lowest number of cases at the beginning of the study, at approximately 6 months, it surpasses TB-Only (which presents

the largest population), see Figure (2.8d). The XDR-TB in the TB-Only subpopulation, throughout the study, maintained a decreasing behavior. The TB-Diabetes subpopulation throughout the study maintained an increasing character in the number of cases. In practice, we recommend special attention to this subpopulation, as diabetic XDR-TB cases outnumber all resistant infected compartments. The TB-HIV/AIDS subpopulation initially has a decreasing number of cases but after approximately 5 years this situation is reversed. We recommend for this subpopulation to take advantage of the decrease in the number of cases at the beginning and to apply control strategies to avoid the growth in the number of cases.

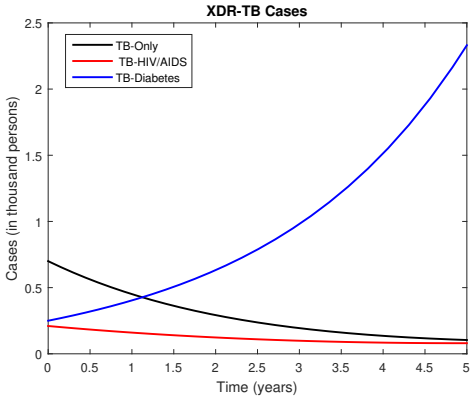
When, we study the compartments of infected by subpopulation, we obtain the following results:

- Drug-sensitive cases outnumber resistance cases except for TB-Diabetes subpopulation. In practice, we have that the epidemic has a greater behavior of being sensitive to treatment than resistant, see Figure (2.9).
- In the TB-Only and TB-HIV/AIDS subpopulations, MDR-TB cases outnumber XDR-TB cases throughout the study, see Figures (2.9a) and (2.9c). This implies that XDR-TB has a lower incidence in this subpopulation. Here, we can in particular note the influence of the follow-up of cases with TB-HIV/AIDS co-infection which among other things controls for non-adherence to treatment.
- In the TB-Diabetes subpopulation, MDR-TB initially outnumbered XDR-TB, but at approximately 1 study time, it began to outpace not only MDR-TB in this subpopulation but also all resistant compartments, see Figures (2.9) and (2.9f). This implies that XDR-TB has a strong incidence in the TB-Diabetes subpopulation.

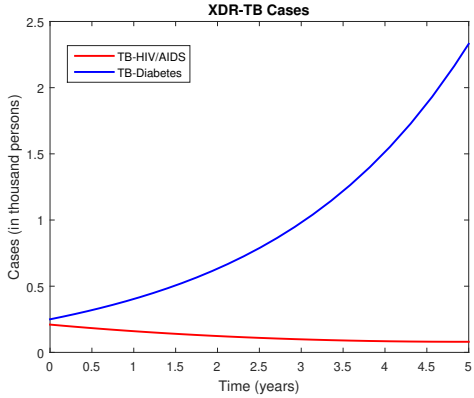
In the study of the recoveries, the highest number was in the TB-Only subpopulation, see Figure (2.10a). This was followed by the TB-Diabetes subpopulation, which outnumbered the TB-HIV/AIDS, see Figure (2.10b). In practice, although diabetics have a higher incidence of resistance, mainly to XDR-TB, they also have a higher number of recoveries. We recommend to control the resistance in this subpopulation to increase the number of recoveries.



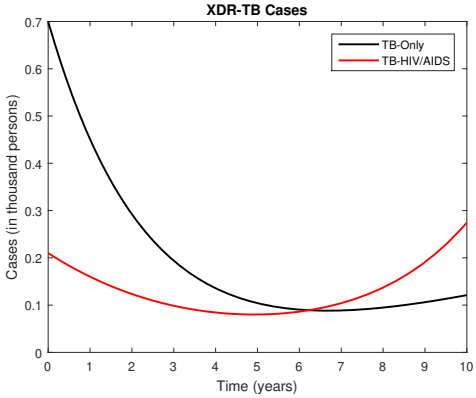
(a) *Comparison of XDR-TB cases between subpopulations, time 10 years.*



(b) *Comparison of XDR-TB cases between subpopulations, time 5 years.*

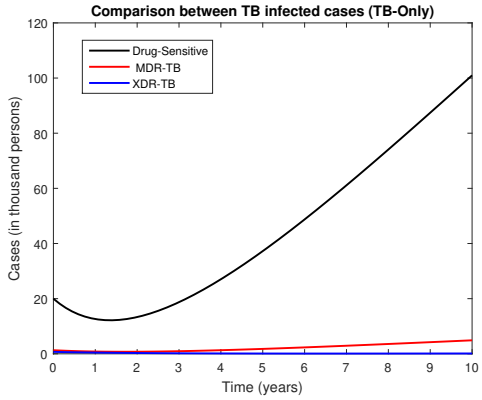


(c) *Comparison of XDR-TB cases between TB-HIV/AIDS and TB-Diabetes subpopulations, time 5 years.*

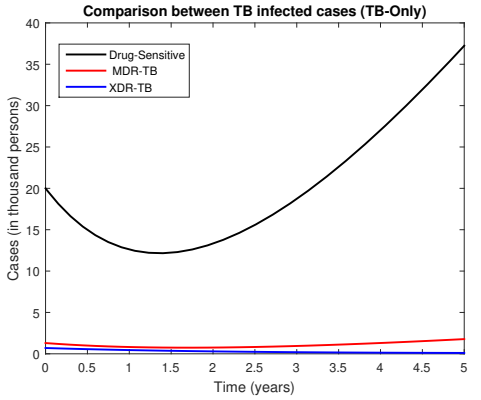


(d) *Comparison of XDR-TB cases between TB-Only and TB-HIV/AIDS subpopulations, time 10 years.*

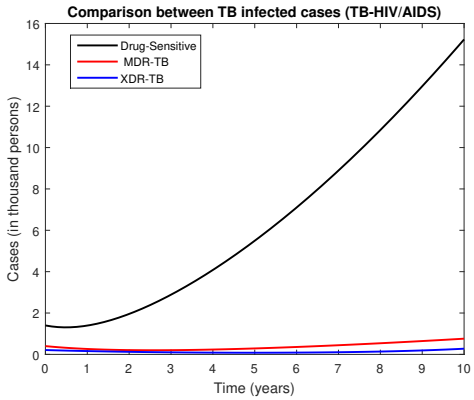
Figure 2.8: *Behavior of XDR-TB cases over time.*



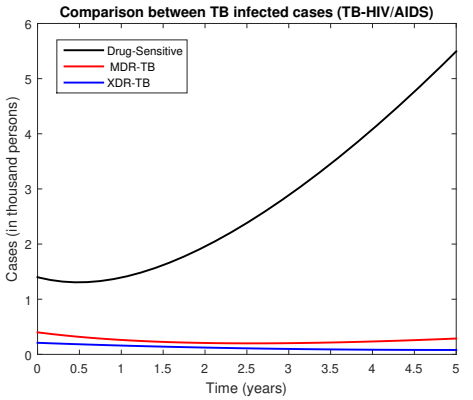
(a) *Comparison between the different types of infected in the TB-Only subpopulation, 10 years.*



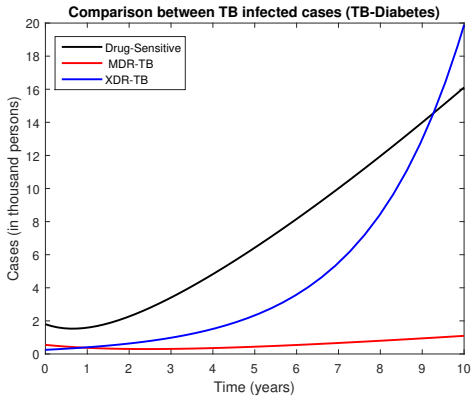
(b) *Comparison between the different types of infected in the TB-Only subpopulation, 5 years.*



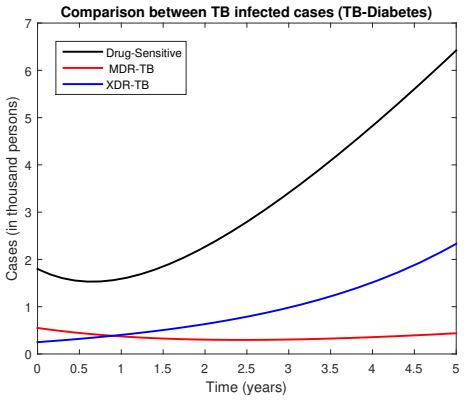
(c) *Comparison between the different types of infected in the TB-HIV/AIDS subpopulation, 10 years.*



(d) *Comparison between the different types of infected in the TB-HIV/AIDS subpopulation, 5 years.*

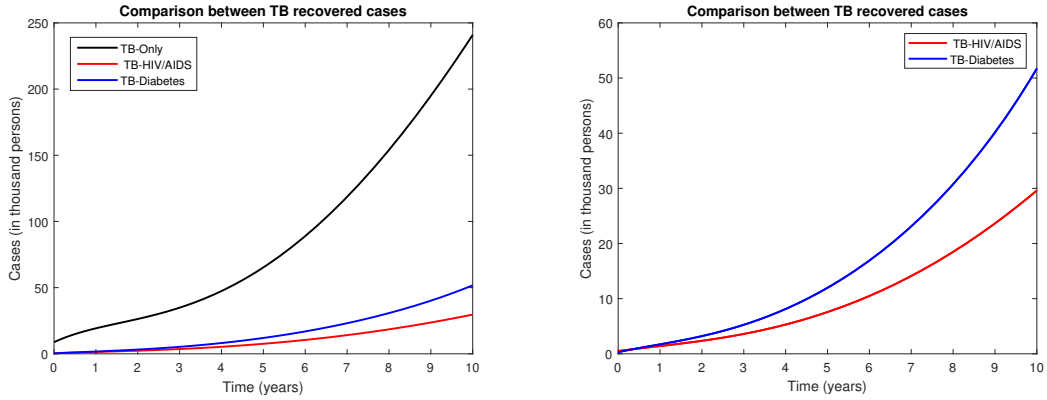


(e) *Comparison between the different types of infected in the TB-Diabetes subpopulation, 10 years.*



(f) *Comparison between the different types of infected in the TB-Diabetes subpopulation, 5 years.*

Figure 2.9: *Comparison of the infected over time.*



(a) *Comparison of recovered in the different subpopulations, 10 years.*

(b) *Comparison of recovered in the different subpopulations, 10 years.*

Figure 2.10: *Behavior of the recovered over time.*

2.6 Partial Conclusions

In this chapter:

- We proposed a new mathematical model for the study of resistance to treatment for tuberculosis in the presence of diabetes and HIV/AIDS. Our main objective is to evaluate the role of diabetes and HIV/AIDS in resistance to TB treatment.
- A mathematical and epidemiology analysis of the model has been presented.
- We computed the basic reproduction number of the model and obtained results that show its relationship with the resistance and recovery parameters.
- We found the sensitivity index of the parameters associated with the transmission, resistance, and recovery with respect to the basic reproduction number. We have that the sensitivity index for the recovered parameters are null or negative, this implies that it may not influence on the basic reproduction number or that its growth causes a decrease in the basic reproduction number.
- We validated our model with data and parameters from the bibliography, in an biologically feasible scenario. Among the results, we obtained that:
  - If we analyze the basic reproduction number with respect to the resistance parameters independently, we have that the basic reproduction number of the TB-Only submodel is greater than unity and for the other submodels it is less than unity. In this case, the basic reproduction number general ($\mathfrak{R}_0 = \max\{\mathfrak{R}_0^T, \mathfrak{R}_0^H, \mathfrak{R}_0^D\}$) is greater than unity and the epidemic will grow and not disappear, see Figure (2.3). If we analyze the $\mathfrak{R}_0$ with respect to the resistance parameters together it is greater than unity, see Figures (2.4a-2.4b). This is evidence of the need to apply control strategies in all subpopulations.
  - The MDR-TB cases in all subpopulations have an analogous asymptotic behavior where they initially decrease and then increase, see Figure (2.7). Given this situation, it is recommended to apply control measures from the beginning in

these compartments to avoid future growth in the number of cases.

– The XDR-TB cases in the TB-Only subpopulation decreased throughout the study. The number of XDR-TB cases in HIV/AIDS subpopulation, initially decreases and then tends to increase. Attention needs to be paid to the TB-Diabetes subpopulation because XDR-TB cases outnumber all resistant compartments, see Figure (2.8). We propose to pay attention to the TB-Diabetes subpopulation because XDR-TB cases outnumber all resistant compartments. Given the results obtained, we propose to monitor the entry into the compartments of the diabetic subpopulation, due to the growth of XDR-TB cases, using strategies such as increasing specialized medical consultations to achieve permanence in treatment, and diabetes testing in the different subpopulations.

Chapter 3

Optimal Control Strategy for the Effectiveness of TB Treatment

3.1 Introduction

Optimal control theory has been used to study the transmission dynamics of TB in [67, 108, 64, 106]. For example, Kim et al. [67] proposed optimal control strategies to reduce the number of patients at high risk for latent and infectious tuberculosis with minimal intervention costs. Numerical simulation with data from the Philippines showed that distancing control is the most efficient control strategy when a single intervention is performed. Jung et al. [64] applied optimal control theory to a two-strain tuberculosis model with aim to reduce the latent and infectious groups with resistant-strain tuberculosis, where the controls are two types of treatments. Bowong [31] proposed an optimal control problem for the transmission dynamics of tuberculosis with controls as a term on chemoprophylaxis to reduce the number of individuals with active TB. Silva et al. [106] incorporated time delays on the diagnosis and beginning of treatment of TB active in a TB model and studied the optimal control problem where controls represent the effort on early detection and the application of chemotherapy or post-exposure vaccine to persistent latent cases. Moualeu et al. [79] proposed an optimal control problem based on the education, diagnosis campaign, and chemoprophylaxis of latent infected with the aim of minimizing the amount of money the Cameroonian government spends on TB control. Silva and Torres [108] applied optimal control theory to a tuberculosis model with the objective of minimizing the cost of interventions, considering reinfection and post-exposure interventions. Lambura et al. [70] presented a mathematical model for the transmission and control of helminth-TB co-interaction, and showed that sanitation is the most effective strategy to control helminth-Mtb co-infection. Liu et al. [73] proposed an optimal control problem to minimize the total number of infectious individuals with the lowest cost and suggested an optimal strategy aiming at exposed and infected populations.

The problems of HIV/AIDS control and TB-HIV/AIDS co-infection with different techniques have become a problem that has been extensively studied by researchers in recent years. For example, Ngina et al. [85] applied optimal control theory to investigate the key roles played by the various HIV treatment strategies and showed that an optimal

controlled treatment strategy would ensure a significant reduction in viral load and HIV transmission in the population and that the protease inhibitor plays a key role in virus suppression. Marsudi et al. [20] incorporated in an HIV model, human education campaign, screening and treatment of infected humans as controls with the goal of minimizing the infected population and slow down the epidemic outbreak of HIV. Tahir et al. [113] extended a mathematical model of TB-HIV/AIDS co-infection to study the optimal control problem, and defined different schemes to minimize and control infection in any population. Boukhouima et al. [6] proposed a fractional epidemic model with a general incidence in order to describe the dynamics of HIV-AIDS infection and formulated a fractional optimal control system to minimize the spread of the disease into the population. Qin et al. [101] presented and solved the optimal control problem for the age-structured HIV model and found the necessary condition for minimization of the viral level and the cost of drug treatment. Agusto and Adekunle [4] used optimal control theory and demonstrated that the application of the combined strategy of prevention of treatment failure in drug-sensitive TB infected individuals and treatment of individuals with drug-resistant TB is the most cost-effective control strategy. Silva and Torres [107] formulated a population model for TB-HIV/AIDS co-infection that considers antiretroviral therapy for HIV infection and treatments for latent and active TB, and used the theory of optimal control to reduce the number of individuals with active TB and AIDS. Awoke and Kassa [27] presented a mathematical model for transmission of TB-HIV/AIDS co-infection that incorporates the change in the prevalence in the population and treatment, proposed optimal control problem to minimize the aggregate cost of the infections and the control efforts, and showed that the treatment control is more effective than the preventive controls.

The study of diabetes control and its relationship to TB has increased in recent decades. For example, Kouidere et al. [26] proposed conducting awareness campaigns based on the severity of complications of diabetes, the importance of a balanced lifestyle, and the correct use of treatment as an optimal control strategy. Chávez et al. [39] formulated a control system for optimal insulin delivery in type I diabetic patients using the linear and quadratic control problem theory. The linear model is used for the glucose-insulin dynamics and the non-linear for the evaluation of the regulatory controller. Kouidere et al. [8] proposed to study an optimal control with delay in state and control variables in the model presented for the authors in [7] where the delay represents the measuring of the extent of interaction with the means of treatment or awareness campaigns.

The aim of this chapter is to present and solve the optimal control problem to reduce TB treatment resistance, taking into account the influence of HIV/AIDS and diabetes.

3.2 Model with Controls, Optimal Control Problem and Analysis

Definition of Controls and its Policy

Our aim with the help of the optimal control theory is to decrease the total number of patients with MDR-TB and XDR-TB during a period of time $[t_0, t_f]$. The control strategy is decomposed in four controls u_0, u_{11}, u_{12} and u_{13} defined as follows:

- $u_0(t)$ (control over reinfection/reactivation)- this refers to preparing patients recovering from TB to avoid possible reinfection/reactivation of the bacteria, scheduling medical consultations and lab tests periodically. Control the entry of new genotypes of TB in the population. Also, to inform patients on how to maintain an active immune system, particularly immunocompromised patients (HIV/AIDS) with adherence to antiretroviral treatment, stimulation of a good (healthy) diet, physical exercise, among others.

- $u_{11}(t)$ (control for TB-Only)- this includes personal respiratory protection, educational programs for public health, and activities that ensure treatment completion to reduce relapse following treatment. Patients receiving treatment for MDR-TB should be monitored to ensure the completion of the treatment. Otherwise, TB infection may become resistant. As part of this control, it is needed to check blood glucose levels and make HIV tests to determine if the person is diabetic and/or HIV positive.

- $u_{12}(t)$ (control for HIV/AIDS cases)- the control will be based on clinical follow-up (we assume all cases are diagnosed), and we consider all cases are using antiretroviral therapy and have a follow-up on their CD4 count and viral load. In particular, from the beginning of treatment for TB, the return of the patient should occur in up to 15 days. Monthly consultations until the end of the TB treatment. Consultations by other members of the multi-professional team, with the objective of promoting treatment adherence and identifying interoccurrences that may interfere with the correct use of TB drugs and antiretrovirals. Another important element is to check blood glucose levels and determine if the person is diabetic.

- $u_{13}(t)$ (control for diabetics cases)- the control is focused on monitoring glycemic parameters throughout TB treatment, and promoting adherence to treatment, identifying interoccurrences that may interfere with the efficacy of TB treatment. Another important factor is to make HIV tests to control the exits of this subpopulation.

In particular, $u_{11}(t)$ is the control in the entrance to compartments I_{T_2}, I_{T_3}, $u_{12}(t)$ is the control in the entrance to compartments I_{H_2}, I_{H_3}, $u_{13}(t)$ is the control in the entrance to compartment I_{D_2}, I_{D_3}, $u_0(t)$ is the control in the entrance to compartments E_T, E_H and E_D compartments by reinfection/reactivation and $(1-u_0)$, $(1-u_{11})$, $(1-u_{12})$ and $(1-u_{13})$ represent the effort that prevents failure of the treatment. System (3.1) shows the incorporation of the controls in the compartments of model (2.5). The Figure (3.1) shows the control dynamics.

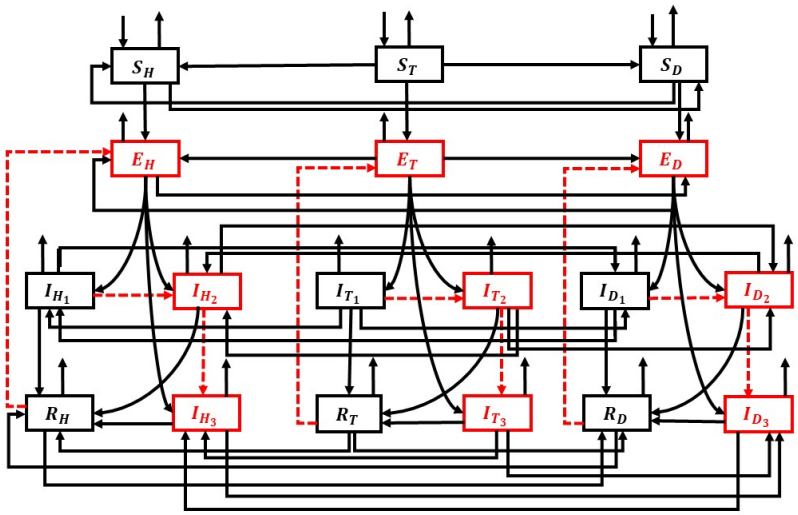


Figure 3.1: *Schematic representation of model with controls, the arrows (discontinued) and boxes red represents the inputs and compartments to be controlled.*

$$\frac{dS_T}{dt} = f_1 = M_T - (\mu + \alpha_H + \alpha_D + \lambda)S_T,$$

$$\frac{dS_H}{dt} = f_2 = M_H + \alpha_H(S_T + S_D) - (\alpha_{HD} + \mu + \mu_H + \omega_H\lambda)S_H,$$

$$\frac{dS_D}{dt} = f_3 = M_D + \alpha_{HD}S_H + \alpha_D S_T - (\alpha_H + \mu + \omega_D\lambda + \mu_D)S_D,$$

$$\frac{dE_T}{dt} = f_4 = \lambda(S_T + (1-u_0)\beta_1^{'}R_T) - (\alpha_H + \alpha_D + \mu + \eta)E_T,$$

$$\frac{dE_H}{dt} = f_5 = \omega_H\lambda(S_H + (1-u_0)\beta_1^{'}R_H) + \alpha_H(E_T + E_D) - (\epsilon_H^*\eta + \mu + \mu_H + \alpha_{HD})E_H,$$

$$\frac{dE_D}{dt} = f_6 = \omega_D\lambda(S_D + (1-u_0)\beta_1^{'}R_D) + \alpha_{HD}E_H + \alpha_D E_T - (\alpha_H + \epsilon_D^*\eta + \mu + \mu_D)E_D,$$

$$\frac{dI_{T_1}}{dt} = f_7 = (1-\beta^*)\eta E_T - ((1-u_{11})l_T + t_H\alpha_H + t_D\alpha_D + \mu + d_T + \eta_{11})I_{T_1},$$

$$\frac{dI_{T_2}}{dt} = f_8 = (1-p_T)\beta^*\eta E_T + (1-u_{11})l_T I_{T_1} - (t_H\alpha_H + t_D\alpha_D + m_T + \mu + t_T^{'}d_T + (1-u_{11})\eta_{14})I_{T_2},$$

$$\frac{dI_{H_1}}{dt} = f_9 = t_H\alpha_H(I_{T_1} + I_{D_1}) + (1-\beta^*)\epsilon_H^*\eta E_H - ((1-u_{12})l_H + \mu + \mu_H + d_{TH} + \eta_{12} + t_{HD}\alpha_{HD})I_{H_1},$$

$$\frac{dI_{H_2}}{dt} = f_{10} = t_H\alpha_H(I_{T_2} + I_{D_2}) + (1-p_H)\beta^*\epsilon_H^*\eta E_H + (1-u_{12})l_H I_{H_1} - (m_H + \mu + \mu_H + t_H^{'}d_{TH} + (1-u_{12})\eta_{15} + t_{HD}\alpha_{HD})I_{H_2},$$

$$\frac{dI_{D_1}}{dt} = f_{11} = t_D\alpha_D I_{T_1} + t_{HD}\alpha_{HD}I_{H_1} + (1-\beta^*)\epsilon_D^*\eta E_D - ((1-u_{13})l_D + t_H\alpha_H + \mu + d_{TD} + \eta_{13} + \mu_D)I_{D_1},$$

$$\frac{dI_{D_2}}{dt} = f_{12} = t_D\alpha_D I_{T_2} + t_{HD}\alpha_{HD}I_{H_2} + (1-p_D)\epsilon_D^*\beta^*\eta E_D + (1-u_{13})l_D I_{D_1} - (m_D + t_H\alpha_H + \mu + t_D^{'}d_{TD} + (1-u_{13})\eta_{16} + \mu_D)I_{D_2},$$

$$
\begin{aligned}
\frac{dI_{T_3}}{dt} &= f_{13} = p_T\beta^*\eta E_T + (1-u_{11})\eta_{14}I_{T_2} - (\eta^*_{11} + t_H\alpha_H + t_D\alpha_D + \mu + t^*_T d_T)I_{T_3},\\
\frac{dI_{H_3}}{dt} &= f_{14} = p_H\beta^*\epsilon^*_H\eta E_H + (1-u_{12})\eta_{15}I_{H_2} + t_H\alpha_H(I_{T_3} + I_{D_3}) - (\eta^*_{12} + t_{HD}\alpha_{HD} + \mu + \mu_H + t^*_H d_{TH})I_{H_3},\\
\frac{dI_{D_3}}{dt} &= f_{15} = p_D\beta^*\epsilon^*_D\eta E_D + (1-u_{13})\eta_{16}I_{D_2} + t_{HD}\alpha_{HD}I_{H_3} + t_D\alpha_D I_{T_3} - (t_H\alpha_H + \eta^*_{13} + \mu + \mu_D + t^*_D d_{TD})I_{D_3},\\
\frac{dR_T}{dt} &= f_{16} = m_T I_{T_2} + \eta_{11}I_{T_1} + \eta^*_{11}I_{T_3} - (\alpha_H + \alpha_D + \mu + (1-u_0)\beta_1'\lambda)R_T,\\
\frac{dR_H}{dt} &= f_{17} = m_H I_{H_2} + \eta_{12}I_{H_1} + \eta^*_{12}I_{H_3} + \alpha_H(R_T + R_D) - (\alpha_{HD} + \mu + \mu_H + (1-u_0)\beta_1'\omega_H\lambda)R_H,\\
\frac{dR_D}{dt} &= f_{18} = m_D I_{D_2} + \eta_{13}I_{D_1} + \eta^*_{13}I_{D_3} + \alpha_D R_T + \alpha_{HD}R_H - (\alpha_H + \mu + \mu_D + (1-u_0)\beta_1'\omega_D\lambda)R_D.
\end{aligned}
\tag{3.1}
$$

Optimal Control Problem and its Analysis

Our objective functional to be minimized is

$$
\begin{aligned}
J(u_0,u_{11},u_{12},u_{13}) = \int_{t_0}^{t_f} &(E_T(t)+E_H(t)+E_D(t)) + (I_{T_2}(t)+I_{H_2}(t)+I_{D_2}(t)) + (I_{T_3}(t)+I_{H_3}(t)+I_{D_3}(t))\\
&+ \frac{1}{2}\left(B_0u_0^2(t) + (B_1+B_4)u_{11}^2(t) + (B_2+B_5)u_{12}^2(t) + (B_3+B_6)u_{13}^2(t)\right)dt.
\end{aligned}
$$

The structure of our functional is consistent with recent works (see [67, 108, 64, 106, 113, 4, 57]).
The coefficients $B_m, m = 0, 1, ..., 6$ represent the constant weight associated with the relative costs of implementing the respective control strategies on a finite time horizon $[t_0, t_f]$ (where the initial time is $t_0 = 0$ and the final time is $t_f = 10$ in years) and consists in the cost induced by the efforts of the four different types of controls. The B_1, B_2 and B_3 are associated with the implementation of control on the MDR-TB and B_4, B_5 and B_6 to the XDR-TB. Given the characteristics of resistance to tuberculosis and its treatment, which in some cases may include hospitalization, high drug costs, the use of other drugs to stimulate the immune system, among others, let's assume that $B_1 < B_4$, $B_2 < B_5$ and $B_3 < B_6$ and these constants cannot be neither zeros nor very large (realistic values). The cost involved in the control about the compartments I_{T_2}, I_{H_2} and I_{D_2} is taken as $\int_{t_0}^{t_f}\frac{B_1u_{11}^2}{2}$, $\int_{t_0}^{t_f}\frac{B_2u_{12}^2}{2}$, $\int_{t_0}^{t_f}\frac{B_3u_{13}^2}{2}$, for I_{T_3}, I_{H_3}, I_{D_3} are $\int_{t_0}^{t_f}\frac{B_4u_{11}^2}{2}$, $\int_{t_0}^{t_f}\frac{B_5u_{12}^2}{2}$, $\int_{t_0}^{t_f}\frac{B_6u_{13}^2}{2}$, for E_T, E_H and E_D are $\int_{t_0}^{t_f}\frac{B_0u_0^2}{2}$. We seek to find the optimal controls u_0^*, u_{11}^*, u_{12}^* and u_{13}^* that satisfy

$$
J(u_0^*,u_{11}^*,u_{12}^*,u_{13}^*) = \min_{U_{ad}} J(u_0,u_{11},u_{12},u_{13}),
\tag{3.2}
$$

where $U_{ad} = \{(u_0,u_{11},u_{12},u_{13}) |\ u_0,u_{11},u_{12},u_{13},$ Lebesgue measurable, $0 \le u_k \le 1,\ k = 0,11,12,13,\ \forall t \in [t_0,t_f]\}$.

The necessary and sufficient conditions of optimal control

We will study the sufficient conditions for the existence of an optimal control for our control system using the conditions in Theorem (4.1) and its corresponding Corollary in

[59]. After that, we will characterize the optimal control functions by using Pontryagin's Maximum Principle and then we derive the necessary conditions for our control problem. We have that solutions of the control system are bounded and non-negative for finite time interval in the biologically feasible region. These results are important to establish the existence of an optimal control.

We denote the vector of states $\vec{x} = [S_T, S_H, S_D, E_T, E_H, E_D, I_{T_1}, I_{T_2}, I_{H_1}, I_{H_2}, I_{D_1}, I_{D_2}, I_{T_3}, I_{H_3}, I_{D_3}, R_T, R_H, R_D]^T$ and the controls vector $\vec{u} = [u_0, u_{11}, u_{12}, u_{13}]^T$.

Theorem 3.2.1. *There is an optimal control $u^* = (u_0^*, u_{11}^*, u_{12}^*, u_{13}^*)$ to problem*

$$\min J(u_0, u_{11}, u_{12}, u_{13}) \quad \textit{subject to model (2.5) with controls}$$

where

$$u^* \in U_{ad}.$$

Proof. We use the requirements of Theorem (4.1) and Corollary (4.1) in [59] to prove the Theorem (3.2.1). Let $l(t, \vec{x}, \vec{u})$ as the right-hand of (2.5) with controls. We will show that the following requirements are satisfied:

I. l is of class C^1 and there is a constant C such that
$|l(t, 0, 0)| \leq C, \quad |l_x(t, \vec{x}, \vec{u})| \leq C(1 + |\vec{u}|), \quad |l_u(t, \vec{x}, \vec{u})| \leq C.$

II. The admissible set $\mathbb{F}$ of all solutions to system (2.5) with controls (3.1) in U_{ad} is non empty;

III. $l(t, \vec{x}, \vec{u}) = a_1(t, \vec{x}) + a_2(t, \vec{x})\vec{u}$;

IV. The control set $U = [0, 1] \times [0, 1] \times [0, 1]$ is closed, convex and compact;

V. The integrand of the objective functional is convex in U.

We can write system (2.5) with controls as

$$l(t, \vec{x}, \vec{u}) = \begin{pmatrix} M_T - (\mu + \alpha_H + \alpha_D + \lambda)S_T \\ M_H + \alpha_H(S_T + S_D) - (\alpha_{HD} + \mu + \mu_H + \omega_H\lambda)S_H \\ M_D + \alpha_{HD}S_H + \alpha_D S_T - (\alpha_H + \mu + \mu_D + \omega_D\lambda)S_D \\ \lambda(S_T + (1-u_0)\beta_1' R_T) - (\alpha_H + \alpha_D + \mu + \eta)E_T \\ \omega_H\lambda(S_H + (1-u_0)\beta_1' R_H) + \alpha_H(E_T + E_D) - (\epsilon_H^*\eta + \mu + \mu_H + \alpha_{HD})E_H \\ \omega_D\lambda(S_D + (1-u_0)\beta_1' R_D) + \alpha_{HD}E_H + \alpha_D E_T - (\alpha_H + \epsilon_D^*\eta + \mu + \mu_D)E_D \\ (1-\beta^*)\eta E_T - ((1-u_{11})l_T + t_H\alpha_H + t_D\alpha_D + \mu + d_T + \eta_{11})I_{T_1} \\ (1-p_T)\beta^*\eta E_T + (1-u_{11})l_T I_{T_1} - (t_H\alpha_H + t_D\alpha_D + m_T + \mu + t_T' d_T + (1-u_{11})\eta_{14})I_{T_2} \\ t_H\alpha_H(I_{T_1} + I_{D_1}) + (1-\beta^*)\epsilon_H^*\eta E_H - ((1-u_{12})l_H + \mu + \mu_H + d_{TH} + \eta_{12} + t_{HD}\alpha_{HD})I_{H_1} \\ t_H\alpha_H(I_{T_2} + I_{D_2}) + (1-p_H)\epsilon_H^*\beta^*\eta E_H + (1-u_{12})l_H I_{H_1} - (m_H + \mu + \mu_H + t_H' d_{TH} + (1-u_{12})\eta_{15} + t_{HD}\alpha_{HD})I_{H_2} \\ t_D\alpha_D I_{T_1} + t_{HD}\alpha_{HD}I_{H_1} + (1-\beta^*)\epsilon_D^*\eta E_D - ((1-u_{13})l_D + t_H\alpha_H + \mu + \mu_D + d_{TD} + \eta_{13})I_{D_1} \\ t_D\alpha_D I_{T_2} + t_{HD}\alpha_{HD}I_{H_2} + (1-p_D)\epsilon_D^*\beta^*\eta E_D + (1-u_{13})l_D I_{D_1} - (m_D + t_H\alpha_H + \mu + \mu_D + t_D' d_{TD} + (1-u_{13})\eta_{16})I_{D_2} \\ p_T\eta E_T + (1-u_{11})\eta_{14}I_{T_2} - (\eta_{11}^* + t_H\alpha_H + t_D\alpha_D + \mu + t_T^* d_T)I_{T_3} \\ p_H\epsilon_H^*\eta E_H + (1-u_{12})\eta_{15}I_{H_2} + t_H\alpha_H(I_{T_3} + I_{D_3}) - (\eta_{12}^* + t_{HD}\alpha_{HD} + \mu + \mu_H + t_H^* d_{TH})I_{H_3} \\ p_D\epsilon_D^*\eta E_D + (1-u_{13})\eta_{16}I_{D_2} + t_{HD}\alpha_{HD}I_{H_3} + t_D\alpha_D I_{T_3} - (t_H\alpha_H + \eta_{13}^* + \mu + \mu_D + t_D^* d_{TD})I_{D_3} \\ m_T I_{T_2} + \eta_{11}I_{T_1} + \eta_{11}^* I_{T_3} - (\alpha_H + \alpha_D + \mu + (1-u_0)\beta_1'\lambda)R_T \\ m_H I_{H_2} + \eta_{12}I_{H_1} + \eta_{12}^* I_{H_3} + \alpha_H(R_T + R_D) - (\alpha_{HD} + \mu + \mu_H + (1-u_0)\beta_1'\omega_H\lambda)R_H \\ m_D I_{D_2} + \eta_{13}I_{D_1} + \eta_{13}^* I_{D_3} + \alpha_H R_T + \alpha_{HD}R_H - (\alpha_H + \mu + \mu_D + (1-u_0)\beta_1'\omega_D\lambda)R_D \end{pmatrix}.$$

Then, we have that $l(t, \vec{x}, \vec{u})$ is of class C^1 by the model construction. Let's

$$|l_u(t,\vec{x},\vec{u})| = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ -\beta_1^{'}\lambda R_T & 0 & 0 & 0 \\ -\beta_1^{'}\omega_H\lambda R_H & 0 & 0 & 0 \\ -\beta_1^{'}\omega_D\lambda R_D & 0 & 0 & 0 \\ 0 & l_T I_{T_1} & 0 & 0 \\ 0 & -l_T I_{T_1} + \eta_{14} I_{T_2} & 0 & 0 \\ 0 & 0 & l_H I_{H_1} & 0 \\ 0 & 0 & -l_H I_{H_1} + \eta_{15} I_{H_2} & 0 \\ 0 & 0 & 0 & l_D I_{D_1} \\ 0 & 0 & 0 & -l_D I_{D_1} + \eta_{16} I_{D_2} \\ 0 & -\eta_{14} I_{T_2} & 0 & 0 \\ 0 & 0 & -\eta_{15} I_{H_2} & 0 \\ 0 & 0 & 0 & -\eta_{16} I_{D_2} \\ \beta_1^{'}\lambda R_T & 0 & 0 & 0 \\ \beta_1^{'}\omega_H\lambda R_H & 0 & 0 & 0 \\ \beta_1^{'}\omega_D\lambda R_D & 0 & 0 & 0 \end{pmatrix},$$

$$l_x(t,\vec{x},\vec{u}) = [\mathbf{A} \mid \mathbf{B}], \quad \text{where}$$

$$
\mathbf{A} = \begin{pmatrix}
-k_{10} & 0 & 0 & 0 & 0 & 0 & -c_1 & -c_1 & -\epsilon_H c_1 \\
\alpha_D & -k_{20} & \alpha_D & 0 & 0 & 0 & -c_2 & -c_2 & -\epsilon_H c_2 \\
\alpha_H & \alpha_{HD} & -k_{30} & 0 & 0 & 0 & -c_3 & -c_3 & -\epsilon_H c_3 \\
\lambda & 0 & 0 & -k_{11} & 0 & 0 & c_4 & c_4 & \epsilon_H c_4 \\
0 & \omega_H\lambda & 0 & \alpha_D & -k_{21} & \alpha_D & c_5 & c_5 & \epsilon_H c_5 \\
0 & 0 & \omega_D\lambda & \alpha_H & \alpha_{HD} & -k_{31} & c_6 & c_6 & \epsilon_H c_6 \\
0 & 0 & 0 & (1-\beta^*)\eta & 0 & 0 & -k_{12}^c & 0 & 0 \\
0 & 0 & 0 & (1-p_T)\beta^*\eta & 0 & 0 & (1-u_{11})l_T & -k_{13}^c & 0 \\
0 & 0 & 0 & 0 & (1-\beta^*)\epsilon_H^*\eta & 0 & t_H\alpha_H & 0 & t_H\alpha_H \\
0 & 0 & 0 & 0 & 0 & (1-\beta^*)\epsilon_D^*\eta & 0 & 0 & t_H\alpha_H \\
0 & 0 & 0 & 0 & 0 & (1-p_D)\epsilon_D^*\beta^*\eta & 0 & t_H\alpha_H & 0 \\
0 & 0 & 0 & p_T\beta^*\eta & 0 & 0 & 0 & (1-u_{11})\eta_{14} & 0 \\
0 & 0 & 0 & 0 & p_H\beta^*\epsilon_H^*\eta & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & p_D\beta^*\epsilon_D^*\eta & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & \eta_{11}-(c_4-c_1) & M_T-(c_4-c_1) & -\epsilon_H(c_4-c_1) \\
0 & 0 & 0 & 0 & 0 & 0 & -(c_5-c_2) & -(c_5-c_2) & \eta_{12}-\epsilon_H(c_5-c_2) \\
0 & 0 & 0 & 0 & 0 & 0 & -(c_6-c_3) & -(c_6-c_3) & -\epsilon_H(c_6-c_3)
\end{pmatrix}
\begin{matrix} \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \end{matrix}
\begin{pmatrix}
-\epsilon_H c_1 \\
-\epsilon_H c_2 \\
-\epsilon_H c_3 \\
\epsilon_H c_4 \\
\epsilon_H c_5 \\
\epsilon_H c_6 \\
0 \\
0 \\
-k_{23}^c \\
0 \\
t_{HD}\alpha_{HD} \\
0 \\
(1-u_{12})\eta_{15} \\
0 \\
-\epsilon_H(c_4-c_1) \\
m_H-\epsilon_H(c_5-c_2) \\
-\epsilon_H(c_6-c_3)
\end{pmatrix},
$$

$$
\mathbf{B} = \begin{pmatrix}
-\epsilon_D c_1 & -\epsilon_D c_1 & -c_1 & -\epsilon_H c_1 & -\epsilon_D c_1 & 0 & 0 & 0 \\
-\epsilon_D c_2 & -\epsilon_D c_2 & -c_2 & -\epsilon_H c_2 & -\epsilon_D c_2 & 0 & 0 & 0 \\
-\epsilon_D c_3 & -\epsilon_D c_3 & -c_3 & -\epsilon_H c_3 & -\epsilon_D c_3 & 0 & 0 & 0 \\
\epsilon_D c_4 & \epsilon_D c_4 & c_4 & \epsilon_H c_4 & \epsilon_D c_4 & (1-u_0)\beta_1'\lambda & 0 & 0 \\
\epsilon_D c_5 & \epsilon_D c_5 & c_5 & \epsilon_H c_5 & \epsilon_D c_5 & 0 & (1-u_0)\beta_1'\omega_H\lambda & 0 \\
\epsilon_D c_6 & \epsilon_D c_6 & c_6 & \epsilon_H c_6 & \epsilon_D c_6 & 0 & 0 & (1-u_0)\beta_1'\omega_D\lambda \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
t_H\alpha_H & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & t_H\alpha_H & 0 & 0 & 0 & 0 & 0 & 0 \\
-k_{32}^c & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
(1-u_{13})l_D & -k_{33}^c & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & -k_{14} & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & t_H\alpha_H & -k_{24} & 0 & 0 & 0 & 0 \\
0 & (1-u_{13})\eta_{16} & t_D\alpha_D & t_{HD}\alpha_{HD} & -k_{34} & 0 & 0 & 0 \\
-\epsilon_D(c_4-c_1) & -\epsilon_D(c_4-c_1) & \eta_{11}^*-(c_4-c_1) & -\epsilon_H(c_4-c_1) & -\epsilon_D(c_4-c_1) & -k_{40} & 0 & 0 \\
-\epsilon_D(c_5-c_2) & -\epsilon_D(c_5-c_2) & -(c_5-c_2) & \eta_{12}^*-\epsilon_H(c_5-c_2) & -\epsilon_D(c_5-c_2) & \alpha_H & -k_{50} & \alpha_H \\
\eta_{13}-\epsilon_D(c_6-c_3) & m_D-\epsilon_D(c_6-c_3) & -(c_6-c_3) & -\epsilon_H(c_6-c_3) & \eta_{13}^*-\epsilon_D(c_6-c_3) & \alpha_D & \alpha_{HD} & -k_{60}
\end{pmatrix},
$$

where $c_1 = \frac{\alpha^* S_T}{N}$, $c_2 = \frac{\omega_H \alpha^* S_H}{N}$, $c_3 = \frac{\omega_D \alpha^* S_D}{N}$, $c_4 = c_1 + \frac{(1-u_0)\beta_1' \alpha^* R_T}{N}$, $c_5 = c_2 + \frac{(1-u_0)\beta_1' \omega_H \alpha^* R_H}{N}$, $c_6 = c_3 + \frac{(1-u_0)\beta_1' \omega_D \alpha^* R_D}{N}$, $k_{10} = \mu + \alpha_H + \alpha_D + \lambda$, $k_{20} = \mu + \mu_H + \alpha_{HD} + \omega_H \lambda$, $k_{30} = \mu + \mu_D + \alpha_H + \omega_D \lambda$, $k_{40} = \mu + \alpha_H + \alpha_D + (1-u_0)\beta_1' \lambda$, $k_{50} = \mu + \mu_H + \alpha_{HD} + (1-u_0)\beta_1' \omega_H \lambda$, $k_{60} = \mu + \mu_D + \alpha_H + (1-u_0)\beta_1' \omega_D \lambda$. The k_{12}^c, k_{13}^c, k_{22}^c, k_{23}^c, k_{32}^c and k_{33}^c represent the k_{12}, k_{13}, k_{22}, k_{23}, k_{32} and k_{33}, with the respective control expressions. We have that $|l(t,0,0)| = |\left(M_T, M_H, M_D, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0\right)^T|$.

All the variables of the model are positive and bounded by definition of the Ω (biologically feasible region). Remember that, $\Omega = \left\{ (S_i, E_i, I_{i_1}, I_{i_2}, I_{i_3}, R_i) \in \mathbb{R}_+^{18}, i = T, H, D : N(t) \leq \frac{M_T + M_H + M_D}{\mu} \right\}$, where $N(t)$ is the total population. Then, there is a constant C such that $|l(t,0,0)| \leq C, \quad |l_x(t,\vec{x},\vec{u})| \leq C(1+|\vec{u}|), \quad |l_u(t,\vec{x},\vec{u})| \leq C$. Thus condition I. is satisfied.

By the construction of the model and the condition I., system (2.5) with controls has a unique solution for constant controls, this implies that condition II. is satisfied.

We can write the system (2.5) with controls as

$$l(t,\vec{x},\vec{u}) = \underbrace{\begin{pmatrix} M_T - (\mu + \alpha_H + \alpha_D + \lambda)S_T \\ M_H + \alpha_H(S_T + S_D) - (\alpha_{HD} + \mu + \mu_H + \omega_H\lambda)S_H \\ M_D + \alpha_{HD}S_H + \alpha_D S_T - (\alpha_H + \mu + \mu_D + \omega_D\lambda)S_D \\ \lambda(S_T + \beta_1' R_T) - (\alpha_H + \alpha_D + \mu + \eta)E_T \\ \omega_H\lambda(S_H + \beta_1' R_H) + \alpha_H(E_T + E_D) - (\epsilon_H^*\eta + \mu + \mu_H + \alpha_{HD})E_H \\ \omega_D\lambda(S_D + \beta_1' R_D) + \alpha_{HD}E_H + \alpha_D E_T - (\alpha_H + \epsilon_D^*\eta + \mu + \mu_D)E_D \\ (1-\beta^*)\eta E_T - (l_T + t_H\alpha_H + t_D\alpha_D + \mu + d_T + \eta_{11})I_{T_1} \\ (1-p_T)\beta^*\eta E_T + l_T I_{T_1} - (\eta_{14} + t_H\alpha_H + t_D\alpha_D + m_T + \mu + t_T' d_T)I_{T_2} \\ t_H\alpha_H(I_{T_1} + I_{D_1}) + (1-\beta^*)\epsilon_H^*\eta E_H - (l_H + \mu + \mu_H + d_{TH} + \eta_{12} + t_{HD}\alpha_{HD})I_{H_1} \\ t_H\alpha_H(I_{T_2} + I_{D_2}) + (1-p_H)\epsilon_H^*\beta^*\eta E_H + l_H I_{H_1} - (\eta_{15} + m_H + \mu + \mu_H + t_H' d_{TH} + t_{HD}\alpha_{HD})I_{H_2} \\ t_D\alpha_D I_{T_1} + t_{HD}\alpha_{HD}I_{H_1} + (1-\beta^*)\epsilon_D^*\eta E_D - (l_D + t_H\alpha_H + \mu + \mu_D + d_{TD} + \eta_{13})I_{D_1} \\ t_D\alpha_D I_{T_2} + t_{HD}\alpha_{HD}I_{H_2} + (1-p_D)\epsilon_D^*\beta^*\eta E_D + l_D I_{D_1} - (\eta_{16} + m_D + t_H\alpha_H + \mu + \mu_D + t_D' d_{TD})I_{D_2} \\ p_T\eta E_T + \eta_{14}I_{T_2} - (\eta_{11}^* + t_H\alpha_H + t_D\alpha_D + \mu + t_T^* d_T)I_{T_3} \\ p_H\epsilon_H^*\eta E_H + t_H\alpha_H(I_{T_3} + I_{D_3}) + \eta_{15}I_{H_2} - (\eta_{12}^* + t_{HD}\alpha_{HD} + \mu + \mu_H + t_H^* d_{TH})I_{H_3} \\ p_D\epsilon_D^*\eta E_D + t_{HD}\alpha_{HD}I_{H_3} + t_D\alpha_D I_{T_3} + \eta_{16}I_{D_2} - (t_H\alpha_H + \eta_{13}^* + \mu + \mu_D + t_D^* d_{TD})I_{D_3} \\ m_T I_{T_2} + \eta_{11}I_{T_1} + \eta_{11}^* I_{T_3} - (\beta_1'\lambda + \alpha_H + \alpha_D + \mu)R_T \\ m_H I_{H_2} + \eta_{12}I_{H_1} + \eta_{12}^* I_{H_3} + \alpha_H(R_T + R_D) - (\beta_1'\omega_H\lambda + \alpha_{HD} + \mu + \mu_H)R_H \\ m_D I_{D_2} + \eta_{13}I_{D_1} + \eta_{13}^* I_{D_3} + \alpha_H R_T + \alpha_{HD}R_H - (\beta_1'\omega_D\lambda + \alpha_H + \mu + \mu_D)R_D \end{pmatrix}}_{a_1(t,\vec{x})} + \underbrace{l_u(t,\vec{x},\vec{u})}_{a_2(t,\vec{x})} \times \underbrace{\begin{pmatrix} u_0 \\ u_{11} \\ u_{12} \\ u_{13} \end{pmatrix}}_{\vec{u}}.$$

Then, $l(t,\vec{x},\vec{u}) = a_1(t,\vec{x}) + a_2(t,\vec{x})\vec{u}$.

This means that condition III. holds. By construction the sets U is closed, convex and compact and condition IV. is satisfied.

Now, we are going to prove the convexity of the integrand in the objective functional

$$f(t,\vec{x},\vec{u}) = E_T(t) + E_H(t) + E_D(t) + I_{T_2}(t) + I_{H_2}(t) + I_{D_2}(t) + I_{T_3}(t) + I_{H_3}(t) + I_{D_3}(t) + \frac{B_0 u_0^2(t)}{2} + \frac{(B_1 + B_4)u_{11}^2(t)}{2} + \frac{(B_2 + B_5)u_{12}^2(t)}{2} + \frac{(B_3 + B_6)u_{13}^2(t)}{2},$$

this implies proving that

$$(1-q)f(t,\vec{x},\vec{u})+qf(t,\vec{x},\vec{v})\geq f(t,\vec{x},(1-q)\vec{u}+q\vec{v}),$$

where $\vec{u}$, $\vec{v}$ are two control vectors with $q\in[0,1]$.

It follows that

$$(1-q)f(t,\vec{x},\vec{u})+qf(t,\vec{x},\vec{v})=$$

$$(1-q)\Bigg(E_T+E_H+E_D+I_{T_2}+I_{H_2}+I_{D_2}+I_{T_3}+I_{H_3}+I_{D_3}+\frac{B_0u_0^2}{2}+\frac{(B_1+B_4)u_{11}^2}{2}+\frac{(B_2+B_5)u_{12}^2}{2}+$$
$$\frac{(B_3+B_6)u_{13}^2}{2}\Bigg)+q\Bigg(E_T+E_H+E_D+I_{T_2}+I_{H_2}+I_{D_2}+I_{T_3}+I_{H_3}+I_{D_3}+\frac{B_0v_0^2}{2}+\frac{(B_1+B_4)v_{11}^2}{2}+\frac{(B_2+B_5)v_{12}^2}{2}+$$
$$\frac{(B_3+B_6)v_{13}^2}{2}\Bigg)=E_T+E_H+E_D+I_{T_2}+I_{H_2}+I_{D_2}+I_{T_3}+I_{H_3}+I_{D_3}+\Bigg(\frac{B_0(qv_0^2+(1-q)u_0^2)}{2}+$$
$$\frac{(B_1+B_4)(qv_{11}^2+(1-q)u_{11}^2)}{2}+\frac{(B_2+B_5)(qv_{12}^2+(1-q)u_{12}^2)}{2}+\frac{(B_3+B_6)(qv_{13}^2+(1-q)u_{13}^2)}{2}\Bigg),$$

and

$$f(t,\vec{x},(1-q)\vec{u}+q\vec{v})=(E_T+E_H+E_D+I_{T_2}+I_{H_2}+I_{D_2}+I_{T_3}+I_{H_3}+I_{D_3}+\frac{B_0}{2}\Big[(1-q)u_0+qv_0\Big]^2+$$
$$\frac{(B_1+B_4)}{2}\Big[(1-q)u_{11}+qv_{11}\Big]^2+\frac{(B_2+B_5)}{2}\Big[(1-q)u_{12}+qv_{12}\Big]^2+\frac{(B_3+B_6)}{2}\Big[(1-q)u_{13}+qv_{13}\Big]^2.$$

Then, we have

$$(1-q)f(t,\vec{x},\vec{u})+qf(t,\vec{x},\vec{v})-f(t,\vec{x},(1-q)\vec{u}+q\vec{v})=$$
$$\frac{B_0}{2}\Big((1-q)u_0^2+qv_0^2-((1-q)u_0+qv_0)^2\Big)+\frac{(B_1+B_4)}{2}\Big((1-q)u_{11}^2+qv_{11}^2-((1-q)u_{11}+qv_{11})^2\Big)+$$
$$\frac{(B_2+B_5)}{2}\Big((1-q)u_{12}^2+qv_{12}^2-((1-q)u_{12}+qv_{12})^2\Big)+\frac{(B_3+B_6)}{2}\Big((1-q)u_{13}^2+qv_{13}^2-((1-q)u_{13}+qv_{13})^2\Big)=$$
$$\frac{B_0}{2}\Big[\sqrt{q(1-q)}u_0-\sqrt{q(1-q)}v_0\Big]^2+\frac{(B_1+B_4)}{2}\Big[\sqrt{q(1-q)}u_{11}-\sqrt{q(1-q)}v_{11}\Big]^2+$$
$$\frac{(B_2+B_5)}{2}\Big[\sqrt{q(1-q)}u_{12}-\sqrt{q(1-q)}v_{12}\Big]^2+\frac{(B_3+B_6)}{2}\Big[\sqrt{q(1-q)}u_{13}-\sqrt{q(1-q)}v_{13}\Big]^2\geq 0.$$

with this, we prove the requirement V. and the proof of the theorem is complete. □

The Pontryagin's Maximum Principle, provides the necessary conditions an optimal control must satisfy. Firstly, the Hamiltonian for the control problem is defined by

$$H=E_T(t)+E_H(t)+E_D(t)+I_{T_2}(t)+I_{H_2}(t)+I_{D_2}(t)+I_{T_3}(t)+I_{H_3}(t)+I_{D_3}(t)+\frac{B_0u_0^2(t)}{2}+\frac{(B_1+B_4)u_{11}^2(t)}{2}+$$
$$\frac{(B_2+B_5)u_{12}^2(t)}{2}+\frac{(B_3+B_6)u_{13}^2(t)}{2}+\sum_{n=1}^{18}\lambda_nf_n,\qquad(3.3)$$

where $\lambda_1, \lambda_2, \cdots, \lambda_{18}$ are the adjoint variables.

Now, we are going to prove the following theorem:

Theorem 3.2.2. *Given an optimal controls $u_0^*, u_{11}^*, u_{12}^*, u_{13}^*$ and associated solutions S_T^{**}, S_H^{**}, S_D^{**}, E_T^{**}, E_H^*, E_D^{**}, $I_{T_1}^{**}$, $I_{T_2}^{**}$, $I_{H_1}^{**}$, $I_{H_2}^{**}$, $I_{D_1}^{**}$, $I_{D_2}^{**}$, $I_{T_3}^{**}$, $I_{H_3}^{**}$, $I_{D_3}^{**}$, R_T^{**}, R_H^{**} and R_D^{**}, that minimizes $J(u_0, u_{11}, u_{12}, u_{13})$ over the domain U_{ad}, there exists adjoint function, $\lambda_n(t)$, $n = 1, .., 18$ that satisfy:*

$$\frac{d\lambda_n}{dt} = -\frac{\partial H}{\partial x_i}, \quad n = 1, ..., 18,$$

where $x_i = S_T, S_H, S_D, E_T, E_H, E_D, I_{T_1}, I_{T_2}, I_{H_1}, I_{H_2}, I_{D_1}, I_{D_2}, I_{T_3}, I_{H_3}, I_{D_3}, R_T, R_H, R_D$. In association with the transversality conditions $\lambda_n(t_f) = 0$ for $n = 1, 2, ..., 18$. Moreover, the following characterization holds

$$\begin{aligned}
u_0^* &= \min\left\{ \max\left\{0, \frac{\beta_1'\lambda\big((\lambda_4 - \lambda_{16})R_T + \omega_H(\lambda_5 - \lambda_{17})R_H + \omega_D(\lambda_6 - \lambda_{18})R_D\big)}{B_0}\right\}, 1\right\},\\
u_{11}^* &= \min\left\{ \max\left\{0, \frac{l_T I_{T_1}(\lambda_8 - \lambda_7) + \eta_{14} I_{T_2}(\lambda_{13} - \lambda_8)}{B_1 + B_4}\right\}, 1\right\},\\
u_{12}^* &= \min\left\{ \max\left\{0, \frac{l_H I_{H_1}(\lambda_{10} - \lambda_9) + \eta_{15} I_{H_2}(\lambda_{14} - \lambda_{10})}{B_2 + B_5}\right\}, 1\right\},\\
u_{13}^* &= \min\left\{ \max\left\{0, \frac{l_D I_{D_1}(\lambda_{12} - \lambda_{11}) + \eta_{16} I_{D_2}(\lambda_{15} - \lambda_{12})}{B_3 + B_6}\right\}, 1\right\}.
\end{aligned} \tag{3.4}$$

Proof. Using Pontryagin's Maximum Principle [100], the adjoint equations are obtained:

$$\begin{aligned}
\frac{d\lambda_1}{dt} &= -\frac{\partial H}{\partial S_T} = \alpha_H(\lambda_1 - \lambda_3) + \alpha_D(\lambda_1 - \lambda_2) + \lambda(\lambda_1 - \lambda_4) + \mu\lambda_1,\\
\frac{d\lambda_2}{dt} &= -\frac{\partial H}{\partial S_H} = \alpha_{HD}(\lambda_2 - \lambda_3) + \omega_H\lambda(\lambda_2 - \lambda_5) + (\mu + \mu_H)\lambda_2,\\
\frac{d\lambda_3}{dt} &= -\frac{\partial H}{\partial S_D} = \alpha_H(\lambda_3 - \lambda_2) + \omega_D\lambda(\lambda_3 - \lambda_6) + (\mu + \mu_D)\lambda_3,\\
\frac{d\lambda_4}{dt} &= -\frac{\partial H}{\partial E_T} = -1 + \alpha_H(\lambda_4 - \lambda_6) + \alpha_D(\lambda_4 - \lambda_5) + \eta((\lambda_4 - \lambda_7) + \beta^*((\lambda_7 - \lambda_8) + p_T(\lambda_8 - \lambda_{13}))) + \mu\lambda_4,\\
\frac{d\lambda_5}{dt} &= -\frac{\partial H}{\partial E_H} = -1 + \alpha_{HD}(\lambda_5 - \lambda_6) + \eta\epsilon_H^*((\lambda_5 - \lambda_9) + \beta^*((\lambda_9 - \lambda_{10}) + p_H(\lambda_{10} - \lambda_{14}))) + (\mu + \mu_H)\lambda_5,\\
\frac{d\lambda_6}{dt} &= -\frac{\partial H}{\partial E_D} = -1 + \alpha_H(\lambda_6 - \lambda_5) + \eta\epsilon_D^*((\lambda_6 - \lambda_{11}) + \beta^*((\lambda_{11} - \lambda_{12}) + p_D(\lambda_{12} - \lambda_{15}))) + (\mu + \mu_D)\lambda_6,\\
\frac{d\lambda_7}{dt} &= -\frac{\partial H}{\partial I_{T_1}} = -1 + t_H\alpha_H(\lambda_7 - \lambda_9) + t_D\alpha_D(\lambda_7 - \lambda_{11}) + \eta_{11}(\lambda_7 - \lambda_{16}) + (1 - u_{11})l_T(\lambda_7 - \lambda_8) +\\
&\quad \frac{\alpha^*}{N}\big((\lambda_1 - \lambda_4)S_T + \omega_H S_H(\lambda_2 - \lambda_5) + \omega_D S_D(\lambda_3 - \lambda_6) + (1 - u_0)\beta_1'(R_T(\lambda_{16} - \lambda_4) +\\
&\quad \omega_H R_H(\lambda_{17} - \lambda_5) + \omega_D R_D(\lambda_{18} - \lambda_6))\big) + (\mu + d_T)\lambda_7,\\
\frac{d\lambda_8}{dt} &= -\frac{\partial H}{\partial I_{T_2}} = -1 + (1 - u_{11})\eta_{14}(\lambda_8 - \lambda_{13}) + t_H\alpha_H(\lambda_8 - \lambda_{10}) + t_D\alpha_D(\lambda_8 - \lambda_{12}) + m_T(\lambda_8 - \lambda_{16}) +\\
&\quad \frac{\alpha^*}{N}\big((\lambda_1 - \lambda_4)S_T + \omega_H S_H(\lambda_2 - \lambda_5) + \omega_D S_D(\lambda_3 - \lambda_6) + (1 - u_0)\beta_1'(R_T(\lambda_{16} - \lambda_4) +
\end{aligned}$$

$$\omega_H R_H(\lambda_{17}-\lambda_5)+\omega_D R_D(\lambda_{18}-\lambda_6))\big)+(\mu+t_T^{'}d_T)\lambda_8,$$

$$\frac{d\lambda_9}{dt}=-\frac{\partial H}{\partial I_{H_1}}=-1+(1-u_{12})l_H(\lambda_9-\lambda_{10})+\eta_{12}(\lambda_9-\lambda_{17})+t_{HD}\alpha_{HD}(\lambda_9-\lambda_{11})+$$
$$\frac{\alpha^*}{N}\epsilon_H\big((\lambda_1-\lambda_4)S_T+\omega_H S_H(\lambda_2-\lambda_5)+\omega_D S_D(\lambda_3-\lambda_6)+(1-u_0)\beta_1^{'}(R_T(\lambda_{16}-\lambda_4)+$$
$$\omega_H R_H(\lambda_{17}-\lambda_5)+\omega_D R_D(\lambda_{18}-\lambda_6))\big)+(\mu+\mu_H+d_{TH})\lambda_9,$$

$$\frac{d\lambda_{10}}{dt}=-\frac{\partial H}{\partial I_{H_2}}=-1+\frac{\alpha^*}{N}\epsilon_H\big((\lambda_1-\lambda_4)S_T+\omega_H S_H(\lambda_2-\lambda_5)+\omega_D S_D(\lambda_3-\lambda_6)+(1-u_0)\beta_1^{'}(R_T(\lambda_{16}-\lambda_4)+$$
$$\omega_H R_H(\lambda_{17}-\lambda_5)+\omega_D R_D(\lambda_{18}-\lambda_6))\big)+t_{HD}\alpha_{HD}(\lambda_{10}-\lambda_{12})+m_H(\lambda_{10}-\lambda_{17})+(1-u_{11})\eta_{15}(\lambda_{10}-$$
$$\lambda_{14})+(\mu+\mu_H+t_H^{'}d_{TH})\lambda_{10},$$

$$\frac{d\lambda_{11}}{dt}=-\frac{\partial H}{\partial I_{D_1}}=-1+\frac{\alpha^*}{N}\epsilon_D\big((\lambda_1-\lambda_4)S_T+\omega_H S_H(\lambda_2-\lambda_5)+\omega_D S_D(\lambda_3-\lambda_6)+(1-u_0)\beta_1^{'}(R_T(\lambda_{16}-\lambda_4)+$$
$$\omega_H R_H(\lambda_{17}-\lambda_5)+\omega_D R_D(\lambda_{18}-\lambda_6))\big)+(1-u_{13})l_D(\lambda_{11}-\lambda_{12})+\eta_{13}(\lambda_{11}-\lambda_{18})+$$
$$t_H\alpha_H(\lambda_{11}-\lambda_9)+(\mu+\mu_D+d_{TD})\lambda_{11},$$

$$\frac{d\lambda_{12}}{dt}=-\frac{\partial H}{\partial I_{D_2}}=-1+\frac{\alpha^*}{N}\epsilon_D\big((\lambda_1-\lambda_4)S_T+\omega_H S_H(\lambda_2-\lambda_5)+\omega_D S_D(\lambda_3-\lambda_6)+(1-u_0)\beta_1^{'}(R_T(\lambda_{16}-\lambda_4)+$$
$$\omega_H R_H(\lambda_{17}-\lambda_5)+\omega_D R_D(\lambda_{18}-\lambda_6))\big)+t_H\alpha_H(\lambda_{12}-\lambda_{10})+m_D(\lambda_{12}-\lambda_{18})+$$
$$(1-u_{13})\eta_{16}(\lambda_{12}-\lambda_{15})+(\mu+\mu_D+t_D^{'}d_{TD})\lambda_{12},$$

$$\frac{d\lambda_{13}}{dt}=-\frac{\partial H}{\partial I_{T_3}}=-1+\frac{\alpha^*}{N}\big((\lambda_1-\lambda_4)S_T+\omega_H S_H(\lambda_2-\lambda_5)+\omega_D S_D(\lambda_3-\lambda_6)+(1-u_0)\beta_1^{'}(R_T(\lambda_{16}-\lambda_4)+$$
$$\omega_H R_H(\lambda_{17}-\lambda_5)+\omega_D R_D(\lambda_{18}-\lambda_6))\big)+\eta_{11}^*(\lambda_{13}-\lambda_{16})+t_D\alpha_D(\lambda_{13}-\lambda_{15})+$$
$$t_H\alpha_H(\lambda_{13}-\lambda_{14})+(\mu+t_T^*d_T)\lambda_{13},$$

$$\frac{d\lambda_{14}}{dt}=-\frac{\partial H}{\partial I_{H_3}}=-1+\frac{\alpha^*}{N}\epsilon_H\big((\lambda_1-\lambda_4)S_T+\omega_H S_H(\lambda_2-\lambda_5)+\omega_D S_D(\lambda_3-\lambda_6)+(1-u_0)\beta_1^{'}(R_T(\lambda_{16}-\lambda_4)+$$
$$\omega_H R_H(\lambda_{17}-\lambda_5)+\omega_D R_D(\lambda_{18}-\lambda_6))\big)+\eta_{12}^*(\lambda_{14}-\lambda_{17})+t_{HD}\alpha_{HD}(\lambda_{14}-\lambda_{15})+$$
$$(\mu+\mu_H+t_H^*d_{TH})\lambda_{14},$$

$$\frac{d\lambda_{15}}{dt}=-\frac{\partial H}{\partial I_{D_3}}=-1+\frac{\alpha^*}{N}\epsilon_D\big((\lambda_1-\lambda_4)S_T+\omega_H S_H(\lambda_2-\lambda_5)+\omega_D S_D(\lambda_3-\lambda_6)+(1-u_0)\beta_1^{'}(R_T(\lambda_{16}-\lambda_4)+$$
$$\omega_H R_H(\lambda_{17}-\lambda_5)+\omega_D R_D(\lambda_{18}-\lambda_6))\big)+\eta_{13}^*(\lambda_{15}-\lambda_{18})+t_H\alpha_H(\lambda_{15}-\lambda_{14})+$$
$$(\mu+\mu_D+t_D^*d_{TD})\lambda_{15},$$

$$\frac{d\lambda_{16}}{dt}=-\frac{\partial H}{\partial R_T}=(1-u_0)\beta_1^{'}\lambda(\lambda_{16}-\lambda_4)+\alpha_H(\lambda_{16}-\lambda_{18})+\alpha_D(\lambda_{16}-\lambda_{17})+\mu\lambda_{16},$$

$$\frac{d\lambda_{17}}{dt}=-\frac{\partial H}{\partial R_H}=(1-u_0)\beta_1^{'}\lambda\omega_H(\lambda_{17}-\lambda_5)+\alpha_{HD}(\lambda_{17}-\lambda_{18})+(\mu+\mu_H)\lambda_{17},$$

$$\frac{d\lambda_{18}}{dt}=-\frac{\partial H}{\partial R_D}=(1-u_0)\beta_1^{'}\lambda\omega_D(\lambda_{18}-\lambda_6)+\alpha_H(\lambda_{18}-\lambda_{17})+(\mu+\mu_D)\lambda_{18}. \tag{3.5}$$

Optimality is when the equations $\frac{\partial H}{\partial u_k}=0$ at u_k^* for $k=0,11,12,13$. Then,

$$\frac{\partial H}{\partial u_0}=B_0u_0+\beta_1^{'}\lambda\big((\lambda_{16}-\lambda_4)R_T+\omega_H(\lambda_{17}-\lambda_5)R_H+\omega_D(\lambda_{18}-\lambda_6)R_D\big)=0,$$

which implies that

$$u_0^*=\frac{\beta_1^{'}\lambda\big((\lambda_4-\lambda_{16})R_T+\omega_H(\lambda_5-\lambda_{17})R_H+\omega_H(\lambda_6-\lambda_{18})R_D\big)}{B_0},$$

on the set $\{t : 0 < u_0^*(t) < 1\}$.

$$\frac{\partial H}{\partial u_{11}} = (B_1 + B_4)u_{11} + l_T I_{T_1}(\lambda_7 - \lambda_8) + \eta_{14} I_{T_2}(\lambda_8 - \lambda_{13})R_D = 0,$$

which implies that

$$u_{11}^* = \frac{l_T I_{T_1}(\lambda_8 - \lambda_7) + \eta_{14} I_{T_2}(\lambda_{13} - \lambda_8)}{B_1 + B_4},$$

on the set $\{t : 0 < u_{11}^*(t) < 1\}$.
Analogously, for the optimal control u_{12}^*, we have

$$\frac{\partial H}{\partial u_{12}} = (B_2 + B_5)u_{12} + l_H I_{H_1}(\lambda_9 - \lambda_{10}) + \eta_{15} I_{H_2}(\lambda_8 - \lambda_{14})R_H = 0.$$

Therefore,

$$u_{12}^* = \frac{l_H I_{H_1}(\lambda_{10} - \lambda_9) + \eta_{15} I_{H_2}(\lambda_{14} - \lambda_{10})}{B_2 + B_5},$$

on the set $\{t : 0 < u_{12}^*(t) < 1\}$. For the control u_{13}^*, we obtain

$$\frac{\partial H}{\partial u_{13}} = (B_3 + B_6)u_{13} + l_D I_{D_1}(\lambda_{11} - \lambda_{12}) + \eta_{16} I_{D_2}(\lambda_{12} - \lambda_{15}) = 0,$$

and this implies that

$$u_{13}^* = \frac{l_D I_{D_1}(\lambda_{12} - \lambda_{11}) + \eta_{16} I_{D_2}(\lambda_{15} - \lambda_{12})}{B_3 + B_6},$$

on the control set $\{t : 0 < u_{13}^*(t) < 1\}$.
Note that the optimality conditions only hold on the interior of the control set.

The second derivative respect to u_k, $k = 0, 11, 12, 13$ are:

$$\frac{\partial^2 H}{\partial u_0^2} = B_0 > 0, \frac{\partial^2 H}{\partial u_{11}^2} = B_1 + B_3 > 0, \quad \frac{\partial^2 H}{\partial u_{12}^2} = B_2 + B_4 > 0 \text{ and } \quad \frac{\partial^2 H}{\partial u_{13}^2} = B_3 + B_6 > 0.$$

□

3.3 Numerical Results

The aim of this section is to simulate the application of the controls in the population. First, the optimality system is numerically solved using the iterative method with the Runge-Kutta fourth-order scheme. We use the forward-backward sweep method for finding the solution of the optimality system which has the state equation (2.5) with controls, adjoint equation (3.5), control chraterization (3.4) and initial/final condition (initial and tranversality conditions). The method starts with initial values for the optimal control and we solve the state system forward in time using Runge-Kutta method of the fourth-order. Following, we solve the adjoint equation backward in time with Runge-Kutta of the fourth-order using the state variables, initial control guess and transversality conditions. The

controls $u_0(t)$, $u_{11}(t)$, $u_{12}(t)$ and $u_{13}(t)$ are updated and used to solve the state and adjoint system respectively. This iterative process continues until that current state, adjoint, and control values converge [4, 71].
For the numerical simulations, we use the values of Tables (2.2)-(2.3). We assume that $B_0 = 200$, $B_1 = 50$, $B_2 = 150$, $B_3 = 75$, $B_4 = 100$, $B_5 = 250$ and $B_6 = 150$ and the control is always applied in the TB-HIV/AIDS subpopulation because tuberculosis is classified as an opportunistic disease and HIV/AIDS cases are monitored by the use of antiretroviral therapy. Also, reinfection/reactivation of TB is always controlled in all strategies because of its impact on treatment resistance. Then, our control strategies are defined as:

- Strategy I. We activate all controls $(u_0(t) > 0, u_{11}(t) > 0, u_{12}(t) > 0, u_{13}(t) > 0)$.

- Strategy II. Combination of $u_0(t)$, $u_{11}(t)$, $u_{12}(t)$ while setting $u_{13}(t) = 0$ $(u_0(t) > 0, u_{11}(t) > 0, u_{12}(t) > 0$ and $u_{13}(t) = 0)$.

- Strategy III. Combination of $u_0(t)$, $u_{12}(t)$, $u_{13}(t)$ while setting $u_{11}(t) = 0$ $(u_0(t) > 0, u_{12}(t) > 0, u_{13}(t) > 0$ and $u_{11}(t) = 0)$.

We are going to study how we start the control process, with highly efficient control (type I) and with minimum value (type II).
Figure (3.2) shows the profiles of the resistance controls $(u_{11}(t), u_{12}(t), u_{13}(t))$ over time for the different strategies and control types.

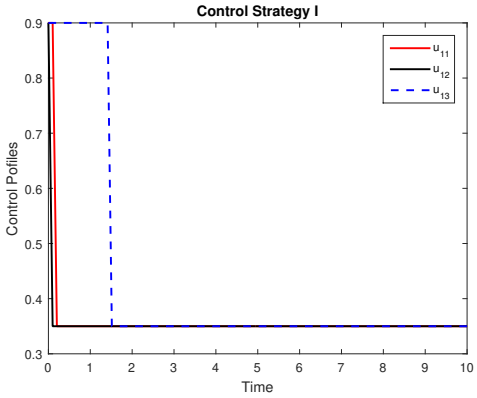
Strategy I. In this strategy all controls are active ($u_0(t) > 0$, $u_{11}(t) > 0$, $u_{12}(t) > 0$ and $u_{13}(t) > 0$). In other words, reinfection/reactivation and resistance are controlled. We show the behavior of the controls over time (3.2a) for control type I and (3.2b) for control type II. It is observed that when this control strategy is implemented, there is a significant decrease in the number of TB resistant compared with the model without control, see Figure (3.3). In the case of MDR-TB, in the different subpopulations before the study year, a decrease in the number of reported cases was observed, see Figures (3.3a)-(3.3c). In the case of XDR-TB, the reduction in the number of cases will occur over a longer period time, but this reduction is significant, mainly in XDR-TB diabetics, which have a strong incidence in the dynamic, see Figure (3.3d)-(3.3f). In the case of MDR-TB and XDR-TB in the TB-HIV/AIDS subpopulation, the control manages to avoid the growth of the number of cases because in the dynamic these compartments tend to decrease initially and then grow. This strategy takes advantage of the decrease in the number of cases and avoids an future growth. The type I control showed better results so it is recommended to start with a high control efficacy and this evolves over time.

Strategy II. Here, we activate the controls $u_0(t) > 0$, $u_{11}(t) > 0$ and $u_{12}(t) > 0$ and $u_{13}(t) = 0$, this means that we control resistance in the TB-HIV/AIDS and TB-Only subpopulations and reinfection/reactivation TB in the full model. The behavior of the controls is shown in Figure (3.2c)-(3.2d). This strategy succeeds in reducing the number of resistant cases, but this reduction is lower than that of strategy I. It is important to keep in mind that the largest number of resistant cases are XDR-TB diabetics and this strategy reduces this compartment but not sufficiently. It is recommended to maintain control over

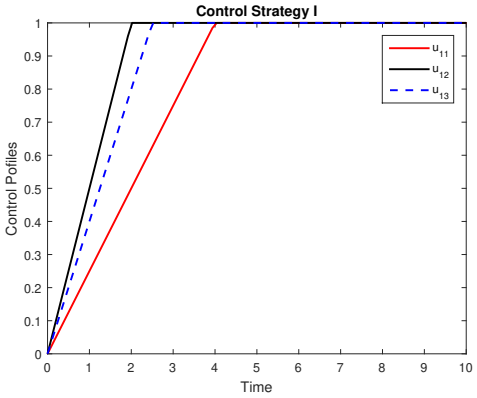
diabetic resistant compartments, due to their impact on resistance dynamic, mainly of XDR-TB. The XDR-TB in the TB-HIV/AIDS and TB-Diabetes subpopulations, the controls decreased the number of cases but did not take advantage of the decrease in the number of cases and the asymptotic behavior was maintained. The type I control was more effective.

Strategy III. This strategy does not control resistance in the TB-Only subpopulation. As in the previous strategies, the objective of reducing resistance in the dynamic is met. Controls applied for XDR-TB cases in HIV/AIDS and diabetic patients reduced the number of cases and asymptotic behavior was maintained, but the results were better than strategy II for the different types of controls. This strategy also failed to take advantage of the decrease in the number of cases, reducing the number of cases but not avoiding future asymptotic growth, see Figures (3.5a), (3.5e) and (3.5f). Here too, controls of type I achieved better results.

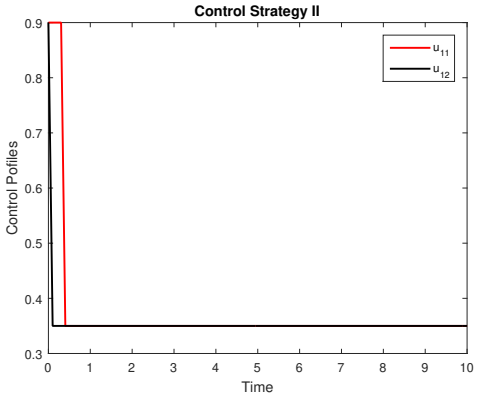
In general, all strategies and types of controls met the objective of reducing the number of cases of MDR-TB and XDR-TB. The most efficient strategy was the strategy I with type I controls. In addition to significantly reducing the number of cases in all resistance compartments, it also takes advantage of the decrease in dynamic and prevents the future growth of cases. In all strategies, type I control showed better results, so it is recommended to start with a high control efficiency. The numerical results in the Subsection (2.5) show the need to reduce XDR-TB in diabetics due to the growth in the number of cases that occurs in this subpopulation, so strategy II does not meet significantly this objective. The strategy II is not recommended because it fails to significantly reduce resistance in diabetics and diabetes is a risk factor for adherence to TB treatment.



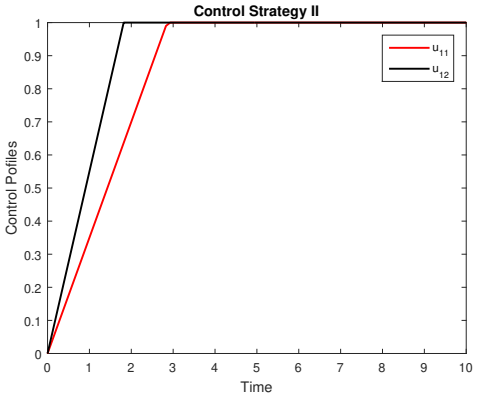
(a) *Controls profiles, strategy I, type I.*



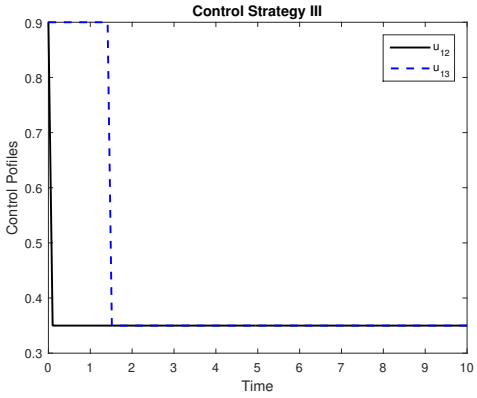
(b) *Controls profiles, strategy I, type II.*



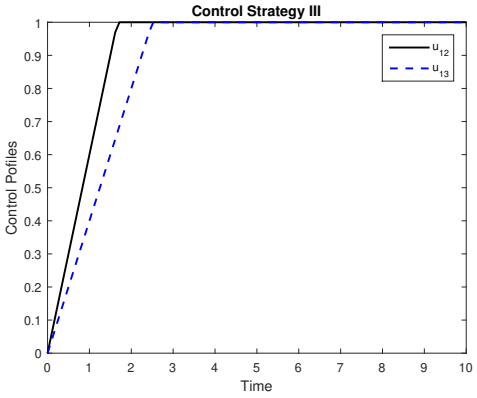
(c) *Controls profiles, strategy II, type I.*



(d) *Controls profiles, strategy II, type II.*

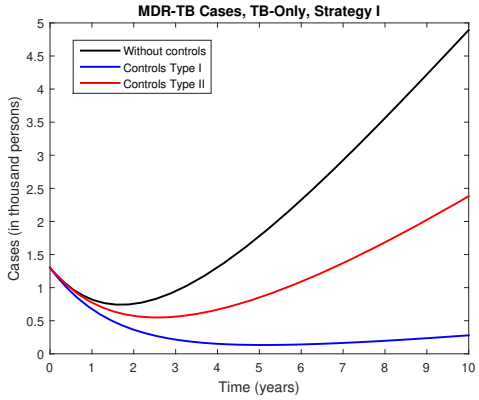


(e) *Controls profiles, strategy III, type I.*

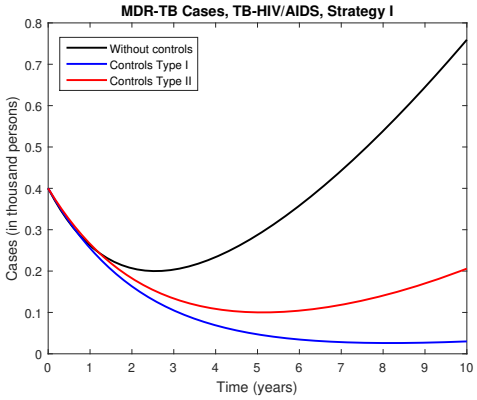


(f) *Controls profiles, strategy III, type II.*

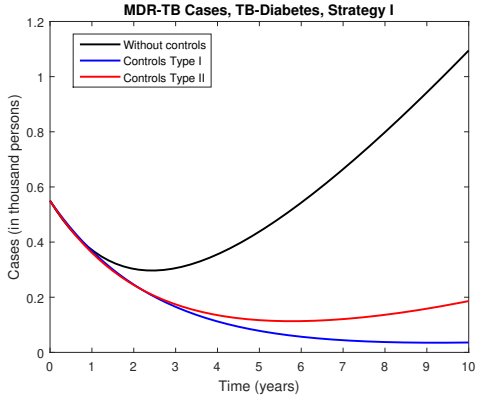
Figure 3.2: *The profiles of the controls associated with resistance in the different strategies and for the different types of controls.*



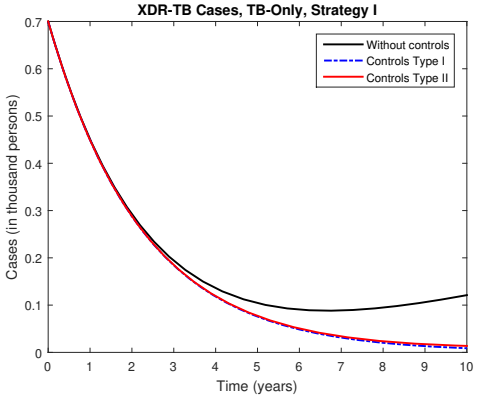
(a) *MDR-TB cases in the TB-Only, study period 10 years.*



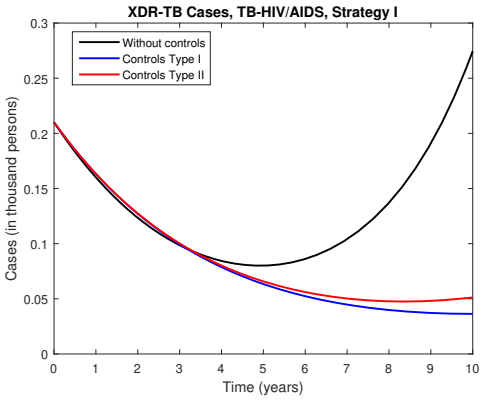
(b) *MDR-TB cases in the TB-HIV/AIDS, study period 10 years.*



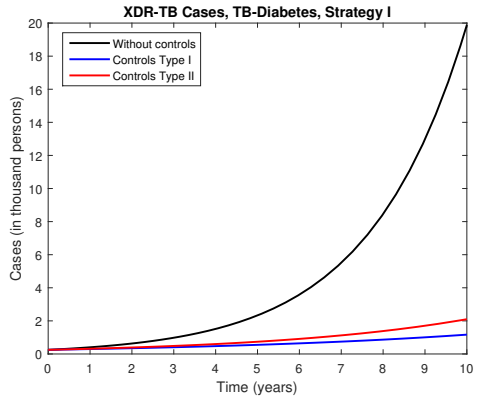
(c) *MDR-TB cases in the TB-Diabetes, study period 10 years.*



(d) *XDR-TB cases in the TB-Only, study period 10 years.*

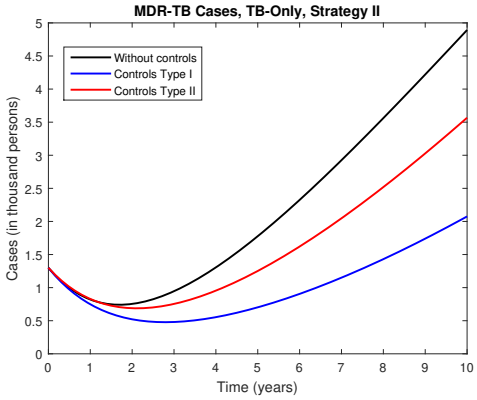


(e) *XDR-TB cases in the TB-HIV/AIDS, study period 10 years.*

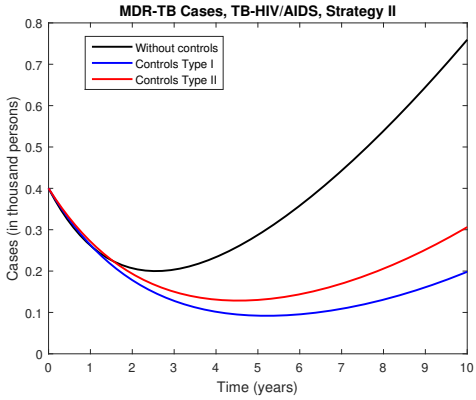


(f) *XDR-TB cases in the TB-Diabetes, study period 10 years.*

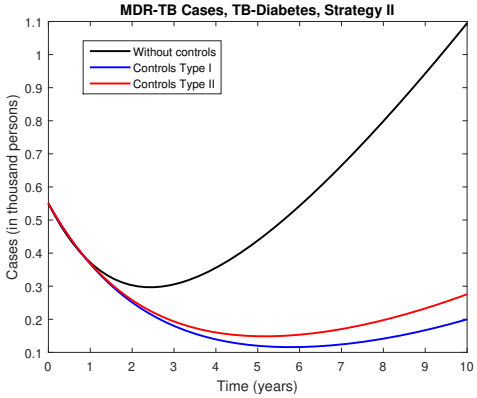
Figure 3.3: *Comparison in the resistance compartments between the types of controls for strategy I.*



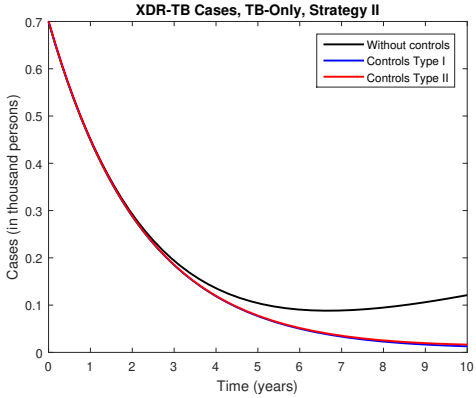
(a) *MDR-TB cases in the TB-Only, study period 10 years.*



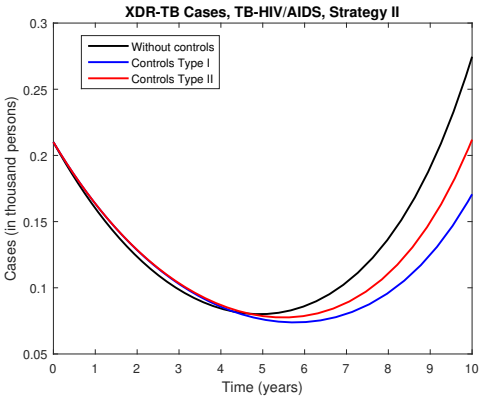
(b) *MDR-TB cases in the TB-HIV/AIDS, study period 10 years.*



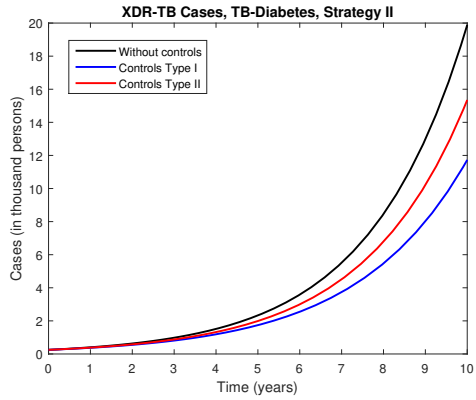
(c) *MDR-TB cases in the TB-Diabetes subpopulation, study period 10 years.*



(d) *XDR-TB cases in the TB-Only subpopulation, study period 10 years.*

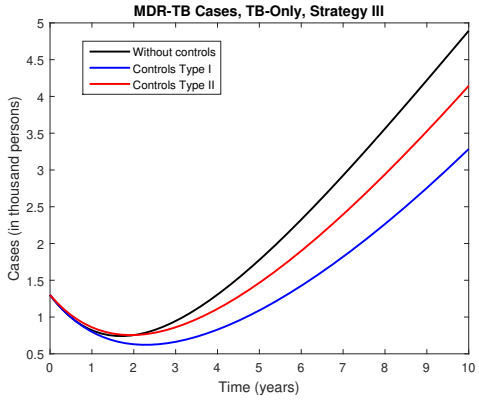


(e) *XDR-TB cases in the TB-HIV/AIDS subpopulation, study period 10 years.*

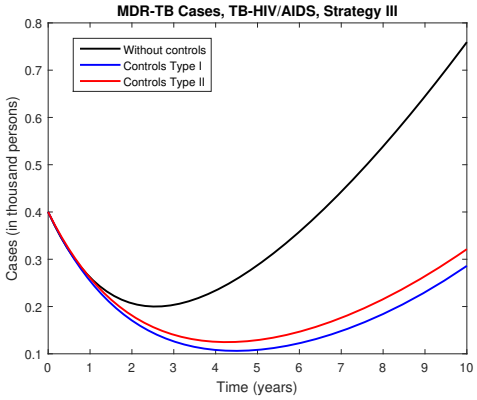


(f) *XDR-TB cases in the TB-Diabetes subpopulation, study period 10 years.*

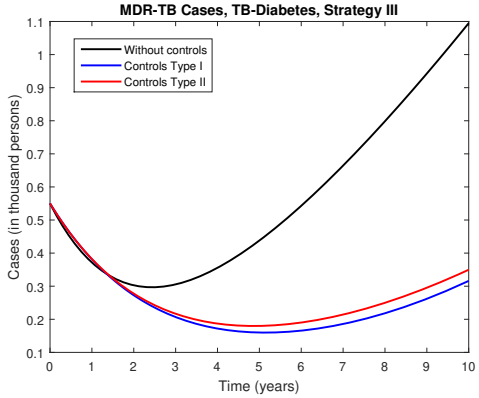
Figure 3.4: *Comparison in the resistance compartments between the types of controls for strategy II.*



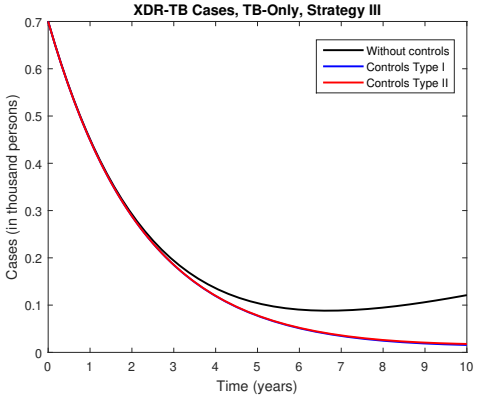
(a) *MDR-TB cases in the TB-Only, study period 10 years.*



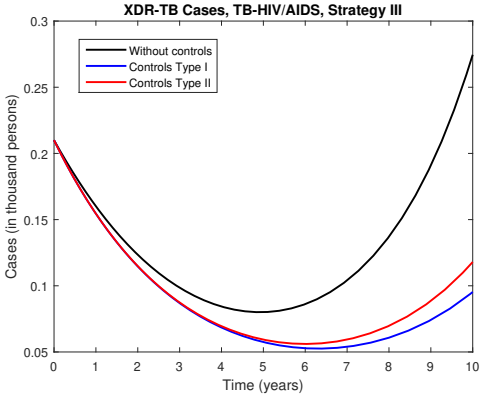
(b) *MDR-TB cases in the TB-HIV/AIDS, study period 10 years.*



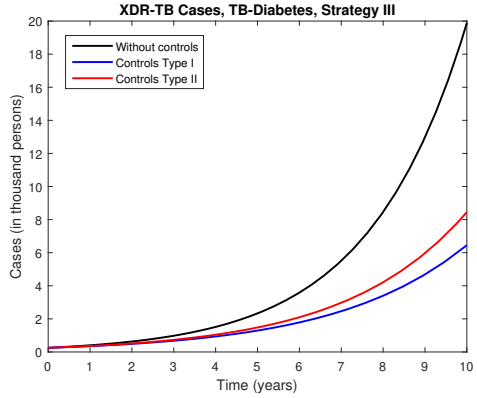
(c) *MDR-TB cases in the TB-Diabetes subpopulation, study period 10 years.*



(d) *XDR-TB cases in the TB-Only subpopulation, study period 10 years.*



(e) *XDR-TB cases in the TB-HIV subpopulation, study period 10 years.*



(f) *XDR-TB cases in the TB-Diabetes subpopulation, study period 10 years.*

Figure 3.5: *Comparison in the resistance compartments between the types of controls for strategy III.*

3.4 Partial Conclusions

In this chapter:

- We studied the optimal control problem to achieve better adherence to treatment, taking into account the influence of HIV/AIDS and diabetes and in order to avoid MDR-TB and XDR-TB.
- The controls are defined as u_0, u_{11}, u_{12} and u_{13} and are based on avoiding reinfection/reactivation of the bacteria and on differentiated care and follow-up in cases who do not suffer from HIV/AIDS neither diabetes, HIV/AIDS and diabetics.
- The optimal control theory was derived analytically by applying the Pontryagin's maximum principle and we demonstrated the existence of optimal control.
- For the computational simulations, we used a fourth-order Runge-Kutta forward/backward scheme. We experimented different control strategies. We presented the results of the resistance compartments (I_{T_2}, I_{H_2}, I_{D_2}, I_{T_3}, I_{H_3} and I_{D_3}).
- We concluded for our scenario that, all strategies with the different types of controls met the objective of reducing the number of resistant cases. The strategy that obtained the best results was the strategy I (activating all controls) with type I controls (starting with high control efficiency), see Figure (3.3). Recommend keeping all subpopulations under control and starting with a maximum control. However, if we have to use only three control, we recommended to use the strategy III, because all the resistance compartments and mainly the diabetic XDR-TB are reduced compared with strategy II. We do not recommend the use of strategy II, since one of the main factors of resistance to TB treatment is diabetes and this strategy did not manage to reduce significantly the number of resistant cases to TB treatment in diabetics.

Chapter 4

Mathematical Model using Fractional-Order Derivatives

4.1 Introduction

In recent years, there has been an increase in the number of papers using fractional order derivatives to epidemics model [23, 82, 22, 81, 119, 11, 120, 102, 55, 65, 96, 56, 34, 104, 103, 60, 105, 15]. For example, Naik et al. [23] developed a fractional-order model for HIV with the impact of prostitution on the population. Naik et al. [82] proposed and studied a fractional order model for HIV transmission with an exposed compartment and divided the infected class of sex workers into conscious and unconscious infectees. Naik et al. [22] using the Caputo and Atangana-Baleanu-Caputo operators presented and analyzed a model for the transmission of the COVID-19 epidemic. Naik [81] studied a SIR structure epidemic model with non-linear fractional-order with Crowley-Martin type functional response and Holling type II treatment rate. Ullah et al. [119] studied the dynamics of tuberculosis with a fractional-order model in the Caputo sense. Fatmawati et al. [11] analyzed a Caputo and Atangana-Baleanu fractional model for tuberculosis dynamics stratified in two age groups. Ullah et al. [120] explored a model for tuberculosis using the Atangana-Baleanu fractional derivative [54].

In the study of TB and HIV/AIDS co-infection we have that, Farman et al. [55] proposed a mathematical model of HIV/AIDS and TB co-infection using the Caputo and Caputo-Fabrizo fractional derivative. Khan et al. explored a Mittag-Leffler fractional HIV/AIDS-TB co-infection model and proved the existence of a unique set of model solutions and Hyers-Ulam stability [54].

In the study of HIV/AIDS we have that, Pinto and Carvalho [96] introduced a fractional-order model for HIV infection, which includes latently infected cells, macrophages, and CTLs. Fatmawati et al. [56] presented a Caputo-derived model for the propagation of HIV/AIDS disease in a sex-stratified population and studied HIV and HCV (hepatitis C virus) co-infection. Carvalho et al. [34] proposed a fractional-order model for the HIV/HCV co-infection dynamics [54].

For the dynamics of diabetes we have that, Saleem et al. [104] presented a fractional-order nonlinear model using the Caputo-Fabrizio derivative for the treatment with insulin

in diabetics. Sakulrang et al. [103] proved that fractional-order differential equation models could give better fits than integer order models with respect to continuous glucose monitoring data from patients with type 1 diabetes [54]. Carvalho et al. [35] developed a non-integer order model for the study of tuberculosis, the impact of diabetes, and multidrug-resistant strains and showed that diabetic individuals with multidrug-resistant tuberculosis require extreme attention due to their rapid growth.

For other epidemics such as Dengue and Ebola, Hamdana and Kilicmana [60] proposed a model of dengue transmission using a fractional-order derivative as the generalization of an integer order model. Shah et al. [105] investigated epidemic model of dengue fever disease with Caputo-Fabrizio fractional derivative. Area et al. [15] presented an Ebola epidemic model using classical and fractional-order derivatives and its comparison with real data [54].

The aim of this chapter is to study the model (2.5) with fractional-order derivatives, taking advantage of the benefits provided by this modeling technique.

4.2 Model Formulation

For this model, the definitions of the variables and parameters of the model (2.5) are maintained. The transmission dynamics is analogous to model (2.5). According to [46], the fractional derivative operator ${}^{c}\mathbb{D}_t^{\alpha}$ has a dimension time$^{-\alpha}$ instead of time^{-1}, so that, due to dimensional analysis, on the right-hand side of the model all parameters of dimension yr^{-1} will have power α. Then, the effectiveness of the TB treatment with the presence of HIV/AIDS and diabetes using Caputo's operator derivative can be expressed as:

$$
\begin{aligned}
{}^{c}\mathbb{D}_t^{\alpha} S_T &= M_T^{\alpha} - (\mu^{\alpha} + \alpha_D^{\alpha} + \alpha_H^{\alpha} + \lambda^{\alpha}) S_T,\\
{}^{c}\mathbb{D}_t^{\alpha} S_H &= M_H^{\alpha} + \alpha_H^{\alpha}(S_T + S_D) - (\alpha_{HD}^{\alpha} + \mu^{\alpha} + \mu_H^{\alpha} + \omega_H \lambda^{\alpha}) S_H,\\
{}^{c}\mathbb{D}_t^{\alpha} S_D &= M_D^{\alpha} + \alpha_{HD}^{\alpha} S_H + \alpha_D^{\alpha} S_T - (\alpha_H^{\alpha} + \mu^{\alpha} + \mu_D^{\alpha} + \omega_D \lambda^{\alpha}) S_D,\\
{}^{c}\mathbb{D}_t^{\alpha} E_T &= \lambda^{\alpha}(S_T + \beta_1^{'} R_T) - (\alpha_D^{\alpha} + \alpha_H^{\alpha} + \mu^{\alpha} + \eta^{\alpha}) E_T,\\
{}^{c}\mathbb{D}_t^{\alpha} E_H &= \omega_H \lambda^{\alpha}(S_H + \beta_1^{'} R_H) + \alpha_H^{\alpha}(E_T + E_D) - (\epsilon_H^{*}\eta^{\alpha} + \mu^{\alpha} + \mu_H^{\alpha} + \alpha_{HD}^{\alpha}) E_H,\\
{}^{c}\mathbb{D}_t^{\alpha} E_D &= \omega_D \lambda^{\alpha}(S_D + \beta_1^{'} R_D) + \alpha_{HD}^{\alpha} E_H + \alpha_D^{\alpha} E_T - (\alpha_H^{\alpha} + \epsilon_D^{*}\eta^{\alpha} + \mu^{\alpha} + \mu_D^{\alpha}) E_D,\\
{}^{c}\mathbb{D}_t^{\alpha} I_{T_1} &= (1 - (\beta^{*})^{\alpha})\eta^{\alpha} E_T - (l_T^{\alpha} + t_D \alpha_D^{\alpha} + t_H \alpha_H^{\alpha} + \mu^{\alpha} + d_T^{\alpha} + \eta_{11}^{\alpha}) I_{T_1},\\
{}^{c}\mathbb{D}_t^{\alpha} I_{T_2} &= (1 - p_T^{\alpha})(\beta^{*})^{\alpha}\eta^{\alpha} E_T + l_T^{\alpha} I_{T_1} - (t_D \alpha_D^{\alpha} + t_H \alpha_H^{\alpha} + m_T^{\alpha} + \mu^{\alpha} + t_T^{'} d_T^{\alpha} + \eta_{14}^{\alpha}) I_{T_2},\\
{}^{c}\mathbb{D}_t^{\alpha} I_{H_1} &= t_H \alpha_H^{\alpha}(I_{T_1} + I_{D_1}) + (1 - (\beta^{*})^{\alpha})\epsilon_H^{*}\eta^{\alpha} E_H - (l_H^{\alpha} + \mu^{\alpha} + \mu_H^{\alpha} + d_{TH}^{\alpha} + \eta_{12}^{\alpha} + t_{HD}\alpha_{HD}^{\alpha}) I_{H_1},\\
{}^{c}\mathbb{D}_t^{\alpha} I_{H_2} &= t_H \alpha_H^{\alpha}(I_{T_2} + I_{D_2}) + (1 - p_H^{\alpha})\epsilon_H^{*}(\beta^{*})^{\alpha}\eta^{\alpha} E_H + l_H^{\alpha} I_{H_1} - (m_H^{\alpha} + \mu^{\alpha} + \mu_H^{\alpha} + t_H^{'} d_{TH}^{\alpha} + \eta_{15}^{\alpha} + t_{HD}\alpha_{HD}^{\alpha}) I_{H_2},\\
{}^{c}\mathbb{D}_t^{\alpha} I_{D_1} &= t_D \alpha_D^{\alpha} I_{T_1} + t_{HD}\alpha_{HD}^{\alpha} I_{H_1} + (1 - (\beta^{*})^{\alpha})\epsilon_D^{*}\eta^{\alpha} E_D - (l_D^{\alpha} + t_H \alpha_H^{\alpha} + \mu^{\alpha} + \mu_D^{\alpha} + d_{TD}^{\alpha} + \eta_{13}^{\alpha}) I_{D_1},\\
{}^{c}\mathbb{D}_t^{\alpha} I_{D_2} &= t_D \alpha_D^{\alpha} I_{T_2} + t_{HD}\alpha_{HD}^{\alpha} I_{H_2} + (1 - p_D^{\alpha})\epsilon_D^{*}(\beta^{*})^{\alpha}\eta^{\alpha} E_D + l_D^{\alpha} I_{D_1} - (m_D^{\alpha} + t_H \alpha_H^{\alpha} + \mu^{\alpha} + \mu_D^{\alpha} + t_D^{'} d_{TD}^{\alpha} + \eta_{16}^{\alpha}) I_{D_2},\\
{}^{c}\mathbb{D}_t^{\alpha} I_{T_3} &= p_T^{\alpha}(\beta^{*})^{\alpha}\eta^{\alpha} E_T + \eta_{14}^{\alpha} I_{T_2} - ((\eta_{11}^{*})^{\alpha} + t_D \alpha_D^{\alpha} + t_H \alpha_H^{\alpha} + \mu^{\alpha} + t_T^{*} d_T^{\alpha}) I_{T_3},\\
{}^{c}\mathbb{D}_t^{\alpha} I_{H_3} &= p_H^{\alpha}(\beta^{*})^{\alpha}\epsilon_H^{*}\eta^{\alpha} E_H + \eta_{15}^{\alpha} I_{H_2} + t_H \alpha_H^{\alpha}(I_{T_3} + I_{D_3}) - ((\eta_{12}^{*})^{\alpha} + t_{HD}\alpha_{HD}^{\alpha} + \mu^{\alpha} + \mu_H^{\alpha} + t_H^{*} d_{TH}^{\alpha}) I_{H_3},\\
{}^{c}\mathbb{D}_t^{\alpha} I_{D_3} &= p_D^{\alpha}(\beta^{*})^{\alpha}\epsilon_D^{*}\eta^{\alpha} E_D + \eta_{16}^{\alpha} I_{D_2} + t_{HD}\alpha_{HD}^{\alpha} I_{H_3} + t_D \alpha_D^{\alpha} I_{T_3} - (t_H \alpha_H^{\alpha} + (\eta_{13}^{*})^{\alpha} + \mu^{\alpha} + \mu_D^{\alpha} + t_D^{*} d_{TD}^{\alpha}) I_{D_3},\\
{}^{c}\mathbb{D}_t^{\alpha} R_T &= m_T^{\alpha} I_{T_2} + \eta_{11}^{\alpha} I_{T_1} + (\eta_{11}^{*})^{\alpha} I_{T_3} - (\alpha_D^{\alpha} + \alpha_H^{\alpha} + \mu^{\alpha} + \beta_1^{'}\lambda^{\alpha}) R_T,\\
{}^{c}\mathbb{D}_t^{\alpha} R_H &= m_H^{\alpha} I_{H_2} + \eta_{12}^{\alpha} I_{H_1} + (\eta_{12}^{*})^{\alpha} I_{H_3} + \alpha_H^{\alpha}(R_T + R_D) - (\alpha_{HD}^{\alpha} + \mu^{\alpha} + \mu_H^{\alpha} + \beta_1^{'}\omega_H \lambda^{\alpha}) R_H,
\end{aligned}
$$

$$
{}^{c}\mathbb{D}_t^{\alpha} R_D = m_D^{\alpha} I_{D_2} + \eta_{13}^{\alpha} I_{D_1} + (\eta_{13}^{*})^{\alpha} I_{D_3} + \alpha_D^{\alpha} R_T + \alpha_{HD}^{\alpha} R_H - (\alpha_H^{\alpha} + \mu^{\alpha} + \mu_D^{\alpha} + \beta_1^{'} \omega_D \lambda^{\alpha}) R_D, \tag{4.1}
$$

where

$$
\lambda^{\alpha} = \frac{(\alpha^{*})^{\alpha} \left(I_{T_1} + I_{T_2} + I_{T_3} + \epsilon_H (I_{H_1} + I_{H_2} + I_{H_3}) + \epsilon_D (I_{D_1} + I_{D_2} + I_{D_3}) \right)}{N},
$$

with initial conditions:
$S_T(0) > 0$, $S_H(0) > 0$, $S_D(0) > 0$, $E_T(0) > 0$, $E_H(0) > 0$, $E_D(0) > 0$, $I_{T_1}(0) > 0$, $I_{T_2}(0) > 0$, $I_{H_1}(0) > 0$, $I_{H_2}(0) > 0$, $I_{D_1}(0) > 0$, $I_{D_2}(0) > 0$, $I_{T_3}(0) > 0$, $I_{H_3}(0) > 0$, $I_{D_3}(0) > 0$, $R_T(0) > 0$, $R_H(0) > 0$, $R_D(0) > 0$ and $\alpha \in (0, 1]$.

Basic Properties of Model

Now, let us prove the existence and positivity of the solution of the system (4.1), and let's find the biologically feasible region. The following results and their proofs can be found in [54].

Existence and Non-Negativity of Solutions

Let's denominate

$$
\begin{aligned}
\Omega_F = \{ x = & (S_T, S_H, S_D, E_T, E_H, E_D, I_{T_1}, I_{T_2}, I_{H_1}, I_{H_2}, I_{D_1}, I_{D_2}, I_{T_3}, I_{H_3}, I_{D_3}, R_T, R_H, R_D) : \\
& S_T, S_H, S_D, E_T, E_H, E_D, I_{T_1}, I_{T_2}, I_{H_1}, I_{H_2}, I_{D_1}, I_{D_2}, I_{T_3}, I_{H_3}, I_{D_3}, R_T, R_H, R_D \geq 0 \}.
\end{aligned}
$$

The following lemma and corollary will be used in the proof of Theorem (4.2.2) and can be found in [89].

Lemma 4.2.1. *(Generalized mean value theorem) Suppose that $f \in C[a, b]$ and ${}^{c}\mathbb{D}_t^{\alpha} f \in C[a, b]$, for $\alpha \in (0, 1]$. Then, $\forall t \in (a, b]$, with $a \leq \epsilon \leq t$ we have*

$$
f(t) = f(a) + \frac{1}{\Gamma(\alpha)} ({}^{c}\mathbb{D}_t^{\alpha} f)(\epsilon)(t - a)^{\alpha},
$$

where $\Gamma(.)$ is the Gamma function.

Corollary 4.2.1.1. *Consider that $f \in C[a, b]$ and ${}^{c}\mathbb{D}_t^{\alpha} f \in C[a, b]$, for $\alpha \in (0, 1]$. Then if*

- *${}^{c}\mathbb{D}_t^{\alpha} f(t) \geq 0$, $\forall t \in (a, b)$, then $f(t)$ is non-decreasing for each $t \in [a, b]$,*
- *${}^{c}\mathbb{D}_t^{\alpha} f(t) \leq 0$, $\forall t \in (a, b)$, then $f(t)$ is non-increasing for each $t \in [a, b]$.*

Theorem 4.2.2. *There is a unique solution $x(t) = (S_T, S_H, S_D, E_T, E_H, E_D, I_{T_1}, I_{T_2}, I_{H_1}, I_{H_2}, I_{D_1}, I_{D_2}, I_{T_3}, I_{H_3}, I_{D_3}, R_T, R_H, R_D)^T$ of the model (4.1) for $t \geq 0$ and the solution will remain in Ω_F.*

Proof. By Theorem (3.1) and Remark (3.2) of [72], we have that the solution in $(0, \infty)$ of the initial value problem (4.1) exists and is unique. Now, we will prove the positivity of the solution of the model (4.1). In order to do this, we need to prove that for every hyperplane bounding the nonnegative orthant, the vector field points to Ω_F. From model (4.1), we

have:

$$
\begin{aligned}
{}^{c}\mathbb{D}_t^{\alpha} S_T\big|_{S_T=0} &= M_T^{\alpha} > 0,\\
{}^{c}\mathbb{D}_t^{\alpha} S_H\big|_{S_H=0} &= M_H^{\alpha} > 0,\\
{}^{c}\mathbb{D}_t^{\alpha} S_D\big|_{S_D=0} &= M_D^{\alpha} > 0,\\
{}^{c}\mathbb{D}_t^{\alpha} E_T\big|_{E_T=0} &= \lambda^{\alpha}(S_T + \beta_1^{'} R_T) \geq 0,\\
{}^{c}\mathbb{D}_t^{\alpha} E_H\big|_{E_H=0} &= \omega_H \lambda^{\alpha}(S_H + \beta_1^{'} R_H) + \alpha_H^{\alpha}(E_T + E_D) \geq 0,\\
{}^{c}\mathbb{D}_t^{\alpha} E_D\big|_{E_D=0} &= \omega_D \lambda^{\alpha}(S_D + \beta_1^{'} R_D) + \alpha_{HD}^{\alpha} E_H + \alpha_D^{\alpha} E_T \geq 0,\\
{}^{c}\mathbb{D}_t^{\alpha} I_{T_1}\big|_{I_{T_1}=0} &= (1 - (\beta^*)^{\alpha})\eta^{\alpha} E_T \geq 0,\\
{}^{c}\mathbb{D}_t^{\alpha} I_{T_2}\big|_{I_{T_2}=0} &= (1 - p_T^{\alpha})(\beta^*)^{\alpha}\eta^{\alpha} E_T + l_T^{\alpha} I_{T_1} \geq 0,\\
{}^{c}\mathbb{D}_t^{\alpha} I_{H_1}\big|_{I_{H_1}=0} &= t_H \alpha_H^{\alpha}(I_{T_1} + I_{D_1}) + (1 - (\beta^*)^{\alpha})\epsilon_H^{*}\eta^{\alpha} E_H \geq 0,\\
{}^{c}\mathbb{D}_t^{\alpha} I_{H_2}\big|_{I_{H_2}=0} &= t_H \alpha_H^{\alpha}(I_{T_2} + I_{D_2}) + (1 - p_H^{\alpha})\epsilon_H^{*}(\beta^*)^{\alpha}\eta^{\alpha} E_H + l_H^{\alpha} I_{H_1} \geq 0,\\
{}^{c}\mathbb{D}_t^{\alpha} I_{D_1}\big|_{I_{D_1}=0} &= t_D \alpha_D^{\alpha} I_{T_1} + t_{HD}\alpha_{HD}^{\alpha} I_{H_1} + (1 - (\beta^*)^{\alpha})\epsilon_D^{*}\eta^{\alpha} E_D \geq 0,\\
{}^{c}\mathbb{D}_t^{\alpha} I_{D_2}\big|_{I_{D_2}=0} &= t_D \alpha_D^{\alpha} I_{T_2} + t_{HD}\alpha_{HD}^{\alpha} I_{H_2} + (1 - p_D^{\alpha})\epsilon_D^{*}(\beta^*)^{\alpha}\eta^{\alpha} E_D + l_D^{\alpha} I_{D_1} \geq 0,\\
{}^{c}\mathbb{D}_t^{\alpha} I_{T_3}\big|_{I_{T_3}=0} &= p_T^{\alpha}(\beta^*)^{\alpha}\eta^{\alpha} E_T + \eta_{14}^{\alpha} I_{T_2} \geq 0,\\
{}^{c}\mathbb{D}_t^{\alpha} I_{H_3}\big|_{I_{H_3}=0} &= p_H^{\alpha}(\beta^*)^{\alpha}\epsilon_H^{*}\eta^{\alpha} E_H + \eta_{15}^{\alpha} I_{H_2} + t_H \alpha_H^{\alpha}(I_{T_3} + I_{D_3}) \geq 0,\\
{}^{c}\mathbb{D}_t^{\alpha} I_{D_3}\big|_{I_{D_3}=0} &= p_D^{\alpha}(\beta^*)^{\alpha}\epsilon_D^{*}\eta^{\alpha} E_D + \eta_{16}^{\alpha} I_{D_2} + t_{HD}\alpha_{HD}^{\alpha} I_{H_3} + t_D \alpha_D^{\alpha} I_{T_3} \geq 0,\\
{}^{c}\mathbb{D}_t^{\alpha} R_T\big|_{R_T=0} &= m_T^{\alpha} I_{T_2} + \eta_{11}^{\alpha} I_{T_1} + (\eta_{11}^{*})^{\alpha} I_{T_3} \geq 0,\\
{}^{c}\mathbb{D}_t^{\alpha} R_H\big|_{R_H=0} &= m_H^{\alpha} I_{H_2} + \eta_{12}^{\alpha} I_{H_1} + (\eta_{12}^{*})^{\alpha} I_{H_3} + \alpha_H^{\alpha}(R_T + R_D) \geq 0,\\
{}^{c}\mathbb{D}_t^{\alpha} R_D\big|_{R_D=0} &= m_D^{\alpha} I_{D_2} + \eta_{13}^{\alpha} I_{D_1} + (\eta_{13}^{*})^{\alpha} I_{D_3} + \alpha_D^{\alpha} R_T + \alpha_{HD}^{\alpha} R_H \geq 0.
\end{aligned} \tag{4.2}
$$

Using the Corollary (4.2.1.1), we have that the solution will remain in Ω_F [54]. □

Biologically Feasible Region

Now, let's prove that Ω^{α} is the biologically feasible region for the model (4.1).

Lemma 4.2.3. *The closed set* $\Omega^{\alpha} = \left\{ (S_i, E_i, I_{i_1}, I_{i_2}, I_{i_3}, R_i) \in \mathbb{R}_{+}^{18}, i = T, H, D : N(t) \leq \frac{M_T^{\alpha} + M_H^{\alpha} + M_D^{\alpha}}{\mu^{\alpha}} \right\}$ *is positively invariant with respect to model (4.1).*

Proof. The fractional derivative in the Caputo sense of the total population is

$$
\begin{aligned}
{}^{c}\mathbb{D}_t^{\alpha} N(t) = {}& {}^{c}\mathbb{D}_t^{\alpha} S_T(t) + {}^{c}\mathbb{D}_t^{\alpha} S_H(t) + {}^{c}\mathbb{D}_t^{\alpha} S_D(t) + {}^{c}\mathbb{D}_t^{\alpha} E_T(t) + {}^{c}\mathbb{D}_t^{\alpha} E_H(t) + {}^{c}\mathbb{D}_t^{\alpha} E_D(t) + {}^{c}\mathbb{D}_t^{\alpha} I_{T_1}(t) + \\
& {}^{c}\mathbb{D}_t^{\alpha} I_{T_2}(t) + {}^{c}\mathbb{D}_t^{\alpha} I_{H_1}(t) + {}^{c}\mathbb{D}_t^{\alpha} I_{H_2}(t) + {}^{c}\mathbb{D}_t^{\alpha} I_{D_1}(t) + {}^{c}\mathbb{D}_t^{\alpha} I_{D_2}(t) + {}^{c}\mathbb{D}_t^{\alpha} I_{T_3}(t) + {}^{c}\mathbb{D}_t^{\alpha} I_{H_3}(t) + \\
& {}^{c}\mathbb{D}_t^{\alpha} I_{D_3}(t) + {}^{c}\mathbb{D}_t^{\alpha} R_T(t) + {}^{c}\mathbb{D}_t^{\alpha} R_H(t) + {}^{c}\mathbb{D}_t^{\alpha} R_D(t),
\end{aligned}
$$

and we have that

$$
{}^{c}\mathbb{D}_t^{\alpha} N(t) + \mu^{\alpha} N(t) \leq M_T^{\alpha} + M_H^{\alpha} + M_D^{\alpha}. \tag{4.3}
$$

To continue the proof, we use the following definitions:

Definition 4.2.1. *The Laplace transform of the Caputo fractional derivatives of the function $\phi(t)$ with order $\alpha > 0$ is defined as*

$$\mathcal{L}\left[{}^{c}\mathbb{D}_{t}^{\alpha}\,\phi(t)\right] = s^{\alpha}\phi(s) - \sum_{v=0}^{n-1}\phi^{v}(0)s^{\alpha-v-1}. \tag{4.4}$$

Definition 4.2.2. *The Laplace transform of the function $t^{\alpha_1-1}\mathbb{E}_{\alpha,\alpha_1}(\pm\lambda t^{\alpha})$ is defined as*

$$\mathcal{L}\left[t^{\alpha_1-1}\mathbb{E}_{\alpha,\alpha_1}(\pm\lambda t^{\alpha})\right] = \frac{s^{\alpha-\alpha_1}}{s^{\alpha}\mp\lambda}, \tag{4.5}$$

where $\mathbb{E}_{\alpha,\alpha_1}$ is two-parameters Mittag-Leffler function $\alpha, \alpha_1 > 0$. Futher, the Mittag-Leffler function satisfies the fallowing equation:

$$\mathbb{E}_{\alpha,\alpha_1}(f) = f\cdot\mathbb{E}_{\alpha,\alpha+\alpha_1}(f) + \frac{1}{\Gamma(\alpha_1)}. \tag{4.6}$$

Applying the Laplace transform to (4.3), we have

$$s^{\alpha}\phi(N) - s^{\alpha-1}\phi(0) \leq \frac{M_T^{\alpha} + M_H^{\alpha} + M_D^{\alpha}}{s} - \mu^{\alpha}\phi(N), \tag{4.7}$$

which further gives

$$\phi(N) \leq \frac{M_T^{\alpha} + M_H^{\alpha} + M_D^{\alpha}}{s(s^{\alpha}+\mu^{\alpha})} + \frac{s^{\alpha-1}}{s^{\alpha}+\mu^{\alpha}}N(0). \tag{4.8}$$

Using the equations (4.4)-(4.6), we assumed that $(S_T(0), S_H(0), S_D(0), E_T(0), E_H(0), E_D(0), I_{T_1}(0), I_{T_2}(0), I_{H_1}(0), I_{H_2}(0), I_{D_1}(0), I_{D_2}(0), I_{T_3}(0), I_{H_3}(0), I_{D_3}(0), R_T(0), R_H(0), R_D(0)) \in \mathbb{R}_{+}^{18}$, then

$$N(t) \leq (M_T^{\alpha} + M_H^{\alpha} + M_D^{\alpha})t^{\alpha}\mathbb{E}_{\alpha,\alpha+1}(-\mu^{\alpha}t^{\alpha}) + N(0)\mathbb{E}_{\alpha,1}(-\mu^{\alpha}t^{\alpha}). \tag{4.9}$$

Using the asymptotic behavior of the Mittag-Leffler function presented in the background theorical (1.1.2), we can observed that $N(t) \to \dfrac{M_T^{\alpha} + M_H^{\alpha} + M_D^{\alpha}}{\mu^{\alpha}}$ when $t \to \infty$.
The Ω^{α} region is well established and all solutions with initial values that belong to Ω^{α} remain in Ω^{α} for each time $t > 0$ [54]. □

Study of the Equilibrium Points and the Basic Reproduction Number

In this subsection, we study the equilibrium points and their relation to the basic reproduction number for the model with fractional-order derivatives. We study by subpopulations and use the next-generation matrix method [51].

TB-Only Submodel

The TB-Only submodel with fractional-order derivatives is:

$$
\begin{aligned}
{}^{c}\mathbb{D}_t^{\alpha} S_T &= M_T^{\alpha} - (\mu^{\alpha} + \alpha_D^{\alpha} + \alpha_H^{\alpha} + \lambda_T^{\alpha}) S_T, \\
{}^{c}\mathbb{D}_t^{\alpha} E_T &= \lambda_T^{\alpha}(S_T + \beta_1^{'} R_T) - (\alpha_D^{\alpha} + \alpha_H^{\alpha} + \eta^{\alpha} + \mu^{\alpha}) E_T, \\
{}^{c}\mathbb{D}_t^{\alpha} I_{T_1} &= (1 - (\beta^*)^{\alpha}) \eta^{\alpha} E_T - (l_T^{\alpha} + t_D \alpha_D^{\alpha} + t_H \alpha_H^{\alpha} + \mu^{\alpha} + d_T^{\alpha} + \eta_{11}^{\alpha}) I_{T_1}, \\
{}^{c}\mathbb{D}_t^{\alpha} I_{T_2} &= (1 - p_T^{\alpha})(\beta^*)^{\alpha} \eta^{\alpha} E_T + l_T^{\alpha} I_{T_1} - (m_T^{\alpha} + \mu^{\alpha} + t_T^{'} d_T^{\alpha} + \eta_{14}^{\alpha} + t_D \alpha_D^{\alpha} + t_H \alpha_H^{\alpha}) I_{T_2}, \\
{}^{c}\mathbb{D}_t^{\alpha} I_{T_3} &= (\beta^*)^{\alpha} p_T^{\alpha} \eta E_T + \eta_{14}^{\alpha} I_{T_2} - ((\eta_{11}^*)^{\alpha} + \mu^{\alpha} + t_T^* d_T^{\alpha} + t_D \alpha_D^{\alpha} + t_H \alpha_H^{\alpha}) I_{T_3}, \\
{}^{c}\mathbb{D}_t^{\alpha} R_T &= m_T^{\alpha} I_{T_2} + \eta_{11}^{\alpha} I_{T_1} + (\eta_{11}^*)^{\alpha} I_{T_3} - (\mu^{\alpha} + \beta_1^{'} \lambda_T^{\alpha} + \alpha_D^{\alpha} + \alpha_H^{\alpha}) R_T,
\end{aligned} \tag{4.10}
$$

with initial conditions:

$$S_T(0) > 0, E_T(0) > 0, I_{T_1}(0) > 0, I_{T_2}(0) > 0, I_{T_3}(0) > 0 \text{ and } R_T(0) > 0.$$

The TB-infection rate for this submodel is

$$\lambda_T^{\alpha} = (\alpha^*)^{\alpha} \frac{\left(I_{T_1} + I_{T_2} + I_{T_3}\right)}{N_T},$$

where

$$N_T = S_T + E_T + I_{T_1} + I_{T_2} + I_{T_3} + R_T.$$

We study the submodel (4.10) in the following region:

$$D_1^{\alpha} = \left\{ (S_T, E_T, I_{T_1}, I_{T_2}, I_{T_3}, R_T) \in \mathbb{R}_+^6 \, : \, N_T(t) \leq \frac{M_T^{\alpha}}{\mu^{\alpha}} \right\}.$$

Using previous methodologies, we have that the solutions of the submodel (4.10), $(S_T(t), E_T(t), I_{T_1}(t), I_{T_2}(t), I_{T_3}(t), R_T(t))$ are bounded and positively invariant in D_1^{α} (biologically feasible region) for all $\alpha \in (0, 1]$.

Disease-Free Equilibrium Point

The disease-free equilibrium point of model (4.10) is given by

$$\epsilon_0^{T_{\alpha}} = \left(S_0^{T_{\alpha}}, 0, 0, 0, 0, 0 \right),$$

where $S_0^{T_{\alpha}} = \dfrac{M_T^{\alpha}}{\mu^{\alpha} + \alpha_D^{\alpha} + \alpha_H^{\alpha}}$.

The basic reproduction number is compute using next-generation matrix method (analogous to the model with ordinary differential equations) and is defined as

$$\mathfrak{R}_0^{T_{\alpha}} = \frac{(\alpha^*)^{\alpha} M_T^{\alpha} \left((1 - (\beta^*)^{\alpha}) \eta^{\alpha} (k_{13}^{\alpha} k_{14}^{\alpha} + l_T^{\alpha} (k_{14}^{\alpha} + \eta_{14}^{\alpha})) + (1 - p_T^{\alpha})(\beta^*)^{\alpha} \eta^{\alpha} k_{12}^{\alpha} (k_{14}^{\alpha} + \eta_{14}^{\alpha}) + k_{12}^{\alpha} k_{13}^{\alpha} (\beta^*)^{\alpha} \eta^{\alpha} p_T^{\alpha} \right)}{N_T (\alpha_D^{\alpha} + \alpha_H^{\alpha} + \mu^{\alpha}) k_{11}^{\alpha} k_{12}^{\alpha} k_{13}^{\alpha} k_{14}^{\alpha}}, \tag{4.11}$$

where $k_{11}^{\alpha} = \alpha_D^{\alpha} + \alpha_H^{\alpha} + \eta^{\alpha} + \mu^{\alpha}$, $k_{12}^{\alpha} = l_T^{\alpha} + t_D\alpha_D^{\alpha} + t_H\alpha_H^{\alpha} + \mu^{\alpha} + d_T^{\alpha} + \eta_{11}^{\alpha}$, $k_{13}^{\alpha} = \mu^{\alpha} + t_T^{'}d_T^{\alpha} + \eta_{14}^{\alpha} + m_T^{\alpha} + t_D\alpha_D^{\alpha} + t_H\alpha_H^{\alpha}$, and $k_{14}^{\alpha} = \mu^{\alpha} + t_T^{*}d_T^{\alpha} + (\eta_{11}^{*})^{\alpha} + t_D\alpha_D^{\alpha} + t_H\alpha_H^{\alpha}$.

Lemma 4.2.4. *(Theorem (2) of [115]) For any $q, r \in \mathbb{Z}_+$, such that $gcd(q, r) = 1$ Let $\alpha = \frac{q}{r}$ and we define $M = r$, then the disease-free equilibrium is locally asymptotically stable if $|\arg(\lambda)| > \frac{\pi}{2M}$ for all roots λ of the associated characteristic equation*

$$Det(diag[\lambda^q\lambda^q\lambda^q\lambda^q\lambda^q\lambda^q] - J(\epsilon_0^{T_\alpha})) = 0, \tag{4.12}$$

where $J(\epsilon_0^{T_\alpha})$ is the jacobian matrix of submodel at $\epsilon_0^{T_\alpha}$. The disease-free equilibrium $\epsilon_0^{T_\alpha}$ is unstable if $\mathfrak{R}_0^{T_\alpha} > 1$.

Proof. The Jacobian of submodel at disease-free equilibrium is

$$\begin{pmatrix} -(\mu^{\alpha} + \alpha_D^{\alpha} + \alpha_H^{\alpha}) & 0 & 0 & 0 & 0 & 0 \\ 0 & -k_{11}^{\alpha} & 0 & 0 & 0 & 0 \\ 0 & (1-(\beta^*)^{\alpha})\eta^{\alpha} & -k_{12}^{\alpha} & 0 & 0 & 0 \\ 0 & (1-p_T^{\alpha})(\beta^*)^{\alpha}\eta^{\alpha} & l_T^{\alpha} & -k_{13}^{\alpha} & 0 & 0 \\ 0 & p_T^{\alpha}(\beta^*)^{\alpha}\eta^{\alpha} & 0 & \eta_{14}^{\alpha} & -k_{14}^{\alpha} & 0 \\ 0 & 0 & \eta_{11}^{\alpha} & m_T^{\alpha} & (\eta_{11}^{*})^{\alpha} & -(\mu^{\alpha} + \alpha_D^{\alpha} + \alpha_H^{\alpha}) \end{pmatrix}.$$

Expanding, $Det(\lambda^q I_6 - J(\epsilon_0^{T_\alpha})) = 0$, where I_6 is the identity matrix of order 6, we obtain the following equation in terms of λ:

$$(-\alpha_D^{\alpha} - \alpha_H^{\alpha} - \mu^{\alpha} - \lambda^q)^2(\lambda^{4q} + b_1\lambda^{3q} + b_2\lambda^{2q} + b_3\lambda^q + b_4) = 0. \tag{4.13}$$

The arguments of the roots of equation $-\alpha_D^{\alpha} - \alpha_H^{\alpha} - \mu^{\alpha} - \lambda^q = 0$ are given by:

$$\arg(\lambda_k) = \frac{\pi}{q} + k\frac{2\pi}{q} > \frac{\pi}{M} > \frac{\pi}{2M},$$

where $k = 0, 1, ..., (q-1)$.

Now, the coefficients of $p(\lambda) = \lambda^{4q} + b_1\lambda^{3q} + b_2\lambda^{2q} + b_3\lambda^q + b_4$ are

$$\begin{aligned}
b_1 =& k_{11}^{\alpha} + k_{12}^{\alpha} + k_{13}^{\alpha} + k_{14}^{\alpha},\\
b_2 =& k_{11}^{\alpha}k_{12}^{\alpha} + k_{11}^{\alpha}k_{13}^{\alpha} + k_{11}^{\alpha}k_{14}^{\alpha} + k_{12}^{\alpha}k_{14}^{\alpha} + k_{13}^{\alpha}k_{14}^{\alpha} - \frac{M_T^{\alpha}(\alpha^*)^{\alpha}\eta^{\alpha}}{N_T(\mu^{\alpha} + \alpha_D^{\alpha} + \alpha_H^{\alpha})},\\
b_3 =& k_{11}^{\alpha}k_{12}^{\alpha}k_{13}^{\alpha} + k_{11}^{\alpha}k_{12}^{\alpha}k_{14}^{\alpha} + k_{11}^{\alpha}k_{13}^{\alpha}k_{14}^{\alpha} + k_{12}^{\alpha}k_{13}^{\alpha}k_{14}^{\alpha} - \frac{M_T^{\alpha}(\alpha^*)^{\alpha}\eta^{\alpha}}{N_T(\mu^{\alpha} + \alpha_D^{\alpha} + \alpha_H^{\alpha})}\big((1-(\beta^*)^{\alpha})(l_T^{\alpha} + k_{13}^{\alpha}) +\\
& (1-p_T^{\alpha})(\beta^*)^{\alpha}\eta_{14}^{\alpha} + (\beta^*)^{\alpha}p_T^{\alpha}((t_T^{'} - t_T^{*})d_T^{\alpha} + (m_T^{\alpha} - (\eta_{11}^{*})^{\alpha}) + \eta_{14}^{\alpha}\big),\\
b_4 =& k_{11}^{\alpha}k_{12}^{\alpha}k_{13}^{\alpha}k_{14}^{\alpha} - \frac{M_T^{\alpha}(\alpha^*)^{\alpha}\eta^{\alpha}}{N_T(\mu^{\alpha} + \alpha_D^{\alpha} + \alpha_H^{\alpha})}\big((1-(\beta^*)^{\alpha})(k_{13}^{\alpha}k_{14}^{\alpha}) + l_T^{\alpha}(k_{14}^{\alpha} + \eta_{14}^{\alpha}) + (1-p_T^{\alpha})k_{12}^{\alpha}(\beta^*)^{\alpha}(k_{14}^{\alpha} +\\
& \eta_{14}^{\alpha}) + k_{12}^{\alpha}k_{13}^{\alpha}(\beta^*)^{\alpha}p_T^{\alpha}\big) = (1-\mathfrak{R}_0^{T}).
\end{aligned}$$

The function $p(\lambda)$ has eigenvalues with negative real part if $b_1, b_2, b_3, b_4 > 0$ and $b_1b_2b_3 > b_1^2b_4 + b_3^2$. All b_i's are greater than zero if $\mathfrak{R}_0^{T_\alpha} < 1$, and the conditions $b_1b_2b_3 >$

$b_1^2 b_4 + b_3^2$ ensure the stability of the disease-free case when $\mathfrak{R}_0^{T_\alpha} < 1$. If $\mathfrak{R}_0^{T_\alpha} < 1$, then the necessary condition fulfill for all the roots of characteristics equation i.e.,$|\arg(\lambda)| > \frac{\pi}{2M}$. Thus, the infection-free equilibrium point is locally asymptotically stable if $\mathfrak{R}_0^{T_\alpha} < 1$. □

This proof can be found in [54].

Endemic Equilibrium Point

To find the endemic point, we apply a methodology analogous to the TB-Only submodel with ODE (2.11). Then, the endemic equilibrium point is $\epsilon_*^{T_\alpha} = (S_{T^\alpha}^*, E_{T^\alpha}^*, I_{T_1^\alpha}^*, I_{T_2^\alpha}^*, I_{T_3^\alpha}^*, R_{T^\alpha}^*)$ where,

$$
\begin{aligned}
S_{T^\alpha}^* &= \frac{M_T^\alpha}{(\lambda_T^\alpha)^* + \alpha_D^\alpha + \alpha_H^\alpha + \mu^\alpha}, \quad E_{T^\alpha}^* = \frac{M_T^\alpha (\lambda_T^\alpha)^* k_{12}^\alpha k_{13}^\alpha k_{14}^\alpha (\alpha_D^\alpha + \alpha_H^\alpha + \beta_1^{'}(\lambda_T^\alpha)^* + \mu^\alpha)}{A_1^\alpha},\\
I_{T_1^\alpha}^* &= \frac{M_T^\alpha (1-(\beta^*)^\alpha)\eta^\alpha (\lambda_T^\alpha)^* k_{13}^\alpha k_{14}^\alpha (\alpha_D^\alpha + \alpha_H^\alpha + \beta_1^{'}(\lambda_T^\alpha)^* + \mu^\alpha)}{A_1^\alpha},\\
I_{T_2^\alpha}^* &= \frac{M_T^\alpha (\lambda_T^\alpha)^* (\alpha_D^\alpha + \alpha_H^\alpha + \beta_1^{'}(\lambda_T^\alpha)^* + \mu^\alpha)(k_{12}^\alpha k_{14}^\alpha (\beta^*)^\alpha \eta^\alpha (1-p_T^\alpha) + k_{14}^\alpha l_T^\alpha (1-(\beta^*)^\alpha)\eta^\alpha)}{A_1^\alpha},\\
I_{T_3^\alpha}^* &= \frac{M_T^\alpha (\lambda_T^\alpha)^* (\alpha_D^\alpha + \alpha_H^\alpha + \beta_1^{'}(\lambda_T^\alpha)^* + \mu^\alpha)(l_T^\alpha \eta_{14}^\alpha (1-(\beta^*)^\alpha)\eta^\alpha + k_{12}^\alpha (\beta^*)^\alpha \eta^\alpha \eta_{14}^\alpha (1-p_T^\alpha) + k_{12}^\alpha k_{13}^\alpha (\beta^*)^\alpha \eta^\alpha p_T^\alpha)}{A_1^\alpha},\\
R_{T^\alpha}^* &= \frac{M_T^\alpha (\lambda_T^\alpha)^* ((1-(\beta^*)^\alpha)\eta^\alpha (k_{13}^\alpha k_{14}^\alpha \eta_{11}^\alpha + l_T^\alpha (k_{14}^\alpha m_T^\alpha + (\eta_{11}^*)^\alpha + \eta_{14}^\alpha) + (1-p_T^\alpha) k_{12}^\alpha (\beta^*)^\alpha \eta^\alpha (k_{14}^\alpha m_T^\alpha + (\eta_{11}^*)^\alpha (\eta_{14}^*)^\alpha) +}{A_1^\alpha}\\
&\frac{k_{12}^\alpha k_{13}^\alpha \eta^\alpha (\eta_{11}^*)^\alpha (\beta^*)^\alpha p_T^\alpha)}{A_1^\alpha},
\end{aligned}
\tag{4.14}
$$

and $A_1^\alpha = (\alpha_D^\alpha + \alpha_H^\alpha + \mu^\alpha + (\lambda_T^\alpha)^*)(\alpha_D^\alpha + \alpha_H^\alpha + \mu^\alpha + \beta_1^{'}(\lambda_T^\alpha)^*) k_{11}^\alpha k_{12}^\alpha k_{13}^\alpha k_{14}^\alpha - (\alpha_D^\alpha + \alpha_H^\alpha + \mu^\alpha + (\lambda_T^\alpha)^*)\beta_1^{'}(\lambda_T^\alpha)^* \big((1-p_T^\alpha) k_{12}^\alpha (\beta^*)^\alpha \eta^\alpha (k_{14}^\alpha m_T^\alpha + (\eta_{11}^*)^\alpha \eta_{14}^\alpha) + (1-(\beta^*)^\alpha)\eta^\alpha (k_{13} k_{14}^\alpha \eta_{11}^\alpha + l_T^\alpha (k_{14} m_T^\alpha + \eta_{11}^\alpha \eta_{14}^\alpha) + k_{12}^\alpha k_{13}^\alpha \beta^\alpha \eta^\alpha \eta_{11}^\alpha p_T^\alpha\big)$.
Applying the analogous methodology to the TB-Ony submodel with ODE (2.3), we have the following lemma:

Lemma 4.2.5. *The TB-Only submodel (4.10) has a unique endemic equilibrium point $\epsilon_*^{T_\alpha}$, whenever $\mathfrak{R}_0^{T_\alpha} > 1$.*

TB-HIV/AIDS Submodel

The TB-HIV/AIDS submodel ($S_T = S_D = E_T = E_D = I_{T_1} = I_{T_2} = I_{D_1} = I_{D_2} = I_{T_3} = I_{D_3} = R_T = R_D = 0$) is determined by

$$
\begin{aligned}
{}^c\mathbb{D}_t^\alpha S_H &= M_H^\alpha - (\alpha_{HD}^\alpha + \mu^\alpha + \mu_H^\alpha + \omega_H \lambda_H^\alpha) S_H,\\
{}^c\mathbb{D}_t^\alpha E_H &= \omega_H \lambda_H^\alpha (S_H + \beta_1^{'} R_H) - (\epsilon_H^* \eta^\alpha + \mu^\alpha + \mu_H^\alpha + \alpha_{HD}^\alpha) E_H,\\
{}^c\mathbb{D}_t^\alpha I_{H_1} &= (1-(\beta^*)^\alpha)\epsilon_H^* \eta^\alpha E_H - (l_H^\alpha + \mu^\alpha + \mu_H^\alpha + d_{TH}^\alpha + \eta_{12}^\alpha + t_{HD}\alpha_{HD}^\alpha) I_{H_1},\\
{}^c\mathbb{D}_t^\alpha I_{H_2} &= (1-p_H^\alpha)(\beta^*)^\alpha \epsilon_H^* \eta^\alpha E_H + l_H^\alpha I_{H_1} - (m_H^\alpha + \mu^\alpha + \mu_H^\alpha + t_H^{'} d_{TH}^\alpha + \eta_{15}^\alpha + t_{HD}\alpha_{HD}^\alpha) I_{H_2},\\
{}^c\mathbb{D}_t^\alpha I_{H_3} &= p_H^\alpha (\beta^*)^\alpha \epsilon_H^* \eta^\alpha E_H + \eta_{15}^\alpha I_{H_2} - ((\eta_{12}^*)^\alpha + \mu^\alpha + \mu_H^\alpha + t_H^* d_{TH}^\alpha + t_{HD}\alpha_{HD}^\alpha) I_{H_3},\\
{}^c\mathbb{D}_t^\alpha R_H &= m_H^\alpha I_{H_2} + \eta_{12}^\alpha I_{H_1} + (\eta_{12}^*)^\alpha I_{H_3} - (\mu^\alpha + \mu_H^\alpha + \beta_1^{'}\omega_H \lambda_H^\alpha + \alpha_{HD}^\alpha) R_H,
\end{aligned}
\tag{4.15}
$$

with non-negative initial conditions and

$$\lambda_H^\alpha = (\alpha^*)^\alpha \frac{\epsilon_H(I_{H_1} + I_{H_2} + I_{H_3})}{N_H},$$

where $N_H = S_H + E_H + I_{H_1} + I_{H_2} + I_{H_3} + R_H$.

The system (4.15) is studied in the following region:

$$D_2^\alpha = \left\{ (S_H, E_H, I_{H_1}, I_{H_2}, I_{H_3}, R_H) \in \mathbb{R}_+^6 \,:\, N_H(t) \leq \frac{M_H^\alpha}{\mu^\alpha} \right\}.$$

It can be easily shown that te solutions $\left(S_H(t), E_H(t), I_{H_1}(t), I_{H_2}(t), I_{H_3}(t), R_H(t)\right)$ of the system are bounded and positively invariant.

The infection-free equilibrium point is $\epsilon_0^{H_\alpha} = \left(S_0^{H_\alpha}, 0, 0, 0, 0, 0\right)$ where $S_0^{H_\alpha} = \frac{M_H^\alpha}{\mu^\alpha + \mu_H^\alpha + \alpha_D^\alpha}$, and

$$\mathfrak{R}_0^{H_\alpha} = \frac{(\alpha^*)^\alpha \epsilon_H \omega_H M_H^\alpha \left((1-(\beta^*)^\alpha)\epsilon_H^* \eta^\alpha (k_{23}^\alpha k_{24}^\alpha + l_H^\alpha (k_{24}^\alpha + \eta_{15}^\alpha)) + (1-p_H^\alpha)\epsilon_H^* (\beta^*)^\alpha \eta^\alpha k_{22}^\alpha (k_{24}^\alpha + \eta_{15}^\alpha) + k_{22}^\alpha k_{23}^\alpha \epsilon_H^* (\beta^*)^\alpha \eta^\alpha p_H^\alpha\right)}{N_H(\alpha_{HD}^\alpha + \mu^\alpha + \mu_H^\alpha) k_{21}^\alpha k_{22}^\alpha k_{23}^\alpha k_{24}^\alpha}, \tag{4.16}$$

where $k_{21}^\alpha = \alpha_{HD}^\alpha + \epsilon_H^* \eta^\alpha + \mu^\alpha + \mu_H^\alpha$, $k_{22}^\alpha = l_H^\alpha + \mu^\alpha + \mu_H^\alpha + d_{TH}^\alpha + \eta_{12}^\alpha + t_{HD}\alpha_{HD}^\alpha$, $k_{23}^\alpha = \mu^\alpha + \mu_H^\alpha + t_H^{'} d_{TH}^\alpha + \eta_{15}^\alpha + m_H^\alpha + t_{HD}\alpha_{HD}^\alpha$, and $k_{24}^\alpha = \mu^\alpha + \mu_H^\alpha + t_H^* d_{TH}^\alpha + (\eta_{12}^*)^\alpha + t_{HD}\alpha_{HD}^\alpha$.

Using an analogous procedure to the TB-Only submodel with FDE (4.10), we obtained the following lemma:

Lemma 4.2.6. *The infection-free equilibrium point, $\epsilon_0^{H_\alpha}$ is asymptotically stable if $\mathfrak{R}_0^{H_\alpha} < 1$ and unstable if $\mathfrak{R}_0^{H_\alpha} > 1$.*

The endemic equilibrium point is given by $\epsilon_*^{H_\alpha} = (S_{H^\alpha}^*, E_{H^\alpha}^*, I_{H_1^\alpha}^*, I_{H_2^\alpha}^*, I_{H_3^\alpha}^*, R_{H^\alpha}^*)$ where,

$$S_{H^\alpha}^* = \frac{M_H^\alpha}{\omega_H(\lambda_H^\alpha)^* + \alpha_{HD}^\alpha + \mu^\alpha + \mu_H^\alpha}, \quad E_{H^\alpha}^* = \frac{M_H^\alpha \omega_H (\lambda_H^\alpha)^* k_{22}^\alpha k_{23}^\alpha k_{24}^\alpha (\alpha_{HD}^\alpha + \omega_H \beta_1^{'} (\lambda_H^\alpha)^* + \mu^\alpha + \mu_H^\alpha)}{A_2^\alpha},$$

$$I_{H_1^\alpha}^* = \frac{M_H^\alpha (1-(\beta^*)^\alpha)\epsilon_H^* \eta^\alpha \omega_H (\lambda_H^\alpha)^* k_{23}^\alpha k_{24}^\alpha (\alpha_{HD}^\alpha + \omega_H \beta_1^{'} (\lambda_H^\alpha)^* + \mu^\alpha + \mu_H^\alpha)}{A_2^\alpha},$$

$$I_{H_2^\alpha}^* = \frac{M_H^\alpha \omega_H (\lambda_H^\alpha)^* (\alpha_{HD}^\alpha + \omega_H \beta_1^{'} (\lambda_H^\alpha)^* + \mu^\alpha + \mu_H^\alpha)(k_{22}^\alpha k_{24}^\alpha \epsilon_H^* (\beta^*)^\alpha \eta^\alpha (1-p_H^\alpha) + k_{24}^\alpha l_H^\alpha (1-(\beta^*)^\alpha)\epsilon_H^* \eta^\alpha)}{A_2^\alpha},$$

$$I_{H_3^\alpha}^* = \frac{M_H^\alpha \omega_H (\lambda_H^\alpha)^* (\alpha_{HD}^\alpha + \omega_H \beta_1^{'} (\lambda_H^\alpha)^* + \mu^\alpha + \mu_H^\alpha)(l_H^\alpha \eta_{15}^\alpha (1-(\beta^*)^\alpha)\epsilon_H^* \eta^\alpha + k_{22}^\alpha (\beta^*)^\alpha \epsilon_H^* \eta^\alpha \eta_{15}^\alpha (1-p_H^\alpha) + k_{22}^\alpha k_{23}^\alpha (\beta^*)^\alpha \epsilon_H^* \eta^\alpha p_H^\alpha)}{A_2^\alpha},$$

$$R_{H^\alpha}^* = \frac{M_H^\alpha \omega_H (\lambda_H^\alpha)^* ((1-(\beta^*)^\alpha)\epsilon_H^* \eta^\alpha)(k_{23}^\alpha k_{24}^\alpha \eta_{12}^\alpha + l_T^\alpha (k_{24}^\alpha m_H^\alpha + (\eta_{12}^*)^\alpha \eta_{15}^\alpha) + (1-p_H^\alpha) k_{22}^\alpha (\beta^*)^\alpha \epsilon_H^* \eta^\alpha (k_{24}^\alpha m_H^\alpha + (\eta_{12}^*)^\alpha \eta_{15}^\alpha) +}{A_2^\alpha}$$

$$\frac{k_{22}^\alpha k_{23}^\alpha (\beta^*)^\alpha \epsilon_H^* \eta^\alpha (\eta_{12}^*)^\alpha p_H^\alpha)}{A_2^\alpha}, \tag{4.17}$$

and $A_2^\alpha = (\alpha_{HD}^\alpha + \mu^\alpha + \mu_H^\alpha + \omega_H(\lambda_H^\alpha)^*)(\alpha_{HD}^\alpha + \mu^\alpha + \mu_H^\alpha + \omega_H(\beta^{'})_1(\lambda_H^\alpha)^*) k_{21}^\alpha k_{22}^\alpha k_{23}^\alpha k_{24}^\alpha - (\alpha_{HD}^\alpha + \mu^\alpha + \omega_H(\lambda_H^\alpha)^*)\beta_1^{'} \omega_H(\lambda_H^\alpha)^* ((1-p_H^\alpha) k_{22}^\alpha (\beta^*)^\alpha \epsilon_H^* \eta^\alpha (k_{24}^\alpha m_H^\alpha + (\eta_{12}^*)^\alpha \eta_{15}^\alpha) + (1-(\beta^*)^\alpha)\epsilon_H^* \eta^\alpha (k_{23}^\alpha k_{24}^\alpha \eta_{12}^\alpha + l_H^\alpha (k_{24}^\alpha m_H^\alpha + (\eta_{12}^*)^\alpha \eta_{12}^\alpha) + k_{22}^\alpha k_{23}^\alpha (\beta^*)^\alpha \epsilon_H^* \eta^\alpha (\eta_{12}^*)^\alpha p_H^\alpha)$.

We apply an analogous procedure to the previous submodel, we have the following

lemma:

Lemma 4.2.7. *The TB-HIV/AIDS submodel (4.15) has a unique endemic equilibrium point* $\epsilon_*^{H_\alpha}$, *whenever* $\mathfrak{R}_0^{H_\alpha} > 1$.

TB-Diabetes Submodel

The TB-Diabetes submodel is obtained when $S_H = S_T = E_H = E_T = I_{H_1} = I_{H_2} = I_{T_1} = I_{T_2} = I_{H_3} = R_H = I_{T_3} = R_T = 0$ and is defined as:

$$
\begin{aligned}
{}^c\mathbb{D}_t^\alpha S_D &= M_D^\alpha - (\alpha_H^\alpha + \mu^\alpha + \mu_D^\alpha + \omega_D\lambda_D^\alpha)S_D,\\
{}^c\mathbb{D}_t^\alpha E_D &= \omega_D\lambda_D^\alpha(S_D + \beta_1^{'}R_D) - (\eta^\alpha + \mu^\alpha + \mu_D^\alpha + \alpha_H^\alpha)E_D,\\
{}^c\mathbb{D}_t^\alpha I_{D_1} &= (1-(\beta^*)^\alpha)\epsilon_D^*\eta^\alpha E_D - (l_D^\alpha + t_H\alpha_H^\alpha + \mu^\alpha + \mu_D^\alpha + d_{TD}^\alpha + \eta_{13}^\alpha)I_{D_1},\\
{}^c\mathbb{D}_t^\alpha I_{D_2} &= (1-p_D^\alpha)\epsilon_D^*(\beta^*)^\alpha\eta^\alpha E_D + l_D^\alpha I_{D_1} - (t_H\alpha_H^\alpha + m_D^\alpha + \mu^\alpha + \mu_D^\alpha + t_D^{'}d_{TD}^\alpha + \eta_{16}^\alpha)I_{D_2},\\
{}^c\mathbb{D}_t^\alpha I_{D_3} &= p_D^\alpha(\beta^*)^\alpha\epsilon_D^*\eta^\alpha E_D + \eta_{16}^\alpha I_{D_2} - ((\eta_{13}^*)^\alpha + t_H\alpha_H^\alpha + \mu^\alpha + \mu_D^\alpha + t_D^*d_{TD}^\alpha)I_{D_3},\\
{}^c\mathbb{D}_t^\alpha R_D &= m_D^\alpha I_{D_2} + \eta_{13}^\alpha I_{D_1} + (\eta_{13}^*)^\alpha I_{D_3} - (\alpha_H^\alpha + \mu^\alpha + \mu_D^\alpha + \beta_1^{'}\omega_D\lambda_D^\alpha)R_D
\end{aligned}
\tag{4.18}
$$

with non-negative initial conditions and

$$\lambda_D^\alpha = (\alpha^*)^\alpha\frac{\epsilon_D(I_{D_1} + I_{D_2} + I_{D_3})}{N_D}$$

where $N_D = S_D + E_D + I_{D_1} + I_{D_2} + I_{D_3} + R_D$.

The system (4.18) will be studied in the following region biologically feasible:

$$D_3^\alpha = \left\{(S_D, E_D, I_{D_1}, I_{D_2}, I_{D_3}, R_D) \in \mathbb{R}_+^6 \,:\, N_D(t) \le \frac{M_D^\alpha}{\mu^\alpha}\right\}.$$

It can be easily shown that solutions $\big(S_D(t), E_D(t), I_{D_1}(t), I_{D_2}(t), I_{D_3}(t), R_D(t)\big)$ of the system are bounded and positively invariant.

The disease-free equilibrium point, $\epsilon_0^{D_\alpha}$, is given by:

$$\epsilon_0^{D_\alpha} = \left(S_0^{D_\alpha}, 0, 0, 0, 0, 0\right),$$

where $S_0^{D_\alpha} = \dfrac{M_D^\alpha}{\mu^\alpha + \mu_2^\alpha + \alpha_H^\alpha}$.

The basic number reproduction is:

$$\mathfrak{R}_0^{D_\alpha} = \frac{(\alpha^*)^\alpha\epsilon_D\omega_D M_D^\alpha\big((1-(\beta^*)^\alpha)\epsilon_D^*\eta^\alpha(k_{33}^\alpha k_{34}^\alpha + l_D^\alpha(k_{34}^\alpha + \eta_{16}^\alpha)) + (1-p_D^\alpha)\epsilon_D^*(\beta^*)^\alpha\eta^\alpha k_{32}^\alpha(k_{34}^\alpha + \eta_{16}^\alpha) + k_{32}^\alpha k_{33}^\alpha\epsilon_D^*(\beta^*)^\alpha\eta^\alpha p_D^\alpha\big)}{N_D(\alpha_H^\alpha + \mu^\alpha + \mu_D^\alpha)k_{31}^\alpha k_{32}^\alpha k_{33}^\alpha k_{34}^\alpha}, \tag{4.19}$$

where $k_{31}^\alpha = \alpha_H^\alpha + \epsilon_D^*\eta^\alpha + \mu^\alpha + \mu_D^\alpha$, $k_{32}^\alpha = l_D^\alpha + \mu^\alpha + d_{TD}^\alpha + \eta_{13}^\alpha + t_H\alpha_H^\alpha + \mu_D^\alpha$, $k_{33}^\alpha = \mu^\alpha + t_D^{'}d_{TD}^\alpha + \eta_{16}^\alpha + m_D^\alpha + t_H\alpha_H^\alpha + \mu_D^\alpha$ and $k_{34}^\alpha = \mu^\alpha + \mu_D^\alpha + t_D^*d_{TD}^\alpha + (\eta_{13}^*)^\alpha + t_H\alpha_H^\alpha$.

The following result is proved by applying the analogous methodology to the TB-Only submodel (4.2).

Lemma 4.2.8. *The infection-free equilibrium point, $\epsilon_0^{D_\alpha}$ is asymptotically stable if $\mathfrak{R}_0^{D_\alpha} < 1$ unstable if $\mathfrak{R}_0^{D_\alpha} > 1$.*

For the TB-Diabetes submodel (4.18) we have the following endemic equilibrium point $\epsilon_*^{D_\alpha} = (S_{D^\alpha}^*, E_{D^\alpha}^*, I_{D_1^\alpha}^*, I_{D_2^\alpha}^*, I_{D_3^\alpha}^*, R_{D^\alpha}^*)$ where,

$$S_{D^\alpha}^* = \frac{M_D^\alpha}{\omega_D(\lambda_D^\alpha)^* + \alpha_H^\alpha + \mu^\alpha + \mu_D^\alpha}, \quad E_{D^\alpha}^* = \frac{M_D^\alpha \omega_D(\lambda_D^\alpha)^* k_{32}^\alpha k_{33}^\alpha k_{34}^\alpha (\alpha_H^\alpha + \omega_D \beta_1^{'}(\lambda_D^\alpha)^* + \mu^\alpha + \mu_D^\alpha)}{A_3^\alpha},$$

$$I_{D_1^\alpha}^* = \frac{M_D^\alpha (1-(\beta^*)^\alpha)\epsilon_H^{*\alpha}\eta^\alpha \omega_D(\lambda_D^\alpha)^* k_{33}^\alpha k_{34}^\alpha (\alpha_H^\alpha + \omega_D \beta_1^{'}(\lambda_D^\alpha)^* + \mu^\alpha + \mu_D^\alpha)}{A_3^\alpha},$$

$$I_{D_2^\alpha}^* = \frac{M_D^\alpha \omega_D(\lambda_D^\alpha)^* (\alpha_H^\alpha + \omega_D \beta_1^{'}(\lambda_D^\alpha)^* + \mu^\alpha + \mu_D^\alpha)(k_{32}^\alpha k_{34}^\alpha (\beta^*)^\alpha \epsilon_D^{*\alpha}\eta^\alpha (1-p_D^\alpha) + k_{34}^\alpha l_D^\alpha (1-(\beta^*)^\alpha)\epsilon_H^{*\alpha}\eta^\alpha)}{A_3^\alpha},$$

$$I_{D_3^\alpha}^* = \frac{M_D^\alpha \omega_D(\lambda_D^\alpha)^* (\alpha_H^\alpha + \omega_D \beta_1^{'}(\lambda_D^\alpha)^* + \mu^\alpha + \mu_D^\alpha)(l_D^\alpha \eta_{16}^\alpha (1-(\beta^*)^\alpha)\epsilon_D^{*\alpha}\eta^\alpha + k_{22}^\alpha \epsilon_D^{*\alpha}(\beta^*)^\alpha \eta^\alpha \eta_{16}^\alpha (1-p_D^\alpha) + k_{32}^\alpha k_{33}^\alpha \epsilon_H^{*\alpha}\eta^\alpha p_D^\alpha)}{A_3^\alpha},$$

$$R_{D^\alpha}^* = \frac{M_D^\alpha \omega_D(\lambda_D^\alpha)^* ((1-(\beta^*)^\alpha)\epsilon_D^{*\alpha}\eta^\alpha (k_{33}^\alpha k_{34}^\alpha \eta_{13}^\alpha + l_D^\alpha (k_{34}^\alpha m_D^\alpha + (\eta_{13}^*)^\alpha \eta_{16}^\alpha) + (1-p_D^\alpha)k_{32}^\alpha \epsilon_H^{*\alpha}(\beta^*)^\alpha \eta^\alpha (k_{34}^\alpha m_D^\alpha + (\eta_{13}^*)^\alpha \eta_{16}^\alpha) +}{A_3^\alpha}$$

$$\frac{k_{32}^\alpha k_{33}^\alpha \epsilon_D^{*\alpha}(\beta^*)^\alpha \eta^\alpha (\eta_{13}^*)^\alpha p_D^\alpha)}{A_3^\alpha}, \tag{4.20}$$

and $A_3^\alpha = (\alpha_H^\alpha + \mu^\alpha + \mu_D^\alpha + \omega_D(\lambda_D^\alpha)^*)(\alpha_H^\alpha + \mu^\alpha + \mu_D^\alpha + \omega_D \beta_1^{'}(\lambda_D^\alpha)^*)k_{31}^\alpha k_{32}^\alpha k_{33}^\alpha k_{34}^\alpha - (\alpha_H^\alpha + \mu^\alpha + \omega_D(\lambda_D^\alpha)^*)\beta_1^{'}\omega_D(\lambda_D^\alpha)^*\big((1-p_D^\alpha)k_{32}^\alpha(\beta^*)^\alpha \epsilon_D^{*\alpha}\eta^\alpha (k_{34}^\alpha m_D^\alpha + (\eta_{13}^*)^\alpha \eta_{16}^\alpha) + (1-(\beta^*)^\alpha)\epsilon_D^{*\alpha}\eta^\alpha (k_{33}^\alpha k_{34}^\alpha \eta_{13}^\alpha + l_D^\alpha (k_{34}^\alpha m_D^\alpha + (\eta_{13}^*)^\alpha \eta_{13}^\alpha) + k_{32}^\alpha k_{33}^\alpha \epsilon_D^{*\alpha}(\beta^*)^\alpha \eta^\alpha (\eta_{13}^*)^\alpha p_D^\alpha\big)$.

Analogously, we obtain the following lemma:

Lemma 4.2.9. *The TB-Diabetes submodel (4.18) has a unique endemic equilibrium point $\epsilon_*^{D_\alpha}$, whenever $\mathfrak{R}_0^{D_\alpha} > 1$.*

Analysis of the Full Model

For the full model (4.1), infection-free equilibrium point is

$$\epsilon_0^{G_\alpha} = (S_0^{T_\alpha}, S_0^{H_\alpha}, S_0^{D_\alpha}, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0),$$

and the basic reproduction number is calculated using next-generation matrix method. The dominant eigenvalues of the next-generation matrix are $\mathfrak{R}_0^{T_\alpha}$, $\mathfrak{R}_0^{H_\alpha}$ and $\mathfrak{R}_0^{D_\alpha}$. Then, the basic reproduction number of the model (4.1) is

$$\mathfrak{R}_0^\alpha = \max\{\mathfrak{R}_0^{T_\alpha}, \mathfrak{R}_0^{H_\alpha}, \mathfrak{R}_0^{D_\alpha}\}.$$

Global Stability

Now, using a methodology analogous to that applied to Model (2.5), we prove the global stability of the infection-free equilibrium point. Following [38], we can rewrite the model (4.1) as

$$\begin{aligned} {}^c\mathbb{D}_t^\alpha S &= F(S, I), \\ {}^c\mathbb{D}_t^\alpha I &= G(S, I), \quad G(S, 0) = 0, \end{aligned} \tag{4.21}$$

where $S \in \mathbb{R}^6_+$ is the vector with uninfected and recovered and $I \in \mathbb{R}^{12}_+$ have the other compartment of the model (4.1).

The disease-free equilibrium is now denoted by $E_0^{G_\alpha} = (S_0^\alpha, 0)$, $S_0^\alpha = (S_0, 0, 0, 0)$, $S_0 = (S_0^{T_\alpha}, S_0^{H_\alpha}, S_0^{D_\alpha})$ where $S_0^{T_\alpha} = \dfrac{M_T^\alpha}{\mu^\alpha + \alpha_D^\alpha + \alpha_H^\alpha}$, $S_0^{H_\alpha} = \dfrac{M_H^\alpha}{\mu^\alpha + \mu_H^\alpha + \alpha_{HD}^\alpha}$ and $S_0^{D_\alpha} = \dfrac{M_D^\alpha}{\mu^\alpha + \mu_D^\alpha + \alpha_H^\alpha}$. The conditions (H_1^α) and (H_2^α) below must be satisfied to guarantee the global asymptotic stability of E_0^G.

$$
\begin{aligned}
(H_1^\alpha) &: \quad \text{For} \quad {}^c\mathbb{D}_t^\alpha S = F(S,0), \quad S_0^\alpha \quad \text{is globally asymptotically stable,} \\
(H_2^\alpha) &: \quad G(S,I) = AI - G^*(S,I), \quad G^*(S,I) \geq 0, \quad \text{for} \quad (S,I) \in \Omega^\alpha,
\end{aligned}
$$

where $A = D_I G(S_0^\alpha, 0)$ ($D_I G(S_0^\alpha, 0)$ is the Jacobian of G at $(S_0^\alpha, 0)$) is a M-matrix (the off-diagonal elements of A are non-negative) and Ω^α is the biologically feasible region.

The following results show the global stability of the infection-free equilibrium point:

Theorem 4.2.10. *The fixed point $E_0^{G_\alpha}$ is a globally asymptotically stable equilibrium (g.a.s) of model (4.1) provided that $\mathfrak{R}_0 < 1$ and that the conditions (H_1^α) and (H_2^α) are satisfied.*

Proof. Let

$$
F(S,0) = \begin{pmatrix}
M_T^\alpha - (\mu^\alpha + \alpha_D^\alpha + \alpha_H^\alpha) S_T \\
M_H^\alpha - (\mu^\alpha + \mu_H^\alpha + \alpha_{HD}^\alpha) S_H \\
M_D^\alpha - (\mu^\alpha + \mu_D^\alpha + \alpha_H^\alpha) S_D \\
0 \\ 0 \\ 0
\end{pmatrix}.
$$

As $F(S,0)$ is a linear equation, then S_0^α is globally stable. Then, (H_1^α) is satisfied.
Let's $\mathbf{A} = [\mathbf{B_1} \mid \mathbf{B_2}]$ where

$$
\mathbf{B_1} = \begin{pmatrix}
-k_{11}^\alpha & 0 & 0 & (\alpha^*)^\alpha & (\alpha^*)^\alpha & (\alpha^*)^\alpha \epsilon_H \\
\alpha_H^\alpha & -k_{21}^\alpha & \alpha_H^\alpha & \omega_H (\alpha^*)^\alpha & \omega_H (\alpha^*)^\alpha & \omega_H (\alpha^*)^\alpha \epsilon_H \\
\alpha_D^\alpha & \alpha_{HD}^\alpha & -k_{31}^\alpha & \omega_D (\alpha^*)^\alpha & \omega_D (\alpha^*)^\alpha & \omega_D (\alpha^*)^\alpha \epsilon_H \\
(1 - (\beta^*)^\alpha) \eta^\alpha & 0 & 0 & -k_{12}^\alpha & 0 & 0 \\
(1 - p_T^\alpha)(\beta^*)^\alpha \eta^\alpha & 0 & 0 & l_T^\alpha & -k_{13}^\alpha & 0 \\
0 & (\beta^*)^\alpha \epsilon_H^* \eta^\alpha & 0 & t_H \alpha_H^\alpha & 0 & -k_{22}^\alpha \\
0 & (1 - p_H^\alpha)(\beta^*)^\alpha \epsilon_H^* \eta^\alpha & 0 & 0 & t_H \alpha_H^\alpha & l_H^\alpha \\
0 & 0 & (1 - (\beta^*)^\alpha) \epsilon_D^* \eta^\alpha & t_D \alpha_D^\alpha & 0 & \alpha_{HD}^\alpha \\
0 & 0 & (1 - p_D^\alpha)(\beta^*)^\alpha \epsilon_D^* \eta^\alpha & 0 & t_D \alpha_D^\alpha & 0 \\
p_T (\beta^*)^\alpha \eta^\alpha & 0 & 0 & 0 & \eta_{14}^\alpha & 0 \\
0 & p_H^\alpha \epsilon_H^* (\beta^*)^\alpha \eta^\alpha & 0 & 0 & 0 & 0 \\
0 & 0 & p_D^\alpha \epsilon_D^* (\beta^*)^\alpha \eta^\alpha & 0 & 0 & 0
\end{pmatrix},
$$

$$\mathbf{B_2} = \begin{pmatrix} (\alpha^*)^\alpha\epsilon_H & (\alpha^*)^\alpha\epsilon_D & (\alpha^*)^\alpha\epsilon_D & (\alpha^*)^\alpha & (\alpha^*)^\alpha\epsilon_H & (\alpha^*)^\alpha\epsilon_2 \\ \omega_H(\alpha^*)^\alpha\epsilon_H & \omega_H(\alpha^*)^\alpha\epsilon_D & \omega_H(\alpha^*)^\alpha\epsilon_D & \omega_H(\alpha^*)^\alpha & \omega_H(\alpha^*)^\alpha\epsilon_H & \omega_H(\alpha^*)^\alpha\epsilon_D \\ \omega_D(\alpha^*)^\alpha\epsilon_H & \omega_D(\alpha^*)^\alpha\epsilon_D & \omega_D(\alpha^*)^\alpha\epsilon_D & \omega_D(\alpha^*)^\alpha & \omega_D(\alpha^*)^\alpha\epsilon_H & \omega_D(\alpha^*)^\alpha\epsilon_D \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & t_H\alpha_H^\alpha & 0 & 0 & 0 & 0 \\ -k_{23}^\alpha & 0 & t_H\alpha_H^\alpha & 0 & 0 & 0 \\ 0 & -k_{32}^\alpha & 0 & 0 & 0 & 0 \\ t_{HD}\alpha_{HD}^\alpha & l_D & -k_{33}^\alpha & 0 & 0 & 0 \\ 0 & 0 & 0 & -k_{14}^\alpha & 0 & 0 \\ \eta_{15}^\alpha & 0 & 0 & t_H\alpha_H^\alpha & -k_{24}^\alpha & t_H\alpha_H^\alpha \\ 0 & 0 & \eta_{16}^\alpha & t_D\alpha_D^\alpha & t_{HD}\alpha_{HD}^\alpha & -k_{34}^\alpha \end{pmatrix},$$

$$\mathbf{I} = \begin{pmatrix} E_T, & E_H, & E_D, & I_{T_1}, & I_{T_2}, & I_{H_1}, & I_{H_2}, & I_{D_1}, & I_{D_2}, & I_{T_3}, & I_{H_3}, & I_{D_3} \end{pmatrix},$$

$$G^*(S,I) = AI^T - G(S,I),$$

$$G^*(S,I) = \begin{pmatrix} G_1^*(S,I) \\ G_2^*(S,I) \\ G_3^*(S,I) \\ G_4^*(S,I) \\ G_5^*(S,I) \\ G_6^*(S,I) \\ G_7^*(S,I) \\ G_8^*(S,I) \\ G_9^*(S,I) \\ G_{10}^*(S,I) \\ G_{11}^*(S,I) \\ G_{12}^*(S,I) \end{pmatrix} =$$

$$\begin{pmatrix} (\alpha^*)^\alpha\left(I_{T_1}+I_{T_2}+I_{T_3}+\epsilon_H(I_{H_1}+I_{H_2}+I_{H_3})+\epsilon_D(I_{D_1}+I_{D_2}+I_{D_3})\right)\left(1-\dfrac{S_T+\beta_1'R_T}{N}\right) \\ \omega_H(\alpha^*)^\alpha\left(I_{T_1}+I_{T_2}+I_{T_3}+\epsilon_H(I_{H_1}+I_{H_2}+I_{H_3})+\epsilon_D(I_{D_1}+I_{D_2}+I_{D_3})\right)\left(1-\dfrac{S_H+\beta_1'R_H}{N}\right) \\ \omega_D(\alpha^*)^\alpha\left(I_{T_1}+I_{T_2}+I_{T_3}+\epsilon_H(I_{H_1}+I_{H_2}+I_{H_3})+\epsilon_D(I_{D_1}+I_{D_2}+I_{D_3})\right)\left(1-\dfrac{S_D+\beta_1'R_D}{N}\right) \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}.$$

Since $S_T + \beta_1' R_T$, $S_H + \beta_1' R_H$ and $S_D + \beta_1' R_D$ are always less than or equal to N, $\frac{S_T + \beta_1' R_T}{N} \leq 1$, $\frac{S_H + \beta_1' R_H}{N} \leq 1$ and $\frac{S_D + \beta_1' R_D}{N} \leq 1$. Thus $G^*(S, I) \geq 0$ for all $(S, I) \in D$. The $E_0^{G_\alpha}$ is a globally asymptotically stable. □

This proof is in [54] and analogous proofs can be found in the bibliographical references [97, 98].

4.3 Numerical Results

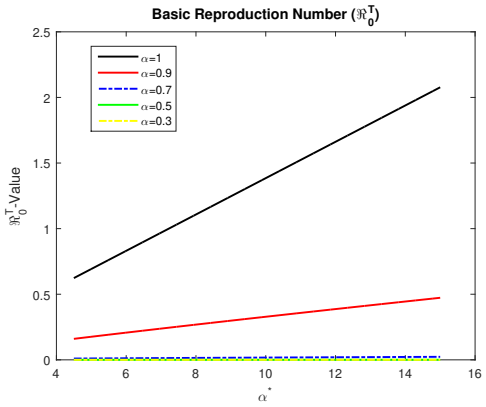
For the simulations, we use different fractional-orders ($\alpha = 0.3, 0.5, 0.7, 0.9, 1.0$) to study the behavior of the basic reproduction number and the resistance compartments. The numerical results of the Caputo derivative are obtained by the predict-evaluate-correct-correct-evaluate (PECE) method of Adams-Bashforth-Moulton type [48, 49, 50], presented in the Subsection (1.1.2) of theoretical background. Here, we use 10 years for the time horizon. The Tables (2.2)-(2.3) show the values used as the initial conditions and parameters for these simulations.

We are going to study the basic reproduction number when we vary $(\alpha^*)^\alpha$ and the resistance parameters in the same intervals as in the ODE study in Section (2.5) for different $\alpha-$values.

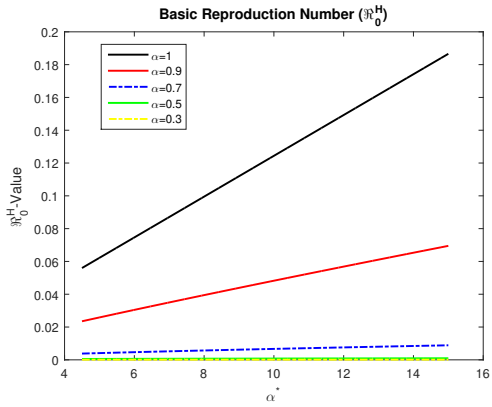
When we vary $(\alpha^*)^\alpha$ (effective contact rate) in the basic reproduction numbers and study the different α-values, we get that: for lower α-values we obtain lower $\mathfrak{R}_0^{T_\alpha}$, $\mathfrak{R}_0^{H_\alpha}$ and $\mathfrak{R}_0^{D_\alpha}$ respectively, see Table (4.1) and Figures (4.1a)-(4.1c). In particular, the $\mathfrak{R}_0^{T_\alpha}$ for the model with $\alpha = 1.0$ it reaches values greater and less than unity. For $\alpha < 1.0$, we have that $\mathfrak{R}_0^{T_\alpha}$ will always be less than the unit. Therefore, we recommend to control the influence of the $(\alpha^*)^\alpha$ in order to keep $\mathfrak{R}_0^{T_\alpha}$ always less than unity. For $\mathfrak{R}_0^{H_\alpha}$ and $\mathfrak{R}_0^{D_\alpha}$, varying $(\alpha^*)^\alpha$ we have that $\mathfrak{R}_0^{H_\alpha} < \mathfrak{R}_0^{D_\alpha}$ for $\alpha > 0.5$, and for $\alpha \leq 0.5$ the opposite situation occurs.

	$\mathfrak{R}_0^{T_\alpha}$		$\mathfrak{R}_0^{H_\alpha}$		$\mathfrak{R}_0^{D_\alpha}$	
α-value	min	max	min	max	min	max
0.3	$2.4314e-05$	$3.4892e-05$	$7.4907e-05$	$1.0735e-04$	$3.7999e-05$	$5.4545e-05$
0.5	$5.3385e-04$	$9.7467e-04$	$5.2741e-04$	$9.6292e-04$	$3.7494e-04$	$6.8415e-04$
0.7	0.0099	0.0232	0.0038	0.0089	0.0039	0.0090
0.9	0.1601	0.4730	0.0235	0.0695	0.03006	0.0905
1.0	0.6232	2.0773	0.0560	0.1866	0.0995	0.3317

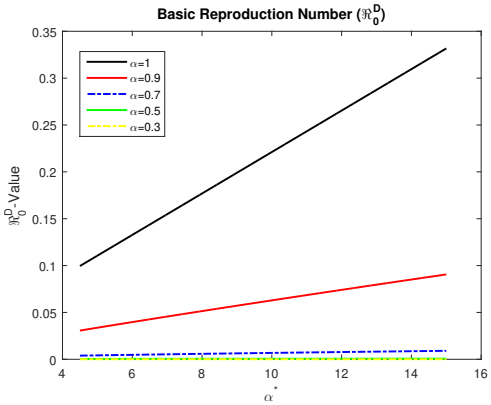
Table 4.1: *Values of the basic reproduction numbers for different α-values varying $(\alpha^*)^\alpha$.*



(a) $\mathfrak{R}_0^{T_\alpha}$ *values varying* $(\alpha^*)^\alpha$ *for different* α*-values.*



(b) $\mathfrak{R}_0^{H_\alpha}$ *values varying* $(\alpha^*)^\alpha$ *for different* α*-values.*



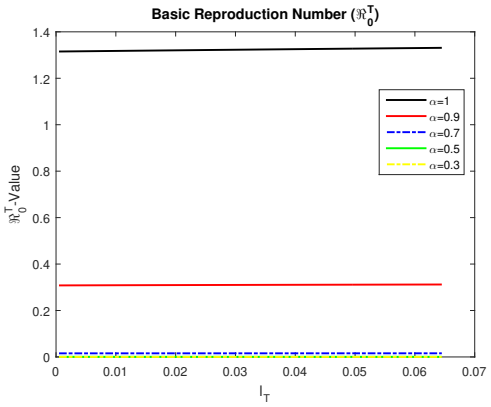
(c) $\mathfrak{R}_0^{D_\alpha}$ *values varying* $(\alpha^*)^\alpha$ *for different* α*-values.*

Figure 4.1: $\mathfrak{R}_0^{T_\alpha}$, $\mathfrak{R}_0^{H_\alpha}$, $\mathfrak{R}_0^{D_\alpha}$ *values varying* $(\alpha^*)^\alpha$ *for different* α*-values.*

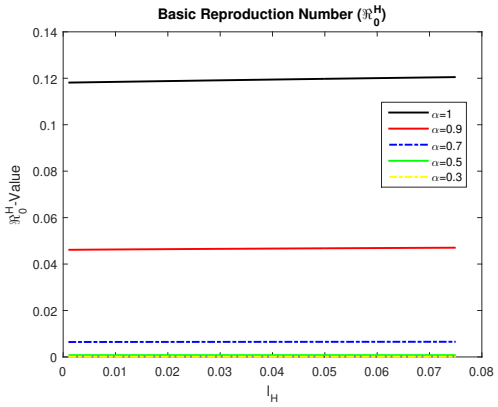
When we vary the parameters $l_T^\alpha, l_H^\alpha, l_D^\alpha, \eta_{14}^\alpha, \eta_{15}^\alpha$ and η_{16}^α and study the basic reproduction numbers for the different α-values, it happens analogous to when we vary $(\alpha^*)^\alpha$, see Table (4.2) and (4.3) and Figures (4.2a)-(4.3c). But, we have that when $\alpha = 1.0$, $\mathfrak{R}_0^{T_\alpha}$ always takes values greater than unity, the same conditions are fulfilled for $\mathfrak{R}_0^{H_\alpha}$ and $\mathfrak{R}_0^D$ with respect to α-values (for $\alpha > 0.5$ implies $\mathfrak{R}_0^{D_\alpha} > \mathfrak{R}_0^{H_\alpha}$ and for $\alpha \leq 0.5$ implies $\mathfrak{R}_0^{D_\alpha} < \mathfrak{R}_0^{H_\alpha}$) and for smaller $\alpha-$values the basic reproduction numbers are smaller.

	$\mathfrak{R}_0^{T_\alpha}$		$\mathfrak{R}_0^{H_\alpha}$		$\mathfrak{R}_0^{D_\alpha}$	
α-value	min	max	min	max	min	max
0.3	$2.1596e-05$	$2.1665e-05$	$9.3579e-05$	$9.3805e-05$	$4.7477e-05$	$4.7751e-05$
0.5	$6.5121e-04$	$6.5682e-04$	$7.6577e-04$	$7.7312e-04$	$6.1631e-04$	$6.2922e-04$
0.7	0.0155	0.0157	0.0064	0.0065	0.0069	0.0072
0.9	0.3080	0.3120	0.0461	0.0470	0.0606	0.0639
1.0	1.3153	1.3311	0.1181	0.1205	0.2095	0.2217

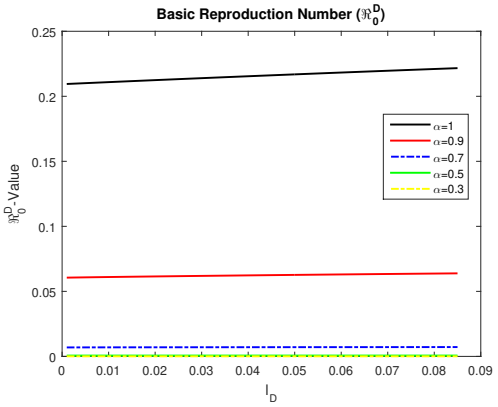
Table 4.2: *Values of the basic reproduction numbers for different* α*-values varying* l_i^α, $i = T, H, D$.



(a) $\mathfrak{R}_0^{T_\alpha}$ *values varying* l_T^α *for different* α*-values.*



(b) $\mathfrak{R}_0^{H_\alpha}$ *values varying* l_H^α *for different* α*-values.*



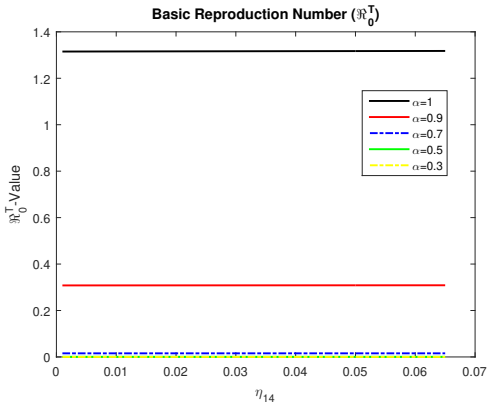
(c) $\mathfrak{R}_0^{D_\alpha}$ *values varying* l_D^α *for different* α*-values.*

Figure 4.2: $\mathfrak{R}_0$ *values varying* l_i^α, $i = T, H, D$ *for different* α*-values.*

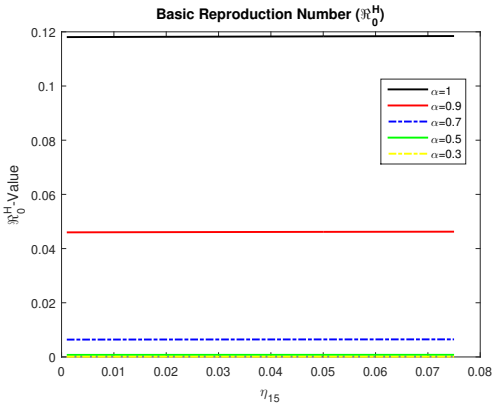
	$\mathfrak{R}_0^T$		$\mathfrak{R}_0^H$		$\mathfrak{R}_0^D$	
α-value	min	max	min	max	min	max
0.3	$2.1599e-05$	$2.1615e-05$	$9.3438e-05$	$9.3710e-05$	$4.7513e-05$	$4.7561e-05$
0.5	$6.5137e-04$	$6.5237e-04$	$7.5462e-04$	$7.7689e-04$	$5.3651e-04$	$5.5168e-04$
0.7	0.0155	0.0156	0.0064	0.0065	0.0065	0.0066
0.9	0.3080	0.3086	0.0460	0.0462	0.0599	0.0602
1.0	1.3151	1.3177	0.1181	0.1184	0.2099	0.2103

Table 4.3: *Values of the basic reproduction numbers for different* α*-values varying* η_{1r}^α, $r = 4, 5, 6$.

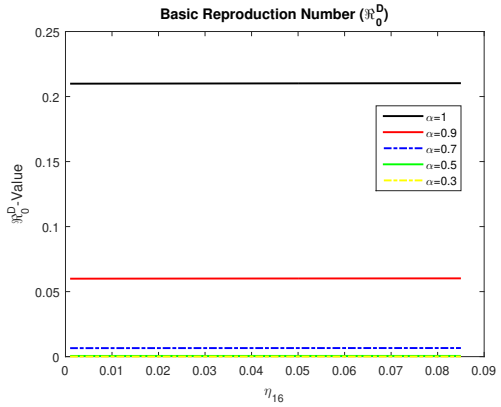
In conclusion, in this case, we must pay attention to the behavior of the basic reproduction number due to its variation with respect to the different α-values and how it influences the transmission of the epidemic. The Table (4.4) shows the values of the basic reproduction numbers for the fractional-orders studied in this scenario, we can see that the basic reproduction numbers increase for higher α-values. Figures (4.4a)-(4.4c) show the graphical behavior of the basic reproduction numbers when we vary the fractional-order. We have that for $\alpha \in [0.9333, 1]$ the $\mathfrak{R}_0^{T_\alpha} \in [0.5043, 1.3156]$, which implies that from these α-values in the scenario under study we should pay attention to this behavior.



(a) $\mathfrak{R}_0^T$ *values varying* η_{14}^α *for different* α*-values.*



(b) $\mathfrak{R}_0^H$ *values varying* η_{15}^α *for different* α*-values.*



(c) $\mathfrak{R}_0^D$ *values varying* η_{16}^α *for different* α*-values.*

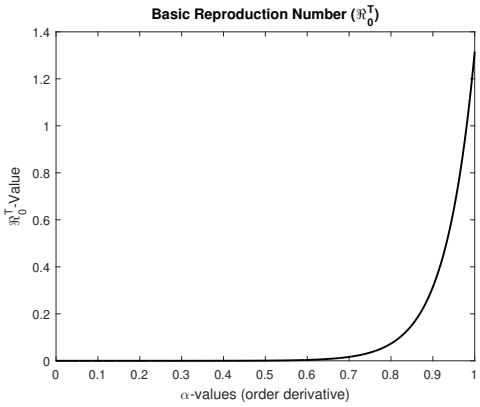
Figure 4.3: $\mathfrak{R}_0$ *values varying* η_{1r}^α, $r = 4, 5, 6$ *for different* α*-values.*

α-value	$\mathfrak{R}_0^{T_\alpha}$	$\mathfrak{R}_0^{H_\alpha}$	$\mathfrak{R}_0^{D_\alpha}$
0.3	$3.0424e-05$	$9.3605e-05$	$4.7543e-05$
0.5	$7.7566e-04$	$7.6631e-04$	$5.4478e-04$
0.7	0.0167	0.0064	0.0066
0.9	0.3136	0.0461	0.0600
1.0	1.3156	0.1182	0.2101

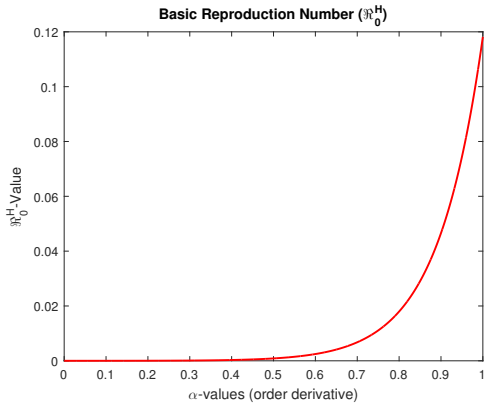
Table 4.4: *Values of* $\mathfrak{R}_0^\alpha$ *for the different* α*-values with the values of the parameters of the Table (2.3).*

The following computational simulations for the resistant compartments and their discussions can be found in [54].

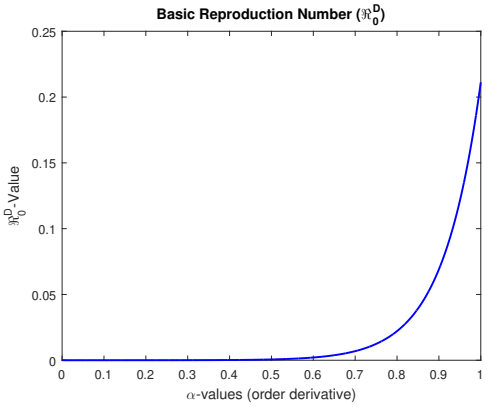
For MDR-TB cases in all subpopulations at the beginning of the study, we have a decrease in the number of cases reported. Initially, fewer cases are reported for the lower α-values (lower α-values imply fewer cases). At about the year of study (depending on the subpopulation) behavior changes and higher α-values report lower numbers of cases, see Figures (4.5b), (4.5d) and (4.5f). Then, a growth begins in all subpopulations of MDR-TB and at the end of the study period, a higher number of cases was reported for the highest α-values, see Figures (4.5a), (4.5c) and (4.5e). The highest number of MDR-TB cases was reported by the TB-Only subpopulation followed by the TB-Diabetes subpopulation throughout the study period and for the different α-values. Due to these results, it is recommended to apply MDR-TB control in all subpopulations at the beginning of the



(a) *Behavior of* $\mathfrak{R}_0^{T_\alpha}$ *for* $\alpha \in (0.00001, 1)$.



(b) *Behavior of* $\mathfrak{R}_0^{H_\alpha}$ *for* $\alpha \in (0.00001, 1)$.



(c) *Behavior of* $\mathfrak{R}_0^{D_\alpha}$ *for* $\alpha \in (0.00001, 1)$.

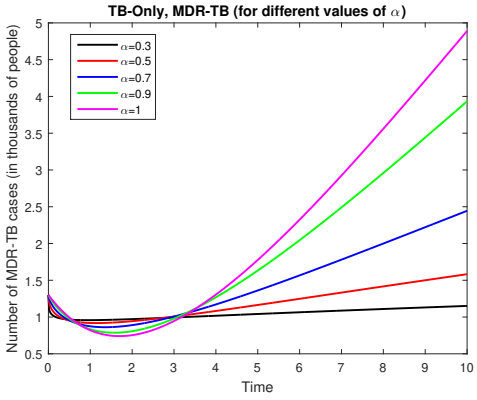
Figure 4.4: *Behavior of* $\mathfrak{R}_0^{\alpha}$ *for* $\alpha \in (0.00001, 1)$.

study period to control the growth in the number of cases [54].

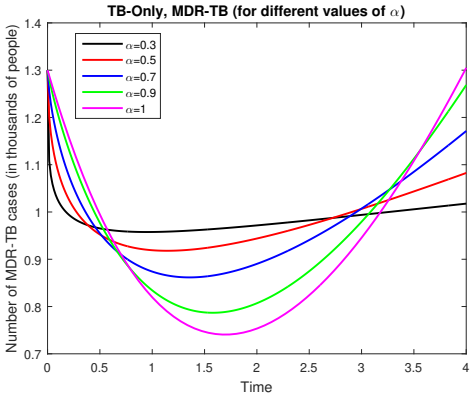
The XDR-TB cases in the TB-Only subpopulation decreased throughout the study period. At the beginning of the study, fewer cases were reported in less time for lower α-values but at the end of the study period, the opposite occurred (higher α-values reported a lower number of cases). We must pay attention when $\alpha = 1.0$ because at the end of the study there is a slight increase in the number of cases, see Figures (4.6a) and (4.6b) [54].

In the TB-HIV/AIDS subpopulation at the beginning of the study, there is a decrease in the number of cases where lower α-values report fewer cases (up to approximately one year of study). Over time, the decrease in the number of cases continues, but now with higher α-values the number of cases is lower. Approximately 5 years into the study, we have an increase in the number of cases for $\alpha > 0.5$ and at the end of the period of study, we can distinguish results for the different α. For $\alpha > 0.5$, higher α-values reported a higher number of cases. For $\alpha \leq 0.5$, the opposite is true, at lower α-values the number of reported cases is higher, see Figures (4.6c) and (4.6d). This event is important to take into account for the application of an effective control strategy in this subpopulation. We recommend applying control from the beginning of the study in order to avoid the growth of cases taking advantage of the initial decrease in these compartments [54].

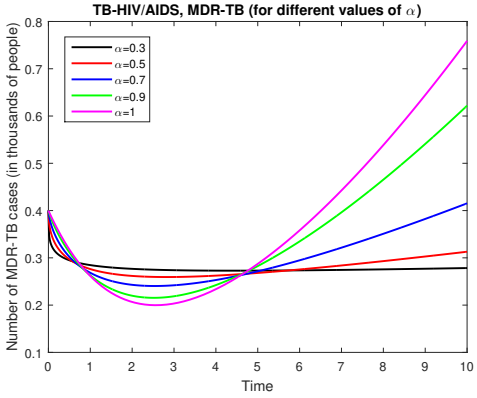
In the TB-Diabetes subpopulation, there is an increase in the number of cases during the entire study period. At the beginning of the study, the highest number of cases was reported for lower α-values, see Figure (4.6e). At the end of the study period, it happens



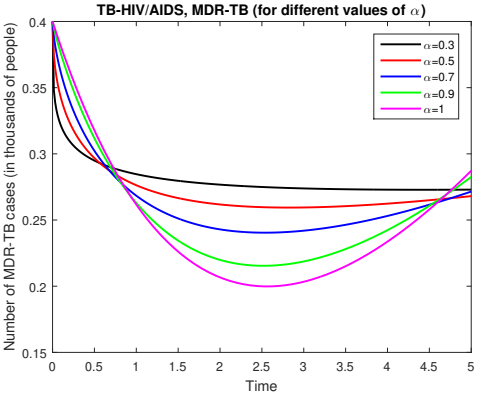
(a) *MDR-TB cases in the TB-Only, study period 10 years.*



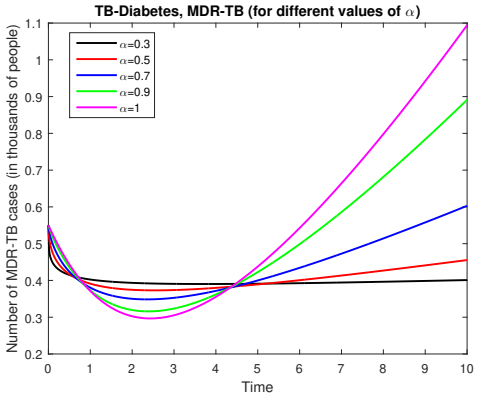
(b) *MDR-TB cases in the TB-Only, study period 4 years.*



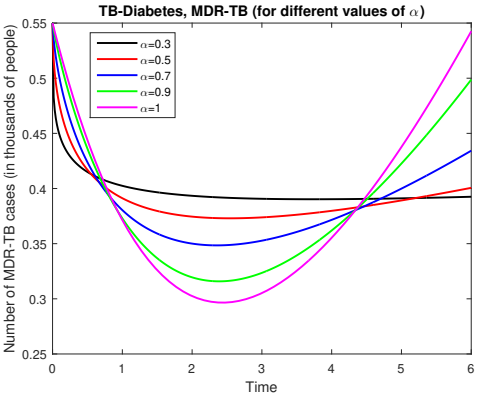
(c) *MDR-TB cases in the TB-HIV/AIDS subpopulation, study period 10 years.*



(d) *MDR-TB cases in the TB-HIV/AIDS subpopulation, study period 5 years.*



(e) *MDR-TB cases in the TB-Diabetes subpopulation, study period 10 years.*

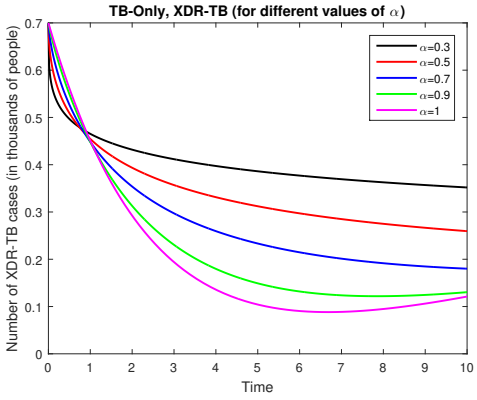


(f) *MDR-TB cases in the TB-Diabetes subpopulation, study period 6 years.*

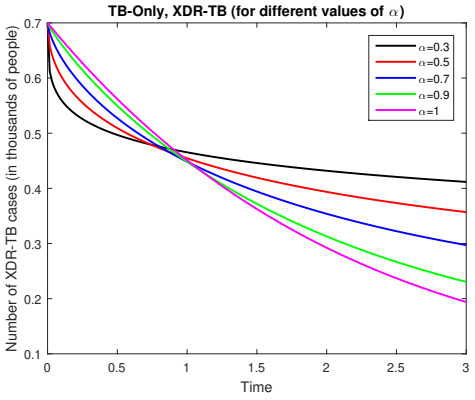
Figure 4.5: *Behavior of MDR-TB cases for different α-values over time.*

that higher α- values report a higher number of cases, see Figure (4.6f). In general, the highest number of XDR-TB cases was reported from the TB-Diabetes subpopulation. We recommend applying an effective control strategy in this subpopulation with the objective of reducing the number of XDR-TB cases due to the growth of cases throughout the study period for all α-values [54].

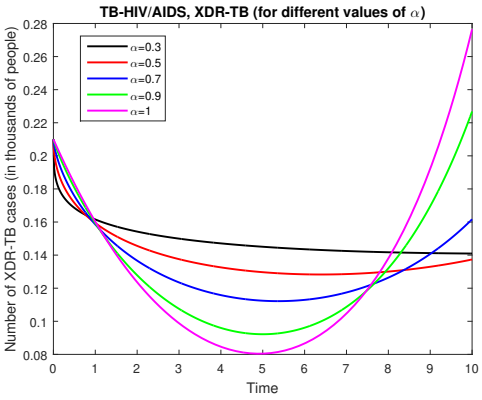
During the computational experimentation, we found that the MDR-TB compartments have a decrease at the beginning of the study period and a growth at the end for the different α-values, which allows us to design a control strategy with the objective of avoiding the growth of the number of cases. For XDR-TB cases, we recommend paying attention to the TB-HIV/AIDS and TB-Diabetes subpopulations due to the growing number of cases. In particular to the diabetic XDR-TB cases because they report the highest number of cases compared to all resistance compartments [54].



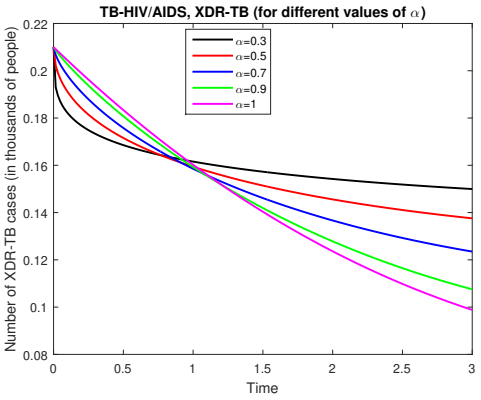
(a) *XDR-TB cases in the TB-Only, study period 10 years.*



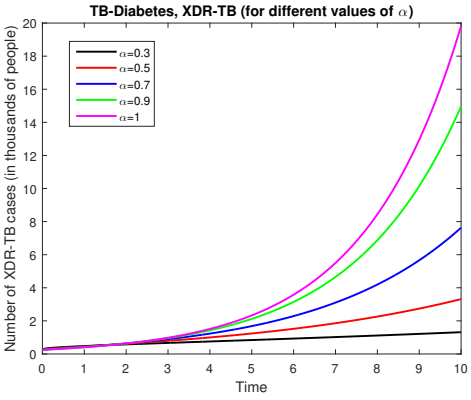
(b) *XDR-TB cases in the TB-Only, study period 3 years.*



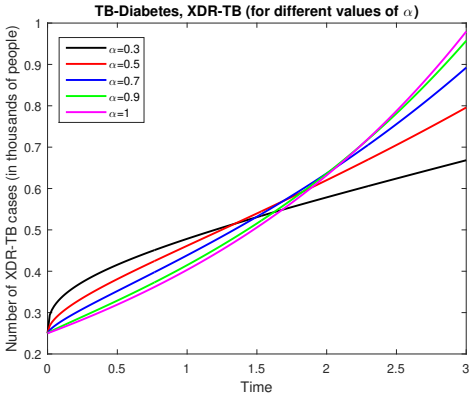
(c) *XDR-TB cases in the TB-HIV/AIDS subpopulation, study period 10 years.*



(d) *XDR-TB cases in the TB-HIV/AIDS subpopulation, study period 3 years.*



(e) *XDR-TB cases in the TB-Diabetes subpopulation, study period 10 years.*



(f) *XDR-TB cases in the TB-Diabetes subpopulation, study period 3 years.*

Figure 4.6: *Behavior of XDR-TB cases for different α-values over time.*

4.4 Partial Conclusions

- The innovative aspect of this chapter is the use of fractional-order derivatives in the Caputo sense to the model presented in Chapter (2).
- We studied MDR-TB and XDR-TB in the different subpopulations TB-Only, TB-HIV/AIDS, and TB-Diabetes and calculated and analyzed the equilibrium points of the different subpopulations (using results of fractional analysis).
- For the computational simulations, we used a predict-evaluate-correct-correct-evaluate (PECE) method in order to study the behavior of the different resistance compartments over time for different α-values.
- Among the results of the simulations, we have that:
  - For the MDR-TB at the beginning of the study, there is a decrease of cases in all subpopulations. Then, the number of cases begins to grow and at the end of the study period in MDR-TB, a higher number of cases is obtained for the higher α-values, see Figure (4.5). For MDR-TB control, we recommended controlling from the beginning of the study to avoid the growth in the number of cases.
  - Throughout the study, the number of XDR-TB cases in the TB-Only subpopulation decreased. At the beginning of the study (before the year of study) for lower α-values, fewer cases are reported, and later in the study, the higher α-values report fewer cases, see Figure (4.6a).
  - The XDR-TB cases in the TB-HIV/AIDS subpopulation initially have a decrease in the number of cases. Approximately 5 years into the study there is a growth in the number of cases for $\alpha > 0.5$ and at the end of the study, there is a differentiated behavior, for $\alpha > 0.5$ the higher α-values reported a higher number of cases and for $\alpha \leq 0.5$ the lower the α-values the higher number of cases reported, see Figure (4.6c). This factor must be taken into account to design an effective control strategy.
  - In the TB-Diabetes subpopulation throughout the study period, there is an increase in the number of XDR-TB cases. At the beginning for lower α-values the number of cases is higher and at the end of the period, the opposite situation occurs, see Figure (4.6e). The diabetics XDR-TB are the highest number of resistance cases compared to all TB treatment resistance compartments. We recommend paying special attention to the control in this compartment due to its growth.
- Computer simulations provide information for an effective design of a control strategy for tuberculosis (treatment resistance and transmission).

Chapter 5

Optimal Control with Fractional-Order Derivatives

5.1 Introduction

The optimal control problem with fractional-order derivatives used in epidemic control has increased in the last decades, due to the advantages of this type of modeling. For example, Bashir and Bilgehana [28] based on a mathematical model with fractional-order derivative in the Caputo sense for COVID-19, formulated and solved a fractional optimal control problem. Sweilam et al. [112] presented an optimal control problem with a fractional-order mathematical model in the Caputo sense, with multiple-delays for the co-infection of HIV/AIDS and malaria. Sweilam et al. [111] studied the optimal control problem for a TB infection model with the presence of diabetes and resistant strains using fractional-order derivatives in the Atangana-Baleanu-Caputo (ABC) sense and presented a new numerical scheme to simulate an optimal fractional-order system with Mittag-Leffler kernels. Rosa and Torres [102] formulated and solved a fractional optimal control problem (FOCP) based on a Caputo fractional-order mathematical model for the transmission of tuberculosis (TB) presented in [121]. Elal et al. [2] used two numerical methods to study the nonlinear fractional optimal control problem for a HIV model. Wang et al. [14] analyzed and designed an optimal control strategy for a Caputo-Fabrizio fractional-order model of the HIV/AIDS epidemic. Kieri and Jafari [66] presented a fractional model for HIV/AIDS with treatment and incorporate three control efforts (effective use of condoms, ART treatment, and behavioral change control) and studied the optimal control problem for different α-values (fractional-order). Sweilam et al. [110] presented a new fractional-order Coronavirus (2019-nCov) mathematical model with modified parameters and an optimal control problems for this model. Jajarmi et al. [62] formulated a new fractional mathematical model using a non-singular derivative operator to study the relationship between diabetes and TB, and introduced four controls in order to reduce the number of infected individuals.

The purpose of this chapter is to present and solve an optimal control problem based on the model (4.1). The novelty lies in the use of fractional order derivative in the model with controls and to take advantage of the benefits of this type of modeling technique.

5.2 Model with Controls, Optimal Control Problem and Analysis

Now, we present the formulation of the problem of optimal control, with fractional-order derivatives in the Caputo sense. We maintain the definition of the controls, coefficients $B_m, m = 0, 1, ..., 6$ and the functional of the optimal control problem with ODE of the Section (3).

$$J(u_0, u_{11}, u_{12}, u_{13}) = \int_{t_0}^{t_f} E_T(t) + E_H(t) + E_D(t) + I_{T_2}(t) + I_{H_2}(t) + I_{D_2}(t) + I_{T_3}(t) + I_{H_3}(t) + I_{D_3}(t) + \frac{1}{2}\left(B_0 u_0^2(t) + (B_1 + B_4)u_{11}^2(t) + (B_2 + B_5)u_{12}^2(t) + (B_3 + B_6)u_{13}^2(t)\right)dt. \tag{5.1}$$

The novelty of the formulation of this problem is that for the constraints, we use the fractional-order derivatives in the Caputo sense and take advantage of all the benefits of this formulation. So, the objective is to find the optimal controls u_0^*, u_{11}^*, u_{12}^* and u_{13}^* that satisfy

$$J(u_0^*, u_{11}^*, u_{12}^*, u_{13}^*) = \min_{U_{ad}} J(u_0, u_{11}, u_{12}, u_{13}), \tag{5.2}$$

where $U_{ad} = \{(u_0, u_{11}, u_{12}, u_{13}) |\ u_0, u_{11}, u_{12}, u_{13},$ Lebesgue measurable, $0 \leq u_k \leq 1,\ k = 0, 11, 12, 13,\ \forall t \in [t_0, t_f]\}$. In this section, we will work with an initial time equal to zero.

The constraints of the control problem is the model (4.1) incorporating the controls and is defined as follows:

$$\begin{aligned}
{}^c\mathbb{D}_t^\alpha S_T = f_1^\alpha &= M_T^\alpha - (\mu^\alpha + \alpha_D^\alpha + \alpha_H^\alpha + \lambda^\alpha)S_T,\\
{}^c\mathbb{D}_t^\alpha S_H = f_2^\alpha &= M_H^\alpha + \alpha_H^\alpha(S_T + S_D) - (\alpha_{HD}^\alpha + \mu^\alpha + \mu_H^\alpha + \omega_H\lambda^\alpha)S_H,\\
{}^c\mathbb{D}_t^\alpha S_D = f_3^\alpha &= M_D^\alpha + \alpha_{HD}^\alpha S_H + \alpha_D^\alpha S_T - (\alpha_H^\alpha + \mu^\alpha + \mu_D^\alpha + \omega_D\lambda^\alpha)S_D,\\
{}^c\mathbb{D}_t^\alpha E_T = f_4^\alpha &= \lambda^\alpha(S_T + (1-u_0)\beta_1^{'}R_T) - (\alpha_D^\alpha + \alpha_H^\alpha + \mu^\alpha + \eta^\alpha)E_T,\\
{}^c\mathbb{D}_t^\alpha E_H = f_5^\alpha &= \omega_H\lambda^\alpha(S_H + (1-u_0)\beta_1^{'}R_H) + \alpha_H^\alpha(E_T + E_D) - (\epsilon_H^*\eta^\alpha + \mu^\alpha + \mu_H^\alpha + \alpha_{HD}^\alpha)E_H,\\
{}^c\mathbb{D}_t^\alpha E_D = f_6^\alpha &= \omega_D\lambda^\alpha(S_D + (1-u_0)\beta_1^{'}R_D) + \alpha_{HD}^\alpha E_H + \alpha_D^\alpha E_T - (\alpha_H^\alpha + \epsilon_D^*\eta^\alpha + \mu^\alpha + \mu_D^\alpha)E_D,\\
{}^c\mathbb{D}_t^\alpha I_{T_1} = f_7^\alpha &= (1-(\beta^*)^\alpha)\eta^\alpha E_T - ((1-u_{11})l_T^\alpha + t_D\alpha_D^\alpha + t_H\alpha_H^\alpha + \mu^\alpha + d_T^\alpha + \eta_{11}^\alpha)I_{T_1},\\
{}^c\mathbb{D}_t^\alpha I_{T_2} = f_8^\alpha &= (1-p_T^\alpha)(\beta^*)^\alpha\eta^\alpha E_T + (1-u_{11})l_T^\alpha I_{T_1} - (t_D\alpha_D^\alpha + t_H\alpha_H^\alpha + m_T^\alpha + \mu^\alpha + t_T^{'}d_T^\alpha +\\
&\quad (1-u_{11})\eta_{14}^\alpha)I_{T_2},\\
{}^c\mathbb{D}_t^\alpha I_{H_1} = f_9^\alpha &= t_H\alpha_H^\alpha(I_{T_1} + I_{D_1}) + (1-(\beta^*)^\alpha)\epsilon_H^*\eta^\alpha E_H - ((1-u_{12})l_H^\alpha + \mu^\alpha + \mu_H^\alpha + d_{TH}^\alpha +\\
&\quad \eta_{12}^\alpha + t_{HD}\alpha_{HD}^\alpha)I_{H_1},\\
{}^c\mathbb{D}_t^\alpha I_{H_2} = f_{10}^\alpha &= t_H\alpha_H^\alpha(I_{T_2} + I_{D_2}) + (1-p_H^\alpha)\epsilon_H^*(\beta^*)^\alpha\eta^\alpha E_H + (1-u_{12})l_H^\alpha I_{H_1} - (m_H^\alpha + \mu^\alpha +\\
&\quad \mu_H^\alpha + t_H^{'}d_{TH}^\alpha + (1-u_{12})\eta_{15}^\alpha + t_{HD}\alpha_{HD}^\alpha)I_{H_2},\\
{}^c\mathbb{D}_t^\alpha I_{D_1} = f_{11}^\alpha &= t_D\alpha_D^\alpha I_{T_1} + t_{HD}\alpha_{HD}^\alpha I_{H_1} + (1-(\beta^*)^\alpha)\epsilon_D^*\eta^\alpha E_D - ((1-u_{13})l_D^\alpha + t_H\alpha_H^\alpha + \mu^\alpha +\\
&\quad \mu_D^\alpha + d_{TD}^\alpha + \eta_{13}^\alpha)I_{D_1},\\
{}^c\mathbb{D}_t^\alpha I_{D_2} = f_{12}^\alpha &= t_D\alpha_D^\alpha I_{T_2} + t_{HD}\alpha_{HD}^\alpha I_{H_2} + (1-p_D^\alpha)\epsilon_D^*(\beta^*)^\alpha\eta^\alpha E_D + (1-u_{13})l_D^\alpha I_{D_1} - (m_D^\alpha + t_H\alpha_H^\alpha +
\end{aligned}$$

$$
\begin{aligned}
&\mu^\alpha + \mu_D^\alpha + t_D^{'} d_{TD}^\alpha + (1-u_{13})\eta_{16}^\alpha) I_{D_2},\\
{}^c\mathbb{D}_t^\alpha I_{T_3} = f_{13}^\alpha =& p_T^\alpha (\beta^*)^\alpha \eta^\alpha E_T + (1-u_{11})\eta_{14}^\alpha I_{T_2} - ((\eta_{11}^*)^\alpha + t_D \alpha_D^\alpha + t_H \alpha_H^\alpha + \mu^\alpha + t_T^* d_T^\alpha) I_{T_3},\\
{}^c\mathbb{D}_t^\alpha I_{H_3} = f_{14}^\alpha =& p_H^\alpha (\beta^*)^\alpha \epsilon_H^* \eta^\alpha E_H + (1-u_{12})\eta_{15}^\alpha I_{H_2} + t_H \alpha_H^\alpha (I_{T_3} + I_{D_3}) - ((\eta_{12}^*)^\alpha + t_{HD}\alpha_{HD}^\alpha + \mu^\alpha + \mu_H^\alpha +\\
&t_H^* d_{TH}^\alpha) I_{H_3},\\
{}^c\mathbb{D}_t^\alpha I_{D_3} = f_{15}^\alpha =& p_D^\alpha (\beta^*)^\alpha \epsilon_D^* \eta^\alpha E_D + (1-u_{13})\eta_{16}^\alpha I_{D_2} + t_{HD}\alpha_{HD}^\alpha I_{H_3} + t_D \alpha_D^\alpha I_{T_3} - (t_H \alpha_H^\alpha + (\eta_{13}^*)^\alpha + \mu^\alpha + \mu_D^\alpha +\\
&t_D^* d_{TD}^\alpha) I_{D_3},\\
{}^c\mathbb{D}_t^\alpha R_T = f_{16}^\alpha =& m_T^\alpha I_{T_2} + \eta_{11}^\alpha I_{T_1} + (\eta_{11}^*)^\alpha I_{T_3} - (\alpha_D^\alpha + \alpha_H^\alpha + \mu^\alpha + (1-u_0)\beta_1^{'}\lambda^\alpha) R_T,\\
{}^c\mathbb{D}_t^\alpha R_H = f_{17}^\alpha =& m_H^\alpha I_{H_2} + \eta_{12}^\alpha I_{H_1} + (\eta_{12}^*)^\alpha I_{H_3} + \alpha_H^\alpha (R_T + R_D) - (\alpha_{HD}^\alpha + \mu^\alpha + \mu_H^\alpha + (1-u_0)\beta_1^{'}\omega_H \lambda^\alpha) R_H,\\
{}^c\mathbb{D}_t^\alpha R_D = f_{18}^\alpha =& m_D^\alpha I_{D_2} + \eta_{13}^\alpha I_{D_1} + (\eta_{13}^*)^\alpha I_{D_3} + \alpha_D^\alpha R_T + \alpha_{HD}^\alpha R_H - (\alpha_H^\alpha + \mu^\alpha + \mu_D^\alpha + (1-u_0)\beta_1^{'}\omega_D \lambda^\alpha) R_D,
\end{aligned}
\tag{5.3}
$$

with

$$
\lambda^\alpha = \frac{(\alpha^*)^\alpha \left(I_{T_1} + I_{T_2} + I_{T_3} + \epsilon_H (I_{H_1} + I_{H_2} + I_{H_3}) + \epsilon_D (I_{D_1} + I_{D_2} + I_{D_3})\right)}{N},
$$

and initial conditions:
$S_T(0) > 0$, $S_H(0) > 0$, $S_D(0) > 0$, $E_T(0) > 0$, $E_H(0) > 0$, $E_D(0) > 0$, $I_{T_1}(0) > 0$, $I_{T_2}(0) > 0$, $I_{H_1}(0) > 0$, $I_{H_2}(0) > 0$, $I_{D_1}(0) > 0$, $I_{D_2}(0) > 0$, $I_{T_3}(0) > 0$, $I_{H_3}(0) > 0$, $I_{D_3}(0) > 0$, $R_T(0) > 0$, $R_H(0) > 0$, $R_D(0) > 0$ and $\alpha \in (0, 1]$.

For this problem, the Hamiltonian is defined as:

$$
\begin{aligned}
H^\alpha =& E_T(t) + E_H(t) + E_D(t) + I_{T_2}(t) + I_{H_2}(t) + I_{D_2}(t) + I_{T_3}(t) + I_{H_3}(t) + I_{D_3}(t) + \frac{B_0 u_0^2(t)}{2} + \frac{(B_1 + B_4)u_{11}^2(t)}{2} +\\
&\frac{(B_2 + B_5)u_{12}^2(t)}{2} + \frac{(B_3 + B_6)u_{13}^2(t)}{2} + \sum_{n=1}^{18} \lambda_n f_n^\alpha,
\end{aligned}
\tag{5.4}
$$

where $\lambda_1, \lambda_2, \cdots, \lambda_{18}$ are the adjoint variables.

Theorem 5.2.1. *If $u_0^*, u_{11}^*, u_{12}^*$ and u_{13}^* are controls of the optimal control problem (5.2), S_T^{**}, S_H^{**}, S_D^{**}, E_T^{**}, E_H^{**}, E_D^{**}, $I_{T_1}^{**}$, $I_{T_2}^{**}$, $I_{H_1}^{**}$, $I_{H_2}^{**}$, $I_{D_1}^{**}$, $I_{D_2}^{**}$, $I_{T_3}^{**}$, $I_{H_3}^{**}$, $I_{D_3}^{**}$ R_T^{**}, R_H^{**} and R_D^{**}, are corresponding optimal paths, them there exists co-state variables $\lambda_n, n = 1, ..., 18$ such that, besides the control system (5.3) is satisfied, the following conditions are satisfied:*

I. co-state equations

$$
\begin{aligned}
{}^c\mathbb{D}_t^\alpha \lambda_1(t^{'}) &= \alpha_D^\alpha(\lambda_3 - \lambda_1) + \alpha_H^\alpha(\lambda_2 - \lambda_1) + \lambda^\alpha(\lambda_4 - \lambda_1) - \mu^\alpha \lambda_1,\\
{}^c\mathbb{D}_t^\alpha \lambda_2(t^{'}) &= \alpha_{HD}^\alpha(\lambda_3 - \lambda_2) + \omega_H \lambda^\alpha(\lambda_5 - \lambda_2) - (\mu^\alpha + \mu_H^\alpha)\lambda_2,\\
{}^c\mathbb{D}_t^\alpha \lambda_3(t^{'}) &= \alpha_H^\alpha(\lambda_2 - \lambda_3) + \omega_D \lambda^\alpha(\lambda_6 - \lambda_3) - (\mu^\alpha + \mu_D^\alpha)\lambda_3,\\
{}^c\mathbb{D}_t^\alpha \lambda_4(t^{'}) &= 1 + \alpha_D^\alpha(\lambda_6 - \lambda_4) + \alpha_H^\alpha(\lambda_5 - \lambda_4) + \eta^\alpha((\lambda_7 - \lambda_4) + (\beta^*)^\alpha((\lambda_8 - \lambda_7) + p_T^\alpha(\lambda_{13} - \lambda_8))) - \mu^\alpha \lambda_4,\\
{}^c\mathbb{D}_t^\alpha \lambda_5(t^{'}) &= 1 + \alpha_{HD}^\alpha(\lambda_6 - \lambda_5) + \eta^\alpha \epsilon_H^*((\lambda_9 - \lambda_5) + (\beta^*)^\alpha((\lambda_{10} - \lambda_9) + p_H^\alpha(\lambda_{14} - \lambda_{10}))) - (\mu^\alpha + \mu_H^\alpha)\lambda_5,\\
{}^c\mathbb{D}_t^\alpha \lambda_6(t^{'}) &= 1 + \alpha_H^\alpha(\lambda_5 - \lambda_6) + \eta^\alpha \epsilon_D^*((\lambda_{11} - \lambda_6) + (\beta^*)^\alpha((\lambda_{12} - \lambda_{11}) + p_D^\alpha(\lambda_{15} - \lambda_{12}))) - (\mu^\alpha + \mu_D^\alpha)\lambda_6,\\
{}^c\mathbb{D}_t^\alpha \lambda_7(t^{'}) &= 1 + t_D \alpha_D^\alpha(\lambda_{11} - \lambda_7) + t_H \alpha_H^\alpha(\lambda_9 - \lambda_7) + \eta_{11}^\alpha(\lambda_{16} - \lambda_7) + (1-u_{11})l_T^\alpha(\lambda_8 - \lambda_7) +\\
&\frac{(\alpha^*)^\alpha}{N}\big((\lambda_4 - \lambda_1)S_T + \omega_H S_H(\lambda_5 - \lambda_2) + \omega_D S_D(\lambda_6 - \lambda_3) + (1-u_0)\beta_1^{'}(R_T(\lambda_4 - \lambda_{16}) +\\
&\omega_H R_H(\lambda_5 - \lambda_{17}) + \omega_D R_D(\lambda_6 - \lambda_{18}))\big) - (\mu^\alpha + d_T^\alpha)\lambda_7,
\end{aligned}
$$

$$
\begin{aligned}
{}^{c}\mathbb{D}_t^{\alpha}\,\lambda_8(t') &= 1+(1-u_{11})\eta_{14}^{\alpha}(\lambda_{13}-\lambda_8)+t_D\alpha_D^{\alpha}(\lambda_{12}-\lambda_8)+t_H\alpha_H^{\alpha}(\lambda_{10}-\lambda_8)+m_T^{\alpha}(\lambda_{16}-\lambda_8)+\\
&\quad\frac{(\alpha^*)^{\alpha}}{N}\big((\lambda_4-\lambda_1)S_T+\omega_H S_H(\lambda_5-\lambda_2)+\omega_D S_D(\lambda_6-\lambda_3)+(1-u_0)\beta_1'(R_T(\lambda_4-\lambda_{16})+\\
&\quad\omega_H R_H(\lambda_5-\lambda_{17})+\omega_D R_D(\lambda_6-\lambda_{18}))\big)-(\mu^{\alpha}+t_T'd_T^{\alpha})\lambda_8,\\
{}^{c}\mathbb{D}_t^{\alpha}\,\lambda_9(t') &= 1+(1-u_{12})l_H^{\alpha}(\lambda_{10}-\lambda_9)+\eta_{12}^{\alpha}(\lambda_{17}-\lambda_9)+t_{HD}\alpha_{HD}^{\alpha}(\lambda_{11}-\lambda_9)+\frac{(\alpha^*)^{\alpha}}{N}\epsilon_H\big((\lambda_4-\lambda_1)S_T+\\
&\quad\omega_H S_H(\lambda_5-\lambda_2)+\omega_D S_D(\lambda_6-\lambda_3)+(1-u_0)\beta_1'(R_T(\lambda_4-\lambda_{16})+\omega_H R_H(\lambda_5-\lambda_{17})\\
&\quad+\omega_D R_D(\lambda_6-\lambda_{18}))\big)-(\mu^{\alpha}+\mu_H^{\alpha}+d_{TH}^{\alpha})\lambda_9,\\
{}^{c}\mathbb{D}_t^{\alpha}\,\lambda_{10}(t') &= 1+\frac{(\alpha^*)^{\alpha}}{N}\epsilon_H\big((\lambda_4-\lambda_1)S_T+\omega_H S_H(\lambda_5-\lambda_2)+\omega_D S_D(\lambda_6-\lambda_3)+(1-u_0)\beta_1'(R_T(\lambda_4-\lambda_{16})+\\
&\quad\omega_H R_H(\lambda_5-\lambda_{17})+\omega_D R_D(\lambda_6-\lambda_{18}))\big)+t_{HD}\alpha_{HD}^{\alpha}(\lambda_{12}-\lambda_{10})+m_H^{\alpha}(\lambda_{17}-\lambda_{10})+(1-u_{11})\eta_{15}^{\alpha}(\lambda_{14}-\\
&\quad\lambda_{10})-(\mu^{\alpha}+\mu_H^{\alpha}+t_H'd_{TH}^{\alpha})\lambda_{10},\\
{}^{c}\mathbb{D}_t^{\alpha}\,\lambda_{11}(t') &= 1+\frac{(\alpha^*)^{\alpha}}{N}\epsilon_D\big((\lambda_4-\lambda_1)S_T+\omega_H S_H(\lambda_5-\lambda_2)+\omega_D S_D(\lambda_6-\lambda_3)+(1-u_0)\beta_1'(R_T(\lambda_4-\lambda_{16})+\\
&\quad\omega_H R_H(\lambda_5-\lambda_{17})+\omega_D R_D(\lambda_6-\lambda_{18}))\big)+(1-u_{13})l_D^{\alpha}(\lambda_{12}-\lambda_{11})+\eta_{13}^{\alpha}(\lambda_{18}-\lambda_{11})+\\
&\quad t_H\alpha_H^{\alpha}(\lambda_9-\lambda_{11})-(\mu^{\alpha}+\mu_D^{\alpha}+d_{TD}^{\alpha})\lambda_{11},\\
{}^{c}\mathbb{D}_t^{\alpha}\,\lambda_{12}(t') &= 1+\frac{(\alpha^*)^{\alpha}}{N}\epsilon_D\big((\lambda_4-\lambda_1)S_T+\omega_H S_H(\lambda_5-\lambda_2)+\omega_D S_D(\lambda_6-\lambda_3)+(1-u_0)\beta_1'(R_T(\lambda_4-\lambda_{16})+\\
&\quad\omega_H R_H(\lambda_5-\lambda_{17})+\omega_D R_D(\lambda_6-\lambda_{18}))\big)+t_H\alpha_H^{\alpha}(\lambda_{10}-\lambda_{12})+m_D^{\alpha}(\lambda_{18}-\lambda_{12})+\\
&\quad(1-u_{13})\eta_{16}^{\alpha}(\lambda_{15}-\lambda_{12})-(\mu^{\alpha}+\mu_D^{\alpha}+t_D'd_{TD})\lambda_{12},\\
{}^{c}\mathbb{D}_t^{\alpha}\,\lambda_{13}(t') &= 1+\frac{(\alpha^*)^{\alpha}}{N}\big((\lambda_4-\lambda_1)S_T+\omega_H S_H(\lambda_5-\lambda_2)+\omega_D S_D(\lambda_6-\lambda_3)+(1-u_0)\beta_1'(R_T(\lambda_4-\lambda_{16})+\\
&\quad\omega_H R_H(\lambda_5-\lambda_{17})+\omega_D R_D(\lambda_6-\lambda_{18}))\big)+(\eta_{11}^*)^{\alpha}(\lambda_{16}-\lambda_{13})+t_D\alpha_D^{\alpha}(\lambda_{15}-\lambda_{13})+\\
&\quad t_H\alpha_H^{\alpha}(\lambda_{14}-\lambda_{13})-(\mu^{\alpha}+t_T^*d_T^{\alpha})\lambda_{13},\\
{}^{c}\mathbb{D}_t^{\alpha}\,\lambda_{14}(t') &= 1+\frac{(\alpha^*)^{\alpha}}{N}\epsilon_H\big((\lambda_4-\lambda_1)S_T+\omega_H S_H(\lambda_5-\lambda_2)+\omega_D S_D(\lambda_6-\lambda_3)+(1-u_0)\beta_1'(R_T(\lambda_4-\lambda_{16})+\\
&\quad\omega_H R_H(\lambda_5-\lambda_{17})+\omega_D R_D(\lambda_6-\lambda_{18}))\big)+(\eta_{12}^*)^{\alpha}(\lambda_{17}-\lambda_{14})+t_{HD}\alpha_{HD}^{\alpha}(\lambda_{15}-\lambda_{14})-\\
&\quad(\mu^{\alpha}+\mu_H^{\alpha}+t_H^*d_{TH}^{\alpha})\lambda_{14},\\
{}^{c}\mathbb{D}_t^{\alpha}\,\lambda_{15}(t') &= 1+\frac{(\alpha^*)^{\alpha}}{N}\epsilon_D\big((\lambda_4-\lambda_1)S_T+\omega_H S_H(\lambda_5-\lambda_2)+\omega_D S_D(\lambda_6-\lambda_3)+(1-u_0)\beta_1'(R_T(\lambda_4-\lambda_{16})+\\
&\quad\omega_H R_H(\lambda_5-\lambda_{17})+\omega_D R_D(\lambda_6-\lambda_{18}))\big)+(\eta_{13}^*)^{\alpha}(\lambda_{18}-\lambda_{15})+t_H\alpha_H^{\alpha}(\lambda_{14}-\lambda_{15})-\\
&\quad(\mu^{\alpha}+\mu_D^{\alpha}+t_D^*d_{TD}^{\alpha})\lambda_{15},\\
{}^{c}\mathbb{D}_t^{\alpha}\,\lambda_{16}(t') &= (1-u_0)\beta_1'\lambda^{\alpha}(\lambda_4-\lambda_{16})+\alpha_D^{\alpha}(\lambda_{18}-\lambda_{16})+\alpha_H^{\alpha}(\lambda_{17}-\lambda_{16})-\mu^{\alpha}\lambda_{16},\\
{}^{c}\mathbb{D}_t^{\alpha}\,\lambda_{17}(t') &= (1-u_0)\beta_1'\lambda^{\alpha}\omega_H(\lambda_5-\lambda_{17})+\alpha_{HD}^{\alpha}(\lambda_{18}-\lambda_{17})-(\mu^{\alpha}+\mu_H^{\alpha})\lambda_{17},\\
{}^{c}\mathbb{D}_t^{\alpha}\,\lambda_{18}(t') &= (1-u_0)\beta_1'\lambda^{\alpha}\omega_D(\lambda_6-\lambda_{18})+\alpha_H^{\alpha}(\lambda_{17}-\lambda_{18})-(\mu^{\alpha}+\mu_D^{\alpha})\lambda_{18},
\end{aligned}
\tag{5.5}
$$

with $t' = t_f - t$.

II. with transversality conditions

$$\lambda_n(t_f)=0,\qquad n=1,\ldots,18. \tag{5.6}$$

III. Optimalitity conditions:

$$H^{\alpha}(S_T^{**},S_H^{**},S_D^{**},E_T^{**},E_H^{**},E_D^{**},I_{T_1}^{**},I_{T_2}^{**},I_{H_1}^{**},I_{H_2}^{**},I_{D_1}^{**},I_{D_2}^{**},I_{T_3}^{**},I_{H_3}^{**},I_{D_3}^{**},R_T^{**},R_H^{**},R_D^{**},\lambda_n,u_k^*)=$$

$$\min_{0\le u_k\le 1} H^{\alpha}(S_T^{**}, S_H^{**}, S_D^{**}, E_T^{**}, E_H^{**}, E_D^{**}, I_{T_1}^{**}, I_{T_2}^{**}, I_{H_1}^{**}, I_{H_2}^{**}, I_{D_1}^{**}, I_{D_2}^{**}, I_{T_3}^{**}, I_{H_3}^{**}, I_{D_3}^{**}, R_T^{**}, R_H^{**}, R_D^{**}, \lambda_n, u_k^*),$$
$$n = 1, ..., 18, \quad k = 0, 11, 12, 13. \tag{5.7}$$

Furthermore, the control functions $u_k^*, k = 0, 11, 12, 13$ are given by

$$u_0^* = \min\left\{ \max\left\{0, \frac{\beta_1'\lambda^{\alpha}\left((\lambda_4-\lambda_{16})R_T + \omega_H(\lambda_5-\lambda_{17})R_H + \omega_D(\lambda_6-\lambda_{18})R_D\right)}{B_0}\right\}, 1\right\},$$
$$u_{11}^* = \min\left\{ \max\left\{0, \frac{l_T^{\alpha} I_{T_1}(\lambda_8-\lambda_7) + \eta_{14}^{\alpha} I_{T_2}(\lambda_{13}-\lambda_8)}{B_1+B_4}\right\}, 1\right\},$$
$$u_{12}^* = \min\left\{ \max\left\{0, \frac{l_H^{\alpha} I_{H_1}(\lambda_{10}-\lambda_9) + \eta_{15}^{\alpha} I_{H_2}(\lambda_{14}-\lambda_{10})}{B_2+B_5}\right\}, 1\right\},$$
$$u_{13}^* = \min\left\{ \max\left\{0, \frac{l_D^{\alpha} I_{D_1}(\lambda_{12}-\lambda_{11}) + \eta_{16}^{\alpha} I_{D_2}(\lambda_{15}-\lambda_{12})}{B_3+B_6}\right\}, 1\right\}, \tag{5.8}$$

where the stationary condition is $\dfrac{\partial H}{\partial u_k} = 0, \quad k = 0, 11, 12, 13.$

Proof. The existence of the optimal control $(u_0^*, u_{11}^*, u_{12}^*, u_{13}^*,)$ and associated optimal solution $(S_T^{**}, S_H^{**}, S_D^{**}, E_T^{**}, E_H^{**}, E_D^{**}, I_{T_1}^{**}, I_{T_2}^{**}, I_{H_1}^{**}, I_{H_2}^{**}, I_{D_1}^{**}, I_{D_2}^{**}, I_{T_3}^{**}, I_{H_3}^{**}, I_{D_3}^{**}, R_T^{**}, R_H^{**}, R_D^{**})$ come from the convexity of the integrand of the functional (5.1) (was proved in Chapter (3)) with respect to the controls $u_k \in U_{ad}, k = 0, 11, 12, 13$ and the Lipschitz property of the state system with respect to state variables $(S_T, S_H, S_D, E_T, E_H, E_D, I_{T_1}, I_{T_2}, I_{H_1}, I_{H_2}, I_{D_1}, I_{D_2}, I_{T_3}, I_{H_3}, I_{D_3}, R_T, R_H, R_D)$. According to the Pontryagin's maximum principle, if $u_k \in U_{ad}, k = 0, 11, 12, 13,$ is an optimal for the problem (5.2)-(5.3) with the initial conditions and t_f fixed, then there is a nontrivial absolutely continuous mapping $\lambda : [0, t_f] \longrightarrow \mathbb{R}^{18}$, $\lambda(t) = (\lambda_1(t), \lambda_2(t), \lambda_3(t), \lambda_4(t), \lambda_5(t), \lambda_6(t), \lambda_7(t), \lambda_8(t), \lambda_9(t), \lambda_{10}(t), \lambda_{11}(t), \lambda_{12}(t), \lambda_{13}(t), \lambda_{14}(t), \lambda_{15}(t), \lambda_{16}(t), \lambda_{17}(t), \lambda_{18}(t))$, called adjoint vector, such that

$$ {}_t^c\mathbb{D}_{t_f}^{\alpha}\, \lambda_n(t) = \frac{\partial H^{\alpha}}{\partial x_l}, \quad n = 1, \cdots, 18, \tag{5.9}$$

where $x_l = S_T$, S_H, S_D, E_T, E_H, E_D, I_{T_1}, I_{T_2}, I_{H_1}, I_{H_2}, I_{D_1}, I_{D_2},I_{T_3}, I_{H_3}, I_{D_3}, R_T, R_H, R_D and H^{α} is the Hamiltonian defined as (5.4). All conditions of (5.6) in $[0, t_f]$ and the transversality conditions $(\lambda_n(t_f) = 0, n = 1, ..., 18)$ are satisfied. The system (5.5) is derived from (5.9) and the optimal control (5.8) are obtained from the minimization condition (5.7). □

5.3 Numerical Results

To numerically solve the optimal control problem, we use a predict-evaluate-correct-correct-evaluate (PECE) method of Adams-Basforth-Moulton for case $(0 < \alpha < 1)$ analogous to the one used in Section (3.3) implemented in MATLAB. First, we solve the system (5.3) using PECE with the initial conditions for the state variables presented in Table (2.2) and a guess for the control in the time interval $[0, t_f]$, and we obtain the values of the state variables. We solve the system (5.5) and the transversality conditions (5.6) with the PECE and the values of the co-state variables $\lambda_n, n = 1, ..., 18$ are obtained. The

controls are updated using a convex combination of the previous control and the value calculated by (5.7). This procedure is repeated iteratively until the stop condition is met, which is that the values of the controls in the previous iteration are very close to those of the current iteration. The case $\alpha = 1.0$ was confirmed using the basic scheme presented in Chapter (3).

The values of the initial conditions and parameters are in Tables (2.2)-(2.3) and the values of the control application costs $B_m, m = 0, ..., 6$ are the same as in Section (3.3). We use the same control strategies defined in Section (3.3) with the objective of studying them with fractional-order derivatives and we apply type I controls because in the ODE control problem presented in Section (3.3) it showed better results.

Strategy I: In the case of MDR-TB, the best results are achieved for $\alpha = 1.0$, and the higher the α-value the more efficient the control behaves. In the case of $\alpha = 0.9$ at the end of the period, it has a growth in the number of cases. In particular, in the case of the TB-Only subpopulation, this achievement does not reach the results obtained with $\alpha = 0.7, 0.5$. For the case $\alpha = 1.0$ in the TB-Only subpopulation, besides showing the best results, it also has a growth at the end of the study period. We recommend paying attention to this behavior to avoid this growth in the number of cases, see Figures (5.1b), (5.1d), and (5.1f).
In XDR-TB in the TB-Only and TB-HIV/AIDS subpopulations, the number of cases was reduced and the future growth of cases was avoided. At the beginning of the study, the best control results were reported for the lowest values of $\alpha-$values but then the opposite situation occurred (higher $\alpha-$values reported a lower number of cases) until the end of the study, see Figures (5.2b) and (5.2d).

For the XDR-TB in the TB-Diabetes subpopulation at the beginning of the study the best results are achieved for the highest $\alpha-$values and it is observed that the lowest of $\alpha-$value under study ($\alpha = 0.3$) achieves the best results, see Figure (5.2f). This strategy showed a strong quantitative reduction in the number of cases in this compartment, which is important due to its impact on the dynamic.

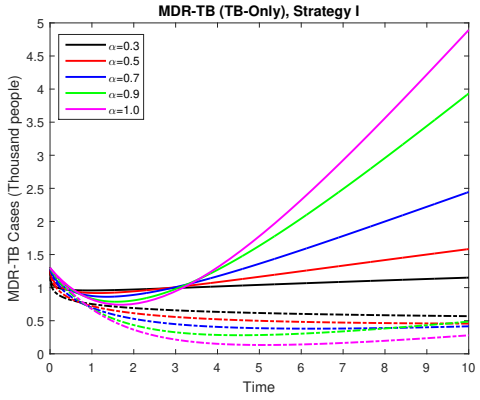
Strategy II: In the MDR-TB in the TB-Only subpopulation, the strategy at the beginning and the end of the period achieves the best results for the lowest $\alpha-$values. In this case, the growth in the number of cases is not avoided and the worst results are achieved for higher $\alpha-$values at the end of the study, see Figure (5.3b). In the TB-HIV/AIDS and TB-Diabetes subpopulations, the best result is achieved for $\alpha = 1.0$. In this subpopulations the highest number of cases are reported for the highest $\alpha-$values and for $\alpha = 0.7, 0.9$ in these subpopulations it occurs that lower α-values will report higher number of cases, see Figures (5.3c) and (5.3f). For all the MDR-TB compartments considering $\alpha \geq 0.5$, we have an increase at the end of the study. In the application of this control strategy, it is recommended to pay attention to the behaviors $\alpha = 0.9, 0.7$ due to the growth in the number of cases at the end of the study.

For XDR-TB in TB-Only at the beginning of the study the reduction of cases was not significant, but for lower $\alpha-$values better results were achieved, and at the end of the period the opposite occurred. This control strategy in this compartment manages to avoid growth at the end of the period for $\alpha = 1.0, 0.9$, see Figures (5.4a) and (5.4b). In the XDR-TB in the TB-HIV/AIDS subpopulation, the increase in the number of cases

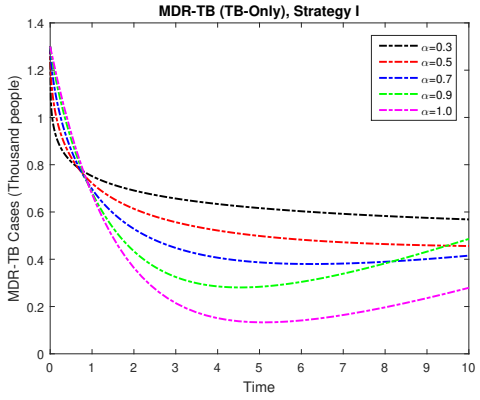
for $\alpha = 0.7, 0.9, 1.0$ is not avoided. The best results at the end of the period are achieved for $\alpha = 0.7, 0.5$ and for $\alpha \leq 0.5$, the higher the $\alpha-$values, the lower the number of cases reported (compared to model without control), see Figures (5.4c) and (5.4d). In TB-Diabetes the asymptotic behavior of the model without control is maintained, but although for all α-values the number of cases is reduced, this reduction is not transcendent because a significant number of diabetic XDR-TB cases are still reported, see Figures (5.4e) and (5.4f).

Strategy III: In this strategy, MDR-TB cases behaved asymptotically as in strategy II, but strategy II reduced further the number of cases reported for all $\alpha-$values, see Figures (5.5a-5.5f). In XDR-TB the opposite is the case, this strategy does not prevent future growth in the number of cases, but manages to reduce the number of XDR-TB more than strategy II, see figures (5.6a-5.6f). In particular for diabetic XDR-TB showed greater effectiveness which is important because this behavior has a great impact on the dynamics of TB resistance and transmission, see Figure (5.6f).

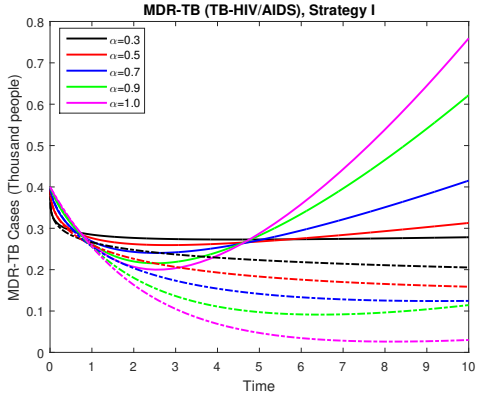
In summary, all strategies succeed in reducing the number of resistant cases for all α-values compared to the model without controls. The most effective strategy is the strategy I because it reduces the number of resistant cases with respect to the other strategies, avoids future growth of resistant cases, and in particular, significantly reduces diabetic XDR-TB which has a strong impact on the resistance and TB transmission. For all compartments, the best results are achieved for higher α-values, except for diabetic XDR-TB. Strategy II is not recommended for any α-value because it continues to report a large number of XDR-TB cases in the TB-Diabetes subpopulation.



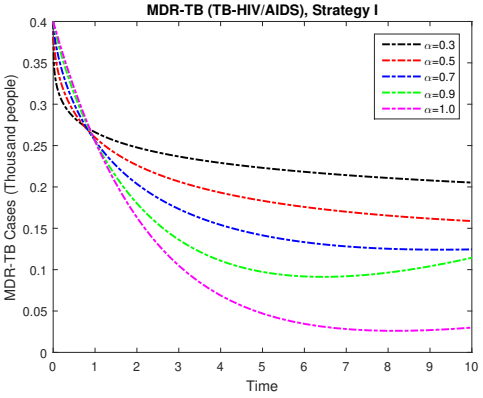
(a) *MDR-TB cases in TB-Only with and without controls for different $\alpha-$values. Strategy I.*



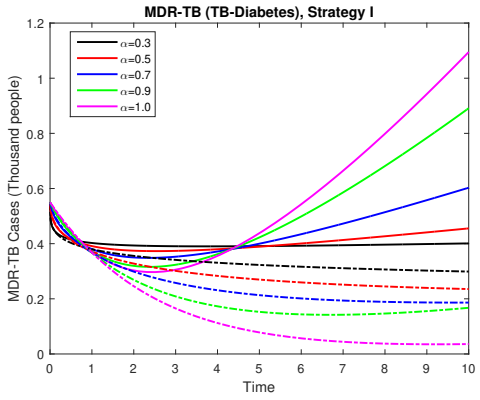
(b) *MDR-TB cases in TB-Only with controls for different $\alpha-$values. Strategy I.*



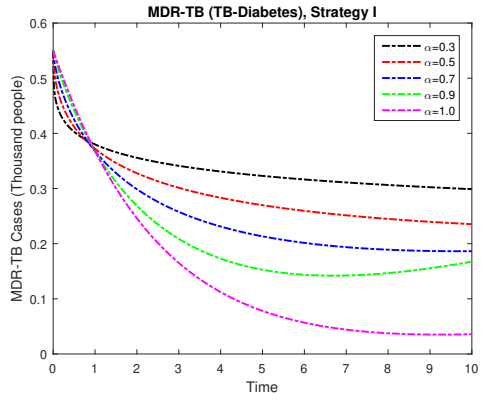
(c) *MDR-TB cases in TB-HIV/AIDS with and without controls for different $\alpha-$values. Strategy I.*



(d) *MDR-TB cases in TB-HIV/AIDS with controls for different $\alpha-$values. Strategy I.*

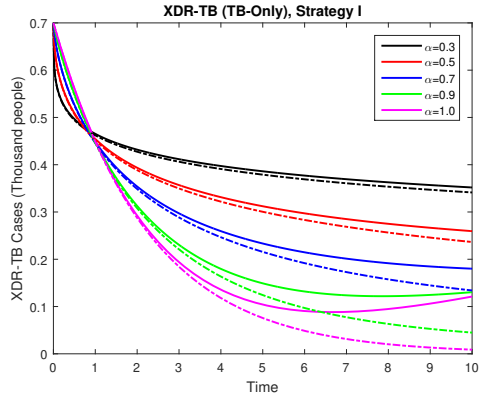


(e) *MDR-TB cases in TB-Diabetes with and without controls for different $\alpha-$values. Strategy I.*

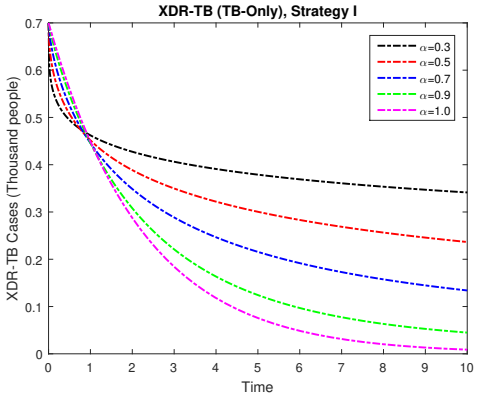


(f) *MDR-TB cases in TB-Diabetes with controls for different $\alpha-$values. Strategy I.*

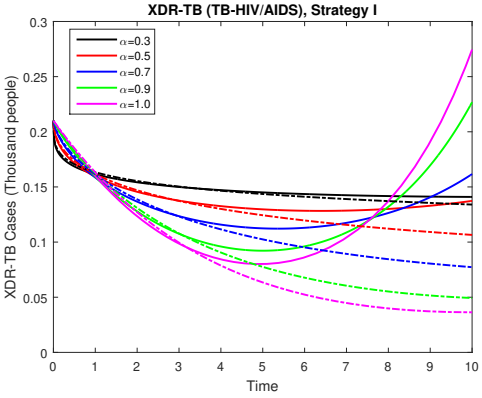
Figure 5.1: *Behavior of MDR-TB cases for different α-values over time. Strategy I.*



(a) *XDR-TB cases in TB-Only with and without controls for different $\alpha-$values. Strategy I.*



(b) *XDR-TB cases in TB-Only with controls for different $\alpha-$values. Strategy I.*



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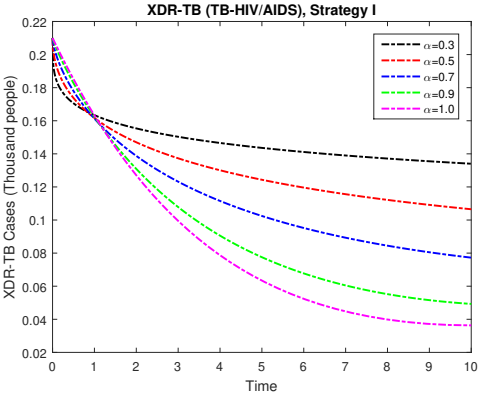
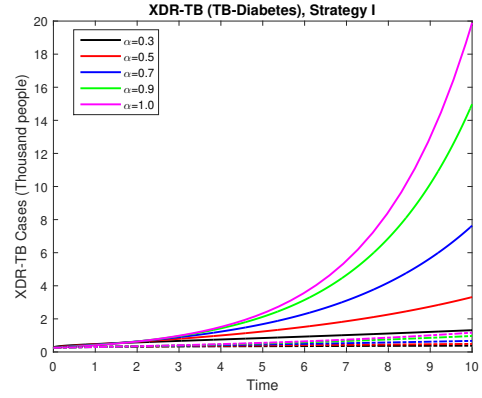
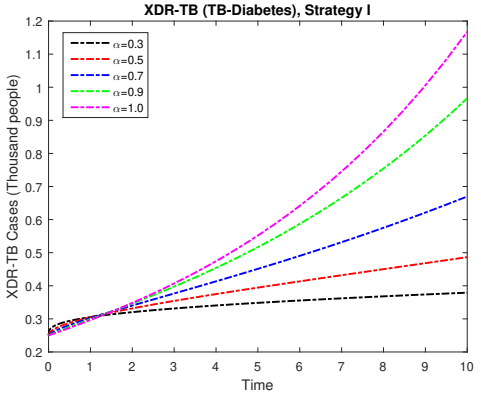


(d) *XDR-TB cases in TB-HIV/AIDS with and without controls for different $\alpha-$values. Strategy I.*

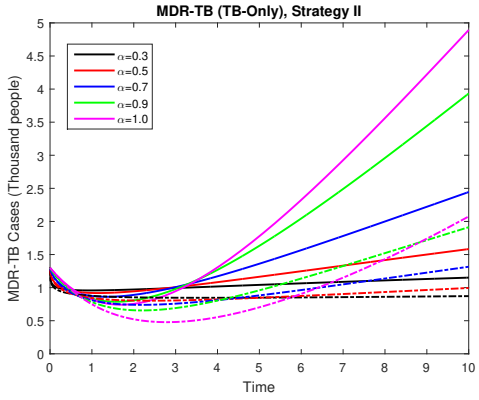


(e) *XDR-TB cases in TB-Diabetes with and without controls for different $\alpha-$values. Strategy I.*

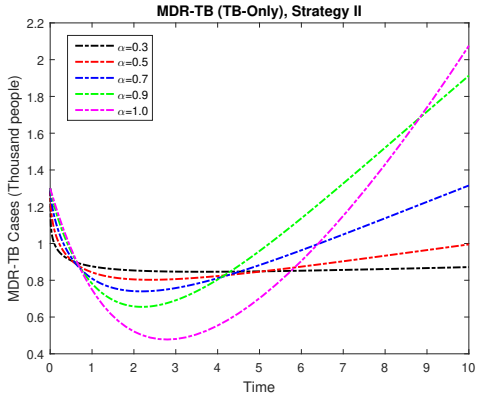


(f) *XDR-TB cases in TB-Diabetes with controls for different $\alpha-$values. Strategy I.*

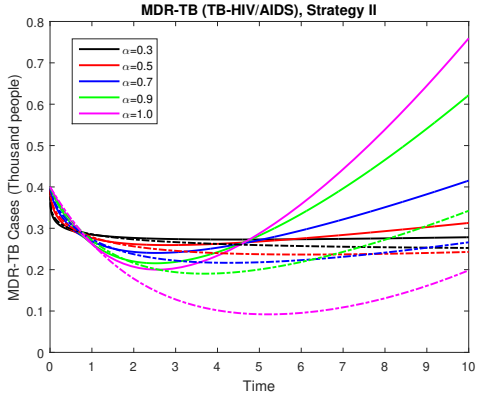
Figure 5.2: *Behavior of XDR-TB cases for different α-values over time. Strategy I.*



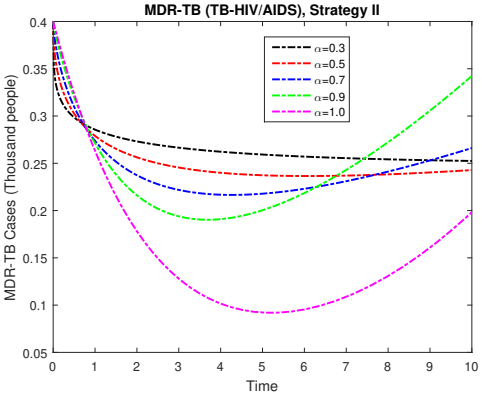
(a) *MDR-TB cases in TB-Only with and without controls for different $\alpha-$values. Strategy II.*



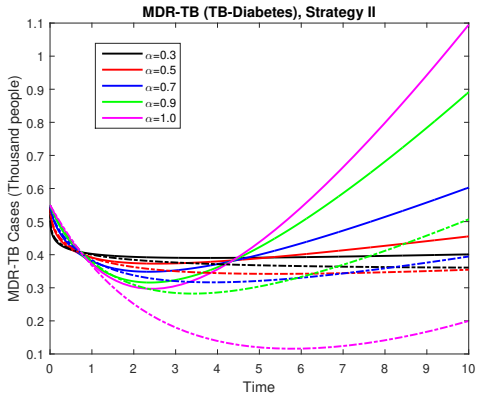
(b) *MDR-TB cases in TB-Only with controls for different $\alpha-$values. Strategy II.*



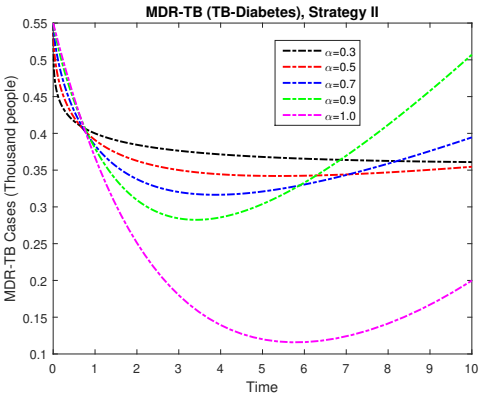
(c) *MDR-TB cases in TB-HIV/AIDS with and without controls for different $\alpha-$values. Strategy II.*



(d) *MDR-TB cases in TB-HIV/AIDS with controls for different $\alpha-$values. Strategy II.*

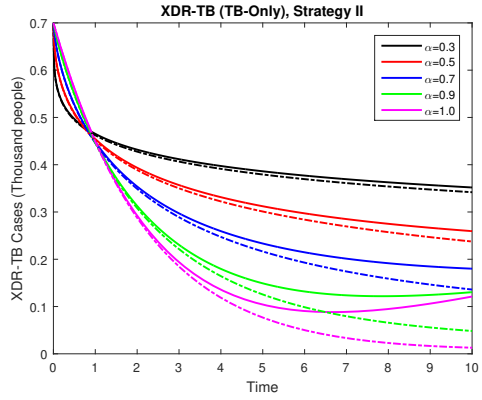


(e) *MDR-TB cases in TB-Diabetes with and without controls for different $\alpha-$values. Strategy II.*

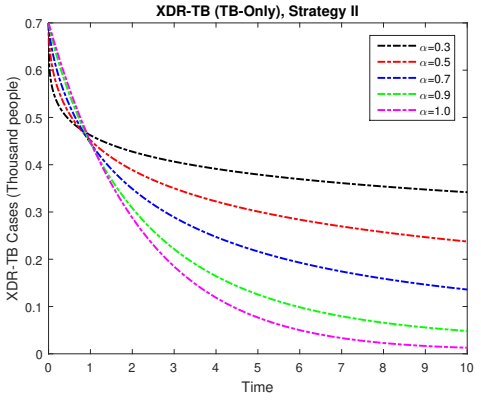


(f) *MDR-TB cases in TB-Diabetes with controls for different $\alpha-$values. Strategy II.*

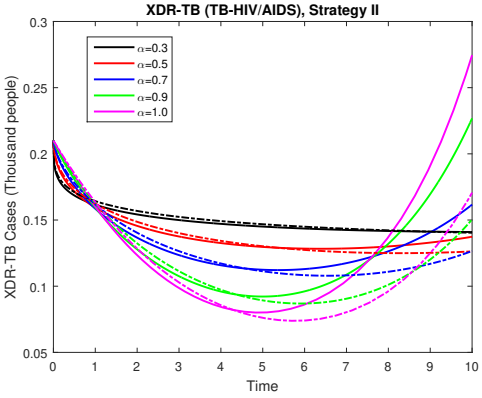
Figure 5.3: *Behavior of MDR-TB cases for different α-values over time. Strategy II.*



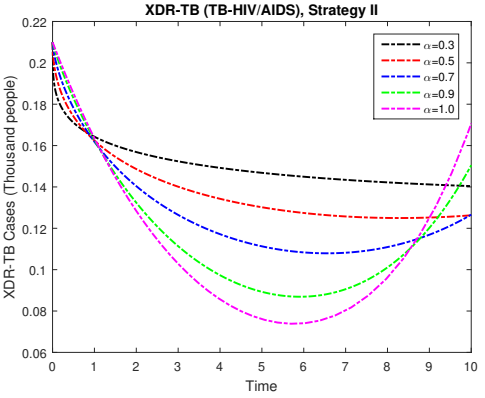
(a) *XDR-TB cases in TB-Only with and without controls for different $\alpha-$values. Strategy II.*



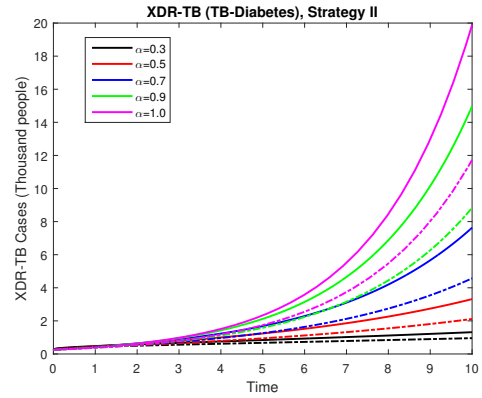
(b) *XDR-TB cases in TB-Only with controls for different $\alpha-$values. Strategy II.*



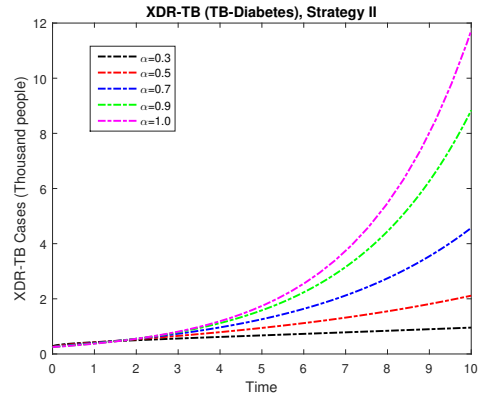
(c) *XDR-TB cases in TB-HIV/AIDS with and without controls for different $\alpha-$values. Strategy II.*



(d) *XDR-TB cases in TB-HIV/AIDS with controls for different $\alpha-$values. Strategy II.*

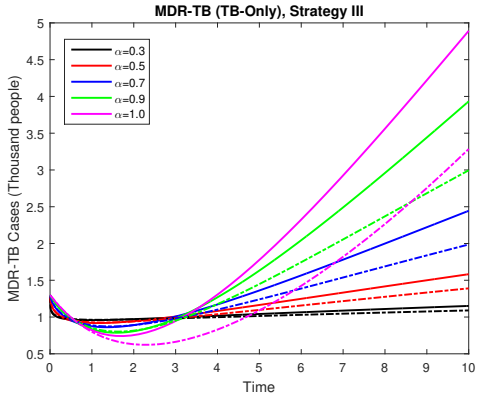


(e) *XDR-TB cases in TB-Diabetes with and without controls for different $\alpha-$values. Strategy II.*

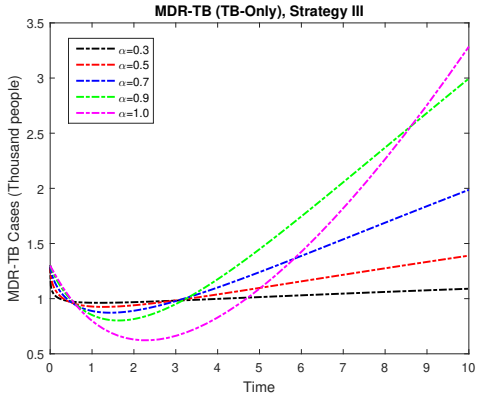


(f) *XDR-TB cases in TB-Diabetes with controls for different $\alpha-$values. Strategy II.*

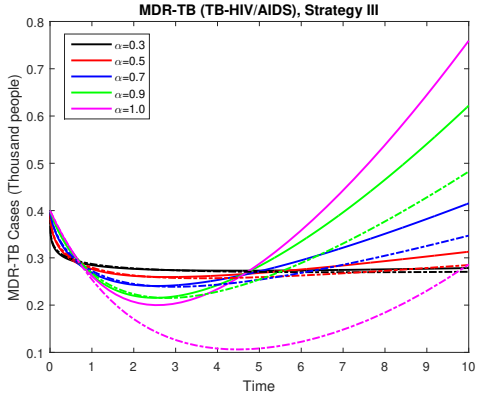
Figure 5.4: *Behavior of XDR-TB cases for different α-values over time. Strategy II.*



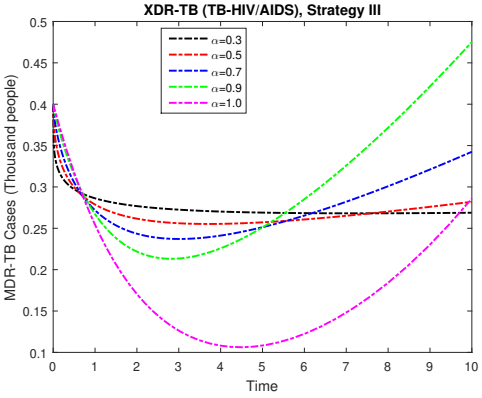
(a) *MDR-TB cases in TB-Only with and without controls for different $\alpha-$values. Strategy III.*



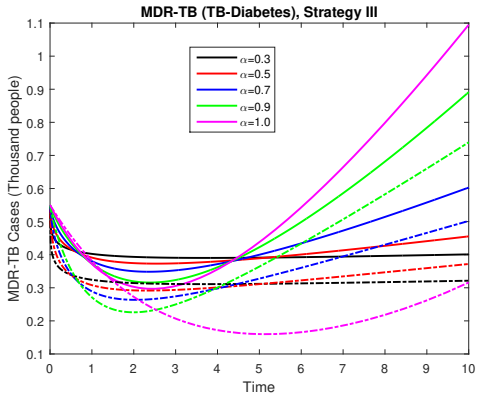
(b) *MDR-TB cases in TB-Only with controls for different $\alpha-$values. Strategy III.*



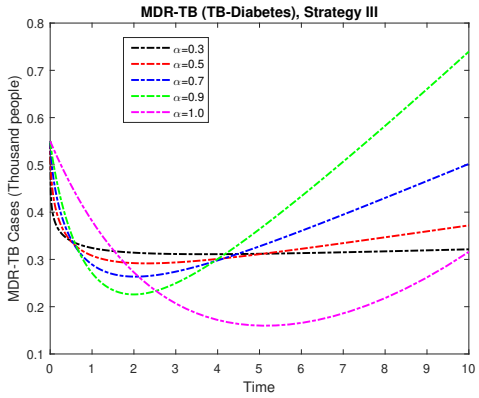
(c) *MDR-TB cases in TB-HIV/AIDS with and without controls for different $\alpha-$values. Strategy III.*



(d) *MDR-TB cases in TB-HIV/AIDS with controls for different $\alpha-$values. Strategy III.*

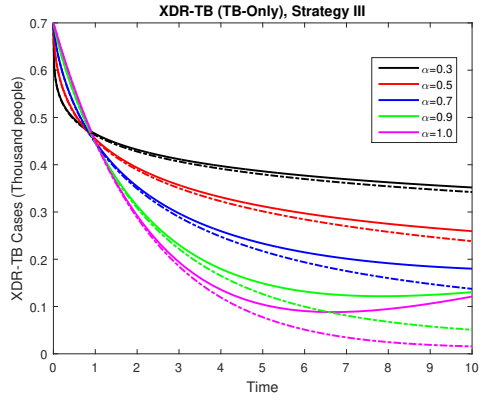


(e) *MDR-TB cases in TB-Diabetes with and without controls for different $\alpha-$values. Strategy III.*

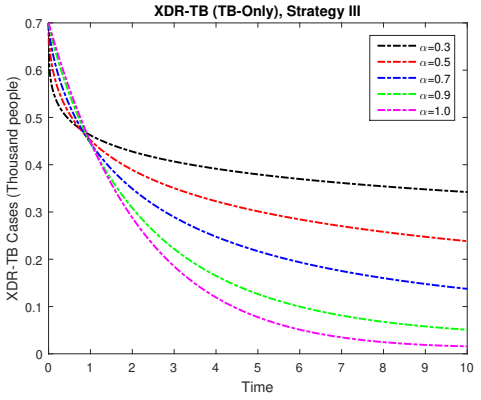


(f) *MDR-TB cases in TB-Diabetes with controls for different $\alpha-$values. Strategy III.*

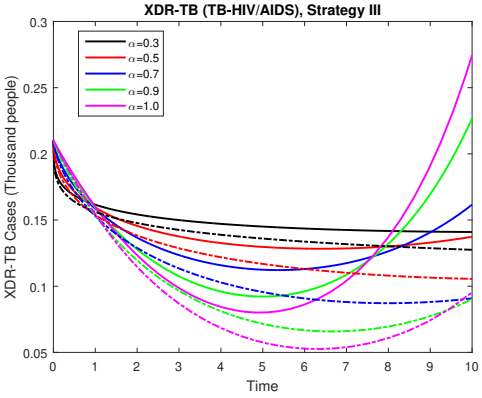
Figure 5.5: *Behavior of MDR-TB cases for different α-values over time. Strategy III.*



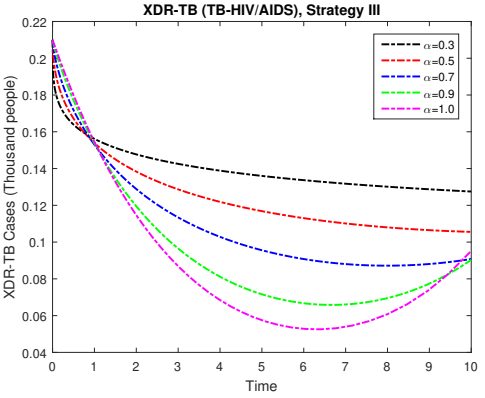
(a) *XDR-TB cases in TB-Only with and without controls for different $\alpha-$values. Strategy III.*



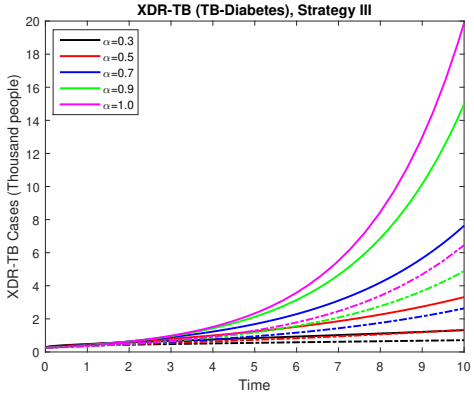
(b) *XDR-TB cases in TB-Only with controls for different $\alpha-$values. Strategy I.*



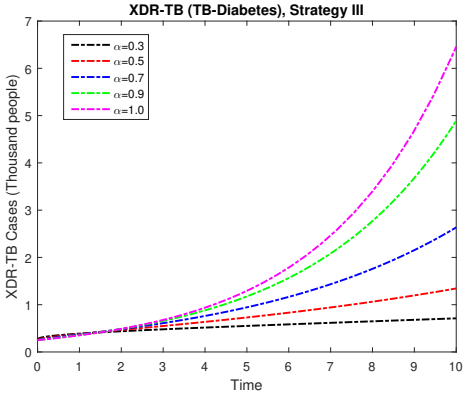
(c) *XDR-TB cases in TB-HIV/AIDS with and without controls for different $\alpha-$values. Strategy III.*



(d) *XDR-TB cases in TB-HIV/AIDS with controls for different $\alpha-$values. Strategy III.*



(e) *XDR-TB cases in TB-Diabetes with and without controls for different $\alpha-$values. Strategy III.*



(f) *XDR-TB cases in TB-Diabetes with controls for different $\alpha-$values. Strategy III.*

Figure 5.6: *Behavior of XDR-TB cases for different α-values over time. Strategy III.*

5.4 Partial Conclusions

In this chapter, we presented a study of an optimal control problem for a model with fractional-order control in the Caputo sense. We presented three control strategies analogous to the optimal control problem with ODE presented in the Subsection (5.2) and studied the different fractional-orders (0.3, 0.5, 0.7, 0.9, and 1.0). We compared the results with respect to the model without control. The strategy that showed the best results is when all controls are activated due to the reduction in all compartments, it manages to avoid future growth in the number of MDR-TB and XDR-TB cases in the TB-Only and TB-HIV/AIDS subpopulations and significantly reduced XDR-TB in diabetic patients, see Figures (5.1a)-(5.2f).

Chapter 6

Conclusions

We presented a new mathematical model for the study of TB treatment efficacy considering the influence of diabetes and HIV/AIDS. Our aim is to examine the impact of diabetes and HIV/AIDS on treatment resistance and transmission of tuberculosis. Based on this model, we studied the optimal control problem to obtain a better adherence to treatment and thus avoid MDR-TB and XDR-TB. The controls are focused on reinfection/reactivation of TB, MDR-TB, and XDR-TB. In order to take advantage of the fractional-order derivative, we studied this model with fractional-order derivatives in the Caputo sense and as a consequence, we used this system as a constraint in the fractional optimal control problem.

We found the basic reproduction number using the next-generation matrix method for the ODE and FDE models. We studied the basic properties of the models such as the existence, uniqueness, and positivity of the solution, and found the biologically feasible regions. Using the respective ODE and FDE techniques, we studied the local stability of the respective infection-free equilibrium points related to the basic reproduction numbers. We proved the global stability of the infection-free equilibrium point. We showed the existence of endemic equilibrium points if the basic reproduction numbers are greater than unity. For the model with ordinary differential equations, we presented results that allow us to know the behavior of the basic reproduction number by submodel (TB-Only, TB-HIV/AIDS and TB-Diabetes), and general model, based on the different joint variations of the resistance and recovery parameters.

We carried out a study of the sensitivity of the parameters with respect to the basic reproduction number, in particular the parameters associated with tuberculosis. We obtained that the recruitment rate and the effective contact rate always have a positive effect on the basic reproduction number and we presented a lemma characterizing the impact of β^* on the basic reproduction number. For the TB-Diabetes submodel in a particular case, we studied the persistence of TB and evidenced the need to apply control strategies.

The optimal control theory for these models is derived analytically by applying Pontryagin's maximum principle and we demonstrated the existence of optimal controlS.

We studied in the numerical simulations the variation of the basic reproduction number concerning the effective contact rate, and we concluded that we must pay attention to this variation in the TB-Only submodel because we can find situations where it can be greater than unity. For the variation with respect to the resistance parameters, it is always greater than unity. This implies that, we should pay attention to tuberculosis transmission in this

subpopulation.

In the numerical simulations of the different resistance compartments, we observed the strong influence that diabetes has on the dynamics and in particular on the XDR-TB so that any control strategy that is applied must comply with the reduction of diabetic XDR-TB given the impact of these cases.

In the optimal control problem, we evaluated different strategies but the one that showed the greatest efficacy was when we activated all the controls (reactivation/reinfection, MDR-TB, and XDR-TB) and starting with high control effectiveness as it reduces all the resistance compartments, avoids future growth of cases, and controls the impact of diabetic XDR-TB.

For the fractional-order model, we studied the basic reproduction number for the different $\alpha-$values. The computational simulations allowed us to observe the behavior of the different compartments for the different $\alpha-$values and this helps us in making decisions for future controls. We can see that for any $\alpha-$values the diabetic XDR-TB has a strong impact on the epidemic.

With the study of fractional optimal control problem in the Caputo sense, using the same strategies of the optimal control problem with ODE, we found that for the different $\alpha-$values the most effective strategy is when we activated all the controls because it meets all the objectives (to reduce the resistance MDR-TB and XDR-TB and avoid future growth of cases) but paying attention to the case when $\alpha = 0.9$ due to its behavior.

This work allows us to study the treatment and transmission of tuberculosis with the presence of diabetes and HIV/AIDS, which are subpopulations vulnerable to infection. It helps to design control strategies and decide how to initiate the control process to reduce the impact of tuberculosis and increase the effectiveness of treatment.

In future work, we will perform parameter estimation using current techniques and computational simulations for real scenarios and study the control problem with $\alpha-$level controls.

References

[1] World Health Organization (WHO). *Global tuberculosis report*. 2017. URL: https://www.who.int/tb/publications/global_report/gtbr2017_main_text.pdf?ua=1 (cit. on p. 1).

[2] F. abd-elal et al. "Computational method for the fractional optimal control HIV infection". In: *Journal of Fractional Calculus and Applications* 7.2 (2016), pp. 121–131. DOI: 10.1051/mmnp/2018015 (cit. on p. 113).

[3] A. Adeboye et al. "A mathematical model for TB/HIV co-infection treatment and transmission mechanism". In: *Mathematical Biosciences and Engineering* 22.4 (2017), pp. 180–192 (cit. on p. 16).

[4] F. B. Agusto and A. I. Adekunle. "Optimal control of a two-strain tuberculosis-HIV/AIDS co-infection model". In: *Biosystems* 119 (2014), pp. 20–44. DOI: 10.1016/j.biosystems.2014.03.006 (cit. on pp. 70, 73, 83).

[5] S. M. Blower et al. "The intrinsic transmission dynamics of tuberculosis epidemics". In: *Nature Medicine* 1.8 (1995), pp. 815–21. DOI: 10.1038/nm0895-815 (cit. on pp. 54, 55).

[6] A. Boukhouima et al. "Stability analysis and optimal control of a fractional HIV-AIDS epidemic model with memory and general incidence rate". In: *European Physical Journal Plus* 136.1 (2019), Art. 103, 20 pp. DOI: 10.1140/epjp/s13360-020-01013-3 (cit. on p. 70).

[7] A. Kouidere et al. "Optimal control strategy for a discrete time to the dynamics of a population of diabetics with highlighting the impact of living environment". In: *Discrete Dynamics in Nature and Society* 2019 (2019), Article ID 6342169. DOI: 10.1155/2019/6342169 (cit. on p. 70).

[8] A. Kouidere et al. "Optimal control strategy with multi-delay in state and control variables of a discrete mathematical modeling for the dynamics of diabetic population". In: *Communications in Mathematical Biology and Neuroscience 2020* 2020.14 (2020), pp. 2052–2541. DOI: 10.28919/cmbn/4486 (cit. on p. 70).

[9] C. R. Stevenson et al. "Diabetes and the risk of tuberculosis: a neglected threat to public health?" In: *Chronic Illness* 3.3 (2007), pp. 228–45. DOI: 10.1177/1742395307081502 (cit. on p. 2).

[10] E. Girardi et al. "The global dynamics of diabetes and tuberculosis: the impact of migration and policy implications". In: *International Journal of Infectious Diseases* 56 (2017). DOI: 10.1016/j.ijid.2017.01.018 (cit. on p. 16).

[11] Fatmawati et al. "A mathematical model of tuberculosis (TB) transmission with children and adults groups: A fractional model". In: *AIMS Mathematics* 5.4 (2020), pp. 2813–2842. DOI: 10.3934/math.2020181 (cit. on p. 91).

[12] G. Guzzetta et al. “Modeling socio-demography to capture tuberculosis transmission dynamics in a low burden setting”. In: *Journal of Theoretical Biology* 289.197-205 (2011). DOI: 10.1016/j.jtbi.2011.08.032 (cit. on p. 15).

[13] H. Ferjouchia et al. “Application of optimal control strategies for physiological model of type 1 diabetes - T1D”. In: *Communications in Mathematical Biology and Neuroscience* 2020 (2020), Article ID 35. DOI: 10.28919/cmbn/4598 (cit. on p. 16).

[14] H. Wang et al. “A Caputo-Fabrizio fractional-order model of HIV/AIDS with a treatment compartment: Sensitivity analysis and optimal control strategies”. In: *Entropy (Basel)* 23.5 (2021), p. 610. DOI: 10.3390/e23050610 (cit. on pp. 14, 113).

[15] I. Area et al. “On a fractional order Ebola epidemic model”. In: *Advances in Difference Equations* 2015 (2015), Article number: 278. DOI: 10.1186/s13662-015-0613-5 (cit. on pp. 91, 92).

[16] L. N. Nkamba et al. “Mathematical model to assess vaccination and effective contact rate impact in the spread of tuberculosis”. In: *Journal of Biological Dynamics* 13.1 (2019), pp. 26–42. DOI: 10.1080/17513758.2018.1563218 (cit. on p. 15).

[17] L. Pealing et al. “Risk of tuberculosis in patients with diabetes: population based cohort study using the UK Clinical Practice Research Datalink”. In: *BMC Med* 13 (2015), p. 135. DOI: 10.1186/s12916-015-0381-9 (cit. on p. 2).

[18] M. Farman et al. “Numerical treatment of a nonlinear dynamical Hepatitis-B model: an evolutionary approach”. In: *The European Physical Journal Plus* 135 (2020), article 941. DOI: 10.1140/epjp/s13360-020-00902-x (cit. on p. 15).

[19] M. Saeedian et al. “Memory effects on epidemic evolution: The susceptible-infected-recovered epidemic model”. In: *PHYSICAL REVIEW E* 95.2 (2017), p. 022409. DOI: 10.1103/PhysRevE.95.022409 (cit. on p. 11).

[20] Marsudi et al. “Optimal control of an HIV model with changing behavior through an education campaign, screening and treatment”. In: *IOP Conference Series: Materials Science and Engineering* (2019) (cit. on p. 70).

[21] O. K. Başoğlu et al. “The oral glucose tolerance test in patients with respiratory infections”. In: *Monaldi Arch Chest Dis* 54.4 (1999), pp. 307–10 (cit. on p. 2).

[22] P. A. Naik et al. “Modeling and analysis of COVID-19 epidemics with treatment in fractional derivatives using real data from Pakistan”. In: *The European Physical Journal Plus* 135 (2020), article 795. DOI: 10.1140/epjp/s13360-020-00819-5 (cit. on p. 91).

[23] P. A. Naik et al. “The role of prostitution on HIV transmission with memory: A modeling approach”. In: *Alexandria Engineering Journal* 59.4 (2020), pp. 2513–2531. DOI: 10.1016/j.aej.2020.04.016 (cit. on p. 91).

[24] P. Baghaei et al. “Diabetes mellitus and tuberculosis facts and controversies”. In: *J Diabetes Metab Disord* 12.1 (2013), p. 58. DOI: 10.1186/2251-6581-12-58 (cit. on p. 2).

[25] J. P. Aparicio and C. Castillo-Chavez. “Mathematical modelling of tuberculosis epidemics”. In: *Mathematical Biosciences and Engineering* 6.2 (2009), pp. 209–37. DOI: 10.3934/mbe.2009.6.209 (cit. on p. 15).

[26] T. D. Awoke and S. M. Kassa. “A new mathematical modeling with optimal control strategy for the dynamics of population of diabetics and its complications with effect of behavioral factors”. In: *Journal of Applied Mathematics* 2020 (2020), Article ID 1943410. DOI: 10.1155/2020/1943410 (cit. on p. 70).

[27] T. D. Awoke and S. M. Kassa. “Optimal control strategy for TB-HIV/AIDS co-infection model in the presence of behaviour modification”. In: *Processes* 6.5 (2018), p. 48. DOI: 10.3390/pr6050048 (cit. on p. 70).

[28] B. A. Baba and B. Bilgehan. “Optimal control of a fractional order model for the COVID - 19 pandemic”. In: *Chaos, Solitons and Fractals* 144 (2021), p. 110678. DOI: 10.1016/j.chaos.2021.110678 (cit. on p. 113).

[29] L. Carvalho de Barros et al. “The memory effect on fractional calculus: an application in the spread of COVID-19”. In: *Computational and Applied Mathematics* 40.3 (2021), p. 72. DOI: 10.1007/s40314-021-01456-z (cit. on pp. 8–11).

[30] C. P. Bhunu, W. Garira, and Z. Mukandavire. “Modeling HIV/AIDS and tuberculosis coinfection”. In: *Mathematical Biosciences and Engineering* 71.7 (2009), pp. 1745–80. DOI: 10.1007/s11538-009-9423-9 (cit. on pp. 16, 47).

[31] S. Bowong. “Optimal control of the transmission dynamics of tuberculosis”. In: *Nonlinear Dynamics* 61.4 (2010), pp. 729–748. DOI: 10.1007/s11071-010-9683-9 (cit. on p. 69).

[32] F. Brauer, C. Castillo-Chavez, and Z. Feng. *Mathematical models in epidemiology*. 1st ed. Springer, New York, NY, 2019 (cit. on p. 2).

[33] R. Figueiredo Camargo and E. Capelas de Oliveira. “Cálculo fracionário”. In: (2015) (cit. on p. 12).

[34] A. R. M. Carvalho, C. M. A. Pinto, and D. Baleanu. “HIV/HCV coinfection model: a fractional-order perspective for the effect of the HIV viral load”. In: *Advances in Difference Equations* 2018 (2018), p. 2. DOI: 10.1186/s13662-017-1456-z (cit. on p. 91).

[35] A. R.M. Carvalho and C. M.A. Pinto. “Non-integer order analysis of the impact of diabetes and resistant strains in a model for TB infection”. In: *Communications in Nonlinear Science and Numerical Simulation* 61 (2018), pp. 104–126. DOI: 10.1016/J.CNSNS.2018.01.012 (cit. on pp. 54, 55, 92).

[36] A. J. F. Cassetone. “Alterações metabólicas associadas ao uso de medicamento antirretroviral em pessoas vivendo com HIV/AIDS: caracterização e desenvolvimento de algoritmos inteligentes aplicados à sua identificação e previsão”. PhD thesis. São Paulo, Brasil: FMUSP, 2017 (cit. on pp. 54, 55).

[37] C. Castillo-Chavez and Z. Feng. “To treat or not to treat: the case of tuberculosis”. In: *Journal of Mathematical Biology* 35.6 (1997), pp. 629–56. DOI: 10.1007/s002850050069 (cit. on pp. 54, 55).

[38] C. Castillo-Chavez, Z. Feng, and W. Huang. “On the computation of $\mathfrak{R}_0$ and its role on global stability”. In: *In: Mathematical Approaches for Emerging and Reemerging Infectious Diseases: An Introduction, Springer-Verlag, New York* (2002), pp. 229–250. DOI: 10.1007/978-1-4613-0065-6 (cit. on pp. 7, 25, 49, 101).

[39] I. Y. Sánchez Chávez, R. Morales-Menéndez, and S. O. Martínez Chapa. “Glucose optimal control system in diabetes treatment”. In: *Applied Mathematics and Computation* 209.1 (2009), pp. 19–30. DOI: 10.1016/j.amc.2008.06.030 (cit. on p. 70).

[40] N. Chitnis, J. M. Hyman, and J. M. Cushing. “Determining important parameters in the spread of malaria through the sensitivity analysis of a mathematical model”. In: *Bulletin of Mathematical Biology* 70.5 (2008), pp. 1272–96. DOI: 10.1007/s11538-008-9299-0 (cit. on p. 51).

[41] T. Cohen et al. “Exogenous re-infection and the dynamics of tuberculosis epidemics: local effects in a network model of transmission”. In: *J. R. Soc. Interface* 4.14 (2007), pp. 523–531 (cit. on pp. 54, 55).

[42] C. Coll et al. “A dynamic model for a study of diabetes”. In: *Mathematical and Computer Modelling: An International Journal* 50.5-6 (2009), pp. 713–716. DOI: 10.1016/j.mcm.2008.12.027 (cit. on p. 16).

[43] G. Delogu, M. Sali, and G. Fadda. “The biology of mycobacterium tuberculosis infection”. In: *Mediterr J Hematol Infect Dis.* 5.1 (2013), e2013070. DOI: 10.4084/MJHID.2013.070 (cit. on p. 1).

[44] O. Diekmann, J. A. P. Heesterbeek, and J. A. J. Metz. “On the definition and the computation of the basic reproduction ratio $\mathfrak{R}_0$ in model for infectious diseases in heterogeneous populations”. In: *Journal of Mathematical Biology* 28 (1990), pp. 365–382 (cit. on p. 23).

[45] O. Diekmann, J. A. P. Heesterbeek, and M. G. Roberts. “The construction of next-generation matrices for compartmental epidemic models”. In: *J. R. Soc. Interface* 7.47 (2010), pp. 873–85. DOI: 10.1098/rsif.2009.0386 (cit. on pp. 4, 23).

[46] K. Diethelm. “A fractional calculus based model for the simulation of an outbreak of dengue fever”. In: *Nonlinear Dynamics* 71 (2013), pp. 613–619. DOI: 10.1007/s11071-012-0475-2 (cit. on p. 92).

[47] K. Diethelm. *The analysis of fractional differential equations.* 1st ed. Springer-Verlag Berlin Heidelberg, 2004 (cit. on pp. 8, 9).

[48] K. Diethelm, N. J. Ford, and A. D. Freed. “A Predictor-Corrector approach for the numerical solution of fractional differential equations”. In: *Nonlinear Dynamics* 29 (2002), pp. 3–22. DOI: 10.1023/A:1016592219341 (cit. on pp. 12, 104).

[49] K. Diethelm, N. J. Ford, and A. D. Freed. “Detailed error analysis for a fractional Adams method”. In: *Numerical Algorithms* 36 (2004), pp. 31–52. DOI: 10.1023/B:NUMA.0000027736.85078.be (cit. on pp. 12, 104).

[50] K. Diethelm and A. D. Freed. *The FracPECE subroutine for the numerical solution of differential equations of fractional order.* Forschung und wissenschaftliches rechnen, 1998, pp. 57–71 (cit. on pp. 12, 104).

[51] P. van den Driessche and J. Watmough. “Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission”. In: *Mathematical Biosciences* 180 (2002), pp. 29–48 (cit. on pp. 5, 23, 95).

[52] R. Durrett. *Probability: Theory and examples.* 5th ed. Cambridge University Press, 2019 (cit. on p. 8).

[53] C. Dye et al. “Prospects for worldwide tuberculosis control under the WHO DOTS strategy. Directly observed short-course therapy”. In: *Lancet* 352.9144 (1998), pp. 1886–1891 (cit. on p. 1).

[54] A. Pietrus E. M. D. Moya and S. M. Oliva. “Mathematical model with fractional order derivatives for tuberculosis taking into account its relationship with HIV/AIDS and diabetes”. In: *Jambura Journal of Biomathematics* 2.2 (2021), pp. 80–95 (cit. on pp. 3, 8, 91–95, 98, 104, 107–110).

[55] M. Farman et al. “Mathematical analysis of fractional order co-Infection TB and HIV model”. In: *International Journal of Analysis and Applications* 18.1 (2020), pp. 16–32 (cit. on p. 91).

[56] Fatmawati, E. M. Shaiful, and M. I. Utoyo. "A fractional-order Model for HIV dynamics in a two-sex population". In: *International Journal of Mathematics and Mathematical Sciences* 2018 (2018), Article ID 6801475. DOI: 10.1155/2018/6801475 (cit. on p. 91).

[57] Fatmawati and H. Tasman. "An optimal treatment control of TB-HIV co-infection". In: *Cogent Mathematics and Statistics* 2016 (2016), Article ID 8261208. DOI: 10.1155/2016/8261208 (cit. on p. 73).

[58] Z. Feng, C. Castillo-Chavez, and A. F. Capurro. "A model for tuberculosis with exogenous reinfection". In: *Theoretical Population Biology* 57.3 (2000), pp. 235–47. DOI: 10.1006/tpbi.2000.1451 (cit. on p. 15).

[59] W. H. Fleming and R. W. Rishel. *Deterministic and stochastic optimal control*. 1st ed. Berlin ; New York : Springer-Verlag, 1975 (cit. on p. 74).

[60] R. Gorenflo, J. Loutchko, and Y. Luchko. "Computation of the Mittag-Leffler function $\mathbb{E}_{\alpha,\beta}(z)$ and its derivatives". In: *Fractional Calculus and Applied Analysis* 5.4 (2002), pp. 491–518 (cit. on pp. 91, 92).

[61] R. I. Hickson, G. N. Mercer, and K. M. Lokuge. "A metapopulation model of tuberculosis transmission with a case study from high to low burden areas". In: *PloS ONE* 7.4 (2012), e34411. DOI: 10.1371/journal.pone.0034411 (cit. on pp. 54, 55).

[62] A. Jajarmi, B. Ghanbari, and D. Baleanu. "A new and efficient numerical method for the fractional modeling and optimal control of diabetes and tuberculosis co-existence". In: *Chaos* 29.9 (2019), p. 093111. DOI: 10.1063/1.5112177 (cit. on p. 113).

[63] C. Y. Jeon and M. B. Murray. "Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies". In: *PLoS Med* 5 (2008), e152. DOI: 10.1371/journal.pmed.0050152 (cit. on p. 2).

[64] E. Jung, S. Lenhart, and Z. Feng. "Optimal control of treatments in a two-strain tuberculosis model". In: *Mathematical Biosciences* 2.4 (2002), pp. 473–482. DOI: 10.3934/dcdsb.2002.2.473 (cit. on pp. 54, 55, 69, 73).

[65] H. Khan et al. "A fractional order HIV-TB coinfection model with nonsingular Mittag-Leffler Law". In: *International Journal of Analysis and Applications* 43.6 (2020), pp. 3786–3806. DOI: 10.1002/mma.6155 (cit. on p. 91).

[66] H. Kheiri and M. Jafari. "Optimal control of a fractional-order model for the HIV/AIDS epidemic". In: *International Journal of Biomathematics* 11.7 (2018), 1850086 (23 pages). DOI: 10.1142/S1793524518500869 (cit. on pp. 12–14, 113).

[67] S. Kim, A. A de Los Reyes, and E. Jung. "Mathematical model and intervention strategies for mitigating tuberculosis in the Philippines". In: *Journal of Theoretical Biology* 443 (2018), pp. 100–112. DOI: 10.1016/j.jtbi.2018.01.026 (cit. on pp. 69, 73).

[68] S. Kumar and S. Jain. "Assessing the effects of treatment in HIV-TB co-infection model". In: *The European Physical Journal Plus* 133 (2018), p. 294. DOI: 10.1140/epjp/i2018-12117-8 (cit. on p. 16).

[69] V. Lakshmikantham, S. Leel, and A. A. Martynyuk. "Stability analysis of nonlinear systems". In: *SIAM Rev* 33.1 (1991), pp. 152–154. DOI: 10.1137/1033038 (cit. on p. 22).

[70] A. G. Lambura et al. "Modeling the effects of helminth infection on the transmission dynamics of mycobacterium tuberculosis under optimal control strategies". In: *Computational and Mathematical Methods in Medicine* 2020 (2020), Article ID 8869377. DOI: 10.1155/2020/8869377 (cit. on p. 69).

[71] S. Lenhart and J. T. Workman. *Optimal control applied to biological models*. 1st ed. Chapman and Hall/CRC, 2007 (cit. on p. 83).

[72] W. Lin. "Global existence theory and chaos control of fractional differential equations". In: *Journal of Mathematical Analysis and Applications* 332.1 (2007), pp. 709–726. DOI: 10.1016/j.jmaa.2006.10.040 (cit. on p. 93).

[73] S. Liu, Y. Bi, and Y. Liu. "Modeling and dynamic analysis of tuberculosis in mainland China from 1998 to 2017: the effect of DOTS strategy and further control". In: *Theoretical Biology and Medical Modelling* 17.1 (2020), p. 6. DOI: 10.3934/mbe.2017021 (cit. on p. 69).

[74] E. F. Long, N. K. Vaidya, and M. L. Brandeau. "Controlling co-epidemics: analysis of HIV and tuberculosis infection dynamics". In: *Operational Research* 56.6 (2008), pp. 1366–1381. DOI: 10.1155/2013/429567 (cit. on p. 16).

[75] A. McIvor, H. Koornhof, and B. D. Kana. "Relapse, re-infection and mixed infections in tuberculosis disease". In: *Pathog Dis* 75.3 (2017). DOI: 10.1093/femspd/ftx020 (cit. on p. 2).

[76] B. K. Mishra and J. Srivastava. "Mathematical model of tuberculosis transmission with reccurent infection and vaccination". In: *Journal of Physics Conference Series* 423.1 (2013), p. 2059. DOI: 10.1088/1742-6596/423/1/012059 (cit. on p. 15).

[77] B. K. Mishra and J. Srivastava. "Mathematical model on pulmonary and multidrug-resistant tuberculosis patients with vaccination". In: *Journal of the Egyptian Mathematical Society* 22.2 (2014), pp. 311–316. DOI: 10.1016/j.joems.2013.07.006 (cit. on p. 15).

[78] D. P. Moualeu et al. "Analysis of the impact of diabetes on the dynamical transmission of tuberculosis". In: *Mathematical and Computer Modelling: An International Journal* 7.3 (2012), pp. 117–146. DOI: 10.1051/mmnp/20127309 (cit. on pp. 16, 54, 55).

[79] D. P. Moualeu et al. "Optimal control for a tuberculosis model with undetected cases in Cameroon". In: *Communications in Nonlinear Science and Numerical Simulation* 20.3 (2015), pp. 986–1003. DOI: 10.1016/j.cnsns.2014.06.037 (cit. on p. 69).

[80] E. D. Moya, A. Pietrus, and S. M. oliva. "A mathematical model for the study of effectiveness in therapy in tuberculosis taking into account associated diseases". In: *Contemporary Mathematics* 2.1 (2021), pp. 77–102 (cit. on pp. 1–3, 15–19, 21, 22, 24–26, 48, 54).

[81] P. A. Naik. "Global dynamics of a fractional-order SIR epidemic model with memory". In: *International Journal of Biomathematics* 13.8 (2020), p. 2050071. DOI: 10.1142/S1793524520500710 (cit. on p. 91).

[82] P. A. Naik, J. Zu, and K. M. Owolabi. "Global dynamics of a fractional order model for the transmission of HIV epidemic with optimal control". In: *Chaos, Solitons and Fractals* 138 (2020), p. 109826. DOI: 10.1016/j.chaos.2020.109826 (cit. on p. 91).

[83] R. Naresh, D. Sharma, and A. Tripathi. "Modelling the effect of tuberculosis on the spread of HIV infection in a population with density-dependent birth and death rate". In: *Mathematical and Computer Modelling* 50.7-8 (2009), pp. 1154–1166. DOI: 10.1016/j.mcm.2009.05.033 (cit. on p. 16).

[84] R. Naresh and A. Tripathi. "Modelling and analysis of HIV-TB co-infection in a variable size population". In: *Mathematical Biosciences and Engineering* 10.3 (2010), pp. 275–286 (cit. on p. 16).

[85] P. Ngina, R. W. Mbogo, and L. S. Luboobi. "Modelling optimal control of In-Host HIV dynamics using different control strategies". In: *Computational and Mathematical Methods in Medicine* 2018 (2018), Article ID 9385080, 18 pages. DOI: 10.1155/2018/9385080 (cit. on p. 69).

[86] F. N. Ngoteya and Y. Nkansah-Gyekye. "Sensitivity analysis of parameters in a competition model". In: *Applied and Computational Mathematics* 4.5 (2015), pp. 363–368. DOI: 10.11648/j.acm.20150405.15 (cit. on p. 51).

[87] A. K. Niazi and S. Kalra. "Diabetes and tuberculosis: a review of the role of optimal glycemic control". In: *J Diabetes Metab Disord* 11 (2012), p. 28. DOI: 10.1186/2251-6581-11-28 (cit. on p. 2).

[88] L. N. Nkamba et al. "Analysis of a mathematical model for tuberculosis with diagnosis". In: *Journal of Applied Mathematics and Computing* 59.1-2 (2018). DOI: 10.1007/s12190-018-1172-1 (cit. on p. 15).

[89] Z. Odibat and N. Shawagfeh. "A fractional calculus based model for the simulation of an outbreak of dengue fever". In: *Applied Mathematics and Computation* 186.1 (2013), pp. 286–293. DOI: 10.1016/j.amc.2006.07.102 (cit. on p. 93).

[90] D. Okuonghae. "A mathematical model of tuberculosis transmission with heterogeneity in disease susceptibility and progression under a treatment regime for infectious cases". In: *Applied Mathematical Modelling* 57.10-11 (2000), pp. 235–47. DOI: 10.1016/j.apm.2013.01.039 (cit. on p. 15).

[91] D. Okuonghae and B. O. Ikhimwin. "Dynamics of a mathematical model for tuberculosis with variability in susceptibility and disease progressions due to difference in awareness level". In: *Frontiers in Microbiology* 6 (2016), p. 1530. DOI: 10.3389/fmicb.2015.01530 (cit. on pp. 1, 15).

[92] D. Okuonghae and B. O. Ikhimwin. "Tuberculosis models with fast and slow dynamics: the role of close and casual contacts". In: *Frontiers in Microbiology* 180.1-2 (2002), pp. 187–205. DOI: 10.1016/S0025-5564(02)00112-8 (cit. on p. 15).

[93] A. Omame, C. U. Nnanna, and S. C. Inyama. "Optimal control and cost-effectiveness analysis of an HPV-Chlamydia trachomatis co-infection model". In: *Acta Biotheoretica* 69.3 (2021), pp. 185–223. DOI: 10.1007/s10441-020-09401-z (cit. on p. 15).

[94] A. Omame and D. Okuonghae. "A co-infection model for oncogenic HPV and TB with optimal control and cost-effectiveness analysis". In: *MedRxiv* (2020). DOI: 10.1101/2020.09.15.20195297 (cit. on p. 15).

[95] World Health Organization. *Global tuberculosis report 2021* (cit. on p. 1).

[96] C. M. A. Pinto and A. R. M. Carvalho. "A latency fractional order model for HIV dynamics". In: *Journal of Computational and Applied Mathematics* 312 (2020), pp. 240–256. DOI: 10.1016/j.cam.2016.05.019 (cit. on p. 91).

[97] C. M. A. Pinto and A. R. M. Carvalho. "Diabetes mellitus and TB co-existence: Clinical implications from a fractional order modelling". In: *Applied Mathematical Modelling* 68 (2019), pp. 219–243 (cit. on pp. 51, 104).

[98] C. M. A. Pinto and A. R. M. Carvalho. "The HIV/TB coinfection severity in the presence of TB multi-drug resistant strains". In: *Ecological Complexity* 32.Part A (2019), pp. 1–20. DOI: 10.1016/j.ecocom.2017.08.001 (cit. on pp. 51, 104).

[99] I. Podlubny. *The analysis of fractional differential equations.* 1st ed. Vol. 198. Academic Press, 1998 (cit. on pp. 8, 9).

[100] L. S. Pontryagin. *Mathematical theory of optimal processes*. 1st ed. CRC Press, 1987 (cit. on p. 80).

[101] C. Qin, X. Wang, and L. Rong. "An age-structured model of HIV latent infection with two transmission routes: Analysis and optimal control". In: *Complexity* 2020 (2020), Article ID 1890320. DOI: 10.1155/2020/1890320 (cit. on p. 70).

[102] S. Rosa and Delfim F. M. Torres. "Optimal control and sensitivity analysis of a fractional order TB model". In: *Statistics, Optimization and Information Computing* 7.3 (2019), pp. 617–625. DOI: 10.19139/soic-2310-5070-836 (cit. on pp. 91, 113).

[103] S. Sakulrang et al. "A fractional differential equation model for continuous glucose monitoring data". In: *Advances in Difference Equations* 2017 (2017), Article number: 150. DOI: 10.1186/s13662-017-1207-1 (cit. on pp. 91, 92).

[104] M. U. Saleem et al. "A Caputo Fabrizio fractional order model for control of glucose in insulin therapies for diabetes". In: *Ain Shams Engineering Journal* 11.4 (2020), pp. 1309–1316. DOI: 10.1016/j.asej.2020.03.006 (cit. on p. 91).

[105] K. Shah, F. Jarad, and T. Abdeljawad. "On a nonlinear fractional order model of dengue fever disease under Caputo-Fabrizio derivative". In: *Alexandria Engineering Journal* 59.4 (2020), pp. 2305–2313. DOI: 10.1016/j.aej.2020.02.022 (cit. on pp. 91, 92).

[106] C. J. Silva, H. Maurer, and Delfim F. M. Torres. "Optimal control of a tuberculosis model with state and control delays". In: *Mathematical Biosciences* 14.1 (2017), pp. 321–337. DOI: 10.3934/mbe.2017021 (cit. on pp. 69, 73).

[107] C. J. Silva and Delfim F. M. Torres. "A TB-HIV/AIDS coinfection model and optimal control treatment". In: *SIAM Journal on Mathematical Analysis* 35.9 (2015), pp. 4639–4663. DOI: 10.3934/dcds.2015.35.4639 (cit. on pp. 47, 54, 55, 70).

[108] C. J. Silva and Delfim F. M. Torres. "Optimal control for a tuberculosis model with reinfection and post-exposure interventions". In: *Mathematical Biosciences* 244.2 (2013), pp. 154–64. DOI: 10.1016/j.mbs.2013.05.005 (cit. on pp. 69, 73).

[109] S. Suchindran, E. S. Brouwer, and A. Van Rie. "Is HIV infection a risk factor for multi-drug resistant tuberculosis? A systematic review". In: *PLoS One* 4.5 (2009), e5561. DOI: 10.1371/journal.pone.0005561 (cit. on p. 2).

[110] N. H. Sweilam, S. M. Al-Mekhlafi, and D. Baleanu. "A hybrid fractional optimal control for a novel Coronavirus (2019-nCov) mathematical model". In: *Journal of Advanced Research* 32 (2021), pp. 149–160. DOI: 10.1016/j.jare.2020.08.006 (cit. on p. 113).

[111] N. H. Sweilam, S. M. AL-Mekhlafi, and D.Baleanu. "Optimal control for a fractional tuberculosis infection model including the impact of diabetes and resistant strains". In: *Journal of Advanced Research* 17 (2019), pp. 125–137. DOI: 10.1016/j.jare.2019.01.007 (cit. on p. 113).

[112] N. H. Sweilam et al. "Optimal control for variable order fractional HIV/AIDS and malaria mathematical models with multi-time delay". In: *Alexandria Engineering Journal* 59.5 (2020), pp. 3149–3162. DOI: 10.1016/j.aej.2020.07.021 (cit. on p. 113).

[113] M. Tahir, S. I. A. Shah, and G. Z. Y. Rogovchenko. "Prevention strategy for superinfection mathematical model tuberculosis and HIV associated with AIDS". In: *Cogent Mathematics and Statistics* 6.1 (2019), Article: 1637166. DOI: 10.1080/25742558.2019.1637166 (cit. on pp. 70, 73).

[114] Tanvi and R. Aggarwal. "Dynamics of HIV-TB co-infection with detection as optimal intervention strategy". In: *International Journal of Non-Linear Mechanics* 120 (2020), p. 03388. DOI: j.ijnonlinmec.2019.103388 (cit. on p. 16).

[115] M. S. Tavazoei and M. Haeri. "Chaotic attractors in incommensurate fractional order systems". In: *Physica D: Nonlinear Phenomena* 237.20 (2008), pp. 2628–2637. DOI: 10.1016/j.physd.2008.03.037 (cit. on p. 97).

[116] G. Teodoro, D. Oliveira, and E. Capelas de Oliveira. "Sobre derivadas fracionárias". In: *Revista Brasileira de Ensino de Física* 40.2 (2018), e2307. DOI: 10.1590/1806-9126-rbef-2017-0213 (cit. on p. 8).

[117] H. R. Thieme. "Persistence under relaxed point-dissipativity (with application to an endemic model)". In: *SIAM Journal on Mathematical Analysis* 24.2 (1993), pp. 407–435. DOI: 10.1137/0524026 (cit. on p. 47).

[118] J. M. Trauer, J. T. Denholm, and E. S. McBryde. "Construction of a mathematical model for tuberculosis transmission in highly endemic regions of the Asia-Pacific". In: *Journal of Theoretical Biology* 358 (2014), pp. 74–84. DOI: 10.1016/j.jtbi.2014.05.023 (cit. on p. 15).

[119] I. Ullah et al. "Investigation of fractional order tuberculosis (TB) model via Caputo derivative". In: *Chaos, Solitons and Fractals* 142 (2011), p. 110479. DOI: 10.1016/j.chaos.2020.110479 (cit. on p. 91).

[120] S. Ullah et al. "A fractional model for the dynamics of tuberculosis (TB) using Atangana-Baleanu derivative". In: *Chaos, Solitons and Fractals* 13.3 (2020), pp. 937–956. DOI: 10.3934/dcdss.2020055 (cit. on p. 91).

[121] W. Wojtak, C. J. Silva, and Delfim F. M. Torres. "Uniform asymptotic stability of a fractional tuberculosis model". In: *Mathematical Modelling of Natural Phenomena* 13.1 (2018), Art 9. DOI: 10.1051/mmnp/2018015 (cit. on p. 113).

[122] M. Zamir, G. Zaman, and A. S. Alshomrani. "Sensitivity analysis and optimal control of anthroponotic cutaneous leishmania". In: *PLoS ONE* 11.8 (2016), e0160513. DOI: 10.1371/journal.pone.0160513 (cit. on pp. 51, 54, 55).

[123] J. Zhang and G. Feng. "Global stability for a tuberculosis model with isolation and incomplete treatment". In: *Computational and Applied Mathematics* 34.3 (2015), pp. 1237–1249. DOI: 10.1007/s40314-014-0177-0 (cit. on p. 15).