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Research Article

A Mathematical Model for the Study of Effectiveness in Therapy in Tuberculosis Taking into Account Associated Diseases

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Abstract: Tuberculosis (TB) remains a major global health problem. We present a deterministic mathematical model for the study of the effectiveness of therapy in TB to determine the impact of HIV/AIDS and diabetes in the spread of the disease and drug resistance. Our model takes into account the relationships between TB, HIV/AIDS, and diabetes and we also study the behavior of multidrug-resistance (MDR-TB) and extensively drug-resistant (XDR-TB). The main mathematical and epidemiology features of the model are investigated. The basic reproduction number ($\mathfrak{R}_0$) in the different sub-populations (diabetics, HIV/AIDS, and those who do not suffer from these diseases) were studied. Conditions were obtained on the model parameters to know when the growth of the parameters associated with resistance to TB treatment has a negative impact on the transmission of TB in the population based on the $\mathfrak{R}_0$ study. It is concluded that MDR-TB and XDR-TB have a negative impact on TB control. Computational simulations show that a greater number of drug-sensitive TB cases with respect to MDR-TB and XDR-TB cases are reported in the infected compartments, and MDR-TB cases surpass XDR-TB cases, except in the diabetes sub-population, which has a growth of XDR-TB cases that surpasses the other compartments of infected of all the sub-populations. It was shown when comparing the sub-populations of diabetes and HIV/AIDS, that although the diabetes sub-population reports a higher number of XDR-TB cases, a lower number of drug-sensitive TB and MDR-TB cases, have a greater number of recovered cases with respect to HIV/AIDS sub-population at the end of the study period. Also, when the XDR-TB cases in the diabetes sub-population exceed the other infected compartments, there is a growth of recovered TB in this sub-population. The results suggest that it is necessary to increase the attention to the diabetic population, which includes improved glucose control, increase the number of specialized medical consultations to achieve permanence in TB treatment and control the entry of individuals to the diabetic compartments by tests of diabetes.

***Keywords*:** diabetes, HIV/AIDS, ordinary differential equations, TB

MSC: 34A12, 92B05, 92D30

1. Introduction

Tuberculosis (TB) is one of the top 10 causes of death worldwide. TB is a chronic bacterial infectious disease

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caused by Mycobacterium TB. The bacteria get released in the air by a carrier with active TB through coughing, sneezing or talking. A 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 [1].

In 2015, there are approximately 10.4 million new TB cases worldwide, 1.4 million TB-induced deaths, and 0.4 million deaths by TB in HIV+ people were registered [2].

TB is treated by two lines of treatment based on antibiotics. Some antibiotics in the first-line of treatment are rifumpcin, isoniazid, pyrazinamide, and ethambutol. The amikacin, capreomycin, cycloserine, azithromycin, clarithromycin, moxifloxacin, and levofloxacin are part of the second-line of treatment. Active cases of TB are treated using first-line drugs rifampicin, isoniazid, pyrazinamide, ethambutol with taken daily for two months and continue a daily intake of rifampicin and isoniazid for a period of four months and exposed cases are treated only with isoniazid [3].

There are six types of multidrug-resistant TB (MDR-TB), more recently appears, extensively resistant TB (XDR-TB) which is a complex resistance [2, 4].

Knowledge about TB is very important for the control of the transmission and this includes the ability to identify causes and understand the transmission path of the disease, recognize the disease, its symptoms, and be aware of available treatment regimes and apply it in a differentiated way [4].

An important risk factor for respiratory diseases including TB is diabetes. Although TB has more incidence in the HIV/AIDS sub-population, diabetes remains a significant factor for TB infections at the population level and in the resistance to TB treatment [5]. An important factor is that diabetes increases TB risk 1.5 to 7.8 times and the relative risk for TB among diabetes patients is 3.11 [6-7]. Diabetes can affect the effectiveness of first-line anti-TB drugs, particularly the use of rifampicin [8]. The TB treatment regimen for diabetics is the same as for the general population at the moment [5]. TB can lead to the development of impaired glucose tolerance (IGT). After recovery from TB, IGT normalizes but it remains an important risk factor for the future development of diabetes [9-10].

The rate of diabetes for HIV patients when they are infected is the same as for the general population. But certain metabolic factors related to HIV, and to HIV therapy can increase the incidence of diabetes over time.

The mathematical models for the study of epidemics have been widely spread, using different techniques and proposing methods to solve them and interpret the results [11-15]. For example, Naik et al. [11] designed a fractional order model for HIV with the presence of prostitution in the population and studied prostitution in the spread of the disease. Naik et al. [12] designed and analyzed a non-linear fractional order model for HIV transmission which included an exposed compartment and divided the infected class of sex workers into conscious and unconscious infected. Farman et al. [13] used evolutionary computational techniques and Padé's approach to give a semi-analytical approach in the treatment of a non-linear model for Hepatitis B. Naik et al. [14] built and studied a model for the transmission of the COVID-19 epidemic of fractional order using the classical operator Caputo and operator Atangana-Baleanu-Caputo. Naik [15] studied an epidemic model of the SIR form with non-linear fractional order with Crowley-Martin type functional response and Holling type II treatment rate. A. Omame et al. [16] presented and studied a model of human papillomavirus (HPV) and Chlamydia trachomatis co-infection and showed that trachomatis prevention controls are the most cost-effective strategies to combat HPV and Chlamydia trachomatis co-infections. A. Omamea and D. Okuonghaeb [17] presented a co-infection model for Oncogenic HPV and TB with cost-effectiveness optimal control analysis and showed that the combination of HPV prevention and TB treatment positively impacts the reduction of oncogenic HPV and co-infection.

The construction of models applied to the study of TB transmission in the community has been intensively researched in the last decades [3, 18-23]. For example, Okuonghae and Ikhimwin [3] extended a mathematical model for the transmission dynamics of TB classifying the latently infected individuals by their level of TB awareness. Zhang and Feng [24] performed an analysis global of a dynamical model for the spread of TB with isolation and incomplete treatment. Trauer et al. [25] presented a mathematical model to simulate TB transmission in highly endemic regions of the Asia-Pacific, and proved that treatment of drug-susceptible TB did not result in decreased rates of MDR-TB, but rather resulted in a modest increase in MDR-TB through strain replacement. Mishra and Srivastava [26] formulated a susceptible-exposed-infectious-quarantine-cured-susceptible with vaccination spatial and temporal model and studied the influence of quarantine and vaccination on the dynamics of TB. Nkamba et al. [23] formulated a mathematical model that evaluated the impact of vaccination on TB transmission and showed that vaccination is not sufficient to control

TB. Nainggolan et al. [22] presented a model of TB transmission with vaccination and showed the effectiveness of vaccination in the control of TB. Egonmwan and Okuonghae [27] proposed a new mathematical model that investigates the impact of diagnosis and treatment of both latent TB infections and active cases on the transmission dynamics of the disease in a population and showed that the treatment rates for latent and active TB cases significantly determines the impact of the fraction of new latent TB cases diagnosed on the burden of the disease in a population. Guzzetta et al. [28] proposed a computational model for TB infection dynamics in an epidemic setting. The main features of the model are age-structured and socio-demographic individual based-model (IBM) and a limitation of this study is the exclusion of socio-demographic processes related to the immigration of individuals from high burden countries.

An important problem for specialists is to study the relationship between HIV and TB, since TB is one of the main causes of death in HIV/AIDS patients. Wang et al. [29] presented a simple model of the interaction between HIV and TB and showed the importance of including HIV characteristics in TB transmission. Long et al. [30] developed two variants of a co-epidemic (TB-HIV/AIDS) model and illustrated the importance of the effects of each disease on the transmission. Roeger et al. [31] constructed the bare-bone model in the simplest settings possible that provides rather general insights into the potential effects of HIV infection on TB and vice versa and suggest that to reduce or control the impact of TB, investing more in reducing the prevalence of HIV. Azeez et al. [32] formulated a mathematical model focused on the dynamics of transmission of TB and HIV co-infection to predict the spread of these diseases in different scenarios. Bhunu et al. [33] presented an HIV/AIDS and TB co-infection model that considers antiretroviral therapy for the AIDS cases and treatment of all forms of TB and concluded that treatment of AIDS cases results in a significant reduction of numbers of individuals progressing to active TB. Naresh et al. [34] proposed a nonlinear mathematical model to study the effect of TB on the spread of HIV infection in a logistically growing human population. Gakkhar and Chavda [35] proposed a mathematical model for the transmission dynamics of HIV-TB within a population of varying size and showed that the increased progression rate from latent to active TB in co-infected individuals may play a significant role in the rising prevalence of TB. Kumar et al. [36] formulated a mathematical model for HIV-TB co-infection dynamics by considering treatments for HIV infection, active TB and co-infection, and showed that when both the diseases are epidemic, the treatment for TB-only-infected individuals is very effective in reducing the total infected population and disease-induced deaths. Tanvi and Aggarwal [37] proposed a non-linear mathematical model for HIV-TB co-infection with a constant time delay parameter defined as the delay in detection and initiation of treatment for co-infected cases. Tanvi et al. [38] a model of HIV-TB co-infection with a non-linear treatment rate for TB was explored and conclude that to reduce the co-infection programs that accelerate TB treatment need to be implemented. Tanvi et al. [39] explored a model of HIV/AIDS and TB co-infection with detection and treatment of both diseases, performed an optimal control analysis using the maximum principle of Pontryagin and showed the importance of accelerating the detection of cases of both diseases along with the treatment to reduce co-infection.

In recent years, scientific work linking TB and diabetes has intensified. Coll et al. [40] presented and analyzed a model for diabetes prevalence with the goal is to estimate the prevalence and impact of diabetes in distinct populations. Moualeu et al. [41] presented a deterministic model for TB in order to determine the impact of diabetes in the spread of the disease and showed that there is a need for increased attention to the chemoprophylaxis of TB latent individuals and diabetic treatment with TB active. Girard et al. [42] presented a study on the impact of migration in the TB transmission on the growing diabetes pandemic. The authors concluded that better access to health care for diabetic patients could decrease the effect of diabetes on TB among migrants. Carvalho et al. [43] formulated a non-integer order model for the study of TB and the impact of diabetes and multi-drug resistant strains in a population. Between the results presented in this paper are that diabetic MDR-TB individuals require extreme attention due to its rapid growth.

The aim of this paper is to present a new mathematical model to study the resistance to TB treatment taking into account the influence of HIV/AIDS and diabetes. The paper is organized as follows: Section 2 presents the model for the study of drug resistance in TB with the presence of HIV/AIDS and diabetes, its mathematical and epidemiological basic properties were studied and the existence and stability conditions of the disease-free equilibrium are deduced; Section 3 is devoted to computational simulations; and Section 4 concludes the paper.

2. Model formulation

The model is composed of 18 compartments and the population is divided into those who do not suffer from HIV/

AIDS and diabetes (index T), HIV/AIDS (index H) and diabetic (index D). The compartments 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 (R_{T_1}, R_{H_1} and R_{D_1}) and TB recovered (R_T, R_H and R_D). For our study, we excluded cases that start with both diseases (HIV/AIDS and diabetes).

The dynamics of the uninfected individuals is given by the following equations:

$$\frac{dS_T}{dt} = M_1 - (\mu + \alpha_1 + \alpha_2 + \lambda_T)S_T,$$

$$\frac{dS_H}{dt} = M_2 + \alpha_2(S_T + S_D) - (\alpha_4 + \mu + \mu_1 + \omega_1\lambda_T)S_H,$$

$$\frac{dS_D}{dt} = M_3 + \alpha_4 S_H + \alpha_1 S_T - (\alpha_2 + \mu + \omega_2\lambda_T + \mu_2)S_D. \tag{1}$$

The M_1, M_2 and M_3 are recruitment rates for those who do not suffer from HIV/AIDS and diabetes, HIV/AIDS and diabetes respectively. 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_4 and it is assumed equal if is acquired for another cause. The rate of an individual acquiring HIV is α_2 and we assume the same for a diabetic. The rate of developing diabetes is α_1.

The TB infection rate is defined as

$$\lambda_T = \alpha^* \frac{I_{T_1} + I_{T_2} + R_{T_1} + \varepsilon_1(I_{H_1} + I_{H_2} + R_{H_1}) + \varepsilon_2(I_{D_1} + I_{D_2} + R_{D_1})}{N},$$

where α^* is the effective contact rate and N is the total population ($N = S_T + S_H + S_D + I_{T_1} + I_{T_2} + I_{H_1} + I_{H_2} + I_{D_1} + I_{D_2} + R_{T_1} + R_{H_1} + R_{D_1} + R_T + R_H + R_D$). The parameters ε_j, $j = 1, 2$ are modifications parameters, modeling the increased infectiousness in HIV/AIDS and diabetics. The natural death rate μ is the same from any compartment. The diabetic uninfected individuals, S_D, HIV/AIDS uninfected individuals, SH, are infected with TB at rate $\omega_1\lambda_T$, $\omega_2\lambda_T$, where ω_1, $\omega_2 > 1$, accounts for increasing infectibility to TB of HIV/AIDS and diabetics respectively. The μ_1 is the death rate from HIV/AIDS and μ_2 is the death rate for diabetes.

The dynamics of the latent individuals, are given by:

$$\frac{dE_T}{dt} = \lambda_T(S_T + \beta_1' R_T) - (\alpha_1 + \alpha_2 + \mu + \eta)E_T,$$

$$\frac{dE_H}{dt} = \omega_1\lambda_T(S_H + \beta_1' R_H) + \alpha_2(E_T + E_D) - (\varepsilon_1^*\eta + \mu + \mu_1 + \alpha_4)E_H,$$

$$\frac{dE_D}{dt} = \omega_2\lambda_T(S_D + \beta_1' R_D) + \alpha_4 E_H + \alpha_1 E_T - (\alpha_2 + \varepsilon_2^*\eta + \mu + \mu_2)E_D. \tag{2}$$

The latent state will be entered by those who come into contact with TB and those who recover (partial immunity). We define ε_j^*, $j = 1, 2$ as the parameters modification associated with resistance to TB treatment in HIV/AIDS and diabetics. We assume that TB-recovered acquire partial immunity and the transmission rate for this class is given by $\beta_1'\lambda_T$, $\beta_1'\omega_1\lambda_T$ and $\beta_1'\omega_2\lambda_T$ with $\beta_1' \leq 1$.

The dynamic of the drug-sensitive TB and MDR-TB individuals, is given by the following equations:

$$\frac{dI_{T_1}}{dt} = (1-\beta^*)\eta E_T - (l_1 + t_1\alpha_1 + t_2\alpha_2 + \mu + d_1 + \eta_{11})I_{T_1},$$

$$\frac{dI_{T_2}}{dt} = (1-p_1)\beta^*\eta E_T + l_1 I_{T_1} - (t_1\alpha_1 + t_2\alpha_2 + m_1 + \mu + t_1' d_1 + \eta_{14})I_{T_2},$$

$$\frac{dI_{H_1}}{dt} = t_2\alpha_2(I_{T_1} + I_{D_1}) + (1-\beta^*)\varepsilon_1^*\eta E_H - (l_2 + \mu + \mu_1 + d_2 + \eta_{12} + t_3\alpha_4)I_{H_1},$$

$$\frac{dI_{H_2}}{dt} = t_2\alpha_2(I_{T_2} + I_{D_2}) + (1-p_2)\beta^*\varepsilon_1^*\eta E_H + l_2 I_{H_1} - (m_2 + \mu + \mu_1 + t_2' d_2 + \eta_{15} + t_3\alpha_4)I_{H_2},$$

$$\frac{dI_{D_1}}{dt} = t_1\alpha_1 I_{T_1} + t_3\alpha_4 I_{H_1} + (1-\beta^*)\varepsilon_2^*\eta E_D - (l_3 + t_2\alpha_2 + \mu + d_3 + \eta_{13} + \mu_2)I_{D_1},$$

$$\frac{dI_{D_2}}{dt} = t_1\alpha_1 I_{T_2} + t_3\alpha_4 I_{H_2} + (1-p_3)\varepsilon_2^*\beta^*\eta E_D + l_3 I_{D_1} - (m_3 + t_2\alpha_2 + \mu + t_3' d_3 + \eta_{16} + \mu_2)I_{D_2}. \quad (3)$$

The η is defined as the natural rate of progression of TB. The β^* represents 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_1 and t_2 are modifications parameters associated with diabetes or HIV infection from the compartments of active TB infection. We assume death from TB with a rate d_1, deaths from the combination TB and HIV/AIDS with a rate d_2 and deaths from the combination TB and diabetes with a rate d_3. It is important to note here that $d_3 \geq d_1$ and $d_2 \geq d_1$ as diabetes and HIV/AIDS experience greater disease induced deaths than their corresponding only TB and we assume death from TB after the use of treatment. The rates l_1, l_2 and l_3 represent the cases that will be MDR-TB (first resistance).The expressions $(1 - p_1)\eta$, $(1 - p_2)\varepsilon_1^*\eta$ and $(1 - p_3)\varepsilon_2^*\eta$ are the cases that in a first infection are going to be MDR-TB and $p_1\eta$, $p_2\varepsilon_1^*\eta$ and $p_3\varepsilon_2^*\eta$ are the cases that are going to be XDR-TB in a first infection. We define t_3 as the parameter of 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} is the recovery rate after being drug-sensitive TB and m_1, m_2 and m_3 is the recovery rate after being MDR-TB. Let's assume that $\eta_{1l} > m_l$ for $l = 1, 2, 3$. The t_l', $l = 1, 2, 3$ are modification parameters associated with TB deaths in MDR-TB cases.

The dynamic of the XDR-TB and recovered individuals, is modeled by the following equations:

$$\frac{dR_{T_1}}{dt} = \eta_{14} I_{T_2} + p_1\beta^*\eta E_T - (\eta_{11}^* + t_1\alpha_1 + t_2\alpha_2 + \mu + t_1^* d_1)R_{T_1},$$

$$\frac{dR_{H_1}}{dt} = p_2\beta^*\varepsilon_1^*\eta E_H + \eta_{15} I_{H_2} + t_2\alpha_2(R_{T_1} + R_{D_1}) - (\eta_{12}^* + t_3\alpha_4 + \mu + \mu_1 + t_2^* d_2)R_{H_1},$$

$$\frac{dR_{D_1}}{dt} = p_3\beta^*\varepsilon_2^*\eta E_D + \eta_{16} I_{D_2} + t_3\alpha_4 R_{H_1} + t_1\alpha_1 R_{T_1} - (t_2\alpha_2 + \eta_{13}^* + \mu + \mu_2 + t_3^* d_3)R_{D_1},$$

$$\frac{dR_T}{dt} = m_1 I_{T_2} + \eta_{11} I_{T_1} + \eta_{11}^* R_{T_1} - (\alpha_1 + \alpha_2 + \mu + \beta_1'\lambda_T)R_T,$$

$$\frac{dR_H}{dt} = m_2 I_{H_2} + \eta_{12} I_{H_1} + \eta_{12}^* R_{H_1} + \alpha_2 (R_T + R_D) - (\alpha_4 + \mu + \mu_1 + \beta_1' \omega_1 \lambda_T) R_H,$$

$$\frac{dR_D}{dt} = m_3 I_{D_2} + \eta_{13} I_{D_1} + \eta_{13}^* R_{D_1} + \alpha_1 R_T + \alpha_4 R_H - (\alpha_2 + \mu + \mu_2 + \beta_1' \omega_2 \lambda_T) R_D. \quad (4)$$

The η_{11}^*, η_{12}^*, and η_{13}^* are the recovery rate after being XDR-TB. Let's assume that $\eta_{1l} > \eta_{1l}^*$ and $m_l > \eta_{1l}^*$ for $l = 1, 2, 3$. The t_1^*, t_2^* and t_3^* represent modification parameters associated with death by TB, death by combination TB-HIV/AIDS and by combination TB-Diabetes after being XDR-TB and we assumed that $t_l^* < 1$ and $t_l^* < t_l'$, $l = 1, 2, 3$.

The parameters description is given in Table 1.

Table 1. Definitions of parameters used in the model (5)

Parameter	Description	Parameter	Description
M_1, M_2, M_3	Recruitment rates	α^*	Effective contact rates for TB infection
α_1	Acquiring diabetes rate	α_2	Acquiring HIV rate
α_4	Diabetes development rate by use of HIV therapy	$\omega_1, \omega_2, \varepsilon_1, \varepsilon_2$	Modification parameters
μ	Natural mortality rate	η	Natural rate of progression to active TB
$t_1, t_2, t_3, t_1^*, t_2^*, t_3^*$	Modification parameters	t_1', t_2', t_3'	Modification parameters
$\varepsilon_1^*, \varepsilon_2^*, \beta_1'$	Modification parameters	l_1, l_2, l_3	Resistant TB development rates
d_1	TB induced death rate	d_2	TB-HIV induced death rate
d_3	TB-Diabetes induced death rate	μ_1, μ_2	Death rate of HIV/AIDS and diabetes respectively.
m_1, m_2, m_3	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_1, p_2, p_3	Rates related to developing XDR-TB resistance

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

$$\frac{dS_T}{dt} = M_1 - (\mu + \alpha_1 + \alpha_2 + \lambda_T) S_T,$$

$$\frac{dS_H}{dt} = M_2 + \alpha_2 (S_T + S_D) - (\alpha_4 + \mu + \mu_1 + \omega_1 \lambda_T) S_H,$$

$$\frac{dS_D}{dt} = M_3 + \alpha_4 S_H + \alpha_1 S_T - (\alpha_2 + \mu + \mu_2 + \omega_2 \lambda_T) S_D,$$

$$\frac{dE_T}{dt} = \lambda_T (S_T + \beta_1' R_T) - (\alpha_1 + \alpha_2 + \mu + \eta) E_T,$$

$$\frac{dE_H}{dt} = \omega_1\lambda_T(S_H + \beta_1^{'}R_H) + \alpha_2(E_T + E_D) - (\alpha_4 + \varepsilon_1^{*}\eta + \mu + \mu_1)E_H,$$

$$\frac{dE_D}{dt} = \omega_2\lambda_T(S_D + \beta_1^{'}R_D) + \alpha_4 E_H + \alpha_1 E_T - (\alpha_2 + \varepsilon_2^{*}\eta + \mu + \mu_2)E_D,$$

$$\frac{dI_{T_1}}{dt} = (1-\beta^{*})\eta E_T - (l_1 + t_1\alpha_1 + t_2\alpha_2 + \mu + d_1 + \eta_{11})I_{T_1},$$

$$\frac{dI_{T_2}}{dt} = (1-p_1)\beta^{*}\eta E_T + l_1 I_{T_1} - (t_1\alpha_1 + t_2\alpha_2 + m_1 + \mu + t_1^{'}d_1 + \eta_{14})I_{T_2},$$

$$\frac{dI_{H_1}}{dt} = t_2\alpha_2(I_{T_1} + I_{D_1}) + (1-\beta^{*})\varepsilon_1^{*}\eta E_H - (l_2 + \mu + \mu_1 + d_2 + \eta_{12} + t_3\alpha_4)I_{H_1},$$

$$\frac{dI_{H_2}}{dt} = t_2\alpha_2(I_{T_2} + I_{D_2}) + (1-p_2)\varepsilon_1^{*}\beta^{*}\eta E_H + l_2 I_{H_1} - (m_2 + \mu + \mu_1 + t_2^{'}d_2 + \eta_{15} + t_3\alpha_4)I_{H_2},$$

$$\frac{dI_{D_1}}{dt} = t_1\alpha_1 I_{T_1} + t_3\alpha_4 I_{H_1} + (1-\beta^{*})\varepsilon_2^{*}\eta E_D - (l_3 + t_2\alpha_2 + \mu + \mu_2 + d_3 + \eta_{13})I_{D_1},$$

$$\frac{dI_{D_2}}{dt} = t_1\alpha_1 I_{T_2} + t_3\alpha_4 I_{H_2} + (1-p_3)\varepsilon_2^{*}\beta^{*}\eta E_D + l_3 I_{D_1} - (m_3 + t_2\alpha_2 + \mu + \mu_2 + t_3^{'}d_3 + \eta_{16})I_{D_2},$$

$$\frac{dR_{T_1}}{dt} = \eta_{14} I_{T_2} + p_1\beta^{*}\eta E_T - (\eta_{11}^{*} + t_1\alpha_1 + t_2\alpha_2 + \mu + t_1^{*}d_1)R_{T_1},$$

$$\frac{dR_{H_1}}{dt} = p_2\beta^{*}\varepsilon_1^{*}\eta E_H + \eta_{15} I_{H_2} + t_2\alpha_2(R_{T_1} + R_{D_1}) - (\eta_{12}^{*} + t_3\alpha_4 + \mu + \mu_1 + t_2^{*}d_2)R_{H_1},$$

$$\frac{dR_{D_1}}{dt} = p_3\beta^{*}\varepsilon_2^{*}\eta E_D + \eta_{16} I_{D_2} + t_3\alpha_4 R_{H_1} + t_1\alpha_1 R_{T_1} - (t_2\alpha_2 + \eta_{13}^{*} + \mu + \mu_2 + t_3^{*}d_3)R_{D_1},$$

$$\frac{dR_T}{dt} = m_1 I_{T_2} + \eta_{11} I_{T_1} + \eta_{11}^{*} R_{T_1} - (\alpha_1 + \alpha_2 + \mu + \beta_1^{'}\lambda_T)R_T,$$

$$\frac{dR_H}{dt} = m_2 I_{H_2} + \eta_{12} I_{H_1} + \eta_{12}^{*} R_{H_1} + \alpha_2(R_T + R_D) - (\alpha_4 + \mu + \mu_1 + \beta_1^{'}\omega_1\lambda_T)R_H,$$

$$\frac{dR_D}{dt} = m_3 I_{D_2} + \eta_{13} I_{D_1} + \eta_{13}^{*} R_{D_1} + \alpha_1 R_T + \alpha_4 R_H - (\alpha_2 + \mu + \mu_2 + \beta_1^{'}\omega_2\lambda_T)R_D, \tag{5}$$

with initial conditions:

$S_T(0) > 0$, $S_H(0) > 0$, $S_D(0) > 0$, $E_T(0) > 0$, $E_H(0) > 0$, $E_D(0) > 0$, $I_{T_1}(0) > 0$, $I_{T_2}(0) > 0$, $I_{H_1}(0) > 0$, $I_{H_2}(0) > 0$, $I_{D_1}(0) > 0$, $I_{D_2}(0) > 0$, $R_{T_1}(0) > 0$, $R_{H_1}(0) > 0$, $R_{D_1}(0) > 0$, $R_T(0) > 0$, $R_H(0) > 0$ and $R_D(0) > 0$.

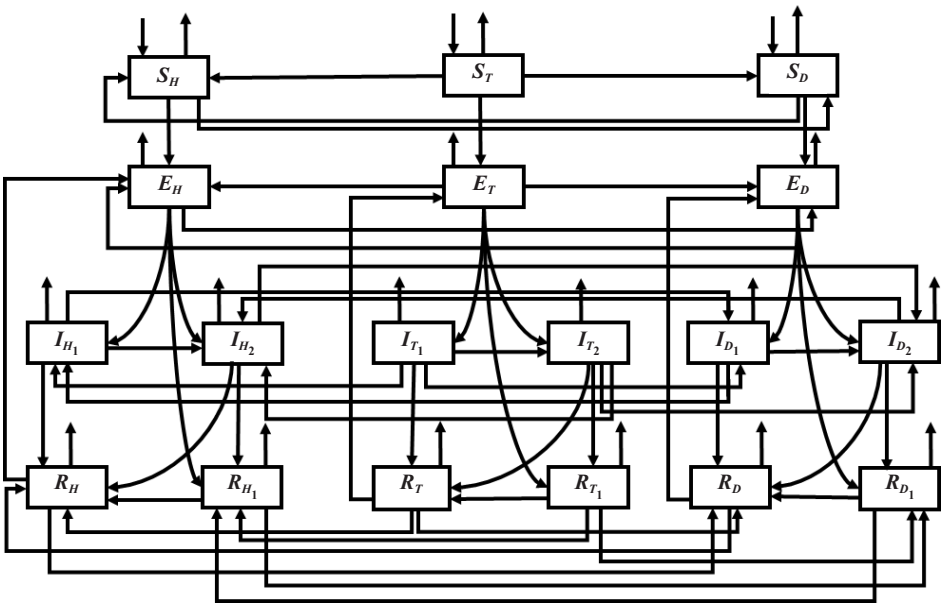

Figure 1. Flowchart of the model (5)

2.1 *Model Analysis*

In this subsection, we demonstrate theorems such as existence, positivity and boundedness of solutions and find the invariant region where the model will be defined (biologically feasible region).

Theorem 2.1 Let the initial data for the model (5) be $S_i(0) > 0$, $E_i(0) > 0$, $I_{i_1}(0) > 0$, $I_{i_2}(0) > 0$, $R_{i_1}(0) > 0$, $R_i(0) > 0$, $i = T, H, D$. Then the solutions $(S_i(t), E_i(t), I_{i_1}(t), I_{i_2}(t), R_{i_1}(t), R_i(t))$, $i = T, H, D$ of the model (5), with positive initial data, will remain positive for all time $t > 0$.

Proof. Let $t_1 = \sup\{t > 0: S_i(0) > 0, E_i(0) > 0, I_{i_1}(0) > 0, I_{i_2}(0) > 0, R_{i_1}(0) > 0, R_i(0) > 0, i = T, H, D\}$.

Let us remark that the first equation of the system (5),

$$\frac{dS_T}{dt} = M_1 - (\mu + \alpha_1 + \alpha_2 + \lambda_T)S_T,$$

can be rewritten as,

$$\frac{d}{dt}\left[S_T(t)\exp\left\{(\mu+\alpha_1+\alpha_2)t + \int_0^t \lambda_T(\tau)d\tau\right\}\right] = M_1 \exp\left\{(\mu+\alpha_1+\alpha_2)t + \int_0^t \lambda_T(\tau)d\tau\right\}. \tag{6}$$

Thus,

$$S_T(t_1)\exp\left\{(\mu+\alpha_1+\alpha_2)t_1 + \int_0^{t_1} \lambda_T(\tau)d\tau\right\} - S_T(0) = \int_0^{t_1} M_1\left[\exp\left\{(\mu+\alpha_1+\alpha_2)y + \int_0^y \lambda_T(\tau)d\tau\right\}\right]dy. \tag{7}$$

So that,

$$S_T(t_1) = S_T(0)\exp\left\{-(\mu+\alpha_1+\alpha_2)t_1 - \int_0^{t_1}\lambda_T(\tau)d\tau\right\} + \exp\left\{-(\mu+\alpha_1+\alpha_2)t_1 - \int_0^{t_1}\lambda_T(\tau)d\tau\right\}$$

$$\times \int_0^{t_1} M_1\left[\exp\left\{(\mu+\alpha_1+\alpha_2)y + \int_0^{y}\lambda_T(\tau)d\tau\right\}\right]dy > 0. \tag{8}$$

Analogously, a similar result can be shown for $S_H(t)$, $S_D(t)$, $E_i(t)$, $I_{i_1}(t)$, $I_{i_2}(t)$, $R_{i_1}(t)$, $R_i(t)$, $i = T, H, D$, for $t > 0$.

Thus, all solutions of the model (5) remain positive for non-negative initial conditions.

Since we work in a population of humans that can not be negative, we need to show that all the variables are always non-negative as well as the solutions of system (5) remain positive always with positive initial conditions. The region where we guarantee this, is called the biologically feasible region.

Lemma 2.2 The closed set

$$D = \left\{(S_i, E_i, I_{i_1}, I_{i_2}, R_{i_1}, R_i) \in \mathbb{R}_+^{18}, i = T, H, D : N(t) \le \frac{M_1+M_2+M_3}{\mu}\right\}$$

is positively-invariant and attracts all positive solutions of the model (5).

Proof. The derivative of N (total population) is

$$\frac{dN}{dt} = M_1 + M_2 + M_3 - \mu N - \mu_1(S_H + E_H + I_{H_1} + I_{H_2} + R_{H_1} + R_H) - \mu_2(S_D + E_D + I_{D_1} + I_{D_2} + R_{D_1} + R_D)$$

$$-\left(d_1(I_{T_1} + t_1' I_{T_2} + t_1^* R_{T_1}) + d_2(I_{H_1} + t_2' I_{H_2} + t_2^* R_{H_1}) + d_3(I_{D_1} + t_3' I_{D_2} + t_3^* R_{D_1})\right).$$

Since $\frac{dN}{dt} \le M_1 + M_2 + M_3 - \mu N,$ it follows that $\frac{dN}{dt} \le 0$, if $N(t) \ge \frac{M_1+M_2+M_3}{\mu}$. Hence, a standard comparison theorem [44] can be used to show that $N(t) \le N(0)\exp\{-\mu t\} + \frac{M_1+M_2+M_3}{\mu}\left(1 - \exp\{-\mu t\}\right)$. In particular, if $N(0) \le \frac{M_1+M_2+M_3}{\mu}$, then $N(t) \le \frac{M_1+M_2+M_3}{\mu}$ for all $t > 0$. Hence, the domain D is positively invariant. Furthermore, if $N(0) > \frac{M_1+M_2+M_3}{\mu}$, then either the solution enters the domain D in finite time or $N(t)$ approaches $\frac{M_1+M_2+M_3}{\mu}$ asymptotically as $t \to \infty$. Hence, the domain D attracts all solutions in R_+^{18}.

The set D is defined as the biologically feasible region. The model (5) is mathematically and epidemiologically well posed in D.

Theorem 2.3 The solutions of model system (5) with non-negative initial conditions exist for all times.

Proof. The right-hand side of the system (5) is locally Lipschitz continuous, and this proved the local existence of the solution. The global existence of the solution follows from a priory bound.

2.2 *Reproduction number basic study*

The basic reproduction number is defined as the number of secondary infections due to a single infection in a completely susceptible population [45].

In this section, the reproduction number, $\mathfrak{R}_0$, is calculated using the next generation method [45-47] for the different sub-populations with the objective of studying transmission in HIV/AIDS, diabetics and in the population that does not suffer from these diseases (TB-only-infected).

We have the TB-only-infected sub-model when $S_H = S_D = E_H = E_D = I_{H_1} = I_{H_2} = I_{D_1} = I_{D_2} = R_{H_1} = R_{D_1} = R_H = R_D = 0$, which is given by

$$\frac{dS_T}{dt} = M_1 - (\mu + \alpha_1 + \alpha_2 + \lambda_T)S_T,$$

$$\frac{dE_T}{dt} = \lambda_T(S_T + \beta_1^{'}R_T) - (\alpha_1 + \alpha_2 + \eta + \mu)E_T,$$

$$\frac{dI_{T_1}}{dt} = (1-\beta^*)\eta E_T - (l_1 + t_1\alpha_1 + t_2\alpha_2 + \mu + d_1 + \eta_{11})I_{T_1},$$

$$\frac{dI_{T_2}}{dt} = (1-p_1)\beta^*\eta E_T + l_1 I_{T_1} - (m_1 + \mu + t_1^{'}d_1 + \eta_{14} + t_1\alpha_1 + t_2\alpha_2)I_{T_2},$$

$$\frac{dR_{T_1}}{dt} = \beta^* p_1\eta E_T + \eta_{14} I_{T_2} - (\eta_{11}^* + \mu + t_1^* d_1 + t_1\alpha_1 + t_2\alpha_2)R_{T_1},$$

$$\frac{dR_T}{dt} = m_1 I_{T_2} + \eta_{11} I_{T_1} + \eta_{11}^* R_{T_1} - (\mu + \beta_1^{'}\lambda_T + \alpha_1 + \alpha_2)R_T, \tag{9}$$

with initial conditions:

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

The TB infection rate for this sub-model is defined as

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

and the total population is given by

$$N_T(t) = S_T + E_T + I_{T_1} + I_{T_2} + R_{T_1} + R_T.$$

Due to biological constraints, the system (9) is studied in the following region:

$$D_1 = \left\{(S_T, E_T, I_{T_1}, I_{T_2}, R_{T_1}, R_T) \in \mathbb{R}_+^6 : N_T(t) \le \frac{M_1}{\mu}\right\}.$$

We can show for this sub-model (9) that the solutions, ($S_T(t)$, $E_T(t)$, $I_{T_1}(t)$, $I_{T_2}(t)$, $R_{T_1}(t)$, $R_T(t)$) are bounded and positively invariant in D_1 (biologically feasible region). The disease free equilibrium point of model (9) is given by

$$\varepsilon_0^T = \left(S_0^T, 0, 0, 0, 0, 0\right),$$

where $S_0^T = \frac{M_1}{\mu + \alpha_1 + \alpha_2}$.

The basic reproduction number is defined as

$$\Re_0^T = \frac{\alpha^* M_1\left((1-\beta^*)\eta(k_{13}k_{14} + l_1(k_{14}+\eta_{14})) + (1-p_1)\beta^*\eta k_{12}(k_{14}+\eta_{14}) + k_{12}k_{13}\beta^*\eta p_1\right)}{N_T(\alpha_1+\alpha_2+\mu)k_{11}k_{12}k_{13}k_{14}}, \tag{10}$$

where $k_{11} = \alpha_1 + \alpha_2 + \eta + \mu$, $k_{12} = l_1 + t_1\alpha_1 + t_2\alpha_2 + \mu + d_1 + \eta_{11}$, $k_{13} = \mu + t_1'd_1 + \eta_{14} + m_1 + t_1\alpha_1 + t_2\alpha_2$ and $k_{14} = \mu + t_1^*d_1 + \eta_{11}^* + t_1\alpha_1 + t_2\alpha_2$. We have the following theorem:

Lemma 2.4 The disease-free equilibrium point ε_0^T is locally asymptotically stable when $\Re_0^T < 1$ and unstable when $\Re_0^T > 1$.

Proof. The Jacobian matrix of the sub-model (9) at ε_0^T is

$$J(\varepsilon_0^T) = \begin{bmatrix} -(\mu+\alpha_1+\alpha_2) & 0 & \frac{-M_1\alpha^*}{N_T(\mu+\alpha_1+\alpha_2)} & \frac{-M_1\alpha^*}{N_T(\mu+\alpha_1+\alpha_2)} & \frac{-M_1\alpha^*}{N_T(\mu+\alpha_1+\alpha_2)} & 0 \\ 0 & -k_{11} & \frac{M_1\alpha^*}{N_T(\mu+\alpha_1+\alpha_2)} & \frac{M_1\alpha^*}{N_T(\mu+\alpha_1+\alpha_2)} & \frac{M_1\alpha^*}{N_T(\mu+\alpha_1+\alpha_2)} & 0 \\ 0 & (1-\beta^*)\eta & -k_{12} & 0 & 0 & 0 \\ 0 & (1-p_1)\beta^*\eta & l_1 & -k_{13} & 0 & 0 \\ 0 & p_1\beta^*\eta & 0 & \eta_{14} & -k_{14} & 0 \\ 0 & 0 & \eta_{11} & m_1 & \eta_{11}^* & -(\mu+\alpha_1+\alpha_2) \end{bmatrix},$$

Trace$[J(\varepsilon_0^T)] = -2(\alpha_1 + \alpha_2 + \mu) - k_{11} - k_{12} - k_{13} - k_{14} < 0$, and its determinant is

$$\text{Det}[J(\varepsilon_0^T)] = -(\alpha_1+\alpha_2+\mu)^2\left(\frac{M_1\alpha^*}{(\alpha_1+\alpha_2+\mu)}((1-\beta^*)\eta(k_{13}k_{14} + l_1(k_{14}+\eta_{14})) + (1-p_1)\beta^*\eta k_{12}(k_{14}+\eta_{14}) + k_{12}k_{13}\beta^*\eta p_1) - k_{11}k_{12}k_{13}k_{14}\right) > 0.$$

If,

$$\frac{(\alpha_1+\alpha_2+\mu)\alpha^* M_1\left((1-\beta^*)\eta(k_{13}k_{14} + l_1(k_{14}+\eta_{14})) + (1-p_1)\beta^*\eta k_{12}(k_{14}+\eta_{14}) + k_{12}k_{13}\beta^*\eta p_1\right)}{N_T}$$

$$< (\alpha_1+\alpha_2+\mu)^2 k_{11}k_{12}k_{13}k_{14},$$

then

$$\frac{M_1\alpha^*\left((1-\beta^*)\eta(k_{13}k_{14} + l_1(k_{14}+\eta_{14})) + (1-p_1)\beta^*\eta k_{12}(k_{14}+\eta_{14}) + k_{12}k_{13}\beta^*\eta p_1\right)}{N_T(\alpha_1+\alpha_2+\mu)k_{11}k_{12}k_{13}k_{14}} < 1.$$

Thus $\Re_0^T < 1$, which means that the eigenvalues of Det$[J(\varepsilon_0^T) - \lambda I] = 0$ (I is the Identity matrix) have negative real parts, implying that ε_0^T is locally asymptotically stable whenever $\Re_0^T < 1$.

Now, we list two conditions that if met, also guarantee the global asymptotic stability of the disease-free equilibrium point.

Following [48], we rewrite the model (9) as

$$\frac{dS}{dt} = F(S, I),$$

$$\frac{dI}{dt} = G(S,I),\ G(S,0) = 0, \tag{11}$$

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 (I_{T_1}, I_{T_2}, R_{T_1}).

The disease-free equilibrium is now denoted by $E_0^T = (S_0^{T*}, 0)$ where $S_0^{T*} = \left(\frac{M_1}{\mu + \alpha_1 + \alpha_2}, 0\right)$.

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

$$H_1 : \text{For } \frac{dS}{dt} = F(S,0),\ S_0^{T*} \text{ is globally asymptotically stable,}$$

$$H_2 : G(S,I) = AI - G^*(S,I),\ G^*(S,I) \geq 0,\ \text{for } (S,I) \in D_1, \tag{12}$$

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

If model (5) satisfies the conditions H_1 and H_2, then the following results holds.

Theorem 2.5 The fixed point E_0^T is a globally asymptotically stable equilibrium of model (9) provided that $\Re_0^T < 1$ and that the conditions H_1 and H_2 are satisfied.

Proof. Let

$$F(S,0) = \begin{pmatrix} M_1 - (\mu + \alpha_1 + \alpha_2)S_T \\ 0 \end{pmatrix}.$$

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

$$A = D_I G(S_T^*, 0) = \begin{pmatrix} -k_{11} & \alpha^* & \alpha^* & \alpha^* \\ (1-\beta^*)\eta & -k_{12} & 0 & 0 \\ (1-p_1)\beta^*\eta & l_1 & -k_{13} & 0 \\ p_1\beta^*\eta & 0 & \eta_{14} & -k_{14} \end{pmatrix},$$

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

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

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

Since

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

Using the threshold quantity, $\Re_0^T$, in (10), we want study the impact of resistance to TB treatment on the dynamics of the disease in a population, and find conditions that characterize these effects. We have

$$\lim_{l_1 \to \infty} \Re_0^T = \frac{\alpha^* M_1 \eta \left(k_{14} + \eta_{14} + p_1 \beta^* (d_1 (t_1' - t_1^*) + (m_1 - \eta_{11}^*))\right)}{N_T (\alpha_1 + \alpha_2 + \mu) k_{11} k_{13} k_{14}} > 0, \tag{13}$$

$$\lim_{\eta_{14} \to \infty} \Re_0^T = \frac{\alpha^* M_1 \eta \left(k_{14} + l_1 + \beta^* (d_1 (1 - t_1^*) + (\eta_{11} - \eta_{11}^*))\right)}{N_T (\alpha_1 + \alpha_2 + \mu) k_{11} k_{12} k_{14}} > 0. \tag{14}$$

If the limits (13-14) are greater than unity, then a high rate of MDR-TB and XDR-TB (l_2, $\eta_{15} \to \infty$) has a negative impact on TB transmission control. That is, if we have

$$\frac{\alpha^* M_1}{N_T (\alpha_1 + \alpha_2 + \mu)} > \frac{k_{11} k_{13} k_{14}}{\eta \left(k_{14} + \eta_{14} + p_1 \beta^* (d_1 (t_1' - t_1^*) + (m_1 - \eta_{11}^*))\right)}, \tag{15}$$

$$\frac{\alpha^* M_1}{N_T (\alpha_1 + \alpha_2 + \mu)} > \frac{k_{11} k_{12} k_{14}}{\eta \left(k_{14} + l_1 + \beta^* (d_1 (1 - t_1^*) + (\eta_{11} - \eta_{11}^*))\right)}. \tag{16}$$

Let

$$\Delta_T = \frac{\alpha^* M_1}{N_T (\alpha_1 + \alpha_2 + \mu)}.$$

These results are summarized in the lemmas below:

Lemma 2.6 The impact of MDR-TB is positive in reducing TB transmission in this sub-population only if

$$\Delta_T < \frac{k_{11} k_{13} k_{14}}{\eta \left(k_{14} + \eta_{14} + p_1 \beta^* (d_1 (t_1' - t_1^*) + (m_1 - \eta_{11}^*))\right)},$$

no impact if

$$\Delta_T = \frac{k_{11} k_{13} k_{14}}{\eta \left(k_{14} + \eta_{14} + p_1 \beta^* (d_1 (t_1' - t_1^*) + (m_1 - \eta_{11}^*))\right)}$$

and a negative impact if

$$\Delta_T > \frac{k_{11} k_{13} k_{14}}{\eta \left(k_{14} + \eta_{14} + p_1 \beta^* (d_1 (t_1' - t_1^*) + (m_1 - \eta_{11}^*))\right)}.$$

Lemma 2.7 The impact of XDR-TB is positive in reducing TB transmission in this sub-population only if

$$\Delta_T < \frac{k_{11}k_{12}k_{14}}{\eta\left(k_{14}+l_1+\beta^*(d_1(1-t_1^*)+(\eta_{11}-\eta_{11}^*))\right)},$$

no impact if

$$\Delta_T = \frac{k_{11}k_{12}k_{14}}{\eta\left(k_{14}+l_1+\beta^*(d_1(1-t_1^*)+(\eta_{11}-\eta_{11}^*))\right)}$$

and a negative impact if

$$\Delta_T > \frac{k_{11}k_{12}k_{14}}{\eta\left(k_{14}+l_1+\beta^*(d_1(1-t_1^*)+(\eta_{11}-\eta_{11}^*))\right)}.$$

We carry out a sensitivity analysis of the parameters associated with resistance (l_1 and η_{14}) by calculating the partial derivatives of $\Re_0^T$ with respect to these parameters and we have

$$\frac{\partial \Re_0^T}{\partial l_1} = \frac{\alpha^* M_1(1-\beta^*)\eta\left(k_{14}(d_1(1-t_1^*)+(\eta_{11}-m_1))+\eta_{14}(d_1(1-t_1^*)+(\eta_{11}-\eta_{11}^*))\right)}{N_T(\alpha_1+\alpha_2+\mu)k_{11}k_{12}^2k_{13}k_{14}}, \tag{17}$$

$$\frac{\partial \Re_0^T}{\partial \eta_{14}} = \frac{\alpha^* M_1\eta\left(((1-\beta^*)l_1+\beta^*(1-p_1)k_{12})((t_1^{'}-t_1^*)d_1+(m_1-\eta_{11}^*))\right)}{N_T(\alpha_1+\alpha_2+\mu)k_{11}k_{12}k_{13}^2k_{14}}. \tag{18}$$

Obviously, it follows that the partial derivative in (17) and (18) are unconditionally greater than zero (using the conditions of the parameters in the construction of the model (5)), i.e., $\frac{\partial \Re_0^T}{\partial l_1} > 0$ and $\frac{\partial \Re_0^T}{\partial \eta_{14}} > 0$. Therefore, the MDR-TB and XDR-TB always has a negative impact on the control of TB transmission in this sub-population.

Analogously, we use the same methodology applied to the sub-model (9) for the sub-model that relates HIV/AIDS to TB (TB-HIV/AIDS) when $S_D = S_T = E_D = E_T = I_{D_1} = I_{D_2} = I_{T_1} = I_{T_2} = R_{T_1} = R_T = R_{D_1} = R_D = 0$ and with non-negative initial conditions. We define the TB infection rate for this sub-model as

$$\lambda_H = \alpha^* \frac{\varepsilon_1(I_{H_1}+I_{H_2}+R_{H_1})}{N_H}$$

and the biologically feasible region is

$$D_2 = \left\{(S_H, E_H, I_{H_1}, I_{H_2}, R_{H_1}, R_H) \in \mathbb{R}_+^6 : N_H(t) \le \frac{M_2}{\mu}\right\}.$$

We have for this sub-model (TB-HIV/AIDS) that the solutions ($S_H(t)$, $E_H(t)$, $I_{H_1}(t)$, $I_{H_2}(t)$, $R_{H_1}(t)$, $R_H(t)$) are bounded and positively invariant in D_2.

The disease-free equilibrium, ε_0^H, is

$$\varepsilon_0^H = \left(S_0^H, 0, 0, 0, 0, 0\right),$$

where $S_0^H = \frac{M_2}{\alpha_4 + \mu + \mu_1}$.

The basic reproduction number is given by

$$\Re_0^H = \frac{\alpha^* \epsilon_1 \omega_1 M_2 \left((1-\beta^*)\epsilon_1^* \eta (k_{23}k_{24} + l_2(k_{24}+\eta_{15})) + (1-p_2)\epsilon_1^* \beta^* \eta k_{22}(k_{24}+\eta_{15}) + k_{22}k_{23}\epsilon_1^* \beta^* \eta p_2\right)}{N_H(\alpha_4+\mu+\mu_1)k_{21}k_{22}k_{23}k_{24}}, \tag{19}$$

where $k_{21} = \alpha_4 + \varepsilon_1^* \eta + \mu + \mu_1$, $k_{22} = l_2 + \mu + \mu_1 + d_2 + \eta_{12} + t_3\alpha_4$, $k_{23} = \mu + \mu_1 + t_2' d_2 + \eta_{15} + m_2 + t_3\alpha_4$, $k_{24} = \mu + \mu_1 + t_2^* d_2 + \eta_{12}^* + t_3\alpha_4$ and $N_H = S_H + E_H + I_{H_1} + I_{H_2} + R_{H_1} + R_H$.

We define H_1 and H_2 as in the sub-model (9) and using the same idea from the demonstration, we get the following results:

Lemma 2.8 The disease-free equilibrium ε_0^H is asymptotically stable when $\Re_0^H < 1$ and is unstable whenever $\Re_0^H > 1$.

Theorem 2.9 The fixed point $E_0^H = (S_0^{H_*}, 0, 0, 0, 0)$ where $S_0^{H_*} = \left(\frac{M_2}{\mu + \alpha_1 + \mu_1}, 0\right)$ is a globally asymptotically stable equilibrium of sub-model (TB-HIV/AIDS) if $\Re_0^H < 1$ and the assumption H_1 and H_2 are satisfied.

We make a procedure analogous to the model (9) for l_2 and η_{15} (MDR-TB and XDR-TB parameters for TB-HIV/AIDS sub-model) and we obtained the following limits:

$$\lim_{l_2 \to \infty} \Re_0^H = \frac{\alpha^* M_2 \omega_1 \varepsilon_1 \varepsilon_1^* \eta \left(k_{24} + \eta_{15} + p_2 \beta^* (d_2(t_2' - t_2^*) + (m_2 - \eta_{12}^*))\right)}{N_H(\alpha_4+\mu+\mu_1)k_{21}k_{23}k_{24}} > 0, \tag{20}$$

$$\lim_{\eta_{15} \to \infty} \Re_0^H = \frac{\alpha^* M_2 \omega_1 \varepsilon_1 \varepsilon_1^* \eta \left(k_{24} + l_2 + \beta^* (d_2(1 - t_2^*) + (\eta_{12} - \eta_{12}^*))\right)}{N_H(\alpha_4+\mu+\mu_1)k_{21}k_{22}k_{24}} > 0. \tag{21}$$

If the limits (20-21) are greater than unity, then a high rate of MDR-TB and XDR-TB (l_2, $\eta_{15} \to \infty$) has a negative impact on TB transmission control. This occurs when

$$\frac{\alpha^* \omega_1 \varepsilon_1 M_2}{N_H(\alpha_4+\mu+\mu_1)} > \frac{k_{21}k_{23}k_{24}}{\varepsilon_1^* \eta \left(k_{24} + \eta_{15} + p_2 \beta^* (d_2(t_2' - t_2^*) + (m_2 - \eta_{12}^*))\right)}, \tag{22}$$

$$\frac{\alpha^* \omega_1 \varepsilon_1 M_2}{N_H(\alpha_4+\mu+\mu_1)} > \frac{k_{21}k_{22}k_{24}}{\varepsilon_1^* \eta \left(k_{24} + l_2 + \beta^* (d_2(1 - t_2^*) + (\eta_{12} - \eta_{12}^*))\right)}. \tag{23}$$

Let

$$\Delta_H = \frac{\alpha^* \omega_1 \varepsilon_1 M_2}{N_H(\alpha_4+\mu+\mu_1)}.$$

These results are summarized in the lemmas below:

Lemma 2.10 The impact of MDR-TB on reducing TB transmission in the HIV/AIDS sub-population is positive only if

$$\Delta_H < \frac{k_{21}k_{23}k_{24}}{\varepsilon_1^* \eta \left(k_{24} + \eta_{15} + p_2 \beta^* (d_2(t_2' - t_2^*) + (m_2 - \eta_{12}^*))\right)},$$

no impact if

$$\Delta_H = \frac{k_{21}k_{23}k_{24}}{\varepsilon_1^*\eta\left(k_{24}+\eta_{15}+p_2\beta^*(d_2(t_2^{'}-t_2^*)+(m_2-\eta_{12}^*))\right)}$$

and a negative impact if

$$\Delta_H > \frac{k_{21}k_{23}k_{24}}{\varepsilon_1^*\eta\left(k_{24}+\eta_{15}+p_2\beta^*(d_2(t_2^{'}-t_2^*)+(m_2-\eta_{12}^*))\right)}.$$

Lemma 2.11 The impact of XDR-TB on reducing TB transmission in the HIV/AIDS sub-population is positive only if

$$\Delta_H < \frac{k_{21}k_{22}k_{24}}{\varepsilon_1^*\eta\left(k_{24}+l_2+\beta^*(d_2(1-t_2^*)+(\eta_{12}-\eta_{12}^*))\right)},$$

no impact if

$$\Delta_H = \frac{k_{21}k_{22}k_{24}}{\varepsilon_1^*\eta\left(k_{24}+l_2+\beta^*(d_2(1-t_2^*)+(\eta_{12}-\eta_{12}^*))\right)}$$

and a negative impact if

$$\Delta_H > \frac{k_{21}k_{22}k_{24}}{\varepsilon_1^*\eta\left(k_{24}+l_2+\beta^*(d_2(1-t_2^*)+(\eta_{12}-\eta_{12}^*))\right)}.$$

We make a sensitivity analysis on the parameters associated with resistance (l_2 and η_{15}) based on the partial derivatives of $\Re_0^H$ with respect to these parameters, giving,

$$\frac{\partial\Re_0^H}{\partial l_2} = \frac{\alpha^* M_2\omega_1\varepsilon_1(1-\beta^*)\varepsilon_1^*\eta\left((k_{24}(d_2(1-t_2^*)+(\eta_{12}-m_2))+\eta_{15}(d_2(1-t_2^*)+(\eta_{12}-\eta_{12}^*))\right)}{N_H(\alpha_4+\mu+\mu_1)k_{21}k_{22}^2k_{23}k_{24}}, \tag{24}$$

$$\frac{\partial\Re_0^H}{\partial \eta_{15}} = \frac{\alpha^* M_2\omega_1\varepsilon_1\varepsilon_1^*\eta\left(((1-\beta^*)l_2+\beta^*(1-p_2)k_{22})((t_2^{'}-t_2^*)d_2+(m_2-\eta_{12}^*))\right)}{N_H(\alpha_4+\mu+\mu_1)k_{21}k_{22}k_{23}^2k_{24}}. \tag{25}$$

Visibly, it follows that the partial derivatives in (24) and (25) are unconditionally greater than zero, i.e., $\frac{\partial\Re_0^H}{\partial l_2} > 0$ and $\frac{\partial\Re_0^H}{\partial \eta_{15}} > 0$. Because of these conditions, MDR-TB and XDR-TB contribute negatively to the control of TB transmission in the HIV/AIDS sub-population.

The sub-model that relates diabetes to TB (TB-Diabetes) is obtained when $S_H = S_T = E_H = E_T = I_{H_1} = I_{H_2} = I_{T_1} = I_{T_2} = R_{H_1} = R_H = R_{T_1} = R_T = 0$ with non-negative initial conditions. The TB infection rate is

$$\lambda_D = \alpha^* \frac{\varepsilon_2(I_{D_1}+I_{D_2}+R_{D_1})}{N_D}$$

and the biologically feasible region is

$$D_3 = \left\{(S_D, E_D, I_{D_1}, I_{D_2}, R_{D_1}, R_D) \in \mathbb{R}^6_+ : N_D(t) \le \frac{M_3}{\mu}\right\}.$$

The solutions of this sub-model (TB-Diabetes), ($S_D(t)$, $I_{D_1}(t)$, $I_{D_2}(t)$, $R_{D_1}(t)$, $R_D(t)$) in D_3 are bounded and positively invariant. The disease-free equilibrium, ε_0^D, is

$$\varepsilon_0^D = \left(S_0^D, 0, 0, 0, 0, 0\right),$$

where $S_0^D = \dfrac{M_3}{\mu + \mu_2 + \alpha_2}$.

The basic reproduction number is given by

$$\Re_0^D = \frac{\alpha^* \varepsilon_2 \omega_2 M_3 \left((1-\beta^*)\varepsilon_2^* \eta (k_{33}k_{34} + l_3(k_{34} + \eta_{16})) + (1-p_3)\varepsilon_2^* \beta^* \eta k_{32}(k_{34} + \eta_{16}) + k_{32}k_{33}\varepsilon_2^* \beta^* \eta p_3\right)}{N_D(\alpha_2 + \mu + \mu_2)k_{31}k_{32}k_{33}k_{34}}, \quad (26)$$

where $k_{31} = \alpha_2 + \varepsilon_2^* \eta + \mu + \mu_2$, $k_{32} = l_3 + \mu + d_3 + \eta_{13} + t_2\alpha_2 + \mu_2$, $k_{33} = \mu + t_3' d_3 + \eta_{16} + m_3 + t_2\alpha_2 + \mu_2$, $k_{34} = \mu + \mu_2 + t_3^* d_3 + \eta_{13}^* + t_2 a_2$ and $N_D = S_D + E_D + I_{D_1} + I_{D_2} + R_{D_1} + R_D$.

We define H_1 and H_2 as in the previous sub-models and using the same idea from the demonstration, we have the following results:

Lemma 2.12 The disease-free equilibrium ε_0^D is asymptotically stable when $\Re_0^D < 1$ and is unstable whenever $\Re_0^D > 1$.

Theorem 2.13 The fixed point $E_0^D = (S_0^{D*}, 0, 0, 0, 0)$ where $S_0^{D*} = \left(\dfrac{M_3}{\mu + \alpha_2 + \mu_2}, 0\right)$ is a globally asymptotically stable equilibrium of sub-model (TB-HIV/AIDS) if $\Re_0^D < 1$ and the assumption H_1 and H_2 are satisfied.

We make a procedure analogous to the previous sub-models for l_3 and η_{16} (MDR-TB and XDR-TB parameters for TB-Diabetes sub-model) and we obtained the following limits:

$$\lim_{l_3 \to \infty} \Re_0^D = \frac{\alpha^* M_3 \omega_2 \varepsilon_2 \varepsilon_2^* \eta \left(k_{34} + \eta_{16} + p_3 \beta^* (d_3(t_3' - t_3^*) + (m_3 - \eta_{13}^*))\right)}{N_D(\alpha_2 + \mu + \mu_2)k_{31}k_{33}k_{34}} > 0, \quad (27)$$

$$\lim_{\eta_{16} \to \infty} \Re_0^D = \frac{\alpha^* M_3 \omega_2 \varepsilon_2 \varepsilon_2^* \eta \left(k_{34} + l_3 + \beta^* (d_3(1 - t_3^*) + (\eta_{13} - \eta_{13}^*))\right)}{N_D(\alpha_2 + \mu + \mu_2)k_{31}k_{32}k_{34}} > 0. \quad (28)$$

A high rate of MDR-TB and XDR-TB (l_3, $\eta_{16} \to \infty$) has a negative impact on the control of TB transmission, if the limits (27-28) are higher than the unit. This occurs when

$$\frac{\alpha^* \omega_2 \varepsilon_2 M_3}{N_D(\alpha_2 + \mu + \mu_2)} > \frac{k_{31}k_{33}k_{34}}{\varepsilon_2^* \eta \left(k_{34} + \eta_{16} + p_3 \beta^* (d_3(t_3' - t_3^*) + (m_3 - \eta_{13}^*))\right)}, \quad (29)$$

$$\frac{\alpha^* \omega_2 \varepsilon_2 M_3}{N_D(\alpha_2 + \mu + \mu_2)} > \frac{k_{31}k_{32}k_{34}}{\varepsilon_2^* \eta \left(k_{34} + l_3 + \beta^* (d_3(1 - t_3^*) + (\eta_{13} - \eta_{13}^*))\right)}. \quad (30)$$

Let

$$\Delta_D = \frac{\alpha^* \omega_2 \varepsilon_2 M_3}{N_D(\alpha_2 + \mu + \mu_2)}.$$

These results are summarized in the lemmas below:

Lemma 2.14 The impact of MDR-TB on reducing TB transmission in the diabetic sub-population is positive only if

$$\Delta_D < \frac{k_{31}k_{33}k_{34}}{\varepsilon_2^*\eta\left(k_{34} + \eta_{16} + p_3\beta^*(d_3(t_3' - t_3^*) + (m_3 - \eta_{13}^*))\right)},$$

no impact if

$$\Delta_D = \frac{k_{31}k_{33}k_{34}}{\varepsilon_2^*\eta\left(k_{34} + \eta_{16} + p_3\beta^*(d_3(t_3' - t_3^*) + (m_3 - \eta_{13}^*))\right)}$$

and a negative impact if

$$\Delta_D > \frac{k_{31}k_{33}k_{34}}{\varepsilon_2^*\eta\left(k_{34} + \eta_{16} + p_3\beta^*(d_3(t_3' - t_3^*) + (m_3 - \eta_{13}^*))\right)}.$$

Lemma 2.15 The impact of MDR-TB on reducing TB transmission in the diabetic sub-population is positive only if

$$\Delta_D < \frac{k_{31}k_{32}k_{34}}{\varepsilon_2^*\eta\left(k_{34} + l_3 + \beta^*(d_3(1 - t_3^*) + (\eta_{13} - \eta_{13}^*))\right)},$$

no impact if

$$\Delta_D = \frac{k_{31}k_{32}k_{34}}{\varepsilon_2^*\eta\left(k_{34} + l_3 + \beta^*(d_3(1 - t_3^*) + (\eta_{13} - \eta_{13}^*))\right)}$$

and a negative impact if

$$\Delta_D > \frac{k_{31}k_{32}k_{34}}{\varepsilon_2^*\eta\left(k_{34} + l_3 + \beta^*(d_3(1 - t_3^*) + (\eta_{13} - \eta_{13}^*))\right)}.$$

The $\Re_0^D$ derivatives with respect to resistance parameters (l_3 and η_{16}) for sensitivity analysis are

$$\frac{\partial \Re_0^D}{\partial l_3} = \frac{\alpha^* M_3 \omega_2 \varepsilon_2 (1 - \beta^*)\varepsilon_2^*\eta\left((k_{34}(d_3(1 - t_3^*) + (\eta_{13} - m_3)) + \eta_{16}(d_3(1 - t_3^*) + (\eta_{13} - \eta_{13}^*))\right)}{N_D(\alpha_2 + \mu + \mu_2)k_{31}k_{32}^2k_{33}k_{34}}, \tag{31}$$

$$\frac{\partial \Re_0^D}{\partial \eta_{16}} = \frac{\alpha^* M_3 \omega_2 \varepsilon_2 \varepsilon_2^*\eta\left(((1 - \beta^*)l_3 + \beta^*(1 - p_3)k_{32})((t_3' - t_3^*)d_3 + (m_3 - \eta_{13}^*))\right)}{N_D(\alpha_2 + \mu + \mu_2)k_{31}k_{32}k_{33}^2k_{34}}. \tag{32}$$

For the conditions on the parameters in the construction of model (5), we have that the derivatives (31) and (32) are

unconditionally greater than zero, i.e., $\frac{\partial \Re_0^D}{\partial l_3} > 0$ and $\frac{\partial \Re_0^D}{\partial \eta_{16}} > 0$. Hence, MDR-TB and XDR-TB negatively impact the control of TB transmission in the diabetic sub-population.

The model (5) has a disease-free equilibrium, given by

$$\varepsilon_0^G = (S_0^T, S_0^H, S_0^D, 0,0,0,0,0,0,0,0,0,0,0,0,0,0,0).$$

We calculate the basic reproduction number as in the previous sub-models by next generation operator method. The dominant eigenvalues of the next generation matrix are $\Re_0^T$, $\Re_0^H$ and $\Re_0^D$.

Thus, the basic reproduction number of the model (5) is given by

$$\Re_0 = \max\{\Re_0^T, \Re_0^H, \Re_0^D\}.$$

Based on the results of the TB-only-infected, TB-HIV/AIDS and TB-Diabetes sub-models, we have conditions for which the MDR-TB and XDR-TB parameters have a positive impact on reducing TB transmission for the full model and we can conclude that MDR-TB and XDR-TB have a negative impact on TB control.

3. Numerical simulations

For the numerical simulations, we use a set of parameters extracted from [3, 20, 24-26, 41, 43] with purposes illustrative and to support the analytical results. After validation with the specialists, we decided to go with the following initial conditions, $S_T = 8741400$, $S_H = 111000$, $S_D = 200000$, $E_T = 557800$, $E_H = 4000$, $E_D = 4500$, $I_{T_1} = 10000$, $I_{T_2} = 500$, $I_{H_1} = 1400$, $I_{H_2} = 100$, $I_{D_1} = 1700$, $I_{D_2} = 150$, $R_{T_1} = 50$, $I_{H_1} = 35$, $R_{D_1} = 20$, $R_T = 8000$, $R_H = 200$ and $R_D = 90$, that do not represent a specific demographic area, but fall within range of actual achievable data. We study the behavior of $\Re_0$ with respect to the effective contagion rate and the parameters associated with MDR-TB and XDR-TB.

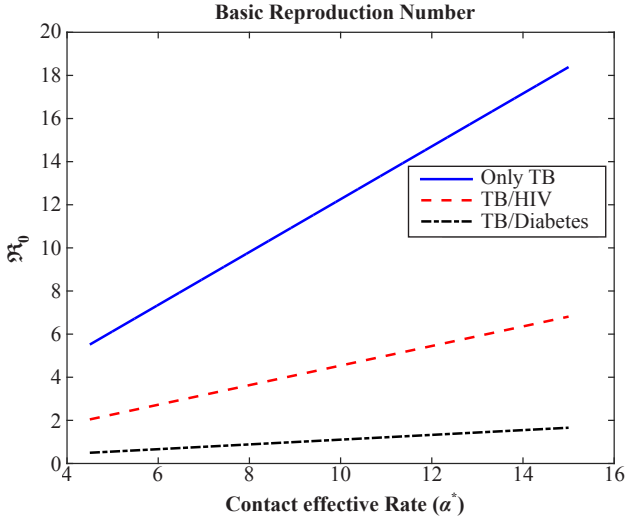

Figure 2. Graph of $\Re_0$ with respect to contact effective rate, α^*, for the different sub-populations, $\alpha^* \in [4.5, 15]$

The $\Re_0^D$ is in the interval [0.4976, 1.6582], $\Re_0^T$ is in [5.5162, 18.3872] and $\Re_0^H$ is in [2.0439, 6.8121]. For the variation of α^*, we can observe that whenever for the sub-populations TB-only-infected and HIV/AIDS we have the

basic reproduction number is greater than unity, then the infection will be able to start spreading in this sub-populations and it is evident that the control of the epidemic is more difficult. In the case of the diabetes sub-population, we can reach values of the basic number of reproduction that are greater than unity and that are less than unity. This implies a decreasing in the number of contagions if there is a reduction of the effective contagion rate, see Figure 2.

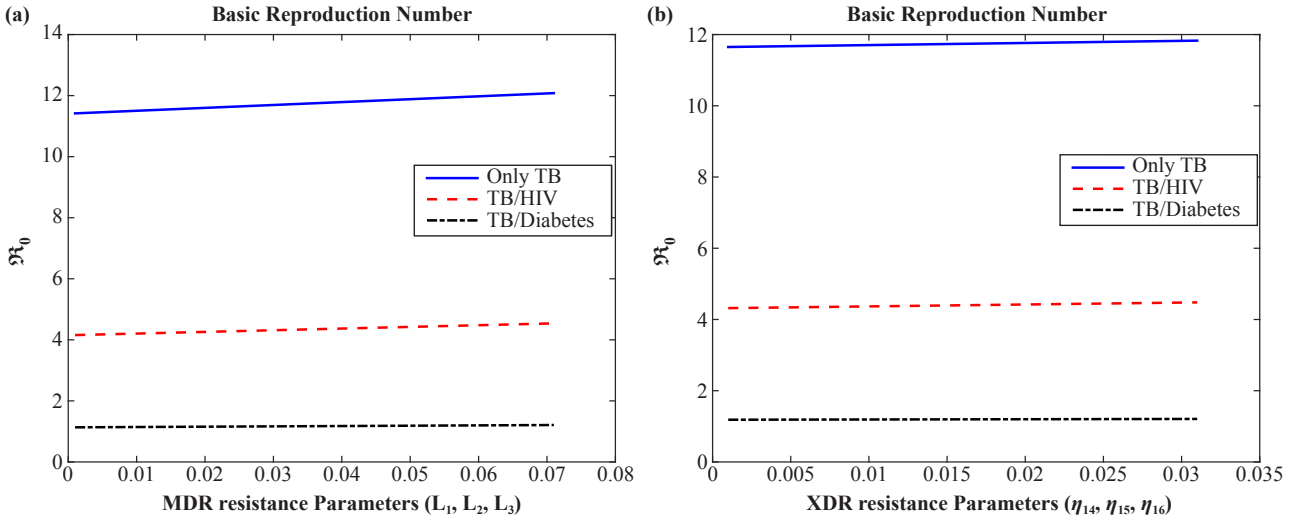

Figure 3. (a) Graphical representation of $\mathfrak{R}_0$ with respect to the MDR-TB parameters (l_1, l_2, l_3), for $l_1 \in [0.0020, 0.065]$, $l_2 \in [0.0021, 0.060]$ and $l_3 \in [0.018, 0.075]$; (b) Graphical representation of $\mathfrak{R}_0$ with respect to the parameters XDR-TB (η_{14}, η_{15}, η_{16}) for $\eta_{14} \in [0.001, 0.035]$, $\eta_{15} \in [0.001, 0.0025]$ and $\eta_{16} \in [0.001, 0.0038]$

In Figure 3, we analyze the response of $\mathfrak{R}_0$ when the parameters that represent MDR-TB and XDR-TB are varied. For Figure 3a, we vary l_1, l_2 and l_3 to study what happens with the basic reproduction number with respect to these parameters that represent the MDR-TB. The $\mathfrak{R}_0^D$ is in [1.1344, 1.2100], $\mathfrak{R}_0^T$ is in [11.4179, 12, 0809] and $\mathfrak{R}_0^H$ is in [4.1557, 4.5389]. In Figure 3b we varied η_{14}, η_{15} and η_{16} (parameters associated with the XDR-TB) and we obtained that $\mathfrak{R}_0^D$ is in [1.1854, 1.2078], $\mathfrak{R}_0^T$ is in [11.6503, 11.8288] and $\mathfrak{R}_0^H$ is in [1.1854, 1.2078].

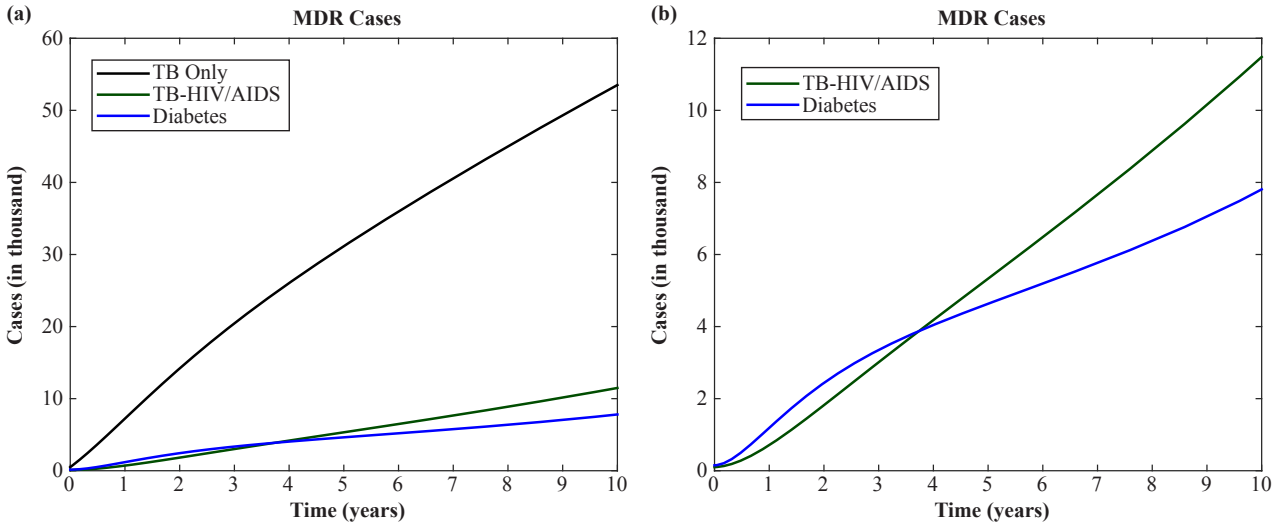

Figure 4. (a) Graphic representation of the MDR-TB cases of the sub-populations; (b) Comparison of MDR-TB cases between the HIV/AIDS and diabetes sub-populations

In both cases, the $\mathfrak{R}_0$ of all the sub-populations remain greater than unity, which shows that growth in the parameters associated with MDR-TB and XDR-TB negatively affects the community. The greatest difficulty in control is found in the TB-only-infected sub-population. However, to control the epidemic it is necessary to control in all sub-populations.

Now, we show the numerical results referring to the study of resistance to TB treatment with the presence of diabetes and HIV/AIDS. Therefore, we present the behavior of drug-sensitive TB, MDR-TB and XDR-TB and recovered cases in the study period of 10 years.

For MDR-TB cases, the highest number of cases is reported in the TB-only-infected sub-population, see Figure 4a. In the initial study period, diabetics cases exceed HIV/AIDS cases, later this situation is reversed, see Figure 4b. In particular, for the control of this resistance, we propose to maintain an internal control in the sub-populations of HIV/AIDS and diabetes.

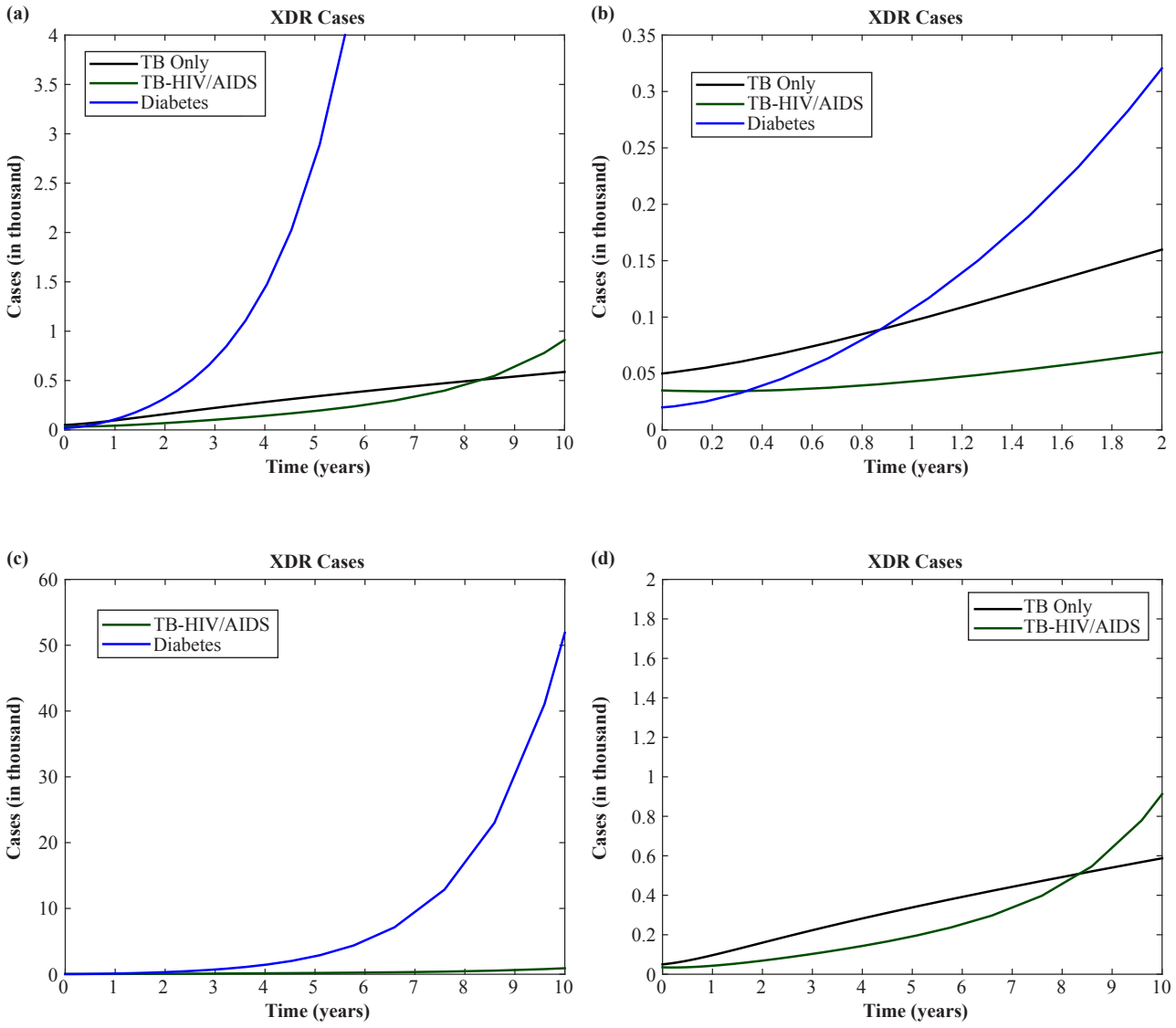

Figure 5. (a) Graphic representation of the XDR-TB cases of the sub-populations; (b) Graphic representation of the XDR-TB cases of the sub-populations for 2 years of study; (c) Comparison of XDR-TB cases between the HIV/AIDS and diabetes sub-populations; (d) Comparison of XDR-TB cases between the HIV/AIDS and TB-only-infected sub-populations

At the beginning of the studied period, the sub-populations remained relatively close respect to the values of XDR-TB cases, approximately 0.9 years later, the XDR-TB cases began to grow in the diabetes sub-population, which until the end of the study exceeded the other populations, see Figures 5a and 5b. At approximately 8 years of the study, the XDR-TB cases of the HIV/AIDS sub-population outnumber the TB-only-infected, see Figure 5d.

For the control of XDR-TB cases, we propose to control the HIV/AIDS and diabetes sub-populations, but mainly the diabetes sub-population from the beginning of the study, in order to avoid uncontrolled growth of cases in this sub-population. Some proposals for control are detection of diabetic cases and HIV/AIDS and carry out counseling to avoid the withdrawal from treatment and monitor the entry of new diabetic cases.

In the comparison between MDR-TB and XDR-TB, for the TB-only-infected and HIV/AIDS sub-populations, a greater number of MDR-TB cases were reported throughout the study period, see Figures 6a and 6b. In the diabetes sub-population, at the beginning of the study, behaved similar to the other sub-populations, but later, approximately in the 6 years of the study, the XDR-TB cases greatly exceed the MDR-TB, see Figure 6c, this shows the need to pay attention to the behavior of XDR-TB cases.

In general, the influence of diabetes on the resistance to TB treatment is evidenced, and the parameters associated with resistance have a negative influence on the control of the epidemic.

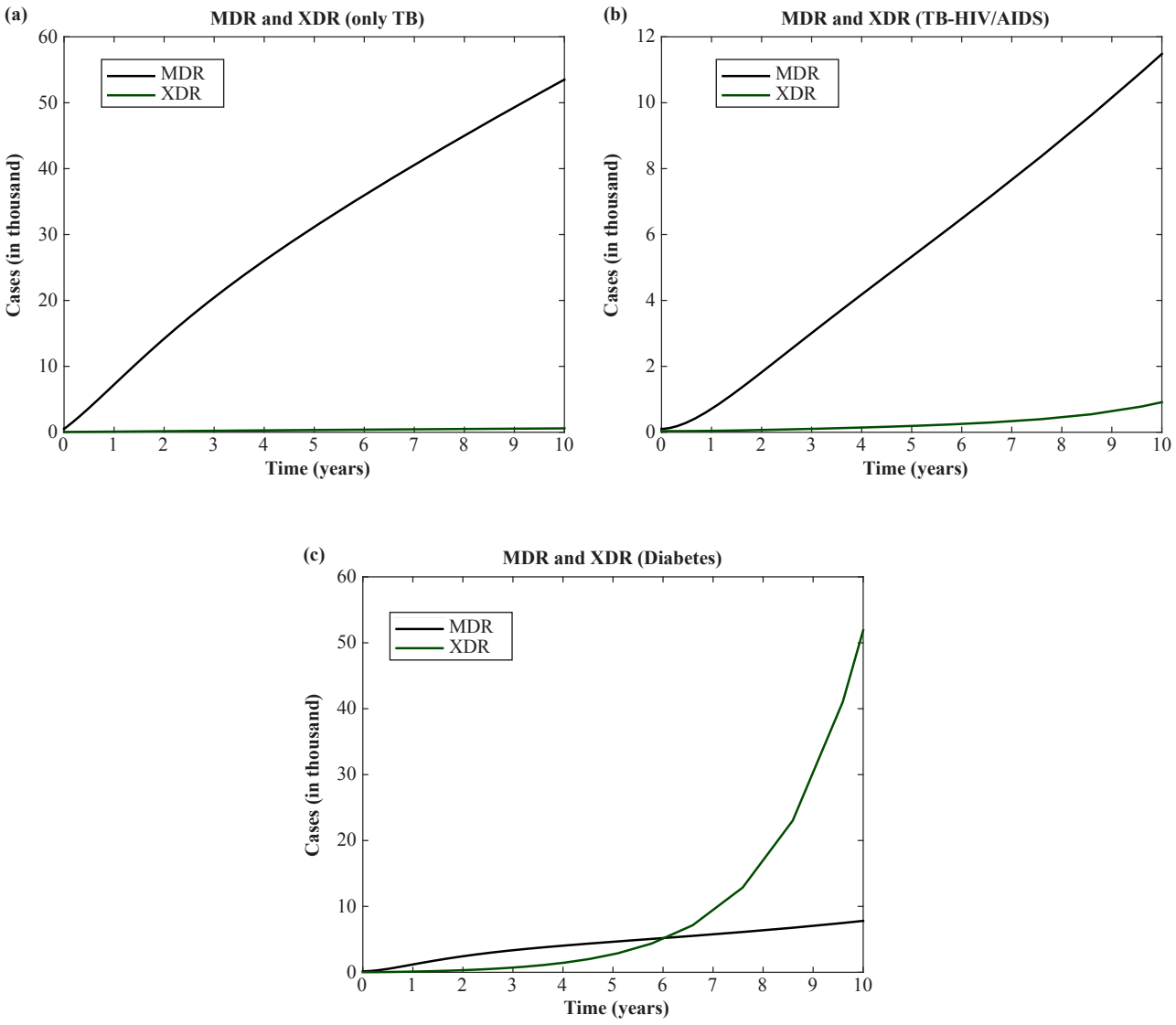

Figure 6. Comparison between of MDR-TB and XDR-TB cases in the different sub-populations. (a) TB-only-infected; (b) HIV/AIDS; (c) Diabetes

In the TB-only-infected and HIV/AIDS sub-populations, the highest number of reported cases is drug-sensitive TB cases, that is, those that will not create resistance to them, followed by MDR-TB and XDR-TB cases respectively, which shows that the largest number of cases recover without becoming resistant to treatment, followed by MDR-TB and XDR-TB cases respectively, which shows that the largest number of cases recover without becoming resistant to treatment, see Figures 7a and 7b. In the case of the sub-population of diabetics, at the beginning of the study, a behavior similar to that of the other sub-populations occurs, but at approximately 6 years of the study, the XDR-TB cases grow, exceeding the MDR-TB and drug-sensitive TB, see Figure 7c. To control resistance to TB drugs, we recommend paying attention mainly to the diabetes sub-population and the entry into this sub-population due to the growth of XDR-TB cases.

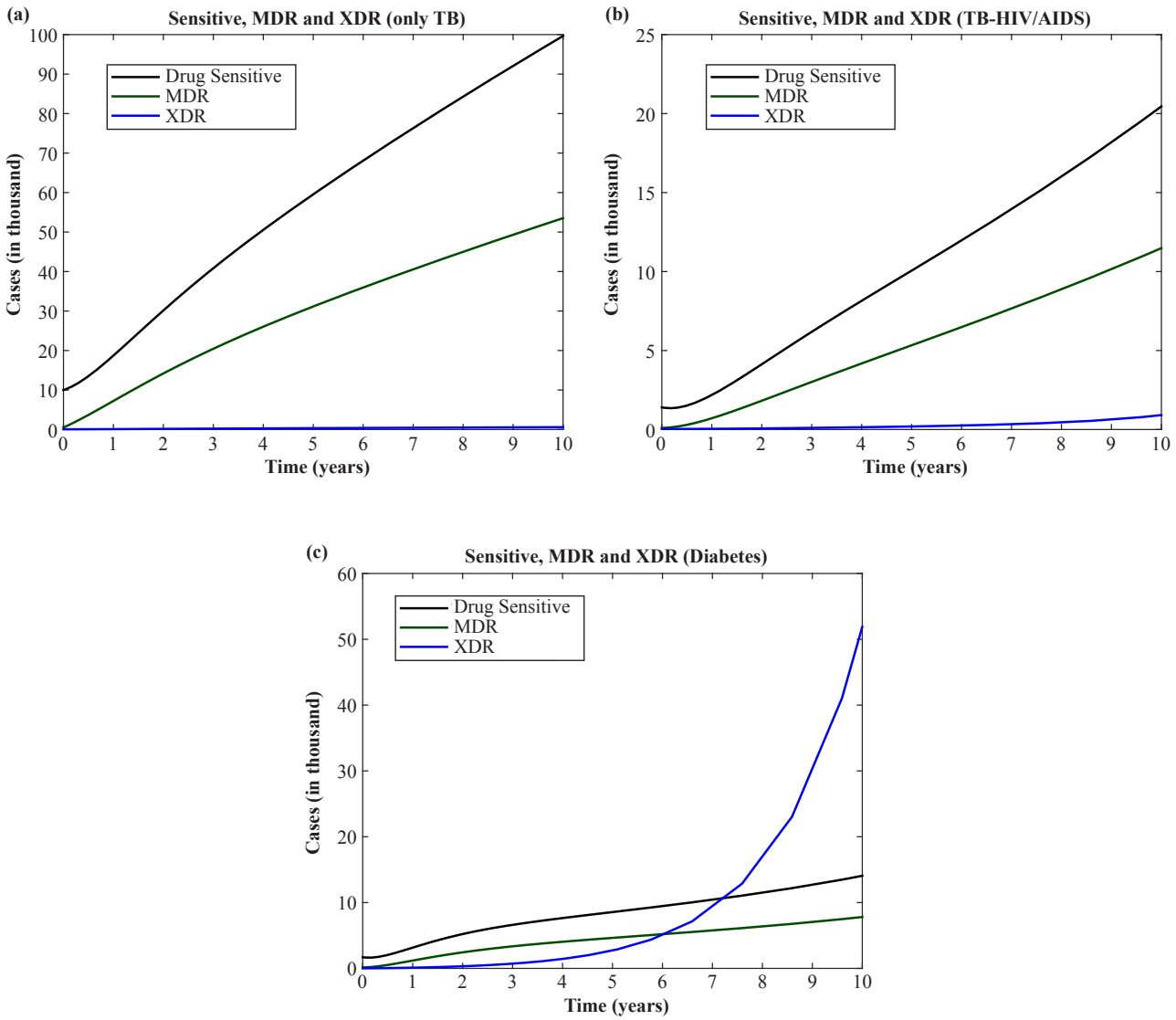

Figure 7. Comparison between the different types of infected (drug-sensitive TB, MDR-TB and XDR-TB) in the different sub-populations. (a) TB-only-infected; (b) HIV/AIDS; (c) Diabetes

The highest number of recovered was reported by the TB-only-infected sub-population, see Figure 8a. In the study of recovered cases in the HIV/AIDS and diabetes sub-populations, approximately 7 years of the study, when XDR-TB diabetics outnumber the other compartments of TB resistance, see Figure 7c, there is a growth of recovered

cases in the diabetes sub-population see Figure 8b. At the end of the study, diabetics recovered outnumber HIV/AIDS, approximately after 9 years of the study, see Figure 8b, despite the fact that at that time of the study they had a greater number of XDR-TB cases, see Figure 5c and a less number of MDR-TB and drug-sensitive TB cases, see Figure 4b and Figure 7.

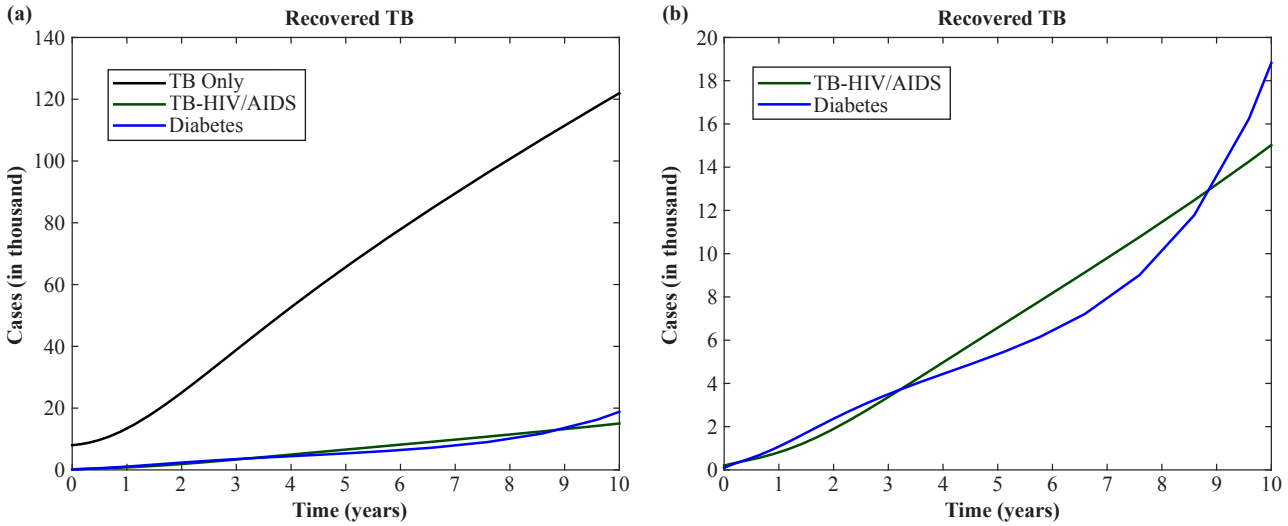

Figure 8. Graphic representation of the recovered cases of the sub-populations. (a) All sub-populations; (b) HIV/AIDS and diabetes sub-populations

4. Conclusions

We propose a new mathematical model for the study of resistance to treatment for TB 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 have computed the reproduction number of the model and its relationship with the parameters associated with resistance to TB treatment has been studied. We have simulated the model's behaviour for biologically reasonable parameters. The study of $\mathfrak{R}_0$ with respect to the MDR-TB and XDR-TB parameters showed that the growth of these parameters affects the control of the epidemic in the community. In the cases of $\mathfrak{R}_0$ with respect to the effective contact rate in the diabetes sub-population, we can find cases in which it is less than one and this means that the number of cases will decrease. In the other sub-populations, the $\mathfrak{R}_0$ for any value of the effective contact rate is greater than unity, this implies that the number of cases will increase and it is necessary to apply control strategies. The computational simulations show the need for extreme care in the diabetes sub-population to XDR-TB cases due to the growth that exceeds the other infected compartments of all sub-populations. The diabetes sub-population at approximately 7 years of the study has a growth of recovered cases despite the fact that XDR-TB cases outperformed the other compartments of infected TB, and approximately after 9 years of the study, diabetics despite having a higher number of XDR-TB cases, and a smaller number of MDR-TB and drug-sensitive TB cases compared to HIV/AIDS, reported a higher number of recovered. This study can help policy planners make decisions for the control of resistance to TB treatment based on the behavior of the sub-populations. We propose to closely monitor the sub-population of diabetics, and the entrance to its compartments by the growth of XDR-TB cases, through glucose control, the increase of specialized medical consultations to achieve permanence in treatment, and test for diabetes in different sub-populations. In future works, we will study the optimal control problem in our model in order to minimize MDR-TB cases and perform computer simulations in real scenarios.

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