The Cursed Duet: Dynamics of HIV-TB Co-infection in South Africa

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Abstract

In South Africa there is an increasing public health concern for the HIV/AIDS pandemic coupled with high tuberculosis (TB) prevalence. The progression of these infectious diseases compliments each other to produce a deadly synergistic effect. This results in devastating morbidity and mortality in communities suffering from HIV/AIDS-TB co-infection. HIV/AIDS-TB spells economic disaster for developing countries, nearly 30% of the annual household income[16]. We use a epidemiological model to explore the co-infection transmission dynamics of HIV/AIDS and tuberculosis in South Africa, specifically in adults aged 15-49. We analyze our model to gauge the extent to which the HIV/AIDS epidemic accentuates the TB epidemic. Will the TB epidemic persist without the presence or prevalence of the HIV/AIDS epidemic? Our parameter values are estimated from demographic data. Sensitivity and uncertainty analysis are employed to determine the parameter value(s) to which the basic reproductive number is most sensitive. We run numerical simulations to predict future trends of both the HIV/AIDS and TB epidemics.

1 Background

1.1 HIV/AIDS

HIV is a retrovirus that primarily infects the $CD4^+T$ cell lymphocytes of the immune system. The virus hijacks the normal cellular function to produce more HIV viruses. The $CD4^+T$ cells are killed directly by the virus infection, by apoptosis due to increased rates of virus production, and by the immune response to the infected cells. HIV infection has stages of development and if untreated will cause a sufficient decline of $CD4^+T$ cells resulting in the loss of cell-mediated immunity. The progression of HIV infection occurs in three stages: the primary infection, acute infection and clinical latency. The clinical latency period is variable but is usually between two weeks and twenty years [3]. A person can be infectious at any stage of HIV progression. The HIV virus can be transmitted by sexual and non-sexual contacts, including unprotected sex, injection needles for drug use, direct blood contact, and mother to baby transmission. Acquired Immunodeficiency Syndrome (AIDS) is characterized by an infection with Human Immunodeficiency Virus (HIV) that has successfully suppressed the immune system leaving an individual more susceptible to and showing symptoms of opportunistic infections [12].

1.2 Tuberculosis

Tuberculosis (TB) is an infectious disease caused primarily by *Mycobacterium tuberculosis*, bacteria that usually infect the lungs (pulmonary TB). Upon infection of the lungs it may spread to lymph nodes, the spine and brain via the circulatory system. A person can be infectious if the bacteria reside in the lungs or throat but usually not infectious if the bacteria infects other parts of the body [14].

TB is usually spread through the air by someone with active TB. Airborne transmission usually results when an individual with active TB sneezes or coughs and the bacteria, in form of tiny droplets, is inhaled by susceptible individuals. The bacteria can persist for up to 48 hours in these tiny air droplets [14]. It is important to understand the difference between TB infection and TB disease. A person can become infected by TB and the bacteria can lie dormant for many years or an entire lifetime [14, 16]. In this dormant stage or latent stage an infected person does not show any symptoms and cannot spread the infection. The progression from the latent stage to the infectious or active stage is either caused externally or resulting from conditions within the organism [11]. TB disease is the result of this progression. A person in the active stage will show symptoms and can transmit the disease.

1.3 Treatment of Tuberculosis and HIV/AIDS

The current drug regiment to treat HIV/AIDS-TB co-infection is the combined use of highly active antiretroviral therapy (HAART) and antituberculosis treatment. Complica-

tions can arise between the interaction of both drug regimens, especially between protease inhibitors (antituberculosis drug) and non-nucleoside reverse transcriptase inhibitors (antiretroviral drug) [16] . There is some protocol to treat HIV/AIDS-TB co-infection: (1) TB treatment takes precedent over HIV infection treatment, (2) if HAART is already in use it must be modified in order to implement the use of TB drug treatment, and (3) if a patient has not started HAART treatment, the timing is crucial [8, 2]. Drug treatment should be monitored for adverse drug reactions.

Preventive measures should involve testing for TB in patients who are infected with HIV in order to start prophylactic treatment. Individuals who are HIV+ and latently infected with TB can reduce the risk of progression to active TB by starting prophylactic treatment [13, 22].

2 Introduction

South Africa has a population of 47,432,000 millions with a life expectancy of 49 and 52 years for males and females respectively [1]. The population growth rate is about 1% [19], with birth rate of 22 per 1,000 and death rate of 18.2 per 1,000 [21].

South Africa experiences 320,000 deaths due to AIDS with approximately 5,300,000 adults aged over 15 with HIV/AIDS [21]. There are 34,000 deaths attributed to TB with 300,000 prevalence in 2005 [21]. About 18.8% of HIV-positive adults (15-49) are infected with TB. An estimated 3 million people die each year from Tuberculosis [14, 11]. About two billion individuals are infected with TB but only about 10% develop active TB [21]. This implies that roughly one-third of the world population acts as a reservoir of this infectious disease [4].

According to WHO (World Health Organization), South Africa has the highest incidence of tuberculosis (Figure 1). Combined with South Africa's high HIV/AIDS prevalence (Figure 2), TB is an increasing public health concern. Individuals who suffer disease that compromises their immune system like HIV/AIDS will have a higher incidence of developing active TB from latent *Mycobacterium tuberculosis* infections [10]. The HIV/AIDS epidemic in South Africa is likely to have caused the increase of TB incidence, thus driving TB proliferation [7]. In the year 2000, 31% of all new TB cases of adults in Africa were attributed to HIV/AIDS [16].

There are more than 5 million people living with HIV/AIDS in South Africa and it is one of the countries with highest percent of people living with the disease (between 18-19%) in the world [9].

HIV/AIDS and TB comprise a synergistic force given the fact that TB is the primary cause of mortality and morbidity in areas of high HIV/AIDS prevalence like South Africa. This deadly interaction is in very literal terms a dual epidemic. Individuals who are both HIV-positive and are latent carriers of TB are 50 times more likely to progress to active TB compared to individuals who are HIV-negative [21]. As mentioned previously HIV/AIDS is the most potent risk factor for TB infection as a result of a compromised immune

system. HIV-positive individuals who are infected with TB are also more infectious to the community [10].

The severity of this increasing public health concern is revealed once you consider the fact that half of all people infected with TB are those people living in areas with HIV/AIDS epidemic [16]. This of course will have a dramatic effect on health care and economic resources. Public health measures that are addressing one need also to consider the control and prevention of the other to combat both epidemics.

We use an epidemiological model to study the dynamics of HIV/AIDS and TB in South Africa. By using current demographic data, we will analyze our model to gauge the extent to which the HIV/AIDS epidemic accentuates the TB epidemic. Will the TB epidemic persist without the presence or prevalence of the HIV/AIDS epidemic? Numerical simulations are used to predict future trends in both the HIV/AIDS and TB epidemics. We conduct sensitivity and uncertainty analysis in order to identify the parameter(s) to which the number of co-infection cases is most sensitive.

This paper is organized as follows: Section 3 introduces our epidemic model; Section 4 computes the disease-free equilibrium point and basic reproductive number for our HIV-TB co-infection model; Section 5 and Section 6 explores the HIV-free model and TB-free model, respectively; Section 7 focuses on the uncertainty and sensitivity analysis of the basic reproductive number, the key to our control strategies; Section 8 gives our numerical solutions; and Section 9 gives our results and conclusions.

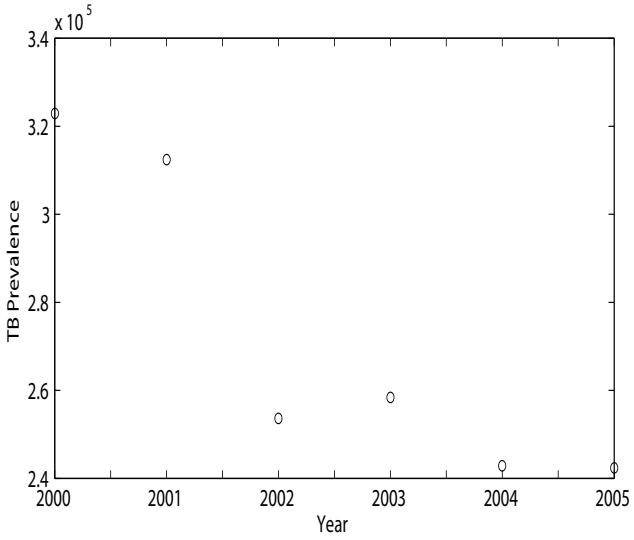

Figure 1: Prevalence of the population in South Africa infected with TB by year (2000-2005). The data was taken from the World Health Organization.

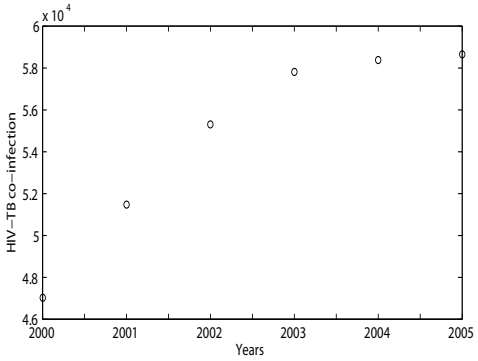

Figure 2: Total number of confirmed HIV-TB coinfection cases in adults aged 15-49 in South Africa by year (2000-2005). The data was taken from the World Health Organization.

3 Model Description

In this section, we present a mathematical model to study the dynamics of HIV-TB coinfection in South Africa. In the model, the population is divided into seven epidemiological classes: Susceptible (S), Latent TB (L), Infectious TB (I), HIV-positive (H), HIV-positive with latent TB (H_L), HIV-positive with infectious TB (H_I), and HIV-positive individuals with other opportunistic infection different from TB (A), in the model H_L and H_I represents the HIV-TB coinfection. The compartment model is shown in (Figure 4). As stated previously in our functional definition of AIDS, an individual who is HIV-positive and is actively infected with TB is an indicator of AIDS; that is, we denote the AIDS class induced by TB as H_I. Also, we consider other opportunistic infections associated with HIV in the A class. We only consider successful treatment for TB.

The susceptible class (S) is composed of individuals aged between 15 to 49 years old, who are neither infected by HIV nor TB. In this model, TB infection is spread between infectious and susceptible individuals through airborne spread (droplets). HIV is also transmitted between infectious and susceptible individuals and no particular route of transmission is assumed (direct sexual contact, exposure to infected body fluids or tissues, etc.) Therefore, susceptible individuals can either be infected with TB by individuals in the epidemiological classes I or H_I and with HIV by individuals in H, H_L, H_I or A. People infected with HIV have an increasing risk for progressive disease to AIDS, (H_I), through TB infection and reactivation of the latent TB infection [16]. HIV also increases the risk of TB progression from reinfection externally caused [16]. The latent class (L) is composed of individuals who have TB infection but can not pass the disease (they are individuals who are infected but not infectious). Consequently, they can be infected with HIV by individuals from the epidemiological classes H, H_L, H_I or A. The active TB class

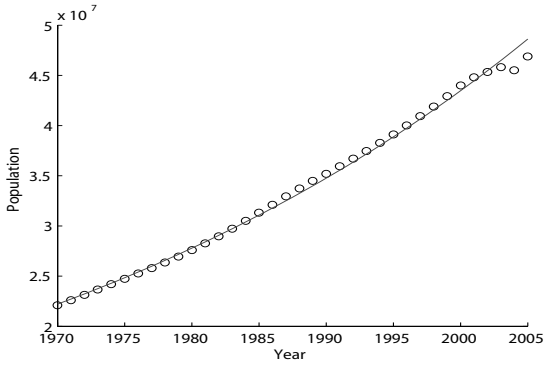

Figure 3: Exponential curve fitting of the total population in South Africa by year (1970-2005). The data was taken from the World Bank.

I is composed of infectious TB individuals. They can be infected with HIV by individuals from H, H_L, H_I or A classes. The HIV class H is composed of individuals who are HIV-positive. Consequently, they can be infected with TB infection by individuals from I or H_I classes. The H_L class are individuals who have HIV-positive and latent TB. Similarly, the H_I class is composed of individuals who have HIV-positive and active TB. Finally, the A class is composed by individuals who have HIV-positive and an opportunistic infection different from TB.

The total population is $N = S + L + I + H + H_L + H_I + A$ where S is the total size of susceptible population, $L + I$ is the total size of TB individuals if HIV was not present in the population, $H + H_L$ is the the HIV population and $(H_I + A)$ is the total number of individuals suffering from AIDS.

Individuals enter the susceptible class at the per-capita rate b and die at the natural per-capita rate μ. Susceptible individuals infected with TB enter the latent period (L) at rate $\beta_1 \left(\frac{I+\delta H_I}{N}\right)$ and the HIV-positive class (H) at the rate $\beta_2 \left(\frac{H+\varepsilon_1 H_L+\varepsilon_2 H_I+\varepsilon_3 A}{N}\right)$ where β_1 and β_2 are the transmission rates per year for TB and HIV respectevely, the quantity $\frac{I+\delta H_I}{N}$ is the probability of contacting an individual infected with TB out of the total population and $\frac{H+\varepsilon_1 H_L+\varepsilon_2 H_I+\varepsilon_3 A}{N}$ is the risk measure associated with levels of HIV in the population; parameter $\delta > 1$ indicates that an individual with HIV and active TB is more infectious to pass TB disease compared with an HIV-negative individual with active TB. The rates $1 \leq \varepsilon_1 \leq \varepsilon_2 \leq \varepsilon_3$ indicate that it is easier to become infected with HIV-positive from an individual with HIV-positive with latent TB or from an individual with AIDS than from an individual infected just with HIV-positive [16]. Individuals who are in the latent class can go back to the susceptible class due to successful treatment for TB at the rate γ_1, die at the rate μ, or progress to the infectious class (I) at the rate κ. Latent TB

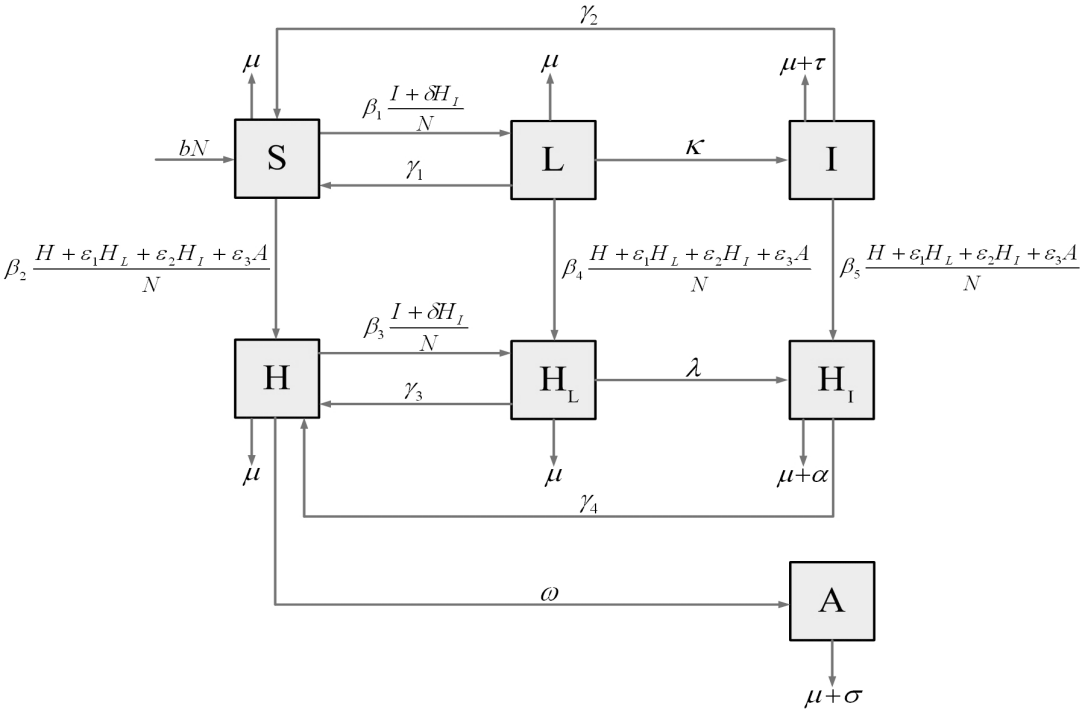

Figure 4: Schematic representation of the flow between the different epidemiological classes.

individuals can also move to the HIV-positive class (H_L) at the rate $\beta_4 \left(\frac{H+\varepsilon_1 H_L+\varepsilon_2 H_I+\varepsilon_3 A}{N}\right)$ where β_4 is the transmission rate for HIV. Infectious TB individuals (I) recover due to successful treatment at the rate γ_2, die from TB at the rate τ, or enter the class (H_I) at the rate $\beta_5 \left(\frac{H+\varepsilon_1 H_L+\varepsilon_2 H_I+\varepsilon_3 A}{N}\right)$ where β_5 is the transmission ratefor HIV. Individuals who are HIV-positive can either be infected with TB or other opportunistic infection. If they are infected with TB, they enter the HIV-positive and latent TB class (H_L) at the rate $\beta_3 \left(\frac{I+\delta H_I}{N}\right)$ where β_3 is the transmission rate. Otherwise, they progress to the AIDS class (A) at the rate ω. Individuals in this class die from both diseases, HIV and any other opportunistic infection, at rate σ. HIV-positive with latent TB individuals go back to the HIV-positive class (H_L) due to successful treatment for TB at the rate γ_3 or progress to AIDS cor HIV-TB co-infection class (H_I) at the rate λ. Individuals infected with HIV-positive and active TB die from HIV and TB at the rate α.

Table 1 describes the parameters, as well as the values used. The model that describes the dynamics of the HIV-TB co-infection is given by the following system of nonlinear

differential equations:

$$
\left\{
\begin{array}{rcl}
\dot{S} &=& bN - \beta_1 S\left(\dfrac{I+\delta H_I}{N}\right) - \beta_2 S\left(\dfrac{H+\varepsilon_1 H_L+\varepsilon_2 H_I+\varepsilon_3 A}{N}\right) - \mu S + \gamma_1 L + \gamma_2 I,\\
\dot{L} &=& \beta_1 S\left(\dfrac{I+\delta H_I}{N}\right) - \beta_4 L\left(\dfrac{H+\varepsilon_1 H_L+\varepsilon_2 H_I+\varepsilon_3 A}{N}\right) - (\gamma_1+\kappa+\mu)L,\\
\dot{I} &=& \kappa L - \beta_5 I\left(\dfrac{H+\varepsilon_1 H_L+\varepsilon_2 H_I+\varepsilon_3 A}{N}\right) - (\gamma_2+\mu+\tau)I,\\
\dot{H} &=& \beta_2 S\left(\dfrac{H+\varepsilon_1 H_L+\varepsilon_2 H_I+\varepsilon_3 A}{N}\right) - \beta_3 H\left(\dfrac{I+\delta H_I}{N}\right) + \gamma_3 H_L + \gamma_4 H_I - (\omega+\mu)H,\\
\dot{H}_L &=& \beta_3 H\left(\dfrac{I+\delta H_I}{N}\right) + \beta_4 L\left(\dfrac{H+\varepsilon_1 H_L+\varepsilon_2 H_I+\varepsilon_3 A}{N}\right) - (\gamma_3+\lambda+\mu)H_L,\\
\dot{H}_I &=& \beta_5 I\left(\dfrac{H+\varepsilon_1 H_L+\varepsilon_2 H_I+\varepsilon_3 A}{N}\right) + \lambda H_L - (\gamma_4+\mu+\alpha)H_I,\\
\dot{A} &=& \omega H - (\mu+\sigma)A,
\end{array}
\right. \tag{1}
$$

with $\dot{N} = bN - \mu N - \tau I - \alpha H_I - \sigma A$.

Table 1: Parameter definitions and values used with the HIV-TB co-infection compartmental epidemic model.

Parameter	Definition	Value	Ref
b	Per-capita birth rate	0.022	[21]
β_1	Infection rate for susceptible individuals by an infectious TB individual per contact per unit time	0.22	[5]
β_2	Infection rate for susceptible individuals by an HIV-positive individual per contact per unit time	0.02	estimated
β_3	Infection rate for HIV-positive individuals by an infectious TB individual per contact per unit time	0.3	estimated
β_4	Infection rate for latent TB individuals by an HIV-positive individual per contact per unit time	0.2	[5]
β_5	Infection rate for infectious TB individuals by an HIV-positive individual per contact per unit time	0.2	estimated
γ_1	Per capita TB recovery rate from L due to TB successful treatment	0.02	[5]
γ_2	Per capita TB recovery rate from I due to TB successful treatment	0.05	[5]
γ_3	Per capita TB recovery rate from H_L to H due to successful TB treatment	0.02	[5]
γ_4	Per capita TB recovery rate from H_I to H due to successful TB treatment	0.02	[16]
κ	Progression rate of latent TB to active TB	0.005	[16]
λ	Progression rate for active TB in HIV positive individuals	0.1	[5]
ω	Rate at which H individuals become A with other opportunistic infections different from TB	0.1	estimated
μ	Per capita natural death rate	0.014	[19]
τ	Per capita death rate due to TB	0.015	[5]
α	Per capita death rate due to H_I	0.05	[17]
σ	Per capita death rate due to A and other opportunistic infections different from TB	0.08	[17]
δ	Coefficient of infectiousness of H_I to pass TB disease	1	estimated
ε_1	Coefficient of infectiousness of H_L to pass HIV-positive disease	1	estimated
ε_2	Coefficient of infectiousness of H_I to pass HIV-positive disease	1	estimated
ε_3	Coefficient of infectiousness of A to pass HIV-positive disease	1	estimated

Parameter ϵ_1 is equal to 1 since the relative infectiousness of latently infected HIV-positive individuals to transmit HIV virus is considered to be the same compared with HIV-positive individuals who are not latently infected. We estimate β_5 to be twice as high as β_2 because active TB individuals are more susceptible to be infected successfully by HIV virus. Individuals who are both HIV-positive and are latent carriers of TB are 50 times more likely to progress to active tuberculosis compared to individuals who are HIV-negative [21].

4 Disease-Free Equilibrium Point and Basic Reproductive Number

4.1 Existence of the Disease-Free Equilibrium Point

Disease-free equilibrium points are steady-state solutions where there is no disease in the population. We have that the non-negative equilibrium population values, in the absence of disease, are $L = 0, I = 0, H = 0, H_L = 0, H_I = 0, A = 0$. Therefore, our model has a disease free equilibrium of $DFE = (S^*, L^*, I^*, H^*, H_L^*, H_I^*, A^*) = (\frac{bN}{\mu}, 0, 0, 0, 0, 0, 0)$. To compute the basic reproductive number, we have to assume the susceptible population is in the demographic steady state and hence $b = \mu$ and the disease-free equlibrium is $(N, 0, 0, 0, 0, 0, 0)$.

4.2 Basic Reproductive Number

We use the next generation operator method as described by van den Driessche et al. in [20] to find the basic reproductive number, R_0, that is defined as the number of secondary cases produced by a "typical" infectious individual during its period of infectiousness in a completely susceptible population at a demographic steady state. We have that F is the vector of rates of appearance of new infections in each compartment and $V = V^- - V^+$, where V^- is a vector of rates of transfer of individuals out of the particular compartment and V^+ is the vector of rates of transfer of individuals into the particular compartment by all other means. For our model, as we supposed constant population, we can use only the equations for S, L, I, H, H_L, H_I, A. Therefore,

$$F = \begin{pmatrix} \beta_1 S\left(\frac{I+\delta H_I}{N}\right) \\ 0 \\ \beta_2 S\left(\frac{H+\varepsilon_1 H_L+\varepsilon_2 H_I}{N}\right) \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

and

$$V = \begin{pmatrix} \beta_4 L\left(\frac{H+\varepsilon_1 H_L+\varepsilon_2 H_I+\varepsilon_3 A}{N}\right) + (\gamma_1+\kappa+\mu)L \\ -\kappa L + \beta_5 I\left(\frac{H+\varepsilon_1 H_L+\varepsilon_2 H_I+\varepsilon_3 A}{N}\right) + (\gamma_2+\mu+\tau)I \\ \beta_3 H\left(\frac{I+\delta H_I}{N}\right) - \gamma_3 H_L - \gamma_4 H_I + (\omega+\mu)H \\ -\beta_3 H\left(\frac{I+\delta H_I}{N}\right) - \beta_4 L\left(\frac{H+\varepsilon_1 H_L+\varepsilon_2 H_I+\varepsilon_3 A}{N}\right) + (\gamma_3+\lambda+\mu)H_L \\ -\beta_5 I\left(\frac{H+\varepsilon_1 H_L+\varepsilon_2 H_I+\varepsilon_3 A}{N}\right) - \lambda H_L + (\gamma_4+\mu+\alpha)H_I \\ -\omega H + (\mu+\sigma)A \end{pmatrix}.$$

Then, we compute the Jacobian matrices for F and V at the disease-free equilibrium point, $DFE = (N, 0, 0, 0, 0, 0, 0)$. The following 6×6 matrices are obtained assuming

$$\mathcal{F} = \begin{pmatrix} 0 & \beta_1 & 0 & 0 & \beta_1\delta & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \beta_2 & \beta_2\varepsilon_1 & \beta_2\varepsilon_2 & \beta_2\varepsilon_3 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

and

$$\mathcal{V} = \begin{pmatrix} \gamma_1+\kappa+\mu & 0 & 0 & 0 & 0 & 0 \\ -\kappa & \gamma_2+\mu+\tau & 0 & 0 & 0 & 0 \\ 0 & 0 & \omega+\mu & -\gamma_3 & -\gamma_4 & 0 \\ 0 & 0 & 0 & \gamma_3+\lambda+\mu & 0 & 0 \\ 0 & 0 & 0 & -\lambda & \gamma_4+\mu+\alpha & 0 \\ 0 & 0 & -\omega & 0 & 0 & \mu+\sigma \end{pmatrix}.$$

The dominant eigenvalue of $\mathcal{F}\mathcal{V}^{-1}$ gives our R_0,

$$R_0 = \max\{R_0^{TB}, R_0^{HIV}\} = \max\left\{\left(\frac{\beta_1}{\gamma_2+\mu+\tau}\right)\left(\frac{\kappa}{\gamma_1+\kappa+\mu}\right), \frac{\beta_2}{\omega+\mu} + \left(\frac{\beta_2\epsilon_3}{\mu+\sigma}\right)\left(\frac{\omega}{\mu+\omega}\right)\right\}.$$

Where R_0^{TB} is the basic reproductive number for TB transmission dynamics which is given by the product of the transmission rate β_1 for susceptible individuals by an active TB individual and the average time $\frac{1}{\gamma_2+\mu+\tau}$ an individual spends in the latent class times the product of the rate κ at which a latent TB individual becomes active TB and the average time $\frac{1}{\gamma_1+\kappa+\mu}$ an individual spends in the latent class. The basic reproductive number for HIV and AIDS transmission dynamics, R_0^{HIV} is given by the product of the transmission rate β_2 for susceptible individuals by a HIV-positive individual and the average of time

$\frac{1}{\mu+\sigma}$ an individual spends in the HIV-positive class plus the product of the transmission rate β_2 by the coefficient of infectiousness of AIDS ϵ_3 times the probability of persistance from the HIV-positive into the AIDS stage $\frac{\omega}{\omega+\mu}$.

As explained previously R_0 is the disease threshold and with the interaction of two diseases we have illustrated the disease threshold can shift from R_0^{HIV} to R_0^{TB} and viceversa. The disease threshold of our entire system is the maximum basic reproductive number, of the TB-free model (R_0^{HIV}) and HIV-free model (R_0^{TB}). The value of our parameters will determine the disease threshold. If we vary certain parameters, the maximum R_0 can change see (figure 6). We also observed, for certain parameter values, increasing the value of the maximum R_0 resulted in a switch, e.g. initially $R_0^{HIV} > R_0^{TB}$ but after increasing R_0^{HIV} to a certain point $R_0^{TB} > R_0^{HIV}$ (figure 6).

For our estimated parameter values, R_0^{HIV} is always greater than R_0^{TB} (figure 5). Decreasing the disease threshold associated with HIV, R_0^{HIV}, below unity will imply that the disease threshold associated with TB, R_0^{TB}, will be below unity.

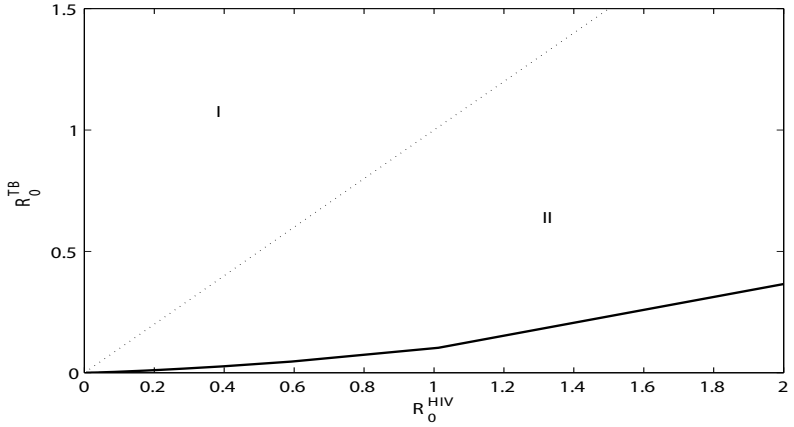

Figure 5: For our estimated parameter values, R_0^{HIV} characterizes our epidemic threshold value. κ=.005; $\beta_1 = 0.22$; $\beta_2 = .02$; $\gamma_1 = .02$; $\gamma_2 = .05$; $\omega = .1$; $\tau = .015$; $\epsilon_3 = 1$; $\sigma = .08$.

In region I of figures 5 and 6, R_0^{TB} is the threshold of the disease dynamics while in region II, R_0^{HIV} is the threshold. For our estimated parameter values, R_0^{HIV} characterizes our epidemic threshold value, as we see in (figure 5).

Varying certain parameters can change the disease threshold, e.g. increasing β_1 can change R_0 from R_0^{HIV} to R_0^{TB} (figure 6).

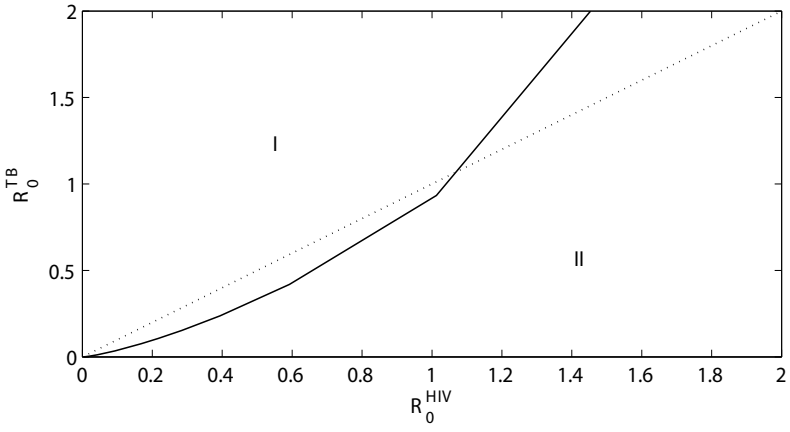

Figure 6: Varying parameter β_1. $\kappa = .005$; $\beta_1 = 2$; $\beta_2 = .02$; $\gamma_1 = .02$; $\gamma_2 = .05$; $\omega = .1$; $\tau = .015$; $\epsilon_3 = 1$; $\sigma = .08$.

5 Uncertainty and Sensitivity Analysis

5.1 Uncertainty Analysis

We performed an uncertainty analysis via Monte Carlo simulations on the basic reproductive number to asses our calculation variability of R_0. Parameter values of κ, β_1, γ_1, μ, γ_2, τ are assigned a probability density functions (PDF), which are taken from reference [15]. We assume $\kappa \sim$ Unif$(a = 0, b = 1)$, $\beta_1 \sim$ Unif$(a = 0, b = 1)$, $\gamma_1 \sim$ Trian$(a = 0.02)$, $\mu \sim$ Unif$(a = 0, b = 1)$, $\gamma_2 \sim$ Trian$(a = 0.05)$, $\tau \sim \exp(a = 0.015, 2)$. For R_0^{HIV}, we assume that $\beta_2 \sim$ Unif$(a = 0, b = 1)$, $\omega \sim \exp(a = 0.1, b = 2)$ and $\sigma \sim$ exp(a=0.08, b=2).

Using Monte Carlo simulations, we obtain a mean value for R_0^{TB} of 0.3375 and for R_0^{HIV} of 2.0424. Since $R_0 = \max\{R_0^{TB}, R_0^{HIV}\}$, we estimate a mean value for R_0 of 2.04. We also find the probability that $R_0 > 1$ is 0.6. This will be validated by our estimate of R_0 in Section 8.

5.2 Sensitivity Analysis

The sensitivity analysis in this section quantifies the effect of changes on R_0. To explore the sensitivity of R_0 to the variability of the parameters for the model, we let ζ represent any of the nonnegative parameters that define R_0 in our model. Considering a small perturbation of ζ by $\Delta\zeta$, a perturbation will occur in R_0 (ΔR_0) as well. The normalized sensitivity index S_ζ is the ratio of the corresponding normalized changes [6]. We define the sensitivity index for parameter ζ as

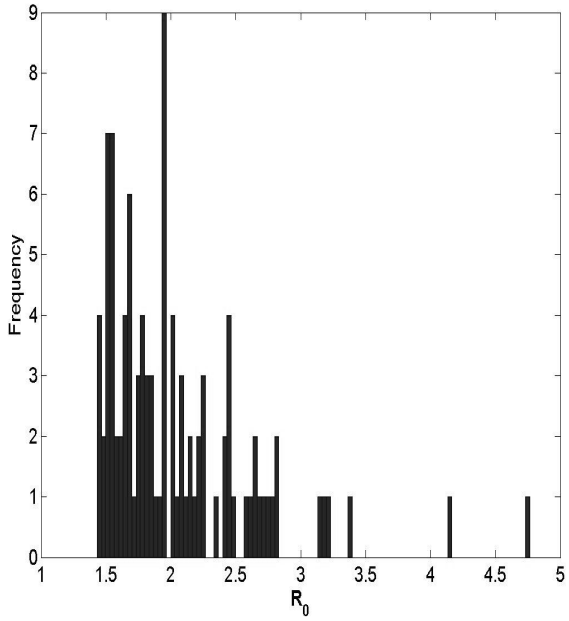

Figure 7: Histogram for R_0 with mean value 2.0424 from Monte Carlo Simulations.

$$S_\zeta = \frac{\Delta R_0}{R_0} / \frac{\Delta \zeta}{\zeta} = \frac{\zeta}{R_0} \cdot \frac{\partial R_0}{\partial \zeta}.$$

Since the basic reproductive number for the model is given by $R_0 = \max\{R_0^{TB}, R_0^{HIV}\}$, we calculate the sensitivity indices in terms of R_0^{TB} and R_0^{HIV}. The following are the sensitivity indices in terms of $R_0^{TB} = \left(\frac{\beta_1}{(\gamma_2 + \mu + \tau))}\right)\left(\frac{\kappa}{(\gamma_1 + \kappa + \mu)}\right)$.

$$
\begin{aligned}
S_\kappa &= \frac{\gamma_1+\mu}{\gamma_1+\kappa+\mu},\\
S_{\beta_1} &= 1,\\
S_{\gamma_1} &= -\frac{\gamma_1}{\gamma_1+\kappa+\mu},\\
S_\mu &= -\frac{\mu(\gamma_1+\gamma_2+\kappa+2\mu+\tau)}{(\gamma_1+\kappa+\mu)(\gamma_2+\mu+\tau)},\\
S_{\gamma_2} &= -\frac{\gamma_2}{\gamma_2+\mu+\tau},\\
S_\tau &= -\frac{\tau}{\gamma_2+\mu+\tau}.
\end{aligned}
$$

The sensitivity indices of $R_0^{HIV} = \dfrac{\beta_2}{\omega+\mu} + \left(\dfrac{\beta_2\epsilon_3}{\mu+\sigma}\right)\left(\dfrac{\omega}{\mu+\omega}\right)$ are

$$
\begin{aligned}
S_{\beta_2} &= 1,\\
S_{\epsilon_3} &= \frac{\epsilon_3\omega}{\mu+\sigma+\epsilon_3\omega},\\
S_\sigma &= -\frac{\sigma\epsilon_3\omega}{(\mu+\sigma)(\mu+\sigma+\epsilon_3\omega)},\\
S_\omega &= \frac{\omega(\epsilon_3\mu-\mu-\sigma)}{(\mu+\omega)(\mu+\sigma+\epsilon_3\omega)},\\
S_\mu &= \mu\left(\frac{1}{\mu+\sigma+\epsilon_3\omega} - \frac{1}{\mu+\sigma} - \frac{1}{\mu+\omega}\right).
\end{aligned}
$$

Using our parameter values $\kappa = 0.005$, $\beta_1 = 0.22$, $\beta_2 = 0.02$, $\gamma_1 = 0.02$, $\gamma_2 = 0.05$, $\tau = 0.015$, $\omega = 0.1$, $\mu = 0.014$, and $\sigma = 0.08$, we compute the sensitivity indices. Table 2 and 3 show the sensitivity indeces and the associated percent needed afect a 1% decrease in R_0. Since the progression rate from latent TB to active TB, the TB recovery rate from latent due to successful treatment, and the TB recovery rate from active due to successful treatment, the trasmission rate for susceptible individuals by an infectious TB individual, and transmission rate Infection rate for susceptible individuals by an HIV-positive individual are some possible interventions strategies, we examine how changes of parameters κ, γ_1, γ_2, β_1, and β_2 affect the basic reproductive numbers, R_0^{TB} and R_0^{HIV}.

Table 2: Sensitivity analysis of R_0^{TB}

Sensitivity index	Value
S_κ	0.8717
S_{β_1}	1
S_{γ_1}	-0.5128
S_μ	-0.5396
S_{γ_2}	-0.6329
S_τ	-0.1898

Table 3: Sensitivity analysis of R_0^{HIV}

Sensitivity index	Value
S_{β_2}	1
S_{ϵ_3}	0.5154
S_σ	-0.0165
S_ω	-0.0136
S_μ	-0.1999

We found that the most sensitive parameters to R_0^{TB} and R_0^{HIV} are β_1 and β_2, respectively.

The sensitivity indeces $S_\beta = 1$ and $\beta_2 = 1$ mean that 1% decrease in β_1 or in β_2 results in a approximately decrease of 1% in R_0^{TB} or R_0^{HIV}, respectively. The sensitivity index $S_\kappa = 0.8717$ means that 1.14% decrease in κ result in a roughly decrease of 1% in R_0^{TB}. The sensitivity index $S_{\gamma_1} = -0.5128$ means that 1.95% increase in γ_1 results in a approximately decrease of 1% in R_0^{TB}. Similarly, the sensitivity index $S_{\gamma_2} = -0.6329$ means that 1.58% increase in γ_2 results in a approximately decrease of 1% in R_0^{TB}. The sensitivity index $S_{\epsilon_3} = 0.5154$ means that 1.9% decrease in ϵ_3 results in a 1% decrease in R_0^{HIV}. Finally, the sensitivity index $S_\omega = -0.01361$ means that 73.5% increase in ω result in a 1% in R_0^{HIV}.

6 Numerical Solutions

6.1 Parameter Estimation Curve Fitting

Most parameter values were obtained from literature and previous TB model manuscripts [5, 17, 18]. In order to obtain estimates for the remaining parameters we perform a curve fit to demographic data. We plotted the number of active TB cases per year in South Africa from the year 2000 to 2005 and fit our solution curve to the data points. In (Table 1) we indicate which parameters were estimated from the curve fit. The following are descriptions of assumptions made for particular parameters.

$b = .022$. The annual growth rate of South Africa was estimated by performing an exponential curve fit to the population data from 1970 to 2005, (figure 3).

$\beta_3 = 0.3$. The transmission rate of TB for HIV-positive individuals is estimated to be relatively higher compared to HIV-negative individuals. HIV-positive individuals are assumed to be more susceptible to infection as a result of a compromised immune system.

$\beta_4 = 0.2$. The transmission rate of HIV for individuals latently infected with tuberculosis is estimated to be the same for individuals who are disease free. Latent individuals are assumed to be no more susceptible to HIV infection because latent tuberculosis does not imply a compromised immune system.

β_5=0.2. The transmission rate of HIV for individuals who are actively infected with tuberculosis is estimated to be relatively higher compared to individuals who are latently infected with tuberculosis and individuals who are disease free.

$\gamma_1 = \gamma_3 = \gamma_4 = 0.02$. All per capita treatment rates except for γ_2 were estimated from the demographic curve fit. Per capita treatment rate for active tuberculosis is assumed to be relatively higher compared to latent infection. Latent infection is asymptomatic and a skin test is required before administering a drug regimen. In the case of active TB, individuals are symptomatic which results in easier diagnosis.

$\kappa = 0.005$. Progression rate to active tuberculosis was estimated from a previous TB manuscript [5]. For HIV-positive individuals who are latently infected with TB, the progression rate to active tuberculosis is estimated to be up to 50 times higher compared to HIV-negative individuals [16].

$\alpha > \sigma > \tau > \mu$. The per capita death rate due to HIV and TB co-infection is assumed to be the higher than any other per capita death rate. We would expect the per capita death rate for individuals suffering active TB infection who have a compromised immune system to be higher. We also assume the per capita death rate for individuals suffering TB with a compromised immune system to higher compared to other opportunistic infections couple with a compromised immune system since TB is the leading cause of death in HIV-infected individuals [21].

$\delta = 1$. Individuals who are co-infected with HIV and active TB are considered to be more infectious to pass tuberculosis compared to individuals who are actively infected with TB. This assumptions is based on the fact that HIV-positive individuals are suffering from a suppressed immune system. The exact value was estimated from curve fit.

$\varepsilon_3 > \varepsilon_2 > \varepsilon_1 > 1$. HIV-positive individuals who are experiencing co-infection are assumed to be more infectious to pass HIV compared to HIV-positive individuals who are not co-infected.

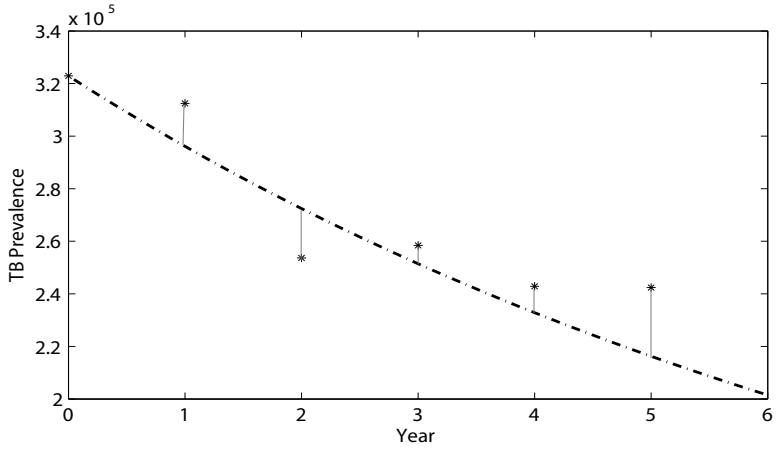

Figure 8: Curve fitting of the TB prevalence in South Africa by year (2000-2006). The data was taken from the World Health Organization.

6.2 Effects of Treatment

Following the protocol of TB-priority treatment we need to gain a qualitative understanding of the timing of treatment. We varied the successful treatment rate γ_2 in order to determine if resources for treatment and management were to be focused on improving successful treatment rate in patients infectious with active tuberculosis. In the hypothetical situation of 100 percent successful treatment of rate, the downward trend observed in the prevalence of active TB cases will still eventually shift and begin to increase (figure 10). Therefore, focusing treatment and control management of just active TB patients will not be effective to continue the TB prevalence decline witnessed between 2000-2005 [21]. This is mainly due to the upward trend of HIV-TB co-infection which continues to experience increasing prevalence.

In order to continue the TB prevalence decline, treatment protocol and management need to consider effective treatment on both patients with active TB and those patients with HIV-TB co-infection. The current HIV-TB co-infection treatment protocol and management is often difficult due to adverse side effects of antiretroviral and antibacterial drug regimes [16]. Effective treatment and management will require a general therapeutic principles. As mentioned in the Background section, treatment of tuberculosis is given precedent and the introduction of antiretroviral drugs should be administered with careful attention to the timing of introduction [16]. According to World Health Organization HIV-positive individuals who are infected with TB experience similar successful treatment rates as witnessed in HIV-negative patients, i.e. the initial response of a 6 month TB treatment therapy in co-infected patients is similar to HIV-negative patients. However, co-infected

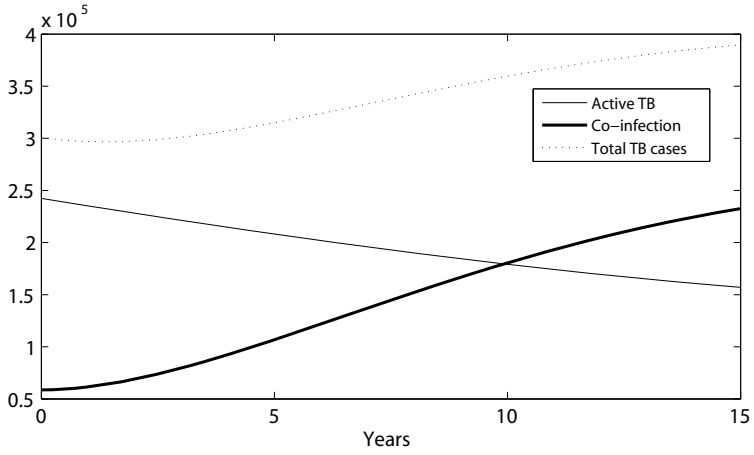

Figure 9: Dynamics of active TB, HIV-TB co-infection, and total TB cases over time.

patients experience higher recurrence rates which some studies suggest is attributed to reinfection rather than treatment failure [16]. Increasing the successful treatment rates of co-infection would be enough to continue the decline of TB prevalence but, in light of adverse drug reactions in HIV-positive patients facing the burden of an intoxicating drug cocktail and high relapse rates, perhaps another measure of disease control might be just as effective and more realistic, e.g. prevention.

Prevention measures of TB disease outbreaks such as treatment of individuals who are latently infected with TB could be an important factor to consider for disease control. As mentioned in the Introduction, HIV-positive individuals who are latently infected with TB are at incredible risk of progressing to active TB. We varied the successful treatment rate of HIV-positive individuals who are latently infected with TB. Increasing this rate results in a continued decline of TB prevalence. This is significant because the South African government could consider a more focused effort on raising awareness of the risk HIV-positive patients face in progressing to active TB. In addition if an individual is tested positive for HIV, he or she should immediately consider a skin test to determine any TB infection. In terms of TB disease control and management, standard protocol of testing for TB infection should be administered to HIV-positive individuals.

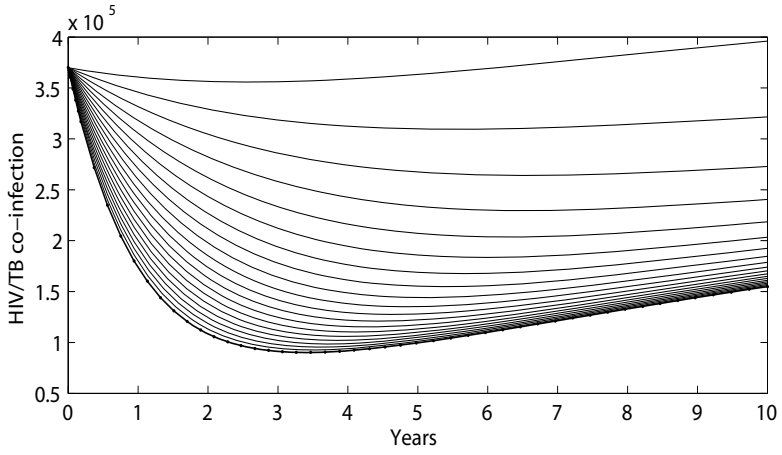

Figure 10: Number of cases of HIV-TB co-infection varying γ_2.

6.3 The Impact of HIV/AIDS on TB epidemic

The current level of HIV prevalence in South Africa is halting the downward trend of total TB cases. This is the result of the continual rise of HIV-TB co-infection (see Figure). As of 2005 the prevalence of HIV-TB co-infection has relatively minimal contribution to the total TB prevalence compared to active TB cases. However, the current rising trend of HIV-TB co-infection will eventually be just as prevalent as active TB cases and in roughly ten years more prevalent (see Figure). The HIV/AIDS epidemic is accentuating the progression of HIV-TB co-infection. If the HIV/AIDS population is reduced TB prevalence will experience a reduction. In the hypothetical situation in which there is no HIV/AIDS in the population, the total TB cases will continue to decrease (see FIgure). We also varied HIV infection rate. Higher HIV infection rate increases the TB prevalence (see figure).

7 Ressults and Conclusions

We developed an epidemiological model to describe the dynamical interaction of the HIV and TB epidemic in South Africa. We analyzed this deterministic model in order to gauge the extent to which the the HIV epidemic accentuates and exacerbates the spread of TB.

The TB-free model is shown to be globally-stable at disease free equilibrium when $R_0^{HIV} < 1$. We identified an unique, locally asymptotically stable endemic equilibrium when $R_0^{HIV} > 1$. The HIV-free model is shown to be locally-stable at the disease free equilibrium when $R_0^{TB} < 1$. For the entire system, R_0 is determined by the $\max R_0^{TB}, R_0^{HIV}$. After further analytical investigation of the disease threshold, R_0^{HIV} is shown to always

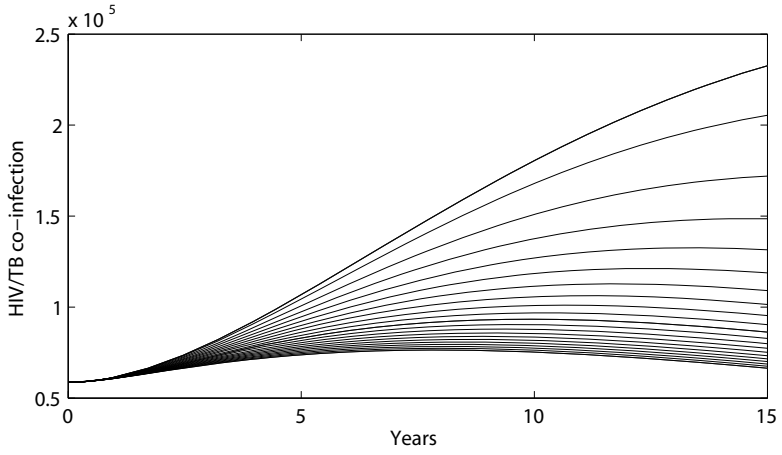

Figure 11: Number of cases of HIV-TB co-infection varying γ_4.

be the maximum basic reproductive number with our estimated parameter values. Therefore, R_0^{HIV} characterizes the disease dynamics of our entire system. The entire system is locally-stable at disease free equilibrium when $\max R_0^{TB}, R_0^{HIV} < 1$.

We conducted uncertainty analysis in order to validate our calculation of R_0. We created distributions of each parameter. We also performed sensitivity analysis since the progression rate from latent TB to active, the TB recovery rate from latent due to successful treatment, and the TB recovery rate from active due to successful treatment are some possible interventions strategies, we examined how changes to parameters κ, γ_1, and γ_2 affect the basic reproductive number. A 1.95% increase in the per capita treatment rate of latent TB infection results in a 1% decrease in R_0. A 1.58% increase of the per capita treatment rate of active TB infection results in a 1% decrease in R_0.

Numerical simulations for the full model where carried out in using estimated parameter values found in literature and estimates obtained from curve fitting demographic data. The results of our numerical simulations identified the declining trend of total tuberculosis cases in South Africa will eventually shift due to HIV-TB co-infection. We expect in about 12 years the HIV-TB co-infection prevalence to be the same as the active TB prevalence. This can be avoided by introducing treatment and management protocols that focus efforts to increase the successful treatment rate of HIV-positive individuals who are latently infected with TB. These individuals are at a significantly high risk to progress to active TB, therefore early case detection of TB in these individuals might impede rising HIV-TB co-infection and stabilize TB prevalence. It is important to recognize that the HIV epidemic in South Africa poses a threat to the stability of TB prevalence.

The impact of the HIV/AIDS epidemic is progressing the TB prevalence. With higher HIV/AIDS population and increased HIV infection rates, TB prevalence persists at in-

creasingly higher levels. HIV-TB co-infection will continue to rise as a result of the HIV/AIDS epidemic.

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