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A DOUBLE AGE-STRUCTURED MODEL OF THE CO-INFECTION OF TUBERCULOSIS AND HIV

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Abstract. After decades on the decline, it is believed that the emergence of HIV is responsible for an increase in the tuberculosis prevalence. The leading infectious disease in the world, tuberculosis is also the leading cause of death among HIV-positive individuals. Each disease progresses through several stages. The current model suggests modeling these stages through a time-since-infection tracking transmission rate function, which, when considering co-infection, introduces a double-age structure in the PDE system. The basic and invasion reproduction numbers for each disease are calculated and the basic ones established as threshold for the disease progression. Numerical results confirm the calculations and a simple treatment scenario suggests the importance of time-since-infection when introducing disease control and treatment in the model.

1. **Introduction.** The connection between the human immunodeficiency virus (HIV) and tuberculosis (TB) has been studied extensively [7, 6, 9]. The HIV epidemic of the 1980s is believed to have caused a surge in the TB prevalence and mortality, especially in countries in central and southern Africa. While both HIV and TB can be contained through treatment, in developing countries, where medical assistance is inferior and awareness and education are lacking, each of the diseases can be deadly. Transition from latent to acute TB can be quicker if HIV is acquired. On the other hand, an HIV-positive individual is more susceptible to TB because of a compromised immune system. 13% of the people who developed TB in 2012 were HIV-positive, which amounts to 1.1 million individuals worldwide. Also, TB is considered to be the most common reason for death from HIV. Hence, both diseases have an effect on each other's prevalence, which makes studying their co-infection important. In fact, the World Health Organization Report on TB has a specific section dedicated to the dynamics between the two diseases [8].

Several mathematical models have investigated the dynamics of a population where both diseases are present. In [12], Wang et. al. look at a time-since infection dependent latent class of TB, separating it from a class of TB-infectious individuals.

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HIV and co-infection with HIV are described with ordinary differential equations. In [2], Currie et. al. develop a statistical model with probability movement between latent and acute stages of TB, which investigates the effectiveness of prevention versus cure for controlling the spread of TB under the influence of HIV. In [11], Sharomi, et. al. present a system of ordinary differential equations that includes latent and acute TB population classes, as well as asymptomatic HIV and AIDS population classes. Adding treatment, and all different possibilities for development of each disease in co-infected individuals, creates a model of a large system of ordinary differential equations. In [5], Kirschner explores the effect of TB and HIV interaction at the cellular level through a system of ordinary differential equations. In a similar manner, Bauer et. al. explore the role of treatment of macrophages in [1]. In [10], Roeger et. al. model the co-infection using latent and acute classes for TB and different stages of HIV with a system of ordinary differential equations. In fact a brief discussion on this paper provoked the currently proposed model.

Both diseases go through several stages of development: acute stage, latency, and reactivation for TB, and acute infection, clinical latency (still contagious), and AIDS for HIV [3, 4]. So far all these stages, as is evident from the given examples of previous work, are modeled using different population classes corresponding to each stage. The current model combines all these stages by using a parameter of time-since-infection for each disease, considering a two-dimensional time-since-infection structure for individuals who are co-infected. To our knowledge, a double time-since-infection (sometimes called age-of-infection) structure has not been considered previously. The mathematical complications that ensue are balanced off by a system of differential equations with fewer variables. Using an age-structured model is important because it allows flexibility when considering strategies for control and treatment. Beyond reducing infectivity and the duration of each stage of the disease, time-since-infection allows us to also consider the effectiveness of the control measure depending on its moment of application within the disease stage itself. The presented model of the dynamics between TB and HIV does not consider vaccination or treatment for either disease.

The article is organized as follows: Section 2 presents the model and Section 3 shows the calculation of the basic reproduction numbers for each disease (R_0^T and R_0^H). Section 3 also contains a theorem that establishes the basic reproduction numbers as thresholds for the stability of the disease free equilibrium. Section 4 presents the calculation of the TB invasion reproduction number, R_H^T, and its biological interpretation. Section 5 presents the same for the HIV invasion reproduction number, R_T^H. Section 6 presents an example in favor of the age-structure used in the current model by comparing its control reproduction numbers, where treatment is applied at different times since infection, to the reproduction numbers of an ODE version of the model. Section 7 presents numerical evidence for verifying the calculated invasion reproduction numbers as thresholds for the disease dynamics. Section 8 is Discussion.

2. **Model.**

The model has the following population classes: $S(t)$ - susceptible individuals, $T(a,t)$ - people who have had tuberculosis for a time units, $H(b,t)$ - people who have been HIV-positive for b time units, $B(a,b,t)$ - individuals with both diseases who have been infected with tuberculosis for a time units and with HIV for b time units. The model is expresses through the following system of differential equations:

$$
\begin{cases}
\dfrac{dS(t)}{dt} = \Lambda - f_S(t)S(t) - g_S(t)S(t) - \mu_S S(t) \\
\dfrac{\partial T(a,t)}{\partial a} + \dfrac{\partial T(a,t)}{\partial t} = -g_T(a,t)T(a,t) - \mu_T(a)T(a,t) \\
\dfrac{\partial H(b,t)}{\partial b} + \dfrac{\partial H(b,t)}{\partial t} = -f_H(b,t)H(b,t) - \mu_H(b)H(b,t) \\
\dfrac{\partial B(a,b,t)}{\partial a} + \dfrac{\partial B(a,b,t)}{\partial b} + \dfrac{\partial B(a,b,t)}{\partial t} = -\mu_B(a,b)B(a,b,t) \\
S(0) = S_0 \\
T(a,0) = T_0(a); T(0,t) = f_S(t)S(t), t > 0 \\
H(b,0) = H_0(b); H(0,t) = g_S(t)S(t), t > 0 \\
B(a,b,0) = B_0(a,b); B(0,b,t) = f_H(b,t)H(b,t), b > 0, t > 0; \\
B(a,0,t) = g_T(a,t)T(a,t), a > 0, t > 0; B(0,0,t) = 0, t > 0,
\end{cases} \tag{1}
$$

where f_i is the rate with which class i is infected with TB and g_i is the rate with which class i is infected with HIV, $i = S, T, H$. Define also $N(t) = S(t) + \int_0^\infty T(a,t)\ da + \int_0^\infty H(b,t)\ db + \int_0^\infty \int_0^\infty B(a,b,t)\ da\ db$, i.e. the total population. The condition $B(0,0,t) = 0$ ensures that no person can be simultaneously infected with both diseases. Then,

$$
\begin{aligned}
f_S(t) &= \frac{\int_0^\infty \alpha^T(a)T(a,t)da}{N(t)} + \frac{\int_0^\infty \int_0^\infty \alpha^B(a,b)B(a,b,t)\ da\ db}{N(t)}, \\
f_H(b,t) &= \gamma_H(b) f_S(t), \\
g_S(t) &= \frac{\int_0^\infty \beta^H(b)H(b,t)db}{N(t)} + \frac{\int_0^\infty \int_0^\infty \beta^B(a,b)B(a,b,t)\ da\ db}{N(t)}, \\
g_T(a,t) &= \gamma_T(a) g_S(t),
\end{aligned} \tag{2}
$$

where $\alpha^T(a)$ is the rate with which TB-infectious people with time-since-infection a infect susceptible individuals, $\beta^H(b)$ is the rate with which HIV-positive people with time-since-infection b infect susceptible individuals. α^B and β^B have the same definition as above, only they may depend on the interplay of progression of both TB and HIV, hence are functions of both a and b. The γ terms imply enhanced susceptibility to disease - TB-positive individuals are more susceptible to HIV ($\gamma_T(a)$) and HIV-positive individuals are more susceptible to acquiring TB ($\gamma_H(b)$). Those enhancements may depend on the progression of the appropriate disease, hence are time-since-infection dependent. $\mu_i, i = S, T, H, B$, are the mortality rates, some being time-since-infection dependent. Λ is the constant recruitment rate of susceptibles.

The following conditions apply:
$T(.,t)$ and $H(.,t) \in W^{1,1}(\mathbb{R}_+)$,
$S(.), T(a,.)$, and $H(b,.) \in C^1(\mathbb{R}_+)$,
$B(.,.,t) \in W^{1,1}(\mathbb{R}_+^2)$,
$T_0(.)$ and $H_0(.) \in L^1(\mathbb{R}_+)$, while $B_0(.,.) \in L^1(\mathbb{R}_+^2)$.
Furthermore, let:
$\alpha^T(.), \alpha^B(.), \beta^H(.), \beta^B(.), \gamma_T(.), \gamma_H(.) \in L^\infty(\mathbb{R})$ and be non-negative.
Therefore, $f_H(.,t), g_T(.,t) \in L^\infty(\mathbb{R})$ and ≥ 0.

We also define $\alpha^T, \alpha^B, \beta^H, \beta^B, \gamma_T$, and $\gamma_H(.)$ to be 0 on $(-\infty, 0)$. This allows us to simplify the expressions for the solutions in the paragraphs below.

Let us also assume that $\exists \underline{\mu} > 0$, such that:
$\mu_S \geq \underline{\mu}$,
$\mu_T(a) \geq \underline{\mu}, \forall a \in [0, \infty)$,
$\mu_H(b) \geq \underline{\mu}, \forall b \in [0, \infty)$, and
$\mu_B(a, b) \geq \underline{\mu}, \forall a, b \in [0, \infty)$.

Furthermore, let us assume that
$\lim_{a\to\infty} T(a, t) = \lim_{b\to\infty} H(b, t) = 0, \forall t \geq 0$,
$\lim_{a\to\infty} B(a, b, t) = 0, \forall b, t \geq 0$, and
$\lim_{b\to\infty} B(a, b, t) = 0, \forall a, t \geq 0$.

Using the method of characteristics,

$$T(a,t) = \begin{cases} T_0(a-t)e^{-\int_0^t g_T(s-t+a,s)+\mu_T(s-t+a)ds}, & a > t \\ f_S(t-a)S(t-a)e^{-\int_0^a g_T(s,s+t-a)+\mu_T(s)ds}, & t > a, \end{cases} \tag{3}$$

$$H(b,t) = \begin{cases} H_0(b-t)e^{-\int_0^t f_H(s-t+b,s)+\mu_H(s-t+b)ds}, & b > t \\ g_S(t-b)S(t-b)e^{-\int_0^b f_H(s,s+t-b)+\mu_H(s)ds}, & t > b. \end{cases} \tag{4}$$

Let:

$$t - a = c, t - b = d, t_0 = \max\{0, c, d\}, \text{ and } B^0(t) := B(t - c, t - d, t).$$

Then $\dfrac{dB^0(t)}{dt} = -\mu_B(t - c, t - d)B^0(t)$, therefore:

$$B^0(t) = B^0(t_0)e^{\int_{t_0}^t \mu_B(s-c,s-d)ds}.$$

The cases will be given by the order of $0, c$, and d for determining t_0.

If $0 > c > d$, then $t < a < b$ and if $0 > d > c$, then $t < b < a$ and $t_0 = 0$. In those cases, the solution is

$$B(a, b, t) = B_0(a - t, b - t)e^{-\int_0^t \mu_B(s-t+a,s-t+b)ds}.$$

If $c > 0 > d$, then $b > t > a$ and if $c > d > 0$, then $t > b > a$, and $t_0 = c$. The solution in those cases has the following expression:

$$\begin{aligned} B(a, b, t) &= B(0, b - a, t - a)e^{-\int_0^a \mu_B(s,s+b-a)ds} \\ &= \gamma_H(b - a)f_S(t - a)H(b - a, t - a)e^{-\int_0^a \mu_B(s,s+b-a)ds}. \end{aligned}$$

If $d > c > 0$, then $t > a > b$ and if $d > 0 > c$, then $a > t > b$, $t_0 = d$. In those cases the solution is:

$$\begin{aligned} B(a, b, t) &= B(a - b, 0, t - b)e^{-\int_0^b \mu_B(s+a-b,s)ds} \\ &= \gamma_T(a - b)g_S(t - b)T(a - b, t - b)e^{-\int_0^b \mu_B(s+a-b,s)ds}. \end{aligned}$$

Then,

$$B(a,b,t) = \begin{cases} B_0(a-t,b-t)e^{-\int_0^t \mu_B(s-t+a,s-t+b)ds}, & \text{if } t < a < b \text{ or } t < b < a \\ B(0,b-a,t-a)e^{-\int_0^a \mu_B(s,s+b-a)ds}, & \text{if } a < t < b \text{ or } a < b < t \\ B(a-b,0,t-b)e^{-\int_0^b \mu_B(s+a-b,s)ds}, & \text{if } b < a < t \text{ or } b < t < a. \end{cases} \tag{5}$$

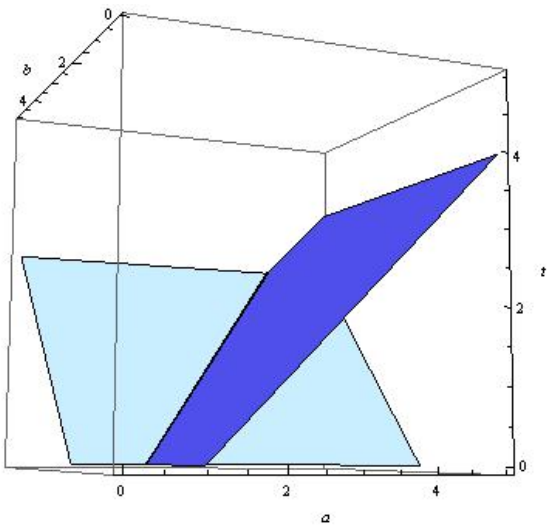

FIGURE 1. A characteristic line from the intersection of the planes $t-a=c$ and $t-b=d$, in the case when $d<c<0$.

Since f, g, γ, and μ are defined to be 0 on $(-\infty, 0)$, the above expression simplifies to:

$$B(a,b,t)=\begin{cases} B_0(a-t,b-t)e^{-\int_0^t \mu_B(s-t+a,s-t+b)ds}, & \text{if } t<a<b \text{ or } t<b<a \\ B(0,b-a,t-a)e^{-\int_0^a \mu_B(s,s+b-a)ds}+ & \\ B(a-b,0,t-b)e^{-\int_0^b \mu_B(s+a-b,s)ds}, & \text{otherwise.} \end{cases} \tag{6}$$

The characteristic lines are the intersections of the planes $t-a=c$ and $t-b=d$ in the $abt-$space. An example of a characteristic line in the case when $t<a<b$ is given by Figure 1 and for the case when $t<b<a$, by Figure 2. Since the solutions in those regions match, the characteristic lines create the region $t<a<b \cup t<b<a$, seen in Figure 3.

It is easy to show that the solution of System 1 is non-negative for all $t \geq 0$. Further, note that:

If $a>t, \lim_{t\to\infty}||T(.,t)||_1=0$, if $b>t, \lim_{t\to\infty}||H(.,t)||_1=0$, and if $t<a<b$ or $t<b<a, \lim_{t\to\infty}||B(.,.,t)||_1=0$. Therefore, when considering solutions at the equilibria, we will only consider the second expressions in (3), (4), and (6).

3. **Basic reproduction numbers.** We calculate the basic reproduction numbers at the disease free equilibrium (DFE) $(\Lambda/\mu^S, 0, 0, 0)$. We assume constant total population size, so let $\mu_S=\mu_T(a)=\mu_H(b)=\mu_B(a,b)$. Then $N(t)=\Lambda/\mu_S$ and hence, for the DFE, $S^0=\Lambda/\mu_S$. The original notation will be kept to help with interpretation. Using (1) and (3), the reproduction number for TB reduces to solving:

$$f_S(t)=\int_0^\infty \alpha^T(a) f_S(t-a) e^{-\int_0^a \mu_T(s)ds}.$$

Note, $H=0$, $B=0$, $\gamma=0$. We look for the solutions of the linear operator at the equilibrium, so solutions of the form $f_S(t)=\bar{f_S}e^{\lambda t}$, where λ is an eigenvalue of the

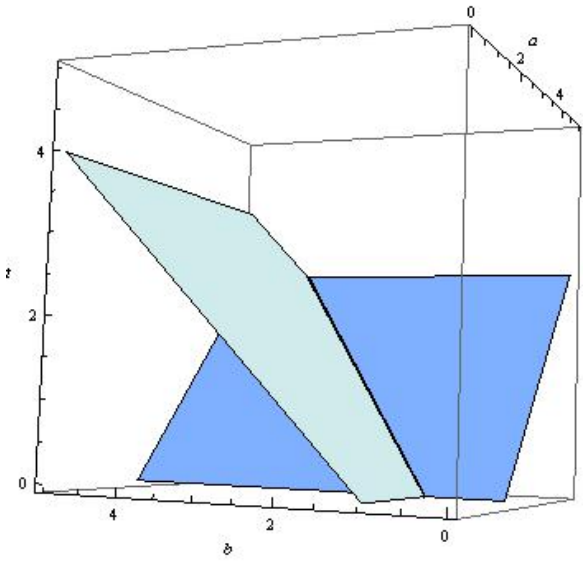

FIGURE 2. A characteristic line from the intersection of the planes $t - a = c$ and $t - b = d$, in the case when $c < d < 0$.

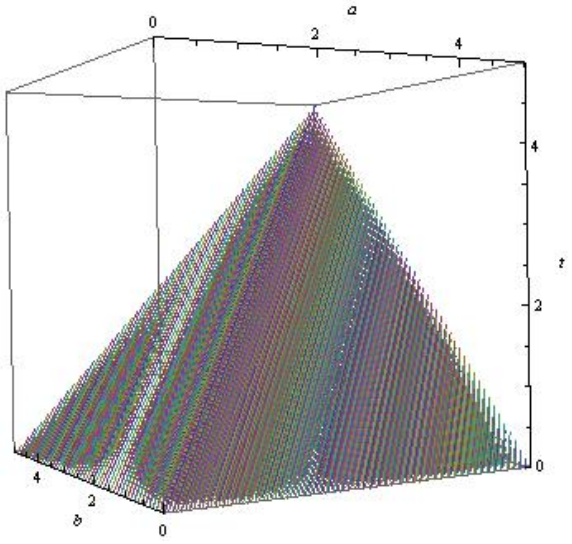

FIGURE 3. A collection of characteristic lines in the region $t < a < b \cup t < b < a$.

linear operator and $\bar{f}_S$ is a positive constant. Substituting in, we can define

$$G(\lambda) := \int_0^\infty \alpha^T(a) e^{-\lambda a} e^{-\int_0^a \mu_T(s)ds} = 1.$$

The characteristic function G is positive, monotonically decreasing, therefore we can define $R_0^T = G(0)$, i.e.

$$R_0^T = \int_0^\infty \alpha^T(a) e^{-\int_0^a \mu_T(s)ds}\, da. \tag{7}$$

If we look at the impression, it simply gives the total number of people a TB-infections individual will infect throughout his/her period of infection. Similarly, with (1) and (4) we get:

$$R_0^H = \int_0^\infty \beta^H(b) e^{-\int_0^b \mu_H(s)ds}\, db. \tag{8}$$

The following theorem uses all assumptions up to now.

Theorem 3.1. *The DFE of (1) is locally asymptotically stable if $R_0^T < 1$ and $R_0^H < 1$ and unstable if either $R_0^T > 1$ or $R_0^H > 1$.*

Proof. Since the total population $N(t)$ is constant, we will reduce the system by eliminating $S(t)$ and following the dynamics of the disease classes. Let $T(a,t) = T^0(a) + y(a,t), H(b,t) = H^0(b) + z(b,t), B(a,b,t) = B^0(a,b) + w(a,b,t)$. The system will be linearized around the DFE and we seek eigenvalues of the linear operator, i.e. we will assume solutions of the type: $y(a,t) = \bar{y}(a)e^{\lambda t}, z(b,t) = \bar{z}(b)e^{\lambda t}$, and $w(a,b,t) = \bar{w}(a,b)e^{\lambda t}$. Note that, since we are considering the DFE, $T^0(a) = H^0(b) = B^0(a,b) = 0$. Also, let $\bar{y} > 0, \bar{z} > 0$, otherwise one of the diseases is not present, which simply reduces the system and is a special case of the argument below. Under these assumptions, system (1), linearized around the DFE, becomes:

$$\begin{cases} \dfrac{\partial \bar{y}(a)}{\partial a} + \lambda \bar{y}(a) = -\mu_T(a)\bar{y}(a) \\ \dfrac{\partial \bar{z}(b)}{\partial b} + \lambda \bar{z}(b) = -\mu_H(b)\bar{z}(b) \\ \dfrac{\partial \bar{w}(a,b)}{\partial a} + \dfrac{\partial \bar{w}(a,b)}{\partial b} + \lambda \bar{w}(a,b) = -\mu_B(a,b)\bar{w}(a,b) \\ \bar{y}(0) = \displaystyle\int_0^\infty \alpha^T(a)\bar{y}(a)\, da + \int_0^\infty \int_0^\infty \alpha^B(a,b)\bar{w}(a,b)\, da\, db \\ \bar{z}(0) = \displaystyle\int_0^\infty \beta^H(b)\bar{z}(b)\, db + \int_0^\infty \int_0^\infty \beta^B(a,b)\bar{w}(a,b)\, da\, db \\ \bar{w}(0,b) = 0 \\ \bar{w}(a,0) = 0. \end{cases} \tag{9}$$

First, it is easy to see that $\bar{w}(a,b) = 0$. Therefore, we can reduce the system to:

$$\begin{cases} \dfrac{\partial \bar{y}(a)}{\partial a} + \lambda \bar{y}(a) = -\mu_T(a)\bar{y}(a) \\ \dfrac{\partial \bar{z}(b)}{\partial b} + \lambda \bar{z}(b) = -\mu_H(b)\bar{z}(b) \\ \bar{y}(0) = \displaystyle\int_0^\infty \alpha^T(a)\bar{y}(a)\, da \\ \bar{z}(0) = \displaystyle\int_0^\infty \beta^H(b)\bar{z}(b)\, da. \end{cases} \tag{10}$$

Let us consider the first equation of (10) and the corresponding boundary condition. It is easy to show that

$$\bar{y}(0) = \int_0^\infty \alpha^T(a)\bar{y}(0) e^{-\int_0^a \lambda + \mu_T(s)\, ds}\, da. \tag{11}$$

Similarly, from the second equation in (10),

$$\bar{z}(0) = \int_0^\infty \beta^H(b)\bar{z}(0)e^{-\int_0^b \lambda+\mu_H(s)\ ds}\ db. \tag{12}$$

Define:

$$K_T(\lambda) := \int_0^\infty \alpha^T(a)e^{-\int_0^a \lambda+\mu_T(s)\ ds}\ da \tag{13}$$

and

$$K_H(\lambda) := \int_0^\infty \beta^H(b)e^{-\int_0^b \lambda+\mu_H(s)\ ds}\ db. \tag{14}$$

Then, (11), (12), (13),and (14) can be combined in the system:

$$A\vec{u} = \vec{0}, \tag{15}$$

where

$$A = \begin{pmatrix} K_T(\lambda) - 1 & 0 \\ 0 & K_H(\lambda) - 1 \end{pmatrix}, \vec{u} = \begin{pmatrix} \bar{y}(0) \\ \bar{z}(0) \end{pmatrix}.$$

λ is an eigenvalue of (10) if and only if $\det(A) = 0$ (see [13]), i.e. the eigenvalues are the solutions of $K_T(\lambda) = 1$ and $K_H(\lambda) = 1$. K_T and K_H are monotonically decreasing functions of λ, $\lim_{\lambda\to\infty} K_T(\lambda) = \lim_{\lambda\to\infty} K_H(\lambda) = 0$, and $\lim_{\lambda\to-\infty} K_T(\lambda) = \lim_{\lambda\to-\infty} K_H(\lambda) = \infty$ for real λ. Therefore, using standard techniques, it is easy to show that $K_T(\lambda) = 1$ has a real solution and this solution is the leading root of the equation. Let us call it λ^T. Same holds for $K_H(\lambda)$, so let us call that dominant eigenvalue λ^H. Further, $K_T(0) = R_0^T, K_H(0) = R_0^H$. Therefore, if $R_0^T < 1$, $\lambda^T < 0$ and if $R_0^H < 1, \lambda^H < 0$. Therefore, if $\lambda_0 = max\{\lambda^T, \lambda^H\}$, λ_0 is the dominant eigenvalue of System 15 and $\lambda_0 < 0$. However, if either $R_0^T > 1$ or $R_0^H > 1$, $\lambda_0 > 0$. Therefore, if both R_0^H and R_0^T are less than 1, the DFE is locally asymptotically stable. If, however, either basic reproduction number is greater than 1, the DFE is unstable. □

4. **Invasion reproduction number for TB, R_H^T.** We consider the HIV-endemic equilibrium, $(S^0, 0, H^0(b), 0)$. Note, we keep our population constant again and $N(t) = N^0 = S^0 + \int_0^\infty H^0(b)\ db$.

Let the following be defined:

$$\begin{aligned} \eta_T(t) &= \int_0^\infty \alpha^T(a)T(a,t)\ da, \\ \eta_B(t) &= \int_0^\infty \int_0^\infty \alpha^B(a,b)B(a,b,t)\ da\ db, \\ \phi_H(t) &= \int_0^\infty \beta^H(b)H(b,t)\ db, \\ \phi_B(t) &= \int_0^\infty \int_0^\infty \beta^B(a,b)B(a,b,t)\ da\ db. \end{aligned} \tag{16}$$

Since we are considering the HIV-endemic equilibrium, we define

$$\phi_H^0 := \int_0^\infty \beta^H(b)H^0(b)\ db. \tag{17}$$

Hence, we can rewrite (2) as:

$$\begin{aligned} f_S(t) &= \frac{\eta_T(t)}{N^0} + \frac{\eta_B(t)}{N^0}, \\ f_H(b,t) &= \gamma_H(b) f_S(t), \\ g_S(t) &= \frac{\phi_H^0}{N^0} + \frac{\phi_B(t)}{N^0}, \\ g_T(a,t) &= \gamma_T(a) g_S(t). \end{aligned} \tag{18}$$

We linearize around the HIV-endemic equilibrium, and the system is reduced to:

$$\begin{cases} T(a,t) = & [\eta_T(t-a) + \eta_B(t-a)] \dfrac{S^0}{N^0} M^T(a) \\ B(a,b,t) = & [\eta_T(t-a) + \eta_B(t-a)] \gamma_H(b-a) \dfrac{H^0(b-a)}{N^0} e^{-\int_0^a \mu_B(s,s+b-a)ds} \\ & + T(a-b,t-b)\gamma_T(a-b) \dfrac{\phi_H^0}{N^0} e^{-\int_0^b \mu_B(s+a-b,s)ds} \\ & = [\eta_T(t-a) + \eta_B(t-a)] \gamma_H(b-a) \dfrac{H^0(b-a)}{N^0} M^B(a,b) \\ & + [\eta_T(t-a-b) + \eta_B(t-a-b)] \dfrac{S^0}{N^0} P^T(a,b), \end{cases} \tag{19}$$

where

$$\begin{aligned} M^T(a) &:= e^{-\int_0^a \gamma_T(s) \frac{\phi_H^0}{N^0} + \mu_T(s)\ ds}, \\ M^B(a,b) &:= e^{-\int_0^a \mu_B(s,s+b-a)ds}, \\ P^T(a,b) &:= e^{-\int_0^{a-b} \gamma_T(s) \frac{\phi_H^0}{N^0} + \mu_T(s)ds} \gamma_T(a-b) \frac{\phi_H^0}{N^0} e^{-\int_0^b \mu_B(s+a-b,s)ds}. \end{aligned}$$

Multiply both sides of the first equation in (19) by $\alpha^T(a)$ and integrate from 0 to ∞ with respect to a. The result is:

$$\eta_T(t) = \int_0^\infty [\eta_T(t-a) + \eta_B(t-a)] \alpha^T(a) \frac{S^0}{N^0} M^T(a) da.$$

Multiply both sides of the second equation in (19) by $\alpha^B(a,b)$ and integrate from 0 to ∞ with respect to a and again, with respect to b. Then,

$$\begin{aligned} \eta_B(t) = & \int_0^\infty \int_0^\infty [\eta_T(t-a-b) + \eta_B(t-a-b)] \times \\ & \alpha^B(a,b) \gamma_H(b-a) \frac{H^0(b-a)}{N^0} M_B(a,b)\ da\ db \\ & + \int_0^\infty \int_0^\infty [\eta_T(t-a-b) + \eta_B(t-a-b)] \alpha^B(a,b) \frac{S^0}{N^0} P^T(a,b)\ da\ db. \end{aligned}$$

We are looking for the eigenvalues of the linear operator, i.e. we are looking for solutions of the type $\eta_i(t) = \bar{\eta_i} e^{\lambda t}, i = T, B$. With some simplifications, the system becomes:

$$\begin{cases} \bar{\eta_T} = \pi_1(\lambda)\bar{\eta_T} + \pi_1(\lambda)\bar{\eta_B} \\ \bar{\eta_B} = \pi_2(\lambda)\bar{\eta_T} + \pi_2(\lambda)\bar{\eta_B} + \pi_3(\lambda)\bar{\eta_T} + \pi_3(\lambda)\bar{\eta_B}, \end{cases} \tag{20}$$

where

$$\pi_1(\lambda) := \int_0^\infty e^{-\lambda a}\alpha^T(a)\frac{S^0}{N^0}M^T(a)da,$$
$$\pi_2(\lambda) := \int_0^\infty \int_0^\infty e^{-\lambda a}\alpha^B(a,b)\gamma_H(b-a)\frac{H^0(b-a)}{N^0}M_B(a,b)\ da\ db,$$
$$\pi_3(\lambda) := \int_0^\infty \int_0^\infty e^{-\lambda(a+b)}\alpha^B(a,b)\frac{S^0}{N^0}P^T(a,b)\ da\ db.$$

The characteristic equation is $\pi_1(\lambda)+\pi_2(\lambda)+\pi_3(\lambda)=1$. Let $G(\lambda)=\sum_{j=1}^3\pi_j(\lambda)$. Then, since G is a monotonic decreasing function of λ, the reproduction number we are looking for is $G(0)$. Further, let $W_H := S^0 + \int_0^\infty \gamma_H(b)H^0(b)\ db$. W_H is the "weighted susceptible to TB population." W_H is a "weighted population," since HIV-positive individuals have higher susceptibility to TB, expressed through the function (weight) $\gamma_H(b)$. Then, with a slight rearrangement,

$$\begin{aligned}
&R_H^T = \\
&\frac{S^0}{W_H}\int_0^\infty \alpha^T(a)M^T(a)\ da\frac{S^0}{N^0}+ \\
&\frac{S^0}{W_H}\int_0^\infty \alpha^T(a)M^T(a)\ da\frac{\int_0^\infty \gamma_H(b)H^0(b)\ db}{N^0}+ \\
&\int_0^\infty\int_0^\infty \frac{\gamma_H(b-a)H^0(b-a)}{W_H}\alpha^B(a,b)M^B(a,b)\ da\ db\frac{S^0}{N^0}+ \\
&\int_0^\infty\int_0^\infty \frac{\gamma_H(b-a)H^0(b-a)}{W_H}\alpha^B(a,b)M^B(a,b)\ da\ db\frac{\int_0^\infty \gamma_H(b)H^0(b)\ db}{N^0}+ \\
&\frac{S^0}{W_H}\int_0^\infty\int_0^\infty \alpha^B(a,b)P^T(a,b)\ da\ db\frac{S^0}{N^0}+ \\
&\frac{S^0}{W_H}\int_0^\infty\int_0^\infty \alpha^B(a,b)P^T(a,b)\ da\ db\frac{\int_0^\infty \gamma_H(b)H^0(b)\ db}{N^0}.
\end{aligned} \tag{21}$$

Note that the sum of the first two terms, the second two terms, and the third two terms are $\pi_1(0), \pi_2(0)$, and $\pi_3(0)$, respectively.

$M^T(a)$ is the probability that an individual who has only TB with time-since-infection a, will not acquire HIV or die. $M^B(a,b)$ is the survival probability for an individual with TB time-since-infection a and HIV time-since-infection b. $P^T(a,b)$ is more involved. $\gamma_T(a-b)\phi_H^0/N^0$ is the rate with which individuals with only TB acquire HIV at TB time-since-infection $a-b$. So, $P^T(a,b)$ is the probability that a TB-positive individual with TB time-since-infection $a-b$ will get infected with HIV and survive as a co-infected individual with TB time-since-infection a and HIV time-since-infection b.

Consider the first term in (21). S^0/W_H is the probability that the first person infected with TB, patient 0, will be from the susceptible population. $\int_0^\infty \alpha^T(a)M^T(a)\ da$ is number of individuals this now TB-positive person will infect before dying or acquiring HIV. S^0/N^0 and $\int_0^\infty \gamma_H(b)H^0(b)\ db/N^0$ determine how many of each TB-susceptible class this initial TB-positive person will infect - susceptibles or HIV-positive individuals, respectively.

The third and fourth terms have similar explanations as above, only this time the initial carrier of TB is originally HIV-positive, given by the probability $\gamma_H(b-a)H^0(b-a)/W_H$, who becomes co-infected.

The fifth and sixth terms count the individuals a person who started in the susceptible class S^0/W_H, acquired TB, and then acquired HIV (integrating P^T gives the probability an individual in the TB class acquires HIV before dying), will infect before dying.

A graphical interpretation of all terms can be seen in Figure 4.

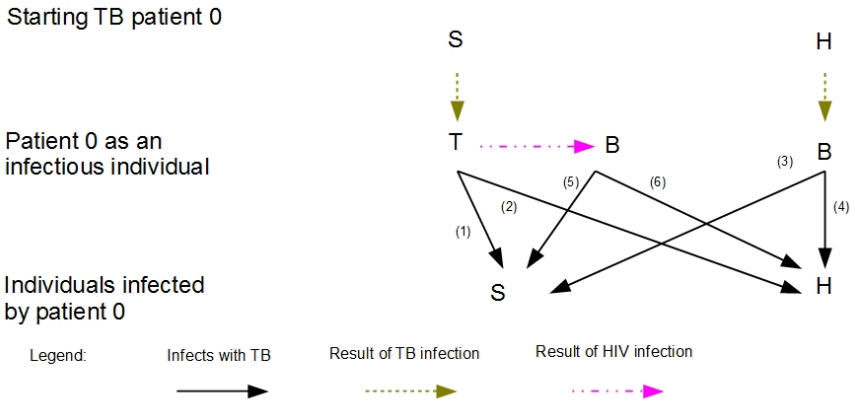

FIGURE 4. Transmission dynamics described by R_H^T. The numbers next to the arrows correspond to the order of the terms in the definition of R_H^T given by (21).

5. **Invasion reproduction number for HIV, R_T^H.** Similarly, we want to calculate the HIV invasion reproduction number at the TB-endemic equilibrium $(S^0, T^0(a), 0, 0)$. We, again, want to keep the population constant, i.e.

$$N^0 = S^0 + \int_0^\infty T^0(a)\ da.$$

We will use the expressions defined in (16). However, let

$$\eta_T^0 := \int_0^\infty \alpha^T(a)T^0(a)\ da.$$

There is a symmetry to the model when considering HIV and TB, so the method for calculating R_T^H is identical to the one used for R_H^T. Furthermore, the interpretation is in parallel with what was done for R_H^T, just inverting the disease and appropriate terms. Hence, R_T^H is given by (22) and the interpretation is sufficiently summarized in Figure 5:

$$\begin{aligned} R_T^H = & \\ & \frac{S^0}{W_T}\int_0^\infty \beta^H(b)D^H(b)\ db\frac{S^0}{N^0} + \\ & \frac{S^0}{W_T}\int_0^\infty \beta^H(b)D^H(b)\ db\frac{\int_0^\infty \gamma_H(a)T^0(a)\ da}{N^0} + \\ & \int_0^\infty\int_0^\infty \beta^B(a,b)D^B(a,b)\frac{\gamma_T(a-b)T^0(a-b)}{W_T}\ da\ db\frac{S^0}{N^0} + \end{aligned}$$

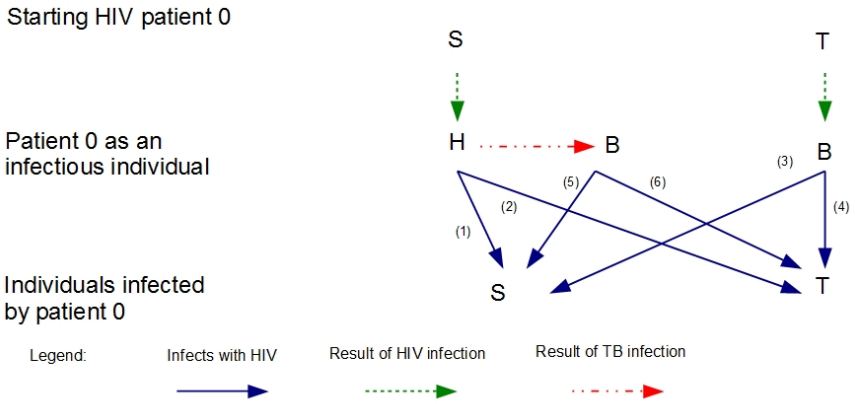

FIGURE 5. Transmission dynamics described by R_T^H. The numbers next to the arrows correspond do the order of the terms in the definition of R_T^H in (22).

$$\int_0^\infty \int_0^\infty \beta^B(a,b)D^B(a,b)\frac{\gamma_T(a-b)T^0(a-b)}{W_T}\,da\,db\frac{\int_0^\infty \gamma_H(a)T^0(a)\,da}{N^0}+$$
$$\frac{S^0}{W_T}\int_0^\infty \int_0^\infty \beta^B(a,b)P^H(a,b)\,da\,db\frac{S^0}{N^0}+ \tag{22}$$
$$\frac{S^0}{W_T}\int_0^\infty \int_0^\infty \beta^B(a,b)P^H(a,b)\,da\,db\frac{\int_0^\infty \gamma_H(a)T^0(a)\,da}{N^0},$$

where

$$W_T := S^0 + \int_0^\infty \gamma_T(a)T^0(a)\,da,$$
$$D^H(b) := e^{-\int_0^b \gamma_H(s)\frac{\eta_T^0}{N^0}+\mu_H(s)\,ds},$$
$$D^B(a,b) := e^{-\int_0^b \mu_B(s+a-b,s)\,ds},$$
$$P^H(a,b) := e^{\int_0^{b-a} \gamma_H(s)\frac{\eta_T^0}{N^0}+\mu_H(s)\,ds}\gamma_H(b-a)\frac{\eta_T^0}{N^0}e^{-\int_0^a \mu_B(s,s+b-a)ds}.$$

6. **Importance of age structure.** Adding time-since-infection to a disease model increases the difficulty of the mathematical analysis. However, by tracking the disease age one can implement more strategies for fighting the disease. In this section, we will present the difference between implementation of TB treatment in the model with time-since-infection versus a simplified total population ordinary differential equation model. We will compare the resulting different values for R_0^T and R_H^T from using the same treatment strategy for either model. The expression for R_0^T when incorporating time-since infection is given by (7) and for R_H^T by (21). For the equivalent, total population ODE model, the expressions are:

$$R_0^{T,ode} = \frac{\alpha^T}{\mu_T}, \tag{23}$$

$$R_H^{T,ode} = \frac{S^0}{N^0}\frac{\alpha^T}{\gamma_T\beta^H\frac{H^0}{N^0}+\mu_T} + \frac{S^0}{N^0}\alpha^B\frac{\gamma_T\beta^H\frac{H^0}{N^0}}{\gamma_T\beta^H\frac{H^0}{N^0}+\mu_T}\frac{1}{\mu_B} + \frac{\gamma_H H^0}{N^0}\alpha^B\frac{1}{\mu_B}, \tag{24}$$

TABLE 1. Parameter values for reproduction number calculations

Parameter	Value
μ	0.02 year^{-1}
γ_T	1
γ_H	1
S^0	100,000 people
H^0	10,000 people
N^0	110,000 people
β^H	0.025 year^{-1}
β^B	0.025 year^{-1}

where $\alpha^T, \alpha^B, \beta^H$, and β^B are constants. The values used for the comparison will be theoretical, used simply to illustrate the importance of considering time-since-infection. We will also introduce two new parameters. ρ is the fraction of TB-infected individuals (we will assume it to be the same for the T and B classes) that are treated. We assume that TB treatment only influences the transmission rate α^T and reduces it by a factor of 5. Furthermore, let θ be the moment in the disease progression when the treatment is implemented. It will not be applied to the ODE reproduction numbers but will be important for the PDE ones. For a fair comparison, all variables will be kept constant besides $\alpha^T(a)$ and $\alpha^B(a,b)$. The parameter values are in Table 1. Let

$$\alpha^T(a) = \alpha^B(a,b) = \begin{cases} 0, \text{if } a < 3 \text{ and } a > 13 \\ 0.175734, \text{if } 3 \leq a \leq 13 \end{cases} \quad \text{years}^{-1}$$

and for the ODE reproduction numbers, $\alpha^T = \alpha^B = 0.03$. The definition of $\alpha^T(a)$ above is constructed in such a way as to equate the R_0^T for both models. A further assumption is that on average people develop active TB 3 years after infection and stop infecting others 10 years after that. Under these assumptions, the control reproduction numbers i.e. the values of the reproduction numbers when we consider treatment, are the following expressions:

$$\begin{aligned}
R_{0,c}^{T,ode} &= \rho \frac{0.2\alpha^T}{\mu_T} + (1-\rho) R_0^{T,ode}, \\
R_{H,c}^{T,ode} &= (1-\rho) R_H^{T,ode} + \\
&\quad \rho \left[\frac{S^0}{N^0} \frac{0.2\alpha^T}{\gamma_T \beta^H \frac{H^0}{N^0} + \mu_T} + \frac{S^0}{N^0} 0.2\alpha^B \frac{\gamma_T \beta^H \frac{H^0}{N^0}}{\gamma_T \beta^H \frac{H^0}{N^0} + \mu_T} \frac{1}{\mu_B} \right] + \\
&\quad \rho \left[\frac{\gamma_H H^0}{N^0} 0.2\alpha^B \frac{1}{\mu_B} \right], \\
R_{0,c}^{T} &= (1-\rho) R_0^{T} + \\
&\quad \rho \left[\int_0^\theta \alpha^T(a) e^{-\int_0^a \mu_T(s) ds} \, da + \int_\theta^\infty 0.2\alpha^T(a) e^{-\int_0^a \mu_T(s) ds} \, da \right], \\
R_{H,c}^{T} &= (1-\rho) R_H^{T} + \\
&\quad \rho \frac{S^0}{N^0} \int_0^\theta \alpha^T(a) M^T(a) \, da +
\end{aligned}$$

TABLE 2. Control Reproduction Numbers Comparison

	No control	$\rho = 0.3$			$\rho = 0.5$			$\rho = 0.6$		
$R_{0,c}^{T,ode}$	1.5	1.14			0.9			0.78		
$R_{H,c}^{T,ode}$	1.5	1.14			0.9			0.78		
		$\theta = 4$	$\theta = 5$	$\theta = 6$	$\theta = 4$	$\theta = 5$	$\theta = 6$	$\theta = 4$	$\theta = 5$	$\theta = 6$
$R_{0,c}^{T}$	1.5	1.18	1.22	1.26	0.97	1.03	1.09	0.86	0.94	1.01
$R_{H,c}^{T}$	1.48	1.16	1.20	1.24	0.95	1.02	1.08	0.85	0.92	1

$$
\begin{aligned}
&\rho\frac{S^0}{N^0}\int_\theta^\infty 0.2\alpha^T(a)M^T(a)\ da+\\
&\rho\int_0^\infty\int_0^\theta \frac{\gamma_H(b-a)H^0(b-a)}{N^0}\alpha^B(a,b)M^B(a,b)\ da\ db+\\
&\rho\int_0^\infty\int_\theta^\infty \frac{\gamma_H(b-a)H^0(b-a)}{N^0}0.2\alpha^B(a,b)M^B(a,b)\ da\ db+\\
&\rho\frac{S^0}{N^0}\int_0^\infty\int_0^\theta \alpha^B(a,b)P^T(a,b)\ da\ db+\\
&\rho\frac{S^0}{N^0}\int_0^\infty\int_\theta^\infty 0.2\alpha^B(a,b)P^T(a,b)\ da\ db.
\end{aligned}
\tag{25}
$$

Table 2 shows the calculations of the control reproduction numbers for different values of ρ and θ. The slightly lower values for $R_{H,c}^T$ are due to the finite support of the integrals. Also, γ_H was taken to be 1, which means that for the purposes of this calculation, and for simplicity, HIV-individuals were not considered more susceptible to tuberculosis. Looking at Table 2, one can see that there are situations when $R_{0,c}^{T,ode}$ and $R_{H,c}^{T,ode}$ are less than 1, while when θ is sufficiently large, $R_{0,c}^T$ and $R_{H,c}^T$ are both greater than 1. In other words, if individuals remain untreated a longer time after developing acute TB, then treatment will not be as effective, and more importantly, will give a false sense of security if the disease is modeled using only ordinary differential equations. This demonstrates the importance of using time-since-infection in the model. More on these results can be read in Section 8.

7. **Numerical simulations.** The numerical simulations explore four scenarios for the interplay between the values of the TB reproduction numbers. The purpose of this section is to verify the role of the reproduction numbers in the population dynamics. Since the system is symmetric, similar observations to the one presented here can be made about the HIV reproduction numbers, therefore they were not simulated. Furthermore, for simplicity, we simulated the ODE reproduction numbers from the previous section: $R_0^{T,ode}$, seen in (23), and $R_H^{T,ode}$, seen in (24). Since treatment is omitted and we are not considering the control reproduction numbers, the ODE ones are sufficient to verify the behavior of the system. The scenarios are the following: $R_0^{T,ode} < 1$ and $R_H^{T,ode} < 1$ (Figure 6), $R_0^{T,ode} > 1$ and $R_H^{T,ode} > 1$ (Figure 7), $R_0^{T,ode} < 1$ and $R_H^{T,ode} > 1$ (Figure 8), and $R_0^{T,ode} > 1$ and $R_H^{T,ode} < 1$ (Figure 9). The parameters were chosen to produce the required values for the reproduction numbers and have little bearing with parameter values from the real world, hence are omitted.

Figures 6 and 7 describe the obvious scenarios: if both reproduction numbers are less than one, TB does not persist, and if both reproduction numbers are greater than one, the disease persists. Figure 8 explores the case when $R_0^{T,ode} < 1$ and $R_H^{T,ode} > 1$. It is a common scenario to use for justifying the computation of the

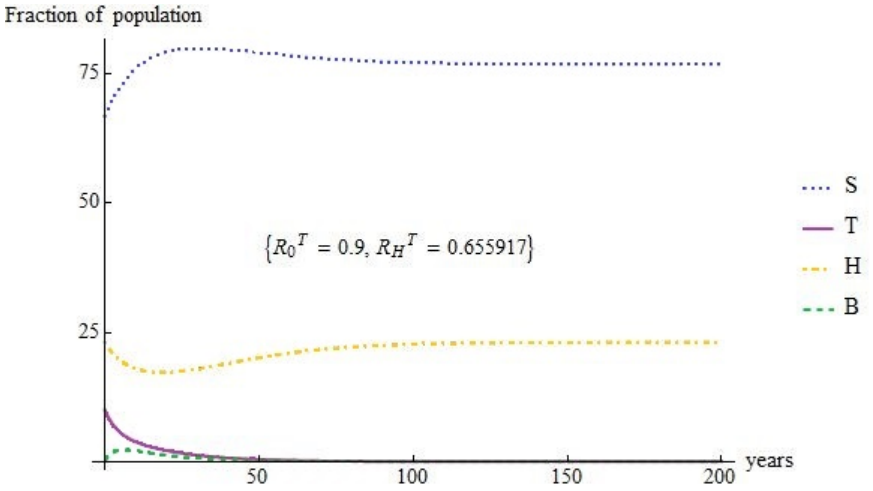

FIGURE 6. The case when $R_0^{T,ode}$ and $R_H^{T,ode} < 1$. TB dies out. The numbers in the center of the graph are $R_0^{T,ode}$ and $R_H^{T,ode}$, respectively.

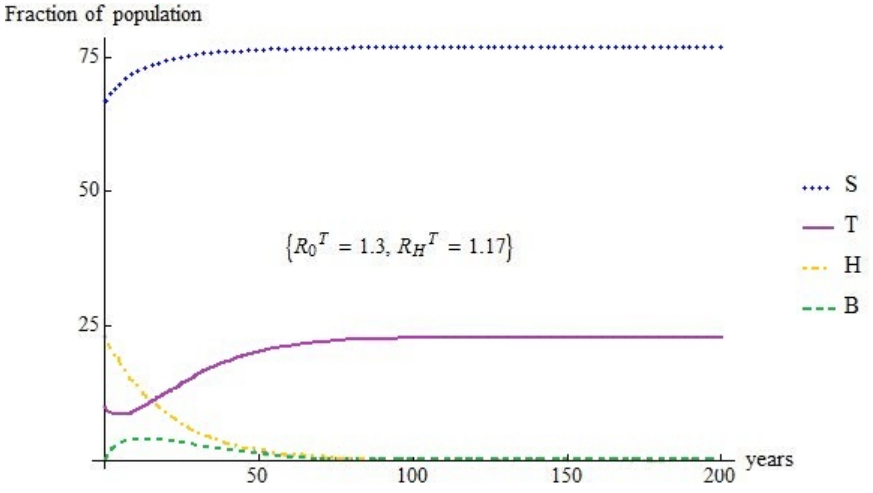

FIGURE 7. The case when $R_0^{T,ode}$ and $R_H^{T,ode} > 1$. TB is persistent. The numbers in the center of the graph are $R_0^{T,ode}$ and $R_H^{T,ode}$, respectively.

invasion reproduction number in the lack of analysis. TB persists, even though the basic reproduction number is less than one, because of the effect of the HIV endemic on the TB epidemic, which is reflected in the invasion reproduction number being greater than one. The last scenario, $R_0^T > 1$ and $R_H^T < 1$ is more interesting. When studying co-infection, it is often assumed that co-infection enhances infectivity (i.e. one would expect that $\alpha_B(a,b)$ is greater in magnitude than $\alpha_T(a)$). However, in this case, since TB and HIV, albeit correlated, are very different diseases in progression and mode of transmission, we cannot estimate with certainty the magnitude of

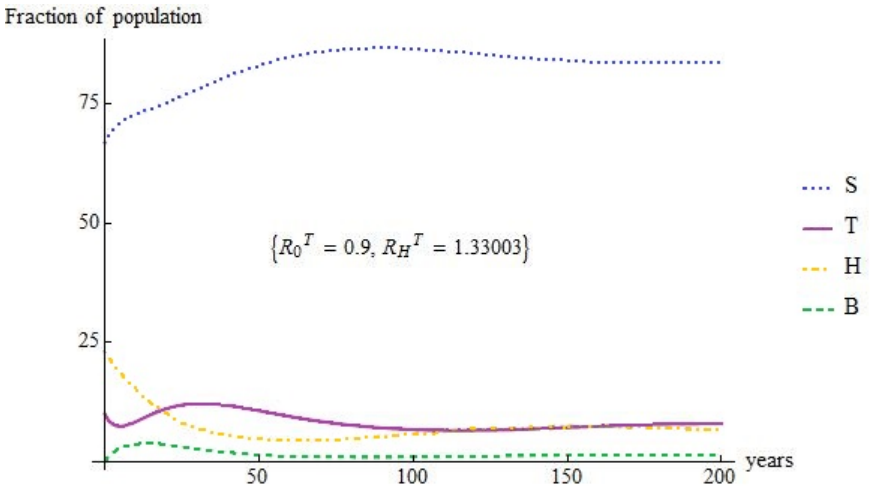

FIGURE 8. The case when $R_0^{T,ode} < 1$ and $R_H^{T,ode} > 1$. TB persists. The numbers in the center of the graph are $R_0^{T,ode}$ and $R_H^{T,ode}$, respectively.

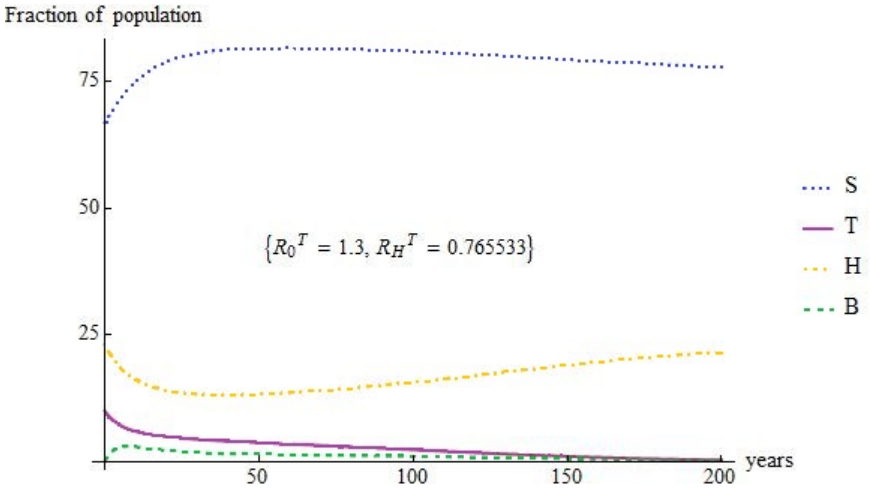

FIGURE 9. The case when $R_0^{T,ode} > 1$ and $R_H^{T,ode} < 1$. TB does not persist. This is an interesting case, which is discussed in Sections 7 and 8.

$\alpha_B(a,b)$ and its relationship with $\alpha_T(a)$, beyond $\alpha_B(a,0) = \alpha_T(a)$. Therefore, it is possible, when considering constant parameters, that $\alpha_B < \alpha_T$, which is reflected in the scenario. Under these conditions TB cannot persist. Of course, this scenario is hypothetical but may be useful when considering treatment and prevention strategies. An interpretation of this result is presented in the next section.

8. **Discussion.** This article presents a double age-structured co-infection model of HIV and TB. The age structure describes time since infection (disease age) for HIV

and TB, and tracks both when considering co-infected individuals. We incorporate a time-since-infection parameter for both HIV and TB since both diseases progress through several stages after acquisition which affect individuals' rate of transmission. Usually, the disease stages are modeled through using different population classes on an ODE system. The age-structure is mathematically more challenging, however allows for more flexibility when modeling the progression of the disease, and especially when implementing treatment and control strategies. A simple example of this phenomenon is given in Section 6. A substantial delay in treatment can produce quite different results if we consider a model of ordinary differential equations versus a time-since-infection model. The ODE model would give us a reduction of the reproduction numbers below 1, which would indicate that the epidemic is dying out, while the PDE model indicates that the reproduction numbers are still greater than 1, hence more effort would be required to control the epidemic. A long delay between the acute stage of tuberculosis and treatment is more usual in developing countries. Since TB is the most dangerous infectious disease in developing regions, accurate models are even more important. The current model is symmetric with respect to TB and HIV. Therefore, delay between treatment for either disease can be an important factor in battling the co-infection and would have to be considered. Still, whether the trade-off between mathematical complexity and control flexibility is worthwhile in practice remains a subject of future investigation.

Regarding the analysis of the current model, the basic and invasion reproduction numbers for each disease are calculated. The basic ones are established as thresholds for stability of the disease free equilibrium (Theorem 3.1). The invasion reproduction numbers are calculated using standard techniques. Analysis of the stability of the endemic equilibria remains topic for future work.

The influence of the invasion reproduction number is suggested by numerically simulating a scenario where TB persists if its basic reproduction number is less than one and its invasion reproduction number is greater than one (Figure 8). Consider Figure 9, the scenario where the TB invasion reproduction number is less than one, while the basic reproduction number is greater than one. It is important to note that the rate of TB transmission by co-infected individuals may not be directly dependent on the rate of TB transmission by individuals with only TB. HIV and TB have different modes of transmission - HIV is a sexually transmitted disease, while TB is airborne. Therefore, for a co-infected individual, the stage of progression of one disease may affect the infectivity of this individual with the other disease. For example, a co-infected person with acute TB may not be as willing to engage in sexual activities, so his sexual contacts will decrease, and hence his HIV infectivity rate. While not realistic in real life, as evident from the increase of TB cases since the introduction of HIV, the case when $R_H^T < 1$ and $R_0^T > 1$ hints at the possible importance of control, treatment, and detection of TB in co-infected individuals, which may reduce their HIV infectivity and vice versa. Furthermore, it is important to mention that the competition of both diseases for susceptible individuals may affect the invasion reproduction numbers for either disease. This is suggested by the persistence of HIV, evident in Figure 9. However, this topic is beyond the current work and will be explored further in the future.

The current article does not explore the shape of the curves that represent the infectivity rates $\alpha^T(a)$ and $\beta^H(b)$. The curves do not simply depend on viral load (for HIV) or bacterial load (for TB) and disease progression but on factors that

would determine the contact rate of individuals at different stages of disease progression. This idea is even more complex when one deals with individuals who are co-infected, because the two diseases have different modes of transmission and when constructing $\alpha^B(a,b)$ and $\beta^B(a,b)$, one has to deal with surfaces rather than just curves. The combination of behavioral changes and levels of infectiousness and how those would influence the transmission curves and surfaces will be explored in the future.

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