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Tuberculosis Model with Exogenous Reinfection and Treatment

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Authors' contributions

This work was carried out in collaboration among all authors. Authors EA, MARENO and IKA assisted in developing the model equations, writing of the draft, numerical simulations and review of the final draft. All authors read and approved the final manuscript.

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Abstract

The epidemiology of tuberculosis model, which includes exogenous reinfection and treatment, is analyzed. We consider both the diagnosed and the undiagnosed individuals as infectious. Since tuberculosis is treatable, we also included the treatment for diagnosed infective. We presented the basic reproduction number and the stability of the disease-free and endemic equilibria. We also analyzed the model when the exogenous re-infection is set to zero. The exogenous re-infection is shown to be capable of supporting multiple equilibria. Lastly, we presented the global stability and numerical simulations of the model.

Keywords: Next-generation matrix; stability; backward bifurcation; reproduction number.

1 Introduction

Tuberculosis (TB) is a type of infectious disease. The causation bacteria for TB is known as *Mycobacterium tuberculosis(M. tb)*. Mostly, it affects the lungs (pulmonary tuberculosis). The bacteria can also affect many

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other parts of the body. These are the central nervous system, the lymphatic system, the spine, or the kidney [1]. According to the Centers for Disease Control and Prevention (CDC) [2], an individual who is exposed to *M tuberculosis* is not able to spread the bacteria to other people right away. Only persons with active TB disease can spread TB bacteria to others. An individual can spread TB to others if active bacteria multiply in his body and cause active TB disease. At this point, he could transmit TB bacteria to susceptible persons. People with active TB are most likely to spread the bacteria to people they spend much time with every day, such as family members, friends, coworkers, or schoolmates. From the global TB report 2019 [1], TB was one of the top 10 causes of death worldwide in 2018. It is also the leading killer of people with HIV and a significant cause of deaths related to antimicrobial resistance. In 2018, there were an estimated 10 (9.0—11.1) million new TB cases worldwide, of which 5.7 million were men, 3.2 million were women, and 1.1 million were children. A higher number of the people who get infected with the *M. tuberculosis* don't progress to the active-TB class during their life. About 30% of individuals who get in touch with active TB patients become infected. TB significantly disturbs a more substantial portion of the population around the world, especially in places where it's more prevalent [3]. Moreover, TB is considered a significant cause of global death compared to other infectious diseases. According to the CDC [4], every year, about 2 billion people are infected with TB, and it claims approximately 2 million lives. TB disease poses an enormous health challenge in some developing countries. The disease kills many youths, young adults and ladies, especially those of childbearing age.

Both latent and active TB is treatable and curable. If TB patients are not treated early, it can kill about 60% of active patients. Further, if TB patients seek treatment, 90% of all cases can be cured [1]. TB patients are not contagious after two weeks of treatment. Since *M. tuberculosis* generally grows slowly, treatment for active infections usually takes six months to 1 year [5]. Generally, active TB cases may be put into two: pulmonary and extrapulmonary. Pulmonary cases affect the lungs. Extrapulmonary TB affects other organs besides the lungs: pleura, lymph nodes, abdomen, joints, and bones. Pulmonary TB cases are the most dominant. The general symptoms of people who are active TB individuals include tiredness, high fever, and coughing. The confirmation of a person with active TB cases requires a particular test using a positive sputum culture. Between 5% to 30% of cases of TB infections are extrapulmonary. Recently infected individuals have a higher likelihood of advancing to the active TB class within five years of the disease. These cases are classified as primary TB cases. A person who proceeds to active TB, many years after infection because of endogenous reactivation and or exogenous re-infection, is classified as secondary active TB cases [6]. Occasional contacts with people with active TB rarely lead to infections [7]. Smith and Moss [8] stated that individuals with TB infection develop a strong immune response during the initial stages. This restrains the propagation of the bacterium and results in partial immunity against more infection. TB is called a slow disease since it takes a long time between the period of exposure and the onset of the illness but a short period during which an infected person can transmit the disease to another person. During the stages where the condition is dormant, individuals cannot spread TB [9]. Many of the secondary infections are due to protracted and close interactions with infectious individuals or due to exogenous re-infection. Another issue that is essential to the epidemiology of TB is the exogenous reinfection, where latently infected individuals acquire new infections from another infectious [10]. However, for most of the age groups, there is a lower chance of acquiring TB due to exogenous reinfection compared to the first time of getting TB infection [11].

Much theoretical work has been written about the analytical dynamics of TB using mathematical models, see [12-19]. The study done by [20,21] is on the modeling of TB transmission with consideration to treatment. Porco and Blower [22] included the aspect of disease relapse into their model. Snider [23] studied a model of TB that includes the aspect of exogenous reinfection, which is quite eminent in sub-Saharan Africa due to the high prevalence of HIV. Research indicates that, although regions of the low incidence of TB has a possibility of reinfection, it is very less compared to the geographical areas of high rate. This means that areas of higher incidence of *M. tuberculosis* are at significant risk of TB reinfection [24]. One of the challenges of controlling TB is because of the high level of infectious people who are undiagnosed in the population. Undiagnosed infectious population refers to the group of infectious people who have pulmonary TB, but it has not been detected [25,26].

We modified and extended the work of Bowong and Kurths [27]. Our model considers the undiagnosed infectious, treatment of identified infectious and disease relapse. This paper is arranged as: Section 2 outlines the schematic diagram and the mathematical model. Section 3 proceeds with the basic reproduction number, the disease-free and endemic equilibria. We also analyzed the model where the exogenous re-infection is set to zero. Global stability was also discussed. Section 4 proceeds with the numerical simulation. Section 5 collects conclusions and discusses the significance of the model's results.

2 The Model

2.1 Model formulation

In this section, we present a model for the transmission of tuberculosis in the human population. We put the population into exclusive sub-populations. These sub-populations are: susceptible $S(t)$, latent individuals (exposed to TB but not infectious) $E(t)$, diagnosed infectious $I(t)$, undiagnosed infectious $J(t)$, and Treated individuals $T(t)$. Λ denotes the recruitment rate. The natural death rate is μ. Both diagnosed and undiagnosed infectious individuals can transmit the disease. Undiagnosed and diagnosed infectious individuals have additional death rates due to the disease represented by d_1 and d_2 respectively. The susceptible individuals are infected when there is adequate contact with the diagnosed or undiagnosed infectious individuals; this is represented mathematically by

$$\lambda = \frac{\beta(I+\varepsilon J)}{N} \tag{1}$$

where β represents the effective contact rate that is enough to transmit the infection. The parameter $\varepsilon > 1$ accounts for the high level of infectiousness of undiagnosed infectious relative to diagnosed infectious. A fraction p of the susceptible individuals undergo a fast progression to the diagnosed and undiagnosed classes. The remainder $(1-p)$ then enters the latent class. A proportion f of individuals that experience fast progression is detected, they move to the diagnosed class. The remaining proportion $(1-f)$ is undetected, and they move to the undiagnosed class. The rate γ represents the effective treatment rate of the individual who has been diagnosed. The undiagnosed infectious can naturally recover. They then join the exposed class at a constant rate of r_2. We also assume further that, a rate q from the undiagnosed individual is later diagnosed. Individuals who did not have effective chemoprophylaxis move to the infectious class at a constant rate of $k(1-r_1)$. Also, individuals who have been exposed to the disease are re-infected (exogenously) if there is an effective contact with infectious individuals. This occurs at a rate of $\sigma(1-r_1)\lambda$ where σ is the reducing factor of the risk of infection because of the immunity acquire for latently infected individuals. Among the exposed individuals, a proportion h of them are diagnosed while the complement part $(1-h)$ is not diagnosed. Since TB does not confer permanent immunity, treated individuals join the latent class at the rate α.

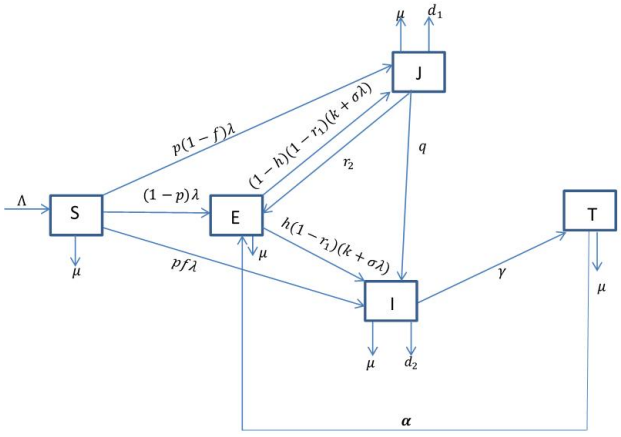


Fig. 1. The schematic diagram for a TB model

The following ordinary differential equation represents the model:

$$\dot{S} = \Lambda - (\lambda + \mu),$$

$$\dot{E} = (1-p)\lambda S + r_2 J + \alpha T - (1-r_1)\sigma\lambda E - A_1 E,$$

$$\dot{I} = pf\lambda S + h(1-r_1)(k+\sigma\lambda)E + qJ - A_2 I, \quad (2)$$

$$\dot{J} = p(1-f)\lambda S + (1-r_1)(1-h)(k+\sigma\lambda)E - A_3 J,$$

$$\dot{T} = \gamma I - A_4 T.$$

where

$$A_1 = \mu + k(1-r_1),\ A_2 = \mu + d_2 + \gamma,\ A_3 = \mu + d_1 + q + r_2,\ A_4 = \mu + \alpha$$

Table 1. List of parameters showing identifying symbol and estimation

Parameters	Symbol	Estimate	Sources
The recruitment rate of susceptible	Λ	$679685/yr$	[28]
Transmission	β	0.8	Assumed
Fast route to active TB	p	9.36432×10^{-4}	[28]
Infectivity of undiagnosed class	ϵ	1.4	Assumed
Reinfection parameter of latently infected individuals	σ	2.38390×10^{-4}	[28]
Slow route to active TB	k	$3.31390 \times 10^{-4}/yr$	[28]
Natural death rate	μ	$0.019896/yr$	[29]
TB mortality of undiagnosed infectious	d_1	$0.413/yr$	[28]
TB mortality of diagnosed infectious	d_2	$0.139/yr$	[28]
Chemoprophylaxis of the latently infected individual	r_1	$0/yr$	[28]
Relapse of recovered individuals	α	8.51257×10^{-2}	[28]
Detection rate of active TB	h	0.828248	[28]
Fast route to diagnosed infections	f	0.5	Assumed
Treatment rate of diagnosed infectious	γ	$0.8625/yr$	[30]
Natural recovery (recovery rate of undiagnosed)	r_2	$0.131140/yr$	[28]
Rate from undiagnosed infectious	q	$0.495896/yr$	[28]

We can represent the system (2) in the compact form as

$$\dot{x} = \varphi(x) - \lambda x$$

$$\dot{y} = \lambda[B_1 x + B_2\langle e_2|y\rangle] + Ay \quad (3)$$

where

$x = S,\ y = (y_1, y_2, y_3, y_4) = (E, I, J, T)^T,\ \varphi(x) = \Lambda - \mu x$, $e_1 = (0, \beta, \beta\epsilon, 0$, $e_2 = (1,0,0,0)$ $e_3 = (0,0,0,1)$, $B_1 = ((1-p), pf, p(1-f),0)^T$,

The force of infection is given by $\lambda = \frac{\langle e_1|y\rangle}{N}$ while the total population is $N = x + y_1 + y_2 + y_3 + y_4 + y_5$

$\langle \cdot \mid \cdot \rangle$ is the usual scalar product and A is the constant matrix

$$A = \begin{bmatrix} -A_1 & 0 & r_2 & \alpha \\ h(1-r_1)k & -A_2 & q & 0 \\ (1-h)(1-r_1)k & 0 & -A_3 & 0 \\ 0 & \gamma & 0 & -A_4 \end{bmatrix}$$

$B_2 = (-(1-r_1)\sigma,\ h(1-r_1)\sigma,\ (1-h)(1-r_1)\sigma,\ 0)^T$

$$-A^{-1} = \frac{1}{\tau}\begin{bmatrix} A_2A_3A_4 & \alpha\gamma A_3 & q\alpha\gamma + A_2A_4r_2 & \alpha A_2A_3 \\ kA_4((1-h)q + hA_3)(1-r_1) & A_4(A_1A_3 - kr_2(1-h)(1-r_1)) & A_4(qA_1 + hkr_2(1-r_1)) & k\alpha(1-r_1)((1-h)q + hA_3) \\ (1-h)(1-r_1)kA_2A_4 & (1-h)(1-r_1)k\alpha\gamma & A_2A_1A_4 - hk\alpha\gamma(1-r_1) & k\alpha A_2(1-h)(1-r_1) \\ k\gamma((1-h)q + hA_3)(1-r_1) & \gamma(A_1A_3 - kr_2(1-h)(1-r_1)) & \gamma(qA_1 + r_2hk(1-r_1)) & A_2(A_1A_3 - kr_2(1-h)(1-r_1)) \end{bmatrix}$$

$\tau = A_3(A_1A_2A_4 - \alpha(1-r_1)hk\gamma) - k(1-h)(1-r_1)(q\alpha r + A_2A_4r_2)$

3 Basic Properties

3.1 Positivity and boundedness of solutions

Since model (2) monitors the humans, all the parameters and state variables should be non-negative and also bounded for all $t > 0$. This means that our model is well-posed and epidemiologically reasonable [31].

Lemma 3.1*:* Let the initial values be $\mathrm{S}(0) > 0, \mathrm{E}(0) \geq 0, \mathrm{I}(0) \geq, \mathrm{J}(0) \geq 0, \mathrm{T}(0) \geq 0$. The solutions $(\mathrm{S}, \mathrm{E}, \mathrm{I}, \mathrm{J}, \mathrm{T})$ of the model (2) are non-negative for all $\mathrm{t} > 0$.

$$\limsup_{t\to\infty} N(t) \leq \frac{\Lambda}{\mu}$$

with $N(t) = S(t) + E(t) + I(t) + J(t) + T(t)$

The proof of this lemma is as follows

$\dot{N} = \Lambda - \mu N - d_1J - d_2I$, we can then deduce that $\dot{N} \leq \Lambda - \mu N$. Integrating the differential inequality yields $N(t) \leq N(0)e^{-\mu t} + \frac{\Lambda}{\mu}(1 - e^{-\mu t})$. In particular $N(t) \leq \frac{\Lambda}{\mu}$ if $N(0) \leq \frac{\Lambda}{\mu}$. On the other hand, if $N(0) \geq \frac{\Lambda}{\mu}$, then $\Lambda - \mu N \leq 0$ and $\dot{N} \leq \Lambda - \mu N(0) \leq 0$, i.e., the total population $N(t)$ will decrease until $N(t) \leq \frac{\Lambda}{\mu}$. Then, the simplex

$$\mathrm{D} = \left\{(S, E, I, J, T)\epsilon\, R_+^5, N(t) \leq \frac{\Lambda}{\mu}\right\} \tag{4}$$

is a compact forward invariant set for the system (2).

Thus, every solution of model (2) with initial conditions in D remains there for $t > 0$.

3.2 The basic reproduction number

The nature of the TB transmission model depends on the basic reproduction number. The basic reproduction number $\mathcal{R}_0$, is an average number of new cases produced by a single infective individual who is introduced into a susceptible population. Model (2) has a disease-free equilibrium given by $E_0 = \left(\frac{\Lambda}{\mu}, 0,0,0,0,0\right)$. Next, we use the next-generation matrix approach developed by Van den Driessche and Watmough [32] to calculate the basic reproduction number, $\mathcal{R}_0$. Let matrix F represent the new infection terms, and matrix V represents the remaining transfer terms. Then

$F = B_1e_1$ and $V = -A$.

The basic reproduction number which is defined as $\rho(FV^{-1})$ is given by

$$\mathcal{R}_0 = \langle e_1|(-A^{-1})B_1\rangle \tag{5}$$

where ρ represents the spectral radius (the dominant eigenvalue in magnitude) of FV^{-1}. The expression $(-A^{-1})$ emphasizes that $(-A^{-1}) \geq 0$ since the matrix A is Metzler Stable.

Using the expression of $(-A^{-1})$, then

$$\mathcal{R}_0 = \frac{\beta[(1-p)R_{01}+pfR_{02}+p(1-f)R_{03}]}{A_3(A_1A_2A_4-\alpha\gamma hk(1-r_1))-k(1-h)(1-r_1)(A_2A_4r_2+\alpha q\gamma)} \tag{6}$$

$R_{01} = \varepsilon k(1-h)(1-r_1)A_2A_4 + A_4k(1-r_1)(q(1-h)+A_2h)$
$R_{02} = \varepsilon k\alpha\gamma(1-h)(1-r_1) - A_4kr_2(1-h)(1-r_1) + A_3A_4A_1$
$R_{03} = \varepsilon(A_2A_1A_4 - hk\alpha\gamma(1-r_1)) + hkr_2A_4(1-r_1) + qA_1A_4$

Lemma 3.2 The disease-free equilibrium E_0 of the model (2) is locally asymptotically stable whenever $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$.

3.3 Endemic equilibria

Let $E^* = (x^*, y^*)$ be any arbitrary endemic equilibrium point of the model system (2). To find the existence of an endemic equilibrium, we equate model (3) to zero, i.e.,

$$\varphi(x^*) - \lambda^* x^* = 0$$

$$\lambda^*[B_1x^* + B_2\langle e_2|y^*\rangle] + Ay^* = 0 \tag{7}$$

where

$$\lambda^* = \frac{\langle e_1|y^*\rangle}{N^*} \tag{8}$$

is the force of infection at the steady-state. Next, we multiply the second equation of (7) by $-A^{-1}$, this gives us

$$\lambda^*[x^*(-A^{-1})B_1 + (-A^{-1})B_2\langle e_2|y^*\rangle - A^{-1}Ay^* = 0$$

$$y^* = \lambda^*[x^*(-A^{-1})B_1 + (-A^{-1})B_2\langle e_2|y^*\rangle] \tag{9}$$

From equation (9), we deduce that

$$\langle e_1|y^*\rangle = \lambda^*[\langle e_1|(-A^{-1})B_1\rangle x^* + \langle e_1|(-A^{-1})B_2\rangle\langle e_2|y^*\rangle] \tag{10}$$

$$\langle e_2|y^*\rangle = \lambda^*[\langle e_2|(-A^{-1})B_1\rangle x^* + \langle e_2|(-A^{-1})B_2\rangle\langle e_2|y^*\rangle] \tag{11}$$

$$\langle e_1|y^*\rangle = \lambda^*[x^*\mathcal{R}_0 + a_1\langle e_2|y^*\rangle]$$

$$\langle e_2|y^*\rangle = \lambda^*[x^*a_2 + a_3\langle e_2|y^*\rangle]$$

Where

$$a_1 = \langle e_1|(-A^{-1})B_2\rangle$$

$$a_2 = \langle e_2|(-A^{-1})B_1\rangle$$

$$a_3 = \langle e_2|(-A^{-1})B_2\rangle$$

Now using equation (11), we prove that

$$\langle e_2|y^*\rangle - a_3\lambda^*\langle e_2|y^*\rangle = \lambda^* x^* a_2$$

$$\langle e_2|y^*\rangle[1 - a_3\lambda^*] = \lambda^* x^* a_2$$

$$\langle e_2|y^*\rangle = \frac{\lambda^* x^* a_2}{1-a_3\lambda^*} \tag{12}$$

Combining equation (10) and the force of infection at the steady-state (8) yields

$$\langle e_1|y^*\rangle = \frac{\langle e_1|y^*\rangle}{N^*}[x^*\mathcal{R}_0 + a_1\langle e_2|y^*\rangle]$$

$$N^* = x^*\mathcal{R}_0 + a_1\langle e_2|y^*\rangle \tag{13}$$

We let $w_1 = (1,0,0,0)$, $w_2 = (0,1,0,0)$, $w_3 = (0,0,1,0)$ and $w_4 = (0,0,0,1)$. Using (9), one can deduce that

$$E^* = \langle w_1|y^*\rangle = \lambda^*[x^*\langle w_1|(-A^{-1})B_1\rangle + \langle w_1|(-A^{-1})B_2\rangle\langle e_2|y^*\rangle]$$

$$I^* = \langle w_2|y^*\rangle = \lambda^*[x^*\langle w_2|(-A^{-1})B_1\rangle + \langle w_2|(-A^{-1})B_2\rangle\langle e_2|y^*\rangle]$$

$$J^* = \langle w_3|y^*\rangle = \lambda^*[x^*\langle w_3|(-A^{-1})B_1\rangle + \langle w_3|(-A^{-1})B_2\rangle\langle e_2|y^*\rangle]$$

$$T^* = \langle w_4|y^*\rangle = \lambda^*[x^*\langle w_4|(-A^{-1})B_1\rangle + \langle w_4|(-A^{-1})B_2\rangle\langle e_2|y^*\rangle]$$

Then, the size of the population can be written as

$$N^* = x^* + \sum_{k=1}^{4}\langle w_k|y^*\rangle$$

$$N^* = x^* + \lambda^*[x^* g_0 + g_1\langle e_2|y^*\rangle] \tag{14}$$

where

$$g_0 = \sum_{k=1}^{4}\langle w_k|(-A^{-1})B_1\rangle,\ g_1 = \sum_{k=1}^{4}\langle w_k|(-A^{-1})B_2\rangle$$

Equalizing (13) and (14), and using (12),

We get

$$x^* R_0 + a_1\frac{\lambda^* x^* a_2}{1 - a_3\lambda^*} = x^* + \lambda^* x^* g_0 + g_1\frac{(\lambda^*)^2 a_2}{1 - a_3\lambda^*}$$

$$R_0 - a_3 R_0\lambda^* + a_1 a_2\lambda^* = 1 - a_3\lambda^* + g_0\lambda^* - a_3 y_0(\lambda^*)^2 + g_1 R_{02}(\lambda^*)^2$$

$$(a_2 g_1 - a_3 y_0)(\lambda^*)^2 + \big(g_0 - a_1 a_2 - a_3(1 - \mathcal{R}_0)\big)\lambda^* + (1 - \mathcal{R}_0) = 0$$

This is represented as

$$d_2(\lambda^*)^2 + d_1(\lambda^*) + d_0 = 0 \tag{15}$$

where

$$d_2 = a_2 g_1 - a_3 y_0,\quad d_1 = g_0 - a_1 a_2 - a_3(1 - \mathcal{R}_0), d_0 = 1 - \mathcal{R}_0$$

The sign of d_2 is positive if $a_2 g_1 > a_3 y_0$ and negative if $a_2 g_1 < a_3 y_0$. Also, it can be realized that the sign of d_0 is positive if $\mathcal{R}_0 < 1$ and negative if $\mathcal{R}_0 > 1$. Thus, the number of real roots of the polynomial (15) depends on the signs d_2, d_1 and d_0. This can be analyzed using the Descartes Rule of Signs on the quadratic $f(\lambda^*) = d_2(\lambda^*)^2 + d_1(\lambda^*) + d_0$ in (15). The various possibilities for the roots of $f(\lambda^*)$ are tabulated in Table 2.

Table 2. Number of possible real roots of $f(\lambda^*)$ for $\mathcal{R}_0 < 1$ and $\mathcal{R}_0 > 1$

Cases	d_2	d_1	d_0	R_0	Number of sign changes	Number of possible real roots
1	−	−	−	$\mathcal{R}_0 > 1$	0	0
	−	−	+	$\mathcal{R}_0 < 1$	1	1
2	+	−	−	$\mathcal{R}_0 > 1$	1	1
	+	−	+	$\mathcal{R}_0 < 1$	2	0,2
3	−	+	−	$\mathcal{R}_0 > 1$	2	0,2
	−	+	+	$\mathcal{R}_0 < 1$	1	1
4	+	+	−	$\mathcal{R}_0 > 1$	1	1
	+	+	+	$\mathcal{R}_0 < 1$	0	0

Lemma 2: The TB model (2)

(i) Could have a unique endemic equilibrium if $\mathcal{R}_0 > 1$ and whenever cases 2 and 4 are satisfied.
(ii) Could have more than one endemic equilibrium if $\mathcal{R}_0 > 1$ and case 3 is satisfied.
(iii) Could have a unique endemic equilibrium if $\mathcal{R}_0 < 1$ and whenever cases 1 and 2 satisfied.
(iv) No endemic equilibria in the other cases.

There exist a possibility of a backward bifurcation since multiple endemic equilibria when $\mathcal{R}_0 < 1$. Backward bifurcation is a situation whereby the stable DFE coexists with a stable endemic equilibrium when $\mathcal{R}_0 < 1$ (see [24, 27, 33, 34, 35]). In general, the existence of backward bifurcation phenomenon means that is that having $\mathcal{R}_0 < 1$ is not enough to control the disease [36]. In such a situation, to eliminate the disease would depend on the initial size of the population [27].

3.4 Absence of exogenous reinfection

In this section, we discuss the situation where there is no exogenous reinfection on the model. In this case $\sigma = 0$ so that $B_2 = 0$. Model (3) then becomes

$$\dot{x} = \varphi(x) - \lambda x$$

$$\dot{y} = \lambda B_1 x + Ay \tag{16}$$

where $\varphi(x)$, λ, B_1 and A are defined as in model (3). Model (16) has the same DFE, E_0, as the model (3). The coefficients of d_2, d_1 and d_0 in (15) reduce to

$$d_2 = 0, \quad d_1 = g_0 \quad \text{and} \quad d_0 = 1 - \mathcal{R}_0 \tag{17}$$

By substituting, (17) into (15), we get the force of infection at the steady-state as

$$\lambda^* = \frac{\mathcal{R}_0 - 1}{g_0}$$

which is positive when $\mathcal{R}_0 > 1$. Then there exists a unique endemic equilibrium $E^*(x^*, y^*)$ where x^* and y^* are given by

$$x^* = \frac{g_0\Lambda}{\mu g_0 + \mathcal{R}_0 - 1}$$

$$y^* = \frac{\Lambda(\mathcal{R}_0-1)(-A^{-1})B_1}{\mu g_0+\mathcal{R}_0-1} \tag{18}$$

From the analysis, model (6) has no endemic equilibrium whenever $\mathcal{R}_0 \leq 1$. This means that our model does not exhibit backward bifurcation when there is no exogenous re-infection.

Theorem 1: In the absence of exogenous re-infection, the disease-free equilibrium of model (2) is globally asymptotically stable in D whenever $\mathcal{R}_0 \leq 1$.

3.5 Analysis of the mass action model

In this section, we consider model (2) with a mass action model while we keep the exogenous re-infections to zero. The force of infection then reduces to $\lambda = \beta(I + \varepsilon J)$. System (2) then becomes

$$\begin{aligned}
\dot{S} &= \Lambda - \beta(I + \varepsilon J)S - \mu S \\
\dot{E} &= \beta S(1-p)(I + \varepsilon J) + r_2 J + \alpha T - A_1 E \\
\dot{I} &= \beta S p f(I + \varepsilon J) + h(1-r_1)kE + qJ - A_2 I \\
\dot{J} &= p\beta(I + \varepsilon J)(1-f)S + k(1-h)(1-r_1)E - A_3 J \\
\dot{T} &= \gamma I - A_4 T
\end{aligned} \tag{19}$$

where A_1, A_2, A_3 and A_4 are defined as in equation (2). The compact form of model (19) is

$$\begin{aligned}
\dot{x} &= \varphi(x) - x\langle e_1|y\rangle \\
\dot{y} &= x\langle e_1|y\rangle B_1 + Ay
\end{aligned} \tag{20}$$

where $\varphi(x), e_1, B_1$ and A are defined as in model (3). The resulting mass action model has the same disease-free equilibrium given by E_0. Using the next-generation matrices, F and V are respectively given by $F = x_0 B_1 e_1$ and $V = -A$ where $x_0 = \frac{\Lambda}{\mu}$. It follows that the associated basic reproduction number for the mass action model without exogenous reinfections is given by

$$\mathcal{R}_1 = x_0\langle e_1|(-A^{-1})B_1\rangle \tag{21}$$

3.5.1 Non-existence of endemic equilibria for $R_0 < 1$

Let $E^* = (x^*, y^*)$ be the positive equilibrium of model (20). We set equation (20) to zero. This yields

$$\begin{aligned}
&\varphi(x^*) - x^*\langle e_1|y^*\rangle = 0 \\
&x^*\langle e_1|y^*\rangle B_1 + Ay^* = 0
\end{aligned} \tag{22}$$

Next, we multiply the second equation of (22) by $-A^{-1}$.

This results

$$\begin{aligned}
&x^*(-A^{-1})B_1\langle e_1|y^*\rangle + (-A^{-1})Ay^* = 0 \\
&y^* = x^*(-A^{-1})B_1\langle e_1|y^*\rangle
\end{aligned} \tag{23}$$

From (23), it implies that

$$\langle e_1|y^*\rangle = x^*\langle e_1|(-A^{-1})B_1\rangle\langle e_1|y^*\rangle \tag{24}$$

We can consider two cases:

Case 1: Considering equation (22), for $\langle e_1|y^*\rangle = 0$ implies that $\varphi(x^*) = 0$ and $-Ay^* = 0$. Since A is non-singular, this gives the disease-free equilibrium E_0.

Case 2: From equation (24)

$$x^* = \frac{1}{\langle e_1|(-A^{-1})B_1\rangle} = \frac{x_0}{\mathcal{R}_0} > 0 \tag{25}$$

when $R_0 > 1$, then $x^* < x_0$, $\varphi(x^*) > 0$ and $y^* = (-A^{-1})B_1\varphi(x^*)$. Hence, model (22) has a unique endemic equilibrium $Q^* = (x^*, y^*)$ where x^* and y^* are given by

$$x^* = \frac{1}{\langle e_1|(-A^{-1})B_1\rangle} = \frac{x_0}{\mathcal{R}_0}$$

$$y^* = (-A^{-1})B_1\,\varphi(x^*) \tag{26}$$

Equation (26) suggests the impossibility of a backward bifurcation since the mass balance model has no endemic equilibrium when $\mathcal{R}_0 \leq 1$.

Next, we establish global stability for the disease-free equilibrium of the mass balance action model without exogenous reinfections.

3.6 Global stability

Theorem 2: If $\mathcal{R}_0 \leq 1$, then model (3) with mass balance incidence in the absence of exogenous reinfection has no positive equilibrium states and the disease-free equilibrium E_0 is globally asymptotically stable on the non-negative orthant R_+^5. This means that the disease naturally dies out.

Proof: Let us consider the following Lasalle-Lyaponuv function

$$\begin{aligned}
V(x,y) &= \frac{1}{x_0}(x - x_0\ln x) + e_1^T(-A^{-1})y - \frac{1}{x_0}(x_0 - x_0\ln x_0)\\
\dot{V}(x,y) &= \frac{1}{x_0}\left(1 - \frac{x_0}{x}\right)\dot{x} + e_1^T(-A^{-1})\dot{y}\\
&= \frac{1}{x_0}\left(1 - \frac{x_0}{x}\right)[\varphi(x) - x\langle e_1|y\rangle] + e_1^T(-A^{-1})[B_1\langle e_1|y\rangle x + Ay]\\
&= \frac{1}{x_0}\left(1 - \frac{x_0}{x}\right)\varphi(x) - \frac{1}{x_0}\left(1 - \frac{x_0}{x}\right)x\langle e_1|y\rangle + e_1^T(-A^{-1})B_1\langle e_1|y\rangle x + e_1^T(-A^{-1})Ay\\
&= \frac{(x - x_0)}{x_0 x}\varphi(x) - \frac{(x - x_0)}{x_0}\langle e_1|y\rangle + e_1^T(-A^{-1})B_1\langle e_1|y\rangle x + e_1^T y\\
&= \frac{(x - x_0)}{x_0 x}\varphi(x) - \frac{x}{x_0}\langle e_1|y\rangle + \langle e_1|y\rangle + e_1^T(-A^{-1})B_1\langle e_1|y\rangle x - e_1^T y\\
&= \frac{(x - x_0)}{x_0 x}\varphi(x) - \frac{x}{x_0}\langle e_1|y\rangle + \frac{\mathcal{R}_0}{x_0}\langle e_1|y\rangle x\\
&= \frac{(x-x_0)}{x_0 x}\varphi(x) + \frac{x}{x_0}\langle e_1|y\rangle(\mathcal{R}_0 - 1)
\end{aligned} \tag{27}$$

Recalling that at the disease-free equilibrium $\Lambda = \mu x_0$, so that $\varphi(x) = \mu(x_0 - x)$, we finally get

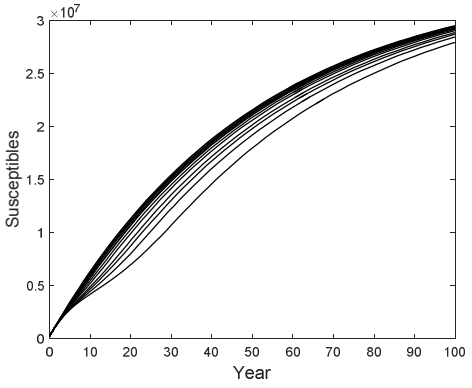
$$\dot{V}(x,y) = \frac{-\mu(x-x_0)^2}{x_0 x} + \frac{x}{x_0}\langle e_1|y\rangle(\mathcal{R}_0 - 1) \tag{28}$$

Thus $\mathcal{R}_0 \leq 1$ ensures that $\dot{V}(x,y) \leq 0$ for all $x, y \geq 0$, and that $\dot{V}(x,y) = 0$ holds when $\mathcal{R}_0 = 1$ for $x = x_0$. It can also be established that the disease-free equilibrium state E_0 is the only fixed point of the system in the space $x = x_0$, therefore the system has no equilibria in D apart from E_0. Therefore using the Lyaponuv-LaSalle's asymptotical stability theorem [36-39], we conclude that the equilibrium state E_0 is globally asymptotically stable in D. This proves the global asymptotic stability on D and then in the non-negative orthant R_+^5.

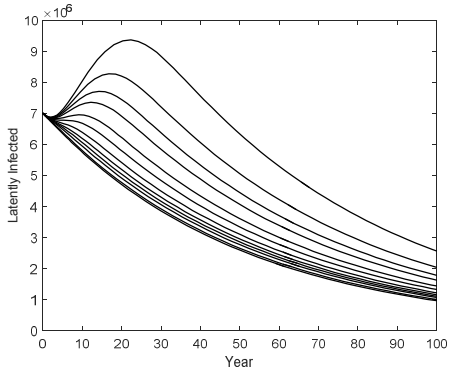
4 Numerical Simulations

In this section, we present the numerical simulation of our model. We used the values in Table 1 for the numerical simulation.

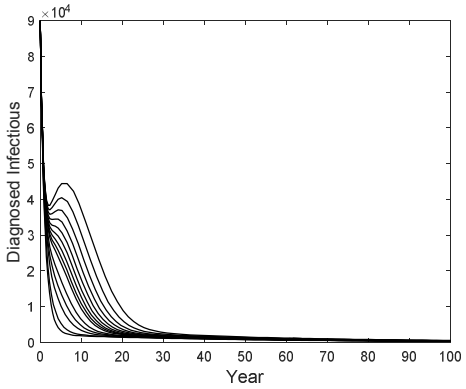
In Fig. 2, we present the numerical simulation of the model (2). It can be seen that the number of susceptible increases, whereas the latently infected, diagnosed infectious, undiagnosed infectious and treated individuals decreases. Also, from Fig. (3a), it can be seen that the number of infectious individuals decreases when $\sigma = 0$ and $\mathcal{R}_0 < 1$. Also, Fig. (3b) shows that the number of infectious individuals increases whenever $\mathcal{R}_0 > 1$. Fig. (4) presents the numerical simulation when the detection rate of active TB is varied. From Fig. 4(a-c), it can be seen that as the detection rate increases, the individuals in the latently infected class, diagnosed and undiagnosed classes also decreases. This implies that the detection of individuals is a critical parameter in the control of tuberculosis.



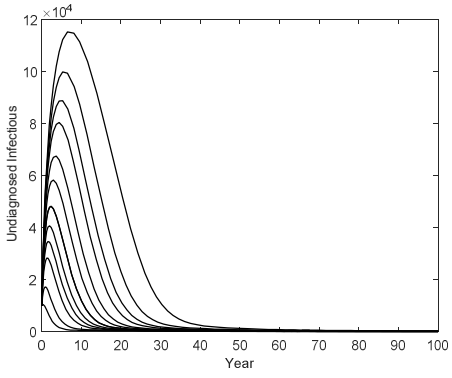
(a)



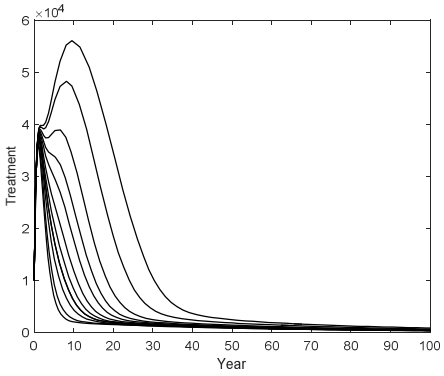
(b)



(c)

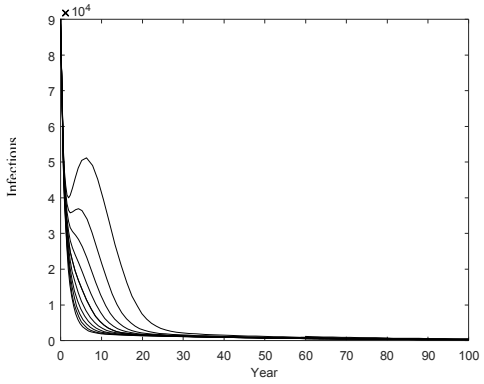


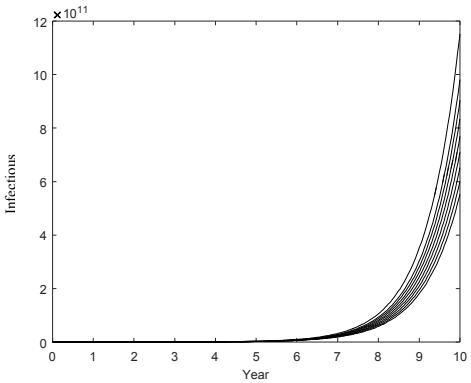
(d)



(e)

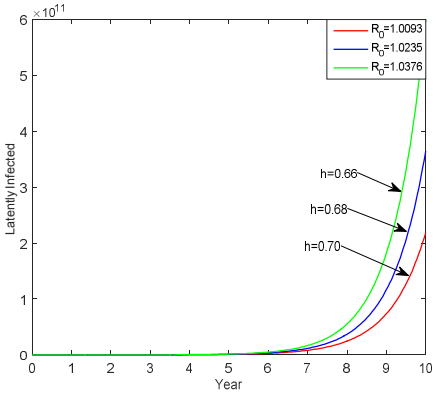
Fig. 2. Simulations results of model system (2). Time series of (a) susceptible, (b) latently infected individuals (c) diagnosed infectious (d) undiagnosed infectious (e) Treatment when $\mathcal{R}_0 < 1$

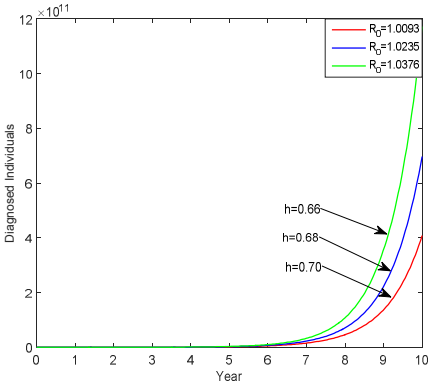




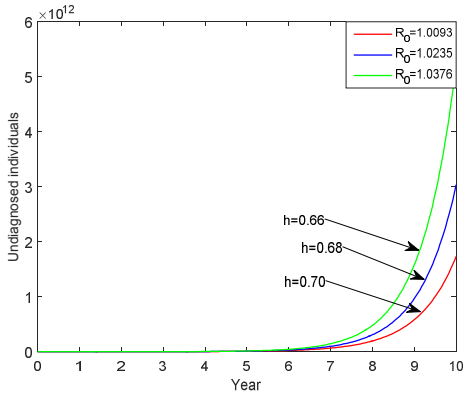
(a) **(b)**

Fig. 3. Time series of model (2) with $\sigma = 0$ showing the number of infected individuals as a function of time when (a)$\mathcal{R}_0 < 1$ (b) $\mathcal{R}_0 > 1$





(a) **(b)**



(c)

Fig. 4. Time series of (a) latently infected individual, (b) diagnosed infectious and (c) undiagnosed infectious of model (2) with $\sigma = 0$ showing the impact of varying h. All other parameters are as in Table 1

5 Discussion and Conclusion

In this section, we present the discussion and conclusion of our work. The model has two infective classes, which are the diagnosed and the undiagnosed classes. The undiagnosed class is significant for the modeling of TB transmission, particularly in developing countries since public health is underdeveloped. According to the studies by Wood et al. [40], about 63% of individuals with pulmonary tuberculosis (PTB) cases are unrecognized (undiagnosed) to TB treatment service. Also among the person with HIV infection, the passive case finding identified only 33% of the number of people with smear-positive TB. They concluded that there is largely unrecognized burden of TB, especially among people with HIV. This means that much effort will have to be put in by public health officials to encourage individuals to go for TB screening.

The treatment class is a very important compartment when modeling and analyzing TB transmission. TB is curable and treatable, but it does not confer permanent immunity after recovery. After a rigorous analysis of the model, it was found that the model may have multiple endemic equilibria when $\mathcal{R}_0 < 1$. This suggests the possible existence of backward bifurcation. On the other hand, by analyzing the model without exogenous re-infection, we realized that there were no multiple endemic equilibria when $\mathcal{R}_0 < 1$. This implies that the backward bifurcation phenomenon is caused by the exogenous re-infection of latently infected and recovered individuals.

Fig. 2 shows the graph of the susceptible, latently infected, diagnosed, undiagnosed and treated individuals when $\mathcal{R}_0 < 1$. It can be seen from Fig. 2 that, when $\mathcal{R}_0 < 1$ the number of susceptible increases whereas the number of latently infected, diagnosed infectious, undiagnosed infectious and Treatment decreases. In Fig. 3(a), the latently infected class with $\sigma = 0$ increases and reaches its maximum, then gradually falls and then reaches a stable state when $\mathcal{R}_0 < 1$. On the other hand, Fig. 3(b) shows that when $\mathcal{R}_0 > 1$ with $\sigma = 0$, the infectious class moves from a steady-state and increases infinitely. However, Fig. 4 shows that with $\sigma = 0$ and the values of h increasing, the latently infected, diagnosed and undiagnosed individuals decreases. This implies that the detection of infectious individuals is crucial in the control of disease transmission.

From the analysis discussed in this paper, more considerable effort should be put in by all stakeholders in the education of the public on TB. This will help to drastically reduce effective contact rates with infectious individuals and more importantly, reduce the number of undiagnosed infectious. Even though the treatment

of TB takes a longer time, people should be educated to stick to their treatment plan since the disease is treatable.

Competing Interests

Authors have declared that no competing interests exist.

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