Source details

Advances in Dynamical Systems and Applications

Scopus coverage years: 2019
(coverage discontinued in Scopus)
Publisher: Research India Publications
ISSN: 0973-5321 E-ISSN: 0974-021X
Subject area: Mathematics: Analysis | Engineering: Computational Mechanics | Mathematics: Geometry and Topology | Mathematics: Applied Mathematics | Mathematics: Control and Optimization | Mathematics: Modeling and Simulation
Source type: Journal

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0.3

SJR 2022
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Advances in Dynamical Systems and Applications.
ISSN 0973-5321, Volume 18, Number 2, (2023) pp. 137-154

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Dynamic Model of Tuberculosis with Diabetes Mellitus

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Abstract

In regions with a high prevalence of low- and middle-income economies, tuberculosis (TB) remains a significant global health concern. Diabetes (DM) has recently emerged as a potential TB risk factor and is expected to substantially increase in the next two decades, further complicating the situation. This study aims to thoroughly assess the TB-DM relationship, focusing on DM's impact on TB transmission dynamics and disability rates. We meticulously examine the mathematical elements of a deterministic TB model tailored for community settings. Our research determines equilibrium points, including the critical epidemic threshold and basic reproduction number. Stability assessments shed light on the model's behavior under varying conditions. Notably, we introduce a novel element in our numerical analysis by exploring DM's influence on TB transmission while considering disability rates associated with diabetes mellitus. Sensitivity studies on key factors influencing disease dynamics enhance our understanding by revealing their relative importance in disease transmission and prevalence. Our mathematical calculations reveal that DM accelerates TB transmission and the emergence of active TB cases within communities. Our work underscores the importance of targeted intervention measures to alleviate the burden of these interconnected diseases. These measures should include chemoprophylaxis for latent TB individuals and specialized treatment plans for DM patients with active TB. To combat TB and DM's co-occurrence, these interventions may involve screening for suspected diabetes, optimizing glucose control, and implementing enhanced clinical and pharmacological monitoring.

Keywords: Tuberculosis, Diabetes, Disease Transmission, Mathematical Model, Intervention Strategies

1 INTRODUCTORY

Despite excellent treatments, tuberculosis (TB) still threatens global health, infecting around one-third of the global population and resulting in 8.8 million new cases and 2 million fatalities annually [1]. The main goal of current TB control techniques is to stop the spread of the disease by quickly detecting and treating persons who have infectious TB. Despite the success of this strategy, TB still exists in many areas, demanding a larger effort to address the disease's societal and human drivers.

Projections predict that between 2000 and 2020, one billion people will become newly infected, 200 million will have TB, and 35 million will pass away from the illness globally [1] if TB control efforts are not substantially strengthened. In 22 "high-burden" nations, primarily in sub-Saharan Africa and Southeast Asia, where co-infection with HIV exacerbates the issue, 80 percent of these cases and fatalities will occur. Most TB infections result in asymptomatic latent infections, with 5–10% developing active TB for a lifetime. For those with HIV, this risk considerably increases.

The World Health Organization's Stop TB Strategy has been widely adopted in high TB burden countries, but the decline in case numbers needs to catch up to expectations. This may be because diagnosis and treatment have taken longer than expected, and risk factors like co-infections, air pollution, alcohol abuse, overcrowding, diabetes, malnutrition, tobacco use, and urbanization have increased [2]. 60% of all deaths worldwide are attributable to diabetes, a major cause of early sickness and mortality. This is due to insufficient insulin synthesis or usage, which causes hyperglycemia and damages many physiological systems [3]. There are two main forms of diabetes: Type 1, which has an unclear origin, and Type 2, which is mostly linked to obesity and inactivity. The prevalence of diabetes varies by area globally, and it is predicted to rise significantly, especially in low- and middle-income countries.

TB and diabetes have a very substantial positive correlation, according to recent epidemiological studies. Diabetes increases the risk of developing tuberculosis (TB) thrice and accounts for 15–25% of TB cases. As DM is frequently identified before TB occurs, diabetes may decrease the immunological response, enabling Mycobacterium tuberculosis infection or disease development [4]. Impairments in host defenses and immune cell functioning may cause an increased incidence of TB in people with diabetes [5,6].

2 DYNAMIC MODEL OF TBC WITH DM

We present a model for the spread of TB in population according to their TB and DM status. The total population at the time t, $N(t)$, is sub-divided into nine classes: non diabetics susceptible individuals (S_1), non-diabetics latently infected individuals (E_1), non-diabetics infected with active TB (I_1), non-diabetics recovered from TB (R_1), diabetics susceptible individuals (S_2), diabetics latently infected individuals (E_2), diabetics infected with active TB (I_2), diabetics recovered from TB (R_2), and treated individuals (T). Thus,

$$N(t) = S_1(t) + E_1(t) + I_1(t) + R_1(t) + S_2(t) + E_2(t) + I_2(t) + R_2(t) + T(t)$$

We assumed that non-diabetics susceptible individuals are recruited through birth, and the recruitment occurs at rate Λ. The TB disease transmission occurs due to contact between susceptible individuals and infectious. Susceptible individuals get the TB disease from individuals with active TB at rate $\lambda = \beta \frac{I_1 + \varepsilon I_2}{N}$. Parameter β is the effective coefficient of TB transmission and parameter $\varepsilon > 1$ accounts for the addition in infectiousness among diabetics infected with active TB (in comparison to non-diabetics infected with active TB).

The natural death rate, μ, is assumed to be positive constant. The class I_1 has additional TB-induced death rates d_1 and the class I_2 has additional TB-induced death rates d_2. The value of d_2 is greater than or equal to d_1 ($d_2 \geq d_1$) as DM experiences more significant disease-induced deaths than their corresponding non-diabetic counterparts [4].

A proportion p_1, with $0 < p_1 < 1$, of non-diabetics susceptible individuals who get active TB infection moves to I_1 class, and the proportion $(1 - p_1)$ becomes latently infected and enters the E_1 class. Once latently infected, an individual can move to T class and follow a treatment. We denote the treatment rate of non-diabetics latent individuals by ψ_1. Non-diabetics latent individuals who do not receive effective treatment develop an active TB at rates σ_1.

Non-diabetics infected with active TB following treatment and move to T class at a rate ω_1. It is assumed that non-diabetics infected with active TB have natural recovery and can become recovered individuals at rate η_1. After following treatment, non-diabetics infectious move to R_1 class with rate $q\delta_1$ Parameter q, with $0 < q < 1$, represents the reduction in risk of infection due to treatment. Ineffective treatment causes non-diabetics infectious relapse into the active TB state at rate $(1 - q)\delta_1$.

Individuals in the classes without DM (those in the S_1, E_1 and R_1) may move to the classes with DM (those in the S_2, E_2, and R_2) at rate α. Non-diabetics infected with active TB acquire DM at rate $\tau\alpha$. Parameter τ is a enhancement factor which increases the progression of non-diabetics infectious to diabetics infectious because of their active TB status [7,8].

When diabetics susceptible individuals interacting with individuals in I_2, they have greater risk of becoming a group infected with active TB at rate $\theta\lambda$ with $\theta > 1$. This is because DM acts as a carrier of TB bacteria [5]. A proportion p_2, with $0 < p_2 < 1$, of diabetics susceptible individuals who get active TB infection moves to I_2 class, and the remainder $(1 - p_2)$ develops a latent TB and moves to the E_2 class.

Let $\psi_2 E_2$ be the number of people with DM latently infected individuals who have received treatment, where ψ_2 is the rate of treatment. Diabetics latent individuals who do not receive effective treatment develop an active TB at rates $\theta\sigma_2$.

Diabetics infected with active TB following treatment and move to T class at a rate ω_1. Thus, diabetics infected individuals with effective treatment progress to recovered at rate $q\delta_2$. But, some individuals may be undergoing ineffective treatment that returns

them to I_2 class with rate $(1-q)\delta_2$. It is assumed that diabetics infected with active TB have natural recovery and can become recovered individuals at rate η_2. DM can cause disability so that diabetics infected with active TB can become disabled at rate γ.

The structure of the model is shown in Figure 1.

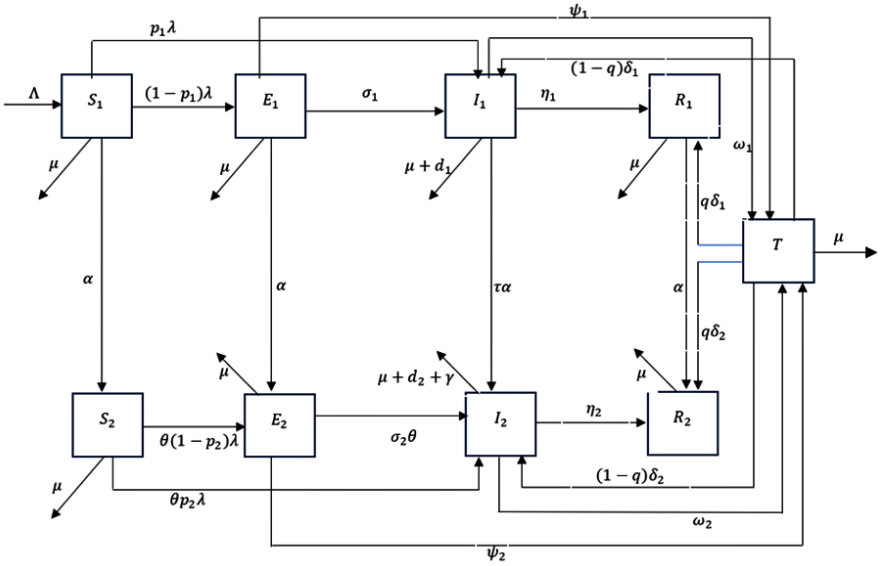

Figure 1. Diagram of TB transition

The dynamics of the population are then described by the system of nonlinear differential equations as follows:

$$
\begin{cases}
\dfrac{dS_1}{dt} = \Lambda - (\mu+\alpha+\lambda)S_1 \\
\dfrac{dE_1}{dt} = (1-p_1)\lambda S_1 - (\mu+\alpha+\sigma_1+\psi_1)E_1 \\
\dfrac{dI_1}{dt} = p_1\lambda S_1 + \sigma_1 E_1 - (\mu+\tau\alpha+d_1+\omega_1+\eta_1)I_1 + (1-q)\delta_1 T \\
\dfrac{dR_1}{dt} = \eta_1 I_1 + q\delta_1 T - (\mu+\alpha)R_1 \\
\dfrac{dS_2}{dt} = \alpha S_1 - (\mu+\theta\lambda)S_2 \\
\dfrac{dE_2}{dt} = \theta(1-p_2)\lambda S_2 + \alpha E_1 - (\mu+\theta\sigma_2+\psi_2)E_2 \\
\dfrac{dI_2}{dt} = \tau\alpha I_1 + \theta p_2\lambda S_2 + \theta\sigma_2 E_2 - (\mu+d_2+\omega_2+\eta_2+\gamma)I_2 + (1-q)\delta_2 T \\
\dfrac{dR_2}{dt} = \alpha R_1 + \eta_2 I_2 + q\delta_2 T - \mu \\
\dfrac{dT}{dt} = \omega_1 I_1 + \omega_2 I_2 + \psi_1 E_1 + \psi_2 E_2 - \mu T - \delta_1 T - \delta_2 T
\end{cases}
\tag{1}
$$

3 ESSENTIAL FEATURES

3.1. Solutions that are constructive and limited

Theorem 3.1. *Let* $S_1(0) > 0, E_1(0) > 0, I_1(0) > 0, R_1(0) > 0, S_2(0) > 0, E_2(0) > 0, I_2(0) > 0, R_2(0) > 0,$ and $T(0) > 0$. *Be the initial data, For any* $t > 0$, *the model (1) solutions* $(S_1, E_1, I_1, R_1, S_2, E_2, I_2, R_2, T)$ *are positive. Furthermore,* $\lim_{t\to\infty} sup\, N(t) \leq \frac{\Lambda}{\mu}$.

Proof: From the first equation of the system (1),

$$\frac{dS_1}{dt} = \Lambda - \big(\mu + \alpha + \lambda(t)\big)S_1,$$

we can write that equation for $t \geq 0$ become

$$\frac{d\big(S_1(t)\big)}{dt} + (\mu + \alpha) \cdot S_1(t) + \lambda(t) \cdot S_1(t) = \Lambda \tag{3}$$

Equation (3) can be written as,

$$\frac{d\big(S_1(t)\big)}{dt} e^{(\mu+\alpha)t+\int_0^t \lambda(u)du} + \big(\mu + \alpha + \lambda(t)\big)S_1(t)e^{(\mu+\alpha)t+\int_0^t \lambda(u)du} = \Lambda e^{(\mu+\alpha)t+\int_0^t \lambda(u)du}$$

$\frac{d}{dt}\left(S_1(t)e^{(\mu+\alpha)t+\int_0^t \lambda(u)du}\right) = \Lambda e^{(\mu+\alpha)t+\int_0^t \lambda(u)du}$Integrating both sides, we would have

$$S_1(t)e^{(\mu+\alpha)t+\int_0^t \lambda(u)du} - S_1(0) = \int_0^t \Lambda e^{(\mu+\alpha)s+\int_0^s \lambda(w)dw}\, ds$$

Thus, the solution would be

$$S_1(t) = e^{-\left((\mu+\alpha)t+\int_0^t \lambda(u)du\right)}\left\{S(0) + \int_0^t \Lambda e^{(\mu+\alpha)s+\int_0^s \lambda(w)dw}\, ds\right\} > 0, \forall t \geq 0$$

Similarly, it can be shown that $E_1(0) > 0, I_1(0) > 0, R_1(0) > 0, S_2(0) > 0, E_2(0) > 0, I_2(0) > 0, R_2(0) > 0,$ and $T(0) > 0$ for all $t \geq 0$.

The sum of the equations in system (1), however, yields

$$\frac{dN(t)}{dt} = \frac{dS_1(t)}{dt} + \frac{dE_1(t)}{dt} + \frac{dI_1(t)}{dt} + \frac{dR_1(t)}{dt} + \frac{dS_2(t)}{dt} + \frac{dE_2(t)}{dt} + \frac{dI_2(t)}{dt} + \frac{dR_2(t)}{dt} + \frac{dT(t)}{dt}$$

$$\frac{dN(t)}{dt} = \Lambda - \mu N(t) - d_1 I_1(t) - (d_2 + \gamma)I_2(t) \tag{4}$$

From equation (4), we get the following inequality

$$\Lambda - (\mu + d_1 + d_2 + \gamma)N(t) \leq \frac{dN(t)}{dt} \leq \Lambda - \mu N(t) \tag{5}$$

Thus,

$$\frac{\Lambda}{\mu + d_1 + d_2 + \gamma} \leq \lim_{t\to\infty} inf\, N(t) \leq \lim_{t\to\infty} sup\, N(t) \leq \frac{\Lambda}{\mu}.$$

So that, $\limsup_{t\to\infty} N(t) \leq \frac{\Lambda}{\mu}$. The proof is complete. ■

3.2. Invariant Region and Existence Solution of the Model

Theorem 3.2. *The feasible set is a positive invariant set over system (1) with initial circumstances in*

$\mathbb{R}_+^9.\ \Omega = \left\{\left(S_1(t), E_1(t), I_1(t), R_1(t), S_2(t), E_2(t), I_2(t), R_2(t), T(t)\right) \in \mathbb{R}_+^9 \,\middle|\, 0 \leq N(t) \leq \frac{\Lambda}{\mu}\right\}$

has the initial condition.

Proof: Let any solution with non-negative initial conditions be $(S_1, E_1, I_1, R_1, S_2, E_2, I_2, R_2, T) \in \mathbb{R}_+^9$ Inequality (5) gives us, we have

$$\frac{dN(t)}{dt} \leq \Lambda - \mu N(t) \tag{6}$$

Inequality (6) can be written as

$$\frac{dN(t)}{dt} e^{\mu t} + \mu N(t) e^{\mu t} \leq \Lambda e^{\mu t}$$

$$\Leftrightarrow \frac{d(N(t)e^{\mu t})}{dt} \leq \Lambda e^{\mu t}$$

Taking the integral of both sides from 0 to t, we obtain

$$N(t) \leq \left[N(0) - \frac{\Lambda}{\mu}\right] e^{-\mu t} + \frac{\Lambda}{\mu} \tag{7}$$

where $N(0)$ represents the initial values of $N(t)$.

System (1) explains the population dynamics. This highlights the non-negative nature of the model variables and parameters at time t. Therefore, inequality (7) has the following lower limit,

$$0 \leq N(t) < \left[N(0) - \frac{\Lambda}{\mu}\right] e^{-\mu t} + \frac{\Lambda}{\mu}$$

Hence, as $t \to \infty$, $0 \leq N(t) \leq \frac{\Lambda}{\mu}$. Therefore, all system (1) practical solutions enter the area,

$\Omega = \left\{\left(S_1(t), E_1(t), I_1(t), R_1(t), S_2(t), E_2(t), I_2(t), R_2(t), T(t)\right) \in \mathbb{R}_+^9 \,\middle|\, 0 \leq N(t) \leq \frac{\Lambda}{\mu}\right\}$.

It shows that the set Ω is a system-positive invariant set (1). This completes the proof. ■

Theorem 3.3. *For every non-negative initial value*

$\left(S_1(0), E_1(0), I_1(0), R_1(0), S_2(0), E_2(0), I_2(0), R_2(0), T(0)\right) \in \Omega$, *For system (1),*

there are always solutions.

Proof: We apply a Lipschitz condition to examine the existence of the model solution.

Let $X = \begin{pmatrix} S_1(t) \\ E_1(t) \\ I_1(t) \\ R_1(t) \\ S_2(t) \\ E_2(t) \\ I_2(t) \\ R_2(t) \\ T(t) \end{pmatrix}$ and $\vartheta(X) = \begin{pmatrix} \dot{S}_1(t) \\ \dot{E}_1(t) \\ \dot{I}_1(t) \\ \dot{R}_1(t) \\ \dot{S}_2(t) \\ \dot{E}_2(t) \\ \dot{I}_2(t) \\ \dot{R}_2(t) \\ \dot{T}(t) \end{pmatrix}$, so the system (1) is rewritten in the following

form

$$\vartheta(X) = AX + P$$

where

$$A = \begin{bmatrix} -(\mu+\alpha+\lambda) & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ (1-p_1)\lambda & -A_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ p_1\lambda & \sigma_1 & -A_2 & 0 & 0 & 0 & 0 & 0 & (1-q)\delta_1 \\ 0 & 0 & \eta_1 & -A_3 & 0 & 0 & 0 & 0 & q\delta_1 \\ \alpha & 0 & 0 & 0 & -(\mu+\theta\lambda) & 0 & 0 & 0 & 0 \\ 0 & \alpha & 0 & 0 & \theta(1-p_2)\lambda & -A_4 & 0 & 0 & 0 \\ 0 & 0 & \tau\alpha & 0 & \theta p_2\lambda & \theta\sigma_2 & -A_5 & 0 & (1-q)\delta_2 \\ 0 & 0 & 0 & \alpha & 0 & 0 & \eta_2 & -\mu & q\delta_2 \\ 0 & \psi_1 & \omega_1 & 0 & 0 & \psi_2 & \omega_2 & 0 & -A_6 \end{bmatrix}, P = \begin{bmatrix} \Lambda \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

Then,

$$\|\vartheta(X_a) - \vartheta(X_b)\| = \left\| \begin{bmatrix} (\mu+\alpha+\lambda)(S_{1b} - S_{1a}) \\ (1-p_1)\lambda|S_{1a} - S_{1b}| + A_1|E_{1b} - E_{1a}| \\ p_1\lambda|S_{1a} - S_{1b}| + \sigma_1|E_{1a} - E_{ab}| + A_2|I_{1b} - I_{1a}| + (1-q)\delta_1|T_a - T_b| \\ \eta_1|I_{1a} - I_{1b}| + A_3|R_{1b} - R_{1a}| + q\delta_1|T_a - T_b| \\ \alpha|S_{1a} - S_{1b}| + (\mu+\theta\lambda)|S_{2b} - S_{2a}| \\ \alpha|E_{1a} - E_{1b}| + \theta(1-p_2)\lambda|S_{2a} - S_{2b}| + A_4|E_{2b} - E_{2a}| \\ \tau\alpha|I_{1a} - I_{1b}| + \theta p_2\lambda|S_{2a} - S_{2b}| + \theta\sigma_2|E_{2a} - E_{2b}| + A_5|I_{2b} - I_{2a}| + (1-q)\delta_2|T_a - T_b| \\ \alpha|R_{1a} - R_{1b}| + \eta_2|I_{2a} - I_{2b}| + \mu|R_{2b} - R_{2a}| + q\delta_2|T_a - T_b| \\ \psi_1|E_{1a} - E_{1b}| + \omega_1|I_{1a} - I_{1b}| + \psi_2|E_{2a} - E_{2b}| + \omega_2|I_{2a} - I_{2b}| + A_6|T_b - T_a| \end{bmatrix} \right\|$$

$$\leq \mu|S_{1b} - S_{1a}| + M_1|E_{1b} - E_{1a}| + M_2|I_{1b} - I_{1a}| + M_3|R_{1b} - R_{1a}| + \mu|S_{2b} - S_{2a}| + M_4|E_{2b} - E_{2a}| + M_5|I_{2b} - I_{2a}| + \mu|R_{2b} - R_{2a}| + M_6|T_b - T_a|$$

$$\leq M(|S_{1b} - S_{1a}| + |E_{1b} - E_{1a}| + |I_{1b} - I_{1a}| + |R_{1b} - R_{1a}| + |S_{2b} - S_{2a}| + |E_{2b} - E_{2a}| + |I_{2b} - I_{2a}| + |R_{2b} - R_{2a}| + |T_b - T_a|)$$

$$\leq M\|\vartheta_a - \vartheta_b\|$$

where

$$A_1 = (\mu+\alpha+\sigma_1+\psi_1)\ A_2 = (\mu+\tau\alpha+d_1+\omega_1+\eta_1) \qquad A_3 = (\mu+\alpha)$$

$A_4 = (\mu + \theta\sigma_2 + \psi_2)$ $A_5 = (\mu + d_2 + \omega_2 + \eta_2 + \gamma)$, and $A_6 = \mu + \delta_1 + \delta_2$.

and

$$M_1 = A_1 + \sigma_1 + \alpha + \psi_1, M_2 = A_2 + \eta_1 + \tau\alpha + \omega_1, M_3 = A_3 + \alpha, M_4 = A_4 + \theta\sigma_2 + \psi_2,$$

$$M_5 = A_5 + \eta_2 + \omega_2, M_6 = A_6 + \delta_1 + \delta_2, \text{and } M = max(\mu, M_1, M_2, M_3, M_4, M_5, M_6)$$

So, the function ϑ satisfies the Lipschitz continuity condition. Thus, based on the restrictions on the state variables, namely $S_1(t) > 0, E_1(t) > 0, I_1(t) > 0, R_1(t) > 0, S_2(t) > 0, E_2(t) > 0, I_2(t) > 0, R_2(t) > 0$, and $T(t) > 0$., it can be concluded that system (1) has a unique solution. ■

3.3. Basic reproduction number

By setting the right-hand sides of the model's equations to zero, model system (1) achieves a state of disease free equilibrium (DFE),

$$DFE = (S_1^0, 0,0,0, S_2^0, 0,0,0,0)$$

with $S_1^0 = \frac{\Lambda}{\mu+\alpha}$ and $S_2^0 = \frac{\alpha\Lambda}{\mu(\mu+\alpha)}$.

The basic reproduction number, $\Re_0$, can be established using the next generation matrix (NGM). Following Driessche and Watmough [9], we have the matrices F and V as follows

$$F = \frac{1}{N_0}\begin{bmatrix} 0 & a_1\beta S_1^0 & 0 & a_1\varepsilon\beta S_1^0 \\ 0 & p_1\beta S_1^0 & 0 & p_1\varepsilon\beta S_1^0 \\ 0 & a_2\theta\beta S_2^0 & 0 & a_2\varepsilon\theta\beta S_2^0 \\ 0 & p_2\theta\beta S_2^0 & 0 & p_2\varepsilon\theta\beta S_2^0 \end{bmatrix} \text{ and } V = \begin{bmatrix} A_1 & 0 & 0 & 0 \\ -\sigma_1 & A_2 & 0 & 0 \\ -\alpha & 0 & A_4 & 0 \\ 0 & -\tau\alpha & -\theta\sigma_2 & A_5 \end{bmatrix}$$

Then, the number $\Re_0$ is given by

$$\Re_0 = \rho(FV^{-1})$$

$$= \frac{1}{N_0}\frac{\beta}{A_1A_2A_4A_5}\big((A_4(\alpha\varepsilon\tau + A_5)(\sigma_1a_1 + A_1p_1) + A_2\theta\varepsilon\alpha\sigma_2a_1)S_1^0 + A_1A_2\theta\varepsilon(\sigma_2a_2\theta + A_4p_2)S_2^0\big)$$

where $a_1 = (1 - p_1)$, $a_2 = (1 - p_2)$, $N_0 = \frac{\Lambda}{\mu}$ and ρ represents the spectral radius.

4 MODEL ANALYSIS

4.1 Stability of DFE

Lemma 4.1. *DFE of system (1) is L.A.S when* $\Re_0 < 1$ *and unstable when* $\Re_0 > 1$.

The system (1) has the following Jacobian matrix at DFE:

$$J = \begin{bmatrix} & \frac{-\beta\mu}{(\mu+\alpha)} & & & & \frac{-\beta\varepsilon\mu}{(\mu+\alpha)} & & \\ & \frac{(1-p_1)\beta\mu}{(\mu+\alpha)} & & & & \frac{(1-p_1)\beta\varepsilon\mu}{(\mu+\alpha)} & & \\ -(\mu+\alpha) & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -A_1 \; \frac{p_1\beta\mu}{(\mu+\alpha)} - A_2 & 0 & 0 & 0 & p_1\frac{\beta\varepsilon\mu}{(\mu+\alpha)} & 0 & 0 \\ 0 & \sigma_1 & 0 & 0 & 0 & 0 & 0 & (1-q)\delta_1 \\ 0 & 0 & \eta_1 & -A_3 & 0 & 0 & 0 & q\delta_1 \\ \alpha & 0 & \frac{-\theta\beta\alpha}{(\mu+\alpha)} & 0 & -\mu & \frac{-\theta\beta\varepsilon\alpha}{(\mu+\alpha)} & 0 & 0 \\ 0 & \alpha & 0 & 0 & -A_4 & 0 & 0 & 0 \\ 0 & 0 & \frac{\theta(1-p_2)\beta\alpha}{(\mu+\alpha)} & 0 & \theta\sigma_2 & \frac{\theta(1-p_2)\beta\varepsilon\alpha}{(\mu+\alpha)} & 0 & (1-q)\delta_2 \\ 0 & 0 & 0 & \alpha & 0 & 0 & -\mu & q\delta_2 \\ 0 & \psi_1 & \tau\alpha + \frac{\theta p_2\beta\alpha}{(\mu+\alpha)} & 0 & \psi_2 & \frac{\theta p_2\beta\varepsilon\alpha}{(\mu+\alpha)} - A_5 & 0 & -A_6 \\ & & 0 & & & \eta_2 & & \\ & & \omega_1 & & & \omega_2 & & \end{bmatrix}$$

The nine roots of the ninth-order polynomial equation are the Jacobian matrix's nine eigenvalues. Explicitly locating the roots is challenging because there are numerous parameters involved. Applying the Routh Hurwitz criteria test, which results in all real parts of polynomial roots being negative if and only if the criterion test conditions are met, is one way to identify the type of polynomial roots.

The basic reproduction number calculates the typical number of new cases of TB that one infection causes in a susceptible population. As a result, when $\Re_0 < 1$, the DFE of the system (1) is locally asymptotically stable (L.A.S). If and $\Re_0 > 1$, TB stay in the community.

Next, we used the result of Castillo-Chavez et al. [10] on the global stability of DFE. We rewrite system (1) as

$$\dot{x}(t) = F(x, y);$$
$$\dot{y}(t) = G(x, y);\ G(x, 0) = 0$$

where

$$x(t) = (S_1(t), S_2(t), R_1(t), R_2(t), T(t))^T \in \mathbb{R}_+^5$$
$$y(t) = \left(E_1(t), I_1(t), E_2(t), I_2(t)\right)^T \in \mathbb{R}_+^4$$

The DFE is now denoted by $E_0 = (x_0, 0)$ where $x_0 = (S_1^0, S_2^0, R_1^0, R_2^0, T^0)$.

The conditions (C_1) and (C_2) below must be met to guarantee E_0 is globally asymptotically stable (G.A.S).

$$C_1\text{: For } \dot{x}(t) = F(x, 0),\ x_0 \text{ is G.A.S,} \quad (2)$$
$$C_2\text{: } G(x, y) = Hy - \tilde{G}(x, y), \tilde{G}(x, y) \geq 0 \text{ for } (x, y) \in \Omega, \quad (3)$$

where H is an M-matrix (the off diagonal elements of H are nonnegative) and Ω is the region where the model makes biological sense. If system (1) satisfies the conditions in Eq. (2) and (3), then the following result holds.

Theorem 4.1. *The point $E_0 = (x_0, 0)$ of system (1) is G.A.S if $\Re_0 < 1$ and the conditions in Eq.* (2) and (3) *are satisfied.*

Proof: From the proof in Lemma 4.1, the DFE is L.A.S when $\Re_0 < 1$. Using system (1), we have

$$F(x,0) = \begin{bmatrix} \Lambda - (\mu+\alpha)S_1 \\ \alpha S_1 - \mu S_2 \\ 0 \\ 0 \\ 0 \end{bmatrix}, C = \begin{bmatrix} -A_1 & (1-p_1)\beta & 0 & (1-p_1)\beta\varepsilon \\ \sigma_1 & p_1\beta - A_2 & 0 & p_1\beta\varepsilon \\ \alpha & \theta(1-p_2)\beta & -A_4 & \theta(1-p_2)\beta\varepsilon \\ 0 & \tau\alpha + \theta p_2\beta & \theta\sigma_2 & \theta p_2\beta\varepsilon - A_5 \end{bmatrix},$$

and

$$\tilde{G}(x,y) = \begin{bmatrix} (1-p_1)\beta I_1\left(1-\frac{S_1}{N}\right) + (1-p_1)\beta\varepsilon I_2\left(1-\frac{S_1}{N}\right) \\ p_1\beta I_1\left(1-\frac{S_1}{N}\right) + p_1\beta\varepsilon I_2\left(1-\frac{S_1}{N}\right) \\ \theta(1-p_2)\beta I_1\left(1-\frac{S_2}{N}\right) + \theta(1-p_2)\beta\varepsilon I_2\left(1-\frac{S_2}{N}\right) \\ \theta p_2\beta I_1\left(1-\frac{S_2}{N}\right) + \theta p_2\beta\varepsilon I_2\left(1-\frac{S_2}{N}\right) \end{bmatrix}$$

Parameter $\theta, \beta, \varepsilon$ is positive constant. The value of p_1 and p_2 are restricted, i.e $0 \leq p_1, p_2 < 1$, then $(1-p_1) \geq 0$ and $(1-p_2) \geq 0$. We know that $0 \leq S_1, S_2 \leq N$.

Let $I_1^0 = I_1(0)$ and $I_2^0 = I_2(0)$, note that $I_1(t) > 0$ if $I_1^0 > 0$ and $I_2(t) > 0$ if $I_2^0 > 0$. We can conclude that $\tilde{G}(x,y) \geq 0$.

Next, using the variation of constant formula, we have

$$0 \leq I_1(t) = e^{Ht} I_1(0) - \int_0^t e^{H(t-s)} \tilde{G}\big(x(s), y(s)\big) ds \leq e^{Ht} I_1(0)$$

Since H is an M-matrix, H has a dominant eigenvalue $m(H)$ with $m(H) < 0$ for $\Re_0 < 1$. Thus

$$\lim_{t\to\infty} \|e^{Ht}\| = 0 \Rightarrow \lim_{t\to\infty} I_1(t) = 0$$

The same calculation is performed for $I_2(t)$, and we have $\lim_{t\to\infty} I_2(t) = 0$.

For $x_1(t) = S_1(t)$,

$$\lim_{t\to\infty} x_1(t) = \lim_{t\to\infty} S_1(t)$$

$$= \lim_{t\to\infty} e^{-\left((\mu+\alpha)t + \int_0^t \lambda(u)du\right)} \left\{ S(0) + \int_0^t \Lambda e^{(\mu+\alpha)s + \int_0^s \lambda(w)dw}\, ds \right\}$$

$$= \frac{\Lambda}{\mu + \alpha} = S_1^0$$

The same calculation is performed for $S_2(t)$, and we have $\lim_{t\to\infty} S_2(t) = \frac{\alpha\Lambda}{\mu(\mu+\alpha)}$.

Since $\lim_{t\to\infty} I_1(t) = 0$ and $\lim_{t\to\infty} I_2(t) = 0$, we have $\lim_{t\to\infty} R_1(t) = \lim_{t\to\infty} R_2(t) = \lim_{t\to\infty} T(t) = 0$.

It is clear that $x_0 = (S_1^0, S_2^0, R_1^0, R_2^0, T^0) = \left(\frac{\Lambda}{\mu+\alpha}, \frac{\alpha\Lambda}{\mu(\mu+\alpha)}, 0,0,0\right)$ is GAS of $\dot{x}(t) = F(x, 0)$.

Both condition in Eq. (2) and (3) are satisfied, so by the above theorem E_0 is G.A.S. ■

4.2 Stability of Endemic Equilibrium (EE)

System (1) has basically two possible endemic equilibria, that is the EE points for non diabetics only and the EE points where both non-diabetics and diabetics exist. Endemic occurs within a population when $I \neq 0$, so we have

$$S_1^* = \frac{\Lambda}{(\mu+\alpha+\lambda)}, E_1^* = \frac{(1-p_1)\lambda S_1^*}{A_1}, I_1^* = \frac{p_1\lambda S_1^* + \sigma_1 E_1^* + (1-q)\delta_1 T^*}{A_2}, R_1^* = \frac{\eta_1 I_1^* + q\delta_1 T^*}{A_3}$$

$$S_2^* = \frac{\alpha S_1^*}{(\mu+\theta\lambda)}, E_2^* = \frac{\theta(1-p_2)\lambda S_2^* + \alpha E_1^*}{A_4}, I_2^* = \frac{\tau\alpha I_1^* + \theta p_2 \lambda S_2^* + \theta\sigma_2 E_2^* + (1-q)\delta_2 T^*}{A_5}$$

$$R_2^* = \frac{\alpha R_1^* + \eta_2 I_2^* + q\delta_2 T^*}{\mu}, T^* = \frac{\omega_1 I_1^* + \omega_2 I_2^* + \psi_1 E_1^* + \psi_2 E_2^*}{A_6}$$

Lemma 4.2. Based on the value of $\Re_0$, model (1) could have

(i) a unique EE whenever $\Re_0 > 1$.

(ii) more than one EE whenever $\Re_0 > 1$.

(iii) a unique EE m whenever $\Re_0 < 1$.

(iv) one or more EE whenever $\Re_0 < 1$.

5 SENSITIVITY ANALYSIS AND NUMERICAL SIMULATION

The parameter values used for numerical simulation are given in Table 1.

Table 1. Numerical values for the parameters of system (1)

Symbol	Value	Source	Symbol	Value	Source
Λ	667685/yr	[11]	ψ_2	0/yr	[15]
β	3	[9]	ω_1	0.7372/yr	[14]
ε	1.1	Assumed	ω_2	0.7372/yr	Assumed
τ	1.01	Assumed	d_1	0.275/yr	[15]
θ	2	[12]	d_2	1.25*d1/yr	[14]
μ	1/53.5/yr	[11]	γ	0.05	[16]
α	9/1000/yr	Assumed	q	0.94	[17]
σ_1	$0.75 * p1$	[13]	η_1	1.07	[17]
σ_2	$0.7 * p1$	Assumed	η_2	0.05	[17]
p_1	0.03	[14]	δ_1	0.14	[17]
p_2	0.06	[14]	δ_2	0.33	[17]
ψ_1	0/yr	[15]			

5.1 Sensitivity Analysis

Sensitivity analysis is used to evaluate the relative importance of model parameters to TB transmission and prevalence. We perform the analysis by calculating the sensitivity indices of number $\Re_0$. We may evaluate the relative change in a state variable when a parameter changes. As the number $\Re_0$ is a differentiable function of the parameters, the sensitivity index can similarly be created using partial derivatives. For instance, the formula for calculating the sensitivity index of $\Re_0$ with regard to the parameter values in Table 1 is as follows.

$$\prod_{\beta}^{\Re_0} = \left(\frac{\partial \Re_0}{\partial \beta}\right)\left(\frac{\beta}{\Re_0}\right) = 1 > 0$$

This reveals that $\Re_0$ is a function that increases and that the parameter significantly affects the transmission of TB. The indices of the remaining parameters are listed in Table 2.

Table 2. Sensitivity indices for the $\Re_0$

Parameter	Index	Parameter	Index	Parameter	Index
Λ	2	α	0.4145	δ_2	0.0046
μ	-2.6174	σ_1	0.1357	ψ_1	0
β	1	σ_2	0.0521	ψ_2	0
ε	0.7976	p_1	0.0036	d_1	-0.1071
τ	0.0008	p_2	0.0089	d_2	-0.0343
θ	0.8102	ω_1	-0.0668	η_1	-0.0275
q	-0.5014	ω_2	-0.4804	η_2	-0.2358
γ	-0.0343	δ_1	-0.0034		

According to Table 2, parameters with negative signs on their sensitivity indices cause

the value of the basic reproduction number to decrease as their values rise, whereas those with positive indications cause the value of $\Re_0$ to rise. The value of the fundamental reproduction number is unaffected by those lacking any indicators.

According to Table 2, the higher risk of developing diabetes and the increased factor of TB susceptibility because of DM lead to an increase in $\Re_0$. The sensitivity index value of 0.4145 indicates that if we raise (lower) the value of by 10%, the value of $\Re_0$ will rise (fall) by 4.145%. Additionally, if we raise (lower) the value of by 10%, the value of $\Re_0$ will rise (fall) by 8.102%.

We can easily see that when the treatment rate ω_2 increasing, the basic reproduction number $\Re_0$ decreases. This means that the treatment of active TB patients in a diabetic population would have a positive impact in TB control. The value of sensitivity index $\omega_2 = -0.4804$ represents that if we increase (decrease) the value of ω_2 by 10% then the value of $\Re_0$ will decrease (increase) by 4.804%.

5.2 Numerical Simulation

For illustrative purposes and to support the analytical results, numerical simulations are run using a set of suitable parameter values from Table 1. The following randomly selected initial conditions were used in all simulations to run the model: $E_1(0) = 557800, E_2(0) = 4500, I_1(0) = 20000, I_2(0) = 1800, R_1(0) = 8000, R_2(0) = 200$, and $T(0) = 200. S_1(0) = 8741400, S_2(0) = 200000$. The transmission rate has been set in all simulations so that there is a case for $\Re_0 > 1$ and for $\Re_0 < 1$. We start by selecting $\beta = 1$. Figure 2 demonstrates that the DFE is locally asymptotically stable after the numerical simulation yields $\Re_0 < 1$. Next, we select $\beta = 3$. Figure 3 demonstrates that the EE is locally asymptotically stable when a numerical simulation yields $\Re_0 > 1$.

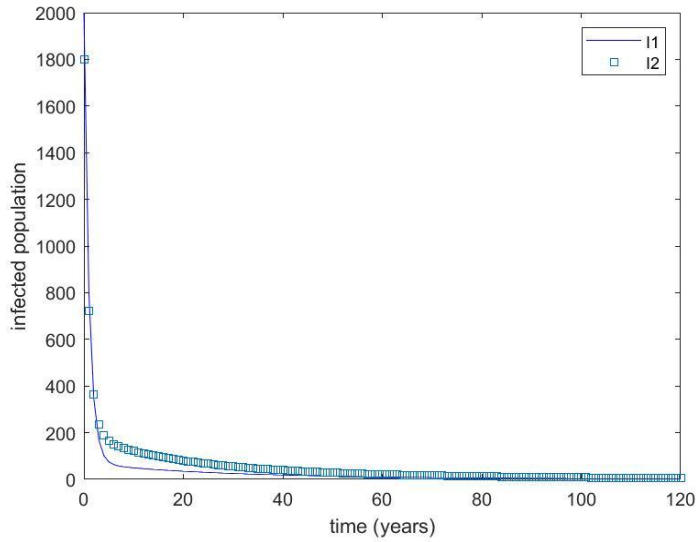

Figure 2. Population graph infecting active TB without DM and with DM when $\beta = 1$

Figure 2 illustrates numerical simulations of model (1) with plots of non-diabetic and diabetic active infected populations (I_1 and I_2) when $\beta = 1$ so that $\Re_0 = 0.7319 < 1$. Figure 2 shows that diabetics (I_2) are more likely to have the infection than non-diabetics (I_1). This indicates that DM increases the number of people with active TB infection. Additionally, Figure 2 demonstrates that as time goes on, both the proportion of TB populations without diabetes and those with diabetes decline. The number of populations with active TB infections will decrease if efforts are made to lessen the interaction rate between those who are vulnerable to TB and those who have the disease. Figure 2 demonstrates that people with active TB infection who do not have diabetes (I_1) get to the disease-free equilibrium point more quickly than people with active TB infection who do have diabetes (I_2). Compared to those with active TB without DM (I_1), those with active TB with DM (I_2) require more time to achieve the disease-free equilibrium point.

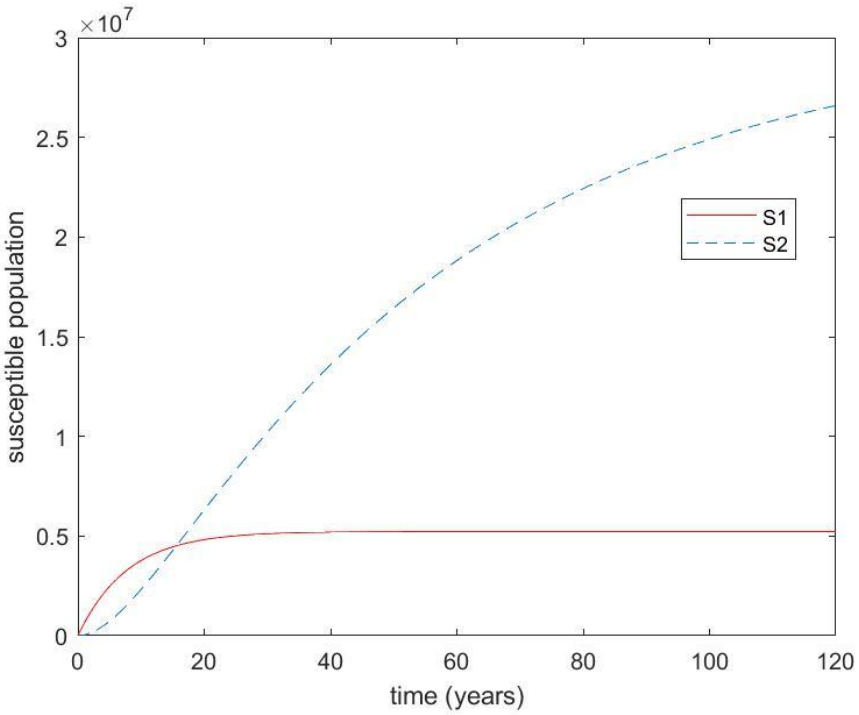

Figure 3. Susceptible population graph without DM and with DM when $\alpha = 0.109$ and $\beta = 3$

Figure 3 displays numerical simulations of model (1) with plots of non-diabetic and susceptible-to-diabetes populations (S_1 and S_2) when $\alpha = 0.109$ and $\beta = 3$ so that $\Re_0 = 4.1621 > 1$. With time, there are more people who are both susceptible to TB without DM and susceptible to TB with DM. High blood sugar sufferers may affect how the TB disease spreads. The spread of the TB disease is aided by raising the values of the parameters and; as can be seen, the resulting $\Re_0$ value is higher than 1. The spread of the TB disease is accelerated by an increase in the number of diabetics.

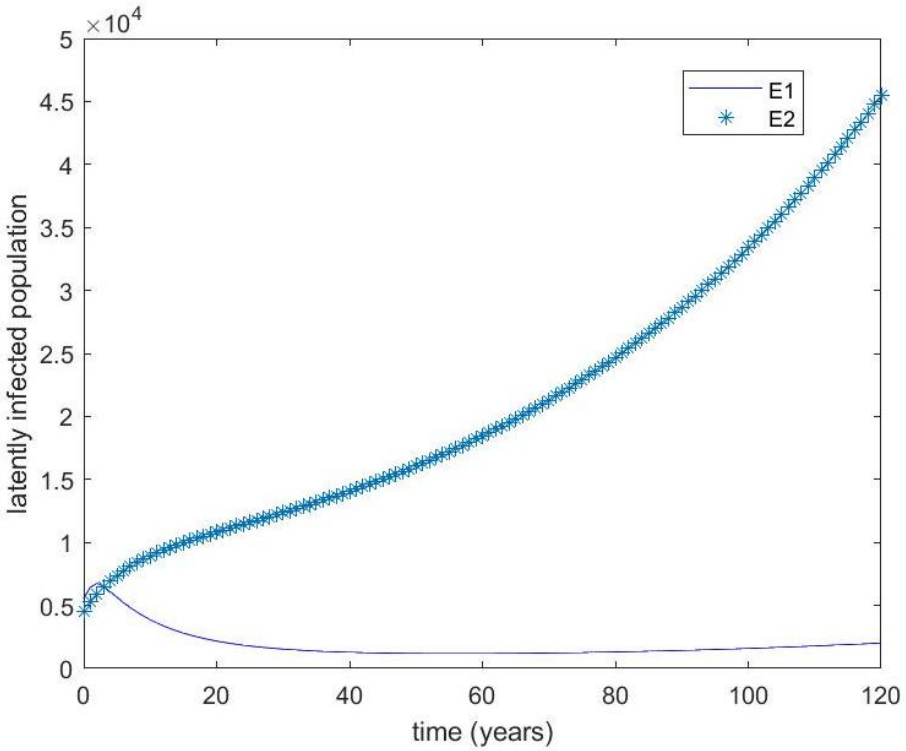

Figure 4. Latently infected population graph without DM and with DM when $\alpha = 0.109$ and $\beta = 3$

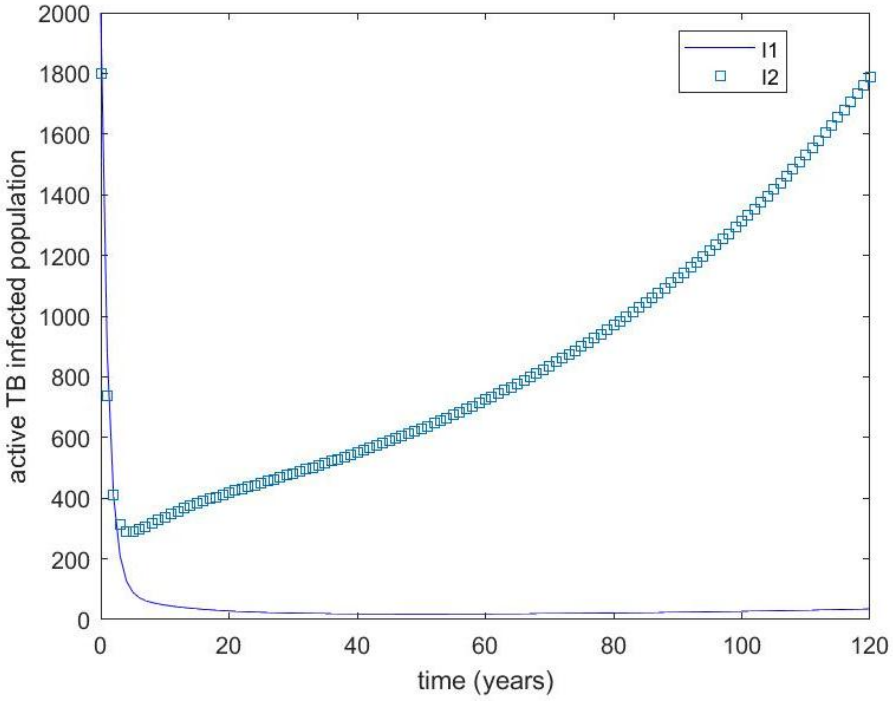

Figure 5. Active TB infected population graph without DM and with DM when $\alpha = 0.109$ and $\beta = 3$

Graphical representations as in Figure 4 and Figure 5 clearly show that an increase of the susceptibility to TB due to DM (α) will generally result in an increases in the number of TB infected individuals with more effect on diabetics latently infected individuals. Thus, DM increases disease transmission.

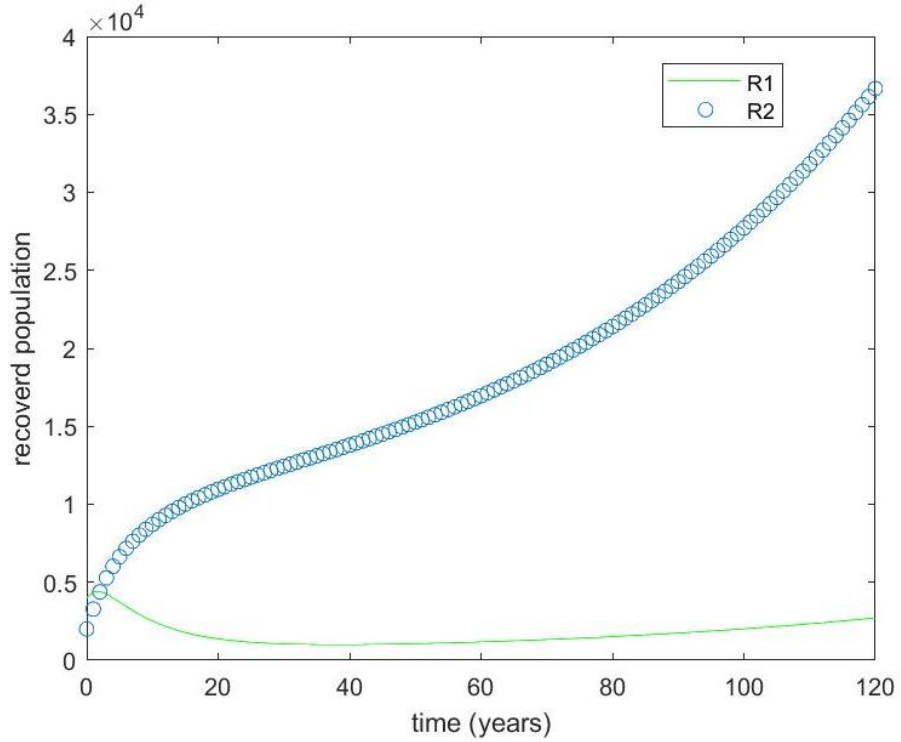

Figure 6. Recovered population graph without DM and with DM when $\beta = 3$

Furthermore, in the presence of treatment, TB control is more effective in communities with diabetics than in the communities with non-diabetics. DM significantly influences the development of TB, so treatment is needed for TB patients with DM. Thus, care for TB patients involves more than just giving the anti-TB treatment. One type of treatment for TB patients is known as the DOTS (Direct Observed Treatment Short Course) strategy. The DOTS (Direct Observed Treatment Short Course) strategy is a management to ensure TB patients swallow anti-TB drugs. To support the DOTS strategy, it requires discipline and compliance from TB patients in their treatment. If treatment compliance is not achieved, then the cure rate as promote by DOTS strategy would not be reached.

Pulmonary TB is one of the most common causes of complications in DM, resulting in the increasing prevalence of DM contributing to the increasing TB epidemic. As more and more people develop diabetes, intervention strategies such as counselling and education campaigns are needed to reduce the spread of TB. Counselling mainly emphasizes diet and physical activity, namely a low-carbohydrate diet and exercise. So, good integration is needed between TB treatment and particular treatment strategies focusing on TB patients with DM.

6 CONCLUSION

A mathematical model for studying the dynamics of TB transmission in a population, considering that some people in the population have diabetes, is presented as a system of ordinary differential equations. Based on the analysis results, a disease-free equilibrium point and an endemic equilibrium point were obtained. The stability of each equilibrium point depends on the system parameters.

Based on the results of the sensitivity test of the $\mathfrak{R}_0$ value to several model parameters, results were obtained which showed that the $\mathfrak{R}_0$ value would increase if the interaction parameter between individuals susceptible to TB and individuals infected with active TB with and without DM (β) were more significant so that the disease would spread in the population. Meanwhile, the $\mathfrak{R}_0$ value will decrease if the value of the rate parameter for individuals infected with TB without DM undergoing treatment (ω_1) and the parameter for the rate of individuals infected with TB with DM undergoing treatment (ω_2) is more significant, which means the infected population will decrease or be free from disease. Based on numerical simulations, it was found that it is necessary to integrate TB treatment and special treatment in treating TB disease with DM to reduce and prevent the spread of TB disease.

ACKNOWLEDGMENT

The Faculty of Science and Mathematics at Diponegoro University, under grant number 22.E/UN7.F8/PP/II/2023, provided funding for this research that was separate from the Indonesian State Revenue and Expenditure Budget.

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