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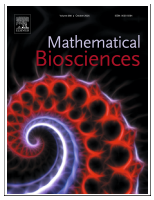

Original research article

Impact of latent delay and environment infection on tuberculosis dynamics in a population

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ABSTRACT

In this paper we explore the impact of latency delay and infection by Mycobacterium tuberculosis in the environment on the spread of tuberculosis in a population. We first derive a delay differential equation model with environmental indirect transmission. We address the well-posenedness and identify the basic reproduction number $\mathcal{R}_0$ of the model. We then discuss the equilibria and their stability in terms of the composite threshold parameter $\mathcal{R}_0$ which determine whether or not the tuberculosis will go extinct of persist in the popolaiton: the disease free equilibrium is globally stable if $\mathcal{R}_0 < 1$, and it becomes unstable if $\mathcal{R}_0 > 1$. In the latter case, there exists a unique endemic equilibrium, which is locally asymptotically stable when τ is sufficiently small; furthermore, we obtain the conditions for the existence of Hopf bifurcation around the endemic equilibrium. The condition implies that the interplay of the latency delay and infection of Mycobacterium tuberculosis in the environment may contribute not only to the TB's persistence but also the way it persists: either as an constant pattern (endemic equilibrium) or as a periodic pattern (oscillation around the endemic equilibrium). We also discuss the epidemiological implication of the mathematical results.

1. Introduction

Tuberculosis (TB) is an ancient infectious disease caused by Mycobacterium tuberculosis (Mtb), yet it remains a major global public health problem. According to the Global Tuberculosis Report 2024 released by the WHO (World Health Organization) [26], there were 10.8 million TB cases in 2022 in the world, including 134 new cases per 100,000 people. The latest research [14] reveals that TB was the leading cause of deaths caused from a single infectious disease in the world in 2022; and after the COVID-19 pandemic, it has caused nearly twice the number of deaths as caused by HIV, reaching a total of 1.13 million deaths.

Spread of TB is mainly through air [18,22]. When active TB carriers cough, sneeze, speak loudly or spit, Mtb in their bodies are expelled from their bodies, first in the air and then landing in the environment. However, studies have shown that Mtb landed in the environment can survive in the environments for months to years [13]. Furthermore, if Mtb attaches to dust particles floating in the air, it can maintain its infectiousness for 8 to 10 days [15]. One may naturally wonder whether Mtb in the environment has an impact on the spread of TB. There have been some works that model the role of Mtb in the environment in the spread of TB [3,7,10]. These models are relatively complex and are all in the form of ordinary differential equation (ODEs) based on the classic epidemic compartment framework; and moreover they focus more on numerical analysis and lack rigorous analysis on disease dynamic.

We note that infectious disease data released by the China Center for Disease Control (CDC) show that the spread of TB in China demonstrate oscillations as seen Fig. 1, which indicates that the highest number of newly reported cases is in early spring, and the lowest number of newly reported cases is in winter.

In fact, in addition to China, TB in nearly 10 countries including South Africa, India, Japan, and Pakistan also demonstrate similar oscillatory patterns [2,4]. Unfortunately, there is no clear medical or biological explanation for such fluctuation patterns of TB dynamics. Some scholars tend to attribute such oscillations to seasonality and have used some periodic ODE models to explain such fluctuations, see, e.g., [11,12,21].

On the other hand, it is well-known that TB has a latent period and the latent phenomenon can be described by delay differential equations (DDEs), and it is also well known that delays often cause oscillations. Realizing this, combined with the above observations, in this paper, we propose a DDE model to describe the transmission dynamics of TB in a population, in which, the Mtb bacteria in the environment and their infections are also incorporated. The constant delay in the DDE model

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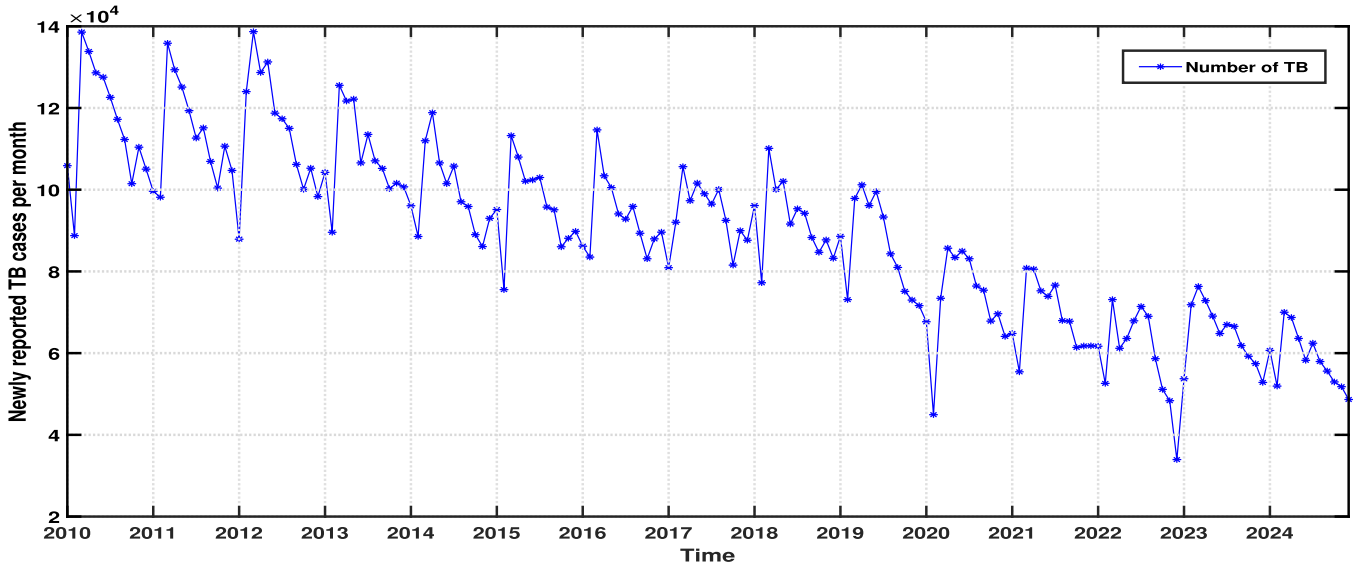


Fig. 1. Newly reported TB cases per month in China between 2010 and 2023.

represents the average latency of TB disease. We hope to gain some further insights into the nonlinear dynamics of TB through the analysis of this delay SEIRB model with environmental indirect transmission and latency delay.

Our main goal is to explore whether that latency and Mtb in the environment could contribute to oscillations in the spread of TB in the population.

The rest of the paper is organized as follows. In Section 2, we formulate the working model and address the well-posedness of the model. In Section 3, we explore the existence of equilibria, especially the existence and uniqueness of an endemic equilibrium and identify the basic reproduction number $\mathcal{R}_0$ of the model. In Section 4, we discuss the global stability of disease-free equilibrium when basic reproduction number $\mathcal{R}_0 < 1$ by constructing a Lyapunov functional, and discuss the local stability of endemic equilibrium when basic reproduction number $\mathcal{R}_0 > 1$ and $\tau = 0$. In Section 5, we study Hopf bifurcations at the endemic equilibrium when basic reproduction number $\mathcal{R}_0 > 1$, using $\tau > 0$ as the bifurcation parameter; we also provide some brief numerical simulations to illustrate our theoretical results. We conclude the paper by Section 6 in which we summarize our main results and discuss some epidemiological implications of the paper.

2. Model formulation

Based on the transmission mechanism of TB, we use $S(t)$, $E(t)$, $I(t)$, and $R(t)$ to represent the numbers of individuals in the susceptible class, latent TB infection (LTBI) class, active TB class and recovered class at time t, respectively. Let $B(t)$ be the population of Mtb bacteria in the environment at time t. Since the Mtb bacteria exhaled from TB carriers, after suspending in the air for a while, typically landed on furnitures, appliances, doors and windows etc. in which they generally cannot replicate, we adopt the following ODE to describe the rate of change of $B(t)$:

$$\frac{\mathrm{d}B}{\mathrm{d}t} = mI - \delta SB - \varepsilon B, \tag{1}$$

where $m > 0$ is the number of Mtb discharged into the environment by an active TB carrier per unit time, $\delta > 0$ is the number of Mtb inhaled by a susceptible individual after encountering Mtb in the environment per unit time, and $\varepsilon > 0$ is the death rate of Mtb.

Assume that the susceptible individuals become LTBI by effective contact with active TB carriers, or by inhaling Mtb in environment. This, together with the simple demographic equation $S'(t) = A - dS$ and a bilinear incidence, the rate of change of $S(t)$ with time is

$$\frac{\mathrm{d}S}{\mathrm{d}t} = A - \beta SI - \eta SB - dS = A - (\beta I + \eta B)S - dS, \tag{2}$$

where $A > 0$ is the constant replenishment rate, $d > 0$ is the natural death rate of population, $\beta > 0$ is the average number of effective contacts of an active TB per unit time, and $\eta > 0$ is the average number of effective contacts of Mtb per unit time.

It is known that TB has a significant latent period and a LTBI individual may not necessarily develop into active TB stage. It is estimated that about $5\,\% - 10\,\%$ of LTBI individuals will eventually progress to active TB stage, and the rest of LTBI may remain in the LTBI stage throughout their lives [5,17,25]. To capture this phenomenon, we follow the ideas in [23,24] to introduce a function

$$P(t) = \begin{cases} 1, & t \in [0, \tau], \\ 1 - k, & t > \tau. \end{cases} \tag{3}$$

to represents the fraction of LTBI individuals remaining in the LTBI class t time units after TB infection. This function $P(t)$ can also be explained as the probability that an infected host still remains in the LTBI class t time units after TB infection. The above form of $P(t)$ accounts for the assumption that, after infection, an infected individual will stay in the LTBI class for at least τ time units; and after τ time units, a fraction k $(0 < k < 1)$ of LTBI will leave the LTBI class and progresses to the active TB class. That is, when $t \geq \tau$, a fraction $1 - k$ of LTBI will still stay in the LTBI class. Then, the population $E(t)$ of the LTBI class at time t can be expressed by the integral

$$E(t) = \int_0^t \Big(\beta I(\theta) + \eta B(\theta)\Big) S(\theta) e^{-d(t-\theta)} P(t-\theta) \mathrm{d}\theta. \tag{4}$$

Here, the term $e^{-d(t-\theta)}$ accounts for the death of LTBI individuals. Due to (3), $E(t)$ can be further distinguished by the cases of $t \leq \tau$ and $t > \tau$. For for $t \leq \tau$,

$$E(t) = \int_0^t \Big(\beta I(\theta) + \eta B(\theta)\Big) S(\theta) e^{-d(t-\theta)} \mathrm{d}\theta,$$

and differentiating this equation gives

$$\frac{\mathrm{d}E}{\mathrm{d}t} = (\beta I + \eta B)S - dE;$$

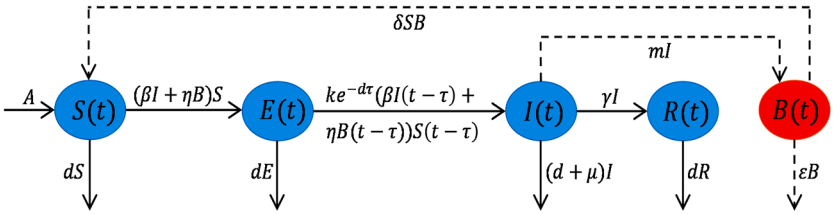


Fig. 2. The flow chart of TB transmission in the population.

For $t > \tau$,

$$E(t) = (1-k)\int_0^{t-\tau}\Big(\beta I(\theta)+\eta B(\theta)\Big)S(\theta)e^{-d(t-\theta)}\mathrm{d}\theta + \int_{t-\tau}^{t}\Big(\beta I(\theta)+\eta B(\theta)\Big)S(\theta)e^{-d(t-\theta)}\mathrm{d}\theta,$$

and differentiating this equation with some reorganization leads to

$$\frac{\mathrm{d}E}{\mathrm{d}t} = (\beta I+\eta B)S - ke^{-d\tau}\Big(\beta I(t-\tau)+\eta B(t-\tau)\Big)S(t-\tau) - dE.$$

The second term in the above equation is nothing but precisely the recruitment rate for the $I(t)$ class, leading to

$$\frac{\mathrm{d}I}{\mathrm{d}t} = ke^{-d\tau}\Big(\beta I(t-\tau)+\eta B(t-\tau)\Big)S(t-\tau) - (d+\mu+\gamma)I, \tag{5}$$

where $\mu > 0$ is the mortality rate due to TB, and $\gamma > 0$ is the recovery rate of active TB. The recovery class $R(t)$ is simply governed by

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \gamma I - dR, \tag{6}$$

Combining the above derivations, we arrive at a model consisting of an ODE system for $t \le \tau$ and a DDE system for $t > \tau$:

$$\begin{cases} \frac{\mathrm{d}S}{\mathrm{d}t} = A - [\beta I+\eta B]S - dS, \\ \frac{\mathrm{d}E}{\mathrm{d}t} = [\beta I+\eta B]S - dE, \\ \frac{\mathrm{d}I}{\mathrm{d}t} = -(d+\mu+\gamma)I, \qquad \text{for} \quad 0 < t \le \tau; \\ \frac{\mathrm{d}R}{\mathrm{d}t} = \gamma I - dR, \\ \frac{\mathrm{d}B}{\mathrm{d}t} = mI - \delta SB - \varepsilon B \end{cases} \tag{7}$$

and

$$\begin{cases} \frac{\mathrm{d}S}{\mathrm{d}t} = A - (\beta I+\eta B)S - dS, \\ \frac{\mathrm{d}E}{\mathrm{d}t} = (\beta I+\eta B)S - ke^{-d\tau}\Big(\beta I(t-\tau)+\eta B(t-\tau)\Big)S(t-\tau) - dE, \\ \frac{\mathrm{d}I}{\mathrm{d}t} = ke^{-d\tau}\Big(\beta I(t-\tau)+\eta B(t-\tau)\Big)S(t-\tau) - (d+\mu+\gamma)I, \qquad \text{for} \quad t > \tau. \\ \frac{\mathrm{d}R}{\mathrm{d}t} = \gamma I - dR, \\ \frac{\mathrm{d}B}{\mathrm{d}t} = mI - \delta SB - \varepsilon B \end{cases} \tag{8}$$

The DDE system (8) can be demonstrated by flow chart given in Fig. 2.

We point out that when $k = 1$ in (3), such a Heaviside-like distribution function switching between 1 and 0 has been used in [23,24] to derive DDE models

For this model (7)-(8), since the unknowns all represent populations, we naturally require that the initial conditions are all nonnegative:

$$(S(0), E(0), I(0), R(0), B(0)) \in \mathbb{R}^5_+ \tag{9}$$

As usual, the first thing we need to confirm for the model is its well-postedness, meaning the existence of a unique nonegative solution to (7)-(8)-(9). We can proceed as below to achieve this.

Firstly, the ODE system (7) is a polynomial system, thus for the given initial condition (9), it has a unique solution $x(t) = (S(t), E(t), I(t), R(t), B(t))$ for all $t > 0$. Then, we use this solution confined on the interval $[0, \tau]$ as the initial function for the DDE system (8); and by the method of steps, we conclude the existence of a unique solution to (7)–(9) for all $t > 0$.

To confirm that the unique solution remains non-negative, again we start with the ODE system (7) under the initial condition (9). Formally treating the first equation in (7) as a linear equation for $S(t)$, one can easily see that $S(t) > 0$ for all $t > 0$. Similarly, from second equation in (7), we can obtain $I(t) = I(0)e^{-(d+\mu+\gamma)t} \ge 0$ for $t > 0$. Once we have confirmed non-negativity of $I(t)$, the 4th and 5th equations, each having a non-negative recruitment, immediately lead to the non-negativity of $R(t)$ and $B(t)$ for $t > 0$. Non-negativity of $E(t)$ is a result of its definition by (4). Now that (8) has a set of non-negative initial functions in $[0, \tau]$, apply [19, P81, Theorem2.1] to (8) for $t \in [\tau, 2\tau]$, we confirm the non-negativity of the solution in $t \in [\tau, 2\tau]$. Repeating the same argument on $[2\tau, 3\tau], \cdots$ we then have proven that the solution remains non-negative with $S(t)$ strictly positive for all $t > 0$.

Next, we show that the solution is ultimate bounded. We first note that the solution on $[0, \tau]$, as the solution to the ODE system (7)–(9), is bounded on $[0, \tau]$, so we only need to show that any solution to the DDE system (8) with non-negative initial functions on $[0, \tau]$ is ultimate bounded. To this end, we add up the four equations of system (8) to obtain (noting the non-negativity of solution of system (8))

$$\frac{\mathrm{d}(S+E+I+R)}{\mathrm{d}t} = A - d(S+E+I+R) - \mu I \le A - d(S+E+I+R).$$

That is, $\lim_{t\to+\infty}\sup(S(t)+E(t)+I(t)+R(t)) \le A/d$. In addition, the last equation of system (8) implies that

$$\frac{\mathrm{d}B}{\mathrm{d}t} = mI - \delta SB - \varepsilon B \le mI - \varepsilon B \le m\frac{A}{d} - \varepsilon B,$$

which implies, by the comparison principle, that $\limsup_{t\to+\infty} B(t) \le mA/d\varepsilon$. Summarizing the above analysis, we have proved the following theorem on the well-posedness of the model (7)–(9).

Theorem 2.1. *The model (7)–(9) is well-posed in the sense that it has a unique solution that exists for all $t > 0$, remains non-negative with $S(t)$ being strictly positive, and is bounded.*

From the proof of Theorem 2.1, we can see that we have actually proved that the set

$$\Gamma = \left\{(S,E,I,R,B) \in R^5_+ : 0 \le S+E+I+R \le \frac{A}{d},\ \ 0 \le B \le \frac{mA}{d\varepsilon}\right\}.$$

is positively invariant for the model system (7)-(8) and it attracts all non-negative solutions of (7)-(8).

Noting that the equations for $E'(t)$ and $R'(t)$ in both (7) and (8) are decoupled from the rest of the equations, we can simply drop them and

just consider the subsystem consisting of the rest of the equations:

$$\begin{cases} \dfrac{\mathrm{d}S}{\mathrm{d}t} = A - [\beta I + \eta B]S - dS, \\ \dfrac{\mathrm{d}I}{\mathrm{d}t} = -(d+\mu+\gamma)I, \qquad \text{for} \quad 0 < t \le \tau; \\ \dfrac{\mathrm{d}B}{\mathrm{d}t} = mI - \delta SB - \varepsilon B \end{cases} \tag{10}$$

and

$$\begin{cases} \dfrac{\mathrm{d}S}{\mathrm{d}t} = A - (\beta I + \eta B)S - dS, \\ \dfrac{\mathrm{d}I}{\mathrm{d}t} = ke^{-d\tau}\Big(\beta I(t-\tau) + \eta B(t-\tau)\Big)S(t-\tau) - (d+\mu+\gamma)I, \qquad \text{for} \quad t > \tau. \\ \dfrac{\mathrm{d}B}{\mathrm{d}t} = mI - \delta SB - \varepsilon B \end{cases} \tag{11}$$

Also, since we are mainly interested in the long term disease dynamics of the model, we will just analyze the DDE system (11) for $t > \tau$ in the rest of the paper.

3. Existence of equilibria

In this section, we mainly focus on the existence of equilibria of (11), as (10) only plays a role of generating initial functions for (11) under (9). It is clear that system (11) always has the disease-free equilibrium $P_0 = (S_0, 0, 0)$ with $S_0 = A/d$. In order to discuss the existence of endemic equilibrium, we set

$$\frac{\mathrm{d}S}{\mathrm{d}t} = \frac{\mathrm{d}I}{\mathrm{d}t} = \frac{\mathrm{d}B}{\mathrm{d}t} = 0$$

in system (11) and then solve the resulting equations to obtain the non-zero equilibrium $P_* = (S_*, I_*, B_*)$ where

$$S_* = \frac{Ake^{-d\tau} - (d+\mu+\gamma)I_*}{dke^{-d\tau}}, \quad B_* = \frac{mI_*}{\delta S_* + \varepsilon},$$

and I_* satisfies the following equation

$$f(I_*) = a_2 I_*^2 + a_1 I_* + a_0 = 0, \qquad I_* \in \left(0, \ \frac{Ake^{-d\tau}}{d+\mu+\gamma}\right)$$

with

$$\begin{aligned} a_2 &= \delta\beta(d+\mu+\gamma)^2, \\ a_1 &= \delta d(d+\mu+\gamma)^2 - (2\beta A\delta k + \beta\varepsilon dk + m\eta dk)(d+\mu+\gamma)e^{-d\tau}, \\ a_0 &= k^2 e^{-2d\tau}\Big[m\eta Ad + A\beta(\delta A + d\varepsilon)\Big]\left(1 - \frac{1}{\mathcal{R}_0}\right) \end{aligned}$$

where

$$\mathcal{R}_0 = \frac{S_0 ke^{-d\tau}}{d+\mu+\gamma}\left[\beta + \frac{\eta m}{\delta S_0 + \varepsilon}\right]$$

which will be explained to be the basic reproduction number of the model later. Obviously, $0 < I_* < Ake^{-d\tau}/(d+\mu+\gamma)$ can ensure that $S_* > 0$. This means that when the equation $f(I_*) = 0$ has positive root in the interval $(0, Ake^{-d\tau}/(d+\mu+\gamma))$, then the non-zero equilibrium solution P_* is a positive equilibrium, that is, an endemic equilibrium. Next, we will discuss the conditions under which the equation $f(I_*) = 0$ has positive root in the interval $(0, \ Ake^{-d\tau}/(d+\mu+\gamma))$. Note that $a_2 > 0$, $f(0) = a_0 > 0$ (resp. < 0) when $\mathcal{R}_0 > 1$. (resp. < 1), and

$$\begin{aligned} f\left(\frac{Ake^{-d\tau}}{d+\mu+\gamma}\right) &= \delta\beta(d+\mu+\gamma)^2 \frac{A^2k^2e^{-2d\tau}}{(d+\mu+\gamma)^2} + m\eta Adk^2e^{-2d\tau} \\ &\quad + \beta A^2\delta k^2 e^{-2d\tau} + \beta A\varepsilon dk^2 e^{-2d\tau} \\ &\quad - d\delta Ake^{-d\tau}(d+\mu+\gamma) - d^2\varepsilon ke^{-d\tau}(d+\mu+\gamma) \\ &\quad + \Big(\delta d(d+\mu+\gamma)^2 - 2\beta A\delta ke^{-d\tau}(d+\mu+\gamma) - \beta\varepsilon dke^{-d\tau} \\ &\quad (d+\mu+\gamma) - m\eta dke^{-d\tau}(d+\mu+\gamma)\Big)\frac{Ake^{-d\tau}}{d+\mu+\gamma} \\ &= \delta\beta A^2k^2e^{-2d\tau} + \delta dAke^{-d\tau}(d+\mu+\gamma) - 2\beta A^2\delta k^2e^{-2d\tau} \\ &\quad - \beta A\varepsilon dk^2e^{-2d\tau} - Am\eta dk^2e^{-2d\tau} + m\eta Adk^2e^{-2d\tau} \\ &\quad + \delta\beta A^2k^2e^{-2d\tau} + \beta A\varepsilon dk^2e^{-2d\tau} - \delta dAke^{-d\tau}(d+\mu+\gamma) \\ &\quad - d^2\varepsilon ke^{-d\tau}(d+\mu+\gamma) \\ &= -d^2\varepsilon ke^{-d\tau}(d+\mu+\gamma) \\ &< 0. \end{aligned}$$

Thus, $f(I_*) = 0$ has no positive real root in the interval $(0, \ Ake^{-d\tau}/(d+\mu+\gamma))$ when $\mathcal{R}_0 < 1$, and has a unique positive real root in interval $(0, \ Ake^{-d\tau}/(d+\mu+\gamma))$ when $\mathcal{R}_0 > 1$.

In particular, when $\mathcal{R}_0 = 1$, we know $a_0 = 0$, and $\delta d(d+\mu+\gamma) = A\delta ke^{-d\tau}(\beta(A\delta + d\varepsilon) + \eta md)/(A\delta + d\varepsilon)$, implying that $f(I_*) = a_2 I_*^2 + a_1 I_* = I_*(a_2 I_* + a_*)$ with

$$a_1 = -k(d+\mu+\gamma)e^{-d\tau}\left(\beta(A\delta + d\varepsilon) + \frac{m\eta d^2\varepsilon}{A\delta + d\varepsilon}\right) < 0.$$

That is, $I^* = -a_1/a_2 > 0$ is a positive root of $f(I_*) = 0$. However, since

$$\frac{Ake^{-d\tau}}{d+\mu+\gamma} - (-\frac{a_1}{a_2}) = -\frac{e^{-d\tau}(\beta\varepsilon dk(A\delta + d\varepsilon) + m\eta dkd\varepsilon)}{\delta\beta(d+\mu+\gamma)(A\delta + d\varepsilon)} < 0,$$

we know that $I^* = -a_1/a_2 \notin (0, \ Ake^{-d\tau}/(d+\mu+\gamma))$, implying that $f(I_*) = 0$ has no positive real root in the interval $(0, \ Ake^{-d\tau}/(d+\mu+\gamma))$ when $\mathcal{R}_0 = 1$.

From the above analysis, we have obtained the following result on the equilibria.

Theorem 3.1. *System (11) always has disease-free equilibrium P_0, and there is a unique endemic equilibrium P_* if and only if $\mathcal{R}_0 > 1$.*

We point out that $\mathcal{R}_0$ is indeed the basic reproduction number of (11), which represents the average number of new cases generated by an active TB infection can produce during the infection. This can been seen by looking at equations for $I'(t)$ and $R'(t)$ of the linearization of (11) at P_0:

$$\begin{cases} \dfrac{\mathrm{d}I}{\mathrm{d}t} = S_0 ke^{-d\tau}[\beta I(t-\tau) + \eta B(t-\tau)] - (d+\mu+\gamma)I \\ \dfrac{\mathrm{d}B}{\mathrm{d}t} = mI - \big(\delta S_0 + \varepsilon\big)B \end{cases} \tag{12}$$

By tracking the duration of infection and new infections and new Mtb produced during this duration, as well as the life span of the Mtb in the environment and new infections Mtb can lead to during the lifetime of Mtb, we then can obtain the basic reproduction number as

$$\begin{aligned} &\frac{1}{d+\mu+\gamma} \cdot S_0 ke^{-d\tau}\beta + \frac{1}{\delta S_0 + \varepsilon} \cdot S_0 ke^{-d\tau}\eta \cdot \frac{1}{d+\mu+\gamma} \cdot m. \\ &= \frac{S_0 ke^{-d\tau}}{d+\mu+\gamma}\left[\beta + \frac{\eta m}{\delta S_0 + \varepsilon}\right] = \mathcal{R}_0. \end{aligned} \tag{13}$$

Here, each term in $\mathcal{R}_0$ has clear epidemiological interpretation: $ke^{-d\tau}$ is the proportion of LTBI that becomes active TB τ time units later after infection, β is the transmission rate of active TB. $1/(d+\mu+\gamma)$ is the average infection period of active TB, η is the transmission rate of Mtb in the environment, $m/(d+\mu+\gamma)$ is the number of Mtb excreted by active TB during their average infection period, $1/(\varepsilon + \delta S_0)$ is the survival period of Mtb in the environment.

4. Stability of equilibria

In this section, we will mainly discuss the stability of disease-free equilibrium P_0 and endemic equilibrium P_* of system (11).

Theorem 4.1. *When $\mathcal{R}_0 \le 1$, the disease-free equilibrium P_0 of system (11) is globally asymptotically stable for any $\tau \ge 0$, and P_0 is unstable when $\mathcal{R}_0 > 1$.*

Proof. The linearized system of system (11) at the disease-free equilibrium $P_0 = (S_0, 0, 0)$ is given by

$$\begin{aligned}
\frac{dS}{dt} &= -dS - S_0(\beta I + \eta B),\\
\frac{dI}{dt} &= -(d+\mu+\gamma)I + S_0 k e^{-d\tau}(\beta I(t-\tau) + \eta B(t-\tau)),\\
\frac{dB}{dt} &= mI - (\delta S_0 + \varepsilon)B,
\end{aligned} \tag{14}$$

which generates the characteristic equation of system (11) at P_0 as

$$\Delta_0(\lambda,\tau) = (\lambda+d)[\lambda^2 + b_{10}(\tau)\lambda + b_{00}(\tau) + (c_{10}(\tau)\lambda + c_{00}(\tau))e^{-\lambda\tau}] = 0$$

with

$$b_{10}(\tau) = d+\mu+\gamma+\delta S_0+\varepsilon, \quad b_{00}(\tau) = (d+\mu+\gamma)(\delta S_0+\varepsilon),$$

$$c_{10}(\tau) = -k\beta S_0 e^{-d\tau}, \qquad c_{00}(\tau) = -k\beta S_0(\delta\frac{A}{d}+\varepsilon)e^{-d\tau} - mk\eta\frac{A}{d}e^{-d\tau}.$$

It is clear that $\Delta_0(\lambda,\tau) = 0$ always has the roots $\lambda = -d < 0$, and other roots are determined by the following equation

$$\Lambda_0(\lambda,\tau) = \lambda^2 + b_{10}(\tau)\lambda + b_{00}(\tau) + (c_{10}(\tau)\lambda + c_{00}(\tau))e^{-\lambda\tau} = 0. \tag{15}$$

Obviously, $\lim_{\lambda\to+\infty}\Lambda_0(\lambda,\tau) = +\infty$, and

$$\Lambda_0(0,\tau) = b_{00}(\tau) + c_{00}(\tau) = \frac{(\delta A + d\varepsilon)(d+\mu+\gamma)}{d}(1-\mathcal{R}_0) < 0$$

when $\mathcal{R}_0 > 1$. Therefore, Eq. (15) has at least a positive real root, implying that P_0 is unstable if $\mathcal{R}_0 > 1$ and $\tau \geq 0$.

In the following, we discuss the stability of P_0 under the condition of $\mathcal{R}_0 \leq 1$. To this end, we construct the following Lyapunov functional

$$V(t) = \frac{e^{d\tau}}{k}(\delta A + d\varepsilon)I + A\eta B + (\delta A + d\varepsilon)\int_{t-\tau}^{t}\big(\beta I(\theta) + \eta B(\theta)\big)S(\theta)d\theta.$$

Then, the derivative of $V(t)$ along positive solutions of system (11) is

$$\begin{aligned}
\frac{dV}{dt} &= \frac{e^{d\tau}}{k}(\delta A + d\varepsilon)(k(\beta I(t-\tau) + \eta B(t-\tau))S(t-\tau)e^{-d\tau} - (d+\mu+\gamma)I)\\
&\quad + A\eta(mI - \delta SB - \varepsilon B) + (\delta A + d\varepsilon)(\beta I(t) + \eta B(t))S(t)\\
&\quad - (\delta A + d\varepsilon)(\beta I(t-\tau) + \eta B(t-\tau))S(t-\tau)\\
&= (\delta A + d\varepsilon)(\beta I(t-\tau) + \eta B(t-\tau))S(t-\tau) - \frac{e^{d\tau}}{k}(\delta A + d\varepsilon)(d+\mu+\gamma)I\\
&\quad + A\eta mI - A\eta\delta SB - A\eta\varepsilon B + (\delta A + d\varepsilon)(\beta I(t) + \eta B(t))S(t)\\
&\quad - (\delta A + d\varepsilon)(\beta I(t-\tau) + \eta B(t-\tau))S(t-\tau)\\
&= (\delta A + d\varepsilon)(\beta I(t) + \eta B(t))S(t) - \frac{e^{d\tau}}{k}(\delta A + d\varepsilon)(d+\mu+\gamma)I\\
&\quad + A\eta mI - A\eta\delta SB - A\eta\varepsilon B\\
&= (\delta A + d\varepsilon)\beta IS + \delta A\eta BS + d\varepsilon\eta BS - \frac{e^{d\tau}}{k}(\delta A + d\varepsilon)(d+\mu+\gamma)I\\
&\quad + A\eta mI - A\eta\delta SB - A\eta\varepsilon B\\
&= (\delta A + d\varepsilon)\beta IS + d\varepsilon\eta BS - \frac{e^{d\tau}}{k}(\delta A + d\varepsilon)(d+\mu+\gamma)I\\
&\quad + A\eta mI - A\eta\varepsilon B.
\end{aligned} \tag{16}$$

Since $S \leq S_0 = \frac{A}{d}$, Eq. (16) can be estimated as

$$\begin{aligned}
\frac{dV}{dt} &\leq (\delta A + d\varepsilon)\beta I\frac{A}{d} + d\varepsilon\eta B\frac{A}{d} - \frac{e^{d\tau}}{k}(\delta A + d\varepsilon)(d+\mu+\gamma)I + A\eta mI - A\eta\varepsilon B\\
&= \frac{(\delta A + d\varepsilon)A\beta}{d}I - \frac{e^{d\tau}}{k}(\delta A + d\varepsilon)(d+\mu+\gamma)I + A\eta mI\\
&= \frac{(\mathcal{R}_0 - 1)(d+\mu+\gamma)(\delta A + d\varepsilon)}{ke^{-d\tau}}I.
\end{aligned}$$

Thus, when $\mathcal{R}_0 < 1$, then $\frac{dV}{dt} < 0$ for $I(t) > 0$, and the global asymptotical stability of P_0 directly follows. For the case of $\mathcal{R}_0 = 1$, we only have $\frac{dV}{dt} \leq 0$, and we need to apply the LaSalle's Invariance Principle to conclude the global asymptotical stability of P_0. To this end, we let M be the maximal invariant set contained in the set $\left\{\phi = (S, I, B) : \frac{dV}{dt} = 0\right\}$. Obviously $P_0 \in M$. Assume $(S, I, B) \in M$. From (16) one can verify that $I = 0$ and $S = A/d$. This together with the invariance of M applied to (11) implies that $B = 0$, and thus, one actually has $(S, I, B) = (A/d, 0, 0) = P_0$. This means that M actually consists of a single point $M = \{P_0\}$. Now, by the LaSalle's Invariance Principle (see, e.g., Hale and Verduyn [8]) and every non-negative solution $(S(t), I(t), B(t))$ of (11) approaches M, that is, $(S(t), I(t), B(t)) \to P_0$ as $t \to \infty$, concluding the global asymptotical stability of P_0 for the case of $\mathcal{R}_0 = 1$.

□

We have seen that when $\mathcal{R}_0 > 1$, the disease free equilibrium P_0 becomes unstable, and based on the biological meaning of $\mathcal{R}_0$, we expect that the disease would become persistent. The following theorem confirms this expectation.

Theorem 4.2. *If $\mathcal{R}_0 > 1$, then both active TB class $I(t)$ and the population of Mtb bacteria in the environment $B(t)$ are uniformly persistent in system (11), in the sense that there is a constant $\epsilon > 0$ such that for any initial value $(S_0, I_0, B_0) \in \mathbb{X}_0 = \{(S, I, B) \in \bar{\Gamma} \mid I > 0\}$. the corresponding solution satisfies*

$$\liminf_{t\to\infty} I(t) \geq \epsilon, \quad \liminf_{t\to\infty} B(t) \geq \epsilon. \tag{17}$$

Proof. Let $X = \mathbb{R}^3_+$ and $X + 0$ be the interior of X: $X_0 = \{\phi = (S, I, B) \in X : I > 0, \text{ and } B > 0\}$. The boundary of X_0 is then $\partial X_0 = X \setminus X_0 = \{\phi = (S, I, B) \in X :, \text{either } I = 0 \text{ or } B = 0\}$. In order to apply the abstract persistence theory in Thieme [20] and Hirsch et al [9], we need to use the set $\Omega_\partial = \{\phi_0 = (S_0, I_0, B_0) \in X : (S(t, \phi_0), I(t, \phi_0), B(t, \phi_0)) \in \partial X_0 \text{ for all } t \geq 0\}$. We show that $\Omega_\partial = \{(S, 0, 0) : S \in \mathbb{R}_+\}$. Firstly, it is clear that $\{(S, 0, 0)\} \subset \Omega_\partial$ for any $S \in \mathbb{R}_+$. Secondly, let $\phi_0 = (S_0, I_0, B_0) \in \Omega_\partial$, we show that $I_0 = 0$ and $B_0 = 0$. Otherwise, either $I_0 > 0$ or $B_0 > 0$. For the former, it follows from the second equation in (10) that $I(t, \phi_0) > 0$, and hence, from the 3rd equation in (10) that $B(t, \phi_0) > -$ for all $t \in [0, \tau]$; then, applying the argument of steps to (11), we further obtain $I(t, \phi) > 0$ and $B(t, \phi) > -$ for all $t \geq \tau$, a contradiction. Similarly, for the latter, positivity of B_0 will lead to $B(t, \phi_0) > 0$ and $I(t, \phi_0) > 0$ for all $t \geq \tau$, also contradicting to $(S(t, \phi_0), I(t, \phi_0), B(t, \phi_0)) \in \partial X_0$ for all $t \geq 0$. Thus, we have shown that $\Omega_\partial = \{(S, 0, 0) : S \in \mathbb{R}_+\}$.

Note that $\mathcal{R}_0$ continuously depends on $S_0 = A/d$. Thus, when $\mathcal{R}_0 > 1$, one can choose $\zeta > 0$ sufficiently small so that

$$\mathcal{R}_0(\zeta) = \frac{(S_0 - \zeta)ke^{-d\tau}}{d+\mu+\gamma}\left[\beta + \frac{\eta m}{\delta(S_0+\zeta)\varepsilon}\right] > 1.$$

For $\theta > 0$, consider the following linear equation:

$$\frac{dS}{dt} = A - dS - S(\beta\theta + \eta\theta) \tag{18}$$

which has a globally asymptotically stable positive equilibrium $S_0(\theta) = A/(d + \beta\theta + \eta\theta)$. Noting that $S_0(0) = S_0 > S_0 - \zeta$, we can chose $\theta > 0$ sufficiently small such that $S_0(\theta) > S_0 - \zeta$. We now prove that for such a $\theta > 0$, there holds (weak persistence)

$$\limsup_{t\to\infty} \max\{I(t, \phi), B(t, \phi)\} > \theta \text{ for all } \phi \in X_0. \tag{19}$$

Otherwise, there would be $\phi \in X_0$ and a $T_1 > 0$ such that the corresponding solution $(S(t), I(t), B(t)) = (S(t, \phi), I(t, \phi), B(t, \phi))$ satisfies $0 < I(t) = I(t, \phi) \leq \theta$ and $0 < B(t) = B(t, \phi) \leq \theta$ for $t \geq T_1$. Then, from the first equation in (11), we have

$$\frac{dS}{dt} \geq A - dS - (\beta\theta + \eta\theta)S = A - (d + \beta\theta + \eta\zeta)S, \quad t \geq T_1,$$

meaning that (18) is a lower comparing equation for the first equation in (11) for large t. Note that $S_0(\theta)$ is globally asymptotically stable for (18) and $S_0(\theta) > S_0 - \zeta$. This together with the comparing principle (see, e.g. [19]) implies that there exists $T_2 > 0$ such that $S(t) > S_0 - \zeta$ for $t \geq T_1 + T_2$. This together with the 2nd equation in (11) leads to

$$\frac{dI}{dt} \geq ke^{-d\tau}(S_0 - \zeta)\Big(\beta I(t-\tau) + \eta B(t-\tau)\Big) - (d+\mu+\gamma)I,$$
$$\text{for} \quad t > T_1 + T_2 + \tau. \tag{20}$$

On the other hand, again from first equation in (11), we know that $\frac{dS}{dt} \geq A - dS$ implying that $\limsup_{t\to\infty} S(t) \leq A/d = S_0$. Thus, for ζ specified above, there exists a $T_3 > 0$ such that $S(t) \leq S_0 + \zeta$ for $t \geq T_3$. Applying this to the 3rd equation in (11) results in

$$\frac{dB}{dt} \geq mI_1(t) - \big(\delta(S_0 + \zeta) + \varepsilon\big)B(t) \text{ , for } t \geq T_3. \tag{21}$$

From (20) and (21), we obtain the following lower comparing system for the 2nd and 3rd equations in (11):

$$\begin{cases} \dfrac{dI_1}{dt} = ke^{-d\tau}[\beta I_1(t-\tau) + \eta B_1(t-\tau)](S_0 - \zeta) - (d+\mu+\gamma)I_1(t), \\ \dfrac{dB_1}{dt} = mI_1(t) - \big(\delta S_0 + \varepsilon + \delta\zeta\big)B_1(t). \end{cases} \tag{22}$$

Again by comparison principe (see, e.g. [19]), we know that $I(t) \geq I_1(t)$ and $B(t) \geq B_1(t)$ for large t. Note that (22) is linear with the basic reproduction number $\mathcal{R}_0(\zeta) > 1$, implying all non-trivial solutions grow exponentially. This together with the comparison result further implies that $I(t)$ and $B(t)$ will also grow exponentially, contradicting to the "otherwise" assumption, and hence proving the claim (19).

From the weak persistence claim (19) and the fact that $S_0 = A/d$ is a globally asymptotically stable equilibrium of $S'(t) = A - dS$, we can conclude that the disease free equilibrium $\{P_0\}$ is an isolated invariant set in X with $W^s(P_0) \cap X_0 = \emptyset$ Clearly, every orbit in Ω_∂ converges to P_0 and $\{P_0\}$ is the only invariant set in Ω_∂. By Thieme [20, Theorem 4.6] and Hirsch et al [9, Theorem 4.3 and Remark 4.3] for a stronger repelling property of the boundary ∂X_0, we conclude that the model system (10)-(11) is indeed uniformly strongly persistent with respect to $(X_0, \partial X_0)$, implying the conclusion of the theorem □

Next we investigate the stability of the endemic equilibriam P_* under the condition $\mathcal{R}_0 > 1$. As in the case of analyzing P_0, we can obtain the characteristic equation of system (11) at the endemic equilibrium P_* as

$$\begin{aligned}\Delta_*(\lambda,\tau) = {} & \lambda^3 + b_{2*}(\tau)\lambda^2 + b_{1*}(\tau)\lambda + b_{0*}(\tau) + (c_{2*}(\tau)\lambda^2 + c_{1*}(\tau)\lambda \\ & + c_{0*}(\tau))e^{-\lambda\tau} = 0\end{aligned} \tag{23}$$

with

$$\begin{aligned}
b_{2*}(\tau) &= d + \mu + \gamma + \delta S_* + \varepsilon + \beta I_* + \eta B_* + d, \\
b_{1*}(\tau) &= (d+\mu+\gamma)(\delta S_* + \varepsilon + \beta I_* + \eta B_* + d) + (\beta I_* + d)\delta S_* \\
&\quad + \varepsilon(\beta I_* + \eta B_* + d), \\
b_{0*}(\tau) &= \beta\delta(d+\mu+\gamma)S_* I_* + (d+\mu+\gamma)\delta d S_* + (\beta I_* + \eta B_* + d)(d+\mu+\gamma)\varepsilon, \\
c_{2*}(\tau) &= -k\beta S_* e^{-d\tau}, \\
c_{1*}(\tau) &= -k\beta\delta S_*^2 e^{-d\tau} - k\beta\varepsilon S_* e^{-d\tau} - mk\eta S_* e^{-d\tau} - dk\beta S_* e^{-d\tau}, \\
c_{0*}(\tau) &= -dk\beta\delta e^{-d\tau} S_*^2 - dk\beta\varepsilon e^{-d\tau} S_* - dmk\eta e^{-d\tau} S_*.
\end{aligned}$$

In the case when $\tau = 0$, Eq. (23) becomes

$$\lambda^3 + \Big(b_2(0) + c_2(0)\Big)\lambda^2 + \Big(b_1(0) + c_1(0)\Big)\lambda + b_0(0) + c_0(0) = 0, \tag{24}$$

where

$$\begin{aligned}
b_{2*}(0) + c_{2*}(0) &= \delta S_* + \varepsilon + d + \beta I_* + \eta B_* + \frac{k\eta S_* B_*}{I_*} > 0, \\
b_{1*}(0) + c_{1*}(0) &= (\beta I_* + \eta B_*)(d+\mu+\gamma) + (\beta I_* + d)\delta S_* + (\beta I_* + \eta B_* + d)\varepsilon \\
&\quad + \frac{dk\eta S_* B_*}{I_*} > 0, \\
b_{0*}(0) + c_{0*}(0) &= \beta\delta S_* I_*(d+\mu+\gamma) + \varepsilon(\beta I_* + \eta B_*)(d+\mu+\gamma) > 0.
\end{aligned}$$

By direct calculation, we can get

$$\begin{aligned}
&\Big(b_2(0) + c_2(0)\Big)\Big(b_1(0) + c_1(0)\Big) - \Big(b_0(0) + c_0(0)\Big) \\
=&\delta\eta S_* B_*(d+\mu+\gamma) + (\delta S_* + \varepsilon + \beta I_* + \eta B_* + d + \frac{k\eta S_* B_*}{I_*})[\frac{dk\eta S_* B_*}{I_*} \\
&+ \beta\delta S_* I_* + d\delta S_* + (\beta I_* + \eta B_*)\varepsilon + d\varepsilon] + (\beta I_* + \eta B_* + d + \frac{k\eta S_* B_*}{I_*}) \\
&(\beta I_* + \eta B_*)(d+\mu+\gamma) \\
>&0.
\end{aligned}$$

Then, the Routh-Hurwitz criterion ensures that all roots of Eq. (24) have negative real parts. That is, the following result holds.

Theorem 4.3. *If $\mathcal{R}_0 > 1$, then the endemic equilibrium P_* of system (11) is locally asymptotically stable for $\tau = 0$.*

In fact, the characteristic roots $\Delta_*(\lambda, \tau) = 0$ have continuous dependence on τ implies that Theorem 4.3 is still true for $\tau > 0$ sufficiently small and $\mathcal{R}_0 > 1$. However, some roots of $\Delta_*(\lambda, \tau) = 0$ also may cross the imaginary axis to the right part as τ increases. We will discuss the behavior of solutions of system (11) as τ increases under the condition of $\mathcal{R}_0 > 1$ in the next subsection.

5. Hopf bifurcation

In order to analyze the behavior of solutions of system (11) as τ increases under the condition of $\mathcal{R}_0 > 1$, we rewrite the characteristic equation $\Delta_*(\lambda, \tau) = 0$ in (23) as

$$P_*(\lambda,\tau) + Q_*(\lambda,\tau)e^{-\lambda\tau} = 0 \tag{25}$$

with

$$\begin{aligned}
P_*(\lambda,\tau) &= \lambda^3 + b_{2*}(\tau)\lambda^2 + b_{1*}(\tau)\lambda + b_{0*}(\tau), \\
Q_*(\lambda,\tau) &= c_{2*}(\tau)\lambda^2 + c_{1*}(\tau)\lambda + c_{0*}(\tau).
\end{aligned}$$

It is clear that $P_*(\lambda, \tau)$ and $Q_*(\lambda, \tau)$ are both analytic function respect to λ and differentiable respect to τ. Following method in Section 2 in [1], through a tedious manipulation, we can obtain

$$\begin{aligned}
&P_*(0,\tau) + Q_*(0,\tau) = b_{0*}(\tau) + c_{0*}(\tau) = \beta\delta S_* I_*(d+\mu+\gamma) + \varepsilon(\beta I_* + \eta B_*) \\
&\qquad (d+\mu+\gamma) > 0, \\
&P_*(i\omega,\tau) + Q_*(i\omega,\tau) = -i\omega^3 - (b_{2*}(\tau) + c_{2*}(\tau))\omega^2 + (b_{1*}(\tau) + c_{1*}(\tau))i\omega \\
&\qquad + b_{0*}(\tau) + c_{0*}(\tau) \neq 0, \\
&\lim_{|\lambda|\to+\infty} \sup \left|\frac{Q_*(\lambda,\tau)}{P_*(\lambda,\tau)}\right| = \lim_{|\lambda|\to+\infty} \sup \left|\frac{c_{2*}(\tau)\lambda^2 + c_{1*}(\tau)\lambda + c_{0*}(\tau)}{\lambda^3 + b_{2*}(\tau)\lambda^2 + b_{1*}(\tau)\lambda + b_{0*}(\tau)}\right| = 0,
\end{aligned}$$

and

$$F_*(\omega,\tau) = |P_*(i\omega,\tau)|^2 - |Q_*(i\omega,\tau)|^2 = \omega^6 + B_2(\tau)\omega^4 + B_1(\tau)\omega^2 + B_0(\tau) \tag{26}$$

with

$$\begin{aligned}
B_2(\tau) &= b_{2*}^2(\tau) - 2b_{1*}(\tau) - c_{2*}^2(\tau), \\
B_1(\tau) &= b_{1*}^2(\tau) - 2b_{2*}(\tau)b_{0*}(\tau) + 2c_{0*}(\tau)c_{2*}(\tau) - c_{1*}^2(\tau), \\
B_0(\tau) &= b_{0*}^2(\tau) - c_{0*}^2(\tau) = (b_{0*}(\tau) - c_{0*}(\tau))(b_{0*}(\tau) + c_{0*}(\tau)) > 0.
\end{aligned}$$

Let $\lambda = i\omega(\omega > 0)$ be a pure imaginary root of Eq. (23), then we have

$$\begin{aligned}
&-i\omega^3 - b_{2*}(\tau)\omega^2 + b_{1*}(\tau)i\omega + b_{0*}(\tau) + (-c_{2*}(\tau)\omega^2 + c_{1*}(\tau)i\omega + c_{0*}(\tau)) \\
&(\cos\omega\tau - i\sin\omega\tau) = 0.
\end{aligned}$$

Separating real and imaginary parts, it follows that

$$\begin{aligned}
b_{1*}(\tau)\omega - \omega^3 &= (c_{0*}(\tau) - c_{2*}(\tau)\omega^2)\sin\omega\tau - c_{1*}(\tau)\omega\cos\omega\tau, \\
b_{2*}(\tau)\omega^2 - b_{0*}(\tau) &= (c_{0*}(\tau) - c_{2*}(\tau)\omega^2)\cos\omega\tau + c_{1*}(\tau)\omega\sin\omega\tau.
\end{aligned} \tag{27}$$

Therefore, we have

$$\begin{aligned}
\cos\omega\tau &= \frac{(c_{0*}(\tau) - c_{2*}(\tau)\omega^2)(b_{1*}(\tau)\omega - \omega^3) + c_{1*}(\tau)\omega(b_{2*}(\tau)\omega^2 - b_{0*}(\tau))}{(c_{0*}(\tau) - c_{2*}(\tau)\omega^2)^2 + c_{1*}^2(\tau)\omega^2}, \\
\sin\omega\tau &= \frac{(c_{0*}(\tau) - c_{2*}(\tau)\omega^2)(b_{2*}(\tau)\omega^2 - b_{0*}(\tau)) - c_{1*}(\tau)\omega(b_{1*}(\tau)\omega - \omega^3)}{(c_{0*}(\tau) - c_{2*}(\tau)\omega^2)^2 + c_{1*}^2(\tau)\omega^2}.
\end{aligned} \tag{28}$$

Setting $\Theta = \omega^2$, then Eq. (26) can be rewritten as

$$G(\Theta) = \Theta^3 + B_2(\tau)\Theta^2 + B_1(\tau)\Theta + B_0(\tau). \tag{29}$$

The derivative of $G(\Theta)$ with respect to Θ is $G'(\Theta) = 3\Theta^2 + 2B_2(\tau)\Theta + B_1(\tau)$. If $B_2^2(\tau) - 3B_1(\tau) < 0$, then $3\Theta^2 + 2B_2(\tau)\Theta + B_1(\tau) = 0$ has no real roots. If $B_2^2(\tau) - 3B_1(\tau) \geq 0$, then $3\Theta^2 + 2B_2(\tau)\Theta + B_1(\tau) = 0$ has two real roots, which are

$$\Theta_1 = \frac{-B_2(\tau) - \sqrt{B_2^2(\tau) - 3B_1(\tau)}}{3}, \quad \Theta_2 = \frac{-B_2(\tau) + \sqrt{B_2^2(\tau) - 3B_1(\tau)}}{3}.$$

The following lemma summarizes the distribution of the roots of Eq. (29) under different conditions.

Lemma 5.1. *Assume that $\mathcal{R}_0 > 1$ and $\tau > 0$.*

(i) If $B_2^2(\tau) - 3B_1(\tau) < 0$, then $G(\Theta) = 0$ has no positive root;
(ii) If $B_2^2(\tau) - 3B_1(\tau) \geq 0$, and $\Theta_2 < 0$, then $G(\Theta) = 0$ has no positive root;
(iii) If $B_2^2(\tau) - 3B_1(\tau) \geq 0$, $\Theta_2 > 0$, and $G(\Theta_2) > 0$, then $G(\Theta) = 0$ has no positive root;
(iv) If $B_2^2(\tau) - 3B_1(\tau) \geq 0$, $\Theta_2 > 0$, and $G(\Theta_2) \leq 0$, then $G(\Theta) = 0$ has at least one positive root.

Proof. In the case when $B_2^2(\tau) - 3B_1(\tau) < 0$, then the equation $G'(\Theta) = 0$ has no real roots. Since the quadratic coefficient of $G'(\Theta)$ is positive, we know $G'(\Theta) > 0$ for all Θ. This implies that $G(\Theta)$ is an increasing function of $\Theta > 0$. Therefore, $B_0(\tau) > 0$ can ensure that $G(\Theta) = 0$ has no positive real root.

In the case when $B_2^2(\tau) - 3B_1(\tau) \geq 0$, then the equation $G'(\Theta) = 0$ has two real roots Θ_1 and Θ_2 with $\Theta_1 \leq \Theta_2$. Obviously, both Θ_1 and Θ_2 are the inflection point of the cubic function $G(\Theta)$. In addition, we know that $\lim_{\Theta\to-\infty} G(\Theta) = -\infty$, $\lim_{\Theta\to+\infty} G(\Theta) = +\infty$, and $G(0) = B_0(\tau) > 0$. In the following, we will discuss the existence of positive real roots for the equation $G(\Theta) = 0$ under different cases based on the above conditions.

Firstly, if $\Theta_2 < 0$, then $\Theta_1 \leq \Theta_2 < 0$, then the cubit function $G(\Theta)$ has no positive extreme point, implying that $G(\Theta)$ is strictly increasing on $[0, +\infty)$. $G(0) = B_0(\tau) > 0$ can ensure that $G(\Theta) = 0$ has no positive root.

If $\Theta_2 > 0$, then $G'(\Theta) = 0$ has at least one positive real root. This implies that the cubic function $G(\Theta)$ has at least one inflection point Θ_2 in the interval $(0, +\infty)$. That is, $G(\Theta)$ is strictly increasing on $[\Theta_2, +\infty)$. The combination of $G(0) = B_0(\tau) > 0$ and $G(\Theta_2) > 0$ ensures that $G(\Theta) = 0$ has no positive real roots. While if $G(\Theta_2) \leq 0$, then the equation $G(\Theta) = 0$ has at least one positive real root. □

If $G(\Theta) = 0$ has no positive roots, then the stability of the endemic equilibrium P_* does not change as τ increases. Therefore, we have the following result:

Theorem 5.1. *Assume that $\mathcal{R}_0 > 1$ and $\tau \geq 0$. Then the endemic equilibrium P_* of system (11) is locally asymptotically stable is one of the following holds:*

(i) $B_2^2(\tau) - 3B_1(\tau) < 0$;
(ii) $B_2^2(\tau) - 3B_1(\tau) \geq 0$, and $\Theta_2 < 0$;
(iii) $B_2^2(\tau) - 3B_1(\tau) \geq 0$, $\Theta_2 > 0$, and $G(\Theta_2) > 0$.

If there exists a positive root for $G(\Theta) = 0$, the stability of endemic equilibrium P_* may change when τ reaches some critical value τ_*. Let Θ_* be the positive root of $G(\Theta) = 0$. Namely, $\omega(\tau_*) = \sqrt{\Theta_*}$ is the unique positive real root of $F_*(\omega, \tau) = 0$. Then we define a set by

$$\Sigma = \{\tau > 0 : B_2^2(\tau) - 3B_1(\tau) \geq 0, \Theta_2 > 0, \text{and} \quad G(\Theta_2) \leq 0\}.$$

That is, for $\tau \in \Sigma$, there exists $\omega = \omega(\tau) > 0$ such that $F_*(\omega, \tau) = 0$.

Let $\theta(\tau) \in (0, 2\pi]$ ($\tau \in \Sigma$) be a solution of the following equations:

$$\cos\theta(\tau) = \frac{(c_{0*}(\tau) - c_{2*}(\tau)\omega^2)(b_{1*}(\tau)\omega - \omega^3) + c_{1*}(\tau)\omega(b_{2*}(\tau)\omega^2 - b_{0*}(\tau))}{(c_{0*}(\tau) - c_{2*}(\tau)\omega^2)^2 + c_{1*}^2(\tau)\omega^2},$$

$$\sin\theta(\tau) = \frac{(c_{0*}(\tau) - c_{2*}(\tau)\omega^2)(b_{2*}(\tau)\omega^2 - b_{0*}(\tau)) - c_{1*}(\tau)\omega(b_{1*}(\tau)\omega - \omega^3)}{(c_{0*}(\tau) - c_{2*}(\tau)\omega^2)^2 + c_{1*}^2(\tau)\omega^2}.$$

Table 1
The values of the parameters in system (11).

Parameters	Value	Unit	Source
A	$\frac{1.6346\times10^7}{12}$	$month^{-1}$	[16]
d	$\frac{0.007^2}{12}$	$month^{-1}$	[16]
μ	4.069×10^{-5}	$month^{-1}$	[29]
γ	0.158	$month^{-1}$	[7]
m	30	$month^{-1}$	[3]
η	(0, 1)	$month^{-1}$	Estimation
k	0.03	$month^{-1}$	Estimation
β	7×10^{-9}	$month^{-1}$	Estimation
δ	9×10^{-8}	$month^{-1}$	Estimation
ε	6.18×10^{-9}	$month^{-1}$	Estimation
τ	8	− − −	Estimation

Then, we conclude that $\omega(\tau)\tau = \theta(\tau) + 2l\pi$. Hence, $i\omega$ is a purely imaginary root of $\Delta_*(\lambda, \tau) = 0$ if and only if τ is a zero of $S_l(\tau)$ for some $l \in \mathbb{N}$, which is defined by

$$S_l(\tau) = \tau - \frac{\theta(\tau) + 2l\pi}{\omega(\tau)}, \quad \tau \in \Sigma, \quad l \in \mathbb{N}.$$

Theorem 2.2 in [1] implies that the following lemma is true.

Lemma 5.2. *Assume that $\omega(\tau)$ is a positive real root of $F_*(\omega, \tau) = 0$ for $\tau \in \Sigma$, and at some $\tau_* \in \Sigma$,*

$$S_l(\tau_*) = 0, \quad \text{for some } l \in \mathbb{N}.$$

Then a pair of simple conjugate pure imaginary roots $\lambda_+(\tau_*) = +i\omega(\tau_*)$, and $\lambda_-(\tau_*) = -i\omega(\tau_*)$ of the characteristic equation $\Delta_*(\lambda, \tau) = 0$ exists at $\tau = \tau_*$ which crosses the imaginary axis from left to right if $\sigma(\tau_*) > 0$ and crosses the imaginary axis from right to left if $\sigma(\tau_*) < 0$, where

$$\sigma(\tau_*) = sign\left\{\frac{dRe(\lambda)}{d\tau}\bigg|_{\lambda=i\omega(\tau_*)}\right\} = sign\{F'_{2\omega}(\omega(\tau_*), \tau_*)\}sign\left\{\frac{dS_l(\tau)}{d\tau}\bigg|_{\tau=\tau_*}\right\} \tag{30}$$

$$= sign\{G'(\Theta_*)\}sign\left\{\frac{dS_l(\tau)}{d\tau}\bigg|_{\tau=\tau_*}\right\}. \tag{31}$$

The identity (30) implies that the transversality condition holds. Therefore, a Hopf bifurcation occurs when $G'(\Theta_*) \neq 0$ and $\tau = \tau_*$, and the following conclusion is obtained according to the Hopf bifurcation theorem.

Theorem 5.1. *Suppose that $\mathcal{R}_0 > 1$ and $G'(\Theta_*) \neq 0$. If $B_2^2(\tau) - 3B_1(\tau) \geq 0$, $\Theta_2 > 0$, and $G(\Theta_2) \leq 0$, then endemic equilibrium P_* of system (11) is locally asymptotically stable for $\tau \in [0, \tau_*)$, and it undergoes a Hopf bifurcation when $\tau = \tau_*$.*

To conclude this section, we will use numerical simulations to demonstrate the result in Theorem 5.1. To this end, we use the parameter values in Table 1 below.

Direct calculation shows that $\mathcal{R}_0 = 3.7045 > 1$, $B_2^2(\tau) - 3B_1(\tau) = 1.9788 \times 10^7 > 0$, $\Theta_2 = 0.01908 > 0$, and $G(\Theta_2) = -1.47006 < 0$, satisfying the conditions in Theorem 5.1. Using Matlab package dde23 with the above parameter values, we accordingly obtain the solution of system (11) that clearly demonstrates periodicity over time t (see in Fig. 3), which supports the conclusion of Theorem 5.1.

We point out that if the transmission by Mtb in the environment is ignored, the long time dynamics of (11) can be different. To see this, we take $\eta = m = \delta = \varepsilon = 0$ and keep the other parameter values still as in Table 1. Then, we find that the periodic solution disappears, replaced by convergence to the endemic equilibrium in an oscillatory way, even though the delay is still present and is even further increased to certain magnitude, as is shown in Fig. 4. However, if τ is too large, from (13), the basic reproduction number $\mathcal{R}_0$ will be reduced to be less that 1, making endemic equilibrium P_* disappear and the disease free equilibrium P_0 regain its stability.

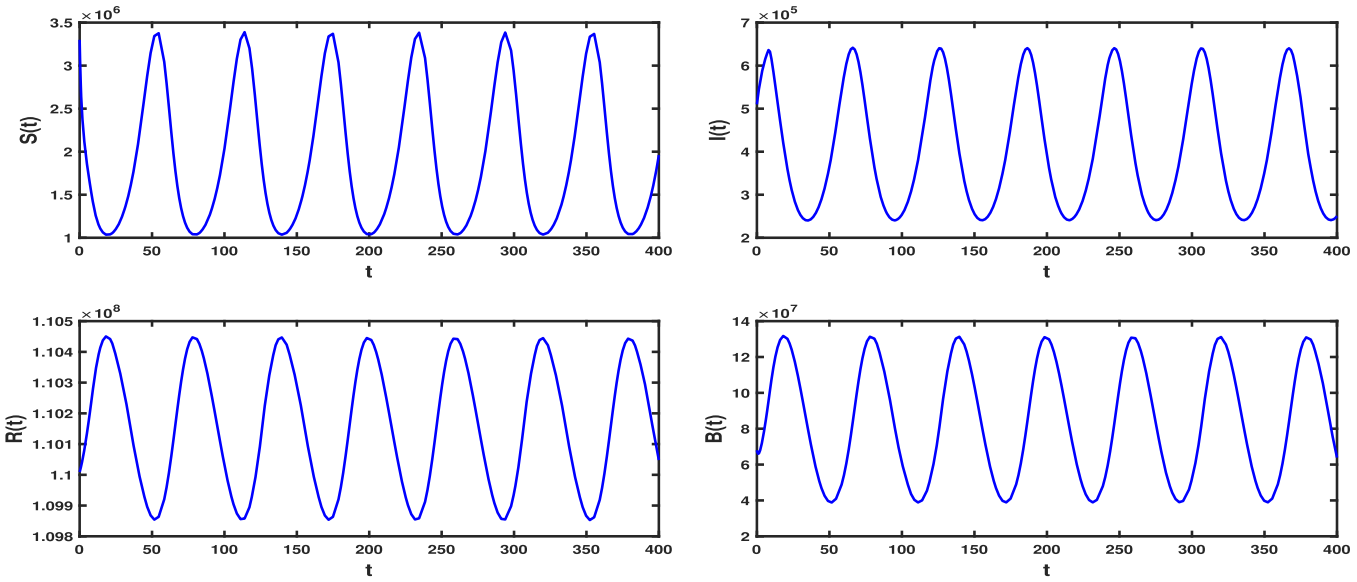
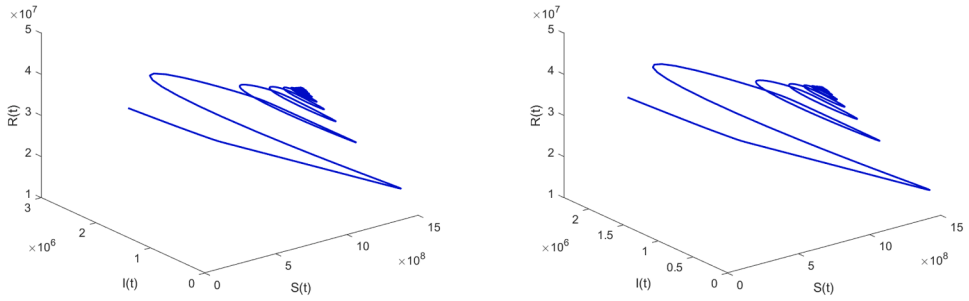


Fig. 3. The solutions of system (11) exhibit periodicity.



(a) $\tau = 8$ (b) $\tau = 12$

Fig. 4. The solutions of system (11) without Mtb in the environment when $\mathcal{R}_0 > 1$ and $\tau > 0$.

6. Conclusion and discussion

In this paper, we have derived and analyzed an SEIRB model for TB epidemic by incorporating and latency delay and environmental indirect transmission. The purpose is to explore the impact of the latent delay and Mtb in the environment on the spreading dynamics of TB in the population. We first confirmed the well-posedness of the new model and identified the basic reproduction number $\mathcal{R}_0$ of system (11). Then we discuss the equilibria of the (11) and determine their stability in terms of $\mathcal{R}_0$. We showed that the basic reproduction number $\mathcal{R}_0$ is the threshold to determine extinction or survival of TB. We proved that the disease-free equilibrium P_0 is globally asymptotically stable if $\mathcal{R}_0 < 1$, and it is unstable if $\mathcal{R}_0 > 1$, leading to occurrence of an unique endemic equilibrium P_*. We further proved the local stability of endemic equilibrium P_* if $\mathcal{R}_0 > 1$ and τ is small, by analyzing the distribution of roots to the related characteristic equation. Finally, we find that the stability of P_* changes as τ increases, and accordingly, system (11) will experience a Hopf bifurcation. Numerical simulations display that system (11) does indeed undergo the Hopf bifurcation if $\mathcal{R}_0 > 1$ at a critical value $\tau = \tau_*$. These results show that in the case of $\mathcal{R}_0 > 1$, TB can persist in the population in two different ways: converging to the endemic equilibrium or periodically oscillating around the endemic equilibrium.

Our modelling and analytical results on the model show that the latent period of TB is a hidden yet crucial factor in the transmission of TB. During this period, infected individuals show no symptoms, but the bacteria may keep replicating in the infected host. Particularly when the immune system weakens, LTBI host can progress to active TB host, making the individual contagious. This delayed pathogenic mechanism allows Mtb to spread stealthily within populations over extended periods: on one hand, LTBI individuals remain undetected and persistent in communities; on the other hand, the prolonged latency ranging from months to years provides the pathogen with opportunities for cross-generational transmission. Thus, the latent period essentially creates a "temporal buffer zone" for Mtbm, extending the time frame for transmission, and this significantly complicates control efforts. This feature stands as a core epidemiological characteristic that makes TB exceptionally difficult to eradicate. We point out that mathematically, if the delay parameter parameter is too large, then $\mathcal{R}_0 < 1$ and the disease free equilibrium P_0 is globally asymptotically stable.

We also point out although the latent delay can cause Hopf bifurcation leading to periodic solutions, this effect is actually mediated by the infection of Mtb in the environment. In fact, when we do not consider the impact of Mtb in the environment on the spread of TB, the solution of system (11) with delay will not show periodic oscillations, which can be seen from [24] and [6]. Even when the bilinear incidence rate is modified to a nonlinear incidence rate, system (11) without considering Mtb in the environment still does not display periodic oscillations [27]. These evidences indicate that Mtb in the environment plays a role for system (11) to produce periodic oscillatory behaviour.

We note that the oscillatory pattern observed in the real-world data from Fig. 1 is not fully consistent with the pattern of oscillations arising from the Hopf bifurcation predicted by the model system (11), as shown

in Fig. 3. We believe this discrepancy is due to the fact that the data in Fig. 3 from China CDC were generated under a series of intervention measures, whereas our model here in this paper only considers possible treatment (reflected by the recovery rate γ) for some cases of active TB cases as the sole intervention. Nevertheless, system (11) at least can demonstrate that the presence of Mtb in the environment may contribute to oscillation of TB cases in a population.

Our results indicate that there is the condition $G'(\Theta_*) \neq 0$ for the occurrence of Hopf bifurcation. Noting that $G(\Theta)$ depends on all model parameters in a complex way, the chances of all these parameters satisfying a single identify $G'(\Theta_*) \neq 0$ is almost zero. This means that one can expect that $G'(\Theta_*) \neq 0$ is generic. Biologically this means that generically, the longer latent delay in TB and the factor environmental transmission are (at least partially) responsible for the long term fluctuations of TB cases. This may partially explain why this disease has existed for such a long time with recurrent pattens. From an epidemiological perspective, the occurrence of sustained oscillation via bifurcation warns us of the possible misleading to the public health agencies and publics in that observing fewer cases in a period does not mean that the disease is truly under control—it may just accounts for some bottom values of the oscillation, and it may soon be followed by an outbreak.

In conclusion, our research shows that Mtb in the environment may change the way TB spreads among the population. In the scenario of periodic TB dynamics, the case numbers at peaks and troughs may provide wrong information that can mislead the publics and public health agencies, affecting their decisions in prevention and control measures. As such, it is worthwhile and indeed crucial to eliminate all possible Mtb in the environment in order to more effectively control the spread of TB in a population. As far as TB control is concerned, in the scenario of stable endemic equilibrium, it would be easy for the public health agencies to implement consistent and sustained control measures such as routine screening, treatment, and vaccination. However, in the scenario of periodic oscillations due to a Hopf bifurcation, more dynamical control measures should be accordingly employed. Such measures include establishing a more sensitive monitoring system, timely capturing the rising trend of the number of cases, increasing the frequency of screening, improving ventilation and regularly disinfecting public places to suppress the occurrence of oscillations.

We point out that in this work, we have adopted a simple form for probability function $P(t)$ in (3) (step function), because this makes the model a little bit more mathematically attractable. Another frequently used form of $P(t)$ is the exponential delay function $e^{-\alpha t}$ which would reduce the model into an ODE system. See [23,24] for this idea to be implemented to reduce the respective models to ODE models. More general than the exponential decay functions is the Gamma functions of the form $P(t) = Ct^{n-1}e^{-\alpha t}$, for which the model can also be reduced to an ODE system. See [28] for such a reduction in an SEI model. How the adoption of these two alternative forms or other forms will affect the disease dynamics remains an open project for future.

To conclude the paper, we would like to mention that the delay dependent factor $e^{-d\tau}$ and the fraction parameter $k \in [0, 1]$ (fraction of LTBI that will leave the LTBI class and progresses to the active TB class) directly impact the basic reproduction number $\mathcal{R}_0$, in a proportional way. The impact of other model parameters on $\mathcal{R}_0$ refelected by (13) clearly offers some insights into how to eradicate/control TB in a population; that is, measures that can decrease the values of k, β, η, m and increase the values of μ, γ, δ, ε can help control TB.

CRediT authorship contribution statement

Hui Cao: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis; **Xianyi Zhao:** Writing – original draft, Investigation; **Xingfu Zou:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization.

Data availability

Just quoted WHO 2024 data for TB cases which is accessble to the public.

Declaration of competing interest

This is paper is theoretical by its nature, mainly containing analytical/mathematical analysis. We confirm that it has never been submitted to other journals for consideration of publications. We also confirm that there is no conflict of interest.

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