Infectious Disease Modelling 9 (2024) 483–500

Contents lists available at ScienceDirect

Infectious Disease Modelling

journal homepage: www.keaipublishing.com/idm

Modelling the preventive treatment under media impact on tuberculosis: A comparison in four regions of China

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ARTICLE INFO

Article history:
Received 14 January 2024
Received in revised form 5 February 2024
Accepted 5 February 2024
Available online 12 February 2024
Handling Editor: Dr Yijun Lou

Keywords:
Latent tuberculosis infection
Preventive treatment
Media impact
Mathematical model
Tuberculosis elimination

ABSTRACT

Preventive treatment for people with latent Tuberculosis infection (LTBI) has aroused our great interest. In this paper, we propose and analyze a novel mathematical model of TB considering preventive treatment with media impact. The basic reproduction number $\mathcal{R}_0$ is defined by the next generation matrix method. In the case without media impact, we prove that the disease-free equilibrium is globally asymptotically stable (unstable) if $\mathcal{R}_0 < 1$ ($\mathcal{R}_0 > 1$). Furthermore, we obtain that a unique endemic equilibrium exists when $\mathcal{R}_0 > 1$, which is globally asymptotically stable in the case of permanent immunity and no media impact. We fit the model to the newly reported TB cases data from 2009 to 2019 of four regions in China and estimate the parameters. And we estimated $\mathcal{R}_0 = 0.5013 < 1$ in Hubei indicating that TB in Hubei will be eliminated in the future. However, the estimated $\mathcal{R}_0 = 1.015 > 1$ in Henan, $\mathcal{R}_0 = 1.282 > 1$ in Jiangxi and $\mathcal{R}_0 = 1.930 > 1$ in Xinjiang imply that TB will continue to persist in these three regions without further prevention and control measures. Besides, sensitivity analysis is carried out to illustrate the role of model parameters for TB control. Our finding reveals that appropriately improving the rate of timely treatment for actively infected people and increasing the rate of individuals with LTBI seeking preventive treatment could achieve the goal of TB elimination. In addition, another interesting finding shows that media impact can only reduce the number of active infections to a limited extent, but cannot change the prevalence of TB.

1. Introduction

Tuberculosis (TB) is a chronic infectious disease that is a major cause of ill health and one of the leading causes of mortality worldwide. The infectious causation of TB is caused by a bacterium called Mycobacterium tuberculosis (M.tb). The M.tb usually attacks people's lungs, but can also affect other parts of the body such as the kidney, spine, and brain. TB is spread through the air

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Peer review under responsibility of KeAi Communications Co., Ltd.

https://doi.org/10.1016/j.idm.2024.02.006

when actively infected people cough, sneeze or spit. According to Global Tuberculosis Report 2022; World Health Organization, 2022) from World Health Organization (WHO), about a quarter of the global population is estimated to have been infected with TB (latent Tuberculosis infection (LTBI), asymptomatic and non-infectious), but most people will not go on to develop active TB disease (about 5–10% of infected latent individuals eventually develop active TB disease, symptomatic and infectious) and some people will clear the infection. Without treatment, the death rate from active TB disease is high (about 50%). Fortunately, about 59%–95% of patients can be cured with currently recommended treatments, which usually require standard 6–24 month course of 4 antibiotics and common drugs including rifampicin and isoniazid (World Health Organization, 2023). Now the only licensed vaccine for prevention of TB disease is the Bacille Calmette-Guérin (BCG) vaccine. However, BCG vaccine is not life-long effective, and the immunity will be weakened and lost with the passage of time. In addition, even vaccination does not mean that it is effective for everyone. The probability of developing active TB disease is much higher among people whose immune system is weak, especially for people living with human immunodeficiency virus (HIV) (Centers for Disease Control and Prevention of America, 2016).

Mathematical modeling studies on the transmission process of infectious diseases are mainly used to provide some meaningful and useful perspectives for the public health policies to prevent or even reduce the spread of diseases. However, TB is an infectious disease with a very complex transmission process and many aspects of the natural history and transmission dynamics of TB remain unclear (White & Garnett, 2010). Many researchers have done a lot of work on the mathematical modeling and analysis of TB. Waaler et al. (1962) proposed the first mathematical model to investigate the epidemiological trend of TB. Li et al. (2022) introduced a TB dynamical model and fitted the data to estimate the parameters, and discussed the optimal control strategies for TB. Das et al. (2020) constructed a TB model with media impact on transmission rate. There are certainly more considerations in the mathematical modeling of TB, including vaccination (Bhunu, Garira, Mukandavire, & Magombedze, 2008; Okuonghae & Omosigho, 2011), treatment and incomplete treatment (Castillo-Chavez & Feng, 1997; Dye & Williams, 2000; Lemmer et al., 2014), fast and slow progression (Aparicio et al., 2002; Cai et al., 2021; Gomes et al., 2007), relapse (Ozcaglar et al., 2012; Ren, 2017), reinfection (Aparicio et al., 2002; Chinnathambi et al., 2021), confection with HIV (Bhunu et al., 2009), drug-resistant strains (Dye & Williams, 2000; Trauer et al., 2014; Wang et al., 2023) and so on.

According to WHO, for people with LTBI, TB preventive treatment can be given to stop the development of active infection (World Health Organization, 2023). And the target of 30 million people receiving preventive treatment worldwide from 2018 to 2022 was proposed at the UN high-level meeting on TB (World Health Organization, 2022). This preventive treatment uses the same drugs for a shorter time, and recent treatment options have shortened the duration of LTBI treatment to only 3 or 6 months. Comparing to at least 6 months of treatment for actively infected population, preventive treatment for people with LTBI has a shorter duration. Therefore, it is less economical and less risky for further development to active infection. The Centers for Disease Control and Prevention (CDC) in the United States also demonstrates this point, and suggests that people with LTBI should be treated to prevent them from developing TB disease (Centers for Disease Control and Prevention of America, 2016). The CDC shows that preventive treatment of LTBI is essential to controlling TB in the United States, because it substantially reduces the risk that LTBI will progress to active TB disease, which aroused our great interest.

To our knowledge, there are still relatively few models considering the treatment for people with LTBI. Castillo-Chavez and Feng (1997), Bhunu, Garira, Mukandavire, and Zimba (2008) and Zhang et al. (2015) only considered a treatment item rE from exposed compartment E to recovered compartment R. In fact, neither preventive treatment for patients with LTBI nor routine treatment for active TB infection is a short-term process and requires at least several months. Therefore, from a modeling perspective, it makes more sense to put the patients being treated into a separate compartment. And there are still a small number of exposed people who are receiving preventive treatment will become actively infected due to reduced immunity for various reasons (World Health Organization, 2022). Therefore, it is very interesting and important to develop mathematical models to study the role of preventive treatment in TB control.

In this paper, we aim to discuss the impact of preventive treatment for people with LTBI in detail. In order to accurately describe the process of preventive treatment, a new compartment T_E is introduced, which represents exposed population receiving preventive treatment. And the preventive treatment is a voluntary disease-protective tool, hence the rate of adoption will be influenced by media. The media can publicize the benefits and necessity of preventive treatment for people with LTBI, thereby influencing more exposed people to receive preventive treatment, especially those with low immunity, which may have a certain positive impact on disease control. Based on this, we further consider the impact of media on the rate of exposed population seeking for preventive treatment.

The structure of this paper is as follows. In section 2, we construct a new TB model considering preventive treatment with media impact, then calculate the basic reproduction number $\mathcal{R}_0$ and discuss the existence of equilibria of the model. Besides, the global stability of equilibria of the model in a special case is investigated in section 3. In section 4, we fit the model to the newly reported TB cases data from 2009 to 2019 of four regions in China and estimate the parameters. And we perform sensitivity analysis and discuss the effects of preventive treatment related parameters on TB control. In the last section, we provide a summary and discussion.

2. Model formulation

To investigate the effects of preventive treatment under media impact, we propose a new mathematical model that the total population (N) associated with epidemiological characteristics of TB is divided into six epidemiological compartments: susceptible (S), individuals infected with TB in the latent (asymptomatic) stage (E), individuals infected with TB in the active stage (I), actively infected individuals receiving treatment (T), exposed individuals receiving preventive treatment (T_E) and recovered (R).

The model is obtained by the following biological assumptions, and its structure is shown by the following diagram (see Fig. 1).

- Actively infected people receiving treatment (T) should be less infectious due to the effects of treatment than those who are not receiving treatment (I), therefore, incidence rate is $\beta S(I+\theta T)$ for $0<\theta<1$ (Li et al., 2022).
- Some people with LTBI (E) will seek for preventive treatment to prevent them from developing active TB disease and a small part of exposed people receiving preventive treatment (T_E) will become actively infected due to weakened immunity for some reasons (World Health Organization, 2023; Centers for Disease Control and Prevention of America, 2016).
- In 2008, Liu and Cui (2008) proposed a *SIRS* model to consider the media impact on the transmission rate, where the media impact is assumed to increase with the total number of infected people with a saturating level, that is, the transmission rate after media alert is $\beta=\beta_1-\beta_2\frac{I}{m+I}$, where $\beta_2\frac{I}{m+I}$ reflects the reduced value of the transmission rate when infectious individuals appear and are reported. Inspired by this work, and considering that the data reported in the media come from the confirmed number (T) of patients with active infections being treated in hospitals, not the actual number of active infections (I), we use the size of compartment T to describe the media impact on encouraging exposed people to receive preventive treatment, that is, the rate of exposed people seeking preventive treatment after media encouragement is $\alpha=\alpha_1+\alpha_2\frac{T}{m+T}$.
- Assume that recovered people have only temporary immunity to TB (Das et al., 2020).

The system of ordinary differential equations corresponding to the process described in Fig. 1 is

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda-\beta S(I+\theta T)+\gamma R-\mu S,\\
\frac{dE}{dt} &= \beta S(I+\theta T)-\left(\alpha_1+\alpha_2\frac{T}{m+T}\right)E-\omega E-\mu E,\\
\frac{dI}{dt} &= \omega E+\varphi T_E-\delta I-d_1 I-\mu I,\\
\frac{dT}{dt} &= \delta I-r_1 T-d_2 T-\mu T,\\
\frac{dT_E}{dt} &= \left(\alpha_1+\alpha_2\frac{T}{m+T}\right)E-\varphi T_E-r_2 T_E-\mu T_E,\\
\frac{dR}{dt} &= r_1 T+r_2 T_E-\gamma R-\mu R.
\end{aligned} \tag{1}$$

The specific definitions of all parameters are as follows. Λ is the recruitment rate. Incidence rate is $\beta S(I+\theta T)$, where β is the transmission rate and θ is the reduction coefficient of TB spread due to treatment ($0<\theta<1$). γ is the rate of recovered who lose immunity and return to be susceptible. μ is the natural death rate while d_1 and d_2 are the disease-induced death rates of compartment I and compartment T, respectively. The impact of media on exposed people seeking preventive treatment is considered by $\alpha=\alpha_1+\alpha_2\frac{T}{m+T}$, where α_1 is the rate of exposed population seeking for preventive treatment before media encouragement, α_2 is the maximum growth rate influenced by media which is assumed to increase with the confirmed

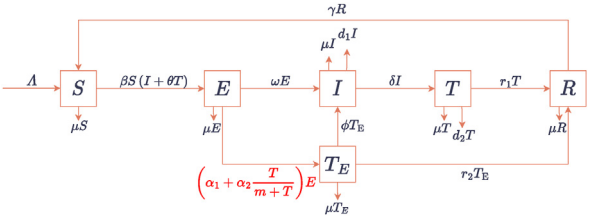


Fig. 1. Illustration of the spread of TB in the population.

number receiving preventive treatment T with a saturating level and m is the half saturation constant. ω is the rate of exposed population becoming actively infected population. φ is the rate of those receiving preventive treatment becoming actively infected. δ is the rate of actively infected population seeking for treatment. r_1 is the treatment rate for compartment T and r_2 is the preventive treatment rate for compartment T_E. All parameters are assumed to be positive constants except $\gamma \geqslant 0$ and $\alpha_2 \geqslant 0$, while $\gamma = 0$ means that recovered people have permanent immunity and $\alpha_2 = 0$ represents no media impact.

Remark 1. Note that the condition $\varphi < \omega$ should be natural by biology, otherwise $\varphi \geqslant \omega$ means that the probability of developing active TB disease among exposed population receiving preventive treatment is higher than those who are not treated, which is unreasonable.

Next, we analyze the dynamics behavior of model (1). For brevity, let $h_1 = \alpha_1 + \omega + \mu$, $h_2 = \delta + d_1 + \mu$, $h_3 = r_1 + d_2 + \mu$, $h_4 = \varphi + r_2 + \mu$, $h_5 = \gamma + \mu$, then model (1) becomes

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \beta S(I + \theta T) + \gamma R - \mu S,\\
\frac{dE}{dt} &= \beta S(I + \theta T) - \alpha_2 \frac{T}{m + T} E - h_1 E,\\
\frac{dI}{dt} &= \omega E + \varphi T_E - h_2 I,\\
\frac{dT}{dt} &= \delta I - h_3 T,\\
\frac{dT_E}{dt} &= \alpha_1 E + \alpha_2 \frac{T}{m + T} E - h_4 T_E,\\
\frac{dR}{dt} &= r_1 T + r_2 T_E - h_5 R.
\end{aligned} \tag{2}$$

2.1. Positivity and boundedness of solutions

To confirm the biological feasibility of model (2), it is essential to disclose that all the state variables are non-negative for all time $t > 0$ and find a suitable feasible region Ω over which the model (2) is analyzed. For this purpose, we have the following results.

Lemma 2.1. *Every solution of model* (2) *with positive initial conditions remains positive in* $\mathbb{R}^6_+$ *as* $t > 0$.

Proof. *From model* (2), *we obtain*

$$\begin{aligned}
\frac{dS}{dt}_{[S=0,E\geqslant 0,I\geqslant 0,T\geqslant 0,T_E\geqslant 0,R\geqslant 0]} &= \Lambda + \gamma R > 0,\\
\frac{dE}{dt}_{[S>0,E=0,I\geqslant 0,T\geqslant 0,T_E\geqslant 0,R\geqslant 0]} &= \beta S(I + \theta T) \geqslant 0,\\
\frac{dI}{dt}_{[S>0,E\geqslant 0,I=0,T\geqslant 0,T_E\geqslant 0,R\geqslant 0]} &= \omega E + \varphi T_E \geqslant 0,\\
\frac{dT}{dt}_{[S>0,E\geqslant 0,I\geqslant 0,T=0,T_E\geqslant 0,R\geqslant 0]} &= \delta I \geqslant 0,\\
\frac{dT_E}{dt}_{[S>0,E\geqslant 0,I\geqslant 0,T\geqslant 0,T_E=0,R\geqslant 0]} &= \alpha_1 E + \alpha_2 \frac{T}{m + T} E \geqslant 0,\\
\frac{dR}{dt}_{[S>0,E\geqslant 0,I\geqslant 0,T\geqslant 0,T_E\geqslant 0,R=0]} &= r_1 T + r_2 T_E \geqslant 0.
\end{aligned} \tag{3}$$

The above rates are all non-negative over the boundary planes of the non-negative cone of $\mathbb{R}^6_+$ (Das et al., 2020). Therefore, all the solution trajectories with positive initial conditions remain in positive region only. □

Lemma 2.2. *The closed set* Ω *defined by*:

$$\Omega = \left\{ (S, E, I, T, T_E, R) \in \mathbb{R}^6_+ : 0 < S + E + I + T + T_E + R \leqslant \frac{\Lambda}{\mu} \right\}$$

is positive invariant and attracting for model (2) with positive initial conditions.

Proof. Define $N=S+E+I+T+T_E+R$, and summing all equations in model (2) yields

$$\frac{dN}{dt}=\Lambda-\mu N-d_1I-d_2T\leqslant\Lambda-\mu N,$$

which implies that $\frac{dN}{dt}\leqslant 0$ if $N(t)\geqslant\frac{\Lambda}{\mu}$. And by the standard comparison theorem (Lakshmikantham et al., 1989),

$$N(t)\leqslant\frac{\Lambda}{\mu}-\left(\frac{\Lambda}{\mu}-N(0)\right)e^{-\mu t}.$$

In fact, we can see that $N(t)\leqslant\frac{\Lambda}{\mu}$ for all $t>0$ if $N(0)\leqslant\frac{\Lambda}{\mu}$, and thus Ω is positive invariant. For $N(0)>\frac{\Lambda}{\mu}$, the solution finally enters the region Ω in finite time or $N(t)$ asymptotically approaches $\frac{\Lambda}{\mu}$ as $t\to\infty$.

Every solution of model (2) with positive initial conditions in Ω remains there for all $t>0$. Therefore, Ω is a positive invariant set and attracts all solutions in $\mathbb{R}^6_+$. □

Throughout this paper, we consider the dynamics of the flow generated by model (2) in region Ω. Hence model (2) is well-posed both in epidemiology and mathematics (Hethcote, 2000).

2.2. Basic reproduction number

Obviously, the disease-free equilibrium of model (2) is calculated as $P^0=\left(S^0,0,0,0,0,0\right)$ where $S^0=\frac{\Lambda}{\mu}$. We use the next generation matrix method to calculate the basic reproduction number (Van den Driessche & Watmough, 2002). Let us consider $X=(E,I,T,T_E)$, and model (2) is written as $\dot{X}=\mathcal{F}-\mathcal{V}$, where

$$\mathcal{F}=\begin{pmatrix}\beta S(I+\theta T)\\0\\0\\0\end{pmatrix},\mathcal{V}=\begin{pmatrix}h_1E+\alpha_2\dfrac{T}{m+T}E\\-\omega E-\varphi T_E+h_2I\\-\delta I+h_3T\\-\alpha_1E-\alpha_2\dfrac{T}{m+T}E+h_4T_E\end{pmatrix}.$$

Jacobian matrices F and V at P^0 of $\mathcal{F}$ and $\mathcal{V}$ are given by

$$F=\begin{pmatrix}0&\frac{\beta\Lambda}{\mu}&\frac{\beta\Lambda\theta}{\mu}&0\\0&0&0&0\\0&0&0&0\\0&0&0&0\end{pmatrix},V=\begin{pmatrix}h_1&0&0&0\\-\omega&h_2&0&-\varphi\\0&-\delta&h_3&0\\-\alpha_1&0&0&h_4\end{pmatrix}.$$

The next generation matrix is

$$FV^{-1}=\begin{pmatrix}\frac{\beta\Lambda(\alpha_1\varphi+h_4\omega)(h_3+\delta\theta)}{h_1h_2h_3h_4\mu}&\frac{\beta\Lambda(h_3+\delta\theta)}{h_2h_3\mu}&\frac{\beta\Lambda\theta}{h_3\mu}&\frac{\beta\Lambda\varphi(h_3+\delta\theta)}{h_2h_3h_4\mu}\\0&0&0&0\\0&0&0&0\\0&0&0&0\end{pmatrix}.$$

The basic reproduction number $\mathcal{R}_0$ is the spectral radius ρ of FV^{-1}, that is,

$$\mathcal{R}_0=\rho(FV^{-1})=\frac{\beta\Lambda(\alpha_1\varphi+h_4\omega)(h_3+\delta\theta)}{h_1h_2h_3h_4\mu}.$$

Using the original parameters, we have

$$\mathcal{R}_0=\frac{\beta\Lambda[\alpha_1\varphi+(\varphi+r_2+\mu)\omega][(r_1+\mu+d_2)+\delta\theta]}{(\alpha_1+\omega+\mu)(\delta+\mu+d_1)(r_1+\mu+d_2)(\varphi+r_2+\mu)\mu}.$$

2.3. Existence of equilibria

Lemma 2.3. *The model* (2) *always exhibits a disease-free equilibrium* P^0, *and possesses a unique endemic equilibrium* P^* *if* $\mathcal{R}_0 > 1$.

Proof. *Define* $\mathcal{X} = I + \theta T$, *and then set*

$$\begin{aligned}
&\Lambda - \beta S\mathcal{X} + \gamma R - \mu S = 0,\\
&\beta S\mathcal{X} - h_1 E - \eta E = 0,\\
&\omega E + \varphi T_{\mathrm{E}} - h_2 I = 0,\\
&\delta I - h_3 T = 0,\\
&\alpha_1 E + \eta E - h_4 T_{\mathrm{E}} = 0,\\
&r_1 T + r_2 T_{\mathrm{E}} - h_5 R = 0,
\end{aligned} \tag{4}$$

where $\eta = \alpha_2 \frac{T}{m+T}$.

Considering $\mathcal{X} = I + \theta T$ as a whole and then by calculations, S, E, I, T, T_{E} and R can be represented by $\mathcal{X}$, that is,

$$\begin{aligned}
S &= \frac{\Lambda(\eta h_2 h_3 h_4 h_5 + h_1 h_2 h_3 h_4 h_5)}{\mathcal{Y}},\\
E &= \frac{\Lambda\mathcal{X}\beta h_2 h_3 h_4 h_5}{\mathcal{Y}},\\
I &= \frac{\Lambda\mathcal{X}\beta(\alpha_1 h_3 h_5\varphi + \eta h_3 h_5\varphi + h_3 h_4 h_5\omega)}{\mathcal{Y}},\\
T &= \frac{\Lambda\mathcal{X}\beta\delta(\alpha_1 h_5\varphi + \eta h_5\varphi + h_4 h_5\omega)}{\mathcal{Y}},\\
T_{\mathrm{E}} &= \frac{\Lambda\mathcal{X}\beta h_2 h_3 h_5(\alpha_1 + \eta)}{\mathcal{Y}},\\
R &= \frac{\Lambda\mathcal{X}\beta(\alpha_1 h_2 h_3 r_2 + \eta h_2 h_3 r_2 + \alpha_1\delta\varphi r_1 + \delta\eta\varphi r_1 + \delta h_4\omega r_1)}{\mathcal{Y}},
\end{aligned} \tag{5}$$

where

$$\mathcal{Y} = (\mathcal{X}\beta + \mu)h_2 h_3 h_4 h_5(h_1 + \eta) - \mathcal{X}\beta\eta(\gamma h_2 h_3 r_2 + \delta\gamma\varphi r_1) - \mathcal{X}\beta(\alpha_1\delta\gamma\varphi r_1 + \delta\gamma h_4\omega r_1 + \alpha_1\gamma h_2 h_3 r_2).$$

Since $h_1 h_2 h_3 h_4 h_5 = (\alpha_1 + \omega + \mu)(\delta + \mu + d_1)(r_1 + \mu + d_2)(\varphi + r_2 + \mu)(\gamma + \mu)$ and the polynomial of $\mathcal{X}\beta h_2 h_3 h_4 h_5(h_1 + \eta)$ contains $\mathcal{X}\beta\eta(\gamma h_2 h_3 r_2 + \delta\gamma\varphi r_1)$ and $\mathcal{X}\beta(\alpha_1\delta\gamma\varphi r_1 + \delta\gamma h_4\omega r_1 + \alpha_1\gamma h_2 h_3 r_2)$, we have $\mathcal{Y} > 0$.

From the fourth equation of (4), we have $I = \frac{h_3 T}{\delta}$. Since $\eta = \alpha_2 \frac{T}{m+T}$ and $\mathcal{X} = I + \theta T$, so $\mathcal{X}, \mathcal{Y}$ can be expressed as a function of T. Therefore, by the fourth equation of (5), state variable T must satisfy

$$T\left(A_1 T^2 + A_2 T + A_3\right) = 0, \tag{6}$$

where

$$\begin{aligned}
A_1 &= \beta(h_3 + \delta\theta)[\alpha_2(\gamma h_2 h_3 r_2 + \delta\gamma\varphi r_1 - h_2 h_3 h_4 h_5) + \alpha_1\gamma h_2 h_3 r_2 + \alpha_1\delta\gamma\varphi r_1 + \delta\gamma h_4\omega r_1 - h_1 h_2 h_3 h_4 h_5] < 0,\\
A_2 &= \alpha_2\delta h_5[\Lambda\beta\varphi(h_3 + \delta\theta) - h_2 h_3 h_4 h_5\mu] + \delta h_1 h_2 h_3 h_4 h_5\mu(\mathcal{R}_0 - 1)\\
&\quad + \beta m(h_3 + \delta\theta)[\alpha_1\gamma h_2 h_3 r_2 + \alpha_1\delta\gamma\varphi r_1 + \delta\gamma h_4\omega r_1 - h_1 h_2 h_3 h_4 h_5]\\
&= \frac{\alpha_2\delta h_2 h_3 h_4 h_5\mu}{\alpha_1\varphi + h_4\omega}[\varphi(\alpha_1 + \omega)(\mathcal{R}_0 - 1) + \mu(\varphi\mathcal{R}_0 - \omega) - \omega r_2] + \delta h_1 h_2 h_3 h_4 h_5\mu(\mathcal{R}_0 - 1)\\
&\quad + \beta m(h_3 + \delta\theta)[\alpha_1\gamma h_2 h_3 r_2 + \alpha_1\delta\gamma\varphi r_1 + \delta\gamma h_4\omega r_1 - h_1 h_2 h_3 h_4 h_5],\\
A_3 &= \delta h_5 m[\Lambda\beta(\alpha_1\varphi + h_4\omega)(h_3 + \delta\theta) - h_1 h_2 h_3 h_4\mu]\\
&= \delta h_1 h_2 h_3 h_4 h_5 m\mu(\mathcal{R}_0 - 1).
\end{aligned}$$

Obviously, $T = 0$ is the root of equation (6). $A_1 < 0$ is always true because the polynomial of $h_2 h_3 h_4 h_5$ contains $\gamma h_2 h_3 r_2 + \delta\gamma\varphi r_1$ and polynomial of $h_1 h_2 h_3 h_4 h_5$ contains $\alpha_1\gamma h_2 h_3 r_2 + \alpha_1\delta\gamma\varphi r_1 + \delta\gamma h_4\omega r_1$. When $\mathcal{R}_0 \leqslant 1$, we have $A_2 < 0$ due to the fact $\varphi < \omega$ and the polynomial of $h_1 h_2 h_3 h_4 h_5$ contains $\alpha_1\gamma h_2 h_3 r_2 + \alpha_1\delta\gamma\varphi r_1 + \delta\gamma h_4\omega r_1$, and $A_3 \leqslant 0$, so equation (6) does not have positive

root. When $\mathcal{R}_0 > 1$, A_2 could be positive or negative, and $A_3 > 0$, equation (6) only has a unique positive root. Hence the required result is obtained. □

3. Stability of equilibria

In this section, we first discuss the global stability of disease-free equilibrium for case $\alpha_2 = 0$ (only preventive treatment is considered without media impact). Then we study the local stability of disease-free equilibrium of model (2) in general. Finally, we investigate the global stability of endemic equilibrium for case $\alpha_2 = 0$ and $\gamma = 0$ (the recovered people have the permanent immunity to TB).

3.1. Stability of disease-free equilibrium

Theorem 3.1. *For case $\alpha_2 = 0$, if $\mathcal{R}_0 < 1$, then disease-free equilibrium P^0 of model (2) is globally asymptotically stable. And if $\mathcal{R}_0 > 1$, then P^0 is unstable.*

Proof. *Construct the following Lyapunov function*:

$$L(t) = B_1E + B_2I + B_3T + B_4T_E + B_5R, \tag{7}$$

where $B_i(i = 1, 2, 3, 4, 5)$ need to be determined suitably in subsequent steps. The derivative of $L(t)$ along the solutions of model (2), together with $S \leqslant S^0$ from the positive invariance Ω, yields

$$\begin{aligned}\dot{L}(t) &= B_1\dot{E} + B_2\dot{I} + B_3\dot{T} + B_4\dot{T}_E + B_5\dot{R}\\ &= B_1[\beta S(I + \theta T) - h_1E] + B_2(\omega E + \varphi T_E - h_2I) + B_3(\delta I - h_3T) + B_4(\alpha_1 E - h_4T_E) + B_5(r_1T + r_2T_E - h_5R)\\ &= (\omega B_2 + \alpha_1 B_4 - h_1B_1)E + (\beta SB_1 - h_2B_2 + \delta B_3)I + (\beta S\theta B_1 - h_3B_3 + r_1B_5)T + (\varphi B_2 - h_4B_4 + r_2B_5)T_E - B_5h_5R\\ &\leqslant (\omega B_2 + \alpha_1 B_4 - h_1B_1)E + \Big(\beta S^0B_1 - h_2B_2 + \delta B_3\Big)I + \Big(\beta S^0\theta B_1 - h_3B_3 + r_1B_5\Big)T + (\varphi B_2 - h_4B_4 + r_2B_5)T_E.\end{aligned}$$

In order to let the coefficient of I be $\mathcal{R}_0 - 1$, and the coefficients of other variables be zero. Set $B_1 = \frac{(\alpha_1\varphi + h_4\omega)(h_3 + \delta\theta)}{h_1h_2h_3h_4}$, and

$$\begin{cases}\omega B_2 + \alpha_1 B_4 - h_1B_1 &= 0,\\ -h_2B_2 + \delta B_3 &= -1,\\ \beta S^0\theta B_1 - h_3B_3 + r_1B_5 &= 0,\\ \varphi B_2 - h_4B_4 + r_2B_5 &= 0.\end{cases} \tag{8}$$

Then we obtain the solution of (8) as

$$\begin{aligned}B_2 &= \frac{\alpha_1h_3r_2 + B_1\delta h_1h_4r_1 + B_1S^0\alpha_1\beta\delta r_2\theta}{\alpha_1h_2h_3r_2 + \alpha_1\delta\varphi r_1 + \delta h_4\omega r_1},\\ B_3 &= \frac{B_1h_1h_2h_4r_1 + B_1S^0\alpha_1\beta h_2r_2\theta - \alpha_1\varphi r_1 - h_4\omega r_1}{\alpha_1h_2h_3r_2 + \alpha_1\delta\varphi r_1 + \delta h_4\omega r_1},\\ B_4 &= \frac{B_1h_1h_2h_3r_2 + B_1\delta h_1\varphi r_1 - B_1S^0\beta\delta\omega r_2\theta - h_3\omega r_2}{\alpha_1h_2h_3r_2 + \alpha_1\delta\varphi r_1 + \delta h_4\omega r_1},\\ B_5 &= \frac{B_1h_1h_2h_3h_4 - \alpha_1h_3\varphi - h_3h_4\omega - B_1S^0\alpha_1\beta\delta\varphi\theta - B_1S^0\beta\delta h_4\omega\theta}{\alpha_1h_2h_3r_2 + \alpha_1\delta\varphi r_1 + \delta h_4\omega r_1}.\end{aligned}$$

Apparently, $B_1 > 0$ and $B_2 > 0$.

Since

$$\begin{aligned}B_1h_1h_2h_4r_1 - \alpha_1\varphi r_1 - h_4\omega r_1 &= \frac{r_1(\alpha_1\varphi + h_4\omega)(h_3 + \delta\theta)}{h_3} - \alpha_1\varphi r_1 - h_4\omega r_1\\ &= \frac{r_1\delta\theta(\alpha_1\varphi + h_4\omega)}{h_3},\end{aligned}$$

then $B_3 > 0$.

Since

$$
\begin{aligned}
&B_1h_1h_2h_3r_2 - h_3\omega r_2 - B_1S^0\beta\delta\omega r_2\theta\\
&= \frac{r_2(\alpha_1\varphi + h_4\omega)(h_3+\delta\theta)}{h_4} - h_3\omega r_2 - B_1S^0\beta\delta\omega r_2\theta\\
&= \frac{r_2\alpha_1\varphi h_3 + r_2\alpha_1\varphi\delta\theta + r_2h_4\omega\delta\theta - B_1S^0\beta\delta\omega r_2\theta h_4}{h_4}\\
&= \frac{r_2\alpha_1\varphi h_3 + r_2\alpha_1\varphi\delta\theta + r_2h_4\omega\delta\theta(1-\mathcal{R}_0)}{h_4},
\end{aligned}
$$

then $B_4 > 0$ when $\mathcal{R}_0 < 1$.

Since

$$
\begin{aligned}
&B_1h_1h_2h_3h_4 - \alpha_1h_3\varphi - h_3h_4\omega - B_1S^0\alpha_1\beta\delta\varphi\theta - B_1S^0\beta\delta h_4\omega\theta\\
&= (\alpha_1\varphi + h_4\omega)(h_3+\delta\theta) - \alpha_1h_3\varphi - h_3h_4\omega - B_1S^0\alpha_1\beta\delta\varphi\theta - B_1S^0\beta\delta h_4\omega\theta\\
&= \delta\theta(\alpha_1\varphi + h_4\omega)(1-\mathcal{R}_0),
\end{aligned}
$$

then $B_5 > 0$ when $\mathcal{R}_0 < 1$.

Therefore, we find the positive coefficients of Lyapunov function $L(t)$, and $\dot{L}(t) = (\mathcal{R}_0 - 1)I < 0$ for $\mathcal{R}_0 < 1$. It follows that there exists a singleton P^0, as the maximal compact invariant set in $\left\{(S,E,I,T,T_E,R)\in\Omega : \dot{L} = 0\right\}$. Using LaSalle's Invariance Principle (La Salle, 1976), every solution of model (2) with initial conditions in Ω approaches P^0 as $t\to\infty$ whenever $\mathcal{R}_0 < 1$. So disease-free equilibrium P^0 of model (2) is globally asymptotically stable if $\mathcal{R}_0 < 1$.

Next, we prove that P^0 is unstable if $\mathcal{R}_0 > 1$. The Jacobian matrix of model (2) at equilibrium P^0 is

$$
J\left(P^0\right) = \begin{pmatrix}
-\mu & 0 & -\frac{\Lambda\beta}{\mu} & -\frac{\Lambda\beta\theta}{\mu} & 0 & \gamma\\
0 & -h_1 & \frac{\Lambda\beta}{\mu} & \frac{\Lambda\beta\theta}{\mu} & 0 & 0\\
0 & \omega & -h_2 & 0 & \varphi & 0\\
0 & 0 & \delta & -h_3 & 0 & 0\\
0 & \alpha_1 & 0 & 0 & -h_4 & 0\\
0 & 0 & 0 & r_1 & r_2 & -h_5
\end{pmatrix}.
$$

The characteristic polynomial of the above Jacobian matrix is

$$
(\lambda+\mu)(\lambda+h_5)\left(\lambda^4 + b_1\lambda^3 + b_2\lambda^2 + b_3\lambda + b_4\right) = 0,
$$

where

$$
\begin{aligned}
b_1 &= h_1 + h_2 + h_3 + h_4,\\
b_2 &= \frac{h_1h_2\mu + h_1h_3\mu + h_1h_4\mu + h_2h_3\mu + h_2h_4\mu + h_3h_4\mu - \Lambda\beta\omega}{\mu},\\
b_3 &= \frac{h_1h_2h_3\mu + h_1h_2h_4\mu + h_1h_3h_4\mu + h_2h_3h_4\mu - \Lambda\beta(\alpha_1\varphi + h_3\omega + h_4\omega + \delta\omega\theta)}{\mu},\\
b_4 &= \frac{h_1h_2h_3h_4\mu - \beta\Lambda(\alpha_1\varphi + h_4\omega)(h_3+\delta\theta)}{\mu} = h_1h_2h_3h_4(1-\mathcal{R}_0).
\end{aligned}
$$

Apparently, we can see that $b_4 < 0$ if $\mathcal{R}_0 > 1$. Therefore, the disease-free equilibrium P^0 is unstable if $\mathcal{R}_0 > 1$ by well known Routh-Hurwitz criterion. □

Remark 2. From the above theorem, the disease-free equilibrium P^0 is globally asymptotically stable when $\mathcal{R}_0 < 1$ for case $\alpha_2 = 0$. Obviously, P^0 is also locally asymptotically stable when $\mathcal{R}_0 < 1$ for case $\alpha_2 = 0$. However, for cases $\alpha_2 = 0$ and $\alpha_2 > 0$, the model (2) has the same disease-free equilibrium point P^0 and Jacobian matrix at P^0, so it should have the same local stability of P^0.

Therefore, we have the following theorem about local stability for P^0 of model (2) in general.

Theorem 3.2. *If $\mathcal{R}_0 < 1$, then disease-free equilibrium P^0 of model (2) is locally asymptotically stable. And if $\mathcal{R}_0 > 1$, then P^0 is unstable.*

3.2. Global stability of endemic equilibrium

Theorem 3.3. *For case $\alpha_2 = 0$ and $\gamma = 0$, if $\mathcal{R}_0 > 1$, then the endemic equilibrium P* of model (2) is globally asymptotically stable.*

Proof. *Note that the first five equations are independent of the sixth in model (2) when $\gamma = 0$, where variable R just appears in the sixth equation of model (2). Therefore, we only need consider the first five equations of model (2) in this special case.*

For endemic equilibrium $P^* = (S^*, E^*, I^*, T^*, {T_E}^*)$ when $\alpha_2 = 0$ and $\gamma = 0$, it satisfies the following equations:

$$\begin{aligned}
&\Lambda - \beta S^*(I^* + \theta T^*) - \mu S^* = 0,\\
&\beta S^*(I^* + \theta T^*) - h_1 E^* = 0,\\
&\omega E^* + \varphi T_E^* - h_2 I^* = 0,\\
&\delta I^* - h_3 T^* = 0,\\
&\alpha_1 E^* - h_4 T_E^* = 0.
\end{aligned} \tag{9}$$

Consider the following Lyapunov function (Huo & Zou, 2016):

$$V(t) = (S - S^* \ln S) + C_1(E - E^* \ln E) + C_2(I - I^* \ln I) + C_3(T - T^* \ln T) + C_4\left(T_E - T_E^* \ln T_E\right),$$

where $C_i (i = 1, 2, 3, 4)$ are positive constants and will be determined later. The derivative of $V(t)$ with respect to time along the solutions of model (2) is calculated as

$$\begin{aligned}
\dot{V}(t) &= \left(1 - \frac{S^*}{S}\right)\dot{S} + C_1\left(1 - \frac{E^*}{E}\right)\dot{E} + C_2\left(1 - \frac{I^*}{I}\right)\dot{I} + C_3\left(1 - \frac{T^*}{T}\right)\dot{T} + C_4\left(1 - \frac{{T_E}^*}{T_E}\right)\dot{T}_E\\
&= \left(1 - \frac{S^*}{S}\right)[\beta S^*(I^* + \theta T^*) + \mu S^* - \beta S(I + \theta T) - \mu S]\\
&\quad + C_1\left(1 - \frac{E^*}{E}\right)\left[\beta S(I + \theta T) - \beta S^*(I^* + \theta T^*)\frac{E}{E^*}\right]\\
&\quad + C_2\left(1 - \frac{I^*}{I}\right)\left[\omega E + \varphi T_E - \left(\omega E^* + \varphi T_E^*\right)\frac{I}{I^*}\right]\\
&\quad + C_3\left(1 - \frac{T^*}{T}\right)\left(\delta I - \delta I^* \frac{T}{T^*}\right) + C_4\left(1 - \frac{{T_E}^*}{T_E}\right)\left(\alpha_1 E - \alpha_1 E^* \frac{T_E}{{T_E}^*}\right)\\
&= \left(1 - \frac{S^*}{S}\right)\left[\beta S^* I^*\left(1 - \frac{S}{S^*}\frac{I}{I^*}\right) + \theta\beta S^* T^*\left(1 - \frac{S}{S^*}\frac{T}{T^*}\right) + \mu S^*\left(1 - \frac{S}{S^*}\right)\right]\\
&\quad + C_1\left(1 - \frac{E^*}{E}\right)\left[\beta S^* I^*\left(\frac{S}{S^*}\frac{I}{I^*} - \frac{E}{E^*}\right) + \theta\beta S^* T^*\left(\frac{S}{S^*}\frac{T}{T^*} - \frac{E}{E^*}\right)\right]\\
&\quad + C_2\left(1 - \frac{I^*}{I}\right)\left[\omega E^*\left(\frac{E}{E^*} - \frac{I}{I^*}\right) + \varphi T_E^*\left(\frac{T_E}{{T_E}^*} - \frac{I}{I^*}\right)\right]\\
&\quad + C_3\left(1 - \frac{T^*}{T}\right)\delta I^*\left(\frac{I}{I^*} - \frac{T}{T^*}\right) + C_4\left(1 - \frac{{T_E}^*}{T_E}\right)\alpha_1 E^*\left(\frac{E}{E^*} - \frac{T_E}{{T_E}^*}\right).
\end{aligned}$$

By denoting

$$\frac{S}{S^*} = x, \frac{E}{E^*} = y, \frac{I}{I^*} = z, \frac{T}{T^*} = l, \frac{T_E}{{T_E}^*} = n,$$

we have

$$
\begin{aligned}
\dot{V}(t) &= -\mu S^*\frac{(1-x)^2}{x} + \left(1-\frac{1}{x}\right)[\beta S^* I^*(1-xz) + \theta\beta S^* T^*(1-xl)] \\
&\quad + C_1\left(1-\frac{1}{y}\right)[\beta S^* I^*(xz-y) + \theta\beta S^* T^*(xl-y)] \\
&\quad + C_2\left(1-\frac{1}{z}\right)[\omega E^*(y-z) + \varphi T_E^*(n-z)] \\
&\quad + C_3\left(1-\frac{1}{l}\right)\delta I^*(z-l) + C_4\left(1-\frac{1}{n}\right)\alpha_1 E^*(y-n) \\
&= -\mu S^*\frac{(1-x)^2}{x} + \beta S^* I^*\left(1-xz-\frac{1}{x}+z\right) + \theta\beta S^* T^*\left(1-xl-\frac{1}{x}+l\right) \\
&\quad + C_1\beta S^* I^*\left(xz-y-\frac{xz}{y}+1\right) + C_1\theta\beta S^* T^*\left(xl-y-\frac{xl}{y}+1\right) \\
&\quad + C_2\omega E^*\left(y-z-\frac{y}{z}+1\right) + C_2\varphi T_E^*\left(n-z-\frac{n}{z}+1\right) \\
&\quad + C_3\delta I^*\left(z-l-\frac{z}{l}+1\right) + C_4\alpha_1 E^*\left(y-n-\frac{y}{n}+1\right) \\
&= -\mu S^*\frac{(1-x)^2}{x} + xz(C_1\beta S^* I^* - \beta S^* I^*) + xl(C_1\theta\beta S^* T^* - \theta\beta S^* T^*) \\
&\quad + y(C_2\omega E^* - C_1\beta S^* I^* - C_1\theta\beta S^* T^* + C_4\alpha_1 E^*) \\
&\quad + z(\beta S^* I^* - C_2\omega E^* - C_2\varphi T_E^* + C_3\delta I^*) \\
&\quad + l(\theta\beta S^* T^* - C_3\delta I^*) + n(C_2\varphi T_E^* - C_4\alpha_1 E^*) \\
&\quad + C_1\beta S^* I^*\left(1-\frac{xz}{y}\right) + C_1\theta\beta S^* T^*\left(1-\frac{xl}{y}\right) + C_2\omega E^*\left(1-\frac{y}{z}\right) \\
&\quad + C_2\varphi T_E^*\left(1-\frac{n}{z}\right) + C_3\delta I^*\left(1-\frac{z}{l}\right) + C_4\alpha_1 E^*\left(1-\frac{y}{n}\right).
\end{aligned}
$$

Variables terms xz, xl, y, z, l and n may have positive coefficients resulting in $\dot{V}(t)$ being positive. Therefore, letting the coefficients of xz, xl, y, z, l and n equal to zero, gives

$$
\begin{aligned}
&C_1\beta S^* I^* - \beta S^* I^* = 0, \\
&C_1\theta\beta S^* T^* - \theta\beta S^* T^* = 0, \\
&C_2\omega E^* - C_1\beta S^* I^* - C_1\theta\beta S^* T^* + C_4\alpha_1 E^* = 0, \\
&\beta S^* I^* - C_2\omega E^* - C_2\varphi T_E^* + C_3\delta I^* = 0, \\
&\theta\beta S^* T^* - C_3\delta I^* = 0, \\
&C_2\varphi T_E^* - C_4\alpha_1 E^* = 0.
\end{aligned} \tag{10}
$$

From first and second equations of (10), it is obviously that $C_1 = 1$. And by applying (9), the last four equations of (10) become

$$
\begin{aligned}
&C_2\omega + C_4\alpha_1 - h_1 = 0, \\
&\beta S^* - C_2 h_2 + C_3\delta = 0, \\
&\theta\beta S^* - C_3 h_3 = 0, \\
&C_2\varphi - C_4 h_4 = 0.
\end{aligned} \tag{11}
$$

We can get a set of solutions of C_i through the last three equations of (11), which is

$$
C_2 = \frac{S^*\beta(h_3+\delta\theta)}{h_2 h_3}, C_3 = \frac{S^*\beta\theta}{h_3}, C_4 = \frac{S^*\beta\varphi(h_3+\delta\theta)}{h_2 h_3 h_4}.
$$

And then substitute them into the first equation of (11), we have

$$C_2\omega + C_4\alpha_1 - h_1 = \frac{S^*\beta h_5(\alpha_1\varphi + h_4\omega)(h_3 + \delta\theta) - h_1h_2h_3h_4h_5}{h_2h_3h_4h_5}.$$

From the first and third equations of (5) when $\alpha_2 = 0(\eta = 0)$ and $\gamma = 0$, we calculate

$$S^* = \frac{h_1h_2h_3h_4}{\beta(\alpha_1\varphi + h_4\omega)(h_3 + \delta\theta)}.$$

Therefore, we have $C_2\omega + C_4\alpha_1 - h_1 = 0$, that is, C_2, C_3, C_4 obtained above are a set of solutions to (11). By substituting into the expression of S^*, we have

$$C_2 = \frac{h_1\,h_4}{\alpha_1\,\varphi + h_4\,\omega}, C_3 = \frac{h_1\,h_2\,h_4\,\theta}{(\alpha_1\,\varphi + h_4\,\omega)\,(h_3 + \delta\,\theta)}, C_4 = \frac{h_1\,\varphi}{\alpha_1\,\varphi + h_4\,\omega}.$$

Therefore,

$$\begin{aligned}
\dot{V}(t) &= -\mu S^*\frac{(1-x)^2}{x} + \beta S^*I^*\left(1-\frac{1}{x}\right) + \theta\beta S^*T^*\left(1-\frac{1}{x}\right) + \beta S^*I^*\left(1-\frac{xz}{y}\right)\\
&\quad + \theta\beta S^*T^*\left(1-\frac{xl}{y}\right) + C_2\omega E^*\left(1-\frac{y}{z}\right) + C_2\varphi T_E^*\left(1-\frac{n}{z}\right) + C_3\delta I^*\left(1-\frac{z}{l}\right) + C_4\alpha_1 E^*\left(1-\frac{y}{n}\right)\\
&= -\mu S^*\frac{(1-x)^2}{x} + \beta S^*I^*\left(1-\frac{1}{x}\right) + \beta S^*I^*\frac{\delta\theta}{h_3}\left(1-\frac{1}{x}\right) + \beta S^*I^*\left(1-\frac{xz}{y}\right)\\
&\quad + \beta S^*I^*\frac{\delta\theta}{h_3}\left(1-\frac{xl}{y}\right) + \left(1-\frac{y}{z}\right)\frac{h_4\omega(h_3+\delta\theta)}{h_3(\alpha_1\varphi+h_4\omega)}\beta S^*I^*\\
&\quad + \left(1-\frac{n}{z}\right)\frac{\alpha_1\varphi(h_3+\delta\theta)}{h_3(\alpha_1\varphi+h_4\omega)}\beta S^*I^* + \left(1-\frac{z}{l}\right)\frac{\delta\theta}{h_3}\beta S^*I^* + \left(1-\frac{y}{n}\right)\frac{\alpha_1\varphi(h_3+\delta\theta)}{h_3(\alpha_1\varphi+h_4\omega)}\beta S^*I^*\\
&= -\mu S^*\frac{(1-x)^2}{x} + \frac{\beta S^*I^*}{h_3(\alpha_1\varphi+h_4\omega)}\left[h_3(\alpha_1\varphi+h_4\omega)\left(1-\frac{1}{x}\right)\right.\\
&\quad + \delta\theta(\alpha_1\varphi+h_4\omega)\left(1-\frac{1}{x}\right) + h_3(\alpha_1\varphi+h_4\omega)\left(1-\frac{xz}{y}\right)\\
&\quad + \delta\theta(\alpha_1\varphi+h_4\omega)\left(1-\frac{xl}{y}\right) + h_4\omega(h_3+\delta\theta)\left(1-\frac{y}{z}\right)\\
&\quad + \alpha_1\varphi(h_3+\delta\theta)\left(1-\frac{n}{z}\right) + \delta\theta(\alpha_1\varphi+h_4\omega)\left(1-\frac{z}{l}\right)\\
&\quad \left. + \alpha_1\varphi(h_3+\delta\theta)\left(1-\frac{y}{n}\right)\right]\\
&= -\mu S^*\frac{(1-x)^2}{x} + \frac{\beta S^*I^*}{h_3(\alpha_1\varphi+h_4\omega)}\left[h_3\alpha_1\varphi\left(1-\frac{1}{x}+1-\frac{xz}{y}+1-\frac{n}{z}+1-\frac{y}{n}\right)\right.\\
&\quad + h_3h_4\omega\left(1-\frac{1}{x}+1-\frac{xz}{y}+1-\frac{y}{z}\right)\\
&\quad + \delta\theta\alpha_1\varphi\left(1-\frac{1}{x}+1-\frac{xl}{y}+1-\frac{n}{z}+1-\frac{z}{l}+1-\frac{y}{n}\right)\\
&\quad \left. + \delta\theta h_4\omega\left(1-\frac{1}{x}+1-\frac{xl}{y}+1-\frac{y}{z}+1-\frac{z}{l}\right)\right].
\end{aligned}$$

The fact that the arithmetical mean is greater than, or equal to the geometrical mean leads to the following results.

- $1-\frac{1}{x}+1-\frac{xz}{y}+1-\frac{n}{z}+1-\frac{y}{n}\leqslant 0$ for $x, y, z, n > 0$ and $1-\frac{1}{x}+1-\frac{xz}{y}+1-\frac{n}{z}+1-\frac{y}{n}=0$ if and only if $x=y=z=n=1$.
- $1-\frac{1}{x}+1-\frac{xz}{y}+1-\frac{y}{z}\leqslant 0$ for $x, y, z > 0$ and $1-\frac{1}{x}+1-\frac{xz}{y}+1-\frac{y}{z}=0$ if and only if $x=y=z=1$.
- $1-\frac{1}{x}+1-\frac{xl}{y}+1-\frac{n}{z}+1-\frac{z}{l}+1-\frac{y}{n}\leqslant 0$ for $x, y, l, n > 0$ and $1-\frac{1}{x}+1-\frac{xl}{y}+1-\frac{n}{z}+1-\frac{z}{l}+1-\frac{y}{n}=0$ if and only if $x=y=z=l=n=1$.
- $1-\frac{1}{x}+1-\frac{xl}{y}+1-\frac{y}{z}+1-\frac{z}{l}\leqslant 0$ for $x, y, z, l > 0$ and $1-\frac{1}{x}+1-\frac{xl}{y}+1-\frac{y}{z}+1-\frac{z}{l}=0$ if and only if $x=y=z=l=1$.

Therefore, $\dot{V}(t)\leqslant 0$ for $x, y, z, l, n > 0$ and $\dot{V}(t) = 0$ if and only if $x = y = z = l = n = 1$, the maximum invariant set of model (2) on the set $\left\{\left(x, y, z, l, n\right) : \dot{V} = 0\right\}$ is the singleton (1, 1, 1, 1, 1). Then, the endemic equilibrium P^* of model (2) is globally asymptotically stable if $\mathcal{R}_0 > 1$ by LaSalle's Invariance Principle (La Salle, 1976). □

Remark 3. From an infectious disease perspective, $\gamma = 0$ means that people have life-long immunity to the disease, that is, a person will get active TB at most once in his life. The above theorem shows that when $\mathcal{R}_0 > 1$, the endemic equilibrium P^* of model (2) is globally asymptotically stable in the case of permanent immunity and no media impact.

4. Numerical simulations

4.1. Parameter estimation and data fitting

Here we fit the model (1) to four sets of data on new TB cases reported annually from 2009 to 2019, respectively. Since the COVID-19 pandemic occurred at the end of 2019, which caused some difficulties and errors in statistical work, we only use data up to 2019. The data came from the four regions of China, that is, Hubei Province, Henan Province, Jiangxi Province and Xinjiang Uygur Autonomous Region, which were available from the Data-Center of China Public Health Science (The Data-center of China Public Health Science, 2023). The actual number of newly reported cases almost all comes from confirmed patients in hospital (Li et al., 2022; Wang et al., 2023), so according to our model (1), the number of newly reported TB cases can be expressed as

$$M(t) = \delta I(t), \tag{12}$$

where the time step is year. And (12) will be used to fit the data of newly reported TB cases each year.

Based on the current research results on TB, some parameters values of model (1) or their ranges are discussed in detail below.

(1) In 2019, the number of new TB cases reported in Hubei Province was 51801, so we set $I(0) = 51801/\delta$. The average permanent population of Hubei Province from 2009 to 2019 was $N = 5.8256 \times 10^7$ (Hubei Provincial Statistics Bureau, 2023), and thus the initial value of susceptible people was assumed to be $S(0) = N - E(0) - I(0) - T(0) - T_E(0) - R(0)$, where $E(0)$, $I(0)$, $T(0)$, $T_E(0)$ and $R(0)$ are later estimated by data fitting.
(2) From 2009 to 2019, the average number of babies born in Hubei Province each year was 6.512×10^5 (Hubei Provincial Statistics Bureau, 2023), and the average lifetime was 76.44 years (China National Bureau of Statistics, 2023). Therefore, we conclude that $\Lambda = 6.512 \times 10^5$ per year and $\mu = 1/76.44 \approx 0.01308$ per year.
(3) We set $\gamma = 0.05$ per year taken from Das et al. (2020).
(4) According to the results in Li et al. (2022) and Wang et al. (2023), we appropriately set the range of β be $[10^{-8}, 10^{-6}]$ per year and the range of θ be [0.001, 1], respectively.
(5) According to Global tuberculosis report 2022 (World Health Organization, 2022), approximately 5%–10% people with latent infection will eventually develop active infection, and the incubation period for active TB infection is approximately 3 months to 2 years (Li et al., 2022). Therefore, we set $\alpha \in [0.5, 4] \times [5\%, 10\%] = [0.025, 0.4]$ per year.
(6) Treatment of active TB infection usually requires 6 months to 2 years and with appropriate treatment (World Health Organization, 2022), and the chance of successful recovery is 59%–95% (Wang et al., 2023), so we set $r_1 \in [0.5, 2] \times [59\%, 95\%] = [0.295, 1.9]$ per year and $d_2 \in [0.5, 2] \times [5\%, 41\%] = [0.025, 0.82]$ per year.
(7) The disease-induced rate d_1 of individuals with active infection (I) should be higher than that of those receiving treatment (T), so we assume $d_1 \in [0.05, 0.9]$ per year.
(8) Preventive treatment for LTBI usually requires 3–6 months (Centers for Disease Control and Prevention of America, 2016; Ying et al., 2023), and the protective effect of preventive anti-TB treatment can reach 60%–90% (Tuberculosis Prevention and Control Center, 2021), therefore, we set $r_2 \in [0.5, 4] \times [60\%, 90\%] = [0.3, 3.6]$ per year.
(9) There is no evidence to show the range of parameters δ, φ, α_1, α_2 and m. We assume that $\delta \in [0.5, 1]$ per year, $\varphi \in [0.001, 0.1]$ per year, $\alpha_1 \in [0.01, 1]$ per year, $\alpha_2 \in [0.001, 1]$ per year and $m \in [10^4, 10^5]$.

Regarding the above initial value $S(0)$, parameters Λ and μ for the other three regions can be estimated similarly based on the data from the Provincial Statistics Bureau (Henan Provincial Statistics Bureau, 2023; Jiangxi Provincial Statistics Bureau, 2023; Statistics Bureau of Xinjiang Uygur Autonomous Region, 2023) and National Bureau of Statistics (China National Bureau of Statistics, 2023), and the specific values can be seen in Table 1.

We estimate the parameters and initial values in model (1) by calculating the minimum sum of square (MSS):

$$MSS = \sum [M(t_i) - data(t_i)]^2,$$

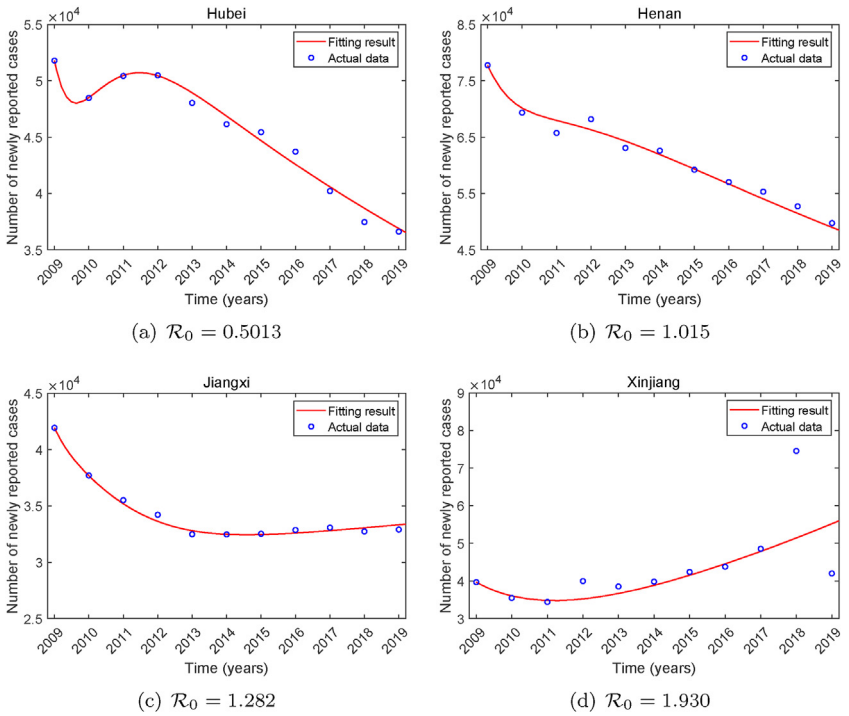
where $t_i = 0, 1, 2, \ldots, 11$ corresponding to $2009 - 2019$.

Table 1
The fitting parameters and initial conditions of model (1) for the four regions of China.

Notation	Value (Hubei)	Value (Henan)	Value (Jiangxi)	Value (Xinjiang)
Λ	6.512×10^5	1.28×10^6	6.076×10^5	3.856×10^5
μ	0.01308	0.01314	0.01316	0.01382
γ	0.05	0.05	0.05	0.05
$\beta \in [10^{-8}, 10^{-6}]$	1.967×10^{-8}	4.0838×10^{-8}	4.9589×10^{-8}	1.9357×10^{-7}
$\theta \in [0.001, 1]$	0.0441	0.0629	0.0434	0.0471
$\omega \in [0.025, 0.4]$	0.0326	0.0496	0.0458	0.0518
$\delta \in [0.5, 1]$	0.8534	0.6491	0.8801	0.6541
$\varphi \in [0.001, 0.1]$	0.0197	0.0353	0.0145	0.0222
$d_1 \in [0.05, 0.9]$	0.1035	0.0816	0.2728	0.1128
$d_2 \in [0.025, 0.82]$	0.0962	0.0597	0.2016	0.0291
$r_1 \in [0.295, 1.9]$	0.8939	0.5433	0.8276	0.6062
$r_2 \in [0.3, 3.6]$	0.9546	0.9069	0.9389	0.8678
$\alpha_1 \in [0.01, 1]$	0.0369	0.2723	0.0141	0.1420
$\alpha_2 \in [0.001, 1]$	0.0090	0.1795	0.0082	0.0164
$m \in [10^4, 10^5]$	10496	14828	15151	36704
$S(0)$	54437094	107909001	43486396	23127003
$E(0)$	2192603	1277436	1024401	630380
$I(0)$	60699	119813	47657	60706
$T(0)$	683491	647811	724378	261929
$T_E(0)$	51992	80102	48038	47742
$R(0)$	830121	565837	159130	672240

The values and intervals of all parameters and the fitting results can be seen in Table 1. The comparison results of the fitting curve of model (1) and the number of newly reported TB cases in Hubei, Henan, Jiangxi and Xinjiang of China from 2009 to 2019 can be seen in Fig. 2 respectively.

It is observed from Fig. 2 that the control situation of TB in the four regions has been different in the past. Since 2009, the annual number of newly reported TB cases in Hubei depicted in Fig. 2(a) has shown a downward trend, and the estimated $\mathcal{R}_0 = 0.5013 < 1$, which indicates that the disease has been effectively controlled and TB in Hubei can be eliminated in the future. The annual newly reported cases of TB in Henan depicted in Fig. 2(b) also show a downward trend, but the estimated



(a) $\mathcal{R}_0 = 0.5013$ (b) $\mathcal{R}_0 = 1.015$

(c) $\mathcal{R}_0 = 1.282$ (d) $\mathcal{R}_0 = 1.930$

Fig. 2. The comparison of the newly reported TB cases in Hubei, Henan, Jiangxi and Xinjiang of China from 2009 to 2019 and fitting results by model (1). All parameters and initial intervals are taken from Table 1.

$\mathcal{R}_0 = 1.015$ is slightly greater than 1, which indicates that newly reported TB cases in Henan will continue to decline, but eventually maintain a low epidemic level in the future, and the government needs to make more efforts to achieve the goal of TB elimination. The annual newly reported cases of TB in Jiangxi depicted in Fig. 2(c) show a trend of first declining and then stabilizing, and the estimated $\mathcal{R}_0 = 1.282 > 1$, which indicates that the annual newly reported cases of TB in Jiangxi may remain at a stable level if there is no external control measures. The annual newly reported cases of TB in Xinjiang depicted in Fig. 2(d) show a trend of first decreasing and then increasing, and the estimated $\mathcal{R}_0 = 1.930 > 1$. The newly reported cases of TB in Xinjiang may grow fast if the government does not take more measures to control TB.

The above analysis shows that the current status of TB control is varied in different regions of China, and TB in some areas such as Hubei Province has been well controlled. The government should adopt control strategies of different strengths according to the severity of TB epidemics in different regions, so as to reduce the burden on the resources and economies.

4.2. Sensitivity analysis

The basic reproduction number $\mathcal{R}_0$ plays a very important role in the control of infectious diseases, and it is interesting and meaningful to explore the effect of parameter α_1 on $\mathcal{R}_0$. The derivative of $\mathcal{R}_0$ with respect to α_1 is obtained as

$$(\mathcal{R}_0)'_{\alpha_1} = \frac{\beta\Lambda[(r_1+\mu+d_2)+\delta\theta]}{(\delta+\mu+d_1)(r_1+\mu+d_2)(\varphi+r_2+\mu)\mu} \frac{[\mu(\varphi-\omega)-\omega r_2]}{(\alpha_1+\omega+\mu)^2}.$$

Then $(\mathcal{R}_0)'_{\alpha_1} < 0$ due to the condition $\varphi < \omega$ (see Remark 1), which means that $\mathcal{R}_0$ is monotonically decreasing as α_1 increases. This suggests that increasing the rate of exposed people seeking for preventive treatment is helpful for TB control and explains why the United Nations is working hard to encourage more people with LTBI to undergo preventive treatment.

Next, by using the method proposed by Chitnis et al. (2008), we perform sensitivity analysis to find sensitive parameter relative to $\mathcal{R}_0$. The normalized forward sensitivity index for α_1, is denoted by $\Gamma_{\alpha_1}^{\mathcal{R}_0}$, which can be defined as

$$\Gamma_{\alpha_1}^{\mathcal{R}_0} = \frac{\partial \mathcal{R}_0}{\partial \alpha_1} \times \frac{\alpha_1}{\mathcal{R}_0}.$$

Similarly, we calculate the sensitivity index of the other parameters, and all calculated results are showed in Table 2 and depicted in Fig. 3.

The sensitivity index shows the normalized effect on $\mathcal{R}_0$ with small changes in the parameter. Positive sensitivity index means that $\mathcal{R}_0$ is an increasing function of the corresponding parameter, while a negative sensitivity index means that $\mathcal{R}_0$ is a decreasing function of the corresponding parameter. For example, $\Gamma_{\alpha_1}^{\mathcal{R}_0} = -0.4$ shows that if α_1 is increased by 10% then $\mathcal{R}_0$ decreases by 4%, while $\Gamma_{\beta}^{\mathcal{R}_0} = 1$ means that $\mathcal{R}_0$ increases by 10% if β is increased by 10%.

From Fig. 3, we can see that β always has positive influence on $\mathcal{R}_0$, which means that reducing the movement of active TB patients in the population is beneficial to control TB. Conversely, δ and α_1 always have negative impact, which implies that improving the rate of timely treatment for actively infected people and appropriately increasing the rate of individuals with LTBI seeking preventive treatment are able to eliminate TB completely. Therefore, the government may take some measures to encourage people with LTBI to positively receive preventive treatment to avoid further development of active infection, and reduce treatment costs to encourage more people with active infection to receive appropriate treatment. These measures can play an active and meaningful role in the prevention and control of TB.

Table 2
Sensitivity index of the basic reproduction number $\mathcal{R}_0$ for the four regions of China. All parameter values used in calculations are taken from Table 1.

Parameter	Hubei	Henan	Jiangxi	Xinjiang
Λ	1	1	1	1
M	−1.1462587878	−1.0605292159	−1.1919206697	−1.0861948264
B	1	1	1	1
Θ	0.0387040257	0.0621466582	0.0353487723	0.0453108344
Ω	0.5399387472	0.6833143467	0.3685208034	0.6874202286
Δ	−0.8346747736	−0.8104872415	−0.7194151335	−0.7925055402
Φ	0.0227324608	0.1624122134	0.0045282165	0.0615359709
d_1	−0.1137304372	−0.109701011	−0.2339502255	−0.1444820166
d_2	−0.002592797	−0.0060216112	−0.0068367095	−0.0020312812
r_1	−0.035601247	−0.0547996874	−0.0280657776	−0.0423148691
r_2	−0.0224240738	−0.1600926442	−0.0044656245	−0.0605713522
α_1	−0.4073890918	−0.644095149	−0.1883948795	−0.6208563137

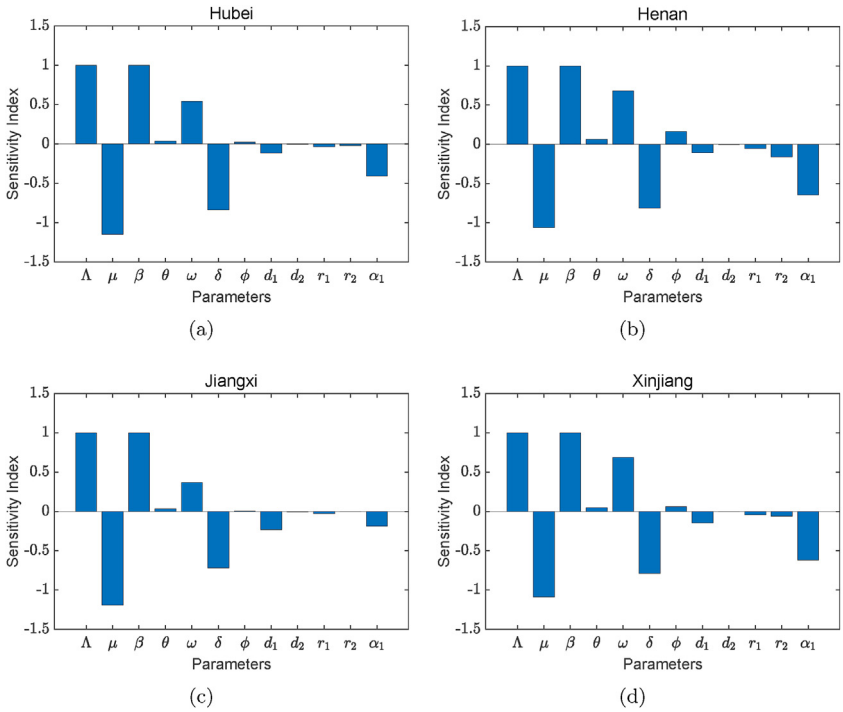


Fig. 3. Sensitivity analysis of the basic reproduction number $\mathcal{R}_0$ for the four regions of China. The specific values of sensitivity index are shown in Table 2.

4.3. *Effect of preventive treatment related parameters*

In this subsection, we take Xinjiang as an example to discuss the impact of preventive treatment related parameters on TB prevention and control.

From the previous discussion, we know that parameter α_1 can change the size of $\mathcal{R}_0$, and thereby affecting the persistence and disappearance of the disease. But the media related parameters α_2 and m can not change $\mathcal{R}_0$. In order to show the different influence of parameters α_1, α_2 and m on the control of TB, next we plot the diagrams of the number of active infections, namely the component I of the endemic equilibrium P^*, as the parameters α_1, α_2 and m change, respectively.

We first plot the bifurcation diagram of I with respect to α_1 by package MATCONT (Dhooge et al., 2003), which is depicted in Fig. 4(a). It shows that as α_1 increases, stable endemic equilibrium P^* disappears, and disease-free equilibrium P^0 changes from unstable to stable. System (1) undergoes a transcritical bifurcation when $\alpha_1 = \alpha_1^* \approx 0.3818$, corresponding to $\mathcal{R}_0 = 1$. Then some solution trajectories of model (1) with different values of α_1 are plotted in Fig. 4(b). They are generated by the same initial conditions and all parameters are exactly the same except parameter α_1. From Fig. 4(b), we can see that the number of

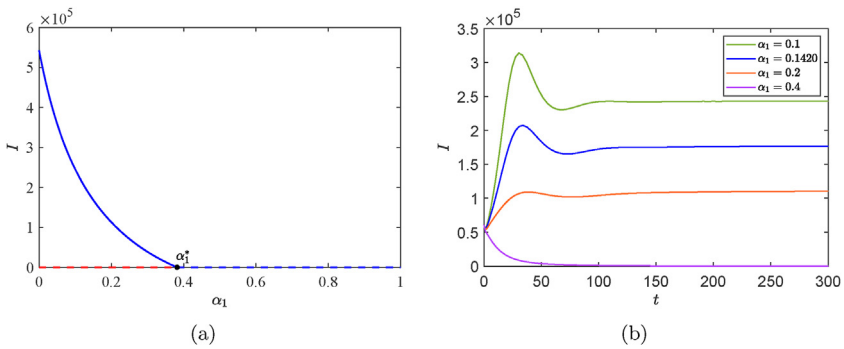


Fig. 4. (a) Bifurcation diagram of component I of P^* with respect to parameter α_1. The threshold value $\alpha_1 = \alpha_1^* = 0.3818$ corresponds $\mathcal{R}_0 = 1$. The dashed and solid curves represent P^0 and P^* respectively, where the blue line expresses stable equilibrium and the red line shows unstable one. (b) Solution trajectories of model (1) with different values of parameter α_1. Other parameter values and the initial value are taken from Table 1 (Xinjiang).

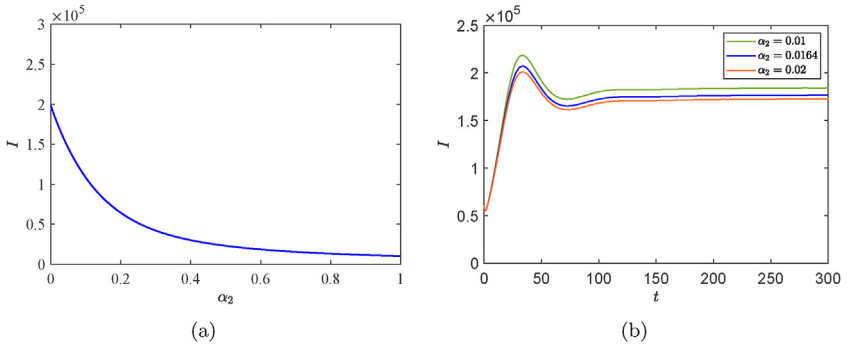


Fig. 5. (a) Diagram of component I of P^* with respect to parameter α_2. The blue solid curve represents stable P^*. (b) Solution trajectories of model (1) with different values of α_2. Other parameter values and the initial value are taken from Table 1 (Xinjiang).

active infections (I) gradually decreases until it disappears as α_1 increases, which further demonstrates that α_1 plays a very important role in the control of TB.

The media related parameters α_2 and m also have an important impact on disease control. We plot the diagram of variable I with respect to α_2 and m respectively, and solution trajectories of I with the same initial conditions for different values of α_2 and m. It can be observed from Fig. 5(a) that the number of I gradually decreases as α_2 increases, but will not disappear completely. This implies that the impact of the media can only reduce the number of actively infected population, but can not achieve the goal of eliminating the disease completely (see Fig. 5(b)). From Fig. 6, we can see that the number of I decreases to a limited extent as m decreases, which shows that two media related parameters α_2 and m have different effects in the control of TB. The effect of m is weaker than α_2 in controlling the number of active infections.

It is interesting to find that three key parameters α_1, α_2 and m have different effects in controlling the number of active infections. The parameter α_1 can change the prevalence of TB and achieve the goal of eliminating TB completely. However, media impact parameters α_2 and m can only reduce the number of active infections to a limited extent, where the effect of m is weaker than α_2, but both can not eliminate the disease completely.

5. Conclusion and discussion

WHO and CDC suggested that people with LTBI should receive preventive treatment to prevent them from developing active TB disease with a higher mortality rate, especially people with low immunity (World Health Organization, 2023; Centers for Disease Control and Prevention of America, 2016). In the age where the media greatly influences us, the media can publicize the benefits and necessity of preventive treatment, thereby influencing more people with LTBI to receive preventive treatment, resulting in a reduction in the number of actively infected population. Therefore, we further consider the media impact on the rate of exposed population seeking for preventive treatment. These motivated us to propose a new TB model (1) considering preventive treatment with media impact to discuss the effect of preventive treatment process.

In the analysis of model (1), the basic reproduction number $\mathcal{R}_0$ is obtained by means of the next generation matrix method, which plays a crucial role. By constructing Lyapunov functions, we proved the global stability of equilibria of model (1) without media impact. In this case, when $\mathcal{R}_0 < 1$, all solutions converge to the disease-free equilibrium, that is, the disease

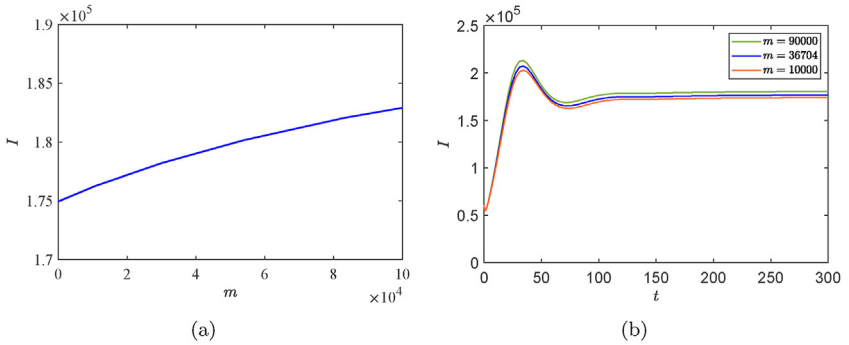


Fig. 6. (a) Diagram of component I of P^* with respect to parameter m. The blue solid curve represents stable P^*. (b) Solution trajectories of model (1) with different values of parameter m. Other parameter values and the initial value are taken from Table 1 (Xinjiang).

will eventually disappear. If $\mathcal{R}_0 > 1$, the system generates a unique endemic equilibrium and it is globally stable in the case of permanent immunity ($\gamma = 0$), that is, the disease will persist.

Firstly, we fit the model (1) to the newly reported TB cases data from 2009 to 2019 of four regions in China based on the MSS method. Then we obtain appropriate parameters values for the model (1), which can be seen in Fig. 2 in detail. We find that the estimated $\mathcal{R}_0 = 0.5013 < 1$ in Hubei Province, indicating that the disease in Hubei will be eliminated in the future. However, the estimated $\mathcal{R}_0 = 1.015 > 1$ in Henan Province, the estimated $\mathcal{R}_0 = 1.282 > 1$ in Jiangxi Province and the estimated $\mathcal{R}_0 = 1.930 > 1$ in Xinjiang Uygur Autonomous Region, indicating that the disease will not be eliminated in these three regions without further additional efforts. Secondly, the sensitivity index of the associated parameters are shown in Table 2 and depicted in Fig. 3. Parameters δ and α_1 in each region are relatively sensitive, that is, appropriately improving the rate of timely treatment for actively infected people and increasing the rate of individuals with LTBI seeking preventive treatment could eliminate TB completely. We also find that α_1 can change the prevalence of the disease and achieve the goal of eliminating diseases (see Fig. 4). Thus the government could take more measures to guide more exposed people to receive preventive treatment, which will be helpful to the control of TB. To consider the media impact on the rate of exposed population seeking for preventive treatment, we plot the diagrams of component I of P^* against media parameters α_2 and m, respectively (see Fig. 5(a) and Fig. 6(a)), and some trajectories of actively infected population for different values of α_2 and m (see Fig. 5(b) and Fig. 6(b)). We find that the number of actively infected population decreases but will not disappear completely as α_2 increases, and the number decreases to a limited extent as m decreases, which means that the effect of m is weaker than α_2 in controlling the number of active infections.

For any infectious disease, controlling the transmission rate and recovery rate can affect the prevalence and disappearance of the disease. TB has some additional characteristics in the prevention and control measures. For example, encouraging more people with LTBI to take preventive treatment could greatly benefit the control of TB. But this also means that the government needs to invest more funds to subsidize preventive treatment, which may cause a large economic burden. Therefore, it is meaningful and worthy of study to establish a joint control strategy to control multiple factors at the same time, to achieve the purpose of controlling TB while minimizing economic costs (Johnson et al., 2018; Nsengiyumva et al., 2022).

In this study, we only obtain the global stability of the equilibria of model (1) in a special case, that is, the saturated term is not considered. And it is also very interesting and meaningful to prove the global stability of the equilibria of the full model (1), which is left as an open issue. TB is an infectious disease with an extremely complicated transmission process, and it is difficult to take all the influencing factors into account. Considering the standard incidence and other more realistic nonlinear incidence might be interesting. It is also interesting to consider other expressions to quantify the impact of media and reported delay caused by the mass media's response duration (Song & Xiao, 2019). Multi-drug resistance is a big problem in tuberculosis treatment and it would be very meaningful to study the impact of drug resistance (Wang et al., 2023).

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Jun Zhang: Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yasuhiro Takeuchi:** Writing – review & editing, Validation, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Yueping Dong:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Zhihang Peng:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Acknowledgments

This work was partially supported by the National Natural Science Foundation of China (Nos. 12371488, 82320108018, 82073673), National Key R&D Program of China (Nos. 2023YFC2306004, 2022YFC2304000) and the Japan Society for the Promotion of Science “Grand-in-Aid 20K03755”.

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