MATHEMATICAL BIOSCIENCES
AND ENGINEERING
Volume **9**, Number **1**, January **2012**

doi:10.3934/mbe.2012.9.111

pp. **111–122**

THRESHOLD DYNAMICS FOR A TUBERCULOSIS MODEL WITH SEASONALITY

Xinli Hu

Department of Applied Mathematics
Xi'an Jiaotong University
Xi'an, 710049 China

(Communicated by Jianhong Wu)

Abstract. In this paper, we investigate a SEILR tuberculosis model incorporating the effect of seasonal fluctuation, where the loss of sight class is considered. The basic reproduction number R_0 is defined. It is shown that the disease-free equilibrium is globally asymptotically stable and the disease eventually disappears if $R_0 < 1$, and there exists at least one positive periodic solution and the disease is uniformly persistent if $R_0 > 1$. Numerical simulations are provided to illustrate analytical results.

1. **Introduction.** Tuberculosis (TB) is a bacterial disease caused by infection with Mycobacterium tuberculosis, which most frequently affects the lungs (pulmonary TB). It is estimated that one-third of the worlds population has been infected with the *M.* tuberculosis, which is a major cause of illness and death worldwide[1]. There are about nine million new TB cases each year, which results in two million deaths, mostly in developing countries. Thus, it is still a very important question using mathematical method to study the transmission dynamics of TB in human populations.

Mathematical models have played a significant role in understanding the complexity of Tuberculosis transmission dynamics[2, 3, 4, 5, 6, 7, 8, 9, 10, 11]. The endemic nature of many communicable diseases is characterized by a wide range of temporal oscillatory patterns: annual or poly-annual periodicity[12, 13]. This behavior depends on the effect of the seasonal fluctuations of the contact rate on the incidence of the disease. Sources of seasonal variation in the contact rate have been attributed to social behavior, such as the timing of the school year, the time series of the incidence of childhood infectious diseases, and seasonal changes in weather conditions. For these reasons, we need to consider possible seasonal patterns in the incidence rate for pulmonary tuberculosis. Seasonal change in the incidence of infectious diseases is a common phenomenon. One of the differences between TB and other infectious diseases is that following primary infection, only a small proportion (about 10%) of individuals develop the progressive disease (active TB). To the best of author's knowledge, the global analysis of tuberculosis models with seasonal fluctuation and fast/slow progression is not well discussed in the literature.

2000 *Mathematics Subject Classification.* Primary: 34C12, 34C25; Secondary: 92D30.

Key words and phrases. Basic reproductive number, periodic solution, seasonal fluctuation, global asymptotic stability, uniform persistence.

Our model, motivated by a TB model in the literature[9], incorporates periodic transmission rate and periodic transferring rate from the exposed to the infectious. We also introduce a new epidemiological class into our model based on the literature[3]. We call the class of loss of sight, which means the infectious that begin their effective therapy in the hospital and never return to the hospital for the spuctrum examinations for many reasons. One reason to introduce this new epidemiological class is that loss of sight usually occur in Sub-Saharan Africa. For example, according to the National Program of Fight against Tuberculosis of Cameroon, about 10% of infectious that begun their therapy treatment become loss of sight. Therefore, this fact cannot be neglected in the TB modeling. The main purpose of this paper is to investigate the basic reproduction number which governs whether the disease dies out or not, and further to examine the relationship between the threshold value obtained here and that for the corresponding system with constant coefficients.

The paper is structured as follows. In Section 2, we present a new TB model with seasonal fluctuation and define the basic reproduction number R_0. In Section 3, we obtain the global properties of the proposed model. There is a unique disease-free equilibrium and the disease always dies out if $R_0 < 1$; while the disease uniformly persists in the population and there is at least one positive periodic solution if $R_0 > 1$. Numerical simulation are provided to validate analytical results in section 4. In the final section, we give the brief conclusions.

2. **Model formulation and basic reproductive number.** In this section, we formulate a TB model incorporating periodic coefficients based on epidemiological status. The whole population is divided into five classes: the susceptible class, the latent/exposed class, the infectious class, the loss of sight class, and the recovered class. The fast and slow progression was considered earlier by some authors to study the transmission of TB [2, 3, 8, 9]. In this paper, we also introduce the fast and slow progression based on the real situation of tuberculosis disease. The standard mass balance incidence expressions $\beta_1(t)SI$ and $\beta_2(t)SL$ to indicate successful transmisssion TB due to nonlinear contacts dynamics in the population by infectious and loss of sight, respectively. The model has the compartmental structure of the $SEILR$ epidemic model, and is described by the following system of nonautonomous differential equations

$$\begin{cases} \dfrac{dS}{dt} = \Lambda - \beta_1(t)SI - \beta_2(t)SL - \mu S, \\ \dfrac{dE}{dt} = (1-p)\beta_1(t)SI + (1-p)\beta_2(t)SL + \theta_1\gamma I - (\mu + k(t))E, \\ \dfrac{dI}{dt} = p\beta_1(t)SI + p\beta_2(t)SL + k(t)E + rL - (\mu + d_1 + \gamma)I, \\ \dfrac{dL}{dt} = \theta_2\gamma I - (\mu + d_2 + r)L, \\ \dfrac{dR}{dt} = \theta_3\gamma I - \mu R, \\ N = S + E + I + L + R, \end{cases} \tag{1}$$

where $S(t)$, $E(t)$, $I(t)$, $L(t)$, and $R(t)$ are the numbers of the susceptible, the latent/exposed, the infectious, the loss of sight, and the recovered individuals at time t, respectively. Λ is the recruitment rate, μ is the natural death rate, and $1/\mu$

is the average lifetime. p is the fraction of fast developing infectious cases, d_1 and d_2 represent the disease-induced death rate in the infectious class and the loss of sight class, respectively. γ is the treatment rate, θ_1, θ_2, and θ_3 are the fractions of entering the latent/exposed, the loss of sight and the recovered, respectively. r is the rate of entering the infectious class from the loss of sight class, and these parameters are positive constants and independent of time t, $p < 1$ and $\theta_1 + \theta_2 + \theta_3 = 1$. We assume that reactivation rate $k(t)$, infection rate $\beta_1(t)$ and $\beta_2(t)$ are periodic positive continuous functions in t with period ω for some $\omega > 0$.

From the fifth equation in (1), we have

$$R(t) = e^{-\mu t}\Big(\int_0^t \theta_3\gamma I(t)e^{\mu t}dt + R(0)\Big)$$

when $I(t)$ attracts to zero, by using the theory of limits, we have $R(t)$ attracts to zero, as $t \to +\infty$; when $I(t)$ attracts to $I^*(t)$, by using the theory of limits, we have $R(t)$ attracts to $R^*(t)$, as $t \to +\infty$, where $I^*(t)$ is a periodic function, and $R^*(t)$ is periodic function. So we omit the fifth equation in (1), and consider the following system:

$$\begin{cases} \dfrac{dS}{dt} = \Lambda - \beta_1(t)SI - \beta_2(t)SL - \mu S, \\ \dfrac{dE}{dt} = (1-p)\beta_1(t)SI + (1-p)\beta_2(t)SL + \theta_1\gamma I - (\mu + k(t))E, \\ \dfrac{dI}{dt} = p\beta_1(t)SI + p\beta_2(t)SL + k(t)E + rL - (\mu + d_1 + \gamma)I, \\ \dfrac{dL}{dt} = \theta_2\gamma I - (\mu + d_2 + r)L, \end{cases} \tag{2}$$

It is obvious that any solution of system (2) with nonnegative initial values is unique and nonnegative.

From (1), we have

$$\frac{dN}{dt} = \Lambda - d_1 I - d_2 L - \mu N \leq \Lambda - \mu N.$$

where $N(t)$ is the total number of the whole population at time t. It is easy to see that the linear differential equation $\dfrac{d\bar{N}}{dt} = \Lambda - \mu\bar{N}$ has a unique equilibrium $N_* = \Lambda/\mu$, which is globally asymptotically stable. The comparison principle [15, Theorem B.1] implies that $N(t)$ is ultimately bounded, and hence, the solutions of system (2) exist globally on the interval $[0, \infty)$. We summarize these discussions in the following theorem.

Theorem 2.1. *System (2) has a unique and bounded solution with the initial value*

$$(S^0, E^0, I^0, L^0) \in X := \mathbb{R}^4_+.$$

Further, the compact set

$$G := \{(S, E, I, L) \in X \ : \ S + E + I + L \leq \Lambda/\mu\}$$

is a positively invariant set, which attracts all positive orbits in X.

In what follows, we introduce the basic reproduction number R_0 for system (2) according to the general procedure presented in [16]. It is easy to see that system (2) has exactly one disease-free equilibrium $P_0(S_0, E_0, I_0, L_0) = (\Lambda/\mu, 0, 0, 0)$ and

the equations for latent/exposed, infectious and loss of sight compartments of the linearized system of model (2) at P_0 are

$$\begin{cases} \dfrac{dE}{dt} = (1-p)\beta_1(t)S_0 I + (1-p)\beta_2(t)S_0 L + \theta_1\gamma I - (\mu + k(t))E, \\ \dfrac{dI}{dt} = p\beta_1(t)S_0 I + p\beta_2(t)S_0 L + k(t)E + rL - (\mu + d_1 + \gamma)I. \\ \dfrac{dL}{dt} = \theta_2\gamma I - (\mu + d_2 + r)L. \end{cases}$$

We obtain

$$F(t) = \begin{pmatrix} 0 & (1-p)\beta_1(t)S_0 & (1-p)\beta_2(t)S_0 \\ 0 & p\beta_1(t)S_0 & p\beta_2(t)S_0 \\ 0 & 0 & 0 \end{pmatrix},$$

and

$$V(t) = \begin{pmatrix} \mu + k(t) & -\theta_1\gamma & 0 \\ -k(t) & \mu + d_1 + \gamma & -r \\ 0 & -\theta_2\gamma & \mu + d_2 + r \end{pmatrix}.$$

Let $\Phi_V(t)$ and $r(\Phi_V(\omega))$ be the monodromy matrix of the linear ω-periodic system $\dfrac{dz}{dt} = V(t)z$ and the spectral radius of $\Phi_V(\omega)$, respectively. Assume $Y(t,s), t \geq s$, is the matrix solution of the linear ω-periodic system

$$\frac{dy}{dt} = -V(t)y. \tag{3}$$

That is, for each $s \in \mathbb{R}$, the 3×3 matrix $Y(t,s)$ satisfies

$$\frac{d}{dt}Y(t,s) = -V(t)Y(t,s), \quad \forall\, t \geq s, \quad Y(s,s) = I,$$

where I is the 3×3 identity matrix. Thus, the monodromy matrix $\Phi_{-V}(t)$ of (3) is equal to $Y(t,0), t \geq 0$.

In view of the periodic environment, we assume that $\phi(s)$, ω-periodic in s, is the initial distribution of infectious individuals. Then $F(s)\phi(s)$ is the rate of new infections produced by the infected individuals who were introduced at time s. Given $t \geq s$, then $Y(t,s)F(s)\phi(s)$ gives the distribution of those infected individuals who were newly infected at time s and remain in the infected compartments at time t. It follows that

$$\psi(t) := \int_{-\infty}^{t} Y(t,s)F(s)\phi(s)ds = \int_0^{\infty} Y(t,t-a)F(t-a)\phi(t-a)da$$

is the distribution of accumulative new infections at time t produced by all those infected individuals $\phi(s)$ introduced at time previous to t.

Let C_ω be the ordered Banach space of all ω-periodic functions from $\mathbb{R}$ to $\mathbb{R}^3$, which is equipped with the maximum norm $||\cdot||$ and the positive cone

$C_\omega^+ := \{\phi \in C_\omega \ : \ \phi(t) \geq 0, \forall\, t \in \mathbb{R}\}$. Then we can define a linear operator $L : C_\omega \to C_\omega$ by

$$(L\phi)(t) = \int_0^{\infty} Y(t,t-a)F(t-a)\phi(t-a)da, \quad \forall\, t \in \mathbb{R}, \quad \phi \in C_\omega. \tag{4}$$

Following [16], we call L the next infection operator, and define the basic reproduction number as $R_0 := r(L)$, the spectral radius of L.

In the special case of $\beta_1(t)\equiv\beta_1, \beta_2(t)\equiv\beta_2$ and $k(t)\equiv k$, $\forall t\geq 0$, we obtain $F(t)\equiv F$, and $V(t)\equiv V$, $\forall t\geq 0$. By [17] (see also [16, Lemma 2.2 (ii)]), we further have

$$R_0 = r(FV^{-1}) = \frac{S_0(p\mu+k)[\beta_1(\mu+d_2+r)+\beta_2\theta_2\gamma]}{(\mu+d_2+r)[(\mu+d_1+\gamma)(\mu+k)-k\theta_1\gamma]-\theta_2\gamma r(\mu+k)}$$

It is easy to verify that system (2) satisfies assumptions $(A1)$-$(A7)$ in [16]. Thus, we have the following result, which will be used in the proof of our main result in section 3.

Lemma 2.2. *([16, Theorem 2.2]) The following statements are valid:*

(i) $R_0 = 1$ *if and only if* $r(\Phi_{F-V}(\omega)) = 1$.
(ii) $R_0 > 1$ *if and only if* $r(\Phi_{F-V}(\omega)) > 1$.
(iii) $R_0 < 1$ *if and only if* $r(\Phi_{F-V}(\omega)) < 1$.

Thus, the disease-free equilibrium P_0 *is locally asymptotically stable if* $R_0 < 1$, *and unstable if* $R_0 > 1$.

3. **Threshold dynamics.** In this section, we will use the method developed in [16] to analyze the threshold dynamics of system (2).

Theorem 3.1. *If the basic reproduction number* $R_0 < 1$, *then the unique disease-free equilibrium* $P_0(\Lambda/\mu, 0, 0, 0)$ *is globally asymptotically stable and if* $R_0 > 1$, *it is unstable.*

Proof. From Lemma 2.2, we know that if $R_0 < 1$, then P_0 is locally asymptotically stable and if $R_0 > 1$, P_0 is unstable. We now prove the global attractivity of P_0 for $R_0 < 1$.

If $(S(t), E(t), I(t), L(t))$ is a nonnegative solution of system (2) in X, then we have

$$\begin{cases} \dfrac{dE}{dt} \leq (1-p)\beta_1(t)S_0 I + (1-p)\beta_2(t)S_0 L + \theta_1\gamma I - (\mu+k(t))E, \\ \dfrac{dI}{dt} \leq p\beta_1(t)S_0 I + p\beta_2(t)S_0 L + k(t)E + rL - (\mu+d_1+\gamma)I. \\ \dfrac{dL}{dt} = \theta_2\gamma I - (\mu+d_2+r)I. \end{cases} \tag{5}$$

Consider the following auxiliary system

$$\frac{dh(t)}{dt} = (F(t)-V(t))h(t). \tag{6}$$

By Lemma 2.2, we know that $R_0 < 1$ if and only if $r(\Phi_{F-V}(\omega)) < 1$. By [19, Lemma 2.1], it follows that there exists a positive, ω-periodic function $\bar{h}(t)$ such that $h(t) = e^{\theta t}\bar{h}(t)$ is a solution of system (6), where $\theta = \dfrac{1}{\omega}\ln r(\Phi_{F-V}(\omega))$. Since $r(\Phi_{F-V}(\omega)) < 1$, θ is a negative constant. Therefore, we have $h(t)\to 0$ as $t\to+\infty$. This implies that the zero solution of system (6) is globally asymptotically stable. For any nonnegative initial value $(E(0), I(0), L(0))^T$ of system (5), there is a sufficiently large $M^* > 0$ such that $(E(0), I(0), L(0))^T \leq M^*\bar{h}(0)$ holds. Applying the comparison principle [15, Theorem B.1], we have $(E(t), I(t), L(t))^T \leq M^* h(t)$, for all $t > 0$, where $M^*h(t)$ is also the solution of system (6). Therefore, we get $E(t)\to 0$, $I(t)\to 0$, and $L(t)\to 0$ as $t\to+\infty$. By the theory of asymptotic autonomous systems [18, Theorem 1.2], it then follows that $S(t)\to\Lambda/\mu$, as $t\to+\infty$. □

Theorem 3.2. *If the basic reproduction number $R_0 > 1$, then the system is uniformly persistent, i.e., there exists a $\delta > 0$ such that any solution $(S(t), E(t), I(t), L(t))$ of system (2) with initial value $(S^0, E^0, I^0, L^0) \in \{(S, E, I, L) \in X \ : \ E > 0, I > 0, L > 0\}$ satisfies*

$$\liminf_{t\to+\infty} S(t) \geq \delta, \liminf_{t\to+\infty} E(t) \geq \delta, \liminf_{t\to+\infty} I(t) \geq \delta, \text{ and } \liminf_{t\to+\infty} L(t) \geq \delta,$$

and system (2) admits at least one positive periodic solution.

Proof. Define

$$X_0 := \{(S, E, I, L) \in X \ : \ E > 0, I > 0, L > 0\}, \qquad \partial X_0 := X \backslash X_0.$$

Let P: $X \to X$ be the Poincaré map associated with system (2), i.e.,

$$P(x^0) = u(\omega, x^0), \qquad \forall\, x^0 \in X,$$

where $u(t, x^0)$ is the unique solution of system (2) with $u(0, x^0) = x^0$. It is easy to see that

$$P^m(S^0, E^0, I^0, L^0) = u(m\omega, (S^0, E^0, I^0, L^0)), \quad \forall m \geq 0.$$

For any $(S^0, E^0, I^0, L^0) \in X_0$, from the first equation of system (2), we have

$$\begin{aligned} S(t) =& e^{-\int_0^t a(s_1)ds_1} \left(S^0 + \Lambda \int_0^t e^{\int_0^{s_2} a(s_1)ds_1} ds_2 \right) \\ \geq& \Lambda e^{-\int_0^t a(s_1)ds_1} \int_0^t e^{\int_0^{s_2} a(s_1)ds_1} ds_2 > 0, \quad \forall t > 0, \end{aligned} \tag{7}$$

where $a(t) := \mu + \beta_1(t)I(t) + \beta_2(t)L(t)$. By [14, Theorem 4.1.1] as generalized to nonautonomous systems, the irreducibility of the cooperative matrix

$$\tilde{M}(t) = \begin{pmatrix} -(\mu + k(t)) & (1-p)\beta_1(t)S(t) + \theta_1\gamma & (1-p)\beta_2(t)S(t) \\ k(t) & p\beta_1(t)S(t) - (\mu + d_1 + \gamma) & p\beta_2(t)S(t) + r \\ 0 & \theta_2\gamma & -(\mu + d_2 + r) \end{pmatrix}$$

implies that $(E(t), I(t), L(t))^T \gg 0, \forall t > 0$. Thus, both X and X_0 are positively invariant. Clearly, ∂X_0 is relatively closed in X.

By Theorem 3.1, the discrete-time system P admits a global attractor in X. Now we prove that P is uniformly persistent with respect to $(X_0, \partial X_0)$. In the case where $R_0 > 1$, we have the following claim:

Claim: *There exists a $\sigma^* > 0$, such that for any $(S^0, E^0, I^0, L^0) \in X_0$ with $||(S^0, E^0, I^0, L^0) - P_0|| \leq \sigma^*$, we have*

$$\limsup_{m\to\infty} d(P^m(S^0, E^0, I^0, L^0), P_0) \geq \sigma^*. \tag{8}$$

If $R_0 > 1$, Lemma 2.2 implies $r(\Phi_{F-V}(\omega)) > 1$. We can choose $\eta > 0$ small enough such that $r(\Phi_{F-V-\eta M}(\omega)) > 1$, where

$$M(t) = \begin{pmatrix} 0 & (1-p)\beta_1(t) & (1-p)\beta_2(t) \\ 0 & p\beta_1(t) & p\beta_2(t) \\ 0 & 0 & 0 \end{pmatrix}.$$

Equation $\dfrac{dS}{dt} = \Lambda - \mu S$ has a unique equilibrium $S_* = \Lambda/\mu$ which is globally attractive in $\mathbb{R}_+$. Note that the perturbed system

$$\frac{dS_\sigma(t)}{dt} = \Lambda - (\beta_1(t)\sigma + \beta_2(t)\sigma + \mu)S_\sigma(t) \tag{9}$$

admits a unique periodic solution

$$S^*_\sigma(t,\sigma)=e^{-\int_0^t(\beta_1(s)\sigma+\beta_2(s)\sigma+\mu)ds}\left(S^*_\sigma(0,\sigma)+\Lambda\int_0^t e^{\int_0^s(\beta_1(u)\sigma+\beta_2(u)\sigma+\mu)du}ds\right),$$

where

$$S^*_\sigma(0,\sigma)=\frac{\Lambda e^{-\int_0^\omega(\beta_1(s)\sigma+\beta_2(s)\sigma+\mu)ds}\int_0^\omega e^{\int_0^s(\beta_1(u)\sigma+\beta_2(u)\sigma+\mu)du}ds}{1-e^{-\int_0^\omega(\beta_1(s)\sigma+\beta_2(s)\sigma+\mu)ds}}.$$

Clearly, $|S_\sigma(t,\sigma)-S^*_\sigma(t,\sigma)|\to 0$, as $t\to\infty$. Thus, $S^*_\sigma(t,\sigma)$ is globally attractive on $\mathbb{R}_+$. From the expression of $S^*_\sigma(0,\sigma)$, it is easy to see that $S^*_\sigma(0,\sigma)$ is continuous in σ. The continuous dependence of the solution $S^*_\sigma(t,\sigma)$ on the initial condition and parameter value implies that $S^*_\sigma(t,\sigma)>S_*-\eta$ holds for sufficiently small σ, and all $t\in[0,\omega]$. By the periodicity of $S^*_\sigma(t,\sigma)$ and constant $S_*-\eta$, we see that $S^*_\sigma(t,\sigma)>S_*-\eta$ holds for sufficiently small σ, and all $t\geq 0$. By the continuity of the solutions with respect to the initial values, there exists a $\sigma^*>0$ such that for all $(S^0,E^0,I^0,L^0)\in X_0$ with $||(S^0,E^0,I^0,L^0)-P_0||\leq\sigma^*$, there holds $||u(t,(S^0,E^0,I^0,L^0))-u(t,P_0)||<\sigma,\forall\, t\in[0,\omega]$. We further claim that

$$\limsup_{m\to\infty} d(P^m(S^0,E^0,I^0,L^0),P_0)\geq\sigma^*. \tag{10}$$

Assume, by contradiction, that (10) does not hold. Then we have

$$\limsup_{m\to\infty} d(P^m(S^0,E^0,I^0,L^0),P_0)<\sigma^*$$

for some $(S^0,E^0,I^0,L^0)\in X_0$. Without loss of generality, we assume that $d(P^m(S^0,E^0,I^0,L^0),P_0)<\sigma^*$, for all $m\geq 0$. It follows that

$$||u(t,P^m(S^0,E^0,I^0,L^0))-u(t,P_0)||<\sigma,\forall\, m\geq 0,\forall\, t\in[0,\omega].$$

For any $t\geq 0$, let $t=m\omega+t'$, where $t'\in[0,\omega)$, and m is the largest integer less than or equal to $\dfrac{t}{\omega}$. Therefore, we have

$$\begin{aligned}&||u(t,(S^0,E^0,I^0,L^0))-u(t,P_0)||\\&=||u(t',P^m(S^0,E^0,I^0,L^0))-u(t',P_0)||<\sigma,\forall\, t\geq 0.\end{aligned}$$

Note that $(S(t),E(t),I(t),L(t))=u(t,(S^0,E^0,I^0,L^0))$. It then follows that $E(t)<\sigma, I(t)<\sigma, L(t)<\sigma,\forall\, t\geq 0$. From the first equations of system (2), we have

$$\begin{cases}\dfrac{dS}{dt}\geq\Lambda-(\beta_1(t)\sigma+\beta_2(t)\sigma+\mu)S,\end{cases} \tag{11}$$

Since the periodic solution $S^*_\sigma(t,\sigma)$ of equation (9) is globally attractive on $\mathbb{R}_+$ and $S^*_\sigma(t,\sigma)>S_*-\eta$, we have $S(t)\geq S_*-\eta$, for sufficiently large t. From the last three equations of system (2), for sufficiently large t, we obtain

$$\begin{cases}\dfrac{dE}{dt}\geq(1-p)\beta_1(t)(S_*-\eta)I+(1-p)\beta_2(t)(S_*-\eta)L-(\mu+k(t))E,\\ \dfrac{dI}{dt}\geq p\beta_1(t)(S_*-\eta)I+p\beta_2(t)(S_*-\eta)L+k(t)E-(\mu+d_1+\gamma)I.\\ \dfrac{dL}{dt}=\theta_2\gamma I-(\mu+d_2+r)L.\end{cases} \tag{12}$$

We then consider the following auxiliary system

$$\begin{cases} \dfrac{d\tilde{E}}{dt}=(1-p)\beta_1(t)(S_*-\eta)\tilde{I}+(1-p)\beta_2(t)(S_*-\eta)\tilde{L}-(\mu+k(t))\tilde{E}, \\ \dfrac{d\tilde{I}}{dt}=p\beta_1(t)(S_*-\eta)\tilde{I}+p\beta_2(t)(S_*-\eta)\tilde{L}+k(t)\tilde{E}-(\mu+d_1+\gamma)\tilde{I}. \\ \dfrac{d\tilde{L}}{dt}=\theta_2\gamma\tilde{I}-(\mu+d_2+r)\tilde{L}. \end{cases} \tag{13}$$

From [19, Lemma 2.1], we know that there exists a positive, ω-periodic function $(\bar{E}(t),\bar{I}(t),\bar{L}(t))^T$ such that $(\tilde{E}(t),\tilde{I}(t),\tilde{L}(t))^T=e^{\zeta t}(\bar{E}(t),\bar{I}(t),\bar{L}(t))^T$ is a solution of system (13), where $\zeta=\dfrac{1}{\omega}\ln r(\Phi_{F-V-\eta M}(\omega))$. Since $r(\Phi_{F-V-\eta M}(\omega))>1$, ζ is a positive constant. Let $t=n\omega$ and n be nonnegative integer, and we get

$$(\tilde{E}(n\omega),\tilde{I}(n\omega),\tilde{L}(n\omega))^T=e^{\zeta n\omega}(\bar{E}(n\omega),\bar{I}(n\omega),\bar{L}(n\omega))^T\to(\infty,\infty,\infty)^T,$$

as $n\to\infty$, since $\omega\zeta>0$ and $(\bar{E}(t),\bar{I}(t),\bar{L}(t))^T>0$. For any nonnegative initial condition $(E(0),I(0),L(0))^T$ of system (12), there exists a sufficiently small $m^*>0$ such that

$(E(0),I(0),L(0))^T\geq m^*(\bar{E}(0),\bar{I}(0),\bar{L}(0))^T$. By the comparison principle [15, Theorem B.1], we have

$(E(t),I(t),L(t))^T\geq m^*(\tilde{E}(t),\tilde{I}(t),\tilde{L}(t))^T$, for all $t>0$. Thus, we obtain $E(n\omega)\to\infty$, $I(n\omega)\to\infty$, and $L(n\omega)\to\infty$ as $n\to\infty$. This leads to a contradiction.

Set

$$M_\partial:=\{(S^0,E^0,I^0,L^0)\in\partial X_0\ :\ P^m(S^0,E^0,I^0,L^0)\in\partial X_0,\forall\ m\geq 0\}.$$

We now show that

$$M_\partial=\{(S,0,0,0)\in X\ :\ S\geq 0\}. \tag{14}$$

It suffices to prove that for any $(S^0,E^0,I^0,L^0)\in M_\partial$, we have $E(m\omega)=I(m\omega)=L(m\omega)=0,\forall m\geq 0$. If it is not true, there exists an $m_1\geq 0$ such that

$$(E(m_1\omega),I(m_1\omega),L(m_1\omega))^T>0.$$

Thus, (7) implies

$$S(t)>0,\forall t>m_1\omega,$$

by replacing the initial time 0 with $m_1\omega$. Similarly, by [14, Theorem 4.1.1] as generalized to nonautonomous systems, it follows that $(E(t),I(t),L(t))^T\gg 0$, $\forall t>m_1\omega$, where the initial value $(E(m_1\omega),I(m_1\omega),L(m_1\omega))^T>0$. Thus, we have

$$(S(t),E(t),I(t),L(t))\in X_0,\ \forall t>m_1\omega,$$

which implies that (14) holds. Clearly, there is exactly one fixed point $P_0=(\Lambda/\mu,0,0,0)$ of P in M_∂. The above claim implies that $P_0(\Lambda/\mu,0,0,0)$ is isolated invariant set in X and $W^s(P_0)\cap X_0=\phi$. Note that every orbit in M_∂ approaches to P_0, and P_0 is acyclic in M_∂. By [20, Theorem 1.3.1], it follows that P is uniformly persistent with respect to $(X_0,\partial X_0)$. By [20, Theorem 3.1.1], the solutions of system (2) are uniformly persistent with respect to $(X_0,\partial X_0)$, that is, there exists a $\delta>0$ such that any solution $(S(t),E(t),I(t),L(t))$ of system (2) with initial value $(S^0,E^0,I^0,L^0)\in X_0$ satisfies $\liminf\limits_{t\to+\infty}S(t)\geq\delta$, $\liminf\limits_{t\to+\infty}E(t)\geq\delta$, $\liminf\limits_{t\to+\infty}I(t)\geq\delta$ and $\liminf\limits_{t\to+\infty}L(t)\geq\delta$. Furthermore, [20, theorem 1.3.6] implies that P has a fixed point $(S^*(0),E^*(0),I^*(0),L^*(0))\in X_0$. Then $S^*(0)\geq 0$, $E^*(0)>0$, $I^*(0)>0$, and $L^*(0)>0$. We further claim that there exists some $\bar{t}\in[0,\omega]$ such that $S^*(\bar{t})>0$.

If it is not the case, $S^*(t)\equiv 0$, for all $t \geq 0$, due to the periodicity of $S^*(t)$. From the first equation of system (2), we get a contradiction. Then we obtain

$$\begin{aligned} S^*(t) = &\exp\left(\int_{\bar{t}}^{t} (\mu + \beta_1(\xi)I(\xi) + \beta_2(\xi)L(\xi))\, d\xi\right) \times \\ &\left(S^*(\bar{t}) + \Lambda \int_{\bar{t}}^{t} \exp\left(\int_{\bar{t}}^{\xi} (\mu + \beta_1(\zeta)I(\zeta) + \beta_2(\zeta)L(\zeta))\, d\zeta\right) d\xi\right) \\ &> 0,\ \forall\, t \in [\bar{t}, \bar{t} + \omega], \end{aligned}$$

The periodicity of $S^*(t)$ implies $S^*(t) > 0$, for all $t \geq 0$. By the last three equations of system (2) and the irreducibility of the cooperative matrix

$$\begin{pmatrix} -(\mu + k(t)) & (1-p)\beta_1(t)S^*(t) + \theta_1\gamma & (1-p)\beta_2(t)S^*(t) \\ k(t) & p\beta_1(t)S^*(t) - (\mu + d_1 + \gamma) & p\beta_2(t)S^*(t) + r \\ 0 & \theta_2\gamma & -(\mu + d_2 + r) \end{pmatrix}$$

It follows $(E^*(t), I^*(t), L^*(t)) \in \mathrm{Int}(\mathbb{R}^3_+), \forall\, t \geq 0$. Therefore, $(S^*(t), E^*(t), I^*(t), L^*(t))$ is a positive ω-periodic solution of system (2). □

4. **Numerical simulations.** From our theoretical results we see that R_0 is a threshold parameter to determine whether or not tuberculosis persists in the population. Our numerical simulations in this section will demonstrate the asymptotical behavior of (2) in different scenarios. We use the method from the reference [16] in our numerical computation of R_0.

In Figure 1, parameters values or functions are $\Lambda = 4, \mu = 0.05, p = 0.08, \gamma = 0.5, d_1 = 0.05, d_2 = 0.04, r = 0.01, \theta_1 = 0.6, \theta_2 = 0.2$, and $\beta_1(t) = a_0(1.1 + \sin\frac{\pi t}{6}), \beta_2(t) = b_0(1.1 + \sin\frac{\pi t}{6}), k(t) = k_0(1 + 0.8\sin\frac{\pi(t-1)}{6}), k_0 = 0.001$.

a_0 and b_0 are used in the simulation to demonstrate the asymptotical behavior of the solutions. For the small $a_0 = 0.03$ and $b_0 = 0.01$ the basic reproductive number is 0.6807. The simulation shows that the disease dies out (see Figure 1). The simulation results are the same as what we got in Theorem 3.1.

For the large $a_0 = 0.05$ and $b_0 = 0.04$ the basic reproductive number is 1.7952. The disease keeps persistent in the population and the simulation suggests that in the case where $R_0 > 1$, every solution with nontrivial initial data is asymptotic to a periodic solution (see Figure 2). From the numerical point of view, there exists a unique global attractive positive periodic solution. It is worth studying the uniqueness and stability of positive periodic solution of model (2) in the case where $R_0 > 1$. We leave these challenging problems for further investigation.

In the following, let $[R_0]$ be the average basic reproduction number of system (2). we take $b_0 = 0.03$ and a_0 varying or $a_0 = 0.03$ and b_0 varying, other parameter values are the same as mentioned above, by numerical computations, we get the curve of the basic reproduction number R_0 and the curve of the average basic reproduction number$[R_0]$ with respect to a_0 and b_0, respectively, in Figure 3. We can see that the basic reproduction number R_0 is always greater than the average basic reproduction number $[R_0]$. So the eradication policy on the basis of the basic reproduction number of the time-averaged system may overestimate the infectious risk of the periodic disease. From Figure 3, we can see that the average basic reproduction number $[R_0]$ is linear about the parameters and the basic reproduction

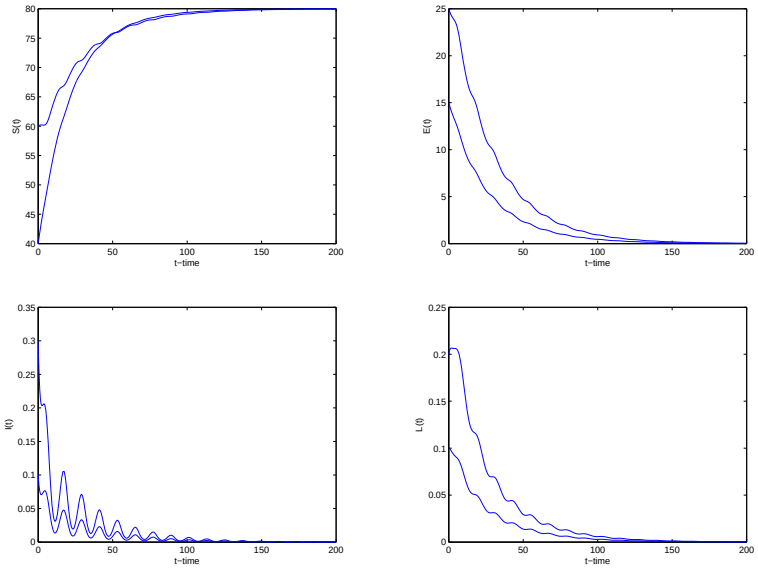

FIGURE 1. The global asymptotic stability of the disease-free equilibrium P_0 when $R_0 = 0.6807$. We choose $a_0 = 0.03, b_0 = 0.01$. Other parameter values are in the text.

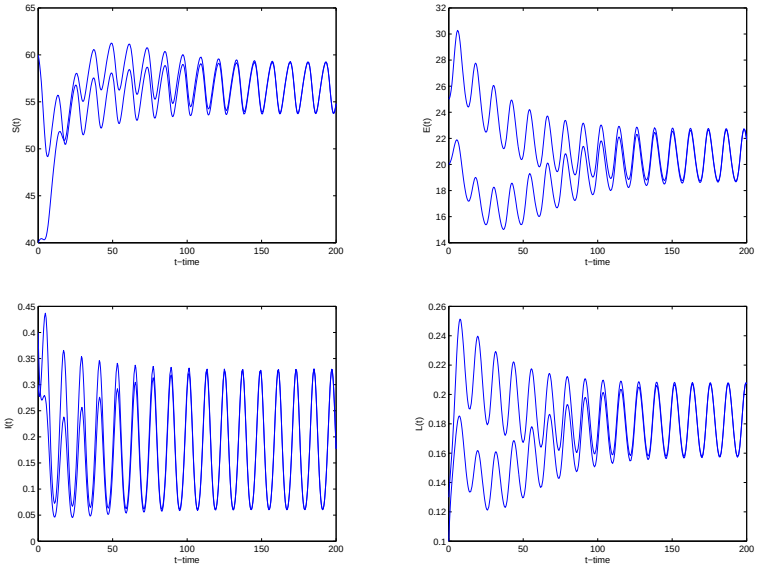

FIGURE 2. The existence of a periodic solution when $R_0 = 1.7952$. We choose $a_0 = 0.05, b_0 = 0.04$. Other parameter values are the same as those in Figure 1.

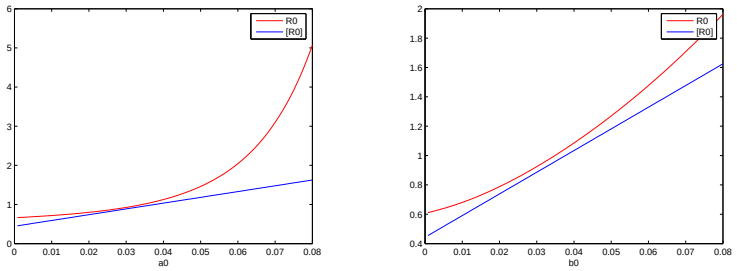

FIGURE 3. The curves of the basic reproduction number R_0 and the average basic reproduction number$[R_0]$ versus a_0 and b_0.

number R_0 is nonlinear about the parameters. For parameters a_0 and b_0, R_0 is more sensitive for parameter a_0. Maybe the loss of sight class transfer from the treatment class and the treatment plays a more important role.

5. **Conclusions.** In this paper, we have formulated a compartmental SEILR model with seasonality. The dynamics of the TB disease transmission are analyzed, and the basic reproductive number R_0 is determined. It is proved that R_0 is the threshold to distinguish the disease extinction or persistence. It shows that the disease-free equilibrium is globally asymptotically stable if $R_0 < 1$, while the disease persists if $R_0 > 1$ and the system has at least one positive periodic solution.

Numerical simulations have been done. First, the simulation results illustrate the analytical results. Second, we compare the average basic reproduction number and the average basic reproduction number. We see that the eradication policy on the basis of the average basic reproduction number may underestimate the infectious risk, so our model is more realistic than the model with constant coefficients. The model and the results can help the public authority improve the national surveillance of TB data. Furthermore, numerical simulations indicate that there may be a unique positive periodic solution which is globally asymptotically stable. We leave these challenging problems for further work.

Acknowledgments. We would like to thank the referees very much for their valuable comments and suggestions.

REFERENCES

[1] D. Bleed, C. Watt and C. Dye, *World health report 2001: Global tuberculosis control*, Technical report, World Health Organization, WHO/CDS/TB/2001.287. Available from: http://whqlibdoc.who.int/hq/2001/WHO_CDS_TB_2001.287.pdf.

[2] S. M. Blower, *The intrinsic transmission dynamics of tuberculosis epidemics*, Nature Medicine, **1** (1995), 815–821.

[3] Samuel Bowong and Jean Jules Tewa, *Mathematical analysis of a tuberculosis model with differential infectivity*, Commun. Nonlinear Sci. Numer. Simul., **14** (2009), 4010–4021.

[4] B. Song, C. Castillo-Chavez and J. P. Aparicio, *Tuberculosis models with fast and slow dynamics: The role of close and casual contacts*, Mathematical Biosciences, **180** (2002), 187–205.

[5] C. C. McCluskey, *Global stability for a class of mass action systems allowing for latency in tuberculosis*, Journal of Mathematical Analysis and Application, **338** (2008), 518–535.

[6] C. C. McCluskey, *Lyapunov functions for tuberculosis models with fast and slow progression*, Mathematical Biosciences and Engineering, **3** (2006), 603–614.

[7] Z. Feng, W. Huang and C. Castillo-Chavez, *On the role of variable latent periods in mathematical models for tuberculosis*, Journal of Dynamics and Differential Equations, **13** (2001), 425–452.
[8] S. M. Blower, P. M. Small and P. C. Hopewell, *Control strategies for tuberculosis epidemics: New models for old problems*, Science, **273** (1996), 497–500.
[9] L. Liu, X.-Q. Zhao and Y. Zhou, *A tuberculosis model with seasonality*, Bull. Math. Biol., **72** (2010), 931–952.
[10] O. Sharomi, C. N. Podder, A. B. Gumel and B. Song, *Mathematical analysis of the transmission dynamics of HIV/TB coinfection in the presence of treatment*, Math. Biosci. Eng., **5** (2008), 145–174.
[11] Y. Zhou, K. Khan, Z. Feng and J. Wu, *Projection of tuberculosis incidence with increasing immigration trends*, J. Theor. Biol., **254** (2008), 215–228.
[12] H. L. Smith, *Subharmonic bifurcation in a S-I-R epidemic model*, J. Math. Biol., **17** (1983), 163–177.
[13] C. J. Duncan, S. R. Duncan and S. Scott, *Oscillatory dynamics of small-pox and the impact of vaccination*, J. Theor. Biol., **183** (1996), 447–454.
[14] H. L. Smith and P. Waltman, "The Theory of the Chemostat. Dynamics of Microbial Competition," Cembridge Studies in Mathematical Biology, **13**, Cambridge Univ. Press, Cambridge, 1995.
[15] H. L. Smith, "Monotone Dynamical Systems: An Introduction to the Theory of Competitive and Cooperative Systems," Mathematical Surveys and Monographs, **41**, American Mathematical Society, Providence, RI, 1995.
[16] W. Wang and X.-Q. Zhao, *Threshold dynamics for compartmental epidemic models in periodic environments*, J. Dynam. Differential Equations, **20** (2008), 699–717.
[17] P. van den Driessche and J. Watmough, *Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission*, Math. Biosci., **180** (2002), 29–48.
[18] H. R. Thieme, *Convergence results and a Poincaré-Bendixson trichotomy for asymptotical autonomous differential equations*, J. Math. Biol., **30** (1992), 755–763.
[19] F. Zhang and X.-Q. Zhao, *A periodic epidemic model in a patchy environment*, J. Math. Anal. Appl., **325** (2007), 496–516.
[20] X.-Q. Zhao, "Dynamical Systems in Population Biology," CMS Books in Mathematics/Ouvrages de Mathématiques de la SMC, **16**, Springer-Verlag, New York, 2003.

Received February 7, 2011; Accepted March 29, 2011.

E-mail address: huxinli1975@yahoo.com.cn