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Research article

Global asymptotic behavior for mixed vaccination strategy in a delayed epidemic model with interim-immune

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Abstract: Vaccination strategy is considered as the most cost-effective intervention measure for controlling diseases. It will strengthen the immunity and reduce the risks of infections. In this paper, a new delayed epidemic model with interim-immune and mixed vaccination strategy is studied. The disease-free periodic solution is obtained by twice stroboscopic mapping and the corresponding dynamical behavior is analyzed. We determine a threshold parameter R_1, the disease-free periodic solution is proved to be global attractive if $R_1 < 1$. We also establish a threshold parameter R_2 for the permanence of the model, i.e., if $R_2 > 1$, the infectious disease will exist persistently. Then, we provide numerical simulations to illustrate our theoretical results intuitively. In particular, a practical application for new-type TB vaccine under mixed vaccination strategy is presented, based on the proposed theory and the data reported by NBSC. The mixed vaccination strategy can achieve the End TB goal formulated by WHO in limited time. Our study will help public health agency to design mixed control strategy which can reduce the burden of infectious diseases.

Keywords: epidemic model; global attractivity; mixed vaccination strategy; delay; interim-immune

1. Introduction

The threat of various infectious diseases always perplexes human society and the battle against infectious diseases has a long history. Nowadays, dozens of species of infectious diseases are spreading among individuals, and more worryingly, it is reported that the number of the newly discovered infectious diseases is increasing around one type annually [1]. For a variety of reasons, such as incessant mutability of viruses, gene defects, diversity and complexity of the transmission routes and so on, in-

fectious diseases are difficult to be deracinated once and for all. However, with the development of health care, the control of infectious diseases has been improved greatly. The prevention and control system of infectious diseases consisted of infectious disease warning, mechanism response, and later control keep humanity off worldwide plague for nearly a century.

For the control of diseases, treatment is just a link. Even worse, improper treatment can lead to the overflow of drug resistance and a higher cost. Immunization saves millions of lives every year and has been widely recognized as one of the world's most successful and cost-effective health interventions. Therefore, the key of disease control is the effective prevention. The research and development for vaccine and corresponding control strategies have made some breakthrough in many malignant infectious diseases. In 1980, with a historic global campaign of surveillance and vaccination, the World Health Assembly declared that smallpox had been eradicated by vaccine. Ebola virus disease (EVD), formerly known as Ebola haemorrhagic fever, was first discovered in 1976 and the existing vaccine rVSV-ZEBOV GP was put into clinical trials in 2015 [2]. The disease can be spread through the contact with the body fluids of infected people, particularly, the custom of burial in some areas plays a significant role in the transmission of Ebola. According to the characteristics, a time-delayed epidemic model is established and the corresponding threshold theory is given [3], and the vaccination strategy of Ebola has been explored theoretically [4]. In Democratic Republic of the Congo (DRC), it is reported that more than $111,000$ people have been vaccinated since the outbreak was declared in August 2018. These vaccines have already been used successfully in the field [5]. Most encouragingly, in 2019, the first malaria vaccine in childhood vaccination is being put into use in selected areas in Africa [6], which will promote the control essentially.

In view of the irreversible damage of population experiment, the most common method of studying infections is establishing reasonable mathematical models. The most commonly used vaccination strategy is constant vaccination, which is perfect in theory [7–10]. However, the major spread vector of infectious diseases is adults who are frequently engaged in social activities. Hence vaccination only for newborns is insufficient to achieve the control of infectious diseases in a limited time [20]. Compared with constant vaccination, pulse vaccination strategy is a more flexible one which can vaccinate different groups in targeted batches. In Central and South America, poliomyelitis and measles have been controlled effectively with pulse vaccination strategy [11–13]. There are many researches on pulse vaccination strategy, which focus on variety of factors. Gao et al. propose a delayed SEIRS epidemic model with pulse vaccination strategy and varying total population size. The threshold conditions of stability for the model are given and proved strictly [14]. In [15], the authors propose a discretization method, which provides a way to design the pulse vaccination strategy with less burden of measurements and related computations. More researches on pulse vaccination strategy can be seen in [16, 17].

With rapid advance of technology, it is possible to combine variety of control strategies together. As a result, a series of mixed control strategies are designed. For infants, the vaccination system is comparatively mature and the physiological indexes are different from the adults, it is necessary to reserve the vaccine program for newborns. Mixed vaccination strategy, consisting of constant and pulse vaccination strategies, combines the beneficial qualities of both and optimizes the prevention effects. An SEIR model with mixed vaccination strategy is proposed by d'Onofrio [18]. Based on Floquet's matrix and numerical simulations, the global asymptotic stability of the eradication solution is given. Gao et al. consider the mixed vaccination strategy with seasonality [19]. In our previous

study, we investigate how the parameters in mixed vaccination strategy control infectious diseases and design various control strategies for tuberculosis in China [20]. This practical research is admitted by Rebecca C Harris et al. [21]. Based on the previous work, we explore the global asymptotic behavior for mixed vaccination strategy with interim-immune in this paper.

When an individual is vaccinated, usually it will take a certain time that the body can make antibodies [22]. An example is HepB, which will be fully effective after thrice vaccination. Actually, this phenomenon should not be ignored to consider this phase in total analysis of infectious diseases. To our knowledge, at present few researchers address this point about mixed vaccination strategy. In this paper, we formulate a delayed epidemic model with interim-immune class for mixed vaccination strategy to analyze and control the dynamical behavior of infectious diseases. Incorporating the interim-immune class into the model increases the difficulties of analyzing the model and solving the solution. In our analysis, we use the twice stroboscopic mapping to calculate disease-free periodic solutions. By the comparison theorem of impulsive differential equation and Lyapunov-like function, we establish two thresholds for global attractivity of the disease-free periodic solution and permanence of the disease, respectively. Some numerical simulations are also given to show the asymptotic behaviour in our model with different thresholds. Furthermore, we present a practical application of mixed vaccination for TB. Basing on the data reported by the National Bureau of Statistics of China, we design a mixed vaccination programme with threshold condition $R_1 < 1$ (i.e., the disease-free periodic solution is globally asymptotically stable), that can finish the End TB Goal formulated by WHO within the allotted time. With our strategy, the End TB Goal will be achieved around 2034.

This paper is organized as follows. In Section 2, some preliminaries and lemmas for model are given. Then we calculate and discuss the disease-free periodic solution and its global asymptotic stability in Section 3. In Section 4, we investigate the permanence of the model and provide relevant threshold condition. In Section 5, some numerical simulations are given to illustrate our results. We conclude with a summary in Section 6.

2. Model formulation and preliminary

Nowadays, with the rapid research and development of new-type vaccines, the range of vaccinated individuals is gradually extending, and effective rate and expiration period of new-type vaccines have also being improved. For instance, new-type vaccine for TB has already passed the phase III clinic trials and will be put into service soon. As a consequence, research is important in the early stage, and then design control strategies. In this section, we formulate an epidemic model with time delay and pulse to analyze the dynamical behavior of mixed vaccination strategy for infectious diseases. This model satisfies the following assumptions:

(1) All coefficients involved in the model are positive constants and $\mathbb{Z}_+$ denotes the set of positive integers.

(2) The birth rate and the death rate are constant and equal. This implies that the total population size remains constant and it is normalized to one.

(3) The vaccine is not fully effective after individuals are just vaccinated, i.e., it will take a certain time that the vaccine is fully effective. Furthermore, the immune efficacy will maintain in the whole life.

Additionally, the disease may recrudesce after recovered. It means that if one has been infected,

the immunity is temporary after recovered. The immunity from recovery is different from vaccine. Yuan et al. considered an SEIRS model with latency and temporary immunity. For their continuous model, the reproduction number and globally asymptotically stability are discussed adequately [23]. Pulse vaccination strategy is introduced into an SEIRS model in [14]. In our study, we extend the general SEIRS epidemic model with the time delay, interim-immune and mixed vaccination strategy as follows:

$$\left\{\begin{array}{l}\left.\begin{array}{ll}\dfrac{dS}{dt} =\mu(1-p)-\beta S I+cR-\mu S,\\ \dfrac{dE}{dt} =\beta S I-\beta e^{-\mu\omega}S(t-\omega)I(t-\omega)\\ \qquad +\sigma\beta V_s I-\sigma\beta e^{-\mu\omega}V_s(t-\omega)I(t-\omega)-\mu E,\\ \dfrac{dI}{dt} =\beta e^{-\mu\omega}S(t-\omega)I(t-\omega)\\ \qquad +\sigma\beta e^{-\mu\omega}V_s(t-\omega)I(t-\omega)-\mu I-\gamma I,\\ \dfrac{dR}{dt} =\gamma I-\mu R-cR,\\ \dfrac{dV_s}{dt} =\mu p-\mu V_s-mV_s-\sigma\beta V_s I,\\ V =1-S-E-I-R-V_s,\end{array}\right\} \begin{array}{l} t\neq nT,\\ n\in\mathbb{Z}_+,\end{array}\\ \left.\begin{array}{l} S(t^+)=(1-p_c)S(t),\\ V_s(t^+)=V_s(t)+p_cS(t),\end{array}\right\} \quad t=nT, n\in\mathbb{Z}_+.\end{array}\right. \tag{2.1}$$

Where $S(t), E(t), I(t), R(t)$ and $V(t)$ denote the proportion of susceptible, exposed, infectious, recovered and vaccinated individuals at time t, respectively. The class V_s denotes the class in which the vaccine is not fully effective. We define this class as the interim-immune class.

In system (2.1), we adopt bilinear incidence rates to describe the infection of disease and parameter β denotes the average number of adequate contacts of an infectious individual per unit time. The birth rate and the death rate are equal and denoted by μ. We use delay parameter to present the incubation period, denoted by ω during which the exposed individual develops, and only after that time the exposed individual becomes an infectious individual. The recurrence rate of $R(t)$ is denoted by c, and the infectious period is $1/\gamma$. We assume that $\mu > c$, that is the natural death rate is higher than the recurrence rate of the disease. The immune efficacy in interim-immune class is measured by $1-\sigma$, where $0 < \sigma < 1$. The parameter m is the rate at which the interim-immune class develops into vaccinated class. Parameters p and p_c are the proportions of constant vaccination for newborns and pulse vaccination for susceptible individuals, respectively.

Obviously, system (2.1) is positively invariant in the set

$$\Omega=\{(S,E,I,R,V_s)\in\mathbb{R}^5_+ : 0\le S,E,I,R,V_s\le 1, 0<S+E+I+R+V_s<1\},$$

with the initial value:

$$\phi(\xi)=(S(\xi),E(\xi),I(\xi),R(\xi),V_s(\xi))\in C([-\tau,0],\mathbb{R}^5_+),\quad \phi(0)>0.$$

Lemma 2.1. *[24] Consider the following delay differential equation:*

$$x'(t)=ax(t-\tau)-bx(t)$$

where $a, b, \tau > 0$ and $x(t) > 0$ for $t \in [-\tau, 0]$. The following hold:

(i) if $a < b$, then $\lim_{t\to\infty} x(t) = 0$,

(ii) if $a > b$, then $\lim_{t\to\infty} x(t) = \infty$.

Lemma 2.2. *Consider the following impulsive differential equations:*

$$\begin{cases} u'(t) = a - bu(t), & t \neq nT, n \in \mathbb{Z}_+, \\ u(t^+) = (1-\theta)u(t), & t = nT, n \in \mathbb{Z}_+, \end{cases} \tag{2.2}$$

where $a > 0, b > 0, 0 < \theta < 1$. Then there exists a unique positive periodic solution of (2.2):

$$u_e(t) = \frac{a}{b} + (u^* - \frac{a}{b})e^{-b(t-nT)}, \quad nT < t \leq (n+1)T,$$

which is globally asymptotically stable, where

$$u^* = \frac{a(1-\theta)(1-e^{-bT})}{b(1-(1-\theta)e^{-bT})}.$$

Lemma 2.3. *Consider the following impulsive differential equations:*

$$\begin{cases} x'(t) = a - bx(t), & t \neq nT, n \in \mathbb{Z}_+, \\ x(t^+) = x(t) + c, & t = nT, n \in \mathbb{Z}_+, \end{cases} \tag{2.3}$$

where $a, b, c > 0$. Then there exists a unique positive periodic solution $x_e(t)$ of (2.3):

$$x_e(t) = \frac{a}{b} + \frac{ce^{-b(t-nT)}}{1-e^{-bT}}, \quad nT < t \leq (n+1)T,$$

which is globally asymptotically stable.

Proof. Integrate and solve the first equation of system (2.3) between pulses:

$$x(t) = \frac{a}{b} + e^{-b(t-nT)}(x(nT) - \frac{a}{b}), \quad nT < t \leq (n+1)T,$$

where $x(nT)$ is the initial value at time nT. Combining with the second equation of system (2.3), we construct the stroboscopic mapping such that

$$x((n+1)T) = \frac{a}{b} + e^{-bT}(x(nT) - \frac{a}{b}) + c \triangleq F(x(nT)), \tag{2.4}$$

where

$$F(u) = \frac{a}{b} + e^{-bT}(u - \frac{a}{b}) + c.$$

Obviously, the mapping F has a unique positive equilibrium:

$$x^* = \frac{a}{b} + \frac{c}{1-e^{-bT}}.$$

It follows the corresponding periodic solution $x_e(t)$ of equation (2.3):

$$x_e(t) = \frac{a}{b} + \frac{ce^{-b(t-nT)}}{1-e^{-bT}}, \quad nT < t \leq (n+1)T.$$

We claim that $x_e(t)$ is globally asymptotically stable. Let $y(t)$ be any solution of (2.3) with initial value $y(0)$, and denote $z(t) = y(t) - x_e(t)$. We obtain the following equation without pulse:

$$\begin{cases} z'(t) = -b(y(t) - x_e(t)) = -bz(t), & t \neq nT, n \in \mathbb{Z}_+, \\ z(t^+) = y(t^+) - x_e(t^+) = z(t), & t = nT, n \in \mathbb{Z}_+. \end{cases} \tag{2.5}$$

The solution of system (2.5) is $z(t) = z(0)e^{-bt}$, and obviously $z(t) \to 0$ when $t \to \infty$. The proof is completed. □

3. Existence and global attractivity of disease-free periodic solutions

In this section, we demonstrate the existence and global attractivity of disease-free periodic solutions of system (2.1). In this case, the infectious individuals are entirely absent from the population, that is, $I(t) = 0$ for all $t \geq 0$. Then system (2.1) can be reduced to the following impulsive system without delay:

$$\left\{ \begin{array}{l} \left.\begin{array}{l} \dfrac{dS}{dt} = \mu(1-p) + cR - \mu S, \\ \dfrac{dE}{dt} = -\mu E, \\ \dfrac{dR}{dt} = -\mu R + cR, \\ \dfrac{dV_s}{dt} = \mu p - \mu V_s - mV_s, \end{array}\right\} \quad t \neq nT, n \in \mathbb{Z}_+, \\ \left.\begin{array}{l} S(t^+) = (1-p_c)S(t), \\ V_s(t^+) = V_s(t) + p_c S(t), \end{array}\right\} \quad t = nT, n \in \mathbb{Z}_+. \end{array} \right. \tag{3.1}$$

Since $R(t)$ and $E(t)$ are not affected by impulsive effects, we have $lim_{t\to\infty}E(t) = 0$ and $lim_{t\to\infty}R(t) = 0$. Now, we are in the position to prove that $S(t)$ and $V_s(t)$ oscillate with period T in synchronization with impulsive vaccination. Consider the following limiting system of system (3.1):

$$\left\{ \begin{array}{l} \left.\begin{array}{l} \dfrac{dS}{dt} = \mu(1-p) - \mu S, \\ \dfrac{dV_s}{dt} = \mu p - \mu V_s - mV_s, \end{array}\right\} \quad t \neq nT, n \in \mathbb{Z}_+, \\ \left.\begin{array}{l} S(t^+) = (1-p_c)S(t), \\ V_s(t^+) = V_s(t) + p_c S(t), \end{array}\right\} \quad t = nT, n \in \mathbb{Z}_+. \end{array} \right. \tag{3.2}$$

Because $V_s(t)$ does not appear in the following impulsive subsystem of (3.2):

$$\begin{cases} \dfrac{dS}{dt} = \mu(1-p) - \mu S, & t \neq nT, n \in \mathbb{Z}_+, \\ S(t^+) = (1-p_c)S(t), & t = nT, n \in \mathbb{Z}_+, \end{cases} \tag{3.3}$$

by Lemma 2.2, the above system (3.3) exists a unique globally asymptotically stable periodic solution $\widetilde{S}(t)$:

$$\widetilde{S}(t) = (1-p) + (s^* - (1-p))e^{-\mu(t-nT)}, \quad nT < t \leq (n+1)T, \tag{3.4}$$

where

$$s^* = \frac{(1-p)(1-p_c)(1-e^{-\mu T})}{1-(1-p_c)e^{-\mu T}}.$$

Then consider the limiting subsystem of (3.2):

$$\begin{cases} \dfrac{dV_s}{dt} = \mu p - \mu V_s - m V_s, \quad t \neq nT, n \in \mathbb{Z}_+, \\ V_s(t^+) = V_s(t) + p_c s^*, \quad t = nT, n \in \mathbb{Z}_+. \end{cases} \tag{3.5}$$

By Lemma 2.3, similarly, system (3.5) exists a unique globally asymptotically stable periodic solution $\widetilde{V}_s(t)$:

$$\widetilde{V}_s(t) = \frac{\mu p}{\mu + m} + \frac{e^{-(\mu+m)(t-nT)} p_c s^*}{1 - e^{-(\mu+m)T}}, \quad nT < t \leq (n+1)T.$$

By

$$S(t) + E(t) + I(t) + R(t) + V_s(t) + V(t) = 1,$$

we have

$$\widetilde{V}(t) = 1 - \widetilde{S}(t) - \widetilde{V}_s(t).$$

Then the disease-free periodic solution of system (2.1) is $(\widetilde{S}(t), 0, 0, 0, \widetilde{V}_s(t), \widetilde{V}(t))$.

Denote

$$R_1 = \frac{\beta e^{-\mu\omega}(\delta - \sigma\delta + \sigma)}{(\mu + r)},$$

where

$$\delta = \frac{\mu(1-p) + c(\mu(1-p) + \sigma\beta)/(\sigma\beta + \mu)}{c + \mu} + \Bigg(\frac{(\mu(1-p) + c(\mu(1-p) + \sigma\beta)/(\sigma\beta + \mu))(1-p_c)(1 - e^{-(c+\mu)T})}{(c+\mu)(1-(1-p_c)e^{-(c+\mu)T})} - \frac{\mu(1-p) + c(\mu(1-p) + \sigma\beta)/(\sigma\beta + \mu)}{c + \mu} \Bigg) \cdot e^{-(c+\mu)T}$$

Theorem 3.1. *If $R_1 < 1$, then the disease-free periodic solution $(\widetilde{S}(t), 0, 0, 0, \widetilde{V}_s(t), \widetilde{V}(t))$ of system (2.1) is globally attractive.*

Proof. In what follows, for the sake of simplicity, let $N_k (k \in \{1, \ldots, 4\})$ be sufficiently large integers such that $N_1 < N_2 < N_3 < N_4$ and all $\varepsilon_k (k \in \mathbb{Z}_+)$ be sufficiently small. Denote

$$M(t) = 1 - V(t) - V_s(t) = S(t) + E(t) + I(t) + R(t),$$

and add the first four equations of system (2.1) to get,

$$\begin{aligned} \frac{dM(t)}{dt} &= \mu(1-p) + \sigma\beta V_s I - \mu M(t) \\ &\leq \mu(1-p) + \sigma\beta - (\mu + \sigma\beta) M(t). \end{aligned} \tag{3.6}$$

Because $V_s(t) \leq 1 - M(t)$ and $I(t) \leq 1$. Then we have

$$\limsup_{t \to \infty} M(t) \leq \frac{\mu(1-p) + \sigma\beta}{\sigma\beta + \mu}. \tag{3.7}$$

Then

$$\begin{aligned} R(t) &= 1 - V(t) - V_s(t) - S(t) - E(t) - I(t) \\ &= M(t) - S(t) - E(t) - I(t) \\ &\le M(t) - S(t) \\ &\le \frac{\mu(1-p) + \sigma\beta}{\sigma\beta + \mu} - S(t). \end{aligned} \tag{3.8}$$

From the first equation of (2.1), we have

$$\begin{aligned} \frac{dS}{dt} &\le \mu(1-p) + c(\frac{\mu(1-p) + \sigma\beta}{\sigma\beta + \mu} - S) - \mu S \\ &\le \mu(1-p) + \frac{c(\mu(1-p) + \sigma\beta)}{\sigma\beta + \mu} - (c+\mu)S. \end{aligned} \tag{3.9}$$

Consider the following comparison impulsive differential system:

$$\begin{cases} z'(t) = \mu(1-p) + \dfrac{c(\mu(1-p) + \sigma\beta)}{\sigma\beta + \mu} - (c+\mu)z(t), & t \ne nT, n \in \mathbb{Z}_+, \\ z(t^+) = (1-p_c)z(t), & t = nT, n \in \mathbb{Z}_+. \end{cases} \tag{3.10}$$

By Lemma 2.2, system (3.10) exists a unique globally asymptotically stable periodic solution:

$$\begin{aligned} z_e(t) = {} & \frac{\mu(1-p) + c(\mu(1-p) + \sigma\beta)/(\sigma\beta + \mu)}{c+\mu} + \left(z^* - \frac{\mu(1-p) + c(\mu(1-p) + \sigma\beta)/(\sigma\beta + \mu)}{c+\mu}\right) \\ & \cdot e^{-(c+\mu)(t-nT)}, \quad nT < t \le (n+1)T, \end{aligned} \tag{3.11}$$

where

$$z^* = \frac{(\mu(1-p) + c(\mu(1-p) + \sigma\beta)/(\sigma\beta + \mu))(1-p_c)(1 - e^{-(c+\mu)T})}{(c+\mu)(1 - (1-p_c)e^{-(c+\mu)T})}.$$

By the comparison theorem of impulsive differential equation [25], there exists an integer N_1 such that

$$S(t) < z(t) < z_e(t) + \varepsilon_1, \quad nT < t \le (n+1)T, \quad n > N_1. \tag{3.12}$$

Then

$$S(t) < z_e(t) + \varepsilon_1 \le z_e((n+1)T) + \varepsilon_1 \triangleq \eta. \tag{3.13}$$

Further, by the third equation of system (2.1), for $t > nT + \omega, n > N_1$, we have

$$I'(t) \le \beta e^{-\mu\omega}((1-\sigma)\eta + \sigma)I(t-\omega) - (\mu+\gamma)I(t). \tag{3.14}$$

Because $R_1 < 1$, for any ε_1 small enough, we have

$$\frac{\beta e^{-\mu\omega}(\delta + \varepsilon_1 - \sigma(\delta + \varepsilon_1) + \sigma)}{\mu + \gamma} < 1,$$

that is

$$\frac{\beta e^{-\mu\omega}(\eta - \sigma\eta + \sigma)}{\mu + \gamma} < 1. \tag{3.15}$$

Consider the following comparison equation respect to Eq (3.14),

$$y'(t) = \beta e^{-\mu\omega}(\eta - \sigma\eta + \sigma)y(t-\omega) - (\mu+\gamma)y(t), \tag{3.16}$$

By Lemma 2.1 and (3.15), we have $\lim_{t\to\infty} y(t) \to 0$ with the initial value $I(\xi)$. Then, there exists an integer N_2 and sufficiently small ε_2, for $t > N_2T + \omega$, such that

$$I(t) \le y(t) < \varepsilon_2. \tag{3.17}$$

By the fourth equation of system (2.1), for $t > N_2T + \omega$, we have

$$\frac{dR(t)}{dt} \le \varepsilon_2\gamma - (\mu + c)R. \tag{3.18}$$

Similarly, by the comparison theorem, there exists an integer N_3, we have

$$R(t) \le \frac{\varepsilon_2\gamma}{\mu + c}, \quad t \ge N_3T. \tag{3.19}$$

In a similar manner, there exists an integer N_4, such that

$$E(t) \le \frac{\beta\varepsilon_2(\eta + \sigma - \sigma\eta)}{\mu}, \quad t > N_4T. \tag{3.20}$$

Since ε_2 is arbitrarily small, it follows form (3.17), (3.19) and (3.20), we obtain that

$$I(t) \to 0, E(t) \to 0, R(t) \to 0, \quad t \to \infty,$$

with initial value $I(\xi), E(\xi)$ and $R(\xi)$. Therefore, it is sufficient to consider the limiting subsystem of system (2.1):

$$\left\{\begin{array}{l} \left.\begin{array}{l} \dfrac{dS}{dt} = \mu(1-p) - \mu S, \\ \dfrac{dV_s}{dt} = \mu p - \mu V_s - mV_s, \end{array}\right\} \quad t \ne nT, n \in \mathbb{Z}_+, \\ \left.\begin{array}{l} S(t^+) = (1-p_c)S(t), \\ V_s(t^+) = V_s(t) + p_cS(t), \end{array}\right\} \quad t = nT, n \in \mathbb{Z}_+. \end{array}\right.$$

By Lemma 2.2 and 2.3, we proved the existence of globally asymptotically stable periodic solution $\widetilde{S}(t)$ and $\widetilde{V}_s(t)$ for subsystem (3.2). Therefore, the disease-free periodic solution $(\widetilde{S}(t), 0, 0, 0, \widetilde{V}_s(t), \widetilde{V}(t))$ is globally attractive. □

4. Permanence

In this section, we will study the permanence of system (2.1).

Definition 4.1. System (2.1) is said to be permanent if there exists a compact region $\Omega_0 \subset int\ \Omega$ such that every solution of system (2.1) will eventually enter and remain in region Ω_0.

Denote

$$R_2 = \frac{\beta e^{-\mu\omega}}{\mu+\gamma}\Big(\frac{\mu(1-p)(1-p_c)(1-e^{-\mu T})}{1-(1-p_c)e^{-\mu T}} + \frac{\sigma\mu p}{\mu+m} + \frac{\sigma p_c(1-p)(1-p_c)(1-e^{-\mu T})}{(1-e^{-(\mu+m)T})(1-(1-p_c)e^{-\mu T})}\Big).$$

Theorem 4.2. *If $R_2 > 1$, then there exists a positive κ such that each positive solution of system (2.1) satisfies $I(t) \geq \kappa$ for t large enough.*

Proof. Rewrite the third equation of system (2.1) by

$$\begin{aligned}\frac{dI(t)}{dt} =& I(t)(\beta e^{-\mu\omega}S(t) + \sigma\beta e^{-\mu\omega}V_s(t) - (\mu+\gamma)) \\ & - \beta e^{-\mu\omega}\frac{d}{dt}\int_{t-\omega}^{t}(S(u)I(u) + \sigma V_s(u)I(u))du.\end{aligned} \tag{4.1}$$

Consider any positive solution $(S(t), E(t), I(t), R(t), V_s(t))$ and define

$$L(t) = I(t) + \beta e^{-\mu\omega}\int_{t-\omega}^{t}(S(u)I(u) + \sigma V_s(u)I(u))du. \tag{4.2}$$

Obviously, $L(t)$ is bounded, that is

$$L(t) \leq 1 + \beta\omega(1+\sigma)e^{-\mu\omega}.$$

Derivate $L(t)$ along the solution of system (2.1):

$$\begin{aligned}L'(t) &= I(t)(\beta e^{-\mu\omega}S(t) + \sigma\beta e^{-\mu\omega}V_s(t) - (\mu+\gamma)) \\ &= (\mu+\gamma)I(t)\Big(\frac{\beta e^{-\mu\omega}(S(t)+\sigma V_s(t))}{\mu+\gamma} - 1\Big).\end{aligned} \tag{4.3}$$

We claim that for any $t_0 > 0$ and any fixed I^*, it is impossible that $I(t) < I^*$ for all $t \geq t_0$. Assuming that the claim is invalid, there is a $t_0 > 0$ such that $I(t) < I^*$ for all $t \geq t_0$. Then, from the first equation of system (2.1), we have

$$\frac{dS(t)}{dt} > \mu(1-p) - (\beta I^* + \mu)S(t). \tag{4.4}$$

Consider the following impulsive differential system for $t \geq t_0$:

$$\begin{cases} v'(t) = \mu(1-p) - (\beta I^* + \mu)v(t), & t \neq nT, n \in \mathbb{Z}_+, \\ v(t^+) = (1-p_c)v(t), & t = nT, n \in \mathbb{Z}_+. \end{cases} \tag{4.5}$$

By Lemma 2.2, system (4.5) exists a unique globally asymptotically stable positive periodic solution

$$\widetilde{v}(t) = \frac{\mu(1-p)}{\beta I^* + \mu} + \Big(v^* - \frac{\mu(1-p)}{\beta I^* + \mu}\Big)e^{-(\beta I^* + \mu)(t-nT)}, \quad nT < t \leq (n+1)T, \tag{4.6}$$

where

$$v^* = \frac{\mu(1-p)(1-p_c)(1-e^{-(\beta I^*+\mu)T})}{(\beta I^* + \mu)(1-(1-p_c)e^{-(\beta I^*+\mu)T})}.$$

By the comparison theorem for impulsive differential equation [25], there exists $t_1 > t_0 + \omega$, when $t > t_1$,

$$S(t) > v(t) \geq \widetilde{v}(t) - \varepsilon_3 \geq v^* - \varepsilon_3 \triangleq \theta_1 > 0. \tag{4.7}$$

Similarly, it follows from the fifth equation of system (2.1) that we have

$$\frac{dV_s(t)}{dt} \geq \mu p - (\mu + m + \sigma\beta I^*)V_s(t). \tag{4.8}$$

Consider the comparison impulsive differential system:

$$\begin{cases} w'(t) = \mu p - (\mu + m + \sigma\beta I^*)w(t), & t \neq nT, n \in \mathbb{Z}_+, \\ w(t^+) = w(t) + p_c\theta_1, & t = nT, n \in \mathbb{Z}_+. \end{cases} \tag{4.9}$$

By Lemma 2.3, system (4.9) exists a unique globally asymptotically stable positive periodic solution

$$\widetilde{w}(t) = \frac{\mu p}{\mu + m + \sigma\beta I^*} + \frac{p_c\theta_1}{1 - e^{-(\mu+m+\sigma\beta I^*)T}} e^{-(\mu+m+\sigma\beta I^*)(t-nT)}. \tag{4.10}$$

Define

$$w^* = \frac{\mu p}{\mu + m + \sigma\beta I^*} + \frac{p_c\theta_1}{1 - e^{-(\mu+m+\sigma\beta I^*)T}}.$$

By the comparison theorem for impulsive differential equation, there exists $t_2 > t_1 + \omega$, when $t > t_2$,

$$V_s(t) > w(t) > \widetilde{w}(t) - \varepsilon_4 \geq w^* - \varepsilon_4 \triangleq \theta_2. \tag{4.11}$$

By (4.3), (4.7) and (4.11), we have

$$L'(t) > (\mu + \gamma)I(t)\Big(\frac{\beta e^{-\mu\omega}}{\mu + \gamma}(\theta_1 + \sigma\theta_2) - 1\Big). \tag{4.12}$$

Because $R_2 > 1$ and for sufficiently small constant $I^* > 0$, we have

$$\begin{aligned} \frac{\beta e^{-\mu\omega}}{\mu + \gamma}\Big(&\frac{\mu(1-p)(1-p_c)(1 - e^{-(\beta I^* + \mu)T})}{1 - (1-p_c)e^{-(\beta I^* + \mu)T}} + \frac{\sigma\mu p}{\mu + m + \sigma\beta I^*} \\ &+ \frac{\sigma p_c(1-p)(1-p_c)(1 - e^{-(\beta I^* + \mu)T})}{(1 - e^{-(\mu+m+\sigma I^*\beta)T})(1 - (1-p_c)e^{-(\beta I^* + \mu)T})}\Big) > 1, \end{aligned} \tag{4.13}$$

that is

$$\frac{\beta e^{-\mu\omega}}{\mu + \gamma}(\theta_1 + \sigma\theta_2) - 1 > 0.$$

Denote

$$I_l = \min_{t \in [t_2, t_2 + \omega]} I(t).$$

We claim that $I(t) \geq I_l$ for $t \geq t_2$. If not, there exists $T > 0$ such that $I(t) \geq I_l$ for $t \in [t_2, t_2 + \omega + T]$, $I(t + \omega + T) = I_l$, and $I'(t + \omega + T) \leq 0$. From the third equation of system (2.1), we have

$$\begin{aligned} I'(t_2 + \omega + T) &\geq \beta e^{-\mu\omega}\theta_1 I_l + \sigma\beta e^{-\mu\omega}\theta_2 I_l - (\mu + \gamma)I_l \\ &= (\mu + \gamma)I_l\Big(\frac{\beta e^{-\mu\omega}}{\mu + \gamma}(\theta_1 + \sigma\theta_2) - 1\Big) > 0. \end{aligned} \tag{4.14}$$

It is a contradiction. By (4.12),

$$L'(t) > (\mu + \gamma)I_l\Big(\frac{\beta e^{-\mu\omega}}{\mu + \gamma}(\theta_1 + \sigma\theta_2) - 1\Big) > 0, \tag{4.15}$$

which implies that $L(t) \to \infty$ as $t \to \infty$. So this contradicts with the boundedness of $L(t)$. Therefore, what we need to consider is the following two cases:

(i) $I(t) \geq I^*$ for t large enough;

(ii) $I(t)$ oscillates about I^* for t large enough.

The case (i) is evident for taking $\kappa = I^*$. It is sufficient to consider case (ii). If $I(t)$ oscillates about I^*, there exists t^* (t^* large enough such that $S(t) \geq \theta_1$ and $V_s(t) \geq \theta_2$ for $t \geq t^*$) and k such that $I(t^*) = I(t^* + k) = I^*$. Denote

$$\kappa = min\{\frac{1}{2}I^*, I^*e^{-(\mu+\gamma)\omega}\}. \tag{4.16}$$

We need to prove that $I(t) \geq \kappa$, for $t > t^*$. Since the positive solution of system (2.1) is ultimately bounded and $I(t)$ is not affected by pulse, $I(t)$ is uniformly continuous. There exists $T_0 > 0$ (T_0 is independent of t^*), we have

$$I(t) \geq \frac{1}{2}I^*, \quad t \in [t^*, t^* + T_0]. \tag{4.17}$$

There are three cases to be discussed.

(1) $k < T_0$. Take $\kappa = \frac{1}{2}I^*$, to achieve our aim obviously.

(2) $T_0 \leq k \leq \omega$. By $I'(t) \geq -(\mu + \gamma)I(t)$, it follows that

$$I(t) \geq I(t^*)e^{-(\mu+\gamma)(t-t^*)} \geq I^*e^{-(\mu+\gamma)\omega}.$$

Take $\kappa = min\{\frac{1}{2}I^*, I^*e^{-(\mu+\gamma)\omega}\}$.

(3) $\omega < k$. In this case, we have

$$\begin{aligned} &I(t) \geq I(t^*)e^{-(\mu+\gamma)(t-t^*)} \geq I^*e^{-(\mu+\gamma)\omega}, \quad t \in [t^*, t^* + \omega], \\ &I(t) \geq I(t^* + k)e^{-(\mu+\gamma)(t-(t^*+k))} \geq I^*e^{-(\mu+\gamma)\omega}, \quad t \in [t^* + \omega, t^* + k]. \end{aligned}$$

Similarly, take $\kappa = min\{\frac{1}{2}I^*, I^*e^{-(\mu+\gamma)\omega}\}$.

Notice that the choice of oscillation interval $[t^*, t^* + k]$ is independent of positive solution of system (2.1), we have $I(t) \geq \kappa$ for t large enough. the proof is completed. □

Theorem 4.3. *If $R_2 > 1$, system (2.1) is permanent.*

Proof. Let $(S(t), E(t), I(t), R(t), V_s(t))$ be any solution of system (2.1) with initial value $(S(\xi), E(\xi), I(\xi), R(\xi), V_s(\xi))$. From the first equation of system (2.1), we have

$$\begin{cases} \dfrac{dS(t)}{dt} \geq \mu(1-p) - (\beta + \mu)S(t), \quad t \neq nT, n \in \mathbb{Z}_+, \\ S(t^+) = (1 - p_c)S(t), \quad t = nT, n \in \mathbb{Z}_+. \end{cases} \tag{4.18}$$

By the impulsive differential comparison theorem,

$$\liminf_{t\to\infty} S(t) \geq \frac{\mu(1-p)(1-p_c)(1-e^{-(\beta+\mu)T})}{(\beta+\mu)(1-(1-p_c)(1-e^{-(\beta+\mu)T}))} \triangleq h,$$

From the fourth equation of system (2.1),

$$\frac{dR(t)}{dt} \geq \gamma m - (\mu + c)R,$$

similarly, we have

$$\liminf_{t\to\infty} R(t) \geq \frac{\gamma m}{\mu + c} \triangleq i.$$

Similarly,

$$E'(t) \geq \beta\theta_1 m + \sigma\beta\theta_2 m - \beta e^{-\mu\omega} - \sigma\beta e^{-\mu\omega} - \mu E(t),$$

we have

$$\liminf_{t\to\infty} E(t) \geq \frac{\beta(\theta_1 m + \sigma\theta_2 m - e^{-\mu\omega} - \sigma e^{-\mu\omega})}{\mu} \triangleq q.$$

At last, consider the fifth equation of system (2.1)

$$\frac{dV_s(t)}{dt} \geq \mu p - (\mu + m + \sigma\beta)V_s(t),$$

and the corresponding comparison impulsive system:

$$\begin{cases} \dfrac{dx(t)}{dt} = \mu p - (\mu + m + \sigma\beta)x(t), & t \neq nT, n \in \mathbb{Z}_+, \\ x(t^+) = x(t) + h, & t = nT, n \in \mathbb{Z}_+. \end{cases}$$

In a similar manner, we have

$$\liminf_{t\to\infty} V_s(t) \geq \frac{\mu p}{\mu + m + \sigma\beta} + \frac{h}{1 - e^{-(\mu+m+\sigma\beta)T}} \triangleq j.$$

Denote

$$\begin{aligned} \Omega_0 = \{&(S(t), E(t), I(t), R(t), V_s(t)), S(t) \geq h, E(t) \geq q, I(t) \geq \kappa, R(t) \geq i, V_s(t) \geq j, \\ &S(t) + E(t) + I(t) + R(t) + V_s(t) \leq 1\}. \end{aligned}$$

Based on the above discussions, every solution of system (2.1) will eventually enter and remain in region Ω_0. Therefore, system (2.1) is permanent. The proof is completed. □

5. Numerical simulations

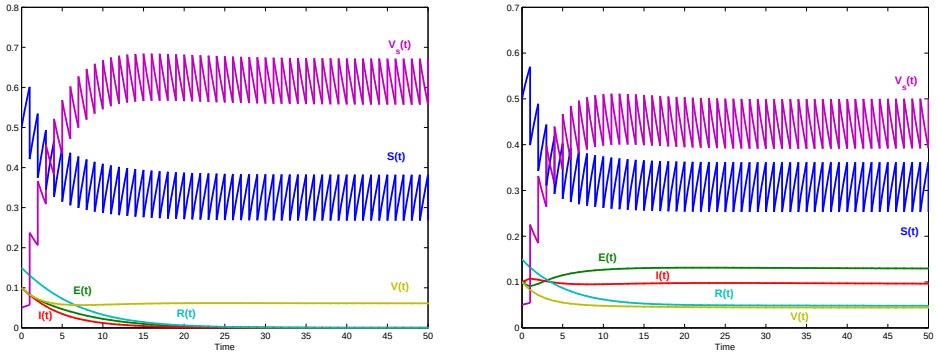
In this section, we present some numerical simulations to illustrate our results presented in previous sections. Particularly, a practical application for new-type TB vaccine is given.

In Figure 1, we make two numerical experiments to simulate asymptotic behavior of the solution of system (2.1) with the conditions of Theorem 3.1 and Theorem 4.3, respectively. In Figure 1(a), under the threshold condition $R_1 < 1$, as time t goes on, all components of solution tend to the disease-free periodic solution of system (2.1). The proportion of infectious individuals denoted by $I(t)$ tends

asymptotically to zero, and in this case, the infectious disease will die out. The parameters are $\mu = 0.2, p = 0.1, \beta = 0.2, c = 0.01, \omega = 1, \sigma = 0.9, v = 0.1, m = 0.02, p_c = 0.3, T = 1$. In Figure 1(b), under the threshold condition $R_2 > 1$, with time t going on, all components of solution maintain above a certain value 'κ'. Therefore, system (2.1) is permanent and infectious disease evolves into endemic disease. The corresponding parameter $\beta = 0.8$, the values of the other parameters are the same as those for Figure 1(a).

Table 1. Parameter values.

Parameter	Value	Resource
μ	0.0143 $year^{-1}$	[26]
c	0.0015 $year^{-1}$	[27]
γ	0.4055 $year^{-1}$	[20]
ω	0.1667 $year$	[27]
β	1.05	Assumed
p	0.6	[27, 28]

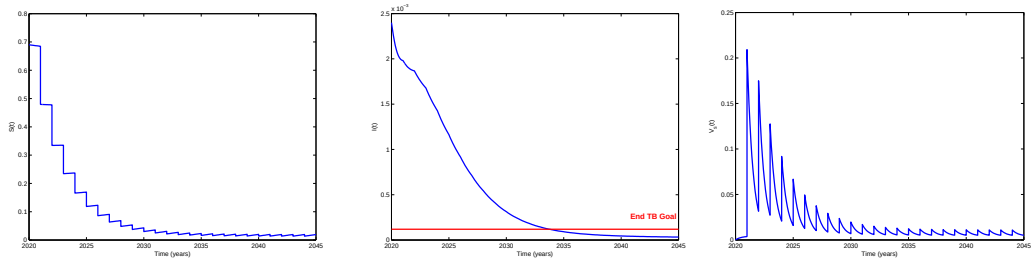


(a) (b)

Figure 1. The movement path of each component of system (2.1) as functions of time t. (a) $R_1 = 0.5128 < 1$, the infectious disease dies out. (b) $R_2 = 1.0940 > 1$, the infectious disease exists permanently.

Since the clinical Phase III for new-type TB vaccine has succeeded, it will be put into practical control soon. The new-type TB vaccine has a wider scope of vaccination and is of a certain interim-immune period, so it is necessary to design the corresponding implementation schedule.

In Figure 2, we present a practical numerical experiment to simulate trend of the control of tuberculosis after new vaccine puts into use. Based on the data reported by the National Bureau of Statistics of China and some parameters estimated by our previous work [20], we make reasonable assumptions which satisfy the model with mixed vaccination strategy in this paper. After primary vaccination, the immune effective rate is 80%, that is, parameter $\sigma = 0.2$. It will take 0.5 year that new vaccine is fully effective, thus the parameter $m = 2$. On the basis of existing constant vaccination strategy, we add impulse-type vaccination strategy with parameters $p_c = 0.3$, and $T = 1$ year. We assume that the mixed



(a) (b) (c)

Figure 2. Time-series of the proportions of susceptible S, infectious I, and interim-immune V_s individuals in system (2.1).

vaccination strategy will be put into use in 2020. Other parameters of the mixed vaccination strategies are shown in Table 1. Using these parameters, we obtain $R_1 = 0.5447$. By Theorem 3.1, infectious disease will die out theoretically. The changing trends of susceptible, infectious, and interim-immune individuals are shown in Figure 2. From Figure 2(b), the proportion of infectious individuals denoted by $I(t)$ declines rapidly, the red solid line represents the End TB goal which raised by WHO in 2015. Under our mixed vaccination strategy, the disease-free periodic solution is globally asymptotically stable and the goal will be achieved around 2034.

6. Conclusions

In the framework of differential equations with time delay and pulse, we formulate a mathematical model with interim-immune class and mixed vaccination strategy to study the dynamical behavior of infectious diseases. Two thresholds for global attractivity of the disease-free periodic solution and permanence of the disease are established, respectively. If $R_1 < 1$, the infectious disease will be controlled and gradually die out. If $R_2 > 1$, system (2.1) is permanent and the infectious disease will evolve into endemic disease. In Section 5, two numerical simulations (Figure 1(a) and (b)) are given to illustrate the asymptotic behavior of infectious disease with different threshold conditions. In view of clinical Phase III new-type TB vaccine has passed and based on practical data in China, we design a mature vaccination programme that can finish the End TB Goal formulated by WHO within the allotted time (Figure 2). The results of numerical experiments are consistent with theoretical analysis that the condition $R_1 = 0.5447 < 1$ will lead to extinction of TB.

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Conflict of interest

All authors declare no conflicts of interest in this paper.

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