DYNAMIC BEHAVIOR AND OPTIMAL SCHEDULING FOR MIXED VACCINATION STRATEGY WITH TEMPORARY IMMUNITY

SIYU LIU\textsuperscript{a}, XUE YANG\textsuperscript{a,b}, YINGJIE BI\textsuperscript{a} AND YONG LI\textsuperscript{*}\textsuperscript{a,b}

\textsuperscript{a} School of Mathematics, Jilin University
Changchun 130012, China
\textsuperscript{b} School of Mathematics and Statistics
and Center for Mathematics and Interdisciplinary Sciences
Northeast Normal University, Changchun 130024, China

(Communicated by Yuan Lou)

1. Introduction. Infectious diseases have become a major public health problem in human society, and it threatens the quality of life seriously. Epidemic models are generally used to describe the transmission process and to design the control strategy since it is an important manner to study infectious diseases. In history, it outbroke malignant diseases repeatedly. In 17th and 18th centuries, smallpox as a scourge in Europe killed at least 150 million people. From the beginning of the 19th century to the end of the 20th century, cholera broke out eight times worldwide [20]. In recent years, bird flu, Ebola and MERS have severely damaged social economy and human survival. The interest in exploring the dynamic behavior and control of disease proliferation has never reduced.

With the development of medical care, some infectious diseases are eradicated or well controlled. In the past few years, because of the isolation and vaccination strategies, the malignant disease can be controlled in an intensive area to prevent it from worsening into an epidemic spreading all over the word. It is worth noting that, compared with these horrible ‘fast’ (acute infectious) diseases, another kind of infectious diseases attracts less attention due to few symptoms, long and variable
latency period, relative low fatality rate and transmission. But there is a high probability that the symptoms of these ‘slow’ (chronic infectious) diseases will be taken for life. A long period of treatment leads to low morbidity and high recurrent infection rate. For example, according to the data released by the National Data of China, the top three annual new reported cases are viral hepatitis, tuberculosis and syphilis [18]. In many areas the ‘slow’ infectious diseases have developed into the stubborn endemic ones.

Prevention is the most critical element in eradicating the infectious diseases. It brings chemotherapy and antibiotics into our infectious disease armamentarium in 20th century. Greater dependency upon vaccination programmes is ever more salient. So a better vaccination strategy and a corresponding optimal scheduling are very important. Some people have applied epidemic models with control theory to present optimal strategy for disease eradication [17, 28]. As more and more control measures are available in actual life, mixed control is used in many applications currently. For instance, the authors of [26] incorporated a control term and evaluated the cost of control strategies by Pontryagin’s maximum principle, both vaccination and isolation were used to reduce cost [12] and the number of infected individuals [13] by means of an optimal control. These models with mixed control are continuous and correspondingly the optimal control theory is relatively perfect.

Nokes and Swinton [21] investigated an interesting strategy in which both constant and pulse vaccination were employed as control measures. A systematic exposition of this strategy based on SEIR model was investigated in [10]. On account of the impulsive effect, the system is discontinuous and the corresponding optimal control problem is difficult to solve in theory [4] though some progress has been achieved for the existence of solutions [2, 3]. But with the help of computational method, the beneficial results for the design of pulse vaccination strategy can also be obtained [27]. In [25], the scheduling problem of different vaccination strategies can be formulated as an unconstrained optimal control problem and solved by dynamic programming. An ingenious work that applies multi-objective minimization to address the multiple impulsive vaccination scheduling problem can be seen in [8].

Our study aims at formulating the mixed vaccination strategy for the chronic disease and providing the optimal scheduling. The local ($\mathcal{R}_0(T) < 1$) and global ($\mathcal{R}_1(T) < 1$) asymptotically stable conditions for the elimination of the disease are studied theoretically. The intricate optimal control problem for impulsive system is transformed into a nonlinear program problem and solved efficiently by numerical method. Numerical simulations show that the exposed and infected populations decrease more rapidly in optimal mixed vaccination strategy than in optimal constant vaccination strategy. It means that we can eradicate the disease in a shorter time under optimal mixed vaccination strategy. It helps greatly to avoid more complex problems like antimicrobial resistance caused by longer treatment period. If the vaccinated population is limited, our optimal scheduling can provide a balanced strategy which the constant vaccination maintains in a moderate level and the number of pulse reaches the maximal boundary while the quantity decreases progressively.

This paper is organized as follows. In Section 2, we formulate an SEIRVS epidemic model with constant and mixed vaccination strategy to investigate the threshold conditions for the elimination of the chronic disease. Theoretical analysis for the stability of the infection-free periodic solution under the mixed vaccination strategy is given. An optimal control problem for the mixed vaccination strategy is built in
Section 3. In Section 4, we transform the optimal control problem into a nonlinear program which can be efficiently solved, and also provide the simulation results. Finally, we conclude the paper with a summary of the main results in Section 5.

2. Dynamics of SEIRVS model under vaccination strategy. Since the chronic infectious disease often has a long and variable latent period, we first formulate an SEIRVS epidemic model to describe the disease under different vaccination strategies.

2.1. Constant vaccination strategy. The vaccination strategy nowadays always focuses on the newborns, like HepB, BCG and so on. In order to explain the current situation of vaccination strategy, we propose a concise but practical epidemic model to describe the dynamics of constant vaccination strategy for the control of the chronic infectious disease. In this model the population is divided into five classes: susceptible ($S$), exposed ($E$), infectious ($I$), recovered ($R$) and vaccinated ($V$), and the model satisfies the following assumptions:

1) The disease can be infected repeatedly.
2) The positive effort of vaccine is limited, and it can’t maintain the whole life.
3) In a stable population, the natural birth rate and death rate are equivalent.

Synthesizing all the situations, the dynamic system of differential equations is given by:

$$\begin{align*}
\frac{dS}{dt} &= (1 - p)\mu + cV + \alpha R - \mu S - \beta SI, \\
\frac{dE}{dt} &= \beta SI - \varepsilon E - \mu E, \\
\frac{dI}{dt} &= \varepsilon E - \mu I - \gamma I, \\
\frac{dR}{dt} &= \gamma I - \mu R - \alpha R, \\
\frac{dV}{dt} &= p\mu - \mu V - cV.
\end{align*}$$

(1)

The population has a constant size, which is normalized to unity:

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

(2)

Here, the parameter $p$ ($0 < p < 1$) indicates the fraction of the newborns vaccinated successfully. $\mu$ is the natural death (birth) rate. Because the positive effort of vaccine is limited, the successfully vaccinated individuals still lose immunity and develop into susceptible at the rate $c$. Once infected, the individuals develop into the exposed class $E$ and the progress to the $I$ class at a rate of $\varepsilon$. The mean infectious period is $1/\gamma$ and the recurrence rate of the disease is $\alpha$. Bilinear incidence $\beta SI$ is applied in this paper.

There is a unique infection-free equilibrium of system (1):

$$E_0(1 - \frac{p\mu}{\mu + c}, 0, 0, 0, \frac{p\mu}{\mu + c}).$$

We can obtain the control reproduction number $R_0$ by using the next generation matrix in [11]

$$R_0 = \rho(FV^{-1}) = \frac{\beta\varepsilon(1 - \frac{p\mu}{\mu + c})}{(\varepsilon + \mu)(\mu + \gamma)} = \frac{\beta\varepsilon[(1 - p)\mu + c]}{(\mu + c)(\varepsilon + \mu)(\mu + \gamma)}.$$  

(3)
where \( \rho \) denotes the spectral radius and the matrices \( F \) and \( V \) are given by
\[
F = \begin{pmatrix}
0 & \beta(1 - \frac{p\mu}{\mu + c}) \\
0 & \alpha \end{pmatrix}, \quad V = \begin{pmatrix}
\varepsilon + \mu & 0 \\
-\varepsilon & \mu + \gamma
\end{pmatrix}.
\]

Each term of \( R_0 \) has clear epidemiological interpretation. \((1 - \frac{p\mu}{\mu + c})\) is the fraction of susceptible population among the total size. \(\varepsilon/(\varepsilon + \mu)\) is the fraction of exposed population becoming infected among those exiting the \(E\) class. \(1/(\mu + \gamma)\) is the mean duration of exiting the \(I\) class. According to the basic reproduction number theorem, the infection-free equilibrium of system (1) is locally stable for \( R_0 \leq 1 \), and this is an important index for the control of disease elimination. By calculating, \( \partial R_0/\partial p < 0 \). Therefore, increasing the fraction of successfully vaccinated infants helps to reduce the chronic disease.

Denote the endemic equilibrium of system (1) as \( E_1(S_e, E_e, I_e, R_e, V_e) \), which is determined by the following equations:
\[
\begin{align*}
(1 - p)\mu + cV_e + \alpha R_e - \mu S_e - \beta S_e I_e &= 0, \\
\beta S_e I_e - \varepsilon E_e - \mu E_e &= 0, \\
\varepsilon E_e - \mu I_e - \gamma I_e &= 0, \\
\gamma I_e - \mu R_e - \alpha R_e &= 0, \\
p\mu - \mu V_e - cV_e &= 0.
\end{align*}
\]

By calculating, the relationship among \( S_e, E_e, R_e, V_e \) and \( I_e \) is:
\[
\begin{align*}
S_e &= \frac{(1 - p)\mu + cV_e + \alpha R_e}{\mu + \beta I_e}, \\
E_e &= \frac{\mu + \gamma}{\varepsilon} I_e, \\
R_e &= \frac{\gamma}{\mu + \alpha} I_e, \\
V_e &= \frac{p\mu}{c + \mu}.
\end{align*}
\]

Substituting them into the second equation in system (1), we know that if \( R_0 > 1 \), there is a unique endemic equilibrium.

The vaccination strategy is aiming at eliminating the disease, then the threshold condition for disease eradication is given as follows.

**Theorem 2.1.** For system (1), the infection-free equilibrium \( E_0(1 - \frac{p\mu}{\mu + c}, 0, 0, 0, \frac{p\mu}{\mu + c}) \) is globally asymptotically stable if \( R_0 \leq 1 \).

**Proof.** For system (1), it follows that \( V = 1 - (S + E + I + R) \),
\[
\begin{align*}
\frac{dS}{dt} + \frac{dE}{dt} + \frac{dI}{dt} + \frac{dR}{dt} &= (1 - p)\mu + c[1 - (S + E + I + R)] - \mu(S + E + I + R) \\
&= (1 - p)\mu + c - (c + \mu)(S + E + I + R).
\end{align*}
\]

Then
\[
\lim_{t \to +\infty} \sup(S + E + I + R) = \frac{(1 - p)\mu + c}{\mu + c}.
\]

The \( S, E, I, R \) class are all non-negative, \( S \leq \frac{(1 - p)\mu + c}{\mu + c} \).
Define the Lyapunov function
\[ L = \varepsilon E + (\varepsilon + \mu)I. \] (6)
Then the derivative of \( L \) with respect to \( t \) along solution of system (1) is given by
\[ L' = [\varepsilon\beta S - (\varepsilon + \mu)(\mu + \gamma)] I \]
\[ = (\varepsilon + \mu)(\mu + \gamma)[R_0 \frac{\mu + c}{(1 - p)\mu + c} S - 1] I. \] (7)
If the condition \( R_0 \leq 1 \) holds, \( L' \leq 0 \) and the proof is completed.

2.2. Mixed vaccination strategy. With the development of medical treatment, there is a special attention on creating safer and more effective vaccines. Thus new vaccines will come with all age groups. Successful vaccine research will require investments well into the next decade [6]. In practical applications, when to achieve the disease elimination goal is another important index of a control strategy. In our previous study [15], the vaccination strategy only for infants cannot reach the goal formulated in limited time. In this section we design a mixed vaccination strategy which is the combination of constant and pulse vaccination to control the disease. In this vaccination strategy, the vaccine is not only for the newborns but also for the susceptible individuals at the same interval time. Through the mixed vaccination strategy, we can get the target in shorter time and avoid more complex problems like antimicrobial resistance caused by longer treatment period.

The system for mixed vaccination strategy is as follows:
\[
\begin{cases}
\frac{dS}{dt} = (1 - p)\mu + cV + \alpha R - \mu S - \beta SI, \\
\frac{dE}{dt} = \beta SI - \varepsilon E - \mu E, \\
\frac{dI}{dt} = \varepsilon E - \mu I - \gamma I, \\
\frac{dR}{dt} = \gamma I - \mu R - \alpha R, \\
V = 1 - S - E - I - R.
\end{cases}
\] (8)

The parameter \( p_c \) \((0 < p_c < 1)\) indicates the fraction of pulse vaccination. The initial value is \((S(0), E(0), I(0), R(0)) \in \Omega = \{(S, E, I, R) \in [0, 1]^4 | 0 \leq S + E + I + R \leq 1\}\). There exists an infection-free periodic solution \((\bar{S}(t), 0, 0, 0)\) in \(\Omega\).

The growth of susceptible class in the time-interval \( t_0 = (n-1)T < t \leq nT \) must satisfy
\[
\frac{dS}{dt} = (1 - p)\mu + c(1 - S) - \mu S. \] (9)
Solving equation (9) yields
\[ S(t) = [S(t_0) - (1 - \frac{p\mu}{c + \mu})]e^{-(c+\mu)(t-t_0)} + (1 - \frac{p\mu}{c + \mu}). \] (10)
Now we can deduce the stroboscopic map \( F \) such that:
\[ S((n + 1)T) = (1 - p_c)\{[S(nT) - (1 - \frac{p\mu}{c + \mu})]e^{-(c+\mu)T} + (1 - \frac{p\mu}{c + \mu})\} = F(S(nT)). \] (11)
It has a unique fixed point

\[ S^* = F(S^*) = \frac{(1 - p_c)(1 - \frac{p\mu}{c + \mu})(e^{(c+\mu)T} - 1)}{e^{(c+\mu)T} - 1 + p_c}. \] (12)

The fixed point \( S^* \) implies that there is a corresponding cycle of period \( T \) in \( S(t) \).

Since, \[ \left| \frac{dF(S(nT))}{dS} \right|_{S(nT)=S^*} = (1 - p_c)e^{-(c+\mu)T} < 1, \] (13)

the fixed point \( S^* \) is locally stable, the sequence \( S(nT) \) must converge to it.

Therefore, by setting \( S(t_0) = S^* \) in (10), we have a complete expression for the infection-free periodic solution over the \( n \)-th time-interval:

\[
\begin{cases}
\tilde{S}(t) = (1 - \frac{p\mu}{c + \mu}) - \frac{p_c e^{(c+\mu)T} (1 - \frac{p\mu}{c + \mu})}{e^{(c+\mu)T} - 1 + p_c} e^{-(c+\mu)(t-t_0)} , \\
\tilde{E}(t) = 0, \quad \tilde{I}(t) = 0, \quad \tilde{R}(t) = 0.
\end{cases} \] (14)

The solution is periodic in time:

\[
\begin{cases}
\tilde{S}(t+T) = \tilde{S}(t), \quad \tilde{E}(t+T) = \tilde{E}(t), \\
\tilde{I}(t+T) = \tilde{I}(t), \quad \tilde{R}(t+T) = \tilde{R}(t).
\end{cases} \] (15)

Define the control reproductive rate of system (8) as follows (see [16]):

\[
\mathcal{R}_0(T) = \frac{\beta \varepsilon}{(\varepsilon + \mu)(\mu + \gamma)T} \int_0^T \tilde{S}(\tau) d\tau = \frac{(1 - \frac{p\mu}{c + \mu}) (e^{(c+\mu)T} - 1)[T(c + \mu) - p_c] + T(1 - \frac{p\mu}{c + \mu})(c + \mu)p_c}{(e^{(c+\mu)T} - 1 + p_c)(c + \mu)} \] (16)

**Theorem 2.2.** If \( \mathcal{R}_0(T) < 1 \), then the periodic infection-free solution \( (\tilde{S}(t), \tilde{E}(t), \tilde{I}(t), \tilde{R}(t)) \) is locally asymptotically stable.

**Proof.** Add small perturbations \( x(t), y(t), z(t), f(t) \) to the periodic solution. Then \( S(t) = \tilde{S}(t) + x(t), E(t) = \tilde{E}(t) + y(t), I(t) = \tilde{I}(t) + z(t), R(t) = \tilde{R}(t) + f(t) \). The linearized equations can be written as:

\[
\begin{pmatrix}
x(t) \\
y(t) \\
z(t) \\
f(t)
\end{pmatrix} = \Phi(t) \begin{pmatrix}
x(0) \\
y(0) \\
z(0) \\
f(0)
\end{pmatrix},
\]

where \( \Phi(t) \) satisfies

\[
\frac{d\Phi}{dt} = \begin{pmatrix}
-c - \mu & -c & -c - \beta \tilde{S} & -c + \alpha \\
0 & -\varepsilon - \mu & \beta \tilde{S} & 0 \\
0 & \varepsilon & -\mu - \gamma & 0 \\
0 & 0 & \gamma & -\mu - \alpha
\end{pmatrix} \Phi(t),
\]
and \( \Phi(0) \) is the identity matrix. When the pulse vaccination comes into effect,
\[
\begin{pmatrix}
x(nT^+) \\
y(nT^+) \\
z(nT^+) \\
f(nT^+)
\end{pmatrix} =
\begin{pmatrix}
1 - p_c & 0 & 0 & 0 \\
0 & 1 & 0 & 0 \\
0 & 0 & 1 & 0 \\
0 & 0 & 0 & 1
\end{pmatrix}
\begin{pmatrix}
x(nT) \\
y(nT) \\
z(nT) \\
f(nT)
\end{pmatrix}.
\]

Hence, if the absolute values of all eigenvalues of
\[
M = \begin{pmatrix}
1 - p_c & 0 & 0 & 0 \\
0 & 1 & 0 & 0 \\
0 & 0 & 1 & 0 \\
0 & 0 & 0 & 1
\end{pmatrix}\Phi(T)
\]

are less than one, the periodic solution \( (\tilde{S}(t), \tilde{E}(t), \tilde{I}(t), \tilde{R}(t)) \) is locally stable [1].

By calculating, we have
\[
\frac{d\Phi}{dt} =
\begin{pmatrix}
(-c - \mu)\varphi_{11} & a_1 & a_2 & a_3 \\
0 & b_1 & b_2 & 0 \\
0 & c_1 & c_2 & 0 \\
0 & d_1 & d_2 & (-\mu - \alpha)\varphi_{44}
\end{pmatrix},
\]

where
\[
a_1 = (-c - \mu)\varphi_{12} - c\varphi_{22} + (-c - \beta\tilde{S})\varphi_{32},
\]
\[
a_2 = (-c - \mu)\varphi_{13} - c\varphi_{22} + (-c - \beta\tilde{S})\varphi_{33} + (-c + \alpha)\varphi_{43},
\]
\[
a_3 = (-c - \mu)\varphi_{14} + (-c + \alpha)\varphi_{44},
\]
\[
b_1 = (-\varepsilon - \mu)\varphi_{22} + \beta\tilde{S}\varphi_{32},
\]
\[
b_2 = (-\varepsilon - \mu)\varphi_{23} + \beta\tilde{S}\varphi_{33},
\]
\[
c_1 = \varepsilon\varphi_{22} + (-\mu - \gamma)\varphi_{32} + c_2 = \varepsilon\varphi_{23} + (-\mu - \gamma)\varphi_{33},
\]
\[
d_1 = \gamma\varphi_{32}, d_2 = \gamma\varphi_{33} + (-\mu - \alpha)\varphi_{43}.
\]

Then the eigenvalues of \( M \) denoted by \( \lambda_1, \lambda_2, \lambda_3 \) and \( \lambda_4 \) are the following:
\[
\lambda_1 = (1 - p_c)e^{-(c + \mu)T} < 1, \quad \lambda_4 = e^{-(\mu + \alpha)T} < 1,
\]
and actually, the stability is determined by the second and third equations of system (8). For the stability, the parameters need to satisfy the following inequality:
\[
\max(|\lambda_2(p, p_c, T, \beta, \varepsilon, \mu, \gamma, \alpha, c), \lambda_3(p, p_c, T, \beta, \varepsilon, \mu, \gamma, \alpha, c)|) < 1. \quad (17)
\]

Based on the theorem of [9], the solution of (17) is:
\[
\frac{\beta \varepsilon}{(\varepsilon + \mu)(\mu + \gamma)T} \int_0^T \tilde{S}(\tau)d\tau < 1.
\]

That is, the periodic infection-free solution \( (\tilde{S}(t), \tilde{E}(t), \tilde{I}(t), \tilde{R}(t)) \) is locally asymptotically stable if \( R_0 < 1 \).

The following theorem is about the global stability of the infection-free periodic solution.
Theorem 2.3. If
\[
\mathcal{R}_1(T) = \frac{(1 - \frac{p\mu}{c + \alpha + \mu})^T - 1)[T(c + \alpha + \mu) - p\epsilon] + T(1 - \frac{p\mu}{c + \alpha + \mu})(c + \alpha + \mu)p\epsilon}{(e^{(c + \alpha + \mu)T} - 1 + p\epsilon)(c + \alpha + \mu)} < 1,
\]
then the infection-free periodic solution \((\tilde{S}(t), \tilde{E}(t), \tilde{I}(t), \tilde{R}(t))\) is globally attractive.

Proof. Since \(V \leq 1 - S\) and \(R \leq 1 - S\), we have
\[
\frac{dS}{dt} = (1 - p\mu + c)S + \alpha R - \mu S - \beta SI \leq (1 - p\mu + (c + \alpha)(1 - S) - \mu S.
\]
We have the following impulsive system:
\[
\begin{align*}
\frac{dX_1}{dt} &= (1 - p\mu + (c + \alpha)(1 - X_1) - \mu X_1, \quad t \neq nT, \\
X_1(t^+) &= (1 - p\epsilon)X_1(t), \quad t = nT, n \in \mathbb{Z}_+, \quad (18) \\
X_1(0) &= S(0).
\end{align*}
\]
Solving the system above, we know that \(X_1(t)\) has analytic solution and \(S(t) \leq X_1(t) \to X_1^*\). And
\[
\begin{align*}
\frac{dE}{dt} &= \beta SI - \varepsilon E - \mu E \leq \beta X_1 I - \varepsilon E - \mu E, \\
\frac{dI}{dt} &= \varepsilon E - \mu I - \gamma I. \quad (19)
\end{align*}
\]
Consider the differential system
\[
\begin{align*}
\frac{dX_2}{dt} &= \beta X_1 X_3 - \varepsilon X_2 - \mu X_2, \\
\frac{dX_3}{dt} &= \varepsilon X_2 - \mu X_3 - \gamma X_3, \quad (20) \\
X_2(0) &= E(0), \\
X_3(0) &= I(0).
\end{align*}
\]
Apply the Kamke’s theorem [7], \(E \leq X_2, I \leq X_3\). If \(\max\{||\phi_1||, ||\phi_2||\} < 1\), the periodic solution of compared system is globally asymptotically stable, where \(\phi_1\) and \(\phi_2\) are defined as ‘Floquet multipliers’.

By calculating we obtain the condition: if \(\mathcal{R}_1(T) < 1\) holds, then \(X_2 \to 0^+, X_3 \to 0^+\) and \(E \to 0^+, I \to 0^+\). According to the comparison principle, the proof is complete.

Those theorems indicate that the control reproduction number (rate) is the key in determining dynamics of the disease and can be used for evaluating control strategies. Once the safer and more effective vaccines come into use, we can design corresponding control strategy by the guide of our study.
3. **Optimal control problem.** System (8) is an epidemic model of mixed vaccination strategy, and the parameter $p$ and $p_c$ are constant. We now add control variables into the system.

\[
\begin{align*}
\frac{dS}{dt} &= (1 - u_1(t))\mu + cV + \alpha R - \mu S - \beta SI, \\
\frac{dE}{dt} &= \beta SI - \varepsilon E - \mu E, \\
\frac{dI}{dt} &= \varepsilon E - \mu I - \gamma I, \\
\frac{dR}{dt} &= \gamma I - \mu R - \alpha R, \\
V &= 1 - S - E - I - R.
\end{align*}
\]

This system is given by the following differential equations:

\[
\begin{align*}
\frac{dS}{dt} &= (1 - u_1(t))\mu + cV + \alpha R - \mu S - \beta SI, \\
\frac{dE}{dt} &= \beta SI - \varepsilon E - \mu E, \\
\frac{dI}{dt} &= \varepsilon E - \mu I - \gamma I, \\
\frac{dR}{dt} &= \gamma I - \mu R - \alpha R, \\
V &= 1 - S - E - I - R. \\
\end{align*}
\]

In system (21), the control function $u_1(t)$ is the fraction of the newborns who enter the vaccinated class. The control function $u_2(t)$ is the fraction of susceptible individuals who enter the vaccinated class at time $nT (n \in Z_+)$. The control functions $u_1(t)$ and $u_2(t)$ are bounded ($a_1 \leq u_1(t) \leq b_1, a_2 \leq u_2(t) \leq b_2$).

For the nonlinear system we established above, the existing approaches to solving it can be classified into indirect and direct methods [23]. Inequality constraints on state variables are difficult to solve in indirect method. So we use a direct dynamic optimization method to solve the optimal problem. More precisely, we define the vector of state variables as

\[
x = \begin{pmatrix}
x_1 \\
x_2 \\
x_3 \\
x_4 \\
x_5
\end{pmatrix} = \begin{pmatrix}
S(t) \\
E(t) \\
I(t) \\
R(t) \\
V(t)
\end{pmatrix}.
\]

(22)

Now, the SEIRVS epidemic model with mixed vaccination strategy can be described by the following dynamic system

\[
\begin{align*}
x(t) &= f(x(t)), \quad t \in (t_k, t_{k+1}], \\
x(t_k^+) &= x(t_k) + Cu_2(t)x(t_k), \quad k = 1, \ldots, N, \\
x(t_0) &= x_0,
\end{align*}
\]

where $f : \mathbb{R}^5 \to \mathbb{R}^5$ represents the epidemic model of mixed vaccination strategy and

\[
C = \begin{pmatrix}
-1 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 \\
1 & 0 & 0 & 0 & 0
\end{pmatrix}.
\]

(23)

Two control functions and the pulse time interval will be optimized.

Generally, we carry out a control strategy in limited time, so the optimal control problem is considered as the question of fixed terminal. The objective function is defined as the minimization of the integral of the infected population in the time horizon $[t_0, t_f]$, and we divide the time horizon $[t_0, t_f]$ into $N$ pieces equally, i.e.,
\[ T = \Delta t_k = (t_f - t_0)/N. \]

The optimal control problem is formulated as follows:

\[
\min_{u_1(t), u_2(t), \Delta t_k} J = \int_{t_0}^{t_f} I(t) dt
\]

subject to:

\[
\begin{cases}
\dot{x}(t) = f(x(t)), t \in (t_k, t_{k+1}], \\
x(t_{k+1}^-) = x(t_k) + C u_2(t) x(t_k), \\
k = 1, \ldots, N, \\
x_{\text{min}} \leq x \leq x_{\text{max}}, \\
a_1 \leq u_1(t) \leq b_1, \\
a_2 \leq u_2(t) \leq b_2, \\
\sum_{k=1}^{N} \Delta t_k = t_f - t_0.
\end{cases}
\]

In a continuous dynamic optimization problem, Pontryagin’s maximum principle can be used to the optimal control analysis. However (24) is an impulsive optimal control problem, and hence the theoretical transversality condition is difficult to give. We try to solve the optimal control problem from the numerical simulation.

4. Numerical simulations. Here, we use the CMSC method [24] to solve the optimal problem. Multiple shooting represents the states with individual shoots over sub-intervals and collocation on finite elements inside each sub-interval [5]. By CMSC method, the original optimal control problem can be transformed into a nonlinear program (NLP) problem, which can be efficiently solved by a NLP solver.

For system (21), it is piecewisely continuous in the time interval \([t_0, t_f]\). \(S(t)\) and \(V(t)\) are continuous in each \(T\)-period and have discontinuities at each pulse vaccination time point \(t_k, k = 1, \ldots, N\). Then, we can take system (21) as a series of \(N\) initial-value problems (IVPs) defined on each \(T\)-period. In order to ensure the stability and accuracy of the numerical solutions, each time interval is divided into \(m\) subintervals. Above all, the continuity conditions are as follows:

\[
\begin{align*}
&x_{k,i} = x(t_{k,i}), \\
&x_{1,0} = x(t_0), \\
&x_{1,1} = \phi(x_{1,0}, \Delta t_{1,1}), \\
&x_{1,2} = \phi(x_{1,1}, \Delta t_{1,2}), \\
&\vdots \\
&x_{1,m-1} = \phi(x_{1,m-2}, \Delta t_{1,m-1}), \\
&x_{2,0} = \phi(x_{1,m-1}, \Delta t_{1,m}) + C u_2(t) \phi(x_{1,m-1}, \Delta t_{1,m}), \\
&x_{2,1} = \phi(x_{2,0}, \Delta t_{2,1}), \\
&\vdots \\
&x_{N,m-1} = \phi(x_{N,m-2}, \Delta t_{N,m-1}), \\
&x_{N,m} = \phi(x_{N,m-1}, \Delta t_{N,m}) + C u_2(t) \phi(x_{N,m-1}, \Delta t_{N,m}).
\end{align*}
\]

(25)
Here, $\phi(x_{k,i-1}, \Delta t_{k,i})$ represents the value of the state trajectory at the end point of the subinterval $\Delta t_{k,i}$. Now optimal control problem (24) is transformed into the following NLP

$$\min_{u_1(t), u_2(t), \Delta t_k} J = (x_{k,i}, \Delta t_k, u_1(t), u_2(t))$$

subject to:

$$\Delta t_k = \sum_{i=1}^{m} \Delta t_{k,i},$$

$$x_{\min} \leq x_{k,i} \leq x_{\max},$$

$$t_{\min} \leq \Delta t_k \leq t_{\max},$$

$$a_1 \leq u_1(t) \leq b_1,$$

$$a_2 \leq u_2(t) \leq b_2,$$

$$\sum_{k=1}^{N} \Delta t_k = t_f - t_0,$$

$$k = 1, \cdots, N, \quad i = 1, \cdots, m. \quad (26)$$

The time horizon of the mixed vaccination strategy in our numerical simulations is 20 years, i.e., $t \in [0, 20]$. And the number of pulse vaccination is from 5 to 10 times, that is, the corresponding pulse period is from 2 to 4 years. The constraints on control $u_1(t)$ and $u_2(t)$ are as follows:

$$0.6 \leq u_1(t) \leq 0.85, \quad 0.1 \leq u_2(t) \leq 0.3. \quad (27)$$

**Table 1. Parameter values**

| Parameter | Value       | Source     |
|-----------|-------------|------------|
| $\mu$     | 0.0143 year$^{-1}$ | [19]        |
| $\varepsilon$ | 6 year$^{-1}$ | [14]        |
| $\alpha$  | 0.0015 year$^{-1}$ | [14]        |
| $c$       | 0.05 year$^{-1}$ | Assumed    |
| $\gamma$  | 0.4055 year$^{-1}$ | Assumed    |
| $\beta$   | 0.4945 | Assumed    |

The comparison between constant vaccination strategy and mixed vaccination strategy with the same cost is shown in Fig. 1. The primary audience of constant vaccination strategy is the newborns. However, annual newborns account for a small part of the total population. Though we can eradicate the disease by constant vaccination strategy theoretically. Constant vaccination strategy still needs to maintain high immunity of newborns for a long time. The newborns and the whole susceptible population can be vaccinated in the same time interval under mixed vaccination strategy, so it is conducive to avoid the disadvantageous factors of vaccination for the high-risk infants. For newborns, the cost of vaccine is usually higher than general vaccine. Let $w$ denote the ratio coefficient of the cost. The values of parameter are presented in Table 1, and the assumption of some parameter values is based on the realistic of tuberculosis because TB is often described as a slow disease [22] and it is one of the most deadly diseases worldwide. With the widespread use of antibiotics, the update of mycobacterium tuberculosis has sped
up a lot. It is difficult for the new vaccine to confer lifelong immunity, so we assume the protection period \((1/c)\) as 20 years. In our simulations, the time unit is year. In Fig. 1, the trends of population under two vaccination strategies with the same cost are shown. From (b) and (c) in Fig. 1, the \(E\) class and \(I\) class decrease more rapidly in mixed vaccination strategy than in constant vaccination strategy after the first pulse vaccination. By calculating, during the mixed vaccination strategy the total number of newly infected cases reduces 227678 per hundred million compared with constant vaccination strategy. Considering TB data of China, it means that the annual newly infected cases decrease by 17%. The cost of treating these people is avoided, and it is a big progress for reducing the burden of chronic diseases.

The populations with optimal mixed vaccination strategy are shown in blue solid lines in Fig. 2, compared with the populations under optimal constant vaccination strategy, as shown in red dashed lines. From Fig. 2, we can clearly see that to minimize infected individuals, the number of pulse and the quantities of both constant and pulse vaccines all reach the maximal boundary. Once the optimal mixed vaccination strategy comes into use, the number of infected individuals decreases more sharply, compared to those of infected individuals under optimal constant vaccination strategy. If our goal is to make the \(I\) class drop to 10% of its initial value, it will take 10.75 years in mixed vaccination strategy and 23.65 years in constant vaccination strategy.

In actual implementation, the investment of medical treatment is restricted. So the quantity of vaccine to population is limited. In Fig. 3, we show the optimal
Figure 2. Comparison between the constant vaccination strategy and optimal mixed vaccination strategy. The red dashed line shows the constant vaccination strategy with $p = 0.85(0.6 \leq p \leq 0.85)$. The blue solid line shows optimal mixed vaccination strategy with $0.6 \leq u_1(t) \leq 0.85, 0.1 \leq u_2(t) \leq 0.3$ and $5 \leq N \leq 10$. All the other parameters are shown in Table 1.

Figure 3. Optimal mixed vaccination strategy under limited vaccinated individuals with $0.6 \leq u_1(t) \leq 0.85, 0.1 \leq u_2(t) \leq 0.3$ and $5 \leq N \leq 10$. All the other parameters are shown in Table 1.
control strategy if the total vaccinated people is less than 4.5% of the total population. From the numerical results, it is obvious that, under limited vaccines, the amount of constant vaccination is remained at a moderate level and the number of pulse reaches the maximal boundary while the quantity decreases progressively.

5. Conclusion. The SEIRVS epidemic model for chronic disease with different vaccination strategies is formulated and its dynamic behaviors are studied. With the development of vaccine, we propose a mixed vaccination strategy for the more effective vaccines correspondingly and provide theoretical basis for eradicating the disease. The local and global asymptotically stable conditions for the elimination of the disease are given in this paper. The optimal control problem of the mixed vaccination strategy is efficiently solved by CMSC method. Numerical simulations show the optimal scheduling of the mixed vaccination strategy. Especially, if the amount of vaccines is not restricted, we should adopt maximum strategy during the procedure. And the simulation results of optimal control also show the case that the total vaccinated people is limited.

Acknowledgments. We thank the reviewer and editor for their useful comments and suggestions. This work was completed with the support by National Basic Research Program of China Grant 2013CB834100, NSFC Grant 11571065, NSFC Grant 11171132 and NSFC Grant 11201173.

REFERENCES

[1] R. M. Anderson and R. M. May, *Infectious Diseases of Humans: Dynamics and Control*, Oxford University Press, 1991.
[2] B. E. Asri, Deterministic minimax impulse control in finite horizon: The viscosity solution approach, ESAIM: Control, Optimisation and Calculus of Variations, 19 (2013), 63–77.
[3] G. Barles, Deterministic impulse control problems, SIAM Journal on Control and Optimization, 23 (1985), 419–432.
[4] A. Bensoussan and J. L. Lions, Impulse control and quasi-variational inequalities, Fruit Growing Research, 1984.
[5] L. T. Biegler, Solution of dynamic optimization problems by successive quadratic programming and orthogonal collocation, Computers & Chemical Engineering, 8 (1984), 243–247.
[6] P. Clayden, S. Collins, C. Daniels, M. Frick, M. Harrington, T. Horn, R. Jefferys, K. Kaplan, E. Lessem, L. McKenna and T. Swan, 2014 Pipeline Report: HIV, Hepatitis C Virus (HCV) and Tuberculosis Drugs, Diagnostics, Vaccines, Preventive Technologies, Research Toward a Cure, and Immune-Based and Gene Therapies in Development, New York, 2014.
[7] W. A. Coppel, *Stability, Asymptotic Behavior of Differential Equations*, American Mathematical Monthly, 1965.
[8] A. R. D. Cruz, R. T. N. Cardoso and R. H. C. Takahashi, Multi-objective design with a stochastic validation of vaccination campaigns, IFAC Proceedings Volumes, 42 (2009), 289–294.
[9] A. d’Onofrio, Stability properties of pulse vaccination strategy in SEIR epidemic model, Mathematical Biosciences, 179 (2002), 57–72.
[10] A. d’Onofrio, Mixed pulse vaccination strategy in epidemic model with realistically distributed infectious and latent times, Applied Mathematics and Computation, 151 (2004), 181–187.
[11] P. V. D. Driessche and J. Watmough, Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission, Mathematical Biosciences, 180 (2002), 29–48.
[12] S. Jana, P. Haldar and T. K. Kar, Mathematical analysis of an epidemic model with isolation and optimal controls, International Journal of Computer Mathematics, 94 (2017), 1318–1336.
[13] T. Khan, G. Zaman and M. I. Chohan, The transmission dynamic and optimal control of acute and chronic hepatitis B, Journal of Biological Dynamics, 11 (2017), 172–189.
[14] J. Li, The spread and prevention of tuberculosis, Chinese Remedies and Clinics, 13 (2013), 482–483.
Mixed vaccination strategy with temporary immunity

1483

[15] S. Liu, Y. Li, Y. Bi and Q. Huang, Mixed vaccination strategy for the control of tuberculosis: A case study in China, Mathematical Biosciences and Engineering, 14 (2017), 695–708.

[16] Z. Lu, X. Chi and L. Chen, The effect of constant and pulse vaccination on SIR epidemic model with horizontal and vertical transmission, Mathematical and Computer Modelling, 36 (2002), 1039–1057.

[17] A. Mubayi, C. Zaleta, M. Martcheva and C. Castillo-Chávez, A cost-based comparison of quarantine strategies for new emerging diseases, Mathematical Biosciences and Engineering, 7 (2010), 687–717.

[18] National Bureau of Statistics of China, Statistical Data of Category A and B Infectious Diseases 2011-2015. Available from: http://data.stats.gov.cn/easyquery.htm?cn=C01.

[19] National Bureau of Statistics of China, China Statistical Yearbook 2016, Birth Rate, Death Rate and Natural Growth Rate of Population, 2016. Available from: http://www.stats.gov.cn/tjsj/ndsj/2016/indexch.htm.

[20] K. E. Nelson and C. M. Williams, Early history of infectious disease: epidemiology and control of infectious diseases, in Infectious Disease Epidemiology: Theory and Practice, Jones and Bartlett Learning, (2014), 3–18.

[21] D. J. Nokes and J. Swinton, The control of childhood viral infections by pulse vaccination, IMA Journal of Mathematics Applied in Medicine & Biology, 12 (1995), 29–53.

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

[23] O. V. Stryk and R. Bulirsch, Direct and indirect methods for trajectory optimization, Annals of Operations Research, 37 (1992), 357–373.

[24] J. Tamimi and P. Li, A combined approach to nonlinear model predictive control of fast systems, Journal of Process Control, 20 (2010), 1092–1102.

[25] E. Verriest, F. Delmotte and M. Egerstedt, Control of epidemics by vaccination, Proceedings of the American Control Conference, 2 (2005), 985–990.

[26] Y. Yang, S. Tang, X. Ren, H. Zhao and C. Guo, Global stability and optimal control for a tuberculosis model with vaccination and treatment, Discrete and Continuous Dynamical Systems - Series B, 21 (2016), 1099–1122.

[27] Y. Yang, Y. Xiao and J. Wu, Pulse HIV vaccination: feasibility for virus eradication and optimal vaccination schedule, Bulletin of Mathematical Biology, 75 (2013), 725–751.

[28] Y. Zhou, J. Wu and M. Wu, Optimal isolation strategies of emerging infectious diseases with limited resources, Mathematical Biosciences and Engineering, 10 (2013), 1691–1701.

Received November 2017; revised February 2018.

E-mail address: siyu15@mails.jlu.edu.cn
E-mail address: yangxuemath@163.com
E-mail address: biyj13@mails.jlu.edu.cn
E-mail address: liyongmath@163.com