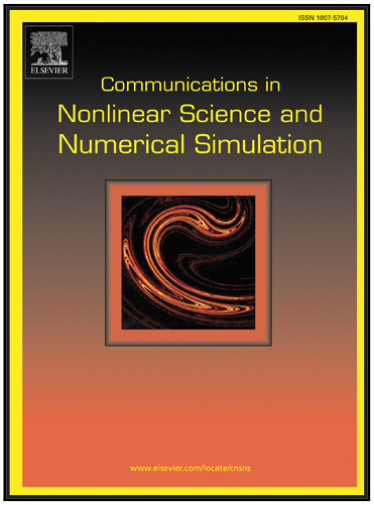

Optimal Vaccination Strategy of A Constrained Time-varying SEIR Epidemic Model

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Highlights

- The optimal vaccination strategy for a constrained time-varying SEIR epidemic model is proposed.
- The computed vaccination strategy can control the epidemic efficiently.
- The comparisons of different cases show that omitting the time-varying factors may result in less optimal even unreasonable control strategy.

Optimal Vaccination Strategy of A Constrained Time-varying SEIR Epidemic Model

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Abstract:

The optimal control strategy for time-varying epidemic models remains a wide open research area. In this paper, the optimal vaccination strategy for a constrained time-varying SEIR (Susceptible, Exposed, Infected and Recovered) epidemic model is solved under the frame of constrained optimal control problems. Three time-varying factors, i.e., seasonally varying incidence coefficient, monotonic decreasing successfully immune rate and monotonic increasing vaccine yield are considered. Constraints on vaccination rate, susceptible population and vaccine supply at each time instant, which are pure-control constraint, pure-state constraint and mixed state-control constraint, respectively, are all taken into consideration. The characterization for the optimal control is derived with the help of the Pontryagin's maximum principle. And optimal control problems are successfully solved by a symplectic pseudospectral method numerically. Numerical results are consistent with the analytical ones. Finally, comparisons of different cases demonstrate that time-varying factors could alter the optimal vaccination strategy, which implies that omitting the time-varying factors may result in less optimal even unreasonable control strategy.

Keywords: SEIR compartmental epidemic model; Time-varying factors; Constrained optimal control problem; Optimal vaccination strategy; Symplectic pseudospectral method

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1. Introduction

Compartmental models in epidemiology are powerful mathematical tools in characterizing and analysing the complex behaviours of epidemics. One of the pioneer works in this field is done by Kermack and McKendrick in 1927 and the famous SIR (susceptible-infectious-recovered) model is proposed [1]. Since then, on the basis of the SIR model, numerous novel epidemic models (such as SIRS [2-3], SEIR [4-5], SEIRS [6] etc.) are developed by introducing new compartments into the classic SIR model. These models are generally governed by ordinary differential equations (ODEs), while in some complicated cases (e.g., taking age structures into consideration) they can be characterized by partial differential equations (PDEs) [7-8].

Researches on compartmental models are generally divided into two categories [9]. The first one is to analyse the property of the mathematical system (such as stability [10-11], bifurcation [12] and so on) and the basic reproduction number is an important concept therein [13][14]. As for the second field, researchers try to obtain optimal control strategies to fight against the disease under the frame of optimal control [15][17]. Vaccination is the most studied measure where the rate of vaccination is generally taken as the control variable and it naturally lies in the range of $[0,1]$. In [18], Neilan determines an optimal vaccination strategy of an SEIR model where a limited supply of vaccines during the whole period is taken into consideration. Adopting the same SEIR model, in contrast to [18], Biswas concentrate on the limited supply of vaccines at each time instant [19]. Moreover, a state constraint is introduced so as to guarantee that the susceptible population is below a certain level during the whole period. The two papers mentioned above both impose a constraint on the supply of vaccines; however, the constraint in the former paper is a pure-state constraint, while the constraint in the latter paper is a mixed state-control constraint. Besides vaccination, treatment [20], quarantine [21],

educational campaign [22][23], etc., are all common measures to control the spread of infectious diseases. And more than one measure can be taken in the control strategy simultaneously. For example, in [24], prevention and two treatment measures are taken to control the Ebola disease. In [11] and [25] vaccination and treatment are both considered as control measures.

The system dynamics in most epidemic control problems are time-independent, in other words the system parameters are considered as constants during the whole period. However, the epidemic models with time-varying parameters could simulate a more real condition. In fact, many researches have investigated the rich nonlinear effects caused by the periodically varying contact rates in epidemic models, and some excellent surveys [26][27][28] have been published. For example, for flu-like infections, the seasonal drivers tend to limit the spread of the virus to particular periods of time of the year. In [29] the optimal vaccination and treatment strategy for seasonally varying flu-like epidemics is explored based on an SIR model. More generally, in [30], the incidence coefficient is modelled as a general function of time, the susceptible population, the infectious population and the total population. Moreover, Pathogens may become resistant to vaccines, i.e., the successfully immune rate decreases as time goes on [31]. In [32] the impact of drug resistance in malaria transmission is analysed and the optimal control analysis is provided. As well as the system parameters, constraints during the control period can be time-dependent. For example, the production yield of a vaccine may be at a low level in the initial stage while the vaccine yield goes up as time goes over. Omitting the time-varying behaviour of the epidemic system may result in improper control strategy.

Structure-preserving methods are highly efficient and accurate for analysing Hamiltonian systems. For system dynamic analysis, Feng proposes the symplectic method for the finite dimensional system [33]. Focusing on the symmetry of the conservative infinite-dimensional damping dynamic systems,

Hu and his co-workers propose the generalized multi-symplectic method [34] which has been successfully employed to the dynamic problems of single-walled carbon nanotube [35] and spatial on-orbit flexible structures [36]. In 1990s, Zhong discovers the simulation relationship between computational mechanics and optimal control [37]. Optimal control problems can be transformed into Hamiltonian systems via Pontryagin's maximum principle or the variational principle [38]. The optimal vaccination strategy can be viewed as a constrained optimal control problem. Recently, Peng et al. developed a series of symplectic pseudospectral methods (SPM) [39][40] for optimal control. The SPM can solve nonlinear optimal control problems with inequality constraints effectively. Three types of constraints, i.e., pure-state, pure-control and mixed state-control can be treated under a uniform frame.

In this paper, we focus on the optimal vaccination strategy of a time-varying SEIR epidemic model. On one hand, the incidence coefficient is seasonally varied; on the other hand, considering the drug resistance, the successfully immune rate by vaccination is considered as a monotonic decreasing function of time. Besides the constraints on the control variable, another two constraints are also taken into consideration. The first one is a pure-state constraint, i.e., an upper bound is imposed on the susceptible population as given in [19]; another one is a time varying mixed state-control constraint, i.e., the vaccine yield is below an upper bound which increases as time goes over.

The remainder of the paper is organized as follows. In Section 2, we start with the basic SEIR model given in [19] and then introduce the time-varying parameters. In Section 3, we formulate optimal vaccination strategy into a constrained optimal control problem. In Section 4, we derive the characterization for optimal vaccination rate using the Pontryagin's maximum principle. In Section 5, we compute the optimal vaccination strategy for the SEIR models with various parameters and

different constraints. And a brief comparison on vaccination strategies based on different models is given. In Section 6, some conclusions are drawn.

2. Formulation of the SEIR model

2.1 The basic SEIR model

The SEIR model is a compartmental model that divides the total population into four compartments related to the epidemic, i.e., the susceptible (S), the exposed (E), the infectious (I) and the recovered (R). The individuals in the S compartment are those who are vulnerable to become infected. An individual is in the E compartment if he is infected but is at the latent period currently, i.e., individuals in this compartment are not able to spread the disease. Infectious individuals are in the I compartment and the immune individuals are in the R compartment. For simplicity, all newborns are considered susceptible, and a susceptible individual may get infected if he contacts with the infectious. Let $S(t)$, $E(t)$, $I(t)$ and $R(t)$ represent the number of individuals in the corresponding compartment at the time t, respectively. Thus, the total population at time t is denoted as $N(t)$ satisfying

$$N(t) = S(t) + E(t) + I(t) + R(t) \tag{1}$$

To characterize the spread of the infectious disease in a certain population, several notations are defined. Let b and d be the natural birth rate and the natural death rate, respectively; let e be the rate the exposed individuals become infectious; g represents the rate the infectious individuals recover; and a refers to the death rate due to the epidemic. The transmission rate is defined as cSI, where c is the incidence coefficient. Following the system dynamics used in Ref [18] and [19], the basic SEIR model can be described as:

$$\begin{cases} \dot{S} = bN - dS - cSI \\ \dot{E} = cSI - (d+e)E \\ \dot{I} = eE - (a+d+g)I \\ \dot{R} = gI - dR \\ \dot{N} = (b-d)N - aI \end{cases} \tag{2}$$

2.2 Introducing vaccination and time-varying parameters into the basic SEIR model

In this paper, we assume that parameters a, b, d, e and g in Eq. (2) are constants during the whole control period, while the parameter c can be varied seasonally. Inspired by Ref [29], trigonometric functions are used to describe the incidence coefficient as follow

$$c(t) = c_0 + c_1 \cos(2\pi t + \varphi_0) \tag{3}$$

where c_0 and c_1 are the average and the amplitude of the incidence coefficient, respectively; $\varphi_0 \in [0, 2\pi)$ is the initial phase.

Let the susceptible individuals be vaccinated at the rate of u. Moreover, we assume the vaccinated individual get immune at the ratio of f, that is, at time t, $u(t)S(t)$ susceptible individuals are vaccinated but only $f(t)u(t)S(t)$ of them proceed to the R compartment permanently. In this paper, considering the drug resistance we model the parameter f as a monotonic decreasing function of time

$$f(t) = f_0 + f_1 \exp(-t/f_2) \tag{4}$$

where f_0, f_1 and f_2 are non-negative real constants. Furthermore, it is seen that $f(0) = f_0 + f_1$ and $\lim_{t\to\infty} f(t) = f_0$.

With the above notations, a modified system dynamics of the SEIR model with vaccination considering time-varying parameters in proposed as follows, and a diagram of the proposed model is given in Fig. 1.

$$\dot{S} = bN - dS - cSI - fuS \tag{5}$$

$$\dot{E} = cSI - (d+e)E \tag{6}$$

$$\dot{I} = eE - (a+d+g)I \tag{7}$$

$$\dot{R} = gI - dR + fuS \tag{8}$$

$$\dot{N} = (b-d)N - aI \tag{9}$$

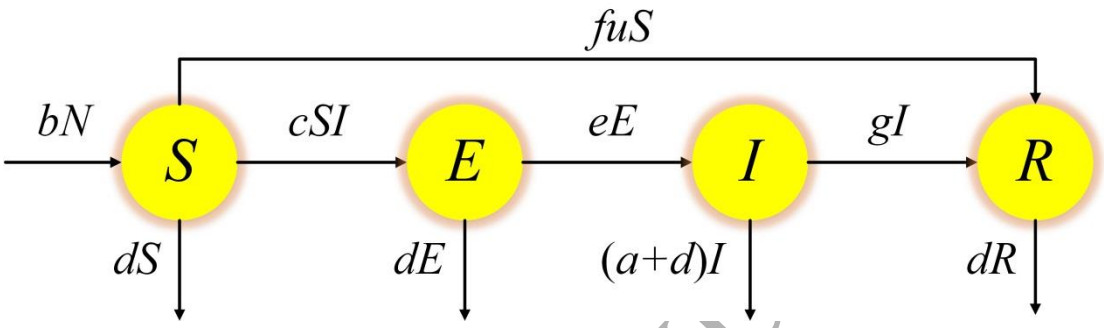

Fig. 1 The diagram of the SEIR compartmental model with vaccination

3. Formulation of the optimal vaccination problem

As mentioned the above, the SEIR epidemic model has been described mathematically as a set of ODEs. Once the initial conditions are given and no vaccination is done (i.e., $u(t) \equiv 0$), an ODE initial value problem can be solved and the population variation in each compartment is obtained. Not limited to this, the spread of the infectious disease can be controlled through reasonable vaccination strategies. In this section, the optimal vaccination problem is solved under the frame of constrained optimal control problems.

To express the number of individuals vaccinated, an extra variable $V(t)$ is introduced

$$\dot{V} = uS \tag{10}$$

where the value of V at the initial time is set to 0. According to realistic condition, the limited supply of vaccines at each time instant can be modelled as follow

$$u(t)S(t) < \Omega(t) \tag{11}$$

where $\Omega(t)$ is a time-dependent upper bound of vaccine supply at each time instant.

Moreover, state constraints can be introduced to keep the infectious population at low level. In this paper, we consider the constraint proposed in [19] as follow

$$S(t) < S_{\max} \tag{12}$$

where $S_{\max}$ is the upper bound of the susceptible population.

Observe Eqs.(5)~(9) and it can be seen that one of these five equations is redundant, that is, if any four variables are known, the fifth one can be obtained according to Eq. (1). In the following problem formulation, we select the state space as $\mathbf{x} = [S\ E\ I\ N]^{\mathrm{T}}$. And the vaccination rate, i.e., $u(t)$ is taken as the control variable. As for the cost functional, a quadratic function in both state and control is selected, which takes both the vaccination consumption and the number of the infectious individuals into consideration. Based on the above descriptions, the optimal vaccination strategy can be formulated as the following optimal control problem with inequality constraints and free terminal states

$$\text{Problem } (\mathbf{P}) \begin{cases} \min J = \int_0^{t_f} \left(AI^2 + u^2\right) \mathrm{d}t \\ s.t. \\ \dot{S} = bN - dS - cSI - fuS \\ \dot{E} = cSI - (d+e)E \\ \dot{I} = eE - (a+d+g)I \\ \dot{N} = (b-d)N - aI \\ S(0) = S_s,\ E(0) = E_s,\ I(0) = I_s \text{ and } N(0) = N_s \\ 0 \le u \le u_{\max} \\ S \le S_{\max} \\ uS \le \Omega \end{cases} \tag{13}$$

where $t_f \in \mathbb{R}^+$ is the terminal time; $A \in \mathbb{R}^+$ is the weight coefficient on the infectious population.

4. Characterization of the optimal control

The existence of the optimal solution and the characterization of the control variable for Problem $(\mathbf{P})$ are well provided in [19]. However, in [19], $u_{\max} > \frac{\Omega}{S}$ always establishes, limiting the

scope of application of the characterization of optimal control therein. In the flowing derivation, we focus on extending the characterization of optimal control to a more general condition. For the existence of optimal solution, interested readers can refer to [19] and the references therein.

Denote the optimal control and corresponding optimal state trajectory for Problem $(\mathbf{P})$ as u^* and $\mathbf{x}^* = \left[S^*, E^*, I^*, N^*\right]^{\mathrm{T}}$, respectively. Next, we derive the optimality system for Problem $(\mathbf{P})$ using the Pontryagin's maximum principle.

The inequality constraints in Problem $(\mathbf{P})$ can be transformed into equality ones with the help of some non-negative parametric parameters, i.e., $\alpha_i \left(i = 1, 2, 3, 4\right)$, as

$$\begin{cases} -u + \alpha_1 = 0 \\ u - u_{\max} + \alpha_2 = 0 \\ S - S_{\max} + \alpha_3 = 0 \\ uS - \Omega + \alpha_4 = 0 \end{cases} \tag{14}$$

And we denote $\boldsymbol{\alpha} = \left[\alpha_1, \alpha_2, \alpha_3, \alpha_4\right]^{\mathrm{T}}$. Hence, the Hamiltonian function for Problem $(\mathbf{P})$ is obtained as follow

$$\begin{aligned} H = {} & AI^2 + u^2 + \lambda_S \left(bN - dS - cSI - fuS\right) \\ & + \lambda_E \left(cSI - \left(d + e\right)E\right) + \lambda_I \left(eE - \left(a + d + g\right)I\right) + \lambda_N \left(\left(b - d\right)N - aI\right) \\ & + \mu_1 \left(-u + \alpha_1\right) + \mu_2 \left(u - u_{\max} + \alpha_2\right) + \mu_3 \left(S - S_{\max} + \alpha_3\right) + \mu_4 \left(uS - \Omega + \alpha_4\right) \end{aligned} \tag{15}$$

where $\boldsymbol{\lambda} = \left[\lambda_S, \lambda_E, \lambda_I, \lambda_N\right]^{\mathrm{T}}$ are costate variables; and $\boldsymbol{\mu} = \left[\mu_1, \mu_2, \mu_3, \mu_4\right]^{\mathrm{T}}$ are non-negative penalty multipliers.

By applying the Pontryagin's maximum principle, the first-order necessary conditions can be derived. The optimality conditions with respect to state, costate and parametric variables result in a two-point boundary value problem (TPBVP) coupled with a nonlinear complementarity problem (NCP) as follow:

$$\dot{\mathbf{x}} = \frac{\partial H}{\partial \boldsymbol{\lambda}} \tag{16}$$

$$\dot{\boldsymbol{\lambda}} = -\frac{\partial H}{\partial \mathbf{x}} \tag{17}$$

$$\boldsymbol{\alpha} \geq \mathbf{0}, \boldsymbol{\mu} \geq \mathbf{0}, \boldsymbol{\alpha}^{\mathrm{T}} \boldsymbol{\mu} = 0 \tag{18}$$

and the optimality condition with respect to control variable is

$$\frac{\partial H}{\partial u} = 0 \tag{19}$$

Eq. (16) is equivalent to the system dynamics. And from Eq. (17), the adjoint system can be derived as follow:

$$\begin{cases} \dot{\lambda}_S = \left(d + cI^* + fu^*\right)\lambda_S - \mu_4 u^* - \mu_3 - cI^*\lambda_E \\ \dot{\lambda}_E = \left(d + e\right)\lambda_E - e\lambda_I \\ \dot{\lambda}_I = cS^*\lambda_S - cS^*\lambda_E + \left(a + d + g\right)\lambda_I + a\lambda_N - 2AI^* \\ \dot{\lambda}_N = -b\lambda_S - \left(b - d\right)\lambda_N \end{cases} \tag{20}$$

with the transversality conditions $\lambda_S\left(t_f\right) = \lambda_E\left(t_f\right) = \lambda_I\left(t_f\right) = \lambda_N\left(t_f\right) = 0$.

The control variable is required to satisfy $0 \leq u \leq u_{\max}$ and $u \leq \frac{\Omega}{S}$. In other words, $0 \leq u \leq \min\left\{u_{\max}, \frac{\Omega}{S}\right\}$ is required to be satisfied. In [19] $u_{\max}$ is set to 1 and $\Omega < S_{\max}$. Hence, $\frac{\Omega}{S} < u_{\max}$ always establishes. In the following derivation, we will extend the result in [19] to a more general condition.

By solving Eq. (19), the optimal control can be expressed as

$$u^* = \frac{fS^*\lambda_S + \mu_1 - \mu_2 - \mu_4 S^*}{2} \tag{21}$$

We first consider the condition where $\frac{\Omega}{S} > u_{\max}$. Under this condition, $u^* < \frac{\Omega}{S^*}$ always establishes, hence, $\mu_4 \equiv 0$. To determine an explicit expression of the optimal control without μ_1 and μ_2, we consider the consider the following three cases :

(1) On the set $\left\{t \middle| 0 < u^* < u_{\max}\right\}$, we have $\mu_1 = \mu_2 = 0$. Hence, the optimal control can be expressed as $u^* = \frac{fS^*\lambda_S}{2}$.

(2) On the set $\left\{t\middle|u^*=0\right\}$, we have $\mu_2=0$. Hence, $0=u^*=\frac{fS^*\lambda_S+\mu_1}{2}$. Since $\mu_1\geq 0$, it is determined that $\frac{fS^*\lambda_S}{2}\leq 0$.

(3) On the set $\left\{t\middle|u^*=u_{\max}\right\}$, we have $\mu_1=0$. Hence, $u_{\max}=u^*=\frac{fS^*\lambda_S-\mu_2}{2}$. Since $\mu_2\geq 0$, it is determined that $\frac{fS^*\lambda_S}{2}\geq u_{\max}$.

Combining the above three cases, the optimal control u^* is characterized as

$$u^*=\max\left\{0,\min\left\{\frac{fS^*\lambda_S}{2},u_{\max}\right\}\right\} \tag{22}$$

Using the similar arguments, we can characterize the optimal control u^* under the condition where $\frac{\Omega}{S}\leq u_{\max}$ as

$$u^*=\max\left\{0,\min\left\{\frac{fS^*\lambda_S}{2},\frac{\Omega}{S^*}\right\}\right\} \tag{23}$$

Considering Eq. (22) and (23) synthetically, the optimal control u^* can be expressed as

$$u^*=\max\left\{0,\min\left\{\frac{fS^*\lambda_S}{2},\frac{\Omega}{S^*},u_{\max}\right\}\right\} \tag{24}$$

An analytical expression of the optimal vaccination rate is already derived in Eq. (24). However, an effective algorithm is still required to solve the nonlinear constrained optimal control problem numerically. In this paper, the SPM developed in [40] is adopted. Since the SPM is the core algorithm for solving the optimal vaccination rate problem, a brief introduction of the SPM is provided in the rest of this section.

For a nonlinear optimal control problem, the SPM first transform the original nonlinear problem into a series of linear-quadratic (LQ) problems with the help of quasilinearization techniques, i.e., the system dynamics and the constraints are linearized while the cost function is expanded up to the second order around nominal trajectories. For each LQ problem, the first-order necessary conditions similar to

Eqs. (16)~(19) are derived, which can be seen as a coupling of a linear two-point boundary value problem (TPBVP) and a linear complementarity problem (LCP). The time domain is divided into several small sub-intervals, and state, costate and parametric variables with each sub-interval are discretized at Legendre-Gauss-Lobatto (LGL) nodes. The variational principle is applied to the second kind of generating function and a set of linear algebraic equations (SLAEs) is obtained. Then the complementarity conditions are imposed at all LGL points and an LCP can be obtained. By proper transformation, state and costate variables are expressed as linear functions of parametric variables. Finally, a standard LCP can be constructed and solved by the Lemek's method. Solutions obtained in current iteration are taken as reference for the next iteration. And the iteration goes on until prescribed convergent criterion is satisfied. For more details of the SPM, interested readers can refer to Refs. [39][40][41].

The SPM has its own merits. For example, it can treat three kinds of constraints, i.e., pure-state, pure-control and mixed state-control under a uniform frame. Coefficient matrices in the SPM are sparse and symmetric due to the benefit of the variational principle, making the proposed method highly efficient. And converged numerical solutions can be obtained after a few iterations since the local pseudospectral method and quasilinearization techniques are used. Based on the above facts, we adopt the SPM to solve optimal control problems numerically in this paper.

5. Numerical simulations

The optimal vaccination strategy problem is already formulated in Section 3. In the following simulation, unless otherwise stated, parameters, constraints and initial conditions of state variables used in each case are set as given in Table 1, just as the same to those in [19].

Table 1

Parameters and their values used in the simulation.

Parameter	Parameter description	Value
a	disease induced death rate	0.2
b	natural birth rate	0.525
c	incidence coefficient	0.001
d	natural death rate	0.5
e	exposed to infectious rate	0.5
f	successfully immune rate	1
A	weight on the infectious population	0.002
t_f	number of years	20
S_s	initial susceptible population	1000
E_s	initial exposed population	100
I_s	initial infectious population	50
R_s	initial recovered population	15
N_s	initial total population	1165
V_s	initial vaccinated population	0
$u_{\max}$	maximum vaccination rate	1
$S_{\max}$	maximum susceptible population	1100
Ω	maximum vaccination supply at each time instant	1000

In this section, we solve five cases to show the impact of time-varying parameters and constraint on the vaccination strategy. In Case 1, no time-varying factor is considered and the parameters used are just like listed in Table 1. In Case 2, the incidence coefficient is considered to be seasonally varying. In Case 3, the drug resistance is considered and the successfully immune rate is decreasing as time goes over. In Case 4, the vaccination supply at each time instant is considered increasing as time goes by. In Case 5, all time varying factors considered in the former cases are taken into consideration simultaneously to simulate a much real condition. To show the effectiveness of the control strategy, controlled solutions along with the uncontrolled solutions are presented in every case. At last, we present a brief comparison of these cases to show the necessarity of considering time-varying factors.

As stated previously, we use the SPM proposed in [40] to solve optimal control problems numerically. In every case, the time domain $\left[0, t_f\right]$ is divided into 40 regular sub-intervals and the degree of the approximation polynomials used in each sub-interval is fixed to five. And the convergent

tolerance in the SPM is set to $\varepsilon = 1.0e-8$. All numerical simulations are performed using the MATLAB (R2016a) software on an Intel® Core™ i7-4710MQ machine with a 2.50 GHz processor and 4 GB of RAM. Finally, it is noted that the uncontrolled trajectories in each case is calculated by the MATLAB built-in package bvp4c with default options.

5.1 Case 1: no time-varying factor is considered

In this case, we take no time-varying factor into consideration. The controlled solutions together with the solutions for uncontrolled problem are presented in Fig. 2. It is seen that the vaccination strategy is effective that E and I decreases rapidly and reach almost zero at the terminal end. Furthermore, S decreases at the initial period then increases but keeps no bigger than $S_{\max}$. However, as for the uncontrolled case, S keeps increasing during the whole period. Since there's no limit on S, variables E and I even exhibit upward tendencies at the terminal end.

In the controlled case, the vaccination rate is 1 at the very beginning period then decreases to the minimum at the eighth year approximately. After that, the control variable keeps increasing and reaches approximately 0.38 at the terminal end. From Fig. 2(e), it is seen that the numerical solution of the control variable is in good agreement with the analytical one as given in Eq.(24), validating the characterization of the optimal control.

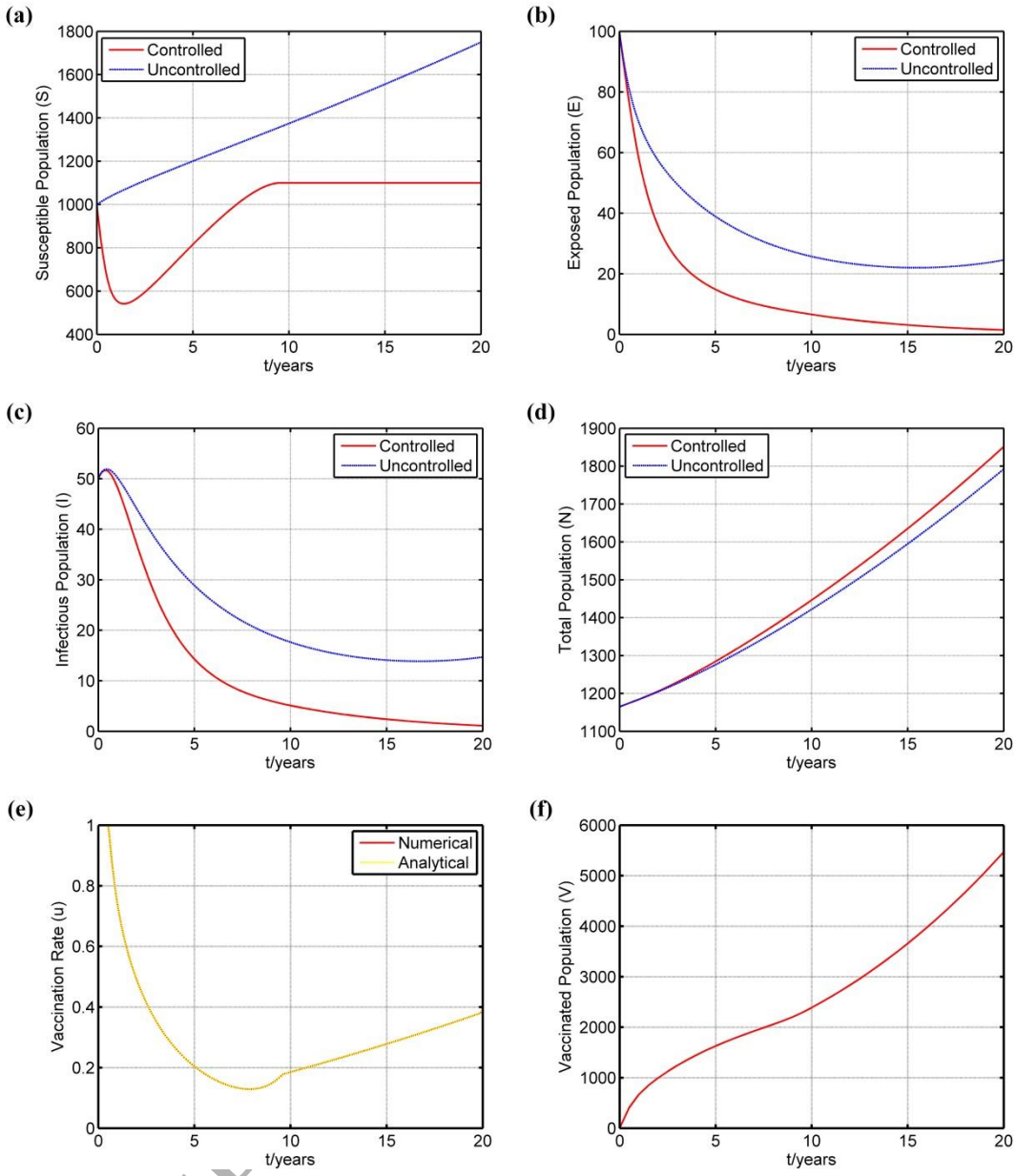

Fig. 2. Case 1: Optimal state trajectories, including (a) the susceptible population, (b) the exposed population, (c) the infectious population and (d) the total population. (e) Optimal vaccination rate. (f) Vaccinated population.

5.2 Case 2: the incidence coefficient is seasonally varying

In this case, the incidence coefficient is considered to be seasonally varying as follow

$$c(t) = 0.001 + 0.0005\cos(2\pi t) \tag{25}$$

It is seen that, for Eq.(25) the initial phase defined in Eq.(3) is set to 0, which indicates that: (1) for $t \in \left(k - \frac{1}{4}, k + \frac{1}{4}\right), k \in \mathbb{Z}$, one has $c(t) > 0.001$; (2) for $t \in \left(k + \frac{1}{4}, k + \frac{3}{4}\right), k \in \mathbb{Z}$, one has

$c(t) < 0.001$. The controlled trajectories along with the uncontrolled ones are given in Fig. 3. It is seen that for both the controlled case and the uncontrolled case, state variables and the control variables show oscillating behaviours around those in Case 1 since the seasonally varying incidence coefficient is introduced. Variables in this case show the identical variation trend with those in Case 1.

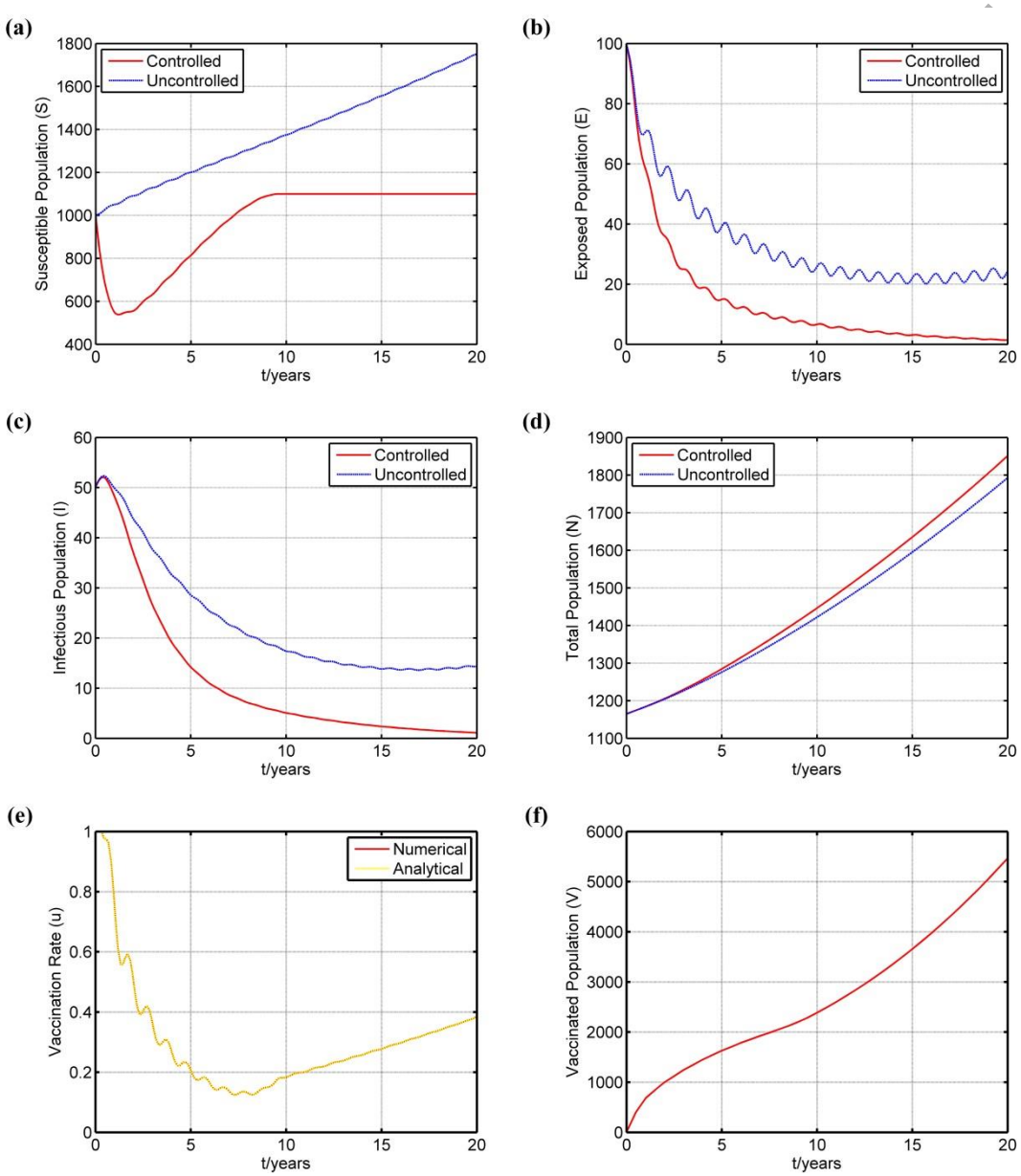

Fig. 3. Case 2: Optimal state trajectories, including (a) the susceptible population, (b) the exposed population, (c) the infectious population and (d) the total population. (e) Optimal vaccination rate. (f) Vaccinated population.

5.3 Case 3: the successfully immune rate is decreasing as time goes over

In this case, drug resistance is taken into consideration. Thus, we model the successfully immune rate as follow

$$f(t) = \exp(-t/50) \tag{26}$$

It is seen that $f(0) = 1$, which indicates that any susceptible individual get immune successfully as long as he is vaccinated at the very beginning. However, the successfully immune rate decreases exponentially as time goes over. The numerical solutions are plotted in Fig. 4. State variables and control exhibit almost the same variation trends as those in Case 1. However, it is found that the control variable in Case 3 is bigger and bigger than that in Case 1 at the late period.

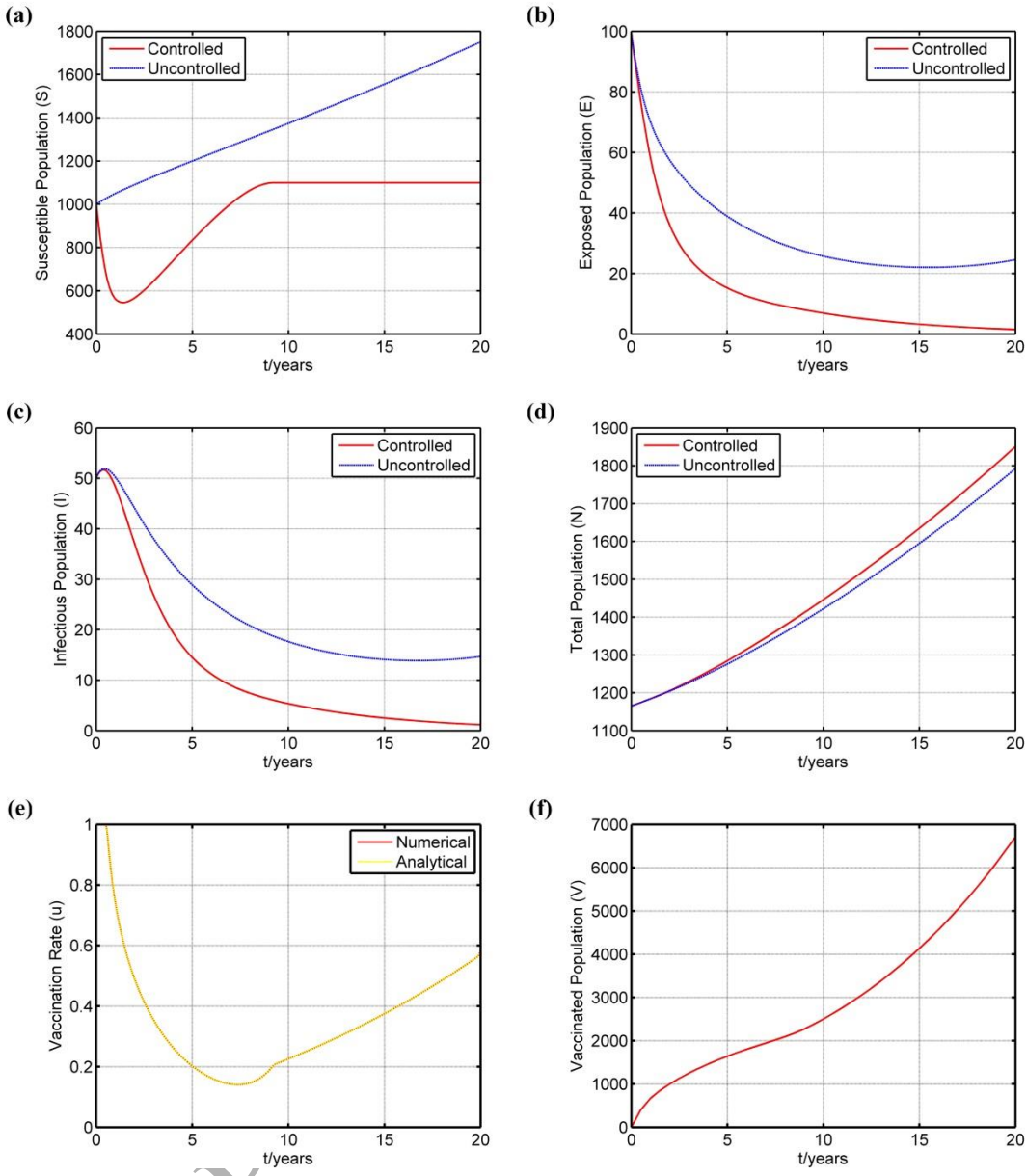

Fig. 4. Case 3: Optimal state trajectories, including (a) the susceptible population, (b) the exposed population, (c) the infectious population and (d) the total population. (e) Optimal vaccination rate. (f) Vaccinated population.

5.4 Case 4: the vaccination supply at each time instant is increasing as time goes over

In the real world, the development and production of vaccines for a new epidemic is usually in slow progress. Thus, the amount of vaccinations available to fight against the epidemic is at a low level at the initial period. Moreover, the yield of vaccines could reach an upper bound at the certain time.

Based on the above facts, we model the vaccination supply at each time instant as a monotonic increasing function

$$\Omega(t) = 1000 - 900\exp(-t/5) \tag{27}$$

Observing Eq. (27) it is seen that $\Omega(0) = 100$ and $\lim_{t\to\infty}\Omega(t) = 1000$. The optimal control and corresponding trajectories are given in Fig. 5. State variables show almost the same variation trend as those in Case 1. However, the control variable shows extremely different behaviour from that in Case 1. In this case, the control is at a low level at the very beginning and keeps increasing until a certain point. After that, the control turns out to decrease then increase, as the same trend in former cases.

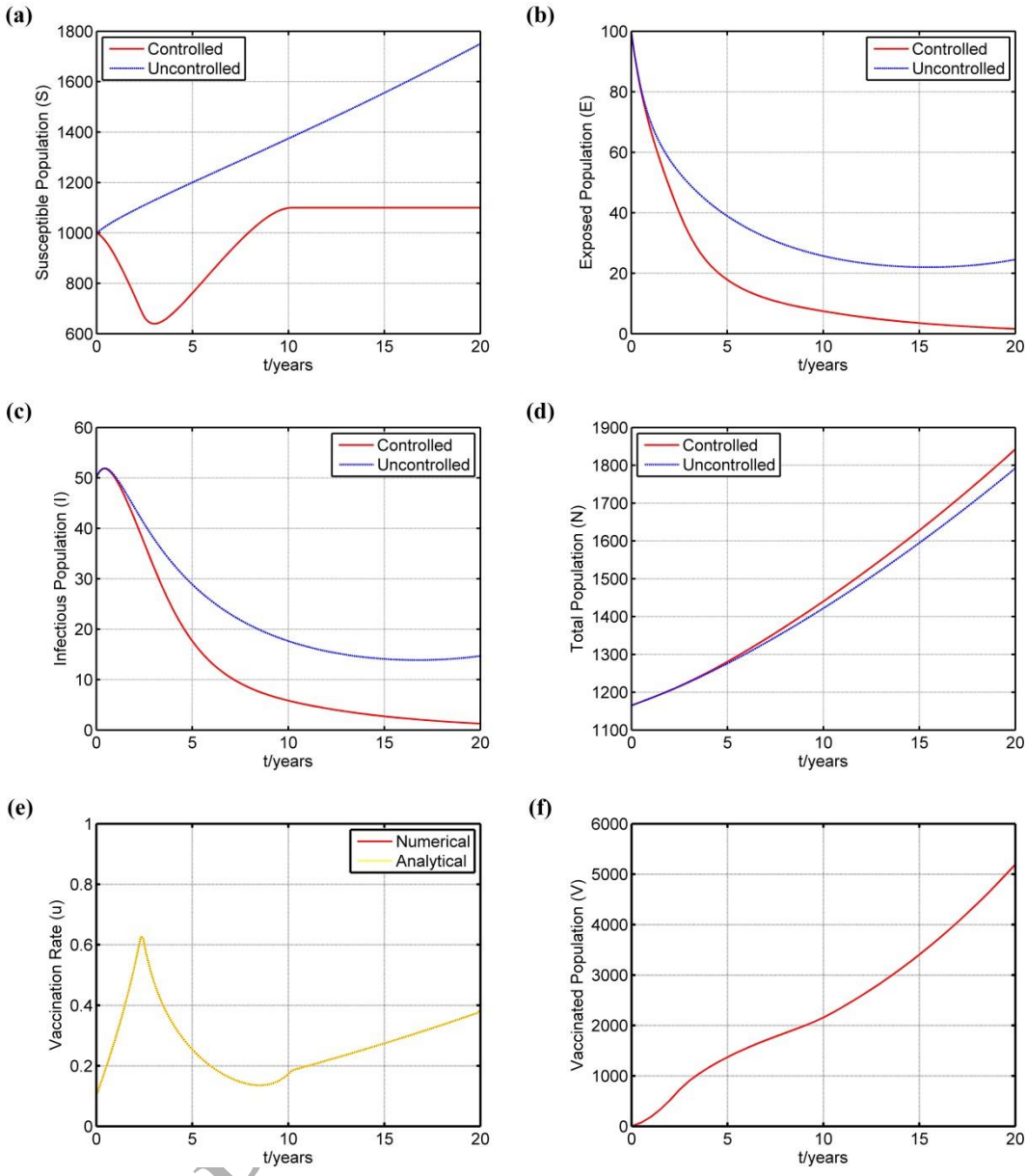

Fig. 5. Case 4: Optimal state trajectories, including (a) the susceptible population, (b) the exposed population, (c) the infectious population and (d) the total population. (e) Optimal vaccination rate. (f) Vaccinated population.

5.5 Case 5: time-varying factors in Case 2~ Case 4 are considered simultaneously

In this case, three time-varying factors involved in Case 2~ Case 4 are all taken into consideration simultaneously. Numerical solutions for sates variables and control variable are plotted in Fig. 6. Still, it is seen that the numerical solution for $u(t)$ is in accordance with the analytical expression given in Eq. (24).

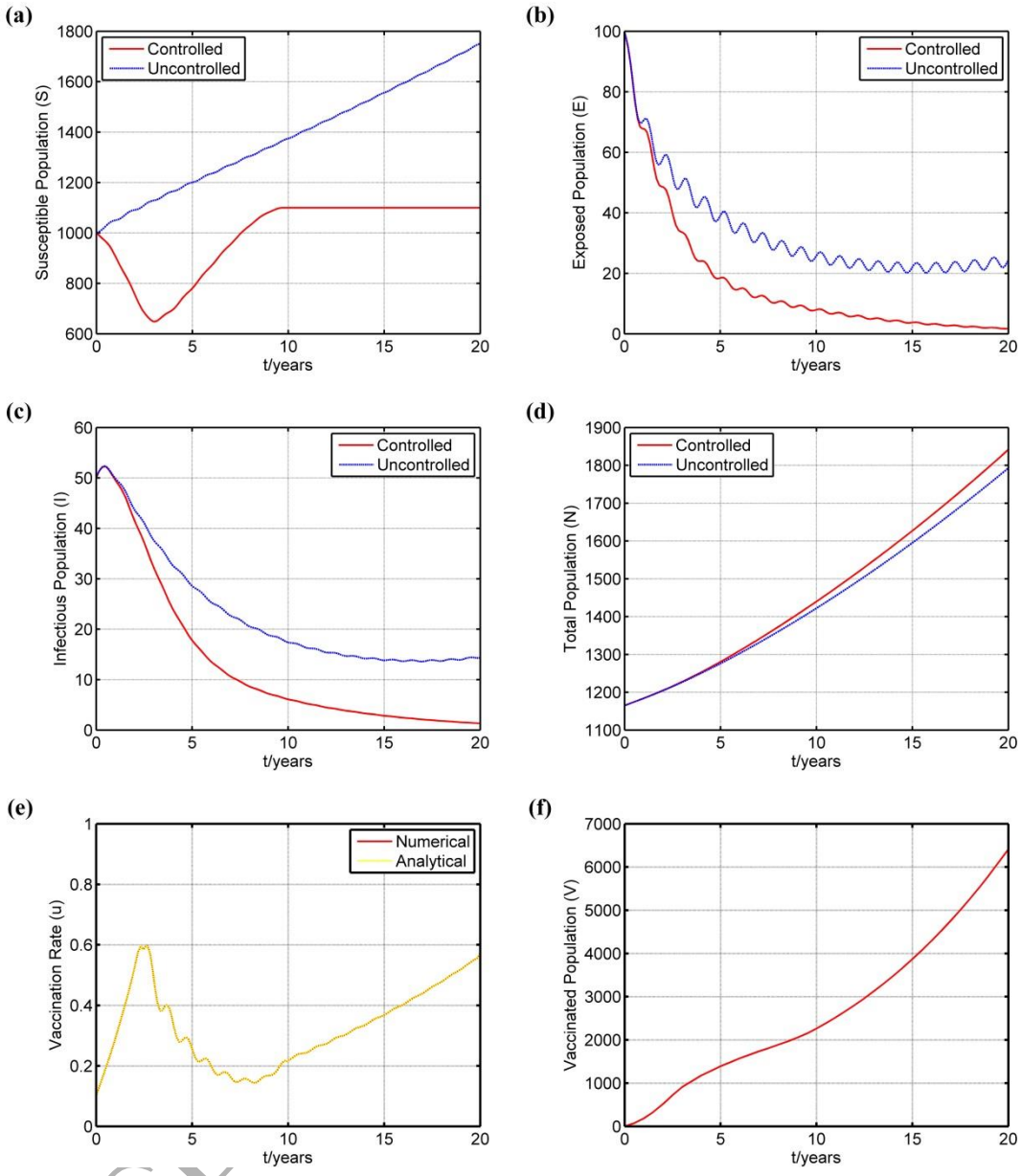

Fig. 6. Case 5: Optimal state trajectories, including (a) the susceptible population, (b) the exposed population, (c) the infectious population and (d) the total population. (e) Optimal vaccination rate. (f) Vaccinated population.

5.6 A brief comparison

The control variable and vaccinated population in each case are replotted in Fig. 7(a) and Fig. 7(b), respectively. Moreover, the terminal state values, terminal vaccinated population and the cost

functional in each case are summarized in Table 2. It is noted that uncontrolled data for Case 1, Case 3 and Case 4 are the same, while uncontrolled data for Case 2 and Case 5 are the same.

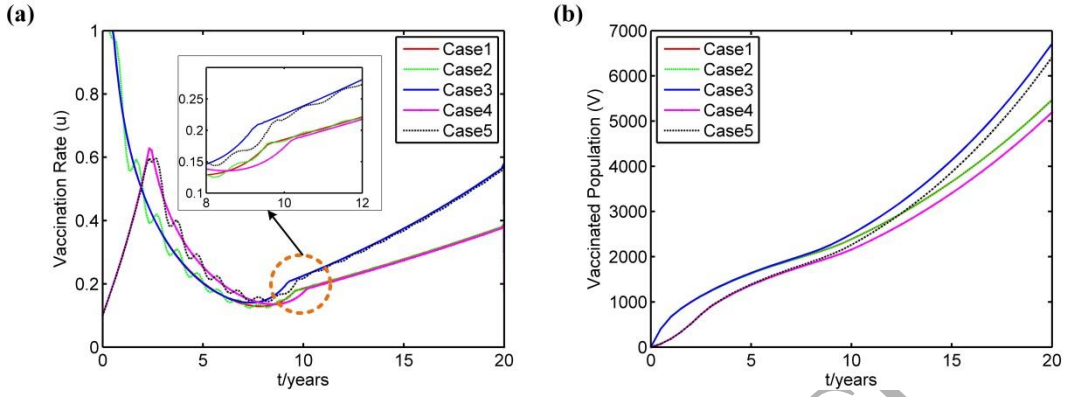

Fig. 7. (a) Control variable and (b) vaccinated population in five cases.

Table 2

Terminal state variables, terminal vaccinated population and cost functional in five cases.

Case No.		$S(t_f)$	$E(t_f)$	$I(t_f)$	$R(t_f)$	$N(t_f)$	$V(t_f)$	Cost functional
Uncontrolled	Case 1, 3 and 4	1750	24.53	14.69	2.86	1792	0	26.97
	Case 2 and 5	1751	24.50	14.35	2.83	1793	0	26.82
Controlled	Case 1	1100	1.45	1.12	748.73	1851	5465	15.86
	Case 2	1100	1.45	1.10	748.75	1851	5466	15.92
	Case 3	1100	1.52	1.17	747.86	1851	6709	16.73
	Case 4	1100	1.65	1.27	739.64	1843	5193	17.72
	Case 5	1100	1.74	1.32	738.62	1842	6411	18.60

When the seasonally varying incidence coefficient is introduced in Case 2, the solutions show oscillating behavior. However, the variation trends of control and state variables and vaccinated population are still in accordance with those in Case 1, to put it more precisely, the solutions in Case 2 oscillate around the solutions in Case 1 seasonally. The cost functional for this case is almost the same to that in Case 1.

In Case 3, it is seen that more individuals are vaccinated than that in Case 1. The control in Case 3 is under the same variation trend with that in Case 1, while there's a growing difference between two cases. This is because the successfully immune rate is monotonically decreasing in Case 3, comparing

to the constant successfully immune rate, more individuals are required to be vaccinated. Correspondingly, the cost functional of Case 3 is bigger than that of Case 1.

In first three cases, the control variable is always going down from 1 at the initial period. However, in Case 4, the control goes up from a low level at the initial period. This is because the vaccination supply is at low level at the very beginning, control has to be kept at a relatively low level to satisfy the constraint as shown in Eq. (11). After going to a certain point, the control begins to decrease and exhibit the similar variation trend to that in Case 1. In this case, more individuals are vaccinated and he cost functional is much bigger than that in the Case 1.

In above five cases, the vaccination rate is more or less different since various time-varying factors are introduced. This enlightens us that omitting the time-varying factors may result in less optimal even unreasonable vaccination strategy.

6. Conclusions

In this paper, the basic SEIR model is extended to a more general one considering time-varying factors. The time-varying factors considered are seasonally varying incidence coefficient, monotonic decreasing successfully immune rate and monotonic increasing vaccine supply. And the optimal vaccination strategy is solved under the frame of nonlinear constrained optimal control. First, the characterization of the vaccination rate is derived with the help of the Pontryagin's maximum principle. Then, the optimal control problem is solved by the symplectic pseudospectral method numerically and the numerical solutions are in good agreement with the analytical ones. Numerical simulations show the obtained vaccination strategy can control the spread of the epidemic efficiently. Moreover, the comparisons between different cases demonstrate time-varying factors could alter the optimal

vaccination strategy, implying that omitting the time-varying factors may result in less optimal even unreasonable vaccination strategy.

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