Journal of Biological Systems
Vol. 21, No. 4 (2013) 1340006 (20 pages)

DOI: 10.1142/S0218339013400068

World Scientific
www.worldscientific.com

OPTIMAL VACCINATION STRATEGIES FOR AN INFLUENZA EPIDEMIC MODEL

QINGWEN HU*
Department of Mathematical Sciences
University of Texas at Dallas
Richardson, TX, 75080, USA
qingwen@utdallas.edu

XINGFU ZOU
Department of Applied Mathematics
University of Western Ontario
London, Ontario, Canada N6A 5B7
xzou@uwo.ca

Received 12 February 2013
Accepted 12 October 2013
Published 20 January 2014

We present an optimal control model for influenza vaccination strategies in an open population. The model is based on an extended Kermack–McKendrick model with the vaccination rate being a measurable function. The objective of this optimal control model is to describe the vaccination strategies so that the total cost arising from vaccination and infections is minimized. We show that the optimal control is a non-singular bang-bang control which has a finite number of switchings. A scheme for the solution of the optimal control problem is formulated using the shooting method. We also carry out numerical simulations to illustrate the general results and to examine the effects of parameters on the optimal vaccination strategy. The simulations show that the ratio of the per capita treatment cost and per capita vaccination cost has a significant effect on the optimal strategy, while the vaccination rate of the newly recruited class turns out to have less effect.

Keywords: Influenza; Vaccination; Optimal Control; Bang-Bang Control; Carathéodory Equations.

1. Introduction

Influenza is an acute respiratory illness that transmits rapidly in seasonal epidemics and incurs human fatalities and monetary expenses. Historical influenza pandemics include the 1889–1890 Russian flu, 1918–1920 Spanish flu, 1957–1958 Asian flu and the 1968–1969 Hong Kong flu.[1] Even the relatively milder 1968–1969 Hong Kong flu killed more than 0.75 million people. Vaccination against influenza is often

*Corresponding author.

recommended for high-risk groups, such as children and the elderly, or for people that have asthma, diabetes or heart diseases. There has been no major pandemic since the 1968 Hong Kong Flu till the 2009 H1N1 influenza pandemic, while the 1977–1978 quasi-pandemic Russian Flu is not considered as a major pandemic. Immunity to previous pandemic influenza strains and vaccination may have limited the spread of the virus and may have helped prevent further pandemic.[1] However, annual influenza outbreaks still result in 250,000–500,000 deaths and the costs of direct and indirect losses caused by influenza are between $1 million and $6 million per 100,000 inhabitants yearly in industrialized countries.[2]

Vaccination has been an important strategy in the control of influenza epidemiology. It is well known that the cost of vaccination is much lower than the cost resulting from infections which may include treatment cost and other indirect losses due to infections. Due to this, vaccination has been an active research topic for several diseases. See, for example, Refs. 1–10 and the references therein.

Optimal control theory has been applied to investigating optimal vaccination strategies since the early 1970s. For example, Hethcote and Waltman[11] considered a Kermack–McKendrick model (KM model) with a general cost functional subject to state constraints, where a dynamic programming technique was employed to construct discretized optimal vaccination schedules. A more complicated model based on the KM model for optimal control of an epidemic, which incorporates distributed latent and incubation periods, was considered by Gupta and Rink.[12] Morton and Wickwire[13] proposed a control model based on the KM model for optimal immunization scheme and obtained an optimal bang-bang control by applying dynamic programming and the Pontaryagin's maximum principle. Di Blasio[14] obtained a synthesis of optimal vaccination for a KM model with quadratic integrand for the objective functional. More recent work can be found, for example, in the references.[15–24]

As remarked in Ref. 17, a simple extension of the KM model by incorporating demographic structure in the host population presents a challenge for the optimal vaccination. Moreover, it is well known that when considering an optimal control problem, the control is typically only assumed to be *measurable* (instead of continuous) function; yet many techniques for epidemic models given by ordinary differential equations require *continuity* for the right-hand sides of such models. As an attempt to overcome the difficulties caused by incorporating demographic structure and by allowing discontinuous control (vaccination strategy), we consider in this paper a simple extended KM model with vaccination on both new recruitments and susceptibles. The objective of the optimal control model is to find an optimal vaccination strategy so that the total costs arising from vaccination infections are minimized.

The rest of this paper is organized as follow. In Sec. 2, we propose an optimal control model where the dynamics of influenza are governed by an extended

KM model with the vaccination policy being a measurable function. We establish the positivity of solutions to this extended KM model in Sec. 3. In Sec. 4, we prove the existence of the optimal control in the space of Lebesgue measurable functions using Filoppov's existence theorem for Lagrange type problems, and describe the characteristics of the optimal vaccination using Pontaryagin's maximal principle. In this section, we also develop a scheme for solving the optimal control. We carry out some numerical simulations in Sec. 5 to illustrate the general results, by which we also explore the sensitivity of the parameters. We conclude the paper in Sec. 6, where we summarize the main results and draw some conclusions.

2. Optimal Control Model for Vaccination Strategies

To this end, we need a basic disease model to describe the dynamics of influenza disease. Influenza disease is caused by virus, as such, we assume all recovered individuals have immunity to the same strain of influenza during the epidemic. As such, SIR or SEIR (if latency is not neglected) models are suitable choices. There have been many such models, but we adopt the strategy of "starting with simple" in our first attempt, by choosing the following classic SIR model:

$$\begin{cases} \dot{S} = k - \mu S - \beta IS, \\ \dot{I} = \beta IS - (\mu + d + r)I, \\ \dot{R} = rI - \mu R. \end{cases} \tag{2.1}$$

Here S, I and R are sub-populations: susceptible, infective and recovered classes, and all parameters are positive constants where k being the recruitment rate (new recruits may include, e.g., new borns and new immigrants), μ is the natural death rate, d is the disease caused death rate, r is the recovery rate and β is the infection rate. Noting that S and I are actually decoupled from R, one only needs to consider the system consisting of the S and I variables:

$$\begin{cases} \dot{S} = k - \mu S - \beta IS, \\ \dot{I} = \beta IS - (\mu + d + r)I. \end{cases} \tag{2.2}$$

For this model, the disease dynamics is fully determined by the basic reproduction number

$$\mathcal{R}_0 = \frac{\beta}{\mu + d + r} \cdot \frac{k}{\mu}, \tag{2.3}$$

in the sense that if $\mathcal{R}_0 < 1$ then the disease will die out; if $\mathcal{R}_0 > 1$ the disease will persist with all positive solutions of (2.2) tending to a unique endemic equilibrium.

When a vaccine is offered to the newly recruited and susceptible individuals at proportions p and u respectively, with $p, u \in [0, 1]$, the model (2.2) is modified to

the following

$$\begin{cases} \dot{S} = k(1-p) - (\mu+u)S - \beta IS, \\ \dot{I} = \beta IS - (\mu+d+r)I, \\ \dot{V} = pk + uS - \mu V, \\ \dot{R} = rI - \mu R. \end{cases} \tag{2.4}$$

Again, the S and I equations are decoupled from the V and R equations, so one only needs to consider the decoupled subsystem:

$$\begin{cases} \dot{S} = k(1-p) - (\mu+u)S - \beta IS, \\ \dot{I} = \beta IS - (\mu+d+r)I. \end{cases} \tag{2.5}$$

If both p and u are constants, this model has the basic reproduction number

$$\mathcal{R}_0^v = \frac{\beta}{\mu+d+r} \cdot \frac{(1-p)k}{\mu+u}, \tag{2.6}$$

and the model has the global threshold dynamics characterized by $\mathcal{R}_0^v$: if $\mathcal{R}_0^v < 1$, then the disease will die out; if $\mathcal{R}_0^v > 1$, the disease will persist with all positive solutions converging to a unique endemic equilibrium. From the formula for $\mathcal{R}_0^v$, it is seen that increasing p or u or both may bring $\mathcal{R}_0^v$ down to a level less than 1, helping eventually eliminate the disease. Indeed, setting $\mathcal{R}_0^v < 1$ and solving this inequality for p or u will give a minimal vaccination rate for newly recruited or susceptible sub-population required to eliminate the disease.

The above are results concerning the long term (asymptotical) disease dynamics. Two issues arise: (i) maintaining constant vaccination rates is in general impractical; (ii) cost is ignored. We now address these two issues by formulating the corresponding model into an optimal control problem. To avoid making the problem too complicated, we keep one of the two vaccination rate to be a constant and allow the other to be time dependent. To be more precise, we assume that the vaccination rate p for new recruits is a constant and let the vaccination rate u for susceptibles be time dependent, taking from the so-called admissible control set

$$\mathcal{U} := \{u \,|\, \text{the map } u : [0,T] \ni t \to u(t) \in [0,q] \text{ is Lebesgue measurable}\}, \tag{2.7}$$

where $T > 0$ is a fixed final time and $q \in [0,1]$ is the maximal vaccination rate.

Let c_q be the cost of vaccinating a susceptible individual and c_σ be the cost of treating an infectious individual. In general, c_σ is much larger than c_q, so $\alpha := c_\sigma/c_q$ is usually very large. With these cost parameters, we introduce the following objective functional

$$\begin{aligned} J_0(u) &= \int_0^T c_q u(t)S(t)dt + \int_0^T (c_\sigma \beta S(t)I(t) + kpc_q)dt \\ &= \int_0^T c_q u(t)S(t)dt + \int_0^T \alpha c_q \beta S(t)I(t)dt + kpc_q T. \end{aligned} \tag{2.8}$$

Here, the first and the third terms on the right side account for the costs for vaccinating the susceptible individuals and new recruits respectively, and the second term reflects the cost for treating the infected individuals. Since we have assumed that $k > 0$ and $p > 0$ are constants, we can indeed drop the last term as well as the parameter c_q in (2.8) and seek control $u(t)$ that minimizes the following new objective functional

$$J(u) = \int_0^T u(t)S(t)dt + \int_0^T \alpha\beta S(t)I(t)dt. \tag{2.9}$$

The above preparation then leads to the following optimal control problem with state constraints:

$$\min_{u\in\mathcal{U}} J(u) = \int_0^T u(t)S(t)dt + \int_0^T \alpha\beta S(t)I(t)dt \tag{2.10}$$

subject to

$$\begin{cases} \dot{S} = k(1-p) - (\mu+u)S - \beta IS, \\ \dot{I} = \beta IS - (\mu+d+r)I, \\ u \in \mathcal{U}, \quad (S(0), I(0)) = (S_0, I_0) \in (0,+\infty)\times(0,+\infty). \end{cases} \tag{2.11}$$

To proceed further, we need to show that the constraint equations in (2.11) will yield positive states $S(t)$ and $I(t)$ for $t \geq 0$, and we do this in the next section.

3. Positivity of Solution of (2.11)

We first explore some basic properties of solutions to (2.11), including existence, uniqueness and positivity of the state variables $S(t)$ and $I(t)$ for $t \geq 0$. To this end, we put $T = +\infty$ in this section. Note that the control u is only a measurable function and is not assumed to be continuous. Therefore, system (2.11) is a set of Carathéodory equations[25] with the right-hand side possibly being discontinuous with respect to the time variable t. Thus, we need to appeal to some results on the initial value problem (IVP) for a Carathéodory equation

$$\begin{cases} \dot{x} = F(t,x), \quad (t,x) \in D \subset \mathbb{R}\times\mathbb{R}^n, \\ x(t_0) = x_0, \end{cases} \tag{3.1}$$

where D is an open set and the function $F(t,x) : \mathbb{R}\times\mathbb{R}^n \to \mathbb{R}$ satisfies the following Carathéodory conditions in the domain D of the (t,x)-space:

(A1) the function $F(t,x)$ is continuous in x for almost all t;
(A2) the function $F(t,x)$ is measurable in t for every x;
(A3) there exists an integrable function $m(t)$ so that $|F(t,x)| \leq m(t)$.

The following lemmas are standard results on existence, uniqueness and continuation of solutions to an initial value problem for a Carathéodory equation, see, e.g., Ref. 26.

Lemma 3.1. *Assume that* $(t_0, x_0) \in D$ *and* $F(t, x)$ *satisfies* (A1)–(A3) *for* $t_0 \le t \le t_0 + a$, $|x - x_0| \le b$. *Then on a closed interval* $[t_0, t_0 + d]$, *where* $d > 0$, *there exists a solution to IVP* (3.1).

Lemma 3.2. *Let* $(t_0, x_0) \in D$. *Assume that* $F(t, x)$ *satisfies* (A1)–(A3) *and there exists a summable function* $l(t)$ *such that*

$$(F(t, x) - F(t, y)) \cdot (x - y) \le l(t)|x - y|^2 \tag{3.2}$$

for every $(t, x), (t, y) \in D$. *Then there exists a unique solution to the IVP* (3.1).

Lemma 3.3. *Let the conditions in Lemma* 3.2 *be satisfied. Then the solution to* (3.1) *can be extended to the boundary of* D.

Making use of the above lemmas, we can obtain the following theorem for (2.11), the proof of which is given in the Appendix.

Theorem 3.1. *Let* $(S_0, I_0) \in (0, +\infty) \times (0, +\infty)$. *Then there exists a unique solution* $(S, I) : \mathbb{R} \ni t \to (S(t), I(t)) \in \mathbb{R}^2$ *for system* (2.11) *with* $(S(t), I(t)) \in (0, +\infty) \times (0, +\infty)$ *for all* $t \ge 0$.

4. Optimal Vaccination Strategies

Let $(S_0, I_0) \in (0, \infty) \times (0, \infty)$ be fixed. By Theorem 3.1, we know that for every $u \in \mathcal{U}$, (2.11) has a uniques solution $(S(t), I(t))$ for all $t > 0$, satisfying $(S(t), I(t)) \in (0, +\infty) \times (0, +\infty)$ for all $t \in [0, +\infty)$. We call $(u(t), S(t), I(t))$ an admissible triple for the objective functional J defined by (2.10). Let Ω be the set of all admissible triples. Obviously Theorem 3.1 shows that Ω is not empty. We now fix $T > 0$, and consider the optimal control problem (2.10) and (2.11), that is, seeking the minimal of J in the admissible set Ω. To this end, and for reader's convenience, we first recall some theoretical results from optimal control theory (see, e.g., Ref. 25).

Let A be a subset of the $t - x$ space $\mathbb{R}^{n+1}$, and $A(t)$ be the projection of A on the x space at t, that is $A(t) = \{x \in \mathbb{R}^n : (t, x) \in A\}$. Let B be a given subset in the $(t_1 - x_1) - (t_2 - x_2)$ space $\mathbb{R}^{n+1} \times \mathbb{R}^{n+1}$. For every $(t, x) \in A$, let $U(t, x)$ be a given subset of the u-space $\mathbb{R}^m$ and $M \subset \mathbb{R}^{1+n+m}$ be the set of all (t, x, u) with $(t, x) \in A$. Let $\tilde{Q}(t, x) \subset \mathbb{R}^{n+1}$ be the set of all (z^0, z) with $z^0 \ge f_0(t, x, u)$, $z = f(t, x, u)$ for some $u \in U(t, x)$, where $f_0(t, x, u)$ and $f(t, x, u)$ are functions for the following optimal control problem of Lagrange type:

$$\begin{aligned} &\text{Minimize } J(x, u) = g(t_1, x_1, t_2, x_2) + \int_{t_1}^{t_2} f_0(t, x(t), u(t))dt \\ &\begin{cases} \dot{x}(t) = f(t, x, u), t \in [t_1, t_2] \text{ a.e.}, \\ (t, x(t)) \in A, u(t) \in U(t, x(t)), (t_1, x(t_1), t_2, x(t_2)) \in B, \end{cases} \end{aligned} \tag{4.1}$$

where $x(t) \in \mathbb{R}^n, u(t) \in \mathbb{R}^m$, x is absolutely continuous, u is measurable in $[t_1, t_2]$ and $f_0(\cdot, x(\cdot), u(\cdot))$ is Lebesgue-integrable in $[t_1, t_2]$ and $g(t_1, x_1, t_2, x_2)$ is lower semicontinuous in B.

We now introduce the Filippov's Existence Theorem for the Lagrange problem (4.1) (see Ref. 25, p. 314).

Theorem 4.1. *Let A and M be compact, B closed, and g lower semicontinuous on B. Assume that $f_0(t, x, u)$ and $f(t, x, u)$ are continuous on M. If for almost all t the sets $\tilde{Q}(t, x)$ with $x \in A(t)$ are convex, then the functional $J(x, u)$ given by* (4.1) *has an absolute minimum in the nonempty class Ω of all admissible pairs $(x(t), u(t))$.*

4.1. *Existence of optimal bang-bang control*

By employing the above result to (2.10) and (2.11), we can obtain the existence of optimal control for this problem, the proof of which is given in the Appendix.

Theorem 4.2. *There exists a solution to the optimal control problem* (2.10) *and* (2.11).

To further characterize the optimal control, we need the following definition.

Definition 4.1. We call $u \in \mathcal{U}$ a bang-bang control if it only assumes its boundary values. We call $t^* \in (0, T)$ a switching time of the bang-bang control $u \in \mathcal{U}$ if $\lim_{t \to t^*} u(t)$ does not exist.

It turns out that the optimal control for (2.10) and (2.11) is such a control:

Theorem 4.3. *The optimal control of* (2.10) *and* (2.11) *is a bang-bang control.*

The proof of this theorem is given in the Appendix.

4.2. *Switching times of bang-bang control*

For a bang-bang control, determining the switching times is obviously of both theoretical and practical importance. Unfortunately, for most such controls, switching times cannot be explicitly obtained, and numeric computations are naturally second choice. As such, computational methods for switching times of a bang-bang control have been widely discussed in the literature, see, for instance, Refs. 27–29.

In many existing works, the number of switching times is typically *assumed* to be finite in the calculations. However, *a priori* information on the finiteness or the number of switching times is essential for implementing a bang-bang control. In this direction, Sussmann[30] obtained an upper bound for the number of switching times for a time-optimal control problem. Wickwire[31,32] and Behncke[17] developed some techniques to obtain the uniqueness of the switching time for their models. However, the aforementioned techniques do not seem to be applicable (at least, directly) to the model in the current paper. In the following, we shall prove that

there is, indeed, only a finite number of switchings for the optimal bang-bang control for (2.10) and (2.11). To this end, we first derive the condition that governs the switching times.

Theorem 4.4. *The optimal bang-bang control u^* of* (2.10) *and* (2.11) *satisfies*

$$u^*(t) = \begin{cases} 0 & \text{if } \lambda_1(t) < 1, \\ q & \text{if } \lambda_1(t) > 1, \end{cases} \tag{4.2}$$

where (λ_1, λ_2) satisfies the adjoint Eqs. (A.2)*.*

The detailed derivation (proof) is given in the Appendix.

The following theorem confirms that there are only finite many switching times for the optimal (bang-bang) control for (2.10) and (2.11).

Theorem 4.5. *If $\alpha > 1$ and $I_0 > 0$, then the optimal control u^* of* (2.10) *and* (2.11) *has a finite number of switchings.*

The proof is given in the Appendix.

4.3. *A shooting method for the optimal control problem*

The optimal bang-bang control for (2.10) and (2.11) confirmed above cannot be obtained explicitly. From the results in Sec. 4 (i.e., Theorems 4.3 and 4.4), we know that solving (2.10) and (2.11) is equivalent to determining the switching times of the bang-bang control. In this section, we develop a scheme for this purpose, by using the idea of shooting proposed in Ref. 27.

Combining the state system (2.11) with the adjoint system (A.2) and the transversality condition (A.10), we have the following system

$$\begin{cases} \dot{S} = k(1-p) - (\mu + u)S - \beta IS, \\ \dot{I} = \beta IS - (\mu + d + r)I, \\ \dot{\lambda}_1 = -u - \alpha\beta I + \lambda_1(\mu + u + \beta I) - \lambda_2\beta I, \\ \dot{\lambda}_2 = -\alpha\beta S + \lambda_1\beta S - \lambda_2(\beta S - \mu - d - r), \\ (S(0), I(0)) = (S_0,\, I_0) \in (0,\, \infty) \times (0,\, \infty), \\ (\lambda_1(T),\, \lambda_2(T)) = (0, 0), \\ u^*(t) = \begin{cases} 0 & \text{if } \lambda_1(t) < 1, \\ q & \text{if } \lambda_1(t) > 1. \end{cases} \end{cases} \tag{4.3}$$

We need to find a set of switching times of u^* so that the optimality system (4.3) is solved. We note that the optimality system (4.3) is not a standard initial value problem for $(S, I, \lambda_1, \lambda_2)$ since only the initial values for (S, I) are given, while for (λ_1, λ_2) it is the terminal values that are prescribed.

Note that $\lambda_1(T) = 0 < 1$. We conclude from Theorem 4.4 and the absolute continuity of λ_1 that $u^*(t) = 0$ for $t \in (t_f, T)$, where t_f is the last switching time of $u^*(t)$. This suggests that we can solve (4.3) *backward*. To this end, let $\tilde{u}(t) = u(T-t)$, $\tilde{S}(t) = S(T-t)$, $\tilde{I}(t) = I(T-t)$, $\tilde{\lambda}_1(t) = \lambda_1(T-t)$ and $\tilde{\lambda}_2(t) = \lambda_2(T-t)$ for all $t \in [0, T]$. Then the optimality system (4.3) is transformed to

$$\begin{cases} \dot{\tilde{S}} = -[k(1-p) - (\mu + \tilde{u})\tilde{S} - \beta\tilde{I}\tilde{S}], \\ \dot{\tilde{I}} = -[\beta\tilde{I}\tilde{S} - (\mu + d + r)\tilde{I}], \\ \dot{\tilde{\lambda}}_1 = \tilde{u} + \alpha\beta\tilde{I} - \tilde{\lambda}_1(\mu + \tilde{u} + \beta\tilde{I}) + \tilde{\lambda}_2\beta\tilde{I}, \\ \dot{\tilde{\lambda}}_2 = \alpha\beta\tilde{S} - \tilde{\lambda}_1\beta\tilde{S} + \tilde{\lambda}_2(\beta\tilde{S} - \mu - d - r), \\ (\tilde{S}(T), \tilde{I}(T)) = (S_0, I_0) \in (0,\infty) \times (0,\infty), \\ (\tilde{\lambda}_1(0), \tilde{\lambda}_2(0)) = (0,0), \\ \tilde{u}^*(t) = \begin{cases} 0 & \text{if } \tilde{\lambda}_1(t) < 1, \\ q & \text{if } \tilde{\lambda}_1(t) > 1. \end{cases} \end{cases} \tag{4.4}$$

Using the shooting method proposed in Ref. 27, for given $(a, b) \in (0,\infty) \times (0,\infty)$, we can solve the following initial value problem (4.5) without the terminal condition for $(\tilde{S}(t), \tilde{I}(t))$:

$$\begin{cases} \dot{\tilde{S}} = -[k(1-p) - (\mu + \tilde{u})\tilde{S} - \beta\tilde{I}\tilde{S}], \\ \dot{\tilde{I}} = -[\beta\tilde{I}\tilde{S} - (\mu + d + r)\tilde{I}], \\ \dot{\tilde{\lambda}}_1 = \tilde{u} + \alpha\beta\tilde{I} - \tilde{\lambda}_1(\mu + \tilde{u} + \beta\tilde{I}) + \tilde{\lambda}_2\beta\tilde{I}, \\ \dot{\tilde{\lambda}}_2 = \alpha\beta\tilde{S} - \tilde{\lambda}_1\beta\tilde{S} + \tilde{\lambda}_2(\beta\tilde{S} - \mu - d - r), \\ (\tilde{S}(0), \tilde{I}(0)) = (a, b) \in (0,\infty) \times (0,\infty), \\ (\tilde{\lambda}_1(0), \tilde{\lambda}_2(0)) = (0,0), \\ \tilde{u}^*(t) = \begin{cases} 0 & \text{if } \tilde{\lambda}_1(t) < 1, \\ q & \text{if } \tilde{\lambda}_2(t) > 1. \end{cases} \end{cases} \tag{4.5}$$

The terminal value $(\tilde{S}_T, \tilde{I}_T)$ of $(\tilde{S}(t), \tilde{I}(t))$ for the initial value problem (4.5) will be implicitly dependent on (a, b). Let $G(a, b) = (\tilde{S}_T, \tilde{I}_T) - (S_0, I_0)$. Then, solving (4.4) is reduced to solving

$$G(a, b) = 0. \tag{4.6}$$

We point out that in general it is difficult, if not impossible, to find an explicit expression for $G(a, b)$, and hence, numerical solutions are naturally sought. In the next section, we will present some results of numerical solutions based on this shooting method.

5. Numerical Results

In this section, we present some numerical results on the solutions of the optimality system (4.4) by using the scheme proposed in Sec. 4.3 based on the shooting method. We are also interested in the impact of the key parameters α (ratio of infection loss and vaccination cost), β (transmission rate), p (vaccination rate for new recruits) and r (recovery rate), so we will present our numerical results for different set of values for these parameters. We prescribe our relative error for implementing the shooting method for (4.6) to be $\mathcal{O}(10^{-8})$. Since the focus here is to illustrate the scheme developed in the preceding section, we do not endeavour to obtain the parameter values from clinic data, to which it is generally not easy to have access. As such, we will take liberty to choose these parameter values to show the feasibility of the scheme. Once the data for a particular flu strain is available, the numerical computation of the switching times for the optimal control can be similarly done.

5.1. *Effect of the ratio of infection losses and the vaccination cost*

We note that the ratio parameter α only appears in the objective function of the optimal control problem (2.10) and (2.11), while other parameters are included in

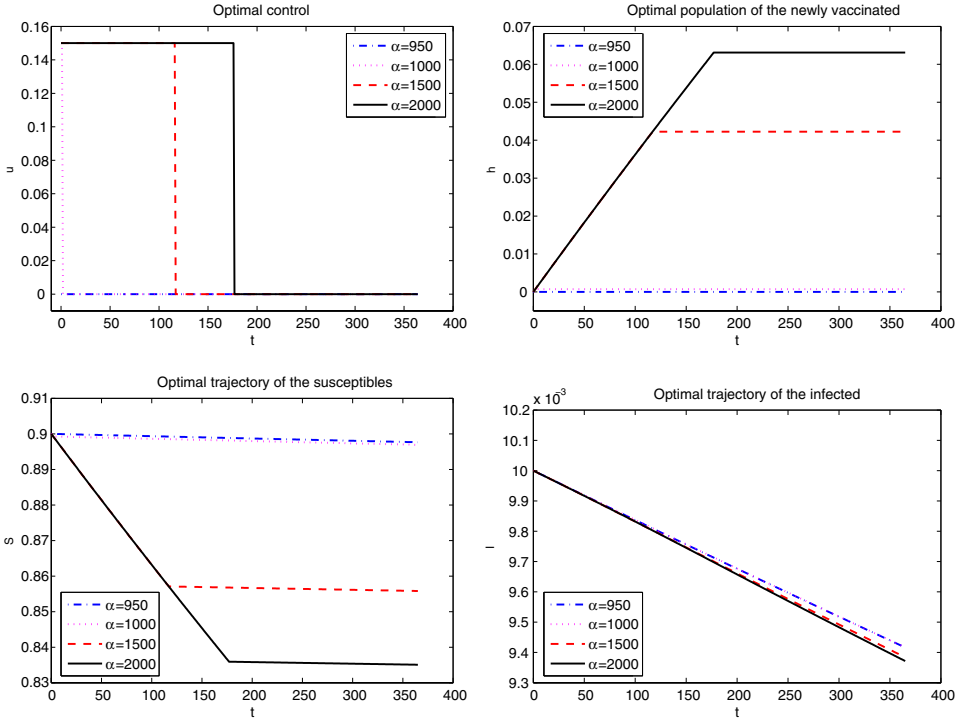

Fig. 1. Numerical results of (4.5) and (4.6) when $S_0 = 0.9$, $I_0 = 0.01$, $\beta = 0.1$, $\mu = 0.01$, $d = 0.04$, $k = 0.015$, $p = 0.5$, $q = 0.15$, $r = 0.1$, and $T = 365$.

the state equations. To explore the effect of α, we fix other parameters $\beta = 0.1, \mu = 0.01, d = 0.04, k = 0.015, p = 0.5, q = 0.15, r = 0.1$. The initial values for S and I are chosen to be $S_0 = 0.9, I_0 = 0.01$ and the $T = 365$.

Figure 1 presents the numerical results for four values of $\alpha \in \{950, 1000, 1500, 2000\}$. For $\alpha \leq 900$, numerical simulations show that the optimal control is identical to zero, which means that no vaccination is needed. If α is large enough, e.g., larger than 950 (see Fig. 1), then there exists a single switching time for the optimal bang-bang control, which indicates that vaccination is needed at the beginning of influenza epidemic. The larger the magnitude of α, the longer the vaccination period and the larger the total vaccinated population given by $h(t) = \int_0^t u(\xi)S(\xi)d\xi$.

5.2. *Effect of the transmission rate on the optimal control*

We are also interested in determining how the transmission rate β affects the optimal vaccination strategies. To this end, we fix $\alpha = 1000$, $\mu = 0.01$, $d = 0.04$, $p = 0.5$, $q = 0.15$, $r = 0.1$, $T = 365$, and let $S_0 = 0.9$, $I_0 = 0.01$. The

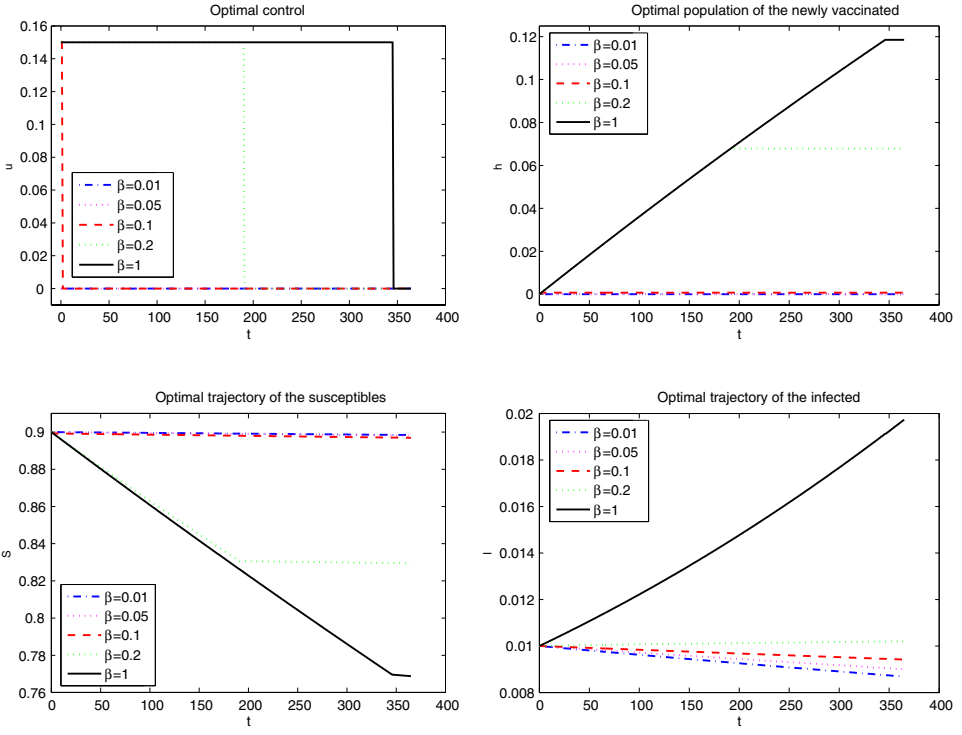

Fig. 2. Numerical results of (4.5) and (4.6) when $S_0 = 0.9$, $I_0 = 0.01$, $\alpha = 1000$, $\mu = 0.01$, $d = 0.04$, $p = 0.5$, $q = 0.15$, $r = 0.1$, $T = 365$.

numerical results for system (4.5) and (4.6) are presented in Fig. 2 for five values of $\beta \in \{0.01, 0.05, 0.1, 0.5, 1\}$.

We can see from the numerical simulations that when the transmission rate is very small (e.g., $\beta \leq 0.01$), the optimal control u^* is identical to zero on $[0, T]$, meaning that no vaccination is needed from the view point of the optimal control; while on the other extreme side, that is, when β is close to 1, vaccination is needed for most of the time. It is also seen that when the vaccination is needed, there exists one switching time for the optimal control. Moreover, when β is close to 1, the populations of vaccinated, susceptible and infected individuals change rapidly in time, in contrast to the case when β is close to 0.01.

5.3. *Effect of vaccination rate p for new recruits on the optimal control*

To see the influence of the vaccination fraction p, we fix $\alpha = 1000, \beta = 0.1, \mu = 0.01, d = 0.04, k = 0.015, q = 0.15, r = 0.1$, $T = 65$ and let $S(0) = 0.9, I(0) = 0.01$.

The numerical simulations are presented in Fig. 3 for (4.5) and (4.6) for $p \in \{0, 0.01, 0.1, 0.5, 1\}$, which seem to suggest that the optimal control, optimal trajectories and the infected populations are not that sensitive to p, in contrast to

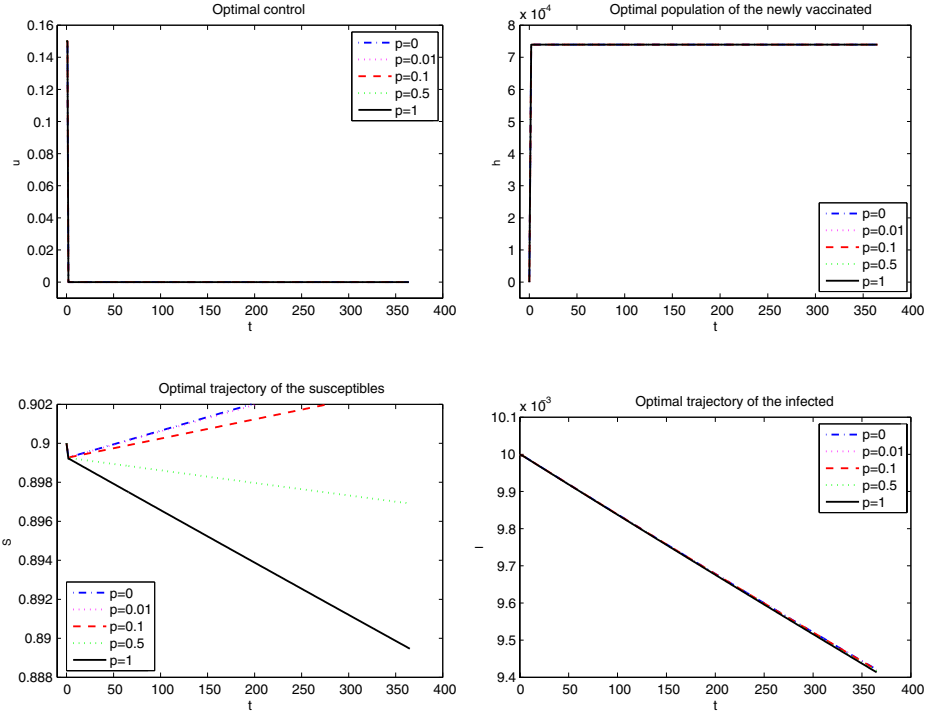

Fig. 3. Numerical results of (4.5) and (4.6) with $S_0 = 0.9$, $I_0 = 0.01$, $\alpha = 1000$, $\beta = 0.1$, $\mu = 0.01$, $d = 0.04$, $k = 0.015$, $q = 0.15$, $r = 0.1$, $T = 365$.

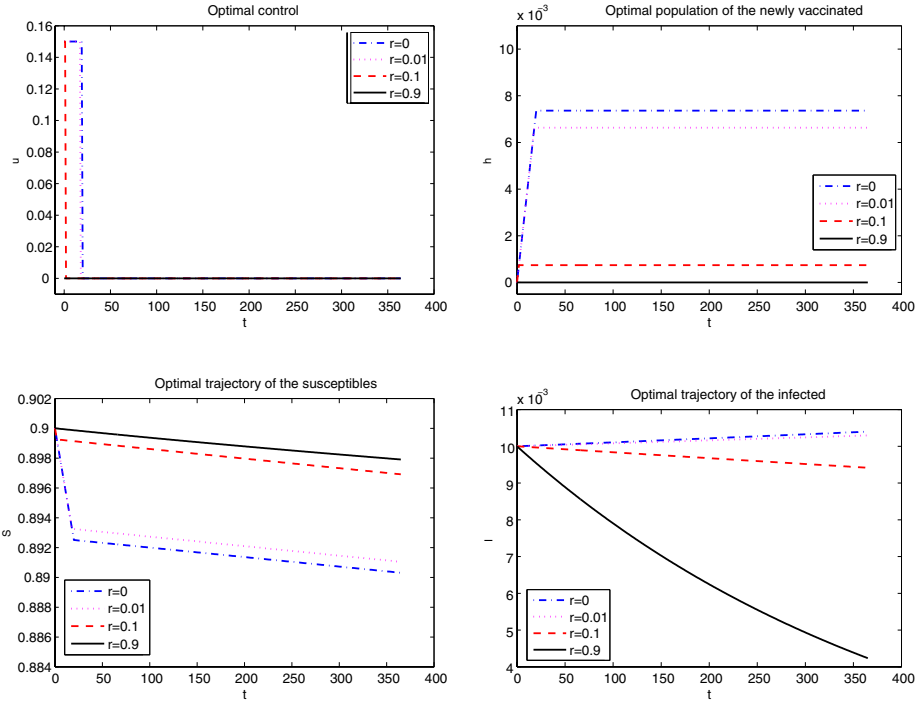

Fig. 4. Numerical results of (4.5) and (4.6) with $S_0 = 0.9$, $I_0 = 0.01$, $\alpha = 1000$, $\beta = 0.1$, $\mu = 0.01$, $d = 0.04$, $k = 0.015$, $p = 0.5$, $q = 0.15$, $T = 365$.

the impact of α and β. This is biologically understandable since both $k(1-p)$ and kp are very small, and hence, the contribution of new recruits is very small.

5.4. *Effect of the recovery rate r*

Figure 4 are results of numerical simulations of (4.5) and (4.6), where the parameters $\alpha = 1000, \beta = 0.1, \mu = 0.01, d = 0.04, k = 0.015, p = 0.5, q = 0.15, T = 365$ and the initial values $S_0 = 0.9, I_0 = 0.01$ are fixed, and the recovery rate r is given four different values: $r \in \{0, 0.01, 0.1, 0.9\}$ to show the effects of the recovery rate r. It is clear from Fig. 4 that the larger the recovery rate is, the shorter the duration of the optimal vaccination time interval will be. In particular, when r is close to 1, the density of the infected population drops rapidly with respect to time t. Even though we are considering vaccination strategies from the view point of optimal control, it is still imaginable that efficient treatment, which would enhance recovery, can also contribute significantly to the control of the disease.

6. Conclusion

In order to model the optimal vaccination strategies during an influenza epidemic, we have proposed in this paper an optimal control model (2.10) and (2.11) where the

objective functional and the state equations are linear with respect to the scalar vaccination rates. We have addressed the well-posedness of the optimal control model, and have proved the existence of the optimal bang-bang control and have derived the characteristics of the bang-bang control including the finiteness of the switching times. Based on a shooting technique, we have formulated a scheme for solving the optimal control problem. We have also provided some numerical results by implementing the scheme, which reveal, in various ways, the impact of some key parameters.

Notice that in our numerical simulations for our model under the given parameter values, only one switching has been observed. According to Theorem 4.4, the uniqueness of switching point is due to the fact that the co-state variable λ_1 is not oscillatory around 1 in a given time period. In a general situation, even finding an upper bound of the switching times of an optimal bang-bang control is very challenging, let alone finding exact times of switching.

The existence of a switching point in our numerical simulations depends sensitively on the magnitude of the transmission rate β, as well as the ratio α of infection losses and the vaccination costs. As is seen in Secs. 5.1 and 5.2, when α or β is sufficiently small, the optimal control is identical to zero; when α or β is sufficiently large, the optimal control has a switching point and vaccination is needed most of the time. The influenza vaccination rate p for new recruits turns out to have less impact on the optimal control than α and β do. Our results also show that if vaccination is needed, it should be applied *as early as possible*, *to the maximal capacity*, as can be seen from the numerical results. Such a conclusion is also obtained in Ref. 17 for some models.

We point out that the solutions of the optimality system (4.3) are sensitive to the initial guesses when shooting method is applied. In this paper, the relative error for shooting method is $\mathcal{O}(10^{-8})$ which is achieved through a basic search method. For more advanced high precision computations of optimality systems, a reader is referred to, e.g., Refs. 28 and 29.

We end this section by pointing out that in this paper we only choose a simple SIR model to start with. There have been many SIR models developed in the literature, with emphasis on various aspects of the disease. For example, some considered more realistic demographic terms, some incorporated other infection mechanism rather than the mass action. There are models containing latent sub-populations and there are also models with relapse sub-populations. Starting from any of these existing models, one can incorporate vaccinations (and possibly treatment) and explore the optimal vaccination strategy in a similar way to this paper. It is in this sense that this paper provides a general frame work for a class of optimal vaccination problems; particularly the shooting method in deriving the scheme for computing the switching times of the optimal control should also be feasible for optimal vaccination problems built on other SIR models.

Acknowledgments

The authors would like to thank the two anonymous reviewers and the handling editors for their comments and suggestions which have helped us improve the paper. Research was partially supported by Mathematics for Information Technology and Complex Systems (MITACS), and by Natural Sciences and Engineering Research Council of Canada (NSERC).

References

1. Hilleman MR, Realities and enigmas of human viral influenza: Pathogenesis, epidemiology and control, *Vaccine* **20**:3068–3087, 2002.
2. Chick SWE, Mamani H, Simchi-Levi D, Supply chain coordination and influenza vaccination, *Oper Res* **56**:1493–1506, 2008.
3. Abakuks A, Optimal immunization policies for epidemics, *Adv Appl Probab* **6**:494–511, 1974.
4. Bauch CT, Galvani AP, Earn DJD, Group interest versus self-interest in smallpox vaccination policy, *Proc Natl Acad Sci* **100**:10564–10567, 2003.
5. Bauch CT, Earn DJD, Vaccination and the theory of games, *Proc Natl Acad Sci* **101**:13391–13394, 2004.
6. Goh BS, Leitmann G, Vincent TL, Optimal control of a prey-predator system, *Math Biosci* **19**:263–286, 1974.
7. Greenhalgh D, Optimal control of an epidemic by ring vaccination, *Comm Statist Stochastic Models* **2**:339–363, 1986.
8. Hadeler KP, Müller J, Optimal harvesting and optimal vaccination, *Math Biosci* **206**:249–272, 2007.
9. May RM, Anderson RM, Spatial heterogeneity and the design of vaccination programs, *Math Biosci* **72**:83–111, 1984.
10. Palache B, New vaccine approaches for seasonal and pandemic influenza, *Vaccine* **26**:6232–6236, 2008.
11. Hethcote HW, Waltman P, Optimal vaccination schedules in a deterministic epidemic model, *Math Biosci* **18**:365–381, 1973.
12. Gupta NK, Rink RE, Optimum control of epidemics, *Math Biosci* **18**:383–396, 1973.
13. Morton R, Wickwire KH, On the optimal control of a deterministic epidemic, *J Appl Probab* **6**:622–635, 1974.
14. Di Blasio G, A synthesis problem for the optimal control of epidemics, *Numer Funct Anal Optim* **2**:347–359, 1980.
15. Andreeva EA, Semykina NA, Optimal control of the spread of an infectious disease taking the incubation period into account, *Comput Math Math Phys* **45**:1133–1139, 2005.
16. Asano E, Gross LJ, Lenhart S, Real LA, Optimal control of vaccine distribution in a rabies metapopulation model, *Math Biosci Eng* **5**:219–238, 2008.
17. Behncke H, Optimal control of deterministic epidemics, *Optim Control Appl Meth* **21**:269–285, 2000.
18. Brauer F, van den Driessche P, Wu J, *Mathematical Epidemiology*, Springer-Verlag, Berlin Heidelberg, 2008.

19. Francis PJ, Optimal tax-subsidy combinations for the flu season, *J Econom Dynam Control* **28**:2037–2054, 2004.
20. Gaff H, Schaefer E, Optimal control applied to vaccination and treatment strategies for various epidemiological models, *Math Biosci Eng* **6**:469–492, 2009.
21. Hansen E, Day T, Optimal control of epidemics with limited resources, *J Math Biol*, 2010, doi:10.1007/s00285-010-0341-0.
22. Hansen E, Day T, Optimal antiviral treatment strategies and the effects of resistance, *Proceedings of the Royal Society B*: *Biological Sciences* **271**:1082–1089, 2011.
23. Hansen E, Day T, Arino J, Wu J, Moghadas SM, Strategies for the use of oseltamivir and zanamivir during pandemic outbreaks, *Canad J Infectious Diseases Med Microbiol* **21**:e28–e63, 2010.
24. Müller J, Optimal vaccination patterns in age-structured populations, *SIAM J Appl Math* **59**:222–241, 1998.
25. Cesari L, *Optimization — Theory and Applications*, Springer-Verlag, 1983.
26. Filippov AF, *Differential Equations with Discontinuous Righthand Sides*, Kluwer Academic Publishers, 1988.
27. Lastman GJ, A shooting method for solving two-point boundary-value problems arising from non-singular bang-bang optimal control problems, *Int J Control* **27**:513–524, 1978.
28. Lee HWJ, Teo KL, Rehbock V, Jennings LS, Control parameterization enhancing technique for time optimal control problems, *Dyn Syst Appl* **6**:243–262, 1997.
29. Liu L, Teo KL, Computational method for a class of optimal switching control problems, *Prog Optimiz* **39**:221–237, 2000.
30. Sussmann HJ, A bang-bang theorem with bounds on the number of switchings, *SIAM J Control Optim* **17**:629–651, 1979.
31. Wickwire K, A note on the optimal control of carrier-borne epidemics, *J Appl Probability* **12**:565–568, 1975.
32. Wickwire K, Optimal immunization rules for an epidemic with recovery, *J Optim Theory Appl* **27**:549–570, 1979.

Appendix: Proofs of Theorems

In this section, we provide the proofs of the main theorems in this paper.

Proof of Theorem 3.1. Let $a > 0, b > 0$ be positive constants and

$$f(t, S, I) = (k(1-p) - (\mu + u(t))S - \beta IS, \beta IS - (\mu + d + r)I),$$

$$D = \{(t, S, I) : 0 \le t \le a, |(S, I) - (S_0, I_0)| \le b\}.$$

Since each coordinate of $f(t, S, I)$ is a polynomial of S, I and u, it is clear that $f(t, S, I)$ satisfies (3.2) and the Carathéodory conditions on D. Then by Lemmas 3.1 and 3.2, there exists a unique solution (S, I) on some interval $[0, c]$, with $0 < c \le a$, to system (2.11) with initial values $S_0 > 0$ and $I_0 > 0$.

Claim 1. $I(t) > 0$ and $S(t) > 0$ for all $t \in [0, c]$. From the second equation of system (2.11) it is clear that $I(t) = I_0 e^{\int_0^t (\beta S(s) - \mu - d - r)ds} > 0$ for all $t \in [0, c]$. Since the function $u(t)$ in (2.11) may not be continuous, the variation-of-constant method can not be applied to prove $S(t) > 0$, and hence we need to seek an alternative way as below.

We first show that $S(t) \geq 0$ for all $t \in (0, c)$. Suppose not. Since $S_0 > 0$, there exist $t_0 \in (0, c)$ and $\epsilon_0 > 0$ small enough so that $S(t_0) = 0$ and $S(t) < 0$ for all $t \in (t_0, t_0 + \epsilon_0)$. We note that in the interval $[0, c]$ the solution (S, I) is absolutely continuous and u is uniformly bounded. Then we can choose $\epsilon \in (0, \epsilon_0)$ small enough so that $\dot{S}(t) = k(1-p) - (\mu + u(t))S(t) - \beta I(t)S(t) > 0$ for almost all $t \in (t_0, t_0 + \epsilon)$. Therefore, we have

$$S(t) = \int_{t_0}^{t} \dot{S}(s)ds > 0 \quad \text{for all } t \in (t_0, t_0 + \epsilon) \subseteq (t_0, t_0 + \epsilon_0).$$

This is a contradiction and hence $S(t) \geq 0$ for all $t \in (0, c)$.

We now show that $S(t) \neq 0$ for all $t \in (0, c)$. Otherwise, there exists $t^* \in (0, c)$ so that $S(t^*) = 0$. By the absolute continuity of S, I and the boundedness of u we know that $\dot{S}(t) = k(1-p) - (\mu + u(t))S(t) - \beta I(t)S(t) > 0$ for almost all t in some open neighborhood $(t^* - \epsilon, t^* + \epsilon) \subseteq (0, c)$ of t^*. Then we have $S(t) = \int_{t^*}^{t} \dot{S}(s)ds < 0$ for all $t \in (t^* - \epsilon, t^*)$. This contradicts the fact that $S(t) \geq 0$ for all $t \in (0, c)$. Therefore, we have $S(t) > 0$ for all $t \in (0, c)$. Similarly, we can show that $S(c) \neq 0$ and hence $S(t) > 0$ for all $t \in [0, c]$. This completes the proof of Claim 1.

Next, we show that (S, I) can be extended to $[0, +\infty)$. Let $[0, c_\infty)$ be the maximal existence interval for (S, I). Then by Claim 1 we have $(S(t), I(t)) \in (0, +\infty) \times (0, +\infty)$ for every $t \in [0, c_\infty)$. If $c_\infty = +\infty$, then the proof is complete. If $c_\infty < +\infty$, then at least one of the limits $\lim_{t \to c_\infty} S(t) = +\infty$ and $\lim_{t \to c_\infty} I(t) = +\infty$ is valid, otherwise, by the claim we conclude that $[0, c_\infty)$ is not the maximal existence interval for (S, I). We distinguish the following three cases:

Case 1. $\lim_{t \to c_\infty} S(t) = +\infty$ and $\lim_{t \to c_\infty} I(t) = +\infty$. By the first equation of system (2.11), we have $\lim_{t \to c_\infty} \dot{S}(t) = -\infty$ which implies that there exists $\epsilon > 0$ such that $S(t)$ is monotonically decreasing on $(c_\infty - \epsilon, c_\infty)$ and hence $\lim_{t \to c_\infty} S(t) < +\infty$. This is a contradiction.

Case 2. $\lim_{t \to c_\infty} S(t) = +\infty$ and $\lim_{t \to c_\infty} I(t) < +\infty$. Then by the first equation of system (2.11) we also have $\lim_{t \to c_\infty} \dot{S}(t) = -\infty$. By Claim 1, we also obtain a contradiction.

Case 3. $\lim_{t \to c_\infty} S(t) < +\infty$ and $\lim_{t \to c_\infty} I(t) = +\infty$. Then by the first equation of system (2.11) we also have $\lim_{t \to c_\infty} \dot{S}(t) = -\infty$. By Claim 1, we also obtain a contradiction.

Therefore we have $c_\infty = +\infty$ and hence the solution (S, I) can be extended for all $t \in [0, +\infty)$ with $(S(t), I(t)) \in (0, +\infty) \times (0, +\infty)$. This completes the proof. □

Proof of Theorem 4.2. Let $(S_0, I_0) \in (0, \infty) \times (0, \infty)$ be given. Adding the $\dot{S}$ and $\dot{I}$ equations in (2.11) leads to $\frac{\mathrm{d}}{\mathrm{d}t}[S(t) + I(t)] \leq k(1-p) - \mu[S(t) + I(t)]$ which implies that $[S(t) + I(t)] \leq [S_0 + I_0] + k(1-p)/\mu =: L$ for $t \geq 0$. Thus, $S(t) \in [0, L]$

and $I(t) \in [0, L]$ for $t \in [0, T]$. Let

$$\begin{cases} f_0 = uS + \alpha\beta SI, \\ f = (k(1-p) - (\mu+u)S - \beta IS, \quad \beta IS - (\mu+d+r)I), \\ g = 0, \\ n = 2, \quad m = 1, \quad t_1 = 0, \quad t_2 = T, \\ (S(0), I(0)) = (S_0, I_0), \\ A = [0, T] \times [0, L] \times [0, L], \\ B = \{0\} \times \{(S_0, I_0)\} \times \{T\} \times \mathbb{R}^2, \\ U = [0, q]. \end{cases}$$

Note that A is compact in $\mathbb{R}^3$, $M = A \times U$ is compact, and $B = \{0\} \times \{(S_0, I_0)\} \times \{T\} \times \mathbb{R}^2$ is closed. Let $\tilde{Q}(t, S, I) \subset \mathbb{R}^3$ be the set of all (z^0, z) with $z^0 \geq f_0(t, S, I, u)$, $z = f(t, S, I, u)$ for some $u \in U$. Let $(t, S, I) \in A$, $(z_1^0, z_1) \in \tilde{Q}(t, S, I)$ and $(z_2^0, z_2) \in \tilde{Q}(t, S, I)$. Then there exist $u_1 \in U, u_2 \in U$ so that

$$\begin{cases} z_1^0 \geq f_0(t, S, I, u_1), \quad z_1 = f(t, S, I, u_1), \\ z_2^0 \geq f_0(t, S, I, u_2), \quad z_2 = f(t, S, I, u_2). \end{cases}$$

We note that both f and f_0 are linear in u. Then for every $s \in [0, 1]$ we have

$$\begin{cases} sz_1^0 + (1-s)z_2^0 \geq f_0(t, S, I, su_1 + (1-s)u_2), \\ sz_1 + (1-s)z_2 = f(t, S, I, su_1 + (1-s)u_2). \end{cases}$$

Note that U is convex, we have $(sz_1^0 + (1-s)z_2^0, sz_1 + (1-s)z_2) \in \tilde{Q}(t, S, I)$ with $su_1 + (1-s)u_2 \in U$. It follows that $\tilde{Q}(t, S, I)$ is convex. Then applying Lemma 4.1, there exists a solution of the optimal control problem (2.10) and (2.11). □

Proof of Theorem 4.3. We prove the theorem by applying the Pontaryagin's maximum principle to (2.10) and (2.11). The Hamiltonian is

$$\begin{aligned} H(S, I, \lambda_1, \lambda_2) = uS + \alpha\beta SI + \lambda_1[k(1-p) - (\mu+u)S - \beta IS] \\ + \lambda_2[\beta IS - (\mu+d+r)I], \end{aligned} \tag{A.1}$$

where $(\lambda_1(t), \lambda_2(t))$ satisfies the adjoint equations

$$\begin{cases} \dot{\lambda}_1 = -\dfrac{\partial H}{\partial S} = -u - \alpha\beta I + \lambda_1(\mu + u + \beta I) - \lambda_2\beta I, \\ \dot{\lambda}_2 = -\dfrac{\partial H}{\partial I} = -\alpha\beta S + \lambda_1\beta S - \lambda_2(\beta S - \mu - d - r). \end{cases} \tag{A.2}$$

Let

$$\psi(t) = \frac{\partial H}{\partial u} = S(t) - \lambda_1(t)S(t). \tag{A.3}$$

Suppose that the optimal control is not bang-bang, that is, u is singular in an open interval $\mathcal{O} \subset [0, T]$. Then $\psi(t) = 0$ for all $t \in \mathcal{O}$. By Theorem 3.1, we know that

$S(t) > 0$ for all $t \in [0, T]$. Then by (A.3) we have $\lambda_1(t) = 1$ for all $t \in \mathcal{O}$. It follows from (A.2) that the equations

$$\begin{cases} \lambda_2 = 1 - \alpha + \dfrac{\mu}{\beta I}, \\ \dot{\lambda}_2 = (1-\alpha)\beta S - \lambda_2(\beta S - \mu - d - r), \end{cases} \tag{A.4}$$

hold for all $t \in \mathcal{O}$. By (A.4) and by the second equation of (2.11) we have

$$\dot{\lambda}_2 = -\frac{\mu}{\beta}\frac{\dot{I}}{I^2} = -\frac{\mu}{\beta}\frac{\beta S - \mu - d - r}{I}, \quad \text{for all } t \in \mathcal{O}. \tag{A.5}$$

Then by (A.4) and (A.5) we have

$$(1-\alpha)\beta S = (1-\alpha)(\beta S - \mu - d - r). \tag{A.6}$$

This is a contradiction since $\mu + d + r \neq 0$ and hence the optimal control is bang-bang. □

Proof of Theorem 4.4. By Theorem 4.3, we know that the optimal control is bang-bang. Then the switching function $\psi(t)$ defined by (A.3) satisfies

$$u^*(t) = \begin{cases} 0 & \text{if } \psi(t) > 0, \\ q & \text{if } \psi(t) < 0. \end{cases} \tag{A.7}$$

By Theorem 3.1, we have $S(t) > 0$ for $t \geq 0$. Then $\psi(t) = S(t) - \lambda_1(t)S(t) > 0$ corresponds to $\lambda_1(t) < 1$ while $\psi(t) = S(t) - \lambda_1(t)S(t) < 0$ corresponds to $\lambda_1(t) > 1$. □

Proof of Theorem 4.5. For notational convenience, we assume, in the proof, that (S, I) and (λ_1, λ_2) are solutions associated with u^* for (2.11) and (A.2), respectively. By Theorem 4.4, if $t^* \in (0, T)$ is a switching time of u^*, then $\lambda_1(t^*) = 1$, where (λ_1, λ_2) satisfies the adjoint equations (A.2). Moreover, by the boundedness of u and the absolute continuity of S, I, λ_1 and λ_2, we have

$$\lim_{t \to t^*} \dot{\lambda}_1(t) = \dot{\lambda}_1(t^*) = \mu + (1 - \alpha - \lambda_2(t^*))\beta I(t^*). \tag{A.8}$$

Then λ_1 is continuously differentiable at t^* and hence on $(0, T)$. By the boundedness of u^* and by (2.11) and (A.2), we obtain

$$\ddot{\lambda}_1(t) = (\lambda_1(t) - \lambda_2(t) - \alpha)\beta\dot{I}(t) + \dot{\lambda}_1(t)(\mu + u^*(t) + \beta I(t)) - \dot{\lambda}_2(t)\beta I(t), \tag{A.9}$$

for almost all $t \in (0, T)$. Therefore, λ_1 is twice continuously differentiable for almost all $t \in (0, T)$.

Now we show that u^* has a finite number of switchings in $(0, T)$. By the way of contradiction, we assume the opposite. Then, by Theorem 4.4, $\lambda_1 - 1$ has infinitely many zeros in $(0, T)$. Consequently there exists a sequence $\{t_n\}_{n=1}^{+\infty} \subset (0, T)$ so

that $\lambda_1(t_n) = 1$ for all $n \in \mathbb{N}$. The boundedness of $\{t_n\}_{n=1}^{+\infty}$ implies that there exists $t_0 \in [0, T]$ so that $\lim_{n\to+\infty} t_n = t_0$ and $\lambda_1(t_0) = \lim_{n\to+\infty} \lambda_1(t_n) = 1$. Since there is no terminal cost and the terminal state is free for (2.10) and (2.11), the transversality condition for the adjoint variable $(\lambda_1(t), \lambda_2(t))$ satisfies

$$(\lambda_1(T), \lambda_2(T)) = (0, 0). \tag{A.10}$$

Since $\lambda_1(t_0) = 1$, it follows from (A.10) that $t_0 \in [0, T)$, and hence

$$\dot{\lambda}_1(t_0) = \lim_{n\to+\infty} \frac{\lambda_1(t_n) - \lambda_1(t_0)}{t_n - t_0} = \lim_{n\to+\infty} \frac{1-1}{t_n - t_0} = 0, \tag{A.11}$$

where $\dot{\lambda}_1(t_0)$ is understood to be the right derivative if $t_0 = 0$. We distinguish two cases:

Case 1. $t_0 \in (0, T)$. It follows from (2.11), (A.2), (A.9) and (A.11) that

$$\begin{aligned}
\lim_{t\to t_0} \ddot{\lambda}_1(t) &= (1 - \lambda_2(t_0) - \alpha)\beta\dot{I}(t_0) - \dot{\lambda}_2(t_0)\beta I(t_0) \\
&= \beta(1 - \lambda_2(t_0) - \alpha)(\beta I(t_0)S(t_0) - (\mu + d + r)I(t_0)) \\
&\quad - \beta(1 - \lambda_2(t_0) - \alpha)\beta S(t_0)I(t_0) - (\mu + d + r)\beta I(t_0)\lambda_2(t_0) \\
&= (\alpha - 1)(\mu + d + r)\beta I(t_0) > 0.
\end{aligned}$$

Thus, there exists $\epsilon > 0$ so that $\ddot{\lambda}_1(t) > 0$ for almost all $t \in (t_0 - \epsilon, t_0 + \epsilon)$. This, together with (A.11), implies that

$$\dot{\lambda}_1(t) = \int_{t_0}^{t} \ddot{\lambda}_1(s)ds = \begin{cases} < 0 & \text{for all } t \in (t_0 - \epsilon, t_0), \\ > 0 & \text{for all } t \in (t_0, t_0 + \epsilon). \end{cases} \tag{A.12}$$

Therefore, $\lambda_1(t) > 1$ for all $t \in (t_0 - \epsilon, t_0 + \epsilon)$ except at $t = t_0$ where $\lambda_1(t_0) = 1$. By Theorem 4.4 there is no switching in the neighbourhood of t_0. This is a contradiction since t_0 is an limit point of the switching times.

Case 2. $t_0 = 0$. In this case, from (2.11), (A.2), (A.9) and (A.11), we can similarly obtain the following for the right-sided limit at t_0:

$$\lim_{t\to t_0^+} \ddot{\lambda}_1(t) = (1 - \alpha)(\mu + d + r)\beta I(t_0) > 0.$$

This, together with (A.11), also implies that there is an $\epsilon > 0$ such that $\lambda_1(t) > 0$ for $t \in (t_0, t_0 + \epsilon)$. That is, there is no switching in $(t_0, t_0 + \epsilon)$, which is a contradiction to the fact that t_0 is an accumulation point of the switching times. This completes the proof. □