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IMPACT OF VACCINE ARRIVAL ON THE OPTIMAL CONTROL OF A NEWLY EMERGING INFECTIOUS DISEASE: A THEORETICAL STUDY

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Dedicated to the memory of our friend and colleague Vincent Hull

(Communicated by Urszula Ledzewicz)

Abstract. When a newly emerging human infectious disease spreads through a host population, it may be that public health authorities must begin facing the outbreaks and planning an intervention campaign when not all intervention tools are readily available. In such cases, the problem of finding optimal intervention strategies to minimize both the disease burden and the intervention costs may be addressed by considering multiple intervention regimes. In this paper, we consider the scenario in which authorities may rely initially only on non-pharmaceutical interventions at the beginning of the campaign, knowing that a vaccine will later be available, at an exogenous and known switching time. We use a two–stage optimal control problem over a finite time horizon to analyze the optimal intervention strategies during the whole campaign, and to assess the effects of the new intervention tool on the preceding stage of the campaign. We obtain the optimality systems of two connected optimal control problems, and show the solution profiles through numerical simulations.

1. Introduction.

In the mathematical theory of epidemic control it is generally assumed that social planners (e. g. governments, public health officers, etc.) choose appropriate strategies to fight epidemic outbreaks when they occur. It is also assumed that they have some intervention tools available, as therapeutic treatments or preventive vaccines. Then, optimal control theory may suggest the *best* plan for implementing such interventions to achieve the best outcome for the chosen strategy during an intervention campaign [1, 3, 27].

A common assumption in the literature is that the set of available tools remains unmodified throughout the whole campaign, from planning time to completion (see [8, 9, 26, 30, 32] for some very recent contributions). However, when a newly emerging human infectious disease spreads through a host population, drugs, treatments and/or vaccine might not be available when public health authorities begin confronting the outbreaks and planning an intervention campaign. In such cases, as

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recent research indicates [12, 28], social planners must often rely on quarantine, isolation, and other non-pharmaceutical interventions to contain outbreaks until new interventions tools are available.

An example of such a scenario is given by the A/H1N1 influenza outbreak in Italy. In March 2009 infection was caused by a novel influenza virus H1N1 that spread from Mexico around the world. During the outbreak, the Italian Ministry of Health activated a web site entitled *La nuova influenza* (the new influenza) to inform the population about the outbreak's status and intervention measures taken [20]. The first step of the control strategy was a containment stage. Among preventive measures considered more effective, there were: early identification of cases in travelers from affected areas, prophylaxis of their close contacts, promotion of hygiene rules and protective actions (e. g. hand washing). In a second stage, they implemented all actions necessary to promote effective availability of the vaccine against the virus. In Italy, the first deaths due to H1N1 influenza were reported in September 2009 [21], and authorities agreed that vaccination activities, according to the availability of the vaccine (and according to the schedule of production of the pharmaceutical industry), had to take place from 15 October to 15 November 2009. The Ministry also determined that once the manufacturer delivered vaccines, they had to be distributed gradually to vaccinate at least 40% of the Italian population [20].

Motivated by the above arguments, we consider the following scenario in this paper: a new generic infectious disease begins to spread in a host population. The disease is mostly unknown, but is apparently transmitted by close interpersonal contacts. The authorities face the emergency by planning an intervention campaign. At the beginning, they may rely on non-pharmaceutical interventions only. We assume that they employ a health-promotion campaign; they aim to reduce the spread of the epidemic via advertising (e. g. papers and television) and counseling, in order to induce people to hygienic or risk-averse behavior. For practical purposes, the campaign cannot be planned day by day, but held for a finite time (say, T), which is considered appropriate by public authorities to face the epidemic. Nevertheless, at time of planning the authorities already know that at an intermediate time (say $t_1 < T$), a vaccine will be available. We assume further that they know the exact value of t_1, because it is assured by the schedule of production of the pharmaceutical industry.

The following questions arise: which is the optimal intervention strategy during the whole campaign $[0, T]$? How will using the vaccine during the time interval $[t_1, T]$ influence the health-promotion campaign during the preceding time interval $[0, t_1]$?

This problem may be addressed by considering two possible intervention regimes. We will analyze the optimal control by using the finite-time horizon two–stage approach described by Tomiyama and Rossana [33, 35]. The method is based on solving two connected optimal control problems, which may be individually solved by the Pontryagin's maximum principle. This approach has been used in several different contexts, both in cases of endogenous and exogenous switching time t_1 (see e. g. [5, 6, 19, 33]), but, as far as we know, in the literature there are no applications of the two–stage approach to management and control of epidemics.

The dynamics inside each regime will be described by epidemic systems with general nonlinear transmission terms proposed by Benchke [3], who studied optimal controls of epidemics with many different methods of intervention, such as vaccination, quarantine and health-promotion campaigns.

The paper is organized as follows: in Section 2 the two–stage optimal control problem is introduced. The necessary conditions are derived in Section 3. In Section 4 we give a short insight about the adopted numerical method. Section 5 is devoted to illustrate and discuss the simulations. Final remarks are given in Section 6.

2. Two-stage disease control campaign.

As mentioned in the introduction, we assume that health authorities must face a newly human infectious disease outbreak. At the time of planning the intervention strategy, the health promotion campaign is the only available control tool. The authorities have to plan the campaign for an appropriate finite time, T. They already know, however, that at an intermediate time, t_1, a vaccine will be ready to be administered to people. Moreover, they are aware of both the costs associated with the health promotion campaign and the future vaccine.

We adopt the model for health campaigns proposed in [3], which is derived by advertising capital models like the Nerlove-Arrow model. Let us denote by $S(t)$ and $I(t)$ the sizes of susceptible and infectious individuals at time t, respectively. Denote by $u(t)$ the control at time t. It measures the efforts for advertising, television and other forms of campaigns, as counseling or hygienic aid. This builds up a capital stock, $w(t)$, which in some sense corresponds to goodwill in marketing.

Hence, in the first stage, that is for $t \in [0, t_1)$, the dynamics is ruled by the following system:

$$\dot{S} = -\phi(w)f(S, I); \quad \dot{I} = \phi(w)f(S, I) - \gamma I; \quad \dot{w} = u(t) - \delta w. \tag{1}$$

The disease transmission is described by the function f, which is assumed to be: positive; nil if susceptibles or infectious are absent; increasing and concave with respect to its arguments, and of almost first-order mass action type i. e.:

$$\begin{array}{ll} f(S, I) = 0, & \text{for } S = 0 \text{ or } I = 0 \\ f(S, I) > 0, & \text{for } S > 0,\ I > 0 \\ f_S, f_I, f_{SI} > 0, & \text{for } S > 0,\ I > 0 \\ f_{SS}, f_{II} \le 0, & \text{for } S \ge 0,\ I \ge 0. \end{array} \tag{2}$$

The efficiency of the campaign is described by the function ϕ. It is assumed that campaign expenditures are increasingly less effective, so that:

$$\begin{array}{l} \phi(0) = 1, \quad 0 < \phi(w) \le 1, \\ \phi'(w) < 0, \ \ \phi''(w) \ge 0, \quad \phi'''(w) \le 0. \end{array} \tag{3}$$

The parameters in (1) are positive constants; γ denotes the removal rate of infectious and δ denotes the rate of forgetting or decay of concern.

Starting from time t_1, a preventive vaccine is available and may potentially be administered to susceptibles. Hence, for the second stage, i.e., for $t \in (t_1, T]$, we have the system:

$$\dot{S} = -\phi(w)f(S, I) - g(S)v(t); \quad \dot{I} = \phi(w)f(S, I) - \gamma I \quad \dot{w} = u(t) - \delta w, \tag{4}$$

where v is the vaccination effort, and the function g describes the efficiency or effectiveness of vaccination [3]. It is assumed that:

$$g(S) \ge 0, \quad g'(S) \ge 0, \quad g'(0) > 0. \tag{5}$$

We assume that the functions f, ϕ and g are sufficiently smooth to guarantee, for given non-negative initial conditions, the existence and uniqueness of the solutions of systems (1) and (4). Examples of functions f, ϕ and g are as follows, where the k_i's are positive constants:

$$f(S,I) = k_1 SI; \tag{6}$$

$$\phi(w) = k_2\, e^{-w}; \tag{7}$$

$$g(S) = k_3 S. \tag{8}$$

Due to technical and financial aspects, the controls are assumed to be bounded by positive constants, that is:

$$0 \le u(t) \le u_0, \qquad 0 \le v(t) \le v_0. \tag{9}$$

The goal here is to minimize epidemic costs, which include care of infectious individuals, economic losses and intervention costs. Hence, the optimal control problem is to minimize the two–stage *objective functional* (or *performance index*):

$$J(u,v) = J_1(u) + J_2(u,v), \tag{10}$$

where

$$J_1(u) = \int_0^{t_1} \left[I(t) + A\, u^2(t)\right] dt, \tag{11}$$

and

$$J_2(u,v) = \int_{t_1}^{T} \left[I(t) + A\, u^2(t) + B\, v^2(t)\right] dt, \tag{12}$$

subject to (1)–(5) and non negative initial data $S(0) = S_0$; $I(0) = I_0$, $w(0) = w_0$. In (11)–(12) the cost of an infectious individual per unit time is normalized to 1, and A and B are two positive weight constants.

We assume that the intervention efforts are increasingly costly and that nonlinear increase may potentially arise at high intervention levels. Unfortunately, we do not have real data, which would help in choosing the best functional form. Therefore, we take quadratic expressions of the control, because they are the simplest and most widely used nonlinear representation of intervention costs (see e.g. [2, 4, 22, 23, 24, 26, 30, 32]). However, we call attention to the fact that it has been argued that other nonlinear functions might provide a better description of the actual cost for vaccination, due to the increase of costs when most of the population is already vaccinated or immune. In such cases dependence on the removed class should be taken into account [17].

We will denote by J^* the minimum value of the objective functional corresponding to the optimal path (u^*, v^*), that is :

$$J^* \equiv J(u^*, v^*) = \min_{\Omega} J(u,v), \tag{13}$$

where Ω is the set of *admissible* controls:

$$\Omega = \left\{(u,v) \in L^1(0,T) \,/\, (u(t),v(t)) \in [0,u_0] \times [0,v_0],\ \forall t \in [0,T]\right\}.$$

By *admissible* we mean that the controls satisfy the constraints, and a corresponding solution exists for the system equation that satisfies the initial and final conditions.

Remark 1. Systems (1) and (4) are completed by the equations for removed individuals, $\dot R = \gamma I$, and $\dot R = \gamma I + g(S)v$, respectively. However, these equations can be studied separately, because the right hand sides of systems (1) and (4), as well as the objective functional, do not depend on R.

Remark 2. System with no controls can be derived from equations (1) and (4) with $w_0 = 0$, $u(t) = 0$ and $v(t) = 0$ for all $t \geq 0$. System with only health campaign is given by the equations (1). We do not explicitly analyze this particular case, because a similar study can be found in [3].

3. **Necessary conditions.**

In this section we derive the necessary conditions following the approach given in [33, 35] for two-stage optimal control problems.
The basic idea is to decompose the original problem into a sequence of two connected Pontryagin problems, one for each of the two–stages of the intervention campaign. The problems are solved backward in time, so that the first problem refers to the second stage, $t \in [t_1, T]$.
Second stage. Given system (4), set the initial conditions:

$$S(t_1) = S_1; \quad I(t_1) = I_1; \quad w(t_1) = w_1, \tag{14}$$

and final conditions,

$$S(T); \quad I(T); \quad w(T); \quad free.$$

Consider the control constraint (9) on $[t_1, T]$. We wish to find admissible optimal controls u^*, v^* which minimize the objective functional (12) over all admissible controls.
We will denote by $S^*(t)$, $I^*(t)$, $w^*(t)$, the corresponding optimal time–profile of the state variables. This is a classical optimal control problem that may be addressed by Pontryagin's maximum principle [31]. The Hamiltonian is given by

$$\begin{aligned} H_2(S, I, w, u, v) = \quad & I(t) + A\, u^2(t) + B\, v^2 - [\phi(w) f(S, I) + g(S) v]\, \lambda_1 + \\ & + [\phi(w) f(S, I) - \gamma I]\, \lambda_2 + (u - \delta w)\, \lambda_3, \end{aligned}$$

where λ_i; $i = 1, 2, 3$, are the adjoint variables. The adjoint equations are given by:

$$\begin{aligned} \dot{\lambda}_1 = \quad & -\tfrac{\partial H_2}{\partial S} = \left[\phi(w) \tfrac{\partial f}{\partial S} + v\, \tfrac{\partial g}{\partial S}\right] \lambda_1 - \phi(w) \tfrac{\partial f}{\partial S} \lambda_2 \\ \dot{\lambda}_2 = \quad & -\tfrac{\partial H_2}{\partial I} = -1 + \phi(w) \tfrac{\partial f}{\partial I} \lambda_1 - \left[\phi(w) \tfrac{\partial f}{\partial I} - \gamma\right] \lambda_2 \\ \dot{\lambda}_3 = \quad & -\tfrac{\partial H_2}{\partial w} = \tfrac{\partial \phi}{\partial w} f \lambda_1 - \tfrac{\partial \phi}{\partial w} f \lambda_2 + \delta \lambda_3. \end{aligned}$$

The state variables are not assigned at the final time T so that we have the transversality equations:

$$\lambda_1(T) = \lambda_2(T) = \lambda_3(T) = 0. \tag{15}$$

In order to illustrate the characterization of the optimal controls u^* and v^*, we consider the optimality conditions:

$$\frac{\partial H_2}{\partial u} = 0, \quad \frac{\partial H_2}{\partial v} = 0,$$

at $u = u^*$ and $v = v^*$, respectively, on the set $\{t \in [t_1, T] : 0 \leq u \leq u_0; 0 \leq v \leq v_0\}$.
That is:

$$u^*(t) = -\frac{\lambda_3}{2A}, \quad v^*(t) = \frac{g(S^*)}{2B} \lambda_1,$$

and, taking into account the bounds on u^*, and v^*, the characterizations are:

$$u^* = \begin{cases} 0 & \text{if } \lambda_3 > 0 \\ -\lambda_3/2A & \text{if } -2A\, u_0 \leq \lambda_3 \leq 0 \\ u_0 & \text{if } \lambda_3 < -2A\, u_0, \end{cases} \tag{16}$$

and

$$v^* = \begin{cases} 0 & \text{if } \lambda_1 < 0 \\ g(S^*)\lambda_1/2B & \text{if } 0 \leq \lambda_1 \leq 2B\, v_0/g(S^*) \\ v_0 & \text{if } \lambda_1 > 2B\, v_0/g(S^*), \end{cases} \tag{17}$$

which, in short form, may be written:

$$u^*(t) = \min\left(\max\left(0, -\lambda_3/2A\right), u_0\right),$$

and

$$v^*(t) = \min\left(\max\left(0, g(S^*)\lambda_1/2B\right), v_0\right).$$

The optimal controls of this first problem depend on the choice of the initial conditions (14), $J_2^* = J_2^*(S_1, I_1, w_1)$. Therefore, the goal of the minimization procedure in the first stage is now to find an admissible control that minimizes the sum of the objective functional (11) and J_2^*. In other words, a terminal index must be included in the objective functional of the first stage. This is the basic idea to analyze the second optimal control problem [35].

First stage. Given system (1), set the initial conditions:

$$S(0) = S_0; \quad I(0) = I_0; \quad w(0) = w_0, \tag{18}$$

and final conditions,

$$S(t_1); \quad I(t_1); \quad w(t_1); \quad free.$$

Consider the control constraint on u, given in (9), on $[0, t_1]$. We wish to find optimal control $u^*(t)$ defined on $[0, t_1]$ which is admissible and minimizes the objective functional:

$$J_{FS}(u) = \int_0^{t_1} \left[I(t) + A\, u^2(t)\right] dt + J_2^*(S(t_1), I(t_1), w(t_1)),$$

over all admissible controls. The Hamiltonian is given by

$$\begin{aligned} H_1(S, I, w, u) = \quad & I(t) + A\, u^2(t) - [\phi(w) f(S, I)]\, \mu_1 + \\ & + [\phi(w) f(S, I) - \gamma I]\, \mu_2 + (u - \delta w)\, \mu_3, \end{aligned}$$

where μ_i; $i = 1, 2, 3$, are the adjoint variables. The adjoint equations are given by:

$$\begin{aligned} \dot{\mu}_1 = \quad & -\tfrac{\partial H_1}{\partial S} = \phi(w) \tfrac{\partial f}{\partial S}\, \mu_1 - \phi(w) \tfrac{\partial f}{\partial S} \mu_2 \\ \dot{\mu}_2 = \quad & -\tfrac{\partial H_1}{\partial I} = -1 + \phi(w) \tfrac{\partial f}{\partial I} \mu_1 - \left[\phi(w) \tfrac{\partial f}{\partial I} - \gamma\right] \mu_2 \\ \dot{\mu}_3 = \quad & -\tfrac{\partial H_1}{\partial w} = \tfrac{\partial \phi}{\partial w} f \mu_1 - \tfrac{\partial \phi}{\partial w} f \mu_2 + \delta \mu_3. \end{aligned}$$

Due to the terminal index, the transversality equations are:

$$\mu_i(t_1) = \frac{\partial J_2^*}{\partial x_i} \left(S^*(t_1), I^*(t_1), w^*(t_1)\right), \tag{19}$$

where $x_1 = S; x_2 = I; x_3 = w$. On the other hand, it is well known that (see, e. g. [10], p. 64)

$$\lambda_i(t_1) = \frac{\partial J_2^*}{\partial x_i} \left(S^*(t_1), I^*(t_1), w^*(t_1)\right),$$

so that the following continuity condition holds

$$\mu_i(t_1) = \lambda_i(t_1); \quad i = 1, 2, 3 \tag{20}$$

In order to illustrate the characterization of the optimal control u^*, we consider the optimality condition:

$$\frac{\partial H_1}{\partial u} = 0,$$

at $u = u^*$, on the set $\{t \in [0, t_1] : 0 \le u \le u_0\}$ and the characterization is the same as in (16), with λ_3 replaced by μ_3.

Remark 3. *(i)* The existence of the optimal control may be established as follows. For any fixed initial state $\left(\overline{S}_1, \overline{I}_1, \overline{w}_1\right)$, the problem set for the second stage, over $[t_1, T]$, is of standard form. The requirements of classical existence theorems (Theorem III 4.1 and Corollary 4.1 in [16]) are satisfied. In particular, it can be easily checked that the integrand of the objective functional is convex with respect to (u, v) and the state equations depend linearly on controls u and v. This ensures the existence of an optimal solution (see [17]). Then, similar arguments also ensure the existence of the optimal control for the first stage, since we have assumed that t_1 is fixed and such that $0 < t_1 < T$, so that the problem for the first stage is also of standard form, where J_2^* is a terminal index. Such an optimal control will minimize J_{FS}. This, together with the continuity condition (20) ensures the existence of an optimal path for (S, I, w) for the whole time interval $[0, T]$.
(ii) An uniqueness result may be established, for sufficiently small time–intervals, by using the approach given in [13, 22] and also employed in [14, 15, 17] for optimal control problems of epidemics and cancer treatment.

4. Numerical method.

Assume that the functions f, ϕ and g are given by (6), (7) and (8), respectively. We solve numerically the two–stage optimal control problem given by the objective functional (10) subject to (9), and the state equations:

$$\dot{S} = -k_1 k_2 e^{-w} SI; \quad \dot{I} = k_1 k_2 e^{-w} SI - \gamma I; \quad \dot{w} = u(t) - \delta w, \tag{21}$$

for $t \in [0, t_1)$, and,

$$\dot{S} = -k_1 k_2 e^{-w} SI - k_3 v(t); \;\; \dot{I} = k_1 k_2 e^{-w} SI - \gamma I; \;\; \dot{w} = u(t) - \delta w, \tag{22}$$

for $t \in (t_1, T]$. We stress that here the contact rate between individuals is assumed to be affected by information produced by the social planner. The exponential relationship (7) describes a quite strong effect due to the information campaign. In principle, other functional forms may be considered. For example, a weaker effect, described by the function $1/(1 + w)$, has been considered in [11].

In order to solve numerically the two-stage optimal control problem, we use an indirect approach (see [7], [34] and the references therein), which leads to the solution of the two boundary value problems.

On the first stage the optimality conditions consist of the control characterization (16), with λ_3 replaced by μ_3, the six ordinary differential equations (21), and the adjoint equations:

$$\begin{aligned}
\dot{\mu}_1 &= \;\; k_1 k_2 e^{-w} I \mu_1 - k_1 k_2 e^{-w} I \mu_2 \\
\dot{\mu}_2 &= \;\; -1 + k_1 k_2 e^{-w} S \mu_1 - \left[k_1 k_2 e^{-w} S - \gamma\right] \mu_2 \\
\dot{\mu}_3 &= \;\; -k_1 k_2 e^{-w} SI \mu_1 + k_1 k_2 e^{-w} SI \mu_2 + \delta \mu_3,
\end{aligned}$$

with initial conditions of the state (18) and final time conditions of the adjoints (19). On the second stage, the optimality conditions consist of the controls characterization (16)-(17), the six ordinary differential equations (22) and the adjoint equations:

$$\begin{aligned}
\dot{\lambda}_1 &= \;\; \left[k_1 k_2 e^{-w} I + k_3 v(t)\right] \lambda_1 - k_1 k_2 e^{-w} I \lambda_2 \\
\dot{\lambda}_2 &= \;\; -1 + k_1 k_2 e^{-w} S \lambda_1 - \left[k_1 k_2 e^{-w} S - \gamma\right] \lambda_2 \\
\dot{\lambda}_3 &= \;\; -k_1 k_2 e^{-w} SI \lambda_1 + k_1 k_2 e^{-w} SI \lambda_2 + \delta \lambda_3,
\end{aligned}$$

with initial conditions of the state (14) and final time conditions of the adjoints (15). The continuity condition (20) connects the two problems.

According to the procedure used in [18] in the multi-stage case, the algorithm consists in proceeding iteratively on the first and second stages, starting from the

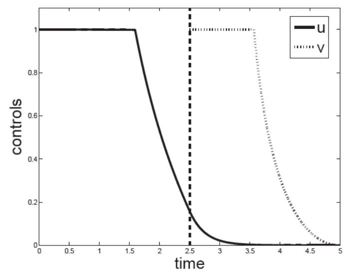


FIGURE 1. Optimal time-profile for the health and vaccination campaigns. The parameter set is given in (23). The initial conditions are: $S(0) = 0.9$, $I(0) = 0.1$, $w(0) = 0$.

second one with an initial guess for the state variables. Within this process the computation of a sequence of boundary value problems with control characterizations is required, that is a family of subproblems where the solution of one problem serves as an initial guess for the neighboring one. In order to solve the problems of this sequence, in each stage we use the so called *forward-backward sweep method*, described in detail in [27].

The process begins with an initial guess on the control variable. Then, the state equations are solved simultaneously forward in time, and next the adjoint equations are simultaneously solved backward in time. The control is updated by inserting the new values of states and adjoints into its characterization, and the process is repeated until convergence occurs. As in [27], the solver used for the state and adjoint systems is a Runge-Kutta fourth order procedure. A MATLAB© code, [29], has been built to perform the simulations.

5. **Simulations and discussion.** Our main goal is to show:
(i) the optimal interventions policy during the whole campaign $[0, T]$;
(ii) how the possibility to use the vaccine during the second stage $[t_1, T]$ may influence the health-promotion campaign during the preceding stage $[0, t_1]$.

We consider an initial scenario in which the majority of the population is susceptible and there is a relatively small fraction of infectious: $S(0) = 0.9$; $I(0) = 0.1$. We assume that the health-authorities consider $T = 5$ (possibly, months) as a reasonable time span to plan the campaign against the outbreak. They start the health campaign ($w(0) = 0$) well aware that a vaccine will be available at time $t_1 = 2.5$.

In our simulations we will take for the other quantities the following values:

$$\begin{array}{c} k_1 = 2, \quad k_2 = 2.2, \quad k_3 = 3, \quad \gamma = 0.1 \quad \delta = 0.01 \\ u_0 = 1, \quad v_0 = 1, \quad A = 0.1, \quad B = 0.001. \end{array} \tag{23}$$

These values are only indicative and do not have any specific biological meaning. More in depth knowledge about the field data certainly would give more realistic parameter values.

The optimal time-profile of the two controls are depicted in Figure 1. It can be seen, as expected, that both interventions must be at the highest possible effort at the beginning. We may also note that it is optimal to continue the health campaign, although at a low and decreasing effort, even when the vaccine is available. The time-profile of the state variables corresponding to this optimal interventions are depicted in Figure 2 (b). A rapid decrease of the susceptible population occurs when

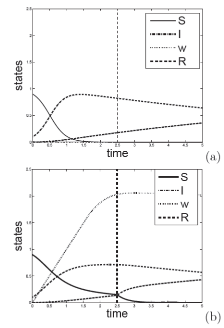


FIGURE 2. (a) Solutions of system (21), without controls. (b) Solutions of systems (21) and (22), corresponding to the optimal interventions. The parameter set is given in (23). The initial conditions are: $S(0) = 0.9$, $I(0) = 0.1$, $w(0) = 0$.

the vaccination campaign starts. Comparing these curves with the uncontrolled case (Figure 2 (a)) it can be seen that the uncontrolled disease spread is characterized by higher and persistent level of infectious.

The effect of interventions on the disease prevalence may be 'measured' by the quantity $\overline{I} = \int_0^T I(t)dt$. In case of simulations depicted in Figure 1 we get $\overline{I} = 3.60$ in absence of interventions and $\overline{I} = 3.00$ when a health campaign and vaccination are used. This means that 16% of infections are prevented due to interventions.

In order to stress the effect of the vaccination campaign on the optimal performance index J^*, given in (13), we have assessed the sensitivity of J^* with respect to B (the vaccination cost parameter) and t_1 (the vaccination campaign starting time). Figure 3 (a) shows J^* as function of B. It can be seen that lower vaccination costs imply better optimal performances. These values are compared with the performance index J_0 that would come by using only the health campaign over $[0, T]$ (in other words, J_0 is the performance index (11) when $t_1 = T$, subject to (21) and the constraint $0 \leq u(t) \leq u_0$ given in (9); we call this case *the no–vaccination case*). It can be seen that for a vaccination cost B one hundred times greater than the health campaign cost A, there is little recourse to vaccination and J^* approaches the optimal value of J_0, say J_0^* (in the plot, $J_0^* \approx 3.26$).
The value of the switching time t_1 is assumed to be exogenous and fixed. In Figure 3 (b) it can be seen J^* as function of t_1. We can deduce that the sooner the vaccine is made available to health authorities, the better the result.

Let us focus now on the first stage. In the absence of any intervention the disease burden over the first stage may be evaluated as $\overline{I_1} = \int_0^{t_1} I(t)dt$. In our case study, with the values given in (23) it follows $\overline{I_1} = 1.78$. Assume now that the social planner decides to follow the optimal path of the *no–vaccination* case. On the first stage, the performance index will be $J_{10} = 1.5922$, so that the result is better, as expected. However, following this path means to plan without taking the vaccine arrival into account. In the next, we want to assess how the performance index during the first stage, J_1, can be influenced by a schedule that does take the vaccine arrival into account. With this aim, we will investigate the dependence of J_1 on the characteristic parameters of the model in the second stage, namely the vaccine cost B, and the vaccine effectiveness rate, k_3. The sensitivity analysis shows that:

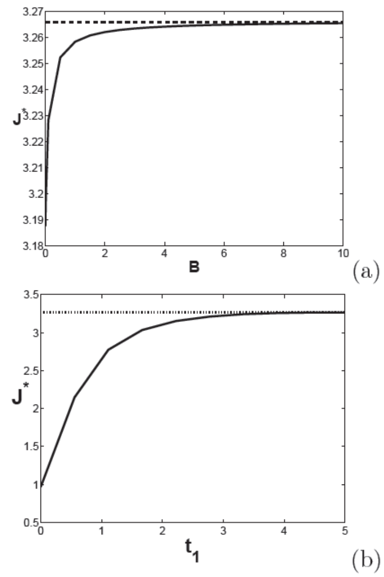
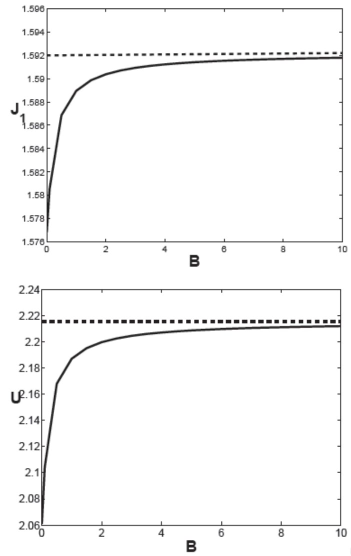


FIGURE 3. Optimal performance index J^* plotted: (a) as function of B; (b) as function of t_1. The other parameter values are given in (23). The initial conditions are: $S(0) = 0.9$, $I(0) = 0.1$, $w(0) = 0$. The dashed lines correspond to the optimal performance index for the no-vaccination case, J_0^*.

(i) The cheaper the vaccine, the better the performance index (for the same effectiveness) not only over the whole period $[0, T]$, where it is optimal, but also on the first stage (Figure 4 (a));
(ii) Compared with the no–vaccination case, optimal schedules over $[0, T]$ obtained by taking the vaccine arrival into account at t_1, require less use of the health campaign (Figure 4 (b)). Nevertheless, the performance index at the first stage will be the same or better (less or equal to 1.5922, see Table 1);
(iii) If the vaccine is very effective and inexpensive, then it will be widely used (in the second stage, when it is available). Consequently, the health campaign will be little used in the first stage. This produces a significant reduction of J_1, from 1.5922 to 1.5768 (reduction of 0.97%), see Table 1, first row.
(iv) If the vaccine is very effective but costly, then it will be used less, and a very small reduction of J_1 will occur, see Table 1, last row.

6. **Final remarks.** In this paper we have considered a specific but common scenario. The health authorities face the emergency of a new infectious disease spreading in a host population. They decide to adopt a health–promotion campaign for an appropriate finite time T. Nevertheless, at time of planning, the authorities already know that a vaccine will be available at an intermediate time, say $t_1 < T$. We assume further that they know the exact value of t_1, because the pharmaceutical industry's schedule of production assures it.

The mathematical investigation has been performed by using the optimal control theory. A two–stage optimal control problem has been introduced and specific epidemic models, with general nonlinear transmission terms, have been considered



(a)

(b)

FIGURE 4. (a) Performance index for the first stage, J_1 plotted as function of B; (b) Total effort provided for the health campaign, $U = \int_0^{t_1} u(t)dt$, plotted as function of B. The other parameter values are given in (23). The initial conditions are: $S(0) = 0.9$, $I(0) = 0.1$, $w(0) = 0$. The dashed lines correspond to the same quantities computed for the no-vaccination case.

$B \setminus k_3$	0.01	0.1	0.5	1	2	3
0.001	1.5922	1.5909	1.5866	1.5831	1.5790	1.5768
0.01	1.5922	1.5918	1.5871	1.5834	1.5793	1.5770
0.1	1.5922	1.5922	1.5911	1.5887	1.5838	1.5805
1	1.5922	1.5922	1.5921	1.5918	1.5906	1.5890
1.1	1.5922	1.5922	1.5921	1.5918	1.5907	1.5892
10	1.5922	1.5922	1.5922	1.5922	1.5920	1.5918

TABLE 1. Values of the performance index J_1, computed for different values of the vaccination cost B and vaccine effectiveness k_3. The other parameter values are given in (23).

for each stage. The necessary conditions have been derived by using the Pontryagin maximum principle and the problem has been solved numerically.

The model provides the optimal schedule of the two interventions over the entire period $[0, T]$. Following the optimal path, the social planner will get the minimum (best) performance index J^*. The possibility to use the vaccine during the second stage will influence use of the health–promotion campaign during the first stage. Generally speaking, the more the vaccine will be used in the second period, the less the health–campaign will be employed in the first. Nevertheless, this will produce a better performance index also during the first stage, though this effect strongly depends on vaccine cost and effectiveness. Thus, the social planner, when planning the use of the health-campaign in the first stage, needs to be aware and take both the cost and effectiveness of the arriving vaccine into account. Ignoring the vaccine arrival means planning interventions at the first stage according to the profile that gives the optimal performance index over $[0,T]$ obtained using only the health–campaign. This will produce, in the first stage, a bigger intervention effort and a worse performance index.

In our approach, we have assumed that the switching time t_1 is exogenous and fixed. In the practice, it may be that planners do not know when the vaccine will be available. This aspect has been considered in [28], where the optimal policy for non–pharmaceutical interventions has been analyzed and the optimization horizon T is assumed to be the vaccine arrival time. To capture the uncertainty, T is assumed to follow an exponential distribution. This leads to a one–stage infinite horizon discounted problem. The two–stage approach proposed in this paper allows to explicitly obtain the optimal policy for vaccination and to assess the impact of vaccine arrival on the previous stage of the intervention campaign. Furthermore, insight into how switching time influences the optimal policy may be obtained by varying t_1, and we have shown how the switching time does affect the optimal performance index.

Another interesting question related to two-stage optimal control problems is to consider the switching time as a control variable and find it optimally. In our case, this means that once the vaccine is available (at time t_1), it might be optimal to begin administering the vaccine to the public later (at $t_2 \in (t_1,T]$). Our analysis shows that vaccination must be administered at the highest possible effort once available. This is in agreement with the result found in [17], where optimal vaccination policies have been investigated for several different epidemic models with SIR and SEIR structure. The authors found that, regardless of the model structure, vaccinating at the highest possible rate as early as possible is essential for controlling an epidemic. This holds if the vaccination is the new available intervention, but different results might come for different interventions as treatment, quarantine, screening, etc.

As mentioned in the introduction, the A/H1N1 influenza outbreak is an example of a scenario for which our approach might be employed. Very recently, modeling control strategies based on social distancing and antiviral treatments has been considered for this kind of disease [25, 32]. The dynamics is described by a high dimensional system of nonlinear ordinary differential equations. Here we have considered oversimplified models, but our approach may be implemented for more realistic (and complex) systems as in [25, 32]. In this way, it will be possible to see how the optimal policies may change in view of vaccine arrival.

All the open questions above will be the subject of further investigations.

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