

# Optimal time–profiles of Public Health Intervention to shape voluntary vaccination for childhood diseases

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## Abstract

In order to seek the optimal time–profiles of Public Health Systems (PHS) Intervention to favor vaccine propensity, we apply optimal control (OC) to a SIR model with voluntary vaccination and PHS intervention. **We focus on short–term horizons, and on both continuous control strategies resulting from the Forward–Backward Sweep (FBS) deterministic algorithm, and piecewise–constant strategies** (which are closer to the PHS way of working) investigated by the Simulated Annealing (SA) stochastic algorithm. For childhood diseases, where disease costs are much larger than vaccination costs, the OC solution sets at its maximum for most of the policy horizon, meaning that the PHS cannot further improve perceptions about the net benefit of immunization. Thus, the subsequent dynamics of vaccine uptake stems entirely from the declining perceived risk of infection (due to declining prevalence) which is communicated by direct contacts among parents, and unavoidably yields a future decline in vaccine uptake. We find that for relatively low communication costs, the piecewise control is close to the continuous control. For large communication costs the SA algorithm converges towards a non–monotone OC that can have oscillations.

**Key-words** *Vaccination, Human behavior, Public Health System, Communication, Optimal Control, Simulated Annealing, Forward–Backward Sweep Method.*

## 1 Introduction

In the last ten years, a new research field in epidemiology has emerged: the *behavioral epidemiology* (BE) of infectious diseases ([Manfredi and d’Onofrio, 2013](#);

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Funk et al., 2010). BE focuses on the feedbacks of human behavior on the transmission and control of infections (Manfredi and d’Onofrio, 2013; Funk et al., 2010). In traditional models (Anderson et al., 1992; Capasso, 1993), individuals are modeled as passive particles randomly interacting according to the mass-action principle (Manfredi and d’Onofrio, 2013; Wang et al., 2016). This assumption inadequately represents contemporary scenarios, where individuals - based on information and rumors on the spread of diseases - modify their social behavior and their propensity to vaccinate (Manfredi and d’Onofrio, 2013; d’Onofrio et al., 2007; Wang et al., 2016). The study of the impact of human decisions on the vaccine uptake under voluntary vaccination is a major area of BE research (Manfredi and d’Onofrio, 2013; Wang et al., 2016; Bauch, 2005)

Indeed, if vaccination is no longer mandatory, then the high degrees of disease control allowed by vaccine-induced herd immunity achieved in the past, jointly with the high standard of health of western societies (Manfredi and d’Onofrio, 2013; d’Onofrio et al., 2011), can favor the spread of *information-dependent* behavior (Manfredi and d’Onofrio, 2013; Buonomo et al., 2013). On the one hand, in periods of low prevalence families might tend to overweight information and rumors on vaccine side-effects and their propensity to vaccinate might decline. On the other hand, periods of high infection prevalence or of outbreaks can enhance the propensity to vaccinate.

BE research has shown that this behavior makes disease elimination unfeasible even when temporarily coverages is near 100% in epochs of high perceived risk, and triggers large recurrent epidemics (Bauch, 2005; Manfredi and d’Onofrio, 2013; d’Onofrio et al., 2007; d’Onofrio et al., 2011).

In (Oraby et al., 2014) it is stressed that some BE models identify vaccine refusal as the *typical* behavior, whereas it should be (as in (d’Onofrio et al., 2007)) the atypical one, as shown by the large vaccine coverages that can be observed worldwide.

In (d’Onofrio et al., 2012) a simple explanation of vaccine acceptance as the typical behavior was proposed: even if vaccination is voluntary the public health system (PHS) can favor vaccine propensity by providing influential information on infection and vaccines. It is the ‘persuasion success’ of PHS efforts that makes vaccine acceptance the typical behavior. Indeed, the model suggests that infection could be eliminated for adequate levels of effort.

A shortcoming of (d’Onofrio et al., 2012) is that the communication effort by the PHS is modeled as constant. In the practice, such effort is not constant, due to a range of epidemiological and economical variables, including the disease burden and the economic and human costs of immunization.

For such a model the determination of a suitable PHS effort that minimizes economic costs under given constraints in a given time-horizon calls for the application of Optimal Control (OC) theory, which is our aim.

Applications of OC theory (Schättler and Ledzewicz, 2012) to classical mathematical epidemiology date back to the seventies (Hethcote and Waltman, 1973;

Morton and Wickwire, 1974; Sethi and Staats, 1978; Wickwire, 1977). Recently, simple deterministic numerical schemes have been introduced (Anița et al., 2011; Lenhart and Workman, 2007) that renewed interest in application of OC to classical mathematical epidemiology (Asano et al., 2008; Buonomo, 2011; Betta et al., 2016; Blayneh et al., 2010; Bolzoni et al., 2014; Demasse et al., 2016; Hansen and Day, 2011; Jung et al., 2009, 2002; Laguzet and Turinici, 2015a; Lee and Castillo-Chavez, 2015; Onyango and Müller, 2014; Rachah and Torres, 2016; Rowthorn and Walther, 2017) and to BE (Kassa and Ouhinou, 2015; Laguzet and Turinici, 2015b; Doutor et al., 2016).

Among the above mentioned deterministic algorithms, we may cite the Forward–Backward sweep (FBS) algorithm (Hackbusch, 1978) and the gradient methods (Anița et al., 2011). **These algorithms are approximation methods built on the necessary conditions obtained by the maximum principle that the control and the state variables need to satisfy (Pontryagin et al., 1962).** In particular, the FBS, which will be used here, provides a numerical approximation to the differential-algebraic system consisting of the state and co-state differential equations and the optimality condition (derived from maximization of the Hamiltonian) which in many problems may be expressed by an algebraic equation.

There is an interesting issue related to the use of optimal solutions in applied problems, which is very important for the study of the PHS effort to favor vaccine uptake. Indeed, in OC theory the control function (generally denoted by  $u(t)$ ) is usually assumed to be a generic Lebesgue integrable function (LIF). Although this assumption is adequate in many domains, it becomes unrealistic when  $u(t)$  is the outcome of a range of human interventions, as for vaccination programmes. The complex machinery of PHS has slow reactions, making impossible to update the strategy on a weekly or even monthly base. In such scenarios, control functions should instead be represented as a well-defined subset of LIFs: piece-wise constant functions (Betta et al., 2016; Faber et al., 2005). Moreover, the intervals where the control  $u(t)$  is constant must be quite long, i.e.  $u(t)$  spans in a finite-dimensional space with low dimension (typically the number of changes of strategy per year times the number of years of the chosen time horizon). This is at variance both with theoretical OC solutions, which are infinite dimensional, and with their numerical approximations, which have large dimensions. Indeed, the numerical approximation of OC requires short timesteps, which are smaller than few days, sometime few hours. This results on the whole time-horizon in a dimension that is finite but is very large.

In this circumstance the original OC problem is transformed into a new problem: finding the global minimum of a real function of a finite number of parameters by using heuristic optimization algorithms, which can be deterministic or stochastic (Banga and Seider, 1996; Schoen, 1991). Among the latter class, one of the most widely adopted is the *Simulated Annealing* (SA) (Kirkpatrick et al., 1983; Faber

et al., 2005; Henderson et al., 2003; Martínez-Alfaro, 2010; Salamon et al., 2002).

Based on these considerations, **in this work we employ the OC theory and SA-based heuristic optimization to assess** how epidemiological and economic factors affect the communication effort of the PHS. Namely, this is done by seeking a time-variable control in the model introduced in (d’Onofrio et al., 2012) such that the costs for the PHS during a given time period are minimized. In particular, our OC problem seeks to minimize total costs due to both the disease burden, vaccination costs (including costs from adverse events) and communication costs.

As in (Bauch, 2005), we consider vaccines targeted at childhood infectious diseases such as measles, mumps and pertussis. In particular, we will focus on short term horizons and investigate the ability of the PHS to effectively increase vaccine uptake in a short time span, departing from an initial situation where vaccine uptake was unsatisfactorily low. This situation was well represented by the case of measles in Italy before the large efforts to expand vaccination carried out in the last decade (d’Onofrio et al., 2012).

This approach will also allow us to show, with a specific example, how two different numerical approaches (the FSB deterministic algorithm and the SA stochastic algorithm) to OC can usefully be employed.

The paper is organized as follows. In Section 2 the model introduced in (d’Onofrio et al., 2012) is reviewed. In Section 3 the OC problem is formulated and parametrized. In Section 4 we determine OC candidate functions by using the FBS algorithm. In Section 5 we validate the nature of global minimum of the candidate OC by employing the SA stochastic algorithm. Concluding remarks follow in Section 6.

## 2 The basic model and PHS intervention

In this section we shortly review models and main results of (d’Onofrio et al., 2011, 2012; Wang et al., 2016; Buonomo et al., 2018). In (d’Onofrio et al., 2011) the following information-dependent SIR model without disease-related fatalities and with non mandatory vaccination at birth was considered:

$$\begin{aligned}\dot{S} &= \mu(1-p) - \mu S - \beta SI \\ \dot{I} &= \beta SI - (\mu + \nu)I \\ \dot{p} &= kp(1-p)(\theta_1 I - p),\end{aligned}\tag{1}$$

where the state variables  $S, I, p$  represent the fraction of susceptible individuals in the population ( $S$ ), the fraction of infectious individuals ( $I$ ), and the proportion of parents of newborns who is favorable to vaccination ( $p$ ), taken as a proxy of vaccine uptake at time  $t$ . The dynamics of the vaccinated fraction, denoted as  $V$ , is linearly depending on  $p(t)$  and it reads as follows:  $\dot{V} = \mu p - \mu V$ . Finally, the dynamics of the removed fraction (represented by the state variable  $R$ ) trivially follows:  $R = 1 - S - I - V$ . Since the dynamics of the pair  $(V, R)$  elementarily derives from the dynamics of the triple  $(S, I, p)$ , in the following we will only focus on the

latter three state variables, as in (d’Onofrio et al., 2011, 2012). The parameters are positive constants:  $\mu$  is the death rate, assumed to be identical to the birth rate;  $\nu$  is the recovery rate;  $\beta$  is the contact rate.

Note that the dynamics of  $p$  is governed by an imitation model (Hofbauer and Sigmund, 1998). This extends the equation for adoption by *imitation* (Mahajan and Peterson, 1985) by including agents’ payoffs. The net payoff gain of immunization ( $\Delta Q$ ) which is perceived from person-to-person contacts has the following general *information-dependent* form introduced in (d’Onofrio et al., 2011):  $\Delta Q = \theta I - \eta p$ , where  $\theta I$ , ( $\theta > 0$ ) defines the perceived risk associated to the disease (taken as prevalence-dependent), while  $\eta p$  ( $\eta > 0$ ) defines the perceived risk of suffering vaccine adverse events (VAE). This risk is taken to be a linear function of actual vaccine uptake  $p$ . The third equation in (1) then follows by setting  $\theta_1 = \theta/\eta$ , which represents a normalized measure of the relative risk of infection compared to the risk of VAE. In this context,  $k$  is the (normalized) index of imitation or *internal* influence. We stress that the imitation game approach in (d’Onofrio et al., 2011), which was based on the classical economy-oriented interpretation of evolutionary game theory, has been given a semi-mechanistic interpretation in (Wang et al., 2016) as the result of a mutual *contagion of ideas* between the group of parents that are favorable to vaccinate their children (whose fraction at time  $t$  is given by  $p(t)$ ) and the group that is not favorable to vaccination (whose fraction at time  $t$  is given by:  $a(t) = 1 - p(t)$ ).

Model (1) admits a ‘behavior-induced’ endemic equilibrium

$$E = (S_e, I_e(\theta), p_e) \equiv \left( \frac{1}{R_0}, \frac{1 - S_e}{1 + \frac{\nu}{\mu} + \theta}, \theta I_e(\theta) \right), \quad (2)$$

where  $R_0 = \beta/(\mu + \nu)$  is the basic reproduction number of SIR model.

Although the equilibrium  $E$  is independent of  $k$ , its stability does. Namely, for sufficiently large values of  $\theta$  one may find intervals  $[k_1(\theta), k_2(\theta)]$  where the infection prevalence shows sustained oscillations, whereas outside of these intervals  $E$  is locally asymptotically stable.

Model (1) was extended in (d’Onofrio et al., 2012) to include the effects of the communication actions by the PHS aimed at increasing vaccine uptake, by assuming that the effort of the PHS per time unit is proportional to the fraction of parents unfavorable to vaccination. The resulting equation for  $p$  is:

$$\dot{p} = k(1 - p)(\theta_1 I - p)p + G(t)(1 - p). \quad (3)$$

In view of the mechanistic interpretation given in (Wang et al., 2016), the term  $G(t)(1 - p)$  is nothing else than the influx of parents that switched their vaccine propensity thanks to the action of the PHS. It is useful to normalize the function  $G$ :

$$\gamma(t) = \frac{G(t)}{k\theta_1},$$

yielding:

$$\dot{p} = k\theta_1(1-p)[(I-\alpha p)p + \gamma(t)], \quad (4)$$

where  $\alpha = 1/\theta_1$  is a measure of the (relative) perceived risk of VAE (i.e., of the propensity to vaccine refusal). The model then reads

$$\begin{aligned} \dot{S} &= \mu(1-p) - \mu S - \beta SI \\ \dot{I} &= \beta SI - (\mu + \nu)I \\ \dot{p} &= k\theta_1(1-p)[(I-\alpha p)p + \gamma(t)]. \end{aligned} \quad (5)$$

Note that in (d'Onofrio et al., 2012) only the case of constant  $\gamma(t)$  was actually considered:  $\gamma(t) = x$ . In particular, if  $x \geq \alpha p_c^2$ , where  $p_c = 1 - 1/R_0$  is the critical immunization threshold (Anderson et al., 1992), then it can be seen that (d'Onofrio et al., 2012)

$$p(t) \rightarrow \min(1, (x/\alpha)^{0.5}), \quad I(t) \rightarrow 0. \quad (6)$$

In other words, there exists a threshold equal to  $\alpha p_c^2$  for  $x$  such that if this threshold is exceeded, i.e. if  $x \geq \alpha p_c^2$ , then  $p(t)$  tends to an equilibrium value  $p_e$  greater than the elimination threshold  $p_c$ , while the prevalence  $I(t)$  tends to zero, so that the infection is eliminated.

On the contrary, if  $x < \alpha p_c^2$ , then there is an endemic equilibrium  $(S_e, I_e, p_e)$  such that (d'Onofrio et al., 2012):

$$\begin{aligned} S_e &= 1/R_0, \\ I_e(p_e) &= \frac{\mu}{\mu + \nu} (p_c - p_e), \end{aligned} \quad (7)$$

and  $p_e$  is given by the unique positive solution of the following equation:

$$p_e (I_e(p_e) - \alpha p_e) + x = 0. \quad (8)$$

That is,

$$p_e(x) = \frac{\frac{\mu p_c}{\mu + \nu} + \sqrt{\frac{\mu^2 p_c^2}{(\mu + \nu)^2} + 4x \left( \alpha + \frac{\mu}{\mu + \nu} \right)}}{2 \left( \alpha + \frac{\mu}{\mu + \nu} \right)}. \quad (9)$$

### 3 The OC problem and parametrization

#### 3.1 The OC problem

We now consider the case in which the PHS attempts to optimally tune its temporal effort in providing information about the infection and vaccines, as represented by the function  $\gamma(t)$ . The aim is to minimize the total cost due to the disease and to the intervention during the time interval  $[0, T]$ , where  $T$  is the finite time horizon. We assume that the public effort is a Lebesgue measurable function such that:

$$0 \leq \gamma(t) \leq \gamma_{max}, \quad \text{for } t \in [0, T]. \quad (10)$$

The upper bound for  $\gamma$  reflects the idea that there are practical limitations on the maximum rate at which information may be spread by the PHS. The cost functional to be minimized includes the following components:

(i) *Enactment cost of the strategy.* We take:

$$J_\gamma = C_\gamma \int_0^T \gamma^2(t) dt, \quad (11)$$

where  $C_\gamma$  is a positive constant weight.

The quadratic cost of the control is the simplest and most widely used nonlinear representation of intervention costs in epidemiology (see e.g. (Blayneh et al., 2010; Chamchod et al., 2014; Choi and Jung, 2014; Lee et al., 2012; Lee and Castillo-Chavez, 2015; Lee et al., 2011; Neilan et al., 2010; Prosper et al., 2011; Rachah and Torres, 2016; Rodrigues et al., 2014; Zhao et al., 2016)). This assumption underlies the idea that costs might increase non-linearly at high intervention levels. Usually the quadratic cost is adopted as *black box* assumption, but in our case it can be somehow justified. Indeed, the per time unit of the PHS effort (denoted by  $j_\gamma(t)$  and whose integral is  $J_\gamma$ ) can be written as follows:

$$j_\gamma(t) = N\mu\gamma(t)a(t)A(\gamma(t), a(t)) \quad (12)$$

where:  $N$  denotes the total population,  $a(t) = 1 - p(t)$  denotes, as mentioned in section 2, the fraction of population adopting the ‘no-vaccine’ strategy,  $N\mu\gamma(t)a(t)$  is the number of parents changing strategy per time unit, and  $A(\gamma, a)$  is the per-capita cost for the PHS to realize strategy switching. This function is such that:

1.  $\partial_\gamma A(\gamma, a) > 0$ , since  $\gamma$  is a measure of the specific speed of strategy-change induced by the actions of the PHS. Thus the larger is this speed, the larger are the costs;
2.  $\partial_a A(\gamma, a) < 0$ , since the smaller (resp. larger) is the proportion of anti-vaccinators the larger (resp. smaller) is the effort needed to convince them to switch strategy. This can be qualitatively justified based on the ‘continuous’ flowing from vaccine hesitancy to vaccine refusal (Larson et al., 2014; Sadaf et al., 2013). Qualitatively: if  $a$  is close to 1 then it is likely that the subjects not-vaccinating their babies are hesitant more than contrary to vaccination; if after intensive action of the NHS  $a$  is close to 0, this suggests that these residual non-vaccinating parents are very likely strongly opponents to vaccination;
3.  $\lim_{a \rightarrow 0^+} A(\gamma, a) = +\infty$ , since when the non-vaccinating parents are very few the effort of the PHS becomes huge and the task unfeasible. This mirrors the historical evidence on smallpox for which it was impossible to eliminate all anti-vaccination groups despite its large mortality rate and also despite the large efforts world-wide to favor smallpox vaccination (Williamson, 2007).

Under the above assumptions, the simplest formulation of function  $A$  is:

$$A(\gamma, a) = \frac{C_\gamma \gamma}{N\mu a},$$

thus yielding the quadratic cost (12). **In this way, the unitary cost tends to considerably grow as  $a$  is very small, but not so much to have  $\lim_{a \rightarrow 0^+} (aA) = +\infty$ . Indeed, in such a case the enactment cost of the strategy may become unbounded. For example, if  $A(\gamma, a) \propto \gamma/a^2$ , then  $j_\gamma \propto \gamma^2/(1-p)$ . Therefore, the presence of such kind of  $j_\gamma$  in the objective functional would preclude the possibility to induce very high levels of vaccinations, which are instead observed in the epidemiological practice.**

(ii) *Direct cost of vaccination.* We take:

$$J_v = K_v \int_0^T N\mu p(t) dt, \quad (13)$$

where  $K_v$  is the average direct cost of vaccine administration per person (including costs of VAE occurring during immunization).

(iii) *Disease related costs.* Assuming an average cost  $K_{in}$  for each new infection, since the number of persons that are infected per time unit is  $N\beta S(t)I(t)$ , it follows that:

$$J_{in} = K_{in} \int_0^T N\beta S(t)I(t) dt. \quad (14)$$

Note that  $I(T)$  does not directly appear in  $J_{in}$ , which could seem suprisingly. However, since  $\beta S(t)I(t) = \dot{I} + (\mu + \nu)I$ , it follows that the above cost can be rewritten as follows:

$$J_{in} = K_{in}N \left( I(T) - I(0) + (\mu + \nu) \int_0^T I(t) dt \right).$$

By setting  $C_v = K_v N\mu$ ,  $C_\varphi = K_{in}N\beta$ , the OC problem may be formalized as follows: *find the optimal control  $\gamma^*(t)$ , defined in the set of admissible controls*

$$\Omega = \{ \gamma \mid \gamma(t) \text{ is Lebesgue measurable on } [0, T], 0 \leq \gamma(t) \leq \gamma_{max} \},$$

such that

$$J(\gamma^*) = \min_{\Omega} J(\gamma),$$

where

$$J(\gamma) = \int_0^T [C_\varphi S(t)I(t) + C_v p(t) + C_\gamma \gamma^2(t)] dt, \quad (15)$$

subject to (5) and initial data

$$S(0) = S_0 \geq 0, \quad I(0) = I_0 > 0, \quad p(0) = p_0 \geq 0, \quad (16)$$

with  $S(0) + I(0) \leq 1$ .



We use the Pontryagin's maximum principle (Pontryagin et al., 1962) and minimize the Hamiltonian given by:

$$H(S, I, p, \gamma, \lambda_1, \lambda_2, \lambda_3, t) = C_\varphi S(t)I(t) + C_v p(t) + C_\gamma \gamma^2(t) + \sum_{i=1}^3 \lambda_i f_i, \quad (17)$$

where  $f_i$ ,  $i = 1, 2, 3$ , represent the right-hand sides of system (5) and  $\lambda_i$ ,  $i = 1, 2, 3$ , are the adjoint variables. The adjoint equations are given by:

$$\dot{\lambda}_1 = -\frac{\partial H}{\partial S}; \quad \dot{\lambda}_2 = -\frac{\partial H}{\partial I}; \quad \dot{\lambda}_3 = -\frac{\partial H}{\partial p}. \quad (18)$$

Note that the third equation of (5) can be written as follows:

$$\dot{p} = k\theta_1 [\alpha p^3 - \alpha p^2 - Ip^2 + Ip + \gamma - p\gamma],$$

implying

$$\begin{aligned} \dot{\lambda}_1 &= -C_\varphi I + \mu\lambda_1 + \beta I\lambda_1 - \beta I\lambda_2 \\ \dot{\lambda}_2 &= -C_\varphi S + \beta S\lambda_1 - \beta S\lambda_2 + (\mu + \nu)\lambda_2 - k\theta_1(1-p)p\lambda_3 \\ \dot{\lambda}_3 &= -C_v + \mu\lambda_1 - k\theta_1\lambda_3 [I - 2\alpha p - 2Ip + 3\alpha p^2 - \gamma]. \end{aligned} \quad (19)$$

The transversality equations are:

$$\lambda_i(T) = 0, \quad i = 1, 2, 3. \quad (20)$$

The existence of the OC solution  $\gamma^*(t)$ , is guaranteed because the requirements of classical existence theorems (i.e. Theorem III 4.1 and Corollary 4.1 in (Fleming and Rishel, 2012)) are satisfied. In particular, it can be easily checked that the integrand of the objective functional is convex with respect to  $\gamma$  and the state system can be written as a linear function of the control with coefficients dependent on time and the state variables. This ensures the existence of an optimal solution (e.g. (Gaff and Schaefer, 2009)).

We remark that a uniqueness result may be established, for sufficiently small time-intervals, by using the approach given in (Fister et al., 1998; Joshi, 2002) and also employed in (Panetta and Fister, 2000, 2003; Gaff and Schaefer, 2009) for OC problems of epidemics and cancer treatment.

Denote by  $(S^*, I^*, p^*)$  the state corresponding to the optimal control  $\gamma^*$ . On the interior of the control set  $\Omega$ , minimizing the Hamiltonian gives:

$$\frac{\partial H}{\partial \gamma} = 0,$$

at  $\gamma^*$ . That is:

$$\gamma^*(t) = \frac{k\theta_1 (p^* - 1) \lambda_3}{2C_\gamma},$$

and, taking into account the bounds on  $\gamma^*$ , the characterization of the OC is:

$$\gamma^* = \begin{cases} 0 & \text{if } k\theta_1(p^* - 1)\lambda_3 < 0 \\ k\theta_1(p^* - 1)\lambda_3/2C_\gamma & \text{if } 0 \leq k\theta_1(p^* - 1)\lambda_3 \leq 2C_\gamma\gamma_{max} \\ \gamma_{max} & \text{if } k\theta_1(p^* - 1)\lambda_3 > 2C_\gamma\gamma_{max}. \end{cases} \quad (21)$$

which, in short form, may be written as follows:

$$\gamma^*(t) = \min(\max(0, k\theta_1(p^* - 1)\lambda_3/2C_\gamma), \gamma_{max}).$$

### 3.2 Parametrization

The description of the parameters and their baseline values (or range) used in the numerical simulations are reported in Table 1. The demographic and epidemiological parameters (i. e.  $\mu, \beta, \nu, R_0, N$ ) are taken from (d'Onofrio et al., 2011; Bauch, 2005). Following (Bauch, 2005), a small immigration/emigration constant flux  $\varepsilon$  is also included to take into the account of immigration of infected individuals, with a positive influx  $+\varepsilon$  in the second equation of (5), compensated by a negative one,  $-\varepsilon$ , in the first equation of (5). The model (5) reads:

$$\begin{aligned} \dot{S} &= \mu(1-p) - \mu S - \beta SI - \varepsilon \\ \dot{I} &= \beta SI + \varepsilon - (\mu + \nu)I \\ \dot{p} &= k\theta_1(1-p)[(I - \alpha p)p + \gamma(t)]. \end{aligned} \quad (22)$$

The introduction of this constant term, obviously, does not modify the optimality conditions found in Section 3.1. Our aim is to investigate the ability of the PHS to increase the vaccination coverage in the short-medium term (as for measles in Italy (d'Onofrio et al., 2012)). Moreover, medium-short horizons were adopted in the OC-based investigations of other kinds of PH interventions concerning infectious diseases (Choi and Jung, 2014; Rodrigues et al., 2014). Thus, the length of the PHS planning horizon has been set to  $T = 10yr$ . In order to emphasize the factors underlying the difficulties to eliminate the infection, we set  $\gamma_{max}$  at levels below the threshold  $\alpha p_c^2$  that would ensure elimination in model (5) with constant  $\gamma$ . In particular in our simulations we will use either  $\gamma_{max} = 0.5\alpha p_c^2$  or  $\gamma_{max} = 0.7\alpha p_c^2$ .

**Remark 3.1.** *Note that the threshold  $\alpha p_c^2$  assumes 'small values' (d'Onofrio et al., 2012), i.e.  $\gamma(t)$  takes values in a 'small' range. However, the impact of this control variable is large. For example, we remind that, in the unconstrained case, if  $\gamma(t)$  even slightly exceeds the 'small' threshold  $\alpha p_c^2$  then it can induce the disease elimination from the target population.*

Moreover, we assume that (i) for  $t \leq 0$  no action has been enacted by the PHS; (ii) at  $t = 0$  the system is (unless otherwise specified) at its behavior-induced endemic equilibrium forced by private information only, i.e. equilibrium (2):

$$(S(0), I(0), p(0)) = E = (S_e, I_e(\theta_1), p_e(\theta_1)).$$

Finally, to remove the complications related with the long waves predicted by the state system in its oscillatory regimes, we only select values of the behavioral parameters  $k, \theta_1$  such that equilibrium  $E$  given in (2) is locally stable. In particular, we consider the following cases that should capture all the relevant situations:

- C1  $(k, \theta_1) = (1/10, 2000)$ , corresponding to relatively slow imitation coefficient and large perceived relative risk of infection;
- C2  $(k, \theta_1) = (1/90, 450)$ , corresponding to very slow imitation and an intermediate perceived relative risk of infection;
- C3  $(k, \theta_1) = (9/10, 4000)$ , corresponding to relatively fast imitation and a very large perceived relative risk of infection;

As for costs parameters, the value of  $K_{in}$  is set to the best estimate of the average cost per measles case estimated for the UK following the societal perspective (Carabin et al., 2002), given by 307 USD. The unit cost of vaccination,  $K_v$ , is computed as follows:  $K_v = K_{vaccine\ dose} + K_{side\ effects}$ , where:  $K_{vaccine\ dose}$  is the cost to deliver a single vaccine dose, which is set to the cost of a unit MMR dose, given by 19 USD, while  $K_{side\ effects}$  is the average direct cost of an episode of adverse event following immunization, which is set to 2.08 USD (Carabin et al., 2002).

As for  $C_\gamma$ , given the lack of field data, we prefer to roughly infer its order of magnitude by the following heuristic reasoning. Let us consider the case of a constant control  $\gamma = x(const.)$ , where  $x \in (0, \alpha p_c^2)$ . In this case, the total cost per unit time at the endemic state  $E$  is given by:

$$\bar{J}(x) = K_v N \mu p_e(x) + K_{in} N \beta S_e I_e(p_e(x)) + C_\gamma x^2.$$

To figure out the order of magnitude of  $C_\gamma$ , we may assume that given a suitable value of  $x$ , the cost to enact the PHS information program is a fraction  $\psi \in (0, 1]$ , having the same order of magnitude of the total costs arising from infection and vaccination, i.e.

$$C_\gamma y^2 = \psi [K_v N \mu p_e(y) + K_{in} N \beta S_e I_e(p_e(y))], \quad (23)$$

implying

$$C_\gamma = \psi \frac{N \mu}{y^2} [K_v p_e(y) + K_{in} (p_c - p_e(y))], \quad (24)$$

which provides a baseline estimate for  $C_\gamma$ .

<i>Symbol</i>	<i>Description</i>	<i>Baseline value or range</i>
$N$	Total population size	$6 \cdot 10^7$
$\mu$	Natural birth/death rate	$5.4757 \cdot 10^{-5} \text{ day}^{-1}$
$\nu$	Recovery rate	$1/10 \text{ day}^{-1}$
$R_0$	Basic reproduction number	10
$\beta$	Contact rate	$R_0(\mu + \nu)$
$\varepsilon$	Emigration/immigration flux	$2.86 \cdot 10^{-8} \text{ day}^{-1}$
$k$	Imitation coefficient	$1/90 \text{ day}^{-1} - 0.9 \text{ day}^{-1}$
$\theta_1$	Relative risk of infection $\theta(M)$	250 – 4000
$\alpha$	Relative risk of vaccination $\alpha(p)$	$1/\theta_1$
$K_{inf}$	Average cost per infection case	307 USD
$K_v$	Average costs per unit immunization	21.08 USD
$C_\varphi$	Total costs of infection	$K_{inf}\beta N$
$C_v$	Total cost of vaccinated	$K_v N \mu$
$C_\gamma$	Parameter tuning intervention cost	See text
$\gamma_{\max}$	Maximum control	$(0.5 - 0.7)\alpha p_c^2$
$S(0)$	Initial value for $S$	$1/10$
$I(0)$	Initial value for $I$	$I_e(\theta_1)$
$p(0)$	Initial value for $p$	$p_e(\theta_1)$

Table 1: Description of parameters and initial data for the OC problem.

## 4 Results: numerical solution of the OC problem by FBS algorithm

### 4.1 Numerical algorithm

In this section the optimality system given by (22), (16), (19), (20) and (21) is solved numerically by the *FBS* algorithm described in (Lenhart and Workman, 2007), and whose convergence is shown in (Hackbusch, 1978) (see also (McAsey et al., 2012)). The process begins with an initial guess on the control variable. Then the state equations (22) with initial data (16) are solved with a forward in time Runge-Kutta routine. Using those new state values, the adjoint equations (19) with final data (20) are solved backward in time with the Runge-Kutta solver. The control is updated by putting the new values of states and adjoints into the characterization (21) and using a convex combination of the previous and current control estimates. **The process is repeated until either convergence occurs or a maximum number of iterations has been reached. In the latter case, the computation process is marked as ‘not converging’.** We built a MATLAB code (Lenhart and Workman, 2007; MATLAB, 2015) to perform the simulations.

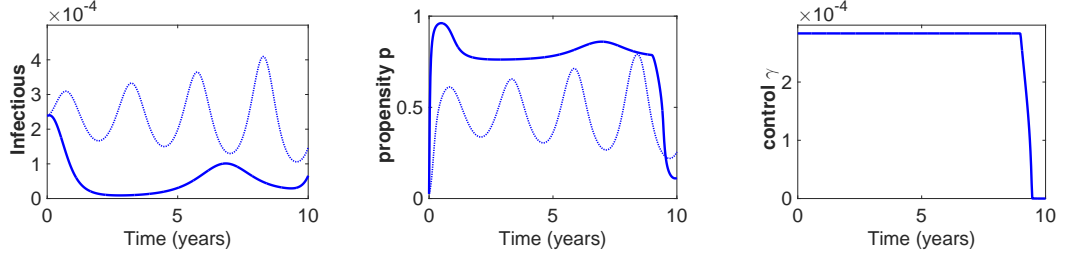


Figure 1: Parameters of case C1 ( $k = 1/10$ ,  $\theta_1 = 2000$ ) and  $\gamma_{\max} = 0.7\alpha p_c^2$ . Left and center plots: dynamics of the system without control (system (22) with  $\gamma = 0$ ) (dotted lines) and the controlled system (solid lines). Right plot: time profile of the optimal control. Initial data correspond to minimum value of  $p$  when the system is uncontrolled, that is:  $S(0) = 0.0999972$ ,  $I(0) = 2.3878 \cdot 10^{-4}$ ,  $p(0) = 0.0256077$ .

## 4.2 The structure of the OC function

As mentioned above, in our simulations we used either  $\gamma_{\max} = 0.5\alpha p_c^2$  or  $\gamma_{\max} = 0.7\alpha p_c^2$ , thereby ruling out the possibility of disease elimination. Further, we set  $\psi = 1$  and  $y = \alpha p_c^2$  in formula (24) to assign a baseline value to communication costs. This gives a parsimonious baseline where the steady-state cost for the PHS communication effort is identical to the steady-state cost for vaccination in the case where infection is eliminated. Indeed, for the chosen  $y$  it is  $p_e(y) = p_c$  in (6)). The OC function resulting from previous hypotheses sets at  $\gamma_{\max}$  for the largest part of the time horizon. This can be seen in right panels of Figures 1, 2, 3, which report the optimal control time profiles. This result follows from the disproportion between the unit cost of the policy (i.e., the sum of the unit vaccination cost and the unit communication cost) and the disease-related unit cost, which remains substantially larger. Close to the end of the horizon the control rapidly switches to zero.

## 4.3 Role of behavioral parameters

We now focus on the interplay between key behavioral parameters (the imitation coefficient  $k$  and the relative risk of infection  $\theta_1$ ) and the control upper bound  $\gamma_{\max}$ , in affecting the system dynamics.

Figure 1 reports the solutions of the controlled system for case C1 in Section 3.2 ( $k = 0.1$ ,  $\theta_1 = 2000$ ),  $\gamma_{\max} = 0.7\alpha p_c^2$ . Initial data correspond to the minimum value of  $p$  for system (22) with  $\gamma = 0$ , i. e.  $p_{\min} = 0.02561$ . The corresponding initial values are  $S(0) = 0.0999$ ,  $I(0) = 2.3878 \cdot 10^{-4}$ . This case is of interest as it represents a worst initial scenario for the public communication campaign, since the vaccine uptake is set at its minimum level (which is generally unknown to the public health planners). Figure 1 shows that despite the unfavorable initial conditions, a good result in the control of the disease is achieved, with a sharp decrease of the

infective prevalence. The next peak in prevalence (occurring seven years after the start of the communication campaign) is more than halved compared to the initial level of prevalence. Moreover, a quite high average vaccine uptake is maintained for most of the intervention horizon.

More in depth, the propensity to vaccinate in the first few months of the program moves from negligible levels to about 95%, which is above the critical vaccination threshold  $p_c = 90\%$ . The propensity starts declining 18 months after the initiation of the programme, setting to quite sub-optimal levels in the range of 80%. Given that  $\gamma^*(t) \approx \gamma_{\max}$  for most of the horizon (Figure 1) – which means that the perceptions about benefits and costs of immunization communicated by the PHS remain constant – it follows that the decline in coverage stems entirely from the changed perceptions of risks communicated among parents through their spontaneous contacts. This perception, indeed, is declining due to the declining prevalence. This favors the relapse of the infection bringing the new wave described above. In turn, this yields - the communication effort being still constant - a moderate relapse of  $p$ . This relapse however just lasts the duration of the epidemic wave, because the subsequent decline in the perceived risk of infection at the end of the wave brings a new phase of low perceived benefit from vaccination. The decline in the propensity to vaccinate follows the disappearance of the epidemic wave with some delay. This lag is essentially related to the magnitude of the imitation speed. Finally, as far as the impact of the control is concerned, we note that although the control  $\gamma(t)$  assumes 'small' values its impact is large. First, as we noticed above, because a good decrease of the disease prevalence and a good increase of the vaccine uptake rate are predicted. Second, in the absence of control the objective functional is  $27.94 * 6 * 10^7 USD$ , whereas in the optimally controlled scenario the cost reduces to  $11.03 * 6 * 10^7 USD$ , i.e. a reduction of 60.52% of the costs.

Figure 2 illustrates case C2 in Section 3.2 ( $k = 1/90$ ,  $\theta_1 = 450$ ). The initial data correspond to the endemic equilibrium (2) of system (1). We in particular compare the effects of different levels of the control upper bound  $\gamma_{\max}$ , which is set to  $\gamma_{\max} = 0.5\alpha p_c^2$  (panel A), and to  $\gamma_{\max} = 0.7\alpha p_c^2$  (panel B), respectively. The optimal dynamics is qualitatively similar to Figure 1. In particular, the larger value of  $\gamma_{\max}$  (panel (B)) promotes a larger vaccine uptake, inducing a lower prevalence and delaying the next epidemics, compared to panel (A). The pattern in the propensity to vaccinate is more regular (indeed almost constant for most of the horizon) compared to Figure 1. This is the consequence of the very low level of the imitation speed, given the short horizon, and the lower perceived risk from infection which, jointly considered, make it negligible the impact of the evolution in the prevalence on vaccination payoff.

Finally, in Figure 3 we consider case C3 in Section 3.2, assuming both a large imitation speed ( $k = 0.9$ ) and a very large perceived risk of infection ( $\theta_1 = 4000$ ), while still comparing the effects of different levels of the control upper bound  $\gamma_{\max}$

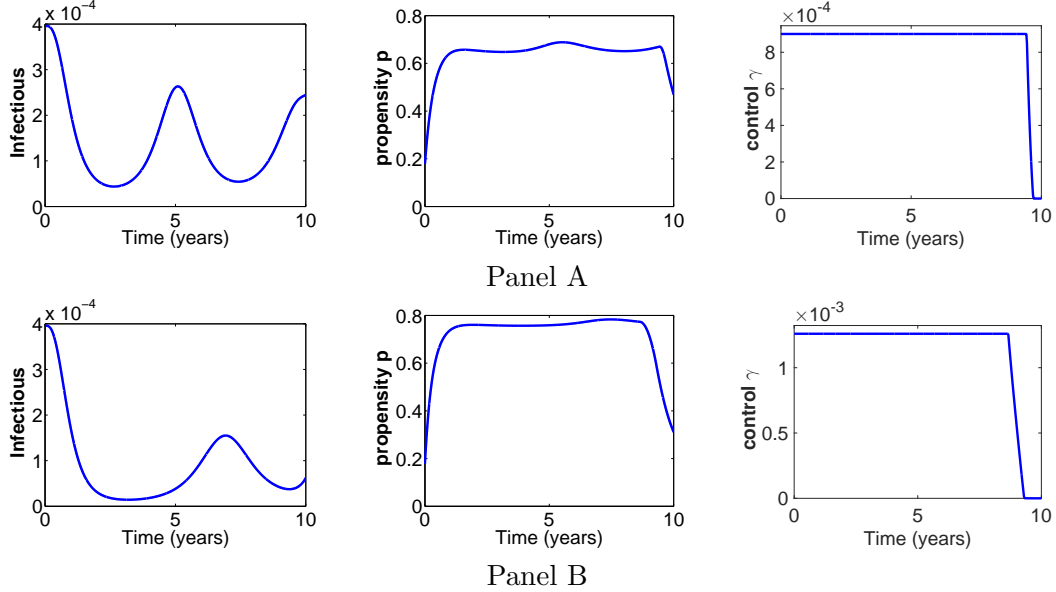


Figure 2: Parameters of case C2 ( $k = 1/90$ ,  $\theta_1 = 450$ ). Panel A:  $\gamma_{\max} = 0.5\alpha p_c^2$ ; Panel B:  $\gamma_{\max} = 0.7\alpha p_c^2$ . The initial data correspond to the endemic equilibrium (2) of system (1).

(panel A vs panel B). The higher perceived risk of infection, compared to Figure 2, allows to achieve higher coverage levels, with temporary peaks as high as 100%. However, these peaks are not maintained, primarily due to the fast decline in the perceived risk of infection but also to the increased perceived risk of vaccine adverse events (caused by the large number of immunizations) whose occurrence is fastly communicated among parents thanks to the large value of the imitation speed. **As in the case of Figure 2 also here the propensity to vaccinate  $p$  achieves larger levels on average, which increases the duration of the post-vaccination *honey-moon* phase (Anderson et al., 1992) by delaying (and mitigating) the onset of the first epidemic wave (see Figure 3, panel (B)).**

These scenarios are representative of the system behavior over a wide spectrum of parameter values.

## 5 Results: numerical solution of the OC by Simulated Annealing

### 5.1 Simulated Annealing for piecewise-constant Control problems

Public health interventions such as programs to favor vaccinations by reducing parental hesitancy or refusal can be very complex and multi-layered (Sadaf et al.,

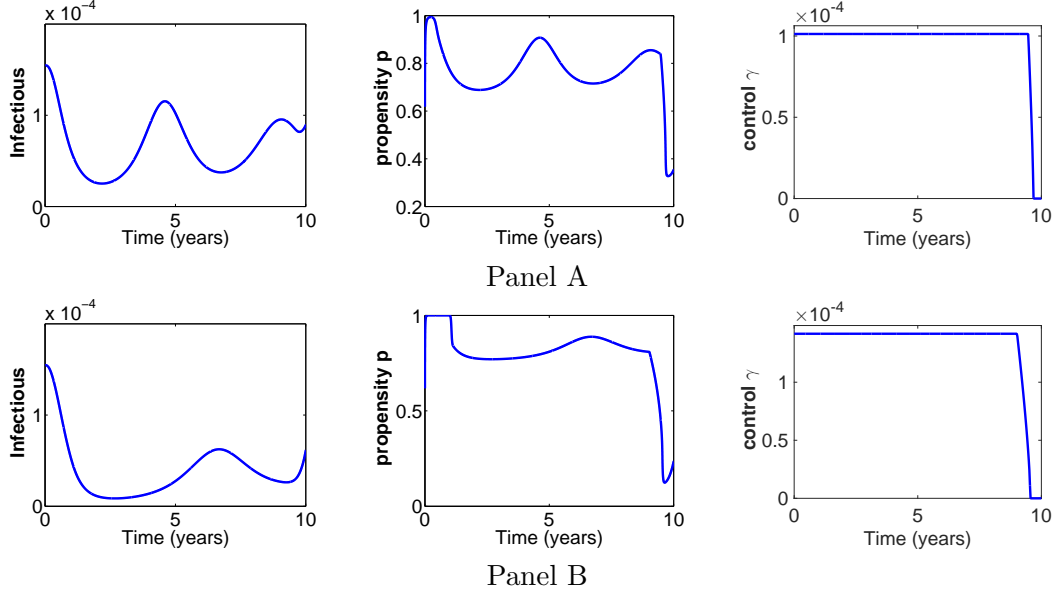


Figure 3: Parameters of case C3 ( $k = 9/10$ ,  $\theta_1 = 4000$ ). Panel A:  $\gamma_{\max} = 0.5\alpha p_c^2$ ; Panel B:  $\gamma_{\max} = 0.7\alpha p_c^2$ . The initial data correspond to the endemic equilibrium (2) of system (1)

2013). Thus, logistic and practical constraints make a time-continuous updating of the policy difficult. Thus, controls **in a given finite time interval**  $[0, t_f]$  should rather be piecewise constant, of the form:

$$u(t) = \sum_{j=0}^{j_{\max}} u_j \text{Ind}(t, [j\tau, (j+1)\tau)), \quad (25)$$

where the  $u_j$  are suitable constants,  $\tau$  is a **positive discretization step**,  $(j_{\max} + 1)\tau = t_f$  and  $\text{Ind}(t, W)$  denotes the indicator function of a given set  $W$ . **Note that the control horizon  $[0, t_f]$  could be discretized by assuming a non constant discretization step. We used a constant step  $\tau$  for the sake of the simplicity and to mimic seasonal PH activity plans.** Then, given the general  $n$ -dimensional ODE control system depending on the control  $u(t)$ :

$$\dot{x}(t) = F(x(t), u(t)), \quad (26)$$

let us seek the control  $u$  that minimizes the functional

$$J(u(\cdot)) = \psi(x(t_f; u(\cdot), x_0), u(t_f)) + \int_0^{t_f} L(x(t; u(\cdot), x_0), u(t)) dt, \quad (27)$$

under constraint

$$u_{\min}(t) \leq u(t) \leq u_{\max}(t), \quad (28)$$



where the control action  $u$  has the form (25) and is enacted on a time interval  $[0, t_f]$ .

By defining the vector  $a = (u_0, \dots, u_N)$ , where  $N = \lceil t_f/\tau \rceil$ , system (26) can be rewritten as the following ODE system depending on the real vector parameter  $a$ :

$$\dot{x}(t) = f(x(t); a). \quad (29)$$

This implies that under a piecewise-constant intervention, the original OC problem transforms into the problem of nonlinear constrained optimization (NCO) of the following function of the real parameter  $a$ :

$$J(a) = \psi_1(x(t_f; a, x_0), a_N) + \int_0^{t_f} L_1(x(t; a, x_0), a) dt, \quad (30)$$

under constraint  $a \in \Omega$ , where (28) yields

$$\Omega = \prod_{i=1}^N \left[ \max_{t \in T_i} u_{\min}(t), \min_{t \in T_i} u_{\max}(t) \right]; \quad T_i = [i\tau, (i+1)\tau].$$

This NCO problem still involves the solution of the dynamical system (29) and the application of functional operators (the integral), which will have to be numerically solved. Traditional numerical algorithms for NCO problems suffer the shortcoming that they often stuck to local minima (Henderson et al., 2003; Salamon et al., 2002). To remedy this drawback, various stochastic optimization algorithms (SOA) exploring the relevant parametric space through a random walk have been proposed (Banga and Seider, 1996; Schoen, 1991).

The SA is one of the most widely adopted SOA and the description is as follows (see (Henderson et al., 2003; Salamon et al., 2002) for further details): the random walk in the SA algorithm is initialized from a value  $a_0 \in \Omega$  which should be sufficiently close to the global minimum  $a^{min}$  (what is called an *educated guess*). Let  $J(a_0)$  denote the corresponding value of the objective function. Then a random value  $a_1$  is drawn in the neighborhood of  $a_0$  from a suitable ‘bell-shaped’ or ‘disk-shaped’ (i.e. uniform on an hypersphere in a given norm) probability density function (PDF)  $\rho$ . If  $a_1$  is suitable (i.e., inside  $\Omega$ ), then the corresponding value  $J(a_1)$  is computed. Unlike deterministic algorithms (where  $a_1$  would be accepted if  $J(a_1) \leq J(a_0)$  and rejected otherwise), in the SA algorithm if

$$J(a_{i+1}) > J(a_i),$$

then  $a_{i+1}$  can be accepted or rejected by a Boltzmann-like probabilistic rule. The rationale for this is exactly avoiding to be stuck at a local minimum.

The probabilistic rule adopted by the SA algorithm is as follows (Henderson et al., 2003; Salamon et al., 2002):

$$\exp\left(-\frac{J(a_{i+1}) - J(a_i)}{k_b T_{m(i)}}\right) < r,$$

where  $r$  is a random number uniformly distributed in  $(0, 1)$ , and  $T_{m(i)}$  is the 'temperature', i. e. an artificial tuning parameter which is gradually decreasing up to zero as  $m(i)$  increases:

$$\lim_{i \rightarrow \infty} T_{m(i)} = 0.$$

In fact, this algorithm is inspired by Statistical Physics, where the reduction of the temperature (annealing) of a system leads it to a state of global minimal energy, here represented by the function to be minimized (Henderson et al., 2003; Salamon et al., 2002). A number of implementations of SA are available using different rules of decreasing  $T_{m(i)}$  and for adjusting the PDF  $\rho$  (Faber et al., 2005; Henderson et al., 2003; Salamon et al., 2002).

## 5.2 Optimal PHS communication plans by SA

**In this section we apply the SA approach to compare the optimal solutions with that provided by the FBS algorithm, and also to find solutions for those parametric values for which FBS failed to converge.** The lack of convergence occurred for large values of the communication cost  $C_\gamma$ . As a further hypothesis, we assume that the communication campaigns enacted by the PHS are updated every three months, so that  $\tau = 90$  days in (25).

We proceed as follows: first, a candidate global optimal solution is discretized at times  $t_0, t_1, \dots, t_n$  to obtain a vector  $l$  (the 'educated guess'). To this aim, when possible, the OC solution produced by the FBS algorithm is employed. Next, we set  $a_0 = l$  and the SA algorithm is run.

If the optimum  $u(t)$  found by the SA algorithm is far from  $\gamma^*$ , then it is reasonable to assume that the candidate solution is not a global minimum. In the contrary case, it would be reasonable to assume that  $\gamma^*(t)$  is the real global minimum.

Since the SA algorithm is a stochastic process, it produces different outputs (in our case, the values of the vector parameter  $a$  and values of the functional  $J$ ) at each run. For this reason, for each set of parameters and initial conditions, the algorithm is applied several times and then it is taken as the candidate optimal control the one corresponding to the smallest evaluated value of  $J$ .

We have performed the SA-based optimizations by using the same parameter values used in the previous section. The left panel of Figure 4 reports both the continuous control  $\gamma^*(t)$  obtained by the FBS algorithm, and the optimal piecewise constant control  $u$  obtained by the SA. It is interesting to note that although the ideal and approximate control have different nature (the former is continuous, the latter is piecewise constant), they overlap very well. As regards the values of the cost functional  $J$ , the minimum observed with the piecewise control is  $J_{SA} = 11.09 \cdot 6 \cdot 10^7$ , while the minimum corresponding to the continuous control is essentially identical:  $J_{FBS} = 11.03 \cdot 6 \cdot 10^7$ . This implies that the idealized solution is well validated by the piece-wise control.

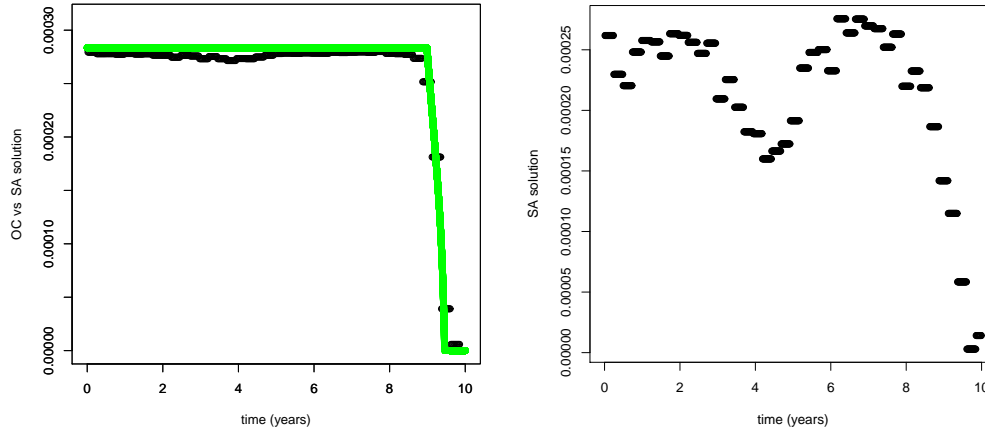


Figure 4: SA-based search for the optimal control. Left Panel: plot of the SA optimal solution vs. the plot of the continuous OC solution. Parameters and initial values as in Figure 1. Right panel: plot of the computed SA optimal solution. The same parameters of the left panel were adopted, but one,  $C_\gamma$ , which is here five times larger than the baseline case.

In the other cases, there is a general agreement of the computed minima  $J$  although in the cases computed by applying SA the value is slightly larger (see Table 2).

The OC solutions obtained for the piece-wise control with the SA algorithm are similar – in our simulations – to the continuous ones obtained by using FBS algorithm. However, some appreciable local deviations and oscillations can be observed. These deviations might be due to the fact that the functional  $J$  close to its minima is quite ‘flat’, thus allowing to local deviations that may be quite significant.

We have also performed further simulations, which could not be performed by using the FBS algorithm due to lack of convergence in the software we used. We have assumed a larger cost coefficient for the control, namely a five-fold larger  $C_\gamma$ . **These larger values of  $C_\gamma$  were employed to assess how the control changed in the case of substantially larger costs for the Public Health campaigns aimed at increasing the propensity to vaccinate.** We have obtained a radically different OC solution compared with the simulations with the baseline  $C_\gamma$  (see right panels of Figures 4, 5, 6). Indeed, in all cases the obtained control was strongly non-monotone. Of course, due to the remarkable increase of the cost associated to the control, all these OC solutions are smaller than the corresponding solutions found in the case with the baseline  $C_\gamma$ . Finally, with regards to the obtained numerical values for  $J$ , in all cases they are larger than the baseline corresponding cases, as reported in Table 2.

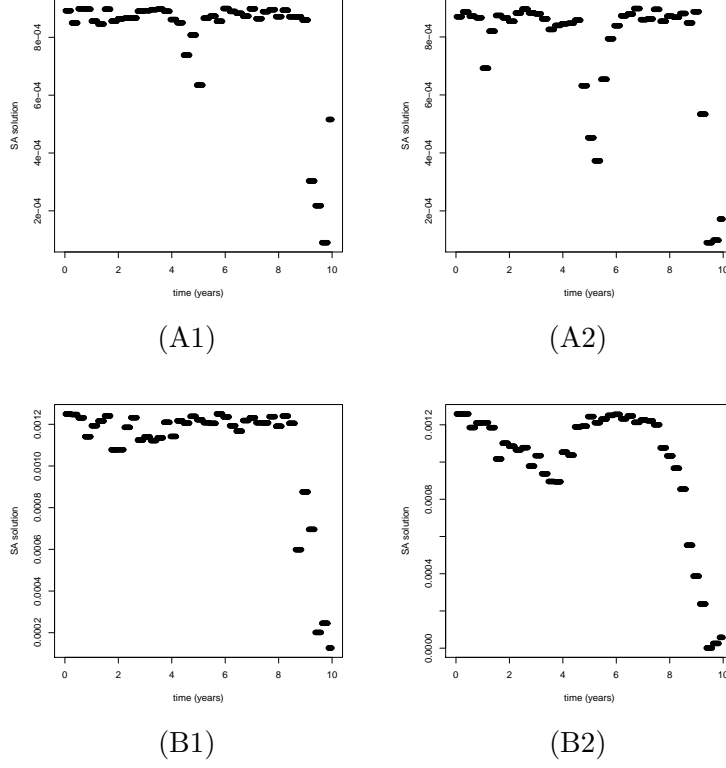


Figure 5: Plots of the computed SA optimal solutions. Parameters of case C2 ( $k = 1/90$ ,  $\theta_1 = 450$ ). Panels A:  $\gamma_{\max} = 0.5\alpha p_c^2$ . Panels B:  $\gamma_{\max} = 0.7\alpha p_c^2$ . Panels (A1) and (B1):  $C_\gamma$  as in Figure 2. Panels (A2) and (B2):  $C_\gamma$  five times larger.

## 6 Concluding remarks

Under voluntary vaccination for childhood diseases, modeling of immunization campaigns is quite complex since coverage is the outcome of parents' decisions. However, the PHS can enact actions aimed at contrasting policy-resistant behaviors by enforcing its role as the most influential provider of information about the infection and vaccines, and related benefits and costs. Our work is aimed at determining the optimal control of the effort of PHS in the framework of Behavioral Epidemiology.

We found that under many circumstances the resulting OC time-profile rapidly sets at its maximum admissible value, where it remains for the largest part of the time horizon. This result follows from the disproportion between the unit cost of the policy (i.e., the sum of the unit vaccination cost and the unit communication cost) and the costs induced by the disease. Indeed, for childhood diseases the latter cost is substantially larger than the former ones. The setting of the control effort at its

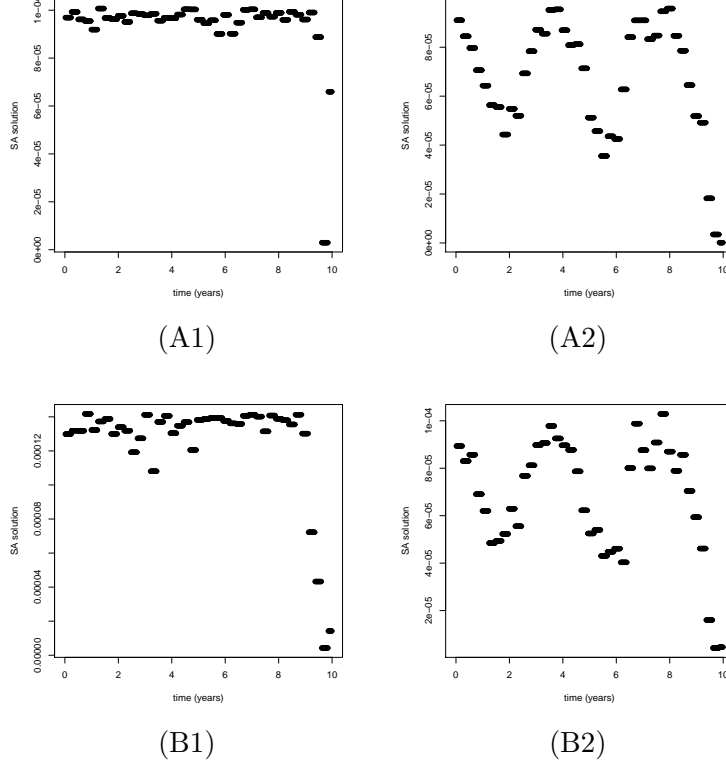


Figure 6: Plots of the median of the computed 101 SA optimal solutions. Parameters of case C3 ( $k = 9/10$ ,  $\theta_1 = 4000$ ). Panels A:  $\gamma_{\max} = 0.5\alpha p_c^2$ . Panels B:  $\gamma_{\max} = 0.7\alpha p_c^2$ . Panels (A1) and (B1):  $C_\gamma$  as in Figure 3. Panels (A2) and (B2):  $C_\gamma$  five times larger.

maximum level means that the perceptions about the net benefit of immunization communicated by the PHS cannot be increased any further. This suggests that the subsequent dynamics stems entirely from the changed perceptions of risks (i.e., mostly the declining perceived risk of infection due to the declining prevalence) communicated among parents through spontaneous contacts. This leads, sooner or later, to a future decline in vaccine uptake triggered by the success in controlling infection during the first phase of the program. Although, in the case of baseline  $C_\gamma$  from mathematical point of view there is not so much difference between the cost associated to a constant control with respect to the cost associated to the OC solution we found, from the practical Public Health viewpoint a difference exists. Indeed, using a constant control even for all the time horizon (i.e. even when our OC solution is zero) implies that one has to maintain a considerable amount of activities (some of which at no cost, e.g. voluntary efforts by GPs), moreover at a cost that is greater than in absence of any work.

Table 2: Key features and results of the simulated scenarios.  $ID_{pm}$  indicates initial data corresponding to minimum value of  $p$  when the system is uncontrolled.  $E_{u0}$  indicates that the initial data correspond to the endemic equilibrium (2) of system (1)

Scenario	$k$	$\theta$	$\frac{\gamma_{max}}{\alpha p_c^2}$	IC	$C_\gamma$	$\frac{J_{SA}}{N}$	$\frac{J_{FBS}}{N}$	$\alpha p_c^2$
Fig. 1 & 4, left	0.1	2000	0.7	$ID_{pm}$	6333	11.09	11.03	$4.05 \cdot 10^{-4}$
Fig. 1 & 4, right	0.1	2000	0.7	$ID_{pm}$	5*6333	16.81	–	$4.05 \cdot 10^{-4}$
Fig. 2 A & 5 (A1)	1/90	450	0.5	$E_{u0}$	320.63	20.12	19.46	$1.8 \cdot 10^{-3}$
Fig. 2 A & 5 (A2)	1/90	450	0.5	$E_{u0}$	5*320.63	24.43	–	$1.8 \cdot 10^{-3}$
Fig. 2 B & 5 (B1)	1/90	450	0.7	$E_{u0}$	320.63	14.65	14.45	$1.8 \cdot 10^{-3}$
Fig. 2 B & 5 (B2)	1/90	450	0.7	$E_{u0}$	5*320.63	20.43	–	$1.8 \cdot 10^{-3}$
Fig. 3 A & 6 (A1)	0.9	4000	0.5	$E_{u0}$	25330	11.83	11.67	$2.02 \cdot 10^{-4}$
Fig. 3 A & 6 (A2)	0.9	4000	0.5	$E_{u0}$	5*25330	14.54	–	$2.02 \cdot 10^{-4}$
Fig. 3 B & 6 (B1)	0.9	4000	0.7	$E_{u0}$	25330	9.52	9.40	$2.02 \cdot 10^{-4}$
Fig. 3 B & 6 (B2)	0.9	4000	0.7	$E_{u0}$	5*25330	14.55	–	$2.02 \cdot 10^{-4}$

We feel that this results **might contribute to clarify** some of the difficulties met by PHS systems in maintaining high coverages for common vaccine preventable infections.

For large PHS action-related costs, we obtained that the OC is non-monotone, in some cases exhibiting oscillations. **Unfortunately, in case of larger  $C_\gamma$  the FBS algorithm did not converge, so that we could not assess, in the continuous case, the effects of the upper limit constraints  $\gamma_{max}$ . However, this is fully done with the SA algorithm.**

As far as the control modeling is concerned, we stressed the relevance of modeling the efforts by the PHS as piecewise constant functions. This called for the use of the SA optimization algorithm.

**Our results show that the OC solutions obtained by using the FBS and those obtained by the SA algorithms stay overall close.** By employing SA algorithm large local deviations and local stochastic fluctuations are observed, which suggests that the minimum corresponding to the OC solution for the considered problem might be quite 'flat'. Therefore, in our problem, even alternative controls that have local remarkable deviations are very close to the global minimum. In this sense, the classical OC solution seems to be relatively robust with respect to deviations imposed by the practical implementation of the communication program.

As far as the modeling of intervention costs are concerned, we provided an example where a quadratic cost – often adopted as a proxy of more complex nonlinear costs – can be justified based on simple PH reasoning. On the other hand, the

field of investigations on public vaccine awareness is very recent and qualitative (Consortium; IMI) so that quantitative studies based on mature data are yet to come.

A limitation of our work is that we adopted a very simple model. Results from a more realistic model including age structure and other kinds of heterogeneity as well as a detailed modeling of the PHS efforts would provide more useful indications to PH policy-makers. **As far as the model of the disease spread is concerned, the first and strongest limitation of our work is that we employed a SIR deterministic model (complemented by an imitation game) without age structure. This model is not fully adequate to quantitative spread and control of an epidemic in the real world. Historically, it was ‘only’ able to provide important qualitative hints to Public Health authorities, and as a base to build more realistic models. Thus the present study has to be understood as a rough ‘first order approximation’ of a real scenario. A slightly better (although insufficient) approximation would require the inclusion of internal (Andersson and Britton, 2012) and external (Øksendal, 2003) randomness. They would require the application of methodologies of stochastic optimal control for, respectively, stochastic differential systems (Fleming and Rishel, 2012, 1975) and for ‘birth and death epidemic processes’ (Lefèvre, 1981; Getz, 1975). In turn both deterministic and stochastic SIR model with and without age structure suffer of a common important limitation: they focus on the spread and control of a single isolated target population. This is seldom the case in the real world, so that a stochastic meta-population approach (Keeling and Rohani, 2011; Ajelli et al., 2010) including age structured social contacts (Melegaro et al., 2017) would be a significant improvement towards providing more realistic suggestions to Public Health authorities.**

**As far as the model of the PHS intervention is concerned,** we stress that here we adopted a practical viewpoint where we defined as effort the control  $\gamma(t)$ , which more realistically should instead be considered as the ‘impact of the effort’. A function or even better a dynamical system connecting the real effort  $E(t)$  and  $\gamma(t)$  should, thus, complete the dynamical system in study. Note, however, that the exact definition and properties of the relationship between  $E(t)$  and  $\gamma(t)$  are both nontrivial. **Another important point is the investigation of more realistic functional forms to describe the per-capita costs for the PHS to realize strategy switching, i.e. the functional  $A(\gamma(t), a(t))$ .**

Summarizing, the present work is only a first and quite elementary step towards the definition of a far more complete model of the impact of PHS efforts to spread the awareness of the importance of vaccines and, as a consequence, to increase vaccine uptake.

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## References

- Marco Ajelli, Bruno Gonçalves, Duygu Balcan, Vittoria Colizza, Hao Hu, José J Ramasco, Stefano Merler, and Alessandro Vespignani. Comparing large-scale computational approaches to epidemic modeling: agent-based versus structured metapopulation models. *BMC infectious diseases*, 10(1):190, 2010.
- Roy M Anderson, Robert M May, and B Anderson. *Infectious diseases of humans: dynamics and control*, volume 28. Wiley Online Library, 1992.
- Hakan Andersson and Tom Britton. *Stochastic epidemic models and their statistical analysis*. Springer, 2012.
- Sebastian Anița, Vincenzo Capasso, and Viorel Arnăutu. *An Introduction to Optimal Control Problems in Life Sciences and Economics*. Birkhäuser/Springer, New York, 2011.
- Erika Asano, Louis J Gross, Suzanne Lenhart, and Leslie A Real. Optimal control of vaccine distribution in a rabies metapopulation model. *Mathematical biosciences and engineering*, 5(2):219–238, 2008.
- Julio R Banga and Warren D Seider. Global optimization of chemical processes using stochastic algorithms. In C Floudas and P M Pardalos, editors, *State of the art in global optimization*, pages 563–583. Springer, 1996.
- Chris T Bauch. Imitation dynamics predict vaccinating behaviour. *Proc. R. Soc. Lond. B Biol. Sci.*, 272(1573):1669–1675, 2005.
- Monica Betta, Marco Laurino, Andrea Pugliese, Giorgio Guzzetta, Alberto Landi, and Piero Manfredi. Perspectives on optimal control of varicella and herpes zoster by mass routine varicella vaccination. *Proc. R. Soc. B*, 283(1826):20160054, 2016.
- Kbenesh W Blayneh, Abba B Gumel, Suzanne Lenhart, and Tim Clayton. Backward bifurcation and optimal control in transmission dynamics of west nile virus. *Bulletin of mathematical biology*, 72(4):1006–1028, 2010.
- Luca Bolzoni, Valentina Tessonni, Maria Groppi, and Giulio A De Leo. React or wait: which optimal culling strategy to control infectious diseases in wildlife. *Journal of mathematical biology*, 69(4):1001–1025, 2014.
- Bruno Buonomo. A simple analysis of vaccination strategies for rubella. *Math. Biosci. Eng.*, 8:677–687, 2011.



- Bruno Buonomo, Alberto d’Onofrio, and Deborah Lacitignola. Modeling of pseudo-rational exemption to vaccination for seir diseases. *Journal of Mathematical Analysis and Applications*, 404(2):385–398, 2013.
- Bruno Buonomo, Giuseppe Carbone, and Alberto d’Onofrio. Effect of seasonality on the dynamics of an imitation–based vaccination model with public health intervention. *Math. Biosci. Eng.*, 15(1):299–321, 2018.
- Vincenzo Capasso. *Mathematical Structures of Epidemic Systems*. Springer, Berlin, 1993.
- Hélène Carabin, W John Edmunds, Ulla Kou, Susan Van den Hof, and Nguyen Van Hung. The average cost of measles cases and adverse events following vaccination in industrialised countries. *BMC Public Health*, 2(1):22, 2002.
- Farida Chamchod, Robert Stephen Cantrell, Chris Cosner, Ali N Hassan, John C Beier, and Shigui Ruan. A modeling approach to investigate epizootic outbreaks and enzootic maintenance of rift valley fever virus. *Bulletin of mathematical biology*, 76(8):2052–2072, 2014.
- Sunhwa Choi and Eunok Jung. Optimal tuberculosis prevention and control strategy from a mathematical model based on real data. *Bulletin of mathematical biology*, 76(7):1566–1589, 2014.
- The ASSET Consortium. Asset. eu action plan on science in society related issues in epidemics and total pandemics. URL [www.asset-scienceinsociety.eu](http://www.asset-scienceinsociety.eu). (Accessed in January 2018).
- Ramses Djidjou Demasse, Jean-Jules Tewa, Samuel Bowong, and Yves Emvudu. Optimal control for an age-structured model for the transmission of hepatitis b. *Journal of mathematical biology*, 73(2):305–333, 2016.
- Alberto d’Onofrio, Piero Manfredi, and Ernesto Salinelli. Vaccinating behaviour, information, and the dynamics of sir vaccine preventable diseases. *Theoretical population biology*, 71(3):301–317, 2007.
- Alberto d’Onofrio, Piero Manfredi, and Piero Poletti. The impact of vaccine side effects on the natural history of immunization programmes: an imitation-game approach. *J. Theor. Biol.*, 273(1):63–71, 2011.
- Alberto d’Onofrio, Piero Manfredi, and Piero Poletti. The interplay of public intervention and private choices in determining the outcome of vaccination programmes. *PLoS ONE*, 7(10):e45653, 2012.
- Paulo Doutor, Paula Rodrigues, Maria do Céu Soares, and Fabio ACC Chalub. Optimal vaccination strategies and rational behaviour in seasonal epidemics. *Journal of mathematical biology*, 73(6-7):1437–1465, 2016.

- Richard Faber, Tobias Jockenhövel, and George Tsatsaronis. Dynamic optimization with simulated annealing. *Computers & chemical engineering*, 29(2):273–290, 2005.
- K Renee Fister, Suzanne Lenhart, and Joseph Scott McNally. Optimizing chemotherapy in an hiv model. *Electronic Journal of Differential Equations*, 1998 (32):1–12, 1998.
- Wendell H Fleming and Raymond W Rishel. *Deterministic and Stochastic Optimal Control*, volume 1 of *Applications of Mathematics*. Springer, Berlin, New York, 1975.
- Wendell H Fleming and Raymond W Rishel. *Deterministic and stochastic optimal control*, volume 1. Springer Science & Business Media, 2012.
- Sebastian Funk, Marcel Salathé, and Vincent AA Jansen. Modelling the influence of human behaviour on the spread of infectious diseases: a review. *Journal of the Royal Society Interface*, page rsif20100142, 2010.
- Holly Gaff and Elsa Schaefer. Optimal control applied to vaccination and treatment strategies for various epidemiological models. *Mathematical biosciences and engineering: MBE*, 6(3):469–492, 2009.
- WM Getz. Optimal control of a birth-and-death process population model. *Mathematical Biosciences*, 23(1-2):87–111, 1975.
- Wolfgang Hackbusch. A numerical method for solving parabolic equations with opposite orientations. *Computing*, 20(3):229–240, 1978.
- Elsa Hansen and Troy Day. Optimal control of epidemics with limited resources. *Journal of mathematical biology*, 62(3):423–451, 2011.
- Darrall Henderson, Sheldon H Jacobson, and Alan W Johnson. The theory and practice of simulated annealing. In Michel Gendreau and Jean-Yves Potvin, editors, *Handbook of metaheuristics*, pages 287–319. Springer, 2003.
- Herbert W Hethcote and Paul Waltman. Optimal vaccination schedules in a deterministic epidemic model. *Mathematical Biosciences*, 18(3-4):365–381, 1973.
- Josef Hofbauer and Karl Sigmund. *Evolutionary games and population dynamics*. Cambridge university press, 1998.
- IMI. Innovative medicine initiative. first innovative medicines initiative ebola projects get underway. URL [www.imi.europa.eu/content/ebola-project-launch](http://www.imi.europa.eu/content/ebola-project-launch). (Accessed in January 2018).
- Hem Raj Joshi. Optimal control of an hiv immunology model. *Optimal control applications and methods*, 23(4):199–213, 2002.

- Eunok Jung, Suzanne Lenhart, and Zhilan Feng. Optimal control of treatments in a two-strain tuberculosis model. *Discrete and Continuous Dynamical Systems Series B*, 2(4):473–482, 2002.
- Eunok Jung, Shingo Iwami, Yasuhiro Takeuchi, and Tae-Chang Jo. Optimal control strategy for prevention of avian influenza pandemic. *Journal of theoretical biology*, 260(2):220–229, 2009.
- Semu Mitiku Kassa and Aziz Ouhinou. The impact of self-protective measures in the optimal interventions for controlling infectious diseases of human population. *Journal of mathematical biology*, 70(1-2):213–236, 2015.
- Matt J Keeling and Pejman Rohani. *Modeling infectious diseases in humans and animals*. Princeton University Press, 2011.
- Scott Kirkpatrick, C Daniel Gelatt, and Mario P Vecchi. Optimization by simulated annealing. *science*, 220(4598):671–680, 1983.
- Laetitia Laguzet and Gabriel Turinici. Global optimal vaccination in the sir model: Properties of the value function and application to cost-effectiveness analysis. *Mathematical biosciences*, 263:180–197, 2015a.
- Laetitia Laguzet and Gabriel Turinici. Individual vaccination as nash equilibrium in a sir model with application to the 2009–2010 influenza a (h1n1) epidemic in france. *Bulletin of mathematical biology*, 77(10):1955–1984, 2015b.
- Heidi J Larson, Caitlin Jarrett, Elisabeth Eckersberger, David MD Smith, and Pauline Paterson. Understanding vaccine hesitancy around vaccines and vaccination from a global perspective: a systematic review of published literature, 2007–2012. *Vaccine*, 32(19):2150–2159, 2014.
- Sunmi Lee and Carlos Castillo-Chavez. The role of residence times in two-patch dengue transmission dynamics and optimal strategies. *Journal of theoretical biology*, 374:152–164, 2015.
- Sunmi Lee, Romarie Morales, and Carlos Castillo-Chavez. A note on the use of influenza vaccination strategies when supply is limited. *Math. Biosci. Eng*, 8(1): 171–182, 2011.
- Sunmi Lee, Michael Golinski, and Gerardo Chowell. Modeling optimal age-specific vaccination strategies against pandemic influenza. *Bulletin of mathematical biology*, 74(4):958–980, 2012.
- Claude Lefèvre. Optimal control of a birth and death epidemic process. *Operations Research*, 29(5):971–982, 1981.

- Suzanne Lenhart and John T Workman. *Optimal Control Applied to Biological Models*. Crc Press, London, 2007.
- Vijay Mahajan and Robert A Peterson. *Models for innovation diffusion*. Sage Publications Inc, 1985.
- Piero Manfredi and Alberto d’Onofrio. *Modeling the Interplay Between Human Behavior and the Spread of Infectious Diseases*. Springer, New York, 2013.
- Horacio Martínez-Alfaro. Using simulated annealing algorithm to solve the optimal control problem. In R Chibante, editor, *Simulated Annealing, Theory with Applications*. InTech, 2010.
- MATLAB. Matlab release 2015a. the mathworks inc. natick, ma., 2015.
- Michael McAsey, Libin Mou, and Weimin Han. Convergence of the forward-backward sweep method in optimal control. *Computational Optimization and Applications*, 53(1):207–226, 2012.
- Alessia Melegaro, Emanuele Del Fava, Piero Poletti, Stefano Merler, Constance Nyamukapa, John Williams, Simon Gregson, and Piero Manfredi. Social contact structures and time use patterns in the manicaland province of zimbabwe. *PloS one*, 12(1):e0170459, 2017.
- Richard Morton and Kenneth H Wickwire. On the optimal control of a deterministic epidemic. *Advances in Applied Probability*, 6(4):622–635, 1974.
- Rachael L Miller Neilan, Elsa Schaefer, Holly Gaff, K Renee Fister, and Suzanne Lenhart. Modeling optimal intervention strategies for cholera. *Bulletin of Mathematical Biology*, 72(8):2004–2018, 2010.
- Bernt Øksendal. *Stochastic differential equations*. Springer, 2003.
- Nelson Owuor Onyango and Johannes Müller. Determination of optimal vaccination strategies using an orbital stability threshold from periodically driven systems. *Journal of mathematical biology*, 68(3):763–784, 2014.
- Tamer Oraby, Vivek Thampi, and Chris T Bauch. The influence of social norms on the dynamics of vaccinating behaviour for paediatric infectious diseases. In *Proc. R. Soc. B*, volume 281, page 20133172. The Royal Society, 2014.
- John Carl Panetta and K Renee Fister. Optimal control applied to cell-cycle-specific cancer chemotherapy. *SIAM Journal on Applied Mathematics*, 60(3):1059–1072, 2000.
- John Carl Panetta and K Renee Fister. Optimal control applied to competing chemotherapeutic cell-kill strategies. *SIAM Journal on Applied Mathematics*, 63(6):1954–1971, 2003.

- Lev S Pontryagin, Vladimir G Boltyanskii, Revaz V Gamkrelidze, and Evgenii F Mishenko. *The Mathematical Theory of Optimal Processes*. (Translated from the russian by Trigoroff, K. N.). Wiley Interscience, New York, 1962.
- Olivia Prosper, Omar Saucedo, Doria Thompson, Griselle Torres-Garcia, Xiaohong Wang, and Carlos Castillo-Chavez. Modeling control strategies for concurrent epidemics of seasonal and pandemic h1n1 influenza. *Mathematical Biosciences and Engineering*, 8(1):141–170, 2011.
- Amira Rachah and Delfim FM Torres. Dynamics and optimal control of ebola transmission. *Mathematics in Computer Science*, 10(3):331–342, 2016.
- Paula Rodrigues, Cristiana J Silva, and Delfim FM Torres. Cost-effectiveness analysis of optimal control measures for tuberculosis. *Bulletin of mathematical biology*, 76(10):2627–2645, 2014.
- Robert Rowthorn and Selma Walther. The optimal treatment of an infectious disease with two strains. *Journal of mathematical biology*, 74(7):1753–1791, 2017.
- Alina Sadaf, Jennifer L Richards, Jason Glanz, Daniel A Salmon, and Saad B Omer. A systematic review of interventions for reducing parental vaccine refusal and vaccine hesitancy. *Vaccine*, 31(40):4293–4304, 2013.
- Peter Salamon, Paolo Sibani, and Richard Frost. *Facts, conjectures, and improvements for simulated annealing*. Siam, 2002.
- Heinz Schättler and Urszula Ledzewicz. *Geometric optimal control: theory, methods and examples*, volume 38. Springer Science & Business Media, 2012.
- Fabio Schoen. Stochastic techniques for global optimization: A survey of recent advances. *Journal of Global Optimization*, 1(3):207–228, 1991.
- Suresh P Sethi and Preston W Staats. Optimal control of some simple deterministic epidemic models. *Journal of the Operational Research Society*, 29(2):129–136, 1978.
- Zhen Wang, Chris T Bauch, Samit Bhattacharyya, Alberto d’Onofrio, Piero Manfredi, Matjaž Perc, Nicola Perra, Marcel Salathé, and Dawei Zhao. Statistical physics of vaccination. *Phys. Rep.*, 664:1–113, 2016.
- K Wickwire. Mathematical models for the control of pests and infectious diseases: a survey. *Theoretical population biology*, 11(2):182–238, 1977.
- Stanley Williamson. *The Vaccination Controversy: The Rise, Reign, and Fall of Compulsory Vaccination for Smallpox*. liverpool University press, 2007.

Songnian Zhao, Yan Kuang, Chih-Hang Wu, David Ben-Arieh, Marcelo Ramalho-Ortigao, and Kaiming Bi. Zoonotic visceral leishmaniasis transmission: modeling, backward bifurcation, and optimal control. *Journal of mathematical biology*, 73 (6-7):1525–1560, 2016.