

# Optimal constant piecewise vaccination and lockdown policies for COVID-19

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## Abstract

We formulate a controlled system of ordinary differential equations, with vaccination and lockdown interventions as controls, to simulate the mitigation of COVID-19. The performance of the controls is measured through a cost functional involving vaccination and lockdown costs as well as the burden of COVID19 quantified in DALYs. We calibrate parameters with data from Mexico City and Valle de Mexico. By using differential evolution, we minimize the cost functional subject to the controlled system and find optimal policies that are constant in time intervals of a given size. The main advantage of these policies relies on its practical implementation since the health authority has to make only a finite number of different decisions. Our methodology to find optimal policies is relatively general, allowing changes in the dynamics, the cost functional, or the frequency the policymaker changes actions.

**Keywords:** COVID-19, Optimal Control, COVAX, Vaccination, WHO-SAGE, DALYs.

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## 1. Introduction

At the date of writing this manuscript, the USA is running its COVID-19 vaccination with Pfizer-BioNTech vaccine. This vaccine development along with Astra-Zeneca, Cansino, Sputnik V, Novavax among others' promise to deliver enough doses for Latin America. In Mexico, particularly, the first stock with around 40 000 shots has arrived past Christmas. In past October, WHO established a recommended protocol for prioritizing access to this pharmaceutical hope giving clear lines about who has to be vaccinated first and why. However, each developed vaccine implies different issues around its application. For example, Pfizer-BioNTech vaccine requires two doses and particular logistics requirements that demand special services. In Mexico, despite Pfizer-BioNTech has been taking the responsibility to capacitate personnel that manage the vaccination, there is an explicit demand for logistics resources that limit the institutions' response. On the hand, nonpharmaceutical interventions (NPIs), like a lockdown, also involve economic costs. Our research in this manuscript explores the effect of two interventions, vaccination and lockdown, to mitigate the propagation of COVID-19.

Among the related literature about the two interventions we deal with in this paper, we can mention the following. The problem of who is vaccinated first, when the number of available shots is limited, has been transformed into an optimal allocation problem of vaccine doses in [1, 2]. These articles give answers to the critical question of how much doses allocate to each different group according to risk and age to minimize the burden of COVID-19. In our study, we take the allocation for granted and consider only the vaccination rate.

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Further, papers modeling NPIs consider the diminish of contact rates—by reducing mobility—or modulating parameters regarding the generation of new infections by linear controls [3, 4], Lockdown–Quarantine [5], shield immunity [6]. In addition, Libotte et. al. reports in [7] optimal vaccination strategies for COVID-19.

Since health services’ response will be limited by the vaccine stock and logistics costs, implementing in parallel NPIs is imminent. We focus on formulating and studying via simulation a Lockdown–Vaccination system by consider the vaccine recently approved by Mexico Health Council. We aim to design a schedule for dose application subject to a given vaccine stock that will be applied in a given period of time. For this purpose, we formulate an optimal control problem that minimizes the burden of COVID-19 in DALYs [8], the cost generated by running the vaccination campaign, and economic damages due to lockdown.

One of the main features of our model is that we consider piecewise constant control policies instead of general measurable control policies —also called permanent controls—to minimize a cost functional. General control policies are difficult to implement since the authority has to make different choices every permanently. The optimal policies we find are constant in each interval of time and hence these policies are easier to implement. To the best of our knowledge, our manuscript is the first optimal control model with both lockdown and vaccination strategies that are easy to implement in the sense described above.

In Section 2, we formulate the basic spread model for COVID19 and calibrate its parameters. Then, Section 3 establishes the lockdown–vaccination model and discusses the regarding reproductive number in Section 4. In Section 5 we describe the optimal control problem which consists in minimizing a cost functional subject to controlled lockdown–vaccination system. The optimal policies we find, by solving numerically the optimal control problem, are presented in Section 6. We conclude with some final comments in Section 7.

## 2. Covid-19 spread dynamics

We split a given population of size  $N$  in the basic SEIR structure with segregated classes according to the manifestation of symptoms. Let  $L, S, E, I_S, I_A, H, R, D$  respectively denote the class of individuals according to their current state, namely

**Lockdown ( $L$ )** All individuals that have low or null mobility and remain under isolation. Thus individuals in this class reduce their contagion probability.

**Suceptible ( $S$ )** Individuals under risk

**Exposed ( $E$ )** Population fraction that hosts SARS-CoV-2 but cannot infect

**Infected-Symptomatic ( $I_S$ )** Population infected fraction with symptoms and reported as confirmed cases

**Infected-Asymptomatic ( $I_A$ )** Infected individuals with transitory or null symptoms and unreported

**Hospitalized ( $H$ )** Infected population that requires hospitalization or intensive care.

**Recover or removed ( $R$ )** Population that recovers from infection and develops partial immunity

**Death ( $D$ )** Population fraction that died due to COVID-19

To fit data of cumulative reported symptomatic cases, we postulate the counter state  $Y_{I_S}$  and make the following assumptions.

**Assumptions 1.** According to above compartment description, we made the following hypotheses.

(A-1) We suppose that at least 30 % of the population is locked down and a fraction of this class eventually moves to the susceptible compartment at rate  $\delta_L$ .

(A-2) Force infection is defined as the probability of acquiring COVID-19 given the contact with a symptomatic or asymptomatic individual. Thus we normalize with respect to alive population  $N^*$ .

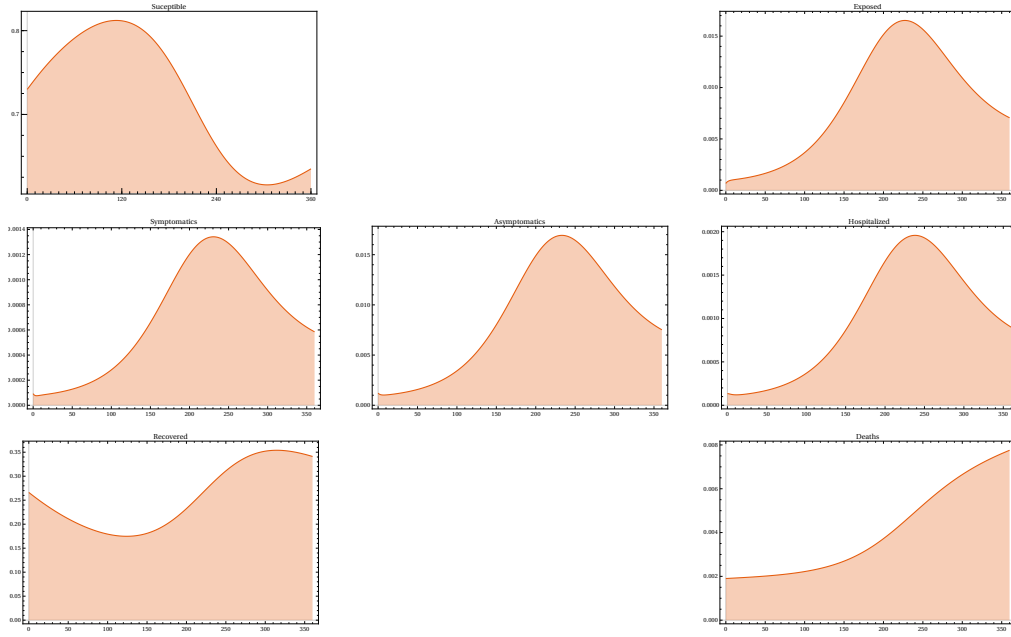


Figure 1: Spread dynamics of COVID-19 according to model in Equation (1).

(A-3) Susceptible individuals become exposed—but not infectious—when they are in contact with asymptomatic or symptomatic individuals. Thus  $\beta_S$  and  $\beta_A$  denote the probabilities of being infectious given the contact with a symptomatic or asymptomatic infectious individuals, respectively.

(A-4) After a period of latency  $1/\kappa = 5.1$  days, an exposed individual becomes infected. Being  $p$  the probability of developing symptoms and  $(1 - p)$  the probability of becoming infectious but asymptomatic. Thus  $p\kappa E$  denotes the exposed individuals that become infectious and develop symptoms.

(A-5) Asymptomatic individuals do not die or stay in the Hospital.

(A-6) A fraction  $\mu_H$  of symptomatic individuals dies due to COVID-19 without hospitalization.

Thus we formulate the following Ordinary Differential Equation (ODE)

$$\begin{aligned}
 S' &= \mu N^* + \delta_R R - (\lambda + \mu) S, \\
 E' &= \lambda(\epsilon L + S) - (\kappa + \mu) E, \\
 I_S' &= p\kappa E - (\gamma_S + \delta_H + \mu_{I_S} + \mu) I_S, \\
 I_A' &= (1 - p)\kappa E - (\gamma_A + \mu) I_A, \\
 H' &= \delta_H I_S - (\gamma_H + \mu_H + \mu) H, \\
 R' &= \gamma_S I_S + \gamma_A I_A + \gamma_H H - (\delta_R + \mu) R, \\
 D' &= \mu_{I_S} I_S + \mu_H H, \\
 \frac{dY_{I_S}}{dt} &= p\kappa E, \\
 \lambda &:= \frac{\beta_A I_A + \beta_S I_S}{N^*}, \\
 N^*(t) &= L + S + E + I_S + I_A + H + R.
 \end{aligned} \tag{1}$$

See Table 1 for notation and references values. [Put here the flow diagram](#)

Parameter	Description
$\mu$	Death rate
$\beta_S$	Infection rate between susceptible and symptomatic infected
$\beta_A$	Infection rate between susceptible and asymptomatic infected
$\lambda_V$	Vaccination rate
$\delta_V^{-1}$	Vaccine-induced immunity
$\varepsilon$	Vaccine efficacy
$\kappa^{-1}$	Average incubation time
$p$	New asymptomatic generation proportion
$\theta$	Proportion of susceptible individuals under lockdown
$\gamma_S^{-1}$	Average time of symptomatic recovery
$\gamma_A^{-1}$	Recovery average time of asymptomatic individuals
$\gamma_H^{-1}$	Recovery average time by hospitalization
$\delta_R^{-1}$	Natural immunity
$\delta_H$	Infected symptomatic hospitalization rate

Table 1: Parameters definition of model in Equation (1).

### 2.1. Parameter calibration

*Bayesian estimation.* We calibrate parameters of our base dynamics (1) via Multichain Montecarlo (MCMC). To this end, we assume that the cumulative incidence of new infected symptomatic cases  $CI_S$  follows a Poisson distribution with mean  $\lambda_t = IC_s(t)$ . Further, following [] we postulate priors for  $p$  and  $\kappa$

$$\begin{aligned}
Y_t &\sim \text{Poisson}(\lambda_t), \\
\lambda_t &= \int_0^t p \delta_e E, \\
p &\sim \text{Uniform}(0.3, 0.8), \\
\kappa &\sim \text{Gamma}(10, 50).
\end{aligned} \tag{2}$$

Figure 2 displays data of cumulative confirmed cases of COVID-19 in Mexico city, and Figure 3 displays the fitted curve of our model in Equations (1) and (2). Table 2 encloses estimated parameters to this setting.

[SDIV 2]  
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Parameter	Median	Reference
$q_r, \epsilon$	0.4, 0.3, 0.1	this study
$\beta_S$	$q_r \times 8.690\,483 \times 10^{-1}$	this study
$\beta_A$	$q_r \times 7.738\,431 \times 10^{-1}$	this study
$\kappa$	0.196\,078\,43	*
$p$	0.1213	*
$\theta$	0.2,	this study
$\delta_L$	0.04	postulated
$\delta_H$	0.2	*
$\delta_V$	0.002\,739\,726\,027\,397\,260\,3	$\delta_V^{-1} = 2$ years CanSinoBIO
$\delta_R$	0.005\,555\,56	$\delta_R^{-1} \approx 180$ days
$\mu$	$3.913\,894 \times 10^{-5}$	**
$\mu_{I_S}$	0.0	
$\mu_H$	0.016\,32	[10]
$\gamma_S$	0.092\,506\,94	*
$\gamma_A$	0.167\,504\,19	*
$\gamma_H$	$5.079\,869 \times 10^{-1}$	*
$\lambda_V$	0.000\,611\,35	
$\varepsilon$	0.7, 0.80, 0.9, 0.95	[PRESS RELESASES]
$N$	26\,446\,435	**
$L_0$	0.266\,260\,097\,021\,127\,96	
$S_0$	0.463\,606\,046\,009\,872	
$E_0$	0.000\,670\,33	*
$I_{S_0}$	$9.283 \times 10^{-5}$	* * *
$I_{A_0}$	0.001\,209\,86	*
$H_0$	$1.341\,579\,69 \times 10^{-4}$	**
$R_0$	$2.661\,259\,39 \times 10^{-1}$	
$D_0$	0.001\,900\,74	**
$X_{vac}^0$	0.0	
$V_0$	0.0	
$Y_{I_S}^0$	0.122\,581\,64	
$B$	0.000\,359\,216\,658\,124\,242\,5	9500 beds/ $N$
$a_{I_S}$	0.002\,012\,775\,543\,825\,648\,6	DALY def
$a_H$	0.001\,411\,888\,738\,103\,725, or $a_H(x) := 0.001\,411\,888\,738\,103\,725 \log(\frac{1}{B-\kappa I_S})$	DALY def [Jo 2020]
$a_D$	7.25	DALY def

Table 2: Model parameters. Values based mainly in [FNEG]

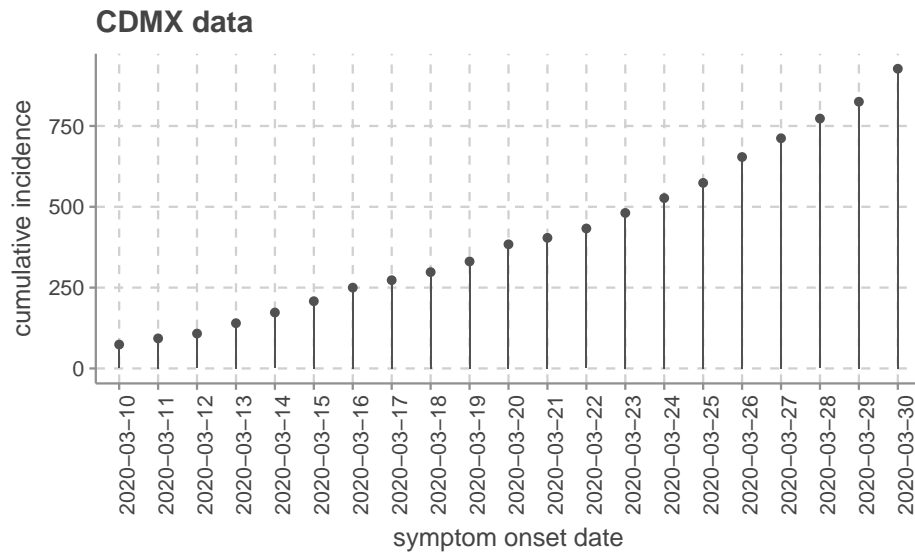


Figure 2: Cumulative new symptomatic and confirmed COVID19 reported cases from Ciudad de Mexico and Valle de Mexico [9] between March, 10, to March 30 of 2020. [https://plotly.com/ AdrianSalcedo/48/](https://plotly.com/AdrianSalcedo/48/)

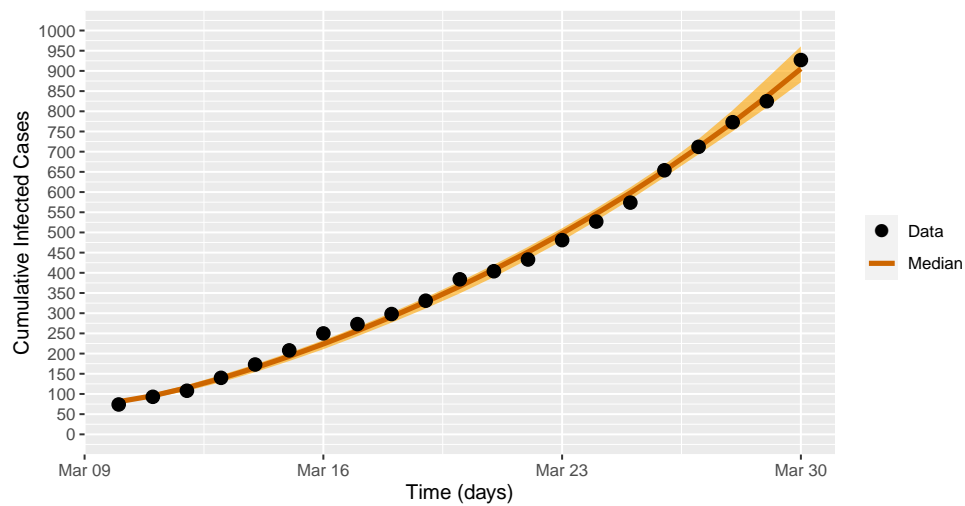


Figure 3: Fit of daily new cases of Mexico city during exponential growth. [https://plotly.com/ AdrianSalcedo/50/](https://plotly.com/AdrianSalcedo/50/)

### 3. Imperfect-preventive COVID-19 vaccination

**Assumptions 2.** According to COVID-19 dynamics in model in Equation (1), we made the following modeling hypotheses about the regarding vaccine.

(VH-1) Vaccine is preventive and only reduce susceptibility.

(VH-2) The vaccination campaign omits testing to detect seroprevalence. Thus Exposed, Infected Asymptomatics and Recovered Asymptomatic individuals are undetected but would obtain a vaccine dose—which in these model represent a waste of resources

(VH-3) Individuals under Lockdown also would be vaccinated

(VH-4) The vaccine is leaky and with efficacy  $\epsilon \in [0.7, .975]$

(VH-5) Vaccine induced immunity last 2 years

(VH-6) Natural immunity last a period of 180 days

**[SDIV 3]**  
Justify this hypothesis  
cite

$$\begin{aligned}
 L' &= \theta \mu N^* - (\epsilon \lambda + \delta_L + \lambda_V + \mu) L \\
 S' &= (1 - \theta) \mu N^* + \delta_L L + \delta_V V + \delta_R R \\
 &\quad - (\lambda + \lambda_V + \mu) S \\
 E' &= \lambda (\epsilon L + (1 - \epsilon) V + S) - (\kappa + \mu) E \\
 I_S' &= p \kappa E - (\delta_H + \gamma_S + \mu_{I_S} + \mu) I_S \\
 I_A' &= (1 - p) \kappa E - (\gamma_A + \mu) I_A \\
 H' &= \delta_H I_S - (\gamma_H + \mu_H + \mu) H \\
 R' &= \gamma_S I_S + \gamma_A I_A + \gamma_H H - (\delta_R + \mu) R \\
 D' &= \mu_{I_S} I_S + \mu_H H \\
 V' &= \lambda_V (S + L) - [(1 - \epsilon) \lambda + \delta_V + \mu] V
 \end{aligned}$$

$$\begin{aligned}
 \frac{dX_{vac}}{dt} &= (u_V(t) + \lambda_V) [L + S + E + I_A + R] \\
 \frac{dY_{I_S}}{dt} &= p \kappa E \\
 \lambda &:= \frac{\beta_A I_A + \beta_S I_S}{N^*}
 \end{aligned} \tag{3}$$

$$\begin{aligned}
 L(0) &= L_0, \quad S(0) = S_0, \quad E(0) = E_0, \\
 I_S(0) &= I_{S_0}, \quad I_A(0) = I_{A_0}, \quad H(0) = H_0, \\
 R(0) &= R_0, \quad D(0) = D_0, \\
 V(0) &= 0, \quad X_{vac}(0) = 0, \\
 X_{vac}(T) &= x_{coverage}, \\
 N^*(t) &= L + S + E + I_S + I_A + H + R + V.
 \end{aligned}$$

### 4. Lockdown-Vaccination reproductive number

The basic reproductive number, which is generally denoted by  $R_0$ , is a threshold quantity with which we can use particular control strategies. The epidemiological interpretation of  $R_0$  is the average number of

secondary cases produced by an infected individual introduced into a population of susceptible individuals. Using Van DenDrishe's [11] definition of reproductive number we obtain

$$R_0 := \frac{\kappa}{(\kappa + \mu)(\delta_L + \mu)} (\mu R_1 + \delta_L) \left[ \frac{p\beta_S}{R_2} + \frac{(1-p)\beta_A}{\gamma_A + \mu} \right],$$

where

$$R_1 = 1 - \theta(1 - \epsilon),$$

$$R_2 = \mu + \delta_H + \gamma_S + \mu_{IS}.$$

The factor  $\frac{p\beta_S}{R_2}$  measures the proportion of new infections generated by a symptomatic infectious individual in the time that it lasts infected. In a similar way, the factor  $\frac{(1-p)\beta_A}{\gamma_A + \mu}$  measures the new infections generated by an asymptomatic infectious individual in the time that it lasts infected. The factor  $\frac{\mu R_1 + \delta_L}{\delta_L + \mu}$  measures the number of individuals in lockdown that leave the lockdown, which can be infected. And finally, the factor  $\frac{\kappa}{\kappa + \mu}$  measures the time of the disease's incubation. If we consider that there is no lockdown, we have that  $R_0$  is reduced to

$$\tilde{R}_0 := \frac{\kappa}{(\kappa + \mu)} \left[ \frac{p\beta_S}{R_2} + \frac{(1-p)\beta_A}{\gamma_A + \mu} \right].$$

Note that we have the relation  $R_0 \leq \tilde{R}_0$ . These indicate that there is greater transmission of the disease if there is no lockdown. [Here Gabriel's R not calculations.](#)<sup>SDIV</sup> Considering assumptions 2, we can establish a vaccine reproductive number, in which individuals who have already been vaccinated can become infected individuals by being in contact with the symptomatic infected. Using Van den Driessche's [11] definition of reproductive number and [12], we obtain

$$R_0^V := \left[ 1 - \frac{\varepsilon\lambda_V}{\mu + \lambda_V + \delta_V} - \frac{\theta\mu(1 - \epsilon)}{\mu + \delta_L + \lambda_V} \right] (\mu R_1 + \delta_L) R_0.$$

The threshold quantity  $R_0^V$  is the reproductive number of infection which can be interpreted as the number of infected people produced by one infected individual introduced into the population in the presence of vaccination.

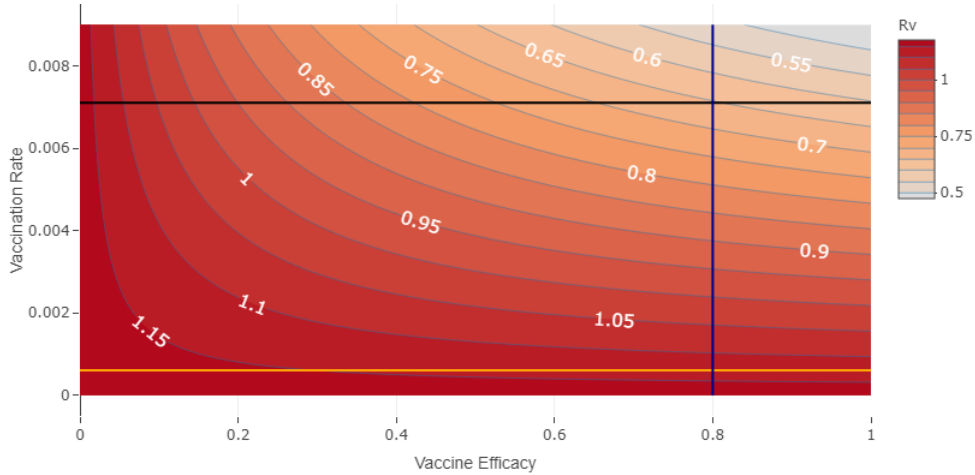


Figure 4: Contour plot of  $R_0^V$  as a function of  $\epsilon$  and  $\lambda_V$  and vaccine-induced immunity average time of half year. orange line represents the value of  $\lambda_{V_{base}} = 0.000611$ , corresponding to a coverage  $x_{coverage} = 0.2$  and a horizon time  $T = 365$  days. Intersection of black line and blue line show a scenario in which it is possible to have the  $R_V = 0.65$ , considering a vaccine efficacy of 0.8 and a vaccination rate of 0.7.

shows the efficacy of the vaccine as a function of the vaccination rate. The blue line,  $\varepsilon = 0.8$ , tells us what value of  $\lambda_V$  to take for which to have the level curve where  $R_0^V < 1$ . In the gray region of the figure 5,

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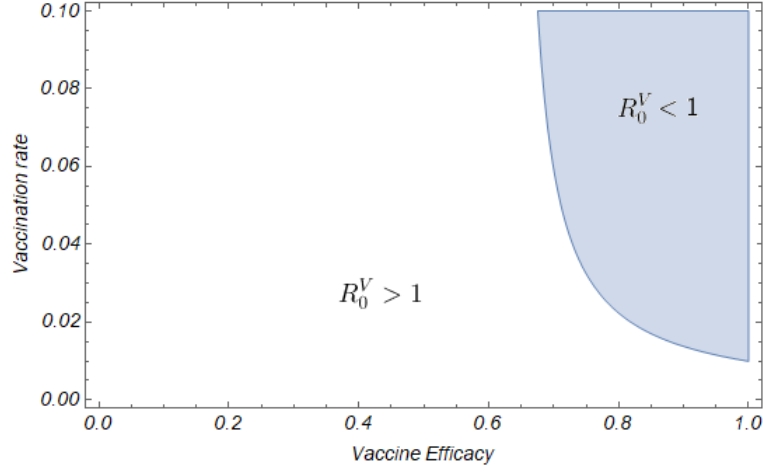


Figure 5: Vaccine efficacy versus vaccination rate feasibility. In the gray shaded region  $R_V < 1$  and in the white region  $R_V > 1$ . Note that, for our scenario, we consider no lockdown individuals. <https://plotly.com/AdrianSalcedo/52/>

111 you can see the values of vaccine efficacy and vaccination rate for which  $R_0^V < 1$ . In this figure, we consider  
 112 that the lockdown effect is not present. If we take  $\varepsilon = 0.2$ , we can see that we always have  $R_0^V > 1$  with  
 which choice of  $\lambda_V$ .

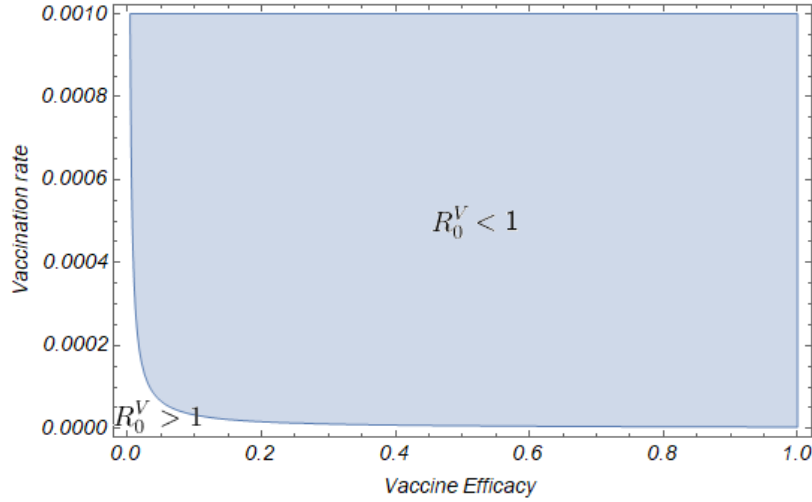


Figure 6: Vaccine efficacy versus vaccination rate feasibility. In the gray shaded region  $R_V < 1$  and in the white region  $R_V > 1$ . Note that, for our scenario, we consider lockdown individuals. <https://plotly.com/AdrianSalcedo/54/>

113 In the figure 6, we take into account that the lockdown effect is present. We can see that the gray region,  
 114  $R_0^V < 1$ , is much larger than in the figure. Note that we can choose smaller values for  $\varepsilon$  and  $\lambda_V$  when we do  
 115 have an individual lockdown.  
 116

## 117 5. Optimal controlled version

118 Now we model vaccination, treatment and lockdown as a optimal control problem. According to dynam-  
 119 ics in Equation (1), we modulate the vaccination rate with a time-dependent control signal  $u_V(t)$ . We add  
 120 compartment  $X_{vac}$  to count all the vaccine applications of lockdownm susceptible, exposed, asymptomatic

121 and recovered individuals. This process is modeled by

$$X'(t) = (\lambda_V + u_V(t))(L + S + E + I_A + R) \quad (4)$$

and describes the number of applied vaccines at time  $t$ . Consider

$$x(t) := (L, S, E, I_S, I_A, H, R, D, V, X_{vac})^\top(t)$$

122 and control signal  $u_v(\cdot)$ . We quantify the cost and reward of a vaccine strategy policy via the penalization  
123 functional

$$J(u_L, u_V) := \int_0^T a_S p \kappa E(r) + a_H \delta_H I_S(r) + a_D [\mu_{I_S} I_S(r) + \mu_H H(r)] + \frac{1}{2} [c_L u_L^2(r) + c_V u_V^2(r)] dr. \quad (5)$$

124 In other words, we assume in functional  $J$  that pandemic cost is proportional to the symptomatic hospitalized  
125 and death reported cases and that a vaccination and lockdown policies implies quadratic consumption of  
126 resources.

127 Further, since we aim to simulate vaccination policies at different coverage scenarios, we impose the  
128 vaccination counter state's final time condition  $X_{vac}(T)$

$$\begin{aligned} x(T) &= (\cdot, \cdot, \cdot, \cdot, \cdot, X_{vac}(T))^\top \in \Omega \\ X_{vac}(T) &= x_{coverage}, \\ x_{coverage} &\in \{\text{Low}(0.2), \text{Mid}(0.5), \text{High}(0.8)\}. \end{aligned} \quad (6)$$

129 Thus, given the time horizon  $T$ , we impose that the last fraction of vaccinated populations corresponds to  
130 20%, 50% or 80%, and the rest of final states as free. We also impose the path constraint

$$\Phi(x, t) := H(t) \leq B, \quad \forall t \in [0, T], \quad (7)$$

131 to ensure that healthcare services will not be overloaded. Here  $\kappa$  denotes hospitalization rate, and  $B$  is the  
132 load capacity of a health system.

133 Given a fixed time horizon and vaccine efficiency, we estimate the constant vaccination rate as the solution  
134 of

$$x_{coverage} = 1 - \exp(-\lambda_V T). \quad (8)$$

135 That is,  $\lambda_V$  denotes the constant rate to cover a fraction  $x_{coverage}$  in time horizon  $T$ . Thus, according to this  
136 vaccination rate, we postulate a policy  $u_v$  that modulates vaccination rate according to  $\lambda_V$  as a baseline.  
137 That is, optimal vaccination amplifies or attenuates the estimated baseline  $\lambda_V$  in a interval  $[\lambda_V^{\min}, \lambda_V^{\max}]$  to  
138 optimize functional  $J(\cdot)$ —minimizing symptomatic, death reported cases and optimizing resources.

139 Our objective is minimize the cost functional (5)—over an appropriated functional space—subject to the  
140 dynamics in equations (1) and (4), boundary conditions, and the path constrain in (7). That is, we search

for vaccination policies  $u_V(\cdot)$ , which solve the following optimal control problem (OCP).

$$\begin{aligned}
\min_{\mathbf{u} \in \mathcal{U}} J(u_L, u_V) &:= \int_0^T a_S p \kappa E(r) + a_H \delta_H I_S(r) + a_D [\mu_{I_S} I_S(r) + \mu_H H(r)] dr + \\
&\quad \int_0^T \frac{1}{2} [c_L u_L^2(r) + c_V u_V^2(r)] dr. \\
\text{s. t.} \\
L' &= \theta \mu N^* - \epsilon \lambda L - u_L(t) L - \mu L \\
S' &= (1 - \theta) \mu N^* + u_L(t) L + \delta_v V + \delta_R R \\
&\quad - [\lambda + (\lambda_V + u_V(t)) + \mu] S \\
E' &= \lambda (\epsilon L + (1 - \epsilon) V + S) - (\kappa + \mu) E \\
I_S' &= p \kappa E - (\gamma_S + \mu_{I_S} + \delta_H + \mu) I_S \\
I_A' &= (1 - p) \kappa E - (\gamma_A + \mu) I_A \\
H' &= \delta_H I_S - (\gamma_H + \mu_H + \mu) H \\
R' &= \gamma_S I_S + \gamma_A I_A + \gamma_H H - (\delta_R + \mu) R \\
D' &= \mu_{I_S} I_S + \mu_H H \\
V' &= (\lambda_V + u_V(t)) S - [(1 - \epsilon) \lambda + \delta_V + \mu] V
\end{aligned} \tag{9}$$

$$\begin{aligned}
\frac{dX_{vac}}{dt} &= (u_V(t) + \lambda_V) [L + S + E + I_A + R] \\
\frac{dY_{I_S}}{dt} &= p \kappa E \\
\lambda &:= \frac{\beta_A I_A + \beta_S I_S}{N^*}
\end{aligned}$$

$$\begin{aligned}
L(0) &= L_0, \quad S(0) = S_0, \quad E(0) = E_0, \quad I_S(0) = I_{S_0}, \\
I_A(0) &= I_{A_0}, \quad H(0) = H_0, \quad R(0) = R_0, \quad D(0) = D_0, \\
V(0) &= 0, \quad X_{vac}(0) = 0, \quad u_V(\cdot) \in [u_{\min}, u_{\max}], \\
X_{vac}(T) &= x_{coverage}, \quad \kappa I_S(t) \leq B, \quad \forall t \in [0, T], \\
N^*(t) &= L + S + E + I_S + I_A + H + R + V
\end{aligned}$$

## 6. Numerical Experiments

### 6.1. Methodology

We simulate a scenario corresponding to a hypothetical but plausible initial conditions and parameters. We integrate model in Equation (9) by classic Runge Kutta scheme and solve the optimization stage with the so called Differential Evolution method. Differential Evolution (DE) [13] is an evolutionary algorithm successfully employed for global optimization [14]. The method is designed to optimize functions  $f : \mathbb{R}^n \rightarrow \mathbb{R}$ . Nevertheless, DE can be applied to optimize a functional as stated in [15]. The method can be coded following Algorithm 1, where an initial random population on the search space  $\mathcal{V}$  of size  $N_p$  is subjected to mutation, crossover and selection. After this process a new population is created which, again would be subjected to the evolutionary process. This process is repeated until some stopping criteria is fulfilled. Finally the best individual (according to some objective function  $f_{ob}$  to optimize) is extracted. These operations are conducted by the operators  $\mathbf{X}_0, \mathbf{M}, \mathbf{C}, \mathbf{S}, \mathbf{x}_{best}$ ; whose explicit form are coded in [16].

In the optimization of this study the mutation scale factor  $F$  and the crossover probability  $C_r$  were taken as 1 and 0.3 respectively, additional  $N_p$  has been taken as 4 times the number of parameters (the dimension

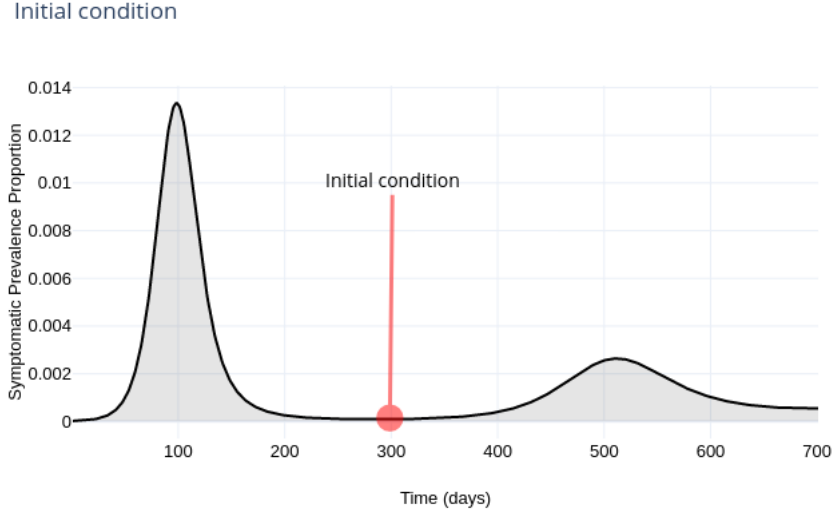


Figure 7: Initial condition scheme. We assume a positive prevalence. Forreference, at the date of write this manuscript, prevalence in CDMX is around 16 000 cases, see <https://plotly.com/sauld/36/> to display a electronic viewer.

of the vector used to describe the two controls—see [15]), which in our case was of 180. As stopping criteria we have used a maximum number of generations which is taken as 5000.

We provide in [17] a GitHub repository with all regarding R and Fortran sources for the sake of reproducibility. This repository also encloses data sources and a Wolfrang Mathematica notebook to reproduce all reported figures.

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**Algorithm 1** Differential Evolution Algorithm

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 $X \leftarrow \mathbf{X}_0(Np, \mathcal{V})$ 
while (the stopping criterion has not been met) do
     $M \leftarrow \mathbf{M}(X, F, \mathcal{V})$ 
     $C \leftarrow \mathbf{C}(X, M, C_r)$ 
     $X \leftarrow \mathbf{S}(X, C, f_{ob})$ 
end while
 $\mathbf{x}_{best} \leftarrow \mathbf{Best}(X, f_{ob})$ 

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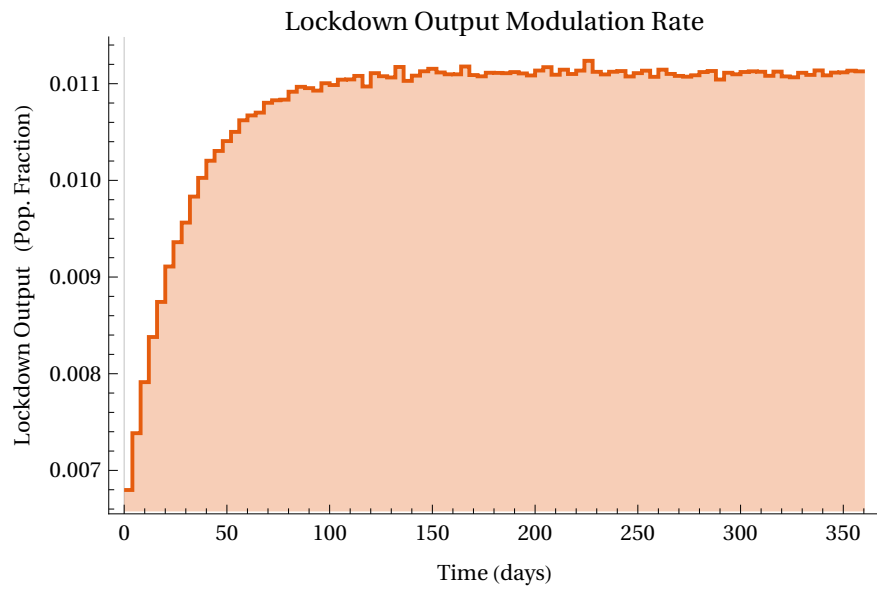


Figure 8: Lockdown modulation signal. [https://plotly.com/ AdrianSalcedo/56/](https://plotly.com/AdrianSalcedo/56/) to display a electronic viewer.

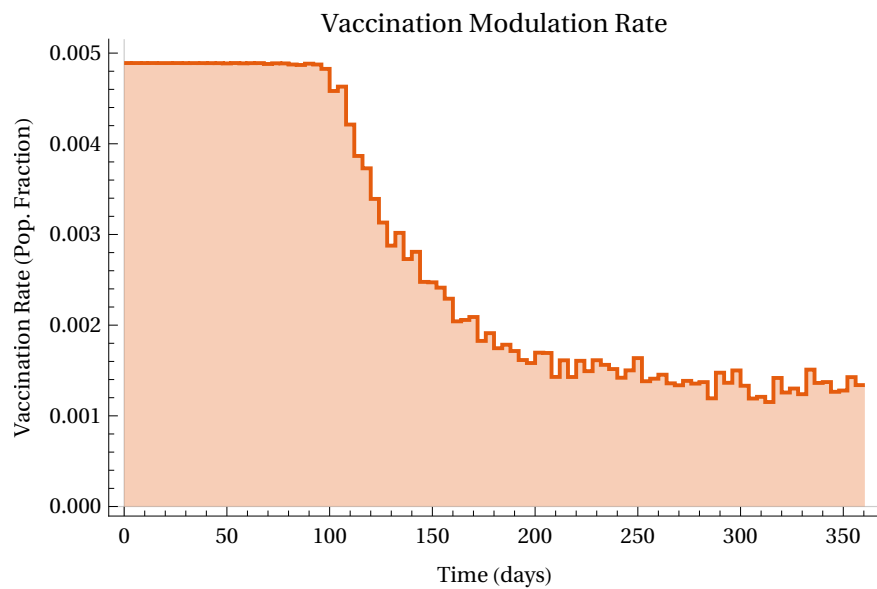


Figure 9: Vaccination rate modulation. [https://plotly.com/ AdrianSalcedo/58/](https://plotly.com/AdrianSalcedo/58/)

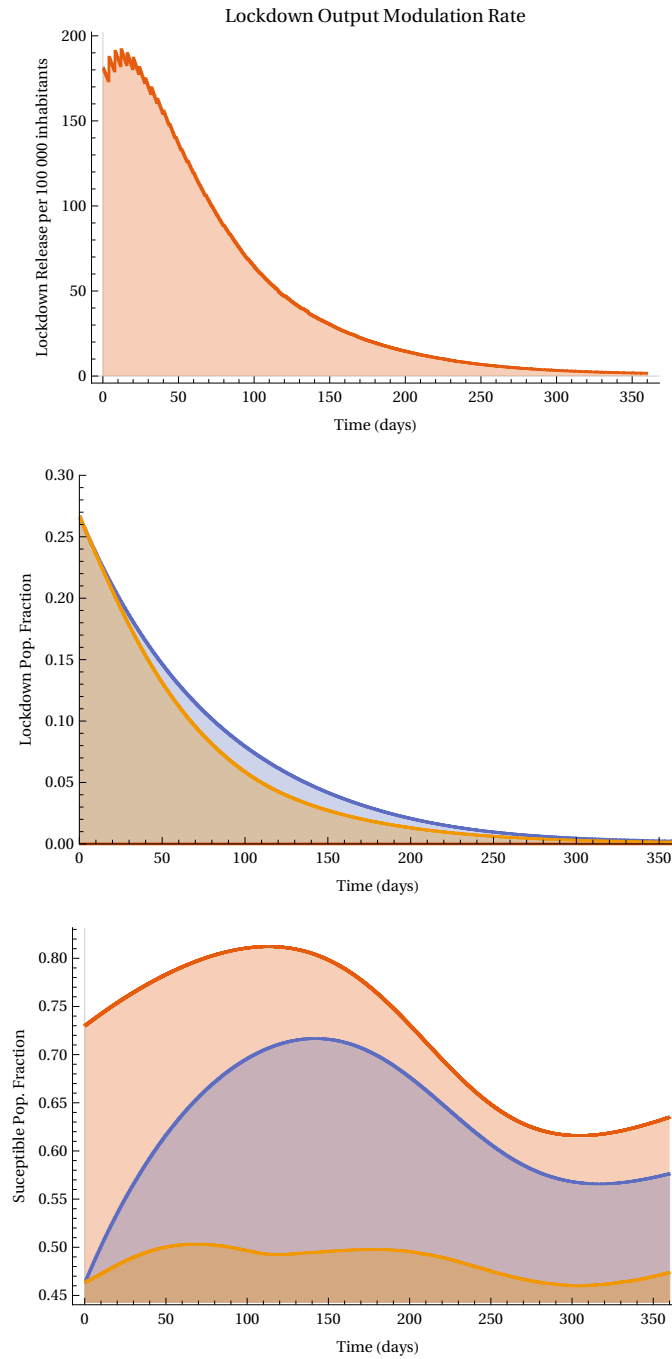


Figure 10: Modulation lock down release. [https://plotly.com/ AdrianSalcedo/60/](https://plotly.com/AdrianSalcedo/60/)

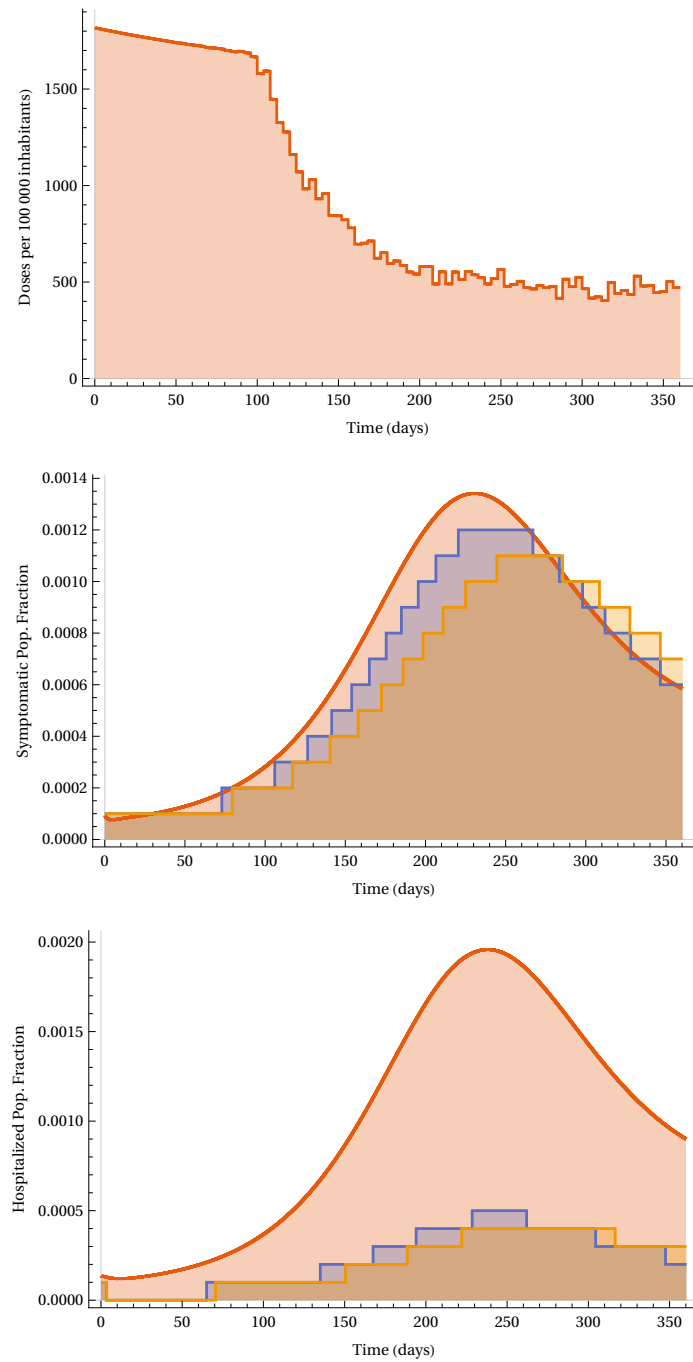


Figure 11: Symptomatic Prevalence and Hospitalization. [https://plotly.com/ AdrianSalcedo/61/](https://plotly.com/AdrianSalcedo/61/)

## 7. Conclusion

Despite that NPIs has been implemented in most countries to mitigate COVID-19, these strategies can not develop immunity. Thus, vaccination becomes the primary pharmaceutical measure. However, this vaccine has to be effective and well implemented in global vaccination programs, and each development implies particular issues. Thus new challenges in distribution, stocks, politics, vaccination efforts, among others, emerge. In this work, we have studied the effect of the combined strategy lockdown-vaccination and our result suggest that the NPIs would be essential to face the new emergent problems with the accepted vaccines.

We see it very important to implement stratification by risk and age. Thus our efforts will be directed in combination with the result presented in this manuscript.

## Data availability

<https://github.com/SaulDiazInfante/NovelCovid19-OptimalPiecewiseControlModelling.git>

## Authors' contributions

**Gabriel A. Salcedo-Varela** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Visualization, Project Administration, Writing–original draft, Writing–review & editing.

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## Conflicts of interest

The authors have no competing interests.

## Appendix A. Existence of optimal policies

In this appendix, we show the existence of optimal policies in the class of *piecewise constant policies*. Consider the following cost functional that we want to minimize

$$\int_0^T C(X(t), u(t)) dt \quad (\text{A.1})$$

subject to the dynamics

$$\dot{X}(t) = f(X(t), u(t)), \quad 0 \leq t \leq T, \quad (\text{A.2})$$

and the initial state  $X(0) = x_0$ . The functions  $u : [0, T] \rightarrow U$  are called *control policies*, where  $U$  is a subset of some Euclidean space. Let  $t_0 < t_1 < \dots < t_n$ , with  $t_0 = 0$  and  $t_n = T$ , be a partition of the interval  $[0, T]$ . We consider piecewise constant policies  $\tilde{u}$  of the form

$$\tilde{u}(t) = a_j \quad t_j \leq t < t_{j+1} \quad (\text{A.3})$$

for  $j = 0, \dots, n-1$ .

**Assumptions 3.** We made the following assumptions.



(A-1) The function  $f$  in the dynamics (A.2) is of class  $C^1$ .

(A-2) The cost function  $C$  in (A.1) is continuous and the set  $U$  is compact.

By Assumption (A-1), the system

$$\dot{X}(t) = f(X(t), a_0), \quad X(0) = x_0, \quad 0 \leq t \leq t_1,$$

has a unique solution  $\tilde{X}_0(t; x_0, a_0)$  which is continuous in  $(x_0, a_0)$ ; see, for instance [18]. Next, put  $x_1 := \tilde{X}_0(t_1; x_0, a_0)$  and consider the system

$$\dot{X}(t) = f(X(t), a_1), \quad X(t_1) = x_1, \quad t_1 \leq t \leq t_2,$$

Again, by Assumption (A-1), the latter system has a unique solution  $\tilde{X}_1(t; x_1, a_1)$  which is continuous in  $(x_1, a_1)$ . By following this procedure, we end up having a recursive solution

$$\begin{aligned} \tilde{X}_{n-1}(t; x_{n-1}, a_{n-1}), \quad t_{n-1} \leq t \leq T, \\ x_{n-1} := \tilde{X}_{n-2}(t_{n-1}; x_{n-2}, a_{n-1}), \end{aligned}$$

where  $\tilde{X}_{n-1}$  is continuous in  $(x_{n-1}, a_{n-1})$ .

For a control  $\tilde{u}$  of the form (A.3) and the corresponding solution path  $\tilde{X}$ , we have

$$\int_0^T C(\tilde{X}(t), \tilde{u}(t)) dt = \sum_{j=0}^{n-1} \int_{t_j}^{t_{j+1}} C(\tilde{X}_j(t), a_j) dt.$$

Notice that each  $\tilde{X}_j$  is a continuous function of  $(a_0, \dots, a_j)$  and  $x_0$ .

By Assumption (A-2), the mapping

$$(a_0, \dots, a_{n-1}) \mapsto \sum_{j=0}^{n-1} \int_{t_j}^{t_{j+1}} C(\tilde{X}_j(t), a_j) dt$$

is continuous. Since each piecewise constant policy  $\tilde{u}$  of the form (A.3) can be identified with the vector  $(a_0, \dots, a_{n-1})$  in the compact set  $U \times \dots \times U$ , the functional (A.1) attains its minimum in the class of piecewise constant policies.

The cost functional (5) and the dynamics (1) are particular cases of (A.1) and (A.2), respectively, and satisfy Assumptions (A-1) and (A-2). Then there exists an optimal vaccination policy of the form (A.3).

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