

# Optimal constant piecewise vaccination policies for COVID-19

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## Abstract

BACKGROUND.

FINDINGS.

IMPLICATIONS.

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

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## 1. Introduction

*Main contribution and its relevance.*

*Background.*

*Vaccine development.*

*Problem setup.*

*Litterature review.*

*Papaer structure.*

## 2. Covid-19 spread dynamics

*Uncontrolled dynamics.* We split the the constant population  $N$  in a base SEIR structure with segregation infected classes according with manifestation of symptoms. We also postulate the extra state  $Y_{IS}$  to fit commulative symptomatic cases reported in the databases from Mexico city during the exponential grow phase. Our dynamics

reads

$$\begin{aligned} L' &= \theta\mu N^* - \epsilon\lambda L - \delta_L L - \mu L, \\ S' &= (1 - \theta)\mu N^* + \delta_L L + \delta_R R - (\lambda + \mu)S, \\ E' &= \lambda(\epsilon L + S) - (\kappa + \mu)E, \\ I'_S &= p\kappa E - (\gamma_S + \delta_H + \underbrace{\mu_{IS}}^{\text{SDIV}} + \mu)I_S, \\ I'_A &= (1 - p)\kappa E - (\gamma_A + \mu)I_A, \\ H' &= \delta_H I_S - (\gamma_H + \mu_H + \mu)H, \\ R' &= \gamma_S I_S + \gamma_A I_A + \gamma_H H - (\delta_R + \mu)R, \\ D' &= \underbrace{\mu_{IS} I_S}_{\text{SDIV}} + \mu_H H, \end{aligned} \tag{1}$$

$$\begin{aligned} \frac{dY_{IS}}{dt} &= p\kappa E, \\ \lambda &:= \frac{\beta_A I_A + \beta_S I_S}{N^*}, \end{aligned}$$

$$N^*(t) = L + S + E + I_S + I_A + H + R.$$

See Table 1 for notation and references values.

*Hypothesis.* We consider that susceptible individuals become infected when they are in contact with asymptomatic individuals and individuals with symptoms, we will propose that a proportion of asymptomatic individuals have a way to get relief and not die. A proportion of individuals infected with symptoms may die from the disease or may be relieved.

We callibrate parameters of our base dynamics in (1) via Multichain Montecarlo (MCMC). To this end, we assume that the comulative 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

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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 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).

$p$  and  $\kappa$

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

Using the reproductive number definition of VanDenDrishe, we obtain

$$R_0 := \frac{N^*(\beta_S p \kappa + \beta_A \kappa (1 - p))}{(\mu - \kappa)(\gamma_S + \mu_{I_S} + \gamma_A + \mu) N^* \mu}$$

Figure 2 displays data of coumulative confirmed cases of COVID-19 of Mexico city, and the fitt of our model in Equations (1) and (2).

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

*Preventive vaccines.*

*Efficacy and vaccine-induced immunity.*

*Actual vaccine stage development.*

*Vaccination reproductive number.*

*Vaccination rate  $\lambda_V$  estimate.*

*Feasibility regions according to efficacy and vaccination rate.*

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

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

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

### 4. Parameter callibration

*Bayesian estimation.*

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	[FENG]
$\gamma_S$	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

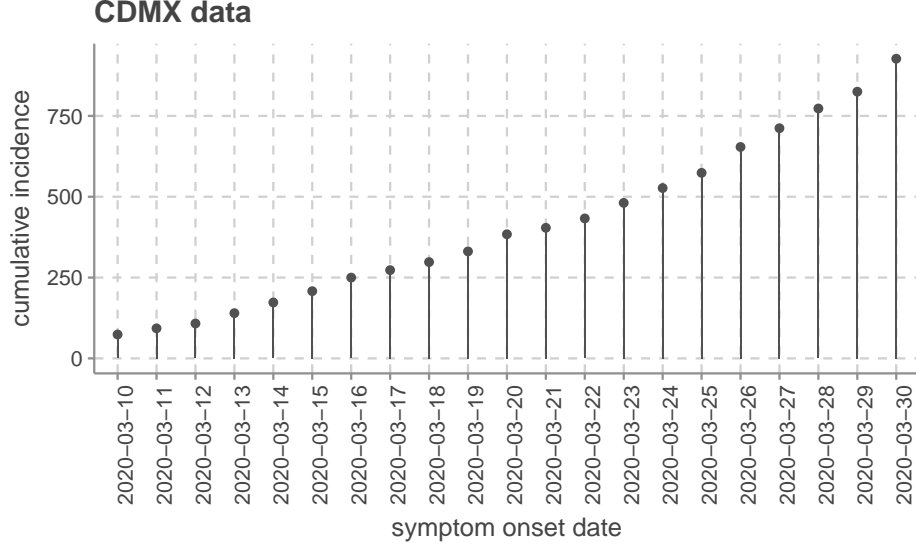


Figure 1: Cumulative new symptomatic and confirmed COVID19 reported cases from Ciudad de Mexico between March, 10, to March 30 of 2020.

## 5. Vaccination reproductive number

## 6. Optimal controlled version

*Controlled Model.* Now we model vaccination, treatment and lockdown as an optimal control problem. According to dynamics in Equation (1), we modulate the vaccination rate with a time-dependent control signal  $u_V(t)$ . We add compartment  $X_{vac}$  to count all the vaccine applications of susceptible, exposed, asymptomatic and recovered individuals. This process is modeled by

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

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

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

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

$$J(u_V) := \int_0^T a_S I_S + a_d D + \frac{1}{2} c_V u_v^2 ds. \quad (5)$$

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

Further, since we aim to simulate vaccination policies at different coverage scenarios, we impose the vaccination counter state's final time condition  $X(T)$

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

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

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

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

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

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

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

Our objective is minimize the cost functional (5)—over an appropriated functional space—subject to the 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

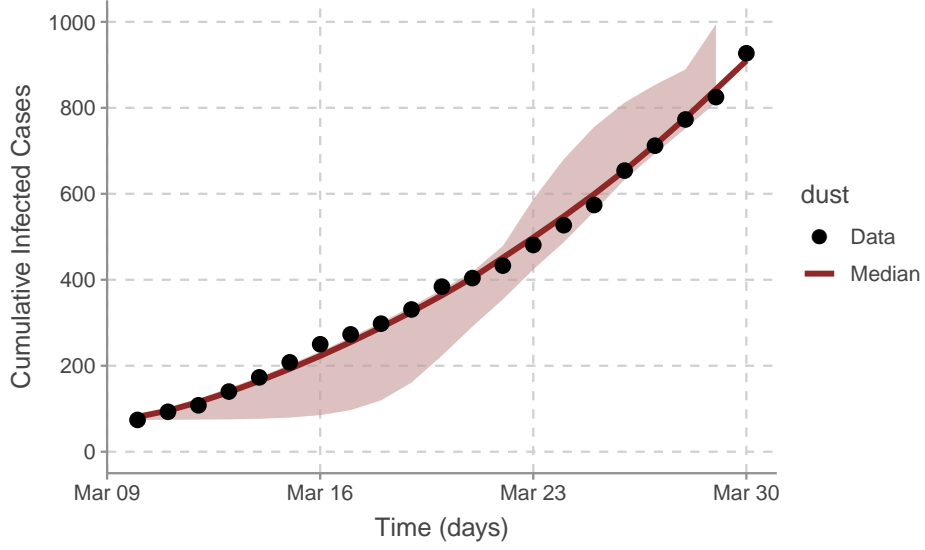


Figure 2: Fit of diary new cases of Mexico city during exponential growth.

problem (OCP).

$$\min_{u \in \mathcal{U}} J(u) := \int_0^T [(a_D \mu_s + a_H \delta_H) I_S(r) + a_{I_S} p \kappa E(r)] dr$$

s. t.

$$\begin{aligned} L' &= \theta \mu N^* - \epsilon \lambda L - u_L(t) L - \mu L \\ S' &= (1 - \theta) \mu N^* + u_L(t) L + \delta_v V + \delta_R R \\ &\quad - [\lambda + (\lambda_V + u_V(t)) + \mu] S \\ E' &= \lambda (\epsilon L + (1 - \epsilon) V + S) - (\kappa + \mu) E \\ I_S' &= p \kappa E - (\gamma_S + \mu_{I_S} + \delta_H + \mu) I_S \\ I_A' &= (1 - p) \kappa E - (\gamma_A + \mu) I_A \\ H' &= \delta_H I_S - (\gamma_H + \mu_H + \mu) H \\ R' &= \gamma_S I_S + \gamma_A I_A + \gamma_H H - (\delta_R + \mu) R \\ D' &= \mu_{I_S} I_S + \mu_H H \\ V' &= (\lambda_V + u_V(t)) S - [(1 - \epsilon) \lambda + \delta_V + \mu] V \end{aligned}$$

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

$$\begin{aligned} L(0) &= L_0, \quad S(0) = S_0, \quad E(0) = E_0, \quad I_S(0) = I_{S_0}, \\ I_A(0) &= I_{A_0}, \quad H(0) = H_0, \quad R(0) = R_0, \quad D(0) = D_0, \\ V(0) &= 0, \quad X_{vac}(0) = 0, \quad u_V(\cdot) \in [u_{\min}, u^{\max}], \\ X_{vac}(T) &= x_{coverage}, \quad \kappa I_S(t) \leq B, \quad \forall t \in [0, T], \\ N^*(t) &= L + S + E + I_S + I_A + H + R + V \end{aligned} \tag{9}$$

## 7. Optimal control problem

## 8. Numerical Results

### Appendix A. Appendix

Consider the following cost functional that we want to minimize

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

subject to the dynamics

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

and the initial state  $X(0) = x_0$ . 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 controls*  $\tilde{u}$  of the form

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

for  $j = 0, \dots, n-1$ . ASSUMPTION 1. ASSUMPTION 2. By Assumption 1, the system

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

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

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

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

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

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

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

Notice that each  $\tilde{X}_j$  is a continuous function of  $(a_0, \dots, a_j)$  and  $x_0$ . Therefore, by Assumption 2, the mapping

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

is continuous.

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