[SDIV 1] edit Abastract

Optimal constant piecewise vaccination and lockdown policies for COVID-19

Gabriel A. Salcedo-Varela[a], Francisco Peñuñuri[b], D. González-Sánchez[c], Saúl Díaz-Infante[c,*]

[a] *Departamento de Matemáticas, Universidad de Sonora, Blvd. Luis Encinas y Rosales S/N, Hermosillo, Sonora, México, C.P. 83000.*
[b] *Facultad de Ingeniería, Universidad Autónoma de Yucatán, A.P. 150, Cordemex, Mérida, Yucatán, México.*
[c] *CONACYT-Universidad de Sonora, Departamento de Matemáticas, Blvd. Luis Encinas y Rosales S/N, Hermosillo, Sonora, México, C.P. 83000.*

Abstract

BACKGROUND.
Vaccine Policies for COVID 19 require that the Nonpahrameceutic Interventions runs in parallel, but in modulation according the the current state of the seroprevalence of SAR-Cov2.
FINDINGS.
IMPLICATIONS.

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

1. Introduction

Background. At the date of writing this manuscript, a Pfizer-Biotech vaccine is implementing in the USA. This vaccine development among Astra-Zeneca, Cansino, Sputnik, Novavax another's promises deliver sufficient doses for Latinoamerica, particularly in Mexico this past Christmas has been arriving the firs stock with around 40 000 amounts. In October, WHO established a recommended protocol for prioritizing access to this pharmaceutical hope, given clear lines about who has to be vaccinated first and why.However, each vaccine development implies different issues to its application. For example, the Pfizer-Biotech vaccine requires two doses and very particularly logistic requirements that demand special services. In Mexico, despite Pfizer taking the responsibility to capacitate and help manage the immunization, we observe an explicit demand for health-logistic resources that limit our institutions' response. Thus our research interest in this manuscript explores the effect of the combined interventions Lockdown-Vaccination to mitigate COVID-19.

Litterature review. The issue of how vaccine first has been traduced as an optimal allocation problem of vaccine doses, we recommend to the interested reader the articles [1, 2]. These articles consider scenarios where the health services response and vaccine stock achieve the given vaccination policy's objectives and respond 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.

Early articles about COVID-19 optimal intervention modeling mainly focus on Nonpharmaceutical interventions (NPIs). Mostly these works understand the control strategy as 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]. Libotte et. al. reports in [7] optimal vaccination strategies for COVID19.

*Corresponding author
Email addresses: a211203745@unison.mx (Gabriel A. Salcedo-Varela), francisco.pa@uady.mx (Francisco Peñuñuri), dgonzalezsa@conacyt.mx (D. González-Sánchez), saul.diazinfante@unison.mx (Saúl Díaz-Infante)

Contribution and main objectives. Our manuscript is the first contribution modeling with optimal control of Lockdown-Vaccination strategies' effect to the best of our knowledge. Since health services' response will be limited by the vaccine stock and logistics, to implement in parallel NPIs is mandatory. We focus on formulating and studying via simulation the system Lockdown-Vaccination with recent and approved vaccine profile by the Mexico Health council and developing optimal policies for the Lockdown release-input and Vaccine application doses.

Vaccine development. According to official Governmental communication in December, Mexico treated 36 000 000 doses Pfizer-Biotech, 76 000 000 doses with Aztra-Seneca 18 000 000 doses of Cansino-BIO. Other developments also are running the third Phase, and with high probability, in the third quarter of 2021, some of these developments will incorporate into Mexico's vaccine portfolio. Despite official agreements, each vaccine's delivery schedule is under uncertainty and-or subject to the approval of COFEPRIS.

Problem setup. The first accepted vaccine —Pfizer-BioNTech's BNT162b2 —has an efficacy above 90 % and requires two doses to achieve immunity. The other mentioned developments have a very similar profile but require different logistic management and stock allocation. Thus, we face designing a schedule of dose application subject to a given vaccine stock that will be applied in a given period. To this end, we formulate an optimal control problem that minimizes the burden of COVID-19 in DALYs [WhoDALY(2020)]. We also optimize the cost generated by the implementation of Vaccination in parallel with Lockdown.

Piecewise optimal policies. Comment about the solution of the underlying Optimal Control Problem 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. Optimal control problems with piecewise constant policies have been studied in different contexts. For instance, a solution method based on the gradient of the cost functional is studied in [8]; convergence results of piecewise constant solutions to permanent solutions in linear-quadratic problems are given in [9]; or, in [10], a general numerical methodology to find piecewise constant solutions is proposed.

[SDIV 2] David

Papaer structure. Afteher this introduction, in Section 2 we formulate the basic spread model for COVID19 and callibrate its parameters. Then, Section 3 establish the lockdown-vacccination model and discusses about the regarding reproductive number in Section 4. Section 5 is the core of our contribution, here we formulate optimal policies for lockdown and vaccination as an optimal controlled problem that we numerically solve and illustrate by Differential Evolution in Section 6. We conclude with perspectives and final commnets in Section 7.

2. Covid-19 spread dynamics

Uncontrolled 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 δ_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 population $N^\star$.

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

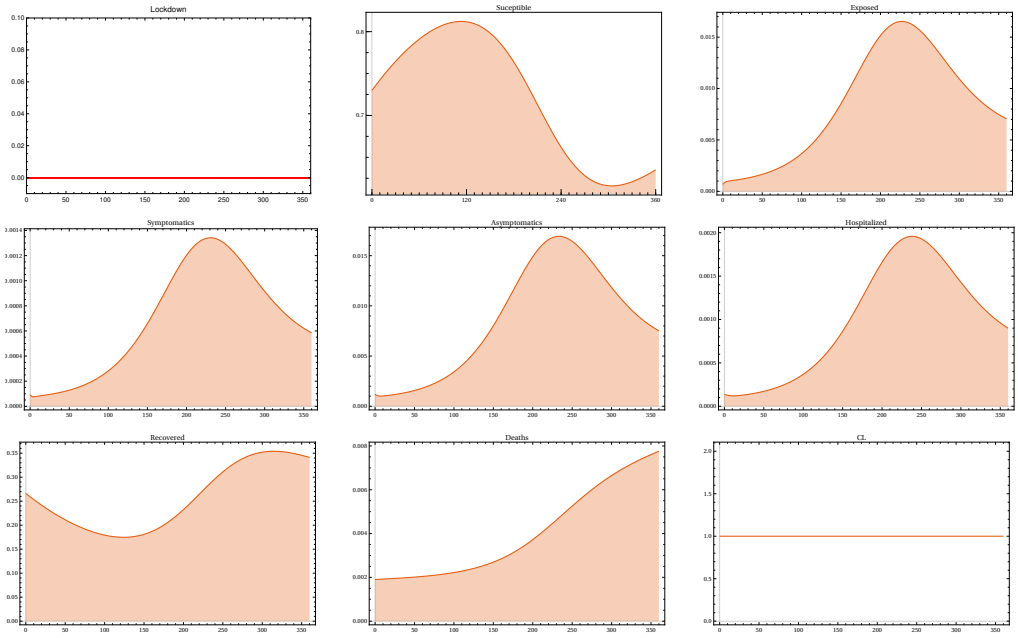
(A-4) After a period of latency $1/\kappa = 5.1$ days, an exposed individual becomes infected. Being p the probability of developing symptoms and $(1-p)$ the probability of becoming infectious but asymptomatic. Thus $p\kappa E$ denotes the exposed individuals that become infectious and develop symptoms.

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

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

Thus we formulate the following Ordinary Differential Equation (ODE)

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



See Table 1 for notation and references values. Put here the flow diagram

[SDIV 3] use WPS

Parameter	Description
μ	Death rate
β_S	Infection rate between susceptible and symptomatic infected
β_A	Infection rate between susceptible and asymptomatic infected
λ_V	Vaccination rate
δ_V^{-1}	Vaccine-induced immunity
ε	Vaccine efficacy
κ^{-1}	Average incubation time
p	New asymptomatic generation proportion
θ	Proportion of individuals under lockdown
γ_S^{-1}	Average time of symptomatic recovery
γ_A^{-1}	Recovery average time of asymptomatic individuals
γ_H^{-1}	Recovery average time by hospitalization
δ_R^{-1}	Natural immunity
δ_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 Pois-

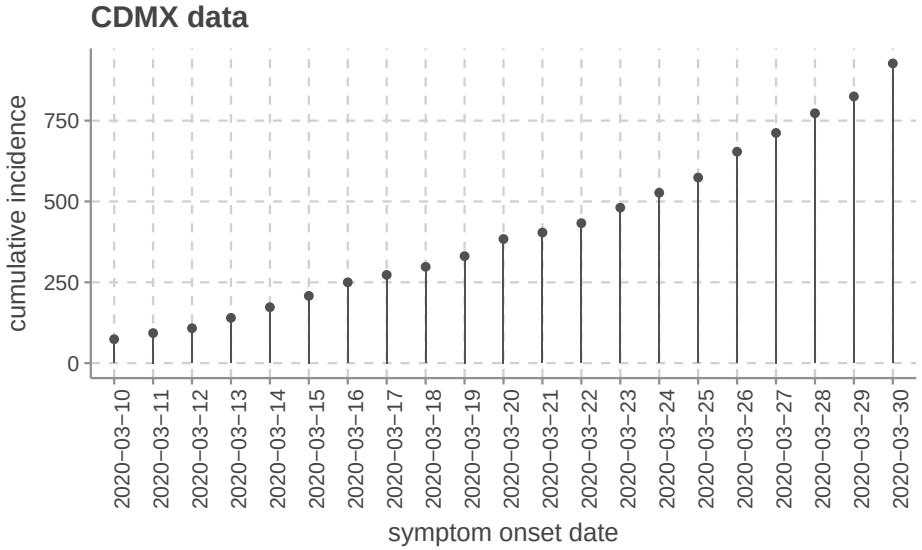


Figure 1: Cumulative new symptomatic and confirmed COVID19 reported cases from Ciudad de Mexico and Valle de Mexico [CITE] between March, 10, to March 30 of 2020.

son distribution with mean $\lambda_t = IC_s(t)$. Further, following [] we postulate priors for p and κ

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

Using Van DenDrishe's [CITE] definition of reproductive number we obtain

[**SDIV 4**] Review this R_0 calculation with Gabriel

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

where

$$\begin{aligned} R_1 &= 1-\theta(1-\epsilon), \\ R_2 &= \mu+\delta_H+\gamma_S+\mu_{I_S} \end{aligned}$$

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

Parameter	Median	Reference
q_r, ϵ	0.4, 0.3, 0.1	this study
β_S	$q_r \times 8.690\,483 \times 10^{-1}$	this study
β_A	$q_r \times 7.738\,431 \times 10^{-1}$	this study
κ	0.196 078 43	*
p	0.1213	*
θ	0.2,	this study
δ_L	0.04	postulated
δ_H	0.2	*
δ_V	0.002 739 726 027 397 260 3	$\delta_V^{-1} = 2$ years CanSinoBIO
δ_R	0.005 555 56	$\delta_R^{-1} \approx 180$ days
μ	$3.913\,894 \times 10^{-5}$	**
μ_{I_S}	0.0	
μ_H	0.016 32	[11]
γ_S	0.092 506 94	*
γ_A	0.167 504 19	*
γ_H	$5.079\,869 \times 10^{-1}$	*
λ_V	0.000 611 35	
ε	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}	9.283×10^{-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^0_{vac}	0.0	
V_0	0.0	
$Y^0_{I_S}$	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]

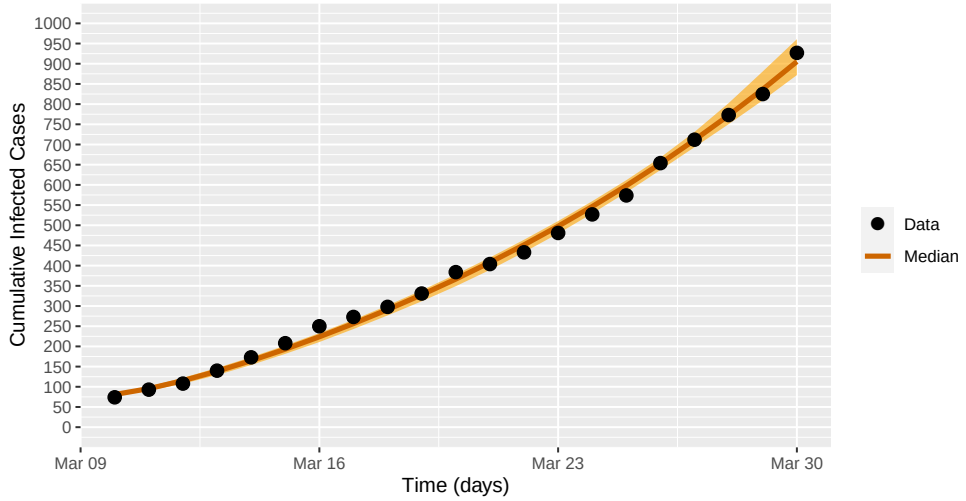


Figure 2: Fit of daily new cases of Mexico city during exponential growth.

3. Imperfect-preventive COVID-19 vaccination

Preventive vaccines.

Efficacy and vaccine-induced immunity.

Actual vaccine stage development.

Vaccination reproductive number.

Vaccination rate λ_V estimate.

Feasibility regions according to efficacy and vaccination rate.

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.

[SDIV 5] Justify this hypothesis cite

(VH-2) The vaccination camping omits testing to detect seroprevalence. Thus Expoxed, 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

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

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

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

4. Lockdown-Vaccination reproductive number

R_0 definition.

No vaccine reproductive number.

Vaccine reproductive number.

Efficacy, coverage and vaccination rate. Here Gabriel's R not calculations.[SDIV]

$$
R_{v0} := \left[1 - \frac{\varepsilon\lambda_V}{\mu + \lambda_V + \delta_V} - \frac{\theta\mu(1-\epsilon)}{\mu + \delta_L + \lambda_V}\right](\mu R_1 + \delta_L)R_0
$$

[SDIV 6] Here counto plots figure as function of efficacy and vaccina tion rate

[1] edit plot range to dis play level RV=1

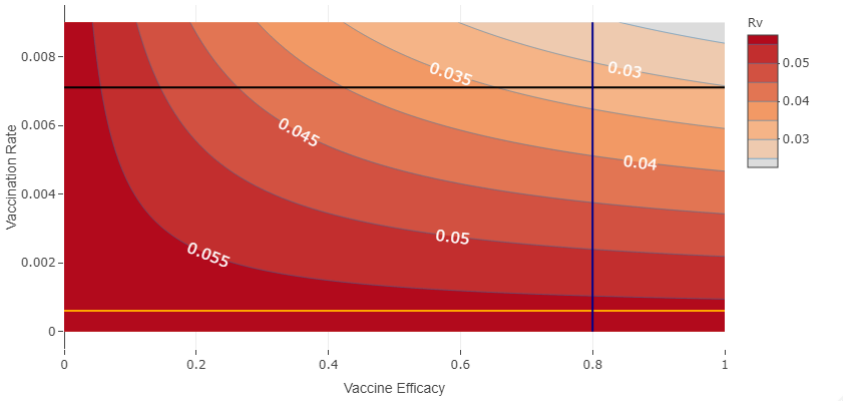


Figure 3: R not contour plot as function of efficacy and vaccination rate.

5. Optimal controlled version

Controlled Model. Now wee model vaccination, treatment and lockdown as a 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 lockdownm susceptible, exposed, asymptomatic and recovered individuals. This process is modeled by

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

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

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

In other words, we assume in functional J that pandemic cost is proportional to the symptomatic hospitalized and death reported cases and that a vaccination and lockdown policies 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 $X_{vac}(T)$

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

[SDIV 7] Write explication in the context of DALYs

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

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

to ensure that healthcare services will not be overloaded. Here κ 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

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

That is, λ_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 λ_V as a baseline. That is, optimal vaccination amplifies or attenuates the estimated baseline λ_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 problem (OCP).

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

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

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

6. Numerical Experiments

Differential Evolution (DE) [12] is an evolutionary algorithm successfully employed for global optimization [13]. The method is designed to optimize functions $f : \mathbb{R}^n \to \mathbb{R}$. Nevertheless, DE can be applied to optimize a functional as stated in [10]. 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 [14].

[SDIV 8] Aqui va tu descripcion Frank.

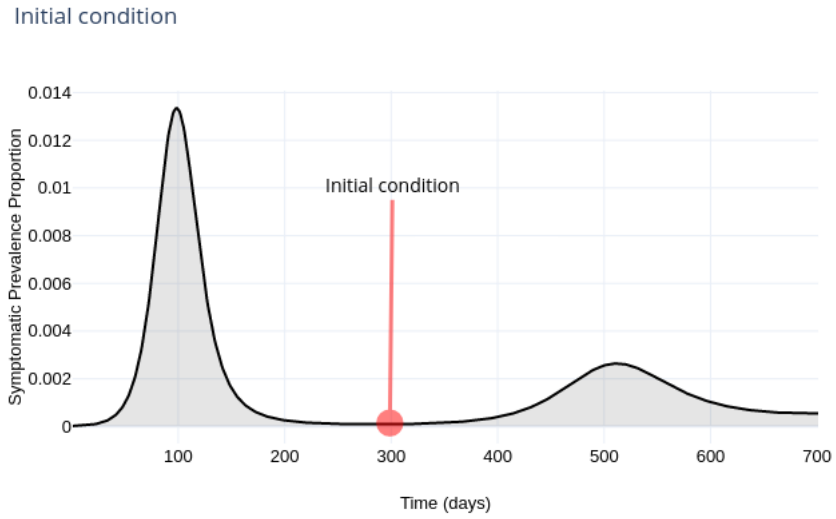


Figure 4: Initial condition scheme. We assume a positive prevelance. Forreference, at the date of write this manuscript, prevalence in CDMX is around 16 000 cases, see https://plotly.com/ sauld/36/ to display a electronic viewer.

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 of the vector used to describe the two controls–see [10]), which in our case was of 180. As stopping criteria we have used a maximum number of generations which is taken as 5000. Whit these values an excellent convergence is achieved as can be seen in figs...

Algorithm 1 Differential Evolution Algorithm

$X \leftarrow \mathbf{X}_0(Np, \mathcal{V})$
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
$\mathbf{x}_{best} \leftarrow \mathbf{Best}(X, f_{ob})$

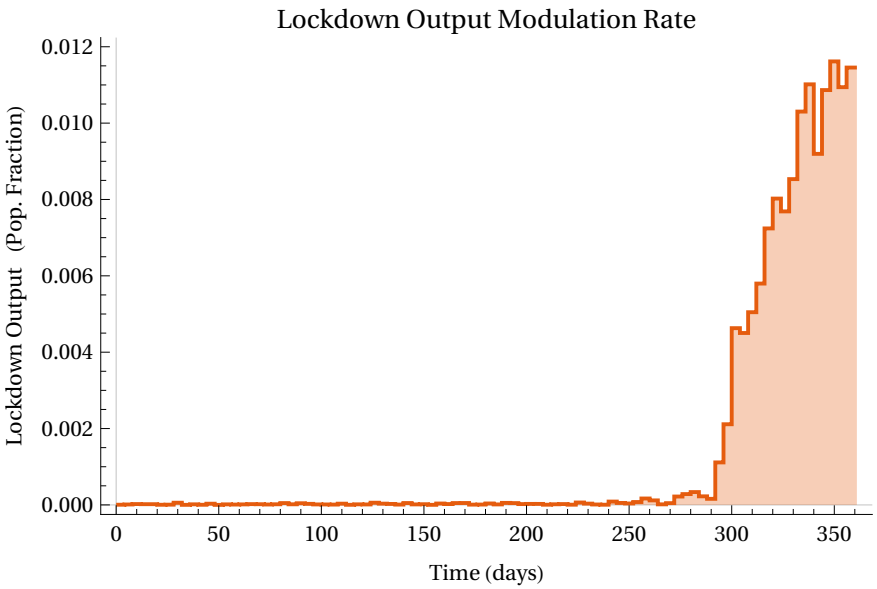


Figure 5: Lockdown modulation signal.

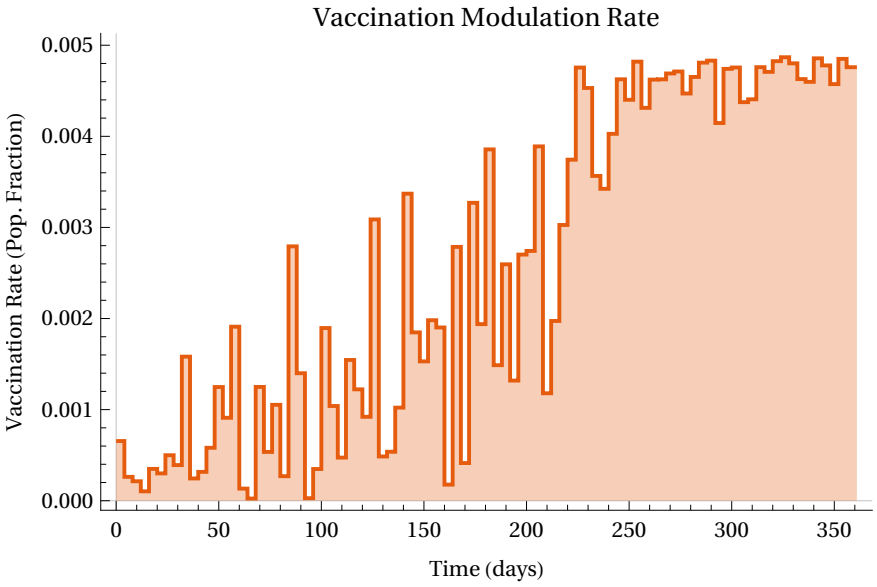


Figure 6: Vaccination rate modulation.

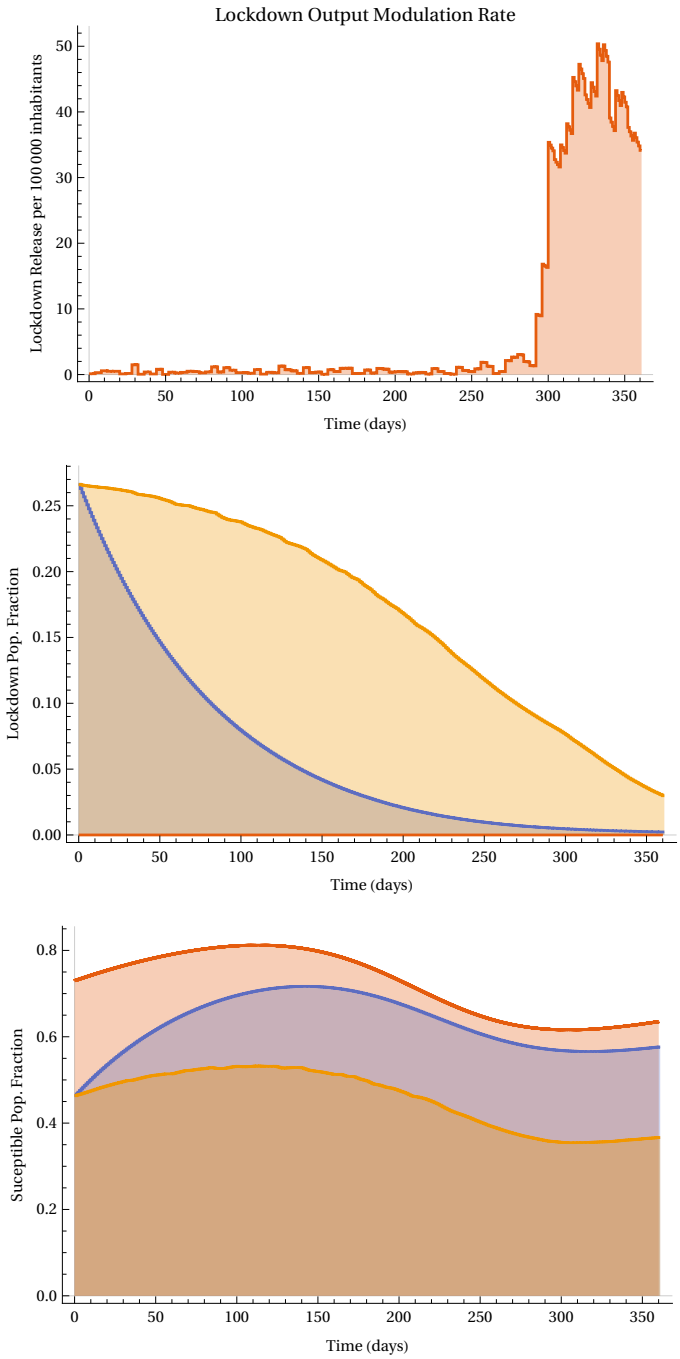


Figure 7: Modulation lock down release.

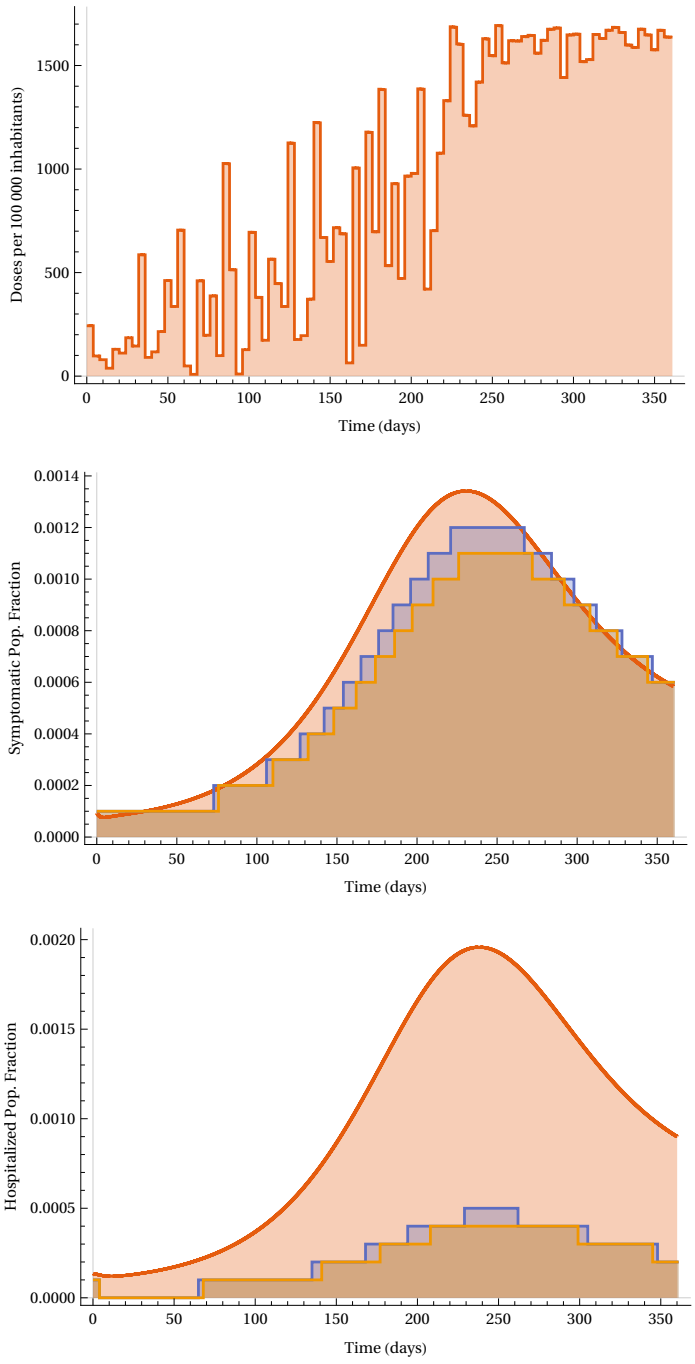


Figure 8: Symptomatic Prevalence and Hozpitalization.

7. Conclusion

Changes (compact)

Author: anonymous

Commented 1

Author: SDIV

Added 2

Commented 8

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

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

subject to the dynamics

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

and the initial state $X(0) = x_0$. The functions $u : [0, T] \to U$ are called *control polices*, where U is a subset of some Euclidean space. Let $t_0 < t_1 < \ldots < t_n$, 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

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

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

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

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

has a unique solution $\tilde{X}_0(t; x_0, a_0)$ which is continuous in (x_0, a_0); see, for instance [15]. Next, put $x_1 := \tilde{X}_0(t_1; x_0, a_0)$ and consider the system

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

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

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

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 $(a_0, \ldots, a_j)$ and x_0.

By Assumption (A-2), the mapping

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

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

The cost functional (5) and the dynamics (9) 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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