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 Bubar(2020) and Matrajt(2020). 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 (see for example Naraigh(2020), Ullah(2020)), Lockdown-Quarantine Manda(l2020), shield immunity Weitz(2020).

Libotte et. al. reports in (Libotte(2020) an Optimal vaccination strategies for COVID19.

1.1. 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

[**SDIV 1**] David

One of the main features of our model is that we consider piecewise constant control policies instead of general measurable control policies. General control policies are difficult to implement since the authority has to make different choices every instant. 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 widely studied: solution method [1], convergence [2].

However, to the best of our knowledge, this is the first application of such policies in epidemics Vaccination-Lockdown control for COVID-19.

Papaer structure.

2. Covid-19 spread dynamics

Uncontrolled dynamics. We split a given population of size N in the base SEIR structure with segregation infected classes according to the manifestation of symptoms. Let $L, S, E, I_S, I_A, H, R, D$ respectively denote the class of an individual according to its current state, namely

Lockdown (L) All individuals that has low or null mobility and that remains under isolation. Thus individual in this class reduce its probability of contagious.

Suceptible (S) Individual under risk

Exposed (E) Population fraction that host SARS-CoV-2 but cannot infect

Infected-Symptomatic (I_S) Population infected fraction with symptoms and reported as confirmed case

Infected-Asymptomatic (I_A) Infected individual whit 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 death by COVID-19

To fit data of cumulative reported symptomatic cases, we postulated the counter state Y_{I_S} and made the following hypothesis.

Hypothesis 1. According to above compartment description, we made the following hypothesis.

(H-1) We suppose that at least 30 %of the population is under lock-down and that eventually a fraction of this class move to the susceptible compartment at rate δ_L.

(H-2) Force infection is defined as the probablity of acquire COVID-19 given the contact with a symptomatic or asympotomatic individual. Thus we normalize under live population $N^\star$

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

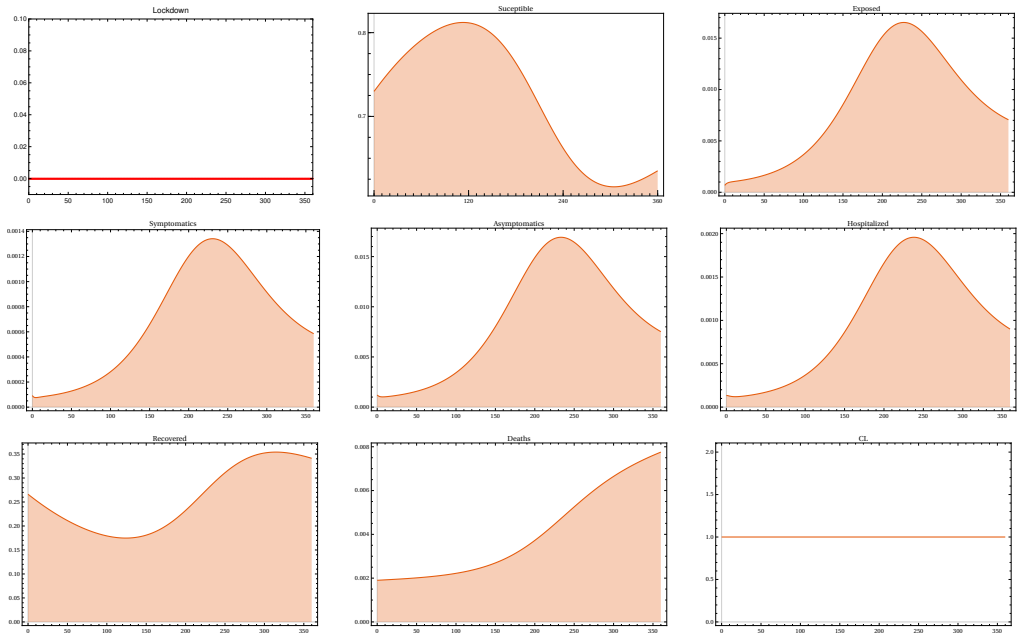
(H-4) After a period of latency of $1/\kappa = 5.1$ days, an exposed individual became infected. Being p the probability of develop symptoms and $(1-p)$ the probability of became infectious but asymptomatic. Thus $p\kappa E$ denotes the event of become infectious and develop symptoms given that the individual has been exposed

(H-5) Asymptomatic individuals not die or get in a Hospital

(H-6) A fraction μ_H of symptomatic individuals die by COVID-19 without hospitalization

Thus we formulate the following Ordinary Differential Equation (ODE)

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



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

[SDIV 2] use WPS

2.1. Parameter calibration

Bayesian estimation. We calibrate parameters of our base dynamics in (1) via Multi-chain Montecarlo (MCMC). To this end, we assume that the cumulative

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).

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 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 the reproductive number definition of Van DenDrishe [CITE], and defining $R_1 = \epsilon\theta - \theta + 1$, $R_2 = \mu + \delta_H + \gamma_S + \mu_{I_s}$ we obtain

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

[SDIV 3] Review this R_0 calculation with Gabriel

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

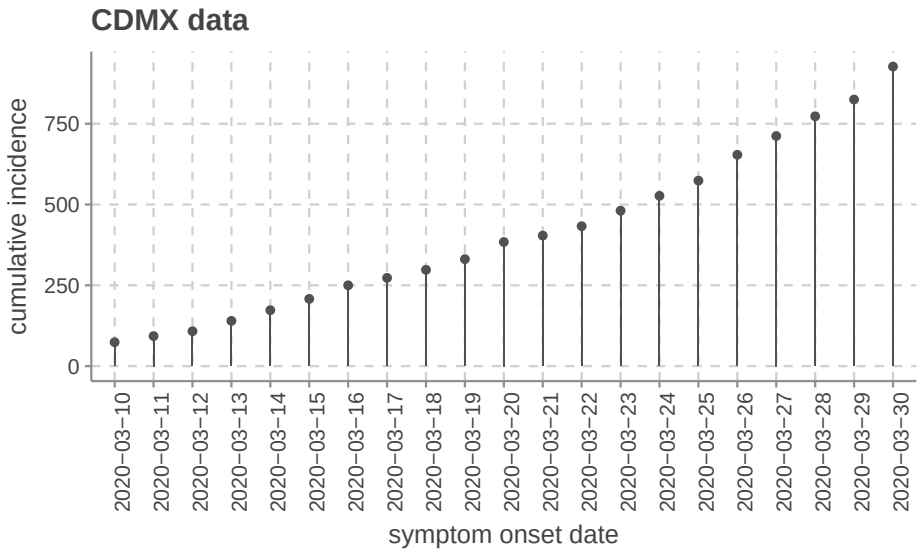


Figure 1: Cumulative new symptomatic and confirmed COVID19 reported cases from Ciudad de Mexico and Valle de Mexico [CITE] between March, 10, to March 30 of 2020.

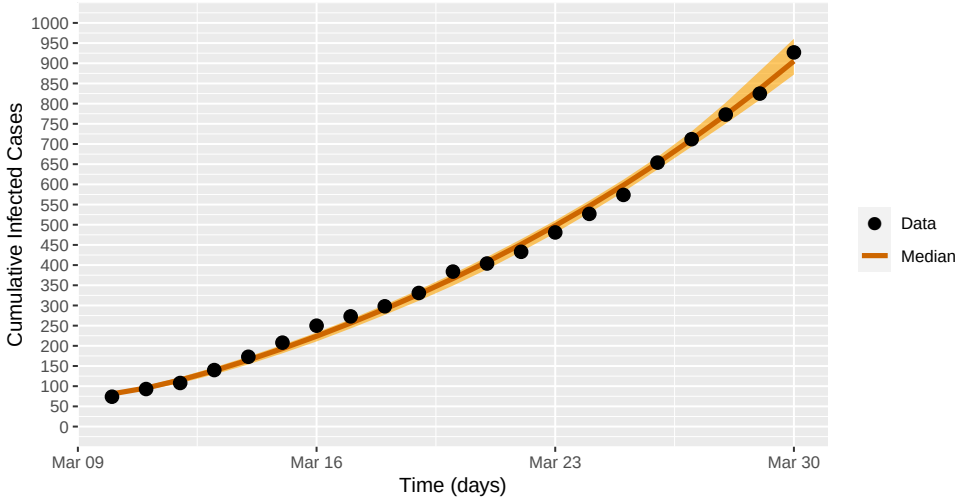


Figure 2: Fit of diary new cases of Mexico city during exponential growth.

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.

Hypothesis 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. 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 $\epsilon \in [0.6, .975]$

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

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

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

4. 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 4] Here countor plots figure as function of efficacy and vaccination rate

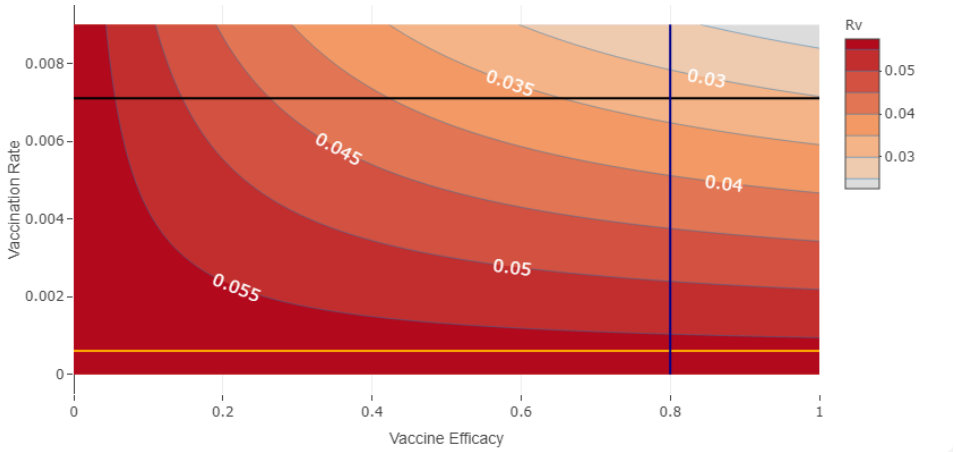


Figure 3: R not contour plot as function of efficacy and vaccination rate.

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 susceptible, exposed, asymptomatic and recovered individuals. This process is modeled by

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

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

$$J(u_L, u_V) := \int_0^T a_S I_S + a_d D + \frac{1}{2}\left(c_L u_L^2 + c_V u_v^2\right) ds. \tag{5}$$

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 differentcoverage scenarios, we impose the vaccination counter state's final time condition $X(T)$

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

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

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

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).

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

s. t.

$$\begin{aligned}
L' &= \theta\mu N^\star - \epsilon\lambda L - u_L(t)L - \mu L \\
S' &= (1-\theta)\mu N^\star + u_L(t)L + \delta_v V + \delta_R R \\
&\quad - \left[\lambda + (\lambda_V + u_V(t)) + \mu\right] S \\
E' &= \lambda(\epsilon L + (1-\varepsilon)V + S) - (\kappa+\mu)E \\
I_S' &= p\kappa E - (\gamma_S + \mu_{I_S} + \delta_H + \mu) I_S \\
I_A' &= (1-p)\kappa E - (\gamma_A + \mu) I_A \\
H' &= \delta_H I_S - (\gamma_H + \mu_H + \mu) H \\
R' &= \gamma_S I_S + \gamma_A I_A + \gamma_H H - (\delta_R + \mu) R \\
D' &= \mu_{I_S} I_S + \mu_H H \\
V' &= (\lambda_V + u_V(t))S - \left[(1-\varepsilon)\lambda + \delta_V + \mu\right] V
\end{aligned} \tag{9}$$

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

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

6. Numerical Experiments

[SDIV 5] Aqui va tu descripcion Frank.

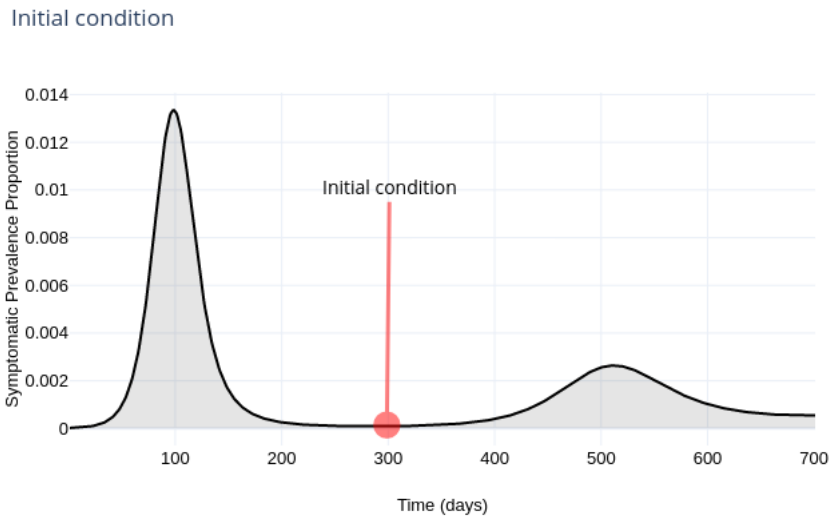


Figure 4: Initial condition scheme. We assume a positive prevelance. Forreference, at the date of write this manuscript, prevalence in CDMX is around 16 000 cases, see https://plotly.com/ sauld/36/ to display a electronic viewer.

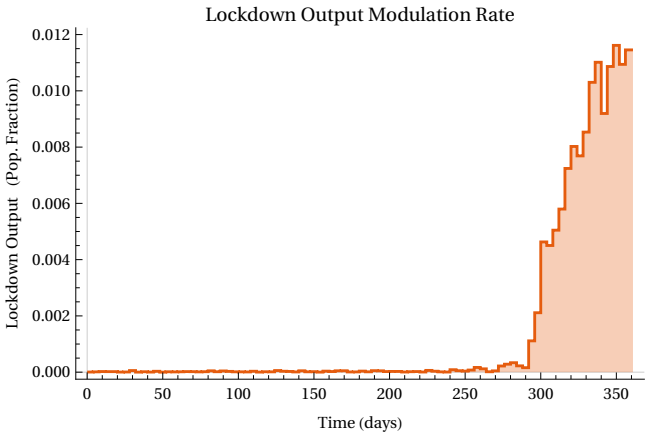


Figure 5: Lockdown modulation signal.

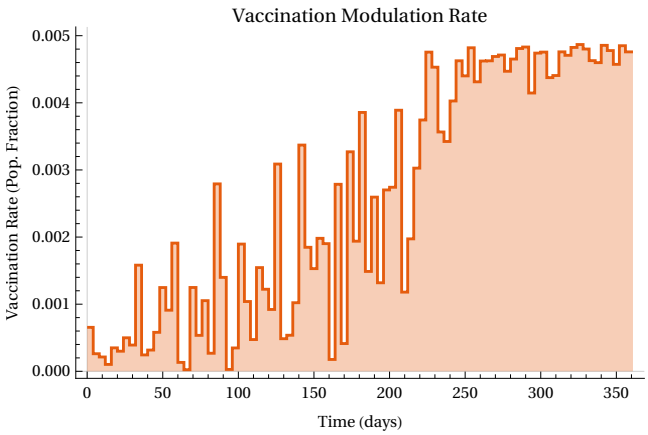


Figure 6: Vaccination rate modulation.

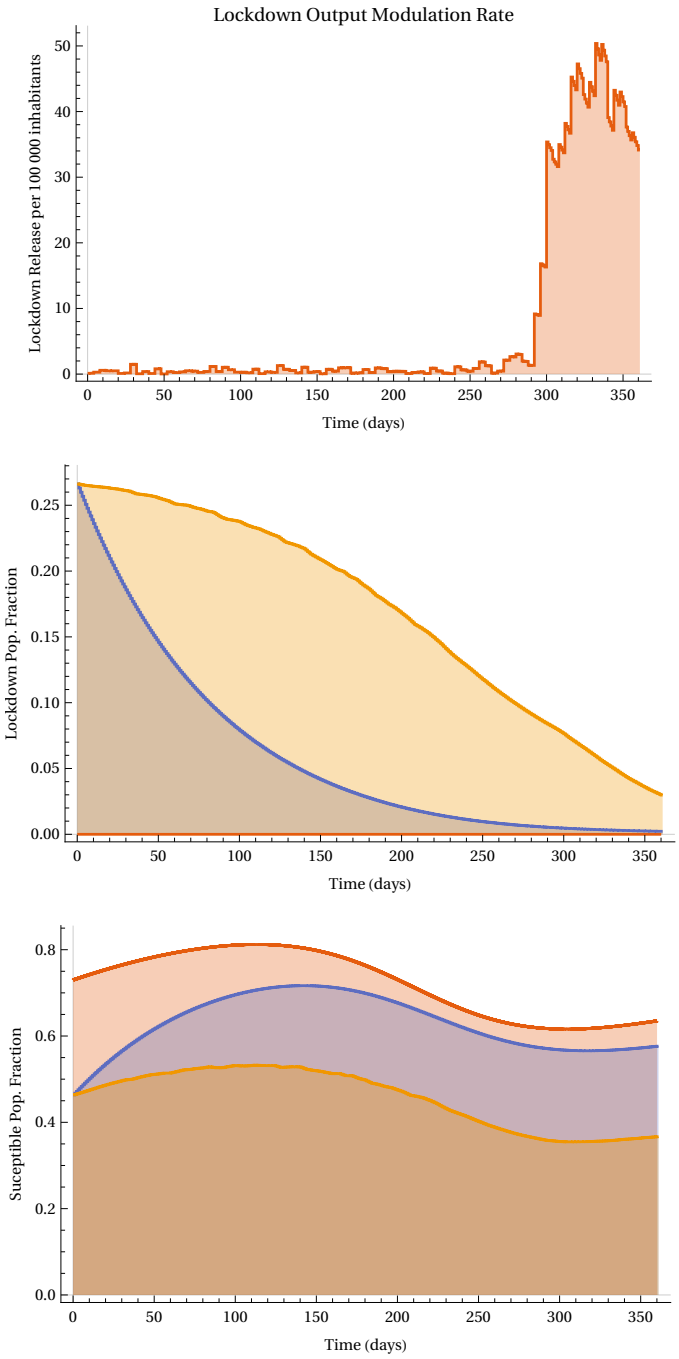


Figure 7: Modulation lock down release.

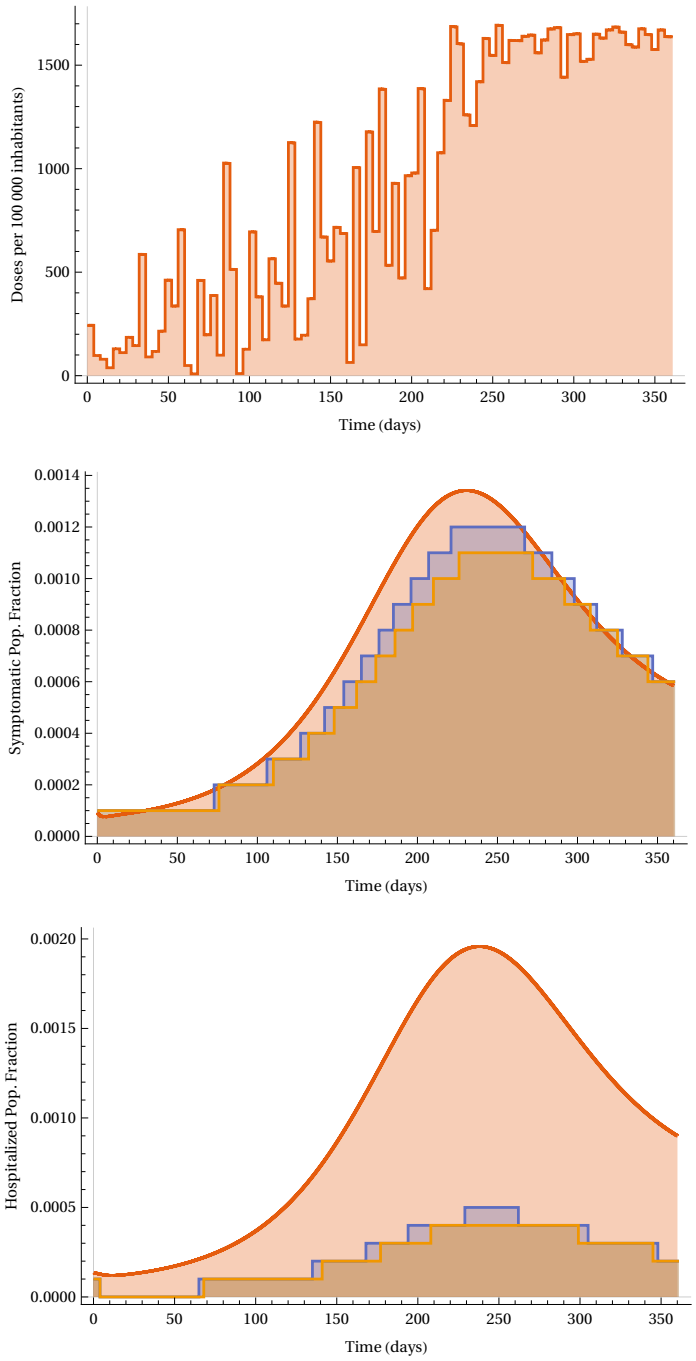


Figure 8: Symptomatic Prevalence and Hozpitalization.

Changes (compact)

Author: anonymous

No changes.

Author: SDIV

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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 1. 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). 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

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

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).

References

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