

1. Introduction

Main contribution and its relevance.

Background.

Piecewise optimal policies. Comment about the solution of the underlying Optimal Control Problem

[SDIV 1]
David

Vaccine development.

Problem setup.

Litterature review.

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.

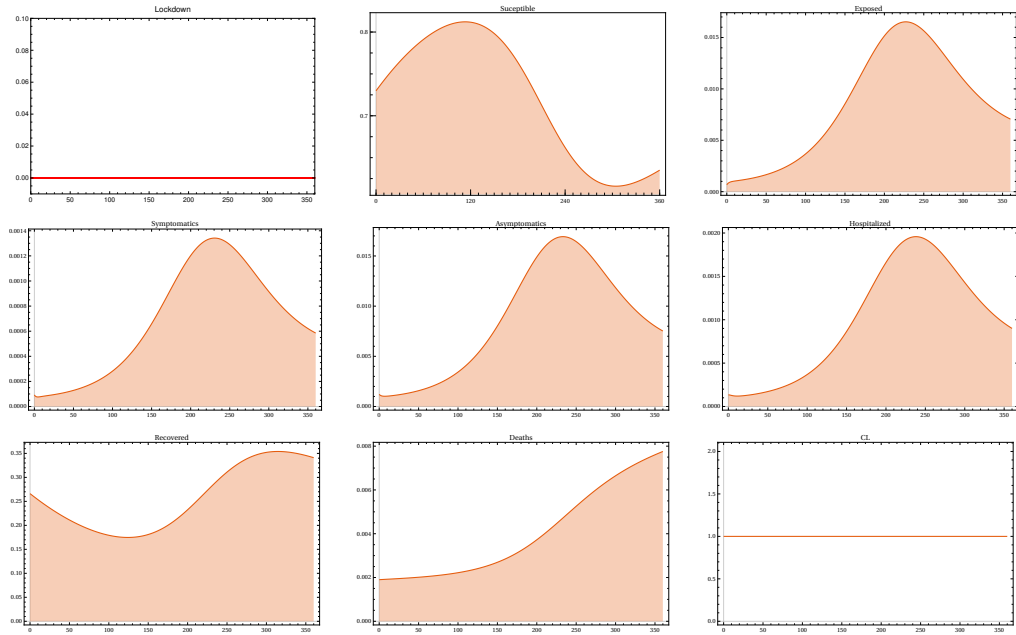
- 33 (H-1) We suppose that at least 30% of the population is under lock-down and
 34 that eventually a fraction of this class move to the susceptible compart-
 35 ment at rate δ_L .
- 36 (H-2) Force infection is defined as the probability of acquire COVID-19 given
 37 the contact with a symptomatic or asympotomatic individual. Thus we
 38 normalize under live population N^*
- 39 (H-3) Susceptible individuals become exposed—but not infectious—when they
 40 are in contact with asymptomatic or symptomatic individuals. Thus β_S ,
 41 β_A denote probability of infectious given the contact with a symptomatic
 42 or asymptomatic infectious individuals.
- 43 (H-4) After a period of latency of $1/\kappa = 5.1$ days, an exposed individual became
 44 infected. Being p the probability of develop symptoms and $(1 - p)$ the
 45 probability of became infectious but asymptomatic. Thus $p\kappa E$ denotes
 46 the event of become infectious and develop symptoms given that the
 47 individual has been exposed
- 48 (H-5) Asymptomatic individuals not die or get in a Hospital
- 49 (H-6) A fraction μ_H of symptomatic individuals die by COVID-19 without hos-
 50 pitalization

51 Thus we formulate the following Ordinary Differential Equation (ODE)

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

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53



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

[SDIV 2]
use WPS

CDMX data

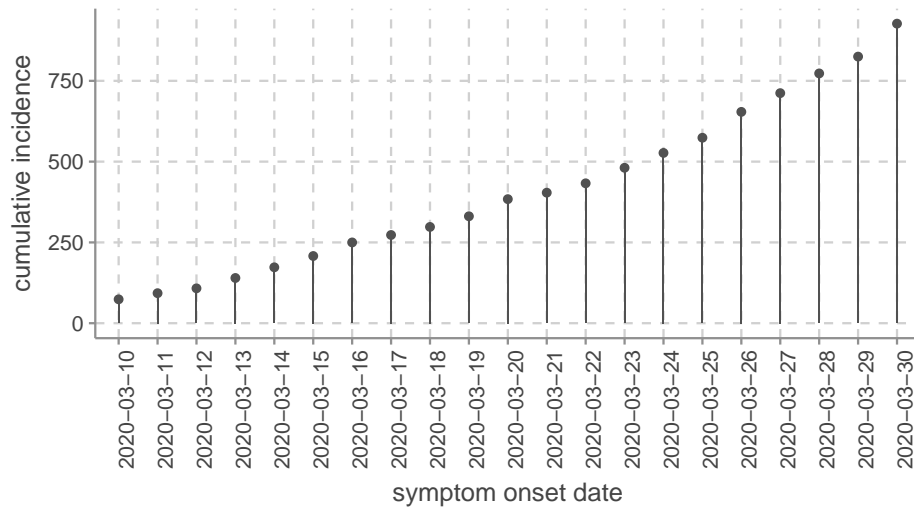


Figure 1: Cumulative new symptomatic and confirmed COVID19 reported cases from Ciudad de Mexico and Valle de Mexico [CITE] between March, 10, to March 30 of 2020.

54

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).

55 2.1. Parameter calibration

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

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

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

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

[SDIV 3]
Review this
 R_0 calcu-
lation with
Gabriel

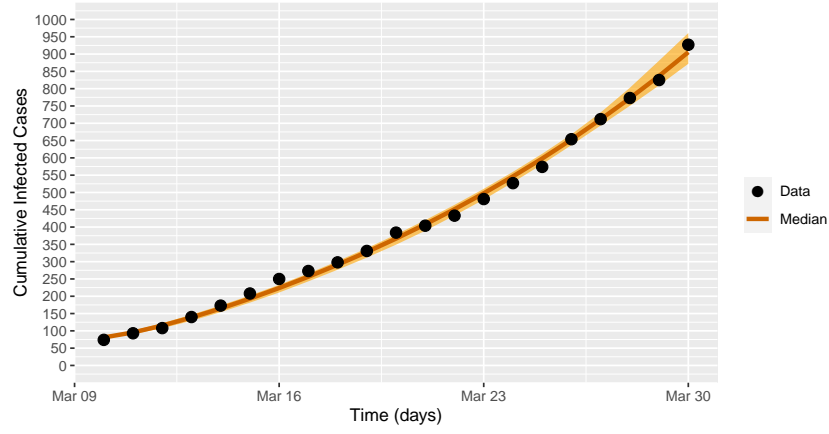


Figure 2: Fit of diary new cases of Mexico city during exponential growth.

60 Figure 2 displays data of coumulative confirmed cases of COVID-19 of Mex-
61 ico city, and Figure 2 displays the fitt of our model in Equations (1) and (2).
62 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	$q_r \times 8.690483 \times 10^{-1}$	this study
β_A	$q_r \times 7.738431 \times 10^{-1}$	this study
κ	0.19607843	*
p	0.1213	*
θ	0.2,	this study
δ_L	0.04	postulated
δ_H	0.2	*
δ_V	0.0027397260273972603	$\delta_V^{-1} = 2$ years CanSinoBIO
δ_R	0.00555556	$\delta_R^{-1} \approx 180$ days
μ	3.913894×10^{-5}	**
μ_{I_S}	0.0	
μ_H	0.01632	[FENG]
γ_S	0.09250694	*
γ_A	0.16750419	*
γ_H	5.079869×10^{-1}	*
λ_V	0.00061135	
ε	0.7, 0.80, 0.9, 0.95	[PRESS RELESASES]
N	26446435	**
L_0	0.26626009702112796	
S_0	0.463606046009872	
E_0	0.00067033	*
I_{S_0}	9.283×10^{-5}	* * *
I_{A_0}	0.00120986	*
H_0	$1.34157969 \times 10^{-4}$	**
R_0	$2.66125939 \times 10^{-1}$	
D_0	0.00190074	**
X_{vac}^0	0.0	
V_0	0.0	
$Y_{I_S}^0$	0.12258164	
B	0.0003592166581242425	9500 beds/ N
a_{I_S}	0.0020127755438256486	DALY def
a_H	0.001411888738103725, or $a_H(x) := 0.001411888738103725 \log(\frac{1}{B-\kappa I_S})$	DALY def [Jo 2020]
a_D	7.25	DALY def

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

63 **3. Imperfect-preventive COVID-19 vaccination**

64 *Preventive vaccines.*

65 *Efficacy and vaccine-induced immunity.*

66 *Actual vaccine stage development.*

67 *Vaccination reproductive number.*

68 *Vaccination rate λ_V estimate.*

69 *Feasibility regions according to efficacy and vaccination rate.*

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

72 (VH-1) Vaccine is preventive and only reduce susceptibility. Justify this hy-
73 pothesis cite

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

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

79 (VH-4) The vaccine is leaky and with efficacy $\epsilon \in [0.6, .975]$

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

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

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

80 4. Vaccination reproductive number

81 R_0 definition.

82 No vaccine reproductive number.

83 Vaccine reproductive number.

84 Efficacy, coverage and vaccination rate.

85 Here Gabriel's R not calculations.^{SDIV}

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

86

[SDIV 4]
Here countor
plots figure
as function
of efficacy
and vaccina-
tion rate

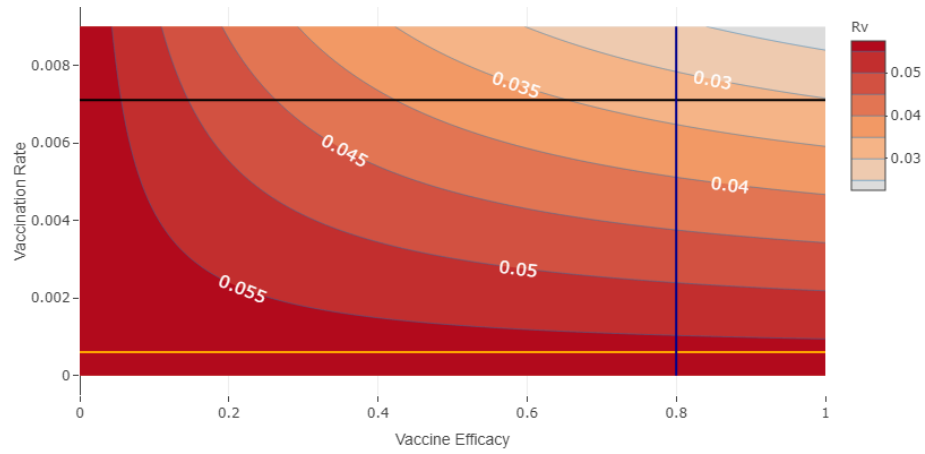


Figure 3: R not contour plot as function of efficacy and vaccination rate.

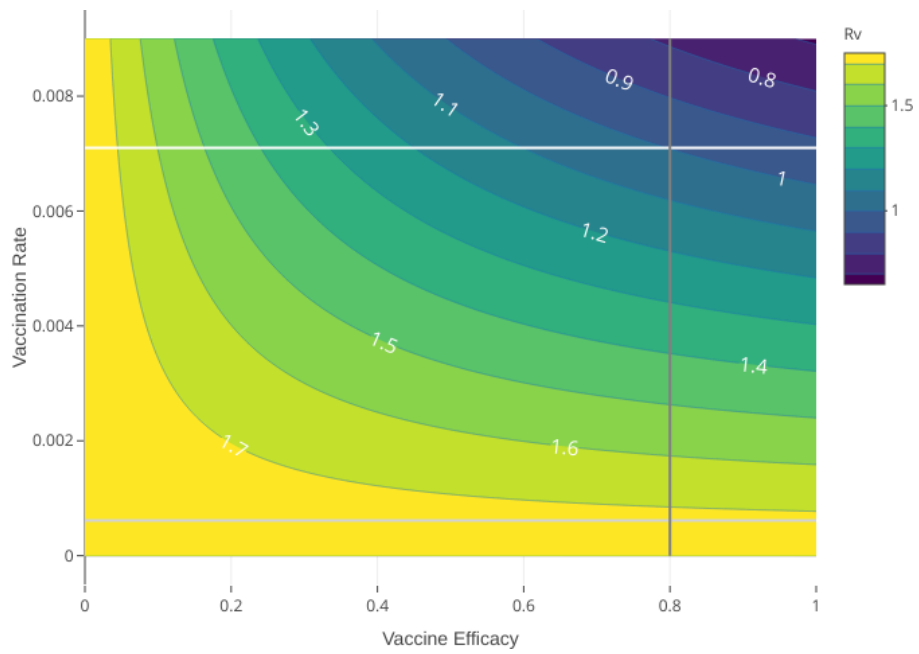


Figure 4: R not contour plot as function of efficacy and vaccination rate.

87 5. Optimal controlled version

88 *Controlled Model.* Now we model vaccination, treatment and lockdown as a
 89 optimal control problem. According to dynamics in Equation (1), we modu-
 90 late the vaccination rate with a time-dependent control signal $u_V(t)$. We add
 91 compartment X_{vac} to count all the vaccine applications of susceptible, exposed,
 92 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

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

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

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

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

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

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

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

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

103 to ensure that healthcare services will not be overloaded. Here κ denotes hos-
 104 pitalization rate, and B is the load capacity of a health system.

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

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

107 That is, λ_v denotes the constant rate to cover a fraction $x_{coverage}$ in time horizon
 108 T . Thus, according to this vaccination rate, we postulate a policy u_v that modu-
 109 lates vaccination rate according to λ_V as a baseline. That is, optimal vaccination
 110 amplifies or attenuates the estimated baseline λ_V in a interval $[\lambda_v^{\min}, \lambda_v^{\max}]$ to
 111 optimize functional $J(\cdot)$ —minimizing symptomatic, death reported cases and
 112 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).

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

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

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

6. Numerical Experiments

[SDIV 5]
Aquí va tu descripción Frank.

Initial condition

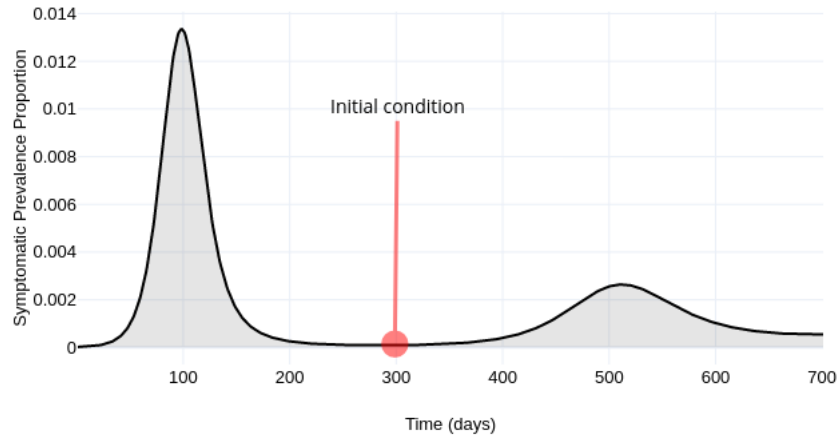


Figure 5: Initial condition scheme. We assume a positive prevalence. For reference, at the date of write this manuscript, prevalence in CDMX is around 16 000 cases, see <https://plotly.com/sauld/36/> to display a electronic viewer.

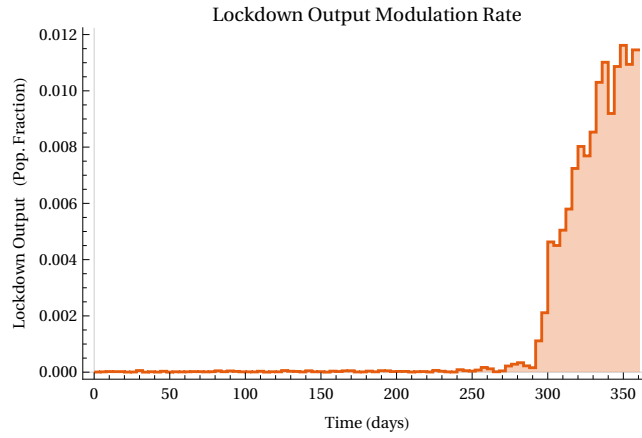


Figure 6: Lockdown modulation signal.

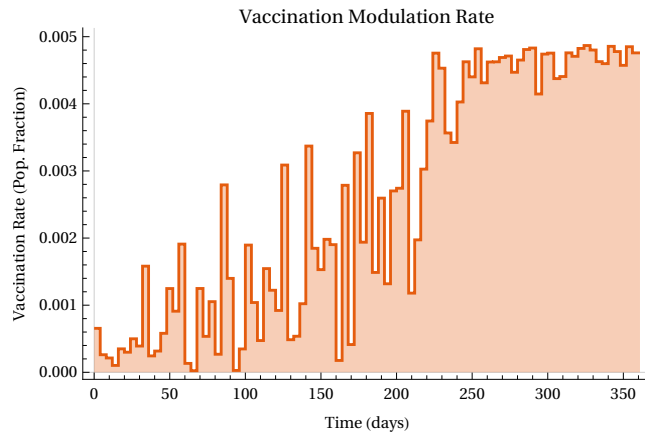


Figure 7: Vaccination rate modulation.

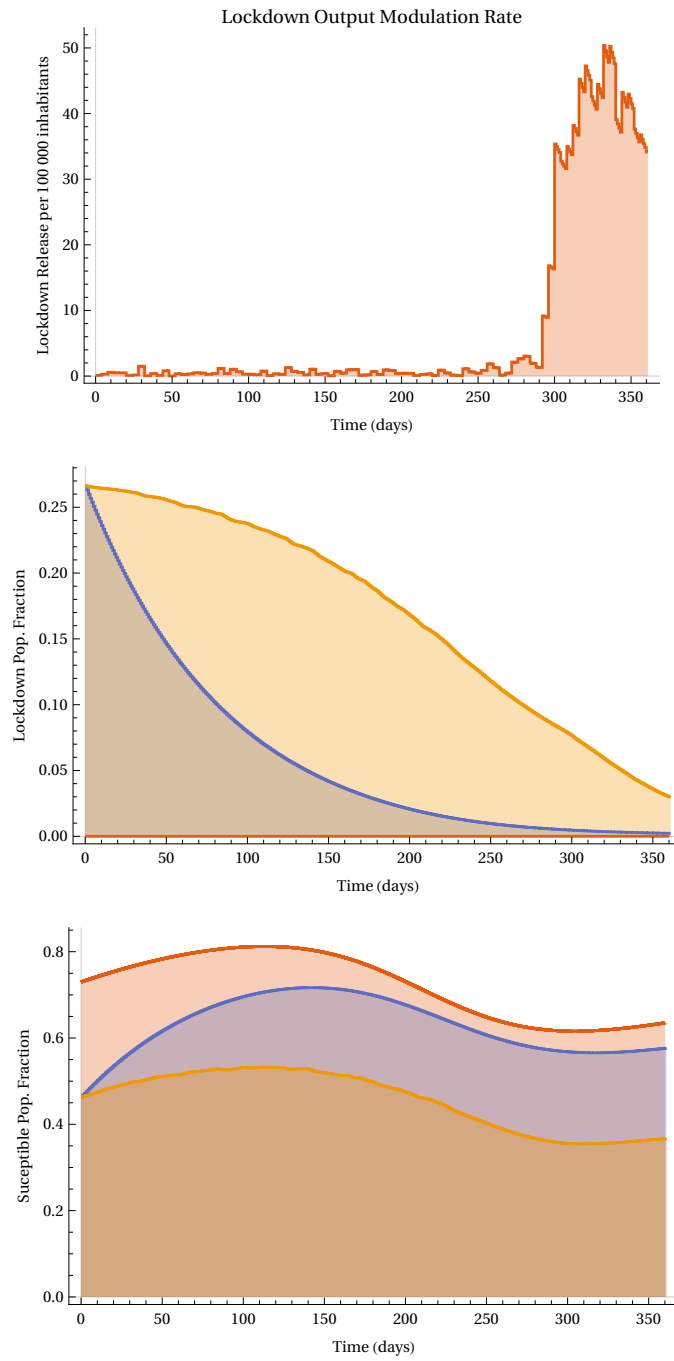


Figure 8: Modulation lock down release.

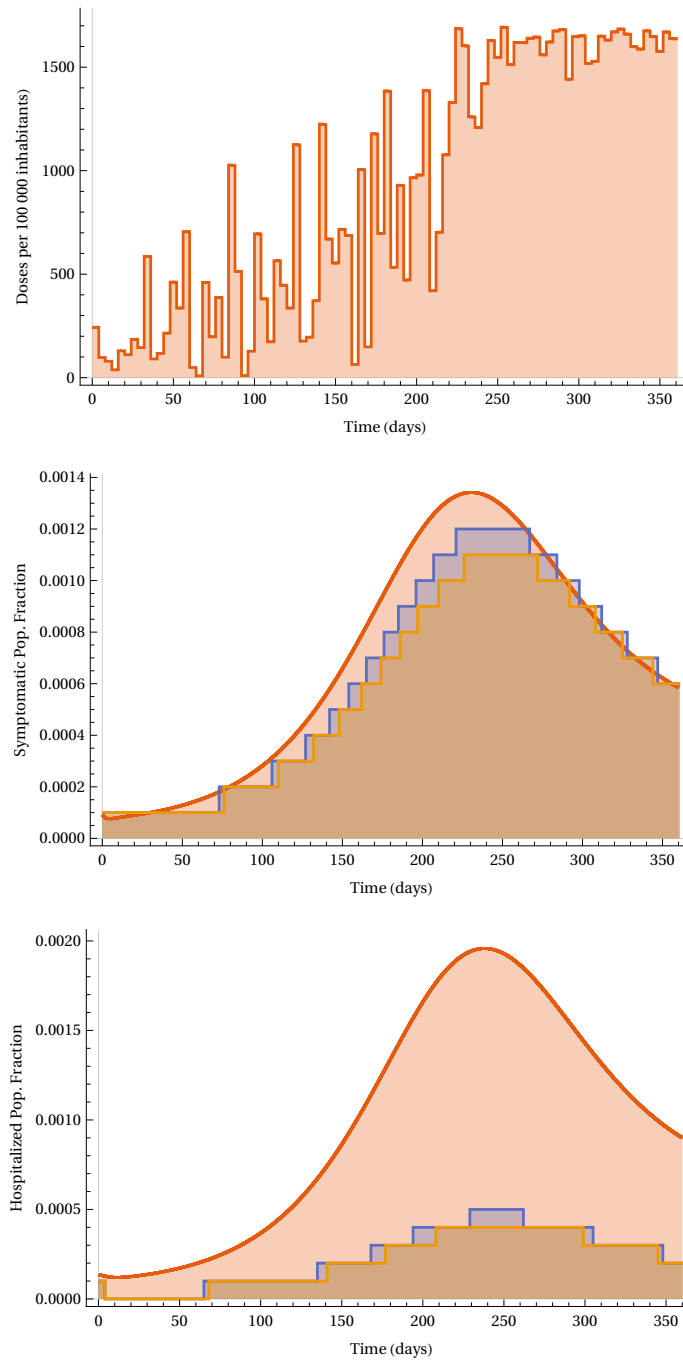


Figure 9: Symptomatic Prevalence and Hospitalization.

119 **Changes (compact)**

120 **Author: anonymous**

121 No changes.

122 **Author: SDIV**

123 Added 2

124 Deleted 2

125 Commented 5

126

127 **Appendix A. Existence of optimal policies**

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

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

131 subject to the dynamics

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

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

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

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

137 **Assumptions 1.** We made the following assumptions.

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

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

140 By Assumption (A-1), the system

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

141 has a unique solution $\tilde{X}_0(t; x_0, a_0)$ which is continuous in (x_0, a_0) . Next, put
142 $x_1 := \tilde{X}_0(t_1; x_0, a_0)$ 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

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

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

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

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

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

147 By Assumption (A-2), the mapping

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

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

151 The cost functional (5) and the dynamics (9) are particular cases of (A.1)
 152 and (A.2), respectively, and satisfy Assumptions (A-1) and (A-2). Then there
 153 exists an optimal vaccination policy of the form (A.3).

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