

## 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.

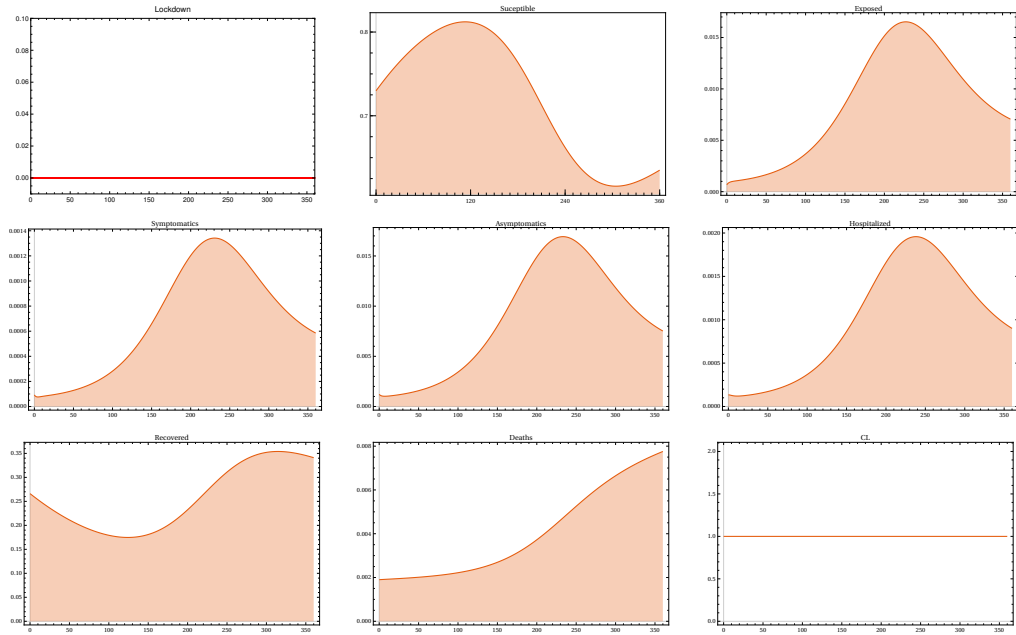
- 33 (H-1) We suppose that at least 30% of the population is under lock-down and  
 34 that eventually a fraction of this class move to the susceptible compart-  
 35 ment at rate  $\delta_L$ .
- 36 (H-2) Force infection is defined as the probability of acquire COVID-19 given  
 37 the contact with a 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  $\beta_S$ ,  
 41  $\beta_A$  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  $\mu_H$  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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See Table 1 for notation and references values. Put here the flow diagram

[SDIV 2]  
use WPS

### CDMX data

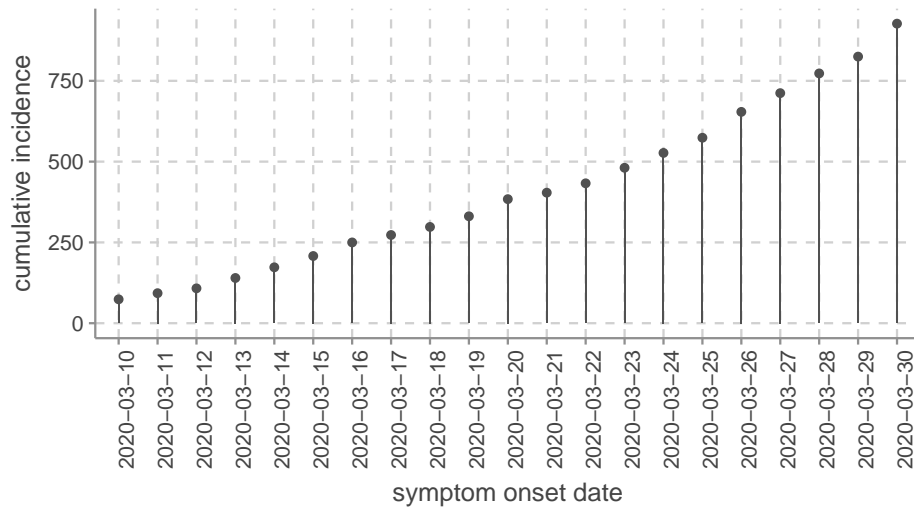


Figure 1: Cumulative new symptomatic and confirmed COVID19 reported cases from Ciudad de Mexico and Valle de Mexico [CITE] between March, 10, to March 30 of 2020.

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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).

### 2.1. Parameter calibration

*Bayesian estimation.* We calibrate parameters of our base dynamics in (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  $\kappa$

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

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

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

**[SDIV 3]**  
Review this  $R_0$  calculation with Gabriel

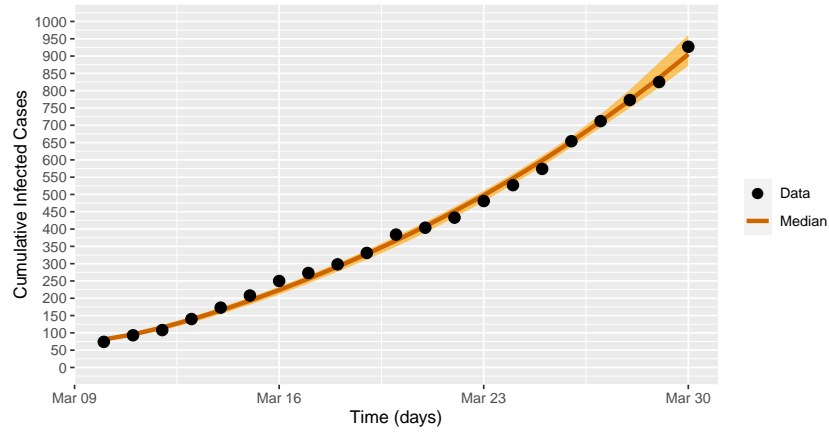


Figure 2: Fit of diary new cases of Mexico city during exponential growth.

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
$q_r, \epsilon$	0.4, 0.3, 0.1	this study
$\beta_S$	$q_r \times 8.690483 \times 10^{-1}$	this study
$\beta_A$	$q_r \times 7.738431 \times 10^{-1}$	this study
$\kappa$	0.19607843	*
$p$	0.1213	*
$\theta$	0.2,	this study
$\delta_L$	0.04	postulated
$\delta_H$	0.2	*
$\delta_V$	0.0027397260273972603	$\delta_V^{-1} = 2$ years CanSinoBIO
$\delta_R$	0.00555556	$\delta_R^{-1} \approx 180$ days
$\mu$	$3.913894 \times 10^{-5}$	**
$\mu_{I_S}$	0.0	
$\mu_H$	0.01632	[FENG]
$\gamma_S$	0.09250694	*
$\gamma_A$	0.16750419	*
$\gamma_H$	$5.079869 \times 10^{-1}$	*
$\lambda_V$	0.00061135	
$\varepsilon$	0.7, 0.80, 0.9, 0.95	[PRESS RELESASES]
$N$	26446435	**
$L_0$	0.26626009702112796	
$S_0$	0.463606046009872	
$E_0$	0.00067033	*
$I_{S_0}$	$9.283 \times 10^{-5}$	* * *
$I_{A_0}$	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  $\lambda_V$  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.<sup>SDIV</sup>

Define  $T_1 = \delta_L + \lambda_V + \mu$ ,  $T_2 = \mu + \lambda_V + \delta_V$ , then

$$R_{v0} := \frac{\mu(\delta_L + R_1 T_2) + \delta_V \delta_L + \lambda_V((1 - \epsilon) + \delta_V)}{T_1 T_2 (\delta_L + \mu R_1)} R_0$$

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



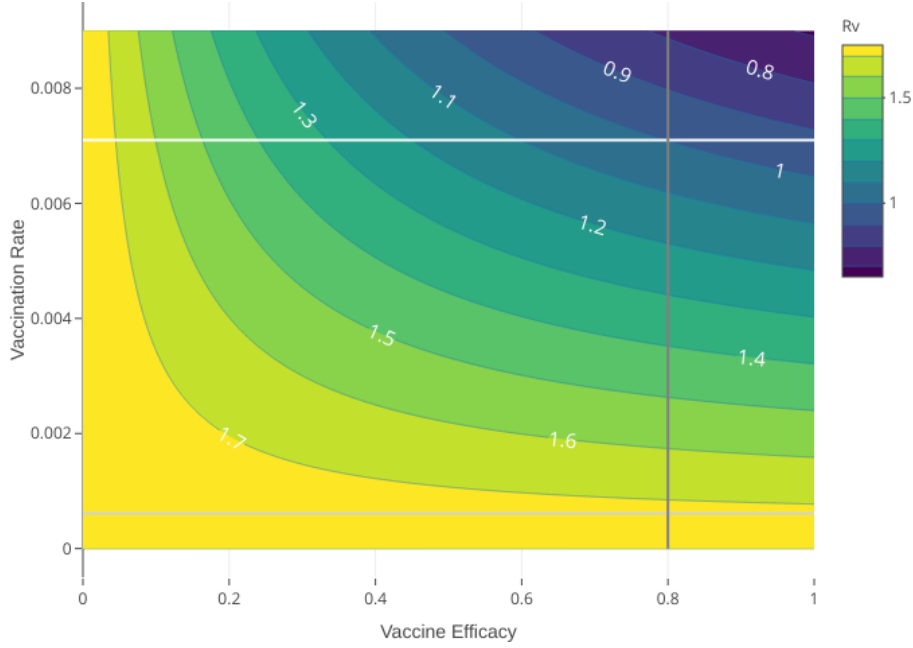


Figure 3: R not contour plot as function of efficacy and vaccination rate.

## 5. Optimal controlled version

*Controlled Model.* Now we 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

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

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

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

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  $X(T)$

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

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

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

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

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

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

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

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

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

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

## 117 6. Numerical Experiments

118

[SDIV 5]  
Aqui va tu  
descripcion  
Frank.

Initial condition

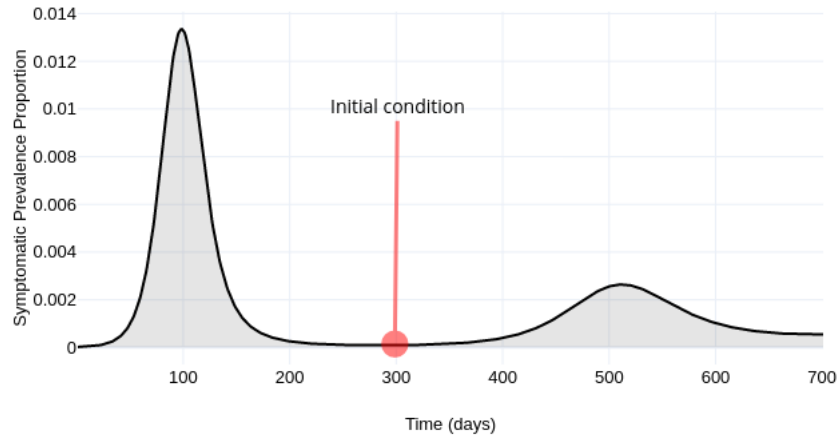


Figure 4: Initial condition scheme. We assume a positive prevalence. For reference, at the date of write this manuscript, prevalence in CDMX is around 16 000 cases, see <https://plotly.com/sauld/36/> to display a electronic viewer.

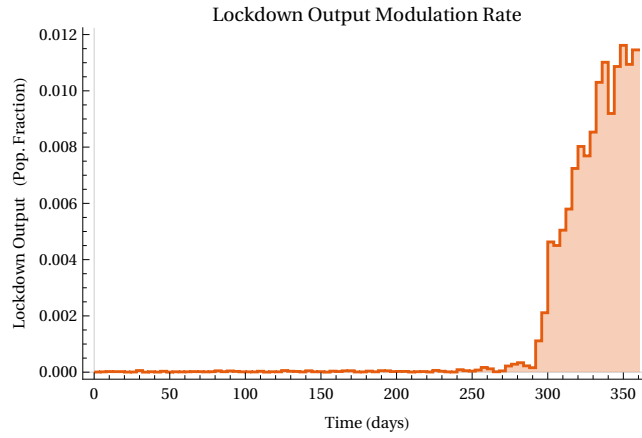


Figure 5: Lockdown modulation signal.

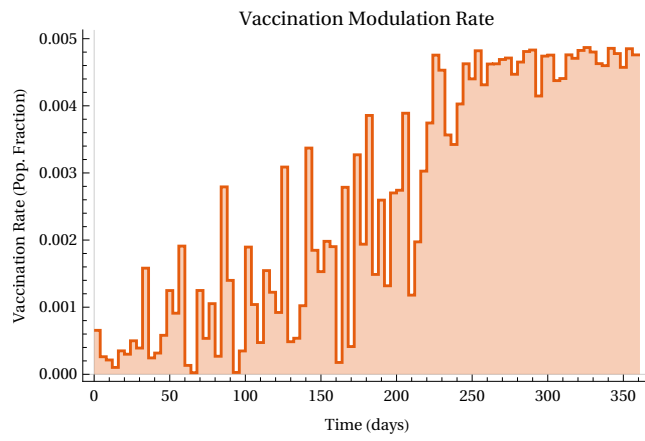


Figure 6: Vaccination rate modulation.

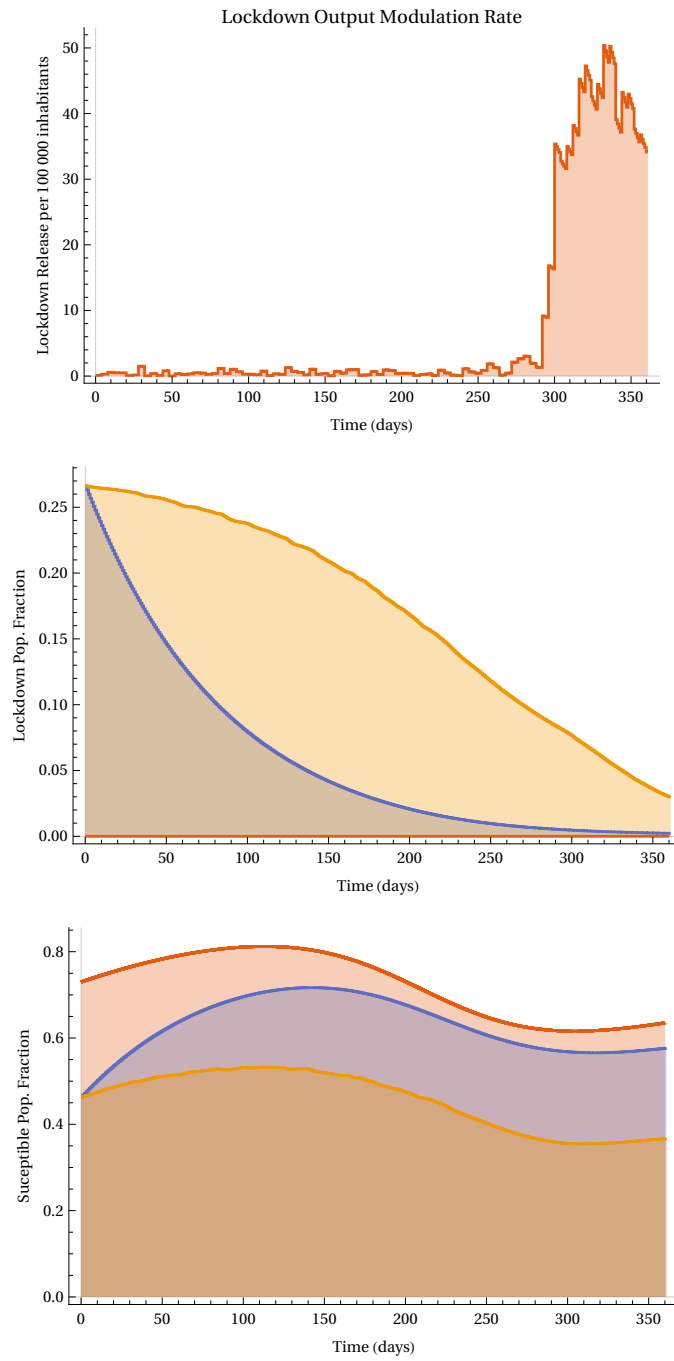


Figure 7: Modulation lock down release.

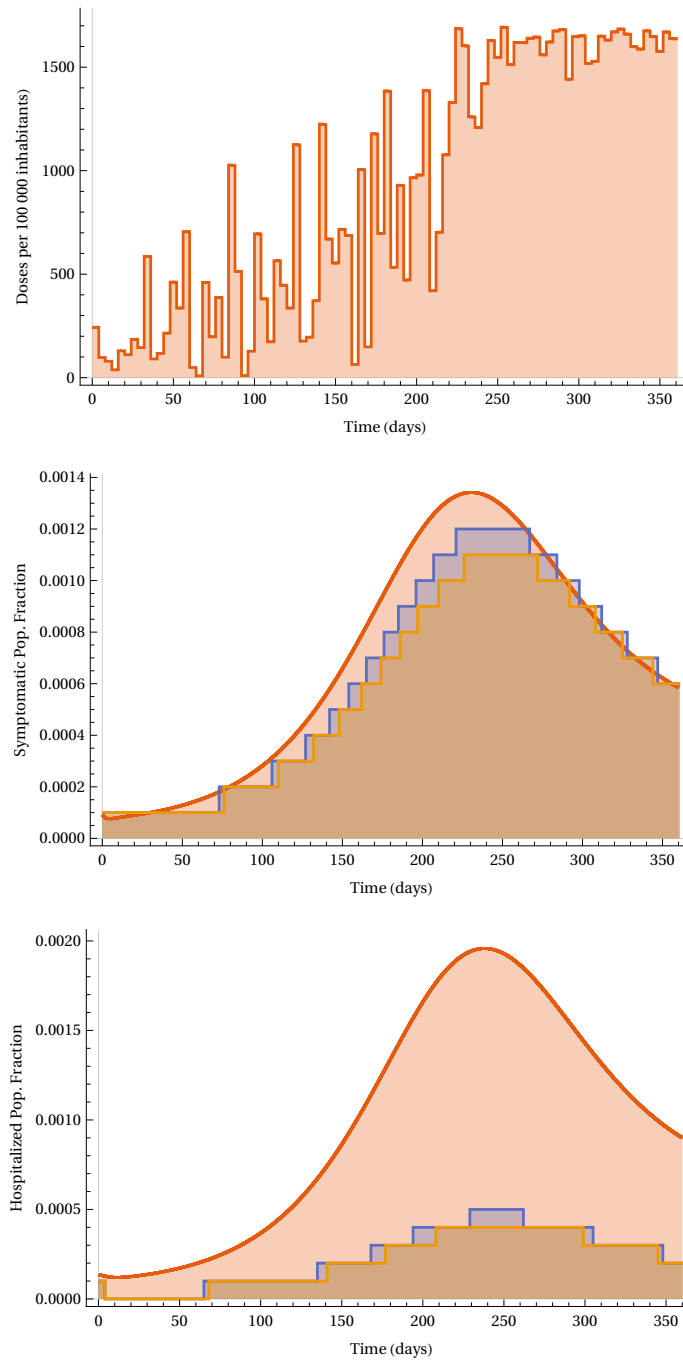


Figure 8: Symptomatic Prevalence and Hospitalization.

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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