Optimal constant picewise vaccination 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.
FINDINGS.
IMPLICATIONS.

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

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_{I_S} to fit commulative symptomatic

*Corresponding author
Email addresses: `adrian.acuna@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)

cases reported in the databases from Mexico city during the exponential grow phase. Our dynamics reads

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

See Table 1 for notation and references values.

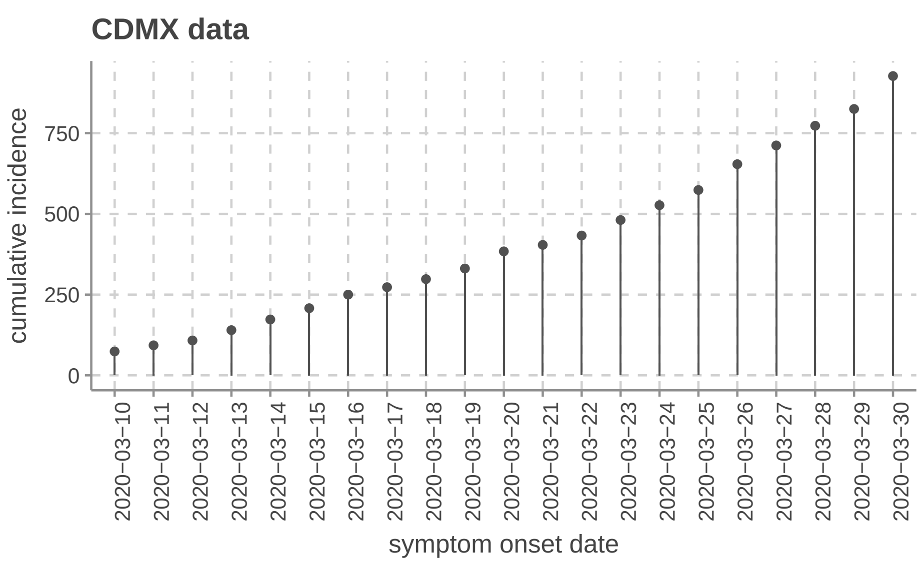

Figure 1: Cummulative new symptomatic and confirmed COVID19 reported cases from Ciudad de Mexico between March, 10, to March 30 of 2020.

Hypothesis. We consider that susceptible individuals become infected when they are in contact with asymptomatic individuals and individuals with symptoms,

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).

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 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 VanDenDrishe, we obtain

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

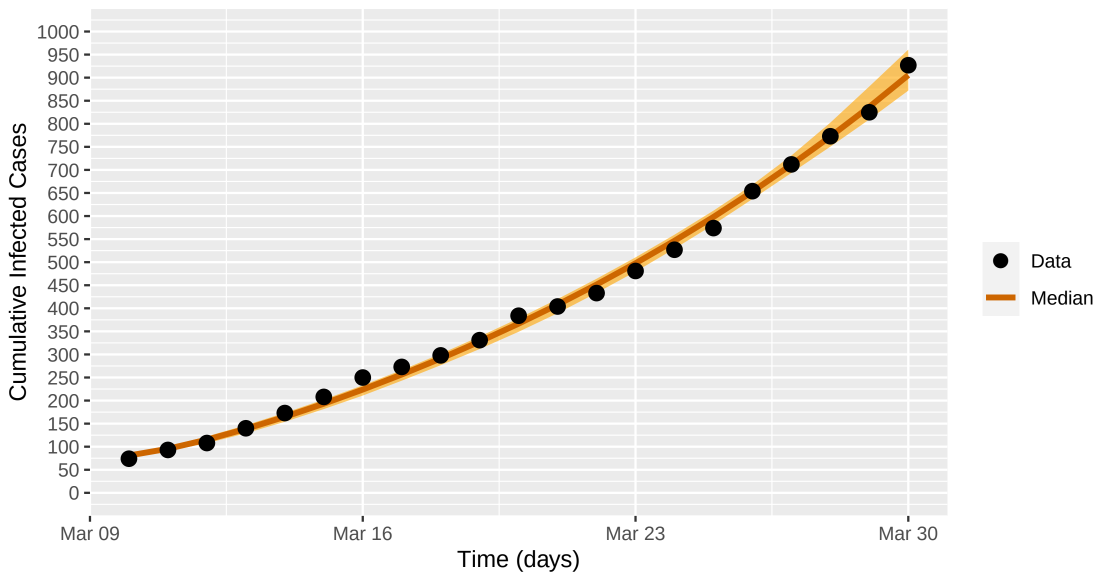

Figure 2: Fit of diary new cases of Mexico city during exponential growth.

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 λ_V estimate.

Feasibility regions according to efficacy and vaccination rate.

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

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

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

4. Parameter callibration

Bayesian estimation.

5. Vaccination reproductive number

R_0 *definition.*

No vaccine reproductive number.

Vaccine reproductive number.

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	$\delta_V^{-1} = 2\,\text{years}$ CanSinoBIO
δ_R	0.005 555 56	$\delta_R^{-1} \approx 180\,\text{days}$
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_{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	$9500\,\text{beds}/N$
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

Efficacy, coverage and vaccination rate.

Here Gabriel's R not calculations.[SDIV]

[SDIV 1] Here countor plots figure as function of efficacy and vaccination rate

$$-\frac{\kappa\,(\epsilon\,\mu\,p\theta\,\beta_A - \epsilon\,\mu\,p\theta\,\beta_s + \epsilon\,p\theta\,\beta_A\delta_H)}{\gamma_A\mu_{I_S}\gamma_A\mu_{I_S}} \tag{4}$$

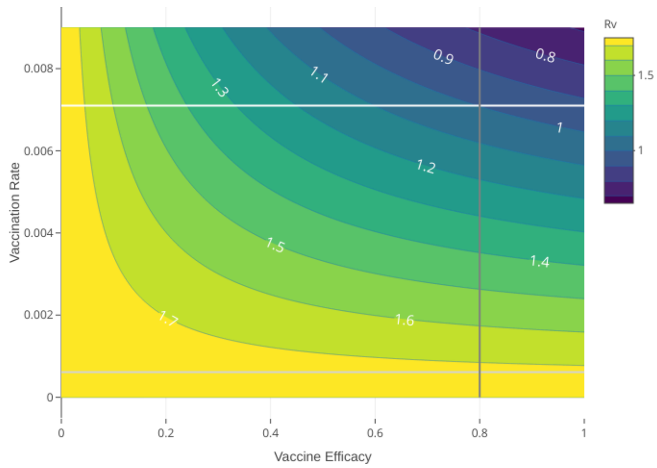

Figure 3: R not contour plot as function of efficacy and vaccination rate

6. 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

$$X'(t) = (\lambda_V + u_V(t))(S + E + I_A + R) \tag{5}$$

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

$$J(u_V) := \int_0^T a_S I_S + a_d D + \frac{1}{2} c_V u_v^2 ds. \tag{6}$$

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 $X(T)$

$$
\begin{aligned}
x(T) &= (\cdot, \cdot, \cdot, \cdot, \cdot, X_{vac}(T))^\top, \in \Omega \\
X_{vac}(T) &= x_{coverage}, \\
x_{coverage} &\in \{\mathrm{Low}(0.2), \mathrm{Mid}(0.5), \mathrm{High}(0.8)\}.
\end{aligned} \tag{7}
$$

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

$$
\Phi(x,t) := \kappa I_S(t) \leq B, \qquad \forall t \in [0,T], \tag{8}
$$

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

$$
x_{coverage} = 1 - \exp(-\lambda_V T). \tag{9}
$$

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 (6)—over an appropriated functional space—subject to the dynamics in equations (1) and (5), boundary conditions, and the path constrain in (8). That is, we search for vaccination policies

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

$$
\begin{aligned}
\min_{u\in\mathcal{U}} J(u) &:= \int_0^T \left[(a_D\mu_s + a_H\delta_H)\, I_S(r) + a_{I_S} p\kappa E(r)\right] dr \\
\text{s. t.}& \\
L' &= \theta\mu N^\star - \epsilon\lambda L - u_L(t)L - \mu L \\
S' &= (1-\theta)\mu N^\star + u_L(t)L + \delta_v V + \delta_R R \\
&\quad - \left[\lambda + (\lambda_V + u_V(t)) + \mu\right] S \\
E' &= \lambda(\epsilon L + (1-\varepsilon)V + S) - (\kappa+\mu)E \\
I_S' &= p\kappa E - (\gamma_S + \mu_{I_S} + \delta_H + \mu)I_S \\
I_A' &= (1-p)\kappa E - (\gamma_A + \mu)I_A \\
H' &= \delta_H I_S - (\gamma_H + \mu_H + \mu)H \\
R' &= \gamma_S I_S + \gamma_A I_A + \gamma_H H - (\delta_R + \mu)R \\
D' &= \mu_{I_S} I_S + \mu_H H \\
V' &= (\lambda_V + u_V(t))S - \left[(1-\varepsilon)\lambda + \delta_V + \mu\right] V
\end{aligned} \tag{10}
$$

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

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

7. Numerical Results

Changes (compact)

Author: anonymous

No changes.

Author: SDIV

Added 1
Deleted 2
Commented 1

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

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

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

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

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

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

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

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

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 $(a_0, \ldots, a_j)$ and x_0. Therefore, by Assumption 2, the mapping

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

is continuous.

References

[1] Yinon M Bar-on, Ron Sender, Avi I Flamholz, Rob Phillips, and Ron Milo. A quantitative compendium of COVID-19 epidemiology. pages 1–51.

[2] Bruno Buonomo. Effects of information-dependent vaccination behavior on coronavirus outbreak: insights from a SIRI model. *Ricerche di Matematica*, 2020.

[3] Anastasia Chatzilena, Edwin van Leeuwen, Oliver Ratmann, Marc Baguelin, and Nikolaos Demiris. Contemporary statistical inference for infectious disease models using Stan. *Epidemics*, 29(February):100367, 2019.

[4] Nicholas G Davies, Adam J Kucharski, Rosalind M Eggo, Amy Gimma, CMMID COVID-19 Working Group, and W. John Edmunds. The effect of non-pharmaceutical interventions on COVID-19 cases, deaths and demand for hospital services in the UK: a modelling study. *medRxiv*, page 2020.04.01.20049908, 2020.

[5] Laura Di Domenico, Giulia Pullano, Chiara E Sabbatini, Pierre-Yves Boëlle, and Vittoria Colizza. Currently under screening at medRxiv Expected impact of lockdown in Île-de-France and possible exit strategies. 2020.

[6] Wandi Ding and Suzanne Lenhart. Introduction to optimal control for discrete time models with an application to disease modeling. In *Modeling paradigms and analysis of disease transmission models*, volume 75, pages 109–119. Amer. Math. Soc., Providence, RI, oct 2010.

[7] Ramses Djidjou-Demasse, Yannis Michalakis, Marc Choisy, Micea T. Sofonea, and Samuel Alizon. Optimal COVID-19 epidemic control until vaccine deployment. *medRxiv*, page 2020.04.02.20049189, 2020.

[8] Neil M Ferguson, Daniel Laydon, Gemma Nedjati-gilani, Natsuko Imai, Kylie Ainslie, Marc Baguelin, Sangeeta Bhatia, Adhiratha Boonyasiri, Zulma Cucunubá, Gina Cuomo-dannenburg, Amy Dighe, Han Fu, Katy Gaythorpe, Will Green, Arran Hamlet, Wes Hinsley, Lucy C Okell, Sabine Van, Hayley Thompson, Robert Verity, Erik Volz, Haowei Wang, Yuanrong Wang, Patrick G T Walker, Caroline Walters, Peter Winskill, Charles Whittaker, Christl A Donnelly, Steven Riley, and Azra C Ghani. Impact of non-pharmaceutical interventions (NPIs) to reduce COVID- 19 mortality and healthcare demand. (March), 2020.

[9] M. H. A. Biswas, L. T. Paiva, and MdR de Pinho. A SEIR model for control of infectious diseases with constraints. *Mathematical Biosciences and Engineering*, 11(4):761–784, 2014.

[10] IHME COVID-19 health service utilization forecasting Team and Christopher JL Murray. Forecasting COVID-19 impact on hospital bed-days,

ICU-days, ventilator-days and deaths by US state in the next 4 months. *medRxiv*, page 2020.03.27.20043752, mar 2020.

[11] Gang Huang, Yasuhiro Takeuchi, Wanbiao Ma, and Daijun Wei. Global Stability for Delay SIR and SEIR Epidemic Models with Nonlinear Incidence Rate. *Bulletin of Mathematical Biology*, 72(5):1192–1207, 2010.

[12] Jiwei Jia, Jian Ding, Siyu Liu, Guidong Liao, Jingzhi Li, B. E.N. Duan, Guoqing Wang, and R. A.N. Zhang. Modeling the control of COVID-19: Impact of policy interventions and meteorological factors. *Electronic Journal of Differential Equations*, 2020:1–21, 2020.

[13] Abdelilah Kaddar, Abdelhadi Abta, and Hamad Talibi Alaoui. A comparison of delayed SIR and SEIR epidemic models. *Nonlinear Analysis: Modelling and Control*, 16(2):181–190, apr 2011.

[14] Qian Li, Biao Tang, Nicola Luigi Bragazzi, Yanni Xiao, and Jianhong Wu. Modeling the impact of mass influenza vaccination and public health interventions on COVID-19 epidemics with limited detection capability. *Mathematical Biosciences*, 325(May):108378, jul 2020.

[15] Gustavo Barbosa Libotte, Fran Sérgio Lobato, Gustavo Mendes Platt, and Antônio José da Silva Neto. Determination of an Optimal Control Strategy for Vaccine Administration in COVID-19 Pandemic Treatment. (November 2019), apr 2020.

[16] Manotosh Mandal, Soovoojeet Jana, Swapan Kumar Nandi, Anupam Khatua, Sayani Adak, and T.K. Kar. A model based study on the dynamics of COVID-19: Prediction and control. *Chaos, Solitons & Fractals*, 136:109889, jul 2020.

[17] Van Kinh Nguyen and Esteban A. Hernandez-Vargas. Parameter Estimation in Mathematical Models of Viral Infections Using R. volume 1836, pages 531–549. 2018.

[18] Jorge Nocedal, Andreas Wächter, and Richard A. Waltz. Adaptive Barrier Update Strategies for Nonlinear Interior Methods. *SIAM Journal on Optimization*, 19(4):1674–1693, jan 2009.

[19] Xinwei Wang, Haijun Peng, Boyang Shi, Dianheng Jiang, Sheng Zhang, and Biaosong Chen. Optimal vaccination strategy of a constrained time-varying SEIR epidemic model. *Communications in Nonlinear Science and Numerical Simulation*, 67:37–48, 2019.