Optimal vaccination preventive policies for COVID 19

Saúl Díaz-Infante [d,*], Adrian Acuña-Zegarra[b], David Baca[b], Daniel Olmos-Liceaga[b]

[a] *Departamento de Matemáticas, COMPLETE*
[b] *Departamento de Matemáticas, División de Posgrado. Universidad de Sonora, 83000, Hermosillo, Mexico.*
[c] *Departamento de Matemáticas, División de Posgrado. ITSON COMPLETE*
[d] *CONACYT-Universidad de Sonora, Rosales y Blvd. Encinas, S/N, 83000, Hermosillo, Mexico.*

Abstract

Abstract

Keywords: Multi-host, persistence, extinction, stochastic perturbation, vector transmission.

1. Introduction

In late December 2019, the appearance of a new virus is reported in Wuhan City, Hubei Province, China. Called SARS-CoV2, it is the virus that causes the 2019 coronavirus disease (COVID-19) and that, very quickly since its appearance, has spread throughout much of the world, causing serious problems for health systems of all the countries in which it is present. On March 11, 2020, the World Health Organization declared the epidemic by COVID-19 as a pandemic, with around 118, 000cases at that time, distributed in 114 countries and with around 4, 291 deaths [WHO-51]. In Latin America, the first detected case of COVID-19 occurred in Brazil on February 26, and in Mexico the first case was reported on February 27, quickly spreading throughout the country.

Various control measures have been implemented in all the countries where the disease is present, with quarantine, isolation, and social distancing being the main ones. Despite the measures that different governments have taken to mitigate the epidemic, it has not been controlled and the number of cases and deaths from the disease continues to increase in many countries of the world. On the other hand, since the appearance of the new coronavirus, the world scientific community has been working hard around this virus, seeking to understand its nature, the mechanisms that the disease follows for its spread as well as vaccines and treatments to control the disease. Once having the proper

*Corresponding author
Email addresses: saul.diazinfante@unison.mx (Adrian Acuña-Zegarra), davidbaca@correo.mx (David Baca), danie@correo (Daniel Olmos-Liceaga)

vaccine and treatment, a major challenge for the health sector is the way in which they should be applied.

To answer many of the doubts that have arisen around the disease, the modeling of the disease using mathematical tools has taken a leading role. In particular, the use of SEIR-type models have been used to study the dynamics of disease spread. Initially, these models have been used to estimate the basic reproductive number associated with the disease, as well as to estimate different parameters involved in its spread, such as contagion rates, incubation periods, and recovery rates. They are also being used to propose and evaluate the effect of various control measures, such as quarantine.

This work, an analysis of the dynamics of the disease when applying preventive vaccination and treatment for COVID-19 are presented. In the first instance, and in order to obtain the most realistic results possible, data provided by the Mexican Ministry of Health are used to estimate the parameters of the proposed model prior to the vaccination model. In this way, we have the possibility of analyzing the effect of the vaccine and treatment, maintaining a base of values for the model parameters, and thus being able to manipulate only the parameters corresponding to vaccination and treatment.

2. Preventive vaccination and treatment mathematical model

To build this model we split the population, initially, in five classes, susceptible (S), exposed (E), symptomatic infected (I_S), asymptomatic infected (I_A) and recovered individuals (R). We consider that a preventive vaccine is applied to the entire population except for symptomatic infected persons. Since the vaccine is preventive, its effect is reflected only in susceptible people, who, when vaccinated, enter the class represented by (V) of vaccinated. In the classes of exposed, infected, asymptomatic, and recovered, the vaccine has no effect.

We also consider that the vaccine is not 100% effective, so vaccinated individuals can be infected by contact with infectious people, but with a lower probability than susceptible individuals. For the population of infectious individuals, we consider the application of treatment and said treated individuals enter the (T) class of treated. We assume that the treatment is also not effective at 100%, so a proportion of treated individuals recovers, and the complement dies. Finally, we consider a class to account for deaths due to illness, represented by (D).

$$
\begin{aligned}
S'(t) &= \mu\bar{N} - \frac{\beta_S I_S + \beta_A I_A}{\bar{N}} S - (\mu + \lambda_V) S + \delta_V V + \delta_R R \\
E'(t) &= \frac{\beta_S I_S + \beta_A I_A}{\bar{N}} S + \epsilon \frac{\beta_S I_S + \beta_A I_A}{\bar{N}} V - (\mu + \delta_E) E \\
I_S'(t) &= p\delta_E E - (\mu + \mu_S + \alpha_S + \lambda_T) I_S \\
I_A'(t) &= (1-p)\delta_E E - (\mu + \alpha_A) I_A \\
R'(t) &= \alpha_S I_S + \alpha_A I_A + \alpha_T T - (\mu + \delta_R) R \\
D'(t) &= \mu_S I_S + \mu_T T \\
V'(t) &= \lambda_V S - \epsilon \frac{\beta_S I_S + \beta_A I_A}{\bar{N}} V - (\mu + \delta_V) V \\
T'(t) &= \lambda_T I_S - (\mu + \alpha_T + \mu_T) T \\
X'(t) &= \lambda_V (S + E + I_A + R)
\end{aligned}
\tag{1}
$$

Where $\bar{N}(t) = S(t) + E(t) + I_S(t) + I_A(t) + R(t) + V(t) + T(t)$ and $N = \bar{N} + D$. Description of the parameters of the system is given in table 3.

Parameter	Description
μ	Birth-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	Reciprocal of the average time the effect of the vaccine lasts
ϵ	Infection reduction factor due vaccine
δ_E	Reciprocal of the Incubation period
p	Proportion of exposed individuals moving to symptomatic infected class
μ_S	Disease-induced death rate for symptomatic infective individuals
α_S	Recovery rate of symptomatic infected
λ_T	Treatment rate
α_A	Recovery rate of asymptomatic infected
α_T	Recovery rate of treatment people
μ_T	Disease-induced death rate for hospitalized individuals

Table 1: Parameters system description

In the next section, an estimation of parameters of a model that contemplates the first two phases of the epidemic is made: evolution of the disease until before the quarantine implementation and the phase that contemplates the quarantine period.

3. Parameter setting

Parameter setting is done in two stages; in both stages, we started off the model (1), which is simplified by adapting it to the stage to be modeled. With the parameters obtained through the adjustment, the value of the basic reproductive number (R_0) will be obtained, defined as the average number of secondary infections generated by an infectious individual, during their entire period of infectivity, when in contact with a population of fully susceptible individuals.

For the second stage analyzed, corresponding to the quarantine period in Mexico and which includes from March 23 to May 31, 2020, we used the model (2) considering one more class, which corresponds to the population of people dying due to disease. Once normalized with respect to the population of living individuals, the model is given by:

$$\begin{aligned} S'(t) &= \mu\bar{N} - \frac{\beta_S I_S + \beta_A I_A}{\bar{N}} S - \mu S + \delta_R R \\ E'(t) &= \frac{\beta_S I_S + \beta_A I_A}{\bar{N}} S - (\mu + \delta_E) E \\ I'_S(t) &= p\delta_E E - (\mu + \alpha_S) I_S \\ I'_A(t) &= (1-p)\delta_E E - (\mu + \alpha_A) I_A \\ R'(t) &= \theta\alpha_S I_S + \alpha_A I_A - (\mu + \delta_R) R \\ D'(t) &= (1-\theta)\alpha_S I_S \end{aligned} \tag{2}$$

where $\bar{\epsilon}$ represents the reduction factor in infection rates due to the quarantine effect.

For the model, the parameters $\mu = 0.653 \times 10^{-6}$ and $\delta_E = 0.196078431$ were set, which correspond to the reciprocals of the half-life, which is 75 years, and the estimated incubation period in 5.1 days [26]. Now, using the next generation matrix method, the basic reproductive number for model (2) is given by:

$$R_{01} = \frac{p\delta_E\beta_S}{(\mu + \alpha_S)(\mu + \delta_E)} + \frac{(1-p)\delta_E\beta_A}{(\mu + \alpha_A)(\mu + \delta_E)}, \tag{3}$$

Using the MCMC method to estimate parameters, we have the following values and their confidence intervals for each estimated parameter.

Parameter	Value
β_S	9.595×10^{-1} $(7.078 \times 10^{-1}, 1.208)$
β_A	9.772×10^{-1} $(7.0833 \times 10^{-1}, 1.180)$
$\bar{\epsilon}$	5.765×10^{-1} $(3.939 \times 10^{-1}, 8.160 \times 10^{-1})$
p	6.040×10^{-2} $(5.031 \times 10^{-2}, 1.048 \times 10^{-1})$
μ_S	1.930×10^{-1} $(9.464 \times 10^{-2}, 3.416 \times 10^{-1})$
α_S	1.017×10^{-1} $(5.685 \times 10^{-2}, 1.797 \times 10^{-1})$
α_A	1.928×10^{-1} $(1.143 \times 10^{-1}, 3.04 \times 10^{-1})$
R_0	5.385 $(4.062, 7.782)$

Table 2: Parameters system description

Parameter	Description
ω	Isolation abandonment rate
$\frac{1}{\gamma}$	Incubation period
$\frac{1}{\eta}$	Recovery rate
β	Probability of contagion
k	Number of contacts between an asymptomatic infected and susceptible individuals
ϵ	Infectiousness reduction factor in exposed individuals
u	Reduction factor in infection force due to the isolation program
μ	Natural death rate
q	Isolation rate

Table 3: Parameter desciption

4. Vaccination and treatment Model Analysis

In this section, we use the parameters estimated in the previous section to analyze Model (1) and the effect of the vaccine and treatment. Some plausible scenarios are presented, depending on the effectiveness of the vaccine and treatment, as well as the rate of vaccination and treatment.

Let

$$\Omega = \{(S, E, I_S, I_A, R, D, V, T) \in \mathbb{R}^8_+ : S + E + I_S + I_A + R + D + V + T = N\}.$$

First, note that for this model we have a closed population, which allows the solutions to be bounded superiorly by the total population. On the other hand, to show the positivity of the solutions with initial conditions $(S(0), E(0), I_S(0), I_A(0), R(0), D(0), V(0), T(0)) \in \mathbb{R}^8_+$, we look at the direction of the vector field on the hypercube faces in the

direction of each variable in the system. For example, consider a point on the hypercube face where the variable $S = 0$ and look at the behavior of the vector field in the direction of the same variable S, to see if the solutions cross the face of the hypercube where we are taking the initial condition. So, notice that if $S = 0$, $S'(t) > 0$, so the solution points into the hypercube. Similarly, consider an initial condition of the form $(S, 0, I_S, I_A, R, D, V, T)$ and note that $E'(t) > 0$ for all $t > 0$, which implies that the solutions of the system with initial conditions of the form $(S, 0, I_S, I_A, R, D, V, T)$ point towards the interior of the hypercube. Similarly, positivity can be tested for the rest of the variables. With this information, we have the following result.

Lemma 1. *The set* $\Omega = \{(S, E, I_S, I_A, R, D, V, T) \in \mathbb{R}^8_+ : S + E + I_S + I_A + R + D + V + T = N\}$ *is a positively invariant set for the system (1).*

Continuing with the analysis of our model, the disease-free equilibrium is $X_0 = (\frac{(\mu+\delta_V)\bar{N}}{\mu+\delta_V+\lambda_V}, 0, 0, 0, 0, \frac{\lambda\bar{N}}{\mu+\delta_V+\lambda_V}, 0)$. Now, using the next-generation matrix method to calculate it [3, 4] we have that the next generation matrix for this model is given by

$$\mathbf{K} = \begin{bmatrix} \frac{\delta_E}{(\mu+\delta_E)}\left(\frac{p\beta_S}{\mu+\alpha_S+\mu_S+\lambda_T}\right)(S^* + \epsilon V^*) & \frac{\beta_S(S^*+\epsilon V^*)}{(\mu+\alpha_S+\mu_S+\lambda_T)\bar{N}} & \frac{\beta_A(S^*+\epsilon V^*)}{(\mu+\alpha_A+\mu_A)\bar{N}} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \tag{4}$$

where $S^* = \frac{(\mu+\delta_V)\bar{N}}{\mu+\delta_V+\lambda_V}$ and $V^* = \frac{\lambda\bar{N}}{\mu+\delta_V+\lambda_V}$. So, the basic reproduction number for this model is

$$R_0 = R_S + R_A \tag{5}$$

with

$$R_S = \frac{p\beta_S\delta_E(\mu + \delta_V + \epsilon\lambda_V)}{(\mu + \delta_E)(\mu + \delta_V + \lambda_V)(\mu + \alpha_S + \mu_S + \lambda_T)},$$
$$R_A = \frac{(1-p)\beta_A\delta_E(\mu + \delta_V + \epsilon\lambda_V)}{(\mu + \delta_E)(\mu + \delta_V + \lambda_V)(\mu + \alpha_A + \mu_A)}.$$

Note that each sum of R_0 represents the contribution of the symptomatic and asymptomatic infected, respectively, to the spread of the disease.

5. Optimal Vaccine policies

According to dynamics in equation (1), we modulate the vaccination rate by a time-dependent control signal $u_V(t)$. Thus, Thus, given the solution of ODE (1) $x(t) := (S, E, I_S, I_A, R, D, V, X)^\top(t)$ and control signal $u_v(\cdot)$, we quantify the cost and reward of a vaccine strategy policy via the penalization function

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

We assume in functional J that pandemic cost is proportional to the symptomatic and deaths 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 $X(\cdot)$

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

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.

Thus our bjective is minimize the cost functional (6)—over appropiated functional space—subjecto to the dynamics in equation (1), boundary conditions, and the path constrain in (8). I other word, we search for vacination policies $u_V(\cdot)$, which solve the following optimal control problem (OCP)

$$\min_{u \in \mathcal{U}} J(u) = \int_0^T a_S I_S(s) + a_d D(s) + \frac{1}{2} c_V u_v^2(s) ds,$$

s.t.

$$\begin{aligned} S'(t) &= \mu \bar{N} - \frac{\beta_S I_S + \beta_A I_A}{\bar{N}} S - (\mu + \lambda_V + u_V(t)) S + \delta_V V + \delta_R R \\ E'(t) &= \frac{\beta_S I_S + \beta_A I_A}{\bar{N}} (S + (1-\epsilon)V) - (\mu + \delta_E) E \\ I_S'(t) &= p \delta_E E - (\mu + \alpha_S) I_S \\ I_A'(t) &= (1-p)\delta_E E - (\mu + \alpha_A) I_A \\ R'(t) &= \theta \alpha_S I_S + \alpha_A I_A - (\mu + \delta_R) R \\ D'(t) &= (1-\theta)\alpha_S I_S \\ V'(t) &= (\lambda_V + u_V(t)) S - (1-\epsilon) \frac{\beta_S I_S + \beta_A I_A}{\bar{N}} V - (\mu + \delta_V) V \\ X'(t) &= \lambda_V (S + E + I_A + R) \end{aligned} \tag{9}$$

$$\begin{aligned} S(0) &= S_0, \ E(0) = E_0, \ I_S(0) = I_{S_0}, \\ I_A(0) &= I_{A_0}, \ R(0) = R_0, \ D(0) = D_0, \\ V(0) &= 0, X(0) = 0, \quad u_V(\cdot) \in [u_\bullet, u^\bullet] \\ X(T) &= x_{coverage}, \quad \kappa I_S(t) \leq B, \qquad \forall t \in [0,T], \\ \bar{N}(t) &= S + E + I_S + I_A + R + V. \end{aligned}$$

6. Numerial experiments

Scenarios. Accordoing with SAGE's documnet [, SAGE] we expolore the following contrafactual scenarios.

Vaccine profile

Vacination policies according to different profiles,namenly:

- efficiency $\epsilon = \{0.1, 0.2, \cdots 0.9\}$.
- vaccine induced immunuity

$$\delta_v^{-1} = \{0.5\,\text{year}, 1.0\,\text{year}, \cdots, \text{lifelong}\}$$

Coverage

We obtained optimal vaccination policies with coverage profiles at

$$x_{covereges} = \{20\%, 50\%, 80\%\}$$

Time horizont

Plausible scenarios at different analytic time horizont

$$T = \{1\,\text{year}, 2\,\text{year}, 10\,\text{year}\}$$

7. Vaccination rate at $T = 2\,\text{years}$, and coverate 0.7

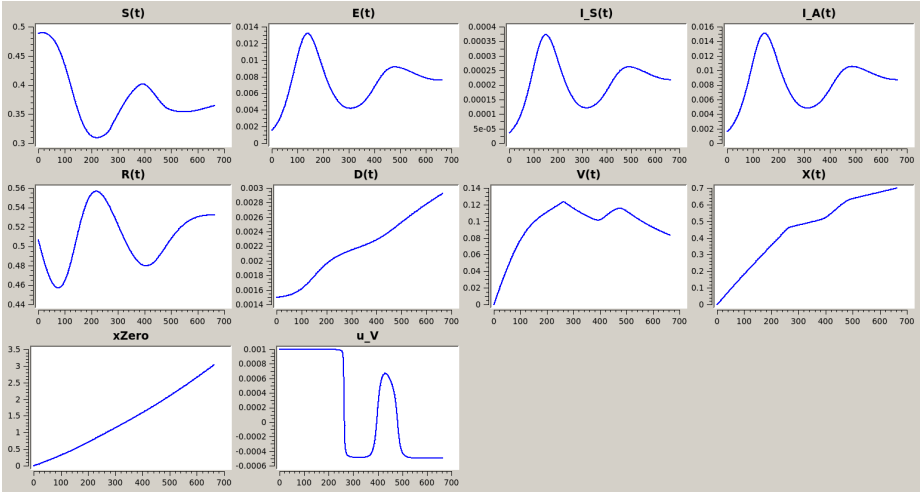

Figure 1: Hight contact rate β.

8. Vaccine immunity

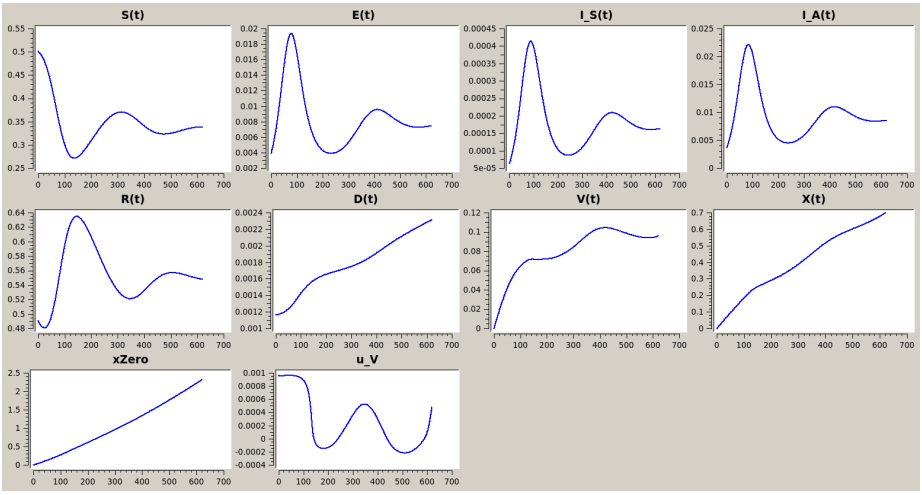

Figure 2: Mid contact rate β.

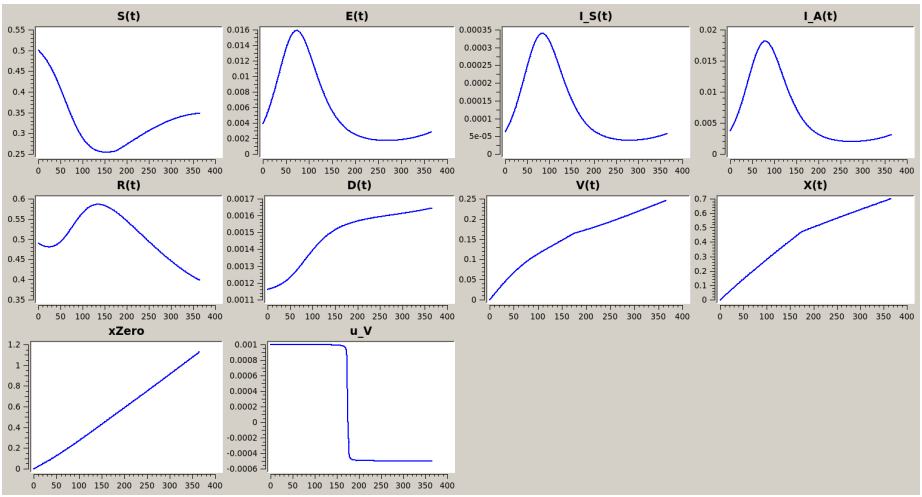

Figure 3: Lifelong immunity.

References

[1] JBacker Jantien A , Klinkenberg Don , Wallinga Jacco . Incubation period of 2019 novel coronavirus (2019-nCoV) infections among travellers from Wuhan, China, 2028 January 2020. Euro Surveill. 2020;25(5):pii=2000062. https://doi.org/10.2807/1560-7917.ES.2020.25.5.2000062.

[2] Biao Tang, Xia Wang, Qian Li, Nicola Luigi Bragazzi, Sanyi Tang, Yanni Xiao, Jianhong Wu Estimation of the transmission risk of 2019-nCov and its implication for public health interventions. Preprint

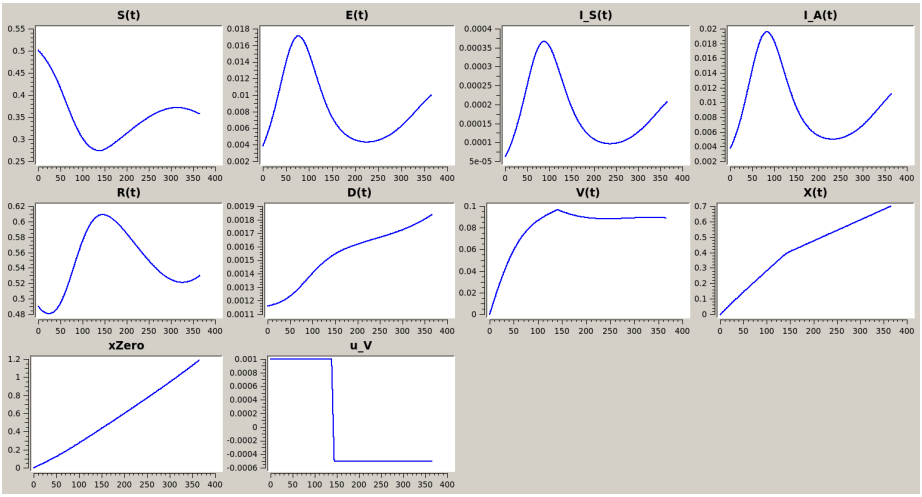

Figure 4: Six months of immunity.

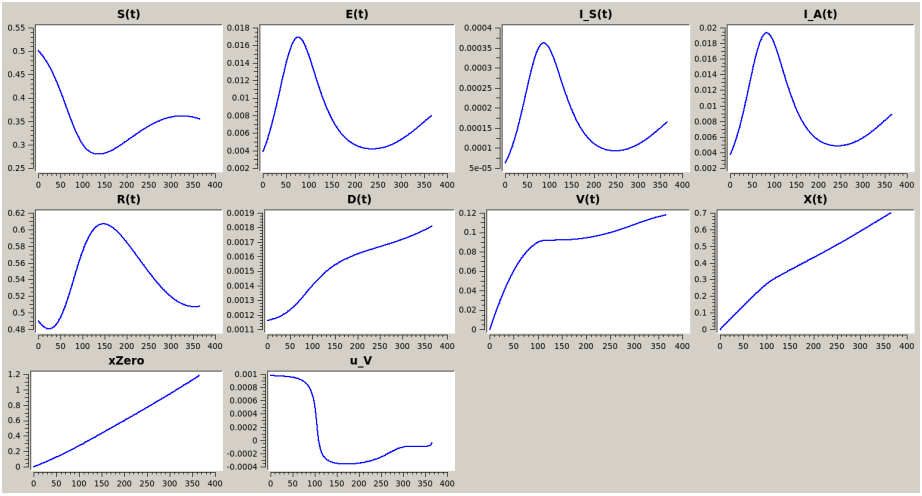

Figure 5: Eight months of immunity.

[3] Diekmann, O., Heesterbeek, J. A. P., & Metz, J. A. (1990). On the definition and the computation of the basic reproduction ratio R 0 in models for infectious diseases in heterogeneous populations. Journal of mathematical biology, 28(4), 365-382.

[4] Van den Driessche, P., & Watmough, J. (2002). Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. Mathematical biosciences, 180(1-2), 29-48.

[5] HERMANOWICZ, Slav W. Forecasting the Wuhan coronavirus (2019-

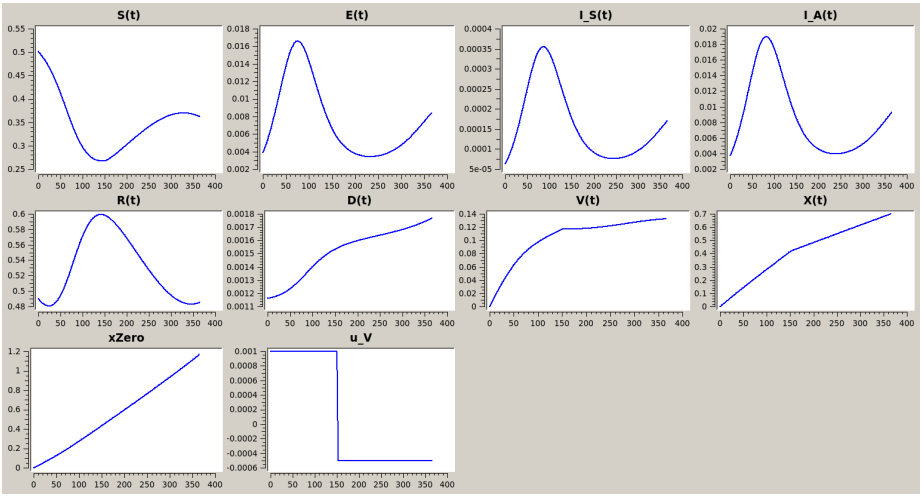

Figure 6: 11 months of immunity.

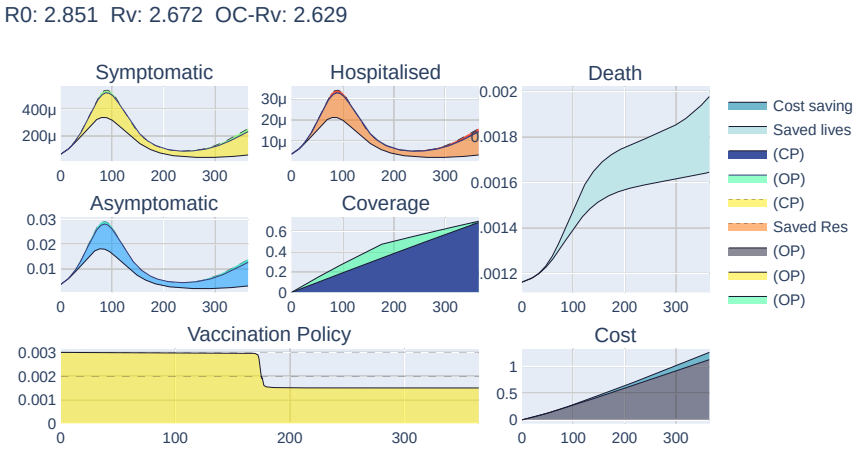

Figure 7: 11 months of immunity.

nCoV) epidemics using a simple (simplistic) model. medRxiv, 2020.

[6] Zhao, S., Ran, J., Musa, S. S., Yang, G., Lou, Y., Gao, D., & He, D. (2020). Preliminary estimation of the basic reproduction number of novel coronavirus (2019-nCoV) in China, from 2019 to 2020: a data-driven analysis in the early phase of the outbreak. bioRxiv 2020; published online Jan 24. DOI, 10(2020.01), 23-916395.

[7] Chen, Y., Cheng, J., Jiang, Y., & Liu, K. (2020). A time delay dynamical model for outbreak of 2019-nCoV and the parameter identification. arXiv preprint arXiv:2002.00418.

[8] Riou, J., & Althaus, C. L. (2020). Pattern of early human-to-human transmission of Wuhan 2019 novel coronavirus (2019-nCoV), December 2019 to January 2020. Eurosurveillance, 25(4).

[9] Wang, F. S., & Zhang, C. (2020). What to do next to control the 2019-nCoV epidemic?. The Lancet, 395(10222), 391-393.

[10] Quilty, B. J., & Clifford, S. (2020). Effectiveness of airport screening at detecting travellers infected with novel coronavirus (2019-nCoV). Eurosurveillance, 25(5).

[11] Imai, N., Cori, A., Dorigatti, I., Baguelin, M., Donnelly, C. A., Riley, S., & Ferguson, N. M. (2020). Report 3: transmissibility of 2019-nCov. Reference Source.

[12] Funk, S., & Eggo, R. M. Early dynamics of transmission and control of 2019-nCoV: a mathematical modelling study.

[13] Wu, J. T., Leung, K., & Leung, G. M. (2020). Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study. The Lancet, 395(10225), 689-697.

[14] Boldog, P., Tekeli, T., Vizi, Z., Dones, A., Bartha, F. A., & Rost, G. (2020). Risk assessment of novel coronavirus COVID-19 outbreaks outside China. Journal of Clinical Medicine, 9(2), 571.

[15] Read, J. M., Bridgen, J. R., Cummings, D. A., Ho, A., & Jewell, C. P. (2020). Novel coronavirus 2019-nCoV: early estimation of epidemiological parameters and epidemic predictions. medRxiv.

[16] Ghosh, U., Kamrujjaman, M., & Ghosh, J. K. (2020). Dynamics of SEAIQR Model with Saturated Type Treatment: A Case Study of Spain COVID-19.

[17] Shaikh, A. S., Shaikh, I. N., & Nisar, K. S. (2020). A Mathematical model of COVID-19 using fractional derivative: Outbreak in India with dynamics of transmission and control.

[18] Liu, M., Ning, J., Du, Y., Cao, J., Zhang, D., Wang, J., & Chen, M. (2020). Modelling the evolution trajectory of COVID-19 in Wuhan, China: Experience and suggestions. Public Health.

[19] Acuna-Zegarra, M. A., Comas-Garcia, A., Hernandez-Vargas, E., Santana-Cibrian, M., & Velasco-Hernandez, J. X. (2020). The SARS-CoV-2 epidemic outbreak: a review of plausible scenarios of containment and mitigation for Mexico. medRxiv.

[20] Acuna-Zegarra, M. A., Santana-Cibrian, M., & Velasco-Hernandez, J. X. (2020). Modeling behavioral change and COVID-19 containment in Mexico: A trade-off between lockdown and compliance. Mathematical Biosciences, 108370.
Rst, G. (2020). Risk assessment of novel coronavirus COVID-19 outbreaks outside China. Journal of Clinical Medicine, 9(2), 571.

[21] Read, J. M., Bridgen, J. R., Cummings, D. A., Ho, A., & Jewell, C. P. (2020). Novel coronavirus 2019-nCoV: early estimation of epidemiological parameters and epidemic predictions. medRxiv.

[22] Ghosh, U., Kamrujjaman, M., & Ghosh, J. K. (2020). Dynamics of SEAIQR Model with Saturated Type Treatment: A Case Study of Spain COVID-19.

[23] Shaikh, A. S., Shaikh, I. N., & Nisar, K. S. (2020). A Mathematical model of COVID-19 using fractional derivative: Outbreak in India with dynamics of transmission and control.

[24] Liu, M., Ning, J., Du, Y., Cao, J., Zhang, D., Wang, J., & Chen, M. (2020). Modelling the evolution trajectory of COVID-19 in Wuhan, China: Experience and suggestions. Public Health.

[25] Acuna-Zegarra, M. A., Comas-Garcia, A., Hernandez-Vargas, E., Santana-Cibrian, M., & Velasco-Hernandez, J. X. (2020). The SARS-CoV-2 epidemic outbreak: a review of plausible scenarios of containment and mitigation for Mexico. medRxiv.

[26] Acua-Zegarra, M. A., Santana-Cibrian, M., & Velasco-Hernandez, J. X. (2020). Modeling behavioral change and COVID-19 containment in Mexico: A trade-off between lockdown and compliance. Mathematical Biosciences, 108370.