Optimal vaccination preventive policies for COVID-19

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Abstract

BACKGROUND At the date, Europe and North America experiments the second wave of COVID-19 causing more than 1 200 000 deaths worldwide. Humanity lacks of successful treatment and the only plausible solution is an effective vaccine. Currently,four are in final phase three trials. If third stage trial results favorable, Pharmaceutics firms estimate big scale production of its vaccine candidates around first 2021 quarter. However, determine the vaccine efficacy, induced immunity response among other essential parameters still are under study and subject to uncertainty. In fact, is possible that first vaccines will not be fully protective. Instead they may reduce the severity of illness, reducing hospitalization and death cases. Further, logistic supply, economical and political implications impose a set of great challenges to develop vaccination policies. PROBEM SETUP For this reason, health decision makers requires tools to evaluate hypothetical scenarios. FINDINGS Our contribution partially answers important modeling questions regarding to WHO Strategic Advisory Group of Experts (SAGE) on Immunization Working Group on COVID-19 Vaccines.

Our results suggest that optimal control theory could be an option tool to develop vaccination policies that satisfies important constrains as coverage horizon time supply restriction. We also report here simulation of vaccination polices with vaccine parameters reported by the most promising alternatives.

COVID-19, which includes vaccination dynamics. We apply optimal control theory to propose optimal vaccine strategies that minimize DALYs. Additionally, we analyze the vaccination reproductive number around the basic reproductive number and the vaccination profile (coverage, efficacy, horizon time, and vaccination rate). Due to the uncertainty about the profile vaccine, our results explore some scenarios regarding efficacy, coverage, induced immunity by vaccination, and natural immunity. Here, we observe that: i) there are strategies that reduce DALYs and cumulative deaths at the horizon time compare to its counterpart with constant vaccination; ii) it is necessary information about vaccine efficacy to design optimal strategies, and iii) ...

Keywords: Optimal Control, COVAX Vaccination, COVID-19.

1. Introduction

In late December 2019, a new virus's appearance is reported in Wuhan City, Hubei Province, China. Called SARS-CoV2, it is the virus that causes the 2019 corona virus disease (COVID-19) and that, very quickly since its appearance, has spread throughout much of the world, causing severe problems to health systems of all the countries in which it is present [1]. On March 11, 2020, the World Health Organization declared the epidemic by COVID-19 as a pandemic when there were around 118,000 cases distributed in

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114 countries, and approximately 4,291 deaths [2]. 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 [3, 4].

Due to the absence of successful treatment and vaccines, several non-pharmaceutical interventions (NPIs) have been implemented in all the countries where the disease is present, with quarantine, isolation, and social distancing being the main ones [5–7]. Despite the measures that different governments have taken to mitigate the epidemic, it has not been controlled in most places, which may be due to the relaxation of mitigation measures. At the date of writing this work, the upturn or regrowth in the number of cases in some countries around the world has been observed. In some places, this behavior is referred to as "second wave". On the other hand, since the new coronavirus appearance, the international scientific community has been working to understand the virus nature. They mainly focus on the spreading mechanisms between individuals, and developing vaccines and treatments to reduce the number of infections and fatality cases. To get a clearer understanding of different vaccination strategies and their consequences on the number of infected individuals, mathematical models have taken a leading role.

The use of various mathematical tools such as SIR and SEIR models has helped to describe epidemics properties around the globe. These models have been used to estimate the basic reproductive number associated with the disease and also different parameters involved in its spread [8–11]. Another use of this kind of model has been addressed to propose and evaluate the effect of various control measures classified as NPIs [4, 9, 12–14].

Currently, vaccine development for COVID-19 is at an advanced stage. It is believed that their distribution will begin in early 2021. However, we consider that, in addition to the vaccine's existence, it is necessary to have a good vaccination strategy. A widely used tool to address this question is the optimal control theory. This mathematical tool is useful to propose scenarios in which the vaccine's application minimizes the damage caused by the disease and its application cost. Some results about it have been applied to control other diseases for humans and animals [15–19]. Optimal control theory has also been used in COVID-19 studies. Most efforts have been invested in finding optimal strategies to evaluate the impact of non-pharmaceutical interventions [20–22]. Optimal control strategies have also being considered in vaccination [23]. In this work, the authors took their optimization based on a basic compartmental model for COVID-19. In their model, deaths due to disease are not considered and vaccination is applied only to susceptible individuals.

In this work, we present a mathematical model to describe the transmission and some vaccination dynamics of COVID-19. Mainly, we focus on using optimal control theory to obtain vaccination strategies in a homogeneous population. Our main objective is to minimize the disability-adjusted life year (DALY) [24]. This quantity is used by the World Health Organization (WHO) to quantify the burden of disease from mortality and morbidity, which is given by the sum of the years of life lost (YLL) and years lost due to disability (YLD). This work's objective is framed within the context of the WHO strategic advisory group of experts (SAGE) on immunization working group on COVID-19 vaccines [25].

Development of COVID-19 vaccines is a major challenge these days. Some research efforts in this direction can be found in [26, 27]. In Mexico, some of the considered vaccines to be applied to the population are Adenovirus Type 5 Vector (Ad5-nCoV) by Cansino Biologics, AZD1222 by AstraZeneca and BNT162b2 by Pfizer and BioNTech. At the current date, these and other vaccines are on the testing phase (phase 3) and there are still some questions about the efficacy of the vaccines. In the United States, an appropriate vaccine to be applied needs to show firm evidence that it protects at least half of those inoculated [28]. At this stage, there are no conclusive results about the efficacy of the vaccines. Also, current work is the immunity time the vaccines will provide to people.

Our work is divided into the following sections. In Section 2, we present our mathematical model, which includes preventive vaccine dynamics. Section 3 includes an analysis of the vaccination reproductive number. Section 4 presents our numerical results regarding optimal vaccination policies. It is important to stress that, with the objective of study COVID-19 dynamics in a specific city and have a set of baseline parameters values, we used the Mexico City plus Mexico state COVID-19 data to estimate some proposed model parameters. We end this work with a conclusions and discussions section.

NO SE VE LA DIFERENCIA RESPECTO A NUESTRO TRABAJO EL QUE NO CONSIDEREN MUERTE NO LO HACE TAN DIFERENTE. RECUERDO QUE SAÚL MENCIONÓ ALGO SOBRE QUE LA FORMA DE HACER CONTROL ES DISTINTA. O DE PLANO NO HAY JAJA....Ohh pues...dejame ser estoy en eso!

2. Mathematical model formulation

In this section, we formulate our baseline mathematical model, which additionally to the transmission dynamics, includes vaccination. In order to build our model, we follow the classical Kermack-McKendrick approach. Figure 1 shows the compartmental diagram of our mathematical model.

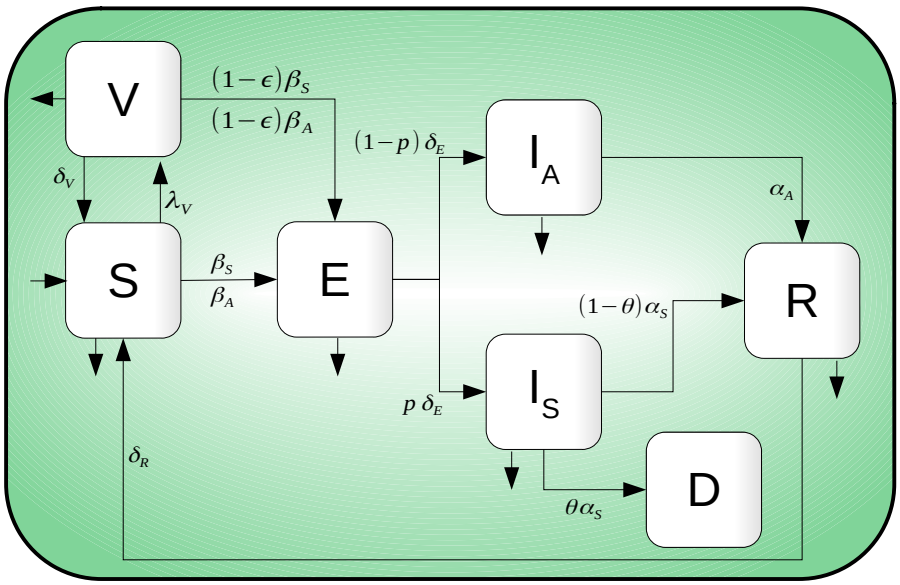

Figure 1: Compartmental diagram of COVID-19 transmission dynamics which including vaccination dynamics. Here, there are seven different classes: Susceptible (S), exposed (E), symptomatic infected (I_S), asymptomatic infected (I_A), recovered (R), death (D) and vaccinated (V) individuals. It is important to mention that I_S represents the proportion of symptomatic individuals who will later report to some health medical center.

Information about reinfection dynamics on COVID-19 disease remains unclear to date. However, to evaluate scenarios related to this dynamic, we assume that reinfection is possible, leading a natural immunity period. We made the following vaccination modeling hypothesis:

(H-1) A vaccine is applied to all alive individuals excepting those with symptoms. Thus, vaccine doses are applied indiscriminately over individuals on the S, E, I_A, and R classes;

(H-2) the regarding vaccine is preventive, that is, only reflects a favorable response in susceptible individuals (S);

(H-3) people will only get one vaccine dose during the campaign;

(H-4) the underlying vaccine is imperfect at level $(1-\epsilon) \in (0.5, 9)$, where ϵ denotes vaccine efficacy. Thus the fraction $(1-\epsilon)$ of vaccinated individuals will not develop artificial immunity and remains susceptible.

Under above hypothesis, our vaccination models is governed by the following system pf ordinary differential equations.

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

where $\bar{N}(t) = S(t) + E(t) + I_S(t) + I_A(t) + R(t) + V(t)$ and $N = \bar{N} + D$. We also include the counter equations

$$\begin{aligned} X'(t) &= \lambda_V(S + E + I_A + R) \\ Y'_{I_S}(t) &= p\delta_E E, \end{aligned} \tag{2}$$

where $X(t)$ counts the accumulated applied vaccine doses at time t, and $Y_{I_S}(t)$ count incidence. Likewise, incidence per day of infected symptomatic individuals at the kth day can be estimated by

$$I_{SA}(k) = Y_{I_S}(k) - Y_{I_S}(k-1) = \int_{k-1}^{k} p\delta_E E dt.$$

We describe the parameters of system (1) in Table 1.

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}	Immunity average time by vaccination
ϵ	vaccine Efficacy
δ_E^{-1}	Average time of the incubation period
p	Proportion of symptomatic individuals
α_S^{-1}	Average output time of symptomatic individuals due to death or recovery
θ	Proportion of symptomatic individuals who die due to the disease
α_A^{-1}	Recovery average time of asymptomatic individuals
δ_R^{-1}	Immunity average time by disease

Table 1: Parameters definition of System (1).

3. Model Analysis

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

In the first instance, it has been shown that the interest region of the state variables of the system is positively invariant and the proof can be found in Appendix B.

Now, an important concept in the analysis of the spread of diseases is the basic reproductive number, defined as the number of secondary infections produced by a typical infected individual, throughout his infectious period, when in contact with a totally susceptible population. For your calculation, and following the works in[29, 30], the basic reproduction number for system (1) is (see Appendix B) fix reference

$$R_V = R_S + R_A \tag{3}$$

with

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

Note that each sum of R_V represents the contribution of the symptomatic and asymptomatic infected, respectively, to the spread of the disease. Following the ideas of Alexander et. al. [31], expression for R_V can be rewritten as

$$R_V = R_0 \left(1 - \frac{\epsilon \lambda_V}{(\mu + \delta_V + \lambda_V)}\right) \tag{4}$$

where R_0 is the basic reproduction number of system without vaccine. Note that $\left(1 - \frac{\epsilon \lambda_V}{(\mu+\delta_V+\lambda_V)}\right) < 1$. Therefore, this factor which saves the parameters corresponding to the application of the vaccine will allow us to modulate the value of R_0. In the first instance, if $R_0 < 1$, then $R_V < 1$. But, if $R_0 > 1$, we wonder if the application of the vaccine can lower R_V value below 1. In this sense, it is easy to prove that, if

$$\lambda_V > \frac{(R_0 - 1)(\mu + \delta_V)}{(\epsilon - 1)R_0 + 1}, \tag{5}$$

for $\epsilon > 1 - (1/R_0)$, it is possible to reduce the value of R_V below one, of course with the necessary conditions in terms of vaccination. That is, there is a region in the parameter space in which it is possible to reduce the value of R_V below one, considering adequate efficacy, vaccination rate and duration of the effect of the vaccine. However, if the inequality (5) is not satisfied, it will not be possible to reduce the value of R_V below 1.

To illustrate the aforementioned, Figure 2 shows the regions where it is possible to reduce the value of R_V. In this case, we set all the system parameters, which are given in table 1 and with $\delta_V = 1/180$, leaving ϵ and λ_V free.

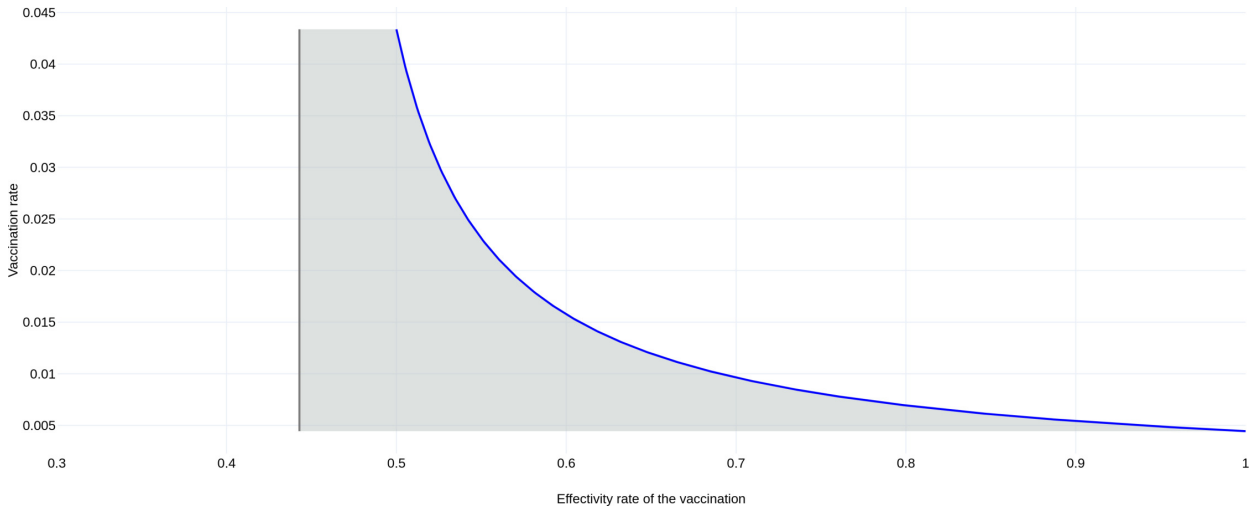

Figure 2: Shaded region corresponds to $R_V > 1$ while white region denotes when $R_V < 1$. This scenario considers a vaccine with 50 percent efficacy, thus an adequate vaccination rate can drive R_V value below one.

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On the other hand, vaccination policies to carry out the application of the same is of utmost importance. Among other factors, the vaccination rate at which the vaccine must be applied in order to achieve a certain coverage of the population within a certain horizon time must be considered. In this sense, we will refer to this vaccination rate as the base vaccination rate and we will denote it as λ_{Vbase} and which is a solution of the equation:

$$x_{coverage} = 1 - \exp(-\lambda_V T). \tag{6}$$

That is, λ_V denotes the constant vaccination rate to cover a fraction $x_{coverage}$ in time horizon T. So, Figure 3, show the contour curves for R_0 considering it as a function of the efficacy of the vaccine (ϵ) and of the vaccination rate (δ_V), considering immunity times due to the vaccine of half year .

Blue line in the graph correspond to the values of λ_{Vbase} and we can see that with this vaccination rate, no matter how effective the vaccine is, it is not possible to reduce the value of R_V below one. Purple lines show a scenario in which it is possible to reduce the R_V value below one, considering a vaccine efficacy of 0.8 and a vaccination rate of 0.7. Figure shows plausible combinations of ϵ and λ_V values in order to reduce the value of R_V below one.

Note that a vaccine efficacy of 50 percent or more is required so that, with an adequate vaccination rate, the R_V value can be reduced below one.

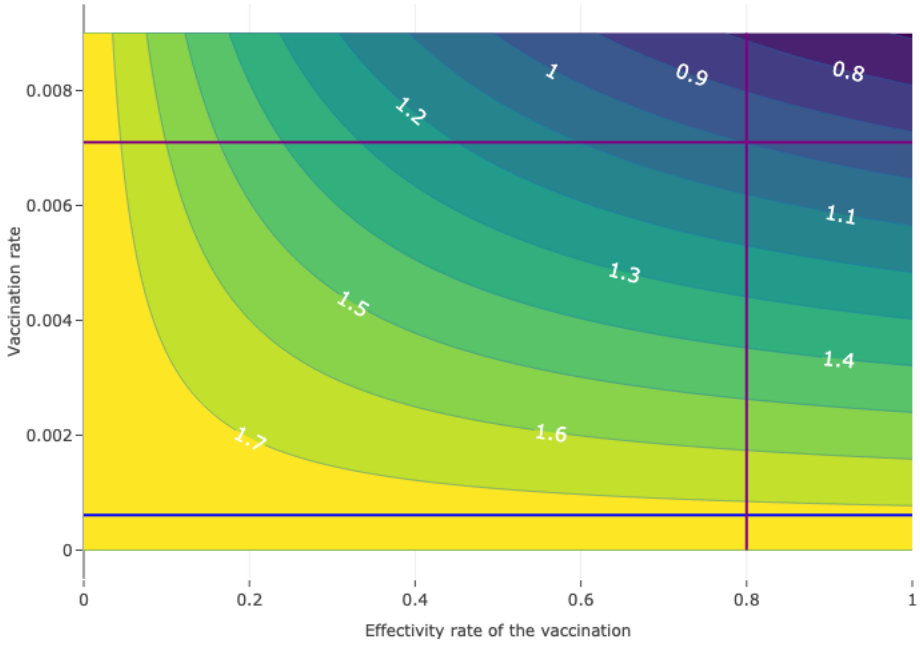

Figure 3: Contour plot of R_V like function of ϵ and λ_V and with immunity average time by vaccination of half year. Blue line represents the value of $\lambda_{Vbase} = 0.000\,611$, corresponding to a coverage $x_{coverage} = 0.2$ and a horizon time $T = 365$. Purple lines show a scenario in which it is possible to reduce the R_V value below one, considering a vaccine efficacy of $\epsilon = 0.8$ and a vaccination rate of $\lambda_V = num0.7$.

In the next section, the optimal control theory will be applied to propose optimal vaccination dynamics that minimize the number of cases of symptomatic infection and deaths due to the disease.

4. Optimal Vaccination policies

Diagram description

According to dynamics in Equations (1) and (2), we modulate the vaccination rate by a time-dependent control signal $u_V(t)$ to achieve an imposed vaccine coverage. That is, according to the components solution of Equations (1) and (2) S, V, X we modulate the vaccination rate λ_V by an additive control $u_V(t)$. Thus, we modify components equations related with S, V, X as

$$\begin{aligned} S'(t) &= \mu\bar{N} - \frac{\beta_S I_S + \beta_A I_A}{\bar{N}} S - (\mu + (\lambda_V + u_V(t))S + \delta_V V + \delta_R R \\ V'(t) &= (\lambda_V + u_V(t))S - (1-\epsilon)\frac{\beta_S I_S + \beta_A I_A}{\bar{N}} V - (\mu + \delta_V)V \\ X'(t) &= (\lambda_V + u_V(t))(S + E + I_A + R). \end{aligned} \tag{7}$$

In order to assure solution of our controlled model we consider the functional space

$$\mathcal{U}[0:T] := \{u_V : [0,T] \to \mathbb{R}, \text{ such that } u_V(\cdot) \text{ bounded and picewise continuous}\}.$$

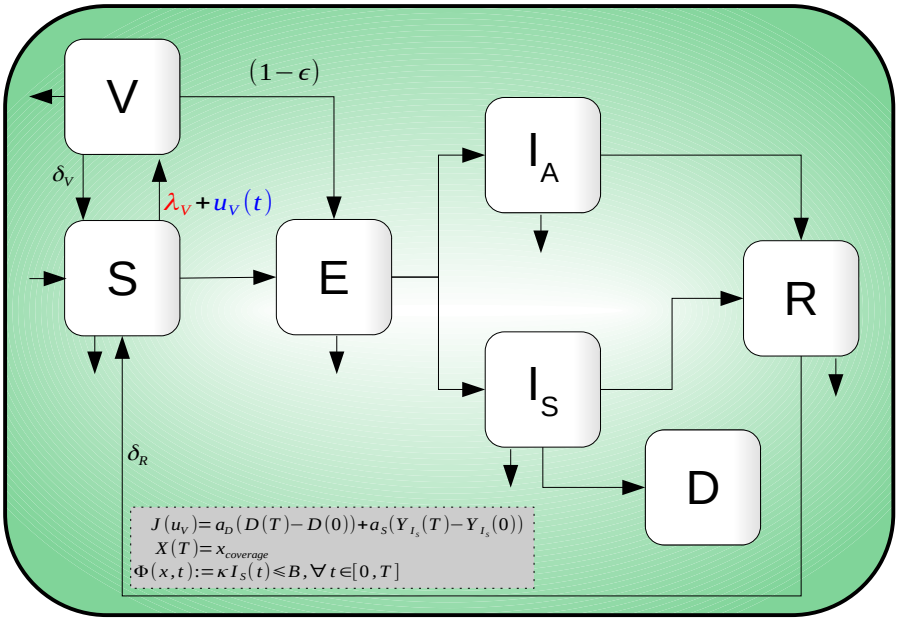

Figure 4: Compartmental diagram of COVID-19 transmission dynamics which including vaccination dynamics and...

Let $x(t) := (S, E, I_S, I_A, R, D, V, X)^\top(t)$ and control signal $u_V(\cdot) \in \mathcal{U}[0,T]$. Following the guidelines of WHO-SAGE modeling questions [25], we quantify the burden of COVID-19, according to the Disability-Adjusted Life Year (DALY) unit. Thus adapting the WHO definition of DALY [24], we optimize the number of year of life lost with a vaccination policy. In other words, we calculate a minimum of the penalization functional

$$J(u_V) = a_D(D(T) - D(0)) + a_S(Y_{I_S}(T) - Y_{I_S}(0)). \tag{8}$$

Here a_S and a_D are parameters related with the units definition of the Years of Life Lost (YLL) due to premature mortality and the Years Lost due to Disability (YLD). We estimate a_D as the mean life expectancy at the age of death, and according to CDMX data, we handle $a_D = 7.5$ years. Parameter a_S is the product of a disability weight (DW) and the average duration of case until remission or death in years, that is, $a_S = DW \times \alpha_S^{-1}$. Here we postulate the disability weight as the arithmetic average of disability weight regarding comorbidities reported in [32]. Thus, our simulations employ $a_S = 0.008\,418\,473$ years. Thus, functional J penalizes the pandemic burden—in Year of Life Lost—due to mortality or disability. We display in Table [*] parameters regarding with the optimal controlled model.

Since we aim to simulate vaccination policies contra factual scenarios following the SAGE modeling guidelines reported in [25], we impose the vaccination counter state's horizon time condition $X(T)$

$$\begin{aligned} x(T) &= (\cdot,\cdot,\cdot,\cdot,\cdot,\cdot,X(T))^\top \in \Omega, \\ X(T) &= x_{coverage}, \\ x_{coverage} &\in \{\text{Low}(0.2), \text{Mid}(0.5), \text{High}(0.8)\}. \end{aligned} \tag{9}$$

Thus, given the time horizon T, we set 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

$$\Phi(x,t) := \kappa I_S(t) \leq B, \qquad \forall t \in [0,T], \tag{10}$$

to ensure that critical symptomatic cases will not overload healthcare services. Here κ denotes hospitalization rate, and B is the load capacity of a health system. We illustrate the main ideas of the above discussion in Figure 4.

Given a fixed time horizon and vaccine with efficacy ϵ, we estimate the constant vaccination rate λ_V as the solution of Equation (6). That is, λ_V estimates the constant rate to cover—with a vaccine dose per individual—population 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.

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Then, optimal vaccination amplifies or attenuates this 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 aim is minimize the cost functional (8)—over an appropriated space—subject to the dynamics in Equations (1) and (7), boundary conditions related with (9), and path constrain (10). That is, we seek for vaccination policies $u_V(\cdot)$, that solve the following optimal control problem (OCP)

$$
\begin{aligned}
&\min_{u_V \in \mathcal{U}[0,T]} J(u_V) = a_D(D(T) - D(0)) + a_S(Y_{I_S}(T) - Y_{I_S}(0)) \\
&\text{s.t.} \\
&f_\lambda := \frac{\beta_S I_S + \beta_A I_A}{\bar{N}} \\
&S'(t) = \mu\bar{N} + \delta_V V + \delta_R R \\
&\qquad - (f_\lambda + \mu + \lambda_V + u_V(t))S \\
&E'(t) = f_\lambda(S + (1-\epsilon)V) - (\mu + \delta_E)E \\
&I_S'(t) = p\delta_E E - (\mu + \alpha_S)I_S \\
&I_A'(t) = (1-p)\delta_E E - (\mu + \alpha_A)I_A \\
&R'(t) = (1-\theta)\alpha_S I_S + \alpha_A I_A - (\mu + \delta_R)R \\
&D'(t) = \theta\alpha_S I_S \\
&V'(t) = (\lambda_V + u_V(t))S - ((1-\epsilon)f_\lambda V + \mu + \delta_V)V \\
&X'(t) = (\lambda_V + u_V(t))(S + E + I_A + R)
\end{aligned}
\tag{11}
$$

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

Table 2 enclose a parameters description regarding with this controlled version.

The classic results on Optimal control assure existence of solution to our (OCP) in Equation (11). Since our aim is the simulation of hypothetical scenarios we refer interested reader to [**? ? ?**] and the reference there in.

Symbol	Description	Ref
a_D	Penalization weight due to premature mortality (YLL) and estimated from CDMX data	[24, 33]
a_S	Penalization weight due to disability (YLD)	[32]
$x_{coverage}$	Covering constraint at time horizon T	[25]
κ	Hospitalization rate	Estimated from CDMX data
B	Health service capacity in number of beds normalized by the whole population N	[33]

Table 2: Parameters regarding controlled version model (OCP) in Equation (11)

5. Numerical experiments

Argument optimal solution.

Numerical Optimization Description.

- Describe IPOP methd and cite BOCOP.
- Cite gitHub repository.

Interpretations of a optimal solution. According to the WHO Strategic Advisory Group of Experts (SAGE) on Immunization Working Group on COVID-19 Vaccines modeling questions presented in [25], our model is capable to explore the following scenarios:

Vaccine profile

Vaccination policies according to different profiles, namely:

- efficacy $\epsilon = \{0.1, 0.2, \cdots 0.9\}$.
- vaccine induced immunity $\delta_V^{-1} = \{0.5\,\text{year}, 1.0\,\text{year}, \cdots, \text{lifelong}\}$.

Coverage

We obtained optimal vaccination policies with coverage profiles at

$$x_{coverage} = \{20\%, 50\%, 80\%\}.$$

Time horizon

Plausible scenarios at time horizon $T = \{1\,\text{year}, 2\,\text{year}, 10\,\text{year}\}$.

To fix ideas, we display in Figure 5 the counterfactual scenario regarding no intervention, constant vaccination policy (CP), and optimal vaccination policy (OP). Dashed lines denote the prevalence of each class according to dynamics with no intervention. Solid lines represent the prevalence according to controlled dynamics with the optimal or constant vaccination policies. Thus, shaded areas respectively denote the gain in mitigation(orange), health resources (red), saved lives (green), coverage (blue), and cost(olive). Here, opaque colors correspond to a constant vaccination policy while translucent colors are related to the gain according to the optimal policy. For example, in the panel titled "Death," the opaque solid line represents the number of accumulated deaths with a constant vaccination policy. The green opaque shaded area is the number of saved lives regarding to CP. Since the translucent green shade area overlaps the opaque green,

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we say that optimal vaccination improves the gain of a constant policy. Further, since the cost (see olive color) of the CP is above OP, we also say that optimal vaccination is cheaper.

Figure 5, shows a scenario where $\mathcal{R}_0 > 1$. Despite $\mathcal{R}_V$ remains below but close to $\mathcal{R}_0$, vaccination reproductive number $\mathcal{R}_V$, suggests constant policies according to the mitigation factor

$$\left(1 - \frac{\epsilon\lambda_V}{\mu + \delta_V + \lambda_V}\right).$$

Fix legend and, subplots titles ar legends for plotly chart figures. Al we need to check if the vaccination signal is multi- plied by the cor- rect factor. Code the generation of EPS figures

Then disease mitigation is strongly related to vaccine efficiency ϵ and vaccination rate λ_V. Following this sort of ideas, Figures 5 and 6 displays the response of the optimal vaccination policy according to three different vaccine efficacies.

Further, given a dynamic with not vaccine intervention and $\mathcal{R}_0 > 1$, $\mathcal{R}_V$ suggests a minimal vaccination rate to drive this dynamic to the disease-free state. In particular, this vaccine efficiency would govern the viability of the constant policy.

6. Optimal Vaccination Policies

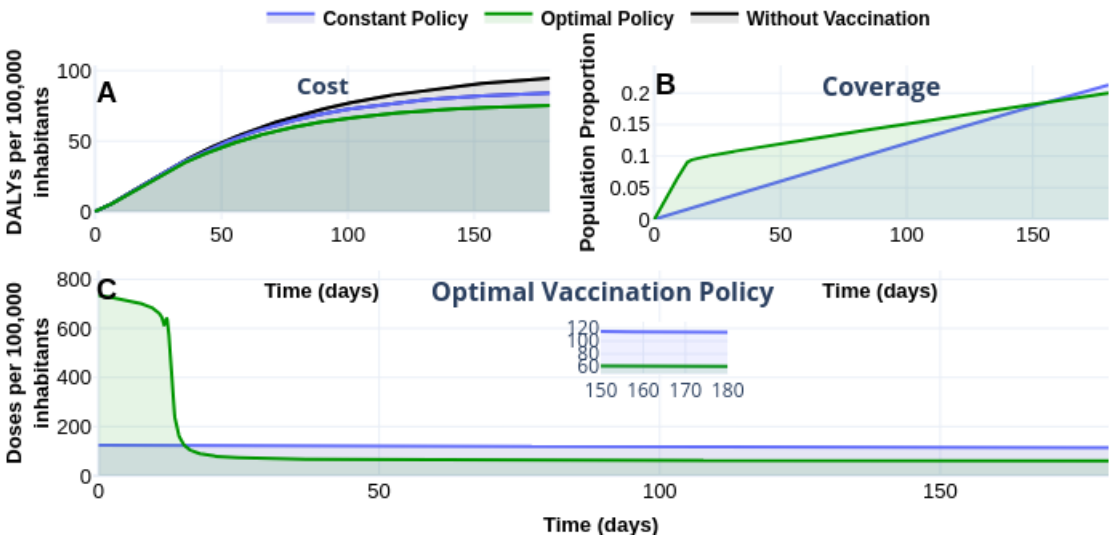

Figure 5: Panel A description. Panel B description. Panel C description. Plotly citation. Implications https://plotly.com/ sauldiazinfante/131/

6.1. Vaccine Profile

Vaccine Efficiency

Vaccine Induced Immunity

6.2. Natural Immunity Hypothesis

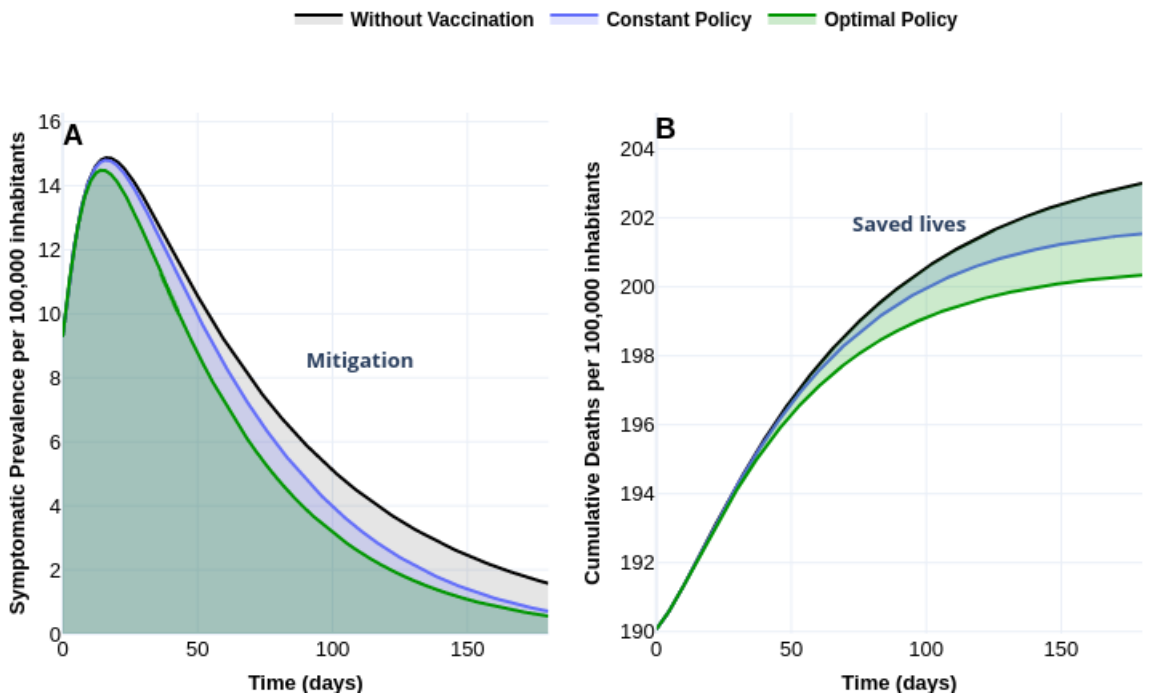

Figure 6: Panel A description. Panel B description. Panel C description. Plotly citation. Implications

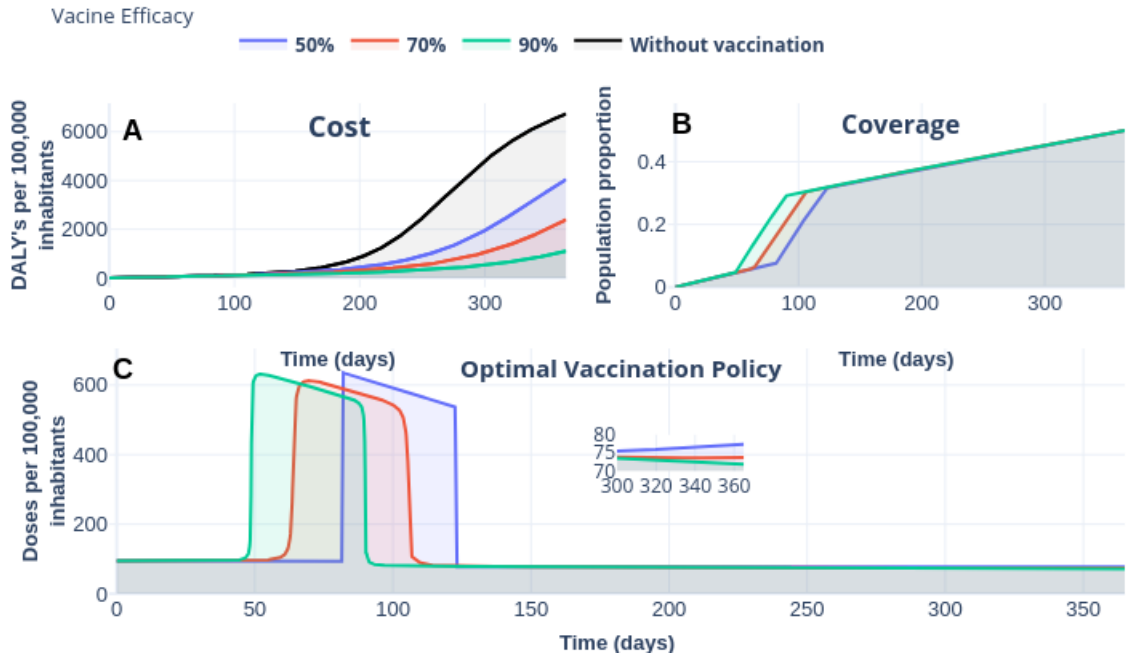

Figure 7: Description panel A. Description panel B. Description Panel C, Implications illustrated https://plotly.com/ sauldiaz-infante/85/

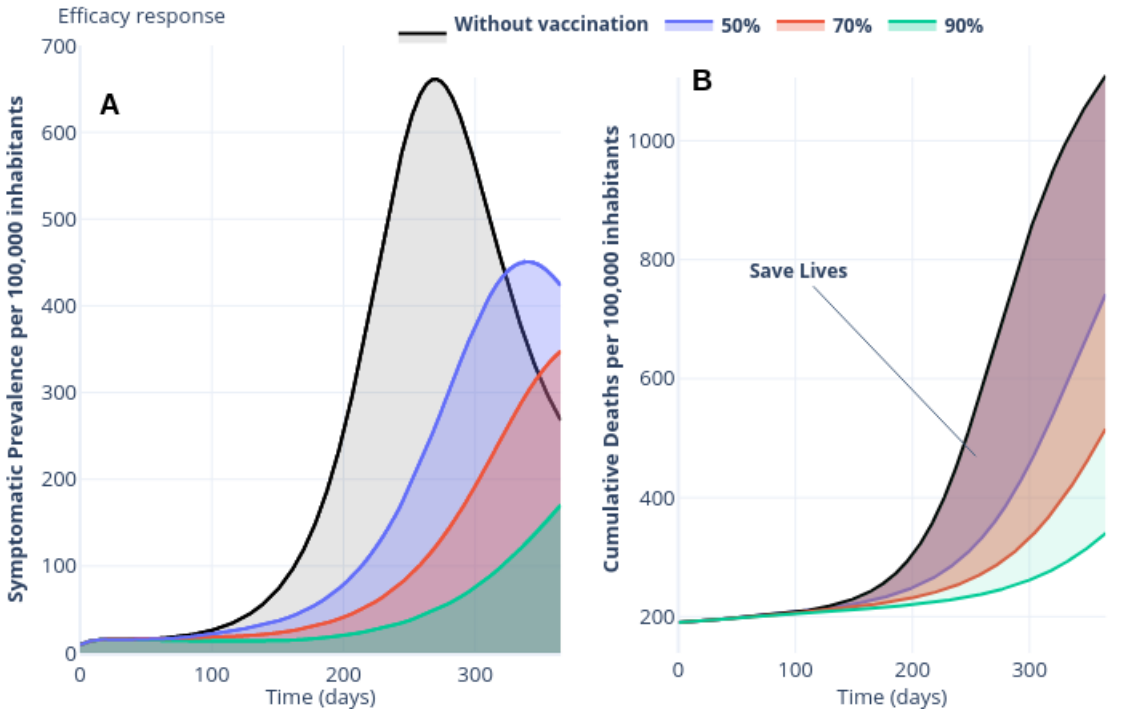

Figure 8: Description panel A. Description panel B. Description panel C. Implications. Explain green translucent layer effect. illustrated

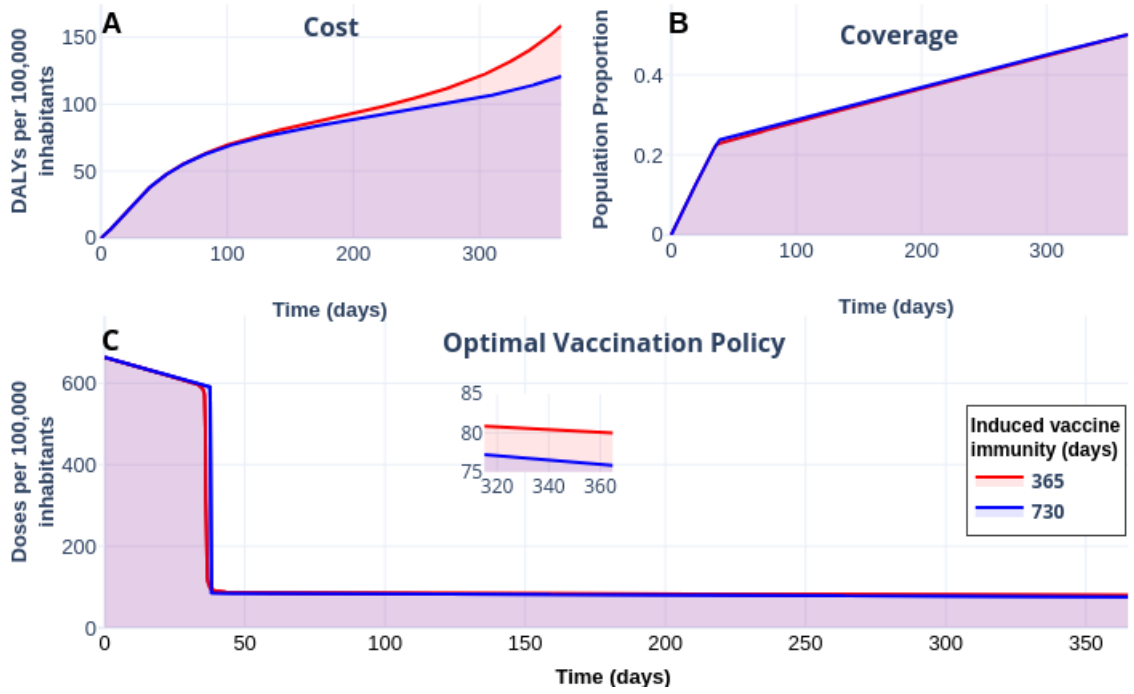

Figure 9: Panel A description. Panel B description. Implication. Cite plotly chart link https://plotly.com/ sauldiazinfante/111/

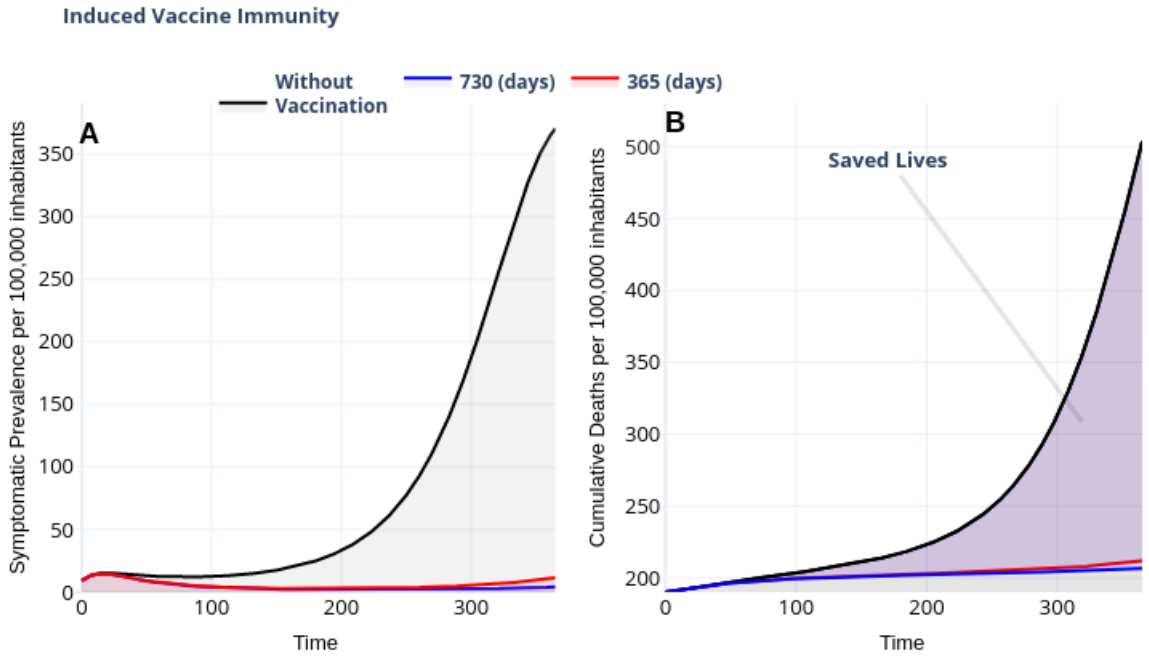

Figure 10: Panel A description. Panel B description. Implication. Cite plotly chart link: https://plotly.com/ sauldiazinfante/123/

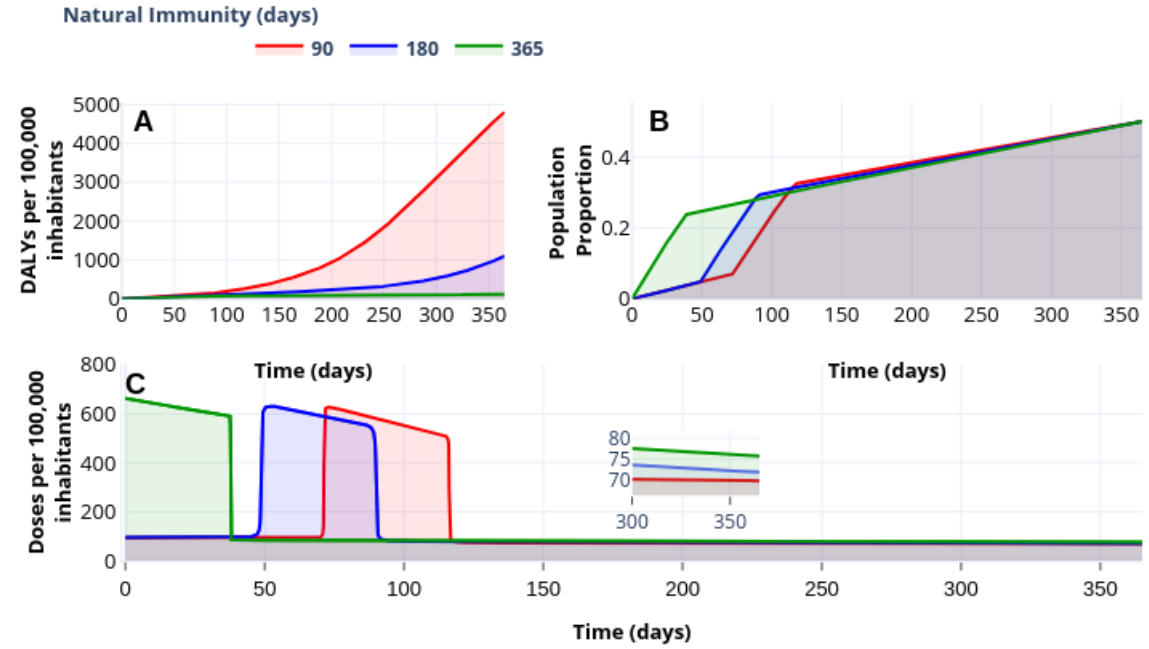

Figure 11: Panel A description, Panel B description, Panel C description, Implications. Plotly-cite: https://plotly.com/ sauldiazinfante/95/

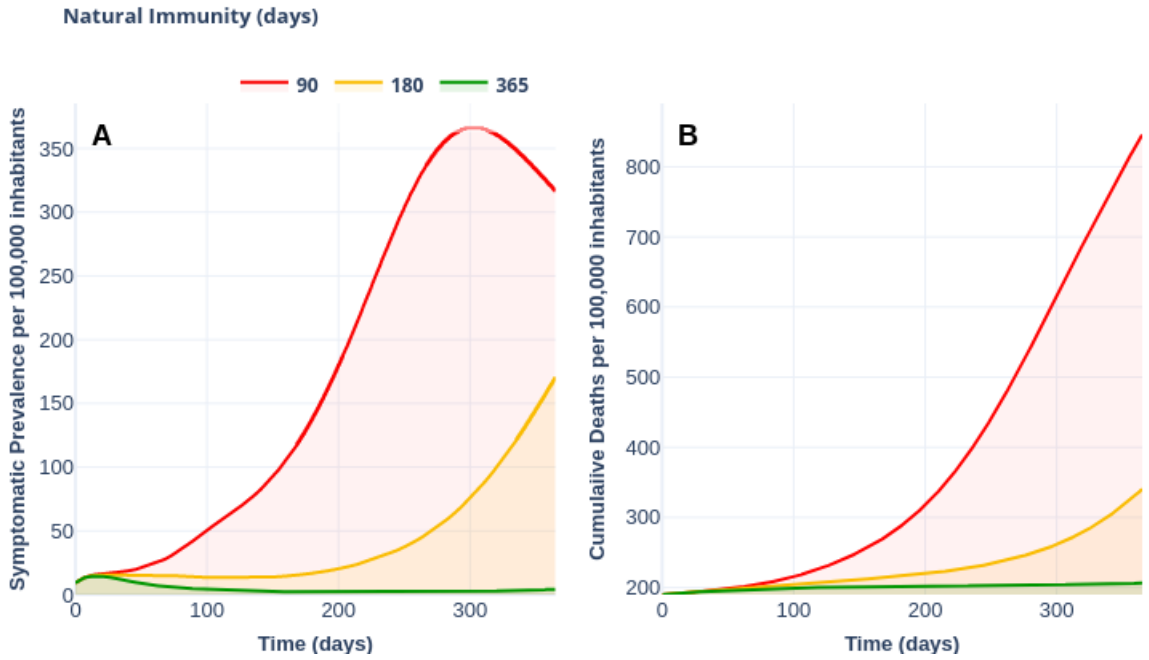

Figure 12: Panel A description, Panel B description, Panel C description, Implications. Plotly: https://plotly.com/ sauldiaz-infante/104/

7. Conclusions and Discussions

Currently, vaccination is the unique strategy to eradicate COVID-19. However, its competence is restricted to several factors such as its distribution, stocks, politics, vaccination efforts among others. A good distribution or application strategy of these drugs is imperative to manage the available resources, especially in developing countries. In order to design optimal vaccination strategies, a mathematical model has been proposed to describe the transmission dynamics of COVID-19, which also includes vaccination dynamics. Our aim is to provide vaccination policies that minimize reported deaths and optimize resource consumption.

Similar to other articles with the same approach, our model presents a reproductive vaccination number ($\mathcal{R}_v$) that depends on $\mathcal{R}_0$ [31]. Here, we can see the importance of the parameters related to vaccination dynamics to reduce $\mathcal{R}_v$. However, according to our simulation parameters setup, to obtain $\mathcal{R}_v < 1$ we need impractical vaccination rates. This last can be improved when implementing NPIs, which can be modeled by transmission contact rates reduction.

To show our scenario of optimal control strategies, we consider Mexico City as the study scenario. Using the data reported by the onset of symptoms, some parameters were estimated, and others from the literature were set. Our results capture the restriction of health care centers that is, do not overcome the available number of beds. Given a target coverage at final time T, we illustrate that an optimal vaccination strategy reduces the number of fatalities compared to the application of the constant vaccination one.

The present work can be extended in different fronts such as i) the evaluation of the inclusion of NPIs at the same time vaccination implementation takes place; ii) the consequences of applying the vaccination strategies during different phases of an outbreak; iii) the effects of using double vaccination doses; iv) the application of different vaccines to distinct groups of individuals, v) vaccine application with knowledge of the percentage of the population that has resulted positive in a seroprevalence study and vi) to improve the efficiency of the optimal control strategies by including a comorbidity class in the model.

Can we say something about the immunity period provided by a vaccine? Does a better knowledge provides with more elements to establish a better control strategy?

We need to include a short discussion of the usual way a control is implemented and the main difference with the approach in this work.

Acknowledgement

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Author contributions

MAAZ . SDIV designed the study, provided oversight for all aspects of the study, developed the controlled modeling framework, developed simulation code for the BOCOP optimization, developed R-scripts for parameters calibration with Stan-R interface and wrote Sections 4 and 5 of the manuscript. DBC DOL

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Appendices

A. Parameter estimation

Mathematical models for COVID-19 have shown that the parameters' values are not necessarily the same in each country. We use COVID-19 data from Mexico City and Mexico state to follow the epidemic curve's initial growth in this work. Consequently, we estimate some parameter values of system (1). To obtain the baseline parameter values, we consider two-stages: i) before and ii) after mitigation measures were implemented. For both stages, we use model (1) with no vaccination dynamics ($\lambda_V = 0$ and $V(0) = 0$), and STAN R-package. This package is used for statistical inference by the Bayesian approach. For the code implementation of our system, we follow the ideas of [34]. For this section, our estimations are focused on three parameters: β_A, β_S and p. Other parameter values are given in Table (3).

Parameter	Value	References
δ_E^{-1}	5.1 days	[35]
α_S^{1}	5.97 days	[4]
α_A^{-1}	10.81 days	[4]
δ_R^{-1}	365 days	
μ^{-1}	70 years	

Table 3: Fixed parameters values of system (1).

For the first stage, the following system is considered:

$$\begin{aligned}
S'(t) &= \mu\bar{N} - \frac{\hat{\beta}_S I_S + \hat{\beta}_A I_A}{\bar{N}} S - \mu S + \delta_R R \\
E'(t) &= \frac{\hat{\beta}_S I_S + \hat{\beta}_A I_A}{\bar{N}} S - (\mu + \delta_E) E \\
I_S'(t) &= p\delta_E E - (\mu + \alpha_S) I_S \\
I_A'(t) &= (1-p)\delta_E E - (\mu + \alpha_A) I_A \\
R'(t) &= (1-\theta)\alpha_S I_S + \alpha_A I_A - (\mu + \delta_R) R \\
D'(t) &= \theta\alpha_S I_S
\end{aligned} \tag{12}$$

where $\bar{N}(t) = S(t) + E(t) + I_S(t) + I_A(t) + R(t)$ and $N = \bar{N} + D$. We use COVID-19 data from the first day of symptoms onset reported (February 19) until March 23, 2020. We also assume that $\theta = 0$ because the first reported death was on March 18, and there were three reported deaths until March 23. The initial values of recovered and dead people are set to zero. Symptomatic class initial value was postulated in one individual, while $E(0)$ and $I_A(0)$ were estimated. Thus, $S(0) = N - (E(0) + I_A(0) + 1)$, where $N = 26\,446\,435$ [33].

we employ a negative-binomial model as the likelihood function with the mean parameter given by incidence solution per day (FALTA). Further, we postulate prior probability distributions according to [] to

For the STAN implementation, by saying that we apply Bayesian MCMC to calibrate model parameters

each parameter and the exposed and asymptomatic classes' initial conditions. Thus, we assume that $\hat{\beta}_A$ and $\hat{\beta}_S$ follows a normal distribution with parameters $\mu = 1$ and $\sigma^2 = 0.13$. Then, p follows a uniform distribution in $(0, 0.25)$, and $E(0)$ and $I_A(0)$ also follow a uniform distribution in $(2, 20)$ and $(2, 10)$, respectively.

We employ the MCMC (Hamilton-..) method from the STAN implementation package []. To this end, we run 5 chains with 100 500 iterations each, burning the first 500, and use 10 000 samples to obtain posterior distributions for $\hat{\beta}_A$, $\hat{\beta}_S$ and p see details and source code in [**?**]. Table 4 shows the confidence interval and posterior median regarding to our calibration. For the second stage, we took a complete month starting

Parameter	95% Confidence Interval	Quantile 50
$\hat{\beta}_S$	$[0.672, 1.1886]$	0.9322
$\hat{\beta}_A$	$[0.501, 0.7851]$	0.6435
p	$[0.061, 0.2206]$	0.1227

Table 4: Confidence interval and median posterior estimated for some parameters of system (12).

the day when mitigation measures were implemented, that is, from March 23 to April 23, 2020. Now, we consider parameter ξ to model the implementation of non-pharmaceutical measures. Thus, system (12) becomes:

$$\begin{aligned}
S'(t) &= \mu\bar{N} - \frac{\xi\hat{\beta}_S I_S + \xi\hat{\beta}_A I_A}{\bar{N}} S - \mu S + \delta_R R \\
E'(t) &= \frac{\xi\hat{\beta}_S I_S + \xi\hat{\beta}_A I_A}{\bar{N}} S - (\mu + \delta_E) E \\
I_S'(t) &= p\delta_E E - (\mu + \alpha_S) I_S \\
I_A'(t) &= (1-p)\delta_E E - (\mu + \alpha_A) I_A \\
R'(t) &= (1-\theta)\alpha_S I_S + \alpha_A I_A - (\mu + \delta_R) R \\
D'(t) &= \theta\alpha_S I_S
\end{aligned} \tag{13}$$

where $\bar{N}(t) = S(t) + E(t) + I_S(t) + I_A(t) + R(t)$ and $N = \bar{N} + D$. At this stage, we consider that $\theta = 0.11$. Here, our objective is to estimate the value of parameter ξ. To do this, we use the median posterior of all the estimated parameters from the first stage (see Table (4)). Other parameter values are given in Table (3). Almost all initial conditions were obtained when solving system (12) with the 10,000 samples (obtained in first stage), after which each solution at the final time (March 23) is saved. We use the median of the saved values. Thus, for system (13), $E(0) = 6587.585$, $I_S(0) = 553.7035$, $I_A(0) = 3149.924$, and $R(0) = 3001.547$. For the initial value of variable D, we consider reported COVID-19 data, then $D(0) = 3$. Therefore $S(0) = N - (E(0) + I_S(0) + I_A(0) + R(0) + D(0))$, with $N = 26446435$. Similar to the first stage, we consider a negative-binomial model as the likelihood function with the mean parameter given by incidence solution per day (FALTA), while that we postulate a uniform distribution in $(0.25, 0.75)$ as a prior probability distribution for the parameter ξ.

For the second stage, we run 5 chains with 100,500 iterations each, discard the first 500, and use 10,000 samples to generate estimates of parameters ξ. Table (5) shows the confidence interval and median posterior estimated for parameter ξ.

Parameter	95% Confidence Interval	Quantile 50
ξ	$[0.3696, 0.4099]$	0.3889

Table 5: Confidence interval and median posterior estimated for parameter ξ of system (13).

Figure 13 shows confidence band for the early phase of the COVID-19 outbreak in Mexico City plus

Mexico state. Here, reported data are shown in blue points, while that solid red line represents quantile 50 of all solutions. The code for both steps is made freely available at...

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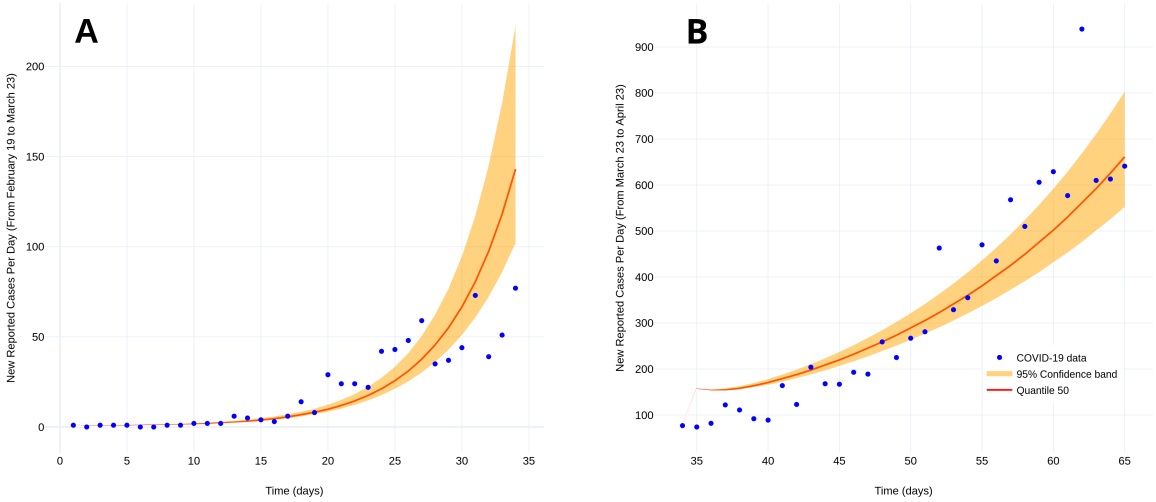

Figure 13: Fitting curves for the early phase of the COVID-19 outbreak in Mexico City plus Mexico state. Panel A shows the outbreak from February 19 to March 23, 2020, while panel B illustrates the outbreak from March 23 to April 23, 2020.

Finally, it is important to mention that our results were implemented considering that the effective transmission contact rates ($\beta_\bullet$) were equal to $\xi\hat{\beta}_\bullet$. This last means that our scenarios consider the first reduction in the effective transmission contact rates by NIPs. Using values in Tables 4 and 5, we build confidence intervals for $\xi\hat{\beta}_\bullet$. These results are shown in Table (6).

Parameter	95% Confidence Interval
$\beta_S = \xi\hat{\beta}_S$	$[0.2483712, 0.48720714]$
$\beta_A = \xi\hat{\beta}_A$	$[0.1851696, 0.32181249]$

Table 6: Confidence interval and median posterior estimated for some parameters of system (12).

$R0$ discussion