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Mathematical Modeling to Study Optimal Allocation of Vaccines against COVID-19 Using an Age-Structured Population

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Abstract: Vaccination against the coronavirus disease 2019 (COVID-19) started in early December of 2020 in the USA. The efficacy of the vaccines vary depending on the SARS-CoV-2 variant. Some countries have been able to deploy strong vaccination programs, and large proportions of their populations have been fully vaccinated. In other countries, low proportions of their populations have been vaccinated, due to different factors. For instance, countries such as Afghanistan, Cameroon, Ghana, Haiti and Syria have less than 10% of their populations fully vaccinated at this time. Implementing an optimal vaccination program is a very complex process due to a variety of variables that affect the programs. Besides, science, policy and ethics are all involved in the determination of the main objectives of the vaccination program. We present two nonlinear mathematical models that allow us to gain insight into the optimal vaccination strategy under different situations, taking into account the case fatality rate and age-structure of the population. We study scenarios with different availabilities and efficacies of the vaccines. The results of this study show that for most scenarios, the optimal allocation of vaccines is to first give the doses to people in the 55+ age group. However, in some situations the optimal strategy is to first allocate vaccines to the 15–54 age group. This situation occurs whenever the SARS-CoV-2 transmission rate is relatively high and the people in the 55+ age group have a transmission rate 50% or less that of those in the 15–54 age group. This study and similar ones can provide scientific recommendations for countries where the proportion of vaccinated individuals is relatively small or for future pandemics.

Keywords: mathematical models; SARS-CoV-2 virus; vaccination; age structure; computational mathematics

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1. Introduction

The COVID-19 pandemic has generated more than 437 million confirmed cases and currently about 5.96 million deaths [1,2]. Various non-pharmaceutical intervention strategies have been designed in order to try to slow down the COVID-19 pandemic [3–6]. The factors that affect SARS-CoV-2's spread around the world are many, and some of their effects are currently uncertain [7–11]. These factors include social behavior, non-pharmaceutical interventions and vaccines. Other important factors include SARS-CoV-2 variants and immunocompetence [12–14]. The study of the dynamics of the spread of SARS-CoV-2 is of paramount importance for public health. Obviously the most important aims are to save lives, and avoid hospitalizations and long term health consequences. Besides these main aspects, the COVID-19 pandemic has had profound economical and psychological impacts on people's lives worldwide.

Forecasting the consequences of the COVID-19 pandemic has been extremely difficult due to the great number of factors that affect its dynamics [15–18]. Moreover, with the

appearance of vaccines against SARS-CoV-2, the forecasting has been even more difficult [19–26]. Forecasting of epidemics related to influenza and other viruses is less difficult, since social behavior has not been changed much due to them, since those viruses are less lethal and/or have been around for a longer time [27–41].

During 2020 and 2021, several countries, including the USA, the UK and European nations, have deployed different vaccination campaigns, and their populations have high percentages of vaccinated people [42]. The vaccine campaigns have been different in different countries due to several factors, such as vaccine availability, prioritization and willingness of people to be vaccinated. The design of a vaccination program needs to take into account different aspects, such as vaccine availability, human resources, vaccination rate, age, geographical factors, immune system, health status and even type of vaccine [6,43–46]. Thus, an optimal vaccination campaign needs to consider the aforementioned factors. The governments of the USA and the UK have implemented different vaccination strategies, and some researchers have been investigating the optimal vaccination programs [47–51]. It has been found that the vaccination rate and the efficacy of the vaccine are the main factors in reducing some health outcomes, such as number of deaths, number of infected and hospitalizations [25,44,45,52–54]. For instance, in [53] the author found that an incidence-minimizing vaccination strategy is highly sensitive to vaccine efficacy, and vaccines with lower efficacy should be administered to teenagers and adults aged 50–59 years. Some researchers have studied the effects of delayed second doses on important health outcomes, such as death [6,48,50,51,55].

National regulatory authorities have granted emergency use authorizations for twenty-two vaccines. Six of those have been approved for emergency or full use by at least one WHO-recognized, stringent regulatory authority [56]. The first vaccine used against SARS-CoV-2 was developed by the Gamaleya Research Institute of Epidemiology and Microbiology in Moscow (widespread use on August 2020); and on December 2020, the United Kingdom granted emergency use authorization for BNT162 developed by Pfizer and BioNTech [57]. The efficacy of the different vaccines against the SARS-CoV-2 vary and also depend on the SARS-CoV-2 variant.

Mathematical models have been used to study many epidemics (including the COVID-19 pandemic) and predict different health outcomes [58–63]. The models can be used to investigate the effects of non-pharmaceutical interventions on important aspects without the need for making forecasts, which is a more complex issue. In this work, we were interested in studying different vaccination strategies in regard to which groups to vaccinate first. Different mathematical models that include vaccinated people and take into account the efficacy of the vaccine have been developed [64–67]. For instance, in [65] the authors proposed a stochastic epidemic model, and they found that white noise can result in the extinction of the disease even with a smaller reproduction number. In all these works it has been shown that vaccination can reduce the burden of the disease. Previous studies have proposed mathematical models to investigate vaccination strategies specifically [6,48,51,55,68]. Some studies found that a delayed second dose strategy might be the optimal strategy under some circumstances and always under the assumption that there is a limit to vaccine availability [6,48,51,53,55]. Countries such as Afghanistan, Haiti and Syria have low percentages of their populations fully vaccinated.

In this article, we develop two nonlinear mathematical models of COVID-19 transmission that take into account the age structure of the population in order to study the optimal vaccination strategy under different situations. We study many scenarios with different vaccine availability levels and levels of vaccine efficacy. The aim of this study is to provide scientific guidelines for countries where the proportions of vaccinated individuals are relatively small, or for future pandemics. Our aim here is not to precisely forecast the COVID-19 pandemic, but rather to understand the effects of using different vaccination strategies on paramount health outcomes, such as number of deaths. That is, we do not present an accurate forecast of the number of deaths at some particular future time. Besides the priority target age group, to design the optimal vaccination strategy there are other

factors to consider. Including all of them in one study is complex and might not provide a clear picture of the effects of all those factors. Choosing a priority target subpopulation is something that governments can relatively easily manage or design. Here we also consider scenarios where the vaccination pace is different; and this is related to vaccine availability, human resources attached to the inoculation process and the willingness of people to be vaccinated [25,69–71]. It is important to mention that many countries currently have low percentages of their populations vaccinated, and obtaining scientific support for designing the optimal vaccination program is of paramount importance under the limitations of vaccine availability. An interesting previous work proposed a continuous age-structured model to study the COVID-19 pandemic [72]. The authors used the age-structured model, since data show that the fatality of the disease is high in elderly people. The authors also studied the impact of a shortage of proper personal protective equipment on the spread of the disease [72]. In [73], the authors developed an interesting agent-based model for COVID-19 disease dynamics where the population has a social structure. These factors, such as age and social, are important for studying the COVID-19 pandemic.

One main advantage of mathematical models is that many different simulations can be done, allowing the investigation of various factors under a variety of scenarios. In this article, we construct two mathematical models based on nonlinear ordinary differential equations, where each variable represents different subpopulations with regard to COVID disease progression, vaccination status and age group. We numerically solve the differential equations with different parameter values in order to provide insight into the optimal vaccination strategy with regard to priority target age group. The models include symptomatic and asymptomatic individuals. The inclusion of asymptomatic people is important, since they are crucial contributors to the dynamics of the COVID-19 pandemic [11,74–88]. Thus, overall, we propose a mathematical approach to investigate a variety of vaccination strategies under different scenarios to consider the variability of situations in different countries where the transmission rates vary due to social behavior, the prevalences of different SARS-CoV-2 variants, and vaccine availability. Health authorities can benefit from the results presented in this study. Thus, this type of study can provide further insights about vaccination strategies against SARS-CoV-2.

2. Materials and Methods

The mathematical models presented here are based on a nonlinear system of ordinary differential equations. The models divide the total population into different subpopulations or compartments based on age group, the COVID-19 progression and vaccination status. The compartments or subpopulations considered are: susceptible, infected (able to infect others), asymptomatic (able to infect others), recovered (not infectious) and vaccinated. The mathematical models consider transitions or flow of individuals through the aforementioned compartments. The models assume that recovered individuals have permanent immunity against reinfection during a period of study that is shorter than one year. In reality this is not totally true, but the percentage of breakthrough cases before one year is very low. We also assume that only susceptible individuals can be vaccinated.

The individuals transit from the susceptible subpopulation to vaccinated if they receive the vaccine. Both models assume a simplification of reality where there are vaccines that are one or two doses. The models consider the possibility of infection for individuals who are vaccinated regardless of whether they are symptomatic or asymptomatic, even though these cases are very low with comparison to infections of unvaccinated people. The mathematical models implicitly assume that transitions follow an exponential distribution. Although this is standard in this type of model, other models consider different distributions, such the Erlang distribution, which makes the models more complex and increases the number of parameters [89–93]. Both mathematical models consider that only symptomatic individuals (vaccinated or not) can die due to COVID-19 [4,94–96]. This last health outcome is of paramount importance for the comparison of different vaccination strategies, and is used in this study and others extensively [4,47–49,51,53,97–100].

The first mathematical model developed is based on a *SIAR*-type epidemiological model. The model includes parameters related to the vaccine efficacy, vaccination pace and vaccine availability. The values of these parameters can be used to generate and investigate infinitely many different scenarios. Thus, we are able to approximate the situations of different places [63,69,70,101–106]. Figure 1 depicts the transits between the different subpopulations based on the disease and the vaccination status of the individuals.

Figure 1. Diagram for the COVID-19 mathematical model including a vaccination program (1). The boxes represent the different classes and the arrows the transitions between these classes.

Next, the first mathematical model is given by the following differential equation $\dot{\mathcal{X}}(t) = F(t, \mathcal{X}(t))$, with

$$\mathcal{X}(t) = (S_1(t), V_1(t), V_{A_1}(t), A_1(t), I_1(t), S_2(t), V_2(t), V_{A_2}(t), V_{I_2}(t), A_2(t), I_2(t), R(t))^t,$$

where $\mathcal{X}$ is the vector of the different states of the subpopulations that compose the total population. Thus, the dynamics of COVID-19 disease in the human population is governed by the following ODE system

$$\begin{aligned} \dot{S}_1(t) &= -\lambda(t)S_1(t) - v_1S_1(t), \\ \dot{V}_1(t) &= -(1-\epsilon)\lambda(t)V_1(t) + v_1S_1(t), \\ \dot{V}_{A_1}(t) &= a(1-\epsilon)\lambda(t)V_1(t) - \gamma V_{A_1}(t), \\ \dot{V}_{I_1}(t) &= (1-a)(1-\epsilon)\lambda(t)V_1(t) - \gamma V_{I_1}(t), \\ \dot{A}_1(t) &= a\lambda(t)S_1(t) - \gamma A_1(t), \\ \dot{I}_1(t) &= (1-a)\lambda(t)S_1(t) - \gamma I_1(t), \\ \dot{S}_2(t) &= -v_2S_2(t) - \lambda(t)S_2(t), \\ \dot{V}_2(t) &= v_2S_2(t) - (1-\epsilon)\lambda(t)V_2(t), \\ \dot{V}_{A_2}(t) &= a(1-\epsilon)\lambda(t)V_2(t) - \gamma V_{A_2}(t), \\ \dot{V}_{I_2}(t) &= (1-a)(1-\epsilon)\lambda(t)V_2(t) - \gamma V_{I_2}(t), \\ \dot{A}_2(t) &= a\lambda(t)S_2(t) - \gamma A_2(t), \\ \dot{I}_2(t) &= (1-a)\lambda(t)S_2(t) - \gamma I_2(t), \\ \dot{R}(t) &= \gamma(1-\delta_1)I_1(t) + \gamma(1-\delta_2)I_2(t) + \gamma(1-\delta_{V_1})V_{I_1}(t) \\ &\quad + \gamma(1-\delta_{V_2})V_{I_2}(t) + \gamma(V_{A_1}(t) + A_1(t) + V_{A_2}(t) + A_2(t)), \end{aligned} \tag{1}$$

and the initial conditions in $t = 0$, written as

$$S_1(0), V_1(0), V_{A_1}(0), A_1(0), I_1(0), S_2(0), V_2(0), V_{A_2}(0), V_{I_2}(0), A_2(0), I_2(0), R(0), \quad (2)$$

and $\dot{D}(t) = \gamma \delta_1 I_1(t) + \gamma \delta_2 I_2(t) + \gamma \delta_{V_1} V_{I_1}(t) + \gamma \delta_{V_2} V_{I_2}(t)$, represents the number of deaths caused by the disease. The expression $\lambda(t)$ is the force of infection, which is given by

$$\lambda(t) = \frac{1}{N} \left(\beta_{I_1} I_1(t) + \beta_{A_1} A_1(t) + \beta_{I_2} I_2(t) + \beta_{A_2} A_2(t) + \beta_{V_{I_1}} V_{I_1}(t) + \beta_{V_{A_1}} V_{A_1}(t) + \beta_{V_{I_2}} V_{I_2}(t) + \beta_{V_{A_2}} V_{A_2}(t) \right), \quad (3)$$

and describes the rate at which a susceptible person becomes infected through interaction with another person who can spread the disease. In this case, it is a linear combination of the classes that can transmit the virus and is measured by the β_s transmission rates.

The state variables, $S_1(t)$ and $S_2(t)$, represent the susceptible subpopulations from the 15–54 and 55+ age groups. When a susceptible and an infectious individual come into infectious contact, the susceptible individual contracts the disease and transitions to the asymptomatic or infected subpopulation. The subpopulations $I_1(t)$, $I_2(t)$, $A_1(t)$ and $A_2(t)$ include individuals that are able to infect others, but the subpopulations $A_1(t)$ and $A_2(t)$ include individuals that are asymptomatic. The model disregards natural births and deaths, since it focuses on a short period for the deployment of the vaccination program.

Both models consider two subpopulations of vaccinated people: The first, $V_1(t)$, includes the individuals that have been vaccinated from the 15–54 age group, and $V_2(t)$ includes those vaccinated from the 55+ age group. Based on the efficacies of the vaccines, those vaccinated can become infected with various probabilities. The first model that we consider assumes a constant proportion vaccination rate, i.e., a proportion of the subpopulations $S_1(t)$ and $S_2(t)$ is vaccinated per day or per unit time. Delivering a specific number of inoculations per day is difficult, since it depends on many factors, such as willingness to be vaccinated, human resources and vaccine availability. Those vaccinated individuals from the 15–54 age group can still get infected and become part of subpopulations $V_{I_1}(t)$ and $V_{A_1}(t)$ (asymptomatic). Similarly, those vaccinated individuals from the 55+ age group can still get infected and become part of subpopulations $V_{I_2}(t)$ and $V_{A_2}(t)$ (asymptomatic). The model assumes that people in states $V_1(t)$, $V_2(t)$, and $R(t)$ are not able to transmit SARS-CoV-2. The compartment $D(t)$ represents the number of deaths due to the SARS-CoV-2 virus.

The mathematical model (1) has an advantage from an analysis point of view, since the positivity of the subpopulations is guaranteed for any time, as we will see in the next section. However, it has the disadvantage that the number of vaccinated people per unit time decreases, since the susceptible population decreases. This does not always occur in reality, since at the beginning of the vaccination programs, it is common to have limited availability of vaccines. Therefore, we propose a second mathematical model where the number of vaccines available per day is fixed. This alternative model has the same subpopulations, but the terms $v_1 S_1$ and $v_2 S_2$ are replaced by v_1 and v_2 . Thus, we achieve a constant fixed number of vaccinations per day or per unit time. From a mathematical point of view, negative values for the susceptible subpopulations $S_1(t)$ and $S_2(t)$ can be obtained. However, to avoid a long simulation time or period of study, negative subpopulations do not arise. In reality what happens is that some part of the population will not be vaccinated due to various reasons. For a long term simulation a more complex model that includes people that are not willing to get vaccinated and demographics is necessary. Figure 2 shows the cumulative number of vaccine doses administered in different countries. If we assume the second mathematical model, the graph should look similar to a line due to the fixed amount of vaccinations per unit time. On the other hand, if the first mathematical model is used, the graph should be similar to an exponential curve due to the fact that the number of inoculations per unit time is proportional to the number of susceptible individuals. Notice

that in the case of USA, the graph can be approximated by a line or even by a quadratic, concave, downward trend, which is the opposite of what happens when the vaccination is proportional to the susceptible subpopulations. Thus, for the USA the second model might be more realistic in order to consider the vaccination program implemented.

Figure 2. Cumulative numbers of vaccine doses administered in different countries.

In this study, we used parameter values that can be found in the scientific articles and on the CDC's website, even though there are some uncertain values, such as the proportion of asymptomatic infections. In this work, we were interested in finding the impact of allocating vaccines to two different age groups. In addition, we considered other factors, such as the vaccination pace, virus transmissibility and vaccine efficacy. All these factors play important roles in the outcomes regarding infections and deaths. In the *in silico* simulations we assumed that the transmission rates of SARS-CoV-2 were constant from the beginning of the period of study. Implicitly, this assumed that social behavior was in a steady state before implementing the vaccination campaign. In reality, it has been mentioned that people might change behavior (on average) when a vaccination program is well advanced due to a perception of less risk [6]. We assumed that social contacts would not change because many health policies would have been already long implemented before the vaccination campaign had begun. We also considered that for a short time horizon of study (less than year), the immunity provided by the vaccines does not diminish.

For the scenarios studied here, we tried to replicate the conditions in the USA just before the vaccination campaign started. However, since the general results are qualitative, the conclusions presented here can be applied to other countries. For the proportion of asymptomatic cases, we chose a conservative approach in which the percentage of asymptomatic infections was 50% [2]. For the parameters related to transmissibility of the different subpopulations, we assumed a variety of values that have been used in some studies [4,81,107–110]. In particular, we assumed that the transmissibility of the 55+ age group is half that of the 15–54 age group. This can be justified by the fact that younger people are less reluctant to stay at home or take preventive measurements. For instance, in South Korea, the 20–29 age group had the highest transmission incidence per capita [53]. On the other hand, the case-fatality rate is highest among the elderly [53]. Thus, based on data related to the USA we assumed a case-fatality rate ten times higher for the 55+ age group compared to the 15–54 age group.

Finally, for the initial conditions we tried to replicate the conditions of the USA, but initial conditions can be changed easily [1]. Moreover, for any country for which the percentages of vaccinated and of recovered people are low, the qualitative results would be similar due to the structure of the population. In Table 1 we present the initial conditions. The initial vaccinated people was taken as zero. Thus, the initial susceptible subpopulation

was given by $S(0) = N(0) - I(0) - A(0) - R(0)$. This can be modified to consider, for instance, that initially some part of the population is vaccinated.

Table 1. Initial conditions for the subpopulations.

Parameter	Symbol	Value
Susceptible 1	$S_1(0)$	149,284,000
Asymptomatic 1	$A_1(0)$	798,000
Infected (symptomatic) 1	$I_1(0)$	798,000
Susceptible 2	$S_2(0)$	112,104,000
Asymptomatic 2	$A_2(0)$	588,000
Infected (symptomatic) 2	$I_2(0)$	588,000
Recovered	$R(0)$	16,000,000
Total population	$N(0)$	300,705,643

Positive Solutions

The mathematical model (1) has been designed for a relative short period, since the behavior of people reluctant to be vaccinated has not been taken into account and this affects the long term dynamics in a crucial way. Despite the mathematical analysis presented in this subsection being more devoted to long term dynamics, it still helps to provide insights into the dynamics of the COVID-19 pandemic, especially the initial part. Thus, we decided to include a brief mathematical analysis of the first proposed model (1). From a fundamental theory of differential equations (see [111,112]), the solution of system (1) exists and it is unique for the initial conditions given by (2). Indeed, the system (1) can be written as $\dot{\mathcal{X}}(t) = F(t, \mathcal{X}(t))$, and it is represented by vector notation as

$$\dot{\mathcal{X}}(t) = (\dot{S}_1(t), \dot{V}_1(t), \dot{V}_{A_1}(t), \dot{V}_{I_1}(t), \dot{A}_1(t), \dot{I}_1(t), \dot{S}_2(t), \dot{V}_2(t), \dot{V}_{A_2}(t), \dot{V}_{I_2}(t), \dot{A}_2(t), \dot{I}_2(t), \dot{R}(t))^t, \quad (4)$$

$$F(t, \mathcal{X}) = \begin{pmatrix} -\lambda(t)S_1(t) - v_1S_1(t) \\ -(1-\epsilon)\lambda(t)V_1(t) + v_1S_1(t) \\ a(1-\epsilon)\lambda(t)V_1(t) - \gamma V_{A_1}(t) \\ (1-a)(1-\epsilon)\lambda(t)V_1(t) - \gamma V_{I_1}(t) \\ a\lambda(t)S_1(t) - \gamma A_1(t) \\ (1-a)\lambda(t)S_1(t) - \gamma I_1(t) \\ -v_2S_2(t) - \lambda(t)S_2(t) \\ v_2S_2(t) - (1-\epsilon)\lambda(t)V_2(t) \\ a(1-\epsilon)\lambda(t)V_2(t) - \gamma V_{A_2}(t) \\ (1-a)(1-\epsilon)\lambda(t)V_2(t) - \gamma V_{I_2}(t) \\ a\lambda(t)S_2(t) - \gamma A_2(t) \\ (1-a)\lambda(t)S_2(t) - \gamma I_2(t) \\ \gamma(1-\delta_1)I_1(t) + \gamma(1-\delta_2)I_2(t) + \gamma(1-\delta_{V_1})V_{I_1}(t) \\ + \gamma(1-\delta_{V_2})V_{I_2}(t) + \gamma(V_{A_1}(t) + A_1(t) + V_{A_2}(t) + A_2(t)) \end{pmatrix}, \quad (5)$$

and the initial conditions showed in (2). We use the following theorem:

Theorem 1. Suppose Ω is an open set in $\mathcal{R} \times \mathbb{R}^n$, and $F : \Omega \rightarrow \mathcal{R}^n$ is continuous, and $F(t, \mathcal{X})$ is locally Lipschitz in $\mathcal{X}$ in each open set in Ω . Then for each $(\mathcal{X}_0, t_0) \in \Omega$ there exists a unique solution of the initial value problem (1) in some open interval containing t_0 .

Proof. See [112] (p. 10). $\square$

Let $\mathcal{S} = C([0, \infty), \mathbb{R}_+^{13})$ be the Banach space of continuous functions mapping the interval $[0, \infty)$ into $\mathbb{R}_+^{13}$ with the sup-norm. The function F given by (5) is defined in

$F : [0, \infty) \times \mathbb{R}_+^{13} \rightarrow \mathbb{R}^{13}$ and is continuous satisfying a local Lipschitz condition. Indeed, if $\psi_1, \psi_2 \in \mathcal{C} \subset \mathcal{S}$, $\mathcal{C}$ being a compact set,

$$\begin{aligned}\psi_1 &= (S_1^1(t), V_1^1(t), V_{A_1}^1(t), A_1^1(t), I_1^1(t), S_2^1(t), V_2^1(t), V_{A_2}^1(t), V_{I_2}^1(t), A_2^1(t), I_2^1(t), R^1(t))^t, \\ \psi_2 &= (S_1^2(t), V_1^2(t), V_{A_1}^2(t), A_1^2(t), I_1^2(t), S_2^2(t), V_2^2(t), V_{A_2}^2(t), V_{I_2}^2(t), A_2^2(t), I_2^2(t), R^2(t))^t,\end{aligned}$$

and $0 < a < b$ such that $t \in [a, b]$, we obtain that

$$\|F(t, \psi_1) - F(t, \psi_2)\| \leq \mathcal{K} \|\psi_1 - \psi_2\|,$$

where $\mathcal{K} > 0$. Then, by Theorem 1 for any $\psi \in \mathcal{S}$ there exists a unique solution $\mathcal{X}(t, \psi)$ of the system (1) such that $\mathcal{X}_0 = \psi$. Since the system of equations given by (1) represents a model of populations from the biological point of view, its solutions must be positive for all positive initial conditions according to (2). Therefore, positivity and boundedness of the solution $X(t)$ of the system (1) in $[0, \infty)$ must be guaranteed. Now, we will show these properties in the following statements.

Theorem 2. *Given the initial conditions $\mathcal{X}(0) > \mathbf{0}$ of the mathematical model (1), the solutions $\mathcal{X}(t)$ of the system (1) are positive for all $t \in [0, \infty)$.*

Proof. From the first equation of system (1), one gets that

$$S_1(t) = S_1(0) \exp \left(- \int_0^t \left[\frac{\lambda(t)}{N} + v_1 \right] dt \right). \quad (6)$$

Therefore, $S_1(t) > 0$ if $S_1(0) > 0$. Thus, from the second equation of system (1), it follows that

$$\dot{V}_1 > -(1 - \epsilon)\lambda(t) \frac{V_1}{N}.$$

Applying the Gronwall inequalities, we obtain that

$$V_1(t) \geq V_1(0) \exp \left(-(1 - \epsilon) \int_0^t \left[\frac{\lambda(t)}{N} \right] dt \right). \quad (7)$$

Accordingly, $V_1(t) > 0$ for $V_1(0) > 0$. In the same way, we can prove that $S_2(t) > 0$ if $S_2(0) > 0$ and $V_2(t) > 0$ for $V_2(0) > 0$. On the other hand, from the equations (third-sixth) and (ninth-twelfth) of model (1) we have

$$\dot{\lambda}(t) = \lambda(t)(p(t) - \gamma),$$

where

$$\begin{aligned}p(t) &= a(1 - \epsilon)\beta_{V_{A_1}} \frac{V_1(t)}{N} + (1 - a)(1 - \epsilon)\beta_{V_{I_1}} \frac{V_1(t)}{N} + a\beta_{A_1} \frac{S_1(t)}{N} + (1 - a)\beta_{I_1} \frac{S_1(t)}{N} \\ &\quad + a(1 - \epsilon)\beta_{V_{A_2}} \frac{V_2(t)}{N} + (1 - a)(1 - \epsilon)\beta_{V_{I_2}} \frac{V_2(t)}{N} + a\beta_{A_2} \frac{S_2(t)}{N} + (1 - a)\beta_{I_2} \frac{S_2(t)}{N}.\end{aligned}$$

Therefore,

$$\lambda(t) = \lambda(0) \exp \left(\int_0^t (p(s) - \gamma) ds \right).$$

Since

$$\lambda(0) = \frac{1}{N} \left(\beta_{I_1} I_1(0) + \beta_{A_1} A_1(0) + \beta_{I_2} I_2(0) + \beta_{A_2} A_2(0) + \beta_{V_{I_1}} V_{I_1}(0) \right. \\ \left. + \beta_{V_{A_1}} V_{A_1}(0) + \beta_{V_{I_2}} V_{I_2}(0) + \beta_{V_{A_2}} V_{A_2}(0) \right),$$

is positive, $\lambda(t) > 0$ for $t \geq 0$. Next, taking the third equation of system (1) and if we suppose that exists a $t_1 > 0$ such that $V_{A_1}(t_1) = 0$ and $\dot{V}_{A_1}(t_1) \leq 0$, one gets

$$0 \geq \dot{V}_{A_1}(t_1) = a(1 - \epsilon)\lambda(t_1) \frac{V_1(t_1)}{N} - \gamma V_{A_1}(t_1) = a(1 - \epsilon)\lambda(t_1) > 0.$$

which is a contradiction. Hence, $V_{A_1}(t) > 0$ for all $t > 0$. With this methodology we can prove that $V_{I_1}(t) > 0$, $A_1(t) > 0$, $I_1(t) > 0$, $V_{A_2}(t) > 0$, $V_{I_2}(t) > 0$, $A_2(t) > 0$, $I_2(t) > 0$ for all $t \geq 0$. Furthermore, $R(t) > 0$ for $t \geq 0$. $\square$

Note: The second mathematical model considers that the amount of vaccine available per day is fixed and the terms $v_1 S_1$ and $v_2 S_2$ are replaced by v_1 and v_2 . Therefore, positivity and boundedness cannot be guaranteed for the second model. However, in practice some part of the population will not be vaccinated and using a relative initial short period of study avoids negative subpopulations.

3. Results

We performed in silico simulations with various scenarios in order to provide a great spectrum of health outcomes under different circumstances. We varied the vaccination pace, transmissibility (to consider different SARS-CoV-2 variants and different social behaviors) and vaccine efficacy (to consider different brands and variants). The transmission rate of SARS-CoV-2 varies depending on non-pharmaceutical interventions and social behavior. We considered two main cases regarding the transmission rate, one with high transmission and another with low transmission. Both cases had constant transmissibility. The numerical simulations were based on the mathematical model (1), and we computed the number of deaths under different scenarios. Table 1 shows the initial conditions and Table 2 the numerical values of the parameters.

Table 2. Parameters' values used in the simulations.

Parameter	Symbol	Value (Days)
Infectious period	$1/\gamma$	7 days [113]
Case fatality ratio (rate) age group 1	δ_1	≈ 0.01 [114]
Case fatality ratio (rate) age group 2	δ_2	≈ 0.1 [114]
Case fatality ratio (rate) vaccinated age group 1	δ_{V1}	$(1 - \epsilon)\delta_1$ assumed [114]
Case fatality ratio (rate) vaccinated age group 2	δ_{V2}	$(1 - \epsilon)\delta_1$ assumed [114]
Probability of being asymptomatic	a	0.5 [2,115]
Efficacy of the vaccines	ϵ_i	90% Varied
Vaccination rate for age group i	v_i	Varied
Fixed number of vaccines	$v_1 + v_2 \approx 1.5 \times 10^6$	Varied

We performed a variety of numerical simulations with different efficacies for the vaccines in order to consider the different types of vaccines and the fact that SARS-CoV-2 variants affect the efficacy of the vaccines. In addition, we considered a variety of inoculation rates, but assumed that these rates were constant over the period of study.

3.1. Scenarios with Proportional Vaccination Rates

The first scenario that we considered is when the vaccination program features a proportional vaccination rate. In this type of program there are more vaccinations of susceptible individuals at the beginning of the period of study. Thus, the maximum number of

doses are required when the vaccination program starts. Figure 3 shows the dynamics of several subpopulations without a vaccination program. The susceptible subpopulations S_1 and S_2 decrease due to the fact that susceptible people get infected and transit to the infected subpopulations (either symptomatic or asymptomatic). The infected subpopulations decrease, since the transmission rate in this scenario is low and the situation is under epidemic control. Figure 4 shows the dynamics of several subpopulations with a proportional vaccination rate program. It can be observed that the susceptible subpopulations S_1 and S_2 decrease faster than the previously considered case since now susceptible individuals transit to the vaccinated subpopulations (V_1 or V_2) and people are still getting infected (but less since there are less susceptible individuals).

Figure 3. Dynamics of several subpopulations without a vaccination program.

Figure 4. Dynamics of several subpopulations with a proportional vaccination rate program. This scenario considers a transmission rate such that the basic reproduction number $\mathcal{R}_0$ is greater than one. We consider a vaccine efficacy of 90%, vaccination rate for age group one (v_1) of 0.05 and vaccination rate for age group two (v_2) of 0.066.

Figure 5 shows the number of deaths and infected individuals from the two different age groups. This scenario considers that the transmission rate of people in the 55+ age group is half of the transmission rate of 15–54 years-old due to the fact that older people in general take more protective measures against getting the virus. In addition, the values of the transmission rate β and the proportion of vaccine devoted to each age group were varied. We considered a vaccine efficacy of 90%, a maximum constant proportional vaccination rate for age group one of $v_1 = 0.05$ and for age group two $v_2 = 0.01$. The rate is higher for 55+ age group in order to take into consideration that there are fewer people in that age group, and therefore, a greater proportion of this subpopulation can be vaccinated under the assumption of limited vaccines. It can be seen, as expected, that increasing

the proportion of vaccinated people for either age group reduces the number of deaths. Moreover, it reduces the number of infected people for each age group. If the proportion v_1 is increased, the number of infected people from age group 1 is reduced more than the number of infected people of the 55+ age group. Conversely, if the proportion v_2 is increased, the number of infected people from the 55+ age group is reduced more than the number of infected people of the 15–54 age group. These results are intuitively correct, but our aim was to find the optimal allocation of vaccines for each age group. Using a constant proportion vaccination rate does not allow one to consider a fixed amount of vaccines per unit time due to the changes in the sizes of the susceptible populations $S_1(t)$ and $S_2(t)$. Despite this, Figure 5 shows that more deaths are averted when the constant proportion vaccination rate v_2 is increased. Thus, the results suggest that first allocating more vaccines to the 55+ age group is better in order to avert more deaths.

Figure 5. Number of deaths and infected individuals from the two different age groups. This scenario considers that the transmission rate of people in the 55+ age group is half of the transmission rate of 15–54 years-old. Vaccine efficacy is assumed 90%, $v_1 = 0.05$ and $v_2 = 0.01$.

Figure 6 shows the number of vaccinated individuals from the 55+ age group at the end of simulation and the total number of vaccinated for each age group. As expected, the vaccinated people for each age group increases uniformly as the constant vaccination rate increases for each age group, respectively. This uniformity does not occur for the infected people in each age group, as can be observed in Figure 5. This is due to the fact that even if the vaccination program does not allocate vaccines for one of the age groups, the number of deaths for that particular age group is reduced, since fewer people from the other group are going to be able to spread the virus. This is what can be called collective societal benefits of vaccinations, and it is related to herd-immunity.

Figure 6. Number of vaccinated individuals from the 55+ age group at the end of simulation and the total number of vaccinated for each age group. The transmission rate of people in the 55+ age group is half of the transmission rate of 15–54 years-old. Vaccine efficacy is assumed 90%, $v_1 = 0.05$ and $v_2 = 0.01$.

3.2. Scenarios with Fixed Numbers of Vaccines

Now, we consider a more realistically accurate vaccination program where the number of vaccines available per unit time is limited or fixed. Thus, the aim is to find the optimal allocation per unit time for this fixed amount of vaccine for each age group. In this case the mathematical model (1) just needs a small change. This alternative model has the same subpopulations, but the terms $v_1 S_1$ and $v_2 S_2$ are replaced by v_1 and v_2 . Thus, we achieve a constant fixed number of vaccines per day. We study here more scenarios than in the previous section since this situation is closer to reality with regard to number of

inoculations per day. We consider different scenarios varying the allocation of vaccines for each age group, the transmission rate with low and high transmission, vaccination pace, the probability of infection for 55+ age group with respect to the 15–54 age group and finally the efficacy of the SARS-CoV-2 vaccine. All these factors vary for each region or country, and thus the qualitative analysis presented here allows the consideration of different situations related to different countries. As has been mentioned, the main metric used here to measure the optimality of the vaccine program is the number of deaths under each vaccination strategy. Next we will evaluate different scenarios considering always a parameter p ($0 \leq p \leq 1$) that denotes the proportion of vaccines allocated to 55+ age group. Conversely, the proportion of vaccines allocated for 15–54 age group is given by $1 - p$; thus a value of $p = 1$ means that all the available vaccines are allocated to 55+ age group.

3.2.1. Scenarios Varying Vaccination Pace

The first scenario that we consider is varying the vaccination pace which translates on varying the amount of vaccines inoculated per unit time (per day) and as well the allocation of vaccines to each age group. Figure 7 shows the number of deaths and the cumulative number of infected people for each age group. We can see that if the proportion of vaccines allocated for one age group is increased then the number of infected people for that specific age group increases. However, the main finding is that increasing the proportion of inoculations in the 55+ age group decreases the total amount of deaths due to SARS-CoV-2. This result suggest that the optimal vaccination program should vaccinate first the people from 55+ age group. The explanation for this is that these people have a higher case fatality rate (CFR). We need to keep in perspective that in this scenario the mathematical model assumes that the probability to get infected for people from 55+ age group is half of that of 15–54 age group. We will vary this probability in other scenarios in order to provide more insightful analysis. Figure 8 shows the number of deaths and the cumulative number of infected people for each age group, but now with a higher SARS-CoV-2 transmission. In this case for low vaccination paces ($\approx 200,000$ – $400,000$ doses per day) the optimal allocation of vaccines is not to first inoculate individuals from the 55+ age group. However, the total number of deaths does not vary significantly when the vaccines are allocated in different proportions among the the age groups. On the other hand, for high vaccination paces ($> 800,000$ doses per day) the optimal strategy to avert more deaths is to allocate the vaccines to people in the 55+ age group. Thus, these scenarios show that the optimal vaccine strategy varies depending on the vaccination pace and the SARS-CoV-2 transmission.

Figure 7. Total number of deaths and the cumulative number of infected people for each age group. This scenario considers a relatively low SARS-CoV-2 transmission rate and vaccine efficacy of 90%. The factors that are varied are the vaccination pace and the proportion of vaccines allocated to each age group.

Figure 8. Total number of deaths and the cumulative number of infected people for each age group. This scenario considers a relatively high SARS-CoV-2 transmission rate and vaccine efficacy of 90%. The factors that are varied are the vaccination pace and the proportion of vaccines allocated to each age group.

3.2.2. Scenarios Varying the Transmission Rate of the 55+ Age Group

The second scenario that we consider is varying the transmission rate of age group 55+ under a low SARS-CoV-2 transmission rate. Figure 9 shows the total number of deaths and the cumulative number of infected people for each age group. We can see on the y-axis the ratio of transmission rate of 15–54 age group and 55+. Thus, the ratio $r = 4$ means that the SARS-CoV-2 transmission rate of 55+ age group is 25% of the one of 15–54 age group. In this case the optimal strategy is to first allocate the vaccines to people in the 55+ age group. Figure 10 shows the case when the SARS-CoV-2 transmission is relatively high. In this case for a large ratio r the optimal strategy is to first vaccinate the people in 15–54 age group. This strategy is the opposite to what some countries have done. On the hand, for low ratio r the optimal strategy to avert more deaths is to allocate the vaccines to people in the 55+ age group. This is explained by the fact that under a high contagiously SARS-CoV-2 and individuals in the 55+ age group highly protected it is better to avoid infections of individuals in 15–54 age group since they are able to spread SARS-CoV-2 faster and then cause more deaths. Thus, having a highly contagious SARS-CoV-2 variant can affect which is the optimal strategy. With regard to total infected cases, the results are similar to those for total deaths.

Figure 9. Total number of deaths and the cumulative number of infected people for each age group. This scenario considers a relatively low SARS-CoV-2 transmission rate. The factors that is varied is the transmission rate of 55+ age group.

Figure 10. Total number of deaths and the cumulative number of infected people for each age group. This scenario considers a relatively high SARS-CoV-2 transmission rate. The factor that is varied is the transmission rate of 55+ age group.

We included one more scenario with higher SARS-CoV-2 transmission to see more clearly how the optimal vaccine strategy varies. Figure 11 shows that the larger the ratio r ,

the more clear it becomes that the optimal strategy is to first vaccinate the people in the 15–54 age group.

Figure 11. Total number of deaths and the cumulative number of infected people for each age group. This scenario considers a high SARS-CoV-2 transmission rate. The factor that is varied is the transmission rate of 55+ age group.

3.2.3. Scenarios Varying SARS-CoV-2 Transmission Rate

The third scenario that we consider is varying the SARS-CoV-2 transmission rate for all age groups. Figure 12 shows the total number of deaths and the cumulative number of infected people for each age group when the transmission ratio is $r = 2$ (transmission rate of 55+ age group is 50%). In this case it is clear that when SARS-CoV-2 transmission rate is not high the the optimal strategy is to first allocate the vaccines to people in the 55+ age group. Figure 13 shows the case when the ratio is $r = 10$. The optimal strategy is still to first vaccinate the people in the 55+ age group. However, the worst outcome is when the allocation of the first vaccines is approximately even (50–90% for the 55+ age group) for both age groups. This result is important for designing the most suitable vaccination strategy.

Figure 12. Total number of deaths and the cumulative number of infected people for each age group. This scenario considers a ratio $r = 2$. The factor that is varied is the SARS-CoV-2 transmission rate.

Figure 13. Total number of deaths and the cumulative number of infected people for each age group. This scenario considers a ratio $r = 10$. The factor that is varied is the SARS-CoV-2 transmission rate.

3.2.4. Scenarios Varying the Efficacy of the Vaccine

The last scenario that we consider is varying the efficacy of the vaccine against SARS-CoV-2 under a relatively high SARS-CoV-2 transmission rate. Figure 14 shows clearly that the optimal strategy is to first allocate the vaccines to people in the 55+ age group. Figure 15 shows the case when the ratio $r = 4$ (transmission rate of 55+ age group is 25%), and the optimal strategy is still to first vaccinate the people in the 55+ age group. However, it can be seen that the worst strategy is to allocate approximately evenly the vaccines between the people of both age groups. This result is important from a public health point of view,

since some countries have implemented similar strategies to allocate the vaccines. Thus, some countries might be causing the worst scenario for averting deaths.

Figure 14. Total number of deaths and the cumulative number of infected people for each age group. This scenario considers a ratio $r = 2$. The factor that is varied is the efficacy of the vaccine.

Figure 15. Total number of deaths and the cumulative number of infected people for each age group. This scenario considers a ratio $r = 4$. The factor that is varied is the efficacy of the vaccine.

4. Discussion and Conclusions

Many countries have strong vaccination campaigns, and large proportions of their populations are fully vaccinated. However, not all countries have well advanced vaccination programs [2,42,101,116–119]. For instance, at this time countries such as Afghanistan, Algeria, Haiti and Turkmenistan have less than 10% of their populations fully vaccinated. Different vaccination campaigns produce different public health outcomes [25,45,51,54,55,69]. The design of an optimal vaccination strategy is a complex problem, since there are many factors that affect the spread of SARS-CoV-2. There are vaccination campaigns that first allocate vaccines to health care workers or elderly people [97]. Thus, governments have implemented a variety of vaccination campaigns.

In this study, we constructed two mathematical models to study the optimal allocation of vaccines between the 15–54 and 55+ age groups. We varied several factors that affect public health outcomes of the vaccination programs. The factors that considered in this study were vaccine availability, vaccine efficacy, SARS-CoV-2 transmission rate, SARS-CoV-2 transmission rate of the 55+ age group and vaccination pace. We assessed the vaccination strategies using cumulative mortality and cumulative infective for each age group. The study of COVID-19 vaccination strategies is crucial to diminish the hospitalizations and deaths related to the COVID-19 pandemic [25,50,51,55,105,120,121].

For most of the scenarios we fixed the efficacy of the vaccine as 90%, even though it has been estimated that two of the most popular vaccines such as Pfizer-BioNTech and Moderna have an efficacy of approximately 95% [50]. It is important to mention that in reality the transmission rate under the current COVID-19 pandemic varies over time. Making a study with a time dependent SARS-CoV-2 transmission rate is extremely complex due to the high variability of social behavior of people. However, this behavior is more stable after more than year into the pandemic. Mathematical models in conjunction with in silico simulations give useful insights regarding the optimal vaccination strategy. In general in this study we considered two SARS-CoV-2 transmission rate scenarios: one with a relatively low one and another one with high. This, helps to apply the results of this study to a variety of countries.

Using two mathematical epidemiological models based on differential equations, we found that for most scenarios the optimal allocation of vaccines is to give the first doses to people in the 55+ age group. This result agrees with previous studies that used a different

mathematical approach [49,122]. However, in particular situations the optimal strategy is to allocate vaccines to the 15–54 age group. This situation occurs whenever the SARS-CoV-2 transmission rate is relatively high and the people in the 55+ age group have a transmission rate 50% or less than that of the 15–54 age group. Another important situation that we found is that when the allocation of vaccines is approximately even between the two age groups, the worst results arise regarding the number of deaths. It is important to remark that despite this result, some countries have implemented this strategy.

The variations in the optimal strategy under different scenarios are partially due to the nonlinearity of the spread of the SARS-CoV-2 and the mathematical model. These nonlinearities have been correctly taken into account in previous studies [51,54,55].

The results presented here are qualitative and are not forecasts about the number of deaths for particular countries. Previous results have proven that accomplishing an accurate forecast regarding the outcomes of the COVID-19 pandemic is a very challenging problem due to the high variability of the social behavior of people [4,20,22–24,123,124]. Besides, including in the numerical simulations accurate vaccination rates is an extremely difficult task due to changes in government policies, the approval of new vaccines and accounting for the resources available for vaccine distribution. Nevertheless, we varied the vaccination rate in order to provide useful information towards improving and designing better vaccination campaigns.

The numerical simulations presented in this study considered a short time period. Thus, these did not deal with the complication of the resistance of a certain sector of the population to getting vaccinated [18,70,125,126].

As in any study involving mathematical models, there were natural limitations due to various reasons including the complexity of the real world. The results of using mathematical models are dependent on the assumptions and the underlying data. Thus, it is important to mention the limitations and hypotheses to avoid reaching wrong conclusions. Nonetheless, the findings are useful to scientifically support health policies [53,127–134]. The models presented here have some assumptions. One important one is that inoculation rates and SARS-CoV-2 transmission rates are time-invariant. We assumed that a steady state of social behavior had been reached before the start of the vaccination campaign, and was maintained during the simulation. The mathematical models presented here do not include demographic factors due to the short time period of study [135,136]. The period of study was assumed to be shorter than one year due to several factors—for instance, the waning of vaccine efficacy and natural immunity. In addition, we did not take into account the resistance of some people to getting vaccinated. If the waning of natural immunity against the SARS-CoV-2 is taken into account, then the developed mathematical models need to be changed. Similarly, if the protection of the vaccine is shorter than 8 months, the model presented here needs to be modified. In summary, more complex mathematical models are necessary to consider the appearance of new SARS-CoV-2 variants and waning immunity [21,54].

The results of this study provide scientific guidelines for countries where vaccination programs are starting or the percentage of vaccinated people is small. The results presented here are based on measuring certain public health outcomes, such as cumulative mortality and cumulative infected. The results presented here help to design optimal vaccination programs under constraints in the vaccine availability.

Finally, the results obtained in this work encourage health authorities to identify which scenario they have before designing the vaccination program. It has been suggested that age groups at higher risk also should be prioritized [55]. However, that vaccination program does not always produce optimal results. Future work should include further analysis of different vaccination programs and other mathematical models to consider other heterogeneities, such as comorbidities. Moreover, depending on ongoing research about the efficacy of the SARS-CoV-2 vaccine, future studies might require considering the waning of the immunity.

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