Improving the worldwide vaccination plans for COVID-19: a comparison of alternative strategies

Joana Correia Rodrigues, joana.s.rodrigues@tecnico.ulisboa.pt
Instituto Superior Técnico, Lisboa, Portugal

Abstract

COVID-19 appeared in December 2019 and quickly spread globally. Although a vaccination campaign started in December 2020, and despite efforts such as COVAX, access to vaccines was unequal across countries. The aim of this study is to quantify and compare the direct health impact of considering global alternative allocation strategies of the available supply of vaccines with different prioritization mechanisms: 1) Age-based demographic prioritization; 2) Case-based epidemiological prioritization; 3) Mixed demographic and epidemiological prioritization.

To achieve this goal, an analysis using country-specific epidemiological data and vaccine effectiveness estimates was performed to compute the alternative number of infections and deaths until the end of 2021 for each strategy. Sensitivity analyses varying vaccine effectiveness were additionally performed.

Among the tested strategies, epidemiological prioritization produced the best results [30.9% (23.7 to 39.6) of infections and 61.6% (50.4 to 75.8) of deaths avoided], allowing for a 5.6% reduction in mortality when compared to the observed vaccine allocation. Contrarily, demographic prioritization yielded the worst results [21.4% (16.1 to 28.5) of infections and 55.4 % (44.7 to 71.2) of deaths avoided].

This study, the first of its kind, proposes an innovative strategy for vaccine allocation that may be superior to the observed distribution, reinforcing the role and articulation of national and international health organizations. These findings have the potential to lead to new global strategies which will be of utmost importance not only for future pandemics, but also for the distribution of new vaccines for the control of SARS-CoV-2 and other viruses' genetic variants.

Keywords: COVID-19, COVID-19 Vaccination, Alternative Strategies, Prioritization Strategies, Global Access, Equity

I BACKGROUND

Coronavirus disease 2019 (COVID-19), a disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the seventh human coronavirus [1], appeared in December 2019, in China. Only 3 months later, on 11 March 2020, the World Health Organization (WHO) declared COVID-19 a pandemic [2] and it has now spread to nearly every country in the world. As of 24 October 2022, there have been 624 235 272 confirmed cases of COVID-19, including 6 555 270 deaths, reported to the WHO [3].

Vaccines have proven to be of extreme importance when managing diseases, by reducing illness and hospitalizations as well as other indirect effects, such as mitigating transmission, and even eradicating some diseases [4]. As waiting for natural herd immunity would take way too long, a quick worldwide immunization program against this pandemic was seen as the finest choice to quicken the reduction of populations' health susceptibility and diminish the social and financial results of COVID-19 widespread. Consequently, a massive global effort was made to discover and produce a vaccine against COVID-19 as quickly as possible.

Since the start of vaccine development, it was clear that in addition to COVID-19 vaccinations, there was also a need to make sure that everyone in the world had access to vaccination in order to put an end to this global public health crisis. That idea was the foundation upon which COVAX was developed. COVAX is the vaccines pillar of the Access to COVID-19 Tools (ACT) Accelerator, an international partnership to hasten the creation of COVID-19 diagnostics, treatments and vaccines as well as ensure equal access to them [5].

On 8 December 2020, the first COVID-19 vaccine was administered to a patient in the United Kingdom [6], marking the beginning of a global immunization process. However, with the model for vaccine distribution being based on an economical competition between countries for limited vaccines, not all countries' have had the same access. Even COVAX struggled to purchase any vaccines and was forced to wait on voluntary donations from high income countries (HICs), failing to achieve its target of having 20% of its target population vaccinated at the end of 2021. Due to the low-income countries' (LICs) shallow economic power and scarce resources, these are mostly dependent on COVAX. Thus, during 2021, HICs had already immunized 75-80% of their population while LICs had only been able to immunize less than 10% [7].

When dealing with a limited supply of vaccines, it is critical to consider worldwide access. Vaccination provides more than just immediate health advantages. For example, it battles some of the socioeconomic consequences of COVID-19 while simultaneously allowing for the virus's spread to be slowed. If the virus continues to spread due to a lack of immunizations in critical areas, there is a larger likelihood that new genetic variations may emerge [8]. Additionally, it is important to analyse which is the strategy of allocation that allows for better outcomes. The WHO has proposed a fair allocation framework for the distribution of vaccines through the COVAX facility in which all countries receive doses in proportion to their population size [9]. However, other prioritization strategies that do not allocate proportionally but are based on the containment of the virus may be more effective.

Several studies have already addressed the matters of the estimation the health impact of the observed vaccine allocation strategy or the comparison strategies of vaccination against COVID-19.

At an international level, Watson et al. [10] estimated the global impact of the first year of vaccination and evaluated how many additional deaths would be prevented by assuring that vaccination would achieve the targets set by COVAX and WHO, i.e., 20% and 40% of the eligible population fully vaccinated globally, respectively. Meslé et al. [11] estimated the number of deaths directly averted in people of 60 years and older as a result of COVID-19 vaccination in the WHO European Region. Numerous other studies evaluated the impact of observed vaccination at the national or regional level [12–17].

Kim and Lee [18] compared real-world epidemiological data from different countries using different strategies of vaccination and vaccines. Both Chapman et al. [19] and Zhou et al. [20] tested different strategies for the allocation of vaccines locally and concluded that the strategy that achieved the best results was when prioritizing vaccination by age and location. Castonguay et al. [21] shows that even though the *ad hoc* principle for vaccine allocation between two areas is that of equity in distribution, there are potential economic and public health benefits in deviating from this allocation, considering equity of outcomes.

However, at the time of writing (September 2022), no studies available focused on the comparison of alternative scenarios for the allocation of vaccines at a global scale. Thus, this study aims to quantify the global health impact of alternative strategies for vaccine allocation and compare them to the observed allocation strategy. Particularly, it aims to study the direct effects of considering demographic and epidemiological prioritization strategies for the distributions of a limited supply of vaccines, considering that there are no border or economic constraints.

According to these objectives, the strategies considered comprise global distributions of vaccines considering: 1) age-based demographic prioritization, 2) case-based epidemiological prioritization and 3) mixed demographic and epidemiological prioritization.

The quantification and comparison of health outcomes will be done by assessing the counterfactual numbers of cases and deaths, based on the direct effect of vaccines.

II METHODOLOGY

The entirety of the analysis was performed using Software R version 4.0.3.

A *Input Data*

The analysis is based on COVID-19 epidemiological and vaccination data available from public data sources. Data were collected from ISO Week 50 of 2020 (start of vaccination) until the end of 2021, for the 180 countries and territories included. Data were structured by weeks and age groups (0-24, 25-49, 50-59, 60-69, 70-79, 80+), in the time period mentioned.

Cases and Deaths

Data regarding cases and deaths were retrieved from two public datasets:

- WHO COVID-19 Detailed Surveillance Data [3];
- Our World in Data (OWID) COVID-19 dataset [22].

WHO data were prioritised as these allowed for weekly counts of cases and deaths by age group, whereas OWID data were not broken down by age group. OWID data were then used for countries that were not included in the WHO dataset or where the number of cases and deaths was significantly lower in the WHO dataset compared to the OWID dataset due to the need of reporting by age group. Then, in countries where OWID data were used, it was necessary to infer the breakdown of total weekly cases and deaths by age group. For this, a weekly distribution pyramid of cases and deaths by age group for each country was used, either based on the age and sex pyramids of cases and deaths for the country, if available, or for the WHO Region, retrieved from the WHO COVID-19 Detailed Surveillance Data Dashboard [3].

Vaccine Uptake

Data regarding vaccine uptake were retrieved from two public datasets:

- European Centre for Disease Prevention and Control (ECDC) – Data on COVID-19 vaccination in the European Union/European Economic Area (EU/EEA) [23];
- OWID COVID-19 dataset [22].

Data from the ECDC dataset were used for the 30 countries in the EU/EEA, and OWID data were used for the rest of the countries. In countries where the vaccine uptake was not sorted out by age group this distribution was inferred, considering that priority groups (health workers, immunocompromised individuals, essential workers, etc.) are vaccinated first, according to the WHO SAGE Roadmap for prioritizing uses of COVID-19 vaccines [24] and then the distribution of vaccines follows an age-descent order. Age groups were assumed completely vaccinated when 90% of its population was vaccinated, to model vaccine hesitancy. Furthermore, when information regarding vaccine manufacturer was not available, a vaccine manufacturer was drawn based on the probability distribution of vaccines by manufacturer of the country. When this distribution was not available, vaccine manufacturers were considered to follow a discrete uniform distribution.

Vaccine Efficacy/Effectiveness

Based on available studies [25–31], there is a substantial waning of Vaccine Effectiveness (VE) in the time period of the study (i.e., over 1 year), so it was considered time-varying. Hence, functions of VE according to week after vaccination, $VE(w)$, both against infection and death, were estimated based on literature [25–38]. A function of VE was used for each of the vaccine manufacturers. Due to the absence of studies, for Inactivated and Protein Subunit vaccines, only one function of VE was made for each these types, instead of manufacturers. Due to lack of data, the following assumptions were additionally made:

- When available, real-world studies that estimated vaccine effectiveness were prioritized. Only when these were not available for the vaccine manufacturer or type in cause, vaccine efficacy estimates from clinical trials were used.
- When the effectiveness waning after the second dose was not available for the whole period of the study, the rest of the VE data points were linearly estimated given the slope of existing data between maximum VE and VE from the last known week from literature.
- Booster shots were considered to have the same waning and replenish effectiveness as a second dose. The first dose is also considered to have the same waning as the second dose.
- VE was considered the same across age groups, across countries and across COVID-19 genetic variants.

The major assumption of this analysis is that only the direct effect of vaccination is considered. Although vaccine effectiveness represents the real-world effect of the vaccines and some authors argue that it also captures some indirect effects [39–41], when evaluating the impact of observed vaccination, the estimate provided by this model is conservative as the indirect effect of vaccination is not taken into account. It is expected that the number of averted events from observed vaccination is even higher, as the vaccine also contributes to a reduction in transmission.

Countries Socio-demographic Information

The population of each country along with its age and sex distribution was retrieved from United Nations – World Population Prospects 2019 [42]. Data regarding income group classification were retrieved from The World Bank [43].

B Alternative Scenarios

Three alternative strategies for the global allocation of vaccines against COVID-19 are considered:

- *Strategy 1 - Age-based Demographic Prioritization*
  Each age group of each country receives vaccines proportionally to its population, and the vaccination follows an age-based prioritization starting by priority (at-risk) groups and then continuing in an age-descent order. Each week, the algorithm developed for the distribution of vaccines in this scenario allocates the limited supply of vaccines in the following order: second doses; boosters (exclusively for 60+ and at-risk individuals that have completed their vaccination scheme 6 months ago) and finally, first doses. This prioritization framework was based on the WHO SAGE Roadmap for prioritizing uses of COVID-19 vaccines [24].
- *Strategy 2 - Case-based Epidemiological Prioritization*
  Each week, vaccines are allocated to countries proportionally to the number of infections reported in the previous week. Then, in each country, vaccines are distributed in the population in an age-descent order giving priority to at-risk groups. In this strategy, countries with higher transmissibility are prioritized. Each week, the algorithm developed for the distribution of vaccines in this scenario allocates the limited supply of vaccines starting by second doses and then, first doses.
- *Strategy 3 - Both Demographic and Epidemiological Prioritization*
  Immunizing high-risk populations to decrease mortality, but also targeting areas where the transmission rates of COVID-19 are high, achieved the best results in some comparison studies [19, 20]. Thus, Strategy 3 aims to cover these two dimensions by allocating 50% of vaccines according to Strategy 1 and 50% of vaccines according to Strategy 2.

It is important to note that, each week, the number of vaccines available is the sum of vaccines that were given in the observed vaccination from all countries. Vaccine supply is not altered, vaccines are simply redistributed globally.

C Mathematical Formulation for Outcomes Estimation

Epidemiology textbooks [44, 45] give one definition for the impact of a protective factor in a population, denominated Population Prevented Fraction (PPF) and defined as in Equation 1. According to Porta [45], the PPF can be defined as *”the proportion of the hypothetical total load of disease (in the population) that has been prevented by exposure to the factor”*. In this case, the factor is the vaccine.

$$PPF = p(1 - RR) \tag{1}$$

Where:

- p is the proportion of population exposed to protection
- RR is the relative risk (or risk ratio)

This definition is the base of the model herein described to measure the impact of each of the vaccination scenarios considered. The number of events, either cases or deaths, that occur in a population with a certain vaccination, $Events(V)$, can be written considering the PPF and the number of events that would occur in a scenario of no vaccination, $Events(NV)$, as shown in Equation 2.

$$Events(V) = Events(NV) - Events(NV) \times PPF \tag{2}$$

The number of events in a scenario of no vaccination is calculated as shown in Equation 3 based on the number of events observed. Then, the number of events for each of the 3 alternative scenarios is calculated as shown in Equation 2.

$$Events(NV) = Events(V) \times \frac{1}{1 - PPF} \tag{3}$$

The PPF can be dissected as the PPF that come from each of the 4 different possible vaccine doses (Equation 4). The four different doses d correspond to the most well-known first and second doses as well as the first additional dose (or first booster) and the second additional dose (or second booster). Those doses are referred to as doses 1 to 4, respectively.

$$PPF = PPF_{d=1} + PPF_{d=2} + PPF_{d=3} + PPF_{d=4} \tag{4}$$

Considering a vaccine effectiveness VE against an event e and vaccine coverage VC, in a certain week w, the PPF from a certain dose d can be written as the sum of products of VE by VC for each of the past weeks and vaccine type/manufacturers v (Equation 5) [46]. In turn, VC can be written as the ratio between the number of individuals vaccinated and the number of individuals from that age group and country (N). It is also important to note that the number of events as well as the PPF are stratified by country and age group, so, such information is not displayed in the equations shown.

$$PPF_{d,w} = \sum_{i=1}^{w-1} \sum_{v} VE_{v,e,d}(i) \times \frac{N_{v,w-i,d}}{N} \tag{5}$$

$N_{v,w-i,d}$ corresponds to the number of individuals that took dose d from vaccine v in week $w - i$ and by the time PPF is being computed (week w) still haven't taken the next dose in the scheme, dose $d+1$.

Thus, the number of events in a counterfactual scenario of no vaccination can be calculated as in Equation 6. Note that the difference between estimating the number of cases or deaths is the consideration of different functions of VE.

$$\begin{gathered} Events(NV) = Events(V) \times \\ \frac{1}{1 - \sum_{d=1}^{4} \sum_{i=1}^{w} \sum_{v} VE_{v,e,d}(i) \times \frac{N_{v,w-i,d}}{N}} \end{gathered} \tag{6}$$

In turn, the number of events in alternative scenarios of vaccination is computed as in Equation 7.

$$\begin{gathered} Events(V) = Events(NV) \times \\ (1 - \sum_{d=1}^{4} \sum_{i=1}^{w} \sum_{v} VE_{v,e,d}(i) \times \frac{N_{v,w-i,d}}{N}) \end{gathered} \tag{7}$$

The number of events directly averted $Events(A)$ by the different COVID-19 vaccination programmes, country and age-stratified, can then be obtained by calculating the difference between the number of events obtained and the events estimated in the no vaccination scenario, shown in Equation 8.

$$Events(A) = Events(NV) - Events(V) \tag{8}$$

D Sensitivity Analysis

Taking into consideration the underlying uncertainty associated with vaccine effectiveness and the multiplicity of assumptions made regarding this variable, a uni-variate sensitivity analysis was performed by varying vaccine effectiveness by $+10$ and -10 percentage points, not going beyond the minimum and the maximum of 0% and 100% of vaccine effectiveness, respectively.

III RESULTS AND DISCUSSION

A summary of the results obtained for each scenario of vaccination can be seen in Table I. This table shows the number of events that would occur in each scenario, as well as the number of events observed, and the percentage of events that would be averted. This percentage is calculated based on the number of events that would occur in the counterfactual scenario of no vaccination. Additionally, this table shows the uncertainty intervals obtained from the sensitivity analysis, considering lower (-10%) and higher ($+10\%$) VE estimates.

In terms of directly averting infections, no alternative scenario of vaccination performed better than the observed. Contrarily, regarding directly averting fatalities, the strategy of case-based epidemiological prioritization (Strategy 2) out-performed the observed and was the best overall. The strategy of allocation of vaccines based on the age pyramid of each country (Strategy 1) was the worst performing strategy both for the prevention of cases and deaths. The reason behind the poor performance of this strategy may be related to the arguments advocated by Castonguay et al. [21]. While equality of distribution is prioritized using Strategy 1, there are benefits in deviating from this rule, in a way that is more closely aligned with another crucial principle, the equity of outcomes, taken into account in Strategy 2. Overall, the results obtained

Table I: Summary of the results by vaccination scenario with sensitivity intervals.

	Cases $(-/+10\%\ \mathrm{VE}^a)$	**Deaths** $(-/+10\%\ \mathrm{VE}^a)$
No Vaccination		
Number of Events	327 737 204 (295 315 489 – 382 658 201)	9 216 368 (7 096 037 – 16 982 890)
Observed		
Number of Events	222 373 578	3 746 908
Percentage of Events Averted	32.15% (24.7 – 41.89)	59.35% (47.2 – 77.94)
Scenario 1		
Number of Events	257 709 262 (247 900 730 – 273 465 228)	4 108 173 (3 925 301 – 4 890 508)
Percentage of Events Averted	21.37% (16.06 – 28.54)	55.43% (44.68 – 71.2)
Scenario 2		
Number of Events	226 636 064 (225 301 366 – 231 151 225)	3 538 144 (3520734 – 4 114 725)
Percentage of Events Averted	30.85% (23.71 – 39.59)	61.61% (50.38 – 75.77)
Scenario 3		
Number of Events	241 902 419 (236 419 044 – 251 896 879)	3 823 903 (3 722 487 – 4 508 971)
Percentage of Events Averted	26.19% (19.94 – 34.17)	58.51% (47.54 – 73.45)

[a] VE - Vaccine Effectiveness

in this study support results previously obtained by other authors which suggested that the pandemic has a degree of spatial heterogeneity which should be taken into account when allocating medical resources, such as vaccines [19–21]. However, the poor performance of Strategy 3 goes against the results obtained in some studies [19, 20]. It is important to note that those are regional studies, performed at a much smaller scale, where the degree of spatial heterogeneity of the severity of the pandemic is not as considerable as globally.

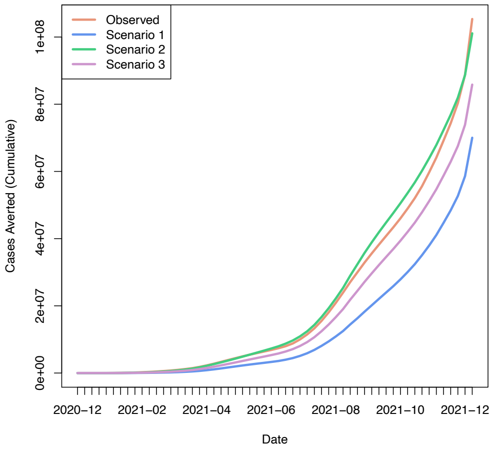
Uncertainty intervals show that the impact of these alternative strategies for vaccination is higher when considering a more pessimistic scenario of VE. In such case, both Strategy 2 and Strategy 3 allow to save more lives, compared to the observed situation. However, on the other hand, for very effective vaccines, the observed strategy performs better than all the others, both in terms of averting cases and averting deaths.

Impact Over Time

Fig. 1 display how each strategy of vaccination behaved over the time-period of the study, regarding the cumulative infections and deaths prevented.

Regarding avoiding deaths, the relative performance of strategies was roughly the same across time, and it is defined right in the first months of vaccination, showing the key role of defining the best prioritization factor as soon as the vaccination campaign starts, in order to save the most lives.

(A) Cases



(B) Deaths

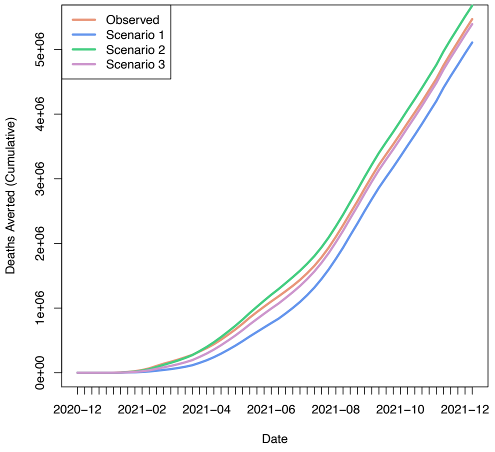
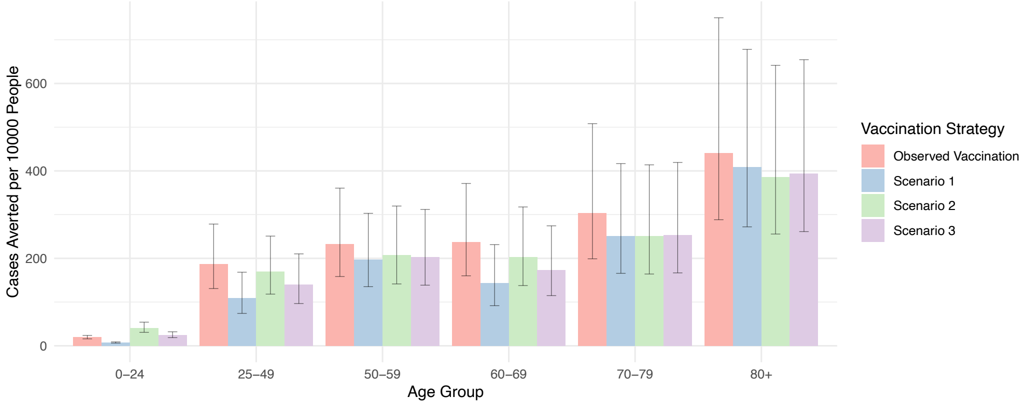


Fig. 1: Cumulative events averted worldwide over time for each vaccination strategy.

However, this is not veracious when it comes to avoided infections. Actually, Strategy 2 performs better than the observed until almost the end of the study period, having only worse results in the last two weeks, when the number of cumulative infections prevented in the observed situation surpasses the number of cumulative infections prevented using Strategy 2. As there were no boosters considered in this allocation of vaccines, at the end of the study period, the algorithm for the distribution is only either finishing vaccination primary series or giving first doses to countries that have low prevalence of COVID-19, as the countries with higher prevalence already have their populations completely vaccinated. As the waning of vaccine effec-

(A) Cases



(B) Deaths

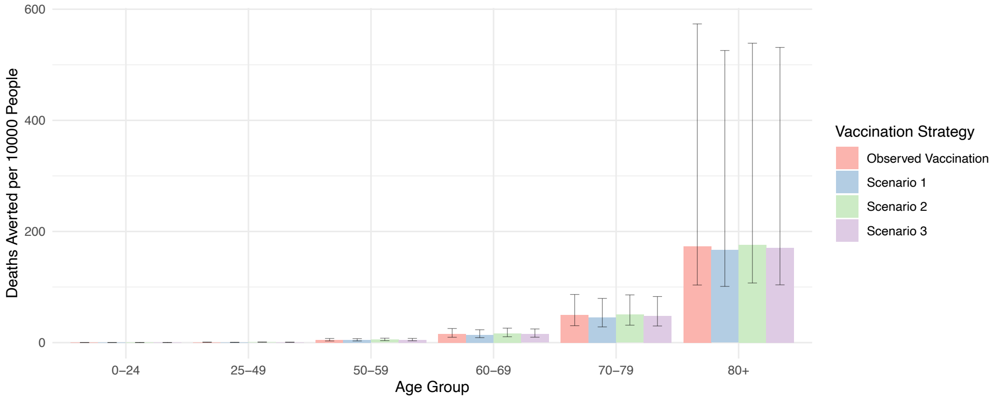


Fig. 2: Comparison of events averted per 10000 people between vaccination scenarios and across age groups (with uncertainty error bars).

tiveness is more prominent against infection, this has an impact in the results obtained for cases, but not for deaths.

Impact Across Age Groups

Bar graphs showing how each scenario performs in terms of cases and deaths averted across age groups can be seen in Fig. 2.

Of the alternative strategies studied, Strategy 1 prevents the most cases amongst older populations. However, as the age decreases, Strategy 1 performs progressively worse. This is natural, as this strategy of vaccination uses age as the main mechanism for prioritization. Further, the observed allocation of vaccines is the one which allows to prevent more cases in almost age groups. Regarding the prevention of fatalities, the impact of Strategy 1 is not so notorious, even for older populations, with Strategy 2 being the best performing across all age groups. While Strategy 1 has the advantage of administering boosters to older populations, Strategy 2 has the advantage of delivering the primary scheme of vaccination when it is most necessary, *i.e.* when cases are starting to rise. The waning of effectiveness of vaccines against death is not as prominent as against infection. Therefore, when it comes to preventing deaths, the marginal gain of the booster dose provided to older populations in Strategy 1 is not enough to account for the right timing of a 2-dose scheme of vaccination supplied in Strategy 2.

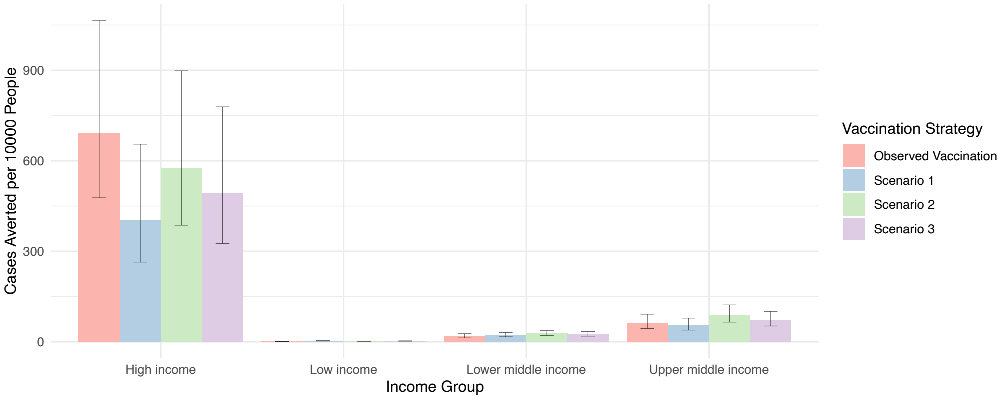
Impact Across Income Groups

Bar graphs showing how each scenario performs in terms of cases and deaths averted across income groups can be seen in Fig. 3.

HICs are the only group of countries that benefit most from the observed distribution of vaccines. As the other scenarios attempt to address disparities in vaccine access, LICs see more advantages in Strategy 1 and Upper Middle Income Countries (UMICs) in Strategy 2. Lower Middle Income Countries (LMICs) benefit most from Strategy 2 when it comes to infections averted, but from Strategy 1 regarding death prevention.

For all vaccination strategies tested, HICs were the ones that benefited most from vaccination, both in terms of preventing infections and deaths. The relative difference between HICs and other income groups is less prominent when concerning the prevention of deaths as these countries are naturally better equipped to deal with the pandemic, having a smaller Infection

(A) Cases



(B) Deaths

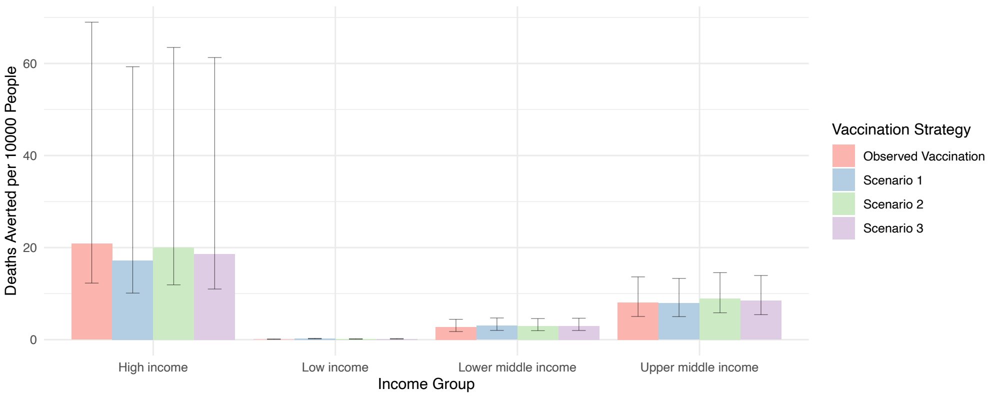


Fig. 3: Comparison of events averted per 10000 people between vaccination scenarios and across income groups (with uncertainty error bars).

Fatality Ratio (IFR) across ages [47], and thus feeling less the impact of vaccination for the prevention of those, when compared to the prevention of infections. It should be noted that this happens as in all strategies tested, HICs were the ones that achieved the highest vaccination rates, as will be discussed below.

Impact by Country

Fig. 4 (A) shows the number of deaths averted against vaccine doses (both per 100 people) for each country and stratified by income group for the observed vaccination strategy.

Due to their economic advantage, HICs were the ones that achieved higher vaccination rates in the observed vaccination. However, some UMICs show the highest impact of vaccination in averting deaths even with lower vaccination rates. As aforementioned, this can happen because of the better healthcare systems of most of HICs compared to the other groups. It is important to note that, while on Fig. 4 (A), the countries with the highest impact on the prevention of deaths appear to be mostly UMICs, other very populous UMICs like China, have pursued a zero-COVID approach, reporting very few deaths, which contributes to the overall impact on deaths shown in Fig. 3 to be higher in HICs. LICs and LMICs show both the lowest vaccination rates and impact in the number of events averted.

Overall, the biggest impact of vaccination was seen in the nations that had administered the most vaccines by the end of 2021 while also easing off on Non-Pharmaceutical Interventions (NPIs), allowing SARS-CoV-2 transmission to rise, *i.e.*, showing high numbers of infections and/or deaths. By contrast, the nations with slower vaccine rollouts as well as those pursuing zero-COVID policies which continued to implement harsher NPIs to stop transmission, saw fewer effects from their vaccination campaigns. These results are in line with the ones obtained by Watson et al. [10]. However, the number of deaths averted by vaccination obtained by these authors (14.4 million) is significantly higher than the estimate provided in the present analysis. This was expected as Watson et al. [10] aims to model both the direct and indirect impact of vaccination. In contrast, the estimates provided by this model are broadly comparable to others focused on the direct effect of vaccination [11–14].

Fig. 4 (B-D) show the number of deaths averted against vaccine doses (both per 100 people) for each country and stratified by income group for the alterna-

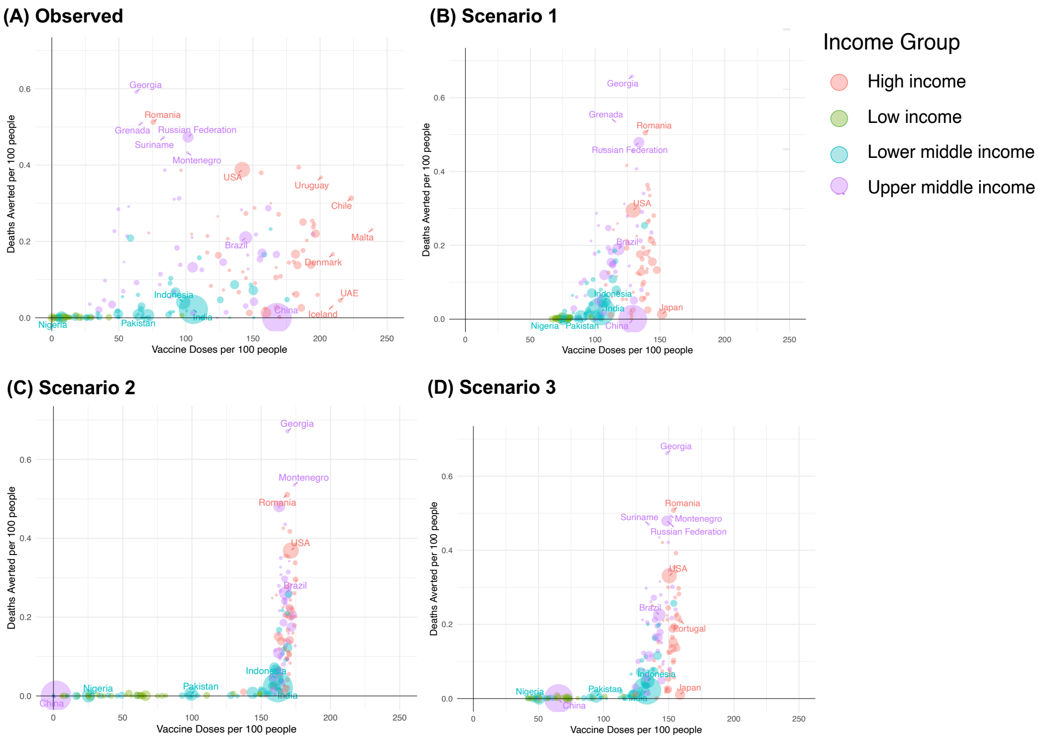


Fig. 4: Deaths averted against vaccine doses (both per 100 people) for each country, stratified by income group, in each vaccination strategy. Point size is proportional to each country's population.

tive vaccination strategies.

Overall, the variability between countries is not as prominent as in the observed vaccination. However, even in alternative scenarios of vaccination, where the financial power of countries was not taken into account, HICs ended up being the ones with the higher vaccination rates, as these countries have older populations and an higher number of reported COVID-19 infections. Nevertheless, the differences were not as striking as in the observed vaccination (Fig. 4 (A)).

Study Limitations

Since the counterfactual situation (*i.e.*, without immunizations) cannot be observed, it is impossible to directly measure the health impact of vaccination programs. Therefore, there are many factors that can influence the results obtained and limit the ability to draw conclusions.

The analysis performed is highly sensitive to the observed number of cases and deaths. Therefore, it is extremely important that these numbers are accurate in order to assess the impact of each vaccination strategy and make comparisons between them. As is known, a high proportion of cases and deaths attributed to COVID-19 were unreported [47, 48]. This tremendously limits the ability to draw conclusions, as it biases the understanding of the true burden of COVID-19. To further exacerbate this limitation, this factor is not homogeneous among countries. Countries in low income settings are the most likely to have higher proportions of under-ascertained infections and deaths [48].

Besides that major factor, many other limitations arise from the poor quality of data. As mentioned previously in this study, many assumptions had to be made regarding event counts and vaccine uptake data, which are likely to affect the accuracy of the results obtained. Moreover, even though vaccines were allocated to at-risk populations in all scenarios of vaccination tested, cases and deaths were not stratified considering this sub-population. Targeting this population first is expected to have an impact in the number of cases and deaths that could not be quantified. All these limitations, that arise from the poor quality of data available, show the importance of national governments in disseminating epidemiological data transparently and accurately.

Additionally, one of the most substantial limitations of the present study is only considering the direct impact of vaccination. It is expected that the number of averted events is even higher, when considering the impact of the observed vaccination strategy, as the vaccine also has other indirect effects, such as a reduction in transmission.

Furthermore, when considering alternative strategies of vaccination, it is expected that re-allocating vaccines alters the course of the pandemic and leads to other indirect effects, such as the appearance (or absence) of new Variants of Concern (VOCs) and changes in policies and strategies of mitigation put in place by national governments, such as NPIs. Similarly, the dimension of healthcare capacity was not considered. This is expected to have limited the results obtained in two manners. First, when confronted with an increase or decrease in cases and deaths, it is expected that healthcare systems respond accordingly, given their capacity. However, it was assumed that healthcare systems responded in a way similar to the observed situation over time. Second, it is assumed that all countries have the necessary human resources and infrastructures required to administer the vaccines allocated to them. This is not always true, as especially LICs are very limited in this aspect.

IV CONCLUSIONS

To our knowledge, this study is among the first to explore the impact of worldwide alternative vaccination strategies against COVID-19 and leverages the knowledge available regarding the importance of globalization in an emergency situation like COVID-19, showing the direct influence it has on health outcomes. However, it should be noted that the impact of vaccination programmes cannot be measured as only the number of infections and deaths averted. The lowest-income populations are the ones that benefit most from immunization, both in terms of health and economy [49]. Future work regarding this and other secondary dimensions is needed in order to fully understand the benefits of a global vaccination campaign.

Regarding the strategies of vaccination explored in this study, the case-based epidemiological prioritizing (Strategy 2) yielded the lowest mortality, whereas age-based demographic prioritization (Strategy 1) performed the poorest. Additionally, contrary to some national studies [19, 20], the strategy that combined both these dimensions (Strategy 3) was not the best performing. Although these results can be affected by the under-reporting of COVID-19 cases and deaths, discussed further below, this highlights that when dealing with a very limited supply of vaccines, the age and priority-based proportional allocation of vaccines is not necessarily the fairest, as the results obtained suggest that it is not the one which allows to save more lives.

Furthermore, the results obtained in Strategy 2, *i.e.*, where boosters were not used, highlights the importance of thoroughly assessing the impact of this additional dose in populations before its administration. As the waning of effectiveness of vaccines is much more prominent for preventing infections compared to deaths, the use of this dose may reveal superfluous and does not allow for the administration of the primary series in populations where the benefit might be greater.

Additionally, future work regarding the frameworks for prioritization can also be done. For the demographic prioritization, the consideration of additional sub-priority groups can be a way to improve, as well as proportional allocation to countries considering their inherent differences in population of these groups, which were not taken into account in this study. For the epidemiological prioritization, other factors that also reveal the need for vaccination such as the resilience of the healthcare systems, may also be interesting to explore. The consideration of regional instead of national ”hotspots” is also a possible source of additional analysis.

Finally, as one of the main limitations of the present work was the lack of complete and reliable data, there are certain strategies that can be employed in future work to lessen the effects of this constraint, such as the use of testing data and excess mortality estimates.

As a conclusion, while there are many ways in which this work can be improved, the present dissertation provides important results and conclusions on the topic of global allocation of vaccines. It is the first study of this kind and it proposes an innovative strategy for vaccine allocation that may be superior to the observed distribution: the epidemiological prioritization. It is also important to mention that the two main limitations of this study (disregarding the indirect effect of vaccines and the underreporting of cases and deaths) are both expected to underestimate the impact of this strategy. Therefore, the positive health impact of this strategy is likely even higher. Additionally, this study reinforces the role and articulation of national and international health organizations. The conclusions drawn here have the broadest applicability in situations where the supply of vaccines is extremely low, such as in the beginning of vaccination programmes. Thus, these findings have the potential to lead to new international strategies which will be of utmost importance not only for future pandemics, but also for the distribution of new vaccines for the control of SARS-CoV-2 and other global infectious agents’ genetic variants.

ACKNOWLEDGEMENTS

This document was written and made publically available as an institutional academic requirement and as a part of the evaluation of the MSc thesis in Biomedical Engineering of the author at Instituto Superior Técnico. The work described herein was performed at Unidade de Epidemiologia (UEPID) of Instituto de Medicina Preventiva e Saúde Pública da Faculdade de Medicina da Universidade de Lisboa (IMP-FML) between February and October of 2022 under the supervision of Dr. Paulo Nicola and the co-supervision of Prof. Mónica Oliveira.

REFERENCES

[1] M. Ciotti *et al.*, “The COVID-19 pandemic,” *Critical Reviews in Clinical Laboratory Sciences*, pp. 365–388, 2020.

[2] Centers for Disease Control and Prevention, “CDC Museum COVID-19 Timeline,” [Accessed: 12.07.2022]. [Online]. Available: https://www.cdc.gov/museum/timeline/covid19.html

[3] World Health Organization, “WHO Coronavirus (COVID-19) Dashboard,” [Accessed: 24.10.2022]. [Online]. Available:

https://covid19.who.int/

[4] A. Schuchat, “Human Vaccines and Their Importance to Public Health,” *Procedia in Vaccinology*, vol. 5, pp. 120–126, 2011.

[5] World Health Organization. COVAX. [Accessed: 27.07.2022]. [Online]. Available: https://www.who.int/initiatives/act-accelerator/covax

[6] BBC. Covid-19 vaccine: First person receives Pfizer jab in UK. [Accessed: 21.04.2022]. [Online]. Available: https://www.bbc.com/news/uk-55227325

[7] V. Pilkington *et al.*, “Global COVID-19 Vaccine Inequity: Failures in the First Year of Distribution and Potential Solutions for the Future,” *Frontiers in Public Health*, vol. 10, 3 2022.

[8] Institute of Tropical Medicine Antwerp. The Unfair Distribution of Vaccines, an Embarassing Déjà Vu. [Accessed: 20.10.2022]. [Online]. Available: https://www.itg.be/E/Article/vaccinongelijkheid-deja-vu

[9] World Health Organization. Fair allocation mechanism for COVID-19 vaccines through the COVAX Facility. [Accessed: 30.09.2022]. [Online]. Available: https://www.who.int/publications/m/item/fair-allocation-mechanism-for-covid-19-vaccines-through-the-covax-facility

[10] O. J. Watson *et al.*, “Global impact of the first year of COVID-19 vaccination: a mathematical modelling study,” *The Lancet Infectious Diseases*, 6 2022.

[11] M. M. Meslé *et al.*, “Estimated number of deaths directly averted in people 60 years and older as a result of COVID-19 vaccination in the WHO European Region, December 2020 to November 2021,” *Eurosurveillance*, vol. 26, 11 2021.

[12] C. Sacco *et al.*, “Estimating averted COVID-19 cases, hospitalisations, intensive care unit admissions and deaths by COVID-19 vaccination, Italy, januaryseptember 2021,” *Eurosurveillance*, vol. 26, 11 2021.

[13] S. Yi *et al.*, “Impact of national Covid-19 vaccination Campaign, South Korea,” *Vaccine*, vol. 40, pp. 3670–3675, 6 2022.

[14] T. Kayano *et al.*, “Number of averted COVID-19 cases and deaths attributable to reduced risk in vaccinated individuals in Japan,” *The Lancet Regional Health - Western Pacific*, vol. 28, p. 100571, 2022.

[15] T. N. Vilches *et al.*, “COVID-19 hospitalizations and deaths averted under an accelerated vaccination program in northeastern and southern regions of the USA,” *The Lancet Regional Health - Americas*, vol. 6, 2022.

[16] A. Shoukat *et al.*, “Lives saved and hospitalizations averted by COVID-19 vaccination in New York City: a modeling study,” *The Lancet Regional Health - Americas*, vol. 5, 2022.

[17] S. M. Moghadas *et al.*, “The Impact of Vaccination on Coronavirus Disease 2019 (COVID-19) Outbreaks in the United States,” *Clinical Infectious Diseases*, vol. 73, pp. 2257–2264, 12 2021.

[18] D. Kim and Y. J. Lee, “Vaccination strategies and transmission of COVID-19: Evidence across advanced countries,” *Journal of Health Economics*, p. 102589, 1 2022.

[19] L. Chapman *et al.*, “Comparison of COVID-19 vaccine prioritization strategies,” 2021, [Preprint - Available at *medRxiv*].

[20] S. Zhou *et al.*, “Optimizing Spatial Allocation of COVID-19 Vaccine by Agent-Based Spatiotemporal Simulations,” *GeoHealth*, vol. 5, 6 2021.

[21] F. M. Castonguay *et al.*, “Spatial Allocation of Scarce COVID-19 Vaccines,” 2021, [Preprint - Available at *medRxiv*].

[22] Our World in Data. COVID-19 dataset. [Accessed: 12.07.2022]. [Online]. Available: https://github.com/owid/covid-19-data/tree/master/public/data

[23] European Centre for Disease Prevention and Control. Data on COVID-19 vaccination in the EU/EEA. [Accessed: 12.07.2022]. [Online]. Available: https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea

[24] World Health Organization. WHO SAGE Roadmap for prioritizing uses of COVID-19 vaccines. [Accessed: 13.09.2022]. [Online]. Available: https://www.who.int/publications/i/item/WHO-2019-nCoV-Vaccines-SAGE-Prioritization-2022.1

[25] D.-Y. Lin *et al.*, “Effectiveness of Covid-19 Vaccines over a 9-Month Period in North Carolina,” *New England Journal of Medicine*, vol. 386, pp. 933–941, 3 2022.

[26] N. Andrews *et al.*, “Duration of Protection against Mild and Severe Disease by Covid-19 Vaccines,” *New England Journal of Medicine*, vol. 386, pp. 340–350, 1 2022.

[27] G. Tonnara *et al.*, “The impact of COVID-19 vaccination program in the Republic of San Marino: focus on effectiveness of Gam-COVID-Vac,” *Clinical Microbiology and Infection*, 7 2022.

[28] J. L. Suah *et al.*, “Waning COVID-19 Vaccine Effectiveness for BNT162b2 and CoronaVac in Malaysia: An Observational Study,” *International Journal of Infectious Diseases*, vol. 119, pp. 69–76, 6 2022.

[29] N. A. Kaabi *et al.*, “Effectiveness of BBIBP-CorV vaccine against severe outcomes of COVID-19 in Abu Dhabi, United Arab Emirates,” *Nature Communications*, vol. 13, 12 2022.

[30] V. L. Richardson *et al.*, “Vaccine effectiveness of CanSino (Adv5-nCoV) COVID-19 vaccine among childcare workers – Mexico, March–December 2021,” *Clinical Infectious Diseases*, 6 2022.

[31] L. J. Abu-Raddad *et al.*, “Waning mRNA-1273 Vaccine Effectiveness against SARS-CoV-2 Infection in Qatar,” *New England Journal of Medicine*, vol. 386, pp. 1091–1093, 3 2022.

[32] N. Dagan *et al.*, “BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting,” *New England Journal of Medicine*, vol. 384, pp. 1412–1423, 4 2021.

[33] A. Jara *et al.*, “Effectiveness of an Inactivated SARS-CoV-2 Vaccine in Chile,” *New England Journal of Medicine*, vol. 385, pp. 875–884, 9 2021.

[34] M. D. Hitchings *et al.*, “Effectiveness of ChAdOx1 vaccine in older adults during SARS-CoV-2 Gamma variant circulation in São Paulo,” *Nature Communications*, vol. 12, 12 2021.

[35] S. González *et al.*, “Effectiveness of the first component of Gam-COVID-Vac (Sputnik V) on reduction of SARS-CoV-2 confirmed infections, hospitalisations and mortality in patients aged 60-79: a retrospective cohort study in Argentina,” *eClinicalMedicine*, vol. 40, 10 2021.

[36] L. Dai *et al.*, “Efficacy and Safety of the RBD-Dimer–Based Covid-19 Vaccine ZF2001 in Adults,” *New England Journal of Medicine*, vol. 386, pp. 2097–2111, 6 2022.

[37] J. Sadoff *et al.*, “Final Analysis of Efficacy and Safety of Single-Dose Ad26.COV2.S,” *New England Journal of Medicine*, vol. 386, pp. 847–860, 3 2022.

[38] H. Chemaitelly *et al.*, “mRNA-1273 COVID-19 vaccine effectiveness against the B.1.1.7 and B.1.351 variants and severe COVID-19 disease in Qatar,” *Nature Medicine*, vol. 27, pp. 1614–1621, 9 2021.

[39] M. E. Halloran *et al.*, “Direct and Indirect Effects in Vaccine Efficacy and Effectiveness,” *American Journal of Epidemiology*, vol. 133, 1991.

[40] J. Clemens *et al.*, “Evaluating new vaccines for developing countries: Efficacy or effectiveness?” *JAMA*, vol. 275, pp. 390–397, 1996.

[41] C. D. Lefebvre *et al.*, “Dissecting the indirect effects caused by vaccines into the basic elements,” *Human Vaccines and Immunotherapeutics*, vol. 11, pp. 2142–2157, 2015.

[42] United Nations - Department of Economic and Social Affairs Population Division. World Population Prospects 2019. [Accessed: 30.05.2022]. [Online]. Available: https://population.un.org/wpp/

[43] The World Bank. Data - World Bank Country and Lending Groups. [Accessed: 04.10.2022]. [Online]. Available: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups

[44] R. A. Spasoff, *Epidemiologic Methods for Health Policy*. Oxford University Press, 1999.

[45] M. Porta, *A Dictionary of Epidemiology*, 5th ed. Oxford University Press, 2008.

[46] G. Hanquet *et al.*, “Vaccine effects and impact of vaccination programmes in post-licensure studies,” *Vaccine*, vol. 31, pp. 5634–5642, 11 2013.

[47] A. T. Levin *et al.*, “Assessing the burden of COVID-19 in developing countries: systematic review, meta-analysis and public policy implications,” *BMJ Global Health*, vol. 7, 2022.

[48] C. Whittaker *et al.*, “Under-reporting of deaths limits our understanding of true burden of covid-19,” *BMJ*, vol. 375, 2021.

[49] A. Y. Chang *et al.*, “The equity impact vaccines may have on averting deaths and medical impoverishment in developing countries,” *Health Affairs*, vol. 37, pp. 316–324, 2 2018.