



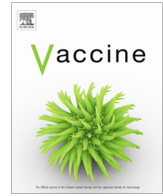
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Measuring the impact of COVID-19 vaccination and immunity waning: A modelling study for Portugal

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ABSTRACT

Vaccination strategies to control COVID-19 have been ongoing worldwide since the end of 2020. Understanding their possible effect is key to prevent future disease spread. Using a modelling approach, this study intends to measure the impact of the COVID-19 Portuguese vaccination strategy on the effective reproduction number and explore three scenarios for vaccine effectiveness waning. Namely, the no-immunity-loss, 1-year and 3-years of immunity duration scenarios. We adapted an age-structured SEIR deterministic model and used Portuguese hospitalisation data for the model calibration. Results show that, although the Portuguese vaccination plan had a substantial impact in reducing overall transmission, it might not be sufficient to control disease spread. A significant vaccination coverage of those above 5 years old, a vaccine effectiveness against disease of at least 80% and softer non-pharmaceutical interventions (NPIs), such as mask usage and social distancing, would be necessary to control disease spread in the worst scenario considered. The immunity duration scenario of 1-year displays a resurgence of COVID-19 hospitalisations by the end of 2021, the same is observed in 3-year scenario although with a lower magnitude. The no-immunity-loss scenario presents a low increase in hospitalisations. In both the 1-year and 3-year scenarios, a vaccination boost of those above 65 years old would result in a 53% and 38% peak reduction of non-ICU hospitalisations, respectively. These results suggest that NPIs should not be fully phased-out but instead be combined with a fast booster vaccination strategy to reduce healthcare burden.

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1. Introduction

During the pre-COVID-19 vaccine period, the pandemic has tested the capacity of health systems to deal with a high influx of COVID-19 patients. In order to reduce disease transmission, most countries opted to implement non-pharmaceutical interventions (NPIs), such as general lockdowns, the closure of schools and the mandatory use of masks, among others [1]. Portugal had two

major lockdowns during the COVID-19 pandemic during 2020 and 2021. The first occurred mid March 2020 during the first SARS-CoV-2 epidemic wave, and the second on January 2021 during the third epidemic wave [2]. During these periods, the public health system was severely stressed with high numbers of hospitalisations. This surge of cases coincided with the appearance of the first cases of the Alpha variant of concern (VOC). This variant was the most commonly identified in the Portuguese population, until the identification of the Delta VOC. This new VOC became dominant, reaching 89.1% of confirmed COVID-19 cases in Portugal by the end of June 2021 [3]. The Delta VOC has been tied to higher disease transmission [4] and severe disease [5,6].

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With the development of COVID-19 vaccines, the focus has changed from the sole use of NPIs to a mixture of both strategies. The COVID-19 vaccines have shown promising effects and mass vaccination programmes were implemented worldwide. Although such programmes are promising, several modelling studies have shown that as vaccination is rolled out, proper vaccine allocation is necessary [7–11] and the maintenance of NPIs is still required to prevent the increase of hospitalisations and deaths, particularly before completing full vaccination [12–16]. In Portugal, vaccination took place in two main phases: the first focused in healthcare professionals and vulnerable individuals (residents in nursing homes, individuals at higher risk of severe disease due to preexisting medical conditions and those 80 years old and over, starting December 2020), and the second one for the general population, organised by age groups, from 79 years old down to 12 years old, starting March 2021. On September 26, 2021, 84% of the population had received the primary complete vaccination scheme [17]. Four vaccines were administered: Cominarty (Pfizer) and Spikevax (Moderna), both in a 2-dose scheme with a 28 day interval, Vaxzevria (Astrazeneca), using a 2-dose schedule with an interval from 8 to 12 weeks, and COVID-19 Janssen, with a single dose. Early estimates, with original virus or during Alpha variant circulation, have shown that these vaccines were highly effective in the real world. Vaccine effectiveness was estimated to be 89.1% against infection and 99% against death in fully vaccinated individuals [18]. Continued monitoring of vaccine effectiveness has however revealed that the vaccines might not grant long-lasting protection. Vaccine induced protection has been shown to last at least 5–6 months [19–21] and older individuals and at risk groups had higher rates of immunity loss [19]. The potential loss of immunity led the Portuguese government to create new boosting vaccine strategies, prioritising individuals at higher risk, including healthcare professionals and older adults aged 65 years old and over.

Mathematical modelling and potential future scenarios development are tools that allow the simulation of the possible healthcare service impact by considering the introduction of new changes to COVID-19 dynamics, namely the appearance of a new VOC, vaccination strategies and immunity loss. Hence, our objectives with this modelling study are twofold. First, to ascertain the change in transmission upon instantaneous complete vaccination, according to the Portuguese vaccination programme, on the effective reproduction number (R_t) and secondly to develop epidemic scenarios of trajectories of COVID-19 intensive care unit cases (ICU) and non-ICU hospitalisations regarding potential waning of both vaccine induced protection and infection induced immunity. The results and conclusions of this study will help to support public health policy making in order to avoid future COVID-19 related healthcare burden.

2. Methods

We have considered a simplified version of the age-structured SEIR model developed in our previous work [22]. Details of the model are described in Appendix A. Individuals start off as susceptible (S) and, upon contact with an infectious individual, they have a probability to become infected. Upon infection, an individual is considered infectious after a period of time given by the average of the latency period for SARS-CoV-2 [23]. After this period an individual can either become symptomatic or asymptomatic with a given probability. Asymptomatic individuals infect at a reduced rate [24]. All asymptomatic individuals are assumed to recover from the infection while symptomatic individuals can either recover or require hospital admission. Hospitalised individuals can either recover, require intensive care or die. Individuals in intensive care units can either die or recover. To assess the effect

of vaccination and immunity loss we added a further branch to the model: susceptible and recovered individuals are vaccinated at rate Y and move to an analogous compartment in the vaccine protected branch of the model. Here we considered that the vaccine is leaky [25], i.e., susceptible vaccinated individuals have reduced probability of being infected upon an infectious contact ($1 - e$) and if infected, have a reduced chance of developing symptoms ($1 - f$). The leaky model has been used in other modelling studies [12] and has been shown to be similar to other approaches when vaccine coverage is high [26]. Vaccinated individuals are similar in all manners to non-vaccinated individuals with the exception of the parameters mentioned above. Vaccinated and recovered individuals lose their vaccine/infection conferred protection at given rates. These individuals are then assumed susceptible. See the supplementary material for more information on model description and parameters.

In the simulations presented, individuals were vaccinated per age-group attempting to capture the progression of the national COVID-19 vaccination programme. Individuals in each age-group were assumed to be vaccinated according to the information available of vaccine coverage, planned vaccination schedule and vaccines recommended for the respective age-group. In the model, we assumed that an individual is protected by the vaccine during a period after completing the vaccination scheme, assuming the targeted coverage described in Table 1 [17]. For the age-groups not corresponding to the ones used in the model a vaccination coverage was assigned which is proportional to their size. For younger age groups a mixture of planned vaccination dates and potential vaccines to be administered were used. Beginning of vaccination in each age-group started two weeks after the beginning of administration of the vaccine in the previous group and was terminated 28 days after, assuming that each age-group received both COVID-19 Janssen vaccine or Spikevax /Cominarty vaccines. Non-calibrated parameters were obtained from COVID-19 literature, while other were obtained by fitting the results of the model to data. The parameters of the model and their description may be found in the supplementary material.

The duration of infection induced immunity and vaccine induced protection are considered in the model and are given by the γ and γ_v parameters, respectively. An individual who loses its vaccine induced protection has the same characteristics as a non-vaccinated individual. In what follows, we will assume that both the infection induced immunity and vaccine induced protection have the same duration.

We fitted the model to the data on hospitalisations both in non-ICU and ICU, by age-group, from January 24, 2021 until September 29, 2021. Changes in contacts due to the introduction and lifting of NPIs and overall changes in population behaviour were estimated using a similar method described in [22,27]. Details of the fitting procedure can be found in the supplementary material.

Table 1

Portuguese vaccination roll-out plan. Beginning and end dates of the vaccination scheme and targeted final vaccination coverage by age-group [17].

Age-group	Begin date	End date	Targeted final vaccination coverage
70+	2021-02-08	2021-08-29	99%
60-69	2021-02-08	2021-08-29	99%
50-59	2021-07-01	2021-09-15	95%
40-49	2021-07-15	2021-09-29	95%
30-39	2021-08-01	2021-10-15	95%
20-29	2021-08-15	2021-10-15	85%
12-19	2021-09-01	2021-10-29	80%

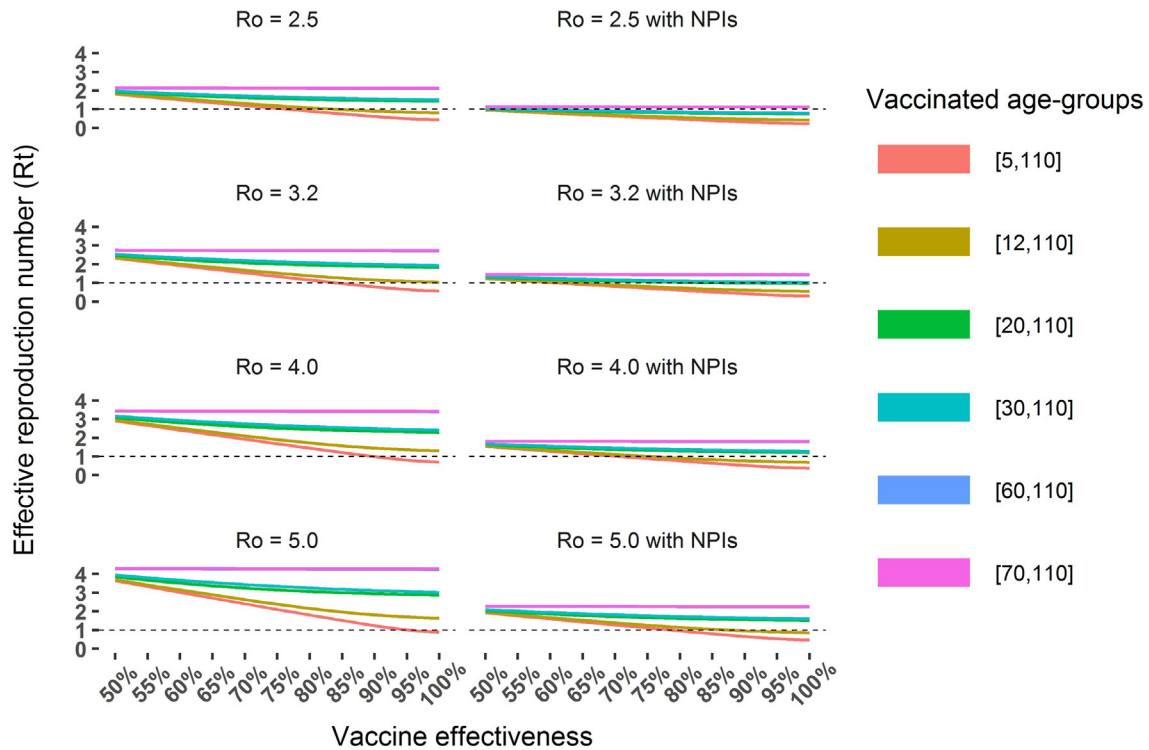


Fig. 1. Effective reproduction number as a function of vaccine coverage (by age-group), vaccine effectiveness and basic reproduction number. Two scenarios were considered: no NPIs in place (left) and overall effective contacts reduced by 47% (right) to take into account social distancing and mask usage [30]. The vaccination coverage was assigned to each age-group according to the final targeted coverage in the Portuguese vaccination plan, presented in Table 1. Coverage of the age group 5–11 was assumed 80%.

In order to assess the impact of the Portuguese vaccination strategy on disease spread, we determined the R_t by the next generation approach [28,29]. We have considered different levels of transmission associated with the presence of the Delta variant: $R_0 = 2.5, 3.2, 4.0$ and 5.0 [4]. Vaccine effectiveness was considered to vary from 50% to 100% by varying e and fixing the parameter f as 0.5, in order to obtain the desired range. We also explored the R_t calculation with and without NPIs in place, such as the use of mask and social distancing. To this end, we assumed a 47% reduction in effective contacts according to mask effectiveness studies [30]. In these calculations we assumed that 11% of the population had already been infected and thus removed from the susceptible group [31]. The remaining susceptible population was then divided into vaccinated and non-vaccinated according to the vaccine coverage plan presented in Table 1. We have also considered the vaccination of those between the ages of 5–11, which is not currently part of the vaccination plan. We assumed a final coverage of 80% in this group. Other parameters used are described in the supplementary material.

Secondly, we developed scenarios of trajectories of COVID-19 hospitalisations for three levels of vaccine induced protection waning. We explored a 1-year and a 3-years vaccine protection duration scenario and a no-loss-of-immunity scenario. Although little information is available about the duration of vaccine induced protection we chose these values according to recent studies that report at least 5–6 months of vaccine protection [19–21]. In each scenario we also explored the effect of giving a booster dose to those above 65 years of age. We assumed that this new vaccination scheme starts on October 11, 2021 and reaches 99% coverage within a month. We also included a 14-day delay to account for immune response.

The increased level of transmission due to the Delta variant was also included in the simulations. This was achieved by changing the value of parameter β , in order to be in line with the R_0 esti-

ated in COVID-19 literature [4] and fixing all other known parameters. For these simulations we assumed an $R_0 = 4$ and that no NPIs were in place after September 30, 2021.

3. Results

In this section we present the results for the R_t impact values and the waning immunity scenarios.

3.1. R_t Impact

Fig. 1 depicts the R_t computations for two scenarios with different levels of vaccine effectiveness, vaccination coverage and an increase of the reproduction number due to the circulation of the Delta variant, R_0^D . We can observe in both scenarios that administering the vaccine to more age-groups has a considerable impact in reducing the effective reproduction number. Moreover, this reduction is more noticeable when all population with 5 or more years is vaccinated.

Fig. 1 also describes the R_t in both scenarios considered, i.e. with and without NPIs in place. In the scenario with no NPIs, we can observe that values of R_t below 1 can only be achieved with the vaccination of at least the age-groups above 12 years old, a vaccine effectiveness above 85% and considering that the Delta variant has a similar transmission dynamics as the original strain ($R_0^D = 2.5$) [32,33]. The results for the scenario with NPIs in place show that an R_t below one can be achieved for all considered levels of transmission. For example, assuming the reproduction number of the Delta variant to be $R_0^D = 5$, the effective reproduction number below 1 is achievable for vaccine effectiveness values above 80%, vaccination of those with 5 or more years of age and with NPIs that induce a 47% reduction in the effective number of contacts, as depicted in the right bottom panel of Fig. 1.

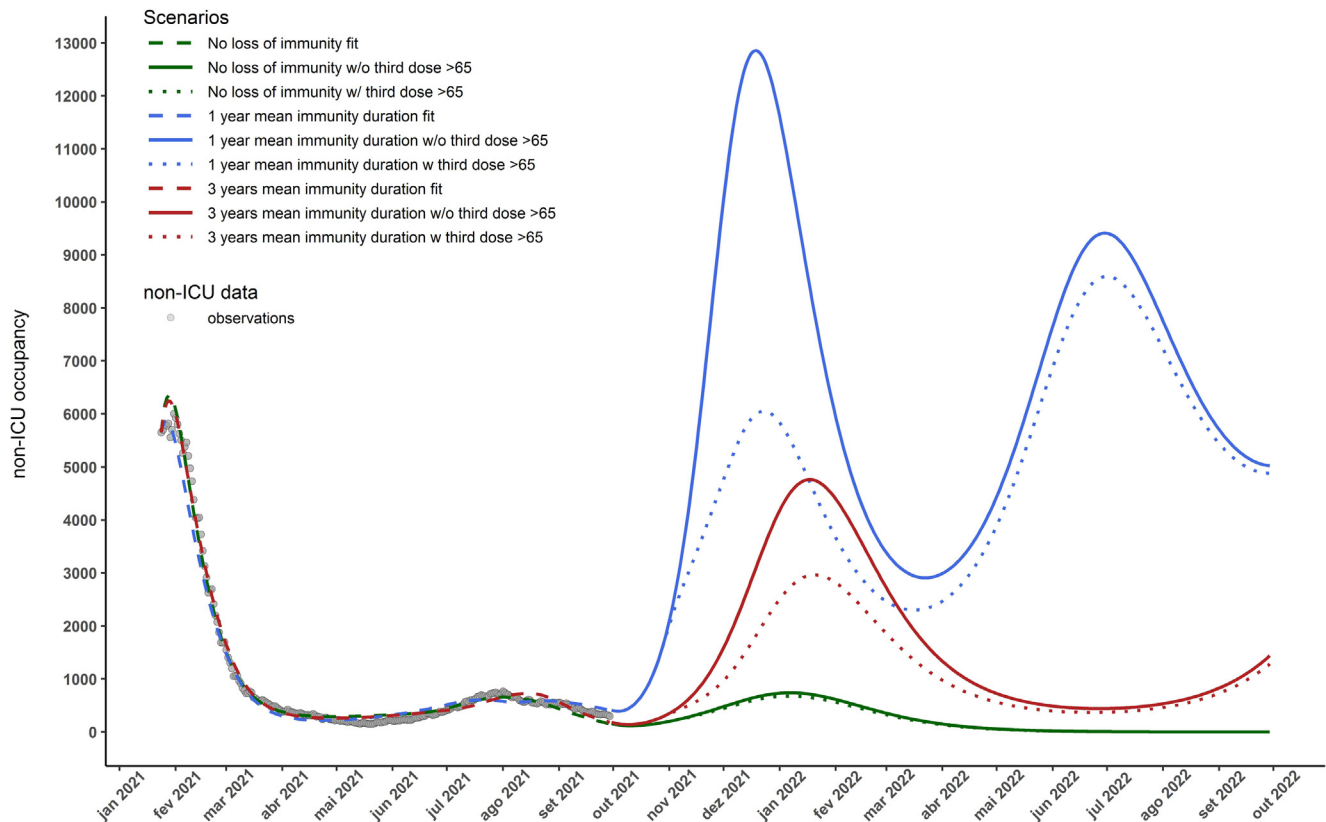


Fig. 2. Number of COVID-19 non-ICU hospitalised cases for the 3 considered scenarios: no loss of vaccine induced protection (green), vaccine effectiveness duration of 1 and 3 years (blue and red respectively). Dashed lines depict the model calibration for each immunity loss scenario, the solid lines represent the trajectory of the total number of non-ICU hospitalisation cases in each scenario. The dotted lines represent the trajectories where a third dose of the vaccine was administered to those above 65 years old and assuming that this group achieves 99% coverage with this new dose within one month of October 11, 2021. It is also assumed that no NPIs are in place after September 30, 2021 and that vaccine/infection granted immunity lasts an equal amount of time and is the same for each age-groups. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.2. Wane simulations

Fig. 2 presents the results for the vaccine protection duration scenarios and booster shots. The 1-year immunity duration scenario displays a new wave of non-ICU hospitalisations at the end of 2021, that can be mitigated by 53% at its peak if a booster shot is administered to those above 65 years of age. The 3-year immunity scenario displays a new wave of hospitalisations with a much smaller magnitude than the previous mentioned scenario but similar to the January 2021 wave. In this scenario the administration of the booster shot to those above 65 years old can reduce the peak non-ICU hospitalisation cases by 38%. The no-immunity-loss scenario also displays a new wave of hospitalisations by the end of 2021, although with a much smaller magnitude than the previous scenarios. It does not exceed 1000 non-ICU occupied beds at its peak. Similar results are obtained for ICU occupations as depicted in Fig. 3. Only in the no-immunity-loss scenario is expected not to exceed the maximum acceptable occupancy of ICU beds (255) by the end of 2021 [34]. More detailed results by age-group of the fitting procedure and simulation scenarios are presented in Appendix B.

4. Discussion

In this study we proposed a model that could capture the dynamics of COVID-19 spread during the period from January 24 to September 30, 2021, i.e., during the implementation of the COVID-19 vaccination programme up to the goal of 84% of vaccine

coverage. The model takes into account the heterogeneous nature of the Portuguese vaccination plan, the lifting and implementation of NPIs and the characteristics of disease complications in each age-group.

The R_t calculations enabled the analysis of possible outcomes of disease spread according to the vaccine effectiveness, vaccine allocation and increased transmission associated with the new Delta variant. By considering a different array of possible values for each of these parameters we were able to explore the R_t uncertainty and investigate possible outcomes of disease transmission. The results suggest that the herd-immunity threshold [35] might be higher than expected according to early assumptions ($R_0 = 2.5$) due to the presence of new and more transmissible variants. On the other hand, herd-immunity might also not be attainable since vaccines do not grant immunity to infection. COVID-19 reports in Portugal highlight that the R_t was estimated as 1.11 for the period between November 29, 2021 and December 3, 2021, vaccination coverage is above 85% in all eligible age-groups and early vaccine effectiveness studies estimate an effectiveness greater than 80% against COVID-19 hospitalisation and mortality and are also effective against SARS-CoV-2 infection with effectiveness close to 53%. Hence, considering the present setting, our results suggest that solely vaccinating the targeted age-groups might not be sufficient to bring the R_t below one and prevent epidemic disease spread, even considering high vaccination coverage rates.

These results are in agreement with other Portuguese modelling studies [12,36] and international studies [13–16] which also present epidemic spread in the presence of vaccination. Consequently the Portuguese government decided to vaccinate those between 5

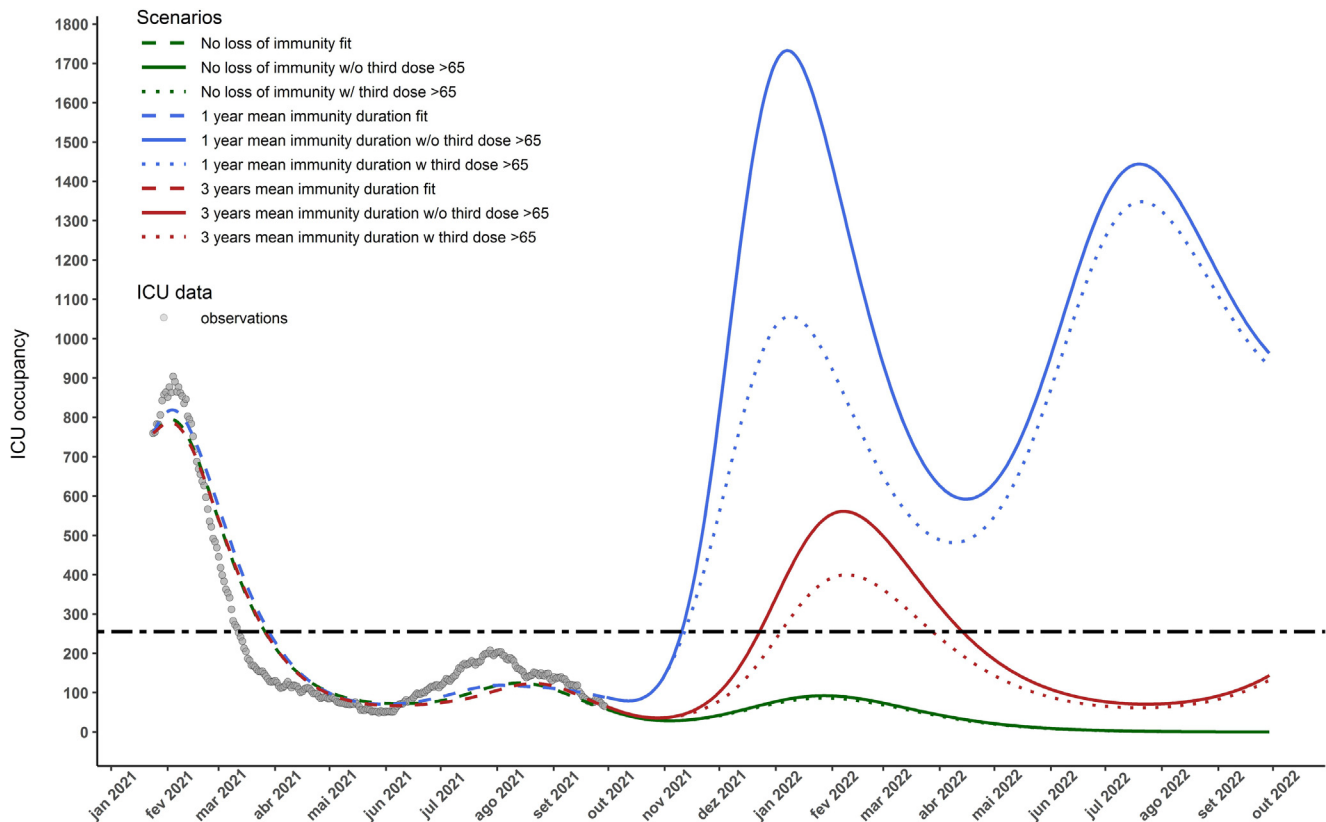


Fig. 3. Number of COVID-19 ICU hospitalised cases for the 3 considered scenarios: no loss of vaccine granted protection (green), vaccine effectiveness duration of 1 and 3 years (blue and red respectively). Dashed lines depict the model calibration for each immunity loss scenario, the solid lines represent the trajectory of the total number of hospitalisation cases in each scenario. The dotted lines represent the trajectories where a third dose of the vaccine was administered to those above 65 years old and assuming that this group achieves 99% coverage with this new dose within one month of October 11, 2021. It is also assumed that no NPIs are in place after September 30th 2021 and that vaccine/infection granted immunity lasts an equal amount of time and is the same for age-group. The horizontal dashed line depicts the ICU capacity of COVID-19 hospitalisations in Portugal. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and 11 years old (during late December 2021), which according to our results would further reduce disease transmission and could even control disease spread in the worst hypothetical scenario considered ($R_0^D = 5$ and no NPIs) if vaccine effectiveness is high (>95%). Additionally under the hypothesis of vaccine immunity waning with time, one must consider that vaccine effectiveness changes throughout the pandemic, independently of vaccine coverage. This means that the impact of vaccine effectiveness and coverage on transmission can be transient in time. Being higher when effectiveness is high (after a booster dose campaign) and lower after more than 5–6 months of complete vaccination scheme. If epidemic control cannot be attained under these conditions, other measures should be adopted. The R_t impact results considering the presence of NPIs show that epidemic control might be feasible under the present setting if soft NPIs are maintained, such as the use of mask and social distancing. We can observe that an $R_t < 1$ can be achieved in the worst scenario ($R_0^D = 5$) with those above 5 years old vaccinated and a vaccine effectiveness above 80%. Furthermore, we plan to update parameter values in these calculations as more detailed information becomes available regarding VOC transmission parameters. In future work we also plan to study the evolution of R_t taking into account the dynamical changes in susceptibility by considering the loss of immunity conferred by both infection and vaccination.

The immunity-loss simulations proposed enabled us to study outcomes of COVID-19 hospitalisations and ICU cases with regard to the uncertain nature of vaccine induced immunity waning and a new planned booster shot. These results show that a new wave of COVID-19 hospitalisations is expected by the end of 2021, and

its magnitude is related to the duration of vaccine protection. We also showed that this wave can be heavily mitigated by administering a booster shot to those above 65 years of age (53% reduction at peak in non-ICU hospitalisations). The 1-year immunity loss scenario displays a possible wave of higher magnitude than past others in both non-ICU and ICU occupied beds, reaching 12,857 non-ICU occupied beds at peak, assuming constant severity. This is a consequence of immunity loss of those that were vaccinated first, which included older individuals and those with higher risk of severe disease. Note also that after this wave a new resurgence is expected by mid 2022 and in this wave the effect of the booster shot is dampened due to the potential immunity loss of those who received the booster dose. It is also important to state that we considered that loss of immunity after the booster dose is also 1 or 3 years, according to each scenario, this assumption will be updated as new data becomes available.

The 3-year immunity duration scenario displays a resurgence of hospitalisations similar to the one observed during the beginning of 2021. In this case, giving a booster to those above 65 years of age also substantially reduces the number of hospitalised individuals (38%). The no-immunity-loss scenario depicts a small size wave of hospitalisations, and since vaccine grants long lasting immunity, the booster shot does not substantially impact the number of hospitalisations. Similar results have been reported by modelling studies that consider the presence of immunity waning, i.e., the presence of immunity loss might result in larger outbreaks, especially in the presence of a VOC with higher transmission [37,38]. Another study suggests that if the rate of administration of booster shots is not high enough, it might lead to a resurgence

of cases, that can be worse than previous waves [39]. It is important to note that our simulations assume a maximum potential of disease spread ($R_0 = 4$), before vaccination and susceptibility and also that vaccine/infection induced immunity waning is age-group independent and no NPIs are introduced, even the use of face mask. This value of R_0 was chosen according to estimated values of the reproduction numbers for the Delta variant [4]. A limitation of the analysis is that vaccinated individuals which lose their vaccine induced protection are assumed to have the same characteristics as non-vaccinated individuals within the same age-group. In a similar way, we assume that individuals who receive a booster shot are equally protected to those who have been vaccinated with a full scheme. Recent studies suggest that a third-dose booster shot increases vaccine protection to levels similar to receiving a complete scheme [40,41] which is in line with the present assumptions.

Our results show that vaccine effectiveness, coverage, vaccination speed and vaccine induced protection waning play key roles in understanding disease spread and healthcare impact. Currently, vaccine allocation, effectiveness and coverage in Portugal have not been enough to control disease spread. Hence, NPIs should be maintained and combined with vaccination programmes that include more age-groups and booster doses. Vaccine effectiveness should be monitored in order to assess scenarios for the periodicity of booster shots. As more data becomes available we will extend the present model to study optimal booster dose schedules according to different scenarios of vaccine induced protection waning and infection induced immunity waning and the impact of new VOC.

This analysis was invoked by questions from Portuguese decision-makers, hence they are time sensitive. Yet, it is useful to reflect on how the results compare with what happened in reality. In the case of Portugal, a mixture of vaccination strategies and NPIs was indeed required to maintain a controlled COVID-19 epidemic activity throughout the autumn of 2021 [42]. Our analysis identified two subsequent waves of hospitalisations. These waves were concurrent in time but with different magnitudes than the ones observed (see supplementary material). This is probably due to various mechanisms: vaccination conferred protection against severe disease decayed slower with time than we anticipated [43], omicron and subsequent variants presented a lower risk of severe disease and immune escape [44]. We would also note that the scenarios presented were designed to provide insights regarding the evolution of the COVID-19 dynamics impact given the assumptions of the model and chosen immunity duration values. Nevertheless, we believe the results provide valuable highlights and show the importance of modeling in supporting decision making with the need to readjust models alongside pandemic evolution. Bosse et al suggested that the combination of mathematical modeling and human judgment can complement each other [45]. To address such challenges, a pre-existing modeling toolkit with easily extendable options is currently being developed.

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Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2022.10.007>.

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