The effect of mixed vaccination rollout strategy: A modelling study

Nico Stollenwerk[a,b], Carlo Delfin S. Estadilla[a,g], Javier Mar[c,d], Joseba Bidaurrazaga Van-Dierdonck[e], Oliver Ibarrondo[c], Rubén Blasco-Aguado[a], Maíra Aguiar[a,b,f,*]

[a]*BCAM-Basque Center for Applied Mathematics, Bilbao, Basque Country, Spain*
[b]*Dipartimento di Matematica, Universitá degli Studi di Trento, Povo, Trento, Italy*
[c]*Osakidetza Basque Health Service, Guipúzcoa, Basque Country, Spain*
[d]*Biodonostia Health Research Institute, Guipúzcoa, Basque Country, Spain*
[e]*Public Health, Basque Health Department, Bilbao, Basque Country, Spain*
[f]*Ikerbasque, Basque Foundation for Science, Bilbao, Basque Country, Spain*
[g]*Preventive Medicine and Public Health Department, University of the Basque Country, Leioa, Basque Country, Spain*

Abstract

Vaccines have measurable efficacy obtained first from vaccine trials. However, vaccine efficacy (VE) is not a static measure and long-term population studies are needed to evaluate its performance and impact. COVID-19 vaccines have been developed in record time and the currently licensed vaccines are extremely effective against severe disease with higher VE after the full immunization schedule.

To assess the impact of the initial phase of the COVID-19 vaccination rollout programmes, we used an extended Susceptible - Hospitalized - Asymptomatic/mild - Recovered ($SHAR$) model. Vaccination models were proposed to evaluate different vaccine types: vaccine type 1 which protects against severe disease only but fails to block disease transmission, and vaccine type 2 which protects against both severe disease and infection. VE

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*Corresponding author

Email addresses: nico.biomath@gmail.com (Nico Stollenwerk), cestadilla@bcamath.org (Carlo Delfin S. Estadilla), franciscojavier.marmedina@osakidetza.eus (Javier Mar), j-bidaurrazaga@euskadi.eus (Joseba Bidaurrazaga Van-Dierdonck), oliver.ibarrondo@gmail.com (Oliver Ibarrondo), rblasco@bcamath.org (Rubén Blasco-Aguado), maguiar@bcamath.org (Maíra Aguiar)

was assumed as reported by the vaccine trials incorporating the difference in efficacy between one and two doses of vaccine administration. We described the performance of the vaccine in reducing hospitalizations during a momentary scenario in the Basque Country, Spain. With a population in a mixed vaccination setting, our results have shown that reductions in hospitalized COVID-19 cases were observed five months after the vaccination rollout started, from May to June 2021. Specifically in June, a good agreement between modelling simulation and empirical data was well pronounced.

1. Introduction

More than two years have passed since a severe respiratory syndrome (COVID-19) caused by a new coronavirus (SARS-CoV-2) was identified by public health authorities in China (World Health Organization, 2020b). Declared as a pandemic by the World Health Organization (WHO) in March 2020 (World Health Organization, 2020c), COVID-19 has spread rapidly around the globe. By October 15 2022, more than 618 million confirmed cases and around 6.5 million deaths were reported globally (World Health Organization, 2020d, 2021). Although disease symptoms range from mild to severe illness needing hospitalization, with age and pre-existing health conditions increasing the likelihood of disease severity manifestation (Aguiar and Stollenwerk, 2020a; Redondo-Bravo et al., 2020), it is now known that a large proportion of COVID-19 cases are asymptomatic, leading to a substantial global underestimation of SARS-CoV-2 infection.

Vaccines against COVID-19 have been developed in record time (Voysey et al., 2021; Polack et al., 2020; Baden et al., 2021; Sadoff et al., 2021) with emergency use authorization granted as early as December 2020. Although these vaccines have varying efficacies, they are found to be extremely effective in preventing severe disease symptoms (Dagan et al., 2021; Hall et al., 2021; Nasreen et al., 2022; Andrews et al., 2022; Florentino et al., 2022). Nonetheless, the so-called sterilizing immunity–occurring when vaccination blocks the transmission of the virus–and the extent of viral infectivity and immune escape of new variants are still being evaluated (Bruxvoort et al., 2021; Hu et al., 2022; Risk et al., 2022; Robles-Fontán et al., 2022). And as the performance of vaccines is driven by their ability to prevent virus trans-

mission, especially in undetected asymptomatic/mild cases (Oran and Topol, 2020; Johansson et al., 2021; Aguiar et al., 2021b), a well-planned strategy to use different COVID-19 vaccines is of major importance to effectively reduce hospitalizations.

Mathematical models convey ideas about the components of host-pathogen interactions and have been intensively used to model the dynamical spreading of COVID-19. Acting as a tool to understand and predict the spread of the disease, and to evaluate the impact of control measures in different epidemiological scenarios, several modelling task forces have been created to assist public health managers and governments during the COVID-19 pandemic. As early as March 2020, a multidisciplinary task force called Basque Modelling Task Force (BMTF) has been created to assist the Basque health managers during the COVID-19 responses. Within the BMTF, a stochastic SHARUCD modelling framework has been developed to describe the COVID-19 epidemic dynamics, giving projections on hospitalizations, Intensive Care Unit (ICU) admissions, and deceased cases. This modelling framework has been used to monitor disease spreading as control measures were relaxed and tightened over time, successfully describing the COVID-19 epidemics in the Basque Country, with accurate weekly predictions reported twice a week to the Basque Government (Aguiar and Stollenwerk, 2020c; Aguiar et al., 2020a,b; Aguiar, 2020; Aguiar et al., 2021a; Stollenwerk et al., 2020).

In this paper, we investigated the impact of the COVID-19 vaccination rollout in the Basque Country, Spain. We considered the initial vaccination rollout phase, from January to June 2021, before SARS-CoV-2 antibodies start to decline, eventually reflecting waning immunity, and before the Delta variant, believed to be more than twice as contagious as previous variants (Liu and Rocklöv, 2021), became dominant. Using results for the BioN-Tech/Pfizer and the Oxford/AstraZeneca vaccine efficacies, a flexible modelling framework is developed to account for differences in efficacy estimations for a single dose and two-dose immunization schedule against infection and hospitalization. Modelling development and extensions are followed by a detailed description of concepts used to analyze epidemiological data of severe COVID-19 cases and vaccine efficacy, where the effect of uneven vaccination rollout plan of action is discussed.

2. Methods

2.1. Modelling COVID-19 in the Basque Country, Spain, prior to vaccination rollout

As an extension of the simple $SHAR$ model, the $SHARUCD$ modelling framework considers populations of susceptible individuals (S), severe cases prone to hospitalization (H), mild, sub-clinical or asymptomatic (A), recovered (R), and patients admitted to the intensive care units (U). The recorded cumulative positive cases, which include all new positive cases for each class of $H, A, U,$ and R, are counted within the C classes. Finally, the model includes the deceased (D) cases (Aguiar and Stollenwerk, 2020c; Aguiar et al., 2020a,b; Aguiar, 2020; Aguiar et al., 2021a).

The deterministic version of the model is given by

$$
\begin{aligned}
\frac{d}{dt}S &= -\beta\frac{S}{N}(H + \phi A + \varrho N), \\
\frac{d}{dt}H &= \eta(1-\nu)\beta\frac{S}{N}(H + \phi A + \varrho N) - (\gamma + \mu)H, \\
\frac{d}{dt}A &= (1-\eta)\beta\frac{S}{N}(H + \phi A + \varrho N) - \gamma A, \\
\frac{d}{dt}R &= \gamma(H + U + A), \\
\frac{d}{dt}U &= \nu\eta\beta\frac{S}{N}(H + \phi A + \varrho N) - (\gamma + \mu)U, \\
\frac{d}{dt}C_H &= \eta\beta\frac{S}{N}(H + \phi A + \varrho N), \\
\frac{d}{dt}C_A &= \xi \cdot (1-\eta)\beta\frac{S}{N}(H + \phi A + \varrho N), \\
\frac{d}{dt}C_R &= \gamma(H + U + \xi A), \\
\frac{d}{dt}C_U &= \nu\eta\beta\frac{S}{N}(H + \phi A + \varrho N), \\
\frac{d}{dt}D &= \mu(H + U),
\end{aligned}
\tag{1}
$$

and includes two important epidemiological parameters: η and ϕ. While the severity ratio η gives the fraction of infected individuals who develop severe symptoms needing to be hospitalized (hence $(1-\eta)$ gives the mild/asymptomatic proportion of infections), the parameter ϕ is a scaling factor used

to differentiate the infectivity $\phi\beta$ of mild/asymptomatic infections from the baseline infectivity β of severe/hospitalized cases. The value of ϕ can be tuned to reflect different situations. A value of $\phi < 1$ reflects the fact that severe cases have larger infectivity than mild cases (e.g. due to enhanced coughing and sneezing), while $\phi > 1$ indicates that asymptomatic individuals and mild cases contribute more to the spread of the infection (e.g., due to their higher mobility and the possibility of interaction) than the severe cases which are more likely to be detected and isolated (Aguiar and Stollenwerk, 2020c).

In the case of COVID-19, ϕ is assumed to be larger than 1, since severe cases are likely hospitalized and isolated while mild/asymptomatic cases are often undetected, hence able to transmit the disease, contributing significantly more to the force of infection than the isolated severe cases.

Able to describe the COVID-19 epidemic in terms of disease spreading, the SHARUCD model gave accurate projections on hospitalizations, ICU admissions, and deceased cases, from March 4, 2020, to December 31, 2020, as shown in Figure 1. The modelling framework has been used to monitor the COVID-19 epidemiological dynamics in the Basque Country while the lockdown measures were tightened and relaxed over time.

The lifting of the lockdown in the summer of 2020 led to an increase in the infection rate with growth factors and momentary reproduction ratio, which determines the boundary when the epidemic will decrease to extinction versus exponential growth of disease cases, hovering around the epidemic threshold (Aguiar et al., 2021a). To evaluate the effect of human mobility and the effect of undetected chains of infection in the post-lockdown phase, the import factor ϱ (neglected while the full lockdown was in place) was taken into consideration as a small proportion of the total population. The import factor ϱ refers to the possibility of susceptible individuals becoming infected by an undetected infection chain (likely coming from an asymptomatic case) that started outside the studied population (Aguiar, 2020; Aguiar et al., 2021a; Mateus et al., 2016a,b).

Note that although this factor was not important during the exponential growth phase in March 2020, undetected imported infections play a major role during the stochastic introduction phase of the virus in naive populations, where only a small number of infections are initially detected. In the scenario of the post-exponential phase, where community transmission is controlled due to lockdown, mobility restrictions and other non-pharmaceutical intervention measures, the import factor can eventually start an isolated out-
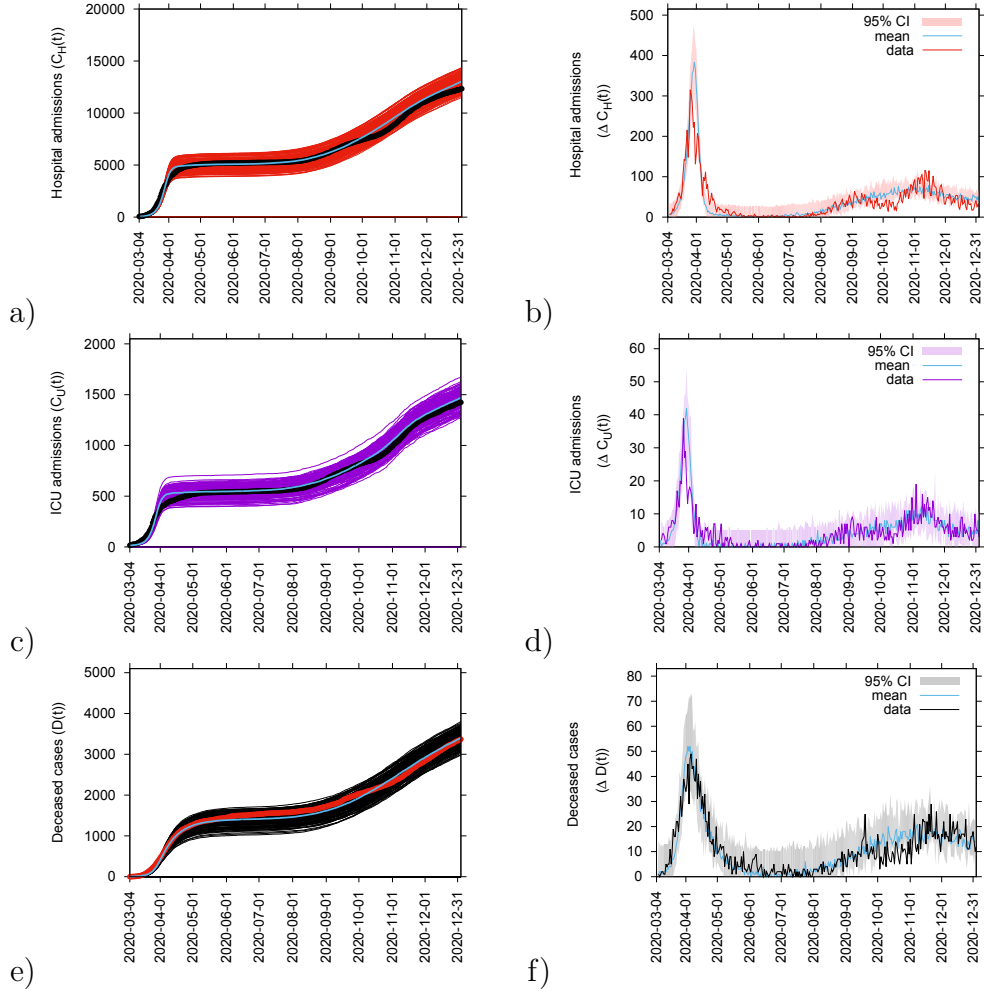
Figure 1: From March 4 to December 31, 2020, on the left-hand side, we plot the ensemble of stochastic realizations of the $SHARUCD$ model for cumulative cases. In a) cumulative hospitalized cases $C_H(\text{t})$, in c) cumulative ICU admissions $C_U(\text{t})$ and in e) deceased cases $D(t)$. The mean of the stochastic realizations is plotted in light blue, coinciding with the deterministic solution of the model. Empirical data are plotted for hospitalizations and ICU admissions (black dots) and deceased cases (red dots). On the right-hand side, we plot the model results for the daily incidences. In b) daily hospitalized cases, in d) daily ICU admissions and in f) daily deceased cases. Empirical data are plotted for hospitalizations (red line), ICU admissions (purple line), and deceased cases (black line). The mean of 200 stochastic realizations is plotted as a light blue line, coinciding with the deterministic solution of the model. The 95% confidence intervals are obtained empirically from 200 stochastic realizations and are plotted as the red, purple, and black shadows for hospitalizations, ICU admissions, and deceased cases, respectively.

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break of variable sizes, depending on the momentary infection rate. However, under the community control scenario, this small factor is not enough to drive the epidemic into a new exponential growth phase of severe cases, see Figure 1.

2.2. Modelling COVID-19 vaccination rollout in the Basque Country

Four COVID-19 vaccines were licensed for emergency use in Europe: two mRNA-type vaccines–BioNTech/Pfizer and Moderna–with initially about 95% vaccine efficacy after a second dose and two viral vector vaccines–Oxford/Astra-Zeneca and Janssen/Johnson & Johnson–with about 70% vaccine efficacy upon full immunization (Dagan et al., 2021; Baden et al., 2021; Voysey et al., 2021; Sadoff et al., 2021).

With different efficacies, COVID-19 vaccines have been remarkably effective in preventing severe forms of the disease after full immunization and have significantly contributed to reducing hospitalizations and deaths worldwide (Nasreen et al., 2022; Andrews et al., 2022; Bruxvoort et al., 2021; Meggiolaro et al., 2022; Sadoff et al., 2022; Yi et al., 2022). However, findings of the natural waning of immunity starting to occur after 3 months of vaccination (Andrews et al., 2022; Robles-Fontán et al., 2022; Risk et al., 2022; Lin et al., 2022; Katikireddi et al., 2022) and the emergence of new variants that may escape the existing vaccine immunity and may lead to reinfection (Stollenwerk et al., 2010) required a continuous vaccination rollout through booster doses to maintain high immunity in the population. As such, the sustainability of mass COVID-19 vaccination has been under debate given the limited resources and the inherent complexity to manage a global vaccine distribution.

This section is divided into three parts. Starting with a brief state-of-the-art on vaccine development and licensing, we evaluated the efficacy of the two most representative COVID-19 vaccines authorized for emergency use in the Basque Country–the BioNTech/Pfizer and the Oxford/AstraZeneca vaccines. The vaccine efficacy estimation results were implemented in the simple SIR model with basic concepts of vaccination coverage and herd immunity presented in detail.

2.2.1. COVID-19 vaccines: from development to approval

Every vaccine must go through extensive and rigorous testing to ensure its safety before using it in a vaccination programme. The pre-clinical phase of vaccine development determines which antigen invokes an immune response

to a given pathogen. This phase is done without testing on humans. If the vaccine triggers a favourable immune response, it will then be tested in human clinical trials which have three phases to assess its safety and to confirm that the vaccine generates an adequate immune response. While Phase I enrols a small number of human volunteers, Phase II enrols several hundred volunteers to further assess its safety and ability to generate an immune response. In a Phase III trial, the vaccine is given to a much larger group of people, often across multiple countries, to determine the relative risk (RR) of the vaccine, i.e. the proportionate reduction of cases among the vaccinated while calculating the risk of disease among the vaccinated and unvaccinated. This reduction is described as the vaccine efficacy (VE) with $VE = 1 - RR$ (Center for Disease Control and Prevention (CDC), 2011; Hightower et al., 1988; Weinberg and Szilagyi, 2010).

After a year of the pandemic, COVID-19 vaccines were approved for emergency use according to current regulatory guidelines and legal requirements (US Food and Drug Administration, 2022). Prompted by a global emergency, the vaccine trials were done at record speed, enrolling similar sample sizes for vaccine and placebo groups. By December 2020, four vaccines were administrated to the Basque population following a specific vaccination schedule and prioritizing risk groups (i.e. according to age or presence of comorbidities). While the mRNA vaccines developed by BioNTech/Pfizer (Dagan et al., 2021) and Moderna (Baden et al., 2021) have reported vaccine efficacy to be over 90% after the second dose, the viral vector vaccines developed by Oxford/AstraZeneca (Voysey et al., 2021) and Janssen/Johnson&Johnson (Sadoff et al., 2021) have reported vaccine efficacy to be around 70% after full immunization.

To measure the efficacy of these vaccines, the studied population are divided into two groups, the vaccinated group consisting of individuals receiving the vaccine (N_v), and the control group, consisting of individuals receiving a placebo solution (N_c) (World Health Organization, 2020a). After the administration of the vaccine and placebo, the number of cases in each group are compared to measure the vaccine efficacy (Center for Disease Control and Prevention (CDC), 2011; Hightower et al., 1988; Weinberg and Szilagyi, 2010). The analysis of the raw vaccine trial data can be done by a Bayesian framework to estimate the efficacy conditioned on the numbers of detected infected in the vaccine group and the placebo group (Aguiar and Stollenwerk, 2017; Aguiar et al., 2016a; Mateus et al., 2015; Aguiar and Stollenwerk, 2020b).

In the following section, we analysed the trial data from the Oxford/Astra-Zeneca and the BioNTech/Pfizer vaccines. We show explicitly the vaccine efficacy as a Bayesian posterior, and from this result, its cumulative distribution function obtaining the confidence intervals in good agreement with reported numbers in the vaccine trials (Voysey et al., 2021; Dagan et al., 2021).

2.2.2. Analysis of the Oxford/AstraZeneca COVID-19 vaccine trial data

With roughly the same sample sizes for the control and the vaccine groups, i.e, $N_v \approx N_c$, the efficacy of Oxford/AstraZeneca COVID-19 vaccine was measured using pooled data from trials from the United Kingdom, Brazil and South Africa (Voysey et al., 2021).

While the control group $N_c = 5829$ reported $I_c = 101$ infected individuals, the vaccine group $N_v = 5807$ counted $I_v = 30$ infected individuals, giving a maximum likelihood estimate for the vaccine efficacy of $\hat{k} = 70\%$. We estimated the vaccine efficacy as a maximum likelihood estimator using the formula

$$\hat{k} = 1 - \frac{ln\left(1 - \frac{I_v}{N_v}\right)}{ln\left(1 - \frac{I_c}{N_c}\right)} \approx 1 - \frac{\left(\frac{I_v}{N_v}\right)}{\left(\frac{I_c}{N_c}\right)},$$

with the approximation valid for small numbers of infected individuals compared to the overall trial size ($I/N \ll 1$), which is well valid in this case. The obtained result confirms the reported estimations for this vaccine trial, see (Voysey et al., 2021). Note that this mathematical approach was previously used to estimate the vaccine efficacy for dengue vaccines (Mateus et al., 2015; Aguiar et al., 2016b; Aguiar and Stollenwerk, 2020b), confirming the efficacies reported during the Phase III trials.

In detail, from the initially susceptible individuals in each group, we estimated the infection rate β from the control group, and the eventually reduced infection rate $(1-k)\beta$ for the vaccine group, with efficacy k, via the processes

$$N_c + I^* \quad \xrightarrow{\beta} \quad I_c + I^*,$$
$$N_v + I^* \quad \xrightarrow{(1-k)\beta} \quad I_v + I^*.$$

The likelihood for the probability of background infection β and, for convenience, respectively the probability of not becoming infected in the control group $\theta_\beta = e^{-\beta T}$ during the study time interval T, i.e. $L(\theta_\beta) = p(I_c|\theta_\beta)$, via

the Bayesian ansatz and the posterior

$$p(\theta_\beta|I_c) = \frac{p(I_c|\theta_\beta)}{p(I_c)}\, p(\theta_\beta)$$

are given. Likewise, in the vaccine group we have θ_β^k, such that we finally obtain the posterior $p(k|I_v, I_c)$ of the vaccine efficacy k only as a function of the trial data, by marginalizing over the internal background infection parameter θ_β, via

$$p(k|I_v, I_c) = \int_0^1 p(k|I_v, \theta_\beta) \cdot p(\theta_\beta|I_c)\, d\theta_\beta.$$

From this, we also obtain its cumulative distribution function $P(k|I_v, I_c)$ to read off medians and confidence intervals, see Figure 2.
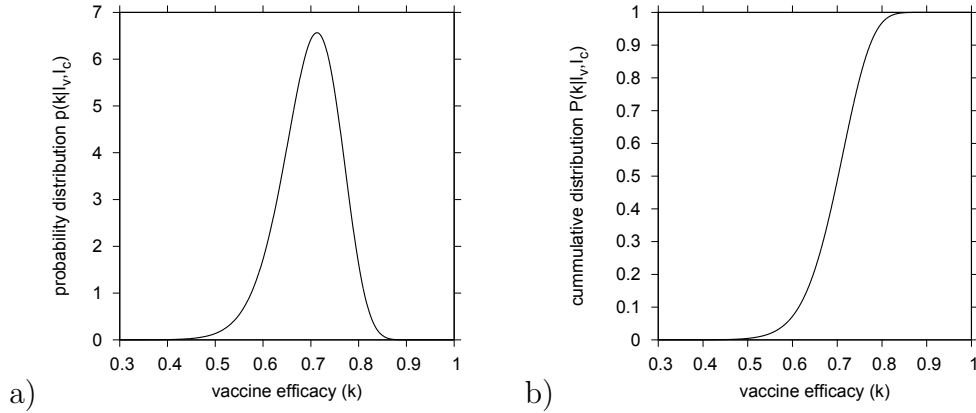
Figure 2: Bayesian analysis of the vaccine efficacy based on the raw trial data of the Oxford/AstraZeneca vaccine available in Voysey et al. (2021). In a) posterior distribution of the vaccine efficacy $p(k|I_v, I_c)$, and in b) its cumulative distribution function $P(k|I_v, I_c)$ to read off median and confidence intervals.

Figure 2a) shows the numerical results for the Oxford/AstraZeneca vaccine efficacy posterior $p(k|I_v, I_c)$, giving a good visual impression of the estimated efficacy and its insecurity (due to the small trial data numbers). Figure 2b) shows the cumulative distribution function $P(k|I_v, I_c)$, from which one can estimate the confidence intervals. From the median of the marginalized posterior $P(k_{0.5}|I_v, I_c) = 0.5$, we obtained the Bayesian estimate of the vaccine efficacy $k_{0.5} = 0.703 = 70.3\%$, and the 95%-confidence interval from

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the 0.025 and 0.975 quantiles, $P(k_{0.025}|I_v, I_c) = 0.025$ for the lower bound $k_{0.025} = 0.559$, and $P(k_{0.975}|I_v, I_c) = 0.975$ for the upper bound $k_{0.975} = 0.805$. These estimations are in good agreement with the values reported for this vaccine trial published in Voysey et al. (2021) (with $70.4\%(95\%$-CI: $54.8-80.6)$), with small differences since we used Bayesian priors being as uninformed as possible. For further details, please see Mateus et al. (2015) and Aguiar and Stollenwerk (2020b).

2.2.3. Analysis of the BioNTech/Pfizer COVID-19 vaccine trial: large-scale population data

Similar to the exercise presented in Section 2.2.2, we estimated the vaccine efficacy for the mRNA vaccine BioNTech/Pfizer based on the results of the first published large-scale population study (Dagan et al., 2021). In this study, data from Israel's largest health care organization, the Clalit Health Service, were used to evaluate the effectiveness of the vaccine after the administration of a first and the second dose, from December 20, 2020, to February 1, 2021, with all newly vaccinated persons matched with unvaccinated controls in a 1:1 ratio setup. Moreover, information on different efficacies for overall infection versus severe cases needing hospitalization is given. Therefore, a preliminary analysis of vaccine efficacy against severe disease needing hospitalization (k_H) and vaccine efficacy against overall infection (k_I) can be performed.

A first inspection of the results from Dagan et al. (2021) already indicated that not only the medians of k_H and k_I could be quite different, but also the confidence intervals could overlap, or in some cases, become disjunct, indicating that future studies will most likely show different efficacies against severe COVID-19 cases needing hospitalization and overall infection. We noted, however, that these differences in the efficacies are mostly observed for individuals receiving a single vaccine dose, while efficacies after the second dose are estimated to be above 90% and remarkably higher than the initial VE estimations obtained after the complete immunization schedule of the Oxford/AstraZeneca vaccine. With $N_v = N_c = 596\ 618$ (and later kept to a good extent to equal group sizes, hence $N_v/N_c \approx 1$), vaccine efficacies can be obtained from the raw data as

$$\hat{k} = 1 - \frac{(\Delta I_v)}{(\Delta I_c)}.$$

Using a refined Bayesian analysis, as described in Section 2.2.2, we com-

pared the vaccine efficacy against hospitalization and infection (Figure 3). For the one-dose vaccination schedule, the two distributions for hospitalizations and overall infections only slightly overlapped. Here, vaccine efficacy against hospitalization $k_{H,1}$ is estimated to be $k_{H,1} = 78\%$ $[61\% - 91\%]$, with a maximum of around 80% (green curve in Figure3a). However, vaccine efficacy against infection $k_{I,1}$ is estimated to be $k_{I,1} = 60\%$ $[53\% - 66\%]$ and has its maximum just below 60% (purple curve in Figure 3a). With two vaccine doses, the efficacy has significantly increased, with the two distributions overlapping. Here, vaccine efficacies against hospitalization $k_{H,2} = 92\%$ $[88\% - 95\%]$ and infection $k_{I,2} = 87\%$ $[55\% - 100\%]$ had maxima around or above 90%, see Figure 3b.
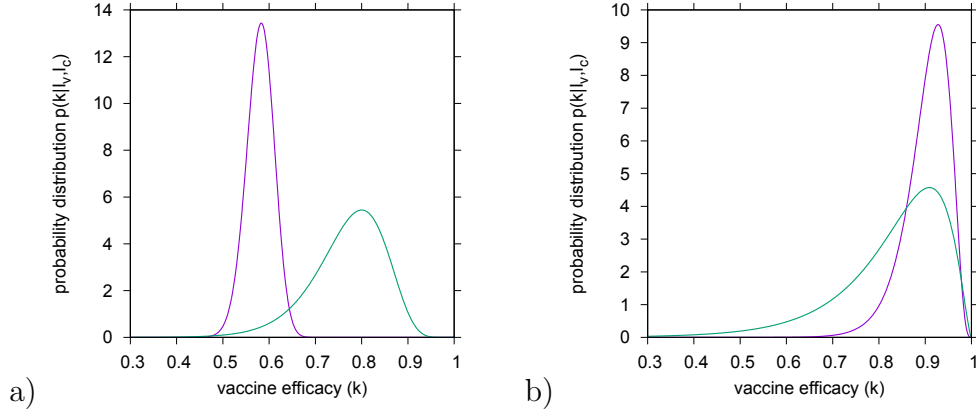

Figure 3: BioNTech/Pfizer vaccine efficacy estimations against hospitalization (k_H) in green and against infection (k_I) in purple. In a) we plotted the vaccine efficacy estimations for a single-dose vaccination $k_{H,1}$ and $k_{I,1}$. A "documented infection" was defined as having a positive PCR test between 21 to 27 days after vaccine administration. In b) we plotted vaccine efficacy estimations for a two-dose vaccination $k_{H,2}$ and $k_{I,2}$. Here, a "documented infection" is defined as having a positive PCR test reported from day 7 after vaccine administration to the end of the trial follow-up. Data were obtained from Dagan et al. (2021).

The efficacy against infection is quite well-measured with confidence intervals between 80% and nearly 100%. However, the small numbers of hospitalizations can lead to wider insecurity of efficacy, with lower bound as low as 50 to 60%. Nevertheless, the bulks of the distributions overlapped well, and for modelling purposes, we assumed that the protections against hospitalization and infection are roughly equal for the two-dose vaccine scenario,

that is, $k_H \approx k_I \approx 92\%$.

2.3. Vaccination coverage to achieve herd immunity: basic concepts using the simple SIR model

The use of vaccines with different efficacies will affect the proportion of individuals needed to be vaccinated in a population to control disease spreading. Aiming to revisit basic concepts of epidemiology, we used a simple SIR model to calculate the vaccination coverage needed to achieve herd immunity by vaccination in a population. As a baseline approach, these concepts will be used later for our refined modelling framework to evaluate the current situation in the Basque Country, Spain, with mixed vaccination coverage of first and second dose, and eventually mixed vaccine efficacies against hospitalization and infection.

From a simple SIR model with

$$\frac{d}{dt}I = \left(\beta \frac{S}{N} - \gamma \right) I,$$

let c be the vaccination coverage of the population N. Hence, we have $S = (1 - c)N$ as the remaining susceptible individuals. We use the condition of zero growth, $\left(\beta \frac{S}{N} - \gamma \right) = \lambda = 0$, as the threshold condition for the vaccination coverage c, that is,

$$0 = \lambda = \left(\beta \frac{S}{N} - \gamma \right) = \beta(1 - c) - \gamma, \tag{2}$$

giving

$$c = 1 - \frac{1}{\left(\frac{\beta}{\gamma} \right)}$$

as the threshold coverage to obtain the population herd immunity $\lambda \leq 0$. This is the classically used formula $c = 1 - 1/\mathcal{R}_0$ for vaccination coverage threshold as a function of the basic reproduction ratio $\mathcal{R}_0$.

With a perfect vaccine $k = 1$, the herd immunity threshold is driven by $\mathcal{R}_0$ of a disease. As an example, for $\beta \approx 3.5\gamma$ (an estimated $\mathcal{R}_0 = 3.5$), we obtained

$$c = 1 - \frac{1}{\left(\frac{\beta}{\gamma} \right)} = 0.714 \approx 70\%$$

vaccine coverage to achieve herd immunity in the population. This value has been frequently mentioned in the public media during the COVID-19 pandemic, however not mentioning that this proportion is obtained by assuming a perfect vaccine (i.e. 100% efficacy).

However, in real life, the situation is more complex, since vaccines are imperfect ($k < 1$) and therefore, herd immunity by vaccination depends not only on the $\mathcal{R}_0$ value but also on the given efficacy of the vaccines administrated in the population. Applied to COVID-19, the already gained immunity via natural infection will eventually play a role in the population coverage needed to achieve the herd immunity status as well. As such, it is important to make some considerations for the use of imperfect vaccines in a population with a significant natural immunity.

2.3.1. Considerations for imperfect vaccines and population immunity by natural infection: the case of the Basque Country

Although useful contributions in this direction have already been provided (see Britton et al. (2020) and Moore et al. (2021), for example) in which models for SARS-CoV-2 consider heterogeneity on the population level or the overall vaccine efficacy, to our knowledge, this is the first modelling exercise considering heterogeneity on vaccine efficacy for a single-dose versus a two-dose immunization schedule, including population immunity by natural infection.

On December 21 2020, vaccination rollout started in the Basque Country reaching, by June 14, 2021, 47.6% vaccination coverage for individuals that have received at least one dose, and 31.3% coverage for complete immunization (Figure 4).

To evaluate the impact of the COVID-19 vaccination, two vaccination models are studied. By considering different vaccines with varying efficacy and coverage, the $SHARUCD$ baseline model, the $SHAR$ framework, is refined to include the uneven vaccination rollout strategy that was placed worldwide.

Results obtained for the Oxford/AstraZeneca vaccine (see Section 2.2.2) and for the BioNTech/Pfizer vaccine (see Section 2.2.3) are implemented into the simple SHAR modelling framework, which was extended to get a qualitative overview of the impact of the COVID-19 vaccination strategy in the Basque Country (and many other European regions).

We applied the model to a momentary epidemiological scenario in the Basque Country, Spain, during the initial phase of the vaccination rollout,
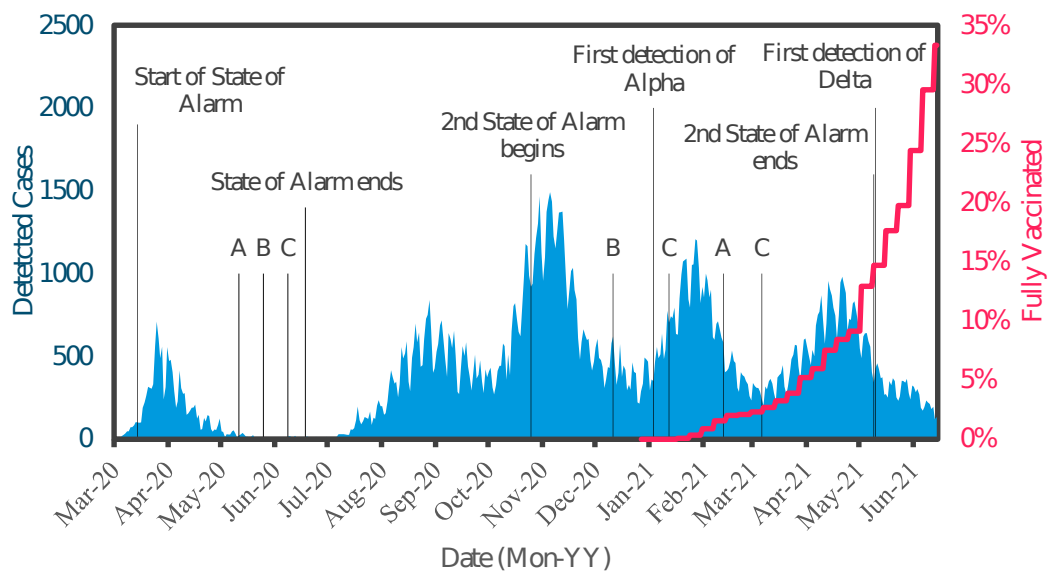
Figure 4: COVID-19 in the Basque Country, Spain. Cases (blue bars) and vaccination rates (red line) are shown from March 2020 to June 2021, before the Delta variant became dominant. Letters A, B, and C indicate levels of mobility restriction: A - mobility allowed municipality of residence, B - mobility allowed within the historical territory of residence, and C - mobility allowed within the Basque Country.

from December 2020 to June 2021. We considered empirical vaccine efficacies ($k < 1$) and a proportion of already naturally immunized persons via a previous natural COVID-19 infection as recorded by the Basque Health Service (Osakidetza).

With a population size of $N = 2.2 \cdot 10^6$, less than 200 000 infections have been reported as of July 1st 2021. Hence, around 10% of the population is considered to be immune prior to the start of the vaccination rollout. We thus consider a pool of default susceptible individuals equal to 90% ($S_0/N \approx 90\%$). Note that this assumption can be modified as new positive cases are detected by counting the current immunized population either by natural infection or by vaccination.

Vaccination coverage was given by $cN = c(S_0 + R(t_0)) = cS_0 + cR(t_0)$ with the recovered $R(t_0)$ at a given time t_0 of analysis, when vaccines were administered in the population independent of the individual previous record of negative or positive PCR tests. Given the non-vaccinated $(1 - c)S_0$ and vaccinated with vaccine efficacy k, i.e. $c \cdot (1 - k)S_0$, where $r = 1 - k$ is the relative risk measured in vaccine trials, we obtained a refined version of the dynamics of infected

$$\frac{d}{dt}I = \left(\beta \frac{S}{N} - \gamma \right) I = \left(\frac{\beta}{N} \left((1 - c)S_0 + c \cdot (1 - k)S_0 \right) - \gamma \right) I.$$

Similarly, as described in Section 2.3, we computed the vaccination coverage threshold by assuming a growth condition of $\lambda = 0$, as in Equation 2. We have

$$c = \frac{1}{k} \left(1 - \frac{1}{\left(\frac{\beta}{\gamma} \cdot \frac{S_0}{N} \right)} \right),$$

showing that while the condition $\frac{S_0}{N} < 1$ reduced the threshold coverage, having $k < 1$ may significantly increase the threshold again.

Here, as shown in Section 2.3, we consider an infection rate of $\beta \approx 3.5\,\gamma$ and a proportion of the susceptible population as $\frac{S_0}{N} \approx 90\%$. By assuming a vaccination rollout using a vaccine with a perfect efficacy ($k = 1$), the value of vaccination coverage to achieve herd immunity is given by

$$c = \left(1 - \frac{1}{\left(\frac{\beta}{\gamma} \cdot \frac{S_0}{N} \right)} \right) = 0.683 \approx 68\%,$$

which is only slightly below the vaccination coverage of $c = 0.714 \approx 71\%$ that was estimated for a 100% susceptible population (see Section 2.3). On the other hand, given imperfect vaccine efficacies ($k < 1$), such as those estimated in Sections 2.2.2 and 2.2.3, the results for the threshold vaccination coverage to achieve herd immunity would be higher. For example, assuming that the efficacy for the BioNTech/Pfizer (BioN/Pf) vaccine is approximately 90% ($k_{BioN/Pf} \approx 90\%$) and that the vaccination rollout in the Basque population has used the BioNTech/Pfizer vaccine only (see Figure 5), we obtained

$$c = \frac{1}{k_{BioN/Pf}} \left(1 - \frac{1}{\left(\frac{\beta}{\gamma} \cdot \frac{S_0}{N} \right)} \right) = 0.758 \approx 76\%,$$

that is, approximately 76% of the Basque population would need to receive two doses to reach the (theoretical) population herd immunity threshold.

Notice that this result was still close to the previously estimated vaccine coverage threshold when using a perfect vaccine. Hence, it would be acceptable to say that, in the considered epidemiological context of the initial vaccination rollout phase, the use of BioNTech/Pfizer vaccine is the most beneficial strategy.

On the other hand, assuming a $k_{OxAZ} \approx 70\%$ efficacy for the Oxford/Astra-Zeneca vaccine, a much large proportion of the population (approximately 97%) would need to receive two doses to reach the herd immunity threshold, that is,

$$c = \frac{1}{k_{OxAZ}} \left(1 - \frac{1}{\left(\frac{\beta}{\gamma} \cdot \frac{S_0}{N} \right)} \right) = 0.975 \approx 97\%.$$

These results are intriguing and must be considered carefully. It is also important to emphasize that the emergence of new COVID-19 variants that can eventually escape immunity conferred by vaccines as well as the natural loss of immunity found to occur after 3 months of vaccination, will lead to different estimations. Moreover, vaccine efficacy is not a static measure, and therefore its evaluation continues with new aspects of disease protection and preconditioning for its use being identified over time (Aguiar et al. (2016c); Aguiar and Stollenwerk (2018); Aguiar (2018); Halstead et al. (2020)).

In the next section, we present a further refined modelling framework to include various aspects of the vaccine heterogeneity, considering not only dif-
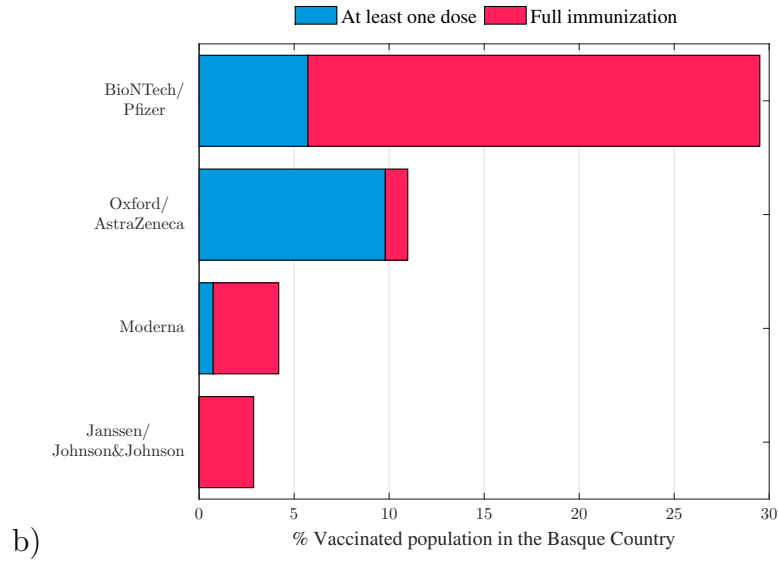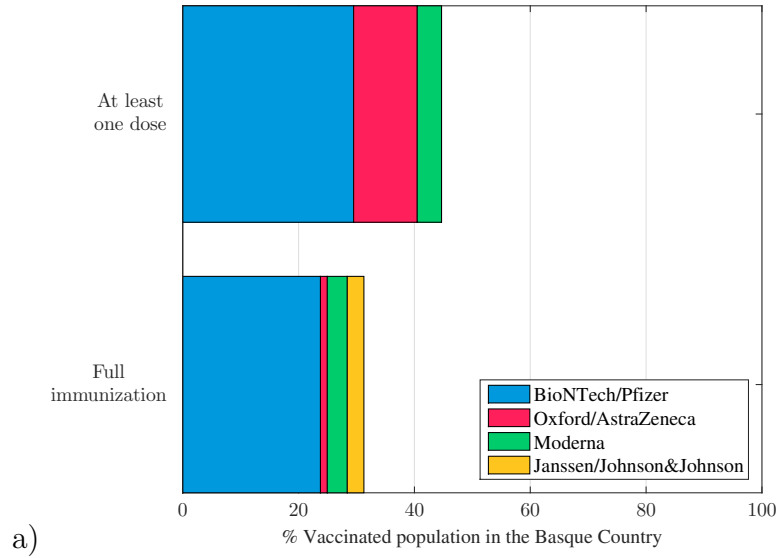
a)

b)

Figure 5: Vaccination rollout in the Basque Country, Spain, from January 1, 2021, to June 14, 2021. Four vaccines were used: BioNTech/Pfizer and Moderna (mRNA vaccines) and Oxford/AstraZeneca and Janssen/Johnson&Johnson (viral vector vaccines). In a) the vaccination coverage of individuals that have received at least one dose of vaccine ($\approx 47.6\%$) and the coverage of individuals that have completed the immunization schedule ($\approx 31.3\%$). In b) the detailed numbers of doses per vaccine type administered given in percentages. Remark: The data on vaccination coverages were first provided by the Basque Health Service (Osakidetza) by May 2021.

ferent efficacies between one or two doses but also their performance against hospitalization and overall infection.

2.4. Modelling COVID-19 vaccination rollout: the baseline SHAR model and extensions

As an extension of the basic SIR model, the $SHAR$ model stratifies the infected class into Hospitalized/severe disease cases (H) and Asymptomatic/mild cases (A). Susceptible (S) individuals become infected, developing either severe disease prone to hospitalization, with a proportion η, or developing a mild infection, potentially asymptomatic, with a proportion $1 - \eta$. The infections due to imported cases (ϱ) are counted as a very small proportion of the population size N.. A scaling factor ϕ is used to differentiate the infectivity $\phi\beta$ of mild/asymptomatic infections with respect to the baseline infectivity β of severe/hospitalized cases. Recovered individuals R are considered resistant to reinfection. The dynamics for the mean values can be written as an ordinary differential equation system (3).

$$
\begin{aligned}
\frac{d}{dt}S &= -\beta\frac{S}{N}(H + \phi A + \varrho N), \\
\frac{d}{dt}H &= \eta\beta\frac{S}{N}(H + \phi A + \varrho N) - \gamma H, \\
\frac{d}{dt}A &= (1 - \eta)\beta\frac{S}{N}(H + \phi A + \varrho N) - \gamma A, \\
\frac{d}{dt}R &= \gamma(H + A).
\end{aligned}
\tag{3}
$$

The vaccination coverage threshold to achieve herd immunity in system 3 can be obtained similarly as presented in Section 2.3.1.

Aiming to evaluate the impact of the initial phase of COVID-19 vaccination rollout in the Basque Country, from December 2020 to June 2021, this framework is extended. Two vaccination models, the vaccine V_1, protecting only against severe disease, but failing to block the transmission of the virus, and the vaccine V_2, protecting only against severe disease and infection, are presented.

2.4.1. Modelling vaccine efficacy against severe disease only: the $SHARV_1$ model

A vaccine which protects against severe disease but not against infection, i.e. failing to block virus transmission, is modelled with a $SHAR$ type model that decreases the risk of vaccinated individuals developing severe disease (r_H) but has no effect against mild/asymptomatic infection. The $SHARV_1$ model is given by 4.

$$\frac{d}{dt}S = -\beta\frac{S}{N}(H + \phi A + \varrho N),$$

$$\frac{d}{dt}S_v = -\beta\frac{S_v}{N}(H + \phi A + \varrho N),$$

$$\frac{d}{dt}H = \eta\beta\frac{S}{N}(H + \phi A + \varrho N) + r_H \cdot \eta\beta\frac{S_v}{N}(H + \phi A + \varrho N) - \gamma H, \quad (4)$$

$$\frac{d}{dt}A = (1-\eta)\beta\frac{S}{N}(H + \phi A + \varrho N) + (1-\eta)\beta\frac{S_v}{N}(H + \phi A + \varrho N)$$

$$+ (1-r_H)\eta\beta\frac{S_v}{N}(H + \phi A + \varrho N) - \gamma A,$$

$$\frac{d}{dt}R = \gamma(H + A),$$

where we distinguish naive susceptibles S and vaccinated susceptibles S_v individuals. While naive individuals S become infected with natural infection rate β or $\phi\beta$, by interacting with a severe or mild infected individual respectively, vaccinated S_v individuals will experience a reduced infection rate $r_1 \cdot \beta$, as described in the vaccine trial analysis above, protected against severe infection, but eventually becoming a mild/asymptomatic case, which is likely to be undetected, and hence, contributing to the force of infection, since they can still transmit the virus.

We extended the $SHARV_1$ model to include the difference in the efficacies between partial and full vaccination. The susceptible population are now stratified into unvaccinated susceptible (S), susceptible vaccinated with a single vaccine dose ($S_{v,1}$), and susceptible fully immunized with two vaccine doses ($S_{v,2}$). Let $k_{H,1}$ be the efficacy of partial vaccination and k_{H_2} be the efficacy of full vaccination. The two-dose $SHARV_1$ model is given by system (5).

$$\frac{d}{dt}S = -\beta\frac{S}{N}(H + \phi A + \varrho N),$$

$$\frac{d}{dt}S_{v,1} = -\beta\frac{S_{v,1}}{N}(H + \phi A + \varrho N),$$

$$\frac{d}{dt}S_{v,2} = -\beta\frac{S_{v,2}}{N}(H + \phi A + \varrho N),$$

$$\frac{d}{dt}H = \eta\beta\frac{S}{N}(H + \phi A + \varrho N) - \gamma H$$

$$+ \sum_{j=1}^{2} r_{H,j} \cdot \eta\beta\frac{S_{v,j}}{N}(H + \phi A + \varrho N), \qquad (5)$$

$$\frac{d}{dt}A = (1 - \eta)\beta\frac{S}{N}(H + \phi A + \varrho N) - \gamma A$$

$$+ \sum_{j=1}^{2}\left[(1 - \eta r_{H,j})\left(\beta\frac{S_{v,j}}{N}(H + \phi A + \varrho N)\right)\right],$$

$$\frac{d}{dt}R = \gamma(H + A).$$

2.4.2. Modelling vaccine efficacy against severe disease and infection: the $SHARV_2$ model

On the other hand, a vaccine which protects against infection and against severe disease is modelled with a $SHAR$ type model that decreases the risks of vaccinated individuals becoming infected (r_I) and from developing severe disease (r_H). The complete $SHARV_2$ model is given by 6. Its dynamical behaviour is very similar to the simple SIR model.

$$\frac{d}{dt}S = -\beta\frac{S}{N}(H + \phi A + \varrho N),$$

$$\frac{d}{dt}S_v = -\beta\frac{S_v}{N}(H + \phi A + \varrho N),$$

$$\frac{d}{dt}H = \eta\beta\frac{S}{N}(H + \phi A + \varrho N) + r_H \cdot \eta\beta\frac{S_v}{N}(H + \phi A + \varrho N) - \gamma H, \qquad (6)$$

$$\frac{d}{dt}A = (1 - \eta)\beta\frac{S}{N}(H + \phi A + \varrho N) + r_I \cdot (1 - \eta)\beta\frac{S_v}{N}(H + \phi A + \varrho N) - \gamma A,$$

$$\frac{d}{dt}R = \gamma(H + A) + (1 - r_I) \cdot \beta\frac{S_v}{N}(H + \phi A + \varrho N).$$

Likewise, we extended the $SHARV_2$ model to incorporate partial and full vaccination efficacy. This is given by system (7).

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$$\frac{d}{dt}S = -\beta\frac{S}{N}(H + \phi A + \varrho N),$$

$$\frac{d}{dt}S_{v,1} = -\beta\frac{S_{v,1}}{N}(H + \phi A + \varrho N),$$

$$\frac{d}{dt}S_{v,2} = -\beta\frac{S_{v,2}}{N}(H + \phi A + \varrho N),$$

$$\frac{d}{dt}H = \eta\beta\frac{S}{N}(H + \phi A + \varrho N) - \gamma H$$

$$+ \sum_{j=1}^{2} r_{H,j} \cdot \eta\beta\frac{S_{v,j}}{N}(H + \phi A + \varrho N), \tag{7}$$

$$\frac{d}{dt}A = (1 - \eta)\beta\frac{S}{N}(H + \phi A + \varrho N) - \gamma A$$

$$+ \sum_{j=1}^{2} [r_{I,j}(1 - \eta) + (r_{I,j} - r_{H,j})\eta]\,\beta\frac{S_{v,j}}{N}(H + \phi A + \varrho N),$$

$$\frac{d}{dt}R = \gamma(H + A) + \sum_{j=1}^{2}(1 - r_{I,j})\beta\frac{S_{v,j}}{N}(H + \phi A + \varrho N),$$

with vaccine coverage $S_{v,1} = c_1 S_0$ for first dose uptake, $S_{v,2} = c_2 S_0$ for second dose uptake, and finally, for non-vaccinated susceptible individuals $S = (1 - (c_1 + c_2))S_0$, with $S_0 = N - R(t_0)$.

The different COVID-19 vaccines in use have features placing them closer to one or the other of these two extreme cases. The analysis of vaccination programmes administrating either vaccine type 1, V_1, and vaccine type 2, V_2, has shown that vaccine performance is driven by the ability of asymptomatic or mild disease cases to transmit the virus, see Aguiar et al. (2021b). It was demonstrated that vaccines protecting against severe disease failing to block virus transmission would not be able to significantly reduce the severe disease burden during the initial stage of a vaccination rollout, leading to an eventual increase in the number of overall infections in a population. However, this modelling exercise was not performed for the simultaneous use of these two vaccine types, V_1 and V_2. Moreover, the differences in vaccine

efficacy observed for a single-dose versus a two-dose vaccination, nor the differences in vaccine efficacy observed for severe disease and infection were never considered.

2.5. Numerical experiments

The parameters used for model simulations are given in Table 1. Results obtained for the BioNTech/Pfizer vaccine, assuming vaccine efficacies reported in Haas et al. (2021), and for the Oxford/AstraZeneca vaccine, assuming vaccine efficacies as reported in Cerqueira-Silva et al. (2022), are compared and shown in Figure 6. For a low vaccination coverage scenario, i.e. with less than 15% of the population receiving at least one vaccine dose, the mixed immunization schedule shows significant differences depending on the assumed type of immunological protection generated after vaccination ($SHARV_1$ protecting against disease only, or $SHARV_2$, protecting against disease and infection). Similar to the results described in Aguiar et al. (2021b), only vaccine type 2 ($SHARV_2$) would significantly reduce the number of hospitalizations during the initial phase of vaccination rollout, while the exclusive use of vaccine type 1 ($SHARV_1$) would notably increase the number of mild/asymptomatic infections, besides having no impact on the number of severe cases for the same time period.

While the BioNTech/Pfizer vaccine has reportedly higher efficacy than the Oxford/AstraZeneca vaccine (see Table 1), the differences between the total hospitalizations and cases are only slight. For example, using a type 2 vaccine with the same efficacy as the BioNTech/Pfizer vaccine will result in 19 619 hospitalizations after 6 months compared to 22 053 for a vaccine with the efficacy of the Oxford/AstraZeneca vaccine.

On the other hand, in a scenario of high vaccine coverage, i.e. with more than 85% of the population receiving at least one vaccine dose, both vaccine types will significantly decrease hospitalizations. While the exclusive use of vaccine type 2 would control the disease spreading and hospitalizations, the exclusive use of a vaccine that only prevents hospitalizations but not infections will result in at least a four-fold increase in mild and asymptomatic cases after 6 months (see Figure 7). Note that in simulations where the proportion of hospitalizations (η) is assumed to be smaller, the increase in mild and asymptomatic cases becomes less pronounced, but are still agreeing with the results presented in Figures 6 and 7.

Results presented here are consistent with the real-life scenario, with an increase of overall infections being reported by the public health authorities

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while vaccination coverages were low, decreasing over time as vaccination coverages became significantly high.

Table 1: Parameter values and initial conditions for the $SHAR$, $SHARV_1$, and $SHARV_2$ models.

| Parameter	Description	Value
β	Transmission rate	0.05
ϕ	Scaling factor for infectivity of mild/asymptomatic cases	1.60
γ	Recovery rate	0.05
η	Proportion of hospitalization	0.45
ρ	Import parameter	e^{-12}
$S(0)$	Initial susceptible	$N - H(0) - A(0) - R(0) - V_1(0) - V_2(0)$
$H(0)$	Initial hospitalized	1 000
$A(0)$	Initial mild/asymptomatic	2 000
$R(0)$	Initial recovered	200 000
$S_{v,1}(0)$	Initial vaccinated with one dose	276 497
$S_{v,2}(0)$	Initial vaccinated with two doses	114 619
N	Total population	2 199 711
Oxford/AstraZeneca (Cerqueira-Silva et al., 2022)		
$k_{I,1}$	Efficacy of partial vaccination against infection	0.504
$k_{I,2}$	Efficacy of full vaccination against infection	0.781
$k_{H,1}$	Efficacy of partial vaccination against hospitalization	0.709
$k_{H,2}$	Efficacy of full vaccination against hospitalization	0.914
$r_{I,1}$	Risk of infection for partially vaccinated	0.496
$r_{I,2}$	Risk of infection for fully vaccinated	0.219
$r_{H,1}$	Risk of hospitalization for partially vaccinated	0.191
$r_{H,2}$	Risk of hospitalization for fully vaccinated	0.086
BioNTech/Pfizer (Haas et al., 2021)		
$k_{I,1}$	Efficacy of partial vaccination against infection	0.577
$k_{I,2}$	Efficacy of full vaccination against infection	0.953
$k_{H,1}$	Efficacy of partial vaccination against hospitalization	0.757
$k_{H,2}$	Efficacy of full vaccination against hospitalization	0.972
$r_{I,1}$	Risk of infection for partially vaccinated	0.423
$r_{I,2}$	Risk of infection for fully vaccinated	0.047
$r_{H,1}$	Risk of hospitalization for partially vaccinated	0.243
$r_{H,2}$	Risk of hospitalization for fully vaccinated	0.028
Vaccination coverage		
$S_{v,1}/N$	Low vaccination scenario, one dose	0.1257
$S_{v,2}/N$	Low vaccination scenario, two doses	0.0521
$S_{v,1}/N$	High vaccination scenario, one dose	0.8785
$S_{v,2}/N$	High vaccination scenario, two doses	0.8563
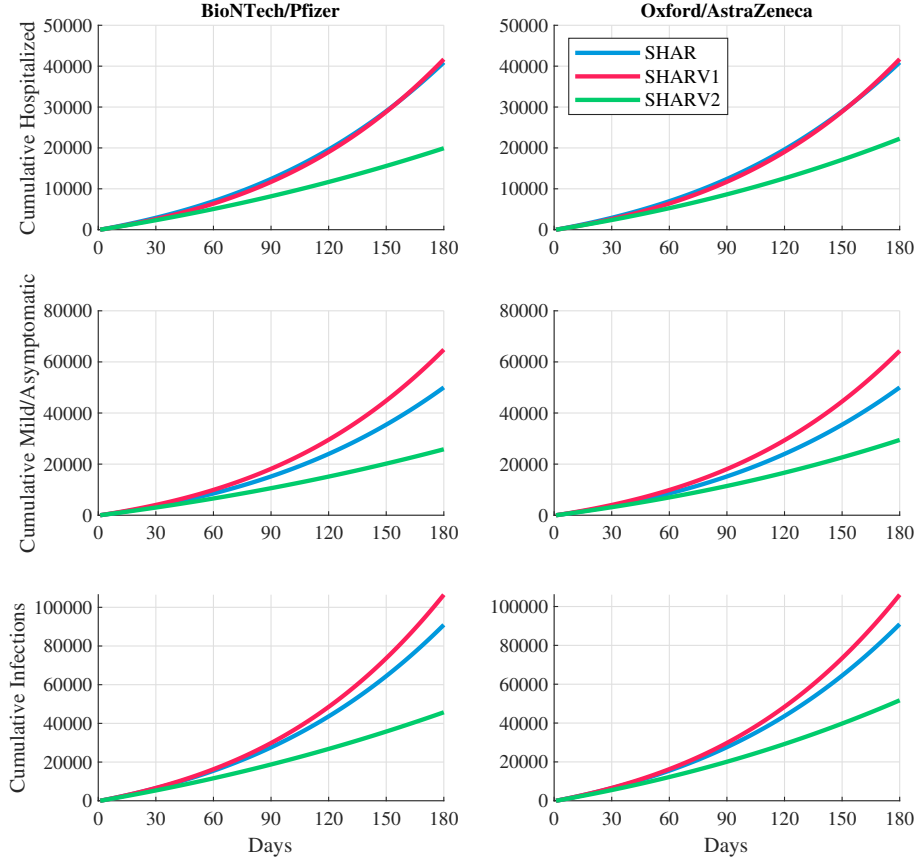
Figure 6: Projected cases and hospitalizations using the models $SHAR$, $SHARV_1$, and $SHARV_2$, with a mixed immunization schedule, given the BioNTech/Pfizer and Oxford/AstraZeneca vaccine, and low vaccine coverage of 13% and 5% for one and two doses, respectively.
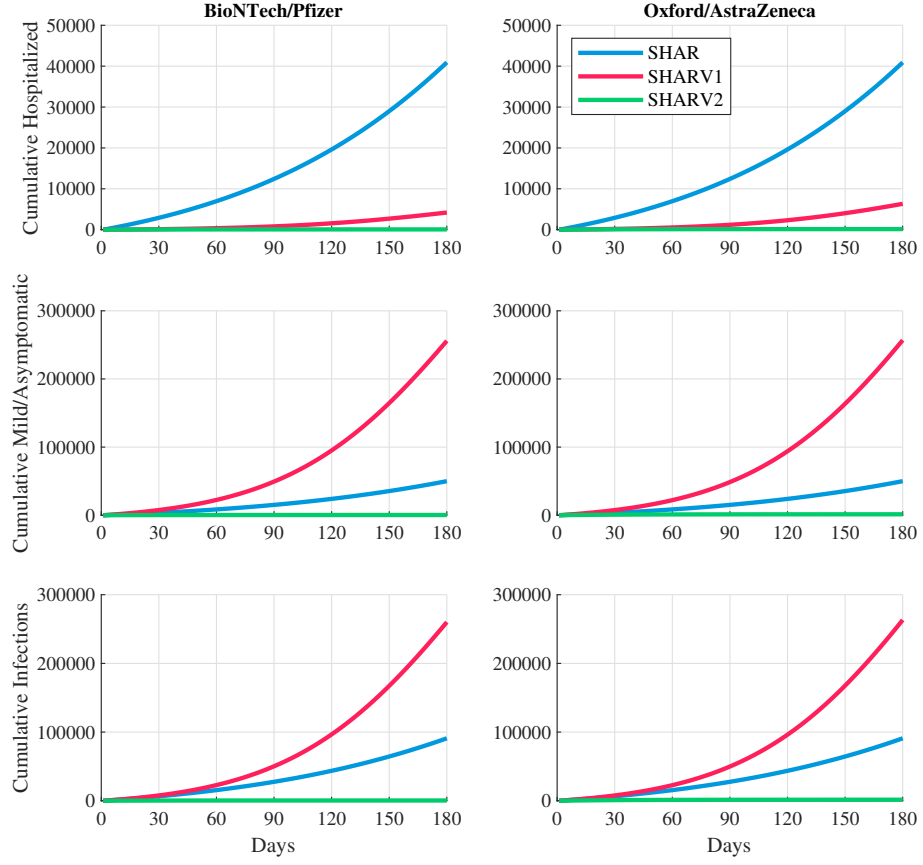
Figure 7: Projected cases and hospitalizations using the models $SHAR$, $SHARV_1$, and $SHARV_2$, with a mixed immunization schedule, given the BioNTech/Pfizer and Oxford/AstraZeneca vaccine, and high vaccine coverage of 88% and 86% for one and two doses, respectively.

2.5.1. Analytical solutions

For analytical insights into the behaviour of the model with a single-dose vaccination and two-dose vaccination compared to the non-vaccination scenario, we consider the dynamics of the disease compartments

$$
\frac{d}{dt}H = \eta\beta\frac{S}{N}(H + \phi A + \varrho N) - \gamma H
$$
$$
+ \sum_{j=1}^{2} r_{H,j} \cdot \eta\beta\frac{S_{v,j}}{N}(H + \phi A + \varrho N),
$$
$$
\frac{d}{dt}A = (1 - \eta)\beta\frac{S}{N}(H + \phi A + \varrho N) - \gamma A
$$
$$
+ \sum_{j=1}^{2} [r_{I,j}(1 - \eta) + (r_{I,j} - r_{H,j})\eta]\,\beta\frac{S_{v,j}}{N}(H + \phi A + \varrho N),
$$

including the vaccination coverage vector $\underline{c} := (c_1, c_2)$ for single-dose and two-dose vaccine administration, and the vaccine efficacy vector $\underline{k} = (k_{H,1}, k_{I,1}, k_{H,2}, k_{I,2})$ for the respective efficacies against hospitalization and infection, after administering one dose or two doses.

The vaccination coverage vector considers the fraction of vaccinated susceptible individuals over the total number of susceptible individuals $S_0 := S + S_{v1} + S_{v2}$, hence $S_{v1} = c_1 \cdot S_0$, $S_{v2} = c_2 \cdot S_0$, and the naive susceptible $S = 1 - (c_1 + c_2) \cdot S_0$.

2.5.2. Stationary state solutions and relative hospitalization reduction

Our model considers an imperfect vaccine with vaccinated individuals able to transmit the disease even when the vaccine is reported with significant efficacy. Moreover, we assume that the COVID-19 herd immunity is not yet reached (see Section 2.3.1), and therefore, we consider $S_0(t_0) =: N - R(t_0)$. The stationary state solution is

$$
\begin{pmatrix} H^* \\ A^* \end{pmatrix} = \frac{\beta\frac{S_0}{N} \cdot \varrho N}{\gamma - \kappa\beta\frac{S_0}{N}} \begin{pmatrix} \eta y \\ (1 - \eta)z \end{pmatrix}
$$

now with vaccination-specific variables

$$
y = 1 - \sum_{j=1}^{2} c_j \cdot k_{H,j}
$$

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and

$$z = 1 + \sum_{j=1}^{2} c_j \frac{\eta k_{H,j} - k_{I,j}}{1 - \eta}$$

using $\kappa := \eta y + \phi(1-\eta)z = \kappa(\underline{c}, \underline{k})$ in the stationary state solution, depending on the vaccination variables y, z and on the SHAR specific parameters η and ϕ.

For the relative reduction of hospitalizations we obtain

$$\frac{H^*(\underline{c}, \underline{k})}{H_0^*} = \frac{1 - (\eta + \phi(1-\eta)) \cdot \frac{\beta}{\gamma}\frac{S_0}{N}}{1 - (\eta y + \phi(1-\eta)z) \cdot \frac{\beta}{\gamma}\frac{S_0}{N}} \cdot y, \tag{8}$$

a surprisingly simple expression, with e.g. the import ϱ cancelling out.

3. Results

Numerical experiments are now conducted in order to analyse the impact of vaccination rollout in the Basque Country, under a mixed vaccination setup, considering vaccination coverage for a population with at least one vaccine dose and vaccination coverage for a population with the complete two-dose immunization schedule. For vaccine types 1 and 2, we show the projections of hospitalizations while using vaccines with different efficacies.

Vaccination coverage is varied monthly, as reported by the Basque Health Service (Osakidetza), and results using vaccine model type 1, $SHARV_1$, and vaccine model type 2, $SHARV_2$, are compared with the scenario without vaccination $SHAR$. With similar results, figure 8 shows the projections obtained when assuming BioNTech/Pfizer efficacy values, whereas figure 9 shows the projections obtained while using the Oxford/AstraZeneca efficacy values.

In detail, for different vaccine efficacies, high or intermediate, and different vaccine generating different types of protection (against disease or both disease and infection), projections for hospitalizations, mild/asymptomatic cases, and total infections are shown. Results obtained by using vaccine type 1 are shown in Figure 10, while Figure 11 presents the results obtained by using vaccine type 2. In both figures, vaccine coverages correspond to the monthly vaccine coverage reported by the Basque Health Service, from January to June 2021.
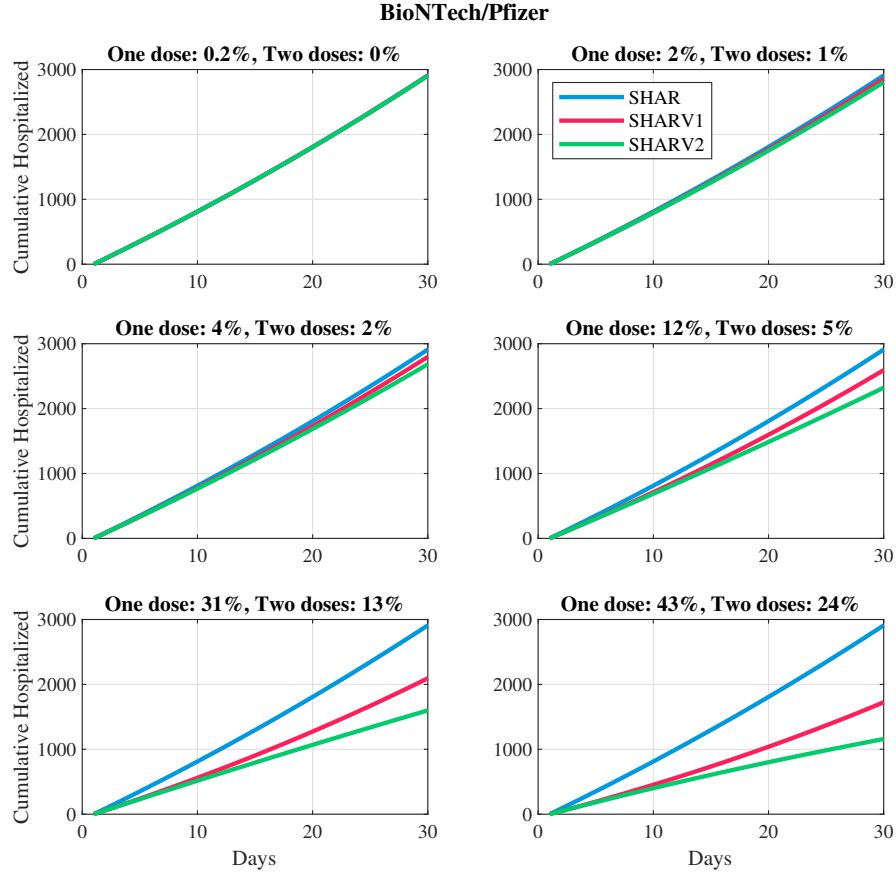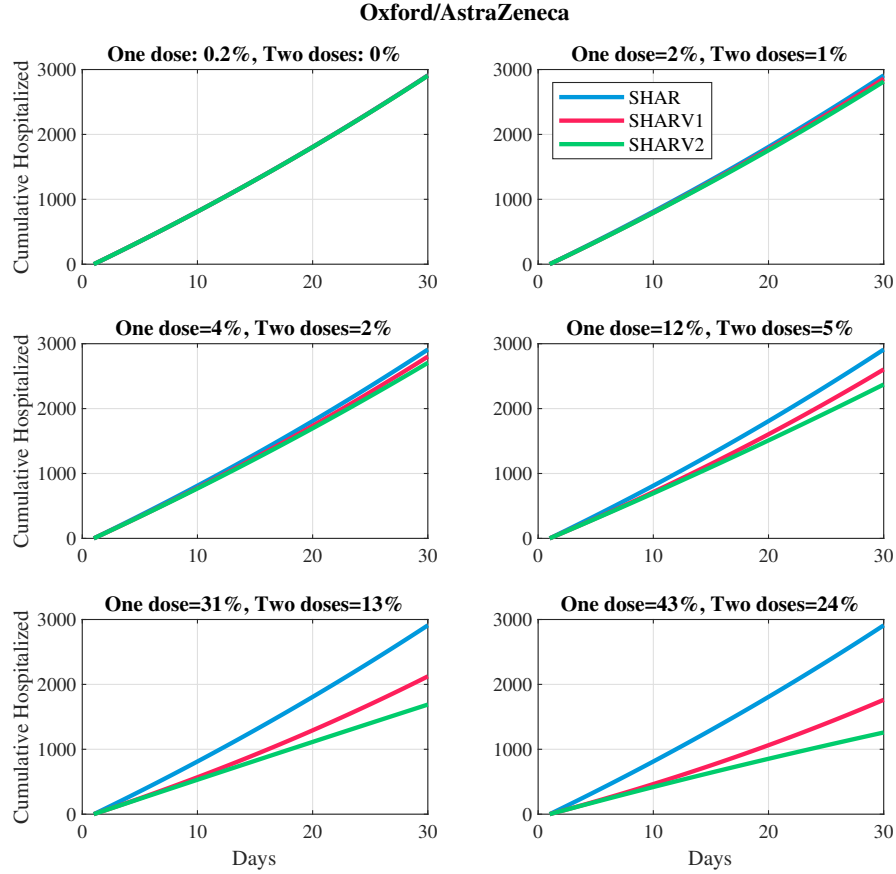
Figure 8: Hospitalization projections from January to June 2021, with varying coverages for single and two-dose vaccination using the reported efficacy for BioNTech/Pfizer. Model results without vaccination are shown in blue. Vaccine coverages for a single and two-dose vaccination are assumed as reported by the Basque Health Service (Osakidetza) in a) January 2021 $(0.2\%, 0\%)$, b) February 2021 $(2\%, 1\%)$, c) March 2021 $(4\%, 2\%)$, d) April 2021 $(12\%, 5\%)$, e) May 2021 $(31\%, 13\%)$, and f) June 2021 $(43\%, 24\%)$. Model outputs are shown in red for $SHARV_1$ and in green for $SHARV_2$ vaccine types.

Oxford/AstraZeneca

Figure 9: Hospitalization projections from January to June 2021, with varying coverages for single and two-dose vaccination using the reported efficacy for Oxford/AstraZeneca. Model results without vaccination are shown in blue. Vaccine coverages for a single and two-dose vaccination are assumed as reported by the Basque Health Service (Osakidetza) in a) January 2021 $(0.2\%, 0\%)$, b) February 2021 $(2\%, 1\%)$, c) March 2021 $(4\%, 2\%)$, d) April 2021 $(12\%, 5\%)$, e) May 2021 $(31\%, 13\%)$, and f) June 2021 $(43\%, 24\%)$. Model outputs are shown in red for $SHARV_1$ and in green for $SHARV_2$ vaccine types.
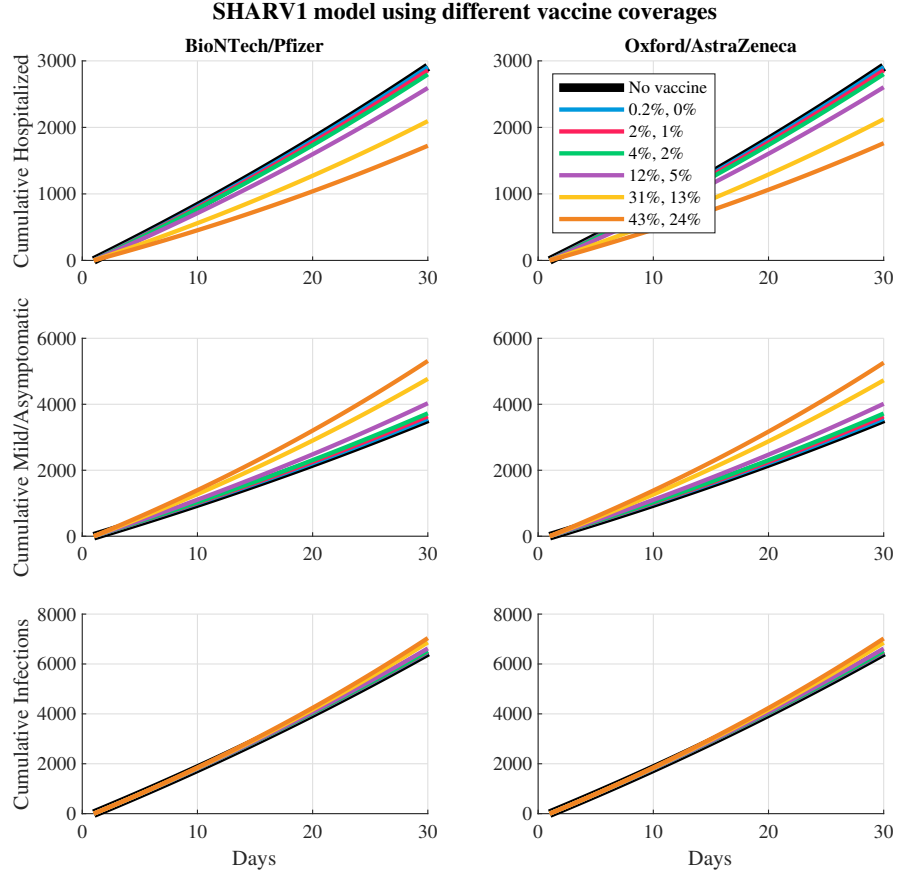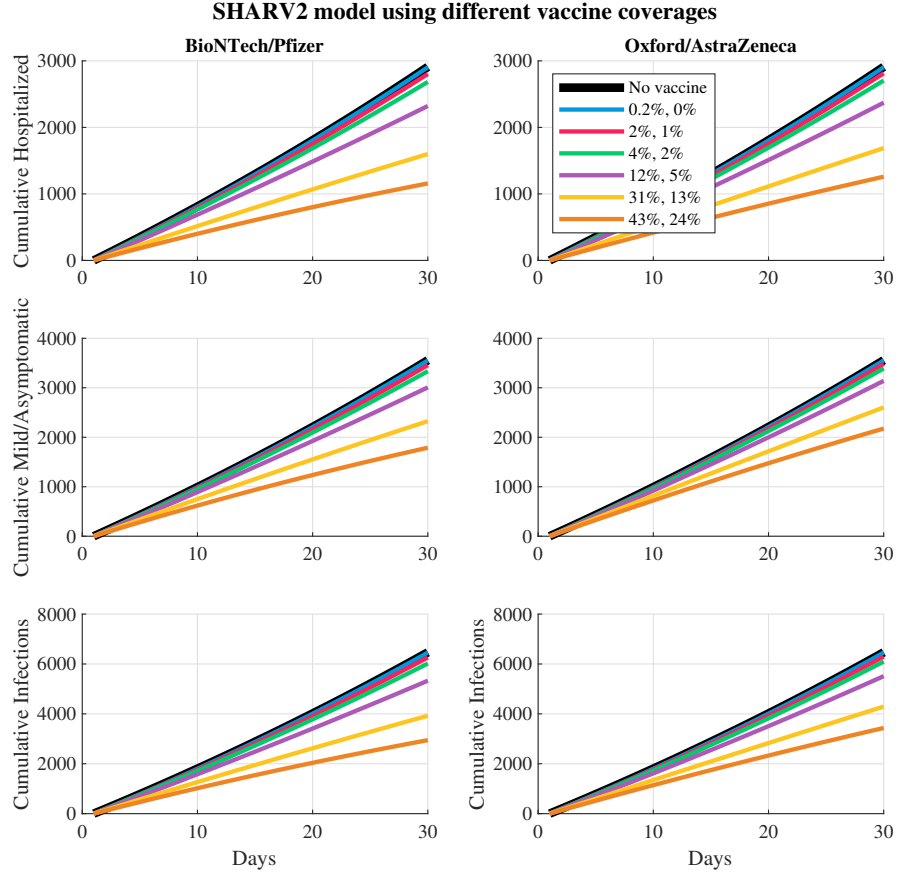
Figure 10: Projected hospitalizations, mild/asymptomatic cases, and total infections using the $SHARV_1$ model (5) for different coverages of the BioNTech/Pfizer and Oxford/AstraZeneca vaccines. Each line corresponds to vaccine coverages equal to x, y as indicated in the legend, where x is the coverage for one dose, and y is the coverage for two doses.

Figure 11: Projected hospitalizations, mild/asymptomatic cases, and total infections using the $SHARV_2$ model (7) for different coverages of the BioNTech/Pfizer and Oxford/AstraZeneca vaccines. Each line corresponds to vaccine coverages equal to x, y as indicated in the legend, where x is the coverage for one dose, and y is the coverage for two doses.

3.1. Vaccination impact in the Basque Country

Here, we evaluate the vaccine impact on severe cases/hospitalizations of COVID-19 in the Basque Country, Spain, from January to June 2021. The momentary population status of remaining susceptibles after one year of pandemic generating natural immunity is known via the official data provided by the Basque Health Department. The overall vaccine efficacy, as well as the reported differences between a single dose and two-dose vaccination scheme, are considered as reported for the vaccination trials, detailed presented in Sections 2.2.2 and 2.2.3.

As vaccine performance is reported in terms of relative risk $r = 1 - k$ and vaccine efficacy k, vaccination is implemented by assuming reduced infectivity $r \cdot \beta$ (for the vaccinated group) against natural infectivity β (for the non-vaccinated group), as measured in vaccine trials and described in Section 2.4. It is important to mention that while the data on vaccination coverages were first provided only on May 23, 2021, the official data on hospitalizations were available weekly, since March 4, 2020. The number of cases reported on January 1st, 2021, was considered the baseline value of severe cases in the Basque Country prior to vaccination. We started with the model projection of the vaccine impact on hospitalization for the end of May 2021, once the vaccination coverages were known.

Two vaccination rollout scenarios are evaluated, and compared with the empirical data of notified hospitalizations, see Figure 12.

First, for the sake of simplicity, we assume a vaccination rollout scenario where BioNTech/Pfizer vaccine type is exclusively used in the population. This assumption is justified by the fact that this vaccine has been the most used vaccine in the Basque Country population, see Figure 5. With significantly lower efficacy for a single vaccine dose than the efficacy for the full immunization schedule with two-dose vaccination, we also consider that in a single vaccination dose regime the efficacy against severe disease needing hospitalization is significantly higher than the efficacy against overall infection, i.e. the so-called sterilizing immunity, occurring when vaccinated individuals cannot transmit the virus, as reported in Dagan et al. (2021).

The reported vaccination coverages for all vaccines in the Basque Country were, as of 23 May 2021, $c_2 = 17.5\%$ for the population that have received the two vaccine dose, and $(c_1 + c_2) = 38.8\%$ for individuals that have received at least one vaccine dose, hence $c_1 = 21.3\%$ refers to single vaccine dose coverage alone, giving the vaccination coverage vector $\underline{c} = (c_1 = 21.3\%, c_2 = 17.5\%)$. With the vaccine efficacy vector given by $\underline{k} = (k_{H,1} = 78\%, k_{I,1} = 60\%, k_{H,2} = $
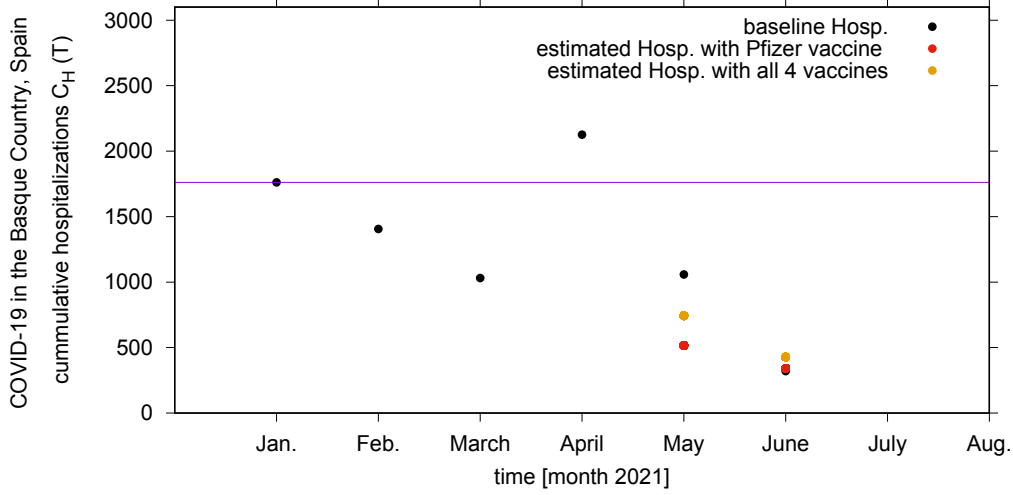
Figure 12: Evaluation of the vaccination impact on hospitalization reduction in the Basque Country. Estimations of hospitalization reductions for May and June 2021 are plotted for two different vaccination rollout scenarios. While the vaccination rollout scenario using exclusively one vaccine type with high efficacy is plotted as red dots, the vaccination rollout scenario using multiple vaccines, with intermediate and high efficacies, simultaneously are plotted as yellow dots. Estimations are compared with the official data on hospitalizations in the Basque Country, from January to June 2021, plotted as black dots.

$92\%, k_{I,2} = 92\%)$, since the BioNTech/Pfizer vaccine was given most often, and the vaccination coverage vector given by $\underline{c} = (c_1 = 21.3\%, c_2 = 17.5\%)$, we obtain the vaccination related variables to be

$$y = 1 - \sum_{j=1}^{2} c_j \cdot k_{H,j} = 1 - (0.21 \cdot 0.78 + 0.18 \cdot 0.92) = 0.6706 \quad ,$$

and by assuming $\eta = 0.08 = 8\%$ for the hospitalization ratio in the Basque Country,

$$z = 1 + \sum_{j=1}^{2} c_j \frac{\eta k_{H,j} - k_{I,j}}{1 - \eta} = 1 - 0.1227 - 0.1656 = 0.7117 \quad .$$

Further, with around 200 000 reported infected cases over the past year, we assume, for the sake of simplicity, that it is roughly the same number of recovered individuals from COVID-19 in the Basque Country, that is,

$$\frac{S_0}{N} \approx \frac{2.2 \cdot 10^6 - 0.2 \cdot 10^6}{2.2 \cdot 10^6} = 2.0/2.2 = 0.909 \quad ,$$

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giving a first approximation for the remaining susceptibility in the study population.

The expected number of hospitalizations $H^*(\underline{c}, \underline{k})$ compared to the baseline hospitalizations notified in January 2021 H_0^*, including a proportionality of reported incidence with the calculated prevalences

$$\frac{C_H(\underline{c}, \underline{k})}{C_{H,0}} = \frac{H^*(\underline{c}, \underline{k})}{H_0^*},$$

gives an evaluation of the vaccination impact from $C_{H,0} = C_H(T = \text{Jan } 2021)$, without vaccination as baseline value, to the values notified in May 2021 as

$$C_H(\underline{c}, \underline{k}) = \frac{H^*(\underline{c}, \underline{k})}{H_0^*} \cdot C_{H,0},$$

with the vaccination coverage reported for May 23, 2021, as $\underline{c} = (c_1 = 21.3\%, \ c_2 = 17.5\%)$, shown as red dot at month 5 in Figure 12.

The estimation for June 2021, is obtained similarly as described above, using the updated vaccination coverages. As of 29 June 2021, the reported vaccination coverages were of $c_2 = 34.1\%$ for the population that have received the two vaccine doses, and $(c_1 + c_2) = 50.9\%$ for individuals that have received at least one vaccine dose, hence $c_1 = 16.8\%$ refers to single vaccine dose coverage alone, giving the vaccination coverage vector $\underline{c}_{n+1} = (c_1 = 16.8\%, \ c_2 = 34.1\%)$.

Results for the evaluation of the vaccination impact on hospitalizations in the Basque Country, Spain while assuming a more realistic scenario of using multiple vaccines with different efficacies are shown as yellow dots in Figure 12. The vaccine variables y and z in Equation 8 have to include now a summation over all applied vaccines, hence $l = 1$ to l_{max}, with $l_{max} = 4$ for the four vaccines administered in the Basque Country. hence, we have

$$y = 1 - \sum_{l=1}^{l_{max}} \sum_{j=1}^{2} c_{j,l} \cdot k_{H,j,l}$$

and

$$z = 1 + \sum_{l=1}^{l_{max}} \sum_{j=1}^{2} c_{j,l} \frac{\eta k_{H,j,l} - k_{I,j,l}}{1 - \eta}.$$

With similar reductions, this result is expected, since the other vaccines—Oxford/AstraZeneca, Moderna and Johnson & Johnson's Janssen vaccines—were used on much smaller scales than the BioNTech/Pfizer vaccine.

Estimations obtained for May 2021 were not satisfactory, since they have predicted a much lower number of severe cases, shown as red and yellow dots, than the official number of hospitalizations, shown as black dots in Figure 12. With an important overestimation of expected hospitalization reduction by vaccination, this outcome can be explained by the large fluctuations observed in the official data from January 2021 to April 2021. There are several reasons to explain this sudden rise of hospitalizations such as the relaxation of hospital admission criteria, which then eventually influenced the data for the following month (see Aguiar et al. (2021a); Stollenwerk et al. (2020); Stollenwerk and Jansen (2010)). Nevertheless, a better result was obtained for June 2021. Although still lower than the notification value, the expected vaccination impact on the hospitalization ratio (red/yellow dots) agrees qualitatively well with the empirical data (black dots) as a positive outcome of this test of concept.

4. Discussion and Conclusion

More than two years have passed since COVID-19 was declared a pandemic by the World Health Organization. The disease has spread rapidly around the world, affecting significantly the collective behaviour of societies by the extreme measures implemented to control disease transmission.

Vaccines against COVID-19 have been developed in record time and are now globally distributed. With varying efficacies, these vaccines are found to be extremely effective in preventing severe disease symptoms and hence, avoiding hospitalization (Dagan et al., 2021; Hall et al., 2021; Nasreen et al., 2022; Andrews et al., 2022). Nevertheless, it is important to mention that vaccine efficacy is not a static measure, with vaccine performance driven by their ability to prevent virus transmission, especially of undetected asymptomatic/mild cases (Oran and Topol, 2020; Johansson et al., 2021; Aguiar et al., 2021b) that are still mobile and able to interact with susceptible individuals, eventually generating severe disease cases. Therefore, a well-planned strategy to use the different COVID-19 vaccines is of major importance to effectively reduce hospitalizations.

In this paper, we investigate the impact of the initial phase of vaccination rollout in the Basque Country, Spain. Two vaccination models, the vaccine V_1, protecting only against severe disease, but fails to block disease transmission, and the vaccine V_2, protecting against severe disease and infection, are studied. These two limiting cases of vaccine type 1 ($SHARV_1$) and vaccine

type 2 ($SHARV_2$) are refined to consider a mixed vaccination rollout scenario with different vaccine efficacies and their effects observed with a single dose versus a two-dose immunization scheme, including population immunity by natural infection. Further, differences in vaccine efficacy against severe disease versus vaccine efficacy against overall infection after the full two-dose immunization regime in the uneven vaccination rollout setting are evaluated.

We study the initial vaccination rollout phase in the Basque Country, from January to June 2021, before SARS-CoV-2 antibodies generated by vaccination start to decline, eventually reflecting waning immunity, and before the Delta variant, believed to be more than twice as contagious as previous variants (Liu and Rocklöv, 2021), became dominant in the population. We use the recent results of vaccine efficacies from large-scale population surveys, and although we have considered simplified assumptions for the remaining levels of susceptibles and the efficacies for mainly one vaccine, results are consistent with the presently available data, since this vaccine accounts for the majority of vaccinated individuals in the Basque country. However, it is important to mention that there is still ample space for further evaluations, including additional stochastic effects as described e.g. in Aguiar et al. (2021a); Stollenwerk et al. (2020); Stollenwerk and Jansen (2010) and appearing also in the large confidence intervals so far observed in the vaccine efficacies in vaccine trials as well as in larger population studies, see e.g. Voysey et al. (2021); Dagan et al. (2021) for other such studies recently published.

Although the vaccination rollouts are advancing fast, a large part of the global population is still covered with a single dose of different vaccines. Therefore, the first dose vaccination regime is still important to be considered in the momentary scenario wherein populations have a large proportion of individuals only being vaccinated with a single dose, still waiting to receive the second vaccine dose.

We have shown that a vaccine that protects against hospitalization but fails to block virus transmission will eventually increase the overall infections, driven by the mobility of asymptomatic and mild cases. This effect is exacerbated as vaccine coverage increases.

The difference in the efficacies between the BioNTech/Pfizer and Oxford/AstraZeneca vaccines only slightly affects the total number of hospitalization and mild cases in our simulations. Both vaccines reduce the number of hospitalizations and cases compared to the no-vaccine scenario under the $SHARV_2$ model assumption. However, under the $SHARV_1$ model, usage of

either vaccine results in more infections overall. These results are consistent with the real-life scenario where an increase in overall infection has been reported by the public health authorities while vaccination coverages were low, decreasing over time as vaccination coverages became significantly high.

Applied to the Basque Country, where the different COVID-19 vaccines used have features placing them closer to one or the other of these two extreme cases—$SHARV_1$ and $SHARV_2$—two vaccination rollout scenarios were evaluated and compared with the empirical data of notified hospitalizations. With a population in a mixed vaccination setting, our results have shown that a reduction of hospitalizations in the Basque Country was initially observed in May 2021, five months after the mass vaccination started, but still with quantitatively unsatisfactory results. Finally, the June values were also quantitatively describing well the observed reduction of hospitalizations in the Basque Country.

Information on COVID-19 vaccine efficacies is updated frequently and the new information can be included in the modelling framework as needed. Studies like this one are, nevertheless, timely and of major importance to understanding the vaccination coverage needed to achieve herd immunity in different settings, including future planning of immunization programmes for new vaccine generations that will likely need to be evaluated under the same settings presented here. It is important, however, to point out that further model refinement will be needed since other factors such as seasonality of respiratory diseases might play an additional role in disease transmission and control. Moreover, new findings and the changing nature of the disease require further extensions of the model to include new epidemiological scenarios such as waning immunity from vaccination, presence of multiple variants, booster doses, and reinfection.

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