Original Article

The role of mild and asymptomatic infections on COVID-19 vaccines performance: A modeling study ☆

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HIGHLIGHTS

- COVID-19 vaccines with different efficacies are reported to be effective against severe disease.
- Vaccine sterilizing immunity is still being evaluated.
- We investigate COVID-19 vaccine performance as vaccine efficacy and vaccine coverage vary.
- Vaccine performance is driven by the ability of asymptomatic infections transmitting the virus.
- Planned strategy to use different COVID-19 vaccines will optimize hospitalization reductions.

GRAPHICAL ABSTRACT
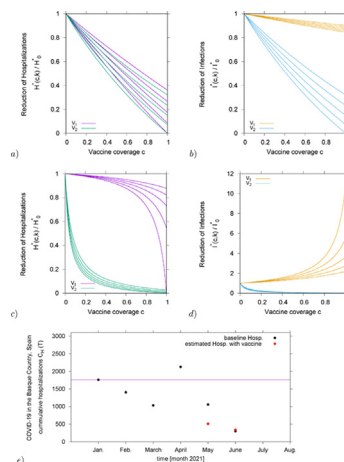
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ABSTRACT

Introduction: Different COVID-19 vaccine efficacies are reported, with remarkable effectiveness against severe disease. The so called sterilizing immunity, occurring when vaccinated individuals cannot transmit the virus, is still being evaluated. It is also unclear to what extent people with no symptoms or mild infection transmit the disease, and estimating their contribution to outbreaks is challenging.
Objective: With an uneven roll out of vaccination, the purpose of this study is to investigate the role of mild and asymptomatic infections on COVID-19 vaccine performance as vaccine efficacy and vaccine coverage vary.
Methods: We use an epidemiological SHAR (Susceptible-Hospitalized-Asymptomatic-Recovered) model framework to evaluate the effects of vaccination in different epidemiological scenarios of coverage and

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Vaccine coverage
Asymptomatic infection

efficacy. Two vaccination models, the vaccine V_1 protecting against severe disease, and the vaccine V_2, protecting against infection as well as severe disease, are compared to evaluate the reduction of overall infections and hospitalizations.

Results: Vaccine performance is driven by the ability of asymptomatic or mild disease cases transmitting the virus. Vaccines protecting against severe disease but failing to block transmission might not be able to reduce significantly the severe disease burden during the initial stage of a vaccination roll out programme, with an eventual increase on the number of overall infections in a population.

Conclusion: The different COVID-19 vaccines currently in use have features placing them closer to one or the other of these two extreme cases, V_1 and V_2, and insights on the importance of asymptomatic infection in a vaccinated population are of a major importance for the future planning of vaccination programmes. Our results give insights on how to best combine the use of the available COVID-19 vaccines, optimizing the reduction of hospitalizations.

Introduction

More than a year has passed since COVID-19 was declared a pandemic by the World Health Organization (WHO). As of beginning of June, 2021, i.e. when this manuscript was submitted, more than 170 million COVID-19 cases worldwide were reported, with around 3.3 million deaths [1]. Number of cases continued to increase and, with eventually substantial global underestimation of SARS-CoV-2 infection, by mid of October 2021 more than 240 million cases and approximately 4.9 million death have been notified by the WHO [2]. COVID-19 symptoms can range from asymptomatic/mild to severe illness, and disease severity and death occurring according to a hierarchy of risks [3], with age and pre-existing health conditions enhancing disease severity. Vaccines against COVID-19 have been developed in record time and are now globally distributed. With different efficacies, those vaccines authorized for emergency use are protecting individuals against severe disease [4–7]. The extent to which COVID-19 vaccines block infection is still being evaluated [8,9]. It is also unclear to what extent people with no symptoms or mild infection transmit the disease, and estimating their contribution to outbreaks is challenging.

According to the WHO, asymptomatically infected individuals are much less likely to transmit the virus than those who develop symptoms [10]. However, recent studies have reported that transmission from asymptomatic individuals was estimated to account for more than 40% of all transmission [11,12]. We use an epidemiological *SHAR* (Susceptible-Hospitalized-Asymptomatic- Recovered) model framework [13] to evaluate the effects of vaccination in different epidemiological scenarios of coverage and efficacy. Results obtained for two vaccination models, the vaccine V_1 protecting against severe disease, and the vaccine V_2, protecting against infection and also severe disease, are compared to the basic SHAR model without vaccination, evaluating the reduction of overall infections and hospitalizations in a population under low or intermediate vaccine coverage.

The different vaccines currently used have features placing them closer to one or the other of these two extreme cases, V_1 and V_2, with the ideal case scenario of perfect vaccine efficacy and complete coverage leading always to an extinction of severe cases. This is a conceptual study to evaluate the performance of vaccines V_1 and V_2 in respect to hospitalization and overall infections reduction. As information on COVID-19 vaccine efficacies are updated frequently, the new reported measures will be included into the modeling framework as needed, once it becomes publicly available [14]. Our results show that in an intermediate scenario of low to medium vaccination coverage and limited vaccine efficacy, vaccine performance will be influenced by the transmission level of mild and asymptomatic cases. If severe disease cases are accounted as the main contributor of disease transmis-

sion in a population, the performance of both vaccines, V_1 and V_2, is observed to be very similar in respect to reduction of hospitalizations, with a minor advantage for V_2 type of vaccine. However, in the case of mild/asymptomatic infections are confirmed to have higher transmission rates than severe/hospitalized cases, V_1 will eventually lead to a higher number of hospitalizations than in a scenario with no vaccine roll out. Although preference to V_2 is desirable, even with a smaller efficacy, a conscientious strategy to administrate simultaneously each vaccine type is needed to optimize hospitalization reductions, knowing that efficacies are also varying according to vaccination doses schedules.

This paper is structured as follows. The second section contains the description of the proposed modeling framework for COVID-19 dynamics, by means of ordinary differential equations and stochastic processes. The third section describes the analysis and simulation results of the proposed models described in Section 2. The last section concludes this work, with a discussion presenting the complete connection of this research with the current vaccination strategy to control COVID-19 spreading and severe disease reduction.

Methods

Using epidemiological models, we analyze three vaccination scenarios of vaccine efficacy and coverage. For the scenario without vaccination, we use the basic *SHAR* model, while for the scenario with vaccination we use the models $SHARV_1$, for vaccine one V_1, protecting against severe disease, and the $SHARV_2$, for vaccine two V_2, protecting against disease and infection. The performance of the vaccines are evaluated in function of vaccine efficacy, vaccine coverage and the role of mild/asymptomatic on disease transmission.

The basic SHAR model

Applied to COVID-19 transmission, the *SHAR* model is an extension of the basic *SIR* (Susceptible-Infected-Recovered) type model, where the infected class is stratified into Hospitalized/severe disease cases (H) and Asymptomatic/mild cases (A). This model was extended to describe the epidemiological situation of COVID-19 in the Basque Country, validated with empirical data and it is, up to date, used by the local public health managers to monitor the impact of intervention measures, the *SHARUCD* modeling framework [13,15,16,18,19]. With infection rate β and recovery rate γ, susceptible S individuals becoming infected can either develop severe disease prone to hospitalization H, with a proportion η, or develop a mild infection, potentially asymptomatic A, with a proportion $(1 - \eta)$. Recovered individuals R are considered resistant

to reinfection. The dynamics for the mean values can be written as ordinary differential equation system

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

where the ratio ϕ is included to differentiate the contribution of asymptomatic/ mild infected individuals to the force of infection ($\phi\beta$) as compared to the contribution of the severe detected cases (β) in a population of size N [13,19].

The SHARV₁ model

The $SHARV_1$ model is an extension of the basic $SHAR$ model described above, with population receiving vaccine V_1 type, protecting against severe disease but unable to block transmission. With a 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 (see e.g. [20–22] for the terminology and analysis in a Bayesian framework).

We distinguish the naive susceptible S individuals prone to natural infection and vaccinated susceptible individuals S_v with a reduced risk of severe disease, but still able to transmit the virus when becoming mild or asymptomatic infected. Here, the hospitalization ratio η in this natural infectivity $\eta\beta$ changes with vaccine uptake $r \cdot \eta\beta$, whereas the mild/asymptomatic infection rate $(1 - \eta)\beta$ is assumed to not be efficiently reduced (in the extreme case, no reduction at all).

The dynamical system of the $SHARV_1$ model is given by

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

(2)

with the term in the dynamics of the asymptomatic infected easily simplified
$(1 - \eta)\beta \frac{S}{N}(H + \phi A) + (1 - \eta)\beta \frac{S_v}{N}(H + \phi A) = (1 - \eta)\beta \frac{S + S_v}{N}(H + \phi A)$,
since neither naive susceptible individuals nor vaccinated susceptible individuals with vaccine V_1 are protected against infection, i.e. are still able to transmit the disease.

The SHARV₂ model

Similarly to the model described above, we now extend the basic $SHAR$ model to obtain the $SHARV_2$ framework for a population receiving vaccine V_2 type, protecting against severe disease and infection, i.e. the so called sterilizing immunity with efficacy k. Note that vaccine V_2 type could eventually have a smaller or larger efficacy k than a vaccine V_1 type, hence we must distinguish vaccine efficacy of V_1 as k_1 from that of V_2 as k_2. For the moment, this difference is not considered since we only evaluate the performance of each vaccine type individually.

For vaccine V_2 type, the vaccinated susceptible individuals S_v have a reduced infection rate for both transitions, the transition into the severe/Hospitalized class H as $r \cdot \eta\beta$, and for the transition into the mild/Asymptomatic class A as $r \cdot (1 - \eta)\beta$.

The dynamical system of the $SHARV_2$ model is given by

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

(3)

Vaccine performance analysis: a conceptual study

For analytical insights into the behaviour of the models with vaccination compared to the non-vaccination scenario, we consider the dynamics of the disease compartments, here in the V_1 case,

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

(4)

including the vaccination coverage c as the fraction of vaccinated susceptible individuals over the total number of susceptible $S_{tot} := S + S_v$, hence $S_v = c \cdot S_{tot}$. In this exercise, we assume that the burning out of susceptible individuals is slow as compared to the disease progression. This assumption is justified when COVID-19 is far from herd immunity, with detected cases being small compared to the overall population, as for example in the Basque Country, with population size of 2.2 million people and less than 200 thousand confirmed cases notified to date. We consider $S_{tot}(t_0) =: S_0$ and hence $S_v(t) \approx c \cdot S_0$ and $S(t) \approx (1 - c) \cdot S_0$.

This is not a limiting assumption, since for any point in time we can assume a certain level of susceptibility, taking already naturally recovered into account, and evaluating the momentary increase or decrease of diseased and infected without and with vaccination impact.

In detail, for the state vector $\underline{x} := (H, A)^{tr}$ we obtain the dynamics where we use

$$y := (1 - c) + rc = 1 - c \cdot k \qquad (5)$$

and

$$z := 1 + \frac{\eta}{1 - \eta}(1 - r)c = 1 + \frac{\eta}{1 - \eta}c \cdot k \qquad (6)$$

for vaccine V_1, but with specific variables y and z all the three models can be analyzed with the same formulation.

The matrix B is explicitly given below (omitting the factor $\frac{S_0}{N}$ since initially $S_0 \approx N$, and note that the infection rate β carries $\frac{S_0}{N}$ in case S_0 is significantly lower than N)

$$B = \beta \begin{pmatrix} \eta y & \phi\eta y \\ (1 - \eta)z & \phi(1 - \eta)z \end{pmatrix} \qquad (7)$$

along with matrix G as

$$G = \gamma \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} \qquad (8)$$

and hence evaluate $J = B - G$ in $\frac{d}{dt}\underline{x} = J\underline{x}$.

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Growth factor of disease spreading or disease decline

For the model $SHARV_1$ we have the above expressions of y and z, which we can call y_1 and z_1, whereas for the basic $SHAR$ model we would obtain $y_0 = 1$ and $z_0 = 1$ which simply disappear in the matrix B. Via the eigenvalue/eigenvector analysis of the matrix J, see [13,15,19] for the notations, we obtain from the dominant eigenvalue the growth factor of disease spreading or disease decline [15]. As opposed to the plain infection rate β for simpler SIR models, the growth rate appears now as a transformed infection rate

$$\tilde{\beta} := (\eta y + \phi(1 - \eta)z)\beta \qquad (9)$$

that can be used for a first inspection of vaccine effects.

To apply the analysis closer to the present epidemiological scenario of COVID-19, we analyze the models including import ϱ as $(H + \phi A + \varrho N)$ in the force of infection and keep the community spreading below exponential growth [16]. Hence we have the dynamical system given by

$$\frac{d}{dt}\begin{pmatrix} H \\ A \end{pmatrix} = (B - G) \cdot \begin{pmatrix} H \\ A \end{pmatrix} + \underline{\varrho} \qquad (10)$$

with matrix $J = B - G$ decomposed into eigenvalue matrix Λ and eigenvector matrix T as $JT = T\Lambda$. From

$$\frac{d}{dt}\underline{x} = T\Lambda T^{-1}\underline{x} + \underline{\varrho} \qquad (11)$$

the time dependent solution is

$$\underline{x}(t) = Te^{\Lambda(t-t_0)}T^{-1}\underline{x}(t_0) + T(e^{\Lambda(t-t_0)} - \mathbb{I})\Lambda^{-1}T^{-1}\underline{\varrho} \qquad (12)$$

with $\mathbb{I}$ as unit matrix, and stationary value $\underline{x}^* = -T\Lambda^{-1}T^{-1} = J^{-1}\underline{\rho}$ with the results given by

$$\begin{pmatrix} H^* \\ A^* \end{pmatrix} = \frac{1}{\kappa}\left[\begin{pmatrix} \eta y(\varrho_1 + \phi\varrho_2) \\ (1-\eta)z(\varrho_1 + \phi\varrho_2) \end{pmatrix} \cdot \frac{1}{-\lambda_1} + \begin{pmatrix} (1-\eta)z\phi\varrho_1 - \eta y\phi\varrho_2 \\ \eta y\varrho_2 - (1-\eta)z\varrho_1 \end{pmatrix} \cdot \frac{1}{-\lambda_2}\right]. \qquad (13)$$

The stationary states for the severe/hospitalized cases (H^*) and overall infection ($I^* = H^* + A^*$) as function of vaccine coverage and efficacy for both vaccines are

$$H^*(c,k) = \frac{\beta\frac{S_0}{N} \cdot \varrho N}{\gamma - \kappa\beta\frac{S_0}{N}} \cdot \eta y \qquad (14)$$

and

$$I^*(c,k) = \frac{\beta\frac{S_0}{N} \cdot \varrho N}{\gamma - \kappa\beta\frac{S_0}{N}} \cdot (\eta y + (1-\eta)z) \qquad (15)$$

with $\kappa := \eta y + \phi(1 - \eta)z$.

The analysis for the vaccine V_2 is done similarly to the analysis for vaccine V_1, obtaining slightly altered vaccination variables $y_2 = 1 - c \cdot k$ (as for the previous case V_1) and $z_2 = y_2 = 1 - c \cdot k$.

The effective infection rate obtained from the growth rates of all three models can be written using the same formulation. For the $SHARV_1$ model we have

$$\tilde{\beta}_1 := (\eta y_1 + \phi(1 - \eta)z_1)\beta \qquad (16)$$

while for the $SHARV_2$ model

$$\tilde{\beta}_2 := (\eta + \phi(1 - \eta))y_2\beta \qquad (17)$$

since $z_2 = y_2$. Finally for the basic $SHAR$ model without vaccination, where $z_0 = y_0 = 1$, we have

$$\tilde{\beta}_0 := (\eta + \phi(1 - \eta))\beta \qquad (18)$$

as result.

The reduction of the effective infection rate due to the vaccine V_2 type is given by

$$\frac{\tilde{\beta}_2}{\tilde{\beta}_0} = y_2 = 1 - c \cdot k \qquad (19)$$

while for V_1 we obtain a slightly more complex situation given by

$$\frac{\tilde{\beta}_1}{\tilde{\beta}_0} = (1 - c \cdot k) + \frac{\phi}{\eta + \phi(1 - \eta)}ck =: (1 - ck) + f(\phi, \eta) \cdot c \cdot k \qquad (20)$$

defining an expression $f(\phi, \eta) := \phi/(\eta + \phi(1 - \eta))$. With a similar result as for V_2, the first term is identical but then reduced by an additional term proportional to $c \cdot \kappa$, which is dependent on the $SHAR$ specific parameters η, the proportion of hospitalizations, and ϕ, the contribution of asymptomatic/mild infections to the force of infection, namely $f(\phi, \eta)$. This factor can become eventually disadvantageous, especially when cases of asymptomatic infection are accounting for most of the transmission ($\phi > 1$).

For this reason, a simple comparison of the growth factors without and with vaccine is not sufficient to evaluate the vaccine performance and vaccination roll out impact, especially when a vaccine protects mainly against severe disease, but leaves the infectivity aspect unanswered. Therefore, we performed the analysis for the present snapshot in time for controlled community spreading, which is obtained after lockdown relaxation, i.e. transmission rate below the epidemic threshold, challenged by imported cases, i.e. expected when mobility is allowed, for both vaccine types analogously. Results are given by Eq. (13), with the respective vaccine specific variables y_i and z_i for each vaccine i.

Stochastic systems formulation and models comparison: SHAR, SHARV_1 and SHARV_2

The deterministic approach described above was obtained via the mean field approximation of the stochastic system and is also used to evaluate the model performance and accuracy to guide the modeling analysis. Similarly as shown for the basic $SHAR$ model in [13], the stochastic versions of the presented models can be given analogously. The stochastic process is given for probabilities of density state vectors $\underline{x}$ as

$$\frac{d}{dt}p(\underline{x}, t) = \sum_{j=1}^{n}\left(Nw_j(\underline{x} + \Delta\underline{x}_j) \cdot p(\underline{x} + \Delta\underline{x}_j, t) - Nw_j(\underline{x}) \cdot p(\underline{x}, t)\right) \qquad (21)$$

For the basic $SHAR$ model with import ϱ and eventual waning immunity α (which matters when e.g. new variants affect natural immunity of the host), densities of the state variables are $x_1 := S/N, x_2 := H/N, x_3 := A/N$ and $x_4 := R/N$, with $\Delta\underline{x}_j := \frac{1}{N} \cdot \underline{r}_j$ defining the shift vectors $\underline{r}_j$ for the $n = 5$ transitions, are given by

$$
\begin{aligned}
w_1(\underline{x}) &= \eta\beta x_1(x_2 + \phi x_3 + \varrho) &,\quad \underline{r}_1 &= (1, -1, 0, 0)^{tr} \\
w_2(\underline{x}) &= (1-\eta)\beta x_1(x_2 + \phi x_3 + \varrho) &,\quad \underline{r}_2 &= (1, 0, -1, 0)^{tr} \\
w_3(\underline{x}) &= \alpha(1 - x_1 - x_2 - x_3) &,\quad \underline{r}_3 &= (-1, 0, 0, 1)^{tr} \\
w_4(\underline{x}) &= \gamma x_2 &,\quad \underline{r}_4 &= (0, 1, 0, -1)^{tr} \\
w_5(\underline{x}) &= \gamma x_3 &,\quad \underline{r}_5 &= (0, 0, 1, -1)^{tr}.
\end{aligned}
\qquad (22)
$$

see e.g. [23–25] for the notations. For the models with vaccination we have to include a fifth state variable $x_5 = S_v/N$ in the state vector. For vaccine V_1, the transitions are

$$
\begin{aligned}
w_6(\underline{x}) &= (1-k)\eta\beta x_5(x_2 + \phi x_3 + \varrho) &,\quad \underline{r}_6 &= (0, -1, 0, 0, 1)^{tr} \\
w_7(\underline{x}) &= (1-\eta)\beta x_5(x_2 + \phi x_3 + \varrho) &,\quad \underline{r}_7 &= (0, 0, -1, 0, 1)^{tr} \\
w_8(\underline{x}) &= k\eta\beta x_5(x_2 + \phi x_3 + \varrho) &,\quad \underline{r}_8 &= (0, 0, -1, 0, 1)^{tr}
\end{aligned}
\qquad (23)
$$

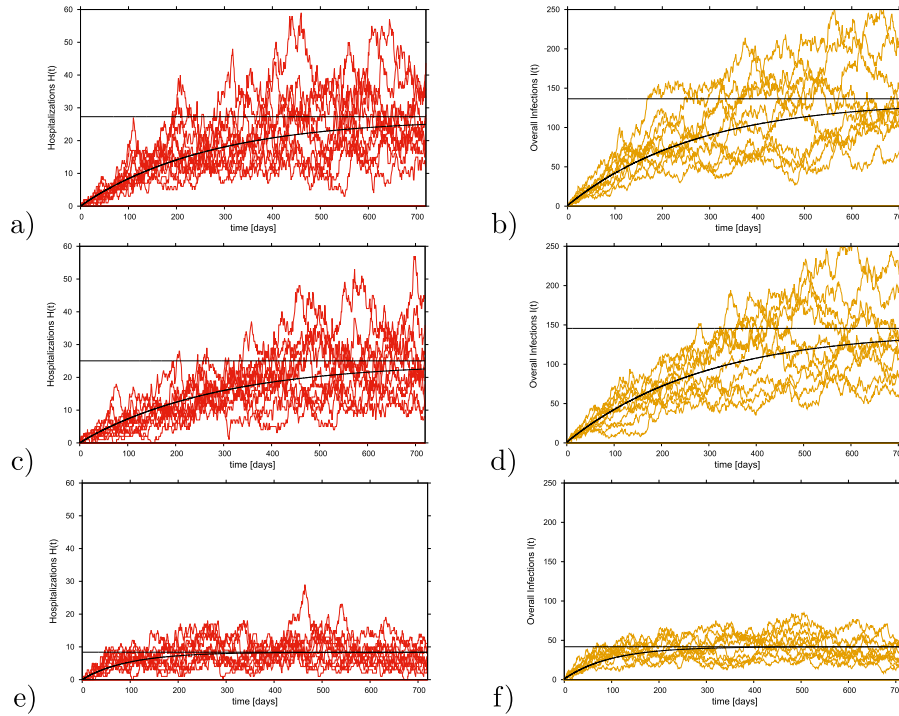while for vaccine V_2 we have the altered transitions

Fig. 1. Stochastic models output comparison. For a population size $N = 2 \cdot 10^6$ and a small import factor $\varrho = e^{-12}$, we plot in red hospitalized cases H and in yellow overall infections $I = (H + A)$ using the following parameter set: $\gamma = 0.05 \, d^{-1}$, $\beta = 0.8 \cdot \gamma$, $\eta = 0.2$, $\phi = 1.2$. Straight black lines give the analytical stationary state results, curvy black lines the mean field approximations of the full systems including $S(t)$ varying with eventual approximation of herd immunity. In a-b) results for the *SHAR* model without vaccination, in c-d) results for the $SHARV_1$ model and in e-f) results for the $SHARV_2$ model with vaccine protecting against disease and infection are shown.

$$
\begin{aligned}
w_6(\underline{x}) &= (1-k)\eta\beta x_5(x_2 + \phi x_3 + \varrho) &, \quad \underline{r}_6 = (0,-1,0,0,1)^{tr} \\
w_7(\underline{x}) &= (1-k)(1-\eta)\beta x_5(x_2 + \phi x_3 + \varrho) &, \quad \underline{r}_7 = (0,0,-1,0,1)^{tr} \\
w_8(\underline{x}) &= k\beta x_5(x_2 + \phi x_3 + \varrho) &, \quad \underline{r}_8 = (0,0,0,-1,1)^{tr}
\end{aligned}
\tag{24}
$$

to complete the formal description of the stochastic processes. The stochastic realizations are obtained via the Gillespie algorithm [26,27].

The models' outcome are shown in Fig. 1, for a scenario of vaccine efficacy of $k = 70\%$ and vaccine coverage of $c = 20\%$. The dynamics of hospitalized cases (H) are plotted in red and the dynamics of overall infected cases ($I = H + A$) are plotted in yellow. Simulation results are shown in Fig. 1 a-b) for the basic *SHAR* model without vaccination. Results for the $SHARV_1$ model, with vaccine protecting against severe disease only, are shown in Fig. 1 c-d) and for the $SHARV_2$ model, with vaccine protecting against disease and infection, are shown in Fig. 1 e-f).

Ten stochastic realizations are plotted. Straight black lines give the analytical stationary state results and curvy black lines the mean field approximation solution of the full systems, including $S(t)$ varying with eventual approximation of herd immunity.

For illustration purposes, we compare the results obtained in the epidemiological scenario where asymptomatic infection is assumed to contribute 20% more to the force of infection than severe hospitalized cases ($\phi = 1.2$). Taking the *SHAR* model as a baseline for comparing the expected reduction of hospitalization and overall infections we observe a slight reduction of overall infected and of severe cases for $SHARV_1$ versus a significant reduction for severe cases and hospitalization for $SHARV_2$.

Results using different assumptions for asymptomatic infection contribution to the overall force of infection (ϕ values) will be discussed in the next section, where we analyze the solution given by the deterministic approach, since large fluctuations observed in the

stochastic system make it difficult to observe in Fig. 1 the differences in vaccine performance.

Results and discussion

The analysis of the proposed models described in Section 2 are shown below as function of vaccination coverage and vaccine efficacy. The role of asymptomatic/mild disease cases are varied to evaluate the performance of the vaccines in respect of hospitalization and overall infections reduction.

Reduction of severe cases/hospitalizations and overall infections as function of vaccination coverage and vaccine efficacy

We analyze the impact of the vaccine V_1 and vaccine V_2 in respect to the reduction of severe/hospitalizations H^* and reduction of overall infections $I^* = (H^* + A^*)$ by changing vaccination coverage c at given vaccine efficacy k over time. We assume a scenario of community transmission controlled, i.e, with non-pharmaceutical interventions able to keep the transmission away from an exponential growth, but under the influence of import, while mobility is still allowed [15,16,18].

The stationary value for hospitalizations and overall infections are given by Eq. (14) and Eq. (15) respectively. We use different definitions of vaccine impact variables y and z for each model, $SHARV_1$, for vaccine V_1, $SHARV_2$, for vaccine V_2, and $SHAR$, with no vaccine, to obtain the uniform description for all models. We obtain for $V_1, y_1 := 1 - c \cdot k$ and $z_1 := 1 + \frac{\eta}{1-\eta}c \cdot k$, and for $V_2, z_2 := y_2$ with given $y_2 := 1 - c \cdot k$. The original value in the *SHAR* model $H_0^* := H^*(c = 0, k)$ without vaccine is given for $c := 0$, no vaccine coverage, hence $z_0 = y_0 = 1$. Further parameters of the *SHAR* type models are described in Section 2.

In Fig. 2 we analyze the ratio of hospitalizations in vaccination and non-vaccination scenarios, hence $H^*(c, k)/H_0^*$. Results obtained
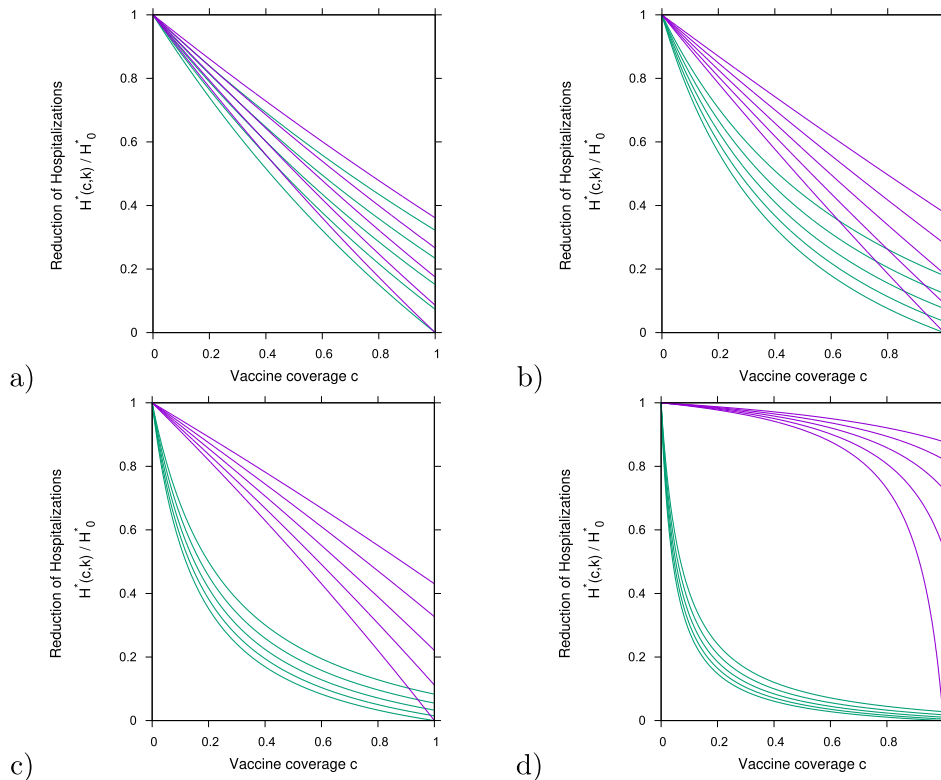
Fig. 2. Reduction of hospitalizations $H^*(c,k)$ for vaccine V_1, in purple and vaccine two V_2, in green, over the non-vaccination scenario of the basic *SHAR* model with import, H_0^*. We plot the results for various vaccine efficacies between $k = 100\%$ (lowest curve in each graph) and $k = 60\%$ (highest curves) in steps of 10%, as function of vaccination coverage c. Varying the infectivity of asymptomatic over the infectivity of severe cases, ϕ, we have in a) $\phi = 0.2$ in b) $\phi = 0.8$, in c) $\phi = 1.1$ and in d) $\phi = 1.245$.

for V_1 are shown in purple and for V_2 in green. From bottom to top vaccine efficacies are varied as $k = 100\%, 90\%, 80\%, 70\%$ and 60%, as continuous function of vaccine coverage $c \in [0, 1]$. To investigate the effect of different transmission rates, we vary the infectivity of asymptomatic/mild cases to be smaller ($\phi < 1$) or larger ($\phi > 1$) than the infectivity of severe/hospitalized cases and we discuss the role of asymptomatic infection on vaccine performance.

By assuming a small infectivity of asymptomatic cases relative to severe cases, $\phi = 0.2$, we observe a very small difference on the performance of V_1 and V_2 (see Fig. 2 a)), with both vaccines reducing severe/hospitalizations nearly linearly as function of vaccine coverage. However, when increasing ϕ closer to unit, in b) $\phi = 0.8$, and beyond, see c) $\phi = 1.1$ and d) $\phi = 1.245$, differences on vaccine performance are observed. Here, only in the limit case of complete coverage $c = 1$ and perfect efficacy $k = 1$, both vaccines would reach extinction of hospitalizations.

In detail, for the $\phi = 0.8$ scenario shown in Fig. 2 b) we have, for vaccine coverage over 60%, some overlapping region of V_1 and V_2, where a higher efficacious V_1, which protects against severe disease without blocking transmission completely, can reduce hospitalizations more than a lower efficacious V_2, which protects against disease and infection. For the $\phi = 1.1$ scenario shown in Fig. 2 c), where mild/asymptomatic cases are transmitting slightly more than severe cases, this effect nearly disappears.

Finally, for the $\phi = 1.245$ scenario shown in Fig. 2 d), where mild/asymptomatic cases are assumed to transmit approximately 25% more than severe/hospitalized cases, significant reductions in hospitalization are reached very fast with V_2 whereas small effects of V_1 can be only observed with a very large vaccination coverage. Here, vaccine efficacy below 60% would have about no effect in the population.

We continue with our analysis, now to also evaluate the reduction in the overall infections. Similarly to the analysis above, we

show for some intermediate cases of ϕ, below unit and above unit, how the overall number of infected $I^* = H^* + A^*$ change with vaccination coverage. In Fig. 3 a) and Fig. 3 b) we plot the ratio of overall infections with and without vaccination, $I^*(c,k)/I_0^*$. In the same way as in Fig. 2, results obtained for V_1 are shown in yellow and for V_2 are shown in blue, for ϕ-values below and above unit, respectively. From bottom to top vaccine efficacies are varied as $k = 100\%, 90\%, 80\%, 70\%$ and 60%, as continuous function of vaccine coverage $c \in [0, 1]$.

COVID-19 vaccines performance: the role of asymptomatic infection in low to medium vaccine coverage scenarios

Estimation of hospitalizations and overall infection reductions are shown in Tables 1 and 2, for V_1 and V_2, respectively. Colors highlight the reductions: above 30% in green, above 10% and below 30% in blue, and below 10% in yellow. Negative reductions, i.e. increasing of cases, are shown in red and were observed only for V_1 in respect the overall infection cases.

Vaccination impact in the Basque Country: data and numerical experiment

In this section, we present the first numerical experiment for this conceptual study. As an exploratory analysis, we evaluate the vaccine impact on severe cases/hospitalizations of COVID-19 in the Basque Country, Spain. Applied to the epidemiological scenario as of June 2021, see Fig. 4a), with vaccination roll out using imperfect vaccines, see Fig. 4b), we consider empirical vaccines efficacy $k < 1$ and a proportion of already naturally immunized persons via previous natural COVID-19 infection as recorded by the public health managers.
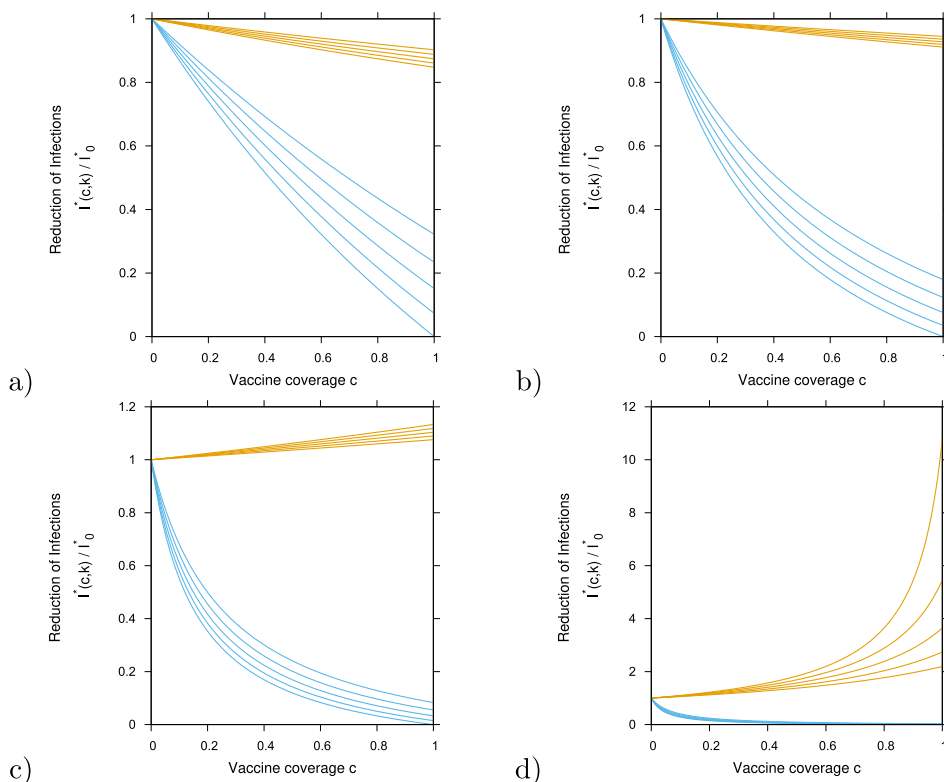
Fig. 3. Reduction of overall infection $I^*(c,k)$, with $I^* := H^* + A^*$, for vaccine V_1, in yellow and vaccine V_2, in blue, over the non-vaccination scenario of the basic *SHAR* model with import, I_0^*. We plot the results for various vaccine efficacies between $k = 100\%$ (lowest curve in each graph) and $k = 60\%$ (highest curves) in steps of 10%, as function of vaccination coverage c. Varying the infectivity of asymptomatic over the infectivity of severe cases, ϕ, we have in a) $\phi = 0.2$ in b) $\phi = 0.8$, in c) $\phi = 1.1$ and in d) $\phi = 1.245$.

Table 1

Estimated reduction of hospitalization (H) and overall infection ($I := (H + A)$) for vaccine V_1, protecting against severe disease but not blocking transmission completely. For different vaccine efficacies, we vary the asymptomatic infection contribution to the overall force of infection. Reduction of hospitalizations and overall infections are shown as percentages for scenarios of low and intermediate vaccination coverage.

Vaccine 1 (protection against severe disease only)									
Estimated reduction of severe disease (H)					Estimated reduction of overall infection (H+A)				
Asymptomatic contribution to the force of infection ($\phi\beta$)	vaccine coverage of 20%		vaccine coverage of 50%		Asymptomatic contribution to the force of infection ($\phi\beta$)	vaccine coverage of 20%		vaccine coverage of 50%	
	vaccine efficacy 70%	vaccine efficacy 90%	vaccine efficacy 70%	vaccine efficacy 90%		vaccine efficacy 70%	vaccine efficacy 90%	vaccine efficacy 70%	vaccine efficacy 90%
$\phi=0.2$	16.00%	21.00 %	39.00%	49.00%	$\phi=0.2$	2.00%	3.00%	6.00%	7.00%
$\phi=0.8$	15.00%	19.00 %	37.00%	47.00%	$\phi=0.8$	3.00%	2.00%	3.00%	4.00%
$\phi=1.1$	13.00%	16.00 %	33.00%	42.00%	$\phi=1.1$	-2.00%	-2.00%	-4.00%	-6.00%
$\phi=1.245$	1.50%	2.00 %	5.00%	7.00%	$\phi=1.245$	-15.00%	-20.00%	-47.00%	-69.00%

With a population size of $N = 2.2 \cdot 10^6$, less than 200 000 infections were reported as of June 15, 2021, i.e. around 10% of the population been already immune prior to vaccination. A pool of default susceptible individuals $S_0/N \approx 90\%$ is considered. Note that this assumption can be modified as new positive cases are detected to be included in the analysis, counting the current immunized population via natural infection or by vaccination at a given time. Vaccination coverage is 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 are administered in the population independently of the individual previous record of negative or positive PCR test.

Assuming the available reported vaccine coverage in the Basque Country from May to June 2021, the baseline number of hospitalizations is assumed to be the number of cumulative hospitalizations notified in January 2021, immediately after the vaccination roll out started in the Basque Country, see purple line in Fig. 4c). We include the present population status of remaining susceptible after one year of natural infection, and for the sake of simplicity, see Fig. 4b), we consider vaccine efficacy against hospitalization as reported in [8]. This assumption is valid since the majority of the Basque population has received the BioNTech/Pfizer vaccine during the vaccination roll out. Results obtained here refer to the

Table 2
Estimated reduction of hospitalization (*H*) and overall infection ($I := (H + A)$) for vaccine V_2, the so called sterilizing vaccine. For different vaccine efficacies, we vary the asymptomatic infection contribution to the force of infection. Reduction of hospitalizations and overall infections are shown as percentages for scenarios of low and intermediate vaccination coverage.

| Vaccine 2 (protection against severe disease and against infection)									
Estimated reduction of severe disease (H)					Estimated reduction of overall infection (H+A)				
Asymptomatic contribution to the force of infection ($\phi\beta$)	vaccine coverage of 20%		vaccine coverage of 50%		Asymptomatic contribution to the force of infection ($\phi\beta$)	vaccine coverage of 20%		vaccine coverage of 50%	
	vaccine efficacy 70%	vaccine efficacy 90%	vaccine efficacy 70%	vaccine efficacy 90%		vaccine efficacy 70%	vaccine efficacy 90%	vaccine efficacy 70%	vaccine efficacy 90%
$\phi=0.2$	19.00%	24.00%	43.00%	53.00%	$\phi=0.2$	19.00%	24.00%	53.00%	53.00%
$\phi=0.8$	33.00%	40.00%	62.00%	71.00%	$\phi=0.8$	33.00%	40.00%	62.00%	71.00%
$\phi=1.1$	54.00%	62.00%	80.00%	86.00%	$\phi=1.1$	54.00%	62.00%	80.00%	86.00%
$\phi=1.245$	79.00%	84.00%	93.00%	95.00%	$\phi=1.245$	79.00%	84.00%	93.00%	95.00%
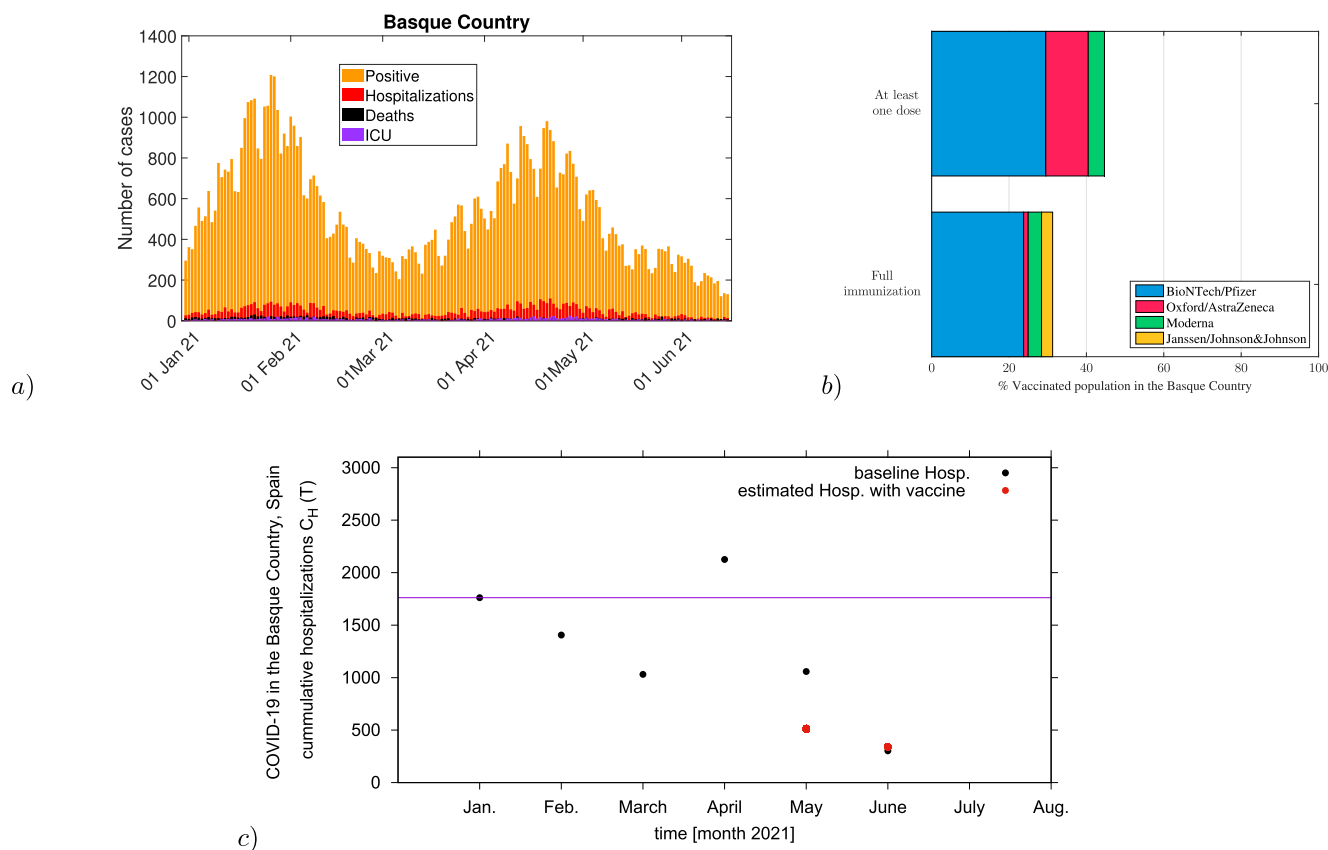
Fig. 4. In a) COVID-19 dynamics in the Basque Country From Jan. 1 to June 15, 2021. Positive PCR cases (in yellow), hospitalizations (in red), ICU admission (in purple) and deceased cases (in black) are shown. In b) the vaccination coverage of individuals that have received at least a single dose of a vaccine ($\approx 47.6\%$) and the coverage of individuals that have completed the immunization schedule ($\approx 31.3\%$) in the Basque Country by June 2021. In c) Evaluation of the vaccination impact on hospitalizations in the Basque Country for May and June 2021 (plotted as red dots) in comparison with the official data on hospitalizations in the Basque Country from January to June 2021 (plotted as black dots). Vaccination coverage of full immunization were fixed to $c = 17.5\%$ and $c = 34.1\%$ as reported in May and June 2021 respectively.

wild type of SARS-CoV-2 variant. Considerations on vaccine performance against new variants of concern (VOCs) and variants of interest (VOIs) are discussed in the Section below.

While Fig. 4a) shows a small decrease of reported severe cases (in red) as vaccination coverage increases, a significant increase of confirmed cases are also observed (yellow), as described in Table 1, for example, for the scenario where asymptomatic cases contribution to the force of infection is considered to be larger than

symptomatic cases, once they are identified and isolated. Our modeling results could describe well these observations, with model predictions being very close to the empirical data for a low/intermediate vaccination coverage scenario, see 4c), where the hospitalizations given the momentary coverages and reported vaccine efficacy is plotted as red dots and the official data on hospitalizations in the Basque Country are plotted as black dots. Our results give insights on the role of mild and asymptomatic infections on

COVID-19 vaccines performance, indicating that asymptomatic disease cases are contributing significantly with disease transmission in the population.

Model limitations and future refinements

From the present analysis, we obtained valid information of the effects of the vaccination scenarios on severe cases, taking especially into account factors like hospitalization ratio, contribution of infectivity of mild or asymptomatic cases, in their interplay with vaccine efficacies, as measured in vaccine trials, and vaccination coverage. The COVID-19 vaccines currently in use share certain features of different protection levels assumed for this study, however, the modeling framework needs some more refinement to describe more accurately the scenario we are living in.

Note that for this exercise we do not consider the effect of new variants. Contrary to what was observed during the initial roll out of the nationwide vaccination program using vaccine efficacy as referred in [8], protection against infection and transmission was highly affected by the new VOCs in circulation, anticipating that vaccination provide transient immunity, i.e., with elimination of the virus being eventually unlikely with the current vaccines in use. In the face of the new VOCs in circulation, e.g. the delta variant, a significant reduction of vaccine effectiveness against SARS-CoV-2 infections was reported to occur over time, but vaccine effectiveness against hospital admissions for infections with the delta variant was kept high overall. Nevertheless, this reduction is expected to be due to waning immunity with time rather than new variant escaping vaccine protection, since the effectiveness against other (non-delta) variants also waned significantly [29].

This is an ongoing work, with information on COVID-19 vaccine efficacies to be updated frequently and included into the refined modeling framework as needed [14]. Considerations of different variants of concern and variants of interest, as well as the detection rates of mild or asymptomatic infected are important to be considered. Nevertheless, studies like the one described here are timely and of major importance to understand the vaccination coverage needed to achieve herd immunity in different settings.

Model extensions to include known risk groups with different hospitalization ratios as well as information of number of individuals vaccinated with one or another vaccine, number of doses and its coverage might be considered, specially for predictions in empirical studies. Additional features have to be taken into account, such as extra compartments for incidence data, ICU admissions and deceased cases. Considerations of different variants and detection rates of mild or asymptomatic infected are also important.

Disentangling vaccination effects from other changing circumstances like seasonality and rapidly varying non-pharmaceutical interventions, upcoming herd immunity due to natural infections and recoveries etc. is still a challenging task, and final statements on when and how to lift other control measure due to increased vaccination levels and impact are soon needed.

Conclusion

The aim of this study was to evaluate the role of mild/asymptomatic infections on COVID-19 vaccine performance as vaccine efficacy and vaccine coverage vary. A simple SHAR model, where infected individuals are either developing severe disease prone to hospitalization (*H*) or developing mild/asymptomatic infection (*A*), with potentially higher mobility and hence more contacts, was extended to investigate reductions of hospitalizations and

overall infections during the vaccination roll out. Two limiting vaccine types were evaluated, vaccine one V_1, protecting against severe disease, and vaccine two V_2, protecting against disease and infection.

The different COVID-19 vaccines currently in use have features placing them closer to one or the other of these two extreme cases, and insights on the importance of asymptomatic infection in a vaccinated population are of major importance for the future planning of vaccination programmes. We study the role of mild/asymptomatic infections during the COVID-19 outbreaks and evaluate their impact on vaccine performance as function of vaccine coverage and efficacy.

Our analysis has shown that in a setting where severe disease cases are assumed to be the main contributor to the spreading of COVID-19 the performance of both vaccines, V_1 and V_2, are able to reduce significantly the number of hospitalizations. A small advantage on the overall reduction of severe disease cases is observed for V_2. Nevertheless, in a setting where mild/asymptomatic cases are the ones accounted to contribute more to the overall infection rate in the population, we observe, in low to intermediate vaccine coverage, an eventual increase of severe cases (in comparison with the no vaccination scenario) for V_1, which although protects against severe disease, fails to block disease transmission. In this scenario, we observe V_1 generating more mild/asymptomatic infections and this effect might contribute to the increase of hospitalizations, specially for non-vaccinated high risk group. While the capacity of asymptomatic to transmit the virus is not well measured, the use of masks and any other non-pharmaceutical interventions are to be considered even for vaccinated individuals, until herd immunity is archived by vaccination and natural infection.

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 in the Basque country. There is, nevertheless, still an ample space for further evaluations, including additional stochastic effects as described e.g. in [16,17,28]. In this study we consider the available information for the BioNTech/Pfizer vaccine [8], assuming that the variations reported eventually capture many aspects of heterogeneous vaccine coverage and efficacies. It is important to mention that, by the time this study was performed, the largest clinical trial reporting on varying efficacies per dose administrated and distinction of protection against hospitalization and infection refers to data from Israel's largest health care organization, used to evaluate the effectiveness of the BNT162b2 mRNA vaccine [8]. As of October 2021, new and relevant data on effectiveness against hospitalization, disease and infection, after one or two doses are already available for the ChAdOX1 and other vaccines that are licensed for emergency use in Europe [29,30].

As a conceptual study, our results give insights on how to best combine the use of the available COVID-19 vaccines, optimizing the reduction of hospitalizations. These results are of major interest, since: i) vaccines are not 100% efficacious, leaving a proportion of the population at risk of acquiring the infections and eventually developing severe disease prone to hospitalization; ii) high vaccine coverage can not be reached immediately in an initial stage of a vaccination roll out programme, and as population immunity grows (by natural infection and vaccination coverage) the challenges of planning vaccine administration decreases, iii) in the case of vaccine waning immunity or even immune escape by new variants, we expect that new vaccine generations will need to be evaluated under the same settings studied here.

CREDIT Author Statement

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Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

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.

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