Supplementary material for "*Distributional cost-utility analysis of vaccines for COVID-19 according to sex, comorbidity and socioeconomic status: a population study*"

The SHARUCD modeling framework

In this section, we present the stochastic SHARUCD modeling framework developed within a modeling task force created to support public health managers during the COVID-19 crisis. As an extension of the basic SHAR (Susceptible-Hospitalized-Asymptomatic-Recovered) model [1], the SHARUCD model was parameterized and validated with empirical data for the Basque Country, Spain, and is used (up until now) to monitor COVID-19 spreading and control throughout the pandemic [2, 1, 3, 4, 5, 6, 7, 8, 9].

This flexible 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 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, including the deceased (D) cases.

Able to describe the COVID-19 epidemic in terms of disease spreading, the SHARUCD model gives accurate projections (see Fig. 1) on hospitalizations, ICU admissions, and deceased cases from March 2020 to December 2020, when vaccination roll-out started. The modeling framework was used to monitor the COVID-19 epidemiological dynamics in the Basque Country while the lockdown measures were relaxed and tightened over time, evaluating also the impact of non-pharmaceutical interventions and social distancing.

To describe the COVID-19 dynamics in the Basque Country, the basic SHAR model was extended by introducing the classes of Intensive Care Unit (ICU) admissions U and of deceased individuals D. Further, for comparison with the available cumulative empirical data, also the cumulative classes for hospitalized C_H, mild/asymptomatic infected C_A, ICU admitted C_U, and recovered C_R were included, counting all incoming cases in the dynamical compartments and neglecting the outflows. A detection ratio ξ for mild/asymptomatic cases was also considered, since a proportion of mild/asymptomatic cases are detected by contact tracing/screening testing, and hence the number of positively tested infections is larger than the notified hospitalized cases.

In this model, disease severity is decided upon infection with a proportion η developing severe infection prone to hospitalization (and $1-\eta$ developing mild/asymptomatic infection). Undetected asymptomatic cases are assumed to transmit the disease more efficiently ($\phi > 1$) than severe cases. Hospitalized individuals can recover, with a recovery rate γ, die, with a mortality rate μ or go to an ICU facility, with an admission rate ν. Here, ICU admission is assumed to be a progression of disease severity after hospitalization.

Letting $\mathbf{x}$ denote the state vector of densities, the master equation for the probabilities $p(\mathbf{x}, t)$ can be expressed in terms of n transitions $w_j(\mathbf{x})$ and small deviations from state $\mathbf{x}$ given by $\Delta\mathbf{x}_j$ as

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

where $\Delta\mathbf{x}_j := \frac{1}{N}\mathbf{r}_j$ for suitable shifting vectors $\mathbf{r}_j$. The stochastic version of the basic SHARUCD model can be formulated through the master equation in the generic form of Eq. (1) with variables $x_1 := S/N$, $x_2 := H/N$, $x_3 := A/N$, $x_4 := R/N$, $x_5 := U/N$, $x_6 := C_H/N$, $x_7 := C_A/N$, $x_8 := C_U/N$ and $x_9 := D/N$ and $x_{10} := C_R/N$. The state vector $\mathbf{x} := (x_1, ..., x_{10})^T$ gives the dynamics for the probabilities $p(\mathbf{x}, t)$, with $n = 10$ different transitions. The

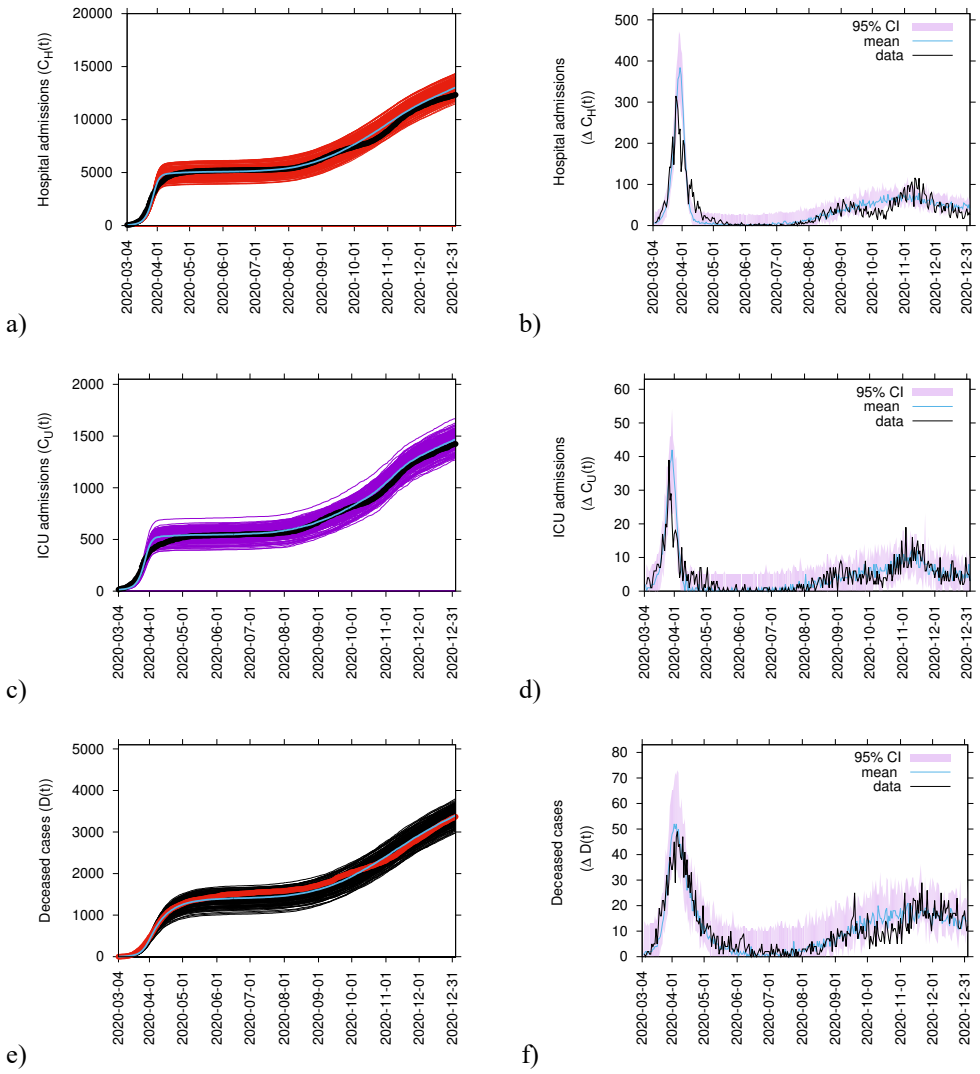


Figure 1: From March 4 to December 31, 2020, on the left-hand side, we plot the ensemble of stochastic realizations of the SHARUCD model for cumulative cases. In a) cumulative hospitalized cases $C_H(t)$, in c) cumulative ICU admissions $C_U(t)$ and in e) cumulative deceases cases $D(t)$. The mean of the stochastic realizations is plotted in light blue. Empirical data are plotted as black dots for hospitalizations and ICU admissions, and red dots for deceased cases. 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 as a black line for all three cases while the mean of 200 stochastic realizations is plotted in light blue. The 95% confidence intervals are obtained empirically from the stochastic realizations and are plotted as light purple shadows. For more information, please see reference [6].

transitions $w_j(\mathbf{x})$ and the corresponding shifting vectors $\mathbf{r}_j$ are given by

$$
\begin{array}{lll}
w_1(\mathbf{x}) = \eta\beta x_1(x_2 + \phi x_3 + \varrho) & , & \mathbf{r}_1 = (1,-1,0,0,0,-1,0,0,0,0)^T \\
w_2(\mathbf{x}) = \xi(1-\eta)\beta x_1(x_2 + \phi x_3 + \varrho) & , & \mathbf{r}_2 = (1,0,-1,0,0,0,-1,0,0,0)^T \\
w_3(\mathbf{x}) = (1-\xi)(1-\eta)\beta x_1(x_2 + \phi x_3 + \varrho) & , & \mathbf{r}_3 = (1,0,-1,0,0,0,0,0,0,0)^T \\
w_4(\mathbf{x}) = \gamma x_2 & , & \mathbf{r}_4 = (0,1,0,-1,0,0,0,0,0,-1)^T \\
w_5(\mathbf{x}) = (1-\xi)\gamma x_3 & , & \mathbf{r}_5 = (0,0,1,-1,0,0,0,0,0,0)^T \\
w_6(\mathbf{x}) = \gamma x_5 & , & \mathbf{r}_6 = (0,0,0,-1,1,0,0,0,0,-1)^T \\
w_7(\mathbf{x}) = \nu x_2 & , & \mathbf{r}_7 = (0,1,0,0,-1,0,0,-1,0,0)^T \\
w_8(\mathbf{x}) = \mu x_2 & , & \mathbf{r}_8 = (0,1,0,0,0,0,0,0,-1,0)^T \\
w_9(\mathbf{x}) = \mu x_5 & , & \mathbf{r}_9 = (0,0,0,0,1,0,0,0,-1,0)^T \\
w_{10}(\mathbf{x}) = \xi\gamma x_3 & , & \mathbf{r}_{10} = (0,0,1,-1,0,0,0,0,0,-1)^T \quad .
\end{array}
\tag{2}
$$

The model was parameterized with empirical data provided by the Basque Health Department and the Basque Health Service (Osakidetza) for each disease-related variable. Parameters were estimated and fixed as the model was able to describe the disease incidence during the exponential phase of the outbreak. The stochastic realizations of the model are calculated via the Gillespie algorithm [8, 7]. To investigate the parameter uncertainties, we calculate numerically the likelihood functions for each parameter conditioned on the others and the data, evaluating distances between simulations and data from all five variables, $D(t)$, $I_{cum}(t)$, $C_H(t)$, $C_U(t)$ and $C_R(t)$, for the exponential phase of the epidemic. The detailed analysis for the parameter estimation and uncertainties via likelihood functions can be found in [2, 1, 9].

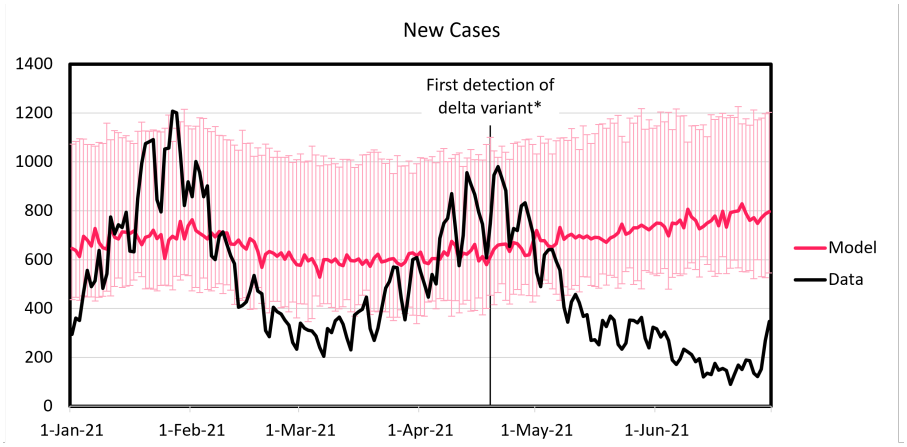
The mean-field ODE system corresponding to the above $w_j(\mathbf{x})$ and $\mathbf{r}_j$ is given in [2, 9] and was used to evaluate the model performance, its accuracy, and to guide the modeling analysis. The deterministic version of the model is hence given by

$$
\begin{cases}
\dot{S} = -\beta\dfrac{S}{N}(H + \phi A + \varrho N), \quad S(0) \geq 0, \\
\dot{H} = \eta\beta\dfrac{S}{N}(H + \phi A + \varrho N) - (\gamma + \nu + \mu)H, \quad H(0) \geq 0, \\
\dot{A} = (1-\eta)\beta\dfrac{S}{N}(H + \phi A + \varrho N) - \gamma A, \quad A(0) \geq 0, \\
\dot{R} = \gamma(H + A + U), \quad R(0) \geq 0, \\
\dot{U} = \nu H - (\gamma + \mu)U, \quad U(0) \geq 0, \\
\dot{C_A} = \xi \cdot (1-\eta)\beta\dfrac{S}{N}(H + \phi A + \varrho N), \quad C_H(0) \geq 0, \\
\dot{C_H} = \eta\beta\dfrac{S}{N}(H + \phi A + \varrho N), \quad C_H(0) \geq 0, \\
\dot{C_R} = \gamma(H + \xi A + U), \quad C_U(0) \geq 0, \\
\dot{C_U} = \nu H, \quad C_U(0) \geq 0, \\
\dot{D} = \mu(H + U), \quad D(0) \geq 0.
\end{cases}
\tag{3}
$$

While modeling simulations started in March 2020, parameters were adjusted with control functions to describe the effects of lockdown implementation and lifting, as well as control measures tightening during the year 2020, using the intitial state and parameter values summarized in Table 1. The framework was calibrated with empirical data and validated with 15 days ahead predictions for the last quarter of 2020. To estimate the number of cases, hospitalizations, ICU admissions, and deaths averted by COVID-19 vaccination, modeling simulations for the following months, from January 2021 to July 2021, were obtained by assuming similar epidemiological conditions as the modeling final setup on December 2020, i.e., without including any extra control to describe the available data. The COVID-19 infection outcomes for this period—defined to be the alternative scenario without vaccination—were collected, and the difference between the model predictions and the official data for each one of the model variables was computed and assumed to measure the epidemiological impact of the initial phase of the vaccination program in the Basque population. By comparing this counterfactual scenario to the official data gathered for the same period (Figures 2-5), we noticed that the effect of vaccination on severe cases started in March 2021, and the number of deaths observed was consistently lower than no-vaccine scenario from April 2021 onwards.

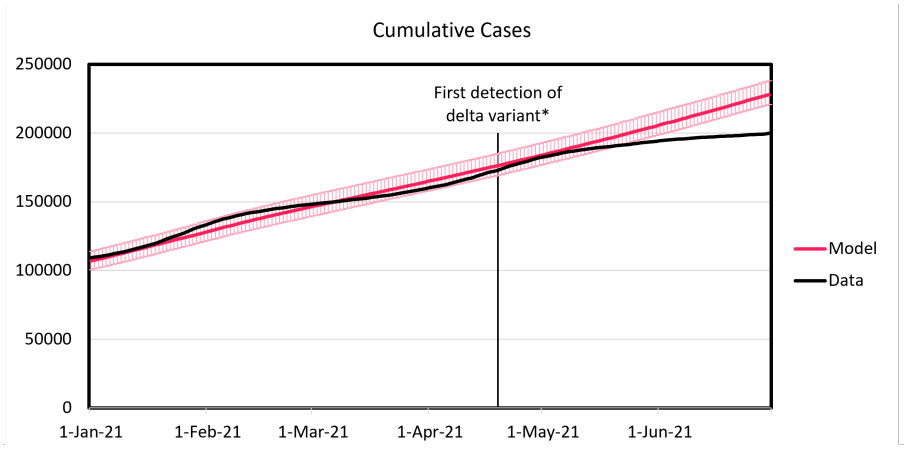
Table 1: Parameter values and initial conditions for the SHARUCD model.

Parameter	Description	Value
β	Transmission rate	$\gamma \times 3.25$
η	Proportion hospitalized after infection	0.0750
ϕ	Scaling factor for infectivity of mild/asymptomatic cases	1.6250
ν	ICU admission rate	0.1130
γ	Recovery rate	0.0515
μ	Disease-induced death rate	0.0205
ξ	Detection ratio of mild/asymptomatic	0.1000
ϱ	Import parameter	e^{-12}
N	Total population	2 207 776
$S(0)$	Initial susceptible individuals	$N - H - A - R - U - D$
$H(0)$	Initial hospitalized individuals	65
$A(0)$	Initial mild/asymptomatic individuals	200
$R(0)$	Initial recovered individuals	0
$U(0)$	Initial ICU-admitted individuals	25
$C_A(0)$	Initial recorded cumulative mild/asymptomatic individuals	40
$C_H(0)$	Initial cumulative hospitalized individuals	57
$C_U(0)$	Initial cumulative ICU-admitted individuals	15
$C_R(0)$	Initial recorded cumulative recovered individuals	0
$D(0)$	Initial deceased individuals	1



While the delta variant was detected in the Basque Country as early as April 2021, the alpha variant continued to be dominant until the end of June 2021.

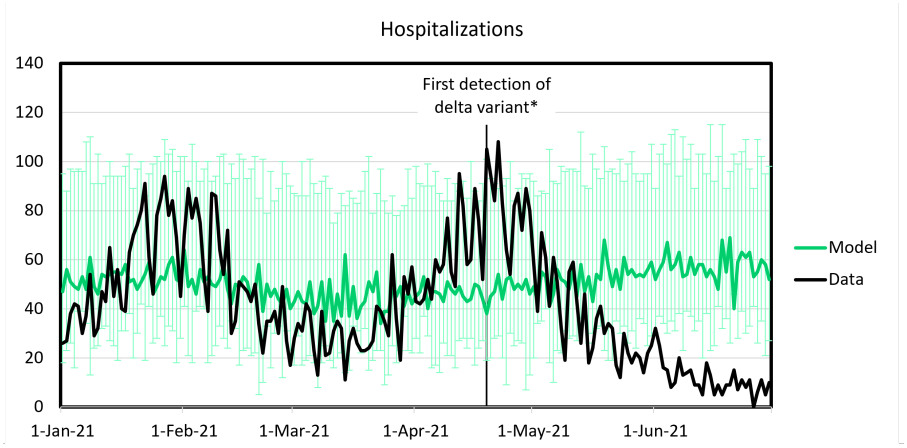
a)



While the delta variant was detected in the Basque Country as early as April 2021, the alpha variant continued to be dominant until the end of June 2021.

b)

Figure 2: a) Model-estimated number of cases in a no-vaccine scenario (red) versus official data (black) from Jan 2021 to Jun 2021. b) Model-estimated cumulative number of cases in a no-vaccine scenario (red) versus official data (black) from Jan 2021 to Jun 2021.



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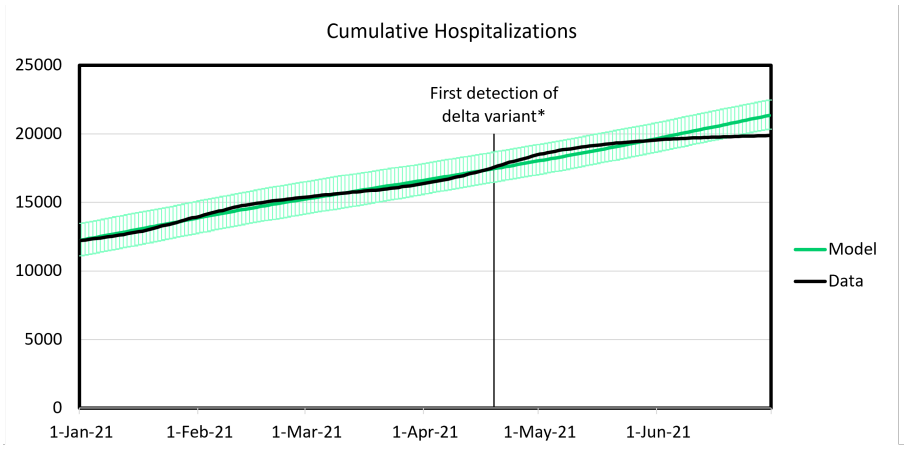
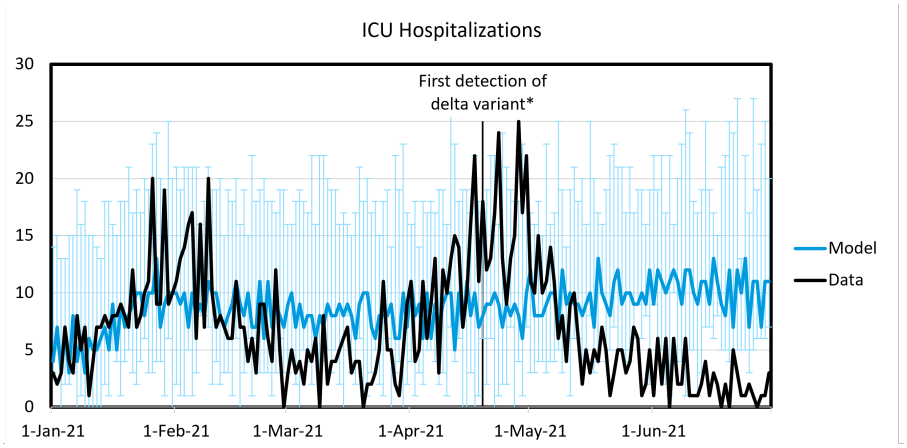


*While the delta variant was detected in the Basque Country as early as April 2021, the alpha variant continued to be dominant until the end of June 2021.

b)

Figure 3: a) Model-estimated number of hospitalizations in a no-vaccine scenario (green) versus official data (black) from Jan 2021 to Jun 2021. b) Model-estimated cumulative number of hospitalizations in a no-vaccine scenario (green) versus official data (black) from Jan 2021 to Jun 2021.



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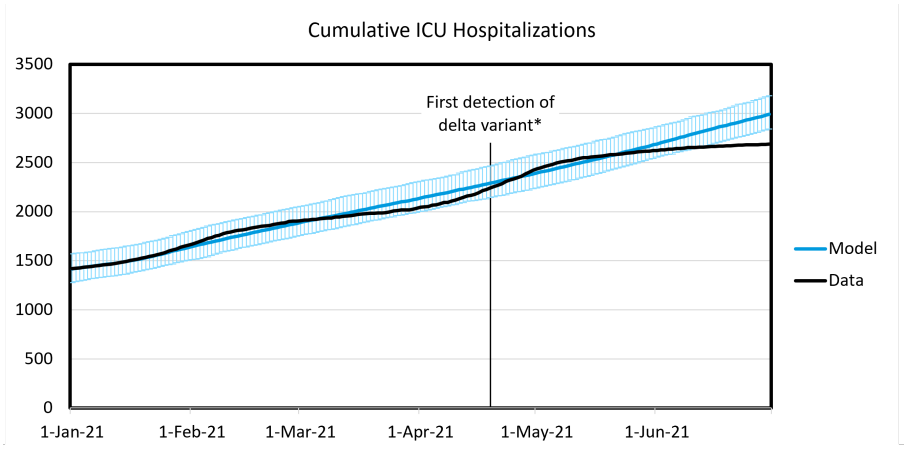
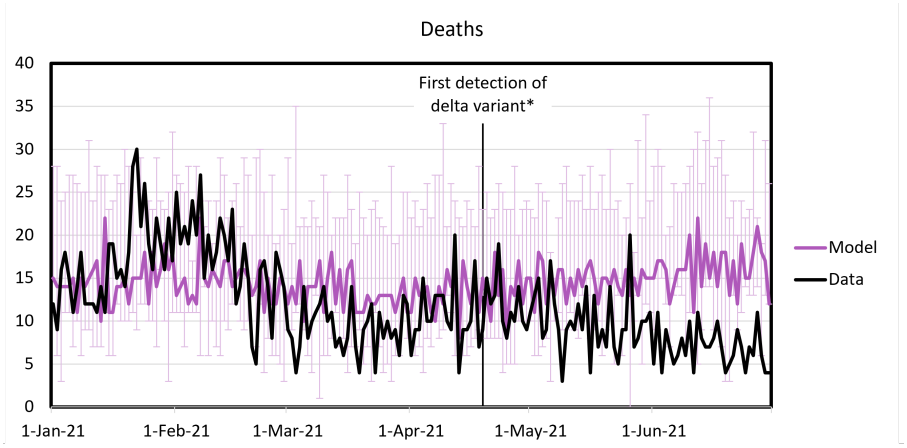


While the delta variant was detected in the Basque Country as early as April 2021, the alpha variant continued to be dominant until the end of June 2021.

b)

Figure 4: a) Model-estimated number of ICU admissions in a no-vaccine scenario (blue) versus official data (black) from Jan 2021 to Jun 2021. b) Model-estimated cumulative number of ICU admissions in a no-vaccine scenario (blue) versus official data (black) from Jan 2021 to Jun 2021.



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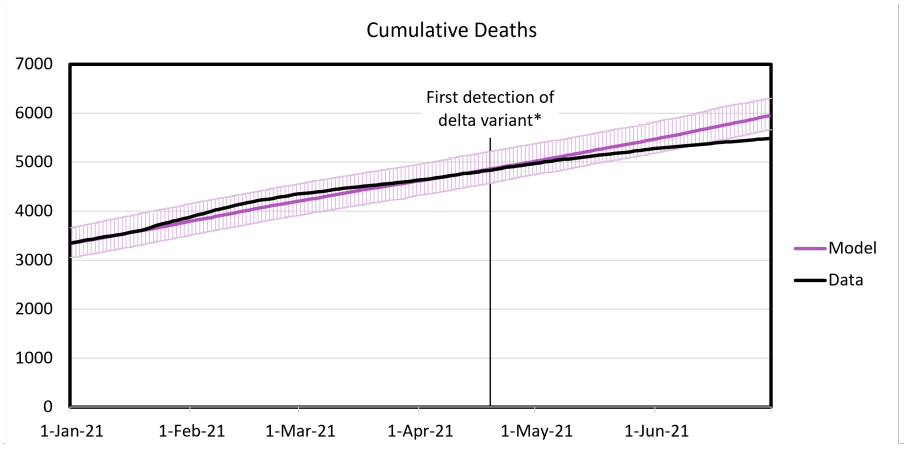

While the delta variant was detected in the Basque Country as early as April 2021, the alpha variant continued to be dominant until the end of June 2021.

b)

Figure 5: a) Model-estimated number of deaths in a no-vaccine scenario (purple) versus official data (black) from Jan 2021 to Jun 2021. b) Model-estimated cumulative number of deaths in a no-vaccine scenario (purple) versus official data (black) from Jan 2021 to Jun 2021.

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Table SM1. Parameters of the Gompertz function used to assign life expectancy.

$$Time\ until\ death = \frac{1}{\beta} ln$$

Where $\alpha = e^{-9 \cdot 579}$ for males $\wedge\ \alpha = e^{-10 \cdot 176}$ for females and $\beta = 0 \cdot 087$ for males $\wedge\ \beta = 0 \cdot 084$ for females.

The equations included a uniformly distributed random factor between 0 and 1 (u) and two parameters α and β that defined the characteristics of the distribution.

Table SM2. Characteristics of individuals in the Basque Country in 2021 disaggregated by socioeconomic status.

		Low income	Medium income	High income	Total
Infection in period	Infected	7,501 (3.11%)	37,325 (3.49%)	40,288 (3.93%)	85,114 (3.64%)
	Not infected	233,506 (96.89%)	1,033,278 (96.51%)	983,597 (96.07%)	2,250,381 (96.36%)
Sex	Hombre	95,844 (39.77%)	496,447 (46.37%)	550,167 (53.73%)	1,142,458 (48.92%)
	Mujer	145,163 (60.23%)	574,156 (53.63%)	473,718 (46.27%)	1,193,037 (51.08%)
Age group	<18	19,242 (7.98%)	63,283 (5.91%)	10,1374 (9.90%)	183,899 (7.87%)
	18-50	74,278 (30.82%)	544,021 (50.81%)	408,087 (39.86%)	1,026,386 (43.95%)
	50-65	50,067 (20.77%)	233,689 (21.83%)	280,591 (27.40%)	564,347 (24.16%)
	>=65	97,420 (40.42%)	229,610 (21.45%)	233,833 (22.84%)	560,863 (24.01%)
Charlson indice at period start (4 levels)	Chln.Nulo	131,945 (56.15%)	723,960 (70.02%)	706,779 (70.95%)	1,562,684 (68.99%)
	Chln.Bajo	72,248 (30.75%)	238,334 (23.05%)	235,054 (23.60%)	545,636 (24.09%)
	Chln.Medio	18,690 (7.95%)	43,765 (4.23%)	35,056 (3.52%)	97,511 (4.31%)
	Chln.Alto	12,101 (5.15%)	27,836 (2.69%)	19,224 (1.93%)	59,161 (2.61%)

Table SM3. Comparison of the expected survival in years predicted by the Spanish Institute of Statistics (INE) in 2019 and the remaining survival estimated by the Gompertz function for men and women.

	Men		Women	
Age, years	**INE**	**Gompertz**	**INE**	**Gompertz**
0	81.02	82.62	86.77	88.01
25	56.51	57.68	62.13	63.03
30	51.64	52.72	57.2	58.05
35	46.8	47.77	52.26	53.08
40	41.93	42.86	47.33	48.13
45	37.1	38	42.46	43.21
50	32.41	33.21	37.65	38.33
55	27.92	28.54	32.94	33.52
60	23.62	24.02	28.36	28.81
65	19.62	19.74	23.91	24.25
70	15.8	15.78	19.53	19.92
75	12.22	12.23	15.2	15.9
80	8.94	9.17	11.2	12.29
85	6.21	6.66	7.69	9.18
90	4.14	4.69	4.87	6.62

Table SM4. Adjustment of mortality hazard ratios (HR) according to Charlson comorbidity index to achieve a population risk of one.

			Bannay[22]	Adjusted HR	
CCI	**Men**	**Women**	**HR**	**Men**	**Women**
0	73.5%	74.1%	1	**0.686**	**0.705**
1-2	23.1%	23.5%	2.435	**1.671**	**1.718**
3-4	2.9%	2.1%	3.798	**2.606**	**2.679**
5-6	0.5%	0.3%	9.481	**6.505**	**6.688**

HR: hazard ratio; CCI: Charlson comorbidity index.

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Table SM5. Unit costs for infection, hospitalization, and intensive care unit admission.

Resource	Unit cost (€)	Infection	Hospitalization	ICU admission
General practitioner consultation	59	2		
Hospitalization	6,840		1	
Hospitalization with ICU	28,829			1
Outpatient services (first visit)	215		1	1
Outpatient services (second visit)	108		8	15
Rehabilitation	5,681			1
Total (€)		118	7,919	36,345

ICU: intensive care unit.

Table SM6. Characteristics of infected and uninfected individuals in the Basque Country during the last quarter of 2020 and the first half of 2021.

	September 2020 to December 2020		January 2021 to June 2021	
	Infected	**Not Infected**	**Infected**	**Not Infected**
Men	34,210 (2.98%)	1,112,476 (97.02%)	41,959 (3.67%)	1,100,499 (96.33%)
Women	38,244 (3.19%)	1,158,928 (96.81%)	43,155 (3.62%)	1,149,882 (96.38%)
Age $<$18 years	7,932 (4.14%)	183,797 (95.86%)	10,546 (5.73%)	173,353 (94.27%)
Age 18-50 years	33,916 (3.29%)	998,477 (96.71%)	42,056 (4.10%)	984,330 (95.90%)
Age 50-65 years	16,912 (3.01%)	544,245 (96.99%)	19,330 (3.43%)	545,017 (96.57%)
Age$\geq$65 years	13,694 (2.45%)	544,885 (97.55%)	13,182 (2.35%)	547,681 (97.65%)
Low income	6,679 (2.77%)	234,797 (97.23%)	7,501 (3.11%)	233,506 (96.89%)
Medium income	32,128 (2.99%)	1,043,585 (97.01%)	37,325 (3.49%)	1,033,278 (96.51%)
High income	33,647 (3.28%)	993,022 (96.72%)	40,288 (3.93%)	983,597 (96.07%)
Charlson 0	49,275 (3.04%)	1,572,181 (96.96%)	59,542 (3.81%)	1,503,142 (96.19%)
Charlson 1-2	17,834 (3.17%)	543,993 (96.83%)	20,627 (3.78%)	525,009 (96.22%)
Charlson 3-4	3,187 (3.18%)	96,929 (96.82%)	30,490 (3.13%)	94,462 (96.87%)
Charlson $>$ 4	2,158 (3.57%)	58,301 (96.43%)	18,950 (3.20%)	57,266 (96.80%)
Total	72,454 (3.1%)	2,271,404 (96.9%)	85,114 (3.6%)	2,250,381 (96.4%)

ICU: intensive care unit.

Table SM7. Characteristics of the intensive care unit admissions in the Basque Country in 2021 in the scenarios with vaccination (observed) and without vaccination (simulated).

Variable		No Vaccination	Vaccination	Difference	%
Total		1579	1274	305	19.3%
Sex	Men	1022	773	249	24.4%
	Women	557	501	56	10.1%
Age group, years	0-29	19	12	7	36.8%
	30-49	236	221	15	6.4%
	50-69	681	475	206	30.2%
	≥70	643	566	77	12.0%
Charlson Comorbidity Index	0	672	487	185	27.5%
	1-2	515	429	86	16.7%
	3-4	207	186	21	10.1%
	>4	185	172	13	7.0%
Socioeconomic status	Low	199	171	28	14.1%
	Medium	694	605	89	12.8%
	High	686	498	188	27.4%

Table SM8. Characteristics of individuals who died in the Basque Country in 2021 in the scenarios with vaccination (observed) and without vaccination (simulated).

Variable		No Vaccination	Vaccination	Difference	%
Total		2617	2136	481	18.4%
Sex	Men	1235	1180	55	4.5%
	Women	1382	956	426	30.8%
Age group, years	0-29	2	2	0	0.0%
	30-49	24	18	6	25.0%
	50-69	381	352	29	7.6%
	≥70	2210	1764	446	20.2%
Charlson Comorbidity Index	0	421	331	90	21.4%
	1-2	841	706	135	16.1%
	3-4	636	467	169	26.6%
	>4	719	632	87	12.1%
Socioeconomic status	Low	306	229	77	25.2%
	Medium	1369	1118	251	18.3%
	High	942	789	153	16.2%

Table SM9. Mean remaining comorbidity-adjusted life expectancy of the population according to age, socioeconomic status and Charlson comorbidity index in the scenarios without and with vaccination.

Population		No Vaccination	Vaccination	Difference
Total		34.791	34.812	0.022
Sex	Men	33.144	33.155	0.011
	Women	36.367	36.400	0.033
Age group, years	10-19	67.880	67.913	0.034
	20-29	57.948	57.978	0.030
	30-39	47.968	47.992	0.024
	40-49	38.235	38.257	0.023
	50-59	28.396	28.419	0.024
	60-69	18.944	18.960	0.016
	70-74	12.492	12.502	0.010
	75-79	9.262	9.267	0.005
	80-84	6.513	6.525	0.012
	85-89	4.571	4.587	0.015
	90-94	3.298	3.315	0.017
	≥95	2.538	2.559	0.021
Socioeconomic status	Low	28.770	28.788	0.019
	Medium	36.340	36.362	0.022
	High	34.588	34.610	0.022
Charlson Comorbidity Index	0	40.527	40.550	0.024
	1-2	25.394	25.413	0.019
	3-4	8.968	8.984	0.017
	>4	5.665	5.677	0.012

Table SM10. Incremental cost and utility mean and confidence intervals with discount using the official and real prices of vaccines.

	Incremental cost with CI € Official prices	Incremental cost with CI € Real prices	Incremental utility with CI QALY
Total	3.75[2.60 ; 4.90]	-0.64[-1.79 ; 0.51]	0.0052[0.0051 ; 0.0054]
Men	-1.64[-3.50 ; 0.21]	-5.45[-7.31 ; -3.60]	0.0029[0.0027 ; 0.0032]
Women	8.92[7.54 ; 10.31]	3.96[2.58 ; 5.35]	0.0074[0.0072 ; 0.0077]
Low SES	7.59[3.33 ; 11.85]	1.82[-2.44 ; 6.08]	0.0055[0.0050 ; 0.0059]
Medium SES	3.47[1.78 ; 5.16]	-0.35[-2.04 ; 1.34]	0.0051[0.0048 ; 0.0054]
High SES	3.14[1.48 ; 4.80]	-1.53[-3.19 ; 0.13]	0.0053[0.0051 ; 0.0056]
CCI 0	3.70[2.72 ; 4.69]	0.36[-0.62 ; 1.35]	0.0047[0.0046 ; 0.0049]
CCI 1-2	5.51[2.76 ; 8.26]	-0.47[-3.22 ; 2.28]	0.0060[0.0055 ; 0.0064]
CCI 3-4	0.89[-10.57 ; 12.35]	-9.08[-20.54 ; 2.38]	0.0088[0.0073 ; 0.0103]
CCI > 4	-6.36[-24.37 ; 11.64]	-16.19[-34.19 ; 1.82]	0.0062[0.0037 ; 0.0088]

Figure 1. Comparison of characteristics of the infected individuals in 2020 and the 2021 simulated population without vaccination.