

## Supplementary material

### Comparative severity of COVID-19 cases caused by Alpha, Delta or Omicron SARS-CoV-2 variants and effect of vaccination

Table S1. Comparison between individuals included and non-included in the study sample in each of the two study periods .....	2
Table S2. Results of sensitivity analyses for the study period of June and July 2021 .....	3
Table S3. Results of sensitivity analyses for the study period of December 2021 and January 2022.....	4
Figure S1. Sample selection and proportions with sequencing information available in each group .....	5
Figure S2. Age distribution of the study population .....	7
Figure S3. Included SARS-CoV-2 infections by week of co-circulation.....	9

**Table S1. Comparison between individuals included and non-included in the study sample in each of the two study periods**

Variable		June and July 2021		December 2021 and January 2022	
		Included (n=17,319)	Non-included (n=851,965)	Included (n=15,850)	Non-included (n=5,054,897)
Hospitalized	Unknown	-	154,425 (18.1)	-	1,243,465 (24.6)
	Yes	2,179 (12.6)	25,721 (3.0)	2,957 (18.7)	60,967 (1.2)
	No	15,140 (87.4)	671,819 (78.9)	12,893 (81.3)	3,750,465 (74.2)
Sequenced		17,319 (100.0)	7,172 (0.8)	15,850 (100.0)	8,917 (0.2)
Age	Unknown	-	73,912 (8.7)	-	764,262 (15.1)
	median(IQR)	35 (22-54 )	29 (20-43 )	49 (34-66 )	41 (28-52 )
Sex	Unknown	-	85 (0.0)	-	725 (0.0)
	Man	8,286 (47.8)	428,730 (50.3)	7,458 (47.1)	2,354,287 (46.6)
	Woman	9,033 (52.2)	423,150 (49.7)	8,392 (53.0)	2,699,885 (53.4)
Completely vaccinated	Unknown	-	141,589 (16.6)	-	368,113 (7.3)
	Yes	6,630 (38.3)	116,210 (13.6)	13,166 (83.1)	3,461,103 (68.5)
	No	10,689 (61.7)	594,166 (69.7)	2,684 (16.9)	1,225,681 (24.2)
Type of vaccine*	Unknown	497 (7.5)	10,645 (9.2)	831 (6.3)	153,515 (4.4)
	Comirnaty	4,334 (65.4)	67,087 (57.7)	8,610 (65.4)	2,362,174 (68.3)
	Spikevax	378 (5.7)	5,577 (4.8)	1,529 (11.6)	420,079 (12.1)
	Vaxzevria	784 (11.8)	18,415 (15.9)	1,542 (11.7)	349,265 (10.1)
	Vaxzevria+ARNm	16 (0.2)	750 (0.7)	77 (0.6)	27,847 (0.8)
	Janssen	613 (9.3)	13,621 (11.7)	356 (2.7)	13,707 (0.4)
	Others	8 (0.1)	115 (0.1)	221 (1.7)	134,516 (3.9)

\* proportion is among the completely vaccinated

**Table S2. Results of sensitivity analyses for the study period of June and July 2021:** Odds Ratio (OR) and 95% Confidence Intervals (95% CI) for the association between: a) SARS-CoV-2 variant Delta vs. Alpha and the odds of hospitalization, stratified by vaccination status and; b) between and vaccination status and the odds of hospitalization, stratified by SARS-CoV-2 variant. Results for the total sample.

<b>Sensitivity Analysis</b>		<b>aOR (95%CI)*</b>	
<b>a)</b>		<b>Unvaccinated</b>	<b>Vaccinated</b>
<b>1. Excluding booster doses from complete vaccination</b>	<b>Delta</b> <b>Alpha</b>	Not performed	
<b>2. Recoding unknown hospitalisation as non-hospitalised</b>	<b>Delta</b> <b>Alpha</b>	Ref. 0.60 (0.50-0.72)	Ref. 0.58 (0.46-0.73)
<b>3. Recoding unknown vaccination as unvaccinated</b>	<b>Delta</b> <b>Alpha</b>	Ref. 0.60 (0.51-0.72)	Ref. 0.58 (0.46-0.73)
<b>4. Alternative definition of hospitalization due to COVID-19</b>	<b>Delta</b> <b>Alpha</b>	Ref. 0.54 (0.44-0.66)	Ref. 0.54 (0.42-0.69)
<b>5. Adjusting by reinfection</b>	<b>Delta</b> <b>Alpha</b>	Ref. 0.57 (0.46-0.69)	Ref. 0.57 (0.45-0.72)
<b>b)</b>		<b>Alpha</b>	<b>Delta</b>
<b>1. Excluding booster doses from complete vaccination</b>	<b>Unvaccinated</b> <b>Vaccinated</b>	Not performed	
<b>2. Recoding unknown hospitalisation as non-hospitalised</b>	<b>Unvaccinated</b> <b>Vaccinated</b>	Ref. 0.16 (0.13-0.21)	Ref. 0.17 (0.14-0.20)
<b>3. Recoding unknown vaccination as unvaccinated</b>	<b>Unvaccinated</b> <b>Vaccinated</b>	Ref. 0.29 (0.23-0.36)	Ref. 0.30 (0.26-0.34)
<b>4. Alternative definition of hospitalization due to COVID-19</b>	<b>Unvaccinated</b> <b>Vaccinated</b>	Ref. 0.15 (0.12-0.20)	Ref. 0.15 (0.13-0.18)
<b>5. Adjusting by reinfection</b>	<b>Unvaccinated</b> <b>Vaccinated</b>	Ref. 0.16 (0.13-0.21)	Ref. 0.16 (0.14-0.19)

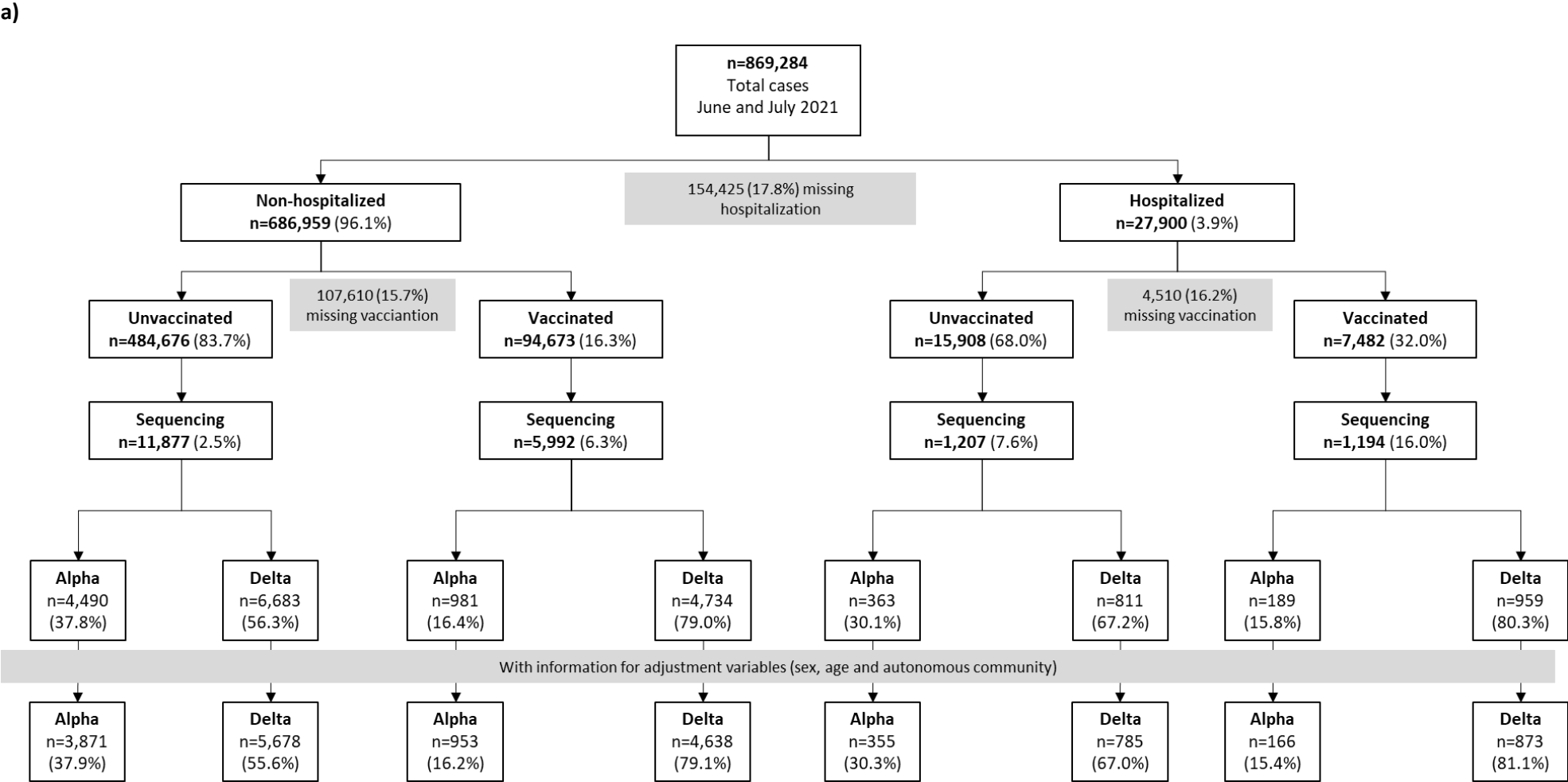
\*aOR: OR adjusted by sex, age, autonomous community and week of co-circulation, including an interaction term with vaccination status (a) or an interaction term with co-circulating variants (b) for the stratified results.

**Table S3. Results of sensitivity analyses for the study period of December 2021 and January 2022:** Odds Ratio (OR) and 95% Confidence Intervals (95% CI) for the association between: a) SARS-CoV-2 variant Delta vs. Alpha and the odds of hospitalization, stratified by vaccination status and; b) between and vaccination status and the odds of hospitalization, stratified by SARS-CoV-2 variant. Results for the total sample.

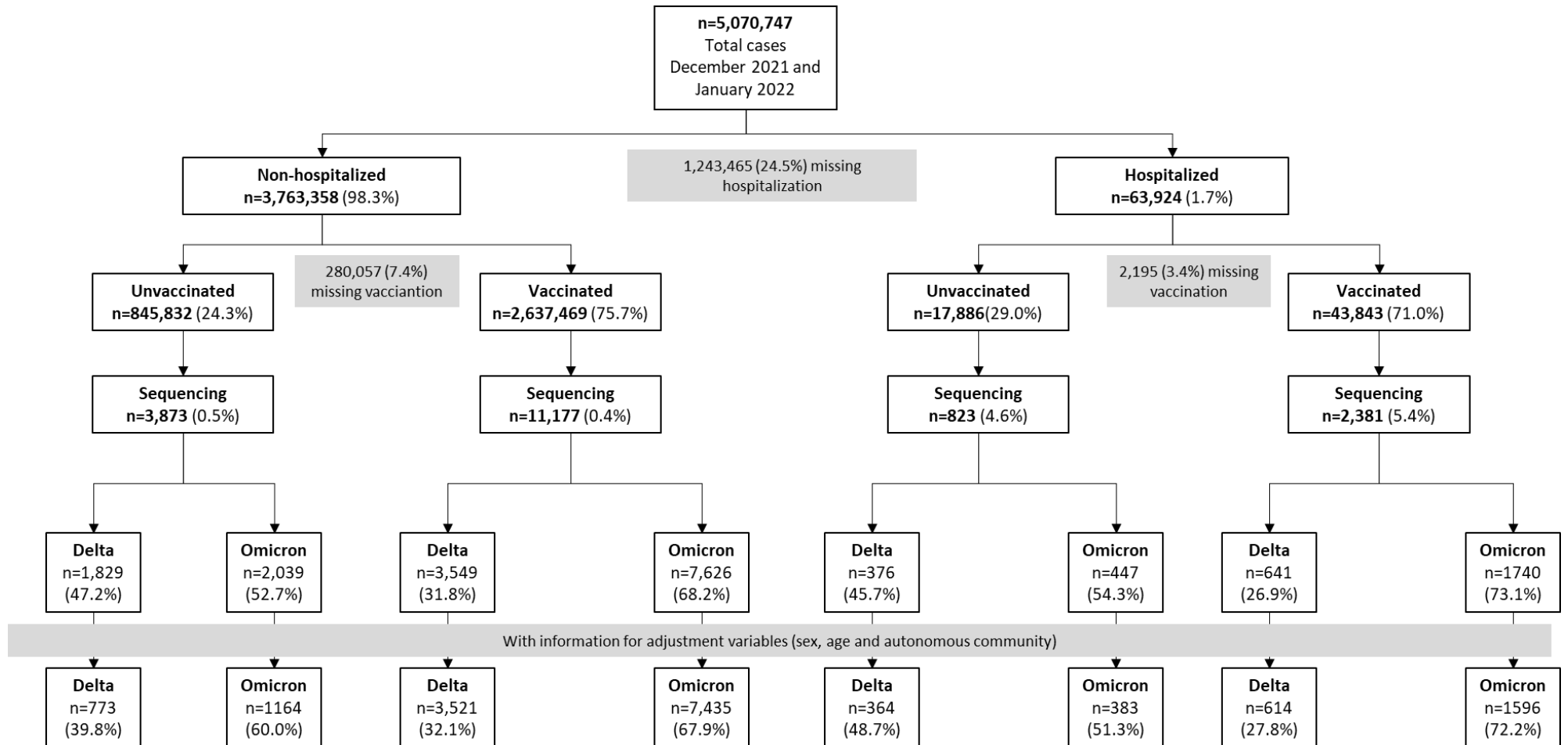
<b>Sensitivity Analysis</b>		<b>aOR (95%CI)*</b>	<b>aOR (95%CI)*</b>
<b>a)</b>		<b>Unvaccinated</b>	<b>Vaccinated</b>
<b>1. Excluding booster doses from complete vaccination</b>	<b>Delta</b>	Ref.	Ref.
	<b>Omicron</b>	0.28 (0.21-0.36)	0.52 (0.42-0.63)
<b>2. Recoding unknown hospitalisation as non-hospitalised</b>	<b>Delta</b>	Ref.	Ref.
	<b>Omicron</b>	0.29 (0.23-0.36)	0.46 (0.39-0.55)
<b>3. Recoding unknown vaccination as unvaccinated</b>	<b>Delta</b>	Ref.	Ref.
	<b>Omicron</b>	0.27 (0.21-0.34)	0.47 (0.40-0.56)
<b>4. Alternative definition of hospitalization due to COVID-19</b>	<b>Delta</b>	Ref.	Ref.
	<b>Omicron</b>	0.26 (0.20-0.34)	0.48 (0.40-0.58)
<b>5. Adjusting by reinfection</b>	<b>Delta</b>	Ref.	Ref.
	<b>Omicron</b>	0.29 (0.22-0.37)	0.49 (0.41-0.59)
<b>b)</b>		<b>Omicron</b>	<b>Delta</b>
<b>1. Excluding booster doses from complete vaccination</b>	<b>Unvaccinated</b>	Ref.	Ref.
	<b>Vaccinated</b>	0.69 (0.57-0.83)	0.37 (0.30-0.45)
<b>2. Recoding unknown hospitalisation as non-hospitalised</b>	<b>Unvaccinated</b>	Ref.	Ref.
	<b>Vaccinated</b>	0.52 (0.45-0.61)	0.33 (0.27-0.39)
<b>3. Recoding unknown vaccination as unvaccinated</b>	<b>Unvaccinated</b>	Ref.	Ref.
	<b>Vaccinated</b>	0.67 (0.57-0.78)	0.38 (0.31-0.46)
<b>4. Alternative definition of hospitalization due to COVID-19</b>	<b>Unvaccinated</b>	Ref.	Ref.
	<b>Vaccinated</b>	0.62 (0.51-0.74)	0.33 (0.27-0.41)
<b>5. Adjusting by reinfection</b>	<b>Unvaccinated</b>	Ref.	Ref.
	<b>Vaccinated</b>	0.62 (0.52-0.74)	0.36 (0.30-0.44)

\*aOR: OR adjusted by sex, age, autonomous community and week of co-circulation, including an interaction term with vaccination status (a) or an interaction term with co-circulating variants (b) for the stratified results.

**Figure S1. Sample selection and proportions with sequencing information available in each group:** a) comparison between Delta and Alpha in June and July 2021; b) comparison between Delta and Omicron in December 2021 and January 2022.

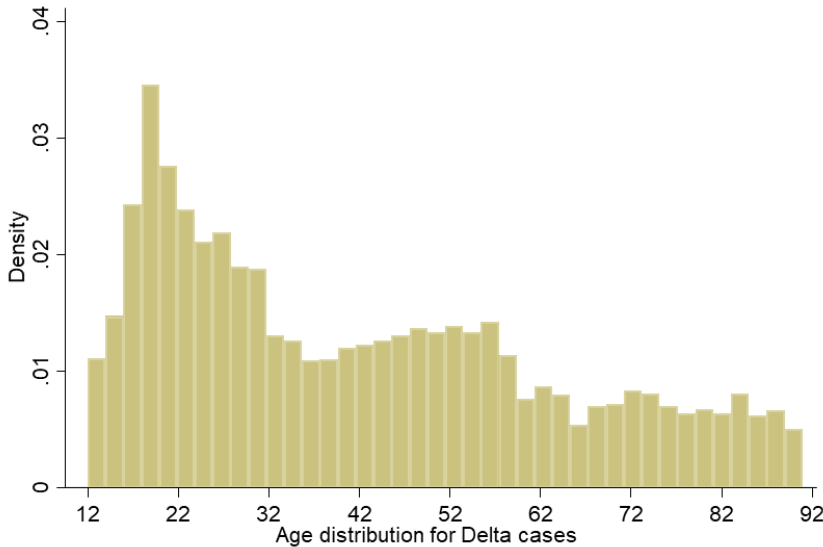
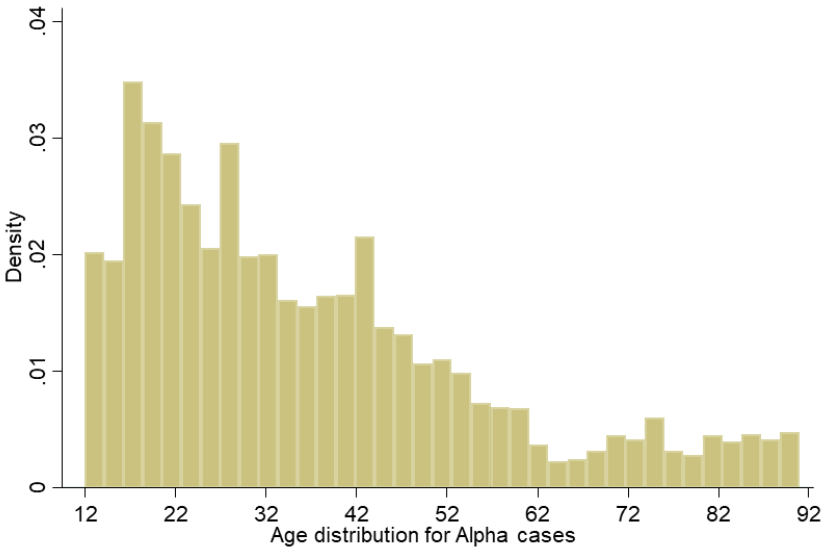


b)

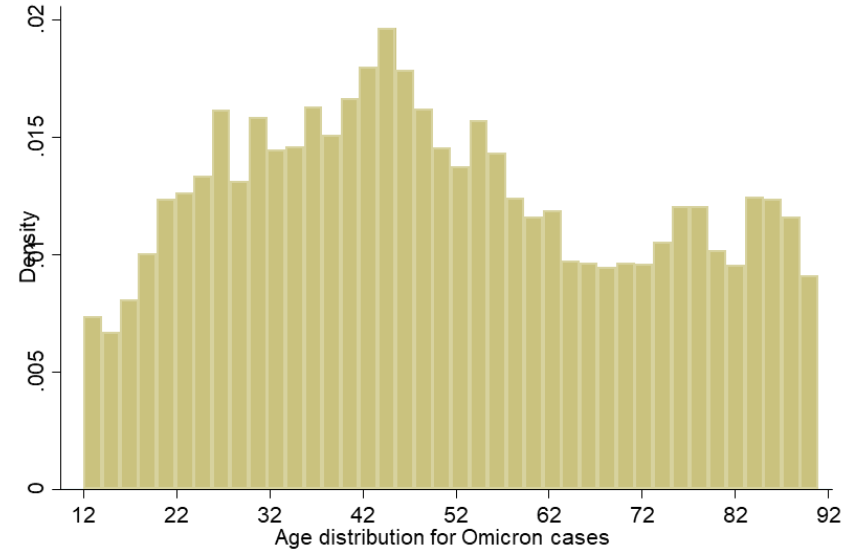
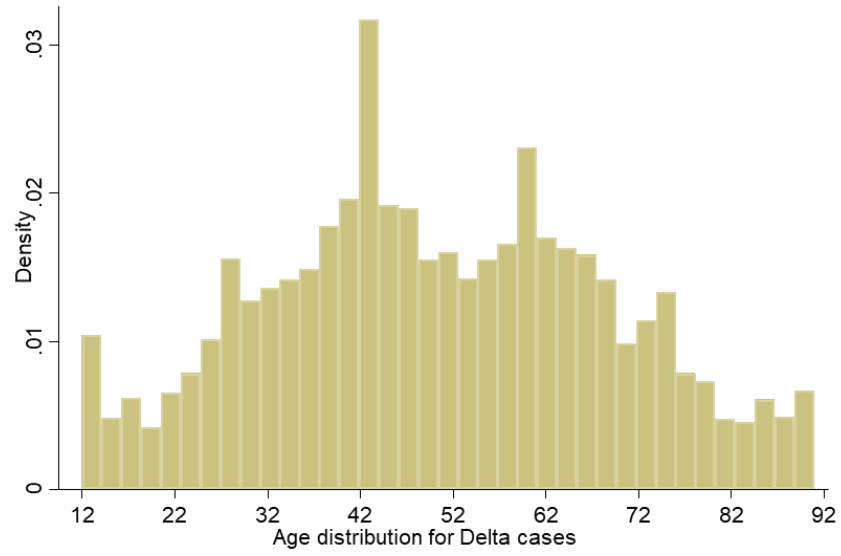


**Figure S2. Age distribution of the study population:** a) for Alpha and Delta cases, Spain, June and July 2021; b) for Delta and Omicron cases, Spain, December 2021 and January 2022

a)

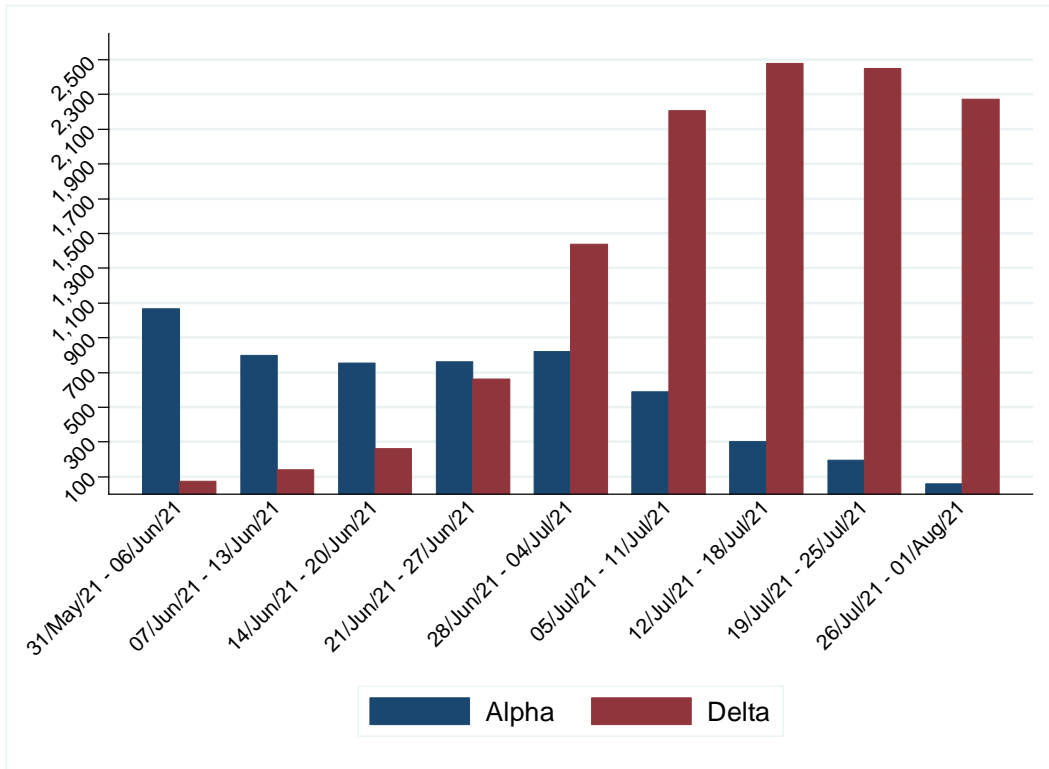


b)



**Figure S3. Included SARS-CoV-2 infections by week of co-circulation:** a) Alpha and Delta cases in Spain, in June and July 2021; b) Delta and Omicron cases in Spain, in December 2021 and January 2022

a)



b)

