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Supplementary appendix

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APPENDIX

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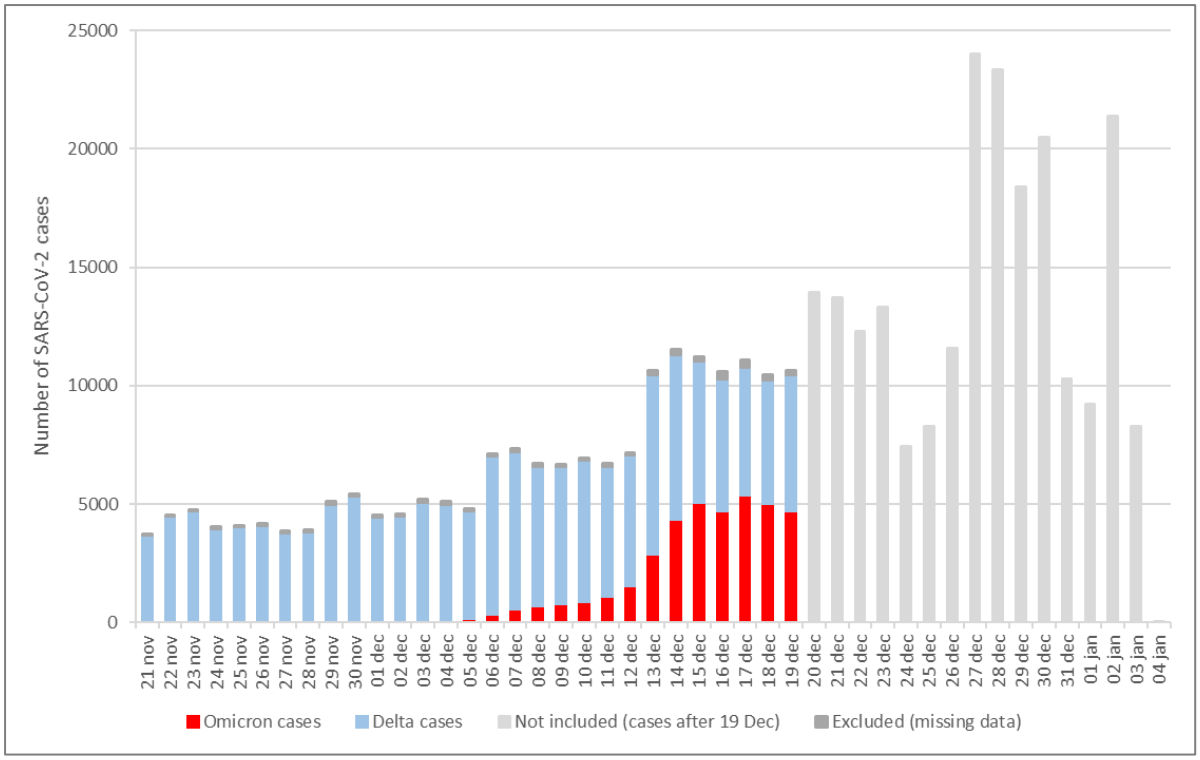
Figure S1. Flow chart for inclusion of the study population of 188,980 SARS-CoV-2 RT-PCR positive individuals between 21 November and 19 December 2021, Denmark.

Inclusion criteria	Flow	SARS-CoV-2 cases	Omicron cases	Delta cases	Omicron hosp.	Delta hosp.		Excluded cases	Excluded hosp.	Exclusion reason
SSI SARS-CoV-2 Surveillance database Linelist sampledates 21.11. to 19.12.2021	↓	192610	38817	153793	222	2279				
Positive Omicron vPCR, or negative or not reported	↓	189888	38817	151071	222	2238	→	2722	41	Omicron vPCR inconclusive due to high Cycle time
Follow-up >=14 dage	↓	189888	38817	151071	222	2238	→	0	0	Follow-up <14 days
Information on name of region	↓	**188980**	38669	150311*	222	2213*	→	908	25	Missing name of region
Healthcare track		15877	2765	2925 neg, 10187	103	274 neg, 806	→	343	21	
Community track		173103	35904	119724 neg, 17475	119	997 neg, 136	→	565	4	

*Delta was defined by either negative (neg.) or not reported Omicron vPCR result (no data in the surveillance system), respectively.



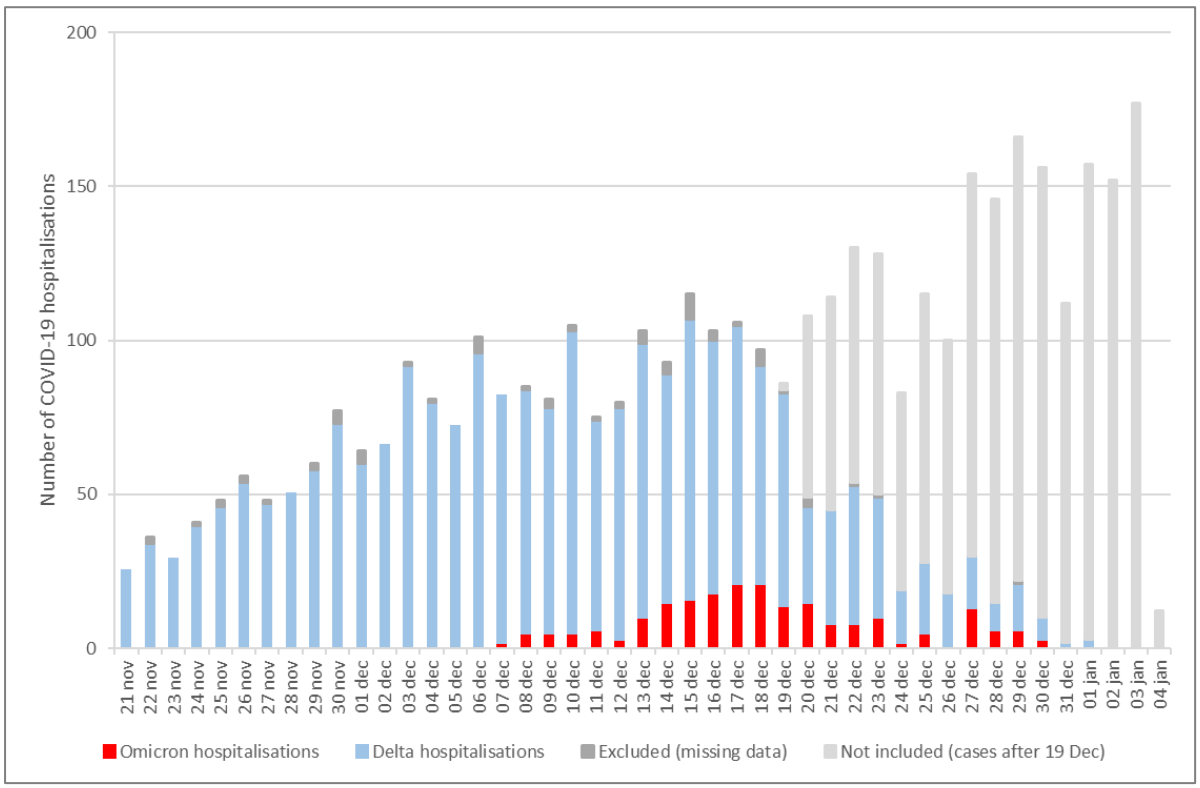


Figure S2. Timeline for cases of infection (test/sample dates, top figure) and COVID-19 hospitalisations (admission dates, bottom figure) by variant in the study population of 188,980 cases of RT-PCR confirmed SARS-CoV-2 infections, between 21 November and 19 December 2021, Denmark. Note that the decrease in number of studied hospitalisations (blue and red bars) after 19 December is by design due to the inclusion of cases until that date. In addition, the apparent increase in number of hospitalisations between 21 November and 19 December is partly due to fact that cases before 21 November were not included in the study, and their associated COVID-19 hospitalisations from 21 November and onwards therefore are not shown in the figure. All studied COVID-19 hospitalisations were followed up for diagnoses and discharge data in the National Patient Registry until 2 February 2022.

Table S1. Further stratification of characteristics of 188,980 cases of RT-PCR confirmed SARS-CoV-2 infections between 21 November and 19 December 2021, Denmark.

	SARS-CoV-2 variant						COVID-19 hospitalisation			
	Overall		<30 years		Reinfected		Overall		Length of stay in hours**	
	Omicron (N=38669)	Delta (N=150311)	Omicron (N=20088)	Delta (N=72437)	Omicron (N=2142)	Delta (N=1886)	Omicron (N=222)	Delta (N=2213)	Omicron median (IQR)	Delta median (IQR)
Vaccination against SARS-CoV-2 (status at infection*)										
None or only one dose	7266 (18.8)	69885 (46.5)	5613 (27.9)	54706 (75.5)	622 (29.0)	1103 (58.5)	54 (24.3)	997 (45.1)	19 (6-41)	28 (9-121)
Infected and not vaccinated	5322 (13.8)	59345 (39.5)	4128 (20.5)	46577 (64.3)	496 (23.2)	978 (51.9)	43 (19.4)	907 (41.0)	19 (6-51)	28 (9-121)
Infected before D1	28 (.1)	1964 (1.3)	27 (.1)	1904 (2.6)	4 (.2)	24 (1.3)	0 (.0)	7 (.3)	-	15 (4-34)
Infected 0-13 days after D1	885 (2.3)	5250 (3.5)	820 (4.1)	4638 (6.4)	33 (1.5)	53 (2.8)	4 (1.8)	24 (1.1)	16 (7-23)	67 (8-177)
Infected 14+ days after D1	826 (2.1)	2800 (1.9)	501 (2.5)	1348 (1.9)	70 (3.3)	39 (2.1)	4 (1.8)	51 (2.3)	39 (28-81)	20 (12-117)
Infected 0-13 days after D2	205 (.5)	526 (.3)	137 (.7)	239 (.3)	19 (.9)	9 (.5)	3 (1.4)	8 (.4)	6 (4-10)	58 (5-148)
Two doses	29922 (77.4)	77441 (51.5)	14111 (70.2)	17501 (24.2)	1460 (68.2)	720 (38.2)	145 (65.3)	1041 (47.0)	12 (6-41)	45 (12-124)
Infected 14+ days after D2	29776 (77.0)	77088 (51.3)	14103 (70.2)	17496 (24.2)	1457 (68.0)	714 (37.9)	143 (64.4)	1029 (46.5)	12 (6-43)	45 (12-124)
Infected 0-13 days after D3	146 (.4)	353 (.2)	8 (.0)	5 (.0)	3 (.1)	6 (.3)	2 (.9)	12 (.5)	14 (3-24)	112 (18-208)
Three doses										
Infected 14+ days after D3	1481 (3.8)	2985 (2.0)	364 (1.8)	230 (.3)	60 (2.8)	63 (3.3)	23 (10.4)	175 (7.9)	25 (7-100)	74 (19-143)

Data are n (%), unless otherwise specified. D1, dose 1; D2, dose 2; D3, dose 3. *Time of infection defined as the RT-PCR positive sample date. ** Not comparable to true length of stays because of truncation until 2 February and inclusion of snapshot data with some stays <12 hours. Nevertheless the data is shown here as a relative comparison by variant. The true length of stay is published by the Danish Health Authority (DHA) based on complete data from the National Patient Registry and does not rely on snapshot data that may include stays <12 hours. For example, the DHA reported a median length of stay of 3.7 days for COVID-hospitalisations of >12hours in September 2021, and 2.6 days for 30-39 year-olds from July to September 2021, both periods where the Delta variant dominated. In comparison, length of stay for 30-39 year-olds in the study population when excluding stays <12 hour, was 45 hours (IQR 20-108) for Delta hospitalisations, which is 1.9 days and thus 2.6-1.9=0.7 days lower than the length reported by DHA.

Table S2. Risk ratio of hospitalisation by infection with SARS-CoV-2 variant Omicron compared to Delta, overall and according to vaccination status, with reduced adjustment compared with main analysis, among 188,980 cases between 21 November and 19 December 2021, Denmark.

	Omicron COVID-19 hospitalisations (n) and COVID-19 hospitalisation RR (95%CI)					
			By vaccination status			
	Main estimate	P value	None or only one dose	Two doses	Three doses	P value
Main crude estimates (see Table 2)	0.39 (0.34,0.45)	<.0001	0.52 (0.40,0.68)	0.36 (0.30,0.43)	0.26 (0.17,0.41)	0.02
Main adjusted estimates (see Table 2)	0.64 (0.56,0.75)	<.0001	0.57 (0.44,0.75)	0.71 (0.60,0.86)	0.50 (0.32,0.76)	0.15
Not adjusted for age	0.50 (0.43,0.58)	<.0001	0.61 (0.47,0.81)	0.49 (0.41,0.59)	0.39 (0.25,0.59)	0.17
Not adjusted for period	0.60 (0.52,0.69)	<.0001	0.54 (0.41,0.70)	0.66 (0.56,0.79)	0.47 (0.31,0.72)	0.18
Not adjusted for sex	0.64 (0.56,0.75)	<.0001	0.57 (0.44,0.75)	0.71 (0.60,0.86)	0.50 (0.32,0.76)	0.15
Not adjusted for comorbidities	0.62 (0.53,0.71)	<.0001	0.54 (0.41,0.72)	0.68 (0.57,0.82)	0.48 (0.31,0.74)	0.15
Not adjusted for region	0.65 (0.56,0.75)	<.0001	0.58 (0.44,0.76)	0.72 (0.60,0.86)	0.48 (0.32,0.74)	0.12
Not adjusted for reinfection status	0.64 (0.56,0.75)	<.0001	0.57 (0.44,0.75)	0.71 (0.60,0.86)	0.50 (0.32,0.76)	0.15

Table S3. Risk ratio of hospitalisation by infection with SARS-CoV-2 variant Omicron compared to Delta using alternative exclusion criterias, adjustments, regression method, and stratification among 188,980 cases between 21 November and 19 December 2021, Denmark.

		Adjusted COVID-19 hospitalisation RR (95%CI)	
Alternative exclusion criterias, adjustments, regression method, and stratification		Omicron hosp.	Main estimate
Main estimate (see Table 2)		222	0.64 (0.56,0.75)
Alternative exclusion criteria			
Excluding AZ or JJ vaccinated cases (1.9%)		222	0.64 (0.55,0.74)
Excluding non-COVID-19 diagnosis, and stays with no data on diagnoses (1%)*		127	0.55 (0.45,0.66)
Excluding stays <=12h, and stays with no data on diagnoses (1%)*		122	0.54 (0.44,0.65)
Excluding reinfected cases		211	0.65 (0.56,0.76)
Excluding early half of cases (14 days: 21 Nov to 4 Dec)		220	0.65 (0.56,0.75)
Alternative adjustments			
Adjusted for ethnicity		222	0.66 (0.57,0.76)
Adjusted for age in 5-year groups		222	0.64 (0.55,0.74)
Adjusted for age as a continuous variable		222	0.66 (0.57,0.76)
Adjusted for age and age (continuous) X vaccination		222	0.64 (0.55,0.74)
Alternativ regression method (logistic regression)		222	0.64 (0.55,0.74)
Alternative stratifications			
Statified by age (years) and comorbidity			*p=0.33*
	0-59y, comorbidity no	122	0.55 (0.45,0.67)
	0-59y, comorbidity yes	46	0.48 (0.35,0.65)
	60+y, comorbidity no	15	0.35 (0.21,0.59)
	60+y, comorbidity yes	39	0.49 (0.36,0.68)
Stratified by age, years			*p=0.0025*
	0-19	31	**1.59 (1.09,2.32)
	20-39	83	0.74 (0.59,0.95)
	40-59	54	0.54 (0.41,0.72)
	60+	54	0.48 (0.36,0.63)
Stratified by reinfection status			*p=0.34*
	Not reinfection	211	0.51 (0.44,0.59)
	Yes reinfection	11	0.37 (0.19,0.73)

*See Methods. Data on diagnoses and length of stay was truncated on 2 February 2022 by data from the National Patient Registry.

** Removing all individuals 0-2 years of age, stays <12hours, and not yet validated stays (ie had no information on length stay), the RR was 1.41 (0.75,2.66). Stratifying the RR 1.59 for 0-19 year-olds further by age the RRs were 1.18 for 0-2y, 0.90 for 3-11y, 2.48 for 12-15y, and 1.26 for 16-19y.

Sensitivity analyses with Table S3

In sensitivity analyses shown in Table S3, we stratified the Omicron RR of hospitalisation by ages above and below 60 years and by comorbidity status in each group and observed no difference in the main effect between the groups. In a further analysis, we used the script algorithm (see Methods section) on 2,416 patients (99%) with information from the National Patient Registry truncated on 2 February 2022, and identified 1,767 patients admitted because of COVID-19 diagnoses, 79 admitted because of respiratory or observational diagnoses, and 570 admitted because of other diagnoses (truncated length of stay was available for all 2,416 patients). Restricting hospitalization to those with COVID-19 diagnoses did not alter the RRs substantially (Table S3). The Omicron RR of hospitalisation were also not altered substantially by excluding the small proportion of cases vaccinated with the Vaxzevria or Johnson & Johnson vaccine, cases in the first half of the study period when Omicron had none or little community spread, when excluding reinfected cases, or when stratifying by reinfection status. Among unvaccinated with and without reinfection there was also no substantially different RR compared with the main estimate (with reinfection: RR 0.80 (95%CI 0.31-2.03), 6 Omicron hospitalisations; without reinfection: RR 0.57, 95%CI 0.43-0.76, 48 Omicron hospitalisations) (all data not shown). Finally, further adjustment of the RR of hospitalisation of Omicron for ethnicity did not affect the RR substantially (Table S3).