Title: Reduced risk of hospitalisation among reported cases of the SARS-CoV-2 Omicron BA.1 variant compared with the Delta variant in Norway, December 2021 – January 2022

Authors:

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Abstract

We included data from 39,524 Omicron and 51,481 Delta cases reported in December 2021 to January 2022. We estimated that Omicron cases had a 73% reduced risk of hospitalisation (aHR: 0.27, 95%CI: 0.20–0.36) compared to Delta. Compared to unvaccinated cases, the reduction in the risk of hospitalisation among vaccinated was lower for Omicron than Delta. The lower risk of hospitalisation associated with Omicron does not necessarily imply reduced burden on hospitals when considering its increased transmissibility and reduced vaccine effectiveness against Omicron infection.

Main text

Background

The Omicron variant of SARS-CoV-2 (Pango lineage B.1.1.529) was first reported in South Africa on 24 November 2021 and was designated as a variant of concern (VOC) by the World Health Organisation on 26 November 2021 [1]. Concern caused by the high transmissibility of Omicron has been augmented by indications that Omicron is poorly neutralized by antibodies in sera from vaccinated and convalescent individuals [2-7], and associated with reduced vaccine effectiveness against COVID-19 compared to the Delta variant [8-11].

The first cases of Omicron BA.1 in Norway were detected in an outbreak following a social gathering on 26 November 2021 [12]. Since then, testing activity has been high [13, 14], and the proportion of screened cases weekly ranged from 49–67% up to early January. Omicron became the dominant circulating variant in late December (Figure 1A).

In order to support the ongoing response to the pandemic, we used linked individual-level data from the Norwegian Preparedness Registry (Beredt C19) [15] to estimate the risk of hospitalisation for reported Omicron cases compared to Delta. We also compared the length of hospital stay (LoS) and estimated the risk of admission to an intensive care unit (ICU) among hospitalised Omicron and Delta cases, and described deaths among the study cohort.

Study population

We extracted data from Beredt C19 on 20 January 2021, allowing 10 days follow-up since last date of positive test. Further details on data sources and definitions can be found in supplementary materials, part 1 (sm1). Ethical approval was granted by Regional Committees for Medical and Health Research Ethics South East (reference number 249509). The need for informed consent was waived.

In our study we included cases infected with Omicron (excluding 241 sub-variant BA.2 cases; all reported in week 1) or Delta, confirmed by PCR screening assays or whole genome sequencing between 6 December (week 49) 2021 and 9 January (week 1) 2022. Overall, 39,524 Omicron (43%) and 51,481 (57%) Delta cases were included. See Table 1 for characteristics of the study cohort.

Our main outcome was admission to hospital ≤2 days before and ≤28 days following a positive SARS-CoV-2 test, where COVID-19 was the reported main cause of hospitalisation. To avoid bias, we excluded 1,474 cases who did not have a national identity number registered and 302 cases hospitalised with another or unknown main cause of admission. We also assessed the representativeness of screened cases (59%) among all reported cases (sm2). The main difference was a higher proportion of cases screened among hospitalised cases compared to non-hospitalised cases (73% vs 59%). This difference is expected to have limited impact on our estimates, given the small proportion of all cases admitted to hospital, and that screening of hospitalised cases did not depend on exposure to Delta or Omicron.

Hospitalisation

Overall, 91 (0.2%) Omicron and 552 (1.1%) Delta cases were hospitalised. The median time from positive test to admission was 1 day (interquartile range (IQR): 0–3) for Omicron cases and 4 days (IQR: 0–7) for Delta.

Using stratified Cox proportional hazard regression (see sm3), we estimated the risk (adjusted hazard ratio, aHR) of hospitalisation for Omicron compared to Delta. The models were stratified by county of residence and sampling date, and further adjusted for age group, sex, country of birth, underlying comorbidities and vaccination status. The stratification allows for the impact of the covariates to be non-proportional among levels, and for each level of a factor to have their own baseline hazard rate.

In our main analysis, Omicron was associated with a 73% reduced risk of hospitalisation (aHR: 0.27, 95%CI: 0.20–0.36) compared with Delta (Table 2). More details on this analysis are provided in sm3.

In Table 2, we present a subgroup analysis with the estimated aHR for hospitalisation for Omicron compared with Delta by the different characteristics. The aHR estimates for several strata indicate a similar association, except for strata with small number of cases and few hospitalisations, for which the results were non-significant, and for some subgroups by vaccination status. We observed interactions between the variant and vaccination status, age group and vaccination status, and underlying comorbidities and vaccination status. We chose not to include them in our main model and investigated them separately in a subgroup analysis by vaccination status (Table 3). We observed a lower reduction in the risk of hospitalisation among Omicron cases compared to Delta for vaccinated individuals, and that protection wanes. The risk of hospitalisation for Omicron cases was 66% lower (95%CI: 22%–83%) for cases vaccinated with two doses 7–180 days before positive test, and 86% lower (95%CI: 69%–94%) for cases vaccinated with three doses ≥7 days before positive test. Among Omicron cases we observed no decrease in the risk of hospitalisation for persons vaccinated with two doses ≥180 days before positive test, compared to unvaccinated (aHR: 0.59, 95%CI: 0.28–1.22). The median time since last dose for cases vaccinated with two doses ≥180 days before positive test was 201 days (interquartile range (IQR): 190–216, maximum 316). The median time since last dose for cases vaccinated with three doses was 22 days (IQR: 12–36, maximum 192).

In Figure 2, we present the 10-day average case hospitalisation rate over time. We see a clear decrease in the case hospitalisation rate in the early part of the plot, corresponding to the roll out of 3rd doses to the elderly population, then a clear further decrease during late December and early January when Omicron superseded Delta.

This latter decrease is of around 70%, which indicates the population level effect is at a similar level to the decrease observed among the cases that were screened for variant. The calculation of case hospitalisation rate discounts the incidence of cases during the latest dates be a factor given by the observed delay between testing and admission to account for potential right censoring [16].

Length of stay in hospital and ICU admission among hospitalised cases

At the end of follow-up 10 of 91 (11%) hospitalised Omicron patients and 80 of 552 (14%) hospitalised Delta patients were still hospitalised. The crude median LoS among Omicron patients was 2.8 days (IQR: 1.6–6.8) compared to 6.5 (IQR: 3.2–12.3) among Delta patients. Using Cox proportional hazard regression stratified for age, sex, vaccination status and number of underlying risk factors (sm3), the aHR for discharge for Omicron patients compared to Delta was 1.44 (95%CI: 0.99–2.07). Assuming exponential distribution of the survival data (sm4), an aHR of 1.44 represents an expected 31% shorter LoS (95%CI: 1% longer – 52% shorter).

Seven Omicron patients (7.7%) were admitted to ICU, compared to 135 (24%) Delta patients. Using Cox proportional hazard regression stratified for age, sex, vaccination status and number of underlying risk factors (sm3), the aHR for the risk of ICU admission for Omicron patients compared to Delta patients was 0.51 (95%CI: 0.20–1.29).

Reported deaths

There were 10 deaths reported among Omicron cases (seven among those non-hospitalised) and 92 among Delta cases (30 among those non-hospitalised). Nine Omicron deaths and 80 Delta were reported as COVID-19 related deaths (sm1). We did not further analyse data on deaths due to small numbers.

Discussion

In this national register-based study, we found that reported Omicron cases (subvariant BA.1) were associated with a 73% lower risk of hospitalisation compared to reported Delta cases. Our findings add to the growing evidence of a lower risk of severe disease among persons infected with Omicron compared to Delta. Results presented in national reports from Denmark [17] and the UK [18] and studies from the USA [19] and Canada [20] estimated a 36–66% reduced risk of hospitalisation. Our preliminary data on LoS and risk of ICU admission also indicate a milder disease trajectory among hospitalised Omicron patients than Delta patients, as reported by others [19], although our analyses for these outcomes is based on a small cohort of hospitalised Omicron patients, and must be interpreted with caution at this early stage.

We detected an interaction between variant and vaccination status in our analysis. In the subgroup analysis, the reduced risk of hospitalisation for Omicron compared to Delta was lower among vaccinated compared to unvaccinated, indicating slightly lower protective effect of the vaccine against hospitalisation for Omicron compared to Delta. The protective effect of the vaccine against hospitalisation due to Omicron was observed in all vaccinated groups, apart from those vaccinated with two doses >180 days since last dose, where the estimate was too uncertain to draw clear conclusions. The third dose of the vaccine was associated with an 86% reduced risk of hospitalisation for Omicron and 88% for Delta compared to their respective unvaccinated cases (with overlapping CIs). These findings concur with reports from UK [18], and are expected based on data from studies that estimated reduced vaccine effectiveness against Omicron infection [8-11] and the benefit of a booster dose [8, 9].

During the study period hospitals functioned within capacity, and the testing strategy in Norway was relatively stable, with a high proportion of reported cases screened (59%). We stratified by sampling date and county of residence, considering differences in testing and screening by time and place. Although we noticed a slightly higher proportion of hospitalised cases being screened compared to non-hospitalised, we believe that this bias is limited. If we assume that we have oversampled hospitalised Delta cases, given the estimated higher risk of hospitalisation, this would cause us to slightly overestimate the reduction in the risk of hospitalisation for Omicron compared with Delta. Conversely, another potential bias could be any systematic differences between the variants among non-diagnosed cases. For example, compared to other VOC Omicron infections may have a higher rate of asymptomatic carriage [21]. Such infections may be less likely to be diagnosed, which could result in an underestimation of the true decreased risk of hospitalisation for Omicron compared to Delta.

Information on severity of infection with new variants is central for decision-making on control measures and strategies. However, considering the increased transmissibility of the Omicron variant and the reduced vaccine effectiveness against Omicron infection, we need to consider that the lower

risk of severe disease associated with Omicron does not necessarily imply reduced burden on hospitals, especially in the event of large waves of infections during the winter season when other viruses also circulate.

Figure and tables

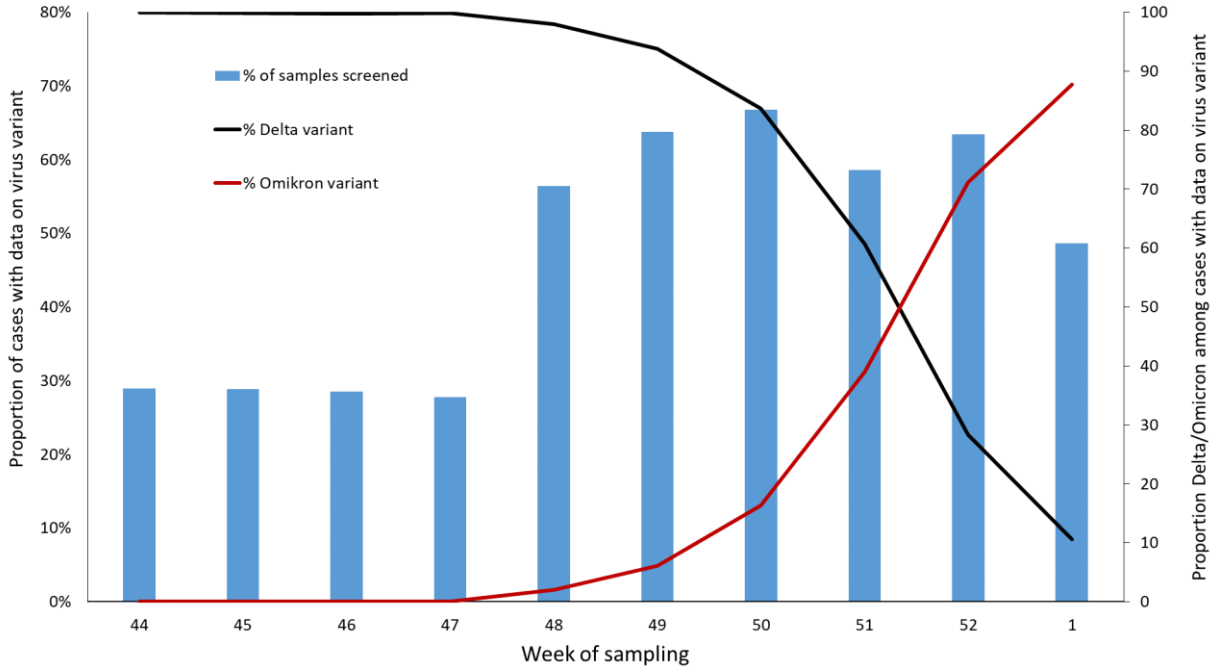

Figure 1 part A. Proportion of SARS-CoV-2 cases with data on virus variant, and proportion with Delta and Omicron by week of sampling for all reported cases, Norway, 1 November 2021 (week 1) - 9 January 2022 (week 1).

Legend/note: Testing activity and screening of cases was enhanced after the detection of the first Omicron cases in Norway (week 48). Variants other than Delta and Alpha were infrequently detected during the study (week 49-1); approximately 55% of all screened cases were Delta, 44% Omicron BA.1 and 0.3 % BA.2 (n=252 in week 1). Note that these numbers refer to all reported cases during this period before we apply our exclusion criteria for our study cohort.

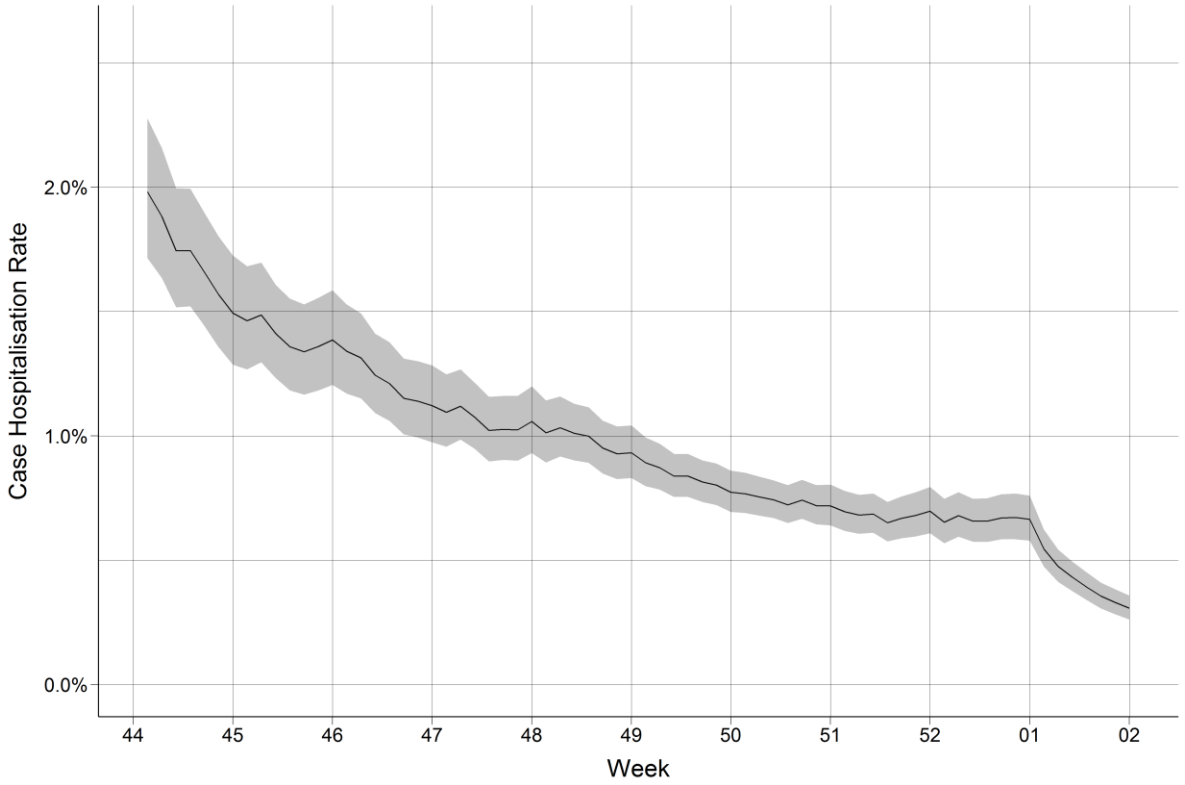

Figure 1 part B. 10-day average case hospitalisation rate (unadjusted) as a function of time from November 2021 to January 2022. The figure shows the fraction of cases that tested positive in the 10 days before the given date that were admitted to hospital. For the last time period we take into account the potential right censoring of admission.

Table 1. Distribution of SARS-CoV-2 cases in study cohort by detected variants for different characteristics and proportion hospitalised, Norway, 6 December 2021 – 9 January 2022.

Characteristic		Study cohort	Variant type (% by characteristic)		Hospitalised cases (% of diagnosed cases)		
			Delta	Omicron	Delta	Omicron	Total
Total		91,005	51,481 (57 %)	39,524 (43 %)	552 (1.1 %)	91 (0.2 %)	643 (0.7 %)
Sex	**Female**	45,262	25,577 (57 %)	19,685 (43 %)	228 (0.9 %)	53 (0.3 %)	281 (0.6 %)
	Male	45,743	25,904 (57 %)	19,839 (43 %)	324 (1.3 %)	38 (0.2 %)	362 (0.8 %)
Age group	**0-29 years**	45,773	25,606 (56 %)	20,167 (44 %)	36 (0.1 %)	11 (0.1%)	47 (0.1 %)
	30-44 years	23,752	13,496 (57 %)	10,256 (43 %)	95 (0.7 %)	14 (0.1 %)	109 (0.5 %)
	45-54 years	11,656	6,537 (56 %)	5,119 (44 %)	80 (1.2 %)	18 (0.4 %)	98 (0.8 %)
	55-64 years	6,334	3,623 (57 %)	2,711 (43 %)	116 (3.2 %)	17 (0.6 %)	133 (2.1 %)
	65-74 years	2,368	1,549 (65 %)	819 (35 %)	96 (6.2 %)	11 (1.3 %)	107 (4.5 %)
	≥75 years	1,122	670 (60 %)	452 (40 %)	129 (19 %)	20 (4.4 %)	149 (13 %)
Country of birth	**Norway**	66,488	38,639 (58 %)	27,849 (42 %)	323 (0.8 %)	52 (0.2 %)	375 (0.6 %)
	Overseas	23,568	12,246 (52 %)	11,322 (48 %)	203 (1.7 %)	34 (0.3 %)	237 (1.0 %)
	Unknown	949	596 (63 %)	353 (37 %)	26 (4.4 %)	5 (1.4 %)	31 (3.3 %)
Risk for severe COVID-19 *	**No underlying comorbidities**	81,036	45,492 (56 %)	35,544 (44 %)	297 (0.7 %)	36 (0.1 %)	333 (0.4 %)
	Medium risk comorbidity	8,667	5,159 (60 %)	3,508 (40 %)	145 (2.8 %)	31 (0.9 %)	176 (2.0 %)
	High risk comorbidity	1,302	830 (64 %)	472 (36 %)	110 (13 %)	24 (5.1 %)	134 (10 %)
Vaccination status at date of positive test	**Not vaccinated**	30,546	22,837 (75 %)	7,709 (25 %)	335 (1.5 %)	15 (0.2 %)	350 (1.2 %)
	One dose <21 days before positive test	517	355 (69 %)	162 (31 %)	8 (2.3 %)	1 (0.6 %)	9 (1.7 %)
	One dose ≥21 days before positive test	6,507	3,935 (60 %)	2,572 (40 %)	9 (0.2 %)	3 (0.1 %)	12 (0.2 %)
	Two doses 7–180 days before positive test **	39,821	17,981 (45 %)	21,840 (55 %)	47 (0.3 %)	26 (0.1 %)	73 (0.2 %)
	Two doses ≥180 days before positive test **	8,351	4,790 (57 %)	3,561 (43 %)	98 (2.1 %)	26 (0.7 %)	124 (1.5 %)
	Three doses ≥7 days before positive test	4,848	1,505 (31 %)	3,343 (69 %)	55 (3.7 %)	20 (0.6 %)	75 (1.6 %)
	Unvaccinated, but with another reported infection 6–12 months prior	415	78 (19 %)	337 (81 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)

** Risk for severe disease based on underlying comorbidities that are associated with a moderate or high risk of serious illness regardless of age. Details on the definitions used are provided in sm1.*

*** Also includes those who had received one dose ≥7 days after their first dose if they had previously been diagnosed with a SARS-CoV-2 infection ≥21 days before vaccination, and those who had received one dose of the Janssen vaccine ≥21 days before positive test. Data on vaccine types is presented in sm1. Overall, 98% of Omicron cases and 96% of Delta cases had received a homologous or mixed regimen of mRNA vaccines.*

Table 2. Hazard ratio estimates for hospitalisation with Omicron variant compared to Delta variant of SARS-CoV-2 overall and by subgroup analysis, Norway, 6 December 2021– 9 January 2022. Hazard ratios were estimated using Cox regression stratified by county of residence and date of sampling and further adjusted for variant, sex, age group, country of birth, underlying comorbidities, and vaccination status at date of positive test.

		Hospitalisation		
		Delta cases (n=51,481)	**Omicron cases (n=39,524)**	**Omicron vs Delta, adjusted hazard ratio (95%CI)**
Overall/Main analysis		552 (1.1 %)	91 (0.2 %)	0.27 (0.20-0.36)
Subgroup analysis by:				
Sex	**Female**	228 (0.9 %)	53 (0.3 %)	0.45 (0.30-0.67)
	Male	324 (1.3 %)	38 (0.2 %)	0.17 (0.11-0.27)
Age group	**0-29 years**	36 (0.1 %)	11 (0.1 %)	0.24 (0.09-0.60)
	30-44 years	95 (0.7 %)	14 (0.1 %)	0.23 (0.11-0.47)
	45-54 years	80 (1.2 %)	18 (0.4 %)	0.40 (0.19-0.85)
	55-64 years	116 (3.2 %)	17 (0.6 %)	0.22 (0.10-0.45)
	65-74 years	96 (6.2 %)	11 (1.3 %)	0.20 (0.07-0.51)
	≥75 years	129 (19 %)	20 (4.4 %)	0.41 (0.17-0.98)
Country of birth	**Norway**	323 (0.8 %)	52 (0.2 %)	0.27 (0.18-0.40)
	Overseas	203 (1.7 %)	34 (0.3 %)	0.23 (0.14-0.38)
	Unknown	26 (4.4 %)	5 (1.4 %)	2.33 (0.13-41.6)
Risk for severe COVID-19 *	**No underlying comorbidities**	297 (0.7 %)	36 (0.1 %)	0.23 (0.15-0.36)
	Medium risk comorbidity	145 (2.8 %)	31 (0.9 %)	0.35 (0.21-0.59)
	High risk comorbidity	110 (13 %)	24 (5.1 %)	0.16 (0.06-0.42)
Vaccination status at date of positive test	**Not vaccinated**	335 (1.5 %)	15 (0.2 %)	0.13 (0.07-0.23)
	One dose <21 days before positive test	8 (2.3 %)	1 (0.6 %)	NA
	One dose ≥21 days before positive test	9 (0.2 %)	3 (0.1 %)	NA
	Two doses 7–180 days before positive test **	47 (0.3 %)	26 (0.1 %)	0.62 (0.31-1.24)
	Two doses ≥180 days before positive test **	98 (2.1 %)	26 (0.7 %)	0.50 (0.25-1.01)
	Three doses ≥7 days before positive test	55 (3.7 %)	20 (0.6 %)	0.19 (0.08-0.43)
	Unvaccinated, but with another reported infection 6–12 months prior	0 (0.0 %)	0 (0.0 %)	NA^

*NA: not available due to small numbers and lack of lack of discordant pairs * Risk for severe disease based on underlying comorbidities that are associated with a moderate or high risk of serious illness regardless of age. Details on the definitions used are provided in sm1.*

*** Also includes those who had received one dose ≥7 days after their first dose if they had previously been diagnosed with a SARS-CoV-2 infection ≥21 days before vaccination, and those who had received one dose of the Janssen vaccine ≥21 days before positive test. Data on vaccine types is presented in sm1. Overall, 98% of Omicron cases and 96% of Delta cases had received a homologous or mixed regimen of mRNA vaccines. When we used a recoded variable for vaccination status including both two-dose categories, regardless the time of last dose, we found an aHR of 0.54 (95%CI: 0.34–0.87).*

^ We had 415 cases that were unvaccinated, but had had another reported infection 6–12 months prior. None of these 415 required hospitalisation. This indicates that prior infection is associated with lower risk of hospitalisation compared to unvaccinated, but estimates were not possible to be calculated due to lack of discordant pairs in our model.

Table 3. Subgroup analysis using stratified cox regression for the risk of hospitalisation by vaccination status among SARS-CoV-2 cases, Norway, 6 December 2021 – 9 December 2022. Hazard ratios for hospitalisation were estimated using Cox regression stratified by county of residence and date of sampling and further adjusted for variant, sex, age group, country of birth, underlying comorbidities at date of positive test.

		Adjusted hazard ratio (95%CI) for hospitalisation					
		Not vaccinated	**One dose <21 days before positive test**	**One dose ≥21 days before positive test**	**Two doses 7–180 days before positive test ****	**Two doses ≥180 days before positive test ****	**Three doses ≥7 days before positive test**
Overall/main analysis		Ref	1.18 (0.59-2.39)	0.22 (0.12-0.41)	0.09 (0.07-0.12)	0.17 (0.14-0.22)	0.10 (0.07-0.14)
Subgroup analysis by:							
Variant	Delta	Ref	1.18 (0.56-2.50)	0.19 (0.09-0.38)	0.07 (0.05-0.10)	0.16 (0.12-0.21)	0.12 (0.09-0.17)
	Omicron	Ref	2.03 (0.24-17.4)	0.71 (0.20-2.51)	0.34 (0.17-0.68)	0.59 (0.28-1.22)	0.14 (0.06-0.31)
Age group	0-29 years	Ref	5.72 (1.26-26.1)	0.16 (0.02-1.16)	0.45 (0.19-1.08)	1.53 (0.47-4.94)	0.57 (0.05-6.63)
	30-44 years	Ref	NA	0.20 (0.05-0.84)	0.07 (0.04-0.13)	0.27 (0.13-0.55)	0.29 (0.10-0.84)
	45-54 years	Ref	1.33 (0.28-6.28)	0.33 (0.08-1.42)	0.09 (0.05-0.16)	0.15 (0.07-0.31)	0.26 (0.11-0.60)
	55-64 years	Ref	1.50 (0.15-14.5)	0.16 (0.02-1.22)	0.05 (0.03-0.10)	0.12 (0.07-0.20)	0.17 (0.08-0.34)
	65-74 years	Ref	2.36 (0.31-18.2)	0.54 (0.11-2.74)	0.17 (0.07-0.42)	0.11 (0.06-0.21)	0.09 (0.04-0.18)
	≥75 years	Ref	3.27 (0.41-25.8)	0.40 (0.08-1.88)	0.29 (0.10-0.83)	0.27 (0.15-0.50)	0.04 (0.02-0.09)
Risk for severe COVID-19 *	No underlying comorbidities	Ref	1.11 (0.50-2.44)	0.28 (0.14-0.58)	0.06 (0.04-0.09)	0.13 (0.08-0.19)	0.03 (0.01-0.07)
	Medium risk comorbidity	Ref	0.64 (0.08-5.05)	0.18 (0.04-0.79)	0.16 (0.10-0.26)	0.20 (0.14-0.30)	0.07 (0.04-0.12)
	High risk comorbidity	Ref	7.96 (0.41-155.7)	1.53 (0.16-14.4)	0.29 (0.08-1.11)	0.87 (0.36-2.08)	0.63 (0.26-1.56)

*NA: not available due to small numbers and lack of lack of discordant pairs. * Risk for severe disease based on underlying comorbidities that are associated with a moderate or high risk of serious illness regardless of age. Details on the definitions of medium- and high-risk categories are provided in sm1.*

*** Also includes those who had received one dose ≥7 days after their first dose if they had previously been diagnosed with a SARS-CoV-2 infection ≥21 days before vaccination, and those who had received one dose of the Janssen vaccine ≥21 days before positive test. Data on vaccine types is presented in sm1. Overall, 98% of Omicron cases and 96% of Delta cases had received a homologous or mixed regimen of mRNA vaccines. When we used a recoded variable for vaccination status including both two-dose categories, regardless the time of last dose, we estimated that Omicron cases vaccinated with two doses had a 50% reduced risk (aHR: 0.50, 95%CI: 0.26–0.96) and Delta cases an 88% reduced risk of hospitalisation (aHR: 0.12, 95%CI: 0.09–0.14) respectively compared to unvaccinated.*

Notes and acknowledgements

Authors' contributions

All co-authors were involved in the conceptualisation of the study. RW drafted the study protocol and coordinated the study. OH, MS, NA, RK, KB and EAB contributed directly to the acquisition of data. LaVe, HB, JeS, OH, MS, NA, JoS, ES, KB and RW contributed to data cleaning, verification and/or preparation. LaVe, HB, ABK, JeS, JoS, ES and RW had access to the final linked dataset. LaVe conducted the statistical analysis for risk of hospitalisation and ABK for length of hospital stay and ICU admission in consultation with HB, JeS, JoS, GR and RW. All co-authors contributed to the interpretation of the results. LaVe, HB and RW drafted the manuscript. All co-authors contributed to the revision of the manuscript and approved the final version for submission.

Conflict of interest

The authors declare that they have no competing interests.

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Data sharing statement

The dataset analysed in the study contains individual-level linked data from various central health registries, national clinical registries and other national administrative registries in Norway. The researchers had access to the data through the national emergency preparedness registry for COVID-19 (Beredt C19), housed at the Norwegian Institute of Public Health (NIPH). In Beredt C19, only fully anonymised data (i.e. data that are neither directly nor potentially indirectly identifiable) are permitted to be shared publicly. Legal restrictions therefore prevent the researchers from publicly sharing the dataset used in the study that would enable others to replicate the study findings. However, external researchers are freely able to request access to linked data from the same registries from outside the structure of Beredt C19, as per normal procedure for conducting health research on registry data in Norway. Further information on Beredt C19, including contact information for the Beredt C19 project manager, and information on access to data from each individual data source, is available at https://www.fhi.no/en/id/infectious-diseases/coronavirus/emergency-preparedness-register-for-covid-19/.

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