COVID-19 Hospitalization Among Children <18 Years by Variant Wave in Norway

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abstract

OBJECTIVES: There is limited evidence on whether the relative severity of coronavirus disease 2019 (COVID-19) in children and adolescents differs for different severe acute respiratory syndrome coronavirus 2 variants. We compare the risk of hospitalization to acute COVID-19 or multisystem inflammatory syndrome in children (MIS-C) among unvaccinated persons <18 years with COVID-19 (cases) between waves of the Alpha, Delta, and Omicron (sublineage BA.1) variants in Norway.

METHODS: We used linked individual-level data from national registries to calculate adjusted risk ratios (aRR) with 95% confidence interval (CI) using multivariable log-binomial regression. We adjusted for variant wave, demographic characteristics, and underlying comorbidities.

RESULTS: We included 10 538 Alpha (21 hospitalized with acute COVID-19, 7 MIS-C), 42 362 Delta (28 acute COVID-19, 14 MIS-C), and 82 907 Omicron wave cases (48 acute COVID-19, 7 MIS-C). The risk of hospitalization with acute COVID-19 was lower in the Delta (aRR: 0.53, 95% CI: 0.30–0.93) and Omicron wave (aRR: 0.40, 95% CI: 0.24–0.68), compared to the Alpha wave. We found no difference in this risk for Omicron compared to Delta. The risk of MIS-C was lower for Omicron, compared to Alpha (aRR: 0.09, 95% CI: 0.03–0.27) and Delta (aRR: 0.26, 95% CI: 0.10–0.63).

CONCLUSIONS: We do not find clear evidence that different variants have influenced the risk of hospitalization with acute COVID-19 among unvaccinated children and adolescents in Norway. The lower risk of this outcome with Omicron and Delta may reflect changes in other factors over time, such as the testing strategy, maternal vaccination and/or hospitalization criteria. The emergence of Omicron has reduced the risk of MIS-C.

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Mr Whittaker conceptualized and designed the study, contributed to data cleaning and linkage between the different registries, conducted the data analysis, drafted the initial manuscript, and reviewed and revised the manuscript; Drs Greve-Isdahl and Suren conceptualized and designed the study, contributed to interpretation of the results, and critically reviewed the manuscript; Dr Bøås conceptualized and designed the study, contributed to data cleaning and interpretation of the results, and critically reviewed the manuscript; Dr Buanes conceptualized and designed the study, coordinated data collection to the Norwegian Intensive Care and Pandemic Registry, contributed to interpretation of the results, and critically reviewed the manuscript; Ms Veneti conceptualized and designed the study, contributed to data cleaning, assisted with the data analysis, contributed to interpretation of the results, and critically reviewed the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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WHAT'S KNOWN ON THIS SUBJECT: There is limited evidence about the potential association between the risk of hospitalization with acute COVID-19 among children and adolescents and different SARS-CoV-2 variants. Preliminary data suggests a lower risk of multisystem inflammatory syndrome in children following infection with Omicron.

WHAT THIS STUDY ADDS: We do not find clear evidence that different SARS-CoV-2 variants have influenced the risk of hospitalization with acute COVID-19 among children and adolescents in Norway. The risk of multisystem inflammatory syndrome was lower in children and adolescents infected with Omicron.

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From late 2020, the emergence and global spread of variants of concern (VOC)[1] of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have shaped the epidemiology of, and ongoing response to, the coronavirus disease 2019 (COVID-19) pandemic. More transmissible VOC have successively superseded their predecessors influencing transmission dynamics, viral virulence, and vaccine effectiveness.[2–8] The emergence of the Omicron variant (Phylogenetic Assignment of Named Global Outbreak Lineages [Pangolin] designation B.1.1.529) in November 2021 instigated a new wave of infections globally.[9]

Most children and adolescents with COVID-19 experience an asymptomatic or mild disease course. However, a small proportion develop severe disease that requires hospitalization, mostly because of acute COVID-19 or multisystem inflammatory syndrome in children (MIS-C), a postinfectious complication of SARS-CoV-2 infection. Death is rare.[10,11]

There is currently limited evidence on whether the relative severity of COVID-19 in children and adolescents differs when infected with different VOC. Studies from England[5] and Denmark[12] did not find clear evidence that the risk of hospitalization because of acute COVID-19 among children and adolescents infected with Omicron differed compared to the Delta variant (Pangolin designation B.1.617.2). One study from the United States reported a reduced risk of hospitalization among children <5 years diagnosed with a SARS-CoV-2 infection during a period of Omicron dominance, compared to the preceding Delta period.[13] Some studies comparing the risk of hospitalization for the Delta variant to earlier VOC have presented descriptive data for younger age groups, without providing age-specific risk estimates.[14,15] Others have been restricted to hospital cohorts, with the reported findings inconsistent between settings.[16–18] In Denmark, the risk of MIS-C did not change among unvaccinated children and adolescents during a wave of Delta infections compared to when the wild-type SARS-CoV-2 variant was circulating.[19] Preliminary data from Denmark[20] and Southeast England[21] have reported a lower risk of MIS-C with Omicron compared to Delta.

Since the beginning of 2021, Norway has experienced 3 COVID-19 waves when different VOC were dominant; Alpha (Pangolin designation B.1.1.7),[4] Delta,[22] and Omicron.[8] We used linked individual-level data from national registries to compare the risk of hospitalization among unvaccinated persons <18 years to COVID-19 between these 3 variant waves.

METHODS

Study Setting

Norway (population <18 years 1.1 million) has had a broad testing strategy for COVID-19 in children and adolescents since autumn 2020. Four pillars of the national pandemic response have been testing, isolation, contact tracing, and quarantine. Through this framework SARS-CoV-2 tests have been available free of charge for everyone, including those with mild or no symptoms, close contacts, and individuals in quarantine. Routine biweekly screening of school children with rapid antigen tests in areas with high transmission was recommended for secondary school students from late August 2021 and for primary school students from November 2021 to January 2022. Positive rapid antigen tests were confirmed with polymerase chain reaction. Further details on the testing strategy for COVID-19 in children and adolescents are described in Supplement A, Section 1. COVID-19 vaccine recommendations for children and adolescents in Norway and data on vaccination coverage are presented in Supplement A, Section 2. From August 2021, pregnant women have been recommended to get vaccinated in the second or third trimester if healthy, and first trimester for women with underlying risk factors.[23]

Data Sources and Study Design

We obtained data through the Norwegian national preparedness registry for COVID-19.[24] The preparedness registry contains individual-level data from different central health registries, national clinical registries, and other national administrative registries. It covers all residents in Norway and includes data on all persons with laboratory-confirmed COVID-19 (cases) in Norway and all hospitalizations, intensive care admissions, and deaths among cases. Further details on the individual registries and data included in this study are presented in Supplement A, Section 1.

We conducted a cohort study, including persons aged <18 years who tested positive for COVID-19 from March 15, 2021 to January 30, 2022, were unvaccinated at date of positive test and had not previously been diagnosed with COVID-19, and had a national identity number registered (the study cohort). We extracted data up to April 12, 2022, a minimum of 72 days of follow-up. This ensures MIS-C diagnoses are not missed.

Definition of Variant Waves

In Norway, SARS-CoV-2 variants are identified on the basis of whole genome sequencing, Sanger partial S-gene sequencing, or polymerase chain reaction screening targeting specific single nucleotide

polymorphisms, insertions, or deletions. The laboratory testing for variants of SARS-CoV-2 in Norway has been described in further detail elsewhere.[25] We identified different variant waves on the basis of the date of the positive test. Variant distribution over time among COVID-19 cases <18 years is presented in Figure 1, with the underlying data available in Supplement B. We defined the Alpha dominant wave as week 11 to 20 (March 15 to May 23) 2021, the Delta dominant wave as week 35 to 48 (August 30 to December 5) 2021, and the Omicron dominant wave as week 2 to 4 (10 to 30 January) 2022. The Omicron wave was not extended beyond week 4 2022 because of the end of the recommendation for routine biweekly screening of school children, gradual downscaling of the national testing strategy, and to ensure analysis when 1 Omicron sublineage (BA.1) was predominant.[26] In models including COVID-19 cases of all ages in Norway, results based on these waves were consistent with analyses based on cases with known variant in periods when 1 variant was superseding another (see Supplement A, Section 3).

Severity Outcomes

Our severity outcomes were: (1) admission to hospital with acute COVID-19 (regardless of main cause of admission) ≤14 days after positive test, (2) admission to hospital ≤14 days after positive test in which acute COVID-19 was the reported main cause of admission, and (3) admission to hospital with MIS-C, defined as patients registered with the International Classification of Diseases, 10th Revision diagnosis code U10.9. Clinical criteria for MIS-C diagnosis in Norway are based on the World Health Organization case definition, as per national pediatric guidelines.[27] Hospitals in Norway functioned within capacity during each variant wave.

Data Analysis

We described the study cohort by variant wave, severity outcome, demographic characteristics, and underlying comorbidities. We also described other outcomes among hospitalized patients including length of stay (LOS) in hospital and admission to an ICU and all deaths in the study cohort. For our 3 severity outcomes, we calculated adjusted risk ratios (aRR) with 95% confidence intervals (CI) using multivariable log-binomial regression. Explanatory variables to analyze differences in our outcomes included variant wave (Alpha, Delta, or Omicron), age (as continuous or categorical

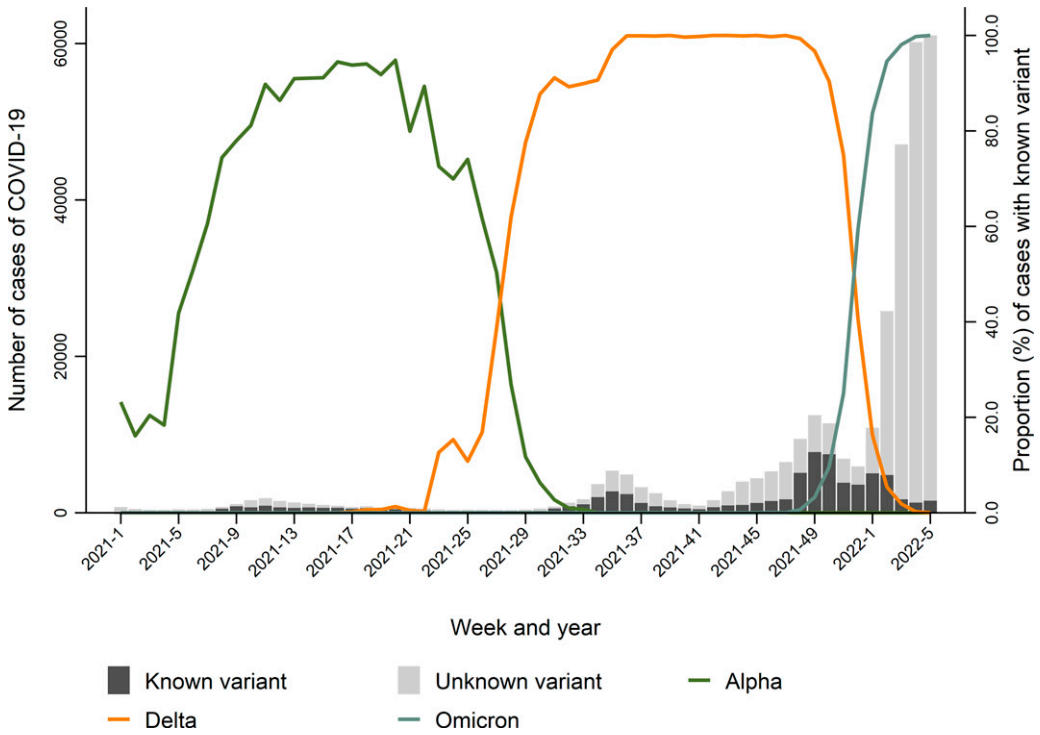

FIGURE 1

Persons aged <18 years diagnosed with COVID-19 in Norway with known and unknown SARS-CoV-2 variant (bars, left y-axis), and proportion with known variant that were the Alpha, Delta, or Omicron variant of concern (lines, right y-axis), by week, January 1, 2021 to February 6, 2022. The data behind the figure are available in Supplement B. During the Alpha wave (week 11to 20, 2021), the proportion of persons diagnosed with COVID-19 that were known to be infected with the Alpha variant ranged from 86% to 95% of those with known variant. However, most other COVID-19 cases with known variant were reported as "probable variant of concern." In Norway, there was minimal circulation of other defined variants of concern (Beta, B.1.351 and Gamma, P.1); thus, it is reasonable to assume that most COVID-19 cases reported as 'probable variant of concern' were also infected with the Alpha variant. Taking these cases into account, the proportion infected with Alpha among those with known variant ranges from 94% to 100% in the Alpha wave.

variable), sex, country of birth, region of residence, and underlying comorbidities. The categorization of explanatory variables is presented in Table 1 and further detailed in Supplement A, Section 1. Explanatory variables were first checked in univariable models. Those with $P < .2$ were further explored in multivariable models. Explanatory variables were further categorized in some models to best fit the data, for example a dichotomous variable for underlying comorbidities (yes or no). We maintained the variant wave variable in each multivariable analysis, even if not significant. We used Akaike Information Criteria and the likelihood ratio test to check model fit. We ran models for each variant combination (Delta versus Alpha, Omicron versus Alpha, Omicron versus Delta) for the entire study cohort, and for the age subgroups <3 months, 3 to 11 months, 1 to 11 years, and 12 to 17 years. For infants <3 months we also described outcomes 1) and 2) among those whose mothers were unvaccinated. For cases 12 to 17 years, we conducted a sensitivity analysis to explore if results were robust when including vaccinated COVID-19 cases and reinfections in this age group (Supplement A, Section 4). Statistical analysis was performed in Stata version 16 (Stata Corporation, College Station, Texas, United States).

Ethics

Ethical approval was granted by Regional Committees for Medical Research Ethics South East Norway, reference number 249509.

RESULTS

Study Cohort

The number of persons aged <18 years diagnosed with COVID-19 was 10 620 during the Alpha wave, 53 724 during the Delta wave and 133 383 during the Omicron wave. Of these, 10 541 (99.3%) Alpha, 53 576 (99.7%) Delta, and 133 042 (99.7%) Omicron cases had a known national identity number. Of these 10 538 (99.9%) Alpha, 42 362 (79.1%) Delta and 83 884 (62.3%) Omicron cases were included in the study cohort as they were unvaccinated at date of positive test and had not been previously diagnosed with COVID-19. Characteristics of the study cohort by variant are presented in Table 1.

Risk of Hospitalization With Acute COVID-19

Overall, 174 (0.1%) cases were hospitalized ≤14 days after positive test, of which 97 with acute COVID-19 as main cause (0.07% of study cohort). Few additional admissions >14 days after positive test were observed (Table 1). Of the 97, 32 (33%) were aged <3 months, 44 (45%) were female, and 83 (86%) had no registered comorbidity.

In the Alpha, Delta, and Omicron waves, 21 (0.2%), 28 (0.07%), and 48 (0.06%) cases <18 years were hospitalized with acute COVID-19 as main cause ≤14 days after positive test, respectively (Table 1, Table 2). The risk of hospitalization with acute COVID-19 as main cause was lower in the Delta (aRR: 0.53, 95% CI: 0.30–0.93) and Omicron wave (aRR: 0.40, 95% CI: 0.24–0.68) compared to the Alpha wave. Among infants <3 months the proportion hospitalized with acute COVID-19 decreased from 14.6% (8 of 55) in the Alpha wave to 5.9% (7 of 118) in the Delta wave and 7.8% (17 of 218) in the Omicron wave. A similar difference between these outcome proportions in the Alpha and Delta waves was observed when restricting the analysis to infants whose mothers were unvaccinated up to 4 weeks after child's birth (Table 3). Results also suggested a decreased risk in children aged 1 to 11 years in the Omicron wave compared to the Alpha wave (aRR: 0.32, 95% CI: 0.13–0.83). We did not observe a difference in the adjusted risk in any age group in the Omicron wave compared to the Delta wave (Table 2). Results for the age group 12 to 17 years were consistent when we included vaccinated COVID-19 cases and adjusted for vaccination status (Supplement A, Section 4). Results for the outcome admission to hospital ≤14 days after positive test regardless of main cause were largely consistent with those for acute COVID-19 as the main cause, although we did observe a decreased risk for cases <18 years in the Omicron wave compared to the Delta wave (aRR: 0.67, 95% CI: 0.48–0.94) (Table 2).

Risk of MIS-C

Twenty-eight cases were diagnosed with MIS-C across the 3 waves (0.02% of study cohort) (Table 2). The median age was 6.5 years (interquartile range [IQR]: 4–9.5; range 1–17), 12 (43%) were female and 26 (93%) had no registered comorbidity. In the Alpha, Delta, and Omicron waves, 7 (0.07%), 14 (0.03%), and 7 (0.008%) cases were diagnosed with MIS-C, respectively (Table 1, Table 2). The risk of MIS-C was lower in the Omicron wave compared to the Alpha (aRR: 0.09, 95% CI: 0.03–0.27) and Delta wave (aRR: 0.26, 95% CI: 0.10–0.63) (Table 2). We did not observe a significant difference in the risk of MIS-C in the Delta wave compared to the Alpha wave.

Length of Hospital Stay, Admission to Intensive Care and Death

The median hospital LOS among cases hospitalized with acute COVID-19 as main cause was 0.8 days (IQR: 0.4–3.2) in the Alpha wave, 1.4 days (IQR: 0.7–3.1) in the

TABLE 1 Characteristics of Persons Aged <18 Years Diagnosed With COVID-19 Who Were Unvaccinated and Also Had Not Previously Been Diagnosed With COVID-19, by Variant Wave, Norway, March 15, 2021 to January 30, 2022

Characteristics	Variant Wave		
	Alpha Dominated Wave (n = 10 538) (%)	Delta Dominated Wave (n = 42 362) (%)	Omicron Dominated Wave (n = 82 907) (%)
Sex			
Male	5118 (48.6)	20 575 (48.6)	39 835 (48.0)
Female	5420 (51.4)	21 787 (51.4)	43 072 (52.0)
Age group			
<3 mo	55 (0.5)	118 (0.3)	218 (0.3)
3–11 mo	212 (2.0)	518 (1.2)	1395 (1.7)
1–11 y	5928 (56.3)	27 999 (66.0)	70 288 (84.8)
12–17 y	4343 (41.2)	13 727 (32.4)	11 006 (13.3)
Median age, y (IQR)	10 (6–1)	10 (7–13)	8 (5–10)
Born in Norway			
Yes, with at least 1 parent born in Norway	5510 (52.3)	29 143 (68.8)	63 225 (76.3)
Yes, 2 parents born outside of Norway	3425 (32.5)	8387 (19.8)	13 121 (15.8)
No	1598 (15.2)	4812 (11.4)	6555 (7.9)
Unknown	5 (<0.1)	20 (<0.1)	6 (<0.1)
Risk for severe COVID-19[a]			
No underlying comorbidities	9732 (92.4)	39 319 (92.8)	77 699 (92.6)
Medium-risk comorbidity	756 (7.2)	2886 (6.8)	5897 (7.0)
High-risk comorbidity	50 (0.5)	178 (0.4)	288 (0.3)
Region of residence[b]			
Southeast	8882 (84.3)	29 564 (69.8)	57 487 (69.3)
West	1265 (12.0)	5033 (11.9)	13 831 (16.7)
Mid	287 (2.7)	4669 (11.0)	8255 (10.0)
North	94 (0.9)	3057 (7.2)	3270 (3.9)
Unknown	10 (<0.1)	39 (<0.1)	64 (<0.1)
Admission to hospital			
No	10 507 (99.7)	42 303 (99.9)	82 819 (99.9)
Yes, ≤14 d after positive test	30 (0.3)	58 (0.1)	86 (0.1)
Yes, 15–28 d after positive test	1 (<0.1)	1 (<0.1)	2 (<0.1)
Admission to hospital with COVID-19 as main cause of admission			
No	10 517 (99.8)	42 334 (99.9)	82 858 (99.9)
Yes, ≤14 d after positive test	21 (0.2)	28 (<0.1)	48 (<0.1)
Yes, 15–28 d after positive test	0 (0.0)	0 (0.0)	1 (<0.1)
Diagnosed with MIS-C			
No	10 531 (99.9)	42 348 (100.0)	82 900 (100.0)
Yes	7 (<0.1)	14 (<0.1)	7 (<0.1)

[a] Risk for severe disease based on underlying comorbidities that are associated with a medium- or high-risk of serious illness regardless of age. Data on comorbidities were based on International Clinical Modification (ICD-10-CM) codes from the Norwegian patient registry, and International Classification of Primary Care, 2nd edition codes from the Norway Control and Payment of Health Reimbursement database. Medium-risk includes chronic liver disease or significant hepatic impairment, immunosuppressive therapy as in autoimmune diseases, diabetes, chronic lung disease including cystic fibrosis and severe asthma which have required the use of high dose inhaled or oral steroids within the past year, obesity with a BMI of ≥35 kg/m^2, dementia, chronic heart and vascular disease (with the exception of high blood pressure), and stroke. High-risk includes having received an organ transplant, immunodeficiency, hematologic cancer in the last 5 years, other active cancers, ongoing or recently discontinued treatment of cancer (especially immunosuppressive therapy, radiation therapy to the lungs or cytotoxic drugs), neurologic or neuromuscular diseases that cause impaired cough or lung function (eg, amyotrophic lateral sclerosis and cerebral palsy), Down syndrome and chronic kidney disease, or significant renal impairment. Further details on the definitions used are provided in Supplement A, Section 1.

[b] Southeast: counties Oslo, Viken, Innlandet, Agder, Vestfold and Telemark; West: counties Vestland and Rogaland; Mid: counties Trøndelag, and Møre and Romsdal; North: counties Nordland, and Troms and Finnmark.

Delta wave, and 1.1 days (IQR: 0.8–2.7) in the Omicron wave. Among the 28 MIS-C cases, the median LOS was 4 days (IQR: 2–6). Data on LOS is not presented by wave for MIS-C cases because of the small number of MIS-C cases in each wave. Across all 3 waves, 6 (6%) cases hospitalized with acute COVID-19 as main cause and 4 (14%) MIS-C cases were admitted to ICU. This equates to 0.007% of diagnosed COVID-19 cases being admitted to ICU for either acute COVID-19 or MIS-C in Norway. At the end of the follow-up, there were no reported deaths among those hospitalized (either for acute COVID-19 or MIS-C), nor within 30 days of positive test among those not hospitalized.

DISCUSSION

In this study we have analyzed national registry data from a setting with a broad COVID-19 testing strategy among children and

TABLE 2 Number of Cases Admitted to Hospital for Acute COVID-19 or MIS-C, and Crude and Adjusted Risk Ratios From Log-Binomial Regression, by Age Group and Variant Wave, Persons Aged <18 Years Diagnosed With COVID-19 Who Were Unvaccinated and Had Also Not Previously Been Diagnosed With COVID-19, Norway, March 15, 2021 to January 30, 2022

		Alpha Wave (wk 11–20 2021)		Delta Wave (wk 35–48 2021)				Omicron Wave (wk 2–4 2022)					
Outcome	Age Group	Number of Outcomes per Cases	%	Number of Outcomes per Cases	%	Crude Risk Ratio Compared to Alpha Wave (95% CI)	Adjusted Risk Ratio Compared to Alpha Wave (95% CI)	Number of Outcomes per Cases	%	Crude Risk Ratio Compared to Alpha Wave (95% CI)	Adjusted Risk Ratio Compared to Alpha Wave (95% CI)	Crude Risk Ratio Compared to Delta Wave (95% CI)	Adjusted Risk Ratio Compared to Delta Wave (95% CI)
Admission to hospital ≤14 d after positive test	<3 mo	10 of 55	18.2	11 of 118	9.3	0.51 (0.23–1.13)	0.43 (0.20–0.97)[d,f]	22 of 218	10.1	0.56 (0.28–1.10)	[a]	1.08 (0.54–2.15)	[a]
	3–11 mo	4 of 212	1.9	6 of 518	1.2	0.61 (0.18–2.15)	[a]	14 of 1395	1.0	0.53 (0.18–1.60)	[a]	0.86 (0.33–2.24)	[a]
	1–11 y	9 of 5928	0.2	25 of 27 999	<0.1	0.59 (0.27–1.26)	1.12 (0.52–2.41)[b,c,d]	44 of 70 288	<0.1	0.41 (0.20–0.84)[f]	0.49 (0.24–1.00) [b,c]	0.70 (0.43–1.14)	0.64 (0.39–1.05)[b,c,d]
	12–17 y	7 of 4343	0.2	16 of 13 727	0.1	0.72 (0.30–1.75)	0.91 (0.37–2.24)[b,c]	6 of 11 006	<0.1	0.34 (0.11–1.01)	[a]	0.47 (0.18–1.19)	[a]
	All <18 y	30 of 10 541	0.3	58 of 42 362	0.1	0.48 (0.31–0.75)[f]	0.70 (0.46–1.08)[b,c]	86 of 82 907	0.1	0.36 (0.24–0.55)[f]	0.48 (0.31–0.72)[b,c,f]	0.76 (0.54–1.06)	0.67 (0.48–0.94)[b,c,f]
Admission to hospital with COVID-19 as main cause of admission ≤14 d after positive test	<3 mo	8 of 55	14.6	7 of 118	5.9	0.41 (0.16–1.07)	[a]	17 of 218	7.8	0.54 (0.24–1.18)	0.50 (0.23–1.09)[e]	1.31 (0.56–3.08)	[a]
	3–11 mo	3 of 212	1.4	3 of 518	0.6	0.41 (0.08–2.01)	[a]	10 of 1395	0.7	0.51 (0.14–1.82)	[a]	1.23 (0.34–4.47)	[a]
	1–11 y	6 of 5928	0.1	10 of 27 999	<0.1	0.35 (0.13–0.97)[f]	0.72 (0.26–2.01)[b,c,d]	18 of 70 288	<0.1	0.25 (0.10–0.64)[f]	0.32 (0.13–0.83)[b,c,f]	0.72 (0.33–1.55)	0.62 (0.28–1.35)[b,c,d,f]
	12–17 y	4 of 4343	<0.1	8 of 13 727	<0.1	0.63 (0.19–2.10)	[a]	3 of 11 006	<0.1	0.30 (0.07–1.32)	[a]	0.47 (0.12–1.76)	[a]
	All <18 y	21 of 10 538	0.2	28 of 42 362	<0.1	0.33 (0.19–0.58)[f]	0.53 (0.30–0.93)[b,c,f]	48 of 82 907	<0.1	0.29 (0.17–0.48)[f]	0.40 (0.24–0.68)[b,c,f]	0.88 (0.55–1.40)	0.76 (0.47–1.23)[b,c,f]
MIS-C	<3 mo	0 of 55	0.0	0 of 118	0.0	—	—	0 of 218	0.0	—	—	—	—
	3–11 mo	0 of 212	0.0	0 of 518	0.0	—	—	0 of 1395	0.0	—	—	—	—
	1–11 y	6 of 5928	0.1	11 of 27 999	<0.1	0.39 (0.14–1.05)	[a]	7 of 70 288	<0.1	0.10 (0.03–0.29)[f]	[a]	0.25 (0.10–0.65)	[a]
	12–17 y	1 of 4343	<0.1	3 of 13 727	<0.1	0.95 (0.10–9.12)	[a]	0 of 11 006	0.0	—	—	—	—
	All <18 y	7 of 10 538	<0.1	14 of 42 362	<0.1	0.50 (0.20–1.23)	[a]	7 of 82 907	<0.1	0.13 (0.04–0.36)[f]	0.09 (0.03–0.27)[b,e]	0.26 (0.10–0.63)	[a]

[a] The crude model was the best model.
[b] Adjusted for age.
[c] Adjusted for underlying comorbidities.
[d] Adjusted for country of birth.
[e] Adjusted for region of residence.
[f] Statistically significant result.
—, Risk ratio not calculated due to zero outcomes in one or both variant waves.

TABLE 3 Admission to Hospital Among Infants Aged <3 Months With COVID-19, by Variant Wave, Age Group and Whether the Mother of the Infant Had Been Vaccinated at Any Time up to 4 Weeks After Birth, Norway, March 15, 2021 to January 30, 2022

Variant Wave	Alpha (%)	Delta (%)	Omicron (%)
All infants aged <3 mo with COVID-19			
Total	55	118	218
Admission to hospital ≤14 d after positive test (% of total)	10 (18.2)	11 (9.3)	22 (10.1)
Admission to hospital with COVID-19 as main cause of admission ≤14 d after positive test (% of total)	8 (14.6)	7 (5.9)	17 (7.8)
Infants aged <3 mo with COVID-19 whose mother was unvaccinated with a COVID-19 vaccine up to 4 wk after child's birth[a]			
Total	54	91	73
Admission to hospital ≤14 d after positive test (% of total)	10 (18.5)	8 (8.9)	11 (15.1)
Admission to hospital with COVID-19 as main cause of admission ≤14 d after positive test (% of total)	8 (14.8)	4 (4.4)	8 (11.0)

[a] Mothers' vaccination status was known for 54 Alpha, 115 Delta, and 215 Omicron cases. For 3 infants diagnosed with COVID-19 in the Delta wave and 6 diagnosed with COVID-19 in the Omicron wave, the mother was unvaccinated but diagnosed with COVID-19 at least 2 weeks before the child's birth.

adolescents. Hospitalization because of acute COVID-19 or MIS-C was infrequent in all 3 waves.

We find no difference in the risk of hospitalization because of acute COVID-19 among persons <18 years in the Omicron wave, compared to the Omicron wave. We did find a lower risk of hospitalization regardless of main cause in the Omicron wave compared to the Omicron wave. However, results for this indicator should be interpreted with caution because it will include patients admitted for non-COVID-19 related causes. Our results are in line with similar national studies from both England[5] and Denmark.[12] Conversely, Omicron has been associated with a reduced risk of hospitalization and intensive care admission compared to Omicron, among children <5 years of age with COVID-19 in the United States.[13] In comparing estimates, the study settings need to be considered, with each conducted in a different population and health care system. In studies including persons of all ages diagnosed with COVID-19, variation in variant-severity estimates from different settings has been reported.[14,15,22] A study from the United States has also suggested an increase in upper respiratory complications among young children since Omicron became dominant.[28] Such changes in the clinical presentation of hospitalized pediatric COVID-19 patients also need to be considered in future hospital capacity planning and management of pediatric patients as Omicron circulates.

Previous studies from the United States and Denmark estimated the incidence of MIS-C (defined based on the case definition from the Centers for Disease Control and Prevention) to be between 1 in 3000 to 1 in 4000 children infected with the wild-type SARS-CoV-2 variant.[29,30] A subsequent study from Denmark found that this risk did not change among unvaccinated children and adolescents during a wave of Omicron infections.[19] We find that the incidence of MIS-C (based on the case definition from the World Health Organization) in Norway during the Omicron wave was approximately 1 in 3000 children with COVID-19 who were unvaccinated and had not been previously diagnosed with COVID-19. This decreased to 1 in 12 000 in the Omicron wave, an estimated 75% decrease (95% CI: 37% to 90%) in risk. This may suggest a lower intrinsic risk of MIS-C for Omicron compared to Delta, which is supported by preliminary data from both Denmark[20] and Southeast England.[21] This is an encouraging finding, especially given evidence that this risk may be further reduced through vaccination. Studies from Denmark and the United States have estimated the effectiveness of 2 doses of the Pfizer-BioNTech BNT162b2 vaccine against MIS-C to be 91% to 94% during periods of Delta dominance.[19,31] It remains to be seen if the same level of vaccine effect against MIS-C is maintained during a period of Omicron dominance. Omicron has been linked to an increase in breakthrough infections[7,32] and lower vaccine effectiveness against some severity outcomes among children and adolescents 5 to 17 years.[33] The lower risk of MIS-C with Omicron must also be taken into account when considering vaccination for children and adolescents.

The proportion of MIS-C cases admitted to ICU in our study is notably lower than reported by others.[11,19,34] Here, differences in the settings, case definition of MIS-C, and the definition of ICU admission need to be considered. For example, our definition of ICU admission will exclude stays in intermediate observation posts in a pediatrics unit.

We find a lower risk of hospitalization because of acute COVID-19 among persons <18 years in the Delta and Omicron waves, compared to the Alpha wave. Although this could reflect a real

decrease in the risk because of the variant, other factors may have influenced these results. An important limitation with severity studies based on persons diagnosed with COVID-19 is that undiagnosed cases will affect reported outcome proportions, whereas systematic differences in undiagnosed cases between groups may affect comparisons. In our study, the testing strategy was further enhanced after the Alpha wave. Thus, a higher proportion of school-age children and adolescents with asymptomatic and mild COVID-19 may have been diagnosed in the Delta and Omicron waves, even if experiences from previous waves suggest that the proportion of children with COVID-19 who were diagnosed was high before routine biweekly screening of school children was recommended (Supplement A, Section 1). Also, maternal vaccination, which has been reported to protect infants from severe COVID-19,[35,36] was first recommended in Norway before the start of the Delta wave. However, the decrease in the proportion of hospitalized infants <3 months between the Alpha and Delta waves was also observed in infants born to unvaccinated mothers. Thus, other factors such as differences in physicians' decisions on whether to hospitalize an infant, may also have influenced our outcomes. The small cohort of infants <3 months, the small number of vaccinated mothers in the Delta wave, and lack of data on important confounders, such as breastfeeding and preterm birth, limited more in-depth analyses of this cohort.

A general limitation with our study is that the small number of outcomes restricted further exploration of our results. Given the low incidence of severe outcomes among children and adolescents with COVID-19, which may be further reduced through vaccination,[19,31,36,37] analyses of pooled data from several countries or meta-analyses may better elucidate differences in the risk of these outcomes between VOC in younger age groups. Also, we analyzed an Omicron wave when the sublineage BA.1 was the dominant circulating variant. Further studies are needed to establish differences in disease severity between different Omicron sublineages.

CONCLUSIONS

We do not find clear evidence that different SARS-CoV-2 variants have influenced the risk of hospitalization with acute COVID-19 among unvaccinated children and adolescents in Norway. Results suggest a decrease in the risk of MIS-C among those infected with the Omicron variant, compared to the Delta and Alpha variant.

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ABBREVIATIONS

aRR: adjusted risk ratio
CI: confidence interval
COVID-19: coronavirus disease 2019
IQR: interquartile range
LOS: length of stay
MIS-C: multisystem inflammatory syndrome in children
MSIS: Norwegian Surveillance System for Communicable Diseases
NIPaR: Norwegian Intensive Care and Pandemic Registry
NPR: Norwegian Patient Register
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
VOC: variant of concern

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