Supplemental Information

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

1.Additional Information on the Data Sources and Definitions

All data in this study came from the national emergency preparedness register, Beredt C19. Beredt C19 contains individual-level data from central health registries, national clinical registries, and other national administrative registries.

1.1 Diagnosed Cases of COVID-19

We included data on diagnosed cases of laboratory-confirmed SARS-CoV-2 infection from the Norwegian Surveillance System for Communicable Diseases (MSIS). Up to January 24, 2022, reinfections were registered if there were ≥6 months between 2 positive sampling dates for an individual. This will thus exclude reinfections within a 6 month period, of which the Omicron variant could be of higher risk.[38,39] From January 25, 2022, reinfections were registered if there were ≥2 months between 2 positive sampling dates for an individual.

We believe that most COVID-19 cases among children and adolescents have been captured by the national testing strategy. Before the Alpha wave, it was recommended that whenever a positive case was detected among children and adolescents, all close contacts should be tested. A close contact was defined as someone who had been <2 meters from the index case for >15 minutes. In many municipalities, public health doctors opted to test everybody in the same class or day care group, to avoid work-intensive contact tracing. At the start of the Alpha wave, recommendations were enhanced, such that whenever an index case was detected, everybody in the same class or day care group should be tested immediately. These testing procedures appeared to capture most of the COVID-19 cases in schools and day care facilities. In November 2020, during a period of relatively high transmission in Oslo, mass testing was conducted in 6 schools that had ongoing outbreaks of COVID-19. A total of 3740 pupils and staff were tested. Of these, 115 had already tested positive through the ordinary tracing and testing procedures. The mass testing revealed an additional 12 COVID-19 cases.

As described in the manuscript, testing was enhanced during the Delta wave. Routine biweekly screening with rapid antigen tests was recommended in areas with high transmission for secondary school students from late August 2021 and from primary school students from November 2021 to January 2022. This probably led to an increase in the diagnosed fraction of cases, although the experiences from previous waves suggest that this proportion was already high during previous waves.

By the end of January 2022, 25% of children and adolescents in Norway had tested positive for COVID-19 at least once. Among children and adolescents of school age (6 to 17 years), the proportion was 30%. In the counties with the highest levels of transmission (Oslo and Viken), the proportion was 44%.

1.2 Laboratory Testing for Variants

Data on virus variants came from the MSIS laboratory database (national laboratory database), which receives SARS-CoV-2 test results from all Norwegian microbiology laboratories. 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.[40]

1.3 National Identity Number

Data on persons with a national identity number was drawn from the national population registry (Folkeregistret). The national identity number was essential to link data from all registries used in the analysis and the country of birth of cases and their parents. The national population registry was also used to identify all deaths in our study cohort during the study period.

1.4 Hospitalization and Intensive Care Admission With Acute COVID-19

We obtained data on hospitalization following a positive polymerase chain reaction test for SARS-CoV-2 from the Norwegian Intensive Care and Pandemic Registry (NIPaR). All Norwegian hospitals report to NIPaR, and reporting is mandatory. Hospitals in Norway functioned within capacity during each variant wave in the study period.

For patients who contracted COVID-19 while admitted to hospital, the time of admission is set to the date of symptom onset, or date of sampling if the patient is asymptomatic. The reported main cause of hospitalization is a clinical assessment. For patients reported with a different main cause than COVID-19, we cannot rule out that COVID-19 may have been a contributing factor for admission. There is no reason to believe, however, that this assessment would differ between patients infected with different variants or

hospitalized in different periods. Full details on the registration of hospitalized patients are available here (in Norwegian): https://helse-bergen.no/norsk-pandemiregister/registrering-i-norsk-pandemiregister-informasjon-til-ansatte.

NIPaR also includes data on patients who have tested positive for COVID-19 and are admitted to an ICU. Patients are registered as ICU patients if they fulfill 1 of 5 categories:

1. LOS >24 hours in intensive care.
2. Require mechanical ventilation.
3. Are transferred between intensive care wards.
4. Persistent administration of vasoactive medication.
5. LOS <24 hours but died during stay in intensive care.

Full details on the registration of ICU patients are available here (in Norwegian): https://helse-bergen.no/norsk-pandemiregister/registrering-i-norsk-pandemiregister-informasjon-til-ansatte.

1.5 Cases of Multisystem Inflammatory Syndrome in Children

The Norwegian Patient Register (NPR) contains health information about all persons who have received treatment, or who are waiting for treatment in public specialist health care services, including private institutions and medical specialists contracted to the regional health authorities. Admission to hospital with multisystem inflammatory syndrome in children (MIS-C) was defined as patients registered in NPR with the International Classification of Diseases, 10th Revision code U10.9. Clinical criteria for the diagnosis of MIS-C cases in Norway are based on World Health Organization guidelines.[41]

1.6 Vaccination status

Data on COVID-19 vaccinations came from the Norwegian Immunisation Registry, SYSVAK. Unvaccinated cases were those who were unvaccinated with a COVID-19 vaccine at date of positive test, and who had also not been previously diagnosed with COVID-19, as reported to MSIS.

1.7 Underlying comorbidities

Data on underlying comorbidities, as stipulated by the national COVID-19 vaccination program, was based on International Classification of Diseases, 10th Revision codes from NPR, and International Classification of Primary Care, 2nd edition codes from the Norway Control and Payment of Health Reimbursement database (Supplemental Table 4). Underlying comorbidities that have been defined as increasing the risk of severe COVID-19 were divided into 2 groups.

- Medium-risk includes people with diseases or conditions that entail a moderate risk of severe COVID-19. This 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 people with diseases or conditions that carry a high risk of severe COVID-19, also in younger individuals. These comorbidities include having received an organ transplant, immunodeficiency, hematological 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, ALS and cerebral palsy), Down syndrome and chronic kidney disease, or significant renal impairment.

In Norway, vaccination was first offered to children and adolescents with severe comorbidities; from February 2021 for 16- to 17-year-olds, June 2021 for 12- to 15-year-olds, and late December for 5- to 11-year-olds. Since August 2021, all 16- to 17-year-olds have been recommended vaccination. All 12- to 15-year-olds and 5- to 11-year-olds have been offered vaccination since September 2021 and January 2022, respectively (Supplemental Table 5). As of March 2022, the Pfizer-BioNTech mRNA vaccine BNT162b2 was the vaccine recommended to be administered to children <18 y as part of the national vaccination program.

Among 16- to 17-year-olds, 1-dose coverage increased from 1.5% in late-August to over 80% by late-October, reaching 89% by January 31, 2022. Two-dose coverage was <5% until late-October, before increasing to over 70% in late-December and reaching 79% by January 31, 2022 (Supplemental Figure 2). Among 12- to 15-year-olds, 1 dose coverage increased from <1.0% in early September to over 70% in early-December, reaching 75% by January 31, 2022. Two--dose coverage reached 5.4% by January 31, 2022 (Supplemental Figure 2). At the end of January 2022, 1.0% of the national population aged 5 to 11 years had received 1 vaccine dose.

To validate the variant wave variable, we ran models for persons of all ages diagnosed with COVID-19 in Norway and compared these to

analyses based on COVID-19 cases with known variant during periods when 1 variant was superseding another (Supplemental Table 6 and Supplemental Table 7). We could not run models based on cases with known variant for just those <18 years, due to the small number of cases with known variant in this age group.

In the analysis of cases with known variant, the Alpha–Delta period was week 18 to 32 2021 and the Delta–Omicron period week 49 2021 to week 1 2022, as used in previous analyses of cases with known variant.[42,43] The variant wave variables were defined as in the main manuscript. We ran a logistic regression model and estimated odds ratios, as opposed to log-binomial regression or Cox regression. Cox regression was not possible as the variant wave variable violated the proportional hazards assumption, while a log-binomial model did not converge in the variant wave analysis. The models are adjusted for variant (wave or known), age group (<1, 1–5, 6–11, 12–15, 16–17, 18–29, 30–44, 45–54, 55–64, 65–74, 75+), sex, vaccination status, county of residence, underlying comorbidities, and country of birth. Vaccination status, county of residence, underlying comorbidities and country of birth were defined as in Veneti et al.[43] The models for known variant are also adjusted for sampling week, which was not included in the variant wave models due to collinearity. We analyzed 3 different outcomes to see if our results remained robust.

Results were consistent, regardless of whether variant wave or known variant was analyzed. Results were also consistent with our previous comparison of Delta and Alpha cases using log-binomial regression (aRR: 0.97, 95% CI: 0.76–1.23)[42] and Delta and Omicron cases using Cox regression (adjusted hazard ratio: 0.27; 95% CI: 0.20–0.36),[42] where the outcome was admission with COVID-19 as main cause of admission.

SUPPLEMENTAL REFERENCES

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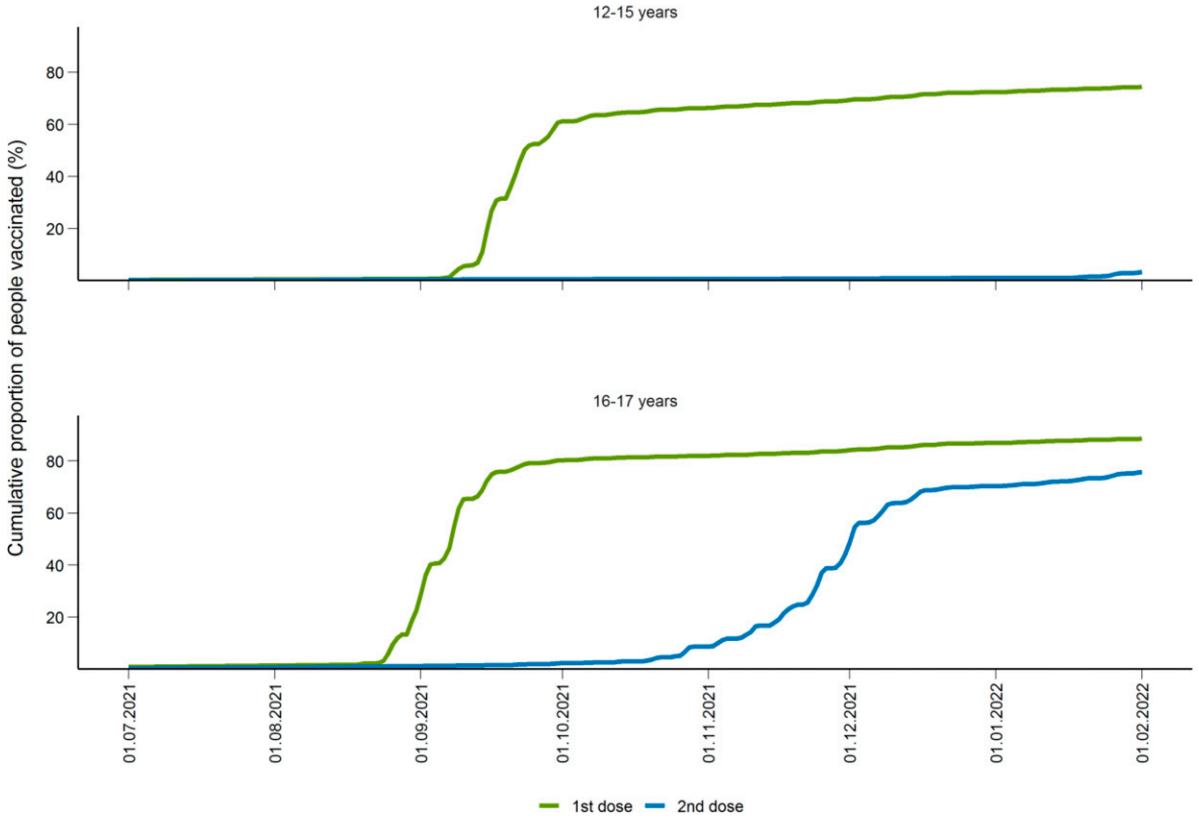

SUPPLEMENTAL FIGURE 2

National vaccination coverage of COVID-19 vaccines in Norway by age group, number of doses and date, persons 12 to 17 Years, July 1, 2021 to January 31, 2022.

SUPPLEMENTAL TABLE 4 ICD-10-CM Codes From the Norwegian Patient Registry and ICPC-2 Codes from the Norway Control and Payment of Health Reimbursement Database Used to Identify Cases With Underlying Comorbidities

Underlying Comorbidity	Specifications	ICD-10-CM Codes	ICPC-2 Codes
Cardiovascular diseases, not including hypertension		I05, I06, I07, I08, I09, I2, I31, I32, I34, I35, I36, I37, I39, I40, I41, I42, I43, I46, I48, I49, I50, I60, I61, I62, I63, I64, I69.1, I69.2, I69.3, I69.4, I69.8, I69.0	K74, K75, K76, K77, K78, K82, K83, K90, K91
Chronic pulmonary diseases, including asthma		J41, J42, J43, J44, J45, J46, J47, J84, J98, E84	R95, R96
Compromised immune function	Organ transplantation, immune deficiency disorders, autoimmune conditions treated with immunosuppressants	Z94.0, Z94.1, Z94.2, Z94.3, Z94.4, Z94.8, D80, D81, D82, D83, D84, G35, M05, M08, M06, M07, M09, M13, M14, K50, K51	
Neurologic and musculoskeletal disorders with compromised lung or cough function		G1, G20, G21, G23, G24, G40.5, G61.0, 70, G71, G80.0, G80.2, G80.3, F72, F73, F84.0, F84.1, Q05.0, Q05.1, Q05.2, Q05.3, Q05.04, Q05.5, Q05.6	
Diabetes		E10, E11, E12, E13, E14	T89, T90
Active cancer treatment or hematologic cancer		C81, C82, C83, C84, C85, C86, C87, C88, C89, C90, C91, C92, C93, C94, C95, C96, D45, D45, D47, C0, C1, C2, C3, C4, C5, C6, C7, C80, D32, D33, D35.2, D35.3, D35.4, D42, D43, D44.2, D44.3, D44.4	
Other risk groups	Dementia, chronic kidney and liver disease, obesity	N18.3, N18.4, N18.5, K70.4, K72, F00, F01, F02, F03, G30, G31, E66	P70, T82

National COVID-19 vaccine recommendations and vaccination coverage among persons 5 to 17 y in Norway.

SUPPLEMENTAL TABLE 5 COVID-19 Vaccine Recommendations for Children and Adolescents 5 to 17 Years up to January 2022, Norway

Age Group, Years	Recommendation for Those With Severe Underlying Disease	Recommendation or Offer for All Within Age Group
16–17	February 2021	August 2021: 2 doses recommended, 8–12 wk interval
12–15	June 2021	September 2021: first dose offered January 2022: second dose offered
5–11	December 2021	January 2022: 2 doses offered, 8–12 wk interval

Estimates among all diagnosed COVID-19 cases by variant wave, compared to cases with known variant.

SUPPLEMENTAL TABLE 6 Crude and Adjusted Odds Ratios From Logistic Regression for Different Outcomes Among COVID-19 Cases, by Variant Wave or Cases With Known Variant, Delta Variant Compared to Alpha Variant, Norway

Outcome	Analysis of Variant Data	Alpha		Delta			
		Number of Outcomes per Cases	%	Number of Outcomes per Cases	%	Crude Odds Ratio Compared to Alpha (95% CI)	Adjusted Odds Ratio Compared to Alpha (95% CI)
Admission to hospital within 14 d of positive test	Variant wave	1440 of 39 523	3.7	2074 of 127 358	1.6	0.44 (0.41–0.47)[a]	1.06 (0.97–1.16)
	Cases with known variant	281 of 12 162	2.3	133 of 8227	1.6	0.69 (0.56–0.86)[a]	0.77 (0.51–1.18)
Admission to hospital with COVID-19 as main cause of admission within 14 d of positive test	Variant wave	1218 of 39 523	3.1	1505 of 127 358	1.2	0.38 (0.35–0.41)[a]	0.96 (0.87–1.06)
	Cases with known variant	242 of 12 162	2.0	108 of 8227	1.3	0.66 (0.52–0.82)[a]	0.80 (0.51–1.28)
Admission to hospital with COVID-19 as main cause of admission or death within 28 d of positive test	Variant wave	1283 of 39 523	3.3	1770 of 127 358	1.4	0.42 (0.39–0.45)[a]	1.00 (0.90–1.10)
	Cases with known variant	256 of 12 162	2.1	120 of 8227	1.5	0.69 (0.55–0.86)[a]	0.75 (0.48–1.18)

[a] Statistically significant.

SUPPLEMENTAL TABLE 7 Crude and Adjusted Odds Ratios From Logistic Regression for Different Outcomes Among COVID-19 Cases, by Variant Wave or Cases With Known Variant, Omicron Variant Compared to Delta Variant, Norway

Outcome	Analysis of Variant Data	Delta		Omicron			
		Number of Outcomes per Cases	%	Number of Outcomes per Cases	%	Crude Odds Ratio Compared With Delta (95% CI)	Adjusted Odds Ratio Compared to Delta (95% CI)
Admission to hospital within 14 d of positive test	Variant wave	2074 of 127 358	1.6	951 of 321 874	0.3	0.18 (0.17–0.19)[a]	0.43 (0.39–0.47)[a]
	Cases with known variant	756 of 51 995	1.5	194 of 40 641	0.5	0.33 (0.28–0.38)[a]	0.33 (0.27–0.41)[a]
Admission to hospital with COVID-19 as main cause of admission within 14 d of positive test	Variant wave	1505 of 127 358	1.2	457 of 321 874	0.1	0.12 (0.11–0.13)[a]	0.29 (0.26–0.33)[a]
	Cases with known variant	551 of 51 995	1.1	107 of 40 641	0.3	0.25 (0.20–0.30)[a]	0.27 (0.21–0.36)[a]
Admission to hospital with COVID-19 as main cause of admission or death within 28 d of positive test	Variant wave	1770 of 127 358	1.4	559 of 321 874	0.2	0.12 (0.11–0.14)[a]	0.31 (0.28–0.35)[a]
	Cases with known variant	611 of 51 995	1.2	126 of 40 641	0.3	0.26 (0.22–0.32)[a]	0.27 (0.21–0.35)[a]

Estimates among all diagnosed COVID-19 cases 12 to 17 y, compared to estimates among unvaccinated cases, Omicron wave compared to Delta wave.
[a] Statistically significant.

SUPPLEMENTAL TABLE 8 Number of Diagnosed COVID-19 Cases Admitted to Hospital for Acute COVID-19 or MIS-C, and Crude and Adjusted Risk Ratios From Log-Binomial Regression, by Age Group, Vaccination Status and Variant Wave, Cases 12 to 17 Years, Norway

		Delta Wave (Week 35 to 48 2021)		Omicron Wave (Week 2 to 4 2022)			
Outcomes	Age Group	Number of Outcomes Per cases	%	Number of Outcomes Per Cases	%	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	Unvaccinated only (main analysis)	16 of 13 727	0.1	6 of 11 006	<0.1	0.47 (0.18–1.19)	[a]
	All cases, including vaccinated and previous infections	20 of 24 888	<0.1	27 of 58 756	<0.1	0.57 (0.32–1.02)	0.83 (0.42–1.64)[b,c]
Admission to hospital with COVID-19 as main cause ≤14 d after positive test	Unvaccinated only (main analysis)	8 of 13 727	<0.1	3 of 11 006	<0.1	0.47 (0.12–1.76)	[a]
	All cases, including vaccinated and previous infections	10 of 24 888	<0.1	7 of 58 756	<0.1	0.30 (0.11–0.78)[e]	0.45 (0.15–1.36)[c]
MIS-C	Unvaccinated only (main analysis)	3 of 13 727	<0.1	0 of 11 006	0.0	—	—
	All cases, including vaccinated and previous infections[d]	5 of 24 888	<0.1	2 of 58 756	<0.1	0.16 (0.03–0.87)[e]	[a]

[a] The crude model was the best model.

[b] Adjusted for age.

[c] Adjusted for vaccination status (vaccinated with at least 1 dose ≥21 d before positive test or previously diagnosed with COVID-19 versus other).

[d] Among the 4 additional MIS-C cases in the 'all cases' cohort, none had completed a 2-dose primary vaccination series ≥7 d before positive test.

This sensitivity analysis was not run for the age group 1 to 11 y, as only 92 cases total in this age group (all but one in the Omicron wave) had received at least 1 vaccine dose before positive test.

[e] Statistically significant.

This sensitivity analysis was not run for the age group 1 to 11 y, as only 92 cases total in this age group (all but one in the Omicron wave) had received at least one vaccine dose before positive test.

— Risk ratio not calculated due to zero outcomes in one or both variant waves.