Supplementary material

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Data sources

We used data from several national registries that were individually linked in the Norwegian preparedness registry (Beredt C19). The data sources and variables used are shown in Table S1. All sources contain individual level data and were linked by using hashed national identity numbers. More information can be found on: https://www.fhi.no/en/id/infectious-diseases/coronavirus/emergency-preparedness-register-for-covid-19/

Table S2. Data sources in the Norwegian preparedness registry (BeredtC19) used in this study and variables retrieved from each source.

Norwegian Abbreviation	Full name of data source	Information provided
DSF	National Population Register	Age, sex, county of residence*, country of birth, date of death
SYSVAK	The National Immunisation Register	Date of vaccination, Vaccine product type
NIPaR	Norwegian Intensive Care and Pandemic Registry	Date of hospitalization and ICU admissionCOVID-19 as the primary diagnosis for admission
MSIS	Norwegian Surveillance System for Communicable Diseases	Date of sample of SARS-CoV-2 positive test
Beredt C19 risikogrupper	Table prepared in BeredtC19 Source: Norwegian Patient Registry (NPR): individual level data from all public specialist health-care services in Norway.	Defines risk groups (see definition below)
NAV - Institution	Norwegian Labour and Welfare Administration (NAV) - Institution	Resident in long-term care facility.
DÅR	Cause of Death Register	COVID-19 associated mortality (death certificate with COVID-19 listed as main or contributing cause of death) and all-cause mortality

* The county of residence was updated in January 2022, which might lead to some errors for individuals who have moved the last half year.

Text S1: Study population

In addition to Figure 1, the text below describes the selection of our study population on the basis of the base population. We removed individuals who had intervals between doses that were not in line with national recommendations (n=1,450), persons who received vaccines that are not part of the Norwegian vaccination program (n=825), those who received a fourth dose before 1st of April 2022 (n=5,095) as the fourth dose was not available in Norway prior to this date, and people with missing data on residency (n=8). Further, we excluded 2,237 individuals who had been hospitalized due to COVID-19 before the start of the study period. Individuals were censored 30 days after a positive test reported in the central registry if no severe event had occurred leading to the full removal of another 14 individuals. Lastly, we excluded 130 individuals due to censoring before they reached 24 weeks of follow-up after the third dose, the reference level for vaccination status, as they did not contribute any time before the end of the study period.

Text S2: Definitions, outcome measures and adjustment variables

The primary outcome measures in our study were i) COVID-19 associated mortality, defined as anyone who died with COVID-19 reported on the death certificate in the Norwegian Cause of Deaths Register and ii) all-cause mortality, including individuals who died of other causes. Secondary outcome measures were iii) COVID-19 associated hospitalization, including only individuals where COVID-19 was the primary reason for hospital admission, and iv) COVID-19 associated ICU admission, including all individuals who were tested positive for SARS-CoV-2 and were admitted to ICU for at least 24 hours, required mechanical ventilatory support (invasive or non-invasive), or needed persistent administration of vasoactive medication. Vaccination status was categorized as a combination of time under risk since the last dose and vaccine type (for the fourth dose) (1): i) third dose, individuals who received the third COVID-19 vaccine dose more than 24 weeks ago to identify the additional benefit of the fourth dose (1), ii) fourth dose, more than seven days after a fourth dose of COVID-19 vaccine, given with either a monovalent or bivalent (BA.1 or BA.4-5) vaccine, given at six-week intervals for the time since vaccination.

To adjust for confounders, several adjustment variables were selected based on the scientific literature and included in our analyses. Our models were stratified for the variables: age-groups (75-79, 80-84, 85-89, and ≥90 years), sex (male, female), region of residence (Innlandet, Trøndelag, Nord-Norge, Oslo & Viken, Agder & Sørøstlandet, Vestlandet), and whether an individual was a resident in a LTCF. We also categorized individuals based on their pre-existing diseases and medical conditions as high risk or medium risk for severe COVID-19 outcome. (2) More details on variables are provided in Table S1 below.

Table S1. Definitions of outcomes and adjustment variables

Variable	Definition
COVID-19 associated deaths	Individuals who died with COVID-19 reported on the death certificate in the Cause of Death Register (DÅR) or notified directly to the Norwegian Surveillance System for Communicable Diseases (MSIS)
All-cause mortality	Individuals who died of any cause
COVID-19 associated hospitalization	Individuals who were hospitalized and where COVID-19 was registered as the primary diagnosis for admission
COVID-19 associated intensive care unit (ICU) admission	Individuals who tested positive for SARS-CoV-2 and were admitted to an ICU (length of stay ≥ 24 h), required mechanical ventilatory support (invasive or non-invasive), or persistent administration of vasoactive medication
High risk group*	Individuals with diseases/conditions that carry a high risk of severe COVID-19 outcomes: - Organ transplant - Immunodeficiency - Haematological cancer in the last five years - Other active cancers - Neurological or neuromuscular diseases that cause impaired cough or lung function (e.g., Amyotrophic lateral sclerosis and cerebral palsy) - Chronic kidney disease, or significant renal impairment.
Medium risk group*	Individuals with diseases/conditions that entail a moderate risk of severe COVID-19: - Chronic liver disease or significant hepatic impairment - Diseases requiring immunosuppressive therapy - 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 body mass index (BMI) of ≥35 kg/m2 - Dementia - Chronic heart and vascular disease (except for high blood pressure) and stroke

*Some underlying medical conditions increase the risk of severe COVID-19 outcomes, regardless of age. These individuals have been prioritized in the vaccination program in Norway. The underlying comorbidities that have been defined as increasing the risk of severe COVID-19 are divided into two groups, high- and medium risk group https://www.fhi.no/contentassets/d07db6f2c8f74fa586e2d2a4ab24dfdf/2020-12-v2-anbefalinger-og-prioriteringer-2-utgave-korrigert-forside.pdf

Time-varying variable included in the Cox-proportional hazard model

Vaccination status was included as a time-varying variable in the Cox proportional hazard model as a combination of time at risk since the third or fourth dose and vaccine type. Each individual entered the study at baseline (1 July 2022) and was grouped according to vaccine and the time since vaccination. Individuals who changed vaccination status during the study were censored without an event in the group that they left and are recorded as a delayed entry in the group into which they were reclassified (see examples table S3). Individuals who received the 5th dose during the study period were censored on the date of the 5th dose. The variable with the time since last vaccine variable was updated accordingly (1). Based on our inclusion criteria, individuals were only included in our analyses as fourth dose recipients >7 days after the administration of the fourth dose (highlighted in blue in the Table S3), to ensure that the partial effect of the vaccine did not affect the comparison. The status of the control group is highlighted in grey in Table S3. The white rows represent a status that is not included in the Cox-proportional hazard model.

Table S3. Vaccination status grouping used for the Cox proportional hazards model, in which individuals were grouped according to their vaccination status during the study period.

Identifier	Start day	End day	Event	Status
Patient 1	0	32		3rd dose > 24 weeks
Patient 1	32	39		4th dose 0-7 days
Patient 1	39	88		4th dose 2-9 weeks
Patient 1	88	112		4th dose 10-17 weeks
Patient 1	112	116		4th dose 18 - 25 weeks
Patient 1	116	158	Primary or secondary outcome	4th dose 18 - 25 weeks
Patient 2	0	11		3rd dose > 24 weeks
Patient 2	11	18		4th dose 0-7 days
Patient 2	18	74		4th dose 2-9 weeks
Patient 2	74	103	Primary or secondary outcome	4th dose 10-17 weeks
Patient 3	0	198		3rd dose > 24 weeks
Patient 4	0	100		3rd dose ≤ 24 weeks
Patient 4	100	198		3rd dose > 24 weeks
Patient 5	0	20		4th dose 2-9 weeks
Patient 5	20	62		4th dose 10-17 weeks
Patient 5	62	104		4th dose 18 - 25 weeks
Patient 5	104	146		4th dose 26 - 33 weeks

The COVID-19 associated events in Norway July 2022 - January 2023

The epidemic curve below displays the overall number of COVID-19 associated death, -hospitalization, -ICU admission as well as all-cause mortality during the study period in Norway.

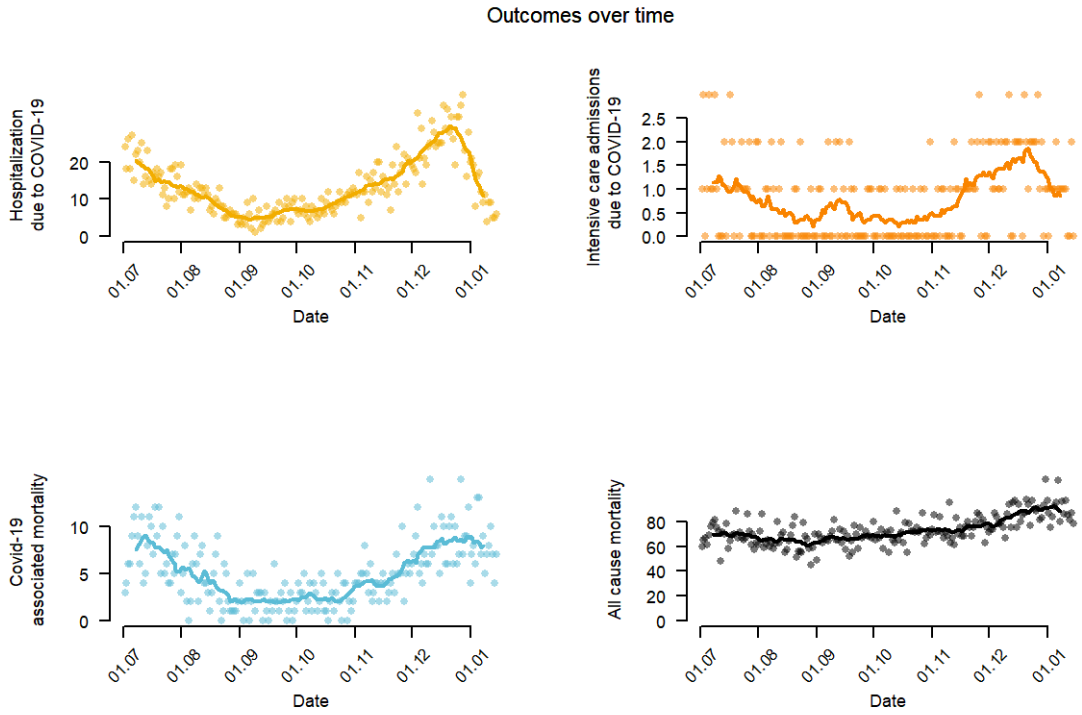

Figure S1. Epidemic curves displaying the number of different outcome measures (COVID-19 related hospitalizations, - intensive care unit admission (ICU), - associated mortality, and all-cause mortality) in Norway between 1 July 2022 and 15 January 2023. Dots represents events per day and line is 14-day rolling average.

SARS-CoV-2 variants in Norway July 2022 – April 2023

The proportion of circulating SARS-CoV-2 variants are displayed over time. The collapsed pangolin name displays the different lineages.

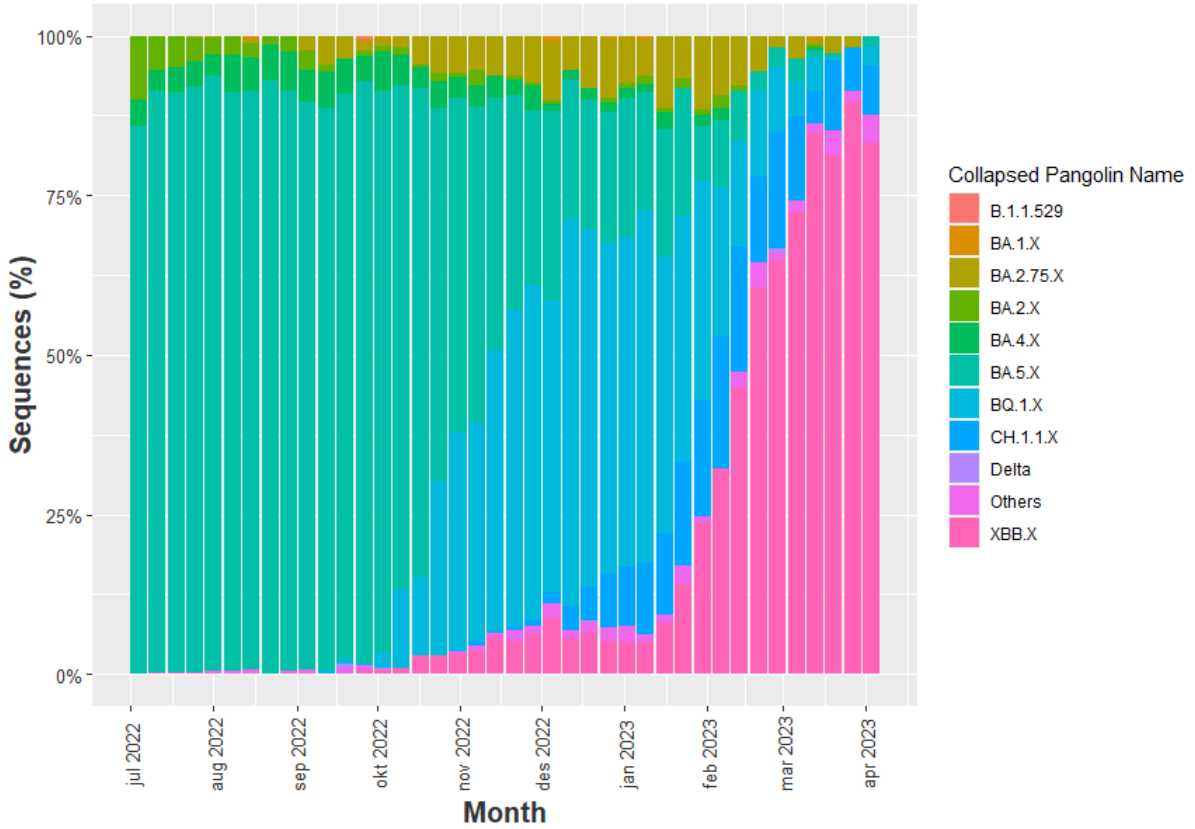

Figure S2. Proportion of different SARS-CoV-2 lineages in Norway between July 2022 and April 2023. The different colours representing the collapsed pangolin names of the different lineages.

Table S4. Sociodemographic characteristics displayed by the number of individuals for the secondary outcome measure COVID-19 associated hospitalization and intensive care unit (ICU), with the time under risk for each event stratified by the vaccine dose.

		Third-dose recipients						Fourth-dose recipients															
								monovalent						BA.1						BA.4-5			
		Person-time		COVID-19 hospitalization		COVID-19 ICU-admission		Person-time		COVID-19 hospitalization		COVID-19 ICU-admission		Person-time		COVID-19 hospitalization		COVID-19 ICU-admission		Person-time		COVID-19 hospitalization		COVID-19 ICU-admission	
		Years	%	n	%	n	%	Years	%	n	%	n	%	Years	%	n	%	n	%	Years	%	n	%	n	%
Gender	Female	50834	56.80%	648	45.73%	24	45.28%	61365	55.22%	409	38.48%	17	34.00%	5314	53.44%	35	40.23%	2	50.00%	2522	54.07%	20	43.48%	0	0.00%
	Male	38718	43.20%	769	54.27%	29	54.72%	49758	44.78%	654	61.52%	33	66.00%	4630	46.56%	52	59.77%	2	50.00%	2143	45.93%	26	56.52%	3	100.00%
Age	75-79	43998	49.10%	462	32.60%	30	56.60%	51701	46.53%	330	31.04%	26	52.00%	5648	56.80%	37	42.53%	3	75.00%	2502	53.64%	16	34.78%	1	33.33%
	80-84	23589	26.30%	378	26.68%	13	24.53%	31723	28.55%	298	28.03%	14	28.00%	2444	24.57%	20	22.99%	0	0.00%	1169	25.07%	7	15.22%	2	66.67%
	85-89	13689	15.30%	330	23.29%	8	15.09%	17388	15.65%	260	24.46%	8	16.00%	1230	12.37%	18	20.69%	0	0.00%	636	13.63%	16	34.78%	0	0.00%
	90+	8275	9.20%	247	17.43%	2	3.77%	10311	9.28%	175	16.46%	2	4.00%	623	6.26%	12	13.79%	1	25.00%	358	8%	7	15.22%	0	0.00%
Region	Innlandet	8305	9.30%	90	6.35%	10	18.87%	9157	8%	53	4.99%	9	18.00%	1145	11.51%	3	3.45%	1	25.00%	409	8.76%	3	6.52%	1	33.33%
	Trøndelag	8205	9.20%	185	13.06%	4	7.55%	10046	9.04%	110	10.35%	2	4.00%	847	8.52%	14	16.09%	0	0.00%	281	6.01%	3	6.52%	0	0.00%
	Nord-Norge	10978	12.30%	91	6.42%	4	7.55%	8403	7.56%	34	3.20%	2	4.00%	1000	10.06%	2	2.30%	0	0.00%	565	12.11%	2	4.35%	0	0.00%
	Oslo & Viken	27028	30.20%	480	33.87%	14	26.42%	38520	34.66%	394	37.06%	16	32.00%	3004	30.21%	27	31.03%	2	50.00%	1924	41.25%	21	45.65%	1	33.33%
	Agder & Sørøstlandet	13006	14.50%	212	14.96%	8	15.09%	16673	15.00%	178	16.75%	7	14.00%	1473	14.81%	13	14.94%	0	0.00%	739	15.85%	10	21.74%	1	33.33%
	Vestlandet	22031	24.60%	359	25.34%	13	24.53%	28324	25.49%	294	27.66%	14	28.00%	2475	24.89%	28	32.18%	1	25.00%	747	16.01%	7	15.22%	0	0.00%
Risk group	None	42089	47%	335	24%	13	25%	51804	46.62%	236	22%	14	28%	4741	48%	15	17%	2	50%	2211	47.40%	11	24%	0	0%
	High	6427	7.20%	217	15.31%	9	16.98%	8469	7.62%	173	16.27%	8	16.00%	698	7.02%	15	17.24%	1	25.00%	334	7%	8	17.39%	0	0.00%
	Medium	41036	45.80%	865	61.04%	31	58.49%	50849	45.76%	654	61.52%	28	56.00%	4505	45.31%	57	65.52%	1	25.00%	2120	45.45%	27	58.70%	3	100.00%
LTCF	No	86319	96.40%	1317	92.94%	53	100.00%	105061	94.55%	1000	94.07%	44	88.00%	9829	98.85%	85	97.70%	4	100.00%	4592	98.44%	43	93.48%	3	100.00%
resident	Yes	3233	3.60%	100	7.06%	0	0.00%	6061	5.45%	63	5.93%	6	12.00%	115	1.16%	2	2.30%	0	0.00%	73	1.56%	3	6.52%	0	0.00%

Long term care facility residents, LTCF; coronavirus disease 2019, COVID-19; third dose recipients: individuals who received their third dose more than 24 weeks ago; fourth dose recipients: individuals who received a fourth COVID-19 bivalent vaccine dose (BA.1 and BA.4-5) or a monovalent vaccine dose (Monovalent); Person time in years, which describes the time under risk for third- and fourth dose recipients until censoring or occurrence of the respective event, number; n.

Results vaccine effectiveness against COVID-19 related mortality and all-cause mortality stratified by residents of long-term care facilities

Table S5: The adjusted hazard ratio (aHR) estimates against COVID-19 associated mortality and all-cause mortality amongst all individuals living in Norway aged ≥75 years. The Cox proportional hazard model is stratified for age, sex, risk group, and county of residence. Due to the recent introduction of the BA.1 and BA.4-5, vaccines estimates could only be calculated for the monovalent vaccines.

Vaccine	Group	aHR (95% CI)
COVID-19 associated mortality		
2-9 weeks after vaccine dose		
Monovalent	non_ltcf	0.33 (0.23 - 0.46)
	ltcf	0.37 (0.24 - 0.59)
BA.1	non_ltcf	0.08 (0.02 - 0.34)
	ltcf	0 (0 - Inf)
BA.4-5	non_ltcf	0.26 (0.12 - 0.56)
	ltcf	0.29 (0.04 - 2.11)
10-17 weeks after vaccine dose		
Monovalent	non_ltcf	0.31 (0.23 - 0.42)
	ltcf	0.43 (0.28 - 0.66)
BA.1	non_ltcf	0.3 (0.16 - 0.57)
	ltcf	0 (0 - Inf)
BA.4-5	non_ltcf	0.24 (0.06 - 0.99)
	ltcf	0 (0 - Inf)
18-25 weeks after vaccine dose		
Monovalent	non_ltcf	0.48 (0.37 - 0.62)
	ltcf	0.78 (0.55 - 1.1)
26-33 weeks after vaccine dose		
Monovalent	non_ltcf	0.5 (0.32 - 0.78)
	ltcf	0.83 (0.49 - 1.39)
34-41 weeks after vaccine dose		
Monovalent	non_ltcf	0.34 (0.08 - 1.38)
	ltcf	0 (0 - Inf)
All-cause mortality		
2-9 weeks after vaccine dose		
Monovalent	non_ltcf	0.48 (0.44 - 0.51)
	ltcf	0.74 (0.67 - 0.81)
BA.1	non_ltcf	0.32 (0.26 - 0.38)
	ltcf	0.33 (0.18 - 0.61)
BA.4-5	non_ltcf	0.37 (0.3 - 0.45)
	ltcf	0.51 (0.31 - 0.82)
10-17 weeks after vaccine dose		
Monovalent	non_ltcf	0.54 (0.51 - 0.58)
	ltcf	0.78 (0.71 - 0.86)
BA.1	non_ltcf	0.35 (0.29 - 0.42)
	ltcf	0.51 (0.31 - 0.84)
BA.4-5	non_ltcf	0.52 (0.37 - 0.72)

	ltcf	0.96 (0.45 - 2.05)
18-25 weeks after vaccine dose		
Monovalent	non_ltcf	0.59 (0.55 - 0.63)
	ltcf	0.81 (0.73 - 0.9)
26-33 weeks after vaccine dose		
Monovalent	non_ltcf	0.68 (0.6 - 0.78)
	ltcf	0.92 (0.78 - 1.08)
34-41 weeks after vaccine dose		
Monovalent	non_ltcf	0.49 (0.33 - 0.72)
	ltcf	0.86 (0.44 - 1.68)

ltcf, long-term care facility residence

The administration over time of the mono- and bivalent COVID-19 vaccines as fourth dose in Norway

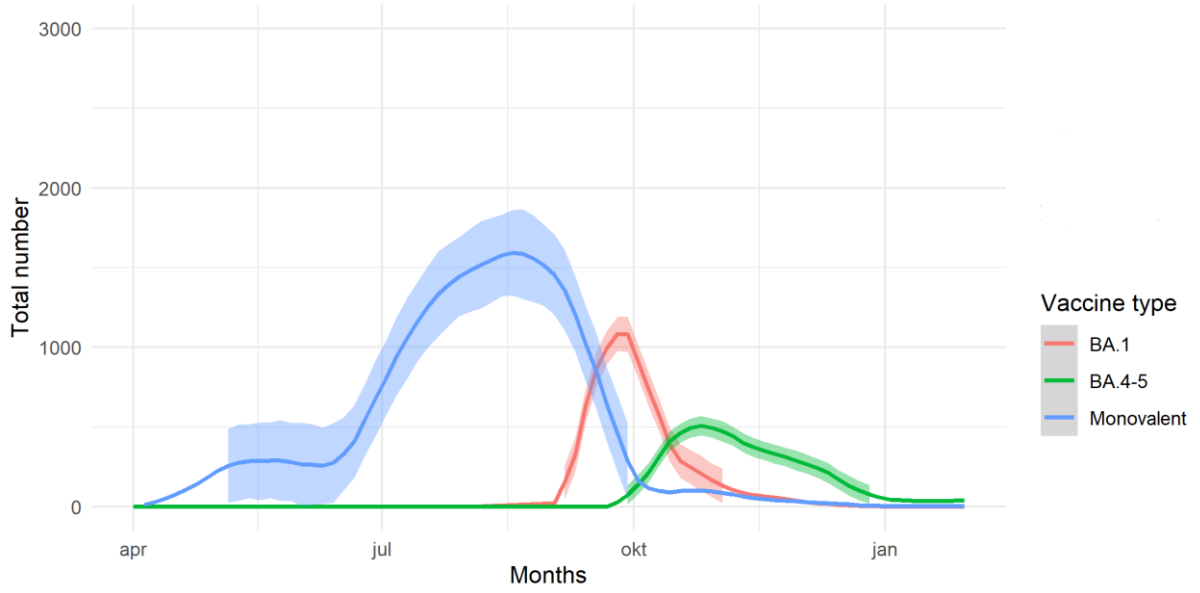

Figure S3. The number of administered mono- and bivalent COVID-19 vaccines (BA.1 and BA.4-5) in Norway between April 2022 and January 2023.

Reference

1. European Centre for Disease Prevention and Control. Protocol for a COVID-19 vaccine effectiveness study using health data registries. Stockholm ECDC; 2023. Report No.: 1.0.

2. Koronavirus—temaside. 2021 [Available from: https://www.fhi.no/sv/smittsomme-sykdommer/corona/.