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Effectiveness and durability of a second COVID-19 booster against severe outcomes among older people in Norway: a population-based cohort study comparing mono- and bivalent booster doses

Melanie Stecher [ORCID] ,[1,2,]* **Anja Bråthen Kristoffersen,[3] Kristian Lie,[1] Svein Rune Andersen,[1] Hinta Meijerink[1] and Jostein Starrfelt[4]**

[1]Department of Infection Control and Vaccines, Norwegian Institute of Public Health, Oslo, Norway, [2]ECDC Fellowship Programme, Field Epidemiology path (EPIET), European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden, [3]Department of Method Development and Analytics, Norwegian Institute of Public Health, Oslo, Norway and [4]Department of Infection Control and Preparedness, Norwegian Institute of Public Health, Oslo, Norway

*Corresponding author. Department of Infection Control and Vaccines, Norwegian Institute of Public Health, Lovisenberggata 8, 0456 Oslo, Norway. E-mail: melanie.stecher@fhi.no

Abstract

Background: Evidence on the durability of the protection of a fourth dose of a monovalent or bivalent messenger ribonucleic acid (mRNA) vaccine against coronavirus disease 2019 (COVID-19) among older people during the predominant Omicron period is needed.

Methods: We performed a population-based cohort study in Norway covering the time from 1 July 2022 to 15 January 2023, including individuals ≥75 years of age who had received at least a third dose. Using Cox proportional hazard models on severe COVID-19-associated outcome measures and all-cause mortality, we estimated the vaccine effectiveness of mono- and bivalent vaccines, comparing fourth- to third-dose recipients (>24 weeks ago). Vaccine status was included as a time-varying covariate and models were adjusted for potential confounders.

Results: We included 408 073 individuals. A fourth dose with either monovalent or bivalent mRNA vaccine showed increased protection against COVID-19-associated mortality relative to a third dose in individuals ≥75 years of age. We estimated a protective effect for the bivalent BA.1 vaccine [adjusted hazard ratio (aHR) 0.08, 95% CI 0.02–0.32] relative to the bivalent BA.4–5 (aHR 0.27, 95% CI 0.14–0.56) and a monovalent dose (aHR 0.34, 95% CI 0.26–0.45) 2–9 weeks after vaccination compared with recipients with a third dose >24 weeks ago. The increased protective effect waned with no added protection for the monovalent vaccine after 33 weeks compared with a third dose.

Conclusions: Our results indicate an increased protective effect of a fourth dose against severe outcomes compared with a third dose, with decreasing effect with time since the last dose.

Keywords: Omicron, SARS-CoV-2, vaccine effectiveness, booster dose, bivalent vaccine

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Key Messages

- A fourth dose with a monovalent or bivalent vaccine (BA.1 or BA.4–5) provided additional protection against severe coronavirus disease 2019 (COVID-19)-related outcomes and all-cause mortality compared with only a third dose (>24 weeks ago) among individuals ≥75 years old in Norway.
- Our results indicate a waning protective effect of the fourth dose with a monovalent vaccine compared with the third dose, starting 10–17 weeks after vaccination.
- After 33 weeks, there was no additional protective effect of a fourth dose with a monovalent vaccine on severe COVID-19-related outcomes compared with a third dose (>24 weeks ago).
- The waning of a fourth dose seems important to consider when defining future COVID-19 booster vaccination strategies.

Introduction

Since December 2021, Omicron (B.1.1.529) has become the dominant severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant globally and a rapid increase in new coronavirus disease 2019 (COVID-19) cases was observed.[1]

Previous studies identified that the Omicron variants BA.4 and BA.5 show a substantial escape from vaccine or infection-induced neutralizing antibodies.[2,3] Thus, the initial monovalent messenger ribonucleic acid (mRNA) booster vaccines based on the original virus (Wuhan) may not provide a long-lasting protection against the new emerging variants.[4–6] However, the immune evasion seems to be less pronounced in individuals with hybrid immunity resulting from prior infection and vaccination.[4,7] To combat the weakened effectiveness of the monovalent BNT162b2 (Comirnaty, Pfizer-BioNTech) and mRNA-1273 (Spikevax, Moderna) COVID-19 vaccines, the bivalent mRNA booster vaccines, covering the original Wuhan virus and BA.4–5 or BA.1, were recently made available in most countries and implemented in the booster vaccination programmes, including for most vulnerable groups such as individuals aged ≥75 years as well as residents of long-term care facilities (LTCFs). The bivalent vaccines are expected to offer a broader immune response able to neutralize Omicron lineages.[8] Previous vaccine effectiveness (VE) studies of fourth doses mainly focused on the monovalent mRNA COVID-19 vaccines and periods prior to the emergence of the subvariants BA.4 and BA.5. Early results indicate that vaccination with the bivalent mRNA boosters as a fourth vaccine dose (second booster) increases protection against COVID-19-associated hospitalization and mortality compared with only receiving three doses (first booster).[9,10] In Norway, the fourth dose of COVID-19 vaccine became available in April 2022 but was not yet recommended for anyone. It was not until 1 July 2022 that a fourth dose was recommended for the most vulnerable groups, including those aged ≥75 years and residents of LTCFs.[11,12] Since September 2022, the adapted bivalent vaccines Comirnaty and Spikevax have become available in the COVID-19 vaccination programme in Norway.[11]

Real-world evidence on the durability of the protection and the effectiveness of the bivalent booster vaccines on severe COVID-19 outcome is needed. Therefore, our study aimed to compare the added protective effect of the fourth dose and the bivalent vaccines against COVID-19-associated mortality and all-cause mortality, COVID-19-associated hospitalization, as well as intensive care unit (ICU) admission among individuals ≥75 years of age in Norway.

Methods
Data collection and study population
We conducted a population-based cohort study and linked data from the National Emergency Preparedness Register (Beredt C19), which contains individual-level data from various registries in Norway. More details about the different data sources and Beredt C19 are provided in the Supplementary Table S2 (available as Supplementary data at *IJE* online). Relevant data was extracted on 13 February covering the study period from 1 July 2022 until 15 January 2023; 1 July 2022 was chosen because this is the date on which when the fourth dose was recommended for the most vulnerable groups in Norway.[12] We included all individuals aged ≥75 years with a national identity number in the Norwegian national registry who had received at least three vaccine doses by 1 July 2022, which comprised the base population. Individuals were excluded based on pre-defined criteria displayed in Figure 1 and Supplementary Text S1 (available as Supplementary data at *IJE* online).

Definition of outcome measures
The primary outcome measures in our study were (i) COVID-19-associated mortality and (ii) all-cause mortality, including individuals who died of other causes. Secondary outcome measures were (iii) COVID-19-associated hospitalization and (iv) COVID-19-associated ICU admission. More detailed information on definitions and adjustment variables is provided in Supplementary Text S1 and Table S1 (available as Supplementary data at *IJE* online).

Statistical analyses
Descriptive analyses were performed to present the socio-demographic characteristics of the overall study population as well as stratified by individuals who received a third dose and/or a fourth dose over the study period. In addition, we calculated the number of severe COVID-19-associated outcome measures and all-cause mortality during the study period. To provide more detailed information about the time at risk, we reported the number of person-years provided by individuals at risk until censoring or the occurrence of each event, stratified by the vaccine dose that individuals received.

Cox proportional hazard models were performed using the *coxph* function from the *survival* R-package[13] to estimate the adjusted hazard ratios (aHRs) on the primary and secondary outcomes measures. We estimated aHRs for individuals who received a fourth dose compared with those who had received the third dose >24 weeks ago. Vaccination status, a combination of time under risk since the last dose and vaccine type (for the fourth dose), was the main predictor and included in the model as a time-varying variable (more details on this time-varying variable are provided in Supplementary Table S3, available as Supplementary data at *IJE* online).[14] All models were stratified using pre-defined strata of age groups, sex, region of residence, risk group and whether an individual was a resident in a LTCF by applying *strata (function)* of the R *survival* package.[13] This allows the covariate combination to have non-proportional differences, i.e. groups are not assumed to have the same baseline hazard over time. The aHR was reported for all levels of the vaccine status factor. As subgroup analysis, we performed an additional Cox proportional hazard model that we stratified by LTCF residents to assess potential differences of lower vaccine-induced protection against the outcome measures among older people living at home and those living in LTCFs. The results are presented as aHRs with 95% confidence intervals (CIs). All analyses were performed using R Version 4.0.2.

Results
Study population
We included a total of 408 073 individuals, of whom 55.7 % (227 290) were female. A total of 23 209 individuals had already received a fourth dose by 1 July 2022. The median time to receive the fourth dose during the study period was 32 days (interquartile range 17–42 days). Detailed socio-demographic characteristics of the study population at baseline and by the vaccine dose that individuals received during the study period are shown in Table 1. Overall, a fourth dose was received by 319 582, of whom 81.1% (259 179) received a monovalent and 18.9% (60 403) a bivalent vaccine. Among bivalent recipients, 57.8% (34 881) and 42.3% (25 522) received a BA.1 and BA.4–5 dose, respectively. The proportion of individuals
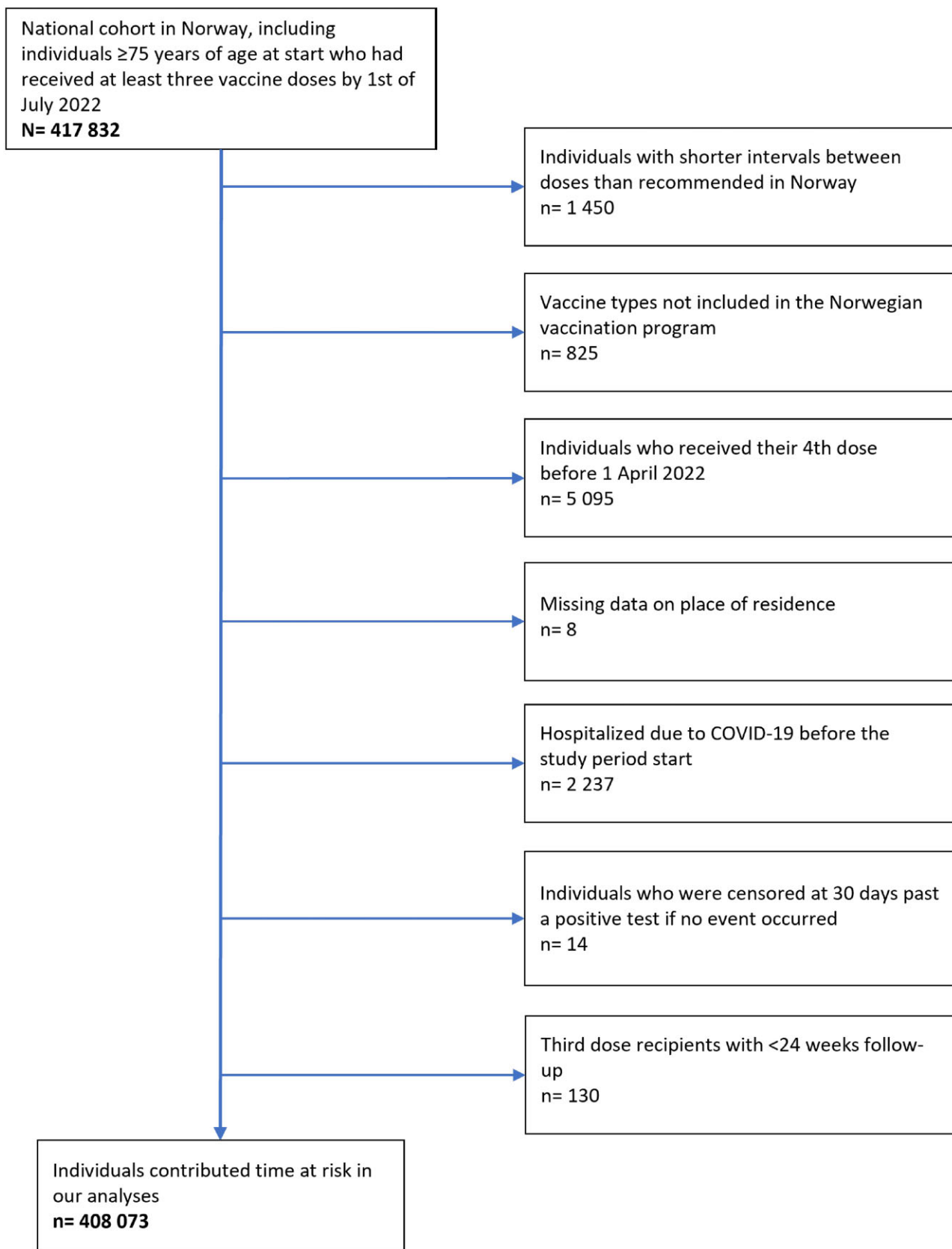
National cohort in Norway, including individuals ≥75 years of age at start who had received at least three vaccine doses by 1st of July 2022
N= 417 832

Individuals with shorter intervals between doses than recommended in Norway
n= 1 450

Vaccine types not included in the Norwegian vaccination program
n= 825

Individuals who received their 4th dose before 1 April 2022
n= 5 095

Missing data on place of residence
n= 8

Hospitalized due to COVID-19 before the study period start
n= 2 237

Individuals who were censored at 30 days past a positive test if no event occurred
n= 14

Third dose recipients with <24 weeks follow-up
n= 130

Individuals contributed time at risk in our analyses
n= 408 073

Figure 1. Flow chart of included individuals who contributed time at risk in our analyses

in the oldest age groups (>85 years) was slightly higher among monovalent recipients (24.8%; 64 007) compared with those who received a bivalent vaccine (BA.1: 18.8%; 6552; BA.4–5: 21.5%; 5494). The groups were comparable regarding high- and medium-risk groups, displayed in Table 1.

Table 1. Socio-demographic characteristics of the study population and stratified for individuals who received a third dose and/or a fourth dose over the study period

| | Study population | | Third-dose recipients[a] | | Fourth-dose recipients | | | | | |
| | | | | | Monovalent vaccine | | BA.1 bivalent vaccine | | BA.4–5 bivalent vaccine | |
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Sex										
Female	227 290	55.70	214 120	55.60	142 665	55.04	18 621	53.38	13 781	54.00
Male	180 783	44.30	170 744	44.40	116 514	44.96	16 260	46.62	11 741	46.00
Age (years)										
75–79	194 594	47.70	191 434	49.70	122 884	47.41	19 733	56.57	13 589	53.24
80–84	111 271	27.30	100 959	26.20	72 288	27.89	8596	24.64	6439	25.23
85–89	63 264	15.50	57 243	14.90	39 867	15.38	4355	12.49	3524	13.81
90+	38 944	9.50	35 228	9.20	24 140	9.31	2197	6.30	1970	7.72
Region										
Innlandet	36 022	8.80	33 868	8.80	22 451	8.66	3808	10.92	2072	8.12
Trøndelag	36 702	9.00	34 878	9	23 618	9.00	3038	9.00	1807	7.00
Nord-Norge	39 775	9.70	38 615	10.00	20 636	7.96	3683	10.56	3264	12.79
Oslo & Viken	133 582	32.70	123 735	32.20	87 962	33.94	10 611	30.42	9809	38.43
Agder & Sørøstlandet	60 375	14.80	56 980	14.80	38 368	14.80	5074	14.55	4052	15.88
Vestlandet	101 617	24.90	96 788	25.10	66 144	25.52	8667	24.85	4518	17.70
Risk group										
None	189 581	46.50	179 726	46.70	120 725	46.58	16 549	47.44	11 973	46.91
Medium	187 608	46.10	176 342	45.80	118 653	45.78	15 865	45.48	11 706	45.87
High	30 884	7.60	28 796	7.50	19 801	7.64	2467	7.07	1843	7.22
LTCF resident										
No	388 227	95.10	367 392	95.50	244 997	94.53	34 472	98.83	25 086	98.29
Yes	19 846	4.90	17 472	4.50	14 182	5.47	409	1.17	436	1.71

LTCF, long-term care facility. *n*, number.
[a] Individuals who received their third dose >24 weeks ago.

Amongst 408 073 individuals, 732 (0.2%) deaths were associated with COVID-19 and 13 430 (3.3%) deaths were not associated with COVID-19. A total of 2613 (0.6%) individuals were hospitalized with COVID-19 as the main reason for admission and 110 (0.03%) individuals were admitted to the ICU. More detailed information about the time at risk until each event occurred stratified by vaccine dose is displayed in Table 2 and Supplementary Table S4 (available as Supplementary data at *IJE* online).

The overall numbers of COVID-19-associated deaths, all-cause mortality, COVID-19-associated hospitalization and ICU admission during the study period in Norway is displayed in the epidemic curve in Supplementary Figure S1 (available as Supplementary data at *IJE* online) and the dominating SARS-CoV-2 variants in Norway in Supplementary Figure S2 (available as Supplementary data at *IJE* online).

Estimates of protection for COVID-19-associated mortality and all-cause mortality

The results of our Cox-regression analyses indicating an additional protective effect against COVID-19-associated mortality of a fourth dose for mono- and bivalent vaccines compared with having received a third dose >24 weeks ago, as all aHRs were <1. A fourth dose of both monovalent and bivalent vaccines show a high protection against COVID-19-associated mortality 2–9 weeks after vaccination. Although not statistically significant, a numerically higher protection was conferred by the BA.1 (aHR 0.08, 95% CI 0.02–0.32) relative to the BA.4–5 (aHR 0.27, 95% CI 0.14–0.56) and a monovalent dose (aHR 0.34, 95% CI 0.26–0.45), as displayed in Figure 2A. A protective effect of a fourth dose relative to a third dose was also identified for the outcome of all-cause mortality (Figure 2B). Receiving a bivalent fourth dose indicate a little higher protective effect (BA.1: aHR 0.33,

95% CI 0.28–0.40; BA.4–5: aHR 0.40, 95% CI 0.33–0.48) during weeks 2–9 after vaccination compared with a monovalent vaccine (aHR 0.55; 95% CI 0.52–0.58).

The protective effect waned over time for both primary outcome measures. After 33 weeks we did not identify an additional protective effect of a fourth dose with a monovalent vaccine on COVID-19-associated mortality (aHR 0.28, 95% CI 0.07–1.14) compared with a third dose >24 weeks ago (Figure 2A and B). The bivalent vaccines were implemented recently and therefore we could not estimate the protective effect after >17 weeks.

The results of the subgroup analysis for LTCF residents did not show any differences for the protective effect of COVID-19-associated mortality and all-cause mortality among individuals who received a fourth dose with a monovalent vaccine. The results are shown in Supplementary Table S5 (available as Supplementary data at *IJE* online).

Estimates of protection for COVID-19-associated hospitalization and ICU admission

Estimates for the secondary outcome measures of COVID-19-associated hospitalization and ICU admission were comparable to the primary outcome measures, elucidating a protective effect of a fourth dose compared with a third dose. We identified a waning of the protective effect for hospitalization after 17 weeks for the monovalent vaccines, with an aHR of 0.31 (95% CI 0.26–0.38) after 2–9 weeks to an aHR of 0.58 (95% CI 0.45–0.73) after 26–33 weeks (Figure 3A). The waning of the protective effect was less pronounced for ICU admission with greater uncertainty of the estimates (Figure 3B). Our results indicate that the protective effect seems to be slightly more pronounced for COVID-19-associated hospitalization compared with COVID-19-associated ICU admission during 2–9 weeks after vaccination. We did not identify differences

Table 2. Socio-demographic characteristics by primary outcome measure of COVID-19-associated mortality and all-cause mortality, with the time under risk in person-years for each event stratified by the vaccine dose

	Third-dose recipients[a]						Fourth-dose recipients																		
							Monovalent vaccine						BA.1 bivalent vaccine						BA.4–5 bivalent vaccine						
	Person-time[b]		COVID-19-associated mortality		All-cause mortality		Person-time[b]		COVID-19-associated mortality		All-cause mortality		Person-time[b]		COVID-19-associated mortality		All-cause mortality		Person-time[b]		COVID-19-associated mortality		All-cause mortality	
	Years	%	n	%	n	%	Years	%	n	%	n	%	Years	%	n	%	n	%	Years	%	n	%	n	%
Sex																								
Female	50 834	56.80%	194	47.90%	3503	53.10%	61 365	55.22%	154	49.52%	3678	57.17%	5314	53.44%	4	50.0%	115	48.12%	2522	54.07%	2	25.0%	82	51.25%
Male	38 718	43.20%	211	52.10%	3095	46.90%	49 758	44.78%	157	50.48%	2755	42.83%	4630	46.56%	4	50.0%	124	51.88%	2143	45.93%	6	75.0%	78	48.75%
Age (years)																								
75–79	43 998	49.10%	79	19.50%	1510	22.90%	51 701	46.53%	57	18.33%	1057	16.43%	5648	56.80%	2	25.0%	61	25.52%	2502	53.64%	4	50.0%	42	26.25%
80–84	23 589	26.30%	70	17.30%	1446	21.90%	31 723	28.55%	58	18.65%	1346	20.92%	2444	24.57%	2	25.0%	41	17.15%	1169	25.07%	0	–	36	22.50%
85–89	13 689	15.30%	102	25.20%	1605	24.30%	17 388	15.65%	82	26.37%	1651	25.66%	1230	12.37%	1	12.5%	73	30.54%	636	13.63%	2	25.0%	42	26.25%
90+	8275	9.20%	154	38.00%	2037	30.90%	10 311	9.28%	114	36.66%	2379	36.98%	623	6.26%	3	37.5%	64	27.00%	358	8.00%	2	25.0%	40	25.00%
Region																								
Innlandet	8305	9.30%	33	8.10%	592	9.00%	9157	8.00%	31	9.97%	570	8.86%	1145	11.51%	3	37.5%	29	12.13%	409	8.76%	0	–	18	11.25%
Trøndelag	8205	9.20%	27	6.70%	604	9.20%	10 046	9.04%	27	8.68%	596	9.26%	847	8.52%	1	12.5%	23	9.62%	281	6.01%	1	12.5%	10	6.25%
Nord-Norge	10 978	12.30%	40	9.90%	739	11.20%	8403	7.56%	22	7.07%	514	7.99%	1000	10.06%	0	0.0%	16	6.69%	565	12.11%	0	–	16	10.00%
Oslo & Viken	27 028	30.20%	132	32.60%	1948	29.50%	38 520	34.66%	109	35.05%	2155	33.50%	3004	30.21%	2	25.0%	68	28.45%	1924	41.25%	3	37.5%	54	33.75%
Agder & Sørøstlandet	13 006	14.50%	46	11.40%	975	14.80%	16 673	15.00%	39	12.54%	975	15.16%	1473	14.81%	0	–	27	11.30%	739	15.85%	3	37.5%	39	24.38%
Vestlandet	22 031	24.60%	127	31.40%	1740	26.40%	28 324	25.49%	83	26.69%	1623	25.23%	2475	24.89%	2	25.0%	76	31.80%	747	16.01%	1	12.5%	23	14.38%
Risk group																								
None	42 089	47.00%	120	29.60%	1929	29.20%	51 804	46.62%	113	36.00%	2010	31.00%	4741	48.00%	3	37.5%	76	31.80%	2211	47.40%	2	25.0%	46	28.75%
Medium	41 036	45.80%	220	54.30%	3622	54.90%	50 849	45.76%	165	53.05%	3555	55.26%	4505	45.31%	4	50.0%	126	52.72%	2120	45.45%	5	62.5%	91	56.88%
High	6427	7.20%	65	16.00%	1047	15.90%	8469	7.62%	33	10.61%	868	13.49%	698	7.02%	1	12.5%	37	15.00%	334	7.00%	1	12.5%	23	14.00%
LTCF resident																								
No	86 319	96.40%	277	68.40%	5096	77.20%	10 5061	94.55%	163	52.41%	3999	62.16%	9829	98.85%	8	100.0%	213	89.12%	4592	98.44%	8	100.0%	137	85.63%
Yes	3233	3.60%	128	31.60%	1502	22.80%	6061	5.45%	148	47.59%	2434	37.84%	115	1.16%	0	–	26	10.88%	73	1.56%	0	–	23	14.38%

LTCF, long-term care facility; COVID-19, coronavirus disease 2019; n, number.
[a] Individuals who received their third dose >24 weeks ago.
[b] The time under risk for third- and fourth-dose recipients until censoring or occurrence of the respective event.
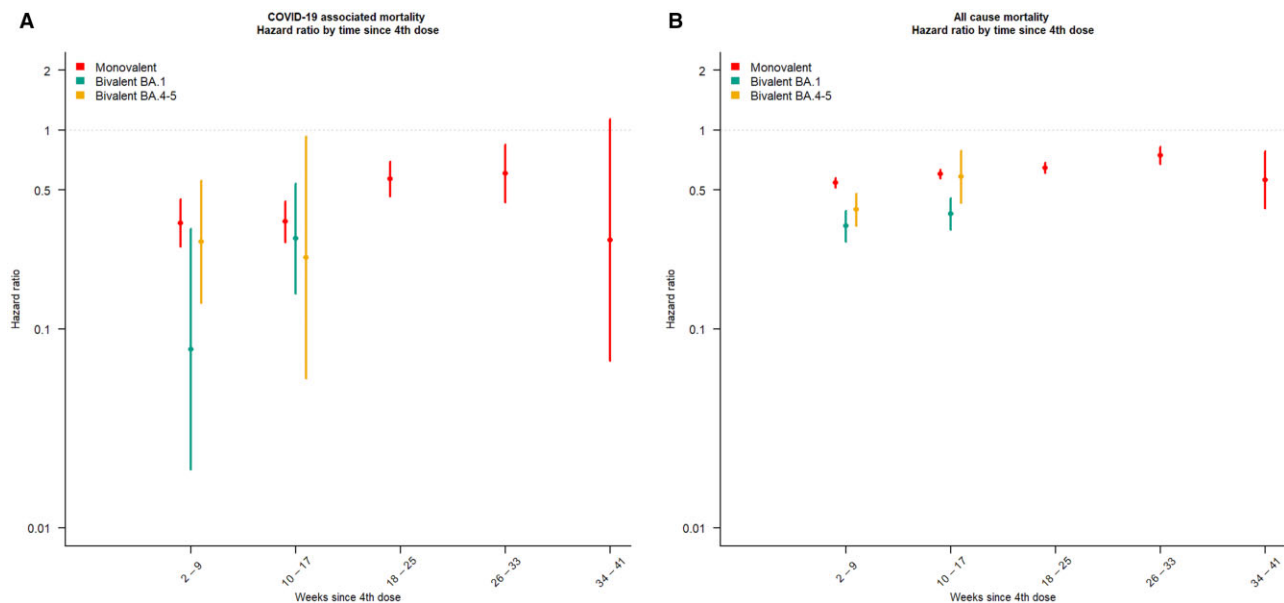
Figure 2. The adjusted hazard ratio (aHR) estimates for (A) COVID-19-associated mortality and (B) all-cause mortality by vaccination with an mRNA booster among all individuals living in Norway with a valid national identity number and aged ≥75 years. Fourth dose, >7 days after a fourth COVID-19 vaccine dose was given with either a monovalent or bivalent (BA.1 or BA.4–5) vaccine. ≥24 weeks since the third dose was used as reference level. The Cox proportional hazard model is stratified for age, sex, risk group, resident in long-term care facility 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 for all vaccination statuses

for the protective effect against ICU admission when comparing bivalent BA.1 with BA.4–5 and monovalent doses (Figure 3A and B).

Discussion

Our population-based cohort study among individuals aged ≥75 years in Norway shows that a fourth dose with a monovalent or bivalent vaccine provided additional protection against severe COVID-19-related outcomes and all-cause mortality than a third dose >24 weeks ago during an Omicron dominating period (Supplementary Figure S2, available as Supplementary data at *IJE* online).

The current recommendations for the bivalent COVID-19 vaccines are mainly based on evidence from immunogenicity studies indicating a greater response against current circulating Omicron lineages.[15,16] But current evidence on the real-world effectiveness of the fourth COVID-19 dose and bivalent vaccines in older people is sparse. Our population-based study provides complementary evidence to existing studies because of the larger study population and longer follow-up.[9,17] In addition, we were able to compare the effect of the different vaccines, BA.1, BA.4–5 and the monovalent vaccine used for the fourth dose over time.

Protective effect for COVID-19-associated outcome measures and all-cause mortality

In our study, we identified high protection against severe COVID-19-associated outcome measures and all-cause mortality for both monovalent and bivalent vaccines (BA.1 and BA.4–5) ≤17 weeks after vaccination, in a period when various Omicron lineages circulated predominantly in Norway. These findings are consistent with previous studies, although different methods, definitions and follow-up times were used, which indicate similar results regarding the protective durability among older people and most vulnerable groups.[17–20]

Comparable levels of protection were identified in a cohort study from Israel covering a shorter follow-up period, which estimated a protective effect for COVID-19-associated mortality (aHR 0.32, 95% CI 0.18–0.58) and hospitalization (aHR 0.28, 95% CI 0.19–0.40) in individuals aged ≥65 years for ≤120 days by comparing individuals who received a bivalent vaccine with those who were unvaccinated.[9] A recent study from Sweden compared the VE of a third and fourth dose against all-cause mortality in individuals aged >80 years and reported a greater protective effect in those living in a LTCF (61%, 95% CI 58–64%) compared with those living at home (50%, 95% CI 46–54%).[17] Whereby stratifying our analysis according to residential status did not appreciably impact our results for a monovalent vaccine on COVID-19-associated mortality and all-cause mortality. Since the group of LTCF residents were prioritized in the vaccination programme and therefore were vaccinated before the bivalent vaccines were introduced, the number of LTCF residents with bivalent vaccines was very low and therefore the protective effect could not be estimated.

The protective effect for all-cause mortality identified in the Swedish study[17] was also found in our analyses. Even though our models were adjusted for demographic data and risk factors for severe COVID-19-associated outcomes, which decreases the risk of bias, we cannot rule out that the protective effect estimates might be overestimated due to the healthy vaccinee bias.[21,22] As all-cause mortality is a relatively unspecific outcome measure, our results can also be biased due to factors that we insufficiently corrected for in our models.

During the winter season, viral infections such as influenza and respiratory syncytial virus are more prevalent, with an increased risk of mortality, particularly among older people and individuals with underlying health conditions. Thus, the results might indicate that vaccination with the updated vaccines before the winter could have provided additional protection against all-cause mortality during the winter season.
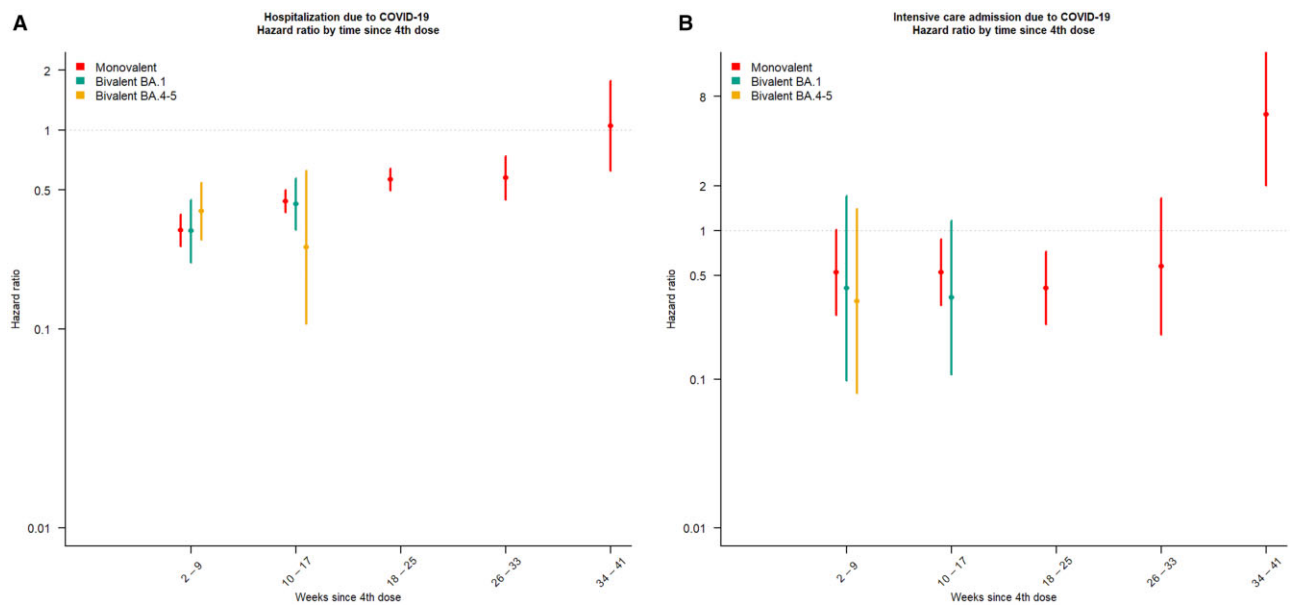
Figure 3. The adjusted hazard ratio (aHR) estimates for COVID-19-associated (A) hospitalization and (B) intensive care unit admission by vaccination with an mRNA booster among all individuals living in Norway with a valid national identity number and aged ≥75 years. Fourth dose, >7 days after a fourth COVID-19 vaccine dose was given with either a monovalent or bivalent (BA.1 or BA.4–5) vaccine. The results of the Cox proportional hazard model are stratified for age, sex, risk group, resident in a long-term care facility 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

Waning of the protective effect against COVID-19-associated severe outcomes

We could not estimate the protective effect of the bivalent vaccine for >17 weeks after vaccination due to the recent introduction of these vaccines. Additionally, the estimated effect for the bivalent vaccines can be biased for the time 10–17 weeks after vaccination due to a different time under risk. Some bivalent recipients in our study had a shorter time at risk and therefore less time for the waning effect to become visible. However, our results indicate a waning protective effect of the fourth dose with a monovalent vaccine compared with the third dose for all vaccines, starting 10–17 weeks after vaccination. A substantial waning immunity after this period was also found in previous studies.[17,23] The waning of a fourth dose among older people seems therefore to be important to consider when defining future booster vaccination strategies.[24,25]

Differences between mono- and bivalent COVID-19 vaccines as fourth dose

Up to now, only limited data have been available to identify differences in VE between bivalent and monovalent vaccines as a fourth dose. Recent findings from North Carolina, USA identified a VE of 61.5% (95% CI 47.1–71.9%) against hospitalization or deaths among individuals aged ≥65 years who received a bivalent dose; the protective effect was 41.2% higher compared with a monovalent dose (20.3%, 95% CI −6.0–40.1%).[18] In our study, we did not identify a clear indication that the bivalent vaccines were superior to a monovalent fourth dose against COVID-19-related outcome measures. However, the protective effect with a bivalent COVID-19 vaccine seemed to be generally slightly higher against all-cause mortality compared with a monovalent vaccine. Nevertheless, this outcome measure is potentially more likely to be biased due to other factors that have not been considered in our models.

Even though we did not identify huge differences between baseline characteristics, such as risk group, sex and age, between third- and fourth-dose recipients, the most vulnerable groups had been prioritized for the fourth-dose roll-out and were vaccinated with a monovalent vaccine due to the availability (see Supplementary Figure S3, available as Supplementary data at *IJE* online), which could also have raised their risk for severe outcome and led to bias of the estimates when comparing mono- and bivalent vaccines.

Some of the latest study findings might indicate that the bivalent vaccines potentially improve and broaden the protection during the Omicron period.[9,18] However, more real-world evidence with longer and larger-sized follow-up data is needed. Therefore, continued monitoring will be important to fully understand the durability of protection of the mono- and bivalent vaccines with the emergence of Omicron sub-lineages and new COVID-19 variants over time.

Limitations

Our study has several limitations. First, the limits of a register-based cohort study should be considered when interpreting the results, as the data were not collected for the purpose of our study only. Second, we should consider that in some cases the outcome of COVID-19-associated mortality may have not directly been caused by SARS-CoV-2. To provide a broader picture of our results, we also included a model on all-cause mortality in our analyses. Third, we could not consider prior infections during the Omicron period because mandatory public testing was stopped mid-January 2022, thus data on infections were no longer reliable after this. Therefore, we could not differentiate between the protective effect of hybrid immunity compared with vaccine-only immunity, which could have led to biased VE estimates.[26,27] However, we excluded individuals who had been previously hospitalized due to COVID-19 to minimize bias. Fourth, even though the models were adjusted for the presence of underlying risk for a severe COVID-19-associated outcome, the

severity of the disease and not only the presence could affect the observed differences of the protective effects. In addition, the number of events was relatively small for mortality and ICU admissions, which could have amplified any differences in the protective effect between monovalent and bivalent vaccines. Fifth, our results present estimates on VE during the predominant Omicron period among individuals ≥75 years old and are not generalizable for other age groups and other time periods. Finally, the number of events in specific strata pertaining to COVID-19-associated mortality and ICU admission outcomes were low, warranting careful consideration when interpreting the results. Nonetheless, the overall protective effect of the COVID-19 vaccines for all outcome measures remained robust during the initial 17 weeks after the fourth dose.

Conclusions

Our analyses provide important evidence on the protective effect and durability of a fourth dose of monovalent and bivalent vaccines BA.1 and BA.4–5 during the predominant Omicron period among individuals ≥75 years of age in Norway. Even though the additional protective effect of the fourth dose waned with time since vaccination, both monovalent and bivalent vaccines showed a high additional protective effect against severe COVID-19 outcomes when compared with a third dose. Our results contribute to the increasing evidence suggesting that the level of protection against severe outcomes seems to wane with the length of time since the last dose within individuals aged ≥75 years.

Ethics approval

This project was performed under the ethics approval that was granted by the Regional Committees for Medical and Health Research Ethics (REC) Southeast (reference number 122745). The Norwegian Institute of Public Health has performed a Data Protection Impact Assessment for Beredt C19.

Data availability

The data sets analysed during the current study come from the national emergency preparedness registry for COVID-19 (Beredt C19), housed at the Norwegian Institute of Public Health. The preparedness registry comprises data from a variety of central health registries, national clinical registries and other national administrative registries. Legal restrictions prevent the researchers from sharing the data set used in the study. 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 the normal procedure for conducting health research on registry data in Norway (https://www.helsedata.no). Further information on the preparedness registry, including access to data from each data source, is available at https://www.fhi.no/en/id/corona/coronavirus/emergency-preparedness-register-for-covid-19/. Code and model results in summary from R are available from the author.

Supplementary data

Supplementary data are available at *IJE* online.

Author contributions

J.S., M.H. and M.S. developed the concept and design for the study. J.S. and M.S. performed data analyses, A.B.K. and M.S. verified the underlying data and model code. M.S. and J.S. interpreted the data and drafted the manuscript. All authors had the opportunity to request data access. All authors read and gave critical feedback on the manuscript and approved the final version.

Conflict of interest

None declared.

References

1. World Health Organization. *Tracking SARS-CoV-2 Variants*. 2023. https://www.who.int/activities/tracking-SARS-CoV-2-variants (28 February 2023, date last accessed).
2. Cele S, Jackson L, Khoury DS *et al.*; COMMIT-KZN Team. Omicron extensively but incompletely escapes Pfizer BNT162b2 neutralization. *Nature* 2022;**602**:654–56.
3. Liu L, Iketani S, Guo Y *et al.* Striking antibody evasion manifested by the Omicron variant of SARS-CoV-2. *Nature* 2022;**602**:676–81.
4. Hachmann NP, Miller J, Collier AY *et al.* Neutralization escape by SARS-CoV-2 Omicron subvariants BA.2.12.1, BA.4, and BA.5. *N Engl J Med* 2022;**387**:86–88.
5. Edara VV, Manning KE, Ellis M *et al.* mRNA-1273 and BNT162b2 mRNA vaccines have reduced neutralizing activity against the SARS-CoV-2 Omicron variant. *Cell Rep Med* 2022;**3**:100529.
6. Lyke KE, Atmar RL, Islas CD *et al.*; DMID 21-0012 Study Group. Rapid decline in vaccine-boosted neutralizing antibodies against SARS-CoV-2 Omicron variant. *Cell Rep Med* 2022;**3**:100679.
7. Bobrovitz N, Ware H, Ma X *et al.* Protective effectiveness of previous SARS-CoV-2 infection and hybrid immunity against the omicron variant and severe disease: a systematic review and meta-regression. *Lancet Infect Dis* 2023;**23**:556–67.
8. Chalkias S, Harper C, Vrbicky K *et al.* A bivalent Omicron-containing booster vaccine against Covid-19. *N Engl J Med* 2022;**387**:1279–91.
9. Arbel R, Peretz A, Sergienko R *et al.* Effectiveness of a bivalent mRNA vaccine booster dose to prevent severe COVID-19 outcomes: a retrospective cohort study. *Lancet Infect Dis* 2023;**23**:914–21.

10. Andersson NW, Thiesson EM, Baum U *et al.* Comparative effectiveness of bivalent BA.4-5 and BA.1 mRNA booster vaccines among adults aged ≥50 years in Nordic countries: nationwide cohort study. 2023;**382**:e075286.

11. Norwegian Institute of Public Health. *Coronavirus Vaccine—Information for the Public.* 2023. https://www.fhi.no/en/id/vaccines/coronavirus-immunisation-programme/coronavirus-vaccine/#booster-doses (28 February 2023, date last accessed).

12. Norwegian Institute of Public Health. *Informasjonsbrev nr 47 om Koronavaksinasjonsprogrammet [Information Letter No. 47 About the Corona Vaccination Programme].* 2022. https://www.fhi.no/publ/brev/informasjonsbrev-nr-47-om-koronavaksinasjonsprogrammet/ (7 July 2023, date last accessed).

13. Therneau TM. *A Package for Survival Analysis in R. R Package Version 3.5-5.* 2023. https://CRAN.R-project.org/package=survival (7 July 2023, date last accessed).

14. European Centre for Disease Prevention and Control. *Protocol for a COVID-19 Vaccine Effectiveness Study Using Health Data Registries: Stockholm ECDC.* Report No.: 1.0. 2023. https://www.ecdc.europa.eu/en/publications-data/protocol-covid-19-vaccine-effectiveness-study-using-health-data-registries.

15. Wang Q, Bowen A, Valdez R *et al.* Antibody response to Omicron BA.4-BA.5 bivalent booster. *N Engl J Med* 2023;**388**:567–69.

16. Zou J, Kurhade C, Patel S *et al.* Neutralization of BA.4–BA.5, BA.4.6, BA.2.75.2, BQ.1.1, and XBB.1 with bivalent vaccine. *N Engl J Med* 2023;**388**:854–57.

17. Nordström P, Ballin M, Nordström A. Effectiveness of a fourth dose of mRNA COVID-19 vaccine against all-cause mortality in long-term care facility residents and in the oldest old: a nationwide, retrospective cohort study in Sweden. *Lancet Reg Health Eur* 2022;**21**:100466.

18. Lin DY, Xu Y, Gu Y *et al.* Effectiveness of bivalent boosters against severe Omicron infection. *N Engl J Med* 2023;**388**:764–66.

19. Tenforde MW, Weber ZA, Natarajan K *et al.* Early estimates of bivalent mRNA vaccine effectiveness in preventing COVID-19-associated emergency department or urgent care encounters and hospitalizations among immunocompetent adults—VISION network, nine states, September-November 2022. *MMWR Morb Mortal Wkly Rep* 2023;**72**:579–88.

20. Andersson NW, Thiesson EM, Baum U *et al.* Comparative effectiveness of the bivalent BA.4–5 and BA.1 mRNA-booster vaccines in the Nordic countries. *medRxiv*; https://doi.org/10.1101/2023.01.19.23284764, 19 January 2923, preprint: not peer reviewed.

21. Hosseini-Moghaddam SM, He S, Calzavara A, Campitelli MA, Kwong JC. Association of influenza vaccination with SARS-CoV-2 infection and associated hospitalization and mortality among patients aged 66 years or older. *JAMA Netw Open* 2022;**5**:e2233730.

22. Nelson JC, Jackson ML, Weiss NS, Jackson LA. New strategies are needed to improve the accuracy of influenza vaccine effectiveness estimates among seniors. *J Clin Epidemiol* 2009;**62**:687–94.

23. Bar-On YM, Goldberg Y, Mandel M *et al.* Protection by a fourth dose of BNT162b2 against Omicron in Israel. *N Engl J Med* 2022;**386**:1712–20.

24. Arregocés-Castillo L, Fernández-Niño J, Rojas-Botero M *et al.* Effectiveness of COVID-19 vaccines in older adults in Colombia: a retrospective, population-based study of the ESPERANZA cohort. *Lancet Healthy Longev* 2022;**3**:e242–52.

25. Ferdinands JM, Rao S, Dixon BE *et al.* Waning of vaccine effectiveness against moderate and severe covid-19 among adults in the US from the VISION network: test negative, case-control study. *BMJ* 2022;**379**:e072141.

26. Malato J, Ribeiro RM, Fernandes E *et al.* Stability of hybrid versus vaccine immunity against BA.5 infection over 8 months. *Lancet Infect Dis* 2023;**23**:148–50.

27. Bozio CH, Butterfield KA, Briggs Hagen M *et al.* Protection from COVID-19 mRNA vaccination and prior SARS-CoV-2 infection against COVID-19-associated encounters in adults during Delta and Omicron predominance. *J Infect Dis* 2023;**227**:1348–63.