



Comparative effectiveness of bivalent BA.4-5 and BA.1 mRNA booster vaccines among adults aged ≥ 50 years in Nordic countries: nationwide cohort study

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ABSTRACT OBJECTIVE

To estimate the effectiveness of the bivalent mRNA booster vaccines containing the original SARS-CoV-2 and omicron BA.4-5 or BA.1 subvariants as the fourth dose against severe covid-19.

DESIGN

Nationwide cohort analyses, using target trial emulation.

SETTING

Denmark, Finland, Norway, and Sweden, from 1 July 2022 to 10 April 2023.

PARTICIPANTS

People aged ≥ 50 years who had received at least three doses of covid-19 vaccine (that is, a primary course and a first booster).

MAIN OUTCOME MEASURES

The Kaplan-Meier estimator was used to compare the risk of hospital admission and death related to covid-19 in people who received a bivalent Comirnaty (Pfizer-BioNTech) or Spikevax (Moderna) BA.4-5 or BA.1 mRNA booster vaccine as a fourth dose (second booster) with three dose (first booster) vaccinated people and between four dose vaccinated people.

RESULTS

A total of 1 634 199 people receiving bivalent BA.4-5 fourth dose booster and 1 042 124 receiving bivalent BA.1 fourth dose booster across the four Nordic countries were included. Receipt of a bivalent BA.4-5 booster as a fourth dose was associated with a comparative vaccine effectiveness against admission

to hospital with covid-19 of 67.8% (95% confidence interval 63.1% to 72.5%) and a risk difference of -91.9 (95% confidence interval -152.4 to -31.4) per 100 000 people at three months of follow-up compared with having received three doses of vaccine (289 v 893 events). The corresponding comparative vaccine effectiveness and risk difference for bivalent BA.1 boosters (332 v 977 events) were 65.8% (59.1% to 72.4%) and -112.9 (-179.6 to -46.2) per 100 000, respectively. Comparative vaccine effectiveness and risk difference against covid-19 related death were 69.8% (52.8% to 86.8%) and -34.1 (-40.1 to -28.2) per 100 000 for bivalent BA.4-5 booster (93 v 325 events) and 70.0% (50.3% to 89.7%) and -38.7 (-65.4 to -12.0) per 100 000 for BA.1 booster (86 v 286) as a fourth dose. Comparing bivalent BA.4-5 and BA.1 boosters as a fourth dose directly resulted in a three month comparative vaccine effectiveness and corresponding risk difference of -14.9% (-62.3% to 32.4%) and 10.0 (-14.4 to 34.4) per 100 000 people for admission to hospital with covid-19 (802 v 932 unweighted events) and -40.7% (-123.4% to 42.1%) and 8.1 (-3.3 to 19.4) per 100 000 for covid-19 related death (229 v 243 unweighted events). The comparative vaccine effectiveness did not differ across sex and age (≤ 70 years) and seemed to be sustained up to six months from the day of vaccination with modest waning.

CONCLUSION

Vaccination with bivalent BA.4-5 or BA.1 mRNA booster vaccines as a fourth dose was associated with reduced rates of covid-19 related hospital admission and death among adults aged ≥ 50 years. The protection afforded by the bivalent BA.4-5 and BA.1 boosters did not differ significantly when directly compared, and any potential difference would most likely be very small in absolute numbers.

Introduction

Fourth dose (that is, second booster) vaccination to improve protection against severe and fatal covid-19 outcomes in target populations are now recommended in many countries. To combat the attenuated efficacy of the original monovalent BNT162b2 (Comirnaty; Pfizer-BioNTech) and mRNA-1273 (Spikevax; Moderna) mRNA covid-19 vaccines observed against the omicron variants compared with other variants,¹⁻³ bivalent mRNA booster vaccines, containing spike sequences from the original (ancestral) SARS-CoV-2 strain and omicron subvariants (BA.4-5 or BA.1), were authorised for use in autumn 2022 and subsequently implemented

WHAT IS ALREADY KNOWN ON THIS TOPIC

The omicron adapted bivalent mRNA booster vaccines containing the original SARS-CoV-2 and omicron BA.4-5 or BA.1 subvariants are now implemented in many covid-19 booster vaccination programmes

Data to evaluate the clinical effectiveness of the bivalent BA.4-5 and BA.1 mRNA booster vaccines against severe covid-19 are limited, and studies on immunogenicity have shown diverging results

WHAT THIS STUDY ADDS

Vaccination of adults aged ≥ 50 years with a bivalent booster vaccine as a fourth dose was associated with lower rates of covid-19 related hospital admission and death at three months of follow-up

Effectiveness was well preserved at six months of follow-up

Any potential difference between the protection afforded by the BA.4-5 and the BA.1 mRNA boosters against severe covid-19 seem to be very small in absolute numbers

in booster vaccination programmes including in the Nordic countries.

Although some clinical studies have shown that the bivalent BA.4-5 and BA.1 mRNA booster vaccines increase neutralising antibody responses against omicron compared with the original monovalent mRNA covid-19 vaccines, others have not.⁴⁻⁸ Data on the effectiveness of the bivalent mRNA booster vaccines to protect against severe covid-19 outcomes are scarce,⁹⁻¹⁵ and previous knowledge on the effectiveness of a fourth covid-19 vaccine dose is mostly based on studies of the monovalent vaccines.¹⁶⁻³² In nationwide cohort analyses in Denmark, Finland, Norway, and Sweden, we assessed the comparative effectiveness of the bivalent BA.4-5 or BA.1 mRNA booster vaccines received as the fourth dose against covid-19 related hospital admission and death among adults aged ≥ 50 years.

Methods

Data sources and source populations

All four Nordic countries hold nationwide demography and healthcare registers with individual level data that can be linked using the country specific unique identifiers assigned to all residents. With linkage of these registers, we obtained information on covid-19 vaccinations and laboratory confirmed SARS-CoV-2 infections and hospital admissions, as well as the presence or absence of selected comorbidities (chronic pulmonary disease, cardiovascular conditions and diabetes, autoimmunity related conditions, cancer, and renal disorders), and demographic variables (age, sex, residency, healthcare occupation, and vital status) (see supplementary tables S1-S2 for further details on registers and definitions of variables). Within each country, we established a source population of people who were known residents and had received at least three vaccine doses (that is, a primary two dose vaccination course and one booster) with the AZD1222 (Vaxzevria; Oxford-AstraZeneca; as part of the primary course only), monovalent (original) BNT162b2, and/or monovalent (original) mRNA-1273 vaccines from 27 December 2020 to 10 April 2023 in Denmark, 7 April 2023 in Finland, 1 April 2023 in Norway, and 31 December 2022 in Sweden (last day of data availability within each country at time of analysis). See supplementary table S3 for a description of ethical approvals/exemptions.

Study cohorts

To be included in our study, people must not have received the third or fourth vaccine dose within 90 days after the second or third dose (to ensure that the received third or fourth doses were truly first or second booster doses), respectively; be younger than a country specific lower age limit of 50 years in Denmark and Sweden, 60 in Finland, and 65 in Norway; or have received the fourth dose before 1 September 2022 in Denmark, 18 July 2022 in Finland, and 1 July 2022 in Norway and Sweden (the last two criteria were defined according to respective health authorities' fourth dose

rollout strategy for the general target population). Omicron BA.5 was the predominant sublineage until late autumn 2022; since then, multiple sublineages have been circulating, primarily sublineages of BQ, BF, and XBB. We classified any fourth vaccine dose according to whether it was a bivalent BA.4-5, bivalent BA.1, or monovalent (original) mRNA booster vaccine regardless of vaccine brand. We considered any comparison that included monovalent fourth dose vaccination as an additional comparison analysis.

Outcomes

We defined covid-19 related hospital admission as admission to hospital as an inpatient with a registered covid-19 related diagnosis and a positive polymerase chain reaction (PCR) test for SARS-CoV-2 (tested positive within 14 days before to two days after the day of admission) (see supplementary table S4 for country specific outcome definitions). We defined covid-19 related death as death within 30 days of a positive PCR test for SARS-CoV-2 in Denmark, Finland, and Sweden, whereas we used covid-19 specific diagnoses registered as the main cause of death in Norway (owing to data availability). The day of admission or death served as the respective event date.

Comparisons

Fourth dose compared with third dose vaccinated

We used a matched design to assess the effectiveness of receipt of a bivalent BA.4-5 or BA.1 mRNA booster vaccine as the fourth dose compared with previous receipt of three monovalent vaccine doses. We matched people who received a fourth dose during follow-up on this vaccination day with those who had not yet received a fourth dose. We matched people (exactly; without replacement) on age (5 year bins), the calendar month of third dose vaccination, and a propensity score including sex, region of residence, vaccination priority groups (that is, people at high risk of severe covid-19 or healthcare workers), selected comorbidities, and previous history of SARS-CoV-2 infection (supplementary table S2). The day the fourth dose was administered within each matched pair served as the index date for both individuals. If people who were included as a matched three dose vaccinated (that is, a reference) individual received a fourth dose later than the assigned index date, they were allowed to potentially re-enter as a fourth dose recipient in a new matched pair on that date. See supplementary figure S1 for a graphical illustration of our matched four versus three dose study design.

Fourth dose comparisons by type of vaccine

We compared the effectiveness of fourth dose vaccination with the bivalent BA.4-5 and BA.1 boosters directly while using stabilised inverse probability of treatment weights to take into account the covariates of calendar month of fourth dose vaccination, age, sex, region of residence, vaccination priority groups, selected comorbidities, and previous history of SARS-CoV-2 infection (supplementary table S2). The day of

Table 1 | Baseline characteristics of study cohorts in four versus three dose and four versus four dose comparisons for estimating effectiveness of bivalent BA.4-5 or BA.1 mRNA booster vaccination as fourth vaccine dose in four Nordic countries. Values are numbers (percentages) unless stated otherwise

Characteristic	Four v three dose vaccinated comparison				Four v four dose vaccinated comparison	
	Matched		Matched		BA.4-5 booster as fourth dose	BA.1 booster as fourth dose
	BA.4-5 booster as fourth dose	Third dose	BA.1 booster as fourth dose	Third dose		
No of individuals						
Total	1 233 741	123 3741	932 846	932 846	1 634 199	1 042 124
Denmark	748 648	748 648	471 810	471 810	1 130 045	567 033
Finland	146 007	146 007	74 690	74 690	156 480	79 333
Norway	87 481	87 481	128 833	128 833	89 670	131 832
Sweden	251 605	251 605	257 513	257 513	258 004	263 926
Mean (SD) age, years						
Denmark	64.5 (10)	64.4 (10.1)	71.3 (10.3)	71.2 (10.4)	65.8 (10)	72.5 (10.5)
Finland	71.6 (7.2)	71.5 (7.2)	71.3 (7.1)	71.2 (7.1)	71.9 (7.4)	71.5 (7.3)
Norway	72.5 (6.4)	72.5 (6.5)	72 (6)	72.1 (6.1)	72.6 (6.5)	72.1 (6)
Sweden	60.8 (7.8)	60.8 (7.8)	60.8 (8)	60.8 (8)	60.9 (7.9)	60.9 (8.1)
Female sex						
Denmark	383 413 (51.2)	378 736 (50.6)	261 828 (55.5)	254 519 (53.9)	582 724 (51.6)	316 979 (55.9)
Finland	79 063 (54.2)	78 338 (53.7)	39 760 (53.2)	39 896 (53.4)	85 151 (54.4)	42 322 (53.3)
Norway	43 966 (50.3)	44 958 (51.4)	65 619 (50.9)	66 113 (51.3)	45 123 (50.3)	67 155 (50.9)
Sweden	130 651 (51.9)	124 228 (49.4)	138 942 (54)	132 471 (51.4)	134 233 (52)	142 887 (54.1)
Calendar period, min to max						
Denmark	23/09/22 to 12/04/23	23/09/22 to 12/04/23	19/09/22 to 12/04/23	19/09/22 to 12/04/23	16/09/22 to 31/03/23	12/09/22 to 30/03/23
Finland	11/08/22 to 07/04/23	11/08/22 to 07/04/23	30/08/22 to 07/04/23	30/08/22 to 07/04/23	04/08/22 to 30/03/23	23/08/22 to 30/03/23
Norway	20/09/22 to 10/04/23	20/09/22 to 10/04/23	13/09/22 to 10/04/23	13/09/22 to 10/04/23	13/09/22 to 01/04/23	06/09/22 to 27/03/23
Sweden	25/07/22 to 31/12/22	25/07/22 to 31/12/22	11/08/22 to 31/12/22	11/08/22 to 31/12/22	18/07/22 to 23/12/22	04/08/22 to 23/12/22
Vaccination priority groups						
Severe covid-19 risk group:						
Denmark	26 395 (3.5)	30 362 (4.1)	33 641 (7.1)	39 104 (8.3)	46 171 (4.1)	53 082 (9.4)
Finland	15 502 (10.6)	14 974 (10.3)	8186 (11.0)	7782 (10.4)	16 598 (10.6)	8677 (10.9)
Norway	715 (0.8)	977 (1.1)	566 (0.4)	576 (0.4)	826 (0.9)	598 (0.5)
Sweden	327 (0.1)	327 (0.1)	808 (0.3)	639 (0.2)	405 (0.2)	914 (0.3)
Healthcare workers:						
Denmark	57 048 (7.6)	67 321 (9.0)	25 484 (5.4)	25 163 (5.3)	88 933 (7.9)	27 418 (4.8)
Finland	3562 (2.4)	3109 (2.1)	1605 (2.1)	1258 (1.7)	4260 (2.7)	1879 (2.4)
Norway	3287 (3.8)	3906 (4.5)	4703 (3.7)	5678 (4.4)	3367 (3.8)	4794 (3.6)
Sweden	26 013 (10.3)	28 989 (11.5)	31 176 (12.1)	33 888 (13.2)	26 977 (10.5)	32 332 (12.3)
Comorbidities						
Autoimmune related condition:						
Denmark	27 983 (3.7)	27 193 (3.6)	20 702 (4.4)	20 812 (4.4)	43 542 (3.9)	25 353 (4.5)
Finland	5848 (4.0)	5223 (3.6)	3237 (4.3)	2651 (3.5)	6318 (4.0)	3451 (4.4)
Norway	2362 (2.7)	2453 (2.8)	3317 (2.6)	3629 (2.8)	2425 (2.7)	3403 (2.6)
Sweden	11 915 (4.7)	11 180 (4.4)	11 787 (4.6)	11 807 (4.6)	12 271 (4.8)	12 115 (4.6)
Cancer:						
Denmark	31 023 (4.1)	30 438 (4.1)	26 920 (5.7)	30 123 (6.4)	50 491 (4.5)	34 407 (6.1)
Finland	14 690 (10.1)	13 293 (9.1)	7144 (9.6)	6758 (9.0)	15 877 (10.1)	7588 (9.6)
Norway	3343 (3.8)	3209 (3.7)	4892 (3.8)	4774 (3.7)	3422 (3.8)	5028 (3.8)
Sweden	12 544 (5.0)	11 600 (4.6)	12 711 (4.9)	12 156 (4.7)	12 967 (5.0)	13 111 (5.0)
Chronic pulmonary disease:						
Denmark	20 900 (2.8)	20 495 (2.7)	20 291 (4.3)	18 928 (4.0)	33 419 (3.0)	25 267 (4.5)
Finland	2860 (2.0)	2932 (2.0)	1488 (2.0)	1456 (1.9)	3078 (2.0)	1578 (2.0)
Norway	9254 (10.6)	9253 (10.6)	13 392 (10.4)	13 471 (10.5)	9471 (10.6)	13 702 (10.4)
Sweden	8730 (3.5)	7525 (3.0)	8932 (3.5)	8109 (3.1)	9014 (3.5)	9230 (3.5)
Cardiovascular condition or diabetes:						
Denmark	57 485 (7.7)	58 302 (7.8)	54 570 (11.6)	55 353 (11.7)	93 538 (8.3)	69 277 (12.2)
Finland	40 780 (27.9)	40 961 (28.1)	22 543 (30.2)	20 652 (27.7)	44 259 (28.3)	24 211 (30.5)
Norway	25 217 (28.8)	24 825 (28.4)	36 235 (28.1)	35 826 (27.8)	25 932 (28.9)	37 096 (28.1)
Sweden	37 559 (14.9)	35 974 (14.3)	39 131 (15.2)	37 798 (14.7)	38 811 (15.0)	40 446 (15.3)
Renal disease:						
Denmark	6781 (0.9)	7463 (1.0)	7003 (1.5)	7910 (1.7)	11 415 (1.0)	9202 (1.6)
Finland	1746 (1.2)	1666 (1.1)	866 (1.2)	818 (1.1)	1939 (1.2)	957 (1.2)
Norway	621 (0.7)	668 (0.8)	918 (0.7)	968 (0.8)	650 (0.7)	938 (0.7)
Sweden	2599 (1.0)	2514 (1.0)	2859 (1.1)	2729 (1.1)	2712 (1.1)	2971 (1.1)
Previous SARS-CoV-2 infection						
After third vaccine dose:						
Denmark	270 003 (36.1)	241 282 (32.2)	141 474 (30.0)	128 299 (27.2)	394 282 (34.9)	168 084 (29.6)

(Continued)

Table 1 | Continued

Characteristic	Four v three dose vaccinated comparison				Four v four dose vaccinated comparison	
	Matched		Matched		BA.4-5 booster as fourth dose	BA.1 booster as fourth dose
	BA.4-5 booster as fourth dose	Third dose	BA.1 booster as fourth dose	Third dose		
Finland	20 613 (14.1)	13 767 (9.4)	7483 (10.0)	6895 (9.2)	22 613 (14.5)	8138 (10.3)
Norway	3637 (4.2)	3362 (3.8)	5463 (4.2)	5378 (4.2)	3742 (4.2)	5617 (4.3)
Sweden	17 716 (7.0)	16 658 (6.6)	19 849 (7.7)	20 430 (7.9)	18 225 (7.1)	20 570 (7.8)
Before third vaccine dose:						
Denmark	41 807 (5.6)	34 872 (4.7)	17 381 (3.7)	14 085 (3.0)	53 468 (4.7)	19 609 (3.5)
Finland	4093 (2.8)	2389 (1.6)	1262 (1.7)	1141 (1.5)	4359 (2.8)	1347 (1.7)
Norway	1254 (1.4)	851 (1.0)	864 (0.7)	627 (0.5)	1300 (1.4)	890 (0.7)
Sweden	34 109 (13.6)	33 642 (13.4)	31 322 (12.2)	30 895 (12.0)	34 751 (13.5)	31 833 (12.1)
No previous infection before third vaccine dose:						
Denmark	436 838 (58.4)	472 494 (63.1)	312 955 (66.3)	329 426 (69.8)	682 295 (60.4)	379 340 (66.9)
Finland	121 301 (83.1)	129 851 (88.9)	65 945 (88.3)	66 654 (89.2)	129 508 (82.8)	69 848 (88.0)
Norway	82 590 (94.4)	83 268 (95.2)	122 506 (95.1)	122 828 (95.3)	84 628 (94.4)	125 325 (95.1)
Sweden	199 780 (79.4)	201 305 (80.0)	206 342 (80.1)	206 188 (80.1)	205 028 (79.5)	211 523 (80.1)
Omicron infection:						
Denmark	260 681 (34.8)	233 387 (31.2)	136 388 (28.9)	123 628 (26.2)	380 263 (33.7)	161 958 (28.6)
Finland	21 064 (14.4)	14 066 (9.6)	7615 (10.2)	7006 (9.4)	23 056 (14.7)	8277 (10.4)
Norway	3337 (3.8)	3070 (3.5)	4917 (3.8)	4810 (3.7)	3427 (3.8)	5040 (3.8)
Sweden	24 237 (9.6)	21 345 (8.5)	24 940 (9.7)	23 627 (9.2)	24 813 (9.6)	25 693 (9.7)
No previous omicron infection:						
Denmark	487 967 (65.2)	515 261 (68.8)	335 422 (71.1)	348 182 (73.8)	749 782 (66.3)	405 075 (71.4)
Finland	124 943 (85.6)	131 941 (90.4)	67 075 (89.8)	67 684 (90.6)	133 424 (85.3)	71 056 (89.6)
Norway	84 144 (96.2)	84 411 (96.5)	123 916 (96.2)	124 023 (96.3)	86 243 (96.2)	126 792 (96.2)
Sweden	227 368 (90.4)	230 260 (91.5)	232 573 (90.3)	233 886 (90.8)	233 191 (90.4)	238 233 (90.3)

SD=standard deviation.

Variable definitions are shown in supplementary table S2.

vaccination with the fourth dose served as the index date. See supplementary figure S2 for a graphical illustration of our weighted four versus four dose study design.

Statistical analysis

For the four versus three dose matched analyses, we used logistic regression to estimate the propensity score of receiving the fourth dose under study given covariates as predictors, with matching on age and calendar month of third dose vaccination and with a calliper width of 0.01 on the propensity score. For the four versus four dose weighted analyses, we used logistic regression to calculate stabilised inverse probability of treatment weights as $((1-p_o)/(1-p_c))/(p_o/p_c)$, with p_o being the crude probability of receiving a bivalent BA.4-5 booster and p_c being the same probability given covariates.

We followed people from day 8 after the index date (to ensure full immunisation among fourth dose recipients) up until the day of an outcome event, 90 days after the index date, death, emigration, or end of the study period, whichever occurred first. Additionally, we censored people with a positive PCR test for SARS-CoV-2 in our follow-up period after 14 and 30 days after the test (as a positive test was part of the outcome ascertainment) for the covid-19 related hospital admission and death outcome analyses, respectively. Moreover, we did not allow inclusion of people with recent SARS-CoV-2 infection (≤ 12 weeks) before the index date (to avoid outcome misclassification). Similarly, for the covid-19 related hospital admission outcome analysis, we did not allow inclusion of people

admitted to hospital with covid-19 any time before the index date. For the four versus three dose matched analyses, we also right censored matched pairs if the reference third dose vaccinated person received a fourth dose (on that day) during follow-up.^{33 34} We used the Kaplan-Meier estimator to estimate cumulative incidences, and from these we calculated the relative (that is, comparative vaccine effectiveness: 1–risk ratio) and absolute risk differences at day 90. We calculated the corresponding 95% confidence intervals by using the delta method. Upper 95% confidence intervals for the comparative vaccine effectiveness estimates were truncated at 100% if higher. We combined country specific estimates by random effects meta-analyses implemented using the *mixmeta* package in R. Counts smaller than five but not zero could not be reported owing to privacy regulations.

Additional analyses

Additional analyses included assessing the effectiveness of a fourth dose with a monovalent mRNA vaccine compared with three dose vaccination and with four dose bivalent booster vaccination, subgrouping according to sex and age ($< \geq 70$ years), and extending follow-up to day 180. In sensitivity analyses of the BA.4-5 versus BA.1 four dose comparison, we firstly included calendar month of third dose vaccination in the weights (to test for residual confounding due to differential waning of the third dose; evaluated in Denmark only) and secondly restricted analysis to people vaccinated after 1 October 2022 (to test for any early vaccinee selection bias not fully captured), as the BA.1-booster was introduced a

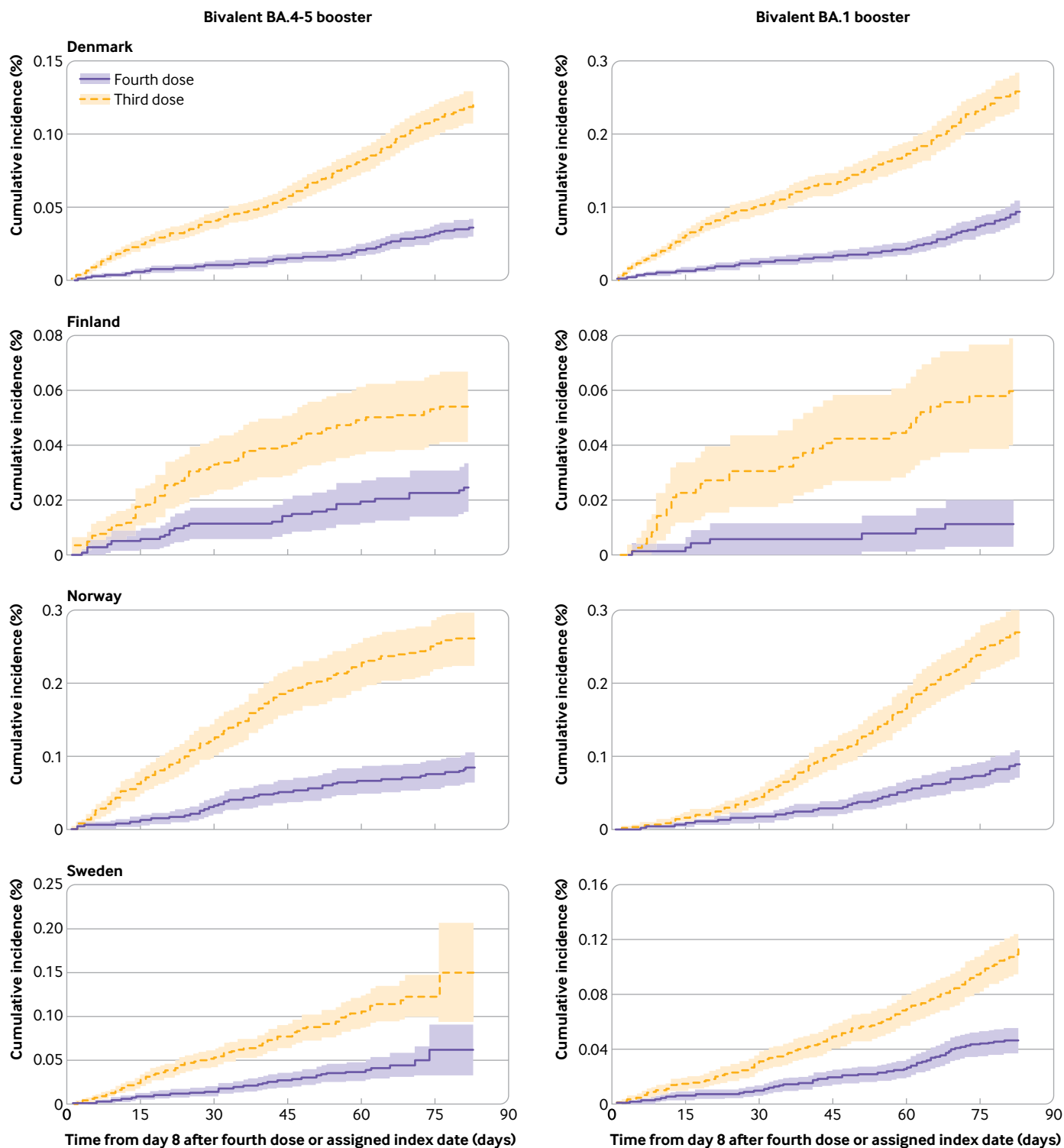


Fig 1 | Cumulative incidence curves of admission to hospital with covid-19, comparing people vaccinated with bivalent BA.4-5 or BA.1 mRNA booster vaccine as fourth dose with those who had received three vaccine doses only in each of four Nordic countries. Matched four dose and three dose vaccinated pairs were followed from day 8 to day 90 after four dose vaccinated people received bivalent booster as fourth dose

few weeks before the BA.4-5 booster. Also, the Nordic fourth dose vaccination rollouts initially prioritised older and vulnerable people, and, as the Danish rollout was initiated in September, this coincided with the authorisation of use of bivalent boosters. In Finland, Norway, and Sweden, these risk groups were

prioritised for vaccination before the respective study periods (during spring 2022).

Patient and public involvement

No patients or members of the public were formally involved in defining the research question, study

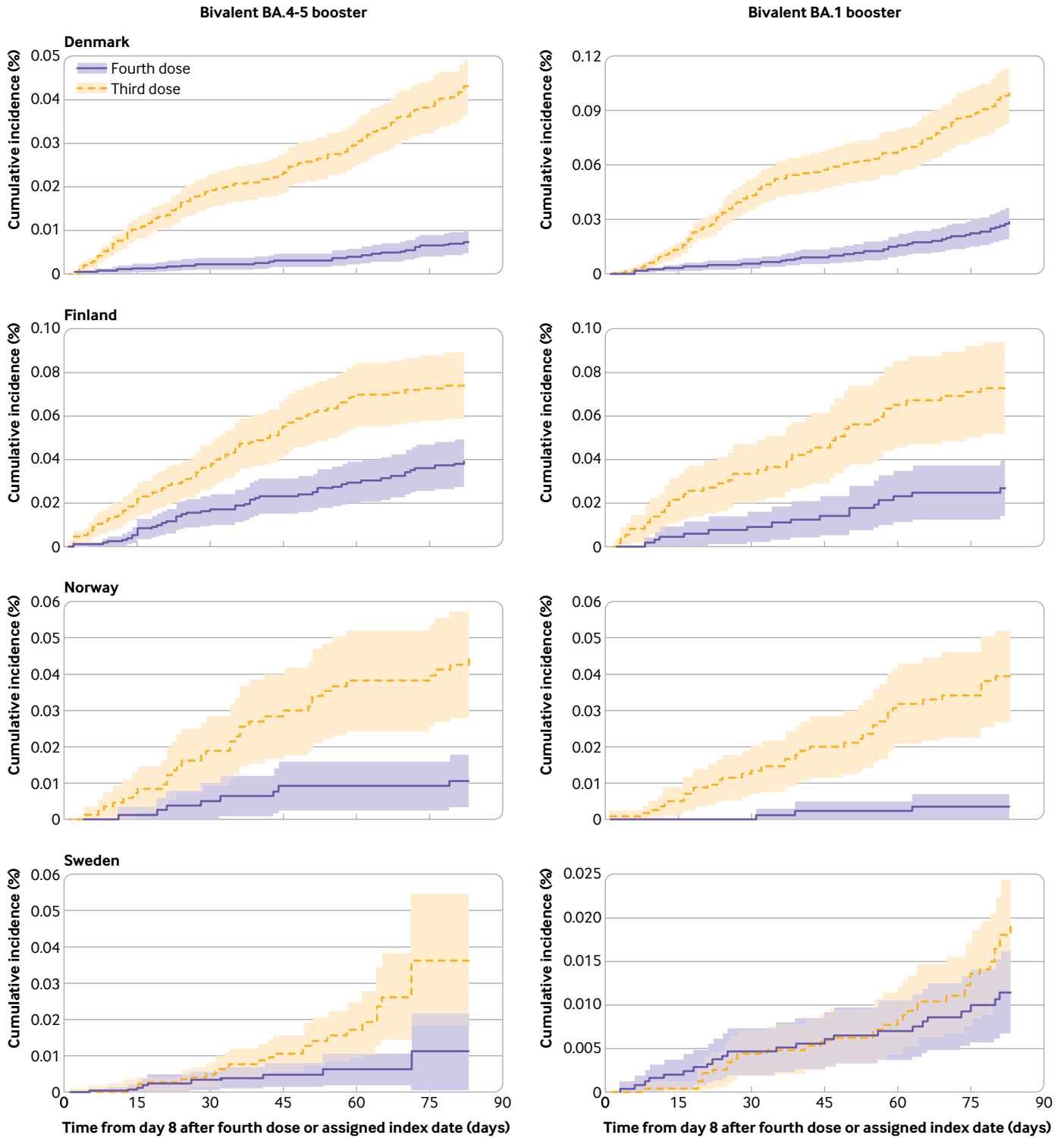


Fig 2 | Cumulative incidence curves of covid-19 related death comparing people vaccinated with bivalent BA.4-5 or BA.1 mRNA booster vaccine as a fourth dose with those who had received three vaccine doses only in each of four Nordic countries. Matched four dose and three dose vaccinated pairs were followed from day 8 to day 90 after four dose vaccinated people received bivalent booster as fourth dose

design, or outcome measures, or in the conduct of the study owing to privacy constrains, funding restrictions, and the short timeline during which the study was conducted. However, we received feedback from one layperson as part of the peer review process.

Results

Study populations

The study cohorts comprised 2 676 323 people who received fourth dose vaccination with a bivalent booster across the four countries; 1 634 199 (61%) had

Table 2 | Risk of covid-19 related hospital admission and death comparing people vaccinated with bivalent mRNA booster vaccine received as fourth dose with those vaccinated with only three doses in four Nordic countries*

	Contributing countries	Events/person years		Risk difference (95% CI) per 100 000 people	Comparative vaccine effectiveness, % (95% CI)
		Four dose vaccinated	Three dose vaccinated		
Hospital admission					
Bivalent BA.4-5 booster:					
All	DK, FI, NO, SE	289/157 024.6	893/155 560.2	-91.9 (-152.4 to -31.4)	67.8 (63.1 to 72.5)
Female	DK, FI, NO, SE	123/81 201.4	421/77 934.4	-83.8 (-150.0 to -17.5)	71.4 (64.3 to 78.4)
Male	DK, FI, NO, SE	166/75 823.2	472/77 625.7	-92.9 (-156.5 to -29.4)	65.0 (55.1 to 74.9)
Age <70 years	DK, FI, NO, SE	73/111 745.4	227/110 941.2	-29.1 (-36.0 to -22.2)	68.4 (59.6 to 77.1)
Age ≥70 years	DK, FI, NO, SE	216/45 279.2	666/44 619.0	-210.4 (-361.9 to -58.8)	67.4 (61.8 to 73.1)
Bivalent BA.1 booster:					
All	DK, FI, NO, SE	332/121 229.6	977/120 173.2	-112.9 (-179.6 to -46.2)	65.8 (59.1 to 72.4)
Female	DK, FI, NO, SE	130/65 260.7	459/62 392.8	-111.3 (-171.1 to -51.5)	75.6 (61.9 to 89.3)
Male	DK, FI, NO, SE	202/55 969.0	518/57 780.5	-110.6 (-184.4 to -36.8)	58.4 (51.3 to 65.6)
Age <70 years	DK, FI, NO, SE	92/77 391.8	199/77 062.0	-31.8 (-49.3 to -14.3)	54.2 (42.5 to 66.0)
Age ≥70 years	DK, FI, NO, SE	240/43 837.8	778/43 111.3	-251.7 (-379.8 to -123.6)	71.4 (59.8 to 83.1)
Death					
Bivalent BA.4-5 booster:					
All	DK, FI, NO, SE	93/159 012.0	325/157 163.0	-34.1 (-40.1 to -28.2)	69.8 (52.8 to 86.8)
Female	DK, FI, NO, SE	40/82 066.3	159/78 647.7	-28.9 (-41.3 to -16.6)	74.1 (53.9 to 94.4)
Male	DK, FI, NO, SE	53/76 945.7	166/78 515.2	-32.6 (-41.6 to -23.7)	68.0 (54.5 to 81.6)
Age <70 years	DK, FI, SE	13/106 242.7	36/105 162.2	-3.7 (-10.1 to 2.7)	62.9 (3.8 to 100.0)
Age ≥70 years	DK, FI, NO, SE	80/45 994.1	287/45 268.3	-104.2 (-169.3 to -39.1)	74.4 (58.4 to 90.3)
Bivalent BA.1 booster:					
All	DK, FI, NO, SE	86/122 646.3	286/121 509.9	-38.7 (-65.4 to -12.0)	70.0 (50.3 to 89.7)
Female	DK, FI, NO, SE	34/65 840.5	137/62 815.9	-37.2 (-61.8 to -12.5)	79.8 (70.3 to 89.2)
Male	DK, FI, SE	52/46 271.6	127/48 331.3	-35.4 (-79.8 to 8.9)	54.7 (30.6 to 78.7)
Age <70 years	DK, FI, SE	10/69 358.3	23/68 905.0	-5.6 (-15.3 to 4.1)	66.8 (39.0 to 94.7)
Age ≥70 years	DK, FI, NO, SE	76/44 509.2	262/43 770.0	-86.9 (-124.9 to -48.8)	70.9 (52.6 to 89.3)

CI=confidence interval; DK=Denmark; FI=Finland; NO=Norway; SE=Sweden.

*Matched pairs were followed up from day 8 after fourth dose vaccination until day 90, an outcome event, three dose reference individual received fourth dose, 14 (for hospital admission) or 30 (for death) days after positive polymerase chain reaction test for SARS-CoV-2, emigration, death, or end of study period, whichever occurred first. Comparisons were matched to take into account year of birth (5 year bins), calendar month of receipt of third vaccine dose, sex, region of residence, vaccination priority groups, selected comorbidities, and previous SARS-CoV-2 infection.

received a bivalent BA.4-5 mRNA booster vaccine and 1042 124 (39%) a bivalent BA.1 mRNA booster vaccine (an additional 911 731 had received a monovalent mRNA booster vaccine). Denmark contributed a relatively larger sample of bivalent mRNA booster vaccinees (a total of 1 697 078; 63% of all included people vaccinated with a bivalent booster) than Finland (235 813; 9%), Norway (221 502; 8%), and Sweden (521 930; 20%) (table 1; supplementary figures S3-S4 and table S5). Slightly more than half of all people who had received a bivalent BA.4-5 or BA.1 booster vaccine within each country cohort were women, with mean ages of approximately 72 years, except in Sweden (approximately 61 years) and for the bivalent BA.4-5 booster vaccinated in Denmark (66 years). The distribution of comorbidities and history of previous SARS-CoV-2 infection was relatively similar between people vaccinated with bivalent BA.4-5 and BA.1 booster within each country. Across countries, the proportion of people with a medical history of cardiovascular disease or diabetes in the overall cohorts was larger in Finland (29%) and Norway (28%) than in Denmark (10%) and Sweden (15%). The matched four versus three dose cohorts consisted of a total of 1 233 741 and 932 846 matched pairs for the bivalent BA.4-5 and BA.1 booster comparisons (corresponding to 75% and 90% of all included bivalent boosted vaccinees), respectively, and characteristics were overall similar to those of the entire bivalent boosted cohorts.

Effectiveness of bivalent booster as fourth dose

The cumulative incidences of covid-19 related hospital admission and death within 90 days of follow-up comparing four dose with three dose vaccinated people were very low (fig 1 and fig 2). Receipt of a fourth vaccine dose with a bivalent BA.4-5 booster was associated with a lower risk of admission to hospital with covid-19 than previous receipt of three vaccine doses (289 v 893 events); the comparative vaccine effectiveness was 67.8% (95% confidence interval 63.1% to 72.5%) and the risk difference was -91.9 (95% confidence interval -152.4 to -31.4) per 100 000 people (table 2). A fourth dose with a bivalent BA.1 booster was similarly associated with lower risks of admission to hospital with covid-19 (332 v 977 events), corresponding to a comparative vaccine effectiveness of 65.8% (59.1% to 72.4%) and a risk difference of -112.9 (-179.6 to -46.2) per 100 000 people. For covid-19 related death, the comparative vaccine effectiveness and risk difference were 69.8% (52.8% to 86.8%) and -34.1 (-40.1 to -28.2) per 100 000 people for bivalent BA.4-5 (93 v 325 events) and 70.0% (50.3% to 89.7%) and -38.7 (-65.4 to -12.0) per 100 000 people for BA.1 boosters (86 v 286 events). The comparative vaccine effectiveness did not differ by sex or age, but the risk difference was greater among people aged ≥70 years than among those who were younger (for example, risk differences for BA.4-5 booster against admission to hospital with covid-19

Table 3 | Risk of covid-19 related hospital admission and death comparing people vaccinated with bivalent BA.4-5 mRNA booster vaccine received as fourth dose with those vaccinated with bivalent BA.1 mRNA booster vaccine received as fourth dose in four Nordic countries*

	Contributing countries	Events/person years		Risk difference (95% CI) per 100 000 people	Comparative vaccine effectiveness, % (95% CI)
		Fourth dose bivalent BA.4-5 booster	Fourth dose bivalent BA.1 booster		
Hospital admission					
All	DK, FI, NO, SE	802/333 522.2	932/229 594.7	10.0 (−14.4 to 34.4)	−14.9 (−62.3 to 32.4)
Female	DK, FI, NO, SE	355/173 218.5	389/125 445.2	10.9 (−7.1 to 28.9)	−5.3 (−32.1 to 21.6)
Male	DK, FI, NO, SE	447/160 303.6	543/104 149.5	8.7 (−31.3 to 48.7)	−1.2 (−54.4 to 52.1)
Age <70 years	DK, FI, NO, SE	165/215 129.7	165/119 986.2	−3.3 (−10.9 to 4.3)	28.0 (5.6 to 50.3)
Age ≥70 years	DK, FI, NO, SE	637/118 392.5	767/109 608.5	17.2 (−38.5 to 73.0)	−17.4 (−71.5 to 36.6)
Death					
All	DK, FI, NO, SE	229/335 719.6	243/231 679.9	8.1 (−3.3 to 19.4)	−40.7 (−123.4 to 42.1)
Female	DK, FI, NO, SE	101/174 193.8	106/126 399.7	6.5 (−10.8 to 23.8)	13.3 (−45.7 to 72.3)
Male	DK, FI, NO, SE	128/161 525.8	137/105 280.1	7.7 (−5.5 to 20.9)	1.9 (−44.7 to 48.6)
Age <70 years	DK, FI, SE	24/208 233.3	17/108 554.2	2.3 (−3.0 to 7.6)	8.7 (−67.8 to 85.3)
Age ≥70 years	DK, FI, NO, SE	205/119 525.1	225/110 887.5	9.8 (−12.3 to 31.8)	6.4 (−38.7 to 51.4)

CI=confidence interval; DK=Denmark; FI=Finland; NO=Norway; SE=Sweden.

*Each person was followed up from day 8 after fourth dose vaccination until day 90, an outcome event, 14 (for hospital admission) or 30 (for death) days after positive polymerase chain reaction test for SARS-CoV-2, emigration, death, or end of study period, whichever occurred first. Comparisons used stabilised inverse probability of treatment weights to take into account year of birth (5 year bins), calendar month of receipt of fourth vaccine dose, sex, region of residence, vaccination priority groups, comorbidities, and previous SARS-CoV-2 infection. Comparative vaccine effectiveness and risk difference point estimates in sex and age subgroup analyses of covid-19 related death are in opposite directions (insignificantly so) to overall estimates because of lack of statistical precision due to few events in country specific analyses and lack of overlap between comparison groups (represented by corresponding wide 95% CIs; see supplementary table S7).

were −210.4 (−361.9 to −58.8) and −29.1 (−36.0 to −22.2) per 100 000 people among those aged ≥70 years and those who were younger, respectively) (supplementary figure S5-S8). Extending follow-up to day 180 resulted in comparative vaccine effectiveness against admission to hospital with covid-19 of 54.9% (49.0% to 60.8%) and 63.5% (49.5% to 77.5%) for the BA.4-5 and BA.1 boosters, respectively (similar for covid-19 related death; supplementary figures S9-S10 and table S6).

Comparative effectiveness between bivalent BA.4-5 and BA.1 boosters as fourth vaccine dose

When comparing bivalent BA.4-5 versus BA.1 boosters directly, the comparative vaccine effectiveness and corresponding risk difference at day 90 were −14.9% (−62.3% to 32.4%) and 10.0 (−14.4 to 34.4) per 100 000 people for admission to hospital with covid-19 (802 v 932 unweighted events) and −40.7% (−123.4% to 42.1%) and 8.1 (−3.3 to 19.4) per 100 000 people for covid-19 related death (229 v 243 unweighted events) (table 3 and fig 3). The direction of the estimates was not uniform across countries (supplementary table S7). Findings were similar with stratification according to sex and age and when follow-up was extended to day 180 (supplementary figures S11-S13 and table S8). Also, the results did not change when we included adjustment for calendar month of third dose vaccination and when we excluded early fourth dose vaccine adopters (supplementary tables S9 and S10).

Comparative effectiveness of monovalent vaccine as fourth dose

Among three dose vaccinated people, at day 90 after receipt of a fourth dose with monovalent vaccine the comparative vaccine effectiveness and risk difference were 57.4% (44.6% to 70.1%) and −86.8 (−152.9 to −20.7) per 100 000 for admission to hospital with covid-19 (326 v 737 events) and 65.4% (36.0% to 94.7%) and −27.8 (−48.5 to −7.0) per

100 000 for covid-19 related death (90 v 254 events) (supplementary figures S14 and S15 and table S11). Sex, age, and extended follow-up analyses were similar to those for the bivalent boosters. Comparing bivalent versus monovalent booster as the fourth dose at day 90 did not result in significant differences in the risk of the severe covid-19 outcomes (for example, comparative vaccine effectiveness for hospital admission was 33.8% (−2.7% to 70.3%) for BA.4-5 and 0.8% (−49.0% to 50.7%) for BA.1 booster versus monovalent vaccination) (supplementary figure S16 and table S12).

Discussion

This study found that fourth dose vaccination (that is, second booster) with the bivalent BA.4-5 or BA.1 mRNA booster vaccines was associated with lower rates of covid-19 related hospital admission and death (comparative vaccine effectiveness of ≥65%) among people from the Nordic countries aged ≥50 years who had previously been vaccinated with three doses of monovalent vaccine (that is, a primary course and a first booster dose). Furthermore, we observed no significant difference in the protection afforded by the bivalent BA.4-5 and BA.1 mRNA booster vaccines as a fourth dose when we compared them directly. Specifically, although severe covid-19 was a very rare event in our Nordic cohorts including 2.68 million people vaccinated with bivalent booster, the 95% confidence interval of the main analysis comparing BA.4-5 with BA.1 bivalent booster vaccines allowed us to conclude that any risk differences in covid-19 hospital admissions would be small, between −14.4 and 34.4 per 100 000 people vaccinated.

Comparison with other studies

Covid-19 vaccination policies recommending the bivalent mRNA boosters as a fourth vaccine dose are mainly supported by studies on immunogenicity, some of which have shown induction of higher antibody

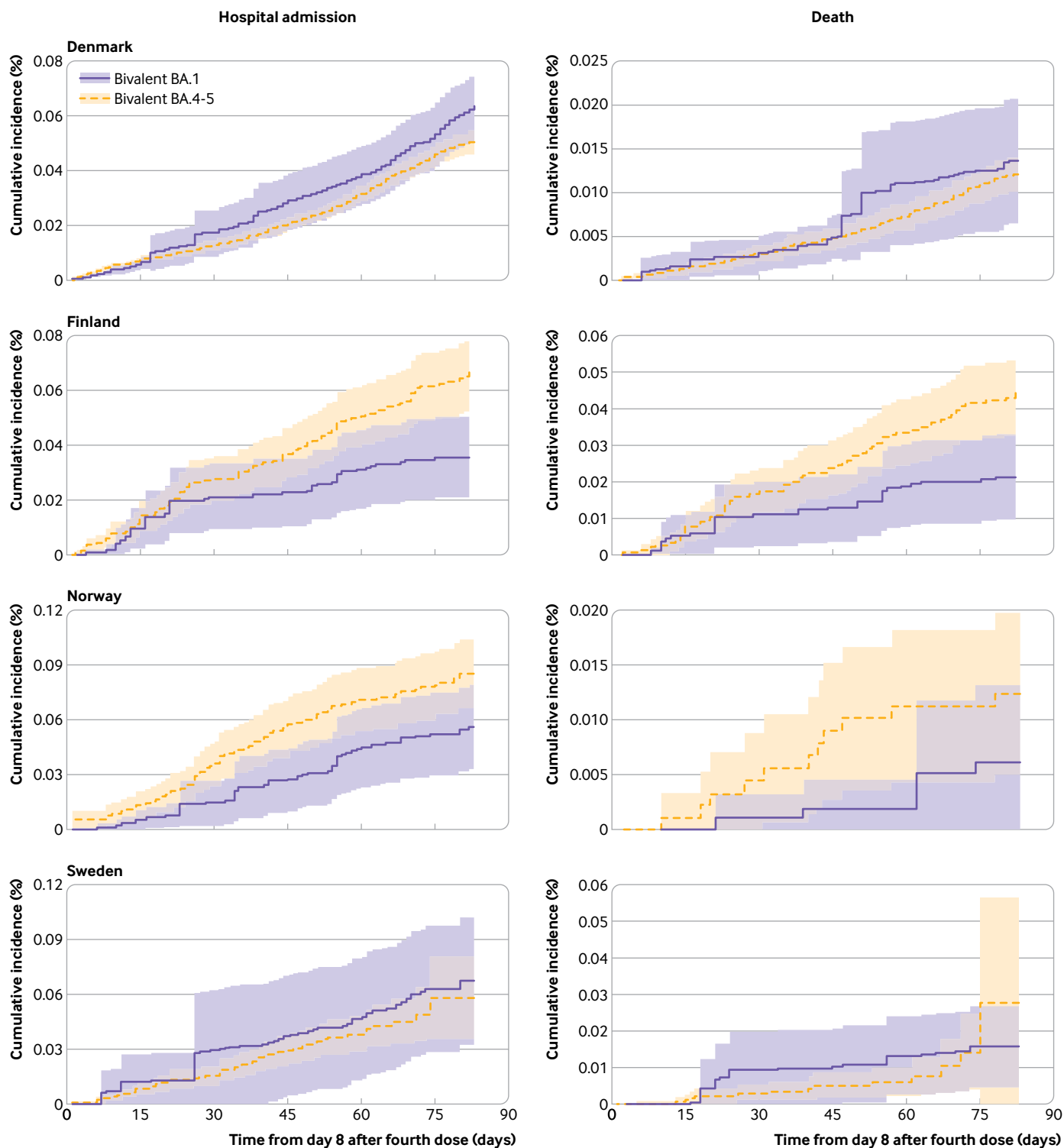


Fig 3 | Cumulative incidence curves of covid-19 related hospital admission and death comparing people vaccinated with bivalent BA.4-5 mRNA booster vaccine as fourth dose with those vaccinated with bivalent BA.1 mRNA booster vaccine as fourth dose in each of four Nordic countries. Each person was followed from day 8 to day 90 after receiving bivalent booster as fourth dose

concentrations against omicron subvariants compared with monovalent boosters.⁴⁻⁸ Previous observational studies of the effectiveness of fourth dose monovalent vaccination also lend some indirect support to these recommendations.¹⁶⁻³²

Although the protection afforded by the bivalent boosters seems to be modest against SARS-CoV-2

infection, with estimates of vaccine effectiveness ranging between 14% and 52%,³⁵⁻³⁷ the protection against severe covid-19 outcomes is likely higher, but data are sparse.⁹⁻¹⁵ Available estimates from the US, Israel, Canada, and England of the effectiveness of the bivalent BA.4-5 and BA.1 boosters against covid-19 related hospital admission, death, or both seem to

Table 4 | Identified reliable studies on vaccine effectiveness of bivalent BA.4-5 and BA.1 booster vaccination

Country	Bivalent booster population size and age	Design	Severe covid-19 outcome	Comparative vaccine effectiveness, % (95% CI)	
Denmark, Finland, Norway, and Sweden*	2 676 323 BA.4-5 or BA.1 boosted (fourth dose) people aged ≥50 years	Cohort analyses	Hospital admission	BA.4-5, 3 months	67.8 (63.1 to 72.5)
			Death		69.8 (52.8 to 86.8)
			Hospital admission	BA.1, 3 months	65.8 (59.1 to 72.4)
			Death		70.0 (50.3 to 89.7)
United States ⁹	884 BA.4-5 boosted (any dose) people aged ≥18 years	Test negative case-control study	Hospital admission	BA.4-5, ≥7 days	≥42 (20 to 58); 59 (44 to 70)†
United States ¹⁰	79 BA.4-5 boosted (any dose) people aged ≥65 years	Test negative case-control study	Hospital admission	BA.4-5, ≥7 days	≥73 (52 to 85); 84 (64 to 93)†
United States† ^{11 12}	1 279 802 BA.4-5 boosted (any dose) people aged ≥12 years	Cohort study	Hospital admission or death§	BA.4-5, 2 weeks	67.4 (46.2 to 80.2)†
				BA.4-5, 20 weeks	38.4 (13.4 to 56.1)†
Israel ¹³	134 215 BA.4-5 boosted (any dose) people aged ≥65 years	Cohort study	Hospital admission	BA.4-5, 4 months	72 (60 to 81)**
			Death		68 (45 to 82)**
Canada ¹⁴	Numbers of included BA.4-5 and BA.1 boosted (≥fourth dose) people aged ≥50 years uncertain¶	Test negative case-control study	Hospital admission or death§	BA.4-5, day 7-29	83 (77 to 88)†
				BA.4-5, day 60-89	81 (72 to 87)†
			Hospital admission or death§	BA.1, day 7-29	86 (82 to 90)†
England ¹⁵	29 954 BA.1 boosted (any dose) people aged ≥50 years	Test negative case-control study	Hospital admission	BA.1, day 90-119	76 (66 to 83)†
				BA.1, week 2-4	53.0 (47.9 to 57.5)
				BA.1, ≥10 weeks	35.9 (31.4 to 40.1)

CI=confidence interval.

*This study. Comparative vaccine effectiveness at 6 months of follow-up for BA.4-5 boosted was 54.9% (49.0% to 60.8%) for hospital admission and 61.3% (35.5% to 87.1%) for death; for BA.1 boosted, estimates were 63.5% (49.5% to 77.5%) and 67.4% (47.7% to 87.2%), respectively.

†Not comparative vaccine effectiveness as booster vaccinated people were compared with unvaccinated people.

‡Initial study from North Carolina in US¹¹ included 1 070 136 BA.4-5 boosted (any dose) people with vaccine effectiveness of 61.8% (48.2% to 71.8%) for hospital admission or death compared with unvaccinated people from day 15-99 after bivalent booster vaccination.

§Combined outcome reported.

¶Specific number of bivalent boosted people across cases and control could not be found; however, study reported 636 cases among bivalent booster vaccinated people.

**Reported as hazard ratio of 0.28 (0.19 to 0.40) for hospital admission and 0.32 (0.18 to 0.58) for death.

be compatible with our findings (table 4).⁹⁻¹⁵ The size of our population enabled the estimation of three month comparative effectiveness with high statistical precision. Moreover, our estimates at six months of follow-up indicated that the additional protection provided by a fourth dose was well preserved with little waning. The estimates of the effectiveness against severe covid-19 of BA.4-5 boosters in North Carolina and BA.1 boosters in the UK was 38.4% (13.4% to 56.1%) after 20 weeks and 35.9% (31.4% to 40.1%) after ≥10 weeks, respectively,^{12 15} and results from Canada indicate a similar modest waning of vaccine effectiveness during 119 days of follow-up (for example, vaccine effectiveness of 76% (66% to 83%) for BA.1 boosters).¹⁴ Additionally, as both the BA.4-5 and BA.1 bivalent boosters were implemented in the Nordic vaccination strategies, we were able to compare these head to head. We found no consistent support for large differences in effectiveness between the two vaccine types. Notably, the precision of our combined Nordic estimates suggests that any potential difference is likely to be small in absolute numbers. For example, the 95% confidence interval for admission to hospital with covid-19 is incompatible with >14 fewer events and >34 excess events per 100 000 among people vaccinated with BA.4-5 compared with BA.1 booster during the first three months after vaccination.

Strengths and limitations of study

A main limitation of this observational study is the lack of controlled randomisation. Therefore, we cannot fully exclude the possibility of residual unmeasured confounding factors being unevenly distributed between compared groups to the extent that such factors were not indirectly adjusted for by

the set of included covariates (that is, proxies). To the best of our knowledge, the assignment of the type of booster as the fourth dose was unselective during the study period, and, except for the initial prioritisation of older and vulnerable people during the study period in Denmark (results did not change when we excluded this period), the analyses should reflect a time when fourth dose vaccination was offered to the general public. Although people were required to fulfil a restrictive set of pre-specified criteria to be considered cases admitted to hospital with covid-19, we cannot exclude the possibility that our outcome definition captured cases in which the infection with SARS-CoV-2 only partly contributed to or coincided with the timing of admission. Similarly, our definition of covid-19 related death as any death occurring within 30 days of a positive SARS-CoV-2 PCR test used in Denmark, Finland, and Sweden was most likely subject to some outcome misclassification. Also, we had no information on at-home antigen testing for SARS-CoV-2 infection, and, although confirmatory PCR testing has generally been advised and people at risk of severe covid-19 have been recommended to have PCR testing if presenting with symptoms, we did not capture all SARS-CoV-2 infections in each country. We reassuringly observed no major differences in the effect estimates for covid-19 related death between Norway (where a covid-19 cause specific definition of death was used) and other countries. In addition, our comparative population based design would tend to mitigate larger differences in this potential outcome misclassification between compared groups as opposed to, for example, analyses using unvaccinated people as a reference group, which would be more prone to bias owing to differences in outcome misclassifications (for example,

greater differences in healthcare contact patterns) and healthy vaccinee bias; also, unvaccinated people do not reflect the targeted population for fourth dose booster vaccination. Moreover, the booster vaccination uptake among ≥ 50 year olds has been high ($>90\%$) in the Nordic countries. Nevertheless, we cannot fully exclude a relative healthy vaccinee bias; our effect estimates with the longer follow-up of 180 days for the four versus three dose vaccinated comparisons would be most susceptible to any such influence. If so, this would suggest that the waning effects we estimated would tend towards being conservative relative to the true waning effects.

Owing to the nature of the healthcare registers in the four Nordic countries, we were able to consider potential confounders on an individual level, which we included by matching or by stabilised inverse probability of treatment weights. However, our direct head-to-head comparison between bivalent and monovalent boosters as a fourth dose was limited by the poorer overlap of calendar periods of use and the need for control thereof (owing to otherwise potential confounding by, for example, differences in waning of third dose, background population infection rates, and circulating variants), resulting in lower statistical precision for some of these analyses. Although fourth dose vaccination with a monovalent vaccine seemed to offer similar protection to the bivalent boosters when we compared the results from the four versus three dose comparisons indirectly (the 95% confidence intervals broadly overlap), these abovementioned factors limit the interpretability of such indirect comparisons of the association estimates. Moreover, given that we controlled for potential confounders through either matching or weighting, results from the individual comparisons should primarily be interpreted separately.

Our results likely have a high degree of generalisability to other similar populations. However, because we assessed the comparative effectiveness against covid-19 related hospital admission and death associated with the bivalent mRNA booster vaccines given as a fourth dose, our results may only indirectly support any evaluation of the effectiveness of these vaccines in other covid-19 vaccination schedule scenarios. As per the study design, we did not examine, and thus our results cannot directly help to inform on, the vaccine effectiveness among people younger than 50; similarly, our estimates may not compare to those in populations with a demographically different composition or in other specific clinical subgroups that were not studied.

Conclusions

Among people aged ≥ 50 years who had received three doses of covid-19 vaccine, vaccination with the bivalent BA.4-5 or BA.1 mRNA boosters as a fourth vaccine dose (that is, second booster) was associated with lower rates of covid-19 related hospital admission and death at three months of follow-up. The effectiveness remained high when we extended follow-up to six

months. In these combined analyses of data from four Nordic countries, the effectiveness of BA.4-5 and BA.1 boosters as a fourth vaccine dose did not differ, and the results indicate that any potential differences in the risk of severe covid-19 outcomes are most likely to be very small in absolute numbers.

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The lead authors (the manuscript's guarantors) affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: Studied participants were anonymised in the data sources used; therefore, direct dissemination to study participants is not possible. The study results will be disseminated to the public and health professionals by a press release written using layman's terms.

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Web appendix: Supplementary appendix