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Comparative effectiveness of monovalent XBB.1.5 containing covid-19 mRNA vaccines in Denmark, Finland, and Sweden: target trial emulation based on registry data

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ABSTRACT

OBJECTIVE To estimate the effectiveness of vaccination with a monovalent covid-19 mRNA vaccine containing the omicron XBB.1.5 subvariant against severe covid-19 disease in Denmark, Finland, and Sweden.

DESIGN Target trial emulation based on registry data.

SETTING Denmark, Finland, and Sweden, 1 October 2023 to 21 April 2024.

PARTICIPANTS Source population of 3 898 264 individuals eligible for vaccination with the XBB.1.5 containing covid-19 mRNA vaccine at the start of the study on 1 October 2023. Study cohort comprised 1 876 282 recipients of an XBB.1.5 containing vaccine during the study period matched with 1 876 282 non-recipients. Individuals were aged ≥65 years (mean age 75.4 years, standard deviation 7.4 years) and had received at least four doses of a previous covid-19 vaccine.

MAIN OUTCOME MEASURES Cumulative incidences of hospital admissions and deaths related to covid-19 in a follow-up period of 24 weeks after immunisation (defined as one week after vaccination) in recipients of an XBB.1.5 containing covid-19 mRNA vaccine and matched non-recipients. Cumulative incidences were used to calculate comparative vaccine effectiveness (1−risk ratio) and risk differences.

RESULTS The associated comparative vaccine effectiveness was 57.9% (95% confidence interval (CI) 49.9% to 65.8%) against hospital admission for covid-19 (1085 *v* 2635 events) and 75.2% (70.6% to 79.9%) against deaths related to covid-19 disease (348 *v* 1458 events) after 24 weeks of follow-up. This result corresponded to 154.7 (95% CI 78.3 to 231.0) hospital admissions for covid-19 and 120.3 (110.5 to 130.2) deaths prevented per 100 000 individuals who were vaccinated with an XBB.1.5 containing vaccine. The associated comparative vaccine effectiveness was similar irrespective of sex, age group (65-74 *v* ≥75 years), number of doses of previous covid-19 vaccines, subgroup of co-administered seasonal influenza vaccines, and period of when either the omicron XBB or BA.2.86 sublineage was predominant. Although the observed reduction in risk was highest during the first weeks after vaccination, comparative vaccine effectiveness was well maintained after 24 weeks of follow-up.

CONCLUSIONS In this study, in adults aged ≥65 years, vaccination with a monovalent XBB.1.5 containing covid-19 mRNA vaccine was associated with reduced rates of hospital admissions for covid-19 and deaths related to covid-19, during the autumn and winter of 2023-24 in Denmark, Finland, and Sweden.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The updated monovalent covid-19 mRNA vaccine containing the omicron XBB.1.5 subvariant was authorised for covid-19 vaccination in the autumn and winter of 2023-24 in many countries

⇒ Evaluations of the clinical effectiveness of the vaccine against severe covid-19 are limited but are needed to support the planning of future covid-19 vaccination strategies

WHAT THIS STUDY ADDS

⇒ During the autumn and winter 2023-24 season in Denmark, Finland, and Sweden, vaccination with a monovalent XBB.1.5 containing vaccine was associated with reduced rates of hospital admissions and deaths related to covid-19 in adults aged ≥65 years

⇒ The associated reduced risk by vaccination with an XBB.1.5 containing vaccine was similar across subgroups and during periods when the omicron XBB or BA.2.86 sublineages were predominant

⇒ Although the associated effectiveness of the vaccine was highest during the first weeks after vaccination, vaccine effectiveness was well maintained after 24 weeks of follow-up

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ The results of the study support the evaluation of the benefits of seasonally updated SARS-CoV-2 sublineage covid-19 vaccines, relevant to the planning of future seasonal covid-19 vaccination programmes

Introduction

The monovalent covid-19 mRNA vaccine containing the omicron XBB.1.5 subvariant was authorised in Europe and the US, and implemented in autumn and winter 2023-24 covid-19 vaccination programmes.[1 2] In Denmark, Finland, and Sweden, the XBB.1.5 containing mRNA vaccine was recommended from 1 October 2023 as an additional dose of covid-19 vaccine to individuals in the general population aged ≥65 years.

Clinical studies have shown that the XBB.1.5 containing mRNA vaccine is immunogenic against the predominant omicron subvariants in the autumn and winter 2023-24 season, including both the XBB and BA.2.86 sublineages (eg, EG.5.1 and JN.1, respectively).[3 4] Evaluations of the effectiveness of the vaccine in preventing severe covid-19

disease, however, are limited and mainly reflect early season short term effectiveness with little follow-up,[5–8] implying no end-of-season estimates. Other shortcomings of the available data include lack of reporting on the absolute effects, in clinically important subgroups (including concurrent seasonal influenza vaccination), with respect to waning immunity and against predominant omicron sublineages, and deaths from covid-19. In three Nordic countries (Denmark, Finland, and Sweden), we estimated the comparative effectiveness of the monovalent XBB.1.5 containing covid-19 mRNA vaccine against hospital admissions for covid-19 and deaths related to covid-19 in a nationwide cohort analysis of adults aged ≥65 years after 24 weeks of follow-up.

Methods

Data sources, study design, and cohort specification

In all three countries (Denmark, Finland, and Sweden), we linked personal and healthcare data in different nationwide registries by using the country specific unique identifiers assigned to all residents. Hence we retrieved individual level information on covid-19 vaccinations, hospital admissions, recorded disease diagnoses, laboratory confirmed SARS-CoV-2 infection by a positive polymerase chain reaction (PCR) test result, and patient characterisitcs (age, sex, residency, healthcare occupation, and vital status; online supplemental tables S1 and S2 have more details).

We designed this non-interventional study based on the target trial emulation framework. Specifically, we compared the rates of hospital admissions and deaths related to covid-19 disease according to whether individuals received or did not receive the XBB.1.5 containing vaccine as an additional covid-19 dose during the study period, 1 October 2023 to 21 April 2024. Online supplemental table S3 lists the key components of the pragmatic target trial specification and emulation.[9 10] In the three Nordic countries, the XBB sublineage (particularly EG.5.1) was predominant until the end of November 2023, and then the BA.2.86 sublineage (particularly JN.1) was predominant for the rest of the study period. The autumn and winter 2023-24 covid-19 wave peaked at around mid-November until mid-December 2023.

Eligibility criteria, assessed at the start of the study period, were specified to construct a cohort representative of the general population targeted for vaccination with the XBB.1.5 containing vaccine during the autumn and winter of 2023-24, according to the national covid-19 vaccination strategies: age ≥65 years, residency in Denmark, Finland, or Sweden (to ensure a linkable identifier), no previous hospital admissions for covid-19 disease at any time, and received ≥4 doses of previous covid-19 vaccines (AZD1222, BNT162b2, or mRNA-1273 vaccines only; AZD1222 as part of the primary vaccination course only).

Outcomes

We defined hospital admissions for covid-19 as any first inpatient hospital admission with a registered diagnosis related to covid-19 and a positive PCR test result for the SARS-CoV-2 virus (positive test result within 14 days before to two days after the day of admission). Death related to covid-19 was defined as any death within 30 days of a positive PCR test result for the SARS-CoV-2 virus. The two outcomes were studied separately; day of admission or death was the respective event date. Online supplemental table S4 has more details of definitions of outcomes.

Procedures

Individuals receiving an XBB.1.5 containing vaccine dose during the study period (1 October 2023 to 21 April 2024) were matched on day 8 after the day of vaccination (ie, after one week, to ensure full immunisation) with individuals who had not received an additional dose up until and including this day. We matched recipients of the XBB.1.5 containing vaccine with non-recipients, 1:1, by exact matching without replacement on age (in five year categories), calendar time of last previous dose of covid-19 vaccine received (in monthly categories; eg, the month of receiving the fourth, fifth, or sixth dose for matched pairs where the XBB.1.5 containing vaccine was given as a fifth, sixth, or seventh dose, respectively), sex, region of residence, vaccination priority groups (ie, individuals considered at high risk of severe covid-19 and healthcare staff), and number of selected comorbidities (by 0, 1, 2, or ≥3 of chronic pulmonary disease, cardiovascular conditions, diabetes, autoimmunity related conditions, cancer, and moderate to severe renal disease; online supplemental table S2 and figure S2) by the number of previous covid-19 vaccine doses received.

The day the XBB.1.5 containing vaccine was given within each matched pair was the index date for both individuals. We followed individuals from one week after the index date for outcome events until 24 weeks of follow-up had passed (ie, 175 days since the index date), receipt of an additional covid-19 vaccine dose, death, emigration, or end of the study period (21 April 2024), whichever occurred first. Also, if an individual who was included as a matched non-recipient received a covid-19 vaccine later than the assigned index date, follow-up was censored for the current matched pair, and the now vaccinated individual could potentially re-enter the study as an XBB.1.5 containing vaccine recipient in a new matched pair on that given date (specifically, day 8 after vaccination) if successfully matched to another non-recipient. Online supplemental figure S1 illustrates our study design.

Table 1 | Characteristics of study cohort before and after matching of recipients and non-recipients of the monovalent covid-19 mRNA vaccine containing the omicron XBB.1.5 subvariant, aged ≥65 years, in Denmark, Finland, and Sweden, for the study period 1 October 2023 to 21 April 2024

	Before matching		After matching	
Characteristic	Vaccine recipients	Non-recipients*	Vaccine recipients	Non-recipients
Total No of individuals:	3 346 650	3 898 264	1 876 282	1 876 282
Denmark	931 467	1 070 440	556 714	556 714
Finland	717 900	1 082 085	514 556	514 556
Sweden	1 697 283	1 745 739	805 012	805 012
Mean (SD) age (years)	76.4 (7.4)	75.5 (7.6)	75.4 (7.4)	75.4 (7.4)
Women	1 816 723 (54.3)	2 115 708 (54.3)	1 018 494 (54.3)	1 018 494 (54.3)
XBB.1.5 containing vaccine dose:†				
Fifth dose	1 441 887 (43.1)	NA	999 771 (53.3)	NA
Sixth dose	1 281 480 (38.3)	NA	700 294 (37.3)	NA
Seventh dose	461 631 (13.8)	NA	175 057 (9.3)	NA
Eighth dose	161 652 (4.8)	NA	1160 (0.1)	NA
Severe covid-19 risk group	697 138 (20.8)	916 576 (23.5)	436 844 (23.3)	436 844 (23.3)
Healthcare workers	135 070 (4.0)	175 036 (4.5)	82 849 (4.4)	82 849 (4.4)
Autoimmune related condition	152 697 (4.6)	164 495 (4.2)	76 312 (4.1)	75 746 (4.0)
Cancer	254 714 (7.6)	283 411 (7.3)	131 504 (7.0)	129 805 (6.9)
Chronic pulmonary disease	137 941 (4.1)	153 121 (3.9)	72 739 (3.9)	70 999 (3.8)
Cardiovascular condition	381 255 (11.4)	410 742 (10.5)	191 727 (10.2)	191 700 (10.2)
Diabetes	273 745 (8.2)	326 861 (8.4)	153 891 (8.2)	155 714 (8.3)
Renal disease	93 121 (2.8)	105 895 (2.7)	45 229 (2.4)	47 494 (2.5)
No of comorbidities:				
0	2 885 554 (86.2)	3 386 853 (86.9)	1 640 061 (87.4)	1 640 061 (87.4)
1	423 273 (12.6)	470 730 (12.1)	219 800 (11.7)	219 800 (11.7)
2	36 210 (1.1)	38 972 (1.0)	16 018 (0.9)	16 018 (0.9)
≥3	1613 (0.0)	1709 (0.0)	403 (0.0)	403 (0.0)

Data are number (%) unless indicated otherwise.
*Individuals eligible for vaccination with the XBB.1.5 containing vaccine as of the start of the study on 1 October 2023.
†XBB.1.5 containing vaccine received as fifth, sixth, seventh, or eighth dose of covid-19 vaccine.
NA, not applicable.

Statistical analysis

We used the Aalen-Johansen estimator to obtain cumulative incidences of the outcomes among recipients and non-recipients of the XBB-1.5 containing vaccine; any death and non-covid-19 related death served as a competing risk for the analysis of hospital admissions and deaths related to covid-19, respectively. Relative (ie, comparative vaccine effectiveness, calculated as 1−risk ratio) and absolute (ie, estimated number of outcome events prevented by vaccination, reported per 100 000 individuals) risk differences were calculated from the cumulative incidences at the 24 week follow-up. The corresponding 95% confidence intervals (CIs) were calculated with the delta method; upper 95% CIs for the comparative vaccine effectiveness estimates were truncated at 100% if higher. We combined country specific estimates by random effects meta-analyses implemented with the mixmeta package in R.[11] This method allows for potential heterogeneity in effect across countries when combined, reflected by the precision of the 95% CIs from the meta-analysis. Counts <5 could not be reported owing to privacy regulations, whereas zero could be reported.

Subgroup analyses were done by sex (women *v* male), age groups (64-75 *v* ≥75 years), number of doses of previous covid-19 vaccines (ie, the XBB.1.5 containing vaccine received as the fifth, sixth, or seventh dose; ≥eighth dose was too few for separate analysis), and seasonal influenza vaccination (co-administered on the same date, received influenza vaccine within one week before to one week after the XBB.1.5 containing vaccine but not on the same day, and no influenza vaccine received within one week before to one week after receipt of the XBB.1.5 containing vaccine). Variant specific comparative effectiveness was assessed at the six week follow-up and by grouping calendar time to before (XBB lineage, mainly EG.5.1 predominant) and after (BA.2.86 lineage, mainly JN.1 predominant) 30 November 2023. Given the short overlap in time where the XBB lineage was predominant and the vaccine was given, the variant specific analysis only had six weeks of follow-up (to standardise follow-up length for the two sublineage periods).

Changes in comparative vaccine effectiveness during follow-up (ie, waning vaccine immunity) were assessed by dividing the follow-up period into three

week intervals for both recipients and non-recipients. This method was used to estimate cumulative incidences with the Aalen-Johansen estimator to obtain estimates for comparative vaccine effectiveness for each three week period separately. These estimates were then meta-analysed and we subsequently fitted a linear regression, where the slope coefficient represented the percentage point change in comparative vaccine effectiveness for each three week period.[12] Sensitivity analyses included not considering death as a competing risk (ie, with the Kaplan-Meier estimator; we also included an analysis of the competing risk as an outcome), starting follow-up three weeks after the index date (to further reduce the potential of transient healthy vaccine effect around the time of vaccination as well as the possible spillover effect from a delay between infection and the onset of severe disease), and examining three negative control outcomes (diverticular disease, clavicle fracture, and low back pain[13]).[14]

Patient and public involvement

No patients or members of the public were formally involved in defining the research question, study design, or outcome measures, or in the conduct of the study, owing to privacy constraints, funding restrictions, and the short timeline during which the study was conducted. Studied participants were anonymised in the data sources used and 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 in layman's language.

Results

Study populations

Table 1 shows the characteristics of the study cohort before and after matching. Online supplemental figure S3 shows a flowchart of the cohort construction and online supplemental figure S4 shows distributions of age and index date by country in density plots. Before matching, the source population comprised 3 898 264 individuals eligible for vaccination with the XBB.1.5 containing covid-19 mRNA vaccine as of the start of the study on 1 October 2023. A total of 3 346 650 monovalent XBB.1.5 containing covid-19 mRNA vaccines were given during the study period. The matched study cohorts comprised 1 876 282 recipients of an XBB.1.5 containing vaccine during the study period (mean age 75.4 years, standard deviation 7.4 years; 54.3% women; 556 714 individuals from Denmark, 514 556 from Finland, and 805 012 from Sweden), matched with 1 876 282 non-recipients. Most XBB.1.5 containing vaccines were given as a fifth covid-19 vaccine dose (53.3%), during October 2023 in Denmark and November 2023 in Finland and Sweden. The distribution of the matched cohort characteristics was similar to that seen before matching.

Effectiveness of XBB.1.5 containing vaccine

Figure 1 shows the 24 week cumulative incidences of hospital admissions and deaths related to covid-19 in recipient versus matched non-recipients of the XBB.1.5 containing vaccine from one week after the vaccination date (online supplemental table S5 shows the number of events and number of individuals at risk during follow-up). The cumulative incidences of severe covid-19 outcomes were low for both recipients and non-recipients. The associated risk of admission to hospital with covid-19, however, was lower for individuals who had received an XBB.1.5 containing vaccine compared with individuals who had not (1085 *v* 2635 events), corresponding to an estimated comparative vaccine effectiveness of 57.9% (95% CI 49.9% to 65.8%) and risk difference per 100 000 individuals of −154.7 (−231.0 to −78.3) at week 24 (table 2). For deaths related to covid-19 (348 *v* 1458), the associated comparative vaccine effectiveness was 75.2% (70.6% to 79.9%), and the risk difference per 100 000 individuals was −120.3 (−130.2 to −110.5). Although comparative vaccine effectiveness was similar irrespective of sex, age group, and number of doses of previous covid-19 vaccines, the absolute risk difference was larger in individuals aged ≥75 years and in individuals who had received a higher number of doses of previous covid-19 vaccines (eg, risk differences against admission to hospital for covid-19 were −249.5, 95% CI −374.3 to −124.8 and −67.5, −100.1 to −34.9 per 100 000 individuals aged ≥75 years and <75 years, respectively). No apparent differences in comparative effectiveness were observed according to co-administration of the seasonal influenza vaccine. For variant specific analyses, we found slightly higher associated point estimates for comparative vaccine effectiveness during the XBB lineage than the BA.2 lineage predominant periods, whereas risk differences were more similar, with large overlaps in 95% confidence intervals.

Figure 2 shows the associated comparative vaccine effectiveness, with follow-up grouped by three week intervals, and the fitted trend line representing the change in effectiveness for each three week period during follow-up. Estimates suggested slightly higher initial reduction in risk, with comparative vaccine effectiveness of 64.5% (95% CI 49.0% to 80.0%) against hospital admission and 82.0% (78.5% to 85.5%) against death related to covid-19 after three weeks of follow-up, with subsequent gradual waning of −1.7 (95% CI −5.5 to 2.1) and −3.6 (−6.6 to −0.7) percentage points every three weeks, respectively.

In sensitivity analyses, where death was not used as a competing risk (online supplemental table S6) and follow-up was started three weeks after vaccination, we found no change in the overall findings (online supplemental table S7). Analysing the competing risk of death as an outcome gave a comparative vaccine effectiveness of 48.6% (36.5%

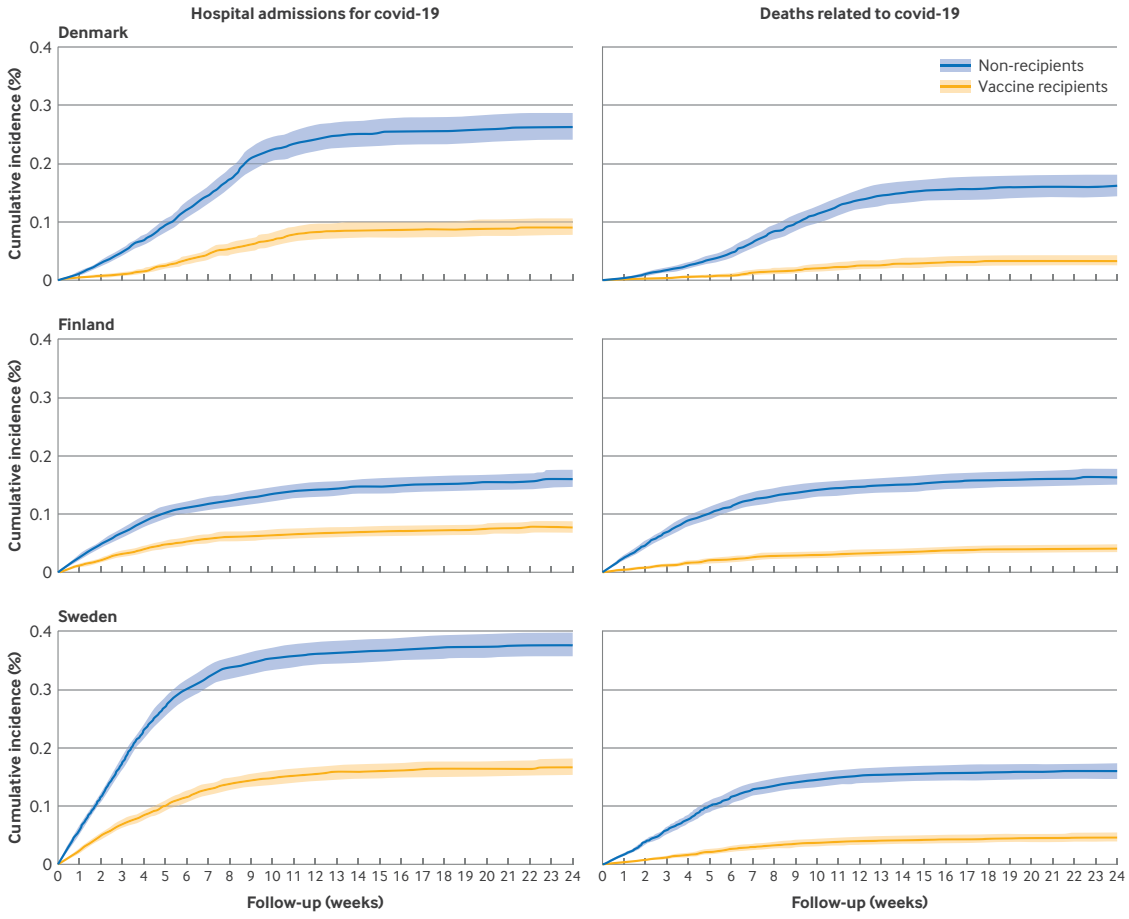


Figure 1 | Cumulative incidence curves for admission to hospital for covid-19 and and deaths related to covid-19 during 24 weeks of follow-up after immunisation (defined as one week after the day of vaccination). Recipients of a monovalent covid-19 mRNA vaccine containing the omicron XBB.1.5 subvariant during autumn and winter of 2023-24 were matched with non-recipients, aged ≥65 years

to 60.7%) with a risk difference of −1333.0 (−1905.3 to −760.7). Receiving the XBB.1.5 containing vaccine was not associated with lower risks of the negative control outcomes of diverticular disease, clavicle fracture, and low back pain (online supplemental table S8)

Discussion

Principal findings

In this multicohort analysis in Denmark, Finland, and Sweden of individuals aged ≥65 years, we found lower rates of hospital admissions for covid-19 and deaths related to covid-19 associated with receiving a dose of a monovalent, XBB.1.5 containing covid-19 mRNA vaccine, compared with those who did not receive a vaccine, during the autumn and winter of 2023-24. Specifically, we estimated a comparative vaccine effectiveness of 58% against hospital admissions and 75% against deaths related to covid-19 after 24 weeks of follow-up. Also, we found that the comparative vaccine effectiveness of the XBB.1.5 containing vaccine did not differ in men and women, or between age groups, number of doses of previous covid-19 vaccines, if seasonal influenza vaccination was co-administered, or between periods when the XBB lineage (eg, 5.1) and BA.2.86 lineage (eg, JN.1) were predominant. Absolute effects were largest for the more vulnerable subgroups, defined by age ≥75 years and having received more doses of previous covid-19 vaccines. Moreover, we found that the associated reduction in risk waned only modestly during follow-up, with well maintained comparative vaccine effectiveness at the end of 24 weeks.

Comparison with other studies

Our results indicated that covid-19 vaccination with the omicron XBB.1.5 subvariant containing vaccine, targeting elderly people, successfully prevented a substantial number of severe covid-19 events in Denmark, Finland, and Sweden during the autumn and winter of 2023-24. Our findings also align with the early short term vaccine effectiveness estimates of the XBB.1.5 containing vaccine.[5–8] With data from a 2.5 week period, from 8 to 26 October 2023, and an average follow-up of 9.9 days, a cohort analysis in Denmark found an early short term vaccine effectiveness of 76% against hospital admission related to covid-19 associated with the XBB.1.5 containing

Table 2 | Risk of hospital admissions for covid-19 and deaths related to covid-19 at 24 weeks of follow-up, comparing recipients with non-recipients of monovalent covid-19 mRNA vaccine containing the omicron XBB.1.5 subvariant, aged ≥65 years, in Denmark, Finland, and Sweden, during the study period 1 October 2023 to 21 April 2024*

		No of events/person years			
	Contributing countries	Vaccine recipients	Non-recipients	Risk difference (95% CI) per 100 000 individuals	Comparative vaccine effectiveness (%, 95% CI)
Hospital admissions for covid-19:					
All participants	Denmark, Finland, and Sweden	1085/324 937	2635/320 935	−154.7 (−231.0 to −78.3)	57.9 (49.9 to 65.8)
Women	Denmark, Finland, and Sweden	511/177 014	1192/175 008	−124.2 (−195.2 to −53.2)	55.4 (50.4 to 60.4)
Men	Denmark, Finland, and Sweden	574/147 923	1443/145 927	−190.0 (−271.6 to −108.4)	60.2 (50.5 to 70.0)
Age <75 years	Denmark, Finland, and Sweden	226/172 332	563/171 845	−67.5 (−100.1 to −34.9)	60.3 (51.9 to 68.7)
Age ≥75 years	Denmark, Finland, and Sweden	859/152 606	2072/149 090	−249.5 (−374.3 to −124.8)	57.6 (47.8 to 67.5)
Fifth dose of vaccine†	Denmark, Finland, and Sweden	454/204 753	1113/202 758	−117.5 (−185.6 to −49.3)	55.3 (43.2 to 67.4)
Sixth dose of vaccine†	Denmark, Finland, and Sweden	455/104 539	1092/103 083	−179.6 (−266.8 to −92.3)	56.7 (51.4 to 61.9)
Seventh dose of vaccine†	Sweden	175/15 506	428/14 957	−378.5 (−470.9 to −286.1)	56.5 (47.3 to 65.8)
Influenza vaccine received on same day‡	Denmark, Finland, and Sweden	416/181 868	1039/179 540	−144.3 (−217.5 to −71.1)	57.5 (48.1 to 67.0)
Influenza vaccine received within 1 week‡	Denmark, Finland	6/4902	29/4848	−182.8 (−317.5 to −48.1)	85.5 (60.8 to 100.0)
No concurrent influenza vaccine received‡	Denmark, Finland, and Sweden	52/25 588	137/25 341	−188.5 (−343.7 to −33.3)	72.3 (54.6 to 89.9)
XBB sublineages predominant§	Denmark, Finland, and Sweden	386/61 938	1110/61 771	−130.6 (−252.6 to −8.7)	75.1 (69.6 to 80.5)
BA.2.86 sublineages predominant§	Denmark, Finland, and Sweden	416/63 158	990/62 987	−89.9 (−144.4 to −35.4)	56.3 (48.5 to 64.0)
Deaths related to covid-19:					
All participants	Denmark, Finland, and Sweden	348/326 382	1458/322 733	−120.3 (−130.2 to −110.5)	75.2 (70.6 to 79.9)
Women	Denmark, Finland, and Sweden	168/177 650	654/175 814	−98.3 (−110.8 to −85.9)	73.4 (68.5 to 78.2)
Men	Denmark, Finland, and Sweden	180/148 731	804/146 919	−147.4 (−169.3 to −125.4)	76.5 (71.7 to 81.4)
Age <75 years	Denmark, Finland, and Sweden	48/172 688	181/172 252	−28.3 (−35.2 to −21.5)	71.7 (62.4 to 81.0)
Age ≥75 years	Denmark, Finland, and Sweden	300/153 694	1277/150 481	−222.7 (−242.2 to −203.2)	76.0 (70.4 to 81.5)
Fifth dose of vaccine†	Denmark, Finland, and Sweden	143/205 322	590/203 474	−83.5 (−122.1 to −44.9)	74.9 (67.4 to 82.3)
Sixth dose of vaccine†	Denmark, Finland, and Sweden	145/105 335	636/104 030	−237.2 (−464.2 to −10.3)	75.6 (71.0 to 80.3)
Seventh dose of vaccine†	Sweden	60/15 724	232/15 229	−277.5 (−354.7 to −200.2)	66.0 (54.4 to 77.5)
Influenza vaccine received on same day‡	Denmark, Finland, and Sweden	178/182 537	790/180 340	−128.2 (−141.9 to −114.4)	76.5 (72.5 to 80.5)
Influenza vaccine received within one week‡	Finland	<5/1216	7/1214	−153.0 (−348.8 to 42.8)	65.8 (18.9 to 100.0)
No concurrent influenza vaccine received‡	Denmark, Finland, and Sweden	19/25 667	91/25 439	−96.7 (−126.0 to −67.4)	81.7 (66.2 to 97.2)
XBB sublineages predominant§	Denmark, Finland, and Sweden	81/62 052	454/61 908	−70.5 (−112.0 to −29.0)	85.7 (80.6 to 90.8)
BA.2.86 sublineages predominant§	Denmark, Finland, and Sweden	126/63 503	588/63 353	−77.3 (−85.0 to −69.5)	78.0 (74.3 to 81.6)

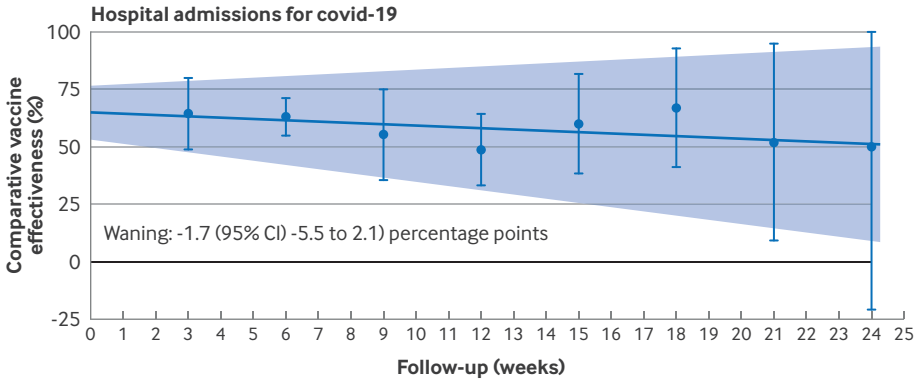
*Individuals were followed for 24 weeks (from one week after the vaccination date), except for estimates by predominant omicron sublineages where individuals were followed for six weeks (online supplemental table S9 shows I^2 statistics from the random effects meta-analyses).

†XBB.1.5 containing vaccine received as fifth, sixth, or seventh dose of vaccine. Risk of covid-19 outcomes could not be studied separately in subgroups of individuals where the XBB.1.5 containing vaccine was received as an eighth dose or higher because of too few events.

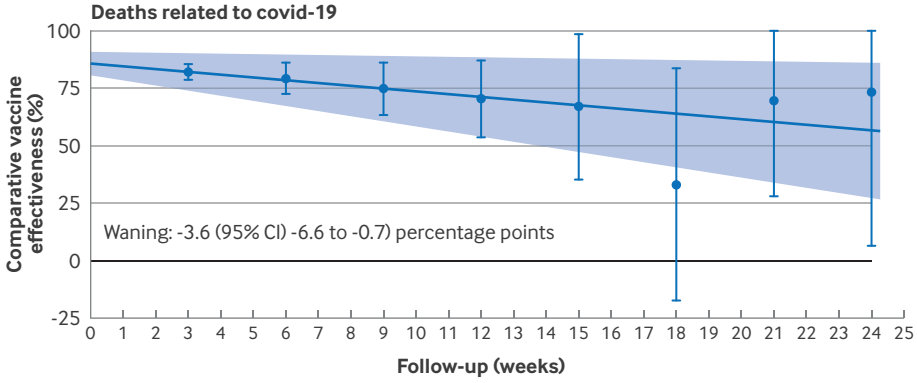
‡Information about influenza vaccination status was only available for three regions in Sweden (ie, the other regions were not included in the influenza co-administration analysis).

§Assessed at six weeks after the start of follow-up (online supplemental table S10 has the results for the overall six week follow-up).

CI, confidence interval.



Time	Weeks 1-3	Weeks 4-6	Weeks 7-9	Weeks 10-12	Weeks 13-15	Weeks 16-18	Weeks 19-21	Weeks 22-24
CVE (%, 95% CI)	64.5 (49.0 to 80.0)	63.1 (54.9 to 71.3)	55.4 (35.6 to 75.1)	48.8 (33.1 to 64.4)	60.1 (38.4 to 81.8)	67.0 (41.3 to 92.8)	52.3 (9.5 to 95.0)	50.1 (-20.9 to 100.0)



Time	Weeks 1-3	Weeks 4-6	Weeks 7-9	Weeks 10-12	Weeks 13-15	Weeks 16-18	Weeks 19-21	Weeks 22-24
CVE (%, 95% CI)	82.0 (78.5 to 85.5)	79.3 (72.4 to 86.1)	74.6 (63.3 to 86.0)	70.3 (53.6 to 87.0)	66.9 (35.3 to 98.4)	33.1 (-17.3 to 83.6)	69.4 (28.1 to 100.0)	73.4 (6.7 to 100.0)

Figure 2 | Waning comparative vaccine effectiveness against admission to hospital for covid-19 and deaths related to covid-19 during 24 weeks of follow-up after immunisation (defined as one week after the day of vaccination). Recipients of a monovalent covid-19 mRNA vaccine containing the omicron XBB.1.5 subvariant during autumn and winter of 2023-24 were compared with matched non-recipients, aged ≥65 years, with follow-up grouped by three week intervals. Waning percentage point estimates represent the trend line in estimates for comparative vaccine effectiveness for each three week period. CVE=comparative vaccine effectiveness; CI=confidence interval

covid-19 vaccine.[6] Similar early season vaccine effectiveness was reported by the VEBIS (Vaccine Effectiveness Burden and Impact Studies) project of >66% against hospital admissions for covid-19 and deaths related to covid-19 (data until 25 November 2023) and from the Netherlands of 71% against hospital admissions related to covid-19 (data until 5 December 2023).[7 8] Based on a test negative case-control design, reports from the UK found that the XBB.1.5 containing vaccine was associated with a comparative vaccine effectiveness peak of 55% against hospital admissions related to covid-19, 2-4 weeks after vaccination in individuals aged ≥65 years.[5 15] Our findings also suggest that the protection provided by the XBB.1.5 containing vaccine was initially high, with an estimated overall comparative vaccine effectiveness after three weeks of follow-up (ie, four weeks from the vaccination date) of 65% and 82% against hospital admissions and deaths related to covid-19, respectively. A similar initial peak in comparative vaccine effectiveness of 66% at four weeks after vaccination with the XBB.1.5 containing vaccine against hospital admissions or deaths related to covid-19 was recently reported in a cohort study from Nebraska, US.[16]

Our results expand on previous evidence by reporting estimates based on long term follow-up data (until 21 April 2024), which facilitates the evaluation of the comparative effectiveness for the entire autumn and winter 2023-24-season and allows assessment of waning of vaccine immunity over a 24 week period. The study adds to the current evidence by our reports of relative and absolute effects and our analysis of a range of clinically important

subgroups of patient characteristics. We also showed that the associated comparative effectiveness of the XBB.1.5 containing vaccine against severe covid-19 outcomes was relatively similar between the periods when the XBB and BA.2.86 sublineages were predominant. Estimates from the UK suggested that vaccination with the XBB.1.5 containing or bivalent BA.4-5 booster mRNA covid-19 vaccine (ie, the XBB.1.5 containing vaccine was not studied separately) had higher relative protection against hospital admissions with XBB sublineages,[15] a tendency also seen for the XBB.1.5 containing vaccine alone in a recent study from the US.[16] Although our results similarly tended towards a higher associated comparative vaccine effectiveness during the period when the XBB rather than the BA.2.86 sublineage was predominant (and more so for hospital admissions than deaths related to covid-19), the difference in absolute risk difference, however, was small, with largely overlapping 95% confidence intervals. Differences could be explained by variations in background transmission rates during the sublineage predominant periods or susceptibility to developing severe disease (eg, more frail individuals) between those contributing to the earlier (XBB sublineage period) rather than the later (BA.2.86 sublineage period) follow-up period, or a combination of these factors. Any indirect comparison of the comparative effectiveness of a covid-19 vaccine against different strains of the SARS-CoV-2 virus is inherently affected by the strong correlation with calendar time.

In contrast with these studies, our results complement the relative effect estimates with estimates of the benefits of vaccination in absolute terms. Specifically, the comparative effectiveness estimates of our primary analysis corresponded to 155 (95% CI 78 to 231) hospital admissions and 120 (111 to 130) deaths related to covid-19 prevented per 100 000 individuals who were vaccinated with an XBB.1.5 containing vaccine in Denmark, Finland, and Sweden. Moreover, although the relative comparative vaccine effectiveness measures were similar, we found larger associated absolute benefits from vaccination with the XBB.1.5 containing vaccine for those aged ≥75 years and for those who had received more doses of previous covid-19 vaccines, reflecting the greater background risk for these subpopulations. Absolute measures of the benefits of vaccination are essential for public health messaging and policy evaluation and planning.

Strengths and limitations of this study

Our study had some limitations. Firstly, we estimated the comparative effectiveness of the XBB.1.5 containing vaccine in routine clinical care in Denmark, Finland, and Sweden. This approach implies lack of controlled randomisation of the intervention, which could be a major limitation. To account for this non-randomisation of intervention in the observational data used in this study, we conditioned on potential key confounders and used an active comparative design where we compared vaccine recipients with individuals who, up until the index (vaccination) date, had undergone the same timely covid-19 vaccination course. For our results to be biased, unmeasured confounding factors would need to be unevenly distributed between the comparison groups and not indirectly considered by the set of included covariates (ie, proxies). Although a relative healthy users bias cannot be ruled out, in the matched cohort, the non-recipient (reference) individual generally received an XBB.1.5 containing vaccine later than the assigned index date. Opting for earlier relative to later in-season vaccination could represent differences in the risk of severe covid-19 disease. We found an associated reduction in risk for the competing risk of death, which is likely because individuals who were close to the end of life did not receive a vaccine. We did not find similar patterns of associated reduction in risk in analyses of negative control outcomes, indicating that healthcare seeking bias was not prevalent in our comparison, but we cannot fully exclude the possibility of residual confounding.

Secondly, our determination of outcomes likely also captured a proportion of patients where infection with the SARS-CoV-2 virus only partly contributed to or coincided with the timing of admission to hospital or death. Thirdly, as part of our outcome definitions, individuals were required to have a positive PCR test result for the SARS-CoV-2 virus, and therefore individuals who were admitted to hospital for covid-19 or who died because of covid-19 but were not tested were missed. Misclassification of outcomes is most likely non-differential between active comparison groups and would tend to skew the results towards the null. Finally, most individuals who received an XBB.1.5 containing vaccine also received their seasonal influenza vaccine on the same day. Hence the 95% confidence intervals for the other subgroups of seasonal influenza vaccination status were more imprecise, also implying that our main estimates primarily reflected co-administration with the seasonal influenza vaccine. This finding is reassuring because co-administration with the influenza vaccine has been speculated to blunt the immune response,[17–22] and if that is the case, our estimates are likely conservative.

Because we studied the general population of adults aged ≥65 years, our results should be generalisable to other similar populations targeted for vaccination with the XBB.1.5 containing vaccine during the autumn and winter of 2023-24. But our results might only indirectly support evaluations in populations not represented in the analyses (eg, individuals aged <65 years, those who received <4 covid-19 vaccine doses before receiving the XBB.1.5 containing vaccine, or individuals previously

admitted to hospital for covid-19). Similarly, analyses were carried out for the autumn and winter 2023-24 season when the XBB sublineages (particularly EG.5.1, until about the end of November 2023) and subsequently the BA.2.86 sublineages (particularly JN.1) were the most prevalent variants. Consequently, how our results relate to the associated reduction in risk of severe covid-19 caused by other subvariants of the SARS-CoV-2 virus is not known.

Conclusions

We found that the monovalent covid-19 mRNA vaccine containing the omicron XBB.1.5 subvariant was associated with reduced rates of hospital admissions and deaths related to covid-19, in individuals aged ≥65 years, over 24 weeks of follow-up, during the autumn and winter of 2023-24 in Denmark, Finland, and Sweden. We found that the associated reduction in risk was similar irrespective of sex, age group, number of doses of previous covid-19 vaccines, subgroup of co-administration of the seasonal influenza vaccine, or when the XBB lineage (eg, 5.1) and BA.2.86 lineage (JN.1) were predominant. Although the associated reduction in risk was highest during the first weeks after vaccination, comparative vaccine effectiveness was well maintained by the end of the 24 weeks of follow-up.

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Ethics approval Denmark: The Danish analyses were performed as surveillance activities analyses as part of the advisory tasks of the governmental institution Statens Serum Institut (SSI) for the Danish Ministry of Health. SSI's purpose is to monitor and fight the spread of disease in accordance with section 222 of the Danish Health Act. According to Danish law, national surveillance activities conducted by SSI do not require approval from an ethics committee. Both the Danish Governmental law firm and the compliance department of SSI have confirmed that the study is fully compliant with all legal, ethical, and IT security requirements, and no further approval procedures are required for such studies. Finland: By Finnish law, the Finnish Institute for Health and Welfare (THL) is the national expert institution to carry out surveillance of the impact of vaccinations in Finland (Communicable Diseases Act, https://www.finlex.fi/en/laki/kaannokset/2016/en20161227.pdf). Neither specific ethical approval of this study nor informed consent from the participants were needed. Sweden: The Swedish analyses were conducted under the Swedish Ethical Review Authority approval 2020-06859, 2021-02186 and conformed to the principles embodied in the Declaration of Helsinki. Register based studies (like this) in Sweden are exempt from obtaining consent to participate.

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