STUDY REPORT

1. TITLE

Effectiveness of monovalent XBB.1.5-containing Covid-19 mRNA vaccine in Denmark, Finland, and Sweden

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2. ABSTRACT

Rationale and background: The Nordic countries of Denmark, Finland, and Sweden, provide a unique setting for the study of Covid-19 vaccine effectiveness. The ubiquitous nationwide demography- and health registers, which include SARS-CoV-2 immunization and surveillance registers, allow for very large study cohorts with near real-time data availability. In the three Nordic countries, the monovalent XBB.1.5-containing Covid-19 vaccine was offered to adults aged 65 years or older during autumn and winter 2023-2024. However, data to inform on the effectiveness are limited.

Research question and objectives: The aim of this project was to evaluate the comparative effectiveness of the monovalent XBB.1.5-containing Covid-19 vaccine in preventing severe Covid-19 outcomes among individuals aged 65 years or older.

Study objectives:

1. To assess the effectiveness of monovalent XBB.1.5-containing Covid-19 vaccine for the prevention of severe Covid-19 related outcomes (Covid-19 related hospitalization or Covid-19 related death).
2. To assess waning of the effectiveness of monovalent XBB.1.5-containing Covid-19 vaccine for the prevention of severe Covid-19 related outcomes (Covid-19 related hospitalization or Covid-19 related death).
3. To assess how the effectiveness of monovalent XBB.1.5-containing Covid-19 vaccine is affected by the coadministration with an influenza vaccine.

Study design and setting: Nationwide register-based cohort analyses in Denmark, Finland, and Sweden, during the study period from 1 October 2023 until 29 February 2024. Using target trial emulation, we compared recipients of a monovalent XBB.1.5-containing Covid-19 vaccine with non-recipients in a matched survival analysis with 12 weeks of follow-up, providing comparative effectiveness estimates.

Population: The study cohorts consisted of all individuals who were at least 65 years of age, were residents in one of the three Nordic countries and had received at least four Covid-19 vaccine doses as of 1 October 2023.

Study size: We expected approximately 3.1 million recipients of an XBB.1.5-containing Covid-19 vaccine as a ≥5th Covid-19 vaccine dose during autumn and winter 2023-2024 across the 3 Nordic

countries. All available data within countries were used and the statistical power of our study is reflected in the 95% CIs of the effectiveness estimates.

Variables: The outcomes of interest were Covid-19 hospitalization and Covid-19 related death. Covariates were variables of demography, comorbidity, and previous Covid-19 vaccination.

Data sources: Nationwide demography- and healthcare registers within each participating country.

Results: The source cohorts comprised 3,066,104 recipients of the XBB.1.5-containing vaccine in the three countries, prior to matching. Most recipients were from Sweden (1,419,714), followed by Denmark (928,226) and Finland (718,164). The matched cohorts consisted of a total of 1,867,448 recipients of the XBB.1.5-containing vaccine during the study period (with a mean age of 75, SD 7.4 years) matched 1:1 with 1,867,448 non-recipients. Most XBB.1.5-containing vaccines were administered as a fifth dose (53.2%) and during October 2023 in Denmark and November 2023 in Finland and Sweden. Overall, characteristics such as age, sex, healthcare worker occupation, and number and type of comorbidities among the matched pairs were similar to those of the unmatched populations.The estimated comparative vaccine effectiveness (CVE) was 60.6% (95% confidence interval [CI]: 46.1% to 75.1%) against covid-19 hospital admission (930 v 2,551 events) and 77.9% (69.2% to 86.7%) against covid-19 related death (301 v 1,326 events) at 12 weeks of follow-up. In absolute terms, this corresponded to an estimated 191.1 (95% CI: 50.2 to 332.1) covid-19 hospital admissions and 109.2 (100.2 to 118.1) deaths prevented per 100,000 recipients of an XBB.1.5-containing vaccine. We did not observe any differences in the CVE across sex, age (65-74/≥75 years), number of previous covid-19 vaccine doses received, seasonal influenza vaccine co-administration, and periods of either omicron XBB (primarily EG.1) or BA.2.86 (primarily, JN.1) lineage dominance. The protection peaked during the first weeks following vaccination, but remained well-preserved by the end of follow-up at 12 weeks.

Discussion: Our findings align with the available evidence, suggesting a high short-term vaccine effectiveness of the XBB.1.5-containing vaccine in preventing severe Covid-19 related outcomes. We expand on previous results by providing autumn and winter 2023-2024-season effectiveness estimates with 12 weeks of follow-up. We further add by evaluating waning of effectiveness and the effectiveness during periods of either XBB (primarily EG.1) or BA.2.86 (primarily, JN.1) lineage dominance and effectiveness within a wide range of population subgroups of relevance to vaccination guideline recommendations.

Given the observational nature of the study, confounding is a potential concern. Thus, we considered key predictors of the outcomes or proxies hereof. The accuracy of our exposure, Covid-19 vaccination, relied on high-quality national vaccination registers. Our outcome definitions most likely also captured

a small proportion of cases where the infection with SARS-CoV-2 only partly contributed to or coincided with the timing of the hospitalization or death. SARS-CoV-2 was ascertained by positive PCR test results. Thus, those who acquired SARS-CoV-2 infection and were hospitalized or died but were not tested were missed. Our active comparative design, however, mitigated concerns that such outcome misclassification differed between compared groups to any larger extent as e.g., opposed to comparisons with individuals never vaccinated with the Covid-19 vaccines. Any misclassification likely tended to skew estimates toward conservative results if differences truly existed.

Both vaccination status and SARS-CoV-2 variants of predominance are strongly correlated with calendar time. This reduces possibilities for a valid direct comparison between effectiveness estimates obtained during different periods of variant predominance (e.g., background transmission rates, time since vaccination and characteristics of the study subjects most likely differ) as well as evaluating longer-term follow-up effectiveness in relation to only one SARS-CoV-2 variant. The majority of the study population received both the influenza and the XBB.1.5-containing Covid-19 vaccine on the same day, meaning that the statistical power of the subgroup analyses within populations not concurrently vaccinated were lower.

Conclusion: We observed reduced rates of Covid-19 related hospital admission and death following vaccination with XBB.1.5-containing covid-19 vaccine in adults aged ≥65 years during autumn and winter 2023-2024 across the three Nordic countries of Denmark, Finland, and Sweden. We found that the protection gained was similar between, sex, age, and number of previous Covid-19 vaccine doses received. Furthermore, we did not observe any differences in vaccine effectiveness after seasonal influenza vaccine co-administration nor during predominance of XBB-lineage (EG.5.1) or BA.2-lineage (JN.1). The protection peaked during the first weeks following vaccination, and remained well-preserved up to 12 weeks of follow-up.

Names and affiliations of principal investigators: Anders Hviid, Pharmacovigilance Research Center, Department of Drug Design and Pharmacology, University of Copenhagen, and Department of Epidemiology Research, Statens Serum Institut, Denmark.

3. MARKETING AUTHORIZATION HOLDER(S)

Not applicable.

4. INVESTIGATORS

All main responsible parties including the main author(s) of the protocol, the principal investigator, a coordinating investigator for each country/organization in which the study was performed and other relevant study sites are presented in the table below.

Name	Professional Title	Over qualifications and role in the study of the organization	Affiliation and address
Lars Bo Nielsen	Director of department	Project management, QA, involvement in scientific tasks, ensuring regulatory anchoring. Overall and contract management	Danish Medicines Agency, Data Analytics Centre, Axel Heides Gade 1, 2300 Copenhagen S, Denmark
Niels Henrik Meedom	Project and contract manager		
Anders Hviid	Professor	Study principal investigator; overall coordination and oversight of the study, responsible for the submission of deliverables	Statens Serum Institut, Department of Epidemiology Research, Artillerivej 5, 2300 Copenhagen S, Denmark
Niklas Andersson	Researcher	Pharmacoepidemiologist; Danish principal investigator, scientific coordination and conduct of Danish analyses, responsible for the meta-analyses of all the site-specific results, literature review, ENCEPP, STROBE compliance, drafting study protocols, reports and manuscripts, submission process, revisions etc.	
Eero Poukka	Researcher	Medical specialist; Finnish principal investigator, local scientific coordination and analyses conduct, review and approval of deliverables, and critical revision of manuscripts.	Finnish Institute for Health and Welfare, Mannerheimintie 166, 00271 Helsinki, Finland
Rickard Ljung	Professor	Senior epidemiologist; Swedish principal investigator, local scientific coordination and analyses conduct, review and approval of deliverables, and critical revision of manuscripts	Swedish Medical Products Agency, Division of Use and Information, SE3751 03 Uppsala, Sweden

The table below presents all named scientific personnel in the study group together with their respective role in the study.

Organization	Name	Function in the study	Description of the function
SSI (DK)	Anders Hviid	Principal investigator	Overall coordination and oversight of the study; responsible for the submission of deliverables

SSI (DK)	Niklas Worm Andersson	Danish principal investigator	Scientific coordination of Danish analyses, drafting study protocols, reports and manuscripts.
SSI (DK)	Emilia Myrup Thiesson	Statistician	Conduct of Danish analyses, meta- analyses of country-specific results.
SSI (DK)	Mie Agermose Gram	Junior epidemiologist	Local project management, literature review, drafting study protocols, reports and manuscripts.
SSI (DK)	Kristyna Faksova	Junior epidemiologist	Local project management, literature review, drafting study protocols, reports and manuscripts.
DKMA (DK)	Elvira Bräuner	Senior epidemiologist	Project management including contribution to discussions about impact of results on regulatory decision-making.
THL (FI)	Tuija Leino	Senior epidemiologist	Local administrative coordination, scientific supervision.
THL (FI)	Eero Poukka	Finnish principal investigator	Scientific coordination of Finnish analyses, drafting study protocols, reports and manuscripts. Approval of deliverables.
THL (FI)	Jori Perälä	Statistician	Conduct of Finnish analyses.
SWE MPA (SE)	Rickard Ljung	Swedish principal investigator	Scientific coordination of Swedish analyses, drafting study protocols, reports and manuscripts. Approval of deliverables.
SWE MPA (SE)	Nicklas Pihlström	Statistician	Conduct of the Swedish analyses.

5. MILESTONES

Milestones	**Planned dates**
Study start	8 January 2024
Study planning meeting	22 January 2024
Study Protocol submission (posted on EU-PAS register when approved by EMA).	25 March 2024
Registration in the EU-PAS Register	25 March 2024
Study Report submission (posted on EU-PAS register when approved by EMA).	8 May 2024
Manuscript(s) ready for submission.	8 July 2024

6. RATIONALE AND BACKGROUND

The emergence of the SARS-CoV-2 Omicron variant in late 2021 raised concerns about the effectiveness of the original monovalent Covid-19 vaccines. Following the adapted bivalent Covid-19 vaccine targeting the Omicron BA.1 and BA.4-5 subvariants, monovalent vaccine targeting the Omicron XBB.1.5 subvariant was developed and authorized for use in the autumn and winter 2023-2024 [1,2]. The XBB.1.5-containing Covid-19 vaccine has been rolled out from 1 October 2023 in Denmark, Finland and Sweden, and recommended for high-risk population groups including all people older than 65 years, in the form of a 5th or 6th Covid-19 vaccine dose, with variation across countries [3].

Evidence on the effectiveness of the monovalent XBB.1.5-containing Covid-19 vaccine is limited. However, a few studies have assessed the short-term effectiveness and immunogenicity of this vaccine. With a limited 2.5-week study period of 8 to 26 October 2023, an early report from Denmark showed a high short-term vaccine effectiveness (VE) of 76% against Covid-19 related hospitalization of the XBB.1.5-containing Covid-19 vaccine, with an average follow-up of only 9.9 days [3]. A screening method-based study conducted in the Netherlands assessed VE of the XBB.1.5 vaccine against Covid-19 related hospitalization and admission to intensive care from 9 October 2023 to 5 December 2023 [4]. The study involved 2,050 hospitalized individuals older than 60 years, of whom 295 (14.4%) had received the XBB.1.5-containing Covid-19 vaccine. The VE was estimated at 70.7% (95% confidence interval [CI]: 66.6 to 74.3) against hospitalization and 73.3% (95% CI: 42.2 to 87.6) against intensive care unit admission[4]. Another study from the USA analyzed data from the Increasing Community Access to Testing SARS-CoV-2 pharmacy testing program to estimate VE for the updated XBB.1.5-containing Covid-19 vaccine, comparing vaccination with an XBB.1.5-containing Covid-19 vaccine as additional Covid-19 vaccine dose against symptomatic SARS-CoV-2 infection versus no additional vaccine dose [5]. The monovalent XBB.1.5-containing Covid-19 vaccine provided 54% (95% CI: 46 to 60%) protection against symptomatic SARS-CoV-2 infection at a median of 52 days after vaccination among adults aged ≥18 years [5]. Similarly, the UK Health Security Agency reported VE of the monovalent XBB.1.5-containing vaccine of 55.4% against hospitalization 2 to 4 weeks after vaccination among those aged 65 years and older in England [6].

A randomized study investigated the immunogenicity of the Moderna XBB.1.5-containing mRNA vaccine administered as a 5th dose [7]. The vaccinated population consisted of adults who previously received a primary series plus a 3rd dose of the original mRNA Covid-19 vaccine, and a 4th dose of the bivalent omicron BA.4-5-containing vaccine. The results showed that monovalent XBB.1.5-containing Covid-19 vaccine provides protection against emerging variants (XBB.1.5, XBB.1.6, XBB.2.3.2, EG.5.1, FL.1.5.1, and BA.2.86) and support the Covid-19 vaccine update to the monovalent XBB.1.5-containing

vaccine [7]. Similarly, findings by Wang et al. confirm that the XBB.1.5-containing monovalent mRNA vaccine markedly increase the magnitude of serum neutralizing antibodies against the prevalent SARS-CoV-2 Omicron subvariants such as XBB.1.5 and EG.5.1 [8].

In summary, the available evidence suggests that the XBB.1.5-containing Covid-19 vaccine can provide additional protection against Covid-19 hospitalization but data are sparse and only short-term follow-up has been assessed.

7. RESEARCH QUESTION AND OBJECTIVES

The aim of this project was to evaluate the comparative effectiveness of the monovalent XBB.1.5-containing Covid-19 vaccine in preventing severe Covid-19 outcomes among individuals aged 65 years or older.

Study objectives:

1. To assess the effectiveness of monovalent XBB.1.5-containing Covid-19 vaccine for the prevention of severe Covid-19 related outcomes (Covid-19 related hospitalization or Covid-19 related death).
2. To assess waning of the effectiveness of monovalent XBB.1.5-containing Covid-19 vaccine for the prevention of severe Covid-19 related outcomes (Covid-19 related hospitalization or Covid-19 related death).
3. To assess how the effectiveness of monovalent XBB.1.5-containing Covid-19 vaccine is affected by the coadministration with an influenza vaccine.

8. AMENDMENTS AND UPDATES

Number	Date	Section	Amendment or update	Reason
1	30/05/2024	Title and 9.1 Study design	Nordic countries specified	To clarify which countries were included in the analysis
2	30/05/2024	Abstract and 10.1.1 General population characteristics	More details on cohort characteristics provided	To provide more details on similar characteristics among matched and non-matched populations
3	30/05/2024	Abstract	Clarification on the end of follow up at 12 weeks	To clarify the end of follow-up period

4	30/05/2024	13. Conclusion	Inclusion of regulatory-oriented interpretation in the conclusion section	To improve readability of the report
5	30/05/2024	11.1 Key results	Added clarification on follow-up periods in CVE estimates and waning of protection estimates	To enhance interpretation of the results

9. RESEARCH METHODS

9.1 Study design

We took advantage of the unique nationwide register data available to us, and constructed country cohorts with individual-level information on dates of vaccination and dates of effectiveness endpoints together with relevant covariate information. All Nordic residents are assigned a unique personal identifier at time of birth or immigration, enabling linkage between registers. The three Nordic countries have universal and tax-financed healthcare systems and reporting to national registers is mandatory, providing near-complete follow-up of all residents over time. The cohort participants were classified according to Covid-19 vaccinations received and followed up using survival analysis. We utilized a comparative design avoiding comparisons with unvaccinated individuals. This reduced concern about selection bias due to inherent differences in who chooses to remain unvaccinated.

The study period started on 1 October 2023. This study start date corresponded to when the XBB.1.5-containing Covid-19 vaccine was offered to the ≥65-year-olds in the three Nordic countries comprising Denmark, Finland, and Sweden. The study period ended on 29 February 2024, corresponding to the last date of data availability at time of analyses.

The research design built on the target trial emulation framework to estimate both relative and absolute effects. Key components of the specification and emulation of the pragmatic target trial of the effectiveness of the monovalent XBB.1.5-containing Covid-19 vaccine against severe Covid-19 using Nordic nationwide registry data are included in table below.

Protocol	Target Trial Specification	Target Trial Emulation
Eligibility criteria	• Aged ≥65 years in Denmark, Finland, and Sweden at start of study period (1 October 2023) • Have a known residency within the specific country at start of study period • Have received at least four Covid-19 vaccine doses (of AZD1222 and/or [original/BA4-5/BA-1 bivalent] mRNA vaccines [AZD1222 as part of the	Same as for the target trial.

	primary vaccination course only]) prior to the start of the study period • No history of Covid-19 hospitalization prior to the start of the study period	
Treatment strategies	1) Receive a monovalent XBB.1.5-containing Covid-19 vaccine at baseline and do not receive additional Covid-19 vaccine doses during follow-up 2) Do not receive a monovalent XBB.1.5-containing Covid-19 vaccine at baseline and continue being a non-recipient during follow-up	Same as for the target trial. We define the date of XBB.1.5-containing Covid-19 vaccine vaccination (that is, the index date) according to the registered date of administration.
Treatment assignment	Individuals are randomly assigned to a strategy at baseline in a 1:1 ratio	Individuals are assigned to the strategy compatible with their treatment received at that time (XBB.1.5 vaccinated and -unvaccinated); randomization is assumed conditional on matching (in a 1:1 ratio) on baseline covariates; XBB.1.5-unvaccinated are assigned the index date of the matched XBB.1.5 vaccine recipient.
Outcomes	Covid-19 hospitalization: inpatient hospitalization with a registered Covid-19-related diagnosis and a positive PCR test for SARS-CoV-2 (within 14 days before to 2 days after the day of admission) Covid-19 death: death within 30 days of a positive PCR test for SARS-CoV-2	Same as for the target trial.
Follow-up	Follow-up for each individual started at day 8 from treatment assignment (to ensure full immunization among XBB.1.5-containing Covid-19 vaccine recipients) and end on day of outcome event, week 12 of follow-up has passed (91 days since the index date), death, emigration, or end of the study period (29 February 2024), whichever occurs first. Data on covid-19 related hospitalization in Sweden was only available until 31 December 2023, so we ended follow-up on day 87 in Sweden for this specific analysis. If individuals who were included as a matched XBB.1.5-containing vaccine non-recipient (i.e., a reference individual) received an XBB.1.5-containing vaccine later than the assigned index date, they were allowed to potentially re-enter as an XBB.1.5-containing vaccine recipient in a new matched pair on that given date and the follow-up for the current pair was censored.	Same as for the target trial.
Causal contrast of interest	Per-protocol	Observational analog to per-protocol effect.
Statistical analysis	The Aalen-Johansen estimator was used to obtain cumulative incidence for each treatment strategy during follow-up (with death as a competing risk). We compared cumulative incidence across treatment strategies by risk ratios (to obtain VE) and risk differences.	Same as for the target trial except observational analogs of per-protocol.

	The Aalen-Johansen estimator was used to estimate VE as 1 – risk ratio at the end of week 12. In addition, person-time since baseline was stratified by consecutive 3-week intervals to estimate changes in VEs per 3-week intervals; these VEs contributed to a meta-regression estimating comparative waning. Subgroup analyses by sex (female/male), age (65-74/≥75 years), number of previous Covid-19 vaccine doses received, and influenza vaccination status were conducted.	

9.2 Setting

Eligibility criteria for study inclusion were:

1) Age of 65 years or older as of the study start,
2) Had a known residency within the specific country at the start of the study period (1 October 2023),
3) Had received at least four Covid-19 vaccine doses (of AZD1222, BNT162b2, or mRNA-1273 vaccines only [AZD1222 as part of the primary vaccination course only; an original/bivalent BA.4-5/BA.1 mRNA vaccine as the fourth/fifth vaccine dose) prior to start of study period,
4) Had no history of Covid-19 hospitalization prior to start of study period.

9.3 Variables

Exposures

The Nordic countries implemented national vaccination campaigns against SARS-CoV-2 from December 27, 2020, providing free vaccinations to all residents. Phased distribution plans were implemented prioritizing vaccination of individuals at highest risk of Covid-19 complications (nursing home residents, healthcare personnel, and individuals of older age). Denmark almost exclusively used mRNA vaccines after full or partial discontinuation of AZD1222 in March 2021 due to serious but rare events of thrombosis with thrombocytopenia. The AZD1222 was similarly halted in Finland and Sweden for the younger population but continued as part of the utilized primary course schedules for the population aged 65 years or more. The mRNA vaccines have been predominantly used in all countries for seasonal dose/additional Covid-19 vaccine vaccinations. Ad26.COV2.S has seen very limited use. The three Nordic countries have vaccinated around 6 times more individuals with BNT162b2 than with mRNA-1273. Prioritized fourth dose vaccination rollouts to the vulnerable elderly and those living in nursing home facilities were initiated in spring 2022 in Finland and Sweden,

and has been offered more broadly to the general population since summer 2022. During autumn and winter 2022-23, the bivalent BA.4-5 and BA.1 mRNA-seasonal vaccines were mainly given as a fourth dose in Denmark and as a fourth or fifth dose in Finland and Sweden. Vaccination with the monovalent XBB.1.5-containing Covid-19 mRNA vaccine mainly as a fifth or a sixth dose was initiated from 1 October 2023 in the three countries.

Outcomes

Covid-19 hospitalization was defined as first inpatient hospitalization with a registered Covid-19-related diagnosis and a positive PCR test for SARS-CoV-2 (within 14 days before to 2 days after the day of admission). We defined Covid-19 death as death within 30 days of a positive PCR test for SARS-CoV-2. In the table below, we provide further country-specific details.

Outcome variable	**Country**	**Data source and details**
Covid-19 hospitalization	Denmark	*The National Patient Register and the Danish Microbiology Database.* Defined as a hospitalization with a PCR positive test for SARS-CoV-2 within 14 days before to 2 days after the admission date, b) inpatient contact or at least 12 hours of contact, and c) a Covid-19 relevant diagnosis code (ICD-10: B342, B342A, B948A, B972, B972A, B972B, B972B1, Z038PA1)
	Finland	*National Care Register for Health Care and the National Infectious Diseases Register.* Defined as a hospitalization with a PCR positive test for SARS-CoV-2 within 14 days before to 2 days after the admission date, b) inpatient hospital contact, and c) a Covid-19 relevant main diagnosis (ICD-10: J00-J22, J46, J80-J84, J851, J86, U071, U072).
	Sweden	*The Swedish Patient Register and the Register on surveillance of notifiable communicable diseases (SmiNet).* Defined as a hospitalization with a PCR positive test for SARS-CoV-2 within 14 days before to 2 days after the admission date, b) inpatient contact or at least 12 hours of contact, and c) a Covid-19 relevant diagnosis code (ICD-10: U071, U072, U109)
Covid-19 death	Denmark	*The Civil Registration System and the Danish Microbiology Database.* Defined as (the date of) death within 30 days after PCR positive test for SARS-CoV-2.
	Finland	*The Finnish Population Information System and the National Infectious Diseases Register.* Defined as (the date of) death within 30 days after PCR positive test for SARS-CoV-2.
	Sweden	*The Total Population Register, the Cause of Death Register, and the Swedish Patient Register and the Register on surveillance of notifiable communicable diseases (SmiNet).* Defined as (the date of) death within 30 days after PCR positive test for SARS-CoV-2.

Covariates

We took the following potential confounders into account by matching: age (using birth cohort), sex, region of residency, calendar time of last mutual vaccine dose (i.e., either 4th dose for the 5 vs 4- or 5th dose for the 6 vs 5-matched pairs etc.), Covid-19 risk groups (at risk of severe Covid-19 due to

comorbidities, healthcare personnel), and selected comorbidities. Further country-specific details of covariate definitions are provided in table below.

Variable	Country	Data source and details	Values/codes
Age	Denmark	*The Civil Registration System.* Recorded birth year. Age defined as the country-specific start date minus birth year.	Categorical (for adjustment, using birth year): 5-year bins Binary (for stratification): </≥ 75 years
	Finland	*The Finnish Population Information System.* Recorded birth year. Age defined as the country-specific start date minus birth year.	
	Sweden	*The Total Population Register.* Recorded birth year. Age defined as the country-specific start date minus birth year.	
Sex	Denmark	*The Civil Registration System.* Defined as registered sex.	Binary: male, female
	Finland	*The Finnish Population Information System.* Defined as registered sex.	
	Sweden	*The Total Population Register.* Defined as registered sex.	
Calendar time period of last mutual vaccine dose	Denmark	*The Danish Vaccination Register.* Defined by the date where the respective vaccine dose examined was administered (e.g., fourth or fifth dose).	Categorical (monthly [up to 33 levels]): 1 (27 December 2020-31 January 2021) to month 49 (February 2024)
	Finland	*The National Vaccination Register.* Defined by the date where the respective vaccine dose examined was administered (e.g., fourth or fifth dose).	
	Sweden	*The National Vaccination Register.* Defined by the date where the respective vaccine dose examined was administered e.g., fourth or fifth dose).	
Region of residency	Denmark	*The Civil Registration System.* Defined by last known address as of study start.	Categorical: Denmark, 5 levels; Finland, 5 levels; Sweden, 9 levels
	Finland	*The Finnish Population Information System.* Defined by last known municipality of residence as of study start.	
	Sweden	*The Total Population Register.* Defined by last known address as of study start.	
Covid-19 risk groups[a]	Denmark	*The Danish Vaccination Register.* Defined as governmentally assigned Covid-19 vaccine priority groups, prioritized according to the risk of severe Covid-19 as well as whether being health and social care workers (last update 24 May 2021).	Categorical (3 levels): Severe Covid-19 risk group, healthcare personnel, others
	Finland	*Register of Social Assistance.* Severe Covid-19 risk group was defined as vulnerable individuals in 24-hours care (binary status per 27 December 2021). *Care register for Health Care (data since 1.1.2015), Special Reimbursement Register (data from 1.1.2018 to*	

Variable	Country	Data source and details	Values/codes
		27.12.2020) Prescription Centre database (data from 1.1.2018 to 27.12.2020. Covid-19 risk group was defined on the basis of national vaccination recommendation [9].	
	Sweden	*Register on persons in nursing homes.* Severe Covid-19 risk group was defined as vulnerable individuals being residents at nursing homes (binary status as of 31 December 2020) *The Longitudinal integrated database for health insurance and labour market studies.* Healthcare personnel defined as healthcare worker occupation status as of 31 October 2018 (binary).	
Comorbidity 1: Chronic pulmonary disease	Denmark	*The National Patient Register.* Defined as primary diagnoses regardless of type of hospital contact registered as of study start (look-back 3 years).	Binary: yes/no (ICD-10 codes: J40-J47, J60–J67, J684, J701, J703, J841, J920, J961, J982, J983)
	Finland	*Care register for Health Care.* Defined as primary or secondary diagnoses registered prior to the start of the study period.	Binary: yes/no (ICD-10 codes: J41-J44, J47)
	Sweden	*National Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact as of study start (look-back 3 years).	Binary: yes/no (ICD-10 codes: E84, J41-J47, J84, J98)
Comorbidity 2: Cardiovascular conditions	Denmark	*The National Patient Register.* Defined as primary diagnoses regardless of type of hospital contact registered as of study start (look-back 3 years).	Binary: yes/no (ICD-10 codes: I110, I130, I132, I20-I23, I420, I426-I429, I48, I500-I503, I508, I509)
	Finland	*Care register for Health Care, Register of Primary Health Care Visits, Special Reimbursement Register and Prescription Centre database.* Defined as primary or secondary diagnoses prior to the start of the study period.	Binary: yes/no (ICD-10 codes: I11–I13, I15, I20–I25)
	Sweden	*National Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient as of study start (look-back 3 years).	Binary: yes/no (ICD-10 codes: I05-I09, I110, I20-I28, I34-I37, I39, I42, I43, I46, I48-I50)
Comorbidity 3: Diabetes	Denmark	*The National Patient Register.* Defined as primary diagnoses regardless of type of hospital contact registered as of study start (look-back 3 years).	Binary: yes/no (ICD-10 codes: E10-E11)
	Finland	*Care register for Health Care, Register of Primary Health Care Visits, Special Reimbursement Register and Prescription Centre database.* Defined as primary or secondary diagnoses prior to the start of the study period or drug prescriptions before 27 December 2020.	Binary: yes/no (ICD-10 codes: E10, E11, E13-E14; ICPC-2 codes: T89, T90; ATC codes: A10A, A10B)
	Sweden	*National Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact as of study start (look-back 3 years).	Binary: yes/no (ICD-10 codes: E10-E14; ATC code: A10)

Variable	Country	Data source and details	Values/codes
		Swedish Prescribed Drug Register. Antidiabetic drugs use defined as ≥2 filled prescriptions as of study start.	
Comorbidity 4: Autoimmunity-related conditions[b]	Denmark	*The National Patient Register.* Defined as primary diagnoses regardless of type of hospital contact registered as of study start (look-back 3 years).	Binary: yes/no (ICD-10 codes: D510, D590, D591, D690, D693, D86, E050, E063, E271, E272, G122G, G35, G610, G700, I00, I01, K50, K51, K743, K900, L12, L40, L52, L80, L93, M05, M06, M08, M300, M313, M315, M316, M32, M33, M34, M35, M45)
	Finland	*Care register for Health Care, Special Reimbursement Register and Prescription Centre database.* Defined as primary or secondary diagnoses as of study start or drug prescriptions before 27 December 2020.	Binary: yes/no (ICD-10 codes: D7081, D7089, D80–D84, E250, E271, E272, E274, E310, E896, D86, K50, K51, L40, M02, M05–M07, M139, M45, M460, M461, M469, M941; ATC-codes: H02AB02, H02AB04, H02AB06, H02AB07, L01BA01, L01XC02, L04AA06, L04AA10, L04AA13, L04AA18, L04AA24, L04AA26, L04AA29, L04AA33, L04AA37, L04AB, L04AC, L04AD01, L04AD02, L04AX01, L04AX03)
	Sweden	*National Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact as of study start (look-back 3 years).	Binary: yes/no (ICD-10 codes: D86, G35, K50, K51, L40, M05-M09, M13, M14, M45)
Comorbidity 5: Cancer	Denmark	*The National Patient Register.* Defined as primary diagnoses regardless of type of hospital contact registered as of study start (look-back 3 years).	Binary: yes/no (ICD-10 codes: C00–C85 (without C44), C88, C90-C96)
	Finland	*Care register for Health Care and Special Reimbursement Register.* Defined as primary or secondary diagnoses registered within 2 years prior to the start of the study period.	Binary: yes/no (ICD-10 codes: C00–C43, C45–C80, C97, D05.1, D39)
	Sweden	*National Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact as of study start (look-back 3 years).	Binary: yes/no (ICD-10 codes: C00-C96 (without C44), D45-D47)
Comorbidity 6: Moderate to severe renal disease	Denmark	*The National Patient Register.* Defined as primary diagnoses regardless of type of hospital contact registered as of study start (look-back 3 years).	Binary: yes/no (ICD-10 codes: I12, I13, N00–N05, N07, N11, N14, N17–N19, Q61)
	Finland	*Care register for Health Care.* Defined as primary or secondary diagnoses prior to the start of the study period.	Binary: yes/no (ICD-10 codes: I12, I13, N00–N05, N07, N08, N11, N14, N18, N19, E102, E112, E142)
	Sweden	*National Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact as of study start (look-back 3 years).	Binary: yes/no (ICD-10 codes: I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61)

Variable	Country	Data source and details	Values/codes
Influenza vaccination status for season 2023–2024	Denmark	*The Danish Vaccination Register.* Defined according to the date of influenza vaccine and XBB.1.5-containing vaccine vaccinations.	Categorical (for subgroup analysis only[c]): co-administered on the same date; received influenza vaccine within 1 week before to 1 week after XBB.1.5-containing vaccine dose administration but not on same date; no influenza vaccine administered within 1 week before to 1 week after of XBB.1.5-containing vaccine dose administration.
	Finland	*The National Vaccination Register.* Defined according to the date of influenza vaccine (VaxigripTetra or InfluvacTetra) and XBB.1.5-containing vaccine vaccinations.	
	Sweden	*The National Vaccination Register.* Defined according to the date of influenza vaccine and XBB.1.5-containing vaccine vaccinations.	

[a] To account for the risk of severe Covid-19, we adjusted for targeted Covid-19 high-risk groups of severe Covid-19, specifically established for each country. In Denmark, the Covid-19 vaccine priority groups were governmentally assigned and individuals were prioritized according to the risk of severe infection (identified by the treating physicians) as well as whether being health or social care workers. In the remaining countries, the variable was constructed based on the identification of vulnerable individuals (as defined by those receiving nursing care or living in nursing homes) and whether being health or social care workers. [b] Autoimmunity-related conditions includes a range disorders such as inflammatory bowel diseases, diseases involving the blood, immune mechanism or endocrine systems, inflammatory rheumatic diseases, psoriasis, lupus erythematosus, multiple sclerosis; subject to country-specific definitions. The selected diagnosis codes to define comorbidities were country-specific, based on inputs from national experts and country-specific registration practices as part of the general national surveillance purposes. This was done as we anticipated that country-specific definitions were likely better at identifying comorbidity-related risk groups within each country than a common set of code definitions. [c] Influenza vaccination status for season 2023–2024 at around time of XBB.1.5-containing vaccine vaccination was not be used for subgroup analyses only.

9.4 Data sources

All data sources are nationwide registers in native format. All study subcontractors had access to their country-specific data and could link data between registers for the purpose of our study. Given the no-to-very-little lag time of the data source, our analyses reflected real-time information. We had a full data availability for all variables (with no missing data; all the exposures, outcomes, or covariates are either present or not) during the study period and as reporting to national registers is mandatory/structurally implemented, this provides a near-complete follow-up of all residents over time.

Country/data source	Details
Denmark	
The Civil Registration System [10]	The register provides the unique personal identifier for all permanent residents of Denmark that allows linkage between all Danish health care registers and civil registrations systems. In addition, it holds general demographic information such as birthdate and sex as well as continuously updated information and dates on historical addresses, immigration and emigration status, and death.
The Danish Vaccination Register [9]	The register holds information on all vaccinations administered in Denmark including vaccination date, type/trade name, dose, and product batch number ever since Nov 15, 2015 (where reporting to the register became mandatory). Specifically related to this study, the Danish Health Agency have provided the governmentally assigned Covid-19 vaccine priority groups that were prioritized groups according to the risk of severe infection as well as whether being health and social care workers.

Country/data source	Details
The Danish Microbiology Database [11]	Information on positive PCR tests for SARS-CoV-2 are obtainable via The Danish Microbiology Database (MiBa) that has data on all microbiology samples analyzed at Danish microbiology departments as well as test results, date of sampling, date of analysis, type of test, and interpretation of test. The SARS-CoV-2 PCR tests are freely available to all individuals in Denmark regardless of symptoms status.
The National Patient Register [12]	The register holds information on all hospital contacts in Denmark including the duration of the contact, and diagnoses, which are assigned by the treating physician and registered according to ICD-10 classification system (since 1994).
Finland	
Finnish Population Information System [13]	The register is held by the Digital and Population Data Services Agency and contains personal data on all permanent residents in Finland such as the unique personal identifier, date of birth, place of residence, date of death, and date of immigration, and emigration.
Register of Social Assistance [14]	The register is held by the Finnish Institute for Health and Welfare and contains information on individuals receiving long-term care and/or social assistance (in e.g., nursing homes, people's own homes or other institutions) including social rehabilitation.
Social and Healthcare Professionals Register [15]	The register holds data on individuals right to act as health care personnel.
National Vaccination Register [16]	The register is based on the Register of Primary Health Care Visits and contains information on all Covid-19 vaccinations administered in Finland including date of vaccination, batch number, and trade name.
National Infectious Diseases Register [17]	The register is held by the Finnish Institute for Health and Welfare and contains information on notifiable diseases in accordance with the Finnish Communicable Diseases Act that must be reported by the laboratories and the treating-physicians, or the physician performing an autopsy and hold information on sample dates of all laboratory-confirmed SARS-CoV-2 infections in Finland
National Care Register for Health Care [18]	The register is held by the Finnish Institute for Health and Welfare and comprises information on all inpatient and outpatient hospital contacts in Finland, including admission and discharge dates, whether hospitalization was planned or acute, codes for discharge diagnoses (according to ICD-10) and surgical procedures, and whether discharged as deceased, to own private residence or other health care facilities.
Special Reimbursement Register and Prescription Centre database	These databases are maintained by the Finnish Social Insurance Institution. The Special Reimbursement Register holds information on individuals entitled to special reimbursement for medical expenses. The Prescription Centre database holds information on individuals using selected medications of interest.
Register of Primary Health Care Visits [19]	The register is held by Finnish Institute for Health and Welfare and holds data on all primary health care services delivered in Finland.
Sweden	
The Total Population Register [20]	The register is held by Statistics Sweden and contains data on the unique personal identifier assigned to all individuals in Sweden plus general demographic information such as date of birth, sex, country of birth, place of residence, and date of immigration and emigration.
The Cause of Death Register [21]	The register holds information on date of death and underlying as well as contributing causes of death.

Country/data source	Details
The Longitudinal Integrated Database For Health Insurance And Labour Market Studies (LISA) [22]	The database is held by Statistics Sweden and holds many socioeconomic variables such as data on occupation which we used to identify whether individuals were health care personnel.
Register On Persons In Nursing Homes [23]	The register is held by the National Board of Health and Welfare and holds data on nursing care given in either nursing homes, own homes or other institutions to elderly and/or persons with physical, psychiatric or intellectual disabilities.
The National Vaccination Register [24]	The register is held by the Public Health Agency of Sweden and contains information on administered Covid-19 vaccines in Sweden including data on date of administration, the specific vaccine products, substance, formulation, batch number and dose number (for repeated doses).
Register On Surveillance Of Notifiable Communicable Diseases (Sminet) [25]	The register is held by the Public Health Agency of Sweden and contains information on notifiable diseases (for which reporting is mandatory) reported by either the analysis performing laboratories, the treating physician or autopsy performing physician, in accordance with the Swedish Communicable Diseases Act. Data included are e.g., date of disease occurrence, date of testing, date of positive test, and diagnoses.
The Swedish Patient Register [26,27]	The register is held by the National Board of Health and Welfare and comprises data on all in- and outpatient hospital specialist care in Sweden including data on dates of admission and discharge, whether hospitalization was planned or acute, codes for discharge diagnoses (recorded according to ICD-10-SE) and surgical procedures, whether discharged as deceased, to own private residence or other health care facilities, and type of department.

9.5 Study size (sample size and power)

We expected approximately 3.1 million individuals would receive a monovalent XBB.1.5-containing Covid-19 vaccine as a ≥fifth Covid-19 vaccine dose during autumn and winter 2023-2024 across the 3 Nordic countries. We utilized all available data to us from the countries' nationwide registers. The statistical power of our study is reflected in the 95% CI of the effectiveness estimates. Based on the Covid-19 VE results from our recent Nordic studies, we expected to have high statistical precision for the outlined main objectives. [28,29]

9.6 Data management

No individual-level data can be or were shared between countries or with EMA. Each country is the sole data owner and controller of their own data. Only aggregated country-specific results were shared and the final country-combined results were generated using meta-analysis. Data management and statistical analyses were conducted using a Common Data Model (CDM). The analytical group in Denmark coded the statistical analyses using R-scripts (R version 4.2.2.). The R-scripts were made available on GitHub (also during the programming phase to facilitate input and comments). The

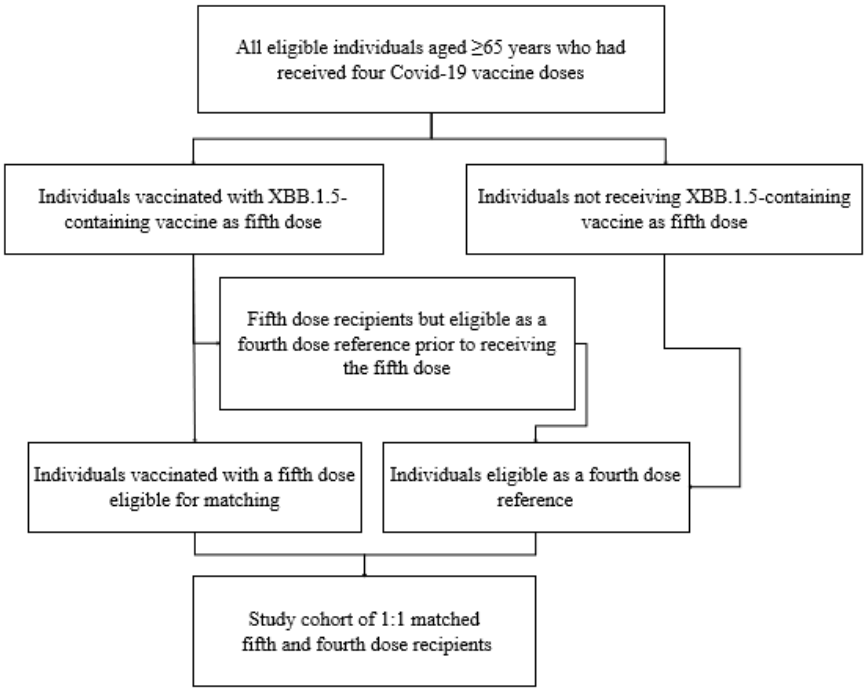
analysts in each of the participating countries then run the R-scripts and returned the output to Denmark for meta-analysis.

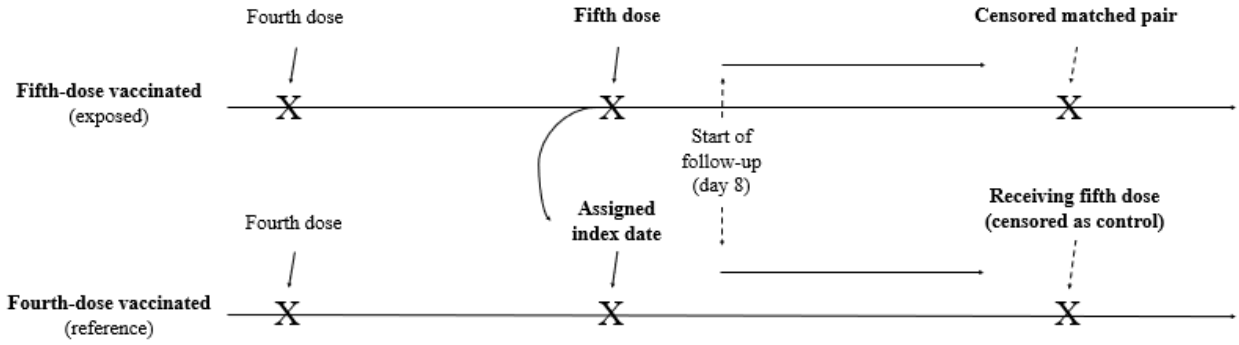
9.7 Data analysis

Procedures

We used a matched study design to evaluate the effectiveness of receiving a monovalent XBB.1.5-containing Covid-19 vaccine in comparison with not receiving a Covid-19 vaccine during the autumn and winter 2023-2024. Individuals who during the study period received an XBB.1.5-containing Covid-19 vaccine were matched on the day of vaccination with individuals who had received the same number of Covid-19 doses prior to study start but had not received an additional dose during the study period. Individuals were matched on age (5-year bins), calendar time of last mutual vaccine dose (e.g., 4th dose for the 5 vs 4- or 5th dose for the 6 vs 5-matched pairs etc.), sex, region of residence, vaccination priority groups (individuals at high-risk of severe Covid-19 and healthcare personnel), and number of selected comorbidities (0, 1, 2, ≥3 of chronic pulmonary disease, cardiovascular conditions, diabetes, autoimmunity-related conditions, cancer, and moderate to severe renal disease). The day the XBB.1.5-containing Covid-19 vaccine was administered within each matched pair served as the index date for both individuals. If individuals who were included as a matched XBB.1.5-containing vaccine non-recipient (i.e., a reference individual) received an XBB.1.5-containing vaccine later than the assigned index date, they were allowed to potentially re-enter as an XBB.1.5-containing vaccine recipient in a new matched pair on that given date and the follow-up for the current pair was censored.

We followed individuals from one week after the index date (to ensure full immunization among XBB.1.5-containing Covid-19 vaccine recipients) up until the day of an outcome event, week 12 of follow-up had passed (91 days since the index date), receipt of an additional Covid-19 vaccine dose, death, emigration, or end of the study period, whichever occurred first. The start of the follow-up period commenced on Day 0, corresponding to eight days after the index date. At the time of running the analyses, data on Covid-19 related hospitalization in Sweden was only available until 31 December 2023, which is why we ended follow-up on day 87 in Sweden for this specific analysis. The figure below illustrates the study cohort construction, as an example of the matching recipients of the XBB.1.5-containing vaccine as a fifth dose with non-recipients (i.e., previously vaccinated with four Covid-19 vaccine doses).





Statistical analysis

We used 1:1 exact matching without replacement with the prespecified covariates to find a precise pairing of individuals having received a monovalent XBB.1.5-containing Covid-19 vaccine to individuals not having received a Covid-19 vaccine.

Cumulative incidences were estimated by the Aalen-Johansen estimator using death as a competing risk, and from these we calculated the CVE as 1 – risk ratio at end of week 12. The corresponding 95%

CI was calculated using the delta method. Country-specific estimates were combined by random-effects meta-analyses using the *mixmeta* package in R.

Comparative waning was estimated using meta-regression [30]. First, we estimated the VEs in consecutive 3-week intervals by stratification on time since XBB.1.5-containing Covid-19 vaccination. Second, we regressed the VE estimates on time-since-vaccination in 3-week intervals using meta-regression in the form of a linear model with an intercept and a slope coefficient. The estimated slope coefficient represented the percentage point change in VE per 3 weeks since start of follow-up.

Subgroup analyses were conducted according to sex, age groups (65-74/≥75 years), number of previous Covid-19 vaccine doses received, and seasonal influenza vaccination status for XBB.1.5-containing Covid-19 vaccine vaccinated (categorized according to 1) co-administered on the same date, 2) received influenza vaccine within 1 week before to 1 week after XBB.1.5-containing vaccine dose administration but not on same date, and 3) no influenza vaccine administered within 1 week before to 1 week after of XBB.1.5-containing vaccine dose administration).

9.8 Supplementary analyses and quality control

Quality control was conducted indirectly to evaluate the validity of our main analyses by 1) making sure that the prevalence of the different schedules and the number of study endpoints match national surveillance dashboards and reports, 2) descriptive and analytical results were compatible with our previous findings, and 3) using a Common Data Model (CDM), by which national register data are standardized to a common structure, format and terminology in order to allow the same statistical programming scripts to be used in each country. The use of a CDM with common statistical programming scripts facilitated efficient use of resources and reproducibility of the statistical analyses. We ensured the scientific quality of the work, by division of review tasks (including statistical code review) and responsibilities in a timely fashion and by adhering to the ENCePP Code of Conduct (see attachment). Although we used exact matching, we also performed matching quality diagnostics to assess the control of matched parameters. We included a sensitivity analysis where we started follow-up after 3 weeks (21 days) after the index date to further reduce the potential of transient healthy vaccinee effect around the time of vaccination as well as a *spill-over effect* of infection from before the index date given that some severe Covid-19 events may take longer time to develop which would bias towards less effectiveness.

10. RESULTS

10.1 Participants and descriptive data

10.1.1 General population characteristics

Table 1 shows the baseline characteristics of the general population study cohorts before and after matching; Figure 1 illustrates the distributions of age and index date in density plots across countries. Prior to matching, the source cohorts comprised 3,066,104 recipients of the XBB.1.5-containing vaccine in the three countries during the study period. The largest number of recipients were from Sweden (1,419,714), followed by Denmark (928,226) and Finland (718,164). The mean age of the recipients prior to matching was 75.9, SD 7.3, and 54.2% were of female sex. Majority had no comorbidities (85.3%) and 13.5% had one comorbidity.

The matched cohorts consisted of a total of 1,867,448 recipients of the XBB.1.5-containing vaccine during the study period and 1,867,448 non-recipients. Most XBB.1.5-containing vaccines were administered as a fifth dose (53.2%) and during October 2023 in Denmark and November 2023 in Finland and Sweden. The mean age of the recipients was 75 years, SD 7.4 years, and 54.3% were of female sex. Majority of recipients had no comorbidities (86.1%) and 12.9 % had one comorbidity. Overall, characteristics such as age, sex, healthcare worker occupation, and number and type of comorbidities among the matched pairs were similar to those of the unmatched populations.

Table 1. Cohort characteristics before and after matching of XBB.1.5-containing vaccine recipients and non-recipients in Denmark, Finland, and Sweden, 1 October 2023 to 29 February 2024.[a]

	Before matching		After matching	
	XBB.1.5-containing vaccine recipients	XBB.1.5-containing vaccine non-recipients[b]	XBB.1.5-containing vaccine recipients	XBB.1.5-containing vaccine non-recipients
Total individuals	3,066,104	3,891,978	1,867,448	1,867,448
Denmark	928,226	1,066,797	554,638	554,638
Finland	718,164	1,079,425	515,538	515,538
Sweden	1,419,714	1,745,756	797,272	797,272
Mean age (SD), years	75.9 (7.3)	75.5 (7.6)	75.4 (7.4)	75.4 (7.4)
Female sex	1,663,305 (54.2)	2,112,686 (54.3)	1,014,154 (54.3)	1,014,154 (54.3)
Dose at which the XBB.1.5-containing vaccine was received				
Fifth dose	1,426,692 (46.5)	NA	992,701 (53.2)	NA

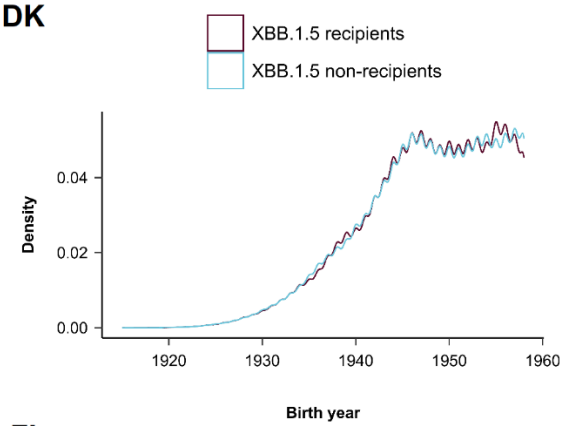
Table 1. Cohort characteristics before and after matching of XBB.1.5-containing vaccine recipients and non-recipients in Denmark, Finland, and Sweden, 1 October 2023 to 29 February 2024.[a]

	Before matching		After matching	
	XBB.1.5-containing vaccine recipients	XBB.1.5-containing vaccine non-recipients[b]	XBB.1.5-containing vaccine recipients	XBB.1.5-containing vaccine non-recipients
Sixth dose	1,247,379 (40.7)	NA	699,321 (37.4)	NA
Seventh dose	389,867 (12.7)	NA	174,593 (9.3)	NA
Eighth dose	2,166 (0.1)	NA	833 (0.0)	NA
Severe Covid-19 risk group	656,591 (21.4)	913,260 (23.5)	436,938 (23.4)	436,938 (23.4)
Healthcare workers	131,005 (4.3)	174,896 (4.5)	82,375 (4.4)	82,375 (4.4)
Autoimmune related condition	147,816 (4.8)	179,573 (4.6)	83,792 (4.5)	82,642 (4.4)
Cancer	251,831 (8.2)	311,467 (8.0)	145,441 (7.8)	143,913 (7.7)
Chronic pulmonary disease	134,147 (4.4)	167,056 (4.3)	79,874 (4.3)	77,840 (4.2)
Cardiovascular condition	357,062 (11.6)	443,241 (11.4)	208,005 (11.1)	207,828 (11.1)
Diabetes	258,747 (8.4)	339,724 (8.7)	159,905 (8.6)	162,666 (8.7)
Renal disease	86,194 (2.8)	112,311 (2.9)	48,296 (2.6)	50,974 (2.7)
Number of comorbidities				
0	2,616,364 (85.3)	3,334,013 (85.7)	1,608,115 (86.1)	1,608,115 (86.1)
1	415,034 (13.5)	514,366 (13.2)	241,565 (12.9)	241,565 (12.9)
2	33,311 (1.1)	41,812 (1.1)	17,340 (0.9)	17,340 (0.9)
≥3	1,395 (0.0)	1,787 (0.0)	428 (0.0)	428 (0.0)

NA denotes not applicable SD standard deviation. [a]Values are numbers (percentages) unless stated otherwise. [b]As of study start, 1 October 2023.

Figure 1. Density plots of the distribution of age and index date across countries.

DK


XBB.1.5 recipients
XBB.1.5 non-recipients
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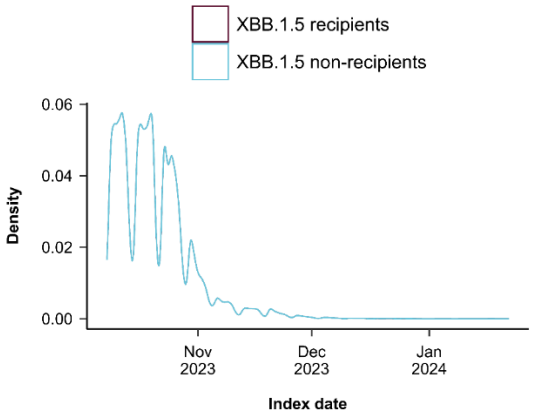
0.04
1920
1930
1940
1950
1960
Birth year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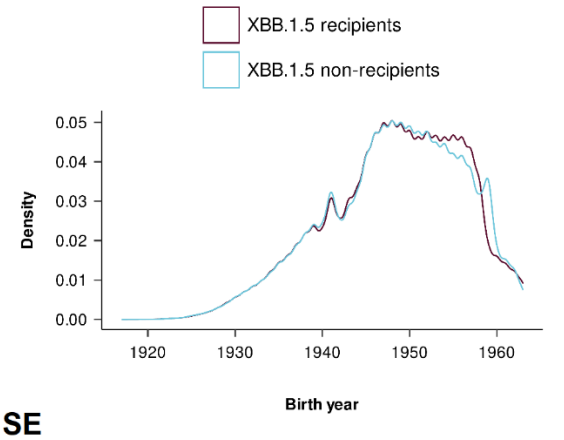
0.04
0.06
Nov 2023
Dec 2023
Jan 2024
Index date

FI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XBB.1.5 non-recipients
Density
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1920
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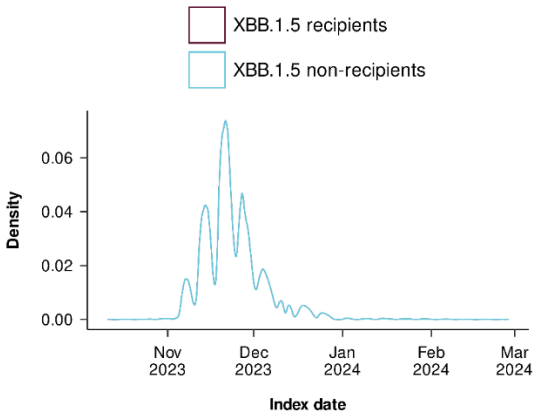
1940
1950
1960
Birth year


XBB.1.5 recipients
XBB.1.5 non-recipients
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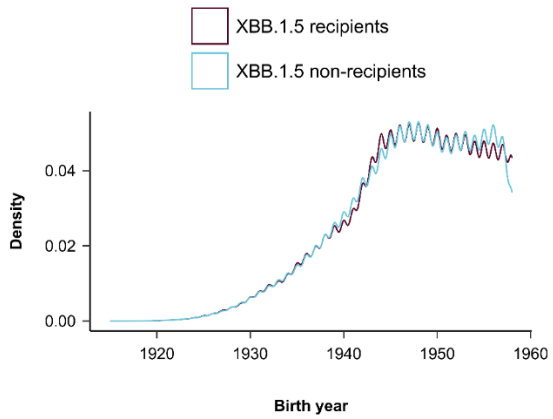
0.04
0.06
Nov 2023
Dec 2023
Jan 2024
Feb 2024
Mar 2024
Index date

SE


XBB.1.5 recipients
XBB.1.5 non-recipients
Density
0.00
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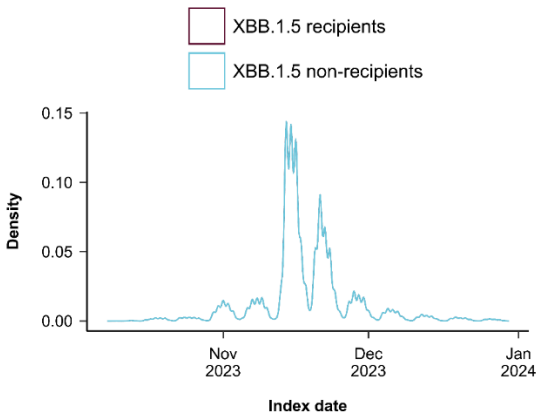
1920
1930
1940
1950
1960
Birth year


XBB.1.5 recipients
XBB.1.5 non-recipients
Density
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0.10
0.15
Nov 2023
Dec 2023
Jan 2024
Index date

10.2 Outcome data and main results

10.2.1 General population comparative vaccine effectiveness

Figure 2 shows the 12-week cumulative incidences of admission to hospital related to Covid-19 and Covid-19 related death in XBB.1.5-containing vaccine recipients versus matched non-recipients from 1 week after the vaccination date. Overall, low cumulative incidences of the outcomes were observed among both recipients and non-recipients.

The number of events and comparative effectiveness estimates are presented in Table 2. The risk of hospital admission with Covid-19 was lower for the recipients of an XBB.1.5-containing vaccine compared with non-recipients corresponding to a CVE of 60.6% (95% CI: 46.1% to 75.1%) and risk difference per 100,000 individuals of –191.1 (95% CI: –332.1 to –50.2) at week 12 (Table 2). The risk of Covid-19 related death was lower among those who received the vaccine compared to those who did not corresponding to a CVE of 77.9% (69.2% to 86.7%) and risk difference of –109.2 (–118.1 to –100.2) per 100,000 individuals. For both outcomes, the CVE was similar for both sexes and, across age groups, and number of previous covid-19 vaccine doses. The risk difference point estimates were larger in males, among individuals aged ≥75 years, and those who previously received higher number of doses. The risk differences against hospital admission with Covid-19 were -160.6 (-301.5 to -19.8) and -214.3 (-366.1 to -62.5) for females and males per 100,000 individuals, respectively, and 194.6 (-271.6 to -117.6) and -86.4 (-160.3 to -12.5) per 100,000 individuals for individuals aged ≥75 and 65-74 years-, respectively; however, the 95% CIs overlapped.

We observed no apparent differences in the CVE based on influenza vaccine co-administration, but as only few individuals received the influenza and the XBB.1.5-containing vaccine in different time points leading to small comparison group, the precision of the 95% CI was notably lower for the other analyzed subgroups. Furthermore, we had only influenza vaccine data from Denmark and Finland. During periods when the omicron XBB (primarily EG.1) or BA.2.86 (primarily, JN.1) lineages were predominant, the estimates of variant-specific CVE against COVID-19 related hospital admission and death at the 6-week follow-up were similar. Although the point estimates for CVE were slightly higher against the XBB-lineage, the 95% CIs overlapped (Table 3 shows the overall results at 6-weeks of follow-up, i.e., without stratifying calendar time according to variant predominance periods).

Figure 3 shows the comparative waning VE of the XBB.1.5-containing vaccine, stratified by 3-week intervals and the per 3-week percentage point change in VE during follow-up is reflected by the trend line. The XBB.1.5-containing vaccine had an initial higher CVE of 65.2% (50.6% to 79.6%) against Covid-19 related hospital admission and 82.7% (79.2% to 86.2%) against Covid-19 related death.

Subsequently, gradual waning of -2.0 (95% CI: -8.8 to 4.8) and -3.7 (-7.5 to 0.2) percentage points against hospitalization and death, respectively, were observed every 3 weeks.

Starting follow-up 21 days after the vaccination date in a sensitivity analysis, provided results that aligned well with the findings of our main analyses (Table 4).

Figure 2. Cumulative incidence curves of admission to hospital and death related to Covid-19, comparing recipients of a monovalent XBB.1.5-containing vaccine during autumn and winter 2023-2024 with matched non-recipients.

Matched XBB.1.5-containing vaccine recipient and non-recipient pairs were followed for a total of 12 weeks after immunization (defined as 1 week after the day of vaccination).

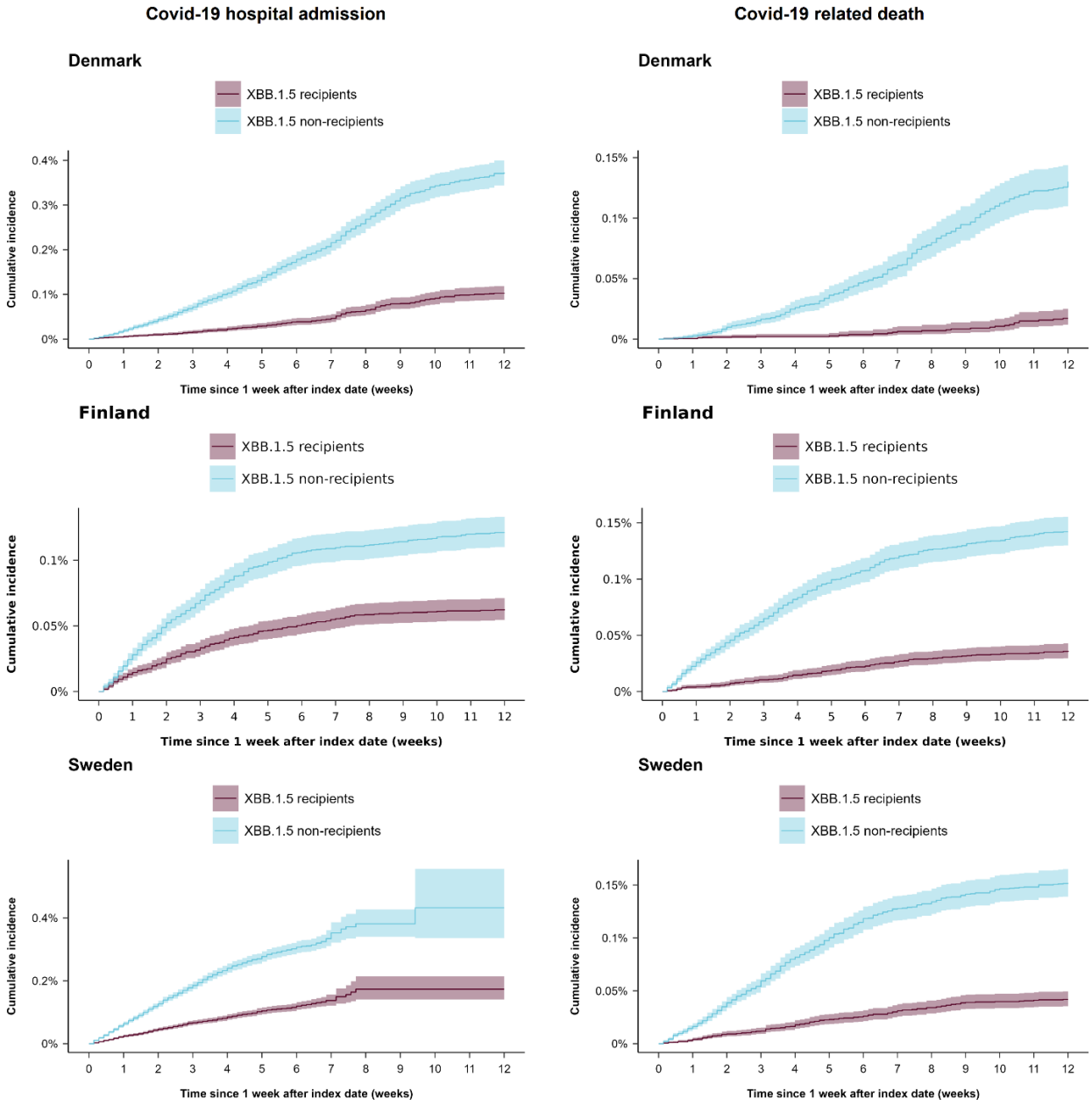

Figure 3. Waning comparative vaccine effectiveness against admission to hospital and death related to Covid-19, comparing recipients of a monovalent XBB.1.5-containing Covid-19 mRNA vaccine during autumn and winter 2023-2024 with matched non-recipients, stratifying follow-up in 3-week intervals.

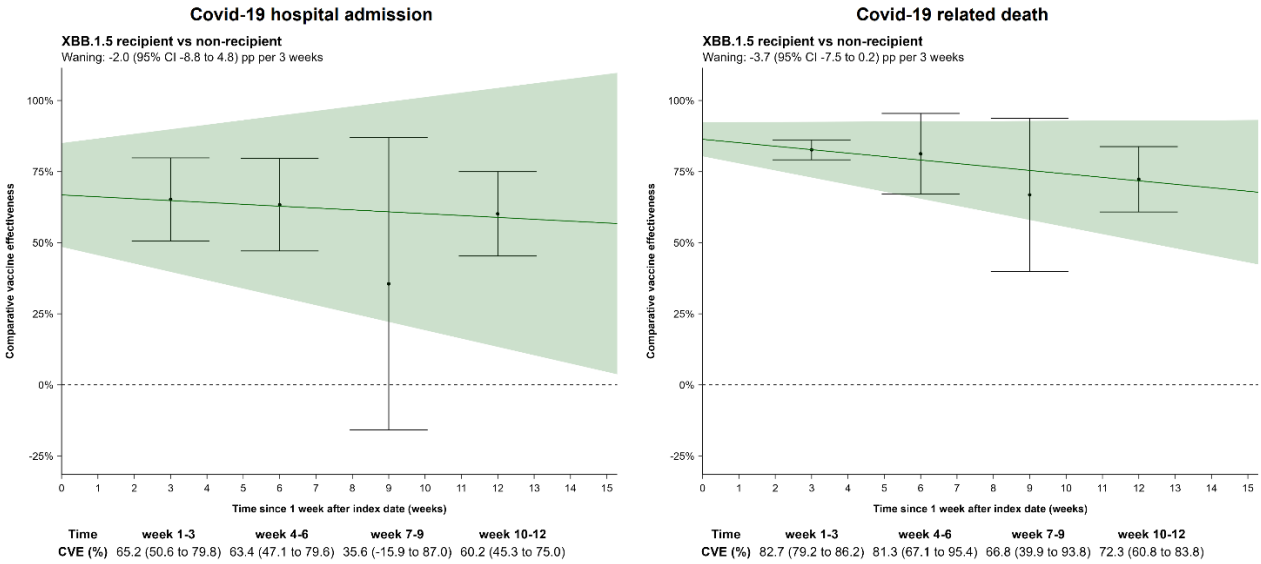

Table 2. Risk of hospital admission and death related to Covid-19 comparing XBB.1.5-containing vaccine recipients with non-recipients in Denmark, Finland, and Sweden, 1 October 2023 to 29 February 2024.[a]

	Contributing countries	Events/person-years		Risk difference (95% CI) per 100,000 individuals	Comparative vaccine effectiveness (95% CI), %
		XBB.1.5-containing vaccine recipients	XBB.1.5-containing vaccine non-recipients		
Covid-19 hospital admission					
All	DK, FI, SE	930/170,115	2,551/168,911	-191.1 (-332.1 to -50.2)	60.6 (46.1 to 75.1)
Female	DK, FI, SE	401/93,130	1,173/92,527	-160.6 (-301.5 to -19.8)	62.4 (47.9 to 77.0)
Male	DK, FI, SE	529/76,985	1,378/76,385	-214.3 (-366.1 to -62.5)	58.8 (44.2 to 73.5)
Age <75 years	DK, FI, SE	189/88,252	532/88,119	-86.4 (-160.3 to -12.5)	58.3 (42.1 to 74.6)
Age ≥75 years	DK, FI, SE	741/81,863	2,019/80,792	-194.6 (-271.6 to -117.6)	62.0 (47.5 to 76.4)
XBB.1.5-containing vaccine received as fifth dose	DK, FI, SE	388/108,684	1,197/107,995	-156.2 (-293.6 to -18.8)	64.6 (51.0 to 78.1)
XBB.1.5-containing vaccine received as sixth dose	DK, FI, SE	385/53,312	965/52,914	-188.4 (-361.6 to -15.2)	57.0 (41.6 to 72.4)
XBB.1.5-containing vaccine received as seventh dose[b]	FI, SE	156/8,086	387/7,969	-248.9 (-490.4 to -7.4)	44.4 (20.2 to 68.7)
Influenza vaccine received on same day	DK, FI	376/108,174	1,100/107,323	-169.1 (-416.4 to 78.3)	61.5 (38.6 to 84.4)
Influenza vaccine received within 1 week	DK, FI	13/3,040	38/3,014	-148.6 (-417.1 to 119.8)	54.3 (20.0 to 88.7)
No concurrent influenza vaccine received	DK, FI	42/13,295	91/13,229	-122.8 (-372.1 to 126.5)	58.5 (31.6 to 85.4)
XBB-lineages prevailing[c]	DK, FI, SE	396/61,813	1,290/61,646	-154.3 (-313.9 to 5.4)	73.6 (60.4 to 86.7)
BA.2.86-lineages prevailing[c]	DK, FI	147/34,112	318/33,949	-158.2 (-318.1 to 1.8)	56.6 (42.8 to 70.4)
Covid-19 death					
All	DK, FI, SE	301/203,402	1,326/201,981	-109.2 (-118.1 to -100.2)	77.9 (69.2 to 86.7)
Subgroups					
Female	DK, FI, SE	146/110,653	596/109,938	-87.3 (-98.3 to -76.2)	76.9 (67.6 to 86.2)
Male	DK, FI, SE	155/92,749	730/92,043	-133.3 (-147.7 to -118.8)	78.9 (69.9 to 87.9)
Age <75 years	DK, FI, SE	35/105,912	159/105,780	-25.9 (-32.1 to -19.8)	77.5 (65.6 to 89.5)
Age ≥75 years	DK, FI, SE	266/97,490	1,167/96,201	-201.6 (-219.4 to -183.9)	78.0 (69.3 to 86.8)
XBB.1.5-containing vaccine received as fifth dose	DK, FI, SE	113/124,819	533/124,148	-75.9 (-111.8 to -40.1)	77.7 (67.5 to 87.9)
XBB.1.5-containing vaccine received as sixth dose	DK, FI, SE	140/67,095	563/66,576	-141.4 (-180.7 to -102.2)	76.9 (66.4 to 87.4)
XBB.1.5-containing vaccine received as seventh dose[b]	SE	48/11,230	225/11,000	-322.4 (-396.6 to -248.1)	82.1 (68.8 to 95.5)
Influenza vaccine received on same day	DK, FI	133/108,526	670/107,752	-112.9 (-125.2 to -100.5)	80.8 (69.0 to 92.6)

Table 2. Risk of hospital admission and death related to Covid-19 comparing XBB.1.5-containing vaccine recipients with non-recipients in Denmark, Finland, and Sweden, 1 October 2023 to 29 February 2024.[a]

	Contributing countries	Events/person-years		Risk difference (95% CI) per 100,000 individuals	Comparative vaccine effectiveness (95% CI), %
		XBB.1.5-containing vaccine recipients	XBB.1.5-containing vaccine non-recipients		
Influenza vaccine received within 1 week	DK, FI	6/3,044	14/3,022	-75.5 (-146.1 to -4.8)	73.5 (42.6 to 100.0)
No concurrent influenza vaccine received	DK, FI	10/13,339	57/13,280	-80.1 (-108.8 to -51.5)	83.8 (67.7 to 99.9)
XBB-lineages prevailing[c]	DK, FI, SE	70/61,934	444/61,796	-45.7 (-54.3 to -37.1)	87.5 (80.3 to 94.6)
BA.2.86-lineages prevailing[c]	DK, FI, SE	131/63,577	572/63,269	-74.5 (-82.3 to -66.6)	77.5 (71.4 to 83.6)

[a]Individuals were followed for 12 weeks (from 1 week after the vaccination date), except for the estimates by prevailing omicron lineages where individuals were followed for 6 weeks and Swedish hospitalization results were measured at ~11.5 weeks . [b]Risk of the Covid-19 outcomes could not be separately studied in subgroups of individuals where the XBB.1.5-containing vaccine was received as an eighth dose due to too few events. [c]Assessed at 6 weeks after start of follow-up; see table 3 for overall 6-week of follow-up results.

Table 3. Risk of hospital admission and death related to Covid-19 at 6 weeks of follow-up comparing XBB.1.5-containing vaccine recipients with non-recipients in Denmark, Finland, and Sweden, 1 October 2023 to 29 February 2024.[a]

Covid-19 outcomes	Contributing countries	Events / person-years		Risk difference (95% CI) per 100,000 individuals	Comparative vaccine effectiveness (95% CI), %
		XBB.1.5-containing vaccine recipients	XBB.1.5-containing vaccine non-recipients		
Hospital admission	DK, FI, SE	787/120,264	2207/119,748	-127.2 (-204.4 to -50.0)	64.1 (49.1 to 79.1)
Death	DK, FI, SE	202/125,511	1022/125,065	-73.4 (-103.0 to -43.8)	83.0 (74.1 to 91.8)

[a]Individuals were followed for 6 weeks (from 1 week after the vaccination date).

Table 4. Risk of hospital admission and death related to Covid-19 comparing XBB.1.5-containing vaccine recipients with non-recipients, 1 October 2023 to 29 February 2024, starting follow-up 21 days after vaccination date.

Covid-19 outcomes	Contributing countries	Events / person-years		Risk difference (95% CI) per 100,000 individuals	Comparative vaccine effectiveness (95% CI), %
		XBB.1.5-containing vaccine recipients	XBB.1.5-containing vaccine non-recipients		
Hospital admission	DK, FI	286/92,640	836/91,727	-137.0 (-385.1 to 111.2)	57.6 (29.8 to 85.5)
Death	DK, FI, SE	212/149,004	879/147,628	-92.2 (-118.3 to -66.2)	76.2 (64.2 to 88.2)

11. DISCUSSION

11.1 Key results

This study provides estimates of CVE against severe Covid-19 outcomes in individuals aged ≥65 years across three Nordic countries during autumn and winter 2023-2024. Overall, lower rates of hospitalization and death related to Covid-19 were observed following receipt of a monovalent XBB.1.5-containing Covid-19 vaccine compared with no receipt. The estimated CVE of XBB.1.5-containing vaccine was 60.6% against Covid-19 related hospital admission and 77.9% against death at 12 weeks of follow-up from 1 week after the vaccination date. The waning of protection afforded by the XBB.1.5-containing vaccine was modest, and the CVE against hospital admission and death was well-preserved, at 60.2% (45.3-75.0) and 72.3% (60.8-83.8) respectively, in the last 3 weeks of follow-up (week 10-12). Additionally, we observed that the CVE was consistent across sex, age, number of previous Covid-19 vaccine doses, seasonal influenza vaccine co-administration subgroups as well as periods of XBB (primarily EG.1) and BA.2.86 (primarily, JN.1) predominance.

11.2 Limitations

Our analyses should be considered in light of a number of limitations.

Given the observational nature of the study, confounding is a potential concern. Thus, we considered key predictors of the outcomes or proxies hereof. The accuracy of our exposure, Covid-19 vaccination, relied on the registered vaccination within the registers and recorded time of administration. To the best of our knowledge, the assignment of the type of the XBB.1.5-containing Covid-19 vaccine was unselective and our study period reflects a time when the vaccine was offered to the general population aged 65 years or older as a ≥fifth Covid-19 vaccine dose.

Our outcome definitions most likely also captured a small proportion of cases where the infection with SARS-CoV-2 only partly contributed to or coincided with the timing of the hospitalization or death. Also, we cannot certify that we captured all Covid-19 related hospitalizations and deaths within each country. SARS-CoV-2 was ascertained by positive PCR test results. Thus, those who acquired SARS-CoV-2 infection and were hospitalized or died but were not tested were missed. Our active comparator design, however, mitigated concerns that such outcome misclassification differed between compared groups to any larger extent as e.g., opposed to comparisons with individuals never vaccinated with the Covid-19 vaccines. Any misclassification would likely tend to skew estimates toward conservative results.

Both vaccination status and SARS-CoV-2 variants of predominance are strongly correlated with calendar time. This reduces possibilities for a valid direct comparison between effectiveness estimates obtained during different periods of variant predominance (e.g., as background transmission rates and population characteristics most likely differ) as well as evaluating longer-term follow-up effectiveness in relation to only one SARS-CoV-2 variant.

Lastly, the majority of the study population received both the influenza and the XBB.1.5-containing Covid-19 vaccine on the same day, meaning that the statistical power of the subgroup analyses within populations not concurrently vaccinated was lower.

11.3 Interpretation

The results of our study support the effectiveness of the seasonal XBB.1.5-containing vaccine in successfully reducing severe Covid-19 outcomes among the elderly population across three Nordic countries from October 2023 to February 2024. Our findings align well with the available evidence, which is, however, only limited to short-term VE [3–6]. Studies conducted in Europe and USA show a high short-term VE of the XBB.1.5-containing vaccine [3–6].

An early-season study from Denmark assessing the XBB.1.5-containing Covid-19 vaccine, reported VE of 76% against Covid-19 related hospitalization. The estimation was, however, based on the average follow-up period of only 9.9 days, from a 2.5-week period of 8 to 26 October 2023 [3]. Similarly, high VE of 70.7% (95% CI: 66.6–74.3) against hospitalization and 73.3% (95% CI: 42.2–87.6) against intensive care unit admission in a study in Netherlands [4]. This study included 295 older adults who received the XBB.1.5. vaccine, out of 2,050 hospitalized individuals, with data until 5 December 2023 [4]. Another study conducted across seven countries in Europe by the VEBIS-EHR (Vaccine Effectiveness Burden and Impact Studies- Electronic Health Records) Network found VE of >66% against covid-19 related hospitalization and death, based on data until 25 November 2023 [31]. Utilizing a test-negative case-control design, studies from the UK estimated the XBB.1.5-containing vaccine to be associated with a CVE-peak of 55% against Covid-19 related hospitalization 2 to 4 weeks following vaccination in adults aged ≥65 years. [6,32]

Our study offers estimates of longer-term CVE given the availability of data until 29 February 2024, covering the entire autumn and winter 2023-2024 season. We provide valuable insights into the waning effects, demonstrating that the protection offered by the vaccine was well-preserved at 12 weeks which suggests only moderate waning in this time-frame. Moreover, we found the comparative effectiveness of the XBB.1.5-containing vaccine against severe Covid-19 outcomes to be relatively

similar between the periods of XBB (primarily EG.1) and BA.2.86 (primarily, JN.1) lineages predominance. Although our results were tending towards higher CVE during the XBB- than the BA.2.86-lineage predominance period, this minor difference was not reflected in the absolute risk estimate, and the 95% CIs largely overlapped. Similarly, a study from the UK suggested that vaccination with either the bivalent BA.4-5 booster or XBB.1.5-containing vaccine (i.e., the two vaccine types not separately analyzed) offered higher protection against hospital admission with XBB-lineages. [32] However, it is important to acknowledge that comparing the effectiveness of Covid-19 vaccines against various SARS-CoV-2 strains is inherently influenced by the strong correlation with calendar time and variations in background population transmission rates.

The matched cohort study design utilized in this study allowed for the estimation of the benefits of vaccination in absolute terms. The estimated CVE corresponds to 191.1 (95%CI, 50.2 to 332.1) hospitalizations and 109.2 (100.2 to 118.1) deaths related to Covid-19 prevented per 100,000 recipients of the XBB.1.5-containing vaccine in the studied population. Despite the similarity of the relative CVE measures, our study shows that the absolute XBB.1.5-containing vaccine benefits vary across subpopulations: higher in those aged ≥75 years, males, and recipients of more prior doses of Covid-19 vaccine. Consequently, supplementing relative measures with absolute measures offers health authorities, clinicians, and patients an assessment of the vaccination benefits that gives greater insights into both the personal risk and the public health burden, insights that the majority of previous studies are lacking.

Finally, this study contributes unique evidence on VE when co-administering with influenza vaccine. We found that the concurrent administration of the XBB.1.5-containing vaccine with seasonal influenza vaccine did not alter the VE, and thus supporting the co-administration vaccination strategy in our population.

11.4 Generalizability

Given the broad inclusion within each Nordic country, our results have a high degree of generalizability to other similar populations. However, our assessment of the comparative effectiveness of monovalent XBB.1.5-containing Covid-19 mRNA-vaccine given as a ≥fifth dose against severe Covid-19 outcomes may only indirectly support any evaluation of the effectiveness of the vaccine within other Covid-19 vaccination schedule scenarios. Our findings may similarly not directly generalize to certain subpopulations not individually studied or to populations with a demographically

different composition. Such subpopulations include for example the general population younger than 65 years old or certain clinical subgroups.

12. OTHER INFORMATION

None.

13. CONCLUSION

We report reduced risk of Covid-19 related hospital admission and death following vaccination with XBB.1.5-containing Covid-19 vaccine in older adults aged ≥65 years following up for 12 weeks during autumn and winter 2023-2024 across the three Nordic countries of Denmark, Finland, and Sweden. We found that the protection gained was similar between, sex, age, and number of previous Covid-19 vaccine doses received. By supplementing relative measures with absolute measure, the results provide health authorities, clinicians, and patients with a more comprehensive assessment of vaccination benefits. Furthermore, this study presents unique evidence on vaccine effectiveness during co-administration with the influenza vaccine. We did not observe any differences in comparative effectiveness with seasonal influenza vaccine co-administration, nor during predominance of either XBB-lineage (EG.5.1) or BA.2.86-lineage (JN.1). The protection peaked during the first weeks following vaccination, and remained well-preserved at 12 weeks of follow-up. Our findings indicate that the concurrent administration of the XBB.1.5-containing vaccine with the seasonal influenza vaccine does not meaningfully alter VE, thereby supporting the co-administration vaccination strategy in our population.

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