STUDY PROTOCOL

1. STUDY INFORMATION

Title	**Effectiveness of monovalent XBB.1.5-containing Covid-19 mRNA vaccines in the Nordic countries**
Protocol version identifier	1
Date of latest version of protocol	8 March 2023
EU PAS Register number	[N/A]
Medicinal products	Spikevax/Omicron XBB.1.5 Comirnaty/Omicron XBB.1.5 Comirnaty Original/Omicron BA.1 (BNT162b2) Comirnaty Original/Omicron BA.4-5 (BNT162b2) Comirnaty Original monovalent (BNT162b2) Spikevax Original/Omicron BA.1 (mRNA-1273 [/Moderna covid-19 vaccine]) Spikevax Original/Omicron BA.4-5 (mRNA-1273 [/Moderna covid-19 vaccine]) Spikevax Original monovalent (mRNA-1273 [/Moderna covid-19 vaccine]) Vaxzevria (ChAdOx1-S [/AZD1222])
Marketing authorization holder(s)	Pfizer/BioNTech Moderna AstraZeneca
Research question and objectives	The aim of this project is to evaluate the comparative effectiveness of the monovalent XBB.1.5-containing Covid-19 vaccines in preventing severe Covid-19 outcomes among individuals aged 65 years or older.
Country(-ies) of study	Denmark, Finland, and Sweden
Authors	Anders Hviid; Kristýna Faksová

2. MARKETING AUTHORIZATION HOLDER(S)

Not applicable.

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3. RESPONSIBLE PARTIES

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 is to be 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 manager and fundraiser		
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 Danish analyses, drafting study protocols, reports and manuscripts. Approval of deliverables.
THL (FI)	Jori Tapio Mikael 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.

4. ABSTRACT

Rationale and background: The Nordic countries of Denmark, Finland, and Sweden, provide a unique setting for the study of Covid-19 vaccination effectiveness. The ubiquitous nationwide demography- and health registers, which includes SARS-CoV-2 immunization and surveillance registers, allows for very large study cohorts with near real-time data availability. The monovalent XBB.1.5-containing Covid-19 vaccines were offered to the adults above 65 years of age during autumn and winter 2023-24. However, data to inform on the effectiveness are limited including when coadministered with an influenza vaccine.

Research question and objectives: The aim of this project is to evaluate the comparative effectiveness of the monovalent XBB.1.5-containing Covid-19 vaccines 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 vaccines 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 vaccines 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 vaccines is affected by the coadministration with an influenza vaccine.

Study design: Nationwide register-based cohort analyses in Denmark, Finland, and Sweden, during the study period from 1 October 2023 until the latest available date in 2024 at time of analyses (e.g., 29 February 2024).

Population: Source cohorts will consist of all individuals who are known residents in the three Nordic countries and have received at least four Covid-19 vaccine doses between 27 December 2020 and latest available date in 2024. The study cohorts will consist of individuals who are at least 65 years of age in Denmark, Finland, and Sweden and eligible to receive an XBB.1.5-containing Covid-19 vaccine as a fifth or sixth dose during the study period.

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

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

Study size: We expect to include at least 3.1 million individuals who have received an XBB.1.5-containing Covid-19 vaccine as a 5th or 6th Covid-19 vaccine dose across the 3 Nordic countries. All available data within countries will be used and the statistical power of our proposed study will be reflected in the 95% CIs of the effectiveness estimates.

Data analysis: Using target trial emulation, we will compare individuals who received a monovalent XBB.1.5-containing Covid-19 vaccine with individuals who did not receive an additional vaccine dose in a matched survival analysis that provides comparative effectiveness estimates while considering a range of covariates.

Milestones: Study start: 8 January August 2024; study planning meeting: 22 January 2024; final first version of study protocol:12 February 2024; study report: 19 April 2024; manuscript draft: 8 July 2024.

5. AMENDMENTS AND UPDATES

Number	Date	Section	Amendment or update	Reason
1	28 February 2024	All	Page numbers added	To improve readability of the document
2	28 February 2024	9.7	Definition of index date and start of follow-up added	To provide clarification on the data analysis approach

6. 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).	12 February 2024
Registration in the EU-PAS Register	12 February 2024
Study Report submission (posted on EU-PAS register when approved by EMA).	19 April 2024
Manuscript(s) ready for submission.	8 July 2024

7. RATIONALE AND BACKGROUND

The emergence of the SARS-CoV-2 Omicron variant in late 2021 quickly raised concerns about the effectiveness of the original monovalent Covid-19 vaccines. Following the adapted bivalent Covid-19 vaccine versions targeting the Omicron BA.1 and BA.4-5 subvariants, monovalent vaccination targeting the Omicron XBB.1.5 subvariant were developed and authorized for use in the autumn and winter 2023-24 [1,2]. The XBB.1.5-containing Covid-19 vaccines have been rolled out from 1 October 2023 in Denmark, Finland and Sweden, and recommended for at-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 vaccines is limited. However, a few studies have assessed the short-term effectiveness and immunogenicity of these vaccines. With a 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 vaccines, but the average follow-up was only 9.9 days [3]. A screening method-based study conducted in the Netherlands assessed Covid-19 VE of the XBB.1.5 vaccines against 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% CI: 66.6–74.3) against hospitalization and 73.3% (95% CI: 42.2–87.6) against intensive care unit admission in the first 57 days following vaccination [4]. Another study by Link-Gelles et al. 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 vaccines, comparing receipt versus no receipt of vaccination against symptomatic SARS-CoV-2 infection [5]. The monovalent XBB.1.5-containing Covid-19 vaccines provided 54% (95% CI : 46–60%) protection against symptomatic SARS-CoV-2 infection at a median of 52 days after vaccination among adults aged ≥18 years [5]. Similarly, UK Health Security Agency reported incremental effectiveness of the monovalent XBB.1.5-containing vaccine at 55.4% against hospitalization 2 to 4 weeks after vaccination among those aged 65 years and older in England [6].

A randomized study by Chalkias and colleagues 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 short termed.

8. RESEARCH QUESTION AND OBJECTIVES

The aim of this project is 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 vaccines 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 vaccines 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 vaccines is affected by the coadministration with an influenza vaccine.

9. RESEARCH METHODS

9.1 Study design

We will take advantage of the unique nationwide register data available to us, and construct 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 will be classified according to Covid-19 vaccinations received and followed up using survival analysis. We

will utilize a comparative design avoiding comparisons with unvaccinated individuals. This will reduce concern about selection bias due to inherent differences in who chooses to remain unvaccinated.

The study period will start in 1 October 2023 in the three countries. This study start date corresponds to when the XBB.1.5-containing Covid-19 vaccine was offered to the 65+ year-olds in the three countries. The study period will end on the last date of data availability at time of analyses during winter or spring 2024.

The overall research design builds on target trial emulation methodologies 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 vaccines against severe Covid-19 using Nordic nationwide registry data are including 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 four or five Covid-19 vaccine doses (of AZD1222 and/or [original/BA4-5/BA-1 bivalent] mRNA vaccines [AZD1222 as part of the primary vaccination course only]) prior to the start of study period • No history of Covid-19 hospitalization prior to the start of study period	Same as for the target trial.
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 unvaccinated 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 will start 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 18 (week 24 if possible) has passed, death, emigration, or end of the study period (date of latest data availability as of 31 March 2024), whichever occurs first.	Same as for the target trial.
Causal contrast of interest	Per-protocol	Observational analog to per-protocol effect.
Statistical analysis	The Aalen-Johansen estimator will be used to obtain cumulative incidence for each treatment strategy during follow-up (with death as a competing risk). We will compare cumulative incidence across treatment strategies by risk ratios (to obtain VE) and risk differences. The Aalen-Johansen estimator will be used to estimate VE as 1 – risk ratio at the end of week 6 and 18 (or 24). In addition, person-time since baseline will be stratified by consecutive 6-week intervals to estimate changes in VEs per 6-week intervals; these VEs will contribute to a meta-regression estimating comparative waning. Subgroup analyses by sex (female/male), age (</≥75 years), and influenza vaccination status.	Same as for the target trial except observational analogs of per-protocol.

9.2 Setting

Eligibility criteria for study inclusion are:

1) Aged of 65 years or older as of the study start
2) Have a known residency within the specific country at start of study period (1 October 2023)
3) Have received four or five 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) 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 workers, 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 vaccines mainly as a fifth or a sixth dose was initiated from 1 October 2023 in the three countries.

Outcomes

Covid-19 hospitalization will be 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 will define 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 will take 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), Covid-19 risk groups (nursing home residents, at risk of severe Covid-19 due to comorbidities), 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[a]	Denmark	*The Danish Vaccination Register.* Defined by the date where the respective vaccine dose examined was administered (i.e., fourth or fifth dose).	Categorical (monthly [up to 33 levels]): 1 (27 December 2020-31 January 2021) to month 49 (January 2024)
	Finland	*The National Vaccination Register.* Defined by the date where the respective vaccine dose examined was administered (i.e., fourth or fifth dose).	
	Sweden	*The National Vaccination Register.* Defined by the date where the respective vaccine dose examined was administered i.e., fourth or fifth dose).	
Region of residency	Denmark	*The Civil Registration System.* Defined by last known address at the country-specific start date for the rollout of the fourth vaccine dose.	Categorical: Denmark, 5 levels; Finland, 5 levels; Sweden, 9 levels
	Finland	*The Finnish Population Information System.* Defined by last known municipality of residence.	

Variable	Country	Data source and details	Values/codes
	Sweden	*The Total Population Register.* Defined by last known address at the country-specific start date for the rollout of the fourth vaccine dose.	
Covid-19 risk groups[b]	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 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 before the start date for the country-specific rollout of the fourth vaccine dose (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 and before first Covid-19 vaccination (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 before the start date for the country-specific rollout of the fourth vaccine dose (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)

Variable	Country	Data source and details	Values/codes
	Sweden	*National Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact and before first Covid-19 vaccination (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 before the start date for the country-specific rollout of the fourth vaccine dose (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 and before first Covid-19 vaccination (look-back 3 years). *Swedish Prescribed Drug Register.* Antidiabetic drugs use defined as ≥2 filled prescriptions during 2020.	Binary: yes/no (ICD-10 codes: E10-E14; ATC code: A10)
Comorbidity 4: Autoimmunity-related conditions[c]	Denmark	*The National Patient Register.* Defined as primary diagnoses regardless of type of hospital contact registered before the start date for the country-specific rollout of the fourth vaccine dose (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 prior start of the follow-up 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 and before first Covid-19 vaccination (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 before the start date for the country-specific rollout of the fourth vaccine dose (look-back 3 years).	Binary: yes/no (ICD-10 codes: C00–C85 (without C44), C88, C90-C96)

Variable	Country	Data source and details	Values/codes
	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 and before first Covid-19 vaccination (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 before the start date for the country-specific rollout of the fourth vaccine dose (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 and before first Covid-19 vaccination (look-back 3 years).	Binary: yes/no (ICD-10 codes: I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61)
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[d]): co-administered on the same date; received influenza vaccine within 1 weeks before to 1 week after XBB.1.5-containing vaccine dose administration but no on same date; no influenza vaccine administered within 1 weeks 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] Due to an 8-10 week lack of hospital register data in Sweden, the country-specific end of study period might be some weeks earlier for the Swedish analyses or we may set on similar end date to unify. [b] To account for the risk of severe Covid-19, we will adjust 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. [c] 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. [d] Influenza vaccination status for season 2023–2024 at around time of XBB.1.5-containing vaccine vaccination will not be used for subgroup analyses only.

9.4 Data sources

All data sources are nationwide registers in native format. All study subcontractors have access to their country-specific data and can link data between registers for the purpose of our study. Given the no-to-very-little lag time of the data source, our analyses will be reflecting real-time information. We will have 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.
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

Country/data source	Details
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.
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 expect to be able to include at least 3.1 million individuals who have received a monovalent XBB.1.5-containing Covid-19 vaccine as a fifth or sixth Covid-19 vaccine dose during autumn and winter 2023-24 across the 3 Nordic countries. We will utilize all available data to us from the countries' nationwide registers. The statistical power of our proposed study will be reflected in the 95% CI of the effectiveness estimates. Based on the data the VE results from our recent Nordic studies, we expect to have high statistical precision for the outlined main objectives [28,29].

9.6 Data management

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

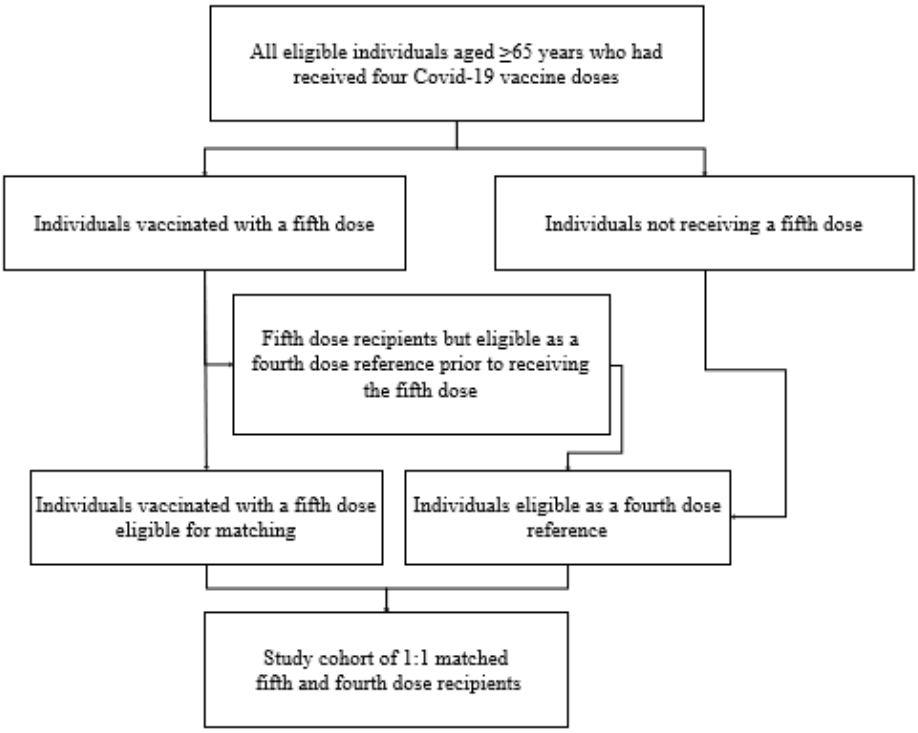
9.7 Data analysis

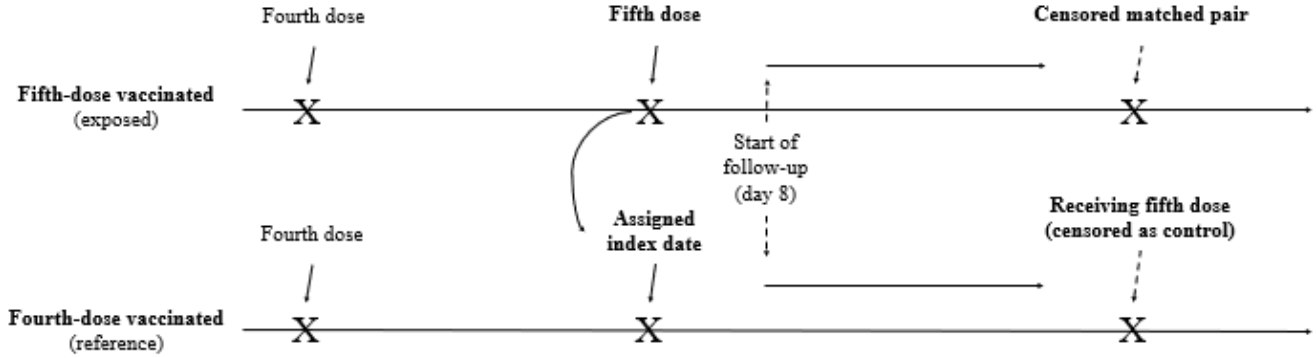
Procedures

We will use 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 2023-24. Individuals who during the study period receive an XBB.1.5-containing Covid-19 vaccine as either a fifth or sixth dose will be matched on the day of vaccination with individuals who have not yet received a fifth or sixth dose, respectively. Individuals will be matched on age (5-year bins), 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), sex, region of residence, vaccination priority groups (i.e., individuals at high-risk of severe Covid-19), 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 will serve as the index date for both individuals. If individuals who were included as a matched XBB.1.5-containing vaccine-unvaccinated individual (i.e., a reference individual) receive an XBB.1.5-containing vaccine later than the assigned index date, they will be 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 will be censored.

We will follow 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, end of week 18 (end of week 24 if possible) since the index date, receipt of additional Covid-19 vaccine dose, death, emigration, or end of the study period, whichever occurs first. The date of vaccination is denoted as the index date. The start of the follow-up period will commence on Day 0, corresponding to eight days after the index date. The figure below illustrates the study cohort construction, as an example of the comparison fifth vs fourth dose.





Statistical analysis

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

Cumulative incidences will be estimated by the Aalen-Johansen estimator using death as a competing risk, and from these we will calculate the comparative VE as 1 – risk ratio at end of week 6 and 18 (or

24). The corresponding 95% CI will be calculated using the delta method. Country-specific estimates will be combined by random-effects meta-analyses implemented using the *mixmeta* package in R.

Comparative waning will be estimated using meta-regression [30]. First, we will estimate the VEs (in the specific comparison being evaluated) in each consecutive 6-week intervals (week 1-6 (day 0-42), 7-12 (day 43-84), 13-18 (day 85-126) and 19-24 (day 127-168)) by stratification on time since XBB.1.5-containing Covid-19 vaccine vaccination. Second, we will regress the VE estimates on time-since-vaccination in 6-week intervals using meta-regression in the form of an intercept and a slope coefficient. The estimated slope coefficient will represent the percentage point change in VE per 6 weeks since vaccination.

Subgroup analyses will be conducted according to sex, age groups (</≥75 years), and influenza vaccination status for XBB.1.5-containing Covid-19 vaccine vaccinated (1)co-administered on the same date, 2) received influenza vaccine within 1 weeks before to 1 week after XBB.1.5-containing vaccine dose administration but no on same date, and 3) no influenza vaccine administered within 1 weeks before to 1 week after of XBB.1.5-containing vaccine dose administration).

9.8 Supplementary analyses and quality control

Quality control will be 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 are 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 will facilitate efficient use of resources and reproducibility of the statistical analyses. We will ensure 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). We will perform matching quality diagnostics to assess the control of matched parameters. We will include a sensitivity analysis where we start 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 *spill-over effect* (that is, prior to the index date) given that some severe Covid-19 events may take longer time to develop.

9.9 Limitations of the research methods

The study has a number of limitations. Given the observational nature of the study, confounding is a potential major concern. Thus, we will consider key predictors of the outcomes or proxies hereof. The

accuracy of our exposure, Covid-19 vaccination, will rely 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 XBB.1.5-containing Covid-19 vaccines was offered to the to the general population aged 65 years or older as fifth and sixth Covid-19 vaccine dose.

Our outcome definitions will most likely also capture 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 will capture all Covid-19 related hospitalizations and deaths within each country. SARS-CoV-2 was ascertained by positive PCR test results and we have no information on at-home antigen testing for SARS-CoV-2. Thus, those who acquired SARS-CoV-2 infection and were hospitalized or died but were not PCR tested will be missed. Our active comparative design, however, mitigates concerns that such outcome misclassification will differ between compared groups to any larger extent as e.g., opposed to comparisons with individuals never vaccinated with the Covid-19 vaccines. Any misclassification will likely tend 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 the possibilities for a valid direct comparison between effectiveness estimates obtained during different periods of variant predominance (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. As such, the analyses will instead reflect evaluations of the initiated Covid-19 vaccination strategies at that given time. In Denmark, Covid-19 hospitalizations peaked on 1 December 2023, when the JN.1 subvariant was predominating.

We expect the majority of the study population will receive 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 will likely be lower.

Given the broad inclusion within each Nordic country, our results will likely 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-vaccines given as a fifth or sixth dose against severe Covid-19 outcomes may only indirectly support any evaluation of the effectiveness of these vaccines 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 other specific clinical subgroups that were not studied.

10. PROTECTION OF HUMAN PARTICIPANTS

No individual-level data will be shared between parties. Country-specific analyses are conducted on pseudo-anonymized data. All parties adhere to GDPR.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Not applicable. Secondary use of data.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Main results expected in the final study report:

- Baseline characteristics-tables, including prior to matching and complementary matching quality diagnostics
- End of week 18 (end of week 24 if possible) cumulative incidence curves-figures for severe Covid-19 outcomes
- Vaccine effectiveness estimates tables for main analysis and influenza co-administration analyses
- Waning vaccine effectiveness figures for severe Covid-19 outcomes

We anticipate one manuscript, and findings will be reported to the general public by institutional press releases upon acceptance in academic peer-review journals or upon uploading to pre-print server (if decided relevant to do so).

We will adhere to the STROBE and ENCEPP guidelines when reporting results and drafting the manuscript(s).

Example of main results table:

	Country-combined measures of association (95% CI) at week 18/24 of follow-up				
	Contributing countries			**XBB.1.5-containing vaccine vaccinated**	
	Contributing countries	**Events/PYRS**	**XBB.1.5-containing**	**RD**	**CVE**

			vaccine unvaccinated		
			Events/PYRS		
Covid-19 hospitalization					
All	XX, XX, XX	XXXX/X, XXX, XXX	XXXX/X, XXX, XXX	XX (XX to XX)	XX (XX to XX)
Subgroups					
Male	XX, XX, XX	XXXX/X, XXX, XXX	XXXX/X, XXX, XXX	XX (XX to XX)	XX (XX to XX)
Female	XX, XX, XX	XXXX/X, XXX, XXX	XXXX/X, XXX, XXX	XX (XX to XX)	XX (XX to XX)
<75 years					
≥75 years					
Influenza vaccine co-administered on the same day					
Influenza vaccine administered within -/ +1 week					
No influenza vaccine administered within -/ +1 week					
Covid-19 death					
All					
Subgroups					
Male					
Female					
<75 years					
≥75 years					
Influenza vaccine co-administered on the same day					
Influenza vaccine administered within -/ +1 week					
No influenza vaccine administered within -/ +1 week					

13. References

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