STUDY PROTOCOL

1. STUDY INFORMATION

Title	**Brand-specific influenza vaccine effectiveness in three Nordic countries: estimates for the 2024-2025 season**
Protocol version identifier	1
Date of latest version of protocol	14 February 2025
EU PAS Register number	EUPAS1000000481
Medicinal products	InfluvacTetra Vaxigrip Tetra Efluelda Tetra Fluad Tetra Flucelvax Tetra
Marketing authorization holder(s)	Abbott Biologicals Sanofi Pasteur Seqirus
Research question and objectives	To provide timely estimates of brand-specific seasonal influenza vaccine effectiveness against laboratory-confirmed and influenza-related outcomes for the 2024-2025 season.
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	**Title**	**Qualifications and role in the study**	**Affiliation and address**
Claus Møldrup	Director of department	Responsible for overall project services and quality assurance	Danish Medicines Agency, Data Analytics Centre, Axel Heides Gade 1, 2300 Copenhagen S, Denmark
Martin Zahle Larsen	Head of unit	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		
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
Ulrike Baum	PhD	Finnish principal investigator, local coordination and analyses conduct, interpretation of results, 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)	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	Epidemiologist	Local project management, literature review, drafting study protocols, reports and manuscripts.
DKMA (DK)	Martin Zahle Larsen	Senior epidemiologist	Project management including contribution to discussions about impact of results on regulatory decision-making.
THL (FI)	Ulrike Baum	Finnish principal investigator, epidemiologist	Local project management. Drafting study protocols, reports and manuscripts. Conduct of Finnish analyses. Approval of deliverables.
THL (FI)	Tuija Leino	Medical specialist	Interpretation of results, review of deliverables, and critical revision of manuscripts.
THL (FI)	Eero Poukka	Medical specialist	Drafting study protocols, reports and manuscripts. Interpretation of results, review of deliverables, and critical revision of manuscripts.
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.
SWE FOHM (SE)	Ulrika Marking	Specialist in infectious diseases	Interpretation of results, review of deliverables, and critical revision of manuscripts.

4. ABSTRACT

Rationale and background: The Nordic countries, Denmark, Finland, and Sweden, provide a unique setting for the study of influenza vaccine effectiveness (IVE). The ubiquitous nationwide demographic and health registers, including vaccination and surveillance data, allow for large study cohorts with near real-time data availability. Seasonal influenza remains a major public health concern, particularly for vulnerable populations such as older adults and individuals at high-risk of serious influenza outcomes. While vaccination is the primary prevention strategy, its effectiveness varies across seasons, virus subtypes, and populations. Data on timely brand-specific IVE are limited.

Research question and objectives: The aim of this project is to evaluate the brand-specific effectiveness of seasonal influenza vaccines in preventing laboratory-confirmed and influenza-related outcomes during the 2024-2025 season in key target populations in Denmark, Finland, and Sweden.

Study objective:

- To provide timely estimates of brand-specific seasonal IVE against laboratory-confirmed and influenza-related outcomes for the 2024-2025 season.

Study design: Nationwide register-based cohort analyses in Denmark, Finland, and Sweden, during the study period from 1 October 2024 until the latest available date in 2025 at time of analyses (e.g., 1 March 2025). We will employ a matched cohort design, utilizing national registers to capture vaccination status, influenza outcomes, and relevant covariates. The study will focus on individuals aged 65 years and older, and adults at high risk of adverse influenza outcomes. IVE will be estimated against laboratory-confirmed influenza, influenza-like illness, hospitalization, ICU admission, and mortality.

Population: Within Denmark, Finland, and Sweden, we will include all individuals aged 65 years and above, and adults at high risk below 65 years of age, who are known residents.

Variables: The primary outcomes are laboratory-confirmed influenza (types A and B, combined and separately), influenza hospitalization, and influenza-related death. The secondary outcomes are hospitalisation for influenza-like-illness, hospitalisation for respiratory infections, ICU admission, and all cause-mortality. Covariates include demographic characteristics and comorbidities.

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

Study size: We expect to include at least 3.2 million individuals who are included in the key target groups for seasonal influenza vaccination 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, vaccinated and unvaccinated cohorts will be compared in matched (1:1) survival analyses to estimate IVE while adjusting for potential confounders. The start of follow-up for matched pairs will be defined as day 14 after vaccination to ensure full immunisation. Sensitivity analyses will include use of negative control outcomes, regression discontinuity analysis, adjustments for prior event rates, and a test-negative case-control design on Danish data (negative test results are currently only available in Denmark).

The findings are aimed at informing regulatory decision-making and vaccination strategies ahead of the 2025-2026 influenza season.

5. AMENDMENTS AND UPDATES

Number	Date	Section	Amendment or update	Reason
1	14.2.2025	9.6 Data management	Added a brief description of the used Common Data Model.	To enhance clarity
2	14.2.2025	9.8 Supplementary analyses and quality control	Added more information on methodological concerns and supplementary analyses.	To provide better overview of the section

6. MILESTONES

Milestone	Planned dates
Project start	1 November 2024
Study planning meeting	15 November 2024
Study Protocol submission to EMA	3 February 2025
Registration in the HMA-EMA Catalogues of real-world data studies	24 February 2025
Study Report submission to EMA	2 May 2025
Manuscript(s) ready for submission to EMA	2 June 2025

7. RATIONALE AND BACKGROUND

Seasonal influenza remains a major public health concern, with a disproportionate impact on older adults aged 65 years and above and individuals who are at increased risk of severe complications, hospitalizations, and mortality associated with influenza infections. Vaccination continues to be the cornerstone of influenza prevention strategies. However, approaches to generate robust estimates of the effectiveness of influenza vaccines has been a subject of extensive research and debate (1).

Several studies have demonstrated moderate effectiveness of seasonal influenza vaccination in elderly populations. Meta-analyses have shown that influenza vaccination is moderately effective against laboratory-confirmed influenza in elderly people during epidemic seasons (2,3). A comprehensive individual participant data meta-analysis by Darvishian et al. examined the effectiveness of seasonal influenza vaccination in community-dwelling elderly people (3). The analysis included 4975 individuals (1829 cases and 3146 controls) from test-negative case-control studies. The researchers observed that influenza vaccination was moderately effective against laboratory-confirmed influenza in elderly people during epidemic seasons when the vaccine matched the circulating type, with a pooled vaccine effectiveness (VE) of 47% (95% CI: 6-70%). Notably, vaccine mismatch or a non-epidemic season was not associated with protection. Significant reductions in influenza-related hospitalizations and mortality have been observed in vaccinated elderly populations (2,4,5). Talbot et al. conducted a prospective observational study over three influenza seasons (2006-2009) to assess the effectiveness of influenza vaccination in preventing hospitalizations in community-dwelling older adults (4). The study included 39 cases and 378 controls. The researchers observed that influenza vaccination was associated with an effectiveness of 61.2% (95% CI: 17.5-81.8%) against laboratory-confirmed influenza hospitalization in adults aged 50 years and older.

The effectiveness of influenza vaccines in high-risk groups is understudied. These populations are at increased risk of severe influenza-related complications, and at the same time their immune systems produce weaker responses to vaccination. A recent study on the effectiveness of 2023 Southern Hemisphere influenza vaccines across eight countries (Argentina, Australia, Brazil, Chile, New Zealand, Paraguay, Thailand, and Uruguay) estimated a pooled vaccine effectiveness of 56.6% (46.2–67.1) against SARI hospitalization among children and adults aged 5–64 years with underlying health conditions. Country-specific estimates varied, ranging from 59.3% (45.9–69.4) in Australia to 28.2% (–44.9 to 64.4) in New Zealand.(6) In immunosuppressed cancer patients, vaccination was associated with lower mortality and reduced risk of influenza-related complications (7), and in RCTs including COPD patients, vaccination was associated with fewer exacerbations (8). In a prospective US evaluation during 2012-16, VE against any influenza was lower among patients with high-risk conditions (41%) than those without (48%; P-for-interaction = 0.02) (9).

VE will vary across different influenza virus subtypes (10,11). A meta-analysis reported pooled VE estimates among older adults of 24% for H3N2, 63% for type B and 62% for H1N1pdm09 (10). In a more recent multi-site evaluation, VE estimates ranged from 26 to 46% against H1N1pdm09, from 2 to 44% against H3N2 and from 50 to 85% against type B. For older adults, VE estimates ranged from 28 to 37% against H1N1pdm09, from 28 to 42% against H3N2 and from 58 to 66% against type B (11).

The moderate effectiveness in the elderly, in part due to the impact of immunosenescence (12), has necessitated the development of more immunogenic vaccine formulations in the form of high-dose vaccines, adjuvanted vaccines and recombinant vaccines. Studies have shown promising results for these enhanced vaccines. For instance, MF59-adjuvanted trivalent inactivated vaccines (MF59-TIV) have demonstrated higher effectiveness in preventing influenza-related hospitalizations and complications compared to non-adjuvanted vaccines in elderly populations (13). Immunosuppressed patients could also benefit from more immunogenic formulations. In an immunosuppressed population, high dose influenza vaccine was more immunogenic than standard dose influenza vaccine against A/H1N1 subtypes but not against H3N2 and B subtypes (14).

The Nordic countries are well-suited to contribute significantly to continuous observational research on influenza VE in target groups. These countries offer unique advantages for conducting such studies due to their comprehensive national health registers, high-quality healthcare systems, and the ability to link various databases using personal identification numbers. In Denmark, a nationwide test-negative case-control study by Emborg et al. utilized Danish health registers to assess the effectiveness of influenza vaccination in individuals aged 65 years and older in the 2015/16 season (15). This study reported VE estimates against H1N1pdm09 of 35.0% (95% CI, 11.1-52.4) and against type B of 4.1% (95% CI: -22.0-24.7). A Finnish-Swedish study by Hergens et al. also used nationwide registers to evaluate the effectiveness of influenza vaccination against laboratory-confirmed influenza in individuals aged 65 years and older during the 2016-2017 season (16). This cohort study included 1,034 and 5,845 cases from Stockholm and Finland, respectively. VEs of 24% (95% CI, 11-35) and 33% (95% CI, 28-38) was reported from Stockholm and Finland, respectively (16).

Despite reassuring observations of moderate effectiveness, especially when the vaccine matches the type and subtype of the circulating influenza virus, some researchers have questioned the universal recommendation of influenza vaccination for populations such as the elderly, calling for more robust study designs, better quality evidence, and the development of more effective vaccines (1,17). It has been argued that many studies, particularly observational ones, have suffered from significant methodological flaws (18). These include selection bias, where healthier individuals are more likely to be vaccinated, and the use of non-specific outcomes like all-cause mortality, which can overestimate vaccine benefits.

The continued evaluation of influenza VE remains important for public health and regulatory decision-making. Despite the widespread use of influenza vaccines, the variability in VE across populations and seasons, virus subtypes, and geographic areas underscores the need for ongoing assessment. This will allow accurate and up-to-date VE data to inform prevention strategies and cost-effectiveness

evaluations, allowing for more efficient allocation of healthcare resources in national immunization programs. Furthermore, seasonal VE studies contribute to the infrastructure and methodologies needed for rapid effectiveness evaluations during potential pandemic situations. By maintaining a robust system for evaluating influenza VE in the European region, the broader goals of public health preparedness and regulatory excellence are also supported. As influenza viruses continue to evolve and use of recent vaccine development platforms such as mRNA-based will increase, continuous assessment of seasonal influenza VE will remain an indispensable tool in the efforts to mitigate the impact of seasonal influenza on vulnerable populations and the national healthcare systems.

8. RESEARCH QUESTION AND OBJECTIVES

We will conduct a large Nordic cohort study combining data from Denmark, Finland, and Sweden to evaluate the brand-specific influenza vaccine effectiveness in preventing influenza outcomes among recommended target groups during the 2024-2025 season (October – April).

Our primary objective is:

- To provide timely estimates of brand-specific seasonal influenza vaccine effectiveness against laboratory-confirmed and influenza-related outcomes for the 2024-2025 season.

The findings are aimed at informing regulatory decision-making and vaccination strategies ahead of the 2025-2026 influenza season.

9. RESEARCH METHODS

9.1 Study design

We will take advantage of the unique nationwide register-data available to us, and construct country-specific 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 birth or immigration, enabling linkage between register data. 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 study period will start on 1st October 2024 in the three countries. This study start date corresponds to the start of the seasonal influenza vaccination program in the three countries. The study period will end on the last date of data availability at time of analyses during spring 2025.

The study design will build on our previous work with Covid-19 vaccination effectiveness in the Nordic countries (19,20). We will utilize a cohort design in a target trial emulation (TTE) framework to estimate both relative and absolute effects. The evaluations in 65+-yr-olds and risk groups 18-64-yr-olds will be designed as two separate target trial emulations. Key components of the specification and emulation of the pragmatic target trials of the effectiveness of brand-specific seasonal IVE using Nordic nationwide register data are included below in Table 1.

Table1. Target trial emulation framework

Protocol	Target Trial Specification	Target Trial Emulation
Eligibility criteria	• Individuals 65+-years-of-age (trial 1) • Individuals in risk groups 18-64-yrs-of-age (trial 2) • Have a permanent residency in Denmark, Finland, or Sweden at start of study period	Same as for the target trials.
Treatment strategies	Vaccination with any of the following influenza vaccines InfluvacTetra, VaxigripTetra, FluadTetra, FluarixTetra or Efluelda Tetra, October 1, 2024 to January 31, 2025 vs vaccination with placebo in the same period.	Same as for the target trials except vaccination with placebo is replaced by no vaccination with any of the vaccines under study.
Treatment assignment	Randomization: Eligible individuals are randomly assigned to receive influenza vaccination with a randomly chosen vaccine brand or no vaccination 1:1	Matching: Eligible individuals who are vaccinated in each country during the study period will be matched 1:1 with individuals who have not yet received a vaccine by age (5-yr bins), sex, region of residence, and presence of comorbidities. Unvaccinated individuals are assigned the index date (date of vaccination) of the matched vaccine recipient.
Outcomes	*Primary:* • Hosp. due to Influenza – Lab. conf + J09-J11 • Lab. conf. Influenza A and B (combined and separately) • Death with influenza – Lab. conf within 30 days before date of death *Secondary:* • Hosp. due to ILI – J09-J11 • Hosp. due to ARI or SARI – J09-J22 • Hosp. due to Influenza with ICU admission • All-cause mortality	Same as for the target trials.
Follow-up	Day 14 after date of vaccination or placebo will serve as the start of follow-up until the day of an outcome event, death, emigration or end of influenza season. Controls are censored if vaccinated.	Day 14 (time zero) after date of vaccination in each matched pair (index date) will serve as the start of follow-up until the day of an outcome event, death, emigration or end of influenza season (or latest possible date of data availability). Pairs are

		censored if controls are vaccinated.
Causal contrast of interest	• Intention to Treat – average effect of treatment assignment in trial population • Per-Protocol Effect – average effect among those who complied with their assigned treatment.	• Modified Per- Protocol Effect – average effect among vaccinated ("do those who get the seasonal influenza vaccination benefit?")
Statistical analysis	VE estimated as 1 - Risk Ratio at week 18 since index date using cumulative incidences from the Aalen-Johansen estimator.	Same as for the target trial. Week 18 subject to change according to data availability. Change will be made before any effectiveness results are estimated.

9.2 Setting

Within Denmark, Finland, and Sweden, we will include all individuals aged 65 years and above, and individuals below 65 years of age at high risk of adverse influenza outcomes, who are known residents. We will analyse each target group in separate cohorts in each country.

Eligibility criteria for study inclusion are:

1) Individuals 65+-years-of-age (trial 1)
2) Individuals in risk groups 18-64-yrs-of-age (trial 2)
3) Have a known residency within the specific country at start of study period

9.3 Variables

Exposures

The Nordic countries conduct annual influenza vaccination campaigns that focus on specific population groups at high risk of severe outcomes from influenza. These groups generally include the elderly, individuals with chronic health conditions, pregnant women, children and healthcare workers (Table 2).

The vaccines are provided free of charge and are typically administered before the peak flu season. In Denmark, vaccines for season 2024/2025 are administered from October 1st, in Finland from September 30th and in Sweden from October 15th. In immunization programmes across the three Nordic countries, the most frequently used quadrivalent inactivated influenza vaccine brands have been InfluvacTetra, VaxigripTetra, FluadTetra, FluarixTetra, and Efluelda Tetra, which are formulated

according to WHO's recommendations. The vaccines contain both seasonal influenza A subtypes, A(H3N2) and A(H1N1) pdm09, and both influenza B lineages, B/Victoria and B/Yamagata. Overview of the country-specific vaccine brands, types and target populations is provided in Table 3. At vaccination at general practitioners, regional vaccination centres or workplaces, individuals are vaccinated with the influenza vaccine available at the location.

An individual is defined as vaccinated starting from and including the day of the first influenza vaccination during the ongoing season, and as unvaccinated if they have yet to receive a first vaccine in the ongoing season.

Table 2. Influenza Vaccination Recommendations in Nordic Countries for season 2024/2025

Country	Target Groups for Influenza Vaccination

Denmark (21)	- Individuals over 65
	- Persons with certain chronic diseases, including:
	  o Persons with chronic lung diseases
	  o Persons with cardiovascular diseases (excluding isolated, well-regulated high blood pressure)
	  o Persons with type 1 or type 2 diabetes
	  o Persons with congenital or acquired immunodeficiency[1]
	  o Persons with impaired respiration due to reduced muscle strength
	  o Persons with chronic liver or kidney disease
	  o Persons with other chronic diseases where the condition, according to the doctor's assessment, leads to an increased risk from Covid-19 or infection[2]
	- Persons with severe obesity (BMI > 35)
	- Persons with other serious diseases or conditions, where the condition, according to the doctor's assessment, poses a serious health risk from Covid-19 or influenza[3]
	- Persons in the same household as individuals with congenital or acquired immunodeficiency, or children at increased risk of severe outcomes from Covid-19 or influenza
	- Pregnant women in the 2nd or 3rd trimester[4]
	- Early retirees

Sweden (22)	- Persons 65 years and above, pregnant women, and persons with certain underlying diseases including:
	  o Persons with chronic lung diseases
	  o Persons with cardiovascular diseases (excluding isolated, well-regulated high blood pressure)

	○ Persons with type 1 or type 2 diabetes ○ Persons with congenital or acquired immunodeficiency[1] ○ Persons with impaired respiration due to reduced muscle strength ○ Persons with chronic liver or kidney disease ○ Persons with other chronic diseases where the condition, according to the doctor's assessment, leads to an increased risk from Covid-19 or infection[2] - Persons with severe obesity (BMI > 35) - Persons with other serious diseases or conditions, where the condition, according to the doctor's assessment, poses a serious health risk from Covid-19 or influenza[3] - Persons in the same household as individuals with congenital or acquired immunodeficiency, or children at increased risk of severe outcomes from Covid-19 or influenza - Pregnant women in the 2nd or 3rd trimester[4] - Health care workers
Finland (23)	- Pregnant women - Individuals aged 65 years or more - Children aged under 7 years - Individuals at risk because of illness or treatment ○ Chronic heart disease ○ Chronic lung disease ○ Chronic metabolic disease ○ Chronic liver disease ○ Chronic kidney disease ○ Immunocompromising conditions due to disease or treatment ○ Down syndrome ○ A neurological disease affecting breathing ○ Psychotic disease ○ Obesity (body mass index > 40) ○ Other condition causing susceptibility for severe influenza - Those close to a person susceptible to serious influenza - Social welfare, healthcare and medical care personnel - Men starting their military service and women starting their voluntary military service

[1]For example, persons with immunoglobulin deficiencies, organ or stem cell transplantation, cancer undergoing chemotherapy, or persons undergoing other immunosuppressive treatment.
[2] For example, persons with severe rheumatological disease, severe neurological disease, or short bowel syndrome.
[3] For example, persons with severe mental illness, Down syndrome, or severe substance abuse.

[4] Pregnant women with other risk factors for a severe course of influenza are recommended to receive the influenza vaccine starting from the first trimester.

Table 3: Overview of vaccine brands used in the national programmes in the Nordic countries in season 2024/2025

Country	Vaccine Brand	Vaccine Type	Target population
Denmark	InfluvacTetra®	QIV, surface antigen	Risk groups above 6 months
			Individuals 65-69 years
	Vaxigrip Tetra®	QIV, split virion	Risk groups above 6 months
			Individuals 65-69 years
	Efluelda Tetra®	QIV, adjuvanted (high-dose)	Clinical trial, 65+
	Fluad Tetra®	QIV, adjuvanted	Elderly 70+
	Flucelvax Tetra®	QIV, surface antigen, cell-based	Individuals with serious allergy to egg, neomycin or gentamycin
Finland	Vaxigrip Tetra®	QIV, split virion	All target groups (incl. 2-6-year-olds)
	Fluenz®	Attenuated live virus, nose spray	Children 2-6 years
	Fluad Tetra®	QIV, adjuvanted	Elderly ≥85y
			Severely immunocompromised ≥50y
	Efluelda Tetra®	QIV, adjuvanted (high-dose)	Outside national vaccination program
Sweden	Vaxigrip Tetra®	QIV, split virion	All target groups (risk groups above 6 months and all above 65)
	InfluvacTetra®	QIV, surface antigen	All target groups (risk groups above 6 months and all above 65)
	Efluelda Tetra®	QIV, adjuvanted (high-dose)	Individuals in long term care facilities (nursery homes for elderly) only

Outcomes

We will estimate VE against the laboratory-confirmed influenza outcomes listed below.

Table 4. Laboratory-confirmed influenza outcomes

Variable	Country	Data source and details
Laboratory-confirmed influenza A	Denmark	*Danish Microbiology Database.* Defined as a laboratory-confirmed positive influenza test with a known subtype of influenza A.
	Finland	*National Infectious Diseases Register.* Defined as a laboratory-confirmed positive influenza test with a known subtype of influenza A.

	Sweden	*Register on surveillance of notifiable communicable diseases (SmiNet).* Defined as a laboratory-confirmed positive influenza test with a known subtype of influenza A.
Laboratory-confirmed influenza B	Denmark	*Danish Microbiology Database.* Defined as a laboratory-confirmed positive influenza B test result.
	Finland	*National Infectious Diseases Register.* Defined as a laboratory-confirmed positive influenza B test result.
	Sweden	*Register on surveillance of notifiable communicable diseases (SmiNet).* Defined as a laboratory-confirmed positive influenza B test result.
Hospitalisation due to influenza	Denmark	*The National Patient Register and the Danish Microbiology Database.* Defined as a hospitalization with a PCR positive test for influenza within 14 days before to 2 days after the admission date, b) inpatient contact or at least 12 hours of contact, and c) influenza-like illness relevant diagnosis code (ICD-10: J09, J10, J11)
	Finland	*National Care Register for Health Care and the National Infectious Diseases Register.* Defined as a hospitalization with a PCR positive test for influenza within 14 days before to 2 days after the admission date, b) inpatient contact, and c) influenza-like illness relevant diagnosis code (ICD-10: J09, J10, J11)
	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 influenza within 14 days before to 2 days after the admission date, b) inpatient contact or at least 12 hours of contact, and c) influenza-like illness relevant diagnosis code (ICD-10: J09, J10, J11)
Influenza-related 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 influenza.
	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 influenza.
	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 influenza.

Furthermore, medically attended outcomes presented in Table 5 will be assessed.

Table 5. Medically attended influenza outcomes

Variable	Country	Data source and details
Influenza-like-illness	Denmark	*The National Patient Register.* Defined as ICD-10 diagnostic codes J09, J10 and J11 used as a primary or secondary diagnosis.
	Finland	*National Care Register for Health Care.* Defined as ICD-10 diagnostic codes J09, J10 and J11 used as a primary diagnosis.
	Sweden	*The Swedish Patient Register.* Defined as ICD-10 diagnostic codes J09, J10 and J11 used as a primary diagnosis.
Hospitalisation for acute respiratory infections (ARI) and severe acute respiratory infections (SARI)	Denmark	*The National Patient Register.* A hospitalised patient is a SARI patient who a) has been admitted to hospital during the study period and has not been discharged to their home or home equivalent, b) inpatient contact or at least 12 hours of contact, and c) a ARI/SARI relevant primary diagnosis code (ICD-10: J09-J22).
	Finland	*National Care Register for Health Care and the National Infectious Diseases Register.* A hospitalised patient is a SARI patient who a) has been admitted to hospital during the study period and has not been discharged to their home or home equivalent, b) inpatient contact or at least 12 hours of contact, and c) a ARI/SARI relevant primary diagnosis code (ICD-10: J09-J22)
	Sweden	*The Swedish Patient Register and the Register on surveillance of notifiable communicable diseases (SmiNet).* A hospitalised patient is a SARI patient who a) has been admitted to hospital during the study period and has not been discharged to their home or home equivalent, b) inpatient contact or at least 12 hours of contact, and c) a ARI/SARI relevant primary diagnosis code (ICD-10: J09-J22)
ICU admission	Denmark	*The National Patient Register and the Danish Microbiology Database.* Defined as admission to an intensive care unit facility during hospitalization for influenza.
	Finland	*Finnish Intensive Care Consortium's Quality Register for Intensive Care, National Care Register for Health Care and the National Infectious Diseases Register.* Defined as admission to an intensive care unit facility during hospitalization for influenza.
	Sweden	*The Swedish Patient Register, Quality Register for Intensive Care and the Register on surveillance of notifiable communicable diseases (SmiNet).* Defined as admission to an intensive care unit facility during hospitalization for influenza.
All-cause mortality	Denmark	*The Civil Registration* Defined as a recording of death in the respective administrative demographic register (vital status is prospectively updated in these registers and also include information on the date of death).
	Finland	*The Finnish Population Information System*

		Defined as a recording of death in the respective administrative demographic register (vital status is prospectively updated in these registers and also include information on the date of death).
	Sweden	*The Total Population Register, the Cause of Death Register* Defined as a recording of death in the respective administrative demographic register (vital status is prospectively updated in these registers and also include information on the date of death).

Covariates

Determinants of vaccination and study outcomes are potential confounders in our studies. The richness of our health registers will allow us to provide detailed characterisations of health and disease status in individuals. We will be able to take the following confounders into account through exact matching: age (5-yr bins), sex, region of residency, and number of selected comorbidities (by 0, 1, 2, or ≥3 of chronic pulmonary disease, cardiovascular conditions, diabetes, autoimmunity-related conditions, cancer, and moderate-to-severe renal disease) as presented in Table 6.

Table 6. List of covariates

Variable	Country	Data source and details	Values/codes
Age	Denmark	*The Civil Registration System.* Recorded birth year. Age defined as 2024 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 2024 minus birth year.	
	Sweden	*The Total Population Register.* Recorded birth year. Age defined as 2024 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.	
Region of residency	Denmark	*The Civil Registration System.* Defined by last known address at the start of the study period.	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 start of the study period.	
Comorbidity 1: Chronic pulmonary disease	Denmark	*The National Patient Register.* Defined as primary or secondary diagnoses registered prior to the start of the study period (look-back 7 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 (look-back 7 years).	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 7 years).	Binary: yes/no (ICD-10 codes: E84, J41-J47, J84, J98)
Comorbidity 2: Cardiovascular conditions	Denmark	*The National Patient Register.* Defined as primary or secondary diagnoses registered prior to the start of the study period (look-back 7 years).	Binary: yes/no (ICD-10 codes: I110, I20-I23, I420, I426-I429, I48, I500-I503, I508, I509, I60–I65)
	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 (look-back 7 years).	Binary: yes/no (ICD-10 codes: I11–I13, I15, I20–I25, I60–I65)
	Sweden	*National Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact prior to the start of the study period (look-back 7 years).	Binary: yes/no (ICD-10 codes: I05-I09, I110, I20-I28, I34-I37, I39, I42, I43, I46, I48-I50, I60–I65)
Comorbidity 3: Diabetes	Denmark	*The National Patient Register.* Defined as primary or secondary diagnoses registered prior to the start of the study period (look-back 7 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 (look-back 7 years).	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 prior to the start of the study period (look-back 7 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 [a]	Denmark	*The National Patient Register.* Defined as primary or secondary diagnoses registered prior to the start of the study period (look-back 7 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,

Variable	Country	Data source and details	Values/codes
			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 to the start of the follow-up or drug prescriptions (look-back 7 years).	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 prior to the start of the study period (look-back 7 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 or secondary diagnoses registered prior to the start of the study period (look-back 7 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 7 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 prior to the start of the study period (look-back 7 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 or secondary diagnoses registered prior to the start of the study period (look-back 7 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 (look-back 7 years).	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 prior to the start of the study period (look-back 7 years).	Binary: yes/no (ICD-10 codes: I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61)

[a] 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.

We provide country specific estimates (by design) and will stratify according to:

- Influenza vaccine brand
- Age groups: individuals <65 years – stratified by 5-yr age bins, ≥65 years – stratified 65 – 75 years of age, and >75 years of age
- Sex

9.4 Data sources

All data sources are nationwide registers in native format. All study investigators have access to their country-specific data and can link data between registers for the purpose of our study. Given the near real-time availability of the data source, our analyses will provide timely evidence. Denmark and Finland 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 complete follow-up of all residents over time. Currently, Sweden has limited access to nationwide influenza vaccination data but will be able to provide data from four regions in Sweden with a combined population of 1,220,00 individuals. These include Uppsala Region (405,000), Jönköping Region (370,000), Blekinge Region (160,000), and Värmland Region (285,000).

Table 7. Overview of individual-level data sources in the three Nordic countries

Country	**Data sources**						
Denmark							
Title	**Info**	**Type**	**Setting**	**Study availability**	**Update**	**Lag**	**Ref**
The Danish Civil Registration System	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.	Register	Nationwide	1968- today	Daily	No lag	(24)

The Danish vaccination register	The register holds information on all vaccinations given in Denmark including information on vaccination date, brand, type, dose, and product batch number ever since November 15, 2015 (when reporting to the register became mandatory).	Register	Nationwide	2020 – today	Daily	No lag	(25)
The National patient registry	The register covers all hospital contacts/visits in Denmark with information on the duration of the contact/visit, department of admission and other hospital characteristics. Treating physician-assigned diagnoses have been registered according to ICD-10 codes since 1995.	Register	Nationwide	1995 - today	Daily	No lag	(26)
The Danish Microbiology Database	Information on positive results of RT-PCR tests for influenza are obtained from The Danish Microbiology Database (MiBa) which holds information on all microbiology samples analysed at Danish departments of microbiology, including information on influenza test results, date of sampling, date of analysis, type of test and interpretation of the test (positive / negative).	Register	Nationwide	2020 – today	Daily	No lag	(27)

Country	**Details of the individual-level data sources**						
Finland							
Title	**Info**	**Type**	**Setting**	**Study availability**	**Update**	**Lag**	**Ref**
Finnish Population Information System	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	Nationwide	1964 - today	Daily	No lag	(28)
National Vaccination Register	The register, which is based on the Register of Primary Health Care Visits, holds information on almost all influenza vaccinations administered in Finland; only influenza vaccinations given by social care givers such as nursing homes might be incompletely covered. Data include the date of vaccination, vaccine batch number and trade name.	Register	Nationwide	2009 - today	Daily	No lag	(29)

Care Register for Health Care	The register comprises information on all in-hospital care (since 1969) and outpatient specialist care (since 1998) in Finland, including admission and discharge dates, whether hospitalisation was planned or acute, codes for discharge diagnoses (according to ICD-10) and surgical procedures, whether discharged as deceased, to own private residence or other health care facilities, type of department and hospital. The register is held by the Finnish Institute for Health and Welfare.	Register	Nationwide	1967 - today	Daily	1-4 weeks	(30)
Register for Primary Health Care Visits	The register is held by Finnish Institute for Health and Welfare and holds data on all primary health care services delivered in Finland.	Register	Nationwide	2011 – today	Daily	No lag	(31)
National Infectious Diseases Register	The register contains information on notifiable diseases which must be reported by the laboratories and the physician treating the patient, or performing an autopsy, in accordance with the Finnish Communicable Diseases Act. All laboratory-confirmed influenza infections are recorded in the National Infectious Diseases Register. The register is held by the Finnish Institute for Health and Welfare.	Register	Nationwide	1995 - today	Daily	0-1 weeks	(32)
Special Reimbursement Register and Prescription Centre database	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. These databases are maintained by the Finnish Social Insurance Institution.	Register	Nationwide	1995 – 2023	Every 6 months	0–6 months	(33)
Finnish Intensive Care Consortium 's Quality Register for Intensive Care	The register includes all intensive care admissions with primary diagnosis (ICD-10).	Register	Nationwide	2020 – today	Daily	No lag	(34)

Country	**Details of the individual-level data sources**						
Sweden							
Title	**Info**	**Type**	**Setting**	**Study availability**	**Update**	**Lag**	**Ref**

Swedish vaccination register	The register will contain information on administered influenza vaccines including data on the date of administration, the specific vaccine products, substance, formulation, batch number and dose number (for repeated doses). The register is held by the Public Health Agency of Sweden.	Register	Nationwide	2026-onwards	Daily	No lag	(35)
Regional vaccination data	Regional data contains information on administered influenza vaccines including data on the date of administration, and the specific vaccine products.	Regional data	Regional	2020-	Ad hoc		
Swedish national inpatient register	The register comprises information on all in-hospital (since 1987) and out-patient (since 2001) specialist care in Sweden including data on admission and discharge dates, whether hospitalisation was planned or acute, codes for discharge diagnoses and surgical procedures, whether discharged as deceased, to own private residence or other health care facilities, type of department, and hospital. For the current study period discharge diagnoses were recorded according to the Swedish clinical modification of the ICD-10 (i.e. ICD-10-SE). The register is held by the National Board of Health and Welfare.	Register	Nationwide	2017 - today	Monthly	2–4 week	(36)
Swedish Prescribed drug register	The Swedish Prescribed Drug Register contains details of all the prescriptions dispensed in Sweden since July 1, 2005. It is updated monthly with around 100 million prescriptions dispensed each year. It covers the entire Swedish population and includes information on unique personal identifier of the patient, age, sex, place of residence, and prescription information on substance, brand name, formulation and package dispensed amount, dosage (in free text) and unique expenditure and reimbursement, date of prescribing and dispensing, practice that has issued the prescription, and prescriber's profession. Drugs are identified by a unique identifier for each specific combination of brand name, substance, formulation, and package. Additionally, all drugs are classified according to the Anatomic Therapeutic Chemical Classification System (ATC). The register only includes filled prescriptions, not medicines sold over the counter, nor medicines administered directly by health-care personnel without prescription. The	Register	Nationwide	2017	monthly	2 weeks	(37)

	register is held by the National Board of Health and Welfare.						
Register on Surveillance of Notifiable Communicable Diseases (Sminet)	The register contains information on notifiable diseases (for which reporting is mandatory) reported by either the analysis-performing laboratories, the treating physician or the autopsy-performing physician, in accordance with the Swedish Communicable Diseases Act. Data include the date of disease occurrence, date of testing, date of positive test and diagnoses. The register is held by the Public Health Agency of Sweden.	Register	Nationwide	2020 - today	Daily	No lag	(38)

Missing data

There are no missing data in this study. All the exposures, outcomes or covariates are either present or not.

9.5 Study size

Below we describe key target group sizes, vaccination coverage and recorded influenza infection incidences in the three Nordic countries for the 2023-2024 season. This provides a good indication of the possible study size for the 2024-2025 season. We expect to include at least 3.2 million individuals who are included in the key target groups for seasonal influenza vaccination across the 3 Nordic countries.

In Denmark, the total population of individuals aged 65 years and older, along with the population at increased risk below 65 years of age, consisted of 1,211 million and 554,780 individuals, respectively, as of 20 December 2024. (39) From 1 October 2024 to 20 December 2024, influenza vaccination coverage in these target groups was 75.6% and 29.2%, respectively. (39) As of 13 January 2025, there were 700 confirmed cases of influenza, including 414 hospitalisations, in older adults above 65 years. (40)

In Finland, the total population of individuals aged 65 years and older was 1,315 million with a vaccine coverage of 61% during the 2023-2024 season. The population at increased risk aged between 18 and 64 years comprised of 0,52 million individuals. The influenza A incidence was 65.5 per 10,000 person-years, and influenza A hospitalisation incidence was 5.4 per 100,000 person-years. As of 20 January 2025, there were 3224 confirmed cases of influenza in the Finnish population, including 81 hospitalisations due to influenza in adults aged 65 years and above. (41,42)

In Sweden, the total population of elderly 65 years and above in the four regions under study comprise of 280,000 individuals, with national influenza vaccination coverage of 69% in the 2023/2024 season. (43)

We will utilize all available data to us from the countries' nationwide registers (Denmark and Finland), and regional data sources (Sweden). The statistical power of our proposed study will be reflected in the 95% CI of the effectiveness estimates. We expect to have robust statistical precision for the most widely used influenza vaccine brands within the current season. (44,45)

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 country-specific results will be shared and combined results will be generated using meta-analysis. Data management and statistical analyses will be conducted using a Common Data Model (CDM), by which national register data are standardised to a common structure, format and terminology in order to allow the same statistical programming scripts to be used in each country. The CDM standardizes the structure of input variables and datasets, ensuring consistency across the three Nordic countries. It is specifically designed to facilitate vaccine effectiveness analyses within the Nordic healthcare setting. The use of a CDM with common statistical programming scripts will facilitate efficient use of resources and reproducibility of the statistical analyses.

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. The country-specific results will be combined using meta-analysis in Denmark.

9.7 Data analysis

Procedures

We will use a matched cohort design to evaluate the effectiveness of seasonal influenza vaccine in comparison with not receiving a seasonal influenza vaccine. Individuals who have received the vaccine will be matched on the day of vaccination with individuals who have not yet received the vaccine. Individuals will be matched on age (5-year bins), sex, region of residence, and selected comorbidities. The day the seasonal vaccine dose was administered within each matched pair will serve as the index date for both individuals. If individuals who were included as a matched non-vaccinated individual

(i.e., a reference individual) receive a vaccine later than the assigned index date, the pair will be right-censored on the day the non-vaccinated individual is vaccinated. In these cases, the non-vaccinated individuals will be allowed to potentially re-enter as vaccine recipients in a new matched pair on that given date.

Statistical analysis

We will follow individuals from day 14 after the index date (to ensure full immunisation) up until the day of an outcome event, death, emigration, or end of the study, whichever occurs first. Additionally, we will censor individuals with a positive PCR test for influenza in our follow-up period 14 and 30 days after the test (as a positive test will be part of the outcome definitions) for the influenza hospitalisation and death outcome analyses, respectively. We will right-censor matched pairs when the reference unvaccinated individual receives a vaccine during follow-up. Cumulative incidences will be estimated by the Aalen-Johansen estimator, and from these we will calculate the comparative VE as 1 – risk ratio at the start of week 18 (depending on data availability) since index date. 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.

9.8 Supplementary analyses and quality control

Confounding-by-indication and healthy vaccinee bias are critical methodological concerns in studies of influenza VE. (46). Confounding by indication would result in an underestimate of true effectiveness if individuals with comorbidities that increase the risk of the study outcome are more likely to get vaccinated. Healthy vaccinee bias occurs when healthy individuals are more likely to get vaccinated while the most frail and sick elderly with the highest risk of the study outcome are not vaccinated, especially at the end of life. In Table 8 below, we present the key possible confounders in studies of effectiveness and how they are likely to be associated with study exposures and outcomes.

Table 8. List of possible confounders in IVE studies

Possible Confounder	Influenza vaccination propensity	Influenza hospitalisation risk	All-Cause Mortality risk	Bias Direction for VE against	Bias direction for VE against

				influenza hospitalisation	all-cause mortality
Comorbidity	↑	↑	↑	Underestimate	Underestimate
High frailty	↓	↑	↑	Overestimate	Overestimate
Healthcare seeking	↑	↑	↓	Underestimate	Overestimate
Healthcare access	↑	↑	↓	Underestimate	Overestimate

The current state-of-the-art in observational vaccination effectiveness estimation is comprised mainly of two study approaches, the test-negative design and TTE. Both approaches seek to mitigate the impact of bias and confounding. Guilin and colleagues (47) evaluated the performance of the two approaches in the evaluation of Covid-19 VE estimation. In data with rich covariate information, they observed similar VE estimates from the two methods. In data with only a few covariates, the test-negative design tended to overestimate the VE, while the target trial emulation underestimated the VE.

To evaluate the potential for biases by healthcare-seeking behaviour or healthcare access, the TTE will be supplemented by a TND study. The TND study is only feasible in Denmark due to lack of test-negative results in Finland and Sweden. Moreover, supplementary analysis comprising of PERR, RDA, and Negative Control Outcomes Analyses will be conducted to allow for comparison and contextualisation of results. Moreover, to strengthen the robustness of findings, triangulation—integrating evidence from multiple analyses with different methodologies—can provide valuable insights into potential biases and enhance the interpretation of results.

Test-Negative Case Control design

The test-negative case-control (TNCC) study design is a variant of the case-control method specifically developed for evaluating VE. (48) Due to unavailability of test negatives data in Finland and Sweden, we will conduct a TNCC study on Danish data only. In this approach, cases are individuals who test positive for influenza, while controls are those who test negative. The TNCC design offers several methodological strengths. It reduces bias from healthcare-seeking behaviour, as both cases and controls sought care and allows for efficient VE estimation during the influenza season. However, the TNCC design also has important limitations. It assumes that influenza vaccine does not affect the risk of other, non-influenza respiratory infections. (48) The design may be subject to bias if cases and

controls differ in disease severity. (49) Moreover, as the use of electronic healthcare records, including register-based data, for identifying cases and controls might cause bias (e.g., misclassification), and active enrolment of study participates is ideal in the TNCC design. (50) However, this increases the cost of the TNCC studies and limits its practicality to estimate VE against rare outcomes. Since a core assumption of the TNCC design is similar healthcare seeking behaviour among those who get tested, there is potential for selection bias if testing practices vary by vaccination status or other patient characteristics.

In the Danish population of individuals who were PCR-tested for influenza during the 2024–2025 season, we will employ a TNCC design to estimate the vaccine effectiveness against influenza infections during the 2024–2025 influenza season. We will exclude negative tests within 7 days of a previous negative test and within 21 days of a subsequent positive test. All tests within 90 days of a previous positive test will be excluded as these likely represent the same episode. Individuals can contribute with a maximum of one negative PCR test, which will be selected at random.

Patients will be considered vaccinated if they received an influenza vaccine at least 14 days before the PCR sample date. Patients will be considered unvaccinated if they have not received the influenza vaccine on the PCR test date or if they have received the influenza vaccine within two weeks before the PCR test date.

Logistic regression models will be used to estimate the odds ratio (OR) with 95% CIs. Our main estimate of interest is the vaccine effectiveness defined by (1−OR) ×100%. The models will be adjusted for age, sex, region of residency and comorbidities. We will assess whether the frequency of testing differs between vaccinated and unvaccinated groups during the season, since differential testing could bias VE estimates. The testing frequency will be visualized in a plot stratified by month and vaccination status.

Prior event rate adjustment

A difference-in-differences approach in the form of prior event rate ratio (PERR) adjustment exists for evaluating healthy vaccinee bias for influenza outcomes. (51) The PERR method is built on the assumption that any differences in event rates unrelated to vaccination between vaccinated and unvaccinated individuals can be observed in the period before vaccination is available. This can be implemented using the pairwise version of PERR. (51)

The matching and censoring criteria from the main TTE analysis will be applied. As before, the day the seasonal vaccine dose was administered within each matched pair will serve as the index date for both individuals. For each individual within a matched pair, the pre-vaccination period will be the start of the 2024/2025 influenza season (1 October 2024) until the index date and the post-vaccination period will start on day 14 following the index date. We will identify individuals who ultimately receive a seasonal influenza vaccine ("future vaccinated") and those who remain unvaccinated ("future unvaccinated"), evaluated at the end of the studied period or on the date of the outcome. Both groups will have the number of outcomes and the amount of person-time measured in the pre-vaccination period (to establish baseline event rates) and in the post-vaccination season (to assess post-vaccination event rates).

The outcome under study is influenza-related hospitalization. Given that influenza hospitalization may be less frequent at the start of the influenza season, we will assess whether sufficient events occur in the pre-vaccination period to produce stable estimates.

We will employ the pairwise version of PERR, which effectively compares the ratio of (current vs. pre-vaccinated) event rates in the vaccinated group to the ratio of (current vs. pre-vaccinated) event rates in the unvaccinated group. Formally:

$$PERR = \frac{\frac{Event\ Rate_{Vaccinated,current}}{Event\ Rate_{Vaccinated,pre\text{-}vaccinated}}}{\frac{Event\ Rate_{Unvaccinated,current}}{Event\ Rate_{Unvaccinated,pre\text{-}vaccinated}}}$$

This ratio-of-ratios approach aims to adjust for pre-existing differences between those who choose vaccination and those who do not.

We will use Poisson regression to estimate event rates during the pre-vaccination and current periods. We will report point estimates and 95% confidence intervals for the PERR-adjusted measure of VE (1-PERR). The precision of these estimates will depend on the number of events in the pre-vaccination period. With high vaccine uptake and the vaccination occurring early in the start of the influenza season, the pre-vaccination period may produce fewer events. PERR results will be interpreted carefully and considered alongside the main matched cohort analyses and other supplementary analysis.

Negative control outcomes (NCO)

To evaluate the possible residual confounding in analysis of influenza vaccine effectiveness, we will analyse the association between influenza vaccination and the following negative control outcomes (NCO) in our main study design: Lower back pain (ICD10: M543-M545), clavicle fracture (ICD10: S420), and diverticulitis (ICD: K57).

Analysing negative control outcomes is a way to assess residual confounding. (70) Negative control outcomes such as lower back pain, clavicle fracture, and diverticulitis are conditions biologically unrelated to both vaccination and influenza. Any association between influenza vaccination and these outcomes would suggest residual confounding e.g. by healthcare seeking behaviour which could bias VE estimates. If no associations are found, it supports the validity of the primary analysis. Significant associations would indicate confounding that requires further adjustment or caution in interpretation. This relies on the assumption that the association between influenza vaccination and the negative control outcome is subject to the same confounders as the association between influenza vaccination and the influenza outcomes. Including negative control outcomes strengthens the study's credibility.

The study population will mirror the primary VE analysis, consisting of individuals aged 65 years or older, and adults under 65 years at high-risk. Vaccinated and unvaccinated individuals will be matched and the start of follow-up for matched pairs will be set at 14 days post-vaccination, ensuring alignment with the primary analysis. The statistical analysis will be conducted in the same way as our main cohort analysis, but negative control outcomes (lower back pain, clavicle fracture, and diverticulitis) will be evaluated instead of the influenza-related outcomes.

The results will be presented as cumulative incidence curves with RD and VE estimates. If no significant associations are found between influenza vaccination and the selected NCOs, this will support the validity of the primary VE analysis and suggest minimal residual confounding. If significant associations are observed, this will indicate residual confounding (e.g., differences in healthcare-seeking behavior) and warrant further exploration or caution in interpreting VE estimates.

Regression discontinuity analysis

For vaccination policies with treatment assignment according to age, regression discontinuity analyses (RDA) can be used to estimate a local average treatment effect (LATE) among individuals whose vaccination status is shifted by an eligibility threshold. Thus, we can estimate the LATE among 60-69-year-olds by comparing the risk in 65-69-yr-olds to the risk in the 60-64-yr-olds. This will provide a valid causal estimate under the assumptions of a) similar baseline risk of the influenza outcome in the two age groups, and b) strict adherence to the age recommendations. If adherence is not strict, we can

use fuzzy regression discontinuity analysis which uses an instrumental variables approach, where the cut-off is an instrument for actual treatment uptake. (52)

While this method can yield robust causal insights under relatively few assumptions, it faces limitations related to sample size, adherence, and external validity. We will interpret RDA findings as part of our broader range of supplementary analyses, recognizing that they estimate a local average treatment effect for compliers in a narrow age interval that may not generalize to the whole population, and should be considered alongside the main cohort findings and other designs (e.g., TNCC, PERR). We will carefully evaluate the number of outcomes in this age range to ensure sufficient power. Even if RDA provides a rigorous causal estimate for the subset near 65, it may not reflect the effect in much older or younger individuals.

We will focus on individuals in an age band of 60-69 years, where the policy recommends seasonal influenza vaccination at age 65. We will extract data on vaccination status at the end of the study period or date of the outcome (yes/no), age (in years), and influenza-related hospitalizations for individuals aged 60–69. This subset ensures that the age threshold of 65 is central in the data, capturing individuals who are just below (60–64) and just above (65–69) the cutoff. Individuals below 65 who are at high-risk will be excluded since they were also offered vaccination. Influenza vaccination will be as assigned as the "treatment" variable. The "instrument" will be a binary indicator of whether an individual's age is ≥65 (the vaccination policy cutoff). This instrument should, in theory, increase the probability of vaccination but is not assumed to directly affect health outcomes other than through vaccination.

The statistical analysis will be conducted using a fuzzy regression discontinuity model. The probability of being vaccinated can be estimated as a function of age relative to 65 (e.g., age − 65) and an indicator for crossing the 65-year threshold. The predicted probability of being vaccinated will then be used to estimate the effect on the outcome of interest (influenza-related hospitalisation). The package *rdrobust* in R can be used to conduct this analysis. We will also construct figures to visualize the discontinuity for outcome and for treatment.

The main assumption is that, aside from the jump in vaccination likelihood at age 65, individuals just below vs. just above 65 should be comparable in terms of health and risk factors. To check this, we will inspect covariate distributions around the cut-off. We also expect to observe a noticeable "jump" in vaccination rates at age 65. If we do not observe this jump, it may indicate that the vaccination policy recommendation has weak influence, and the instrument's strength may be inadequate.

Testing frequency

Tracking the frequency of influenza testing among vaccinated and unvaccinated individuals during follow-up provides insights into residual healthcare utilization or access bias. Testing rates can be compared between the groups to identify discrepancies that could influence VE estimates. We will assess testing frequency among vaccinated and unvaccinated individuals and stratify by calendar month to evaluate whether they are consistent across both groups and months, or driven by specific factors (e.g., timing patterns in a situation of increased testing activity during high influenza season). Ideally, we want the testing frequency to be similar. The results will be presented as the number of tests per group and calendar month, in a table or a graph. These steps ensure that any observed associations between vaccination and outcomes are not unduly influenced.

Sensitivity analysis before full immunization

We will conduct a sensitivity analysis using the primary cohort design (TTE approach) to evaluate vaccine effectiveness (VE) with an alternative time zero. The objective is to determine whether there is a difference in the incidence of influenza hospitalizations when time zero is set at the day of vaccination (Day 0) versus the day of full immunization (Day 14). Accordingly, we will estimate VE for the period from Day 0 to Day 14, and from Day 0 until the end of follow-up, to assess any potential effect of early events on our vaccine effectiveness estimates.

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 vaccination schedule 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. We will perform matching quality diagnostics to assess the control of matched parameters.

9.9 Limitations of the research methods

The statistical power of brand-specific estimates may be limited for the vaccines that are less frequently procured, hence used, in a given country. The statistical precision of our estimates will depend on the seasonal incidence of infections which varies and the uptake of the different influenza vaccine brands.

Cohort studies are susceptible to confounding due to differences in vaccinated persons compared to unvaccinated persons. Confounding due to differences in healthcare seeking behaviour, or to differences in risk of severe disease, can be substantial and can challenge the estimation of the true vaccine effect. We will assess the possible impact of confounding carefully by implementing different supplementary analyses each with unique strengths and weaknesses allowing for triangulation of our findings to support a nuanced interpretation of the results.

Due to only regional availability of influenza vaccination data in Sweden, the majority of the study population is expected to be from Denmark and Finland. We expect near-real time data availability from Denmark and Finland. In Sweden we expect to be able to receive data at one time point – timed later in the data analysis process to ensure that the largest number of influenza vaccinated is included and we have a full representation of the influenza season, without delaying reporting of results.

The timing of vaccination relative to influenza virus circulation can influence VE estimates. Individuals vaccinated earlier or later in the season might experience different levels of exposure to circulating viruses, leading to time-related heterogeneity in effects that is not represented by our VE estimates.

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 after matching, of two separate cohorts of 65+-year-olds (trial 1) and18-64 years-of-age at increased risk (trial 2)
- Figures of cumulative incidence curves for vaccinated and unvaccinated, per country, outcome, brand and trial
- Brand-specific effectiveness estimates-tables with stratified analyses (age, sex, comorbidity, Covid-19 status, influenza vaccination history)
- Supplementary analyses results

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 a pre-print server (if decided relevant to do so). The study protocol and study report deliverables will be made public in the HMA-EMA Catalogue of RWD studies when approved by EMA. We will adhere to the STROBE and ENCePP guidelines for the conduct of observational studies and for scientific independence and transparency.

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