FEASIBILITY REPORT

1. STUDY INFORMATION

Title	Brand-specific influenza vaccine effectiveness in three Nordic countries: feasibility assessment
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 document the feasibility of conducting annual brand-specific seasonal influenza vaccine effectiveness studies in Denmark, Finland, and Sweden.
Countries 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 feasibility report, 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 roles 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

This feasibility report evaluates the potential for conducting annual brand-specific influenza vaccine effectiveness (IVE) studies in Denmark, Finland, and Sweden, utilizing the unique capabilities of Nordic health registries. These registries enable linkage of vaccination data, influenza-related clinical outcomes, and relevant covariates across healthcare settings, providing a robust framework for observational vaccine research.

The assessment demonstrates the availability of comprehensive nationwide, individual-level data on vaccination and health outcomes in Denmark and Finland, with partial regional coverage in Sweden. Data sources capture vaccination details by brand, laboratory-confirmed influenza cases, and clinical outcomes, while supporting subgroup evaluations by age and target groups. The report identifies key elements for timely high quality IVE studies, including linked data on covariates, such as comorbidities, and availability of near real-time surveillance.

The Nordic setting's proven capability in collaborative vaccine effectiveness studies, such as those conducted during the Covid-19 pandemic, underscores its suitability for brand-specific IVE evaluations. Challenges include the current unavailability of Swedish national data on influenza vaccinations, and lag times in data availability. Limitations in test-negative data in Sweden and Finland impacts the feasibility of test-negative case-control designs. The use of target trial emulation, supplemented by negative control outcomes, regression discontinuity, and prior event rate adjustment analyses are recommended to address potential confounding and bias.

This assessment concludes that the Nordic health registries together with appropriate methodology provide a strong foundation for conducting timely brand-specific IVE studies, that can support vaccination strategy evaluations and inform public health and regulatory decision-making.

5. AMENDMENTS AND UPDATES

Number	Date	Section	Amendment or update	Reason
1	31.1.2025	10. Study designs 11. Conclusion	Updated structure of the Study Designs section Revised conclusion section	Per feedback from EMA
2	10.2.2025	10. Study designs	Table 16: Clarification on study designs and supplemental analyses	To ensure better overview of the study designs

6. MILESTONES

Milestones	**Planned dates**
Project start	1 November 2024
Study planning meeting	15 November 2024
Feasibility report submission	6 January 2025
Registration in the HMA-EMA Catalogues	14 February 2025

7. DATA SOURCES IN DENMARK, FINLAND AND SWEDEN

This section provides an overview of the healthcare and data systems in Denmark, Finland, and Sweden, assessing their suitability for influenza vaccine effectiveness (VE) studies based on data quality and availability.

The three Nordic countries Denmark, Finland, and Sweden comprise a total population of approximately 22 million inhabitants. (1) They share a common welfare model that provides universal, tax-funded healthcare to their populations. Each country operates a wide range of government-maintained population-based registries, containing individual-level data on demographics and healthcare. (2) These registries can be linked through a personal key, the unique personal identification number assigned to all residents in the Nordic countries since the establishment of national civil registry systems between 1964–1969. (3,4) These identifiers enable individual-level data linkage across various healthcare and demographic registries, allowing researchers to pool data into a single, large study cohort, enhancing statistical power and enabling robust research with less selection bias over longer time periods. (2) Norway is not participating in the current collaboration, but would be a welcome addition for future seasonal evaluations, if near-real time access to the needed data sources, including influenza vaccinations, are possible.

This coordinated use of Nordic health registries offers significant advantages for epidemiological studies, particularly when examining rare outcomes, due to the large study populations and the ability to follow individuals over extended periods and in near real-time. (2)

7.1. The Nordic setting – a proven setting for vaccine effectiveness monitoring and evaluation

During the pandemic, the Nordic countries (Denmark, Finland, Norway and Sweden) have collaborated on the conduct of large effectiveness- and safety studies of the Covid-19 vaccines. (5–8) This collaboration has consistently produced rapid and impactful evidence to the benefit of public health- and regulatory agencies nationally, regionally and globally. Nordic collaborations have been at the forefront with respect to the analyses of the association between the viral vector vaccines and thromboembolism with thrombocytopenia syndrome (TTS) (9), and the association between the mRNA vaccines and myocarditis (8), informing vaccination policies in the respective countries. In the context of the European Medicines Agency (EMA) and related to vaccine effectiveness, the collaboration has conducted a comprehensive evaluation of vaccine effectiveness across Denmark, Sweden and Finland, including “Comparative effectiveness of the monovalent XBB.1.5-containing

covid-19 mRNA vaccine across three Nordic countries" (10) and "Comparative effectiveness of bivalent BA.4-5 or BA.1 mRNA booster vaccines among immunocompromised individuals across three Nordic countries: A nationwide cohort study". (11) These studies demonstrated the feasibility of conducting rapid effectiveness studies in the Nordic setting on newly introduced vaccines as well as seasonal vaccines. (12)

Collaboration among Nordic countries on observational vaccine effect studies has been well-established for some time. In the context of human papillomavirus vaccination, Denmark and Sweden have conducted extensive evaluations of the risk of autoimmune diseases, neurological conditions and thromboembolic events. (13–15) The Nordic countries have also demonstrated the ability to collaborate with sites across Europe and globally. (16,17)

7.2. Fit-for-purpose data for conducting influenza vaccine effectiveness studies

Denmark

Denmark has a well-established system for national influenza surveillance, primarily coordinated by the Statens Serum Institut (SSI). (18) SSI monitors the incidence of influenza to indicate the start and end of the flu season, to assess the severity of the flu season, to isolate and characterize the circulating flu viruses in the population, and to assess the effectiveness of seasonal influenza vaccines. (18) Table 1 provides an overview of available data sources for vaccine effectiveness studies.

Table 1. Overview of individual-level data sources in Denmark

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	Register	Nationwide	1968- today	Daily	No lag	(19)

	well as continuously updated information and dates on historical addresses, immigration and emigration status, and death.						
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	(20)
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	(21)
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	(22)

Laboratory confirmed influenza

The occurrence of laboratory-confirmed influenza is monitored through the Danish Microbiology Database (MiBa), which records all influenza-related test results from microbiology departments across the country. (23) This database enables the tracking of weekly influenza cases, specifically the number of patients testing positive for influenza A or B. This information enables us estimate vaccine effectiveness against laboratory-confirmed influenza outcomes including laboratory-confirmed

influenza A or B. SSI maintains an interactive influenza dashboard, where the data are updated on a weekly basis during influenza season. (24) However, the testing strategy for influenza is less comprehensive than it was during the Covid-19 pandemic. As a result, influenza-related test results are limited to a subset of individuals, likely those who sought hospital care with symptoms resembling influenza. Therefore, many individuals might have had less severe influenza without testing positive.

Table 2. Lab-confirmed influenza cases per season and influenza type, population of Denmark (last update 2025-01-02)

Season	Influenza type	Number
2023/2024	INFLA	18799
2023/2024	INFLB	402
2024/2025	INFLA	1710
2024/2025	INFLB	162

Table 3. Lab-confirmed influenza cases per season and influenza type, target groups for seasonal vaccination, Denmark (last update 2025-01-02)

Season	Influenza type	Target group	Number
2023/2024	INFLA	65+	4839
2023/2024	INFLA	high risk 18-64	1673
2023/2024	INFLB	65+	18
2023/2024	INFLB	high risk 18-64	27
2024/2025	INFLA	65+	393
2024/2025	INFLA	high risk 18-64	148
2024/2025	INFLB	65+	6
2024/2025	INFLB	high risk 18-64	16

Vaccination

In Denmark, free influenza vaccination is offered to target groups. (25) In the 2024/2025 influenza season, publicly funded vaccination is offered at regional vaccination centres and at the Danish Doctors' Vaccination Service providers. (26) In total, there are 326 vaccination sites across Denmark. (26) Moreover, influenza vaccination is provided in selected workplaces. It is not possible to get vaccinated at the pharmacies this season, but it has been in previous seasons. (25) All vaccinations are recorded in the Danish Vaccination Register (DDV) which is updated on a daily basis (27) and include vaccines administered at workplaces. Methodological considerations related to the utilization of the DDV in vaccine effectiveness studies are outlined below in the *Methodological considerations* section (Table 9). The register provides information about the vaccination date and vaccine brand. On 9 October 2024, SSI launched the yearly interactive influenza vaccination dashboard providing data on regional vaccine uptake for each target group and gender. (28)

Severe influenza outcomes

National information about ICD-10 codes related to hospital admissions, outpatient visits, and emergency room contacts are available from the Danish National Patient Registry. (30) Information about ICD-10 codes and date and time of admission will be used to define severe influenza outcomes. Methodological considerations related to the internal validity of cohort studies conducted with data from the Danish National Patient Registry are outlined below in the *Methodological considerations* section (Table 10).

Finland

Finland has a hybrid influenza surveillance system allowing the Finnish Institute for Health and Welfare (THL) to monitor the prevalence of influenza in the population combining traditional syndromic sentinel surveillance and analyses of electronic health records. (31) The surveillance system is based on laboratory analyses of respiratory specimens, on communicable disease notifications filed by doctors and laboratories as well as on data about primary health care visits, hospitalizations and vaccinations. (31) Table 4 provides an overview of available data sources for vaccine effectiveness studies.

Table 4. Overview of individual-level data sources in Finland

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	(32)
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	(33)
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	Register	Nationwide	1967 - today	Daily	1-4 weeks	(34)

	and hospital. The register is held by the Finnish Institute for Health and Welfare.						
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	(35)
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	(36)
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 - today	Every 6 months	0–6 months	(37)
Register of Social Assistance	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.	Register	Nationwide	1985-today	Once per year	One year	(38)
Finnish Intensive Care Consortium 's Quality Register for	The register includes all intensive care admissions with primary diagnosis (ICD-10).	Register	Nationwide	2020 – today	Daily	No lag	(39)

Intensive Care							

Vaccination

In Finland, seasonal influenza vaccination is recommended to more than half of the Finnish population. As part of the national vaccination program, seasonal influenza vaccination is offered free of charge to children younger than 7 years, adults aged 65 years and above, military conscripts, pregnant women, social and health care workers, people in institutional settings, people at risk of severe influenza disease because of an underlying chronic illness or immunosuppressive treatment, and people close to a person at particularly high risk of severe influenza disease. (40) In addition, occupational and private health care services provide seasonal influenza vaccination outside the national vaccination program.

Almost all influenza vaccinations are recorded in the Finnish Vaccination Register which is updated daily. (33) Only influenza vaccinations given by social care givers such as nursing homes might be covered incompletely. Methodological considerations related to the utilization of the vaccination register in vaccine effectiveness studies are outlined below in the *Methodological considerations* section (Table 9). The register records the vaccination date, batch number and vaccine brand. A register-based real-time follow-up of the 2024-2025 influenza vaccination campaign by age group and wellbeing services county is available online. (41)

Laboratory-confirmed influenza

In Finland, in accordance with the Communicable Diseases Act, all microbiological laboratories must report all influenza-positive findings, which are then recorded in the Finnish Infectious Diseases Register. This register enables the tracking of influenza cases, specifically the number of patients testing positive for influenza A or B. Table 5 summarizes the number of laboratory-confirmed influenza cases in 2022-2023, 2023-2024 and 2024-2025 (last update 2024-12-12). An overview of the number of laboratory-confirmed influenza cases by either month, age group or wellbeing services county is also available online. (42) These data enable estimation of vaccine effectiveness against laboratory-confirmed influenza, combining the two types as well as distinguishing between type A and B.

In general, the laboratory confirmation of mild cases is considered not necessary if more than 48 hours have passed since symptom onset. (43) Severe cases and severely immunocompromised cases are, however, recommended to be laboratory confirmed. Testing practices (including timeliness of healthcare seeking) have thus a great impact on which influenza infections are detected and included by a case definition based on laboratory confirmation. Ultimately, laboratory-confirmed influenza is a highly specific but not very sensitive outcome measure for influenza infection and estimation of vaccine effectiveness. However, the sensitivity for severe influenza infection can be assumed to be high. Unfortunately, negative test results are not yet available for register-based influenza vaccine effectiveness studies. The likelihood of testing and the test positivity rate is thus still unknown. Negative test results are recorded in Kanta, a nationwide set of digital services that store citizens' social welfare and health care data. (44) After careful examination and validation of the data structure these records are planned to become available sometime in the future.

Table 5. Laboratory-confirmed influenza cases per season (from October to April) and influenza type in Finland (last update 2024-12-12)

Season	Influenza type	Number
2022/2023	INFLA	13528
2022/2023	INFLB	1775
2023/2024	INFLA	10239
2023/2024	INFLB	1050
2024/2025	INFLA	321
2024/2025	INFLB	45

Severe influenza outcomes

The Finnish Care Register for Health Care (34) comprises information on all in-hospital care and outpatient specialist care in Finland. Diagnostic codes (ICD-10 codes) and the date and time of hospital admission will be used to define severe influenza outcomes. The information whether a hospitalized patient was treated in an intensive care unit (ICU) will be derived from the Finnish Intensive Care Consortium's Quality Register for Intensive Care. (39) Methodological considerations related to the

utilization of these registers in vaccine effectiveness studies are outlined below in the *Methodological considerations* section (Table 10).

Sweden

Sweden has a well-established system for national influenza surveillance, primarily coordinated by the Public Health Agency of Sweden. The Public Health Agency of Sweden monitors the incidence of influenza to indicate the start and end of the flu season, to assess the severity of the flu season, to isolate and characterize the circulating flu viruses in the population, and to assess the effectiveness of seasonal influenza vaccines.

Table 6. Overview of individual-level data sources in Sweden

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	(45)
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	(46)
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	Register	Nationwide	2017	monthly	2 weeks	(47)

	personnel without prescription. The 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	(48)

Vaccination

The Swedish national vaccination register was implemented in 2013. (45,49) The data collection is administered by the Public Health Agency of Sweden. Reporting to the register is mandatory for all vaccinations given within the national immunization program (childhood vaccinations and pneumococci for elderly) and vaccination against Covid-19.

The Swedish national vaccination register is regulated under a legislation issued by the Swedish government and can among others be used for evaluation and planning of health care services, monitoring public health and for research. The register is a health data register and data may not be accessed by data providers or patients, hence it cannot be regarded as a complete Immunisation Information System. The data is confidential and protected by the Secrecy Act (chapter 9, §4). This act stipulates that data become confidential on transmission to the Public Health Agency of Sweden. However, research is one of the stipulated areas for which data from the Swedish vaccination register may be used, given ethical approval is granted by the Swedish Ethical Review Authority.

The national vaccination register contains eleven variables with information on the vaccinated, the vaccine and the vaccinator (Table 7). Dose number was included in the register from 1 January 2021. Registered information on the vaccinator is most often on the regional health care authority responsible for the vaccination and to a less extent the actual health care facility giving the vaccination.

Table 7. Variables of the Swedish national vaccination register

Variable	**Variable name**	**Variable definition**
Information on the vaccinated		
Personal identity		
Date of birth		
Place of Residence		Place of Residence at time of vaccination
Sex		
Information on the vaccine		
Date of vaccination		Date when the vaccination was given
Vaccine product name		Vaccine product name
Vaccine unique identifier		NPLID
Batch number		Vaccine product Batch
Dose number		Dose number
Vaccine type or disease		Disease or disease the vaccine is intended for
Information on the vaccinator		
Responsible health care organisation		

Extending the national vaccination register to become a comprehensive register of all vaccinations

A recent Swedish Government Official Reports (50) suggested a more comprehensive national vaccination register, where vaccinations that are not a part of the national programmes, including seasonal influenza vaccines, would be included. This is however yet to be considered and handled by the Swedish government. There are no estimations of when a more comprehensive register, including influenza vaccinations, may be available. Currently, influenza vaccination data from four regions in Sweden are available with a 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).

Laboratory confirmed influenza

The occurrence of laboratory-confirmed influenza is monitored through the Register on Surveillance of Notifiable Communicable Diseases (SmiNet), which records all influenza-related test results from

microbiology departments across the country. (48) This database enables the tracking of weekly influenza cases, specifically the number of patients testing positive for influenza A or B. This information enables us to estimate vaccine effectiveness against laboratory-confirmed influenza outcomes including laboratory-confirmed influenza A or B. The Public Health Agency of Sweden maintains an interactive influenza dashboard, where the data are updated on a weekly basis during influenza season. (51) However, the testing strategy for influenza is less comprehensive than it was during the Covid-19 pandemic. As a result, influenza-related test results are likely limited to a subset of individuals, likely those who sought hospital care with symptoms resembling influenza. Therefore, many individuals might have had less severe influenza without testing positive.

Table 8. Lab-confirmed influenza cases per season and influenza type, population of Sweden (last update 2024-12-16)

Season	Influenza type	Number
2023/2024	INFLA	15308
2023/2024	INFLB	1152
2024/2025	INFLA	379
2024/2025	INFLB	42

In Sweden, a total of 421 confirmed cases of influenza have been reported during the current influenza season. Of these, 90 percent were attributed to influenza A, while 10 percent were identified as influenza B. Further subtyping of influenza A cases revealed that 83 percent were subtype A(H1) pdm09, and 17 percent were subtype A(H3), based on a total of 186 subtyped influenza A samples. Among the influenza B cases, all six samples that underwent lineage typing were identified as lineage B/Victoria. An analysis of the confirmed cases indicates that 39 percent were individuals aged 65 years or older, with 17 percent aged 80 years or older.

7.3. Data sources related methodological considerations

This section outlines the methodological considerations for conducting cohort and case-control studies (e.g. test-negative study design) in the Nordic settings. The study designs are further elaborated in Section 10.

Table 9. Methodological Considerations Related to the Internal Validity of Cohort and Case-Control Studies Conducted with Data from Nordic Vaccination Registers

Completeness	The vaccination registers in Denmark, Finland, and Sweden provide varying levels of completeness. Denmark's register contains nationwide data on all vaccinations since 2015, including privately funded vaccinations if reported. Finland's register covers vaccinations from the public primary care sector, private and occupational sectors (since 2021), and secondary care (since 2019), though social caregiver-administered vaccinations (e.g., in nursing homes) may be incompletely covered. Sweden's national vaccination register was implemented in 2013 but only mandates reporting for vaccinations included in national immunization programs (e.g. childhood vaccinations, Covid-19 vaccines). Seasonal influenza vaccinations are not yet comprehensively recorded at the national level but are captured regionally (4 regions included).
Selection bias	The universal healthcare systems in Denmark, Finland, and Sweden ensure equal access to publicly funded vaccinations, reducing the risk of selection bias related to socioeconomic factors such as income level or employment status.
Information bias	In all three countries, vaccination registers provide high-quality data, but potential misclassification of vaccination status may occur due to reporting delays or errors by healthcare providers. In Denmark and Finland, inconsistencies in recording batch numbers and vaccine brand names have been noted for earlier years, though these issues have improved over time. In Sweden, data on influenza vaccinations is only available regionally, but this is unlikely to introduce information bias.
Confounding	The Nordic vaccination registers can be linked to other national registries (e.g. hospital, prescription, and demographic registers) using unique personal identifiers, enabling control for confounders such as comorbidities, healthcare-seeking behaviour, and vaccination history. However, unmeasured confounders, such as lifestyle factors may still pose challenges in observational studies.

Table 10. Methodological Considerations Related to the Internal Validity of Cohort Studies Conducted with Data from Nordic Hospital Care and Infectious Disease Surveillance Registers

Completeness	The Nordic hospital care registers capture comprehensive data on in-hospital care, with coverage spanning several decades. These registers provide near-complete health histories for specialized care, supporting life-course epidemiology across large populations. Private hospital data may be less consistently included, and milder primary care influenza cases are not captured in hospital-based datasets. Infectious disease surveillance systems in the region also provide national coverage of laboratory-confirmed influenza cases, though variations in testing practices can affect completeness.
Selection bias	The population-based nature of the Nordic healthcare systems, with universal access, minimizes selection bias related to socioeconomic factors, insurance status, or care-seeking behaviours. However, surveillance systems relying on laboratory-confirmed cases may introduce bias related to testing behaviours and recommendations.
Information bias	Misclassification of outcomes may arise from inaccuracies in diagnostic coding or delays in receiving laboratory results. This is particularly relevant for older patients, where the initial diagnosis may not include influenza if symptoms are atypical or masked by chronic conditions. While Nordic registers are generally reliable, there may be underreporting of private healthcare services or self-funded treatments. Testing strategies for influenza also differ across regions and seasons, which leads to incomplete reporting of influenza cases, especially during periods of low testing.
Confounding	Nordic health data systems enable linkage of hospital care registers with vaccination, population, and prescription registers using unique personal identifiers. This facilitates control for many confounders, such as comorbidities, healthcare-seeking behaviour, and vaccination history. However, unmeasured confounders, such as frailty, general health status, and social determinants, may still pose challenges.

8. TARGET GROUPS FOR SEASONAL INFLUENZA VACCINATION

Overview of influenza immunisation recommendations for 2024/2025 season (e.g., by age/risk group) in the Denmark, Finland, and Sweden are presented in Table 11.

Table 11. Influenza Vaccination Recommendations in Nordic Countries

Country	Target Groups for Influenza Vaccination
Denmark (25)	- 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 (52)	- 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) 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] - Health care workers

Finland (40)	- Pregnant women
	- Individuals aged 65 years or more
	- Children aged under 7 years (< 7 years)
	- Individuals at-risk groups because of illness or treatment
	  o Chronic heart disease
	  o Chronic lung disease
	  o Chronic metabolic disease
	  o Chronic liver disease
	  o Chronic kidney disease
	  o Immunocompromising conditions due to disease or treatment
	  o Down syndrome
	  o A neurological disease affecting breathing
	  o Psychotic disease
	  o Obesity (body mass index > 40)
	  o 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.

Feasibility of conducting IVE studies in children and pregnant women

Evaluating IVE in children and pregnant women is associated with additional challenges.

Denmark

In the 2021/22 influenza season, vaccination was introduced for the first time for children aged 2–6 years in Denmark. (53,54) While the vaccine effectiveness (VE) for non-hospitalized children in this cohort was estimated at 62.4% (95% confidence interval: 50.5–74.1), vaccine uptake was relatively low, reaching only 29% in the first season. (53)

Over the subsequent influenza seasons, vaccination coverage in this age group declined further, with uptake dropping to 22% in 2022/23 and 16% in 2023/24. (55) A register-based study conducted by the Statens Serum Institut highlighted that vaccination rates were higher among younger children (2–3 years) and those with chronic conditions. However, parental attitudes toward vaccination shifted. (55,56) Findings from surveys and interviews indicated that parents were increasingly less concerned about the risk of influenza infection and less inclined to vaccinate their children solely to protect others. (55)

Given the declining support for the program, the Danish Health Authority concluded that maintaining vaccination for healthy children in this age group would require significant resources and extraordinary efforts. As a result, the influenza vaccination offers for children aged 2–6 years without underlying health conditions was discontinued in the 2024 season. However, vaccination remains available for vulnerable children, who are offered and encouraged to receive the vaccine. (55)

Despite challenges in uptake, the availability of comprehensive health registries in Denmark provides a valuable framework for conducting IVE studies in children. Focusing on vulnerable populations where vaccination remains a priority could yield meaningful insights into vaccine effectiveness and contribute to public health strategies.

Influenza vaccination is routinely recommended for pregnant women in Denmark due to the increased risk of severe influenza-related complications during pregnancy. (25) Vaccination is offered during the second and third trimesters as part of the national influenza vaccination program. Pregnant women who also belong to one of the other risk groups for severe influenza disease are recommended to be vaccinated already in the 1st trimester. (25)

A large cohort study in Denmark demonstrated that maternal immunization with the trivalent inactivated influenza vaccine (TIV) significantly reduced the risk of laboratory-confirmed influenza and influenza-related hospitalizations in pregnant women. Additionally, infants born to vaccinated mothers experienced a lower incidence of influenza infections during their first six months of life.

Importantly, the study found no association between vaccination and adverse pregnancy outcomes, including preterm birth and low birth weight, supporting the vaccine's safety profile. (57)

The feasibility of conducting IVE studies in pregnant women in Denmark is enhanced by the country's comprehensive health registry system. These registries enable linkage of vaccination data with maternal and neonatal health outcomes, allowing for robust evaluations of vaccine effectiveness against influenza-related morbidity and adverse pregnancy outcomes. Furthermore, Denmark's well-established data infrastructure supports the longitudinal monitoring necessary for IVE studies linking maternal vaccination with infant outcomes.

Finland

Seasonal influenza vaccination for children was added in 2007 to the Finnish National Vaccination Program. At first, vaccination was recommended only to children aged 6 to 35 months. In 2018, the recommendation was extended to 3- to 6-year-olds. Since the 2015/16 season, 2- to 6-year-old children (or their legal guardians) can choose between a live-attenuated nasal spray vaccine and an inactivated injectable vaccine.

The national recommendation is non-preferential with respect to type of vaccine. In recent seasons, the vaccination coverage in children has been roughly constant, ranging between 31% and 37%. (58) Despite the non-preferential recommendation, the majority of vaccinated 2- to 6-year-olds receive the live-attenuated vaccine. The vaccination coverage of the inactivated vaccine has been continuously decreasing from 5% in 2019–2020 to 2% in 2023–2024. (58)

The effectiveness of seasonal influenza vaccination in children has been routinely assessed in the past based solely on the available register data using a cohort study approach. (58,59) However, the rarity of severe outcomes in this population and the low coverage of injectable vaccine has only allowed robust estimation of the effectiveness of the live-attenuated nasal spray vaccine against laboratory-confirmed influenza.

Seasonal influenza vaccination for pregnant women (including all trimesters of pregnancy) was added in 2010 to the Finnish National Vaccination Program. Because there is no Finnish register of past and ongoing pregnancies, the evaluation of vaccination coverage and vaccine effectiveness has not yet been conducted in real-time.

Past (unpublished) analyses of vaccination coverage among pregnant women utilized the Finnish Medical Birth Register, which contains data on live births and stillbirths, as well as data on the mothers. (60) The data become available with a delay of up to 1 year after childbirth and thus with a delay of 1 to 2 years after the beginning of pregnancy. The vaccination coverage among pregnant women has been continuously improving and was estimated at 46% for the 2019/20 season.

A Finnish register-based cohort study utilizing the Medical Birth Register and the Register of Induced Abortions demonstrated the perinatal safety of maternal vaccination with the 2009/10 pandemic influenza vaccine. (61) In principle, an effectiveness study could have been conducted similarly. Unfortunately, the study failed to include pregnancies terminated by spontaneous abortion, which is recorded in the Care Register of Health Care but without data on the embryo's/fetus' gestational age.

Recently, the Register of Primary Health Care Visits has been utilized to identify all women who visit maternity clinics and thus are likely pregnant. However, the exact timing of a pregnancy is at the moment not identifiable hindering accurate real-time analyses of maternal vaccination coverage and vaccine effectiveness.

Sweden

No recent research available demonstrating feasibility due to the lack of available nationwide recordings of influenza vaccinations in Sweden.

9. BRAND-SPECIFIC VACCINATION DATA

Below we present country-specific information on influenza vaccine uptake, and vaccine brands used in the current and previous seasons. In Denmark, Influvac Tetra, Vaxigrip Tetra, and Fluad Tetra and Vaxigrip Tetra were the most frequently administered vaccines in the seasons 2023/2024 and 2024/2025, respectively. Similarly, Vaxigrip Tetra was the most frequently administered vaccine brand over the two seasons in Finland, and 2023/2024 season in Sweden. Data for the current season from Sweden are not available in a real time, but will be available in the form of a one-time output in spring 2025 to support effectiveness evaluations.

Denmark

Figure 1. Seasonal influenza vaccine uptake rates by vaccine brands for seasons 2023/2024 and 2024/2025 (last update 2025-01-02)

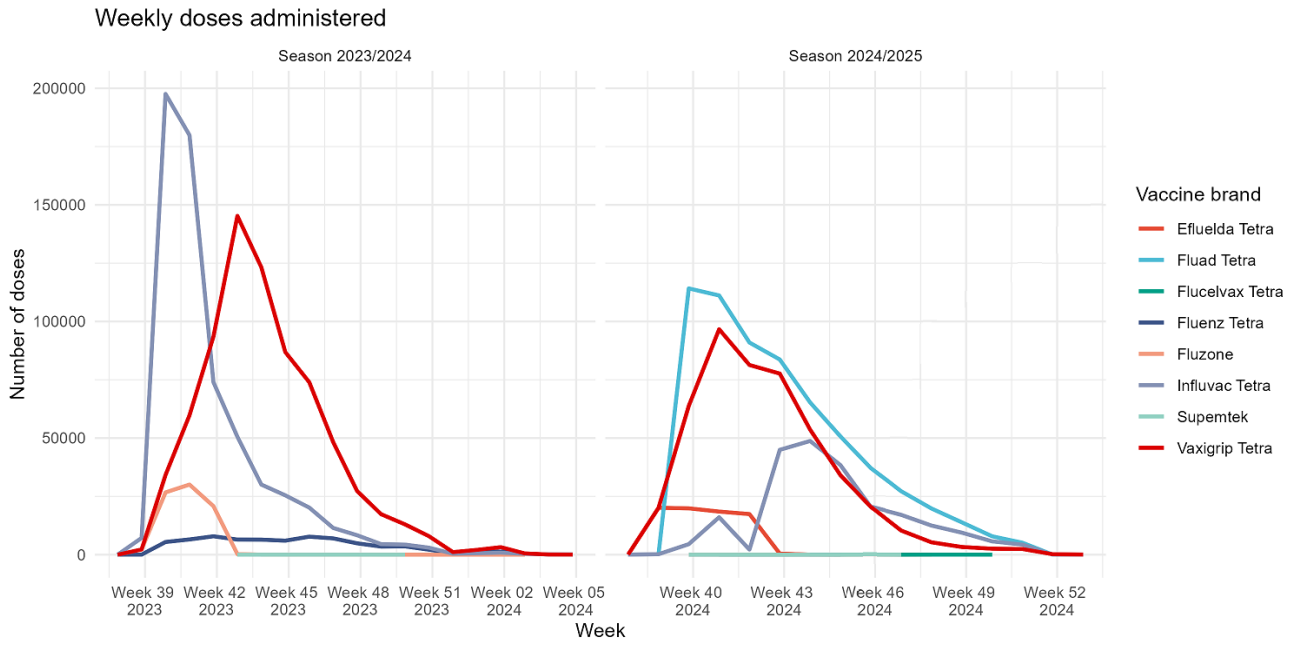


Table 12. Overview of vaccine brands used in the current and 2023/2024 season, Denmark

Season	Vaccine Brand	Vaccine Type	Target population
2024-2025	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
	Eflulda 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
2023-2024	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
	Fluenz Tetra®	Attenuated live virus, nose spray	Children 2-6 years
	Fluzone®	QIV, adjuvanted	Elderly 70+
	Supemtek®	quadrivalent, recombinant, prepared in cell culture	Individuals with serious allergy to egg, neomycin or gentamycin

*QIV = quadrivalent inactivated vaccine

Finland

Figure 2. Seasonal influenza vaccine uptake rates by vaccine brands for seasons 2023/2024 and 2024/2025 (as of 2024-12-13)

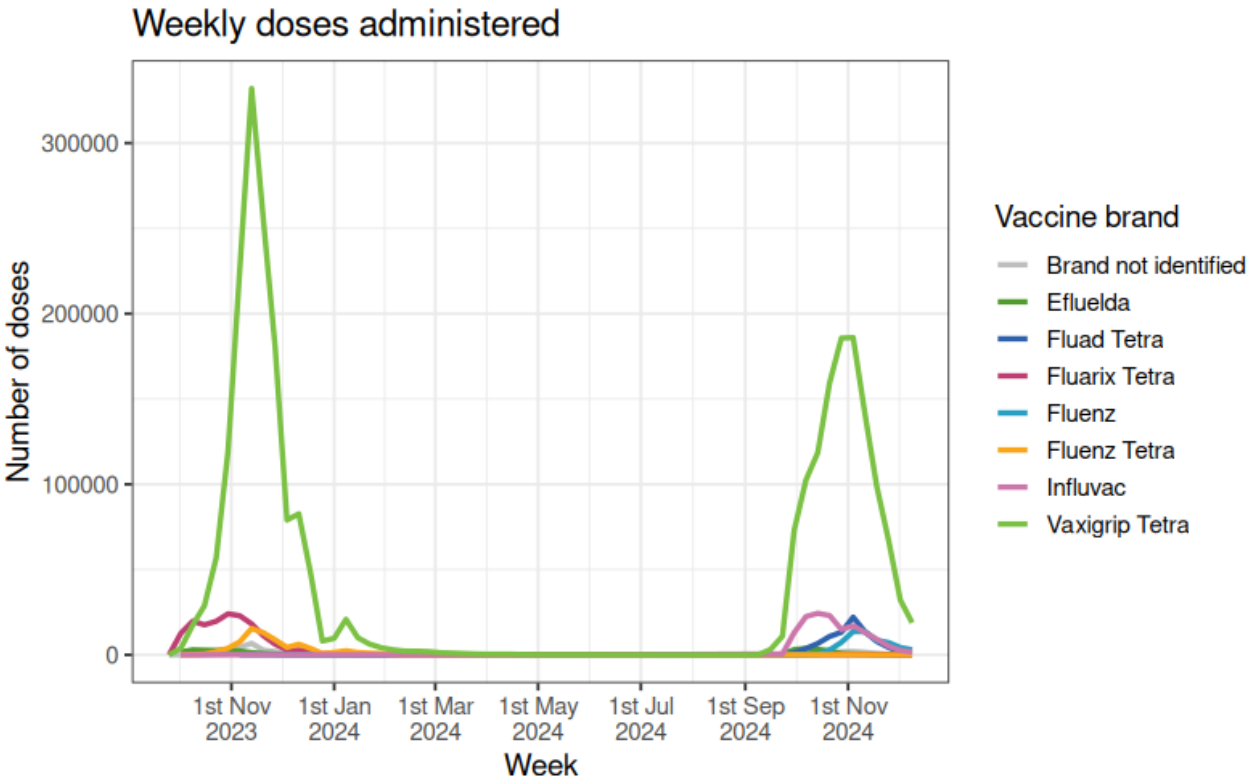


Table 13. Overview of vaccine brands used in the current and 2023/2024 season, Finland

Season	Vaccine Brand	Vaccine Type	Target population
2024-2025	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
2023-2024	Vaxigrip Tetra®	QIV, split virion	All target groups (incl. 2-6-year-olds)
	Fluenz Tetra®	Attenuated live virus, nose spray	Children 2-6 years

Efluelda Tetra®	QIV, adjuvanted (high-dose)	Outside national vaccination program
Fluarix Tetra®	QIV, split virion	Outside national vaccination program
Influvac®	TIV, split virion	Outside national vaccination program

Sweden

Figure 3. Seasonal influenza vaccine uptake rates by vaccine brands for season 2023/2024

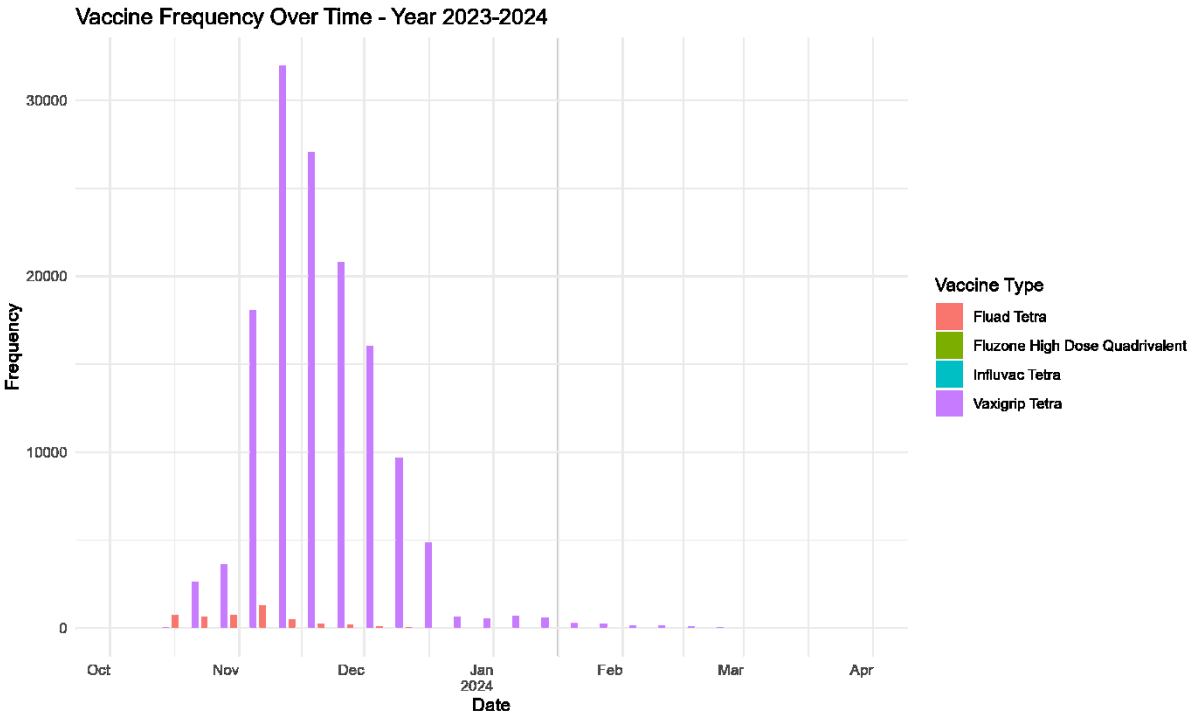


Table 14. Overview of vaccine brands used in the current season, Sweden

Season	Vaccine Brand	Vaccine Type	Target population
2024-2025	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

10. STUDY DESIGNS FOR SEASONAL IVE STUDIES

10.1 Study design considerations for studies on IVE

Randomized controlled trials (RCTs) are widely regarded as the "gold standard" in clinical research due to their ability to provide valid causal inference through randomization. However, RCTs with clinical endpoints are not routinely conducted to assess seasonal influenza vaccine effectiveness (IVE). Instead, immunological evaluations of antibody titres following vaccination are often used as proxies for studies with clinical endpoints.

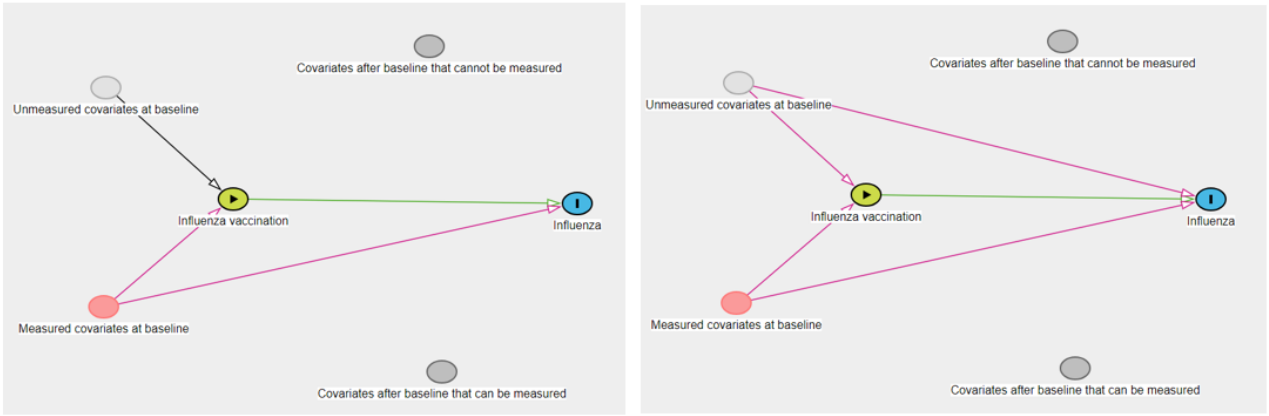
Observational studies, in contrast, provide the evidence base for public health and regulatory decision making on seasonal vaccination policies. These studies are particularly valuable for understanding how well seasonal influenza vaccination policies performs in real-world conditions. Despite their importance, observational studies are subject to potential biases and confounding, which must be carefully addressed to ensure reliable results.

Confounding-by-indication and healthy vaccinee bias are critical methodological concerns in studies of influenza vaccine effectiveness. (62) 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 15 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 15. List of possible confounders in IVE studies

Possible Confounder	Influenza vaccination propensity	Influenza hospitalisation risk	All-Cause Mortality risk	Bias Direction for VE against influenza hospitalisation	Bias direction for VE against all-cause mortality
Comorbidity	↑	↑	↑	Underestimate	Underestimate
High frailty	↓	↑	↑	Overestimate	Overestimate
Healthcare seeking	↑	↑	↓	Underestimate	Overestimate
Healthcare access	↑	↑	↓	Underestimate	Overestimate

Another way of visualising potential sources of confounding and bias is to draw a directed acyclic graph (DAG). Below we present DAGs showing our causal assumptions about the relationships between influenza vaccination, influenza outcomes, measured and unmeasured covariates at baseline and measured and unmeasured covariates after baseline (intercurrent events).



The left DAG demonstrates a scenario where causal inference is possible through adjustment of measured baseline covariates. Here, the measured baseline covariates provide a sufficient adjustment set for estimating the causal effect of vaccination on influenza outcomes, despite the presence of paths through unmeasured baseline covariates, because adjusting for measured covariates blocks all backdoor paths. A backdoor path occurs when exposure and outcome are connected through covariates that could create a spurious association – such as when a common cause affects both vaccination and influenza outcomes (the common cause is then termed a confounder). In contrast, the right DAG shows a scenario where unmeasured confounding prevents unbiased causal effect estimation, as adjusting for measured baseline covariates still leaves unblocked backdoor paths through the unmeasured baseline covariates. The post-baseline covariates in both scenarios are included to highlight the possibility of informative censoring.

The current state-of-the-art in observational vaccination effectiveness estimation is comprised mainly of two study approaches, the test-negative design and target trial emulation framework. The test-negative design is widely used to routinely estimate seasonal IVE, while target trial emulation framework has been used for Covid-19 VE estimation. Both approaches seek to mitigate the impact of bias and confounding. Guilin and colleagues (63) 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.

10.2 Overview of possible study designs

10.2.2 Cohort design using an emulated target trial approach

The emulated target trial approach can be used to evaluate VE by mimicking the structure and principles of a RCT using observational data. (67) This approach aims to minimize biases typically associated with observational studies by explicitly defining the eligibility criteria, treatment strategies, follow-up, and outcome assessment as they would be in an RCT. One of its primary strengths is the ability to emulate a causal framework, thereby enhancing the interpretability of results. By specifying a clear causal question and aligning the analysis with this framework, the emulated target trial can approximate the effects of vaccination more robustly than traditional observational methods. (67) The success of the emulated approach relies heavily on the quality and completeness of the observational data. Missing data, misclassification, or incomplete capture of confounders can compromise the validity of the findings. Moreover, unlike RCTs, this design cannot fully eliminate confounding due to unmeasured factors or control for biases arising from healthcare access or health-seeking behaviours.

Table 16. 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	Same as for the target trials.

	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	
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.

Analytical choices in target trial emulation

Matching and inverse probability of treatment weighting (IPTW) are widely used to address confounding. (68,69) The methods can ensure comparability between vaccinated and unvaccinated groups. Both methods aim to account for differences in characteristics such as age, sex and comorbidities.

Matching in VE studies involves pairing vaccinated and unvaccinated individuals based on their propensity scores or specific covariates, ensuring balance in confounders between groups. Matching helps isolate the effect of vaccination by creating groups with comparable covariate characteristics, thereby enhancing the internal validity of the study. However, in the context of influenza vaccines, matching can reduce the sample size, especially if the overlap in characteristics between vaccinated and unvaccinated individuals is limited. This can be a significant limitation in studies aiming to assess VE in subpopulations or for rare outcomes like severe influenza-related hospitalization. Furthermore, the exclusion of unmatched individuals may limit generalizability. When matching, VE can be interpreted as the effect among those who chose to get vaccinated.

IPTW in VE studies is used to balance covariates across vaccinated and unvaccinated groups without excluding individuals. By assigning weights based on the inverse probability of vaccination, IPTW creates a pseudo-population where the distribution of confounders is similar across groups. The intuition behind IPTW is that individuals who are unlikely to get vaccinated based on their covariates but get vaccinated anyway are upweighted, while individuals who are likely to get vaccinated based on their covariates but remain unvaccinated are also upweighted. Retaining all individuals ensures efficient use of available data, preserving statistical power to estimate VE across multiple outcomes, such as influenza-like illness, hospitalization, or mortality. However, the sensitivity of IPTW to extreme weights, often arising in datasets with very high or very low vaccination probabilities, poses challenges including instability and increased variance of estimates. When weighting, VE can be interpreted as the effect if the whole population had chosen to get vaccinated.

Both methods face challenges in relation to potential unmeasured confounding, such as health status and the risk of collider bias, where the decision to seek care and be tested (the inclusion criteria in TND) is influenced by both vaccination and outcome risk.

In conclusion, both matching and IPTW are valuable for addressing confounding in influenza VE studies. Matching offers intuitive balancing but at the cost of reduced sample size and generalizability, while IPTW retains the full sample but requires careful handling of extreme weights. Both methods also require the identification of a time zero (start of follow-up). For vaccinated individuals, date of vaccination or immunization (1-2 weeks after vaccination) is time zero. When matching, the matched pair (vaccinated and unvaccinated individual) is assigned the same time zero. When weighting, the unvaccinated individuals can be assigned time zeros sampled from the distribution of vaccination dates among the vaccinated. The choice of time zero—either the date of vaccination or the immunization date (14 days after vaccination)—can influence study results. Using the date of vaccination ensures precision and alignment with recorded data but may misclassify early events occurring before immunity develops. In contrast, using the immunization date reflects the period of vaccine-induced protection but requires approximations regarding when this protection takes effect, as the exact time of immunity development can vary among individuals.

An emulated target trial approach should ideally be supplemented by additional analyses with different strengths and weaknesses to evaluate potential biases. 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. By

comparing outcomes across complementary approaches, we can assess the consistency of findings and identify possible sources of residual confounding or bias. This multi-method strategy allows for a more comprehensive contextualization of the vaccine effectiveness estimates and supports more reliable conclusions about the study's findings. In the section below, we present possible supplementary analyses which could enhance the contextualisation of the results.

10.2.3 Supplementary analyses

Test-negative case control design

The test-negative case-control (TND) design is a variant of the case-control method specifically developed for evaluating VE. (64) In this approach, cases are individuals who test positive for influenza, while controls are those who test negative, among patients presenting with influenza-like illness (ILI). The TND offers several methodological strengths. It reduces bias from healthcare-seeking behaviour, as both cases and controls sought care for ILI and allows for efficient VE estimation during the influenza season. However, the TND also has important limitations. It assumes that influenza vaccine does not affect the risk of non-influenza ILI. (64) The design may be subject to bias if cases and controls differ in disease severity. (65) Moreover, as use of register-based data for identifying cases and controls might cause bias, and active enrolment of study participates is ideal in TND. (66) However, this increases the cost of the TND studies and limits its practicality to estimate VE against rare outcomes. Since a core assumption of the TND 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. Finally, by design the TND cannot assess VE against all-cause outcomes.

Prior event rate adjustment

A difference-in-differences approach in the form of prior event rate ratio (PERR) adjustment exist for evaluating healthy vaccinee bias for influenza outcomes. (72) The PERR method is built on the assumption that the outcome event rate in the vaccinated and unvaccinated individuals should be similar in the period prior to study start, before vaccination is possible. This can be implemented using the pairwise version of PERR which estimates the current vs prior association in vaccinated and unvaccinated individuals, respectively. (72) The period from when the 2022/23 influenza season

ended and until before vaccination begins for the 2023/24 season could be used. However, the results should be interpreted carefully. A key weakness in our setting will be the expected rarity of influenza outcomes outside of the season which results in imprecise estimates of bias. Additionally, vaccinated individuals are likely to get influenza vaccination in repeated seasons and may carry cross-reactive immunity from the last vaccine into the prior period, and unvaccinated individuals are likely to remain unvaccinated through successive seasons and may carry infection induced immunity from a previous season into the prior period.

Regression discontinuity analysis

For vaccination policies with treatment assignment according to age, regression discontinuity analyses (RDA) can be used to estimate VE in the age groups just below and above the age threshold for vaccination recommendation. Thus, we could estimate the IVE among 60-69-year-olds as an intention-to-treat effect by comparing the risk in 65-69-yr-olds to the risk in the 60-64-yr-olds. This would 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. The main limitations of these approaches are statistical power and the question of generalizability of the VE in this narrower age-groups.

Negative control outcomes

Analysing negative control outcomes is a valuable 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, ensuring more reliable VE estimates.

Negative control period

Evaluating documented influenza infection during the first X days of follow-up as a negative control period where vaccination is unlikely to have produced a protective effect but where the effect of

vaccination is expected to be confounded similarly to the main outcome. If a strong protective effect is found in the first 7 days after vaccination, this indicates bias.

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 (e.g., tests per person-time) can be compared between the groups to identify discrepancies that could influence VE estimates. Differences in testing frequency can also be assessed within subgroups (e.g., age, comorbidities, or region of residency) to evaluate whether they are consistent across populations or driven by specific factors. Ideally, we want the testing frequency to be similar. Additionally, testing timing patterns can be examined to detect temporal biases, such as increased testing shortly after vaccination. These steps ensure that any observed associations between vaccination and outcomes are not unduly influenced by differences in healthcare utilization, strengthening the reliability of VE estimates.

10.3 Conclusion on study designs

In conclusion, a cohort study design utilising the TTE framework will be the primary study approach to estimate the IVE in our study. This approach is feasible in all three countries as high-quality complete data are available. 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. In Table 16 we summarise the strengths, limitations and feasibility of these study designs in the Nordic settings.

Table 16. Overview of strengths and limitations of the suggested study designs and supplemental analyses

Study Design	Pros	Cons	Feasibility in Nordic Register Setting
Cohort design using the TTE framework	Mimics RCT structure using observational data; can reduce bias if appropriately designed; provides an	Dependent on data quality; susceptible to unmeasured confounding; potential biases from healthcare	Feasible with detailed register data; relies on high data quality and completeness.

	interpretable causal framework.	access and health-seeking behaviours; methodologically complex.	
Test-Negative Case-Control (TND)	Reduces bias from healthcare-seeking behaviour; efficient VE estimation during influenza season; well-established method.	Assumes influenza vaccine does not affect other respiratory pathogens; potential selection bias if testing differs by vaccination status or over time; cannot be used for all-cause outcomes.	Only feasible in Denmark. Not feasible due to unavailability of test negative results in Finland and Sweden.
Supplemental analyses	**Pros**	**Cons**	**Feasibility in Nordic Register Setting**
Prior Event Rate Adjustment (PERR)	Adjusts for pre-vaccination differences in outcome rates, providing a valid causal estimate under the assumption of stable relative differences in outcome rates before and after vaccination among the comparison groups.	Limited power due to the rarity of influenza outcomes outside the season; potential confounding from cross-reactive immunity and infection-induced immunity; susceptible to calendar time related changes in health-care seeking behaviour.	Feasible, but limited power due to seasonal variability of influenza outcomes.
Regression Discontinuity Analysis	Provides valid causal estimate when vaccination eligibility is based on age; suitable for simple intention-to-treat analysis of individuals just above and below threshold.	Limited generalizability to broader population; requires strict adherence to age thresholds; potential issues with statistical power.	Feasible with access to age-specific vaccination data in registers.
Negative Control Outcomes Analysis	Detects residual confounding by examining outcomes (e.g., lower back pain, clavicle fracture,	Outcomes must be truly unrelated to vaccination or risk misinterpretation.	Feasible if these diagnoses are well-coded in national registers.

	diverticulitis) unrelated to vaccination and influenza. Null findings support validity of VE estimates.	Rare events may limit power. Confounders for influenza may not map exactly to these outcomes, complicating interpretation.	

11. CONCLUSION

This feasibility report confirms the strong potential for conducting annual brand-specific seasonal influenza vaccine effectiveness (IVE) studies in Denmark, Finland, and Sweden. The Nordic countries benefit from comprehensive, population-based health registries that allow for linkage of vaccination data, clinical outcomes, and covariates. Denmark and Finland provide nationwide data with extensive coverage, while Sweden offers partial regional data that complements the broader Nordic collaboration.

In addition to documenting the feasibility of IVE studies, this report also presents data on vaccine uptakes in Denmark, Finland and Sweden (only regional data), as well as laboratory-confirmed influenza cases across the countries, which is useful to inform study development and their potential power. These datasets further underscore the capability of the Nordic registries to support stratified analyses by vaccine brand, target groups, and clinical outcomes. However, estimates on brand-specific VE may be limited by smaller sample sizes for less frequently administered vaccine brands, reducing statistical power and leading to less precise estimates. This challenge will be acknowledged when interpreting findings.

While the Nordic countries' data infrastructure is well-suited for IVE studies, certain challenges remain, such as the limited availability of certain datasets, including test-negative data in Sweden and Finland, and the varying scope of regional data in Sweden. 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 recommend TTE as the primary study approach that is feasible in all three countries. To assess the possible impact of healthcare seeking bias, healthy vaccinee bias, and confounding, supplemental analyses are recommended, as described above. Nevertheless, the proven capacity of these countries for collaborative vaccine effectiveness studies—exemplified during the Covid-19 pandemic—underscores their suitability for brand-specific IVE studies.

This report concludes that the Nordic health registries together with appropriate methodology provide a scientifically rigorous and operationally feasible platform for brand-specific IVE evaluations. Such a platform can support vaccination policy assessments and can meaningfully inform public health and regulatory decision-making, aligning with the European Medicines Agency's requirements for reliable and timely evidence.

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