STUDY REPORT

1. TITLE

Brand-specific influenza vaccine effectiveness in three Nordic countries: estimates for the 2024-2025 season

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TABLE OF CONTENTS

2. ABSTRACT

Rationale and background: The Nordic countries, Denmark, Finland, and Sweden, provide a unique setting for the study of influenza vaccine effectiveness (VE). 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. Limited data on timely brand-specific influenza VE are available to support annual decision-making by the European Medicines Agency on the performance of seasonal influenza vaccines.

Research question and objectives: The aim of this study was 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 influenza VE 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 21 March 2025. We employed target trial emulation with a matched cohort design, utilizing national registers to capture vaccination status, influenza outcomes, and relevant covariates. The study focused on individuals aged 65 years and older, and adults at high risk of adverse influenza outcomes. VE was estimated against laboratory-confirmed influenza, influenza-like illness, hospitalization, ICU admission, and mortality.

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

Study size: We included 3.3 million individuals who were in the key target groups for seasonal influenza vaccination across the 3 Nordic countries. All available data within countries was used and the statistical power of the study was reflected in the 95% CIs of the effectiveness estimates.

Variables: The primary outcomes were laboratory-confirmed influenza (types A and B, combined and separately), influenza hospitalization, and influenza-related death. The secondary outcomes were hospitalisation for influenza-like-illness, hospitalisation for respiratory infections, ICU admission, and all cause-mortality. Covariates included demographic characteristics and comorbidities. We included quadrivalent influenza vaccine brands administered during the 2024–2025 season in the three

countries comprising Vaxigrip Tetra (standard-dose split virion), Influvac Tetra (standard-dose subunit), Fluad Tetra (adjuvanted standard-dose subunit), and Efluelda Tetra (high-dose split virion).

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

Data analysis: Vaccinated and unvaccinated cohorts were compared in matched (1:1) survival analyses to estimate VE while adjusting for potential confounders. The start of follow-up for matched pairs was defined as day 14 after vaccination to ensure full immunisation. Sensitivity analyses included 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 only available in Denmark).

Results: The matched cohorts **of individuals aged 65 years and older** for the analysis of influenza hospitalization consisted of a total of 1,164,686 recipients of a seasonal influenza vaccine during the study period (mean age 75.4, SD 7.3 years) and 1,164,686 non-recipients. Most recipients were from Finland (611,174) and Denmark (529,082), followed by Sweden (24,430). The most frequently used vaccine brand was Vaxigrip Tetra (688,822 doses) followed by Fluad Tetra (402,490 doses,), Efluelda Tetra (37,246 doses) and Influvac Tetra (36,098 doses). The sizes of the matched cohorts for other outcomes were similar, with minor differences according to the exclusion of prior events for each outcome.

At week 18 of follow up, the estimated VE against overall laboratory-confirmed influenza was 39.7% (36.1-43.2) with a risk difference of -167.8 (-199.4 to -136.1) per 100,000 individuals. Against laboratory-confirmed influenza A, the overall estimated VE was 38.1% (31.3-44.8) with a risk difference of -160.0 (-312.3 to -7.8) per 100,000 individuals. Against laboratory-confirmed influenza B, the overall estimated VE was 63.7% (44.2-83.1) with a risk difference of -4.4 (-6.7 to -2.0) per 100,000 individuals. The overall VE against influenza hospitalization was 46.8% (40.8-52.9) with a risk difference of -60.2 (-217.0 to 96.6) per 100,000 individuals. The overall VE against influenza-related death was 63.2% (53.6-72.8) with a risk difference of -19.9 (-32.1 to -7.6) per 100,000 individuals. Where estimable, the vaccine brand Efluelda Tetra (high-dose) showed the highest VE against the primary outcomes, followed by Fluad Tetra (adjuvanted) and Influvac Tetra vaccines.

The vaccines had an initial VE of 61.6% (46.8-76.3) against laboratory confirmed influenza, 65.7% (36.9 to 94.4) against influenza hospitalization and 74.9% (19.5% to 100%) against influenza- related death at 3 weeks of follow-up. Subsequently, gradual waning of -7.2 (-10.9 to 3.6), -6.5 (-10.5 to 2.5), and -4.4 (-12.6 to 3.8) percentage points against laboratory confirmed influenza, hospitalization, and death, respectively, were observed every 3 weeks on average.

The matched cohorts of **adults below 65 years of age at high risk** for the analysis of influenza hospitalization consisted of a total of 210,566 recipients of a seasonal influenza vaccine during the study period (mean age 53.1, SD 10.4 years) and 210,566 non-recipients. Most recipients were from Finland (105,069) and Denmark (103,542), followed by Sweden (1,955). The most frequently used vaccine brand was Vaxigrip Tetra (155,600 doses), followed by Influvac Tetra (50,935 doses), Efluelda Tetra (2,186 doses), and Fluad Tetra (1,827 doses). The sizes of the matched cohorts for other outcomes were similar, with minor differences according to the exclusion of prior events for each outcome.

At week 18 of follow up and for all brands pooled, the estimated VE against overall laboratory-confirmed influenza was 12.4% (3.7 to 21.1) with a risk difference of -56.1 (-118.4 to 6.1) per 100,000 individuals. Against laboratory-confirmed influenza A, the estimated VE was 6.9% (-2.9 to 16.6) with a risk difference of -27.3 (-70.4 to 15.7) per 100,000 individuals. Against laboratory-confirmed influenza B, the estimated VE was 46.2% (24.4 to 68.1) with a risk difference of -17.7 (-42.7 to 7.3) per 100,000 individuals. The VE against influenza hospitalization was 20.1% (-27.8 to 68.0) with a risk difference of -13.7 (-33.2 to 5.9) per 100,000 individuals. The overall VE against influenza-related death was 15.1% (-51.8 to 81.9) with a risk difference of -1.0 (-6.9 to 5.0) per 100,000 individuals. Age, sex, and vaccine brand-stratified estimates were not provided due to limited number of events in this cohort.

Discussion: This study provides estimates of influenza VE against laboratory-confirmed and medically attended influenza outcomes in individuals aged ≥65 years and adults <65 years at high risk across three Nordic countries during the 2024/25 season. Among older adults, we observed moderate VE: 39.7% against laboratory-confirmed influenza, 46.8% against hospitalization, and 63.2% against influenza-related death at 18 weeks of follow-up. Enhanced vaccines (Efluelda Tetra and Fluad Tetra) showed higher VE than standard-dose or unadjuvanted vaccines where estimable. In the high-risk <65 cohort, VE was lower (12.4% against laboratory-confirmed influenza).

We conducted supplementary analyses comprising negative control outcomes, regression discontinuity analysis, adjustments for prior event rates, and a test-negative design on Danish data only. Although there were limitations such as varying data completeness across countries, and limited power for brand-specific VE in younger high-risk adults, our findings were directionally similar across multiple supplementary analyses, but with method-dependent discrepancies. Despite this, triangulating these results support a protective effect of seasonal influenza vaccination, particularly among older adults.

Our VE estimates are consistent with recent European evidence from the VEBIS and DRIVE studies, though differences in case definitions and healthcare-seeking behavior may explain some variability. Notably, the use of enhanced vaccines in the 65+ group this season may have contributed to improved VE compared to previous seasons. Brand-specific findings support the preferential use of high-dose and adjuvanted vaccines in older adults.

These results are likely generalizable to similar populations and healthcare systems in Europe with high data source completeness and comparable vaccination strategies. However, they reflect the specific virus circulation and vaccine composition of the 2024/2025 season and may not be directly transferable to other seasons or subpopulations not studied.

Conclusion: This multi-country register-based study provides brand-specific and generic estimates of influenza VE in the elderly and among high-risk groups during the 2024/2025 season in the Nordic region. Seasonal influenza vaccination was moderately effective in reducing the risk of laboratory-confirmed influenza and severe outcomes—particularly among individuals aged ≥65 years, with adjuvanted and high-dose vaccines offering superior protection. VE among high-risk adults under 65 years was lower, possibly reflecting different testing practices. These findings reinforce the value of enhanced vaccines for older adults. Continued annual monitoring using Nordic health registries and other available European data sources remains crucial for informing evidence-based vaccination strategies and regulatory decision-making.

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3. MARKETING AUTHORIZATION HOLDER(S)

Not applicable.

4. INVESTIGATORS

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

Name	**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)	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.

5. 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

6. 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 published up to July 13, 2014. 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 in the influenza season 2023-2024. 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), based on Cochrane reviews of studies published up to 2017. (7,8) In a prospective US evaluation during 2012-2016, 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 of studies published up to 2015, 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, during October 2022 to January 2023 (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, based on systematic review of studies published up to 2016 (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, based on systematic review of studies up to 2019 (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 2015-2016 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) were 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, including by vaccine brand and type, the broader goals of public health preparedness and regulatory excellence are also supported. Methodological and data source considerations to support the feasibility of this endeavour have been provided as part of this research. (19)

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.

7. RESEARCH QUESTION AND OBJECTIVES

We conducted 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 – March).

Study objective:

- 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.

8. AMENDMENTS AND UPDATES

Number	Date	Section	Amendment or update	Reason
1	2/6/2025	Abstract and methods	Added more details on the vaccine types.	To provide more details on the brands and types of vaccines included in the analysis.
2	2/6/2025	Results	Added information about pairwise censoring.	To provide clarification on the applied censoring.

9. RESEARCH METHODS

9.1 Study design

We took advantage of the unique nationwide register-data available to us, and constructed 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 started on the 1st of October 2024 in the three countries. This study start date corresponded to the start of the seasonal influenza vaccination program in the three countries. The study period ended on the 21st of March 2025.

The study design is built on our previous work with Covid-19 vaccine effectiveness in the Nordic countries (20,21). We utilized a cohort design in a target trial emulation (TTE) framework to estimate both relative and absolute effects. The evaluations in adults aged 64 and older, and risk groups 18-64-yr-olds was 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 influenza VE 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, Efluelda Tetra, Flucelvax, and Fluenz, October 1, 2024 to March 21, 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 were vaccinated in each country during the study period were 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 were 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) served 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 were censored if controls were vaccinated.
Causal contrast of interest	• Intention to Treat – average effect of treatment assignment in trial population	• Modified Per- Protocol Effect – average effect among vaccinated ("did those who get the

	• Per-Protocol Effect – average effect among those who complied with their assigned treatment.	seasonal influenza vaccination benefit?")
Statistical analysis	VE estimated as 1 - Risk Ratio at week 18 since the start of follow-up using cumulative incidences from the Aalen-Johansen estimator.	Same as for the target trial.

9.2 Setting

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

Eligibility criteria for study inclusion were:

1) All individuals 65+-years-of-age (including those at high risk due to comorbidities) (trial 1)
2) Individuals in risk groups 18-64-yrs-of-age (trial 2)
3) Had a known residency within the specific country at start of study period (trial 1 and 2)

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 were 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 influenza vaccine brands were Vaxigrip Tetra (standard-dose split virion), Influvac Tetra (standard-dose subunit), Fluad Tetra (adjuvanted standard-dose subunit), and Efluelda Tetra (high-dose split virion) vaccines, which were formulated according to WHO's recommendations. The vaccines contained 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 were vaccinated with the influenza vaccine available at the location.

An individual was defined as vaccinated starting from and including the day of the first influenza vaccination during the ongoing season, and as unvaccinated if they had yet to receive a first vaccine in the ongoing season. Individuals receiving vaccines outside of the 2024/2025 seasonal vaccination program were excluded. Vaccinations without recorded influenza brand were censored during the study period. This season's influenza vaccines received before October 1, 2024 were excluded.

Exposures – The DANFLU-2 trial

In Denmark, in the 2024/2025 season, there is an ongoing pragmatic trial DANFLU-2 comparing high-dose (HD, Efluelda Tetra) versus standard-dose (SD) influenza VE. To preserve the integrity of the trial and avoid compromising blinding, we will not be disclosing any Denmark-only VE estimates related to these treatment arms at this stage. These estimates can be made available upon publication of the DANFLU-2 trial results, expected in August or September 2025.

DANFLU-2 is an individually randomized, registry-based trial comparing HD versus SD influenza vaccine effectiveness in adults 65+ years across Denmark (2022/23-2024/25), with over 332,000 participants randomized (152k of which were randomized during the 2024/25 season). During this period in Demark, HD was only available via DANFLU-2 (with SD used as standard of among those 65+), while the 2024/25 season introduced adjuvanted vaccine for those aged 70+. Any SD used in 70+ would therefore have been from DANFLU-2. This unique distribution means that any national-level analysis of vaccine performance stratifying HD and SD would effectively reveal DANFLU-2 trial outcomes before the planned final readout (particularly with the vast majority of SD in the 2024/25 season administered as part of DANFLU-2).

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

Country	Target Groups for Influenza Vaccination
Denmark (22)	- 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 (23)	- 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 (24)	- Pregnant women
	- Individuals aged 65 years or more
	- Children aged under 7 years
	- Individuals at risk 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.

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, subunit	Risk groups above 6 months
			Individuals 65-69 years
	Vaxigrip Tetra®	QIV, split virion	Risk groups above 6 months
			Individuals 65-69 years, DANFLU-2 clinical trial
	Eflueldа Tetra®	QIV, high-dose	DANFLU-2 clinical trial, 65+
	Fluad Tetra®	QIV, adjuvanted	Elderly 70+
	Flucelvax Tetra®	QIV, subunit, cell-based	Individuals with serious allergy to egg, neomycin or gentamycin
Finland	InfluvacTetra®	QIV, subunit	Outside national vaccination program
	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
	Eflueldа Tetra®	QIV, 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, subunit	All target groups (risk groups above 6 months and all above 65)
	Eflueldа Tetra®	QIV, high-dose	Individuals in long term care facilities (nursery homes for elderly) only

Outcomes

We estimated VE against the laboratory-confirmed influenza outcomes listed below. Individuals were excluded if an event had occurred 90 days before the index start date (October 1, 2024).

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.

Variable	Country	Data source and details
	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 were 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 Quality Register, 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*

Variable	Country	Data source and details
		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 were potential confounders in our study. The richness of our health registers allowed us to provide detailed characterisations of health and disease status in individuals. We were 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. Date of birth was used in supplementary analysis.	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. Date of birth was used in supplementary analysis.	
	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.	

Variable	Country	Data source and details	Values/codes
	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.	
	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–I64, 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–I64, 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–I64, 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)

Variable	Country	Data source and details	Values/codes
	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, 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)

Variable	Country	Data source and details	Values/codes
	Finland	*Care register for Health Care and Special Reimbursement Register.* Defined as primary or secondary diagnoses registered within 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 combined country estimates and in the cohort of individuals aged 65 years and above we stratified according to:

- Influenza vaccine brand for primary outcomes
- Age groups: 65 – 75 years of age, and >75 years of age
- Sex

9.4 Data sources

All data sources were nationwide registers in native format. All study investigators have access to their country-specific data and could link data between registers for the purpose of our study. Given the near real-time availability of the data source, our analyses provided timely evidence. Denmark and Finland had 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 provided complete follow-up of all residents over time. Currently, Sweden has no national registration of administered influenza vaccination and was able to provide data from Uppsala Region (405,000 inhabitants).

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	(25)
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	(26)
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	(27)
The Danish Microbiolo	Information on positive results of RT-PCR tests for influenza are obtained from The Danish Microbiology	Register	Nationwide	2020 – today	Daily	No lag	(28)

gy Database	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).						

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	(29)
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	(30)
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	(31)

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	(32)
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	(33)
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	(34)
Finnish Intensive Care Quality Register	The register includes all intensive care admissions with primary diagnosis (ICD-10).	Register	Nationwide	2020 – today	Daily	No lag	(35)

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	Register	Nationwide	2026-onwards	Daily	No lag	(36)

	repeated doses). The register is held by the Public Health Agency of Sweden.						
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	(37)
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	Register	Nationwide	2017	monthly	2 weeks	(38)

	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 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	(39)

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. We expected to include at least 3.3 million individuals who were 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. (40) From 1 October 2024 to 20 December 2024, influenza vaccination coverage in these target groups was 75.6% and 29.2%, respectively. (40) As of 13 January 2025, there were 700 confirmed cases of influenza, including 414 hospitalisations, in older adults above 65 years. (41)

In Finland, the total population of individuals aged 65 years and older was 1.343 million with a vaccine coverage of 58% during the 2024-2025 season. The population at increased risk aged between 18 and 64 years comprised of 0.4 million individuals, with vaccine coverage of 33%. 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. (42,43)

In Sweden, the total population of elderly 65 years and above in the region under study comprised of 78,594 individuals, with national influenza vaccination coverage of 42% in the 2023/2024 season. (44) The population at increased risk aged between 18 and 64 years comprised of 27,015 individuals in Uppsala region, with a vaccine coverage of 8%.

We utilized all data available to us from the countries' nationwide registers (Denmark and Finland), and regional data sources (Sweden). The statistical power of our study is reflected in the 95% CI of the effectiveness estimates. We expected to have robust statistical precision for the most widely used influenza vaccine brands within the 2024/2025 season. (45,46)

9.6 Data management

No individual-level data could or were shared between countries or with EMA. Each country is the sole data owner and controller of their own data. Only country-specific results were shared and combined results were generated using meta-analysis. Data management and statistical analyses were 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 facilitates efficient use of resources and reproducibility of the statistical analyses.

The analytical group in Denmark coded the statistical analyses using R-scripts (R version 4.2.2.). The R-scripts were made available on GitHub (also during the programming phase to facilitate input and comments). The analysts in each of the participating countries then ran the R-scripts and returned the output to Denmark. The country-specific results were combined using meta-analysis in Denmark.

9.7 Data analysis

Procedures

We used a matched cohort design to evaluate the effectiveness of seasonal influenza vaccine in comparison with not receiving a seasonal influenza vaccine. Individuals who received the vaccine were matched on the day of vaccination with individuals who had not yet received the vaccine. Individuals were matched on age (5-year bins), sex, region of residence, selected comorbidities in the cohort of individuals below 65 years at high risk, and comorbidity count in the cohort of individuals aged 65 years and older. When analysing the cohort of individuals at high risk under 65, individuals can match on multiple comorbidities. The day the seasonal vaccine dose was administered within each matched pair served as the index date for both individuals. If individuals who were included as a matched non-vaccinated individual (i.e., a reference individual) received a vaccine later than the assigned index date, the pair was right-censored on the day the non-vaccinated individual is vaccinated. In these cases, the non-vaccinated individuals were allowed to potentially re-enter as vaccine recipients in a new matched pair on that given date.

Statistical analysis

We followed 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 occurred first. Additionally, censored individuals with a positive PCR test for influenza in our follow-up period 14 and 30 days after the test (as a positive test is part of the outcome definitions) for the influenza hospitalisation and death outcome analyses, respectively. We right-censored matched pairs when the reference unvaccinated individual received a vaccine during follow-up. Cumulative incidences were estimated by the Aalen-Johansen estimator, and from these we calculated the VE as 1 – risk ratio at the start of week 18 (day 126) since the start of follow-up. The corresponding 95% CI were calculated using the delta method. Country-specific estimates were 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. (47). 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. Individuals with high frailty are considered as very ill and/or close to death, which may be associated with lower uptake of vaccination.

Table 8. List of possible confounders in influenza VE 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

The current state-of-the-art in observational vaccination effectiveness estimation is comprised mainly of two study approaches, the test-negative design (TND) and TTE. Both approaches seek to mitigate the impact of bias and confounding. Guilin and colleagues (48) 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 was supplemented by a TND study. The TND study was only feasible in Denmark due to lack of test-negative results in Finland and Sweden. Moreover, supplementary analysis comprising of Prior event rate ratio (PERR) adjustment, Regression discontinuity analysis (RDA), and Negative control outcomes analyses were conducted in the cohort of individuals aged 65 and older 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 Design (TND)

The TND is a variant of the case-control method specifically developed for evaluating VE. (49) Due to unavailability of test negatives data in Finland and Sweden, we conducted a TND study on Danish data only. In this approach, cases were individuals who tested positive for influenza, while controls were those who tested negative. The TND 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 TND also has important limitations. It assumes that influenza vaccine does not affect the risk of other, non-influenza respiratory infections. (49) The design may be subject to bias if cases and controls differ in disease severity. (50) Moreover, as the use of electronic healthcare records, including register-based data, for identifying cases and controls might cause bias (e.g., misclassification), active enrolment of study participates is ideal in the TND. (51) 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.

In the Danish population of individuals who were PCR-tested for influenza during the 2024–2025 season, we employed a TND to estimate the vaccine effectiveness against influenza infections during the 2024–2025 influenza season. We excluded 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 were excluded as these likely represented the same episode. Individuals could contribute with a maximum of one negative PCR test, which was selected at random.

Individuals were considered vaccinated if they received an influenza vaccine at least 14 days before the PCR sample date. Individuals were considered unvaccinated if they had not received the influenza vaccine on the PCR test date or if they had received the influenza vaccine within two weeks before the PCR test date. Individuals with a PCR sample date between their influenza vaccination date and 14 days after their influenza vaccination date, as well as individuals with a PCR sample date more than 18 weeks after their influenza vaccination, were excluded.

Logistic regression models were used to estimate the odds ratio (OR) with 95% CIs. Our main estimate of interest was the vaccine effectiveness defined by (1−OR) ×100%. The models were adjusted for age, sex, region of residency, comorbidities, and week of test. We assessed whether the frequency of testing differed between vaccinated and unvaccinated groups during the season, since differential testing could bias VE estimates. The testing frequency is visualized in a plot by weekly counts of positive tests in each country.

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. (52) 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. (52)

The matching and censoring criteria from the main TTE analysis were applied. As before, the day the seasonal vaccine dose was administered within each matched pair served as the index date for both individuals. For each individual within a matched pair, the pre-vaccination period was the start of the 2024/2025 influenza season (1 October 2024) until the index date and the post-vaccination period started on day 14 following the index date. We identified individuals who ultimately receive a seasonal influenza vaccine ("future vaccinated") and those who remained unvaccinated ("future unvaccinated"), evaluated at the end of the studied period or on the date of the outcome. Both groups had 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 was influenza-related hospitalization. Given that influenza hospitalization may have been less frequent at the start of the influenza season, we assessed whether sufficient events occurred in the pre-vaccination period to produce stable estimates.

We employed 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 used Poisson regression to estimate event rates during the pre-vaccination and current periods. We report point estimates and 95% confidence intervals for the PERR-adjusted measure. The precision of these estimates depended 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 were 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 analysed 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). We required a 90-day gap from a previous diagnosis of diverticulitis in an attempt to capture only incident cases.

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 could 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 could 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 design's credibility.

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

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

Regression discontinuity analysis

For vaccination policies with treatment assignment according to a strict age-cut off, regression discontinuity analyses (RDA) can be used to estimate a local average treatment effect (LATE) among individuals whose vaccination status is dependent on an eligibility threshold. Thus, we can estimate the LATE among 60-69-year-olds by comparing the risk of those under 65 years of age to those over 65 years of age. This provides 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. (53)

While this method can yield robust causal insights under relatively few assumptions, it faces limitations related to sample size, adherence, and external validity. We interpreted 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., TND, PERR). We carefully evaluated 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 focused on individuals in an age band of 60-69 years, where the policy recommends seasonal influenza vaccination at age 65. We extracted data on vaccination status at the end of the study period or date of the outcome (yes/no), age, and influenza-related hospitalizations for individuals aged 60–69. This subset ensured that the age threshold of 65 is central in the data, capturing individuals who were just below and just above the cutoff. Influenza vaccination was assigned as the "treatment" variable. The "instrument" was a binary indicator of whether an individual's age was ≥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 was conducted using a fuzzy regression discontinuity model. The probability of being vaccinated was 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 was then used to estimate the effect on the outcome of interest (influenza-related hospitalisation). The package *rdrobust* in R was used to conduct this analysis. The function *rdrobust* in the package was used to perform separate local-linear regressions of the outcome and the treatment indicator on either side of the 65-year cutoff and apply a triangular kernel weighting that gives greatest weight to observations nearest

the threshold; bandwidths were selected via the package's default mean-squared-error-optimal procedure. We also constructed figures to visualize the discontinuity for outcome and for treatment.

The main assumption was 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 inspected covariate distributions around the cut-off. We also expected to observe a noticeable "jump" in vaccination rates at age 65. If we did not observe this jump, it may had indicated that the vaccination policy recommendation had 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 healthcare access bias. Testing rates can be compared between the groups to identify discrepancies that could influence VE estimates. We assessed testing frequency among vaccinated and unvaccinated individuals to evaluate whether they are consistent across both groups, or driven by specific factors (e.g., timing patterns in a situation of increased testing activity during peak influenza season). Ideally, we want the testing frequency to be similar. The results are presented as the number of positive tests per group and calendar week in a figure. This helps evaluating if observed associations between vaccination and outcomes are unduly influenced by testing frequency.

Sensitivity analysis before full immunization

We conducted 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 estimated 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 was conducted indirectly to evaluate the validity of our main analyses by 1) making sure that the timing 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 were standardized to a common structure, format and terminology in order to allow the same statistical programming scripts to be used in each country. The use of a CDM with common statistical programming scripts facilitated efficient use of resources and reproducibility of the statistical analyses. We ensured the scientific quality of the work, by division of review tasks (including statistical code review) and responsibilities in a timely fashion and by adhering to the ENCePP Code of Conduct. We performed matching quality diagnostics to assess covariate balancing.

10. RESULTS

10.1 Individuals aged 65 and older

10.1.1 Participants and descriptive data

Tables 9 and 10 show the baseline characteristics of the general population study cohorts for influenza hospitalization analysis before and after matching; Figure 1 outlines the selection of cohort participants; Figure 2 illustrates the distributions of age and index date in density plots across countries. Prior to matching, the source cohorts comprised 1,611,962 recipients of the seasonal influenza vaccine in the three countries during the study period. The largest number of recipients were from Denmark (826,766), Finland (752,350), followed by Sweden (32,846). The most frequently used vaccine brand was Vaxigrip Tetra (854,562 doses accounting for 53% of total vaccines administered), followed by Fluad Tetra (659,153 doses, 40.9%) (Table 9).

The matched cohorts consisted of a total of 1,164,686 recipients of the seasonal influenza vaccine for the estimation of VE against influenza hospitalization during the study period (with a mean age 75.4 SD 7.3 years) and 1,164,686 non-recipients. Most recipients were from Finland (611,174) and Denmark (529,082), followed by Sweden (24,430).
The most frequently used vaccine brand was Vaxigrip Tetra (688,822 doses, 59.1%), followed by Fluad Tetra (402,490 doses, 34.6%), Efluelda Tetra (37,246 doses, 3.2%), and Influvac Tetra (36,098 doses, 3.1%) (Table 10). Characteristics among the matched pairs were overall similar to those of the unmatched populations. The baseline characteristics for other outcomes are similar, with minor differences according to the exclusion of prior events.

Table 9. Baseline characteristics before matching of study cohort comparisons for estimating effectiveness of the seasonal influenza vaccines against influenza hospitalization in Denmark, Finland and Sweden, 1 October 2024 to 21 March 2025.[a]

	Seasonal recipient	Non-recipient[b]
No. individuals		
Total	1,611,962	2,520,189
Denmark	826,766	1,129,872
Finland	752,350	1,311,727
Sweden	32,846	78,590
Mean age (SD), years	75.9 (7.3)	75.3 (7.4)
Female sex	890,814 (55.3)	1,382,276 (54.8)
Influvac Tetra	44,795 (2.8)	
Vaxigrip Tetra	854,562 (53.0)	
Efluelda Tetra	51,871 (3.2)	
Fluarix Tetra	46 (0.0)	
Fluad Tetra	659,153 (40.9)	
Flucelvax Tetra	40 (0.0)	
Fluenz Tetra	3 (0.0)	
Fluenz	15 (0.0)	
Fluzone	6 (0.0)	
Autoimmune related conditions	91,001 (5.6)	129,219 (5.1)
Cancer	216,473 (13.4)	314,711 (12.5)
Chronic pulmonary disease	86,937 (5.4)	120,588 (4.8)
Cardiovascular condition	441,175 (27.4)	670,035 (26.6)
Diabetes	163,374 (10.1)	256,511 (10.2)
Renal disease	46,608 (2.9)	68,725 (2.7)
Comorbidity count		
0	857,776 (53.2)	1,389,682 (55.1)
1	520,209 (32.3)	784,994 (31.1)
2	184,682 (11.5)	273,596 (10.9)
2+	49,295 (3.1)	71,917 (2.9)

[a] Values are numbers (percentages) unless stated otherwise.

[b] Individuals eligible for influenza vaccination as of the start of the study on 1 October 2024.

Table 10. Baseline characteristics 14 days after matching of study cohort comparisons for estimating effectiveness of the seasonal influenza vaccines against influenza hospitalization in Denmark, Finland and Sweden, 1 October 2024 to 21 March 2025.[a,c]

	Seasonal recipient	Non-recipient[b]
No. individuals		
Total	1,164,686	1,164,686
Denmark	529,082	529,082
Finland	611,174	611,174
Sweden	24,430	24,430
Mean age (SD), years	75.4 (7.3)	75.4 (7.3)
Female sex	647,756 (55.6)	647,756 (55.6)
Influvac Tetra	36,098 (3.1)	
Vaxigrip Tetra	688,822 (59.1)	
Efluelda Tetra	37,246 (3.2)	
Fluarix Tetra	0 (0.0)	
Fluad Tetra	402,490 (34.6)	
Flucelvax Tetra	20 (0.0)	
Fluenz	10 (0.0)	
Autoimmune related conditions	61,727 (5.3)	58,011 (5.0)
Cancer	150,410 (12.9)	142,635 (12.2)
Chronic pulmonary disease	56,345 (4.8)	54,110 (4.6)
Cardiovascular condition	311,783 (26.8)	317,891 (27.3)
Diabetes	117,826 (10.1)	123,804 (10.6)
Renal disease	30,427 (2.6)	32,150 (2.8)
Comorbidity count		
0	635,941 (54.6)	635,941 (54.6)
1	367,483 (31.6)	367,483 (31.6)
2	128,104 (11.0)	128,104 (11.0)
2+	33,158 (2.8)	33,158 (2.8)

[a] Values are numbers (percentages) unless stated otherwise.
[b] Individuals eligible for influenza vaccination as of the start of the study on 1 October 2024.
[c] Per study design, we applied a pairwise censoring if a reference individual received a vaccine. This led to 329160 matched pairs experiencing censoring prior to start of follow up at 14 days after vaccination due to quick vaccine uptake.

Figure 1. Flowchart of cohort construction.

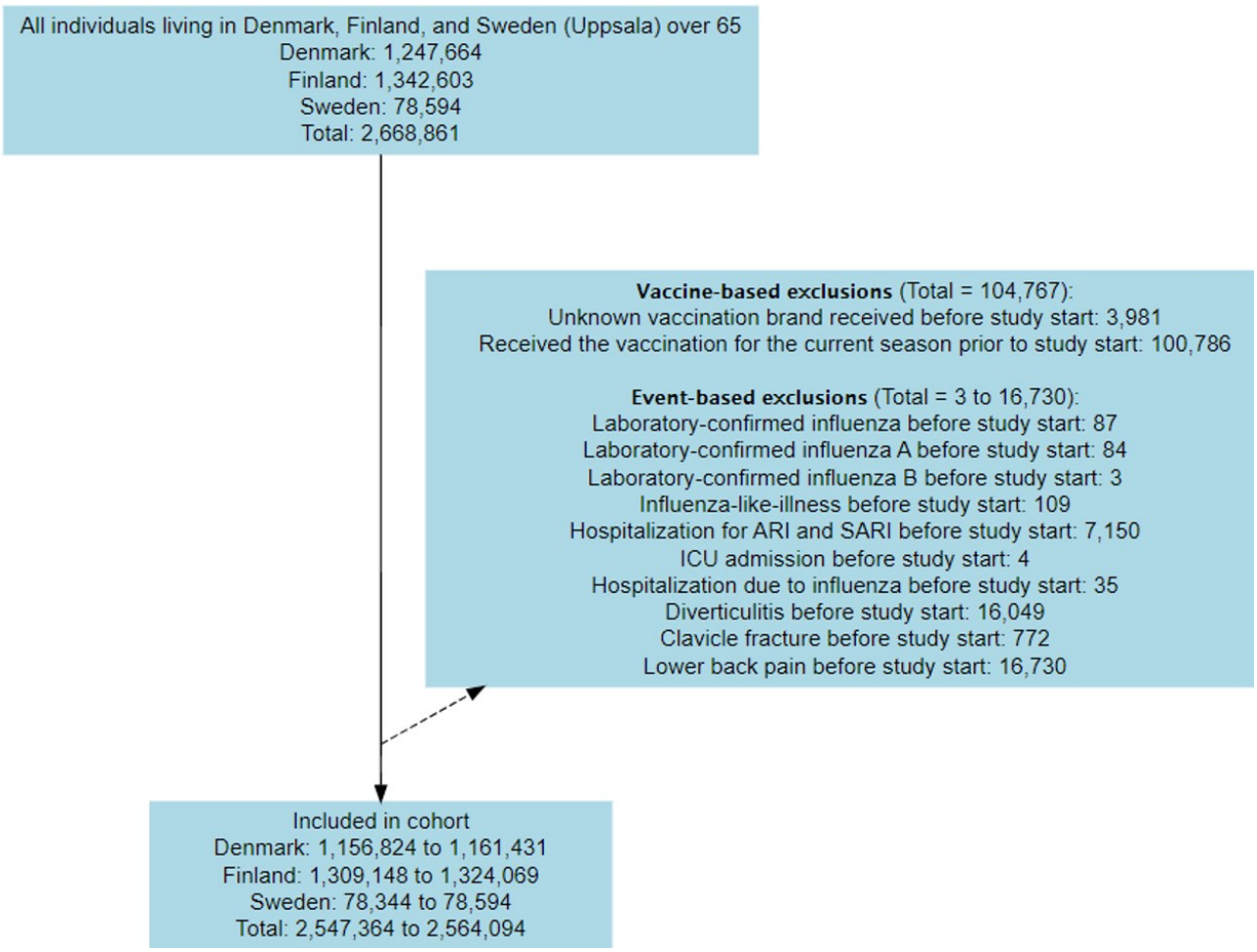
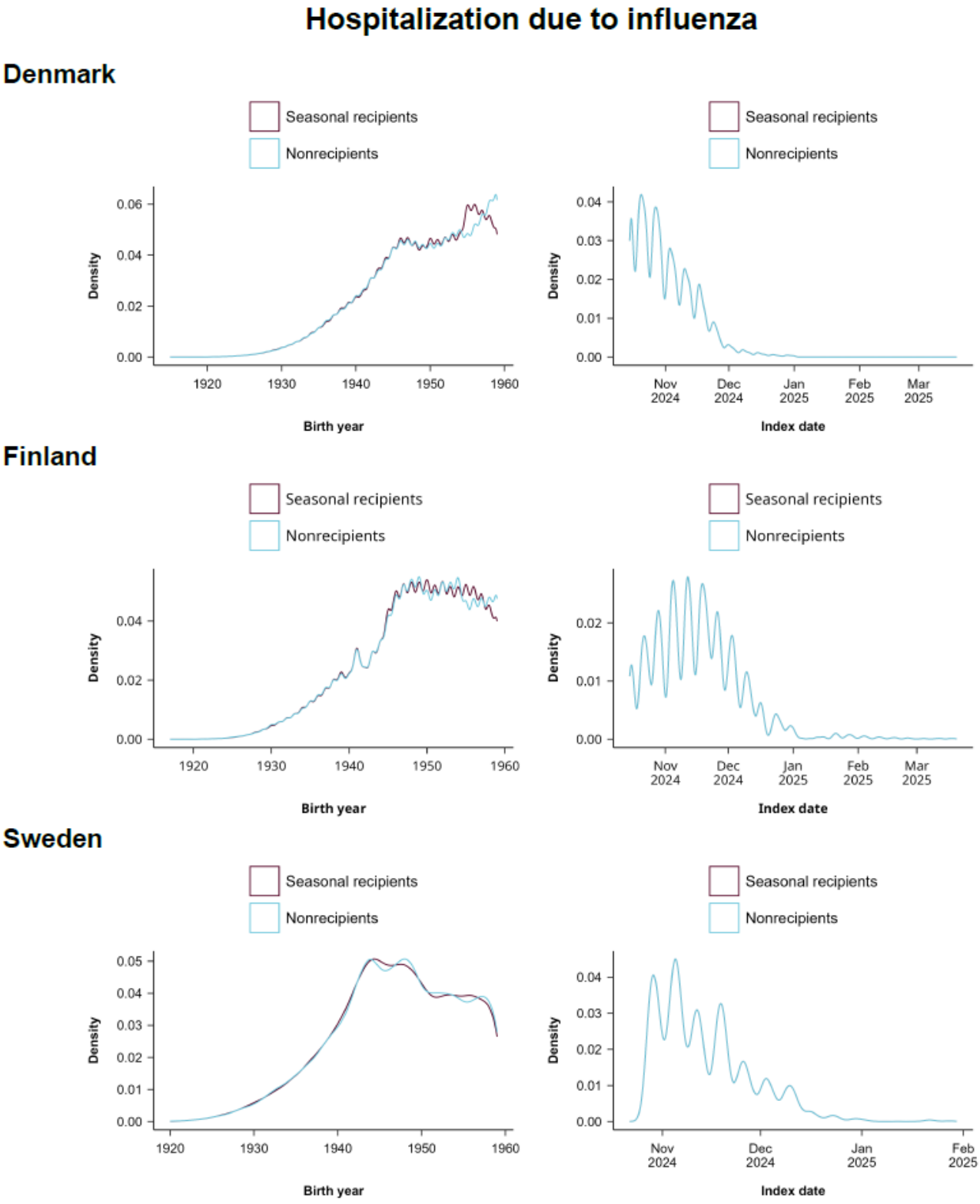


Figure 2. Density plots of the distribution of age and index date for influenza hospitalization across the three countries.



10.1.2 Outcome data and main results

10.1.2.1 Primary outcomes

Figures 3 - 7 show the 18-week cumulative incidences of laboratory- confirmed influenza, influenza hospitalization, and death among vaccine recipients versus matched non-recipients from 2 weeks after the vaccination date. Tables 11-17 show the risk of influenza related primary outcomes comparing seasonal recipients with non-recipients at day 126 (week 18), by sex, age group, and vaccine brand in Denmark and Finland. Due to limited data availability, Sweden did not contribute to the estimates at day 126, but contributed to the estimates of selected outcomes at day 84 (week 12). Figure 13 presents the risks of primary and secondary outcomes at day 84 (week 12) in Denmark, Finland and Sweden.

Laboratory-confirmed influenza (types A and B, and overall)

Vaccine recipients had lower cumulative incidence of laboratory-confirmed influenza when compared to non-recipients, especially for influenza A, with patterns consistent across countries. Cumulative incidences of laboratory-confirmed influenza B remained very low throughout the season in Denmark and Finland, reflecting its limited circulation during the study period, and could not be estimated for Sweden (Figures 3-5).

The risk of overall laboratory confirmed influenza was lower for the recipients of the seasonal influenza vaccine compared with non-recipients. The VE estimate against laboratory-confirmed influenza was 39.7% (36.1 to 43.2) with a risk difference of -167.8 (-199.4 to -136.1) per 100,000 individuals. The highest VE of 52.7% (30.5 to 74.9) and 52.5% (-1.5 to 100.0) was observed for Efluelda Tetra, and Influvac Tetra, respectively, however based on low numbers of events among vaccine recipients. VE for Fluad Tetra and Vaxigrip Tetra was 45.8% (35.0 to 56.5), and 36.2% (30.9 to 41.6), respectively. The highest risk difference of -312.1 (-545.2 to -79.0) per 100,000 individuals was estimated for Fluad Tetra. The VE estimates were similar across the two age groups (Table 11). At day 84, the VE was 50.9% (43.7 to 58.2) with a risk difference of −81.8 (−92.4 to −71.1) per 100,000 individuals, based on results from Denmark, Finland, and Sweden (Figure 13).

Against laboratory-confirmed influenza A, the overall estimated VE was 38.1% (31.3 to 44.8) with a risk difference of -160.0 (-312.3 to -7.8) per 100,000 individuals. Efluelda Tetra showed the highest VE at 49.9% (26.4 to 73.4), followed by Fluad Tetra at 40.5% (31.7 to 49.2), Vaxigrip Tetra at 36.9% (95%

CI: 30.1 to 43.8), and Influvac Tetra at 33.0% (–10.8 to 76.8). The highest risk difference of -234.7 (-272.9 to -196.6) per 100,000 individuals was estimated for Fluad Tetra. The VE estimates were comparable between the two age groups (Table 11). At day 84, the VE was 47.7% (33.7 to 61.6) with a risk difference of –75.3 (–90.7 to –59.9) per 100,000 individuals, based on results from Denmark, Finland, and Sweden (Figure 13).

Against laboratory-confirmed influenza B, the overall estimated VE was 63.7% (44.2 to 83.1) with a risk difference of -4.4 (-6.7 to -2.0) per 100,000 individuals. The brand-specific VE was 77.4% (59.0 to 95.8) and 40.0% (95%CI: -6.7 to 86.6) for Vaxigrip Tetra and Fluad Tetra, respectively. VE for other vaccines could not be estimated due to the limited number of laboratory-confirmed influenza B events occurring in these smaller subgroups of vaccine brand recipients. The risk difference of -5.2 (-8.0 to -2.3) per 100,000 individuals for Vaxigrip Tetra was substantially smaller compared to those of the previous two outcomes. The VE was higher in the <75 years age group compared to the ≥75 age group (Table 11).

Figure 3. Cumulative incidence curves of overall laboratory-confirmed influenza, comparing recipients of influenza vaccine during the 2024-2025 season with matched non-recipients.

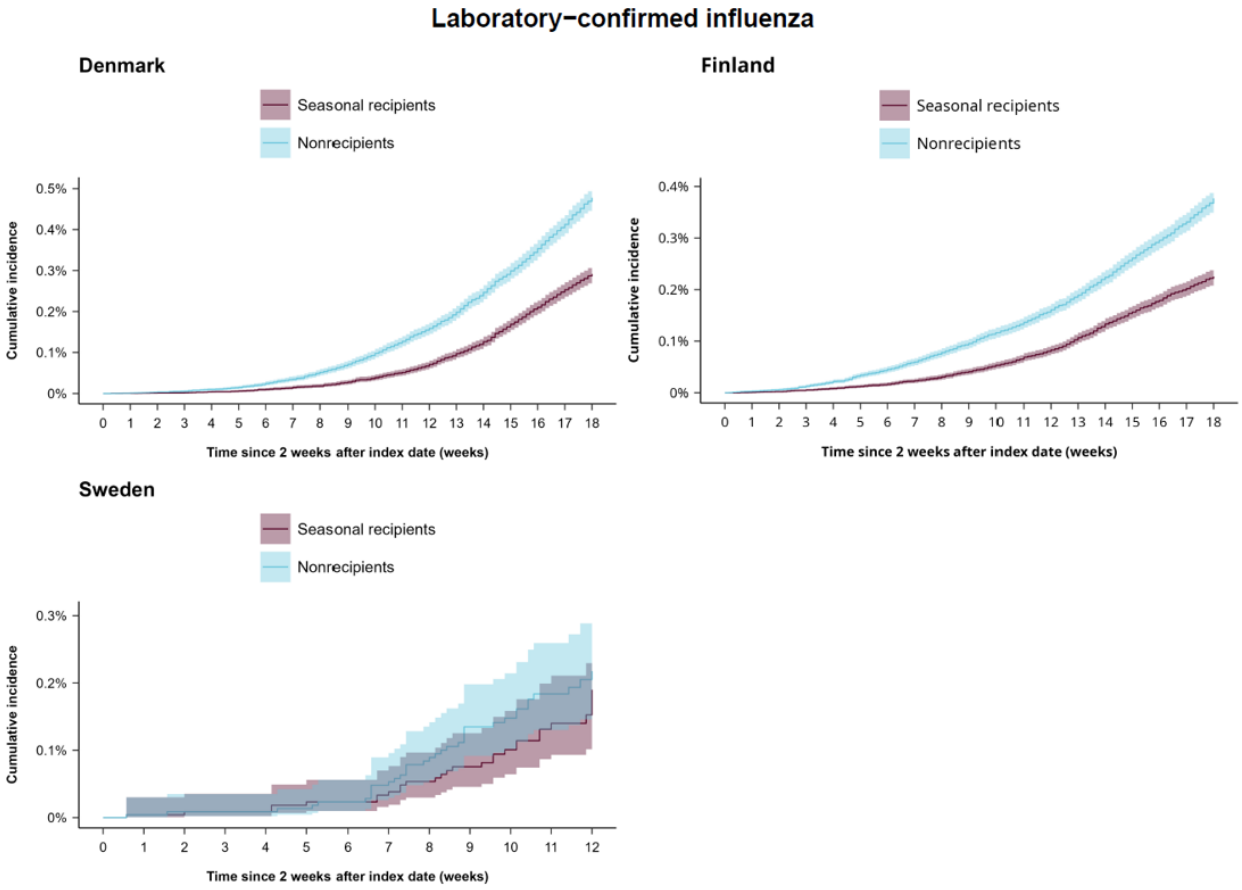


Figure 4. Cumulative incidence curves of laboratory-confirmed influenza A, comparing recipients of influenza vaccine during 2024-2025 season with matched non-recipients.

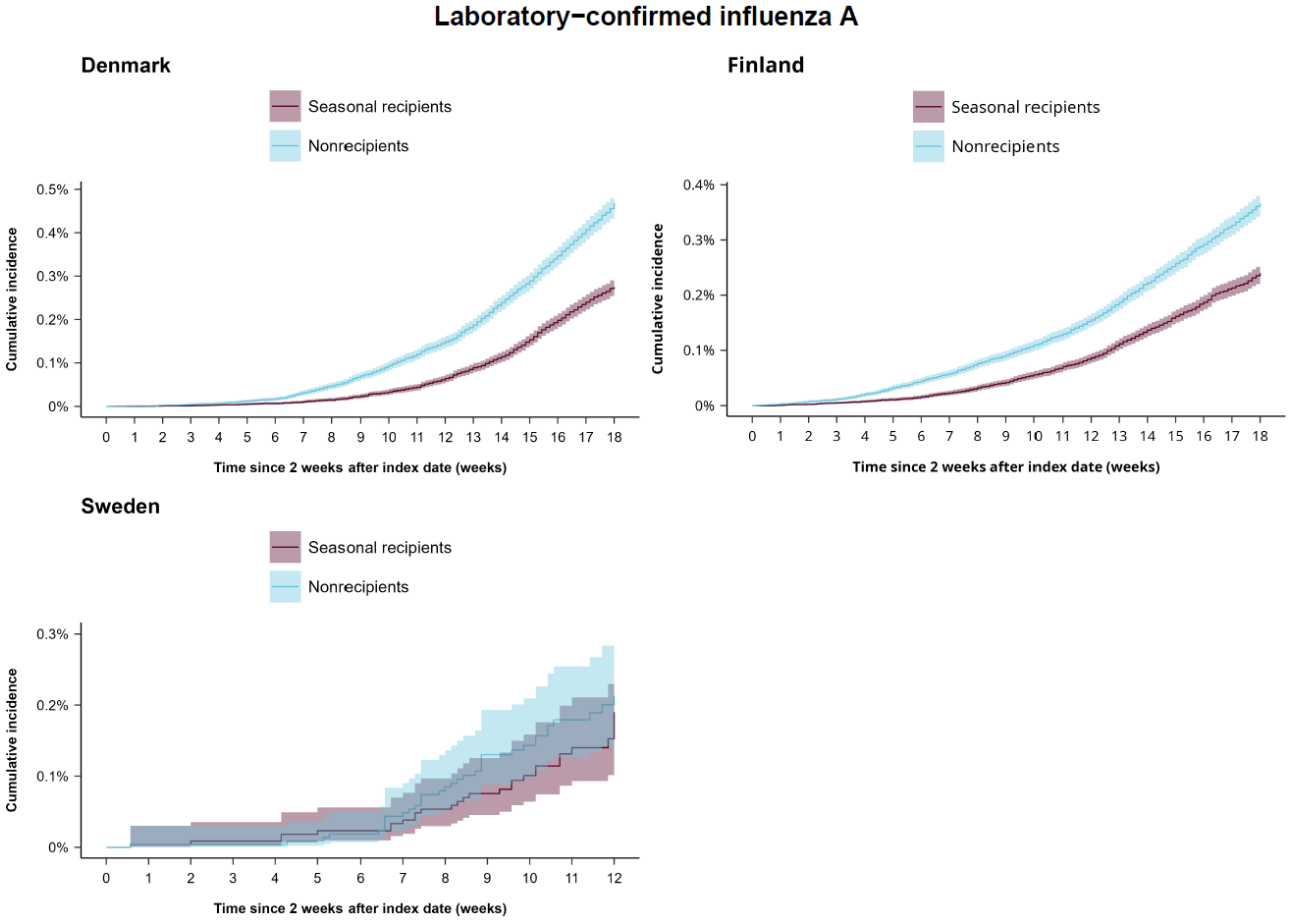


Figure 5. Cumulative incidence curves of laboratory-confirmed influenza B, comparing recipients of influenza vaccine during 2024-2025 season with matched non-recipients.

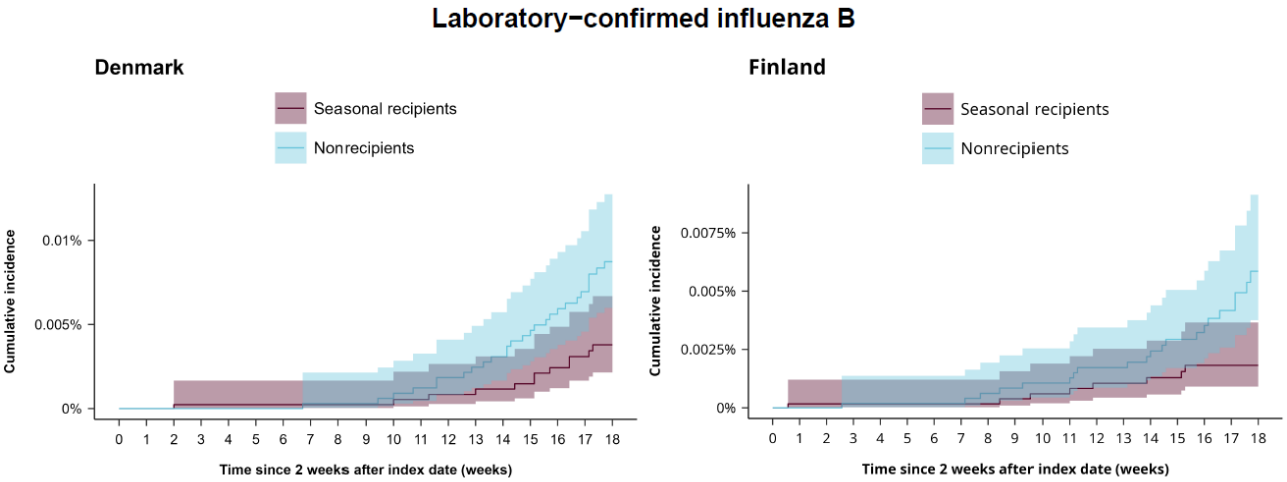


Table 11. Risk of laboratory-confirmed influenza comparing seasonal recipients with non-recipients at day 126 (week 18) in Denmark and Finland, 1 October 2024 to 21 March 2025[b]

		Events / person-years			
	Contributing countries	**Recipients**	**Non-recipients**	**Risk difference (95% CI) per 100,000 individuals**	**Vaccine effectiveness (95% CI)**
Seasonal recipients – Overall laboratory-confirmed influenza					
All	DK, FI	1810 / 271,972	3010 / 270,375	-167.8 (-199.4 to -136.1)	39.7 (36.1 to 43.2)
Female	DK, FI	968 / 151,675	1619 / 150,893	-163.6 (-189.1 to -138.1)	40.2 (35.4 to 45.1)
Male	DK, FI	842 / 120,297	1391 / 119,482	-171.7 (-224.8 to -118.7)	39.0 (33.8 to 44.3)
Age <75 years	DK, FI	685 / 140,918	1146 / 140,524	-123.4 (-159.5 to -87.2)	39.9 (33.7 to 46.1)
Age ≥75 years	DK, FI	1125 / 131,054	1864 / 129,850	-213.8 (-253.7 to -173.9)	39.7 (35.2 to 44.2)
Efluelda Tetra	DK, FI	28 / 7,467	54 / 7,412	-117.7 (-251.9 to 16.6)	52.7 (30.5 to 74.9)
Fluad Tetra	DK, FI	783 / 89,092	1382 / 88,224	-312.1 (-545.2 to -79.0)	45.8 (35.0 to 56.5)
Influvac Tetra	DK, FI	75 / 9,856	113 / 9,835	-251.8 (-648.3 to 144.7)	52.5 (-1.5 to 100.0)
Vaxigrip Tetra	DK, FI	924 / 165,550	1461 / 164,896	-121.7 (-144.3 to -99.1)	36.2 (30.9 to 41.6)

Table 11. Risk of laboratory-confirmed influenza comparing seasonal recipients with non-recipients at day 126 (week 18) in Denmark and Finland, 1 October 2024 to 21 March 2025[b]

		Events / person-years			
	Contributing countries	Recipients	Non-recipients	Risk difference (95% CI) per 100,000 individuals	Vaccine effectiveness (95% CI)
Seasonal recipients - Laboratory-confirmed influenza A					
All	DK, FI	1805 / 272,004	2943 / 270,414	-160.0 (-312.3 to -7.8)	38.1 (31.3 to 44.8)
Female	DK, FI	960 / 151,657	1585 / 150,898	-156.1 (-201.1 to -111.0)	39.0 (34.0 to 44.0)
Male	DK, FI	845 / 120,347	1358 / 119,516	-162.7 (-328.1 to 2.7)	36.9 (26.2 to 47.6)
Age <75 years	DK, FI	667 / 140,981	1115 / 140,590	-120.4 (-173.9 to -66.9)	39.6 (33.7 to 45.4)
Age ≥75 years	DK, FI	1138 / 131,023	1828 / 129,824	-202.4 (-364.9 to -39.8)	37.7 (26.5 to 48.8)
Efluelda Tetra	DK, FI	29 / 7,364	53 / 7,308	-76.4 (-287.0 to 134.2)	49.9 (26.4 to 73.4)
Fluad Tetra	DK, FI	783 / 89,068	1346 / 88,208	-234.7 (-272.9 to -196.6)	40.5 (31.7 to 49.2)
Influvac Tetra	DK, FI	79 / 9,920	91 / 9,899	-77.3 (-185.7 to 31.0)	33.0 (-10.8 to 76.8)
Vaxigrip Tetra	DK, FI	914 / 165,644	1453 / 164,991	-127.2 (-166.4 to -88.1)	36.9 (30.1 to 43.8)
Seasonal recipients - Laboratory-confirmed influenza B					
All	DK, FI	20 / 272,033	48 / 270,543	-4.4 (-6.7 to -2.0)	63.7 (44.2 to 83.1)
Female	DK, FI	11 / 151,643	27 / 150,928	-4.0 (-7.0 to -1.0)	62.7 (36.4 to 89.1)
Male	DK, FI	9 / 120,390	21 / 119,616	-4.4 (-8.0 to -0.8)	66.9 (39.5 to 94.3)
Age <75 years	DK, FI	10 / 140,958	27 / 140,598	-5.2 (-8.5 to -1.9)	73.2 (49.1 to 97.3)
Age ≥75 years	DK, FI	10 / 131,075	21 / 129,945	-3.6 (-6.9 to -0.3)	57.9 (25.8 to 90.1)
Fluad Tetra	DK, FI	11 / 89,043	17 / 88,223	-2.4 (-6.7 to 1.9)	40.0 (-6.7 to 86.6)
Vaxigrip Tetra	DK, FI	8 / 165,598	28 / 165,001	-5.2 (-8.0 to -2.3)	77.4 (59.0 to 95.8)

[b] Due to limited availability of data in Sweden, only data from Denmark and Finland were included in this analysis. Data from Sweden are presented below in Figure 13 with a shorter time of follow-up (up to 84 days).

Influenza hospitalization

Vaccine recipients had a lower cumulative incidence of influenza hospitalization than non-recipients, with patterns consistent across countries (Figure 6).

The risk of influenza hospitalization was lower for the recipients of the seasonal influenza vaccine compared with non-recipients. The overall VE against influenza hospitalization was 46.8% (40.8 to 52.9) with a risk difference of -60.2 (-217.0 to 96.6) per 100,000 individuals. VE for Fluad Tetra was 48.2% (40.8 to 55.6), followed by 43.6% (23.7 to 63.6) for Vaxigrip Tetra, and 30.6% (-7.8 to 69.1) for Influvac Tetra.

Estimates for Efluelda Tetra and Influvac Tetra were based on data from Denmark only (Table 12). At day 84, the VE was 54.0% (45.7 to 62.2) with a risk difference of −26.2 (−45.0 to −7.4) per 100,000 individuals, based on results from Denmark, Finland, and Sweden (Figure 13).

Figure 6. Cumulative incidence curves of influenza hospitalization, comparing recipients of influenza vaccine during 2024-2025 season with matched non-recipients.

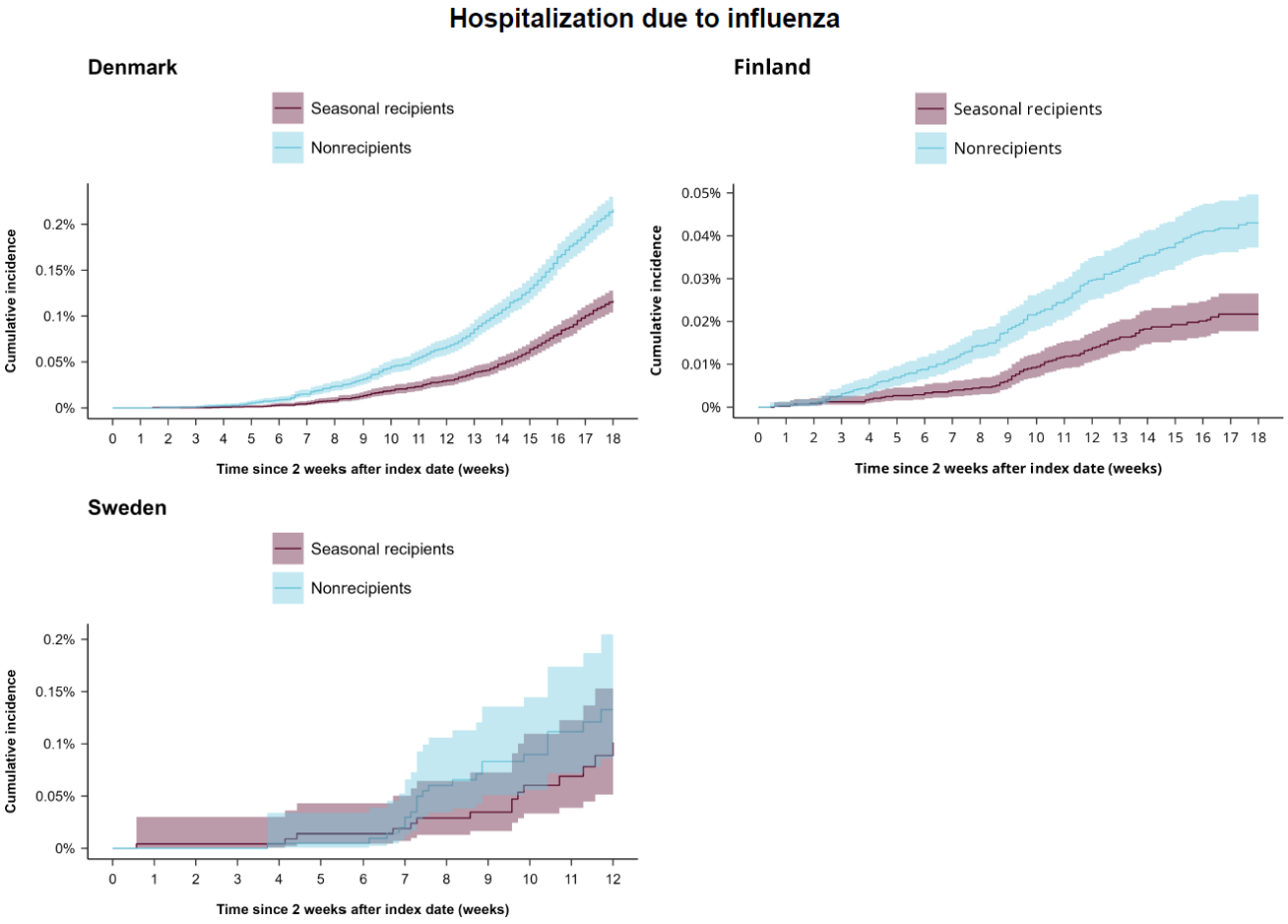


Table 12. Risk of influenza hospitalization comparing seasonal recipients with non-recipients at day 126 (week 18) in Denmark and Finland, 1 October 2024 to 21 March 2025[b]

		Events / person-years			
	Contributing countries	Recipients	Non-recipients	Risk difference (95% CI) per 100,000 individuals	Vaccine effectiveness (95% CI)
Seasonal recipients - Hospitalization due to influenza					
All	DK, FI	459 / 271,855	868 / 270,312	-60.2 (-217.0 to 96.6)	46.8 (40.8 to 52.9)
Female	DK, FI	229 / 151,619	441 / 150,882	-56.4 (-214.3 to 101.5)	47.3 (38.9 to 55.7)
Male	DK, FI	230 / 120,237	427 / 119,431	-64.7 (-220.1 to 90.7)	46.3 (37.7 to 55.0)
Age <75 years	DK, FI	169 / 140,884	295 / 140,522	-35.1 (-177.9 to 107.7)	43.6 (32.8 to 54.3)
Age ≥75 years	DK, FI	290 / 130,971	573 / 129,790	-89.5 (-272.0 to 93.0)	49.0 (41.8 to 56.3)
Efluelda Tetra [c]	DK	X / X	X / X	X	X
Fluad Tetra	DK, FI	286 / 88,996	551 / 88,151	-77.2 (-250.3 to 96.0)	48.2 (40.8 to 55.6)
Influvac Tetra	DK	23 / 9,292	34 / 9,275	-41.9 (-104.5 to 20.8)	30.6 (-7.8 to 69.1)
Vaxigrip Tetra	DK, FI	138 / 165,472	251 / 164,847	-22.3 (-29.9 to -14.7)	43.6 (23.7 to 63.6)

[b] Due to limited availability of data in Sweden, only data from Denmark and Finland were included in this analysis. Data from Sweden are presented below in Figure 13 with a shorter time of follow-up (up to 84 days).

[c] Results for Efluelda Tetra are temporarily redacted to avoid unblinding of the ongoing pragmatic trial DANFLU2 on this vaccine brand in Denmark – results will be made available when the pragmatic trial stops follow-up in late August / early September 2025.

Influenza-related death

Vaccine recipients had lower cumulative incidence of influenza- related death when compared to non-recipients, with patterns consistent across Denmark and Finland. Cumulative incidences could not be estimated in Sweden due to limited number of events (Figure 7).

The risk of influenza- related death was lower for the recipients of the seasonal influenza vaccine compared with non-recipients. The overall VE against influenza-related death was 63.2% (53.6 to 72.8) with a risk difference of -19.9 (-32.1 to -7.6) per 100,000 individuals. The highest VE of 65.8% (54.6 to 76.9) and the lowest risk difference of -40.6 (-52.3 to -28.9) per 100,000 individuals was afforded by Fluad Tetra. VE for Vaxigrip Tetra was 45.2% (-13.9 to 100.0). Higher VE and lower risk difference was observed in the ≥75 years age group compared to the <75 years age group. Estimates

from Sweden and for other influenza vaccines could not be provided due to limited number of events (Table 13).

Figure 7. Cumulative incidence curves of influenza death, comparing recipients of influenza vaccine during 2024-2025 season with matched non-recipients.

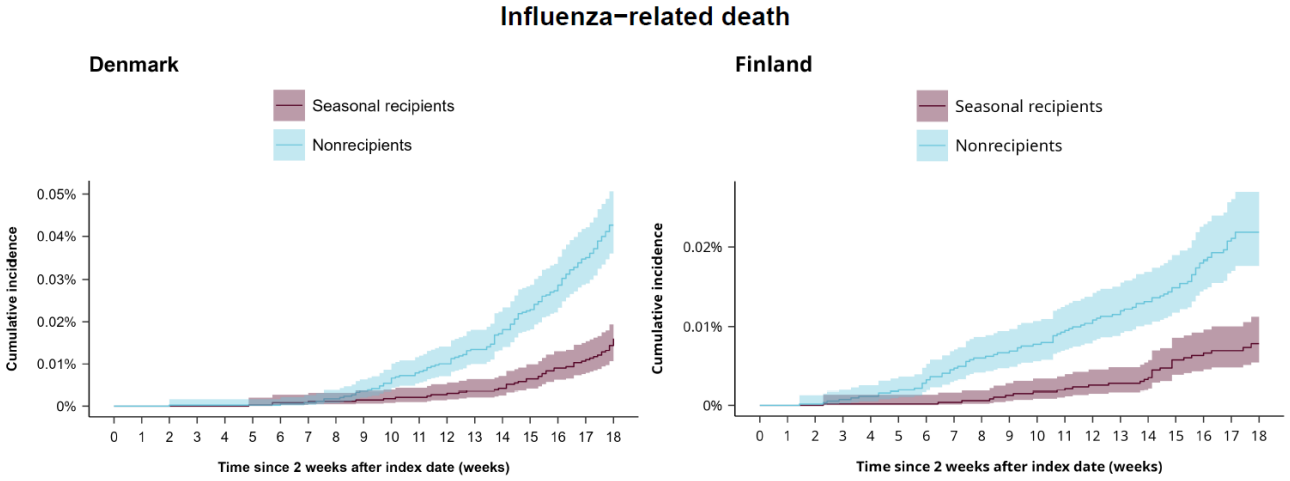


Table 13. Risk of influenza death comparing seasonal recipients with non-recipients at day 126 (week 18) in Denmark and Finland, 1 October 2024 to 21 March 2025[b]

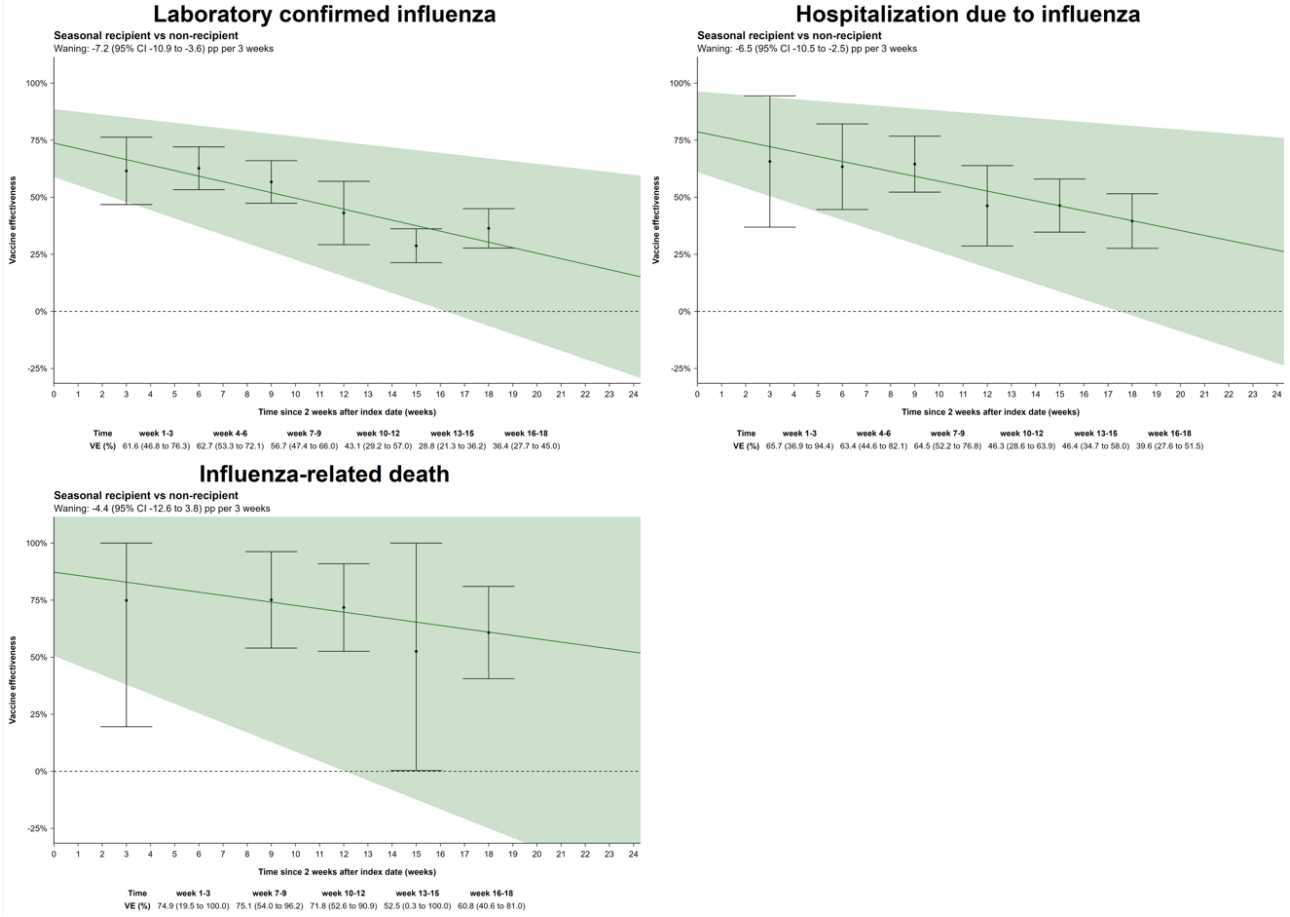
		Events / person-years			
	Contributing countries	Recipients	Non-recipients	Risk difference (95% CI) per 100,000 individuals	Vaccine effectiveness (95% CI)
Seasonal recipients - Influenza-related death					
All	DK, FI	79 / 272,092	222 / 270,595	-19.9 (-32.1 to -7.6)	63.2 (53.6 to 72.8)
Female	DK, FI	36 / 151,702	107 / 150,994	-17.7 (-30.6 to -4.8)	65.0 (51.6 to 78.4)
Male	DK, FI	43 / 120,390	115 / 119,601	-21.5 (-32.3 to -10.6)	61.8 (48.2 to 75.4)
Age <75 years	DK, FI	26 / 140,968	51 / 140,620	-5.4 (-9.9 to -0.9)	45.3 (19.1 to 71.6)
Age ≥75 years	DK, FI	53 / 131,124	171 / 129,975	-34.8 (-57.9 to -11.7)	68.5 (58.7 to 78.3)
Fluad Tetra	DK, FI	49 / 89,194	147 / 88,374	-40.6 (-52.3 to -28.9)	65.8 (54.6 to 76.9)
Vaxigrip Tetra	DK, FI	30 / 165,545	66 / 164,939	-6.0 (-15.9 to 4.0)	45.2 (-13.9 to 100.0)

		Events / person-years			
	Contributing countries	**Recipients**	**Non-recipients**	**Risk difference (95% CI) per 100,000 individuals**	**Vaccine effectiveness (95% CI)**

[b] Due to limited availability of data in Sweden, only data from Denmark and Finland were included in this analysis. Data from Sweden are presented below in Figure 13 with a shorter time of follow-up (up to 84 days).

Figure 8 shows the waning of the seasonal influenza VE, stratified by 3-week intervals with the per 3-week percentage point change in VE during follow-up estimated by the trend line. The vaccine had an initial VE of 61.6% (46.8 to 76.3) against laboratory confirmed influenza, 65.7% (36.9 to 94.4) against influenza hospitalization and 74.9% (19.5 to 100) against influenza- related death at week 3. Subsequently, gradual waning of -7.2 (-10.9 to -3.6), -6.5 (-10.5 to 2.5), and -4.4 (-12.6 to 3.8) percentage points against laboratory confirmed influenza, hospitalization, and death, respectively, were observed every 3 weeks.

Figure 8. Waning vaccine effectiveness against laboratory confirmed influenza, hospitalization and death related to influenza, comparing recipients of seasonal influenza vaccine with matched non-recipients during 2024/2025 influenza season stratifying follow-up in 3-week intervals.



10.1.2.2 Secondary outcomes

The VE estimates at day 126 (week 18) are based on results from Denmark and Finland. Due to limited data availability, Sweden did not contribute to the estimates at day 126, but contributed to the estimates of selected outcomes at day 84. Figure 13 presents the risks of primary and secondary outcomes at day 84 (week 12) in Denmark, Finland and Sweden.

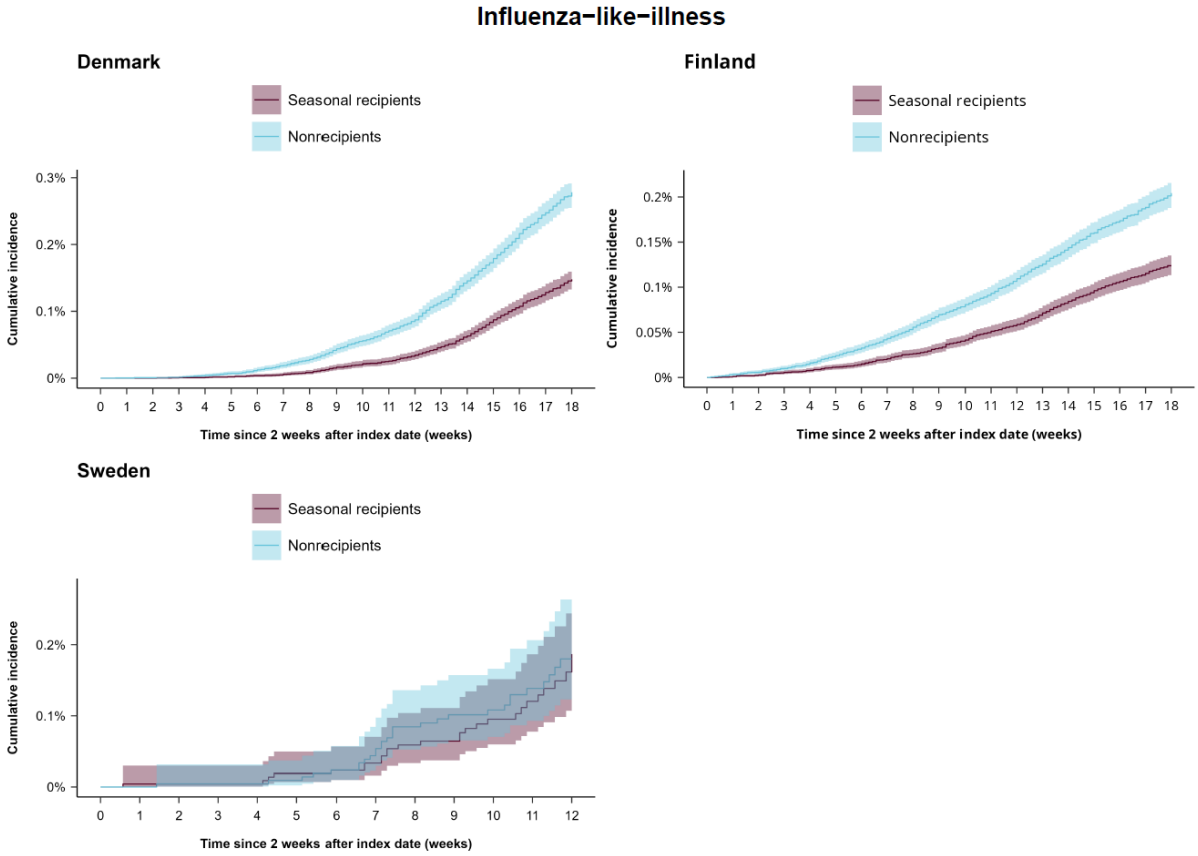
Influenza-like-illness

Vaccine recipients had lower cumulative incidence than non-recipients of influenza-like illness, with patterns consistent across countries (Figure 9).

The risk of influenza-like illness was lower for the recipients of the seasonal influenza vaccine compared with non-recipients. The VE afforded by the seasonal influenza vaccine was 43.3% (36.0 to

50.6) with a risk difference of -105.4 (-250.7 to 40.0) per 100,000 individuals. (Table 14). At day 84, the VE was 48.5% (29.8 to 67.3) with a risk difference of −51.5 (−59.8 to −43.2) per 100,000 individuals, based on results from Denmark, Finland, and Sweden (Figure 13).

Figure 9. Cumulative incidence curves of influenza-like illness, comparing recipients of influenza vaccine during 2024-2025 season with matched non-recipients.

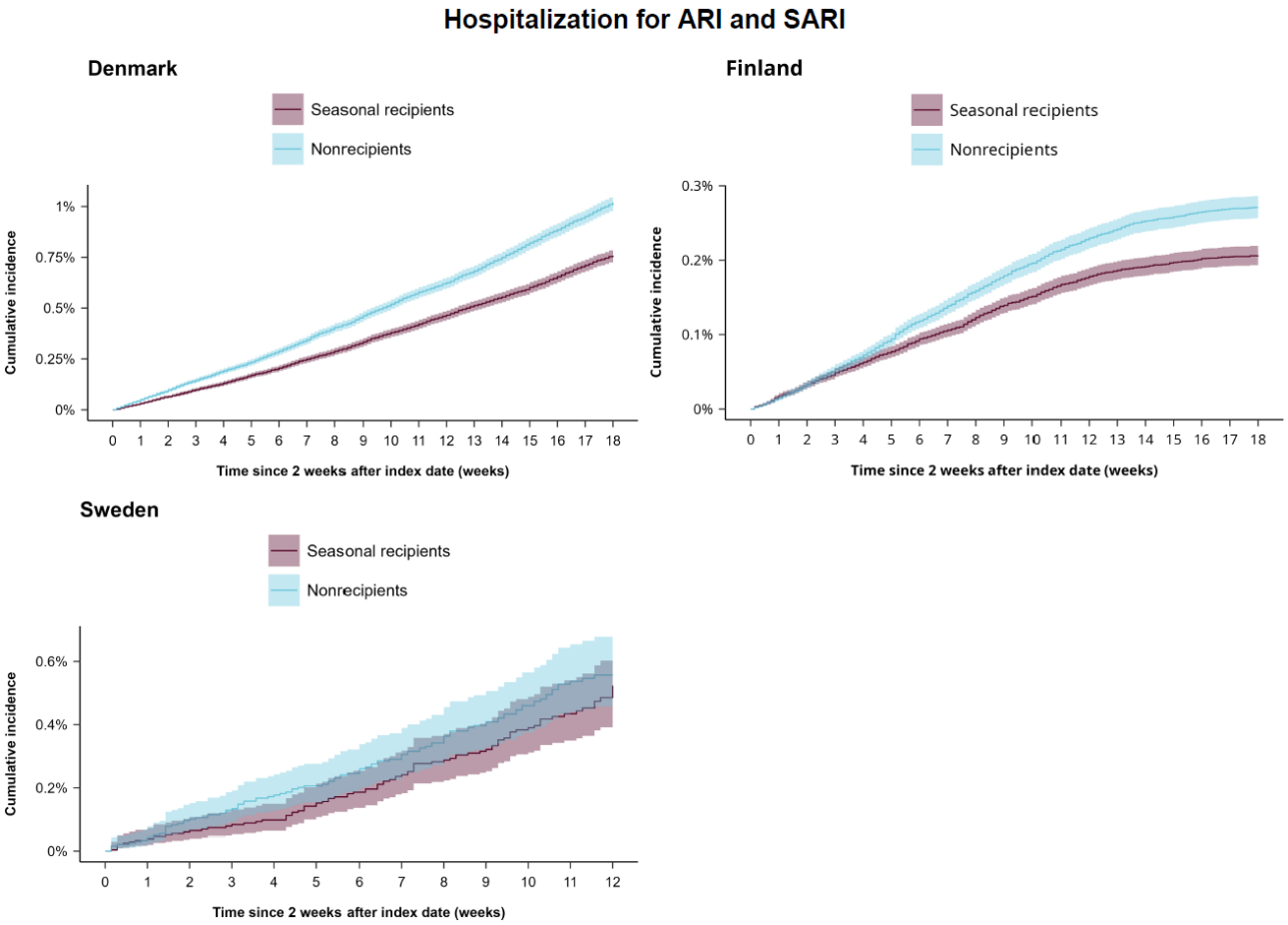


Hospitalisation for respiratory infections (ARI, SARI)

Vaccine recipients had lower cumulative incidence of hospitalization for ARI and SARI than non-recipients. The difference was more pronounced in Denmark, where overall incidence was higher and the curves continued to diverge over time, while in Finland the difference was smaller and plateaued mid-season (Figure 10).

The risk of hospitalization for ARI and SARI was lower for the recipients of the seasonal influenza vaccine compared with non-recipients. The VE afforded by the seasonal influenza vaccine was 25.2% (21.9 to 28.4) with a risk difference of -162.2 (-398.7 to 74.3) per 100,000 individuals (Table 14). At day 84, the VE was 24.2% (20.3 to 28.0) with a risk difference of −92.2 (−175.0 to −9.3) per 100,000 individuals, based on results from Denmark, Finland, and Sweden (Figure 13).

Figure 10. Cumulative incidence curves of hospitalization for ARI and SARI, comparing recipients of influenza vaccine during 2024-2025 season with matched non-recipients.

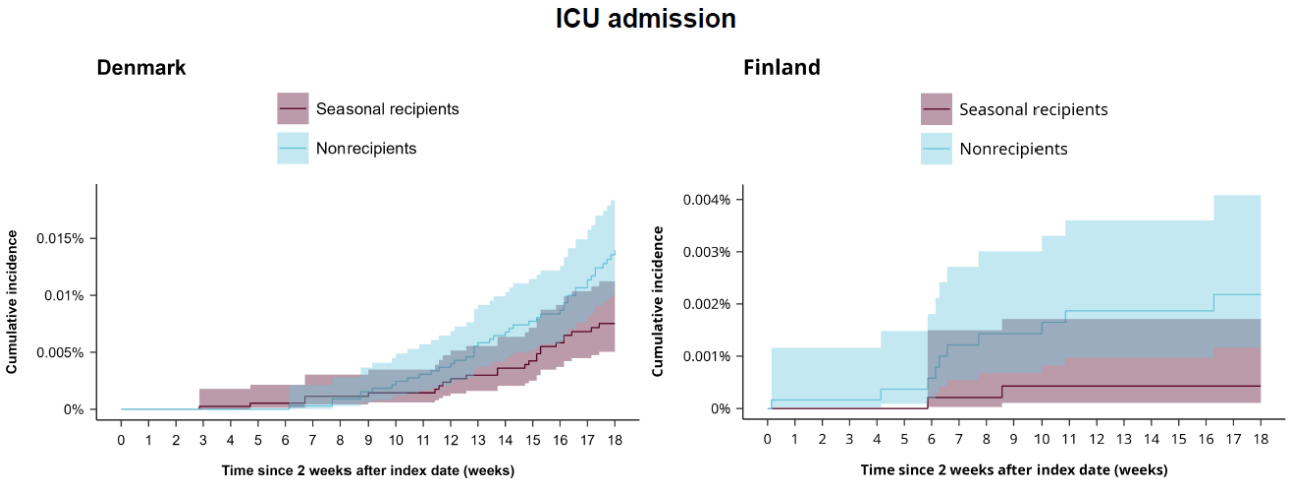


ICU admission

Vaccine recipients had lower cumulative incidence of ICU admission than non-recipients. ICU admissions were rare in both countries, and the difference between the groups were more evident in Denmark, while in Finland the estimates were imprecise due to a low number of cases. Cumulative incidence in Sweden could not be estimated due to a low number of cases (Figure 11).

The risk of ICU admission was lower for the recipients of the seasonal influenza vaccine compared with non-recipients. The VE afforded by the seasonal influenza vaccine was 62.6% (29.1 to 96.2) with a risk difference of -3.4 (-7.7 to 0.9) per 100,000 individuals (Table 14). Estimates from Sweden could not be provided due to limited number of events.

Figure 11. Cumulative incidence curves of ICU admission, comparing recipients of influenza vaccine during 2024-2025 season with matched non-recipients.



All-cause mortality

Vaccine recipients had lower cumulative incidence of all-cause mortality than non-recipients, with patterns consistent across countries (Figure 12).

The risk of all-cause mortality was lower for the recipients of the seasonal influenza vaccine compared with non-recipients. The VE afforded by the seasonal influenza vaccine was 42.2% (34.6 to 49.9) with a risk difference of -829.1 (-1,136.3 to -521.9) per 100,000 individuals (Table 14). At day 84, the VE was 44.2% (35.8 to 52.6) with a risk difference of −598.9 (−764.2 to −433.6) per 100,000 individuals, based on results from Denmark, Finland, and Sweden (Figure 13).

Figure 12. Cumulative incidence curves of all-cause mortality, comparing recipients of influenza vaccine during 2024-2025 season with matched non-recipients.

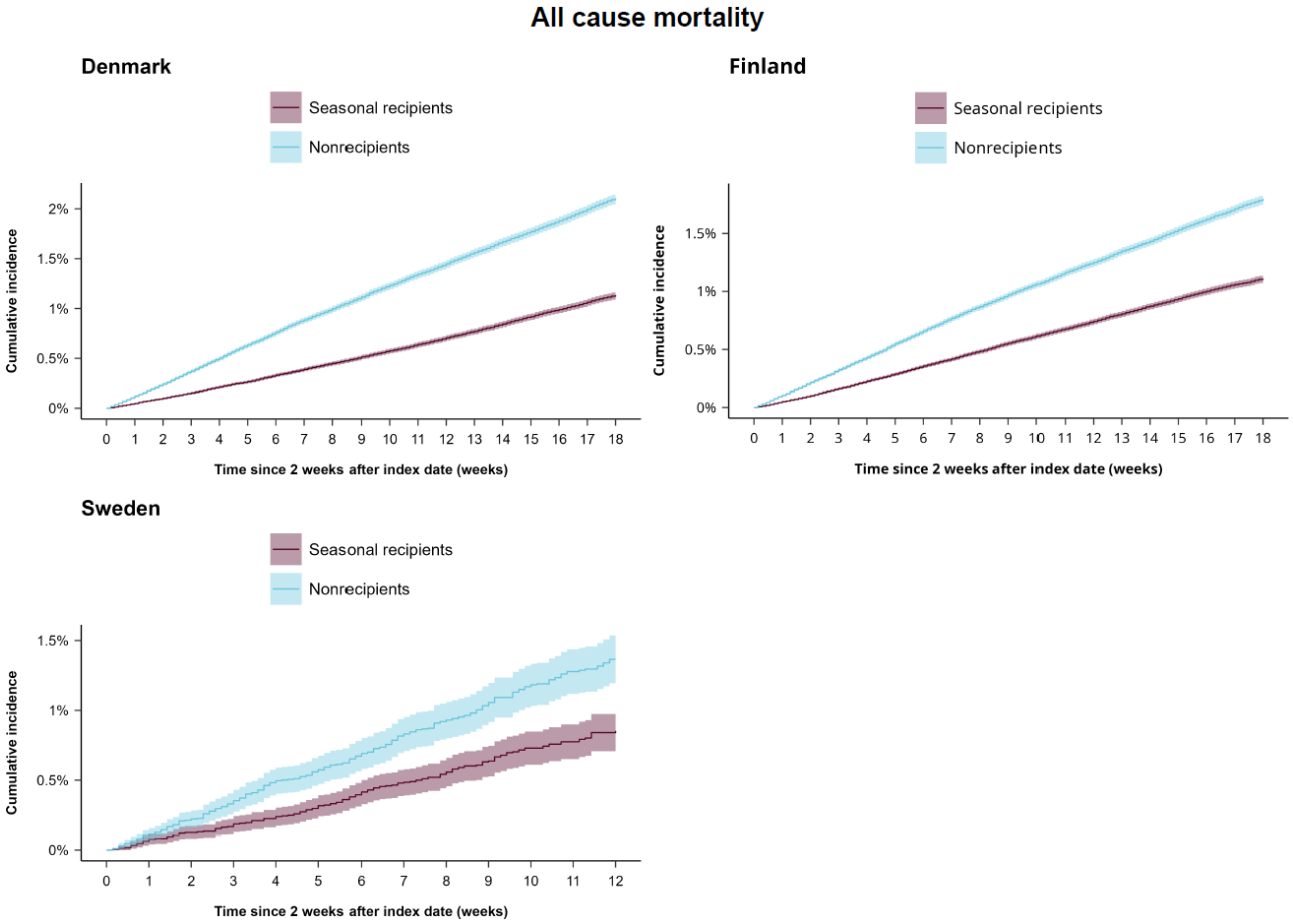


Table 14. Risk of influenza related secondary outcomes comparing seasonal recipients with non-recipients at day 126 (week 18) in Denmark and Finland, 1 October 2024 to 21 March 2025[b]

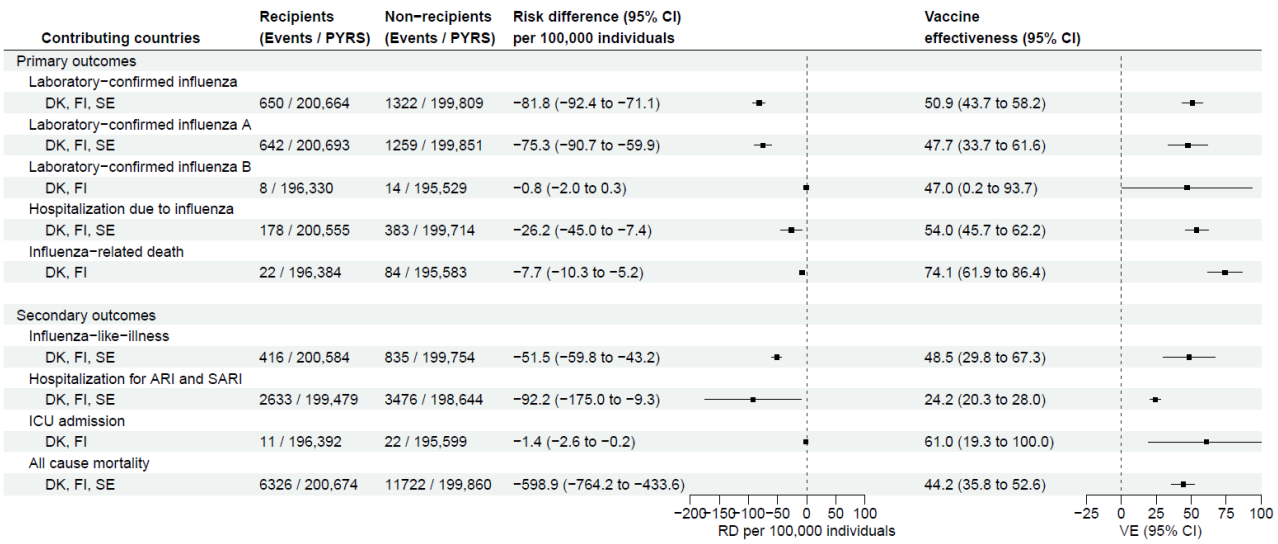
		Events / person-years			
	Contributing countries	**Recipients**	**Non-recipients**	**Risk difference (95% CI) per 100,000 individuals**	**Vaccine effectiveness (95% CI)**
Seasonal recipients - Influenza-like-illness					
All	DK, FI	978 / 271,906	1734 / 270,371	-105.4 (-250.7 to 40.0)	43.3 (36.0 to 50.6)
Seasonal recipients - Hospitalization for ARI and SARI					
All	DK, FI	3545 / 270,332	4736 / 268,794	-162.2 (-398.7 to 74.3)	25.2 (21.9 to 28.4)
Seasonal recipients - ICU admission					

Table 14. Risk of influenza related secondary outcomes comparing seasonal recipients with non-recipients at day 126 (week 18) in Denmark and Finland, 1 October 2024 to 21 March 2025[b]

	Contributing countries	Events / person-years		Risk difference (95% CI) per 100,000 individuals	Vaccine effectiveness (95% CI)
		Recipients	Non-recipients		
All	DK, FI	26 / 272,088	53 / 270,606	-3.4 (-7.7 to 0.9)	62.6 (29.1 to 96.2)
Seasonal recipients - All cause mortality					
All	DK, FI	8822 / 272,095	15441 / 270,596	-829.1 (-1,136.3 to -521.9)	42.2 (34.6 to 49.9)

[b] Due to limited availability of data in Sweden, only data from Denmark and Finland were included in this analysis. Data from Sweden are presented above in Figure 13 with a shorter time of follow-up (up to 84 days).

Figure 13. Risk of primary and secondary outcomes comparing seasonal vaccine recipients with non-recipients at day 84 (week 12) in Denmark, Finland, and Sweden, 1 October 2024 to 21 March 2025.



10.1.3 Results of supplementary analyses

All supplementary analyses presented below were conducted to investigate the study cohort of individuals aged 65 years and above.

Test-Negative Design

We identified 1,853 cases (laboratory confirmed influenza) and 29,721 controls (confirmed negative tests). Table 15 shows the covariate distribution between cases and controls. Of these tests, we identified 19,313 recipients of seasonal influenza vaccine and 14,261 non-recipients. The mean age was 78.4 (SD 7.8 years) and 77.8 (SD 8.1) among recipients and non-recipients, respectively (Table 16). Among the non-recipients, there were 1,708 cases (laboratory confirmed influenza) and 12,553 controls. Among the vaccine recipients, there were 2,145 cases of laboratory-confirmed influenza, and 17,168 controls. The estimated VE was 39.5% (34.9 to 43.8), which is close to our meta-analysed main analysis estimate of 39.7% (36.1 to 43.2) (Table 17). The Danish estimate from our main analysis was 39.0% (34.0 to 44.1), which is also close to the estimated VE from this analysis.

Table 15. Baseline characteristics of cases and controls in a test negative design analysis of seasonal influenza vaccines in Denmark, 1 October 2024 to 21 March 2025.[a]

	Cases	Controls
No. individuals		
Total	3,853	29,721
Denmark	3,853	29,721
Mean age (SD), years	77.0 (7.9)	78.3 (7.9)
Female sex	1,961 (50.9)	15,341 (51.6)
Autoimmune related conditions	372 (9.7)	2,946 (9.9)
Cancer	635 (16.5)	6,153 (20.7)
Chronic pulmonary disease	744 (19.3)	6,537 (22.0)
Cardiovascular condition	1,290 (33.5)	10,582 (35.6)
Diabetes	478 (12.4)	3,609 (12.1)
Renal disease	301 (7.8)	2,635 (8.9)
Comorbidity count		
0	1,443 (37.5)	9,945 (33.5)
1	1,371 (35.6)	10,689 (36.0)
2	737 (19.1)	6,177 (20.8)
2+	302 (7.8)	2,910 (9.8)

[a]Values are numbers (percentages) unless stated otherwise.

Table 16. Baseline characteristics in a test negative design supplementary analysis of seasonal influenza vaccines in Denmark, 1 October 2024 to 21 March 2025.[a]

	Seasonal recipient	Non-recipient
No. individuals		
Total	19,313	14,261
Denmark	19,313	14,261
Mean age (SD), years	78.4 (7.8)	77.8 (8.1)
Female sex	9,885 (51.2)	7,417 (52.0)
Autoimmune related conditions	1,994 (10.3)	1,324 (9.3)
Cancer	4,067 (21.1)	2,721 (19.1)
Chronic pulmonary disease	4,465 (23.1)	2,816 (19.7)
Cardiovascular condition	6,835 (35.4)	5,037 (35.3)
Diabetes	2,286 (11.8)	1,801 (12.6)
Renal disease	1,665 (8.6)	1,271 (8.9)
Comorbidity count		
0	6,296 (32.6)	5,092 (35.7)
1	7,076 (36.6)	4,984 (34.9)
2	4,051 (21.0)	2,863 (20.1)
2+	1,890 (9.8)	1,322 (9.3)

[a]Values are numbers (percentages) unless stated otherwise.

Table 17. Risk of laboratory-confirmed influenza comparing seasonal recipients with non-recipients in Denmark using a test negative case control design, 1 October 2024 to 21 March 2025.

Seasonal recipients		Non-recipients			
Cases	Controls	Cases	Controls	Crude VE (95% CI)	Adjusted VE (95% CI)
2145	17168	1708	12553	8.2 (1.7 to 14.2)	39.5 (34.9 to 43.8)

Sensitivity analysis before full immunization

In the sensitivity analysis starting follow-up from the day of vaccination (day 0), vaccine effectiveness (VE) against laboratory-confirmed influenza was 39.6% (35.7 to 43.5), closely aligned with the main analysis estimate of 39.7% (36.1 to 43.2) from day 14 onward. VE during the 0–13 days post-vaccination was 40.2% (3.6 to 76.8). For influenza A, VE was 39.6% (33.2 to 46.0) from day 0 and

57.0% (30.9 to 83.1) in the first 13 days. For influenza B, estimates were more uncertain due to few cases (Table 18).

Hospitalization due to influenza also showed consistent estimates. VE was estimated at 51.1% (44.9 to 57.3) from day 0 and 81.9% (54.0 to 100.0) during days 0–13. Similarly, VE against influenza-related death was 66.2% (56.1 to 76.2) from day 0, matching closely with the main analysis estimate of 63.2% (53.6 to 72.8). Only a few (<5) influenza-related deaths were observed during the 0–13-day in Finland, resulting in an inconclusive estimate (Table 18).

Table 18. Risk of influenza related outcomes comparing seasonal recipients with non-recipients in Denmark, Finland and Sweden when starting follow-up from day of vaccination (day 0).

		Events / person-years			
	Contributing countries	**Recipients**	**Non-recipients**	**Risk difference (95% CI) per 100,000 individuals**	**Vaccine effectiveness (95% CI)**
Seasonal recipients - Laboratory-confirmed influenza					
0-13	DK, FI	17 / 49,955	28 / 49,960	-0.8 (-1.8 to 0.2)	40.2 (3.6 to 76.8)
Start follow-up from day 0	DK, FI	1485 / 302,036	2481 / 300,269	-127.9 (-150.3 to -105.5)	39.6 (35.7 to 43.5)
Seasonal recipients - Laboratory-confirmed influenza A					
0-13	DK, FI	15 / 49,949	35 / 49,956	-1.4 (-2.4 to -0.3)	57.0 (30.9 to 83.1)
Start follow-up from day 0	DK, FI	1469 / 302,064	2450 / 300,322	-128.2 (-271.0 to 14.6)	39.6 (33.2 to 46.0)
Seasonal recipients - Laboratory-confirmed influenza B					
0-13	DK	<5 / 23,974	<5 / 23,953	-0.2 (-6,198.1 to 6,197.8)	54.2 (-55.9 to 100.0)
Start follow-up from day 0	DK, FI	17 / 302,091	36 / 300,397	-2.3 (-4.2 to -0.5)	55.3 (29.0 to 81.6)
Seasonal recipients - Influenza-like-illness					
0-13	DK, FI	10 / 49,950	23 / 49,954	-0.8 (-1.7 to 0.1)	56.3 (23.7 to 88.8)
Start follow-up from day 0	DK, FI	832 / 302,003	1502 / 300,251	-88.2 (-230.8 to 54.5)	44.5 (33.2 to 55.7)
Seasonal recipients - Hospitalization for ARI and SARI					
0-13	DK, FI, SE	522 / 50,821	891 / 50,820	-32.9 (-57.1 to -8.7)	45.3 (27.4 to 63.2)
Start follow-up from day 0	DK, FI	3784 / 300,483	5226 / 298,717	-170.6 (-402.0 to 60.7)	26.5 (23.4 to 29.6)
Seasonal recipients - ICU admission					

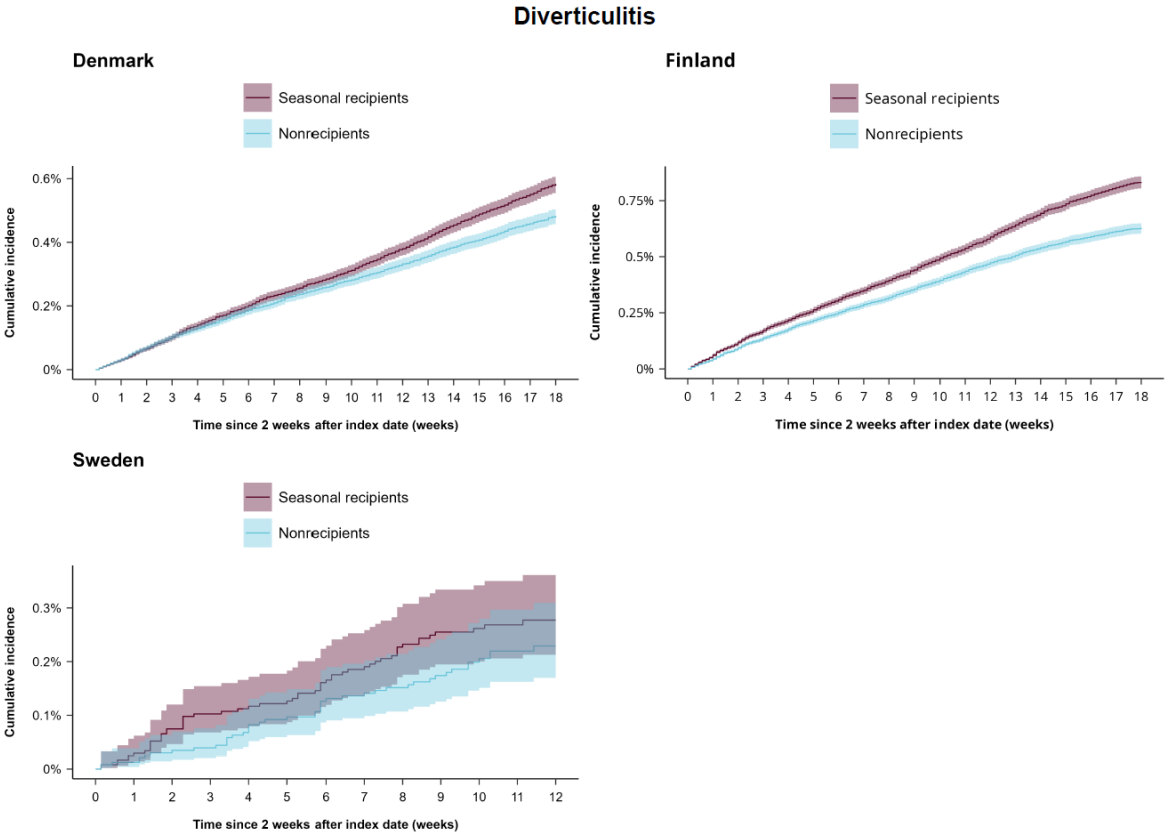
Table 18. Risk of influenza related outcomes comparing seasonal recipients with non-recipients in Denmark, Finland and Sweden when starting follow-up from day of vaccination (day 0).

		Events / person-years			
	Contributing countries	**Recipients**	**Non-recipients**	**Risk difference (95% CI) per 100,000 individuals**	**Vaccine effectiveness (95% CI)**
Start follow-up from day 0	DK, FI	21 / 302,170	37 / 300,483	-1.6 (-2.9 to -0.3)	55.9 (12.7 to 99.1)
Seasonal recipients - Hospitalization due to influenza					
0-13	DK, FI	2 / 49,975	10 / 49,978	-0.6 (-1.1 to -0.1)	81.9 (54.0 to 100.0)
Start follow-up from day 0	DK, FI	355 / 301,986	727 / 300,236	-52.7 (-202.5 to 97.2)	51.1 (44.9 to 57.3)
Seasonal recipients - Influenza-related death					
0-13	FI	<5 / 26,001	<5 / 26,026	0.0 (-6,198.0 to 6,198.0)	-0.2 (-100.0 to 100.0)
Start follow-up from day 0	DK, FI	59 / 302,152	174 / 300,457	-15.2 (-21.8 to -8.6)	66.2 (56.1 to 76.2)

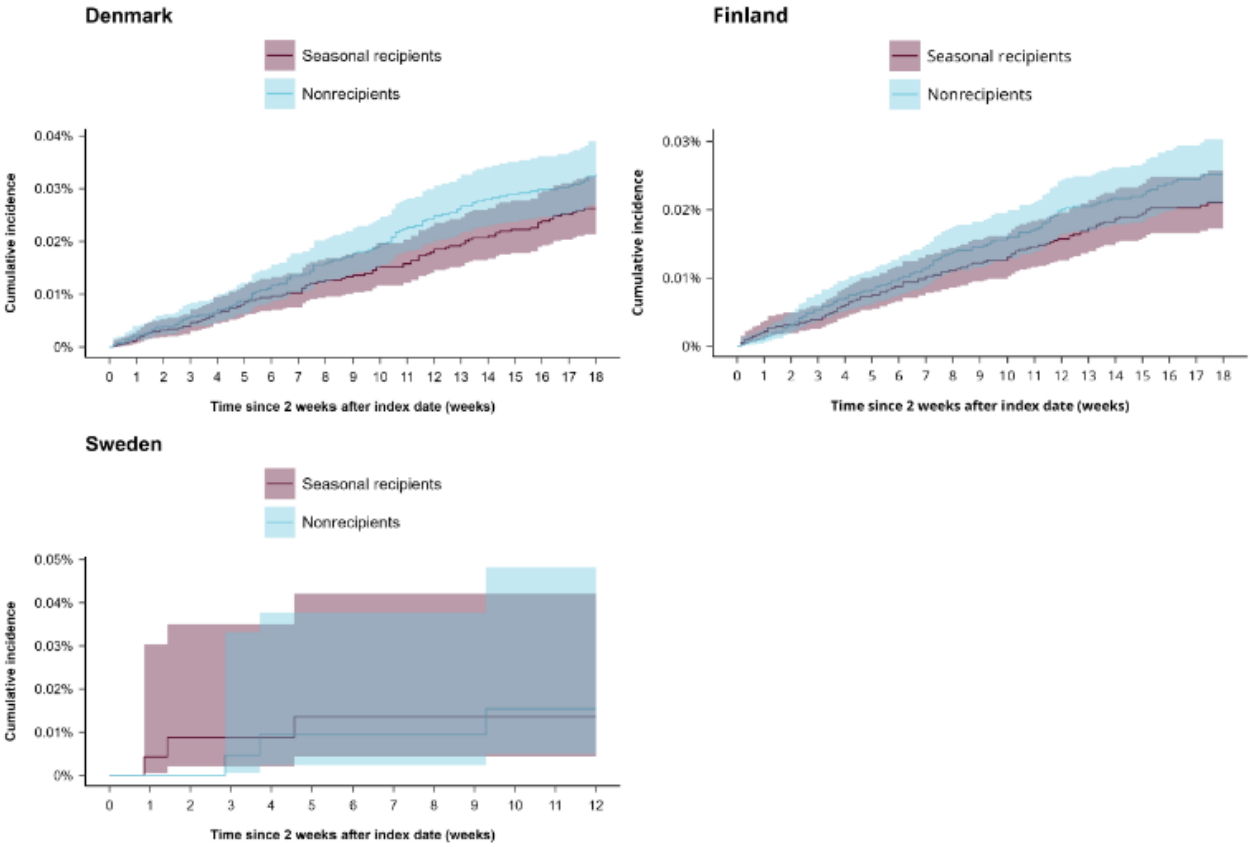
Negative control outcomes

To assess residual confounding, we examined three negative control outcomes: diverticulitis, clavicle fracture, and lower back pain. For diverticulitis and lower back pain, the cumulative incidence was consistently higher among vaccine recipients compared to non-recipients across all countries (Figure 14), with negative vaccine effectiveness estimates of –26.7% (–38.0 to –15.5) and –21.4% (–33.7 to –9.1), respectively (Table 18). In contrast, clavicle fractures showed a small protective association (VE: 18.2%, 2.3 to 34.1).

Figure 14. Cumulative incidence curves of negative control outcomes (diverticulitis, clavicle fracture, lower back pain), comparing recipients of influenza vaccine during 2024-2025 season with matched non-recipients.



Clavicle fracture



Lower back pain

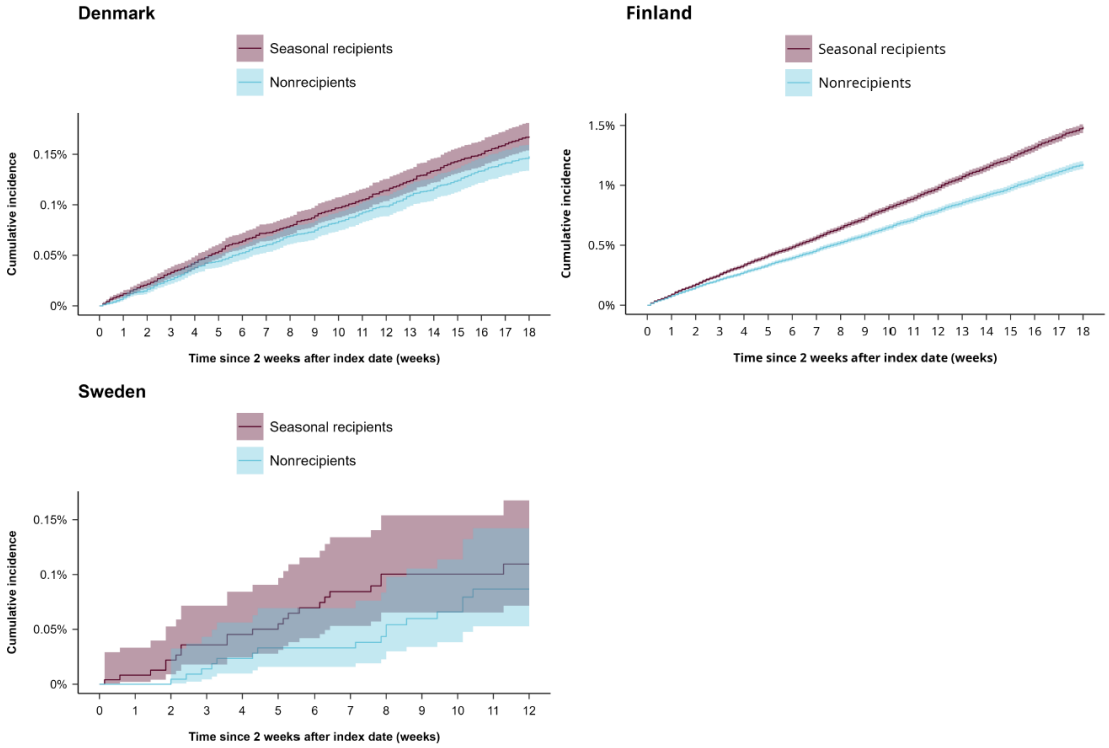


Table 18. Risk of negative control outcomes comparing seasonal recipients with non-recipients in Denmark, Finland and Sweden.

		Events / person-years			
	Contributing countries	**Recipients**	**Non-recipients**	**Risk difference (95% CI) per 100,000 individuals**	**Vaccine effectiveness (95% CI)**
Seasonal recipients - Diverticulitis					
All	DK, FI	5786 / 268,043	4566 / 266,782	151.7 (-18.2 to 321.7)	-26.7 (-38.0 to -15.5)
Seasonal recipients - Clavicle fracture					
All	DK, FI	191 / 271,977	231 / 270,490	-5.0 (-10.0 to -0.1)	18.2 (2.3 to 34.1)
Seasonal recipients - Lower back pain					
All	DK, FI	7078 / 267,402	5667 / 266,180	163.6 (-151.2 to 478.4)	-21.4 (-33.7 to -9.1)

Prior event rate adjustment (PERR)

We conducted a PERR analysis using a difference-in-differences approach that compared pre- and post-vaccination event rates for influenza-related hospitalization in Denmark and Finland. The PERR estimate was 0.77 (0.13 to 5.85) in Denmark and 0.21 (0.03 to 1.01) in Finland, indicating a lower relative risk of hospitalization in the vaccinated group after adjusting for pre-vaccination differences (Table 19). These results are consistent with a protective effect of vaccination, although the wide confidence intervals reflect limited statistical power due to low event counts in the pre-vaccination period. While the findings align with the direction of effect observed in the primary matched cohort analysis—providing some reassurance that residual confounding from healthy vaccinee bias is unlikely to fully account for the observed VE estimates—the limited number of events in the pre-period renders this estimate imprecise.

Table 19. Prior event rate ratio estimates for influenza related hospital admission in Denmark and Finland.

Seasonal recipient events		Nonrecipient events					
Pre-period	Post period	Pre-period	Post period	Total individuals in pre-period	Total individuals in post period	Country	Prior event rate ratio (95%)
5	105	<5	197	745451	611705	Denmark	0.77 (0.13 to 5.85)
<5	413	<5	802	723807	528529	Finland	0.21 (0.03 to 1.01)

Regression discontinuity analysis (RDA)

We conducted a fuzzy RDA centred around the age threshold of 65 years to estimate the local average treatment effect (LATE) of influenza vaccination eligibility on influenza-related hospitalisations among individuals aged 60–69 years in Denmark and Finland. A triangular kernel weighting was used to give the greatest weight to observations near the 65-year cut off. A band width of 1.21 years for Finland and 1.65 years for Denmark was observed using the MSE-optimal method at each side of the cut off.

We observed a discontinuity in the probability of vaccination at the age eligibility threshold in both countries. In Denmark, from an approximate visual inspection of Figure 15, the predicted probability of the two local linear fits just above and below the cut off shows an increase of the probability of vaccination from approximately 30% to over 50% at age 65. This is reflected in the first stage estimate of 0.23 (0.22 to 0.24), that gives the percentage point change of these two probabilities. In Finland, a smaller yet evident increase was seen at the threshold (from approximately 28% to 35%), with a first-stage estimate of 0.07 (0.06 to 0.09) (Figure 15).

Despite the observed changes in vaccination uptake around the age 65 threshold, the estimated effect of vaccination eligibility on influenza-related hospitalisation was not statistically significant in either country. In Denmark, the LATE (represented as percentage point difference) was -0.0007 (-0.0032 to 0.0018), and in Finland, the LATE was 0.0026 (-0.0027 to 0.0078) (Table 21). These estimates suggest that, while age-based policy increased vaccination uptake, the modest increase in vaccination probability at the 65-year cut off and the limited number of events did not translate into a measurable

percentage point change in the risk of influenza-related hospitalisation among individuals just above versus just below the eligibility age.

Baseline characteristics were generally well balanced across the 60–69 age band, with individuals who received the seasonal influenza vaccine being slightly older on average (65.3 vs. 63.8 years) and more likely to have underlying health conditions (e.g., cardiovascular disease: 16.1% vs. 12.1%) (Table 20). As expected, vaccinated individuals had higher comorbidity burden, consistent with risk-based prioritisation within the age bands.

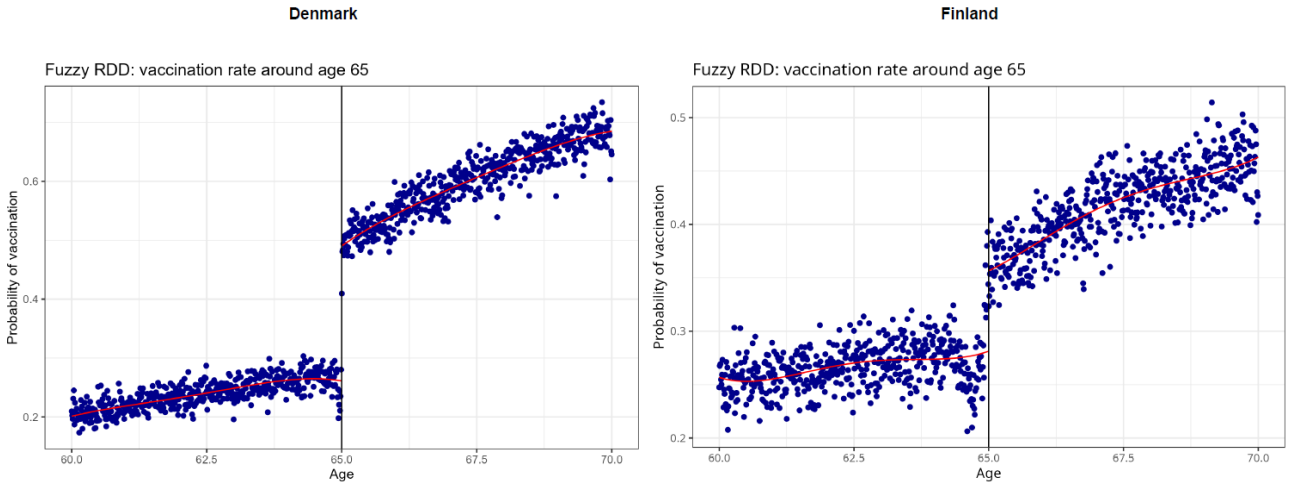
Table 20. Baseline characteristics of the cohort participants for comparisons for estimating effectiveness of seasonal influenza vaccines in Denmark and Finland among individuals 60-69 years of age using regression discontinuity analyses. Values are numbers (percentages) unless stated otherwise.

	Seasonal recipient	Non-recipient
No. individuals		
Total	465,159	799,379
Denmark	252,297	382,797
Finland	212,862	416,582
Mean age (SD), years	65.3 (2.8)	63.8 (2.8)
Female sex	256,303 (55.1)	385,854 (48.3)
Autoimmune related conditions	28,750 (6.2)	28,328 (3.5)
Cancer	44,569 (9.6)	48,104 (6.0)
Chronic pulmonary disease	22,067 (4.7)	17,905 (2.2)
Cardiovascular condition	74,977 (16.1)	96,947 (12.1)
Diabetes	43,834 (9.4)	53,800 (6.7)
Renal disease	7,341 (1.6)	7,879 (1.0)
Comorbidity count		
0	294,389 (63.3)	596,196 (74.6)
1	128,311 (27.6)	160,605 (20.1)
2	35,167 (7.6)	36,176 (4.5)
2+	7,292 (1.6)	6,402 (0.8)

Table 21. Regression discontinuity analysis to find local average treatment effect of offering the influenza vaccination at 65 on influenza related hospital admission in Denmark and Finland.

Country	Band width	Kernel	Polynomial order	Local jump in vaccination probability (First stage estimate) (95% CI)	Local average treatment effect (95% CI)
Denmark	1.65	Triangular	1	0.23 (0.22 to 0.24)	-0.0007 (-0.0032 to 0.0018)
Finland	1.21	Triangular	1	0.07 (0.06 to 0.09)	0.0026 (-0.0027 to 0.0078)

Figure 15. Fuzzy regression discontinuity analysis plot of age and probability of vaccination in Denmark and Finland.



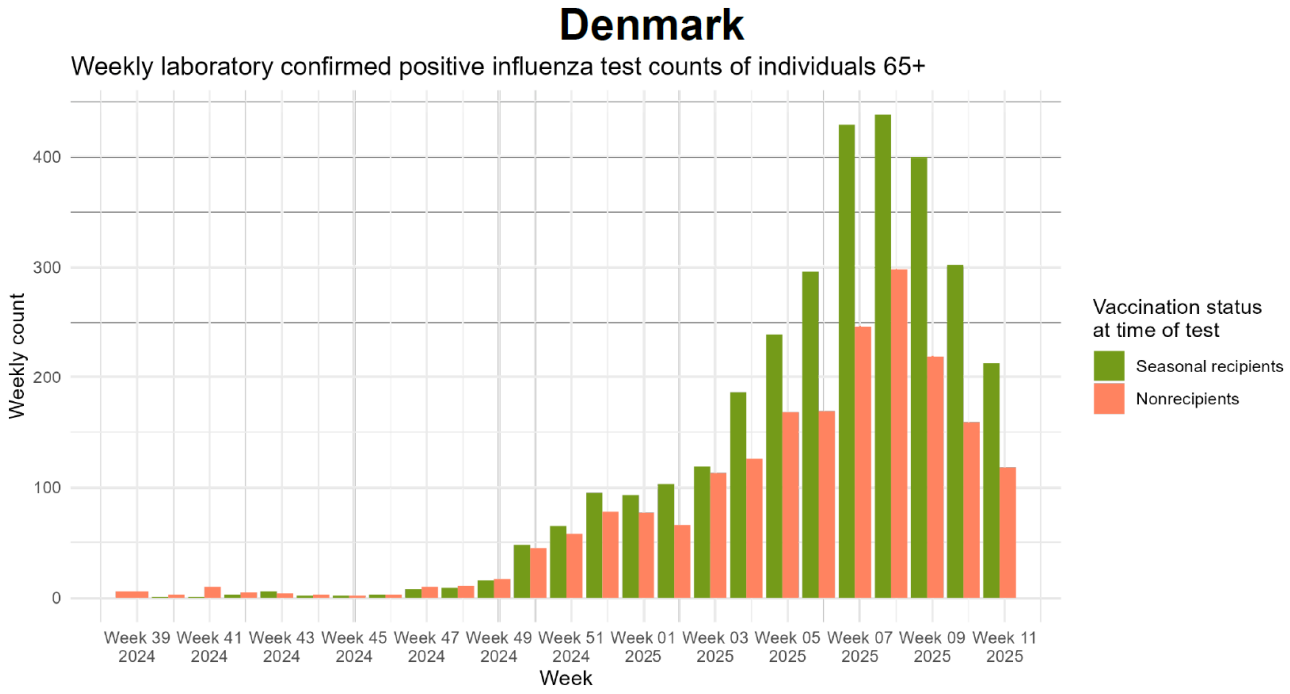
Testing frequency

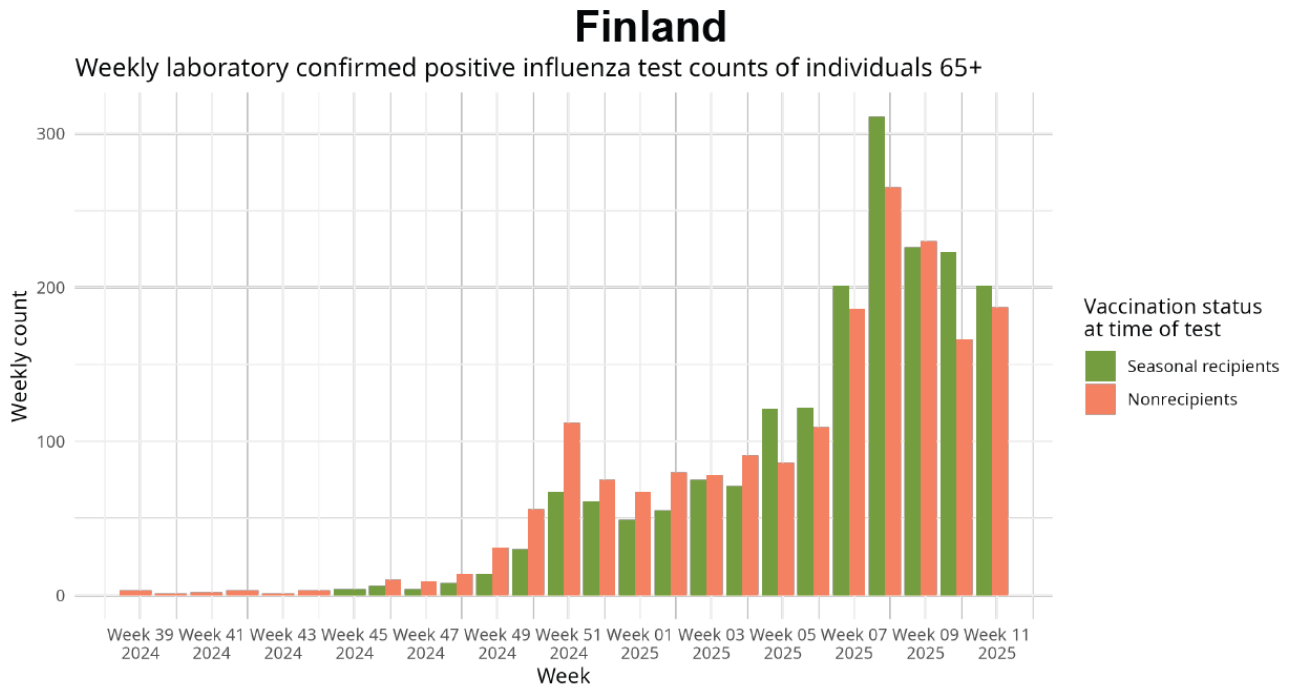
Figures 16 illustrates the weekly numbers of positive influenza tests for vaccinated and unvaccinated individuals from week 39 2024 through week 11 2025 in Denmark and Finland, and week 4 in Sweden.

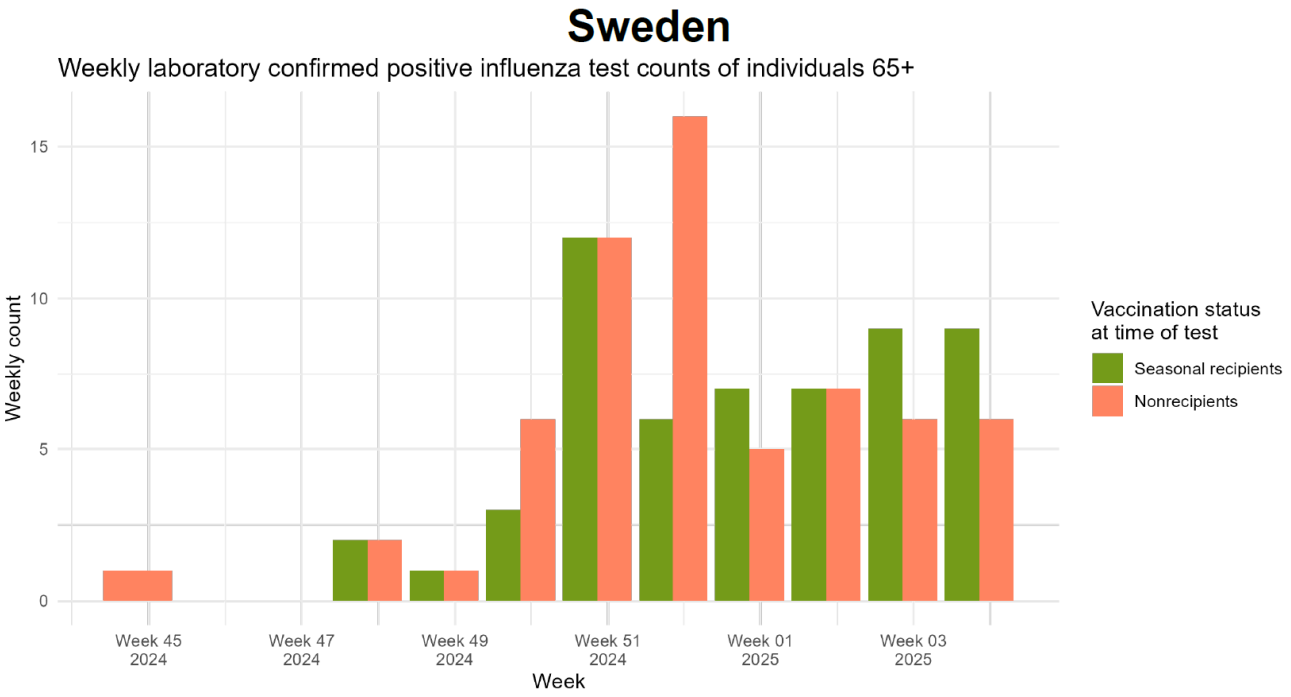
Positive-test counts started to increase from week 50, peaking at week 8 when influenza activity was the highest, accounting for approximately 440 positive tests among the vaccinated, and 300 tests among the unvaccinated in Denmark and 310 and 270, respectively, in Finland. The positive test

frequency among the two groups followed the same increasing trend in Denmark and Finland, aligning with the season's peak and the number of positive cases throughout the season (Figure 16).

Figure 16. Weekly counts of laboratory-confirmed positive tests among vaccinated and unvaccinated individuals aged 65 years and older in Denmark, Finland, and Sweden, by week of test, 2024–2025 season. [c]







[c] Follow-up in Sweden to week 4 only, due to limited data availability.

10. 2 Adults at high risk below 65 years of age

10.2.1 Participants and descriptive data

Tables 22 and 23 show the baseline characteristics of the general high-risk population study cohorts for influenza hospitalization analysis before and after matching; Figure 17 outlines the selection of cohort participants; Figure 18 illustrates the distributions of age and index date in density plots across countries. In order to have a common high-risk definition across countries, high risk individuals are defined as individuals under 65 who have had one or more of the predefined comorbidities. Moreover, in contrast to the main cohort analysis, instead of matching on comorbidity count, individuals were also matched on the specific comorbidities.

Prior to matching, the source cohorts comprised 234,264 recipients of the seasonal influenza vaccine in the three countries during the study period. The largest number of recipients were from Finland (116,380), Denmark (115,839), followed by Sweden (2,045). The most frequently used vaccine brand was Vaxigrip Tetra (173,745 doses accounting for 74.2 % of total vaccines administered), followed by Influvac Tetra (55,372, 23.6%) (Table 22).

The matched cohorts consisted of a total of 210,566 recipients of the seasonal influenza vaccine for the estimation of influenza hospitalization during the study period (with a mean age 53.1 SD 10.4 years) and 210,566 non-recipients. The most recipients were from Finland (105,069), Denmark (103,542), followed by Sweden (1,955).

The most frequently used vaccine brand was Vaxigrip Tetra (155,600 doses accounting for 73.9 % of total vaccines administered before matching), followed by Influvac Tetra (50,935 doses, 24.2%), Efluelda Tetra (2,186 doses, 1%), and Fluad Tetra (1,827 doses, 0.9%) (Table 23).

Characteristics among the matched pairs were overall similar to those of the unmatched populations. The cohort characteristics for other outcomes are similar, with minor differences according to the exclusion of prior events for each outcome.

Table 22. Baseline characteristics before matching of high-risk below 65 years of age cohort comparisons for estimating effectiveness of the seasonal influenza vaccines in Denmark, Finland and Sweden, 1 October 2024 to 21 March 2025.[a]

	Seasonal recipient	Non-recipient[b]
No. individuals		
Total	234,264	754,793
Denmark	115,839	380,238
Finland	116,380	347,540

Table 22. Baseline characteristics before matching of high-risk below 65 years of age cohort comparisons for estimating effectiveness of the seasonal influenza vaccines in Denmark, Finland and Sweden, 1 October 2024 to 21 March 2025.[a]

	Seasonal recipient	Non-recipient[b]
Sweden	2,045	27,015
Mean age (SD), years	53.1 (10.4)	50.0 (12.1)
Female sex	133,906 (57.2)	385,053 (51.0)
Influvac Tetra	55,372 (23.6)	
Vaxigrip Tetra	173,745 (74.2)	
Efluelda Tetra	2,425 (1.0)	
Fluarix Tetra	68 (0.0)	
Fluad Tetra	2,056 (0.9)	
Flucelvax Tetra	13 (0.0)	
Fluenz or Fluenz Tetra	8 (0.0)	
Autoimmune related conditions	61,916 (26.4)	205,216 (27.2)
Cancer	47,023 (20.1)	142,764 (18.9)
Chronic pulmonary disease	31,946 (13.6)	98,622 (13.1)
Cardiovascular condition	69,026 (29.5)	209,119 (27.7)
Diabetes	64,499 (27.5)	186,914 (24.8)
Renal disease	10,942 (4.7)	33,270 (4.4)
Comorbidity count		
1	190,703 (81.4)	649,354 (86.0)
2	36,879 (15.7)	91,418 (12.1)
2+	6,682 (2.9)	14,021 (1.9)

[a] Values are numbers (percentages) unless stated otherwise.

[b] Individuals eligible for influenza vaccination as of the start of the study on 1 October 2024.

Table 23. Baseline characteristics after matching of high-risk below 65 years of age cohort comparisons for estimating effectiveness of the seasonal influenza vaccines in Denmark, Finland and Sweden, 1 October 2024 to 21 March 2025.[a,c]

	Seasonal recipient	Non-recipient[b]
No. individuals		
Total	210,566	210,566
Denmark	103,542	103,542
Finland	105,069	105,069
Sweden	1,955	1,955
Mean age (SD), years	52.9 (10.5)	52.8 (10.4)
Female sex	118,859 (56.4)	118,859 (56.4)
Influvac Tetra	50,935 (24.2)	
Vaxigrip Tetra	155,600 (73.9)	
Efluelda Tetra	2,186 (1.0)	
Fluarix Tetra	0 (0.0)	

	Seasonal recipient	Non-recipient[b]
Fluad Tetra	1,827 (0.9)	
Flucelvax Tetra	12 (0.0)	
Fluenz	6 (0.0)	
Autoimmune related conditions	55,233 (26.2)	55,233 (26.2)
Cancer	41,747 (19.8)	41,747 (19.8)
Chronic pulmonary disease	27,670 (13.1)	27,670 (13.1)
Cardiovascular condition	61,659 (29.3)	61,659 (29.3)
Diabetes	57,356 (27.2)	57,356 (27.2)
Renal disease	9,244 (4.4)	9,244 (4.4)
Comorbidity count		
1	173,530 (82.4)	173,530 (82.4)
2	32,136 (15.3)	32,136 (15.3)
2+	4,900 (2.3)	4,900 (2.3)

[a] Values are numbers (percentages) unless stated otherwise.
[b] Individuals eligible for influenza vaccination as of the start of the study on 1 October 2024.
[c] Per study design, we applied a pairwise censoring if a reference individual received a vaccine. This led to 22229 matched pairs experiencing censoring prior to start of follow up at 14 days after vaccination due to quick vaccine uptake.

Figure 17. Flowchart of cohort construction.

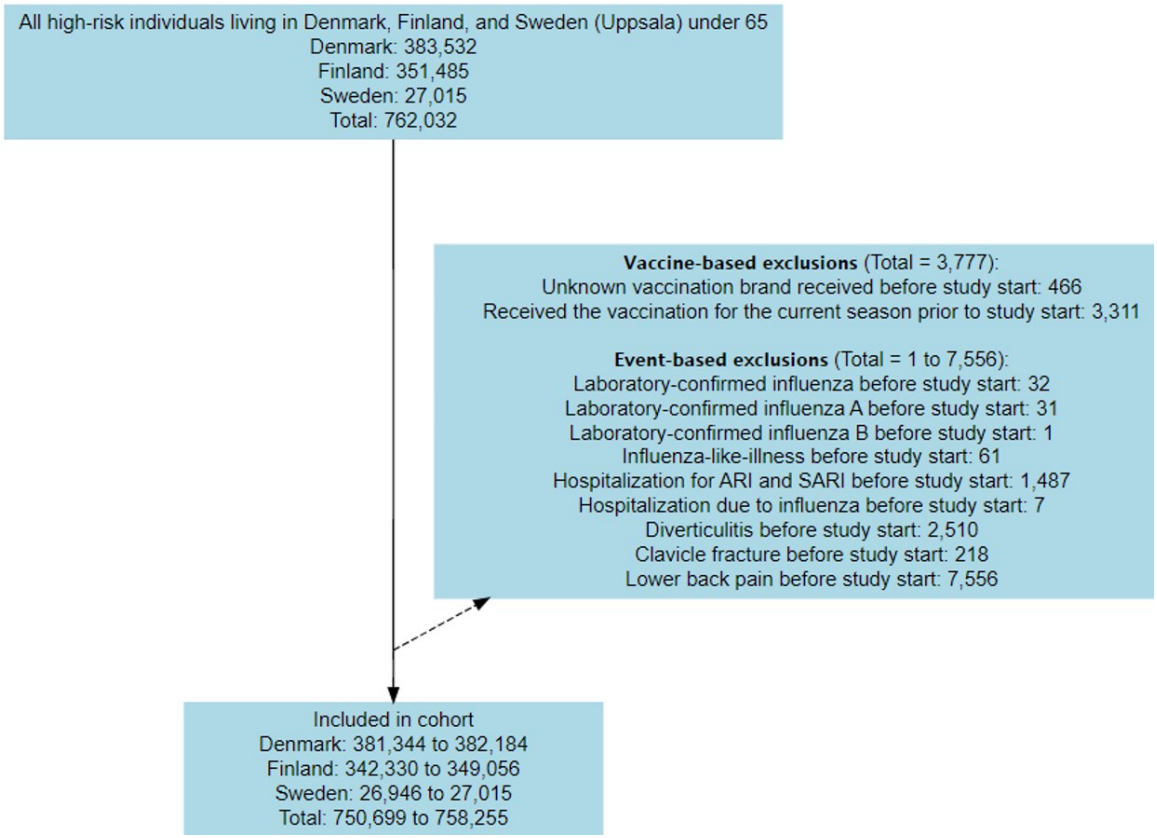
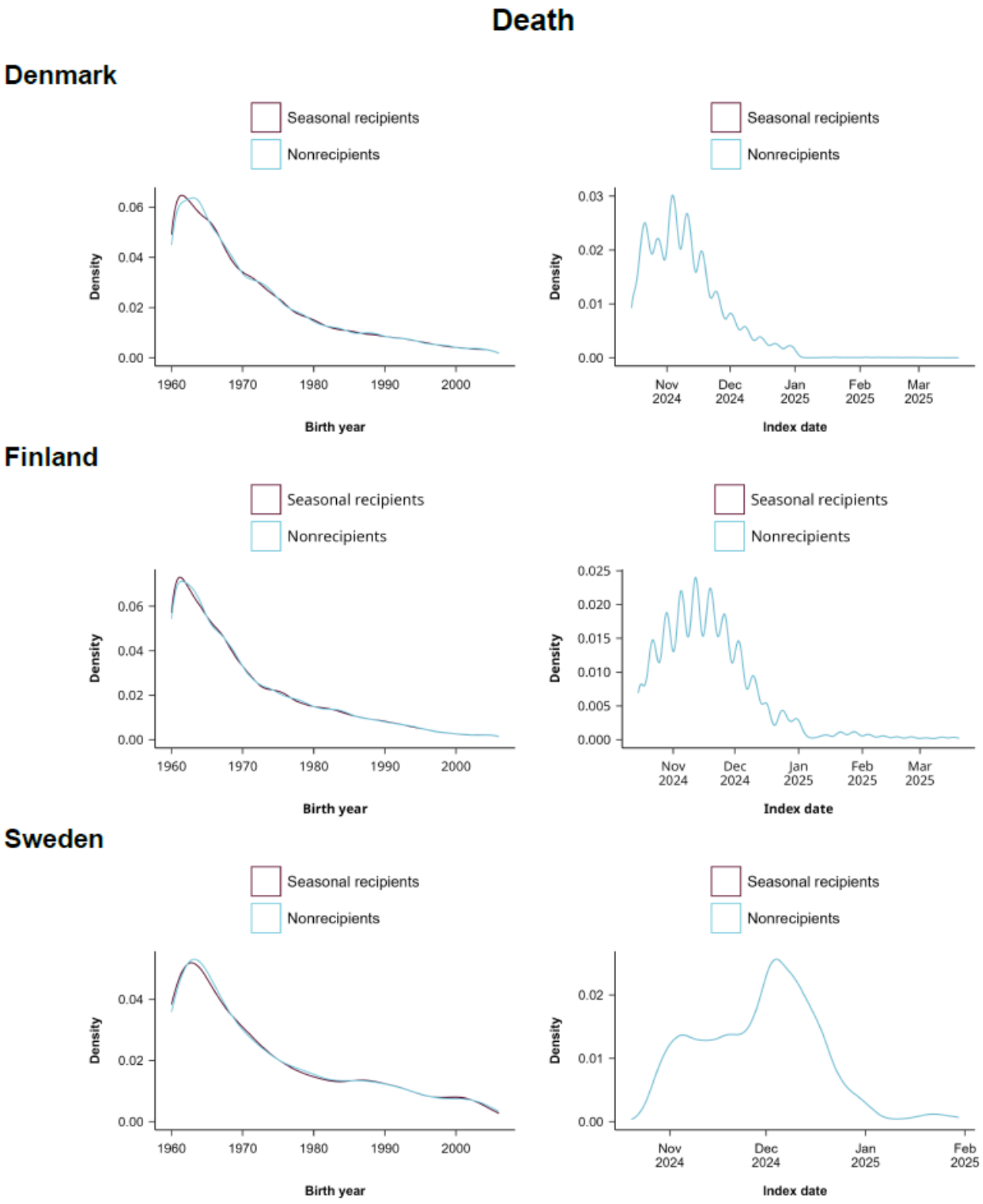


Figure 18. Density plots of the distribution of age and index date for influenza-related death among high-risk individuals below 65 years of age across the three countries.



10.2.2 Outcome data and main results

10.2.2.1 Primary outcomes

Figures 19 - 23 show the 18-week cumulative incidences of laboratory- confirmed influenza, influenza hospitalization, and influenza death among vaccine recipients versus matched non-recipients from 2 weeks after the vaccination date, among individuals at high risk below 65 years of age. Tables 24 and 25 show the risk of influenza related primary outcomes comparing seasonal recipients with non-recipients at day 126 (week 18), in Denmark and Finland. Due to limited data availability, Sweden did not contribute to the estimates at day 126, but contributed to the estimates of selected outcomes at day 84. Figure 28 presents the risks of primary and secondary outcomes at day 84 (week 12) in Denmark, Finland and Sweden. Age, sex, and vaccine brand-stratified estimates were not provided due to limited number of events in this cohort.

Laboratory-confirmed influenza (types A and B, and overall)

Vaccine recipients had lower cumulative incidence of overall laboratory-confirmed influenza, as well as influenza A, when compared to non-recipients, with patterns consistent in Denmark and Finland (Figures 19-21).

The risk of overall laboratory-confirmed influenza was lower for the recipients of the seasonal influenza vaccine compared with non-recipients. The overall VE afforded by the seasonal influenza vaccine was 12.4% (3.7 to 21.1) with a risk difference of -56.1 (-118.4 to 6.1) per 100,000 individuals (Table 24). At day 84, the VE was 19.2% (6.7 to 31.7) with a risk difference of −36.8 (−62.9 to −10.7) per 100,000 individuals, based on results from Denmark, Finland, and Sweden (Figure 28).

The risk of laboratory-confirmed influenza A was lower for the recipients of the seasonal influenza vaccine compared with non-recipients. The VE afforded by the seasonal influenza vaccine was 6.9% (-2.9 to 16.6) with a risk difference of -27.3 (-70.4 to 15.7) per 100,000 individuals (Table 24). At day 84, the VE was 26.0% (14.9 to 37.1) with a risk difference of −53.3 (−80.3 to −26.4) per 100,000 individuals, based on results from Denmark, Finland, and Sweden (Figure 28).

The risk of laboratory-confirmed influenza B was lower for the recipients of the seasonal influenza vaccine compared with non-recipients. The VE afforded by the seasonal influenza vaccine was 46.2% (24.4 to 68.1) with a risk difference of -17.7 (-42.7 to 7.3) per 100,000 individuals (Table 24). This estimate, however, relies on a lower number of events (37), compared with the number of events of the two previous laboratory-confirmed outcomes (853 and 752, respectively) (Table 24).

Figure 19. Cumulative incidence curves of overall laboratory-confirmed influenza, comparing recipients of influenza vaccine during 2024-2025 season with matched non-recipients among individuals at high risk below 65 years of age.

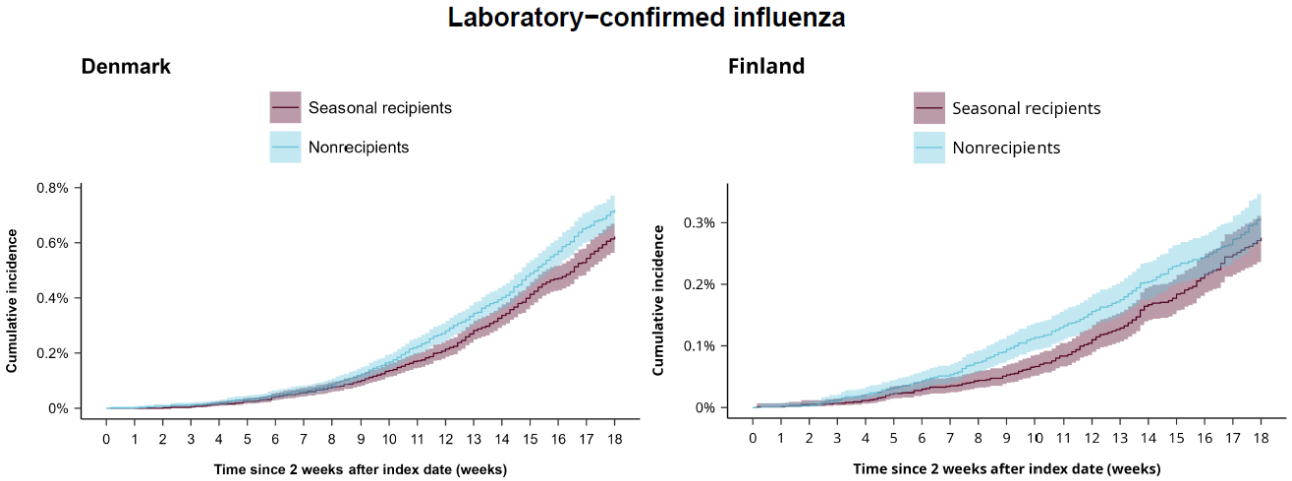


Figure 20. Cumulative incidence curves of laboratory-confirmed influenza A, comparing recipients of influenza vaccine during 2024-2025 season with matched non-recipients among individuals at high risk below 65 years of age.

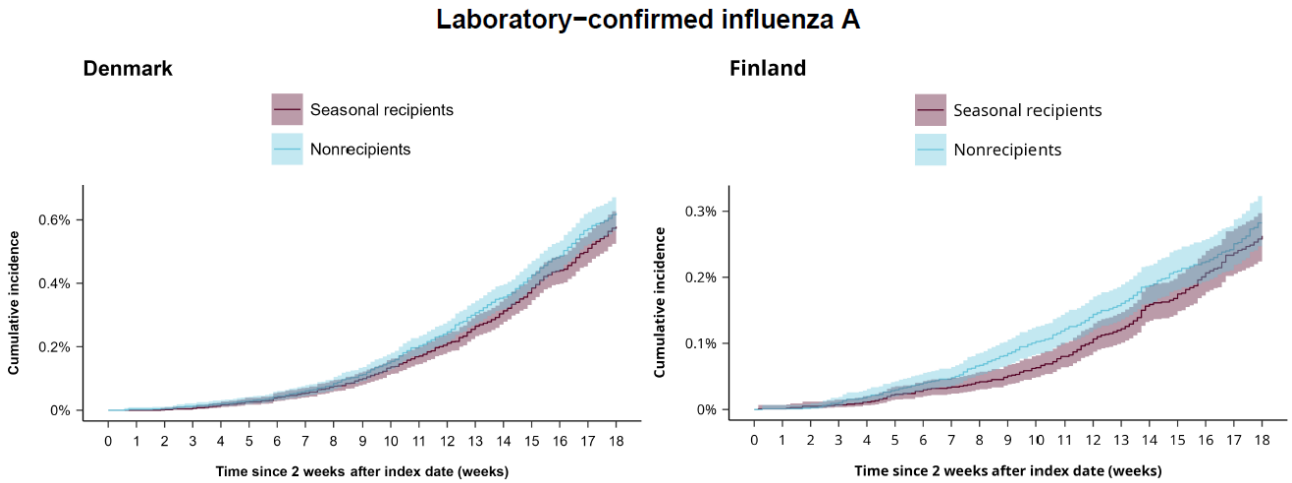


Figure 21. Cumulative incidence curves of laboratory-confirmed influenza B, comparing recipients of influenza vaccine during 2024-2025 season with matched non-recipients among individuals at high risk below 65 years of age.

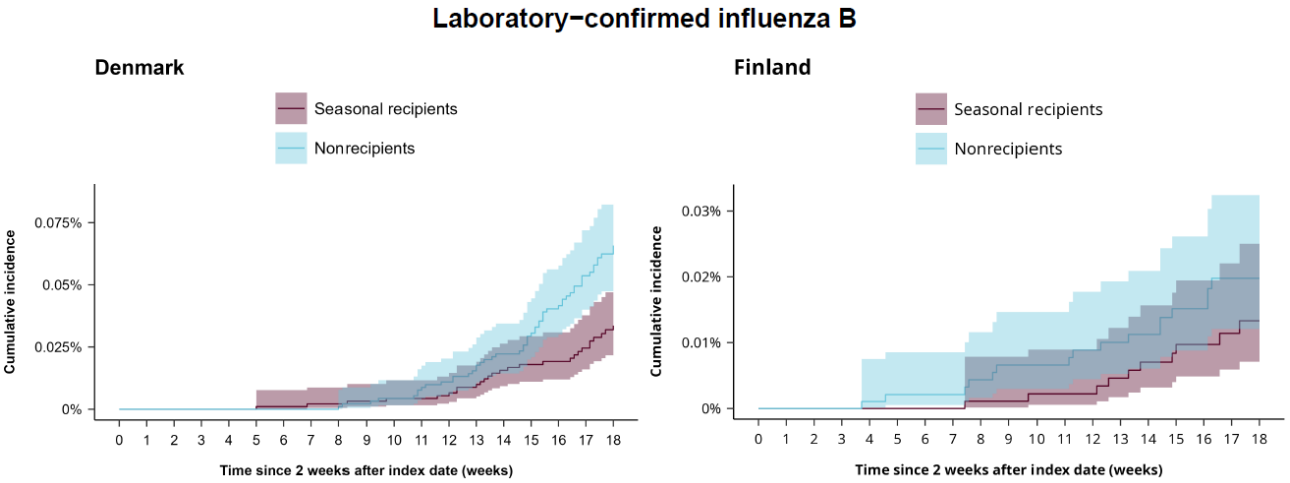


Table 24. Risk of laboratory-confirmed influenza comparing seasonal recipients with non-recipients at day 126 (week 18) among individuals at high risk below 65 years of age in Denmark and Finland, 1 October 2024 to 21 March 2025.

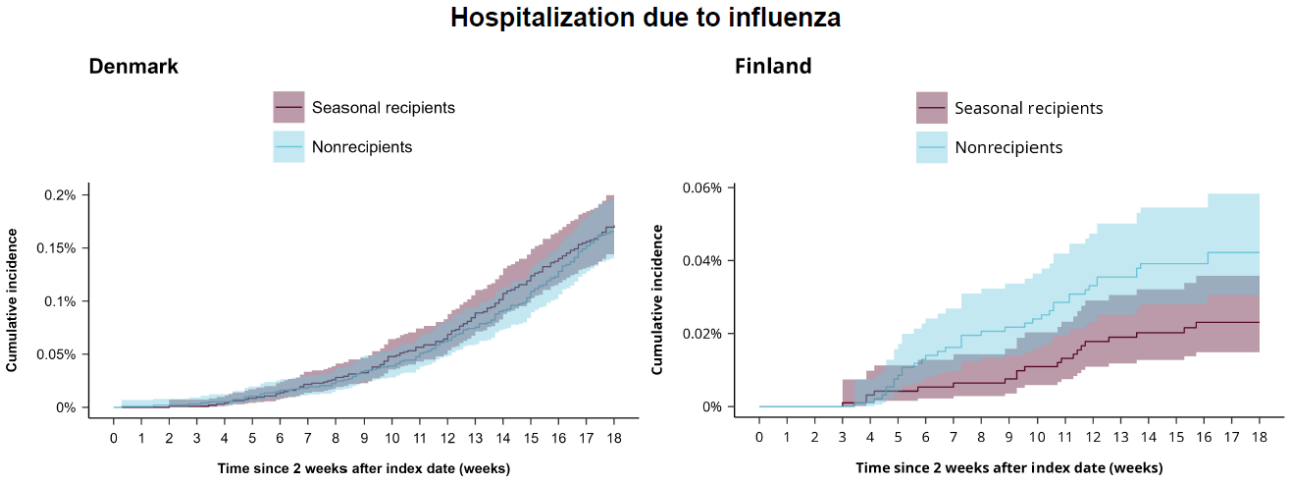
		Events / person-years			
	Contributing countries	**Recipients**	**Non-recipients**	**Risk difference (95% CI) per 100,000 individuals**	**Vaccine effectiveness (95% CI)**
Seasonal recipients - Laboratory-confirmed influenza					
All	DK, FI	736 / 60,103	853 / 60,017	-56.1 (-118.4 to 6.1)	12.4 (3.7 to 21.1)
Seasonal recipients - Laboratory-confirmed influenza A					
All	DK, FI	690 / 60,082	752 / 60,004	-27.3 (-70.4 to 15.7)	6.9 (-2.9 to 16.6)
Seasonal recipients - Laboratory-confirmed influenza B					
All	DK, FI	37 / 60,133	69 / 60,077	-17.7 (-42.7 to 7.3)	46.2 (24.4 to 68.1)

Influenza hospitalization

Compared to Denmark, hospitalizations in Finland were less frequent overall, and while vaccine recipients consistently showed lower incidence, the difference remained small with wider uncertainty intervals (Figure 22).

The risk of influenza hospitalization was lower for the recipients of the seasonal influenza vaccine compared with non-recipients, although not significantly. The VE afforded by the seasonal influenza vaccine was 20.1% (-27.8 to 68.0) with a risk difference of -13.7 (-33.2 to 5.9) per 100,000 individuals (Table 25). At day 84, the VE was 20.0% (−28.3 to 68.3) with a risk difference of −7.2 (−26.3 to 11.9) per 100,000 individuals, based on results from Denmark, Finland, and Sweden (Figure 28).

Figure 22. Cumulative incidence curves of influenza hospitalization, comparing recipients of influenza vaccine during 2024-2025 season with matched non-recipients among individuals at high risk below 65 years of age.



Influenza-related death

The risk of influenza-related death was lower for the recipients of the seasonal influenza vaccine compared with non-recipients, although not significantly (Figure 23). The VE afforded by the seasonal influenza vaccine was 15.1% (-51.8 to 81.9) with a risk difference of -1.0 (-6.9 to 5.0) per 100,000 individuals (Table 25).

Figure 23. Cumulative incidence curves of influenza-related death, comparing recipients of influenza vaccine during 2024-2025 season with matched non-recipients among individuals at high risk below 65 years of age.

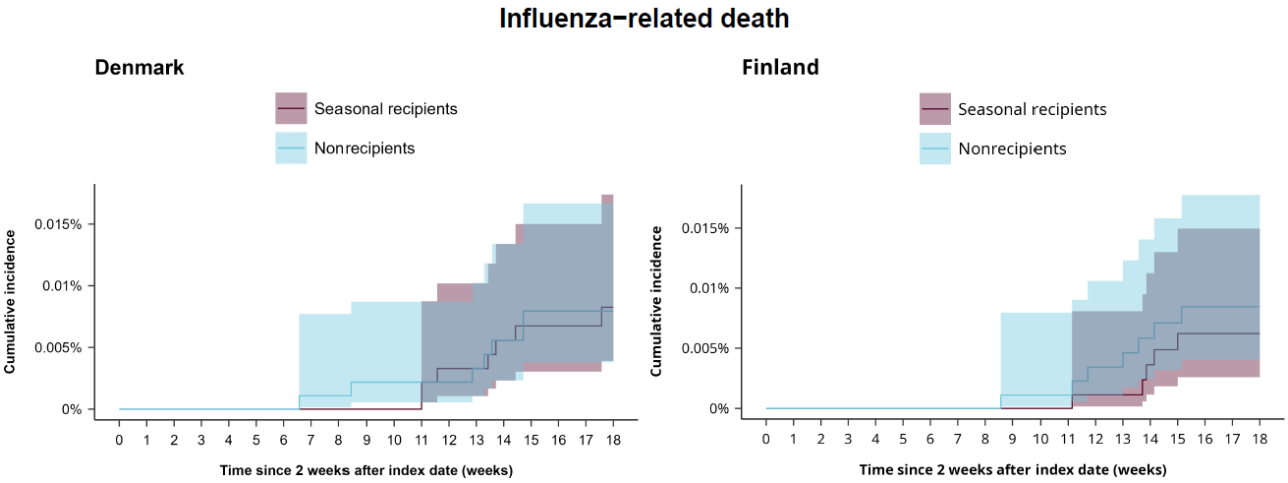


Table 25. Risk of influenza-related hospitalization and death comparing seasonal recipients with non-recipients at day 126 (week 18) among individuals at high risk below 65 years of age in Denmark and Finland, 1 October 2024 to 21 March 2025.

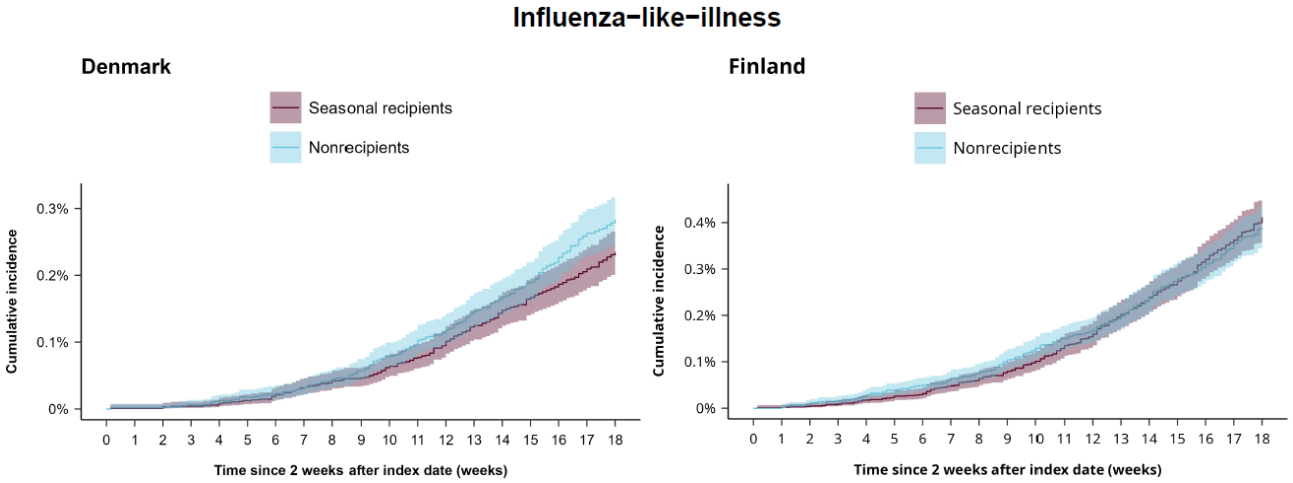
	Contributing countries	Events / person-years: Recipients	Events / person-years: Non-recipients	Risk difference (95% CI) per 100,000 individuals	Vaccine effectiveness (95% CI)
Seasonal recipients - Hospitalization due to influenza					
All	DK, FI	166 / 60,094	177 / 60,033	-13.7 (-33.2 to 5.9)	20.1 (-27.8 to 68.0)
Seasonal recipients - Influenza-related death					
All	DK, FI	12 / 60,151	14 / 60,097	-1.0 (-6.9 to 5.0)	15.1 (-51.8 to 81.9)

10.2.2.2 Secondary outcomes

Influenza-like-illness

The risk of influenza-like illness was lower for the recipients of the seasonal influenza vaccine compared with non-recipients, although not significantly (Figure 24). The VE afforded by the seasonal influenza vaccine was 6.1% (-16.7 to 28.8) with a risk difference of -17.0 (-83.3 to 49.3) per 100,000 individuals (Table 26).

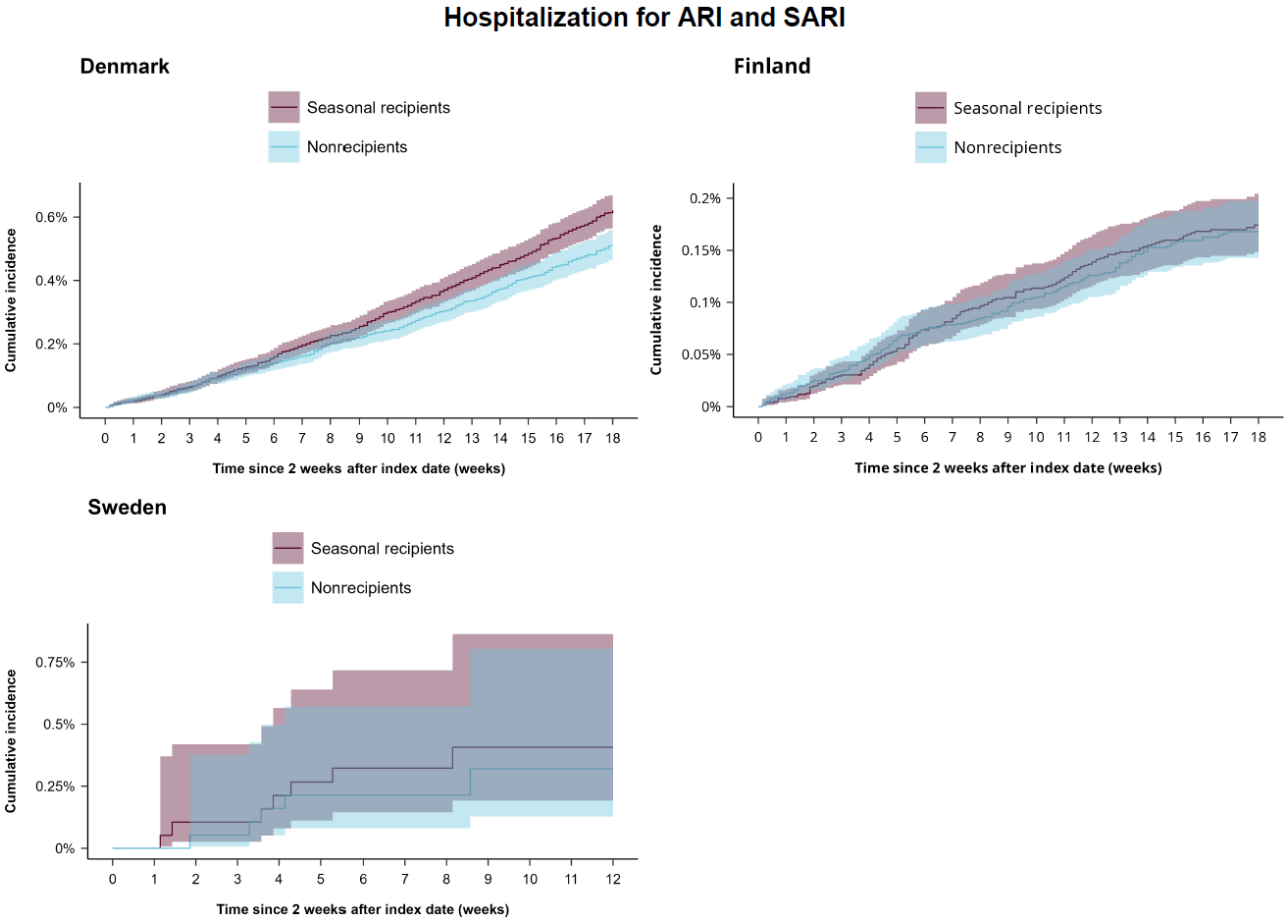
Figure 24. Cumulative incidence curves of influenza-like illness, comparing recipients of influenza vaccine during 2024-2025 season with matched non-recipients among individuals at high risk below 65 years of age.



Hospitalization for respiratory infections (ARI, SARI)

Among individuals in Denmark and Finland, the incidence of hospitalization for ARI and SARI was slightly higher among vaccine recipients (698 events per 59,771 person-years) than non-recipients (597 events per 59,725 person-years), although not significantly, corresponding to a risk difference of 57.4 (–114.0 to 228.7) per 100,000 individuals. The VE was estimated at –15.2% (–32.3 to 2.0), suggesting no significant protective effect of the seasonal vaccine for this outcome (Table 26). At day 84, the VE was −18.2% (−33.9 to −2.6) with a risk difference of 36.2 (−14.4 to 86.8) per 100,000 individuals based on results from Denmark, Sweden and Finland (Figure 28).

Figure 25. Cumulative incidence curves of hospitalization for ARI, SARI, comparing recipients of influenza vaccine during 2024-2025 season with matched non-recipients among individuals at high risk below 65 years of age.

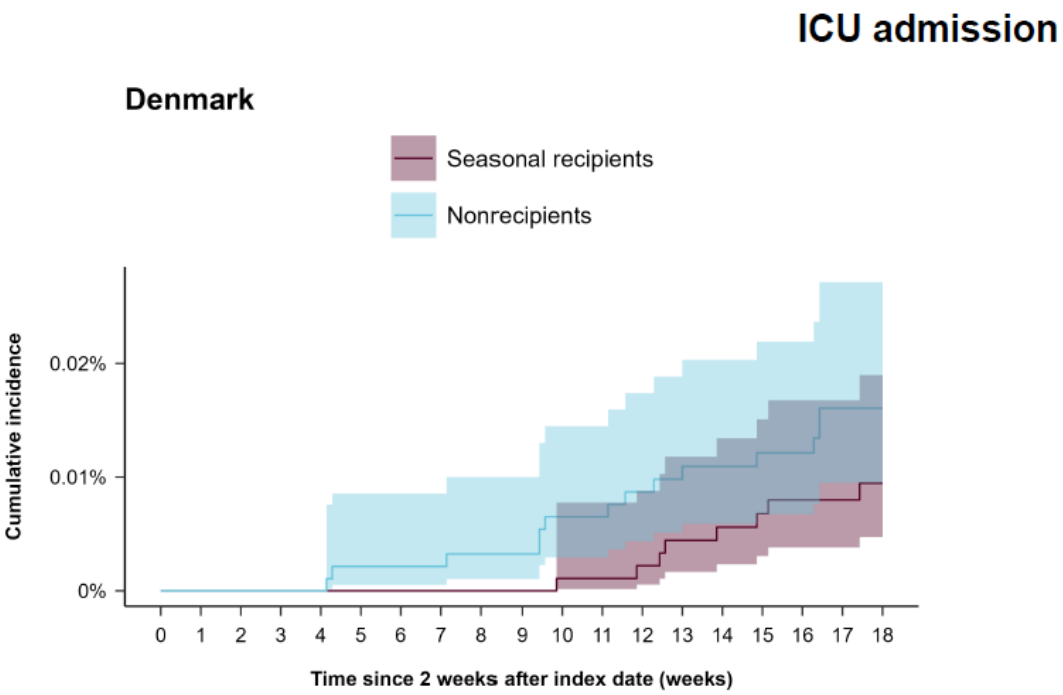


ICU admission

In Denmark, vaccine recipients had lower cumulative incidence of ICU admission compared to non-recipients. The overall ICU admission remained low throughout the season, with only Denmark being able to contribute with events for an analysis. A visible divergence between groups emerged around week 10 and continued through week 18. Cumulative incidence of ICU admission could not be estimated in Finland and Sweden, due to low number of events (Figure 26).

The risk of ICU admission was lower for the recipients of the seasonal influenza vaccine compared with non-recipients. The VE afforded by the seasonal influenza vaccine was 41.1% (-10.6 to 92.9) with a risk difference of -6.6 (-6,204.6 to 6,191.4) per 100,000 individuals (Table 26).

Figure 26. Cumulative incidence curves of ICU admission comparing recipients of influenza vaccine during 2024-2025 season with matched non-recipients among individuals at high risk below 65 years of age.



All cause-mortality

The risk of all-cause mortality was lower for the recipients of the seasonal influenza vaccine compared with non-recipients (Figure 27). The VE afforded by the seasonal influenza vaccine was 30.6% (22.7 to 38.5) with a risk difference of -127.0 (-166.5 to -87.6) per 100,000 individuals (Table 26). At day 84, the VE was 32.0% (22.9 to 41.2) with a risk difference of −87.4 (−117.8 to −57.1) per 100,000 individuals, based on results from Denmark, Finland, and Sweden (Figure 28).

Figure 27. Cumulative incidence curves of all-cause mortality comparing recipients of influenza vaccine during 2024-2025 season with matched non-recipients among individuals at high risk below 65 years of age.

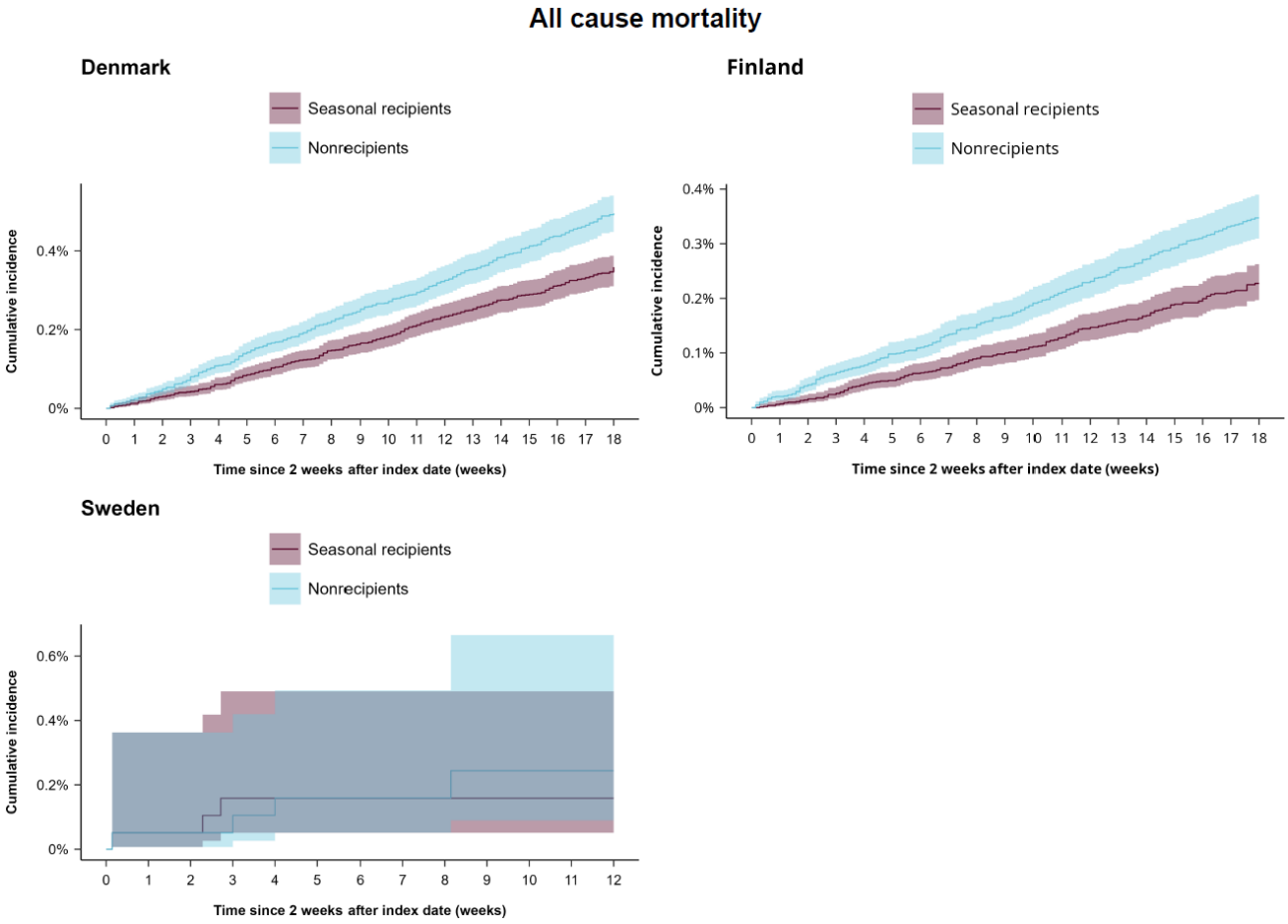


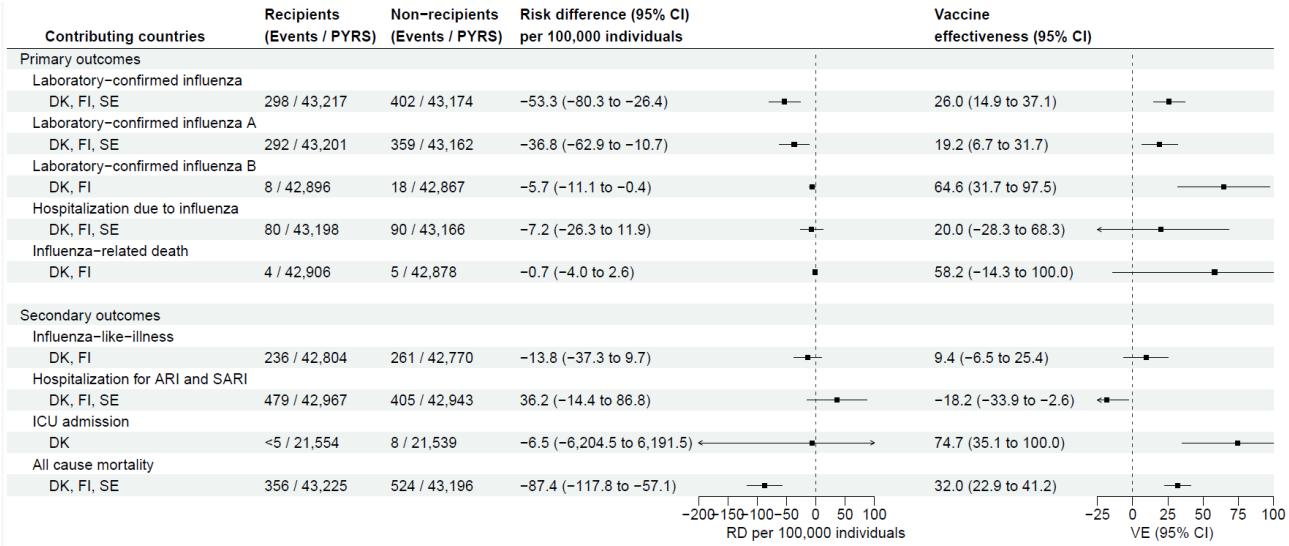
Table 26. Risk of influenza-related secondary outcomes comparing seasonal recipients with non-recipients at day 126 (week 18) among individuals at high risk below 65 years of age in Denmark and Finland, 1 October 2024 to 21 March 2025.

		Events / person-years			
	Contributing countries	Recipients	Non-recipients	Risk difference (95% CI) per 100,000 individuals	Vaccine effectiveness (95% CI)
Seasonal recipients - Influenza-like-illness					
All	DK, FI	515 / 59,975	546 / 59,907	-17.0 (-83.3 to 49.3)	6.1 (-16.7 to 28.8)
Seasonal recipients - Hospitalization for ARI and SARI					
All	DK, FI	698 / 59,771	597 / 59,725	57.4 (-114.0 to 228.7)	-15.2 (-32.3 to 2.0)
Seasonal recipients - ICU admission					
All	DK	8 / 30,775	14 / 30,746	-6.6 (-6,204.6 to 6,191.4)	41.1 (-10.6 to 92.9)
Seasonal recipients - All cause mortality					

Table 26. Risk of influenza-related secondary outcomes comparing seasonal recipients with non-recipients at day 126 (week 18) among individuals at high risk below 65 years of age in Denmark and Finland, 1 October 2024 to 21 March 2025.

		Events / person-years			
	Contributing countries	Recipients	Non-recipients	Risk difference (95% CI) per 100,000 individuals	Vaccine effectiveness (95% CI)
All	DK, FI	508 / 60,154	740 / 60,099	-127.0 (-166.5 to -87.6)	30.6 (22.7 to 38.5)

Figure 28. Risk of primary and secondary outcomes comparing seasonal vaccine recipients with non-recipients at day 84 (week 12) among individuals at high risk below 65 years of age in Denmark, Finland, and Sweden, 1 October 2024 to 21 March 2025.



10.2.3 Results of Supplementary Analyses

In a supplementary analysis using the test-negative design restricted to Denmark, we identified 2,278 cases (laboratory confirmed influenza) and 9,260 controls (confirmed negative tests). Table 27 shows the covariate distribution between cases and controls. Of these tests, we identified 3,439 recipients of seasonal influenza vaccine and 8,099 non-recipients. The mean age was 53.1 (SD 10.7 years) and 48.3 (SD 12.6) among recipients and non-recipients, respectively (Table 28). Among the non-recipients,

there were 1,685 cases (laboratory confirmed influenza) and 6,414 controls. Among the vaccine recipients, there were 593 cases of laboratory-confirmed influenza, and 2,846 controls. The estimated VE among high-risk individuals 18-64-yrs-of-age was 36.6% (29.1% to 43.4%) (Table 29). This is very different than our meta-analysed main analysis VE estimate of 12.4% (3.7% to 21.2%). The Danish VE of 13.4% (3.3% to 23.6%) from the main analysis is also very different.

Table 27. Baseline characteristics of cases and controls in a test negative design supplementary analysis of seasonal influenza vaccines in Denmark. Values are numbers (percentages) unless stated otherwise.

	Cases	Controls
No. individuals		
Total	2,278	9,260
Denmark	2,278	9,260
Mean age (SD), years	48.0 (12.7)	50.2 (12.1)
Female sex	1,318 (57.9)	5,242 (56.6)
Autoimmune related conditions	688 (30.2)	2,555 (27.6)
Cancer	377 (16.5)	2,172 (23.5)
Chronic pulmonary disease	808 (35.5)	3,122 (33.7)
Cardiovascular condition	425 (18.7)	2,007 (21.7)
Diabetes	348 (15.3)	1,485 (16.0)
Renal disease	195 (8.6)	965 (10.4)
Comorbidity count		
1	1,810 (79.5)	6,910 (74.6)
2	389 (17.1)	1,772 (19.1)
2+	79 (3.5)	578 (6.2)

Table 28. Baseline characteristics in a test negative design supplementary analysis of seasonal influenza vaccines in Denmark. Values are numbers (percentages) unless stated otherwise.

	Seasonal recipient	Non-recipient
No. individuals		
Total	3,439	8,099
Denmark	3,439	8,099
Mean age (SD), years	53.1 (10.7)	48.3 (12.6)
Female sex	2,006 (58.3)	4,554 (56.2)
Autoimmune related conditions	950 (27.6)	2,293 (28.3)
Cancer	858 (24.9)	1,691 (20.9)

Table 28. Baseline characteristics in a test negative design supplementary analysis of seasonal influenza vaccines in Denmark. Values are numbers (percentages) unless stated otherwise.

	Seasonal recipient	Non-recipient
Chronic pulmonary disease	1,321 (38.4)	2,609 (32.2)
Cardiovascular condition	749 (21.8)	1,683 (20.8)
Diabetes	562 (16.3)	1,271 (15.7)
Renal disease	359 (10.4)	801 (9.9)
Comorbidity count		
1	2,403 (69.9)	6,317 (78.0)
2	763 (22.2)	1,398 (17.3)
2+	273 (7.9)	384 (4.7)

Table 29. Risk of positive test of influenza comparing seasonal recipients with non-recipients in Denmark using a test negative case control design.

Seasonal recipients		Non-recipients			
Cases	**Controls**	**Cases**	**Controls**	**Crude VE (95% CI)**	**Adjusted VE (95% CI)**
593	2846	1685	6414	20.7 (12.1 to 28.5)	36.6 (29.1 to 43.4)

11. DISCUSSION

11.1 Key results

This study provides estimates of VE against laboratory-confirmed (primary) and medically-attended influenza (secondary) outcomes in two cohorts - in individuals aged ≥65 years and adults below 65 years of age at high risk across three Nordic countries during 2024/2025 influenza season.

We included 1,164,686 vaccine recipients ≥65 years of age. The most frequently used vaccine brand was Vaxigrip Tetra (688,822 doses) followed by Fluad Tetra (402,490 doses), Efluelda Tetra (37,246

doses), and Influvac Tetra (36,098 doses). The estimated VE against overall laboratory-confirmed influenza for all brands was 39.7%, 46.8% against influenza hospitalization, and 63.2% against influenza-related death at 18 weeks of follow up. Where estimable, the vaccine brand Efluelda Tetra (high-dose) showed the highest VE against the primary outcomes, followed by Fluad Tetra (adjuvanted) and Influvac Tetra vaccines.

We included 210,566 vaccine recipients at high risk below 65 years of age. The most frequently used vaccine brand was Vaxigrip Tetra (155,600 doses) followed by Influvac Tetra (50,935 doses), Efluelda Tetra (2,186 doses), and Fluad Tetra (1,827 doses). The estimated VE against overall laboratory-confirmed influenza for all brands was 12.4%, followed by a VE of 20.1% against influenza hospitalization, and 15.1% against influenza-related death at 18 weeks of follow up. Due to low number of outcome events and the smaller size of this cohort, brand-specific VE were not estimated.

Notable differences in the widths of the RD and VE confidence intervals can be observed and have to do with their distinct statistical properties. Relative measures, as those constructed to estimate VE, tend to be more stable across populations and less influenced by differences in baseline risk. Absolute measures, RDs, however, vary directly with each setting's baseline incidence. As a result, when pooling results across countries with different underlying risks, the between country heterogeneity inflates the RD variance and yields wider CIs compared to RRs.

For example, in our meta-analysis for hospitalization, the overall vaccine effectiveness was 46.8% (40.8-52.9), whereas the risk difference was -60.2 (-217.0 to 96.6) per 100,000. Country-specific VEs were very consistent (Denmark 46.0% (39.1 to 52.9); Finland 49.6% (37.1 to 62.0)), yielding narrow CIs for these relative measures. By contrast, the absolute RDs differed substantially (Denmark –99.3 (–119.6 to –79.1) per 100,000; Finland –21.3 (–28.9 to –13.8) per 100,000) because each country's baseline incidence varied. When these heterogeneous RDs are pooled under a random-effects model, with precise estimates that are far apart, the between-country variance inflates the RD's overall CI, making it much wider than the CI for the VE.

11.2 Limitations

Our results should be interpreted in light of a number of limitations.

The statistical precision of brand-specific estimates was limited for the vaccines that are less frequently procured and used in a given country. The statistical precision of our estimates depended on the seasonal incidence of infections which varied throughout the influenza season, and the uptake of the different influenza vaccine brands. Moreover, in Denmark and Finland there were age-specific differences in the type of vaccines that the cohort participants received, which could introduce

selection bias. In Denmark, people aged 70 years and older received the adjuvanted standard-dose vaccine Fluad Tetra, while those aged 65–69 years were offered the non-adjuvanted standard-dose vaccine Influvac Tetra. In addition, a subset of people aged 65 and older took part in a pragmatic clinical trial study where they were randomly allocated either the high-dose Efluelda Tetra or a standard-dose vaccine. In Finland, Fluad Tetra has been recommended and offered free of cost to all adults aged 85 years and older, while all other adults received the non-adjuvanted standard-dose vaccine Vaxigrip Tetra. Moreover, enhanced influenza vaccines were available for out-of-pocket purchase. The limited size of the cohort of high-risk individuals under 65 years of age did not allow for a meaningful estimation of brand-specific VE for any outcomes.

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

Due to data availability of only the Uppsala region in Sweden, the majority of the study population was from Denmark and Finland. We had near-real time data availability from Denmark and Finland, with follow-up until March 21, 2025 to ensure that the largest number of influenza-vaccinated were included and we had a full representation of the influenza season, without delaying reporting of results. In Sweden we were only able to receive data until January 31, 2025. However, the inclusion of Sweden demonstrates our ability to include multiple countries in a common analysis. It is likely that Sweden in a couple of years will have influenza vaccination data available on the national level. However, there are yet no decisions taken to include influenza vaccination data in the national vaccination register.

The timing of vaccination relative to influenza virus circulation could influence VE estimates. Individuals vaccinated earlier or later in the season might have experienced different levels of exposure to circulating viruses, leading to time-related heterogeneity in effects. Thus, our VE estimates should be interpreted in the specific context of the 2024/2025 season.

Only a limited proportion of individuals below 65 years of age at high risk who were eligible for influenza vaccination were vaccinated. This may have been due to the fact that individuals below 65 years of age in Denmark do not receive an invitation for influenza vaccination, and therefore they did not get vaccinated despite being in the high-risk group. Lastly, our definition of high-risk included history of one or more of the predefined comorbidities. Additional discussion on challenges, and

mitigation thereof, of brand-specific influenza vaccine effectiveness studies can be found in the ROC27 Feasibility report (19).

11.3 Interpretation

The results of our study support the moderate effectiveness of the seasonal influenza vaccines in successfully reducing laboratory-confirmed and medically attended influenza outcomes among individuals aged 65 and older, and, to a lesser extent, also below 65 years of age at high risk across three Nordic countries from October 2024 to March 2025. Our findings align well with the available evidence, which are, however, limited to short follow-up time and largely based on TND as compared to our main study design. (54–57) While much of this existing evidence relies on TND, we chose a cohort design using the TTE framework as our main study design for its feasibility across the three Nordic countries and its strength in supporting causal interpretation using comprehensive register data including providing both relative and absolute measures of vaccine effectiveness. Unlike TND, which is restricted to individuals who seek testing and was only feasible in Denmark, the TTE approach allows for broader population-level inclusion and evaluation of a wider range of outcomes, including those not directly linked to testing. (19)

Our overall VE estimates are in line with recent European studies. Rose et al. reported interim VE estimates from eight European studies covering 17 countries during the same 2024–2025 season during a period up to 31 January 2025. (54) Their findings, based on a test-negative study design, indicated VE ranging from 40–53% in primary care and 34–52% in hospital settings for all ages, with generally lower estimates in older adults, especially against A(H3N2), the dominant subtype this season. Specifically, for Denmark, the estimated VE from hospital settings in their study against all laboratory confirmed influenza was 44% (28 to 57) in the 18-64 years-olds, and 55% (47 to 62) among people aged 65 years and older. (54)

Overall, in our study with a study period until 21 March 2025, we observed lower VE in both cohorts compared to the study by Rose et al. (54) We estimated VE of 12.4% (3.7 to 21.1) among the 18-64 years-olds, and 39.7% (36.1 to 43.2) among those aged ≥65 years, against overall-laboratory confirmed influenza, based on our TTE. This could be due to a different case definition applied in their study, which conditioned on sudden onset of symptoms with fever, myalgia and respiratory symptoms among hospitalised patients, compared to only a positive test in our study, or the fact that we have a longer study period. At day 84, we observed similar VE of 50.9% (43.7 to 58.2) among those aged ≥65 years. Moreover, we observed higher VE of 63.7% against influenza B than against influenza A

among those aged ≥65 years, and VE of 46.2% (24.2 to 68.1) among the 18-64 years-olds, although circulation of B viruses was limited this season. (54)

Furthermore, our findings can also be interpreted in the context of a multicentre VEBIS study by Maurel et al.**,** which assessed influenza vaccines effectiveness in the 2022–2023 season using a large test-negative study across 10 European countries. (55) Against influenza A, overall VE was 39% (31 to 46), including 40% (29 to 49) among 15–64-year-olds and 30% (11 to 44) among those aged ≥65 years. We estimated VE of 6.9% among the below 65 years-olds at high risk based on our TTE, which is substantially lower.

This difference may be due to the choice of our main study design as compared to the test-negative study design. In the TND, the healthcare seeking behaviour and access to testing for influenza among the study participants is expected to be relatively high as compared to the general population. In the high-risk population, if those vaccinated also tend to get tested more, this could explain the discrepancy we observe between the matched cohort design and the TND in our study. In the cohort design, if vaccinated are tested more, this can lead to an underestimate of VE. In contrast, in the TND, testing more can lead to a proportionally larger group of vaccinated among the controls (those that test-negative). This can lead to an overestimate of the VE. It is likely that the true estimate lies in between the 12.4% and the 36.6%.

Furthermore, the lower estimated VE among the younger adults at high risk as compared to those aged ≥65 years may reflect greater immune responsiveness in older adults due to the use of enhanced vaccines (high dose, adjuvanted) this season in the Nordic countries.

Our main VE estimates against influenza A (38.1%) as well as our VE estimate using a test-negative design against laboratory-confirmed influenza (39.5%) in individuals aged ≥65 years, were slightly higher than the estimates in the VEBIS study. (55)

This divergence is further illustrated in the most recent VEBIS interim report for the 2023/24 season, which reported VE against influenza A of 39% in primary care settings and 36% in hospital settings among individuals aged ≥65 years, which was lower compared to the VE they estimated for younger adults in the same settings. In contrast, our study showed higher VE in the older group, suggesting that timely access to enhanced vaccines and high coverage in the Nordic countries may yield improved real-world effectiveness.(56)

Our findings also build on previous evidence from Halme et al., who assessed trivalent influenza VE across seasons 2015-2018 in Finnish seniors comparing active test-negative and register-based designs. (57) Their reported VE for register-based cohorts (register-based TND and cohort design) ranged from 13% to 48% in seasons 2015-2018, depending on the dominant strain and season. In line with those results, our register-based approaches using matched comparisons and TND provided very similar estimates, demonstrating the utility of linked national health registers for timely VE monitoring. Similar to Denmark, based on the availability of near real-time nationwide register data, the register-based cohort design is the method of choice in Finland to continue the annual surveillance of influenza vaccine effectiveness.

A key strength of our study is the availability of brand-specific estimates for the primary outcomes in the cohort of individuals aged ≥65 years. A systematic review of nine real world evidence studies (7 February 2020 to 6 September 2021) comprising approximately 53 million participants, highlight the public health importance of adjuvanted and high-dose vaccines in the prevention of influenza. (58) The study showed that an adjuvanted trivalent influenza vaccine was more effective than conventional influenza vaccines and equally effective as high-dose influenza vaccine in reducing influenza-related outcomes in adults aged ≥65 years over several consecutive influenza seasons. (58)

Our findings are also consistent with those of Stuurman et al., who evaluated brand-specific influenza VE as part of the DRIVE project during the 2021–2022 season. (59) Despite limited virus circulation during the COVID-19 pandemic, the study highlighted the feasibility of brand-level VE monitoring across Europe. While point estimates were imprecise in older adults due to low case numbers, and adjuvanted or high-dose vaccines were unavailable, VE for Vaxigrip Tetra reached up to 81% in some settings. (59) Our study extends this work by providing more precise, season-specific estimates during a period of active influenza circulation and broad vaccine use. Overall, The Nordic health registries together with appropriate methodology provide a strong foundation for conducting timely brand-specific influenza VE studies, that can support vaccination strategy evaluations and inform public health and regulatory decision-making.

Triangulation of results

To assess the robustness of our findings and strengthen causal interpretation, we conducted several supplementary analyses alongside the main target trial emulation. Across designs, the findings were directionally similar and support the conclusion that seasonal influenza vaccination was effective in reducing the risk of influenza and its complications among individuals aged 65 and older, although there were some method-dependent discrepancies.

The observation of substantial VE in the 0-13 days post-vaccination, including a notably high VE against hospitalization 81.9% (54.0 to 100.0), warrants careful interpretation regarding bias. Given that this period precedes full immunity and hospitalisation occurs days after infection, this early effect likely reflects selection rather than direct vaccine protection or strong bias. Symptomatic individuals will likely postpone vaccination, disproportionately removing those already progressing towards testing and hospitalization from the vaccinated cohort. It is possible that some of this observed early effect, may be transient and not fully persist throughout the entire follow-up period. However, we cannot exclude the possibility that some of the effect reflects consistent differences between recipients and non-recipients, which biases the influenza VE results upwards.

The test-negative design analysis yielded VE estimate of 39.5%—nearly identical to the TTE estimate of 39.7% (39.0% for Denmark)—providing reassurance against confounding by healthcare-seeking behaviour. The prior event rate ratio analysis further supported a protective association, adjusting for baseline risk differences, although not significantly, likely due to a low number of events.

The regression discontinuity analysis, while showing an increase in vaccine uptake at the age 65 eligibility threshold—most so in Denmark—did not detect a significant effect on hospitalisation. This likely reflects low event rates and limited power within the narrow age band, rather than a contradiction of the main findings.

When considering all-cause mortality, we caution against using it as a negative control outcome for influenza vaccine effectiveness studies. It is highly unlikely that the specific set and strength of unmeasured confounders for the association between vaccination and all-cause mortality are the same as those for the association between vaccination and influenza outcomes. Therefore, while the VE against all-cause mortality is highly likely to be biased upwards, the VE estimate against all-cause mortality itself is difficult to use for direct calibration due to the likely divergence in confounding structures. However, we cannot exclude that the biased effect on all-cause mortality is also reflected to some extent in the influenza VE estimates.

The findings on diverticulitis and lower back pain, suggest residual confounding, potentially related to differences in healthcare-seeking behaviour or underlying health status, which could bias the influenza VE results towards underestimating vaccine protection. The finding on clavicle fractures, suggest residual confounding acting in the opposite direction, potentially indicative of a 'healthy vaccinee effect' where vaccinated individuals may be healthier or less prone to injury than their unvaccinated counterparts. Such confounding could bias the influenza VE results towards overestimating vaccine protection.

Negative control outcomes are useful for gauging the potential for confounding and bias. However, we caution against the use of these negative control outcome VE estimates for direct calibration of the influenza VE results (60). Such calibration would rely on the critical assumption that the specific unmeasured confounding factors associated with the negative control outcomes are the same, and act with the same strength, as those associated with the risk of influenza itself. The diverging results for the different negative control outcomes make this assumption questionable.

Our analyses of negative control outcomes and all-cause mortality reveal that seasonal vaccine recipients and non-recipients in the Nordic countries are not similar with respect to factors not included in our study. As mentioned above, the degree to which this reflects confounding in our influenza specific estimates is not clear. However, the direction of bias is most likely to be towards overestimating the effectiveness against influenza outcomes in the 65+-yr-olds. For the high-risk group, differences in testing practices are more likely to produce measurable confounding, as witnessed by the discrepancy between the VE from the matched cohort analysis and the VE from the TND.

Overall, these complementary analytical approaches indicated moderate protection from seasonal influenza vaccination among individuals aged 65 and older in the 2024–2025 season. The protection in the high-risk 18-64 age group is likely lower, and caution is emphasized when interpreting VE estimates for this group due to the method-dependent discrepancies in results that we have observed.

11.4 Generalizability

Given the broad inclusion of data within Denmark and Finland, and partly Sweden, our results likely have a high degree of generalizability to other populations with similar demographics and healthcare systems. However, our results pertain specifically to the 2024/2025 influenza season, reflecting both the circulating strains, the particular influenza activity of that period and the timing of the vaccination program roll-outs in relation to the peak of the influenza burden. As such, these findings cannot be directly extended beyond this specific season, and we advise that vaccine effectiveness evaluations such as ours are routinely conducted for each influenza season. Furthermore, they may not directly generalize to subpopulations not individually studied or to populations with markedly different demographic compositions. For instance, individuals younger than 65 years of age who are not at risk of severe influenza outcomes which includes both health-care workers and individuals offered employer-sponsored vaccinations.

12. OTHER INFORMATION

None.

13. CONCLUSION

This multi-country register-based study provides estimates of influenza VE in the elderly and among high-risk groups during the 2024/2025 season in the Nordic region, including by vaccine brand. Seasonal influenza vaccination was moderately effective in reducing the risk of laboratory-confirmed influenza and severe outcomes—particularly among individuals aged ≥65 years, with adjuvanted and high-dose vaccines offering superior protection. VE among high-risk adults under 65 years was lower, possibly reflecting different testing practices. These findings reinforce the value of enhanced vaccines for older adults. Continued annual monitoring using Nordic health registries remains crucial for informing evidence-based vaccination strategies and regulatory decision-making.

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