Study Report

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DARWIN EU® - Proof-of-concept: Preparedness for annual seasonal influenza vaccine effectiveness studies - Vaccine coverage and incidence of influenza-related outcomes

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Version 3.0

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Public

CONTENTS

Study title	DARWIN EU® - Proof-of-concept: Preparedness for annual seasonal influenza vaccine effectiveness studies - Vaccine coverage and incidence of influenza-related outcomes
Study report version	V3.0
Date	10/02/2025
EUPAS number	EUPAS1000000803
Active substance	Influenza vaccine (ATC: J07BB)
Medicinal product	Not applicable
Research question and objectives	The aim of this study was to assess the availability, quality, and completeness of fit-for-purpose data sources that record seasonal influenza vaccine exposure, including brand where available, as well as influenza-related clinical outcomes and covariates relevant for influenza vaccine effectiveness studies. The specific objectives of this study were: 1. To estimate the period prevalence of influenza vaccination in the general population for each influenza season from 2015/16 to 2023/24, overall and stratified by age group and sex. 2. To characterise influenza vaccine use within each influenza season by month of vaccination, vaccine brand, and route of administration, stratified by age group and sex. 3. To describe the baseline demographic characteristics, comorbidities, immunocompromised status, and receipt of other vaccinations of individuals receiving any influenza vaccine in each influenza season. 4. To describe the background incidence rates of influenza-related clinical outcomes, hospitalisations, and deaths in the general population, and crude incidence rates of influenza-related clinical outcomes, hospitalisations, and deaths in the vaccinated and unvaccinated populations, overall and stratified by age group and sex in each influenza season.
Countries of study	Croatia, Denmark, Finland, Norway, Spain, The United Kingdom
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LIST OF ABBREVIATIONS

Acronyms/term	Description
AIDS	Acquired immunodeficiency syndrome
ARI	Acute Respiratory Infection
ATC	Anatomical Therapeutic Chemical
CC	Coordination centre
CDM	Common Data Model
CI	Confidence Intervals
CPRD GOLD	Clinical Practice Research Datalink GOLD
DARWIN EU®	Data Analysis and Real-World Interrogation Network
DK-DHR	Danish Data Health Registries
ECDC	European Centre for Disease Prevention and Control
EHR	Electronic Health Records
EMA	European Medicines Agency
EU	European Union
EUPAS	EU Post-Authorisation Studies Register
FinOMOP-THL	Finnish Care Register for Health Care
GDPR	General Data Protection Regulation
GP	General Practitioner
HIV	Human immunodeficiency virus
ICD	International Classification of Diseases
IQR	Interquartile Range
ILI	Influenza-Like Illness
IP	Inpatient
IRB	Institutional Review Board
IVE	Influenza Vaccine Effectiveness
NAJS	Croatian National Public Health Information System
NLHR	Norwegian Linked Health Registry data
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
OP	Outpatient
RSV	Respiratory Syncytial Virus
RxNorm	Medical prescription normalised
SARI	Severe Acute Respiratory Infection
SIDIAP	The Information System for Research in Primary Care
SNOMED	Systematized Nomenclature of Medicine

Acronyms/term	Description
UK	The United Kingdom
VEBIS	Vaccine Effectiveness, Burden, and Impact Studies
VMP	Vaccine Monitoring Platform
WHO	World Health Organisation

1. TITLE

DARWIN EU® - Proof-of-concept: Preparedness for annual seasonal influenza vaccine effectiveness studies - Vaccine coverage and incidence of influenza-related outcomes

2. DESCRIPTION OF THE STUDY TEAM

Study team role	Names	Organisation
Principal Investigator	Anna Saura-Lazaro Amy Lam	University of Oxford
Data Scientist	Marta Alcalde-Herraiz Edward Burn	University of Oxford
Clinical Domain Expert	Albert Prats-Uribe	University of Oxford
Study Manager	Natasha Yefimenko	Erasmus MC
Data source	**Names**	**Data Partner Organisation***
NAJS	Jakov Vuković Anamaria Jurčević Ivan Pristaš Marko Čavlina Karlo Pintarić Antea Jezidžić Helena Ivanković	Croatian Institute of Public Health
DK-DHR	Elvira Bräuner Susanne Bruun	Danish Medicines Agency
FinOMOP-THL	Toni Lehtonen Laura Salonen Petteri Hovi Toni Susi	Finnish Institute for Health and Welfare
NLHR	Hedvig Marie Egeland Nordeng Saeed Hayati Nhung Trinh	University of Oslo
SIDIAP	Agustina Giuliodori Picco Irene López Sánchez Laura Granés González Anna Palomar Cros	IDIAP JGol
CPRD GOLD	Antonella Delmestri	University of Oxford

*Data partners do not have an investigator role. Data partners execute code at their data source, review, and approve their results.

3. ABSTRACT

Title

DARWIN EU® - Proof-of-concept: Preparedness for annual seasonal influenza vaccine effectiveness studies - Vaccine coverage and incidence of influenza-related outcomes

Rationale and background

Revisions to the European Medicines Agency (EMA) Guideline on Influenza Vaccines, generating robust real-world evidence on influenza vaccine effectiveness (IVE) has become a priority. This study assessed the feasibility of using DARWIN EU® data sources to conduct annual IVE studies and to understand the extent to which these data sources can reliably capture influenza vaccination, brand information, relevant covariates, and influenza-related outcomes.

Research question and objectives

The study aimed to assess the availability, quality, and completeness of seasonal influenza vaccine-related information across multiple data sources to inform potential future IVE studies. Specific objectives were to:

1. Estimate the period prevalence of seasonal influenza vaccination in the general population.
2. Characterise influenza vaccine use, including month of vaccination, brand, and administration route.
3. Describe demographic and clinical characteristics of influenza vaccine recipients.
4. Describe background incidence rates of influenza-related clinical outcomes, hospitalisations, and deaths in the general population, and crude rates in vaccinated and unvaccinated populations.

Methods

Study design

- Population-level drug utilisation study (Objective 1)
- Patient-level characterisation (Objective 2 and 3)
- Population-level descriptive epidemiology study (Objective 4)

Population

The study included all individuals present in each data source for at least one influenza season during the period 01/10/2015–30/04/2024 (or the end of available data). Individuals with missing age or sex were excluded. For Objective 3, individuals required to have ≥365 days of prior observation, and for Objective 4, ≥28 days.

Variables

Exposure (Objective 2-4): Influenza vaccine

Outcome (Objective 1): Receipt of influenza vaccine

Outcome (Objective 4): Primary outcomes: symptom-based clinical syndromes (Influenza-like illness (ILI), acute respiratory infection (ARI), and severe acute respiratory infection (SARI)), all-cause and respiratory/influenza-related hospitalisation, and all-cause and respiratory/influenza-related death; secondary outcomes: diagnosis-based acute respiratory infections (broader definition) and influenza

Covariates for characterisation (Objective 2): Month of vaccination, vaccine brand, route of administration

Covariates for characterisation (Objective 3): Demographics, comorbidities, receipt of other vaccines

Covariates for stratification (Objective 1, 2, and 4): Age group (<6 years, 6–17 years, 18–64 years, ≥65 years), sex

Statistical analysis

Influenza vaccination prevalence (Objective 1) was calculated as annual period prevalence with binomial 95% confidence intervals. Vaccine use and type (Objective 2) and characteristics of vaccine recipients (Objective 3) were summarised using counts and proportions. Background incidence rates of influenza-related outcomes in the general population and crude rates in vaccinated and unvaccinated groups (Objective 4) were estimated per 100,000 person-years with 95% Poisson confidence intervals, with a 28-day washout applied for repeated outcomes (except death). Analyses used the *IncidencePrevalence* and *CohortCharacteristics* R packages, applying a minimum cell count of <5.

Data sources

1. Croatia: Croatian National Public Health Information System (NAJS)
2. Denmark: Danish Data Health Registries (DK-DHR)
3. Finland: Finnish Care Register for Health Care (FinOMOP-THL)
4. Norway: Norwegian Linked Health Registry data (NLHR)
5. Spain: The Information System for Research in Primary Care (SIDIAP)
6. The United Kingdom: Clinical Practice Research Datalink GOLD (CPRD GOLD)

Study size

No sample size was calculated, as this was a descriptive study which did not test a specific hypothesis. Based on a preliminary feasibility assessment, the expected number of record counts for influenza vaccine ranged from 2,533,000 (NAJS) to 29,155,500 (CPRD GOLD).

Results

Influenza vaccination prevalence ranged between approximately 11% and 22% from 2015/16 to 2019/20 across data sources, with small increases over time in DK-DHR and FinOMOP-THL and more stable trends in SIDIAP and CPRD GOLD. A marked increase occurred during the COVID-19 pandemic, beginning in 2020/21 in DK-DHR, FinOMOP-THL, NLHR, and SIDIAP and in 2021/22 in CPRD GOLD, reaching approximately 30% in some data sources. Prevalence subsequently declined but generally remained slightly above pre-pandemic levels. The highest prevalence was recorded in FinOMOP-THL and the lowest was observed in NAJS. Adults ≥65 years consistently showed the highest prevalence (>50% since 2020/21, except in NAJS, where the maximum was 27%). Prevalence among children <6 years increased in DK-DHR but remained stable or declined slightly elsewhere. NAJS and NLHR reported the lowest vaccination levels among children <6 years. Most vaccinations were administered between October and December. Complete brand information was available only in DK-DHR and FinOMOP-THL, and complete route information in these two and NAJS. Most vaccines were administered by injection, with nasal formulations used mainly in children <6 years. Vaccine recipients were predominantly older adults (median age 60–72 years) and female (53–59%). Common comorbidities included hypertension (20–81%), cardiac conditions (13–50%), diabetes mellitus (11–35%), asthma (8–24%), and cancer (9–25%), consistent with targeted risk groups. Pneumococcal vaccination was the most commonly observed prior vaccination. Co-administration of influenza and COVID-19 vaccines increased markedly from 2021/22 and peaked during 2021–2023, declining thereafter.

Among influenza-related clinical outcomes, ARI, followed by diagnosis-based acute respiratory infection (broader definition), were the most frequently recorded, whereas ILI, SARI, and influenza diagnoses were rare. Incidence rates of respiratory outcomes were generally stable over time, except for a notable drop in 2020/21 in most data sources. Rates were highest among older adults (≥65 years) and young children (<6

years), as well as in females for most respiratory outcomes. All-cause hospitalisation and death were largely stable, with slight increases in mortality between 2019 and 2022 in several data sources. Hospitalisation was more common among females, while death was generally more common among males, and both outcomes occurred more frequently among older adults. Influenza-related hospitalisation and death were infrequent.

Discussion

This study demonstrates that several European data sources within DARWIN EU® have sufficiently detailed information to monitor influenza vaccination prevalence and influenza-related clinical outcomes. Consistent temporal trends with pandemic-related surge and alignment with World Health Organisation estimates support the reliability of the underlying data. Complete brand and route information was limited to a subset of data sources, and symptom-based outcomes, such as ARI, were generally captured more frequently than diagnosis-based outcomes. The low frequency of ILI and influenza diagnoses likely reflects restrictive clinical definitions and limited laboratory confirmation.

For future IVE studies, data sources with complete brand and route information or robust hospital linkage may be especially valuable for analyses requiring product-specific or severe-outcome assessment. Continued refinement of phenotypes and harmonisation of outcome definitions across data partners are crucial to ensure comparability. Symptom-based outcomes may help mitigate this variability, given their reduced dependence on clinical judgement and coding compared to diagnosis-based outcomes. Taken together, these considerations may enhance the ability of these data sources to contribute high-quality, policy-relevant IVE evidence in Europe.

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Study deliverable	Timelines (planned)	Timelines (actual)
Final Study Protocol	September 2025	29 August 2025
Creation of Analytical code	September 2025	21 September 2025
Execution of Analytical Code on the data	October 2025	16 October 2025
Draft Study Report	December 2025	10 December 2025
Final Study Report	January 2025	To be confirmed by EMA

6. RATIONALE AND BACKGROUND

In 2016, during the revision of the European Medicines Agency (EMA) Guideline on Influenza Vaccines[1] by the Vaccine Working Party and the Committee for Medicinal Products for Human Use, European experts agreed that the optimal way to monitor the performance of influenza vaccines was to generate high-quality vaccine effectiveness data. Given that vaccine composition is adapted annually to match circulating strains, and that small clinical trials on immunogenicity and safety are not always informative, non-interventional influenza vaccine effectiveness (IVE) studies can provide insights into how protective the vaccines are in real-world settings, including in populations not included in these trials. Results of IVE studies may also provide additional information to indicate specific concerns, which may trigger public health and regulatory actions.

Several European public initiatives and public-private partnerships have attempted to generate robust IVE data.[2-5] Providing annual evidence specific for each brand has proven challenging due to several factors:

(a) unpredictable use of several brands in a fragmented influenza vaccine market within the European Union (EU); (b) issues with reaching a sufficient sample size in individual data sources for meaningful evidence from prospective studies; and (c) challenges for vaccine manufacturers in accessing data, including exposure data held by public health agencies.

The research agenda of the Vaccine Monitoring Platform (VMP), a collaboration between the European Medicines Agency (EMA) and the European Centre for Disease Prevention and Control (ECDC), includes several research questions indicating the need for real-world evidence on influenza vaccines.[6] This study contributed to informing the EMA on the feasibility to conducting IVE studies within the DARWIN EU® network. The aim of such IVE studies was to provide robust evidence to support decision-making by the EMA and the EMA Emergency Task Force.

To address the research need arising from the background outlined above, this study assessed the prevalence of influenza vaccination across participating data sources for each influenza season, with particular interest in information of influenza vaccines.. Influenza season is typically defined as October to April. **Table 1** summarises national influenza vaccination recommendations in selected European countries, highlighting age groups and clinical indications to guide study age stratification and patient characterisation. The study also investigated the availability of records in terms of influenza-related outcomes to inform feasibility of future IVE studies.

Table 1. Recommendation on influenza vaccination in selected European countries.

Country	Paediatric population	Elderly population	Special population with clinical relevance
Croatia (as of Nov 2023) [7]	- 6 months to 18 years of age who receive long-term therapy with drugs containing acetylsalicylic acid	- 65 years of age and above	- Pregnant individuals - Individuals with chronic diseases [a]
Denmark (as of June 2023) [8]	- 2 to 6 years of age	- 65 years of age and above	- Pregnant individuals - Chronically ill individuals [b]
Finland (as of June 2025) [9]	- 6 months to 6 years of age	- 65 years of age and above	- Pregnant individuals - Individuals at risk due to illness or treatment
Norway (as of August 2024) [10]	- Premature at birth from 6 months to 5 years of age	- 65 years of age and above	- Pregnant individuals - Individuals with chronic clinical conditions [c]
Spain (as of July 2024) [11]	- 6 to 59 months of age - 5 to 18 years of age with higher risk of complications - 5 to 18 years of age who receive long-term treatment with acetylsalicylic acid	- 60 years of age or above	- Pregnant individuals - Women up to 6 months postpartum and without vaccination during pregnancy - Adults, up to 59 years of age, with risk conditions [d] - Smokers - Individuals with celiac disease. - Cerebrospinal fluid fistula and cochlear implant (or waiting for one)

Country	Paediatric population	Elderly population	Special population with clinical relevance
The United Kingdom (as of August 2024) [12]	- 2 to 3 years of age - Eligible school aged children, from reception (4/5 years of age) to year 11 (15/16 years of age)	- 65 years of age and above	- Pregnant individuals - Individuals aged 6 months or older within clinical risk groups [e]

a. Chronic diseases include heart and lung diseases, chronic metabolic diseases (including diabetes mellitus), chronic kidney disease, haemoglobinopathies and immune system impairment (including human immunodeficiency virus (HIV) infection), and, especially in children, impaired lung function (cystic fibrosis, chronic asthma, bronchopulmonary dysplasia) and congenital defects.

b. Chronically ill individuals include chronic lung diseases, cardiovascular diseases (except isolated, well-regulated high blood pressure), diabetes type 1 or 2, congenital or acquired immunodeficiency, e.g., individuals with immunoglobulin deficiencies, organ or stem cell transplantation, cancer in treatment with chemotherapy, or individuals undergoing other immunosuppressive treatment, impaired respiration due to reduced muscle strength, chronic liver or kidney disease, chronic diseases where the condition means that influenza or COVID-19 poses a serious health risk, e.g., individuals with severe rheumatological syndrome, severe neurological disease or short bowel syndrome, obesity (BMI>35), other serious diseases or conditions that mean that influenza or COVID-19 poses a serious health risk, e.g., individuals with severe mental illness, Down syndrome, or severe substance abuse.

c. Chronic clinical conditions include chronic lung disease (including asthma), cardiovascular disease (other than well-regulated high blood pressure), type 1 or type 2 diabetes, liver failure or renal failure, chronic neurological disease or injury, impaired immune function due to disease or treatment (e.g., organ transplant, cancer, HIV, rheumatoid arthritis, and other diseases), morbid obesity (body mass index over 40), other serious or chronic diseases where influenza is a serious health risk, after individual assessment by a doctor (e.g., individuals with congenital chromosomal abnormalities, genetic syndromes, and complex chromosomal abnormalities not classified elsewhere).

d. Risk conditions include diabetes mellitus and Cushing's syndrome, morbid obesity (body mass index ≥40 in adults, ≥35 in adolescents, or ≥3 standard deviations in childhood), chronic cardiovascular, neurological, or respiratory diseases, including bronchopulmonary dysplasia, cystic fibrosis, and asthma, chronic kidney disease and nephrotic syndrome, hemoglobinopathies and anaemias or haemophilia, other coagulation disorders and chronic haemorrhagic disorders, as well as recipients of blood-derived products and multiple transfusions, asplenia or severe splenic dysfunction, chronic liver disease, including chronic alcoholism, severe neuromuscular diseases, immunosuppression (including primary immunodeficiencies and those due to HIV infection or drugs, as well as in transplant recipients and complement deficiency), cancer and malignant blood disorders, chronic inflammatory disease, disorders and diseases that lead to cognitive dysfunction: Down syndrome, dementias, and others.

e. Clinical risk groups include chronic respiratory disease, chronic heart disease and vascular disease, chronic kidney disease, chronic liver disease, chronic neurological disease, diabetes and adrenal insufficiency, immunosuppression, asplenia or dysfunction of the spleen, and morbid obesity (class III obesity).

7. RESEARCH QUESTION AND OBJECTIVES

Research question

The aim of this study was to assess the availability, quality, and completeness of influenza vaccine-related records within selected data sources with seasonal influenza vaccine exposure, including brand, where available, as well as influenza-related clinical outcomes and covariates relevant for IVE studies.

Objectives

The specific objectives of this study were:

1. To estimate the period prevalence of influenza vaccination in the general population for each influenza season from 2015/16 to 2023/24, overall and stratified by age group and sex.
2. To characterise influenza vaccine use within each influenza season by month of vaccination, vaccine brand, and route of administration, stratified by age group and sex.

3. To describe the baseline demographic characteristics, comorbidities, immunocompromised status, and receipt of other vaccinations of individuals receiving any influenza vaccine in each influenza season.
4. To describe the background incidence rates of influenza-related clinical outcomes, hospitalisations, and deaths in the general population, and the crude incidence rates of influenza-related clinical outcomes, hospitalisations, and deaths in the vaccinated and unvaccinated populations, overall and stratified by age group and sex in each influenza season.

8. RESEARCH METHOD

8.1. Study design

A cohort study was conducted using routinely collected health data from six data sources from six countries across Europe and in five EU member states.

The study comprised of:

- Population-level drug utilisation study: assessing the period prevalence of influenza vaccination in the general population for each influenza season from 2015/16 to 2023/24 (Objective 1).
- Patient-level characterisation: assessing the use and type of influenza vaccine in terms of month of vaccination, brand, and route of administration (Objective 2); and describing baseline characteristics of influenza vaccine recipients in terms of demographics, comorbidities, immunocompromised status, as well as other vaccinations (Objective 3) for each influenza season from 2015/16 to 2023/24.
- Population-level descriptive epidemiology study: describing the background incidence of influenza-related clinical outcomes in the general population, and crude incidence of influenza-related clinical outcomes in the vaccinated and unvaccinated populations for each influenza season from 2015/16 to 2023/24 (Objective 4).

Figure 1 to **Figure 4** illustrate the Harper diagrams corresponding to each objective, with the index date (Day 0) specified in each figure.

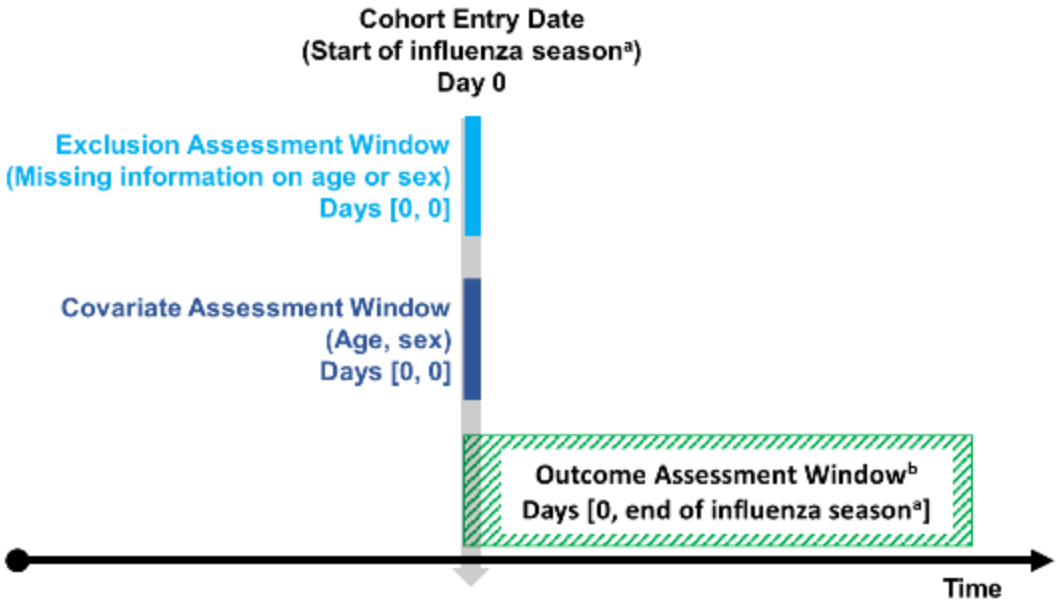


Figure 1. HARPER diagram for population-level drug utilisation study on influenza vaccine (Objective 1).

a. Influenza season was defined from 1st of October to 30th of April.
b. Outcome was defined as influenza vaccine.

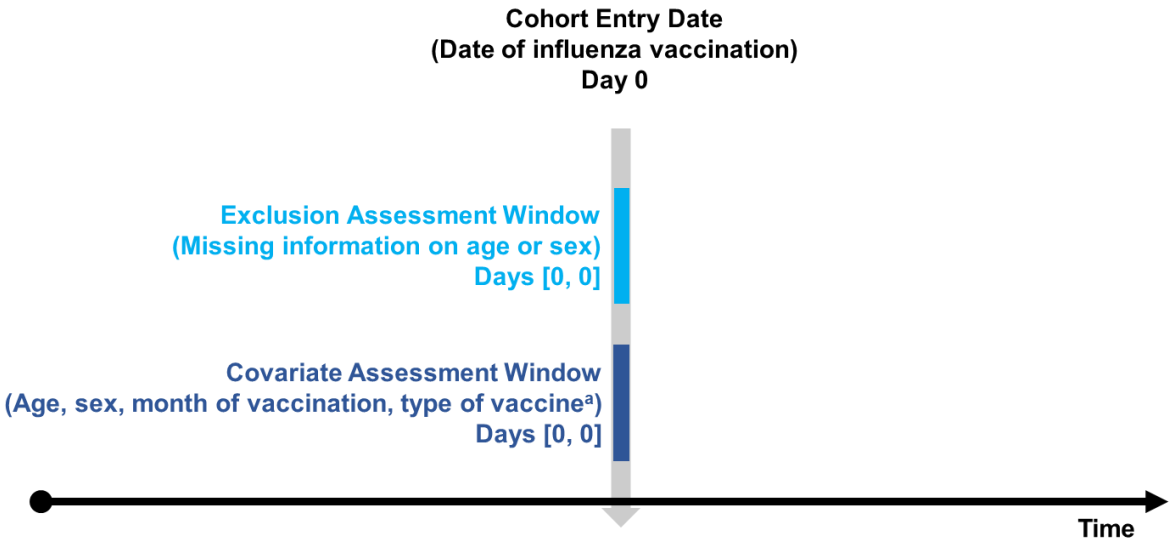


Figure 2. HARPER diagram for patient-level characterisation on use and type of influenza vaccine (Objective 2).

a. Covariates on type of vaccine include vaccine brand and route of administration.

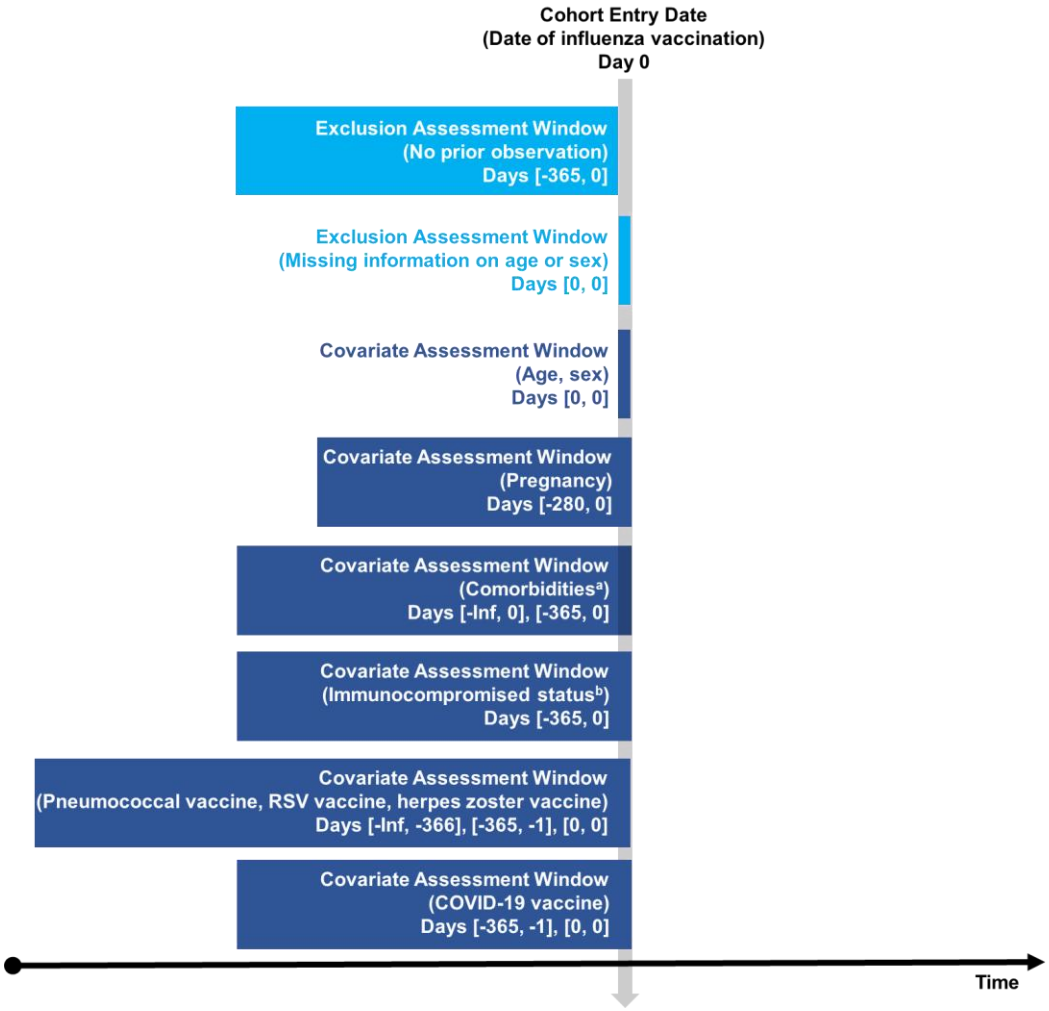


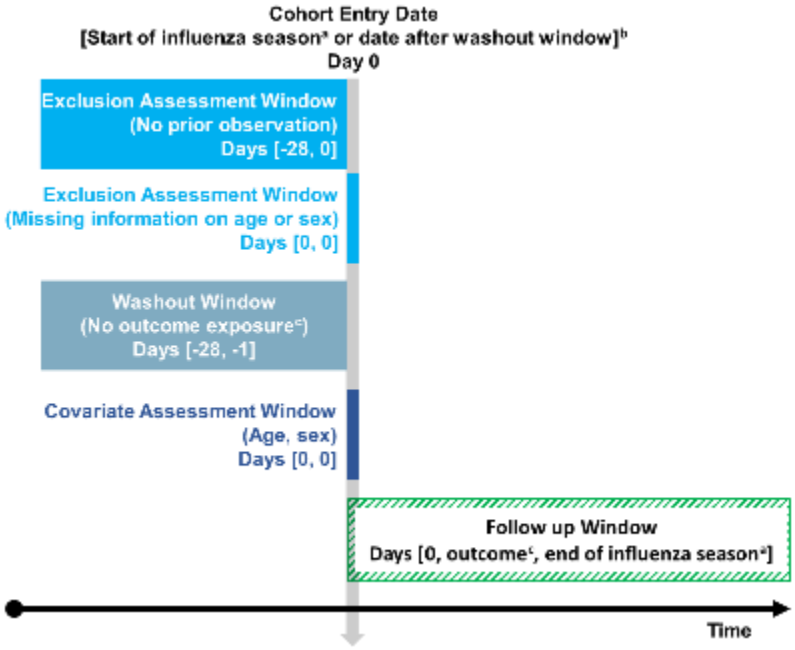
Figure 3. HARPER diagram for patient-level characterisation of influenza vaccine recipients (Objective 3).

a. Covariates of interest for patient characterisation included anaemia, asplenia, asthma, chronic liver disease, cardiovascular diseases, diabetes, hypertension, obesity, neuromuscular disorders, renal disease, dementia, stroke, rheumatological diseases, cancer, lung disease excluding asthma and chronic obstructive pulmonary disease, tuberculosis, and chronic obstructive pulmonary disease. Only anaemia, cancer, obesity, and tuberculosis were evaluated within the assessment window [-365, 0] because these conditions may represent more acute, evolving, or transient health states.

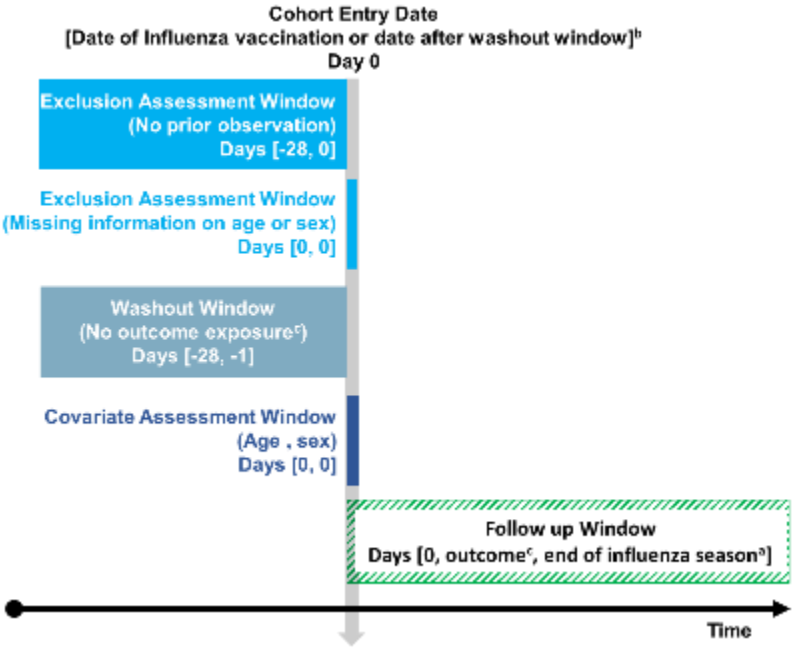
b. Immunocompromised status was defined as follows:
   - Individuals were considered immunocompromised if they have a record of any of the following conditions with assessment window [-365, 0]:
     - HIV/Acquired immunodeficiency syndrome (AIDS)
     - Haematological malignancies
     - Solid malignancies
     - Other intrinsic immune conditions
   - Individuals were also considered immunocompromised if they received antineoplastic or immunomodulating agents with assessment window [-183, 0].
   - Additionally, individuals treated with systemic corticosteroids during the same 183-day period were considered immunocompromised if they also had a record of any of the following conditions with assessment window [-365, 0] relative to the index date of receiving influenza vaccine:
     - Organ transplantation
     - Rheumatologic or inflammatory conditions, including rheumatoid arthritis, inflammatory bowel disease, or systemic lupus erythematosus

RSV= Respiratory Syncytial Virus

A


Cohort Entry Date
[Start of influenza season[a] or date after washout window][b]
Day 0
Exclusion Assessment Window
(No prior observation)
Days [-28, 0]
Exclusion Assessment Window
(Missing information on age or sex)
Days [0, 0]
Washout Window
(No outcome exposure[c])
Days [-28, -1]
Covariate Assessment Window
(Age, sex)
Days [0, 0]
Follow up Window
Days [0, outcome[c], end of influenza season[a]]
Time

B


Cohort Entry Date
[Date of Influenza vaccination or date after washout window][b]
Day 0
Exclusion Assessment Window
(No prior observation)
Days [-28, 0]
Exclusion Assessment Window
(Missing information on age or sex)
Days [0, 0]
Washout Window
(No outcome exposure[c])
Days [-28, -1]
Covariate Assessment Window
(Age , sex)
Days [0, 0]
Follow up Window
Days [0, outcome[c], end of influenza season[a]]
Time

C

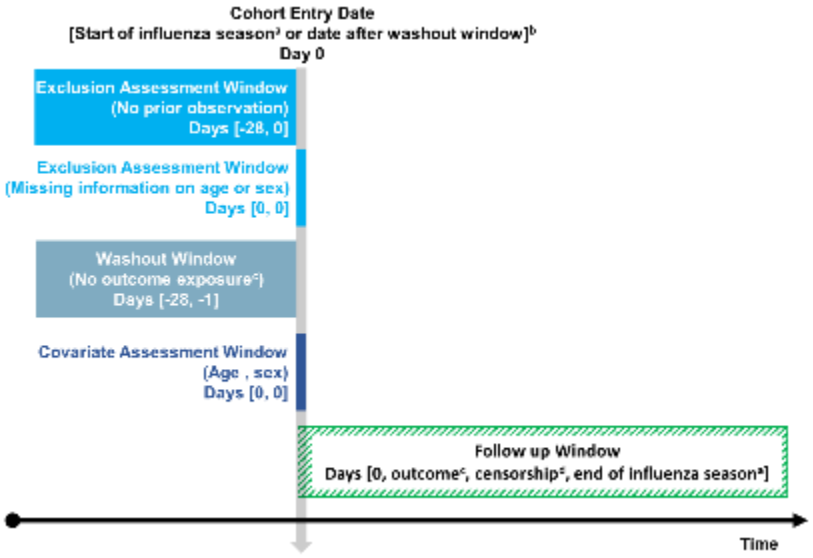


Figure 4. HARPER diagram for population-level descriptive epidemiology study of influenza-related clinical outcomes (Objective 4), in (A) general population, (B) vaccinated population, and (C) unvaccinated population.

a. Influenza season was defined from 1st of October to 30th of April.
b. Cohort entry date was defined as start of influenza season or date after washout window, whichever comes later. Re-entry of individual to denominator cohort within the same influenza season was allowed, after the post-outcome exposure washout window.
c. Outcomes included influenza-related clinical outcomes, with clinical syndromes such as influenza-like illness (ILI), acute respiratory infection (ARI), severe acute respiratory infection (SARI), hospitalisation, and death defined as primary outcomes, and condition-based records of influenza and acute respiratory infections defined as secondary outcomes.
d. Censorship was applied to unvaccinated population when individuals receive influenza vaccine.

8.2. Follow-up

Objective 1: Population-level drug utilisation on influenza vaccine

Follow-up for prevalence estimation began on the start of influenza season (1st of October), for each influenza season during the study period 2015/16–2023/24.

Follow-up ended on the end of the influenza season (30th April), for each influenza season during the study period 2015/16–2023/24.

Prevalence required an appropriate denominator population and contributed observation time to first be identified. Study participants in the denominator population began contributing person time-at-risk, as described above. Prevalence was only estimated for those intervals where the data source captured the complete interval, that is, prevalence of the influenza season was only estimated when the data source is in observation for the entire influenza season. Prevalence was also only estimated in individuals who were present in the data source throughout the entire influenza season.

An example of entry and exit into the denominator population is shown in **Figure 5**. In this example, person ID 1 started the observation period before the start of the influenza season and the observation period ended after the end of the influenza season, so this person contributed the complete study period, and was included in the denominator for this influenza season. Person IDs 2, 3, and 4 either started the observation period after the start of the influenza season or end the observation period before the end of influenza season. These three individuals did not have complete observation periods throughout the entire influenza season and therefore did not contribute to the denominator cohort for this influenza season. Lastly, person ID 5 had two observation periods in the data source, where the observation period was not complete for this influenza season. Person ID 5 did not contribute to the denominator cohort for this influenza season.

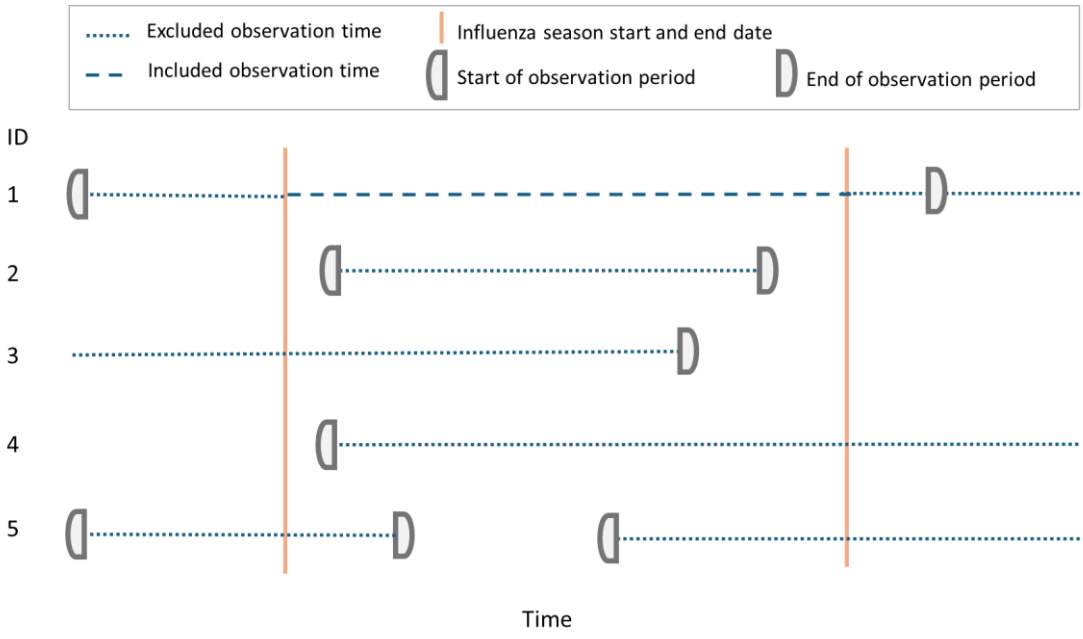


Figure 5. Included observation time for the denominator population for population-level drug utilisation on influenza vaccine (Objective 1).

Objective 4: Population-level descriptive epidemiology of influenza-related outcomes

For the general population, follow-up for incidence estimation began, for each influenza season, on the latest of:

- the start of the influenza season (1st October), or
- the start of the individual's observation period.

Follow-up ended at the earliest of:

- the end of the influenza season (30th April),
- the end of the individual's observation period, or
- the occurrence of an outcome of interest, including death.

Multiple outcomes (other than death) could have been recorded per individual during each influenza season. A 28-day washout period was applied to avoid counting recurrent or prolonged episodes as separate events. Only outcomes of the same type occurring at least 28 days apart were considered distinct incident events.

Eligible individuals could have contributed to more than one influenza season, provided they met the inclusion criteria for each.

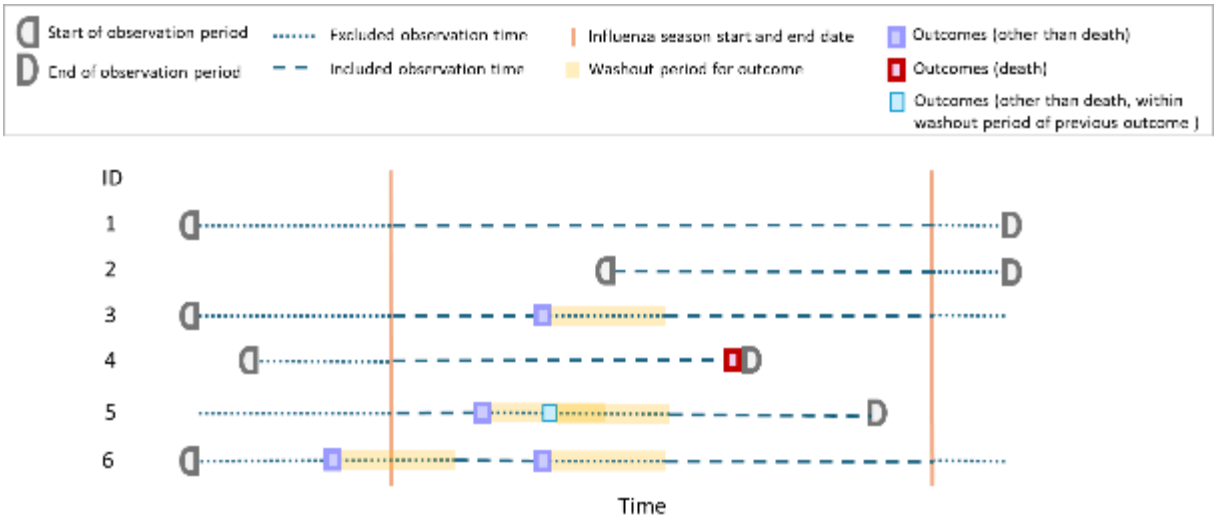
Figure 6A shows six hypothetical individuals to illustrate how follow-up and outcome assessment were conducted for incidence estimation of influenza-related outcomes in the general population. Person ID 1 was observed throughout the entire influenza season but did not experience any outcome and therefore contributed person-time only. Person ID 2 was similar but entered observation after the influenza season had already started and contributed person-time from that point onward. Person ID 3 had full observation during the season and experienced a non-fatal outcome, which is counted as an incident event. After the 28-day washout period, this individual re-entered observation time and could have contributed additional person-time. Person ID 4 contributed person-time until the date of death, which was also recorded as an outcome. Person ID 5 experienced a non-fatal outcome, followed by another similar outcome within the 28-day washout period. The second event as not considered incident, and the individual did not re-enter observation time until the washout period of that second event was completed. Finally, person ID 6 represented an individual who had an outcome before the start of the influenza season and therefore did not contribute to observation time until the washout period had been completed.

Figure 6B presents eight hypothetical individuals to illustrate how follow-up and outcome assessment were conducted in the vaccinated population. For vaccinated individuals, follow-up began on the date of influenza vaccination within each influenza season. The application of follow-up rules and time windows otherwise followed the same logic as for the general population. Follow-up ended at the earliest of: the end of the influenza season (30th April), the end of the individual's observation period, or death. As with the general population, individuals could have experienced multiple influenza-related outcomes during follow-up, provided they were separated by at least 28 days. Only outcomes of the same type occurring 28 days or more apart were considered distinct incident events. Individuals could have contributed to multiple influenza seasons if they received an influenza vaccine in more than one season and met the inclusion criteria.

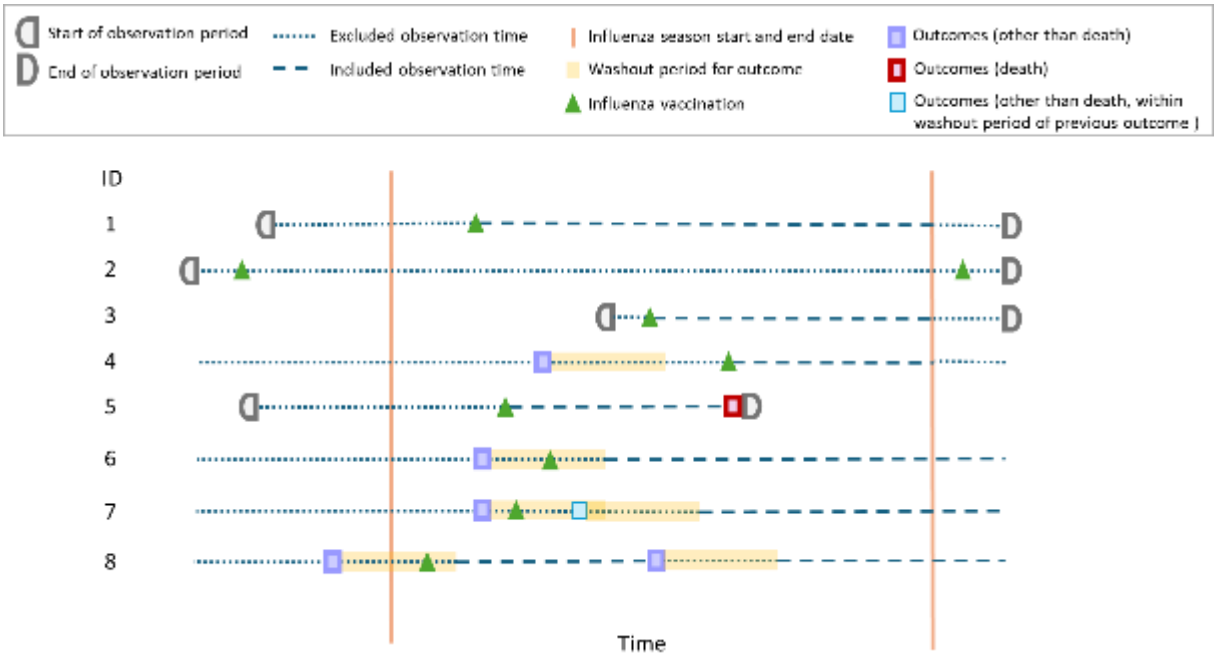
Figure 6C presents eight hypothetical individuals to illustrate how follow-up and outcome assessment were conducted in the unvaccinated population. For unvaccinated individuals, follow-up began on the start date of influenza season. The application of follow-up rules and time windows otherwise followed the same logic as for the general population. Follow-up ended at the earliest of: the end of the influenza season (30th April), the end of the individual's observation period, receipt of influenza vaccination, or death. As with the general population, individuals could have experienced multiple influenza-related outcomes during follow-

up, provided they were separated by at least 28 days. Only outcomes of the same type occurring 28 days or more apart were considered distinct incident events.

A



B



C

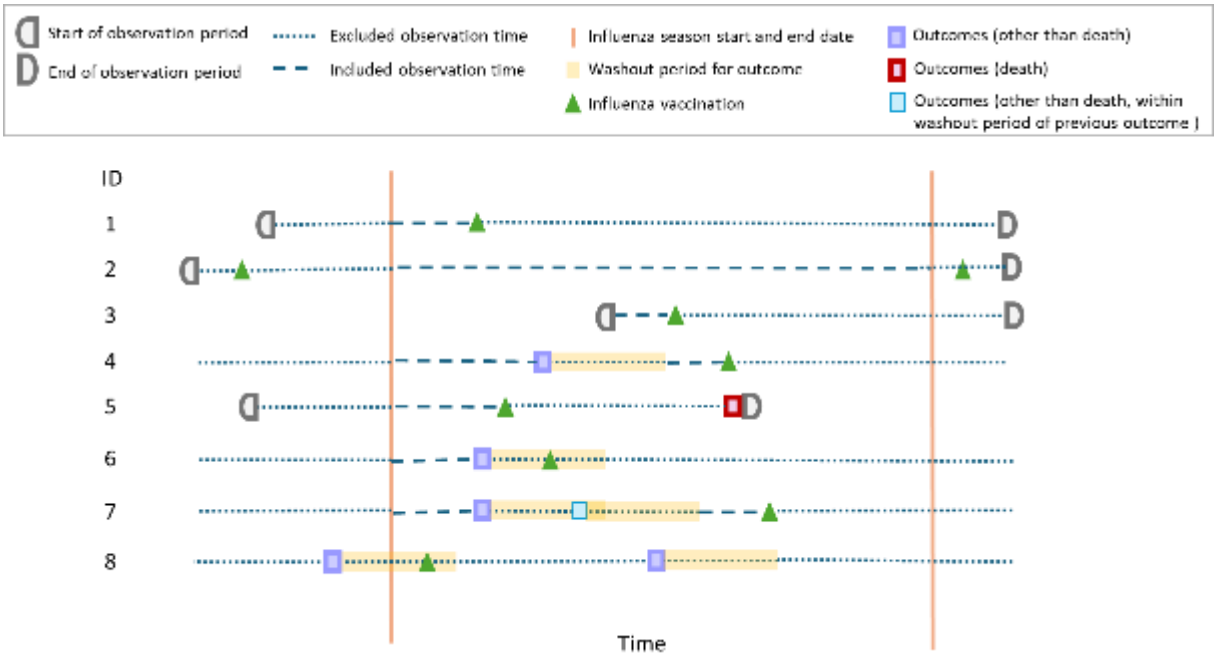


Figure 6. Included observation time for the denominator population for population-level descriptive epidemiology of respiratory infection outcome (Objective 4), in (A) general population, (B) vaccinated population, and (C) unvaccinated population.

8.3. Study population with inclusion and exclusion criteria

Objective 1: Population-level drug utilisation on influenza vaccine

Inclusion criteria

- All individuals present in each influenza season (1st October–30th April) during the study period of 01/10/2015 to 30/04/2024 (or the latest available date)

Exclusion criteria

- Individuals with missing information on sex and age

Objective 2: Patient-level characterisation on use and type of influenza vaccine

Inclusion criteria

- All individuals receiving influenza vaccine in each influenza season during the period of 01/10/2015 to 30/04/2024 (or the latest available date)

Exclusion criteria

- Individuals with missing information on sex and age

Objective 3: Patient-level characterisation of influenza vaccine recipients

Inclusion criteria

- All individuals receiving influenza vaccine in each influenza season during the period of 01/10/2015 to 30/04/2024 (or the latest available date)
- Minimum 365 days of available history before index date

Exclusion criteria

- Individuals with missing information in sex and age

Objective 4: Population-level descriptive epidemiology of influenza-related outcomes

Inclusion criteria

- All individuals with at least one of the defined influenza-related outcomes in each influenza season during the period of 01/10/2015 to 30/04/2024 (or the latest available date)

Exclusion criteria

- Individuals with missing information in sex and age

8.4. Study setting and data sources

Table 2. Data sources.

Country	Name of Data source	Health Care setting	Type of Data	Number of active individuals	Calendar period covered by each data source	Contributing to
Croatia	NAJS	Nationwide registry	EHR	4.3M	2014–01/2025	All objectives
Denmark	DK-DHR	Nationwide registry	EHR	5.98M	1995–11/2024	All objectives
Finland	FinOMOP-THL	Nationwide registry	EHR	5.7M	2011–10/2024	All objectives
Norway	NLHR	Nationwide registry	EHR	5.55M	2008–12/2023	All objectives
Spain	SIDIAP	Regional, primary care and hospital setting	EHR	5.95M	2006–06/2023	All objectives
The United Kingdom	CPRD GOLD	Nationwide, primary care	EHR	2.63M	1987–12/2024	All objectives

CPRD= Clinical Practice Research Datalink; DK-DHR= Danish Data Health Registries; EHR= Electronic Health Record; FinOMOP-THL= Finnish Care Register for Health Care; M= Million; NAJS= National Public Health Information System; NLHR= Norwegian Linked Health Registry data; SIDIAP= The Information System for Research in Primary Care

This study was conducted using routinely collected data from five nationwide registry-based data sources and one regional primary care data source with linked secondary care in the DARWIN EU® network of data partners, covering six European countries in five EU member states. All data were a priori mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM).

Data sources

1. Croatia: Croatian National Public Health Information System (NAJS)
2. Denmark: Danish Data Health Registries (DK-DHR)
3. Finland: Finnish Care Register for Health Care (FinOMOP-THL)
4. Norway: Norwegian Linked Health Registry data (NLHR)
5. Spain: The Information System for Research in Primary Care (SIDIAP)
6. The United Kingdom (UK): Clinical Practice Research Datalink GOLD (CPRD GOLD)

Data source justification and key characteristics

Croatian National Public Health Information System (NAJS)

NAJS was included in this study because it is a nation-wide registry data source that provides relevant information on the influenza vaccine coverage in the general population.

Based on a preliminary feasibility assessment, the expected number of record counts for influenza vaccine in NAJS was 2,533,000.

Moreover, data availability and follow-up in NAJS was sufficient, as data availability in NAJS started in 2014, and the date of the most recent data extraction was 01/2025 (as of 07/2025), which aligned with the study period. The median follow-up of the first observation period in NAJS was 3,640 days (Interquartile Range (IQR) 3,110–3,740), taken from portal.

There were some specific limitations present in NAJS. First, information on the brand of influenza vaccine was not available. Second, accurate vaccination data were only available from 2020 onwards with the introduction of the centralised eVaccination records. Prior to this, vaccination data were sourced from general practitioners' EHR systems, which may have been affected by underreporting. Accordingly, the study period for NAJS started in 10/2020 to 04/2024. In addition, hospitalisation data were unavailable after 2022; consequently, hospitalisation outcomes 2022/23 and 2023/24 were not presented in NAJS.

Lastly, NAJS had blanket approval, which made the execution of this study feasible within the proposed study timelines.

Danish Data Health Registries (DK-DHR)

DK-DHR was included in this study because it is a nation-wide registry data source that provides relevant information on the influenza vaccine in the general population.

Based on a preliminary feasibility assessment, the expected number of record counts for influenza vaccines in DK-DHR was 17,206,000.

Moreover, data availability and follow-up in DK-DHR was sufficient, as data availability in DK-DHR started in 1995, and the date of most recent data extraction was 11/2024 (as of 07/2025), which aligned with the study period. The median follow-up of the first observation period in DK-DHR was 7,920 days (IQR 2,610–10,900).

There were no study specific limitations present in DK-DHR.

Lastly, DK-DHR had blanket approval, which made the execution of this study feasible within the proposed study timelines.

Finnish Care Register for Health Care (FinOMOP-THL)

FinOMOP-THL was included in this study because it is a nation-wide registry data source that provides relevant information on the influenza vaccine in the general population.

Based on a preliminary feasibility assessment, the expected number of record counts for influenza vaccines in FinOMOP-THL was 15,202,400.

Moreover, data availability and follow-up in FinOMOP-THL was sufficient, as data availability in FinOMOP-THL started in 2011, and the date of most recent data extraction was 10/2024 (as of 07/2025), which aligned with the study period. The median follow-up of the first observation period in FinOMOP-THL was 5,020 days (IQR 4,030–5,020).

There were some study specific limitations present in FinOMOP-THL, namely: cause of death was not available in the data and therefore death due to a respiratory or influenza-related cause was defined as death where a clinical outcome occurred within 14 days prior.

Lastly, Institutional Review Board (IRB) approval for FinOMOP-THL was estimated to take one week, which made the execution of this study feasible within the proposed study timelines.

Norwegian Linked Health Registry data (NLHR)

NLHR was included in this study because it is a nation-wide registry data source that provides relevant information on the influenza vaccine in the general population.

Based on a preliminary feasibility assessment, the expected number of record counts for influenza vaccines in NLHR was 6,437,800.

Moreover, data availability and follow-up in NLHR was sufficient, as data availability in NLHR started in 2008, and the date of most recent data extraction was 12/2023 (as of 07/2025), which aligned with the study period. The median follow-up of the first observation period in NLHR was 5,840 days (IQR 5,230–5,840).

There were some study specific limitations present in NLHR, namely: absence of data on brand of influenza vaccine and, due to data availability, the study period for NLHR was 10/2018 to 04/2023.

Lastly, IRB approval for NLHR was estimated to take 3 weeks, which made the execution of this study feasible within the proposed study timelines.

The Information System for Research in Primary Care (SIDIAP)

SIDIAP was included in this study because it is a regional primary care and hospital data source that provides relevant information on the influenza vaccine in the general population.

Based on a preliminary feasibility assessment, the expected number of record counts for influenza vaccine in SIDIAP was 15,469,800.

Moreover, data availability and follow-up in SIDIAP was sufficient, as data availability in SIDIAP started in 2006, and the date of most recent data extraction was 06/2023 (as of 07/2025), which aligned with the study period. The median follow-up of the first observation period in SIDIAP was 5,670 days (IQR 2,220–6,390).

There were some study specific limitations present in SIDIAP, namely: absence of data on brand of influenza vaccine; cause of death not available in the data and therefore death due to a respiratory or influenza-related cause was defined as death where a clinical outcome occurred within 14 days prior; due to data availability, the study period for SIDIAP was 10/2015 to 04/2023. In addition, hospitalisation data were unavailable for the first half of 2023; consequently, hospitalisation outcomes were not shown for the 2022/23 season in SIDIAP.

Lastly, IRB approval for SIDIAP was estimated to take one month, which made the execution of this study feasible within the proposed study timelines.

Clinical Practice Research Datalink GOLD (CPRD GOLD)

CPRD GOLD was included in this study because it is a nation-wide primary care data source that provides relevant information on the influenza vaccine in the general population.

Based on a preliminary feasibility assessment, the expected number of record counts for influenza vaccine in CPRD GOLD was 29,155,500.

Moreover, data availability and follow-up in CPRD GOLD was sufficient, as data availability in CPRD GOLD started in 1987, and the date of most recent data extraction was 12/2024 (as of 07/2025), which aligned with the study period. The median follow-up of the first observation period in CPRD GOLD was 2,150 days (IQR 727–4,930).

There were some study specific limitations present in CPRD GOLD, namely: absence of data on brand of influenza vaccine; cause of death not available in the data and therefore death due to a respiratory or influenza-related cause was defined as death where a clinical outcome occurred within 14 days prior; no hospitalisation data available in CPRD GOLD and therefore, outcome of SARI and hospitalisation were assessed in objective 4.

Lastly, IRB approval for CPRD GOLD was estimated to take one week, which made the execution of this study feasible within the proposed study timelines.

Information on the data sources used in this study is provided in **ANNEXES I and II**.

8.5. Study period

The study period was from 01/10/2015 to 30/04/2024, or up to the most recent influenza season with complete data for the full interval in each contributing data source. In the NAJS data source, accurate vaccination data only became available from 2020 with the start of the centralised eVaccination records; therefore, the study period for NAJS began on 01/10/2020. Similarly, in the NLHR data source, accurate drug data only became available from 2018; therefore, the study period for NLHR began on 01/10/2018. For NLHR and SIDIAP, the study period ended on 30/04/2023.

8.6. Variables

8.6.1. Exposure

Objective 2: Patient-level characterisation on use and type of influenza vaccine

In this objective, exposure to the influenza vaccine was defined as the presence of a record for an influenza vaccine. In case of multiple records identified for the same individuals within a given influenza season, only the first recorded vaccination was considered.

Objective 3: Patient-level characterisation of influenza vaccine recipients

In this objective, exposure to the influenza vaccine was defined as the presence of a record for an influenza vaccine. In case of multiple records identified for the same individuals within a given influenza season, only the first recorded vaccination was considered.

Objective 4: Population-level descriptive epidemiology of influenza-related outcome

In this objective, population-level descriptive epidemiology of influenza-related outcomes was conducted in the general population, the influenza-vaccinated, and unvaccinated population.

In the influenza-vaccinated population, exposure to the influenza vaccine was defined as the presence of a record of an influenza vaccine. In case of multiple records identified for the same individuals within a given influenza season, only the first recorded vaccination was considered.

In the influenza-unvaccinated population, exposure to the influenza vaccine, defined as the presence of a record of an influenza vaccine, led to censorship of individuals for the remainder of that season.

The code lists used for the identification of exposure are described in **Table S1** in **ANNEX III**.

8.6.2. Outcome

Objective 1: Population-level drug utilisation on influenza vaccine

The outcome for this objective was overall influenza vaccination, defined as the presence of a record of an influenza vaccine. In case of multiple records identified for the same individuals within a given influenza season, only the first recorded vaccination was considered.

Objective 4: Population-level descriptive epidemiology of influenza-related outcome

The primary outcomes for this objective were:

- Influenza-like illness (ILI)
- Acute respiratory infection (ARI)
- Severe acute respiratory infection (SARI)
- All-cause hospitalisation
- Respiratory/influenza-related hospitalisation
- All-cause death

- Respiratory/influenza-related death

Definitions for the clinical syndromes ILI, ARI, and SARI have been adapted from the definitions developed by the Vaccine Effectiveness, Burden, and Impact Studies (VEBIS) working group of the ECDC.[3] For this study, and taking into account data availability, they were defined as follows:

- ILI was defined as a clinical presentation with at least one of the following systemic symptoms:
    - fever or feverishness
    - malaise
    - headache
    - myalgia

  and at least one of the following respiratory symptoms on the same date:
    - cough
    - sore throat
    - shortness of breath
- ARI was defined as the presence of at least one of the following respiratory symptoms:
    - cough
    - sore throat
    - shortness of breath
    - coryza
- SARI was defined as a hospitalised individual presenting with at least one of the following symptoms:
    - cough
    - fever
    - shortness of breath
    - anosmia, ageusia, or dysgeusia

  These symptoms had to occur within 14 days prior to or at the time of hospital admission.

Given the potential challenges in phenotyping ILI, ARI, and SARI based on the VEBIS definitions, and the variability in data availability across data sources, we proposed two alternative proxy outcomes to be used as secondary outcomes:

- Influenza, defined by condition codes explicitly indicating influenza
- Acute respiratory infection (broader definition), defined not by clinical symptoms, but by broader condition codes encompassing a wider range of acute respiratory infections than influenza alone

These proxy outcomes were selected to enhance feasibility and ensure consistent outcome ascertainment across data sources, while still capturing the burden of influenza-related illness.

As all outcomes were treated as incident events, and multiple episodes per individual were allowed, other than death, a 28-day washout period was applied for ILI, ARI, SARI, influenza, and acute respiratory infection (broader definition) to distinguish separate events.

Regarding hospitalisation and death outcomes, we aimed to distinguish between all-cause and respiratory/influenza-related hospitalisation and death, where possible. We defined a composite outcome

combining hospitalisation or death with a prior clinical outcome (e.g., ILI, ARI, SARI, influenza, or acute respiratory infection (broader definition)). In such cases, we attributed the hospitalisation or death to a respiratory or influenza-related cause if the clinical outcome occurred within 14 days prior to the hospitalisation or death date.

The code lists used for the identification of symptoms for the definition of clinical syndromes, secondary outcomes, and hospitalisation are described in **Table S2** in **ANNEX III**.

8.6.3. Covariates, including confounders, effect modifiers, intercurrent events, and other variables

The following covariates, assessed on the index date [0, 0], defined as start of influenza season, namely 1st of October each year within the study period, were used for stratification:

- Sex
- Age groups
    - Below 6 years
    - 6–17 years
    - 18–64 years
    - 65 years and above
- Influenza season

Objective 2: Patient-level characterisation on use and type of influenza vaccine

The following covariates were used to characterise use of vaccine, assessed on the index date [0,0], defined as date of influenza vaccination:

- Month of vaccination

The following covariates were used to characterise type of vaccine, assessed on the index date [0,0], defined as date of influenza vaccination:

- Vaccine brand
- Route of administration
    - Injectable
    - Nasal

We classified the code lists of influenza vaccines by brand and route of administration for each concept, using the relationships between concepts. However, the characterisation of vaccine recipients by brand and route depended on the availability of this information in each data source, as not all data sources had mapped their data to concepts containing the relationship to brands and routes.

The following covariates were used for stratification, assessed on the index date [0, 0]:

- Age groups
    - Below 6 years
    - 6–17 years
    - 18–64 years
    - 65 years and above
- Sex

- Influenza season

Objective 3: Patient-level characterisation of influenza vaccine recipients

The following covariates were used to characterise influenza vaccine recipients on the index date [0, 0], defined as date of influenza vaccination:

- Sex
- Age groups
    - Below 6 years
    - 6–17 years
    - 18–64 years
    - 65 years and above

The following covariates were used to characterise influenza vaccine recipients, with the assessment window [-280, 0] (when data was available):

- Pregnancy, defined by condition codes indicating an ongoing pregnancy or pregnancy outcome.

The following covariates were used to characterise influenza vaccine recipients, with the assessment window [-Inf, 0] and [-365, 0]:

- Anaemia, asplenia, asthma, chronic liver disease, cardiovascular diseases, diabetes, hypertension, obesity, neuromuscular disorders, renal disease, dementia, stroke, rheumatological diseases, cancer, lung disease excluding asthma and chronic obstructive pulmonary disease, tuberculosis, chronic obstructive pulmonary disease. Only anaemia, cancer, obesity, and tuberculosis were evaluated within the assessment window [-365, 0] because these conditions may represent more acute, evolving, or transient health states.

Immunocompromised status was defined as follows:

- Individuals were considered immunocompromised if they have a record of any of the following conditions with assessment window [-365, 0]:
    - HIV/AIDS
    - Haematological malignancies
    - Solid malignancies
    - Other intrinsic immune conditions
- Individuals were also considered immunocompromised if they received antineoplastic or immunomodulating agents with assessment window [-183, 0].
- Additionally, individuals treated with systemic corticosteroids during the same 183-day period were considered immunocompromised if they also had a record of any of the following conditions with assessment window [-365, 0] relative to the index date of receiving influenza vaccine:
    - Organ transplantation
    - Rheumatologic or inflammatory conditions, including rheumatoid arthritis, inflammatory bowel disease, or systemic lupus erythematosus

Information regarding following vaccines was collected, with the assessment window [-Inf, -366], [-365, -1], [0, 0]:

- Pneumococcal vaccine, respiratory syncytial virus (RSV) vaccine, herpes zoster vaccine

Information regarding following vaccines was collected, with the assessment window [-365, -1], [0, 0]:

- COVID-19 vaccine

Objective 4: Population-level descriptive epidemiology of influenza-related outcome

The following covariates were used for stratification, with the assessment window at index date [0, 0], defined as the start of the influenza season, namely 1st of October each year within the study period for the general population, or the date of influenza vaccination for the vaccinated population:

- Age groups
    - Below 6 years
    - 6–17 years
    - 18–64 years
    - 65 years and above
- Sex

8.7. Study size

No sample size was calculated, as this was a drug utilisation study which did not test a specific hypothesis. In addition, we used already collected available data to estimate influenza vaccination prevalence. Thus, the sample size was driven by the availability of data for individuals with influenza vaccination. Based on a preliminary feasibility assessment (as of 22/05/2025), the estimated number of influenza vaccine records in each data source were as follows: NAJS (2,533,000), DK-DHR (17,206,000), FinOMOP-THL (15,202,400), NLHR (6,437,800), SIDIAP (15,469,800), and CPRD GOLD (29,155,500).

8.8. Data transformation

Analyses were conducted separately for each data source. Before study initiation, test runs of the analyses were performed on a subset of the data sources and quality control checks were performed. Once all the tests passed (see **ANNEX IV**), the final study codes package was released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally executed the analytics against the OMOP CDM in R Studio and reviewed and approved the, by default, aggregated results.

The study results of all data sources were checked, after which they were made available to the team, and the dissemination phase started. All results were locked and timestamped for reproducibility and transparency.

8.9. Statistical methods

8.9.1. Main summary measures

Descriptive statistics were used to summarise influenza vaccination prevalence, characteristics of vaccines, characteristics of vaccine recipients, and influenza-related clinical outcomes across data sources. Vaccination prevalence was estimated as the proportion of individuals vaccinated within each influenza season and reported with 95% confidence intervals (CI). Categorical variables were summarised using counts and percentages, while continuous variables were described using medians and interquartile ranges. Incidence rates for clinical outcomes were calculated per 100,000 person-years and reported with 95% CI.

8.9.2. Main statistical methods

In data sources where individuals had multiple observation periods, only the first period was included in the analysis.

R-packages

The prevalence of influenza vaccination (objective 1) and incidence of respiratory infection outcome (objective 4) were calculated based on OMOP CDM mapped data using the *IncidencePrevalence* R package.[15] Patient characteristics of influenza vaccine recipients (objective 2 and 3) were given based on OMOP CDM mapped data using the *CohortCharacteristics* R package.[16]

Prevalence calculations for population-level drug utilisation on influenza vaccine (Objective 1)

Prevalence of influenza vaccine was calculated as annual period prevalence, which summarised the total number of individuals who received an influenza vaccine during a given influenza season divided by the population under observation during that season. Therefore, period prevalence gave the proportion of individuals exposed at any time during a specified interval. Binomial 95% CI were calculated.

Patient-level characterisation on type of vaccine (Objective 2)

Characterisation on type of vaccine, including brand and route of administration, and characterisation on use of vaccine in terms of month of vaccination was provided in influenza vaccine recipients for each influenza season. Covariates were extracted on the index date, which was defined as date of influenza vaccination.

Patient-level characterisation of influenza vaccine recipients (Objective 3)

Patient characterisation by pre-defined conditions/vaccines of interest before/on index date (date of influenza vaccination) was provided in influenza vaccine recipients for each influenza season. Covariates were extracted for the following time intervals: pregnancy was assessed from -280 days to index date; pre-defined conditions on comorbidities were assessed from anytime to index date, and from -365 days to index date; immunocompromised status was defined by multiple conditions with a different assessment window, as stated above in **Section 8.6.3**; receipt of pre-selected vaccines was assessed from anytime to -366 days, from -365 days to one day prior to influenza vaccination, and on the date of influenza vaccination (pneumococcal vaccine, RSV vaccine, herpes zoster vaccine), and from -365 days to one day prior to influenza vaccination, and on the date of influenza vaccination (COVID-19 vaccine). List of pre-defined covariates of interest are given in **Section 8.6.3**.

Incidence calculations for population-level descriptive epidemiology of influenza-related outcomes (Objective 4)

Annual incidence rates of the selected pre-specified influenza-related outcomes were described as the number of individuals with the outcome of interest per 100,000 person-years of the population at risk (background incidence rate in the general population and crude incidence rates in the vaccinated and unvaccinated population) for each influenza season. Study participants who entered the denominator population contributed person-time from the start of follow-up until the earliest of the following events: occurrence of the outcome, death, end of observation, or end of the influenza season. Multiple outcomes were allowed, with participants' time contributions paused during a defined outcome washout period of 28 days. Participants without outcome exposure contributed time-at-risk as continuously until censoring. Time-at-risk of individuals who die was censored at the time of death. Similarly, time-at-risk of individuals who were lost to follow-up was censored at the time of loss to follow-up (i.e., last contact). Subjects with data until the end of the study period without experiencing outcome were administratively censored at the end of the influenza season. For analysis in unvaccinated population, individuals receiving influenza vaccine were censored at the date of vaccination. Incidence rates were given together with Poisson 95% CI.

8.9.3. Missing values

Individuals with missing information in sex and age were excluded.

8.9.4. Sensitivity analysis

Table 3. Sensitivity analyses – rationale, strengths, and limitations.

	What is being varied? How?	Why? (What do you expect to learn?)	Strengths of the sensitivity analysis compared to the primary	Limitations of the sensitivity analysis compared to the primary
Period prevalence estimation on influenza vaccination (objective 1): removing requirement of full-year contribution of individuals	Main analysis: **full-year contribution of individuals was required** for denominator cohort entry. Sensitivity analysis: **full-year contribution of individuals was not required** for denominator cohort entry.	This is to ensure the prevalence reflects the actual population at risk throughout the influenza season and avoid bias caused by individuals with short observation times.	This could avoid selection bias, where requiring full year contribution may remove individuals at risk.	Sensitivity analysis without full contribution requirement may lead to inconsistent time-at-risk and therefore, interpretation of result in period prevalence would be difficult.
Definition of influenza-related outcomes SARI and hospitalisation and death with influenza-related cause (objective 4): additional assessment window for symptoms prior to hospital admission/date of death	Main analysis: pre-defined symptoms must occur within **14 days** prior to or at the time of hospital admission for SARI/date of death. Sensitivity analysis: pre-defined symptoms must occur within **10 days** prior to or at the time of hospital admission for SARI/date of death.	The World Health Organisation uses an assessment window of 10 days for the symptoms prior to hospital admission/date of death.	A narrower assessment window of symptoms was needed to provide a more specific definition SARI/influenza-related death.	Using 14 days for an assessment window, as proposed in main analysis, would align with the definition used in VEBIS. In reality, there might be a delay in healthcare seeking behaviour from the symptom onset that could be recorded from GP to hospital admission.

8.10. Deviations from the protocol

None.

9. RESULTS

The full set of results for this study is available through an interactive web-application ShinyApp at EUPAS1000000803.

The ShinyApp is structured into seven main tabs, each providing specific study outputs and supporting information:

1. Background: provides a brief description of the study, including the rationale, background, and objectives.
2. Study data sources: includes a snapshot subtab with a table summarising key metadata for each study data source.

3. Codelists: contains two subtabs:
    - Cohort code use: displays codes from the study code list used to define the study phenotypes observed on the day of cohort entry for each study data source. Hospitalisation cohort code use for NAJS could not be included due to memory limitations in the data source.
    - Cohort count: presents the counts of records and individuals identified using these code lists for each study data source. The cohort counts displayed here correspond to the period from 10/2015 to 04/2024 and are not broken down by influenza season.
4. Vax Prevalence: includes the results for Objective 1 and contains two subtabs:
    - Prevalence: displays population-level prevalence rates in both table (raw data) and plot formats.
    - Prevalence attrition: shows the stepwise inclusion and exclusion criteria leading to the final analytical population for prevalence analyses.
5. Vax Use Characterisation: includes the results for Objective 2 and contains four subtabs:
    - Demographic Characteristics
    - Vax month: Contains data in table and plot format.
    - Brand: Contains data in table and plot format.
    - Route: Contains data in table and plot format.
6. Vax Recipients Characterisation: includes the results for Objective 3 and contains one subtab that displays selected patient-level variables at different time windows before and at the index date.
7. Outcomes Incidence Rates: includes the results for Objective 4 and contains two subtabs:
    - Incidence: displays population-level incidence rates in both table (raw data) and plot formats.
    - Incidence attrition: shows the stepwise inclusion and exclusion criteria leading to the final analytical population for incidence analyses.

9.1. Participants

During the entire study period, the number of identified influenza vaccine recipients per influenza season ranged from 315,680 to 353,067 in NAJS, 584,326 to 1,660,806 in DK-DHR, 881,057 to 1,851,213 in FinOMOP-THL, 656,100 to 1,347,773 in NLHR, 749,257 to 1,155,277 in SIDIAP, and 662,310 to 986,045 in CPRD GOLD (**Table 4**).

Table 4. Number of influenza vaccine recipients in each influenza season by study objective and data source.

Variable level	Study objective	Additional requirement [a]	Data sources					
			NAJS	DK-DHR	FinOMOP-THL	NLHR	SIDIAP	CPRD GOLD
Influenza season 2015/16								
Total number of eligible population	Nil	Nil	–	5,470,540	5,598,479	–	5,923,709	5,373,232
Total number of influenza vaccine recipients	1 (sensitivity analysis), 2	Nil	–	584,326	881,057	–	788,633	986,045
	1	Full year contribution of individual	–	572,570	874,381	–	775,027	912,376
	3	With prior medical history of 365 days	–	583,882	870,463	–	783,756	945,915
	4	With prior medical history of 28 days	–	584,298	880,991	–	788,162	981,865
Influenza season 2016/17								
Total number of eligible population	Nil	Nil	–	5,494,647	5,608,607	–	5,930,824	4,701,076
Total number of influenza vaccine recipients	1 (sensitivity analysis), 2	Nil	–	681,483	1,034,825	–	771,389	859,312
	1	Full year contribution of individual	–	667,676	1,026,729	–	757,789	809,349
	3	With prior medical history of 365 days	–	680,851	1,020,622	–	767,180	820,837
	4	With prior medical history of 28 days	–	681,459	1,034,714	–	770,951	854,850
Influenza season 2017/18								
Total number of eligible population	Nil	Nil	–	5,512,263	5,611,265	–	5,967,490	4,370,477
Total number of influenza vaccine recipients	1 (sensitivity analysis), 2	Nil	–	738,647	1,084,991	–	751,752	832,499
	1	Full year contribution of individual	–	723,596	1,076,271	–	737,274	795,623
	3	With prior medical history of 365 days	–	737,848	1,070,028	–	747,033	797,231
	4	With prior medical history of 28 days	–	738,609	1,084,884	–	751,188	828,753
Influenza season 2018/19								
Total number of eligible population	Nil	Nil	–	5,522,012	5,611,274	5,409,285	6,015,417	4,179,881

Variable level	Study objective	Additional requirement [a]	Data sources					
			NAJS	DK-DHR	FinOMOP-THL	NLHR	SIDIAP	CPRD GOLD
Total number of influenza vaccine recipients	1 (sensitivity analysis), 2	Nil	–	808,383	1,200,459	656,100	749,257	832,463
	1	Full year contribution of individual	–	793,332	1,191,676	649,420	735,757	805,370
	3	With prior medical history of 365 days	–	807,229	1,183,093	654,440	743,311	797,213
	4	With prior medical history of 28 days	–	808,341	1,200,343	655,794	748,561	828,822
Influenza season 2019/20								
Total number of eligible population	Nil	Nil	–	5,528,837	5,614,093	5,430,057	6,046,121	4,016,143
Total number of influenza vaccine recipients	1 (sensitivity analysis), 2	Nil	–	859,093	1,190,490	811,575	810,110	792,902
	1	Full year contribution of individual	–	846,216	1,181,762	803,810	793,067	752,493
	3	With prior medical history of 365 days	–	857,837	1,172,806	809,752	802,568	759,814
	4	With prior medical history of 28 days	–	859,057	1,190,348	811,309	809,317	789,202
Influenza season 2020/21								
Total number of eligible population	Nil	Nil	4,252,637	5,531,151	5,608,873	5,472,084	6,051,833	3,635,999
Total number of influenza vaccine recipients	1 (sensitivity analysis), 2	Nil	353,067	1,287,971	1,577,596	995,877	1,155,277	704,830
	1	Full year contribution of individual	351,480	1,269,639	1,567,418	987,250	1,135,794	663,695
	3	With prior medical history of 365 days	351,984	1,286,778	1,561,329	994,488	1,147,827	677,810
	4	With prior medical history of 28 days	352,784	1,287,923	1,577,455	995,672	1,154,268	702,735
Influenza season 2021/22								
Total number of eligible population	Nil	Nil	4,278,612	5,571,908	5,620,608	5,496,137	6,085,548	3,321,261
Total number of influenza vaccine recipients	1 (sensitivity analysis), 2	Nil	315,680	1,660,806	1,851,213	1,347,773	1,085,664	964,297
	1	Full year contribution of individual	310,837	1,638,198	1,836,836	1,335,131	1,068,984	931,075
	3	With prior medical history of 365 days	314,676	1,657,675	1,833,656	1,345,086	1,079,610	928,888

Variable level	Study objective	Additional requirement [a]	Data sources					
			NAJS	DK-DHR	FinOMOP-THL	NLHR	SIDIAP	CPRD GOLD
	4	With prior medical history of 28 days	315,627	1,660,682	1,851,038	1,347,471	1,085,117	961,556
Influenza season 2022/23								
Total number of eligible population	Nil	Nil	4,283,201	5,614,292	5,636,888	5,546,487	6,076,748	3,100,477
Total number of influenza vaccine recipients	1 (sensitivity analysis), 2	Nil	327,381	1,546,047	1,691,923	1,311,669	1,007,047	837,288
	1	Full year contribution of individual	322,041	1,523,613	1,677,943	1,298,807	991,441	811,468
	3	With prior medical history of 365 days	326,899	1,541,950	1,675,831	1,308,719	1,001,284	807,442
	4	With prior medical history of 28 days	327,231	1,545,900	1,691,676	1,311,340	1,006,486	835,062
Influenza season 2023/24								
Total number of eligible population	Nil	Nil	4,294,969	5,633,022	5,673,754	–	–	3,033,924
Total number of influenza vaccine recipients	1 (sensitivity analysis), 2	Nil	316,538	1,421,636	1,662,264	–	–	662,310
	1	Full year contribution of individual	311,457	1,402,563	1,648,728	–	–	632,685
	3	With prior medical history of 365 days	316,062	1,418,809	1,645,229	–	–	638,637
	4	With prior medical history of 28 days	316,456	1,421,560	1,661,972	–	–	659,879

a. Additional requirements were applied according to the objectives and outcomes of interest, as stated in study protocol. For objective 1, full-year contribution of denominator population was introduced to ensure the estimated prevalence reflected the actual population at risk throughout the influenza season and to avoid bias based by individuals with short observation times. For objective 3, prior history of 365 days was required to ensure adequate length of follow up to capture and describe individuals' baseline characteristics. For objective 4, to align with a washout period of 28 days for each outcome of interest, a prior history of 28 days was required for observation.

– indicates a value not applicable because the period falls outside the study window for this database

CPRD= Clinical Practice Research Datalink; DK-DHR= Danish Data Health Registries; FinOMOP-THL= Finnish Care Register for Health Care; NAJS= National Public Health Information System; NLHR= Norwegian Linked Health Registry data; SIDIAP= The Information System for Research in Primary Care.

9.2. Main results

9.2.1. Objective 1: Population-level drug utilisation on influenza vaccine

Figure 7 shows the prevalence of influenza vaccination among the general population across participating data sources from the 2015/16 to the 2023/24 influenza seasons.

Between 2015/16 and 2019/20, vaccination prevalence ranged from around 11% to 22% across most data sources with available data. DK-DHR increased from 10.7% (95% CI 10.7–10.7) in 2015/16 to 15.6% (95% CI 15.6–15.7) in 2019/20, while FinOMOP-THL rose from 15.9% (95% CI 15.8–15.9) to 21.4% (95% CI 21.3–21.4) over the same period. SIDIAP and CPRD GOLD remained broadly stable during these years with prevalences of approximately 13% and 20%, respectively. NLHR had available data starting from the 2018/2019 season, reaching a prevalence of 15.1% (95% CI 15.0–15.1) in 2019/20. From the 2018/19 season onward, FinOMOP-THL consistently reported the highest vaccination prevalence.

Notable increases in vaccination prevalence were observed in the 2021/22 season in DK-DHR, FinOMOP-THL, NLHR, and SIDIAP, with prevalence reaching around 30% or higher in DK-DHR and FinOMOP-THL. In CPRD GOLD, a similar increase was observed in the 2021/22 season, also reaching approximately 30% prevalence. Following this peak during the COVID-19 pandemic period, vaccination prevalence began to slightly decline again across all data sources.

NAJS reported the lowest vaccination prevalence among all data sources. The first available estimate was 8.4% (95% CI 8.4–8.5) in the 2020/21 season, followed by slightly lower values in subsequent seasons, reaching 7.4% (95% CI 7.3–7.4) in 2023/24.

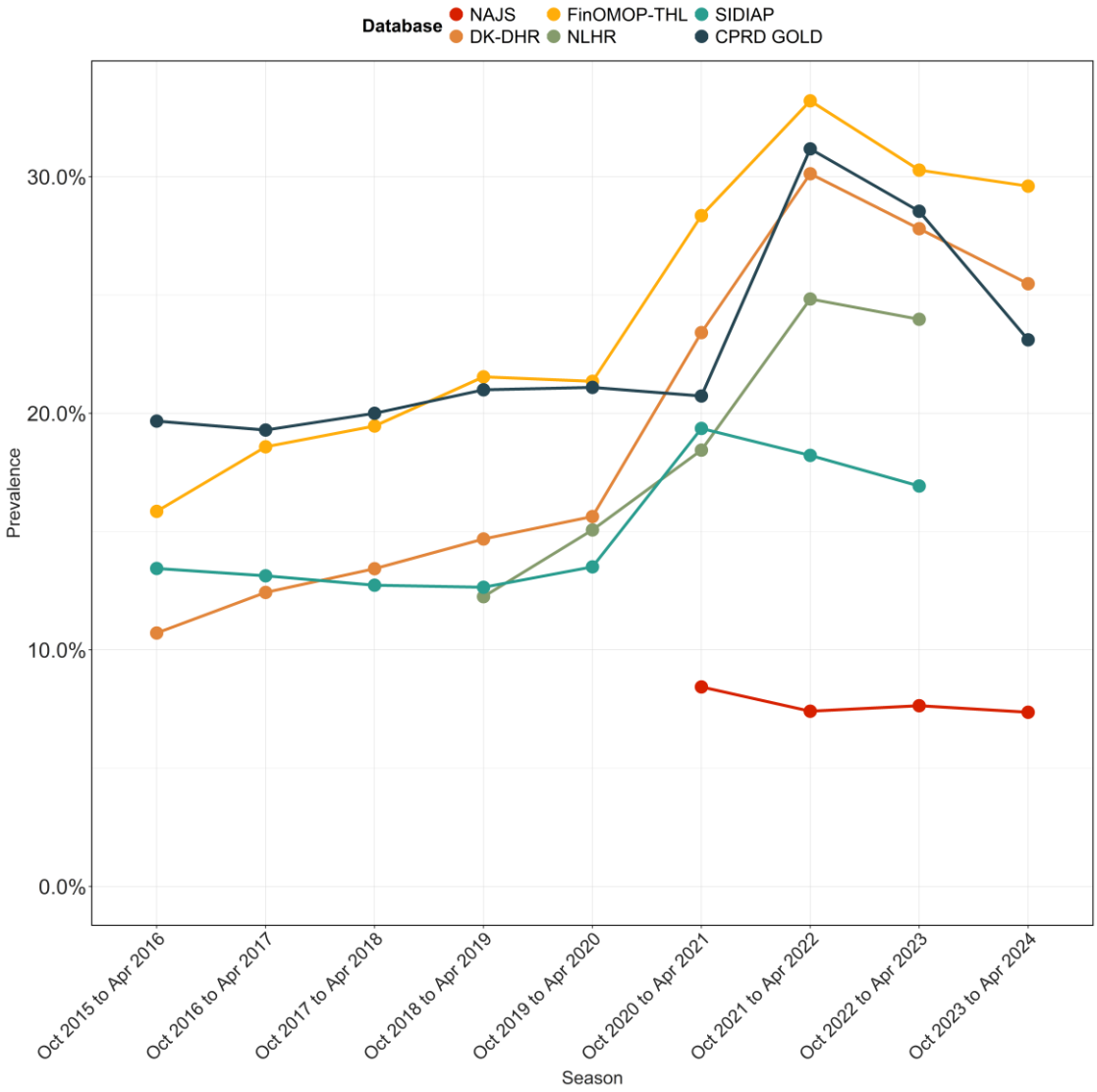


Figure 7. Prevalence of influenza vaccination in the general population from 2015/16 to 2023/24 influenza seasons by data source.

CPRD= Clinical Practice Research Datalink; DK-DHR= Danish Data Health Registries; FinOMOP-THL= Finnish Care Register for Health Care; NAJS= National Public Health Information System; NLHR= Norwegian Linked Health Registry data; SIDIAP= The Information System for Research in Primary Care

When stratified by sex (**Figure 8**), influenza vaccination prevalence was consistently higher among females compared to males across all data sources, with a smaller difference in NAJS than in the other data sources.

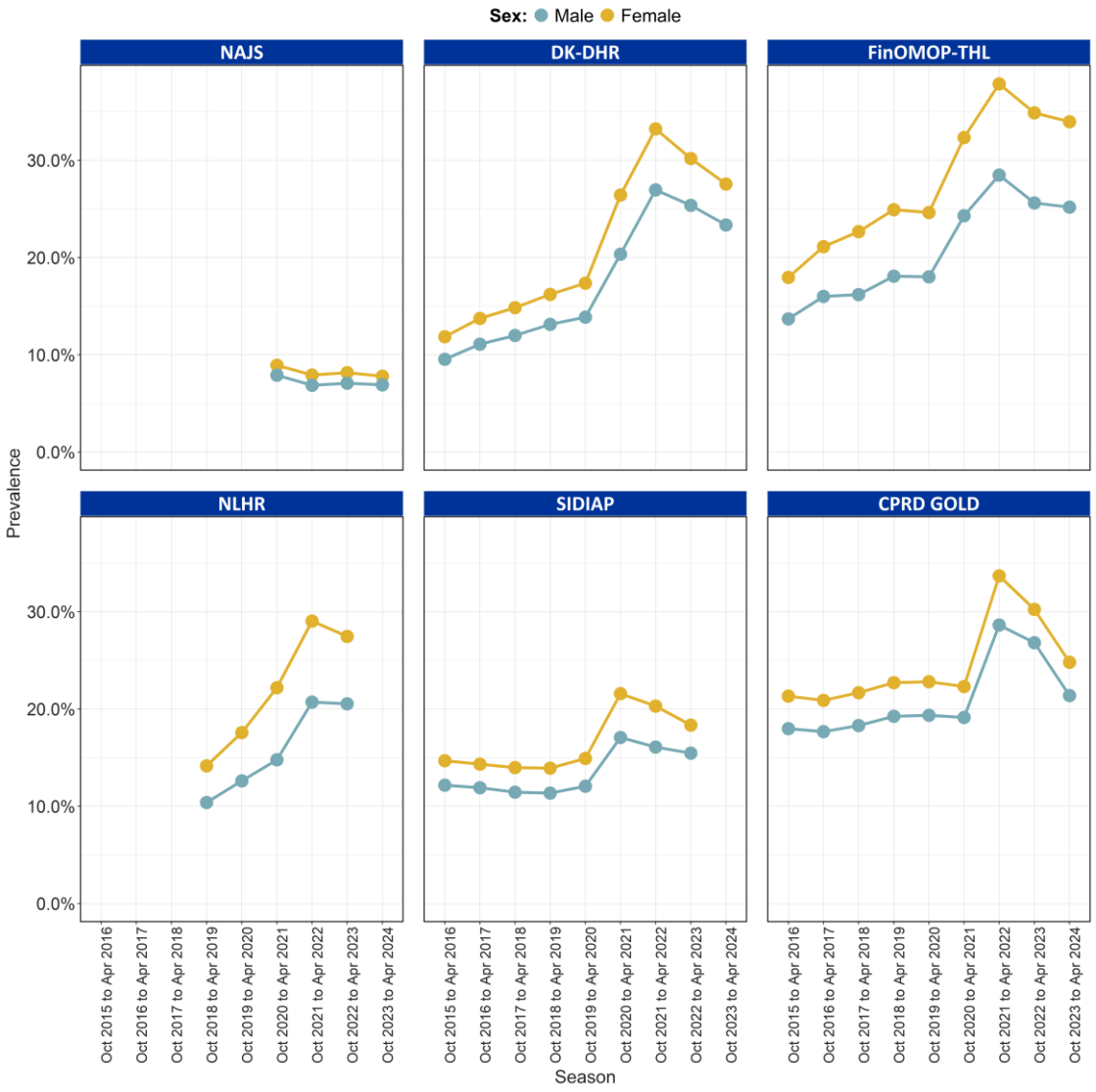


Figure 8. Prevalence of influenza vaccination in the general population from 2015/16 to 2023/24 influenza seasons by sex and data source.

CPRD= Clinical Practice Research Datalink; DK-DHR= Danish Data Health Registries; FinOMOP-THL= Finnish Care Register for Health Care; NAJS= National Public Health Information System; NLHR= Norwegian Linked Health Registry data; SIDIAP= The Information System for Research in Primary Care

When stratified by age group (**Figure 9**), influenza vaccination prevalence was consistently higher among the oldest age group (≥65 years) across all data sources. During the study period, prevalence in this age group ranged from 24.9% to 27.2% in NAJS, 44.0% to 81.8% in DK-DHR, 43.3% to 62.8% in FinOMOP-THL, 38.4% to 63.9% in NLHR, 48.0% to 62.6% in SIDIAP, and 51.4% to 68.1% in CPRD GOLD. Notably, CPRD GOLD showed a decline in prevalence among adults aged ≥65 years in the 2020/21 season followed by a sharp increase in 2021/22. The age group with the second-highest vaccination prevalence varied by data source: in FinOMOP-THL it was the youngest group (<6 years), with prevalence ranging from 17.6% to 38.1%; in NAJS, DK-DHR, NLHR, and SIDIAP, it was the 18–64-year group (2.8–3.9% in NAJS; 3.5–19.2% in DK-DHR; 8.9–21.0% in NLHR; 4.9–11.1% in SIDIAP). However, in DK-DHR, vaccination prevalence among the youngest group (<6 years) increased markedly in 2021/22 to 24.5%, surpassing that of the 18–64-year group. In CPRD GOLD, the youngest age group (<6 years) had the second-highest prevalence until 2020/21 (22.7–27.8%),

after which it was overtaken by the 6–17-year group, which reached 35.2% in 2023/24. Interestingly, among children aged under six years, influenza vaccination prevalence did not increase substantially following the emergence of COVID-19 compared with the oldest age group, except in DK-DHR. In CPRD GOLD, prevalence in this group even showed a slight decrease. NAJS and NLHR had the lowest levels of vaccination among children <6 years, with prevalence below 1.5% across all seasons with available data.

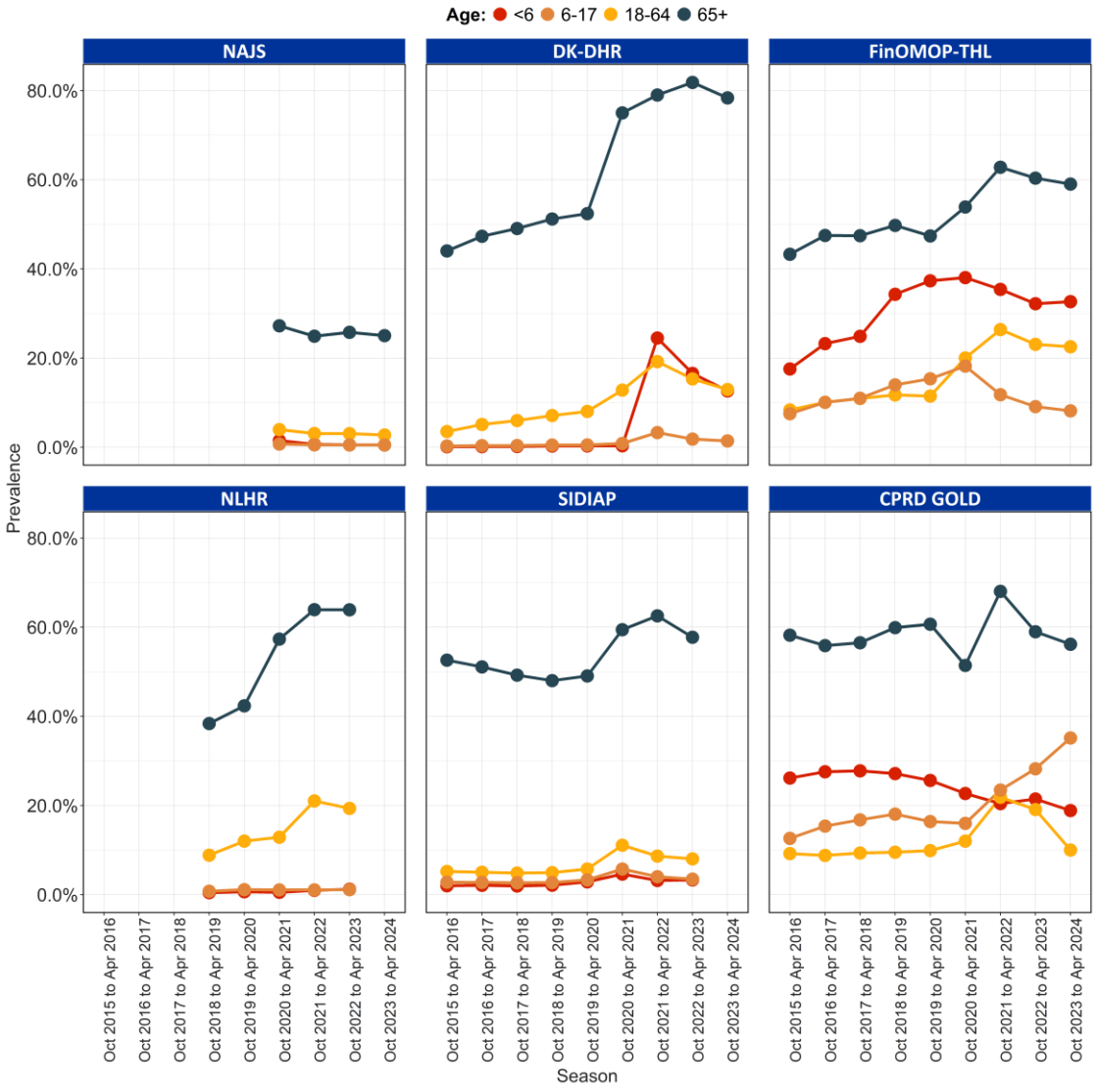


Figure 9. Prevalence of influenza vaccination in the general population from 2015/16 to 2023/24 influenza seasons by age group and data source.

CPRD= Clinical Practice Research Datalink; DK-DHR= Danish Data Health Registries; FinOMOP-THL= Finnish Care Register for Health Care; NAJS= National Public Health Information System; NLHR= Norwegian Linked Health Registry data; SIDIAP= The Information System for Research in Primary Care

9.2.2. Objective 2: Patient-level characterisation on use and type of influenza vaccine

Figure 10 illustrates the monthly temporal pattern of influenza vaccination uptake across participating data sources over multiple influenza seasons. In all data sources, vaccination activity was highly concentrated in the early months of each influenza season, with the majority of vaccinations administered between October and December. Specifically, vaccination uptake peaked in October in CPRD-GOLD, DK-DHR, and NLHR, and in November in FinOMOP-THL and SIDIAP, followed by a rapid decline from December onwards, reaching minimal levels by January. This seasonal pattern remained consistent throughout the study period, with limited variation between influenza seasons, except for 2019/20 in DK-DHR, when most vaccinations were administered in November instead of October, and for the 2015/16, 2020/21, and 2022/23 seasons in SIDIAP, where vaccinations were more evenly distributed between October and November. Among the seasons available for NAJS, there was greater variability: uptake peaked in October in 2020/21 and 2022/23, while in 2021/22 and 2023/24 it peaked in November.

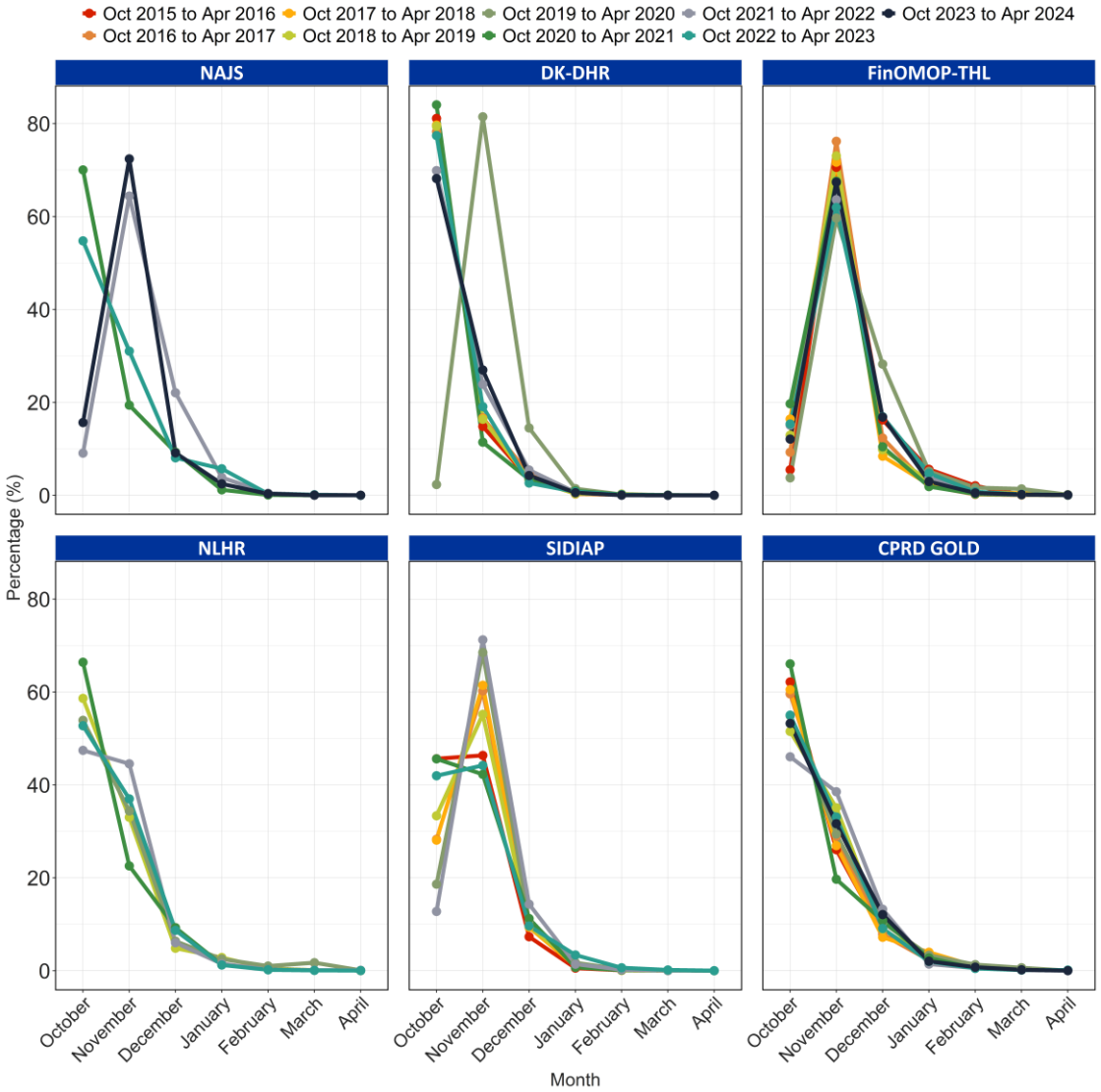


Figure 10. Monthly distribution of influenza vaccination uptake within each influenza season from 2015/16 to 2023/24, by data source.

CPRD= Clinical Practice Research Datalink; DK-DHR= Danish Data Health Registries; FinOMOP-THL= Finnish Care Register for Health Care; NAJS= National Public Health Information System; NLHR= Norwegian Linked Health Registry data; SIDIAP= The Information System for Research in Primary Care

No striking differences were found by sex (**Figure S1** in **ANNEX V**) or by age group (**Figure S2** in **ANNEX V**). In DK-DHR, NLHR, and CPRD GOLD, the oldest age group appeared to receive vaccinations earlier in the season, with a clear peak in October, whereas among younger age groups, vaccination uptake was more evenly distributed between October and December.

Figure 11 shows the distribution of influenza vaccine brands across influenza seasons and data sources. Only DK-DHR and FinOMOP-THL contained detailed information on vaccine brand. In DK-DHR, during the first season (2015/16), the main vaccine administered was Afluria, representing up to 95% of the vaccines administered. In the following seasons, the predominant vaccines were Vaxigrip and Influvac, ranging from 25.2% to 54.0% and 40.7% to 57.6%, respectively, across influenza seasons. The use of Fluenz began in 2021/22 peaking at 6.5% and declined thereafter. In FinOMOP-THL, during the first season (2015/16), the main vaccines administered were Vaxigrip (48.2%) and Fluarix (50.4%). In the 2016/17 and 2017/18 seasons, Influvac predominated, accounting for over 90% of vaccinations. From the 2018/19 season onwards, Vaxigrip became the predominant vaccine, representing more than 85% of administered vaccines. Beginning in the 2020/21 season, Fluarix started to increase in use, rising from approximately 4% to 9% in the 2023/24 season. The use of Fluenz represented between 1% and 7% of vaccinations across influenza seasons, with the highest proportions observed in the 2019/20 season.

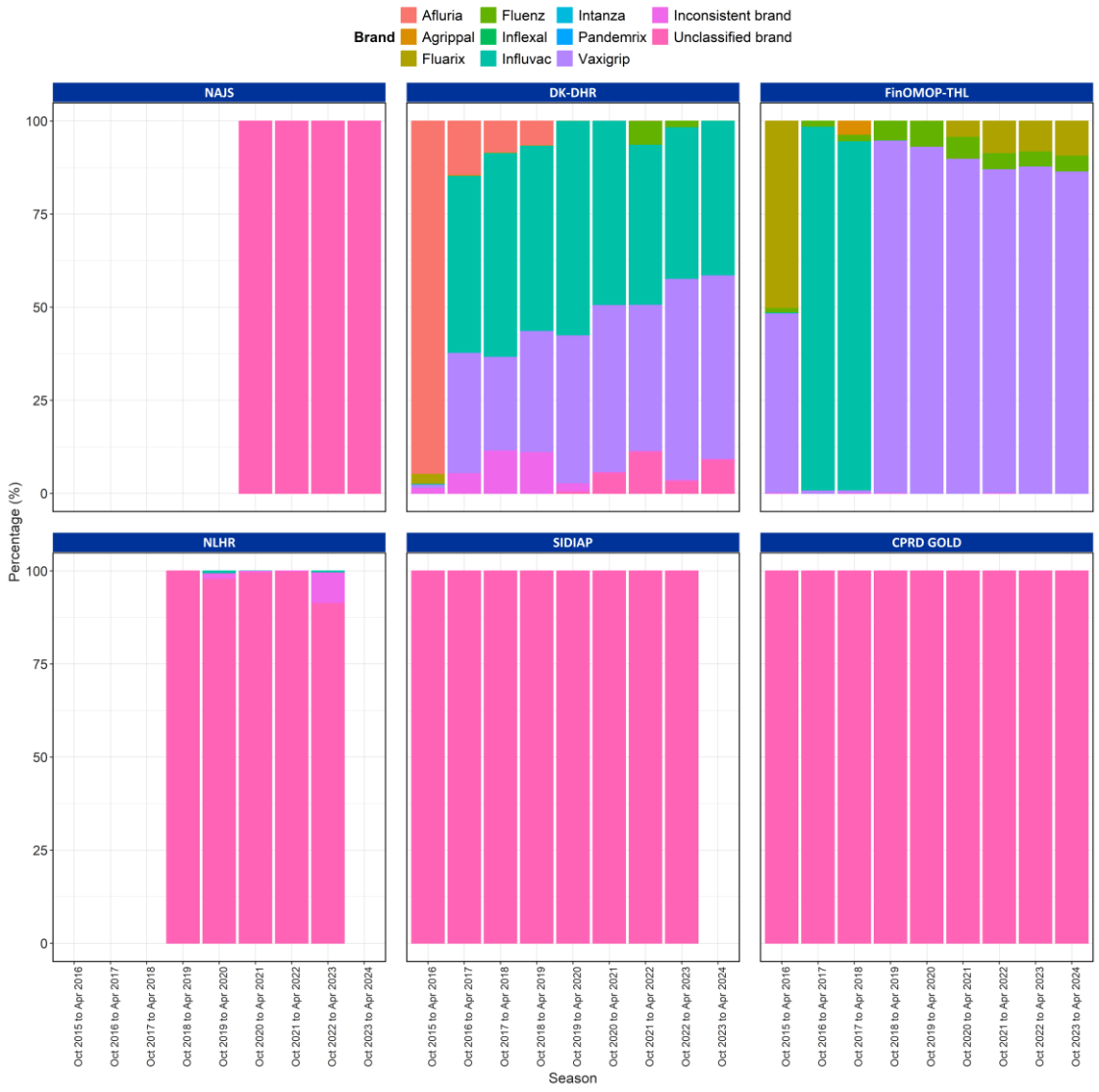


Figure 11. Distribution of influenza vaccine brands by influenza season (2015/16–2023/24) and data source.

Inconsistent brand refers to individuals with more than one vaccination record on the same date that contains conflicting information on the vaccine brand.

CPRD= Clinical Practice Research Datalink; DK-DHR= Danish Data Health Registries; FinOMOP-THL= Finnish Care Register for Health Care; NAJS= National Public Health Information System; NLHR= Norwegian Linked Health Registry data; SIDIAP= The Information System for Research in Primary Care

No striking differences were observed by sex (**Figure S3** in **ANNEX V**). When stratified by age group (**Figure S4** in **ANNEX V**), the main differences were observed for the Fluenz brand in both DK-DHR and FinOMOP-THL. In DK-DHR, Fluenz accounted for 99% of vaccinations when it was first introduced during the season 2021/22 among the youngest age group (<6 years) and for 66% of vaccinations among those aged 6–17 years. In FinOMOP-THL, Fluenz represented 49% or more of vaccinations among the youngest vaccine recipients from the 2018/19 season onwards and 10–23% among those aged 6–17 years. Very few Fluenz vaccines (<0.04%) were administered among individuals aged 18 years and older in both data sources. Conversely, in FinOMOP-THL, Fluarix was rarely administered to individuals under 18 years of age, with a maximum of 0.14% among children <6 years and 3.7% among those aged 6–17 years. Additionally, in DK-DHR, Vaxigrip and Influvac were rarely administered to children under six years of age (<0.6%) from the 2021/22 season onwards.

Figure 12 shows the distribution of influenza vaccine administration routes across influenza seasons and data sources. Only NAJS, DK-DHR, and FinOMOP-THL contained fully detailed information on vaccine route. In all three data sources, the vast majority of vaccines (over 90%) were administered by injection. In DK-DHR and FinOMOP-THL, nasal vaccines accounted for between 1% and 7%, with the highest proportions observed during the 2021/22 season in DK-DHR and during the 2019/20 season in FinOMOP-THL. In NAJS, nasal vaccines represented less than 1% across seasons. In CPRD GOLD, data were available from the 2019/20 season onwards, showing that most vaccines were injectable, ranging from 66% to 79%. No records of nasal vaccination were found, and between 11% and 24% of individuals had inconsistent route information due to multiple influenza vaccine codes with different route categories recorded on the same dates. NLHR contained very limited data on vaccine route, and SIDIAP did not include this information.

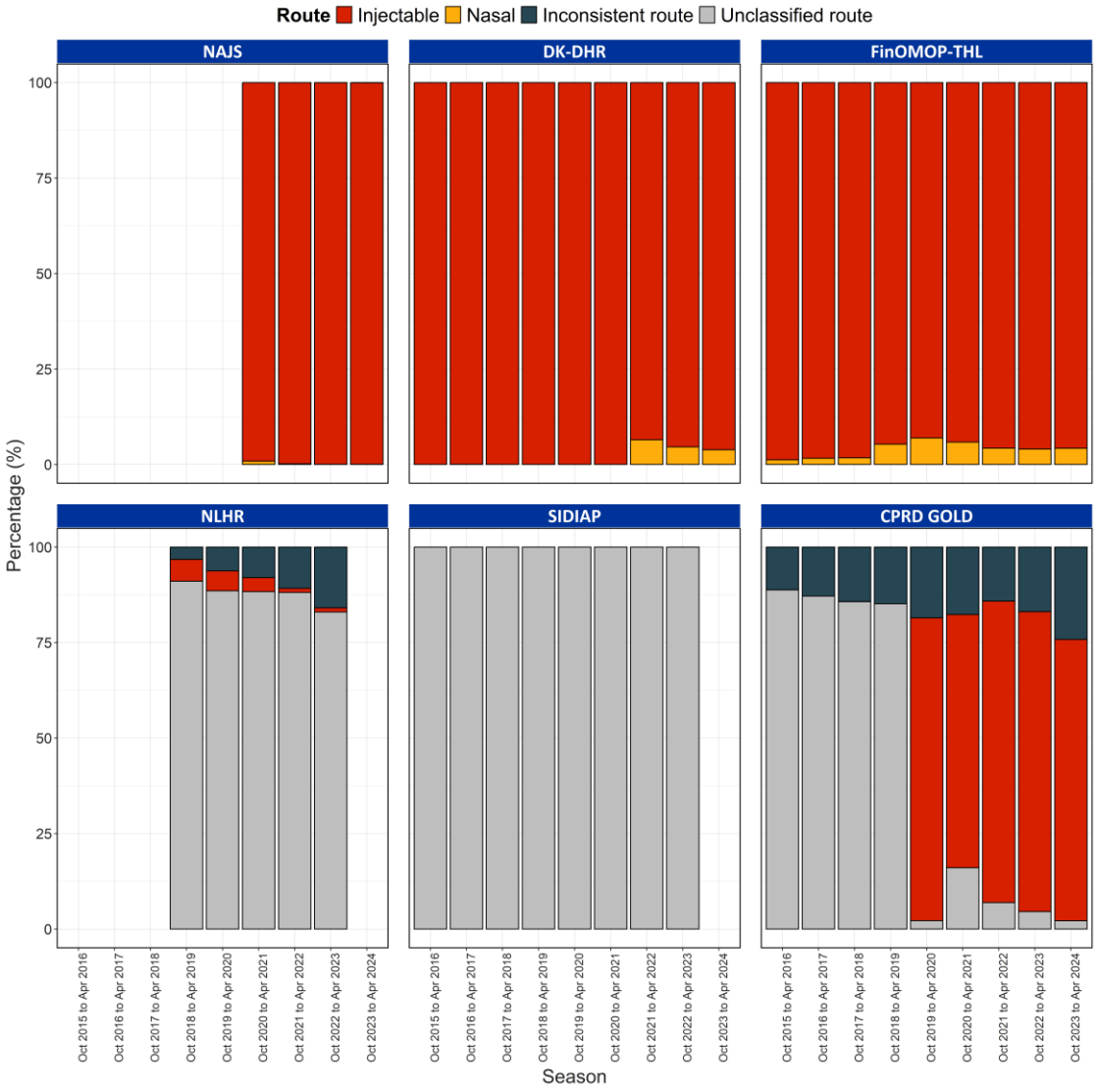


Figure 12. Distribution of influenza vaccine routes by influenza season (2015/16–2023/24) and data source.

Inconsistent route refers to individuals with more than one vaccination record on the same date that contains conflicting information on the vaccine route.
CPRD= Clinical Practice Research Datalink; DK-DHR= Danish Data Health Registries; FinOMOP-THL= Finnish Care Register for Health Care; NAJS= National Public Health Information System; NLHR= Norwegian Linked Health Registry data; SIDIAP= The Information System for Research in Primary Care

No striking differences were found by sex (**Figure S5** in **ANNEX V**). When stratified by age group (**Figure S6** in **ANNEX V**), in DK-DHR, from the 2021/22 season onwards, nasal vaccines accounted for over 98% of vaccinations among the youngest group (<6 years) and over 66% among those aged 6–17 years. In FinOMOP-THL, nasal vaccines accounted for 49% or more of vaccinations among the youngest individuals from the 2018–2019 season onwards and for 10–23% among those aged 6–17 years. Very few nasal vaccines (<0.04%) were administered among individuals aged 18 years and older in both data sources.

9.2.3. Objective 3: Patient-level characterisation of influenza vaccine recipients

Tables 5–13 describe the baseline demographic characteristics, pre-defined clinical conditions, and receipt of other vaccines of interest among influenza vaccine recipients across different data sources and influenza seasons from 2015/16 to 2023/24. The median age at the date of vaccination ranged from 69 years (IQR: 62–77) to 71 years (IQR: 65–78) in NAJS, 66 years (IQR: 51–75) to 72 years (IQR: 66–79) in DK-DHR, 60 years (IQR: 33–72) to 66 years (IQR: 41–74) in FinOMOP-THL, 63 years (IQR: 46–73) to 67 years (IQR: 51–75) in NLHR, 68 years (IQR: 55–77) to 72 years (IQR: 63–81) in SIDIAP, and 61 years (IQR: 44–71) to 66 years (IQR: 43–75) in CPRD GOLD across seasons. The median age at vaccination decreased by 1–4 years during the 2020/21 season, except in NLHR where median age at vaccination increased by 3 years. Females accounted for a higher proportion of vaccinated individuals than males across all data sources and seasons, representing 53% to 59% of all vaccinated individuals.

Clinical conditions

The proportion of pregnant individuals among influenza vaccine recipients varied across data sources but remained relatively stable over time. FinOMOP-THL consistently reported the highest proportions, ranging from 1.9% to 3.0% across influenza seasons, followed by NLHR, where pregnancy accounted for 1.6% to 2.2% of vaccinated individuals. NAJS reported the lowest proportions, with values of 0.2% or below.

The pre-defined clinical conditions most frequently recorded among influenza vaccine recipients were largely consistent across data sources and influenza seasons. Hypertension, cardiac conditions, diabetes mellitus, asthma, and cancer were among the most common comorbidities in all data sources, although prevalence levels varied. Across data sources, hypertension affected approximately 20–81% of vaccinated individuals, and cardiac conditions ranged between 13% and 50%, diabetes mellitus between 11% and 35%, asthma between 8% and 24%, and cancer between 9% and 25%. NAJS and SIDIAP generally reported the highest prevalence estimates across conditions, while CPRD GOLD showed the lowest. Certain comorbidities were more specific to individual data sources: for example, obesity and lung disease were more prominent in SIDIAP, anaemia was notable in NAJS, NLHR, and SIDIAP, and chronic renal disease was more frequent in CPRD GOLD.

Across all data sources, the proportion of influenza vaccine recipients identified as immunocompromised remained relatively stable over time, with some variation between data sources. The highest prevalence was consistently observed in NAJS and NLHR. The proportion of immunocompromised individuals ranged 16.0–17.2% in NAJS and 14.0–15.9% in NLHR across influenza seasons, followed by DK-DHR (9.1–12.9%). In FinOMOP-THL, prevalence ranged from 7.5% to 9.3%, while in SIDIAP, it ranged from 5.1% to 5.9%. CPRD GOLD consistently reported the lowest proportions, ranging between 2.9% and 4.0%.

Receipt of other vaccines

Across all data sources and influenza seasons, prior receipt of other vaccines more than one year before the influenza vaccination was common, particularly for pneumococcal vaccination. The prevalence of previous pneumococcal vaccination increased over time in most data sources. In NAJS, prevalence rose from 0.9% in 2020/21 to 3.8% in 2023/24, remaining the lowest across all data sources. In DK-DHR and FinOMOP-THL, the proportion of influenza vaccine recipients with a prior pneumococcal vaccine rose from 1.6% in 2015/16 to 65.3% in 2023/24 and from 10.0% to 26.1%, respectively. A similar increasing trend was

observed in NLHR, with values ranging from 2.0% in 2019/20 to 19.4% in 2022/23. In SIDIAP and CPRD GOLD, pneumococcal vaccination remained consistently higher, ranging from 40.2–48.8% and 39.0–55.6% across seasons, respectively. Prior herpes zoster vaccination was far less common. It was most frequent in CPRD GOLD, increasing from about 5% in earlier seasons to nearly 20% by 2023/24. In contrast, it represented 0.7–2.1% of recipients in FinOMOP-THL and below 0.7% in DK-DHR and NLHR, with that rarely recorded in NAJS and SIDIAP. No RSV vaccinations were identified in any data source during the study period until after the 2022/23 season, where very rare cases of RSV vaccination were observed in DK-DHR and FinOMOP-THL.

Regarding vaccines administered within one year prior to influenza vaccination, pneumococcal vaccination was again the most frequently recorded, though proportions varied across data sources. In NAJS, between 0.4% and 2.4% of recipients had received a pneumococcal vaccine during the preceding year. In DK-DHR, this proportion ranged from 0.7% to 28.6%, with the highest levels observed in 2020/21. In FinOMOP-THL, this ranged between 2.3% and 8.1%, in NLHR, between 1.3% and 12.2%, and in SIDIAP, between 2.5% and 4.4%. In CPRD GOLD, proportions ranged from 1.5% to 5.9%. Herpes zoster vaccination remained infrequent, with proportions below 4.1% in CPRD GOLD and below 1% elsewhere. COVID-19 vaccination appeared in the data starting from the 2020/21 season. The proportion of influenza vaccine recipients who had also received a COVID-19 vaccine during the prior year rose sharply in 2021/22, reaching 92.7% in NAJS, 92.3% in DK-DHR, 90.9% in FinOMOP-THL, 98.7% in NLHR, 96.6% in SIDIAP, and 88.2% in CPRD GOLD. These proportions declined gradually in subsequent seasons, to 70.4% (NAJS), 90.4% (DK-DHR), 82.9% (FinOMOP-THL), 90.0% (NLHR), 82.8% (SIDIAP), and 77.0% (CPRD GOLD), respectively, in 2022/23, and further to 6.1% (NAJS), 30.8% (DK-DHR), 15.9% (FinOMOP-THL), and 45.6% (CPRD GOLD) in 2023/24 (with no data available for NLHR and SIDIAP).

Co-administration of other non-COVID-19 vaccines on the same day as the influenza vaccine was relatively uncommon across all data sources, with pneumococcal vaccination being the most frequent (generally <10%), except for DK-DHR, which peaked at 26.8% in 2020/21. Herpes zoster vaccination was rare, representing <1.5% in CPRD GOLD and <0.1% elsewhere. In contrast, co-administration of COVID-19 and influenza vaccines became increasingly common after the rollout of COVID-19 vaccination programmes. During the 2021/22 season, same-day receipt of both vaccines was reported for 13.0% of influenza vaccine recipients in FinOMOP-THL, 32.7% in SIDIAP, and 45.6% in CPRD GOLD. Co-administration increased further during 2022/23, reaching 63.2% in DK-DHR, 24.7% in FinOMOP-THL, 67.9% in SIDIAP, and 58.6% in CPRD GOLD. In 2023/24, proportions declined slightly to 46.1% in FinOMOP-THL and 52.8% in CPRD GOLD but rose to 65.3% in DK-DHR. Co-administration of COVID-19 and influenza vaccines was uncommon in NAJS and NLHR, with proportions below 2.5%.

Table 5: Baseline characteristics of influenza vaccine recipients by data source for influenza season 2015/16.

Variable name	Variable level	Estimate name	Database			
			DK-DHR	FinOMOP-THL	SIDIAP	CPRD GOLD
Demographics index date						
Number subjects	–	N	583,882	870,463	783,756	945,915
Sex	Female	N (%)	325,401 (55.73%)	499,046 (57.33%)	432,815 (55.22%)	516,614 (54.62%)
	Male	N (%)	258,481 (44.27%)	371,417 (42.67%)	350,941 (44.78%)	429,301 (45.38%)
Age	–	Median [Q25 – Q75]	72 [66 – 79]	66 [41 – 74]	72 [63 – 81]	66 [43 – 75]
		Mean (SD)	70.73 (13.36)	57.07 (24.71)	68.65 (17.81)	56.04 (26.53)
		Range	1 to 109	1 to 108	1 to 108	1 to 107
Immunocompromised -365 to 0						
	Immunocompromised	N (%)	75,009 (12.85%)	80,883 (9.29%)	42,049 (5.37%)	36,653 (3.87%)
Pregnancy -280 to 0						
	Pregnancy	N (%)	4,346 (0.74%)	24,015 (2.76%)	6,592 (0.84%)	17,858 (1.89%)
Comorbidities -inf to 0						
	Acute renal disease	N (%)	10,200 (1.75%)	24,319 (2.79%)	37,501 (4.78%)	11,028 (1.17%)
	Anaemia	N (%)	39,175 (6.71%)	41,490 (4.77%)	139,587 (17.81%)	64,035 (6.77%)
	Asplenia	N (%)	1,344 (0.23%)	460 (0.05%)	<5	1,135 (0.12%)
	Asthma	N (%)	139,790 (23.94%)	91,635 (10.53%)	63,685 (8.13%)	120,662 (12.76%)
	Cancer	N (%)	143,890 (24.64%)	94,773 (10.89%)	106,531 (13.59%)	94,435 (9.98%)
	Cardiac conditions	N (%)	195,902 (33.55%)	215,990 (24.81%)	267,534 (34.13%)	163,469 (17.28%)
	Chronic liver disease	N (%)	7,868 (1.35%)	5,490 (0.63%)	46,978 (5.99%)	13,042 (1.38%)
	Chronic renal disease	N (%)	14,298 (2.45%)	10,190 (1.17%)	104,651 (13.35%)	112,366 (11.88%)
	COPD	N (%)	94,517 (16.19%)	28,940 (3.32%)	88,387 (11.28%)	58,292 (6.16%)
	Dementia	N (%)	19,981 (3.42%)	30,317 (3.48%)	46,999 (6.00%)	19,154 (2.02%)
	Diabetes mellitus	N (%)	105,274 (18.03%)	153,985 (17.69%)	183,798 (23.45%)	134,788 (14.25%)
	Hypertension	N (%)	272,229 (46.62%)	263,182 (30.23%)	359,541 (45.87%)	221,460 (23.41%)
	Lung disease	N (%)	78,403 (13.43%)	27,232 (3.13%)	103,998 (13.27%)	43,841 (4.63%)

Variable name	Variable level	Estimate name	Database			
			DK-DHR	FinOMOP-THL	SIDIAP	CPRD GOLD
	Neuromuscular disorders	N (%)	1,323 (0.23%)	1,411 (0.16%)	1,092 (0.14%)	1,215 (0.13%)
	Obesity	N (%)	51,090 (8.75%)	25,808 (2.96%)	171,010 (21.82%)	82,570 (8.73%)
	Rheumatologic diseases	N (%)	24,618 (4.22%)	25,715 (2.95%)	14,994 (1.91%)	15,787 (1.67%)
	Stroke	N (%)	52,138 (8.93%)	30,881 (3.55%)	36,815 (4.70%)	23,605 (2.50%)
	Tuberculosis	N (%)	1,312 (0.22%)	651 (0.07%)	2,422 (0.31%)	1,166 (0.12%)
Comorbidities -365 to 0						
	Acute renal disease	N (%)	1,973 (0.34%)	8,945 (1.03%)	11,753 (1.50%)	3,713 (0.39%)
	Anaemia	N (%)	14,586 (2.50%)	28,958 (3.33%)	59,571 (7.60%)	19,020 (2.01%)
	Cancer	N (%)	64,779 (11.09%)	73,386 (8.43%)	39,669 (5.06%)	29,635 (3.13%)
	Tuberculosis	N (%)	220 (0.04%)	322 (0.04%)	325 (0.04%)	194 (0.02%)
Vaccines -inf to -366						
	Herpes zoster vaccine	N (%)	105 (0.02%)	6,195 (0.71%)	<5	45,747 (4.84%)
	Pneumococcal vaccine	N (%)	9,148 (1.57%)	86,635 (9.95%)	337,605 (43.08%)	512,770 (54.22%)
	RSV vaccine	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vaccines -365 to -1						
	COVID-19 vaccine	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Herpes zoster vaccine	N (%)	407 (0.07%)	5,063 (0.58%)	<5	31,266 (3.31%)
	Pneumococcal vaccine	N (%)	4,201 (0.72%)	57,289 (6.58%)	30,430 (3.88%)	27,104 (2.87%)
	RSV vaccine	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vaccines index date						
	COVID-19 vaccine	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Herpes zoster vaccine	N (%)	7 (0.00%)	191 (0.02%)	0 (0.00%)	13,504 (1.43%)
	Pneumococcal vaccine	N (%)	1,063 (0.18%)	26,228 (3.01%)	35,718 (4.56%)	23,935 (2.53%)
	RSV vaccine	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

COPD= Chronic Obstructive Pulmonary Disease; CPRD= Clinical Practice Research Datalink; DK-DHR= Danish Data Health Registries; FinOMOP-THL= Finnish Care Register for Health Care; Q= Quartile; NAJS= National Public Health Information System; RSV= Respiratory Syncytial Virus; SD= Standard Deviation; SIDIAP= The Information System for Research in Primary Care

Table 6: Baseline characteristics of influenza vaccine recipients by data source for influenza season 2016/17.

Variable name	Variable level	Estimate name	Data sources			
			DK-DHR	FinOMOP-THL	SIDIAP	CPRD GOLD
Demographics index date						
Number individuals	–	N	680,851	1,020,622	767,180	820,837
Sex	Female	N (%)	378,662 (55.62%)	586,589 (57.47%)	423,513 (55.20%)	447,206 (54.48%)
	Male	N (%)	302,189 (44.38%)	434,033 (42.53%)	343,667 (44.80%)	373,631 (45.52%)
Age	–	Median [Q25 – Q75]	72 [64 – 79]	66 [37 – 74]	72 [63 – 81]	65 [36 – 74]
		Mean (SD)	69.42 (14.49)	55.62 (25.43)	68.82 (17.95)	54.38 (27.49)
		Range	1 to 108	0 to 108	1 to 109	1 to 107
Immunocompromised -365 to 0						
	Immunocompromised	N (%)	84,687 (12.44%)	91,893 (9.00%)	42,585 (5.55%)	31,243 (3.81%)
Pregnancy -280 to 0						
	Pregnancy	N (%)	5,602 (0.82%)	29,770 (2.92%)	7,175 (0.94%)	14,642 (1.78%)
Comorbidities -inf to 0						
	Acute renal disease	N (%)	12,196 (1.79%)	31,773 (3.11%)	41,157 (5.36%)	9,873 (1.20%)
	Anaemia	N (%)	45,060 (6.62%)	50,917 (4.99%)	147,638 (19.24%)	53,572 (6.53%)
	Asplenia	N (%)	1,498 (0.22%)	545 (0.05%)	<5	954 (0.12%)
	Asthma	N (%)	162,865 (23.92%)	109,920 (10.77%)	66,079 (8.61%)	102,806 (12.52%)
	Cancer	N (%)	165,457 (24.30%)	113,034 (11.08%)	113,138 (14.75%)	79,964 (9.74%)
	Cardiac conditions	N (%)	221,788 (32.58%)	254,689 (24.95%)	276,369 (36.02%)	138,163 (16.83%)
	Chronic liver disease	N (%)	9,279 (1.36%)	7,174 (0.70%)	50,984 (6.65%)	12,711 (1.55%)
	Chronic renal disease	N (%)	16,716 (2.46%)	12,388 (1.21%)	114,251 (14.89%)	91,161 (11.11%)
	COPD	N (%)	107,043 (15.72%)	33,849 (3.32%)	90,030 (11.74%)	49,695 (6.05%)
	Dementia	N (%)	24,244 (3.56%)	36,463 (3.57%)	47,209 (6.15%)	16,042 (1.95%)
	Diabetes mellitus	N (%)	118,433 (17.39%)	175,003 (17.15%)	187,090 (24.39%)	114,435 (13.94%)
	Hypertension	N (%)	311,515 (45.75%)	314,548 (30.82%)	366,485 (47.77%)	184,048 (22.42%)
	Lung disease	N (%)	89,792 (13.19%)	33,191 (3.25%)	115,818 (15.10%)	37,557 (4.58%)

Variable name	Variable level	Estimate name	Data sources			
			DK-DHR	FinOMOP-THL	SIDIAP	CPRD GOLD
	Neuromuscular disorders	N (%)	1,527 (0.22%)	1,643 (0.16%)	1,172 (0.15%)	1,019 (0.12%)
	Obesity	N (%)	61,482 (9.03%)	33,408 (3.27%)	190,783 (24.87%)	72,169 (8.79%)
	Rheumatologic diseases	N (%)	27,980 (4.11%)	29,781 (2.92%)	15,783 (2.06%)	13,509 (1.65%)
	Stroke	N (%)	58,193 (8.55%)	37,608 (3.68%)	37,622 (4.90%)	20,103 (2.45%)
	Tuberculosis	N (%)	1,538 (0.23%)	781 (0.08%)	2,443 (0.32%)	956 (0.12%)
Comorbidities -365 to 0						
	Acute renal disease	N (%)	2,322 (0.34%)	10,547 (1.03%)	11,929 (1.55%)	2,901 (0.35%)
	Anaemia	N (%)	15,906 (2.34%)	32,453 (3.18%)	59,737 (7.79%)	15,444 (1.88%)
	Cancer	N (%)	74,086 (10.88%)	83,007 (8.13%)	40,493 (5.28%)	24,397 (2.97%)
	Tuberculosis	N (%)	239 (0.04%)	336 (0.03%)	302 (0.04%)	162 (0.02%)
Vaccines -inf to -366						
	Herpes zoster vaccine	N (%)	611 (0.09%)	11,415 (1.12%)	<5	67,334 (8.20%)
	Pneumococcal vaccine	N (%)	13,773 (2.02%)	138,326 (13.55%)	351,446 (45.81%)	456,087 (55.57%)
	RSV vaccine	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vaccines -365 to -1						
	COVID-19 vaccine	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Herpes zoster vaccine	N (%)	182 (0.03%)	8,356 (0.82%)	0 (0.00%)	22,784 (2.78%)
	Pneumococcal vaccine	N (%)	10,144 (1.49%)	76,649 (7.51%)	34,051 (4.44%)	21,211 (2.58%)
	RSV vaccine	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vaccines index date						
	COVID-19 vaccine	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Herpes zoster vaccine	N (%)	<5	285 (0.03%)	0 (0.00%)	12,412 (1.51%)
	Pneumococcal vaccine	N (%)	5,500 (0.81%)	30,463 (2.98%)	23,989 (3.13%)	15,538 (1.89%)
	RSV vaccine	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

COPD= Chronic Obstructive Pulmonary Disease; CPRD= Clinical Practice Research Datalink; DK-DHR= Danish Data Health Registries; FinOMOP-THL= Finnish Care Register for Health Care; Q= Quartile; NAJS= National Public Health Information System; RSV= Respiratory Syncytial Virus; SD= Standard Deviation; SIDIAP= The Information System for Research in Primary Care

Table 7: Baseline characteristics of influenza vaccine recipients by data source for influenza season 2017/18.

Variable name	Variable level	Estimate name	Data sources			
			DK-DHR	FinOMOP-THL	SIDIAP	CPRD GOLD
Demographics index date						
Number individuals	–	N	737,848	1,070,028	747,033	797,231
Sex	Female	N (%)	410,298 (55.61%)	630,004 (58.88%)	415,122 (55.57%)	434,551 (54.51%)
	Male	N (%)	327,550 (44.39%)	440,024 (41.12%)	331,911 (44.43%)	362,680 (45.49%)
Age	–	Median [Q25 – Q75]	71 [63 – 78]	65 [35 – 74]	72 [63 – 81]	65 [36 – 74]
		Mean (SD)	68.72 (15.03)	54.91 (25.72)	68.94 (18.07)	54.06 (27.45)
		Range	1 to 109	1 to 109	1 to 110	1 to 109
Immunocompromised -365 to 0						
	Immunocompromised	N (%)	89,916 (12.19%)	95,667 (8.94%)	42,745 (5.72%)	30,392 (3.81%)
Pregnancy -280 to 0						
	Pregnancy	N (%)	6,288 (0.85%)	31,512 (2.94%)	8,998 (1.20%)	13,366 (1.68%)
Comorbidities -inf to 0						
	Acute renal disease	N (%)	13,434 (1.82%)	37,674 (3.52%)	44,217 (5.92%)	10,427 (1.31%)
	Anaemia	N (%)	48,161 (6.53%)	57,422 (5.37%)	152,599 (20.43%)	51,247 (6.43%)
	Asplenia	N (%)	1,606 (0.22%)	635 (0.06%)	<5	925 (0.12%)
	Asthma	N (%)	178,056 (24.13%)	119,626 (11.18%)	66,961 (8.96%)	99,477 (12.48%)
	Cancer	N (%)	180,358 (24.44%)	122,635 (11.46%)	118,555 (15.87%)	77,303 (9.70%)
	Cardiac conditions	N (%)	237,551 (32.20%)	274,125 (25.62%)	280,410 (37.54%)	133,131 (16.70%)
	Chronic liver disease	N (%)	10,405 (1.41%)	7,965 (0.74%)	54,064 (7.24%)	13,966 (1.75%)
	Chronic renal disease	N (%)	18,271 (2.48%)	13,802 (1.29%)	120,489 (16.13%)	83,364 (10.46%)
	COPD	N (%)	115,169 (15.61%)	35,642 (3.33%)	90,005 (12.05%)	48,519 (6.09%)
	Dementia	N (%)	24,953 (3.38%)	40,612 (3.80%)	46,779 (6.26%)	15,254 (1.91%)
	Diabetes mellitus	N (%)	126,421 (17.13%)	181,179 (16.93%)	185,686 (24.86%)	109,697 (13.76%)
	Hypertension	N (%)	334,906 (45.39%)	336,969 (31.49%)	367,704 (49.22%)	173,992 (21.82%)

Variable name	Variable level	Estimate name	Data sources			
			DK-DHR	FinOMOP-THL	SIDIAP	CPRD GOLD
	Lung disease	N (%)	97,201 (13.17%)	36,426 (3.40%)	125,576 (16.81%)	36,190 (4.54%)
	Neuromuscular disorders	N (%)	1,730 (0.23%)	1,808 (0.17%)	1,284 (0.17%)	999 (0.13%)
	Obesity	N (%)	69,091 (9.36%)	38,189 (3.57%)	201,296 (26.95%)	70,492 (8.84%)
	Rheumatologic diseases	N (%)	30,070 (4.08%)	31,819 (2.97%)	16,402 (2.20%)	13,236 (1.66%)
	Stroke	N (%)	61,165 (8.29%)	41,035 (3.83%)	37,807 (5.06%)	19,411 (2.43%)
	Tuberculosis	N (%)	1,687 (0.23%)	870 (0.08%)	2,474 (0.33%)	906 (0.11%)
Comorbidities -365 to 0						
	Acute renal disease	N (%)	2,258 (0.31%)	11,479 (1.07%)	12,459 (1.67%)	2,941 (0.37%)
	Anaemia	N (%)	16,165 (2.19%)	34,157 (3.19%)	58,666 (7.85%)	14,377 (1.80%)
	Cancer	N (%)	80,012 (10.84%)	86,816 (8.11%)	41,427 (5.55%)	23,299 (2.92%)
	Tuberculosis	N (%)	254 (0.03%)	317 (0.03%)	311 (0.04%)	165 (0.02%)
Vaccines -inf to -366						
	Herpes zoster vaccine	N (%)	830 (0.11%)	17,476 (1.63%)	<5	85,836 (10.77%)
	Pneumococcal vaccine	N (%)	23,129 (3.13%)	182,710 (17.08%)	360,210 (48.22%)	432,881 (54.30%)
	RSV vaccine	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vaccines -365 to -1						
	COVID-19 vaccine	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Herpes zoster vaccine	N (%)	150 (0.02%)	3,788 (0.35%)	5 (0.00%)	23,255 (2.92%)
	Pneumococcal vaccine	N (%)	22,446 (3.04%)	86,476 (8.08%)	22,924 (3.07%)	17,033 (2.14%)
	RSV vaccine	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vaccines index date						
	COVID-19 vaccine	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Herpes zoster vaccine	N (%)	5 (0.00%)	106 (0.01%)	0 (0.00%)	12,076 (1.51%)
	Pneumococcal vaccine	N (%)	6,158 (0.83%)	27,001 (2.52%)	18,897 (2.53%)	9,684 (1.21%)
	RSV vaccine	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

COPD= Chronic Obstructive Pulmonary Disease; CPRD= Clinical Practice Research Datalink; DK-DHR= Danish Data Health Registries; FinOMOP-THL= Finnish Care Register for Health Care; Q= Quartile; NAJS= National Public Health Information System; RSV= Respiratory Syncytial Virus; SD= Standard Deviation; SIDIAP= The Information System for Research in Primary Care

Table 8: Baseline characteristics of influenza vaccine recipients by data source for influenza season 2018/19.

Variable name	Variable level	Estimate name	Data sources				
			DK-DHR	FinOMOP-THL	NLHR	SIDIAP	CPRD GOLD
Demographics index date							
Number individuals	–	N	807,229	1,183,093	654,440	743,311	797,213
Sex	Female	N (%)	448,294 (55.53%)	691,668 (58.46%)	374,021 (57.15%)	413,744 (55.66%)	433,301 (54.35%)
	Male	N (%)	358,935 (44.47%)	491,425 (41.54%)	280,419 (42.85%)	329,567 (44.34%)	363,912 (45.65%)
Age	–	Median [Q25 – Q75]	71 [62 – 78]	65 [32 – 73]	66 [49 – 75]	72 [63 – 81]	65 [38 – 74]
		Mean (SD)	67.89 (15.58)	53.25 (26.79)	61.16 (19.02)	68.68 (18.43)	54.81 (27.22)
		Range	1 to 109	1 to 108	1 to 108	1 to 109	1 to 106
Immunocompromised -365 to 0							
	Immunocompromised	N (%)	99,036 (12.27%)	98,162 (8.30%)	103,025 (15.74%)	43,113 (5.80%)	30,953 (3.88%)
Pregnancy -280 to 0							
	Pregnancy	N (%)	7,597 (0.94%)	33,310 (2.82%)	12,112 (1.85%)	10,345 (1.39%)	11,690 (1.47%)
Comorbidities -inf to 0							
	Acute renal disease	N (%)	14,977 (1.86%)	44,680 (3.78%)	5,172 (0.79%)	47,269 (6.36%)	12,126 (1.52%)
	Anaemia	N (%)	51,759 (6.41%)	66,094 (5.59%)	82,089 (12.54%)	158,284 (21.29%)	53,186 (6.67%)
	Asplenia	N (%)	1,765 (0.22%)	724 (0.06%)	0 (0.00%)	<5	909 (0.11%)
	Asthma	N (%)	196,289 (24.32%)	133,229 (11.26%)	119,390 (18.24%)	70,244 (9.45%)	98,632 (12.37%)
	Cancer	N (%)	199,413 (24.70%)	137,710 (11.64%)	145,246 (22.19%)	124,485 (16.75%)	81,665 (10.24%)
	Cardiac conditions	N (%)	255,454 (31.65%)	304,199 (25.71%)	254,548 (38.90%)	285,664 (38.43%)	136,437 (17.11%)
	Chronic liver disease	N (%)	11,423 (1.42%)	9,632 (0.81%)	5,170 (0.79%)	58,370 (7.85%)	16,154 (2.03%)
	Chronic renal disease	N (%)	19,457 (2.41%)	15,771 (1.33%)	14,749 (2.25%)	125,161 (16.84%)	83,205 (10.44%)
	COPD	N (%)	124,198 (15.39%)	38,746 (3.27%)	71,663 (10.95%)	91,648 (12.33%)	50,226 (6.30%)
	Dementia	N (%)	25,417 (3.15%)	43,534 (3.68%)	16,577 (2.53%)	46,256 (6.22%)	15,023 (1.88%)

Variable name	Variable level	Estimate name	Data sources				
			DK-DHR	FinOMOP-THL	NLHR	SIDIAP	CPRD GOLD
	Diabetes mellitus	N (%)	135,154 (16.74%)	194,360 (16.43%)	88,922 (13.59%)	186,965 (25.15%)	112,638 (14.13%)
	Hypertension	N (%)	361,508 (44.78%)	371,587 (31.41%)	272,881 (41.70%)	371,289 (49.95%)	178,830 (22.43%)
	Lung disease	N (%)	105,583 (13.08%)	41,791 (3.53%)	17,864 (2.73%)	138,003 (18.57%)	38,086 (4.78%)
	Neuromuscular disorders	N (%)	1,972 (0.24%)	2,036 (0.17%)	1,045 (0.16%)	1,550 (0.21%)	1,035 (0.13%)
	Obesity	N (%)	77,767 (9.63%)	44,958 (3.80%)	38,555 (5.89%)	212,064 (28.53%)	71,871 (9.02%)
	Rheumatologic diseases	N (%)	32,716 (4.05%)	34,564 (2.92%)	56,388 (8.62%)	17,212 (2.32%)	13,796 (1.73%)
	Stroke	N (%)	64,189 (7.95%)	45,235 (3.82%)	36,867 (5.63%)	38,422 (5.17%)	20,112 (2.52%)
	Tuberculosis	N (%)	1,858 (0.23%)	904 (0.08%)	1,210 (0.18%)	2,560 (0.34%)	950 (0.12%)
Comorbidities -365 to 0							
	Acute renal disease	N (%)	2,373 (0.29%)	12,442 (1.05%)	3,892 (0.59%)	12,388 (1.67%)	3,321 (0.42%)
	Anaemia	N (%)	16,644 (2.06%)	37,193 (3.14%)	43,481 (6.64%)	57,311 (7.71%)	14,404 (1.81%)
	Cancer	N (%)	87,021 (10.78%)	93,636 (7.91%)	89,417 (13.66%)	41,604 (5.60%)	24,126 (3.03%)
	Tuberculosis	N (%)	260 (0.03%)	294 (0.02%)	226 (0.03%)	315 (0.04%)	142 (0.02%)
Vaccines -inf to -366							
	Herpes zoster vaccine	N (%)	1,006 (0.12%)	23,855 (2.02%)	0 (0.00%)	7 (0.00%)	114,574 (14.37%)
	Pneumococcal vaccine	N (%)	42,225 (5.23%)	266,446 (22.52%)	15 (0.00%)	362,820 (48.81%)	434,335 (54.49%)
	RSV vaccine	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vaccines -365 to -1							
	COVID-19 vaccine	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Herpes zoster vaccine	N (%)	178 (0.02%)	1,766 (0.15%)	146 (0.02%)	0 (0.00%)	21,162 (2.65%)
	Pneumococcal vaccine	N (%)	23,749 (2.94%)	81,122 (6.86%)	8,431 (1.29%)	21,450 (2.89%)	12,299 (1.54%)
	RSV vaccine	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vaccines index date							
	COVID-19 vaccine	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Herpes zoster vaccine	N (%)	7 (0.00%)	141 (0.01%)	16 (0.00%)	0 (0.00%)	10,849 (1.36%)

Variable name	Variable level	Estimate name	Data sources				
			DK-DHR	FinOMOP-THL	NLHR	SIDIAP	CPRD GOLD
	Pneumococcal vaccine	N (%)	6,509 (0.81%)	21,177 (1.79%)	14,321 (2.19%)	21,240 (2.86%)	13,187 (1.65%)
	RSV vaccine	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

COPD= Chronic Obstructive Pulmonary Disease; CPRD= Clinical Practice Research Datalink; DK-DHR= Danish Data Health Registries; FinOMOP-THL= Finnish Care Register for Health Care; Q= Quartile; NAJS= National Public Health Information System; NLHR= Norwegian Linked Health Registry data; RSV= Respiratory Syncytial Virus; SD= Standard Deviation; SIDIAP= The Information System for Research in Primary Care

Table 9: Baseline characteristics of influenza vaccine recipients by data source for influenza season 2019/20.

Variable name	Variable level	Estimate name	Data sources				
			DK-DHR	FinOMOP-THL	NLHR	SIDIAP	CPRD GOLD
Demographics index date							
Number individuals	–	N	857,837	1,172,806	809,752	802,568	759,814
Sex	Female	N (%)	479,667 (55.92%)	683,001 (58.24%)	466,853 (57.65%)	447,861 (55.80%)	412,611 (54.30%)
	Male	N (%)	378,170 (44.08%)	489,805 (41.76%)	342,899 (42.35%)	354,707 (44.20%)	347,203 (45.70%)
Age	–	Median [Q25 – Q75]	71 [61 – 78]	64 [30 – 74]	64 [46 – 74]	72 [61 – 81]	66 [42 – 75]
		Mean (SD)	67.19 (16.05)	52.60 (27.37)	59.46 (19.48)	67.57 (19.22)	55.90 (26.45)
		Range	1 to 109	0 to 108	1 to 109	1 to 111	1 to 107
Immunocompromised -365 to 0							
	Immunocompromised	N (%)	101,621 (11.85%)	99,784 (8.51%)	124,187 (15.34%)	47,394 (5.91%)	30,087 (3.96%)
Pregnancy -280 to 0							
	Pregnancy	N (%)	7,973 (0.93%)	34,949 (2.98%)	18,090 (2.23%)	12,836 (1.60%)	10,504 (1.38%)
Comorbidities -inf to 0							
	Acute renal disease	N (%)	15,867 (1.85%)	49,816 (4.25%)	10,045 (1.24%)	53,197 (6.63%)	13,572 (1.79%)
	Anaemia	N (%)	53,177 (6.20%)	71,372 (6.09%)	111,424 (13.76%)	174,258 (21.71%)	52,451 (6.90%)
	Asplenia	N (%)	1,751 (0.20%)	796 (0.07%)	0 (0.00%)	11 (0.00%)	869 (0.11%)
	Asthma	N (%)	205,841 (24.00%)	136,620 (11.65%)	156,624 (19.34%)	80,636 (10.05%)	96,313 (12.68%)
	Cancer	N (%)	211,825 (24.69%)	141,561 (12.07%)	177,180 (21.88%)	138,350 (17.24%)	81,062 (10.67%)
	Cardiac conditions	N (%)	263,232 (30.69%)	313,067 (26.69%)	305,710 (37.75%)	307,534 (38.32%)	133,804 (17.61%)
	Chronic liver disease	N (%)	12,246 (1.43%)	10,482 (0.89%)	7,191 (0.89%)	68,098 (8.49%)	17,710 (2.33%)
	Chronic renal disease	N (%)	19,911 (2.32%)	17,011 (1.45%)	19,791 (2.44%)	134,136 (16.71%)	77,695 (10.23%)
	COPD	N (%)	125,808 (14.67%)	39,004 (3.33%)	87,542 (10.81%)	98,637 (12.29%)	49,455 (6.51%)
	Dementia	N (%)	25,503 (2.97%)	47,293 (4.03%)	19,962 (2.47%)	47,453 (5.91%)	14,471 (1.90%)

Variable name	Variable level	Estimate name	Data sources				
			DK-DHR	FinOMOP-THL	NLHR	SIDIAP	CPRD GOLD
	Diabetes mellitus	N (%)	137,433 (16.02%)	195,090 (16.63%)	105,799 (13.07%)	199,785 (24.89%)	111,318 (14.65%)
	Hypertension	N (%)	376,867 (43.93%)	375,742 (32.04%)	324,118 (40.03%)	396,978 (49.46%)	174,457 (22.96%)
	Lung disease	N (%)	108,361 (12.63%)	44,197 (3.77%)	24,593 (3.04%)	160,879 (20.05%)	37,010 (4.87%)
	Neuromuscular disorders	N (%)	2,073 (0.24%)	2,128 (0.18%)	1,316 (0.16%)	1,896 (0.24%)	1,069 (0.14%)
	Obesity	N (%)	83,363 (9.72%)	48,729 (4.15%)	53,154 (6.56%)	238,213 (29.68%)	71,397 (9.40%)
	Rheumatologic diseases	N (%)	33,888 (3.95%)	35,075 (2.99%)	71,849 (8.87%)	19,380 (2.41%)	13,554 (1.78%)
	Stroke	N (%)	64,828 (7.56%)	47,620 (4.06%)	43,972 (5.43%)	41,134 (5.13%)	19,848 (2.61%)
	Tuberculosis	N (%)	1,828 (0.21%)	974 (0.08%)	1,566 (0.19%)	2,816 (0.35%)	933 (0.12%)
Comorbidities -365 to 0							
	Acute renal disease	N (%)	2,520 (0.29%)	13,251 (1.13%)	6,013 (0.74%)	13,262 (1.65%)	3,547 (0.47%)
	Anaemia	N (%)	16,445 (1.92%)	38,007 (3.24%)	62,212 (7.68%)	60,937 (7.59%)	13,843 (1.82%)
	Cancer	N (%)	89,800 (10.47%)	93,310 (7.96%)	107,419 (13.27%)	44,661 (5.56%)	23,933 (3.15%)
	Tuberculosis	N (%)	255 (0.03%)	287 (0.02%)	241 (0.03%)	335 (0.04%)	161 (0.02%)
Vaccines -inf to -366							
	Herpes zoster vaccine	N (%)	1,199 (0.14%)	24,254 (2.07%)	188 (0.02%)	6 (0.00%)	126,658 (16.67%)
	Pneumococcal vaccine	N (%)	60,169 (7.01%)	316,219 (26.97%)	16,212 (2.00%)	386,932 (48.21%)	399,353 (52.57%)
	RSV vaccine	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vaccines -365 to -1							
	COVID-19 vaccine	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Herpes zoster vaccine	N (%)	221 (0.03%)	1,613 (0.14%)	323 (0.04%)	5 (0.00%)	21,498 (2.83%)
	Pneumococcal vaccine	N (%)	23,795 (2.77%)	58,693 (5.00%)	20,994 (2.59%)	25,518 (3.18%)	16,502 (2.17%)
	RSV vaccine	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vaccines index date							
	COVID-19 vaccine	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Herpes zoster vaccine	N (%)	6 (0.00%)	114 (0.01%)	25 (0.00%)	0 (0.00%)	9,175 (1.21%)

Variable name	Variable level	Estimate name	Data sources				
			DK-DHR	FinOMOP-THL	NLHR	SIDIAP	CPRD GOLD
	Pneumococcal vaccine	N (%)	8,101 (0.94%)	19,018 (1.62%)	22,110 (2.73%)	27,598 (3.44%)	16,265 (2.14%)
	RSV vaccine	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

COPD= Chronic Obstructive Pulmonary Disease; CPRD= Clinical Practice Research Datalink; DK-DHR= Danish Data Health Registries; FinOMOP-THL= Finnish Care Register for Health Care; Q= Quartile; NAJS= National Public Health Information System; NLHR= Norwegian Linked Health Registry data; RSV= Respiratory Syncytial Virus; SD= Standard Deviation; SIDIAP= The Information System for Research in Primary Care

Table 10: Baseline characteristics of influenza vaccine recipients by data source for influenza season 2020/21.

Variable name	Variable level	Estimate name	Data sources					
			NAJS	DK-DHR	FinOMOP-THL	NLHR	SIDIAP	CPRD GOLD
Demographics index date								
Number individuals	–	N	351,984	1,286,778	1,561,329	994,488	1,147,827	677,810
Sex	Female	N (%)	192,368 (54.65%)	731,068 (56.81%)	898,492 (57.55%)	591,311 (59.46%)	646,614 (56.33%)	366,498 (54.07%)
	Male	N (%)	159,616 (45.35%)	555,710 (43.19%)	662,837 (42.45%)	403,177 (40.54%)	501,213 (43.67%)	311,312 (45.93%)
Age	–	Median [Q25 – Q75]	69 [62 – 77]	70 [60 – 76]	60 [33 – 72]	67 [51 – 75]	68 [55 – 77]	63 [43 – 73]
		Mean (SD)	67.06 (15.09)	66.36 (15.62)	52.17 (25.40)	61.96 (18.19)	63.86 (19.84)	55.00 (25.52)
		Range	1 to 106	1 to 110	0 to 109	1 to 107	1 to 112	1 to 107
Immunocompromised -365 to 0								
	Immunocompromised	N (%)	56,530 (16.06%)	136,347 (10.60%)	117,716 (7.54%)	158,485 (15.94%)	58,089 (5.06%)	21,989 (3.24%)
Pregnancy -280 to 0								
	Pregnancy	N (%)	736 (0.21%)	8,875 (0.69%)	37,724 (2.42%)	19,281 (1.94%)	15,487 (1.35%)	6,190 (0.91%)
Comorbidities -inf to 0								
	Acute renal disease	N (%)	11,145 (3.17%)	22,364 (1.74%)	62,251 (3.99%)	16,649 (1.67%)	66,564 (5.80%)	11,783 (1.74%)
	Anaemia	N (%)	63,766 (18.12%)	72,412 (5.63%)	86,353 (5.53%)	149,946 (15.08%)	218,476 (19.03%)	43,599 (6.43%)
	Asplenia	N (%)	657 (0.19%)	2,148 (0.17%)	969 (0.06%)	0 (0.00%)	32 (0.00%)	695 (0.10%)
	Asthma	N (%)	36,945 (10.50%)	284,049 (22.07%)	171,860 (11.01%)	201,233 (20.23%)	114,584 (9.98%)	80,092 (11.82%)
	Cancer	N (%)	68,724 (19.52%)	302,312 (23.49%)	176,070 (11.28%)	235,588 (23.69%)	176,972 (15.42%)	65,886 (9.72%)
	Cardiac conditions	N (%)	157,676 (44.80%)	359,370 (27.93%)	380,075 (24.34%)	406,483 (40.87%)	374,400 (32.62%)	105,107 (15.51%)
	Chronic liver disease	N (%)	12,094 (3.44%)	17,606 (1.37%)	13,891 (0.89%)	10,504 (1.06%)	96,593 (8.42%)	16,582 (2.45%)
	Chronic renal disease	N (%)	18,264 (5.19%)	25,335 (1.97%)	19,793 (1.27%)	26,701 (2.68%)	147,954 (12.89%)	56,317 (8.31%)
	COPD	N (%)	47,334 (13.45%)	156,000 (12.12%)	44,522 (2.85%)	113,708 (11.43%)	114,602 (9.98%)	36,312 (5.36%)
	Dementia	N (%)	8,901 (2.53%)	31,054 (2.41%)	50,919 (3.26%)	26,918 (2.71%)	47,648 (4.15%)	10,315 (1.52%)

Variable name	Variable level	Estimate name	Data sources					
			NAJS	DK-DHR	FinOMOP-THL	NLHR	SIDIAP	CPRD GOLD
	Diabetes mellitus	N (%)	104,108 (29.58%)	187,730 (14.59%)	232,752 (14.91%)	148,311 (14.91%)	236,812 (20.63%)	85,203 (12.57%)
	Hypertension	N (%)	270,688 (76.90%)	531,435 (41.30%)	457,342 (29.29%)	443,665 (44.61%)	510,798 (44.50%)	144,088 (21.26%)
	Lung disease	N (%)	37,450 (10.64%)	140,398 (10.91%)	54,057 (3.46%)	32,924 (3.31%)	213,296 (18.58%)	30,382 (4.48%)
	Neuromuscular disorders	N (%)	824 (0.23%)	2,976 (0.23%)	2,587 (0.17%)	1,774 (0.18%)	2,498 (0.22%)	877 (0.13%)
	Obesity	N (%)	34,446 (9.79%)	123,756 (9.62%)	66,234 (4.24%)	78,173 (7.86%)	323,367 (28.17%)	54,087 (7.98%)
	Rheumatologic diseases	N (%)	14,369 (4.08%)	47,689 (3.71%)	43,252 (2.77%)	98,038 (9.86%)	25,969 (2.26%)	10,859 (1.60%)
	Stroke	N (%)	16,626 (4.72%)	86,825 (6.75%)	55,317 (3.54%)	60,472 (6.08%)	47,579 (4.15%)	15,303 (2.26%)
	Tuberculosis	N (%)	1,449 (0.41%)	2,563 (0.20%)	1,044 (0.07%)	2,112 (0.21%)	3,712 (0.32%)	697 (0.10%)
Comorbidities -365 to 0								
	Acute renal disease	N (%)	3,649 (1.04%)	3,515 (0.27%)	14,808 (0.95%)	7,630 (0.77%)	15,330 (1.34%)	2,932 (0.43%)
	Anaemia	N (%)	38,571 (10.96%)	20,967 (1.63%)	43,003 (2.75%)	78,985 (7.94%)	66,743 (5.81%)	9,787 (1.44%)
	Cancer	N (%)	55,232 (15.69%)	122,280 (9.50%)	112,666 (7.22%)	139,119 (13.99%)	53,081 (4.62%)	18,198 (2.68%)
	Tuberculosis	N (%)	686 (0.19%)	326 (0.03%)	276 (0.02%)	314 (0.03%)	413 (0.04%)	105 (0.02%)
Vaccines -inf to -366								
	Herpes zoster vaccine	N (%)	13 (0.00%)	1,645 (0.13%)	27,683 (1.77%)	451 (0.05%)	16 (0.00%)	104,019 (15.35%)
	Pneumococcal vaccine	N (%)	3,012 (0.86%)	76,719 (5.96%)	371,843 (23.82%)	41,095 (4.13%)	461,158 (40.18%)	301,558 (44.50%)
	RSV vaccine	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vaccines -365 to -1								
	COVID-19 vaccine	N (%)	298 (0.08%)	181 (0.01%)	419 (0.03%)	458 (0.05%)	62 (0.01%)	1,043 (0.15%)
	Herpes zoster vaccine	N (%)	6 (0.00%)	368 (0.03%)	2,159 (0.14%)	317 (0.03%)	0 (0.00%)	12,216 (1.80%)
	Pneumococcal vaccine	N (%)	1,369 (0.39%)	367,415 (28.55%)	110,613 (7.08%)	121,216 (12.19%)	38,193 (3.33%)	17,134 (2.53%)
	RSV vaccine	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vaccines index date								
	COVID-19 vaccine	N (%)	91 (0.03%)	12 (0.00%)	76 (0.00%)	121 (0.01%)	6 (0.00%)	55 (0.01%)

Variable name	Variable level	Estimate name	Data sources					
			NAJS	DK-DHR	FinOMOP-THL	NLHR	SIDIAP	CPRD GOLD
	Herpes zoster vaccine	N (%)	<5	24 (0.00%)	125 (0.01%)	18 (0.00%)	0 (0.00%)	3,150 (0.46%)
	Pneumococcal vaccine	N (%)	591 (0.17%)	345,198 (26.83%)	35,007 (2.24%)	60,680 (6.10%)	48,191 (4.20%)	9,636 (1.42%)
	RSV vaccine	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

COPD= Chronic Obstructive Pulmonary Disease; CPRD= Clinical Practice Research Datalink; DK-DHR= Danish Data Health Registries; FinOMOP-THL= Finnish Care Register for Health Care; Q= Quartile; NAJS= National Public Health Information System; NLHR= Norwegian Linked Health Registry data; RSV= Respiratory Syncytial Virus; SD= Standard Deviation; SIDIAP= The Information System for Research in Primary Care

Table 11: Baseline characteristics of influenza vaccine recipients by data source for influenza season 2021/22.

Variable name	Variable level	Estimate name	Data sources					
			NAJS	DK-DHR	FinOMOP-THL	NLHR	SIDIAP	CPRD GOLD
Demographics index date								
Number individuals	–	N	314,676	1,657,675	1,833,656	1,345,086	1,079,610	928,888
Sex	Female	N (%)	172,385 (54.78%)	920,787 (55.55%)	1,053,903 (57.48%)	777,777 (57.82%)	608,142 (56.33%)	504,613 (54.32%)
	Male	N (%)	142,291 (45.22%)	736,888 (44.45%)	779,753 (42.52%)	567,309 (42.18%)	471,468 (43.67%)	424,275 (45.68%)
Age	–	Median [Q25 – Q75]	70 [64 – 78]	66 [51 – 75]	60 [39 – 73]	63 [46 – 73]	70 [61 – 79]	61 [46 – 72]
		Mean (SD)	68.78 (13.99)	60.24 (21.83)	54.75 (23.39)	59.29 (18.54)	67.03 (18.15)	55.63 (23.23)
		Range	1 to 107	1 to 111	1 to 109	1 to 108	1 to 113	1 to 107
Immunocompromised -365 to 0								
	Immunocompromised	N (%)	50,243 (15.97%)	151,577 (9.14%)	146,339 (7.98%)	188,024 (13.98%)	60,224 (5.58%)	26,529 (2.86%)
Pregnancy -280 to 0								
	Pregnancy	N (%)	363 (0.12%)	11,041 (0.67%)	36,705 (2.00%)	23,896 (1.78%)	11,039 (1.02%)	5,391 (0.58%)
Comorbidities -inf to 0								
	Acute renal disease	N (%)	11,324 (3.60%)	26,975 (1.63%)	79,003 (4.31%)	22,742 (1.69%)	69,261 (6.42%)	14,420 (1.55%)
	Anaemia	N (%)	62,850 (19.97%)	82,772 (4.99%)	108,080 (5.89%)	195,222 (14.51%)	217,909 (20.18%)	54,886 (5.91%)
	Asplenia	N (%)	661 (0.21%)	2,289 (0.14%)	1,157 (0.06%)	0 (0.00%)	40 (0.00%)	748 (0.08%)
	Asthma	N (%)	34,044 (10.82%)	348,413 (21.02%)	206,891 (11.28%)	257,501 (19.14%)	102,972 (9.54%)	91,159 (9.81%)
	Cancer	N (%)	65,128 (20.70%)	340,020 (20.51%)	218,696 (11.93%)	290,793 (21.62%)	187,258 (17.34%)	83,747 (9.02%)
	Cardiac conditions	N (%)	149,071 (47.37%)	395,867 (23.88%)	464,557 (25.34%)	492,143 (36.59%)	383,393 (35.51%)	131,080 (14.11%)
	Chronic liver disease	N (%)	12,376 (3.93%)	19,995 (1.21%)	18,808 (1.03%)	13,675 (1.02%)	101,505 (9.40%)	22,959 (2.47%)
	Chronic renal disease	N (%)	18,756 (5.96%)	26,882 (1.62%)	24,529 (1.34%)	31,921 (2.37%)	154,721 (14.33%)	65,540 (7.06%)
	COPD	N (%)	45,479 (14.45%)	164,074 (9.90%)	53,329 (2.91%)	130,778 (9.72%)	115,175 (10.67%)	43,468 (4.68%)
	Dementia	N (%)	9,759 (3.10%)	33,384 (2.01%)	66,718 (3.64%)	31,685 (2.36%)	50,010 (4.63%)	12,041 (1.30%)

Variable name	Variable level	Estimate name	Data sources					
			NAJS	DK-DHR	FinOMOP-THL	NLHR	SIDIAP	CPRD GOLD
	Diabetes mellitus	N (%)	99,836 (31.73%)	205,077 (12.37%)	281,530 (15.35%)	172,105 (12.80%)	241,468 (22.37%)	105,816 (11.39%)
	Hypertension	N (%)	251,181 (79.82%)	590,763 (35.64%)	580,468 (31.66%)	536,993 (39.92%)	525,148 (48.64%)	186,064 (20.03%)
	Lung disease	N (%)	36,243 (11.52%)	156,970 (9.47%)	64,580 (3.52%)	41,751 (3.10%)	209,079 (19.37%)	34,341 (3.70%)
	Neuromuscular disorders	N (%)	798 (0.25%)	3,454 (0.21%)	3,213 (0.18%)	2,245 (0.17%)	2,741 (0.25%)	1,070 (0.12%)
	Obesity	N (%)	33,418 (10.62%)	150,106 (9.06%)	86,496 (4.72%)	114,757 (8.53%)	321,974 (29.82%)	83,710 (9.01%)
	Rheumatologic diseases	N (%)	13,465 (4.28%)	52,375 (3.16%)	52,146 (2.84%)	121,624 (9.04%)	26,686 (2.47%)	13,143 (1.41%)
	Stroke	N (%)	16,831 (5.35%)	93,248 (5.63%)	68,957 (3.76%)	71,402 (5.31%)	50,313 (4.66%)	19,775 (2.13%)
	Tuberculosis	N (%)	1,397 (0.44%)	2,770 (0.17%)	1,245 (0.07%)	2,623 (0.20%)	3,440 (0.32%)	927 (0.10%)
Comorbidities -365 to 0								
	Acute renal disease	N (%)	3,079 (0.98%)	4,331 (0.26%)	18,126 (0.99%)	8,740 (0.65%)	16,194 (1.50%)	3,580 (0.39%)
	Anaemia	N (%)	34,954 (11.11%)	21,654 (1.31%)	50,863 (2.77%)	93,356 (6.94%)	65,651 (6.08%)	10,492 (1.13%)
	Cancer	N (%)	49,220 (15.64%)	131,646 (7.94%)	136,601 (7.45%)	164,503 (12.23%)	54,124 (5.01%)	20,846 (2.24%)
	Tuberculosis	N (%)	525 (0.17%)	301 (0.02%)	293 (0.02%)	387 (0.03%)	347 (0.03%)	129 (0.01%)
Vaccines -inf to -366								
	Herpes zoster vaccine	N (%)	10 (0.00%)	2,370 (0.14%)	25,286 (1.38%)	879 (0.07%)	14 (0.00%)	130,576 (14.06%)
	Pneumococcal vaccine	N (%)	3,367 (1.07%)	679,836 (41.01%)	449,852 (24.54%)	196,451 (14.61%)	490,939 (45.47%)	361,919 (38.97%)
	RSV vaccine	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vaccines -365 to -1								
	COVID-19 vaccine	N (%)	291,536 (92.65%)	1,530,497 (92.33%)	1,667,215 (90.92%)	1,327,219 (98.67%)	1,042,383 (96.55%)	819,608 (88.24%)
	Herpes zoster vaccine	N (%)	25 (0.01%)	1,076 (0.06%)	2,424 (0.13%)	355 (0.03%)	6 (0.00%)	10,828 (1.17%)
	Pneumococcal vaccine	N (%)	1,494 (0.47%)	235,726 (14.22%)	65,268 (3.56%)	66,694 (4.96%)	31,827 (2.95%)	13,674 (1.47%)
	RSV vaccine	N (%)	0 (0.00%)	5 (0.00%)	<5	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vaccines index date								
	COVID-19 vaccine	N (%)	4,623 (1.47%)	6,414 (0.39%)	237,568 (12.96%)	5,115 (0.38%)	352,670 (32.67%)	423,670 (45.61%)

Variable name	Variable level	Estimate name	Data sources					
			NAJS	DK-DHR	FinOMOP-THL	NLHR	SIDIAP	CPRD GOLD
	Herpes zoster vaccine	N (%)	<5	101 (0.01%)	257 (0.01%)	16 (0.00%)	11 (0.00%)	1,011 (0.11%)
	Pneumococcal vaccine	N (%)	576 (0.18%)	93,264 (5.63%)	7,428 (0.41%)	22,242 (1.65%)	12,853 (1.19%)	3,096 (0.33%)
	RSV vaccine	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

COPD= Chronic Obstructive Pulmonary Disease; CPRD= Clinical Practice Research Datalink; DK-DHR= Danish Data Health Registries; FinOMOP-THL= Finnish Care Register for Health Care; Q= Quartile; NAJS= National Public Health Information System; NLHR= Norwegian Linked Health Registry data; RSV= Respiratory Syncytial Virus; SD= Standard Deviation; SIDIAP= The Information System for Research in Primary Care

Table 12: Baseline characteristics of influenza vaccine recipients by data source for influenza season 2022/23.

Variable name	Variable level	Estimate name	Data sources					
			NAJS	DK-DHR	FinOMOP-THL	NLHR	SIDIAP	CPRD GOLD
Demographics index date								
Number individuals	–	N	326,899	1,541,950	1,675,831	1,308,719	1,001,284	807,442
Sex	Female	N (%)	178,682 (54.66%)	843,912 (54.73%)	972,276 (58.02%)	743,215 (56.79%)	549,518 (54.88%)	430,088 (53.27%)
	Male	N (%)	148,217 (45.34%)	698,038 (45.27%)	703,555 (41.98%)	565,504 (43.21%)	451,766 (45.12%)	377,354 (46.73%)
Age	–	Median [Q25 – Q75]	71 [64 – 78]	69 [56 – 76]	62 [41 – 74]	64 [48 – 74]	70 [61 – 78]	61 [44 – 71]
		Mean (SD)	69.25 (13.81)	63.53 (19.87)	56.05 (23.20)	60.25 (18.51)	67.05 (17.51)	54.05 (24.00)
		Range	1 to 108	1 to 112	1 to 107	1 to 109	1 to 114	1 to 108
Immunocompromised -365 to 0								
	Immunocompromised	N (%)	54,222 (16.59%)	150,746 (9.78%)	141,818 (8.46%)	187,408 (14.32%)	57,008 (5.69%)	24,415 (3.02%)
Pregnancy -280 to 0								
	Pregnancy	N (%)	470 (0.14%)	7,269 (0.47%)	32,311 (1.93%)	20,663 (1.58%)	8,506 (0.85%)	4,378 (0.54%)
Comorbidities -inf to 0								
	Acute renal disease	N (%)	12,978 (3.97%)	27,146 (1.76%)	77,743 (4.64%)	26,700 (2.04%)	64,414 (6.43%)	12,354 (1.53%)
	Anaemia	N (%)	71,151 (21.77%)	81,124 (5.26%)	108,208 (6.46%)	200,296 (15.30%)	198,247 (19.80%)	45,951 (5.69%)
	Asplenia	N (%)	732 (0.22%)	2,253 (0.15%)	1,165 (0.07%)	0 (0.00%)	40 (0.00%)	656 (0.08%)
	Asthma	N (%)	36,553 (11.18%)	326,377 (21.17%)	200,801 (11.98%)	256,533 (19.60%)	95,037 (9.49%)	79,793 (9.88%)
	Cancer	N (%)	71,365 (21.83%)	352,138 (22.84%)	218,446 (13.04%)	301,355 (23.03%)	179,582 (17.94%)	71,656 (8.87%)
	Cardiac conditions	N (%)	159,056 (48.66%)	401,240 (26.02%)	455,729 (27.19%)	500,443 (38.24%)	356,869 (35.64%)	108,778 (13.47%)
	Chronic liver disease	N (%)	14,154 (4.33%)	20,421 (1.32%)	18,904 (1.13%)	14,098 (1.08%)	101,962 (10.18%)	21,101 (2.61%)
	Chronic renal disease	N (%)	21,845 (6.68%)	27,609 (1.79%)	24,859 (1.48%)	33,328 (2.55%)	138,447 (13.83%)	51,454 (6.37%)
	COPD	N (%)	47,992 (14.68%)	165,119 (10.71%)	50,454 (3.01%)	131,632 (10.06%)	106,541 (10.64%)	35,098 (4.35%)
	Dementia	N (%)	11,149 (3.41%)	34,144 (2.21%)	67,496 (4.03%)	33,251 (2.54%)	37,350 (3.73%)	9,039 (1.12%)

Variable name	Variable level	Estimate name	Data sources					
			NAJS	DK-DHR	FinOMOP-THL	NLHR	SIDIAP	CPRD GOLD
	Diabetes mellitus	N (%)	108,048 (33.05%)	208,427 (13.52%)	266,493 (15.90%)	171,780 (13.13%)	225,832 (22.55%)	90,480 (11.21%)
	Hypertension	N (%)	262,431 (80.28%)	605,770 (39.29%)	575,930 (34.37%)	543,818 (41.55%)	490,644 (49.00%)	159,349 (19.74%)
	Lung disease	N (%)	39,894 (12.20%)	155,270 (10.07%)	63,132 (3.77%)	44,784 (3.42%)	198,374 (19.81%)	30,503 (3.78%)
	Neuromuscular disorders	N (%)	866 (0.26%)	3,510 (0.23%)	3,194 (0.19%)	2,273 (0.17%)	2,556 (0.26%)	941 (0.12%)
	Obesity	N (%)	35,677 (10.91%)	143,522 (9.31%)	90,378 (5.39%)	123,001 (9.40%)	305,037 (30.46%)	68,008 (8.42%)
	Rheumatologic diseases	N (%)	14,697 (4.50%)	52,714 (3.42%)	49,900 (2.98%)	124,432 (9.51%)	25,688 (2.57%)	11,545 (1.43%)
	Stroke	N (%)	18,473 (5.65%)	95,844 (6.22%)	66,932 (3.99%)	73,099 (5.59%)	45,260 (4.52%)	15,895 (1.97%)
	Tuberculosis	N (%)	1,522 (0.47%)	2,680 (0.17%)	1,153 (0.07%)	2,473 (0.19%)	3,220 (0.32%)	706 (0.09%)
Comorbidities -365 to 0								
	Acute renal disease	N (%)	3,460 (1.06%)	4,658 (0.30%)	16,407 (0.98%)	9,665 (0.74%)	15,629 (1.56%)	3,043 (0.38%)
	Anaemia	N (%)	39,033 (11.94%)	21,647 (1.40%)	50,988 (3.04%)	93,346 (7.13%)	62,198 (6.21%)	9,435 (1.17%)
	Cancer	N (%)	52,560 (16.08%)	137,250 (8.90%)	135,253 (8.07%)	168,295 (12.86%)	55,338 (5.53%)	18,862 (2.34%)
	Tuberculosis	N (%)	500 (0.15%)	307 (0.02%)	271 (0.02%)	381 (0.03%)	331 (0.03%)	102 (0.01%)
Vaccines -inf to -366								
	Herpes zoster vaccine	N (%)	45 (0.01%)	3,135 (0.20%)	22,679 (1.35%)	1,195 (0.09%)	16 (0.00%)	105,968 (13.13%)
	Pneumococcal vaccine	N (%)	4,752 (1.45%)	870,488 (56.45%)	440,951 (26.32%)	253,475 (19.37%)	463,725 (46.31%)	319,461 (39.57%)
	RSV vaccine	N (%)	0 (0.00%)	<5	<5	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vaccines -365 to -1								
	COVID-19 vaccine	N (%)	230,090 (70.39%)	1,393,324 (90.36%)	1,389,568 (82.92%)	1,177,792 (90.00%)	828,697 (82.76%)	621,594 (76.98%)
	Herpes zoster vaccine	N (%)	44 (0.01%)	6,444 (0.42%)	13,913 (0.83%)	673 (0.05%)	1,140 (0.11%)	17,372 (2.15%)
	Pneumococcal vaccine	N (%)	5,608 (1.72%)	85,637 (5.55%)	40,286 (2.40%)	42,044 (3.21%)	25,427 (2.54%)	47,280 (5.86%)
	RSV vaccine	N (%)	0 (0.00%)	<5	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vaccines index date								
	COVID-19 vaccine	N (%)	3,791 (1.16%)	974,015 (63.17%)	413,259 (24.66%)	30,868 (2.36%)	679,672 (67.88%)	472,880 (58.57%)

Variable name	Variable level	Estimate name	Data sources					
			NAJS	DK-DHR	FinOMOP-THL	NLHR	SIDIAP	CPRD GOLD
	Herpes zoster vaccine	N (%)	<5	314 (0.02%)	410 (0.02%)	62 (0.00%)	416 (0.04%)	541 (0.07%)
	Pneumococcal vaccine	N (%)	3,374 (1.03%)	126,722 (8.22%)	4,636 (0.28%)	24,876 (1.90%)	1,885 (0.19%)	2,714 (0.34%)
	RSV vaccine	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

COPD= Chronic Obstructive Pulmonary Disease; CPRD= Clinical Practice Research Datalink; DK-DHR= Danish Data Health Registries; FinOMOP-THL= Finnish Care Register for Health Care; Q= Quartile; NAJS= National Public Health Information System; NLHR= Norwegian Linked Health Registry data; RSV= Respiratory Syncytial Virus; SD= Standard Deviation; SIDIAP= The Information System for Research in Primary Care

Table 13: Baseline characteristics of influenza vaccine recipients by data source for influenza season 2023/24.

Variable name	Variable level	Estimate name	Data sources			
			NAJS	DK-DHR	FinOMOP-THL	CPRD GOLD
Demographics index date						
Number individuals	–	N	316,062	1,418,809	1,645,229	638,637
Sex	Female	N (%)	170,933 (54.08%)	773,633 (54.53%)	950,236 (57.76%)	344,791 (53.99%)
	Male	N (%)	145,129 (45.92%)	645,176 (45.47%)	694,993 (42.24%)	293,846 (46.01%)
Age	–	Median [Q25 – Q75]	71 [65 – 78]	70 [58 – 77]	62 [41 – 74]	64 [27 – 75]
		Mean (SD)	69.75 (13.78)	64.81 (19.24)	56.19 (23.23)	53.17 (27.70)
		Range	1 to 108	1 to 109	0 to 108	1 to 109
Immunocompromised -365 to 0						
	Immunocompromised	N (%)	54,230 (17.16%)	146,404 (10.32%)	142,453 (8.66%)	21,944 (3.44%)
Pregnancy -280 to 0						
	Pregnancy	N (%)	604 (0.19%)	6,369 (0.45%)	31,126 (1.89%)	3,394 (0.53%)
Comorbidities -inf to 0						
	Acute renal disease	N (%)	13,589 (4.30%)	26,721 (1.88%)	79,652 (4.84%)	11,584 (1.81%)
	Anaemia	N (%)	75,778 (23.98%)	77,148 (5.44%)	112,890 (6.86%)	37,885 (5.93%)
	Asplenia	N (%)	751 (0.24%)	2,144 (0.15%)	1,154 (0.07%)	569 (0.09%)
	Asthma	N (%)	36,855 (11.66%)	308,038 (21.71%)	206,915 (12.58%)	62,014 (9.71%)
	Cancer	N (%)	73,663 (23.31%)	344,093 (24.25%)	221,527 (13.46%)	65,196 (10.21%)
	Cardiac conditions	N (%)	158,835 (50.25%)	389,799 (27.47%)	463,494 (28.17%)	100,241 (15.70%)
	Chronic liver disease	N (%)	15,049 (4.76%)	19,579 (1.38%)	20,415 (1.24%)	17,150 (2.69%)
	Chronic renal disease	N (%)	23,586 (7.46%)	27,586 (1.94%)	25,928 (1.58%)	51,578 (8.08%)
	COPD	N (%)	47,913 (15.16%)	157,071 (11.07%)	51,208 (3.11%)	30,852 (4.83%)
	Dementia	N (%)	11,784 (3.73%)	34,147 (2.41%)	66,150 (4.02%)	10,052 (1.57%)
	Diabetes mellitus	N (%)	109,907 (34.77%)	201,439 (14.20%)	265,458 (16.14%)	80,037 (12.53%)
	Hypertension	N (%)	256,726 (81.23%)	586,080 (41.31%)	589,509 (35.83%)	134,414 (21.05%)

Variable name	Variable level	Estimate name	Data sources			
			NAJS	DK-DHR	FinOMOP-THL	CPRD GOLD
	Lung disease	N (%)	41,063 (12.99%)	148,860 (10.49%)	64,720 (3.93%)	28,013 (4.39%)
	Neuromuscular disorders	N (%)	922 (0.29%)	3,517 (0.25%)	3,294 (0.20%)	870 (0.14%)
	Obesity	N (%)	36,857 (11.66%)	145,957 (10.29%)	100,613 (6.12%)	52,967 (8.29%)
	Rheumatologic diseases	N (%)	14,969 (4.74%)	51,868 (3.66%)	49,651 (3.02%)	10,123 (1.59%)
	Stroke	N (%)	18,730 (5.93%)	91,169 (6.43%)	66,375 (4.03%)	15,372 (2.41%)
	Tuberculosis	N (%)	1,565 (0.50%)	2,508 (0.18%)	1,131 (0.07%)	603 (0.09%)
Comorbidities -365 to 0						
	Acute renal disease	N (%)	3,597 (1.14%)	4,623 (0.33%)	16,092 (0.98%)	2,976 (0.47%)
	Anaemia	N (%)	42,488 (13.44%)	20,821 (1.47%)	52,224 (3.17%)	8,727 (1.37%)
	Cancer	N (%)	54,054 (17.10%)	130,824 (9.22%)	136,191 (8.28%)	17,491 (2.74%)
	Tuberculosis	N (%)	503 (0.16%)	294 (0.02%)	262 (0.02%)	70 (0.01%)
Vaccines -inf to -366						
	Herpes zoster vaccine	N (%)	91 (0.03%)	9,024 (0.64%)	32,398 (1.97%)	122,132 (19.13%)
	Pneumococcal vaccine	N (%)	11,846 (3.75%)	926,613 (65.31%)	428,979 (26.08%)	339,581 (53.18%)
	RSV vaccine	N (%)	0 (0.00%)	5 (0.00%)	<5	0 (0.00%)
Vaccines -365 to -1						
	COVID-19 vaccine	N (%)	19,302 (6.11%)	437,043 (30.80%)	260,802 (15.85%)	290,916 (45.55%)
	Herpes zoster vaccine	N (%)	59 (0.02%)	11,272 (0.79%)	11,759 (0.71%)	25,838 (4.05%)
	Pneumococcal vaccine	N (%)	7,582 (2.40%)	66,276 (4.67%)	37,275 (2.27%)	29,315 (4.59%)
	RSV vaccine	N (%)	0 (0.00%)	7 (0.00%)	<5	0 (0.00%)
Vaccines index date						
	COVID-19 vaccine	N (%)	2,191 (0.69%)	926,918 (65.33%)	759,176 (46.14%)	336,992 (52.77%)
	Herpes zoster vaccine	N (%)	0 (0.00%)	151 (0.01%)	184 (0.01%)	2,161 (0.34%)
	Pneumococcal vaccine	N (%)	4,220 (1.34%)	401 (0.03%)	8,059 (0.49%)	2,186 (0.34%)
	RSV vaccine	N (%)	0 (0.00%)	<5	0 (0.00%)	0 (0.00%)

COPD= Chronic Obstructive Pulmonary Disease; CPRD= Clinical Practice Research Datalink; DK-DHR= Danish Data Health Registries; FinOMOP-THL= Finnish Care Register for Health Care; Q= Quartile; NAJS= National Public Health Information System; RSV= Respiratory Syncytial Virus; SD= Standard Deviation

9.2.4. Objective 4: Population-level descriptive epidemiology of influenza-related clinical outcomes

General population

ILI, ARI, SARI, acute respiratory infection (broader definition), and influenza

Figure 13 presents the incidence rates of the primary outcomes (ARI, ILI, and SARI) and the secondary outcomes (acute respiratory infection (broader definition) and influenza) among the general population across participating data sources from the 2015/16 to the 2023/24 influenza seasons. Data for SARI are not shown for CPRD GOLD, as hospitalisation data were not available for this data source.

Overall, ARI and acute respiratory infection (broader definition) were the most frequently observed outcomes across all data sources and seasons, with incidence rates ranging between 2,000 and 47,500 and between 1,000 and 21,000 cases per 100,000 person-years, respectively. FinOMOP-THL recorded the highest rates of acute respiratory infection (broader definition), with values exceeding 20,000 cases per 100,000 person-years in some seasons, whereas NAJS reported the highest ARI rates, with more than 45,000 cases per 100,000 person-years in most seasons with available data. A marked decrease in both ARI and acute respiratory infection (broader definition) was observed in SIDIAP and CPRD GOLD during the 2020/21 season, followed by an increase in subsequent seasons. Incidence of ARI and acute respiratory infection (broader definition) also dropped during the 2020/21 season in DK-DHR and NLHR albeit with less magnitude. In contrast, FinOMOP-THL displayed the opposite pattern, with a sharp rise in acute respiratory infection (broader definition) during the 2020/21 and 2021/22 seasons. For NAJS, although data prior to 2020 were not available, an increase after 2020/21 was also observed, particularly for ARI.

Compared with ARI and acute respiratory infections (broader definition), ILI, SARI, and influenza were less frequent, with incidence rates generally remaining below 1,000 per 100,000 person-years across all data sources. Exceptions included influenza in NLHR, which exceeded 1,000 cases per 100,000 person-years in some seasons; ILI in NAJS, which approached 2,000 cases per 100,000 person-years in certain seasons; and SARI in NAJS, which surpassed 3,800 cases per 100,000 person-years. However, hospitalisation cohort in NAJS include secondary day-care encounters that were mapped to inpatient care; therefore, all hospitalisation-related rates do not exclusively represent inpatient admissions and should not be directly compared with hospitalisation rates from the other data sources. ILI incidence was particularly low in DK-DHR, SIDIAP, and CPRD GOLD. Influenza incidence in DK-DHR and CPRD GOLD was also low, with rates below 170 cases per 100,000 person-years.

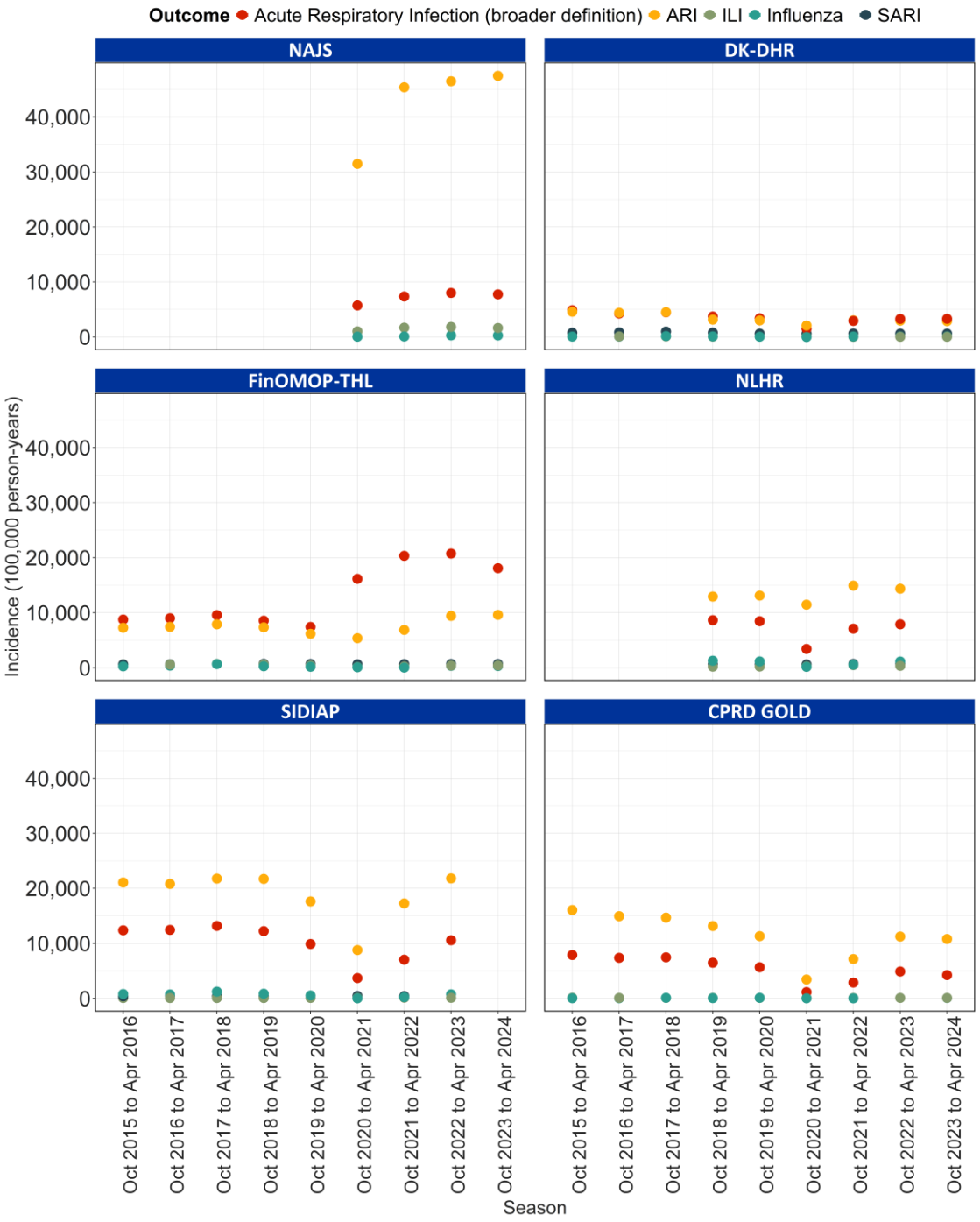


Figure 13. Incidence rates of primary outcomes (ILI, ARI, and SARI) and secondary outcomes (acute respiratory infection (broader definition), and influenza) in the general population from 2015/16 to 2023/24 influenza seasons by data source.

Data for SARI are not shown for CPRD GOLD, as hospitalisation data were not available for this data source. In NAJS, SARI estimates for 2022/23 and 2023/24 are also not presented because hospitalisation data were unavailable after 2022. Estimates for SARI are also not shown for the 2022/23 season in SIDIAP, as hospitalisation data were unavailable for the first half of 2023.
ARI = Acute Respiratory Infection; CPRD= Clinical Practice Research Datalink; DK-DHR= Danish Data Health Registries; FinOMOP-THL= Finnish Care Register for Health Care; ILI = Influenza-Like Illness; NAJS= National Public Health Information System; NLHR= Norwegian Linked Health Registry data; SARI = Severe Acute Respiratory Infection; SIDIAP= The Information System for Research in Primary Care

When stratified by sex (**Figure S7** in **ANNEX V**), the overall trend remained similar, although females had slightly higher incidence rates for most outcomes compared with males across all data sources. When stratified by age groups (**Figure S8** in **ANNEX V**), incidence rates for ARI were generally highest among the youngest individuals (<6 years), except in DK-DHR, where the highest rates were observed among the oldest age group. In contrast, incidence rates for acute respiratory infection (broader definition) were often highest among the oldest group (≥65 years), except in FinOMOP-THL and CPRD GOLD, where the highest rates were observed among the youngest individuals. In SIDIAP, ARI incidence was higher than that of acute respiratory infection (broader definition) among the youngest individuals, whereas among the oldest group, acute respiratory infection (broader definition) showed higher rates than ARI. In FinOMOP-THL and NLHR, incidence rates for ARI and acute respiratory infection (broader definition) were similar among the oldest age group. Similarly, incidence rates for ILI, SARI, and influenza were highest among the youngest (<6 years) and oldest (≥65 years) age groups across all data sources, except for ILI in NAJS, where rates were lowest in the oldest group, and for influenza in NAJS, where the second-highest incidence after the oldest group was observed among adults aged 18–64 years.

Hospitalisation and death

Figure 14 presents the incidence rates of all-cause hospitalisation, all-cause death, influenza-related hospitalisation, and influenza-related death across participating among the general population across participating data sources from the 2015/16 to the 2023/24 influenza seasons. Data for hospitalisation outcomes are not shown for CPRD GOLD, as hospitalisation data were not available for this data source.

Overall, incidence rates for all-cause hospitalisation ranged from approximately 10,000 to 54,000 per 100,000 person-years across data sources and seasons. NAJS reported rates more than double those observed in the other data sources because, as previously noted, the hospitalisation cohort includes secondary day-care encounters that were mapped to inpatient care. Excluding NAJS, rates were highest in DK-DHR, followed by FinOMOP-THL, NLHR, and SIDIAP. Across most data sources, incidence rates remained relatively stable over time, except for DK-DHR, which showed higher rates in 2015/16 to 2018/19, followed by a decline from 2018/19 to 2019/20 and stabilisation thereafter. Influenza-related hospitalisation had lower incidence rate compared with all-cause hospitalisation. Excluding NAJS, the remaining data sources reported rates below 2,100 per 100,000 person-years. Where data were available, a decrease was observed during the 2019/20–2020/21 seasons.

The incidence of all-cause death remained low across all data sources, ranging approximately between 750 and 1,600 per 100,000 person-years. A slight increase was observed from the 2019/20 season in CPRD GOLD, the 2020/21 season in SIDIAP, and the 2021/22 season in DK-DHR, FinOMOP-THL, and NLHR, while NAJS showed a decrease from 2022/23 onwards. Influenza-related deaths occurred at lower rates than all-cause deaths, remaining below 370 per 100,000 person-years across all data sources, with NAJS reporting the highest rates. Notably, influenza-related deaths showed a marked increase in SIDIAP during the 2019/20 and 2020/21 seasons, before returning to previous levels in 2021/22, with a similar rise observed in NAJS, DK-DHR, FinOMOP-THL, and NLHR during the 2021/22 season.

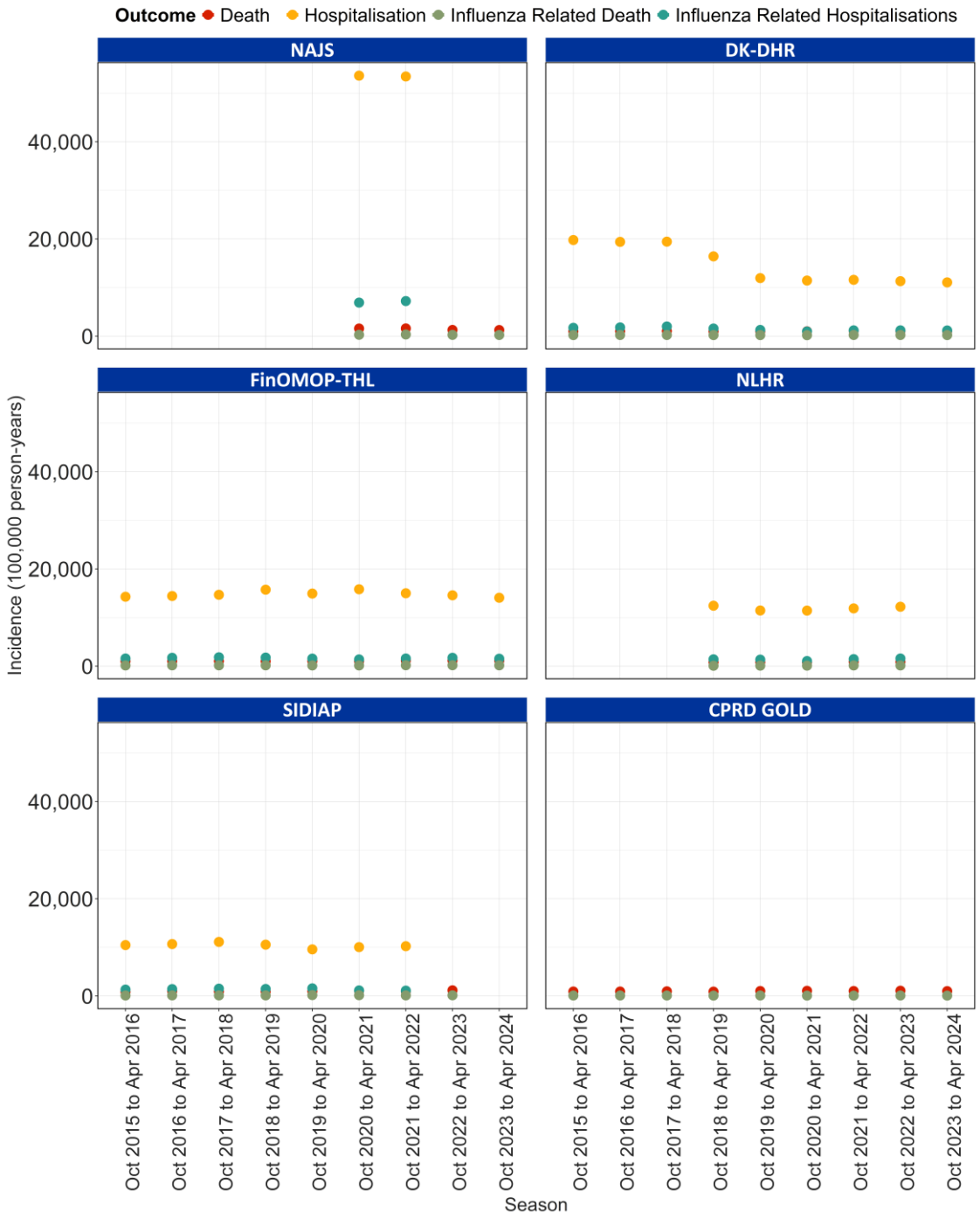


Figure 14. Incidence rates of all-cause hospitalisation, all-cause death, influenza-related hospitalisation, and influenza-related death in the general population from 2015/16 to 2023/24 influenza seasons by data source.

Data for hospitalisation outcomes are not shown for CPRD GOLD, as hospitalisation data were not available for this data source. In NAJS, estimates for hospitalisation outcomes for 2022/23 and 2023/24 are also not presented because hospitalisation data were unavailable after 2022. Estimates for hospitalisation outcomes are also not shown for the 2022/23 season in SIDIAP, as hospitalisation data were unavailable for the first half of 2023.
CPRD= Clinical Practice Research Datalink; DK-DHR= Danish Data Health Registries; FinOMOP-THL= Finnish Care Register for Health Care; NAJS= National Public Health Information System; NLHR= Norwegian Linked Health Registry data; SIDIAP= The Information System for Research in Primary Care

When stratified by sex (**Figure S9** in **ANNEX V**), overall trends were similar for both males and females. However, females had slightly higher incidence rates of all-cause hospitalisation compared with males across all data sources with available data. A similar pattern was observed for influenza-related hospitalisation, with rates slightly higher among females in FinOMOP-THL and NLHR. In contrast, influenza-related hospitalisation incidence was higher among males in DK-DHR and SIDIAP, as was the incidence of all-cause death in all data sources except NLHR. Similarly, the incidence of influenza-related death was generally higher in the male population. When stratified by age groups (**Figure S10** in **ANNEX V**), the incidence of all-cause hospitalisation was highest among individuals aged ≥65 years. The incidence of all-cause death was similarly highest among the oldest group, remaining very low among children and younger adults. Similar differences by age group were observed for both influenza-related hospitalisation and influenza-related death.

Unvaccinated and vaccinated population

The unvaccinated and vaccinated populations showed overall temporal and age/sex patterns that were similar to those observed in the general population (**Figures S11–S22** in **ANNEX V**). Absolute incidence rates were higher in the vaccinated population for several outcomes, particularly acute respiratory infection (broader definition), hospitalisation, and mortality, likely reflecting their older age distribution and higher burden of chronic conditions, consistent with the target groups for seasonal influenza vaccination. As this study is descriptive, crude rates in unvaccinated and vaccinated groups are presented for contextual reference only. These differences reflect underlying population characteristics and should not be interpreted as indicators of vaccine effect.

9.3. Sensitivity analyses

When removing the requirement for full-year contribution in the estimation of period prevalence, prevalence estimates were slightly lower; however, no striking differences in results were observed compared with the main analysis. For SARI, using the 10-day window definition instead of 14 days resulted in marginally lower incidence rates, but overall trends remained consistent. Similarly, results for influenza-related hospitalisation (10-day window) and influenza-related death (10-day window) were slightly lower but comparable to the main analyses (14-day window). Full results can be explored in the ShinyApp EUPAS1000000803.

10. DISCUSSION

10.1. Key results

Influenza vaccination prevalence ranged between approximately 11% and 22% from 2015/16 to 2019/20 across participating data sources with available data, with small increases over time in DK-DHR and FinOMOP-THL and more stable trends in SIDIAP and CPRD GOLD. A sharp increase was observed from the 2020/21 season in DK-DHR, FinOMOP-THL, NLHR, and SIDIAP, and from the 2021/22 season in CPRD GOLD, reaching up to approximately 30% in some data sources. Following these peaks, vaccination prevalence declined slightly. Throughout most of the study period, the highest prevalence was recorded in FinOMOP-THL, while the lowest was observed in NAJS.

Prevalence of influenza vaccination was highest among individuals aged 65 years or older (often exceeding 60% since 2020/21 season, except in NAJS, where the highest prevalence was 27%), followed by children under 6 years in DK-DHR (since the 2021/22 season), FinOMOP-THL, and CPRD GOLD (until the 2020/21 season), and individuals aged 18–64 years in NAJS, DK-DHR (until the 2021/21 season), NLHR, and SIDIAP, and individuals aged 6–17 years in CPRD GOLD since the 2021/22 season. NAJS and NLHR reported the lowest vaccination levels among children under six years. Notably, although influenza vaccination

prevalence increased across most age groups since the 2020/21 season, it did not rise among children under six years, except in DK-DHR. In CPRD GOLD, prevalence in this group even showed a slight decline.

Most vaccinations were administered between October and December of each influenza season, with peaks of vaccination typically observed in October or November. Fully detailed brand information on influenza vaccines was available only in DK-DHR and FinOMOP-THL, and complete information on route was available in these two data sources and in NAJS. The majority of influenza vaccines were administered by injection, while the nasal formulation was primarily used in individuals under 6 years.

Influenza vaccine recipients were predominantly older adults, with a median age ranging from 60 to 72 years across data sources. Females consistently accounted for a higher proportion of recipients (53–59%). Among all data sources, NAJS and SIDIAP included the oldest and the population with the most comorbidities. The most commonly recorded chronic conditions included hypertension, cardiac conditions, diabetes mellitus, asthma, and cancer, which were typical target groups for influenza vaccination recommendations. Pneumococcal vaccination was the most commonly observed prior vaccination. COVID-19 vaccine co-administration was first observed in 2021 and peaked during 2021–2023, followed by a decline in the most recent influenza seasons.

When considering influenza-related clinical outcomes in the general population as background incidence rates, ARI (from the primary outcome, defined by the presence of respiratory symptoms in VEBIS) and acute respiratory infections (from the secondary outcome, defined by a broader condition record of acute respiratory infection) were the most frequently observed outcomes. In contrast, incidence rates for ILI, SARI, and influenza were notably lower. Incidence rates of respiratory outcomes remained mostly stable throughout the study period, except for temporary drop during the 2020/21 season in all data sources with available data, except FinOMOP-THL, which showed the opposite pattern. Rates of ARI were generally highest among the youngest individuals (<6 years), whereas incidence rates for acute respiratory infection (broader definition) were often highest among individuals aged ≥65 years. For most respiratory outcomes, rates were also higher in females than males. All-cause hospitalisation and death in the general population remained generally stable over time, with a slight increase in all-cause mortality observed from the 2019/20 season in CPRD GOLD, the 2020/21 season in SIDIAP, and the 2021/22 season in DK-DHR, FinOMOP-THL, and NLHR. Influenza-related hospitalisation and death were infrequent. All-cause hospitalisation was more common among females, whereas all-cause and influenza-related deaths were generally more common among males. Both hospitalisation and death occurred generally more frequently among older adults aged ≥65 years.

10.2. Strengths and limitations of the research methods

The results estimated from this study reflect only the populations represented in the included data sources. EHR have certain inherent limitations because they are collected primarily for clinical purposes rather than for research use. Despite this, four of the six data sources included in the current study (NAJS, DK-DHR, FinOMOP-THL, and NLHR) were nationwide data sources containing both primary and secondary healthcare data, and therefore the results generated are broadly representative of influenza vaccination prevalence (Objective 1) at the population level. The remaining two data sources (SIDIAP and CPRD GOLD) were primary care data sources, with one (SIDIAP) having additional linkage to hospital data. These two data sources provided good population representativeness and valuable insights into influenza vaccine prevalence, thereby supporting the assessment of data availability for future vaccine effectiveness and safety studies.

Due to limitations in data availability across different data sources, prevalence estimates for influenza vaccination were not available for all influenza seasons during the study period (2015/16 to 2023/24), particularly due to the requirement for full-year data contribution for prevalence estimation, affecting NLHR and SIDIAP. Additionally, in NAJS, accurate vaccination data were only available from 2020 onwards

with the introduction of the centralised eVaccination records, so the study period started on 1st October 2020. Similarly, in NLHR, drug records were only available from 2018, and the study period started on 1st October 2018. As summarised in **Section 8.4**, this limitation applied to the following data sources (brackets denote influenza seasons contributed by each data source): NAJS (2020/21 to 2023/24), NLHR (2018/19 to 2022/23), and SIDIAP (2015/16 to 2022/23).

The influenza season was defined as October through April of the following year, so we reported season-specific prevalences in this study. However, influenza vaccinations may also occur outside the pre-specified influenza season. This is particularly relevant for Norway and the UK, where the beginning of the influenza season can fall in September. In the UK, for example, pregnant individuals and children are vaccinated in September, meaning that these vaccinations were not captured in this study.

In the current study design, if an individual received more than one influenza vaccination within the same influenza season, only the first vaccination was considered. During study execution, we observed a number of individuals with multiple vaccination records on the same date, including cases with multiple brand or route categories recorded. In such cases, these individuals were defined as having received influenza vaccinations with inconsistent brand or route information. Future IVE studies should consider such situations to ensure high data quality.

In this study, the route of administration (Objective 2) was derived from the dosage form of the recorded concept, rather than using the route table within the OMOP CDM, as not all data sources had this table fully populated. This approach required data mapping with sufficient granularity to identify dosage form information. While this may be considered a limitation of the methodology used to identify route of administration, this aligned with the main purpose of the current study, which was to assess data quality preparedness for future IVE studies. Route of administration may also serve as a proxy for influenza vaccine brand in specific situations, namely for products with an exclusive route (e.g., nasal versus injectable) and in seasons where a limited number of brands were available; however, this would require careful validation and consideration of temporal changes in product availability. Furthermore, influenza vaccine brand information (Objective 2) was not available in NAJS, NLHR, SIDIAP, and CPRD GOLD. Frequency of capture of certain vaccine information will also help inform the feasibility of including specific data sources in future IVE studies.

In the patient-level characterisation of influenza vaccine recipients (Objective 3), we considered clinical conditions associated with an increased risk of influenza or at risk of severe complications following infection as variables of interest. However, in practice, the indications for influenza vaccination are not limited to clinical conditions; they also include non-clinical factors such as being a cohabitant or caregiver of an immunosuppressed person, healthcare professionals, workers in institutions providing care for chronically ill or elderly individuals, and individuals working in essential public services. These groups are at close contact with persons vulnerable to influenza and are therefore eligible for vaccination. Such non-clinical conditions could not be captured and were not characterised in this study.

We applied a pragmatic approach to identify pregnancy status in the patient-level characterisation of influenza vaccine recipients, using a proxy of pregnancy-related codes recorded within 280 days (the standard pregnancy duration) before the vaccination date to identify women who were pregnant at the time of vaccination. We acknowledge that this approach may also capture women whose pregnancy ended before vaccination, however it was preferred to minimise the risk of missing pregnant individuals.

Additionally, the current definition of herpes zoster vaccination included both specific herpes zoster vaccine codes (identified by brand) and non-specific zoster vaccine codes. Efforts were made to exclude those with dosage forms corresponding to varicella vaccines rather than zoster. However, some varicella vaccinations may have been captured under the broader codes which is consistent with the observation that a few source codes for varicella vaccine were mapped to herpes zoster vaccine. Nevertheless, most

influenza vaccine recipients were older adults, which aligns with the primary indication for herpes zoster vaccination.

Hospitalisation data were also unavailable in CPRD GOLD. Consequently, outcomes such as SARI, all-cause hospitalisation, and influenza- or respiratory-related hospitalisation (Objective 4) were not assessed in CPRD GOLD. During study execution, it was identified that hospitalisation data in SIDIAP was unavailable for the first half of 2023; therefore, incidence estimates for hospitalisation-related outcomes were not estimated for the 2022/23 season. A similar issue occurred in NAJS, where complete hospitalisation data were unavailable for the 2022/23 and 2023/24 seasons. In addition, the hospitalisation cohort in NAJS included secondary day-care encounters that were mapped to inpatient care, leading to overestimation of incidence rates for real hospitalisation-related outcomes in this data source, including SARI, all-cause hospitalisation, and influenza-related hospitalisation. This study aimed to explore the completeness of influenza vaccine-related data in the included data sources. The results, including missingness of influenza-related outcomes, will help inform the feasibility of including specific data sources in future IVE studies.

In the incidence estimation of influenza-related outcomes (Objective 4), results should be interpreted with caution. The current study aimed to provide a crude descriptive analysis of the background rates of influenza-related outcomes in the general population, and crude incidence rates in vaccinated and unvaccinated populations for reference purposes only. No direct comparisons between populations should be made. This was a characterisation study with no intention to estimate vaccine effectiveness or infer causality. No methods were applied to measure or minimise confounding or related biases to account for the differences between the vaccinated and unvaccinated individuals. Therefore, the crude incidence rates of influenza-related outcomes in vaccinated and unvaccinated populations cannot and should not be compared or interpreted as proxies for vaccine effects. Additionally, when planning future IVE studies, a post-vaccination grace period should be incorporated into the outcome analysis.

10.3. Interpretation

The prevalence of influenza vaccination showed some slight increasing trends in some data sources between 2015 and 2019. During 2020–2022, prevalence was notably influenced by the COVID-19 pandemic, with all data sources showing a marked increase in prevalence during the 2020/21 and 2021/22 seasons, followed by a slight decline in subsequent years.

As mentioned in the introduction, influenza vaccination recommendations were in general consistent across countries, but vaccine prevalence relied heavily on national vaccination policies and the payment or reimbursement schemes. Information on influenza vaccination policies during the influenza seasons from 2017/18 to 2023/24 is summarised in **Table 14**.[17] In all included countries, older adults were covered under the national influenza vaccination policy and were provided vaccination free of charge. This helps explain the generally higher prevalence of influenza vaccination among individuals aged 65 years or above across all included data sources. Conversely, children were eligible for free influenza vaccination in Denmark, Finland, and the UK, but not in Croatia, Norway, or Spain during most of the study period (2015/16 to 2023/24). This likely explains the relatively low prevalence of influenza vaccination observed in NAJS, NLHR, and SIDIAP.

Table 14. National policy on influenza vaccination for influenza seasons 2017/18–2023/24.

	Countries					
	Croatia	Denmark	Finland	Norway	Spain	The United Kingdom
Beginning of influenza vaccination [a]	October or November	October [c]	October	September or October	October	September [d] or October
End of influenza vaccination [a]	March	January or March	December or April	January or April	January or February	February or March
Payment scheme for vaccination [b]	Free of charge for indicated population	Free of charge for indicated population	Free of charge for indicated population	Free of charge for residents in long-term care facilities; free of charge for children with certain chronic conditions until 2021/22	Free of charge for indicated population	Free of charge for indicated population
Indicated population – Older adults [b]	Yes	Yes	Yes	Yes	Yes	Yes
Indicated population – Children [b]	Children with certain chronic conditions	Yes, since 2020/21	Yes	Children with certain chronic condition	Children with certain chronic condition; children in general since 2022/23	Yes

a. The duration of influenza vaccination available in each country depends on the year of influenza season and depends on the population at risk.
b. Information was only available for 2020/21–2023/24 influenza seasons.
c. Postponed to November in the 2019/20 influenza season (https://en.ssi.dk/news/epi-news/2019/no-26---2019)
d. In the UK, pregnant individuals and children are vaccinated in September.

In most of the included countries the influenza vaccination programme began in October, except for Norway where vaccination was available as early as September in some influenza seasons. Despite the earlier availability, most vaccinations were administered from October onward. [17, 18] In the UK, pregnant individuals and children are often vaccinated in September, so these vaccinations were not captured in this study. Careful definition of the influenza season for each country will be needed when designing future IVE studies. It should also be noted that vaccination peaks observed in November rather than October should not be interpreted as delayed uptake. The timing of the campaign plays a key role; for example, if the programme began in mid-October, there were fewer days available for vaccination in October compared with November.

We further reviewed and compared the prevalence of influenza vaccination estimated in this study with annual influenza vaccination prevalence data reported by the World Health Organisation (WHO), focusing on older adults (≥65 years) to ensure comparability and facilitate interpretation.[19] In Croatia, influenza vaccination prevalence remained low, ranging from 28% to 32% between 2020 and 2024, consistent with the low prevalence observed in NAJS in this study. It is important to note that in Croatia, the influenza vaccine is free for individuals aged 65 years and older, but the number of available doses per year is limited. For example, despite having around 900,000 individuals aged ≥65 years, only about 500,000 doses were

ordered for all age groups in the 2023/24 season. In contrast, higher prevalence was recorded in the Nordic countries and Western Europe. In Denmark, WHO data showed an increase from approximately 50% in 2018 to over 80% by 2023, aligning with our estimates from DK-DHR. Finland showed a similar rise, from around 40% in 2018 to over 60% in 2024, matching the FinOMOP-THL estimates. In Norway, WHO data reported an increase from 34% to around 65% over the same period, consistent with estimates derived from NLHR. For Spain, prevalence among older adults increased gradually from around 55% in 2018 to 68% in 2024, in line with the results observed in SIDIAP. Overall, results from the current study aligned well with WHO figures for influenza vaccination prevalence, with both the estimates and trends (an increasing trend peaking during the COVID-19 pandemic, followed by a slight decrease) following the patterns reported by WHO, except for findings from CPRD GOLD and SIDIAP. While WHO data indicated that influenza vaccination prevalence in the UK remained consistently high (over 70%) between 2018 and 2024, the findings from the current study showed a lower prevalence, ranging approximately from 50% to 70% during the same period. This difference likely reflects the characteristics of CPRD GOLD, a primary care data source covering about 4.1% of the UK population, with most practices located in Scotland and Wales since 2019. Consequently, the results from CPRD GOLD in this study may not be fully representative of the overall influenza vaccination prevalence in the UK in recent years, in addition to the early initiation of vaccination programme in UK. However, given that this study primarily serves as a feasibility and preparedness assessment for future IVE studies, national representativeness is less critical than aspects such as data completeness, consistency of outcome definitions, and availability of vaccine brand and route information. Regarding SIDIAP, estimates were slightly lower compared to national figures for Spain. This is consistent with the fact that influenza vaccine prevalence in Catalonia has historically been lower than the Spanish average, particularly among younger populations.[20]

In general, we observed higher influenza vaccination prevalence among older adults, one of the target groups of vaccination, and among females. This finding aligns with a systematic review showing higher seasonal influenza vaccination prevalence among female populations.[21] Furthermore, we observed a higher prevalence of baseline comorbidities among vaccinated individuals. For example, up to 35% of vaccinated individuals had diabetes, around 50% had cardiac conditions, and up to 80% had hypertension. These findings suggest that influenza vaccine recipients generally had more chronic comorbidities at baseline, which aligns with the higher vaccination prevalence observed among older adults and individuals with chronic health conditions targeted by influenza vaccination recommendations.

During the 2020/21 and 2021/22 influenza seasons, there was a marked increase in influenza vaccination prevalence across all included data sources with available data. This rise during the COVID-19 pandemic is consistent with the figures published by the ECDC.[22] When examining vaccination prevalence stratified by age group, a notable exception was observed in CPRD GOLD, where a decline among individuals aged 65 years or above occurred during the 2020/21 influenza season, followed by a sharp increase in the subsequent season. This finding does not align with published literature on influenza vaccination prevalence among older adults in the UK during the COVID-19 pandemic.[23] We found that nearly 30% of individuals in this age group were vaccinated before the beginning of October in the 2020/21 season and were therefore not captured under the influenza season definition applied in this study.[24] Additionally, during study implementation, we identified a mapping issue affecting a code used since 2019. To address this, the corresponding source code and relevant procedure codes for influenza vaccination were incorporated into the phenotype definitions. It is also important to note that, aside from pandemic-related effects, the increase observed in FinOMOP-THL is partly attributable to improved data capture from private service providers beginning in 2019. This primarily influences estimates for working-age adults, who often receive influenza vaccinations through occupational health services.

Since 2021, the WHO has recommended the same-day co-administration of seasonal influenza and COVID-19 vaccines.[25] This recommendation has been adopted in all countries included in the current study, and a positive correlation has been observed between COVID-19 vaccine prevalence and influenza vaccination

prevalence.[26] Indeed, since the 2021/22 influenza season, an increasing number of same-day co-administrations of seasonal influenza and COVID-19 vaccines have been observed. COVID-19 vaccination was recorded in 13.0–45.6% of influenza vaccine recipients in three data sources (FinOMOP-THL, SIDIAP, CPRD GOLD) during the 2021/22 season, rising to 24.7–67.9% across all available data sources (DK-DHR, FinOMOP-THL, SIDIAP, CPRD GOLD) by the 2022/23 season.

In addition to co-administration policies, the increased intention to vaccinate following the COVID-19 pandemic may also have contributed to the rise in influenza vaccination prevalence.[27] However, despite the surge observed in the 2020/21 season, this increase was not sustained in subsequent years. Prevalence declined in recent seasons, with a smaller decrease observed in Denmark, Finland, and Norway, and a more notable reduction in the UK. One potential explanation for this decline could be vaccine fatigue and growing vaccine hesitancy driven by misinformation and increasing public scepticism toward healthcare systems over time.[28, 29]

To date, few vaccine effectiveness studies have included detailed information on influenza vaccine brands. A previous European initiative, the Development of Robust and Innovative Vaccine Effectiveness (DRIVE) project,[4] is a good example of a successful public-private partnership investigating brand-specific estimates of influenza vaccine effectiveness.[30, 31] However, challenges remain in achieving adequate sample sizes to support stratified analyses. Moreover, although the test-negative design can help reduce potential bias related to healthcare-seeking behaviour, this study design limits the generalisability of results to broader populations.[32] The current study aimed to assess the feasibility of obtaining brand information from population-wide healthcare data to enable pragmatic real-world observational study designs. However, our findings indicated that brand information was available only in a limited number of nationwide registries. Despite this limitation, the results still suggest the feasibility of conducting brand-specific analyses in selected countries where data quality is sufficient. Challenges remain particularly in handling variations in vaccine brands across different influenza seasons and in identifying comparable study populations for future IVE studies.

The WHO has set a target of 75% influenza vaccination prevalence among target risk populations, including older adults, individuals with chronic conditions, and children aged 6–24 months, in line with World Health Assembly Resolution 56.19 established in 2003. However, as of the 2020/21 influenza season, among EU/European Economic Area countries, only Denmark had achieved the 75% prevalence target in the older adult population, which is consistent with the findings of the current study.[22] Achieving this 75% target would help to reduce the substantial number of influenza cases and deaths that place significant burden on public health systems and the broader economy. An epidemiological modelling study estimated that reaching this target in four European countries (the UK, Spain, France, and Italy) could prevent approximately 918,200 influenza cases, 16,300 hospitalisations, and more than 6,000 deaths, resulting in savings of around €84 million in direct medical costs.[33] These findings highlighted the importance of improving influenza vaccination prevalence across Europe to protect vulnerable populations and reduce the burden on healthcare systems.

The current study also aimed to contextualise the background rates of influenza-related clinical outcomes within each of the included data sources. We examined the incidence rates of ILI, ARI, and SARI as defined in the ECDC VEBIS projects, where these outcomes are primarily defined based on the presence of symptoms with varying criteria. To further explore data availability and the capacity of each data source to capture relevant outcomes, we additionally included secondary outcomes for acute respiratory infection (broader definition) and influenza, defined using diagnostic codes representing broader respiratory infection categories and influenza-specific codes.

From our results, the incidence rate of ARI was higher than that of acute respiratory infection (broader definition) in NAJS, CPRD GOLD, NLHR, and SIDIAP, whereas the opposite was observed in FinOMOP-THL. The incidence rates of acute respiratory infection (broader definition) and ARI were similar in DK-DHR.

Although DK-DHR, FinOMOP-THL, and NLHR are nationwide data sources containing primary care data, the highest ARI rates were observed in NAJS, CPRD GOLD, and SIDIAP. This likely reflects differences in symptom recording practices across settings, as ARI relies on symptom-based coding, which is likely to be more commonly captured in primary care-centred systems.

A substantial drop in both ARI and acute respiratory infection (broader definition) was observed in CPRD GOLD and SIDIAP during the 2020/21 influenza season, likely due to the public health measures related to the COVID-19 pandemic. Previous research has reported a decrease in influenza circulation during the pandemic due to the implementation of non-pharmaceutical interventions.[34] However, given that ARI and acute respiratory infection (broader definition) were defined mainly by symptom or diagnostic codes without specification for influenza infection, it is theoretically possible that these codes also captured cases of COVID-19 infection during that period. A similar drop in ARI and acute respiratory infection (broader definition) was observed in DK-DHR and NLHR, suggesting that the effect was likely due to the overall impact of the COVID-19 pandemic rather than specific data source characteristics. In contrast, FinOMOP-THL showed a sudden increase in the incidence of acute respiratory infection (broader definition) during the 2020/21 season. While this may reflect the coding of COVID-19 cases as acute respiratory infections, it could also be explained by an influx of data from private outpatient and occupational care into the FinOMOP-THL data source since 2020. Therefore, the increase in acute respiratory infection (broader definition) incidence in FinOMOP-THL during 2020/21 should be interpreted with caution. The substantially higher incidence of acute respiratory infection (broader definition) compared with ARI in FinOMOP-THL may also indicate differences in diagnostic coding practices relative to other data sources. These observations underscore the need for caution when interpreting influenza-related outcomes during the pandemic period in future IVE studies. Both a true reduction in non-COVID respiratory infections due to non-pharmaceutical measures and the classification of COVID-19 as ARI or acute respiratory infection (broader definition) could bias effectiveness estimates. Careful outcome definitions, exclusion of COVID-19 episodes where appropriate, and sensitivity analyses across pre- and post-pandemic periods will be crucial to ensure robust and comparable IVE assessments.

Serious outcomes such as SARI, which require hospitalisation, were generally rare in most included data sources. Outcomes of all-cause hospitalisation and death remained stable throughout the study period, with the exception of DK-DHR, which showed a greater declining trend in hospitalisations over time than in other data sources, particularly in the 2018/19 and 2019/20 seasons. This pattern may warrant attention, as it is likely to be the result from changing recording system in the data source. Since 2019, records from inpatient hospitalisation have been derived from a customised algorithm instead of direct record of visit type. Upon confirmation with DK-DHR, there has been a stable trend of hospital visits over the study period, regardless of visit type (inpatient visit/outpatient visit/emergency room visit). Despite such, the observed gradual decrease in influenza-related hospitalisation during the COVID-19 pandemic among the included data sources aligns with existing literature.[35] It is also worth noting that the high hospitalisation rates observed in NAJS appear to be influenced by how certain episodes were mapped. The data source confirmed that a category of multi-day secondary day-care encounters had been classified as inpatient episodes because their duration spanned more than one calendar day, even though they do not involve an overnight stay. These episodes account for roughly 20–50% of the hospitalisations recorded in NAJS each year. Thus, hospitalisation incidence rates for NAJS in this study should therefore be interpreted with caution and should not be compared directly with those from other data sources. Hospitalisation-related outcomes should also not be used as effectiveness outcomes for future IVE studies in this data source unless appropriately re-mapped.

The study also assessed the incidence of influenza-related outcomes among vaccinated and unvaccinated populations. It is important to emphasise that incidence rates between these two groups should not be compared directly to infer vaccine effectiveness, as the patient-level characteristics and medical histories of vaccinated individuals differ substantially from those of unvaccinated individuals (e.g., vaccinated

individuals have higher frequency of conditions indicated for influenza vaccination and different health seeking behaviours due to underlying comorbidities). As such, the two groups are inherently non-comparable with respect to outcomes.

Regarding data availability for outcomes and preparedness of data sources for future IVE studies, symptom-based outcomes were generally captured more consistently across data sources. This enabled more reliable identification of ARI compared with acute respiratory infection (broader definition) based solely on diagnosis codes, resulting in higher incidence rates and better completeness, particularly among data sources that include primary care and general practice records. ILI was rarely observed, likely due to its requirement for a very specific combination of symptoms. Influenza diagnoses were also uncommon, possibly reflecting the lack of laboratory confirmation data. It is also important to note that differences in coding practices across data sources may affect comparability and the precision of future effectiveness estimates. In this context, symptom-based outcomes may help reduce variability introduced by diagnosis codes, which are more dependent on clinical judgement and coding practices.

This study establishes a descriptive framework for consistent cross-country monitoring of influenza vaccination prevalence, characterising vaccinated populations, and estimating crude incidence rates of influenza-related clinical outcomes in real-world settings. Few studies have extensively reviewed nationwide influenza vaccination prevalence alongside background rates of influenza-related clinical outcomes. The current study provides valuable information to validate the robustness of influenza vaccine data quality together with comparison to official WHO and ECDC statistics. It also offers important insights into the feasibility of future IVE studies incorporating vaccine brand and route of administration, thereby supporting preparedness of data sources for studies with higher granularity, consistent with the research agenda of the EMA/ECDC Vaccine Monitoring Platform to strengthen real-world evidence on influenza vaccination.

10.4. Generalisability

The study included data sources from six European countries (Croatia, Denmark, Finland, Norway, Spain, and the UK), covering different regions across Europe. These data sources represented diverse healthcare settings, including two primary care data sources and four nationwide data sources with linked registries. However, the findings from this study reflect only the situation within the specific regions, settings, and time periods covered by each data source and should not be generalised to other countries or data sources.

The current study estimated the annual prevalence of influenza vaccination in the general population. It is important, however, to interpret these results in the context of differing national influenza vaccination policies, including the timing of vaccination campaigns, which in some countries may begin slightly earlier than the influenza season defined in this study. The requirement for full-year data contribution of individuals within each data source for the estimation of annual influenza vaccination prevalence may have restricted the population at risk, and therefore, the estimates may not fully represent the true prevalence in the respective countries. Nevertheless, this requirement helps minimise bias from individuals with short observation periods (e.g., immortal time bias). In view of this, additional sensitivity analysis on estimation of annual influenza vaccination prevalence without full-year data contribution requirement was conducted, which has shown similar results with slightly lower prevalence estimates.

Although several data sources were nationwide, specific subpopulations, such as institutionalised individuals, those receiving only private healthcare, or recent migrants, may be underrepresented, which could limit generalisability within countries.

It should also be noted that, although the study provides estimates of the incidence of influenza-related outcomes in the general population, among those who were vaccinated, and in the unvaccinated population, these results should not be compared directly between groups. As shown by the table on vaccination recommendations and national policies across countries, the characteristics of vaccinated and

unvaccinated populations differ substantially at baseline in terms of comorbidities and health seeking behaviours. The reported incidence rates represent crude estimates within each population and were not adjusted to account for potential confounding or related biases.

11. CONCLUSION

This multi-data source characterisation demonstrated generally slightly increasing or stable trends in influenza vaccination prevalence from 2015 to 2019, followed by a notable rise during 2020–2022 coinciding with the COVID-19 pandemic, and a subsequent slight decline. Prevalence was consistently highest among older adults and higher in females, and between-country variation largely reflected differences in national influenza vaccination policies. From a data-preparedness perspective, detailed vaccine brand information was available only in DK-DHR and FinOMOP-THL, and detailed route information was available in these two data sources as well as in NAJS. Symptom-based outcomes (ARI) were generally captured more frequently than diagnosis-based outcomes (acute respiratory infection (broad definition), influenza). Certain data considerations, such as the absence of hospitalisation data in CPRD GOLD, the temporary gap in hospital records in NAJS and SIDIAP, and occasional code-mapping inconsistencies, should be considered when selecting data sources and refining phenotypes for future analyses.

For future IVE studies, several considerations may help strengthen study design and optimise the use of these data sources. Data sources with more complete information on vaccine brand, route of administration, or with hospital linkage may be particularly valuable for analyses requiring brand stratification or severe outcomes. Continued refinement and validation of phenotypes, building on the work undertaken in this study, together with harmonised outcome definitions across data partners are crucial to ensure consistency and comparability. Symptom-based outcomes may help mitigate this variability, given their reduced dependence on clinical judgement and coding compared to diagnosis-based outcomes. Taken together, these considerations, alongside attention to country-specific vaccination campaign timing, may enhance the ability of these data sources to contribute reliable and policy-relevant estimates in future IVE studies.

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13. ANNEXES

ANNEX I. Description of data sources

Croatian National Public Health Information System (NAJS)

#	Section	Description
1	Data source identification and country	NAJS (Croatian National Public Health Information System) Croatia
2	Data partner information section	Croatian Institute of Public Health Department of Data Science and Analytics
3	Coverage and timespan	Data collection since: 1998 Extent: Nation-wide. Geographic coverage covers whole Croatia, with various levels of resolution for different registries. Current estimates for the population in Croatia will be available at: https://podaci.dzs.hr/hr/podaci/stanovnistvo/procjena-stanovnistva/ for each year.
4	Healthcare setting / type of data	Primary care – General Practitioner, and secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care. Primary care – gps, and secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care. For both inpatient and outpatient setting diagnoses, medication, procedures, and measurements are captured. The year of availability of information depends on the setting • 2014-2025 for biochemical lab tests in primary care from EHR patients records (measurements with results) • 2015-2025 for primary care data from EHR patient records (conditions, procedures, and drug prescriptions) • 2015- 2024 for inpatient hospital data from EHR administrative records (conditions, procedures, measurements without results and drug administrations) • 2016-2025 for health risk assessment data entered by GPs (measurements with results - height, weight…) • 2016-2024 for secondary conciliatory care data from EHR administrative records (conditions, procedures, measurements without results and drug administrations) • 2016-2022 for emergency care data from EHR patient records (conditions) • 2017-2025 for hospital records from registry data (conditions and procedures) • 2020-2025 for vaccination data from EHR patient records
5	Data collection process	Inpatient hospital billing systems, and Other. Data is entered by clinicians at healthcare contact, then combined by CIPH into the NAJS database and integrated with registries for public health purposes.
6	General representativeness	The data is collected from the evidence of public health records collected for public health purposes, as the majority of health care in Croatia is public and under single health insurance provider. Personal details are collected to a better extent for insured individuals compared to uninsured patients, who are excluded in the ETL process.
7	Data content /source coding	Medication prescriptions are recorded with ATC codes with an additional 3 digit code denoting the package. Diagnoses with ICD10 codes (Australian modification). Procedures with local source codes. Lab results with local source codes.
8	Data Harmonization	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. Records from 2017 include insured patients with reliable IDs. Uninsured patients do not have reliable IDs. For example, if a patient changed her status from insured to uninsured, or vice versa, she could be counted several times, as could tracking records from before 2017 and after. By using the unique personal identifier for Croatian citizens, it can be checked and verified.
9	Quality control (data source specific)	There is a network of registry personnel (leaders, administrators, coders, sources) working on data coverage and other quality dimensions. An analytical team routinely checks for erroneous entries in hospital records, removing double entries, false dates, and overlapping stays. Entries

#	Section	Description
		without enough data or with obviously erroneous dates from primary care analysis are being excluded.
10	Linkage	The national death registry is updated yearly, with one year lag, but the fact of someone's death (just the date) is updated daily, without the cause of death or any other additional details. Primary care is updated weekly and hospital level care monthly. Specific registries are included in NAJS (e.g., diabetes registry), where inclusion criteria vary across these registries.
11	Vital status	NAJS is linked to the national death registry.
12	Limitations	Hospital data is available from 2017 onwards. This is often used as start of data collection, while laboratory and GP data is captured before that (since 2014 and 2015 respectively). The total and active person count in the NAJS data is larger than the current population of Croatia. This explained by: a) the person table included deceased and all previously insured people and b) there is no information about insurance ending, c) healthcare is also used by people with dual citizenship from neighbouring countries It is known that a lot of people emigrated (300k-400k) and weren't included in the last population census but still are in the NAJS database. There is also an influx of immigrant workers that are insured and registered but weren't included in the census. In-hospital administrations are managed via paper drug charts and hospital discharge summaries are currently not captured into NAJS. Reliability of hospital drug administration data is less reliable than prescription data from primary care, with some drugs (monoclonal antibodies / precision medicine drugs) that require additional approval not being recorded at all. In-hospital administrations are managed via paper drug charts and hospital discharge summaries are currently not captured into NAJS.
13	Main references	No main reference provided.
14	Link to HMA-EMA catalogue and data source webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1111155 Website: https://www.hzjz.hr/nacionalni-javnozdravstveni-informacijski-sustav-najs/

Danish Data Health Registries (DK-DHR)

Danish health data (DK-DHR) is collected, stored, and managed in national health registers at the Danish

#	Section	Description
1	Data source identification and country	DK-DHR (Danish Data Health Registries) Denmark
2	Data partner information section	Danish Medicines Agency (DKMA) Data Analytics Centre (DAC)
3	Coverage and timespan	Data collection since: 1995 Extent: Nation-wide. The data is representative of the entire Danish population.
4	Healthcare setting / type of data	Community pharmacists, and secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care. The following data elements are collected: diagnosis (including rare diseases and pregnancy data), hospital admissions, discharge and ICU data, Cause of death, Drug prescriptions, dispensing, vaccination and contraception, Procedures (surgical and non-surgical hospital), and Sociodemographic information (sex and age only).
5	Data collection process	Outpatient electronic health records, and Inpatient hospital electronic health records, and Registries, and Other. All causes of deaths, all retrieved drug prescriptions, all records of vaccinations, all hospital inpatient and outpatients contacts including disease diagnoses and hospital surgical and non-surgical

#	Section	Description
		procedures, histologically confirmed incident cancers, laboratory test results for the entire Danish population from 1/1/1995 onwards.
6	General representativeness	The data is representative of the entire Danish population. Healthcare is free in Denmark, so we do not expect any bias in data collection based on socio-economic status.
7	Data content /source coding	Diagnoses and causes of death are collected using the ICD-10 vocabulary. ATC and RxNorm are used for Drugs. SNOMED codes are used for Procedures.
8	Data Harmonization	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. No.
9	Quality control (data source specific)	The data we have received relating to nationwide Danish Health Data registries offer an opportunity for large-scale, population-based studies with several advantages 1) Their large size improves the precision of estimates and enables the study of rare exposures and outcomes with long-term latency, 2) Inclusion of nearly all individuals in the target population ensures that the data reflect routine clinical care and all clinical segments of the source population, 3) Data are collected independently of each research study, thus minimising certain types of bias, e.g., non-response, and the influence from attention to the research question on the diagnostic process. Before the source data is sent to us, the Danish Health Data Authority runs and does comprehensive checks of the registry table data validity of the variables, breaks in data, changes in variable coding, missingness, etc. We perform checks of missingness/completeness in relation to requested variables. In essence, we are receiving a dump of a mirror of the data that is controlled by the SDS. The documentation performed by SDS is available online, in Danish primarily https://www.esundhed.dk/Dokumentation (all variables), but also in English https://sundhedsdatastyrelsen.dk/da/english/health_data_and_registers/national_health_registers
10	Linkage	There is no linkage in this data source.
11	Vital status	The Cause of Death registry (DAR) is used, the cause of death is collected using ICD-10 codes.
12	Limitations	DK-DHR has the following limitations, which may be relevant confounders for certain complex Darwin EU studies: - We lack information on key socio-economic status (SES) factors, such as occupation, education, and income. These variables may be important for analysis in some studies. - We only have complete data on lifestyle factors (such as smoking status and weight) for pregnant individuals. - We have no information on patient contacts in primary care (visits to the GP). Consequently, the incidence of chronic diseases like Type 2 Diabetes (T2D) and asthma must be determined using drug prescriptions as a proxy. Stillborn children will not have any records in our CDM. This means that e.g., birth length of stillborns is not recorded.
13	Main references	Schmidt M, Schmidt SAJ,Adelborg K,Sundbøll J,Laugesen K,Ehrenstein V,Sørensen HT "The Danish health care system and epidemiological research: from health care contacts to database records." Clinical epidemiology (2019): 31372058
14	Link to HMA-EMA catalogue and data source webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1111217 Website: https://sundhedsdatastyrelsen.dk/da/english/health_data_and_registers/healthdatadenmark

Finnish Care Register for Health Care (FinOMOP-THL)

#	Section	Description
1	Data source identification and country	FinOMOP-THL (Finnish Care Register for Health Care) Finland

#	Section	Description
2	Data partner information section	Finnish Institute for Health and Welfare (THL) The Department of Data and Analytics
3	Coverage and timespan	Data collection since: 1998 Extent: Nation-wide. The current CDM population comprises all persons having been alive and residing in Finland since the beginning of 2011.
4	Healthcare setting / type of data	Primary care – General Practitioner, and primary care specialists (e.g., paediatricians), and secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care, and other (specify). THL maintains health registers that cover both public and private, primary, and specialised inpatient, urgent and outpatient health care encounters in Finland, starting from 2011. The entire public sector and private inpatient encounters have been included since 2011, while private outpatient encounters, including occupational care, are included since 2020. Since 1998, the Care Register for Health Care (TerveysHilmo) has covered both public outpatient and inpatient specialized care and private inpatient care. Since 2009, the Finnish National Vaccination Register has covered all vaccinations from the public sector and from a large part of private vaccination providers, with the data coverage from both sections being very good to complete from 2020 onwards. Since 2011, the Register of Primary Health Care Visits (AvoHilmo) has covered public primary care. Since 2020, the register has also covered private outpatient care and occupational care. In addition, the CDM also contains positive COVID-19 test results from the Finnish National Infectious Diseases Register. The register itself covers all laboratory confirmations for around 70 specific microbes from 1995 onwards, but only COVID-19 has currently been mapped to the CDM. The CDM also includes prescription records from multiple different sources. Both Care Register for Health Care and Register of Primary Health Care Visits contain very basic prescription data recorded during health care encounters that include just the ATC-code and trade name of medication. More comprehensive prescription data from Kanta Prescription Centre, maintained by Social Insurance Institution of Finland (Kela), has been integrated into the CDM since its 2024 release. The Kanta Prescription records are based electronic prescriptions, which were adopted by most public health care providers in 2010 and by most private providers by 2017.
5	Data collection process	Outpatient electronic health records, and Inpatient hospital electronic health records, and Registries. Data is entered by clinicians upon healthcare contact and processed by THL (Kela in the case of Kanta Prescription Centre).
6	General representativeness	The THL data has national coverage and is therefore well representative of the Finnish population. Using the complete population as a basis for the person table also serves to facilitate calculations on a population level, e.g., incidence rates.
7	Data content /source coding	The following coding systems have been OMOP-mapped, typically to a good level of completeness: ICD10fi Finnish Extension, ICPC-2, ATC, Toimenpideluokitus (procedure classification adapted from the Nordic Classification of Surgical Procedures (NCSP)), Terveydenhuollon erikoisalat (Hilmo specific provider speciality), Rokotustapa (AR/YDIN National classification for vaccine administration), Tupakointistatus (AR/YDIN National classification for smoking status). Vaccinations are identified on product level based on batch number, trade name, vaccine title, and ATC-code. This is mapped on brand and type in the OMOP CDM.
8	Data Harmonization	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. Each patient in THL has a unique identifier.
9	Quality control (data source specific)	The source data collection undergoes a structural and semantic validation before entry into the source database. Additionally, some coded variables undergo quality assessment against the respective code systems post entry into the database. The source registers are also assessed for completeness and coverage, with the aim of improving future collection in the areas where data is lacking.

#	Section	Description
10	Linkage	THL is already a linkage of multiple Finnish registries (see above).
11	Vital status	The National Population registry data forms the basis for forming the patient population. This ensures an up-to-date location (municipality of residence) of patients, as well as complete death occurrences (although not the cause of death).
12	Limitations	All drug records in the CDM are currently based on prescriptions. Kanta Prescription Centre also includes information on drug dispensings, but these have not currently been converted into OMOP CDM. Depending on the type of the medication, a single prescription can be for up to two years dosage of the drug. This means a patient can have up to two-year breaks between observations while actively using the drug. Observation of a prescription also does not mean that the patient necessarily bought or used the medication. The CDM does not currently have meaningful end dates or days of supply for drug exposure. This information is not available for Care Register for Health Care or Register of Primary Health Care Visits, and for Kanta Prescription Centre it is only available in unstructured, free-form format that has not been converted into OMOP CDM. The source system for prescription drug data is only available to the DP until Dec-2023, therefore drug_exposure records from this source are only available in that time range. Not all private health care records are covered for the CDM's entire follow-up time from 2011 onwards. For Register of Primary Health Care Visits and Finnish National Vaccination Register, records from private health care have been available from 2020 onwards. For Kanta Prescription Centre, the coverage of private health care records has been good from 2017 onwards. The inclusion of private health care mainly presents itself as an increase in the number of observations, meaning that it has to be accounted for when interpreting any time series data from the CDM.
13	Main references	Häkkinen, Pirjo; Mölläri, Kaisa; Saukkonen, Sanna-Mari; Väyrynen, Riikka; Mielikäinen, Lasse; Järvelin, Jutta "Hilmo - Sosiaali- ja terveydenhuollon hoitoilmoitus 2020 : Määrittelyt ja ohjeistus : Voimassa 1.1.2020 alkaen" Terveyden ja hyvinvoinnin laitos (2019):
14	Link to HMA-EMA catalogue and data source webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1111187;https://catalogues.ema.europa.eu/data-source/1111191 Website: https://thl.fi/en/statistics-and-data/data-and-services/register-descriptions;https://www.kanta.fi/en/research-and-knowledge-management

Norwegian Linked Health Registry data (NLHR)

#	Section	Description
1	Data source identification and country	NLHR (Norwegian Linked Health Registry data) Norway
2	Data partner information section	University of Oslo Faculty of Mathematics and Natural Science – Department of Pharmacy
3	Coverage and timespan	Data collection since: 2008 Extent: Nation-wide. Norway has a universal public health care system, consisting of primary and specialist health care services covering a population of approximately 5.4 million inhabitants.
4	Healthcare setting / type of data	Primary care – General Practitioner, and primary care specialists (e.g., paediatricians), and secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care. The following registries are included: the Medical Birth Registry of Norway (MBRN), the Norwegian Prescription Registry (NorPD), the Norwegian Patient Registry (NPR), Norway Control and Payment of Health Reimbursement (KUHR), the Norwegian Surveillance System for Communicable Diseases (MSIS), the Norwegian Immunisation Registry (SYSVAK), the National Death Registry, and the National Registry (NR).

#	Section	Description
5	Data collection process	Registries. Many population-based health registries were established in the 1960s, with use of unique personal identifiers facilitating linkage between registries. Data in these health registries are used for health analysis, health statistics, improving the quality of healthcare, research, administration, and emergency preparedness.
6	General representativeness	The NLHR data covers the full Norwegian population.
7	Data content /source coding	NPR: ICD-10 for diagnosis, ATC and some special codes for drug use, Norwegian codes for clinical procedures (surgery (NCSP), medicine (NCMP) and diagnostic imaging, image-guided intervention, and nuclear medicine (NCRP)). KUHR: ICD-10 and ICPC-2 and ICPC-2B for diagnosis/procedure. NorPD: ATC. SYSVAK and MSIS: national classifications. MBRN: custom classifications by questionnaires (incl. check box variables in Maternity health care card)
8	Data Harmonization	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. Linkage between the registries was facilitated using project-specific person IDs generated from unique personal identification assigned at birth or immigration for all legal residents in Norway.
9	Quality control (data source specific)	In-house data quality checks of rates of common conditions, drug exposures, and outcomes. We compare obtained rates with official national statistics (e.g., birth statistics, yearly rates of drug dispensing, and diagnosis by age and gender). We also review missing data and outliers and inform registry holders of any unusual patterns.
10	Linkage	The NLHR is, by definition, a linkage of datasets. Helsedata.no is one central portal to apply for 11 national health registries, including all the registries that have been mapped to the OMOP CDM.
11	Vital status	The national death registry is linked.
12	Limitations	No database-specific limitations documented. General limitations for the data type applicable.
13	Main references	Mitter VR, Lupattelli A,Bjørk MH,Nordeng HME "Identification and characterization of migraine in pregnancy: A Norwegian registry-based cohort study." Cephalalgia : an international journal of headache (2024): 38663979
14	Link to HMA-EMA catalogue and data source webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1000000409 Website: https://www.mn.uio.no/farmasi/english/research/groups/pharma-safe/

The Information System for Research in Primary Care (SIDIAP)

#	Section	Description
1	Data source identification and country	SIDIAP (The Information System for the Development of Research in Primary Care) Catalunya, Spain
2	Data partner information section	IDIAPJGol
3	Coverage and timespan	Data collection since: 2006 Extent: Regional. SIDIAP is a database of primary care electronic health records of the population of Catalonia, North-East Spain. It contains pseudo-anonymised records of more than 8 million people , of which 6.1 million are active as of 2022, representing around 76% of the Catalan population.
4	Healthcare setting / type of data	Primary care – General Practitioner, and hospital inpatient care. SIDIAP captured data includes routine visits, socio-demographics, diagnoses, laboratory tests, drugs (prescribed and dispensed), referrals, sick leaves and lifestyle information.

#	Section	Description
5	Data collection process	Outpatient electronic health records, and Inpatient hospital electronic health records, and Other. Data is entered by primary care physicians upon healthcare contact, supplemented with hospital discharge records. The Institut Catala de la Salut (Catalan Health Institute) is the data controller.
6	General representativeness	It was previously shown that the captured SIDIAP population is highly representative of the entire Catalan region in terms of geographic, age, and sex distributions.
7	Data content /source coding	SIDIAP data covers all services that occur at the Primary Care Centres, as well as support services, such as sexual and reproductive health or home end-of-life care. Drugs are coded in ATC-WHO terminology in the source data. Health outcomes are captured in ICD-10CM codes. The SIDIAP contains all laboratory tests and results performed in primary health centres. Demographics, geographical, as well as socio-economic factors are recorded for each patient.
8	Data Harmonization	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. No.
9	Quality control (data source specific)	Internal and external validation processes are carried out to determine the data quality of the SIDIAP information at each data update. These include stratifying the data by geographical regions and year in order to identify differences in data collection that need to be harmonized (e.g., recording of specific information under different codes). The measurement units of variables measuring one characteristic are also homogenized (e.g., transformation of the data from every laboratory that measures haemoglobin to grams per decilitre). Visual inspection of all data included in the database by week is also conducted, allowing one to see temporal patterns in the registry of a certain variable. With this information, the SIDIAP team can issue recommendations to researchers about the most common variable(s) where certain information is recorded (e.g., there are several variables with information concerning the women's menopausal status and with these visual inspection tools the SIDIAP team can inform the researchers about which related variables have the largest number of records and could be more helpful to capture menopause). Data availability (longitudinally and reliability), plausibility (range checks and unusual values), and consistency are inspected through visualisation tools. In addition, before accessing the data for a requested project, research teams have access to a quality-control report. This document contains counts, years, percentiles, maximums and minimums, incidences, and prevalence of the data requested for the project, allowing detection of inconsistencies in the data extraction prior to data delivery. External validation processes of the SIDIAP database mainly include assessing the data recorded in SIDIAP through linkage to external gold standard data sources, by analysing free text, or by sending questionnaires to health professionals.
10	Linkage	SIDIAP is linked to a hospital discharge database, pharmacy dispensation, and primary care laboratories. It can also be linked to other registries in Catalonia on a project by project basis.
11	Vital status	Mortality is fully captured in SIDIAP. The cause of death is not available, but can be linked to the Spanish death registry on a project by project basis.
12	Limitations	The SIDIAP data is not representative of individuals not using public primary care, and conditions that are usually followed by specialist care might not be properly captured. In addition, there is limited information on lifestyle variables. Patients are followed until Death or when transferring to another primary health care centre that does not contribute to SIDIAP.
13	Main references	Recalde M, Rodríguez C,Burn E,Far M,García D,Carrere-Molina J,Benítez M,Moleras A,Pistillo A,Bolíbar B,Aragón M,Duarte-Salles T "Data Resource Profile: The Information System for Research in Primary Care (SIDIAP)." International journal of epidemiology (2022): 35415748

#	Section	Description
14	Link to HMA-EMA catalogue and data source webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/50190 Website: https://www.sidiap.org/index.php/en

Clinical Practice Research Datalink GOLD (CPRD GOLD)

#	Section	Description
1	Data source identification and country	CPRD GOLD (Clinical Practice Research Datalink GOLD) United Kingdom
2	Data partner information section	University of Oxford NDORMS
3	Coverage and timespan	Data collection since: 1987 Extent: Nation-wide. CPRD GOLD consists of patients in contributing practices using Vision software. Historically this covered the whole of the UK, but the number of contributing practices in the England is dropping. In January 2025 only 3 practices from England were a part of CPRD GOLD, while historical patient data were from the whole of the UK, and will continue to be so. In the future, no practices from England will be present, only practices from Scotland, Wales, and Northern Ireland.
4	Healthcare setting / type of data	Primary care – General Practitioner, and primary care specialists (e.g., paediatricians), and secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care. CPRD GOLD data include patient demographics, biological measurements, clinical symptoms and diagnoses, referrals to specialist/hospital and their outcome, laboratory tests/results, and prescribed medications.
5	Data collection process	Outpatient electronic health records. Data are entered by clinicians into the EHR. Data is processed by CPRD that provides data releases for research.
6	General representativeness	CPRD GOLD has been assessed and found to be broadly representative of the UK general population in terms of age and sex. In CPRD GOLD January 2025 release there were 2,730,707 current acceptable patients (i.e., registered at currently contributing practices that use Vision software, excluding transferred out, deceased patients, and those flagged by CPRD as not acceptable for clinical research for data quality issues). This equals to 4.07%, based on the UK population estimates of 67,026,300 from the Office of National Statistics (mid-2023). Current patients are mainly from Scotland, Wales, and Northern Ireland. Historically, GOLD does contain data from England as well.
7	Data content /source coding	Gemscript, Read, dm+d
8	Data Harmonization	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. In GOLD, a patient can be registered under different ID numbers upon changing practice or re-registration. Researchers are not able to identify these patients, as the data are anonymised. However, GOLD covers less than 5% of the current UK GP practices and it is unlikely that an individual who does change GP practice ends up in another GP practice which uses the Vision software and accepts the CPRD data collection agreement. The very small number of duplicated IDs will have different observation periods and should not have an impact on the data analyses.
9	Quality control (data source specific)	CPRD GOLD only includes practices whose data quality is assessed to be up-to-standard (UTS). Each practice is associated to an UTS date set when the data quality standards become satisfactory, and CPRD recommend using only longitudinal data starting from this UTS date.

#	Section	Description
		Every time CPRD collect the EHR from a practice, checks are run for the data quality standards, and if they are not adequate, the EHR is not accepted. When the data quality becomes acceptable again, CPRD updates the practice UTS date. CPRD also checks data quality standards at the patient level, and associates each patient with a flag, reporting if its data are acceptable for clinical research. Only patients with acceptable data quality are included in the population to be mapped to CDM.
10	Linkage	CPRD GOLD can be linked to several sources, however our Oxford OMOP CDM is only linked to the CPRD GOLD Ethnicity Record and to the CPRD Townsend Deprivation Index at the Practice Level.
11	Vital status	Vital status is retrieved from the GP records. Population registry (ONS) data can be requested on a study-by-study basis and linked. This data only covers England and is planned to be mapped to OMOP in the future. The cause of death is not captured.
12	Limitations	The main limitation is due to the fact that CPRD GOLD is limited to GP records, and although it contains information on referrals and discharge letters, it may not fully capture specific hospital information. Events from hospital and specialist care are not covered.
13	Main references	Sanchez-Santos MT, Axson EL,Dedman D,Delmestri A "Data Resource Profile Update: CPRD GOLD." International journal of epidemiology (2025): 40499193
14	Link to HMA-EMA catalogue and data source webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1111113 Website: https://www.cprd.com/data/primary-care-data/cprd-gold

ANNEX II. Fitness for use assessment

Data source justification for inclusion and key characteristics

Croatian National Public Health Information System (NAJS)

NAJS was included in this study because it is a nation-wide registry data source that provides relevant information on the influenza vaccine prevalence in the general population.

Based on a preliminary feasibility assessment, the expected number of record counts for influenza vaccine in NAJS was 2,533,000.

Moreover, data availability and follow-up in NAJS was sufficient, as data availability in NAJS started in 2014, and the date of the most recent data extraction was 01/2025 (as of 07/2025), which aligned with the study period. The median follow-up of the first observation period in NAJS was 3,640 days (Interquartile Range (IQR) 3,110–3,740), taken from portal.

There were some specific limitations present in NAJS. First, information on the brand of influenza vaccine was not available. Second, accurate vaccination data were only available from 2020 onwards with the introduction of the centralised eVaccination records. Prior to this, vaccination data were sourced from general practitioners' EHR systems, which may have been affected by underreporting. Accordingly, the study period for NAJS started in 10/2020 to 04/2024.

Lastly, NAJS had blanket approval, which made the execution of this study feasible within the current study timelines.

Danish Data Health Registries (DK-DHR)

DK-DHR was included in this study because it is a nation-wide registry data source that provides relevant information on the influenza vaccine in the general population.

Based on a preliminary feasibility assessment, the expected number of record counts for influenza vaccines in DK-DHR was 17,206,000.

Moreover, data availability and follow-up in DK-DHR was sufficient, as data availability in DK-DHR started in 1995, and the date of most recent data extraction was 11/2024 (as of 07/2025), which aligned with the study period. The median follow-up of the first observation period in DK-DHR was 7,920 days (IQR 2,610–10,900).

There were no study specific limitations present in DK-DHR.

Lastly, DK-DHR had blanket approval, which made the execution of this study feasible within the current study timelines.

Finnish Care Register for Health Care (FinOMOP-THL)

FinOMOP-THL was included in this study because it is a nation-wide registry data source that provides relevant information on the influenza vaccine in the general population.

Based on a preliminary feasibility assessment, the expected number of record counts for influenza vaccines in FinOMOP-THL was 15,202,400.

Moreover, data availability and follow-up in FinOMOP-THL was sufficient, as data availability in FinOMOP-THL started in 2011, and the date of most recent data extraction was 10/2024 (as of 07/2025), which aligned with the study period. The median follow-up of the first observation period in FinOMOP-THL was 5,020 days (IQR 4,030–5,020).

There were some study specific limitations present in FinOMOP-THL, namely: cause of death was not available in the data and therefore death due to a respiratory or influenza-related cause was defined as death where a clinical outcome occurred within 14 days prior.

Lastly, IRB approval for FinOMOP-THL was estimated to take one week, which made the execution of this study feasible within the current study timelines.

Norwegian Linked Health Registry data (NLHR)

NLHR was included in this study because it is a nation-wide registry data source that provides relevant information on the influenza vaccine in the general population.

Based on a preliminary feasibility assessment, the expected number of record counts for influenza vaccines in NLHR was 6,437,800.

Moreover, data availability and follow-up in NLHR was sufficient, as data availability in NLHR started in 2008, and the date of most recent data extraction was 12/2023 (as of 07/2025), which aligned with the study period. The median follow-up of the first observation period in NLHR was 5,840 days (IQR 5,230–5,840).

There were some study specific limitations present in NLHR, namely: absence of data on brand of influenza vaccine and, due to data availability, the study period for NLHR started in 10/2018 to 04/2023.

Lastly, IRB approval for NLHR was estimated to take 3 weeks, which made the execution of this study feasible within the current study timelines.

The Information System for Research in Primary Care (SIDIAP)

SIDIAP was included in this study because it is a regional primary care and hospital data source that provides relevant information on the influenza vaccine in the general population.

Based on a preliminary feasibility assessment, the expected number of record counts for influenza vaccine in SIDIAP was 15,469,800.

Moreover, data availability and follow-up in SIDIAP was sufficient, as data availability in SIDIAP started in 2006, and the date of most recent data extraction was 06/2023 (as of 07/2025), which aligned with the study period. The median follow-up of the first observation period in SIDIAP was 5,670 days (IQR 2,220–6,390).

There were some study specific limitations present in SIDIAP, namely: absence of data on brand of influenza vaccine; cause of death not available in the data and therefore death due to a respiratory or influenza-related cause was defined as death where a clinical outcome occurred within 14 days prior; due to data availability, the study period for SIDIAP was 10/2015 to 04/2023.

Lastly, IRB approval for SIDIAP was estimated to take one month, which made the execution of this study feasible within the current study timelines.

Clinical Practice Research Datalink GOLD (CPRD GOLD)

CPRD GOLD was included in this study because it is a nation-wide primary care data source that provides relevant information on the influenza vaccine in the general population.

Based on a preliminary feasibility assessment, the expected number of record counts for influenza vaccine in CPRD GOLD was 29,155,500.

Moreover, data availability and follow-up in CPRD GOLD was sufficient, as data availability in CPRD GOLD started in 1987, and the date of most recent data extraction was 12/2024 (as of 07/2025), which aligned with the study period. The median follow-up of the first observation period in CPRD GOLD was 2,150 days (IQR 727–4,930).

There were some study specific limitations present in CPRD GOLD, namely: absence of data on brand of influenza vaccine; cause of death not available in the data and therefore death due to a respiratory or influenza-related cause was defined as death where a clinical outcome occurred within 14 days prior; no hospitalisation data available in CPRD GOLD and therefore, outcome of SARI and hospitalisation were assessed in objective 4.

Lastly, IRB approval for CPRD GOLD was estimated to take one week, which made the execution of this study feasible within the current study timelines.

ANNEX III: Study code lists

Table S1. List of ingredients for the ATC 4th-level class code Influenza vaccines (J07BB).

Concept Name	Ingredient Concept ID	Vocabulary	Include descendants
A/Hong Kong/4801/2014 (H3n2) - Like Virus	36878800	RxNorm Extension	Yes
influenza A virus (H1N1) antigen	46275993	RxNorm	Yes
influenza B virus antigen	46275999	RxNorm	Yes
influenza A virus (H3N2) antigen	46275996	RxNorm	Yes
influenza A virus vaccine, A-Texas-50-2012 (H3N2)-like virus	45776076	RxNorm	Yes
influenza B virus vaccine, B-Massachusetts-2-2012-like virus	43531944	RxNorm	Yes
influenza B virus vaccine, B-Wisconsin-1-2010-like virus	42873961	RxNorm	Yes
influenza A virus vaccine, A-Victoria-361-2011 (H3N2)-like virus	42873956	RxNorm	Yes
influenza virus vaccine, inactivated A-Victoria-210-2009 X-187 (H3N2) (A-Perth-16-2009) strain	40225028	RxNorm	Yes
influenza virus vaccine, live attenuated, A-Perth-16-2009 (H3N2) strain	40225038	RxNorm	Yes
influenza A-California-7-2009-(H1N1) v-like virus vaccine	40166605	RxNorm	Yes
influenza B virus vaccine B/Brisbane/60/2008 antigen	40164828	RxNorm	Yes
Influenza Virus Surface Antigen, Inactivated, Strain B / Phuket / 3073/2013 & ndash; Analogue strain B / Utah / 9/2014, Wild Type	36878953	RxNorm Extension	Yes
Influenza Virus Surface Antigens, strain A / Switzerland / 9715293/2013 H3N2 - Analogue Strain Nib-88	36879025	RxNorm Extension	Yes
Antigens Surface Of Virus Influenza, strain A / Switzerland / 9715293/2013 H3N2 - Analogue Strain A / Switzerland / 9715293/2013, Nib-88	36879013	RxNorm Extension	Yes
Influenza Virus Fragmented, Inactivated, Strain A / Switzerland / 9715293/2013 H3N2 - Analogue Strain A / Switzerland / 9715293/2013, Nib-88	36879023	RxNorm Extension	Yes
Influenza Virus Surface Antigen, Inactivated, Strain A / Switzerland / 9715293/2013 H3N2 - Analogue Strain A / South Australia / 55/2014 Type Wild	36879091	RxNorm Extension	Yes
Antigens Surface Of Virus Influenza, strain B / Brisbane / 9/2014 Wild Type	36879093	RxNorm Extension	Yes
Influenza Virus Surface Antigen, strain A / Victoria / 361/2011 H3N2 - Derived Strain Used Ivr-165	36878619	RxNorm Extension	Yes
Influenza Virus Fragmented, Inactivated, Strain A / Switzerland / 9715293/2013 H3N2 - Analogue Strain A / South Australia / 55/2014 Ivr-175	36878617	RxNorm Extension	Yes
Influenza Virus Fragmented, Inactivated, Strain B / Phuket / 3073/2013	36878713	RxNorm Extension	Yes

Table S2. Code list for influenza-related symptoms, secondary outcomes, and hospitalisation.

Phenotype	Concept id	Concept name	Vocabulary	Domain
ageusia	44782579	Loss of taste anterior two thirds of tongue	SNOMED	Observation
ageusia	45765564	Loss of taste posterior one third of tongue	SNOMED	Observation
ageusia	4239971	Taste-blindness	SNOMED	Observation
ageusia	44783807	Hemiageusia	SNOMED	Observation
ageusia	1332786	Loss of smell or taste	PPI	Observation
ageusia	4289517	Loss of taste	SNOMED	Observation
anosmia	4044243	Mucosal anosmia	SNOMED	Condition
anosmia	4185711	Loss of sense of smell	SNOMED	Observation
anosmia	1332786	Loss of smell or taste	PPI	Observation
coryza	4309214	Purulent rhinitis	SNOMED	Condition
coryza	4313430	Hypertrophic rhinitis	SNOMED	Condition
coryza	4316066	Rhinitis medicamentosa	SNOMED	Condition
coryza	4100047	Granulomatous rhinitis	SNOMED	Condition
coryza	1340461	Exacerbation of rhinitis	OMOP Extension	Condition
coryza	4031046	Purulent nasal discharge	SNOMED	Condition
coryza	4270705	Ulcerative rhinitis	SNOMED	Condition
coryza	35609917	FeverPAIN (Fever in last 24 hours, Purulence, Attend rapidly under 3 days, Inflamed tonsils, No cough and/or coryza) Clinical Score	SNOMED	Measurement
coryza	42873159	Irritant rhinitis	SNOMED	Condition
coryza	4274037	Catarrhal nasal discharge	SNOMED	Condition
coryza	4276172	Nasal discharge	SNOMED	Condition
coryza	4091370	Postnasal discharge on posterior wall of pharynx	SNOMED	Condition
coryza	4316067	Rhinitis sicca	SNOMED	Condition
coryza	4101701	Atrophic rhinitis	SNOMED	Condition
coryza	4327870	Gustatory rhinitis	SNOMED	Condition
coryza	4165268	Obstructive rhinitis	SNOMED	Condition
coryza	4320791	Rhinitis	SNOMED	Condition
coryza	4245453	Necrotic rhinitis	SNOMED	Condition
coryza	4177553	Mixed rhinitis	SNOMED	Condition
coryza	260427	Common cold	SNOMED	Condition
coryza	4305500	Vasomotor rhinitis	SNOMED	Condition
coryza	4049223	Acute irritant rhinitis	SNOMED	Condition

Phenotype	Concept id	Concept name	Vocabulary	Domain
coryza	4051475	Rhinitis caseosa	SNOMED	Condition
coryza	4149990	Nasal discharge present	SNOMED	Observation
coryza	3654569	Mucopurulent discharge from nose	SNOMED	Condition
coryza	619759	Rhinosinusitis	SNOMED	Condition
coryza	4329087	Acute rhinosinusitis	SNOMED	Condition
coryza	604304	Rhinoconjunctivitis	SNOMED	Condition
coryza	37311132	Foul smelling discharge from nose	SNOMED	Condition
coryza	257683	Posterior rhinorrhea	SNOMED	Condition
cough	3657556	Recently performed mobilisation with intent to cause cough	SNOMED	Observation
cough	4048098	Cough with fever	SNOMED	Condition
cough	42868844	I wake at night because of coughing in the past 7 days [FACIT]	LOINC	Observation
cough	4048759	Brassy cough	SNOMED	Condition
cough	4009942	Postural cough	SNOMED	Condition
cough	4142946	Sounds unaffected by cough	SNOMED	Meas Value
cough	4109381	Persistent cough	SNOMED	Condition
cough	4311574	Post-tussive vomiting	SNOMED	Condition
cough	44806100	Episodic dry cough	SNOMED	Condition
cough	36203801	Date of cough onset	LOINC	Observation
cough	4010220	Cough fracture of ribs	SNOMED	Condition
cough	4140570	Sounds clear with cough	SNOMED	Meas Value
cough	4126096	Croupy cough	SNOMED	Condition
cough	4188217	Cough after eating	SNOMED	Condition
cough	36203802	Cough duration	LOINC	Observation
cough	4090569	Painful cough	SNOMED	Condition
cough	4094147	Cough when swallowing	SNOMED	Condition
cough	4117283	Does cough up sputum	SNOMED	Condition
cough	4270340	Increasing frequency of cough	SNOMED	Condition
cough	4271318	Spasmodic cough	SNOMED	Condition
cough	4323688	Cough at rest	SNOMED	Condition
cough	4234105	Tussive syncope	SNOMED	Condition
cough	4059020	Morning cough	SNOMED	Condition
cough	4059018	Night cough present	SNOMED	Observation
cough	40767150	Over the past 3 months, I have coughed [PhenX]	LOINC	Observation
cough	40767161	My cough makes me tired [PhenX]	LOINC	Observation

Phenotype	Concept id	Concept name	Vocabulary	Domain
cough	42868913	I have been coughing in the past 7 days [FACIT]	LOINC	Observation
cough	4183272	Tussive fremitus	SNOMED	Observation
cough	4038065	Cough aggravates symptom	SNOMED	Observation
cough	4077128	Barking cough	SNOMED	Condition
cough	44789249	Reflux cough	SNOMED	Condition
cough	601499	Headache after cough	SNOMED	Condition
cough	1340293	Exacerbation of cough	OMOP Extension	Condition
cough	4103332	Effective cough	SNOMED	Condition
cough	4059017	Productive cough-yellow sputum	SNOMED	Condition
cough	4087179	Character of cough	SNOMED	Observation
cough	4144596	Pain provoked by coughing	SNOMED	Condition
cough	4128391	Cough - urge incontinence of urine	SNOMED	Condition
cough	4038519	Dry cough	SNOMED	Condition
cough	4102774	Productive cough	SNOMED	Condition
cough	4167374	Respiratory tract congestion and cough	SNOMED	Condition
cough	4243802	Hacking cough	SNOMED	Condition
cough	40767160	My cough hurts [PhenX]	LOINC	Observation
cough	40482863	Postviral cough	SNOMED	Condition
cough	4239599	Characteristic of cough	SNOMED	Observation
cough	1332774	Cough	PPI	Observation
cough	4060224	Productive cough -clear sputum	SNOMED	Condition
cough	4058584	Evening cough	SNOMED	Condition
cough	40767166	My cough or breathing is embarrassing in public [PhenX]	LOINC	Observation
cough	4294425	Purpura due to prolonged vomiting and/or coughing	SNOMED	Condition
cough	35626060	Cough strength	SNOMED	Observation
cough	4122567	Does cough	SNOMED	Condition
cough	4060051	Productive cough -green sputum	SNOMED	Condition
cough	35811619	Cough on most days	UK Biobank	Observation
cough	254761	Cough	SNOMED	Condition
cough	4199298	Decreased coughing	SNOMED	Condition
cough	4266704	Early morning cough	SNOMED	Condition
cough	4310540	Post-tussive crackles	SNOMED	Condition
cough	40767164	My cough or breathing disturbs my sleep [PhenX]	LOINC	Observation

Phenotype	Concept id	Concept name	Vocabulary	Domain
cough	4137801	Coughing	SNOMED	Observation
cough	4196430	Unexplained cough	SNOMED	Condition
cough	4182587	Paroxysmal cough	SNOMED	Condition
dysgeusia	436235	Taste sense altered	SNOMED	Observation
dysgeusia	4082438	Abnormal taste in mouth	SNOMED	Condition
fever	4152339	Rapid fall of fever	SNOMED	Condition
fever	4328373	Pyrexia of unknown origin	SNOMED	Condition
fever	4009878	Spiking fever	SNOMED	Condition
fever	4048097	Feverish cold	SNOMED	Observation
fever	4158332	Irregular fever	SNOMED	Condition
fever	4087625	Pattern of fever	SNOMED	Observation
fever	36716728	Fever due to infection	SNOMED	Condition
fever	4093995	Rising phase of fever	SNOMED	Condition
fever	4158329	Gradual rise of fever	SNOMED	Condition
fever	4152340	Gradual fall of fever	SNOMED	Condition
fever	4260205	Hyperpyrexia	SNOMED	Condition
fever	4166729	Disorder characterized by fever	SNOMED	Condition
fever	4268842	Pattern of fever - finding	SNOMED	Condition
fever	4164645	Fever with chills	SNOMED	Condition
fever	4093996	Slightly remittent fever	SNOMED	Condition
fever	4086665	Biphasic fever	SNOMED	Condition
fever	4094001	Fever defervescence	SNOMED	Condition
fever	437663	Fever	SNOMED	Condition
fever	440637	Relapsing fever	SNOMED	Condition
fever	4086663	Plateau phase of fever	SNOMED	Condition
fever	4299794	Intermittent fever	SNOMED	Condition
fever	36712667	Viral fever	SNOMED	Condition
fever	38001557	Fever	DRG	Observation
fever	4268846	Phase of fever - finding	SNOMED	Condition
fever	4127282	Low grade pyrexia	SNOMED	Condition
fever	21495024	Date of fever onset	LOINC	Observation
fever	4086664	Falling phase of fever	SNOMED	Condition
fever	4087626	Phase of fever	SNOMED	Observation
fever	4087016	Prolonged fever	SNOMED	Condition
fever	4154923	Acute rise of fever	SNOMED	Condition
fever	4274502	Remittent fever	SNOMED	Condition
fever	1616342	Acute illness with fever	LOINC	Observation

Phenotype	Concept id	Concept name	Vocabulary	Domain
fever	1332834	A fever/feverish	PPI	Observation
fever	4158330	Continuous fever	SNOMED	Condition
fever	136030	Sweating fever	SNOMED	Condition
fever	4086666	Fever, diurnal variation	SNOMED	Condition
fever	35609917	FeverPAIN (Fever in last 24 hours, Purulence, Attend rapidly under 3 days, Inflamed tonsils, No cough and/or coryza) Clinical Score	SNOMED	Measurement
fever	444413	Febrile convulsion	SNOMED	Condition
fever	377101	Simple febrile seizure	SNOMED	Condition
fever	762948	Simple febrile seizure, non-refractory	SNOMED	Condition
fever	765872	Complex febrile seizure, refractory	SNOMED	Condition
fever	762914	Complex febrile seizure, non-refractory	SNOMED	Condition
fever	4143868	Recurrent febrile convulsion	SNOMED	Condition
fever	762947	Simple febrile seizure, refractory	SNOMED	Condition
fever	374168	Complex febrile seizure	SNOMED	Condition
fever	4048098	Cough with fever	SNOMED	Condition
headache	4264837	Characteristic of headache	SNOMED	Observation
headache	4038024	Headache character	SNOMED	Observation
headache	1340345	Exacerbation of headache	OMOP Extension	Condition
headache	3179785	Intractable headache	Nebraska Lexicon	Condition
headache	378253	Headache	SNOMED	Condition
headache	4105365	Sick headache	SNOMED	Condition
headache	40768081	Because of your headaches on how many days in the last 3 months did you miss family, social, or leisure activities [PhenX]	LOINC	Observation
headache	40772101	Bothered by headaches in last 4 weeks [Reported.PHQ]	LOINC	Observation
headache	42870248	I am bothered by headaches in the past 4 weeks [FACIT]	LOINC	Observation
headache	4036624	Throbbing headache	SNOMED	Condition
headache	43530648	New daily persistent headache	SNOMED	Condition
headache	762152	Intractable episodic cluster headache	SNOMED	Condition
headache	40326905	Unilateral headache	SNOMED	Condition
headache	38000976	Headaches w/o MCC	DRG	Observation
headache	43530641	Primary thunderclap headache	SNOMED	Condition

Phenotype	Concept id	Concept name	Vocabulary	Domain
headache	762084	Intractable episodic tension-type headache	SNOMED	Condition
headache	376382	Tension-type headache	SNOMED	Condition
headache	4195951	Nasal headache	SNOMED	Condition
headache	3043250	Headache [Minimum Data Set]	LOINC	Observation
headache	42539583	Acute headache	SNOMED	Condition
headache	373755	Thunderclap headache	SNOMED	Condition
headache	40768080	Because of your headaches on how many days in the last 3 months was your productivity in house-hold work reduced by half or more [PhenX]	LOINC	Observation
headache	4147325	Frontal headache	SNOMED	Condition
headache	4038025	Aching headache	SNOMED	Condition
headache	377545	Episodic tension-type headache	SNOMED	Condition
headache	43530640	Hypnic headache	SNOMED	Condition
headache	374922	Idiopathic stabbing headache	SNOMED	Condition
headache	40768078	Because of your headaches on how many days in the last 3 months was your productivity at work or school reduced by half or more [PhenX]	LOINC	Observation
headache	4315023	Ocular headache	SNOMED	Condition
headache	21493489	Headaches [NDI]	LOINC	Observation
headache	4172302	Sinus headache	SNOMED	Condition
headache	37016725	Frequent headache	SNOMED	Condition
headache	605546	Unilateral left sided headache	SNOMED	Condition
headache	40768077	Because of your headaches on how many days in the last 3 months did you miss work or school [PhenX]	LOINC	Observation
headache	42868773	I get headaches in the past 7 days [FACIT]	LOINC	Observation
headache	4012515	Viral headache	SNOMED	Condition
headache	4038026	Shooting headache	SNOMED	Condition
headache	4037300	Parietal headache	SNOMED	Condition
headache	35811428	Degree bothered by headaches in the last 3 months	UK Biobank	Observation
headache	605547	Unilateral right sided headache	SNOMED	Condition
headache	4037298	Headache site	SNOMED	Condition
headache	4037891	Bilateral headache	SNOMED	Condition
headache	40483832	Orthostatic headache	SNOMED	Condition
headache	763746	Postural headache	SNOMED	Condition
headache	601499	Headache after cough	SNOMED	Condition

Phenotype	Concept id	Concept name	Vocabulary	Domain
headache	36716799	Frequent episodic tension-type headache	SNOMED	Condition
headache	38000975	Headaches w MCC	DRG	Observation
headache	4134454	Vascular headache	SNOMED	Condition
headache	40767654	I get headaches or stomach aches when I am at school [SCARED-R]	LOINC	Observation
headache	4036622	Generalized headache	SNOMED	Condition
headache	4212985	Temporal headache	SNOMED	Condition
headache	43530760	Daily headache	SNOMED	Condition
headache	44790934	Increased frequency of headaches	SNOMED	Condition
headache	4044236	Low pressure headache	SNOMED	Condition
headache	42869282	I am bothered by headaches in the past 7 days [FACIT]	LOINC	Observation
headache	4036953	Morning headache	SNOMED	Condition
headache	35819519	Headache	UK Biobank	Observation
headache	37016721	Intermittent headache	SNOMED	Condition
headache	4140381	Occipital headache	SNOMED	Condition
headache	4271776	Headache character - finding	SNOMED	Condition
headache	375527	Headache disorder	SNOMED	Condition
headache	37020024	I had a headache in past 7 days [PROMIS.PEDS]	LOINC	Observation
headache	4309592	Aural headache	SNOMED	Condition
headache	40480081	Paroxysmal hemicrania	SNOMED	Condition
headache	3170444	Occipital pain	Nebraska Lexicon	Condition
headache	4115407	Frontal sinus pain	SNOMED	Condition
headache	4103477	Maxillary sinus pain	SNOMED	Condition
headache	42535475	Episodic paroxysmal hemicrania	SNOMED	Condition
headache	40480082	Hemicrania continua	SNOMED	Condition
malaise	4202045	Postviral fatigue syndrome	SNOMED	Condition
malaise	4214612	Muscle fatigue	SNOMED	Condition
malaise	1340332	Exacerbation of fatigue	OMOP Extension	Condition
malaise	40764345	How would you rate your fatigue on average in past 7 days [PROMIS]	LOINC	Observation
malaise	40764631	On how many days was your fatigue worse in the morning in past 7 days [PROMIS]	LOINC	Observation
malaise	37016959	Management of fatigue	SNOMED	Observation
malaise	4347293	Severe systemic illness respiratory muscle fatigue	SNOMED	Condition

Phenotype	Concept id	Concept name	Vocabulary	Domain
malaise	439926	Malaise and fatigue	SNOMED	Observation
malaise	40764588	Due to your fatigue were you less effective at work (include work at home) in past 7 days [PROMIS]	LOINC	Observation
malaise	40764639	I feel fatigued during the past 7 days [PROMIS]	LOINC	Observation
malaise	4063119	Peripheral muscle fatigue	SNOMED	Condition
malaise	40764598	Did fatigue make you less effective at home in past 7 days [PROMIS]	LOINC	Observation
malaise	36204164	Bothered by fatigue over the past 2 weeks [KCCQ]	LOINC	Observation
malaise	42868897	I feel fatigued in the past 7 days [FACIT]	LOINC	Observation
malaise	3035035	Fatigue [CCC]	LOINC	Observation
malaise	4209103	Accommodative fatigue	SNOMED	Condition
malaise	40764638	What was the level of your fatigue on most days in past 7 days [PROMIS]	LOINC	Observation
malaise	40770521	I needed help doing my usual activities because of my fatigue in the past 7 days [NeuroQol]	LOINC	Observation
malaise	4319130	Neuromuscular fatigue	SNOMED	Observation
malaise	40764622	How much were you bothered by your fatigue on average in past 7 days [PROMIS]	LOINC	Observation
malaise	1616921	Fatigue panel [R-Outcomes]	LOINC	Observation
malaise	4260261	Level of fatigue	SNOMED	Observation
malaise	4092860	Rapid fatigue of gait	SNOMED	Observation
malaise	607123	Reduced level of fatigue	SNOMED	Observation
malaise	40764581	How hard was it for you to carry on a conversation because of your fatigue in past 7 days [PROMIS]	LOINC	Observation
malaise	36204163	Fatigue limited your ability to do what you wanted over the past 2 weeks [KCCQ]	LOINC	Observation
malaise	4223659	Fatigue	SNOMED	Observation
malaise	4193374	Central muscle fatigue	SNOMED	Condition
malaise	4193763	High frequency muscle fatigue	SNOMED	Condition
malaise	1333026	Unusual fatigue	PPI	Observation
malaise	40766817	Fatigue --resting	LOINC	Observation
malaise	4279937	Low frequency muscle fatigue	SNOMED	Condition
malaise	4272240	Malaise	SNOMED	Observation
malaise	40768638	Loss of energy or fatigue [DI-PAD]	LOINC	Observation

Phenotype	Concept id	Concept name	Vocabulary	Domain
malaise	40770515	I felt fatigued in the past 7 days [NeuroQol]	LOINC	Observation
malaise	765190	Asthenia due to disease	SNOMED	Observation
malaise	437113	Asthenia	SNOMED	Observation
myalgia	4319324	Polymyalgia	SNOMED	Condition
myalgia	4318397	Intercostal myalgia	SNOMED	Condition
myalgia	4150129	Musculoskeletal pain	SNOMED	Condition
myalgia	4184119	Pain on movement of skeletal muscle	SNOMED	Condition
myalgia	4298555	Epidemic cervical myalgia	SNOMED	Condition
myalgia	4150130	Muscle tension pain	SNOMED	Condition
myalgia	42870055	I am bothered by muscle pains in the past 7 days [FACIT]	LOINC	Observation
myalgia	4092930	Musculoskeletal chest pain	SNOMED	Condition
myalgia	442752	Muscle pain	SNOMED	Condition
myalgia	4344370	Viral myalgia	SNOMED	Condition
myalgia	42869098	I have joint pain or muscle cramps in the past 7 days [FACIT]	LOINC	Observation
myalgia	1340400	Exacerbation of muscle pain	OMOP Extension	Condition
myalgia	1333131	Unusually strong muscle pains/aches	PPI	Observation
myalgia	37167238	Pain in muscle of lower leg	SNOMED	Condition
myalgia	37167229	Pain in muscle of forearm	SNOMED	Condition
myalgia	37167237	Pain in muscle of upper arm	SNOMED	Condition
myalgia	37167226	Pain in muscle of hand	SNOMED	Condition
shortness_of_breath	40757972	Shortness of breath or trouble breathing with exertion in last 7 days [MDSv3]	LOINC	Observation
shortness_of_breath	40757974	Shortness of breath or trouble breathing when lying flat in last 7 days [MDSv3]	LOINC	Observation
shortness_of_breath	4091788	Dyspnea raising arms	SNOMED	Condition
shortness_of_breath	40767184	My breathing makes it difficult to do things such as walk up hills, carrying things up stairs, light gardening such as weeding, dance, play bowls or play golf [PhenX]	LOINC	Observation
shortness_of_breath	1176427	Considering your shortness of breath over the past 7 days, rate the amount of difficulty you had when walking (faster than your usual speed) for 50 steps without stopping [PROMIS]	LOINC	Observation
shortness_of_breath	4212233	Dyspnea after eating	SNOMED	Condition
shortness_of_breath	4248284	Dyspnea, class IV	SNOMED	Condition

Phenotype	Concept id	Concept name	Vocabulary	Domain
shortness_of_breath	1175569	Considering your shortness of breath over the past 7 days, rate the amount of difficulty you had when walking up 30 stairs (3 flights) without stopping [PROMIS]	LOINC	Observation
shortness_of_breath	1989377	I am embarrassed by my shortness of breath in past 7 days	LOINC	Observation
shortness_of_breath	312437	Dyspnea	SNOMED	Condition
shortness_of_breath	4244276	Paroxysmal dyspnea	SNOMED	Condition
shortness_of_breath	3046714	Inability to lie flat due to shortness of breath [Minimum Data Set]	LOINC	Observation
shortness_of_breath	42529081	Dyspnea [ALSFRS-R]	LOINC	Observation
shortness_of_breath	4066850	Dyspnea leaning over	SNOMED	Condition
shortness_of_breath	4217021	Dyspnea, class II	SNOMED	Condition
shortness_of_breath	42869104	I have difficulty breathing when I am exposed to cold temperatures in the past 7 days [FACIT]	LOINC	Observation
shortness_of_breath	36204166	Bothered by shortness of breath over the past 2 weeks [KCCQ]	LOINC	Observation
shortness_of_breath	1176335	Considering your shortness of breath over the past 7 days, rate the amount of difficulty you had when carrying something weighing 10-20 lbs (about 4.5-9 kg, like a large bag of groceries) from one room to another [PROMIS]	LOINC	Observation
shortness_of_breath	1176118	Considering your shortness of breath over the past 7 days, rate the amount of difficulty you had when scrubbing the floor or counter [PROMIS]	LOINC	Observation
shortness_of_breath	1175177	Considering your shortness of breath over the past 7 days, rate the amount of difficulty you had when moderate-intensity leisure activity (bicycling on level terrain, etc.) [PROMIS]	LOINC	Observation
shortness_of_breath	40767185	My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per H, play tennis or swim [PhenX]	LOINC	Observation
shortness_of_breath	36304302	Shortness of breath during assessment period [CMS Assessment]	LOINC	Observation
shortness_of_breath	1176014	Considering your shortness of breath over the past 7 days, rate the amount of difficulty you had when lifting something weighing less than 5 lbs (about 2 kg, like a houseplant) [PROMIS]	LOINC	Observation
shortness_of_breath	1176142	Considering your shortness of breath over the past 7 days, rate the amount of difficulty you had when walking up	LOINC	Observation

Phenotype	Concept id	Concept name	Vocabulary	Domain
		10 stairs (1 flight) without stopping [PROMIS]		
shortness_of_breath	1175881	Considering your shortness of breath over the past 7 days, rate the amount of difficulty you had when low-intensity leisure activity (gardening, etc.) [PROMIS]	LOINC	Observation
shortness_of_breath	1175867	Considering your shortness of breath over the past 7 days, rate the amount of difficulty you had when talking while walking [PROMIS]	LOINC	Observation
shortness_of_breath	4041664	Difficulty breathing	SNOMED	Condition
shortness_of_breath	35810535	Shortness of breath walking on level ground	UK Biobank	Observation
shortness_of_breath	4206307	Paroxysmal nocturnal dyspnea	SNOMED	Condition
shortness_of_breath	45765605	Difficulty eating due to breathlessness	SNOMED	Observation
shortness_of_breath	40772106	Bothered by shortness of breath in last 4 weeks [Reported.PHQ]	LOINC	Observation
shortness_of_breath	1175340	Considering your shortness of breath over the past 7 days, rate the amount of difficulty you had when walking up 20 stairs (2 flights) without stopping [PROMIS]	LOINC	Observation
shortness_of_breath	1175420	Considering your shortness of breath over the past 7 days, rate the amount of difficulty you had when dining out [PROMIS]	LOINC	Observation
shortness_of_breath	4065915	Dyspnea, class I	SNOMED	Condition
shortness_of_breath	3043375	Shortness of breath [Minimum Data Set]	LOINC	Observation
shortness_of_breath	4094132	Nocturnal dyspnea	SNOMED	Condition
shortness_of_breath	36204167	Sleep sitting up in a chair or with at least 3 pillows to prop you up because of shortness of breath over the past 2 weeks [KCCQ]	LOINC	Observation
shortness_of_breath	1176272	Considering your shortness of breath over the past 7 days, rate the amount of difficulty you had when making a bed [PROMIS]	LOINC	Observation
shortness_of_breath	1175514	Considering your shortness of breath over the past 7 days, rate the amount of difficulty you had when taking a bath without help [PROMIS]	LOINC	Observation
shortness_of_breath	1988842	Frequency of shortness of breath in past 7 days	LOINC	Observation
shortness_of_breath	4263848	Dyspnea on exertion	SNOMED	Condition
shortness_of_breath	1175124	Considering your shortness of breath over the past 7 days, rate the amount	LOINC	Observation

Phenotype	Concept id	Concept name	Vocabulary	Domain
		of difficulty you had when sweeping or mopping [PROMIS]		
shortness_of_breath	1988500	Shortness of breath in general in past 7 days	LOINC	Observation
shortness_of_breath	1175667	Considering your shortness of breath over the past 7 days, rate the amount of difficulty you had when walking up 5 stairs without stopping [PROMIS]	LOINC	Observation
shortness_of_breath	1175588	Considering your shortness of breath over the past 7 days, rate the amount of difficulty you had when lifting something weighing 5-10 lbs (about 2-4.5 kg, like a basket of clothes) [PROMIS]	LOINC	Observation
shortness_of_breath	1989668	I get upset when I can't do something because of my shortness of breath in past 7 days	LOINC	Observation
shortness_of_breath	4219335	Dyspnea, class III	SNOMED	Condition
shortness_of_breath	1988655	Duration of shortness of breath in past 7 days	LOINC	Observation
shortness_of_breath	1175874	Considering your shortness of breath over the past 7 days, rate the amount of difficulty you had when walking 10 steps/paces on flat ground at a normal speed without stopping [PROMIS]	LOINC	Observation
shortness_of_breath	1175579	Considering your shortness of breath over the past 7 days, rate the amount of difficulty you had when walking (faster than your usual speed) for at least 1 mile (a little more than 1.5 km) without stopping [PROMIS]	LOINC	Observation
shortness_of_breath	40757695	Shortness of breath	LOINC	Observation
shortness_of_breath	40757973	Shortness of breath or trouble breathing when sitting at rest in last 7 days [MDSv3]	LOINC	Observation
shortness_of_breath	40767186	My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sport [PhenX]	LOINC	Observation
shortness_of_breath	1175216	Considering your shortness of breath over the past 7 days, rate the amount of difficulty you had when walking (faster than your usual speed) for 1/2 mile (almost 1 km) without stopping [PROMIS]	LOINC	Observation
shortness_of_breath	1988563	Intensity of shortness of breath in past 7 days	LOINC	Observation
shortness_of_breath	4128689	Difficulty taking deep breaths	SNOMED	Observation

Phenotype	Concept id	Concept name	Vocabulary	Domain
shortness_of_breath	1340318	Exacerbation of dyspnea	OMOP Extension	Condition
shortness_of_breath	4097311	Inspiratory dyspnea	SNOMED	Condition
shortness_of_breath	40768564	Condition causing difficulty with breathing [PhenX]	LOINC	Observation
shortness_of_breath	1176255	Considering your shortness of breath over the past 7 days, rate the amount of difficulty you had when walking 1/2 mile (almost 1 km) on flat ground at a normal speed without stopping [PROMIS]	LOINC	Observation
shortness_of_breath	1175934	Considering your shortness of breath over the past 7 days, rate the amount of difficulty you had when carrying something weighing less than 5 lbs (about 2 kg, like a houseplant) from one room to another [PROMIS]	LOINC	Observation
shortness_of_breath	1175311	Considering your shortness of breath over the past 7 days, rate the amount of difficulty you had when getting in or out of a car [PROMIS]	LOINC	Observation
shortness_of_breath	1176456	Considering your shortness of breath over the past 7 days, rate the amount of difficulty you had singing or humming [PROMIS]	LOINC	Observation
shortness_of_breath	1175767	Considering your shortness of breath over the past 7 days, rate the amount of difficulty you had when putting on socks or stockings [PROMIS]	LOINC	Observation
shortness_of_breath	1175255	Considering your shortness of breath over the past 7 days, rate the amount of difficulty you had when walking 50 steps/paces on flat ground at a normal speed without stopping [PROMIS]	LOINC	Observation
shortness_of_breath	1175742	Considering your shortness of breath over the past 7 days, rate the amount of difficulty you had when lifting something weighing more than 20 lbs (about 9 kg, like a medium-sized suitcase) [PROMIS]	LOINC	Observation
shortness_of_breath	1333230	Difficulty breathing or shortness of breath	Observation	PPI
shortness_of_breath	4144682	Expiratory dyspnea	SNOMED	Condition
shortness_of_breath	40760356	Exertion level causing shortness of breath during assessment period [CMS Assessment]	LOINC	Observation
shortness_of_breath	1175423	Considering your shortness of breath over the past 7 days, rate the amount of difficulty you had when dressing yourself without help [PROMIS]	LOINC	Observation

Phenotype	Concept id	Concept name	Vocabulary	Domain
shortness_of_breath	1176316	Considering your shortness of breath over the past 7 days, rate the amount of difficulty you had when preparing meals [PROMIS]	LOINC	Observation
shortness_of_breath	1175441	Considering your shortness of breath over the past 7 days, rate the amount of difficulty you had when standing for at least 5 minutes [PROMIS]	LOINC	Observation
shortness_of_breath	1176274	Considering your shortness of breath over the past 7 days, rate the amount of difficulty you had when carrying something weighing 5-10 lbs (about 2-4.5 kg, like a basket of clothes) from one room to another [PROMIS]	LOINC	Observation
shortness_of_breath	1176270	Considering your shortness of breath over the past 7 days, rate the amount of difficulty you had when lifting something weighing 10-20 lbs (about 4.5-9 kg, like a large bag of groceries) [PROMIS]	LOINC	Observation
shortness_of_breath	1175121	Considering your shortness of breath over the past 7 days, rate the amount of difficulty you had when washing dishes [PROMIS]	LOINC	Observation
shortness_of_breath	4060052	Dyspnea at rest	SNOMED	Condition
shortness_of_breath	36714269	Breathlessness care	SNOMED	Observation
shortness_of_breath	4219740	Borg Breathlessness Score finding	SNOMED	Condition
shortness_of_breath	36685571	mMRC (modified Medical Research Council) dyspnoea scale grade 4	SNOMED	Condition
shortness_of_breath	4148800	Platypnea	SNOMED	Condition
shortness_of_breath	36685568	mMRC (modified Medical Research Council) dyspnoea scale grade 1	SNOMED	Condition
shortness_of_breath	36685570	mMRC (modified Medical Research Council) dyspnoea scale grade 3	SNOMED	Condition
shortness_of_breath	4190875	Breathless - strenuous exertion	SNOMED	Condition
shortness_of_breath	4223034	Borg Breathlessness Score: 3 moderate	SNOMED	Condition
shortness_of_breath	4223035	Borg Breathlessness Score: 4 somewhat severe	SNOMED	Condition
shortness_of_breath	4195694	Acute respiratory distress syndrome	SNOMED	Condition
shortness_of_breath	35610140	eMRC (extended Medical Research Council) dyspnoea scale grade 2	SNOMED	Condition
shortness_of_breath	4059022	Breathless - mild exertion	SNOMED	Condition
shortness_of_breath	4223036	Borg Breathlessness Score: 5 severe	SNOMED	Condition
shortness_of_breath	4220640	Borg Breathlessness Score: 6 severe (+)	SNOMED	Condition

Phenotype	Concept id	Concept name	Vocabulary	Domain
shortness_of_breath	4223037	Borg Breathlessness Score: 7 very severe	SNOMED	Condition
shortness_of_breath	4010972	Trepopnea	SNOMED	Condition
shortness_of_breath	4310172	Medical Research Council Dyspnoea scale grade 4	SNOMED	Condition
shortness_of_breath	4220641	Borg Breathlessness Score: 9 very, very severe (almost maximal)	SNOMED	Condition
shortness_of_breath	4154698	Transient respiratory distress with sepsis	SNOMED	Condition
shortness_of_breath	1340509	Progression of acute respiratory distress syndrome	OMOP Extension	Condition
shortness_of_breath	4024118	Pulmonary insufficiency following trauma	SNOMED	Condition
shortness_of_breath	4192279	Medical Research Council Dyspnoea scale grade 5	SNOMED	Condition
shortness_of_breath	4223038	Borg Breathlessness Score: 8 very severe (+)	SNOMED	Condition
shortness_of_breath	4253185	Unable to complete a sentence in one breath	SNOMED	Condition
shortness_of_breath	36685569	mMRC (modified Medical Research Council) dyspnoea scale grade 2	SNOMED	Condition
shortness_of_breath	35610142	eMRC (extended Medical Research Council) dyspnoea scale grade 5a	SNOMED	Condition
shortness_of_breath	35610144	eMRC (extended Medical Research Council) dyspnoea scale grade 5b	SNOMED	Condition
shortness_of_breath	4178416	Increasing breathlessness	SNOMED	Condition
shortness_of_breath	4307188	Medical Research Council Dyspnoea scale grade 3	SNOMED	Condition
shortness_of_breath	4087166	Labored breathing	SNOMED	Condition
shortness_of_breath	35610139	eMRC (extended Medical Research Council) dyspnoea scale grade 1	SNOMED	Condition
shortness_of_breath	35610141	eMRC (extended Medical Research Council) dyspnoea scale grade 3	SNOMED	Condition
shortness_of_breath	36685567	mMRC (modified Medical Research Council) dyspnoea scale grade 0	SNOMED	Condition
shortness_of_breath	4059021	Breathless - moderate exertion	SNOMED	Condition
shortness_of_breath	4308377	Short of breath dressing/undressing	SNOMED	Condition
shortness_of_breath	4310059	Medical Research Council Dyspnoea scale grade 1	SNOMED	Condition
shortness_of_breath	4222444	Borg Breathlessness Score: 1 very slight	SNOMED	Condition
shortness_of_breath	315361	Orthopnea	SNOMED	Condition
shortness_of_breath	4223033	Borg Breathlessness Score: 2 slight	SNOMED	Condition
shortness_of_breath	4047610	Gasping for breath	SNOMED	Condition

Phenotype	Concept id	Concept name	Vocabulary	Domain
shortness_of_breath	4222446	Borg Breathlessness Score: 10 maximal	SNOMED	Condition
shortness_of_breath	4158346	Respiratory distress	SNOMED	Condition
shortness_of_breath	4191650	Acute respiratory distress	SNOMED	Condition
shortness_of_breath	35610143	eMRC (extended Medical Research Council) dyspnoea scale grade 4	SNOMED	Condition
shortness_of_breath	4193263	Medical Research Council Dyspnoea scale grade 2	SNOMED	Condition
sore_throat	4241328	Phlegmonous pharyngitis	SNOMED	Condition
sore_throat	4197268	Nasopharyngitis	SNOMED	Condition
sore_throat	42868901	I have pain in my mouth, throat or neck in the past 7 days [FACIT]	LOINC	Observation
sore_throat	23798	Acute laryngopharyngitis	SNOMED	Condition
sore_throat	4170621	Vesicular pharyngitis	SNOMED	Condition
sore_throat	4109893	Acute phlegmonous pharyngitis	SNOMED	Condition
sore_throat	4226263	Pharyngitis	SNOMED	Condition
sore_throat	3181166	Aphthous pharyngitis	Nebraska Lexicon	Condition
sore_throat	4273688	Atrophic pharyngitis	SNOMED	Condition
sore_throat	25297	Acute pharyngitis	SNOMED	Condition
sore_throat	4112499	Pharyngitis sicca	SNOMED	Condition
sore_throat	4036632	Has a sore throat	SNOMED	Observation
sore_throat	1332836	Sore or painful throat	PPI	Observation
sore_throat	4247910	Gangrenous pharyngitis	SNOMED	Condition
sore_throat	4337956	Hypertrophic pharyngitis	SNOMED	Condition
sore_throat	4110358	Acute gangrenous pharyngitis	SNOMED	Condition
sore_throat	4112343	Acute viral pharyngitis	SNOMED	Condition
sore_throat	259153	Pain in throat	SNOMED	Condition
sore_throat	4240728	Suppurative pharyngitis	SNOMED	Condition
sore_throat	4190176	Ulcerative pharyngitis	SNOMED	Condition
sore_throat	4051490	Glandular fever pharyngitis	SNOMED	Condition
sore_throat	4193318	Infective pharyngitis	SNOMED	Condition
sore_throat	4110512	Influenza with pharyngitis	SNOMED	Condition
sore_throat	4131441	Exudative pharyngitis	SNOMED	Condition
sore_throat	4147326	Sore throat	SNOMED	Condition
sore_throat	4112342	Acute ulcerative pharyngitis	SNOMED	Condition
sore_throat	4035987	Viral pharyngitis	SNOMED	Condition
acute_respiratory_infections	4175297	Lower respiratory tract infection	SNOMED	Condition
acute_respiratory_infections	45768730	Severe acute respiratory infection	SNOMED	Condition

Phenotype	Concept id	Concept name	Vocabulary	Domain
acute_respiratory_infections	4193169	Viral respiratory infection	SNOMED	Condition
acute_respiratory_infections	40491473	Recurrent lower respiratory tract infection	SNOMED	Condition
acute_respiratory_infections	46273463	Upper respiratory tract infection caused by Influenza virus	SNOMED	Condition
acute_respiratory_infections	4085100	Viral upper respiratory tract infection	SNOMED	Condition
acute_respiratory_infections	4181583	Upper respiratory infection	SNOMED	Condition
acute_respiratory_infections	257011	Acute upper respiratory infection	SNOMED	Condition
acute_respiratory_infections	46270491	Upper respiratory tract infection caused by Influenza A	SNOMED	Condition
acute_respiratory_infections	4110479	Recurrent upper respiratory tract infection	SNOMED	Condition
acute_respiratory_infections	4006969	Acute respiratory disease	SNOMED	Condition
acute_respiratory_infections	4183609	Influenzal acute upper respiratory infection	SNOMED	Condition
acute_respiratory_infections	4170143	Respiratory tract infection	SNOMED	Condition
acute_respiratory_infections	4112341	Acute respiratory infections	SNOMED	Condition
acute_respiratory_infections	4173813	Infection of lower respiratory tract and mediastinum	SNOMED	Condition
acute_respiratory_infections	4307774	Acute lower respiratory tract infection	SNOMED	Condition
acute_respiratory_infections	4207187	Viral lower respiratory infection	SNOMED	Condition
acute_respiratory_infections	46270122	Upper respiratory tract infection caused by H1N1 influenza	SNOMED	Condition
acute_respiratory_infections	40482863	Postviral cough	SNOMED	Condition
acute_respiratory_infections	37016926	Influenza caused by Influenza A virus subtype H5	SNOMED	Condition
acute_respiratory_infections	25297	Acute pharyngitis	SNOMED	Condition
acute_respiratory_infections	4112357	Acute purulent bronchitis	SNOMED	Condition
acute_respiratory_infections	4049238	Acute infection of tonsillar remnant	SNOMED	Condition
acute_respiratory_infections	37394477	Influenza due to pandemic influenza virus	SNOMED	Condition
acute_respiratory_infections	4173734	Acute pansinusitis	SNOMED	Condition
acute_respiratory_infections	435840	Acute epiglottitis without obstruction	SNOMED	Condition
acute_respiratory_infections	4321233	Viral epiglottitis	SNOMED	Condition
acute_respiratory_infections	4229623	Acute abscess of maxillary sinus	SNOMED	Condition
acute_respiratory_infections	4109898	Acute gangrenous tonsillitis	SNOMED	Condition
acute_respiratory_infections	4051610	Adult acute epiglottitis and supraglottitis	SNOMED	Condition
acute_respiratory_infections	4052544	Acute viral bronchiolitis	SNOMED	Condition
acute_respiratory_infections	37394476	Influenza due to zoonotic influenza virus	SNOMED	Condition

Phenotype	Concept id	Concept name	Vocabulary	Domain
acute_respiratory_infections	4048517	Acute bronchopneumonia	SNOMED	Condition
acute_respiratory_infections	4035960	Acute bronchiolitis with bronchospasm	SNOMED	Condition
acute_respiratory_infections	4069712	Acute pleuropericarditis	SNOMED	Condition
acute_respiratory_infections	4207471	Infective laryngitis	SNOMED	Condition
acute_respiratory_infections	4243668	Acute obliterating bronchiolitis	SNOMED	Condition
acute_respiratory_infections	36714388	Influenza caused by seasonal influenza virus	SNOMED	Condition
acute_respiratory_infections	4154698	Transient respiratory distress with sepsis	SNOMED	Condition
acute_respiratory_infections	4216201	Acute suppuration of nasal sinus	SNOMED	Condition
acute_respiratory_infections	139850	Acute frontal sinusitis	SNOMED	Condition
acute_respiratory_infections	4110362	Recurrent acute tonsillitis	SNOMED	Condition
acute_respiratory_infections	4112524	Acute exudative bronchiolitis	SNOMED	Condition
acute_respiratory_infections	4052543	Acute viral bronchitis	SNOMED	Condition
acute_respiratory_infections	4028389	Infectious disease of lung	SNOMED	Condition
acute_respiratory_infections	46270121	Pneumonia caused by Influenza A virus subtype H1N1	SNOMED	Condition
acute_respiratory_infections	40481087	Viral sinusitis	SNOMED	Condition
acute_respiratory_infections	4173027	Acute laryngitis and/or tracheitis	SNOMED	Condition
acute_respiratory_infections	4120324	Acute lingual tonsillitis	SNOMED	Condition
acute_respiratory_infections	4304374	Influenza caused by Influenza C virus	SNOMED	Condition
acute_respiratory_infections	4110358	Acute gangrenous pharyngitis	SNOMED	Condition
acute_respiratory_infections	4048489	Recurrent acute sinusitis	SNOMED	Condition
acute_respiratory_infections	4124677	Infectious disorder of bronchus	SNOMED	Condition
acute_respiratory_infections	4105773	Acute epiglottitis	SNOMED	Condition
acute_respiratory_infections	4341520	Acute interstitial pneumonia	SNOMED	Condition
acute_respiratory_infections	4080680	Influenza caused by Influenza B virus	SNOMED	Condition
acute_respiratory_infections	4105409	Acute abscess of frontal sinus	SNOMED	Condition
acute_respiratory_infections	4273095	Acute tracheitis without obstruction	SNOMED	Condition
acute_respiratory_infections	433513	Acute epiglottitis with obstruction	SNOMED	Condition
acute_respiratory_infections	4121450	Infectious disorder of trachea	SNOMED	Condition
acute_respiratory_infections	37394479	Influenza with pneumonia due to seasonal influenza virus	SNOMED	Condition
acute_respiratory_infections	4014329	Suppurative tonsillitis	SNOMED	Condition
acute_respiratory_infections	4035987	Viral pharyngitis	SNOMED	Condition
acute_respiratory_infections	443449	Acute laryngitis with obstruction	SNOMED	Condition
acute_respiratory_infections	437903	Acute tracheitis	SNOMED	Condition
acute_respiratory_infections	4198127	Viral pleurisy	SNOMED	Condition

Phenotype	Concept id	Concept name	Vocabulary	Domain
acute_respiratory_infections	31601	Acute laryngotracheitis with obstruction	SNOMED	Condition
acute_respiratory_infections	42536748	Infection causing tracheitis in neonate	SNOMED	Condition
acute_respiratory_infections	4296469	Acute empyema of maxillary sinus	SNOMED	Condition
acute_respiratory_infections	36676221	Influenza caused by Influenza A virus subtype H3N2	SNOMED	Condition
acute_respiratory_infections	4245453	Necrotic rhinitis	SNOMED	Condition
acute_respiratory_infections	4112348	Acute edematous laryngitis	SNOMED	Condition
acute_respiratory_infections	4112350	Acute catarrhal laryngitis	SNOMED	Condition
acute_respiratory_infections	46269741	Bronchiolitis caused by influenza virus	SNOMED	Condition
acute_respiratory_infections	4051239	Acute empyema of frontal sinus	SNOMED	Condition
acute_respiratory_infections	320651	Severe acute respiratory syndrome	SNOMED	Condition
acute_respiratory_infections	40483537	Influenza caused by Influenza A virus	SNOMED	Condition
acute_respiratory_infections	4154776	Whooping cough-like syndrome	SNOMED	Condition
acute_respiratory_infections	4198126	Infective pleurisy	SNOMED	Condition
acute_respiratory_infections	4240728	Suppurative pharyngitis	SNOMED	Condition
acute_respiratory_infections	260134	Croup	SNOMED	Condition
acute_respiratory_infections	260427	Common cold	SNOMED	Condition
acute_respiratory_infections	255566	Acute tracheitis with obstruction	SNOMED	Condition
acute_respiratory_infections	4112342	Acute ulcerative pharyngitis	SNOMED	Condition
acute_respiratory_infections	4198240	Viral tonsillitis	SNOMED	Condition
acute_respiratory_infections	4243199	Acute bronchitis with obstruction	SNOMED	Condition
acute_respiratory_infections	4267869	Acute abscess of ethmoidal sinus	SNOMED	Condition
acute_respiratory_infections	31597	Acute laryngotracheitis	SNOMED	Condition
acute_respiratory_infections	256723	Pneumonia and influenza	SNOMED	Condition
acute_respiratory_infections	4248811	Healthcare associated severe acute respiratory syndrome	SNOMED	Condition
acute_respiratory_infections	763012	Pneumonia due to Influenza A virus subtype H1N1	SNOMED	Condition
acute_respiratory_infections	765607	Influenza due to Influenza A virus with upper respiratory signs	SNOMED	Condition
acute_respiratory_infections	23798	Acute laryngopharyngitis	SNOMED	Condition
acute_respiratory_infections	4240333	Acute empyema of nasal sinus	SNOMED	Condition
acute_respiratory_infections	4215773	Acute bronchiolitis with obstruction	SNOMED	Condition
acute_respiratory_infections	37117932	Acute sinusitis caused by virus	SNOMED	Condition
acute_respiratory_infections	4149333	Acute empyema of ethmoidal sinus	SNOMED	Condition
acute_respiratory_infections	4295288	Fibrinopurulent pleurisy	SNOMED	Condition
acute_respiratory_infections	4112349	Acute ulcerative laryngitis	SNOMED	Condition
acute_respiratory_infections	4112355	Acute fibrinous bronchitis	SNOMED	Condition

Phenotype	Concept id	Concept name	Vocabulary	Domain
acute_respiratory_infections	4051498	Acute simple laryngitis	SNOMED	Condition
acute_respiratory_infections	46269726	Bronchopneumonia due to virus	SNOMED	Condition
acute_respiratory_infections	4200018	Acute viral laryngotracheitis	SNOMED	Condition
acute_respiratory_infections	4081225	Acute suppuration of maxillary sinus	SNOMED	Condition
acute_respiratory_infections	141323	Acute maxillary sinusitis	SNOMED	Condition
acute_respiratory_infections	4193914	Seropurulent pleurisy	SNOMED	Condition
acute_respiratory_infections	4197404	Acute bronchitis with bronchospasm	SNOMED	Condition
acute_respiratory_infections	4009160	Acute suppuration of sphenoidal sinus	SNOMED	Condition
acute_respiratory_infections	4248810	Healthcare associated influenza disease	SNOMED	Condition
acute_respiratory_infections	4143092	Hospital acquired pneumonia	SNOMED	Condition
acute_respiratory_infections	4309214	Purulent rhinitis	SNOMED	Condition
acute_respiratory_infections	4110506	Pneumonia caused by pleuropneumonia-like organism	SNOMED	Condition
acute_respiratory_infections	4112664	Influenza with laryngitis	SNOMED	Condition
acute_respiratory_infections	4110512	Influenza with pharyngitis	SNOMED	Condition
acute_respiratory_infections	4049241	Acute membranous laryngitis	SNOMED	Condition
acute_respiratory_infections	4048195	Pediatric acute epiglottitis and supraglottitis	SNOMED	Condition
acute_respiratory_infections	4009042	Acute abscess of nasal sinus	SNOMED	Condition
acute_respiratory_infections	260123	Acute sinusitis	SNOMED	Condition
acute_respiratory_infections	4067213	Acute suppuration of frontal sinus	SNOMED	Condition
acute_respiratory_infections	4186568	Influenzal bronchopneumonia	SNOMED	Condition
acute_respiratory_infections	4225318	Viral pneumonia with AIDS (acquired immunodeficiency syndrome)	SNOMED	Condition
acute_respiratory_infections	40482414	Acute infective adenoiditis	SNOMED	Condition
acute_respiratory_infections	42872723	Influenza caused by Influenza A virus subtype H7	SNOMED	Condition
acute_respiratory_infections	4193318	Infective pharyngitis	SNOMED	Condition
acute_respiratory_infections	4266367	Influenza	SNOMED	Condition
acute_respiratory_infections	45768913	Influenza caused by Influenza A virus subtype H7N9	SNOMED	Condition
acute_respiratory_infections	36676238	Pneumonia caused by Influenza A virus	SNOMED	Condition
acute_respiratory_infections	37206139	Acute bronchitis co-occurrent with wheeze	SNOMED	Condition
acute_respiratory_infections	4050869	Atypical pneumonia	SNOMED	Condition
acute_respiratory_infections	24660	Acute tonsillitis	SNOMED	Condition
acute_respiratory_infections	40484544	Influenza caused by Influenza A virus subtype H1N1	SNOMED	Condition

Phenotype	Concept id	Concept name	Vocabulary	Domain
acute_respiratory_infections	42872724	Influenza caused by Influenza A virus subtype H9	SNOMED	Condition
acute_respiratory_infections	1340298	Exacerbation of croup	OMOP Extension	Condition
acute_respiratory_infections	4147376	Acute abscess of sphenoidal sinus	SNOMED	Condition
acute_respiratory_infections	4148204	Acute tracheobronchitis	SNOMED	Condition
acute_respiratory_infections	443747	Acute laryngotracheitis without obstruction	SNOMED	Condition
acute_respiratory_infections	36676233	Influenza caused by Influenza A virus subtype H5N1	SNOMED	Condition
acute_respiratory_infections	137900	Acute sphenoidal sinusitis	SNOMED	Condition
acute_respiratory_infections	4109893	Acute phlegmonous pharyngitis	SNOMED	Condition
acute_respiratory_infections	4109899	Acute suppurative laryngitis	SNOMED	Condition
acute_respiratory_infections	4048492	Acute subglottic laryngitis	SNOMED	Condition
acute_respiratory_infections	3178885	Secondary pneumonia	Nebraska Lexicon	Condition
acute_respiratory_infections	37394478	Influenza due to seasonal influenza virus	SNOMED	Condition
acute_respiratory_infections	4099298	Acute empyema of sphenoidal sinus	SNOMED	Condition
acute_respiratory_infections	4170141	Acute fibrinous laryngotracheobronchitis	SNOMED	Condition
acute_respiratory_infections	4208807	Acute infective bronchitis	SNOMED	Condition
acute_respiratory_infections	260125	Acute bronchiolitis	SNOMED	Condition
acute_respiratory_infections	4278083	Viral tracheitis	SNOMED	Condition
acute_respiratory_infections	30133	Acute laryngitis	SNOMED	Condition
acute_respiratory_infections	36714570	Influenza caused by pandemic influenza virus	SNOMED	Condition
acute_respiratory_infections	4220386	Suppurative laryngitis	SNOMED	Condition
acute_respiratory_infections	4112343	Acute viral pharyngitis	SNOMED	Condition
acute_respiratory_infections	4109897	Acute catarrhal tonsillitis	SNOMED	Condition
acute_respiratory_infections	4112922	Loculated empyema	SNOMED	Condition
acute_respiratory_infections	46270318	Pneumonia caused by Influenza virus	SNOMED	Condition
acute_respiratory_infections	761988	Infection of larynx	SNOMED	Condition
acute_respiratory_infections	4269219	Acute suppuration of ethmoidal sinus	SNOMED	Condition
acute_respiratory_infections	4279922	Septic bronchitis	SNOMED	Condition
acute_respiratory_infections	141056	Acute ethmoidal sinusitis	SNOMED	Condition
acute_respiratory_infections	37396171	Severe acute respiratory syndrome of upper respiratory tract	SNOMED	Condition
acute_respiratory_infections	4215807	Infective pneumonia acquired prenatally	SNOMED	Condition
acute_respiratory_infections	4093292	Viral pharyngoconjunctivitis	SNOMED	Condition

Phenotype	Concept id	Concept name	Vocabulary	Domain
acute_respiratory_infections	4112351	Acute phlegmonous laryngitis	SNOMED	Condition
acute_respiratory_infections	607085	Influenza caused by Influenza A virus subtype H2	SNOMED	Condition
acute_respiratory_infections	4329087	Acute rhinosinusitis	SNOMED	Condition
acute_respiratory_infections	40479600	Inflammation of larynx caused by virus	SNOMED	Condition
acute_respiratory_infections	4105601	Purulent bronchitis	SNOMED	Condition
acute_respiratory_infections	443410	Infective pneumonia	SNOMED	Condition
acute_respiratory_infections	4238808	Empyema of pleura	SNOMED	Condition
acute_respiratory_infections	4142174	Pulmonary nematodiasis	SNOMED	Condition
acute_respiratory_infections	261326	Viral pneumonia	SNOMED	Condition
acute_respiratory_infections	46273416	Acute adenoiditis	SNOMED	Condition
acute_respiratory_infections	4109896	Acute ulcerative tonsillitis	SNOMED	Condition
acute_respiratory_infections	4112009	Acute erythematous tonsillitis	SNOMED	Condition
acute_respiratory_infections	4110361	Acute viral tonsillitis	SNOMED	Condition
acute_respiratory_infections	260139	Acute bronchitis	SNOMED	Condition
acute_respiratory_infections	4058712	Viral bronchitis	SNOMED	Condition
acute_respiratory_infections	4208810	Acute infective tracheobronchitis	SNOMED	Condition
acute_respiratory_infections	4116487	Basal pneumonia	SNOMED	Condition
acute_respiratory_infections	4114030	Left upper zone pneumonia	SNOMED	Condition
acute_respiratory_infections	4135197	Hypostatic bronchopneumonia	SNOMED	Condition
acute_respiratory_infections	255848	Pneumonia	SNOMED	Condition
acute_respiratory_infections	4205578	Peribronchial pneumonia	SNOMED	Condition
acute_respiratory_infections	4273378	Interstitial pneumonia	SNOMED	Condition
acute_respiratory_infections	4228277	Pneumonia with AIDS (acquired immunodeficiency syndrome)	SNOMED	Condition
acute_respiratory_infections	4048052	Necrotizing bronchopneumonia	SNOMED	Condition
acute_respiratory_infections	40660059	All quality actions for the applicable measures in the community-acquired pneumonia (cap) measures group have been performed for this patient (Deprecated)	HCPCS	Observation
acute_respiratory_infections	40757921	Pneumonia in last 7 days [MDSv3]	LOINC	Observation
acute_respiratory_infections	1340380	Exacerbation of interstitial pneumonia	OMOP Extension	Condition
acute_respiratory_infections	4293463	Community acquired pneumonia	SNOMED	Condition
acute_respiratory_infections	4116488	Left lower zone pneumonia	SNOMED	Condition
acute_respiratory_infections	2617502	Pneumonia: patient documented to have received antibiotic within 4 hours of presentation (Deprecated)	HCPCS	Observation
acute_respiratory_infections	4195014	Lymphoid interstitial pneumonia	SNOMED	Condition

Phenotype	Concept id	Concept name	Vocabulary	Domain
acute_respiratory_infections	4102253	Right middle zone pneumonia	SNOMED	Condition
acute_respiratory_infections	43020558	Cavitary pneumonia	SNOMED	Condition
acute_respiratory_infections	4025165	Abscess of lung with pneumonia	SNOMED	Condition
acute_respiratory_infections	4248029	Granulomatous pneumonia	SNOMED	Condition
acute_respiratory_infections	4111119	Hemorrhagic bronchopneumonia	SNOMED	Condition
acute_respiratory_infections	4245006	Bilateral bronchopneumonia	SNOMED	Condition
acute_respiratory_infections	4138769	Bilateral basal pneumonia	SNOMED	Condition
acute_respiratory_infections	4153356	Postobstructive pneumonia	SNOMED	Condition
acute_respiratory_infections	38001039	Simple pneumonia & pleurisy w MCC	DRG	Observation
acute_respiratory_infections	4048518	Confluent bronchopneumonia with abscess formation	SNOMED	Condition
acute_respiratory_infections	256722	Bronchopneumonia	SNOMED	Condition
acute_respiratory_infections	4280213	Unresolved lobar pneumonia	SNOMED	Condition
acute_respiratory_infections	4133224	Lobar pneumonia	SNOMED	Condition
acute_respiratory_infections	4114031	Right upper zone pneumonia	SNOMED	Condition
acute_respiratory_infections	4245499	Pleurobronchopneumonia	SNOMED	Condition
acute_respiratory_infections	38001041	Simple pneumonia & pleurisy w/o CC/MCC	DRG	Observation
acute_respiratory_infections	2617503	Pneumonia: patient not documented to have received antibiotic within 4 hours of presentation (Deprecated)	HCPCS	Observation
acute_respiratory_infections	38001040	Simple pneumonia & pleurisy w CC	DRG	Observation
acute_respiratory_infections	4117114	Right lower zone pneumonia	SNOMED	Condition
acute_respiratory_infections	4175598	Catarrhal pneumonia	SNOMED	Condition
acute_respiratory_infections	4001167	Acute ulcerative gastroenteritis complicating pneumonia	SNOMED	Condition
acute_respiratory_infections	4046011	Focal pneumonia	SNOMED	Condition
acute_respiratory_infections	4048519	Confluent pneumonia	SNOMED	Condition
acute_respiratory_infections	4236311	Bilateral pneumonia	SNOMED	Condition
acute_respiratory_infections	4310964	Hypostatic pneumonia	SNOMED	Condition
acute_respiratory_infections	4311555	Desquamative interstitial pneumonia	SNOMED	Condition
acute_respiratory_infections	4044215	Nonspecific interstitial pneumonia	SNOMED	Condition
acute_respiratory_infections	4145369	Lingular pneumonia	SNOMED	Condition
acute_respiratory_infections	4212120	Unresolved pneumonia	SNOMED	Condition
acute_respiratory_infections	4148529	Primary atypical interstitial pneumonia	SNOMED	Condition
acute_respiratory_infections	1340436	Exacerbation of pneumonia	OMOP Extension	Condition
acute_respiratory_infections	4284985	Organized pneumonia	SNOMED	Condition
acute_respiratory_infections	4322625	Gangrenous pneumonia	SNOMED	Condition

Phenotype	Concept id	Concept name	Vocabulary	Domain
acute_respiratory_infections	4051335	Hemorrhagic pneumonia	SNOMED	Condition
acute_respiratory_infections	4276663	Terminal bronchopneumonia	SNOMED	Condition
acute_respiratory_infections	4110056	Chronic obstructive pulmonary disease with acute lower respiratory infection	SNOMED	Condition
acute_respiratory_infections	42537960	Influenza with CNS disorder	SNOMED	Condition
acute_respiratory_infections	4252885	Influenza with encephalopathy	SNOMED	Condition
influenza_outcome	4252885	Influenza with encephalopathy	SNOMED	Condition
influenza_outcome	4299935	Myocarditis caused by influenza virus	SNOMED	Condition
influenza_outcome	4183609	Influenzal acute upper respiratory infection	SNOMED	Condition
influenza_outcome	40483537	Influenza caused by Influenza A virus	SNOMED	Condition
influenza_outcome	4080680	Influenza caused by Influenza B virus	SNOMED	Condition
influenza_outcome	36714570	Influenza caused by pandemic influenza virus	SNOMED	Condition
influenza_outcome	3169660	Postinfluenza syndrome	Nebraska Lexicon	Condition
influenza_outcome	46269706	Otitis media caused by Influenza virus	SNOMED	Condition
influenza_outcome	46269742	Myocarditis caused by Influenza A virus	SNOMED	Condition
influenza_outcome	46269769	Otitis media caused by Influenza A virus	SNOMED	Condition
influenza_outcome	256723	Pneumonia and influenza	SNOMED	Condition
influenza_outcome	4146943	Encephalitis caused by Influenza virus	SNOMED	Condition
influenza_outcome	46269736	Gastroenteritis caused by Influenza virus	SNOMED	Condition
influenza_outcome	46269705	Otitis media caused by Influenza A virus subtype H1N1	SNOMED	Condition
influenza_outcome	3655653	Myelitis caused by Influenza A virus	SNOMED	Condition
influenza_outcome	46269737	Gastroenteritis caused by Influenza A virus	SNOMED	Condition
influenza_outcome	46269741	Bronchiolitis caused by influenza virus	SNOMED	Condition
influenza_outcome	46273463	Upper respiratory tract infection caused by Influenza virus	SNOMED	Condition
influenza_outcome	36676233	Influenza caused by Influenza A virus subtype H5N1	SNOMED	Condition
influenza_outcome	45770619	At risk of influenza related complication	SNOMED	Observation
influenza_outcome	46270121	Pneumonia caused by Influenza A virus subtype H1N1	SNOMED	Condition
influenza_outcome	46270318	Pneumonia caused by Influenza virus	SNOMED	Condition
influenza_outcome	46274061	Encephalopathy caused by Influenza A virus	SNOMED	Condition

Phenotype	Concept id	Concept name	Vocabulary	Domain
influenza_outcome	763012	Pneumonia due to Influenza A virus subtype H1N1	SNOMED	Condition
influenza_outcome	4304374	Influenza caused by Influenza C virus	SNOMED	Condition
influenza_outcome	37016926	Influenza caused by Influenza A virus subtype H5	SNOMED	Condition
influenza_outcome	46270123	Myocarditis caused by Influenza A virus subtype H1N1	SNOMED	Condition
influenza_outcome	42872724	Influenza caused by Influenza A virus subtype H9	SNOMED	Condition
influenza_outcome	37394476	Influenza due to zoonotic influenza virus	SNOMED	Condition
influenza_outcome	40484544	Influenza caused by Influenza A virus subtype H1N1	SNOMED	Condition
influenza_outcome	42537960	Influenza with CNS disorder	SNOMED	Condition
influenza_outcome	37394477	Influenza due to pandemic influenza virus	SNOMED	Condition
influenza_outcome	765607	Influenza due to Influenza A virus with upper respiratory signs	SNOMED	Condition
influenza_outcome	4266367	Influenza	SNOMED	Condition
influenza_outcome	320752	Influenza with non-respiratory manifestation	SNOMED	Condition
influenza_outcome	46270124	Encephalopathy caused by Influenza A virus subtype H1N1	SNOMED	Condition
influenza_outcome	4108226	Acute myocarditis - influenzal	SNOMED	Condition
influenza_outcome	4112824	Influenza with gastrointestinal tract involvement	SNOMED	Condition
influenza_outcome	36676238	Pneumonia caused by Influenza A virus	SNOMED	Condition
influenza_outcome	46270122	Upper respiratory tract infection caused by H1N1 influenza	SNOMED	Condition
influenza_outcome	4110512	Influenza with pharyngitis	SNOMED	Condition
influenza_outcome	37394478	Influenza due to seasonal influenza virus	SNOMED	Condition
influenza_outcome	42872723	Influenza caused by Influenza A virus subtype H7	SNOMED	Condition
influenza_outcome	607085	Influenza caused by Influenza A virus subtype H2	SNOMED	Condition
influenza_outcome	46274030	Gastroenteritis caused by Influenza A virus subtype H1N1	SNOMED	Condition
influenza_outcome	4112664	Influenza with laryngitis	SNOMED	Condition
influenza_outcome	4186568	Influenzal bronchopneumonia	SNOMED	Condition
influenza_outcome	46270491	Upper respiratory tract infection caused by Influenza A	SNOMED	Condition

Phenotype	Concept id	Concept name	Vocabulary	Domain
influenza_outcome	36676221	Influenza caused by Influenza A virus subtype H3N2	SNOMED	Condition
influenza_outcome	45768913	Influenza caused by Influenza A virus subtype H7N9	SNOMED	Condition
influenza_outcome	4042202	Post-influenza encephalitis	SNOMED	Condition
influenza_outcome	37394479	Influenza with pneumonia due to seasonal influenza virus	SNOMED	Condition
influenza_outcome	36714388	Influenza caused by seasonal influenza virus	SNOMED	Condition
influenza_outcome	4248810	Healthcare associated influenza disease	SNOMED	Condition
hospitalisation	38004283	General Acute Care Women Hospital	NUCC	Visit
hospitalisation	38004277	Long Term Care Hospital	NUCC	Visit
hospitalisation	38004274	Substance Use Disorder Rehabilitation Hospital Unit	NUCC	Visit
hospitalisation	38004288	Military Hospital	NUCC	Visit
hospitalisation	262	Emergency Room and Inpatient Visit	Visit	Visit
hospitalisation	9201	Inpatient Visit	Visit	Visit
hospitalisation	38004286	Rehabilitation Children Hospital	NUCC	Visit
hospitalisation	38004275	Chronic Disease Hospital Unit	NUCC	Visit
hospitalisation	581379	Inpatient Critical Care Facility	CMS Place of Service	Visit
hospitalisation	38004515	Hospital	Medicare Specialty	Visit
hospitalisation	38004282	General Rural Acute Care Hospital	NUCC	Visit
hospitalisation	38004276	Chronic Disease Children Hospital	NUCC	Visit
hospitalisation	38004280	General Acute Care Critical Access Hospital	NUCC	Visit
hospitalisation	38004287	Special Hospital	NUCC	Visit
hospitalisation	8971	Inpatient Psychiatric Facility	CMS Place of Service	Visit
hospitalisation	32760	Isolation in inpatient setting	Visit	Visit
hospitalisation	32254	Hospital-Swing Beds	UB04 Typ bill	Visit
hospitalisation	32037	Intensive Care	Visit	Visit
hospitalisation	581383	Inpatient Cardiac Care Facility	CMS Place of Service	Visit
hospitalisation	38004284	Psychiatric Hospital	NUCC	Visit
hospitalisation	38004279	General Acute Care Hospital	NUCC	Visit
hospitalisation	38004290	Military General Acute Care Hospital	NUCC	Visit
hospitalisation	581384	Inpatient Nursery	CMS Place of Service	Visit

Phenotype	Concept id	Concept name	Vocabulary	Domain
hospitalisation	8717	Inpatient Hospital	CMS Place of Service	Visit
hospitalisation	8913	Psychiatric Facility-Partial Hospitalization	CMS Place of Service	Visit
hospitalisation	38004270	Epilepsy Hospital Unit	NUCC	Visit
hospitalisation	38004291	Military General Acute Care Operational (Transportable) Hospital	NUCC	Visit
hospitalisation	38004285	Rehabilitation Hospital	NUCC	Visit
hospitalisation	38004281	General Acute Care Children Hospital	NUCC	Visit

ANNEX IV. Operational and reporting considerations

DATA MANAGEMENT

Data management

All data sources have previously mapped their data to the OMOP common data model. This enables the use of standardised analytics and using DARWIN EU tools across the network since the structure of the data and the terminology system is harmonised. The OMOP CDM was developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail on the wiki page of the CDM: https://ohdsi.github.io/CommonDataModel and in The Book of OHDSI: http://book.ohdsi.org.

The analytic code for this study was written in R and used standardized analytics wherever possible. Each data partner executed the study code against their data source containing patient-level data and then returned the results (csv files) which only contained aggregated data. The results from each of the contributing data sites were then combined in tables and figures for the study report.

Data storage and protection

For this study, participants from various EU member states processed personal data from individuals which was collected in national/regional electronic health record data sources. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All data sources used in this study were already used for pharmaco-epidemiological research and had a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses were run, which generated non-identifiable aggregate summary results.

The output files were stored in the DARWIN Remote Research Environment. These output files did not contain any data that allow identification of individuals included in the study. The RRE implemented further security measures to ensure a high level of stored data protection to comply with the local implementation of the General Data Protection Regulation (GDPR) (EU) 679/20161 in the various member states.

QUALITY CONTROL

General data source quality control

A number of open-source quality control mechanisms for the OMOP CDM have been developed (see Chapter 15 of The Book of OHDSI http://book.ohdsi.org/DataQuality.html). In particular, it was expected that data partners would have run the OHDSI Data Quality Dashboard tool (https://github.com/OHDSI/DataQualityDashboard). This tool provides numerous checks relating to the conformance, completeness, and plausibility of the mapped data. Conformance focuses on checks that describe the compliance of the representation of data against internal or external formatting, relational, or computational definitions, completeness in the sense of data quality is solely focused on quantifying missingness, or the absence of data, while plausibility seeks to determine the believability or truthfulness of data values. Each of these categories has one or more subcategories and are evaluated in two contexts: validation and verification. Validation relates to how well data align with external benchmarks with expectations derived from known true standards, while verification relates to how well data conform to local knowledge, metadata descriptions, and system assumptions.

Study specific quality control

When defining drug cohorts, non-systemic products were excluded from the list of included codes summarised on the ingredient level. A pharmacist reviewed the codes of the influenza vaccine.

When defining cohorts for indications, a systematic search of possible codes for inclusion was identified using *CodelistGenerator* R package (https://github.com/darwin-eu/CodelistGenerator). This software allowed the user to define a search strategy and using this then queried the vocabulary tables of the OMOP common data model so as to find potentially relevant codes. In addition, the *PhenotypeR* package (https://ohdsi.github.io/PhenotypeR) was run to assess the use of different codes across the data sources contributing to the study and identify any codes potentially omitted in error.

The study code was based on two R packages currently being developed to (1) estimate Incidence and Prevalence (*IncidencePrevalence*) and (2) characterise drug utilisation using the OMOP common data model (*CohortCharacteristics)*. These packages included numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing. The R package was made publicly available via GitHub.

ANNEX V: Supplemental figures

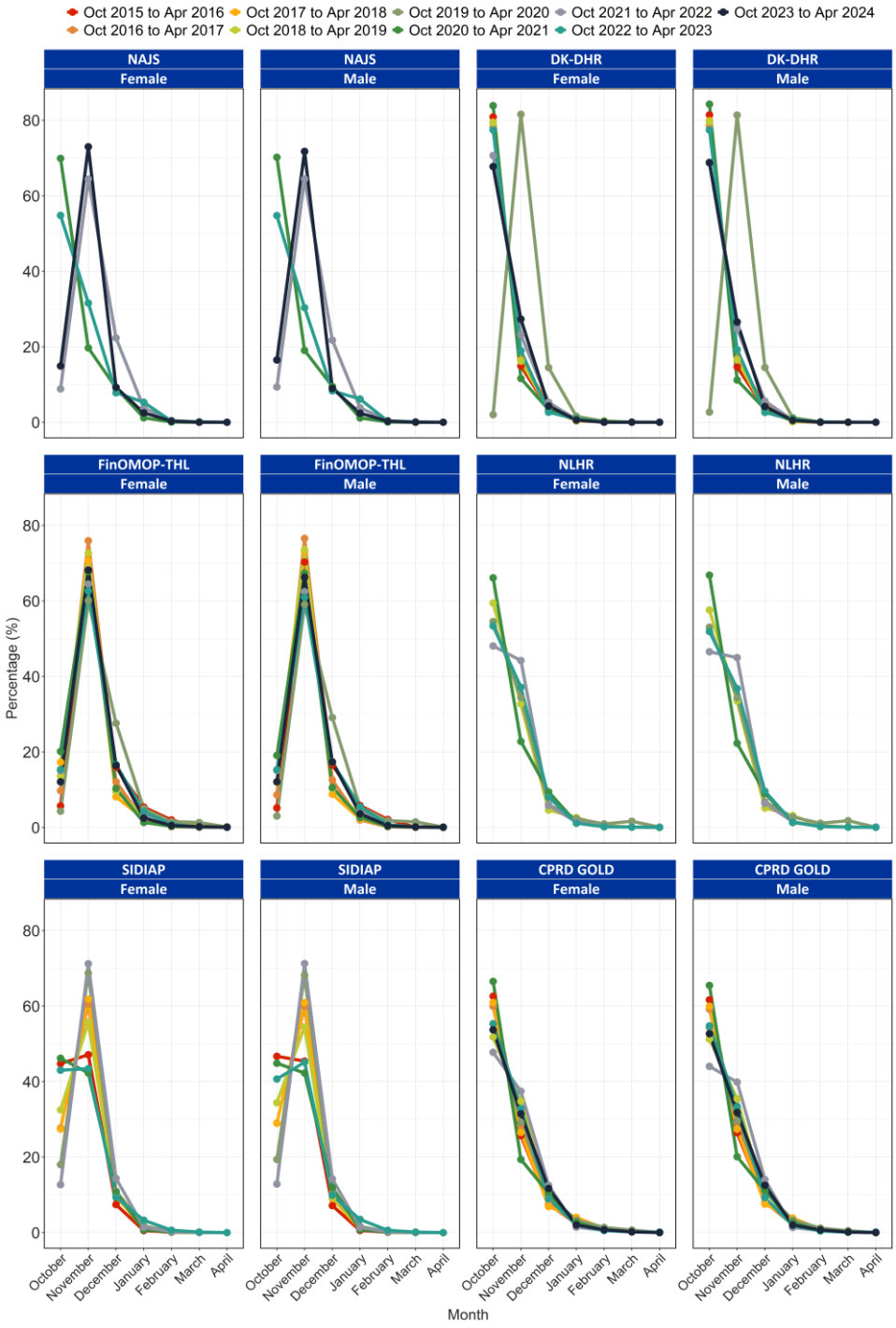

Figure S1. Monthly distribution of influenza vaccination uptake within each influenza season from 2015/16 to 2023/24, by sex and data source.

CPRD= Clinical Practice Research Datalink; DK-DHR= Danish Data Health Registries; FinOMOP-THL= Finnish Care Register for Health Care; NAJS= National Public Health Information System; NLHR= Norwegian Linked Health Registry data; SIDIAP= The Information System for Research in Primary Care

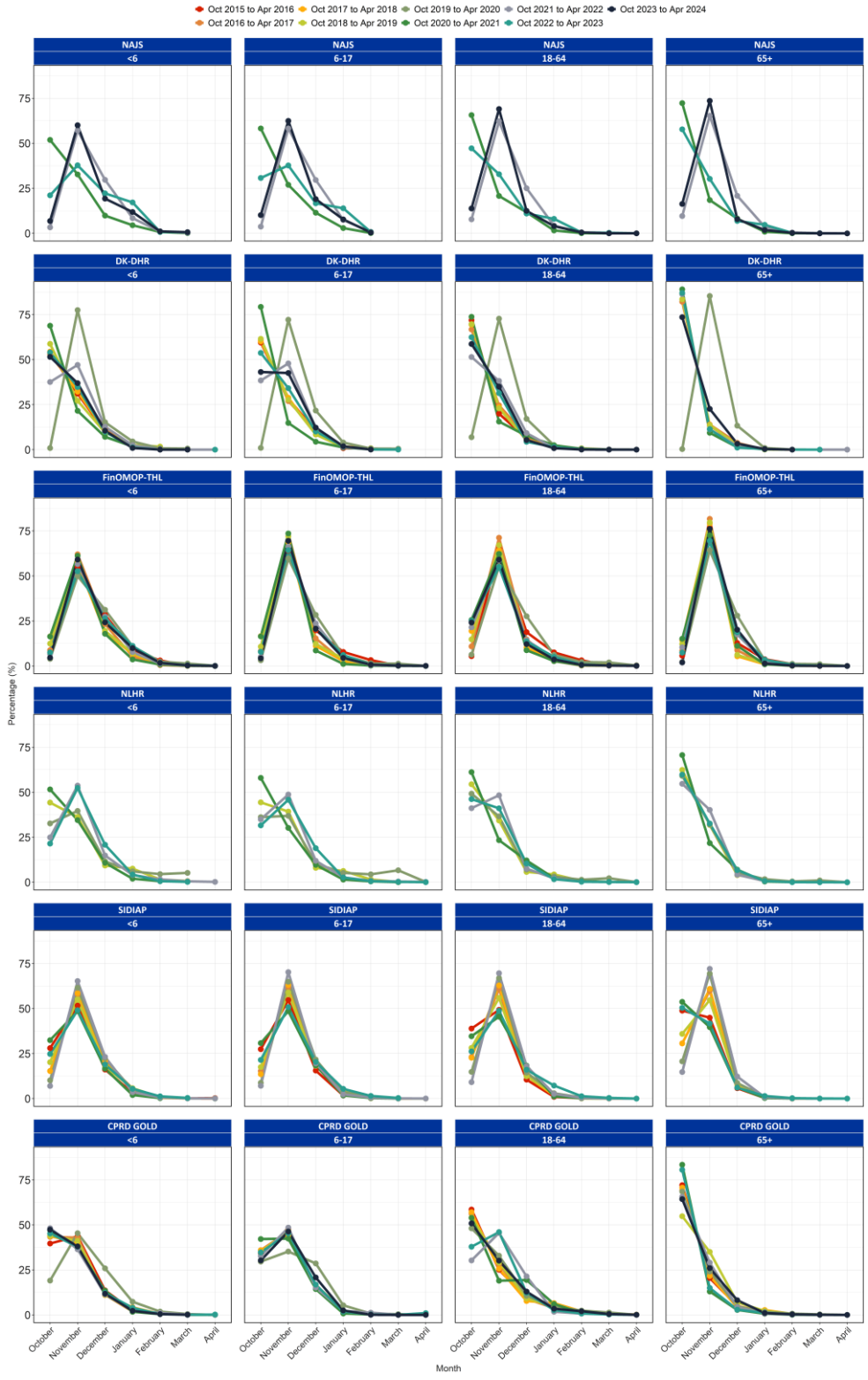

Figure S2. Monthly distribution of influenza vaccination uptake within each influenza season from 2015/16 to 2023/24, by age group and data source.

CPRD= Clinical Practice Research Datalink; DK-DHR= Danish Data Health Registries; FinOMOP-THL= Finnish Care Register for Health Care; NAJS= National Public Health Information System; NLHR= Norwegian Linked Health Registry data; SIDIAP= The Information System for Research in Primary Care

Figure S3. Distribution of influenza vaccine brands by influenza season (2015/16–2023/24), sex, and data source.

Inconsistent brand refers to individuals with more than one vaccination record on the same date that contains conflicting information on the vaccine brand.
CPRD= Clinical Practice Research Datalink; DK-DHR= Danish Data Health Registries; FinOMOP-THL= Finnish Care Register for Health Care; NAJS= National Public Health Information System; NLHR= Norwegian Linked Health Registry data; SIDIAP= The Information System for Research in Primary Care

Figure S4. Distribution of influenza vaccine brands by influenza season (2015/16–2023/24), age group, and data source.

Inconsistent brand refers to individuals with more than one vaccination record on the same date that contains conflicting information on the vaccine brand.

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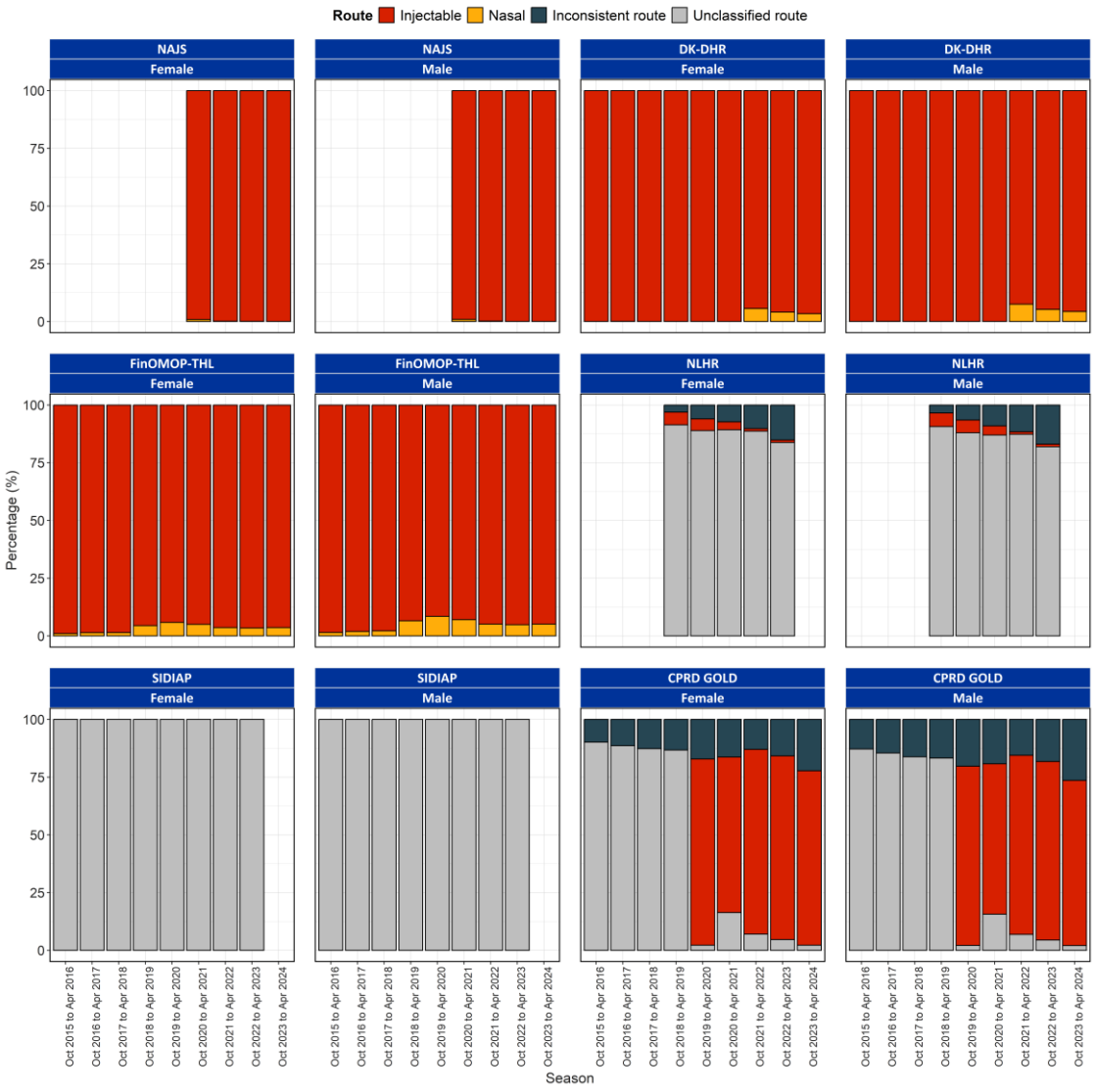

Figure S5. Distribution of influenza vaccine routes by influenza season (2015/16–2023/24), sex, and data source.

Inconsistent route refers to individuals with more than one vaccination record on the same date that contains conflicting information on the vaccine route.
CPRD= Clinical Practice Research Datalink; DK-DHR= Danish Data Health Registries; FinOMOP-THL= Finnish Care Register for Health Care; NAJS= National Public Health Information System; NLHR= Norwegian Linked Health Registry data; SIDIAP= The Information System for Research in Primary Care

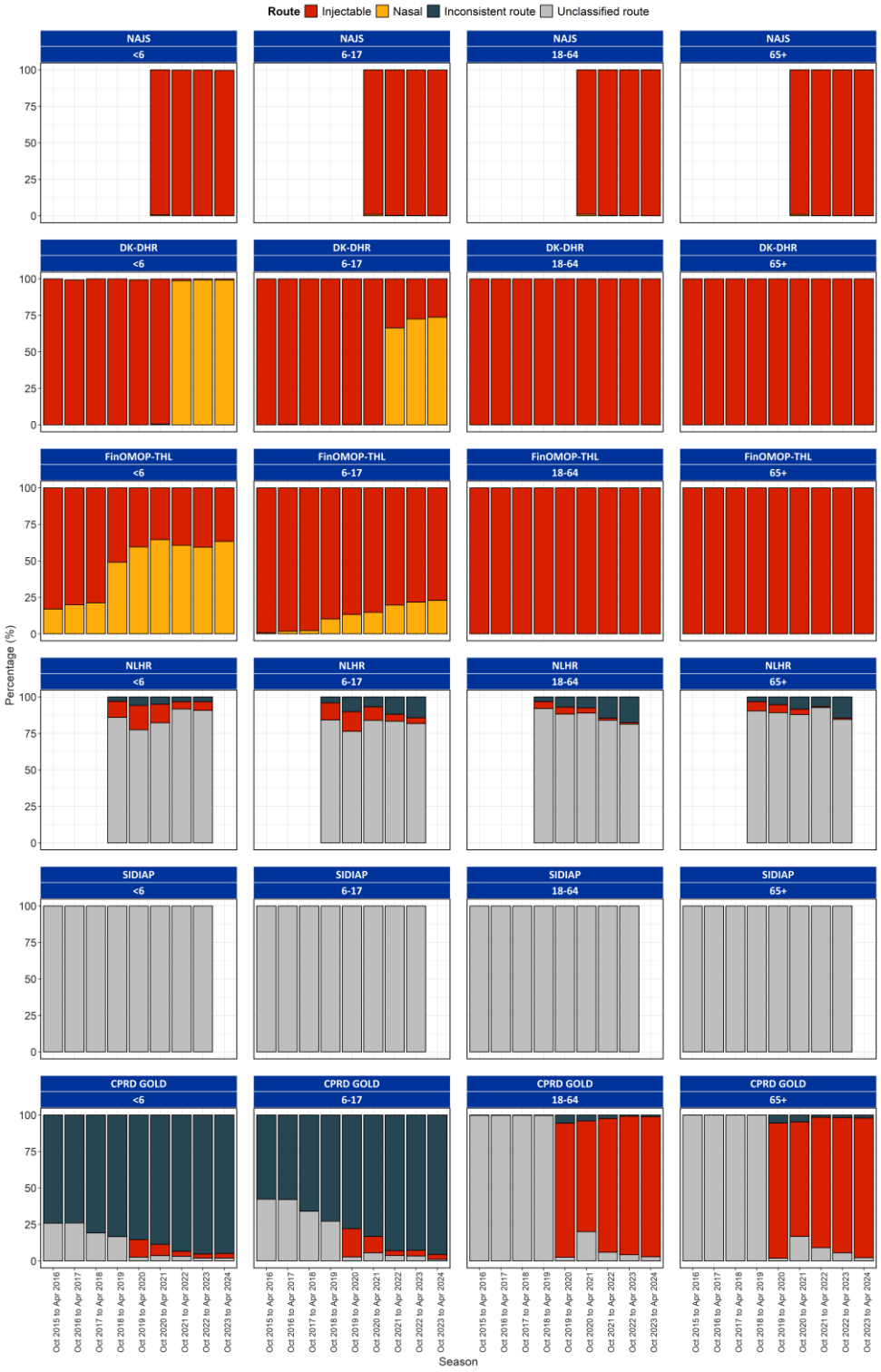

Figure S6. Distribution of influenza vaccine routes by influenza season (2015/16–2023/24), age group, and data source.

Inconsistent route refers to individuals with more than one vaccination record on the same date that contains conflicting information on the vaccine route.
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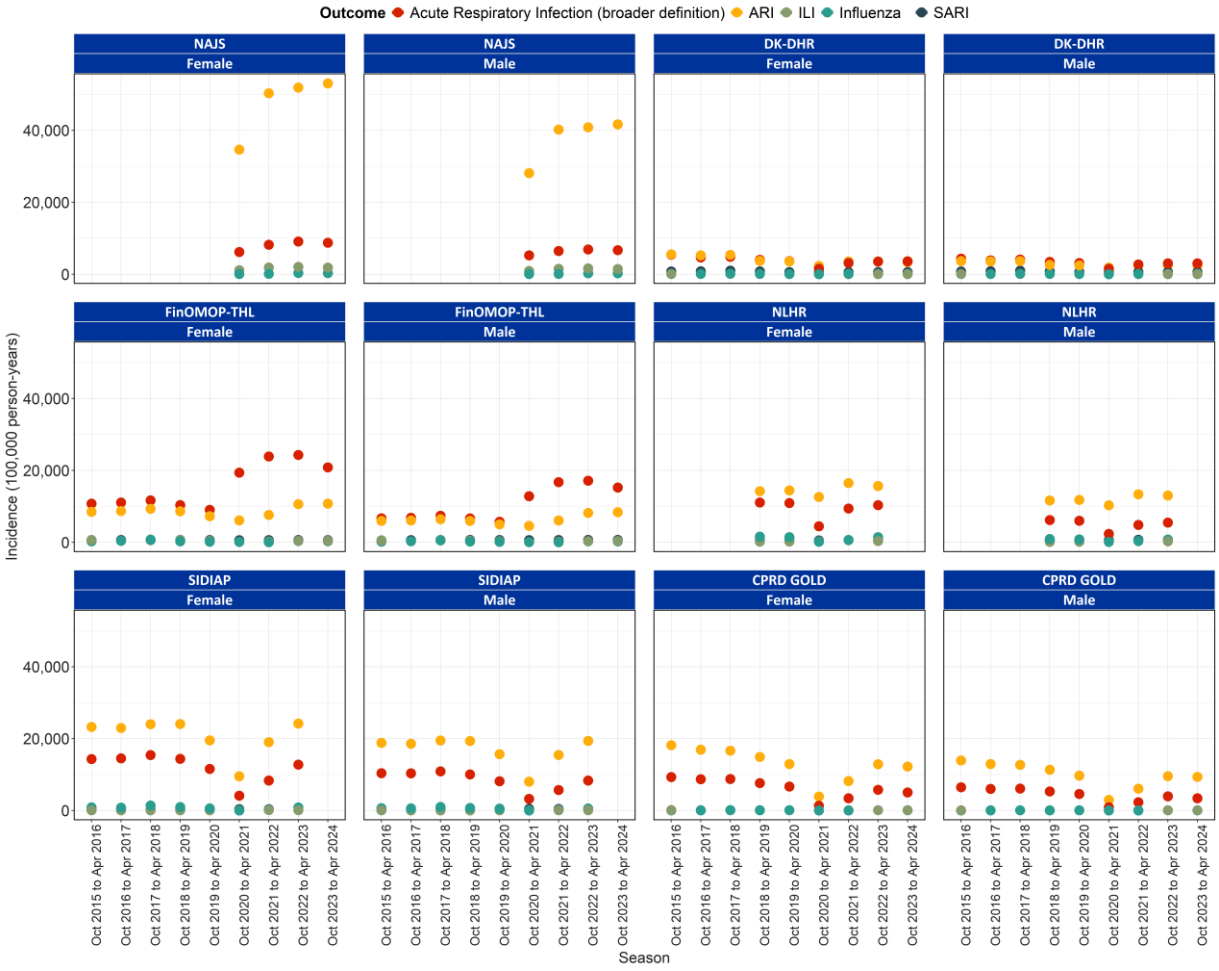

Figure S7. Incidence rates of primary outcomes (ILI, ARI, and SARI) and secondary outcomes (acute respiratory infection (broader definition), and influenza) in the general population from 2015/16 to 2023/24 influenza seasons by sex and data source.

Data for SARI are not shown for CPRD GOLD, as hospitalisation data were not available for this data source. In NAJS, SARI estimates for 2022/23 and 2023/24 are also not presented because hospitalisation data were unavailable after 2022. Estimates for SARI are also not shown for the 2022/23 season in SIDIAP, as hospitalisation data were unavailable for the first half of 2023.
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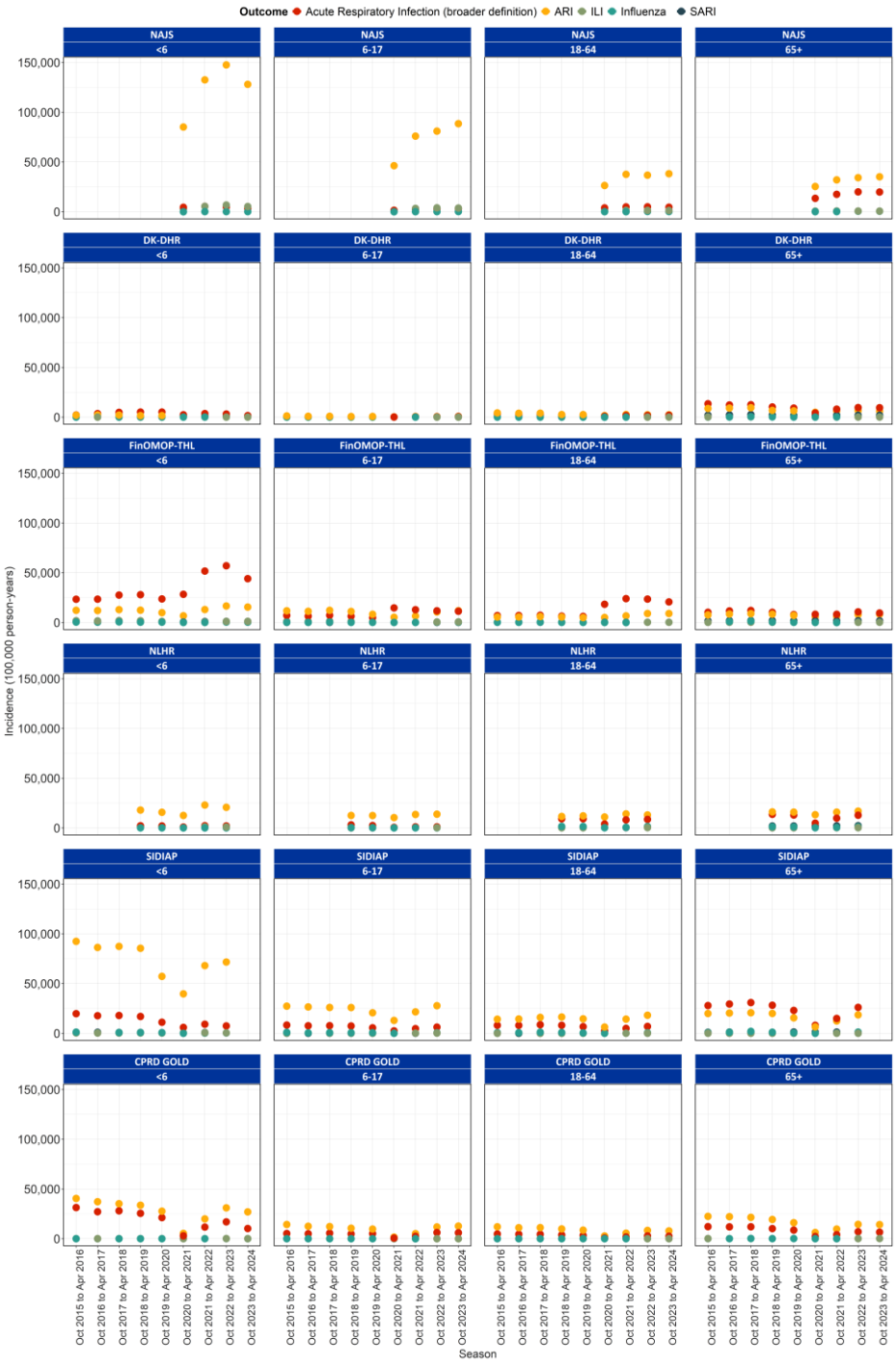

Figure S8. Incidence rates of primary outcomes (ILI, ARI, and SARI) and secondary outcomes (acute respiratory infection (broader definition), and influenza) in the general population from 2015/16 to 2023/24 influenza seasons by age group and data source.

Data for SARI are not shown for CPRD GOLD, as hospitalisation data were not available for this data source. In NAJS, SARI estimates for 2022/23 and 2023/24 are also not presented because hospitalisation data were unavailable after 2022. Estimates for SARI are also not shown for the 2022/23 season in SIDIAP, as hospitalisation data were unavailable for the first half of 2023.
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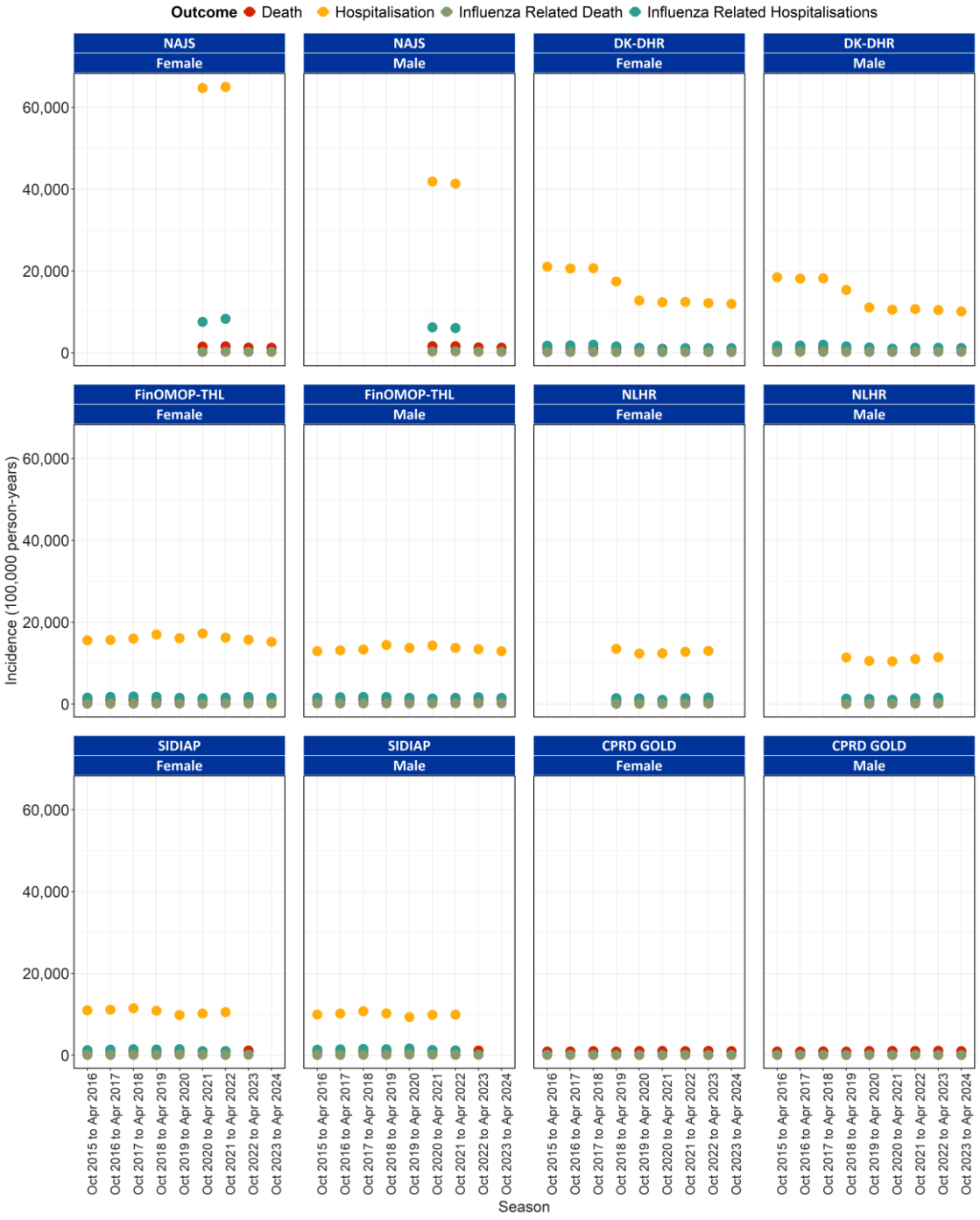

Figure S9. Incidence rates of all-cause hospitalisation, all-cause death, influenza-related hospitalisation, and influenza-related death in the general population from 2015/16 to 2023/24 influenza seasons by sex and data source.

Data for hospitalisation outcomes are not shown for CPRD GOLD, as hospitalisation data were not available for this data source. In NAJS, estimates for hospitalisation outcomes for 2022/23 and 2023/24 are also not presented because hospitalisation data were unavailable after 2022. Estimates for hospitalisation outcomes are also not shown for the 2022/23 season in SIDIAP, as hospitalisation data were unavailable for the first half of 2023.
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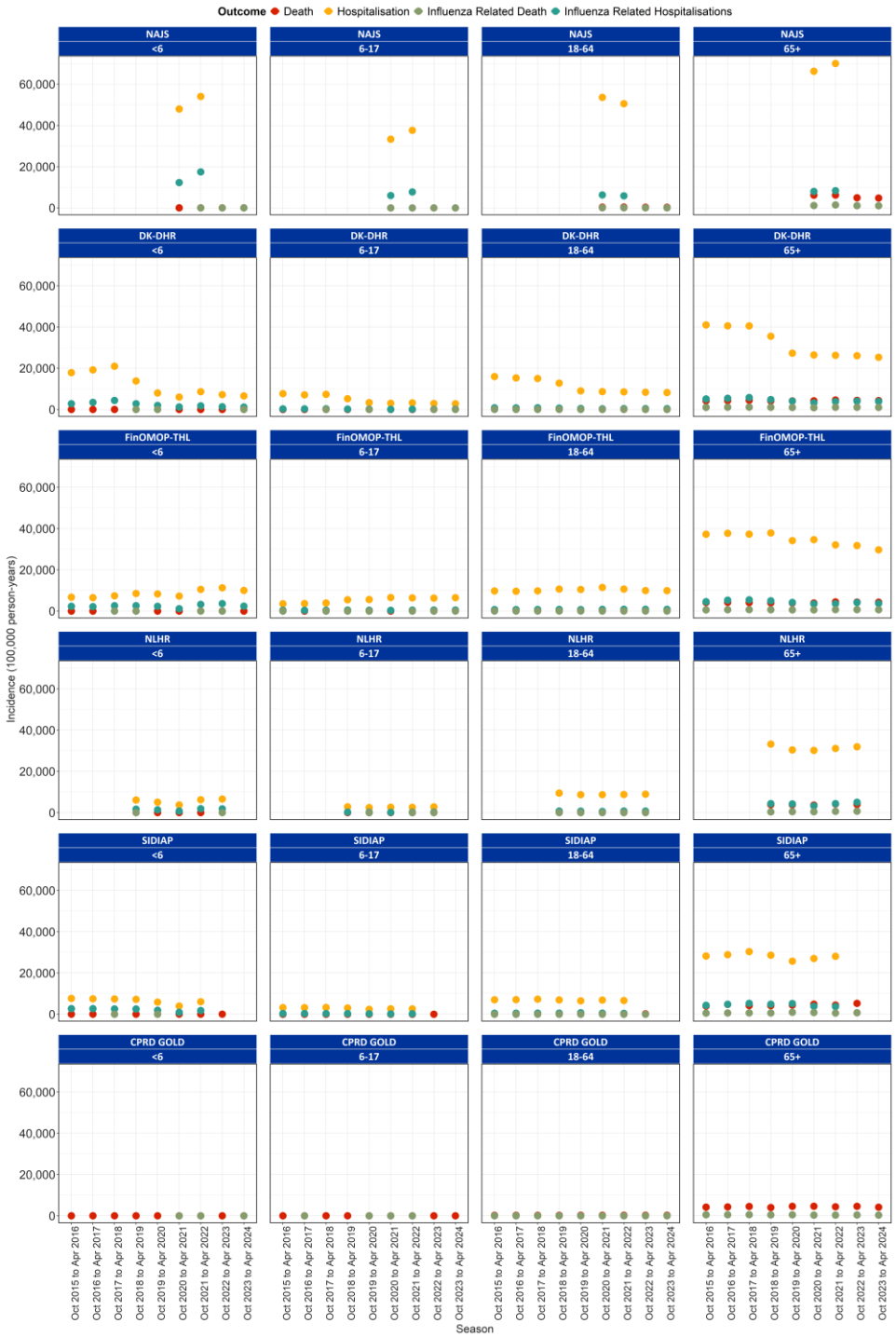

Figure S10 Incidence rates of all-cause hospitalisation, all-cause death, influenza-related hospitalisation, and influenza-related death in the general population from 2015/16 to 2023/24 influenza seasons by age group and data source.

Data for hospitalisation outcomes are not shown for CPRD GOLD, as hospitalisation data were not available for this data source. In NAJS, estimates for hospitalisation outcomes for 2022/23 and 2023/24 are also not presented because hospitalisation data were unavailable after 2022. Estimates for hospitalisation outcomes are also not shown for the 2022/23 season in SIDIAP, as hospitalisation data were unavailable for the first half of 2023.
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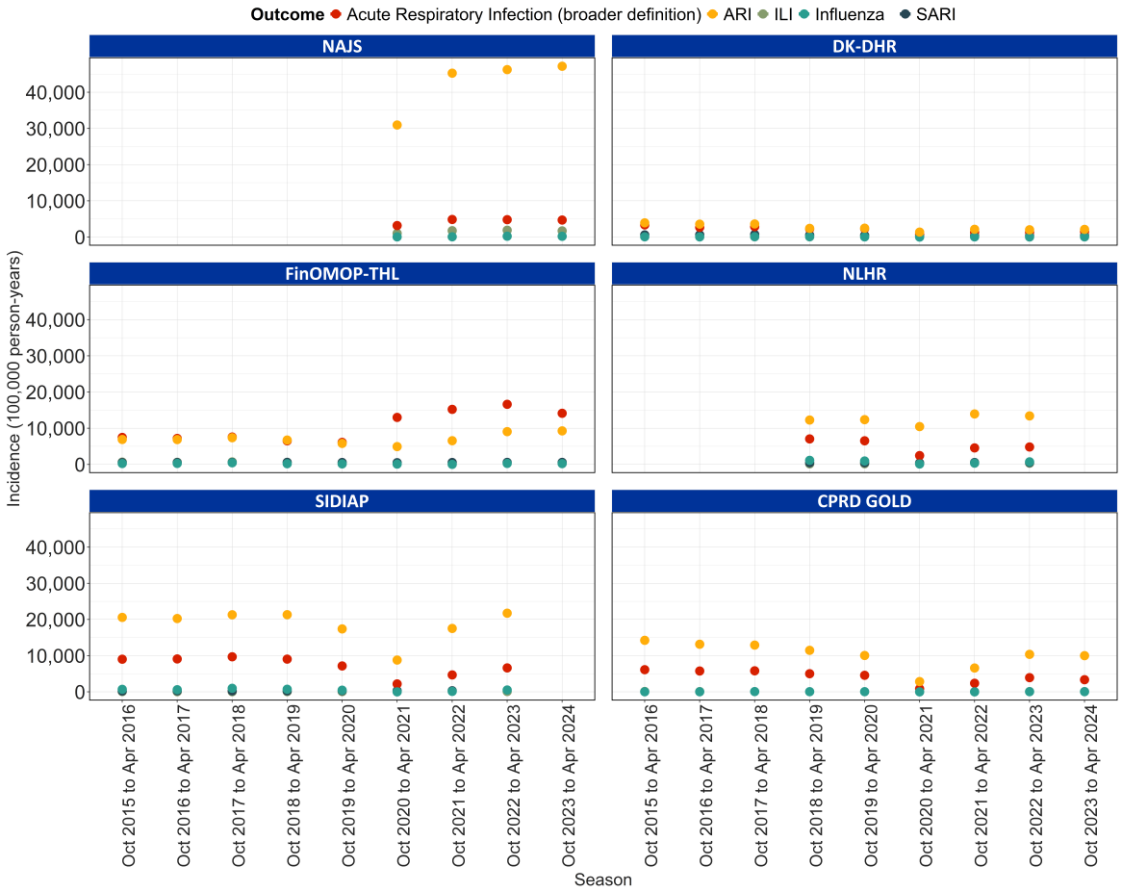

Figure S11. Incidence rates of primary outcomes (ILI, ARI, and SARI) and secondary outcomes (acute respiratory infection (broader definition), and influenza) in the influenza unvaccinated population from 2015/16 to 2023/24 influenza seasons by data source.

Data for SARI are not shown for CPRD GOLD, as hospitalisation data were not available for this data source. In NAJS, SARI estimates for 2022/23 and 2023/24 are also not presented because hospitalisation data were unavailable after 2022. Estimates for SARI are also not shown for the 2022/23 season in SIDIAP, as hospitalisation data were unavailable for the first half of 2023.
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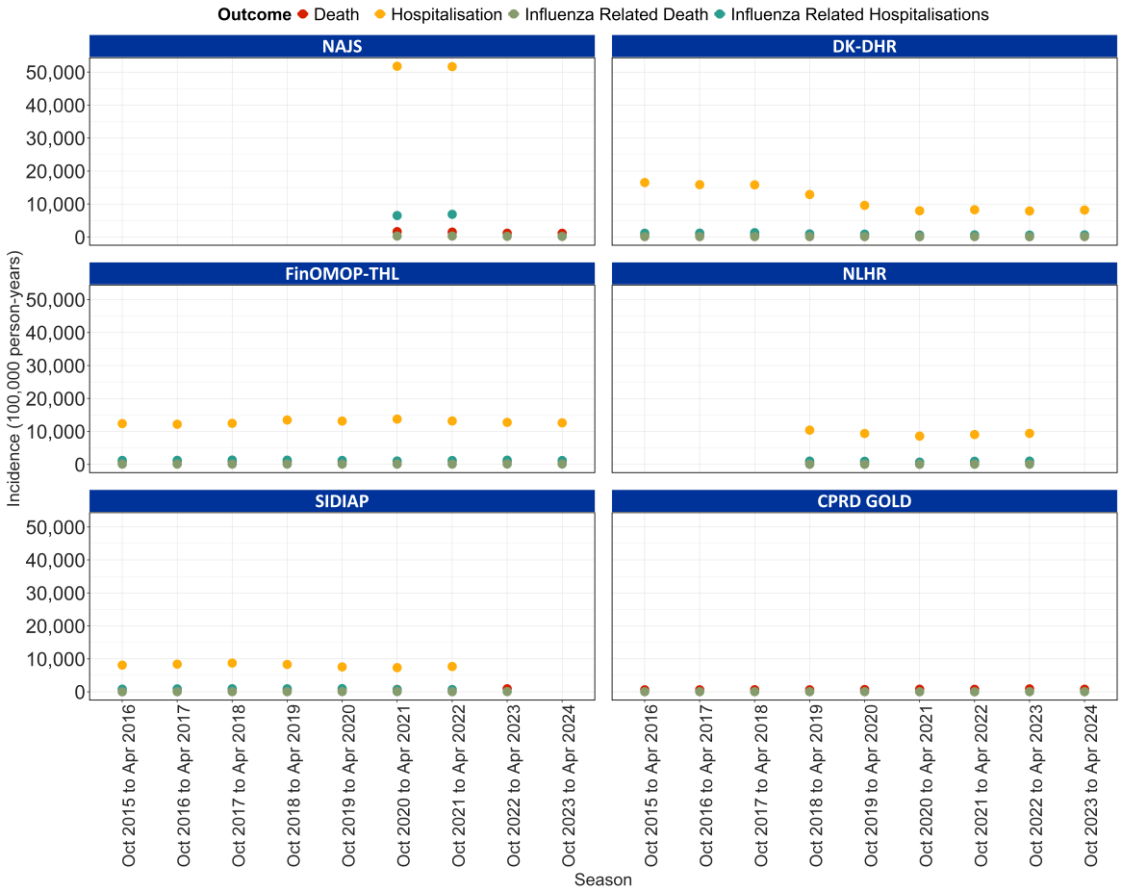

Figure S12. Incidence rates of all-cause hospitalisation, all-cause death, influenza-related hospitalisation, and influenza-related death in the influenza unvaccinated population from 2015/16 to 2023/24 influenza seasons by data source.

Data for hospitalisation outcomes are not shown for CPRD GOLD, as hospitalisation data were not available for this data source. In NAJS, estimates for hospitalisation outcomes for 2022/23 and 2023/24 are also not presented because hospitalisation data were unavailable after 2022. Estimates for hospitalisation outcomes are also not shown for the 2022/23 season in SIDIAP, as hospitalisation data were unavailable for the first half of 2023.
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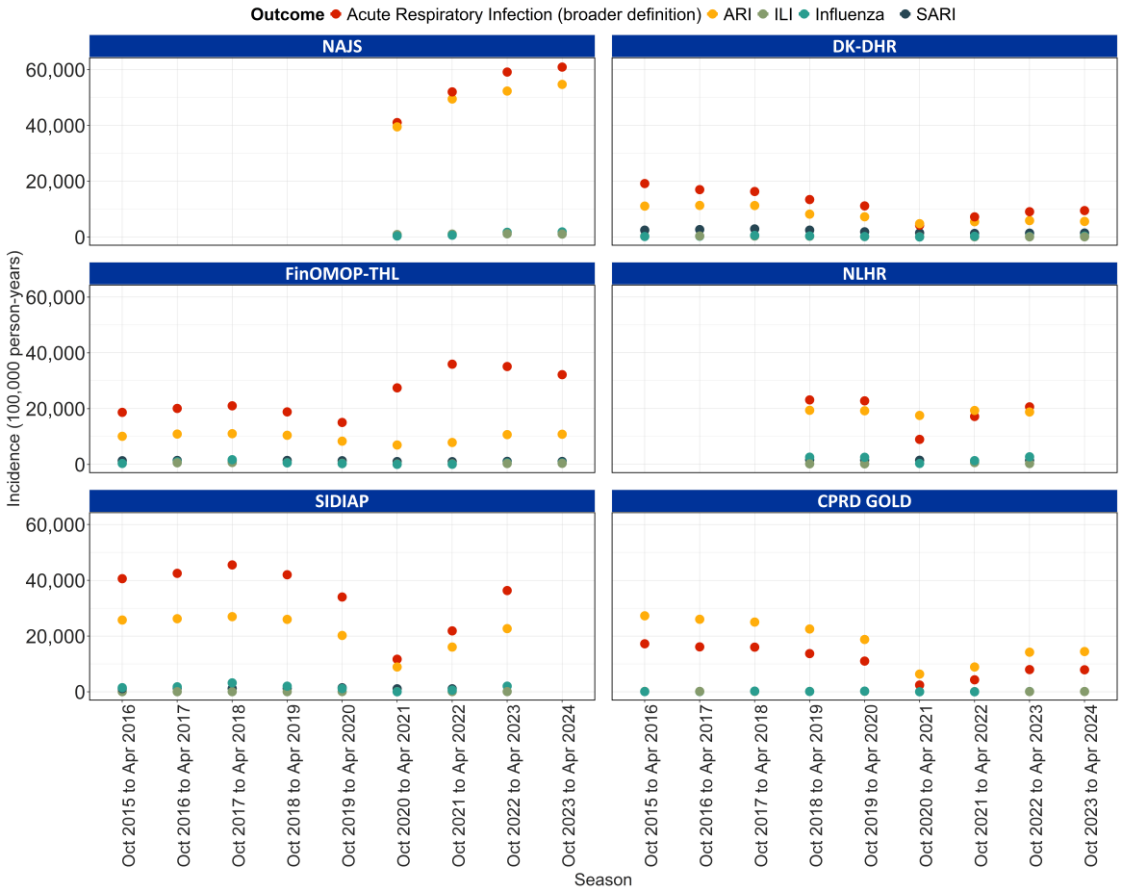

Figure S13. Incidence rates of primary outcomes (ILI, ARI, and SARI) and secondary outcomes (acute respiratory infection (broader definition), and influenza) in the influenza vaccinated population from 2015/16 to 2023/24 influenza seasons by data source.

Data for SARI are not shown for CPRD GOLD, as hospitalisation data were not available for this data source. In NAJS, SARI estimates for 2022/23 and 2023/24 are also not presented because hospitalisation data were unavailable after 2022. Estimates for SARI are also not shown for the 2022/23 season in SIDIAP, as hospitalisation data were unavailable for the first half of 2023.
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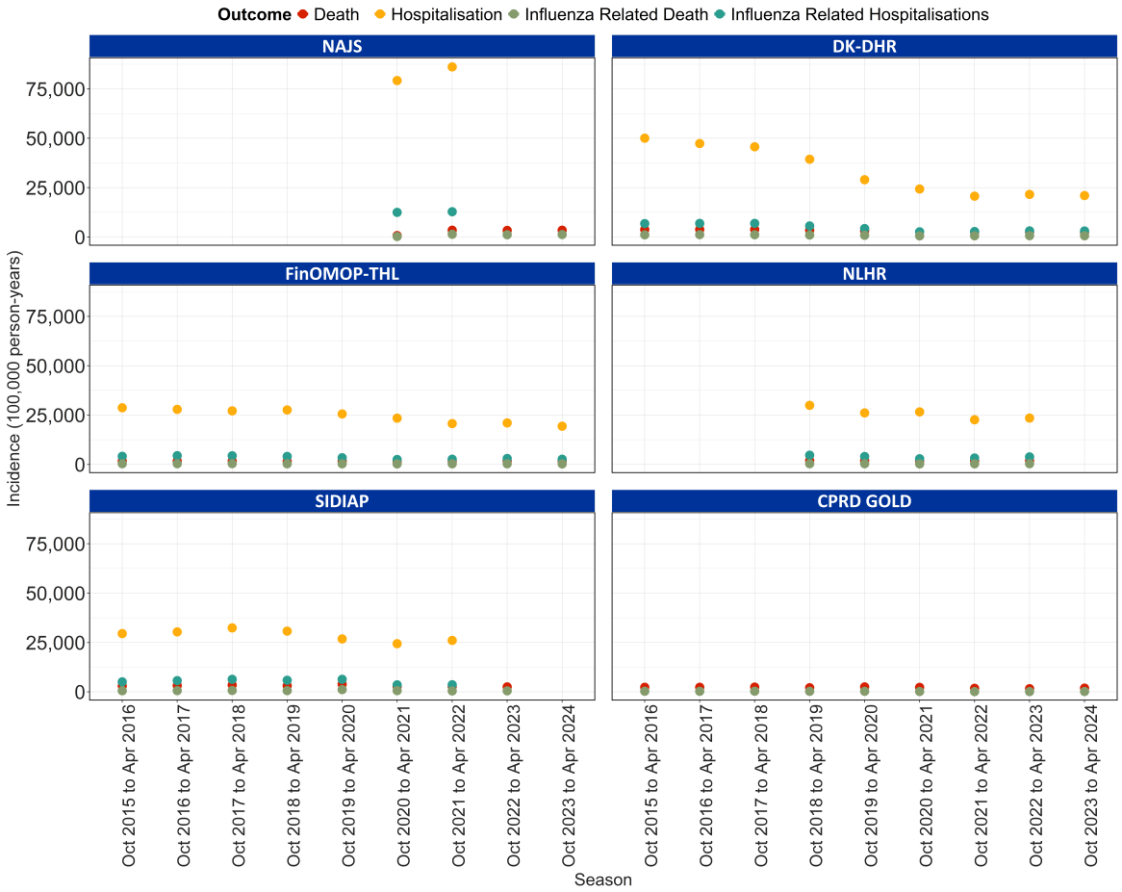

Figure S14. Incidence rates of all-cause hospitalisation, all-cause death, influenza-related hospitalisation, and influenza-related death in the influenza vaccinated population from 2015/16 to 2023/24 influenza seasons by data source.

Data for hospitalisation outcomes are not shown for CPRD GOLD, as hospitalisation data were not available for this data source. In NAJS, estimates for hospitalisation outcomes for 2022/23 and 2023/24 are also not presented because hospitalisation data were unavailable after 2022. Estimates for hospitalisation outcomes are also not shown for the 2022/23 season in SIDIAP, as hospitalisation data were unavailable for the first half of 2023.
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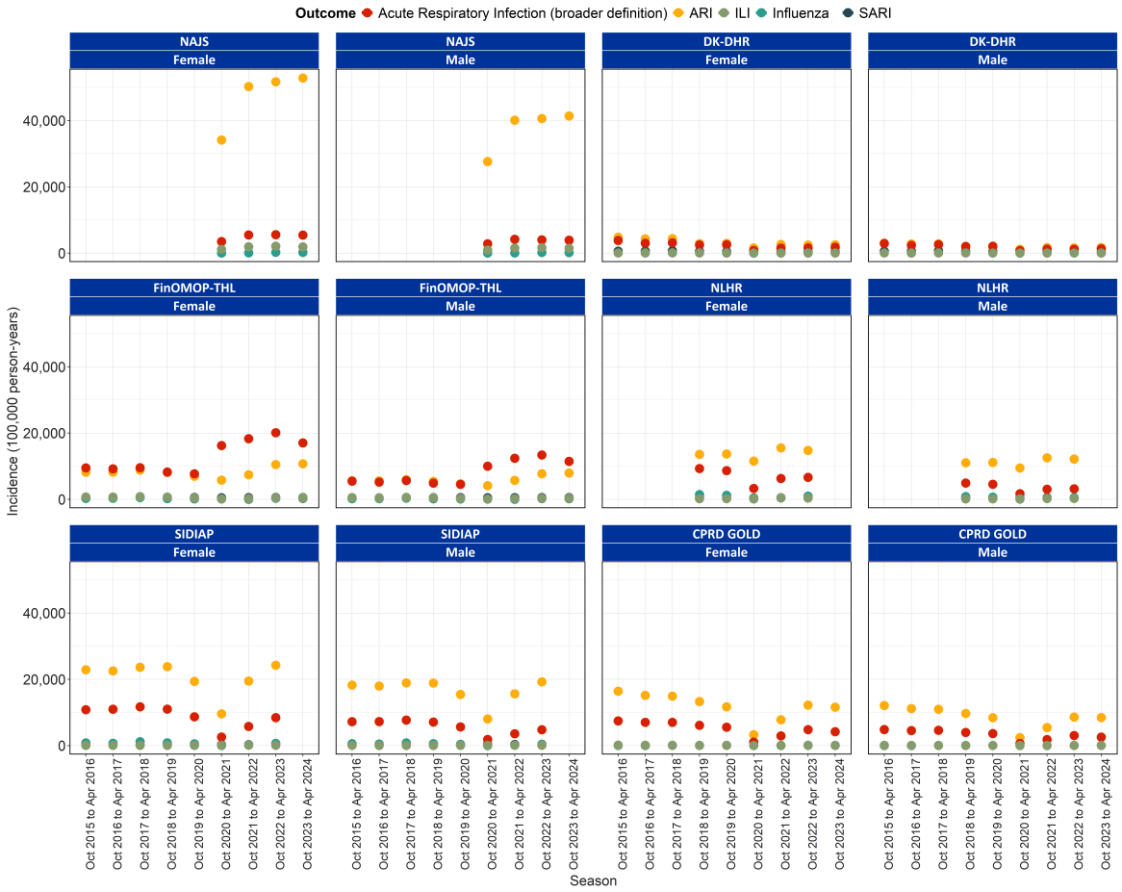

Figure S15. Incidence rates of primary outcomes (ILI, ARI, and SARI) and secondary outcomes (acute respiratory infection (broader definition), and influenza) in the influenza unvaccinated population from 2015/16 to 2023/24 influenza seasons by sex and data source.

Data for SARI are not shown for CPRD GOLD, as hospitalisation data were not available for this data source. In NAJS, SARI estimates for 2022/23 and 2023/24 are also not presented because hospitalisation data were unavailable after 2022. Estimates for SARI are also not shown for the 2022/23 season in SIDIAP, as hospitalisation data were unavailable for the first half of 2023.
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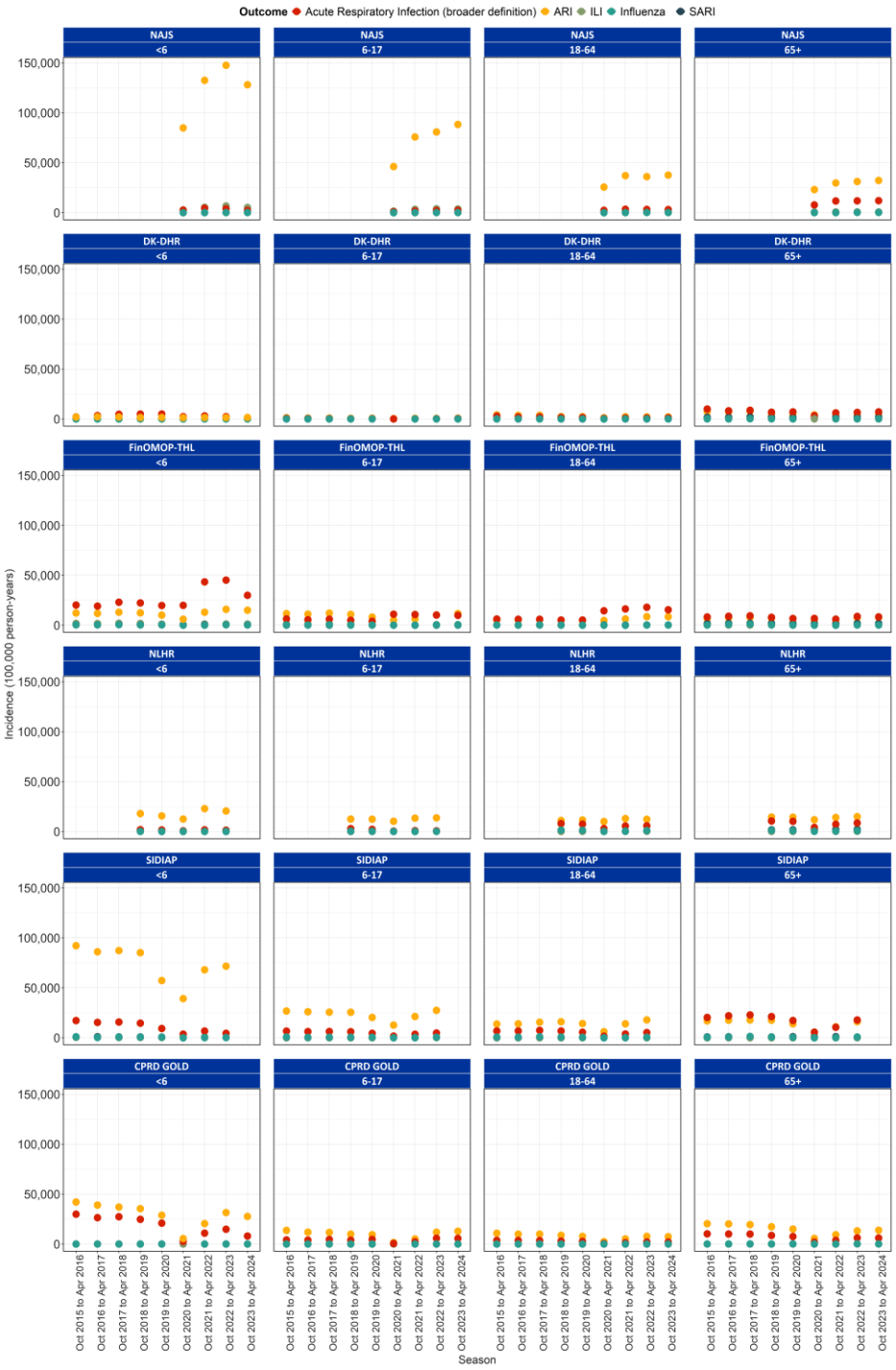

Figure S16. Incidence rates of primary outcomes (ILI, ARI, and SARI) and secondary outcomes (acute respiratory infection (broader definition), and influenza) in the influenza unvaccinated population from 2015/16 to 2023/24 influenza seasons by age group and data source.

Data for SARI are not shown for CPRD GOLD, as hospitalisation data were not available for this data source. In NAJS, SARI estimates for 2022/23 and 2023/24 are also not presented because hospitalisation data were unavailable after 2022. Estimates for SARI are also not shown for the 2022/23 season in SIDIAP, as hospitalisation data were unavailable for the first half of 2023.
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Figure S17. Incidence rates of all-cause hospitalisation, all-cause death, influenza-related hospitalisation, and influenza-related death in the influenza unvaccinated population from 2015/16 to 2023/24 influenza seasons by sex and data source.

Data for hospitalisation outcomes are not shown for CPRD GOLD, as hospitalisation data were not available for this data source. In NAJS, estimates for hospitalisation outcomes for 2022/23 and 2023/24 are also not presented because hospitalisation data were unavailable after 2022. Estimates for hospitalisation outcomes are also not shown for the 2022/23 season in SIDIAP, as hospitalisation data were unavailable for the first half of 2023.
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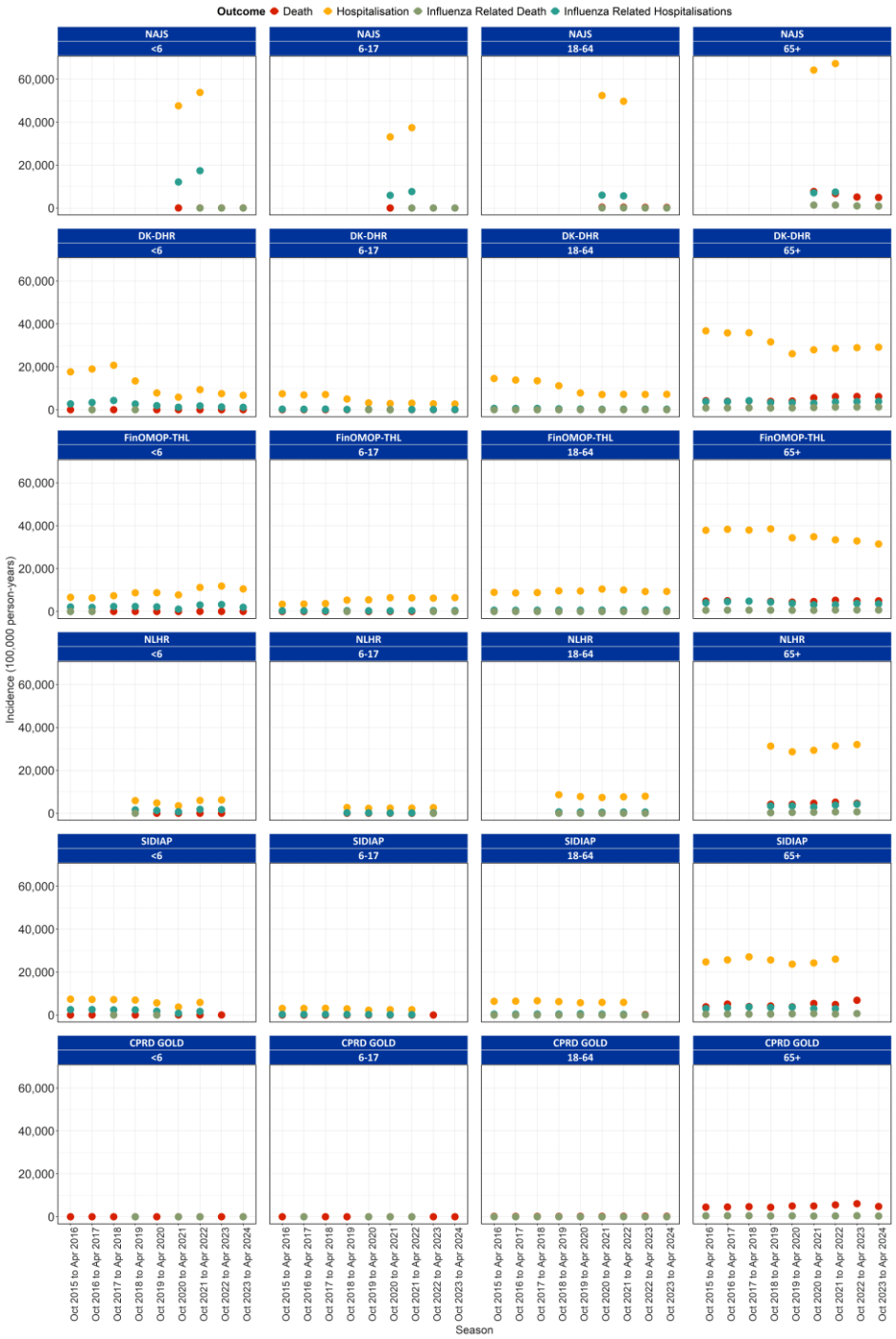

Figure S18. Incidence rates of all-cause hospitalisation, all-cause death, influenza-related hospitalisation, and influenza-related death in the influenza unvaccinated population from 2015/16 to 2023/24 influenza seasons by age group and data source.

Data for hospitalisation outcomes are not shown for CPRD GOLD, as hospitalisation data were not available for this data source. In NAJS, estimates for hospitalisation outcomes for 2022/23 and 2023/24 are also not presented because hospitalisation data were unavailable after 2022. Estimates for hospitalisation outcomes are also not shown for the 2022/23 season in SIDIAP, as hospitalisation data were unavailable for the first half of 2023.
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Figure S19. Incidence rates of primary outcomes (ILI, ARI, and SARI) and secondary outcomes (acute respiratory infection (broader definition), and influenza) in the influenza vaccinated population from 2015/16 to 2023/24 influenza seasons by sex and data source.

Data for SARI are not shown for CPRD GOLD, as hospitalisation data were not available for this data source. In NAJS, SARI estimates for 2022/23 and 2023/24 are also not presented because hospitalisation data were unavailable after 2022. Estimates for SARI are also not shown for the 2022/23 season in SIDIAP, as hospitalisation data were unavailable for the first half of 2023.
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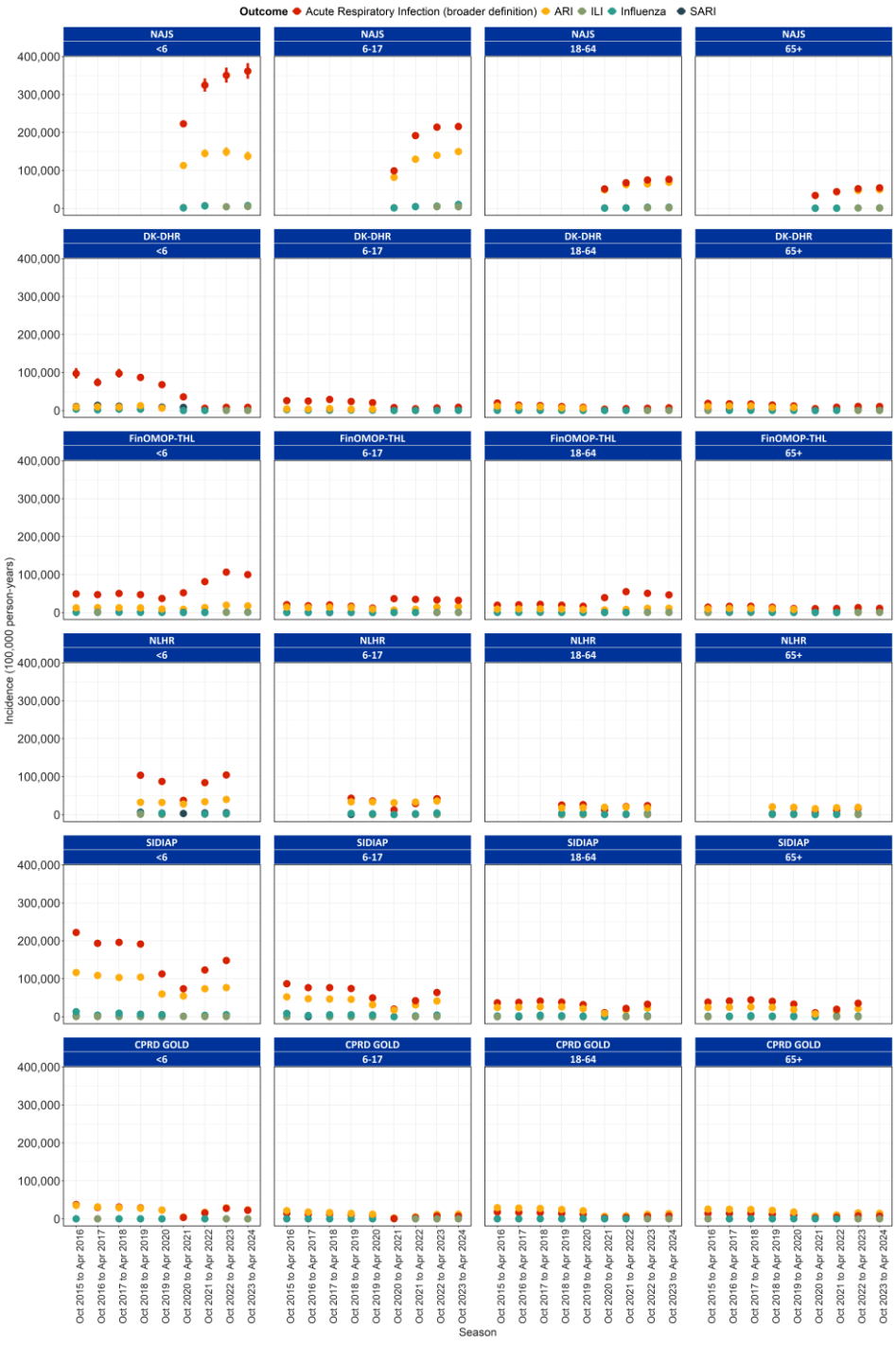

Figure S20. Incidence rates of primary outcomes (ILI, ARI, and SARI) and secondary outcomes (acute respiratory infection (broader definition), and influenza) in the influenza vaccinated population from 2015/16 to 2023/24 influenza seasons by age group and data source.

Data for SARI are not shown for CPRD GOLD, as hospitalisation data were not available for this data source. In NAJS, SARI estimates for 2022/23 and 2023/24 are also not presented because hospitalisation data were unavailable after 2022. Estimates for SARI are also not shown for the 2022/23 season in SIDIAP, as hospitalisation data were unavailable for the first half of 2023.
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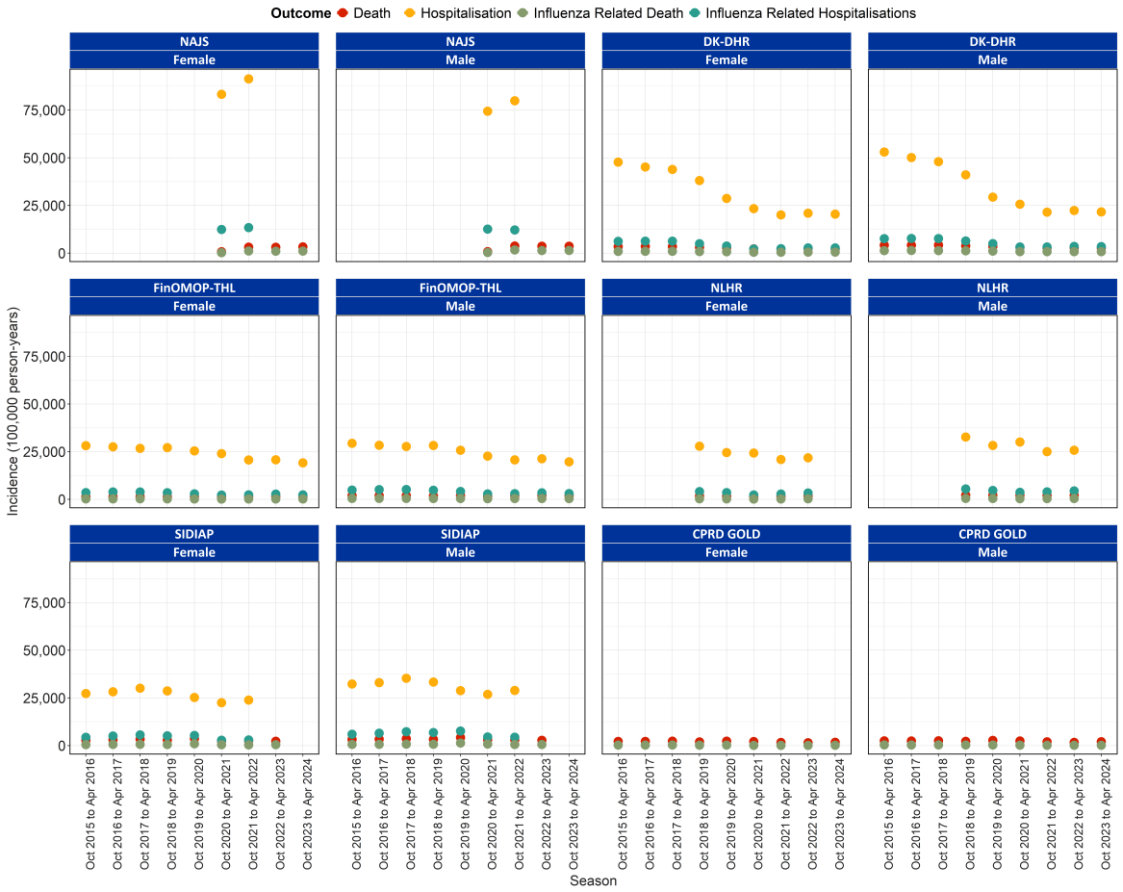

Figure S21. Incidence rates of all-cause hospitalisation, all-cause death, influenza-related hospitalisation, and influenza-related death in the influenza vaccinated population from 2015/16 to 2023/24 influenza seasons by sex and data source.

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Figure S22. Incidence rates of all-cause hospitalisation, all-cause death, influenza-related hospitalisation, and influenza-related death in the influenza vaccinated population from 2015/16 to 2023/24 influenza seasons by age group and data source.

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ANNEX V: Glossary

Additional definitions are available in the EMA Glossary of terms https://www.ema.europa.eu/en/about-us/glossaries.

Aggregated Data

Data collected and combined from multiple sources to generate summary information, typically anonymised.

Benefit-Risk Assessment

Evaluation of the positive therapeutic effects of a medicine compared to its risks (e.g., side effects).

Common Data Model (CDM)

A standardized data structure that enables data from multiple sources to be harmonized, making analysis consistent and reproducible. DARWIN EU® utilises the OMOP CDM maintained by the OHDSI community.

Complex Studies (C3)

Studies requiring the development or customisation of specific study designs, protocols, and Statistical Analysis Plans (SAPs), with extensive collection or extraction of data. Examples include etiological studies measuring the strength and determinants of an association between an exposure and the occurrence of a health outcome in a defined population considering sources of bias, potential confounding factors, and effect modifiers.

Coordination Centre (CC)

The central hub responsible for managing and overseeing the activities within DARWIN EU®. It is based at Erasmus University Medical Centre in Rotterdam, the Netherlands.

Data Access

The process of obtaining permission to use specific datasets for regulatory or scientific studies.

Data Quality Framework

A set of standards and procedures to ensure accuracy, completeness, timeliness, and consistency of data used in DARWIN EU®.

Data Source

A database or repository of structured health-related data, such as electronic health records (EHRs), insurance claims, or registries.

DARWIN EU®

The European Medicines Agency's (EMA) federated network of real-world data sources designed to generate evidence to support regulatory decision-making.

EMA (European Medicines Agency)

The regulatory body responsible for the evaluation and supervision of medicinal products in the EU, overseeing DARWIN EU®.

Evidence Generation

The process of analysing real-world data to produce scientific information that can inform healthcare or regulatory decisions.

Federated Network

A data infrastructure where data remain at their original location but can be analysed in a harmonised way across multiple partners using a common model and tools.

GDPR (General Data Protection Regulation)

The EU regulation governing the protection of personal data and privacy, crucial to how DARWIN EU® handles health data.

Health Technology Assessment (HTA)

A systematic evaluation of properties and impacts of health technology, often using DARWIN EU® data to support assessments.

Metadata

Descriptive information about a data source (e.g., its content, quality, and structure), essential for identifying relevant databases in DARWIN EU® studies.

Off-the-Shelf Studies (OTS)

Studies for which a standard protocol per study/analysis type and standardised analytics may be developed and applied or adapted, typically relating to a descriptive research question. This includes studies on disease epidemiology, for example, the estimation of the prevalence or incidence of health outcomes in defined time periods and population groups, or drug utilisation studies at the population or patient level.

OHDSI (Observational Health Data Sciences and Informatics)

An open-science collaborative community that develops tools and standards (including the OMOP CDM) to enable large-scale analytics of observational health data. OHDSI provides the technical and scientific foundation for DARWIN EU®'s analytical ecosystem.

Patient-Level Data

Data related to individuals, de-identified, used for longitudinal or detailed analyses.

OMOP (Observational Medical Outcomes Partnership)

A common data model (CDM) that standardises the structure and content of observational healthcare data, enabling systematic analysis across disparate datasets. DARWIN EU® uses the OMOP CDM to ensure interoperability and consistency in real-world evidence generation.

Real-World Data (RWD)

Data relating to individual health status or healthcare delivery that is collected from routine clinical practice rather than from randomised controlled trials.

Real-World Evidence (RWE)

Clinical evidence derived from the analysis of RWD, used to inform decisions by regulators, payers, or clinicians.

Regulatory Decision-Making

The process by which authorities like EMA assess data to authorise, monitor, or modify the use of medicines in the EU.

Routine Repeated Studies (RR)

Studies that are either Off-the-Shelf or Complex studies repeated on a regular basis, following the same protocol and study code, but with updated data and/or different data partners.

Study Protocol

A detailed plan describing how a specific real-world study will be conducted, including objectives, design, data sources, and analyses.

Very Complex Studies (C4)

Studies which cannot rely only on electronic health care databases, or which would require complex methodological work, for example, due to the occurrence of events that cannot be defined by existing diagnosis codes, including events that do not yet have a diagnosis code, where it may be necessary to combine a diagnosis code with other data such as results of laboratory investigations. These studies might require the collection of data prospectively, or the inclusion of new (not previously onboarded) data sources.