Study Report

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DARWIN EU® - Association between varicella vaccines (V), measles-mumps-rubella-varicella vaccines (MMRV), and encephalitis in paediatric recipients

26/05/2026

Version 5.0

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Public

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Study title	DARWIN EU® - Association between varicella vaccines (V), measles-mumps-rubella-varicella vaccines (MMRV), and encephalitis in paediatric recipients.
Study report version	V5.0
Date	26/05/2026
EUPAS number	EUPAS1000000813
Active substance	Varicella vaccines (V), measles-mumps-rubella-varicella vaccines (MMRV) for use in children and adolescents.
Medicinal product	NA
Research question and objectives	This study aimed to evaluate the association between varicella vaccines (V)/measles-mumps-rubella-varicella vaccines (MMRV) and the occurrence of encephalitis in paediatric populations. Specifically, the study had three objectives: 1. To describe V/MMRV vaccine uptake by vaccine type, dose, brand, age group, country, and to describe the characteristics of vaccine recipients. 2. To describe the background rates of encephalitis in the general paediatric population, and to estimate the crude incidence rates of encephalitis following varicella infection. 3. To assess the association between varicella infection and encephalitis among children and adolescents aged 9 months to 18 years by age group and country. 4. To assess the association between V/MMRV vaccines and encephalitis among children and adolescents aged 9 months to 18 years by age group and country.
Countries of study	Denmark, Finland, Norway, and Spain
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LIST OF ABBREVIATIONS

Acronyms/term	Description
AIDS	acquired immunodeficiency syndrome
AESIs	Adverse events of special interest
ATC	Anatomical Therapeutic Chemical
CDM	Common Data Model
CC	Coordination centre
CI	Confidence Interval
CPRD	Clinical Practice Research Datalink
DARWIN EU®	Data Analysis and Real-World Interrogation Network
DK-DHR	Danish Data Health Registries
DQD	Data Quality Dashboard
DRE	Digital Research Environment
EHR	Electronic Health Records
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EUPAS	EU Post-Authorisation Studies Register
FinOMOP-THL	Finnish Institute for Health and Welfare
GDPR	General Data Protection Regulation
GP	General Practitioner
ICD	International Classification of Diseases
IP	Inpatient
IPCI	Integrated Primary Care Information
IRB	Institutional Review Board
IR	Incidence rate
IRR	Incidence rate ratio
MMR	Measles-Mumps-Rubella (vaccines)
MMRV	Varicella-containing Measles-Mumps-Rubella (vaccines)
MSIS	Norwegian Surveillance System for Communicable Diseases
NLHR	Norwegian Linked Health Registry data
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
OP	Outpatient
PRAC	Pharmacovigilance Risk Assessment Committee
PY	Person years
RxNorm	Medical prescription normalized

Acronyms/term	Description
RWE	Real World Evidence
RWD	Real World Data
SCCS	Self-controlled case series
SCID	Severe combined immunodeficiency
SCRI	Self-controlled risk interval
SIDIAP	The Information System for Research on Primary Care
SIVAMIN	Spanish Ministry of Health Vaccination Information System
SmPC	Summary of Product Characteristics
SNOMED	Systematized Nomenclature of Medicine
SOC	System Organ Class
V	Varicella vaccines
VAERS	Vaccine Adverse Event Reporting System
VZV	Varicella-zoster virus
WHO	World Health Organisation

1. TITLE

DARWIN EU® - Association between varicella vaccines (V), measles-mumps-rubella-varicella vaccines (MMRV), and encephalitis in paediatric recipients.

2. DESCRIPTION OF THE STUDY TEAM

Study team role	Names	Organisation
Principal Investigator	Xintong Li Annika Jödicke	University of Oxford University of Oxford
Data Scientist	Martí Català Sabaté Mike Du	University of Oxford University of Oxford
Clinical Domain Expert	Anna Saura Lazaro Daniel Prieto-Alhambra	University of Oxford University of Oxford
Epidemiologist	Xintong Li Annika Jödicke Martí Català Sabaté	University of Oxford University of Oxford University of Oxford
Statistician	Martí Català Sabaté	University of Oxford
Study Manager	Natasha Yefimenko	Erasmus Medical Centre
Data source	**Names**	**Data Partner Organisation***
Danish Data Health Registries (DK-DHR)	Elvira Bräuner Susanne Bruun	Danish Medicines Agency
Finnish Care Register for Health Care (FinOMOP-THL)	Toni Lehtonen Laura Salonen Petteri Hovi	Finnish Institute for Health and Welfare (THL)
Norwegian Linked Health Registry data (NLHR)	Nhung Trinh Hedvig Nordeng Saeed Hayati	University of Oslo
The Information System for Research on Primary Care (SIDIAP)	Laura Granes Gonzalez Anna Palomar Cros Agustina Giuliodori Picco Irene Lopez Sanchez	IDIAP JGOL

*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® - Association between varicella vaccines (V), measles-mumps-rubella-varicella vaccines (MMRV), and encephalitis in paediatric recipients

Rationale and background

Varilrix and *Varivax* are authorised for prevention of varicella infection (chickenpox) in adults, children, and adolescents aged 9 – 12 months and older. Both vaccines contain live-attenuated varicella virus (OKA strain).

The EMA Pharmacovigilance Risk Assessment Committee (PRAC) reviewed the risk of encephalitis associated with these vaccines following a report of a fatal case in a paediatric recipient of *Varilrix* (PRAC meeting highlights June 2025), leading to an update of the product information to further describe the severity of the risk of encephalitis for both varicella vaccines licensed in Europe (see: New product information wording – July 2025). These vaccines are widely used across the European Union (EU), and encephalitis is listed as an adverse reaction in their product information based on rare reports during post-marketing surveillance; however this risk should be better characterised, as observational evidence is scarce.

Cases of encephalitis with fatal outcome are extremely rare given the extensive use of varicella vaccines. Data from US spontaneous reports showed <1 case per million doses administered.[1] Encephalitis is also a recognised but rare complication following severe varicella infection, in about 1–2 cases per 10,000 infected children and adolescents, and with a higher risk in immunocompromised individuals.[2] Considering the severity of encephalitis and the regulatory context, further investigation is needed.

Objectives

This study aimed to evaluate the association between varicella vaccines (V)/ measles-mumps-rubella-varicella vaccines (MMRV) and the occurrence of encephalitis in paediatric populations.

The specific objectives of this study were:

1. To describe V/MMRV vaccine uptake by vaccine type, dose, brand, age group, country, and to describe the characteristics of vaccine recipients.
2. To describe the background rates of encephalitis in the general paediatric population, and to estimate the crude incidence rates (IRs) of encephalitis following varicella infection.
3. To assess the association between varicella infection and encephalitis among children and adolescents aged 9 months to 18 years by age group and country.
4. To assess the association between V/MMRV vaccines and encephalitis among children and adolescents aged 9 months to 18 years by age group and country.

Methods

Study design

Descriptive analyses were conducted to describe vaccine uptake and coverage (including dose uptake and brand) and background IRs of encephalitis. A self-controlled risk intervals (SCRI) analyses was conducted to assess the association between varicella vaccination or varicella infection and encephalitis.

Population

The study population included all individuals aged between 9 months and 18 years who were present in the data sources during the study period from 1st January 2017 until the latest date of data availability, with at

least 365 days of data availability (reduced to 90 days for children ≤1 years) before index date. For Objective 4, we required children and adolescents to receive at least one dose of V or MMRV vaccines during the study period.

For the SCRI analysis, children and adolescents who were not eligible for vaccination, including children and adolescents with contraindications or a record of previous varicella infection, were excluded. Children and adolescents with a record of another live vaccine in the 28 days before or after receipt of a V or MMRV vaccine, which was the minimum allowable interval for live vaccines, were also excluded.

Variables

Exposure:

In Objective 3, the primary exposure was varicella infection.

In Objectives 1 and 4, exposure was defined based on the dose of V/MMRV vaccine.

Outcome:

The outcome of interest was encephalitis. Two definitions of the outcome were used: encephalitis (any) included any type of encephalitis; encephalitis (unspecified/vaccination) included unspecific encephalitis and encephalitis due to varicella or vaccination. A 90-day washout period was used to define incident encephalitis in the primary analysis.

Data sources

1. Denmark: Danish Data Health Registries (DK-DHR)
2. Finland: Finnish Care Register for Health Care (FinOMOP-THL)
3. Norway: Norwegian Linked Health Registry data (NLHR)
4. Spain: The Information System for Research on Primary Care (SIDIAP)

Statistical analysis

All analyses were conducted separately for each data source and were carried out in a federated manner, allowing analyses to be run locally without sharing patient-level data. To comply with data privacy regulation, cell counts <5 were suppressed.

Results from all analyses were presented separately for each data source. If FinOMOP-THL and SIDIAP, where varicella vaccine was included in the national vaccination scheme, had event counts ≥5 for the respective analyses for SCRI, we pooled the effect estimates across two data sources using random effect meta-analyses.

Objective 1

We estimated the annual vaccine uptake and coverage of children and adolescents vaccinated in the relevant age group for each vaccine type, dose, and brand. We then described the characteristics of vaccine recipients, including age at vaccination, sex, history of other live-attenuated vaccines, and history of encephalitis.

Objective 2

Crude IRs per 100,000 person years, with the 95% confidence Interval (95% CI), of encephalitis were estimated among a cohort of children and adolescents with a recorded varicella infection, restricted to the first 28 days post diagnosis.

Background rates of encephalitis per 100,000 person-years, with 95% CI, were estimated for the study period, stratified by age group.

Objectives 3 and 4

Incidence rate ratios (IRRs) were estimated using a SCRI design, comparing rates of encephalitis in the immediate time after vaccination/varicella infection (risk interval: from 5 to 28 days after vaccination/infection) to unexposed time (control interval: from 50 to 90 days after vaccination/infection).

Sensitivity analyses included alternative definitions of the risk and control intervals, alternative definition of encephalitis, and removal of follow-up time requirements.

Results

Following the introduction of universal varicella vaccination in Finland in 2017, first-dose coverage among children aged <2 years increased from 12.87% in 2017 to 82.18% in 2024. In parallel, first-dose coverage also increased in Spain from 70.06% in 2017 to 89.16% in 2024. Two-dose coverage by age 7 increased from 6.64% to 72.18% between 2017 and 2024 in Finland, and from 32.94% to 83.64% in Spain.

Crude background IRs of encephalitis (any) during the study period were 6.42/100,000 person-years (95% CI 5.90–6.98) in DK-DHR, 13.75 (95% CI 12.94–14.60) in FinOMOP-THL, 7.46 (95% CI 6.85–8.12) in NLHR, and 4.68 (95% CI 4.21–5.18) in SIDIAP. Rates were generally stable over time, with slightly lower estimates observed during 2020–2021.

Encephalitis cases within 28 days after varicella infection were rare (8 in DK-DHR, 8 in FinOMOP-THL, 9 in NLHR, and <5 in SIDIAP). In the SCRI analysis of varicella infection, the age- and season-adjusted IRR for encephalitis (any) was 6.39 (95% CI 0.69–58.88) in NLHR. In the other data sources, event numbers were too small to generate effect estimates.

In the SCRI analysis of varicella vaccination, sufficient sample size was only available in FinOMOP-THL and SIDIAP. Among first-dose recipients, the age- and season-adjusted IRR for encephalitis (any) was 1.55 (95% CI 0.53–4.50) in FinOMOP-THL and 1.01 (95% CI 0.20–5.04) in SIDIAP, with a pooled estimate of 1.36 (95% CI 0.56–3.31). Among second-dose recipients, corresponding IRRs were 0.24 (95% CI 0.02–3.05) and 0.49 (95% CI 0.05–4.76), respectively, with a pooled estimate of 0.36 (95% CI 0.07–1.95). Sensitivity analyses results were in line with the main analysis.

Discussion

Overall, encephalitis following varicella vaccination was rare, and meta-analysed estimates did not show significant associations between varicella vaccination and encephalitis, while suggesting a role for varicella infection in the occurrence of encephalitis.

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Study deliverable	Timelines (planned)	Timelines (actual)
Final Study Protocol	November 2025	27/11/2025
Creation of Analytical code	November 2025	24/11/2025–16/12/2025
Execution of Analytical Code on the data	December 2025	17/12/2025–22/01/2026
Draft Study Report	January 2026	16/02/2026
Final Study Report	February 2026	20/03/2026

6. RATIONALE AND BACKGROUND

Varilrix and *Varivax* are authorised for vaccination against varicella infection (chickenpox) in children and adolescents aged 9 – 12 months and older, and in adults. Both vaccines contain live-attenuated varicella virus (OKA strain).

Known adverse reactions include injection site reactions (pain, redness, swelling, or itching), fever, and mild rash. In rare cases, more serious adverse events have been reported, including allergic reactions, such as anaphylaxis, and transmission of the vaccine virus, particularly in immunocompromised individuals, for whom the vaccines are contraindicated.

In June 2025 EMA's Pharmacovigilance Risk Assessment Committee (PRAC) reviewed the risk of encephalitis associated with the two varicella vaccines, *Varilrix* and *Varivax*, following a report of a fatal outcome in a paediatric recipient of *Varilrix* (see: PRAC meeting highlights June 2025). Encephalitis is an uncommon but serious condition inflammation (swelling) of the brain, which can be life-threatening.[2] Varicella vaccines are widely used across the European Union (EU), and encephalitis is listed as an adverse reaction in their product information, based on rare reports during post-marketing surveillance.

The EU-Summary of Product Characteristics (SmPC) includes encephalitis:

- *Varilrix*: System Organ Class (SOC) Nervous system disorders: encephalitis, cerebrovascular accident, seizure, cerebellitis, cerebellar-like symptoms (including transient gait disturbance and transient ataxia)
- *Varivax*: SOC Infections and infestations: Encephalitis, […], aseptic meningitis

At its July 2025 meeting, PRAC recommended updating the product information of *Varilrix* and *Varivax* to further describe the severity of the risk of encephalitis (PRAC meeting highlights July 2025; New product information wording – July 2025).

Varicella (V) vaccines are also authorised as part of/in fixed combinations in measles, mumps, rubella, and varicella (MMRV) vaccines. In July 2025, PRAC considered that "the product information of MMRV vaccines should also be updated in line with varicella vaccines".

Fatal cases of encephalitis remain very rare, given the extensive exposure to the V (and MMRV) vaccines.[1] Encephalitis has also been reported as a complication from severe varicella infection.[3]

However, there is currently a very limited number of studies assessing the incidence rates (IRs) of encephalitis after vaccination or examining the association between varicella vaccines and encephalitis. One study using the Vaccine Adverse Event Reporting System (VAERS) from the US reported that during 2006–2020, 40,684 adverse event reports were received after over 132 million doses distributed.[1] Among

those, the reporting rate of encephalitis, calculated as per 100,000 doses of varicella vaccines distributed, was 0.06. One study that used the self-controlled risk interval design in administrative claims data from Taiwan, found no increased risk of encephalitis during the 1–42 days post-varicella vaccination, with an adjusted incidence rate ratio (IRR) of 1.00 (95% CI: 0.62–1.60).[4]

Considering the severity of the outcome and the limited availability of observational evidence, further investigation is needed, including the generation of timely real-world evidence (RWE) on the association between varicella vaccination and encephalitis risk in the paediatric population.

This study aimed to advance broader public health understanding of this rare but serious adverse event following varicella immunisation.

7. RESEARCH QUESTION AND OBJECTIVES

Research questions

This study aimed to evaluate the association between the use of varicella vaccines (V)/measles-mumps-rubella-varicella vaccines (MMRV) and the occurrence of encephalitis among paediatric populations.

Research objectives

The specific objectives of this study were:

1. To describe V/MMRV vaccine uptake by vaccine type, dose, brand, age group, country, and to describe the characteristics of vaccine recipients.
2. To describe the background rates of encephalitis in the general paediatric population, and to estimate the crude IRs of encephalitis following varicella infection.
3. To assess the association between varicella infection and encephalitis among children and adolescents aged 9 months to 18 years by age group and country.
4. To assess the association between V/MMRV vaccines and encephalitis among children and adolescents aged 9 months to 18 years by age group and country.

8. RESEARCH METHODS

8.1. Study design

Population-level descriptive analyses were conducted to study vaccine uptake and coverage (including dose uptake and brand) and background IRs of encephalitis. We then conducted self-controlled risk intervals (SCRI) analyses to assess the association between varicella vaccination or infection and encephalitis.

8.1.1. Descriptive analyses

The study comprised several descriptive analyses:

In Objective 1, we assessed vaccine uptake and vaccine coverage among children and adolescents eligible for varicella vaccination. Vaccine uptake was estimated as the absolute number of children and adolescents who have received a specified vaccine dose(s) at a specified “age milestone”, e.g. their 2nd birthday.[5] Vaccination coverage was measured as the proportion of eligible children and adolescents who received the number of vaccine doses as recommended per national schedule in the relevant age group/at the relevant age milestone.[5] We also described the age and sex distribution of vaccinated children and adolescents at the time of vaccination.

In Objective 2, we described the IR of encephalitis in the general population (i.e. regardless of infection status) and in the immediate time following varicella infection.

8.1.2. Self-controlled Risk Interval (SCRI) analyses

The SCRI design was used to assess the association between varicella infection and encephalitis (Objective 3) and the association between V/MMRV vaccines and encephalitis (Objective 4) among children and adolescents.

The self-controlled case series (SCCS) and SCRI study designs have been developed and are widely used in vaccine safety studies, including studies on the safety of varicella vaccines.[4] Briefly, SCRI are an intra-individual study design which compares event rates (here: encephalitis) in the immediate time following vaccination ("risk window") to event rates in control windows. The resulting incidence rate ratios (IRRs) provide an estimate of the relative risk associated with vaccination.

The main advantage of this method is that the estimation is within individuals, and no separate controls are required.[6] This is particularly useful for studies on vaccines where suitable unvaccinated controls are difficult to identify due to, for example, wide vaccine coverage in the targeted population or age group. By its intra-individual design, SCRI accounts for time-stable confounding, and analyses can be adjusted for time-varying covariates, such as age and season. The study design is illustrated in **Figure 1** below. Risk and control windows were selected based on previous studies on encephalitis and varicella vaccines.[4,7,8]

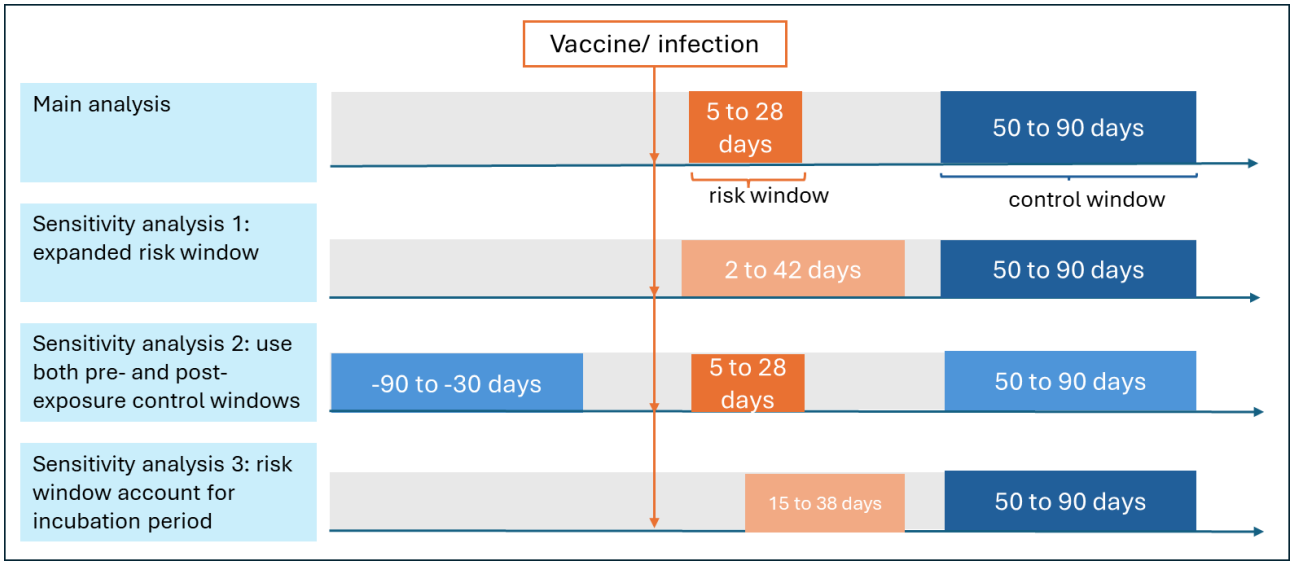

Figure 1. Illustration of the study design of the SCRI analyses.

8.2. Follow-up

Objective 1

Analyses of varicella vaccine coverage/uptake and individual characterisation were conducted from the start of the study period until the latest date of data availability.

For each analysis, individual's follow-up started at the earliest time they met all inclusion criteria. Follow-up ended when the individual reached the respective age milestones for vaccine coverage/uptake assessment. Follow-up was censored at death, end of observation period (the latest available data), recording of a contraindication for life-attenuated virus vaccination, or varicella infection.

Objective 2

For the analyses of the background IRs of encephalitis, follow-up started at the earliest time each individual meets all inclusion criteria. End of follow-up was defined as the earliest of occurrence of encephalitis, loss to follow-up, death, end of observation period (the latest available data), or age >18years.

For the analyses of the crude IRs of encephalitis following varicella infection, follow-up started on the date of varicella infection. End of follow-up was defined as: occurrence of encephalitis, loss to follow-up, death, end of observation period (the latest available data), or 42 days after varicella infection, whichever occurred first.

Objective 3

For the SCRI analysis, follow-up started at 90 days prior to varicella infection and ended at 90 days after varicella infection.

Objective 4

For the SCRI analysis, follow-up started at 90 days prior to vaccination and ended at 90 days after vaccination.

8.3. Study population with inclusion and exclusion criteria

Objective 1

Vaccine uptake and coverage

Study population:

Denominator*:* children and adolescents eligible for live-attenuated varicella virus vaccination.

Numerator: children and adolescents who received at least one dose of varicella vaccines (V) or measles-mumps-rubella-varicella vaccines (MMRV) during the study period.

Inclusion criteria:

- Aged between 9 months and 18 years during the study period.
- At least 365 days data availability (reduced to 90 days for children ≤1 years) before contribution to the denominator population.

Exclusion criteria:

- Children and adolescents with a history of contraindications for life-attenuated virus vaccination (i.e. acquired immunodeficiency syndrome (AIDS) or symptomatic HIV infection, immunosuppression due to leukaemia, lymphoma, generalised malignancy, severe combined immunodeficiency (SCID), immunosuppressive therapy, and transplantation) prior to vaccination.
- Children and adolescents with previous varicella infection diagnosis.

Objective 2

Background rates of encephalitis

Study population:

Denominator: children and adolescents.

Numerator: number of incident cases of encephalitis.

Inclusion criteria:

- Aged between 9 months and 18 years during the study period.
- At least 365 days of data availability (reduced to 90 days for children ≤1 years) before contribution to the denominator population.

Crude incidence rates of encephalitis after varicella infection

Study population:

Denominator: children and adolescents who received a varicella infection diagnosis.

Numerator: number of incident cases of encephalitis.

Inclusion criteria:

- Aged between 9 months and 18 years during the study period.
- At least 365 days data availability (reduced to 90 days for children ≤1 years) before starting to contribute to person-time.
- A record of varicella infection during the study period.

Objective 3

Study population: children and adolescents with varicella infection and a record of encephalitis within 90 days before or after index date.

Inclusion criteria:

- Aged between 9 months and 18 years during the study period.
- Records of varicella infection during the study period.
- At least 365 days data availability (reduced to 90 days for children ≤1 years) before index date of varicella infection.
- At least 90 days of follow-up data availability after index date.
- At least one record of incident encephalitis during the follow-up period.

Objective 4

Study population: children and adolescents vaccinated with at least one dose of varicella vaccines (V), measles-mumps-rubella-varicella vaccines (MMRV), and a record of encephalitis within 90 days before or after index date.

Inclusion criteria:

- Aged between 9 months and 18 years during the study period.
- Received at least one dose of varicella vaccines (V), measles-mumps-rubella-varicella vaccines (MMRV) during the study period.
- Have at least 365 days data availability (reduced to 90 days for children ≤1 years) before index date (V or MMRV vaccination).
- Have at least 90 days of follow-up data availability after index date.
- Have at least one record of incident encephalitis during the follow-up period.

Exclusion criteria:

- Children and adolescents with a history of contraindications to vaccination with V/MMRV prior to index date: acquired immunodeficiency syndrome (AIDS) or symptomatic HIV infection, immunosuppression due to leukaemia, lymphoma, generalised malignancy, severe combined immunodeficiency (SCID), immunosuppressive therapy, and transplantation.

- Received another live-attenuated vaccination (including MMR) within 90 days before and after index date. Vaccination on the same date is allowed.
- Children and adolescents with varicella infection any time prior to index date of vaccination.

8.4. Study setting and data sources

Table 1. 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
Denmark	Danish Data Health Registries (DK-DHR)	Hospital care	Registries	5.72m	1995-01-01 to 2024-11-07	All objectives
Finland	Finnish Care Register for Health Care (FinOMOP-THL)	Primary care, Hospital care	Registries	5.58m	2011-01-01 to 2024-10-09	All objectives
Norway	Norwegian Linked Health Registry data (NLHR)	Primary care, hospital care	Registries	5.27m	2008-01-01 to 2023-12-31	All objectives
Spain	The Information System for Research on Primary Care (SIDIAP)	Primary care, hospital care	EHR	5.86m	2006-01-01 to 2024-12-31	All objectives

*Active individuals reported as number of individuals under observation at 2017-01-01. EHR=Electronic health records.

This study was conducted using routinely collected data from four data sources in the DARWIN EU® network of data partners from four European countries, of which three are EU member states. All data were a priori mapped to the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM).

Data sources

1. Denmark: Danish Data Health Registries (DK-DHR)
2. Finland: Finnish Care Register for Health Care (FinOMOP-THL)
3. Norway: Norwegian Linked Health Registry data (NLHR)
4. Spain: The Information System for Research on Primary Care (SIDIAP)

Data sources selection

These data sources fulfil the criteria required in terms of data quality, completeness, and timeliness, while covering different regions of Europe.

When it comes to assessing the reliability of data sources, the data partners are asked to describe their internal data quality process on the source data as part of the DARWIN EU® onboarding procedure. To further ensure data quality, we utilised the *Achilles* tool, which systematically characterises the data and generates data characteristics such as age distribution, condition prevalence per year, and data density.

Data density includes information on 1) monthly record counts by data domain (which offers insights into data collection patterns and the start date of each data source) and 2) measurement value distribution (i.e. min, max, quartiles for numeric values per measurement concept and per unit and counts for discrete measurement-value pairs). The latter can be compared against expectations for the data based on predefined standards, historical trends, or known epidemiological patterns to identify potential anomalies or inconsistencies. Additionally, the data quality dashboard (DQD) provides more objective checks on plausibility of data completeness, consistency, and conformity across the data sources.

In terms of relevance, the selection of data sources was based on the availability of data on varicella vaccines in children and adolescents, countries in which varicella vaccine is included in the vaccination scheme, as well as settings where encephalitis would be recorded (primary care linked to hospital data/national registries). In addition, the data sources were chosen considering their ability to support timely institutional review board (IRB) approvals, thus ensuring alignment with the timeline established by stakeholders for the conduct of this study.

The DARWIN EU® portal, as well as information from the onboarding documents, were used to assess whether data sources have information on varicella vaccines in children and adolescents. Data within the DARWIN EU® portal is maintained up to date by extracting the release dates for each dataset in the network and monitoring when data are out-of-date with the expected refresh cycle (typically quarterly or every 6 months). In addition, it is important to have clear understanding of the time covered by each released data source, as this can vary across different domains. To facilitate this, the *CDMOnboarding* (and *Achilles*) packages contain a 'data density' plot. This plot displays the number of records per OMOP domain monthly. This allows getting insights into when data collection started, when new sources of data were added, and until when data was included. In addition, at the time of inviting data partners, they were informed about study objectives and asked whether they could participate in the study.

More general-purpose diagnostic tools, *CohortDiagnostics*[9] and *DrugExposureDiagnostics*[10], have been developed. The *CohortDiagnostics* package provides additional insights into cohort characteristics, record counts, and index event misclassification. The *DrugExposureDiagnostics* package evaluates ingredient-specific attributes and patterns in drug exposure records. Upon finalisation of the study protocol and creation of the disease and drug cohorts of interest by DARWIN EU® Coordination Centre, these packages were executed in each data sources by each data partners.

Data source justification and key characteristics

The data sources selection was based on

- Feasibility counts for varicella vaccinations
- Complete recording of other vaccines of interest, e.g. MMR vaccine
- Availability of records of encephalitis in children and adolescents
- Setting(s) that would include both vaccination and diagnosis and recording of severe encephalitis, such as primary care data linked to hospital records (SIDIAP) or population-level, national registries (DK-DHR, NLHR, FinOMOP-THL)
- If available, data sources from a country/region where varicella vaccination is implemented in the national immunisation programme

Among data sources with reasonable feasibility counts (>1000 individuals), two data sources (FinOMOP-THL, SIDIAP) are from countries where varicella vaccination is included in national immunisation programmes.

In Finland, varicella vaccines were introduced to the national vaccination schedule in 2017. The first varicella vaccine dose is recommended at 18 months (while MMR is recommended between 12 – 18

months), followed by MMRV or MMR+V at age 6 years. A “catch-up” vaccination is offered if children and adolescents did not receive 2 varicella vaccine doses by the age of 12 years.[11,12]

In Catalonia, Spain, varicella vaccines were incorporated into the routine childhood vaccination schedule in 2016: A first varicella vaccine dose is recommended at the age of 15 month (MMR vaccination at 12 months), followed by MMRV or MMR+V between the age of 3 – 4years. Similar to Finland, a “catch-up” vaccination is offered if children and adolescents did not receive 2 varicella vaccine doses by the age of 12 years.[13,14]

In Denmark and Norway, varicella vaccines are not included in the national vaccination programme for children and adolescents.

Based on these criteria, DK-DHR, FinOMOP-THL, NLHR, and SIDIAP were invited to participate in the study. Feasibility was also assessed for the Clinical Practice Research Datalink GOLD (CPRD GOLD) and Integrated Primary Care Information (IPCI) data sources, but both data sources were not included due to (comparably) smaller feasibility counts and lack of information on hospital diagnoses.

Additional information on the data sources used in this study is provided in **Annex I**. Details on the selection of data sources and fit-for-purpose assessment are available in **Annex II**.

8.5. Study period

The study period was from 01/01/2017 to the most recent data available for each contributing data source. In NLHR, the availability of the data starts at 01/01/2018.

8.6. Variables

8.6.1. Exposure

In both Finland and Spain, where varicella vaccines are included in the national vaccination program, a first dose of varicella-only vaccine (V) is recommended after a first dose of MMR, and a second dose of varicella vaccine is recommended to be administrated on the same date with MMR as MMR+V or as the tetravalent vaccine (MMRV). Specifically, the following study cohorts were defined for this study:

Primary Exposure – First Vaccine Dose

- First dose of varicella-only vaccine (V), administered without MMR on the same date, referred to as [D1(V)]

Primary Exposure – Second Vaccine Dose

- Second dose of varicella vaccine, administered with MMR on the same date (MMR +V), or as tetravalent vaccine (MMRV), referred to as [D2(MMRV)]

Secondary Exposure:

- First dose of varicella vaccine (V), administered with MMR on the same date (MMR + V), or as tetravalent vaccine (MMRV), referred to as [D1(MMRV)]
- Any first dose varicella vaccine, including D1(V) and D1(MMRV), referred to as [D1(any)].
- Second dose of varicella-only vaccine (V), administered without MMR on the same date, referred to as [D2(V)]
- Any secondary varicella vaccine, including D2(V) and D2(MMRV), referred to as [D2(any)].

For Objectives 2 and 3, incident varicella infection, defined as the first varicella infection record without any previous record in the individual’s history, was included as exposure.

The preliminary concept sets used for the identification of exposures are described in **Annex III**. These codes were then refined during the study execution following the DARWIN EU® phenotyping standard processes, which involve the review of code lists by clinical experts and pharmacists and the review of phenotypes and vaccine cohorts after their execution in the participating data sources. Only varicella vaccines used in children and adolescents were included in this study.

8.6.2. Outcome

For Objective 1, the analysis described:

- Vaccine uptake, defined as the absolute number of children and adolescents who received a specified varicella vaccine dose(s) among eligible children.[5]
- Vaccination coverage, defined as the proportion of children that received the specified number of varicella vaccine doses in the relevant age group by age milestones (e.g. by the time of their 2nd birthday) among the eligible children.[5]

For Objectives 2 to 4, the outcome of interest is encephalitis. Encephalitis was identified using the phenotype developed in a previous DARWIN EU® study (DARWIN EU® – Background incidence rates of selected vaccine adverse events of special interest (AESIs)). The code list used for the identification of outcomes are described in **Annex IV**.

Two definitions of encephalitis included:

a.) “Encephalitis (any)”: this used the “narrow” cohort from the AESI study

b.) “Encephalitis (unspecified/vaccination)”: this started from the “narrow” cohort from the AESI study and excluded concepts that had a specific cause listed that was not relevant for this study. Therefore, unspecific encephalitis and encephalitis due to varicella or vaccination were included. This phenotype was developed during the implementation stage.

A 90-day washout period was used to define incident encephalitis in the primary analysis.

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

Objective 1

The vaccine uptake and coverage were estimated in the following age groups as age milestones (roughly 12 months after the recommended vaccination schedules in the four countries):

- 1st dose: by 2nd birthday
- 2nd dose: by 7th birthday; by 13th birthday; by 18th birthday

Birthdays were calculated based on the available date of birth for DK-DHR, FinOMOP-THL, and NLHR, and using the first day of the month of birth for SIDIAP.

The following variables were used for stratification in estimating vaccine uptake and coverage:

- Vaccine type: V, MMRV
- Vaccine brand (when available): *Varivax, Varilrix, ProQuad, Priorix-Tetra*
- Vaccine dose: 1st dose, 2nd dose

We characterised vaccine recipients based on the vaccine cohorts defined in **8.6.1. Exposure**.

The covariates for the characterisation of newly vaccinated children are as follows:

- Age groups: 9 months – 23 months, 2 – 6 years, 7 – 11 years, 12 – 18 years
- Sex: male, female

- History of varicella vaccine: type, dose, brand
- History of other live-attenuated vaccines: MMR, varicella vaccine, rotavirus vaccine, flu vaccines (nasal spray), polio vaccine (oral)
- History of encephalitis

Objective 2

The following variables were used for stratification:

- Age groups: 9 months – 23 months, 2 – 6 years, 7 – 11 years, 12 – 18 years
- Calendar years: 2017 – 2019, 2020 – 2024
- Seasons: Jan – Mar, Apr – Jun, Jul – Sep, Oct – Dec (year-season specific rates was reported)

Objectives 3 and 4

Variables that were adjusted as time-varying confounder in the SCRI analysis:

- Age: as age band
- Season: 4 seasons (Jan – Mar, Apr – Jun, Jul – Sep, Oct – Dec)
- The following variables were used for stratification:
- Age stratification: 9 months – 23 months, 2 – 6 years, 7 – 11 years, 12 – 18 years
- Calendar year: 2017 – 2019, 2020 – 2024
- Objective 4 only: Vaccine brand (when available and if sample size allows): *Varivax, Varilrix, ProQuad, Priorix-Tetra*

8.7. Study size

The following table summarises the feasibility counts of varicella vaccine and encephalitis for included data sources.

Table 2. Feasibility counts of exposure and outcomes for included data sources.

Data source	Vaccine (person count)			Encephalitis (record count)	
	Varicella vaccine	MMRV vaccine	MMR vaccine	Infants and toddlers (28d – 23m)	Children (2–18 yr)
DK-DHR	141,500 Varivax: 19,600 Varilrix: 3,800	5,200	2,675,900	400	2,500
FinOMOP-THL	1,393,100 Varivax: 523,000 Varilrix: 54,900	237,400	1,333,600	500	3,400
NLHR	10,200		756,700	300	1,400
SIDIAP	762,700		1.4M*	100	400

*SIDIAP mapped MMR as vaccines of measles, mumps, and rubella as three separate records.
MMRV=measles-mumps-rubella-varicella (vaccines); MMR=measles-mumps-rubella (vaccines); DK-DHR=Danish Data Health Registries; FinOMOP-THL=Finnish Care Register for Health Care; NLHR=Norwegian Linked Health Registry data; SIDIAP=The Information System for Research on Primary Care.

Objectives 1 and 2

No sample size was calculated, as these objectives are descriptive and did not test a specific hypothesis. In addition, we used already collected data to estimate vaccination uptake/coverage and background rates for encephalitis. Thus, the sample size was driven by the availability of data for children and adolescents with varicella vaccination, varicella infection, and encephalitis records. Based on a preliminary feasibility assessment, the expected number of persons counts for varicella vaccination in the data sources included in this study range from 1.4 million (FinOMOP-THL) to 10,200 (NLHR). Feasibility record counts for encephalitis range from 100 (SIDIAP) to 500 (FinOMOP-THL) in infants/toddlers aged 1 – 23 months and from 400 (SIDIAP) to 3,400 (FinOMOP-THL) in children and adolescents aged 2 – 11 years. Individual counts for varicella infection were 11,400 (DK-DHR, no primary care settings included) and 49,300, 161,200, and 589,700 for FinOMOP-THL, NLHR, and SIDIAP, respectively.

Objectives 3 and 4

Sample size for SCRI was estimated assuming: a risk period of 30 days, a total follow-up of 365 days, alpha 0.05, and 80% power. An SCCS nested in a cohort of vaccine-exposed subjects would need a total of 82 cases/events for the scenario if IRR was 2.5, 20 cases/events for the scenario if IRR was 5, and 8 cases/events for the scenario if IRR was. With an estimated incidence rate of encephalitis of 1 to 10 per 100,000 person-years (PY), this study would need the following number of vaccinated children and adolescents to identify the 82 and/or 20 events previously estimated:

- IR 1/100,000 PY and IRR 2.5: approximately 8.2 million vaccinated children and adolescents would be needed to identify 82 cases.
- IR 10/100,000PY and IRR 2.5: approximately 820,000 vaccinated children and adolescents would be needed to identify 82 cases.
- IR 1/100,000PY and IRR 5: approximately 2 million vaccinated children and adolescents would be needed to identify 20 cases.
- IR 10/100,000PY and IRR 5: approximately 200,000 vaccinated children and adolescents would be needed to identify 20 cases.

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 III**), 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

In Objective 1, vaccine uptake was measured as number of people who received the vaccine of interest, and vaccine coverage was measured as percentage of people who received the vaccine among those eligible for a vaccination.

In Objective 2, IRs were estimated.

In Objectives 3 and 4, adjusted IRR was assessed.

8.9.2. Main statistical methods .

Objective 1

This objective described vaccine uptake of V/MMRV, by vaccine type, dose, brand, country, and described the characteristics of vaccine recipients.

We estimated the vaccine uptake and coverage of children vaccinated in the relevant age group for each vaccine type, dose, and brand (when available). Vaccine uptake was estimated as the absolute number of children and adolescents who received a specified vaccine dose(s) among eligible children and adolescents. Vaccination coverage was measured as the percentage/proportion of children and adolescents who received the specified number of vaccine doses in the relevant age group/at the relevant age milestone among the eligible children and adolescents.

We reported the overall and annual vaccine uptake and coverage in each data source.

We then described the characteristics of vaccine recipients, as defined in section **8.6.1. Exposure**, including age at vaccination, sex, history of other live-attenuated vaccines, and history of encephalitis.

R-packages

All analyses were based on OMOP CDM mapped data using R packages for standard analytics developed by DARWIN EU®. We used the *IncidencePrevalence* R package[15] (with the addition of some custom code, if needed) to estimate vaccine uptake and coverage. The characterisation of vaccine recipients used the *CohortCharacteristics* R package.

Objective 2

This objective described the background rates of encephalitis in a paediatric population, as well as estimated crude IRs of encephalitis after varicella infection.

We estimated the background rates of encephalitis during the study period, stratified by age groups (9 months – 23 months, 2 – 6 years, 7 – 11 years, 12 – 18 years) (event rates per 100,000 person years, with 95% Confidence Intervals (CIs)). Standardisation was not conducted, as the European Standard Population typically used for age-sex standardisation of background rates is only available for 5-year age bands, which does not align with the age groups used in this study.

We estimated the crude IRs of encephalitis within 28 days after varicella diagnosis (event rates per 100,000 person years, with 95% CIs).

R-packages

All analyses were based on OMOP CDM mapped data using R packages for standard analytics developed by DARWIN EU®. We used the *IncidencePrevalence* R package[15] to estimate crude IRs and background rates.

Objectives 3 and 4

We conducted a SCRI analysis, which compared the rate of events during the pre-defined risk interval to the rate during the pre-defined control interval.

First, we planned to perform diagnostics to test the assumptions for self-controlled design, which included:

- Event-dependent exposures[16]
    - A key assumption is that subsequent exposures should not appreciably be affected by previous events.

- This can be examined by plotting the distribution of the interval between exposure and event time. If a peak or trough in events prior to exposure is apparent, the presence of short-term event-dependent exposures is suspected.

- Event-dependent observation periods
  - If the event increases the probability of death, then there is a chance that observation periods could be cut short as a direct result of the event.
  - This can be examined by histograms of the times from event to end of observation, for those whose observation times are censored, and those are not separately. If a spike is apparent close to zero in the censored data histogram, the presence of event-dependent observation periods is suspected.

Table 3. Specification of planned analyses.

Hypothesis:	To assess the association between varicella infection, V/MMRV vaccines, and encephalitis among children and adolescents aged 9 months to 18 years by age group and country.
Exposure contrast:	Immediate time after exposure of interest (risk window) compared to unexposed (both pre-and-post exposure) time (control window) In Objective 3, the exposure was varicella infection. In Objective 4, the following exposures were defined: Primary vaccine Exposure (main analysis): • D1(V) (first dose of varicella-only vaccine, without MMR on the same date) • D2(MMRV) (second dose as MMRV or MMR+V) Secondary vaccine exposures were included: • D1(MMRV) • D1(any) • D2(V) • D2(any)
Outcome:	Incident encephalitis
Analytic software:	*SCCS* R package with custom code adaptations (if needed) Conditional IRR and corresponding 95% CIs of incident encephalitis between the risk window and the control window was estimated using Conditional Poisson regression.
Model(s):	Two modes were used: • encephalitis ~ infection/vaccine + age • encephalitis ~ infection/vaccine + age + season Follow-up: [-90, 90] days Index date of infection/vaccination: [0, 0] days Risk interval (primary): [5, 28] days[17] Control intervals: [50, 90] days Age adjustment: age bands Season: 4 seasons (Jan – Mar, Apr – Jun, Jul – Sep, Oct – Dec)
Confounding adjustment method	
	• Self-controlled risk interval (intra-individual) study design, accounting for time-stable confounding

	• Adjustment for age and calendar time
Subgroup Analyses	
	The following subgroup analyses were conducted for primary vaccine exposure (V1_V, V2_MMRV) and varicella infection exposure: • Age stratification: 9 months – 23 months, 2 – 6 years, 7 – 11 years, 12 – 18 years • Calendar year: 2017 – 2019, 2020 – 2024 • Apply to vaccine exposure: If sample size allowed, we planned to perform SCRI for V1_V stratified by vaccine brand (for data sources where this information was available)
Sensitivity analyses	
	• Secondary (extended) risk interval: [2,42] • Include both pre- and post-index control interval: [-90,-30] days and [50, 90] • Risk interval that accounts for incubation period: [15, 38] • Restrict to first ever encephalitis event only • Remove requirement of 90 days available follow-up time after vaccination

V=Varicella vaccines; MMRV=Measles-Mumps-Rubella-Varicella vaccines; IRR=Incidence rate ratio; SCCS=Self-controlled Case Series.

8.9.3. Missing values

We excluded individuals with missing age or sex.

8.9.4. Sensitivity analysis

Five sensitivity analyses were planned for Objectives 3 and 4. The following table describes the planned sensitivity analyses.

Table 4. Planned sensitivity analyses.

	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
Sensitivity analysis 1	Risk interval extended from [5, 28] days to [2, 42] days[17]	Duration of "exposure effect" after vaccination unclear based on immunological effect and previous literature	Longer risk window would capture additional events that are missed (underestimated) in shorter risk window	Events that are included in addition might be "too early" or "too late" to be immunologically related to vaccination (potential overestimation)
Sensitivity analysis 2	Use a combination of pre- and post-index control interval: from -90 to -30 day prior to index and from 50 to 90 day post-index date.	To test if there is any impact on the choice of control interval, especially under the potential for event dependent exposure.	Increase sample size as longer person time will be included	To minimise the potential bias from event-dependent exposure.
Sensitivity analysis 3	Risk interval of [15,38] days post-index	To account to the incubation period of encephalitis	Capture later onset encephalitis to account for the incubation period.	Cases occurred close to index day will not be included.

	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
Sensitivity analysis 4	First incident of encephalitis included only	SCCS assumption test: having previous encephalitis may change the likelihood of having subsequent encephalitis	SCCS assumption test	Smaller sample size.
Sensitivity analysis 5	Removal of the requirement of 90days available follow-up time after vaccination	This requirement might exclude children and adolescents with fatal encephalitis (if there were any) who then might not have the 90days follow-up	Does not include or condition on "future" follow-up time as inclusion criterion (remove the selection bias)	Might lead to reduced follow-up durations after vaccination, which potentially limits the identification of encephalitis cases after vaccination

SCRI=Self-controlled Risk Interval, SCCS=Self-controlled Case Series.

8.10. Deviations from the protocol

In the study protocol, we planned to conduct diagnostics to the SCRI assumptions. However, in the study, we identified very few numbers of individuals with both exposure and the outcome of interest in the risk/control window. Conducting the diagnostics, such as plotting time between index and event, would result in small cell count below 5. Therefore, to comply with data privacy regulation, we were not able to conduct these diagnostics.

While we planned to conduct stratified analysis by age group and calendar year, we were not able to conduct these analyses in the main analysis due to the low counts.

9. RESULTS

The full set of results for this study is available through an interactive web-application (ShinyApp) at EUPAS1000000813.

9.1. Participants

In DK-DHR, we identified a total of 38,907 varicella-containing vaccine records among 22,597 individuals aged between 9 months and 18 years. After applying the criteria of (1) no receipt of another live-attenuated vaccine within 28 days before or after the date of administration of the varicella-containing vaccine; (2) no additional record of a varicella-containing vaccine within 90 days; (3) a minimum prior observation period; (4) vaccination during the study period (2017 onwards); and (5) no contraindication to varicella-containing vaccine, we included 12,723 doses contributed by 11,506 children. (**Table 5**)

In FinOMOP-THL, 887,440 records from 586,570 children were identified. After applying the inclusion and exclusion criteria, we included 764,272 doses contributed by 526,858 children.

In NLHR, 13,025 records from 7,488 children were identified. After applying the inclusion and exclusion criteria, we included 5,426 doses contributed by 4,869 children.

In SIDIAP, 1,417,099 records from 842,597 children were identified. After applying the inclusion and exclusion criteria, we included 879,817 doses contributed by 566,154 children.

Table 5. Attrition of the vaccinated cohort, by data sources.

Reason	Variable name			
	number of vaccine records	number of subjects	excluded records	excluded subjects
DK-DHR; vaccinated				
Only first or second dose vaccine between age of 9 months and 18 years	38,907	22,597		
Require not receiving another live-attenuated vaccine during -28 to -1 days prior or 1-28 days after vaccination	25,221	16,305	13,686	6,292
Require 0 intersections with cohort varicella. Intersection window: -90 to -1 days relative to cohort start date	17,723	16,013	7,498	292
Require 0 intersections with cohort MMRV. Intersection window: -90 to -1 days relative to cohort start date	17,594	16,012	129	<5
Require minimum prior observation	17,027	15,496	567	516
Cohort start date after 2017-01-01	12,956	11,728	4,071	3,768
Cohort start date before 2025-12-31	12,956	11,728	0	0
Remove individuals with a prior contraindication	12,723	11,506	233	222
FinOMOP-THL; vaccinated				
Only first or second dose vaccine between age of 9 months and 18 years	887,440	586,570		
Require not receiving another live-attenuated vaccine during -28 to -1 days prior or 1-28 days after vaccination	832,886	562,808	54,554	23,762
Require 0 intersections with cohort varicella. Intersection window: -90 to -1 days relative to cohort start date	820,827	561,428	12,059	1,380
Require 0 intersections with cohort MMRV. Intersection window: -90 to -1 days relative to cohort start date	820,773	561,428	54	0
Require minimum prior observation	806,703	552,446	14,070	8,982
Cohort start date after 2017-01-01	766,035	527,792	40,668	24,654
Cohort start date before 2025-12-31	766,035	527,792	0	0
Remove individuals with a prior contraindication	764,272	526,858	1,763	934
NLHR; vaccinated				
Only first or second dose vaccine between age of 9 months and 18 years	13,025	7,488		
Require not receiving another live-attenuated vaccine during -28 to -1 days prior or 1-28 days after vaccination	8,406	5,375	4,619	2,113
Require 0 intersections with cohort varicella. Intersection window: -90 to -1 days relative to cohort start date	5,950	5,326	2,456	49
Require 0 intersections with cohort MMRV. Intersection window: -90 to -1 days relative to cohort start date	5,950	5,326	0	0
Require minimum prior observation	5,671	5,072	279	254
Cohort start date after 2017-01-01	5,671	5,072	0	0
Cohort start date before 2025-12-31	5,671	5,072	0	0
Remove individuals with a prior contraindication	5,426	4,869	245	203

Reason	Variable name			
	number of vaccine records	number of subjects	excluded records	excluded subjects
SIDIAP; vaccinated				
Only first or second dose vaccine between age of 9 months and 18 years	1,417,099	842,597		
Require not receiving another live-attenuated vaccine during -28 to -1 days prior or 1-28 days after vaccination	1,392,863	835,353	24,236	7,244
Require 0 intersections with cohort varicella. Intersection window: -90 to -1 days relative to cohort start date	1,352,780	834,629	40,083	724
Require 0 intersections with cohort MMRV. Intersection window: -90 to -1 days relative to cohort start date	1,352,780	834,629	0	0
Require minimum prior observation	1,234,501	774,642	118,279	59,987
Cohort start date after 2017-01-01	882,626	567,731	351,875	206,911
Cohort start date before 2025-12-31	882,626	567,731	0	0
Remove individuals with a prior contraindication	879,817	566,154	2,809	1,577

DK-DHR=Danish Data Health Registries; FinOMOP-THL=Finnish Care Register for Health Care; NLHR=Norwegian Linked Health Registry data; SIDIAP=The Information System for Research on Primary Care; MMRV=measles-mumps-rubella-varicella (vaccines)

9.2. Descriptive data

First dose vaccination

The characteristics of first dose vaccine recipients are presented in **Table 6**.

We identified a total of 11,398 eligible first-dose recipients in DK-DHR, 510,256 in FinOMOP-THL, 4,835 in NLHR, and 468,721 in SIDIAP.

Among the first-dose recipients, the median age at vaccination was 2 years, interquartile range (IQR) [1–4] years in DK-DHR, 1 [1–5] in FinOMOP-THL, 3 [1–8] in NLHR, and 1 [1–3] in SIDIAP.

The proportion of females was similar across all four data sources: 49.3% in DK-DHR, 49.0% in FinOMOP-THL, 50.7% in NLHR, and 48.5% in SIDIAP.

Most children received their first-dose varicella-containing vaccine as a monovalent varicella vaccine: 85.4% in DK-DHR, 86.4% in FinOMOP-THL, 91.3% in NLHR, and 86.3% in SIDIAP. Vaccine brand information was only available in DK-DHR and FinOMOP-THL, with Varivax being the most commonly recorded.

Most children had received one dose of MMR vaccine (median 1, IQR 1–1) before receiving the varicella-containing vaccine, except in NLHR.

Second dose vaccination

The characteristics of second dose vaccine recipients are presented in **Table 7**.

We identified a total of 1,325 second-dose vaccine recipients in DK-DHR, 254,016 in FinOMOP-THL, 591 in NLHR, and 411,096 in SIDIAP.

The median age at vaccination (IQR) was 2 [1–3] years in DK-DHR, 6 [6–7] in FinOMOP-THL, 3 [2–6] in NLHR, and 3 [3–10] in SIDIAP.

In DK-DHR and NLHR, most children received the second dose as a monovalent V vaccine (83.70% and 92.05%, respectively), whereas in FinOMOP-THL and SIDIAP most children received their second dose as MMRV (varicella vaccine administered with MMR on the same date or as tetravalent vaccine) (72.93% and

62.19%, respectively). In FinOMOP-THL, 71.80% received ProQuad. We were not able to determine whether children in SIDIAP received the vaccine as MMR+V or a quadrivalent MMRV product.

Table 6. Characteristics of first dose vaccine recipients.

Variable name	Variable level	Estimate name	Dose			
			1			
			Data source name			
			DK-DHR	FinOMOP-THL	NLHR	SIDIAP
Number subjects		N	11,398	510,256	4,835	468,721
Age		Median [Q25 – Q75]	2 [1 – 4]	1 [1 – 5]	3 [1 – 8]	1 [1 – 3]
Age group	0 to 1	N (%)	5,201 (45.63%)	265,922 (52.12%)	1,357 (28.07%)	301,598 (64.34%)
	2 to 6	N (%)	5,004 (43.90%)	171,768 (33.66%)	1,984 (41.03%)	74,857 (15.97%)
	7 to 11	N (%)	634 (5.56%)	58,114 (11.39%)	742 (15.35%)	73,020 (15.58%)
	12 to 17	N (%)	559 (4.90%)	14,452 (2.83%)	752 (15.55%)	19,246 (4.11%)
Sex	Female	N (%)	5,620 (49.31%)	250,018 (49.00%)	2,453 (50.73%)	227,234 (48.48%)
	Male	N (%)	5,778 (50.69%)	260,235 (51.00%)	2,382 (49.27%)	241,487 (51.52%)
	Unknown	N (%)		<5		
Cohort start date		Median [Q25 – Q75]	2022-05-04 [2020-10-28 – 2023-07-06]	2019-09-17 [2018-03-29 – 2022-02-24]	2021-02-15 [2019-07-02 – 2022-11-16]	2020-07-24 [2018-06-06 – 2022-10-24]
Vaccine type	MMRV	N (%)	1,667 (14.63%)	69,220 (13.57%)	422 (8.73%)	64,100 (13.68%)
	V	N (%)	9,731 (85.37%)	441,036 (86.43%)	4,413 (91.27%)	404,621 (86.32%)
Brand	Unknown (MMRV)	N (%)	377 (3.31%)	37 (0.01%)	422 (8.73%)	64,100 (13.68%)
	Unknown (V)	N (%)	642 (5.63%)	4,755 (0.93%)	4,413 (91.27%)	404,621 (86.32%)
	Varilrix (MMRV)	N (%)	223 (1.96%)	144 (0.03%)		
	Varilrix (V)	N (%)	1,409 (12.36%)	1,263 (0.25%)		

Variable name	Variable level	Estimate name	Dose			
			1			
			Data source name			
			DK-DHR	FinOMOP-THL	NLHR	SIDIAP
	Varivax (MMRV)	N (%)	1,067 (9.36%)	31,636 (6.20%)		
	Varivax (V)	N (%)	7,680 (67.38%)	435,018 (85.25%)		
	ProQuad (MMRV)	N (%)		37,403 (7.33%)		
Prior observation days		Median [Q25 – Q75]	782 [459 – 1,491]	642 [553 – 1,850]	1,326 [628 – 2,908]	482 [457 – 1,126]

DK-DHR=Danish Data Health Registries; FinOMOP-THL=Finnish Care Register for Health Care; NLHR=Norwegian Linked Health Registry data; SIDIAP=The Information System for Research on Primary Care. MMRV=varicella-containing vaccine, administered with MMR on the same date (MMR +V), or as tetravalent vaccine (MMRV); MMR=measles-mumps-rubella (vaccines); V=varicella (vaccines); Prior observation days=number of days since the individual entered the data source.

Table 7. Characteristics of second dose vaccine recipients.

Variable name	Variable level	Estimate name	Dose			
			2			
			Data source name			
			DK-DHR	FinOMOP-THL	NLHR	SIDIAP
Number subjects		N	1,325	254,016	591	411,096
Age		Median [Q25 – Q75]	2 [1 – 3]	6 [6 – 7]	3 [2 – 6]	3 [3 – 10]
Age group	0 to 1	N (%)	642 (48.45%)	613 (0.24%)	148 (25.04%)	525 (0.13%)
	2 to 6	N (%)	582 (43.92%)	187,729 (73.90%)	315 (53.30%)	278,225 (67.68%)
	7 to 11	N (%)	56 (4.23%)	28,167 (11.09%)	86 (14.55%)	94,131 (22.90%)
	12 to 17	N (%)	45 (3.40%)	37,507 (14.77%)	42 (7.11%)	38,215 (9.30%)
Sex	Female	N (%)	647 (48.83%)	125,310 (49.33%)	298 (50.42%)	199,563 (48.54%)
	Male	N (%)	678 (51.17%)	128,705 (50.67%)	293 (49.58%)	211,533 (51.46%)
	Unknown	N (%)		<5		

Variable name	Variable level	Estimate name	Dose			
			2			
			Data source name			
			DK-DHR	FinOMOP-THL	NLHR	SIDIAP
Cohort start date		Median [Q25 – Q75]	2022-08-01 [2020-08-22 – 2023-09-30]	2022-02-11 [2020-05-27 – 2023-05-29]	2021-09-02 [2020-02-04 – 2023-01-12]	2021-09-07 [2019-10-16 – 2023-05-04]
Vaccine type	MMRV	N (%)	216 (16.30%)	185,255 (72.93%)	47 (7.95%)	255,659 (62.19%)
	V	N (%)	1,109 (83.70%)	68,761 (27.07%)	544 (92.05%)	155,437 (37.81%)
Brand	Unknown (MMRV)	N (%)	21 (1.58%)	<5	47 (7.95%)	255,659 (62.19%)
	Unknown (V)	N (%)	47 (3.55%)	739 (0.29%)	544 (92.05%)	155,437 (37.81%)
	Varilrix (MMRV)	N (%)	19 (1.43%)	42 (0.02%)		
	Varilrix (V)	N (%)	220 (16.60%)	925 (0.36%)		
	Varivax (MMRV)	N (%)	176 (13.28%)	2,820 (1.11%)		
	Varivax (V)	N (%)	842 (63.55%)	67,097 (26.41%)		
	ProQuad (MMRV)	N (%)		182,390 (71.80%)		
Prior observation days		Median [Q25 – Q75]	732 [484 – 1,381]	2,240 [2,200 – 2,511]	1,214 [706 – 2,178]	1,169 [1,104 – 3,082]

DK-DHR=Danish Data Health Registries; FinOMOP-THL=Finnish Care Register for Health Care; NLHR=Norwegian Linked Health Registry data; SIDIAP=The Information System for Research on Primary Care. MMRV varicella-containing vaccine, administered with MMR on the same date (MMR +V), or as tetravalent vaccine (MMRV); MMR=measles-mumps-rubella (vaccines); V=varicella (vaccines); Prior observation days=number of days since the individual entered the data source.

9.3. Main results

9.3.1. Objective 1: Vaccine uptake and coverage

Table 8 and **Figure 2** present vaccine coverage and uptake rates across the four data sources from 2017 to 2024.

First dose vaccination

In FinOMOP-THL, since the introduction of the varicella vaccine in 2017, we observed a consistent increase in vaccine uptake and coverage. First-dose vaccine coverage among children aged <2 years increased from 12.87% in 2017 to 82.18% in 2024. In SIDIAP, where the vaccine was introduced in 2016, first-dose vaccine coverage among children aged <2 years was 70.06% in 2017 and 89.16% in 2024. Uptake and coverage in

DK-DHR and NLHR, where varicella vaccination is not included in the national vaccination programs, was substantially lower, below 5%.

Second dose vaccination

We assessed second-dose coverage at the age milestones of 7th, 13th, and 17th birthdays: In FinOMOP-THL, two-dose coverage by the 7th birthday increased from 6.64% in 2017 to 72.18% in 2024. In SIDIAP, two-dose coverage by the 7th birthday increased from 32.94% in 2017 to 83.64% in 2024. Second-dose coverage by the 13th and 17th birthdays was lower than the estimates at the 7th birthday. In 2024, in FinOMOP-THL, second-dose coverage by the 13th and 17th birthdays was 25.39% and 12.25%, respectively. In SIDIAP, second-dose coverage by the 13th and 17th birthdays in 2024 was 68.83% and 62.85%, respectively. Similarly to the first dose, second-dose uptake and coverage in DK-DHR and NLHR was low. Within each age milestone, the vaccine uptake of two-dose increased within FinOMOP-THL and SIDIAP.

Table 8. Yearly vaccine uptake and coverage.

Calendar year	Data source name							
	DK-DHR		FinOMOP-THL		NLHR		SIDIAP	
	Estimate name							
	Uptake	Coverage	Uptake	Coverage	Uptake	Coverage	Uptake	Coverage
First dose (2 birthday)								
2017	158	0.27%	7,112	12.87%	0	0.00%	33,178	70.06%
2018	231	0.38%	32,066	60.13%	105	0.19%	43,151	89.16%
2019	344	0.57%	37,161	72.93%	272	0.50%	42,838	89.54%
2020	459	0.75%	37,053	76.94%	314	0.59%	40,795	88.89%
2021	1,067	1.76%	37,013	80.10%	316	0.59%	38,719	87.51%
2022	1,352	2.23%	37,640	80.34%	269	0.52%	36,109	87.13%
2023	1,638	2.60%	40,954	82.14%	370	0.71%	37,156	89.30%
2024	1,485	2.96%	28,418	82.18%	<5	–	36,537	89.16%
Second dose (7 birthday)								
2017	57	0.09%	3,819	6.64%	0	0.00%	11,773	32.94%
2018	44	0.07%	5,791	10.19%	9	0.02%	11,916	32.41%
2019	79	0.13%	13,727	24.03%	54	0.10%	10,738	29.66%
2020	133	0.23%	26,048	45.87%	77	0.14%	10,390	26.03%
2021	284	0.49%	31,870	56.09%	142	0.26%	11,954	26.10%
2022	472	0.81%	35,736	64.46%	232	0.43%	32,052	63.58%
2023	867	1.40%	38,072	70.57%	339	0.67%	42,637	82.10%
2024	1,046	1.97%	28,634	72.18%	<5	–	43,174	83.64%
Second dose (13 birthday)								
2017	34	0.05%	888	1.51%	0	0.00%	11,069	42.65%
2018	31	0.05%	2,024	3.47%	<5	–	16,036	63.40%
2019	80	0.12%	4,699	7.94%	21	0.04%	17,393	64.06%
2020	148	0.22%	5,716	9.83%	40	0.07%	19,047	64.65%

Calendar year	Data source name							
	DK-DHR		FinOMOP-THL		NLHR		SIDIAP	
	Estimate name							
	Uptake	Coverage	Uptake	Coverage	Uptake	Coverage	Uptake	Coverage
2021	48	0.07%	7,208	12.41%	62	0.11%	20,846	64.39%
2022	69	0.11%	9,322	16.05%	92	0.16%	22,971	70.51%
2023	130	0.20%	12,591	21.68%	110	0.21%	25,196	70.47%
2024	113	0.21%	11,245	25.39%	<5	–	26,199	68.83%
Second dose (17 birthday)								
2017	18	0.03%	516	0.87%	0	0.00%	5,524	14.79%
2018	16	0.02%	729	1.25%	16	0.03%	5,955	17.27%
2019	31	0.05%	1,046	1.81%	33	0.06%	6,140	19.53%
2020	42	0.06%	1,348	2.31%	32	0.06%	7,865	26.70%
2021	60	0.09%	1,957	3.32%	54	0.09%	11,648	41.84%
2022	71	0.11%	3,238	5.56%	64	0.12%	16,574	60.95%
2023	129	0.19%	6,125	10.30%	72	0.14%	17,805	60.85%
2024	197	0.34%	5,494	12.25%	<5	–	19,810	62.85%

DK-DHR=Danish Data Health Registries; FinOMOP-THL=Finnish Care Register for Health Care; NLHR=Norwegian Linked Health Registry data; SIDIAP=The Information System for Research on Primary Care. "–": When the vaccine uptake is lower than 5, we did not report the vaccine coverage.

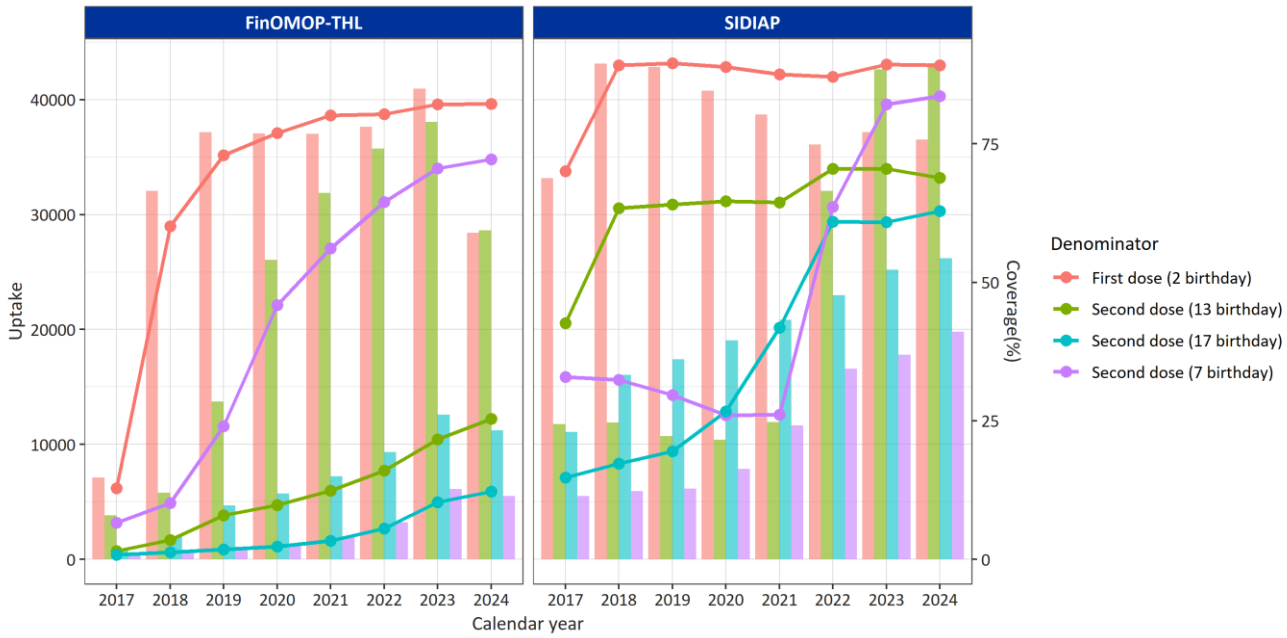

Figure 2. Vaccine uptake (bar plot, axis on the left) and coverage (line chart, axis on the right).

FinOMOP-THL=Finnish Care Register for Health Care; SIDIAP=The Information System for Research on Primary Care.

9.3.2. Objective 2. Incidence rates of encephalitis

Background incidence rates of encephalitis

We estimated the background IRs of encephalitis (both definitions, see **Section 8.6.2.**) per 100,000 person-years.

The background IRs for encephalitis (any) over the entire study period were 6.42 (95% CI 5.90–6.98) in DK-DHR, 13.75 (95% CI 12.94–14.60) in FinOMOP-THL, 7.46 (95% CI 6.85–8.12) in NLHR, and 4.68 (95% CI 4.21–5.18) in SIDIAP.

Background IRs for encephalitis without a specific cause were 4.91 (95% CI 4.45–5.40), 12.04 (95% CI 11.28–12.84), 5.67 (95% CI 5.13–6.24), and 3.19 (95% CI 2.81–3.62) in DK-DHR, FinOMOP-THL, NLHR, and SIDIAP, respectively.

Table 9 presents the background IRs of encephalitis by calendar year. Within each data source, IRs were stable during the study period, with slightly lower estimates reported during 2020–2021, reflecting reduced healthcare access during the pandemic.

Figure 3 shows the IRs stratified by age group. In DK-DHR, FinOMOP-THL, and NLHR, IRs were similar across all age groups during the study period. In SIDIAP, we observed higher IRs in the younger age groups in most of the years.

Table 9. Background incidence rates of encephalitis by calendar year.

Incidence start date	Data source name											
	DK-DHR			FinOMOP-THL			NLHR			SIDIAP		
	Estimate name											
	Outcome (N)	Incidence 100,000 person-years [95% CI]	Person-years	Outcome (N)	Incidence 100,000 person-years [95% CI]	Person-years	Outcome (N)	Incidence 100,000 person-years [95% CI]	Person-years	Outcome (N)	Incidence 100,000 person-years [95% CI]	Person-years
Encephalitis (any)												
2017-01-01	79	7.18 (5.68 – 8.94)	1,100,922.38	148	14.32 (12.11 – 16.83)	1,033,221.46	46	4.32 (3.16 – 5.76)	1,065,489.09	41	4.11 (2.95 – 5.57)	998,310.96
2018-01-01	69	6.28 (4.89 – 7.95)	1,098,705.19	155	15.09 (12.81 – 17.66)	1,026,971.94	77	7.21 (5.69 – 9.02)	1,067,476.27	67	6.74 (5.22 – 8.56)	994,257.81
2019-01-01	84	7.67 (6.12 – 9.50)	1,095,104.33	147	14.44 (12.20 – 16.97)	1,018,226.09	82	7.71 (6.13 – 9.57)	1,063,970.71	38	3.83 (2.71 – 5.26)	991,181.86
2020-01-01	62	5.66 (4.34 – 7.26)	1,095,333.41	115	11.37 (9.39 – 13.65)	1,011,440.91	80	7.52 (5.96 – 9.36)	1,063,691.98	28	2.82 (1.87 – 4.08)	992,864.15
2021-01-01	56	5.14 (3.88 – 6.67)	1,089,708.74	119	11.91 (9.87 – 14.25)	999,061.64	72	6.83 (5.34 – 8.60)	1,054,711.05	35	3.57 (2.49 – 4.97)	980,102.08
2022-01-01	68	6.26 (4.86 – 7.93)	1,086,772.00	137	13.84 (11.62 – 16.36)	990,232.56	77	7.34 (5.79 – 9.18)	1,048,872.87	47	4.87 (3.58 – 6.48)	964,856.32
2023-01-01	70	6.44 (5.02 – 8.14)	1,086,525.63	153	15.62 (13.24 – 18.30)	979,436.71	114	11.66 (9.62 – 14.00)	978,035.45	60	6.28 (4.79 – 8.08)	956,077.78
2024-01-01										50	5.27 (3.91-6.95)	948,552.13
Encephalitis (unspecified/vaccination)												

Incidence start date	Data source name											
	DK-DHR			FinOMOP-THL			NLHR			SIDIAP		
	Estimate name											
	Outcome (N)	Incidence 100,000 person-years [95% CI]	Person-years	Outcome (N)	Incidence 100,000 person-years [95% CI]	Person-years	Outcome (N)	Incidence 100,000 person-years [95% CI]	Person-years	Outcome (N)	Incidence 100,000 person-years [95% CI]	Person-years
2017-01-01	60	5.45 (4.16 – 7.02)	1,100,927.28	135	13.07 (10.96 – 15.46)	1,033,224.80	32	3.00 (2.05 – 4.24)	1,065,493.04	26	2.60 (1.70 – 3.82)	998,320.78
2018-01-01	44	4.00 (2.91 – 5.38)	1,098,710.98	141	13.73 (11.56 – 16.19)	1,026,975.22	64	6.00 (4.62 – 7.66)	1,067,479.25	49	4.93 (3.65 – 6.52)	994,265.32
2019-01-01	64	5.84 (4.50 – 7.46)	1,095,109.84	136	13.36 (11.21 – 15.80)	1,018,228.51	65	6.11 (4.72 – 7.79)	1,063,974.99	28	2.83 (1.88 – 4.08)	991,184.50
2020-01-01	49	4.47 (3.31 – 5.91)	1,095,336.73	102	10.09 (8.22 – 12.24)	1,011,444.43	60	5.64 (4.30 – 7.26)	1,063,696.79	18	1.81 (1.07 – 2.87)	992,867.62
2021-01-01	39	3.58 (2.54 – 4.89)	1,089,712.53	101	10.11 (8.23 – 12.28)	999,066.30	49	4.65 (3.44 – 6.14)	1,054,716.83	22	2.24 (1.41 – 3.40)	980,106.72
2022-01-01	54	4.97 (3.73 – 6.48)	1,086,775.80	120	12.12 (10.05 – 14.49)	990,236.50	61	5.82 (4.45 – 7.47)	1,048,876.51	35	3.63 (2.53 – 5.04)	964,861.46
2023-01-01	56	5.15 (3.89 – 6.69)	1,086,528.72	125	12.76 (10.62 – 15.21)	979,442.42	85	8.69 (6.94 – 10.75)	978,041.54	42	4.39 (3.17 – 5.94)	956,083.23
2024-01-01										30	3.16 (2.13 – 4.52)	948,558.13

DK-DHR=Danish Data Health Registries; FinOMOP-THL=Finnish Care Register for Health Care; NLHR=Norwegian Linked Health Registry data; SIDIAP=The Information System for Research on Primary Care.

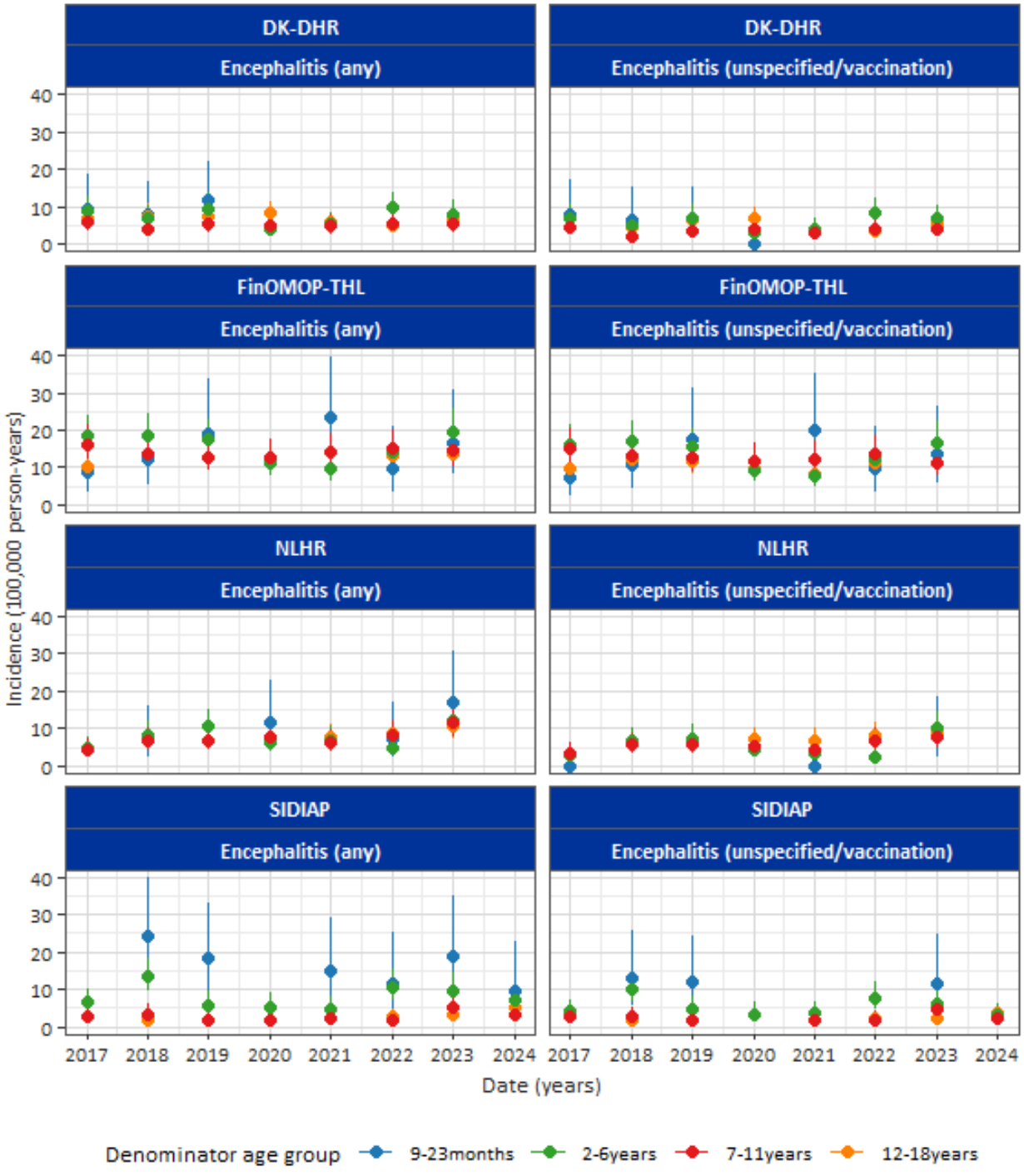

Figure 3. Background incidence rates stratified by age groups.

DK-DHR=Danish Data Health Registries; FinOMOP-THL=Finnish Care Register for Health Care; NLHR=Norwegian Linked Health Registry data; SIDIAP=The Information System for Research on Primary Care.

Incidence rates of Encephalitis after varicella infection

We estimated the IRs of encephalitis during the 28 days after varicella infection. During the study period, 8 encephalitis cases were identified during the 28-day period in DK-DHR, 8 cases were identified in FinOMOP-THL, 9 cases were identified in NLHR, and less than 5 in SIDIAP. The overall IRs of encephalitis (any) per 100,000 person-years were 3,369. (95% CI 1,454.50–6,638.28) in DK-DHR, 1,303. (95% CI 562.84–2,568.80) in FinOMOP-THL, and 216. (95% CI 98.78–410.08) in NLHR.

Table 10. Incidence rates of encephalitis after varicella infection.

Data source name							
DK-DHR		FinOMOP-THL		NLHR		SIDIAP	
Outcome (N)	Incidence per 100,000 person-years [95% CI]	Outcome (N)	Incidence per 100,000 person-years [95% CI]	Outcome (N)	Incidence per 100,000 person-years [95% CI]	Outcome (N)	Incidence per 100,000 person-years [95% CI]
Encephalitis (any)							
8	3,369 (1,454.50 – 6,638.28)	8	1,303 (562.84 – 2,568.80)	9	216 (98.78 – 410.08)	<5	–
Encephalitis (unspecific/vaccination)							
8	3,368 (1,454.24 – 6,637.13)	8	1,303 (562.83 – 2,568.72)	9	216. (98.78 – 410.08)	<5	–

DK-DHR=Danish Data Health Registries; FinOMOP-THL=Finnish Care Register for Health Care; NLHR=Norwegian Linked Health Registry data; SIDIAP=The Information System for Research on Primary Care. "–": When the event number is lower than 5, we did not report incidence rate.

9.3.3. Objective 3. Association between varicella infection and encephalitis

Table 11 presents the association between encephalitis and varicella infection in the main SCRI analysis. Across the four data sources, 3,010 (DK-DHR), 7,758 (FinOMOP-THL), 53,050 (NLHR), and 36,882 (SIDIAP) individuals met the inclusion criteria of having a diagnosis of varicella during the study period. Of those, less than five individuals had a record of encephalitis within either the risk or the control window.

In NLHR, a total of 6 individuals were included for the analysis of Objective 3. The age- and season-adjusted IRR was 6.39 (95% CI 0.69–58.88). While the CI is large (due to small sample size), this point estimate is pointing towards a potential positive association between varicella infection and encephalitis.

In FinOMOP-THL, zero individuals were identified. Less than five individuals were identified in DK-DHR and SIDIAP, and IRRs could not be estimated.

Table 11. Association between varicella infection and encephalitis.

CDM name	Variable name				
	Number subjects	Control window	Risk window	Age model	Age and season model
	N	Time (days)	Time (days)	IRR [95%CI]	IRR [95%CI]
Encephalitis(any)					
NLHR	6	240	138	6.83 [0.76 – 61.14]	6.39 [0.69 – 58.88]
Encephalitis (unspecified/vaccination)					
NLHR	6	240	138	6.83 [0.76 – 61.14]	6.39 [0.69 – 58.88]

DK-DHR=Danish Data Health Registries; FinOMOP-THL=Finnish Care Register for Health Care; NLHR=Norwegian Linked Health Registry data; SIDIAP=The Information System for Research on Primary Care; IR=Incidence Rate; IRR=Incidence Rate Ratio

9.3.4. Objective 4. Association between V/MMRV vaccines and encephalitis

A total of 4,336 (DK-DHR), 742,810 (FinOMOP-THL), 2,551 (NLHR), and 843,781 (SIDIAP) doses of varicella vaccine were included in the analysis. Among them, the number of children who received the vaccine and experienced the study outcome within the exposure/control window were more than 5 in only FinOMOP-THL and SIDIAP, allowing for IRRs estimates in only these data sources. (**Table 12**)

In FinOMOP-THL, 15 individuals were included in the first-dose analysis (D1 (any)), with 8 events observed in the control window, and 7 events observed in the risk window. In the second-dose analysis (D2 (any)), 7 events were observed in the control window, and less than 5 events were observed in the risk window.

In SIDIAP, 13 individuals were included in the first-dose analysis, with 8 events observed in the control window, and 5 events observed in the risk window. In the second-dose analysis, we observed less than 5 events in both the control and the risk windows.

Among first-dose vaccine recipients (D1(any)), the age- and season-adjusted IRR of encephalitis (any) were 1.55 (95% CI 0.53–4.50) in FinOMOP-THL and 1.01 (95% CI 0.20–5.04) in SIDIAP. The meta-analysed estimate from these two data sources was 1.36 (95% CI 0.56–3.31).

Among the children who received the monovalent varicella vaccine as the first dose (D1 (V)), adjusted IRR of encephalitis (any) was 1.42 (95% CI 0.44–4.56) in FinOMOP-THL, 0.87 (95% CI 0.13–5.68) in SIDIAP, and the meta-analysed estimate was 1.24 (95% CI 0.46–3.34).

Among second-dose recipients (D2 (any)), the age- and season-adjusted IRR was 0.24 (95% CI 0.02–3.05) in FinOMOP-THL and 0.49 (95% CI 0.05–4.76) in SIDIAP. The meta-analysed estimate from these two data sources was 0.36 (95% CI 0.07–1.95).

The IRR among those who received MMRV as a second-dose (D2 (MMRV)) was only computable in FinOMOP-THL, with an estimate of 0.24 (95% CI 0.02–3.05).

Table 12. Association between V/MMRV vaccines and encephalitis, by vaccine dose.

CDM name	Exposure	Variable name							
		Control window			Risk window			Age model	Age and season model
		Event	Time (days)	IR	Event	Time (days)	IR	IRR [95%CI]	IRR [95%CI]
Encephalitis (any)									
FinOMOP-THL	D1 (any)	8	600	0.01	7	345	0.02	1.48 [0.54 – 4.09]	1.55 [0.53 – 4.50]
	D1 (V)	7	520	0.01	6	299	0.02	1.46 [0.49 – 4.36]	1.42 [0.44 – 4.56]
	D2 (any)	7	320	0.02	<5	184	–	0.24 [0.03 – 1.98]	0.24 [0.02 – 3.05]
	D2 (MMRV)	5	240	0.02	<5	138	–	0.34 [0.04 – 2.92]	0.24 [0.02 – 3.05]
SIDIAP	D1 (any)	8	520	0.02	5	299	0.02	1.07 [0.35 – 3.26]	1.01 [0.20 – 5.04]
	D1 (V)	7	440	0.02	<5	253	–	0.98 [0.29 – 3.33]	0.87 [0.13 – 5.68]
	D2 (any)	<5	200	–	<5	115	–	0.43 [0.05 – 3.82]	0.49 [0.05 – 4.76]
Meta-analysis	D1 (any)							1.28 [0.60 – 2.71]	1.36 [0.56 – 3.31]
	D1 (V)							1.22 [0.54 – 2.77]	1.24 [0.46 – 3.34]
	D2 (any)							0.32 [0.07 – 1.45]	0.36 [0.07 – 1.95]
Encephalitis (unspecified/vaccination)									
FinOMOP-THL	D1 (any)	6	480	0.01	6	276	0.02	1.71 [0.55 – 5.30]	1.83 [0.48 – 6.97]
	D1 (V)	5	440	0.01	6	253	0.02	2.05 [0.63 – 6.72]	2.29 [0.58 – 9.05]
	D2 (any)	6	280	0.02	<5	161	–	0.28 [0.03 – 2.37]	0.46 [0.04 – 5.02]
	D2 (MMRV)	<5	200	–	<5	115	–	0.43 [0.05 – 3.82]	0.46 [0.04 – 5.02]
SIDIAP	D1 (any)	<5	200	–	<5	115	–	1.14 [0.19 – 6.82]	0.99 [0.07 – 13.18]
Meta-analysis	D1 (any)							1.52 [0.58 – 3.96]	1.61 [0.49 – 5.28]

DK-DHR=Danish Data Health Registries; FinOMOP-THL=Finnish Care Register for Health Care; NLHR=Norwegian Linked Health Registry data; SIDIAP=The Information System for Research on Primary Care; IR=Incidence Rate; IRR=Incidence Rate Ratio; D1=Dose 1; D2=dose 2; MMRV=measles-mumps-rubella-varicella (vaccines);MMR=measles-mumps-rubella (vaccines); V=varicella (vaccines). "–": When the event number is lower than 5, we did not report incidence rate.

9.4. Sensitivity analyses

For the analyses of Objectives 3 and 4, five sensitivity analyses were conducted, as shown in **Table 4**. The full results of the sensitivity analyses are presented in **Annex V**. This section reports the results of the sensitivity analyses for those data sources where the main analysis could be conducted, which are NLHR for Objective 3 and FinOMOP-THL and SIDIAP for Objective 4.

Objective 3: Sensitivity analyses in NLHR

Figure 4 summarises the results for these analyses. In the sensitivity analyses where we included an extra pre-index period into the control window (sensitivity analysis 2), the adjusted IRR was 12.40 (95% CI 1.35–114.03) for encephalitis (any) and 12.40 (95% CI 1.35–114.03) for the restricted definition of encephalitis (unknown/vaccination-related codes).

When using a risk window of 15–38 days post infection to account for the incubation period (sensitivity analysis 3), the adjusted IRR was 6.40 (95% CI 1.14–35.93) for encephalitis (any) and 6.40 (95% CI 1.14–35.93) for the restricted definition.

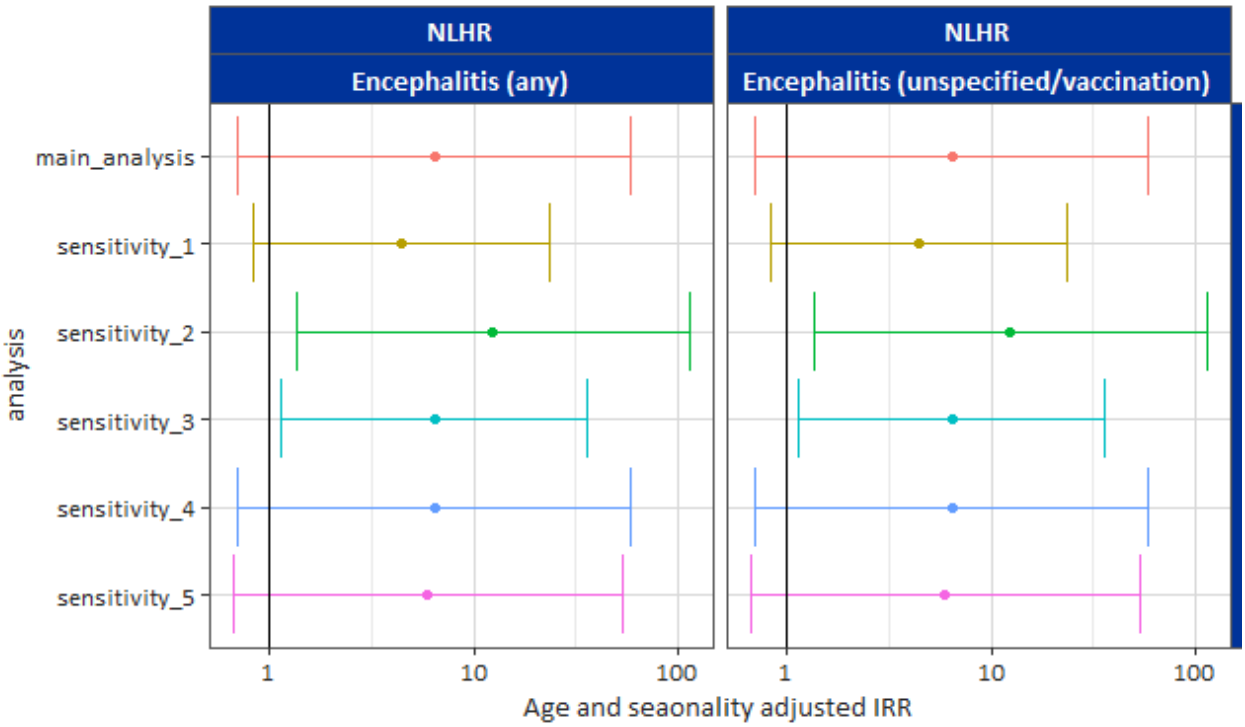

Figure 4. Sensitivity analyses of Objective 3.

NLHR=Norwegian Linked Health Registry data; IRR=Incidence Rate Ratio.

Objective 4: Sensitivity analyses in FinOMOP-THL, SIDIAP

In the sensitivity analyses of Objective 4, the results were consistent with the main analysis, as shown in **Figure 5**.

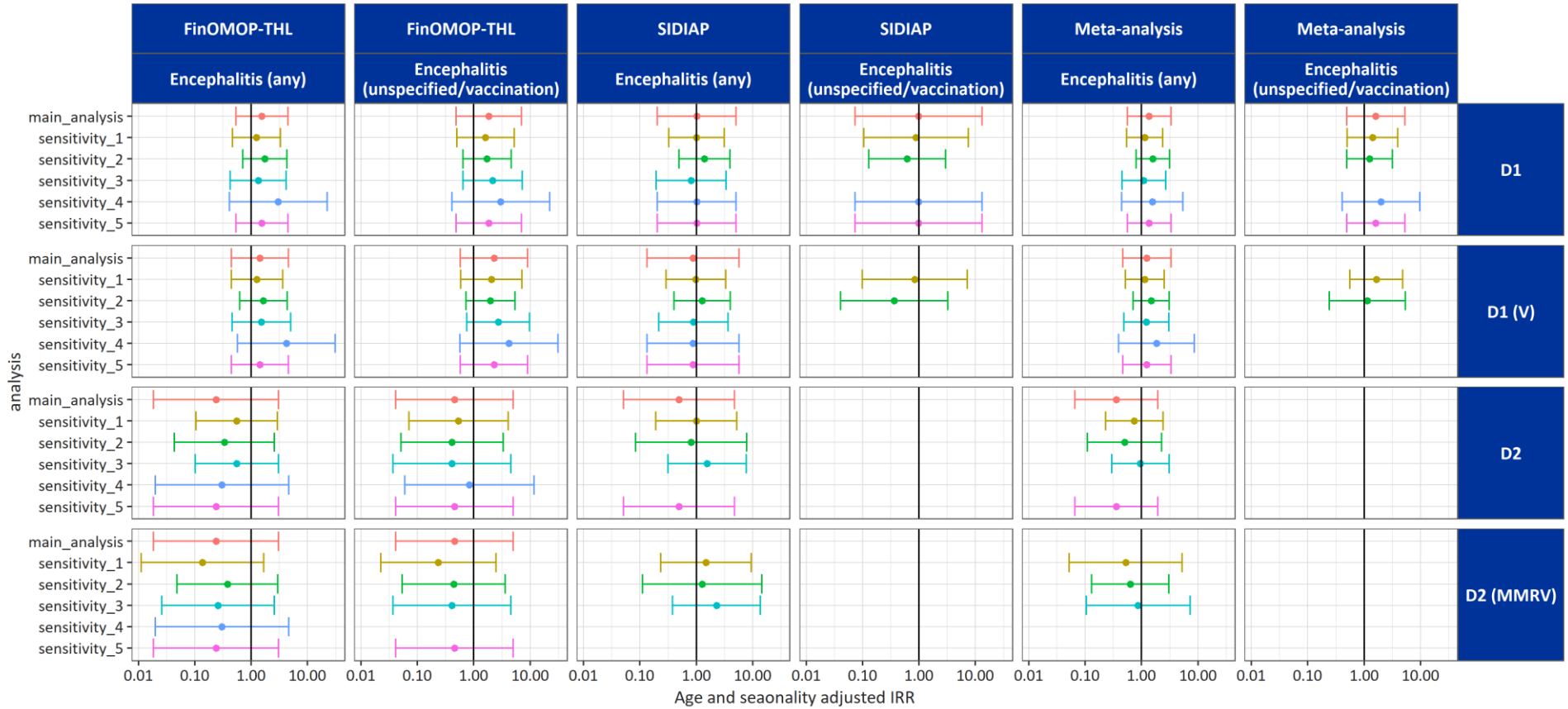

Figure 5. Sensitivity analyses of Objective 4.

FinOMOP-THL=Finnish Care Register for Health Care; SIDIAP=The Information System for Research on Primary Care; IRR=Incidence Rate Ratio; MMRV=measles-mumps-rubella-varicella (vaccines); MMR=measles-mumps-rubella (vaccines); V=varicella (vaccines); D1=dose 1; D2= dose 2.

10. DISCUSSION

10.1. Key results

Across four large European healthcare data sources (DK-DHR, FinOMOP-THL, NLHR, and SIDIAP), we estimated varicella vaccine uptake and coverage, background IRs of encephalitis, the association between varicella infection and encephalitis, and the association between varicella vaccination and encephalitis. Among the four European countries included, Finland and Spain recommend varicella vaccination in the national immunisation schedule.

Since the introduction of universal varicella vaccination in Finland in 2017, vaccine uptake and coverage increased steadily, with first-dose coverage among children aged <2 years rising from 12.87% in 2017 to 82.18% in 2024. In Spain (SIDIAP), first-dose coverage was already high in 2017 (70.06%) and remained stable, reaching 89.16% in 2024. Two-dose coverage by age 7 increased markedly in both countries over time, although coverage by ages 13 and 17 remained lower.

In Finland and Catalonia (Spain), most children received their first dose vaccine at age of 1, in line with the recommendation schedule. Median age of second dose was 6 in Finland and 3 in Spain, again in line with the recommendation schedule (at 6 in Finland and between 3 and 4 in Spain).

Background IRs of encephalitis were low and generally stable throughout the study period in all data sources, with slightly lower rates observed during 2020–2021, likely reflecting reduced healthcare utilisation during the COVID-19 pandemic and interruptions in infection transmission pathways.[18] Age-stratified analyses showed lower rates in younger age groups.

Encephalitis occurring within 28 days after varicella infection was rare. In the SCRI analyses evaluating the association between varicella infection and encephalitis, we were only able to generate IRRs in NLHR. While the IRR suggested an increased risk (6.39, 95% CI 0.69–58.88), it was based on small numbers.

In the SCRI analysis evaluating the association between varicella vaccination and encephalitis, only Finland and Spain had sufficient number of cases for estimation. CIs were wide, suggesting no increased risk after both the first (IRR 1.24, 95% CI 0.46–3.34) and the second dose (IRR 0.36, 95% CI 0.07–1.95). Sensitivity analyses results were in line with results observed in the main analysis.

Overall, encephalitis following varicella vaccination was rare, and no consistent evidence of increased risk was observed, whereas varicella infection may be positively associated with encephalitis, but estimates are imprecise and should be interpreted cautiously.

10.2. Strengths and limitations of the research methods

Data

The study was informed by routinely collected health care data; as such, data quality issues and missingness of information must be considered. In particular, mild forms of varicella infection might be treated at home without children and adolescents being presented to general practitioners (GPs) or paediatricians. In such cases, the data would potentially miss records of varicella infections, and the study population of children and adolescents eligible for varicella vaccination may include children and adolescents with (undocumented) varicella infection. This could potentially underestimate vaccine uptake and vaccine coverage. Likewise, under-reported (milder) varicella infections in the data sources could have potentially led to an overestimation of incidence rates of encephalitis following varicella infection.

The DK-DHR data source does not include primary care records, therefore only severe (hospitalised) cases of varicella were captured in this data source.

Varicella vaccination is included in the national immunisation schedule in Finland and Spain, with vaccination records of high completeness in the Finnish and Spanish data sources included in this study.

The date of birth is available in DK-DHR, FinOMOP-THL, and NLHR. In SIDIAP only the month/year of birth are recorded for privacy reasons. We used the first day of the respective month of birth as a proxy.

In addition, the documentation of comorbidities (leading to contraindication for vaccination with live-attenuated vaccines), necessary for individual-level vaccine recipient characterisation and used as exclusion criteria in this study, may vary across data sources.

Methods

Vaccine uptake and coverage

We estimated vaccine uptake and coverage in children and adolescents eligible for vaccination following the commonly used definitions (i.e. the denominator only includes children and adolescents "susceptible" to varicella, that is, without a record of varicella diagnosis). This might lead to higher rates compared to figures published by public health agencies/authorities in the respective age groups.[19,20] In addition, the vaccine coverage calculation is anchoring the day of birth, which implicitly required the children to survive to that age milestone to be included. Therefore, if a child died before the milestone birthday, the child would not be included in the analysis.

Crude incidence and background rates

IRs estimated in this study were stratified by age group. However, no standardisation for age and sex was done, as the age bands available for the European Standard Populations (reference population for standardisation) do not match the age bands of interest for this study (e.g. 9 months – 2 years). Therefore, these rates should not be used to calculate absolute risk differences, as they do not account for differences in the underlying populations, which would lead to confounded estimates.

While observed-to-expected analyses based on age-sex standardised background IRs are often used in pharmacovigilance, for our research question this approach would not adequately control for confounding. Moreover, previous methodological work assessing bias and precision of background rates comparison methods for vaccine safety monitoring showed that, despite good discrimination, most analyses had a tendency to overestimate risks, with 20% – 100% type 1 error, but low (0% – 20%) type 2 error in large data sources.[21] In the current study, we used background IRs of encephalitis and crude IRs of encephalitis after varicella infection to contextualise the IRs findings (pointing towards "relative risk") from SCRI analyses in the light of the ("absolute") event rates per 100,000 person years.

Self-controlled risk interval design

As described in **Section 8.1.2.** above, the SCRI study design has been developed to assess vaccine safety when suitable (unvaccinated) controls are difficult to identify.[6] The advantage of the self-controlled design is that it controls for time-stable confounding.

Importantly, self-controlled designs aim to answer the question of whether the exposure is associated with the outcome in the specific time window. This needs to be taken into account when interpreting the results.

The self-controlled design is subject to specific assumptions, including: "event-dependent exposure", [16] that subsequent exposures should not be affected by previous events; and "event-dependent observation periods", that the length of observation period should not be affected by previous events. If the event increases the probability of death, then there is a chance that observation periods could be shorter as a direct result of the event. For the current study, the first assumption could have been violated, as an encephalitis event may lead to delay vaccination. We conducted several sensitivity analyses to test different control windows, as well as restricting to the first ever encephalitis diagnosis.

The SCRI design is restricted to the study population who received the vaccine of interest, as well as having the study outcome. In the preliminary feasibility assessment, we saw that encephalitis records were rare in the paediatric population, which may result in an underpowered estimate in our analyses.

10.3. Interpretation

Uptake and coverage

Data from the Finland national vaccination register dashboard showed that first-dose varicella vaccine coverage among children born in 2017 was 80.9%, ranging from 56.2% in Ostrobothnia to 87.0% in North Savo. Coverage increased to 84.2–88.5% among children born in 2018–2022.[19] Second-dose coverage was not available from the dashboard.

A previous study using the same Finnish data source reported overall coverage of 87.0% for children born in 2016 and 85.1–86.9% for those born in 2017-2020.[11] Second-dose coverage was 58% in the 2016 cohort, with no data available for later cohorts at the time of publication (2023). Catch-up vaccination coverage declined with earlier birth cohorts, with first-dose coverage ranging from 82% (2015 cohort) to 18% (2006 cohort) and second-dose coverage from 64% to 10%, respectively.

Differences between our estimates and previous reports likely reflect different coverage definitions. Our estimates were based on vaccination by a specified age within a calendar year, whereas previous studies used birth-cohort definitions. Children vaccinated after age of two and those receiving other live-attenuated vaccines around the index vaccination were excluded to align with the Summary of Product Characteristics (SmPC) recommendations and to define a population eligible for vaccination under routine programme conditions. However, applying these criteria led to the exclusion of a proportion of children, which impacted in particular the Danish and Norwegian data sources. This should be taken into account when interpreting the results, as the estimates may differ from those reflecting broader vaccination practices.

Based on data from the Spanish Ministry of Health Vaccination Information System (SIVAMIN),[20] varicella vaccine coverage in Spain in 2024 was 96.9% for the first dose and 92.3% for the second dose. Among adolescents, defined as those aged 12 years old, vaccine coverage was 20.77% in 2024. Coverage for the first and second doses was relatively consistent across regions, whereas adolescent coverage varied substantially across the country. In 2024, adolescent coverage ranged from 1.63% in Ceuta to 59.91% in Castile–La Mancha. In Catalonia, first- and second-dose varicella vaccine coverage in 2024 was 95.96% and 90.96%, respectively, while adolescent coverage was 17.79%.

Vaccine coverage estimates from the current study were slightly lower than publicly reported figures. In 2024, we estimated first-dose coverage by the second birthday and second-dose coverage by the seventh birthday to be 89.16% and 83.64%, respectively. These differences are likely attributable to the more restrictive definition of eligible vaccination used in our analyses, including the exclusion of doses administered within 28 days before or after another live-attenuated vaccine, as well as the incorporation of age-specific criteria in the coverage definitions.

In both the Finnish data and the Spanish data, the second-dose coverage was lower when using a higher age milestone (e.g. by 17th birthday vs. by 7th birthday). This was because that the denominator of vaccine coverage was the number of children who reached the age milestone. With the higher age milestone, we included children who were born before the introduction of these vaccines into the national schedule. Therefore, they are less likely to have received the two doses according to the current schedule.

Encephalitis background incidence rates

In this study, we estimated background IRs of encephalitis using two outcome definitions across four European data sources. Overall, the crude rates were broadly comparable across countries, although some variation was observed, which is likely attributable to differences in the epidemiology of viruses with the

potential of causing encephalitis, healthcare systems, coding practices, and data capture across primary and secondary care settings. Rates of encephalitis without a specified cause were generally lower than those for any encephalitis, reflecting the more restrictive case definition.

Background rates within each data source remained relatively stable over the study period. The slightly lower rates observed during 2020 and 2021 are consistent with findings from other studies and are likely explained by reduced healthcare utilisation and changes in care-seeking behaviour during the COVID-19 pandemic, and interruptions in infection transmission pathways.[18] Age-stratified analyses showed consistently lower encephalitis rates among younger age groups across all data sources. This pattern is consistent with previously reported age distributions of encephalitis and provides reassurance that the observed rates reflect expected epidemiological patterns.

Varicella infection and risk of encephalitis

Varicella is an acute infectious disease caused by varicella-zoster virus, with primary infection results in varicella (chickenpox). Varicella infection can occasionally lead to severe neurological complications, including encephalitis. It has been estimated that encephalitis occurs approximately 1 per 30,000 – 50,000 varicella cases.[22] This condition can affect adults and infants and is more common and severe in those who are immunocompromised.[22–24] Another review of infectious encephalitis estimated that the annual incidence of infectious encephalitis due to varicella zoster virus was 0.2–0.4 per 100,000.[25]

In the NLHR data, we identified only a very small number of children with varicella infection and encephalitis (6 in the main analysis) eligible for inclusion in the SCRI analysis. As a result, the analysis was underpowered and provided wide CIs. Nevertheless, the point estimate of the IRR was high, suggesting a potential increased risk of encephalitis following varicella infection, although this finding should be interpreted with caution.

In the DK-DHR data source, only secondary care data were available for analysis. Given that varicella is more commonly diagnosed and managed in primary care settings, or even not reported to the GP, this limitation has likely led to underestimation of varicella infections, resulting in a potential overestimation of incidence rates of encephalitis following varicella infection.

Conversely, the very limited number of varicella infection cases identified in the FinOMOP-THL and SIDIAP data may reflect genuinely low rates of varicella infection in regions where the varicella vaccine has been incorporated into the national immunisation programme. For example, in Finland, a previous study found that the incidence rate of varicella cases had decreased by more than 90% since the introduction of the varicella vaccination programme.[11] Earlier data from Spain also showed that in the regions where varicella vaccine was included in routine vaccination programmes, a reduction of 78% in the hospitalisation rate due to varicella was observed.[26] However, the assessment on effectiveness of the varicella vaccination campaigns to reduce varicella infections was outside the scope of the our study.

Future studies could address these limitations by extending the study period to include the years prior to the introduction of the varicella vaccination programme, thereby increasing the number of observable cases and improving statistical power.

Safety of varicella vaccination and encephalitis

A number of countries have implemented universal childhood varicella vaccination programmes over the past 30 years. However, strategies differ in terms of the number of doses, type of vaccine(s) recommended, age at vaccination, and interval between doses.[27] While the effectiveness of the varicella vaccine in reducing varicella incidence and varicella-related hospitalisation has been documented,[11,28,29] more evidence on the real-world safety of varicella vaccines, particularly with respect to rare neurological outcomes such as encephalitis, is needed.

In an overview paper including 17 reviews of varicella vaccine safety among children aged 9 months to 6 years, the authors suggested that mild local and systemic reactions were relatively common, whiles serious adverse reactions were rare. Despite the methodological limitations of review studies included in the overview, such as deemed 'critically low' quality due to lack of pre-specified study protocol, non-comprehensive search strategies, lack of details in reasons for exclusion, and lack of risk of bias assessment, the authors concluded that there was substantial evidence underpinning the safety of varicella vaccination.[30,31] Importantly, encephalitis and other severe neurological complications were reported very infrequently, with no consistent evidence suggesting a causal association with vaccination.

A study analysed 22 years of global post-marketing surveillance data for VARIVAX vaccine, using passive safety reports maintained by the vaccine manufacture, and found that serious events were extremely rare with no new safety signals.[32]

A study conducted in the US study using the Vaccine Adverse Event Reporting System (VAERS) reported that during the period 2006–2020, 40,684 adverse event reports were received after over 132 million doses distributed.[1] Among those, the reporting rate of encephalitis, calculated as per 100,000 doses of varicella vaccines distributed, was 0.06 for both the single antigen varicella vaccine and the quadrivalent measles, mumps, rubella, varicella vaccine.

One study used the self-controlled risk interval design in administrative claims data from Taiwan and studied multiple outcomes after varicella vaccine during 2004 to 2014. The study included over 1 million of children who received the vaccine (single dose) and found no increased risk of encephalitis during the 1–42 days post-varicella vaccination, with an adjusted IRR of 1.00 (95% CI: 0.62–1.60).[4]

In our study, analyses stratified by vaccine dose (first dose, second dose) were underpowered; nevertheless, we observed a lower point estimate of the IRR following the second dose (IRR 0.36, 95% CI 0.07–1.95) compared with the first dose (IRR 1.24, 95% CI 0.46–3.34).

From a public health perspective, the findings from this study provided additional real-world evidence on the safety of varicella vaccination in routine immunisation programmes. Although the analyses were underpowered to detect a rare adverse event such as encephalitis, we did not find evidence of a positive association between varicella vaccination and encephalitis across the included data sources. Together with the well-documented available evidence on the effectiveness of varicella vaccines, these findings may be informative for immunisation programmes evaluation, while underscoring the importance of pharmacovigilance to identify rare outcomes.

10.4. Generalisability

This study included data sources from four European countries: Denmark, Finland, Norway, and Spain, two of which had incorporated varicella-containing vaccines into their national immunisation programmes. As the analyses were based on populations captured within these specific data sources, the results reflect only the included populations and may not be generalisable to other countries or settings. In addition, substantial heterogeneity across countries is expected due to differences in vaccination schedules, recommendations, and healthcare systems.

The use of electronic health records and national registries also entails inherent limitations, as these data were collected primarily for clinical and administrative purposes rather than for research. Furthermore, information on vaccine brand was only available in some data sources; therefore, brand-specific results could not be reported in the SCRI analysis. As a consequence, potential differences in risk profiles between vaccine brands could not be evaluated and may have been obscured in the pooled estimates.

11. CONCLUSION

Overall, encephalitis following varicella vaccination was rare, and meta-analysed estimates did not show significant associations between varicella vaccination and encephalitis, while suggesting a role for varicella infection in the occurrence of encephalitis.

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13. ANNEXES

ANNEX I. Description of data sources

Danish Data Health Registries (DK-DHR)

Danish health data (DK-DHR) is collected, stored, and managed in national health registers at the Danish Health Data Authority, and covers the entire population which makes it possible to study the development of diseases and their treatment over time. There are no gaps in terms of gender, age, and geography in Danish health data due to mandatory reporting on all patients from cradle to grave, in all hospitals and medical clinics. Personal identification numbers enable linking of data across registers, so DK-DHR has data on all Danes throughout their lives, regardless of whether they have moved around the country. High data quality due to standardization, digitization, and documentation means that Danish health data is not based on interpretation. The Danish Health Data Authority is responsible for the national health registers and for maintaining and developing standards and classifications in the Danish healthcare system. Legislation ensures balance between personal data protection and use. In the present data base, DK-DHR has access to the following registries for the entire Danish population of 5.9 million persons from 1st January 1995: The central Person Registry (CPR), The National Patient Registry (LPR), The Register of Pharmaceutical Sales (LSR), The National Cancer Register (CAR), The Cause of Death registry (DAR), The Clinical Laboratory Information Register (LAB), COVID-19 test and vaccination Registries (SSI-OVD, SSI-DDV), The complete Vaccination registry (DDV_all). All data registered from 1st January 1995 was be included.

Finnish Care Register for Health Care (FinOMOP-THL)

FinOMOP-THL covers both public and private, primary, and specialised inpatient 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. The main content of the THL CDM is The Finnish Care Register for Health Care (fi: Hoitoilmoitusrekisteri, HILMO). It is a continuation of the former Hospital Discharge Register, which originally gathered data on patients discharged from hospitals. The Care Register has comprehensive data on the use of services and service users from Finnish public inpatient and outpatient primary and specialised care nationwide. Since 1998 the register has covered both public outpatient and inpatient specialized care and private inpatient care (TerveysHilmo). From 2011 the register has covered public primary care (AvoHilmo). From 2020 the register has covered private outpatient care and occupational care. In addition, the CDM also contains the vaccination data from the Finnish National Vaccination Register, and positive COVID-19 test results from the Finnish National Infectious Diseases Register, which is maintained by FinOMOP-THL. The CDM is currently produced from the above-mentioned and limited to observation periods commencing after 1st January 2011. The National Population registry is also used as a source for the CDM. The National Population registry data forms the basis for forming the patient population. This ensures up-to-date location (municipality of residence) of patients as well as complete death occurrences (although not the cause of death). Using the complete population as a basis for the person table also serves to facilitate calculations on a population level, e.g. incidence rates. The current CDM population comprises all persons having been alive and residing in Finland since the beginning of 2011.

Norwegian Linked Health Registry data (NLHR)

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. 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. Norwegian Linked Health Registry data (NLHR) harmonized data from the following registries: 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). Linkage between the registries was facilitated using project-specific person ID generated from unique personal identification assigned at birth or immigration for all legal residents in Norway. In brief: MBRN stores information about the pregnancy, the mother, father and child; NPR records diagnosis in secondary care (e.g. hospital); KUHR contains information about diagnosis and contact in primary care (e.g. GPs and outpatient specialists) – to be included in third release; NorPD recorded all medications dispensed outside of hospitals; MSIS collects test results of communicable diseases (e.g. Sars-Cov-2); SYSVAK recorded vaccinations.

The Information System for Research in Primary Care (SIDIAP)

The Information System for Research in Primary Care (SIDIAP) is a clinical database of anonymized patient records in Catalonia, Spain. The Spanish public healthcare system covers more than 98% of the population, and more than two thirds of the Catalan population see their GP at least once a year. The computerisation of the primary care patient records of the Catalan Health Institute (CHI) was complete in 2005. SIDIAP was designed to provide a valid and reliable database of information from clinical records of patients registered in primary care centres for use in biomedical research. SIDIAP contains data of anonymized patients' healthcare records for nearly six million people (approximately 80% of the Catalan population) registered in 287 primary care practices throughout Catalonia since 2005. It includes data collected by health professionals during routine visits in primary care, including anthropometric measurements, clinical diagnoses (International Classification of Diseases 10th revision ICD-10), laboratory tests, prescribed and dispensed drugs, hospital referrals, demographic, and lifestyle information. It was previously shown that SIDIAP population is highly representative of the entire Catalan region in terms of geographic, age, and sex distributions. The high quality of these data has been previously documented, and SIDIAP has been successfully applied to epidemiological studies of key exposures and outcomes. Quality checks to identify duplicate patient IDs are performed centrally at each SIDIAP database update. Checks for logical values and data harmonisation are performed. For biochemistry data, consistency for measurements taken in different laboratories is assessed, and unit conversion is undertaken when needed.

ANNEX II. Fitness for use assessment

Data source justification for inclusion and key characteristics:

Danish Data Health Registries (DK-DHR)

DK-DHR was included in this study because it is national registry that provides complete capture of vaccination in children and adolescents, as well as coverage of secondary care settings that would see severe cases of encephalitis and severe varicella.

Based on a preliminary feasibility assessment, the expected number of person counts for varicella vaccines was 141,500 (all age groups), with vaccine-brand level information for *Varivax* and *Varilrix* being available for 19,600 and 3,800, respectively. Record counts for encephalitis were low, with around 400 and 2500 records being recorded in infants/toddlers (1months – 2years) and children and adolescents (2 – 11years), respectively. Denmark does not include varicella vaccination in the national vaccination program for children and adolescents.

Data availability and follow-up in DK-DHR was sufficient, as the date of most recent data extraction was 01/2025. Individuals are registered in DK-DHR at birth or at entry into the country, which allows for data availability prior to the first vaccine dose. DK-DHR records each individual's date of birth, which allows for accurate age calculation.

Study specific limitations included that the DK-DHR data cut currently used for DARWIN EU® does not include primary care conditions, e.g. non-severe varicella infection and/or contraindications to life-attenuated vaccination (but prescription/secondary care diagnoses has cover most of the latter).

Lastly, DK-DHR has blanket approval/IRB approval for drug safety studies in the context of DARWIN EU®, which made the execution of this study feasible within the study timelines.

Finnish Care Register for Health Care (FinOMOP-THL)

FinOMOP-THL was the second data partner contributing to this study. It is national registry that provides capture of vaccination (varicella) in children and adolescents, as well as coverage of secondary care settings that would see severe cases of encephalitis.

Feasibility assessment showed an expected number of person counts for varicella vaccines of 1,393,100 (all age groups), with vaccine-brand level information for *Varivax* and *Varilrix* being available for 523,000 and 54,900, respectively. Person counts were 237,400 for MMRV vaccines. Record counts for encephalitis were around 500 and 3,400 records in infants/toddlers and children and adolescents, respectively.

Finland introduced varicella vaccines into the national vaccination schedule in 2017. The first varicella vaccine dose is recommended at 18 months (while MMR is recommended between 12 – 18 months), followed by MMRV or MMR+V at age 6 years. A "catch-up" vaccination is offered if children and adolescents did not receive 2 varicella vaccine doses by the age of 12 years.

Data availability and follow-up in FinOMOP-THL was sufficient, as the date of most recent data extraction was 10/2024. There were no study specific limitations present: FinOMOP-THL had the exact dates of birth for the entire Finnish population, which allowed for accurate calculation of age. For newborns, the unique personal identifier and information on date of birth and sex of the child are sent to the Finnish Population Information System by the maternity hospital within days from the live birth. This allowed for data availability prior to the first vaccine dose.

Lastly, FinOMOP-THL needed to retrieve IRB approval for this study, with approval timelines typically ranging between 1–3 months. The execution of this study in FinOMOP-THL was therefore feasible within the study timelines.

Norwegian Linked Health Registry data (NLHR)

NLHR was the third national registry that was included in this study. It provides complete capture of vaccination (varicella and MMR) in children and adolescents, as well as coverage of secondary care settings that would see severe cases of encephalitis.

Based on a preliminary feasibility assessment, the expected number of person counts for varicella vaccines was 10,200 (all age groups), with no vaccine-brand level information for *Varivax* and *Varilrix* being available. Person counts for MMR vaccines were 756,700. Record counts for encephalitis were 300 and 1,400 records in infants/toddlers and children and adolescents, respectively.

Norway does not include varicella vaccination in the national vaccination program for children and adolescents. Varicella vaccine is however recommended after nine months of age for children and adolescents who are about to start immunosuppressive treatment or have a treatment break, who are going to undergo an organ transplant, close contacts of individuals who are at risk of severe varicella infection if infected, and HIV-positive individuals without immunodeficiency.[33] Recommended varicella vaccination in these individuals are: Two doses; minimum 6 weeks apart after 12 months of age, 3 months apart if given at 9–12 months. High-risk individuals may need extra doses.

The vaccine cannot be given to individuals with severely compromised immune function, such as those with congenital immunodeficiency or those receiving very high doses of immunosuppressive therapy.

The overall incidence of varicella in Norway is unknown. Varicella-zoster virus (VZV) infection is only notifiable to the Norwegian Surveillance System for Communicable Diseases (MSIS) when it involves infection of the central nervous system. Encephalitis caused by VZV has been notifiable to MSIS since 1975, and, as of 1 July 2012, cases are reported under the broader category of viral infections of the central nervous system. Between 1977 and 2024, a total of 1,357 cases of serous meningitis/encephalitis and other conditions with VZV detected in cerebrospinal fluid have been reported to MSIS.

Data availability and follow-up in NLHR was limited to the period of 2018 – 2023. While the registry has the exact dates of birth for the entire Norwegian population, and all legal residents are being enrolled at birth or immigration, the current data cut onboarded for DARWIN EU® only included children and adolescents who resided/were born in Norway between 2018 – 2023.

Lastly, NLHR had IRB approval in place for this drug safety study, using the data cut onboarded for DARWIN EU®, which made the execution of this study feasible within the study timelines.

The Information System for Research on Primary Care (SIDIAP)

SIDIAP is a primary care data source from Catalonia, Spain, which can be linked to secondary care/hospital data in the region. It therefore provides both complete capture of vaccination (varicella and MMR) in children and adolescents, as well as coverage of the secondary care settings that would see severe cases of encephalitis.

Feasibility (person) counts for varicella vaccines retrieved for SIDIAP were 762,700 (all age groups), with no vaccine-brand level information for *Varivax* and *Varilrix* being available. Person counts for MMR vaccines were 1.4 million, with SIDIAP having mapped their MMR as three separate records vaccines of measles, mumps, and rubella, respectively. Record counts for encephalitis were low, with 100 and 400 records in infants/toddlers and children and adolescents, respectively.

In Catalonia, the varicella vaccines were incorporated into the routine childhood vaccination schedule in 2016: A first varicella vaccine dose is recommended at the age of 15 month (MMR vaccination at 12 months), followed by MMRV or MMR+V between the age of 3 – 4years. Similar to Finland, a “catch-up” vaccination is offered if children and adolescents did not receive 2 varicella vaccine doses by the age of 12 years.

Data in SIDIAP is available from the start of the planed study period (2017), but follow-up is limited to the date of most recent data extraction, which was 06/2023. As SIDIAP only had the month of birth available, the actual date of birth for this study was defined as the first day of the respective month of birth. Newborns are registered in the public health system directly by public healthcare facilities for births that took place in public facilities. Individuals are automatically incorporated into SIDIAP if they are registered in the public health system and have been assigned to a primary care centre of the Catalan Health Institute (only those primary care centres are in SIDIAP). However, it is not unusual to give birth in a private healthcare facility but then go to public primary care for paediatric visits; in such cases children and adolescents are enrolled a few weeks after birth.

SIDIAP needed to retrieve IRB approval for this study, with approval timelines typically ranging between 1–3 months. The execution of this study in SIDIAP was therefore feasible within the study timelines.

ANNEX III. Operational and reporting considerations

DATA MANAGEMENT

Data management

All data sources have previously mapped their data to the OMOP common data model. This enabled the use of standardised analytics and using DARWIN EU® tools across the network since the structure of the data and the terminology system was 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 individual 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, personal data from individuals in various EU member states were processed, using information collected from 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 have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control were adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses were run, which generate non-identifiable aggregate summary results.

The output files are stored in the DARWIN EU® Digital Research Environment (DRE). These output files do not contain any data that allow identification of subjects included in the study. The DRE implements 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

Data source 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 is expected that data partners will have run the OHDSI *DataQualityDashboard* 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 vaccine cohorts (V, MMRV), varicella infection diagnoses, and contraindications, a systematic search of possible codes for inclusion was be identified using *CodelistGenerator* R package (https://github.com/darwin-eu/CodelistGenerator). This software allows 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. A pharmacist reviewed the codes of the vaccines of interest, while 2 clinical epidemiologists reviewed the codes for varicella infection and contraindications.

In addition, the *CohortDiagnostics* R package (https://github.com/OHDSI/CohortDiagnostics) was ran 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 be based on R packages currently developed for DARWIN EU®, including *IncidencePrevalence* and *CohortCharacterisation,* using the OMOP common data model. These packages included numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing. The SCRI analyses used the *SCCS* package.

The study code was made publicly available via GitHub.

ANNEX IV. Code list for study outcomes definition

Concept ID	Concept Name
Encephalitis (unspecified/vaccination)	
374021	Acute disseminated encephalomyelitis
43530701	Acute disseminated encephalomyelitis following infectious disease
44806551	Acute encephalitis
4249574	Acute hemorrhagic leukoencephalitis
4009332	Acute necrotizing encephalitis
4047619	Acute viral encephalitis
4318558	Autoimmune encephalitis
4141686	Bickerstaff's brainstem encephalitis
4041671	Brainstem encephalitis
4088249	Encephalitis lethargica
4147498	Encephalitis, myelitis and encephalomyelitis
373189	Encephalomyelitis
4088248	Epidemic encephalitis
4047626	Focal encephalitis
36715541	Infection causing encephalomyelitis
374020	Infective encephalitis
4041673	Limbic encephalitis
4174766	Lymphocytic meningoencephalitis
4322814	Meningoencephalitis
762645	Meningoencephalitis caused by virus
765827	Multiphasic acute disseminated encephalomyelitis
379792	Post-immunization encephalitis
372615	Post-infectious encephalitis
379798	Post-infectious encephalomyelitis
4105201	Post mixed vaccination encephalitis
443802	Postvaccinal encephalomyelitis
380322	Postvaricella encephalitis
4249132	Primary encephalitis
4324751	Primary viral encephalitis
4206037	Pyogranulomatous meningoencephalomyelitis
761989	Recurrent acute disseminated encephalomyelitis
372547	Viral encephalitis
Encephalitis (any)	
4147586	Acute adenoviral encephalitis
4221266	Acute adenoviral meningoencephalitis

Concept ID	Concept Name
374021	Acute disseminated encephalomyelitis
43530701	Acute disseminated encephalomyelitis following infectious disease
44806551	Acute encephalitis
4249574	Acute hemorrhagic leukoencephalitis
4009332	Acute necrotizing encephalitis
4047619	Acute viral encephalitis
4210628	Adenoviral encephalitis
4324289	Allergic encephalitis
4176250	Allergic encephalomyelitis
4045979	Amebic encephalitis
4102195	Arbovirus encephalitis
4318558	Autoimmune encephalitis
764228	Autoimmune encephalitis caused by N-methyl D-aspartate receptor antibody
4045977	Bacterial encephalitis
40483321	Bacterial meningoencephalitis
4141686	Bickerstaff's brainstem encephalitis
4041671	Brainstem encephalitis
439725	California encephalitis virus infection
4213372	California encephalitis virus infection neuroinvasive disease
4047470	Chronic echovirus meningoencephalitis
4047623	Chronic viral encephalitis
381794	Congenital syphilitic encephalitis
4306458	Cytomegalovirus encephalitis
438069	Disorder caused by Venezuelan equine encephalitis virus
440332	Eastern equine encephalitis virus infection
4221064	Eastern equine encephalitis virus neuroinvasive disease
4221192	Eastern equine encephalitis virus non-neuroinvasive disease
378143	Encephalitis
45757204	Encephalitis caused by Actinomyces
36715969	Encephalitis caused by Alphavirus
36716017	Encephalitis caused by Coenurus cerebralis
36716014	Encephalitis caused by Echinococcus granulosus
443881	Encephalitis caused by European subtype of tick-borne encephalitis virus
376905	Encephalitis caused by Far Eastern tick-borne encephalitis virus
36715988	Encephalitis caused by Hendra virus
376026	Encephalitis caused by Herpesvirus
4322568	Encephalitis caused by human herpes simplex virus

Concept ID	Concept Name
40479557	Encephalitis caused by human herpesvirus 6 infection
4146943	Encephalitis caused by Influenza virus
4221661	Encephalitis caused by Langat virus
36717188	Encephalitis caused by Nipah virus
36715978	Encephalitis caused by Polyoma virus
4302794	Encephalitis caused by protozoa
443543	Encephalitis caused by rickettsia
36715986	Encephalitis caused by Rubulavirus
36716010	Encephalitis caused by Schistosoma
36716011	Encephalitis caused by Schistosoma haematobium
36716013	Encephalitis caused by Schistosoma japonicum
36716012	Encephalitis caused by Schistosoma mansoni
4217555	Encephalitis caused by Siberian tick-borne encephalitis virus
36716016	Encephalitis caused by Taenia solium
37016847	Encephalitis caused by tick-borne encephalitis virus
36716007	Encephalitis caused by Trypanosoma brucei
37110324	Encephalitis caused by Venezuelan equine encephalomyelitis virus
4088249	Encephalitis lethargica
4147498	Encephalitis, myelitis and encephalomyelitis
4222250	Encephalitis with AIDS (acquired immunodeficiency syndrome)
373189	Encephalomyelitis
4220014	Encephalomyelitis caused by lymphocytic choriomeningitis virus
375185	Encephalomyelitis due to rubella
4228612	Encephalomyelitis with AIDS (acquired immunodeficiency syndrome)
4041669	Enteroviral encephalitis
4320933	Enteroviral encephalomyelitis
4210015	Eosinophilic meningoencephalitis
4302798	Eosinophilic meningoencephalitis caused by Angiostrongylus cantonensis
4088248	Epidemic encephalitis
4047626	Focal encephalitis
4047625	Fungal encephalitis
4042201	Granulomatous amebic encephalitis
37311983	Henipavirus encephalitis
4047622	Herpes simiae encephalitis
4045976	Herpes zoster encephalitis
4296460	Herpetic acute necrotizing encephalitis
4161950	Human immunodeficiency virus encephalitis

Concept ID	Concept Name
4324541	Ilheus virus encephalitis
36715541	Infection causing encephalomyelitis
4041670	Infectious mononucleosis encephalitis
374020	Infective encephalitis
4227852	Jamestown Canyon virus encephalitis
381789	Japanese encephalitis virus disease
4230601	Keystone virus encephalitis
4044937	Kumlinge virus encephalitis
4265323	La Crosse encephalitis
434866	Late effects of viral encephalitis
4045978	Late syphilitic encephalitis
4041673	Limbic encephalitis
35622353	Limbic encephalitis with contactin-associated protein-like 2 antibodies
36676495	Limbic encephalitis with dipeptidyl-peptidase 6 antibodies
35607961	Limbic encephalitis with leucine-rich glioma-inactivated 1 antibodies
37399546	Limbic encephalitis with N-methyl-D-aspartate receptor antibodies
4077718	Listeria meningoencephalitis
4174766	Lymphocytic meningoencephalitis
4166858	Measles inclusion body encephalitis
380632	Meningococcal encephalitis
4322814	Meningoencephalitis
46269919	Meningoencephalitis caused by Acanthamoeba
380941	Meningoencephalitis caused by human herpes simplex virus
4180433	Meningoencephalitis caused by Naegleria
4027838	Meningoencephalitis caused by Rubella virus
762645	Meningoencephalitis caused by virus
375475	Meningoencephalitis due to acquired toxoplasmosis
45757219	Meningoencephalitis due to Blastomyces dermatitidis
46269920	Meningoencephalitis due to Chagas disease
46270062	Meningoencephalitis due to free-living ameba
765827	Multiphasic acute disseminated encephalomyelitis
378065	Mumps encephalitis
4220632	Mumps meningoencephalitis
442611	Murray Valley encephalitis
35622800	Mycoplasma pneumoniae encephalitis
4236144	Nairoviral encephalitis
4289603	Negishi encephalitis

Concept ID	Concept Name
4169939	Neuroinvasive Cache Valley encephalitis virus infection
4219689	Neuroinvasive Powassan encephalitis virus infection
4214943	Neuroinvasive St. Louis encephalitis virus infection
4215383	Neuroinvasive Venezuelan equine encephalitis virus infection
4310991	Neuroinvasive Western equine encephalitis virus infection
35622805	Non-herpetic acute limbic encephalitis
4309568	Non-neuroinvasive Western equine encephalitis virus infection
4312671	Paraneoplastic encephalitis
4310021	Paraneoplastic encephalomyelitis
40481971	Paraneoplastic limbic encephalitis
4103103	Polioencephalitis
4102198	Post BCG vaccination encephalitis
4103109	Post cholera vaccination encephalitis
4105200	Post diphtheria vaccination encephalitis
4100112	Post hepatitis A vaccination encephalitis
4104690	Post hepatitis B vaccination encephalitis
379792	Post-immunization encephalitis
372615	Post-infectious encephalitis
379798	Post-infectious encephalomyelitis
4042202	Post-influenza encephalitis
4103116	Post influenza vaccination encephalitis
377487	Post measles encephalitis
4102199	Post measles vaccination encephalitis
4105201	Post mixed vaccination encephalitis
4103115	Post mumps vaccination encephalitis
4103108	Post paratyphoid vaccination encephalitis
4103111	Post pertussis vaccination encephalitis
4103110	Post plague vaccination encephalitis
4103114	Post polio vaccination encephalitis
4103112	Post rabies vaccination encephalitis
4100111	Post rubella vaccination encephalitis
4100109	Post smallpox vaccination encephalitis
4100108	Post tetanus vaccination encephalitis
36676401	Post-transplant acute limbic encephalitis
4103107	Post typhoid vaccination encephalitis
4100110	Post typhus vaccination encephalitis
443802	Postvaccinal encephalomyelitis

Concept ID	Concept Name
380322	Postvaricella encephalitis
4103113	Post yellow fever vaccination encephalitis
4215521	Powassan encephalitis virus infection
4216883	Powassan virus non-neuroinvasive disease
4042200	Primary amebic encephalitis
4176017	Primary amebic encephalitis caused by Naegleria fowleri
4249132	Primary encephalitis
4324751	Primary viral encephalitis
4120303	Progressive congenital rubella encephalomyelitis
4002949	Progressive rubella panencephalitis
4206037	Pyogranulomatous meningoencephalomyelitis
4252714	Q fever encephalitis
4041672	Rasmussen syndrome
763040	Rasmussen syndrome, refractory
761989	Recurrent acute disseminated encephalomyelitis
4042197	Rhabdovirus encephalitis
4213917	Rio Bravo viral encephalitis
4047620	Rocio virus encephalitis
4100107	Rubella encephalitis
4035637	Simian B encephalomyelitis
4227853	Snowshoe hare virus encephalitis
36674282	Steroid-responsive encephalopathy associated with autoimmune thyroiditis
440023	St. Louis encephalitis virus infection
443579	St. Louis encephalitis virus non-neuroinvasive disease
4009925	Subacute adenoviral encephalitis
37017071	Subacute adenoviral encephalitis co-occurrent with human immunodeficiency virus infection
4222717	Subacute adenoviral encephalitis with AIDS (acquired immunodeficiency syndrome)
373408	Subacute sclerosing panencephalitis
378349	Syphilitic encephalitis
4318863	Systemic lupus erythematosus encephalitis
4044936	Tensaw encephalitis
378136	Toxic encephalitis
4327502	Toxic encephalitis caused by thallium
40480147	Toxic encephalomyelitis
4103105	Toxoplasma encephalitis
4324130	Trypanosomiasis with encephalitis
4238921	Tuberculous encephalitis

Concept ID	Concept Name
4150516	Tuberculous meningoencephalitis
4233538	Van Bogaert's sclerosing leukoencephalitis
4220454	Venezuelan equine encephalitis virus non-neuroinvasive disease
372547	Viral encephalitis
380942	Western equine encephalitis
373692	West Nile encephalitis

ANNEX V. Sensitivity Analysis Results

Five different sensitivity analyses were conducted in Objectives 3 and 4:

1. Secondary (extended) risk interval: [2,42]
2. Include both pre- and post-index control interval: [-90,-30] days and [50, 90]
3. Risk interval that account for incubation period: [15, 38]
4. Restrict to first ever encephalitis event only
5. Remove requirement of 90 days available follow-up time after vaccination

Table 1. Sensitivity analysis results in Objective 3.

Analysis	CDM name	Outcome	Age-season adjusted IRR
Main analysis	NLHR	Encephalitis (any)	6.39 (0.69 – 58.88)
Main analysis	NLHR	Encephalitis (unspecified/vaccination)	6.39 (0.69 – 58.88)
Sensitivity 1	NLHR	Encephalitis (any)	4.39 (0.82 – 23.45)
Sensitivity 1	NLHR	Encephalitis (unspecified/vaccination)	4.4 (0.83 – 23.49)
Sensitivity 2	NLHR	Encephalitis (any)	12.41 (1.35 – 114.03)
Sensitivity 2	NLHR	Encephalitis (unspecified/vaccination)	12.41 (1.35 – 114.03)
Sensitivity 3	NLHR	Encephalitis (any)	6.40 (1.14 – 35.93)
Sensitivity 3	NLHR	Encephalitis (unspecified/vaccination)	6.40 (1.14 – 35.93)
Sensitivity 4	NLHR	Encephalitis (any)	6.39 (0.69 – 58.88)
Sensitivity 4	NLHR	Encephalitis (unspecified/vaccination)	6.39 (0.69 – 58.88)
Sensitivity 5	NLHR	Encephalitis (any)	5.94 (0.66 – 53.65)
Sensitivity 5	NLHR	Encephalitis (unspecified/vaccination)	5.94 (0.66 – 53.65)

DK-DHR=Danish Data Health Registries; FinOMOP-THL=Finnish Care Register for Health Care; NLHR=Norwegian Linked Health Registry data; SIDIAP=The Information System for Research on Primary Care; IR=Incidence Rate; IRR=Incidence Rate Ratio.

Table 2. Sensitivity analysis results in Objective 4.

Analysis	CDM name	Outcome	Exposure	Age-season adjusted IRR
Main analysis	FinOMOP-THL	Encephalitis (any)	D1	1.55 (0.53 – 4.50)
Main analysis	SIDIAP	Encephalitis (any)	D1	1.01 (0.20 – 5.04)
Main analysis	FinOMOP-THL	Encephalitis (any)	D1 (V)	1.42 (0.44 – 4.56)
Main analysis	SIDIAP	Encephalitis (any)	D1 (V)	0.87 (0.13 – 5.68)
Main analysis	FinOMOP-THL	Encephalitis (any)	D2	0.24 (0.02 – 3.05)
Main analysis	SIDIAP	Encephalitis (any)	D2	0.49 (0.05 – 4.76)
Main analysis	FinOMOP-THL	Encephalitis (any)	D2 (MMRV)	0.24 (0.02 – 3.05)
Main analysis	FinOMOP-THL	Encephalitis (unspecified/vaccination)	D1	1.83 (0.48 – 6.97)
Main analysis	SIDIAP	Encephalitis (unspecified/vaccination)	D1	0.99 (0.07 – 13.18)
Main analysis	FinOMOP-THL	Encephalitis (unspecified/vaccination)	D1 (V)	2.29 (0.58 – 9.05)
Main analysis	FinOMOP-THL	Encephalitis (unspecified/vaccination)	D2	0.46 (0.04 – 5.02)

Analysis	CDM name	Outcome	Exposure	Age-season adjusted IRR
Main analysis	FinOMOP-THL	Encephalitis (unspecified/vaccination)	D2 (MMRV)	0.46 (0.04 – 5.02)
Main analysis	Meta-analysis	Encephalitis (any)	D1	1.36 (0.56 – 3.31)
Main analysis	Meta-analysis	Encephalitis (any)	D1 (V)	1.24 (0.46 – 3.34)
Main analysis	Meta-analysis	Encephalitis (any)	D2	0.36 (0.07 – 1.95)
Main analysis	Meta-analysis	Encephalitis (unspecified/vaccination)	D1	1.61 (0.49 – 5.28)
Sensitivity 1	FinOMOP-THL	Encephalitis (any)	D1	1.25 (0.47 – 3.31)
Sensitivity 1	SIDIAP	Encephalitis (any)	D1	1.00 (0.32 – 3.12)
Sensitivity 1	FinOMOP-THL	Encephalitis (any)	D1 (V)	1.27 (0.45 – 3.61)
Sensitivity 1	SIDIAP	Encephalitis (any)	D1 (V)	0.98 (0.29 – 3.32)
Sensitivity 1	FinOMOP-THL	Encephalitis (any)	D2	0.55 (0.11 – 2.9)
Sensitivity 1	SIDIAP	Encephalitis (any)	D2	1.00 (0.19 – 5.21)
Sensitivity 1	FinOMOP-THL	Encephalitis (any)	D2 (MMRV)	0.14 (0.01 – 1.65)
Sensitivity 1	SIDIAP	Encephalitis (any)	D2 (MMRV)	1.47 (0.23 – 9.34)
Sensitivity 1	FinOMOP-THL	Encephalitis (unspecified/vaccination)	D1	1.61 (0.5 – 5.22)
Sensitivity 1	SIDIAP	Encephalitis (unspecified/vaccination)	D1	0.88 (0.10 – 7.45)
Sensitivity 1	FinOMOP-THL	Encephalitis (unspecified/vaccination)	D1 (V)	2.05 (0.59 – 7.17)
Sensitivity 1	SIDIAP	Encephalitis (unspecified/vaccination)	D1 (V)	0.84 (0.10 – 7.15)
Sensitivity 1	FinOMOP-THL	Encephalitis (unspecified/vaccination)	D2	0.54 (0.07 – 4.10)
Sensitivity 1	FinOMOP-THL	Encephalitis (unspecified/vaccination)	D2 (MMRV)	0.24 (0.02 – 2.47)
Sensitivity 1	Meta-analysis	Encephalitis (any)	D1	1.14 (0.54 – 2.38)
Sensitivity 1	Meta-analysis	Encephalitis (any)	D1 (V)	1.14 (0.51 – 2.51)
Sensitivity 1	Meta-analysis	Encephalitis (any)	D2	0.74 (0.23 – 2.40)
Sensitivity 1	Meta-analysis	Encephalitis (any)	D2 (MMRV)	0.52 (0.05 – 5.26)
Sensitivity 1	Meta-analysis	Encephalitis (unspecified/vaccination)	D1	1.40 (0.50 – 3.92)
Sensitivity 1	Meta-analysis	Encephalitis (unspecified/vaccination)	D1 (V)	1.64 (0.56 – 4.82)
Sensitivity 2	FinOMOP-THL	Encephalitis (any)	D1	1.74 (0.70 – 4.32)
Sensitivity 2	SIDIAP	Encephalitis (any)	D1	1.39 (0.49 – 3.94)
Sensitivity 2	FinOMOP-THL	Encephalitis (any)	D1 (V)	1.65 (0.63 – 4.35)
Sensitivity 2	SIDIAP	Encephalitis (any)	D1 (V)	1.26 (0.40 – 3.97)
Sensitivity 2	FinOMOP-THL	Encephalitis (any)	D2	0.34 (0.04 – 2.58)
Sensitivity 2	SIDIAP	Encephalitis (any)	D2	0.81 (0.08 – 7.75)
Sensitivity 2	FinOMOP-THL	Encephalitis (any)	D2 (MMRV)	0.38 (0.05 – 2.98)
Sensitivity 2	SIDIAP	Encephalitis (any)	D2 (MMRV)	1.27 (0.11 – 14.45)
Sensitivity 2	FinOMOP-THL	Encephalitis (unspecified/vaccination)	D1	1.72 (0.64 – 4.60)
Sensitivity 2	SIDIAP	Encephalitis (unspecified/vaccination)	D1	0.62 (0.13 – 2.95)
Sensitivity 2	FinOMOP-THL	Encephalitis (unspecified/vaccination)	D1 (V)	1.98 (0.73 – 5.36)

Analysis	CDM name	Outcome	Exposure	Age-season adjusted IRR
Sensitivity 2	SIDIAP	Encephalitis (unspecified/vaccination)	D1 (V)	0.36 (0.04 – 3.26)
Sensitivity 2	FinOMOP-THL	Encephalitis (unspecified/vaccination)	D2	0.41 (0.05 – 3.31)
Sensitivity 2	FinOMOP-THL	Encephalitis (unspecified/vaccination)	D2 (MMRV)	0.44 (0.05 – 3.59)
Sensitivity 2	Meta-analysis	Encephalitis (any)	D1	1.58 (0.80 – 3.14)
Sensitivity 2	Meta-analysis	Encephalitis (any)	D1 (V)	1.48 (0.71 – 3.09)
Sensitivity 2	Meta-analysis	Encephalitis (any)	D2	0.50 (0.11 – 2.26)
Sensitivity 2	Meta-analysis	Encephalitis (any)	D2 (MMRV)	0.63 (0.13 – 3.02)
Sensitivity 2	Meta-analysis	Encephalitis (unspecified/vaccination)	D1	1.24 (0.49 – 3.15)
Sensitivity 2	Meta-analysis	Encephalitis (unspecified/vaccination)	D1 (V)	1.14 (0.24 – 5.40)
Sensitivity 3	FinOMOP-THL	Encephalitis (any)	D1	1.33 (0.43 – 4.17)
Sensitivity 3	SIDIAP	Encephalitis (any)	D1	0.81 (0.19 – 3.37)
Sensitivity 3	FinOMOP-THL	Encephalitis (any)	D1 (V)	1.51 (0.46 – 5.00)
Sensitivity 3	SIDIAP	Encephalitis (any)	D1 (V)	0.89 (0.22 – 3.64)
Sensitivity 3	FinOMOP-THL	Encephalitis (any)	D2	0.56 (0.10 – 3.04)
Sensitivity 3	SIDIAP	Encephalitis (any)	D2	1.54 (0.31 – 7.68)
Sensitivity 3	FinOMOP-THL	Encephalitis (any)	D2 (MMRV)	0.26 (0.03 – 2.59)
Sensitivity 3	SIDIAP	Encephalitis (any)	D2 (MMRV)	2.27 (0.38 – 13.65)
Sensitivity 3	FinOMOP-THL	Encephalitis (unspecified/vaccination)	D1	2.16 (0.64 – 7.25)
Sensitivity 3	FinOMOP-THL	Encephalitis (unspecified/vaccination)	D1 (V)	2.71 (0.75 – 9.77)
Sensitivity 3	FinOMOP-THL	Encephalitis (unspecified/vaccination)	D2	0.41 (0.04 – 4.55)
Sensitivity 3	FinOMOP-THL	Encephalitis (unspecified/vaccination)	D2 (MMRV)	0.41 (0.04 – 4.55)
Sensitivity 3	Meta-analysis	Encephalitis (any)	D1	1.10 (0.45 – 2.67)
Sensitivity 3	Meta-analysis	Encephalitis (any)	D1 (V)	1.21 (0.49 – 3.01)
Sensitivity 3	Meta-analysis	Encephalitis (any)	D2	0.95 (0.30 – 3.06)
Sensitivity 3	Meta-analysis	Encephalitis (any)	D2 (MMRV)	0.87 (0.11 – 7.21)
Sensitivity 4	FinOMOP-THL	Encephalitis (any)	D1	3.01 (0.41 – 22.17)
Sensitivity 4	SIDIAP	Encephalitis (any)	D1	1.01 (0.20 – 5.04)
Sensitivity 4	FinOMOP-THL	Encephalitis (any)	D1 (V)	4.2 (0.57 – 30.93)
Sensitivity 4	SIDIAP	Encephalitis (any)	D1 (V)	0.87 (0.13 – 5.68)
Sensitivity 4	FinOMOP-THL	Encephalitis (any)	D2	0.30 (0.02 – 4.64)
Sensitivity 4	FinOMOP-THL	Encephalitis (any)	D2 (MMRV)	0.30 (0.02 – 4.64)
Sensitivity 4	FinOMOP-THL	Encephalitis (unspecified/vaccination)	D1	3.01 (0.41 – 22.17)
Sensitivity 4	SIDIAP	Encephalitis (unspecified/vaccination)	D1	0.99 (0.07 – 13.18)
Sensitivity 4	FinOMOP-THL	Encephalitis (unspecified/vaccination)	D1 (V)	4.20 (0.57 – 30.93)
Sensitivity 4	FinOMOP-THL	Encephalitis (unspecified/vaccination)	D2	0.83 (0.06 – 11.69)
Sensitivity 4	Meta-analysis	Encephalitis (any)	D1	1.55 (0.44 – 5.43)

Analysis	CDM name	Outcome	Exposure	Age-season adjusted IRR
Sensitivity 4	Meta-analysis	Encephalitis (any)	D1 (V)	1.84 (0.39 – 8.6)
Sensitivity 4	Meta-analysis	Encephalitis (unspecified/vaccination)	D1	1.99 (0.41 – 9.66)
Sensitivity 5	FinOMOP-THL	Encephalitis (any)	D1	1.55 (0.53 – 4.50)
Sensitivity 5	SIDIAP	Encephalitis (any)	D1	1.01 (0.20 – 5.04)
Sensitivity 5	FinOMOP-THL	Encephalitis (any)	D1 (V)	1.42 (0.44 – 4.56)
Sensitivity 5	SIDIAP	Encephalitis (any)	D1 (V)	0.87 (0.13 – 5.68)
Sensitivity 5	FinOMOP-THL	Encephalitis (any)	D2	0.24 (0.02 – 3.05)
Sensitivity 5	SIDIAP	Encephalitis (any)	D2	0.49 (0.05 – 4.76)
Sensitivity 5	FinOMOP-THL	Encephalitis (any)	D2 (MMRV)	0.24 (0.02 – 3.05)
Sensitivity 5	FinOMOP-THL	Encephalitis (unspecified/vaccination)	D1	1.83 (0.48 – 6.97)
Sensitivity 5	SIDIAP	Encephalitis (unspecified/vaccination)	D1	0.99 (0.07 – 13.18)
Sensitivity 5	FinOMOP-THL	Encephalitis (unspecified/vaccination)	D1 (V)	2.29 (0.58 – 9.05)
Sensitivity 5	FinOMOP-THL	Encephalitis (unspecified/vaccination)	D2	0.46 (0.04 – 5.02)
Sensitivity 5	FinOMOP-THL	Encephalitis (unspecified/vaccination)	D2 (MMRV)	0.46 (0.04 – 5.02)
Sensitivity 5	Meta-analysis	Encephalitis (any)	D1	1.36 (0.56 – 3.31)
Sensitivity 5	Meta-analysis	Encephalitis (any)	D1 (V)	1.24 (0.46 – 3.34)
Sensitivity 5	Meta-analysis	Encephalitis (any)	D2	0.36 (0.07 – 1.95)
Sensitivity 5	Meta-analysis	Encephalitis (unspecified/vaccination)	D1	1.61 (0.49 – 5.28)

DK-DHR=Danish Data Health Registries; FinOMOP-THL=Finnish Care Register for Health Care; NLHR=Norwegian Linked Health Registry data; SIDIAP=The Information System for Research on Primary Care; IR=Incidence Rate; IRR=Incidence Rate Ratio; D1=Dose 1; D2=dose 2; MMRV=measles-mumps-rubella-varicella (vaccines);MMR=measles-mumps-rubella (vaccines); V=varicella (vaccines).

ANNEX VI. 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.