DARWIN EU® - Encephalitis risk in pediatric varicella vaccine recipients

First published: 06/11/2025

Last updated: 18/12/2025

Study Ongoing

Administrative details

EU PAS number

EUPAS1000000813

Study ID

1000000813

DARWIN EU® study

Yes

Study countries

- [ ] Denmark
- [ ] Finland
- [ ] Norway
- [ ] Spain

Study description

Varilrix and Varivax are authorised for the prevention of varicella infection (chickenpox) in adults, children, and adolescents aged 9–12 months of age and older. Both vaccines contain the live-attenuated varicella virus (OKA strain). In June 2025, 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. Varicella vaccines are widely used across the EU, and encephalitis is listed as an adverse reaction in their product information, based on rare reports during post-marketing surveillance, however, 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. Encephalitis is also a recognised but rare complication following severe varicella infection itself, in about 1–2 cases per 10,000 infected children and adolescents, with a higher risk in immunocompromised individuals. Considering the seriousness of encephalitis and the regulatory context, further investigation is needed.

Study status

Ongoing

Research institutions and networks

Institutions

Department of Medical Informatics - Health Data Science, Erasmus Medical Center (ErasmusMC)

Netherlands

First published: 03/11/2022

Last updated: 02/05/2024

Institution | Educational Institution | ENCePP partner

Networks

Data Analysis and Real World Interrogation Network (DARWIN EU®)

- [ ] Belgium
- [ ] Croatia
- [ ] Denmark
- [ ] Estonia
- [ ] Finland
- [ ] France
- [ ] Germany
- [ ] Greece
- [ ] Hungary
- [ ] Italy
- [ ] Netherlands
- [ ] Norway
- [ ] Portugal
- [ ] Spain
- [ ] Sweden
- [ ] United Kingdom

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Last updated: 30/04/2025

Network

Contact details

Study institution contact

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Study contact

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Primary lead investigator

Xintong Li

Primary lead investigator

Study timelines

Date when funding contract was signed

Planned: 14/07/2025

Study start date

Planned: 28/11/2025

Actual: 28/11/2025

Date of final study report

Planned: 27/02/2026

Sources of funding

- EMA

Study protocol

DARWIN EU_Protocol_P4-C3-003_Varicella vaccine_V4.0.pdf (1.15 MB)

Regulatory

Was the study required by a regulatory body?

Yes

Is the study required by a Risk Management Plan (RMP)?

Not applicable

Methodological aspects

Study type

Study type list

Study topic:

Disease /health condition

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Drug utilisation

Safety study (incl. comparative)

Data collection methods:

Secondary use of data

Study design:

Population-level descriptive analysis will be conducted to study the vaccine uptake, patient characterisations, and background rates for encephalitis. We will then conduct the self-controlled risk intervals analyses to assess the association between vaccination,varicella infection, and encephalitis.

Main study objective:

1. To describe the vaccine uptake of V/MMRV by vaccine type, dose, brand, 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/chickenpox diagnosis.
3. To assess the association between V/MMRV vaccines and varicella infection (chickenpox) with encephalitis among children and adolescents aged 9 months to 18 years by age group and country

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Anatomical Therapeutic Chemical (ATC) code

(J07BK) Varicella zoster vaccines

Varicella zoster vaccines

(J07BD54) measles, combinations with mumps, rubella and varicella, live attenuated

measles, combinations with mumps, rubella and varicella, live attenuated

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Medical condition to be studied

Encephalitis

Population studied

Short description of the study population

The study population will include all individuals aged between 9 months and 18 years who are present in the data source 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 will require children and adolescents to receive at least one dose of varicella vaccines (V) or measles-mumps-rubella-varicella vaccines (MMRV) during the study period.
For the SCRI analysis, children and adolescents who are not eligible for vaccination, including children and adolescents with contraindications (acquired immunodeficiency syndrome (AIDS) or symptomatic HIV infection, immunosuppression due to leukaemia, lymphoma, generalised malignancy, severe combined immunodeficiency (SCID), immunosuppressive therapy, and transplantation) or a record of previous varicella infection will be excluded. Children and adolescents with a record of another live vaccine in the 28 days before or after study vaccine administration, which is the minimum allowable

interval for live vaccines, will also be excluded.

Age groups

- **Paediatric Population (< 18 years)**
  - Neonate
    - Preterm newborn infants (0 – 27 days)
    - Term newborn infants (0 – 27 days)
  - Infants and toddlers (28 days – 23 months)
  - Children (2 to < 12 years)
  - Adolescents (12 to < 18 years)

Study design details

Setting

This study will be conducted using routinely collected data from one primary care data source linked to hospital data, and three national registries in the DARWIN EU® network of data partners from four European countries. All data were a priori mapped to the OMOP CDM.

Outcomes

For Objective 1, the analysis will describe:

• Vaccine uptake, defined as the absolute number of children and adolescents who received a

specified varicella vaccine dose(s) among eligible children.

• 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.

For objectives 2 to 4, the outcome of interest is encephalitis. Encephalitis will be 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)).
Two definitions of encephalitis will be included:
a.) “Any encephalitis”: this will use the “narrow” cohort from the AESI study
b.) “Unspecific encephalitis and encephalitis due to varicella or varicella containing vaccination will
be included”: this will start from the “narrow” cohort from the AESI study and exclude concepts
that have a specific cause listed that is not relevant for this study. Therefore. unspecific encephalitis
and encephalitis due to varicella or vaccination will be included. This phenotype will be developed
during the implementation stage.

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Data sources

Data source(s)

Danish Health Data Registries

Norwegian Linked Health registry at University of Oslo

The Information System for Research in Primary Care (SIDIAP)

Data source(s), other

Finnish Care Register for Health Care

Use of a Common Data Model (CDM)

CDM mapping

Yes

CDM Mappings

CDM name

OMOP

CDM website

https://www.ohdsi.org/Data-standardization/

CDM version

https://ohdsi.github.io/CommonDataModel/index.html

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

No