Population-based retrospective nested case-control study evaluating effectiveness of GARDASIL™ /GARDASIL™9 against adult-onset recurrent respiratory papillomatosis (AoRRP) in Sweden, Denmark, and Norway (V503-088)

First published: 05/10/2022

Last updated: 21/05/2025

Study Ongoing

Administrative details

EU PAS number

EUPAS48452

Study ID

50312

DARWIN EU® study

No

Study countries

- [ ] Denmark
- [ ] Norway
- [ ] Sweden

Study description

Adult-onset Recurrent Respiratory Papillomatosis (AoRRP) and juvenile-onset Recurrent Respiratory Papillomatosis (JoRRP) are rare medical conditions where human papillomavirus (HPV) types 6 and 11 cause wart-like growths in the larynx. GARDASIL™ and GARDASIL™9 are vaccines that target HPV types 6 and 11.

This study will utilize data from national registries in Sweden, Denmark, and Norway to determine if vaccination with GARDASIL™ or GARDASIL™9 reduces the incidence of AoRRP.

The study has 2 parts: (1) a population-based nested case-control study that allows the selection of controls from the same underlying population at risk as the disease cases in females aged 15 to 29 years

(2) an ecological study using registry data to assess annual age-standardized incidence rates of JoRRP and AoRRP separately for juveniles (0-14 years) and adults (15-29 years) and by gender (males and females).

The primary objective of the study is to assess if the odds of AoRRP are lower among females fully vaccinated with GARDASIL/GARDASIL 9 before the age of 17 years versus those unvaccinated.

Study status

Ongoing

Research institutions and networks

Institutions

Merck Sharp & Dohme LLC

United States

First published: 01/02/2024

Last updated: 08/07/2025

Institution | Pharmaceutical company

Karolinska Institutet

Sweden

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Institution | Educational Institution

Cancer Registry of Norway

Danish Cancer Research Society

Contact details

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Primary lead investigator

Clinical Trials Disclosure Merck Sharp & Dohme LLC

Primary lead investigator

Study timelines

Date when funding contract was signed
Actual: 15/01/2021

Study start date
Planned: 15/12/2022

Actual: 26/10/2021

Data analysis start date
Planned: 15/05/2025

Actual: 15/05/2025

Date of final study report
Planned: 15/10/2025

Sources of funding

- Pharmaceutical company and other private sector

More details on funding

Merck Sharp & Dohme LLC

Study protocol

V503-088-00-v2.1-Protocol_final redaction.pdf(513.37 KB)

V503-088-01-v1-final-redaction.pdf(722.91 KB)

Regulatory

Was the study required by a regulatory body?

No

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

Not applicable

Methodological aspects

Study type

Study type list

Study topic:

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Disease epidemiology

Effectiveness study (incl. comparative)

Data collection methods:

Secondary use of data

Study design:

The study design includes population-based nested case control study, and population-based ecological study

Main study objective:

The main objective is to assess if the odds of AoRRP among females fully vaccinated with GARDASIL™ or GARDASIL™9 before the age of 17 years versus those unvaccinated.

Study Design

Non-interventional study design

Ecological

Other

Non-interventional study design, other

Population-based nested case-control study

Study drug and medical condition

Name of medicine

GARDASIL

GARDASIL 9

Name of medicine, other

- human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)
- human papillomavirus vaccine [types 6, 11, 16, 18, 31, 33, 45, 52, 58] (recombinant, adsorbed)

Anatomical Therapeutic Chemical (ATC) code

(J07BM01) papillomavirus (human types 6, 11, 16, 18)
papillomavirus (human types 6, 11, 16, 18)
(J07BM03) papillomavirus (human types 6, 11, 16, 18, 31, 33, 45, 52, 58)
papillomavirus (human types 6, 11, 16, 18, 31, 33, 45, 52, 58)

Additional medical condition(s)

Recurrent respiratory papillomatosis

Population studied

Short description of the study population

Inclusion Criteria:
Primary objective: All females 15-29 years of age after 2006 and eligible for HPV vaccination at <17 years of age, i.e., birth cohorts 1990 and later.
Secondary objective: All individuals (males and females) 0-29 years of age between the following calendar years and birth cohorts:
- Sweden: 2000 – 2021 (birth cohort, 1971 – 2021)
- Denmark: 1997 – 2022 (birth cohort, 1968 – 2022)
- Norway: 2008 – 2022 (birth cohort, 1979 – 2022)

Exclusion Criteria:
- Subjects who receive a first diagnosis of RRP before age 15 will be excluded for primary analysis

- Subjects who immigrated to Sweden or Denmark after 2006, or to Norway after 2008, and age 9 years
- Subjects who receive the bivalent vaccine Cervarix

Age groups

Term newborn infants (0 – 27 days)

Infants and toddlers (28 days – 23 months)

Children (2 to < 12 years)

Adolescents (12 to < 18 years)

Adults (18 to < 46 years)

Estimated number of subjects

15000000

Study design details

Setting

Nordic population, patient, and vaccine registries

Comparators

For each case of AoRRP, 10 control subjects free of this diagnosis will be randomly selected from the underlying population at risk in the respective countries, using incidence density sampling procedures. Matching criteria will be age at diagnosis, calendar year, region where case was diagnosed, and length of follow-up.

Outcomes

Primary objective: A subject will be defined as having a first case of AoRRP if she has > or = 1 hospitalization or outpatient record with diagnosis registered

as ICD-10 code D14.1 along with appropriate topography/morphology or SNOMED/Norpat codes as deemed necessary by experts, between 15-29 years of age.

Secondary objective:
All subjects will be defined as having a case of JoRRP if he/she has > or = 1 hospitalization or outpatient record with diagnosis registered as D14.1 along with appropriate topography/morphology or SNOMED/Norpat codes as deemed necessary by experts, with a first diagnosis of this condition before 15 years of age.

All subjects will be defined as having a case of AoRRP if he/she has > or = 1 hospitalization or outpatient record with diagnosis registered as D14.1 along with appropriate topography/morphology or SNOMED/Norpat codes as deemed necessary by experts, with a first diagnosis of this condition after 15 years of age and before 30 years of age.

Data analysis plan
Primary objective: Conditional logistic regression will be used for estimation of odds ratios (ORs) and corresponding 95% confidence intervals in the pooled analysis using 1-step approach, with adjustment for clustering and adjustment for relevant covariates; all measured with similar high accuracy in each country. Descriptive statistics will be calculated for the epidemiological measures of interest for cases and controls for age, education level (subject/mother), and income (individual/family) using t-test or chi-2-test for differences in continuous and categorical variables, as appropriate.

Secondary Objective: Annual age-standardized incidence rates (ASIRs) of JoRRP and AoRRP will be calculated, stratified by age group, gender, and calendar period and the p-values from the test for calendar year trends for these rates

will be estimated. Confidence intervals will be calculated.

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)

Sweden National Prescribed Drugs Register / Läkemedelsregistret

The Cancer Registry of Norway

Data source(s), other

- National Vaccination Registry and Swedish Vaccination Registry (SVEVAC), Sweden
- Total Population Registry and National Patient Registry, Sweden
- Longitudinal Integrated database for Health insurance and Labour market studies (LISA), Sweden
- Multigenerational registry, Sweden
- Population Registry (Danish Civil Registration System), Denmark
- National Patient Registry and National Health Service Registry, Denmark
- National Prescription Register, Denmark
- Statistics Denmark

- Pathology Register, Denmark
- National population registry, Norway
- Norwegian patient registry
- Norwegian Prescribed Drug Registry
- Norwegian Immunisation Registry (SYSVAK)
- Statistics Norway

Data sources (types)

Disease registry

Electronic healthcare records (EHR)

Non-interventional study

Other

Population registry

Data sources (types), other

Prospective patient-based data collection and exposure registry

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Yes

Check completeness

Yes

Check stability

Unknown

Check logical consistency

Yes

Data characterisation

Data characterisation conducted

Yes