PAES INFORMATION

Title	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.
Protocol Version identifier	V503-088-01-v1
Date of last version of protocol	Aug 31, 2022
HMA-EMA Catalogue of Real-World Data:	EUPAS48452
Active substance:	Each dose of Quadrivalent Human Papillomavirus Recombinant Vaccine (GARDASIL®, G4) contains 20 µg HPV 6 L1 VLP, 40 µg HPV 11 L1 VLP, 40µg HPV 16 L1 VLP, and 20 µg HPV 18 L1 VLP, along with 225 µg of alum. Each dose of Nonavalent Human Papillomavirus Recombinant Vaccine (GARDASIL®9, G9) contains 30 µg HPV 6 L1 VLP, 40 µg HPV 11 L1 VLP, 60µg HPV 16 L1 VLP, 40 µg HPV 18 L1 VLP, 20 µg HPV 31 L1 VLP, 20 µg HPV 33 L1 VLP, 20 µg HPV 45 L1 VLP, 20 µg HPV 52 L1 VLP, and 20 µg HPV 58 L1 VLP, along with 500 µg of alum.
Medicinal product(s):	G4: Quadrivalent Human Papillomavirus Recombinant Vaccine G9: Nonavalent Human Papillomavirus Recombinant Vaccine
Joint PAES	No

Research question and objectives	**Primary Objective:** To assess if the odds of AoRRP are lower among females fully vaccinated with GARDASIL/GARDASIL9 before the age of 17 years versus those unvaccinated. **Secondary Objectives:** 1) To assess annual age-standardized incidence rates of AoRRP (ages 15-29 years) among males and females. 2) To assess annual age-standardized incidence rates of juvenile-onset recurrent respiratory papillomatosis (JoRRP) (ages 0-14 years) among males and females.
Country(-ies) of study	Sweden, Denmark, and Norway
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Merck Final Repository (REDS) Date	01-AUG-2024
Date of Health Authority Approval of Protocol	N/A

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LIST OF ABBREVIATIONS

AE	*Adverse event*
AoRRP	*Adult-onset Recurrent Respiratory Papillomatosis*
ASIR	*Age-Standardized Incidence Rate*
ATC	*Anatomical Therapeutic Chemical*
CI	*Confidence Interval*
CT	*Chlamydia Trachomatis*
CRN	*Cancer Registry of Norway*
EGW	*External Genital Warts*
EMA	*European Medicines Agency*
FDA	*Food and Drug Administration*
GPP	*Good Pharmacoepidemiology Practice*
HPV	*Human Papillomavirus*
ICD-10	*International Classification of Disease, 10th Modification*
IEC	*Independent Ethics Committee*
ISERP	*Independent Safety Epidemiology Review Panel*
IRB	*Institutional Review Board*
JoRRP	*Juvenile-onset Recurrent Respiratory Papillomatosis*
KI	*Karolinska Institutet*
LISA	*Longitudinal Integrated database for Health insurance and Labour market studies*
MBR	*Medical Birth Register*
NBHW	*National Board of Health and Welfare*
NorPD	*Norwegian Prescription Database*
NPR	*National Patient Register*
OPC	*Oropharyngeal Cancer*
OR	*Odds Ratio*
PASS	*Post-Authorization Safety Study*
PIN	*Personal Identification Number*
PQC	*Product Quality Complaint*
RR	*Relative Risk*
RRP	*Recurrent Respiratory Papillomatosis*
SAP	*Statistical Analysis Plan*
SCR	*Swedish Cancer Register*
SD	*Standard Deviation*
SNOMED	*Systemized Nomenclature of Medicine*
SOP	*Standard Operating Procedure*
SYSVAK	*Norwegian Immunization Registry*
SQI	*Significant Quality Issue*

1 RESPONSIBLE PARTIES

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Supplier/Collaborator	PPD
Shared responsibilities	1) Drafting of protocol, 2) Execution of study, 3) Interpretation of results, and 4) Drafting of study report

2 ABSTRACT

Title	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.
Protocol Number / Version	V503-088-01-v1
Date	18Jul2024
Author	PPD
Rationale & Background	Recurrent respiratory papillomatosis (RRP) is a medical condition where HPV types 6 and 11 cause wart-like growths in the larynx. The condition is rarely fatal but associated with high morbidity. Current treatment only offers temporary symptomatic relief. There is an expectation that HPV vaccination targeting types 6 and 11 will reduce incidence of RRP. To date, no study has evaluated the effectiveness of HPV vaccination against AoRRP. Due to the low incidence of AoRRP, a randomized controlled trial to evaluate the efficacy of HPV vaccination against RRP would be prohibitively large and complex. The comprehensive national registry systems of Sweden, Denmark, and Norway afford the opportunity to evaluate the effectiveness of GARDASIL/GARDASIL 9 in lowering the risk of AoRRP in the female population with minimal biases due to completeness and representativeness of the data.

Research Question(s) & Objective(s)	**Primary Objective:** 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. The study success criterion requires demonstration that the odds ratio comparing unvaccinated to vaccinated females be ≥3.0 and the lower bound of 95% CI be ≥1.33. **Secondary Objectives:** 1) To assess annual age-standardized incidence rates of AoRRP (ages 15-29 years) among males and females. 2) To assess annual age-standardized incidence rates of JoRRP (ages 0-14 years) among males and females. **Exploratory Objectives:** To assess factors associated with risk of AoRRP.
Study Design	Population-based nested case-control study (primary objective); Population-based ecological study (secondary objectives)
Population	**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) **Exploratory objective:** Same population as the primary objective.

Variables	**Exposure definition:** Full receipt of GARDASIL/GARDASIL 9 vaccination regimen for effectiveness evaluation (2 or 3 doses according to age at vaccination). **Outcome definitions:** • First diagnosis of AoRRP (females only) identified from national registries for primary analysis. • First diagnosis of JoRRP and AoRRP (males and females) from national registries for incidence rates assessment in secondary analyses. **Covariates:** Vaccination age, history of external genital warts (EGW), and sociodemographic variables (education level, income).
Data Sources	Nordic population, patient, and vaccine registries.
Study Size	Sample size **Primary objective (nested case-control study):** Cases: <50 AoRRP cases in each country. Controls: 10 controls per case will be selected. **Secondary objectives (ecological study):** Descriptive/no power calculation. Entire age eligible population during specified calendar years in Sweden, Denmark, and Norway will be eligible.
Data Analysis	**Power calculation for primary objective:** A total of 60 AoRRP cases from Sweden, Denmark, and Norway will provide the study with approximately 80% power to detect an odds ratio equal to 3.0 with a corresponding lower bound of 95% CI of odds ratio equal to 1.33. **Primary analysis:** Conditional logistic regression for estimation of ORs and corresponding 95% CIs. In the main analysis, only vaccination before 17 years of age will be considered as exposure.

Milestones	**Planned Date**
Start of data collection:	26Oct2021 (Actual)
End of data collection:	3Q2024
Final report of study results:	1Q2025

3 AMENDMENTS AND UPDATES

Update no	Date	Section of Study Protocol	Update	Reason	CORE DRC Approval Date	CORE DRC Version No
1	13Mar22	7.1, 7.6.2, 7.10	Case and control matching criteria	Regulatory agency feedback	25Apr22	2.0
		7.6.3, 7.10	Covariates	Regulatory agency feedback	25Apr22	2.0
		7.8, 7.10	Sample size and power	Regulatory agency feedback	25Apr22	2.0
2	31Aug22	PAES Information	Changed the quantity of alum for GARDASIL®9 vaccine to 500 µg.	Due to an error in the previous version of the protocol.	n/a	2.1
		7.6.2, 7.6.3	Changed the case definition for the secondary objective and the covariate definition to match the case definition for the primary objective (≥ 1 instead of >1 hospitalization or outpatient record).	To correct the case definition of the secondary objective and covariate.	n/a	2.1
3	21Jun23	4	Milestone dates updated.	Due to data collection period extension.	27Jul23	3.0
		7.1, 7.2, Annex 2 (Tables 2, 3, and 5; Figures 2 and 3)	Data collection period extended to 2021.	Inclusion of most recent data available from registries.	27Jul23	3.0
		7.8	Inserted description of strategy to pool data with other Nordic countries to improve power/precision.	Pre-specify analysis approach.	27Jul23	3.0

Update no	Date	Section of Study Protocol	Update	Reason	CORE DRC Approval Date	CORE DRC Version No
4	23Nov23	7.8	Provided number of confirmed AoRRP cases in the Sweden registries and estimated power.	Estimated study power in Sweden alone is <80%.	18Jul24	4.0
5	12Feb24	6.12	Included additional study limitation	Acknowledge that younger birth cohorts have high herd protection.	18Jul24	4.0
6	05May24	All sections	Major amendment made to the protocol. Data from Denmark and Norway will be added to the study.	Insufficient power with data from Sweden alone. The protocol is now in harmony with the Juvenile RRP (JoRRP) protocol.	18Jul24	4.0
		1	Additional principal investigators added, sponsor information updated.	Due to combination of Sweden, Denmark, and Norway data.	18Jul24	4.0
		2	Amended the study population and updated sample size/power estimates.	Due to combination of Sweden, Denmark, and Norway data.	18Jul24	4.0
		4	Milestone dates updated.	Due to delay caused by the decision to combine Sweden, Denmark, and Norway data to attain	18Jul24	4.0

Update no	Date	Section of Study Protocol	Update	Reason	CORE DRC Approval Date	CORE DRC Version No
				adequate power for the analysis.		
		5, 6, 7.1, 7.2, 7.7, 7.9, 7.10, Annex 1, Annex 2	Amended these sections to include information from Denmark and Norway.	Due to combination of Sweden, Denmark, and Norway data.	18Jul24	4.0
		7.1	Cohort: Added justification to use the age group 15-29 years for the AoRRP protocol. Added Table 1 and Figure 1 to describe the ages, birth cohorts, and calendar years of coverage of included participants from Sweden, Denmark, and Norway.	Clarification of ages, birth cohorts, and calendar years of coverage of included participants from Sweden, Denmark, and Norway.	18Jul24	4.0
		7.1	Cases: Updated this section to highlight different case definitions for Sweden, Denmark, and Norway for more accurately capturing AoRRP cases in those countries along with a justification for this approach.	Clarification and description of case definition.	18Jul24	4.0
		7.6.1	Added a clarification that a person will be classified as unexposed if they did not receive even a single dose of Gardasil prior to being selected as a case or control in the study.	To clarify exposure.	18Jul24	4.0

Update no	Date	Section of Study Protocol	Update	Reason	CORE DRC Approval Date	CORE DRC Version No
		7.6.2	Added use of topography/morphology or SNOMED/Norpat codes from pathology registries to define AoRRP cases.	To clarify outcome definition.	18Jul24	4.0
		7.8	Updated the power calculation, sample size estimates, and Table 2, which describes estimated power based on varying the effect size, vaccination coverage, and number of AoRRP cases. Provided a justification to pool data from Sweden, Norway, and Denmark.	Due to combination of Sweden, Denmark, and Norway data.	18Jul24	4.0

4 MILESTONES

Milestone	Planned Date
Registration in the HMA-EMA Catalogue of Real-World Data	04Oct2022 (Actual)
Start of data collection	26Oct2021 (Actual)
End of data collection	3Q2024
Final report of study results	1Q2025

5 RATIONALE AND BACKGROUND

Background

Recurrent respiratory papillomatosis (RRP) is a generally benign, self-limiting disease, characterized by the appearance of papillomatous lesions anywhere in the aero-digestive tract; however, the vast majority of lesions (>95%) are detected in the larynx [1] [2]. Most RRP cases (>90%) are caused by HPV types 6 and 11[1]. Despite being rare, the health and economic burden associated with RRP is substantial. Nearly 20% of RRP patients experience aggressive disease requiring >40 lifetime procedures, and some patients may undergo >100 surgeries in their lifetime [3]. Further, malignant transformation of RRP occurs in 3 to 7% of patients [4].

Adult-onset RRP (AoRRP) is most often diagnosed between ages 20-40 years [3]. In cases of AoRRP, causal HPV infections are likely acquired through sexual behavior like other HPV related diseases [5]. The risk factors for AoRRP are only partially described and the mechanisms involved appear to be dominated by sexually acquired oral HPV infection transmitted horizontally between adults [5]. Risk factors for RRP are largely unknown. Limited number of studies evaluating AoRRP incidence have reported estimates that ranged from approximately 0.5 per 100,000 in Denmark and Norway to 1.8 per 100,000 in the US [6] [7] [8].

Juvenile-onset RRP (JoRRP) is most often diagnosed between ages 2-4 years[3]. In cases of JoRRP, the likely route of HPV transmission is from mother to child during labor. Numerous age cut points have been used to define JoRRP cases, typically ranging from 11 to 17 years. In Denmark, children born to mothers with external genital warts (EGW) were found to have ~230-fold increased risk compared to children born to mothers without genital warts [9]. Studies focused on JoRRP have reported incidence ranging from 0.2 to 4.3 per 100,000 across several countries, including Denmark, Norway, South Africa, Canada and the US[6] [8] [10] [11] [12] [13]. A recent US study focusing on JoRRP found a pre-vaccination incidence of 2 per 100,000 births in 23 US states, but this may have been an underestimation due to technical problems in case ascertainment and using national (versus state level) denominator data[14].

Given the high attribution of targeted HPV types 6 and 11, high GARDASIL/GARDASIL 9 vaccine effectiveness is expected against RRP. A recent Australian surveillance study found that the incidence rate of JoRRP declined from 0.16 per 100,000 in 2012 to 0.02 per 100,000 in 2016 (p=0.03) following introduction of an extensive GARDASIL vaccination program [15]. This program initially targeted females 12-26 years in 2007-2009, and achieved very high coverage, e.g., >85% of girls <16 years of age received at least one dose. Among 15 incident JoRRP cases observed in this study, none of the mothers of these cases received vaccination prior to pregnancy, and 20% had a maternal history of external genital warts. Further, 13/15 of the affected children were born vaginally, and all genotyped cases (n=7) were either HPV6 (n=4) or HPV11 (n=3) positive [15]. Similarly, investigators recently reported a significant decline in the incidence of JoRRP following HPV vaccine introduction in the United States, from 2 per 100,000 births (in 2004-2005 birth cohort) to 0.5 per 100,000

births (in 2012-2013 birth cohort), which the authors suggest is most likely due to GARDASIL vaccination[14]. No publications exist focused on the evaluation of AoRRP incidence trends in settings with early introduction of GARDASIL or GARDASIL 9.

Rationale

Despite this medical condition being rare, the health and economic burden associated with RRP is substantial due to the high number of surgeries required in management of each RRP case. During the period 2004 to 2007, the mean annual cost for managing JoRRP and AoRRP cases in the US (2010 US dollars) was estimated to be 123 million and 48 million, respectively [16]. As there is currently no cure, treatment focuses on maintaining voice quality and airway patency[17]. A similar percentage of children and adults with RRP experience aggressive disease requiring >40 lifetime procedures (19% and 17%, respectively) [3].

Due to the low incidence of JoRRP and AoRRP, it is not feasible to conduct a randomized controlled trial to evaluate the efficacy of HPV vaccination in reducing the incidence of RRP. However, an observational (real-world) study to assess whether GARDASIL/GARDASIL 9 vaccination is associated with a reduction in the risk of RRP in vaccinated compared to unvaccinated populations is feasible, especially in the Scandinavian region (Denmark, Norway, and Sweden). These countries have established comprehensive systems of registries nationwide that can be linked by a personal identification number (PIN) at an individual level within each country. These registry systems afford the opportunity to evaluate the population-based, real-world, effectiveness of GARDASIL/GARDASIL 9 against RRP with minimal biases due to completeness and representativeness of the data. The Nordic registries are a reputable and trusted source of data by regulatory authorities and other public health stakeholders. These registries have previously been used to conduct post-licensure surveillance studies of GARDASIL [18], which has been shown to be highly effective against high-grade cervical lesions and invasive cervical cancer in the real-world using Swedish and Danish registry information [19] [20] [21] [22] [23]. Also, long-term effectiveness of GARDASIL through at least 14 years has been demonstrated in an extension of the FUTURE II study based on registry information from Nordic countries, including Sweden, Denmark, and Norway[24]; this study extension was conducted as a commitment to the FDA and the EMA. Besides national registries, Sweden, Denmark, and Norway have similar demographic characteristics, universal healthcare, healthcare expenditure, and public healthcare systems [25] [26]. All three countries introduced GARDASIL in their national vaccination programs with the quadrivalent vaccine providing protection against HPV types 6 and 11 which cause RRP. Moreover, the proportion of sexually active 15-year-old girls (30-40%) [27] and the median age at initiation of sexual activity (16-17 years) [28] is similar in these three countries. These factors lead to a homogenous population regarding risk of HPV infection and related diseases and permit pooling of data across these countries to assess the effect of HPV vaccination on a rare outcome such as RRP.

Since initial licensure of GARDASIL in 2006, many countries have implemented publicly funded vaccination programs. GARDASIL was approved in October 2006 in Sweden, and the Swedish free-of-charge national HPV vaccination program (targeting all girls born 1999

or later and attending the 5th or 6th grade; ages 10-12 years) was introduced in 2010. After public purchasing procedures, large-scale vaccination with high coverage of GARDASIL was achieved in 2012. Fully subsidized catch-up vaccination for girls aged 13-17 years has been available in Sweden since 2012, and partially subsidized for the same age group since 2007. In 2015, a 2-dose schedule (with doses administered 6 months apart) was recommended for females <14 years of age, and in 2020, males were included in the school-based national immunization program, with switch to use of GARDASIL 9 in 2020 as well. In Denmark, the earliest primary vaccination cohorts (girls 12 years of age since 2009) and catch-up cohorts (girls 13-15 years of age from 2008 to 2012) are now in their mid to late 20's. In 2012, another catch-up program (targeting females up to age 27 years) was implemented, with the oldest targeted females now being in their mid-30's. Vaccination coverage across targeted birth cohorts (1985+) in Denmark is >70%, but low (~5% to 10%) in cohorts born during the 1970s to the mid-1980s. In Norway, an organized school-based HPV vaccination program was initiated in 2009, in which girls approximately 12 years of age (i.e., attending the seventh grade) were offered GARDASIL in a three-dose schedule (until 2017). The first cohort targeted was girls born in 1997, with coverage >70%. Cervarix (recombinant HPV bivalent [types 16 and 18] vaccine) is currently used in Norway (since 2017).

Here, we propose a national, population registry-based case-control study investigating GARDASIL/GARDASIL 9 effectiveness against AoRRP. For the purpose of this proposed study, we will use the term "Gardasil" in the protocol to represent either GARDASIL (G4, quadrivalent vaccine) or GARDASIL 9 (G9, nonavalent vaccine), unless otherwise specified. Demonstration of Gardasil effectiveness against AoRRP would support the recommendation to administer vaccination to prevent a serious disease caused by HPV types 6 and 11, which is rarely fatal, but associated with high morbidity. Additionally, estimation of the annual incidence of JoRRP and AoRRP (evaluated separately) before and after Gardasil introduction would provide an ecologic perspective on the impact of Gardasil vaccination in the Nordic countries and could also help inform future studies focused on the evaluation of Gardasil effectiveness against JoRRP.

6 RESEARCH QUESTIONS AND OBJECTIVES

Primary Objective

To assess if the odds of AoRRP are lower among females fully vaccinated with Gardasil before the age of 17 years versus those unvaccinated. *

* In case-control studies, the odds (likelihood) of exposure are typically assessed among cases of a disease and compared with controls. However, given that the odds ratio is the same regardless of how it is defined in terms of marginal probabilities (i.e., probability of exposure given disease or probability of disease given exposure are statistically equivalent), we have chosen to express it as the latter (probability of disease given exposure) to provide a measure of the protective effect of vaccination against RRP. Additionally, given the rare outcome of RRP and the use of incidence density sampling, odds ratio estimates will be interpreted as the corresponding relative risks.

Secondary Objectives:

1) To assess annual age-standardized incidence rates of AoRRP (ages 15-29 years) among males and females in Sweden, Denmark, and Norway.

2) To assess annual age-standardized incidence rates of JoRRP (ages 0-14 years) among males and females in Sweden, Denmark, and Norway.

Exploratory Objectives:

1) To assess factors associated with risk of AoRRP, including history of external genital warts and socioeconomic factors.

7 RESEARCH METHODS

7.1 Study Design

Primary Objective: Nested Case-Control Study

Setting: Sweden, Denmark, Norway.

In all Nordic countries, registries have been established to capture disease and vaccination history, as well as other demographic data. Importantly, all registry data can be linked by a unique PIN that is assigned to each resident at birth (or at the time of immigration) and does not change through the resident's lifetime. Therefore, existing infrastructure and registry systems are an excellent resource for monitoring the burden of HPV-related disease in the general population. Registries are accurate, complete, and have high population coverage, thereby minimizing some biases inherent in observational studies, such as selection of the study population, recall bias, and lack of access to complete medical records.

Design: Population-based nested case-control study. A nested case-control design allows the selection of controls from the same underlying population at risk as the cases, therefore reducing confounding and selection bias. This design is used for studies of rare diseases and is particularly advantageous for studies of biologic precursors of disease [29].

Cohort: AoRRP cases are most often diagnosed between ages 20-40 years [3] and causal HPV infections are likely acquired through sexual behavior like other HPV related diseases [5]. Several age-based cut points have been proposed to distinguish JoRRP from AoRRP (ranging from 11 to 17 years). In this proposed study, we used a cut point of 15 years for AoRRP based on expert opinions that RRP diagnosed before the age of 15 years are likely due to HPV infections acquired during birth from mothers and HPV infections at 15 years and older ages are likely acquired through sexual transmission. The median age at first intercourse among Scandinavian women was 16 years in Denmark and 17 years in Norway and Sweden [28]. An upper age of below 30 (i.e., study including 15-29-year-olds) was chosen by the study team since Gardasil is most efficacious when administered at younger ages.

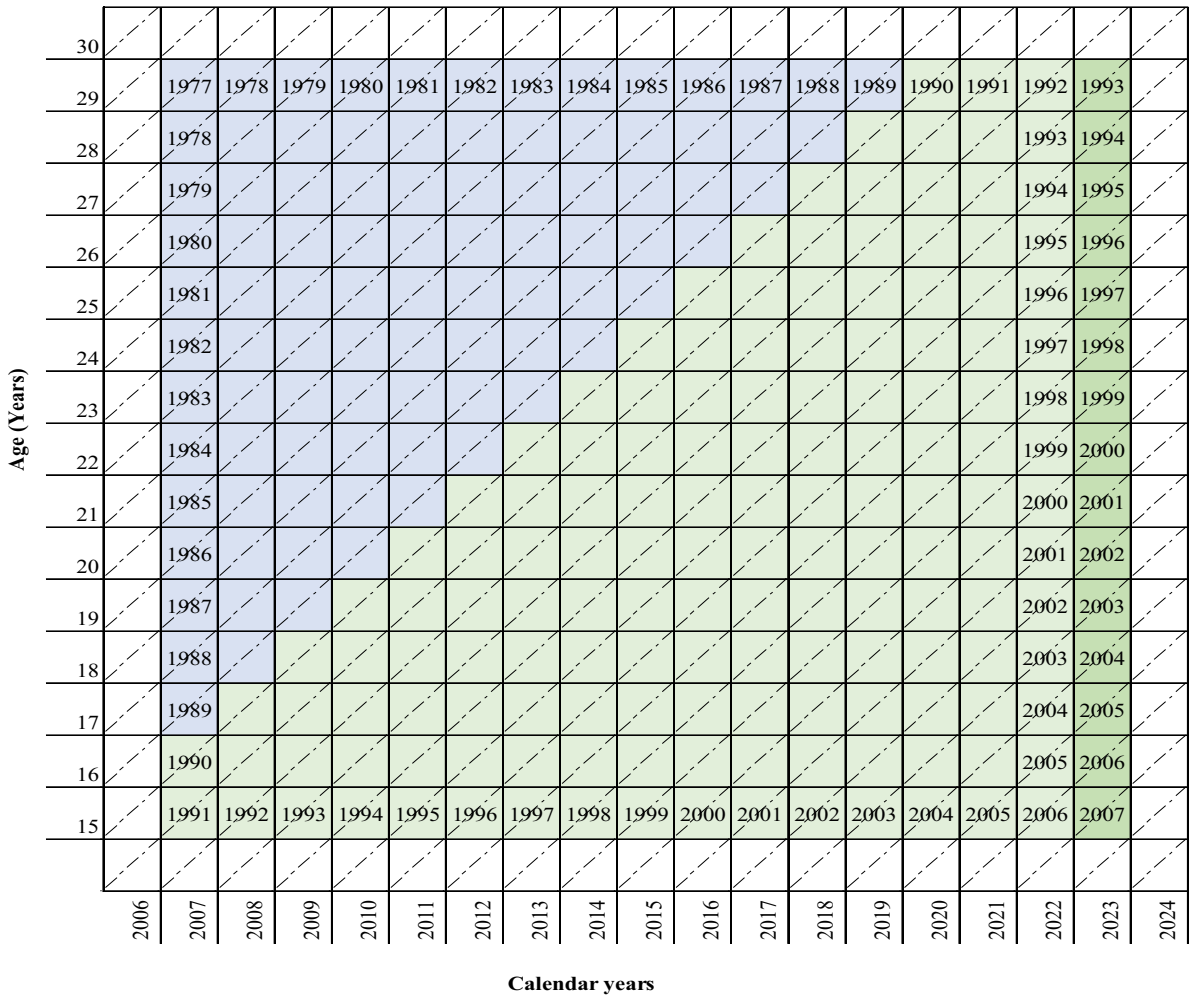
Gardasil was not available in Sweden, Denmark, and Norway until 2006. Therefore, we plan to capture the cohort of girls/women aged 15 to 29 years beginning 2006 till the most recent registry data are available from each country, which currently is 2021 for Sweden and 2022 for Denmark and Norway. A description and rationale for the age groups, birth cohorts, and calendar years of coverage included for the three participating countries is provided in Table 1 and Figure 1 below.

Table 1 Description of age groups, birth cohorts, and calendar years of the participants included in the primary and secondary analysis.

Country	Age at diagnosis	Birth cohort	Calendar year – study period
Primary analysis (Exposure: HPV vaccination at < 17 years of age)			
Sweden	15 – 29 years	1990 – 2006	2006 through 2021
Denmark	15 – 29 years	1990 – 2007	2006 through 2022
Norway	15 – 29 years	1990 – 2007	2006 through 2022
Secondary analysis (All available data)			
Sweden	0 – 29 years	1971 – 2021	2000 through 2021
Denmark	0 – 29 years	1968 – 2022	1997 through 2022
Norway	0 – 29 years	1979 – 2022	2008 through 2022

In Figure 1 below, age of participants is represented on the y-axis (horizontal grid lines), calendar year is represented on the x-axis (vertical grid lines), and the birth cohort is represented by the diagonal grid lines and years of birth labelled in the cells. The shaded green areas represent the ages, birth cohorts, and calendar years for the participants included in the study for the primary analysis. Light green shade represents Sweden (with participants followed from the beginning of 2006 through to the end of 2021). Dark green shade represents additional years of coverage for ascertainment of AoRRP outcomes, from the beginning of 2006 through to the end of 2022. Grey shaded areas represent birth cohorts from eligible ages and calendar years of coverage that will not be included in the study as they represent participants who may have received HPV vaccine after 17 years of age. Eligible participants from earlier birth cohorts enter and exit the study period early. For example, a 16-year-old girl born in 1990 will enter the study in 2006 and exit the study in 2019 after reaching the age of 29 years.

Figure 1 Lexis diagram to visualize the ages, birth cohorts, and calendar years of coverage of included participants from Sweden, Denmark, and Norway.



As described in Section 5 (above), since 2012 in Sweden, females ages 10-12 years have been targeted for vaccination as part of school-based program, with fully subsidized catch-up vaccination up to age 17 years (partially subsidized for females ages 13-17 years since 2007). In Denmark, vaccination of girls 12 years of age started in January 2009, and catch-up vaccination of girls 13-15 years of age started in October 2008. In 2012, another catch-up program (targeting females up to age 27 years) was implemented. HPV vaccination program was initiated in Norway in 2009, in which girls approximately 12 years of age (i.e., attending the seventh grade) were offered Gardasil in a three-dose schedule (until 2017). Males were not included (or only recently included) in national immunization programs during the study period in Sweden, Denmark, and Norway and therefore due to very low coverage it is not feasible to include males in the study.

Cases: Within the specified cohort, AoRRP (females only) cases (first diagnosis) will be identified from national registries using the ICD-10 code D14.1 (benign neoplasm of larynx). The date of first diagnosis is the index date for AoRRP cases. Compared to JoRRP, other benign laryngeal conditions such as laryngeal granulomas and nodules associated with

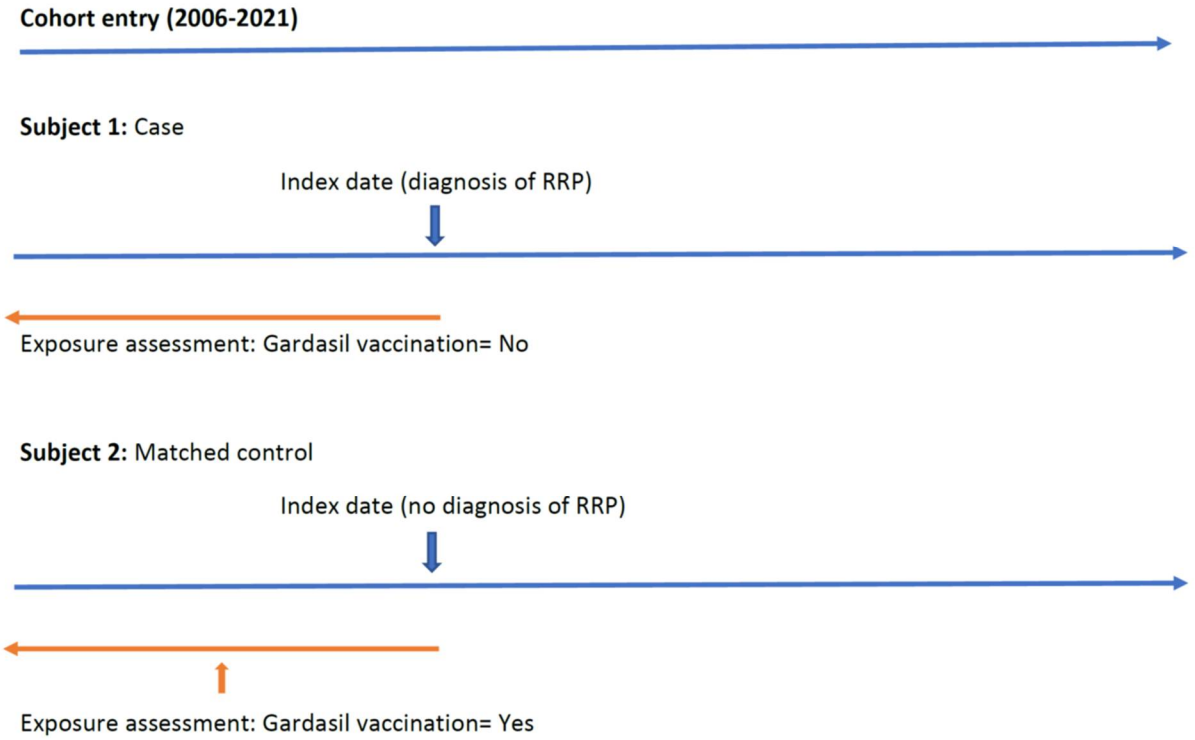
behaviors such as smoking are likely to be more common among adults and may result in misclassification of the AoRRP outcome based on the use of D14.1 code alone. Therefore, we will use the best practices for accurate ascertainment of AoRRP cases from registries in each participating country to minimize biases after consulting experts and clinicians and reviewing the cases. In countries where topography/morphology codes are available/complete in the cancer/pathology registry, AoRRP definition will require D14.1 and/or appropriate topography/morphology codes.

In Sweden, local experts have confirmed that ICD-10 diagnosis code D14.1 (especially subcode A representing "larynx papilloma") is used for diagnosis of RRP and should be used to ascertain AoRRP cases. Experts have recommended use of appropriate topography and SNOMED (Systematized Nomenclature of Medicine) codes to ascertain AoRRP cases more accurately in Denmark. When available and complete, appropriate topography and Norpat (Norwegian Pathology Code system) codes should be used in conjunction with D14.1 to identify AoRRP cases in Norway. Using this approach, we expect the accuracy of RRP diagnosis to be high in Sweden, Denmark, and Norway. The larynx is the site of the vast majority of RRP cases [1] [2], which supports focusing on "benign neoplasm of larynx" rather than other additional sites (ensuring both high sensitivity and specificity of diagnosis).

Where available, the subcode D14.1A will be explored in a subgroup/sensitivity analysis, as this may be more specific for RRP according to clinician expert input. Additionally, cases of D14.1 and/or D14.1A that have at least one associated treatment or procedural code, e.g., DQB10 (Endoscopic extirpation), UDQ25 (Microlaryngoscopy with biopsy), or UDQ22 (Microlaryngoscopy), will also be explored in a subgroup/sensitivity analysis, with similar expectation that this will be more specific for RRP.

Controls: For each case of AoRRP, 10 control subjects free of this diagnosis, at the time of the case's diagnosis, will be identified from the respective countries where cases were diagnosed. As the number of controls per case increases beyond 4, improvement in statistical power diminishes [30]. However, given that data for additional controls are readily available in this database study, 10 controls per case will be selected. Cases and controls will be matched on age (+/- 1 year) at diagnosis, calendar year, and the region where case was diagnosed. By design of the study (nested case-control), cases and controls will also be matched according to length of follow-up in the registries. Controls will be selected from the population at risk at the point in time when a case is diagnosed with RRP. All controls who met the matching criteria will be assigned a random number using SAS statistical software (SAS Institute Inc, Cary, NC) procedures. Then, 10 controls for each case will be selected at random from the pool of eligible controls. Controls will be assigned the same index date as the case to which they are matched. Figure 2 provides an example of case/control subject selection nested within population-based cohort (2006-2021) in this study.

Figure 2 Example of case/control subject selection nested within population-based cohort (2006-2021) in this study. Subject 1 is classified as a case without exposure to Gardasil prior to the index (diagnosis) date, and subject 2 is an eligible matched control with exposure to Gardasil prior to the index date.



Exposure assessment: The exposure of interest is GARDASIL or GARDASIL 9 vaccination prior to the index date for each case and matched controls. GARDASIL is a quadrivalent vaccine that is effective against HPV types 6/11/16/18, while GARDASIL 9 is a nonavalent vaccine that is effective against HPV types 6/11/16/18/31/33/45/52/58.

Exposure will be defined in 2 ways:

1. Exposure in primary objective: Fully vaccinated with Gardasil (yes/no) before the age of 17 years. A female will be classified as exposed if she received 3 doses of Gardasil (administered at recommended intervals of 0, 2, and 6 months) or 2 doses if <15 years of age (administered at recommended interval of 0 and 6-12 months). For a 3-dose schedule, the minimum intervals are 4 weeks between dose 1 and dose 2 and 12 weeks between dose 2 and dose 3. For a 2-dose schedule, the minimum interval is 5 months between doses. A female will be classified as unexposed if she did not receive even a single dose of Gardasil prior to being selected as a case or control in the study.
2. Exposure in sensitivity analysis: Gardasil vaccination (yes/no). A female who received at least one dose of Gardasil prior to the index date will be classified as exposed.

The vaccine registries in Sweden, Denmark, and Norway accurately capture vaccination [31], greatly reducing the risk of exposure misclassification and providing the foundation for a robust observational study. Prior studies relying on Nordic registries for measurement of Gardasil exposure (in relation to risk of anogenital diseases, including cervical cancer) have been conducted successfully in recent years [21] [32].

Secondary Objectives: Ecological Study

Design: Descriptive/ecologic study using nationwide registry data to assess annual age-standardized incidence rates of JoRRP (0-14 years) and AoRRP (15-29 years) by gender.

Cohort: Male and female residents of Sweden, Denmark, and Norway (ages 0-29 years), during the following periods (Table 1):

- Sweden: 2000 – 2021 (birth cohort, 1971 – 2021)
- Denmark: 1997 – 2022 (birth cohort, 1968 – 2022)
- Norway: 2008 – 2022 (birth cohort, 1979 – 2022)

Cases: RRP cases will be identified from national registries using the case definitions for the participating countries as described above.

Exposure assessment: There is no exposure for ecologic study (secondary objective).

7.2 Setting

The study population is identified using the Total Population Registry in each of the Nordic countries, for information on birth year, migration status, and date of death in each of the respective countries. The registries have full coverage of the Swedish, Danish, and Norwegian populations.

Nested case-control study (primary objective)

The study population is female residents of Sweden, Denmark, and Norway (ages 15-29 years) between 2006 and the latest years of coverage, in primary analysis focusing on those eligible/had a chance to get vaccinated before age 17 years. A description of the ages, birth cohorts, and calendar years of coverage for the included participants is provided in Table 1 and Figure 1.

Ecological study (secondary objective)

The study population is children, women and men living in Sweden, Denmark, and Norway (0-29 years of age) between the following calendar years and birth cohorts (Table 1):

- Sweden: 2000 – 2021 (birth cohort, 1971 – 2021)
- Denmark: 1997 – 2022 (birth cohort, 1968 – 2022)

- Norway: 2008 – 2022 (birth cohort, 1979 – 2022)

7.3 Inclusion Criteria

- The study subject must be alive and reside in Sweden, Denmark, or Norway as defined through the Total Population Registry of the respective countries at some point during the time period specified. Subjects will be censored at date of emigration (where applicable), and upon date of death (where applicable).

- The study subject must be of the appropriate age range (15-29 years) for AoRRP (primary objective).

- Only females are eligible to be included for the primary objective (due to low coverage of Gardasil vaccination among males during study period), whereas both genders are eligible to be included for the secondary objectives.

- To be considered as a potential case of RRP (for either primary or secondary objective), a study subject must have at least one first diagnosis of RRP (as defined in Section 7.1) in the appropriate country-specific registry, during the specified time period of focus.

7.4 Exclusion Criteria

- Subjects who receive a first diagnosis of RRP before age 15 will be excluded for primary analysis, as this more likely reflects a maternally transmitted juvenile-onset case, rather than a sexually transmitted adult-onset case.

- Subjects who immigrated to Sweden or Denmark after 2006, or to Norway after 2008, and age 9 years will be excluded as vaccination exposure status is unknown, and follow-up in registries may be insufficient to determine if incident case is truly new onset (primary objective).

- Subjects who receive the bivalent vaccine Cervarix (recombinant HPV bivalent [types 16 and 18] vaccine, GlaxoSmithKline) will be excluded since it provides no protection against the causative HPV types (6 and 11) in RRP (primary objective).

7.5 Stratification

Stratified analyses, statistical adjustment, and/or assessment of interaction will be performed for the primary objective according to the following factors:

1) Age at vaccination (girls/women vaccinated before 17 years of age or after 17 years of age compared to unvaccinated). Primary objective/analysis will focus on evaluation of vaccine effectiveness among females vaccinated before 17 years of age.

2) Personal history of external genital warts (yes/no).

Stratified analyses for the secondary objective will be performed according to calendar year, gender, and age.

7.6 Variables

All the below variables are intended to be analyzed as categorical variables for primary analysis. Where applicable, continuous covariates such as income or number of years of education, will be categorized into standard categories.

Validation: Analyses will be carried out using the ICD-10 code D14.1 (benign tumor of the larynx), and if needed, the equivalent codes to D14.1 in the predecessor ICD system ICD-9 and ICD-7. In countries where available/complete from the pathology/cancer registry, appropriate topography/morphology or SNOMED/Norpat codes (identified in consultation with sub-specialist clinical experts) will also be used to increase specificity of the outcome definition in primary analyses, as discussed in Section 7.1 (Case definition) above. Specificity may also be increased by using ICD-10 code D14.1A, when available. Descriptive statistics of the combinations of diagnostic and procedural codes for all the cases in the dataset will be provided. Study investigators will further work with local clinician expert(s) as needed, to investigate and define which combination of procedural codes (e.g., DQB10, UDQ25, or UDW22) for RRP may provide further specificity to validate the outcome. Depending on exact case numbers available from the registries, the plan is to perform this procedure for all cases identified.

Otorhinolaryngologists/phoniatricians as well as other experts in RRP, HPV, epidemiology, and biostatistics external to the study have provided valuable input on the study design and case ascertainment and will continue to be consulted as needed throughout the study. These experts will play an important role in the validation process, performing case profile review (blinded to vaccination status) to ensure accurate identification and characterization of AoRRP cases. A Scientific Review Committee with expertise in RRP, HPV, epidemiology, and biostatistics has been formed to provide an independent review of study findings, including interpretation of results.

7.6.1 Exposure

A subject will be defined as fully vaccinated and exposed if she has received 2 or 3 doses (depending on age group-specific dose regimen recommendation) of HPV vaccine with GARDASIL or GARDASIL 9 as defined through the ATC code J07BM01 or J07BM03. Among individuals who initiated vaccination prior to 15 years of age, receipt of 2 doses administered at 0 and 6-12 months is considered fully vaccinated, whereas among individuals who initiate vaccination after 15 years of age, 3 doses administered at 0, 2, and 6 months is considered fully vaccinated. Sensitivity analysis will be performed where individuals will be classified as exposed/vaccinated if they received at least one vaccine dose. The study primary objective/analysis will focus on evaluation of vaccine effectiveness among females fully vaccinated before age 17 years. A female will be classified as unexposed if she did not receive even a single dose of Gardasil prior to being selected as a case or control in the study. Sensitivity analyses will be performed evaluating effectiveness irrespective of age at vaccination, and among those vaccinated at older ages (≥17 years).

7.6.2 Outcomes

Detailed case definitions for primary and secondary objectives for each participating country are provided in Section 7.1.

Nested case-control study (primary objective)

Definition of AoRRP case: A subject will be defined as having a first case of AoRRP if she has ≥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 [33].

Selection of controls: random selection of 10 controls per case 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.

Ecological study (secondary/exploratory objective)

- All subjects will be defined as having a case of JoRRP if he/she has ≥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 ≥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.

7.6.3 Covariates

In an observational study, where exposure is not randomized, it is important to explicitly express which association is being investigated, and a priori motivate which covariates are proposed for inclusion/exclusion and why. To this end, an Annex to this Protocol has been prepared which lists in detail subject matter expertise reasoning and motivation regarding potential confounders, specifically for the proposed association of study: potential effectiveness of HPV vaccination against AoRRP. Therein, a closer discussion on variables of consideration, the size of associations when known, and potential causal mechanisms supporting a confounding theory are discussed (Annex 1). For all covariates, missing data will be labeled as “Missing” and included as a separate category in the statistical analysis.

Covariates (potential confounders and/or effect modifiers):

1) Genital warts: External genital warts (EGW) or anogenital warts (AGWs) are, like RRP, caused by HPV6 and HPV11. History of EGWs is therefore expected to be a strong risk factor for RRP, with HPV6/11 infection being the likely causative agent for both conditions. It is important to consider that adjustment for EGWs may attenuate the estimated vaccine effect on RRP because some of the vaccine effect on RRP may be attributed to the EGW covariate. It is also possible that maternal history of EGWs may be associated with risk of AoRRP. An individual will be defined as having EGWs based on ≥1 hospitalization or outpatient record with diagnosis registered as A63 with subcodes, and/or a prescription for a pharmaceutical against anogenital warts (ATC codes D06BB10 [imiquimod] and/or D06BB04 [podophyllotoxin], as validated in Levàl et al, 2012 and Herweijer et al, 2014) [31] [34].

2) History of chlamydia infection: EGW is the only sexually transmitted disease which may be comprehensively investigated in Swedish and Danish registries; the other STDs such as *Chlamydia trachomatis* (CT), gonorrhea, or syphilis are protected by law which limits the possibility of tracing individuals with a history of such diagnoses. It is possible to study certain antibiotics such as doxycycline which is drug of choice in treatment of genital CT infection, however this drug is also used in some cases of upper respiratory tract infection in the age group of this study entailing poor specificity of this as proxy for genital infection. In a subset of study population from Norway, Chlamydia infections will be retrieved from the Norwegian Prescription Database based on treatment with doxycycline (ATC code J01AA02).

3) Age at vaccination (before 17 years of age vs 17 years or older): Given the importance of age at vaccination (i.e., vaccination is exclusively prophylactic, and risk of HPV exposure increases with age), the primary objective is focused on evaluation of effectiveness among females fully vaccinated before 17 years of age.

4) Education level of subject/mother (highest level achieved) will be categorized as low/medium/high according to the Swedish, Danish, and Norwegian system of number of school years.

5) Annual individual/family income will be categorized in tertiles or quantiles relative to the general female population of the respective Nordic country and corresponding age structure from the KI team's previous study on HPV vaccine uptake in relation to parents' country of birth, education and income, there were 2.2%, 3.9% and 3.1% missing data for mothers and 4.2%, 6.6% and 6.4% missing data for fathers, respectively [35]. Overall, missing data in this specific field represented a small but definable category which is feasible to be studied as a measure of study participants who are e.g., underserved or lack demographic information due to immigration.

7.7 Data Sources

This is an observational study that will use nationwide data from various registries and databases in Sweden, Denmark, and Norway to monitor incidence rates of upper airway

HPV-related diseases over time. The diseases of interest are collected prospectively on a routine basis and recorded in the registries, thereby allowing the opportunity to conduct retrospective studies.

All registry data can be linked by a unique personal identification number (PIN) that is assigned to each resident at birth (or at the time of immigration into the countries) and does not change through the resident's lifetime. Therefore, the existing infrastructure and registry systems in Nordic countries are an excellent resource for monitoring the burden of HPV-related disease in the general population. The registries in Nordic countries are accurate, complete, and have high population coverage, thereby minimizing some biases inherent in observational studies, such as selection of the study population, recall bias, and lack of access to complete medical records [36] [37] [38].

The study will be conducted using only structured secondary data. The data sources for this study include population, cancer, and vaccine registries. Examples of the data that may be available from these types of registries are shown below for each participating country.

Data sources for this study include for **Sweden** the following population, patient, and vaccine registries:

Total Population Registry

- date of birth
- gender
- migration status
- date of death, if applicable

National Patient Registry

- diagnosis of RRP (both JoRRP and AoRRP)
- diagnosis of external genital warts (own and maternal)
- treatment codes DQB10 (Endoscopic extirpation), UDQ25 (Microlaryngoscopy with biopsy), UDQ22 (Microlaryngoscopy)

Prescribed Drug Registry (PDR)

- ATC code (HPV vaccine: J07BM01 [GARDASIL-4] and J07BM03 [GARDASIL-9], genital warts treatment: D06BB10 and D06BB04)
- date(s) of administration
- other types of information from PDR relevant to understand dosing pattern of relevant products

National Vaccination Registry and Swedish Vaccination Registry (SVEVAC)

- type of vaccine received
- brand name
- date(s) of administration

Multigenerational registry

- index data for linking to mothers of cases and controls in the primary objective to obtain maternal history of EGW

LISA database

- education level of the subject
- parental education level
- individual and household income

Data sources for this study include for **Denmark** the following population, patient, and vaccine registries:

Population Registry (Danish Civil Registration System) (includes information on all residents in Denmark and is daily updated with information on emigration, immigration, death)

- date of birth
- gender
- migration status
- date of death, if applicable

National Patient Registry (contains information on all diagnoses and treatment/procedures related to admissions to hospitals (since 1978) and outpatient clinics (since 1995)

- diagnosis of RRP (both JoRRP and AoRRP)
- date(s) of RRP diagnosis
- procedure and treatment codes in relation to RRP
- diagnoses of genital warts (GWs)

- date(s) of GWs

National Health Service Registry (contains information on all HPV vaccination given free of charge

- type of HPV vaccine received
- number of doses
- dates of administration

National Prescription Register (contains information on all redeemed prescription in Denmark since 1995 - including HPV vaccines bought at own cost)

- type of HPV vaccine received
- number of doses
- dates of administration
- prescription of Podophyllotoxin (drug of choice in Denmark for treatment of GWs)
- dates of administration

Statistics Denmark

- educational level
- income

Pathology Register

- Topography/SNOMED codes in relation to RRP
- Date(s) of RRP diagnosis

Data sources for this study include for **Norway** the following population, patient, and vaccine registries:

National population registry

- Date of birth
- Gender
- Migration, if applicable
- Date of death, if applicable
- Index data for linking to mothers of cases and controls in the primary objective, e.g., to obtain maternal history of vaccination.

Norwegian patient registry

- Diagnosis, including date, of RRP
- Treatment codes, including dates, DQB10 (Endoscopic extirpation), UDQ25 (Microlaryngoscopy with biopsy), UDQ22 (Microlaryngoscopy)
- Diagnosis, including date, of AGW (own and maternal)

Norwegian cancer registry

- Norpat codes on morphology/topography to increase specificity of RRP diagnosis (if feasible)

Norwegian Prescribed Drug Registry

- ATC code (HPV vaccine: J07BM01 Gardasil-4, J07BM02 Cervarix, J07BM03 Gardasil-9), genital warts treatment: D06BB10 Imiquimod and D06BB04 Podophyllotoxin, chlamydia treatment: J01AA02 Doxycycline
- Date(s) of administration
- Other types of information relevant to understand dosing pattern of relevant products

Norwegian Immunisation Registry (SYSVAK)

- Type of HPV vaccine (Gardasil/Gardasil9/Cervarix)
- Date(s) of administration

Statistics Norway

- Education level (subject/parents)
- Annual individual and family income

7.7.1 Study Procedures

The proposed study is non-interventional in nature and does not entail any risk to the study participant, apart from the possibility of integrity breach through accessing public records. Therefore, it must be subject to approval from the ethics review committees in each of the respective countries to mandate this access. All study investigators/research institutions have substantial experience in handling similar studies in an integrity-assured manner and numerous safeguards are in place to maintain confidentiality of information on the study subjects. Also, all data are pseudonymized and the researcher does not have access to the underlying identifiers as these are protected separately by the data holder authority.

7.8 Study Size

Power analysis for the primary objective (nested case-control study):

Estimated power to evaluate the primary objective is presented in this section. Our primary hypothesis is that AoRRP risk is lower among females fully vaccinated with Gardasil before age 17 years versus those who are never vaccinated before case/control selection. This could be also stated as AoRRP risk is higher among females unvaccinated for HPV compared to those who are vaccinated at age < 17 years. The statistical criterion for success requires that the odds ratio (OR) for this comparison be ≥3.0 and lower bound of the 95% confidence interval (CI) for the OR be ≥1.33. In observational studies, high effect estimates are considered important to demonstrate strong associations and to assess causality. Conventionally, odds ratios of <2 are considered to represent weaker associations by epidemiologists, as it may not be possible to judge whether the association can be entirely accounted for by bias [39]. A threshold of 3.0 is therefore proposed to establish the effectiveness of Gardasil vaccination in preventing RRP. Prior Nordic registry studies reported Gardasil effectiveness against genital warts ranging from 38%-88% (equivalent to ORs of 1.6-8.3) and cervical intraepithelial neoplasia grade 2+ ranging from 22%-82% (equivalent to ORs of 1.3-4.0) with higher effect among females vaccinated at younger age.

Based on prior available information (i.e., publicly available gross statistics on ICD codes for otorhinolaryngological diseases), the Sponsor's power calculations (summarized below) at first suggested that it may be possible to test this hypothesis in Sweden alone. However, at the time when this protocol was initially drafted, the exact number of cases were not known and therefore it was noted that a decision to conduct the analysis would be made once data were received from the registries, i.e., when the exact number of cases occurring in relevant birth cohorts was confirmed.

Estimated number of AoRRP cases:

The number of possible AoRRP cases (identified using ICD-10 code D14.1) occurring after Gardasil introduction in Sweden, Denmark, and Norway (among females eligible for vaccination before 17 years of age) were estimated by accessing publicly available gross statistics on ICD-10 codes for otorhinolaryngological diseases, and without assessing the proportion of vaccinated individuals among cases and controls, or conducting any preliminary analyses evaluating the association between HPV vaccination and RRP. Initial case counts from Sweden were expected to be between 30 and 60; recent assessment of the total number of cases in the birth cohorts of interest were 46. In Denmark, the estimated number of possible AoRRP cases (identified using ICD-10 code D14.1) occurring after Gardasil introduction was estimated to be between 50 to 90 in eligible birth cohorts. After applying appropriate topography and SNOMED codes to improve specificity, the number of AoRRP cases will be < 50. In Norway, the estimated number of possible AoRRP cases identified in the Norwegian Patient Registry among females ages 15-29 years for the calendar years 2006-2020 (using ICD-10 code D14.1) and birth cohorts of interest (1990+) is between 40 to 70 cases. These numbers will likely be lower after using appropriate topography/morphology (Norpat) codes to improve specificity (also <50).

Power calculations:

Study power was estimated according to varying number of AoRRP cases (from 40 to 80), effect size (odds ratio from 3.0 to 4.0), and weighted female vaccination coverage (20 to 30%) with constant alpha-level of 0.05, control/case ratio of 10 in the age range of focus (Table 1). To detect a true OR of 3.0 with an overall vaccination coverage of 25% in all three countries combined, approximately 60 AoRRP cases would be needed to achieve a power of at least 80%, which would not be possible by including data from individual countries alone. Precision was also considered by specifying that the analyses for the primary objective be powered to detect an OR of at least 3.0, with a lower bound for the confidence interval of at least 1.33, which is equivalent to lower bound of 95% CI of vaccine effectiveness >25%. Preliminary estimates of vaccination coverage among females in the proposed age group (<17 years) obtained from public registries are ~20% for Sweden, ~50% for Denmark, and ~25% for Norway, and is expected to be at least 25% overall. By pooling data from Sweden, Denmark, and Norway for the primary analysis, the estimated combined number of AoRRP cases occurring after Gardasil introduction in these three countries (birth cohorts 1990+) is expected to be above 60 with >80% power assuming true odds ratio of 3.0 and 25% vaccination coverage (Table 2). Previously, individual level registry data were successfully pooled across multiple Nordic countries (Denmark, Finland, and Sweden) in a case-control study evaluating risk of male breast cancer in association with finasteride use [40].

In Sweden, Denmark and Norway, the attribution of HPV types contributing to HPV-related diseases (including RRP) is similar, and the median age of sexual debut among females is also similar (~16 years) [28]. As expected, prior studies in these countries have reported similar vaccine effectiveness against HPV-related diseases, including against cervical cancer in Sweden and Denmark, i.e., 88% and 86% effectiveness among females who were vaccinated at <17 years of age, respectively [20] [21]. Also, in a very recent Norwegian analysis focusing on Gardasil vaccine effectiveness against CIN2+, investigators reported 82% effectiveness among females vaccinated <17 years of age (lower compared with estimates above but expected given the higher attribution of HPV types other than 16 and 18 in cervical precancer versus cancer) [41].

Table 2 Power estimates according to varying number of cases of AoRRP (from 40 to 80), effect size (odds ratio from 3.0 to 4.0), and vaccination coverage (20-30%), with constant alpha-level of 0.05, lower bound of 95% confidence interval >1.33, control/case ratio of 10.

True effect size	**% Vaccine coverage**	**Number of AoRRP cases**								
		40	45	50	55	60	65	70	75	80
OR = 3	20	0.40	0.46	0.48	0.52	0.57	0.60	0.61	0.65	0.68
	25	0.67	0.71	0.76	0.76	0.80	0.82	0.82	0.85	0.87
	30	0.85	0.87	0.88	0.91	0.92	0.93	0.94	0.95	0.96
OR = 3.5	20	0.48	0.55	0.60	0.65	0.68	0.71	0.75	0.75	0.80
	25	0.77	0.79	0.83	0.86	0.87	0.90	0.92	0.93	0.93
	30	0.91	0.93	0.94	0.95	0.96	0.97	0.98	0.98	0.98
OR = 4	20	0.57	0.63	0.68	0.74	0.76	0.79	0.83	0.85	0.87
	25	0.84	0.86	0.89	0.92	0.93	0.94	0.95	0.96	0.97
	30	0.95	0.96	0.97	0.98	0.98	0.99	0.99	0.99	0.99

Regarding evaluation of Gardasil effectiveness against JoRRP, the Sponsor has similarly proposed including additional data from Denmark and Norway due to study power limitations in Sweden alone.

7.9 Data Management

Prior to initiating this study, a common data model will be prepared along with transfer agreement for Denmark to receive data from Sweden and Norway, including preparation of a clear management plan for data handling to ensure protection of subject privacy. The data management of the variables will be performed before sending the final data to Denmark. Because of legal restrictions, Danish investigators will not be able to transfer the data out of Denmark. Therefore, all data will be received and analyzed by Danish investigators.

All data collected for the study should be recorded accurately, promptly, and legibly. For primary data collection, the investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. For data not obtained from a primary source (i.e., secondary data, such as claims and electronic health records), the investigator is responsible for reviewing data quality and relevance to the best of the investigator's knowledge. By signing this protocol either electronically or written, the investigator confirms that the quality and relevance of data has been assessed to meet the minimum requirements for all study objectives.

If this study has been outsourced, the institutional policies of the supplier should be followed for development of data management plans. However, the supplier should ensure compliance with Good Pharmacoepidemiology Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the study.

Data Management Software and Hardware (per country):

Sweden

- SAS version 9.4 will be used for data management and statistical analyses.
- Stata version 18.0 will be used for statistical analyses.
- R may be used for complimentary statistical analyses and generation of graphs.
- All hardware utilized in the study is procured through central KI purchasing procedures and follow strict regulations on performance and capacity.

Norway

All data management and statistical computing on registry data delivered to the project will be performed in the most recent version of Stata (currently 18.0 MP (StataCorp) or R, using syntax scripts generated by the CRN study team. All syntax that influences the dataset (data management) or generates results (analyses) is stored in the project data script folder on CRN's secure server. Syntax files will be numbered according to the order in which they should be run. All syntax written by one member of the CRN study team is checked by another member of the CRN study team. All output (results) is also assessed by the CRN study team, and any unexpected result is investigated further to double-check that no scripting error has occurred. Tables and figures are transferred to the report template by one member of the CRN study team and the transfer is checked by another member of the CRN study team. All data management, analyses or other data procedures are logged, including information on when the procedure took place and who performed the procedure.

Denmark

A data management plan will be developed to guide and instruct the data manager on the project. This will include a list of the registers used (see section 7.4) and a detailed instruction on the criteria for data extraction from each register. Furthermore, the steps listed in section 7.7 will be part of the data management plan. All steps in data management plan will be gone through between the data manager and investigator before execution and evaluated after execution. The SAS software and the R statistical software will be used in the data management.

Description of Data Preparation and Methods for Data Retrieval and Collection:

Sweden: All data retrieval is documented and traceable through the formal data specification orders exchanged with the registry data holders before data delivery, inclusive of exact variable and format lists. Data collection will take place from Swedish registry data holders through the import of SAS.7bdat format and/or CSV files. Only electronic data will be used, there are no paper-based data in this project. No eCRFs are applicable. Data quality checking will occur right after delivery from the registry data holder, ensuring that requested data are logical and transparent. Data cleaning will be done using SAS version 9.4 and documented through log files and validation procedures as described below. Statistical analyses will be performed using softwares specified above.

Denmark: All data collected in this project are electronic data derived from existing registers (section 7.4). Data will be collected according to the specified criteria in the data management plan i.e., specified age intervals, specified diagnoses etc. that will be developed for this protocol. No data collector will be used in this protocol.

Norway: Data collection will take place from Norwegian registry data holders through the import of CSV and/or dta files. Each registry will securely transfer data to the delivery unit at the CRN, including:

- RRP incidence data from the Norwegian Patient Registry (NPR)
- HPV vaccination status from the Norwegian Immunisation Registry (SYSVAK)
- Prescription data from the Norwegian Prescribed Drug Registry
- Sociodemographic data from Statistics Norway
- Norpat codes from the Norwegian Cancer Registry (CRN)
- Population data from the National Population Registry

Only electronic data will be used, there are no paper-based data in this project. Data received from each registry will be documented by a data-in procedure, including quality checks of incoming data and documentation of data reception and links to the application for data, the data file itself and any documentation accompanying the data file. Data-in and its associated forms are stored in the project data documentation folder. General quality checks of incoming data are carried out to ensure that the data delivery coincides with the data application, e.g., that all the expected variables have been included and contain the expected information, and that the correct number of individuals have been included. Checks will be carried out and any errors reported to the delivering registry within 2 weeks of receipt of data. Any new deliveries of data will be documented by the data-in procedure. All raw data received from the registries will be stored on CRN's secure server as they were delivered to the project, with access restricted to project members only. All data and associated files are backed up regularly and automatically. Data cleaning will be done using Stata or R and documented through syntax scripts and validation procedures as described above.

7.10 Programming Quality

Good programming standards should be followed during all programming associated with the study. No error statements should occur when programs are run. Warning statements should be avoided whenever possible. If warning statements do appear, they should be accompanied by explanatory text, stating why they do not represent a program. A Programming Information Document should be drafted that describes:

- the order by which the SAS or other software programs were run;
- a description of the SAS or other software programs;
- the program's name, location, and author;
- the date of creation and modification where applicable;
- the name and location of the SAS or other software datasets input and output; and
- the purpose of the program.

Data validation should occur throughout the data management and analysis process. Data quality checks may include, but are not limited to, programming checks by an individual who is not main programmer for the study, internal dataset consistency, consistency between datasets, external checks with other available databases for verification of items such as birthdates and vaccination dates and checks to ensure that protocol and SAP criteria were met. If validation checks were not satisfied, then an examination of the problem should be performed on the dataset or datasets in question and the problem resolved. All data validation, quality checks, and resolution of issues identified should be recorded on a standardized form used for this study.

Institution will retain copies of electronic versions of the analytic datasets and programs, and computer printouts. This includes any relevant computer code that produces the basis of tables, discussions, graphs, or interpretations in the study report.

The procedures are applicable to all study programing, tables and figures associated with study final report, and additional analyses requested by MSD.

7.11 Data Analysis

Data Pooling

Data from the three Nordic countries will be pooled by developing a common data model. The list of variables, including the primary exposure, outcome, and covariates will be defined and a data dictionary will be created. Variable types, names, and formats will be standardized. An indicator variable for the country (Sweden/Norway/Denmark) and unique study IDs will be generated. Datasets from the three countries will be concatenated and checked for consistency and errors, including logic checks.

Primary Objective: Nested Case-Control Study

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. Each case subject and her controls constitute a risk stratum, or a risk set matched on age at diagnosis, calendar year, and region where case was diagnosed. The distribution of these factors is therefore equalized in the model by design, which removes the need for adjusting for these factors so long as the risk strata are retained. For controls with longer follow-up than the case to which they are matched, the follow-up will be truncated to match that of the case. Regarding education level and income, it was decided not to match on these factors, as they may be of interest to study as confounders or effect modifiers.

To account for prevalent RRP cases undiagnosed at the time of vaccination, a buffer period of 6 months will be applied in sensitivity analyses, where cases occurring among individuals within this time period (from last vaccination dose) will not be considered. This approach of applying buffer period is consistent with prior analyses conducted in Nordic and other

regions to assess vaccine effectiveness in relation to diseases with long latency and/or diagnostic delay [19] [20].

When the outcome of a study is rare, which is the case for RRP, the OR approximates the risk ratio (or relative risk, RR) [42]. Further, incidence density sampling (i.e. random sampling of controls from the available population still at-risk at the particular point in time of the case's diagnosis) also ensures that ORs are a direct estimate of the hazard ratio, again interpretable as the risk ratio in our study [43]. ORs obtained through the conditional logistic regression model will therefore be interpreted as the corresponding RR.

To further increase specificity, the primary analysis will be restricted to AoRRP cases identified using ICD-10 code D14.1 along with appropriate topography/morphology or SNOMED/Norpat codes when available and complete and deemed necessary by experts.

Primary Objective(s): Calculation of Epidemiological Measure(s) of Interest

Descriptive statistics will be calculated for the cases and controls in terms of 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. Conditional logistic regression will be conducted for estimation of ORs and corresponding 95% confidence intervals, with adjustment for relevant covariates. For a detailed discussion of covariates of interest, please see Annex 1, which lists subject matter expertise analysis of the association of interest, and potential confounding thereto. Annex 1 also motivates closely the inclusion of covariates described here below.

In case-control studies, it is the odds of exposure which is typically assessed among cases of a disease and then compared with odds of exposure among controls. However, the odds ratio is the same regardless of how it is defined in terms of marginal probabilities, i.e., probability of exposure given disease or probability of disease given exposure are statistically and technically equivalent. As per standard practice, it was therefore chosen to express ORs as the probability of disease given exposure, to provide a measure of the association between vaccine receipt and disease outcome.

Potential confounders such as highest level of family income and highest level of education achieved by the mother and/or subject income/education (tentatively in tertiles relative to the general age-matched population of the respective countries) will be adjusted for when investigating the primary objective, through inclusion in the conditional logistic regression. Given that most young adult females in their late teens/early 20s in Nordic countries have a similar level of education (i.e., almost all complete high school) and income is often limited due to being in school, adjustment for individual-level income and education will be considered and the decision of which variables to include in the model will depend on association of these variables with RRP outcome, and consideration of collinearity. Additionally, confounder assessment based on G-estimation may be undertaken if considered appropriate following discussion between the Sponsor and investigators.

Sensitivity analyses will be conducted in relation to the primary objective to assess the impact of: vaccine exposure definition (fully vaccinated versus ≥1 vaccine dose), age at

vaccination (any age and ≥17 years), applying buffer period between vaccination and disease onset of 6 months (from last dose), outcome definition (ICD-10 code D14.1 only versus cases [of D14.1] that have appropriate topography/morphology or SNOMED/Norpat codes, and cases [of D14.1] with at least one associated treatment/procedural code and/or specified with subcode D14.1.A/"larynx papilloma"), restricted to Gardasil use only (as exposure), and personal history of EGW (yes versus no). OR estimates from the regression model will be inspected in terms of point estimates and precision, for comparison with results from the main analysis. Effect size (OR) estimates are expected to vary across most sensitivity analyses. For example, effectiveness may be higher among females that are fully vaccinated, vaccinated at younger age (prior to sexual debut), without history of EGW, and in analyses including a buffer period and more restrictive outcome definition. For transparency, all pre-planned analyses are described here.

There will be no adjustment for multiple comparisons in this study. Analyses have been pre-specified, discriminating between primary and sensitivity analyses, and all results will be reported.

Secondary Objective: Calculation of Epidemiological Measure(s) of Interest

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. New cases of JoRRP or AoRRP will be the numerator for the calculation of incidence rates. The denominator will be the accumulated person-time in each calendar year for which the data are analyzed. As this is a highly robust measure over time and the entire population is sampled, it may not be necessary to include confidence intervals; however, given the small number of cases per calendar year, confidence intervals will be calculated.

Overall incidence rates will be adjusted for age according to European Standard Population, because of the larger proportion of older age groups in Nordic countries compared to the World Standard Population.

Exploratory Objective: Calculation of Epidemiological Measure(s) of Interest (e.g., hazard ratios, incidence rates, test/retest reliability)

Risk factors for AoRRP will be explored in the VE analysis conditional logistic regression model to evaluate if they are independently statistically significantly associated with the outcome of RRP, with all other factors held constant. Specifically, vaccination exposure will be at the reference level, i.e., the analysis of risk factor status will effectively be restricted to non-vaccinated individuals.

7.12 Quality Control

By signing this protocol, all parties agree to following applicable standard operating procedures (SOPs). All parties also agree to ensuring all existing and new study personnel are appropriately trained to ensure the study is conducted and data are generated, documented, and reported in compliance with the protocol, Good Pharmacoepidemiology

Practice (GPP), Good Pharmacovigilance Practices (GVP), and all applicable federal, state, and local laws, rules, and regulations. All parties should maintain transparency and open communication in order to effectively manage the study and proactively mitigate any risks.

The Sponsor may conduct routine or for-cause audits to ensure oversight and conduct of the study are completed in accordance with the protocol, quality standards (e.g., GPP and GVP), and applicable laws and regulations. If a significant quality issue (SQI) is identified at any time during the conduct of the study, it must be escalated to the Sponsor immediately. A SQI is any issue with the potential to negatively impact, either directly or indirectly, the rights, safety and well-being of patients or study participants and/or the integrity of the data. In the event an audit or SQI results in corrective or preventive actions, all parties are expected to appropriately implement the action plan in a timely manner.

7.13 Limitations of the Research Methods

This is a register-based study which relies on the use of a proxy codes rather than medical records. It is thus limited in terms of density of data, such that there is not access to all medical details for each case. There is also no available explicit information on lifestyle factors such as smoking and sexual behavior; however, there are several proxy variables that may serve to adjust for potential confounding (Annex 1). However, the bias introduced by these limitations is expected to be minimal for this study, because the Nordic registries have high accuracy, completeness, and in addition high population coverage. Furthermore, these potential limitations are not likely to change, so the results will be comparable throughout the study period. Additionally, with use of registry data from three different countries in the pooled analysis, some variables may need to be adapted to be able to combine information as it is not identical in all registers. Consistent with the related JoRRP study, this will be achieved via development of a common data model, involving collaboration between all Nordic country investigators.

Among the birth cohorts eligible to be vaccinated <17 years of age (i.e., 1990+), herd protection is expected to be greater than among older birth cohorts with lower vaccination coverage. Therefore, it is possible that in the study primary analysis (restricted to 1990+ birth cohorts) vaccine effect estimates may be lower due to lower infection rates among unvaccinated individuals resulting from indirect (herd) protection.

Given that the main cause of RRP globally is infection with HPV type 6 or 11, results are expected to be generalizable. With the proposed study population design, there is restriction in analytical format as having access to the full baseline cohort will yield many technical advantages. The risk for misclassification of exposure to vaccination is minimized through the substantial in-house knowledge of combination of vaccination registries. Nonetheless there is a small but existing risk of non-differential misclassification of outcome. Generalizability is maximized through the population-based sampling frame and allowing all eligible study participants alive and resident in Sweden, Denmark, and Norway at the appropriate time to enter. Also, in recent years, especially the post-vaccination introduction era, Sweden, Denmark, and Norway have experienced high immigration, which may further increase generalizability of study results. The magnitude of random error is minimized in the

ecological study through including a very large group of subjects. Yet, it is acknowledged that the rarity of the outcome may lead to some challenges in precision, despite the large baseline study sample size.

7.14 Methods to Minimize Bias

A register-based proxy for definition of outcome (JoRRP and AoRRP) will be used, i.e., ICD-10 code D14.1, which in Sweden is used to register the disease category "benign tumor of the larynx". To increase specificity, the full set of D14.1 cases available will be augmented with appropriate topography/morphology or SNOMED/Norpat codes when available, complete, and recommended by experts. Additionally, in sensitivity analyses, diagnostic and treatment codes described above will be applied to also improve specificity. Given that granulomas of the larynx are largely occurring in middle-age, male smokers, it is suggested that benign tumors of the larynx, other than HPV-associated papilloma, in the specified age ranges (i.e., 0-29 years) and restricted to females, will be very rare. If a misclassification of outcome due to using D14.1 would sometimes occur, it will likely lead to bias towards the null, which means that if vaccine effectiveness against RRP is observed, the true effect is likely greater.

Given the rarity of RRP, and the strong registration of healthcare in the Nordic countries, it is believed that virtually all cases of RRP will be identified by the above algorithm. The risk that a control selected at random from the underlying population is a false negative, i.e., a missed case of RRP, should be negligible.

All immigrant females to Sweden, Denmark and Norway (after age 9) will be excluded to ensure there is no misclassification of exposure, which removes the risk that subjects who have received HPV vaccination outside of these countries are mis-classified as non-vaccinated and ensures a minimum of six years of individual follow-up in the registries prior to case eligibility (at age 15) for exclusion of prevalent RRP cases.

Furthermore, adjustment for potential confounders will be employed in the conditional logistic regression model, for factors that are shown to be associated with both exposure and outcome (see Annex 1 for details). The spectrum of confounding factors can be determined both a priori/empirically, through subject matter knowledge and literature review, but also (once data on potential confounders are collected) by investigation of variables in the regression model, whereby covariates are examined in terms of whether their removal from the model substantially (e.g., by ≥10%) alters the width of the confidence interval for the observed (odds ratio) association between exposure and outcome in the actual model (nota bene: this is thus not forward selection, which only evaluates association between covariate and outcome and applying a threshold of e.g. $p<0.05$ to call a variable a "confounder" – this would not be methodologically correct.)

8 PROTECTION OF HUMAN SUBJECTS

Prior to study initiation, appropriate approvals will be obtained from relevant authorities overseeing the study, e.g., Institutional Review Boards or Data Protection Agencies.

8.1 Informed Consent

Informed consent is not needed for this registry-based study, as there is no intervention or interaction with subjects, and subjects will not be identified.

9 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse Event (AE) and Product Quality Complaint (PQC) Reporting Language for Non-Interventional Study Protocols

Adverse Event and Product Quality Complaint Reporting

This is a non-interventional database study based on secondary use of data collected for other purposes. No administration of any therapeutic or prophylactic agent is required in this protocol. No reporting of individual adverse events or product quality complaints to regulatory agencies is planned for this database study because there is no access to individual patient/subject records, and it is not possible to assess the causality of individual cases. The investigator should refer to their institution's policy or local laws and regulations regarding reporting of any suspected adverse reactions and product quality complaints.

Any health outcomes (if collected per section 7.6.2), including any that qualify as adverse events, will be summarized as part of any interim analysis (including safety analysis, if required) and in the final study report, which will be provided to regulatory agencies by the Sponsor as required. Any relevant safety information will be summarized, and the Sponsor will include in the appropriate Periodic Safety Update Report (PSUR)/Periodic Benefit Risk Evaluation Report (PBRER) and/or Development Safety Update Reports (DSUR) if required.

10 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The primary results of this research study will be externally disseminated in a manuscript submitted to a peer-reviewed, scientific journal, abstract/presentation at a scientific conference or symposium, or results posted on the HMA-EMA Catalogue of Real-World Data. Any publication related to the study will need to be reviewed/approved by the Sponsor prior to submitting results externally. Any publication resulting from this work will adhere to the procedures and pre-specified analysis plans within this protocol.

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12 ANNEXES

Annex 1 Graphical And Numerical Overview Of Potential Confounding In Assessment Of Hpv Vaccine Effectiveness Against Adult-Onset Rrp

Definitions:

Study exposure: HPV vaccination with GARDASIL or GARDASIL 9, below called HPV vaccination.

Study outcome: Adult-onset recurrent respiratory papillomatosis, below called RRP.

Primary objective: Estimate odds ratio (OR) of RRP (yes/no) given HPV vaccination (yes/no).

Power: The study has ≥80% power to detect an OR of 3.0 with a lower bound of the 95% confidence interval of ≥1.33, assuming at least 60 cases of AoRRP are observed.

Main association of interest:

The hypothesis is that HPV vaccination is negatively associated with the odds (likelihood) of RRP. Factors that may act as confounders to this association are considered, below. That is, factors associated with both exposure and outcome in such a way that an observed association between the two is partially or completely confounded.

Potential confounders:

Factors that are established to be associated with exposure/HPV vaccination in Nordic countries (Sweden, Denmark, and Norway):

1) Socioeconomic status:

In studies evaluating factors associated with uptake of HPV vaccination in the Nordic region, low education and low-income level of parent(s) were found to be associated with lower vaccine uptake [44][35]. Statistically significant associations (95% CIs excluded null) were observed when focusing on girls in the free of charge school-based program (hazard ratio [HR] or odds ratio [OR] estimates ranging from: 0.75 to 0.92 for low education and from 0.67 to 0.87 for low income in Denmark and Sweden, respectively) and the subsidized program in Sweden (HR=0.53 for low income and HR=0.32 for low education). Additionally, in Denmark, investigators assessed association between vaccine uptake and country of birth and found that uptake was significantly lower if born outside of Denmark (OR=0.49, 95% CI=0.42-0.57) [44]. Similarly, in Sweden, investigators assessed association between vaccine uptake and country of birth and found that uptake was significantly lower if born outside of Sweden (OR=0.49, 95% CI=0.48-0.50) [35].

2) Sexual behavior:

In a Swedish study examining acceptability of HPV vaccination in young adult women (up to age 30), investigators found that subjects with >1 sexual partner, a below median age of sexual debut, and defining themselves as bisexual were more willing to accept HPV vaccination than comparison groups. Effect sizes (ORs) were modest, ranging from 1.15 to 1.69, but statistically significant. Investigators also found that subjects who self-identified as being at high risk of a sexually transmitted infection (STI) were more willing to accept HPV vaccination (OR=2.0, 95% CI=1.56-2.17) [45].

It is difficult *a priori* to conclude that individuals with a previous history of STI may have an interest in vaccination against an STI. This case might be particularly existent for subjects with own, or maternal history of external genital warts, where the subject may then obtain vaccination against HPV/EGW which also incidentally protects against RRP. Therefore, there may be a positive association with previous sexual activity/previous EGW and likelihood of exposure in this study. However, the strength of the association is expected to be small-moderate.

In this context, it is important to note that a wide body of literature has addressed the possibility of riskier sexual behavior after HPV vaccination receipt. In this case, sexual habits could act as a mediator of the association between HPV vaccination and RRP and should not be adjusted for. However, no substantial evidence exists that suggests uptake of HPV vaccination leads to riskier sexual behavior, whereas on the contrary many studies have found no indications of change in behavior [46] [47] [48] [49] [50] [51] [52] [53].

3) Smoking:

There have been no comprehensive studies showing an association between smoking habits and willingness to vaccinate against HPV in the Nordic countries. An association between smoking and HPV vaccination can therefore be questioned.

Factors that are established to be <u>associated with outcome/RRP diagnosis</u> receipt in Nordic countries (Sweden, Denmark, and Norway):

There are no comprehensive local studies performed that analyzed risk factors for AoRRP due to rarity of the outcome. A recent international systematic review found that evidence about disease risk factors for RRP is limited but supported that the patient's smoking and sexual behavior are involved [54].

1) Sexual behavior:

The review concluded that "compared with disease-free controls, patients with RRP have a significantly higher median number of lifetime sexual partners" but also acknowledged that additional studies have mixed findings and conclusive evidence is lacking [54].

No large studies have been identified evaluating the association between sexual contacts and risk of RRP. A small study including 25 RRP patients [55], which is cited in the review by

Welschmeyer and Berke, reported an OR of 2.11 (95% CI=1.02-4.39) for RRP development in patients with more than 25 lifetime sexual partners versus in those with 0-5.

2) Smoking habits:

A study from 1989[56] is frequently cited as showing that smoking is a risk factor for RRP in adults. However, there are no robust statistical analyses presented in this report and more recent publications have not found an association with severity of disease. Yet, it remains a clinical observation that adult RRP patients tend to be smokers, and therefore, from a qualitative perspective, smoking may be considered potentially/somewhat associated with risk of RRP.

3) Socioeconomic status (SES):

While lower SES (of parents) has been found to be associated with risk of juvenile-onset RRP, to our knowledge, no studies exist confirming an association between SES and risk of RRP in adults (in Nordic countries or similar resource settings). One could speculate that subjects with higher SES may however be more prone to seek healthcare due to having a hoarse voice – the primary physical symptom in adult-onset RRP. However, it could be equally speculated that in a country with a strong tax-funded healthcare system, young women aged 15-29 years with a hoarse voice would be prone to seek healthcare attention regardless of social background, as the cost is very low to the individual whereas the social stigma would be equal. It could therefore be posited that SES be associated with risk of RRP through surveillance bias, but the strength of this association would be unknown.

Conclusions on potential confounders:

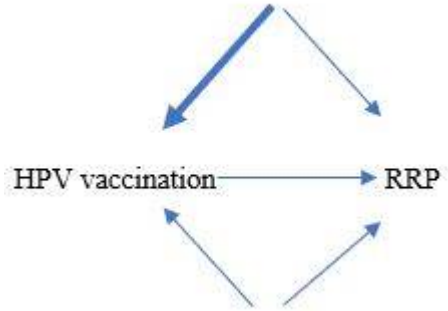
Although **socioeconomic status** appears to be moderately-strongly associated with exposure, there is no evidence suggesting it is associated with outcome. If there is an association with RRP as an outcome, it should be modest in size. However, in the interest of obtaining the best evidence, this association should be evaluated formally, and it is therefore planned to include this factor as a potential confounder in the analysis.

Regarding **sexual behavior**, the association with HPV vaccine exposure appears to be weak, whereas that with RRP (outcome) is stronger. This is expected given that causal HPV infection is acquired sexually. In Sweden, riskier sexual behavior was positively associated with willingness to be vaccinated, and therefore bias (due to this confounder) may be expected to be towards the null. Although number of sexual partners cannot explicitly be adjusted for in the proposed register-based study, age of vaccination will be accounted for in the analysis and minimal bias due to sexual behavior would be expected among those vaccinated at younger ages (<17 years), which is defined as exposure in the study primary analysis. Additionally, medical information regarding history of external genital warts (EGW) pre-vaccination may be obtained and used as a proxy for sexual behavior with particular relevance to risk of acquisition of low-risk types of HPV. EGW history is unique as the only STI where individual level register data is validated and available in all countries.

Finally, for **smoking habits**, the size of the association and thus potential for confounding due to this factor appears to be modest at most. Nordic registers cannot be used to define individual smoking status as this type of lifestyle factor is not systematically reported to national healthcare registries, especially not among subjects so young (in older age groups, there are proxy codes for smoking-related diagnoses and drugs that could be utilized but these are not relevant here). However, the inclusion of socioeconomic status is expected to serve as at least a partial proxy for smoking behavior, as previously used in HPV vaccine effectiveness studies [20]. It is believed that this approach adequately addresses potential confounding by this factor.

Directed acyclic graph (DAG) appropriate for the study

Socioeconomic status (proxy for sexual behavior and smoking)



History of EGW (proxy for sexual behavior, association expected to be weaker in females vaccinated below 17 years of age)

Note: Thickness of line indicates relative strength of association. Insufficient data exists on effect size expected for history of EGW in association with RRP (current study will provide these estimates).

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Annex 2 Table And Figure Shells For Rrp Study (Primary And Secondary Objectives)

Table 3 Number of new cases and incidence rates of recurrent respiratory papillomatosis, by calendar years (2000-2021)

Gender and age group	2000			2001			2002			2003			2004			2005		
	No. of cases	Incidence Rate (per 100,000 subjects)		No. of cases	Incidence Rate (per 100,000 subjects)		No. of cases	Incidence Rate (per 100,000 subjects)		No. of cases	Incidence Rate (per 100,000 subjects)		No. of cases	Incidence Rate (per 100,000 subjects)		No. of cases	Incidence Rate (per 100,000 subjects)	
Women																		
All ages																		
0-14																		
15-29																		
0-4																		
5-9																		
10-14																		
15-19																		
20-24																		
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0-16																		
17-29																		
Men																		
All ages																		
0-14																		
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0-4																		
5-9																		
10-14																		
15-19																		
20-24																		
25-29																		
0-16																		
17-29																		

Table 3, continued.

Gender and age group	2006			2007			2008			2009			2010			2011		
	No. of cases	Incidence Rate (per 100,000 subjects)		No. of cases	Incidence Rate (per 100,000 subjects)		No. of cases	Incidence Rate (per 100,000 subjects)		No. of cases	Incidence Rate (per 100,000 subjects)		No. of cases	Incidence Rate (per 100,000 subjects)		No. of cases	Incidence Rate (per 100,000 subjects)	
Women																		
All ages																		
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5-9																		
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15-19																		
20-24																		
25-29																		
0-16																		
17-29																		

Table 3, continued.

Gender and age group	2012			2013			2014			2015			2016			2017		
	No. of cases	Incidence Rate (per 100,000 subjects)		No. of cases	Incidence Rate (per 100,000 subjects)		No. of cases	Incidence Rate (per 100,000 subjects)		No. of cases	Incidence Rate (per 100,000 subjects)		No. of cases	Incidence Rate (per 100,000 subjects)		No. of cases	Incidence Rate (per 100,000 subjects)	
Women																		
All ages																		
0-14																		
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25-29																		
0-16																		
17-29																		

Table 3, continued.

Gender and age group	2018			2019			2020			2021		
	No. of cases	Incidence Rate (per 100,000 subjects)		No. of cases	Incidence Rate (per 100,000 subjects)		No. of cases	Incidence Rate (per 100,000 subjects)		No. of cases	Incidence Rate (per 100,000 subjects)	
Women												
All ages												
0-14												
15-29												
0-4												
5-9												
10-14												
15-19												
20-24												
25-29												
0-16												
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All ages												
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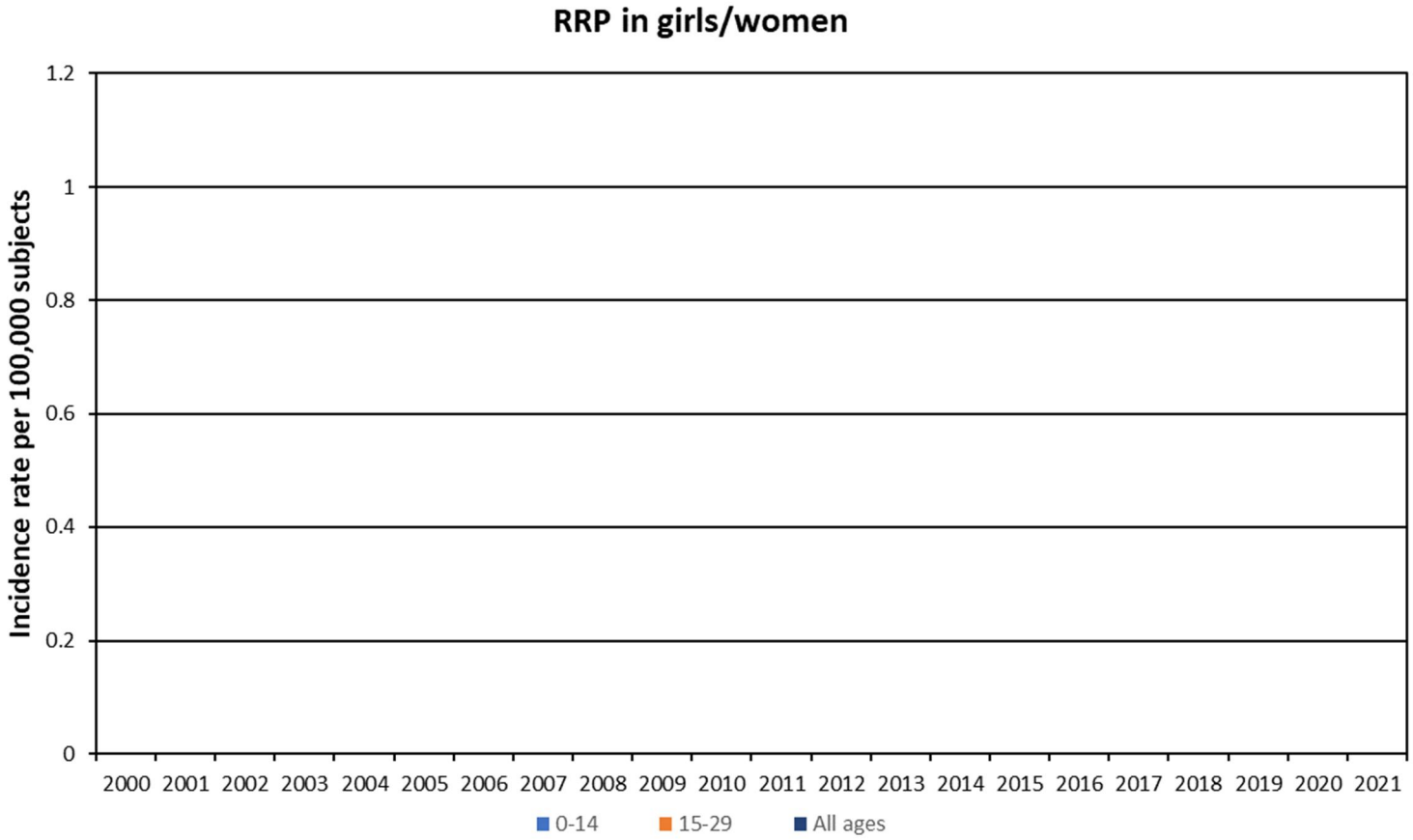
15-29												
0-4												
5-9												
10-14												
15-19												
20-24												
25-29												
0-16												
17-29												

Note: Age groups and calendar years may be combined if the number of cases in the cells is small.

Separate tables will be prepared for Sweden, Denmark, and Norway, and adapted to reflect the calendar years of coverage in those countries.

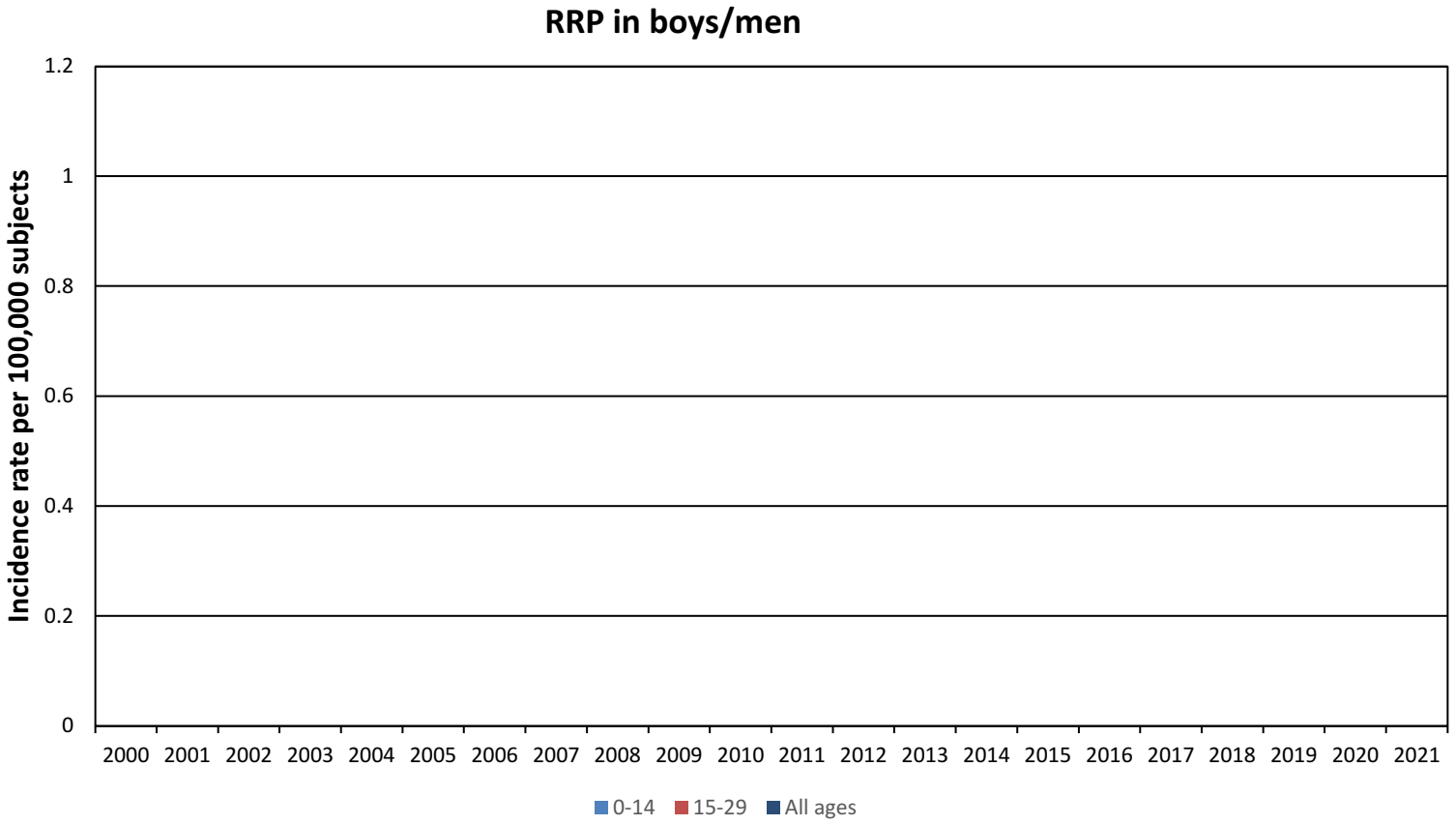
Figure 3 Overall age-adjusted and age-specific incidence rates of recurrent respiratory papillomatosis (RRP) among girls/women by year (2000-2021)



Note: Calendar years may be combined if the number of cases in is small.

Separate figures will be prepared for Sweden, Denmark, and Norway, and adapted to reflect the calendar years of coverage in those countries.

Figure 4 Overall age-adjusted and age-specific incidence rates of recurrent respiratory papillomatosis (RRP) among boys/men by year (2000-2021)



Note: Calendar years may be combined if the number of cases in is small.

Separate figures will be prepared for Sweden, Denmark, and Norway, and adapted to reflect the calendar years of coverage in those countries.

Table 4 Characteristics of study population, AoRRP cases, and control subjects

	Study population, **No. (%)**	AoRRP cases, **No. (%)**	Controls, **No. (%)**
Total			
Age, years, mean (SD)			
Education level			
Low			
Medium			
High			
Missing			
Income level			
Low			
Medium			
High			
Missing			
Highest level of education achieved by mother*			
Low			
Medium			
High			
Missing			
Highest annual household family income level‡			
Low			
Medium			
High			
Missing			
Study Site			
Sweden			
Denmark			
Norway			
Country of birth			
Study site			
Other country			
Missing			
Own history of EGW			
Yes			
No			
Missing			
Maternal history of EGW			
Yes			
No			
Missing			
Length of follow-up in registries, years, mean (SD)			

AoRRP = adult-onset recurrent respiratory papillomatosis; EGW = external genital warts; SD = standard deviation

*****Education level of mother at index date.

‡Based on average level between 2006 (the start year of HPV vaccination) and the index date.

Table 5 Number of cases and odds ratio for recurrent respiratory papillomatosis (RRP) by HPV vaccination status

HPV vaccination status	**AoRRP**			
	No. of cases[1]	No. of controls[2]	Crude OR (95% CI)	Adjusted OR[3] (95% CI)
Fully Vaccinated[4]			Ref.	Ref.
Unvaccinated				

AoRRP = adult-onset recurrent respiratory papillomatosis; CI = confidence interval; HPV= human papillomavirus; ICD-10 = international classification of disease, 10th modification; OR = odds ratio; Ref. = reference.

[1] All study participants who acquired a first diagnosis of AoRRP as defined for each country.
[2] 10 controls matched on attained age, region of diagnosis and calendar year of case's diagnosis.
[3] Adjustment factors considered for inclusion include education level, income level, country of birth, own history of external genital warts (EGW), and maternal history of EGW.
[4] A female who received 3 doses (or 2 doses administered at 0 and 6-12 months if <15 years of age) of GARDASIL or GARDASIL 9 before age 17 will be classified as exposed and those who did not receive any dose will be considered unexposed.

Notes on Table 5:

1. Separate tables will be prepared with outcome defined using: a) subcode D14.1.A, and b) code D14.1 and/or subcode D14.1A with at least one appropriate procedural code, i.e. DQB10 (Endoscopic extirpation), UDQ25 (Microlaryngoscopy with biopsy), and/or UDQ22 (Microlaryngoscopy).

2. Separate tables will be prepared considering: a) age at vaccination (≥17 years vs. any age at vaccination) and b) own history of external genital warts (yes/no).

3. Separate tables will be prepared with exposure defined as receiving at least one dose of Gardasil vaccine.

4. Separate tables will be prepared applying buffer period between vaccination and disease of 6 months (from last dose).

5. Separate tables will be prepared focusing on Gardasil use only as exposure.

Annex 3 Administrative And Regulatory Details

Confidentiality:

Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence if applicable such information will be divulged to Institutional Review Board, Ethics Review Committee or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), Institutional Review Board/Independent Ethics Committee (IRB/IEC), or Regulatory Agency representatives may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

Administrative:

Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor or through a secure password-protected electronic portal provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this

information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Pharmacoepidemiology Practice and all applicable federal, state and local laws, rules and regulations relating to the conduct of the study.

The investigator also agrees to allow monitoring, audits, Institutional Review Board/Independent Ethics Committee review and regulatory agency inspection of study-related documents and procedures and provide for direct access to all study-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The Investigator shall prepare and maintain complete and accurate study documentation in compliance with Good Pharmacoepidemiology Practice, standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the study, provide all data, and, upon completion or termination of the study, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory agencies. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the study documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the study in accordance with their institution's records retention schedule which is compliant with all applicable regional and national laws and regulatory requirements. If an institution does not have a records retention schedule to manage its records long-term, the investigator must maintain all documentation and records relating to the conduct of the study for 5 years after final report or first publication of study results, whichever comes later, per GPP guidelines. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. All study documents shall be made available if required by relevant regulatory authorities. The investigator must consult with the Sponsor prior to discarding study and/or subject files.

The investigator will promptly inform the Sponsor of any regulatory agency inspection conducted for this study.

Persons debarred from conducting or working on studies by any court or regulatory agency will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center study (including multinational). When more than one study site is open in an EU country, the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different sites in that Member State, according to national regulations. For a single-center study, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the study report that summarizes the study results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the study in the study's final report. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of study methods, appropriate enrollment of subject cohort, timely achievement of study milestones). The Protocol CI must be a participating study investigator.

Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), as well as the European Medicines Agency GVP Module VIII, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to one or more study registries such as the HMA-EMA Catalogue of Real-World Data. The Sponsor of this study will review this protocol and submit the information necessary to fulfill these requirements for all post-marketing safety and efficacy studies. Information posted will allow subjects to identify potentially appropriate primary data collection studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAMA/FDAAA and EMA GVP Module VIII are that of the Sponsor and agrees not to submit any information about this study or its results to a study registry without consulting with the Sponsor.

13 SIGNATURES

13.1 Sponsor's Representative

PRINTED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

I agree to conduct this study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other project plans and documents referenced from this protocol); changes from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Pharmacoepidemiology Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any adverse events and product quality complaints as defined in the Safety and Product Quality Complaint Reporting and Related Procedures section. I understand that information that identifies me will be used and disclosed as described in the protocol and the Use and Disclosure of Personal Data notice provided to me, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

PRINTED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.3 Supplier

I agree to conduct this study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol); changes from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Pharmacoepidemiology Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any adverse events and product quality complaints as defined in the Safety and Product Quality Complaint Reporting and Related Procedures section. I understand that information that identifies me will be used and disclosed as described in the protocol and in order to perform any agreement between myself and the Sponsor, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

PRINTED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	