PAES INFORMATION

Title	Population-based retrospective nested case-control study evaluating effectiveness of GARDASIL™ against adult-onset recurrent respiratory papillomatosis in Sweden
Protocol Version identifier	2.1
Date of last version of protocol	September 30, 2021
EU PAS Register No:	Study not registered
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
Product reference:	V501 and V503
Procedure number:	NIS009722
Marketing authorisation holder(s) (MAH)	Merck Sharp & Dohme B.V.
Joint PAES	No

Research question and objectives	Primary Objective: To assess if the odds of AoRRP is lower among females fully vaccinated with Gardasil/Gardasil 9 before age 17 years versus those unvaccinated. Secondary Objectives: 1) To assess annual incidence rates of AoRRP among males and females in Sweden since 2000. 2) To assess annual incidence rates of JoRRP among males and females in Sweden since 2000.
Country(-ies) of study	Sweden
Author	PPD Principal Investigator, Dept of Laboratory Medicine, Division of Pathology, Karolinska Institutet, S-141 86 Stockholm, Sweden, PPD PPD Principal Scientist, Merck Sharp & Dohme LLC, 126 East Lincoln Ave., P.O. Box 2000, Rahway, NJ 07065 PPD
Marketing authorisation holder(s) including MAH Contact Person	Merck Sharp & Dohme B.V. PPD Molenstraat 110 5342 CC Oss Netherlands PPD
Merck Final Repository (REDS) Date	31-AUG-2022
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*
ATC	*Anatomical Therapeutic Chemical*
CT	*Chlamydia Trachomatis*
EGW	*External Genital Warts*
EMA	*European Medical Association*
FDA	*Food and Drug Administration*
HPV	*Human Papillomavirus*
ICD-10	*International Classification of Disease, 10th Modification*
IEC	*Independent Ethics Committee*
ISERP	*Independent Safety Epidemiology Review Panel*
JoRRP	*Juvenile-onset Recurrent Respiratory Papillomatosis*
KI	*Karolinska Institutet*
LISA	*Longitudinal Integrated database for Health insurance and Labour market studies (LISA)*
MBR	*Medical Birth Register*
NBHW	*National Board of Health and Welfare*
NPR	*National Patient Register*
PASS	*Post-Authorization Safety Study*
PIN	*Personal Identification Number*
RRP	*Recurrent Respiratory Papillomatosis*
SAP	*Statistical Analysis Plan*
SCR	*Swedish Cancer Register*
SOP	*Standard Operating Procedure*

1 RESPONSIBLE PARTIES

Principal investigator	PPD Principal Investigator Dept of Laboratory Medicine, Division of Pathology, Karolinska Institutet, S-141 86 Stockholm, Sweden PPD
Coordinating investigator for each country in which the study is to be performed	Sweden: PPD Dept of Laboratory Medicine, Division of Pathology, Karolinska Institutet, S-141 86 Stockholm, Sweden PPD
Sponsor contacts	PPD Executive Director, Epidemiology Tel: PPD E-mail: PPD PPD Principal Scientist, Epidemiology Tel: PPD E-mail: PPD
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™ against adult-onset recurrent respiratory papillomatosis in Sweden
Protocol Number / Version	2.0
Date	April 25, 2022
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.
Research Question(s) & Objective(s)	Primary Objective: To assess if the odds of AoRRP is lower among females fully vaccinated with Gardasil/Gardasil 9 before age 17 years versus those unvaccinated. Secondary Objectives: 1) To assess annual incidence rates of AoRRP among males and females in Sweden since 2000. 2) To assess annual incidence rates of JoRRP among males and females in Sweden since 2000.
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 between 2006 and 2019 (able to be vaccinated <17 years of age), i.e. birth cohorts 1990-2003. Secondary objective: All individuals 0-29 years of age between 2000 and 2019, i.e. birth cohorts 1971-2017.
Variables	Exposure definition: Full receipt of GARDASIL/GARDASIL 9 vaccination regimen (2 or 3 doses according to age at vaccination). Outcome definitions: - First diagnosis of AoRRP (female only) and JoRRP (male/female) identified from national registries using ICD-10 code D14.1 (benign neoplasm of larynx).
Data Sources	Nordic population, patient, and vaccine registries.
Study Size	Sample size Primary objective (nested case-control study): - AoRRP: ~52 cases, 10 controls per case (i.e. ~520 controls) Secondary objectives (ecological study): descriptive/no power calculation - Population size for assessment of AoRRP and JoRRP: ~6,510,000 females/males
Data Analysis	Power calculation for primary objective (estimated 52 AoRRP cases and 520 controls) AoRRP: study is 81% powered to detect a RR=>3.0 with a lower bound of the 95% confidence interval >1.33; equivalent to lower bound of 95% CI of vaccine effectiveness >25% (to be confirmed prior to analysis).

Milestones:	
Start of data collection:	2Q2022
End of data collection:	3Q2022
Final report of study results:	1Q2023

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
2	13Mar22	7.6.3, 7.10	Covariates	Regulatory agency feedback	25Apr22	2.0
3	13Mar22	7.8, 7.10	Sample size and power	Regulatory agency feedback	25Apr22	2.0

4 MILESTONES

Milestone	Planned Date
Registration in the EU PAS register	2Q2022
Start of data collection	2Q2022
End of data collection	3Q2022
Final report of study results	1Q2023

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].

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, similar to other HPV related diseases [4]. The risk factors for AoRRP are only partially described and the mechanisms involved appear to be dominated by oral HPV sexual transmission horizontally between adults [4]. There is a clear gap of knowledge in terms of risk factors for this disease, but smoking has been implicated. Studies focused on evaluation of incidence of AoRRP are limited; however, reported estimates range from approximately 0.5 per 100,000 in Denmark and Norway to 1.8 per 100,000 in the US [5] [6] [7].

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 [8]. 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 [5] [7] [9] [10] [11] [12]. 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 [13].

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 [14]. 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 [14]. 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 [13]. 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 generally required in management of each RRP case, the estimated annual cost of managing JoRRP and AoRRP in the US (2004-2007) was reported at $123 million and $48 million, respectively [15]. As there is currently no cure, treatment focuses on maintaining voice quality and airway patency [16]. 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 [17], which has been shown to be highly effective against high-grade cervical lesions and invasive cervical cancer in the real-world using Swedish registry information [18] [19]. 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 Sweden and other Nordic countries [20]; this study extension was conducted as a commitment to the FDA and the EMA.

With population of >10 million, Sweden is the largest Scandinavian country, with expected greater annual number of RRP cases than Denmark or Norway. 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. Unlike in some settings where HPV vaccination coverage was immediately high following vaccine introduction, in Sweden coverage increased gradually from ~20% (for 1990 birth-cohort) to ~80% (for 1999+ birth-cohorts). In 2015, a 2-dose schedule (with doses administered at 0 and 6 months) 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.

Prior studies in Sweden have successfully been conducted focusing on GARDASIL vaccine effectiveness against high-grade cervical lesions and cancer [18] [19], using National Patient Registry information to accurately identify cases (using international classification of disease, 10th [ICD 10] revision codes) [21], and also involving generational linkage of registry information for children and their parent(s) [22]. Thus, we here propose a national, population register-based case-control study investigating GARDASIL/GARDASIL 9 effectiveness against AoRRP. Demonstration of GARDASIL/GARDASIL 9 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 Sweden, and could also help inform future studies focused on the evaluation of GARDASIL/GARDASIL 9 effectiveness against JoRRP.

6 RESEACH QUESTION AND OBJECTIVES

Primary Objective

To assess if the odds of AoRRP is lower among females fully vaccinated with GARDASIL/GARDASIL 9 before age 17 years versus those unvaccinated. *

* In case-control studies, the odds (likelihood) of exposure is 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 incidence rates of AoRRP among males and females in Sweden since 2000.

2) To assess annual incidence rates of JoRRP among males and females in Sweden since 2000.

Exploratory Objective

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

7 RESEARCH METHODS

7.1 Study Design

Nested case-control study (primary objective)

Setting: Sweden.

In all Nordic countries, including Sweden, 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 [23].

Cohort: GARDASIL was not available in Sweden until late 2006, therefore we plan to capture the cohort of girls/women ages 15 to 29 years during the period 2006 to 2019.

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). Females vaccinated at age 17 in 2007 would then be age 29 by end of study follow-up period (2019), which is the rationale for this upper age limit.

Also, males were not included in the Swedish HPV national immunization program during the study period and therefore due to very low coverage it is not feasible to include males in the study.

Cases: Within the specified cohort, AoRRP (female 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.

In Sweden, local otorhinolaryngology/phoniatrician expertise has confirmed that D14.1 is the ICD-10 code used for diagnosis of RRP. Recently, investigators from Australia found that cases of RRP identified using this code had positive predictive value (PPV) of 98.1%, with no additional RRP cases found using other codes [24]. It is therefore expected that the accuracy of RRP diagnosis using this approach would also be very high in Sweden. 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 (representing "larynx papilloma") will be explored in a subgroup/sensitivity analyses, as this may be even 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), 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 cohort. As the number of controls per case increases beyond 4, improvement in statistical power diminishes [25]. 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 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 1] provides an example of case/control subject selection nested within population-based cohort (2006-2019) in this study.

Exposure assessment: The exposure of interest is GARDASIL or GARDASIL 9 vaccination prior to the index date for each case and matched controls.

Exposure will be defined in 2 ways:

1. Exposure in primary objective: Fully vaccinated with GARDASIL/GARDASIL 9 (yes/no) before age 17 years. A female who received 3 doses (or 2 doses administered at 0 and 6-12 months if <15 years of age) of GARDASIL/GARDASIL 9 will be classified as exposed.

2. Exposure in sensitivity analysis: GARDASIL/GARDASIL 9 vaccination (yes/no) before age 17 years. A female who received at least one dose of GARDASIL/GARDASIL 9 prior to the index date will be classified as exposed.

The vaccine registries in Sweden accurately capture vaccination [26], greatly reducing the risk of exposure misclassification and providing the foundation for a robust observational study. Prior studies relying on Swedish registries for measurement of GARDASIL/GARDASIL 9 exposure (in relation to risk of anogenital diseases, including cervical cancer) have been conducted successfully in recent years [18] [19].

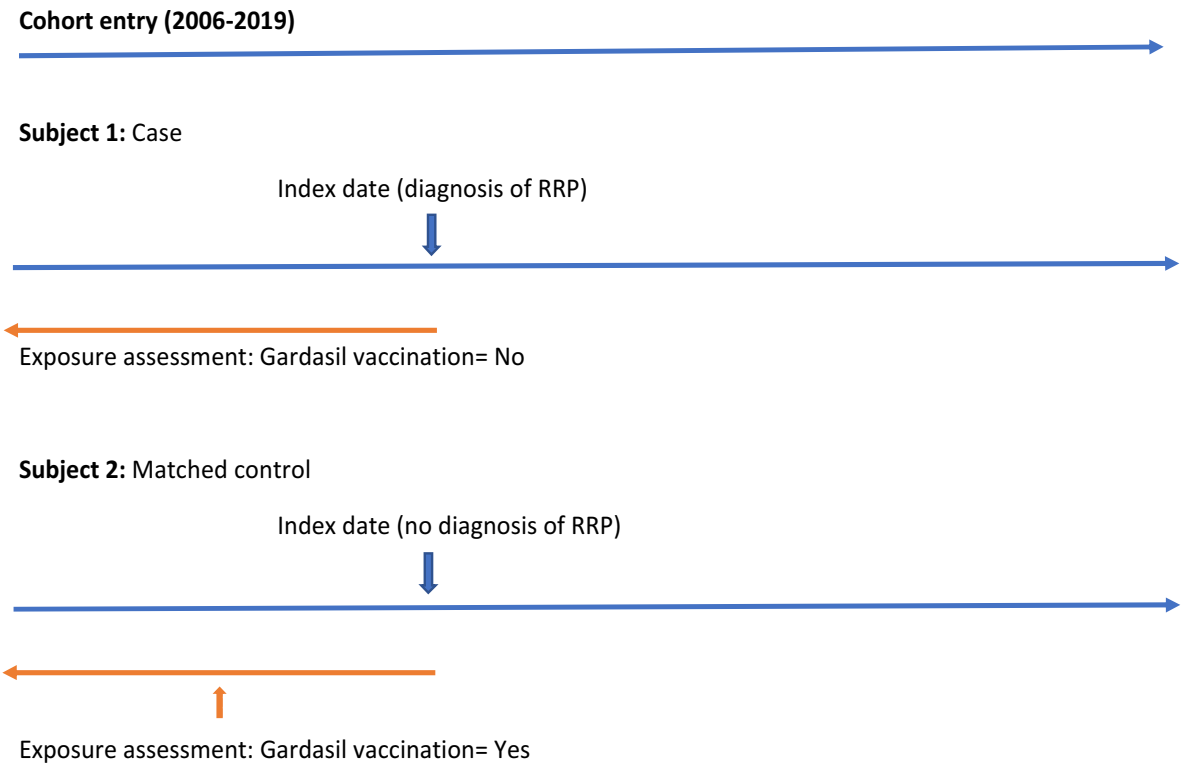

Figure 1 Example of case/control subject selection nested within population-based cohort (2006-2019) in this study. Subject 1 is classified as a case without exposure to GARDASIL/GARDASIL 9 prior to the index (diagnosis) date, and subject 2 is an eligible matched control with exposure to GARDASIL/GARDASIL 9 prior to the index date.

Ecological study (secondary objective)

Design: Descriptive/ecologic study using nationwide registry data to assess annual age-standardized incidence rates of RRP, separately for juveniles (0-14 years) and adults (15-29 years), and by gender.

Cohort: Male and female residents of Sweden (ages 0-29 years), during the period 2000 to 2019.

Cases: RRP cases will be identified from national registries using the ICD-10 code D14.1 (benign neoplasm of larynx).

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

7.2 Setting

The study population is identified using the Swedish Total Population Registry, for information on birth year and migration status, as well as the Swedish National Cause of Death registry, for date of death. The two registers have full coverage of the Swedish Population.

Nested case-control study (primary objective)

The study population is female residents of Sweden (15-29 years of age) between 2006 and 2019, i.e. birth cohort 1977-2003 (or 1990-2003, in primary analysis focusing on those vaccinated before age 17 years).

Ecological study (secondary objective)

The study population is children, women and men living in Sweden (0-29 years of age) during 2000 to 2019, i.e. birth cohort 1971-2019.

Based on existing datasets available at Karolinska Institutet (KI) (covering the period of 2006-2017), preliminary estimates of population cohort sizes for evaluation of AoRRP (males and females, ages 15-29 years) and evaluation of JoRRP and AoRRP combined (males and females, ages 0-29 years) are 3,641,315 individuals and 6,145,123 individuals, respectively. See [Table 1], below. Note that an additional 2 years of data (2018-2019) will be available for the actual study.

Table 1 Cohort size for evaluation of AoRRP and JoRRP/AoRRP combined.

	Total Number	Female	Male
1) AoRRP cohort	3,641,315	1,959,645 (53.8%)	1,681,670 (46.2%)
2) JoRRP/AoRRP cohort	6,145,123	3,220,154 (52.4%)	2,924,969 (47.6%)

7.3 Inclusion Criteria

- The study subject must be alive and resident in Sweden as defined through the Total Population Registry 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/GARDASIL 9 vaccination among males during study period), whereas both genders are eligible to be included for the secondary objective.

- To be considered as a potential case of JoRRP and AoRRP (for either primary or secondary objective), a study subject must have at least one first diagnosis coded with D14.1 in the National Patient Registry, during the specified time period of focus.

7.4 Exclusion Criteria

- Subjects who receive a first diagnosis of D14.1 (benign tumor of the larynx) before age 15 will be excluded, as this more likely reflects a maternally transmitted juvenile-onset case, rather than a sexually transmitted adult-onset case (primary objective).

- Subjects who immigrated to Sweden after 2006 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 (GlaxoSmithKline, <1% of all HPV vaccinated subjects in Sweden) will be excluded since it provides no effectiveness against the causative HPV types (6 and 11) in RRP (primary objective).

- Subjects above age 30 will be excluded since GARDASIL/GARDASIL 9 exposure in this group is too low to expect any effectiveness observed (both primary and secondary objectives).

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 (before 17 years of age vs 17 years or older). 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 year, gender, and age.

7.6 Variables

All the below variables are intended to be analyzed as categorical variables. 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. 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 and UDW22) for RRP may provide further specificity to validate the outcome. Depending on exact case numbers available from the registers, the plan is to perform this procedure for at least 33% of the total case load (i.e., ~20-30 cases).

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 including advising on use of ICD-10 code D14.1, 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 that use of ICD-10 code D14.1 alone is specific and appropriate for characterizing cases of AoRRP. A Scientific Review Committee with expertise in RRP, HPV, epidemiology, and biostatistics will be 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 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 also 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. 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

Nested case-control study (primary objective)

Definition of cases:

- A subject will be defined as having a first case of AoRRP if she has ≥1 hospitalization or outpatient record with diagnosis registered as D14.1, between 15-29 years of age [24].

Selection of controls: random selection of 10 controls per case from the underlying population at risk, using incidence density sampling procedures. Matching criteria will be age at diagnosis, calendar year, length of follow-up in the registries, and region where case was diagnosed.

Ecological study (secondary objective)

Definition of cases:

- 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, 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, 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, a Supplement 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 (Supplement 1).

Covariates (potential confounders and/or effect modifiers):

- An individual will be defined as having EGW 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 and/or D06BB04, as validated in Levàl et al, 2012 and Herweijer et al, 2014) [26] [27]. EGW is the only sexually transmitted disease which may be comprehensively investigated in Swedish registries; the other STD's such as *Chlamydia trachomatis* (CT), gonorrhea or syphilis are protected by a special 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.

- 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.

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

- Annual individual/family income will be categorized in tertiles or quantiles relative to the general female population of Sweden of corresponding age structure [28]. The average income in 2020 for Swedish females aged 20 years was SEK 114,000 (USD 13,340) and for Swedish females aged 29 years was SEK 267,000 (USD 31,243).

Missing data for covariates will be included as variable categories marked "Missing" and will be included as separate categories in the statistical analysis. 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 [29]. 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

Data sources for this study include 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

7.7.1 Study Procedures

The here 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 ERA to mandate this access. KI has 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

Sample Size and Power: Estimated power to evaluate the primary objective (i.e., hypothesis that AoRRP risk is lower among females fully vaccinated with GARDASIL or GARDASIL 9 before age 17 years versus those who are unvaccinated) is presented in this section. The statistical criterion for success requires that the odds ratio be >3.0 and lower bound of the 95% confidence interval for the odds ratio be >1.33. Based on available information, the Sponsor's power calculations (summarized below) supports testing of this hypothesis; however, the exact number of cases is not known and therefore a decision to conduct the analysis will be made once data are received from the registries, i.e., exact number of cases occurring in relevant birth cohorts is confirmed. This assessment will be made prior to conducting any analyses. If due to low number of cases, study power is not sufficient, then the analysis will not be performed until additional cases are available.

The estimated number of possible RRP cases (identified using ICD-10 code D14.1) occurring after GARDASIL introduction in Sweden (among females eligible for vaccination before 17

years of age; birth cohorts 1990 to 2003) is ~50. Study power was estimated according to varying number of cases (30 to 60) and effect size (odds ratio/relative risk from 3 to 4), with constant alpha-level of 0.05, control/case ratio of 10, and weighted female vaccination coverage/exposure rate of 30% in the age range of focus [Table 2]. For reasons of data sharing and integrity (cell counts <5 cases being suppressed), only a range of possible number of cases is known at this time. With 52 cases originating from 1990-2003 birth cohorts (high end of estimated range), the estimated power assuming true odds ratio of 3.0 is 81%. Precision was also taken into account 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%. This level of precision is attainable within the study power calculation assuming at least 52 incident AoRRP cases are observed in the cohort of interest. It is important to note that these approximate counts were generated for the purpose of power estimation only through accessing publicly available gross statistics on ICD codes for otorhinolaryngological diseases, and that no preliminary analyses evaluating the association between HPV vaccination and RRP have been performed.

In observational studies, high effect estimates are considered important to demonstrate strong associations and to assess causality. Conventionally, relative risks of <2 are considered to represent weaker associations by epidemiologists, as it may not be possible to judge whether or not the association can be entirely accounted for by bias [30]. A threshold of 3.0 is therefore proposed to establish the effectiveness of GARDASIL/GARDASIL 9 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%-75% (equivalent to ORs of 1.3-4.0) with higher effect among females vaccinated at younger age. Based on the preliminary possible RRP case counts for Sweden, provided by the study Principal Investigator (Dr. Karin Sundstrom from Karolinska Institutet), this study is expected to be sufficiently powered to assess GARDASIL/GARDASIL 9 vaccine effectiveness against AoRRP [Table 2]; however, this will need to be confirmed once actual number of cases is confirmed. The power of the study will be calculated once data are received from the registries, and the exact number of cases occurring in relevant birth cohorts is confirmed. This assessment of whether the study is adequately powered to proceed with addressing the study primary objective will be made prior to conducting any analyses and without knowledge of vaccination status of cases. If due to low number of cases, study power is not sufficient, then the analysis will not be performed until adequate numbers of cases are available in the Swedish Registries. As an alternative approach to waiting for additional cases to accrue in Sweden, the Sponsor may also consider conducting a pooled analysis including additional data from other similar Nordic countries (Denmark and/or Norway); where registries similar to those in Sweden are available. The pooled analysis would combine patient level data from the countries and utilize the same protocol. The Sponsor has confirmed that the same ICD-10 code (D14.1) is appropriate for identification of RRP cases in Denmark and Norway as well. 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 [31].

Regarding evaluation of GARDASIL/GARDASIL 9 effectiveness against JoRRP, the case load will not be sufficient in Sweden alone, so to ensure adequate study power the Sponsor may also consider conducting a pooled analysis including additional data from Denmark and/or Norway. The sample size and power estimation will be included in a separate protocol.

Table 2 Power estimates according to varying number of cases of AoRRP (from 30 to 60) and effect size (odds ratio from 3.0 to 4.0), with constant alpha-level of 0.05, lower bound of 95% confidence interval >1.33, control/case ratio of 10, and vaccination coverage of 30%.

True Effect Size	Cases of AoRRP			
	30	40	50	60
OR=3	0.55	0.72	0.77	0.85
OR=3.5	0.72	0.84	0.90	0.94
OR=4	0.82	0.91	0.96	0.98

Note: For OR=3, >80% power would be achieved with 52 cases.

7.9 Data Management

All data collected for the study should be recorded accurately, promptly, and legibly. The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate by the Swedish register data holder, to the best of his/her knowledge.

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.

7.10 Data Analysis

Statistical Methods

Conditional logistic regression will be used for estimation of odds ratios (ORs) and corresponding 95% confidence intervals, with adjustment for relevant covariates. Each case subject and her controls constitute a risk stratum, or a risk set matched on age at diagnosis, calendar year, length of follow-up in the registries, 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 [18] [19].

When the outcome of a study is rare, which is the case for RRP, the OR approximates the risk ratio (or relative risk, RR) [32]. 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 [33]. ORs obtained through the conditional logistic regression model will therefore be interpreted as the corresponding RR.

It is expected that use of ICD-10 code D14.1 will be highly accurate for diagnosis of RRP; however, to further increase its specificity, the plan is also to perform sensitivity analyses restricted to RRP cases with related diagnostic or other treatment procedures, and/or subcode D14.1.A, as described above.

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 Supplement 1, which lists subject matter expertise analysis of the association of interest, and potential confounding thereto. Supplement 1 also motivates closely the inclusion of covariates described here below.

In case-control studies, it is actually 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 Swedish age-matched population) 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 Sweden 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 KI 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 versus cases [of D14.1] that have 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(s): Calculation of Epidemiological Measure(s) of Interest

For the ecological study over two decades, age-standardized incidence rates (ASIRs) of JoRRP and AoRRP will be calculated, stratified by age group and calendar period. 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.

Exploratory Objective(s): 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.

7.11 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), 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 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.

7.12 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. On the other hand, there is excellent systematicity, and generalizability due to the structural nature of the register sampling frame. 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 (Supplement 1).

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 Karolinska Institutet proprietary HPV vaccination algorithm and substantial in-house knowledge of combination of 3 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 at the appropriate time to enter. In recent years, especially the post-vaccination introduction era, Sweden has experienced a large immigration proportion, such that the proportion of Swedes with a foreign background is now 24.1% - foreign background defined as either having been born outside of Sweden, or having both parents born outside of Sweden. 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.

7.13 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". Therefore, the full set of D14.1 cases available will be used in main analysis, augmented (in sensitivity analyses) with diagnostic and treatment codes described above. 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 Swedish healthcare, 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 actually a false negative, i.e. a missed case of RRP, should be negligible.

All immigrant females to Sweden (after age 9) will be excluded, so as to ensure there is no misclassification of exposure, which removes the risk that subjects who have actually received HPV vaccination outside of Sweden are mis-classified as non-vaccinated, and also 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 Supplement 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

8.1 Informed Consent

This study will operate under the Swedish law regulating access to health register data for the purpose of research for the greater good, i.e. societal need. According to Swedish legal and ethical standards, such studies may be conducted under exemption from individual informed consent if the study is very large, the risk to the participant is very low (i.e. the study is non-interventional in nature), and the need for new knowledge is clear. First, the researcher applies to the Ethical Review Authority of Sweden for permission to perform the study.

When the ERA gives approval, the researcher applies to the relevant health data holder (typically the Swedish National Board of Health and Welfare) and obtains a pseudonymized dataset with the requested data. If the project may need updates, the pseudonymization code key may be retained by the data holder authority (typically the National Swedish statistics agency Statistics Sweden) for a maximum of three years, upon active application for such retention. Otherwise, the code key is destroyed after three months. Once the data has been extracted and transferred to the researcher, the researcher may carry out the intended research on the data. Ethical amendment applications to the ERA may enable further modifications and amendments to the data handed out. Informed consent is not required for this study.

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. Any health outcomes (if collected per section 4.1), 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.

If an investigator elects to spontaneously report any suspected adverse reactions or product quality complaints, they should be reported via fax to Local DPOC [+46 (0)8 578 139 00], in English using an AE and PQC report form for reporting to worldwide regulatory agencies as appropriate.

10 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

It is anticipated that this study will yield 2 or more manuscripts to be published in a peer-reviewed scientific journal. It is anticipated that this study will yield 1 or more conference abstracts to be submitted to scientific conferences of note in the field of oncology, epidemiology and/or virology. Any publications related to the study will need to be reviewed/approved by the Sponsor prior to submitting results externally.

The Risk Management Safety Team (RMST) Lead /Clinical Safety Risk Manager (CSRM) Physician will be notified if any safety data are generated in the final study report or any interim report. The safety and conclusion sections of the final study report or interim report must be reviewed by the RMST Lead/CSRM Physician prior to finalization of the report. The review by the CSRM Physician must occur prior to any release of results to the public domain in the form of abstracts, posters, presentations or manuscripts.

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12 ANNEXES

ANNEX 1 LIST OF STAND-ALONE DOCUMENTS

No.	Title
1.	AE/PQC Reporting Form

ANNEX 2 GRAPHICAL AND NUMERICAL OVERVIEW OF POTENTIAL CONFOUNDING IN ASSESSMENT OF HPV VACCINE EFFECTIVENESS AGAINST ADULT-ONSET RRP

Definitions:

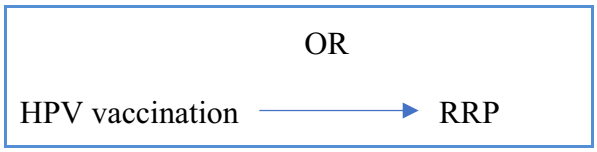
Study exposure: HPV vaccination with GARDASIL or GARDASIL 9, below called HPV vaccination.

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 52 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 Sweden [29]:

1. Socioeconomic status: in *subsidized* vaccination program for girls age 13-17 years 2007-2012

    - Country of birth (Hazard Ratio (HR) = 0.49, 95% confidence interval (CI)=0.48-0.50) for vaccine receipt if birth country other than Sweden)

    - Education level of parents (HR=0.32, 95% CI=0.31-0.33) for vaccine receipt if lowest tertile of education)

    - Income level of parents (HR=0.53, 95% CI=0.52-0.54) for vaccine receipt if lowest tertile of income)

2. Socioeconomic status: in free-of-charge, school-based program for girls age 11-18 years 2012 and onwards

    - Country of birth (HR=0.82, 95% CI=0.81-0.83) for vaccine receipt if birth country other than Sweden)

    - Education level of parents (HR=0.92, 95% CI=0.91-0.94) for vaccine receipt if lowest tertile of education)

    - Income level of parents (HR=0.87, 95% CI=0.85-0.88) for vaccine receipt if lowest tertile of income)

Here it is observed that country of birth and socioeconomic status (defined as education and income) are associated with the exposure, of moderate-strong degree depending on age and calendar period of exposure.

3. Sexual behavior:

    - There has been one study in Sweden published indicating higher hypothetical acceptability of HPV vaccination in young adult women up to age 30 [28].

    - Subjects with >1 sexual partner, a below median age of sexual debut, and defining themselves as bisexual were found to be more willing to accept HPV vaccination than comparison groups. Effect sizes (ORs) were modest, ranging from 1.15 to 1.69, but statistically significant (95% CIs excluded null).

    - 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).

    - It is difficult a priori to exclude 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 [34] [35] [36] [37] [38] [39] [40] [41].

4. Smoking

    - There have been no comprehensive studies showing an association between smoking habits and willingness to vaccinate against HPV in Sweden or elsewhere. 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 Sweden:

- No comprehensive local studies performed, due to rarity of 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 [42].

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.

    - No large studies have been identified evaluating the association between sexual contacts and risk of RRP. A small study including 25 RRP patients [43], 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 [44] 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 Sweden 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 age 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:

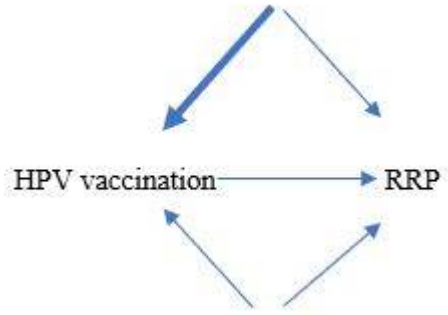
Although **socioeconomic status** appears to be moderately-strongly associated with exposure, there is no evidence suggesting it is associated with outcome. If there is an association with RRP as an outcome, it should be modest in size. However, in the interest of obtaining the best evidence, this association 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.

Finally, for **smoking habits**, the size of the association and thus potential for confounding due to this factor appears to be modest at most. Swedish 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 [19]. 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 3 TABLE AND FIGURE SHELLS FOR RRP STUDY (PRIMARY AND SECONDARY OBJECTIVES)

Table 3 Number of new cases and incidence rates of recurrent respiratory papillomatosis (RRP, defined as a first receipt of code D14.1) in Sweden, by calendar years 2000-2019

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												
25-29												
Men												
All ages												
0-14												
15-29												
0-4												
5-9												
10-14												
15-19												
20-24												
25-29												

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																		
0-14																		
15-29																		
0-4																		
5-9																		
10-14																		
15-19																		
20-24																		
25-29																		
Men																		
All ages																		
0-14																		
15-29																		
0-4																		
5-9																		
10-14																		
15-19																		
20-24																		
25-29																		

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																		
15-29																		
0-4																		
5-9																		
10-14																		
15-19																		
20-24																		
25-29																		
Men																		
All ages																		
0-14																		
15-29																		
0-4																		
5-9																		
10-14																		
15-19																		
20-24																		
25-29																		

Table 3, continued.

Gender and age group	2018			2019		
	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						
Men						
All ages						
0-14						
15-29						
0-4						
5-9						
10-14						
15-19						
20-24						
25-29						

Figure 2 Overall age-adjusted and age-specific incidence rates of recurrent respiratory papillomatosis (RRP, defined as a first receipt of code D14.1) among women in Sweden, by year 2000-2019

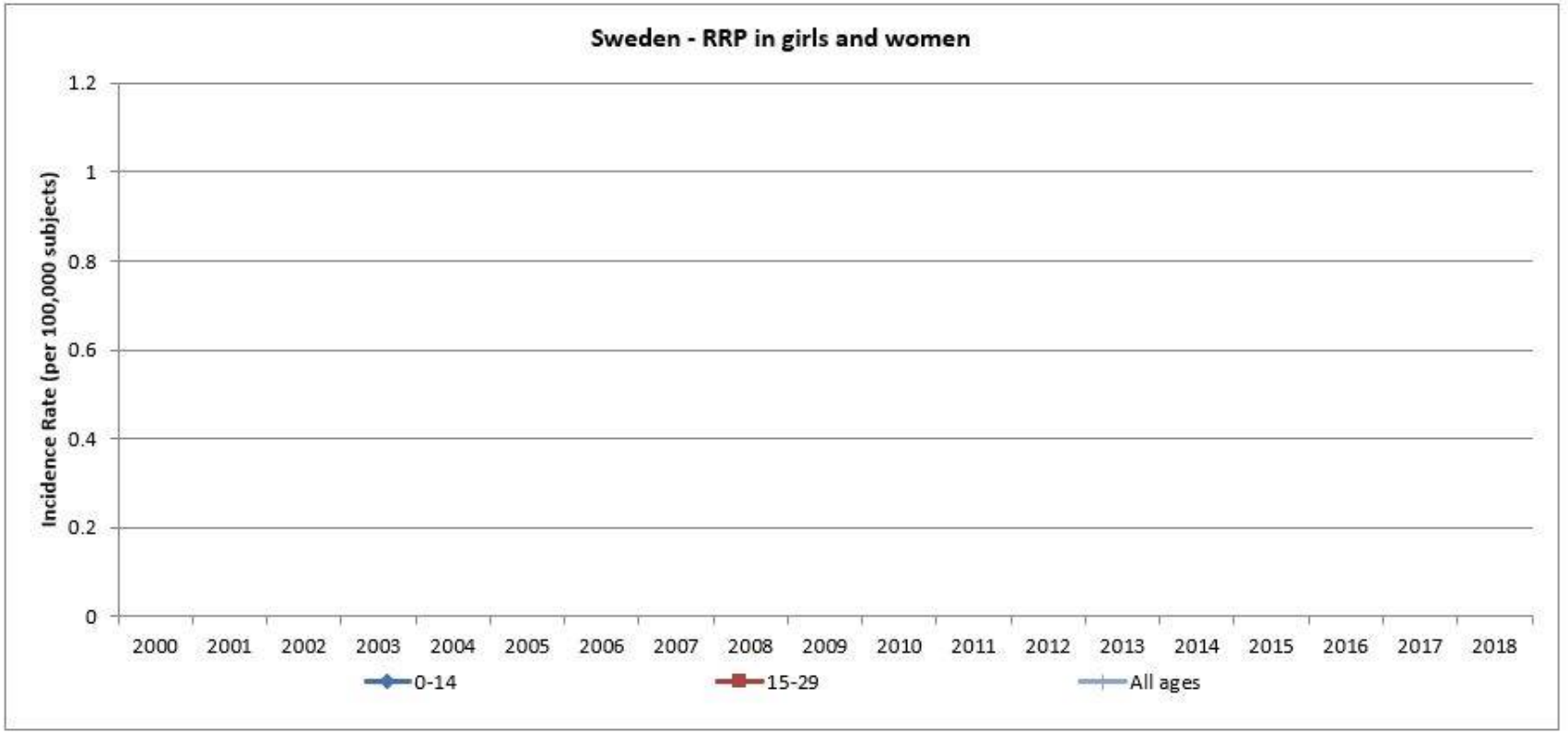

Figure 3 Overall age-adjusted and age-specific incidence rates of recurrent respiratory papillomatosis (RRP, defined as a first receipt of code D14.1) among men in Sweden, by year 2000-2019

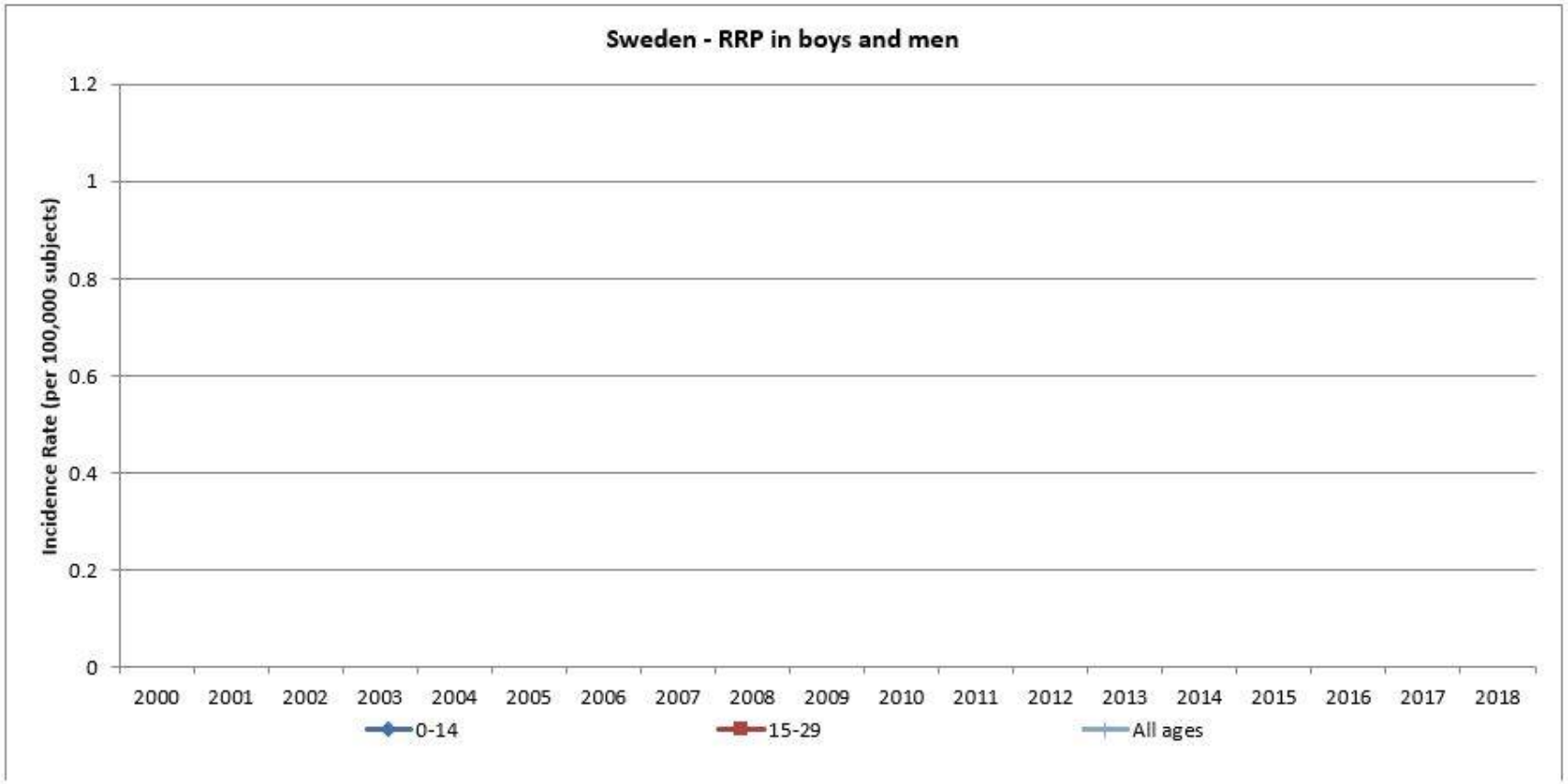

Table 4 Characteristics of study population, AoRRP cases, and control subjects.

	Study population, **No. (%)**	AoRRP cases, **No. (%)**	Controls, **No. (%)**
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			
Country of birth			
Sweden			
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, 2006-2019

HPV vaccination status	**AoRRP (ICD-10 code: D14.1)**			
	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 D14.1 after age 15 years are included.
[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, 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.

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/GARDASIL 9 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 4 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, Merck, as 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), the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to the Clinical Trials Data Bank, such as ENCePP. Merck, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAMA/FDAAA mandated studies. Information posted will allow subjects to identify potentially appropriate 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 are that of the Sponsor and agrees not to submit any information about this study or its results to the Clinical Trials Data Bank.

ANNEX 5 QUALIFIED PERSON FOR PHARMACOVIGILANCE (QPPV)

Dr Guy Demol
EU Qualified Person for Pharmacovigilance
Tel: PPD
Fax: PPD
Email: PPD

MERCK SHARP & DOHME
Hertford Road
Hoddesdon
Hertfordshire EN11 9BU
Telephone PPD

Deputy QPPVs:
PPD
Tel: PPD GSM: PPD , Fax: PPD
Email: PPD
PPD
Tel: PPD GSM: PPD , Fax: PPD
Email: PPD

Emergency/Out of Hours: GSM numbers above or via PPD

Dear Sir/Madam

Re: EU QPPV Signature Page for PASS

INN:
Product:
Protocol No.:
Epidemiology No.:
Protocol Date:
MAH:

In line with the Guideline on Good PharmacoVigilance Practice (GVP), Module VIII – Post-Authorisation Safety Studies (PASS) and according to MSD internal SOPs, this study has been reviewed and approved by the European Qualified Person for Pharmacovigilance.

Yours faithfully

Dr Guy Demol
Associate Vice President,
EU Qualified Person for Pharmacovigilance

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	