PRODUCT: V501/V503	PROTOCOL/AMENDMENT VERSION NO.: V503-095-00-v3
REVOPS ID NO: NIS102781 EPIDEMIOLOGY NO.(PE STUDIES ONLY): 08039.022	CORE DRC APPROVAL DATE: 18MAR2024

PAES INFORMATION

Title	Nested case-control study evaluating effectiveness of immunization of girls and women of childbearing potential with GARDASIL™/GARDASIL™ 9 against juvenile-onset recurrent respiratory papillomatosis (JoRRP) in Sweden, Denmark, and Norway
Protocol Version identifier	V503-095-00-v3
Date of last version of protocol	Aug 28, 2023
HMA-EMA Catalogue of Real-World Data:	To be 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
Joint PAES	No
Research question and objectives	Primary Objective: To assess if the odds of JoRRP are lower among children whose biologic mothers were fully vaccinated with Gardasil/Gardasil 9 at least one year prior to delivery versus unvaccinated mothers.
Country(-ies) of study	Sweden, Norway, Denmark

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Marketing authorisation holder(s) including MAH Contact Person	Merck Sharp & Dohme B.V. PPD Molenstraat 110 5342 CC Oss Netherlands Tel: PPD Email: PPD
Merck Final Repository (REDS) Date	18-JUL-2024
Date of Health Authority Approval of Protocol	N/A

PRODUCT: V501/V503	PROTOCOL/AMENDMENT VERSION NO.: V503-095-00-v3
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LIST OF ABBREVIATIONS

AE	*Adverse event*
AoRRP	*Adult-onset Recurrent Respiratory Papillomatosis*
CI	*Confidence Interval*
EGW	*External Genital Warts*
EMA	*European Medicines Agency*
EU	*European Union*
FDA	*Food and Drug Administration*
GPP	*Good Pharmacoepidemiology Practice*
HPV	*Human Papillomavirus*
HR	*Hazard Ratio*
ICD	*International Classification of Disease*
IEC	*Independent Ethics Committee*
IRB	*Institutional Review Board*
JoRRP	*Juvenile-onset Recurrent Respiratory Papillomatosis*
OR	*Odds Ratio*
PAES	*Post-Authorization Effectiveness Study*
PASS	*Post-Authorization Safety Study*
PIN	*Personal Identification Number*
PPV	*Positive Predictive Value*
PQC	*Product Quality Complaint*
RR	*Relative Risk*
RRP	*Recurrent Respiratory Papillomatosis*
SD	*Standard Deviation*
SNOMED	*Systemized Nomenclature of Medicine*
SOP	*Standard Operating Procedure*
SQI	*Significant Quality Issue*
STI	*Sexually Transmitted Infections*
VE	*Vaccination Exposure*

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1 RESPONSIBLE PARTIES

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Supplier/Collaborator	PPD Sweden Cancer Registry of Norway, Norway Danish Cancer Society, Denmark
Shared responsibilities	1) Authoring of protocol, 2) Execution of study, 3) Interpretation of results, and 4) Drafting of study report

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2 ABSTRACT

Title	Nested case-control study evaluating effectiveness of immunization of girls and women of childbearing potential with GARDASIL™/GARDASIL™ 9 against juvenile-onset recurrent respiratory papillomatosis (JoRRP) in Sweden, Denmark, and Norway
Protocol Number / Version	V503-095-00-v3
Date	18Mar2024
Authors	PPD 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 of mothers, targeting types 6 and 11, will reduce incidence of RRP in their children.
Research Question(s) & Objective(s)	Primary Objective: To assess if the odds of JoRRP are lower among children whose biologic mothers were fully vaccinated with GARDASIL/GARDASIL 9 at least one year prior to delivery versus unvaccinated mothers.
Study Design	Population-based nested case-control study
Population	Primary objective: Children 0-9 years of age between 2008 and 2018 or later, born to mothers with opportunity to receive GARDASIL/GARDASIL 9, i.e. birth cohorts 2008 to 2018+.

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Variables	Exposure definition: Fully vaccinated with GARDASIL/GARDASIL 9 according to schedule (2 or 3 doses according to age at vaccination) in biologic mother of child. Outcome definitions: - First diagnosis of JoRRP from national registries using ICD-10 code D14.1 (benign neoplasm of larynx).
Data Sources	Nordic population, patient, and vaccine registries.
Study Size	Primary objective (nested case-control study): - JoRRP: ~200 cases, ~100 controls per case (i.e. ~20,000 controls)
Data Analysis	Power calculation for primary objective (estimated 200 JoRRP cases and 20,000 controls) JoRRP: study is 94% powered to detect a RR=>3.0 with a lower bound of the 95% confidence interval of >1.33; equivalent to lower bound of 95% CI of vaccine effectiveness >25% (sample size and study power to be confirmed prior to initiating analysis).
Milestones	**Planned Date**
Start of data collection:	03Mar2023 (Actual)
End of data collection:	4Q2024
Final report of study results:	1Q2025

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3 AMENDMENTS AND UPDATES

Update no	Date	Section of Study Protocol	Amendment or Update	Reason	CORE DRC Approval Date	CORE DRC Version No
1	30Jun23	4	Updated data collection and final report timelines.	Revised milestones from PIs regarding data acquisition from respective registries.	27Jul23	2
		7.1	In Study Design Section of protocol, it was stated that "cases and controls will be matched as closely as possible on age of mother" without specifying age difference. The protocol has been updated to specify in this section that age difference will be +/- 1 year.	Additional information added on matching criteria (maternal age) of cases and controls.	27Jul23	2
		7.1	In Study Design Section of protocol, it was stated that "cases and controls will also be matched on calendar year of diagnosis and according to length of follow-up in the registries." The protocol has been modified, removing mention of matching on "length of follow-up in the registries."	Investigators will not explicitly match on number of years of follow-up.	27Jul23	2

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Update no	Date	Section of Study Protocol	Amendment or Update	Reason	CORE DRC Approval Date	CORE DRC Version No
		7.2.2, 7.7.1	Exclusion criteria was added specifying that subjects/children whose mother received Cervarix (bivalent HPV vaccine) will be excluded from the study.	Cervarix does not target HPV types 6/11 and so not expected to prevent RRP.	27Jul23	2
		7.2.2	Added specific exclusion criteria that any child (case or control subject) who previously received any HPV vaccine will be excluded from analysis.	Focus of analysis is assessment of maternal vaccination in prevention of JoRRP.	27Jul23	2
		7.2.3, 7.3.1, 7.7.2	Inclusion of stratification according to time since vaccination of mother to ≤10 years and >10 years.	Attempt to explore durability of protection.	27Jul23	2
		9	Reference to Outcomes Section number was previously incorrect (“7.6.2” replaced with “7.3.2” in revised draft).	Correction of minor typographical error.	27Jul23	2
		6.2, 7.4, 7.7.3	Added exploratory objective to assess mother-child pairs, according to JoRRP and AoRRP history.	Explore concordant and discordant pairs according to RRP history	27Jul23	2

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Update no	Date	Section of Study Protocol	Amendment or Update	Reason	CORE DRC Approval Date	CORE DRC Version No
				(i.e., mother-child pairs).		
		7.2.3, 7.3.1, 7.7.2	Inclusion of stratification according to time since vaccination of mother to ≤10 years and >10 years.	Attempt to explore durability of protection.	27Jul23	2
		9	Reference to Outcomes Section number was previously incorrect ("7.6.2" replaced with "7.3.2" in revised draft).	Correction of minor typographical error.	27Jul23	2
		6.2, 7.4, 7.7.3	Added exploratory objective to assess mother-child pairs, according to JoRRP and AoRRP history.	Explore concordant and discordant pairs according to RRP history (i.e., mother-child pairs).	27Jul23	2
2	23Nov23	7.1, 7.3, 7.3.2, 7.7.1, 7.10	Add requirement for appropriate topography/morphology code in addition to D14.1 (to define outcome) in settings where this information is available/complete from pathology register.	Determined that these codes can be retrieved from pathology register in some settings.	18Mar2024	3

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4 MILESTONES

Milestone	**Planned Date**
Start of data collection	03Mar2023 (Actual)
Registration in the HMA-EMA Catalogue of Real-World Data	3Q2024
End of data collection	4Q2024
Final report of study results	1Q2025

5 RATIONALE AND BACKGROUND

Background

Recurrent respiratory papillomatosis (RRP) is a self-limiting disease, characterized by the appearance of papillomatous lesions that are generally benign, occurring 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].

Juvenile-onset RRP (JoRRP) is most often diagnosed between ages 2-4 years [3]. In cases of JoRRP, the route of HPV transmission is from mother to child during labor. Numerous age cut points have been used to define the upper age limit for 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 of JoRRP compared to children born to mothers without genital warts [4]. 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] [6] [7] [8] [9] [10]. A recent US study focusing on JoRRP found an incidence of 2 per 100,000 births in 23 US states prior to the introduction of HPV vaccination, but this may have been an underestimate due to technical problems in case ascertainment and using national (versus state level) denominator data [11].

Given the high attribution of targeted HPV types 6 and 11, high GARDASIL (recombinant HPV quadrivalent [types 6, 11, 16 and 18] vaccine) and GARDASIL 9 (recombinant HPV nonavalent [types 6, 11, 16, 18, 31, 33, 45, 52 and 58] vaccine) 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 [12]. 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 [12]. 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 [11].

In evaluating the impact/effectiveness of GARDASIL against JoRRP it is important to consider the unique mechanism of acquisition of causal HPV infections, i.e., mother to child transmission during delivery. To observe an effect, the vaccinated female must become pregnant and deliver a child with sufficient opportunity to develop JoRRP, considering also that the peak age of JoRRP onset is between 2 to 4 years. The earliest cohort of girls vaccinated in school-based programs (10-13 years of age) in 2007 would reach a maximum age of 23-26 years (1992-1995 birth cohorts) in 2020, with few cases of JoRRP expected to be diagnosed among children born to mothers from these birth cohorts at this point in time. But considering the rapid decline in JoRRP already observed in the United States and in

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Australia, where average maternal age at birth of first child is mid- to late-20s, this suggests that the majority of mothers whose children received protection were vaccinated in the older "catch-up" age range, up to 26 years of age.

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 in the US (2004-2007) was reported at $123 million [13]. As there is currently no cure, treatment focuses on maintaining voice quality and airway patency [14]. Among children diagnosed with JoRRP, approximately 19% experience aggressive disease requiring >40 lifetime procedures [3].

There is currently no available practical prevention approach for JoRRP, thus it is important to assess the effectiveness of HPV vaccination against this disease. Due to the low incidence of JoRRP, it is not feasible to conduct a randomized controlled trial to evaluate the efficacy of HPV vaccination in reducing the incidence of RRP and may not be considered ethically justifiable given the established benefits to vaccine recipients. However, an observational (real-world) study to assess whether GARDASIL/GARDASIL 9 vaccination is associated with a reduction in the risk of JoRRP in children of vaccinated compared to unvaccinated mothers is feasible, especially in the Nordic region (Denmark, Norway, and Sweden), with combined population size of >21 million individuals. 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 JoRRP 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 [15], which has been shown to be highly impactful in reducing incidence of genital warts and effective and in preventing high-grade cervical lesions and invasive cervical cancer in the real-world using Swedish and Danish registry information [16] [17] [18] [19] [20]. The 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 [21]; this study extension was conducted as a commitment to the FDA and the EMA. Additionally, a long-term effectiveness study of GARDASIL 9, which is an extension of the GARDASIL 9 pivotal efficacy study, is also ongoing as a commitment to the FDA and EMA, and long-term effectiveness has been demonstrated through 8 years in an interim analysis [22].

Prior studies in the Nordic region have successfully been conducted focusing on GARDASIL vaccine effectiveness against high-grade cervical lesions and cancer [16] [17] [18] using National Patient Registry information to accurately identify cases (using international classification of disease, 10th [ICD 10] revision codes) [23] [24], and also involving generational linkage of registry information for children and their parent(s) [25] [26] [27]. Thus, we here propose a national, population register-based case-control study investigating

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GARDASIL/GARDASIL 9 effectiveness against JoRRP. Demonstration of GARDASIL/GARDASIL 9 effectiveness against JoRRP 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.

The current protocol, focusing on JoRRP, is adapted from a similar protocol focusing on vaccine effectiveness against adult-onset RRP (AoRRP) in Nordic countries, including Sweden, Denmark, and Norway.

6 RESEARCH QUESTION AND OBJECTIVES

6.1 Primary Objective

To assess if the odds of JoRRP are lower among children whose biologic mothers were fully vaccinated with GARDASIL/GARDASIL 9 at least one year prior to delivery versus unvaccinated mothers.*

* 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 JoRRP. Additionally, given the rare outcome of JoRRP and the use of incidence density sampling, odds ratio estimates will be interpreted as the corresponding relative risks.

6.2 Exploratory Objectives

1) To assess risk factors for JoRRP, including maternal history of external genital warts, mode of delivery, maternal smoking status, and socioeconomic factors.

2) To assess mother-child pairs, according to JoRRP and AoRRP history.

7 RESEARCH METHODS

7.1 Study Design

Nested case-control study (primary objective)

Setting: Sweden, Norway, and Denmark.

In 2006, the U.S. Food and Drug Administration and European Medicines Agency approved the use of GARDASIL. National HPV vaccination programs in Scandinavian countries (Denmark, Norway, and Sweden) were instituted in subsequent years (~2008 or afterward) for young female adolescents, with catch-up vaccination programs for cohorts of older adolescents, teens, and/or young women in Denmark and Sweden. In Denmark, GARDASIL

was used from October 2008 to February 2016, Cervarix (recombinant HPV bivalent [types 16 and 18] vaccine) from February 2016 to November 2017, and GARDASIL 9 since November 2017 (currently in use). The national HPV vaccination program targeting girls aged 12 years (primary cohort) was introduced in 2009, with fully subsidized catch-up vaccination for girls 13-15 years of age available since 2008, and girls/women up to 27 years of age since 2012. In Sweden, national HPV vaccination program using GARDASIL was introduced in 2010, with large-scale vaccination and high coverage achieved in 2012, with GARDASIL 9 being used since 2020. 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 Norway, the HPV vaccination program was initiated in 2009, in which girls approximately 12 years of age were offered GARDASIL in a three-dose schedule (until 2017). Catch-up vaccination was offered in Norway during the period 2016–2019 to women born between 1991 and 1996. Since 2017, Cervarix has been used in Norway. In 2015, a 2-dose schedule (with doses administered at 0 and 6 months) was recommended for females ≤14 years of age in Denmark and Sweden.

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. The ability to link registry information for children and their mothers in Sweden, Norway, and Denmark enables assessment of vaccine effectiveness against JoRRP, i.e., maternal vaccination status prior to delivery can be compared between case and control subjects. 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 case-control study nested within a cohort of children born to mothers with opportunity to be vaccinated with GARDASIL/GARDASIL 9 at least one year prior to delivery. 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 [28].

Cohort: GARDASIL was not available in eligible Nordic countries (Sweden, Norway, and Denmark) until late 2006, therefore we plan to capture the cohort of children (0-9 years) born to mothers' during the period 2008 to 2018 or later (birth cohorts 2008 to 2018+), i.e., JoRRP cases whose mother had opportunity to be vaccinated prior to becoming pregnant. The most recent registry data available from each country will be collected, e.g., 2018 or later. In the sections below, 2020 is listed as end date of follow-up period; however, the most recent data available in each country will be used.

Cases: Within the specified cohort, JoRRP cases (first diagnosis) will be identified from national registries using the ICD-10 code D14.1 (benign neoplasm of larynx). In countries

where topography/morphology codes are available/complete in the cancer/pathology registry, JoRRP definition will require both code D14.1 and appropriate topography/morphology codes. The date of birth is the index date for JoRRP cases.

D14.1 is the ICD-10 code used for diagnosis of RRP in Nordic and other countries and will be used to capture cases of JoRRP for the primary analysis. Recently, investigators from Australia found that cases of JoRRP identified using this code had positive predictive value (PPV) of 98.1%, with no additional RRP cases identified using other codes [29]. It is therefore expected that the accuracy of RRP diagnosis using this code would also be very high in Sweden, Norway, and Denmark. 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). In countries where available from the pathology/cancer registry, appropriate topography/morphology codes (identified in consultation with sub-specialist clinical experts) will also be used to increase specificity of the primary JoRRP case definition. In countries where topography/morphology codes cannot be accessed/incomplete within pathology/cancer registry, the subcode D14.1A (representing "larynx papilloma") will be explored in a subgroup/sensitivity analysis, as this may also be even more specific for RRP according to sub-specialist clinical 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 even more specific for RRP.

Controls: For each case of JoRRP, up to 100 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 [30]. However, given that data for additional controls are readily available in this database study, effort will be made to identify 100 controls per case. Cases and controls will be matched as closely as possible on age of mother (+/- 1 year), sex of child, and region where case was diagnosed. By design of the study (nested case-control), cases and controls will also be matched on calendar year of diagnosis. Controls will be selected from the population at risk at the point in time when a case is diagnosed with JoRRP. All controls who meet the matching criteria will be assigned a random number using SAS statistical software (SAS Institute Inc, Cary, NC) procedures. Then, 100 controls for each case will be selected at random from the pool of eligible controls. Controls will be assigned the same index date (date of birth) as the case to which they are matched. [Figure 1] provides an example of case/control subject selection nested within population-based cohort in this study.

Exposure assessment: The exposure of interest is GARDASIL or GARDASIL 9 vaccination in mother, one year prior to delivery, for each case and matched controls (see Figure 1 below).

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Exposure will be defined in 2 ways:

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

2. Exposure in sensitivity analysis: GARDASIL/GARDASIL 9 vaccination (yes/no). A female/mother who received at least one dose of GARDASIL/GARDASIL 9 one year prior to delivery will be classified as exposed.

While suggestive evidence exists that one dose of GARDASIL/GARDASIL 9 may provide a similar level of protection against the respective HPV target types (compared with those who are fully vaccinated), final results from short-term randomized controlled trials addressing this question are not yet available and waning immunity remains a concern. For this reason, the primary analysis focusses on children of females that are fully vaccinated.

The vaccine registries in Sweden, Norway and Denmark accurately capture vaccination, 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/GARDASIL 9 exposure have been conducted successfully in recent years [16] [17] [18] [31].

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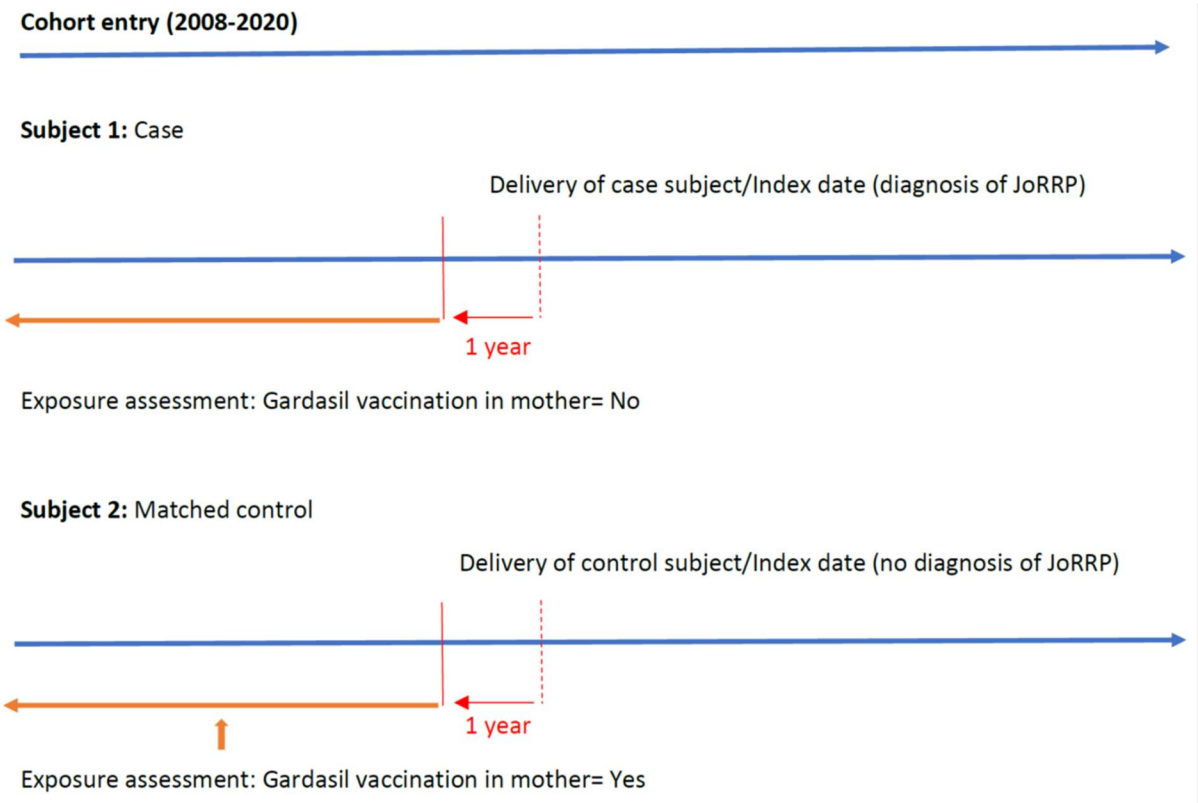

Figure 1 Example of Case/Control Subject Selection and Exposure Assessment, Nested Within Population-Based Cohort in this Study.

Subject 1 is classified as a case without maternal history of exposure to GARDASIL/GARDASIL 9 ≥1 year prior to delivery, and subject 2 is an eligible matched control with maternal history of exposure to GARDASIL/GARDASIL 9 ≥1 year prior to delivery.

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 registers have full coverage of the Swedish, Danish, and Norwegian populations.

The study population includes male/female children (0-9 years of age) from Sweden, Norway, and Denmark during time period 2008 to 2020, whose mother had the opportunity to be fully vaccinated with GARDASIL/GARDASIL 9 at least one year prior to delivery, i.e., birth cohorts 2008-2020.

7.2.1 Inclusion Criteria

- Birth cohorts 2008 to 2020
- The study subject (child) must be born and resident in Sweden, Denmark or Norway as defined through the Total Population Registry for their entire life, to ensure incident JoRRP case is truly new onset.
- The study subject must be between 0 to 9 years of age (due to direct HPV-vaccine receipt at ages 10-12 years) through school-based programs in some countries.

7.2.2 Exclusion Criteria

A flow diagram to highlight the exclusion criteria is shown in Figure 2 below.

- Children whose mother immigrated to Sweden, Denmark, or Norway both after 2006 and after age 9 years will be excluded as vaccination exposure status is unknown.
- Since the hypothesis of HPV transmission is that it occurs in mothers giving birth to biological children, adopted children will be excluded from the analysis as vaccination status of the actual, biological mother will be missing.
- Children whose mother received the bivalent vaccine Cervarix will be excluded since it provides no effectiveness against the causative HPV types (6 and 11) in RRP.
- Any child (case or control subject) who previously received any HPV vaccine will be excluded from analysis.

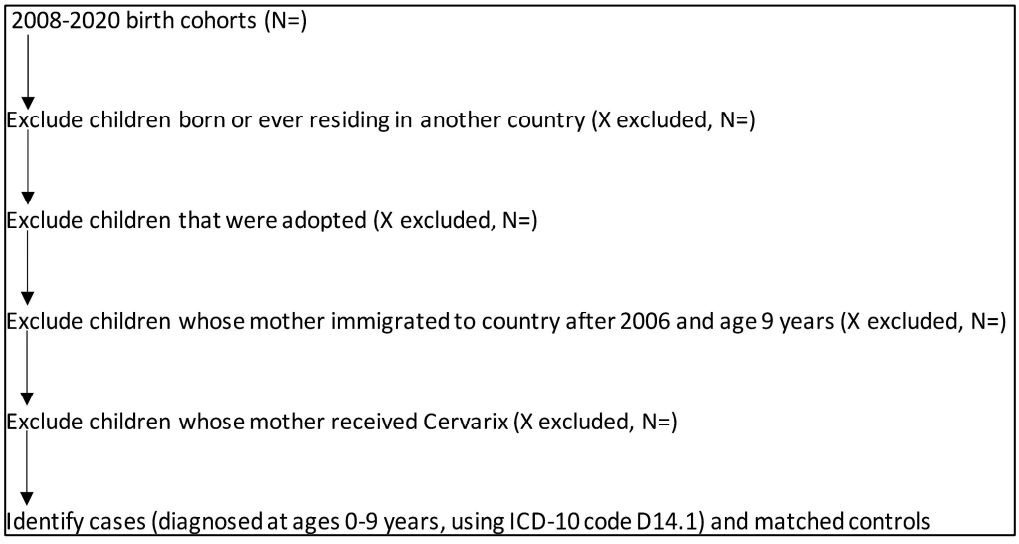

Figure 2 Flow Diagram Describing Steps to be Used in Creation of Data Set for Each Country, Based on Listed Inclusion/Exclusion Criteria

7.2.3 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 of mother (before 17 years of age vs 17 years or older)

2) Time since vaccination of mother (≤10 years vs >10 years)

3) Maternal history of external genital warts prior to delivery (yes/no)

7.3 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: Primary 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 codes (identified in consultation with sub-specialist clinical experts) will also be used to increase specificity of the outcome definition in primary analyses. There will be no medical chart review; however, 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. 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 including advising on use of ICD-10 code D14.1 and will continue to be consulted as needed throughout the study. 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.

7.3.1 Exposure

A subject's mother 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. 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, according to age at vaccination (<17 years vs. ≥17 years), and time since vaccination (≤10 years vs. >10 years). While higher effectiveness may be expected among females vaccinated as children (e.g., <14 years), few cases of JoRRP have occurred among children born to mothers from 1992+ birth cohorts (i.e., vaccinated at age 13 in 2007 or later), which may be expected considering that the average maternal age at birth of first child is ~29 years in Nordic countries.

7.3.2 Outcomes

Health outcomes are defined as clinical events or outcomes which may be represented as diagnoses, treatment or procedures.

Definition of cases:

- A subject will be defined as having JoRRP if he/she has ≥1 hospitalization or outpatient record with diagnosis registered as D14.1, with appropriate topography/morphology codes (where possible to obtain from pathology/cancer registry), between 0-9 years of age [29].

Selection of controls: random selection of up to 100 controls per case from the underlying population at risk, using incidence density sampling procedures. Matching criteria will be age of mother (+/- 1 year), sex of child, calendar year of case diagnosis, and region where case was diagnosed.

7.3.3 Covariates

In an observational study, where exposure is not randomized, it is important to explicitly express which association is being investigated, and *a priori* explain which covariates are proposed for adjustment 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. 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).

Covariates (potential confounders and/or effect modifiers):

- An individual (mother) will be defined as having EGW based on ≥1 hospitalization or outpatient record, and/or a prescription for a pharmaceutical against anogenital warts as validated in studies performed in the Nordic region [32] [33].

- Method of delivery (vaginal versus cesarean section). Evidence is inconsistent regarding whether birth by cesarean section is protective against JoRRP [14].

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

- Smoking status of the mother at first prenatal visit will be assessed (yes/no).

- Annual family income will be categorized in tertiles or quantiles relative to the general female population of Sweden, Denmark, and Norway of corresponding age structure.

- Mother's country of birth (Sweden/Norway/Denmark or other).

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

7.4 Data Sources

The study will be conducted using only structured secondary data.

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

Central Population Registry

- date of birth (subject/mother)
- gender
- migration status (subject/mother)
- date of death, if applicable

National Patient Registry

- diagnosis of JoRRP
- date of diagnosis
- diagnosis of external genital warts (maternal)
- diagnosis of AoRRP (maternal)

Pregnancy/Birth Registry

- mode of delivery (vaginal or caesarean section)
- smoking status of the mother during index pregnancy (1st antenatal visit)

Prescription Registry (covers women vaccinated outside program)

- type of HPV vaccine (dates of administration)
- number of doses
- dates of administration
- genital warts treatment (Podyphyllotoxin)
- date(s) of diagnosis

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The National Health Insurance Service Registry (covers girls/women vaccinated free of charge)

- type of HPV vaccine received
- number of doses
- date(s) of administration

Family database

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

Statistics Denmark

- education level of mother
- household/family income

Pathology Register

- topography/SNOMED codes in relation to RRP

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

Total Population Registry

- date of birth (subject/mother)
- gender
- migration status (subject/mother)
- date of death, if applicable

National Patient Registry

- diagnosis of JoRRP
- date of diagnosis
- diagnosis of external genital warts (maternal)
- diagnosis of AoRRP (maternal)

Medical Birth Registry

- mode of delivery (vaginal or caesarean section)
- smoking status of the mother during index pregnancy (1st antenatal visit)

Prescribed drug Registry (covers women vaccinated outside program)

- type of HPV vaccine (dates of administration)
- no. of doses
- dates of administration
- genital warts treatment (Podyphyllotoxin)

SVEVAC/National Vaccination Registry (covers girls/women vaccinated free of charge)

- type of HPV vaccine received
- no. of doses
- date(s) of administration

Multi-generation registry

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

LISA (Swedish Longitudinal integrated database for health insurance and labour market studies)

- education level of mother
- household/family income

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

The National Population Registry of Norway ("Folkeregisteret")

- date of birth (subject/mother)
- gender
- migration status
- date of death, if applicable
- index data for linking to mothers of cases and controls in the primary objective to obtain relevant maternal information

The National Patient Registry in Norway (NPR)

- diagnosis of JoRRP (date of diagnosis)
- diagnosis of external genital warts (maternal) (date(s) of diagnosis)
- diagnosis of AoRRP (maternal)

The Medical Birth Registry of Norway (MBRN)

- mode of delivery (vaginal or caesarean section)
- smoking status of the mother during index pregnancy (1st antenatal visit)

Norwegian Cancer Registry

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

Norwegian Prescribed Drug Registry

- Prescription(s) for HPV vaccine (type of vaccine)
- Prescription(s) for genital warts treatment (maternal) (Podophyllotoxin, Imiquimod, Sinecathecins)
- Date(s) of prescription(s)

The Norwegian Immunization Registry (SYSVAK)

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

Statistics Norway (SSB)

- education level of mother
- household/family income

7.4.1 Study Procedures

The proposed study is non-interventional in nature and does not entail any risk to the study participants, 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.

7.5 Study Size

Sample Size and Power: Estimated power to evaluate the primary objective (i.e., hypothesis that JoRRP risk is lower among children whose biologic mother was fully vaccinated with GARDASIL or GARDASIL 9 one year prior to delivery versus those 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) support 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.

The estimated number of possible JoRRP cases (identified using ICD-10 code D14.1) occurring after GARDASIL introduction in Sweden, Denmark, and Norway (among children

born to mothers with opportunity to receive HPV vaccination prior to delivery; birth cohorts 2008 to 2020) is approximately 100, 50, and 50, respectively (total=200). Study power was estimated according to varying number of cases (100 to 300) and effect size (odds ratio from 3 to 4) and overall female vaccination exposure rate (5% to 10%) in the maternal birth cohorts of interest, with constant alpha-level of 0.05, and control/case ratio of 10 or 100 [Table 1]. With 200 cases originating from 2008-2020 birth cohorts, the estimated power assuming true odds ratio of 3.0 is 92% (10 controls per case) and 94% (100 controls per case). Precision was also taken into account by specifying that the analyses for the primary objective be powered to detect an odds ratio 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% confidence interval of vaccine effectiveness ≥25%. This level of precision is attainable within the study power calculation assuming ≥120 incident JoRRP cases are observed (with 100 controls per case) or ≥140 incident JoRRP cases are observed (with 10 controls per case) in the cohort of interest. Herd protection was not considered in evaluation of study power for two reasons: 1) In the Nordic region, the average maternal age at birth of first child is ~29 years and in older birth cohorts vaccination rates are much lower, and 2) Males, who are typically the vectors of infection, were not targeted for vaccination until very recently. To examine the potential effect of herd protection and test this assumption, age-standardized incidence rates of JoRRP will be calculated according to maternal vaccination status to assess changes in incidence in pre- and post-vaccination periods among children of unvaccinated mothers, e.g., through calculation of annual percent change.

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 [34]. A threshold of 3.0 is therefore proposed to establish the effectiveness of GARDASIL/GARDASIL 9 vaccination in preventing JoRRP. 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 JoRRP case counts for Sweden, Denmark and Norway provided by the study Principal Investigators (Dr. Karin Sundstrom from Karolinska Institutet, Dr. Susanne Kjær from Danish Cancer Society Research Center, and Dr. Ståle Nygård from Cancer Registry of Norway), this study is expected to be sufficiently powered to assess GARDASIL/GARDASIL 9 vaccine effectiveness against JoRRP [Table 1]; however, this will need to be re-evaluated 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 determined. 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 mothers' 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 cases are available in the Nordic Registries or until a point at which the feasibility of accruing sufficient cases would need to be reassessed.

Table 1 Power Estimates According to Varying Number of Cases of JoRRP (From 100 to 300), Effect Size (Odds Ratio From 3.0 to 4.0), and Vaccination Coverage (5% to 10%), With Constant Alpha-Level of 0.05, Lower Bound of 95% Confidence Interval >1.33, And Control/Case Ratio of 10 or 100

True Effect Size	Vaccine Coverage	Cases of JoRRP 100	125	150	175	200	225	250	300
Control/case ratio of 10									
OR=3	5%	0.68	0.76	0.82	0.87	0.92	0.93	0.96	0.98
	10%	0.86	0.93	0.92	0.98	0.99	0.99	1	1
OR=3.5	5%	0.83	0.90	0.93	0.96	0.98	0.99	0.99	1
	10%	0.96	0.99	0.99	1	1	1	1	1
OR=4	5%	0.92	0.96	0.98	0.99	1	1	1	1
	10%	0.99	1	1	1	1	1	1	1
Control/case ratio of 100									
OR=3	5%	0.72	0.80	0.86	0.91	0.94	0.96	0.97	0.98
	10%	0.90	0.95	0.98	0.99	0.99	1	1	1
OR=3.5	5%	0.86	0.92	0.96	0.97	0.99	0.99	1	1
	10%	0.98	0.99	1	1	1	1	1	1
OR=4	5%	0.95	0.98	0.99	1	1	1	1	1
	10%	0.99	1	1	1	1	1	1	1

Note: For OR=3 and 5% vaccination coverage, >80% power would be achieved with 140 cases with 10 controls per case and 120 cases with 100 controls per case.

7.6 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.

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.

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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.

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Description of Data Preparation and Methods for Data Retrieval and Collection (per country):

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.

Norway

- Data collection will take place from Norwegian registry data holders through the import of CSV and/or data 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 should 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.

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.
- A data management plan will be developed for this protocol.
- No data collector is used in this protocol.

7.7 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.

7.8 Data Analysis

7.8.1 Statistical Methods

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. Children whose mother received the bivalent vaccine, even in combination with GARDASIL or GARDASIL 9, will be excluded from the analysis. Similarly, in the primary analysis, children whose mother had history of genital warts prior to vaccination will be excluded as vaccination is exclusively prophylactic, i.e., there is no therapeutic effect against HPV infection or related disease.

Each case subject and his/her controls constitute a risk stratum, or a risk set matched on age of mother, sex of child, 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. Regarding mode of delivery, history of maternal genital warts, maternal smoking status, 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.

When the outcome of a study is rare, which is the case for JoRRP, the OR approximates the risk ratio (or relative risk, RR) [35]. 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 [36]. 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, where possible, effort will be made to further increase specificity, applying appropriate topography/morphology codes. We also plan to perform sensitivity analyses restricted to RRP cases with related diagnostic or other treatment procedures, and/or subcode D14.1.A, as described above.

7.8.2 Primary Objective: Calculation of Epidemiological Measures of Interest

Descriptive statistics will be calculated for the cases and controls in terms of age of child at diagnosis, age of mother at the time of delivery, mode of delivery, maternal genital warts history, maternal smoking status, education level (mother), family income, and mother's

country of birth 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 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 mode of delivery, as well highest level of family income and education achieved by the mother (tentatively in tertiles relative to the general age-matched population in each of the respective countries) will be adjusted for when investigating the primary objective, through inclusion in the conditional logistic regression. 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 (<17 years versus ≥17 years), 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”), time since vaccination (≤10 years versus >10 years), and maternal history of EGW prior to delivery (yes versus no). To assess if older vaccinated women are a higher risk group, history of genital warts will also be presented separately among vaccinated women (i.e., history of genital warts prior to vaccination), stratified according to attained age at time of vaccination and compared with history of genital warts among unvaccinated women with same attained age. In the analysis, the group of women with history of genital warts prior to vaccination will be considered separately, if appropriate, i.e., assuming history of genital warts is not strongly associated with HPV vaccine uptake. If vaccination is found to be effective in preventing JoRRP among children whose mother had history of EGWs prior to delivery then it would suggest that vaccination not only prevents acquisition of infection in the mother but also prevents transfer of infection from infected mother to child, e.g., through maternal transfer of antibodies or other mechanism. 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), and without history of EGW.

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.

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7.8.3 Exploratory Objectives: Calculation of Epidemiological Measures of Interest

Risk factors for JoRRP will be explored in the VE analysis conditional logistic regression model to evaluate if they are independently statistically significantly associated with the outcome of JoRRP, with all other factors held constant. Specifically, vaccination exposure will be at the reference level (i.e., unvaccinated).

Information will be presented on biological mother-child pairs, focusing on concordant and discordant pairs for JoRRP and AoRRP (history of diagnosis, identified using ICD-10 code D14.1), e.g., preparation of summary 2x2 table (if possible). Due to strict data protection regulation in Europe, it is not possible to include exact counts if <5 in an individual cell.

7.9 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.

7.10 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 certain lifestyle factors of the mother, such as sexual behavior; however, there are several proxy variables that may serve to adjust for potential confounding (Annex 1). Additionally, with use of registry data from three different countries, some variables may need to be adapted to be able to combine information as it is not identical in all registers. This will be achieved via development of a common data model, involving collaboration between all Nordic country investigators.

Given that the main cause of JoRRP 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 substantial knowledge and experience utilizing vaccination registries by investigators in each of the respective countries. Nonetheless there is a small but existing risk of non-differential misclassification of the outcome. Generalizability is maximized through the population-based sampling frame and allowing all eligible study participants who are alive and reside 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.

7.11 Methods to Minimize Bias

A register-based proxy for definition of outcome (JoRRP) will be used, i.e., ICD-10 code D14.1, which in all countries (Sweden, Denmark, and Norway) is used to register the disease category “benign tumor of the larynx”. Where possible, appropriate topography/morphology codes for RRP will also be applied to further increase outcome specificity. Additionally, in sensitivity analyses, diagnostic and treatment codes described above will be applied to also improve specificity in settings where topography/morphology codes cannot be accessed in the pathology or cancer registry. 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, among children (ages 0-9 years), 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 JoRRP is observed, the true effect is likely greater.

Given the rarity of JoRRP, and the strong registration of Swedish, Danish, and Norwegian healthcare, it is believed that virtually all cases of JoRRP 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 subjects whose mother immigrated to Sweden, Denmark, or Norway (after age 9) will be excluded, to ensure there is no misclassification of exposure, which removes the risk that mothers who have received HPV vaccination outside of their country are mis-classified as non-vaccinated. Also, to ensure that prevalent cases of JoRRP are excluded, subjects (children) born or ever living in another country will not be eligible, as follow-up in registries may be insufficient to determine if incident case is truly new onset.

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.

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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 7.3.2), 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. Any publication related to the study will need to be reviewed/approved by the Sponsor prior to submitting results externally.

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12 ANNEXES

Annex 1 OVERVIEW OF POTENTIAL CONFOUNDING IN ASSESSMENT OF HPV VACCINE EFFECTIVENESS AGAINST JUVENILE-ONSET RRP

Definitions:

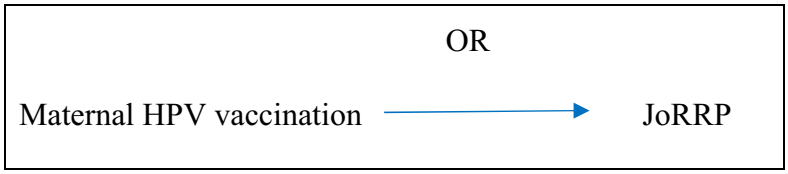
Study exposure: Maternal HPV vaccination with GARDASIL or GARDASIL 9, below called HPV vaccination.

Study outcome: Juvenile-onset recurrent respiratory papillomatosis.

Primary objective: Estimate odds ratio (OR) of JoRRP (yes/no) given HPV vaccination in biologic mother (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 120 cases of JoRRP are observed.

Main association of interest:



The hypothesis is that maternal HPV vaccination is negatively associated with the odds (likelihood) of JoRRP. 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. Given that causal HPV infections in cases of JoRRP are acquired vertically (from mother-to-child during delivery), many of the same factors considered here as confounders in evaluating the association between HPV vaccination and JoRRP are the same as those considered in evaluating the association between HPV vaccination and AoRRP.

Potential confounders or effect modifiers:

Factors that may be associated with exposure/HPV vaccination in Nordic countries:

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 [37] [38]. 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) [37].

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) [39].

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 [40] [41] [42] [43] [44] [45] [46] [47] [48].

3. Pregnancy delivery method

There have been no studies showing an association between method of delivery (vaginal versus cesarean section) and willingness to vaccinate against HPV in Nordic region or elsewhere. An association between method of delivery and HPV vaccination can therefore be questioned.

4. Maternal history of external genital warts

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 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.

5. Maternal smoking history

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

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Factors that may be associated with outcome/JoRRP diagnosis in Nordic countries:

1. Socioeconomic status

Lower socioeconomic status (of parents) has been found to be associated with elevated risk of JoRRP in studies conducted outside of the Nordic region. For example, in a large database of publicly and privately insured patients in the United States, investigators reported that incidence was higher in publicly insured patients compared with those with private insurance (3.21 vs 1.98 per 100 000, respectively) [9]. Also, in a Canadian cross-sectional study of JoRRP patients from the Hospital for Sick Children in Toronto, investigators showed that approximately half of patients were below the poverty line [49]. Considering that HPV 6 and 11 infection is the cause of most RRP cases, a potential explanation for these findings is that parents' socioeconomic status is associated with risk of cervical HPV infection. In a large study combining data from five separate case-control studies conducted in Spain, Columbia, and Brazil (n=1,184 women), investigators assessed risk factors for cervical HPV infection and reported statistically significant lower risk among women with higher levels of education and family income in all countries [50]. To our knowledge, there have been no studies showing an association between mother's country of birth and child's risk of JoRRP in Nordic region or elsewhere.

2. Sexual behavior

Causal HPV 6 and 11 infections in JoRRP cases are acquired vertically (mother-to-child), thus maternal sexual behavior, HPV infection/AoRRP risk is expected to be associated with elevated risk of JoRRP in children, i.e., considered a relevant proxy. A recent international systematic review focused on RRP risk factors concluded that information is limited, but supported that sexual behavior is important for AoRRP risk, which is relevant for JoRRP given that causal infections are acquired from the mother [51]. 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. A small study including 25 AoRRP patients [52], which is cited in the review by Welschmeyer and Berke, reported an OR of 2.11 (95% CI=1.02-4.39) for AoRRP development in patients with more than 25 lifetime sexual partners versus in those with 0-5.

3. Pregnancy delivery method

Evidence is inconsistent regarding whether birth by cesarean section is protective against JoRRP [4] [53] [54]. In a Danish retrospective cohort study focused on evaluation of maternal characteristics associated with JoRRP, investigators did not report a statistically significant lower risk associated with cesarean delivery (elective cesarean, RR=0.86, 95% CI=0.27-2.76; acute cesarean, RR=0.73, 95% CI=0.26-2.02) [4]. However, in a separate US study [53], investigators reported that out of 109 JoRRP cases, only a single case (<1%) was delivered by cesarean section, while the expected cesarean section rate was between 10% and 25%. Similarly, in a more recent US study, out of 208 JoRRP patients where delivery method

was known, it was reported that >90% were delivered vaginally, which is much higher than the 2018 US national average of 68% [54]. An exploratory aim of the current study is to assess potential risk factors of JoRRP, including method of delivery.

4. Maternal history of genital warts

The lead risk factor for JoRRP is a maternal history of genital warts. Most children who develop RRP are born to mothers with genital warts [55]. In the same Danish retrospective cohort study cited above, children born to mothers with history of genital warts were found to have ~230-fold increased risk of JoRRP compared to children born to mothers without history of genital warts (RR=231.4, 95% CI=135.3-395.9) [4]. Investigators also reported that longer delivery (≥10 hours versus <10 hours) was associated with a two-fold greater risk of JoRRP (RR=2.0, 95% CI=1.1-3.5), which suggests vertical transmission of HPV infection during delivery [4].

5. Maternal smoking history

In the Danish retrospective cohort study cited above that focused on evaluation of maternal characteristics associated with JoRRP, investigators did not observe any association between maternal smoking status at first prenatal visit and risk of JoRRP (RR=1.00, 95% CI=0.55-1.82).

Conclusions on potential confounders:

Socioeconomic status (income/education) appears to be moderately-strongly associated with exposure; however, there have been no studies conducted in the Nordic region assessing association with outcome of JoRRP. Studies conducted in other regions (Canada and the U.S.) support an association and it is likely that an association also exists in the Nordic region. Country of birth has been found to be strongly associated with HPV vaccine uptake in Denmark but an association with JoRRP has not been assessed. In the interest of obtaining the best evidence, this association and association between socioeconomic status and JoRRP should be evaluated formally. It is therefore planned to include these factors as potential confounders in the analysis.

Regarding **sexual behavior**, the association with HPV vaccine exposure appears to be weak, whereas that with AoRRP (proxy for JoRRP) is stronger. 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, the analysis will include adjustment for income, education and smoking as a proxy for sexual behavior. Additionally, analyses will be performed separately considering history of genital warts prior to vaccination. Stratified analyses will also be conducted by age at vaccination, as minimal bias due to sexual behavior would be expected among those vaccinated at younger ages.

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While at least some association between **method of delivery** and JoRRP appears likely, it is unknown if any association exists with vaccine uptake. This variable will therefore be explored as a potential confounder in the analysis.

Considering that **maternal history of external genital warts** is so strongly associated with outcome of JoRRP and likely lies on the causal pathway (i.e., maternal acquisition of HPV types 6/11, progression to EGW, and transmission of causal HPV infection to child during delivery), it may not be appropriate to adjust for this variable in evaluation of vaccine effectiveness. Stratified analyses will be performed according to maternal history of EGW prior to delivery (yes/no).

Finally, while **maternal smoking** will be explored as a potential confounder in the analysis, prior studies do not suggest it is a risk factor for JoRRP or show an association with willingness to vaccinate against HPV. However, smoking may serve as a proxy for risky sexual behavior, along with income and education.

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Annex 2 TABLE AND FIGURE SHELLS FOR RRP STUDY (PRIMARY OBJECTIVE)

Table 2 Characteristics of Study Population, JoRRP Cases, and Control Subjects (prepared separately for each country)

	Study population, **No. (%)**	JoRRP cases, **No. (%)**	Controls, **No. (%)**
Age of child, years, mean (SD)			
Age of mother at delivery, years, mean (SD)			
Highest level of education achieved by mother*			
Low			
Medium			
High			
Missing			
Highest annual household family income level‡			
Low			
Medium			
High			
Missing			
Mother's country of birth			
Current country of residence			
Other country			
Missing			
Method of delivery			
Vaginal			
Cesarean			
Missing			
Maternal history of EGW			
Yes			
No			
Missing			
Maternal smoking status at first prenatal visit			
Yes			
No			
Missing			

EGW = external genital warts; JoRRP = juvenile-onset recurrent respiratory papillomatosis; 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.

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Table 3 Number of Cases and Odds Ratio for Recurrent Respiratory Papillomatosis (RRP) by GARDASIL/GARDASIL 9 Vaccination Status, 2008-2020

GARDASIL/ GARDASIL 9 vaccination status	**JoRRP (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				

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

[1] All study participants who acquired a first diagnosis of D14.1 before age 10 years and appropriate topography/morphology code (if available from pathology/cancer registry).
[2] Up to 100 controls matched on age of mother, sex of subject, and region of diagnosis.
[3] Adjustment factors considered for inclusion include maternal education level, family income level, maternal smoking status, mother's country of birth, and method of delivery.
[4] A mother who received 3 doses (or 2 doses administered at 0 and 6-12 months if <15 years of age) of GARDASIL or GARDASIL 9 one year prior to delivery, without history of genital warts prior to vaccination, will be classified as exposed.

Notes on Table 3:

1. In countries where topography/morphology codes cannot be obtained from pathology or cancer registry, 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: a) considering age at vaccination (<17 years vs. ≥17 years), b) considering time since vaccination of mother (≤10 years vs >10 years), c) considering maternal history of genital warts prior to delivery (yes/no), and d) irrespective of maternal history of genital warts prior to delivery/vaccination. In the event that there are <5 counts in an individual cell of any stratified table, it will not be possible to include exact counts due to strict data protection regulation in Europe.

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 focusing on GARDASIL use only as exposure.

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Annex 3 ADMINISTRATIVE AN 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), 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. The Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. The Sponsor 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.

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13 SIGNATURES

13.1 Sponsor's Representative

PRINTED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

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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	

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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. 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	