STUDY PROTOCOL

TITLE PAGE

Division: Research and Development

Information Type: Study Protocol

Title:	Efficacy/Effectiveness of Cervarix against grade 3 cervical intraepithelial neoplasia or worse (CIN3, CIN3+) and cervical cancer. A systematic review and meta-regression analysis.
Compound Number:	GSK580299
Effective Date:	22 Feb 2024
Subject:	Infection, vaccines, premalignant lesions, cancer
Author(s):	PPD
Indication Studied:	HPV-related cervical premalignant lesions and cervical cancer

STUDY INFORMATION

Title	Efficacy/Effectiveness of Cervarix against grade 3 cervical intraepithelial neoplasia or worse (CIN3, CIN3+) and cervical cancer. A systematic review and meta-regression analysis
Protocol version identifier	221785 (EPI-HPV-101 VE DB)
Date of last version of protocol	29 August 2023
EU PAS (ENCEPP) register number	Study not registered
Active substance	Human papillomavirus vaccine [types 16, 18] ATC code: J07BM02
Medicinal product	CERVARIX HUMAN PAPILLOMAVIRUS VACCINE [TYPES 16, 18] (RECOMBINAN T, ADJUVANTED, ADSORBED)
Product reference	EU/1/07/419/001-012
Procedure number	EMEA/H/C/000721
Marketing authorisation holder(s)	GlaxoSmithKline Biologicals S.A
Research question and objectives	Evaluate Efficacy/Effectiveness of Cervarix against grade 3 cervical intraepithelial neoplasia or worse (CIN3+) Objective: To conduct a meta-analysis and meta-regression analyses on the efficacy/effectiveness of CERVARIX on cervical cancer and CIN3 or worse (CIN3+) to provide estimates of the effect size adjusting by covariates such as age at vaccination, time since vaccination, study design, or analytical cohort (HPV baseline status of participants).
Country(-ies) of study	NA
Author	PPD , Sr Epidemiology Lead

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	GlaxoSmithKline Biologicals S.A Rue De L'institut 89; B-1330, Rixensart, Belgium
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LIST OF ABBREVIATIONS

AIC	Akaike Information Criterion
AIS	Adenocarcinoma In Situ
Al (OH)3	Aluminium hydroxide
ASO4	Adjuvant with aluminium hydroxide and 3-O-desacyl-4'-monophosphoryl lipid A.
ATP-E	According-to-protocol cohort for Efficacy
CENTRAL	Central Register for Clinical Trials
CIN	Cervical Intraepithelial Neoplasia
CIN3	Cervical Intraepithelial Neoplasia Grade 3
CIN3+	Cervical Intraepithelial Neoplasia Grade 3 or worse
DNA	Deoxyribonucleic Acid
EMBASE	Excerpta medica Database
EU	European Union
GDS	Global Data Sheet
GSK	GlaxoSmithKline
HPV	Human Papillomavirus
HR	Hazard Ratio
HR HPV	High-Risk Human Papillomavirus
HSIL	High-grade squamous intraepithelial lesions
IARC	International Agency for Research on Cancer
IRR	Incident Relative Risk (or Risk Ratio)
LEEP	Loop electrosurgical excision procedure
LiPA	Line probe assay
LR HPV	Low-Risk Human Papillomavirus
LSIL	Low-Grade Squamous Intraepithelial Lesion
mITT	Modified intention to treat
MPL	3-O-desacyl-4'-monophosphoryl lipid A
NIP	National Immunization Program
NGS	Next generation sequencing
OR	Odds Ratio
Pap test	Papanicolaou test

PCR	Polymerase chain reaction
PPV	Positive predictive value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomised Controlled Trial
REML	Restricted maximum likelihood
ROBINS-I	Risk of Bias in Non-randomized Studies of Interventions
RoS2	Risk of bias 2
RR	Relative Risk (or Risk Ratio)
SCC	Squamous Cell Carcinoma
SIL	Squamous Intraepithelial Lesion
SLR	Systematic literature review
SmPc	Summary of Product Characteristics
TVC	Total Vaccinated Cohort
VE	Vaccine efficacy/effectiveness
VLPs	Virus-like particles
WHO	World Health Organization

TRADEMARK INFORMATION

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Aimmugen
Cecolin
Gardasil (Silgard)
Gardasil 9
Walrinvax

1. RESPONSIBLE PARTIES

NA

1.1. SPONSOR SIGNATORY

Title: Efficacy/Effectiveness of Cervarix against grade 3 cervical intraepithelial neoplasia or worse (CIN3, CIN3+) and cervical cancer. A systematic review and meta-regression analysis.

Compound Number: GSK580299

Dora Navarro **Primary Author/NI Scientific Lead**	Date (DD Month YYYY)
Huifeng Yun **Therapy Area Leader/+1 Manager**	Date (DD Month YYYY)

Note: Not applicable if an eSignature process is used to get the sponsor approval.

2. SYNOPSIS

Title

Efficacy/Effectiveness of CERVARIX against grade 3 cervical intraepithelial neoplasia or worse (CIN3, CIN3+) and cervical cancer. A systematic review and meta-regression analysis.

Rationale and background

CERVARIX is composed of recombinant C-terminally truncated HPV-16 L1 and HPV-18 L1 proteins, assembled into VLPs adjuvanted with the GSK proprietary adjuvant AS04 [EMA , 2023].

Long-term efficacy and immunogenicity information is already part of CERVARIX´s label. However, as NIPs with universal CERVARIX vaccination are being rolled out, and observational studies are being developed, real-world and long-term follow-up of clinical trials data on the long-term effects of CERVARIX are accruing and becoming available [EMA, 2023].

With the aim of collecting all published evidence and given that the new available data have not been generated by GSK, a systematic literature review and meta-analysis was conducted, including critical appraisal of the data to assess its quality, and robustness.

Research question and Objectives

Research question: What is the efficacy/effectiveness of the human papillomavirus vaccination with CERVARIX in girls and women against human papillomavirus on cervical cancer and grade 3 CIN or worse?

Objectives: To conduct a meta-analysis and meta-regression analyses on the efficacy/effectiveness of CERVARIX on cervical cancer and CIN3 or worse (CIN3+) to provide estimates of the effect size adjusting by covariates such as age at vaccination, time since vaccination, study design, or analytical cohort (HPV baseline status of participants).

Study Design

Meta-analysis/meta-regression.

Population: HPV vaccine eligible females among the general population

Intervention: human papillomavirus vaccination with the bivalent HPV vaccine (CERVARIX)

Comparator: Comparators in RCTs can be other vaccines and in observational studies, the comparator can be an unvaccinated cohort.

Outcome: efficacy/effectiveness of CERVARIX to prevent cervical cancer and CIN3 or worse (CIN3+) as provided by the retrieved publications.

When vaccine efficacy or effectiveness results are not available in the selected papers but a measure of effect is provided instead, vaccine efficacy/effectiveness will be determined (including 95% confidence interval) from the relevant measure of effect: OR, RR or Rate Ratio, HR, IRR, as cervical cancer below 25 years of age is rare and therefore, these measures of effect offer a reasonable approximation of the RR. Hence, depending on the reported measure of effect, vaccine efficacy/effectiveness will be calculated as VE=(1-OR)*100; VE=(1-RR)*100; VE=(1-HR)*100, or VE=(1-IRR)*100.

Population

HPV vaccine eligible females among the general population.

Note: In some observational studies included in the meta-analysis, the control arm consists of HPV unvaccinated women among non-HPV vaccine eligible women (i.e., older age groups) or from birth cohorts before the inception of the HPV vaccination program.

Variables

Outcome*:* efficacy/effectiveness of CERVARIX to prevent cervical cancer and CIN3 or worse (CIN3, CIN3+) as provided by the retrieved publications.

Endpoints*:* CIN3, CIN3+, AIS, invasive cervical cancer

Covariates to be considered in the meta-regression:

- TVC/TVC naïve: This is a binary variable and reflects whether the analytical cohort was the total vaccinated cohort (irrespective of the baseline HPV status) or the total vaccinated cohort naïve (HPV-negative at baseline).
- Age at first vaccination: This variable represents the age at which the participant received the first vaccine dose. Age will be modelled as a continuous variable. Non-linearity will be checked.
- Time since vaccination (time of follow-up): This variable is the time that passed between when the participant received the first dose of the vaccine and the conduct of the study as described by the selected paper.
- HPV type: vaccine efficacy/effectiveness is expressed against different HPV types. Including those that are vaccine-specific (i.e., HPV 16/18) or non-vaccine types, or even composite indexes (i.e., 12 HR HPV types). For the purpose of this study, the meta-analysis and meta-regression will be planned to answer research questions that entail two scenarios concerning HPV type i.e., “HPV 16/18” or “Irrespective of HPV type”.
- Study design: This variable will have two values: RCT and observational that includes observational studies such as cohort studies and longitudinal population-based surveillance studies.
- Study correlation: This is a dummy variable created to adjust for potential correlation in studies. For instance, some study may contribute data from participants vaccinated at different age groups and two different analysis approaches (i.e., TVC naïve and

TVC); in other instances, different studies may provide data from the same population but with different analytical approach (TVC naïve and TVC, respectively) and different components (RCT and observational study for vaccine efficacy and vaccine effectiveness, respectively) or combinations of both.

Data sources

Studies published in journal articles between 1 January 2000 to 21 June 2022. The following databases have been screened: PubMed, EMBASE, Scopus, and Cochrane CENTRAL.

No geographical limits, or race restrictions have been applied to the selection of articles. Studies with the following design have been included: RCTs and observational studies (cohort, cross-sectional, case-control, longitudinal, population-based surveillance).

Study size

NA

Data analysis

A systematic literature review has been conducted and a quantitative synthesis of the findings will be pursued to determine a summary point estimate of the long-term efficacy/effectiveness of CERVARIX on the selected endpoints. Simple meta-analyses will be first performed followed by univariate meta-regression analyses by the variables of interest, and multivariate meta-regression analyses within different scenarios.

3. AMENDMENTS AND UPDATES

NA

4. MILESTONES

Milestone	Planned date
Start of data collection	21 June 2022
End of data collection	21 June 2022
Final report of study results	15 February 2024*

*The date when the report is planned to be completed.

5. RATIONALE AND BACKGROUND

In the general population, HPV infection appears to be relatively common. Exposure to HPV usually occurs during adolescence in the first years after initiation of sexual activity. The highest prevalence of HPV is in women younger than 25 years of age, corresponding to the onset of exposure through sexual activity. Prevalence then steadily declines [Peto, 2004]. Sexual intercourse is the primary route of transmission of genital HPV infection and rates of transmission of HPV between males and females in heterosexual couples vary widely across studies [Kero, 2019].

Long-term persistent infection with high-risk HPV types enhances the risk for oncogenic progression and can result in invasive cancer. Normally, the HPV infection resolves within 2 years and in over 90% of the cases it is not detected within 5 to 7 years [Schiffman, 2016].

HPV infection is commonly found in the anogenital tract of human beings with and without clinical lesions. Unresolved HPV infection, currently defined as persistent presence of HPV DNA in repeated testing of cervical specimens, may result in cervical cancer. From infection to cancer, the time lag may range up to 4 decades, making the initiating infections and precursor lesions of cervical cancer (i.e., CIN or SIL) an appropriate target for screening and early detection.

High-risk HPV types have been established as the main cause of cervical cancer and its precursor lesions [Walboomers, 1999; Muñoz, 2003; Cogliano, 2005]. Of the more than 40 HPV types that infect the anogenital region, 14 are considered as high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) because of their frequent association with cervical cancer and pre-invasive lesions[Cogliano, 2005; Cuzick, 2014]. HPV-16 and 18 are responsible for 70% of cervical cancers worldwide. HPV 31, 33, 45, 52, and 58 are responsible for another 20% of cases. Worldwide, the prevalence of HPV 16/18 infection among women with normal cytology is 3.9%, and 69.4% among women with cervical cancer. Only a small percentage of cervical cancer cases have shown to be associated with infection by the remaining high-risk HPVs [Bruni, 2023].

HPV16 and HPV 18 infections and cervical lesions tend to progress more rapidly to cancer in comparison to other high-risk HPV types. HPV 16, HPV 18 and HPV 45 are detected significantly more commonly in SCC than in HSIL [Clifford, 2003a; Clifford, 2003b; Jaisamrarn, 2013; Skinner, 2016a].

Cervical cancer is the fourth most common cancer among women worldwide, with estimated over 600 000 new cases and over 340 000 deaths in 2020, and a crude incidence of 15.6 cases per 100 000 population. Cervical cancer is the second most common female cancer in women aged 15 to 44 years, globally. There is a high degree of variation in incidence and mortality rates among regions of the world predominantly due to differences in the availability of cervical screening programs and treatment. In 2020 in Europe, it was estimated that over 58 000 new cervical cancer cases were diagnosed annually, and almost 26 000 women died from the disease [Bruni, 2023]. Other anogenital HPV-related cancers include anal cancer and cancers of the vulva and the vagina, and penile cancer. All of these are preceded by precursor lesions and HPV 16 is the most common type detected.

In recent decades, there has been a significant increase in the incidence of HPV-positive head and neck cancers, particularly in oropharyngeal tumors.

Because sexual activity constitutes the current paradigm for high-risk HPV acquisition, prophylactic vaccination is recommended before the sexual debut, in some countries as early as 9 years of age [Meites, 2016].

CERVARIX is composed of recombinant C-terminally truncated HPV 16 L1 and HPV 18 L1 proteins, assembled into vVLPs adjuvanted with the GSK proprietary adjuvant AS04.

The HPV 16 L1 VLP and HPV 18 L1 VLP proteins constitute the active ingredient of the vaccine and are produced with a recombinant Baculovirus expression system. The AS04 adjuvant is composed of an aluminum salt, Al(OH)3 and MPL. The MPL immunostimulant is a detoxified derivative of the lipopolysaccharide of the gram-negative bacterium Salmonella Minnesota R595 strain.

CERVARIX´s current SmPC includes indications "for the prevention of premalignant ano-genital lesions (cervical, vulvar, vaginal and anal) and cervical and anal cancers causally related to certain oncogenic HPV types."

Long-term efficacy and immunogenicity information is already part of CERVARIX´s label. However, as NIPs with universal CERVARIX vaccination are being rolled out, and observational studies are being developed, real-world and long-term follow-up of clinical trials data on the long-term effects of CERVARIX are accruing and becoming available.

With the aim of collecting all published information and given that the new available data has not been generated by GSK, it was decided to conduct a systematic literature review and meta-analysis, including critical appraisal of the data to assess its quality, and robustness. The systematic literature review has been completed, including the risk of bias assessment, and a quantitative synthesis is pursued.

6. RESEARCH QUESTION AND OBJECTIVE(S)

RESEARCH QUESTION

What is the efficacy/effectiveness of the HPV vaccination with CERVARIX of girls and women against HPV on cervical cancer and grade 3 CIN or worse?

OBJECTIVE

To perform a meta-analysis/meta-regression analysis to provide estimates of the effect size of CERVARIX on cervical cancer and CIN3 or worse (CIN3+) while adjusting for covariates such as age at vaccination, time since vaccination (time of follow-up), or type of analytical cohort (HPV baseline status of participants), and study design.

The analysis will be designed to respond to the following questions:

- What is the combined efficacy/effectiveness of CERVARIX on CIN3+ caused by vaccine HPV types?
- What is the combined efficacy/effectiveness of CERVARIX on CIN3+ caused by any HPV type?
- What is the efficacy of CERVARIX on CIN3+ caused by vaccine HPV types?

- What is the effectiveness of CERVARIX on CIN3+ caused by vaccine HPV types? (Observational studies only)
- What is the efficacy of CERVARIX on CIN3+ caused by any HPV type?
- What is the effectiveness of CERVARIX on CIN3+ caused by any HPV type? (Observational studies only)

The covariates to be considered in the meta-regression are:

- TVC/TVC naïve: This is a binary variable and reflects whether the analytical cohort was the total vaccinated cohort (irrespective of the baseline HPV status) or the total vaccinated cohort naïve (HPV-negative at baseline).
- Age at first vaccination*:* This variable represents the age at which the participant received the first vaccine dose. Age will be modelled as a continuous variable. Non-linearity will be checked.
- Time since vaccination (time of follow-up): This variable is the time that passed between when the participant received the first dose of the vaccine and the conduct of the study as described by the selected paper.
- HPV type: vaccine efficacy/effectiveness is expressed against different HPV types. Including those that are vaccine-specific (i.e., HPV 16/18) or non-vaccine types, or even composite indexes (i.e., 12 high-risk HPV types). For the purpose of this study, the meta-analysis and meta-regression will be planned to answer research questions that entail two scenarios concerning HPV type: “HPV 16/18” or “Irrespective of HPV type”.
- Study design: This variable will have two values, RCT and observational that includes observational studies such as cohort studies and longitudinal population-based surveillance studies.

  Additionally, an additional technical variable will be considered in the model to take into account the correlation between the results of the patients within the same study:

- Study correlation: Some study may contribute data from participants vaccinated at different age groups and two different analysis approaches (i.e., TVC naïve and TVC); in other instances, different studies may provide data from the same population but with different analytical approach (TVC naïve and TVC, respectively) and different components (RCT and observational studies for vaccine efficacy and vaccine effectiveness, respectively) or combinations of both. Studies sub-groups considered in the meta-regression containing the same subjects or subjects within the same study will be given the same value in the study correlation variable.

7. RESEARCH METHODS

7.1. Study Design

This study has been conceived as a systematic review to collect non-GSK data stemming mainly from long-term follow-up studies of RCTs, long-term observational studies and data from national surveillance from countries that implemented CERVARIX in their NIPs and that have been accruing over time.

Selected RCTs in this systematic literature review had an intervention arm giving CERVARIX and an active comparator arm. In each of the trials, the comparator was a hepatitis -A vaccine, provided by GSK, (HAVRIX-based investigational formulation) in case of PATRICIA Vaccine Trial [Lehtinen, 2012],, and Costa Rica Vaccine Trial [Shing, 2022].. In a study conducted on Japanese women, the Japan-licensed HAV (Aimmugen; The Chem-Sero-Therapeutic Research Institute, Kumamoto, Japan) was the control vaccine used [Konno, 2014]. This type of vaccine is supposed to have no effect on the outcome of interest and has been used to have the same type of procedure for the active and control groups and for blinding purposes.

In the case of observational studies, the comparator arm used to determine vaccine effectiveness was a control group of unvaccinated participants.

The objective of the present study is to determine effectiveness of CERVARIX (and not comparative effectiveness vs. any other HPV vaccine). The respective comparators (be it an active comparator or an arm of unvaccinated participants) are considered to have no effect on the outcome of interest (CIN3+).

7.2. Study Population and Setting

Eligibility criteria

Studies were eligible if they compared the protection conferred by CERVARIX to prevent cervical cancer and CIN3 or worse (CIN3+) between CERVARIX vaccinated and non-vaccinated participants, be it a comparator arm in the case of RCTs (efficacy), or unvaccinated participants in case of observational/population-based surveillance/longitudinal studies (effectiveness).

Vaccination has been considered if participants received at least one dose of the vaccine.

No geographical limits, or race restrictions applied to the selection of articles.

Inclusion criteria

All studies that meet the following criteria were included:

- Studies that report CERVARIX efficacy (randomized controlled trials, RCTs) or effectiveness (observational studies) against cervical cancer and/or CIN3 or worse (CIN3+).

- Studies that have a comparator group receiving either placebo or another vaccine, or a control group of unvaccinated participants.
- The intervention group was considered as vaccinated if participants received at least one dose of the vaccine.
- Studies published in journal articles between 1 January 2000 to 21 June 2022. The following databases were screened: PubMed, EMBASE, Scopus, and Cochrane CENTRAL.
- Studies with the following design could be included: randomized controlled trials and observational studies (cohort, cross-sectional, case-control, longitudinal, population-based surveillance)
- Journal articles with abstract in the following languages: English, French, Spanish, Portuguese, German, and Italian.

Exclusion criteria

Systematic reviews, reviews, modelling, economic studies (including cost-effectiveness and comparative effectiveness), letters to the editor, case reports, and case series were excluded. Conference abstracts and proceedings were excluded. Studies that have unreliable data for the extraction were excluded. Grey literature was not included.

7.3. Variables

7.3.1. Covariates to be included in the meta-regression.

The following variables were designed to be included in the meta-regression analyses with the aim to allow for certain known confounders/effect modifiers (i.e., age at first vaccination, time since vaccination, type of analytical cohort). For most studies outcomes were reported for vaccine types but also "irrespective of HPV type". Smaller vaccine effects are expected for any HPV type than for those types that are the vaccine target (i.e., HPV16/18) and this variable has been introduced to create the different scenarios that will respond to the formulated research questions.

In addition, as some correlation is expected in some studies that are analyzed at the same time, a dummy variable will be created (i.e., study correlation, see Section 6) to address this aspect.

- TVC/TVC naïve: This is a binary variable and reflects whether the analytical cohort was the total vaccinated cohort (irrespective of the baseline HPV status) or the total vaccinated cohort naïve (HPV-negative at baseline).
- Age at first vaccination*:* This variable represents the age at which the participant received the first vaccine dose. Age will be modelled as a continuous variable. Non-linearity will be checked.
- Time since vaccination (time of follow-up): This variable is the time that passed between when the participant received the first dose of the vaccine and the conduct of the study.

- HPV type: vaccine efficacy/effectiveness is expressed against different HPV types. Including those that are vaccine-specific (i.e., HPV 16/18) or non-vaccine types, or even composite indexes (i.e., 12 high-risk HPV types). For the purpose of this study, the meta-analysis and meta-regression will be planned to answer research questions that entail two scenarios concerning HPV type: “HPV 16/18” or “Irrespective of HPV type”
- Study design: This variable will have two values: RCT and observational that includes observational studies such as cohort studies and longitudinal population-based surveillance studies.

7.3.2. Exposure definitions

In this study, the exposure is vaccination with CERVARIX. For this study, a participant is considered as vaccinated if received at least one dose of the vaccine.

Selected RCTs in this systematic literature review had an intervention arm giving CERVARIX and an active comparator arm (see Section 7.1). Since the hepatitis A vaccine is not supposed to have any effect on CIN3+, subjects receiving this vaccine will be considered as non-exposed.

In the case of observational studies, the comparator arm used to determine vaccine effectiveness was a control group of unvaccinated participants, who will also be considered as non-exposed.

In the RCTs in this systematic review, CERVARIX vaccination was the intervention of the trial. Therefore, vaccination was registered within the trial. In observational studies that were post-hoc studies of clinical trials, the same procedure was followed. For longitudinal studies corresponding to surveillance of national immunization programs, individual vaccination status was retrieved from national registers and in some instances, when individual vaccination status was not available, researchers modelled the specific probability that a woman was vaccinated from the official national statistics for vaccination with three doses in the general population (i.e., [Rebolj, 2022]).

In Table 3 the different age categories for the meta-analysis/meta-regression are shown.

7.3.3. Outcome definitions

The outcome for this study is the vaccine efficacy/effectiveness of CERVARIX to prevent cervical cancer and CIN3 or worse (CIN3+) as provided by the retrieved publications.

However, when vaccine efficacy or effectiveness results were not available in the selected papers but a measure of effect was provided instead, vaccine efficacy/effectiveness was estimated (including 95% confidence interval) from the relevant measure of effect: i.e., OR, IRR, as cervical cancer below 25 years of age is rare [Teixeira, 2021] and therefore, these measures of effect offer a reasonable approximation of the RR [Viera, 2008]. In those cases, vaccine efficacy/effectiveness was calculated as VE=(1-OR)*100, or VE=(1-IRR)*100.

In those studies where HPV type was determined, relevant and specific DNA sequencing and bioinformatic techniques were used (i.e., PCR SPF10-LiPA25 and type specific PCR for HPV 16 and HPV 18 DNA, SPF10-DEIA, NGS followed by custom Torrent Suite plugin analysis, Hybrid Capture 2 test, PCR SPF10-LiPA24). Cytology and histopathology for CIN cases were mainly reviewed by an independent pathology committee, usually masked to the vaccine allocation.

7.3.4. Confounders and effect modifiers

Post hoc studies of clinical trials and observational and longitudinal studies stemming from surveillance of NIPs were likely subject to the following confounders:

- Age at first vaccination (HPV acquisition, prevalent infection, or baseline HPV status).
- Sexual behavior (HPV acquisition, prevalent infection, or baseline HPV status).
- Time since vaccination or time of follow-up (immunogenicity, duration of protection).
- Age at first cervical screening.
- Healthcare seeking behavior.
- Socioeconomic factors.

Some of these variables are well known effect modifiers. For instance, vaccine effectiveness is higher in younger participants, as the vaccine has proven less effective if there is an HPV prevalent infection at vaccination. Therefore, “age at first vaccination” and "sexual behavior” are proxy variables for "HPV baseline status”, as the current accepted paradigm for HPV acquisition is sexual activity. The earlier the sexual debut, the earlier the acquisition. This is the reason why the HPV vaccine is recommended in early adolescence, anticipating to the commencement of sexual activity. “Time since vaccination" is also expected to be an effect modifier as immunity wanes over time. Therefore, the longer the follow-up, the lower the vaccine effectiveness expected. This is particularly relevant for the long-term cohort studies (up to 10-11 years of follow-up).

Healthcare seeking behavior can also confound the estimation of vaccine effectiveness by establishing a different risk of detecting premalignant lesions and cancer between the participants. For example, if unvaccinated participants are half as likely to get screened than the more health-conscious vaccinated ones, vaccine effectiveness might result smaller since lesions may be more numerous among vaccinated due to lower detection in the unvaccinated participants. In retrospective nationwide observational studies this is quite unlikely as both interventions are part of national routine vaccination and cervical screening programs, respectively, and relevant birth cohorts, either vaccinated or not, are invited to uptake cervical screening. In other observational studies and RCTs, periodical follow-up visits were planned in the studies for CERVARIX-vaccinated and -unvaccinated participants.

The PPV of cytology for advanced cervical lesions decreases among vaccinated women and this decrease is larger for women vaccinated at younger ages [Lei, 2020]. In all studies included in the selection for the quantitative synthesis, participants were tested for cervical HPV DNA with molecular techniques. The only study relaying on cytological and histological examination was the Scottish study [Palmer, 2019] and the results corresponded to their first smear test or colposcopy examination or for the few women with more than one at the first year of screening, the most severe record was selected. All birth cohorts were invited for cervical screening at 20 years of age as part of the national cervical screening program.

Most studies adjusted for other demographic and socioeconomic factors (i.e., deprivation index, rurality scores) that are known confounders.

Nonetheless, residual confounding cannot be completely ruled out.

Please refer to Section 7.8 for further information on the steps followed for risk of bias and quality assessment.

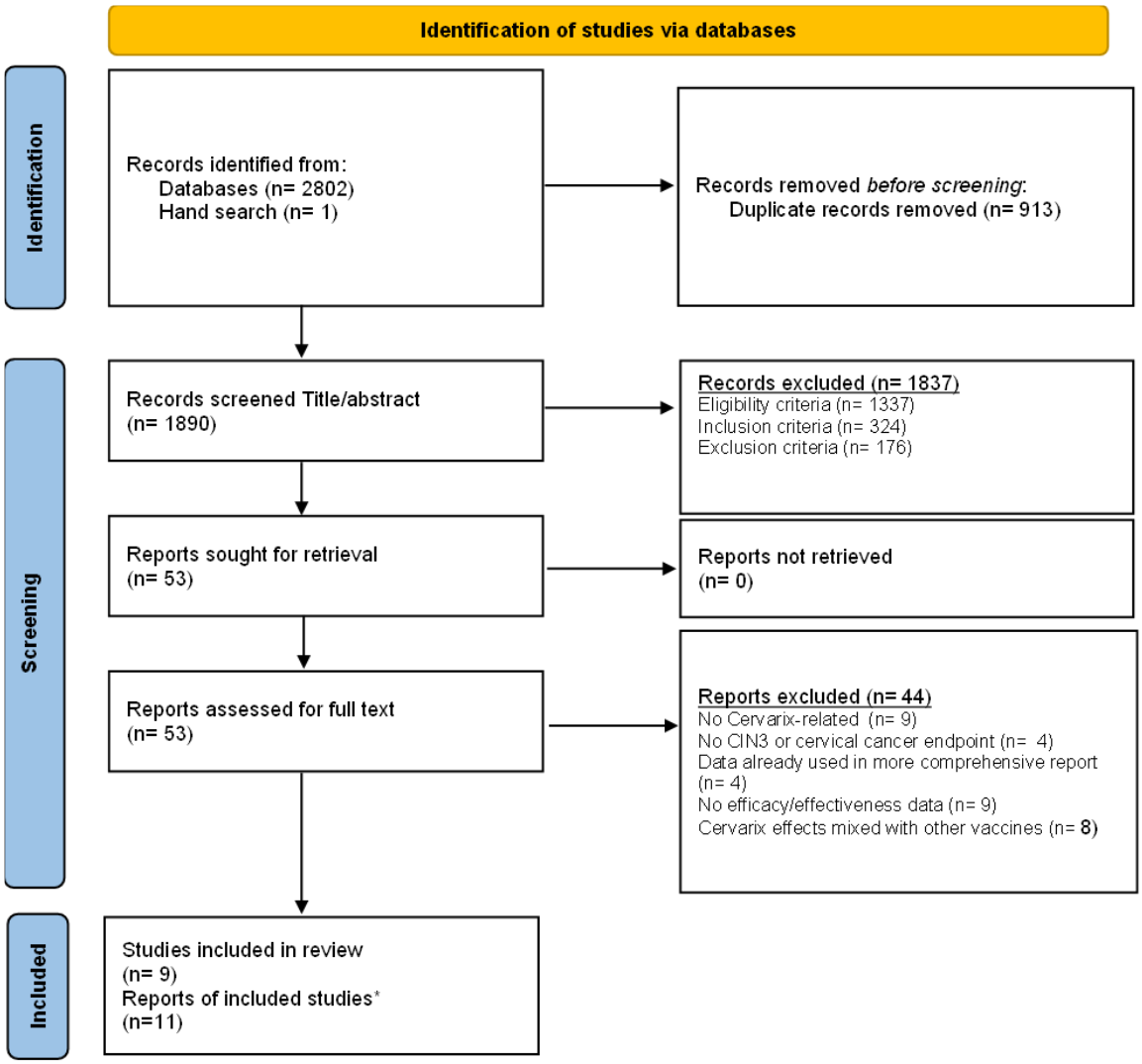
For RCTs most of the confounders were addressed per the study design. However, certain degree of residual confounding could be expected even in well-designed and conducted clinical trials.

7.4. Data sources

7.4.1. PRISMA 2020 flow diagram

The search flow and the selected studies scheme is presented in Figure 1:

Figure 1 PRISMA 2020 flow diagram



Note: (*) denotes two studies that had both a vaccine efficacy and a vaccine effectiveness component
n: number of reports.
List of reports sought for retrieval is provided in Table 15.

7.4.2. Characteristics of studies selected.

Data extraction was performed over 9 selected manuscripts consisting of 11 reports [two papers reported both on vaccine efficacy and vaccine effectiveness as studies had a first part as a follow-up of RCTs and a second part that included an unvaccinated cohort (observational study)].

Table 1 Summary of characteristics of potentially included studies in the quantitative analysis.

Author, Year	Country	Study period	Study design	Study population	Age at first vaccination	Vaccine coverage	Number of doses	Type of outcomes	Case-counting start
[Wheeler, 2012]	Multicountry (US, Australia, Belgium, Brazil, Canada, Finland, Germany, Italy, Philippines, Spain, Taiwan, Thailand, UK)	June 2004-June 2008	RCT (4-year follow-up)	Females with no more than 6 lifetime sexual partners (not applied in Finland), regardless of their baseline HPV DNA status, HPV-16 or HPV-18 serostatus, or cytology. N=16 114, 11 644, and 18 644 women were included in the ATP-E (vaccine N=8067, control N=8047), TVC naïve (vaccine N=5824, control n=5820), and TVC cohorts (vaccine N=9319, control N=9325), respectively. 16% of participants (3034 of 18 644) were lost to follow-up by the end of the study	15-25 y	NA	Participants considered for the analysis 3 doses-ATP-E cohort at least 1 dose: TVC-naïve and TVC	Vaccine efficacy	Day after 1st vaccination for TVC-naïve and TVC, and the day after 3rd vaccination for ATP-E cohort
[Lehtinen, 2012]	Multicountry (US, Australia, Belgium, Brazil, Canada, Finland, Germany,	June 2004-June 2008	RCT (4-year follow-up)	Females with no more than 6 lifetime sexual partners (not applied in Finland), regardless of their baseline HPV DNA status, HPV-16 or HPV-18 serostatus, or cytology. Completed study: TVC, N= 7798 HPV arm, N=7811 control arm	15-25 y	NA	Participants considered for the analysis •3 doses-ATP-E cohort	Vaccine efficacy	Day after 1st vaccination for TVC-naïve and TVC, and the day after 3rd

Author, Year	Country	Study period	Study design	Study population	Age at first vaccination	Vaccine coverage	Number of doses	Type of outcomes	Case-counting start
	Italy, Philippines, Spain, Taiwan, Thailand, UK)			TVC-naïve, N= 1879 HPV arm, N= 2315 control arm ATP-E, N= 6815 HPV arm, N=6769 control arm			•at least 1 dose: TVC-naïve and TVC		vaccination for ATP-E cohort
[Konno, 2014]	Japan	October 2009- April 2013	RCT (4-year follow-up)	Healthy females not screened before enrollment with respect to baseline serological, cytological, or HPV DNA status TVC-combined, N=519 HPV arm, N=521 control arm ATP cohort for efficacy-combined, N=499 HPV arm, N=498 control arm TVC naïve-combined, N=281 HPV arm, N=284 control arm	20-25 y	NA	Participants considered for the analysis if at least 1 dose: TVC-naïve and TVC	Vaccine efficacy	Day after receipt of the first vaccine dose for the TVC-naïve and TVC (up to 4 y follow-up)
[Lehtinen, 2017]	Finland	Enrolment: June 2003/2005 and May 2004 to April 2005. Follow-up: 2009 to 2015	Cohort study	18-19 y unvaccinated women N=15627 16-17 y vaccinated women N=2401 PATRICIA trial 16-17 y vaccinated women N= 64 HPV-012 trial	15-25 y PATRICIA trial 10-25 y HPV-012 trial	NA	Participants considered for the analysis if at least 1 dose (TVC)	Vaccine effectiveness	Day after 1st vaccination (up to 10 years post vaccination follow-up)
[Porras, 2020]	Costa Rica	June 2004-Dec 2005 (RCT); Follow-up March 2009-July 2012 (Total 11 years)	RCT (up to year 4) and Cohort study (no randomization) (up to year 11)	Healthy women (HPV 16/18 DNA-negative at months 0 and 6, who did not have biopsy or LEEP during the vaccination phase) N= 2635 in HPV vaccine group N=2677 in control group (0-4 y RCT) N=2073 HPV vaccine group and N=2530 unvaccinated group in cohort analysis (7-11 y)	18-25 y	NA	3 doses	Vaccine efficacy Vaccine effectiveness	Day after 1st vaccination (up to year 11 of follow-up)

Author, Year	Country	Study period	Study design	Study population	Age at first vaccination	Vaccine coverage	Number of doses	Type of outcomes	Case-counting start
[Shing, 2022]	Costa Rica	June 2004-Dec 2005 (RCT); Follow-up March 2009-July 2012 (Total 11 years)	RCT (up to year 4) and Cohort study (no randomization) (up to year 11)	Healthy women (HPV 16/18 DNA-negative at months 0 and 6, who did not have biopsy or LEEP during the vaccination phase) N= 3491 in HPV vaccine group and N=3512 in control arm (CIN3+ endpoint, years 1-4 follow-up) N= 2826 in HPV vaccine group and N=2592 unvaccinated control arm (CIN3+ endpoint, years 7-11 follow-up) Note: Analyses included all participants with at least one follow-up visit in the respective period and excluded participants with a previous endpoint (CIN2+, CIN3+) (ie, modified intention-to-treat cohort).	18-25 y	NA	At least 1 dose (mITT)	Vaccine efficacy Vaccine effectiveness	Day after 1st vaccination (up to year 11 of follow-up)
[Palmer, 2019]	Scotland (UK)	Between 1 January 1988 and 5 June 1996 for screening. Extraction date August 2017	Retrospective population-based study	Routine vaccinated girls 12-13 y (born between 1 January 1988 and 5 June 1996); catch-up campaign vaccinated women (born 1991-94, age 14-17 at vaccination); unvaccinated women (born 1988-90, age 18-20 in 2008) screened at age 20 N= 138 692 screened women at age 20	12-13 y 14 y 15 y 16 y 17 y ≥ 18 y	90% at age 13 (1995 birth cohort)	3, 2, or 1 dose	OR	NA
[Falcaro, 2021]	England (UK)	January 2006-June 2019, data extraction on 26 January 2021	Retrospective population-based database study	Vaccine eligible women (7 birth cohorts), Unvaccinated cohort (born between May 1, 1989 and Aug 31, 1990) 13·7 million-years of follow-up of women aged 20 years to younger than 30 years in the three vaccinated cohorts.	12-13 y 14-16 y 16-18 y	Routine cohort: 85.9%-90.6% for 2008-09 and 2011-12 Catch-up cohort:	At least 1 dose, 3 doses	Adjusted IRR	NA

Author, Year	Country	Study period	Study design	Study population	Age at first vaccination	Vaccine coverage	Number of doses	Type of outcomes	Case-counting start
						55.6% to 81.9% 1 dose: 60.5% to 88.7% 3 doses: 44.8% to 84.9%			
[Rebolj, 2022]	England (UK)	2013-2018	Retrospective population-based database study	Women eligible for catch-up vaccination (14-17 y) and received High-risk-HPV test at 25 y N=64274 overall results of women tested; N=42384 genotyped results	Vaccinated cohort 24-25 years; Unvaccinated cohort 26-29 y	40%-75% depending on the birth cohort	Data on individual vaccination status unavailable	Vaccine effectiveness	NA

ATP-E: According-to-protocol cohort for Efficacy, CIN3+: Cervical Intraepithelial Neoplasia Grade 3, DNA: Deoxyribonucleic Acid, HPV: Human Papillomavirus, IRR: Incident Relative Risk (or Risk Ratio), OR: Odds ratio, LEEP: loop electrosurgical excision procedure, mITT: modified intention to treat, N: number, NA: Not applicable, UK: United Kingdom, TVC: total vaccinated cohort.

Table 2 Outcomes and endpoints of the selected studies

Author, Year	Endpoint	HPV type	Time since vaccination (years)	CIN3+ definition
[Wheeler, 2012]	CIN3+	HPV non-vaccine type composite index (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68)	4	CIN3, adenocarcinoma in situ, or invasive carcinoma
[Lehtinen, 2012]	CIN3+ AIS	HPV16 HPV18 HPV 16/18 Irrespective of HPV type	4	CIN3, adenocarcinoma in situ, or invasive carcinoma
[Konno, 2014]	CIN3+	Irrespective of HPV type	4	Not defined
[Lehtinen, 2017]	CIN3+	HPV16 HPV18 HPV16/18 HPV16/31/33/35/52/58 HPV/31/33/35/52/58 HPV31/33/35/39/45/52/58/59/68 HPV31/33/45 HPV6/11/16/18/31/33/45/51/74 HPV6/11/31/33/45/51/74 HPV34/35/39/40/42/43/44/52/53/54/56/58/59/66/68/70/73 Irrespective of HPV type All types (excluding HPV16/18) Total (original FCR registered CIN3+ diagnoses) Total All (re-review of histopathological block retrieval and re-analysis)	10	CIN3+ includes intraepithelial neoplasia grade three and invasive cancer
[Porras, 2020]	CIN3+	HPV16/18	4 7 9 11	CIN3+
[Shing, 2022]	CIN3+	HPV16/18 HPV31/33/45 HPV types other than HPV 16, 18, 31, 33, or 45 Irrespective of HPV type	1-4 7-11 1-11	CIN3+

Author, Year	Endpoint	HPV type	Time since vaccination (years)	CIN3+ definition
[Palmer, 2019]	CIN3+	Histological diagnosis (no HPV testing results)	2 3 4 5 6 7-8	CIN3+ (glandular neoplasia or cancer)
[Falcaro, 2021]	CIN3 Cervical cancer	Histological diagnosis (no HPV testing results)	2-4 4-6 7-8	NA (only CIN3 and cervical cancer endpoints)
[Rebolj, 2022]	CIN3+ Cervical cancer	HPV 16/18 High-risk HPV (16,18 ,31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) HPV31/33/35/39/45/51/52/56/58/59/66/68	7-11	Not defined

Abbreviations: CIN3: Cervical Intraepithelial Neoplasia Grade 3, CIN3+: Cervical Intraepithelial Neoplasia Grade 3 or worse, HPV: Human Papillomavirus, NA: Not applicable.

7.4.3. Rationale for selection of studies and endpoints for the meta-regression

The following parameters were considered for the inclusion of the studies in the meta-analysis/meta-regression analyses. Findings of those studies not included in the quantitative synthesis will be presented in the narrative review.

1. **Endpoint:** CIN3+. Results on other endpoints [i.e., CIN3, AIS, or cervical cancer were reported by very few papers (one, one, and two papers respectively)]. Therefore CIN3+ was selected as endpoint for the meta-regression [Lehtinen, 2012; Konno, 2014; Lehtinen, 2017; Palmer, 2019; Porras, 2020; Shing, 2022; Rebolj, 2022].
2. **Outcome:** Vaccine efficacy/Vaccine effectiveness as reported by the different studies. In study by Palmer et al., vaccine effectiveness is calculated for as (1-OR)*100 (the measure of effect provided by the paper is OR) [Palmer, 2019]. In a study by Falcaro et al., vaccine effectiveness is calculated as (1-IRR)*100 (the measure of effect provided by the paper is IRR) [Falcaro, 2021].
3. **Number of doses**. The information for the number of doses injected needed to be reported in the paper. For the analysis, the groups vaccinated with "3 doses" and "At least 1 dose" from different studies will be pooled together if at least 75% of the participants of the "At least 1 dose" group received 3 doses of the vaccine. This is the case for the following studies:
   - **[Lehtinen, 2012]** (PATRICIA trial): The decision is to include data pertaining to the TVC because, although the data used for regulatory purposes were those of the ATP-E cohort, the TVC data are more relevant from a public health perspective (sic. paper). The TVC includes all women who received at least one vaccine dose and were evaluable for efficacy, irrespective of baseline HPV DNA, cytological status, and serostatus. TVC, N=18 644 participants, of which at least 86.4% received 3 doses of the study vaccine (ATP-E cohort) (supplementary material). Data belonging to the TVC naïve cohort (TVC naïve, HPV negative at baseline) will also be included as a covariate in the meta-regression models.
   - **[Lehtinen, 2017].** According to the paper, the analysis was made on the Finnish TVC that was aligned with the PATRICIA trial [Lehtinen, 2012] of which this cohort was part. In addition, the text says that all HPV-012 participants (N=64) received 3 doses of the HPV vaccine. Therefore, we consider that in this observational study participants receiving at least 3 doses of the HPV vaccine, are at least 75% of the TVC. Since some of the participants in this study are also participants (Finnish sites) to the PATRICIA trial [Lehtinen, 2012], it is agreed to only include it in the analyses for observational studies alone.
   - **[Konno, 2014].** The TVC cohort was used for the analysis and included all women who received at least 1 vaccine dose. The ATP cohort for efficacy includes women with no or low-grade cytological abnormality at month 0, who met the eligibility criteria, complied with protocol procedures, had received all 3 vaccine doses, and had data available concerning the efficacy end point assessed. The ATP cohort represented 96.1% of the TVC. Therefore, data from this paper can be pooled together with "3 doses" data as meets the threshold of

at least 75% of participants vaccinated with 3 doses. Data belonging to the TVC naïve cohort (HPV negative at baseline) will also be included as a covariate in the meta-regression models.

4. **Age at first vaccination.** The decision was to stratify by age in those studies with this data available to increase the number of observations allowing a more robust model. This is to use the most granular results at the level of the studies in terms of age groups. For example, if the VE was reported for 3 age categories in a study, the three VE results will be used in the meta-regression.
5. **Time since vaccination** (time from the analysis to vaccination or time of follow-up).
6. **CIN3+, HPV31/33/35/39/45/51/52/56/58/59/66/68 (common non-vaccine types endpoint), Vaccine effectiveness/vaccine efficacy.** There are very few papers reporting on non-vaccine types, one is an RCT and the other is an observational study. A decision was made not to pursue meta-regression for this endpoint of non-vaccine types. Description of the findings will be presented in the narrative review.
7. **Cervical cancer, Histological diagnosis (no HPV testing results), Vaccine effectiveness**. There are only two papers [Falcaro, 2021; Rebolj, 2022] referring to the same population and there is certain possibility of overlapping in the birth cohorts of interest. In addition, vaccine effectiveness against cervical cancer in a study [Rebolj, 2022] did not reach statistical significance due to the small number of cases. Therefore, results from these papers referring to the outcome cervical cancer will not be included in the meta-regression and will be included in the narrative alone.
8. For the **CIN3+ vaccine effectiveness meta-regression** focusing on the endpoint "Irrespective of the HPV type" the decision is to also include a study as the vaccine effectiveness is calculated as overall since the endpoints are histology-based (no direct HPV testing of the samples) [Palmer, 2019]. Another study will also be included since vaccine effectiveness refers to 14 high-risk HPV types, which are considered the most relevant oncogenic types and responsible for cervical cancer (up to 99% of cervical cancer is caused by the high-risk HPV types) [Rebolj, 2022]. Therefore, this paper will be considered that reports the outcome "irrespective of the HPV type) [Dunne, 2007].
9. **Choice of the analysis group: TVC cohort and TVC-naïve cohort.** The TVC cohort is the cohort closest to the real world (regardless of their HPV baseline status) and more relevant from the public health perspective.
10. However, differences for vaccine efficacy/effectiveness between both cohorts are significant. Therefore, a decision was made to conduct meta-regression having each of them independently (binary covariate) to highlight how important it is for increased protection to vaccinate girls and teenagers before sexual debut (the natural path of acquiring an HPV infection).

A decision was made to determine summary point estimates for RCTs and observational studies alone, and also the combined effects of RCTs and observational data pooled together. This approach allows a sensitivity analysis considering the different scenarios: different study design and different vaccine outcomes (vaccine efficacy/effectiveness against vaccine types HPV16/18 or irrespective of HPV type).

Table 3 Final outcomes and endpoints for the meta-regression analysis

Author, Year	Endpoint	HPV type	N of doses	Age at first vaccination	Time since vaccination (years)
Analysis 1_CIN3+, HPV16/18 RCT/Obs combined					
RCT, Vaccine efficacy					
[Lehtinen, 2012]	CIN3+	HPV 16/18	At least 1 dose (TVC and TVC naïve)	15-17 y 18-20 y 21-25 y	0-4
[Porras, 2020]	CIN3+	HPV 16/18	At least 1 dose (TVC naïve)	18-25 y	0-4
Observational; population-based surveillance, Vaccine effectiveness					
[Shing, 2022]	CIN3+	HPV 16/18	At least 1 dose (TVC)	18-25 y	7-11
[Rebolj, 2022]	CIN3+	HPV 16/18	3 doses	14-17 y	7-11
Analysis 2_CIN3+, Irrespective of HPV type RCT/Obs combined					
RCT, Vaccine efficacy					
[Konno, 2014]	CIN3+	Irrespective of HPV type	At least 1 dose (TVC and TVC naïve)	20-25 y	0-4
[Lehtinen, 2012]	CIN3+	Irrespective of HPV type	At least 1 dose (TVC and TVC naïve)	15-17 y 18-20 y 21-25 y	0-4
Observational; population-based surveillance, Vaccine effectiveness					
[Palmer, 2019]	CIN3+	Histological diagnosis (no HPV testing results). Considered as “irrespective of HPV type”	3 doses	12-13 y 14 y 15 y 16 y 17 y ≥18 y	0-8 0-6 0-5 0-4 0-3 0-2
[Shing, 2022]	CIN3+	Irrespective of HPV type	At least 1 dose	18-25 y	7-11
[Rebolj, 2022]	CIN3+	High-risk-HPV (16,18 ,31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68). Considered as “irrespective of HPV type”	3 doses	14-17 y	7-11
Analysis 3_CIN3+, HPV16/18 RCT					
RCT, Vaccine efficacy					
[Lehtinen, 2012]	CIN3+	HPV 16/18	At least 1 dose (TVC and TVC naïve)	15-17 y 18-20 y	0-4

Author, Year	Endpoint	HPV type	N of doses	Age at first vaccination	Time since vaccination (years)
				21-25 y	
[Porras, 2020]	CIN3+	HPV 16/18	At least 1 dose (TVC naïve)	18-25 y	0-4
[Shing, 2022]	CIN3+	HPV 16/18	At least 1 dose (TVC)	18-25 y	0-4
Analysis 4_CIN3+, HPV16/18, Obs, Vaccine effectiveness					
[Lehtinen, 2017]	CIN3+	HPV16/18	At least 1 dose	16-17 y	0-10
[Shing, 2022]	CIN3+	HPV16/18	At least 1 dose	18-25 y	7-11
[Rebolj, 2022]	CIN3+	High-risk-HPV (16,18 ,31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68). Considered as "irrespective of HPV type"	3 doses	14-17 y	7-11
Analysis 5_CIN3+, Irrespective of HPV type, RCT, Vaccine efficacy					
[Konno, 2014]	CIN3+	Irrespective of HPV type	At least 1 dose (TVC and TVC naïve)	20-25 y	0-4
[Lehtinen, 2012]	CIN3+	Irrespective of HPV type	At least 1 dose (TVC and TVC naïve)	15-17 y 18-20 y 21-25 y	0-4
[Shing, 2022]	CIN3+	Irrespective of HPV type	At least 1 dose (TVC)	18-25 y	1-4
Analysis 6_CIN3+, Irrespective of HPV type, Obs, Vaccine effectiveness					
[Lehtinen, 2017]	CIN3+	Irrespective of HPV type	At least 1 dose	16-17 y	0-10
[Palmer, 2019]	CIN3+	Histological diagnosis (no HPV testing results). Considered as "irrespective of HPV type"	3 doses	12-13 y 14 y 15 y 16 y 17 y ≥18 y	0-8 0-6 0-5 0-4 0-3 0-2
[Shing, 2022]	CIN3+	Irrespective of HPV type	At least 1 dose	18-25 y	7-11
[Rebolj, 2022]	CIN3+	High-risk-HPV (16,18 ,31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68). Considered as "irrespective of HPV type"	3 doses	14-17 y	7-11

Abbreviations: CIN3+: Cervical Intraepithelial Neoplasia Grade 3 or worse, HPV: Human Papillomavirus, N: Number, Obs: observational studies, RCT: randomized control trial, TVC: Total Vaccinated Cohort

7.4.4. Research questions and corresponding meta-regression datasets

The different questions that will be addressed by the meta-regression analyses and the corresponding parameters and selection of studies are described below:

1. What is the combined efficacy/effectiveness of CERVARIX on CIN3+ caused by vaccine HPV types?

Analysis 1.

- Endpoint: CIN3+.
- HPV type considered: HPV16/18.
- Type of studies considered: Combined RCT/Observational studies.

Table 4 Studies included in the meta-regression for Analysis 1

Author	Year	Study design	Study correlation	TVC	TVC naïve	Age first vaccination (years)	Endpoint	Time since vaccination (Time follow-up) (years)
Lehtinen	2012	RCT	A	1	0	15-17	CIN3+	0-4
Lehtinen	2012	RCT	A	1	0	18-20	CIN3+	0-4
Lehtinen	2012	RCT	A	1	0	21-25	CIN3+	0-4
Lehtinen	2012	RCT	A	0	1	15-17	CIN3+	0-4
Lehtinen	2012	RCT	A	0	1	18-20	CIN3+	0-4
Lehtinen	2012	RCT	A	0	1	21-25	CIN3+	0-4
Porras	2020	RCT	B	0	1	18-25	CIN3+	0-4
Shing	2022	Obs	B	1	0	18-25	CIN3+	7-11
Rebolj	2022	Obs	F	1	0	14-17	CIN3+	7-11

Abbreviations: CIN3+: Cervical Intraepithelial Neoplasia Grade 3 or worse, Obs: Observational study, RCT: randomized control trial, TVC: Total Vaccinated Cohort.
A, B, F: values of dummy variable "study correlation".

Study by Konno et al., is not included in this analysis as it reports vaccine efficacy "irrespective of HPV type" [Konno, 2014]. An RCT by Shing et al., is not included since participants overlap with those from another study by Porras et al.[Shing, 2022; Porras, 2020] (although the analytical cohort is different in both cases, 3 doses of vaccine and HPV negative at baseline in study by Porras et al [Porras, 2020] and at least 1 dose and modified-intention-to-treat in Shing et al. [Shing, 2022]). A study by Palmer et al., is not included in this analysis as results are based in cytology and histological diagnosis as Scotland does not use HPV testing for the triage of low-grade cytology [Palmer, 2019]. Therefore, results from Palmer et al., have been considered as "irrespective of HPV type" [Palmer, 2019]. The data from Lehtinen et al., 2017 is not included in analysis 1 since the participants in the study partially overlapped with those from Lehtinen et al., 2012, which was chosen for the analysis [Lehtinen, 2012; Lehtinen, 2017].

2. What is the combined overall efficacy/effectiveness of CERVARIX on CIN3+ caused by any HPV type?

Analysis 2.

- Endpoint: CIN3+;
- HPV type considered: irrespective of HPV type.
- Type of studies considered: Combined RCT/Observational studies.

Table 5 Studies included in the meta-regression for Analysis 2

Author	Year	Study design	Study correlation	TVC	TVC naïve	Age first vaccination (years)	Endpoint	Time since vaccination (Time follow-up) (years)
Lehtinen	2012	RCT	A	1	0	15-17	CIN3+	0-4
Lehtinen	2012	RCT	A	1	0	18-20	CIN3+	0-4
Lehtinen	2012	RCT	A	1	0	21-25	CIN3+	0-4
Lehtinen	2012	RCT	A	0	1	15-17	CIN3+	0-4
Lehtinen	2012	RCT	A	0	1	18-20	CIN3+	0-4
Lehtinen	2012	RCT	A	0	1	21-25	CIN3+	0-4
Konno	2014	RCT	C	1	0	20-25	CIN3+	0-4
Konno	2014	RCT	C	0	1	20-25	CIN3+	0-4
Shing	2022	Obs	B	1	0	18-25	CIN3+	7-11
Palmer	2019	Obs	D	1	0	12-13	CIN3+	0-8
Palmer	2019	Obs	D	1	0	14	CIN3+	0-6
Palmer	2019	Obs	D	1	0	15	CIN3+	0-5
Palmer	2019	Obs	D	1	0	16	CIN3+	0-4
Palmer	2019	Obs	D	1	0	17	CIN3+	0-3
Palmer	2019	Obs	D	1	0	≥18	CIN3+	0-2
Rebolj	2022	Obs	F	1	0	14-17	CIN3+	7-11

Abbreviations: CIN3+: Cervical Intraepithelial Neoplasia Grade 3 or worse, Obs: Observational study, RCT: randomized control trial, TVC: Total Vaccinated Cohort
A, B, C, D, F: values of dummy variable "study correlation".

A RCT by Konno et al., was included in this analysis as it reports vaccine efficacy "irrespective of HPV type" [Konno, 2014]. A study by Palmer et al., is included as observational study since it also reports vaccine effectiveness irrespective of HPV type [Palmer, 2019]. A RCT by Porras et al., is not included in this analysis as it reports on vaccine efficacy against CIN3+ caused by HPV 16/18 [Porras, 2020]. An observational study by Lehtinen et al., 2017, is not included as participants partially overlap with those from another study (RCT) by Lehtinen et al., 2012 [Lehtinen, 2012; Lehtinen, 2017].

3. What is the efficacy of CERVARIX on CIN3+ caused by vaccine HPV types?

Analysis 3.

- Endpoint: CIN3+

- HPV type considered: HPV16/18

Type of study considered: RCT.

Table 6 Studies included in the meta-regression for Analysis 3

Author	Year	Study design	Study correlation	TVC	TVC naïve	Age first vaccination (years)	Endpoint	Time since vaccination (Time follow-up) (years)
Lehtinen	2012	RCT	A	1	0	15-17	CIN3+	0-4
Lehtinen	2012	RCT	A	1	0	18-20	CIN3+	0-4
Lehtinen	2012	RCT	A	1	0	21-25	CIN3+	0-4
Lehtinen	2012	RCT	A	0	1	15-17	CIN3+	0-4
Lehtinen	2012	RCT	A	0	1	18-20	CIN3+	0-4
Lehtinen	2012	RCT	A	0	1	21-25	CIN3+	0-4
Porras	2020	RCT	B	0	1	18-25	CIN3+	0-4
Shing	2022	RCT	B	1	0	18-25	CIN3+	0-4

Abbreviations: CIN3+: Cervical Intraepithelial Neoplasia Grade 3 or worse, RCT: randomized control trial, TVC: Total Vaccinated Cohort

A, B: values of dummy variable "study correlation".

A study by Shing et al., is included here as it reports vaccine efficacy against HPV 16/18 from different analytic cohort than Porras et al. [Shing, 2022; Porras, 2020] (i.e., TVC vs TVC naïve in study by Porras et al. [Porras, 2020])

4. What is the effectiveness of CERVARIX on CIN3+ caused by vaccine HPV types? Observational studies only

Analysis 4.

- Endpoint: CIN3+
- HPV type considered: HPV 16/18
- Type of study considered: observational studies.

Table 7 Studies included in the meta-regression for Analysis 4

Author	Year	Study design	Study correlation	TVC	TVC naïve	Age first vaccination (y)	Endpoint	Time since vaccination (Time follow-up) (y)
Shing	2022	Obs	B	1	0	18-25	CIN3+	7-11
Lehtinen	2017	Obs	G	1	0	16-17	CIN3+	0-10
Rebolj	2022	Obs	F	1	0	14-17	CIN3+	7-11

Abbreviations: CIN3+: Cervical Intraepithelial Neoplasia Grade 3 or worse, Obs: Observational study, TVC: Total Vaccinated Cohort

B, G, F: values of dummy variable "study correlation".

A study by Lehtinen et al., is included in this analysis as it reports vaccine effectiveness against HPV 16/18. [Lehtinen, 2017].

5. What is the efficacy of CERVARIX on CIN3+ caused by any HPV type?

Analysis 5.

- Endpoint: CIN3+.
- HPV type: irrespective of HPV type.
- Type of study considered RCT.

Table 8 Studies included in the meta-regression for Analysis 5

Author	Year	Study design	Study correlation	TVC	TVC naïve	Age first vaccination (years)	Endpoint	Time since vaccination (Time follow-up) (years)
Lehtinen	2012	RCT	A	1	0	15-17	CIN3+	0-4
Lehtinen	2012	RCT	A	1	0	18-20	CIN3+	0-4
Lehtinen	2012	RCT	A	1	0	21-25	CIN3+	0-4
Lehtinen	2012	RCT	A	0	1	15-17	CIN3+	0-4
Lehtinen	2012	RCT	A	0	1	18-20	CIN3+	0-4
Lehtinen	2012	RCT	A	0	1	21-25	CIN3+	0-4
Konno	2014	RCT	C	1	0	20-25	CIN3+	0-4
Konno	2014	RCT	C	0	1	20-25	CIN3+	0-4
Shing	2022	RCT	B	1	0	18-25	CIN3+	0-4

Abbreviations: CIN3+: Cervical Intraepithelial Neoplasia Grade 3 or worse, TVC: Total Vaccinated Cohort
A, B, C: values of dummy variable "study correlation".

6. A study by Shing et al., is included in this analysis as it reports vaccine efficacy irrespective of HPV type. [Shing, 2022]. What is the effectiveness of CERVARIX on CIN3+ caused by any HPV type?

Analysis 6.

- Endpoint: CIN3+
- HPV type considered: irrespective of HPV type.
- Type of study considered: Observational studies.

Table 9 Studies included in the meta-regression for Analysis 6

Author	Year	Study design	Study correlation	TVC	TVC naïve	Age first vaccination (years)	Endpoint	Time since vaccination (Time follow-up) (years)
Shing	2022	Obs	B	1	0	18-25	CIN3+	7-11
Lehtinen	2017	Obs	G	1	0	16-17	CIN3+	0-10
Palmer	2019	Obs	D	1	0	12-13	CIN3+	0-8
Palmer	2019	Obs	D	1	0	14	CIN3+	0-6
Palmer	2019	Obs	D	1	0	15	CIN3+	0-5
Palmer	2019	Obs	D	1	0	16	CIN3+	0-4
Palmer	2019	Obs	D	1	0	17	CIN3+	0-3
Palmer	2019	Obs	D	1	0	≥18	CIN3+	0-2
Rebolj	2022	Obs	F	1	0	14-17	CIN3+	7-11

Abbreviations: CIN3+: Cervical Intraepithelial Neoplasia Grade 3 or worse, Obs: Observational study, TVC: Total Vaccinated Cohort

B, D, G, F: values of dummy variable "study correlation".

A study by Lehtinen et al., [Lehtinen, 2017] is included in this analysis as it reports on vaccine effectiveness irrespective of HPV type.

Note: For observational studies, unless it is clearly specified in the methods section of the paper, a TVC approach was considered (irrespective of the baseline HPV status). This is the case of the population-based surveillance studies (i.e., [Palmer, 2019; Rebolj, 2022]) that report on results of the HPV national immunization program that obviously does not include pre-vaccination cervical screening.

7.4.5. Potential confounders and effect modifiers

By selecting the studies according to different selection criteria and taking into account important confounders/effect modifiers in the meta regression, the analyses do take into account effects of the main well-known confounders/effect modifiers. Please see Section 7.3.4 and Section 7.8.

7.4.6. Other potential sources of bias

Expected sources of bias for observational studies are:

- Selection bias: selection of participants could be influenced by participant´s characteristic or outcome (i.e., if the unvaccinated arm presents differences in the characteristics and/or age than the vaccinated arm).
- Information bias: bias related to measurements in the intervention and of the outcome (methods for the identification of the outcome, time between vaccination and outcome and baseline status to rule out outcomes due to pre-existing infection at a given dose)

RCTs may be also subject to bias arising from the randomization process, deviations from intended intervention, missing outcome data, and bias in the selection of reported results. Bias has been assessed. Please see Section 7.8 for more details on the risk of bias assessment.

7.5. Study size

NA

This was not conceived as a confirmatory study. There is not a prior hypothesis to test and therefore it is not necessary to establish a sample size that has sufficient power to reject the null hypothesis. However, since two of the observational studies are nationwide surveillance studies (including several birth cohorts) and the other observational and follow-up of RCTs studies included high number of participants that allowed statistically significant vaccine efficacy/effectiveness estimates, precision of the estimates produced by the meta-regression results is expected to be sufficient.

The cohort sizes for the different studies included in the meta-regression and the correspondent vaccine effect estimates and precision intervals are presented in Table 10.

Table 10 Vaccine effects on different endpoints

Author, Year	N* (overall)	Age at first vaccination (years)	N (age group)	Endpoints	Vaccine effects % (95%CI)
[Lehtinen, 2012]	**TVC, N=18644** Vaccine arm, n=9319 Control arm, n=9325 **TVC-naïve, N=11644** Vaccine arm, n=5824 Control arm, n=5820	15-25 15-25 15-25 15-25 15-17 18-25 18-20 21-25 15-17 18-25 18-20 21-25 15-17 18-25 18-20 21-25 15-17 18-25 18-20 21-25	NA	VEFC against CIN3+ associated with HPV-16/18 in TVC-naïve VEFC against CIN3+ associated with HPV-16/18 in TVC VEFC against all CIN3+ (irrespective of HPV type in the lesion and including lesions with no HPV DNA detected) in the TVC-naïve VEFC against all CIN3+ (irrespective of HPV type in the lesion) in the TVC VEFC against CIN3+ associated with HPV-16/18 in TVC-naïve VEFC against CIN3+ associated with HPV-16/18 in TVC-naïve VEFC against CIN3+ associated with HPV-16/18 in TVC-naïve VEFC against CIN3+ associated with HPV-16/18 in TVC-naïve VEFC against CIN3+ associated with HPV-16/18 in TVC VEFC against CIN3+ associated with HPV-16/18 in TVC VEFC against CIN3+ associated with HPV-16/18 in TVC VEFC against CIN3+ associated with HPV-16/18 in TVC VEFC against all CIN3+ (irrespective of HPV type in the lesion and including lesions with no HPV DNA detected) in the TVC-naïve VEFC against all CIN3+ (irrespective of HPV type in the lesion and including lesions with no HPV DNA detected) in the TVC-naïve VEFC against all CIN3+ (irrespective of HPV type in the lesion and including lesions with no HPV DNA detected) in the TVC-naïve VEFC against all CIN3+ (irrespective of HPV type in the lesion and including lesions with no HPV DNA detected) in the TVC-naïve VEFC against all CIN3+ (irrespective of HPV type in the lesion) in the TCV VEFC against all CIN3+ (irrespective of HPV type in the lesion) in the TCV VEFC against all CIN3+ (irrespective of HPV type in the lesion) in the TCV VEFC against all CIN3+ (irrespective of HPV type in the lesion) in the TCV	100 (85.5, 100) 45.7 (22.9, 62.2) 93.2 (78.9, 98.7) 45.6 (28.8, 58.7) 100 (69.4, 100) 100 (67.8, 100) 100 (39.5, 100) 100 (-4.6, 100) 80.5 (55.6, 92.7) 24.2 (-14.1, 50.0 56.3 (13.6, 79.1) -10.1 (-90.5, 36.1) 91.5 (65.9, 99.0) 95.1 (69.3, 99.9) 90.6 (35.5, 99.8) 100 (51.4, 100) 65.5 (42.5, 80.0) 33.1 (7.5, 51.9) 49.5 (13.9, 71.2) 19.5 (-22.7, 47.4)
[Konno, 2014]	**TVC combined, N=1040** Vaccine arm, n=519 Control arm, n=521 **TVC-naïve combined,** N=565	20-25	NA	VEFC against CIN3+ irrespective of the HPV type in the TVC-naive (over the combined 4-y study period of initial and follow-up studies) VEFC against CIN3+ irrespective of the HPV type in the TVC (over the combined 4-y study period of initial and follow-up studies)	100 (-417.0, 100) 36.4 (-57.8, 75.7)

Author, Year	N* (overall)	Age at first vaccination (years)	N (age group)	Endpoints	Vaccine effects % (95%CI)
	Vaccine arm, n=281 Control arm, n=284				
[Lehtinen, 2017]	**N=18092** Vaccinated arm, n=2465 Unvaccinated arm, n=15627	16-17	NA	VEFT against CIN3+ caused by HPV16 VEFT against CIN3+ caused by HPV18 VEFT against CIN3+ caused by HPV16/18 VEFT against CIN3+ caused by HPV16/31/33/35/52/58 VEFT against CIN3+ caused by HPV/31/33/35/52/58 (excluding co-infections with HPV16) VEFT against CIN3+ caused by A9=HPV31/33/35/52/58 and A7=HPV39/45/59/68, (excluding co-infections with 16/18) VEFT against CIN3+ caused by HPV31/33/45 VEFT against CIN3+ caused by HPV6/11/16/18/31/33/45/51/74 (all protected types) VEFT effectiveness against CIN3+ caused by HPV6/11/31/33/45/51/74 (all protected types excluding co-infections with 16/18) VEFT against CIN3+ caused by HPV34/35/39/40/42/43/44/52/53/54/56/58/59/66/68/70/73 (all non-protected types excluding co-infections with 16/18) VEFT against CIN3+ caused by all detected HPV types VEFT against CIN3+ caused by all detected HPV types (HPV positive and HPV negative baseline, excluding co-infections with 16/18) VEFT against CIN3+ caused by Total (original FCR registered CIN3+ diagnoses) VEFT against CIN3+ caused by Total All, irrespective of HPV type, this includes the re-review of histopathological block retrieval and re-analysis	22 (-160, 73) 100 (-1500, 100) 27 (-140, 74) 53 (-48, 83) 100 (-65, 100) 100 (-55, 100) 100 (-120,100) 50 (-60, 82) 100 (-120, 100) 100 (-480, 100) 56 (-38, 84) 100 (-55, 100) 59 (-26, 85) 66 (8.4, 88)
[Porras, 2020]	**Analytical cohort (0-4 y), N=5312**	18-25	NA	VEFC against CIN3+ caused by HPV 16/18 at year 4 post-vaccination (analytical cohort with original control group)	66.4 (-175, 97.3)

Author, Year	N* (overall)	Age at first vaccination (years)	N (age group)	Endpoints	Vaccine effects % (95%CI)
	Vaccine arm, n=2635 Control arm, n=2677 **Analytical cohort (7-11 y), N=4603** Vaccinated arm, n=2073 Unvaccinated arm, n=2530			VEFT against CIN3+ caused by HPV 16/18 at year 7 post-vaccination (analytical cohort with unvaccinated new control group) VEFT against CIN3+ caused by HPV 16/18 at year 9 post-vaccination (analytical cohort with unvaccinated new control group) VEFT against CIN3+ caused by HPV 16/18 at year 11 post-vaccination (analytical cohort with unvaccinated new control group)	100 (-40.1, 100) 100 (44.0, 100) 100 (78.8, 100)
[Shing, 2022]	**Analytical cohort (1-4 y), N=7003** Vaccine arm, n=3491 Control arm, n=3512 **Analytical cohort (7-11 y), N=5418** Vaccine arm, n=2826 Unvaccinated arm, n=2592	18-25	NA	VEFC against incident CIN3+ irrespective of HPV type (combined 4-year period) VEFC against incident CIN3+ caused by HPV16 or HPV18 (combined 4-year period) VEFC against incident CIN3+ caused by HPV 31,33, or 45 (excluding HPV 16 or 18 coinfection) (combined 4-year period) VEFC against incident CIN3+ caused by HPV types other than HPV 16, 18, 31, 33, or 45 (combined 4-year period)	25.2 (-5.0, 46.9) 52.9 (22.4, 72.1) -16.1 (-149.0, 45.3) -17.4 (-123.2, 37.8)
				VEFT against incident CIN3+ irrespective of HPV type (combined years 7-11 period) VEFT against incident CIN3+ caused by HPV16 or HPV18 (combined years 7-11 period) VEFT against incident CIN3+ caused by HPV 31,33, or 45 (excluding HPV 16 or 18 coinfection) (combined years 7-11 period) VEFT against incident CIN3+ caused by HPV types other than HPV 16, 18, 31, 33, or 45 (combined years 7-11 period) VEFT against incident CIN3+ irrespective of HPV type (combined 11-year period) VEFT against incident CIN3+ caused by HPV16 or HPV18 (combined 11-year period) VEFT against incident CIN3+ caused by HPV 31,33, or 45 (excluding HPV 16 or 18 coinfection) (combined 11-year period) VEFT against incident CIN3+ caused by HPV types other than HPV 16, 18, 31, 33, or 45 (combined 11-year period)	14.4 (-23.4, 40.7) 86.9 (65.3, 96.1) 36.9 (-36.2, 71.6) -135.0 (-329.8, -33.5) 19.5 (-3.3, 37.5) 67.9 (51.1, 80.4) 16.6 (-40.6, 52.4) -81.7 (-190.6, -19.9)
[Palmer, 2019]	**N=138692** 0 doses, n=64026 1 dose, n=2051 2 doses, n=4135 3 doses, n=68480	12-13 14 15 16 17	N=16200 N=5409 N=16532 N=17511 N=8711	VEFT against CIN3+ [a, b] VEFT against CIN3+ VEFT against CIN3+ VEFT against CIN3+ VEFT against CIN3+	86 (75, 92) 82 (57, 93) 71 (56, 81) 73 (59, 82) 45 (17, 64)

Author, Year	N* (overall)	Age at first vaccination (years)	N (age group)	Endpoints	Vaccine effects % (95%CI)
		≥18	N=4117	VEFT against CIN3+	15 (-37, 48)
		≤17	N=15678	VEFT against CIN3+, born ≥ 1991 (unvaccinated)	18 (-7, 37)
		12-13	N=48348	VEFT against CIN3, born 1995-1996 (unvaccinated)	100 (69, 100)
[Rebolj, 2022]	**N=108138** Vaccinated, n=64274 Unvaccinated, n=43863	14-17	NA	VEFT against High-risk-HPV positive CIN3+ (High-risk-HPV+/cytology+ primary screening test)[c] VEFT against HPV 16/18-related CIN3+ VEFT against CIN3+ by "Other" HPV-related (excludes co-infections with HPV 16/18[d] VEFT against cervical cancer	79 (73,83) 87 (80, 91) 57 (25, 75) 64 (-91, 93)

Abbreviations: CIN3+: Cervical Intraepithelial Neoplasia Grade 3 or worse, HPV: Human Papillomavirus, N: Number (Overall), n: Number of participants in each arm, NA: Not applicable, RCT: randomized control trial, TVC: Total Vaccinated Cohort, VEFC: Vaccine efficacy, VEFT: Vaccine effectiveness

a. Participants received at least 1 dose of vaccine.

b. Vaccine effectiveness calculated as VE=(1-OR)*100

c. **14** High-risk-HPV types: 16,18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68

d. **"**Other" 12 High-risk-HPV types: 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68

*Overall number of participants in the cohort divided into different arms within the study.

7.6. Data management

NA

7.7. Data analysis

Heterogeneity among selected studies is expected to be large, given the differences in settings (e.g., time at first vaccination, time of follow-up, study design, etc.) that are known to influence vaccine efficacy/effectiveness but a decision was made to pursue a quantitative synthesis exercise. To consider these factors in the calculation of global estimates, meta-regression models will be fitted. They will provide summary point estimates for vaccine efficacy/effectiveness for every scenario while adjusting for relevant covariates (i.e., correcting for study differences due to different levels of covariates). Residual heterogeneity not explained by the multiparametric model will be shown in the statistical outputs. If this heterogeneity is still large, it will be discussed and acknowledged among the limitations of the study.

Meta-regression allows the effects of multiple factors to be investigated simultaneously. It examines if characteristics of studies are associated with the magnitude and direction of the effect in the selected studies. The outcome variable will be the effect estimate. The explanatory variables are characteristics of studies that might influence the size of the effect. These are often called “potential effect modifiers” or covariates. For this analysis, the outcome variable will be the effect estimate (CERVARIX efficacy/effectiveness). The explanatory variables will be study design (RCT/observational), age at first vaccination, the type of analytical cohort, and time since vaccination. Note that to increase the precision of the estimates, when possible, we will split studies in different sub-studies given differences in terms of covariates. The correlations between the different sub-studies of a study will be taken into account in all subsequent analyses.

Meta-regression models will be fitted using a frequentist approach. For each question considered, the following strategy will be used:

- First a meta-analysis will be fitted (using the rma.mv function from R) using a REML estimation procedure allowing for Random Effect).
- Univariate meta-regressions (with Random Effect and REML) will be fitted to assess the impact of each covariate independently.
- A multivariate meta-regression (with Random Effect and REML) will then be considered. Covariate selection for this model will be performed via an R function called multi-model inference which is examining the predictor combination providing the best fit (AIC to measure the goodness of fit of the models will be applied). The data-driven multiparametric models will allow for prediction of covariates with impact on decision-making for vaccine policies.

7.7.1. Rationale

Meta-regression is a generalization of the meta-analysis that allows assessing the relationship between specific study-level covariates, such as age or time since vaccination, and the effect size. In particular, it may take into account the heterogeneity of the results that may come from different levels of covariates of the different studies. Meta-regression may be performed under the fixed-effect or the random-effects model, but in most cases the latter is appropriate [Borenstein, 2009].

7.7.2. Regression

Regression is a statistical method that assesses the relationship between covariates and the dependent variable in a particular study.

- Determine b0 (the intercept) and b1 (the slope) such that the sum of the squares of the residuals (yi - ŷi) is minimized.
- The slope is calculated according to the following formula: $b_1 = \frac{\sum(y_i-\bar{y})(x_i-\bar{x})}{\sum(x_i-\bar{x})^2}$

Where $\bar{x}$ and $\bar{y}$ are the means of the variables x and y respectively.

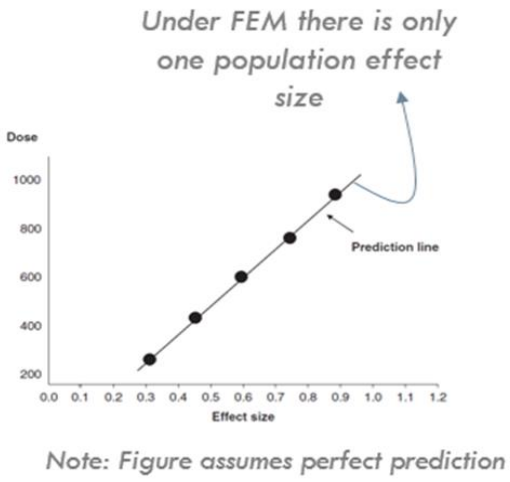
7.7.3. Fixed-effect and random-effect meta-regression:

The goal of fixed-effect meta-regression it to estimate $y_i = \beta_0 + \beta_1 x_{1i} + \varepsilon_i$ by minimizing the sum of the weighted sum of the squares of the residuals, i.e., $\sum w_i(y_i - \bar{y})^2$

The slope of the covariate is given by $\beta_1 = \frac{\sum w_i(y_i-\bar{y})(x_i-\bar{x})}{\sum w_i(x_i-\bar{x})^2}$

Where, $w_i = \frac{1}{{\sigma_i}^2}$

Figure 2 Meta-Regression (Fixed Effect)



Reference: [Borenstein, 2009].

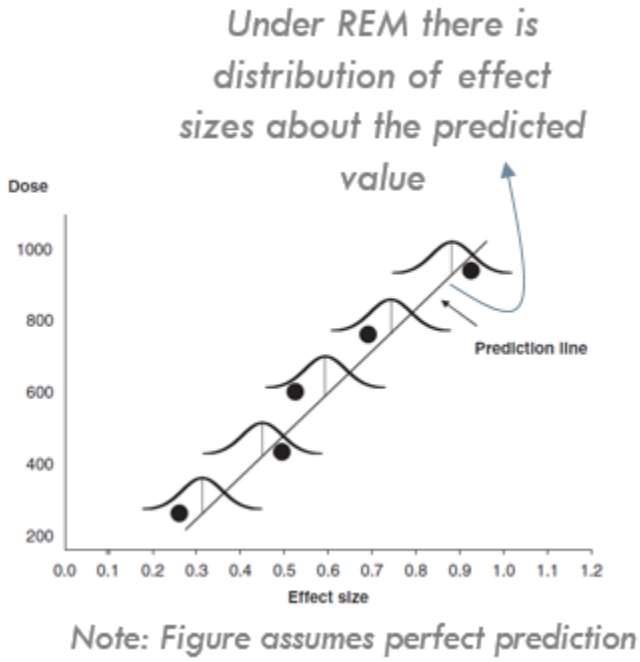
Estimate $y_i = \beta_0 + \beta_1 x_{1i} + \zeta_i + \varepsilon_i$ by minimizing the sum of the weighted sum of the squares of the residuals, i.e., $\sum w_i^*(y_i - \bar{y})^2$

The slope of the covariate is given by $\beta_1 = \frac{\sum w_i^*(y_i - \bar{y})(x_i - \bar{x})}{\sum w_i^*(x_i - \bar{x})^2}$

Where, $w_i^* = \frac{1}{\sigma_i^2 + \tau^2}$

In this study, meta-regression will always have random effects and vaccine efficacy/effectiveness will be modelled as the log of the relative risk [log(1-VE)] as normally distributed.

Figure 3 Meta-Regression (Random Effect)



Reference: [Borenstein, 2009].

7.7.4. Statistical testing

Significance of each covariate introduced into the model will be assessed using the Z-test and subsequent p-values will be evaluated.

7.7.5. Statistical significance

In this whole analysis, the statistical significance will be at p=0.05. However, this study is not considered as confirmatory and no prior hypothesis has been formulated. There is no intention to adjust for multiplicity. Confidence intervals will be two-sided and will be at a 95% level.

7.7.6. Software

Analyses will be performed using the "metafor" package in R.

7.7.7. Primary analysis

7.7.7.1. Main Analytical approach

The following scheme will be followed to answer the research questions and scenarios as described in section 7.4.4 .

Multiparametric meta-regressions adjusting for the following covariates: age at first vaccination, study design (RCT vs observational), analytical cohort (TVC vs TVC naïve), and time since vaccination (time of follow-up). An AIC (estimator of prediction error) approach will be used to assess the quality of the models for every given dataset allowing a data-driven selection of the best model. One model will be selected for each of the 6 questions assessed:

- What is the combined efficacy/effectiveness of CERVARIX on CIN3+ caused by vaccine HPV types?
- What is the combined overall efficacy/effectiveness of CERVARIX on CIN3+ caused by any HPV type?
- What is the efficacy of CERVARIX on CIN3+ caused by vaccine HPV types?
- What is the effectiveness of CERVARIX on CIN3+ caused by vaccine HPV types? (Observational studies only)
- What is the efficacy of CERVARIX on CIN3+ caused by any HPV type?
- What is the effectiveness of CERVARIX on CIN3+ caused by any HPV type? (Observational studies only)

However, prior to this, the following preliminary analyses will be considered:

1. Classical random effect meta-analysis without adjusting for covariates.
2. Univariate meta-regression with random effect of each potential covariate, e.g., age at first vaccination, study design (RCT vs observational), analytical cohort (TVC vs TVC naïve), and time since vaccination (time of follow-up)

Graphical representations for results from univariate and multivariate models will be produced.

This stepwise approach to the analysis will allow to understand the specific effects of individual covariates (univariate analysis) on the outcome in the different scenarios and, through selection of the best models, multiparametric analysis will permit to combine the effect of those covariates with strong influence on the outcome relevant for decision-making.

7.7.7.2. Sensitivity analyses

As described in Section 7.4.5 the analysis will be conducted following different scenarios (i.e., analyzing RCTs or observational studies independently, and pooling together data corresponding to both study designs) to assess how different values of the independent variables affect the outcome variable. In addition, uni-, and multivariate models will be considered.

7.7.8. Secondary analysis/Exploratory analysis

NA

7.7.9. Summary of all analyses

Table 11 Summary of analyses

Study	Study design	Analytical cohort		Age at first vaccination (y)	HPV type		Time since vaccination (y)	Analysis 1	Analysis 2	Analysis 3	Analysis 4	Analysis 5	Analysis 6
		TVC	TVC naïve		HPV 16/18	Irrespective HPV type							
[Lehtinen, 2012]	RCT	X		15-17	X	X	4	X	X	X		X	
[Lehtinen, 2012]	RCT	X		18-20	X	X	4	X	X	X		X	
[Lehtinen, 2012]	RCT	X		21-25	X	X	4	X	X	X		X	
[Lehtinen, 2012]	RCT		X	15-17	X	X	4	X	X	X		X	
[Lehtinen, 2012]	RCT		X	18-20	X	X	4	X	X	X		X	
[Lehtinen, 2012]	RCT		X	21-25	X	X	4	X	X	X		X	
[Konno, 2014]	RCT	X		20-25		X	4		X	X		X	
[Konno, 2014]	RCT		X	20-25		X	4		X			X	
[Porras, 2020]	RCT		X	18-25	X		4	X		X			
[Shing, 2022]	RCT	X		18-25	X	X	4			X		X	
[Lehtinen, 2017]	Observational	X		16-17	X	X	10				X		X
[Palmer, 2019]	Observational	X		12-13		X	7-8		X				X
[Palmer, 2019]	Observational	X		14		X	6		X				X
[Palmer, 2019]	Observational	X		15		X	5		X				X
[Palmer, 2019]	Observational	X		16		X	4		X				X
[Palmer, 2019]	Observational	X		17		X	3		X				X
[Palmer, 2019]	Observational	X		≥18		X	2		X				X
[Rebolj, 2022]	Observational	X		14-17	X	X	7-11	X	X		X		X
[Shing, 2022]	Observational	X		18-25	X	X	7-11	X	X		X		X

HPV: Human Papillomavirus, RCT: randomized control trial, TVC: Total Vaccinated Cohort.

7.8. Quality control and Quality Assurance

The systematic review was conducted in accordance with the PRISMA checklist /and in compliance to the Cochrane Handbook of Systematic Review of Interventions [Higgins, 2023; PRISMA, 2023] and the Joanna Briggs Institute Manual for Evidence Synthesis [Jordan, 2019].

Expected sources of bias for observational studies are

- Selection bias: selection of participants could be influenced by participant´s characteristic or outcome.
- Information bias: bias related to measurements in the intervention and of the outcome (methods for the identification of the outcome, time between vaccination and outcome and baseline status to rule out outcomes due to pre-existing infection at a given dose)
- confounding: assessing the probability of differences between the two study groups.

The risk of bias was assessed by two different tools:

- Cochrane risk of bias for randomized controlled trails (RoB2) [The Cochrane Collaboration, 2022a]
- Cochrane ROBINS-I tool for observational epidemiological studies specifically designed for use in systematic reviews [The Cochrane Collaboration, 2022b]

Every report was assessed using the relevant tool. For those papers that report both on RCTs and observational studies (long-term follow-up of clinical trials), the appropriate tool was used to assess the quality of each component.

After completion of the assessment, the “robvis” visualisation tool was used to produce the figure for the overall assessment [McGuinness, 2020].

7.8.1. Quality assessment of randomized controlled trials

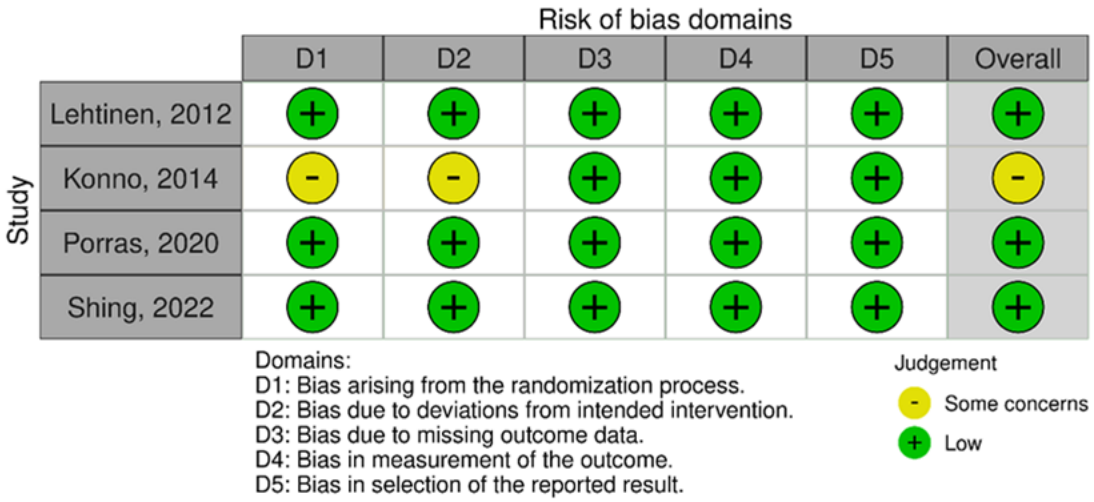
The Cochrane RoB2 tool was applied to the selected RCTs and three studies showed low risk bias whereas the study by Konno et al., presented some concerns in the randomization and deviations from intended intervention domain because a) this study is a post hoc follow-up of an RCT and the follow-up was not blinded. However, laboratory staff that assessed the outcome was blinded to the vaccination status. Therefore, a great impact on the efficacy was not expected; b) the study was not powered to evaluate vaccine efficacy against CIN3+, the reason why this result showed wide confidence intervals. The latter will be addressed when conducting the adjusting in the meta-regression analysis [Konno, 2014; The Cochrane Collaboration, 2022a].

Follow-up post hoc studies of RCTs by Lehtinen et al., Porras et al., and Shing et al., presented low risk of bias. The main feature for these studies is that double blinding was kept beyond the 3-year RCT duration up to the end of the 4-year follow-up (48 months). Therefore, participants, study personnel and investigators were blinded to the treatment

allocation [Lehtinen, 2012; Porras, 2020; Shing, 2022]. In contrast, this was not the case for Konno et al., where the blinding was broken at the end of the RCT at 36 months. Therefore, participants and carers were aware of the intervention allocation during the follow-up period. This is why this study had the overall judgement of presenting "some concerns". However, laboratory staff were blinded to the intervention which prevents bias at the diagnosis and assessment of the outcome, and ultimately was expected not to have influenced the efficacy assessment. Another important aspect is that the Konno, 2014 study was not powered to evaluate vaccine effectiveness against CIN3+. Hence, the large 95% confidence intervals for the results on this outcome (Table 10). This was addressed in the analysis phase (meta-regression) [Konno, 2014].

Overall, completeness of all follow-up studies was quite high, and losses were not selective, leaving both arms balanced at completion of the study.

Table 12 Risk of bias of RCTs from the systematic review



Source: [McGuinness, 2020]
The table was prepared using the robvis tool.

7.8.2. Quality assessment of observational studies

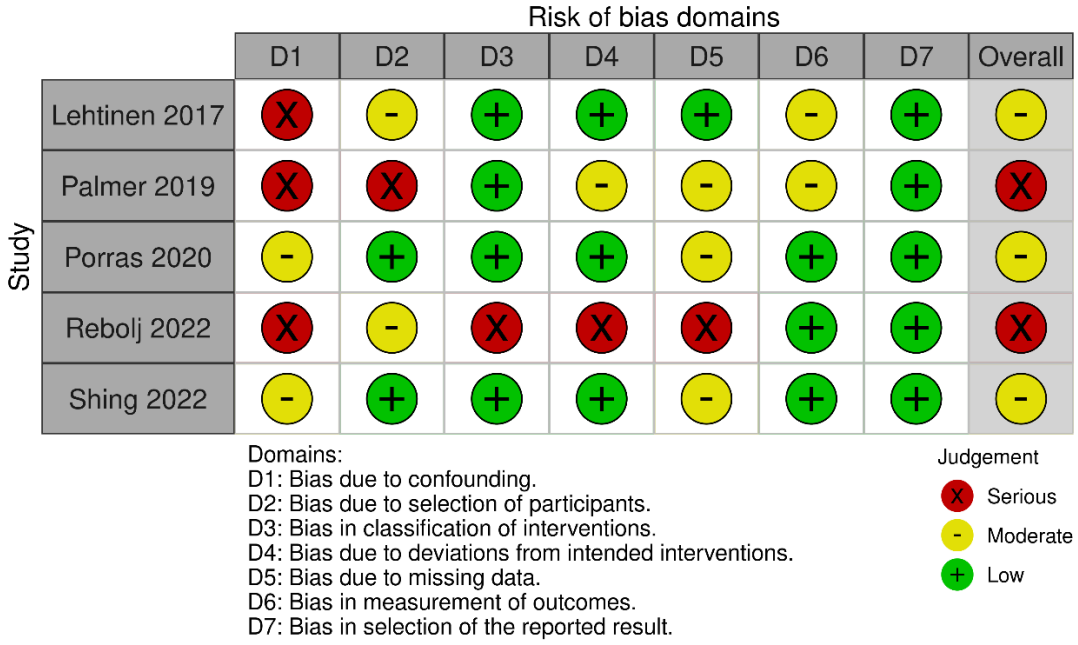
The Cochrane ROBINS I tool for non-interventional studies was used to assess the risk of bias of observational studies and surveillance of national immunization programs studies [The Cochrane Collaboration, 2022b].

All the included studies were considered to have at least moderate risk of bias, and two of the five studies included were at high (serious) risk of bias. These two studies that were at serious risk of bias had one or two domains at high risk (mainly confounding and information of outcome) [Palmer, 2019; Rebolj, 2022]. Uptake of screening in fully vaccinated women aged 20 or 21 years was 51%, and only 23% in unvaccinated women and this may have overestimated vaccine effectiveness [Palmer, 2019]. On the other hand, authors adjusted by immunization status and age at which the first dose was

administered, and by year of birth in unvaccinated women, respectively. The analysis also adjusted for socioeconomic status (deprivation and rurality score) [Palmer, 2019]. In the study by Rebolj et al., individual vaccination status was unknown. The age and calendar year specific probability that a woman was vaccinated was estimated from the official national statistics for vaccination with three doses in the general population, available by school cohort. However, these two studies were population-based retrospective cohort studies limiting the risk of selection bias. The overall judgement was that both studies addressed bias and confounding in an appropriate manner in the analytical phase considering the limitations of the retrospective population-based registry linked study design [Palmer, 2019; Rebolj, 2022].

An important source of confounding of observational studies is related to HPV acquisition. The population-based studies did not determine HPV-baseline status to assess for prevalent infection at the time of vaccination as pre-vaccination cervical screening is not standard of care. To address this, studies allowed for buffer time between the vaccination and outcome assessment (cervical screening). Other important source of confounding in observational studies determining HPV vaccine effectiveness is differences in risk of HPV acquisition between vaccinated and unvaccinated participants. In those observational studies other than stemming from national surveillance, baseline characteristics of the participants were assessed, most importantly in relation to sexual behavior and activity and adjusted for [Porras, 2020; Shing, 2022] and in other instances, sexual debut age was very similar between the vaccinated and unvaccinated arms [Lehtinen, 2017].

Table 13 Risk of bias of observational studies from the systematic review



Source: [McGuinness, 2020].
The table was prepared using the robvis tool.

As expected, a certain degree of bias was found among observational studies since it is well known that they are subject to several sources of bias and confounding that have been evaluated and assessed with this tool. The keys for interpretation of the results are as follows:

Low		The study is comparable to a well-performed randomized trial with regard to this domain
Moderate		The study is sound for a non-randomized study with regard to this domain but cannot be considered comparable to a well-performed randomized trial
Serious		The study has some important problems

In any case, a decision was made not to discard any observational study, to adjust for covariates instead, and to acknowledge the limitations of the studies.

7.9. Limitations of the research methods

7.9.1. Data

7.9.1.1. Methodology of SLR

A SLR suffers from intrinsic limitations. It can only review what is found, and an element of publication bias is always present, which will reflect in the meta-analysis. Other limitations include the unavailability of data or language barriers.

7.9.1.2. Data availability

Absence of data about important covariates (needed for the meta-regression) can be a major limitation in the assessment of heterogeneity in meta-regressions.

The data included in the analysis is based on a systematic literature review. As such the analysis is limited by the detail and granularity of the data provided in published manuscripts.

7.9.1.3. Number of studies and power of analysis

In a meta-regression framework, the unit of analysis is the study, so the regression performance is determined by the number of studies in the meta-analysis, which is sometimes relatively low. Consequently, one should not expect much statistical power from the meta-regression, depending on the number of covariates included in the model [Bartolucci, 1994].

The power of a statistical analysis is limited, i.e., based on the available data. Consequently, if a covariate is not found to be significant, we cannot conclude that there is no effect of that covariate. i.e., there may be a true effect but there may be insufficient evidence to demonstrate the effect with the available data.

7.9.1.4. Assessment of publication bias

Publication bias occurs when published studies differ systematically from all conducted studies in relation with a topic. Publication bias arises when papers with statistically significant or positive results in a certain direction are more likely to be published than papers with non-statistically significant or negative results [Jordan, 2019], translating into a threat to the validity of the systematic review.

The minimal number of studies recommended for assessment of publication bias with existing tools (i.e., funnel plot, statistical test for funnel plot asymmetry, etc.) should be at least ten to ensure sound statistical power [Higgins, 2023; Jordan, 2019]. However, the assessment of studies to be included (7 papers) is below ten. Therefore, this analysis was not conducted.

7.9.2. Methodology

7.9.2.1. Interpretation of associations and confounding variables

The associations derived from meta-regression are observational and have a less rigorous interpretation than the associations obtained within a single study, particularly when averages of patients' characteristics are used as covariates in the regression.

- Aggregation bias occurs when the relationship with patient averages across trials may not be the same as the relationship with patients within trial.
- Bias by confounding (association with one of the study characteristics that reflects a true association with another known or unknown correlated characteristic) is a particular problem in meta-regression.

7.9.2.2. Assumptions of linearity and normality

In the majority of meta-regressions, there is no attempt to verify the underlying assumptions of normality of the residuals, or the linearity of covariates.

7.9.2.3. Assumptions on creation of age groups

The data included in the analysis is based on a systematic literature review. As such the analysis is limited by the detail and granularity of the data provided in published manuscripts.

7.9.2.4. Potential post-hoc data dredging

The principal pitfall in meta-regression is data-dredging.

- There are only a few studies included, and many characteristics that can explain heterogeneity. Each of these characteristics could potentially be analyzed, until associations are found. Such multiple or post hoc analyses lead to a high chance of false positive conclusions.
- Post hoc conclusions should be regarded as hypothesis generating, to be investigated in other data sets. However, in meta-analysis, the totality of evidence has been accumulated and there is no such external validation.
- Pre-specification of the covariates (prior to the literature search) to be investigated helps protecting against false positive conclusions. However, in order to be truly pre-specified, a protocol should be drawn up without knowledge of any of the relevant literature, which is not really achievable in practice since experts have already strong scientific rationales.
- The number of covariates should be limited, to limit the false positive conclusions. Also a possibility is Bonferroni adjustment to the significance level for each covariate inclusion [Wasserstein, 2016].
- Unfortunately, in practice, after pre-specifying covariates, researchers often discover that for the originally chosen covariates, the information is not available, or that other new important covariates that have not been pre-specified should be included in the analysis.

This study is exploratory and should not be regarded as more than hypothesis generating.

7.9.3. Study closure / Non interpretability of results

NA

7.10. Other aspects

NA

8. PROTECTION OF HUMAN SUBJECTS

8.1. Ethical approval and subject consent

This study will not enroll study participant and will only use aggregated data.

This study will comply with all applicable laws regarding participant privacy. No direct subject contact or primary collection of individual human subject data will occur. Study results will be in tabular form and aggregate analyses that omits subject identification, therefore informed consent, ethics committee or IRB approval are not required. Any publications and reports will not include subject identifiers.

8.2. Participant confidentiality

NA

9. LEGAL BASIS FOR PROCESSING INDIVIDUAL HUMAN DATA

Not applicable as no individual data used in this study.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study does not have safety objectives.

There is no potential to collect serious and non-serious AEs, pregnancy exposures, or incidents related to any GSK product, as the minimum criteria of identifiable patient, reporter, exposure and event needed to collect and report individual case safety reports are not present in the data source.

Reporting of adverse events/reactions (Spontaneous Events)

The use of automated methods for data extractions means there is no potential to collect serious and non-serious AEs, pregnancy exposures, or incidents related to any GSK product during the conduct of this research, as the minimum criteria of identifiable patient, reporter, exposure and event, needed to collect and report individual case safety reports are not present in the data source.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Results will be communicated to Authorities since the study falls within any obligation (i.e., Article 46 submission) or public disclosure.

Results will be published in a manuscript, if scientifically relevant after the variation and discussions with the regulatory authorities have ended.

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Annex 1 LIST OF STAND-ALONE DOCUMENTS

None.

Annex 2 Tables

Table 14 Estimated vaccine effects of pooled data in the different scenarios

Analysis	VE (Meta-analysis)	VE (Univariate meta-regression)	VE (Multivariate meta-regression)
Analysis 1			
Analysis 2			
Analysis 3			
Analysis 4			
Analysis 5			
Analysis 6			

Table 15 List of papers sought for retrieval

Paper
[Acuti Martellucci, 2021]
[Apter, 2015]
[Arbyn, 2016]
[Beachler, 2016]
[Brotherton, 2012]
[Brown, 2009]
[Cameron, 2017a]
[Cameron, 2017b]
[Casajuana-Pérez, 2022]
[Chen, 2020]
[Clark, 2021]
[De Carvalho, 2010]
[Del Mistro, 2021]
[Donken, 2021]
[Falcaro, 2021]
[Hallowell, 2018]
[Harari, 2016]
[Hariri, 2015]
[Harper, 2006]
[Hildesheim, 2014]
[Hiramatsu, 2022]
[Ikeda, 2021]
[Johnson Jones, 2020]
[Khatun, 2012]
[Kjaer, 2021]
[Konno, 2018]
[Konno, 2010]
[Konno, 2014]

Paper
[Lehtinen, 2012]
[Lehtinen, 2017]
[Naud, 2014]
[Onuki, 2022]
[Paavonen, 2009]
[Palmer, 2019]
[Porras, 2020]
[Powell, 2012]
[Racey, 2020]
[Rana, 2013]
[Rebolj, 2022]
[Romanowski, 2009]
[Roteli-Martins, 2012]
[Ryser, 2019]
[Shiko, 2020]
[Shing, 2022]
[Silverberg, 2020]
[Skinner, 2014]
[Skinner, 2016b]
[Szarewski, 2012]
[Tota, 2020]
[Tota, 2021]
[Tozawa-Ono, 2021]
[Wheeler, 2012]
[Yagi, 2021]

Annex 3 Figures

Figure 4 Predicted efficacy/effectiveness of CERVARIX on CIN3+ given age and different categories of covariates.

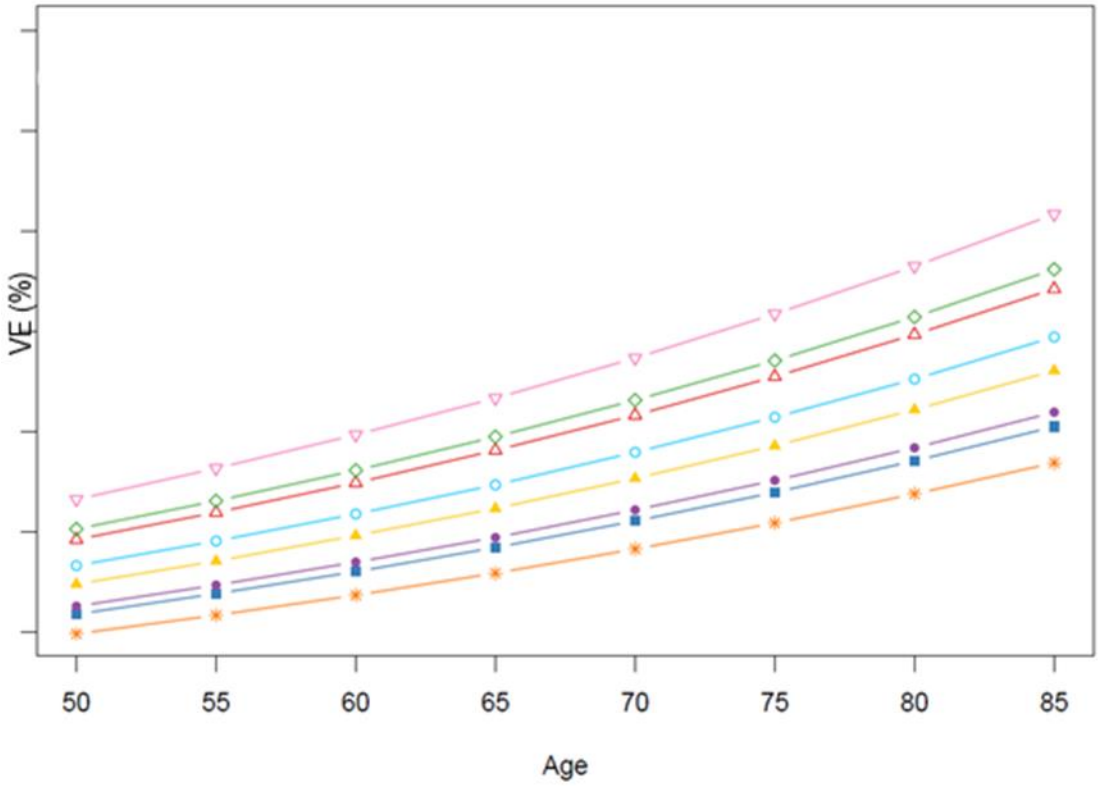


Figure 5 Estimated VE (with 95% Confidence interval) in the 6 different questions (study design/endpoint) without adjusting for covariates (marginal effects).

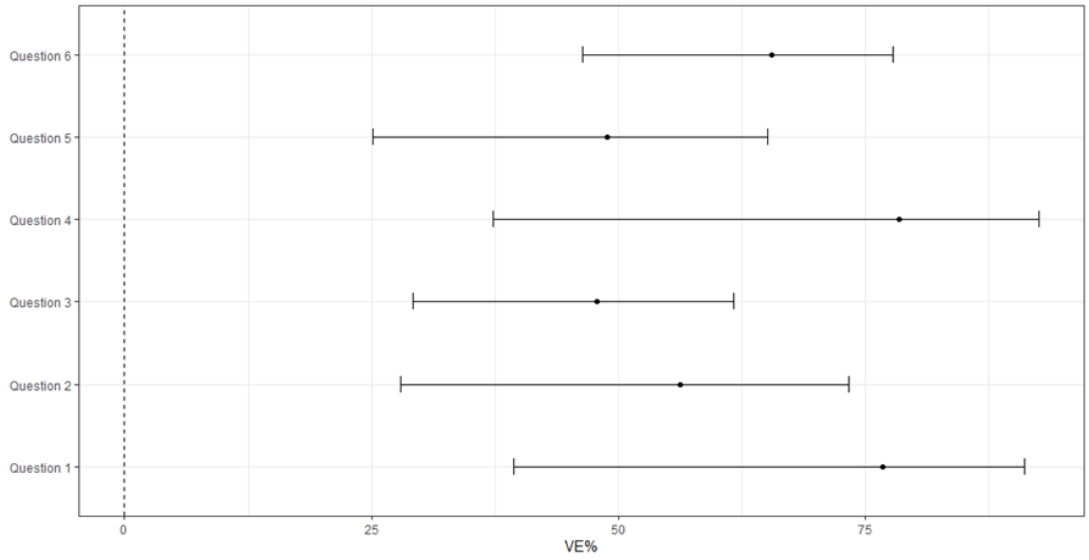
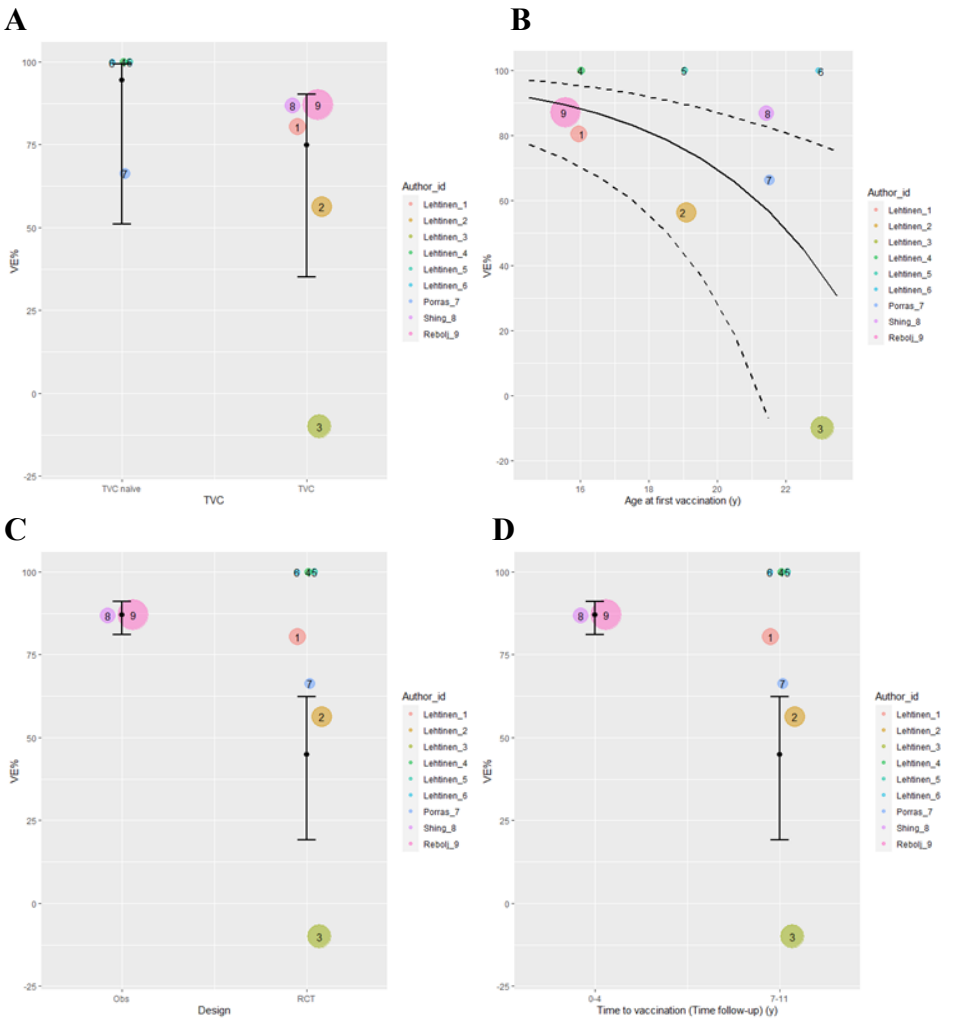
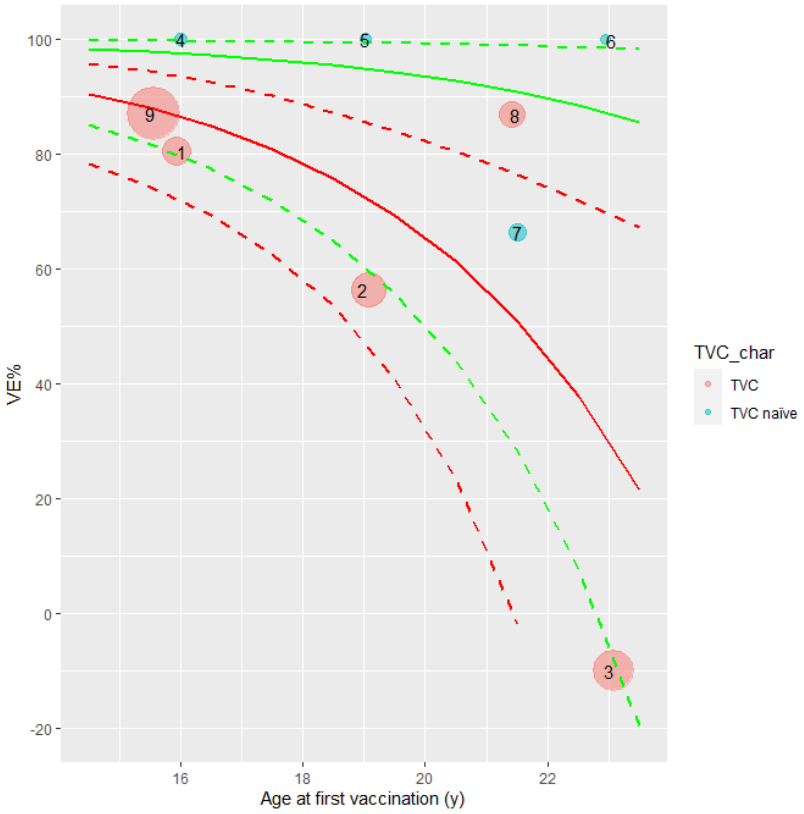


Figure 6 Vaccine effects of pooled data from RCT and/or observational studies



(A) analytical cohort, B) age at first vaccination, C) study design, and D) time since vaccination (time of follow-up)

Figure 7 Vaccine effects of pooled data from RCT and/or observational studies adjusted by age at first vaccination and by analytical cohort



Annex 4 ENCePP Checklist for study protocols

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☐	☐	☐	
1.1.2 End of data collection[2]	☐	☐	☐	
1.1.3 Progress report(s)	☐	☐	☐	
1.1.4 Interim report(s)	☐	☐	☐	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
1.1.6 Final report of study results.	☐	☒	☐	

Comments:

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g., to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	
2.1.2 The objective(s) of the study?	☒	☐	☐	
2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	

1 Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

2 Date from which the analytical dataset is completely available

Section 2: Research question	Yes	No	N/A	Section Number
2.1.5 If applicable, that there is no a priori hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	Yes	No	N/A	Section Number
3.1 Is the study design described? (e.g., cohort, case-control, cross-sectional, other design)	☒	☐	☐	
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☐	☐	☒	
3.4 Does the protocol specify measure(s) of association? (e.g., risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	
3.5 Does the protocol describe the approach for the collection and reporting of AEs/adverse reactions? (e.g., AEs that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☒	☐	☐	
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	
4.2.2 Age and sex	☒	☐	☐	

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.3 Country of origin	☒	☐	☐	
4.2.4 Disease/indication	☒	☐	☐	
4.2.5 Duration of follow-up	☒	☐	☐	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria)	☒	☐	☐	

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g., operational details for defining and categorizing exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	
5.2 Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy, use of validation sub-study)	☒	☐	☐	
5.3 Is exposure categorized according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g., dose, duration)	☐	☐	☒	
5.5 Is exposure categorized based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	
6.3 Does the protocol address the validity of outcome measurement? (e.g., precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g., HRQoL, QALYs, DALYS, health care services utilization, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g., confounding by indication)	☒	☐	☐	
7.2 Does the protocol address selection bias? (e.g., healthy user/adherer bias)	☒	☐	☐	
7.3 Does the protocol address information bias? (e.g., misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	

Comments:

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g., collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	

Comments:

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	
9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	
9.1.3 Covariates and other characteristics?	☒	☐	☐	
9.2 Does the protocol describe the information available from the data source(s) on:	☐	☐	☐	
9.2.1 Exposure? (e.g., date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	
9.2.2 Outcomes? (e.g., date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	
9.2.3 Covariates and other characteristics? (e.g., age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	
9.3 Is a coding system described for:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.1 Exposure? (e.g., WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g., International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g., based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	
10.3 Are descriptive analyses included?	☒	☐	☐	
10.4 Are stratified analyses included?	☒	☐	☐	
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☐	☒	
11.2 Are methods of quality assurance described?	☒	☐	☐	
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	
12.1.2 Information bias?	☒	☐	☐	
12.1.3 Residual/unmeasured confounding? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	
12.2 Does the protocol discuss study feasibility? (e.g., study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☐	☒	

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☐	☐	☒	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☐	☐	☒	

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g., to regulatory authorities)?	☒	☐	☐	
15.2 Are plans described for disseminating study results externally, including publication?	☐	☐	☒	

Comments:

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Reason for signing: Approved	Name: PPD Role: Author Date of signature: 21-Feb-2024 10:48:41 GMT+0000

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 22-Feb-2024 08:19:00 GMT+0000

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