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NON-INTERVENTIONAL STUDY REPORT

TITLE PAGE

Division: Research and Development

Information Type: Non-Interventional Study Report

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:	01 March 2024
Subject:	Infection, vaccines, premalignant lesions, cancer.
Authors:	PPD
Indication Studied:	Prevention of 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
Date of last version of protocol	05 February 2024
EU PAS (ENCEPP) register number	EUPAS1000000026
Active substance	Human papillomavirus vaccine [types 16, 18] ATC code: J07BM02
Medicinal product	CERVARIX human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed).
Product reference	EU/1/07/419/001-012
Procedure number	EMEA/H/C/000721
Marketing authorization holder	GlaxoSmithKline Biologicals S.A.
Joint PASS	No
Research question and objectives	Evaluate efficacy/effectiveness of CERVARIX against grade 3 cervical intraepithelial neoplasia or worse (CIN3+). • To conduct a systematic literature review of the long-term efficacy/effectiveness of CERVARIX on cervical cancer and CIN3 or worse (CIN3+). • 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), and study design.
Country(-ies) of study	NA.

Author	PPD, Sr Epidemiology Lead, Epidemiology (VEO).

MARKETING AUTHORISATION HOLDER(S)

Marketing authorization holder(s)	GlaxoSmithKline Biologicals S.A, Rue De L'institut 89; B-1330, Rixensart, Belgium.
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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
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Date (DD Month YYYY)

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

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LIST OF ABBREVIATIONS

AEs	Adverse events
AIC	Akaike information criterion
AIN	Anal intraepithelial neoplasia
AIN1	Anal intraepithelial neoplasia grade 1
AIN2	Anal intraepithelial neoplasia grade 2
AIN3	Anal intraepithelial neoplasia grade 3
AIS	Adenocarcinoma in situ
Al(OH)3	Aluminium hydroxide
ASO4	Adjuvant with aluminium hydroxide and 3-O-desacyl-4'-monophosphoryl lipid A.
ATC	Anatomical therapeutic chemical
ATP-E	According-to-protocol for efficacy cohort
PPD	
CENTRAL	Central register for clinical trials
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
CIN3	Cervical intraepithelial neoplasia grade 3
CIN3+	Cervical intraepithelial neoplasia grade 3 or worse
CVT	Costa Rica Vaccine Trial
PPD	
DNA	Deoxyribonucleic acid
EMBASE	Excerpta medica database
EMEA	Europe, Middle East, and Africa
EU	European Union

EU PAS	European Union electronic Register of Post-Authorization
FCR	Finnish Cancer Registry
GSK	GlaxoSmithKline Biologicals SA
HAV	Hepatitis A virus
HPV	Human papillomavirus
HR HPV	High-risk human papillomavirus
HSIL	High-grade squamous intraepithelial lesion
IRB	Institutional review board
IRR	Incident relative risk (or risk ratio)
LEEP	Loop electrosurgical excision procedure
LR HPV	Low-risk human papillomavirus
LSIL	Low-grade squamous intraepithelial lesion
MeSH	Medical subject headings
mITT	Modified intention to treat
PPD	
MPL	3-O-desacyl-4’-monophosphoryl lipid A
NA	Not applicable
NIP	National immunization program
PPD	
Pap test	Papanicolaou test
PASS	Post-authorization safety study
PICO	Population, intervention, comparison and outcome.
PPV	Positive predictive value
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
RCT	Randomized controlled trial

REML	Restricted maximum likelihood
RoB2	Risk of bias 2 tool
ROBINS-I	Risk of bias in non-randomized studies - of interventions
RR	Relative risk (or risk ratio)
SCC	Squamous cell carcinoma
SIL	Squamous intraepithelial lesion
SmPC	Summary of product characteristics
TVC	Total vaccinated cohort
UK	United Kingdom
US	United States
VE	Vaccine effectiveness
VLPs	Virus-like particles
Vs.	Versus
WHO	World Health Organization

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1. RESPONSIBLE PARTIES

NA.

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.

Keywords

Human papillomavirus (HPV), cancer, Cervical Intraepithelial Neoplasia Grade 3 (CIN3+), vaccine, efficacy, effectiveness.

Rationale and background

CERVARIX is composed of recombinant C-terminally truncated HPV-16 L1 and HPV-18 L1 proteins, assembled into Virus-like particles (VLPs) adjuvanted with the GSK proprietary adjuvant AS04.

Long-term efficacy and immunogenicity information is already part of CERVARIX´s label. However, as National Immunization Program (NIP) 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 compiling all published evidence and given that the new available data have not been generated by GlaxoSmithKline Biologicals SA (GSK), a systematic literature review and meta-analysis/meta-regression analysis was conducted, including critical appraisal of the data to assess its quality, and robustness.

Research questions and objectives

Research question: What is the efficacy/effectiveness of the (HPV) vaccination with CERVARIX in girls and women against HPV on (CIN3) or worse (CIN3+)?

Objectives:

- To conduct a systematic literature review of the long-term efficacy/effectiveness of CERVARIX on cervical cancer and CIN3 or worse (CIN3+).
- 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), and study design.

Study design:

Systematic literature review and meta-analysis/meta-regression analysis.

Setting:

See “Variables and data sources”.

Participants and study size:

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 and data sources:

Outcome:

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

Endpoints:

CIN3, CIN3+, Adenocarcinoma in situ (AIS), invasive cervical cancer.

Covariates to be considered in the meta-regression analysis:

- TVC (total vaccinated cohort) /TVC naïve: This is a binary variable and reflects whether the analytical cohort was the TVC (irrespective of the baseline HPV status) or the TVC 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 modeled as a continuous variable.
- 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 Human Papillomavirus [HR HPV] types). For the purpose of this study, the meta-analysis and meta-regression analysis were planned to answer research questions that entailed two scenarios concerning HPV type: “HPV 16/18” or “Irrespective of HPV type”.
- Study design: This variable has two values: Randomized controlled trial (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 studies for vaccine efficacy and vaccine effectiveness [VE], 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, Excerpta medica Database (EMBASE), Scopus, and Cochrane Central Register for Clinical Trials (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).

Results

After in-depth assessment of the selected papers for the full-text review, 9 papers were determined to remain in the study [Wheeler, 2012; Lehtinen, 2012; Konno, 2014; Lehtinen, 2017; Palmer, 2019; Porras, 2020; Falcaro, 2021; Rebolj, 2022; Shing, 2022]. Of them, 5 papers corresponded to RCTs [Wheeler, 2012; Lehtinen, 2012; Konno, 2014; Porras, 2020; Shing, 2022]. The papers by Porras et al. and Shing et al. had also an observational component (up to 11 years of follow-up of the original RCT, replacing the comparator arm by a control arm of unvaccinated participants). The study by Lehtinen et al was a ten-year follow-up observational study. The papers by Palmer et al., Falcaro et al., and Rebolj et al, reported on national surveillance data of the CERVARIX national implementation program (retrospective population-based register linked studies) in Scotland and England [Lehtinen, 2017; Palmer, 2019; Porras, 2020; Falcaro, 2021; Shing, 2022; Rebolj, 2022].

Results from this systematic review and quantitative synthesis have shown that CERVARIX is an efficacious vaccine in preventing advanced cervical premalignant lesions and cervical cancer in adolescent girls and women vaccinated at 12- 25 years.

This statement holds true across different study types, whether follow-up of RCTs or real-world observational studies, or combinations of both types of studies, the pooled vaccine effects (unadjusted for covariates) ranged from 48% to 78%, regardless of HPV deoxyribonucleic acid (DNA) classification.

Furthermore, we evaluated covariate adjusted vaccine effects by performing meta-regression analysis. We identified strong predictors. Vaccine effects were higher in younger age at first vaccination of the participants, in the TVC naïve population (HPV negative at baseline) compared to the TVC (irrespective of the HPV baseline status), and the shorter the time since vaccination (time of follow-up). Results of CERVARIX´s long-term effects (either from RCTs, or observational studies, or both designs combined) against CIN3+ caused by HPV 16/18 types or by any HPV type were consistent across all the analyses.

These identified covariates explained an important part of the heterogeneity in efficacy/effectiveness leading to good predictions relevant for decision-making.

Discussion

Results from this systematic review and quantitative synthesis have shown that CERVARIX is an efficacious and effective vaccine in preventing advanced cervical premalignant lesions and cervical cancer in adolescent girls and women vaccinated at 12 to 25 years.

This statement holds true across different study types, whether follow-up of RCTs or real-world observational studies, or combinations of both types of studies, the pooled vaccine effects ranged from 48% to 78%, regardless of HPV type.

High efficacy of CERVARIX had already been observed against CIN3+ (93% [95%CI, 79-99]) in initial clinical trials with three doses of the vaccine among HPV naïve women, irrespective of HPV type [Hildesheim, 2014]. However, this is the first time that long-term effects against CIN3+ and cervical cancer are evaluated, including real-world data.

In this systematic review and meta-regression analysis, the greatest CERVARIX effects (either vaccine efficacy or effectiveness) were found in the youngest age groups assessed, with many of the studies showing decreased vaccine effects among recipients who initiated vaccination at a later age. These greater vaccine effects of CERVARIX at younger age are most likely due to the administration of the vaccine before the exposure to HPV as the current paradigm for HPV acquisition is sexual activity. In this respect, larger vaccine effects were found in studies when the analytical cohort included participants who were HPV DNA negative at enrolment (TVC naïve), confirming findings from pivotal clinical trials that demonstrated higher efficacy when the vaccine was administered before exposure to HPV. This was also evident in the population-based studies (i.e., Palmer et al) where participants vaccinated at 17 years were more than three times as likely to be diagnosed with CIN3+ than those vaccinated at 12-13 years [Palmer, 2019].

This systematic review has also uncovered long-term broad protection of CERVARIX against CIN3+ caused by non-vaccine types, both from follow-up studies of RCTs and observational studies.

Our analysis estimated consistent CERVARIX vaccine effects in 4-year follow-ups of clinical trials, and up to over 10-11 years in observational and population-based studies, showcasing the translation of the observed long-term immunogenicity to long standing vaccine effects against advanced cervical premalignant lesions and cervical cancer, to the point that cervical cancer was drastically reduced and almost disappeared after the CERVARIX NIP implementation in some settings [Falcaro, 2021; Rebolj, 2022]. Furthermore, long-term seropositivity seems to be higher when the vaccine is given at younger age compared to older age groups, particularly those aged 25 years or older [Schwarz, 2017]. Nevertheless, our meta-regression analysis unveiled that age at

vaccination was impactful on VE when pooling data from observational studies, irrespective of the HPV type.

It has been postulated that the broad immunity observed after CERVARIX vaccination (including cross-protection), and the lesser HPV 18 L1-specific antibody waning compared to Gardasil and Gardasil 9 may be attributable to the adjuvant. The aluminium hydroxide and 3-O-desacyl-4'-monophosphoryl lipid A (AS04) adjuvant has shown to enhance the antigen-specific T cell response, cytokine release, and consequently, B cell response and antibodies, by activating antigen-presenting cells. Several studies pointed to the adjuvants capacity to induce a more effective affinity maturation of antibodies [Roy, 2023].

VE studies are instrumental to comprehend how vaccines perform in real settings. VE is affected by vaccine efficacy, specific vaccination policies and real-world conditions of administration, and population-level vaccine coverage. Variations in policies respect to recommendations in terms of age at vaccination has undoubtedly an impact on VE. This systematic review and meta-regression analysis have demonstrated that CERVARIX is more effective when administered at younger ages. Overall, these findings may raise awareness for policy- makers and the wider community to initiating HPV vaccination at the youngest recommended age with the confidence that it will evoke a more effective and long-lasting response.

Future research is warranted to understand the impact of CERVARIX on other population groups (i.e., men), and long-term effects on additional HPV-related premalignant lesions and cancers. Methodologically, the importance of controlling for confounding by factors interrelated to vaccination and outcomes (i.e., sexual activity) has proven important.

Conclusions

The results of this study provide strong evidence of CERVARIX confers long-term protection to prevent HPV-related advanced cervical premalignant lesions (CIN3, AIS, CIN3+) and cervical cancer, both in controlled environments (i.e., RCTs), but also in real-world settings. Moreover, these vaccine effects have shown to be larger among populations that were HPV naïve at the time of vaccination, and subsequently, the younger the age at first vaccination. CERVARIX effectiveness against cervical cancer endpoints was particularly high when implemented in nationwide immunization programs with elevated routine vaccination coverage and catch-up campaigns including multiple age cohorts. The policy implications of these findings, reinforcing an early and extensive HPV vaccination, hold promise for attaining the World Health Organization (WHO) goals for cervical cancer elimination [World Health Organization, 2020].

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Marketing authorization holder

GlaxoSmithKline Biologicals S.A.

Names and affiliations of principal investigators

NA.

3. AMENDMENTS AND UPDATES

None.

4. MILESTONES

Milestone	Planned date	Actual date
Start of data collection	21 June 2022	21 June 2022
End of data collection	21 June 2022	21 June 2022
Final report of study results	15 February 2024*	01 March 2024

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

5. RATIONALE AND BACKGROUND

5.1. HPV-RELATED ANOGENITAL DISEASE

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 HR HPV types enhances the risk for oncogenic progression and can result in invasive cancer [Della Fera, 2021]. 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.

HR 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 HR 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 HR HPVs [Bruni, 2023].

Within the HR HPV types, there is a wide variation in the prevalence of infection and association with different grades of lesions. Both HPV 16 and HPV 18 types rise in prevalence as lesion severity increases from LSIL, HSIL including CIN to SCC [Clifford, 2005; Tjalma, 2013]. HPV 16 and HPV 18 infections and cervical lesions tend to progress more rapidly to cervical cancer in comparison to other HR 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 program 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].

Anal HPV infection may result in anal lesions and cancer. Approximately 88% of the cases are associated with HPV infection worldwide [Alemany, 2015]. In 2020, worldwide, approximately 50 900 new cases and around 19 300 deaths were reported annually. The incidence seems to be increasing in more developed regions [Bray, 2018; Bruni, 2023;]. HPV 16 is the most common type detected (73% of all HPV-positive tumours) followed by HPV-18 (approximately 5% of cases). HPV DNA is also detected in most precancerous anal lesions AIN; 91.5% in AIN1 and 93.9% in AIN2/AIN3). In affluent countries, the incidence is highest among women compared to men [De Vuyst, 2009; de Martel, 2020; Bruni, 2023].

Other anogenital HPV-related cancers include cancers of the vulva and the vagina in women and penile cancer in men, accounting for a global crude incidence of 1.17, and 0.46 per 100 000 women per year, and 0.92 per 100 000 men per year, respectively [Bruni, 2023]. 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. It is today well established that HPV is associated with a proportion of head and neck cancers along with tobacco and alcohol, and in particular with oropharyngeal cancer. Current evidence suggests that HPV 16 is the most frequent type that is associated with tonsil cancer (including Waldeyer ring cancer), base of tongue cancer and other oropharyngeal cancer sites [Chaturvedi, 2018; Haeggblom, 2019; Ndiaye, 2014]. Early stages of the disease (precursor lesions) are not easily detected as there is no equivalent to the Pap test; a biopsy is required to confirm the cases [Näsman, 2020].

The LR HPV types 6 and 11 cause 90% of genital warts and some low-grade CIN. Among the non-cancerous HPV-associated preventable conditions, besides genital warts there is also recurrent respiratory papillomatosis unequivocally linked to HPV 6 and 11.

Because sexual activity constitutes the current paradigm for HR HPV acquisition, prophylactic vaccination is recommended before the sexual debut, in some countries as early as 9 years of age [Meites, 2016]. As HR HPV infection has also been associated to anogenital warts and several cancer types in men (i.e., oropharyngeal, penile, and anal cancer [Bruni, 2023], and more recently to prostate cancer [Lawson, 2020], gender-neutral HPV vaccination [Vänskä, 2020], has been introduced in several countries throughout the world.

WHO has set up the first global health strategy for the elimination of cervical cancer as a public health problem. Part of the strategic actions is to achieve by 2030, 90% of girls fully vaccinated with an HPV vaccine by the age of 15 years [World Health Organization, 2020].

5.2. PROJECT 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.

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 aluminium 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” for use from the age of 9 years.

Long-term efficacy and immunogenicity information is already part of CERVARIX´s label. However, as NIP 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 compiling all published evidence and given that the new available data have not been generated by GSK, a systematic literature review and meta-analysis/meta-regression analysis have been conducted, including critical appraisal of the data to assess its quality, and robustness.

6. RESEARCH QUESTION AND OBJECTIVES

6.1. RESEARCH QUESTION

What is the efficacy/effectiveness of the HPV vaccination with CERVARIX in girls and women against HPV on cervical cancer and CIN3 or worse (CIN3+)?

To address the literature search, the following PICO strategy was established:

Population*:* Vaccine eligible females among the general population.

Intervention: HPV vaccination with the bivalent HPV vaccine (CERVARIX).

Comparator: Not applicable. Note: This study did not compare vaccine efficacy/effectiveness of CERVARIX with other products. However, 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.

However, when vaccine efficacy or effectiveness results were not available in the selected papers but a measure of effect was provided instead, VE was determined (including 95% CI) from the relevant measure of effect: i.e., Odds Ratio, 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]. Hence, depending on the reported measure of effect, VE was calculated as VE=(1-odds ratio)*100 , or VE=(1-IRR)*100.

6.2. OBJECTIVES

To conduct a systematic literature review on the long-term efficacy/effectiveness of CERVARIX on cervical cancer and CIN3 or worse (CIN3+).

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), and study design.

The analysis has been designed to respond to the following questions:

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

7. RESEARCH METHODS

7.1. Study Design

This study has been conceived as a systematic review to mainly collect non-GSK data stemming 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. The aim was to analyze these data in a systematic and synthetic manner.

Selected RCTs in this systematic literature review had an intervention arm giving CERVARIX and an active comparator arm. In each of them, the comparator was a hepatitis A vaccine, provided by GSK (HAVRIX based investigational formulation) in case of studies by Lehtinen et al., (PATRICIA Vaccine Trial) [Lehtinen, 2012], and Shing et al., [Shing, 2022]and Porras et al., (CVT)[Porras, 2020]. In Konno, 2014, the Japan-licensed HAV (Aimmugen; The Chem-Sero-Therapeutic Research Institute, Kumamoto, Japan) was the control vaccine in the Japanese trial. 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 [Konno, 2014].

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

The objective of the present study is to determine efficacy/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/Participants and Setting

7.2.1. 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 RCT (efficacy), or unvaccinated participants in case of observational/population-based surveillance/longitudinal studies (effectiveness).

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

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

7.2.2. Inclusion criteria

All studies that meet the following criteria were included:

- Report CERVARIX efficacy (RCTs) or effectiveness (observational studies) against cervical cancer and/or CIN3 or worse (CIN3+).
- 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 CERVARIX.
- Journal articles published between 1 January 2000 to 21 June 2022. Databases: PubMed, EMBASE, Scopus, and Cochrane CENTRAL were consulted.
- It included RCTs and observational studies (cohort, cross-sectional, case-control, longitudinal, population-based surveillance).
- Restricted to journal articles with abstract in the following languages: English, French, Spanish, Portuguese, German, and Italian.

7.2.3. Exclusion criteria

Systematic reviews, reviews, modeling, 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

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

Endpoints*:* CIN3, CIN3+, AIS, invasive cervical cancer. Based on the number of reports on cervical endpoints, a decision was made to focus on CIN3+ for the quantitative synthesis.

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., HPV 16/18) 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 was created (i.e., study correlation) to address this aspect.

- TVC/TVC naïve: This is a binary variable and reflects whether the analytical cohort was the TVC (irrespective of the baseline HPV status) or the TVC naïve (HPV negative at baseline).
- Age at first vaccination: This variable represents the age at which the participant received the first vaccine dose. Age was modeled as a continuous variable.
- 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 analysis were planned to answer research questions that entailed two scenarios concerning HPV type: “HPV 16/18” or “Irrespective of HPV type”.
- Study design: This variable had 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 studies 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 (RCTs and Observational studies for vaccine efficacy and VE, respectively) or combinations of both.

7.4. Data Sources

7.4.1. Search terms

The literature search was based on the following concepts articulating different search terms:

Concept 1

“papillomavirus vaccine”, “papillomavirus vaccination”, “HPV vaccine”, “HPV vaccination”, “CERVARIX”, “bivalent human papillomavirus vaccine”.

Concept 2

“program* evaluation”, “population surveillance”, “sentinel surveillance”, “vaccine effectiveness”, “vaccine efficacy”.

Concept 3

"high-grade cervical intraepithelial neoplasia", "cervical intraepithelial neoplasia grade 3", "high-grade CIN", "cervical severe dysplasia", "cervical severe dyskaryosis", "cervical carcinoma in-situ" "uterine cervical neoplasm", "CIN 3", "cervical invasive carcinoma", "high-grade squamous intraepithelial lesion", "HSIL".

Included MeSH and Emtree terms when available. Hand-search of references of relevant papers were also performed.

Note: Asterisk (*) is a truncation symbol to broaden results in the selected databases that allows to look for variations of words. They can be used in a keyword search to retrieve alternate word endings (i.e., program* will retrieve "program", "programs", "programme", "programmes", etc).

Table 1 Search terms for the different databases

Keyword	MeSH (PubMed)	Emtree (EMBASE)	Scopus
papillomavirus vaccine	"Papillomavirus Vaccines"[Mesh]	Human papilloma virus vaccine'/exp	papillomavirus vaccine
papillomavirus vaccination	No MeSH term	No Emtree term	papillomavirus vaccination
HPV vaccine	"Papillomavirus Vaccines"[Mesh]	No Emtree term	HPV vaccine
HPV vaccination	"Papillomavirus Vaccines"[Mesh]	'hpv vaccination'/exp	HPV vaccination
CERVARIX	No MeSH term	No Emtree term	CERVARIX
bivalent human papillomavirus vaccine	No MeSH term	'bivalent human papillomavirus vaccine'	"bivalent human papillomavirus vaccine"
program* evaluation	"Program Evaluation"[Mesh]	'program evaluation'/exp	"program* evaluation"
population surveillance	"Population Surveillance"[Mesh]	'population surveillance'/exp	"population surveillance"
sentinel surveillance	"Sentinel Surveillance"[Mesh]	'sentinel surveillance'/exp	"sentinel surveillance"
vaccine efficacy	"Vaccine Efficacy"[Mesh]	'vaccine efficacy'	"vaccine efficacy"
vaccine effectiveness	"Vaccine Efficacy"[Mesh]	'vaccine effectiveness'/exp	"vaccine effectiveness"
cervical intraepithelial neoplasia grade 3	"Cervical Intraepithelial Neoplasia"[Mesh] "Uterine Cervical Neoplasms"[Mesh]	'cervical intraepitelial neoplasia 3'/exp	cervical intraepithelial neoplasia
cervical severe dysplasia	"Cervical Intraepithelial Neoplasia"[Mesh] "Uterine Cervical Dysplasia"[Mesh]	'uterine cervix dysplasia'/exp	cervical dysplasia
cervical severe dyskariosis	"Cervical Intraepithelial Neoplasia"[Mesh]	No Emtree term	cervical severe dyskariosis
uterine cervical neoplasm	"Uterine Cervical Neoplasms"[Mesh]	'uterine cervix cancer'/exp	uterine cervical neoplasm
uterine cervical carcinoma	No MeSH term	uterine cervical carcinoma	uterine cervix carcinoma
high-grade CIN	No MeSH term	No Emtree term	high-grade CIN
high-grade squamous intraepithelial lesion	"Squamous Intraepithelial Lesions"[Mesh]	'high grade squamous intraepithelial lesion of the cervix'/exp	high-grade squamous intraepithelial lesion
high-grade cervical intraepithelial neoplasia	No MeSH term	'uterine cervix carcinoma in situ'/exp	high-grade cervical intraepithelial neoplasia
cervical carcinoma in-situ	"Cervical Intraepithelial Neoplasia"[Mesh]	'uterine cervix carcinoma in situ'/exp	cervical carcinoma in-situ
CIN 3	"Cervical Intraepithelial Neoplasia"[Mesh]	No Emtree term	CIN 3
cervical invasive carcinoma/cancer	No MeSH term	'uterine cervix cancer'/exp	cervical invasive carcinoma/cancer
HSIL	"Cervical Intraepithelial Neoplasia"[Mesh]	No Emtree term	HSIL

Abbreviations: CIN 3= Cervical intraepithelial neoplasia grade 3, EMBASE= Excerpta medica database, HSIL= High-grade squamous intraepithelial lesion, HPV= Human papillomavirus.

7.4.2. Search strategy

Pubmed

"Papillomavirus Vaccines" [mesh] OR "papilloma virus vaccin*"[tw] OR "papillomavirus vaccin*"[tw] OR "hpv vaccin*"[tw] OR CERVARIX[tw] **AND** (vaccine[tw] AND (efficacy[tw] OR effectiveness[tw])) OR ("program* evaluation*"[tw] OR "Program Evaluation"[Mesh] OR "population surveillance"[tw] OR "Population Surveillance"[Mesh] OR "sentinel surveillance"[tw] OR "Sentinel Surveillance"[Mesh] OR "Vaccine Efficacy"[mesh]) **AND** "Uterine cervical dysplasia"[mesh] OR "Squamous intraepithelial lesions"[mesh] OR "Cervical intraepithelial neoplasia"[mesh] OR "Uterine cervical neoplasms"[mesh] OR "uterine cervical carcinoma*"[tw] OR "uterine cervix carcinoma*"[tw] OR "cervical invasive carcinoma"[tw] OR "cervical invasive cancer"[tw] OR "high-grade CIN"[tw] OR "cervical intraepithelial neoplas*"[tw] OR "CIN 3"[tw] OR "HSIL"[tw] OR ((cervical[tw] OR cervical[tw]) AND (dysplasia*[tw] OR dyskaryosis[tw])) **AND** (Humans[mesh] OR human*[tw]) **NOT** review[Publication Type] **AND** (“2000/01/01”[Date - Publication]:”2022/06/22”[Date - Publication]).

Filters:

- Humans.
- from 01/01/2000 to 21/06/2022.
- Not conference abstract, conference paper, or review.

EMBASE

(('wart virus vaccin*' OR 'papillomavirus vaccin*' OR 'papilloma virus vaccin*' OR 'hpv vaccin*' OR CERVARIX):ti,ab,kw OR 'hpv vaccination'/exp OR ' Human papilloma virus vaccine'/exp) **AND** 'vaccine effectiveness'/exp OR 'drug efficacy'/exp OR 'sentinel surveillance'/exp OR 'program evaluation'/exp OR 'population surveillance'/exp OR 'program* evaluation':ti,ab,kw OR ((population NEAR/5 surveillance):ti,ab,kw) OR 'sentinel surveillance':ti,ab,kw OR ((vaccine NEAR/5 efficacy):ti,ab,kw) **AND** 'cervical intraepithelial neoplasia 3'/exp OR 'uterine cervix dysplasia'/exp OR 'uterine cervix tumor'/exp OR 'uterine cervix cancer'/exp OR 'high grade squamous intraepithelial lesion of the cervix'/exp OR 'uterine cervix carcinoma in situ'/exp OR ('uterine cervix carcinoma*' OR 'high-grade CIN' OR 'CIN 3' OR 'HSIL' OR cervical near/3 dysplasia* OR cervix near/3 dysplasia* OR 'cervical severe dyskariosis'):ti,ab,kw **AND** [humans]/lim NOT 'conference abstract'/it OR 'conference paper'/it OR 'review'/it **AND** [01-05-2000]/sd NOT [22-06-2022]/sd.

Filters:

- Humans.
- From 01/01/2000 to 21/06/2022.
- Not conference abstract, conference paper, or review.

Scopus

((((TITLE-ABS-KEY (("wart virus vaccin*" OR "papillomavirus vaccin*" OR "papilloma virus vaccin*" OR "hpv vaccin*" OR CERVARIX) AND ((vaccine or program*)w/5 (efficacy OR effectiveness or impact)) OR ("population surveillance" OR "sentinel surveillance") AND (("cervical intraepithelial neoplasia" w/2 3) or ("uterine cervi*" w/1 (carcinoma* or neoplasm*)) or "high-grade CIN" or "CIN 3" or "high-grade squamous intraepithelial lesion*" or "HSIL" or ((cervical or cervical) w/2 (dysplasia* or dyskaryosis or "invasive carcinoma")))))) AND (TITLE-ABS-KEY ((human*)))) AND NOT (((DOCTYPE (re) OR DOCTYPE (cp)))) AND (PUBYEAR > 1999).

Filters:

- Title, Abstract, Keywords.
- Humans.
- From 01/01/2000 to 21/06/2022.
- Not conference abstract, conference paper, or review.

Cochrane CENTRAL

(CERVARIX): ti,ab,kw OR (bivalent human papillomavirus vaccine):ti,ab,kw

Filters:

- Content type: Trials.
- Cochrane Library publication date: Between Jan 2000 and Jun 2022.
- CENTRAL Trials only original publication year: All years.
- Search word variations.

7.4.3. Data collection and extraction

Search strategy and search strings were reviewed by the Medical Librarian at GSK. A reviewer searched in the databases. Endnote® was used as reference manager tool and Microsoft Excel® was the software selected for references export and data extraction. References retrieved from each database were exported via Excel to Endnote® where the duplicates were removed. Single papers were exported back to Excel and the first screening of titles and abstracts took place, including reasons for exclusion. Title and abstracts were screened by one reviewer PPD and selected full-text reports were screened by two independent reviewers PPD also highlighting the reasons for exclusion. Disagreements were resolved by a third reviewer PPD. When several papers referred to the same population (even partially) and scope, the most recent paper was selected.

Two independent reviewers extracted the data PPD, and the extracted data were cross-checked and confirmed. Discrepancies were resolved by consensus discussion and there were no final disagreements.

Data extraction focused on the following fields and variables:

- Reference: First author, title of the paper, publication year, inclusion/exclusion criteria used for participants to the study.
- Methods: Country of the study, study period, study design, study objectives, setting, study population (criteria), age range/group, number of doses, vaccine coverage, endpoint.
- Vaccine efficacy/effectiveness/Impact or Measure of effect: Number of vaccinated, number of unvaccinated (or control), time points of analysis (time of follow-up since vaccination), outcome ((vaccine effect/Effect %), odds ratio, IRR), 95%CI (upper and lower bounds), p value, diagnostic method/cytology/histopathology, odds ratio (first dose, second dose, third dose), vaccine efficacy/effectiveness (first dose, second dose, third dose).
- Funding (declared for the study).
- Other vaccine effects.
- Comments to quality.
- CIN3+ definition.
- Comments 2 (any other comment).

7.5. Bias

7.5.1. Inter-rater reliability. Cohen´s kappa coefficient calculation

Studies that determine the agreement between two or more observers usually include a statistic to account for bias due to subjectivity in the interpretation by the observers, as these may agree or disagree only by chance [Viera, 2005]. Inter-reviewer agreement (inter-rater reliability) denotes the degree of agreement when a measurement is repeated under identical conditions by different raters. It was determined using the Cohen´s kappa coefficient. The Cohen´s kappa statistic measures inter-rater reliability (also called interobserver agreement) and has the assumption that raters are deliberately chosen, as this is the case of the present study where two reviewers PPD assessed which papers remained in the study after full-text review (see Table 12 in Section 11). However, the kappa coefficient does not differentiate the various types or sources of disagreement.

The results were as follows:
Simple kappa coefficient=82.3% (95%CI, 63.1-100).
Interpretation: Near perfect agreement.

Note: The Kappa statistic varies from 0 to 1, where:
0 = agreement equivalent to chance
0.1 – 0.20 = slight agreement.
0.21 – 0.40 = fair agreement.
0.41 – 0.60 = moderate agreement.
0.61 – 0.80 = substantial agreement.
0.81 – 0.99 = near perfect agreement
1 = perfect agreement.

7.5.2. Potential sources of bias

Expected sources of bias for observational studies are:

- **Selection bias:** Selection of participants could be influenced by participants' characteristics or outcome (i.e., if the unvaccinated arm presents differences in the characteristics and/or age compared to 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. See Section 7.8.

7.5.3. Confounders and effect modifiers

Post hoc studies of clinical trials and observational and longitudinal studies stemming from surveillance of NIP 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 (including race/ethnicity).

Some of these variables are well known effect modifiers. For instance, the younger the participant, the higher is the VE and the vaccine has proved 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 VE 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 VE by establishing a different risk of detecting premalignant lesions and cancer between the participants [Glasziou, 2022]. For example, if unvaccinated participants are half as likely to get screened than the more health-conscious vaccinated ones, VE 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 smear test or biopsy at the first year of screening, the most severe result 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.

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.

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

7.5.4. 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 10 to ensure sound statistical power [Higgins, 2022; Jordan, 2019]. However, the number of studies to be potentially included in this assessment (7 papers) is below 10. Therefore, this analysis was not conducted.

7.6. Study Size

This section was NA. This study was not conceived as a confirmatory study. There was not a prior hypothesis to test and therefore it was not necessary to establish a sample size that had sufficient power to reject the null hypothesis. However, since two of the selected

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 analyses results is expected to be sufficient.

The cohort sizes for the different studies included in the meta-regression analyses and the correspondent vaccine effect estimates and precision intervals are presented in Table 9.

7.7. Data Analysis

After in-depth assessment of the selected papers for the full-text review, 9 papers were determined to remain in the study [Wheeler, 2012; Lehtinen, 2012; Konno, 2014; Lehtinen, 2017; Palmer, 2019; Porras, 2020; Falcaro, 2021; Rebolj, 2022; Shing, 2022]. Of them, 5 papers corresponded to RCTs [Wheeler, 2012; Lehtinen, 2012; Konno, 2014; Porras, 2020; Shing, 2022]. The papers by Porras et al, and Shing et al, had also an observational component (up to 11 years of follow-up of the original RCT, replacing the comparator arm by a control arm of unvaccinated participants). The study by Lehtinen, 2017 was a ten-year follow-up observational study. The papers by Palmer et al, Falcaro et al, and Rebolj et al, reported on national surveillance data of the CERVARIX national implementation program (retrospective population-based register linked studies) in Scotland and England [Lehtinen, 2017; Palmer, 2019; Porras, 2020; Falcaro, 2021; Shing, 2022; Rebolj, 2022].

A detailed examination of the different parameters of the study was carried out and a decision was made to pursue a quantitative synthesis of the long-term effects of CERVARIX on clinical endpoints (Table 2). In relation to the papers to be included in the statistical analysis, previous decisions were made:

1. To determine summary point estimates for RCTs and observational studies alone, and the combined effects of RCTs and observational data pooled together. This approach allowed a sensitivity analysis to explore variations in vaccine effects depending on the study design.
2. **Endpoint**: CIN3+ was the endpoint for the analysis, given that enough number of the selected papers reported on it. Information on other endpoints (i.e., CIN3, AIS, or invasive cervical cancer) were included in the qualitative synthesis as few papers reported on them.
3. **Outcome**: Vaccine efficacy/effectiveness as reported by the different studies. VE was calculated for Palmer, 2019 as (1-odds ratio)*100 (the measure of effect provided by the paper is odds ratio) [Palmer, 2019]. For Falcaro, 2021, VE is calculated as (1-IRR)*100 (the measure of effect provided by the paper is IRR) [Falcaro, 2021].
4. **Choice of the analytic cohort**: TVC cohort and TVC-naïve cohort. The TVC cohort is the cohort closest to the real world (regardless of their HPV baseline status and receiving at least one dose of the vaccine) and more relevant from the public health perspective. However, differences for vaccine efficacy/effectiveness between both cohorts are significant. Therefore, a decision was made to conduct meta-regression

analysis 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). Another analytic cohort in some studies was the ATP-E cohort that consisted of participants that received 3 doses of the vaccine and were HPV naïve at first vaccination. This analytical cohort was not considered for the quantitative synthesis for the reasons mentioned above.

5. **Number of doses of CERVARIX**: The groups vaccinated with "3 doses" and "At least 1 dose" from different studies were pooled together in the quantitative synthesis if at least 75% of the participants of the "At least 1 dose" group received 3 doses of the vaccine. This decision affects studies like Lehtinen et al, 2012 [Lehtinen, 2012] (86.4% of participants in the TVC received 3 doses of the vaccine), Lehtinen et al, 2017 [Lehtinen, 2017], (at least 75% of the participants received 3 doses of the vaccine), Konno et al, 2014 [Konno, 2014] (96.1% of the participants in the TVC received 3 doses of the vaccine), Palmer et al [Palmer, 2019] (91.7% of participants received 3 doses of the vaccine).
6. **Age at first vaccination**: The decision was to stratify by age in those studies with this data available to increase the number of units allowing a more robust model. For example, if the vaccine effects were reported for three age categories in a study, the three vaccine effects results were used in the meta-regression analysis.
7. **Time since vaccination**: Time from the analysis to vaccination or time of follow-up.
8. **HPV type:** Some papers reported on non-vaccine types. A decision was made to stratify effects by "vaccine types" (HPV 16/18) and "irrespective of HPV type". When studies reported vaccine effects based on histological diagnosis alone (i.e., Palmer, 2019) or against a composite index of 14 HR HPV types (considered the most relevant oncogenic types as up to 99% of cervical cancer is caused by these HR HPV types), it was considered that these studies reported the outcome "irrespective of HPV type".

An aspect to consider when conducting systematic reviews and aiming to a quantitative synthesis is heterogeneity. Heterogeneity is the variation in the true effect studied in systematic reviews. This variability is inherent to pooling together different studies and it is partly due to chance (random error), and partially owed to systematic differences between the studies (study design, different populations, different evaluation and measurement of outcomes, etc.) [Schroll, 2011]. Effect estimates can vary from study to study owed to real differences (between-study variability) and because of chance (within-study variability).

Heterogeneity among selected studies was expected to be large, given the differences in settings (e.g., time at first vaccination, time of follow-up, study design, etc.) and are known to influence vaccine efficacy/effectiveness but a decision was made to pursue a quantitative synthesis exercise. To take into account these factors in the calculation of global estimates, meta-regression analysis models were fitted. They provided summary point estimates for vaccine efficacy/effectiveness 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 is shown in the statistical outputs (ANNEX 2). If this heterogeneity is still large, it is discussed and acknowledged among the limitations of the study.

Meta-regression analysis 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 is 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 was the effect estimate (CERVARIX efficacy/effectiveness). The explanatory variables were 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, studies have been split in different sub-groups given the differences in terms of covariates. The correlations between the different sub-groups of a study were considered in all subsequent analyses.

Covariates considered in the meta-regression analysis:

- TVC/TVC naïve: This is a binary variable and reflects whether the analytical cohort was the TVC (irrespective of the baseline HPV status) or TVC naïve (HPV negative at baseline).
- Age at first vaccination: This variable represents the age at which the participant received the first vaccine dose. Age was modeled as a continuous variable. Non-linearity was 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 (For example, 14 HR HPV types). For the purpose of this study, the meta-analysis and meta-regression analysis were planned to answer research questions that entailed two scenarios concerning HPV type: "HPV 16/18" or "Irrespective of HPV type".
- Study design: This variable had 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 Observation studies for vaccine efficacy and VE, respectively) or combinations of both.

Table 2 Outcomes and endpoints of the selected studies

Author, Year	Endpoint	HPV type	Time since vaccination (y)	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, AIS, or invasive carcinoma
Lehtinen, 2012	CIN3+ AIS	HPV16 HPV18 HPV 16/18 Irrespective of HPV type	4	CIN3, AIS, 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 or worse
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	CIN 3 or worse

Author, Year	Endpoint	HPV type	Time since vaccination (y)	CIN3+ definition
Palmer, 2019	CIN3+	Histological diagnosis (no HPV testing results)	2 3 4 5 6 7-8	CIN3 or worse (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 HR-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: AIS= Adenocarcinoma in situ, CIN3= Cervical intraepithelial neoplasia grade 3, CIN3+= Cervical intraepithelial neoplasia grade 3 or worse, FCR= Finnish cancer registry, HPV= Human papillomavirus.HR HPV= High-risk human papillomavirus, NA= Not applicable, y=Years.

7.7.1. Primary Analysis

7.7.1.1. Main Analytical approach

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

- First a meta-analysis was fitted (using the rma.mv function from R software using a REML estimation procedure allowing for Random Effect) without adjusting for covariates.
- Univariate meta-regression analyses (with Random Effect) were fitted to assess the impact of each covariate independently.
- A multiparametric meta-regression analysis (with Random Effect and REML) was then considered. Covariate selection for this model was performed via an R function called multimodal inference which is examining the predictor combination providing the best fit (AIC to measure the goodness of fit of the models was applied). Multiparametric meta-regression analysis 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 was used to assess the predictiveness of the models for every given dataset allowing a data-driven selection of the best model. One model was selected for each of the 6 questions assessed:

Analysis 1

- What is the combined efficacy/effectiveness of CERVARIX on CIN3+ caused by vaccine HPV types? (RCTs and Observational studies combined).

Analysis 2

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

Analysis 3

- What is the efficacy of CERVARIX on CIN3+ caused by vaccine HPV types? (RCTs only).

Analysis 4

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

Analysis 5

- What is the efficacy of CERVARIX on CIN3+ caused by any HPV type? (RCTs only).

Analysis 6

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

7.7.1.2. Data handling conventions/data transformations

NA

7.7.1.3. Sensitivity analyses

As described in Section 7.7, the analysis was 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 multiparametric models were considered.

7.7.2. Secondary analysis/Exploratory analysis

NA.

7.7.3. Amendments to statistical plan

NA.

7.8. Quality Control and Quality Assurance

The risk of bias of the systematic literature review was assessed by two different tools:

- Cochrane risk of bias for RCTs (RoB2) [The Cochrane Collaboration, 2022a].
- Cochrane ROBINS-I tool for observational epidemiological studies, specifically designed for use in systematic reviews [Sterne, 2016; The Cochrane Collaboration, 2022b].

Every report was assessed using the relevant tool. For those papers that reported both on RCTs and observational studies (i.e., post hoc 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].

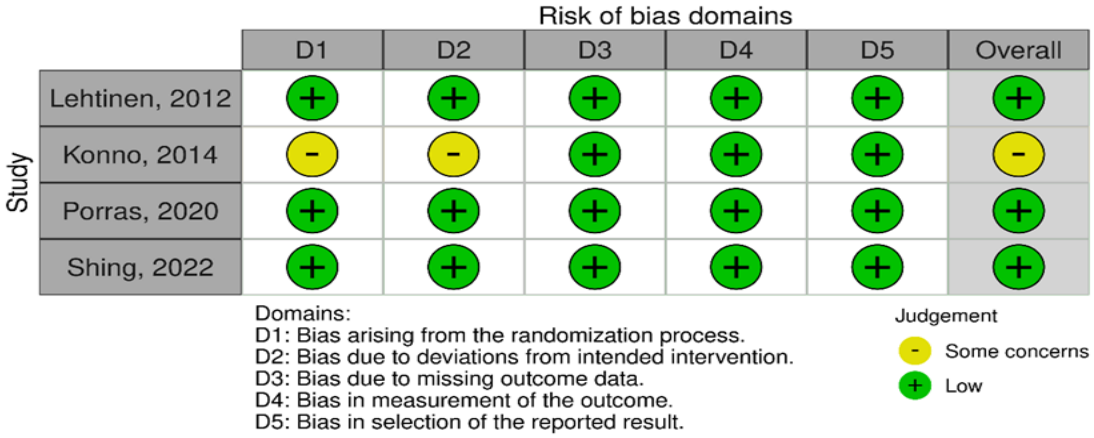
No studies were excluded based on quality. Instead, a decision was made to conduct meta-regression analyses adjusting for covariates and discussing and acknowledging the limitation of the studies. The results of the bias assessment are descriptively summarized below.

7.8.1. Quality assessment of RCTs

Follow-up post- hoc studies of RCTs by Lehtinen, 2012; Porras, 2020, and Shing, 2022 presented low risk of bias (Table 3 and Table 4). The main feature of 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 intervention allocation. In contrast, this was not the case for Konno, 2014 where the blinding was broken at the end of the primary 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, the fact of follow-up unblinding was expected not to have influenced the efficacy assessment. Another important aspect is that the Konno, 2014 study was not powered to evaluate VE against CIN3+. Hence the large 95% CIs for the results on this outcome (Table 9). This aspect was addressed in the analysis phase (meta-regression analysis).

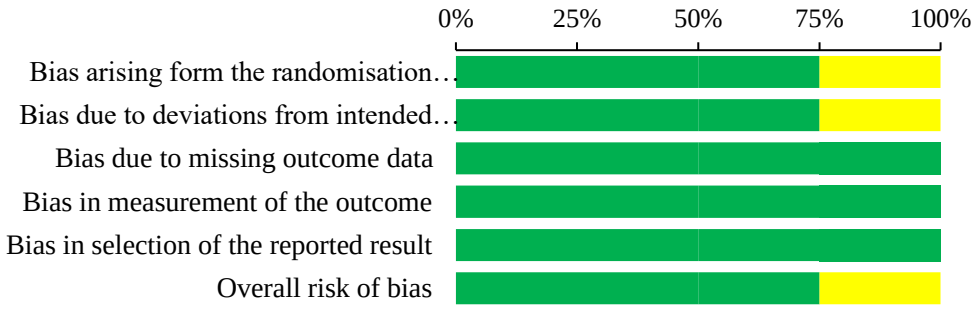
Overall, completeness of all follow-up studies was quite high, and losses were not selective, leaving both arms balanced at completion of the study.

Table 3 Risk of bias assessment of RCTs from the systematic review



Source: [McGuinness, 2020]

Table 4 Summary of quality assessment rating regarding bias (RCTs)



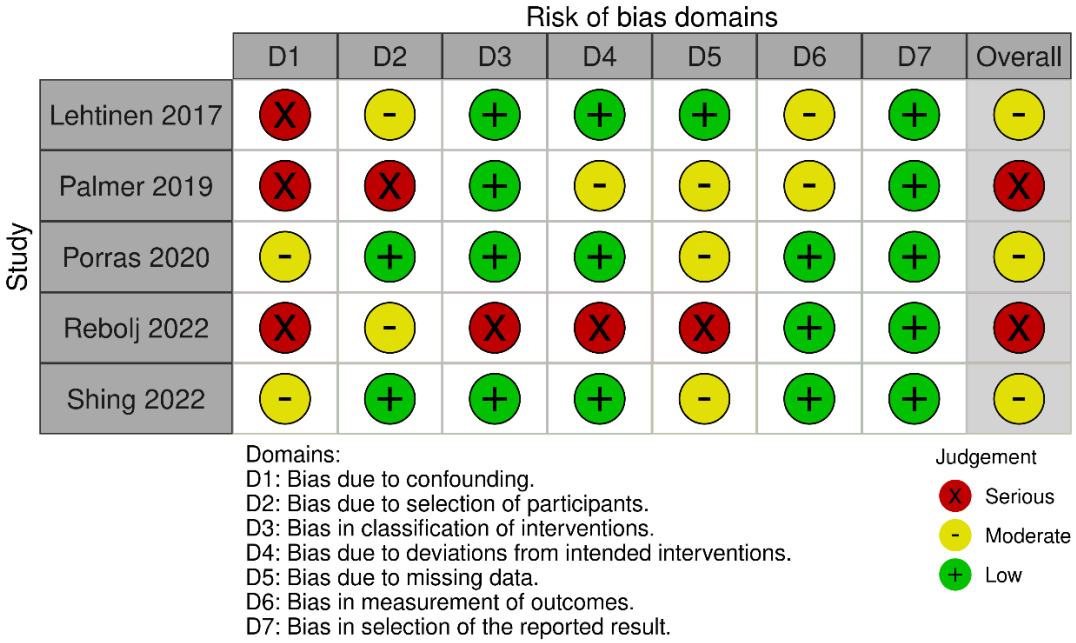
Source: [McGuinness, 2020]
Note: The 0-100% scale represents the global risk of bias attributable to every bias domain and overall, for all included RCTs

7.8.2. Quality assessment of observational studies

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 [Palmer, 2019; Rebolj, 2022] (Table 5 and Table 6). These two studies that were at serious risk of bias had one or two domains at high risk (mainly confounding and information of outcome). 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 VE [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). In 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. Nevertheless, 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].

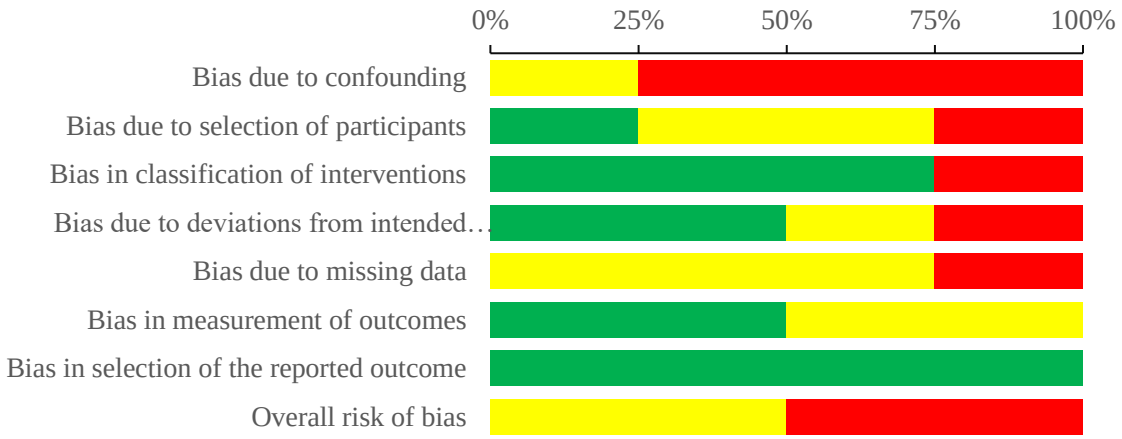
An important source of confounding in observational studies is related to HPV acquisition. The population-based studies did not determine HPV baseline status to assess for prevalent infection at the time of vaccination as pre-vaccination cervical screening is not standard of care. To address this, many studies allowed for buffer time between the vaccination and outcome assessment (cervical screening). Other relevant source of confounding in observational studies determining HPV VE is differences in risk of HPV acquisition between vaccinated and unvaccinated participants. In those 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 (i.e., Porras, Shing) and in other instances, sexual debut age was very similar between the vaccinated and unvaccinated arms [Lehtinen, 2017].

Table 5 Risk of bias of observational studies from the systematic review



Source: [McGuinness, 2020]

Table 6 Summary of quality assessment rating regarding bias (Obs)



Source: [McGuinness, 2020]
Note: The 0-100% scale represents the global risk of bias attributable to every bias domain and overall, for all selected observational studies

Table 7 Interpretation of results of the risk of bias assessment for observational studies

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

Funding was declared in all selected papers. The PATRICIA trial [Lehtinen, 2012], and the Japanese trial [Konno, 2014] were funded and coordinated by GlaxoSmithKline Biologicals. The Finnish observational study [Lehtinen, 2017] received funding from GlaxoSmithKline Biologicals and the Academy of Finland. The CVT follow-up studies [Porras, 2020; Shing, 2022] were funded by the US National Cancer Institute with funding support from the National Institutes of Health Office of Research on Women's Health. GSK contributed vaccines to this trial. The Scottish study [Palmer, 2019] was part of the routine work of Health Protection Scotland (Scottish National Health Service). The British studies [Falcaro, 2021; Rebolj, 2022] were carried out by Public Health England in collaboration with Cancer Research UK.

8. PROTECTION OF HUMAN PARTICIPANTS

8.1. Ethical approval and participant consent

This study complied with all applicable laws regarding participant privacy. No direct subject contact or primary collection of individual human subject data occurred. Study results are in tabular form and presented as aggregate analyses that omit subject identification, therefore informed consent, ethics committee or IRB approval was not required. Any publications and reports do not include subject identifiers.

8.2. Participant confidentiality

NA.

9. RESULTS

9.1. Search results and characteristics of selected studies

Across the searches through the databases, 2803 potentially eligible articles were identified (including one article retrieved by hand search), Figure 1. Of them, 913 duplicates were removed. Records were screened (n=1890) and n=1837 were excluded based on the eligibility, inclusion, or exclusion criteria. After title and abstract screening, n=53 papers were included for full-text review. Of these, 9 met the inclusion criteria. Of them, 5 studies were follow-up of RCTs [Wheeler, 2012; Lehtinen, 2012; Konno, 2014;

Porras, 2020; Shing, 2022], 3 studies were retrospective population-based registry linked studies [Palmer, 2019; Falcaro, 2021; Rebolj, 2022] and 1 study was an observational post-hoc long-term follow-up of an RCT [Lehtinen, 2017] Table 8 and Table 9. Two of the RCTs had also an observational component [Porras, 2020; Shing, 2022]. Studies were conducted in Japan [Konno, 2014], Costa Rica [Porras, 2020; Shing, 2022], Finland [Lehtinen, 2017], Scotland [Palmer, 2019], England [Falcaro, 2021; Rebolj, 2022], and in multicountry sites [Lehtinen, 2012; Wheeler, 2012).

The majority of studies stratified by age at first vaccination, although age groups varied considerably (Table 9). Seven studies were selected for the quantitative synthesis [Lehtinen, 2012; Konno, 2014; Lehtinen, 2017; Palmer, 2019; Porras, 2020; Shing, 2022; Rebolj, 2022] whereas two studies remained for the narrative review alone [Wheeler, 2012; Falcaro, 2021] (Table 10).

This systematic review and meta-analysis/meta-regression analysis included data on CERVARIX effects on CIN3+ from roughly 290 000 participants aged 12 to 25 years at vaccination, and up to 11 years of follow-up. Population-based HPV surveillance data from England added 13.7 million-years of follow-up in relation to VE against CIN3, and cervical cancer.

In the 4-year follow-up of the PATRICIA trial [Lehtinen, 2012], the overall vaccine efficacy against CIN3+ caused by HPV 16/18 reached its highest in the TVC-naïve [V efficacy= 100% (95%CI, 85.5-100)], and ATP-E cohort [V efficacy= 91.7% (95%CI, 66.6-99.1)] whereas, vaccine efficacy was lower [V efficacy= 45.7% (95%CI, 22.9-62.2) in the TVC whose participants received at least one dose of CERVARIX and were sexually active (Table 9). When stratified by age, usually vaccine efficacy decreased as vaccination age of participants increased (Table 9).

Konno et al, determined vaccine efficacy against CIN3+ caused by any HPV type at 100% (95%CI, -417.0-100) in the TVC naïve cohort, and 36.4% (95%CI,- 57.8-75.7) in the TVC cohort [Konno, 2014] (Table 9).

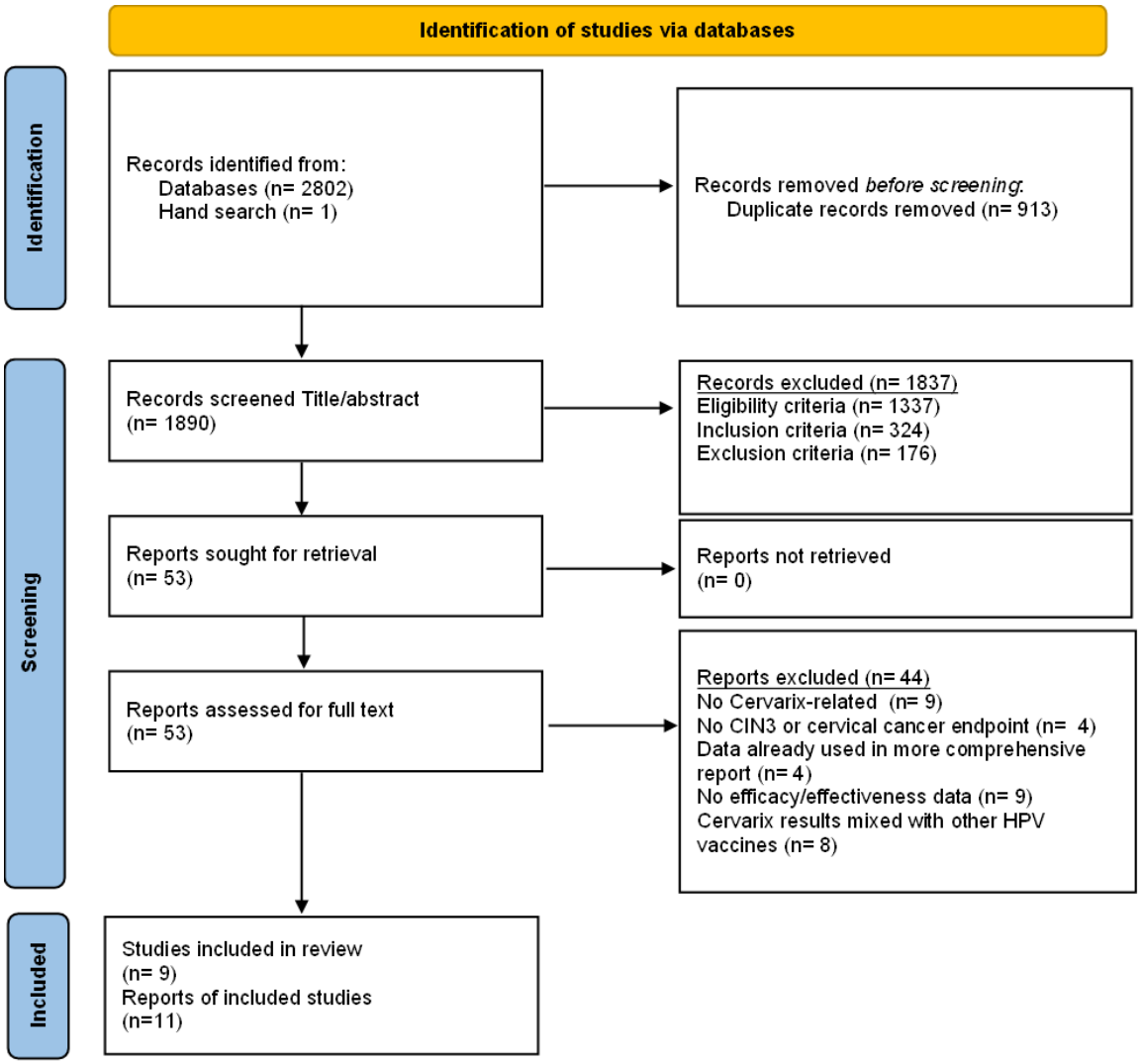
The 4-year post-vaccination analysis of the Costa Rica Vaccine Trial that Porras et al. conducted, established vaccine efficacy against CIN3+ caused by HPV 16/18 at 66.4% (95%CI, -175-97.3), and VE in a post-hoc observational study up to 11 years of follow-up at 100% (95%CI, 78.8-100). The analytical cohort for the 4-year follow-up was composed of women that were HPV 16/18 naïve and did not have CIN2+ or any LEEP treatment at enrollment (Table 9).

With a different analytical approach of the Costa Rica Vaccine Trial, Shing and colleagues established vaccine efficacy against incident CIN3+ caused by HPV 16/18 at 52.9% (95%CI, 22.4-72.1) in the 4-year follow-up of the trial in the TVC. Vaccine efficacy was 25.2% (95%CI, -5.0-46.9), irrespective of the HPV type. The observational post-hoc 7-11 years post-vaccination follow-up found VE of 86.9% (95%CI, 65.3-91.1) against incident CIN3+ caused by HPV 16/18, whereas VE declined to 14.4% (95%CI, -23.4-40.7) when it was caused by any HPV type (Table 9).

In the 10-year follow-up observational study of the Finnish component of the PATRICIA and HPV-012 trials, Lehtinen and colleagues [Lehtinen, 2017] determined VE against CIN3+ irrespective of HPV type at 66% (95%CI, 8.4-88) (Table 9).

The VE against CIN3+ of three doses of CERVARIX in the population-based study carried out by Palmer and colleagues in Scotland [Palmer, 2019] was estimated at 86% (95%CI, 75-92) in the 12-13 years at vaccination age-group, decreasing in older vaccinated birth cohorts.

Figure 1 PRISMA flow diagram



Abbreviations: CIN3= Cervical intraepithelial neoplasia grade 3, n=number of reports, HPV= Human Papillomavirus, PRISMA= Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Note: Two papers (i.e., Porras, Shing) included reports both on vaccine efficacy and vaccine effectiveness (observational component) [Porras, 2020; Shing, 2022].

Table 8 Summary of characteristics of selected studies

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	Multi-country (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-naive (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	Multi-country (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. Completed study: TVC, n= 7798 HPV arm, n=7811 control arm TVC-naïve, n= 1879 HPV arm, n= 2315 control arm ATP-E, n= 6815 HPV arm, n=6769 control arm	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

Author, Year	Country	Study period	Study design	Study population	Age at first vaccination	Vaccine coverage	Number of doses	Type of outcomes	Case-counting start
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) and the day after 3rd vaccination for ATP-E cohort
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 first vaccination (up to 10 years post vaccination follow-up)
Porras, 2020	Costa Rica	June 2004-December 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 first 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-December 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)	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+) (i.e., modified intention-to-treat cohort).	18-25 y	NA	At least 1 dose (mITT)	Vaccine efficacy Vaccine effectiveness	Day after first 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= 138692 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

Author, Year	Country	Study period	Study design	Study population	Age at first vaccination	Vaccine coverage	Number of doses	Type of outcomes	Case-counting start
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 1 May 1989 and 31 August 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: 55.6% to 81.9% 1 dose: 60.5% to 88.7% 3 doses: 44.8% to 84.9%	At least 1 dose, 3 doses	Adjusted IRR	NA
Rebolj, 2022	England (UK)	2013-2018	Retrospective population-based database study	Women eligible for catch-up vaccination (14-17 y) and received HR-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

Abbreviations: ATP-E= According-to-protocol for efficacy cohort, DNA= Deoxyribonucleic acid, HPV= Human papillomavirus, HR HPV= High-risk human papillomavirus, IRR= Incident relative risk (or Risk Ratio), mITT= Modified intention to treat, N= Total (Overall), n= number of participants in each arm, NA= Not applicable, UK=United Kingdom, US=United States, RCT= Randomized controlled trial, y=years.

Table 9 Vaccine effects reported on different endpoints

Author, Year	N (overall)	Age at first vaccination (y)	N (age group)	Endpoints	Vaccine effects % (95%CI)
Wheeler, 2012	ATP-E[a], N=16114 vaccine arm, n=8067 control arm, n=8047 TVC[b], N=18644 vaccine arm, n=9319 control arm, n=9325 TVC-naïve[c], N=11644 vaccine arm, n=5824 control arm, n=5820	15-25	NA	Vaccine efficacy against CIN3+ associated with a composite of 12 non-vaccine HPV types, with or without HPV-16/18 co-infection, in the ATP-E cohort. Vaccine efficacy against CIN3+ associated with a composite of 12 non-vaccine HPV types excluding HPV-16/18 co-infection, in the ATP-E cohort. Vaccine efficacy against CIN3+ associated with a composite of 12 non-vaccine HPV types, with or without HPV-16/18 co-infection, in the TVC-naïve. Vaccine efficacy against CIN3+ associated with a composite of 12 non-vaccine HPV types, excluding HPV-16/18 co-infection, in the TVC-naive. Vaccine efficacy against CIN3+ associated with a composite of 12 non-vaccine HPV types, with or without HPV-16/18 co-infection, in the TVC. Vaccine efficacy against CIN3+ associated with a composite of 12 non-vaccine HPV type, excluding HPV-16/18 co-infection, in the TVC	73.8 (48.3, 87.9) 62.1 (21.8, 82.9) 91.4 (65.0, 99.0) 81.9 (17.1, 98.1) 47.5 (22.8, 64.8) 40.0 (1.1, 64.2)
Lehtinen, 2012	ATP-E, N=16114 vaccine arm, n=8067 control arm, n=8047 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 15-25 15-25 15-25 15-25 15-25 15-25 15-25 15-25 15-25 15-17 18-25 18-20 21-25 15-17 18-25	NA	Vaccine efficacy against CIN3+ associated with HPV-16/18 in TVC-naïve. Vaccine efficacy against CIN3+ associated with HPV-16/18 in TVC. Vaccine efficacy against CIN3+ associated with HPV-16/18 in ATP-E cohort. Vaccine efficacy against CIN3+ associated with HPV-16 in ATP-E cohort. Vaccine efficacy against CIN3+ associated with HPV-18 in ATP-E cohort. Vaccine efficacy against all CIN3+ (irrespective of HPV type in the lesion and including lesions with no HPV DNA detected) in the TVC-naïve. Vaccine efficacy against all CIN3+ (irrespective of HPV type in the lesion) in the TVC. Vaccine efficacy against all AIS HPV 16/18-related in the TVC-naïve. Vaccine efficacy against all AIS HPV 16/18-related in the TVC. Vaccine efficacy against all AIS irrespective of HPV DNA in the lesion in the TVC-naïve. Vaccine efficacy against all AIS irrespective of HPV DNA in the lesion in the TVC. Vaccine efficacy against AIS associated with HPV-16/18 in ATP-E cohort. Vaccine efficacy against AIS associated with HPV-16 in ATP-E cohort. Vaccine efficacy against AIS associated with HPV-18 in ATP-E cohort. Vaccine efficacy against CIN3+ associated with HPV-16/18 in TVC-naïve. Vaccine efficacy against CIN3+ associated with HPV-16/18 in TVC-naïve.	100 (85.5, 100) 45.7 (22.9, 62.2) 91.7 (66.6, 99.1) 90.2 (59.7, 98.9) 100 (-8.2, 100) 93.2 (78.9, 98.7) 45.6 (28.8, 58.7) 100 (15.5, 100) 70.0 (-16.6, 94.7) 100 (31.0, 100) 76.9 (16.0, 95.8) 100 (-8.6, 100) 100 (48.4, 100) 100 (-3768.9, 100) 100 (69.4, 100) 100 (67.8, 100)

Author, Year	N (overall)	Age at first vaccination (y)	N (age group)	Endpoints	Vaccine effects % (95%CI)
		18-20		Vaccine efficacy against CIN3+ associated with HPV-16/18 in TVC-naïve.	100 (39.5, 100)
		21-25		Vaccine efficacy against CIN3+ associated with HPV-16/18 in TVC-naïve.	100 (-4.6, 100)
		15-17		Vaccine efficacy against CIN3+ associated with HPV-16/18 in TVC.	80.5 (55.6, 92.7)
		18-25		Vaccine efficacy against CIN3+ associated with HPV-16/18 in TVC.	24.2 (-14.1, 50.0)
		18-20		Vaccine efficacy against CIN3+ associated with HPV-16/18 in TVC.	56.3 (13.6, 79.1)
		21-25		Vaccine efficacy against CIN3+ associated with HPV-16/18 in TVC.	-10.1 (-90.5, 36.1)
		15-17		Vaccine efficacy against all CIN3+ (irrespective of HPV type in the lesion and including lesions with no HPV DNA detected) in the TVC-naïve.	91.5 (65.9, 99.0)
		18-25		Vaccine efficacy against all CIN3+ (irrespective of HPV type in the lesion and including lesions with no HPV DNA detected) in the TVC-naïve.	95.1 (69.3, 99.9)
		18-20		Vaccine efficacy against all CIN3+ (irrespective of HPV type in the lesion and including lesions with no HPV DNA detected) in the TVC-naïve.	90.6 (35.5, 99.8)
		21-25		Vaccine efficacy against all CIN3+ (irrespective of HPV type in the lesion and including lesions with no HPV DNA detected) in the TVC-naïve.	100 (51.4, 100)
				Vaccine efficacy against all CIN3+ (irrespective of HPV type in the lesion) in the TVC.	65.5 (42.5, 80.0)
				Vaccine efficacy against all CIN3+ (irrespective of HPV type in the lesion) in the TVC.	33.1 (7.5, 51.9)
				Vaccine efficacy against all CIN3+ (irrespective of HPV type in the lesion) in the TVC.	49.5 (13.9, 71.2)
				Vaccine efficacy against all CIN3+ (irrespective of HPV type in the lesion) in the TVC.	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 vaccine arm, n=281 control arm, n=284	20-25	NA	Vaccine efficacy against CIN3+ irrespective of the HPV type in the TVC-naive (over the combined 4-y study period of initial and follow-up studies).	100 (-417.0, 100)
				Vaccine efficacy against CIN3+ irrespective of the HPV type in the TVC (over the combined 4-y study period of initial and follow-up studies).	36.4 (-57.8, 75.7)

Author, Year	N (overall)	Age at first vaccination (y)	N (age group)	Endpoints	Vaccine effects % (95%CI)
Lehtinen, 2017	N=18092 vaccinated arm, n=2465 unvaccinated arm, n=15627	16-17	NA	Vaccine effectiveness against CIN3+ caused by HPV16. Vaccine effectiveness against CIN3+ caused by HPV18. Vaccine effectiveness against CIN3+ caused by HPV16/18. Vaccine effectiveness against CIN3+ caused by HPV16/31/33/35/52/58. Vaccine effectiveness against CIN3+ caused by HPV/31/33/35/52/58 (excluding co-infections with HPV16). Vaccine effectiveness against CIN3+ caused by A9=HPV31/33/35/52/58 and A7=HPV39/45/59/68, (excluding co-infections with 16/18). Vaccine effectiveness against CIN3+ caused by HPV31/33/45. Vaccine effectiveness against CIN3+ caused by HPV6/11/16/18/31/33/45/51/74 (all protected types). Vaccine effectiveness against CIN3+ caused by HPV6/11/31/33/45/51/74 (all protected types excluding co-infections with 16/18). Vaccine effectiveness 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), Vaccine effectiveness against CIN3+ caused by all detected HPV types. Vaccine effectiveness against CIN3+ caused by all detected HPV types (HPV positive and HPV negative baseline, excluding co-infections with 16/18). Vaccine effectiveness against CIN3+ caused by Total (original FCR registered CIN3+ diagnoses). Vaccine effectiveness 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 vaccine arm, n=2635 control arm, n=2677 Analytical cohort (7-11 y), N=4603 vaccinated arm, n=2073 unvaccinated arm, n=2530	18-25	NA	Vaccine efficacy against CIN3+ caused by HPV 16/18 at year 4 post-vaccination (analytical cohort with original control group) Vaccine effectiveness against CIN3+ caused by HPV 16/18 at year 7 post-vaccination (analytical cohort with unvaccinated new control group). Vaccine effectiveness against CIN3+ caused by HPV 16/18 at year 9 post-vaccination (analytical cohort with unvaccinated new control group). Vaccine effectiveness against CIN3+ caused by HPV 16/18 at year 11 post-vaccination (analytical cohort with unvaccinated new control group).	66.4 (-175, 97.3) 100 (-40.1, 100) 100 (44.0, 100) 100 (78.8, 100)

Author, Year	N (overall)	Age at first vaccination (y)	N (age group)	Endpoints	Vaccine effects % (95%CI)
Shing, 2022	Analytical cohort (1-4 y), N=7003 vaccine arm, n=3491 control arm, n=3512 Analytical cohort (7-11 y), N=5418 vaccinated arm, n=2826 unvaccinated arm, n=2592	18-25	NA	Vaccine efficacy against incident CIN3+ irrespective of HPV type (combined 4-year period). Vaccine efficacy against incident CIN3+ caused by HPV16 or HPV18 (combined 4-year period). Vaccine efficacy against incident CIN3+ caused by HPV 31,33, or 45 (excluding HPV 16 or 18 coinfection) (combined 4-year period). Vaccine efficacy against incident CIN3+ caused by HPV types other than HPV 16, 18, 31, 33, or 45 (combined 4-year period). Vaccine effectiveness against incident CIN3+ irrespective of HPV type (combined years 7-11 period). Vaccine effectiveness against incident CIN3+ caused by HPV16 or HPV18 (combined years 7-11 period). Vaccine effectiveness against incident CIN3+ caused by HPV 31,33, or 45 (excluding HPV 16 or 18 coinfection) (combined years 7-11 period). Vaccine effectiveness against incident CIN3+ caused by HPV types other than HPV 16, 18, 31, 33, or 45 (combined years 7-11 period). Vaccine effectiveness against incident CIN3+ irrespective of HPV type (combined 11-year period). Vaccine effectiveness against incident CIN3+ caused by HPV16 or HPV18 (combined 11-year period). Vaccine effectiveness against incident CIN3+ caused by HPV 31,33, or 45 (excluding HPV 16 or 18 coinfection) (combined 11-year period). Vaccine effectiveness against incident CIN3+ caused by HPV types other than HPV 16, 18, 31, 33, or 45 (combined 11-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) 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 (unvaccinated) n=64026 1 dose, n=2051 2 doses, n=4135 3 doses, n=68480	12-13 14 15 16 17 ≥18 ≤17 12-13	N=16200 N=5409 N=16532 N=17511 N=8711 N=4117 N=15678 N=48348	Vaccine effectiveness against CIN3+[c,d,e] Vaccine effectiveness against CIN3+ Vaccine effectiveness against CIN3+ Vaccine effectiveness against CIN3+ Vaccine effectiveness against CIN3+ Vaccine effectiveness against CIN3+ Vaccine effectiveness against CIN3+, born ≥ 1991 (unvaccinated). Vaccine effectiveness against CIN3, born 1995-1996 (unvaccinated).	86 (75, 92) 82 (57, 93) 71 (56, 81) 73 (59, 82) 45 (17, 64) 15 (-37, 48) 18 (-7, 37) 100 (69, 100)

Author, Year	N (overall)	Age at first vaccination (y)	N (age group)	Endpoints	Vaccine effects % (95%CI)
Falcaro, 2021	13.7 million-years of follow-up	12-13 14-16 16-18 12-13 14-16 16-18	NA	Vaccine effectiveness against CIN3[f] Vaccine effectiveness against CIN3 Vaccine effectiveness against CIN3 Vaccine effectiveness against cervical cancer Vaccine effectiveness against cervical cancer. Vaccine effectiveness against cervical cancer.	97 (96, 98) 75 (72, 77) 39 (36, 41) 87 (72, 94) 62 (52, 71) 34 (25, 41)
Rebolj, 2022	N=108138 vaccinated, n=64274 unvaccinated, n=43863	14-17	NA	Vaccine effectiveness against HR-HPV positive CIN3+ (HR-HPV+/cytology+ primary screening test)[g]. Vaccine effectiveness against HPV 16/18-related CIN3+. Vaccine effectiveness against CIN3+ by "Other" HPV-related (excludes co-infections with HPV 16/18)[h]. Vaccine effectiveness against cervical cancer.	79 (73, 83) 87 (80, 91) 57 (25, 75) 64 (-91, 93)

a Participants received 3 doses of vaccine and were HPV DNA negative at baseline.
b Participants received at least 1 dose of vaccine, irrespective of baseline HPV DNA status.
c Participants received at least 1 dose of vaccine and were HPV DNA negative at baseline.
d Vaccine effectiveness calculated as VE=(1-odds ratio)*100.
e Results for 3 doses of vaccine.
f Vaccine effectiveness calculated as VE=(1-IRR)*100. (Adjusted IRR model 3).
g 14 HR-HPV types: 16,18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68.
h "Other" 12 HR-HPV types: 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68.

Abbreviations: AIS= Adenocarcinoma in situ, ATP-E= According-to-protocol for efficacy cohort, DNA= Deoxyribonucleic Acid, FCR= Finnish cancer registry, HPV= Human papillomavirus, HR HPV= High-risk human papillomavirus, IRR= Incident relative risk (or risk ratio), N= Total (overall), n= Number of participants in each arm, NA= Not applicable, TVC= Total vaccinated cohort UK=United Kingdom, US=United States, RCT= Randomized controlled trial, y=years.

Table 10 Final outcomes and endpoints for the meta-regression analyses

Author, Year	Endpoint	HPV type	N of doses	Age at first vaccination	Time since vaccination (y)
Analysis 1_CIN3+, HPV16/18 RCT/Observational 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/Observational 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+	HR-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

Author, Year	Endpoint	HPV type	N of doses	Age at first vaccination	Time since vaccination (y)
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 21-25 y	0-4
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, Observational, 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+	HPV16/18	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, Observational, 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+	HR-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: HPV= Human papillomavirus, HR HPV= High-risk Human papillomavirus, TVC= Total vaccinated cohort, RCT= Randomized controlled trial, y=years.

9.2. Results of primary analyses

Statistical outputs for all analyses are included in ANNEX 2 at the end of this document.

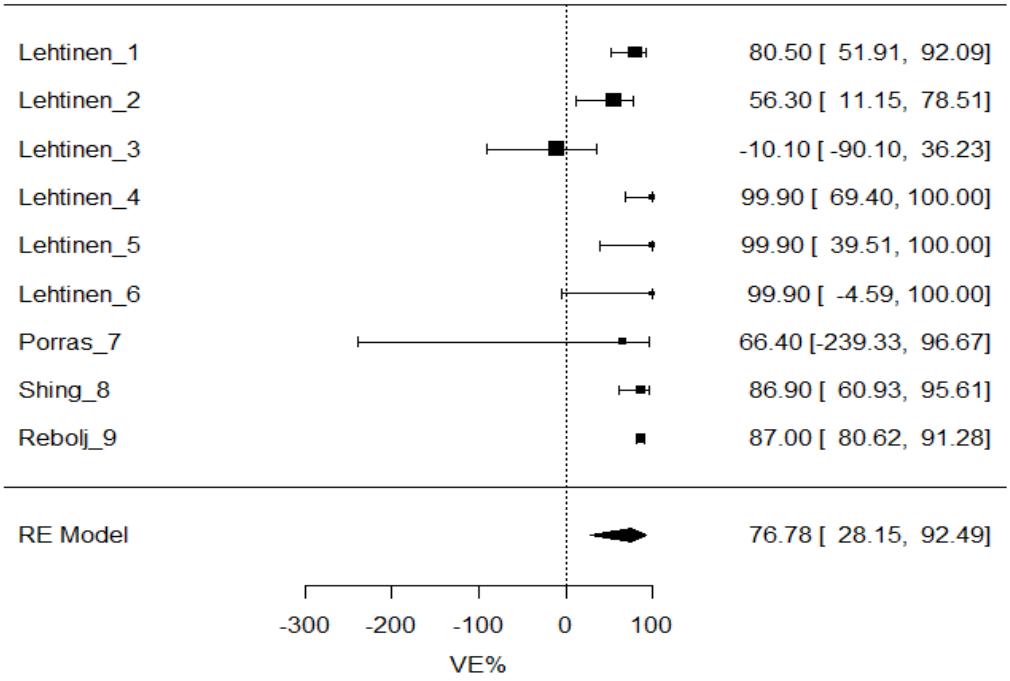
9.2.1. Analysis 1: What is the combined efficacy/effectiveness of CERVARIX on CIN3+ caused by vaccine HPV types? (RCTs and Observational studies combined)

This analysis studied the combined effects of follow-up studies of RCT ([Lehtinen, 2012], including the TVC naïve and TVC; [Porras, 2020], TVC naïve) and observational studies ([Shing, 2022], TVC; [Rebolj, 2022], TVC) of CERVARIX on CIN3+ caused by HPV 16/18 types. The rationale behind the selection of studies for this dataset was to include RCTs and observational studies with outcome results on HPV 16/18 types. We excluded Lehtinen, 2017 from this analysis because participants partially overlapped with Lehtinen, 2012 [Lehtinen, 2012; Lehtinen, 2017]. The observational component of Shing, 2022 was included to consider the long-term follow-up of the CVT, although participants partially overlap with those of Porras, 2020, but with a different approach to the analytical cohort. The "study correlation" variable was used to account for the partial overlapping [Porras, 2020; Shing, 2022].

1. **Meta-analysis***. Pooled vaccine effects were determined at vaccine effect= 76.78 (95%CI, 28.15-92.49) (Figure 2).

*Meta-analysis was done on the log relative risk scale assuming normality. Then results were back transformed to the vaccine effect scale. Therefore, some differences may be found in 95%CI between the pooled vaccine effects provided in the datasets and those estimated in the meta-analysis.

Figure 2 Pooled estimated vaccine effects of CERVARIX on CIN3+ caused by HPV 16/18 types (Analysis 1)



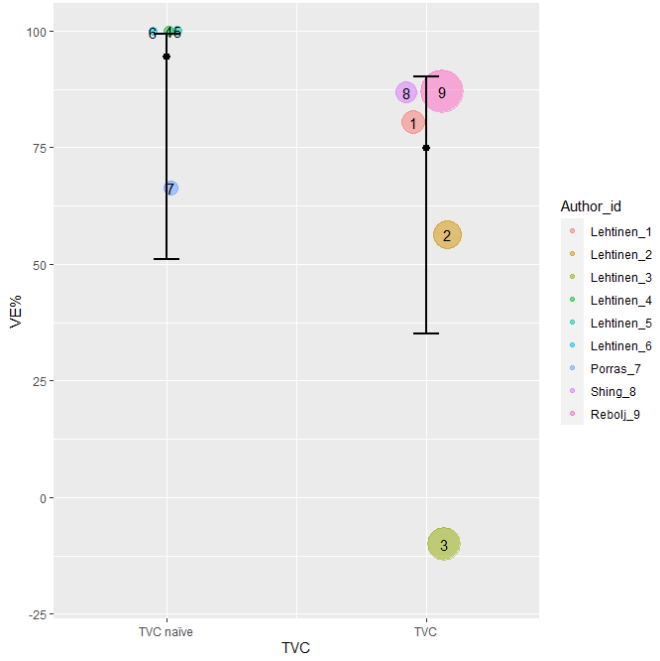
Note for interpretation of graphs:
Lehtinen 1= Lehtinen 2012, age at first vaccination 15-17 years, TVC, time since vaccination 0-4 years.
Lehtinen 2= Lehtinen 2012, age at first vaccination 18-20 years, TVC, time since vaccination 0-4 years.
Lehtinen 3= Lehtinen 2012, age at first vaccination 21-25 years, TVC, time since vaccination 0-4 years.
Lehtinen 4= Lehtinen 2012, age at first vaccination 15-17 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 5= Lehtinen 2012, age at first vaccination 18-20 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 6= Lehtinen 2012, age at first vaccination 21-25 years, TVC naïve, time since vaccination 0-4 years.
Porras 7= Porras 2020, age at first vaccination 18-25 years, TVC naïve, time since vaccination 0-4 years.
Shing 8= Shing 2022, age at first vaccination 18-25 years, TVC, time since vaccination 7-11 years.
Rebolj 9= Rebolj 2022, age at first vaccination 14-17 years, TVC, time since vaccination 7-11 years.
Abbreviations: VE=Vaccine effects, RE=random effects.
Reference: [Lehtinen, 2012; Porras, 2020; Shing, 2022; Rebolj, 2022].

The most remarkable aspect of this meta-analysis was that the lower limit of the 95%CI for some individual vaccine effect estimates are negative. This was the case of the Porras, 2020 study that showed a very wide 95%CI. In case of the Lehtinen, 2012 study, the point estimate for vaccine effect corresponding to the age group 21-25 years at first vaccination (Lehtinen 3), was negative whereas vaccine effect=100% for all age groups in the TVC naïve cohort for this particular study, indicated within-trial variability[Lehtinen, 2012]. Negative lower limits occured only for wide confidence intervals and were not given much weight in the model given their uncertainty and thus, it does not largely contribute to the pooled effect. Therefore, the pooled estimate for vaccine effect of all RCTs and observational studies against CIN3+ caused by HPV 16/18 types was vaccine effect=76.78 (95%CI, 28.15-92.49).

2. Univariate meta-regression analysis.

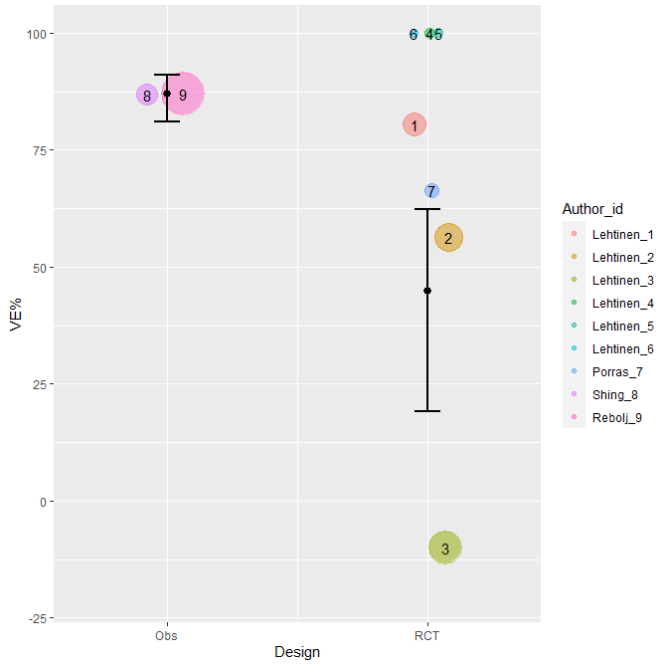
Results from this analysis showed that the variables “age at first vaccination” (p=0.0086), “study design” (RCT follow-up vs. observational study, p=0.0011) and “time since vaccination” (0-4 years vs. 7-11 years, p=0.0011) presented strong association with the outcome vaccine effect (i.e., small p values in the univariate meta-regression analysis model). All estimates suggests that the vaccine effect decreases with age at first vaccination, it is lower in randomized trials compared with observational studies, and it is larger when time since vaccination is “0-4” years (RCTs) compared to “7-11” years (observational studies). vaccine effect is also larger when the analytical cohort is the TVC naïve (participants HPV negative at baseline). Figures below show the observed and the predicted vaccine effect (black line with 95%CI) as a function of the univariate covariates. Size of the bubbles is proportional to the inverse of the variance (corresponds to the weight in classical meta-analysis).

Figure 3 Univariate effect of analytical cohort on vaccine efficacy/effectiveness (Analysis 1)



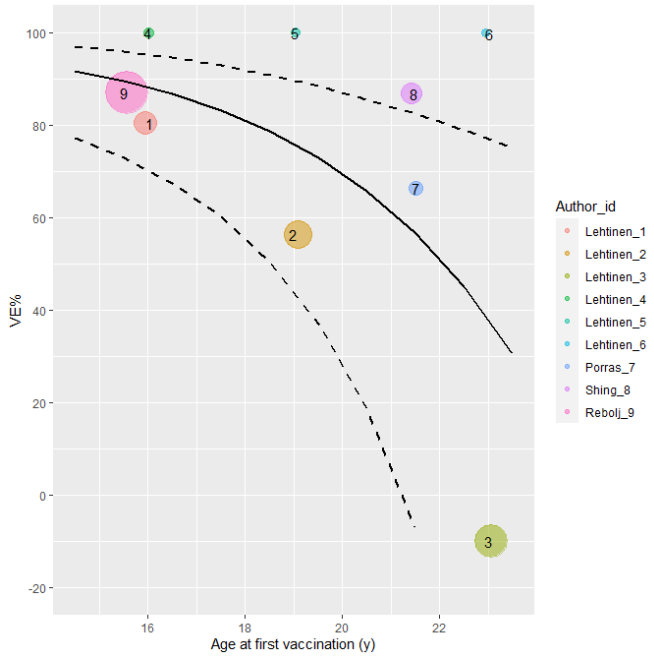
Note for interpretation of graphs:
Lehtinen 1= Lehtinen 2012, age at first vaccination 15-17 years, TVC, time since vaccination 0-4 years.
Lehtinen 2= Lehtinen 2012, age at first vaccination 18-20 years, TVC, time since vaccination 0-4 years.
Lehtinen 3= Lehtinen 2012, age at first vaccination 21-25 years, TVC, time since vaccination 0-4 years.
Lehtinen 4= Lehtinen 2012, age at first vaccination 15-17 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 5= Lehtinen 2012, age at first vaccination 18-20 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 6= Lehtinen 2012, age at first vaccination 21-25 years, TVC naïve, time since vaccination 0-4 years.
Porras 7= Porras 2020, age at first vaccination 18-25 years, TVC naïve, time since vaccination 0-4 years.
Shing 8= Shing 2022, age at first vaccination 18-25 years, TVC, time since vaccination 7-11 years.
Rebolj 9= Rebolj 2022, age at first vaccination 14-17 years, TVC, time since vaccination 7-11 years.
Abbreviations: VE=Vaccine effect, TVC=total vaccinated cohort,id=identity.
Reference: [Lehtinen, 2012; Porras, 2020; Shing, 2022; Rebolj, 2022]

Figure 4 Univariate effect of study design on vaccine efficacy/effectiveness (Analysis 1)



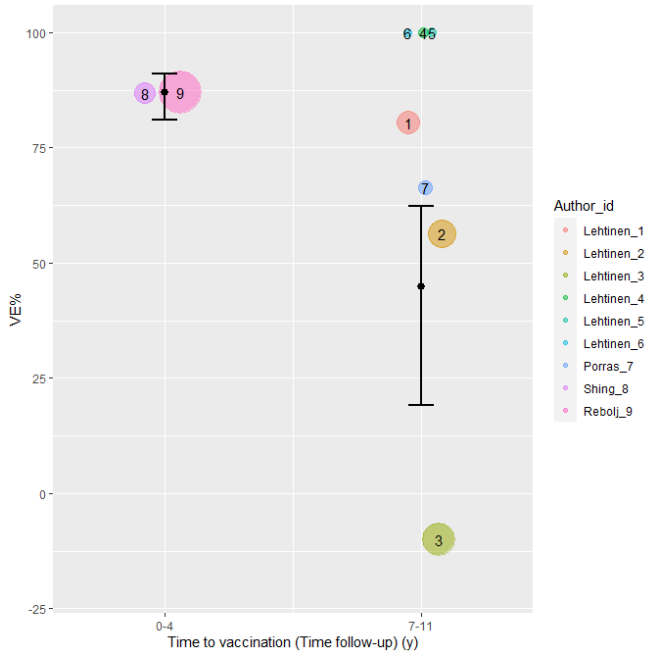
Note for interpretation of graphs:
Lehtinen 1= Lehtinen 2012, age at first vaccination 15-17 years, TVC, time since vaccination 0-4 years.
Lehtinen 2= Lehtinen 2012, age at first vaccination 18-20 years, TVC, time since vaccination 0-4 years.
Lehtinen 3= Lehtinen 2012, age at first vaccination 21-25 years, TVC, time since vaccination 0-4 years.
Lehtinen 4= Lehtinen 2012, age at first vaccination 15-17 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 5= Lehtinen 2012, age at first vaccination 18-20 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 6= Lehtinen 2012, age at first vaccination 21-25 years, TVC naïve, time since vaccination 0-4 years.
Porras 7= Porras 2020, age at first vaccination 18-25 years, TVC naïve, time since vaccination 0-4 years.
Shing 8= Shing 2022, age at first vaccination 18-25 years, TVC, time since vaccination 7-11 years.
Rebolj 9= Rebolj 2022, age at first vaccination 14-17 years, TVC, time since vaccination 7-11 years.
Abbreviations: VE=Vaccine effect, id=identity, Obs=observational studies, RCT=randomized control trials.
Reference: [Lehtinen, 2012; Porras, 2020; Shing, 2022; Rebolj, 2022].

Figure 5 Univariate effect of age at first vaccination on vaccine efficacy/effectiveness (Analysis 1)



Note for interpretation of graphs:
Lehtinen 1= Lehtinen 2012, age at first vaccination 15-17 years, TVC, time since vaccination 0-4 years.
Lehtinen 2= Lehtinen 2012, age at first vaccination 18-20 years, TVC, time since vaccination 0-4 years.
Lehtinen 3= Lehtinen 2012, age at first vaccination 21-25 years, TVC, time since vaccination 0-4 years.
Lehtinen 4= Lehtinen 2012, age at first vaccination 15-17 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 5= Lehtinen 2012, age at first vaccination 18-20 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 6= Lehtinen 2012, age at first vaccination 21-25 years, TVC naïve, time since vaccination 0-4 years.
Porras 7= Porras 2020, age at first vaccination 18-25 years, TVC naïve, time since vaccination 0-4 years.
Shing 8= Shing 2022, age at first vaccination 18-25 years, TVC, time since vaccination 7-11 years.
Rebolj 9= Rebolj 2022, age at first vaccination 14-17 years, TVC, time since vaccination 7-11 years.
Abbreviations: VE=vaccine effect, id=identity, y= years.
Reference: [Lehtinen, 2012; Porras, 2020; Shing, 2022; Rebolj, 2022]

Figure 6 Univariate effect of time since vaccination (time of follow-up) on vaccine efficacy/effectiveness (Analysis 1)



Note for interpretation of graphs:
Lehtinen 1= Lehtinen 2012, age at first vaccination 15-17 years, TVC, time since vaccination 0-4 years.
Lehtinen 2= Lehtinen 2012, age at first vaccination 18-20 years, TVC, time since vaccination 0-4 years.
Lehtinen 3= Lehtinen 2012, age at first vaccination 21-25 years, TVC, time since vaccination 0-4 years.
Lehtinen 4= Lehtinen 2012, age at first vaccination 15-17 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 5= Lehtinen 2012, age at first vaccination 18-20 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 6= Lehtinen 2012, age at first vaccination 21-25 years, TVC naïve, time since vaccination 0-4 years.
Porras 7= Porras 2020, age at first vaccination 18-25 years, TVC naïve, time since vaccination 0-4 years.
Shing 8= Shing 2022, age at first vaccination 18-25 years, TVC, time since vaccination 7-11 years.
Rebolj 9= Rebolj 2022, age at first vaccination 14-17 years, TVC, time since vaccination 7-11 years.
Abbreviations: VE=vaccine effect, id=identity, y= years.
Reference: [Lehtinen, 2012; Porras, 2020; Shing, 2022; Rebolj, 2022].

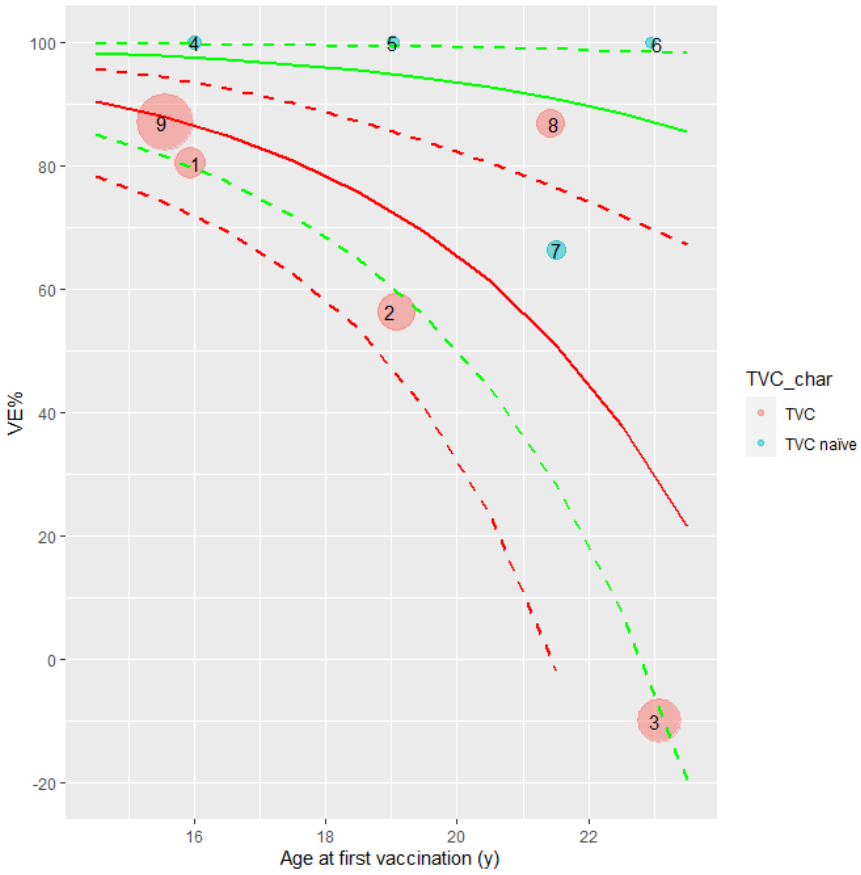
3. Multiparametric meta-regression analysis

All possible combinations of predictors were evaluated and compared using AIC (data-driven approach) to find the best model, and which predictors were the most important ones. This data-driven exploration conducted to a final model that includes the "age at first vaccination" and "analytical cohort" variables. After adjusting for the analytical cohort (TVC vs. TVC naïve), "age at first vaccination" resulted as the most impactful variable on the outcome (p=0.0092). It is also interesting to mention that time since vaccination was not selected as one of the two main explanatory factors, which may indicate persistence of the effect of the vaccine over time. The heterogeneity explained by the selected model was R^2*= 62.18%.

The following figure shows the predictions (with 95% Confidence intervals, dotted line) from this data-driven selected model adjusting for "age at first vaccination" and "analytical cohort". Red and green curves represent the predicted vaccine effect as a function of age for TVC and TVC naïve populations. Red and blue bubbles represent the

observed VEs of the studies with TVC and TVC naïve population, respectively. Size of the bubbles is proportional to the inverse of the variance (it corresponds to the weight in a classical meta-analysis). Observed values seem to be relatively well approximated by the multiparametric model.

Figure 7 Results of data-driven multiparametric meta-regression analysis model (Analysis 1)



Note for interpretation of graphs:
Lehtinen 1= Lehtinen 2012, age at first vaccination 15-17 years, TVC, time since vaccination 0-4 years.
Lehtinen 2= Lehtinen 2012, age at first vaccination 18-20 years, TVC, time since vaccination 0-4 years.
Lehtinen 3= Lehtinen 2012, age at first vaccination 21-25 years, TVC, time since vaccination 0-4 years.
Lehtinen 4= Lehtinen 2012, age at first vaccination 15-17 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 5= Lehtinen 2012, age at first vaccination 18-20 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 6= Lehtinen 2012, age at first vaccination 21-25 years, TVC naïve, time since vaccination 0-4 years.
Porras 7= Porras 2020, age at first vaccination 18-25 years, TVC naïve, time since vaccination 0-4 years.
Shing 8= Shing 2022, age at first vaccination 18-25 years, TVC, time since vaccination 7-11 years.
Rebolj 9= Rebolj 2022, age at first vaccination 14-17 years, TVC, time since vaccination 7-11 years.
Abbreviations: VE=Vaccine effect, TVC=total vaccinated cohort, y=years.
Reference: [Lehtinen, 2012; Porras, 2020; Shing, 2022; Rebolj, 2022].

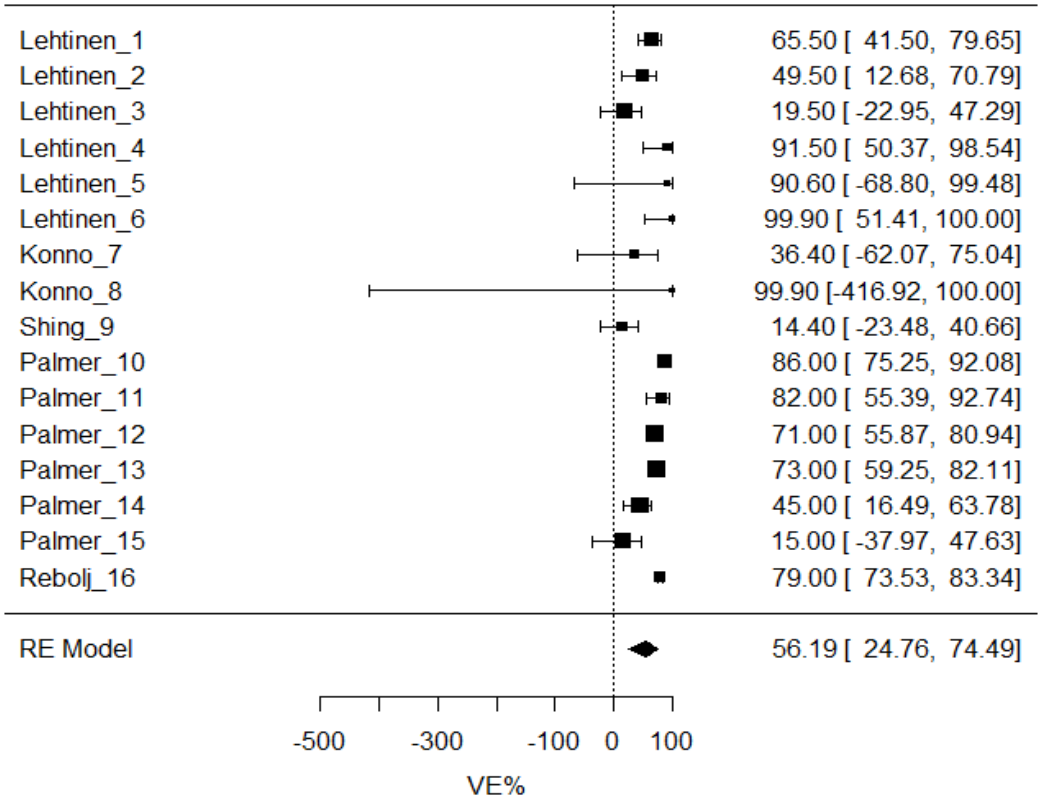
9.2.2. Analysis 2: What is the combined overall efficacy/effectiveness of CERVARIX on CIN3+ caused by any HPV type? (RCTs and Observational studies combined).

This analysis studied the combined effects of follow-up studies of RCT ([Lehtinen, 2012], including the TVC naïve and TVC; [Konno, 2014], TVC and TVC naïve) and observational studies ([Shing, 2022], TVC; [Palmer, 2019], TVC; [Rebolj 2022], TVC) of CERVARIX on CIN3+ caused by any HPV type. The rationale behind the selection of studies for this dataset was to include RCTs and observational studies with outcome results irrespectively of the causing HPV type. We excluded Lehtinen, 2017 of this analysis because participants partially overlapped with Lehtinen, 2012 [Lehtinen, 2012; Lehtinen, 2017]. The observational component of Shing, 2022 was included to consider the long-term follow-up of the CVT, as Porras, 2020 only reports on HPV 16/18 types [Porras, 2020; Shing, 2022].

1. **Meta-analysis***. Pooled vaccine effects were determined at vaccine effect= 56.19 (95%CI, 24.76-74.49) (Figure 8).

*Meta-analysis was done on the log relative risk scale assuming normality. Then results were back transformed to the vaccine effect scale. Therefore, some differences may be found in 95%CI between the pooled vaccine effects provided in the datasets and those estimated in the meta-analysis.

Figure 8 Pooled estimated vaccine effects of CERVARIX on CIN3+ caused by any HPV type (Analysis 2)



Note for interpretation of graphs:
Lehtinen 1= Lehtinen 2012, age at first vaccination 15-17 years, TVC, time since vaccination 0-4 years.
Lehtinen 2= Lehtinen 2012, age at first vaccination 18-20 years, TVC, time since vaccination 0-4 years.
Lehtinen 3= Lehtinen 2012, age at first vaccination 21-25 years, TVC, time since vaccination 0-4 years.
Lehtinen 4= Lehtinen 2012, age at first vaccination 15-17 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 5= Lehtinen 2012, age at first vaccination 18-20 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 6= Lehtinen 2012, age at first vaccination 21-25 years, TVC naïve, time since vaccination 0-4 years.
Konno 7= Konno 2014, age at first vaccination 20-25 years, TVC, time since vaccination 0-4 years.
Konno 8= Konno 2014, age at first vaccination 20-25 years, TVC naïve, time since vaccination 0-4 years.
Shing 9= Shing 2022, age at first vaccination 18-25 years, TVC, time since vaccination 7-11 years.
Palmer 10= Palmer 2019, age at first vaccination 12-13 years, TVC, time since vaccination 0-8 years.
Palmer 11= Palmer 2019, age at first vaccination 14 years, TVC, time since vaccination 0-6 years.
Palmer 12= Palmer 2019, age at first vaccination 15 years, TVC, time since vaccination 0-5 years.
Palmer 13= Palmer 2019, age at first vaccination 16 years, TVC, time since vaccination 0-4 years.
Palmer 14= Palmer 2019, age at first vaccination 17 years, TVC, time since vaccination 0-3 years.
Palmer 10= Palmer 2019, age at first vaccination ≥18 years, TVC, time since vaccination 0-2 years.
Rebolj 16= Rebolj 2022, age at first vaccination 14-17 years, TVC, time since vaccination 7-11 years.
Abbreviations: VE=Vaccine effect, RE=random effects.
Reference: [Lehtinen, 2012; Konno, 2014; Palmer, 2019; Shing, 2022; Rebolj, 2022].

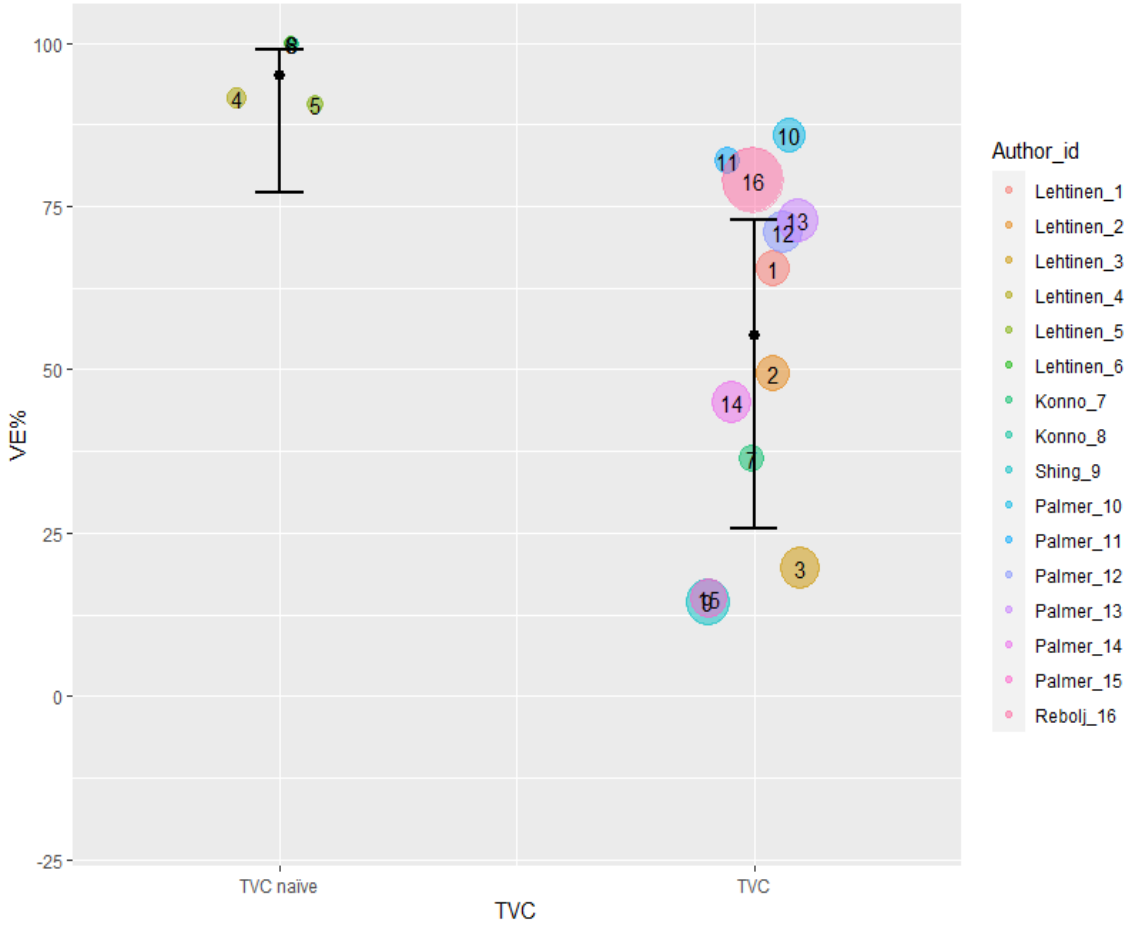
The most remarkable aspect of this meta-analysis is that the lower limit of the 95%CI for some individual vaccine effect estimates is negative. This is especially relevant for Konno, 2014 (TVC naïve cohort) (Konno 8), as already described in Section 7.8.1

[Konno, 2014]. However, the combined pooled estimate reached statistical significance and the lower limit is above "0" [vaccine effect= 56.19 (95%CI, 24.76-74.49].

2. Univariate meta-regression analysis

Results from this analysis showed that the variables "analytical cohort" (TVC vs. TVC naïve, p=0.0104), "age at first vaccination" (p<0.001), and "time since vaccination" (0-4 years vs. 7-11 years, p<0.001), presented strong association with the outcome vaccine effect (small p values in the univariate meta-regression analysis model). All estimates (with exception of "time since vaccination") suggests that the vaccine effect decreases with age at first vaccination, it is lower in randomized trials compared with observational studies, and it is higher as time since vaccination increases. vaccine effect is also clearly larger when the analytical cohort is the TVC naïve (participants HPV negative at baseline). Figures below show the observed and the predicted vaccine effect (black line with 95%CI) as a function of the univariate covariates. Size of the bubbles is proportional to the inverse of the variance (it corresponds to the weight in a classical meta-analysis).

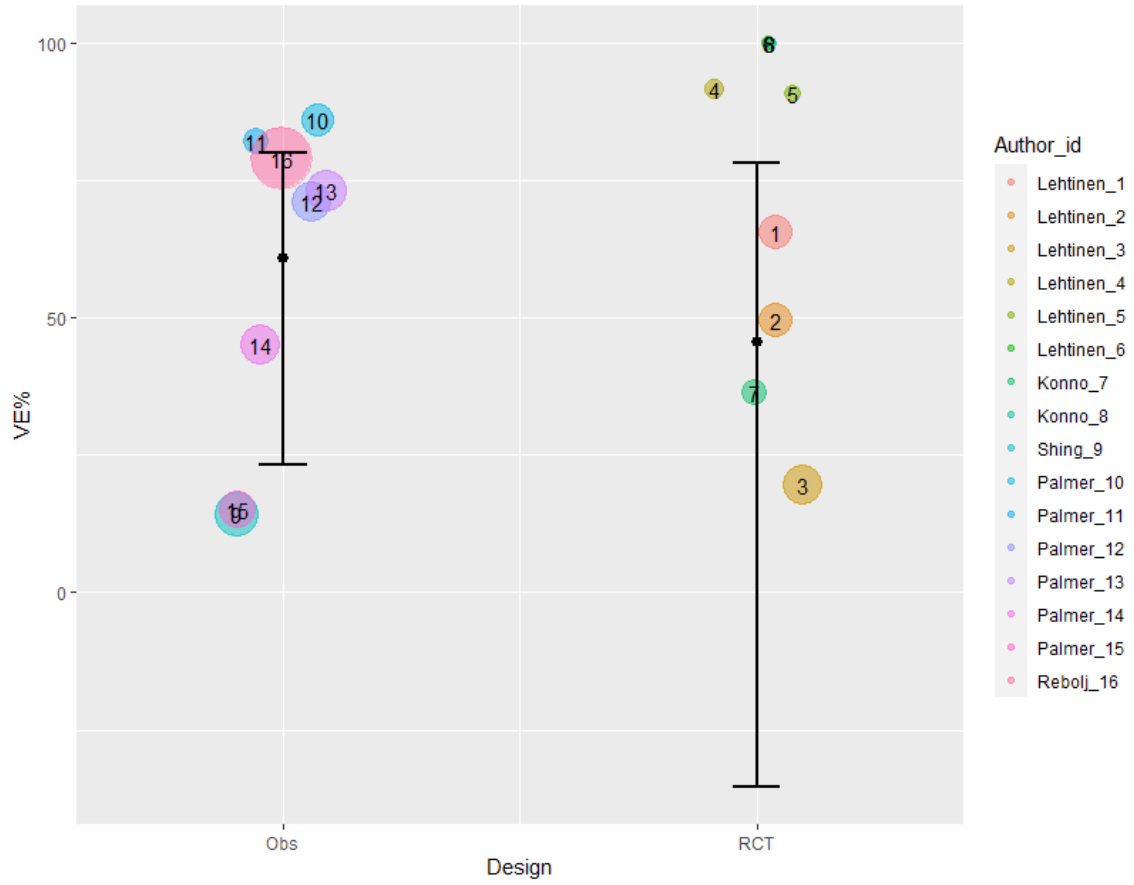
Figure 9 Univariate effect of analytical cohort on vaccine efficacy/effectiveness (Analysis 2)



Note for interpretation of graphs:
Lehtinen 1= Lehtinen 2012, age at first vaccination 15-17 years, TVC, time since vaccination 0-4 years.
Lehtinen 2= Lehtinen 2012, age at first vaccination 18-20 years, TVC, time since vaccination 0-4 years.

Lehtinen 3= Lehtinen 2012, age at first vaccination 21-25 years, TVC, time since vaccination 0-4 years.
Lehtinen 4= Lehtinen 2012, age at first vaccination 15-17 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 5= Lehtinen 2012, age at first vaccination 18-20 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 6= Lehtinen 2012, age at first vaccination 21-25 years, TVC naïve, time since vaccination 0-4 years.
Konno 7= Konno 2014, age at first vaccination 20-25 years, TVC, time since vaccination 0-4 years.
Konno 8= Konno 2014, age at first vaccination 20-25 years, TVC naïve, time since vaccination 0-4 years.
Shing 9= Shing 2022, age at first vaccination 18-25 years, TVC, time since vaccination 7-11 years.
Palmer 10= Palmer 2019, age at first vaccination 12-13 years, TVC, time since vaccination 0-8 years.
Palmer 11= Palmer 2019, age at first vaccination 14 years, TVC, time since vaccination 0-6 years.
Palmer 12= Palmer 2019, age at first vaccination 15 years, TVC, time since vaccination 0-5 years.
Palmer 13= Palmer 2019, age at first vaccination 16 years, TVC, time since vaccination 0-4 years.
Palmer 14= Palmer 2019, age at first vaccination 17 years, TVC, time since vaccination 0-3 years.
Palmer 10= Palmer 2019, age at first vaccination ≥18 years, TVC, time since vaccination 0-2 years.
Rebolj 16= Rebolj 2022, age at first vaccination 14-17 years, TVC, time since vaccination 7-11 years.
Abbreviations: VE=Vaccine effect, id=identity, TVC=total vaccinated cohort.
Reference: [Lehtinen, 2012; Konno, 2014; Palmer, 2019; Shing, 2022; Rebolj, 2022]

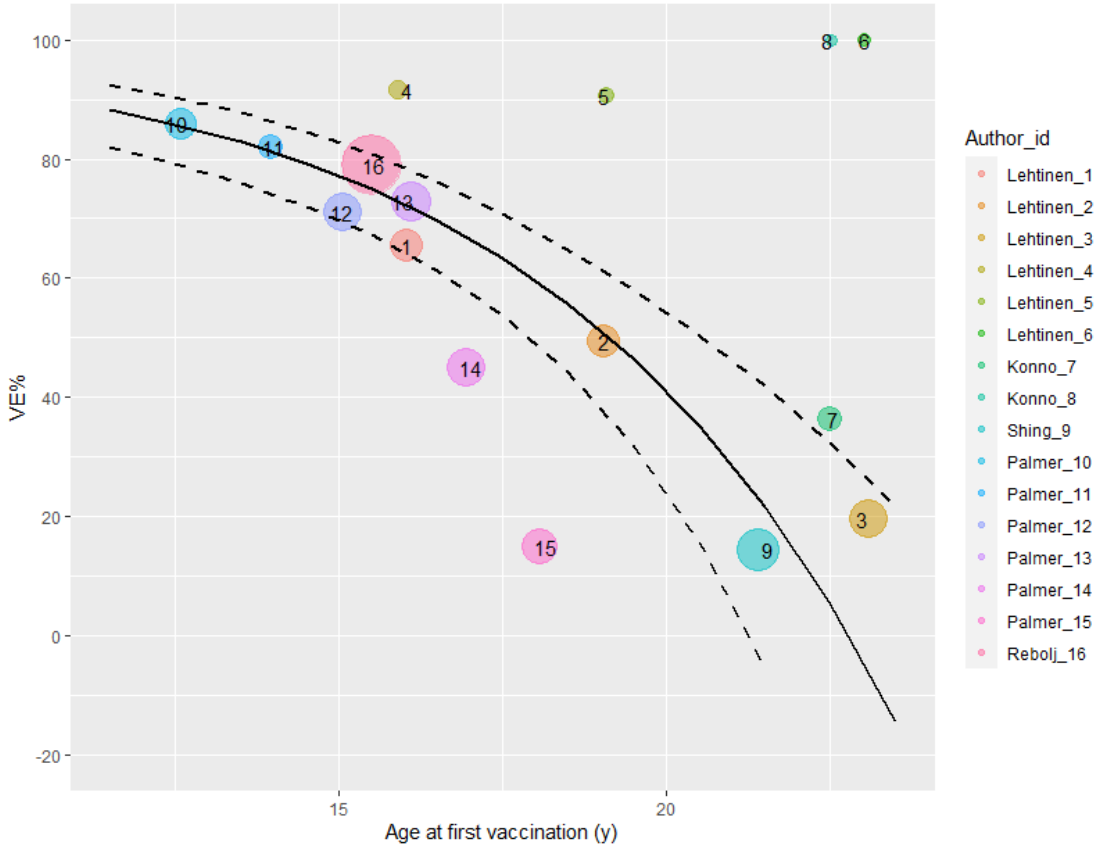
Figure 10 Univariate effect of study design on vaccine efficacy/effectiveness (Analysis 2)



Note for interpretation of graphs:
Lehtinen 1= Lehtinen 2012, age at first vaccination 15-17 years, TVC, time since vaccination 0-4 years.
Lehtinen 2= Lehtinen 2012, age at first vaccination 18-20 years, TVC, time since vaccination 0-4 years.
Lehtinen 3= Lehtinen 2012, age at first vaccination 21-25 years, TVC, time since vaccination 0-4 years.
Lehtinen 4= Lehtinen 2012, age at first vaccination 15-17 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 5= Lehtinen 2012, age at first vaccination 18-20 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 6= Lehtinen 2012, age at first vaccination 21-25 years, TVC naïve, time since vaccination 0-4 years.

Konno 7= Konno 2014, age at first vaccination 20-25 years, TVC, time since vaccination 0-4 years.
Konno 8= Konno 2014, age at first vaccination 20-25 years, TVC naïve, time since vaccination 0-4 years.
Shing 9= Shing 2022, age at first vaccination 18-25 years, TVC, time since vaccination 7-11 years.
Palmer 10= Palmer 2019, age at first vaccination 12-13 years, TVC, time since vaccination 0-8 years.
Palmer 11= Palmer 2019, age at first vaccination 14 years, TVC, time since vaccination 0-6 years.
Palmer 12= Palmer 2019, age at first vaccination 15 years, TVC, time since vaccination 0-5 years.
Palmer 13= Palmer 2019, age at first vaccination 16 years, TVC, time since vaccination 0-4 years.
Palmer 14= Palmer 2019, age at first vaccination 17 years, TVC, time since vaccination 0-3 years.
Palmer 10= Palmer 2019, age at first vaccination ≥18 years, TVC, time since vaccination 0-2 years.
Rebolj 16= Rebolj 2022, age at first vaccination 14-17 years, TVC, time since vaccination 7-11 years.
Abbreviations: VE=Vaccine effect, id=identity, Obs= Observational, RCT= randomized controlled trial.
Reference: [Lehtinen, 2012; Konno, 2014; Palmer, 2019; Shing, 2022; Rebolj, 2022]

Figure 11 Univariate effect of age at first vaccination on vaccine efficacy/effectiveness (Analysis 2)



Note for interpretation of graphs:
Lehtinen 1= Lehtinen 2012, age at first vaccination 15-17 years, TVC, time since vaccination 0-4 years.
Lehtinen 2= Lehtinen 2012, age at first vaccination 18-20 years, TVC, time since vaccination 0-4 years.
Lehtinen 3= Lehtinen 2012, age at first vaccination 21-25 years, TVC, time since vaccination 0-4 years.
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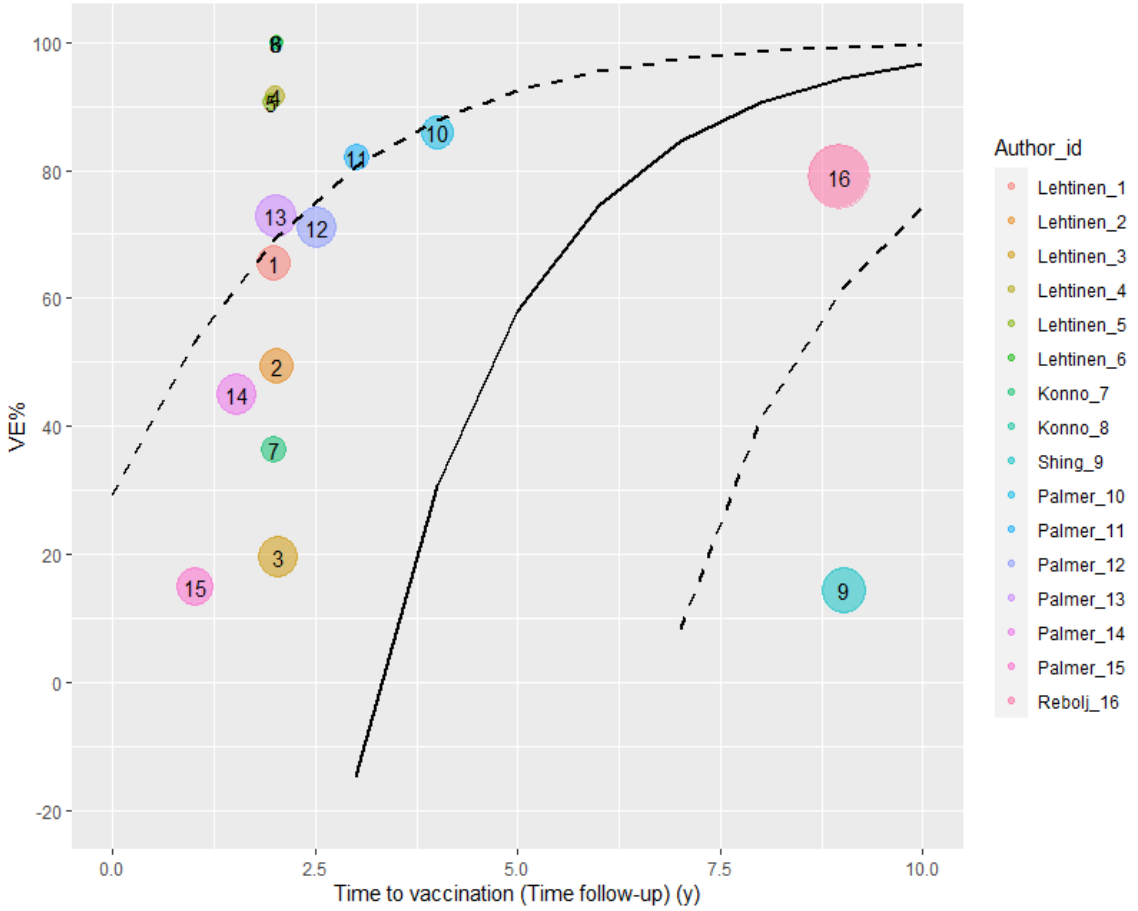
Lehtinen 5= Lehtinen 2012, age at first vaccination 18-20 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 6= Lehtinen 2012, age at first vaccination 21-25 years, TVC naïve, time since vaccination 0-4 years.
Konno 7= Konno 2014, age at first vaccination 20-25 years, TVC, time since vaccination 0-4 years.
Konno 8= Konno 2014, age at first vaccination 20-25 years, TVC naïve, time since vaccination 0-4 years.
Shing 9= Shing 2022, age at first vaccination 18-25 years, TVC, time since vaccination 7-11 years.
Palmer 10= Palmer 2019, age at first vaccination 12-13 years, TVC, time since vaccination 0-8 years.
Palmer 11= Palmer 2019, age at first vaccination 14 years, TVC, time since vaccination 0-6 years.

Palmer 12= Palmer 2019, age at first vaccination 15 years, TVC, time since vaccination 0-5 years.
Palmer 13= Palmer 2019, age at first vaccination 16 years, TVC, time since vaccination 0-4 years.
Palmer 14= Palmer 2019, age at first vaccination 17 years, TVC, time since vaccination 0-3 years.
Palmer 10= Palmer 2019, age at first vaccination ≥18 years, TVC, time since vaccination 0-2 years.
Rebolj 16= Rebolj 2022, age at first vaccination 14-17 years, TVC, time since vaccination 7-11 years.
Abbreviations: VE=Vaccine effect, id=identity, y=years.
Reference: [Lehtinen, 2012; Konno, 2014; Palmer, 2019; Shing, 2022; Rebolj, 2022].

Figure 12 Univariate effect of time since vaccination (time of follow-up) on vaccine efficacy/effectiveness (Analysis 2)



Note for interpretation of graphs:
Lehtinen 1= Lehtinen 2012, age at first vaccination 15-17 years, TVC, time since vaccination 0-4 years.
Lehtinen 2= Lehtinen 2012, age at first vaccination 18-20 years, TVC, time since vaccination 0-4 years.
Lehtinen 3= Lehtinen 2012, age at first vaccination 21-25 years, TVC, time since vaccination 0-4 years.
Lehtinen 4= Lehtinen 2012, age at first vaccination 15-17 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 5= Lehtinen 2012, age at first vaccination 18-20 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 6= Lehtinen 2012, age at first vaccination 21-25 years, TVC naïve, time since vaccination 0-4 years.
Konno 7= Konno 2014, age at first vaccination 20-25 years, TVC, time since vaccination 0-4 years.
Konno 8= Konno 2014, age at first vaccination 20-25 years, TVC naïve, time since vaccination 0-4 years.
Shing 9= Shing 2022, age at first vaccination 18-25 years, TVC, time since vaccination 7-11 years.
Palmer 10= Palmer 2019, age at first vaccination 12-13 years, TVC, time since vaccination 0-8 years.
Palmer 11= Palmer 2019, age at first vaccination 14 years, TVC, time since vaccination 0-6 years.
Palmer 12= Palmer 2019, age at first vaccination 15 years, TVC, time since vaccination 0-5 years.
Palmer 13= Palmer 2019, age at first vaccination 16 years, TVC, time since vaccination 0-4 years.
Palmer 14= Palmer 2019, age at first vaccination 17 years, TVC, time since vaccination 0-3 years.

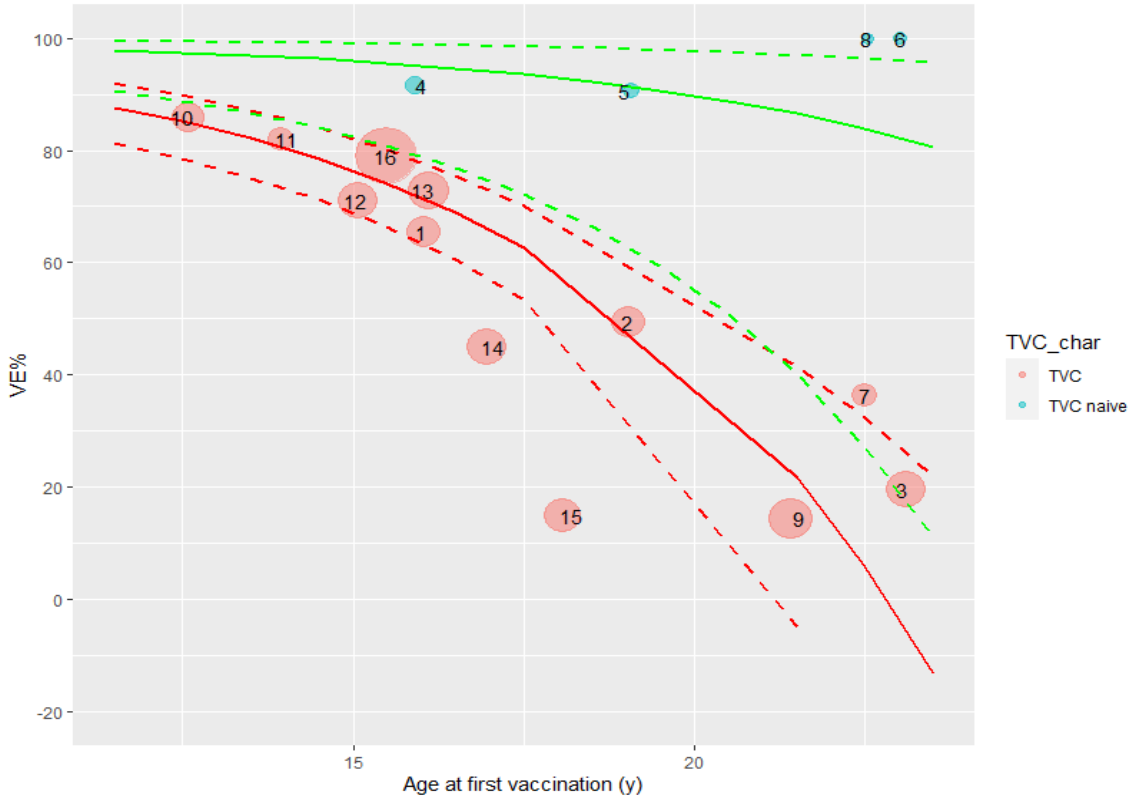
Palmer 10= Palmer 2019, age at first vaccination ≥18 years, TVC, time since vaccination 0-2 years.
Rebolj 16= Rebolj 2022, age at first vaccination 14-17 years, TVC, time since vaccination 7-11 years.
Abbreviations: VE=Vaccine effect, id=identity, y=years.
Reference: [Lehtinen, 2012; Konno, 2014; Palmer, 2019; Shing, 2022; Rebolj, 2022].

3. Multiparametric meta-regression analysis

All possible combinations of predictors were evaluated and compared using AIC (data-driven approach) to find the best model, and which predictors were the most important ones. This data-driven exploration conducted to a final model that includes the "age at first vaccination" and "analytical cohort" variables. After adjusting for the analytical cohort (TVC vs. TVC naïve), "age at first vaccination" resulted as the most impactful variable on the outcome (p<0.001). The heterogeneity explained by the selected model was R^2*= 87.47%.

The following figure shows the predictions (with 95% Confidence intervals, dotted line) from this data-driven selected model adjusting for "age at first vaccination" and "analytical cohort". Red and green curves represent the predicted vaccine effect as a function of age for TVC and TVC naïve populations. Red and blue bubbles represent the observed vaccine effects of the studies with TVC and TVC naïve population, respectively. Size of the bubbles is proportional to the inverse of the variance (it corresponds to the weight in a classical meta-analysis).

Figure 13 Results of the data-driven multiparametric meta-regression analysis model (Analysis 2)



Note for interpretation of graphs:
Lehtinen 1= Lehtinen 2012, age at first vaccination 15-17 years, TVC, time since vaccination 0-4 years.

Lehtinen 2= Lehtinen 2012, age at first vaccination 18-20 years, TVC, time since vaccination 0-4 years.
Lehtinen 3= Lehtinen 2012, age at first vaccination 21-25 years, TVC, time since vaccination 0-4 years.
Lehtinen 4= Lehtinen 2012, age at first vaccination 15-17 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 5= Lehtinen 2012, age at first vaccination 18-20 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 6= Lehtinen 2012, age at first vaccination 21-25 years, TVC naïve, time since vaccination 0-4 years.
Konno 7= Konno 2014, age at first vaccination 20-25 years, TVC, time since vaccination 0-4 years.
Konno 8= Konno 2014, age at first vaccination 20-25 years, TVC naïve, time since vaccination 0-4 years.
Shing 9= Shing 2022, age at first vaccination 18-25 years, TVC, time since vaccination 7-11 years.
Palmer 10= Palmer 2019, age at first vaccination 12-13 years, TVC, time since vaccination 0-8 years.
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Palmer 12= Palmer 2019, age at first vaccination 15 years, TVC, time since vaccination 0-5 years.
Palmer 13= Palmer 2019, age at first vaccination 16 years, TVC, time since vaccination 0-4 years.
Palmer 14= Palmer 2019, age at first vaccination 17 years, TVC, time since vaccination 0-3 years.
Palmer 10= Palmer 2019, age at first vaccination ≥18 years, TVC, time since vaccination 0-2 years.
Rebolj 16= Rebolj 2022, age at first vaccination 14-17 years, TVC, time since vaccination 7-11 years.
Abbreviations: VE=Vaccine effect, id=identity, TVC=total vaccinated cohort, y=years.
Reference: [Lehtinen, 2012; Konno, 2014; Palmer, 2019; Shing, 2022; Rebolj, 2022].

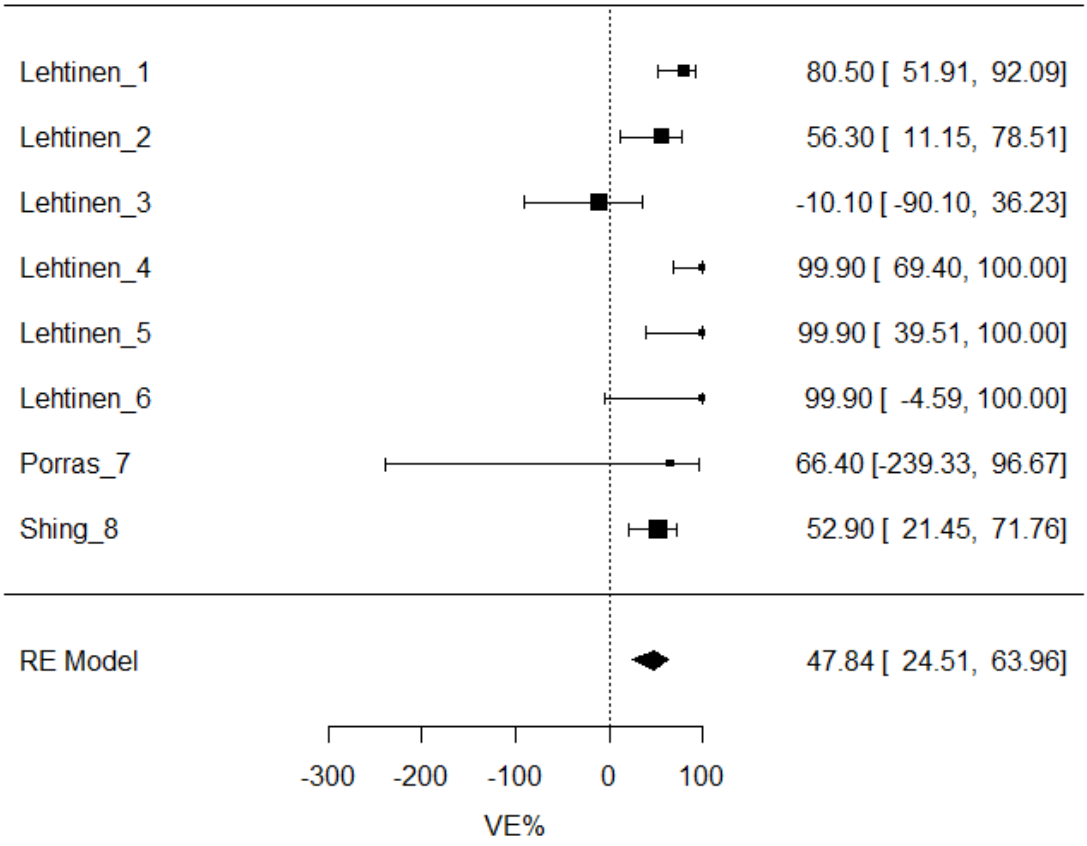
9.2.3. Analysis 3: What is the efficacy of CERVARIX on CIN3+ caused by vaccine HPV types? (RCTs only)

This analysis studied the combined effects of follow-up studies of RCT ([Lehtinen, 2012], including the TVC naïve and TVC; [Porras, 2020], TVC naïve; [Shing, 2022], TVC) of CERVARIX on CIN3+ caused by HPV 16/18 types. The rationale behind the selection of studies for this dataset was to include RCTs with outcome results on HPV 16/18 types. The RCT follow-up component of Shing, 2022 was included to consider the long-term follow-up of the CVT, although participants partially overlap with those of Porras, 2020, but with a different approach to the analytical cohort [Porras, 2020; Shing, 2022] . The “study correlation” variable was used to account for the partial overlapping.

1. **Meta-analysis***. Pooled vaccine efficacy was determined at vaccine efficacy= 47.84% (95%CI, 24.51-63.96) (Figure 14).

*Meta-analysis is done on the log relative risk scale assuming normality. Then results are back transformed to the vaccine effects scale. Therefore, some differences may be found in 95%CI between the pooled vaccine efficacy provided in the datasets and those estimated in the meta-analysis.

Figure 14 Pooled estimated Vaccine efficacy of CERVARIX on CIN3+ caused by HPV 16/18 types (Analysis 3)



Note for interpretation of graphs:
Lehtinen 1= Lehtinen 2012, age at first vaccination 15-17 years, TVC, time since vaccination 0-4 years.
Lehtinen 2= Lehtinen 2012, age at first vaccination 18-20 years, TVC, time since vaccination 0-4 years.
Lehtinen 3= Lehtinen 2012, age at first vaccination 21-25 years, TVC, time since vaccination 0-4 years.
Lehtinen 4= Lehtinen 2012, age at first vaccination 15-17 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 5= Lehtinen 2012, age at first vaccination 18-20 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 6= Lehtinen 2012, age at first vaccination 21-25 years, TVC naïve, time since vaccination 0-4 years.
Porras 7= Porras 2020, age at first vaccination 18-25 years, TVC naïve, time since vaccination 0-4 years.
Shing 8= Shing 2022, age at first vaccination 18-25 years, TVC, time since vaccination 1-4 years.
Abbreviations: VE=Vaccine efficacy, RE=random effects.
Reference: [Lehtinen, 2012; Porras, 2020; Shing, 2022]

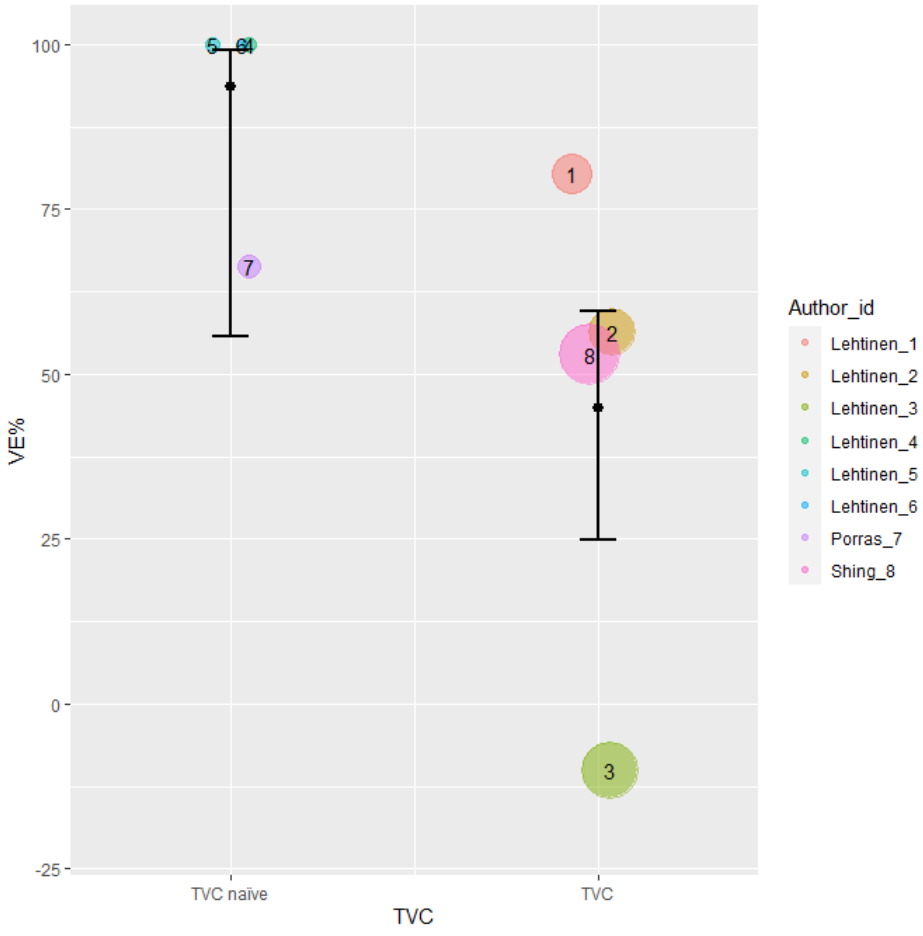
The most remarkable aspect of this meta-analysis is that the lower limit of the 95%CI for some individual vaccine efficacy estimates is negative. This is the case of the Porras 2020 study that shows a very wide 95% CI. In case of the Lehtinen, 2012 study, the point estimate for vaccine efficacy corresponding to the age group 21-25 years at first vaccination (Lehtinen 3), is negative whereas vaccine efficacy=100% for all age groups in the TVC naïve cohort, indicating within-trial variability [Lehtinen, 2012]. Negative lower limits occur only for wide confidence intervals. As wide negative confidence intervals are not given much weight in the model, the corresponding studies do not

largely contribute to the pooled effect. Therefore, the pooled estimate for vaccine efficacy of all RCTs against CIN3+ caused by HPV 16/18 types was vaccine efficacy= 47.84 (95%CI, 24.51-63.96).

2. Univariate meta-regression analysis

Results from this analysis showed that the variables “age at first vaccination” (p=0.0136), and “analytical cohort” (TVC vs. TVC naïve, p=0.0751) presented association (even if weak for the “analytical cohort” variable) with the outcome vaccine efficacy (small p values in the univariate meta-regression analysis model). All estimates suggests that the vaccine efficacy decreases with age at first vaccination and is lower in the TVC population (irrespective of HPV baseline status of participants). Figures below show the observed and the predicted vaccine efficacy (black line with 95%CI) as a function of the univariate covariates. Size of the bubbles is proportional to the inverse of the variance (it corresponds to the weight in a classical meta-analysis).

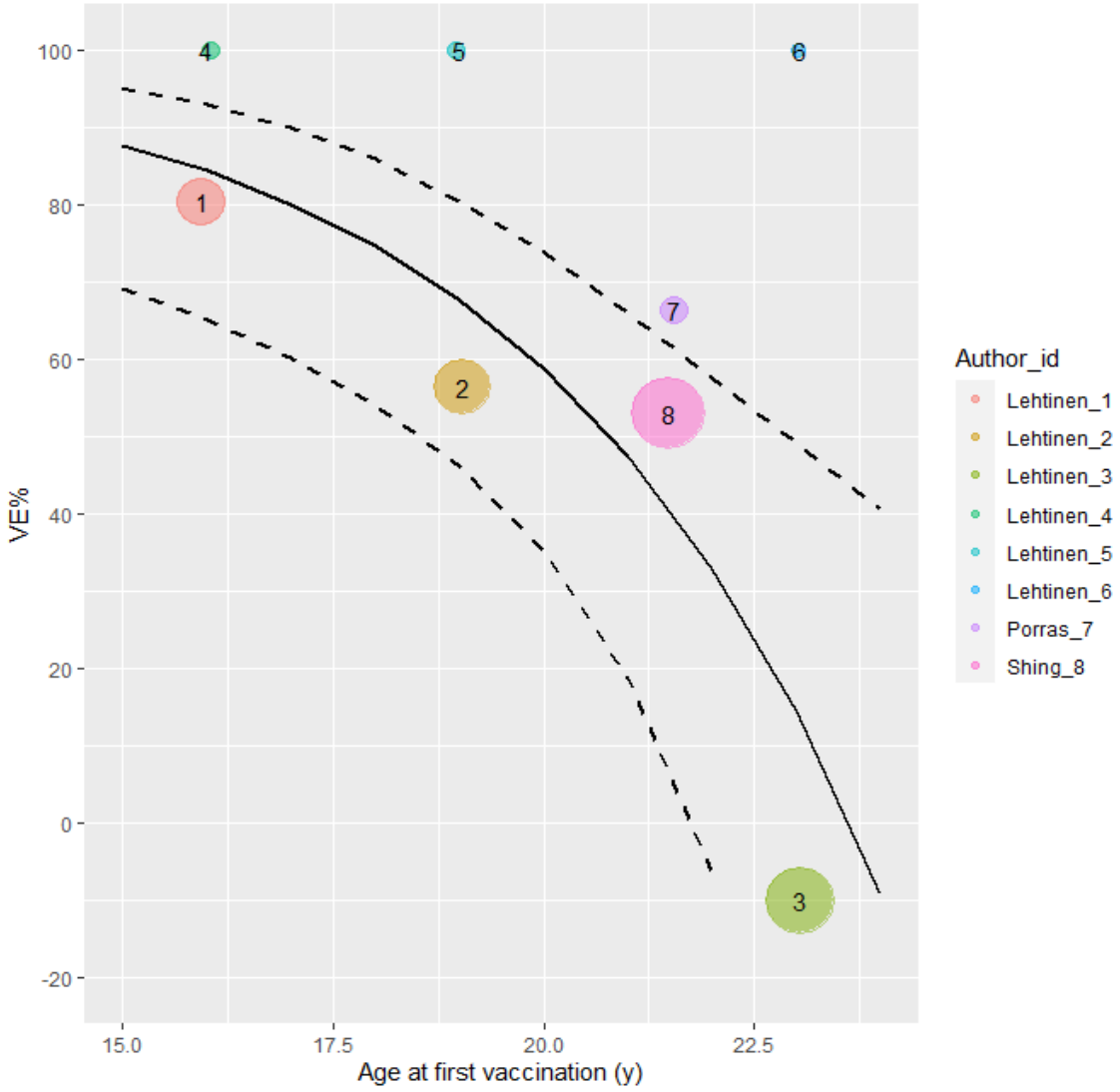
Figure 15 Univariate effect of analytical cohort on vaccine efficacy (Analysis 3)



Note for interpretation of graphs:
Lehtinen 1= Lehtinen 2012, age at first vaccination 15-17 years, TVC, time since vaccination 0-4 years.
Lehtinen 2= Lehtinen 2012, age at first vaccination 18-20 years, TVC, time since vaccination 0-4 years.
Lehtinen 3= Lehtinen 2012, age at first vaccination 21-25 years, TVC, time since vaccination 0-4 years.
Lehtinen 4= Lehtinen 2012, age at first vaccination 15-17 years, TVC naïve, time since vaccination 0-4 years.

Lehtinen 5= Lehtinen 2012, age at first vaccination 18-20 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 6= Lehtinen 2012, age at first vaccination 21-25 years, TVC naïve, time since vaccination 0-4 years.
Porras 7= Porras 2020, age at first vaccination 18-25 years, TVC naïve, time since vaccination 0-4 years.
Shing 8= Shing 2022, age at first vaccination 18-25 years, TVC, time since vaccination 1-4 years.
Abbreviations: VE=Vaccine efficacy, id=identity, TVC=total vaccinated cohort.
Reference: [Lehtinen, 2012; Porras, 2020; Shing, 2022].

Figure 16 Univariate effect of age at first vaccination on vaccine efficacy (Analysis 3)



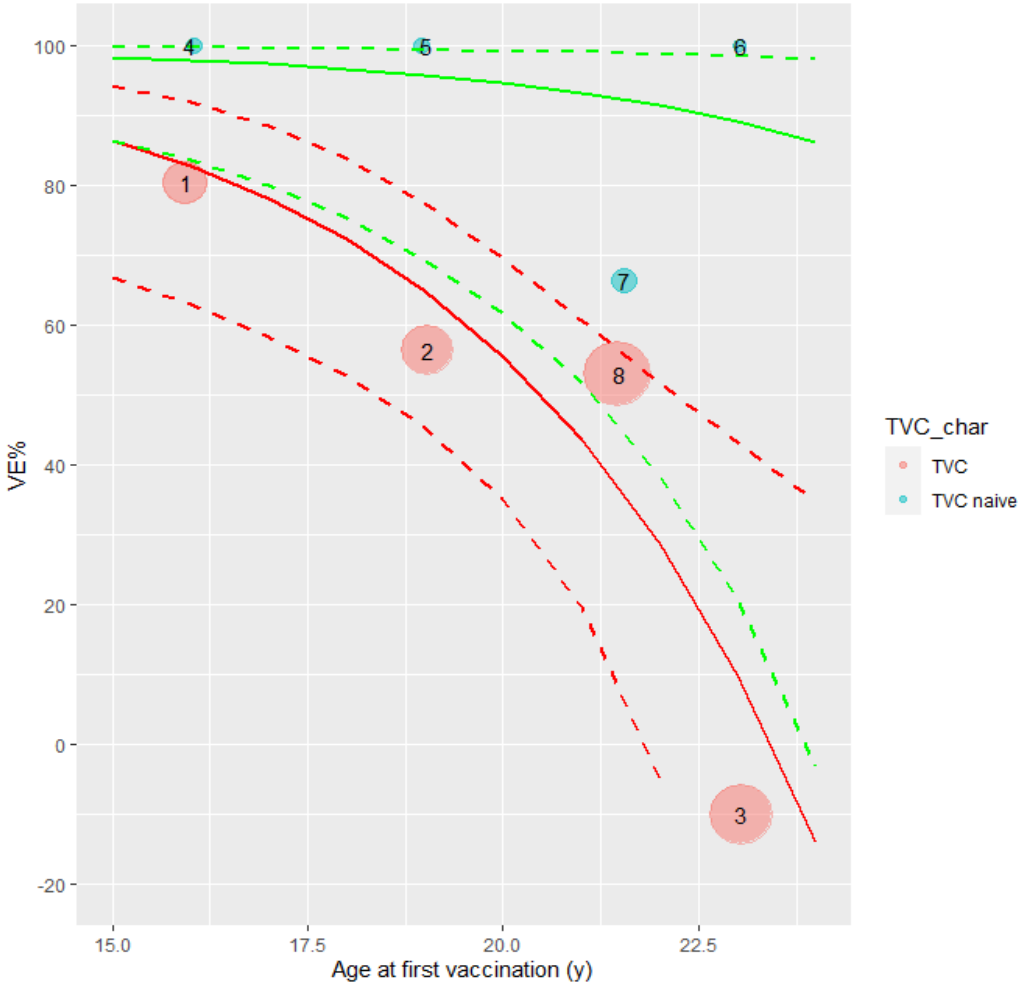
Note for interpretation of graphs:
Lehtinen 1= Lehtinen 2012, age at first vaccination 15-17 years, TVC, time since vaccination 0-4 years.
Lehtinen 2= Lehtinen 2012, age at first vaccination 18-20 years, TVC, time since vaccination 0-4 years.
Lehtinen 3= Lehtinen 2012, age at first vaccination 21-25 years, TVC, time since vaccination 0-4 years.
Lehtinen 4= Lehtinen 2012, age at first vaccination 15-17 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 5= Lehtinen 2012, age at first vaccination 18-20 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 6= Lehtinen 2012, age at first vaccination 21-25 years, TVC naïve, time since vaccination 0-4 years.
Porras 7= Porras 2020, age at first vaccination 18-25 years, TVC naïve, time since vaccination 0-4 years.
Shing 8= Shing 2022, age at first vaccination 18-25 years, TVC, time since vaccination 1-4 years.
Abbreviations: VE=Vaccine efficacy, id=identity, y=years.
Reference: [Lehtinen, 2012; Porras, 2020; Shing, 2022].

3. Multiparametric meta-regression analysis

All possible combinations of predictors were evaluated and compared using AIC (data-driven approach) to find the best model, and which predictors were the most important ones. This data-driven exploration conducted to a final model that includes the "age at first vaccination" and "analytical cohort" variables. After adjusting for the analytical cohort (TVC vs. TVC naïve), "age at first vaccination" resulted as the most impactful variable on the outcome (p=0.02). The heterogeneity explained by the selected model was R^2*= 92.95%.

The following figure shows the predictions (with 95% Confidence intervals, dotted line) from this data-driven selected model adjusting for "age at first vaccination" and "analytical cohort". Red and green curves represent the predicted vaccine efficacy as a function of age for TVC and TVC naïve populations. Red and blue bubbles represent the observed vaccine efficacies of the studies with TVC and TVC naïve population, respectively. Size of the bubbles is proportional to the inverse of the variance (it corresponds to the weight in classical meta-analysis). Observed values seem to be relatively well approximated by the multiparametric model.

Figure 17 Results of the data-driven multiparametric meta-regression analysis model (Analysis 3)



Note for interpretation of graphs:
Lehtinen 1= Lehtinen 2012, age at first vaccination 15-17 years, TVC, time since vaccination 0-4 years.
Lehtinen 2= Lehtinen 2012, age at first vaccination 18-20 years, TVC, time since vaccination 0-4 years.
Lehtinen 3= Lehtinen 2012, age at first vaccination 21-25 years, TVC, time since vaccination 0-4 years.
Lehtinen 4= Lehtinen 2012, age at first vaccination 15-17 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 5= Lehtinen 2012, age at first vaccination 18-20 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 6= Lehtinen 2012, age at first vaccination 21-25 years, TVC naïve, time since vaccination 0-4 years.
Porras 7= Porras 2020, age at first vaccination 18-25 years, TVC naïve, time since vaccination 0-4 years.
Shing 8= Shing 2022, age at first vaccination 18-25 years, TVC, time since vaccination 1-4 years.
Abbreviations: VE=Vaccine efficacy, id=identity, TVC=total vaccinated cohort, y=years.
Reference: [Lehtinen, 2012; Porras, 2020; Shing, 2022].

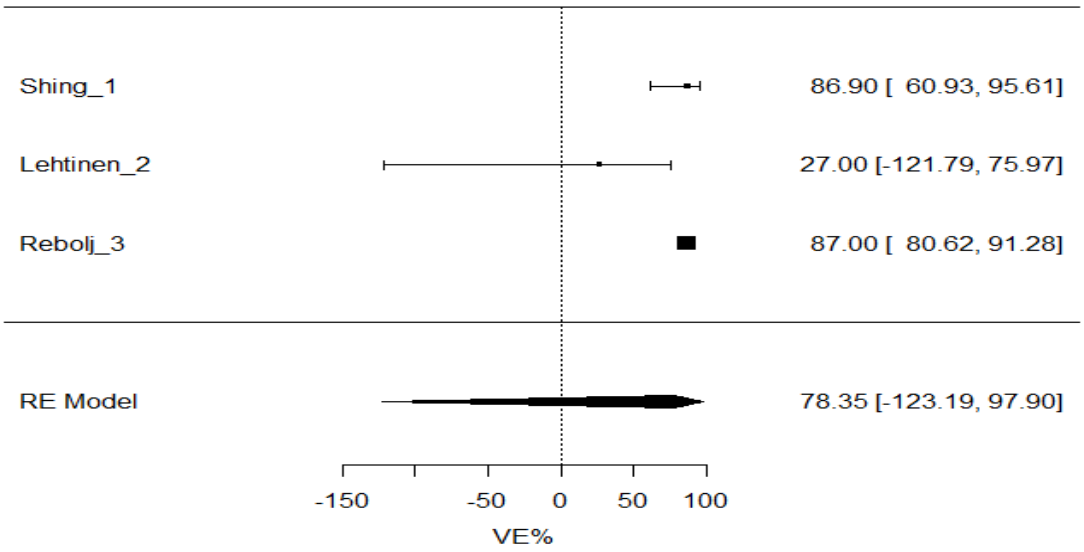
9.2.4. Analysis 4: What is the effectiveness of CERVARIX on CIN3+ caused by vaccine HPV types? (Observational studies only)

This analysis studied the combined effects of follow-up studies of observational studies ([Shing, 2022], TVC; [Lehtinen, 2017], TVC; [Rebolj, 2022], TVC) of CERVARIX on CIN3+ caused by HPV 16/18 types. The rationale behind the selection of studies for this dataset was to include observational studies with outcome results on HPV 16/18 types. Shing et al was included (instead of the observational component of Porras, 2020) to align with the other observational studies that used the TVC as analytical cohort.

1. **Meta-analysis***. Pooled VE were determined at VE=78.35 (95%CI, -123.19, 97.90) (Figure 18).

*Meta-analysis is done on the log relative risk scale assuming normality. Then results are back transformed to the vaccine effects scale. Therefore, some differences may be found in 95%CI between the pooled VE provided in the datasets and those estimated in the meta-analysis.

Figure 18 Pooled estimated VEs of CERVARIX on CIN3+ caused by HPV 16/18 types (Analysis 4)



Note for interpretation of graphs:

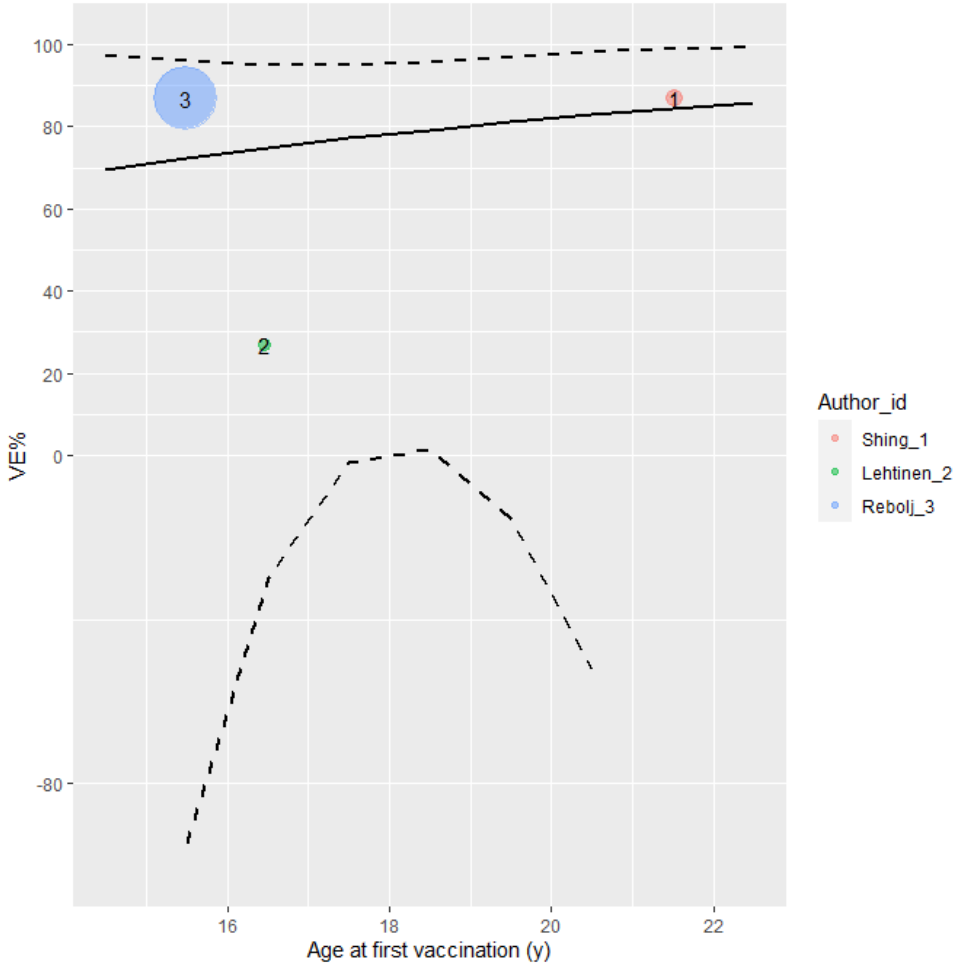
Shing 1= Shing 2022, age at first vaccination 18-25 years, TVC, time since vaccination 7-11 years.
Lehtinen 2= Lehtinen 2017, age at first vaccination 16-17 years, TVC, time since vaccination 0-10 years.
Rebolj 16= Rebolj 2022, age at first vaccination 14-17 years, TVC, time since vaccination 7-11 years.
Abbreviation: VE=vaccine effects, RE=random effects.
Reference: [Lehtinen, 2017; Shing, 2022; Rebolj, 2022].

The most remarkable aspect of this meta-analysis is that the lower limit of 95%CI for an individual VE estimate is negative. This is the case of the Lehtinen 2017 [Lehtinen 2] study that shows a very wide 95%CI [Lehtinen, 2017].

2. Univariate meta-regression analysis

Results from this analysis did not detect a strong univariate association between individual covariates and the outcome (VE) probably due to the small number of studies. Figures below show the observed and the predicted VE (black line with 95%CI) as a function of the univariate covariates. Size of the bubbles is proportional to the inverse of the variance (it corresponds to the weight in a classical meta-analysis).

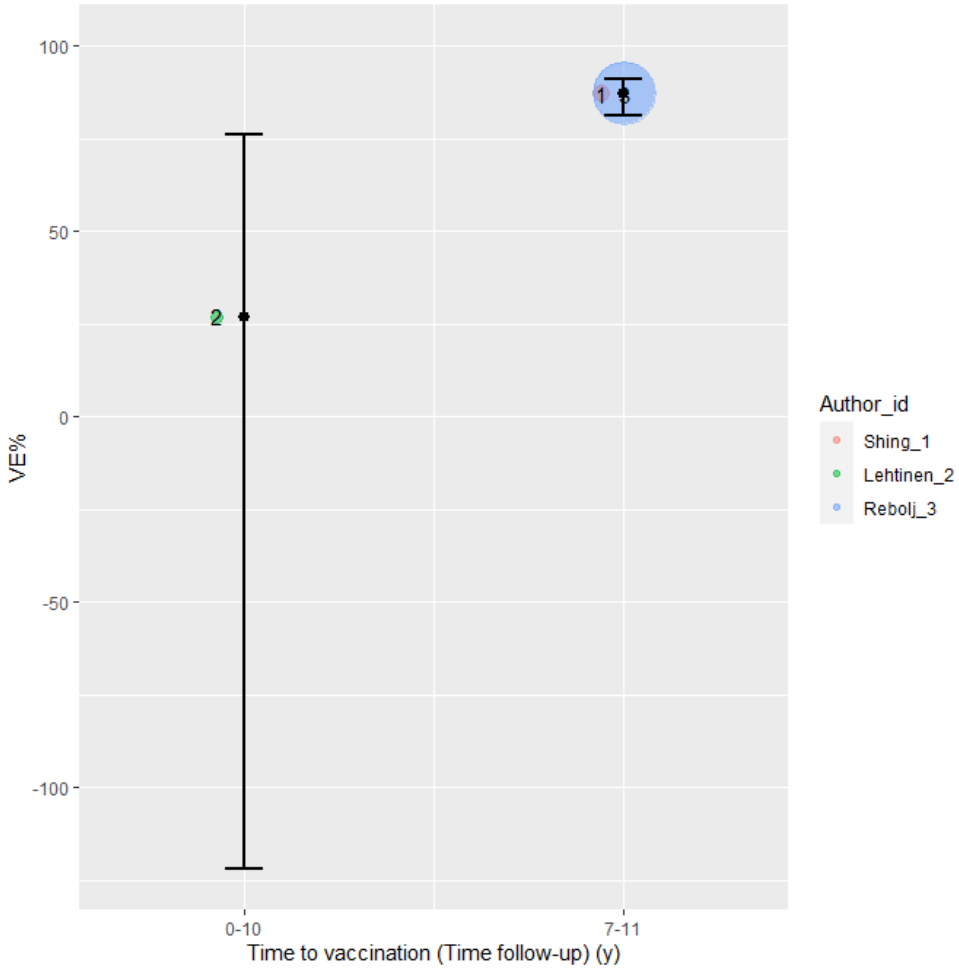
Figure 19 Univariate effect of age at first vaccination on vaccine effectiveness (Analysis 4)



Note for interpretation of graphs:
Shing 1= Shing 2022, age at first vaccination 18-25 years, TVC, time since vaccination 7-11 years.

Lehtinen 2= Lehtinen 2017, age at first vaccination 16-17 years, TVC, time since vaccination 0-10 years.
Rebolj 16= Rebolj 2022, age at first vaccination 14-17 years, TVC, time since vaccination 7-11 years.
Abbreviations: VE=Vaccine effect, id=identity, y=years.
Reference: [Lehtinen, 2017; Shing, 2022; Rebolj, 2022].

Figure 20 Univariate effect of time since vaccination (time of follow-up) on vaccine effectiveness (Analysis 4)



Note for interpretation of graphs:
Shing 1= Shing 2022, age at first vaccination 18-25 years, TVC, time since vaccination 7-11 years.
Lehtinen 2= Lehtinen 2017, age at first vaccination 16-17 years, TVC, time since vaccination 0-10 years.
Rebolj 16= Rebolj 2022, age at first vaccination 14-17 years, TVC, time since vaccination 7-11 years.
Abbreviations: VE=Vaccine effect, id=identity, y=years.
Reference: [Lehtinen, 2017; Shing, 2022; Rebolj, 2022].

3. Multiparametric meta-regression analysis

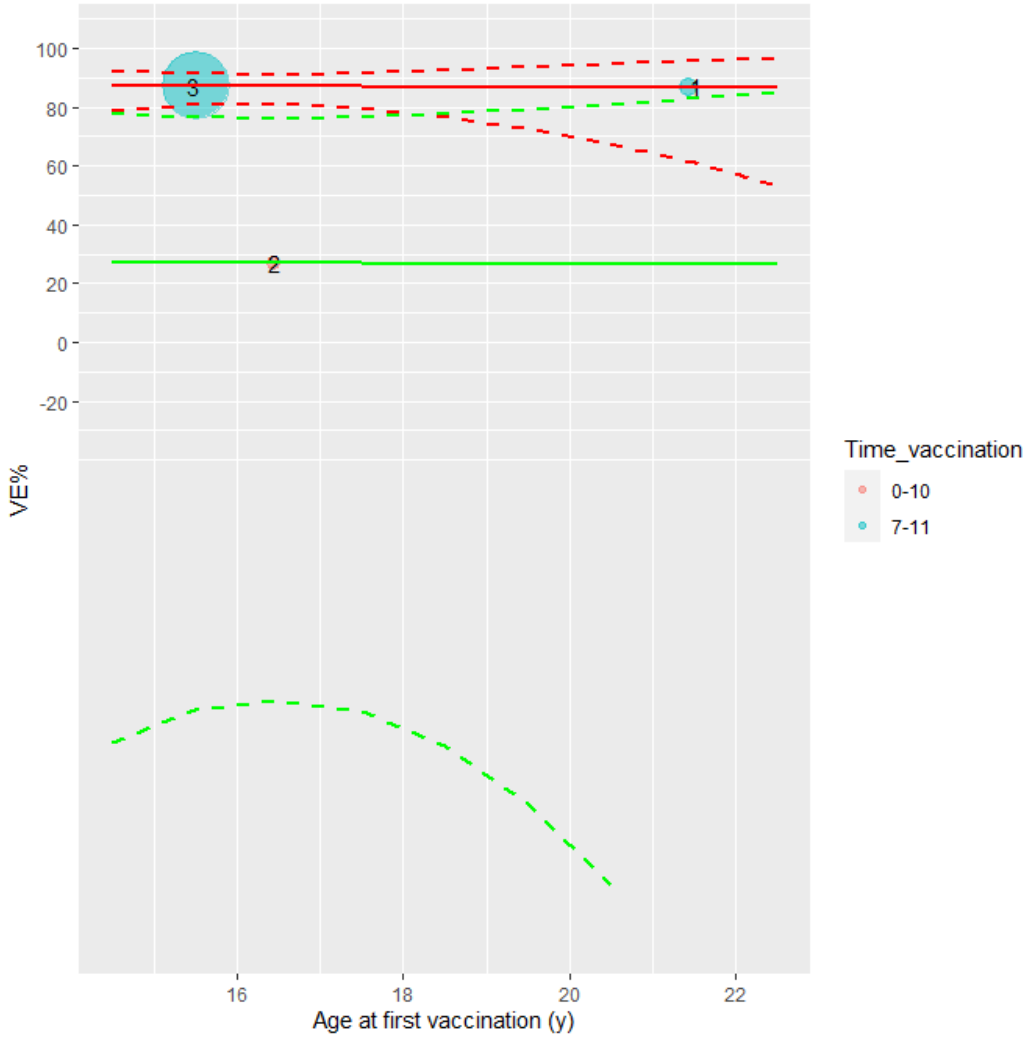
All possible combinations of predictors were evaluated and compared using AIC (data-driven approach) to find the best model, and which predictors were the most important ones. The analysis revealed that the model including “age at first vaccination” and “time since vaccination” showed a strong correlation between the two covariates. When these two covariates are included in the model, it becomes unstable, and the variance of the

random effect makes it uninterpretable. Adjusting for covariates for this specific question is not meaningful.

The heterogeneity explained by the selected model was R^2*= 100%. However, this result should be interpreted cautiously as the model was unable to properly estimate the random effect likely because of the small number of studies included in the analysis with respect to the two covariates considered.

The following figure shows the predictions (with 95% Confidence intervals, dotted line) from this data-driven selected model adjusting for “age at first vaccination” and “time since vaccination”. Red and green curves represent the predicted VE as a function of age for the time since vaccination. Red and blue bubbles represent the observed VE of the studies with different time since vaccination, respectively. Size of the bubbles is proportional to the inverse of the variance (it corresponds to the weight in a classical meta-analysis).

Figure 21 Results of the data-driven multiparametric meta-regression analysis model (Analysis 4)



Note for interpretation of graphs:
Shing 1= Shing 2022, age at first vaccination 18-25 years, TVC, time since vaccination 7-11 years.
Lehtinen 2= Lehtinen 2017, age at first vaccination 16-17 years, TVC, time since vaccination 0-10 years.
Rebolj 16= Rebolj 2022, age at first vaccination 14-17 years, TVC, time since vaccination 7-11 years.
Abbreviations: VE=Vaccine effect, y=years.
Reference: [Lehtinen, 2017; Shing, 2022; Rebolj, 2022].

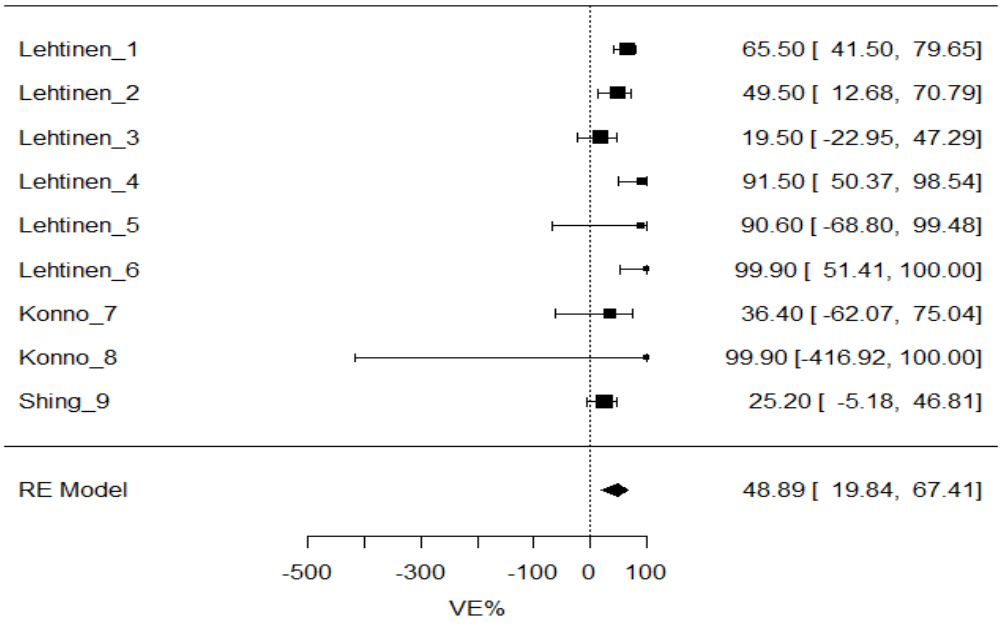
9.2.5. Analysis 5: What is the efficacy of CERVARIX on CIN3+ caused by any HPV type? (RCTs only)

This analysis studied the combined effects of follow-up studies of RCT ([Lehtinen, 2012], including the TVC naïve and TVC; [Konno, 2014], TVC and TVC naïve; [Shing, 2022], TVC) of CERVARIX on CIN3+ caused by any HPV type. The rationale behind the selection of studies for this dataset was to include RCTs with outcome results irrespective of the HPV types. The RCT follow-up TVC component of Shing, 2022 was included to consider the long-term follow-up of the CVT [Shing, 2022]. Since results from Konno, 2014 for the two analytical cohorts (TVC naïve and TVC) were included, the "study correlation" variable was used to account for the partial overlapping [Konno, 2014]. Overall, this approach was followed to maximize the amount of information for this analysis.

1. **Meta-analysis***. Pooled vaccine efficacy were determined at vaccine efficacy= 48.89 (95%CI, 19.84-67.41)

*Meta-analysis is done on the log relative risk scale assuming normality. Then results are back transformed to the vaccine effects scale. Therefore, some differences may be found in 95%CI between the pooled vaccine efficacy provided in the datasets and those estimated in the meta-analysis.

Figure 22 Pooled estimated vaccine efficacy of CERVARIX on CIN3+ caused by any HPV type (Analysis 5)



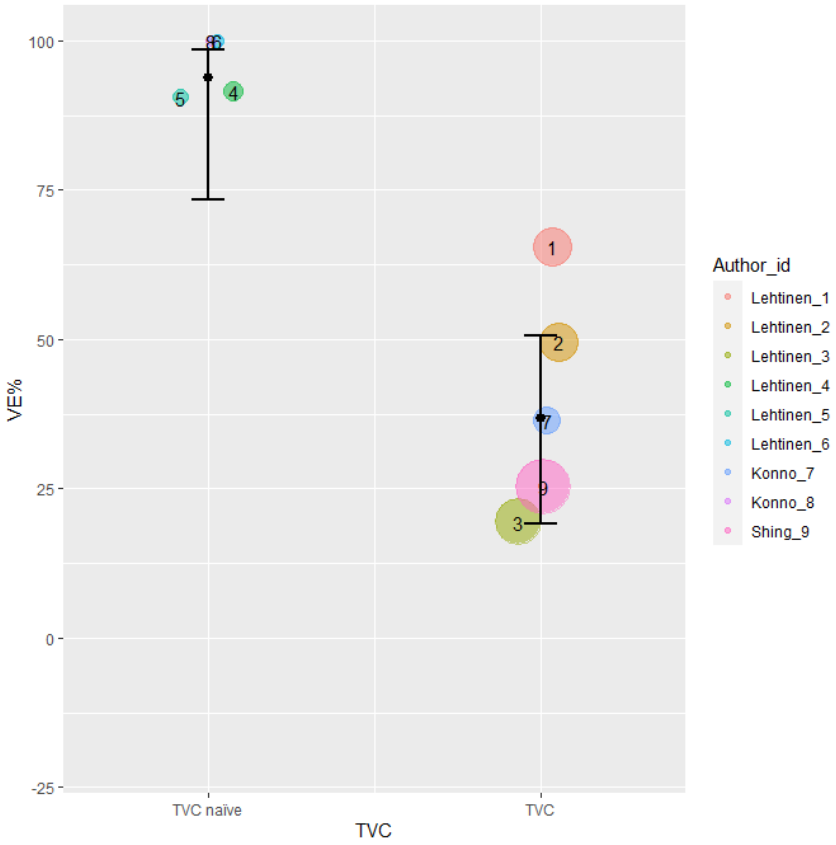
Note for interpretation of graphs:
Lehtinen 1= Lehtinen 2012, age at first vaccination 15-17 years, TVC, time since vaccination 0-4 years.
Lehtinen 2= Lehtinen 2012, age at first vaccination 18-20 years, TVC, time since vaccination 0-4 years.
Lehtinen 3= Lehtinen 2012, age at first vaccination 21-25 years, TVC, time since vaccination 0-4 years.
Lehtinen 4= Lehtinen 2012, age at first vaccination 15-17 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 5= Lehtinen 2012, age at first vaccination 18-20 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 6= Lehtinen 2012, age at first vaccination 21-25 years, TVC naïve, time since vaccination 0-4 years.
Konno 7= Konno 2014, age at first vaccination 20-25 years, TVC, time since vaccination 0-4 years.
Konno 8= Konno 2014, age at first vaccination 20-25 years, TVC naïve, time since vaccination 0-4 years.
Shing 9= Shing 2022, age at first vaccination 18-25 years, TVC, time since vaccination 1-4 years.
Abbreviations: VE=Vaccine efficacy, RE=random effects.
Reference: ([Lehtinen, 2012; Konno, 2014; Shing, 2022].

The most relevant feature of this Forest plot is that the lower limit of the 95%CI for some individual vaccine efficacy estimates is negative. This is especially relevant for Konno 2014 (TVC naïve cohort) (Konno 8), as already described in Section 7.8.1 [Konno, 2014]. Therefore, due to the strong weight of other studies, the combined pooled estimate reached vaccine efficacy=48.89 (95%CI, 19.84-67.41).

2. Univariate meta-regression analysis

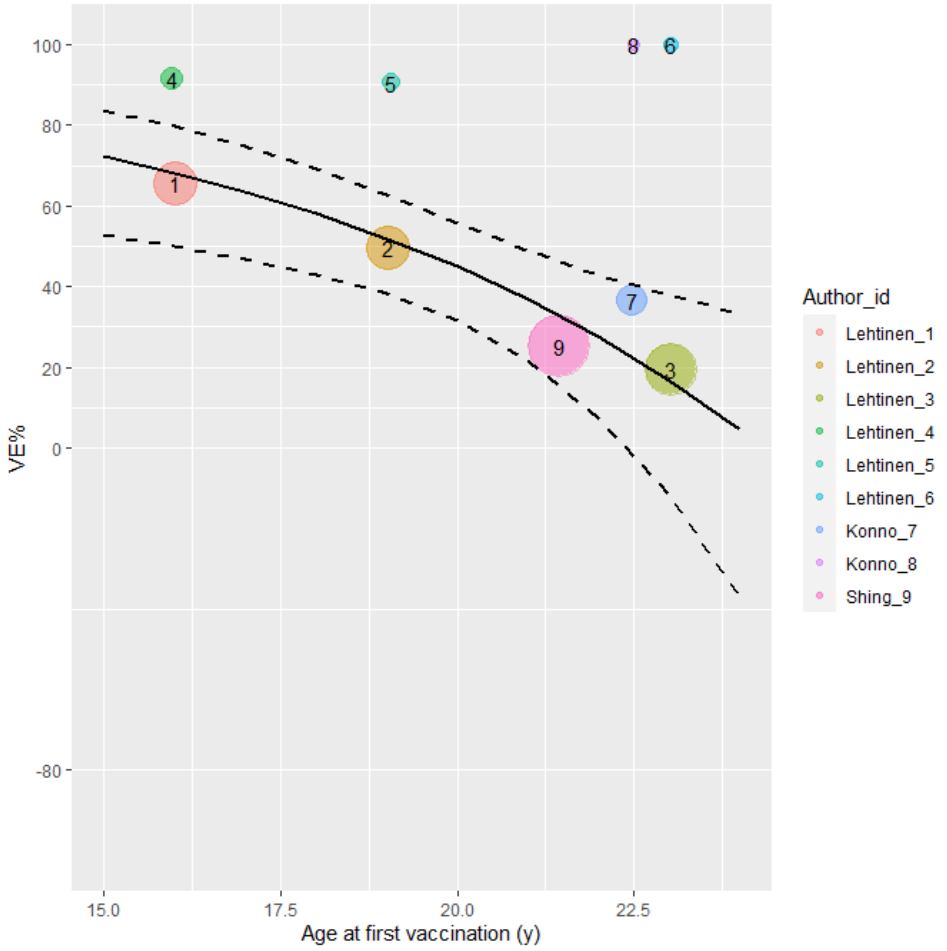
Results from this analysis showed that the variables “age at first vaccination” (p=0.0168), and “analytical cohort” (TVC vs. TVC naïve, p=0.0172) presented association with the outcome vaccine efficacy (small p values in the univariate meta-regression analysis model). All estimates suggests that the vaccine efficacy decreases with age at first vaccination, and is lower in the TVC population (irrespective of HPV baseline status of participants) compared to the TVC naïve (HPV negative at baseline). Figures below show the observed and the predicted vaccine efficacy (black line with 95%CI) as a function of the univariate covariates. Size of the bubbles is proportional to the inverse of the variance (it corresponds to the weight in a classical meta-analysis).

Figure 23 Univariate effect of analytical cohort on vaccine efficacy (Analysis 5)



Note for interpretation of graphs:
Lehtinen 1= Lehtinen 2012, age at first vaccination 15-17 years, TVC, time since vaccination 0-4 years.
Lehtinen 2= Lehtinen 2012, age at first vaccination 18-20 years, TVC, time since vaccination 0-4 years.
Lehtinen 3= Lehtinen 2012, age at first vaccination 21-25 years, TVC, time since vaccination 0-4 years.
Lehtinen 4= Lehtinen 2012, age at first vaccination 15-17 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 5= Lehtinen 2012, age at first vaccination 18-20 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 6= Lehtinen 2012, age at first vaccination 21-25 years, TVC naïve, time since vaccination 0-4 years.
Konno 7= Konno 2014, age at first vaccination 20-25 years, TVC, time since vaccination 0-4 years.
Konno 8= Konno 2014, age at first vaccination 20-25 years, TVC naïve, time since vaccination 0-4 years.
Shing 9= Shing 2022, age at first vaccination 18-25 years, TVC, time since vaccination 1-4 years.
Abbreviations: VE=Vaccine efficacy, id=identity, TVC=total vaccinated cohort.
Reference: [Lehtinen, 2012; Konno, 2014; Shing, 2022].

Figure 24 Univariate effect of age at first vaccination on vaccine efficacy (Analysis 5)



Note for interpretation of graphs:
Lehtinen 1= Lehtinen 2012, age at first vaccination 15-17 years, TVC, time since vaccination 0-4 years.
Lehtinen 2= Lehtinen 2012, age at first vaccination 18-20 years, TVC, time since vaccination 0-4 years.
Lehtinen 3= Lehtinen 2012, age at first vaccination 21-25 years, TVC, time since vaccination 0-4 years.
Lehtinen 4= Lehtinen 2012, age at first vaccination 15-17 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 5= Lehtinen 2012, age at first vaccination 18-20 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 6= Lehtinen 2012, age at first vaccination 21-25 years, TVC naïve, time since vaccination 0-4 years.
Konno 7= Konno 2014, age at first vaccination 20-25 years, TVC, time since vaccination 0-4 years.
Konno 8= Konno 2014, age at first vaccination 20-25 years, TVC naïve, time since vaccination 0-4 years.
Shing 9= Shing 2022, age at first vaccination 18-25 years, TVC, time since vaccination 1-4 years.
Abbreviations: VE=Vaccine efficacy, id=identity, y=years.
Reference: [Lehtinen, 2012; Konno, 2014; Shing, 2022].

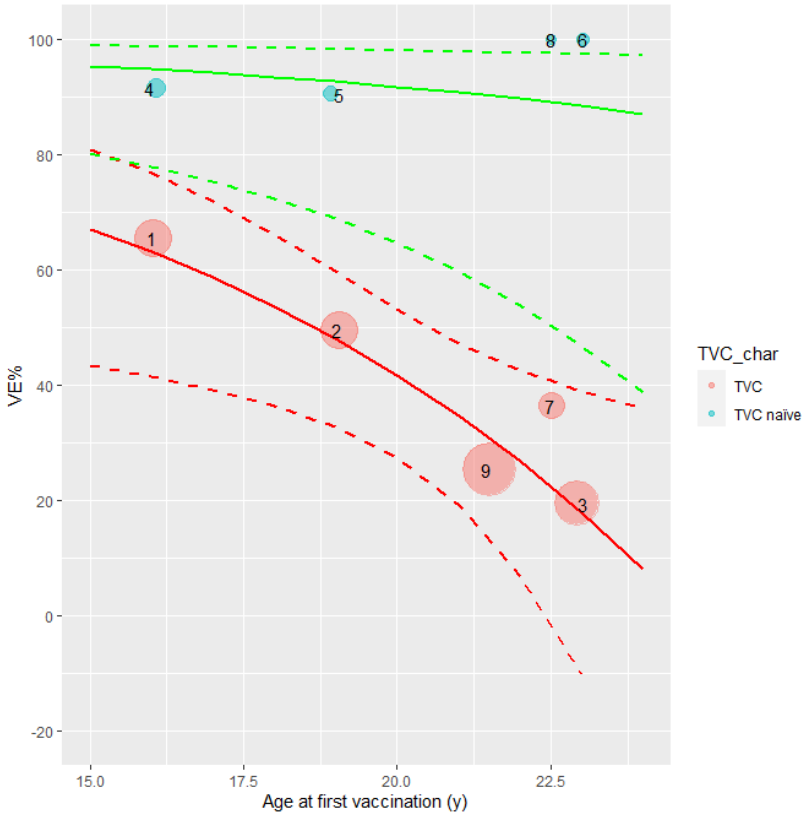
3. Multiparametric meta-regression analysis

All possible combinations of predictors were evaluated and compared using AIC (data-driven approach) to find the best model, and which predictors were the most important ones. This data-driven exploration conducted to a final model that includes the "age at first vaccination" and "analytical cohort" variables. After adjusting for the "analytical cohort", vaccine efficacy decreased with age at first vaccination.

The heterogeneity explained by the selected model was R^2*= 100%. This optimistic value is because the estimated between-trial variability is equal to "0". Therefore, the interpretation of this result should be prudent. However, as shown in Figure 25, the model is predicting the data very well.

The following figure shows the predictions (with 95% Confidence intervals, dotted line) from this data-driven selected model adjusting for "age at first vaccination" and "analytical cohort". Red and green curves represent the predicted vaccine efficacy as a function of age for the time since vaccination. Red and blue bubbles represent the observed vaccine efficacies of the studies with TVC and TVC naïve population, respectively. Size of the bubbles is proportional to the inverse of the variance (it corresponds to the weight in a classical meta-analysis). Observed values seem to be relatively well approximated by the multiparametric model.

Figure 25 Results of the data-driven multiparametric meta-regression analysis model (Analysis 5)



Note for interpretation of graphs:
Lehtinen 1= Lehtinen 2012, age at first vaccination 15-17 years, TVC, time since vaccination 0-4 years.
Lehtinen 2= Lehtinen 2012, age at first vaccination 18-20 years, TVC, time since vaccination 0-4 years.
Lehtinen 3= Lehtinen 2012, age at first vaccination 21-25 years, TVC, time since vaccination 0-4 years.
Lehtinen 4= Lehtinen 2012, age at first vaccination 15-17 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 5= Lehtinen 2012, age at first vaccination 18-20 years, TVC naïve, time since vaccination 0-4 years.
Lehtinen 6= Lehtinen 2012, age at first vaccination 21-25 years, TVC naïve, time since vaccination 0-4 years.
Konno 7= Konno 2014, age at first vaccination 20-25 years, TVC, time since vaccination 0-4 years.
Konno 8= Konno 2014, age at first vaccination 20-25 years, TVC naïve, time since vaccination 0-4 years.
Shing 9= Shing 2022, age at first vaccination 18-25 years, TVC, time since vaccination 1-4 years.

Abbreviations: VE=Vaccine efficacy, TVC=total vaccinated cohort, y=years.
Reference: [Lehtinen, 2012; Konno, 2014; Shing, 2022].

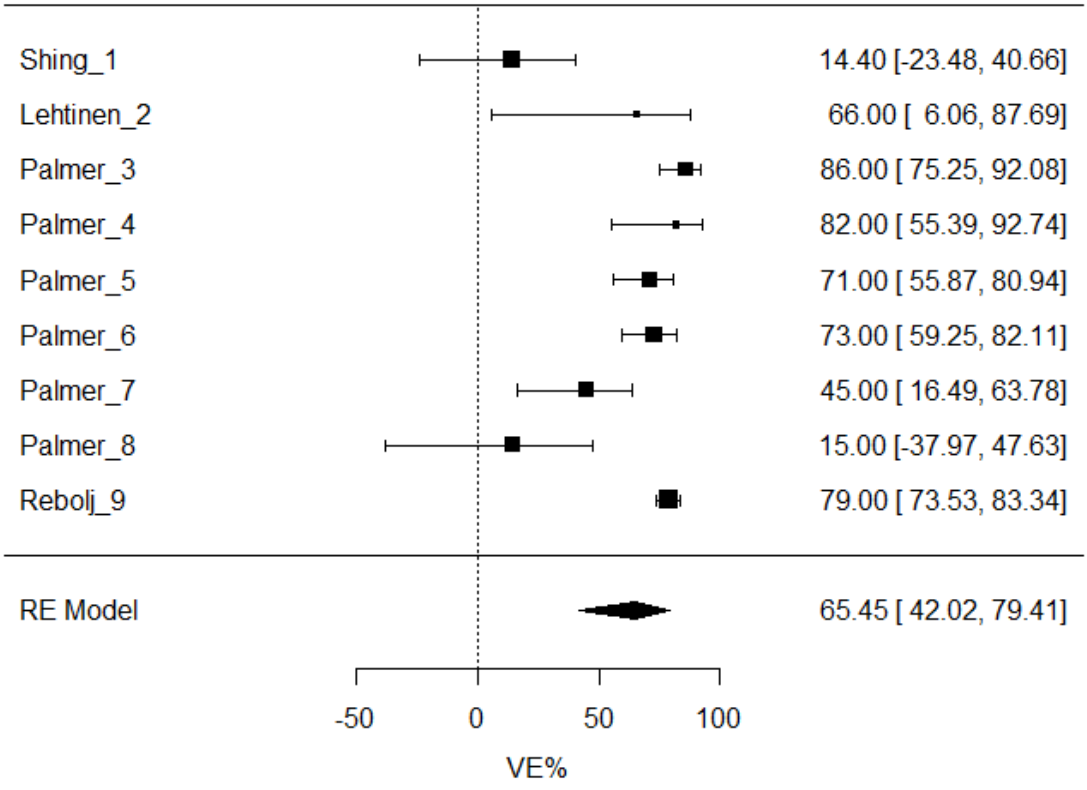
9.2.6. Analysis 6. What is the effectiveness of CERVARIX on CIN3+ caused by any HPV type? (Observational studies only)

This analysis studied the combined effects of observational studies ([Shing, 2022], TVC; [Lehtinen, 2017], TVC; [Palmer, 2019], TVC; [Rebolj, 2022], TVC) of CERVARIX on CIN3+ caused by any HPV type. The rationale behind the selection of studies for this dataset was to include observational studies with outcome results irrespective of the causing HPV type. The long-term follow-up TVC component of Shing, 2022 was included to consider the long-term follow-up of the CVT. Overall, this approach was followed to maximize the amount of information for this analysis.

1. **Meta-analysis***. Pooled VE were determined at VE= 65.45 (95%CI, 42.02-79.41)

*Meta-analysis is done on the log relative risk scale assuming normality. Then results are back transformed to the VE scale. Therefore, some differences may be found in 95%CI between the pooled VE provided in the datasets and those estimated in the meta-analysis.

Figure 26 Pooled estimated VEs of CERVARIX on CIN3+ caused by any HPV type (Analysis 6)



Note for interpretation of graphs:
Shing 1= Shing 2022, age at first vaccination 18-25 years, TVC, time since vaccination 7-11 years.
Lehtinen 2= Lehtinen 2017, age at first vaccination 16-17 years, TVC, time since vaccination 0-10 years.

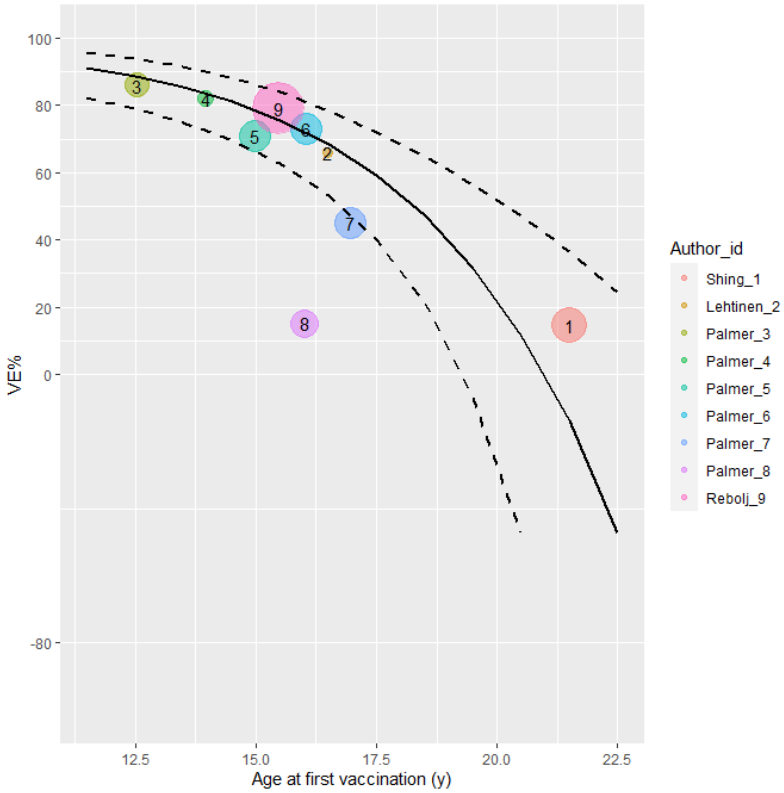
Palmer 3= Palmer 2019, age at first vaccination 12-13 years, TVC, time since vaccination 0-8 years.
Palmer 4= Palmer 2019, age at first vaccination 14 years, TVC, time since vaccination 0-6 years.
Palmer 5= Palmer 2019, age at first vaccination 15 years, TVC, time since vaccination 0-5 years.
Palmer 6= Palmer 2019, age at first vaccination 16 years, TVC, time since vaccination 0-4 years.
Palmer 7= Palmer 2019, age at first vaccination 17 years, TVC, time since vaccination 0-3 years.
Palmer 8= Palmer 2019, age at first vaccination ≥18 years, TVC, time since vaccination 0-2 years.
Rebolj 9= Rebolj 2022, age at first vaccination 14-17 years, TVC, time since vaccination 7-11 years.
Abbreviations: VE=vaccine effects, RE=random effect.
Reference: [Lehtinen, 2017; Palmer, 2019; Shing, 2022; Rebolj, 2022].

The most relevant feature of this Forest plot is that the lower limit of the 95%CI for some individual VE estimates is negative. This is especially relevant for Palmer 8 ([Palmer, 2019], age at first vaccination ≥18 years). As wide confidence intervals are not given much weight in the model the corresponding studies may not largely contribute to the pooled effect. Therefore, due to the strong contribution of large studies such as Palmer (for the younger age groups) and Rebolj [Palmer, 2019; Rebolj, 2022], the combined pooled estimate reached VE=65.45 (95%CI, 42.02-79.41).

2. Univariate meta-regression analysis

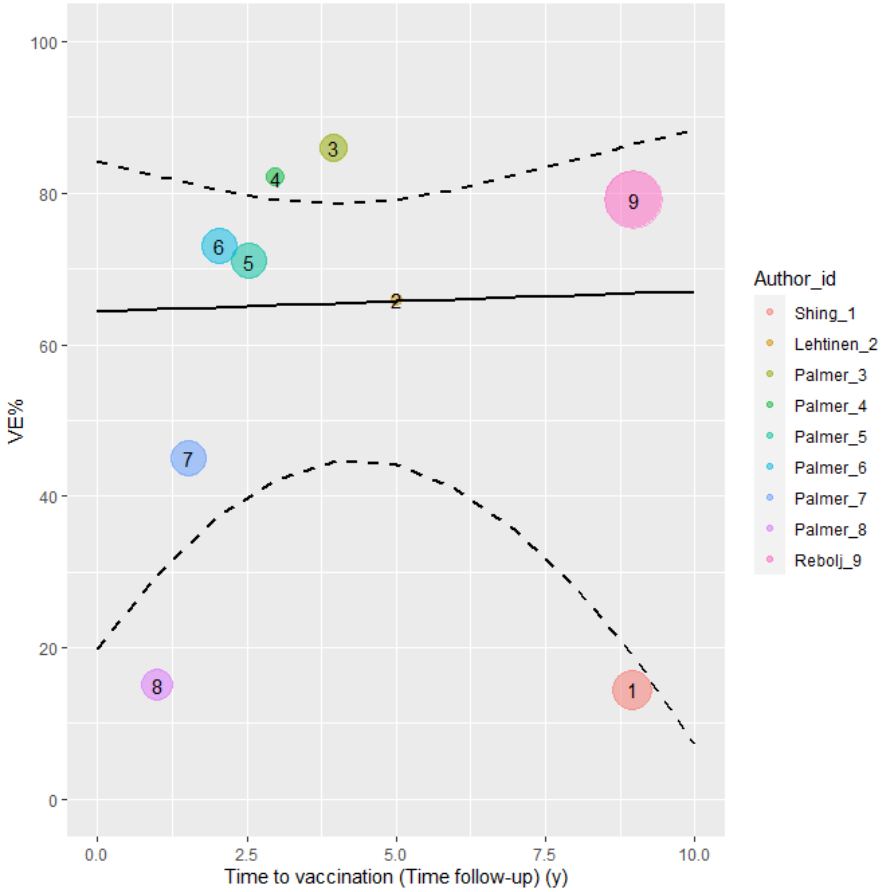
Results from this analysis showed that the variable “age at first vaccination” (p=0.0018), presented association with the outcome VE (i.e., small p values in the univariate meta-regression model). The estimate is positive, suggesting that the VE decreases as age at first vaccination increases. However, “time since vaccination” (time of follow-up) is not associated with VE (p=0.9273). Figures below show the observed and the predicted VE (black line with 95%CI) as a function of the univariate covariates. Size of the bubbles is proportional to the inverse of the variance (it corresponds to the weight in a classical meta-analysis).

Figure 27 Univariate effect of age at first vaccination on vaccine effectiveness (Analysis 6)



Note for interpretation of graphs:
Shing 1= Shing 2022, age at first vaccination 18-25 years, TVC, time since vaccination 7-11 years.
Lehtinen 2= Lehtinen 2017, age at first vaccination 16-17 years, TVC, time since vaccination 0-10 years.
Palmer 3= Palmer 2019, age at first vaccination 12-13 years, TVC, time since vaccination 0-8 years.
Palmer 4= Palmer 2019, age at first vaccination 14 years, TVC, time since vaccination 0-6 years.
Palmer 5= Palmer 2019, age at first vaccination 15 years, TVC, time since vaccination 0-5 years.
Palmer 6= Palmer 2019, age at first vaccination 16 years, TVC, time since vaccination 0-4 years.
Palmer 7= Palmer 2019, age at first vaccination 17 years, TVC, time since vaccination 0-3 years.
Palmer 8= Palmer 2019, age at first vaccination ≥18 years, TVC, time since vaccination 0-2 years.
Rebolj 9= Rebolj 2022, age at first vaccination 14-17 years, TVC, time since vaccination 7-11 years.
Abbreviations: VE=Vaccine effect, id=identity, y=years.
Reference: [Lehtinen, 2017; Palmer, 2019; Shing, 2022; Rebolj, 2022].

Figure 28 Univariate effect of time since vaccination (time of follow-up) on vaccine effectiveness (Analysis 6)



Note for interpretation of graphs:
Shing 1= Shing 2022, age at first vaccination 18-25 years, TVC, time since vaccination 7-11 years.
Lehtinen 2= Lehtinen 2017, age at first vaccination 16-17 years, TVC, time since vaccination 0-10 years.
Palmer 3= Palmer 2019, age at first vaccination 12-13 years, TVC, time since vaccination 0-8 years.
Palmer 4= Palmer 2019, age at first vaccination 14 years, TVC, time since vaccination 0-6 years.
Palmer 5= Palmer 2019, age at first vaccination 15 years, TVC, time since vaccination 0-5 years.
Palmer 6= Palmer 2019, age at first vaccination 16 years, TVC, time since vaccination 0-4 years.
Palmer 7= Palmer 2019, age at first vaccination 17 years, TVC, time since vaccination 0-3 years.
Palmer 8= Palmer 2019, age at first vaccination ≥18 years, TVC, time since vaccination 0-2 years.
Rebolj 9= Rebolj 2022, age at first vaccination 14-17 years, TVC, time since vaccination 7-11 years.
Abbreviations: VE=Vaccine effect, id=identity, y=years.
Reference: [Lehtinen, 2017; Palmer, 2019; Shing, 2022; Rebolj, 2022].

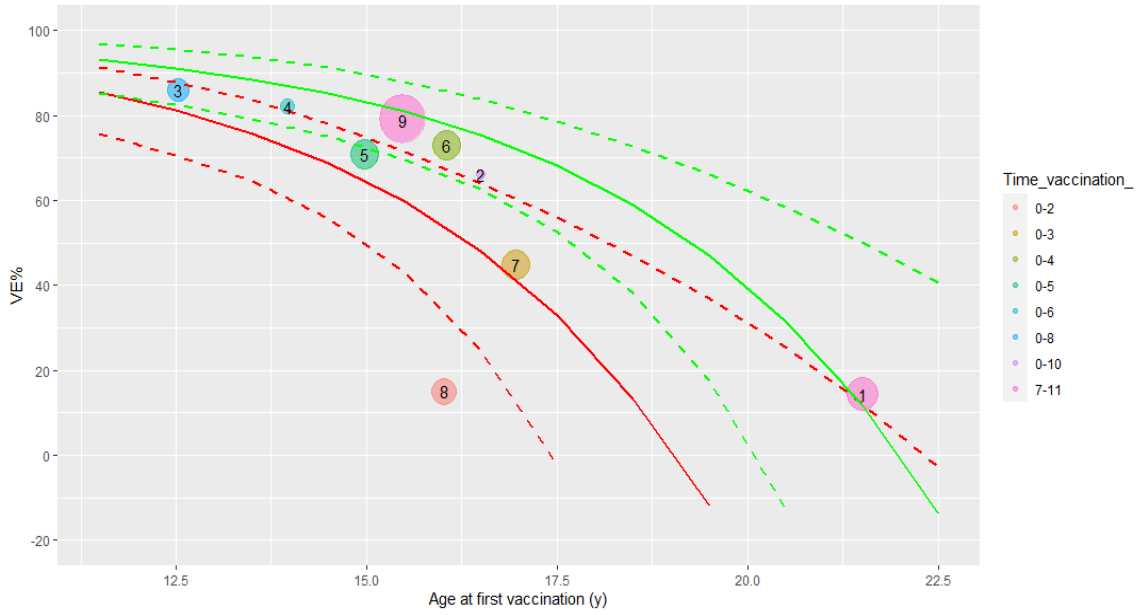
3. Multiparametric meta-regression analysis

All possible combinations of predictors were evaluated and compared using AIC (data-driven approach) to find the best model, and which predictors were the most important ones. This data-driven exploration conducted to a final model that includes the “age at first vaccination” and “time since vaccination” (time of follow-up) variables. The model fitted the data well and did not present extremely high correlation between variables. After adjusting for the “time since vaccination”, VE decreased with age at first vaccination.

The heterogeneity explained by the selected model was R^2*= 82.59%.

The following figure shows the predictions (with 95% Confidence intervals, dotted line) from this data-driven selected model adjusting for "age at first vaccination" and "time since vaccination" for two selected values of time. Red and green curves represent the predicted VE as a function of age for the time since vaccination (the "0-2" years of "time since vaccination" corresponds to the red curve, and the "7-11" years of "time since vaccination" is depicted by the green curve). Colors of the different bubbles represent the observed VEs of the studies with different time since vaccination. Size of the bubbles is proportional to the inverse of the variance (it corresponds to the weight in a classical meta-analysis). As observed in the graph VE decreases with age at first vaccination and it is lower among the "7-11" years of follow-up group. Even if the time of follow-up is shorter in this age group, the "0-2" years of time since vaccination group [Palmer, 2019], represents those vaccinated at older age (≥ 18 years) whereas the "7-11" years of follow-up group were vaccinated at a younger age (14-17 years).

Figure 29 Results of the data-driven multiparametric meta-regression analysis model (Analysis 6)



Red and green curves represent the predicted VE as a function of age for the time since vaccination (the "0-2" years of "time since vaccination" corresponds to the red curve, and the "7-11" years of "time since vaccination" is depicted by the green curve).

Note for interpretation of graphs:
Shing 1= Shing 2022, age at first vaccination 18-25 years, TVC, time since vaccination 7-11 years.
Lehtinen 2= Lehtinen 2017, age at first vaccination 16-17 years, TVC, time since vaccination 0-10 years.
Palmer 3= Palmer 2019, age at first vaccination 12-13 years, TVC, time since vaccination 0-8 years.
Palmer 4= Palmer 2019, age at first vaccination 14 years, TVC, time since vaccination 0-6 years.
Palmer 5= Palmer 2019, age at first vaccination 15 years, TVC, time since vaccination 0-5 years.
Palmer 6= Palmer 2019, age at first vaccination 16 years, TVC, time since vaccination 0-4 years.
Palmer 7= Palmer 2019, age at first vaccination 17 years, TVC, time since vaccination 0-3 years.
Palmer 8= Palmer 2019, age at first vaccination ≥18 years, TVC, time since vaccination 0-2 years.
Rebolj 9= Rebolj 2022, age at first vaccination 14-17 years, TVC, time since vaccination 7-11 years.
Abbreviations: VE=Vaccine effect, y=years.
Reference: [Lehtinen, 2017; Palmer, 2019; Shing, 2022; Rebolj, 2022].

9.2.7. Overall results

Using meta-regression analysis of individually published point estimates for vaccine efficacy/effectiveness, the following question have been addressed:

Q1: What is the combined efficacy/effectiveness of CERVARIX on CIN3+ caused by vaccine HPV types? Combined RCTs and Observational studies

Q2: What is the combined overall efficacy/effectiveness of CERVARIX on CIN3+ caused by any HPV type? Combined RCT and Observational studies

Q3: What is the efficacy of CERVARIX on CIN3+ caused by vaccine HPV types? RCTs only

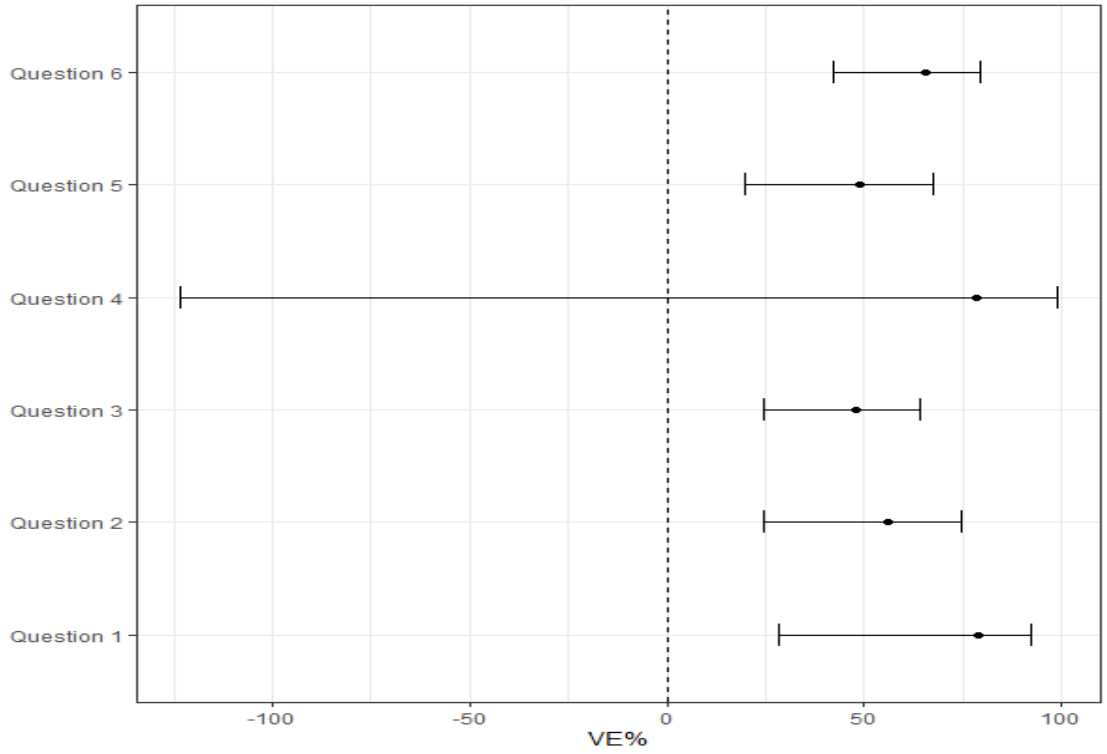
Q4: What is the effectiveness of CERVARIX on CIN3+ caused by vaccine HPV types? Observational studies only

Q5: What is the efficacy of CERVARIX on CIN3+ caused by any HPV type? RCTs only

Q6: What is the effectiveness of CERVARIX on CIN3+ caused by any HPV type? Observational studies only

The following graph represents the different pooled vaccine effect estimates (including 95%CI) obtained by simple meta-analysis and thus, without adjusting for covariates.

Figure 30 Pooled vaccine effects from unadjusted meta-analysis



Abbreviation: VE=Vaccine effect.

Irrespectively of the question, the unadjusted vaccine effect was large in every scenario (within a range of vaccine effect from 48% to 78%).

When adjusting for covariates:

1. Results are consistent across all the analyses, CERVARIX´s effects (either from RCTs, or observational studies, or both designs combined) against CIN3+ caused by HPV 16/18 types or by any HPV type, and were higher the younger the age at the first vaccination of the participants, in the TVC naïve population (HPV negative at baseline) compared to the TVC (irrespective of the HPV baseline status), and the shorter the follow-up (shorter time since vaccination).
2. These identified covariates explained most part of the heterogeneity leading to good predictions relevant for decision-making.

9.3. Secondary outcomes

The systematic literature review unveiled effects of CERVARIX on other endpoints (i.e., CIN3, AIS, cervical cancer), herd effects, and cross-protection. Since there were not enough individual records as to conduct a quantitative synthesis, a brief description of the findings is included.

Vaccine effects of CERVARIX on CIN3 and cervical cancer

Falcaro and colleagues [Falcaro, 2021] determined the VE of CERVARIX after its implementation as part of the NIP in England from 2008 to 2012. The immunization was deployed as a school-based routine vaccination program directed towards girls 12-13 years old and there were also catch-up campaigns for older adolescents (14-18 years). Results from this nationwide population-based study revealed a VE on CIN3 ranging from 97% (95%CI, 96%-98%) among the 12-13 years old vaccinated cohort, through 75% (95%CI, 72%-77%) in the 14-16 years old group, to 39% (95%CI, 36%-41%) in the 16-18 years old vaccinated cohort (Table 9).

Furthermore, the researchers estimated the VE of the program on cervical cancer at 87% (95%CI, 72%-94%) among students vaccinated at 12-13 years, through 62% (95%CI, 52%-71%) in the cohort vaccinated at 14-16 years, to 34% (95%CI, 25%-41%) in the 16-18 years old vaccinated group [Falcaro, 2021].

The authors concluded that they observed a substantial reduction in the incidence of cervical cancer and CIN3 after the introduction of the universal vaccination program with CERVARIX in England, especially among women offered the vaccine at 12-13 years. They affirmed that the vaccine almost eliminated cervical cancer in women born since 01 September 1995. Part of this success was likely due to the high annual vaccine coverage in England that for 2008–09 and 2011–12 ranged between 85.9% and 90.6% in the routine cohorts [Falcaro, 2021].

These results are very important because this was the first time ever that real-world HPV VE on cervical cancer was reported for CERVARIX.

Rebolj et al, reported VE results on cervical cancer corresponding to 14-17 years old adolescents vaccinated in England through the catch-up campaign. Overall VE against cervical cancer among this population group was established at 64% (95%CI, -91%-93%). However, results were not statistically significant (p=0.14) as number of cases was small (n=32). Vaccine coverage in the catch-up cohort ranged from 40% to 75%, depending on the birth cohort [Rebolj, 2022].

Vaccine effects of CERVARIX on CIN3+ caused by non-vaccine types.

Wheeler et al. investigated the vaccine efficacy on CIN3+ caused by non-vaccine types (a composite index of 12 HR HPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) as part of the PATRICIA trial (Table 9). The vaccine efficacy in the TVC-naïve (participants who were HPV negative at baseline and received at least one dose of the vaccine) was 81.9% (95%CI, 17.1-98.1) and 40.0% (95%CI, 1.1-64.2) in the TVC (participants who received at least one dose of the vaccine, irrespective of their HPV baseline status). VE against CIN3+ caused by non-vaccine types reached 62.1% (95%CI, 21.8-82.9) in the ATP-E cohort (participants who received three doses of the vaccine and were HPV negative at baseline). In all the above cases, the analysis excluded HPV 16/18 co-infection [Wheeler, 2012].

These results are relevant because underpin cross-protection and effectiveness of CERVARIX on advanced lesions and cervical cancer (CIN3+) caused by non-vaccine HPV types [Wheeler, 2012].

Vaccine effects of CERVARIX on AIS.

Lehtinen and colleagues reported vaccine efficacy against AIS HPV 16/18-related of 100% (95%CI, 15.5-100) in the TVC naïve whereas it was 70% (95%CI, -16.6-94.7) in the TVC. Vaccine efficacy against AIS irrespective of HPV DNA in the lesion in the TVC naïve and TVC, was 100% (95%CI, 31.0-100) and 76.9% (95%CI, 16.0-95.8), respectively [Lehtinen, 2012].

Other vaccine effects.

Our systematic review also identified herd effects of CERVARIX on CIN3 as reported by Palmer et al. (Table 9). These authors investigated the impact of CERVARIX introduction in the NIP in Scotland among unvaccinated cohorts born in 1995 and 1996 (the same age than vaccine-eligible cohorts, 12-13 years old), and found a VE against CIN3 estimated at 100% (95%CI, 69-100) compared with unvaccinated women born in 1988-1990. Most likely these effects relate to high vaccine coverage as the vaccine uptake among the 1995 birth cohort (13 years at vaccination) was 90% [Palmer, 2019].

9.4. Adverse events/adverse reactions

There was 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 safety was not an objective of the study.

10. DISCUSSION

10.1. Key results

Results from this systematic review and quantitative synthesis have shown that CERVARIX is an efficacious and effective vaccine in preventing advanced cervical premalignant lesions and cervical cancer in adolescent girls and women vaccinated at 12 to 25 years.

This statement holds true across different study types, whether follow-up of RCTs or real-world observational studies, or combinations of both types of studies, the pooled vaccine effects ranged from 48% to 78%, regardless of HPV DNA classification (Table 11).

High efficacy of CERVARIX had already been observed against CIN3+ (93% [95%CI, 79-99]) in initial clinical trials with three doses among HPV naïve women, irrespective of HPV type [Hildesheim, 2014]. However, this is the first time that long-term effects (4 years for RCTs, and 10-11 years for observational studies) against CIN3+ and cervical cancer are evaluated, including real-world data.

In this systematic review and meta-regression analysis, we found the greatest vaccine effects (either vaccine efficacy and/or effectiveness) in the youngest age groups assessed, with many of the studies showing decreased vaccine effects among recipients who initiated vaccination at a later age. These greater vaccine effects of CERVARIX at younger age are most likely due to the administration of the vaccine before the exposure to HPV as the current paradigm for HPV acquisition is sexual activity. In this respect, we found larger vaccine effects in studies when the analytical cohort included participants who were HPV DNA negative at enrolment (TVC naïve), confirming findings from pivotal clinical trials that demonstrated higher efficacy when the vaccine was administered before exposure to HPV. This was also evident in the population-based studies (i.e., Palmer et al.) where participants vaccinated at 17 years were more than three times as likely to be diagnosed with CIN3+ than those vaccinated at 12-13 years (Odds ratio= 0.55 [95%CI, 0.36-0.83] vs. Odds ratio=0.14 [95%CI, 0.08-0.25], respectively) [Palmer, 2019].

This systematic review has also uncovered long-term broad protection of CERVARIX against CIN3+ caused by non-vaccine types, both from follow-up studies of RCTs and observational studies.

Long-term immunogenicity of CERVARIX had been already demonstrated in vaccinated adolescents 16-17 years old whose neutralizing antibodies to HPV 16/18 were consistently high up to 12 years post-vaccination across all age strata (18-45 years), and 6- to 12-fold higher when compared with Gardasil [Mariz, 2021]. The clinical implications of these findings were uncertain, but our analysis estimated consistent CERVARIX vaccine effects in 4-year follow-ups of clinical trials, and up to over 10-11 years in observational and population-based studies, showcasing the translation of the observed long-term immunogenicity to long standing vaccine effects against CIN3+ and cancer, to the point that cervical cancer was drastically reduced and almost disappeared

after the CERVARIX NIP implementation in some settings [Falcaro, 2021; Rebolj, 2022]. Furthermore, long-term seropositivity seems to be higher when the vaccine is given at younger age compared to older age groups, particularly those aged 25 years or older [Schwarz, 2017]. Nevertheless, our meta-regression analysis unveiled that time since vaccination was impactful on VE when pooling data from observational studies, irrespective of the HPV type (Table 11). Further, results from the univariate models for combined effects (RCTs and observational studies) irrespective of HPV type (Analysis 2) showed higher vaccine effects for long-term follow-up observational studies compared to RCTs as most likely these results were driven by the large nationwide population-based studies in the dataset (i.e., Palmer and Rebolj) [Palmer, 2019; Rebolj, 2022].

It has been postulated that the broad immunity observed after CERVARIX vaccination (including cross-protection), and the lesser HPV 18 L1-specific antibody waning compared to Gardasil and Gardasil 9 may be attributable to the adjuvant. The AS04 adjuvant has shown to enhance the antigen-specific T cell response, cytokine release, and consequently, B cell response and antibodies, by activating antigen-presenting cells. Several studies pointed to the adjuvants´ capacity to induce a more effective affinity maturation of antibodies [Roy, 2023].

VE studies are instrumental to comprehend how vaccines perform in real settings. VE is affected by vaccine efficacy, specific vaccination policies and real-world conditions of administration, and population-level vaccine coverage. Variations in policies respect to recommendations in terms of age at vaccination has undoubtedly an impact on VE. This systematic review and meta-regression analysis have demonstrated that CERVARIX is more effective when administered at younger ages. Overall, these findings may raise awareness for policy- makers and the wider community to initiating HPV vaccination at the youngest recommended age with the confidence that it will evoke a long-lasting and effective response.

Future research is warranted to understand the long-term impact of CERVARIX on other population groups (i.e., men), and additional HPV-related premalignant lesions and cancers. Methodologically, the importance of controlling for confounding by factors interrelated to vaccination and outcomes (i.e., sexual activity) has proven important.

Table 11 Pooled long-term vaccine effects and impactful covariates.

Analysis	Outcome	Meta-analysis Vaccine Effect (95%CI)	Meta-regression analysis Impactful covariates
HPV 16/18			
Analysis 1 (RCTs, Observational studies)	Combined vaccine effects	76.78% (28.15-92.49)	Age at first vaccination, Analytic cohort[1].
Analysis 3 (RCTs)	Vaccine efficacy	47.84% (24.51-63.96)	Age at first vaccination, Analytic cohort[1].
Analysis 4 (Observational studies)	Vaccine effectiveness	78.35% (-123.19-97.90)	NA[2].
Irrespective of HPV type			
Analysis 2 (RCTs, Observational studies)	Combined vaccine effects	56.19% (24.76-74.49)	Age at first vaccination, Analytic cohort[1].
Analysis 5 (RCTs)	Vaccine efficacy	48.89% (19.84-67.41)	Age at first vaccination, Analytic cohort[1].
Analysis 6 (Observational studies)	Vaccine effectiveness	65.45% (42.02-79.41)	Age at first vaccination, Time since vaccination.

Abbreviation: CI= confidence interval, HPV=Human papillomavirus, RCT= randomized controlled trial, NA=not applicable.

1 Analytic cohorts: Total Vaccinated Cohort (TVC, irrespective of HPV baseline status) and Total Vaccinated Cohort naïve (TVC-naïve cohort, HPV-naïve at baseline)

2 The data-driven multiparametric meta-regression selection did not identify any stable model

10.2. Limitations

A systematic literature review suffers from intrinsic limitations mainly concerning the ability to retrieve all available information.

Many studies included in this systematic review were considered to have some degree of risk of bias. This was particularly true for the observational studies and was mainly inherent to the observational design itself. Nevertheless, all studies acknowledged limitations and used different approaches and methods to address bias and confounding to ensure robustness about their conclusions. Moreover, observational studies are necessary to demonstrate real-world vaccine effects and often, they are the only ethical method.

In relation to the meta-regression analysis, the unit of analysis is the study, so the regression performance is determined by the number of studies in the meta-analysis, which in this study was relatively low. The power of the statistical analysis is limited depending 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 available evidence may be insufficient to demonstrate the effect with the actual data. Further, non-linearity for the covariate “age at first vaccination” was not checked given the small number of observations.

10.3. Interpretation of results

1. Results were consistent across all the analyses, CERVARIX´s long-term effects (either from RCTs, or observational studies, or both designs combined) against CIN3+ caused by HPV 16/18 types or by any HPV type, and were higher the younger the age at the first vaccination of the participants, in the TVC naïve population (HPV negative at baseline) compared to the TVC (irrespective of the HPV baseline status), and the shorter the follow-up (shorter time since vaccination).
2. These identified covariates explained most part of the heterogeneity leading to good predictions relevant for decision-making.

10.4. Generalizability

Findings from this systematic review can be extrapolated across settings since studies were conducted in high-, and low-, and middle-income countries (i.e., PATRICIA trial, Costa Rica Vaccine Trial). However, HPV VE is affected by population-level vaccine coverage and age at sexual debut and thus, influenced by cultural differences. Vaccine effects may be different in settings with low vaccine coverage and early initiation of sexual activity.

11. OTHER INFORMATION

Table 12 List of full papers assessed for inclusion (n=53).

Paper	Reviewer 1 (PP)		Reviewer 2 PPD	
	Yes	No	Yes	No
Acuti, 2021		X		X
Apter, 2015	X			X
Arbyn, 2016		X		X
Beachler, 2016		X		X
Brotherton, 2012		X		X
Brown, 2009		X		X
Cameron, 2017a		X		X
Cameron, 2017b	X			X
Casajuana-Pérez, 2022		X		X
Chen, 2020		X		X
Clark, 2021		X		X
De Carvalho, 2010		X		X
Del Mistro, 2021		X		X
Donken, 2021		X		X
Falcaro, 2021	X		X	
Hallowell, 2018		X		X
Harari, 2016		X		X
Hariri, 2015		X		X
Harper, 2006		X		X
Hildesheim, 2014		X		X
Hiramatsu, 2022		X		X
Ikeda, 2021		X		X
Johnson Jones, 2020		X		X
Khatun, 2012		X		X
Kjaer, 2021		X		X
Konno, 2018		X		X
Konno, 2010		X		X
Konno, 2014	X		X	
Lehtinen, 2012	X		X	
Lehtinen, 2017	X		X	
Naud, 2014		X		X
Onuki, 2022		X		X
Paavonen, 2009	X			X
Palmer, 2019	X		X	
Porras, 2020	X		X	
Powell, 2012		X		X
Racey, 2020		X		X
Rana, 2013		X		X
Rebolj, 2022	X		X	
Romanowski, 2009		X		X

Paper	Reviewer 1 (BB)		Reviewer 2 (DN)	
Roteli-Martins, 2012		X		X
Ryser, 2019		X		X
Shiko, 2020		X		X
Shing, 2022	X		X	
Silverberg, 2020		X		X
Skinner, 2014		X		X
Skinner, 2016b		X		X
Szarewski, 2012		X		X
Tota, 2020		X		X
Tota, 2021		X		X
Tozawa-Ono, 2021		X		X
Wheeler, 2012	X		X	
Yagi, 2021		X		X

Abbreviation: PPD

12. CONCLUSIONS

The results of this study provide strong evidence of CERVARIX successfully conferring long-term protection to prevent HPV-related advanced cervical premalignant lesions (CIN3, CIN3+) and cervical cancer, both in controlled environments (i.e., RCTs), but also in real-world settings. Moreover, these vaccine effects have shown to be larger among populations that were HPV naïve at the vaccine uptake, and subsequently, the younger the age at first vaccination. CERVARIX effectiveness against cervical cancer endpoints was particularly high when implemented in nationwide immunization programs with elevated routine vaccination coverage and catch-up campaigns, including multiple age cohorts. The policy implications of these findings, reinforcing an early and extensive HPV vaccination, hold promise for attaining the WHO goals for cervical cancer elimination [World Health Organization, 2020].

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

No.	Document Reference No	Date	Title
1.	TMF-16313057	22 February 2024	Protocol.
2.	TMF-18576732	12 February 2024	Important publications referenced in the report.
3.	TMF-17751068	06 Feb 2024	Study administrative table.
4	Obtained once study report core text is final	Obtained once study report core text is final	Sponsor signature page.

ANNEX 2. ADDITIONAL INFORMATION

Statistical outputs for meta-analysis, univariate analysis and multiparametric models

<u>Question 1:</u> What is the combined efficacy/effectiveness of CERVARIX on CIN3+ caused by vaccine HPV types? Combined RCT and Observational studies.

Results

1. Classical meta-analysis (no covariates)

Yi=log(1-VEi) is the log relative risk for each study and vi its variance.

```
mod0 <- rma.mv(yi,vi,
+                 slab = Author_id,
+                 data = dat,
+                 random = ~ 1 | Correlation,
+                 method = "REML",test="t")
```

```
            estim    sqrt  nlvls  fixed       factor
sigma^2    0.6207  0.7878      3     no  Correlation
estimate      se     tval  df    pval    ci.lb    ci.ub
 -1.4600  0.4898  -2.9810   8  0.0176  -2.5894  -0.3306  *
```

2. Univariate meta-regression

We first perform univariate meta-regressions

```
mod_u1 <- rma.mv(yi,vi, mods=~cov,
+                 slab = Author_id,
+                 data = dat,
+                 random = ~ 1 | Correlation,
+                 method = "REML",test="t")
```

Estimated coefficients (fixed effects) from the univariate meta-analysis are showed below

```
                    estimate     se   tval df   pval   ci.lb  ci.ub
TVC                   1.5037 1.0533 1.4277  7 0.1964 -0.9869 3.9943
age                   0.2362 0.0654 3.6114  7 0.0086  0.0816 0.3909
Design_RCT            1.4456 0.2734 5.2882  7 0.0011  0.7992 2.0921
Time_vaccination0_4   1.4456 0.2734 5.2882  7 0.0011  0.7992 2.0921
```

Univariate models in more details

sigma^2 represents the between-correlation variability

TVC (TVC vs TVC naive)

```
            estim    sqrt  nlvls  fixed       factor
sigma^2    0.5897  0.7679      3     no  Correlation

         estimate      se     tval  df    pval    ci.lb    ci.ub
intrcpt   -2.8815  1.1057  -2.6060   7  0.0351  -5.4962  -0.2669  *
TVC        1.5037  1.0533   1.4277   7  0.1964  -0.9869   3.9943
```

AGE (years)

```
            estim    sqrt  nlvls  fixed       factor
sigma^2    0.4580  0.6767      3     no  Correlation


         estimate      se     tval  df    pval    ci.lb    ci.ub
intrcpt   -5.9155  1.3086  -4.5203   7  0.0027  -9.0100  -2.8211  **
age        0.2362  0.0654   3.6114   7  0.0086   0.0816   0.3909  **
```

Design (RCT vs Obs)

```
            esteem    sqrt  nlvls  fixed       factor
sigma^2    0.0000  0.0000      3     no  Correlation


            estimate      se      tval  df    pval    ci.lb    ci.ub
intrcpt      -2.0393  0.1913  -10.6585   7  <.0001  -2.4917  -1.5869  *
**
Design_RCT    1.4456  0.2734    5.2882   7  0.0011   0.7992   2.0921
**
```

Time since vaccination

```
           estim    sqrt  nlvls  fixed       factor
sigma^2    0.0000  0.0000      3     no  Correlation


                     estimate      se      tval  df    pval    ci.lb    ci.ub
intrcpt               -2.0393  0.1913  -10.6585   7  <.0001  -2.4917  -1.5869
***
Time_vaccination0_4    1.4456  0.2734    5.2882   7  0.0011   0.7992   2.0921
**
```

3. Multiple (multiparametric) meta-regression

First, it is important to check the correlation between the different covariates

```
                      TVC   age Design_RCT Time_vaccination0_4 Correlation
TVC                  1.00 -0.15      -0.48               -0.48          0.31
age                 -0.15  1.00       0.17                0.17         -0.38
Design_RCT          -0.48  0.17       1.00                1.00         -0.77
Time_vaccination0_4 -0.48  0.17       1.00                1.00         -0.77
Correlation          0.31 -0.38      -0.77               -0.77          1.00
```

Full model (including all covariates)

```
mod_full <- rma.mv(yi,vi, mods=~TVC+age+Design+Time_vaccination, #Desig
n is confounded with the random effect!
+                     slab = Author_id,
+                     data = dat,
+                     random = ~ 1 | Correlation,
+                     method = "REML",test="t")

            estim    sqrt  nlvls  fixed       factor
sigma^2    7.0709  2.6591      3     no  Correlation

           estimate      se     tval  df    pval     ci.lb    ci.ub
intrcpt   -12.4393  2.9223  -4.2568   5  0.0080  -19.9512  -4.9274  **
TVC         4.7165  1.6534   2.8526   5  0.0357    0.4663   8.9667   *
age         0.2370  0.0711   3.3340   5  0.0207    0.0543   0.4197   *
DesignRCT   5.0429  1.8960   2.6598   5  0.0449    0.1691   9.9166   *
```

```
mod_full2 <- rma.mv(yi,vi, mods=~TVC+age+Design+Time_vaccination, #Desi
gn is confounded with the random effect!
+                     slab = id,
+                     data = dat,
+                     random = ~ 1 | id,
+                     method = "REML",test="t")
           estim    sqrt  nlvls  fixed  factor
sigma^2    0.2081  0.4562      9     no      id

           estimate      se     tval  df    pval     ci.lb    ci.ub
intrcpt     -7.3703  2.0326  -3.6260   5  0.0151  -12.5953  -2.1453  *
TVC          2.3846  1.1044   2.1593   5  0.0833   -0.4542   5.2234  .
age          0.1690  0.0903   1.8701   5  0.1204   -0.0633   0.4012
DesignRCT    0.9653  0.5711   1.6904   5  0.1517   -0.5026   2.4332
```

Multi-model inference

These are the top 5 models according to the AIC criterion

```
Model selection table
   (Int)    age Dsg Tim_vcc   TVC df  logLik  AIC delta weight
12     + 0.1690   +         2.385  5 -10.106 30.2  0.00  0.262
16     + 0.1690   +       + 2.385  5 -10.106 30.2  0.00  0.262
14     + 0.1690           + 2.385  5 -10.106 30.2  0.00  0.262
10     + 0.2213             2.227  4 -11.804 31.6  1.40  0.130
11     +          +         2.375  4 -12.225 32.5  2.24  0.085


mod_sel <- rma.mv(yi,vi, mods=~TVC+age,
+                     slab = Author_id,
+                     data = dat,
+                     random = ~ 1 | Correlation,
+                     method = "REML",test="t")


           estim    sqrt  nlvls  fixed       factor
sigma^2    0.2348  0.4845      3     no  Correlation

         estimate      se     tval  df    pval     ci.lb    ci.ub
intrcpt   -7.4391  1.5950  -4.6639   6  0.0035  -11.3420  -3.5362  **
TVC        1.6866  1.0409   1.6203   6  0.1563   -0.8605   4.2336
age        0.2345  0.0620   3.7818   6  0.0092    0.0828   0.3862  **
```

Question 2: What is the combined overall efficacy/effectiveness of CERVARIX on CIN3+ caused by any HPV type? Combined RCT and Observational studies

Results

1. Classical meta-analysis (no covariates)

Yi=log(1-VEi) is the log relative risk for each study and vi its variance.

```
mod0 <- rma.mv(yi,vi,
+                  slab = Author_id,
+                  data = dat,
+                  random = ~ 1 | Correlation,
+                  method = "REML",test="t")


            estim    sqrt  nlvls  fixed       factor
```

```
sigma^2    0.2759  0.5252      5     no  Correlation

Model Results:

estimate      se     tval  df    pval    ci.lb    ci.ub
 -0.8252  0.2537  -3.2532  15  0.0053  -1.3659  -0.2846  **
```

2. Univariate meta-regression

We first perform univariate meta-regressions.

```
mod_u1 <- rma.mv(yi,vi, mods=~cov,
+                 slab = Author_id,
+                 data = dat,
+                 random = ~ 1 | Correlation,
+                 method = "REML",test="t")
```

Estimated coefficients (fixed effects) from the univariate meta-analisys are showed below

```
           estimate     se    tval df   pval   ci.lb   ci.ub
TVC          2.2115 0.7485  2.9547 14 0.0104  0.6062  3.8168
age          0.1898 0.0284  6.6909 14 0.0000  0.1290  0.2506
Design_RCT   0.3260 0.5781  0.5639 14 0.5818 -0.9140  1.5659
time        -0.5024 0.1038 -4.8416 14 0.0003 -0.7249 -0.2798
```

Univariate models in more details

sigma^2 represents the between-correlation variability

TVC (TVC vs TVC naive)

```
            estim    sqrt  nlvls  fixed       factor
sigma^2    0.2872  0.5359      5     no  Correlation

         estimate      se     tval  df    pval    ci.lb    ci.ub
intrcpt   -3.0150  0.7851  -3.8401  14  0.0018  -4.6990  -1.3311  **
TVC        2.2115  0.7485   2.9547  14  0.0104   0.6062   3.8168   *
```

AGE (years)

```
            estim    sqrt  nlvls  fixed       factor
sigma^2    0.0384  0.1960      5     no  Correlation

         estimate      se     tval  df    pval    ci.lb    ci.ub
intrcpt   -4.3252  0.5250  -8.2380  14  <.0001  -5.4513  -3.1992  ***
age        0.1898  0.0284   6.6909  14  <.0001   0.1290   0.2506  ***
```

Design (RCT vs Obs)

```
            estim    sqrt  nlvls  fixed       factor
sigma^2    0.3336  0.5776      5     no  Correlation

            estimate      se     tval  df    pval    ci.lb    ci.ub
intrcpt      -0.9354  0.3430  -2.7271  14  0.0164  -1.6710  -0.1997  *
Design_RCT    0.3260  0.5781   0.5639  14  0.5818  -0.9140   1.5659
```

Time since vaccination

```
            estim    sqrt  nlvls  fixed       factor
sigma^2    3.8382  1.9591      5     no  Correlation

         estimate      se     tval  df    pval    ci.lb    ci.ub
```

```
intrcpt    1.6427  1.0162   1.6165  14  0.1283  -0.5368   3.8222
time      -0.5024  0.1038  -4.8416  14  0.0003  -0.7249  -0.2798  ***
**
```

3. Multiple (multiparametric) meta-regression

First, it is important to check the correlation between the different covariates

```
                TVC   age Design_RCT  time Correlation
TVC            1.00 -0.34      -0.58  0.25        0.46
age           -0.34  1.00       0.59 -0.09       -0.50
Design_RCT    -0.58  0.59       1.00 -0.43       -0.80
time           0.25 -0.09      -0.43  1.00        0.34
Correlation    0.46 -0.50      -0.80  0.34        1.00
```

Full model (including all covariates)

```
mod_full <- rma.mv(yi,vi, mods=~TVC+age+Design+Time_vaccination, #Desig
n is confounded with the random effect!
+                     slab = Author_id,
+                     data = dat,
+                     random = ~ 1 | Correlation,
+                     method = "REML",test="t")

            estim    sqrt  nlvls  fixed       factor
sigma^2    0.0000  0.0000      5     no  Correlation

           estimate      se     tval  df    pval    ci.lb    ci.ub
intrcpt     -5.8094  0.8296  -7.0025  11  <.0001  -7.6353  -3.9834  ***
TVC          1.6530  0.7521   2.1978  11  0.0503  -0.0024   3.3084    .
age          0.2057  0.0256   8.0463  11  <.0001   0.1495   0.2620  ***
DesignRCT   -0.4357  0.2005  -2.1734  11  0.0525  -0.8769   0.0055    .
time        -0.0623  0.0205  -3.0363  11  0.0113  -0.1074  -0.0171    *
```

Multi-model inference

These are the top 5 models according to the AIC criterion

```
   (Intrc)    age Desgn     time   TVC df  logLik  AIC delta weight
10       + 0.1678               1.886  4 -10.306 28.6  0.00  0.372
16       + 0.2020     + -0.06086 1.675  6  -8.754 29.5  0.90  0.238
14       + 0.1692       -0.03819 1.953  5  -9.891 29.8  1.17  0.208
12       + 0.1812     +         1.750  5 -10.144 30.3  1.68  0.161
8        + 0.2091     + -0.06221        5 -12.168 34.3  5.72  0.021
```

In the following we show the results of the top model (including age and TVC).

```
mod_sel <- rma.mv(yi,vi, mods=~TVC+age,
+                     slab = Author_id,
+                     data = dat,
+                     random = ~ 1 | Correlation,
+                     method = "REML",test="t")


            estim    sqrt  nlvls  fixed       factor
sigma^2    0.0346  0.1859      5     no  Correlation
```

```
          estimate      se     tval  df    pval    ci.lb    ci.ub
intrcpt   -5.9787  0.8741  -6.8402  13  <.0001  -7.8670  -4.0904  ***
TVC        1.7618  0.7472   2.3577  13  0.0347   0.1475   3.3761    *
age        0.1847  0.0281   6.5812  13  <.0001   0.1241   0.2454  ***
```

Question 3: What is the efficacy of CERVARIX on CIN3+ caused by vaccine HPV types? RCTs only

Results

1. Classical meta-analysis (no covariates)

Yi=log(1-VEi) is the log relative risk for each study and vi its variance.

```
mod0 <- rma.mv(yi,vi,
+                 slab = Author_id,
+                 data = dat,
+                 random = ~ 1 | Correlation,
+                 method = "REML",test="t")
```

```
            estim    sqrt  nlvls  fixed       factor
sigma^2    0.0000  0.0000      2     no  Correlation

estimate      se     tval  df    pval    ci.lb    ci.ub
 -0.6508  0.1563  -4.1630   7  0.0042  -1.0205  -0.2812  **
```

2. Univariate meta-regression

We first perform univariate meta-regressions

```
mod_u1 <- rma.mv(yi,vi, mods=~cov1,
+                 slab = Author_id,
+                 data = dat,
+                 random = ~ 1 | Correlation,
+                 method = "REML",test="t")
```

Estimated coefficients (fixed effects) from the univariate meta-analisys are showed below

```
    estimate     se   tval df   pval   ci.lb  ci.ub
TVC   2.1677 1.0082 2.1502  6 0.0751 -0.2991 4.6346
age   0.2430 0.0704 3.4497  6 0.0136  0.0706 0.4153
```

Univariate models in more details

sigma^2 represents the between-correlation variability

TVC (TVC vs TVC naive)

```
            estim    sqrt  nlvls  fixed       factor
sigma^2    0.0000  0.0000      2     no  Correlation
          estimate      se     tval  df    pval    ci.lb    ci.ub
intrcpt   -2.7651  0.9957  -2.7772   6  0.0321  -5.2014  -0.3288  *
TVC        2.1677  1.0082   2.1502   6  0.0751  -0.2991   4.6346  .
```

AGE (years)

```
            estim    sqrt  nlvls  fixed       factor
sigma^2    0.0478  0.2186      2     no  Correlation

         estimate      se     tval  df    pval    ci.lb    ci.ub
intrcpt   -5.7440  1.4898  -3.8557   6  0.0084  -9.3893  -2.0987  **
age        0.2430  0.0704   3.4497   6  0.0136   0.0706   0.4153   *
```

3. Multiple (multiparametric) meta-regression

First, it is important to check the correlation between the different covariates

```
               TVC  age Correlation_n
TVC              1 0.00          0.00
age              0 1.00          0.35
Correlation_n    0 0.35          1.00
```

Full model (including all covariates)

```
mod_full <- rma.mv(yi,vi, mods=~TVC+age,
+                      slab = Author_id,
+                      data = dat,
+                      random = ~ 1 | Correlation,
+                      method = "REML",test="t")


            estim    sqrt  nlvls  fixed       factor
sigma^2    0.0156  0.1249      2     no  Correlation


         estimate      se     tval  df    pval     ci.lb    ci.ub
intrcpt   -7.6375  1.7604  -4.3385   5  0.0074  -12.1628  -3.1123  **
TVC        2.1134  1.0097   2.0932   5  0.0905   -0.4820   4.7088   .
age        0.2357  0.0700   3.3671   5  0.0200    0.0558   0.4156   *
```

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

Results

1. Classical meta-analysis (no covariates)

Yi=log(1-VEi) is the log relative risk for each study and vi its variance.

```
mod0 <- rma.mv(yi,vi,
+                  slab = Author_id,
+                  data = dat,
+                  random = ~ 1 | id,
+                  method = "REML",test="t")


Variance Components:

            estim    sqrt  nlvls  fixed  factor
sigma^2    0.6783  0.8236      3     no      id
```

```
Model Results:

estimate      se     tval  df    pval    ci.lb   ci.ub
 -1.5304  0.5423  -2.8221   2  0.1060  -3.8636  0.8029
```

2. Univariate meta-regression

We first perform univariate meta-regressions.

```
mod_u1 <- rma.mv(yi,vi, mods=~cov1,
+                 slab = Author_id,
+                 data = dat,
+                 random = ~ 1 | id,
+                 method = "REML",test="t")
```

Estimated coefficients (fixed effects) from the univariate meta-analisys are showed below

```
                      estimate     se    tval df   pval   ci.lb  ci.ub
age                    -0.0949 0.2913 -0.3256  1 0.7996 -3.7965 3.6068
Time_vaccination7-11   -1.7246 0.5984 -2.8821  1 0.2126 -9.3279 5.8786
```

Univariate models in more details

sigma^2 represents the between-correlation variability

AGE (years)

```
           estim    sqrt  nlvls  fixed  factor
sigma^2   1.5178  1.2320      3     no      id

         estimate      se     tval  df    pval     ci.lb    ci.ub
intrcpt    0.1839  5.2146   0.0353   1  0.9776  -66.0735  66.4412
age       -0.0949  0.2913  -0.3256   1  0.7996   -3.7965   3.6068
```

Time since vaccination (years)

```
           estim    sqrt  nlvls  fixed  factor
sigma^2   0.0000  0.0000      3     no      id

         estimate      se     tval  df    pval     ci.lb    ci.ub
intrcpt    1.8410  1.2979   1.4185   1  0.3909  -14.6506  18.3327
time      -0.4312  0.1496  -2.8821   1  0.2126   -2.3320   1.4697
```

3. Multiple (multiparametric) meta-regression

First, it is important to check the correlation between the different covariates

```
      age time
age  1.00 0.36
time 0.36 1.00
```

Full model (including all covariates)

```
mod_full <- rma.mv(yi,vi, mods=~age+ Time_vaccination,
+                   slab = Author_id,
+                   data = dat,
+                   random = ~ 1 | id,
+                   method = "REML",test="t")
```

```
            estim    sqrt  nlvls  fixed  factor
sigma^2    0.0000  0.0000      3     no      id

                      estimate      se     tval  df    pval     ci.lb    ci.ub
intrcpt                -0.3358  1.7282  -0.1943   1  0.8778  -22.2941  21.6225
age                     0.0013  0.0989   0.0129   1  0.9918   -1.2559   1.2584
Time_vaccination7-11   -1.7242  0.5991  -2.8781   1  0.2129   -9.3364   5.8880
```

Question 5: What is the efficacy of CERVARIX on CIN3+ caused by any HPV type? RCTs only

Results

1. Classical meta-analysis (no covariates)

Yi=log(1-VEi) is the log relative risk for each study and vi its variance.

```
mod0 <- rma.mv(yi,vi,
+                  slab = Author_id,
+                  data = dat,
+                  random = ~ 1 | id,
+                  method = "REML",test="t")

            estim    sqrt  nlvls  fixed  factor
sigma^2    0.1286  0.3586      9     no      id


estimate      se     tval  df    pval    ci.lb    ci.ub
 -0.6712  0.1951  -3.4397   8  0.0088  -1.1211  -0.2212  **
```

2. Univariate meta-regression

We first perform univariate meta-regressions.

```
mod_u1 <- rma.mv(yi,vi, mods=~cov1,
+                  slab = Author_id,
+                  data = dat,
+                  random = ~ 1 | id,
+                  method = "REML",test="t")
```

Estimated coefficients (fixed effects) from the univariate meta-analisys are showed below

```
                     estimate     se   tval df   pval   ci.lb  ci.ub
 TVC                   2.3139 0.7451 3.1055  7 0.0172  0.5520 4.0758
 age                   0.1370 0.0439 3.1200  7 0.0168  0.0332 0.2409
 Time_vaccination1-4   0.3592 0.2206 1.6280  7 0.1476 -0.1625 0.8809
```

Univariate models in more details

sigma^2 represents the between-correlation variability

TVC

```
            estim    sqrt  nlvls  fixed       factor
sigma^2    0.0090  0.0950      3     no  Correlation
```

```
          estimate      se     tval  df    pval    ci.lb    ci.ub
intrcpt   -2.7720  0.7407  -3.7422   7  0.0072  -4.5235  -1.0204  **
TVC        2.3139  0.7451   3.1055   7  0.0172   0.5520   4.0758   *
```

AGE (years)

```
           estim    sqrt  nlvls  fixed       factor
sigma^2    0.0000  0.0000      3     no  Correlation


          estimate      se     tval  df    pval    ci.lb    ci.ub
intrcpt   -3.3357  0.9108  -3.6622   7  0.0080  -5.4895  -1.1819  **
age        0.1370  0.0439   3.1200   7  0.0168   0.0332   0.2409   *
```

Time since vaccination (years)

```
           estim    sqrt  nlvls  fixed       factor
sigma^2    0.0000  0.0000      3     no  Correlation


                     estimate      se     tval  df    pval    ci.lb    ci.ub
intrcpt               -0.6496  0.1358  -4.7841   7  0.0020  -0.9706  -0.3285  *
*
Time_vaccination1-4    0.3592  0.2206   1.6280   7  0.1476  -0.1625   0.8809
```

3. Multiple (multiparametric) meta-regression

First, it is important to check the correlation between the different covariates

```
                     TVC   age Time_vaccination0_4 Correlation_n

TVC                 1.00  0.05              -0.32          0.06

age                 0.05  1.00              -0.16          0.50

Time_vaccination0_4 -0.32 -0.16               1.00         -0.19

Correlation_n       0.06  0.50              -0.19          1.00
```

Full model (including all covariates)

```
mod_full <- rma.mv(yi,vi, mods=~TVC+age+Time_vaccination0_4, #Design is
confounded with the random effect!
+                      slab = Author_id,
+                      data = dat,
+                      random = ~ 1 | id,
+                      method = "REML",test="t")
```

```
           estim    sqrt  nlvls  fixed  factor
sigma^2    0.0000  0.0000      9     no      id

                     estimate      se     tval  df    pval    ci.lb    ci.ub
intrcpt               -4.5124  1.1610  -3.8867   5  0.0116  -7.4968  -1.5280  *
TVC                    1.9335  0.7601   2.5437   5  0.0517  -0.0204   3.8875  .
age                    0.1064  0.0466   2.2843   5  0.0712  -0.0133   0.2262  .
Time_vaccination0_4   -0.1383  0.2310  -0.5987   5  0.5755  -0.7321   0.4555


            estim    sqrt  nlvls  fixed  factor
sigma^2    0.0000  0.0000      9     no      id

          estimate      se     tval  df    pval    ci.lb    ci.ub
intrcpt   -4.7832  1.0692  -4.4737   6  0.0042  -7.3995  -2.1670  **
TVC        1.9614  0.7587   2.5851   6  0.0415   0.1049   3.8179   *
age        0.1141  0.0448   2.5464   6  0.0437   0.0045   0.2237   *
```

Question 6: What is the effectiveness of CERVARIX on CIN3+ caused by any HPV type? Observational studies only

Results

1. Classical meta-analysis (no covariates)

Yi=log(1-VEi) is the log relative risk for each study and vi its variance.

```
mod0 <- rma.mv(yi,vi,
+                 slab = Author_id,
+                 data = dat,
+                 random = ~ 1 | id,
+                 method = "REML",test="t")

            estim    sqrt  nlvls  fixed  factor
sigma^2    0.3754  0.6127      9     no      id


estimate      se     tval  df    pval    ci.lb    ci.ub
 -1.0627  0.2244  -4.7349   8  0.0015  -1.5802  -0.5451  **
```

2. Univariate meta-regression

We first perform univariate meta-regressions.

```
mod_u1 <- rma.mv(yi,vi, mods=~cov1,
+                 slab = Author_id,
+                 data = dat,
+                 random = ~ 1 | id,
+                 method = "REML",test="t")
```

Estimated coefficients (fixed effects) from the univariate meta-analysis are showed below

```
     estimate     se    tval df   pval   ci.lb   ci.ub
age    0.2562 0.0526  4.8730  7 0.0018  0.1319  0.3805
time  -0.5361 0.1078 -4.9745  7 0.0016 -0.7909 -0.2813
```

Univariate models in more details

sigma^2 represents the between-correlation variability

AGE (years)

```
            estim    sqrt  nlvls  fixed       factor
sigma^2    0.1073  0.3275      4     no  Correlation


         estimate      se     tval  df    pval    ci.lb    ci.ub
intrcpt   -5.3768  0.9245  -5.8161   7  0.0007  -7.5628  -3.1908  ***
age        0.2562  0.0526   4.8730   7  0.0018   0.1319   0.3805   **
```

Time since vaccination (years)

```
            estim    sqrt  nlvls  fixed       factor
sigma^2    4.0960  2.0238      4     no  Correlation


         estimate      se     tval  df    pval    ci.lb    ci.ub
intrcpt    2.4152  1.2263   1.9694   7  0.0896  -0.4847   5.3150   .
time      -0.5361  0.1078  -4.9745   7  0.0016  -0.7909  -0.2813  **

            estim    sqrt  nlvls  fixed  factor
sigma^2    0.4419  0.6647      9     no      id


         estimate      se     tval  df    pval    ci.lb    ci.ub
intrcpt   -1.0334  0.4144  -2.4936   7  0.0414  -2.0134  -0.0534  *
time      -0.0076  0.0808  -0.0946   7  0.9273  -0.1987   0.1834
```

3. Multiple (multiparametric) meta-regression

First, it is important to check the correlation between the different covariates

```
               age time Correlation_n
age           1.00 0.44         -0.37
time          0.44 1.00          0.08
Correlation_n -0.37 0.08          1.00
```

Full model (including all covariates)

```
mod_full <- rma.mv(yi,vi, mods=~age+time,
+                     slab = Author_id,
+                     data = dat,
+                     random = ~ 1 | id,
+                     method = "REML",test="t")

            estim    sqrt  nlvls  fixed  factor
sigma^2    0.0654  0.2557      9     no      id


         estimate      se     tval  df    pval    ci.lb    ci.ub
intrcpt   -4.7697  0.8304  -5.7438   6  0.0012  -6.8017  -2.7378  **
age        0.2551  0.0542   4.7102   6  0.0033   0.1226   0.3877  **
time      -0.0936  0.0406  -2.3077   6  0.0605  -0.1928   0.0056   .
```

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
MAH contact person	PPD

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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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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.

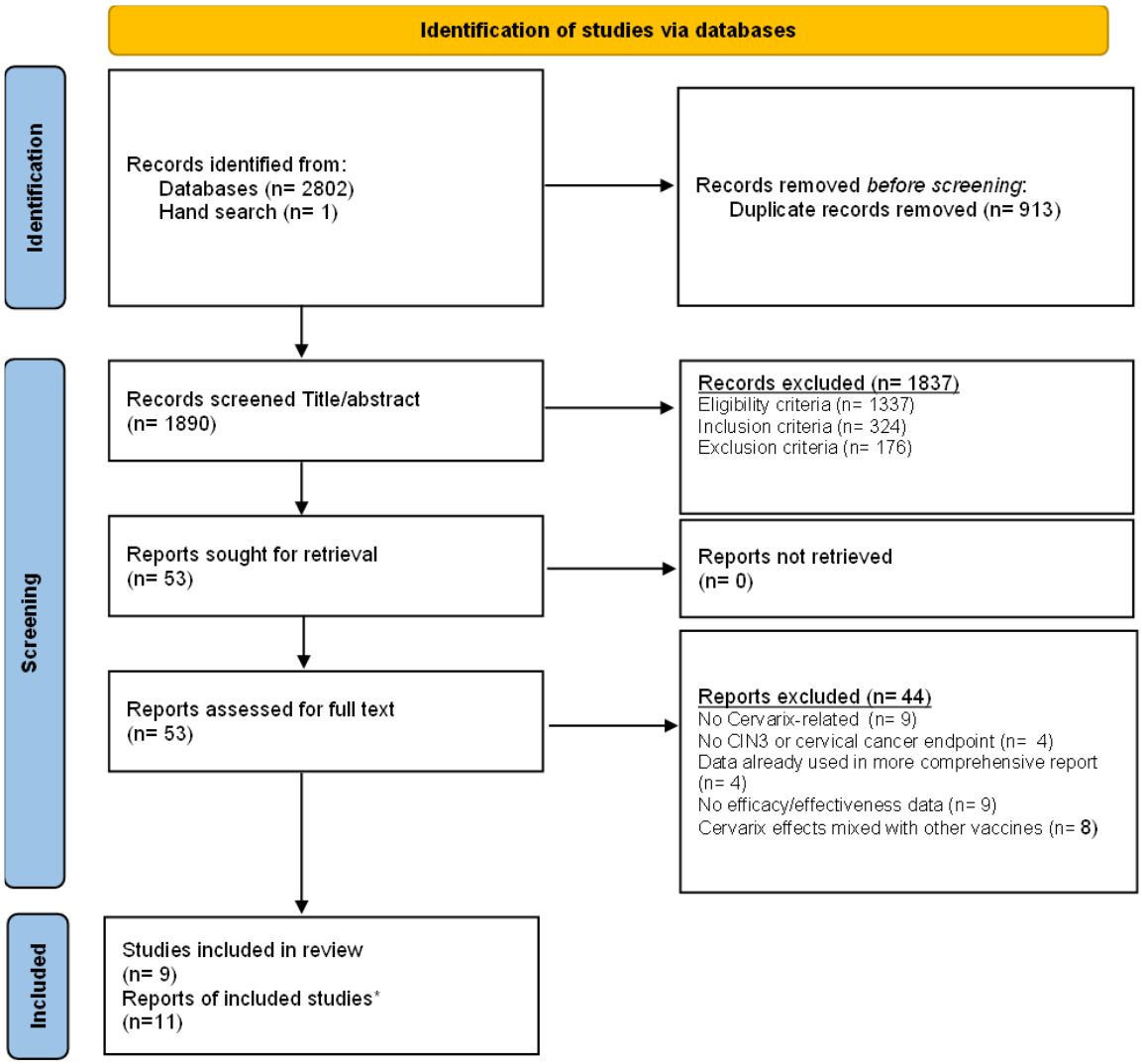
For RCTs most of the confounders were addressed per the study design. However, certain degree of residual confounding could be expected even in well-designed and conducted clinical trials.

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]	79 (73,83)
				VEFT against HPV 16/18-related CIN3+	87 (80, 91)
				VEFT against CIN3+ by "Other" HPV-related (excludes co-infections with HPV 16/18[d]	57 (25, 75)
				VEFT against cervical cancer	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.

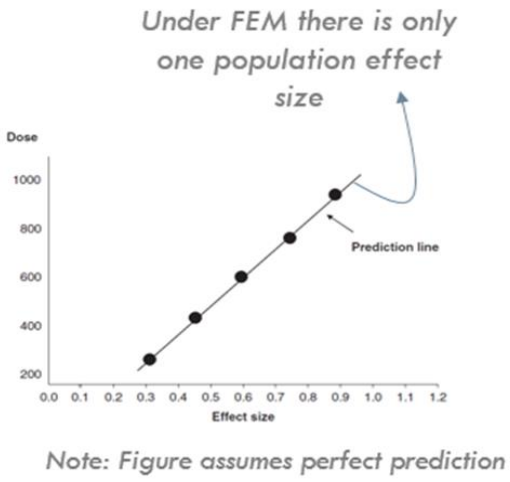
7.7.3. Fixed-effect and random-effect meta-regression:

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].

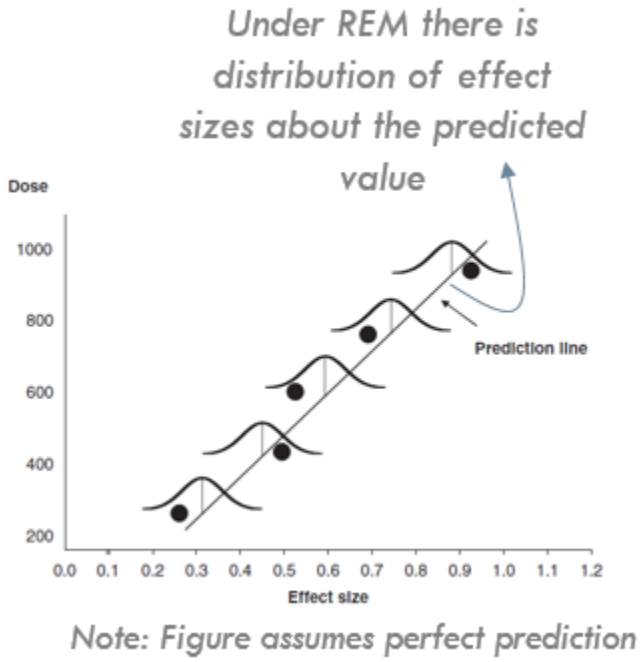
Estimate $y_i = \beta_0 + \beta_1 x_{1i} + \zeta_i + \varepsilon_i$ by minimizing the sum of the weighted sum of the squares of the residuals, i.e., $\sum w_i^*(y_i - \bar{y})^2$

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

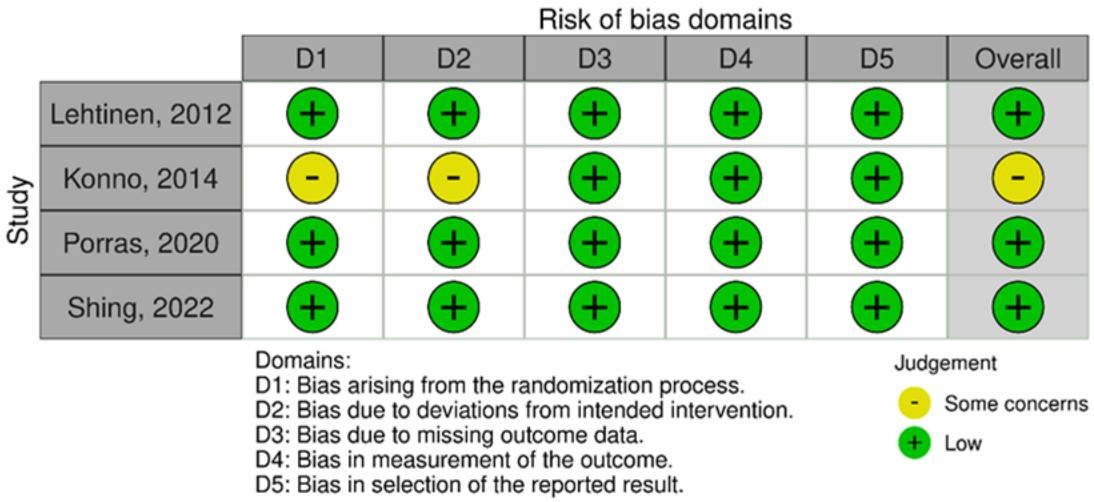
The Cochrane RoB2 tool was applied to the selected RCTs and three studies showed low risk bias whereas the study by Konno et al., presented some concerns in the randomization and deviations from intended intervention domain because a) this study is a post hoc follow-up of an RCT and the follow-up was 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

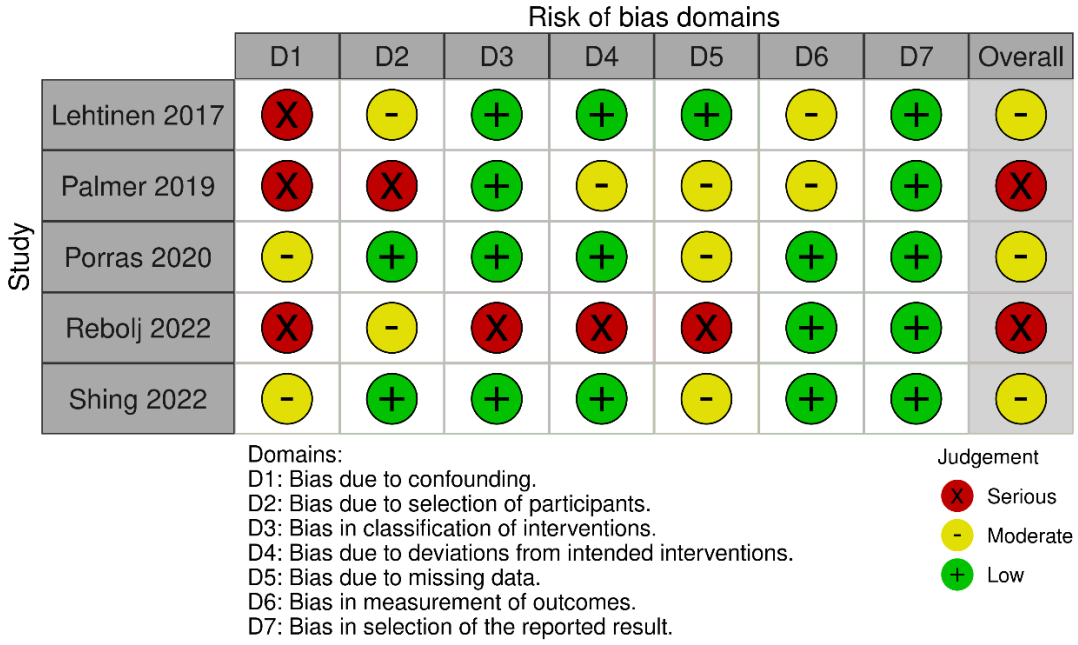
The Cochrane ROBINS I tool for non-interventional studies was used to assess the risk of bias of observational studies and surveillance of national immunization programs studies [The Cochrane Collaboration, 2022b].

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.

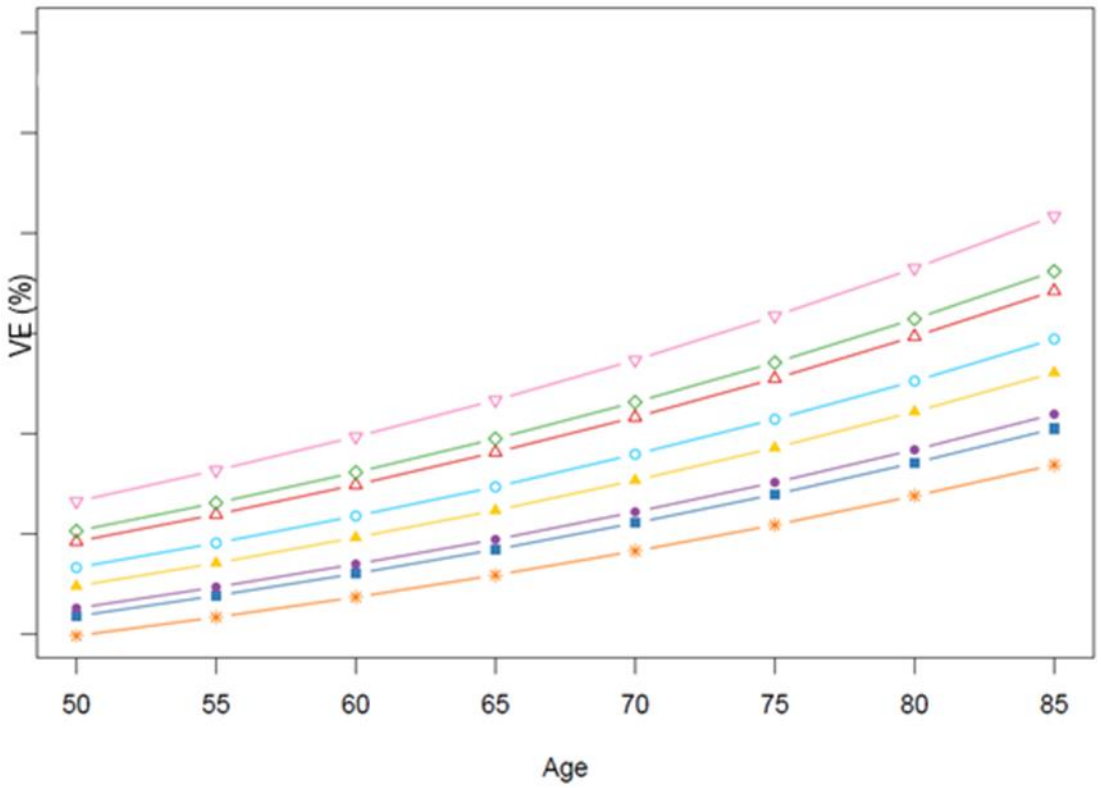


Figure 5 Estimated VE (with 95% Confidence interval) in the 6 different questions (study design/endpoint) without adjusting for covariates (marginal effects).

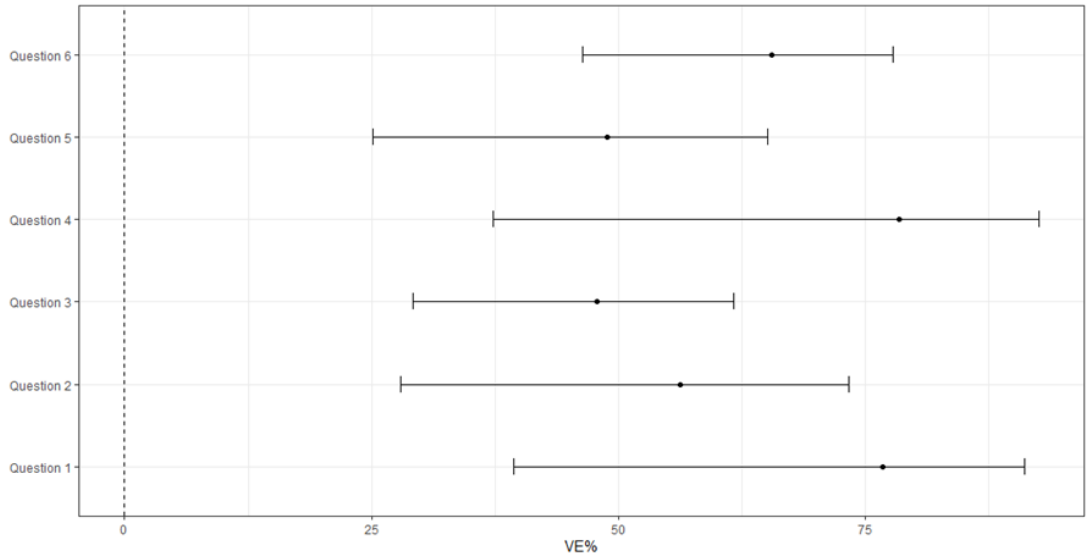
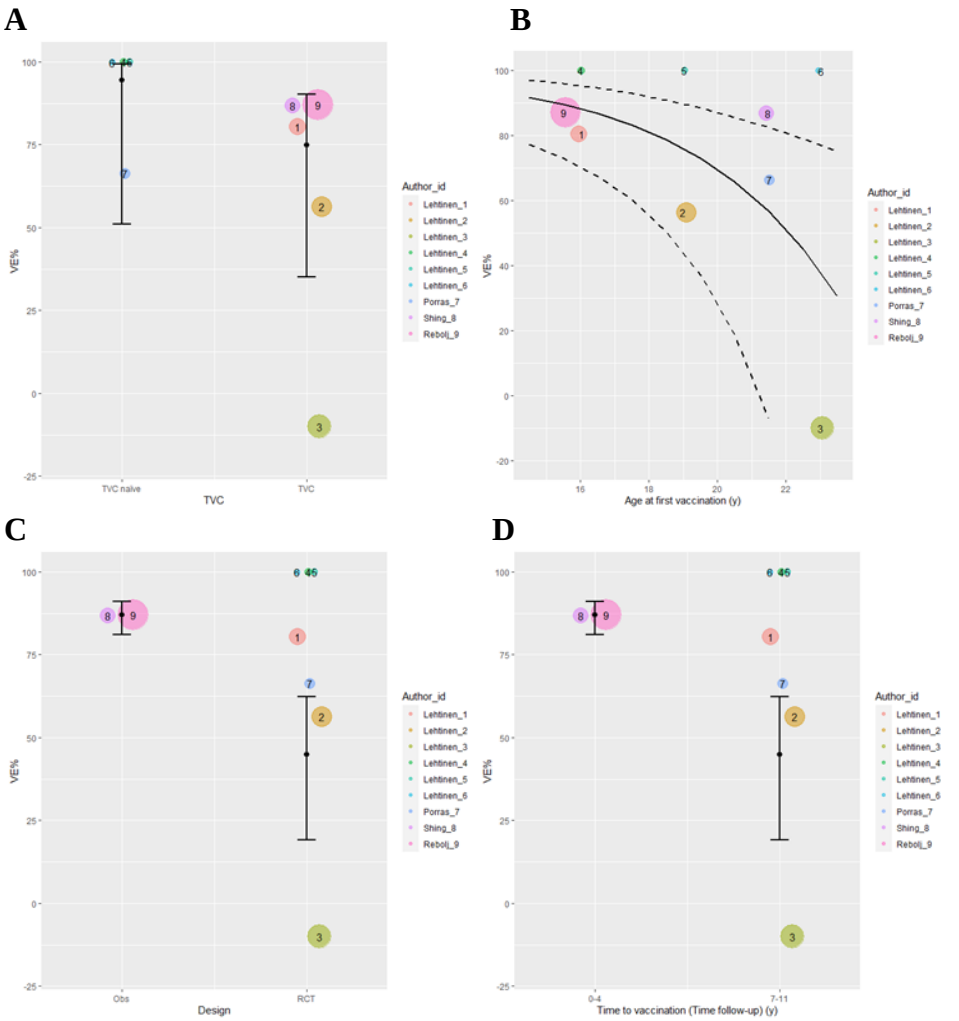
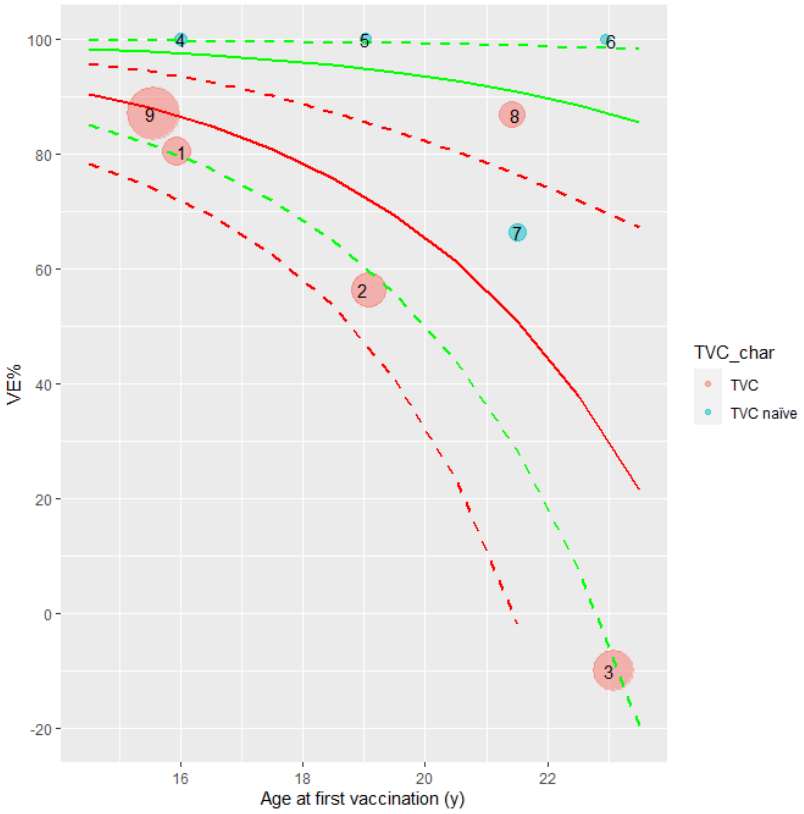


Figure 6 Vaccine effects of pooled data from RCT and/or observational studies



(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:

Signature Page for 221785 TMF-16313057 v3.0

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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