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[Intervention Review]

Human papillomavirus (HPV) vaccination in women with conisation

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ABSTRACT

Rationale

Cervical cancer is the fourth most common cancer affecting women worldwide, caused by persistent infection with oncogenic human papillomavirus (HPV) types. While HPV infections usually resolve spontaneously, persistent infections with high-risk HPV types can progress to premalignant glandular or — mostly — squamous intraepithelial lesions, usually classified in cervical intraepithelial neoplasia (CIN). Women with CIN 2 and CIN 3 (i.e. high-grade CIN) typically undergo cervical conisation to remove precancerous cervical lesions. While conisation is effective, there is a risk of recurrence and progression to invasive cervical cancer. Additionally, women who have undergone conisation are at higher risk of HPV-associated anogenital precancerous lesions and cancers in other locations.

HPV vaccination is an important measure to prevent HPV-related cancer. It is unclear to what extent HPV vaccination offers protection to women with conisation. Of note, the term 'with conisation' is interchangeably used for all time points of HPV vaccination relative to the conisation procedure for the purpose of this review.

Objectives

To investigate the benefits and harms of HPV vaccination (given shortly before, at, or after conisation) in comparison to no HPV vaccination in women with conisation.

Search methods

We searched CENTRAL, MEDLINE, Embase, and Clarivate Web of Science (May 2023). We also searched ClinicalTrials.gov to identify ongoing studies.

Eligibility criteria

We included randomised controlled trials (RCTs) and non-randomised studies of interventions (NRSI) if they compared an HPV vaccine (nonavalent, quadrivalent, or bivalent) with no HPV vaccine, placebo, or other vaccines not directed against HPV in women of any age with conisation for treating precancerous lesions following HPV infection.

Outcomes

Critical outcomes: CIN 2+ (irrespective of HPV type and related to HPV 16/18), CIN 3+ (irrespective of HPV type and related to HPV 16/18), incident invasive cervical cancer (irrespective of HPV type and related to HPV 16/18), persistent HPV infection (irrespective of HPV type and related to HPV 16/18) and incident HPV infection (irrespective of HPV type and related to HPV 16/18).

Risk of bias

We evaluated RCTs using the Cochrane RoB 2 tool and NRSI using the 'Risk of Bias in Non-randomised Studies of Interventions' tool (ROBINS-I).

Synthesis methods

Two review authors independently screened, extracted data, and assessed risk of bias. We used random-effects meta-analyses for our primary analyses. We rated the certainty of evidence using the GRADE approach.

Included studies

The search identified 13 studies (2 RCTs, 11 NRSI), with 21,453 women with conisation. Studies were conducted in Europe (10), China (1), South Korea (1), and Iran (1), and published between 2013 and 2023. The length of follow-up after conisation was up to 36 months in RCTs and up to greater than 60 months in NRSI.

Eight studies included women older than 25 years. The remaining studies included women across different age groups (range 17 to greater than 50 years). In 10 studies, the treatment for cervical lesions included loop electrosurgical excision procedures or large loop excision of the transformation zone as the conisation procedure. The spectrum of precancerous lesions (in terms of baseline characteristics) varied widely between women.

Seven studies used the quadrivalent HPV vaccine, one used the nonavalent HPV vaccine, four used various HPV vaccine types, and one did not specify the HPV vaccine type. All studies compared the HPV vaccine with no intervention.

Synthesis of results

Critical outcomes

HPV vaccination compared to no HPV vaccination in women with conisation may reduce the risk of CIN 2+ (evidence from RCTs: risk ratio (RR) 0.40, 95% confidence interval (CI) 0.26 to 0.63; 2 RCTs, 420 women; evidence from NRSI: hazard ratio (HR) 0.49, 95% CI 0.27 to 0.89; 5 NRSI, 19,059 women; odds ratio (OR) 0.23, 95% CI 0.05 to 0.97; 3 NRSI, 928 women; RR 0.24, 95% CI 0.13 to 0.46; 3 NRSI, 1027 women; low-certainty evidence).

There were similar results for CIN 2+ (related to HPV 16/18) (evidence from NRSI: RR 0.38, 95% CI 0.21 to 0.68; 7 NRSI, 2970 women; low-certainty evidence).

Effects on CIN 3+ varied between studies. One study suggested similar effects to CIN 2+ favouring HPV vaccination (evidence from NRSI: OR 0.20, 95% CI 0.10 to 0.60; 1 NRSI, 285 women; low-certainty evidence), while the remaining evidence was very uncertain (evidence from NRSI: RR 0.53, 95% CI 0.15 to 1.90; 2 NRSI, 17,472 women; very low-certainty evidence).

The evidence on CIN 2+ (related to HPV 16/18) based on RCT evidence was very uncertain.

The evidence on CIN 3+ (related to HPV 16/18), incident invasive cervical cancer (irrespective of HPV type), and persistent HPV infections (irrespective of HPV type and related to HPV 16/18) was very uncertain.

Adverse events

One RCT reported minor local reactions (redness and rash: 127/138 (92%) women; headache: 11/138 (8%) women) and severe allergies (2/158 (1%) women).

Authors' conclusions

HPV vaccination given around the time of conisation in comparison to no HPV vaccination in women with conisation may reduce the risk of CIN 2+ and CIN 2+ (related to HPV 16/18; evidence based on NRSI). Effects on CIN 3+ (irrespective of HPV type) varied, with one NRSI suggesting similar effects to CIN 2+, while the remaining evidence was very uncertain. The evidence on other outcomes was predominantly very uncertain or inconclusive. Overall, the existing evidence for HPV vaccination in women with conisation is largely based on NRSI with serious or critical risk of bias and low- to very low-certainty evidence. Evidence from RCTs is limited (i.e. only two RCTs are available). Additional RCTs with a placebo intervention in the control group to evaluate the efficacy and safety of HPV vaccination (particularly with the nonavalent vaccine) as an adjuvant to conisation would provide more robust evidence. Future RCTs should also aim to assess how effects of vaccination around the time of conisation vary according to whether a previous HPV vaccine for primary prevention was received, timing of HPV vaccination related to conisation, and different age groups.

Funding

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Registration

PROSPERO (CRD42023428998)

PLAIN LANGUAGE SUMMARY

How effective are human papillomavirus vaccines for women who had or undergo a surgical procedure to remove abnormal cells in the cervix, and do they have any unwanted effects?

Key messages

- Human papillomavirus (HPV) vaccination in comparison to no HPV vaccination in women with conisation (removal of a cone of tissue that contains abnormal cells, also known as cone biopsy) may reduce the risk of precancerous cervical cell changes (primarily CIN 2+).
- Due to limitations in data, we are not sure whether HPV vaccination (given shortly before, at, or after conisation) in comparison to no HPV vaccination in women with conisation affects cervical cancer risk or persistent HPV infection.
- Further high-quality studies are needed to assess the effectiveness and unwanted effects of HPV vaccination in women with conisation. These trials should also consider specific groups, such as women who had received HPV vaccination before and different age groups.

What is human papillomavirus and how is it treated?

Cervical cancer (cancer in the neck of the womb) is the fourth most common cancer affecting women worldwide. It is caused by persistent infection with specific types of human papillomavirus (HPV). While HPV infections are common and usually resolve without any problems, persistent HPV infections can progress to abnormal cell changes in the cervix (that is, precancerous conditions), called cervical intraepithelial neoplasia (CIN). These precancerous conditions can be classified as low-grade lesions (called CIN 1) and high-grade lesions (called CIN 2 and CIN 3). While low-grade lesions usually resolve spontaneously without treatment, high-grade lesions have a higher chance of progressing to cervical cancer. CIN 3 corresponds to carcinoma in situ (abnormal cells confined to where they first occurred), and adenocarcinoma in situ (abnormal cells that have moved to glands); it is well accepted that these immediately precede cervical cancer.

There are more than 200 types of HPV, and over 40 of them infect the genital area. Seven in 10 cervical cancers are caused by HPV types 16 and 18. Women diagnosed with CIN 2 and CIN 3 are usually considered for cervical conisation (also known as cone biopsy), a surgical procedure to remove abnormal cells to prevent progression to cervical cancer.

In Europe, there are three approved HPV vaccines: a bivalent (which protects against two HPV types), quadrivalent (which protects against four HPV types), and nonavalent (which protects against nine HPV types) vaccine. HPV vaccination is used to prevent cervical cancer, but its effectiveness for women with conisation remains uncertain. Of note, we use the term 'with conisation' interchangeably to refer to whenever the HPV vaccination was given around the time of the conisation procedure, that is, before, at, or after the procedure.

What did we want to find out?

We wanted to find out how effective HPV vaccination is for women who had or undergo conisation to remove precancerous cervical lesions, and if it has any unwanted effects.

What did we do?

We searched for studies that examined the effects of HPV vaccination in women of any age with conisation to treat precancerous cervical cell changes caused by HPV. We summarised the results, assessed their reliability, and rated our confidence in the evidence.

What did we find?

We found 13 studies that included 21,453 women with conisation. The studies varied in design and quality. Most studies were conducted in Europe (10 studies) and used the quadrivalent (seven studies) or nonavalent (one study) HPV vaccine. Some studies monitored women for more than 60 months.

Main results

- HPV vaccination in comparison to no HPV vaccination in women with conisation may reduce the risk of precancerous lesions. However, results have to be interpreted with caution.
- We are not sure whether HPV vaccination in comparison to no HPV vaccination in women with conisation has an effect on cervical cancer and persistent HPV infection.
- There were no data for new HPV infections, adenocarcinoma in situ, and quality of life, and the remaining evidence was mostly inconclusive.
- Unwanted effects included minor reactions (redness and rash: 92 in every 100 women; headache: 8 in every 100 women) and severe allergies (1 in every 100 women).

What are the limitations of the evidence?

The evidence was mainly from studies that had potential problems with how they were conducted. Only two studies were designed to produce more robust evidence. The studies did not provide enough information to know whether a previous HPV vaccination means that another vaccination and its timing in relation to the conisation procedure gives different results. We also need to know more about the effects on different age groups.

How up to date is this evidence?

The evidence is current to May 2023.

SUMMARY OF FINDINGS

Summary of findings 1. Human papillomavirus (HPV) vaccination compared to no HPV vaccination in women with conisation

Human papillomavirus (HPV) vaccination compared to no HPV vaccination in women with conisation

Patient or population: women with conisation

Setting: any setting

Intervention: HPV vaccine (nonavalent, quadrivalent, bivalent)

Comparison: no vaccination

Outcome, study design	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no vaccine	Risk with vaccine				
Outcome: CIN 2+ (irrespective of HPV type)						
RCTs (follow-up: 24–36 months)	233 per 1000	93 per 1000 (61 to 147)	RR 0.40 (0.26 to 0.63)	420 (2 studies)	⊕⊕⊕⊕ Low^a	The evidence from 2 RCTs is of low certainty, but suggests that HPV vaccination may reduce the risk of CIN 2+.
NRSI (follow-up: ≥ 12 to > 60 months)	53 per 1000	27 per 1000 (15 to 48)	HR 0.49 (0.27 to 0.89)	19,059 (5 studies)	⊕⊕⊕⊕ Low^b	The evidence from 5 NRSI is of low certainty, but suggests that HPV vaccination may reduce the risk of CIN 2+.
	120 per 1000	30 per 1000 (7 to 117)	OR 0.23 (0.05 to 0.97)	928 (3 studies)	⊕⊕⊕⊕ Low^b	The evidence from 3 NRSI is of low certainty, but suggests that HPV vaccination may reduce the risk of CIN 2+.
	84 per 1000	20 per 1000 (11 to 39)	RR 0.24 (0.13 to 0.46)	1027 (3 studies)	⊕⊕⊕⊕ Low^b	The evidence from 3 NRSI is of low certainty, but suggests that HPV vaccination may reduce the risk of CIN 2+.
Outcome: CIN 2+ (HPV 16/18)						
RCTs (follow-up: 36 months)	45 per 1000	5 per 1000 (0 to 91)	RR 0.11 (0.01 to 2.03)	178 (1 study)	⊕⊕⊕⊕ Very low^{c,d}	The evidence from 1 RCT is of very low certainty about the effect of HPV vaccination on CIN 2+ (HPV 16/18).

NRSI (follow-up: 14.2–42 (medi- an) months)	50 per 1000	19 per 1000 (10 to 34)	RR 0.38 (0.21 to 0.68)	2970 (7 studies)	⊕⊕⊕⊕ Low^b	The evidence from 7 NRSI is of low certainty, but suggests that HPV vaccination may reduce the risk of CIN 2+ (HPV 16/18).
Outcome: CIN 3+ (irrespective of HPV type)						
RCTs	No evidence from RCTs available					
NRSI (follow-up: ≥ 12–36 (median) months)	78 per 1000	17 per 1000 (8 to 48)	OR 0.20 (0.10 to 0.60)	285 (1 study)	⊕⊕⊕⊕ Low^b	The evidence from 1 NRSI is of low certainty, but suggests that HPV vaccination may reduce the risk of CIN 3+.
	28 per 1000	15 per 1000 (4 to 54)	RR 0.53 (0.15 to 1.90)	17,472 (2 studies)	⊕⊕⊕⊕ Very low^{b,d}	The evidence from 2 NRSI is of very low certainty about the effect of HPV vaccination on CIN 3+.
Outcome: CIN 3+ (HPV 16/18)						
RCTs	No evidence from RCTs available					
NRSI (follow-up: 36 (median) months)	29 per 1000	2 per 1000 (0 to 47)	RR 0.08 (0.01 to 1.63)	344 (1 study)	⊕⊕⊕⊕ Very low^{b,d}	The evidence from 1 NRSI is of very low certainty about the effect of HPV vaccination on CIN 3+ (HPV 16/18).
Outcome: incident invasive cervical cancer (irrespective of HPV type)						
RCTs (follow-up: 24 months)	10 per 1000	2 per 1000 (0 to 59)	RR 0.25 (0.01 to 6.11)	242 (1 study)	⊕⊕⊕⊕ Very low^{a,d}	The evidence from 1 RCT is of very low certainty about the effect of HPV vaccination on incident invasive cervical cancer.
NRSI (follow-up: ≥ 12 months)	1 per 1000	1 per 1000 (0 to 4)	RR 0.85 (0.20 to 3.69)	17,128 (1 study)	⊕⊕⊕⊕ Very low^{b,e}	The evidence from 1 NRSI is of very low certainty about the effect of HPV vaccination on incident invasive cervical cancer.
Outcome: incident invasive cervical cancer (HPV 16/18)						
RCTs	No evidence from RCTs available					
NRSI	No evidence from NRSI available					

Outcome: persistent HPV infection (irrespective of HPV type)						
RCTs	No evidence from RCTs available					
NRSI (follow-up: 6–30 months)	169 per 1000	113 per 1000 (72 to 177)	RR 0.67 (0.43 to 1.05)	765 (2 studies)	⊕⊕⊕⊕ Very low ^{b,d}	The evidence from 2 NRSI is of very low certainty about the effect of HPV vaccination on persistent HPV infection.
Outcome: persistent HPV infection (HPV 16/18)						
RCTs	No evidence from RCTs available					
NRSI (follow-up: 33.1–36 months)	98 per 1000	96 per 1000 (65 to 143)	RR 0.98 (0.66 to 1.46)	907 (2 studies)	⊕⊕⊕⊕ Very low ^{b,d}	The evidence from 2 NRSI is of very low certainty about the effect of HPV vaccination on persistent HPV infection (HPV 16/18).
Outcome: incident HPV infection (irrespective of HPV type and related to HPV 16/18)						
RCTs	No evidence from RCTs available					
NRSI	No evidence from NRSI available ^f					
Outcome: any serious adverse event						
RCTs	No evidence from RCTs available					
NRSI	No evidence from NRSI available					
Outcome: any adverse event						
RCTs	1 RCT reported minor local reactions (redness and rash, 127/138 women (92%); headache, 11/138 women (8%)) in the HPV vaccine group. Additionally, 2/158 women (1%) allocated to the treatment arm were excluded from the analysis population due to severe allergies. There were no data for the comparator group.					
NRSI	No evidence from NRSI available					

CIN: cervical intraepithelial neoplasia; **CI:** confidence interval; **HPV:** (high-risk) human papillomavirus (diagnosed by HPV testing); **NRSI:** non-randomised studies of interventions; **RCT:** randomised controlled trial.

Grades of evidence after the GRADE working group:

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

^a Downgraded two levels for risk of bias (RCTs): very serious concerns regarding randomisation, deviations from intended interventions, missing outcome data, and selection of the reported results.

^b Downgraded two levels for risk of bias (NRSI): very serious concerns regarding confounding, selection of participants into study, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported results.

^c Downgraded one level for risk of bias (RCT): serious concerns regarding randomisation, deviations from intended interventions, missing outcome data, and selection of the reported results.

^d Downgraded two levels for imprecision: 95% CI indicates the possibility of considerably fewer or more events.

^e Downgraded one level for imprecision: 95% CI is consistent with the possibility of fewer or more events.

^f One study reported incident HPV infections in combination with persistent HPV infections [1].

Heterogeneity quantified using the I^2 statistic was moderate (outcomes: CIN 2+ HPV 16/18 (NRSI)) to high (outcomes: CIN 2+ (NRSI)) in some meta-analyses and the wide prediction intervals incorporated potential harm, benefit, and no difference. However, the effects of individual studies are consistent in direction. Therefore, we did not downgrade for inconsistency.

BACKGROUND

Description of the condition

Cervical cancer is the fourth most common cancer affecting women worldwide. It particularly impacts countries with a low Human Development Index, where mortality rates are up to six times higher compared to countries with a very high Human Development Index [2, 3]. Cervical cancer is caused by persistent infections with oncogenic (tumour-causing) types of human papillomavirus (HPV). More than 200 types of HPV have been identified and more than 40 types of them infect the genital tract. Whereas HPV 16 and 18 are the two primary oncogenic types that are responsible for 71% of cervical cancers, HPV 31, 33, 45, 52, and 58 account for an additional 18% of cervical cancers [4]. HPV 6 and 11 are non-oncogenic and cause 90% of anogenital warts [5].

While HPV infections are common and usually resolve without any consequences, persistent infections with high-risk HPV types can progress to premalignant glandular or squamous intraepithelial lesions (cervical dysplasia). From a histopathological perspective, the squamous lesions are classified as cervical intraepithelial neoplasia (CIN) and graded as CIN 1 (referring to low-grade squamous intraepithelial lesion), CIN 2 (referring to high-grade squamous intraepithelial lesion), and CIN 3 (referring to high-grade squamous intraepithelial lesion and carcinoma in situ) [5, 6]. While low-grade lesions (CIN 1) usually regress spontaneously, CIN 2 and 3 lesions have a higher potential to progress to cervical cancer. CIN 3, along with adenocarcinoma in situ, is well-accepted as the pathological state that immediately precedes invasive cervical cancer [6]. Studies on HPV vaccination often use composite outcomes, for example, CIN 2⁺ which typically includes CIN 2, CIN 3, and cervical cancer; or CIN 3⁺ which typically includes CIN 3 and cervical cancer [5, 7, 8]. However, these composite outcomes are not reported consistently; for example, CIN 2+ classifications sometimes include only the precancerous lesions CIN 2 and CIN 3 [9].

a: the '+' indicates 'CIN 2 or worse' or 'CIN 3 or worse'.

Description of the intervention and how it might work

HPV vaccination is an important measure to prevent cancer. In Europe, three intramuscularly administered HPV vaccines, namely a bivalent (Cervarix), quadrivalent (Gardasil 4), and nonavalent (Gardasil 9) vaccine, are approved for use [10, 11, 12, 13]. All licenced HPV vaccines use virus-like particles from the L1 structural protein, which induce HPV antibodies in the serum that can prevent HPV-related diseases [5]. While all three HPV vaccines target the high-risk oncogenic HPV types 16 and 18, the nonavalent HPV vaccine (Gardasil 9) targets five additional (oncogenic) HPV types (31, 33, 45, 52, and 58). Furthermore, quadrivalent (Gardasil 4) and nonavalent (Gardasil 9) HPV vaccines target the non-oncogenic HPV types 6 and 11.

This review evaluates HPV vaccination (given shortly before, at, or after conisation) in women with conisation. While HPV vaccines are highly effective when given prior to sexual debut as a primary prevention strategy (e.g. through routine or catch-up immunisation programmes) [14], their impact in the context of conisation, which may be considered a form of secondary prevention, remains uncertain.

Surgical treatments, such as conisation, indicate major changes in inflammatory response in the cervix and reduced levels of tumour necrosis factor- α and other pro-inflammatory cytokines. This anti-inflammatory microenvironment may negatively impact the development of persistent infections. Administering the HPV vaccine at this stage may prevent new or recurrent infections, comparable to effects observed in healthy individuals [15, 16, 17]. Additionally, HPV vaccination may help prevent infections from other HPV types to which women who have undergone conisation have not yet been exposed. It may also limit the spread of the virus from sites with low malignant potential to the transformation zone [18]. Nevertheless, HPV virus-like particle-based vaccines are unlikely to induce regression of established cervical dysplasia because the L1 protein is not expressed in the basal cells of infected epithelium where virus infection is thought to be maintained [18]. Beyond the uncertainties surrounding these mechanisms, other factors, such as age, vaccine type, and timing, may also further influence the potential benefits of HPV vaccination in women with conisation [2].

Next to preventive HPV vaccines, there is a growing focus on the development of specifically designed therapeutic HPV vaccines aimed at treating existing HPV-related diseases. While development is still ongoing, the present review focussed exclusively on licenced HPV vaccines for preventive use (i.e. the bivalent, quadrivalent, and nonavalent HPV vaccine) [19].

Why it is important to do this review

Little is known about the degree and duration of naturally acquired immunity after the first infection with HPV [20, 21]. Although infections with one HPV type may provide some natural protection against that particular HPV type, most likely, they do not provide much protection against other HPV types [22]. The serological response after HPV vaccination is stronger than the response after natural infection, providing people with long-term protection against vaccine-targeted HPV types [5].

Women diagnosed with CIN 2+ typically undergo cervical conisation to remove precancerous cervical lesions to prevent disease progression [23]. Conisation, also known as cervical cone excision or cone biopsy, is a surgical procedure to remove a cone-shaped piece of tissue from the cervix. The size and depth of the cone removed depends on the extent of the cervical lesion and the surgical method. Excisional methods include cold knife conisation, laser conisation, electrosurgical loop procedures (loop electrosurgical excision procedures or large loop excision of the transformation zone) and needle or straight wire excision of the transformation zone [23, 24]. Although eliminating high-risk HPV infection is not the treatment goal of conisation, many such women have achieved elimination of infection [25]. While the effectiveness of conisation has been demonstrated, the risk of recurrence of precancerous cervical lesions after five years is 6% for CIN 3+ and 16.5% for CIN 2+ [26]. Furthermore, women receiving conisation show a higher risk than the general population of developing invasive cervical cancer in the long-term follow-up after treatment [27]. Additionally, women who have undergone conisation are at higher risk of developing HPV-associated anogenital precancerous lesions and cancers in other locations [28].

While HPV vaccination has beneficial effects against new infections from vaccine-targeted HPV types, it is unclear to what extent HPV vaccination offers protection when given to women with

conisation to treat precancerous lesions. Therefore, this review aimed to investigate the efficacy, effectiveness, and safety by including and evaluating randomised controlled trials (RCTs) and non-randomised studies of interventions (NRSI) on HPV vaccination (given shortly before, at, or after conisation) in women with conisation. Of note, for the purposes of this review, the term 'with conisation' is used interchangeably to refer to all time points of HPV vaccination relative to the conisation procedure, whether the vaccination occurred before, during, or after the procedure. Several reviews suggest that HPV vaccination may benefit women with conisation [15, 29, 30, 31, 32, 33]. However, methodological concerns and outdated data raise the need for a methodologically robust systematic review of the current evidence.

OBJECTIVES

To investigate the benefits and harms of HPV vaccination (given shortly before, at, or after conisation) in comparison to no HPV vaccination in women with conisation.

METHODS

Criteria for considering studies for this review

Types of studies

We searched for RCTs, including cluster-randomised trials and cross-over trials, as this study design, if performed appropriately and under ideal conditions of clinical care, provides the best evidence for efficacy questions. In addition, we included NRSI, as we expected to find only a few RCTs [34, 35]. NRSI were 1. studies in which participants (individuals or clusters of individuals) were allocated to different groups (intervention and control group) using methods that were not random and 2. observational studies (i.e. prospective cohort studies (i.e. prospective follow-up; HPV vaccination received after study start and consent for participation) and retrospective cohort studies (i.e. no prospective follow-up; HPV vaccination received in the past before participants were enrolled in the study)) with a control group and case-control studies. In observational studies, group allocation is determined by factors outside the investigator's control, allowing the assessment of the HPV vaccine's effectiveness under typical clinical care conditions [34, 35].

We excluded single-arm studies without any control group (such as case reports and case series), review articles, laboratory and animal studies, pharmacokinetic studies, and in-vitro studies.

We included full-text journal publications, preprint articles, and results published in the trial registry if there was sufficient information on study design, characteristics of participants, interventions, and outcomes.

We excluded citations reported in abstract form only (due to limited information on study methods), theses, editorials, letters, and comments. We did not apply any limitations concerning the length of follow-up.

Types of participants

We included studies investigating women of any age who receive conisation (excisional surgery) due to precancerous cervical lesions with any of the following procedures: loop electrosurgical excision procedure/large loop excision of the transformation zone; needle

excision of the transformation zone/straight wire excision of the transformation zone; cold knife conisation; and laser conisation.

We excluded studies investigating males; women with other HPV-related lesions (non-cervical lesions); and women with cancer, with HIV or other immunocompromised/immunosuppressed conditions (e.g. rheumatism). Furthermore, we excluded ablative therapies, including laser ablation, cryotherapy, and cold coagulation.

Types of interventions

Interventions

We included the following vaccines.

- Nonavalent HPV vaccine (Gardasil 9, 9vHPV)
- Quadrivalent HPV vaccine (Gardasil, 4vHPV)
- Bivalent HPV vaccine (Cervarix, 2vHPV)

For the purposes of this review, we defined HPV vaccination related to conisation as an HPV vaccine given shortly (i.e. four months or less^b) before, at, or after conisation (up to 12 months after conisation as 'adjuvant' intervention to conisation).

^bOf note, the protocol did not define a specific time window for the inclusion of studies that include women who receive the HPV vaccination before conisation [36].

We excluded studies where the HPV vaccine was administered for the primary prevention of cervical cancer in the general population to avoid potential misinterpretation between primary prevention in the general population and the prevention of disease recurrence in women with conisation.

Comparator

We compared the eligible HPV vaccines with the following.

- No HPV vaccination
- Placebo intervention (containing no active agent)
- Another non-HPV vaccine.

Outcome measures

We included critical outcomes (suggested prospectively by experts of the HPV Working Group) in [Summary of findings 1](#) and assessed the certainty of evidence according to the GRADE approach.

Timing of outcome measurement

We collected information on outcomes from all time points reported in the publications. If only a few studies contributed data to an outcome, we pooled different time points, provided the studies had produced valid data and pooling of different time points was clinically reasonable. If a study provided multiple suitable time points for the same outcome, we selected the longest follow-up.

Critical outcomes

Efficacy and effectiveness outcomes

- Presence of histologically confirmed cervical lesions (as defined by the World Health Organization [5, 6]) after conisation^c:
 - CIN 2+ (irrespective of HPV type)
 - CIN 2+ (related to HPV 16/18)

- CIN 3+ (irrespective of HPV type)
- CIN 3+ (related to HPV 16/18)

For this review, we included for the composite outcome CIN 2+ studies reporting either CIN 2, CIN 3, and cervical cancer, or only the precancerous lesions CIN 2 and CIN 3, sometimes also classified as high-grade squamous intraepithelial lesion. The composite outcome CIN 3+ included studies reporting CIN 3 and cervical cancer.

- Incident invasive cervical cancer (irrespective of HPV type)
- Incident invasive cervical cancer (related to HPV 16/18)
- Persistent HPV infection^d (irrespective of HPV type)
- Persistent HPV infection (related to HPV 16/18)
- Incident HPV infection^e (irrespective of HPV type)
- Incident HPV infection (related to HPV 16/18)

^cThe '+' indicates 'CIN 2 or worse' or 'CIN 3 or worse'.

^dPersistent HPV infection is defined as the presence of type-specific HPV DNA on repeated clinical biological samples over at least six months (starting at baseline, i.e. time of conisation).

^eDetection of a new HPV infection (defined as the presence of type-specific HPV DNA) at six months or later after conisation.

Important outcomes

Efficacy and effectiveness outcomes

- Presence of CIN 2 (irrespective of HPV type)
- Presence of CIN 3 (irrespective of HPV type)
- Presence of adenocarcinoma in situ
- Mortality (all-cause and cancer-related)
- Presence of vulvar intraepithelial neoplasia (VIN) 2+/vaginal intraepithelial neoplasia (VaIN) 2+
- Quality of life (as measured by validated instruments or scales)

Safety outcomes

- Any serious adverse events
- Any adverse pregnancy outcomes observed during the studies
- Vaccine-related adverse effects, including:
 - local reactions (e.g. swelling, redness, pain/tenderness)
 - systemic reactions (e.g. fever, fatigue)
 - any other reported adverse effects related to the vaccine

Search methods for identification of studies

An information specialist conducted comprehensive systematic literature searches for relevant studies. A second information scientist peer-reviewed the complete electronic search strategies following the recommendation of PRESS (Peer Review of Electronic Search Strategies [37]) and validated by checking whether the strategy identified studies already known.

We did not use any date or language restrictions in the electronic searches. For each database, we documented the search interface used, date of search, search strategy, and number of search results. Search strategies for the databases mentioned below were adapted from the MEDLINE (Ovid) strategy.

Electronic searches

We conducted the searches for published studies in the following electronic databases on the 25 and 26 May 2023.

- Cochrane Central Register of Controlled Trials (CENTRAL) (via Cochrane Library/Wiley), Issue 5, 2023
- MEDLINE (ALL) (via Ovid)
- Embase (via Ovid)
- Web of Science
- BIOSIS Citation Index (via Clarivate)

We searched for ongoing studies or unpublished completed studies in ClinicalTrials.gov (<https://clinicaltrials.gov>).

Search strategies are provided in [Supplementary material 1](#).

Searching other resources

We used relevant studies and systematic reviews to search for additional references via the PubMed similar articles function, and forward and backward citation tracking. We reviewed reference lists of relevant studies and systematic reviews and contacted experts in the field to enquire about any further relevant studies or unpublished data that may not have been retrieved by the electronic searches. Further, we conducted a search of websites of regulatory agencies (European Medicines Agency and Food and Drug Administration). For the included studies, we searched Retraction Watch (<https://retractiondatabase.org/>) and PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) on 7 July 2025 to identify associated retractions or published errata.

Data collection and analysis

Selection of studies

Two review authors (from PK, ET, TB, or CS) independently screened the titles and abstracts of the citations identified by the searches. Two review authors (from PK, ET, TB, or CS) independently checked the full texts of potentially relevant studies and documented reasons for exclusions. We resolved disagreements by consensus, or with a third review author if necessary (TB).

We piloted the 'title and abstract screening' process on a random subset of 50 search results. We piloted the 'full-text screening' process on five included studies. The complete screening process was conducted in Covidence [38].

Data extraction and management

Two review authors (PK, TB, ET, LG, or CS) independently extracted data using a customised and piloted data extraction form. We resolved disagreements by discussion.

We extracted the following information, if reported.

- General information: author and year of publication, study type
- Study characteristics: start and end of study (including follow-up time), sample size (total and for each study arm), funding sources, conflict of interest, geographical setting
- Participant characteristics: age, type of precancerous lesion, whether HPV vaccination was received before the development of the disease (i.e. received for primary prevention and not related to conisation), number of pregnancies/births

- Intervention: type of vaccine, number of doses, timing of first vaccination related to conisation
- Control intervention: no intervention, placebo intervention (e.g. no active product, only the adjuvant of the HPV vaccine), or another non-HPV vaccine
- Outcomes: as defined in [Outcome measures](#), number and reasons for participants unavailable for outcome measurements (non-attendees)

Risk of bias assessment in included studies

Two review authors (from PK, LG, or CS) independently assessed risk of bias of each individual study on an outcome level for all critical outcomes, using the longest reported follow-up. The effect of interest was the assignment of intervention (the 'intention-to-treat effect'). We resolved disagreements by consensus, or with a third review author if necessary (TB).

We assessed bias in RCTs using the RoB 2 tool as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* [39]. For the assessment, we considered the following domains:

- bias arising from the randomisation process;
- bias due to deviations from intended interventions;
- bias due to missing outcome data;
- bias in measurement of the outcome; and
- bias in selection of the reported result.

We judged each domain and overall risk of bias as 'low risk of bias', 'some concerns', or 'high risk of bias' [40, 41]. We conducted the assessment using guidance documents and an adapted version of the RoB Excel Tool available at <https://www.riskofbias.info>.

We evaluated bias in NRSI according to the 'Risk of Bias in Non-randomised Studies of Interventions' tool (ROBINS-I) as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* [39]. For the assessment, we considered the following domains:

- bias due to confounding (i.e. age, CIN grade, HPV type, contraceptive prescriptions, screening history, sexual history, number of births);
- bias in selection of participants into the study (e.g. inception bias);
- bias in classification of the interventions;
- bias due to deviations from intended interventions (i.e. second conisation procedure);
- bias due to missing data;
- bias in measurement of outcomes;
- bias in selection of the reported result; and
- overall bias [42, 43].

We judged each domain and overall risk of bias as 'low', 'moderate', 'serious', or 'critical' risk of bias. We conducted the assessment using guidance documents available at <https://www.riskofbias.info>.

We included all studies, regardless of the risk of bias judgement, in the meta-analyses^f.

^fAlthough the protocol excluded studies with a critical risk of bias from the analyses [36], we included them following consultation

with the HPV Working Group and considered them in sensitivity analyses.

Measures of treatment effect

We conducted meta-analyses separately for each vaccine and for each vaccine effect ratio (e.g. risk ratio (RR), hazard ratio (HR), incidence rate ratio (IRR), or odds ratio (OR)), as well as separately for RCTs and NRSI. We summarised the precision of the pooled effect estimates from meta-analyses with the corresponding 95% confidence interval (CI). Additionally, we expressed vaccine effect estimates (efficacy or effectiveness) as percentages and calculated as follows: **vaccine efficacy or effectiveness (VE) = (1 - vaccine effect ratio) × 100**. Thereby, we used the adjusted vaccine effect ratio as reported in the primary study including OR, RR, HR, or IRR. We summarised the precision of the vaccine effect estimate (efficacy or effectiveness) with the corresponding 95% CI. Vaccine effect estimates greater than 0% suggest a protective effect of the vaccine.

We planned to present continuous outcomes as mean differences (MDs) with 95% CI when studies used the same scales. When studies used different scales, we planned to use the standardised mean difference (SMD) with 95% CI.

For NRSI, we used the adjusted data. Where adjusted data were not available, we extracted the unadjusted data as reported in the study. For RCTs, we used unadjusted data.

Unit of analysis issues

The unit of analysis was the individual study participant. We planned to incorporate multi-arm, cluster-randomised, and cross-over studies following the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* [44].

Dealing with missing data

We analysed data, if possible, on an intention-to-treat basis or according to recently developed recommendations for systematic reviewers for addressing missing data in clinical studies [45]. We did not contact the authors of trials to obtain any missing data.

Reporting bias assessment

We planned to examine funnel plots and use appropriate statistical tests (i.e. Egger's test) to determine publication bias provided 10 or more studies were available for pooling on the same outcome [46].

Synthesis methods

We pooled dichotomous outcomes of vaccine effect estimates and continuous outcomes by applying the inverse variance method. We conducted meta-analyses using the random-effects model. We used the Hartung-Knapp adjustment for random-effects meta-analyses when there were three or more studies [47, 48], and for ad hoc correction, we used the 95% CI of the classic random-effects model or the Hartung-Knapp meta-analysis (whichever was wider) [49].

To estimate the between-study variance, we used the restricted maximum likelihood method [50]. We conducted meta-analyses with the statistical software R (version 4.2.2) using the package meta [51, 52]. A narrative description, including tables reporting the outcomes across studies, aimed to synthesise the direction and size of any observed effects in the absence of a meta-analysis.

Investigation of heterogeneity and subgroup analysis

We evaluated different types of heterogeneity (owing to different clinical characteristics, methodological diversity, or small-study effects) using the I^2 statistic and the Chi^2 test using the following thresholds to interpret the I^2 statistic [45].

- 0% to 40%: might not be important
- 30% to 60% may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% or greater: considerable heterogeneity

Additionally, we calculated 95% prediction intervals for assessing heterogeneity in meta-analyses with more than three studies indicating the 95% probability range of a future study with similar characteristics to those included in the meta-analysis [53].

The protocol predefined the sensitivity analyses and subgroup analyses [36]. We conducted sensitivity analyses and subgroup analyses for critical outcomes regardless of the measured statistical heterogeneity.

We planned subgroup analyses for critical outcomes using the random-effects model to investigate clinical heterogeneity for the following characteristics.

- Characteristics of the population: age; conisation procedure; grade of CIN at conisation
- Characteristics of the intervention: type of HPV vaccine; timing related to conisation; number of doses; ascertainment of vaccination status (e.g. self-reported, medical record) in NRSI
- Characteristics of the setting: geographic location (e.g. low Human Development Index versus very high Human Development Index)
- Length of follow-up time: less than 12 months and 12 months or greater

The selection of the subgroups and sensitivity analyses was guided by the experts of the HPV Working Group and informed by previously published systematic reviews in the field of HPV vaccination [14, 32]. In particular, age-related differences may play an important role in the development of HPV-related diseases, considering previous exposures to HPV types throughout life. In the same vein, the available HPV vaccines cover different oncogenic HPV types and, therefore, may show differences in protection of HPV-related diseases. The geographic location, which is known to impact HPV incidence and HPV mortality rates, was also considered in the definition of subgroup analyses [2, 3].

Equity-related assessment

We did not examine equity-related characteristics in this review.

Sensitivity analysis

If possible, we considered the following sensitivity analyses (for critical outcomes only).

- Risk of bias assessment (exclusion of studies with critical risk of bias)
- Effect size (studies with inexplicably high or low effects)
- Study design (prospective NRSI, retrospective NRSI)

For the available analyses, we conducted both fixed-effect and random-effects meta-analyses.

Certainty of the evidence assessment

We used GRADEpro GDT to create [Summary of findings 1](#) [54, 55]. We included the following outcomes that were *prioritised* a priori.

- CIN 2+ (irrespective of HPV type and related to HPV 16/18)
- CIN 3+ (irrespective of HPV type and related to HPV 16/18)
- Incident invasive cervical cancer (irrespective of HPV type and related to HPV 16/18)
- Persistent HPV infection (irrespective of HPV type and related to HPV 16/18)
- Incident HPV infection (irrespective of HPV type and related to HPV 16/18)

We used the GRADE approach to assess the certainty of the evidence for the outcomes listed above. The GRADE approach uses five domains (risk of bias, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty in the body of evidence for each prioritised outcome.

We downgraded our certainty of evidence as follows.

- Serious (one level) or very serious (two levels) risk of bias
- Serious (one level) or very serious (two levels) inconsistency
- Serious (one level) or very serious (two levels) uncertainty about directness
- Serious (one level) or very serious (two levels) imprecise or sparse data
- Serious (one level) or very serious (two levels) probability of reporting bias

The GRADE system uses the following levels when assigning the certainty of evidence.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
- Low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

We followed the current GRADE guidance for these assessments in its entirety as recommended in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* [54]. We used the overall risk of bias judgement to inform our decision on downgrading for risk of bias. In accordance with the GRADE guidelines for NRSI assessed with ROBINS-I, we also started the assessment with high certainty of evidence [56]. The results per outcome are presented in [Summary of findings 1](#) as suggested by the GRADE Working Group. We phrased the findings and certainty in the evidence as suggested in the informative statement guidance [57]. Two review authors (PK, CS) independently conducted the GRADE assessments. We resolved any disagreements by discussion and consensus involving a third review author, if needed (WS).

Consumer involvement

Consumers were not involved in this review.

RESULTS

Description of studies

Results of the search

The literature search identified 3203 records. Additionally, we identified 543 registry entries on ClinicalTrials.gov. Searches of

reference lists resulted in no additional relevant records. After removing duplicates (via Systematic Review Accelerator) [58], 2378 records remained. During title and abstract screening, we judged 2300 records to be irrelevant. We proceeded to full-text screening with 78 records. From these, we excluded 57 records and listed one study as awaiting classification (Figure 1). Finally, we included 13 records contributing data to the outcomes of this review (13 studies (2 RCTs and 11 NRSI)) and listed seven ongoing studies (4 RCTs and 3 NRSI) (Supplementary material 5). The flow of records, including the reasons for exclusions, is illustrated in Figure 1 [59].

Figure 1. Study flow diagram.

NRSI: non-randomised studies of interventions; RCT: randomised controlled trial.

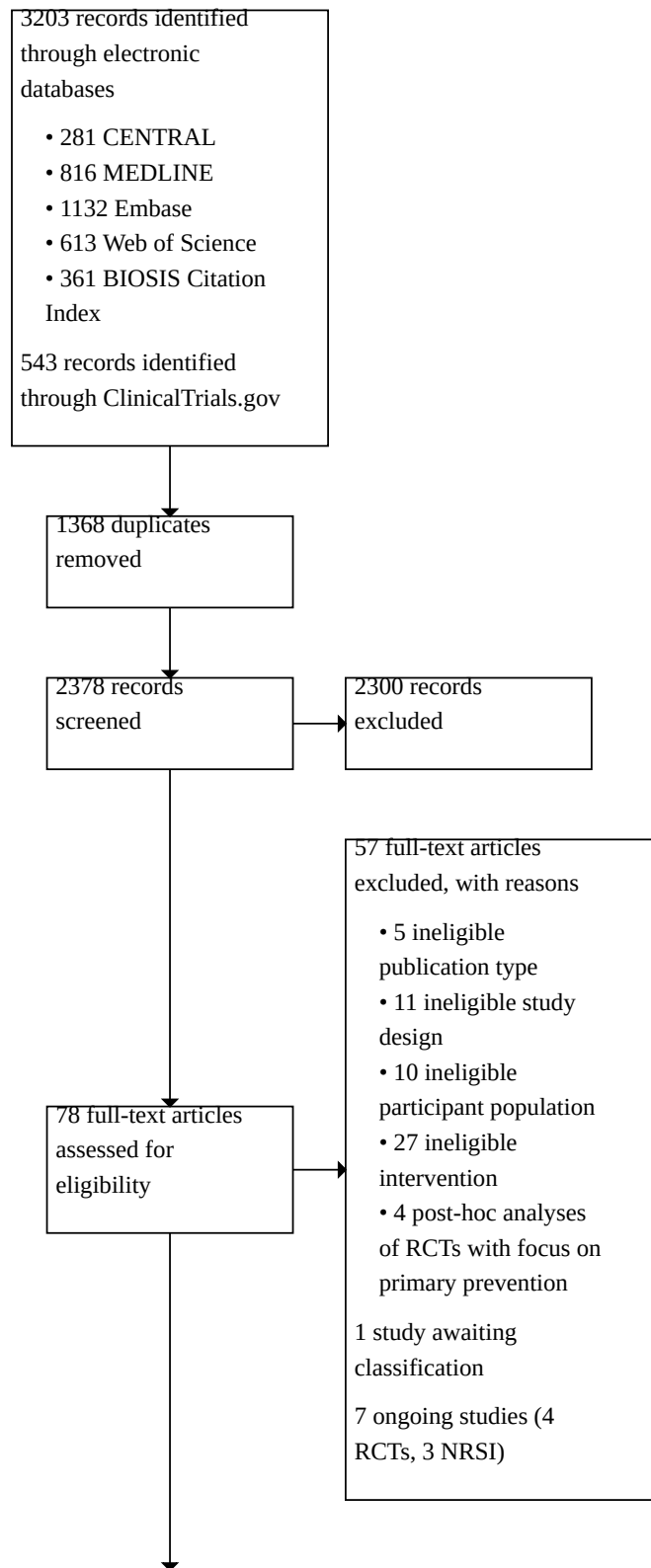
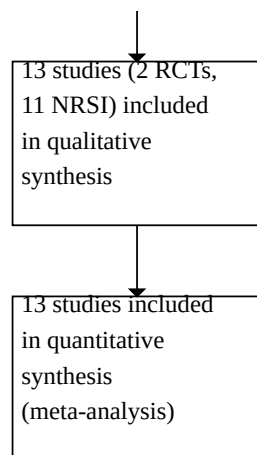


Figure 1. (Continued)



Included studies

The review includes 13 studies, the details of which are provided in [Table 1](#) and [Supplementary material 2](#).

Baseline study characteristics

We found two RCTs (Karimi-Zarchi 2020 [60]; Pieralli 2018 [61]), three prospective NRSI (Chen 2023 [62]; Ghelardi 2018 [63]; Sand 2020 [64]), and eight retrospective NRSI (Bogani 2020 [65]; Casajuana-Perez 2022 [66]; Del Pino 2020 [25]; Gomez de la Rosa 2021 [67]; Henere 2022 [1]; Kang 2013 [68]; Ortega-Quiñonero 2019 [69]; Petrillo 2020 [70]), enrolling 21,453 women with conisation.

Ten studies were in Europe (Bogani 2020; Casajuana-Perez 2022; Del Pino 2020; Ghelardi 2018; Gomez de la Rosa 2021; Henere 2022; Ortega-Quiñonero 2019; Petrillo 2020; Pieralli 2018; Sand 2020); and one each in China (Chen 2023), South Korea (Kang 2013), and Iran (Karimi-Zarchi 2020). They were published between 2013 (Kang 2013) and 2023 (Chen 2023). The length of follow-up after conisation was 24 months (Karimi-Zarchi 2020) and 36 months (Pieralli 2018) in the RCTs. In NRSI, median follow-up times for the primary outcome CIN 2+ ranged between 12 months (Sand 2020) and greater than 60 months (Bogani 2020).

We assessed all included studies for potential conflicts of interest. One study reported funding by the vaccine manufacturer (Casajuana-Perez 2022).

Participant characteristics

Eight studies included women older than 25 years (Bogani 2020; Casajuana-Perez 2022; Del Pino 2020; Gomez de la Rosa 2021; Henere 2022; Kang 2013; Ortega-Quiñonero 2019; Petrillo 2020). The remaining five studies included women across different age groups, ranging from 17 to greater than 50 years of age (Chen 2023; Ghelardi 2018; Karimi-Zarchi 2020; Pieralli 2018; Sand 2020).

In 10 studies, the treatment for cervical lesions included loop electrosurgical excision procedure/large loop excision of the transformation zone as surgical procedures (Bogani 2020; Casajuana-Perez 2022; Chen 2023; Del Pino 2020; Ghelardi 2018; Gomez de la Rosa 2021; Henere 2022; Kang 2013; Ortega-Quiñonero

2019; Petrillo 2020), and one study included loop electrosurgical excision procedure and cold-knife conisation (Karimi-Zarchi 2020). Two studies did not specify the conisation procedure (Pieralli 2018; Sand 2020).

Some studies reported lesions based on clinical assessment that led to the recommendation for conisation, while other studies used pathology reports of the actual conisation specimens for reporting these baseline data. Therefore, the spectrum of (precancerous) lesions at baseline varied widely: normal, CIN 1, CIN 2, CIN 3, or cervical cancer.

In total, four studies reported explicitly that prior HPV vaccination (i.e. an HPV vaccine given not related to conisation) was an exclusion criterion (Chen 2023; Kang 2013; Ortega-Quiñonero 2019; Sand 2020). In the remaining studies, information on prior HPV vaccination (given as primary prevention) was lacking.

Interventions and comparators

Timing of the application of the first dose in relation to conisation varied. The HPV vaccines were administered after (up to six months) conisation (Bogani 2020; Del Pino 2020; Ghelardi 2018; Gomez de la Rosa 2021; Kang 2013; Petrillo 2020; Pieralli 2018), at the time of conisation (Karimi-Zarchi 2020), or either (shortly) *before* (range 1 to 4 months) or *after* (1 to 12 months) conisation (Henere 2022; Ortega-Quiñonero 2019; Sand 2020).

Two studies described the timing of HPV vaccination related to the conisation (i.e. after conisation and before or after conisation), but did not report the exact time frame (e.g. months) between conisation and HPV vaccination (Casajuana-Perez 2022; Chen 2023).

The studies used the quadrivalent HPV vaccine (Bogani 2020; Chen 2023; Ghelardi 2018; Kang 2013; Karimi-Zarchi 2020; Petrillo 2020; Pieralli 2018), the nonavalent HPV vaccine (Henere 2022), or various HPV vaccine types (Casajuana-Perez 2022; Del Pino 2020; Gomez de la Rosa 2021; Ortega-Quiñonero 2019). One study did not specify the HPV vaccine type (Sand 2020).

Six studies gave three doses of the HPV vaccines (68% or greater of women; Bogani 2020; Casajuana-Perez 2022; Del Pino 2020; Henere 2022; Kang 2013; Karimi-Zarchi 2020). The remaining studies did not specify the proportion of women receiving one, two, or three doses. All studies compared the HPV vaccines with no intervention.

Of note, a small proportion of women received the bivalent HPV vaccines. Bogani 2020 reported that 7% of women received the bivalent HPV vaccine, while Petrillo 2020 indicated that 2% of women received the bivalent HPV vaccine.

Excluded studies

Overall, we excluded 57 full-text records. Reasons included ineligible publication type (five), ineligible study design (11), ineligible participant population (10), ineligible intervention (27), and post-hoc analysis of RCTs with focus on primary prevention (four). Detailed reasons for exclusion during full-text screening are provided in [Supplementary material 3](#).

Studies awaiting classification

One study is awaiting classification (see [Supplementary material 4](#)).

Ongoing studies

Seven studies are ongoing (see [Supplementary material 5](#)).

Risk of bias in included studies

We assessed the risk of bias for two RCTs contributing results to our critical outcomes using the RoB 2 tool [40, 41]. The RoB 2 judgements for the two RCTs account for all critical outcomes and are available in [Supplementary material 7](#). We judged one RCT to have overall some concerns, mainly due to issues regarding the randomisation procedure (i.e. insufficient description of the randomisation procedure), deviations from intended interventions, missing outcome data, and the selection of the reported results (i.e. no protocol or registration provided) (Pieralli 2018). The other RCT was at overall high risk of bias, mainly due to major concerns regarding missing outcome data (i.e.

high dropout rates in the control group) and concerns regarding deviations from intended interventions, and the selection of the reported results (Karimi-Zarchi 2020).

We assessed risk of bias for the 11 NRSI using the ROBINS-I tool [42]. The ROBINS-I judgements also account for all critical outcomes and are available in [Supplementary material 8](#). We judged 10 NRSI to have an overall serious risk of bias, mainly due to confounding (which was in most cases not sufficiently considered), measurement of the outcomes (e.g. differences in follow-up time between groups), selection of participants into the study, and risk for selection of the reported results (Bogani 2020; Casajuana-Perez 2022; Chen 2023; Gomez de la Rosa 2021; Del Pino 2020; Ghelardi 2018; Kang 2013; Ortega-Quiñonero 2019; Petrillo 2020; Sand 2020). One NRSI was at overall critical risk of bias due to important uncontrolled confounding (e.g. uncontrolled differences in participant characteristics at baseline) (Henere 2022).

Synthesis of results

Human papillomavirus vaccine compared to no intervention

[Supplementary material 9](#) provides an overview of all outcome data extracted at the study level. An overview of the effects of the intervention for each critical and important outcome is presented in [Supplementary material 10](#).

Critical outcomes

CIN 2+ (irrespective of HPV type)

The risk of CIN 2+ may be reduced among vaccinated women with conisation (evidence from RCTs: RR 0.40, 95% CI 0.26 to 0.63; 2 RCTs, 420 women; low-certainty evidence; Karimi-Zarchi 2020; Pieralli 2018; evidence from NRSI: HR 0.49, 95% CI 0.27 to 0.89; 5 NRSI, 19,059 women; low-certainty evidence; Bogani 2020; Casajuana-Perez 2022; Gomez de la Rosa 2021; Kang 2013; Sand 2020; OR 0.23, 95% CI 0.05 to 0.97; 3 NRSI, 928 women; low-certainty evidence; Chen 2023; Del Pino 2020; Ortega-Quiñonero 2019; RR 0.24, 95% CI 0.13 to 0.46; 3 NRSI, 1027 women; low-certainty evidence; Ghelardi 2018; Henere 2022; Petrillo 2020) ([Summary of findings 1](#); [Figure 2](#); [Figure 3](#); [Supplementary material 9](#)).

Figure 2. Randomised controlled trials: CIN 2+ (irrespective of HPV type).

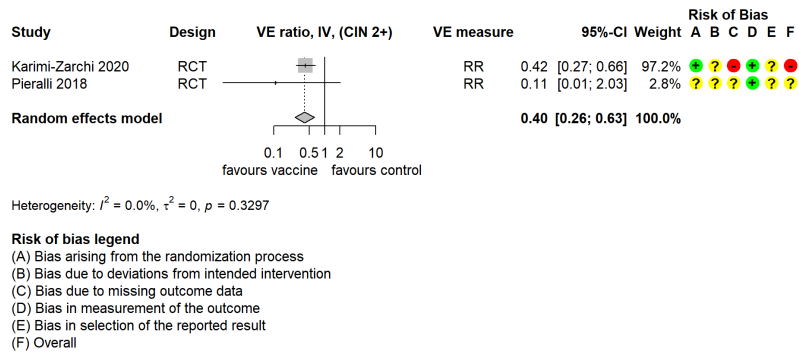
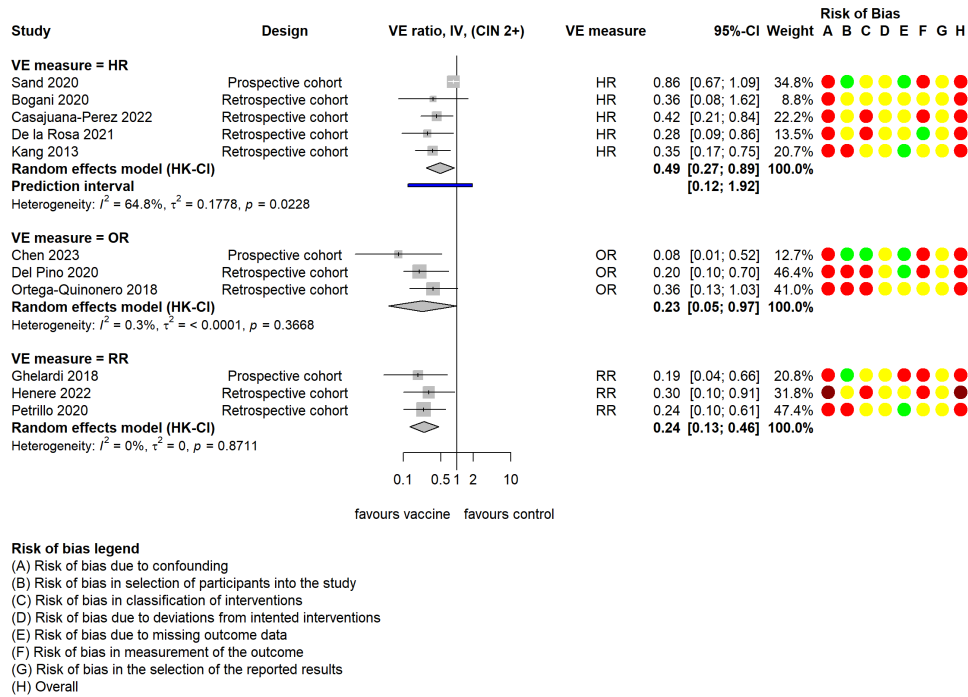


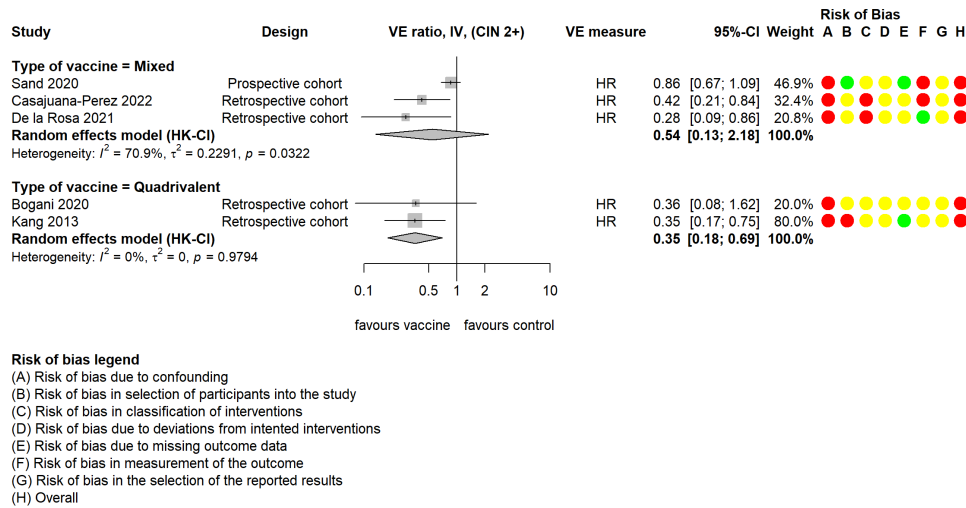
Figure 3. Non-randomised studies of interventions: CIN 2+ (irrespective of HPV type)



Subgroup analyses

We found no subgroup differences according to type of HPV vaccine, as indicated by the overlapping 95% CI when comparing the subgroups (Figure 4).

Figure 4. Non-randomised studies of interventions: CIN 2+ (irrespective of HPV type), subgroup analyses (type of vaccine)

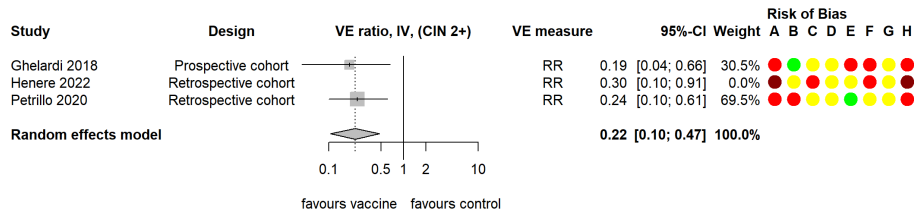


Sensitivity analyses

Sensitivity analyses were possible based on risk of bias (excluding studies with critical risk of bias). The effect was similar to the

primary analysis for CIN 2+ (irrespective of HPV type), with slightly wider CIs. The sensitivity analysis did not alter the interpretation of the result (Figure 5; Supplementary material 11).

Figure 5. Non-randomised studies of interventions: CIN 2+ (irrespective of HPV type), sensitivity analyses



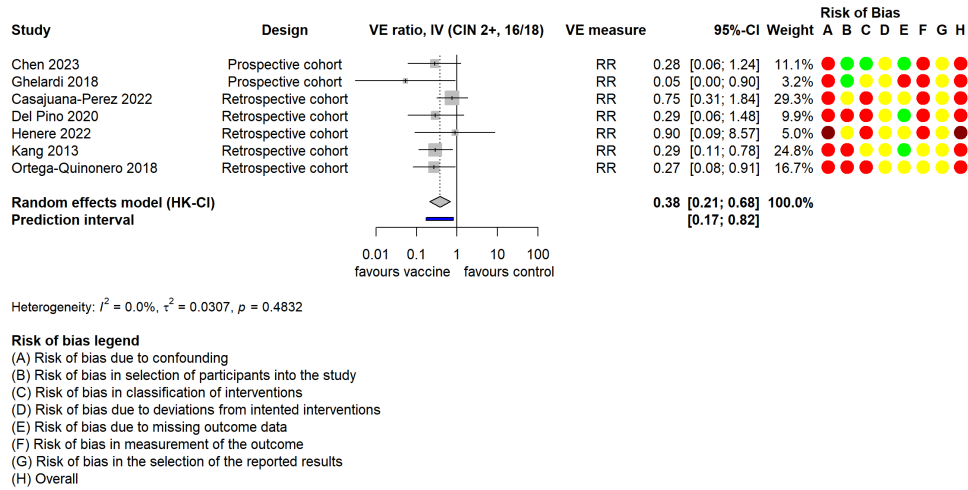
Risk of bias legend
 (A) Risk of bias due to confounding
 (B) Risk of bias in selection of participants into the study
 (C) Risk of bias in classification of interventions
 (D) Risk of bias due to deviations from intended interventions
 (E) Risk of bias due to missing outcome data
 (F) Risk of bias in measurement of the outcome
 (G) Risk of bias in the selection of the reported results
 (H) Overall

CIN 2+ (related to HPV 16/18)

The risk of CIN 2+ (HPV 16/18) may be reduced based on evidence from NRSI among vaccinated women with conisation. The risk for CIN 2+ (HPV 16/18) was very uncertain based on evidence from one RCT, since the CIs included both a considerably decreased and increased risk for CIN 2+ (HPV 16/18) among vaccinated women

(evidence from RCTs: RR 0.11, 95% CI 0.01 to 2.03; 1 RCT, 178 women; very low-certainty evidence; Pieralli 2018; evidence from NRSI: RR 0.38, 95% CI 0.21 to 0.68; 7 NRSI, 2970 women; low-certainty evidence; Casajuana-Perez 2022; Chen 2023; Del Pino 2020; Ghelardi 2018; Henere 2022; Kang 2013; Ortega-Quifonero 2019) (Summary of findings 1; Figure 6 (single study result for RCT not included); Supplementary material 9).

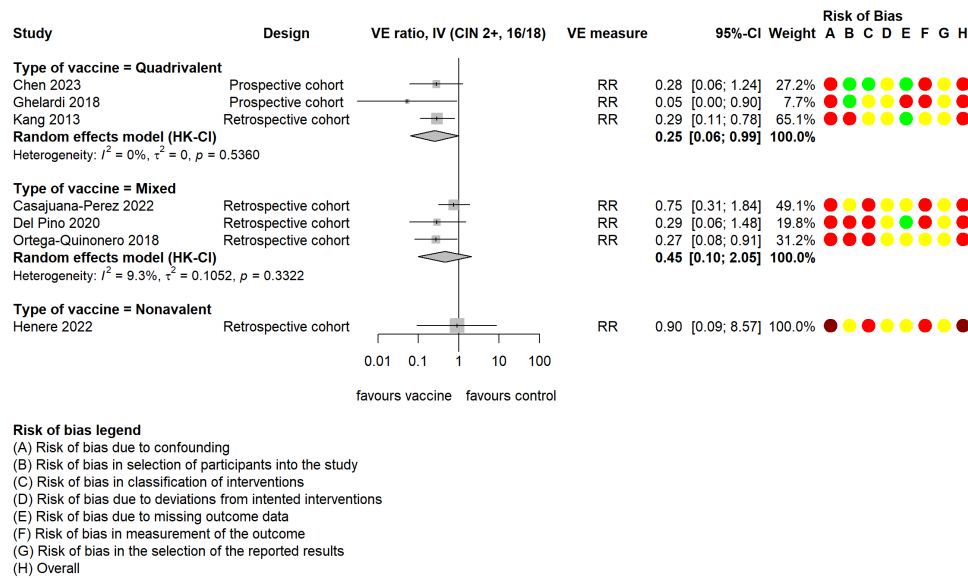
Figure 6. Non-randomised studies of interventions: CIN 2+ (related to HPV 16/18)



Subgroup analyses

We found no subgroup differences according to type of HPV vaccine, as indicated by the overlapping 95% CI when comparing the subgroups (Figure 7).

Figure 7. Non-randomised studies of interventions: CIN 2+ (related to HPV 16/18), subgroup analyses (type of vaccine)

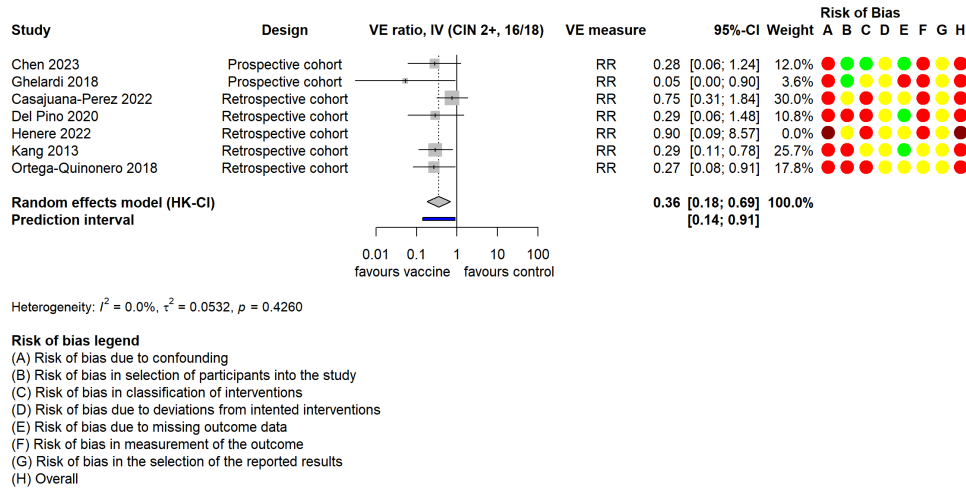


Sensitivity analyses

Sensitivity analyses were possible based on risk of bias (excluding studies with critical risk of bias). The effect was similar to the

primary analysis for CIN 2+ (related to HPV 16/18), with slightly wider CIs. The sensitivity analysis did not alter the interpretation of the result (Figure 8; Supplementary material 11).

Figure 8. Non-randomised studies of interventions: CIN 2+ (related to HPV 16/18), sensitivity analyses

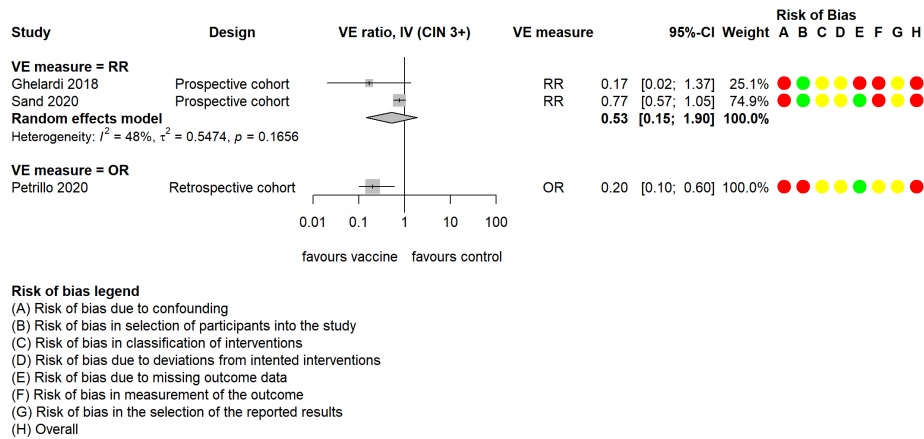


CIN 3+ (irrespective of HPV type)

Effects on CIN 3+ varied between studies. The risk of CIN 3+ may be reduced based on evidence from one NRSI among vaccinated women with conisation (evidence from NRSI: OR 0.20, 95% CI 0.10 to 0.60; 1 NRSI, 285 women; low-certainty evidence; Petrillo 2020). The evidence of the two remaining studies was very uncertain

about the effect of HPV vaccination on CIN 3+ in women with conisation. Although the pooled point estimate suggested there may be an effect in favour of vaccinated women, the CIs were wide and included a considerably decreased and increased risk for CIN 3+ (evidence from NRSI: RR 0.53, 95% CI 0.15 to 1.90; 2 NRSI, 17,472 women; very low-certainty evidence; Ghelardi 2018; Sand 2020) (Summary of findings 1; Figure 9; Supplementary material 9).

Figure 9. Non-randomised studies of interventions: CIN 3+ (irrespective of HPV type)



Subgroup and sensitivity analyses

There were insufficient data for conducting informative subgroup or sensitivity analyses.

CIN 3+ (related to HPV 16/18)

The evidence is very uncertain about the effect of HPV vaccination on CIN 3+ (related to HPV 16/18) in women with conisation as only one NRSI contributed data (RR 0.08, 95% CI 0.01 to 1.63; 1 NRSI, 344 women; very low-certainty evidence; Ghelardi 2018) (Summary of findings 1; Supplementary material 9).

Invasive cervical cancer (irrespective of HPV type)

The evidence is very uncertain about the effect of HPV vaccination on invasive cervical cancer in women with conisation. The CIs included both a considerably decreased and increased risk of invasive cervical cancer among vaccinated women (evidence from RCTs: RR 0.25, 95% CI 0.01 to 6.11; 1 RCT, 242 women; very low-

certainty evidence; Karimi-Zarchi 2020; evidence from NRSI: RR 0.85, 95% CI 0.20 to 3.69; 1 NRSI, 17,128 women; very low-certainty evidence; Sand 2020) (Summary of findings 1; Supplementary material 9).

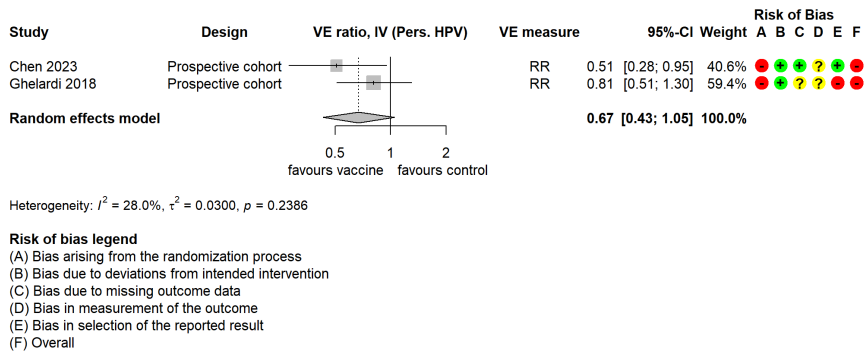
Invasive cervical cancer (related to HPV 16/18)

None of the studies assessed this outcome.

Persistent human papillomavirus infection (irrespective of HPV type)

The evidence is very uncertain about the effect of HPV vaccination on persistent HPV infection in women with conisation. Although the pooled point estimate suggested there may have been a small effect in favour of vaccinated women, the CIs were wide and included values around the null effect (evidence from NRSI: RR 0.67, 95% CI 0.43 to 1.05; 2 NRSI, 765 women; very low-certainty evidence; Chen 2023; Ghelardi 2018) (Summary of findings 1; Figure 10; Supplementary material 9).

Figure 10. Non-randomised studies of interventions: persistent HPV infection (irrespective of HPV type)



Subgroup and sensitivity analyses

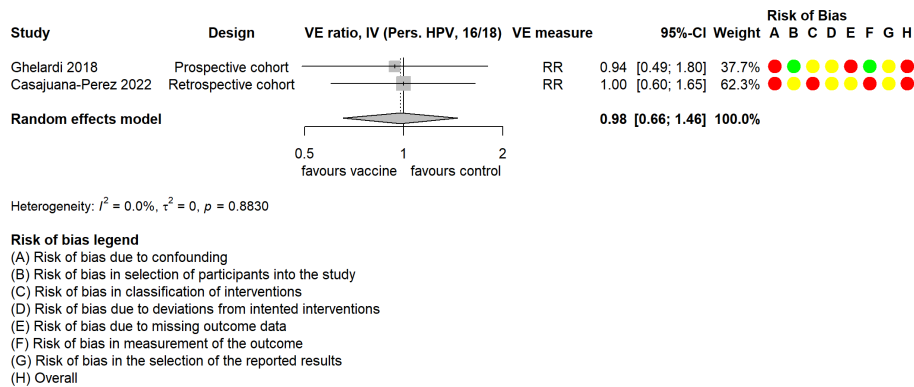
There was insufficient data for conducting informative subgroup or sensitivity analyses.

Persistent human papillomavirus infection (related to HPV 16/18)

The evidence is very uncertain about the effect of HPV vaccination on persistent HPV infection (related to HPV 16/18) in women with

conisation. The CIs included both a considerably decreased and increased risk for HPV infection (HPV 16/18) among vaccinated women (evidence from NRSI: RR 0.98, 95% CI 0.66 to 1.46; 2 NRSI, 907 women; very low-certainty evidence; Casajuana-Perez 2022; Ghelardi 2018) (Summary of findings 1; Figure 11; Supplementary material 9).

Figure 11. Non-randomised studies of interventions: persistent HPV infection (related to HPV 16/18)



Subgroup and sensitivity analyses

There were insufficient data for conducting informative subgroup or sensitivity analyses.

Incident human papillomavirus infection (irrespective of HPV type and related to HPV 16/18)

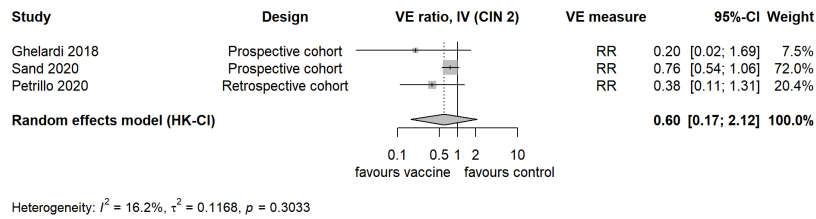
None of the studies assessed these outcomes (only in combination with persistent infections) (Henere 2022).

Important outcomes

CIN 2 (irrespective of HPV type)

The evidence is inconclusive about the effect of HPV vaccination on CIN 2 in women with conisation. The CIs included both a considerably decreased and increased risk for CIN 2 among vaccinated women (evidence from NRSI: RR 0.60, 95% CI 0.17 to 2.12; 3 NRSI, 17,757 women; Ghelardi 2018; Petrillo 2020; Sand 2020) (Figure 12; Supplementary material 9).

Figure 12. Non-randomised studies of interventions: CIN 2 (irrespective of HPV type)



Subgroup and sensitivity analyses

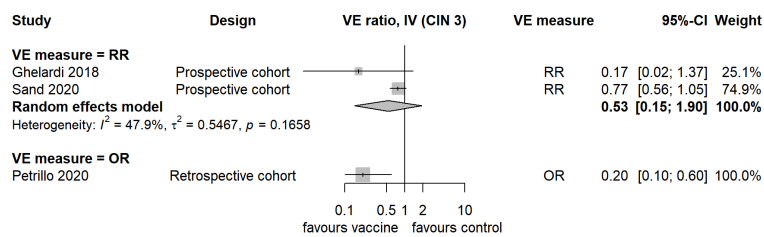
There were insufficient data for conducting informative subgroup or sensitivity analyses.

CIN 3 (irrespective of HPV type)

Effects on CIN 3 varied between studies. The risk of CIN 3 may be reduced based on evidence from one NRSI among vaccinated

women with conisation (evidence from NRSI: OR 0.20, 95% CI 0.10 to 0.60; 1 NRSI, 285 women; Petrillo 2020). The evidence of the two remaining studies was inconclusive. The CIs included both a considerably decreased and increased risk of CIN 3 among vaccinated women (evidence from NRSI: RR 0.53, 95% CI 0.15 to 1.90; 2 NRSI, 17,472 women; Ghelardi 2018; Sand 2020) (Figure 13; Supplementary material 9).

Figure 13. Non-randomised studies of interventions: CIN 3 (irrespective of HPV type)



Subgroup and sensitivity analyses

There were insufficient data for conducting informative subgroup or sensitivity analyses.

Adenocarcinoma in situ

None of the studies assessed this outcome.

Mortality (all-cause and cancer-related)

The evidence is inconclusive about the effect of HPV vaccination on mortality in women with conisation (evidence from NRSI: RR 0.52, 95% CI 0.16 to 1.67; 1 NRSI, 17,128 women; Sand 2020) (Supplementary material 9).

VIN 2+/VaIN 2+

The evidence is inconclusive about the effect of HPV vaccination on VIN 2+ and VaIN 2+ in women with conisation. One RCT reported that there were no events of VIN 2+ or VaIN 2+ observed (effect measure not calculable; 1 RCT, 178 women; Pieralli 2018) (Supplementary material 9).

Quality of life

None of the studies assessed quality of life.

Any serious adverse events

None of the studies reported serious adverse events.

Any adverse pregnancy outcomes observed during the studies

None of the studies assessed adverse pregnancy outcomes.

Vaccine-related adverse effects

One RCT reported vaccine-related adverse effects including minor local reactions (redness and rash: 127/138 (92%) women; headache: 11/138 (8%) women). Additionally, 2/158 (1%) women were excluded from the analysis population due to severe allergies. There were no data for the comparator group (Karimi-Zarchi 2020) (Supplementary material 9).

Reporting biases

There are registered studies that are ongoing. Currently, we do not suspect any publication bias to be present for any of the outcomes.

DISCUSSION

Summary of main results

This review aimed to investigate the efficacy, effectiveness, and safety of HPV vaccination (given shortly before, at, or after conisation) in women with conisation due to cervical lesions.

We identified two RCTs including 420 women and 11 NRSI including 21,033 women with conisation. Of the predefined critical outcomes of this review, the studies reported data on CIN 2+ and CIN 3+ (irrespective of HPV type and related to HPV 16/18),

invasive cervical cancer (irrespective of HPV type), and persistent HPV infection (irrespective of HPV type and related to HPV 16/18). Furthermore, the studies also reported data for outcomes considered important, namely: CIN 2 (irrespective of HPV type), CIN 3, VIN 2+/VaIN 2+, mortality, and vaccine-related adverse effects.

Our analyses show that HPV vaccination in comparison to no HPV vaccination may reduce the risk of CIN 2+ (irrespective of HPV type, based on RCTs and NRSI) and CIN 2+ (related to HPV 16/18) (based on NRSI only). Of note, despite differences in design and potential biases, RCTs and NRSI showed similar findings for CIN 2+ (irrespective of HPV type), which may strengthen confidence in the results. However, these similarities could also be a consequence of biases that may have led to an overestimation or underestimation of the effects. Effects on CIN 3+ (irrespective of HPV type) varied between studies, with one NRSI suggesting similar effects to CIN 2+ favouring HPV vaccination, while the remaining evidence was very uncertain (based on NRSI). The effect estimates for CIN 2+ (related to HPV 16/18) based on one RCT and CIN 3+ (related to HPV 16/18) based on one NRSI were very uncertain, with CIs overlapping the null effect. Due to the low- to very low-certainty evidence, results should be interpreted with caution.

The effect on persistent HPV infections (irrespective of HPV type and related to HPV 16/18) was very uncertain. Likewise, we observed no discernible impact of HPV vaccination on the prevention of invasive cervical cancer (irrespective of HPV type) in both RCTs and NRSI.

Moreover, the evidence for the important (i.e. non-critical) outcomes CIN 2 (irrespective of HPV type), VIN 2+/VaIN 2+, and mortality was inconclusive. This can be attributed to some outcomes only being measured by one study or that there was a low event rate, or both. Effects on CIN 3 varied between studies, with one NRSI suggesting similar effects to CIN 2+ favouring HPV vaccination, while the remaining evidence was inconclusive. One RCT reported minor local reactions (redness and rash: 127/138 (92%) women; headache: 11/138 (8%) women) in the HPV vaccine group. Additionally, 2/158 (1%) women were excluded from the analysis population due to severe allergies. There were no data for the comparator group.

Limitations of the evidence included in the review

The evidence summarised in this review applies to the use of the HPV vaccines in women with conisation across a wide age range and across different types of vaccines.

We could not determine the optimal timing for HPV vaccination when given as an adjuvant to conisation. Although some studies suggest it may be more beneficial to be vaccinated before conisation, the available study pool did not allow us to conduct subgroup analyses according to the timing of HPV vaccination in relation to conisation. However, Sand 2020, including more than 17,000 women with surgical treatment for precancerous lesions, found that women vaccinated before conisation (within three months) had a lower risk for developing recurrent diseases compared to women who were not vaccinated. Women vaccinated after conisation (up to 12 months) showed a similar risk compared to women who were not vaccinated. These findings were similar to the results of Henere 2022 (i.e. in favour of vaccination before conisation). Controversially, as surgical treatment may induce changes in the microenvironment of the inflammatory

tissue similar to those seen in women without HPV infection, there could be potential advantages in administering the vaccine postoperatively [71].

Given that widespread HPV vaccination programmes for primary prevention are now well established in most European countries [72, 73], it is unclear whether the results of the included studies can be transferred to a predominantly immunised population. Only four studies explicitly excluded women with a history of HPV vaccination, while the remaining studies did not provide detailed information on prior vaccination status. None of the identified studies specifically included women who were previously vaccinated. However, due to insufficient reporting of the included studies, we cannot rule out the possibility that some women may have been previously vaccinated. Nevertheless, HPV vaccination, particularly with the nonavalent HPV vaccine, could help prevent infections from other HPV types to which women who have undergone conisation have not yet been exposed. It may also limit the spread of the virus from sites with low malignant potential to the transformation zone [18].

Diagnostic uncertainty due to complex diagnostic pathways (including cytology, HPV testing, and histological findings) may be another limitation in the interpretation of the results (Casajuan-Perez 2022; Henere 2022; Pieralli 2018). Furthermore, there are possible limitations based on variability in protection depending on the range of different types of virus-like particles included in the respective HPV vaccines. For example, only Henere 2022 focused on women who exclusively received the nonavalent vaccine (Gardasil 9), which is designed to provide broader protection. However, this retrospective study was at critical risk of bias (Supplementary material 8), and did not differentiate between incident and persistent infections during the follow-up. However, we identified two ongoing RCTs that are investigating the nonavalent HPV vaccine (Gardasil 9) in women with local conservative treatment for CIN (Supplementary material 5). The results for one of these studies were scheduled to be released in summer 2025 [74].

In addition, one study published in Russian is awaiting classification due to methodological uncertainties and the pending formal translation. The study favours HPV vaccination over no HPV vaccination in women with conisation for the outcome "recurrence of CIN", which generally aligns with our results (Zarochentseva 2021 [75]; Supplementary material 4).

We assessed the certainty of the evidence for prioritised outcomes presented in Summary of findings 1 according to GRADE [54]. We found CIN 2+ (irrespective and respective of HPV 16/18) to be of low-certainty evidence. The certainty of the evidence for persistent HPV infection (irrespective of HPV type) and invasive cervical cancer (irrespective of HPV type) was very low. Downgrading was due to concerns regarding imprecision and risk of bias. Our findings primarily pertain to the quadrivalent and bivalent HPV vaccines, and not the nonavalent HPV vaccine. However, we opted not to downgrade due to the indirect nature of the evidence. The decision not to downgrade was influenced by the continued use of the bivalent HPV vaccine, particularly [72].

The assessment of publication bias proved difficult. There are registered studies that are ongoing. Currently, we do not suspect any publication bias to be present for any of the outcomes.

The NRSI were at serious or critical risk of bias based on the ROBINS-I bias assessment tool. The risk of bias was attributed, at least partially, to the presence of confounders (including unadjusted differences in baseline characteristics between intervention and control groups) or suboptimal selection of participants in the included studies. Specifically, age differences between women who were vaccinated and those who were not vaccinated might affect the risk of recurrence of the disease. In four studies, vaccinated women were younger than those who were not vaccinated, and increased recurrence of disease could partly be a result of older age (Bogani 2020; Ortega-Quiñero 2019; Petrillo 2020; Sand 2020). Not all studies reported adjusted analyses for these differences, and some analyses may not have accounted for all relevant confounders, potentially limiting the comparability of effect estimates across the included studies. The variability in diagnostic methods, length of follow-up, types of HPV vaccines, and the timing of HPV vaccination in relation to surgical treatment among the studies could also have influenced the effect estimate. The length of follow-up was 30 months (based on studies reporting median follow-up time), so we could not assess whether the effect would be sustained in the long term and to what extent the suggested benefits observed in this review can be translated to cervical cancer and mortality.

Limitations of the review processes

To avoid potential bias in the review process, we committed ourselves to conducting this systematic review closely to the guidance provided in the *Cochrane Handbook for Systematic Reviews of Interventions* [39]. In addition, we calculated our findings with fixed- and random-effects meta-analyses. Observed differences in effect estimates between the fixed- and random-effects meta-analyses (e.g. for CIN 2 and CIN 3) may indicate the presence of small-study effects (Supplementary material 11). Although the subgroup analyses according to the type of vaccine showed consistent results, the number of studies included in these subgroups was often low. Data for incident and persistent HPV infection were scarce. Although four of 13 studies reported on HPV infection (Casajuana-Perez 2022; Chen 2023; Ghelardi 2018; Henere 2022), one was not included in our meta-analyses (Henere 2022), because this study did not distinguish between incident and persistent infections. Studies did not report data following the intention-to-treat principle. Further, we could not exclude that we missed unpublished or unregistered studies. However, we conducted forward and backward citation tracking and checked reference lists of included studies and systematic reviews, which should ensure that we included the most important studies. Further, we did not search the World Health Organization International Clinical Trials Registry Platform (ICTRP), which may have resulted in missing registered or unpublished studies. Finally, risk of bias assessment is always subjective to some extent and, therefore, other reviewers might have come to different conclusions. We tried to minimise subjectivity by having pairs of review authors conduct independent assessments and allowing for an in-depth team discussion of the results of the risk of bias judgements.

Agreements and disagreements with other studies or reviews

There are several reviews on HPV vaccination in women with conisation to prevent cervical cancer [15, 29, 30, 31, 32, 33]. Kechagias and colleagues focused on the effects of HPV vaccination

on the risk of HPV infection and recurrent diseases in individuals with local surgical treatment [32]. This review did not incorporate more-recent studies, such as Henere 2022, Casajuana-Perez 2022, and Chen 2023. However, the authors also concluded that HPV vaccination may reduce the risk of recurrence of CIN and their GRADE assessment indicated that "the data were inconclusive". Furthermore, the review stressed that "the effect of HPV vaccination on the risk of HPV infection treated surgically is unclear because of the scarcity of data and the moderate to high overall risk of bias of the available studies".

Lichter and colleagues included six studies in their systematic review and meta-analysis (1 RCT, 5 NRSI) and reported on multiple CIN and non-cervical outcomes [33]. Another systematic review and meta-analysis, published by Jentschke and colleagues, included 10 studies (1 RCT, 9 NRSI) and reported results similar to our review regarding the risk of recurrence of CIN 2+ (the only outcome assessed in the review) [15]. The review assessed risk of bias using the RoB 2 tool, which is the current standard bias tool for RCTs and not specifically tailored to capture biases in NRSI. Di Donato and colleagues included 11 studies [30]. The review assessed risk of bias with the ROBINS-I tool for all studies (including RCTs). They did not perform a GRADE assessment. Bartels and colleagues retrieved data from five studies for their meta-analysis on the risk of recurrence of CIN 2+ [29]. They did not perform a GRADE assessment, and used the Jadad system to assess risk of bias (this system has been used historically, but is no longer recommended by the *Cochrane Handbook for Systematic Reviews of Interventions*) [39, 76]. Eriksen and colleagues concluded that HPV vaccination post-treatment was associated with a significantly reduced risk of CIN 2+ recurrence when using unadjusted estimates from NRSI and RCTs [31]. There was no risk reduction on CIN 2+ recurrence when the review considered only studies with low risk of bias.

Overall, the findings of these reviews are in alignment with our review, indicating that the current evidence for HPV vaccination in women with conisation is mainly based on NRSI, with only two RCTs being available.

AUTHORS' CONCLUSIONS

Implications for practice

Human papillomavirus (HPV) vaccination in comparison to no HPV vaccination in women with conisation may reduce the risk of cervical intraepithelial neoplasia (CIN) 2+ (irrespective of HPV type), CIN 2+ (related to HPV 16/18) (only shown in non-randomised studies of interventions (NRSI)). Effects on CIN 3+ (irrespective of HPV type) varied between studies, with one NRSI suggesting similar effects to CIN 2+ favouring HPV vaccination, while the remaining evidence was very uncertain (based on NRSI). The evidence on HPV vaccination in comparison to no HPV vaccination on CIN 2+ (related to HPV 16/18) (based on evidence from one randomised controlled trial (RCT)), CIN 3+ (related to HPV 16/18), invasive cervical cancer (irrespective of HPV type), persistent HPV infections (irrespective of HPV type), and persistent HPV infection (related to HPV 16/18) was very uncertain (due to very serious concerns in risk of bias and imprecision).

The evidence was inconclusive for CIN 2, VIN 2+/VaIN 2+, and mortality. Effects on CIN 3 varied between studies, with one NRSI suggesting similar effects to CIN 2+ favouring HPV vaccination, while the remaining evidence was inconclusive. Only one RCT

comparing HPV vaccination to no HPV vaccination reported severe allergies (two cases) and minor local reactions to the HPV vaccine.

This review is under a service contract with the European Health and Digital Executive Agency (HaDEA) and aims to support EU Member States in their decision-making on national vaccination programmes. The evidence presented in this review has to be balanced with additional factors, such as values and preferences, resources, equity, acceptability, and feasibility.

Implications for research

Overall, the existing evidence for HPV vaccination in women with conisation is predominantly derived from NRSI with serious or critical risk of bias and low- or very low-certainty evidence. Evidence from RCTs is very limited (i.e. only two RCTs are available). Additional adequately powered RCTs with a placebo intervention in the control group and longer follow-up to reliably evaluate the efficacy and safety of HPV vaccination (particularly the nonavalent vaccine) as an adjuvant to conisation would provide more informative evidence.

As highlighted in this review, there is a lack of data on harms, such as serious adverse events. There is also a need for ongoing efforts to standardise the assessment of safety and efficacy outcomes to ensure better comparability across studies. Additionally, future RCTs should take into account relevant subgroups, such as HPV vaccination status (whether a previous HPV vaccine for primary prevention was received), timing of HPV vaccination related to conisation, and different age groups.

SUPPLEMENTARY MATERIALS

Supplementary materials are available with the online version of this article: [10.1002/14651858.CD016121](https://doi.org/10.1002/14651858.CD016121).

Supplementary material 1 Search strategies

Supplementary material 2 Characteristics of included studies

Supplementary material 3 Characteristics of excluded studies

Supplementary material 4 Characteristics of studies awaiting classification

Supplementary material 5 Characteristics of ongoing studies

Supplementary material 6 Data package

Supplementary material 7 Risk of bias in RCTs (RoB 2)

Supplementary material 8 Risk of bias in NRSI (ROBINS-I)

Supplementary material 9 Overview of effect estimates for reported outcomes

Supplementary material 10 Outcome data at study level

Supplementary material 11 Sensitivity analysis summary table

ADDITIONAL INFORMATION

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Editorial and peer-reviewer contributions

The following people conducted the editorial process for this article.

- Sign-off Editor (final editorial decision): Dr Jo Morrison, Department of Gynaecological Oncology, GRACE Centre, Musgrove Park Hospital, Somerset NHS Foundation Trust, Taunton, UK
- Managing Editors (selected peer reviewers, provided editorial guidance to authors, edited the article): Elizabeth Royle and Liz Bickerdike, Cochrane Central Editorial Service
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments and supported editorial team): Lisa Wydrzynski and Addie-Ann Smyth, Cochrane Central Editorial Service
- Copy Editor (copy editing and production): Anne Lawson, Cochrane Central Production Service
- Peer-reviewers (provided comments and recommended an editorial decision): Esra Bilir, MD, MSc Department of Obstetrics and Gynecology, University Hospitals Schleswig-Holstein, Campus Kiel, Kiel, Germany; Department of Gynecologic Oncology, Koç University School of Medicine, Istanbul, Turkey; Department of Global Health, Koç University Graduate School of Health Sciences, Istanbul, Turkey (clinical/content review); Yoon K Loke, University of East Anglia (consumer review); Jo-Ana Chase, Quality Assurance Editor, Cochrane Central Editorial Service (methods review); Ina Monsef, Cochrane Evidence Synthesis Unit (ESU) Germany, Institute of Public Health, Faculty of Medicine and University Hospital Cologne, University of Cologne, Germany (search review). One additional peer reviewer provided statistical peer review but chose not to be publicly acknowledged.

Contributions of authors

PK: title and abstract and full-text screening, risk of bias assessment, GRADE assessment, statistical analysis, drafting the review, final approval of the version to be published

CS: conception and methodology, conducting the title and abstract and full-text screening, data extraction, risk of bias assessment, GRADE assessment, drafting the review, final approval of the version to be published

WS: statistical analysis, feedback on review findings and review draft, final approval of the version to be published

TB: title and abstract and full-text screening, data extraction, final approval of the version to be published

LG: screening of additional records, risk of bias assessment, feedback on review findings and review draft, final approval of the version to be published

MRM: clinical expertise, feedback on review findings and review draft, final approval of the version to be published

KG: conception of the search strategy, feedback on review findings and review draft, final approval of the version to be published

ET: title and abstract and full-text screening, data extraction, final approval of the version to be published

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Registration and protocol

Registration: PROSPERO, CRD42023428998.

Data, code and other materials

As part of the published Cochrane review, the following information is made available: search strategy for each database ([Supplementary material 1](#)); characteristics of included studies ([Supplementary material 2](#)); reasons for excluded references at full-text screening ([Supplementary material 3](#)); references and reasons of studies awaiting classification ([Supplementary material](#)

[4](#)); characteristics of ongoing studies ([Supplementary material 5](#)); references of studies included, excluded at full-text screening, awaiting classification, and additional references ([Supplementary material 6](#)); overview of effect estimates for reported outcomes ([Supplementary material 9](#)); risk of bias in randomised controlled trials (RoB 2) ([Supplementary material 7](#)); risk of bias in non-randomised studies of interventions (ROBINS-I) ([Supplementary material 8](#)); and outcome data at study level ([Supplementary material 10](#)).

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ADDITIONAL TABLES

Table 1. Overview of included studies and synthesis table illustrating key study characteristics, ordering studies based on study type

Study characteristics				Participant characteristics		Intervention				Control
Author, year	Country	Follow-up time (months after conisation)	Number total (I/C)	Age, median (range), mean ± SD	Conisation diagnosis or indication for conisation	Conisation procedure	Time of 1st dose	Number of doses	Type of vaccine	
RCTs										
Kari-mi-Zarchi 2020	Iran	24 months ^a	242 (138/104)	32.6 (SD 4.9) years	Diagnosis at conisation or indication for conisation (unclear): CIN 1 (I/C): 45 (32.6%) vs 35 (33.7%) CIN 2 (I/C): 50 (36.2%) vs 35 (33.7%) CIN 3(I/C): 43 (31.2%) vs 34 (32.6%)	LEEP, CKC (no other details)	At conisation (2nd and 3rd dose ≤ 6 months)	3 doses: 75% 2 doses: 25.4% 1 dose: 0%	Quadrivalent (100%)	No intervention
Pieralli 2018	Italy	36 months ^a	178 (89/89)	32 (range 23–44) years	Diagnosis based on conisation or indication for conisation (unclear): LSIL: 30 (16.9%) and HSIL: 148 (83.1%) (overall)	Conisation (no other details)	After conisation 3 months	3 doses (no other details)	Quadrivalent (100%)	No intervention
NRSI: prospective design										
Chen 2023	China	30 months (median)	423 (148/273)	20–45 years	Diagnosis at conisation: CIN 2 (I/C): 20 (13.5%)/42 (15.38%) CIN 3 (I/C): 128 (86.5%)/231 (84.6%)	LEEP (100%)	After conisation (no other details)	3 doses planned (no other details)	Quadrivalent (100%)	No intervention
Ghelardi 2018	Italy	≥ 24; 36 months (median)	344 (172/172)	18–45 years	Diagnosis at conisation: CIN 2 (I/C): 6 (3.5%)/3 (1.7%)	LEEP (100%)	After conisation ≤ 1 month	3 doses planned (no other details)	Quadrivalent (100%)	No intervention

Table 1. Overview of included studies and synthesis table illustrating key study characteristics, ordering studies based on study type (Continued)

						CIN 3 (I/C): 163 (94.8%)/167 (97.1%)				
						CC (I/C): 3 (1.7%)/2 (1.2%)				
Sand 2020	Denmark	≥ 12 months ^b	17,128 (2074/15,054)	I: 28 (range 17–51) years C: 32 (range 17–51) years	Diagnosis at conisation: CIN 2+ (I/C): 1508 (73%)/10,895 (72%)	Conisation (no other details)	Before (3 months) or after (≤ 12 months) conisation	NR	NR	No intervention
NRSI: retrospective design										
Bogani 2020	Italy (multicentre)	> 60 months	300 (100/200)	33.4 (range 24–44) years	Diagnosis at conisation: CIN 2 (I/C): 54 (54%)/106 (53%) CIN 3(I/C): 46 (46%)/94 (47%)	LEEP (100%)	After conisation ≤ 6 months	3 doses: 68% 2 doses: 18% NR: 14%	Quadrivalent (93%), bivalent (7%)	No intervention
Casajua-na-Perez 2022 (VENUS study)	Spain	32.9 months (median)	563 (277/286)	36.9 (SD 8.2) years	Diagnosis at conisation or indication for conisation (unclear): LSIN/CIN 1 (I/C): 17 (6%)/16 (5.8%) HSIL/CIN 2-3 (I/C): 266 (94%)/261 (94.2%)	LEEP (100%)	Before or after conisation (no other details)	3 doses: 92.0% 2 doses: 5.8% 1 dose: 2.2%	Quadrivalent, bivalent (no other details)	No intervention
Gomez de la Rosa 2021	Spain	≥ 48 months	331 (160/171)	37.5 (SD 7.9) years	Diagnosis at conisation: CIN 2 (I/C): 89 (55.6%)/79 (44.4%) CIN 3 (I/C): 71 (44.4%)/76 (55.6%)	LEEP (100%)	After conisation ≤ 6 months	NR	Quadrivalent, bivalent (no other details)	No intervention
Del Pino 2020 ^c	Spain	21.7 months (median)	265 (153/112)	39.8 (SD 10.3) years	Diagnosis at conisation: Normal (I/C): 12 (7.8%)/14 (12.5%)	LEEP (100%)	After conisation ≤ 6 months	3 doses: 77.1% 2 doses: 10.5%	Quadrivalent (4%), bivalent (20%), nonava-	No intervention

Table 1. Overview of included studies and synthesis table illustrating key study characteristics, ordering studies based on study type (Continued)

					LSIL/CIN 1 (I/C): 17 (11.1%)/13 (11.6%)			1 dose: 4.6%	lent (64%), NR (12%)	
					HSIL/CIN 2-3 (I/C): 124 (81.1%)/85 (75.9%)			NR: 7.8%		
Henere 2022	Spain	20.2 months (mean)	398 (306/92)	40.8 (SD 10.3) years	Diagnosis at conisation: Normal (I/C): 27 (8.8%)/14 (15.2%) HSIL (I/C): 257 (84%)/ 60 (65.2%) LSIL (I/C): 22 (7.2%)/18 (19.6%)	LEEP/LLETZ (100%)	Before (4 months) or after (5 months) conisation	3 doses: 91.8% 2 doses: 6.2% 1 dose: 2.0%	Non-avalent (100%)	No intervention
Kang 2013	South Korea	> 24; 42 months (median)	737 (360/377)	36.7 (SD 5.8)	Diagnosis at conisation: CIN 2 (I/C): 54 (15%)/71 (19%) CIN 3 (I/C): 306 (85%)/306 (81%)	LEEP (100%)	After conisation ≤ 6 months	3 doses: 100%	Quadri-valent (100%)	No intervention
Ortega-Quiñero 2019	Spain	14.2 months (median)	242 (103/139)	I: 33 (range 28–38) years C: 39 (31–50) years	Diagnosis at conisation: CIN 2 (I/C): 51 (49.5%)/55 (39.6%) CIN 3 (I/C): 52 (50.5%)/84 (60.4%)	LEEP (100%)	Before (1 month) or after (1 month) conisation	3 doses planned (no other details)	Quadri-valent (32%), bivalent (68%),	No intervention
Petrillo 2020	Italy	≥ 24 months	302 (182/103)	I: 38 (range 30–44) years C: 41 (range 36–49) years	Diagnosis at conisation: Normal (I/C): 1 (0.6%)/1 (0.9%) CIN 1 (I/C): 3 (1.8%)/2 (1.7%) CIN 2 (I/C): 96 (53.0%)/57 (50.9%) CIN 3 (I/C): ^d 72 (39.8%)/45 (40.2%) CIS (I/C): ^d 9 (5.0%)/7 (6.3%)	LEEP (100%)	After conisation ≤ 1 month	NR	Quadri-valent (98%), bivalent (2%)	No intervention

C: control group (no HPV vaccine); CC: cervical cancer; CIN: cervical intraepithelial neoplasia; CIS: carcinoma in situ; CKC: cold-knife conisation; HSIL: high-grade squamous intraepithelial lesions (cytological diagnosis); HPV: human papillomavirus; I: intervention group (HPV vaccine); LEEP: loop electrosurgical excision procedure; LLETZ: large loop excision of the transformation zone; LSIL: low-grade squamous intraepithelial lesion; NR: not reported; NRSI: non-randomised studies of interventions; RCT: randomised controlled trial.

^a Unclear if mean or median.

^b First follow-up 12 months after conisation until diagnosis of CIN 2+, second conisation, death, emigration or end of follow-up (30 June 2016), whichever came first.

^c This study is retrospective in design (while labelled as prospective in the publication) by the authors (Del Pino 2020).

^d The authors reported CIN 3 and CIS separately.

INDEX TERMS**Medical Subject Headings (MeSH)**

*Conization; Human Papillomavirus Viruses; *Papillomavirus Infections [prevention & control]; *Papillomavirus Vaccines [administration & dosage]; Randomized Controlled Trials as Topic; *Uterine Cervical Dysplasia [prevention & control] [surgery] [virology]; *Uterine Cervical Neoplasms [prevention & control] [virology]

MeSH check words

Adult; Female; Humans