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TECHNICAL REPORT

Efficacy, effectiveness and safety of HPV vaccination in women with conisation: a systematic review and meta-analyses

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Abbreviations

2v	Bivalent
9v	Nonavalent
4v	Quadrivalent
AIS	Adenocarcinoma in situ
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
CIS	Carcinoma in situ
CKC	Cold knife conisation
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HPV	Human papillomavirus
HSIL	High-grade squamous intraepithelial lesion
ITT	Intention-to-treat
IRR	Incidence rate ratio
LEEP	Loop electrosurgical excision procedure
LLETZ	Large loop excision of the transformation zone
LSIL	Low-grade squamous intraepithelial lesion
NETZ	Needle excision of the transformation zone
NITAG	National Immunisation Technical Advisory Group
NRSI	Non-randomised studies of the effects of interventions
OR	Odds ratio
PRESS	Peer review of electronic search strategies
RCT	Randomised controlled trial
RD	Risk difference
RoB	Risk of Bias
ROBINS-I	Risk Of Bias In Non-randomised Studies of Interventions
RR	Risk ratio
SWETZ	Straight wire excision of the transformation zone
VaIN	Vaginal intraepithelial neoplasia
VE	Vaccine efficacy (RCT) or effectiveness (NRSI)
VIN	Vulvar intraepithelial neoplasia
WHO	World Health Organization

Executive summary

Cervical cancer is the fourth most common cancer affecting women worldwide. It is caused by persistent infection with oncogenic 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. HPV 16 and 18 are the two primary oncogenic types and are responsible for 71% of cervical cancers, and HPV 31, 33, 45, 52 and 58 together account for 18% of cervical cancers.

While HPV infections are common and usually resolve without any consequences, persistent infections with high-risk HPV 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 (mild dysplasia referring to low-grade squamous intraepithelial lesion [LSIL]), CIN 2 (moderate dysplasia referring to high-grade squamous intraepithelial lesion [HSIL]), and CIN 3 (severe dysplasia referring to HSIL, carcinoma in situ [CIS]). CIN 3+ includes CIN3 (CIS) and is, along with adenocarcinoma in situ (AIS), well-accepted as the pathological state that immediately precedes invasive cervical cancer.

HPV vaccination is an important measure to prevent cancer. In Europe, three HPV vaccines bivalent (Cervarix), quadrivalent (Gardasil 4) and nonavalent (Gardasil 9) are approved for use. All three vaccines target the high-risk oncogenic HPV types 16 and 18, and the nonavalent vaccine (Gardasil 9) also targets the five additional (oncogenic) HPV types 31, 33, 45, 52 and 58.

Women diagnosed with CIN 2+ typically undergo cervical conisation (a surgical procedure) to remove precancerous cervical lesions to prevent disease progression. The administration of the HPV vaccine in women who have undergone conisation is grounded in the rationale of preventing reactivation or reinfections by the same HPV type, while also offering protection against new infections by other vaccine-targeted types.

The objective of this review was to investigate the efficacy, effectiveness and safety of HPV vaccination in women undergoing conisation compared with those not receiving a HPV vaccination. HPV vaccination related to conisation was defined for the purposes of this study as HPV vaccine given shortly (i.e. four months or less) before, at or after conisation (as 'adjuvant' intervention to conisation, secondary prevention). We conducted meta-analyses separately for randomised controlled trial (RCTs) and non-randomised studies of the effects of interventions (NRSI).

The review found that the use of HPV vaccines in comparison to not using them in women with conisation may reduce the risk of CIN 2+ and CIN3+ (both irrespective of HPV type) and CIN 2+ (related to HPV 16/18). However, confidence in the effect estimates is limited. The evidence on the effect of HPV vaccination in comparison to no vaccination on CIN3+ (related to HPV 16/18), invasive cervical cancer, persistent HPV infections (irrespective of HPV type) and persistent HPV infection (related to HPV 16/18) was very uncertain.

The evidence for the effect of HPV vaccine in women with conisation was inconclusive for the outcomes CIN 2, CIN 3, VIN 2+ and VaIN 2+ and mortality. There were no data available for incident HPV infections (irrespective of HPV type and related to HPV 16/18), AIS and quality of life. One RCT comparing vaccinated women with women who did not receive a vaccine reported severe allergies (two cases) and minor local reactions to the HPV vaccine. Subgroup analyses according to type of vaccine were only possible for CIN 2+ (irrespective of HPV type and related to HPV 16/18). No differences were identified.

Overall, the existing evidence related to the HPV vaccine in women with conisation is predominantly derived from NRSI with serious or critical risk of bias. Evidence from RCTs is very limited, i.e. only two RCTs are available. Further additional RCTs with a placebo intervention in the control group to evaluate the efficacy of HPV vaccines (particularly the nonavalent vaccine) as an adjuvant to conisation would provide more robust evidence. These RCTs should additionally consider the HPV vaccination status of the women concerned (in terms of primary prevention). Moreover, it would be crucial to extend follow-up times to the generation of robust data on the incidence of cervical cancer and cancer-related mortality.

Summary of findings

Table 1. Summary of findings

Outcome No. of participants (studies)	Relative effect (95%-CI)	Anticipated absolute effects§			Certainty	Assessment
		Without HPV vaccine	With HPV vaccine	Risk difference		
Outcome: CIN 2+ (irrespective of HPV type)						
2 RCTs (420)	VE: 59.5% (37.1–73.9) Effect ratio: 0.41 (0.26–0.63)	23.3%	9.6%	138 fewer per 1 000 (from 173 fewer to 86 fewer)	⊕⊕◯◯ Low[a]	The evidence from RCTs is of low certainty, but shows that the HPV vaccine may largely reduce the risk of CIN 2+
11 NRSI (21014)	VE: 65.6% (48.7–76.9) Effect ratio: 0.34 (0.23–0.51)	5.6%	1.9%	37 fewer per 1 000 (from 43 fewer to 28 fewer)	⊕⊕◯◯ Low[b]	The evidence from NRSI is of low certainty, but shows that the HPV vaccine may reduce the risk of CIN 2+
Outcome: CIN 2+ (HPV 16/18)						
1 RCT (178)	VE: 89% (-103.0–99.0) Effect ratio: 0.11 (0.01–2.03)	4.5%	0.5%	40 fewer per 1 000 (from 44 fewer to 46 more)	⊕◯◯◯ Very low[c,d]	The evidence from one RCT is of very low certainty about the effect of the HPV vaccine on CIN 2+ (HPV 16/18)
7 NRSI (2970)	VE: 67.9% (30.9–85.1) Effect ratio: 0.32 (0.15–0.69	5.0%	1.6%	34 fewer per 1 000 (from 42 fewer to 15 fewer)	⊕⊕◯◯ Low[b]	The evidence from NRSI is of low certainty, but shows that the HPV vaccine may reduce the risk of CIN 2+ (HPV 16/18)
Outcome: CIN 3+ (irrespective of HPV type)						
2 NRSI (629)	VE: 80.5% (55.5–91.4) Effect ratio: 0.20 (0.09–0.45)	5.1%	1.0%	41 fewer per 1 000 (from 46 fewer to 28 fewer)	⊕⊕◯◯ Low[b]	The evidence from NRSI is of low certainty but shows that the HPV vaccine may reduce the risk of CIN 3+.
Outcome: CIN 3+ (HPV 16/18)						
1 NRSI (344)	VE: 91% (-63.0–99.0) Effect ratio: 0.08 (0.01–1.63)	2.9%	0.2%	27 fewer per 1 000 (from 29 fewer to 18 more)	⊕◯◯◯ Very low[b,d]	The evidence from NRSI is of very low certainty about the effect of the HPV vaccine on persistent HPV infection (HPV 16/18)
Outcome: Invasive cervical cancer						
1 RCT (242)	VE: 75% (-511.0–99.0) Effect ratio: 0.25 (0.01–6.11)	1.0%	0.2%	7 fewer per 1 000 (from 10 fewer to 49 more)	⊕◯◯◯ Very low[a,d]	The evidence from one RCT is of very low certainty about the effect of the HPV vaccine on invasive cervical cancer
1 NRSI (17128)	VE: 15% (-269.0–80.0) Effect ratio: 0.85 (0.20–3.69)	0.1%	0.1%	0 fewer per 1 000 (from 1 fewer to 3 more)	⊕◯◯◯ Very low[b,e]	The evidence from NRSI is of very low certainty about the effect of the HPV vaccine on invasive cervical cancer
Persistent HPV infection (irrespective of HPV type)*						
2 NRSI (765)	VE: 32.9% (-4.8–57.0) Effect ratio: 0.67 (0.43–1.05)	16.9%	11.3%	56 fewer per 1 000 (from 96 fewer to 8 more)	⊕◯◯◯ Very low[b,d]	The evidence from NRSI is of very low certainty about the effect of the HPV vaccine on persistent HPV infection
Persistent HPV infection (HPV 16/18)*						
2 NRSI (907)	VE: 2.3% (-45.6–34.5) Effect ratio: 0.98 (0.66–1.46)	8.1%	7.6%	2 fewer per 1 000 (from 33 fewer to 45 more)	⊕◯◯◯ Very low[b,d]	The evidence from NRSI is of very low certainty about the effect of the HPV vaccine on persistent HPV infection (HPV 16/18)

Grades of evidence after the Grading of Recommendations, Assessment, Development and Evaluation (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.
Explanations of the certainty of evidence:
a. Risk of bias downgraded by two levels (RCTs): major concerns regarding the randomisation, deviations from intended interventions, missing outcome data, and selection of the reported results.
b. Risk of bias downgraded by two levels (NRSI): major concerns regarding confounding, selection of participants into the study, classification of the interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported results.
c. Risk of bias downgraded by one level (RCT): concerns regarding randomisation, deviations from intended interventions, missing outcome data, and selection of the reported results.
d. Imprecision downgraded by two levels: 95%-CI indicates the possibility of considerably fewer or more events.
e. Imprecision downgraded by one level: 95%-CI is consistent with the possibility of fewer or more events.
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, effects single studies are consistent in direction. Therefore, inconsistency was not downgraded.

CIN: Cervical Intraepithelial Neoplasia, CI: Confidence Interval, HPV: (High-Risk) Human Papillomavirus (diagnosed by HPV testing), NRSI: Non-randomised studies of the effects of interventions, RCT: Randomised controlled trial, VE: Vaccine Efficacy (RCT) or Effectiveness (NRSI)

§Differences in the estimated magnitude of the treatment effect between RCTs and NRSI are common taking into account that RCTs evaluate the efficacy of a intervention under ideal conditions and NRSI are often used to measure the effectiveness of an intervention in 'real world' scenarios. Moreover, factors other than study design per se may contribute to different results of RCTs and NRSI (1-3).

**No evidence from RCTs available.*

1. Background

Little is known about the degree and duration of naturally acquired immunity after the first infection with HPV [13, 14]. Although infections with one HPV type may provide some natural protection against that particular HPV type, they most likely do not provide protection against other HPV types [15]. The serological response after HPV vaccination is stronger than the response after natural infection, providing people with long-term direct protection against vaccine-targeted HPV types [6].

Women diagnosed with CIN 2+ typically undergo cervical conisation to remove precancerous cervical lesions to prevent disease progression [16]. 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 as well as on the surgical method. Excisional methods include cold knife conisation, laser conisation, electrosurgical loop procedures (loop electrosurgical excision procedures [LEEP] or large loop excision of the transformation zone [LLETZ]) and needle or straight wire excision of the transformation zone (NETZ and SWETZ, respectively) [16, 17]. Although eliminating high-risk HPV is not the treatment goal of conisation, many such women have achieved elimination of infection [18]. While the effectiveness of conisation has been demonstrated, the risk of recurrence of precancerous cervical lesions after five years is 6% (CIN 3+) and 16.5% (CIN 2+) respectively (19). Furthermore, women receiving conisation show a higher risk than the general population of developing invasive cervical cancer in the long-term after treatment (20).

Although HPV vaccines have been shown to protect against new infections and reinfections from vaccine-targeted HPV types in HPV-naïve individuals, it is unclear whether the vaccines offer protection when given to women undergoing conisation to treat precancerous lesions.

2. Objectives

This systematic review and meta-analysis aims to investigate the efficacy, effectiveness and safety of HPV vaccination in women with conisation compared with not vaccinating this group. . This review is registered in the international Prospective Register of Systematic Reviews (PROSPERO, https://www.crd.york.ac.uk/prospero/, CRD42023428998).

3. Review methods

3.1 Types of studies

To assess the efficacy, effectiveness and safety of HPV vaccination in women with conisation, we included RCTs, as this study design, if performed appropriately, provides the best evidence for clinical questions.

We also included NRSI defined as (i) studies in which participants (individuals or clusters of individuals) are allocated to different groups (intervention and control group) using methods that are not random and (ii) observational studies, i.e. prospective and retrospective cohort studies with a control group and case control studies. In observational studies the allocation to a group is determined by factors outside the investigator's control which can bias the selections of participants into the study.

We excluded single-arm studies (such as case reports and case series), review articles, laboratory and animal studies, pharmacokinetic studies and in-vitro studies.

We included the following formats, if sufficient information was available on study design, characteristics of participants, interventions, and outcomes: (i) full-text journal publications, (ii) preprint articles and (iii) results published in trial registries.

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 to the length of follow-up.

3.2 Types of participants

We included studies investigating female participants of any age who receive conisation (excisional surgery) due to precancerous cervical lesions with the following procedures: (i) loop electrosurgical excision procedure / large loop excision of the transformation zone, (ii) needle excision of the transformation zone / straight wire excision of the transformation zone, (iii) cold knife conisation and (iv) laser conisation.

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

3.3 Types of interventions

We included (i) nonavalent HPV vaccine (Gardasil 9, 9vHPV), (ii) quadrivalent HPV vaccine (Gardasil, 4vHPV) and (iii) bivalent HPV vaccine (Cervarix, 2vHPV). Eligible vaccines had to be approved or expected to be approved in EU or EU countries (for primary prevention). HPV vaccination related to conisation was defined for the purposes of this study as HPV vaccine given shortly (i.e. four months or less) before, at or after conisation (as "adjuvant" intervention to conisation, secondary prevention).

Studies where the HPV vaccine was administered for the primary prevention of cervical cancer in the general population were not included in the main analyses. This decision was made to avoid potential misinterpretation between primary prevention in the general population and the prevention of disease recurrence in women who underwent conisation. However, these studies, specifically four post-hoc analyses, are presented in Annex J to offer a comprehensive overview within this clinical field of research. We compared the eligible HPV vaccine with (i) no vaccination or (ii) placebo vaccination (containing no active agent, the adjuvant of the HPV vaccine, or another non-HPV vaccine).

3.4 Types of outcome measures

We evaluated a wide range of primary and secondary outcomes. Moreover, prioritised primary outcomes were used to inform the Summary of Findings Table (Table 1) according to the GRADE approach.

3.4.1 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 was clinically reasonable.

3.4.2 Primary outcome measures

Efficacy and effectiveness outcomes

We assessed the following primary efficacy and effectiveness outcomes:

- Incident of histologically-confirmed precancerous cervical lesions (as defined by the WHO [6]) after conisation:
  - CIN 2 (irrespective of HPV type)
  - CIN 2+ (irrespective of HPV type) (prioritised outcome)
  - CIN 2+ (related to HPV 16/18) (prioritised outcome)
  - CIN 3 (irrespective of HPV type)
  - CIN 3+ (irrespective of HPV type) (prioritised outcome)
  - CIN 3+ (related to HPV 16/18) (prioritised outcome)
  - Adenocarcinoma in situ (AIS).
- Incident of invasive cervical cancer (with or without HPV 16/18) (prioritised outcome)
- Persistent HPV infection[i](irrespective of HPV type) (prioritised outcome)
- Persistent HPV infection (related to HPV 16/18) (prioritised outcome)
- Incident HPV infection[ii] (related to HPV 16/18) (prioritised outcome)
- Incident HPV infection (irrespective of HPV type) (prioritised outcome).

[i] Persistent HPV infection defined as the presence of type-specific HPV DNA on repeated clinical biological samples over a period of at least six months (starting at baseline, i.e. time of conisation).

[ii] Detection of a new HPV infection (defined as the presence of type-specific HPV DNA) at six month or later (≥ 6 months) after conisation.

3.4.3 Secondary outcome measures

Efficacy and effectiveness outcomes

- Mortality (all-cause and cancer-related)
- Incident 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 (i) local reactions (e.g. swelling, redness, pain/tenderness); (ii) systemic reactions (e.g. fever, fatigue) and (iii) any other reported harm related to the vaccine.

3.5 Search methods for identification of studies

3.5.1 Literature searches

An information specialist conducted comprehensive systematic literature searches for relevant studies. The complete electronic search strategies were peer-reviewed by a second information specialist following the recommendation of PRESS (Peer Review of Electronic Search Strategies [21]) and validated by checking whether the strategy identifies studies already known.

We did not use any date or language restrictions in the electronic searches. For each database, the search interface used, date of search, search strategy as well as number of search results were documented.

Search strategies for the databases mentioned below were adapted from the Medline strategy and are presented in Annex A.

3.5.2 Searches for published studies

Searches for published studies were conducted in the following electronic data sources on the 25 and 26 of May 2023:

- Medline (ALL) (via Ovid)
- Cochrane Central Register of Controlled Trials (CENTRAL) (via Cochrane Library/Wiley)
- Embase (via Ovid)
- Web of Science Science/ Citation Index Expanded, BIOSIS Citation Index (via Clarivate).

3.5.3 Searches for unpublished and ongoing studies

Searches for ongoing studies or unpublished completed studies were performed in ClinicalTrials.gov [www.clinicaltrials.gov].

3.5.4 Supplementary searches

We used relevant studies and/or systematic reviews to search for additional references via the Pubmed similar articles function[iii] and forward and backward citation tracking. Reference lists of relevant studies and systematic reviews were reviewed and experts in the field were contacted to enquire about any further relevant studies or unpublished data that may not have been retrieved by the electronic searches. Further, a search in sources including websites of regulatory agencies (European Medicines Agency and Food and Drug Administration) was conducted.

3.6 Data collection and analysis

3.6.1 Study selection and management

Titles and abstracts of the citations identified by the searches were independently screened by two reviewers (title and abstract screening and full texts of all potentially relevant articles were obtained. Full texts were also independently checked for eligibility by two reviewers and reasons for exclusions were documented (full text screening). Any disagreements were resolved by consensus, moderated by a third reviewer, if necessary.

[iii] https://www.nlm.nih.gov/bsd/disted/pubmedtutorial/020_190.html

The 'title and abstract screening' were piloted on a random subset of 50 search results. The 'full text screening' were piloted on five included studies. The complete screening process was conducted in Covidence (https://www.covidence.org/home).

3.6.2 Data extraction

Two review authors extracted data independently, using a customised data extraction form. We solved 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
- Participants characteristics: Age, type of precancerous lesion, whether HPV vaccination was received before the development of the disease (i.e. received for primary prevention in the past and not related to conisation), number of pregnancies/births
- Intervention: Type of vaccine, number of doses, timing of first vaccination related to conisation
- 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 under 3.1.4, number and reasons for participants not available for outcome measurements (non-attendees).

3.6.3 Assessment of risk of bias in included studies

The risk of bias of each individual study was assessed on outcome level by two reviewers and is presented in the 'risk of bias' tables. Any disagreements were resolved by consensus, moderated by a third reviewer, if necessary.

Bias in a RCT was evaluated according to the revised Cochrane risk of bias tool for randomised trials (RoB 2) considering the following domains: (i) bias arising from the randomisation process; (ii) bias due to deviations from intended interventions; (iii) bias due to missing outcome data; (iv) bias in measurement of the outcome; and (v) bias in selection of the reported result. These domains were judged with 'low risk of bias' or 'some concerns' or 'high risk of bias' (22, 23).

Bias in a NRSI was evaluated according to the 'Risk of Bias in Non-randomised Studies of Interventions' tool (ROBINS-I) considering the following domains: (i) bias due to confounding (e.g. age, screening history, socioeconomic differences); (ii) bias in selection of participants into the study (e.g. inception bias); (iii) bias in measurement of the intervention; (iv) bias due to deviations from intended intervention; (v) bias due to missing data; (vi) bias in measurement of outcomes; (vii) bias in selection of the reported result; and (viii) overall bias (24). Domains were judged as 'low' or 'moderate' or 'serious' or 'critical' risk of bias. All studies - regardless the risk of bias judgement - were included in the meta-analyses.

3.6.4 Unit of analysis

The unit of analysis was the individual study participant.

3.6.5 Dealing with missing data

Data were analysed, if possible, on an intention-to-treat (ITT) basis or according to recently developed recommendations for systematic reviewers for addressing missing data in clinical studies [25].

3.6.6 Assessment of reporting biases

A funnel plot and appropriate statistical tests (i.e. Egger's test) for small study effects was planned if ≥ 10 studies were available addressing the same outcome [26]. Furthermore, we minimised the impact of publication bias by ensuring a comprehensive search for eligible studies including searches in the trial registry.

3.6.7 Measures of treatment effect

Vaccine effect estimates (in terms of efficacy or effectiveness) were expressed in percentage and calculated as follows: vaccine efficacy or effectiveness (VE) = (1 – vaccine effect ratio) × 100. Thereby, we used the vaccine effect ratio as reported in the primary study including odds ratio (OR), risk ratio (RR), hazard ratio (HR), or incidence rate ratio (IRR). The precision of the vaccine effect estimate (in terms of efficacy or effectiveness) were summarised with the corresponding 95% confidence interval (CI). Vaccine effect estimates greater than 0% suggest a protective effect of the vaccine.

Where adjusted data were available in NRSI:, these data were used; where adjusted data were not available, we extracted the unadjusted data as reported in the study. In RCT, we used unadjusted data.

3.6.8 Assessment of heterogeneity

Different types of heterogeneity (owing to different clinical characteristics, methodological diversity or small study effects) were evaluated and statistically quantified based on I^2 and the statistical test chi square [25]. The following thresholds were used to interpret an I^2:

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

Additionally, we also 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 [27].

Sensitivity analyses and subgroup analyses were pre-defined in the protocol for primary outcomes, irrespective of the measured statistical heterogeneity.

3.6.9 Data synthesis

We conducted meta-analyses separately for RCTs and NRSI. Dichotomous outcomes of vaccine effect estimates and continuous outcomes were pooled by applying the inverse variance method. The Hartung-Knapp adjustment was used for random-effects meta-analyses with three or more studies [28, 29] 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) [30]. Meta-analyses were conducted using both the random-effects and fixed-effect model. The results of this systematic review are based on the effect estimates calculated with the random-effects model.

To estimate the between-study variance, we used the restricted maximum likelihood method [31]. Meta-analyses were conducted with the statistical software *R* (version 4.2.2) using the package meta [32, 33]. A narrative description synthesised the direction and size of any observed effects in the absence of a meta-analysis.

3.6.10 Subgroup analysis

We planned subgroup analyses for primary 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
- Other relevant characteristics if enough data are available: e.g. socioeconomic status, ethnicity, number of pregnancies/births, number of sexual partners, comorbidities.

Characteristics of the intervention

- Type of HPV vaccine: nonavalent HPV vaccine (Gardasil 9, 9vHPV), quadrivalent HPV vaccine (Gardasil, 4vHPV), bivalent HPV vaccine (Cervarix, 2vHPV)
- Timing related to treatment: before conisation, at conisation, six months or less (≤ 6 months) after conisation, between seven and 12 months after conisation
- Number of doses: one dose, two doses, three doses (independent of time between doses), three doses (administered at baseline (0), one and six months)
- Ascertainment of vaccination status (e.g. self-reported, medical record) in NRSI.

Characteristics of the setting

- Geographic location (e.g. low-middle income and high-income countries).

Length of follow-up time

- < 12 months and ≥ 12 months.

3.6.11 Sensitivity analysis

Where possible, the following sensitivity analyses were considered (for primary 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).

3.7 Summary of findings and certainty of the evidence assessment

We used the GRADEpro Guideline Development Tool to create a summary of findings table. According to Chapter 14 of the Cochrane Handbook for Systematic Reviews of Interventions, the 'most critical and/or important health outcomes, both desirable and undesirable,' should be included in the summary of findings table [34, 35]. We included the following outcomes prospectively prioritised by the experts of the HPV Working Group:

- 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)
- Persistent HPV infection (irrespective of HPV type)
- Persistent HPV infection (related to HPV 16/18)
- Incident HPV infection (irrespective of HPV typ)
- Incident HPV infection (related to HPV 16/18)
- Invasive cervical cancer.

3.7.1 Assessment of certainty in the evidence

We used the GRADE approach to assess the certainty in 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 (- 1) or very serious (- 2) risk of bias
- Serious (- 1) or very serious (- 2) inconsistency
- Serious (- 1) or very serious (- 2) uncertainty about directness
- Serious (- 1) or very serious (- 2) imprecise or sparse data
- Serious (- 1) or very serious (- 2) probability of reporting bias.

The GRADE system used the following criteria for assigning grade 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 the Cochrane Handbook for Systematic Reviews of Interventions, Chapter 14 [34]. We used the overall risk of bias judgement to inform our decision on downgrading for risk of bias., We also started with a high certainty of evidence in accordance with the GRADE guidelines for NRSI assessed with ROBINS-I [36]. The results per outcome are presented in a Summary of Findings Table as suggested by the GRADE Working Group. We phrased the findings and certainty in the evidence as suggested in the informative statement guidance [37]. The GRADE assessments were conducted independently by two reviewers. Any disagreements were resolved by discussion and consensus involving a third person, if needed.

4. Review results

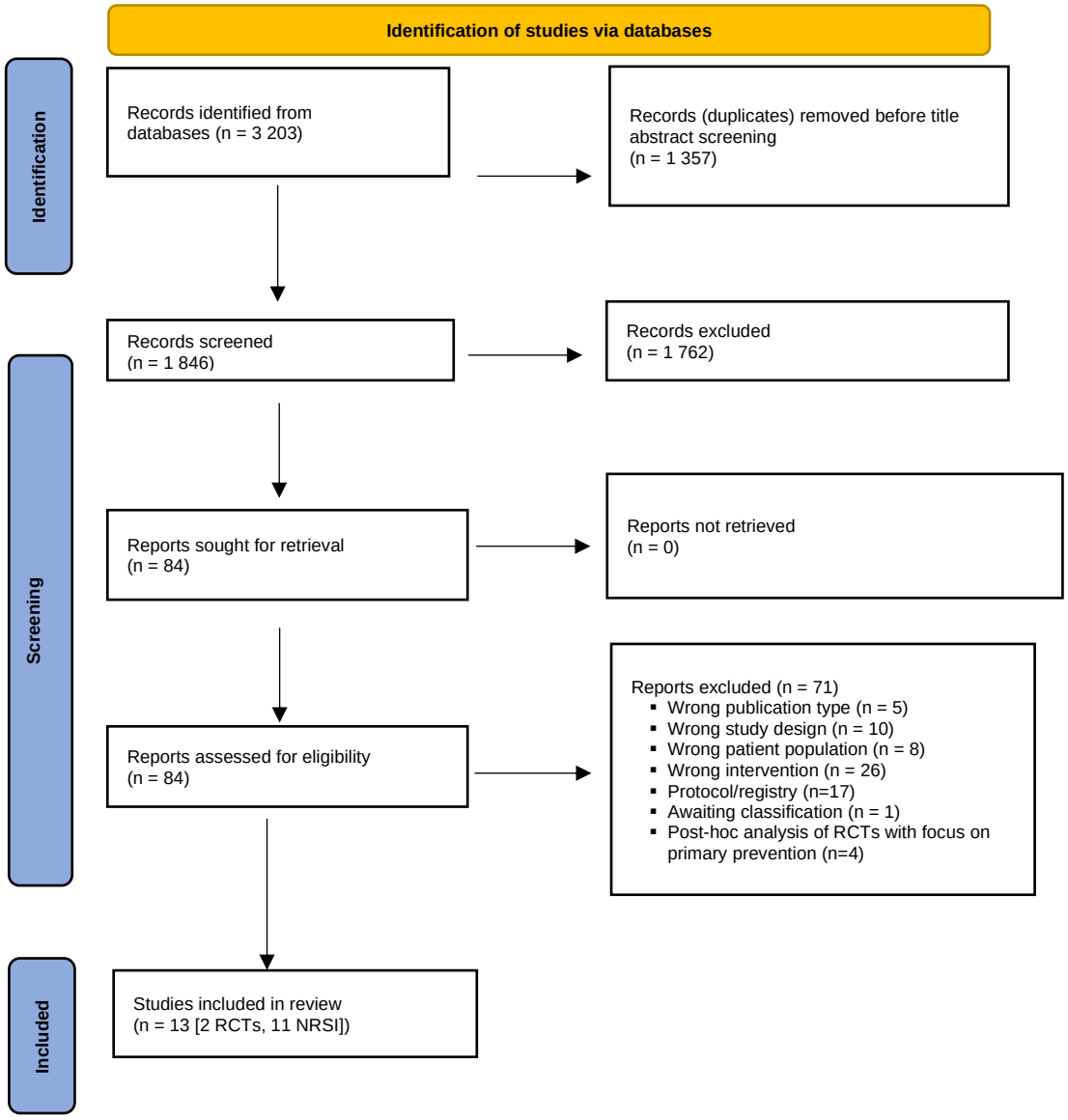
4.1 Description of studies

4.1.1 Results of the search

The literature search resulted in 3 203 records. No records were identified via additional searches of reference lists. After removing duplicates, 1 846 records remained. During title and abstract screening, we judged 1 762 records to be irrelevant. We proceeded to full-text screening with 84 records. From these 84 records, we excluded 71 records (Annex C). Detailed reasons for exclusion are provided in Annex C. Finally, we included 13 records (two RCTs and 11 NRSI) contributing data to the outcomes of this review. The flow of records including reasons for exclusion is illustrated in Figure 1.

In total, 541 registry entries were identified with six of them examining the effect of HPV vaccination to reduce the recurrence of CIN after local surgical treatment. Four studies are ongoing and two have an unknown status (Annex B).

Figure 1. PRISMA 2020 flow diagram [38]



4.2 Study characteristics

Baseline study characteristics

Thirteen studies were included in this review, the details of which are provided in Table 2. We found two RCTs [39, 40], three prospective [41-43] and eight retrospective [18, 44-50] cohort studies enrolling a total of 21 453 women with conisation.

Studies were conducted in Europe (n=10 [18, 40, 42-47, 49, 50]), China (n=1 [41]), South Korea (n=1 [48]) and Iran (n=1 [39]) and published between 2013 [49] and 2023 [41]. The length of follow-up after treatment was 24 [39] and 36 [40] month in RCTs. In NRSI, median follow-up times for the primary outcome CIN 2+ ranged between 12 [43] and > 60 [44] month.

All included studies were assessed for potential conflicts of interest. In one study [45], there were connections in terms of funding by the vaccine manufacturer.

Patient characteristics

Eight studies included women older > 25 years of age [18, 44-50]. The remaining five studies included participants across different age groups, ranging from 18 to > 50 years of age [39-43].

In most studies, the treatment for cervical lesions included LEEP/LLETZ as surgical procedures (n=10 [18, 41, 42, 44-50]) or LEEP and cold-knife conisation (n = 1 [39]). The conisation procedure was not specified in two studies [40, 43].

The spectrum of (precancerous) lesions in terms of baseline characteristic varied widely (normal, CIN1, CIN 2, CIN 3 or cervical cancer). The heterogeneity observed is due to variations in how baseline characteristics were defined: Some studies reported the patient characteristics in terms of the recommendation or clinical need for conisation and other studies use the actual conisation specimens for baseline data.

In total, four studies [41, 43, 48, 49] explicitly reported that a prior HPV vaccination (i.e. an HPV vaccine not related to conisation) was an exclusion criteria. In the remaining studies, information on prior HPV vaccination (in terms of primary prevention) was lacking.

Interventions and comparators

The time of the first vaccination dose in relation to conisation varied. Vaccination was administered up to six months after conisation (n=7 [18, 40, 42, 44, 46, 48, 50]), at the time of conisation (n=1 [39]) or included both either (shortly) before (range one to four months) and after (one to 12 months) conisation (n=3 [43, 47, 49]).

Two studies described the timing of the vaccine 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 vaccination (n=2 [41, 45]).

The studies used either the quadrivalent vaccine (> 90% of women, n=7 [39-42, 44, 48, 50]), the nonavalent vaccine (100% of women, n=1 [47]), or various vaccine types (n=4 [18, 45, 46, 49]). The vaccine type was not specified in one study (n=1 [43]).

Three doses of the HPV vaccine were given in six studies (> 68% of women, n=6 [18, 39, 44, 45, 47, 48]. The remaining studies did not specify the proportion of women receiving one, two or three doses. All studies compared the vaccine with no intervention.

Table 2. Key study characteristics

Study characteristics				Patient characteristics			Intervention			Control
Author, year, funding	Country, recruitment time	Follow-up time (in months after conisation)	N total (I/C)	Age, [years] median (range), mean±SD	Type of (precancerous) lesion and information on prior HPV vaccination status	Conisation Procedure	Time of vaccination (1st dose)	Doses of vaccination	Type of vaccination	
RCT										
Karimi-Zarchi 2020 (39) (public funding)	Iran 10/11–11/15	24§	242 (138/104)	32.6±4.9	**Vaccine (138) vs. No-vaccine (104)** ***Conisation diagnosis or indication for conisation (unclear):*** CIN 1: 45 (32.6%) vs. 35 (33.7%) CIN 2: 50 (36.2%) vs. 35 (33.7%) CIN 3: 43 (31.2%) vs. 34 (32.6%) **Positive resection margin:** NR **Prior HPV vaccination status: unknown**	LEEP, CKC (no other details)	**At conisation** (2nd and 3rd dose ≤ 6 mos)	3 doses: 75% 2 doses: 25.4% 1 dose: 0%	Quadrivalent 100%)	No intervention
Pieralli 2018 (40) (public funding)	Italy 11/13–10/14	36§	178 (89/89)	32 (23–44)	**Vaccine (89) vs. No-vaccine (89)** ***Conisation diagnosis or indication for conisation (unclear):*** LSIL: 30 (16.9%) and HSIL: 148 (83.1%) (overall) **Positive resection margin:** NR **Prior HPV vaccination status: unknown**	Conisation (no other details)	**After conisation** 3 mos	3 doses (no other details)	Quadrivalent 100%)	No intervention
NRSI: prospective design										
Chen 2023 (41) (public funding)	China 09/17–04/20	30 (median)	423 (148/273)	20–45	**Vaccine (148) vs. No-vaccine (273)** ***Conisation diagnosis:*** CIN 2: 20 (13.5%) / 42 (15.38%) CIN 3: 128 (86.5%) / 231 (84.6%) **Positive resection margin:** Only patients with negative resection margins included. **Exclusion criteria: prior HPV vaccination**	LEEP (100%)	**After conisation** (no other details)	3 doses planned (no other details)	Quadrivalent (100%)	No intervention
Ghelardi 2018 (42) SPERANZA Project (no funding)	Italy 01/13–03/17	≥24; 36 (median)	344 (172/172)	18–45	**Vaccine (172) vs. No-vaccine (172)** ***Conisation diagnosis:*** CIN 2: 6 (3.5%) / 3 (1.7%) CIN 3: 163 (94.8%) / 167 (97.1%) CC: 3 (1.7%) / 2 (1.2%) **Positive resection margin:** 28 (16.3%) / 24 (13.9%) **Prior HPV vaccination status: unknown**	LEEP (100%)	**After conisation** ≤ 1 mos	3 doses planned (no other details)	Quadrivalent (100%)	No Intervention
Sand 2019 (43) (public funding)	Denmark 10/06–06/12	≥12°	17128 (2074/150514)	I: 28 (17–51) C: 32 (17–51)	**Vaccine (2074) vs. No-vaccine (15054)** ***Conisation diagnosis:*** CIN 2+: 1508 (73%) / 10895 (72%) **Positive resection margin:** NR **Exclusion criteria: prior HPV vaccination**	Conisation (no other details)	**Before** (3 mos) **or after** (≤ 12 mos) **conisation**	NR	NR	No intervention

Study characteristics				Patient characteristics			Intervention			Control
NRSI: retrospective design										
Bogani 2020 (44) (no funding)	Italy (multicentre) 01/10–12/14	>60	300 (100/200)	33.4 (24–44)	**Vaccine (100) vs. No-vaccine (200)** ***Conisation diagnosis:*** CIN 2: 54 (54%) / 106 (53%) CIN 3: 46 (46%) / 94 (47%) **Positive resection margin:** 24 (24%) / 49 (24.5%) **Prior HPV vaccination status: unknown**	LEEP (100%)	**After conisation** ≤ 6 mos	3 doses: 68% 2 doses: 18% NR: 14%	Quadrivalent (93%), Bivalent (7%)	No intervention
Casajuana -Perez 2022 (45) **VENUS Study** (pharmaceutical funding)	Spain 01/09–01/19	32.9 (median)	563 (277/286)	36.9±8.2	**Vaccine (277) vs. No-vaccine (286)** ***Conisation diagnosis or indication for conisation (unclear):*** LSIN/CIN 1: 17 (6%) / 16 (5.8%) HSIL/CIN 2-3: 266 (94%) / 261 (94.2%) **Positive resection margin:** 56 (20.2%) / 47 (16.6%) **Prior HPV vaccination status: unknown**	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
De la Rosa 2021 (46) (no funding)	Spain 01/12–06/15	≥48	331 (160/171)	37.5±7.9	**Vaccine (160) vs. No-vaccine (171)** ***Conisation diagnosis:*** CIN 2: 89 (55.6%) / 79 (44.4%) CIN 3: 71 (44.4%) / 76 (55.6%) **Positive resection margin:** 72 (44.9%) / 85 (49.7%) **Prior HPV vaccination status: unknown**	LEEP (100%)	**After conisation** ≤ 6 mos	NR	Quadrivalent, Bivalent (no other details)	No intervention
Del Pino 2020[#] (18) (public funding)	Spain 01/13–07/18	21.7 (median)	265 (153/112)	39.8±10.3	**Vaccine (153) vs. No-vaccine (112)** ***Conisation diagnosis:*** Normal: 12 (7.8%) / 14 (12.5%) LSIL/CIN 1: 17 (11.1%) / 13 (11.6%) HSIL/CIN 2-3: 124 (81.1%) / 85 (75.9%) **Positive resection margin:** 59 (38.6%) / 32 (28.6%) **Prior HPV vaccination status: unknown**	LEEP (100%)	**After conisation** ≤ 6 mos	3 doses: 77.1% 2 doses: 10.5% 1 dose: 4.6% NR: 7.8%	Quadrivalent (4%), Bivalent (20%), Nonavalent (64%), NR (12%)	No Intervention
Henere 2022 (47) (public funding)	Spain 07/16–12/19	20.2 (mean)	398 (306/92)	40.8±10.28	**Vaccine (306) vs. No vaccine (92)** ***Conisation diagnosis:*** Normal: 27 (8.8%) / 14 (15.2%) HSIL: 257 (84%) / 60 / (65.2%) LSIL: 22 (7.2%) / 18 (19.6%) **Positive resection margin:** 119 (38.9%) / 33 (35.9%) **Prior HPV vaccination status: unknown**	LEEP/LLETZ (100%)	**Before** (4 mos) **or after** (5 mos) **conisation**	3 doses: 91.8% 2 doses: 6.2% 1 dose: 2.0%	Nonavalent (100%)	No intervention
Kang 2013 (48) (public funding)	South Korea 08/07–07/10	>24; 42 (median)	737 (360/377)	36.7±5.8	**Vaccine (360) vs. No-vaccine (377)** ***Conisation diagnosis:*** CIN 2: 54 (15%) / 71 (19%) CIN 3: 306 (85%) / 306 (81%) **Positive resection margin:** 63 (17.5%) / 73 (19.3%) **Exclusion criteria: prior HPV vaccination**	LEEP (100%)	**After conisation** ≤ 6 mos	3 doses: 100%	Quadrivalent (100%)	No intervention

Study characteristics				Patient characteristics			Intervention			Control
Ortega- Quinonero 2018 (49) (unclear funding)	Spain 01/11–05/15	14.2 (median)	242 (103/139)	I: 33 (28–38) C: 39 (31–50)	**Vaccine (103) vs. No-vaccine (139)** ***Indication for conisation:*** CIN 2: 51 (49.5%) / 55 (39.6%) CIN 3: 52 (50.5%) / 84 (60.4%) **Positive resection margin:** 26 (25.2%) /36 (25.9%) **Exclusion criteria: prior HPV vaccination**	LEEP (100%)	**Before** (1 mos) **or after** (1 mos) **conisation**	3 doses planned (no other details)	Quadrivalent (32%), Bivalent (68%),	No intervention
Petrillo 2020 (50) (no funding)	Italy 01/12–06/17	≥24	302 (182/103)	I: 38 (30–44) C: 41 (36–49)	**Vaccine (182) vs. No-vaccine (103)** ***Conisation diagnosis:*** Normal: 1 (0.6%) / 1 (0.9%) CIN 1: 3 (1.8%) / 2 (1.7%) CIN 2: 96 (53.0%) / 57 (50.9%) CIN 3:* 72 (39.8%) / 45 (40.2%) CIS:*9 (5.0%) / 7 (6.3%) **Positive resection margin:** 13 (7.1%) / 15 (12.9%) **Prior HPV vaccination status: unknown**	LEEP (100%)	**After conisation** ≤ 1 mos	NR	Quadrivalent (98%)	No Intervention

C: Control group (no vaccine or placebo 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: (High-Risk) Human Papillomavirus (diagnosed by HPV testing), I: Intervention group (HPV vaccine), LEEP: Loop electrosurgical excision procedure, LLETZ: Large loop excision of the transformation zone, LSIL: Low-grade Squamous Intraepithelial Lesion, Mos: Months, N: Number, NR: Not reported, NRSI: Non-randomised studies of the effects of interventions, RCT: Randomized controlled trial, Y: Years

§ Unclear if mean or median.

 # This study (Del Pino 2020) is falsely declared as prospective study by the authors.

° First follow-up 12 months after conisation until diagnosis of CIN2+, second conisation, death, emigration or end of follow-up (30 June 2016), whichever came first.

** The authors reported CIN3 and CIS separately*

4.3 Risk of bias in included studies

We assessed the risk of bias for two RCTs contributing results to our primary outcomes using the RoB 2 tool [22, 23]. The RoB 2 judgements for the two RCTs account for all primary outcomes (see 3.1.4.2) and are available in Figure 2 and Annex D. We judged one RCT [40] as having some overall concerns, mainly due to some 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). The other RCT [39] was judged to have an overall high risk of bias, mainly due to major concerns regarding missing outcome data (i.e. high drop-out rates in the control group) and some concerns regarding deviations from intended interventions, and the selection of the reported results.

The risk of bias for the 11 NRSI was assessed using the ROBINS-I tool [24]. The ROBINS-I judgements also account for all primary outcomes (see section 3.1.4.2) and are available in Figure 3 and Annex E. We judged nine NRSI to have an overall serious risk of bias, mainly due to confounding (which was in most cases not sufficiently considered), the selection of participants into the study, measurement of the outcomes (e.g. no blinding and expected differences in follow-up time between groups), and the selection of the reported results [18, 41-45, 48-50]. Two NRSI were judged as having overall critical risk of bias, mainly due to very problematic confounding (e.g. uncontrolled differences in patient characteristics at baseline) and the selection of reported results [46, 47].

Figure 2. RoB2 in RCTs (applies to all outcomes)

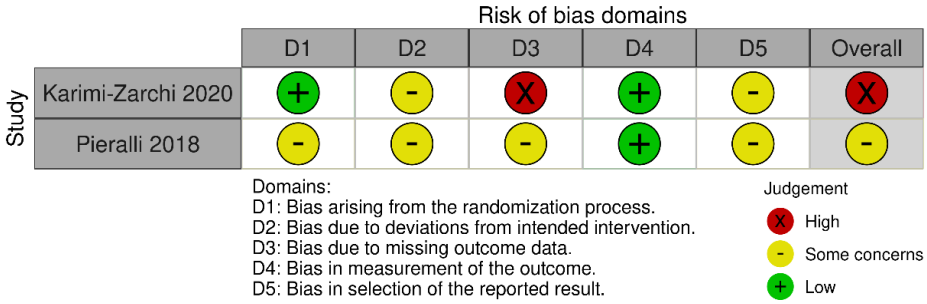
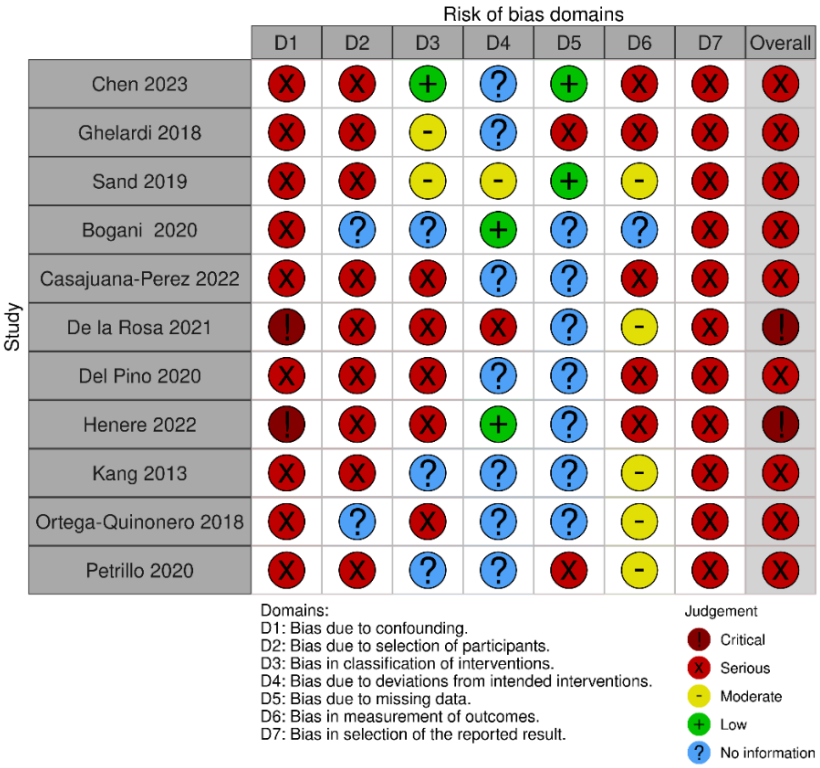


Figure 3. ROBINS-I Tool NRSI (applies to all outcomes)



4.4 Effects of interventions

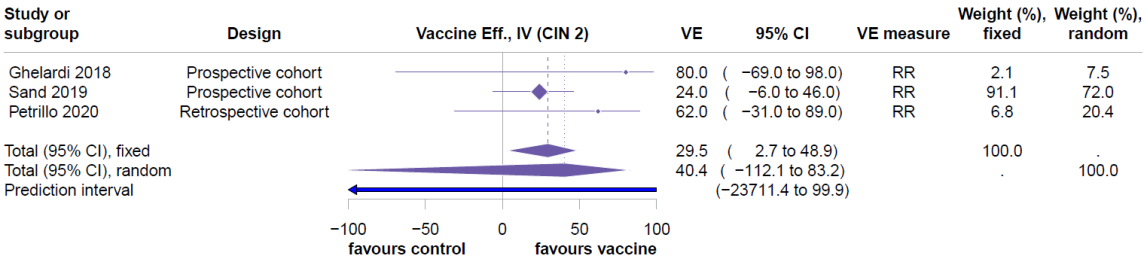
AnnexAn overview of all outcome data extracted at the study level is provided in Annex F. An overview of the effect of intervention for each primary and secondary outcome is presented in Table 3.

4.4.1 Primary outcomes

CIN 2 (irrespective of HPV type)

The evidence is inconclusive about the effect of the vaccine on CIN 2 .The 95%-CI includes both, a considerably decreased and increased risk for CIN 2 among vaccinated women. The only evidence from NRSI that is available showed: VE (%) 40.4, 95%-CI -112.1 to 83.2, 3 NRSI. 17 757 participants [42, 43, 50]; Figure 4, Table 3.

Figure 4. CIN 2



Test for heterogeneity: τ^2=0.12; χ^2=2.39, df=2, P=0.30; I^2=16%
Test for overall effect (fixed effect): Z = −2.13, P = 0.03
Test for overall effect (random effects): t_2 = −1.75, P = 0.22

Subgroup analyses and sensitivity analysis

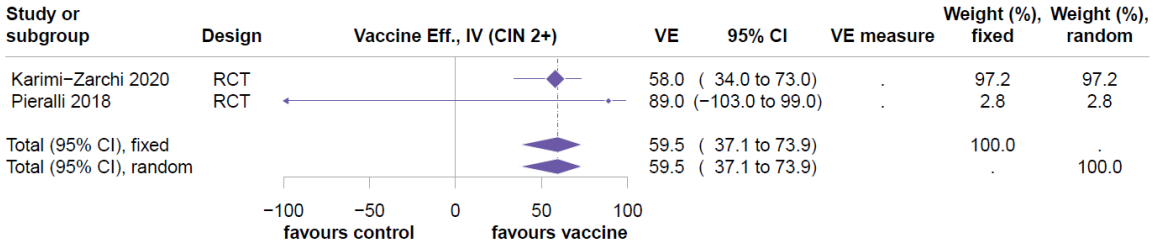
There were insufficient data for conducting informative subgroup or sensitivity analyses.

CIN 2+ (irrespective of HPV type)

The risk of CIN 2+ may be reduced among vaccinated patients. Evidence from RCTs showed: VE (%) 59.5, 95%-CI 37.1 to 73.9, 2 RCTs, 420 participants, low certainty of evidence [39, 40]; evidence from NRSI: VE (%) 65.6, 95%-CI 48.7 to 76.9, 11 NRSI, 21 014 participants, low certainty of evidence [18, 41-50]; Figure 5A and B, Table 3.

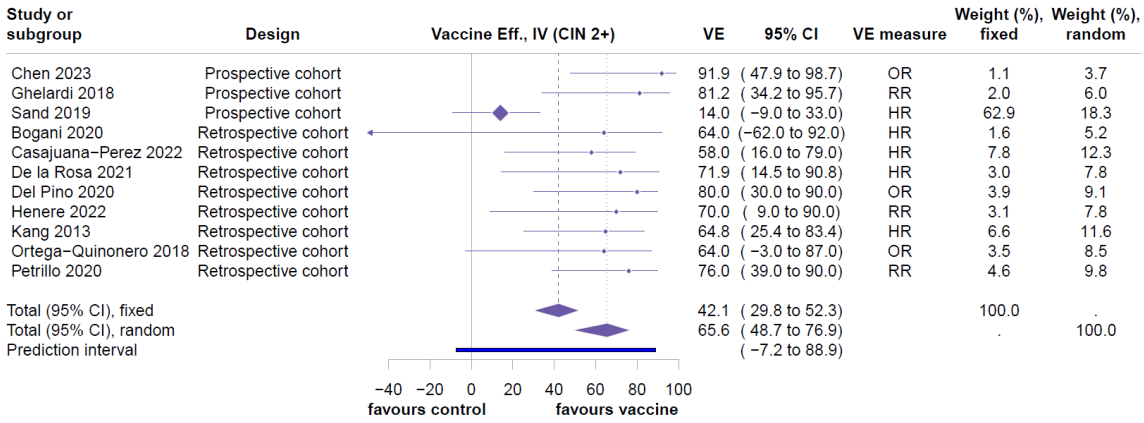
Figure 5. CIN 2+

A. CIN 2+ (RCTs)



Test for heterogeneity: τ^2=0; χ^2=0.95, df=1, P=0.33; I^2=0%
Test for overall effect (fixed effect): Z = −4.02, P < 0.001
Test for overall effect (random effects): Z = −4.02, P < 0.001

B. CIN 2+ (NRSI)



Test for heterogeneity: τ^2=0.21; χ^2=31.96, df=10, P < 0.001; I^2=69%
Test for overall effect (fixed effect): Z = −5.55, P < 0.001
Test for overall effect (random effects): t_{Inf} = −5.24, P < 0.001

Subgroup analyses

We found no subgroup differences according to type of vaccine. The 95%-CI in the subgroups overlapped, which was reflected by large P values for the test for subgroup differences (Annex H).

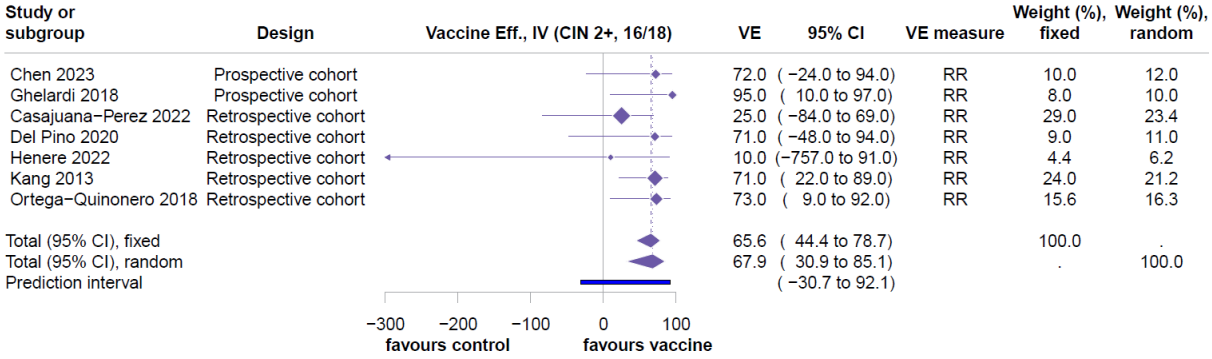
Sensitivity analyses

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) and did not alter the interpretation of the result (Annex I).

CIN 2+ (related to HPV 16/18)

The risk for CIN 2+ (HPV 16/18) may be reduced based on evidence from NRSI among vaccinated patients. The risk for CIN 2+ (HPV 16/18) is very uncertain based on evidence from one RCT, since the 95%-CI includes both a considerably decreased and increased risk for CIN 2+ (HPV 16/18) among vaccinated women. Evidence from RCTs showed: VE (%) 89.0, 95%-CI -103.0 to 99.0, 1 RCT, 178 participants, very low certainty of evidence [39]; evidence from NRSI: VE (%) 67.9, 95%-CI 30.9 to 85.1, seven NRSI, 2 970 participants, low certainty of evidence [18, 41, 42, 45, 47-49]; Figure 6 (single study result for RCT not included), Table 3.

Figure 6. CIN 2+ (HPV 16/18)



Test for heterogeneity: τ^2=0.20; χ^2=8.95, df=6, P=0.18; I^2=33%
Test for overall effect (fixed effect): Z = −4.36, P < 0.001
Test for overall effect (random effects): t_6 = −3.63, P = 0.01

Subgroup analyses

We found no subgroup differences according to type of vaccine. The 95%-CI in the subgroups overlapped, which was reflected by large P values for the test for subgroup differences (Annex I).

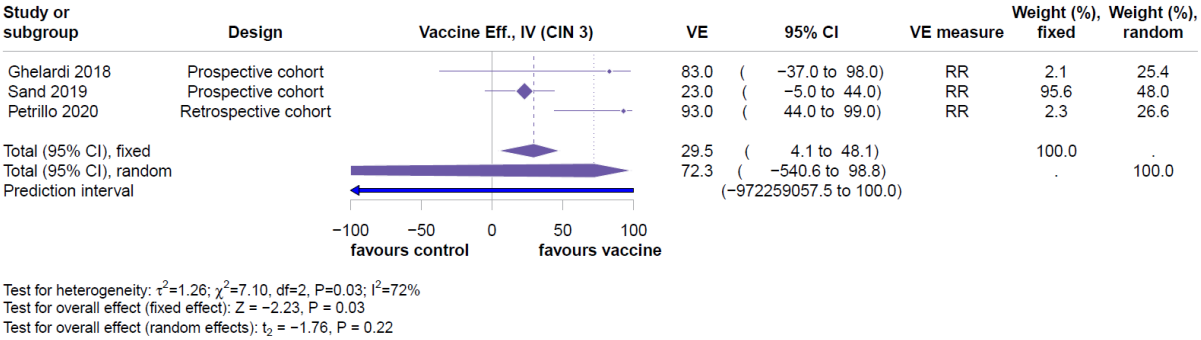
Sensitivity analyses

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) and did not alter the interpretation of the result (Annex I).

CIN 3 (irrespective of HPV type)

The evidence is inconclusive about the effect of the vaccine on CIN 3. The 95%-CI includes both a considerably decreased and increased risk for CIN 3 among vaccinated women. The only evidence from NRSI available shows: VE (%) 72.3, 95%-CI -540.6 to 98.8, three NRSI, 17 757 participants [42, 43, 50]; Figure 7, Table 3.

Figure 7. CIN 3



Test for heterogeneity: τ^2=1.26; χ^2=7.10, df=2, P=0.03; I^2=72%
Test for overall effect (fixed effect): Z = −2.23, P = 0.03
Test for overall effect (random effects): t_2 = −1.76, P = 0.22

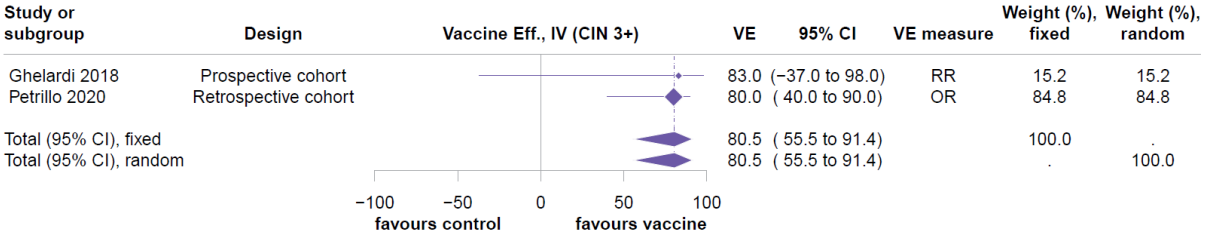
Subgroup analyses and sensitivity analysis

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

CIN 3+ (irrespective of HPV type)

The risk of CIN 3+ recurrence may be reduced among vaccinated patients. The only evidence available from NRSI shows: VE (%) 80.5, 95%-CI 55.5 to 91.4, two NRSI, 629 participants [42, 50]; Figure 8, Table 3**.**

Figure 8. CIN 3+



Test for heterogeneity: τ^2=0; χ^2=0.02, df=1, P=0.89; I^2=0%
Test for overall effect (fixed effect): Z = −3.88, P < 0.001
Test for overall effect (random effects): Z = −3.88, P < 0.001

Subgroup analyses and sensitivity analysis

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 the vaccine on CIN 3+ (related to HPV 16/18). The only available evidence from NRSI shows: VE (%) 91.0, 95%-CI -63.0 to 99.0, one NRSI, 344 participants, very low certainty of evidence [42]; Table 3.

Adenocarcinoma in situ (AIS)

None of the studies assessed this outcome.

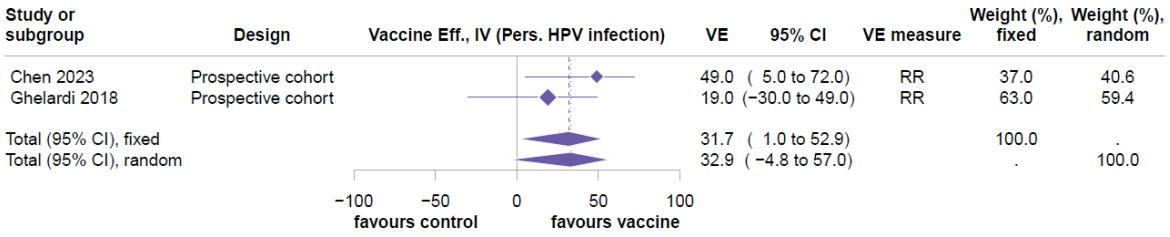
Invasive cervical cancer (with or without HPV 16/18)

The evidence is very uncertain about the effect of the vaccine on invasive cervical cancer (with or without HPV 16/18). The 95%-CIs includes both, a considerably decreased and increased risk for invasive cervical cancer (with or without HPV 16/18) among vaccinated women. Evidence from RCTs show: VE (%) 75.0, 95%-CI -511.0 to 99.0, one RCT, 242 participants, very low certainty of evidence [39]; evidence from NRSI shows: VE (%) 15.0, 95%-CI -269.0 to 80.0, one NRSI, 17 128 participants, very low certainty of evidence [51]; Table 3**.**

Persistent HPV infection (irrespective of HPV type)

The evidence is very uncertain about the effect of the vaccine on persistent HPV infection. Although the pooled point estimate suggests that there may be a small effect in favour of vaccinated women, the 95%-CI is wide and includes values around the null effect. The only evidence available from NRSI shows: VE (%) 32.9, 95%-CI -4.8 to 57.0, two NRSI, 765 participants, very low certainty of evidence [41, 42]; Figure 9, Table 3.

Figure 9. Persistent HPV infection

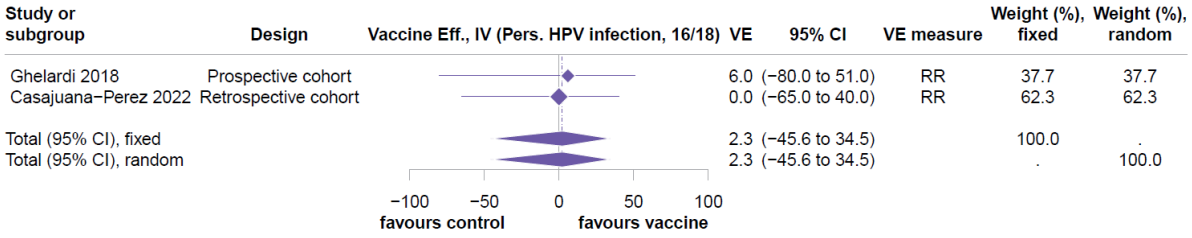


Test for heterogeneity: τ^2=0.03; χ^2=1.39, df=1, P=0.24; I^2=28%
Test for overall effect (fixed effect): Z = −2.01, P = 0.04
Test for overall effect (random effects): Z = −1.75, P = 0.08

Persistent HPV infection (related to HPV 16/18)

The evidence is very uncertain about the effect of the vaccine on persistent HPV infection (related to HPV 16/18). The 95%-CI includes both, a considerably decreased and increased risk for HPV infection (HPV 16/18) among vaccinated women. The only evidence available from NRSI shows: VE (%) 2.3, 95%-CI -45.6 to 34.5, two NRSI, 907 participants, very low certainty of evidence [42, 45]; Figure 10, Table 3.

Figure 10. Persistent HPV infection (HPV 16/18)



Test for heterogeneity: τ^2=0; χ^2=0.02, df=1, P=0.88; I^2=0%
Test for overall effect (fixed effect): Z = −0.11, P = 0.91
Test for overall effect (random effects): Z = −0.11, P = 0.91

Incident HPV infection (irrespective of HPV type)

None of the studies assessed this outcome (only in combination with persistent infections) [47].

Incident HPV infection (related to HPV 16/18)

None of the studies assessed this outcome.

4.4.2 Secondary outcomes

Mortality (all cause and cancer-related)

The evidence is inconclusive about the effect of the vaccine on mortality. The only available evidence from NRSI shows: VE (%) 48.0, 95%-CI -67.0 to 84.0, one study, 17 128 participants [43]; Table 3.

VIN 2+ / VaIN 2+

The evidence is inconclusive about the effect of the vaccine on VIN 2+ and VaIN 2+. One RCT reported that no events of VIN 2+ or VaIN 2+ were observed: VE not calculable, one RCT, 178 participants [40]; Table 3.

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

Vaccine-related adverse effects including minor local reactions (redness, headache, rash; n=127 women) and severe allergies (n=2 women) were reported in one RCT comparing the HPV vaccine with no intervention: VE not calculable, one RCT, 138 participants included in vaccine group [39]; Table 3.

Table 3. Overview of effect estimates for all outcomes

Study type (participants)	Event rates		Relative effect (95%-CI)	Risk difference
	HPV Vaccine	Control		
CIN 2 (irrespective of HPV type)*				
3 NRSI (17 757)	42/2 428	365/15 329	VE: 40.4% (-112.1 to 83.2) Effect ratio: 0.60 (0.17 to 2.12)	**10 fewer per 1 000** (from 20 fewer to 7 more)
CIN 2+ (irrespective of HPV type) (prioritised outcome)				
2 RCTs (420)	23/227	45/193	VE: 59.5% (37.1 to 73.9) Effect ratio: 0.41 (0.26 to 0.63)	**138 fewer per 1 000** (from 173 fewer to 86 fewer)
11 NRSI (21 014)	136/4 035	953/16 979	VE: 65.6% (48.7 to 76.9) Effect ratio: 0.34 (0.23 to 0.51)	**37 fewer per 1 000** (from 43 fewer to 28 fewer)
CIN 2+ (HPV 16/18) (prioritised outcome)				
1 RCT (178)	0/89	4/89	VE: 89% (-103 to 99.0) Effect ratio: 0.11 (0.01 to 2.03)	**40 fewer per 1 000** (from 44 fewer to 46 more)
7 NRSI (2 970)	23/519	72/1 451	VE: 67.9% (30.9 to 85.1) Effect ratio: 0.32 (0.15 to 0.69)	**34 fewer per 1 000** (from 42 fewer to 15 fewer)
CIN 3 (irrespective of HPV type)*				
3 NRSI (17 757)	45/2 428	420/15 329	VE: 72.3% (-540.6 to 98.8) Effect ratio: 0.28 (0.01-6.40)	**20 fewer per 1 000** (from 27 fewer to 148 more)
CIN 3+ (irrespective of HPV type)* (prioritised outcome)				
2 NRSI (629)	3/354	14/275	VE: 80.5% (55.5 to 91.4) Effect ratio: 0.20 (0.09 to 0.45)	**41 fewer per 1 000** (from 46 fewer to 28 fewer)
CIN 3+ (HPV 16/18)* (prioritised outcome)				
1NRSI (344)	0/172	5/172	VE: 91% (-63.0 to 99.0) Effect ratio: 0.08 (0.01 to 1.63)	**27 fewer per 1 000** (from 29 fewer to 18 more)
VIN 2+ / VaIN 2+				
1 RCT (178)	0/89	0/89	NA	NA
Invasive cervical cancer				
1 RCT (242)	0/138	1/104	VE: 75% (-511.0 to 99.0) Effect ratio: 0.25 (0.01 to 6.11)	**7 fewer per 1 000** (from 10 fewer to 49 more)
1 NRSI (17 128)	2/2 074	17/15 054	VE: 15% (-269.0 to 80.0) Effect ratio: 0.85 (0.20 to 3.69)	**0 fewer per 1 000** (from fewer 1 to 3 more)
Persistent HPV infection (irrespective of HPV type)* (prioritised outcome)				
2 NRSI (765)	38/320	75/445	VE: 32.9% (-4.8 to 57.0) Effect ratio: 0.67 (0.43 to 1.05)	**56 fewer per 1 000** (from 96 fewer to 8 more)
Persistent HPV infection (HPV 16/18)* (prioritised outcome)				
2 NRSI (907)	43/449	45/458	VE: 2.3% (-45.6 to 34.5) Effect ratio: 0.98 (0.66 to 1.46)	**2 fewer per 1 000** (from 33 fewer to 45 more)
Mortality*				
1 NRSI (17 128)	3/2 074	42/15 054	VE: 48% (-67.0 to 84.0) Effect ratio: 0.52 (0.16 to 1.67)	**27 fewer per 1 000** (32 fewer to 20 more)
Vaccine-related adverse effects				
1 RCT (242)	129/138	NA	NA	**NA**

CI: Confidence Interval, CIN: Cervical Intraepithelial Neoplasia, HPV: (High-Risk) Human Papillomavirus (diagnosed by HPV testing), NA: Not applicable, NRSI: Non-randomised studies of the effects of interventions, RCT: Randomised controlled trial, VaIN: Vaginal intraepithelial neoplasia, VE: Vaccine Efficacy, VIN: Vulvar intraepithelial neoplasia
**No evidence from RCTs available.*

5. Discussion

This review aimed to investigate the efficacy, effectiveness and safety of the HPV vaccine in reducing the recurrence of precancerous cervical lesions and other patient-relevant outcomes in women undergoing conisation due to cervical lesions.

We identified two RCTs including 420 women and 11 NRSI including 21 033 women with conisation. From the prioritised primary endpoints 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 and persistent HPV infection (irrespective of HPV type and related to HPV 16/18). Furthermore, the studies also reported data for the non-prioritised endpoints: CIN 2 and CIN 3 (both irrespective of HPV type), VIN 2+ / VaIN 2+, mortality and vaccine-related adverse events.

Our analyses show that the HPV vaccination compared to no vaccination may reduce the risk of CIN 2+ irrespective of HPV type (RCTs: VE (%) 59.5, 95%-CI 37.1 to 73.9, RD 138 per 1 000, 2 RCTs, 420 participants, low certainty of evidence; NRSI: VE (%) 65.6, 95%-CI 48.7 to 76.9, RD 37 per 1 000, 11 NRSI, 21014 participants, low certainty of evidence), CIN 2+ related to HPV 16/18 (evidence based on NRSI (RCTs: VE (%) 89.0, 95%-CI -103.0 to 99.0, RD 40 per 1 000, 1 RCT, 178 participants, very low certainty of evidence; NRSI: VE (%) 67.9, 95%-CI 30.9 to 85.1, RD 34 per 1 000, 7 NRSI, 2 970 participants, low certainty of evidence) and CIN 3+(irrespective of HPV type) (evidence based on NRSI: VE (%) 80.5, 95%-CI 55.5 to 91.4, RD 41 per 1 000, 2 NRSI, 629 participants, low certainty of evidence).

The effect estimates for CIN 3+ (related to HPV 16/18) was very uncertain: VE (%) 91, 95%-CI -63.0 to 99.0, RD 27 per 1 000, one NRSI, 344 participants, very low certainty of evidence. The number of persistent HPV infections (irrespective of HPV type and related to HPV 16/18) between women with HPV vaccine and no vaccine was also very uncertain: VE (%) 32.9, 95%-CI -4.8 to 57.0, RD 56 per 1 000, two NRSI, 765 participants, very low certainty of evidence and VE (%) 2.3, 95%-CI -45.6 to 34.5, RD two per 1 000, two NRSI, 907 participants, very low certainty of evidence, respectively. Likewise, we observed no discernible impact of the HPV vaccine on the prevention of invasive cervical cancer in both RCTs and NRSI: VE (%) 75, 95%-CI -511.0 to 99.0, RD seven per 1 000, one RCT, 242 participants, very low certainty of evidence and VE (%) 15.0, 95%-CI -269.0 to 80.0, RD 0 per 1 000, one NRSI, 17 128 participants, very low certainty of evidence, respectively.

Moreover, the evidence for the non-prioritised outcomes CIN 2 and CIN 3 (irrespective of HPV type), , VIN 2+ and VaIN 2+ and mortality was inconclusive. This can be attributed to the fact that some outcomes were only measured by a single study, and/or that events occurred at a low rate. One RCT reported severe allergies (n=2) and minor local reactions (n=127) to the HPV vaccines (n total receiving vaccine=138).

Overall completeness and applicability of evidence

The evidence summarised in this review applies to the use of the HPV vaccine 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 get vaccinated before treatment, the available study pool did not allow us to conduct subgroup analyses according to the timing of vaccination in relation to conisation. However, a recent follow-up by Sand et al. [43] including more than 17 000 women undergoing surgical treatment for precancerous lesions, found that women vaccinated before conisation (within three months) had a lower risk for developing recurrent disease 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. Although these findings were similar to the results of Henere et al. [47] (i.e. in favour of vaccination before conisation), these study data could not be considered in subgroup analyses in the current systematic review due to methodological limitations of the comparisons. Controversially, as surgical treatment may induce changes in the microenvironment of the inflammatory tissue similar to those seen in patients without HPV infection, there could be potential advantages in administering the vaccine postoperatively [52].

Taking into account that widespread HPV vaccination programmes have now become established in various European countries [53-55], it is unclear whether the results of the included studies can be transferred to a predominantly immunised population. Also, the applicability of our findings for subgroups, such as immunocompromised or older people, who have a relevant risk of an inadequate immune response to vaccination, must be applied with caution.

Diagnostic uncertainty including complex diagnostic pathways (including cytology, HPV testing and histological finding) may be another limitation in the interpretation of the results [40, 45, 47]. Furthermore, possible limitations regarding vaccine efficacy and effectiveness for different HPV types need to be considered when interpreting the results of this review. For example, only one study [47] focused on women who exclusively received the nonavalent vaccine (Gardasil 9), which is designed to provide broader protection. However, this retrospective study was judged

with a critical risk of bias (Annex E) and did not differentiate between incident and persistent infections during the follow-up. However, we identified two ongoing RCTs [56-58] that investigate the nonavalent prophylactic HPV vaccine (Gardasil 9) in patients with local conservative treatment for CIN. The results for one of these studies [56] were scheduled to be released in the middle of 2023. However, to date, no results have been published.

Furthermore, we conducted additional meta-analyses of four post-hoc analyses of RCTs [51, 59-61] not designed to evaluate the effect of vaccination in relation to conisation. In these studies, participants had been vaccinated in the past, and the purpose of this vaccine was primary prevention of cervical cancer (Annex J). The results of these four post-hoc analysis in which the immunised study participants where compared with those who had been vaccinated with a placebo and subsequently required conisation, align closely with the findings observed in the present systematic review, where the vaccine was administered as an 'adjuvant' intervention to conisation.

Certainty of the evidence

We assessed the certainty of evidence for prioritised outcomes presented in the Summary of Findings table according to GRADE [34]. We found CIN 2+ (irrespective and respective of HPV 16/18) and CIN 3+ (irrespective of HPV type) to have low certainty evidence. The certainty of the evidence for CIN 3+ (related to HPV 16/18), persistent HPV infection and invasive cervical cancer was very low. Downgrading was due to very serious or serious imprecision and a very serious to serious risk of bias (Table 1). Our findings primarily pertain to the quadrivalent and bivalent vaccine types, and not the nonavalent vaccine, however, we opted not to downgrade due to the indirect nature of the evidence. The decision not to downgrade was particularly influenced by the continued use of the bivalent vaccine[54].

Assessing the risk of publication bias was difficult. There are registered studies that are ongoing. Currently, we do not suspect any publication bias to be present, for any of the outcomes. A funnel plot for the outcome CIN 2+ (irrespective of HPV type) is presented in Annex K.

The NRSI were of serious or critical risk of bias based on the ROBINS-I bias assessment tool, and only four studies provided adjusted data for some outcomes [18, 43, 46, 48]. The risk of bias is attributed, at least partially, to the presence of confounders (including 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 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 [43, 44, 49, 50]. Additionally, confounding factors, such as smoking, which is associated with a higher risk of recurrence, were not accounted for in the current study pool. 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 median length of follow-up was 30 months (based on studies reporting median follow-up time), so we could not assess whether the effect estimate would be sustained in the long term.

Potential biases in the review process

To avoid potential bias in the review process, we committed ourselves to conducting this systematic review according to published guidance provided by the Cochrane Handbook for Systematic Reviews of Interventions [62]. 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. Although the subgroup analyses according to the type of vaccine showed consistent results, the number of included studies in these subgroups was often low. Data for incident and persistent HPV infection were scarce. Although four [41, 42, 45, 47] of 13 studies reported on HPV infection, one was not included in our meta-analyses, because this study [47] did not distinguish between incident and persistent infections. Studies did not report data following the ITT principle.

Agreements and disagreements with other studies or reviews

There are several reviews analysing the HPV vaccine in women with conisation to prevent cervical cancer [63-67]. Kechagias et al. [63] focused on the effects of HPV vaccination on the risk of HPV infection and recurrent diseases in individuals undergoing local surgical treatment. This review did not incorporate more recent studies, such as Henere et al. [47], Casajuana-Perez et al. [45] and Chen et al. [41]. However, the authors also concluded that the HPV vaccination may reduce the risk of recurrence of CIN and their GRADE assessment indicated that "the data were inconclusive". Furthermore, this 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 et al. [66] included six studies in their systematic review and meta-analysis (one RCT, five NRSI) and reported on multiple CIN and non-cervical outcomes. Another systematic review and meta-analysis, published by Jentschke et al. [58], included ten studies (one RCT, nine NRSI) and reported results similar to our review regarding the risk of recurrence of CIN 2+ (the only outcome assessed in this study). The risk of bias in NRSI in this review was assessed using the RoB 2 tool, which is the gold standard bias tool for RCTs and not specifically tailored to capture biases in NRSI. Di Donato et al. [67] included 11 studies. Risk of bias was assessed with the ROBINS-I tool for all studies (including RCTs). A GRADE assessment was not carried out. Bartels et al. [68] retrieved data from only five studies for their meta-analysis on the risk of recurrence of CIN 2+. A GRADE assessment was not performed, and the RoB tool used (JADAD) has been used historically, but is not recommended any longer by the Cochrane Handbook for Systematic Reviews of Interventions [62]. Eriksen et al. [65] 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. No risk reduction on CIN 2+ recurrence was reported when only studies with low risk of bias were considered in this review.

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

6. Conclusions

The use of HPV vaccines in comparison to not using HPV vaccines in women with conisation may reduce the risk of CIN 2+ (irrespective of HPV type and related to HPV 16/18) and CIN 3+ (irrespective of HPV type). However, our confidence in the effect estimates is limited. The effect of HPV vaccination in comparison to no vaccination on CIN 3+ (related to HPV 16/18), invasive cervical cancer, persistent HPV infections (irrespective of HPV type) and persistent HPV infection (related to HPV 16/18) was very uncertain.

The evidence was inconclusive for CIN 2, CIN 3, VIN 2+ and VaIN 2+ and mortality. There were no data available for incident HPV infections (irrespective of HPV type and related to HPV 16/18), AIS and quality of life. One RCT comparing vaccinated women with women who did not receive a vaccine reported severe allergies (two cases) and minor local reactions to the HPV vaccine. Subgroup analyses according to type of vaccine were only possible for CIN 2+ (irrespective of HPV type and related to HPV 16/18). No differences were identified.

Overall, the existing evidence for the HPV vaccine in women with conisation is predominantly derived from NRSI with serious or critical risk of bias. Evidence from RCTs is very limited, i.e. only two RCTs are available. Additional RCTs with a placebo intervention in the control group to evaluate the efficacy of HPV vaccines (particularly the nonavalent vaccine) as an adjuvant to conisation may provide more reliable evidence. These RCTs should additionally consider the HPV vaccination status (in terms of primary prevention). Moreover, it would be crucial to extend the follow-up times to ensure the generation of robust data on the incidence of cervical cancer and cancer-related mortality.

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65. Eriksen DO, Jensen PT, Schroll JB, Hammer A. Human papillomavirus vaccination in women undergoing excisional treatment for cervical intraepithelial neoplasia and subsequent risk of recurrence: A systematic review and meta-analysis. Acta Obstet Gynecol Scand. 2022;101(6):597-607.

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Annex A. Search Strategies

Medline [Ovid]

Date run: 25.05.2023

#	Searches	Results
1	exp Papillomavirus Vaccines/	10 112
2	(exp Papillomavirus Infections/ or exp Papillomaviridae/) and exp Vaccines/	9 428
3	((Vaccin* or Immuniz* or immunis*) adj5 (Hpv* or Human Papilloma Virus* or Human Papillomavirus*)).ti,ab,kf.	14 404
4	(Cervarix or Gardasil or Gardasil9 or Cecolin).ti,ab,kf.	720
5	or/1-4	16 401
6	Conization/	1 168
7	coni?ation$.ti,ab,kf.	2 665
8	(excision* or electroexcision* or surg* or electrosurg* or LEEP or LLETZ or NETZ or SWETZ).ti,ab,kf.	2 433 297
9	*Electrosurgery/mt [Methods]	869
10	Uterine Cervical Dysplasia/su	1 793
11	Uterine Cervical Dysplasia/th [Therapy]	687
12	Neoplasm Recurrence, Local/pc [Prevention & Control]	8 994
13	Uterine Cervical Neoplasms/su	10 453
14	Secondary Prevention/	22 615
15	secondary prevention.ti,ab,kf.	22 391
16	or/6-15	2 481 586
17	5 and 16	**816**

CENTRAL (via Cochrane Library/Wiley)

Date run: 26.05.2023

#	Searches	Results
1	MeSH descriptor: [Papillomavirus Vaccines] explode all trees	548
2	([mh "Papillomavirus Infections"] OR [mh Papillomaviridae]) AND [mh Vaccines]	601
3	((Vaccin* or Immuniz* or immunis*) NEAR/5 (Hpv* or Human Papilloma Virus* or Human Papillomavirus*))	10 190
4	(Cervarix OR Gardasil OR Gardasil9 OR Cecolin):ti,ab,kw	245
5	#1 OR #2 OR #3 OR #4	10 232
6	MeSH descriptor: [Conization] this term only	38
7	(conisation* OR conization*):ti,ab,kw	207
8	((excision* or electroexcision* or surg* or electrosurg* or LEEP or LLETZ or NETZ or SWETZ)):ti,ab,kw	308 140
9	MeSH descriptor: [Electrosurgery] explode all trees and with qualifier(s): [methods - MT]	129
10	MeSH descriptor: [Uterine Cervical Dysplasia] explode all trees and with qualifier(s): [surgery - SU]	113
11	MeSH descriptor: [Uterine Cervical Dysplasia] explode all trees and with qualifier(s): [therapy - TH]	49
12	MeSH descriptor: [Neoplasm Recurrence, Local] explode all trees and with qualifier(s): [prevention & control - PC]	1 021
13	MeSH descriptor: [Uterine Cervical Neoplasms] explode all trees and with qualifier(s): [surgery - SU]	417
14	MeSH descriptor: [Secondary Prevention] explode all trees	4 006
15	secondary prevention:ti,ab,kw	7 837
16	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	315 521
17	#5 AND #16	**281**

Embase (via Ovid)

Date run: 25.05.2023

#	Searches	Results
1	'human papilloma virus vaccine'/exp	17 667
2	((vaccin* OR immuniz* OR immunis*) NEAR/5 (hpv* OR 'human papilloma virus*' OR 'human papillomavirus*')):ti,ab,kw	18 828
3	cervarix:ti,ab,kw OR gardasil:ti,ab,kw OR gardasil9:ti,ab,kw OR cecolin:ti,ab,kw	1 076
4	#1 OR #2 OR #3	24 258
5	'uterine cervix conization'/exp	4 134
6	coni$ation?:ti,ab,kw	282
7	excision*:ti,ab,kw OR electroexcision*:ti,ab,kw OR surg*:ti,ab,kw OR electrosurg*:ti,ab,kw OR leep:ti,ab,kw OR lletz:ti,ab,kw OR netz:ti,ab,kw OR swetz:ti,ab,kw	3 323 630
8	'uterine cervix dysplasia'/exp/dm_su,dm_th	733
9	'uterine cervix tumor'/exp/dm_su	15 836
10	'secondary prevention'/de	34 150
11	'secondary prevention':ti,ab,kw	36 049
12	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	3 379 400
13	#4 AND #12	1 585
14	#13 NOT ('conference abstract'/it OR 'conference paper'/it OR 'conference review'/it)	1 234
15	#14 AND [embase]/lim	**1 132**

Web of Science

Web of Science Core Collection: Citation Indexes

Date run: 26.05.2023

#	Searches	Results
1	TS=("Papillomavirus Vaccines")	660
2	TS=(("Papillomavirus Infections" OR Papillomaviridae) AND Vaccines)	269
3	TS=(((Vaccin* OR Immuniz* OR immunis*) NEAR/5 (Hpv* OR "Human Papilloma Virus*" OR "Human Papillomavirus*")))	14 190
4	TS=((Cervarix OR Gardasil OR Gardasil9 OR Cecolin))	687
5	#4 OR #3 OR #2 OR #1	14 391
6	TS=(conisation* OR conization*)	2 488
7	TS=((excision* OR electroexcision* OR surg* OR electrosurg* OR LEEP OR LLETZ OR NETZ OR SWETZ))	2 022 051
8	TS=("secondary prevention")	23 984
9	#6 OR #7 OR #8	2 045 253
10	#9 AND #5	613
11	#9 AND #5	**613**

BIOSIS Citation Index

Date run: 26.05.2023

#	Searches	Results
1	TS=("Papillomavirus Vaccines")	211
2	TS=(("Papillomavirus Infections" OR Papillomaviridae) AND Vaccines)	6 564
3	TS=(((Vaccin* OR Immuniz* OR immunis*) NEAR/5 (Hpv* OR "Human Papilloma Virus*" OR "Human Papillomavirus*")))	7 782
4	TS=((Cervarix OR Gardasil OR Gardasil9 OR Cecolin))	487
5	#1 OR #2 OR #3 OR #4	9 096
6	TS=(conisation* OR conization*)	1 523
7	TS=((excision* OR electroexcision* OR surg* OR electrosurg* OR LEEP OR LLETZ OR NETZ OR SWETZ))	1 852 379
8	TS=("secondary prevention")	9 292
9	#6 OR #7 OR #8	1 861 180
10	#5 AND #9	**361**

Annex B. Study registry entries

Study ID / country	Register link	Type of study / Planed sample size	Status
NCT03979014 / (NOVEL Trial) Great Britain	https://clinicaltrials.gov/study/NCT03979014	RCT / 1 000	status unknown; estimated study completion date: 07/2023
NL7938 / (VACCINE study) Netherlands	https://www.onderzoekmetmensen.nl/en/trial/22561	RCT / 750	ongoing; estimated study completion date: unknown
NCT03848039 / Italy	https://clinicaltrials.gov/study/NCT03848039	RCT / 1 220	ongoing; estimated study completion date: 05/2028
NCT05085093 / China	https://clinicaltrials.gov/study/NCT05085093	NRSI / 414	ongoing; estimated study completion date: 05/2028
NCT01393470 / Finland	https://clinicaltrials.gov/study/NCT01393470	NRSI / 10 000	ongoing; estimated study completion date: 12/2024
NCT02937155 / Canada	https://clinicaltrials.gov/study/NCT02937155	NRSI / 100	status unknown; estimated study completion date: 09/2023

Annex C. Publications excluded by full-text

Wrong publication type (n=5)

1. Dessole M, Petrillo M, Tinacci E, Capobianco G, Cossu A, Muresu N, et al. Effectiveness of HPV vaccine in women undergoing LEEP for cervical dysplasia. J Prev Med Hyg. 2019;60(3):E1-E384.
2. Mayrand MHB, Trottier H, Guedon AC. Vaccination did not reduce the risk of a second HSIL after excisional treatment for HSIL in a cohort of Canadian women. J Low Genit Tract Dis. 2017;21(2):S16-S7.
3. Vinnytska A. EP1090 Use of HPV-vaccine in prevention of recurrent HSIL after LEEP in women of reproductive age. Int J Gynecol Cancer. 2019;29(Suppl 4):A571-A.
4. Volodko N, Makuh H, Petronchak O, Huley R, Palyha I, Soboljeva V, editors. The Vaccination With Bivalent HPV Vaccine Cervarix After Electrosurgical Conization Prevents The Recurrent HPV Infection In Patients With High Grade Cervical Intraepithelial Neoplasia. Int J Gynecol Cancer. 2016: Lippincott Williams & Wilkins.
5. Garland SM. Does the Hpv-16/18 As04-adjuvanted vaccine benefit women with cervical disease? J Low Genit Tract Dis. 2013;17(6):S110-S1.

Wrong study design (n=10)

1. Zou M, Liu H, Liu H, Wang M, Zou Z, Zhang L. Vaccinating women previously treated for human papillomavirus-related cervical precancerous lesions is highly cost-effective in China. Front Immunol. 2023;14:1119566.
2. Chaiken S, Bruegl A, Caughey A, Munro E. HPV vaccination following loop electrical excision procedure (LEEP) for cervical intraepithelial neoplasia: A cost-effectiveness analysis (134). Gynecol Oncol. 2022; 166:S83-S4.
3. Li K, Yin R, Li Q, Wang D. Analysis of HPV distribution in patients with cervical precancerous lesions in Western China. Medicine. 2017;96(29).
4. Ehret A, Bark VN, Mondal A, Fehm TN, Hampl M. Regression rate of high-grade cervical intraepithelial lesions in women younger than 25 years. Arch Gynecol Obstet. 2023;307(3):981-90.
5. Gonzalez-Bosquet E, Gibert M, Serra M, Hernandez-Saborit A, Gonzalez-Fernandez A. Candidate HPV genotypes not included in the 9-valent vaccine for prevention of CIN 2–3. Int J Gynecol Cancer. 2020;30(7).
6. Chaiken SR, Bruegl AS, Caughey AB, Emerson J, Munro EG. Adjuvant Human Papillomavirus Vaccination After Excisional Procedure for Cervical Intraepithelial Neoplasia: A Cost-Effectiveness Analysis. Obstet Gynecol. 2023;141(4):756-63.
7. Giannella L, Delli Carpini G, Di Giuseppe J, Prandi S, Tsiroglou D, Ciavattini A. Age-related changes in the fraction of cervical intraepithelial neoplasia grade 3 related to HPV genotypes included in the nonavalent vaccine. J Oncol. 2019;2019.
8. Chao A, Jao MS, Huang CC, Huang HJ, Cheng HH, Yang JE, et al. Human papillomavirus genotype in cervical intraepithelial neoplasia grades 2 and 3 of Taiwanese women. Int J Cancer. 2011;128(3):653-9.
9. Bogani G, Pinelli C, Chiappa V, Martinelli F, Lopez S, Ditto A, Raspagliesi F. Age-specific predictors of cervical dysplasia recurrence after primary conization: analysis of 3,212 women. J Gynecol Oncol. 2020;31(5).
10. Bogani G, Lalli L, Sopracordevole F, Ciavattini A, Ghelardi A, Simoncini T, et al. Development of a nomogram predicting the risk of persistence/recurrence of cervical dysplasia. Vaccines. 2022;10(4):579.

Wrong patient population (n=8)

1. Einstein MH, Kadish AS, Burk RD, Kim MY, Wadler S, Streicher H, et al. Heat shock fusion protein-based immunotherapy for treatment of cervical intraepithelial neoplasia III. Gynecol Oncol. 2007;106(3):453-60.
2. Robertson G, Robson SJ. Excisional Treatment of Cervical Dysplasia in Australia 2004–2013: A Population-Based Study. J Oncol. 2016;2016.
3. Hammer A, Mejlgaard E, Gravitt P, Høgdall E, Christiansen P, Steiniche T, Blaakær J. HPV genotype distribution in older Danish women undergoing surgery due to cervical cancer. Acta Obstet Gynecol Scand. 2015;94(11):1262-8.
4. Paraskevaidis E, Athanasiou A, Paraskevaidi M, Bilirakis E, Galazios G, Kontomanolis E, et al. Cervical pathology following HPV vaccination in Greece: a 10-year HeCPA observational cohort study. In Vivo. 2020;34(3):1445-9.
5. Shibata T, Takata E, Sakamoto J, Shioya A, Yamada S, Takakura M, Sasagawa T. A retrospective study of immunotherapy using the cell wall skeleton of Mycobacterium bovis Bacillus Calmette-Guérin (BCG-CWS) for cervical cancer. Medicine. 2022;101(52).
6. Lonky NM, Xu L, Da Silva DM, Felix JC, Chao C. Human papillomavirus vaccination history and diagnosis of cervical intraepithelial neoplasia grade≥ 2 severe lesions among a cohort of women who underwent colposcopy in Kaiser Permanente Southern California. Am J Obstet Gynecol. 2021;225(6):656. e1-. e11.
7. Ghelardi A, Marrai R, Bogani G, Sopracordevole F, Bay P, Tonetti A, et al. Surgical treatment of vulvar HSIL: adjuvant HPV vaccine reduces recurrent disease. Vaccines. 2021;9(2):83.
8. Haupt RM, Wheeler CM, Brown DR, Garland SM, Ferris DG, Paavonen JA, et al. Impact of an HPV6/11/16/18 L1 virus-like particle vaccine on progression to cervical intraepithelial neoplasia in seropositive women with HPV16/18 infection. Int J Cancer. 2011;129(11):2632-42.

Wrong intervention (n=26)

1. Salvadó A, Miralpeix E, Solé-Sedeno JM, Kanjou N, Lloveras B, Duran X, Mancebo G. Predictor factors for conservative management of cervical intraepithelial neoplasia grade 2: Cytology and HPV genotyping. Gynecol Oncol. 2021; 162(3):569-74.
2. Foster L, Robson SJ. Association between a national quality improvement program and excisional treatment of cervical dysplasia in Australia. J Obstet Gynecol Res. 2018;44(11):2085-90.
3. Park Y-C, Ouh Y-T, Sung M-H, Park H-G, Kim T-J, Cho C-H, et al. A phase 1/2a, dose-escalation, safety and preliminary efficacy study of oral therapeutic vaccine in subjects with cervical intraepithelial neoplasia 3. J Gynecol Oncol. 2019;30(6).
4. Hallez S, Simon P, Maudoux F, Doyen J, Noël J-C, Beliard A, et al. Phase I/II trial of immunogenicity of a human papillomavirus (HPV) type 16 E7 protein–based vaccine in women with oncogenic HPV-positive cervical intraepithelial neoplasia. Cancer Immunol Immunother. 2004;53:642-50.
5. Harper DM, Nieminen P, Donders G, Einstein MH, Garcia F, Huh WK, et al. The efficacy and safety of Tipapkinogen Sovacivec therapeutic HPV vaccine in cervical intraepithelial neoplasia grades 2 and 3: Randomized controlled phase II trial with 2.5 years of follow-up. Gynecol Oncol. 2019;153(3):521-9.
6. Kim TJ, Jin H-T, Hur S-Y, Yang HG, Seo YB, Hong SR, et al. Clearance of persistent HPV infection and cervical lesion by therapeutic DNA vaccine in CIN3 patients. Nat Commun. 2014;5(1):5317.
7. Trimble CL, Morrow MP, Kraynyak KA, Shen X, Dallas M, Yan J, et al. Safety, efficacy, and immunogenicity of VGX-3100, a therapeutic synthetic DNA vaccine targeting human papillomavirus 16 and 18 E6 and E7 proteins for cervical intraepithelial neoplasia 2/3: a randomised, double-blind, placebo-controlled phase 2b trial. Lancet. 2015;386(10008):2078-88.
8. Kuroki LM, James-Nywening L, Wu N, Liu J, Powell MA, Thaker PH, Massad LS. High-grade cervical dysplasia after negative loop electrosurgical excision procedure. J Low Genit Tract Dis. 2016;20(4):300.
9. Grześ B, Heimrath J, Ciszek M. Minimally invasive surgery with the complementing immunotherapy in the treatment of intraepithelial neoplasia of cervix in women of child-bearing age. Onkol Pol. 2011;14:125-30.
10. Morrow MP, Kraynyak KA, Sylvester AJ, Dallas M, Knoblock D, Boyer JD, et al. Clinical and immunologic biomarkers for histologic regression of high-grade cervical dysplasia and clearance of HPV16 and HPV18 after immunotherapy. Clin Cancer Res. 2018;24(2):276-94.
11. Pruski D, Przybylski M, Millert-Kalinska S, Zmaczynski A, Jach R. Histopathological discrepancies between colposcopy-directed biopsy and LEEP-conization observed during SARS-CoV-2 pandemic. Ginek Pol. 2023;94(1):12-8.
12. Tinelli A, Guido M, Zizza A, Pellegrino M, Greco M, Vergara D, et al. The mRNA-HPV test utilization in the follow up of HPV related cervical lesions. Curr Pharm Des. 2013;19(8):1458-65.
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14. Santa María-Ortiz J, Álvarez-Silvares E, Bermúdez-González M, Lavandeira SG, Mosquera MP, Cambeiro BC. Importance of surgical margins affected in cervical uterine conization. Ginec Obstet México. 2020;88(09):586-97.
15. Alvarez RD, Huh WK, Bae S, Lamb Jr LS, Conner MG, Boyer J, et al. A pilot study of pNGVL4a-CRT/E7 (detox) for the treatment of patients with HPV16+ cervical intraepithelial neoplasia 2/3 (CIN2/3). Gynecol Oncol. 2016;140(2):245-52.
16. García-Espinosa B, Nieto-Bona M, Rueda S, Silva-Sánchez LF, Piernas-Morales M, Carro-Campos P, et al. Genotype distribution of cervical human papillomavirus DNA in women with cervical lesions in Bioko, Equatorial Guinea. Diag Pathol. 2009;4:1-8.
17. Kang WD, Kim SM. Human papillomavirus genotyping as a reliable prognostic marker of recurrence after loop electrosurgical excision procedure for high-grade cervical intraepithelial neoplasia (CIN2-3) especially in postmenopausal women. Menopause. 2016;23(1):81-6.
18. Frazer IH, Quinn M, Nicklin JL, Tan J, Perrin LC, Ng P, et al. Phase 1 study of HPV16-specific immunotherapy with E6E7 fusion protein and ISCOMATRIX™ adjuvant in women with cervical intraepithelial neoplasia. Vaccine. 2004;23(2):172-81.
19. Huang HJ, Tung HJ, Yang LY, Chao A, Tang YH, Chou HH, et al. Role of human papillomavirus status after conization for high-grade cervical intraepithelial neoplasia. Int J Cancer. 2021;148(3):665-72.
20. Bagarazzi ML, Yan J, Morrow MP, Shen X, Parker RL, Lee JC, et al. Immunotherapy against HPV16/18 generates potent TH1 and cytotoxic cellular immune responses. Sci Trans Med. 2012;4(155):155ra38-ra38.
21. Bhuyan PK, Dallas M, Kraynyak K, Herring T, Morrow M, Boyer J, et al. Durability of response to VGX-3100 treatment of HPV16/18 positive cervical HSIL. Hum Vaccin Immunother. 2021;17(5):1288-93.
22. Byun JM, Jeong DH, Kim YN, Jung EJ, Lee KB, Sung MS, Kim KT. Persistent HPV-16 infection leads to recurrence of high-grade cervical intraepithelial neoplasia. Medicine. 2018;97(51).
23. Harper DM, Nieminen P, Donders G, Einstein MH, Garcia F, Huh WK, et al. The efficacy and safety of Tipapkinogen Sovacivec therapeutic HPV vaccine in cervical intraepithelial neoplasia grades 2 and 3: Randomized controlled phase II trial with 2.5 years of follow-up. Gynecol Oncol. 2019;153(3):521-9.
24. Einstein M, Roden R, Ferrall L, Chang Y-N, Blomer A, Wu T, Ma MJ. Safety run-in of intramuscular pNGVL4a-Sig/E7 (detox)/HSP70 and TA-CIN vaccination as the treatment for HPV16 (+) ASCUS, ASC-H, LSIL/CIN-1 (315). Gynecol Oncol. 2022;166:S165.
25. de Vos van Steenwijk PJ, Ramwadhdoebe TH, Löwik MJ, van der Minne CE, Berends-van der Meer DM, Fathers LM, et al. A placebo-controlled randomized HPV16 synthetic long-peptide vaccination study in women with high-grade cervical squamous intraepithelial lesions. Cancer Immunol Immunother. 2012;61:1485-92.
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Protocol or registry entry (n=17)

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Awaiting classification (n=1)

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Post-hoc analysis of RCTs with focus on primary prevention (n=4)

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Annex D. Risk of bias in RCTs (ROB2)

RoB 2 Tool (RCTs).

Study	Randomisation	Deviations from intervention	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall risk of bias
Karimi-Zarchi 2020	Low[1]	Some concerns[2]	High[3]	Low[4]	Some concerns[5]	High
Pieralli 2018	Some concerns[6]	Some concerns[7]	Some concerns[8]	Low[9]	Some concerns[10]	Some concerns

[1]Quote: "Three hundred and twelve women were randomised to the intervention group or the control group through a computer-generated random table of quadruple block numbers (block size of four) [...] One nurse who was not involved in the research prepared the coded envelopes allocated the women into two groups".
[2]Comment: Carers and people delivering the intervention were aware of group assignment. Nine women in the intervention group received one dose of the vaccine only. Therefore, deviations from intended interventions cannot be fully excluded. No appropriate analysis was done.
[3]Comment: Flow chart provided, but missing data differs between groups. Higher dropout rate in control group. No methods to control missing data described (i.e. no appropriate analysis to control for missing data used)
[4]Comment: Method of measuring the outcome probably appropriate. Measurement or ascertainment probably does not differ between groups. The main investigator and the gynaecologist who assessed the outcomes were blinded to the group allocation.
[5]Comment: Registration retrospective, but no protocol available.
[6]Quote: "The randomised numbers were assigned in an unreadable computer file by clinicians and biologists", Comment: Randomisation procedure not sufficiently described and insufficient information regarding baseline differences. Sequence allocation concealed.
[7]Quote: "[…] the study was not blind", Comment: Carers and people delivering the intervention were aware of group assignment. The authors did not mention deviations from intended interventions (unclear and therefore, deviations from intended interventions cannot be fully excluded). Unclear whether or not an appropriate analysis was done.
[8]Comment: Authors did not provide information regarding potential missing data.
[9]Comment: Method of measuring the outcome probably appropriate. Colposcopists, biologists and physicians were blinded.
[10]Comment: No study protocol or registration provided.

Annex E. Risk of bias in NRSI (ROBINS-I)

ROBINS-I Tool (NRSI)

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Prospective cohort study								
Chen 2023	Serious (Confounding variables measured; probably not all relevant confounders considered)	Serious (Allocation based on patient preference)	Low (Vaccination status prospectively retrieved and probably recorded from study team; time points of vaccination alike between participants; participants received probably all scheduled doses; participants received the same vaccine type)	No information (Probably no blinding; no information regarding additional treatments)	Low (Missing data; number of participants with missing outcome data small)	Serious (Unclear blinding of outcome assessments; assessment appropriate and comparable between groups; follow-up time similar between groups)	Serious (No protocol)	**SERIOUS**
Ghelardi 2018	Serious (Confounding variables measured; probably not all relevant confounders considered)	Serious (Allocation based on patient preference)	Moderate (Vaccination status probably prospectively retrieved and probably recorded from study team; time points of vaccination alike between participants; unclear if all participants received all schedules doses; participants received the same vaccine type)	No information (Probably no blinding; no information regarding additional treatments)	Serious (Missing data; reasons for missing participant data insufficiently described)	Serious (Unclear blinding of outcome assessments; assessment appropriate and comparable between groups; follow-up time similar between groups)	Serious (No protocol)	**SERIOUS**
Sand 2019	Serious (Confounding variables measured; age, education and year of conisation different between groups; analysis to control differences described; probably not all relevant confounders considered)	Serious (No information regarding patient allocation, probably patient preferences; sensitivity analysis done for the different years of follow-up)	Moderate (Vaccination status from national database + prescription registry; time points of vaccination differ between participants; vaccine type and doses unclear)	Moderate (No blinding; some women received second conisation, but balanced between groups and adjusted)	Low (Data retrieved from reliable databases that probably have a completed follow up)	Serious (Unclear blinding of outcome assessments; assessment appropriate and comparable between groups; follow-up time similar between groups)	Serious (No protocol)	**SERIOUS**

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Retrospective cohort study								
Bogani 2020	Serious (Confounding variables measured in sample without matching; differences for age, BMI, high risk HPV types, positive margins, and HPV persistence were identified; analysis to control differences described; probably not all relevant confounders considered)	No information (No information regarding patient allocation, probably patient preference; sample retrospectively selected; no information regarding the start of follow-up)	No information (Retrieval of vaccination status unclear; vaccination time points alike between most participants; numbers of doses differ slightly between participants; missing information regarding the dose for some vaccinated participants; most participants received the same vaccine type)	Low (No blinding; secondary conisations were accounted as outcome)	No information	No information (Retrospective study; assessment appropriate and comparable between groups; unclear if follow-up times between groups were comparable)	Serious (No protocol)	**SERIOUS**
Casajuana-Perez 2022	Serious (Confounding variables measured; probably not all relevant confounders considered)	Serious (Allocation probably based on patient preference; sample retrospectively selected; start of follow-up differs between groups)	Serious (Vaccination status retrieved from medical report; time points of vaccination differ between participants; numbers of doses differ slightly between participants; vaccine types differ between participants, unclear numbers)	No information (No blinding; some women received second conisation, unclear if second conisations were accounted as outcome; unclear group distribution of second conisations)	No information (Missing data likely; insufficiently described)	Serious (Retrospective study; assessment appropriate and comparable between groups; follow-up time was different between groups)	Serious (No protocol)	**SERIOUS**
De la Rosa 2021	Critical (Confounding variables measured; difference in age and CIN classes identified; no analysis to control differences described; probably not all relevant confounders considered)	Serious (Allocation based on patient preference; sample retrospectively selected)	Serious (Vaccination status retrieved from medical report; time points of vaccination probably alike between participants; unclear number of doses; vaccine types differ between participants, unclear numbers)	Serious (No blinding; some women received second conisation; unclear numbers)	No information	Moderate (Retrospective study; assessment appropriate and comparable between groups; follow-up time similar between groups)	Serious (No protocol)	**CRITICAL**
Del Pino 2020	Serious (Confounding variables measured; numerical difference in positive margins, but not significant; probably not all relevant confounders considered)	Serious (Allocation based on patient preference; sample retrospectively selected)	Serious (Vaccination status retrieved from medical records; time points of vaccination differ between participants; doses differ between participants; vaccine types differ between participants)	No information (No blinding; some women received second conisation, unclear if second conisations were accounted as outcome; unclear group distribution of second conisations)	No information	Serious (Retrospective study; assessment appropriate and comparable between groups; follow-up time differed between groups)	Serious (No protocol)	**SERIOUS**

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Henere 2022	Critical (Confounding variables measured; HSIL/LSIL and negative surgical specimen diagnosis different between groups and not adjusted; Probably not all relevant confounders considered)	Serious (Allocation based on patient preference; sample retrospectively selected)	Serious (Vaccination status retrieved from medical report; time points of vaccination differ between participants; doses differ between participants; participants received the same vaccine type)	Low (No blinding; secondary conisations were accounted as outcome)	No information	Serious (Retrospective study; not all participants were histologically confirmed; length of follow-up timediffered slightly between groups)	Serious (No protocol)	**CRITICAL**
Kang 2013	Serious (Confounding variables measured; probably not all relevant confounders considered)	Serious (Allocation based on patient preference; sample retrospectively selected)	No information (Vaccination status probably from patient records; time points of vaccination probably alike between participants; unclear if all participants received all schedules doses; participants received the same vaccine type)	No information (No blinding; no information regarding additional treatments)	No information	Moderate (Retrospective study; assessment appropriate and comparable; unclear if follow-up differed between groups)	Serious (No protocol)	**SERIOUS**
Ortega-Quinonero 2018	Serious (Confounding variables measured; numerical difference in age and CIN-Classes but none are significant; probably not all relevant confounders considered)	No information (No information regarding patient allocation, probably patient preference; sample retrospectively selected; start of follow-up similar between groups)	Serious (Reporting of vaccination status unclear; time points of vaccination differ between participants; unclear if all participants received all schedules doses; vaccine types differ between participants	No information (No blinding; no information regarding additional treatments)	No information	Moderate (Retrospective study; assessment appropriate and comparable; unclear if follow-up time differed between groups)	Serious (No protocol)	**SERIOUS**
Petrillo 2020	Serious (Confounding variables measured; age different between groups and not adjusted; probably not all relevant confounders considered)	Serious (Allocation based on patient preference; start of follow-up differs between groups)	No information (Reporting of vaccination status unclear; time points of vaccination alike between participants; unclear if all participants received all schedules doses; the majority participants received the same vaccine type)	No information (No blinding; no information regarding additional treatments)	Serious (Participant data missing; reasons insufficiently described)	Moderate (Retrospective study; assessment appropriate and comparable, unclear if follow-up differed between groups)	Serious (No protocol)	**SERIOUS**

Annex F. Outcome data at study level

Study	Age, y	Time of vaccination (before/after conisation)	Outcome measure	Time of outcome measurement (months after conisation)	Vaccine N Events/Total	No Vaccine N Events/Total
RCTs						
Karimi-Zarchi 2020	32.6±4.9	At conisation	CIN 2+ (CIN 2-3)	24	23/138	41/104
			Invasive cervical cancer		0/138	1/104
			Vaccine related AE (redness, headache, rash)		129/138	-
Pieralli 2018	32 (23-44)	After	CIN 2+	36	0/89	4/89
			CIN 2+ (HPV 16/18)		0/89	4/89
			VIN 2+ / VaIN 2+		0/89	0/89
NRSI: prospective design						
Chen 2023	20 - 45	After	CIN 2+	30	3/148	29/273
			CIN 2+ (HPV 16/18)		2/148	13/273
			Persistent HPV infection		12/148	43/273
Ghelardi 2018	18 - 45	After	CIN 2	≥24; 36 (median)	1/172	5/172
			CIN 2+		2/172	11/172
			CIN 2+ (HPV 16/18)		0/172	9/172
			CIN 3		1/172	6/172
			CIN 3+		1/172	6/172
			CIN 3+ (HPV 16/18)		0/172	5/172
			Persistent HPV infection	6	26/172	32/172
			Persistent HPV infection (HPV 16/18)		16/172	17/172
Sand 2019	30 (17-51)	Before+after (80%)	CIN 2	≥12‡	37/2 074	354/15 054
			CIN 2+		82/2 074	777/15 054
			CIN 3		43/2 074	406/15 054
			Cervical cancer		2/2 074	17/15 054
			Mortality		3/2 074	42/15 054
NRSI: retrospective design						
Bogani 2020	33.4 (24-44)	After	CIN 2+ (HSIL)	>60	2/100	11/200
Casajuana-Perez 2022	36.9±8.2	Before+after (70%)	CIN 2+	33.1 (17.6)	12/277	28/286
			CIN 2+ (HPV 16/18)		8/277	11/286
			Persistent HPV infection (HPV 16/18)		27/277	28/286
De la Rosa 2021	37.5 ±7.9	After	CIN 2+ (CIN 2-3)	48	4/160	16/171
Del Pino 2020	39.8±10.3	After (90%)	CIN 2+ (CIN 2-3/HSIL)	I: 18.5 (10.3-77.2)	5/153	12/112
			CIN 2+ (HPV 16/18)	C: 24.3 (8-59.9)	2/153	5/112
Henere 2022	40.8±10.28	Before+after (65%)	CIN 2+**	6.1 (2.1)	5/306	4/92
			Persistent/incident HPV infection		115/306	38/92
			CIN 2+	20.2 (10.6)	6/306	6/92
			CIN 2+ (HPV 16/18)		3/306	1/92
			Persistent/incident HPV infection		58/306	17/92
Kang 2013	36.7±5.8	After	CIN 2+ (CIN 2-3)	42 (median)	9/360	27/377
			CIN 2+ (CIN 2-3, HPV 16/18)		5/360	18/377
Ortega-Quinonero 2018	I: 33 (28-38) C: 39 (31-50)	Before+after (50%)	CIN 2+	14.2 (6-24)	5/103	22/139
			CIN 2+ (HPV 16/18)		3/103	15/139
Petrillo 2020	I: 39 (30-44) C: 41 (36-49)	After	CIN 2	≥24	4/182	6/103
			CIN 2+		6/182	14/103
			CIN 3		1/182	8/103
			CIN 3+		2/182	8/103

AE: Adverse event, C: Control group (no vaccine or placebo vaccine), CIN: Cervical Intraepithelial Neoplasia, HPV: (High-Risk) Human Papillomavirus (diagnosed by HPV testing), HSIL: High-grade Squamous Intraepithelial Lesions (cytological diagnosis), I: Intervention group (HPV vaccine), N: Number, NR: Not reported, RCT: Randomised controlled trial, VaIN: Vaginal intraepithelial neoplasia, VIN: Vulvar intraepithelial neoplasia, Y: Years

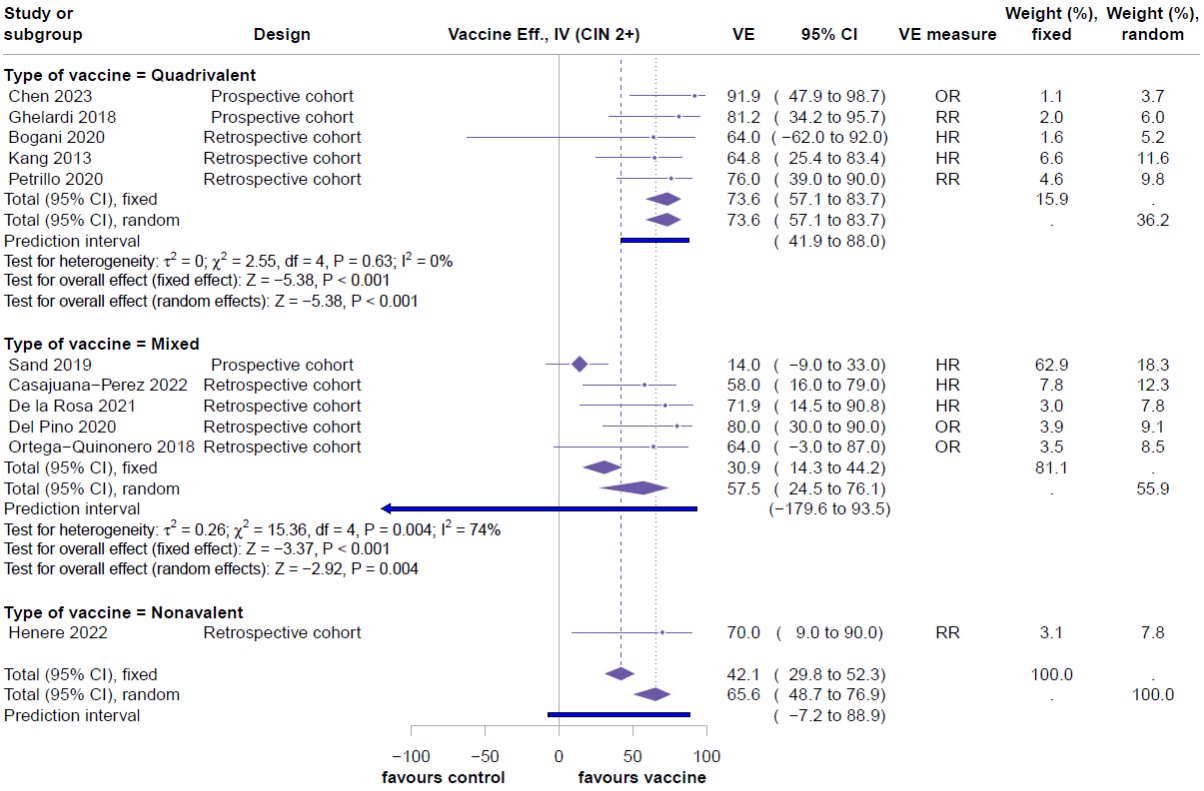
** The 129 events include two events classified as "severe allergies due to vaccine".*

***Defined as second conisation, recurrent/persistent.*

‡ Follow-up was starting 12 months after conisation.

Annex G. Subgroup analysis (CIN 2+)

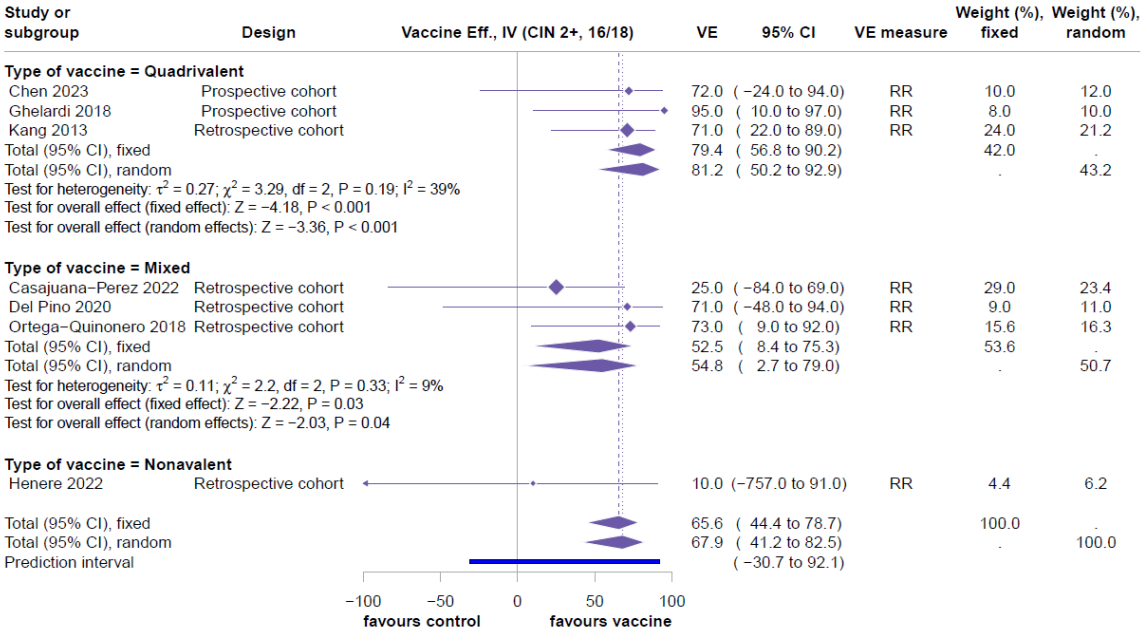
Type of vaccine



Test for heterogeneity: τ^2=0.21; χ^2=31.96, df=10, P < 0.001; I^2=69%
Test for overall effect (fixed effect): Z = −5.55, P < 0.001
Test for overall effect (random effects): Z = −5.24, P < 0.001
Test for subgroup differences (fixed effect): χ^2 = 14.05, df = 2, P < 0.001
Test for subgroup differences (random effects): χ^2 = 1.55, df = 2 P = 0.46

Annex H. Subgroup analysis (CIN 2+, HPV 16/18)

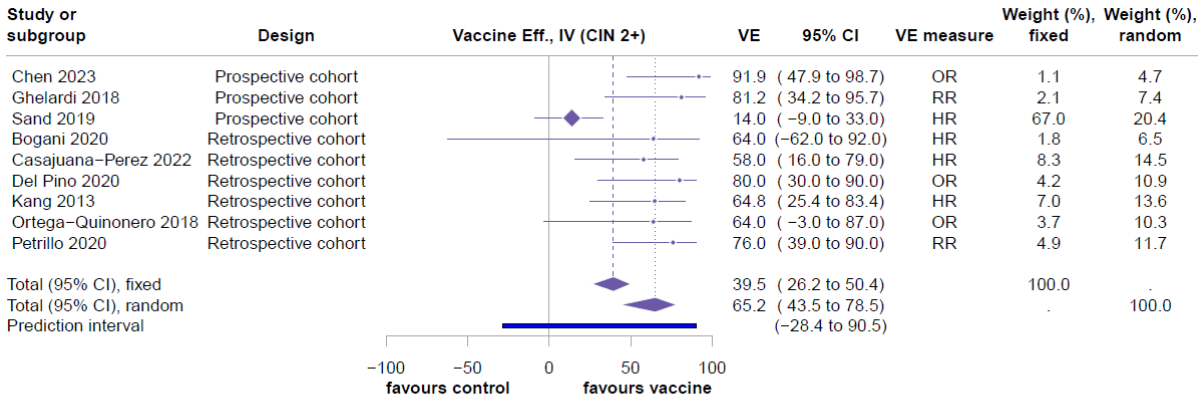
Type of vaccine



Test for heterogeneity: τ^2=0.20; χ^2=8.95, df=6, P=0.18; I^2=33%
Test for overall effect (fixed effect): Z = −4.36, P < 0.001
Test for overall effect (random effects): Z = −3.68, P < 0.001
Test for subgroup differences (fixed effect): χ^2 = 3.46, df = 2, P = 0.18
Test for subgroup differences (random effects): χ^2 = 2.65, df = 2 P = 0.27

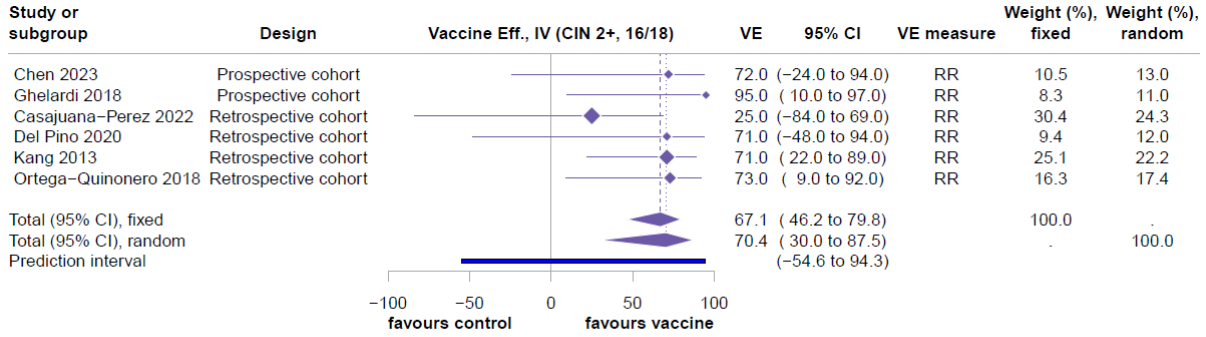
Annex I. Sensitivity analysis (studies with critical risk of bias excluded)

CIN 2+



Test for heterogeneity: τ^2=0.25; χ^2=28.79, df=8, P < 0.001; I^2=72%
Test for overall effect (fixed effect): Z = −4.94, P < 0.001
Test for overall effect (random effects): t_8 = −5.04, P = 0.001

CIN 2+, HPV 16/18



Test for heterogeneity: τ^2=0.24; χ^2=8.24, df=5, P=0.14; I^2=39%
Test for overall effect (fixed effect): Z = −4.44, P < 0.001
Test for overall effect (random effects): t_5 = −3.64, P = 0.01

Annex J. Overview of post-hoc analyses of RCTs

We identified four post-hoc analyses from RCTs data with vaccination at randomisation before the development of the disease. Study characteristics, bias assessment and results are presented below:

Key study characteristics

Study characteristics				Patient characteristics			Intervention			Control
Author, Year	Country, recruitment time	Follow-up time (months after conisation)	N total (I/C)	Age, y median (range), mean±SD	Type of (precancerous) lesion and information on prior HPV vaccination status	Conisation procedure	Time of vaccination (1st dose)	Doses of vaccination	Type of vaccination	
Post-hoc analysis of RCTs										
Garland 2016 (59) (pharmaceutical funding)	Multinational (14 countries) 05/04 – 06/05	NR§	454 (190/264)	21.1±4.1	**Vaccine (190) vs. Placebo (264)** (characteristics at RCT enrollment are provided, not at conisation) **Vaccination at randomisation before the development of the disease**	LEEP, CKC (no other details)	**Before conisation** 19.1 (1.5-46.5)	3 doses (no other details)	Bivalent (100%)	Placebo (Hepatitis A)
Hildesheim 2016 (60) (public + pharmaceutical funding)	Costa Rica 06/04 – 12/05	27.3 (median)	311 (142/169)	18 – 25	**Vaccine (142) vs. Placebo (169)** (characteristics at RCT enrollment are provided, not at conisation) **Vaccination at randomisation before the development of the disease**	LEEP (100%)	**Before conisation** 28.2 (median)	3 doses: 80% 2 doses: 12.4% 1 dose: 7.4%	Bivalent (100%)	Placebo (Hepatitis A)
Joura 2012 (61) (pharmaceutical funding)	Multinational (24 countries) 12/01 – 05/03	NR	1 350 (587/763)	19.9±2.0	**Vaccine (587) vs. Placebo (763)** (characteristics at RCT enrollment are provided, not at conisation) **Vaccination at randomisation before the development of the disease**	LEEP (84.7%), CKC (12.5%), other (2.8%)	**Before conisation** no other details	3 doses: 99.7% 2 doses: 0.3% 1 dose: 0%	Quadrivalent (100%)	Placebo (aluminum hydroxyl-phosphate)
Zhao 2020 (51) (public + pharmaceutical funding)	China 10/08 – NR	50 (median)	168 (86/80)	18 – 25	**Vaccine (86) vs. Placebo (80)** (characteristics at RCT enrollment are provided, not at conisation) **Vaccination at randomisation before the development of the disease**	LEEP, CKC (no other details)	**Before conisation** 17 (4.0- 30.0)	3 doses (no other details)	Bivalent (100%)	Placebo (aluminum hydroxide)

C: Control group (no vaccine or placebo vaccine), CKC: Cold knife conisation, HPV: (High-Risk) Human Papillomavirus (diagnosed by HPV testing), HSIL: High-grade Squamous Intraepithelial Lesions (cytological diagnosis), I: Intervention group (HPV vaccine), LEEP: Loop electrosurgical excision procedure, N: Number, NR: Not reported, RCT: Randomised controlled trial, Y: Years
§Unclear if mean or median.

Risk of bias (ROBINS-I)

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Post-hoc analysis of RCTs								
Garland 2016	Critical (No sufficient information on confounding; however, authors describe that baseline criteria were not comparable; no analysis to control differences described; probably not all relevant confounders considered)	Serious (Allocation not random due to post-hoc design; start of follow-up differs between groups)	Moderate (Vaccination status retrieved from study report; time points of vaccination alike between participants; unclear if all participants received all scheduled doses; the report of primary study indicates that number of scheduled doses differed between participants; participants received the same vaccine type)	No information (Unclear blinding; in the study report of the primary study and the registry entry only investigators and participants are described to be blinded; no information regarding additional treatments)	No information	Serious (Outcome assessments probably blinded; assessments appropriate and comparable between groups; follow-up times differ between groups)	Critical (Post hoc analysis, not prospectively defined)	**CRITICAL**
Hildesheim 2016	Serious (Confounding variables measured; lifetime partner and cytology show numeric differences; no analysis to control differences described; probably not all relevant confounders considered)	Serious (Allocation not random due to post-hoc design; start of follow-up differs between groups)	Moderate (Vaccination status retrieved from study report; time points of vaccination probably alike between participants; unclear if all participants received all scheduled doses; the report of primary study indicates that number of scheduled doses differed between participants; participants received the same vaccine type)	Low (Study team, participants and outcome assessors probably blinded; therefore, no relevant deviations from intended interventions are expected)	No information	Serious (Outcome assessments blinded; assessment appropriate and comparable between groups; follow-up times differ between groups)	Critical (Post hoc analysis, not prospectively defined)	**CRITICAL**
Joura 2012	Serious (Confounding variables measured; probably not all relevant confounders considered)	Moderate (Allocation not random due to post-hoc design; start of follow-up differs slightly between groups)	Low (Vaccination status retrieved from study report; time points of vaccination alike between participants; the majority of participants received all scheduled doses, participants received the same vaccine type)	No information (Unclear blinding; in the study report of the primary study and registry entry state only investigators and participants are blinded; no information regarding additional treatments)	No information	Moderate (Unclear blinding of outcome assessments; assessment appropriate and comparable between groups; follow-up alike between groups)	Critical (Post hoc analysis, not prospectively defined)	**CRITICAL**

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Zhao 2020	Serious (Confounding variables measured; probably not all relevant confounders considered)	Moderate (Allocation not random due to post-hoc design; start of follow-up probably similar between groups group)	Moderate (Vaccination status retrieved from study report; time points of vaccination alike between participants; unclear if all participants received scheduled doses; based on the report of the primary study, not all participants received all scheduled doses; participants received the same vaccine type)	Low (Participants, care provider, investigator, outcomes Assessor blinded; therefore, no relevant deviations from intended interventions are expected)	Moderate (Missing data; number of participants with missing outcome comparable between groups)	Low (Outcome assessments blinded; assessment appropriate and comparable between groups; follow-up time similar between groups)	Critical (Post hoc analysis, not prospectively defined)	**CRITICAL**

Outcome data at study level of excluded post-hoc analysis of RCTs with focus on primary prevention

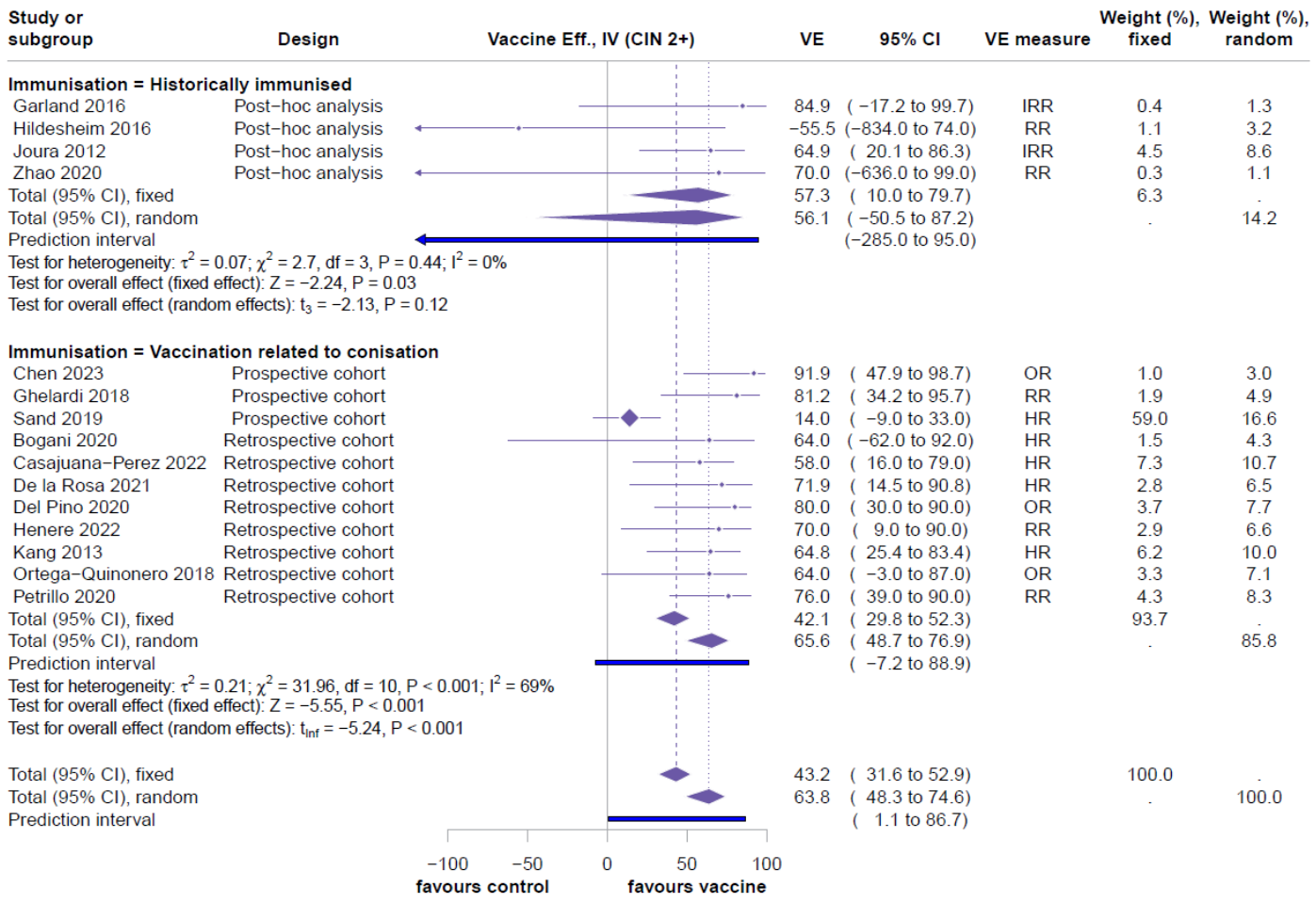
Study	Age, y	Time of vaccination	Outcome measure	Time of outcome measurement (months after conisation)	Vaccine N Events/Total	No Vaccine N Events/Total
Post-hoc analysis of RCTs						
Garland 2016	21.1±4.1	Before the development of the disease for primary prevention (unclear how many months or years the women received the vaccine prior to conisation due to cervical lesions)	CIN 2	NR	1/190	9/264
			CIN 2+		1/186	7/249
			CIN 2+ (HPV 16/18)		0/186	2/250
			VIN 2+		0/190	0/264
			VaIN 2+		1/190	1/264
Hildesheim 2016	18-25		CIN 2+	I: 31.8 (19.6-39.8) C: 23.9 (11.5-39.8)	3/142	2/169
			CIN 2+ (HPV 16/18)		3/142	1/169
			Persistent HPV infection (HPV 16/18)		4/142	6/169
			Incident HPV infection (HPV 16/18)		4/142	8/169
Joura 2012	19.9±2.0		CIN 2	NR	5/474	13/592
			CIN 2+		8/474	26/592
			CIN 2+ (HPV 16/18 + 6/11)		1/474	3/592
			CIN 3+		3/474	13/592
			CIN 3+ (HPV 16/18)		0/474	0/592
			VIN 2+ / VaIN 2+		3/474	5/589

Study	Age, y	Time of vaccination	Outcome measure	Time of outcome measurement (months after conisation)	Vaccine N Events/Total	No Vaccine N Events/Total
Zhao 2020	18-25		CIN 2	50	0/80	1/73
			CIN 2+		0/80	1/73
			CIN 2+ (HPV 16/18)		0/80	1/73
			CIN 3		0/80	0/73
			CIN 3+		0/80	0/73
			CIN 3+ (HPV 16/18)		0/80	0/73
			AIS		0/80	0/73
			Invasive cervical cancer		0/80	0/73
			Persistent HPV infection		inconclusive	
			Incident HPV infection		inconclusive	
			VaIN 2+		1/80	0/73

AIS: Adenocarcinoma in situ, C: Control group (no vaccine or placebo vaccine), CIN: Cervical Intraepithelial Neoplasia, HPV: (High-Risk) Human Papillomavirus (diagnosed by HPV testing), I: Intervention group (HPV vaccine), N: Number, NR: Not reported, RCT: Randomised controlled trial, VaIN: Vaginal intraepithelial neoplasia, VIN: Vulvar intraepithelial neoplasia, Y: Years

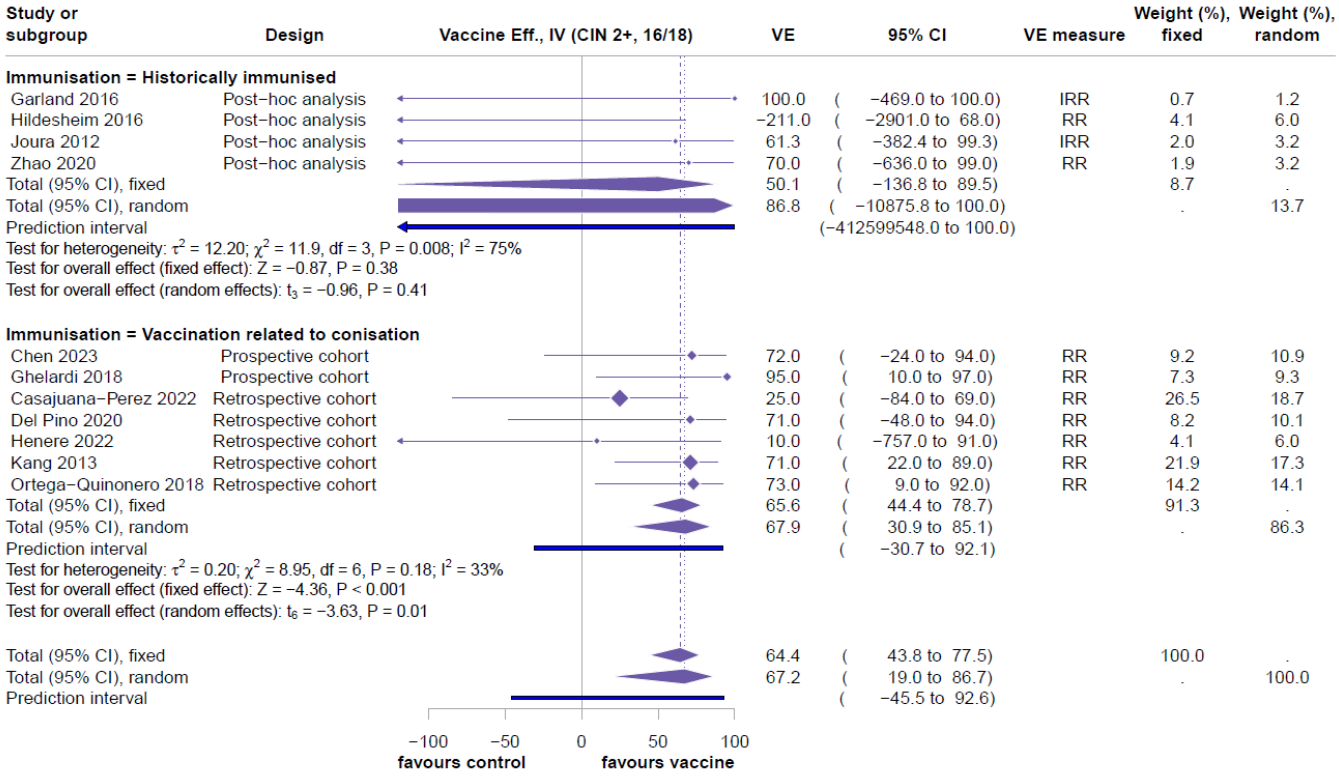
Effects of interventions for outcome CIN 2+ post-hoc analysis of RCTs (vaccination before the development of the disease) compared to the effects of studies providing vaccination related to conisation

A. CIN 2+



Test for heterogeneity: τ^2=0.18; χ^2=35.26, df=14, P=0.001; I^2=60%
Test for overall effect (fixed effect): Z = −5.94, P < 0.001
Test for overall effect (random effects): t_{Inf} = −5.59, P < 0.001
Test for subgroup differences (fixed effect): χ^2 = 0.60, df = 1, P = 0.44
Test for subgroup differences (random effects): χ^2 = 0.31, df = 1 P = 0.58

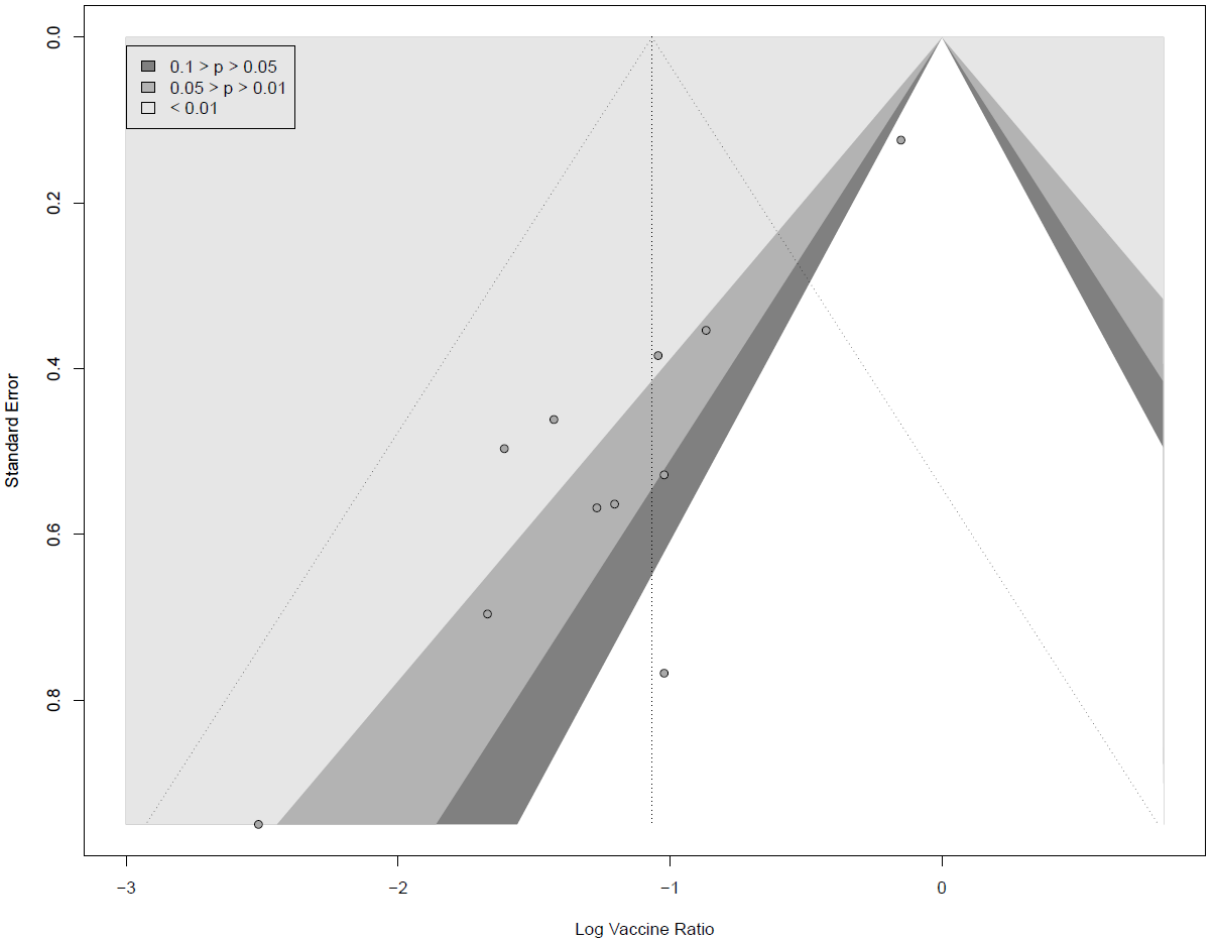
B. CIN 2+, HPV 16/18



Test for heterogeneity: τ^2=0.33; χ^2=21.06, df=10, P=0.02; I^2=53%
Test for overall effect (fixed effect): Z = −4.42, P < 0.001
Test for overall effect (random effects): t_{10} = −2.75, P = 0.02
Test for subgroup differences (fixed effect): χ^2 = 0.20, df = 1, P = 0.65
Test for subgroup differences (random effects): χ^2 = 0.17, df = 1 P = 0.68

Annex K. Funnel plot

Funnel plot for the outcome CIN 2+ (irrespective of HPV type) (HPV vaccine vs. no intervention, 11 studies)



The horizontal scale of the funnel plot presents the effect sizes of the individual study included in the analysis and is plotted against the study size on the vertical axis (plotted on a logarithmic scale). The true intervention effect ratio is presented as the dashed vertical line (random-effect model). The outer dashed lines indicate the triangular region within 95% of studies are expected to lie using the random-effect model [69].

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