

RESEARCH ARTICLE

Effect of human papillomavirus (HPV) vaccination on HPV infection and recurrence of HPV related disease after local surgical treatment: A systematic review and meta-analysis

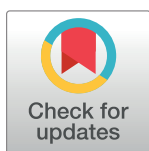
Qinxue Cao¹, Yantao Hou², Chaoyang Wang^{3†*}, Juntao Yin^{4†*}

1 Department of Obstetrics and Gynecology, Huaihe Hospital, Henan University, Henan, China, **2** Henan Technical Institute, School of Mechanical and Electrical Engineering, Zhengzhou, China, **3** Department of General Surgery, Huaihe Hospital, Henan University, Henan, China, **4** Department of Pharmacy, Huaihe Hospital, Henan University, Henan, China

☞ These authors contributed equally to this work.

‡ These authors also contributed equally to this work.

* yinjuntao811@163.com (JY); wangcy202402@126.com (CW)



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Citation: Cao Q, Hou Y, Wang C, Yin J (2024) Effect of human papillomavirus (HPV) vaccination on HPV infection and recurrence of HPV related disease after local surgical treatment: A systematic review and meta-analysis. PLoS ONE 19(12): e0312128. <https://doi.org/10.1371/journal.pone.0312128>

Editor: Mehmet Demirci, Kırklareli Üniversitesi, TÜRKİYE

Received: August 15, 2024

Accepted: October 1, 2024

Published: December 31, 2024

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Data Availability Statement: All relevant data are within the paper and its [Supporting Information](#) files.

Funding: This research was funded by grant from Science and Technology Department of Henan Province (Award Number 112102310306). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Abstract

Background

The prophylactic vaccines available to protect against infections by human papillomavirus (HPV) are well tolerated and highly immunogenic. This systematic review and meta-analysis aimed to explore the efficacy of HPV vaccination on the risk of HPV infection and recurrent diseases related to HPV infection in individuals undergoing local surgical treatment.

Methods

A literature search was performed using PubMed/MEDLINE, Embase, the Cochrane Library, Scopus, Web of Science, and bioRxiv/medRxiv from inception to July 15, 2024. Randomized controlled trials (RCTs) reporting the effect of HPV vaccination on HPV infection and recurrence of HPV related disease after local surgical treatment vs no HPV vaccination were included. The primary outcome measure was risk of recurrence cervical high-grade squamous intraepithelial lesion (HSIL) after local surgical treatment, with follow-up as reported by individual studies. Included studies were assessed for risk of bias using the Revised Cochrane risk-of-bias (RoB 2.0 tool). Pooled risk ratios (RR) and 95% confidence intervals (CI) were calculated. No restrictions were applied on language, the date of publication, age, sex, and country. All analyses were carried out using the Review Manager 5 software (version 5.4).

Results

Eight RCTs (n = 3068) met the inclusion criteria. The risk of cervical HSIL recurrence was not reduced in individuals who were vaccinated compared with those who were not

Competing interests: The authors have declared that no competing interests exist.

vaccinated (RR 0.92, 95% CI: 0.66–1.27; $I^2 = 40\%$). However, HPV vaccination reduced the risk of recurrence of cervical HSIL related to the HPV types HPV16/18, but uncertainty was large (RR 0.57, 95% CI: 0.18–1.84; $I^2 = 29\%$).

Conclusions

Adjuvant HPV vaccination after surgical excision is not associated with a reduced risk of recurrent HSIL overall or a reduced risk of recurrent lesions caused by the most oncogenic strains (HPV16/18). Therefore, HPV vaccination should not be considered for adjuvant treatment in patients undergoing surgical excision.

Introduction

With the vaccination of human papillomavirus (HPV) vaccines, cervical cancer prophylaxis has been revolutionized [1]. Cervical cancer could be virtually eliminated by increasing HPV vaccines coverage and efforts to improve cervical cancer screening [2]. HPV vaccines can prevent HPV infection and related diseases in children before puberty, but cannot eliminate existing lesions and are ineffective against already existing lesions caused by HPV [3–7].

Women undergoing local surgery for cervical high-grade squamous intraepithelial lesion (HSIL) have been identified as a target high-risk population, and can benefit from vaccination with adjuvant vaccines to prevent cervical cancer. Cervical HSILs are the precursor condition to cervical cancer [8]. Patients with cervical HSIL on a cervical biopsy followed by a negative conization specimen are particularly susceptible to HPV infection and may be reinfected quickly [8,9]. These women are also at high risk of recurrent cervical HSIL and other malignancies associated with HPV infection [10–12], and repeated conisations may carry an increased risk of adverse reproductive outcomes [13–16].

The VENUS study demonstrates that HPV vaccination elicits a stronger immune response than natural infection [17]. Natural immunity from induced antibodies appears to weaken with the passage of time, while it was reported that vaccines can provide protection against reinfection or reactivation in seropositive individuals with prior clearance of the infection [18–20]. This vaccination may confer beneficial effects against new infections and reinfections from the same HPV type shortly after treatment, although this effect is unlikely to promote the clearance of an established infection in isolation. The potential of the vaccine to enhance the efficacy of local surgical treatment and promote viral clearance remains unknown.

Evidence of the efficacy of vaccination against human papillomavirus after conization is inconsistent. Two randomized controlled trials (RCTs) showed a reduced recurrence rate of cervical HSIL [21,22]. However, other studies reached contrary conclusions and suggested no benefit [23–25].

This meta-analysis aimed to assess the effect of HPV vaccines on the risk of HPV infection and recurrence of preinvasive disease related to HPV infection after local surgical treatment for cervical diseases.

Materials and methods

Protocol and registration

This systematic review was registered with the International prospective register of systematic reviews (PROSPERO, CRD42024512507), and was conducted in strict accordance with the

recommendations of the Cochrane Handbook [26] and the updated Preferred Reporting Items for Systematic Reviews of Interventions (PRISMA) guidelines [27].

Eligibility criteria

When the outcomes of the same studies were reported in different publications, the study with the largest sample size was enrolled in this meta-analysis. Inclusion criteria were predetermined and organized in accordance with the PICOS acronym: Participants (P): patients with cervical HSIL who have undergone local surgical treatment; Intervention (I): HPV vaccine; Control (C): no HPV vaccine; Outcomes (O): recurrence of cervical HSIL after local surgery related to HPV; recurrence of cervical LSIL, and cervical HSIL related to HPV16/18 types; and HPV infections after treatment; and Study design (S): included only RCTs. Cohort studies, matched case-control series, reviews, and studies lacking of information on outcomes, were excluded. No restrictions were imposed on language, the date of publication, age, sex, and country.

The study included all RCTs that reported HPV infection rates or recurrence of diseases related to HPV infection after local surgery for genital diseases related to HPV in vaccinated individuals. And only those studies that also reported the results of an unvaccinated cohort as control group were enrolled in this review. No restrictions were imposed on language, region, publication time, participant demographics, or publication status. Studies were enrolled independent of surgical technique, type of vaccine, and timing of vaccination.

Search strategy

A comprehensive literature search was conducted in PubMed/Medline, EMBASE, the Cochrane Library databases, Scopus, Web of Science, and bioRxiv/medRxiv (from inception to July 15, 2024). Two independent reviewers (QXC and JTY) formulated the search strategy and screened the studies. The Cochrane-validated filter for randomized controlled trials was applied [28]. The search strategy was adjusted based on descriptors in each database. In addition, references of all included studies were also manually searched to determine any potentially qualified studies.

Study screening and selection

Two authors (Q.X.C. and C.Y.W.) performed independently the screening and selection of the studies. The inconsistencies were resolved by a third author (J.T.Y.). The first step was to import the research papers from the designated database into EndNote X20 and deleted the duplicate items. After excluding irrelevant studies by evaluating their titles and abstracts, the full texts of the studies were read. If the information of studies located in databases was incomplete, the corresponding author was contacted by data extractors (J.T.Y. and C.Y.W.) via email for relevant information.

Data extraction

If the studies met the eligibility criteria, data were extracted by two independent investigators (Q.X.C. and C.Y.W.) in a prespecified data extraction form. The data extraction form included the following items: the first author's name, the publication year, the region in which the study was conducted, the mean age of the participants, type of vaccine, Vaccination timing, Follow-up duration, outcomes, recurrence, and associated factors were all included in the data extraction form.

Quality assessment

Risk of bias was evaluated by two investigators independently (QXC and CYW) according to the updated Cochrane risk-of-bias tool (RoB-2.0 tool) for randomized controlled trials [29,30]. Disagreements between investigators were discussed or solved by a third investigator (JTY).

Definitions of outcomes

The primary outcome was recurrence of cervical HSIL after local surgery related to HPV. Secondary outcomes included cervical HSIL related to HPV16/18 types, recurrence of cervical LSIL, and HPV infections after treatment.

Statistical analysis

The data from randomized controlled trials were pooled, which reported the effect of vaccination shortly before, at the time of, or within 12 months after the local surgery. We used crude data for the primary outcome, and sensitivity and subgroup analyses.

We estimated each pooled effect size by using risk ratio (RR) and corresponding 95% confidence interval (CI) with a fixed- or random- effect model based on the Mantel-Haenszel method [31]. Statistical heterogeneity was evaluated using the χ^2 test ($P < 0.10$) and was quantified using I^2 [32,33].

When more than 10 studies reported a certain outcome, visual inspection of the funnel plot and Egger's test were used to evaluate the effects of publication bias [34]. The method of "trim and fill" was adopted to assess the effect of publication bias if publication bias was detected.

To identify possible sources of heterogeneity, a leave-one-out sensitivity analysis [31] was conducted for the primary outcome (risk of recurrence of cervical HSIL after local surgery). A series of subgroup analyses were also carried out to identify sources of heterogeneity and differences in pooled estimates for the primary outcome (risk of recurrence of cervical HSIL after local surgery) based on timing of vaccination (up to three months before vs at the time of or up to 12 months after treatment) and vaccine type (Cervarix vs Gardasil vs Gardasil-9). All statistical analyses were carried out with the Review Manager 5 software (version 5.4).

Results

Characteristics of the included studies

There were 11362 studies were identified. All of them were screened for inclusion by title and abstract assessment, and 10 full-text articles were screened for eligibility. No other studies were retrieved from the reference lists of enrolled studies. Of these, 2 were ruled out because of the study design (not RCT) [35,36]. Thus, 8 studies with 3068 participants, all peer-reviewed studies, met the criteria for inclusion and were included into the review (Fig 1; Table 1) [21,22,24,25,37–40]. All of the 8 studies were assessed as low risk of bias according to the revised Cochrane RoB-2.0 tool (Fig 2).

AIN anal intraepithelial neoplasia, *CIN* cervical intraepithelial neoplasia, *CKC* cold knife conisation, *HPV* human papilloma virus, *HSIL* high-grade squamous intraepithelial neoplasia, *ICC* invasive cervical cancer, *LLETZ* large loop excision of the transformation zone, *LSIL* low-grade squamous intraepithelial neoplasia, *MSM* men who have sex with men, *N/A* not applicable, *RCT* randomised controlled trial, *VIN/VaIN* vulvar intraepithelial neoplasia/vaginal intraepithelial neoplasia.

Recurrence of cervical HSIL

The analysis for risk of recurrence of cervical HSIL after local surgery showed that no significant difference was observed in RR of cervical HSIL recurrence between vaccinated participants at the time of treatment and unvaccinated participants (6 studies, 1376 participants; RR 0.92, 95% CI: 0.66–1.27, $I^2 = 40\%$) (Fig 3). Sensitivity analysis (one-by-one elimination method) showed that all of the six results remained statistically no significant (Table 2).

Subgroup analysis was conducted based on type of vaccine. No significant difference in RR of recurrence of cervical HSIL between the two groups in studies that used the Cervarix vaccine (three studies, 838 participants; RR 1.60, 95% CI: 0.68–3.78, $I^2 = 38\%$), the Gardasil vaccine (two studies, 352 participants; RR 0.53, 95% CI: 0.07–4.23, $I^2 = 58\%$), or the Gardasil-9 vaccine (one studies, 187 participants; RR 0.67, 95% CI: 0.36–1.24; Fig 4).

Another subgroup analysis was carried out by timing of vaccination. Vaccination before treatment did not reduce the risk of recurrence of cervical HSIL, (2 studies, 685 participants; RR 1.23, 95% CI: 0.15–10.10, $I^2 = 67\%$; Fig 5A), nor did vaccination at the time of or after treatment reduce the risk of cervical HSIL recurrence despite the high degree of uncertainty (4 studies, 692 participants; RR 0.81, 95% CI: 0.57–1.15; $I^2 = 12\%$; Fig 5B).

Recurrence of cervical HSIL related to HPV16/18

HPV vaccination did not reduce the risk of cervical HSIL recurrence related to HPV16/18 (4 studies, 1050 participants; RR 0.57, 95% CI: 0.18–1.84, $I^2 = 29\%$; Fig 6).

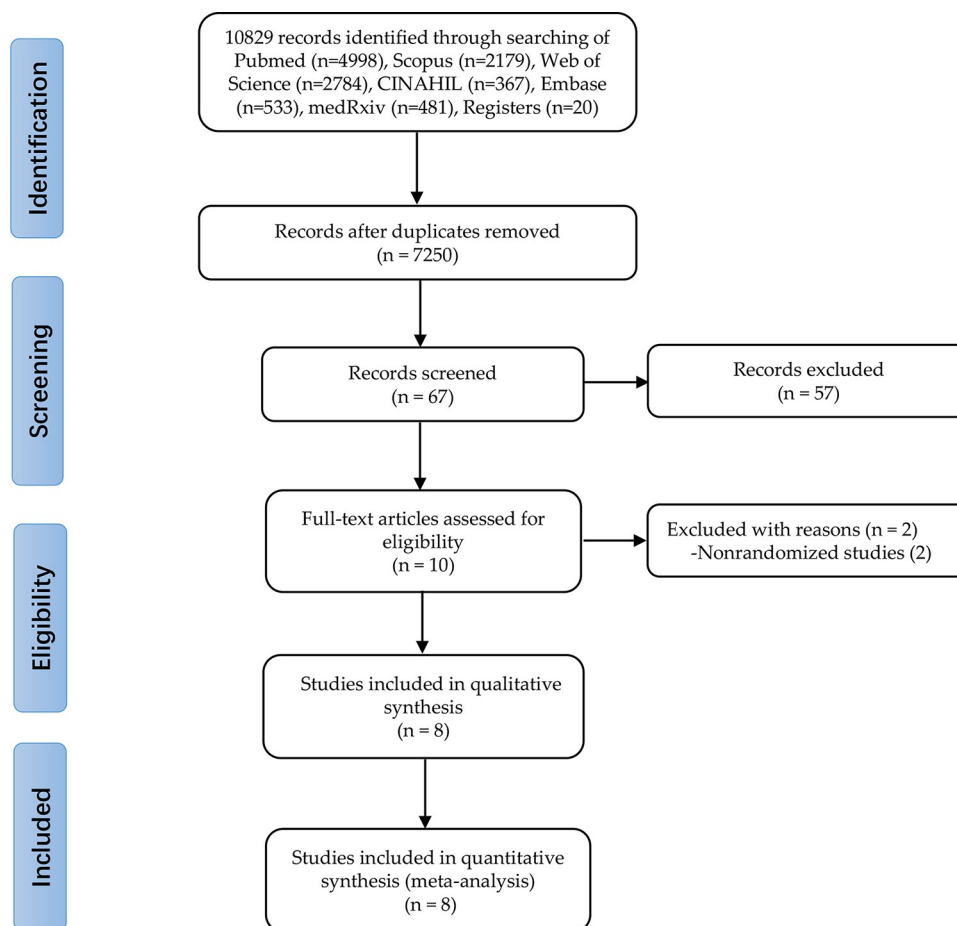


Fig 1. Research selection procedure based on the PRISMA flowchart.

<https://doi.org/10.1371/journal.pone.0312128.g001>

Table 1. Characteristics and outcomes of studies included in this study.

Study ID	Country	Population	Intervention	Comparison	Vaccination timing	Follow-up duration	Outcomes†	Recurrence		
								HSIL	HSIL related to HPV16/18	LSIL
Firnhaber et al, [37] 2021	South Africa	180 women living with HIV with 1 year of follow-up [Vaccine group 90 –Non-vaccine Group 90] Age: 39.2 (mean) [Vaccine Group 40.1 –Non-Vaccine Group 39.1] CIN grade: 86 CIN2, 93 CIN3, 1 Inadequate [Vaccine group: 40 CIN2, 46 CIN3, 1 Inadequate–Non-Vaccine Group 49 CIN2, 44 CIN3]	LEEP	Quadrivalent vaccine [3 doses] vs No HPV vaccination	1 months Before treatment	26 months (minimum)	CIN2 CIN3 HSIL	28/ 87:27/ 87	-	-
Garland et al, [38] 2016	Multi-national (14 countries)	454 women treated for cervical lesions [Vaccine group 190 – Non-vaccine Group 264] Age: N/A	LLETZ, Conization	Bivalent vaccine [doses N/A] vs Hepatitis A vaccine	19.1 (1.5–46.5) and 26.5 (0.8–48.3) months before the treatment	47.3 (median)	CIN1+ CIN2+ HSIL LSIL CIN1+ HPV 16–18 CIN2+ HPV 16–18 CIN1 CIN2 Abnormal cytology VIN/VaIN 1 + VIN/VaIN 2 +	1/ 159:4/ 215	0/174:1/ 234	27/ 101:21/ 110
Hildesheim et al, [39] 2016	Costa Rica	311 women treated for high grade cervical disease [Vaccine group 142 – Non-vaccine Group 169] Age: N/A CIN Grade: 154 normal, 67 LSIL, 87 HSIL [Vaccine group 1 Inadequate, 57 Normal, 36 LSIL, 47 HSIL–Non-vaccine group 1 Inadequate, 97 Normal, 31 LSIL, 40 HSIL]	LLETZ	Bivalent vaccine [3 doses 80%, 2 doses 12.4%, 1 dose 7.4%] vs Hepatitis A vaccine	28.2 months (median) Before treatment	27.3 months (median)	CIN2+ * CIN2+ HPV 16–18 * HSIL HSIL+ HPV 16–18 * LSIL Abnormal cytology Persistent HPV Infection Incident HPV infection	10/ 142: 4/169	3/142:2/ 169	33/142: 31/169

(Continued)

Table 1. (Continued)

Study ID	Country	Population	Intervention	Comparison	Vaccination timing	Follow-up duration	Outcomes†	Recurrence		
								HSIL	HSIL related to HPV16/18	LSIL
Joura et al, [40] 2012	Multi-national (13 countries)	1350 women treated for cervical disease [Vaccine group 587 – Non-vaccine Group 763] Age: 19.8 (mean) [Vaccine group 19.9 – Non-vaccine Group 19.8] CIN grade: 113 ASCUS, 23 ASCH, 232 LSIL, 65 HSIL [Vaccine group 47 ASCUS, ASCH 13, 112 LSIL, 36 HSIL Non vaccine group 65 ASCUS, 10 ASCH, 120 LSIL, 29 HSIL]	LLETZ (84.7%), Conization (13%), Cryotherapy (0.7%), Other (2.1%)	Quadrivalent vaccine [585/587 3 doses, 2/587 2 doses] vs 225 g aluminum Hydroxyphosphate sulfate	Before the treatment	44 months (maximum)	CIN1+ CIN2+ CIN1+ HPV 16–18 CIN2+ HPV 16–18 CIN1 CIN2 CIN3 VIN/VaIN 1 + VIN/VaIN 2 + Genital warts	-	-	-
Karimi-Zarchi et al, [20] 2020	Iran	242 women treated for CIN1 or high grade CIN (CIN2-3) [Vaccine group 138 – Non-vaccine Group 104] Age: 32.59 (mean) [Vaccine Group 31.7 – Non-Vaccine Group 33.04] CIN grade: 80 CIN1, 85 CIN2, 77 CIN3 [Vaccine group: 45 CIN1, 50 CIN2, 43 CIN3 – Non-Vaccine Group 35 CIN1, 35 CIN2, 34 CIN3]	LLETZ, CKC, Ablation	Quadrivalent vaccine [35/138 2 doses, 103/138 3 doses] vs No HPV vaccination	At the time of treatment	24 months (minimum)	CIN1+ CIN2+ CIN1 ICC	-	-	-
Karita et al, [23] 2022	United States	187 women who were previously treated for anal or vulvar HSIL and HSIL-free [Vaccine group 104 – Non-vaccine Group 83] Age: 55 (mean) [Vaccine Group 30.1 – Non-Vaccine Group 29.8] HSIL grade: 187 [Vaccine group: 104 Normal Non-Vaccine Group 83 Normal]	NI	9vHPV [3 doses] vs No HPV vaccination	Before the treatment	48 months (maximum)	HSIL	15/104: 18/83	-	-

(Continued)

Table 1. (Continued)

Study ID	Country	Population	Intervention	Comparison	Vaccination timing	Follow-up duration	Outcomes†	Recurrence		
								HSIL	HSIL related to HPV16/18	LSIL
Pieralli et al, [19] 2018	Italy	178 women treated for CIN with negative HPV test, cytology, and colposcopy 3 months after treatment [Vaccine Group 89 – Non-vaccine Group 89] Age: 32 (mean) [Vaccine Group 32.1 – Non-vaccine Group 31.8] CIN grade: 30 LSIL, 148 HSIL	N/A	Quadrivalent vaccine [3 doses] vs No HPV vaccination	3 months after treatment	36 months (minimum)	CIN1+ CIN2+ HSIL HSIL+ HPV 16–18 LSIL CIN1+ HPV 16–18 CIN2+ HPV 16–18 CIN1 Abnormal cytology VIN/VaIN 1 + VIN/VaIN 2 +	0/89:4/89	0/89:4/89	3/89:8/89
Zhao et al, [22] 2020	China	166 women treated for cervical lesions [Vaccine group 86 – Non-vaccine Group 80] Age: 18–25	LLETZ, Conization	Bivalent vaccine vs Aluminum hydroxide	17 months (median) before the treatment	50 months (median)	CIN1+ CIN2+ HSIL HSIL+ HPV 16–18 LSIL CIN2+ HPV 16–18 CIN1 CIN2 CIN3 VIN/VaIN 1 + VIN/VaIN 2 +	1/80: 1/73	0/80: 0/73	2/80: 1/73

*median (range), #mean (SD)

† The outcome was confirmed by histology in most of the studies, * Describes studies where outcome was determined by either histology or cytology.

<https://doi.org/10.1371/journal.pone.0312128.t001>

Recurrence of cervical LSIL

No significant difference in RR of cervical LSIL recurrence between participants who were vaccinated at the time of treatment and unvaccinated participants (four studies, 853 participants; RR 1.20, 95% CI: 0.88–1.64, $I^2 = 18\%$; Fig 7).

Publication bias

The funnel plot exhibited no asymmetry of studies examining HSIL recurrence for the assessment of publication bias, which indicates that there was no publication bias detected in our study (Fig 8).

Discussion

The findings of this review indicate that adjuvant HPV vaccination at the time of local excision for cervical intraepithelial neoplasia (CIN) cannot reduce the risk of recurrence of cervical HSIL or LSIL. Moreover, HPV vaccination cannot reduce the risk of recurrence of cervical

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Firnhaber 2021	+	+	+	+	+	+	?
Garland 2016	+	+	+	+	+	+	?
Hildesheim 2016	+	+	+	+	+	+	?
Joura 2012	+	+	+	+	+	+	?
Karimi-Zarchi 2020	+	+	+	+	+	?	+
Karita 2022	+	+	+	+	+	+	?
Pieralli 2018	+	+	+	+	+	?	?
Zhao 2020	+	+	+	+	+	+	?

Fig 2. Risk of bias assessment was performed using the Cochrane Risk of Bias RoB2.0 tool.

<https://doi.org/10.1371/journal.pone.0312128.g002>

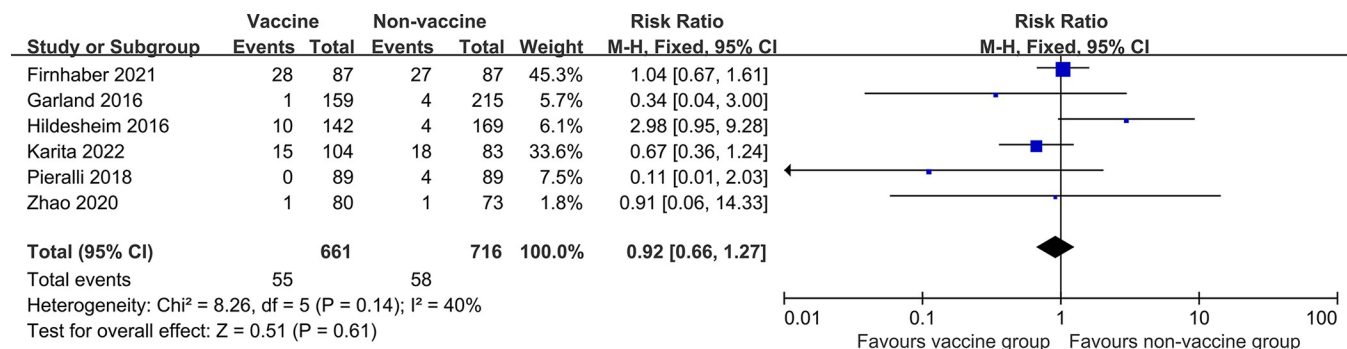


Fig 3. Forest plots assessing risk of recurrence of cervical HSIL between human papillomavirus (HPV) vaccinated and non-vaccinated groups after local conservative treatment for cervical intraepithelial neoplasia, irrespective of HPV type.

<https://doi.org/10.1371/journal.pone.0312128.g003>

HSIL related to the HPV16/18. In studies that used the vaccine Cervarix, Gardasil, or Gardasil-9 respectively, no significant difference was shown in RR of recurrence of cervical HSIL between the two groups. Vaccination before treatment did not reduce the risk of recurrence of cervical HSIL, nor did vaccination at the time of or after treatment reduce the risk of cervical HSIL recurrence. Therefore, HPV vaccination should not be considered for adjuvant treatment in patients receiving local surgical treatment. The potential reasons for the observed lack of efficacy include differences in the timing of vaccination, the participants studied, or the nature of surgical treatment, which may also be the reason for heterogeneity.

To the best of our knowledge, our study is the first meta-analysis of RCTs to evaluate the effect of adjuvant HPV vaccination on the risk of cervical HSIL recurrence in individuals treated with local surgery. Whilst CIN2/3 is widely accepted as a surrogate marker for cervical cancer vaccine efficacy in studies of prophylactic or therapeutic HPV vaccines [41,42], and is generally be incorporated in HSIL according to the Bethesda System for Reporting Cervical Cytology (TBS), it is a poor predictor of progression [43,44]. After implementation of the new guidelines, conservative management became more frequent, and is now used for more than half of women with CIN2 [44]. Therefore, in this review, we chose recurrence of cervical HSIL rather than CIN2/3 after local surgical treatment as the primary outcome.

Up to now, there have been eight meta-analyses attempting to pool the evidence [45–52]. However, our findings on pooled estimates were in inconsistent with the outcomes of these meta-analyses, and our analysis sparked worries about data quality. All of the eight studies focused primarily on the CIN2/3 recurrence after local surgery, rather than cervical HSIL.

Table 2. Sensitivity analysis of Crude Risk Ratio (RR) Associated for cervical HSIL recurrence between participants who were vaccinated at the time of treatment and those who were unvaccinated.

Leave-one-out sensitivity analysis for cervical HSIL recurrence				
Estimates for Crude RR				
Removed study	RR	95% Lower CI	95% Upper CI	<i>p</i>
Firnhaber et al. 2021 [37]	0.98	0.76	1.27	= 0.10
Garland et al. 2016 [38]	1.02	0.82	1.28	> 0.10
Hildesheim et al. 2016 [39]	0.92	0.73	1.16	> 0.10
Karita et al. 2022 [23]	1.09	0.86	1.38	> 0.10
Pieralli et al. 2018 [19]	1.04	0.83	1.30	> 0.10
Zhao et al. 2020 [22]	1.00	0.80	1.25	= 0.10
Overall	1.00	0.80	1.25	> 0.10

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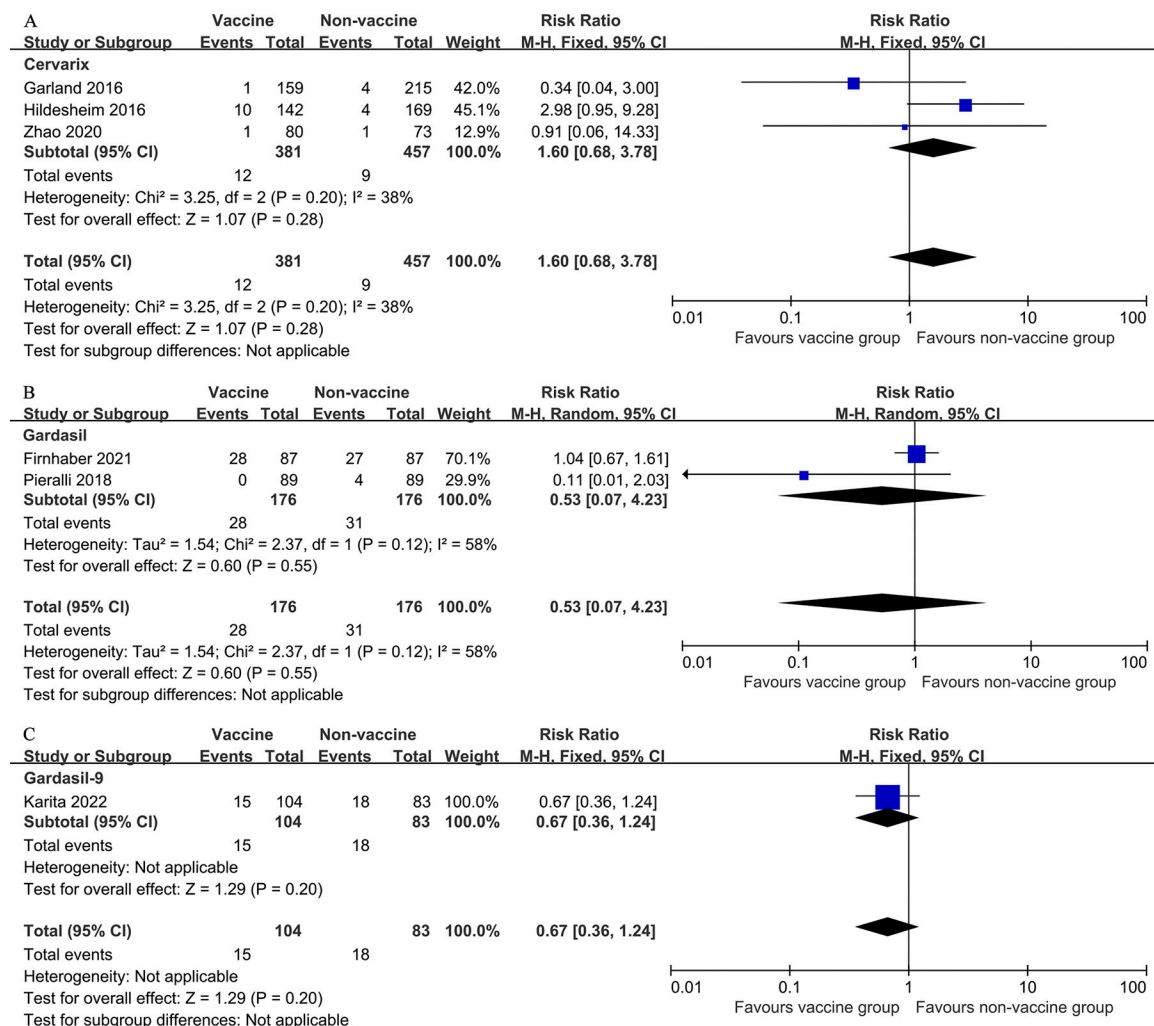


Fig 4. Forest plots demonstrating the subgroup analyses for the primary outcome (HSIL recurrence after local surgical treatment for cervical intraepithelial neoplasia) based on vaccine type.

<https://doi.org/10.1371/journal.pone.0312128.g004>

Additionally, these studies included case control and cohort studies in addition to randomized controlled trials.

Our meta-analysis comprehensively assessed the effect of adjuvant HPV vaccination after surgical excision for cervical and other non-cervical diseases related to HPV infection, and rigorously assessed the risk of bias and heterogeneity. This analysis only enrolled RCTs in which vaccines were administered at the time of or after local surgery, which made potential inaccurate assessment of effect estimates eliminated and lowered heterogeneity. We examined the quality of the studies enrolled in our meta-analysis using the updated Cochrane RoB 2.0 tool. We also assessed the publication bias in this meta-analysis, and conducted analyses irrespective of HPV type and analyses for HPV16/18. We also performed two subgroup analyses based on timing of vaccination and type of vaccine. The results of which were basically consistent with the overall effect, proving the robustness of the conclusions.

However, the findings of our study should be interpreted with caution, as this study also has several limitations. Firstly, vaccinated participants might be younger than unvaccinated individuals, and the increased risk of disease recurrence may be partly due to older age. Secondly,

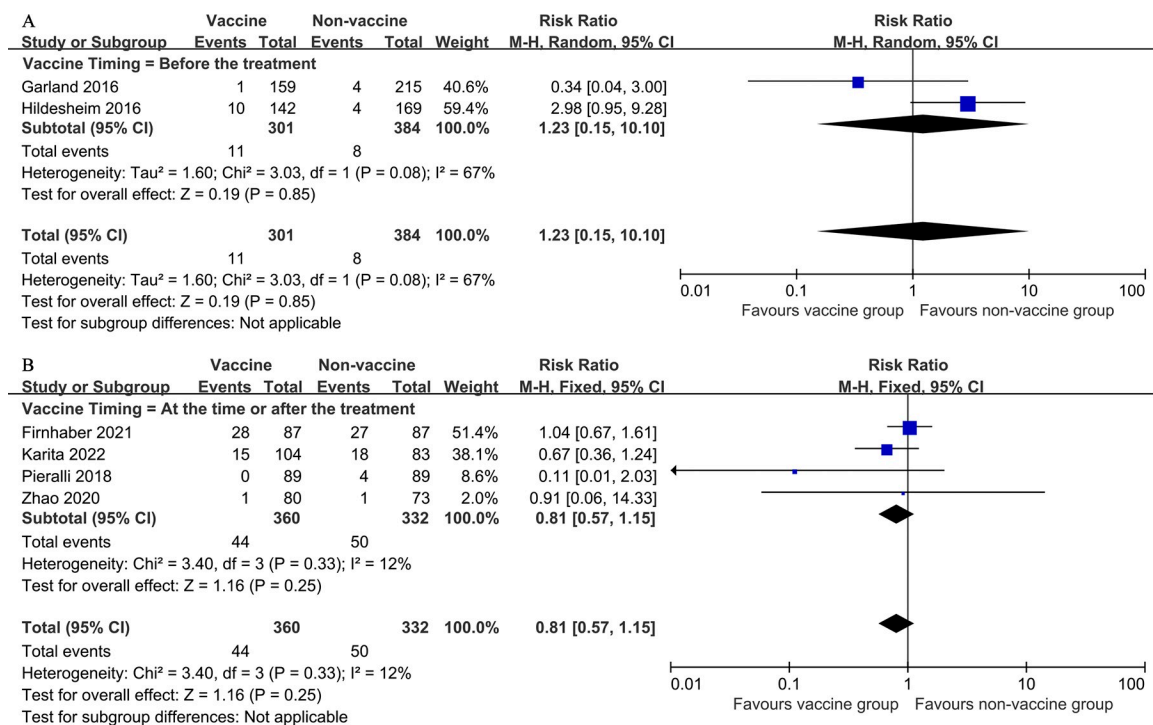


Fig 5. Forest plots demonstrating the subgroup analyses for the primary outcome (HSIL recurrence after local surgical treatment for cervical intraepithelial neoplasia) based on vaccination timing. A, Before the treatment. B, At the time or after the treatment.

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confounding factors (such as smoking and drinking) that are associated with a higher risk of recurrence were not controlled in some studies. Thirdly, in each study, participants were vaccinated at different time points before or after local treatment for cervical intraepithelial neoplasia. Fourthly, the time period during which the enrolled studies were conducted might lead to bias because the staging system, terms and definitions may change with the passage of time. The enrolled studies were carried out over a long period, and populations can be recruited using the Bethesda or recently evolving ASCCP terminology. Finally, variability in length of follow-up (follow-ups of all the 8 enrolled studies were 24–64 months), diagnostic methods, timing of HPV vaccination, and type of HPV vaccine across studies might affect the accuracy of the effect estimates. The risk of cervical HSIL recurrence was lower with a median follow-up of >24 months, despite large uncertainty. Although the most frequent recurrence occurred within the first 24 months [53], the uneven length of follow-up is inherent defect of this study and similar

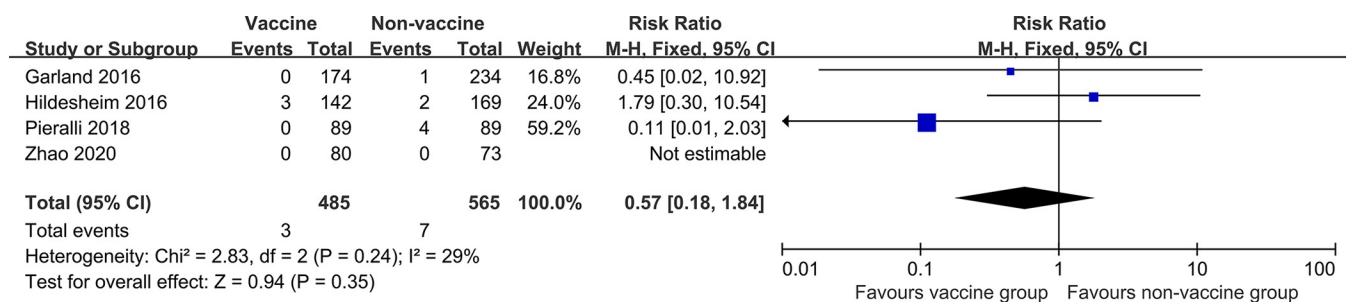


Fig 6. Forest plots assessing risk of recurrence of cervical HSIL between human papillomavirus (HPV) vaccinated and non-vaccinated groups after local treatment for cervical intraepithelial neoplasia, related to HPV types HPV16/18.

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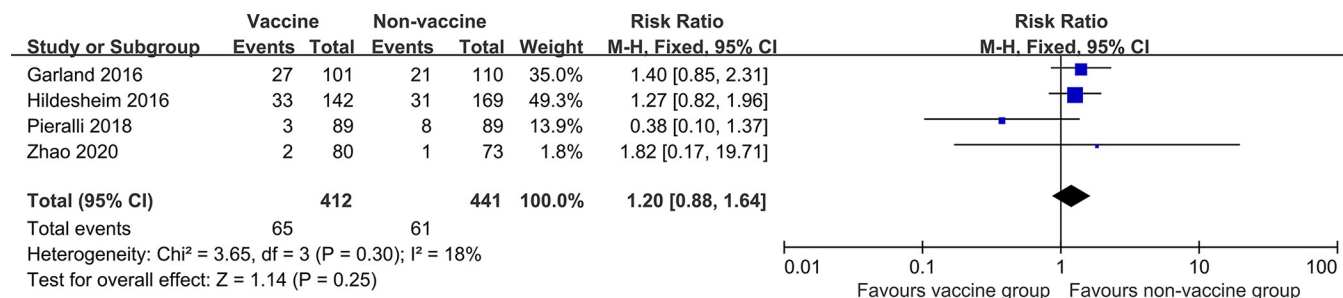


Fig 7. Forest plots assessing risk of recurrence of cervical LSIL between human papillomavirus (HPV) vaccinated and non-vaccinated groups after local treatment for cervical intraepithelial neoplasia, irrespective of HPV type.

<https://doi.org/10.1371/journal.pone.0312128.g007>

studies; moreover, future disease episodes may not be associated with the originally, treated disease and confound estimates of (potential) vaccine impact. Therefore, large scale, high quality randomized controlled trials with follow-up ≥ 24 months are needed to provide more definitive evidence for the effect of HPV vaccination on the risk of HPV infection and recurrent diseases related to HPV infection in individuals undergoing local surgical treatment.

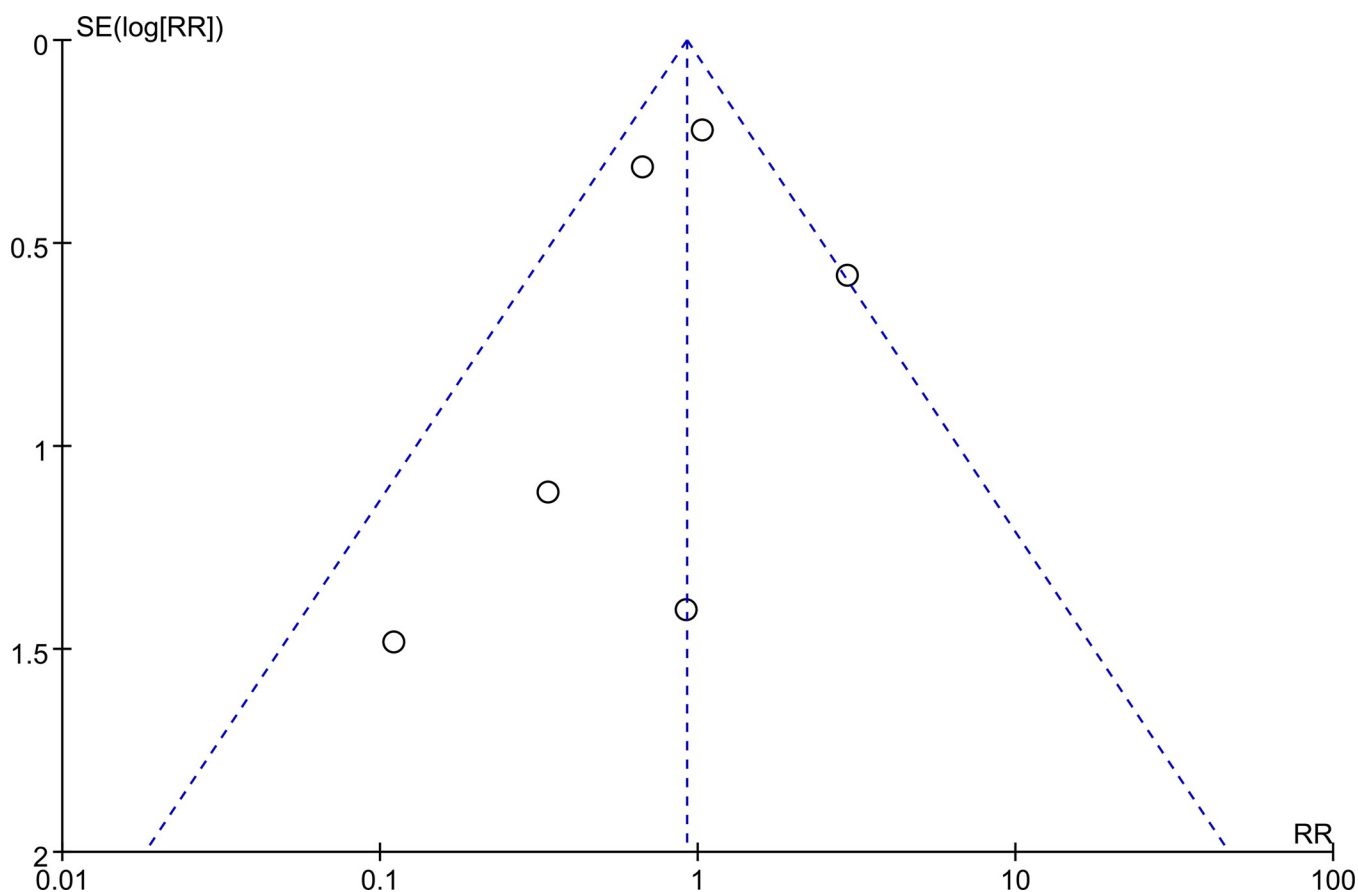


Fig 8. Funnel plot of studies examining cervical HSIL recurrence for the assessment of publication bias.

<https://doi.org/10.1371/journal.pone.0312128.g008>

Conclusions

In conclusion, adjuvant HPV vaccination after local surgical treatment for CIN is not associated with a reduced risk of HSIL recurrence overall or a reduced risk of recurrent lesions due to the most carcinogenic strains (HPV16/18). Therefore, HPV vaccination should not be considered for adjuvant treatment in patients receiving local surgical treatment.

Supporting information

S1 Checklist. PRISMA 2020 checklist.

(DOCX)

S1 File.

(XLSX)

S1 Graphical abstract.

(TIF)

Author Contributions

Conceptualization: Qinxue Cao, Juntao Yin.

Formal analysis: Qinxue Cao, Yantao Hou, Chaoyang Wang.

Funding acquisition: Juntao Yin.

Methodology: Yantao Hou, Chaoyang Wang, Juntao Yin.

Writing – original draft: Qinxue Cao.

Writing – review & editing: Yantao Hou, Chaoyang Wang, Juntao Yin.

References

1. Goldstone SE, Giuliano AR, Palefsky JM, Lazcano-Ponce E, Penny ME, Cabello RE, et al. Efficacy, immunogenicity, and safety of a quadrivalent HPV vaccine in men: results of an open-label, long-term extension of a randomised, placebo-controlled, phase 3 trial. *Lancet Infect Dis*. 2022; 22(3):413–425. [https://doi.org/10.1016/S1473-3099\(21\)00327-3](https://doi.org/10.1016/S1473-3099(21)00327-3) PMID: 34780705
2. Rahangdale L, Mungo C, O'Connor S, Chibwesha CJ, Brewer NT. Human papillomavirus vaccination and cervical cancer risk. *BMJ*. 2022; 379:e070115. <https://doi.org/10.1136/bmj-2022-070115> PMID: 36521855
3. Bruni L, Diaz M, Barrionuevo-Rosas L, Herrero R, Bray F, Bosch FX, et al. Global estimates of human papillomavirus vaccination coverage by region and income level: a pooled analysis. *Lancet Glob Health*. 2016; 4(7):e453–463. [https://doi.org/10.1016/S2214-109X\(16\)30099-7](https://doi.org/10.1016/S2214-109X(16)30099-7) PMID: 27340003
4. Mo Y, Ma J, Zhang H, Shen J, Chen J, Hong J, et al. Prophylactic and Therapeutic HPV Vaccines: Current Scenario and Perspectives. *Front Cell Infect Microbiol*. 2022; 12:909223. <https://doi.org/10.3389/fcimb.2022.909223> PMID: 35860379
5. Rebolj MA-OX, Pesola FA-O, Mathews CA-O, Mesher DA-O, Soldan KA-O, Kitchener HA-O. The impact of catch-up bivalent human papillomavirus vaccination on cervical screening outcomes: an observational study from the English HPV primary screening pilot. *Br J Cancer*. 2022; 127(1532–1827 (Electronic)):278–287. <https://doi.org/10.1038/s41416-022-01791-w> PMID: 35347326
6. Palmer TJ, Kavanagh K, Cuschieri K, Cameron R, Graham C, Wilson A, Roy K. Invasive cervical cancer incidence following bivalent human papillomavirus vaccination: a population-based observational study of age at immunization, dose, and deprivation. *J Natl Cancer Inst*. 2024; 116(6):857–865. <https://doi.org/10.1093/jnci/djad263> PMID: 38247547
7. Middeldorp M, Duijster JW, van de Kasstelee J, van der Klis FRM, de Melker HE. Immune response following a two-dose schedule of bivalent HPV vaccination among girls and boys. *Front Immunol*. 2024; 15:1327770. <https://doi.org/10.3389/fimmu.2024.1327770> PMID: 38343547
8. Hughes KC, Herring TA, Song JN, Gately RV, Przybyl LM, Ogilvie RP, et al. Cervical High-Grade Squamous Intraepithelial Lesion Burden and Standard of Care Treatment Effectiveness and Safety in the

- United States, 2008–2018: The EACH-WOMAN Project. *J Low Genit Tract Dis*. 2023; 27(2):105–112. <https://doi.org/10.1097/LGT.0000000000000719> PMID: 36815642
9. Viveros-Carreño D, Mora-Soto N, Rodríguez J, Rauh-Hain JA, Ramírez PT, López Varón M, et al. Recurrence After Biopsy-Confirmed Cervical High-Grade Intraepithelial Lesion Followed by Negative Conization: A Systematic Review and Meta-analysis. *J Low Genit Tract Dis*. 2024; 28(1):26–31. <https://doi.org/10.1097/LGT.0000000000000779> PMID: 37924263
 10. Kalliala I, Athanasiou A, Veroniki AA, Salanti G, Efthimiou O, Raftis N, et al. Incidence and mortality from cervical cancer and other malignancies after treatment of cervical intraepithelial neoplasia: a systematic review and meta-analysis of the literature. *Ann Oncol*. 2020; 31(2):213–227. <https://doi.org/10.1016/j.annonc.2019.11.004> PMID: 31959338
 11. Zhang Y, Ni Z, Wei T, Liu Q. Persistent HPV infection after conization of cervical intraepithelial neoplasia—a systematic review and meta-analysis. *BMC Womens Health*. 2023; 23(1):216. <https://doi.org/10.1186/s12905-023-02360-w> PMID: 37138261
 12. Giannini A, Di Donato V, Sopracordevole F, Ciavattini A, Ghelardi A, Vizza E, et al. Outcomes of High-Grade Cervical Dysplasia with Positive Margins and HPV Persistence after Cervical Conization. *Vaccines (Basel)*. 2023; 11(3):698. <https://doi.org/10.3390/vaccines11030698> PMID: 36992282
 13. Kyrgiou M, Athanasiou A, Paraskevaïdi M, Mitra A, Kalliala I, Martin-Hirsch P, et al. Adverse obstetric outcomes after local treatment for cervical preinvasive and early invasive disease according to cone depth: systematic review and meta-analysis. *BMJ*. 2016; 354:i3633. <https://doi.org/10.1136/bmj.i3633> PMID: 27469988
 14. Kyrgiou M, Athanasiou A, Kalliala IEJ, Paraskevaïdi M, Mitra A, Martin-Hirsch PP, et al. Obstetric outcomes after conservative treatment for cervical intraepithelial lesions and early invasive disease. *Cochrane Database Syst Rev*. 2017; 11(11):Cd012847. <https://doi.org/10.1002/14651858.CD012847> PMID: 29095502
 15. Athanasiou A, Veroniki AA, Efthimiou O, Kalliala I, Naci H, Bowden S, et al. Comparative effectiveness and risk of preterm birth of local treatments for cervical intraepithelial neoplasia and stage IA1 cervical cancer: a systematic review and network meta-analysis. *Lancet Oncol*. 2022; 23(8):1097–1108. [https://doi.org/10.1016/S1470-2045\(22\)00334-5](https://doi.org/10.1016/S1470-2045(22)00334-5) PMID: 35835138
 16. Lieb JA, Mondal A, Lieb L, Fehm TN, Hampf M. Pregnancy outcome and risk of recurrence after tissue-preserving loop electrosurgical excision procedure (LEEP). *Arch Gynecol Obstet*. 2023; 307(4):1137–1143. <https://doi.org/10.1007/s00404-022-06760-5> PMID: 36068362
 17. Casajuana-Pérez A, Ramírez-Mena M, Ruipérez-Pacheco E, Gil-Prados I, García-Santos J, Bellón-Del Amo M, et al. Effectiveness of Prophylactic Human Papillomavirus Vaccine in the Prevention of Recurrence in Women Conized for HSIL/CIN 2–3: The VENUS Study. *Vaccines (Basel)*. 2022; 10(2):288. <https://doi.org/10.3390/vaccines10020288> PMID: 35214747
 18. Olsson SE, Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Wheeler CM, et al. Evaluation of quadrivalent HPV 6/11/16/18 vaccine efficacy against cervical and anogenital disease in subjects with serological evidence of prior vaccine type HPV infection. *Hum Vaccin*. 2009; 5(10):696–704. <https://doi.org/10.4161/hv.5.10.9515> PMID: 19855170
 19. Luna J, Plata M, Gonzalez M, Correa A, Maldonado I, Nossa C, et al. Long-term follow-up observation of the safety, immunogenicity, and effectiveness of Gardasil™ in adult women. *PLoS One*. 2013; 8(12):e83431. <https://doi.org/10.1371/journal.pone.0083431> PMID: 24391768
 20. Cho J, Kim EM, Kim J, Shin JY, Kim EH, Park JH, et al. Effect of the human papillomavirus vaccine on the risk of genital warts: a nationwide cohort study of Korean adolescent girls. *Epidemiol Health*. 2024; 46:e2024040. <https://doi.org/10.4178/epih.e2024040> PMID: 38549356
 21. Pieralli A, Bianchi C, Auzzi N, Fallani MG, Bussani C, Fambrini M, et al. Indication of prophylactic vaccines as a tool for secondary prevention in HPV-linked disease. *Arch Gynecol Obstet*. 2018; 298(6):1205–1210. <https://doi.org/10.1007/s00404-018-4926-y> PMID: 30306310
 22. Karimi-Zarchi M, Allahqoli L, Nehmati A, Kashi AM, Taghipour-Zahir S, Alkatout I. Can the prophylactic quadrivalent HPV vaccine be used as a therapeutic agent in women with CIN? A randomized trial. *BMC Public Health*. 2020; 20(1):274. <https://doi.org/10.1186/s12889-020-8371-z> PMID: 32106837
 23. Sand FL, Kjaer SK, Frederiksen K, Dehlendorf C. Risk of cervical intraepithelial neoplasia grade 2 or worse after conization in relation to HPV vaccination status. *Int J Cancer*. 2020; 147(3):641–647. <https://doi.org/10.1002/ijc.32752> PMID: 31648368
 24. Zhao S, Hu S, Xu X, Zhang X, Pan Q, Chen F, Zhao F. Impact of HPV-16/18 AS04-adjuvanted vaccine on preventing subsequent infection and disease after excision treatment: post-hoc analysis from a randomized controlled trial. *BMC Infect Dis*. 2020; 20(1):846. <https://doi.org/10.1186/s12879-020-05560-z> PMID: 33198657

25. Karita HCS, Magaret A, Schouten J, Mao C, Huh W, Grieco V, et al. Effect of Human Papillomavirus Vaccine to Interrupt Recurrence of Vulvar and Anal Neoplasia (VIVA): a Randomized, Placebo-Controlled Trial. *Open Forum Infect Dis*. 2022; 9:S100. <https://doi.org/10.1093/ofid/ofac492.179>
26. Dobyns EL, Carpenter TC, Durmowicz AG, Stenmark KR. Chapter 13—Acute Respiratory Failure. In: Chernick V, Boat TF, Wilmott RW, Bush A, editors. *Kendig's Disorders of the Respiratory Tract in Children* (Seventh Edition). Philadelphia: W.B. Saunders; 2006. p. 224–242.
27. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021; 372:n71. <https://doi.org/10.1136/bmj.n71> PMID: 33782057
28. Julian H, LassersonToby, Jackie C, David T, James T, Ella F, Rachel C. Standards for the conduct and reporting of new Cochrane Intervention Reviews, reporting of protocols and the planning, conduct and reporting of updates: Cochrane; 2022. Available from: <https://community.cochrane.org/mecir-manual>.
29. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *Bmj*. 2016; 355:i4919. <https://doi.org/10.1136/bmj.i4919> PMID: 27733354
30. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019; 366:i4898. <https://doi.org/10.1136/bmj.i4898> PMID: 31462531
31. Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, Thomas J. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Rev*. 2019; 10(10):Ed000142. <https://doi.org/10.1002/14651858.ED000142> PMID: 31643080
32. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003; 327(7414):557–560. <https://doi.org/10.1136/bmj.327.7414.557> PMID: 12958120
33. Viechtbauer W. Confidence intervals for the amount of heterogeneity in meta-analysis. *Stat Med*. 2007; 26(1):37–52. <https://doi.org/10.1002/sim.2514> PMID: 16463355
34. Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ*. 2011; 343:d4002. <https://doi.org/10.1136/bmj.d4002> PMID: 21784880
35. Del Pino M, Martí C, Torras I, Henere C, Munmany M, Marimon L, et al. HPV Vaccination as Adjuvant to Conization in Women with Cervical Intraepithelial Neoplasia: A Study under Real-Life Conditions. *Vaccines* (Basel). 2020; 8(2):245. <https://doi.org/10.3390/vaccines8020245> PMID: 32456136
36. Kang WD, Choi HS, Kim SM. Is vaccination with quadrivalent HPV vaccine after loop electrosurgical excision procedure effective in preventing recurrence in patients with high-grade cervical intraepithelial neoplasia (CIN2-3)? *Gynecol Oncol*. 2013; 130(2):264–268. <https://doi.org/10.1016/j.ygyno.2013.04.050> PMID: 23623831
37. Firnhaber C, Swarts A, Jezile V, Mulongo M, Goeieman B, Williams S, et al. Human Papillomavirus Vaccination Prior to Loop Electroexcision Procedure Does Not Prevent Recurrent Cervical High-grade Squamous Intraepithelial Lesions in Women Living With Human Immunodeficiency Virus: A Randomized, Double-blind, Placebo-controlled Trial. *Clin Infect Dis*. 2021; 73(7):e2211–e2216. <https://doi.org/10.1093/cid/ciaa1456> PMID: 32975556
38. Garland SM, Paavonen J, Jaisamrarn U, Naud P, Salmerón J, Chow SN, et al. Prior human papillomavirus-16/18 AS04-adjuvanted vaccination prevents recurrent high grade cervical intraepithelial neoplasia after definitive surgical therapy: Post-hoc analysis from a randomized controlled trial. *Int J Cancer*. 2016; 139(12):2812–2826. <https://doi.org/10.1002/ijc.30391> PMID: 27541373
39. Hildesheim A, Gonzalez P, Kreimer AR, Wacholder S, Schussler J, Rodriguez AC, et al. Impact of human papillomavirus (HPV) 16 and 18 vaccination on prevalent infections and rates of cervical lesions after excisional treatment. *Am J Obstet Gynecol*. 2016; 215(2):212.e1–.e15. <https://doi.org/10.1016/j.ajog.2016.02.021> PMID: 26892991
40. Jura EA, Garland SM, Paavonen J, Ferris DG, Perez G, Ault KA, et al. Effect of the human papillomavirus (HPV) quadrivalent vaccine in a subgroup of women with cervical and vulvar disease: Retrospective pooled analysis of trial data. *BMJ* (Online). 2012; 344(7851):e1401. <https://doi.org/10.1136/bmj.e1401> PMID: 22454089
41. Shing JZ, Hu S, Herrero R, Hildesheim A, Porras C, Sampson JN, et al. Precancerous cervical lesions caused by non-vaccine-preventable HPV types after vaccination with the bivalent AS04-adjuvanted HPV vaccine: an analysis of the long-term follow-up study from the randomised Costa Rica HPV Vaccine Trial. *Lancet Oncol*. 2022; 23(7):940–949. [https://doi.org/10.1016/S1470-2045\(22\)00291-1](https://doi.org/10.1016/S1470-2045(22)00291-1) PMID: 35709811

42. Alouini S, Pichon C. Therapeutic Vaccines for HPV-Associated Cervical Malignancies: A Systematic Review. *Vaccines (Basel)*. 2024; 12(4):428. <https://doi.org/10.3390/vaccines12040428> PMID: 38675811
43. Tainio K, Athanasiou A, Tikkinen KAO, Aaltonen R, Cárdenas J, Hernández, et al. Clinical course of untreated cervical intraepithelial neoplasia grade 2 under active surveillance: systematic review and meta-analysis. *BMJ*. 2018; 360:k499. <https://doi.org/10.1136/bmj.k499> PMID: 29487049
44. Skorstengaard M, Lynge E, Suhr J, Napolitano G. Conservative management of women with cervical intraepithelial neoplasia grade 2 in Denmark: a cohort study. *Bjog*. 2020; 127(6):729–736. <https://doi.org/10.1111/1471-0528.16081> PMID: 31880054
45. Lichter K, Krause D, Xu J, Tsai SHL, Hage C, Weston E, et al. Adjuvant Human Papillomavirus Vaccine to Reduce Recurrent Cervical Dysplasia in Unvaccinated Women: A Systematic Review and Meta-analysis. *Obstet Gynecol*. 2020; 135(5):1070–1083. <https://doi.org/10.1097/AOG.0000000000003833> PMID: 32282601
46. Jentschke M, Kampers J, Becker J, Sibbertsen P, Hillemanns P. Prophylactic HPV vaccination after conization: A systematic review and meta-analysis. *Vaccine*. 2020; 38(41):6402–6409. <https://doi.org/10.1016/j.vaccine.2020.07.055> PMID: 32762871
47. Di Donato V, Caruso G, Petrillo M, Kontopantelis E, Palaia I, Perniola G, et al. Adjuvant HPV Vaccination to Prevent Recurrent Cervical Dysplasia after Surgical Treatment: A Meta-Analysis. *Vaccines (Basel)*. 2021; 9(5):410. <https://doi.org/10.3390/vaccines9050410> PMID: 33919003
48. Bartels HC, Postle J, Rogers AC, Brennan D. Prophylactic human papillomavirus vaccination to prevent recurrence of cervical intraepithelial neoplasia: a meta-analysis. *International Journal of Gynecologic Cancer*. 2020; 30(6):777–782. <https://doi.org/10.1136/ijgc-2020-001197> PMID: 32276936
49. Kechagias KS, Kalliala I, Bowden SJ, Athanasiou A, Paraskevaidi M, Paraskevaidis E, et al. Role of human papillomavirus (HPV) vaccination on HPV infection and recurrence of HPV related disease after local surgical treatment: systematic review and meta-analysis. *BMJ*. 2022; 378:e070135. <https://doi.org/10.1136/bmj-2022-070135> PMID: 35922074
50. 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. <https://doi.org/10.1111/aogs.14359> PMID: 35470865
51. Petráš M, Dvořák V, Lomozová D, Máčalík R, Neradová S, Dlouhý P, et al. Timing of HPV vaccination as adjuvant treatment of CIN2+ recurrence in women undergoing surgical excision: a meta-analysis and meta-regression. *Sex Transm Infect*. 2023; 99(8):561–570. <https://doi.org/10.1136/sextrans-2023-055793> PMID: 37553234
52. Di Donato V, Caruso G, Bogani G, Cavallari EN, Palaia G, Perniola G, et al. HPV Vaccination after Primary Treatment of HPV-Related Disease across Different Organ Sites: A Multidisciplinary Comprehensive Review and Meta-Analysis. *Vaccines (Basel)*. 2022; 10(2):239. <https://doi.org/10.3390/vaccines10020239> PMID: 35214697
53. Arbyn M, Redman CWE, Verdoodt F, Kyrgiou M, Tzafetas M, Ghaem-Maghami S, et al. Incomplete excision of cervical precancer as a predictor of treatment failure: a systematic review and meta-analysis. *Lancet Oncol*. 2017; 18(12):1665–1679. [https://doi.org/10.1016/S1470-2045\(17\)30700-3](https://doi.org/10.1016/S1470-2045(17)30700-3) PMID: 29126708