

REVIEW

Prophylactic HPV vaccines reduce recurrence rates after conization of CIN: a clinical research review

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Abstract

Cervical conization serves as the primary and effective treatment for high-grade squamous intraepithelial lesions (HSIL). Following conization, recurrence of cervical intraepithelial neoplasia (CIN) and persistent human papillomavirus (HPV) infection remain key factors contributing to the onset and progression of cervical cancer. Current evidence indicates that prophylactic HPV vaccination in HSIL/CIN2+ patients significantly reduces recurrence rates, thus lowering the risk of complications from repeat treatments. This strategy successfully integrates both primary and secondary prevention, broadening the clinical application of HPV vaccination. This review consolidates data from existing clinical studies and proposes directions for future research to inform post-conization management of HSIL.

Keywords

Prophylactic HPV vaccine; Conization; CIN; Recurrence; Clinical studies

1. Introduction

According to 2023 cancer statistics [1], the United States is expected to report 13,960 new cases of cervical cancer and 4310 related deaths. Squamous intraepithelial lesions (SIL) of the cervix, a group of cervical abnormalities closely linked to invasive cervical cancer, are strongly associated with persistent high-risk HPV infection [2]. With ongoing advancements in cervical cancer screening and early diagnosis, the detection rate of HPV-related HSIL/CIN2+ has significantly increased [3]. Recommended treatments for HSIL currently include excisional therapy, ablative therapy and cryotherapy [4]. Although most cases of cervical HSIL show successful outcomes, 7%–25% of patients may experience residual or recurrent lesions [5, 6], resulting in an elevated risk of cervical or vaginal cancer compared to the general population [7].

Persistent HPV infection and reinfection after conization are critical risk factors for lesion recurrence and progression, with up to 77.5% postoperative recurrences linked to high-risk HPV persistence [8, 9]. Thus, in addition to rigorous post-treatment monitoring, reducing the recurrence of cervical HSIL/CIN2–3 has emerged as a major clinical challenge.

Prophylactic HPV vaccines, a primary prevention strategy for cervical cancer, have been extensively validated for safety and efficacy [10–12]. However, their effectiveness in women already infected with HPV remains a subject of debate. Recent meta-analyses indicate that HPV vaccination before or after conization for HSIL/CIN2–3 significantly reduces the likelihood of HPV reinfection and associated lesion outcomes, thereby improving prognosis [13–15]. International expert consensus guidelines now recommend HPV vaccination for post-conization patients [16, 17]. Several large-scale clinical

trials, including observational studies, randomized controlled trials (RCTs) and *post-hoc* analysis, have demonstrated that HPV vaccination can reduce the risk of CIN2+ recurrence. Nonetheless, challenges remain within these studies. This article reviews the current research landscape, identifies existing issues and proposes directions for future studies.

2. Currently available HPV vaccines

HPV vaccines play a critical role in reducing HPV infections and the associated cancer incidence. While the HPV vaccination rate (≥ 1 dose) among American adolescents rose from 71.5% in 2019 to 75.1% in 2020, this remains below optimal levels and significantly short of the 2030 goal of vaccinating 90% of girls by age 15. As of October 2024, six HPV vaccines have been licensed, all of which are prophylactic and based on L1 virus-like particles (VLPs) self-assembly. However, these vaccines differ in expression systems and adjuvants, as detailed in Table 1.

3. Why prophylactic HPV vaccines can prevent post-conization recurrence?

Prophylactic HPV vaccines cannot eliminate active persistent HPV infections or residual HPV-associated dysplastic tissue following surgery. However, they can effectively prevent new HPV infections from different types and reinfections by the same HPV type. The mechanisms by which HPV vaccines reduce disease recurrence after cervical surgery remain unclear. Several hypotheses have been proposed to explain their protective effect in individuals already infected with HPV.

TABLE 1. Characteristics of the six licensed HPV vaccines.

HPV vaccine	Cecolin®	Walvax®	Cervarix®	Gardasil®	Gardasil-9®	Cervavac®
VLP type	16/18	16/18	16/18	6/11/16/18	6/11/16/18/31/33/45/52/58	6/11/16/18
Expression system	<i>Escherichia coli</i>	<i>Pichia pastoris</i>	Insect cell-Baculovirus	<i>Saccharomyces cerevisiae</i>	<i>Saccharomyces cerevisiae</i>	<i>Hanseniaspora</i>
Adjuvant	Alum	Alum	AS04	Alum	Alum	Alum
Immunization schedule	0, 1, 6 mon	0, 2, 6 mon	0, 1, 6 mon	0, 2, 6 mon	0, 2, 6 mon	0, 2, 6 mon
Dosage	2 doses (9–14) or 3 doses (15–45)	2 doses (9–14) or 3 doses (15–30)	2 doses (9–14) or 3 doses (15+)	2 doses (9–13) or 3 doses (14+)	2 doses (9–14) or 3 doses (15+)	2 doses (9–14) or 3 doses (15+)
Market approval date	2019	2022	2007	2006	2014	2022 (marketed only in India)
Target population	9–45	9–30	9–45	9–45	9–45	9–45

VLP: virus-like particles; HPV: human papillomavirus.

3.1 Prevention of new infections

Following HPV infection, the body generates neutralizing antibodies targeting the L1 and L2 capsid proteins of the virus. Prophylactic HPV vaccines are developed using recombinant DNA technology to produce the L1 protein, which induces the production of neutralizing antibodies to prevent future infections [18]. Antibody levels generated in response to natural infection are generally low, even at their peak [19, 20]. In contrast, vaccine-induced antibody levels are theoretically much higher than those resulting from natural infection, whether from viral spread of an existing infection or new exposure. Additionally, from an immunological perspective, cervical surgery induces local inflammation, similar to that seen in HPV-uninfected patients. In this microenvironment, vaccination may provide protection against HPV infection. Moreover, the anti-inflammatory microenvironment following surgery may hinder persistent HPV infection, while the removal of persistent HPV lesions creates a favorable setting for post-surgical vaccination [21–23].

3.2 Inhibition of latent HPV reactivation

Latent HPV infection, characterized by previously undetectable viral levels, has been proposed to be suppressed by HPV vaccination, although the exact mechanisms remain uncertain [24].

3.3 Enhancement of immune mechanisms

The host's immune response to HPV determines whether an infection is cleared or becomes persistent. Immunocompromised individuals exhibit reduced immunogenicity to HPV vaccines, resulting in lower rates of protective antibody responses. Several independent predictors of residual or recurrent disease have been identified, including autoimmune disorders, human immunodeficiency virus (HIV) infection, hepatitis B or C, malignancies, diabetes, genetic disorders and organ transplants [25]. HPV vaccines stimulate cell-mediated immunity, which

may contribute to preventing recurrent infections [26]. Consequently, there is a rationale for exploring the potential benefits of vaccination in individuals with a history of HPV-related disease.

3.4 Cross-protection against other HPV types

Earlier studies have demonstrated that HPV vaccination can prevent infections by other HPV types and related diseases in individuals already infected with HPV. Hildesheim's study identified a subgroup of women who may particularly benefit from vaccination: those exposed to new HPV infections after treatment [27]. In this subgroup, the study showed significant vaccine efficacy against new infections and oncogenic infections linked to HPV types 31, 33 and 45, with suggestive evidence of efficacy against infections by HPV types 16 and 18. These findings suggest that post-conization vaccination may effectively prevent infections by HPV types distinct from the initial infection.

4. Safety of prophylactic HPV vaccination after conization

Vaccine safety assessments typically encompass both local injection site reactions and systemic responses. HPV vaccines have generally demonstrated a favorable safety profile in studies [28]. The World Health Organization (WHO) Global Advisory Committee on Vaccine Safety (GACVS) classifies HPV vaccines as extremely safe [29]. Common local reactions include redness and pain, while systemic reactions primarily consist of mild fever, dizziness, headache, nausea and fatigue. Most of these symptoms resolve spontaneously without intervention, and no significant differences in adverse events have been observed across different vaccine doses [30].

However, there are no direct clinical studies evaluating the safety of HPV vaccination specifically in the post-conization context. Post-conization patients may experience complica-

tions such as bleeding, infection or tissue damage. Additionally, some studies suggest that post-conization patients may undergo temporary immune suppression, which could potentially affect their immune response to vaccination [31, 32]. Despite this, none of the clinical studies reviewed reported severe adverse reactions in post-conization patients receiving the HPV vaccine. Any serious adverse events would likely have been documented in the literature.

Overall, HPV vaccines have been extensively validated for safety across various populations. A six-year follow-up study of individuals vaccinated with the nonavalent HPV vaccine found no significant increase in the risk of conditions such as Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyneuropathy (CIPD) or stroke across age or sex groups [33]. Furthermore, the latest WHO position paper confirmed that HPV vaccination does not elevate the risk of severe adverse events or negative pregnancy outcomes [34]. The recommended vaccination age range for HPV vaccines is 9–45 years. While younger individuals may still fall within the immunization schedule age range, the safety of co-administration with other vaccines has been a focus of research. Studies from Mexico, Canada and the United States have shown that simultaneous or sequential administration of the HPV vaccine with inactivated vaccines (e.g., meningococcal conjugate vaccine (MCV4), tetanus-diphtheria-acellular pertussis (Tdap) vaccine, hepatitis A/B vaccines) or live attenuated vaccines (e.g., chimeric yellow fever-dengue tetravalent dengue vaccine (CYD-TDV)) does not impair the immune response to any of the vaccines [35–37].

5. Current clinical research status on HPV vaccines for preventing recurrence of CIN following surgical intervention

5.1 *Post-hoc* analysis of RCTs

In 2012, Joura EA published a retrospective analysis based on the global multicenter phase III clinical trials, FUTURE I and FUTURE II, which involved the quadrivalent HPV vaccine [38]. The study included 587 recipients of the quadrivalent vaccine and 763 placebo recipients who underwent cervical conization. Preoperative HPV vaccination was found to significantly reduce the risk of recurrence of CIN1, CIN2 and CIN3 by 48.3%, 64.9% and 73.5%, respectively, at ≥ 60 days post-conization, with all differences being statistically significant. Additionally, the study demonstrated that preoperative vaccination reduced the risk of other HPV-related lesions, such as vaginal, vulvar lesions and genital warts. In 2016, Garland S.M.'s research team conducted a retrospective analysis of the global multicenter PATRICIA study, which involved 18,644 individuals aged 15–25 who received the bivalent HPV vaccine [39]. This analysis indicated that the bivalent vaccine provided 88.2% protection against CIN2+ recurrence after 60 days or more post-surgery (95% confidence interval (CI): 14.8–99.7), regardless of baseline HPV DNA types. However, a retrospective analysis by Allan Hildesheim in the same year, based on a Costa Rican study, found that vaccine administration did not provide protection against postoperative HPV infection

or CIN lesions [27]. This discrepancy may be attributed to the low recurrence rate of HSIL after conization in the trial, which hindered comprehensive analysis, potentially contributing to the inconsistent study outcomes. The differing results highlight the lower evidence quality inherent in retrospective studies. Thus, further research and validation are necessary before these findings can be applied as significant clinical practice guidelines.

5.2 Retrospective cohort studies

In 2013, South Korean researchers published the first retrospective study involving 737 patients aged 20–45 who underwent loop electrosurgical excision procedure (LEEP) for CIN2–3 [40]. Of these, 360 patients received the quadrivalent HPV vaccine post-LEEP, while 377 did not. All participants began receiving the vaccine one week post-surgery, with a median follow-up duration of 3.5 years. The study revealed that, regardless of HPV type, the vaccine group had 9 cases of CIN recurrence, while the non-vaccine group had 27 cases. The recurrence rate for lesions associated with HPV types covered by the quadrivalent vaccine was 8.5% in the non-vaccine group and 2.5% in the vaccine group, with this difference being statistically significant. A Cox multivariate regression model identified lack of vaccination post-LEEP as an independent risk factor for CIN2–3 recurrence, suggesting that HPV quadrivalent vaccine administration after treatment significantly reduces recurrence risk.

Substantial evidence supporting the postoperative protective effects of the HPV vaccine has emerged, primarily from retrospective studies. In 2021, Gómez de la Rosa AG conducted a study comparing recurrence rates after 4 years of follow-up for 160 patients who received the HPV vaccine (bivalent or quadrivalent) post-LEEP and 171 who did not [41]. The non-vaccine group had a CIN2–3 recurrence rate of 9.4%, while the vaccine group had a significantly lower rate of 2.5%. In the following year, Andrea Casajuana-Pérez's study included 277 patients who received the HPV vaccine post-cone biopsy for HSIL/CIN2–3 and 286 who did not [42]. The study demonstrated a 57% reduction in the risk of HSIL persistence/recurrence in the vaccine group compared to non-recipients. Despite differences in age distribution and some data bias, effectively reduces the risk of HSIL recurrence after conization. Thus, administering the HPV vaccine post-treatment should be considered as a preventive or adjunctive therapeutic measure.

Conversely, a retrospective study from Denmark followed 17,126 post-conization patients, and found that women who received the HPV vaccine before and after conization had a slightly lower risk of CIN2+ recurrence compared to those who did not. However, the results did not reach statistical significance (hazard ratio (HR)_{adjusted} = 0.86, 95% CI: 0.67–1.09) [43]. Despite an adequate sample size sourced from the Danish national database, the findings contradicted previous studies. The researchers suggested that the lack of statistical significance might be due to the inclusion of patients with CIN3 pathology post-surgery but not CIN2. Thus, further research and discussion are needed to clarify the impact of post-conization HPV prophylactic vaccination on cervical epithelial

lesions.

5.3 Prospective cohort studies

Italy's first prospective cohort study (SPERimentazione ANTi-HPV Zona Apuana, SPERANZA) enrolled female patients aged 18–45 with cervical HSIL/CIN2+ or cervical cancer stage Ia1 who underwent LEEP treatment and were subsequently vaccinated with the quadrivalent HPV vaccine. The vaccine was administered within 30 days post-surgery, with the second and third doses given at 2 and 6 months. The vaccine group consisted of 174 patients, while the control group had 176 patients. After 4 years of follow-up, the study demonstrated that administering the quadrivalent HPV vaccine within 30 days post-conization significantly reduced the risk of subsequent HSIL recurrence by 81.2% (95% CI, 34.3–95.7) [44]. No high-grade CIN cases related to the vaccine HPV types were observed post-surgery, indicating a vaccine efficacy of 100%.

In 2020, Spain conducted a prospective study involving 265 post-conization patients, with follow-up assessments every 6 months over a 24-month period [45]. Each follow-up included HPV testing and vaginal colposcopy evaluation. Among the 153 patients who received the HPV vaccine, 19.6% received the bivalent vaccine, 4.6% received the quadrivalent vaccine, and 64.1% received the nonavalent vaccine, while 11.8% were unsure of the vaccine type. The vaccine group showed a significantly lower HSIL recurrence rate (3.3%) compared to the control group (10.7%) ($p = 0.015$), with vaccinated women exhibiting a 4.5-fold lower risk of persistent/recurrent HSIL. Del Pino's analysis further calculated the efficacy of prophylactic HPV vaccines in reducing post-conization HPV persistence or recurrence, revealing that HPV vaccines effectively reduced the risk of postoperative viral infection ($p = 0.021$). Although the study did not restrict the type or timing of HPV vaccination, the findings provide compelling evidence supporting the benefit of HPV vaccination in post-conization patients, offering valuable insight into vaccine administration policies.

In the same year, Italy conducted a single-center prospective study involving 181 patients who received the quadrivalent HPV vaccine, 3 patients who received the bivalent vaccine, and 116 patients who refused vaccination. After a 2-year follow-up post-LEEP, univariate analysis showed that HPV vaccination significantly reduced the risk of persistent/recurrent HSIL (odds ratio (OR): 0.3, 95% CI: 0.1–0.8, $p = 0.021$) [46]. A study from Sun Yat-sen University Affiliated First Hospital in China also found that the quadrivalent HPV vaccine reduced the risk of disease recurrence post-conization, involving 423 patients. Of these, 148 were in the vaccine group and 273 in the control group. The results were consistent with the findings of the previous three studies, with no statistically significant differences between the two groups, except for education level [47].

These four prospective studies provide higher levels of evidence, and consistently suggest that post-conization HPV vaccination reduces the risk of cervical lesion recurrence. However, limitations such as small sample sizes, non-randomized designs, and short follow-up periods warrant further investigation.

5.4 RCTs in medical research

RCTs represent the gold standard for clinical research, minimizing selection bias and confounding factors, thereby offering higher levels of evidence. In 2018, Italy reported a prospective RCT involving 178 patients under 45 years of age who had negative follow-up results for HPV, liquid-based cytology, and vaginal colposcopy three months after conization surgery. These patients were randomly assigned in a 1:1 ratio to the vaccine group or control group. The control group received only follow-up examinations, while the vaccine group received the quadrivalent HPV vaccine at 0, 2 and 6 months. The results showed that among the 89 patients in the follow-up group, 12 had recurrences (13.5%, 12/89), whereas in the vaccine group, only 3 patients had recurrences (3.4%, 3/89), with a statistically significant difference between the two groups ($p < 0.05$) [48].

In October 2021, Firnhaber C conducted a single-center, randomized, double-blind, placebo-controlled Phase III trial involving 180 HIV-co-infected patients with HSIL in Johannesburg, South Africa [49]. Participants were randomly assigned to either the vaccine or placebo group. At baseline and week 4, they received either the quadrivalent HPV vaccine or 0.9% saline, with cervical tissue or cytology assessments performed at weeks 26 and 52. The study found no statistically significant differences between the two groups regarding the recurrence of high-grade cervical lesions based on histological or cytological evaluations. The discrepancy with previous studies is likely due to the patients' concurrent HIV infection. Despite receiving antiretroviral therapy, participants showed considerable immunosuppression prior to surgery. Furthermore, the majority of patients had atypical squamous cells where HSIL could not be excluded (ASC-H) or HSIL diagnoses on colposcopy, with HIV-positive individuals generally presenting larger, more diffuse lesions. Postoperative pathological analysis revealed that 91 patients had positive margins, potentially contributing to the study's divergent results. Another limitation was the use of the quadrivalent HPV vaccine, and the outcomes might differ if a nonavalent HPV vaccine had been used.

Several ongoing RCTs are investigating the potential of HPV vaccines to reduce post-conization recurrence. In 2020, van de Laar RLO initiated a randomized, double-blind, multicenter, placebo-controlled trial involving 750 patients scheduled for LEEP surgery due to CIN2–3 [50]. Participants were randomly assigned to either the vaccine or placebo group, with the vaccine group receiving the first dose of the nonavalent HPV vaccine on the day of surgery, and the placebo group receiving 0.9% saline. Follow-up HPV and cytology assessments were conducted 24 months later. The study also stratified participants by age to assess the impact of age on postoperative recurrence rates and the protective effects of the vaccine across different age groups. The study's completion date is pending, and its results are highly anticipated. A search in the National Institutes of Health (NIH)'s global clinical trial database (<https://clinicaltrials.gov/>) revealed three ongoing RCTs focusing on reducing post-conization recurrence through HPV vaccination. The HOPE9 study (NCT03848039), a phase III trial in Italy, involves nine hospitals and includes patients

aged 18 and above with histologically confirmed CIN2+ or cervical invasive carcinoma (stage < Ia). In this study, the vaccine group receives the nonavalent HPV vaccine perioperatively, while the placebo group is administered sterile water injections. A five-year follow-up will assess CIN recurrence rates, HPV infection, and time to disease recurrence, with the study set to conclude in May 2028. The COVENANT study, a randomized placebo-controlled trial, aims to evaluate whether the nonavalent HPV vaccine can reduce HSIL recurrence in HIV-positive women post-conization. This study plans to enroll 536 participants aged 25 and older, with preliminary completion scheduled for March 2025. The NOVEL study, a randomized controlled trial across the UK, Sweden and Finland, will enroll 1000 patients aged 18–55 with histologically confirmed HSIL. Participants will be randomized into a vaccine plus conization group and a conization-only group, with the vaccine group receiving the nonavalent HPV vaccine post-conization. After a two-year follow-up, the study will compare HPV clearance, reinfection rates, and recurrence of high-grade intraepithelial lesions between the groups.

In summary, the majority of studies indicate that HPV vaccination reduces the risk of post-conization CIN recurrence and sustained HPV infection. However, consensus has not yet been reached regarding optimal vaccine administration timing, dosage, formulation, age of vaccination and economic factors.

Vaccination timing varies across studies with all suggesting either pre- or post-conization administration. Among three Phase III vaccine trials conducted pre-conization, one study indicated that vaccination did not prevent HPV infection after treatment, while the other two showed a significant reduction in CIN2+ recurrence, ranging from 61% to 85% [27, 38, 39]. In these studies, vaccines administered pre- and/or post-conization resulted in a 23% to 69% reduction in CIN2+ recurrence rates [41–43]. In the six studies where vaccination occurred post-conization, reduction rates ranged from 65% to 100% [40, 44–46, 48, 51]. These findings suggest HPV vaccination, regardless of whether it is administered before or after treatment, can reduce the risk of CIN2+ recurrence. In July 2017, the Catalonia Autonomous Region in Spain legislated the free provision of the nonavalent HPV vaccine to women who underwent surgery for HSIL from July 2016 onwards. The first dose can be given either preoperatively or immediately postoperatively, with the full three-dose regimen completed at 0, 2 and 6 months. The Catalonia Health Department stresses the importance of promptly administering the vaccine once HSIL is diagnosed, regardless of whether the vaccination occurs pre- or postoperatively.

A previous study by Del Pino, found that patients vaccinated with bivalent, quadrivalent or nonavalent HPV vaccines exhibited similar protective effects against recurrent HSIL, irrespective of vaccine formulation. Furthermore, the standard three-dose HPV vaccination schedule (administered at 0 months, 1–2 months and 6 months) demonstrated statistically significant differences in outcomes between patients who completed the full course and those who received one or two doses [45]. In a U.S. study by Johnson Jones ML in 2008, which included 2731 unvaccinated women, 325 women who received three doses, 108 who received two doses, and 136 who received

one dose, the estimated vaccine efficacy for one, two, and three doses was 47%, 55% and 74%, respectively, compared to unvaccinated individuals [52]. Current research suggests that completing the full three-dose HPV vaccine series is more effective in preventing lesion recurrence. However, Grade A evidence is lacking, and further RCTs are needed to provide more conclusive data.

Additionally, Jentschke *et al.* [53] compared patients under 25 years of age with those aged 25 and older who received HPV vaccination post-HSIL treatment. The relative risks for sustained CIN2+ or recurrence were 0.47 (95% CI: 0.28–0.80) and 0.52 (95% CI: 0.41–0.65), respectively, with no significant difference between the age groups [53]. Due to the limited available research, further studies are necessary to determine the optimal timing, dosages, formulations, and age for vaccination, as well as the health and economic implications of HPV vaccination.

6. Can a single dose of prophylactic HPV vaccine prevent the recurrence of CIN after conization?

In 2022, the WHO's Strategic Advisory Group of Experts on Immunization (SAGE), updated its position on HPV vaccination, informed by several observational and ecological studies, as well as one RCT [54–57]. The updated guidelines propose a single-dose vaccination regimen for both females and males aged 9 to 20, a shift from the 2017 WHO position paper [34]. The UK Joint Committee on Vaccination and Immunisation (JCVI) endorsed this recommendation, incorporating a single-dose vaccine into its national immunization program. Central to this strategy is the durability of protection, which hinges on the persistence of type-specific antibodies at levels sufficient to prevent ongoing HPV infection. Early studies have shown that although antibody levels following a single dose of Cervarix are lower than those after two or three doses, these levels remain stable for up to 11 years of follow-up [58]. To further assess the long-term immunogenicity of a single-dose quadrivalent HPV vaccine, Partha Basu's team conducted a study involving 17,729 girls aged 10–18, with serological samples collected at various time points over a 10-year period. Among them, 324 participants received one dose, 190 received two doses, 167 received three doses and 352 were unvaccinated. Neutralizing antibody titers were measured in each group. At 12 months post-vaccination, the geometric mean titer (GMT) of anti-HPV16 antibodies in the single-dose group was 9.72 IU/mL (95% CI, 8.3–11.37). At 120 months, the GMT remained virtually unchanged (9.90 IU/mL; 95% CI, 8.76–11.19), 2.05 times higher (95% CI, 1.34–3.16) than in the unvaccinated group. The antibody dynamics for HPV18, HPV6 and HPV11 mirrored those of HPV16 [59]. This study, alongside data from the Costa Rica Vaccine Trial (CVT) [55], underscores the long-term immunogenicity and efficacy of a single dose, suggesting that it can provide lasting protection. Moreover, numerous studies have demonstrated the effectiveness of a single dose in preventing cervical histological and cytological abnormalities, though there is variability in its efficacy against CIN2+, high-grade lesions and low-grade cytological abnormalities. Some studies report comparable

protection with one, two and three doses [56, 60], while others indicate that a single dose is slightly less effective than two or three doses [52, 61–64]. A few studies even suggest that a single dose may offer limited or no protection [65].

Despite the absence of clinical trials specifically investigating the efficacy of a single-dose HPV vaccine in preventing recurrence after cervical conization, previous studies on its effectiveness in preventing HPV infection, CIN, and genital warts and measuring of immunogenicity indicate that it remains a viable option for post-conization prevention.

7. Discussion

Cervical conization is a classic surgical procedure for diagnosing and treating cervical precancerous lesions, playing a critical role in reducing the incidence and mortality of cervical cancer [66]. However, due to the persistence and diversity of HPV infection, the post-surgical viral clearance is closely linked to disease prognosis [67], significantly impacting the cure rate and raising concerns among clinicians. Women who have undergone treatment for cervical lesions are at higher risk for subsequent cervical cancer development, yet there is still a lack of effective methods to promote post-surgical HPV clearance. HPV vaccines, as the most effective primary prevention strategy for cervical cancer, have been proven to be both safe and effective. Many countries have included HPV vaccination for eligible populations in their national immunization programs. Meanwhile, the potential therapeutic effects of these vaccines have become a research focus globally. Increasing evidence suggests that HPV vaccination can reduce the risk of recurrent cervical lesions in women treated with conization for HSIL.

A retrospective study involving 77 patients who underwent hysterectomy for CIN2+ or early-stage cervical cancer revealed that approximately 90% of these cases were attributed to HPV genotypes covered by the nonavalent HPV vaccine. Additionally, among patients who developed vulvar, vaginal or anal lesions post-surgery, about 90% of these lesions were also associated with vaccine-covered HPV types. This highlights the potential of the prophylactic nonavalent HPV vaccine in the treatment of HPV-related diseases, suggesting that even after cervical removal, vaccination may help prevent and manage lower genital tract lesions, including those in the vulva, vagina and anus [68].

Despite these findings, the WHO position paper on HPV vaccines has yet to offer specific recommendations regarding vaccination for individuals who have undergone surgical treatment for cervical lesions. Several key issues and gaps in current knowledge remain unresolved.

Clinical research gaps: A limited number of studies have focused on the reduction of HSIL recurrence post-conization with HPV vaccination. Most of these studies are single-center, small-sample and retrospective, which may affect the reliability and applicability of their findings. Additionally, variations in vaccination timing, vaccine types, doses and follow-up durations across studies further hinder the generalizability of the results. To overcome these limitations, future research should prioritize multicenter, large-sample and cross-sectional studies.

Insufficient cohort studies: In recent years, cohort studies have been relatively scarce. It is essential to clarify that interventional and observational studies each have their specific clinical applications. Although cohort studies typically provide lower than levels of evidence compared to RCTs, their findings often reflect real-world outcomes more accurately. Therefore, large-scale, long-term observational cohort studies should be prioritized to enhance our understanding of HPV vaccination in post-treatment settings.

Quality of RCTs: Several existing RCTs suffer from sub-optimal reporting quality, including issues with insufficient participant inclusion and, in some cases, design flaws. Future research should focus on improving the standardization of RCT protocols, implementation procedures, and reporting formats to ensure greater rigor and credibility in study findings.

Given these challenges and gaps, future studies should aim to provide clearer, more comprehensive guidance on the role of HPV vaccination following cervical lesion treatments. Such research will be critical in shaping evidence-based clinical practices moving forward.

8. Conclusion

Based on existing research, the majority of studies support the inclusion of prophylactic HPV vaccination as part of a post-treatment strategy to prevent recurrence in patients treated for CIN. This approach has the potential to reduce the risk of recurrence and its associated adverse outcomes, making it a valuable component of post-treatment management. This emerging perspective is expected to influence future HPV vaccination policies. However, due to the absence of large-scale, well-designed prospective RCTs, further research is needed before prophylactic HPV vaccination can be conclusively established as an effective method for preventing recurrence in patients following CIN treatment.

AVAILABILITY OF DATA AND MATERIALS

The data are contained within this article.

AUTHOR CONTRIBUTIONS

XL—conceptualization, writing-original draft, investigation, funding acquisition. QLR—writing-review & editing, project administration, funding acquisition.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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