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Original Research Article

Efficacy of bivalent, quadrivalent and nonavalent vaccines against human papillomavirus and cervical intraepithelial lesions: A systematic review

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Abstract

Purpose: *To investigate the effectiveness of bivalent (2v), quadrivalent (4v) and nonavalent (9v) vaccines against human papillomavirus (HPV) and cervical intraepithelial neoplasia (CIN).*
Methods: *This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria and involved an electronic search of studies published from 2018 to 2023. The efficacy of each vaccine was evaluated by comparing the number of vaccinated individuals with the number of positive cases using a 95 % confidence interval (CI).*
Results: *The overall effectiveness of the 2v, 4v and 9v vaccines against CIN was 87.23 %, 99.85 and 97.7 %, respectively. Based on 95 % CIs, the vaccine efficacies for CIN 1, CIN 2, CIN 3 and > 6 months of persistent infection were 87.4, 86.2, 88.08 and 95.92 % for the 2v vaccine; 99.56, 100, 100 and 75.9 % for the 4v vaccine; and 98, 96.3, 99 and 96 % for the 9v vaccine, respectively. The 4vHPV vaccine was the most effective against HPV types in terms of protection against different stages of CIN. However, the 9vHPV vaccine was highly effective and offered protection against most HPV types.*
Conclusion: *The 9vHPV vaccine is highly effective and thus an ideal choice for HPV and CIN as it offers protection against most HPV types.*

Keywords: *Human papillomavirus, HPV vaccines, Efficacy, Cervical intraepithelial neoplasia, Cervical intraepithelial lesions*

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INTRODUCTION

Infectious diseases that spread via vaginal, oral, or anal intercourse are known as sexually transmitted diseases (STDs) [1]. One of the most common STDs is caused by human papillomavirus (HPV), which affects the skin and the vaginal, anal and oropharyngeal mucous membranes [2–4]. The HPV is a double-stranded DNA virus and a member of the Papillomaviridae

family, which currently comprises 29 genera and over 100 species [4–8]. To date, over 200 HPV genotypes have been reported, with each species comprising many genotypes [9]. The primary genotypes known to cause cancer are those of the Alpha genus, whereas those of the Beta and Gamma genera often cause asymptomatic infections. These genotypes are classified as high risk (HPV types 16, 18, 31, 33, 35, 35, 39, 45, 51, 52, 56, 58, 59, 68 and 82), low risk (HPV types 6, 11, 40, 42, 43, 44, 44, 54, 61, 70, 72 and 81), or possibly high risk (HPV types 26, 34, 53, 57, 66, 69, 73, and 84) [10,11].

Genital HPV infections can present a wide array of clinical symptoms, ranging from asymptomatic to malignant indications [12]. Benign warts can spread across the mouth, cervix, vagina, anal and anogenital areas, urinary meatus and pubis [13]. Despite being asymptomatic, these are responsible for HPV transmission during intercourse [14]. Cutaneous warts are benign epithelial lesions that occur anywhere on the skin surface and usually affect the hands, feet, neck and face [15,16]. They are harmless and spread through skin contact, often among young people and children [13].

In most cases, HPV infections cause cervical dysplasia, also known as cervical intraepithelial neoplasia (CIN). This refers to an abnormal epithelial growth on the surface of the cervix, resulting in morphological deformity of cells and loss of normal tissue structure [17]. Cervical intraepithelial neoplasia is a type of precancerous lesion that can be divided into three stages: CIN 1 (low-grade intraepithelial lesion; mild dysplasia), CIN 2 (high-grade squamous intraepithelial lesion; moderate dysplasia) and CIN 3 (high-grade squamous intraepithelial lesion; severe dysplasia; carcinoma *in situ*). If these dysplasias are not detected in the initial phase, they may develop into squamous cell carcinoma of the epithelial cells or adenocarcinoma *in situ* of the endocervical glands [18]. Both men and women are HPV carriers and transmitters. Although men can be infected with the virus, most cases are asymptomatic [19]. In addition to respiratory papillomatosis, men may develop cutaneous warts in the anal, oropharyngeal and penile regions.

In 2020, cervical cancer ranked fourth globally in terms of all-cause mortality and is the ninth most common tumor to be diagnosed worldwide [20-22]. Vaccines against HPV have been developed because of the link between cervical cancer and the virus [23]. Currently, the bivalent (2vHPV), quadrivalent (4vHPV) and nonavalent (9vHPV) HPV vaccines are the three most commonly used HPV vaccines worldwide [24,25]. Two doses (0 and 6 months, respectively) of the 2vHPV and 9vHPV vaccines are required for males and females aged 9 – 14 years, whereas three doses (0, 1 – 2 and 6 months, respectively) are administered to individuals 15 years and older [26–29]. On the other hand, the 2vHPV vaccines target HPV types 16 and 18, the 4vHPV vaccines target HPV types 6, 11, 16 and 18, while the 9vHPV vaccines target HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58. These vaccines demonstrate higher efficacy against CIN, thereby lowering the incidence of cervical cancer in the general population [26]. This review therefore assessed the efficacy of three distinct vaccines against HPV and CIN.

METHODS

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) criteria [30]. The search strategy was based on the following eligibility criteria: original research articles (multicenter, randomized, double-blind, controlled clinical trials); baseline studies on vaccination efficacy; studies based on bivalent, tetravalent, or nonavalent vaccines; studies that used a placebo or another vaccine as a control group; articles written in English language and published up to March 20, 2023; and studies with a follow-up period of less than 10 years. The exclusion criteria were as follows: scientific studies published before 2010; studies that exclusively involved male participants, which are irrelevant to the efficacy of the three HPV vaccines; trials with a quality score < 6 on the Critical Appraisal Skills Programme (CASP) checklist [31,32]; articles that did not discuss the efficacy of vaccines; and articles that did not evaluate the efficacy of the vaccines against CIN 1, CIN 2, and CIN 3.

An electronic search in PubMed, Scopus and Web of Science databases using the keywords “human papillomavirus”, “vaccine efficacy”, “cervical cancer” or “HPV vaccine” identified studies published between 2018 and 2023 (five years). The articles were selected by reading their abstracts and titles, both of which had to be appropriate for the topic. Figure 1 shows a flow diagram summarizing the literature search.

The scientific evidence quality of the publications was assessed using the CASP checklist, which is designed to critically appraise clinical evidence from randomized controlled trials [31,32]. This checklist, which contains 11 valid questions for understanding a clinical trial, is divided into three sections viz: validity of trial results, magnitude of

effect of the results, as well as precision and applicability of the results. Three independent authors (FA, HG, and AB) searched and removed any duplicate articles. After eliminating 105 publications that did not meet the eligibility criteria, 112 were selected from the first search (Figure 1). Independent reviewers extracted data from the selected articles using an established procedure. The authors submitted the selected articles for assessment by an unbiased advisor before their final inclusion in the study. In cases of disagreement or opposing opinions, a final decision was made through discussion until a consensus was reached.

An efficacy analysis was performed for the per-protocol efficacy group of participants, which comprised participants who were not infected with HPV at the time of vaccination and received all three doses within one year. This method ensured accurate information regarding vaccine efficacy. The efficacy of each vaccine was determined by comparing the total number of vaccines in each group with the number of positive cases for each condition using a 95 % confidence interval (CI).

RESULTS

Two studies conducted on the 2vHPV vaccine were included [33,34]. The study conducted by Zhu *et al* comprised 5780 patients between 18 and 25 years of age [33]. The results indicated efficacies of 96.8 % (95 % CI: 88 – 99.6) against > 6 months of persistent infection (cases: two vaccinated vs. 63 control individuals); 93.3 % (95 % CI: 56.2 – 99.8) against CIN 1 (cases: 1 vaccinated vs. 15 control individuals); and 87.3 % (95 % CI: 5.5 – 99.7) against CIN 2+ (cases: 1 vaccinated vs. 8 control individuals) in the per-protocol efficacy population. Porras *et al*. studied 4603 individuals between 18 and 25 years of age and obtained vaccine efficacies of 94.9 % (95 % CI: 73.7 – 99.4) against CIN 3 (cases: 2 vaccinated vs. 36 control individuals) and 97.4 % (95 % CI: 88 – 99.6) against CIN 2 (cases: 2 vaccinated vs. 72 control individuals) [34].

In addition, three 4vHPV vaccine studies were included: one descriptive, single-arm, open-label trial [35] and two randomized, double-blind, placebo-controlled effectiveness trials [36,37]. An analysis of 2602 women between 20 and 25 years of age for over 72 months showed that 21 individuals in the control (placebo) group and none in the vaccine group developed HPV types 6, 11, 16 and 18-related cervical lesions. This indicated 100 % (95 % CI: 70.9 – 100) vaccine efficacy in the per-protocol efficacy population [36]. Additionally, the efficacy against > 6 months of persistent infection was 75.9 % (95 % CI: 43.5 – 91.1) in the per-protocol efficacy population. The efficacy of the vaccine against HPV types 6, 11, 16 and 18 in 5493 women between 16 and 23 years of age during 168 months of follow-up was 98.7 % (95 % CI: 92.9 – 100) compared with the placebo [37].

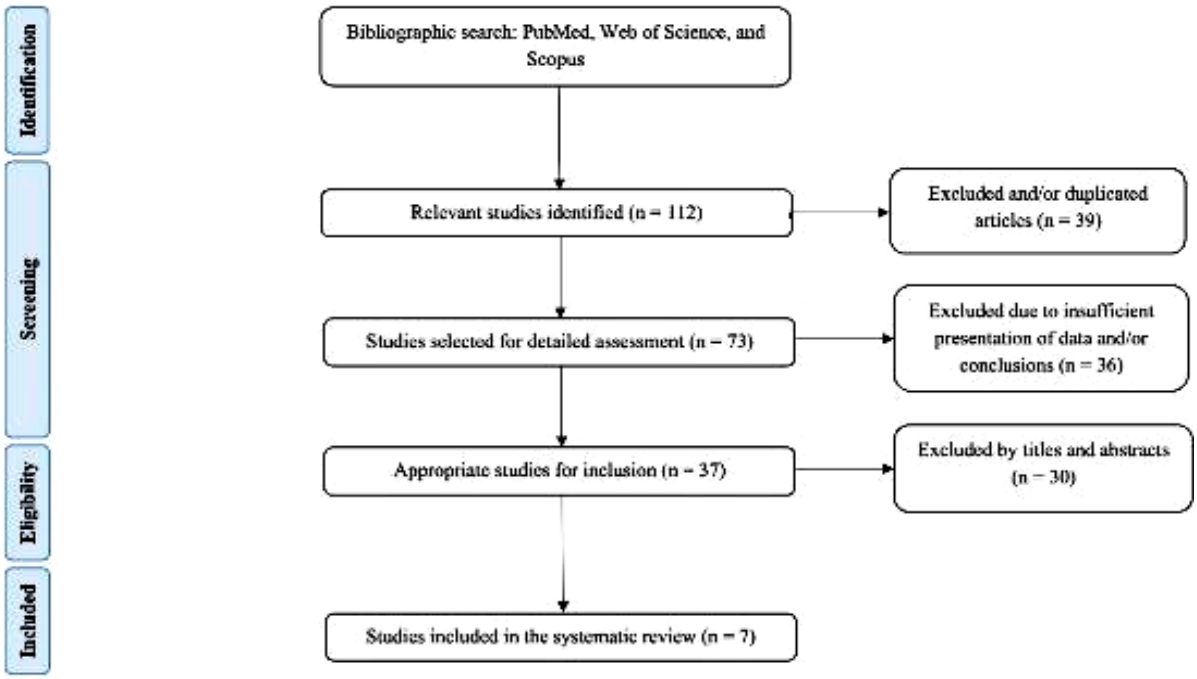

Figure 1: A PRISMA flowchart depicting the literature search and selection process for the systematic review

Furthermore, in the per-protocol efficacy population of 1030 women between 17 and 26 years of age, the vaccine showed 100 % (95 % CI: 0.0 – 0.1) efficacy against cervical lesions of any grade caused by all the HPV types covered [35].

Also, two 9vHPV vaccination studies included in this review were both randomized, double-blind, placebo-controlled trials that examined vaccine efficacy against CIN [38,39]. In a study of 1717 patients between 16 and 26 years of age, the 9vHPV group had a 100 % lower incidence of cervical cancer of any grade than that in the 4vHPV vaccine group (95 % CI: 71.5 – 98.7; cases: 7 in the 4vHPV group vs. none in the 9vHPV group) [38]. The efficacy of the 9vHPV vaccine against > 6 months of persistent infection by HPV types 31, 33, 45, 52 and 58 was 95.8 % (95 % CI: 87.8 – 98.9; 3 infected persons in the 9vHPV group vs. 67 in the 4vHPV group). In addition, in a study of 4744 women between 16 and 26 years of age, one patient with CIN 3 was reported in the 9vHPV group compared to 45 patients with CIN 1 and CIN 3 in the 4vHPV group [39]. The overall efficacy of the 9vHPV vaccine against cervical cancer of any grade was 98 % (95 % CI: 88.9 – 99.9) compared to that of 4vHPV. The 9vHPV efficacy against HPV-related persistent infections (HPV types 31, 33, 45, 52 and 58) was 95.2 % (95 % CI: 92.7 – 97.0; cases: 424 in the 4vHPV group vs. 22 in the 9vHPV group). The results of seven studies on the efficacy of the 2vHPV, 4vHPV, and 9vHPV vaccines are discussed in Table 1 and Table 2.

DISCUSSION

In this review, efficacy was evaluated exclusively in per-protocol efficacy groups. Overall, the studies included the cumulative incidence of vaccine efficacy in two participant groups: those who received three vaccine doses and were initially HPV-free, and those who received at least one dose and were infected with a specific HPV type. HPV vaccines demonstrate high levels of efficacy in preventing persistent viral infections [40–43]. In studies involving women (16 – 26 years of age) from two different nations, the overall efficacy of 2vHPV vaccines against CINs was 87.23 % after evaluating the effectiveness of each trial against grades 1, 2 and 3 squamous lesions [33,34]. The efficacy values, determined by a 95 % CI, were 87.4 % for CIN 1, 86.2 % for CIN 2, 88.08 % for CIN 3 and 95.92 % for > 6 months of persistent infection [33,34]. Among the three vaccines, 2vHPV vaccine demonstrated the lowest efficacy against CIN and the second highest incidence of systemic and local (at the injection site) adverse effects. Studies on patients (16 – 26 years of age) from different countries have reported that the overall effectiveness of the 4vHPV vaccine against CIN is 99.85 %. The 4vHPV vaccine provides protection against CIN crossmatching for HPV types 31 and 45 [35–37].

The overall effectiveness of 9vHPV vaccine against CIN in women (16 – 26 years of age) from different countries was 97.7 % after analyzing the effectiveness of each trial against grade 1, 2 and 3 squamous lesions [38,39]. Studies comparing the efficacies of 4vHPV and 9vHPV showed that the latter was more effective overall for HPV types 6, 11, 16 and 18, and protected against HPV types 31 and 45 [38,39]. Individuals who received the 4vHPV vaccine exhibited the lowest risk of adverse effects, both locally and systemically [44,45]. While most individuals in the 9vHPV vaccination group experienced adverse effects, the most prevalent manifestations were headaches and pyrexia [46]. No deaths or serious adverse events were associated with this vaccine [47,48].

Europe is the only continent in which all nations include HPV vaccinations in their schedules [49], whereas Africa has the fewest countries (only 11 countries) providing HPV vaccines to girls [50]. The data from this systemic review highlight the significance of incorporating these vaccines into vaccination schedules, as the benefits serve as incentives for the public to vaccinate. Long-term follow-ups are necessary to evaluate the sustained effectiveness of these vaccines. None of the studies in this systematic review had follow-up periods >10 years. However, extending the follow-up time entails greater costs as it requires conducting diagnostic and control tests.

Males are also carriers of HPV and there is a 40 % correlation between high-risk HPV types and penile cancer [51]. However, males are not eligible for free HPV vaccinations [52]. The effectiveness of HPV vaccines in males needs to be studied, as insufficient data is available to indicate whether these vaccines can successfully prevent oropharyngeal, anal and penile cancers. Studies should focus on the 2vHPV vaccine, which has been poorly evaluated in males. After evaluating the long-term efficacy and immune response to a single dose of HPV vaccine, patients receiving one dose were reported to show better outcomes than those receiving two or three doses. Large observational studies from Costa Rica and India have indicated that single-dose HPV vaccinations provide long-term protection equivalent to multidose regimens [53,54]. The potential increase in vaccination

Table 1: Characteristics of clinical trials of three different types of HPV vaccines included in the systematic review

Author; Year; Country	Type of study	Study population; Age	Vaccination status: number of individuals	Objectives	Results
Zhu *et al*, 2019; China [33]	Multicenter, double-blind, randomized, controlled trial	5780; 18–25 years	2vHPV: 2523 Placebo: 2534	Assessed the effectiveness, immunogenicity and safety of the 2vHPV vaccine during 84 months of follow-up	The efficacies were 93.3% for CIN 1, 87.3% for CIN 2 and 96.8% for >6 months of persistent infection. Severe AEs were observed in 1.85% of the vaccine group and 2.7% of the control group
Porras *et al*, 2020; Costa Rica [34]	Randomized, double-blind, placebo-controlled trial	4603; 18–25 years	2vHPV: 2073	Evaluated the effectiveness and safety of the 2vHPV vaccine during 132 months of follow-up	The efficacies were 97.4% for CIN 2 (2 vs. 72) and 94.9% for CIN 3 (2 vs. 36). Pain, swelling, erythema, and pruritus were the injection site AEs (67.4% control, 68% 2vHPV); headache and pyrexia were the systemic AEs (41.1% control, 43.9% 2vHPV)
Sakamoto *et al*, 2019; Japan [35]	Open-label, single-arm descriptive trial	1030; 17–26 years	4vHPV: 1030	Evaluated the effectiveness and safety of the 4vHPV vaccine for 48 months of follow-up	The efficacy against CIN related to HPV 6, 11, 16 and 18 was 100% (0 vs. 21). Pain (11.5%), swelling (3.9%), pruritus (24%), and erythema (1.2%) were the injection site AEs (8.6% 4vHPV); headache (2.3%), malaise (1.7%) and pyrexia (1.3%) were the systemic AEs (14.5% 4vHPV)
Wei *et al*, 2019; China [36]	Randomized, double-blind, placebo-controlled, safety and efficacy study	2602; 20–25 years	4vHPV: 1308	Evaluated the effectiveness of the 4vHPV vaccine for 72 months of follow-up	The efficacy against CIN related to HPV 6, 11, 16, and 18 was 100% (0 vs. 21). The efficacy against >6 months of persistent infection by HPV 6, 11, 16 and 18 was 75.9% (7 vs 28)
Kjaer *et al*, 2020; Denmark, Iceland, Norway, and Sweden [37]	Randomized, double-blind, placebo-controlled trial	5493; 16–23 years	4vHPV: 2650 Placebo: 1843	Evaluated the effectiveness of the 4vHPV vaccine for 168 months of follow-up	The efficacy against CIN related to HPV 6, 11, 16 and 18 was 98.7% (0 vs 21)

2vHPV: bivalent HPV vaccine; 4vHPV: quadrivalent HPV vaccine; 9vHPV: nonavalent HPV vaccine; AEs: adverse events; CIN: cervical intraepithelial neoplasia; HPV: human papillomavirus

Table 2: Characteristics of clinical trials of three different types of HPV vaccines included in the systematic review *(continued)*

Author; Year; Country	Type of study	Study population; Age	Vaccination status: number of individuals	Objectives	Results
Garland *et al*, 2018; Japan, Hong Kong, South Korea, Taiwan, and Thailand [38]	Randomized, double-blind, 4vHPV vaccine-controlled study	1717; 16–26 years	9vHPV: 858 4vHPV: 859	Assessed the effectiveness, immunogenicity, and safety of the 9vHPV vaccine during 54 months of follow-up	The efficacy against CIN related to HPV 31, 33, 45, 52 and 58 was 100% (0 vs 7). The efficacy against >6 months of persistent infection by HPV 31, 33, 45, 52 and 58 was 95.8% (3 vs 67). Pain, swelling, erythema and pruritus were the injection site AEs (85.5% and 80.2%); headache and pyrexia were the systemic AEs (43.8% 9vHPV and 45.7% 4vHPV).
Ruiz-Sternberg *et al*, 2018; Brazil, Chile, Colombia, Mexico, and Peru [39]	Randomized, double-blind, 4vHPV vaccine-controlled trial	4744; 16–26 years	9vHPV: 2372 4vHPV: 2372	Assessed the effectiveness, immunogenicity, and safety of the 9vHPV vaccine during 58 months of follow-up	The efficacy against CIN related to HPV 31, 33, 45, 52 and 58 was 98% (1 vs 45). The efficacy against >6 months of persistent infection by HPV 31, 33, 45, 52 and 58 was 95.2% (22 vs 424). Pain, edema, erythema, and pruritus were the injection site AEs (89.6% 9vHPV and 84.2% 4vHPV); headache, dizziness, nausea and pyrexia were the systemic AEs (61.4% 9vHPV vs 60.6% 4vHPV).

2vHPV: bivalent HPV vaccine; 4vHPV: quadrivalent HPV vaccine; 9vHPV: nonavalent HPV vaccine; AEs: adverse events; CIN: cervical intraepithelial neoplasia; HPV: human papillomavirus

rates could be attributed to the possibility of administering fewer doses.

Limitations of this study

This systematic review was limited by the lack of previously published reports with a follow-up period of >10 years. Therefore, it was difficult to accurately evaluate the efficacy of the vaccines because the risk of CIN decreased with shorter durations.

CONCLUSION

The 4vHPV vaccine is the most effective against HPV types in terms of protection against different stages of CIN. However, the 9vHPV vaccine is highly effective and offers protection against most HPV types. Thus, the 9vHPV vaccine is an ideal choice, because it is effective against a wider range of HPV types.

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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