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Comparative effectiveness and immunogenicity of single-dose and multi-dose human papillomavirus vaccination: a systematic review

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Abstract

Introduction Administering a single dose of the human papillomavirus vaccine substantially reduces costs and simplifies distribution. However, due to inconsistent findings in the existing research, there is an ongoing debate regarding the efficacy of a single-dose HPV vaccine regimen. Therefore, this systematic review investigated the effects of different HPV vaccine administration frequencies.

Methods We conducted a comprehensive search in the Cochrane Library, Embase, MEDLINE (accessed via PubMed), and CINAHL databases using MeSH and Emtree terms, with the assistance of a professional librarian. We included articles published until April 2024 without restrictions on publication year. We independently performed screening, data extraction, and quality appraisal using the Risk of Bias 2 for randomized controlled trial. This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist.

Results Six publications derived from four unique randomized controlled trials were included in this review. These studies reported on immunogenicity outcomes from 6 to 132 months after HPV vaccination. Although the total number of participants across studies was 29,415, some studies reported overlapping cohorts and the sample size should not be interpreted as additive. Reported geometric mean concentrations (GMC) for single-dose recipients ranged from 2.17 to 176 EU/mL, and for three-dose recipients from 7.92 to 1045.37 EU/mL, depending on the vaccine type, assay, and follow-up time point. The HPV infection incidence rates were 0.0%–1.8% and 0.0%–0.9%, whereas vaccine efficacy was 53.9%–100.0% and 72.6%–100.0% for 1 and 3 doses, respectively.

Conclusions The findings indicate that, although single-dose vaccination generates lower antibody levels, it still offers substantial protection against HPV infection. This suggests that a single-dose approach could serve as a practical and cost-effective alternative in resource-constrained settings, addressing economic and logistical challenges associated with multi-dose schedules.

Trial registration PROSPERO registration ID # CRD42024509046.

Keywords Cervix cancer prevention, Human papillomavirus virus, Papillomavirus vaccine, Systematic review, Vaccine efficacy

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Introduction

The human papillomavirus (HPV) vaccine was first authorized in 2006 and approved after several stages of clinical trials [1, 2]. HPV vaccination is a crucial public health strategy aimed at preventing HPV-related diseases, including cervical cancer, by reducing or eliminating HPV infections. HPV is classified into high-risk and low-risk types, with 14 specific types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) currently considered high risk due to their potential to cause cancer in humans [3]. Beyond types 16 and 18, which account for over 70% of cervical cancer cases in women [4], HPV is also linked to various other conditions, including cancers of the vulva, vagina, penis, anus, and oropharynx, as well as genital warts and respiratory papillomatosis [5–7]. Cervical cancer is a common cancer type among women, with approximately 660,000 new cases and 350,000 deaths reported in 2022 [8]. In Asia, the incidence of cervical cancer is approximately 604,000 cases, with 170,000 related deaths, nearly double the figures observed in Europe or the United States [9]. Along with screening, HPV vaccination is crucial for preventing cervical cancer [10].

The HPV vaccines currently available include Cervarix (GlaxoSmithKline Biologicals, London, UK), Gardasil, Gardasil 9 (Merck & Co., Rathway, NJ, USA), and Cecolin (Xiamen Innovax Biotech CO., LTD., Xiamen, China), all of which demonstrate high immunogenicity and efficacy [11–13]. The vaccine was initially approved with a 3-dose regimen administered over 6 months based on large-scale randomized clinical trials (RCTs). According to the latest WHO position paper [14], individuals aged 9–20 years may receive either a single dose or two doses of the HPV vaccine, depending on national immunization schedules. For immunocompromised individuals, a three-dose schedule is still recommended. A study by Hull et al. [15] indicated that 90% of cervical cancer deaths occur in low- and middle-income countries (LMICs), yet only 26% of those countries have implemented HPV vaccine programs. In Asian LMICs where HPV vaccination is not available or not included in the national schedule, the burden of HPV-related diseases remains significant. Therefore, improving access to HPV vaccine programs is essential to save more lives in these regions.

HPV vaccination has been introduced in less than 30% of LMICs, whereas more than 85% of high-income countries have successfully implemented the vaccine into their national immunization schedules [6]. Efforts are underway to address these issues; however, the current multi-dose regimen poses challenges regarding cost, time, and logistical complexities [16].

A single dose of the HPV vaccine offers several advantages including effectiveness, cost efficiency, and logistical simplification [12]. A single dose provides similar protective effects against HPV-16/18 as the traditional 2-or 3-dose regimens, demonstrating comparable efficacy in preventing cervical lesions associated with HPV infection. Additionally, a single dose offers a sustained immune response and protective effects for over 10 years post-vaccination. These results support the WHO guidelines, demonstrating that a single dose can provide a similar level of protection as multiple doses [10]. The cost efficiency of a single dose is particularly important for LMICs. Reducing the number of doses makes vaccination programs more affordable and accessible, thereby potentially increasing vaccination coverage and impact on public health. Additionally, implementing a single-dose regimen simplifies logistics, making it easier to distribute and administer the vaccine in remote or underserved areas. This approach helps reduce healthcare system burdens. It also enhances the feasibility of widespread immunization, especially in underserved regions [15, 16]. While prior systematic reviews—such as the Cochrane review for WHO [17] and Whitworth et al. [18]—have addressed the efficacy of single-dose HPV vaccination, this review offers an updated synthesis that includes the most recent long-term immunogenicity data, standardizes antibody measures using GMCs, and highlights comparative effectiveness from diverse global trial settings. Our analysis incorporates post-hoc data from extended follow-up studies, thereby contributing novel insights to the evolving evidence base. Administering a single-dose regimen of the HPV vaccine can significantly reduce vaccine supply costs and streamline delivery, thus enhance the accessibility and sustainability of HPV vaccination [14]. The relationship between HPV vaccine dosage and its efficacy has been a subject of continuous research since the vaccine's development. Recent studies have indicated that a single dose may provide comparable protective effects [19, 20]. However, understanding the long-term immune response and efficacy associated with varying vaccination regimens requires the integration and review of the latest data. This study systematically reviews the existing literature on the relationship between HPV vaccine efficacy and dosage, synthesizing scientific evidence to inform vaccination guidelines. By doing so, it aims to establish clear recommendations on HPV vaccine dosages and strengthen the foundation for public health strategies.

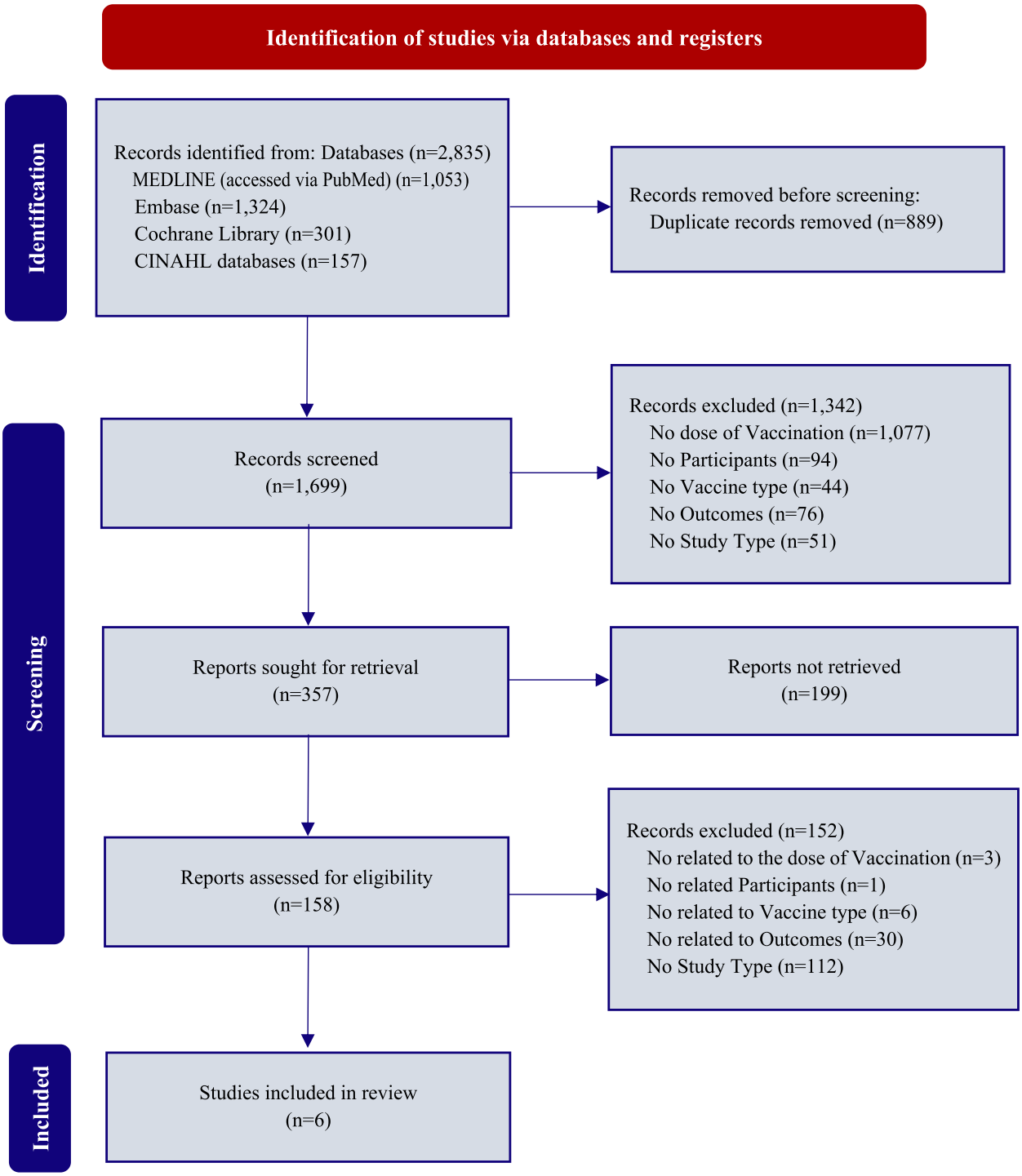

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the article selection process

Methods

Design

This systematic review was prospectively registered in the PROSPERO database (CRD42024509046) [21] and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Fig. 1) [22].

Search strategy

In collaboration with a university librarian, we conducted a comprehensive search of studies published until April

2024. We used electronic records obtained from the Cochrane Library, Embase, MEDLINE (accessed via PubMed), and CINAHL databases, incorporating MeSH and Emtree terms to ensure thorough coverage (Supplemental Table S1). Our searches included combinations of free text words and index terms using Boolean operators such as "HPV," "Human Papillomavirus viruses [MeSh]," "wart virus/de," "Human Papillomavirus vaccine/de," and "MM Vaccines +." The search yielded 301 (Cochrane Library), 1,324 (Embase), 1,053 (PubMed), and 157 (CINAHL) records. The search strategies for every electronic database were shown in the supplementary (Supplementary S1).

Eligibility criteria and study selection

Two researchers independently evaluated the retrieved studies using predefined data extraction forms. In cases of disagreement, a consensus was reached through discussion. The study designs included in this systematic review were limited to RCTs.

The inclusion and exclusion criteria were based on the population (patient), intervention, comparison, outcome (PICO) framework. The population (P) in this study comprised girls and boys aged ≥ 9 years. Immunocompromised individuals were excluded. The participants received at least 1 dose of the licensed HPV vaccine (Cervarix, Gardasil, or Gardasil 9). Intervention (I) was defined as an administration of a single dose of a licensed HPV vaccine. Comparisons (C) were made between single-dose vaccination and no vaccination (placebo), single-dose and 2-dose vaccination, single-dose and 3-dose vaccination, and single-dose and 2-or 3-dose vaccination. The outcomes (O) included immunological indicators, specifically geometric mean concentration (GMC), and clinical indicators such as the incidence of high-risk HPV infection and vaccine efficacy. While the primary outcome of interest was vaccine efficacy, immunogenicity outcomes were also extracted and synthesized when reported in conjunction with efficacy measures.

Data extraction

The extracted data included basic information about the studies (authors, publication year, country of study, and study design), vaccines (type, product name, and number of doses), and participants (sex, age, and number of participants). The variables confirmed through mediation included GMC and clinical outcomes such as the incidence of HPV infections and vaccine efficacy. Figure 1 displays a flowchart of the literature selection process. To ensure consistency of the extracted data, two researchers independently conducted the extractions. In cases of disagreement, adjustments were made by reaching a consensus.

Risk of bias assessment

A quality assessment of the literature was independently conducted by two researchers using the Risk of Bias 2 (RoB 2) tool for RCTs [23] as described in the Cochrane handbook for systematic reviews of interventions. In cases of disagreement, adjustments were made by reaching a consensus. Six publications from four unique randomized controlled trials were assessed for the risk of bias using the RoB 2 tool. The following domains were evaluated: 1) bias arising from the randomization process; 2) bias due to deviations from intended interventions; 3) bias due to missing outcome data; 4) bias in the measurement of the outcome; 5) bias in the selection of the reported results; and 6) overall risk of bias based on the evaluations of these 5 domains. Responses to questions within the RoB 2 tool include "Yes," "Probably yes," "Probably no," "No," and "Not applicable." The risk of bias in each domain was generated using an algorithm based on these responses, and the assessment results were categorized as "Low risk of bias" if all domains was assessed as having low risk, "Some concerns" if at least 1 domain was assessed as having some concerns with no domain assessed as having high risk, and "High risk of bias" if at least 1 domain was assessed as having high risk [23]. Although prior assessments such as the Cochrane review rated the Safaeian and Sankaranarayanan studies as low risk of bias, we judged them as having serious risk due to critical post-hoc design modifications and substantial protocol deviations. Specifically, the early suspension of randomization and subsequent cohort-based analyses resulted in potential selection bias and lack of allocation concealment, which are considered serious under the RoB 2.0 framework.

Results

Study characteristics

Although the total sample size across all studies was 29,415, overlapping cohorts from the Costa Rica and India trials were accounted for to prevent double-counting, and data were synthesized at the trial level. After excluding duplicates, 1,699 studies were extracted from the databases. After screening the titles and abstracts, 158 studies were evaluated for eligibility. Ultimately, 6 publications derived from four unique randomized controlled trials were included in this systematic review following the described search strategy in Fig. 1. All 6 studies were RCTs, with 1, 1, 2, and 2 studies conducted in Kenya, Canada, Costa Rica, and India, respectively.

Table 1 Characteristics of the included studies

Author (year)	Country	Period	F/U	Vaccine Type	Dose	Sex	Age (years)	Number of patients	Outcomes	Risk of bias					
										D1	D2	D3	D4	D5	D6
Barnabas et al. (2023) [24]	Africa	2018–2021	3Y	Cervarix Gardasil 9	1	F	15–20	2,275	Incidence of HPV infection & VE	+	+	+	+	+	+
Gilca et al. (2018) [25]	Québec	2016–2018	6 M	Cervarix Gardasil 9	1, 2	F, M	9–10	371	GMC	+	+	+	+	+	+
Kreimer et al. (2020) [26]	Costa Rica	2004–2018	9/11Y	Cervarix	1, 2, 3	F	18–25	7,466	Incidence of HPV infection & VE, GMC	!	!	+	+	+	!
Joshi et al. (2023) [27]	India	2012–2022	10Y	Gardasil	1, 2, 3	F	10–18	14,277	GMC	+	!	+	+	+	!
Sankaranarayanan et al. (2018) [28]	India	2009–2017	48 M	Gardasil	1, 2, 3	F	10–18	19,303	Incidence of HPV infection	−	−	−	+	−	−
Safaeian et al. (2013) [29]	Costa Rica	2004–2012	4Y	Gardasil	1, 2, 3	F	18–25	1,539	GMC	+	+	+	+	+	−

Abbreviations: *F/U* flow-up, *M* male, *F* female, *RCT* randomized controlled trial, *HPV* human papillomavirus, *VE* vaccine efficacy, *GMC* geometric mean concentration, *Y* year, *M* month, *D1* randomization process, *D2* deviations from the intended interventions, *D3* missing outcome data, *D4* measurement of the outcome, *D5* Selection of the reported result, *D6* overall

Total Number of patients: 29,415

These studies had a combined total of 29,415 patients (Table 1). Notably, the studies by Kreimer and Safaeian are based on the same cohort from the Costa Rica Vaccine Trial (CVT), and the studies by Sankaranarayanan and Joshi are from the IARC India trial. These overlapping cohorts were accounted for in our synthesis to avoid double-counting participants. Although all six publications were derived from randomized controlled trials, the studies from Costa Rica [26, 29] and India [27, 28] involved post-hoc analyses of participants based on cohort assignments after the suspension of randomization. These analyses are therefore more akin to prospective cohort studies and differ in design from trials such as KEN SHE, which maintained full random allocation.

Risk of bias

Two studies were assessed as having a low risk of bias [24, 25], 2 studies were assessed as having some concerns [26, 27], and 2 studies were assessed as having a high risk of bias [28, 29] (Table 1).

Vaccine type, number of doses, and outcomes

Two of the included studies had comparisons between bivalent and nonavalent vaccines and 2 studies confirmed the efficacy of quadrivalent vaccines. Additionally, 2 studies confirmed the effectiveness of bivalent vaccines. Regarding outcomes, GMC (Table 2) and HPV infection incidence (Table 3) were assessed in 3 studies each. In studies that assessed GMC, bivalent, quadrivalent, and nonavalent vaccines were administered in single, 2, and 3 doses, and outcomes at 6, 18, 36, 48, and 120 months post-vaccination were analyzed according to vaccine type and number of doses. In the studies that assessed the incidence of HPV infection and vaccine efficacy, bivalent, quadrivalent, and nonavalent vaccines were administered in single, 2, or 3 doses, and the outcomes at 36, 48, and 84 months post-vaccination were evaluated based on vaccine type and number of doses.

Across the six included RCTs, single-dose HPV vaccination demonstrated sustained immunogenicity and high efficacy over follow-up periods ranging from 36 to 48 months. Although geometric mean concentration (GMC) was generally lower in the single-dose group compared to multi-dose groups, seropositivity remained high, indicating a durable immune response. These findings support the potential of single-dose regimens as a viable alternative to multi-dose schedules.

The results of these studies confirmed that even a single dose induced a sustained immune response and provided long-term protection. In addition to vaccine efficacy, Kreimer et al. [26]'s study also reported immunogenicity outcomes stratified by the number of doses. Their findings demonstrated that although antibody concentration was lower in the single-dose group, seropositivity for HPV-16 and HPV-18 remained high over time, indicating sustained immune response.

Discussion

HPV infection is one of the most common sexually transmitted infections worldwide. Most sexually active individuals are likely to contract it at least once in their lifetime. Although many infections resolve spontaneously, persistent HPV infection can cause a range of health problems including cancer. [30]. HPV is a leading cause of cervical cancer and is associated with other cancers, such as vaginal, anal, oropharyngeal, and penile cancers, making prevention crucial for both males and females [31, 32]. The HPV vaccine has demonstrated high efficacy in preventing high-risk HPV types, leading to a substantial reduction in the incidence of HPV-related diseases, including cervical cancer, over the long term [33–35]. Globally, cervical cancer is the second most prevalent cancer type among women, with particularly high incidence and mortality rates in LMICs due to limited access to early screening and treatment [15, 36, 37]. This underscores the vital importance of preventive measures. Thus, preventing HPV infection through vaccination and consequently reducing the incidence of cervical cancer and other HPV-related diseases is a crucial public health objective.

The WHO has developed guidelines to assist countries in implementing and managing effective immunization programs [38]. These guidelines advocate for international collaborations to enhance HPV vaccine distribution and provide technical and financial support for immunization initiatives [39]. According to the WHO guidelines, the HPV vaccine was initially approved for a 3-dose regimen [38]. However, based on immunogenicity data, a 2-dose regimen was later approved for adolescents, and currently, a single-dose regimen is also recommended [40]. The 3-dose regimen has demonstrated very high immunogenicity, with the strongest immune responses being observed in females aged 9–15 years [41]. In studies involving women aged 18–45 years, the 3-dose regimen showed seropositivity rates of 100% for HPV-16 and 98% for HPV-18 at 66 months post-vaccination [42]. In a study that compared immunogenicity outcomes, the 2-dose vaccination regimen demonstrated non-inferior or higher GMCs compared with the 3-dose regimen [43–46], and protection against HPV-16/18-related pre-cervical cancer was confirmed with fewer than 3 doses [47]. Despite these advantages, multiple doses involve higher vaccination costs, multiple hospital visits, and a need for additional healthcare personnel to manage the dosing schedule, which can cause strains on other

Table 2 Geometric mean concentrations of anti-HPV antibodies according to vaccine type and number of vaccinations

Study (year)	Month	Vaccine type	HPV	Dose	GMC (EU/mL) (95% CI)	Sero-positive (%)	*P*-value
Gilca et al. (2018) [25]	6	9 V	HPV 6	1	6.4 (5.6–7.3)	100.0	< 0.05
				2	375.9 (334.6–422.2)	100.0	< 0.05
			HPV 11	1	6.9 (6.0–7.9)	100.0	< 0.05
				2	525.2 (470.1–586.8)	100.0	< 0.05
			HPV 16	1	30.3 (27.1–33.8)	100.0	< 0.05
				2	1174.5 (1049–1315)	100.0	< 0.05
			HPV 18	1	13.7 (12.2–15.3)	100.0	< 0.05
				2	593.9 (527.7–668.3)	100.0	< 0.05
			HPV 31	1	22.6 (19.9–25.7)	100.0	< 0.05
				2	1163.0 (1033–1309)	100.0	< 0.05
			HPV 33	1	36.8 (32.9–41.2)	100.0	< 0.05
				2	1970.6 (1746–2224)	100.0	< 0.05
			HPV 45	1	26.0 (23.0–29.5)	100.0	< 0.05
				2	1230 (1085–1395)	100.0	< 0.05
			HPV 52	1	39.1 (33.8–45.1)	100.0	< 0.05
				2	1095 (981–1222)	100.0	< 0.05
			HPV 58	1	70.3 (62.9–78.5)	100.0	< 0.05
				2	1859 (1673–2065)	100.0	< 0.05
	6	2 V	HPV 16	1	16.7(13.3–21.0)	100.0	< 0.05
			HPV 18	1	11.7(9.4–14.7)	100.0	< 0.05
Kreimer et al. (2020) [26]	132	2 V	HPV 16	1	176(145–214)	100.0	
			HPV 18	1	109(89–133)	100.0	
Safaeian et al. (2013) [29]	48	2 V	HPV 16	1	137.49 (106.16–178.07)	100.0	< 0.001
				2	519.99 (422.02–640.70)	100.0	< 0.001
				3	748.25 (647.63–864.49)	100.0	
			HPV 18	1	70.21 (54.37–90.67)	100.0	< 0.001
				2	304.97 (237.76–391.18)	100.0	< 0.001
				3	334.55 (285.31–392.30)	100.0	
Joshi et al. (2023) [27]	18	4 V	HPV 6	1	2.29 (1.90–2.72)	100.0	< 0.05
				3	28.62 (24.41–33.55)	100.0	
			HPV 11	1	3.41 (2.84–4.09)	94.6	< 0.05
				3	36.70 (31.35–42.97)	100.0	
			HPV 16	1	8.4 (7.07–9.98)	98.6	< 0.05
				3	129.36 (113.12–147.94)	100.0	
			HPV 18	1	2.53 (2.10–3.05)	97.3	< 0.05
				3	33.22 (27.85–39.62)	100.0	
	36		HPV 6	1	2.27 (1.90–2.72)	99.3	< 0.05
				3	17.07 (14.03–20.76)	100.0	
			HPV 11	1	3.38 (2.80–4.07)	94.7	< 0.05

Table 2 (continued)

Study (year)	Month	Vaccine type	HPV	Dose	GMC (EU/mL) (95% CI)	Sero-positive (%)	*P*-value
				3	20.81 (17.09–25.34)	100.0	
			HPV 16	1	7.94 (6.66–9.46)	98.0	< 0.05
				3	77.27 (65.63–90.98)	100.0	
			HPV 18	1	2.44 (2.05–2.90)	98.0	< 0.05
				3	19.03 (15.39–23.54)	100.0	
	120		HPV 6	1	2.17 (1.92–2.45)	96.9	< 0.05
				2	5.87 (5.01–6.87)	100.0	< 0.05
				3	7.92 (6.73–9.32)	100.0	
			HPV 11	1	3.37 (2.99–3.81)	93.5	< 0.05
				2	10.21 (8.85–11.79)	98.9	< 0.05
				3	10.11 (8.61–11.88)	100.0	
			HPV 16	1	9.90 (8.76–11.19)	96.0	< 0.05
				2	34.74 (30.40–39.70)	100.0	< 0.05
				3	35.40 (30.44–41.16)	100.0	
			HPV 18	1	2.58 (2.26–2.95)	96.9	< 0.05
				2	6.64 (5.58–7.90)	97.9	< 0.05
				3	8.13 (6.78–9.75)	100.0	

Abbreviations: *HPV* human papillomavirus, *CI* confidence interval, *GMC* geometric mean concentration, *4 V* quadrivalent, *9 V* nonavalent. All GMC values are reported in EU/mL unless otherwise stated. Joshi et al. uses IU/mL

health services [48, 49]. Conversely, a single-dose regimen offers several benefits such as lower vaccine costs; enhanced cost-effectiveness from reduced workforce resources; improved vaccination rates through a simplified schedule; easier logistics and distribution; long-term protection; and comparable preventive efficacy [19, 50]. Recent modelling from India projected that nationwide adoption of a one-dose policy could avert roughly 1.6 million cervical-cancer cases and save about US $200 million in programme costs over the next three decades compared with a two-dose schedule [51]. The present study also determined that single-dose HPV vaccination elicited an immune response similar to that of multi-dose vaccination, highlighting its potential as a viable alternative in health policy and vaccination programs [24–29]. Nevertheless, head-to-head comparisons across bivalent, quadrivalent and nonavalent formulations are scarce, and differences in adjuvant systems or L1-VLP content may partially explain the wide GMC ranges observed between trials. An added complication is that studies used disparate laboratory methods—from ELISA to pseudovirion-based neutralisation assays—making direct GMC comparisons challenging and underscoring the need for harmonised WHO International Standards [52]. Safaeian et al. [29] reported that HPV-16/18 antibody positivity remained at 100% across all dose groups for 48 months. Barnabas et al. [24] observed high vaccine efficacy across all dosage groups, suggesting comparable clinical effectiveness. Kreimer et al. [26] confirmed long-term protection against HPV-16/18 with a single dose, noting sustained antibody levels. Yet their extension study documented markedly lower cross-neutralising antibodies against HPV-31 and HPV-45 after a single dose, underscoring concerns that dose reduction may attenuate cross-protection [16]. The WHO Strategic Advisory Group of Experts (SAGE) also acknowledged these concerns in its 2022 recommendation, noting that while single-dose schedules may be introduced where operational advantages exist, the evidence for cross-protection—particularly against non-vaccine oncogenic types such as HPV-31, 33, and 45—remains limited and warrants further investigation before broader adoption [53]. Joshi et al. [27] found that a single dose elicited robust immune responses, with antibody titers similar to those observed

Table 3 Incidence of HPV infection according to vaccine type and number of vaccinations

Study(year)	Month	Vaccine type/Dose		Incidence of HPV-16/18 infection per 100 women-years (95% CI)	Incidence of HPV-16/18/31 33/45/52/58 infection per 100 women-years (95% CI)	Vaccine efficacy (95% CI)	*P*-value
Barnabas et al. (2023) [24]	36	Experimental Group	2 V/1	0.16 (0.02–0.58)		97.5 (90.0–99.4)	< 0.001
			9 V/1	0.08 (0–0.44)	0.61 (0.20–1.42)[a]	95.5 (89.0–98.2)	< 0.001
		Control Group		6.70 (5.24–8.44)	13.8 (11.0–17.0)[a]		
Kreimer et al. (2020) [26]	132	Experimental Group	2 V/1	1.8 (0.3–5.8)		53.9 (–571 to 92.4)	0.17
			2 V/2	1.6 (0.1–7.7)		58.4 (–110 to 97.9)	0.33
			2 V/3	0.6 (0.3–1.1)		84.9 (69.8–93.2)	
		Control Group		3.9 (3.1–4.9)			
Sankaranarayanan et al. (2018) [28]	84	Experimental Group	4 V/1	1.6 (1.1–2.3)	5.7 (4.6–6.8)[b]		
			4 V/2	0.9 (0.5–1.7)	4.5 (3.4–5.8)[b]		
			4 V/3	0.9 (0.5–1.7)	5.1 (3.9–6.5)[b]		
		Control Group		6.2 (5.0–7.6)	7.7 (6.4–9.2)[b]		

Abbreviations: *HPV* human papilloma virus, *CI* confidence interval, *2 V* bivalent, *4 V* quadrivalent, *9 V* nonavalent

[a] HPV-16/18/31/33/45/52/58 infection

[b] HPV-31/33/45 infection

in 3-dose regimens. In the study by Gilca et al. [25], both 2-valent and 9-valent vaccines were evaluated. One month after the first dose, standardized antibody GMC were 16.7 IU/mL for HPV-16 and 11.7 IU/mL for HPV-18 in the 2-valent group, which were comparable to those in the 9-valent group.

Safaeian et al. [29] demonstrated that both the single-dose and multi-dose groups exhibited high and stable efficacy against HPV-16/18 infections over 48 months. Kreimer et al. [26] further emphasized that seropositivity remained stable for years even with a single dose, reinforcing the argument for long-term protection through simplified regimens. Nonetheless, only a handful of trials have so far reported histologically confirmed CIN2 + outcomes; ongoing ESCUDDO and DoRIS studies are expected to clarify whether single-dose schedules sustain protection against high-grade lesions in the longer term [52]. The immunogenicity profiles support the potential for reduced-dose strategies while acknowledging slightly lower antibody concentration [41]. This is consistent with other studies that showed maintenance of seropositivity for 36 months, long-term immune response, and prevention of cervical cancer with a single dose, alongside antibody response persistence for up to 10 years post-vaccination [53–56]. Kreimer et al. [19] conducted a pooled analysis of the Costa Rica Vaccine and PATRICIA trials, revealing that even a single dose of the bivalent vaccine provided comparable protection to two or three doses over four years, though higher doses induced stronger antibody responses. This finding further supports the viability of single-dose schedules, especially in resource-limited settings. Kreimer et al. [26] and Sankaranarayanan et al. [28] reported that single-dose HPV vaccination provided protection against HPV infection comparable to that of multi-dose vaccination. This indicated that reducing vaccination schedules can be effective, potentially simplifying vaccination strategies significantly. Barnabas et al. [24] demonstrated that single-dose HPV vaccination exhibited high efficacy in preventing HPV infection, comparable to multi-dose vaccination. This trial also used an immunobridging approach that aligned antibody thresholds in 15- to 20-year-old Kenyan girls with those seen in 9- to 14-year-olds from earlier pivotal studies, thereby supporting extrapolation to the primary vaccination age group [44–47]. While this finding aligns with modeling projections by Prem et al. [57], it is important to note that Prem's study was based on simulation modeling, not empirical clinical trial data. The WHO currently recommends a single-dose or two-dose schedule for individuals under 20 years of age, depending on local policies. This shift from the previous multi-dose schedule aims to enhance coverage and reduce logistical burdens globally [58, 59]. However, it should be noted that the WHO formally recommends a two-dose schedule beginning at age 9. A single-dose regimen is permitted as an off-label option for girls and boys aged 9–20 years, particularly in settings where implementation of a full schedule may be constrained.

This recommendation is supported by evidence from various population studies indicating that single-dose HPV vaccination elicits an immune response and maintains long-term antibody stability comparable to those of multi-dose vaccination [24–29, 60–63]. Consequently, the WHO Strategic Advisory Group of Experts (SAGE)

concluded in 2022 that countries may introduce a single-dose schedule when the operational advantages outweigh the marginal immunologic gains from additional doses, with the proviso that the guidance will be re-evaluated as ten-year effectiveness data mature [57]. Burger et al. [64]'s study underscored the importance of adopting single-dose HPV vaccination promptly, highlighting that delaying its introduction can potentially increase the incidence of preventable cancers by 7.2%–9.6%. In this context, while newer HPV vaccines such as Cecolin have gained approval in several Asian countries, we did not identify any eligible studies on reduced-dose schedules of these vaccines that met our inclusion criteria. As more peer-reviewed data become available, future reviews should aim to incorporate findings on these emerging vaccine platforms. Furthermore, De Carvalho et al. [65] reported high cost-effectiveness of single-dose HPV vaccination regimens compared with multi-dose regimens. Overall, these findings suggest that single-dose HPV vaccination offers a feasible solution to address logistical challenges associated with multi-dose regimens in resource-limited settings, such as those in LMICs.

The findings underscored the effectiveness and cost efficiency of single-dose HPV vaccination, which facilitated a broader vaccine uptake. This approach not only improved the delivery of health services, but also helped reduce health disparities, ensuring more equitable access to preventive measures against HPV-related diseases. In addition, the efficacy and long-term protection of multi-dose HPV vaccination has traditionally been supported by strong evidence. However, findings from emerging research, including those from the present study, demonstrate that a single-dose regimen provides comparable and durable protection against HPV infection, aligning closely with the results of multi-dose schedules. Therefore, in specific contexts, such as those outlined by the WHO guidelines aimed at maximizing global vaccination coverage and reducing HPV-related cancer incidence, a single-dose approach may merit consideration. In addition to the findings from randomized controlled trials, several observational studies have also reported high effectiveness of single-dose HPV vaccination. These real-world studies, conducted in diverse populations, have shown results consistent with those from RCTs, further supporting the use of simplified dosing schedules in various contexts.

Despite the advantages of single-dose vaccination identified in this study, controversy continues owing to several disadvantages. To address these uncertainties, strong safety monitoring after rollout is essential so that we can quickly detect any increase in serious pre-cancer lesions among single-dose recipients. Such monitoring can draw on national passive-reporting systems such as the U.S. Vaccine Adverse Event Reporting System [66], Europe's EudraVigilance [67], and the WHO VigiBase [68], as well as active-surveillance networks like the Vaccine Safety Datalink [69] and linkage of immunization files with cervical-screening or cancer registries to track high-grade lesions over time [70]. These include relatively low efficacy, concerns about the sustainability of the preventive effect, and the limited amount of research data available [71].

This systematic review also had several limitations akin to the controversies aforementioned. This study built on previous research conducted among restricted populations across several countries. Given the diversity in political and economic contexts, vaccination rates, disease prevalence, and healthcare system characteristics in different countries, it is essential to interpret these findings considering each country's peculiarities. Therefore, caution should be exercised when extrapolating the results of this study to broader populations. Furthermore, the findings from 1 country may not be applicable universally, highlighting the need for additional research. Future studies should examine diverse populations across multiple countries to establish conclusions that are more widely applicable. Priority should be given to immunocompromised individuals, male recipients and co-administration with other adolescent vaccines, all of which remain under-represented in current evidence. Including boys in single-dose programmes could accelerate herd-immunity gains and directly reduce HPV-related oropharyngeal cancer in men, but fewer than one-third of LMIC schedules currently target males, highlighting a crucial research and policy gap [72]. Additionally, the issue of cross-protection against non-vaccine HPV types following single-dose vaccination warrants further discussion. Existing evidence suggests that while single-dose regimens provide strong protection against HPV-16 and HPV-18, their effectiveness against other high-risk types—such as HPV-31, HPV-33, and HPV-45—may be significantly lower, particularly with the bivalent vaccine. For instance, Cuschieri et al. [16]'s study reported reduced cross-protection in women who received only one dose of the bivalent vaccine. A recent network meta-analysis estimated that protection against non-vaccine oncogenic types could be up to 20% lower after one dose versus two or three doses, although wide confidence intervals reflect limited event numbers [73].

Given the high prevalence of non-vaccine HPV types in certain regions, this limitation must be taken into account when developing national immunization strategies. Future studies should evaluate cross-protection outcomes over longer follow-up periods and in diverse populations to confirm the broader protective benefits of single-dose schedules. In summary, this comprehensive

systematic review significantly contributes to the promotion of HPV vaccination programs and equity in public health. By explicitly resolving cohort overlap and post-hoc design concerns highlighted by previous reviewers, the present synthesis also enhances methodological transparency and reproducibility.

Conclusions

In this systematic review, we synthesized findings from six publications derived from four unique randomized controlled trials (RCTs) to assess the effectiveness of single-dose HPV vaccination compared to multiple-dose regimens. While the combined sample size across these publications was 29,415 participants, some studies reported on overlapping cohorts; therefore, participant numbers are not additive.

This systematic review confirms that single-dose HPV vaccination, despite lower antibody concentrations, provides substantial protection. Given its cost-effectiveness and simplified logistics, a single-dose strategy is a practical alternative, especially in LMICs. Future research should explore long-term durability and cross-protection across diverse populations.

Abbreviations

HPV	Human papillomavirus
RCTs	Randomized clinical trials
WHO	World Health Organization
LMICs	Low- and middle-income countries
GMC	Geometric mean concentration

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

All authors contributed to form the study design. MJ and IJ performed the research method, data collection and curation, quality assessment, data analysis, and manuscript preparation.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This research was conducted after receiving an exemption from review by the Institutional Review Board (IRB) of Chung-Ang University (CAUH No. 2208–005-517).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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