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Systematic Review

Comparative Effectiveness, Duration of Protection, And Safety of Licensed Human Papillomavirus Vaccines with Special Reference to the Indian Context: A Systematic Review

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Abstract

Background: Human papillomavirus (HPV) infection is the necessary cause of cervical cancer, which remains a major public health burden in India, with 127,526 new cases and 79,906 deaths reported in 2022, accounting for approximately one quarter of global cervical cancer mortality. Prophylactic HPV vaccines are central to primary prevention strategies; with India recently integrating HPV vaccination into its Universal Immunisation Programme (UIP) using CERVAVAC®, the first indigenously developed quadrivalent HPV vaccine, a rigorous comparative evaluation of licensed vaccines with respect to effectiveness, duration of protection, and safety is urgently needed to guide Indian vaccination policy.

Objectives: To comparatively evaluate approved HPV vaccines with respect to effectiveness, duration of protection, and safety.

Methods: A systematic review was conducted in accordance with PRISMA 2020 guidelines. PubMed/MEDLINE, Embase, Scopus, and the Cochrane Library were searched from inception to October 2025. Randomised controlled trials (RCTs), long-term follow-up studies, and high-quality observational studies evaluating licensed bivalent, quadrivalent, and nonavalent HPV vaccines were eligible. Risk of bias was assessed using the Cochrane Risk of Bias 2 (RoB-2) tool and the Newcastle–Ottawa Scale (NOS). Certainty of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. A narrative synthesis was performed due to clinical and methodological heterogeneity.

Results: Forty-eight studies met the inclusion criteria. All licensed HPV vaccines demonstrated high efficacy against persistent HPV-16/18 infection and near-complete protection against vaccine-type–associated cervical intraepithelial neoplasia grade 2 or above (CIN2+) in HPV-naïve populations. Protection was sustained for at least 10–12 years with standard dosing schedules. Population-based studies confirmed real-world reductions in HPV prevalence, genital warts, and high-grade cervical lesions, with evidence of herd protection. Reduced-dose and single-dose schedules showed promising short- to medium-term effectiveness; however, certainty of evidence was low. All vaccines demonstrated a consistently favourable safety profile with no increased risk of serious adverse events.

Conclusions: All approved HPV vaccines, including CERVAVAC®, are highly effective, provide durable protection, and have excellent safety profiles, supporting their use within India's Universal Immunisation Programme. Differences between formulations are primarily attributable to breadth of HPV type coverage. Continued post-licensure surveillance of CERVAVAC® and long-term evaluation of reduced-dose and single-dose strategies are essential to inform evidence-based vaccination policy in India and other LMICs.

Keywords: Human papillomavirus; HPV vaccination; vaccine effectiveness; duration of protection; vaccine safety; CERVAVAC®; India; Universal Immunisation Programme; systematic review.

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Introduction

Human papillomavirus (HPV) infection is firmly established as the necessary cause of cervical cancer and one of the most important contributors to infection-related malignancy globally. India bears a disproportionate share of this burden: with 127,526 new cervical cancer cases and 79,906 deaths recorded in 2022, India accounts for approximately one quarter of global cervical cancer mortality, making it the second most common cancer among Indian women. Persistent infection with oncogenic HPV types, particularly HPV-16 and HPV-18, accounts for the majority of cervical cancer cases in India and worldwide, and also plays a substantial role in the pathogenesis of anogenital and oropharyngeal cancers. [1,2]

Despite advances in cervical cancer screening and treatment, the disease continues to pose a major public health challenge in India and other low- and middle-income countries (LMICs). Limited access to organised screening programmes, low awareness, socio-cultural barriers, delayed diagnosis, and healthcare delivery inequities between urban and rural populations contribute to persistently high incidence and mortality, particularly in states such as Tamil Nadu, Mizoram, and Meghalaya where age-standardised rates are highest.[3,4] In addition to cervical cancer, HPV infection is implicated in malignancies of the anus, vulva, vagina, penis, and oropharynx, reflecting the broad clinical and public health significance of HPV disease for Indian practitioners.[5]

The development of prophylactic HPV vaccines based on virus-like particle (VLP) technology has transformed primary prevention strategies globally and in India. Early randomised controlled trials (RCTs) demonstrated that bivalent and quadrivalent vaccines provide high-level protection against persistent HPV-16 and HPV-18 infection and associated precancerous lesions when administered prior to viral exposure.[6–8]

The introduction of the nonavalent vaccine further expanded oncogenic coverage.[14,15] Of particular significance to India is the development of CERVAVAC® by the Serum Institute of India — the country's first indigenously produced quadrivalent HPV vaccine — which received Drug Controller General of India (DCGI) approval in January 2023 and has since been incorporated into India's Universal Immunisation Programme (UIP), targeting approximately 10 million girls annually.

Evidence from long-term follow-up studies has demonstrated durable vaccine-induced protection with persistent antibody responses documented for more than a decade following vaccination.[13–16] Population-based studies internationally have reported substantial declines in HPV prevalence, genital warts, and high-grade cervical lesions, along with indirect herd protection.[17–20,40] The landmark Indian cluster-randomised trial by Basu et al. (2021), involving 17,729 girls aged 10–18 years across India with 10-year follow-up, provides critical evidence specific to the Indian population.[19] Several clinically relevant questions remain, including differences in vaccine formulations, durability of protection, safety profiles, and the emerging interest in reduced-dose and single-dose vaccination strategies, particularly in resource-constrained settings. [21–23]

Existing systematic reviews have evaluated HPV vaccine effectiveness and safety in global populations — notably Drolet et al. (2019), who assessed population-level herd protection, and Subasinghe et al. (2020), who examined long-term real-world effectiveness — but none has specifically evaluated licensed HPV vaccines, including CERVAVAC®, with explicit contextualisation for Indian clinical practice and the Universal Immunisation Programme. The present systematic review addresses this gap by comparatively evaluating all approved HPV vaccines with respect to effectiveness, duration of protection, and safety, with specific reference to the Indian context

Methodology

Study Design and Reporting Framework: This study was conducted as a systematic review designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement to ensure transparency, reproducibility, and methodological rigour. A review protocol was developed a priori.

Eligibility Criteria: Eligibility criteria were specified using the Population, Intervention, Comparator, Outcomes, and Study design (PICOS) framework.

Inclusion Criteria: Studies were included if they evaluated (1) females and/or males of any age, including immunocompromised individuals and studies conducted in Indian or South Asian populations; (2) approved prophylactic HPV vaccines (bivalent, quadrivalent, or nonavalent), including CERVAVAC®, using one-, two-, or three-dose schedules; (3) a comparator group (placebo, no vaccination, alternative formulation, or different dosing schedule); and (4) at least one outcome related to vaccine effectiveness or efficacy against persistent HPV infection, HPV-related clinical endpoints, duration of protection, immunogenicity, or safety. Eligible study designs

included RCTs, long-term follow-up studies of RCTs, and high-quality observational studies.

Exclusion criteria: Excluded studies included case reports, case series, narrative reviews, systematic reviews, meta-analyses, editorials, letters, and conference abstracts without full data; animal or in-vitro studies; studies evaluating experimental or non-approved vaccines; studies not reporting relevant outcomes; and duplicate publications where a more complete report was available.

Information Sources and Search Strategy: An extensive literature search was undertaken in PubMed/MEDLINE, Embase, Scopus, and the Cochrane Library from database inception to October 2025. Search strategies combined Medical Subject Headings (MeSH) controlled vocabulary with free-text keywords.

The full PubMed/MEDLINE search strategy is provided below. Analogous strategies using Emtree terms were applied in Embase.

Reference lists of included articles, key systematic reviews, and World Health Organization (WHO) policy documents were manually screened for additional eligible studies.

Supplementary Box 1. PubMed/MEDLINE Search Strategy (searched October 2025)

Database: PubMed/MEDLINE | Date of search: October 2025

#1 "Papillomavirus Vaccines"[MeSH Terms]
#2 "papillomavirus vaccine*"[tiab] OR "HPV vaccine*"[tiab] OR "human papillomavirus vaccine*"[tiab]
#3 "Gardasil"[tiab] OR "Cervarix"[tiab] OR "Silgard"[tiab] OR "Gardasil 9"[tiab] OR "CERVAVAC"[tiab]
#4 #1 OR #2 OR #3

#5 "Vaccine Efficacy"[MeSH Terms] OR "Treatment Outcome"[MeSH Terms]
#6 "vaccine efficac*"[tiab] OR "vaccine effectiveness"[tiab] OR "real-world effectiveness"[tiab]
#7 #5 OR #6

#8 "Immunologic Memory"[MeSH Terms] OR "Antibodies, Viral"[MeSH Terms]
#9 "duration of protection"[tiab] OR "long-term protection"[tiab] OR "antibody persistence"[tiab] OR "immunogenicity"[tiab]
#10 #8 OR #9

#11 "Vaccine Safety"[MeSH Terms] OR "Adverse Drug Reaction Reporting Systems"[MeSH Terms]
#12 "safety"[tiab] OR "adverse event*"[tiab] OR "adverse effect*"[tiab] OR "tolerability"[tiab] OR "post-licensure surveillance"[tiab]
#13 #11 OR #12

#14 "Uterine Cervical Neoplasms"[MeSH Terms] OR "Papillomavirus Infections"[MeSH Terms]
#15 "cervical intraepithelial neoplasia"[tiab] OR "CIN"[tiab] OR "genital wart*"[tiab] OR "condyloma*"[tiab] OR "HPV infection"[tiab]
#16 #14 OR #15

#17 #4 AND (#7 OR #10 OR #13 OR #16)

Filters applied: English language | Humans | Study types: Clinical Trial, RCT, Observational Study, Cohort Study, Systematic Review (for reference list checking only)

Study Selection, Data Extraction, and Risk of Bias Assessment: All retrieved records were exported to Zotero for duplicate removal. Two reviewers independently screened titles and abstracts, followed by full-text assessment against predefined criteria. Disagreements were resolved through discussion and consensus.

Data were extracted independently using a standardised form capturing study characteristics, population details, vaccine formulation, dosing schedule, follow-up duration, effectiveness/immunogenicity outcomes, and safety data. Risk of bias was assessed using the Cochrane RoB-2 tool for RCTs and the Newcastle–Ottawa Scale (NOS) for observational studies. Certainty of evidence was assessed at the outcome level using the GRADE approach.

Data Synthesis: Given anticipated heterogeneity in study populations, vaccine formulations, dosing schedules, and outcome definitions, findings were synthesised narratively, organised by vaccine type and outcome domain. No quantitative meta-analysis was undertaken.

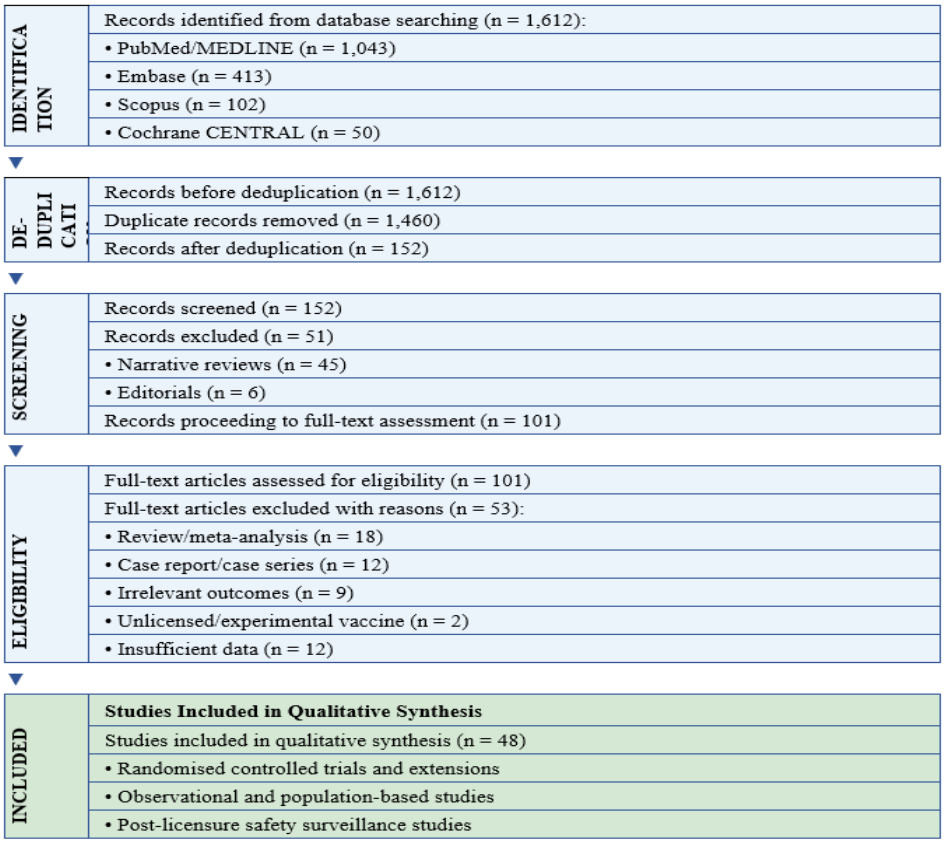
Ethical Approval: Ethical approval for this systematic review was obtained from the Institutional Ethics Committee of the authors'

institution (details provided in the First Page file). As this study involved analysis of previously published literature only and did not involve direct patient participation, data collection, or any clinical intervention, individual informed consent was not required. The review was conducted in accordance with the Declaration of Helsinki and ICMR National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017.

Results

Study Selection: The literature search yielded 1,612 records across four databases (PubMed/MEDLINE, n = 1,043; Embase, n = 413; Scopus, n = 102; Cochrane CENTRAL, n = 50). Following removal of 1,460 duplicates, 152 records underwent title and abstract screening, of which 51 were excluded (narrative reviews, n = 45; editorials, n = 6).

Of 101 full-texts assessed for eligibility, 53 were excluded for the following reasons: review or meta-analysis (n = 18), case report or case series (n = 12), irrelevant outcomes (n = 9), unlicensed or experimental vaccine (n = 2), and insufficient data (n = 12). Forty-eight studies met the inclusion criteria and were included in the qualitative synthesis, as illustrated in the PRISMA 2020 flow diagram (Figure 1).



PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Figure 1: PRISMA 2020 Flow Diagram

Study Characteristics: The 48 included studies spanned diverse geographic settings including multinational, European, North American, Australian, and Asian populations, enrolling adolescents and adults of both sexes. Vaccine formulations evaluated included bivalent (HPV-16/18), quadrivalent (HPV-6/11/16/18), and nonavalent (HPV-6/11/16/18/31/33/45/52/58) preparations. Two studies are of particular relevance to the Indian context: the cluster-randomised trial by Basu et al. (2021) — the largest HPV vaccine trial conducted in India, enrolling 17,729 girls aged 10–18 years with 10-year follow-up — and the pivotal phase 2/3 immunogenicity trial of CERVAVAC® conducted across 12 tertiary care hospitals in India. Vaccination schedules included standard three-dose regimens as well as reduced-dose and single-dose strategies. Follow-up duration ranged from 18 months to more than 12 years. Primary outcomes assessed included persistent HPV infection, cervical intraepithelial neoplasia (CIN), genital warts, duration of protection, immunogenicity, and safety (Table 1). Multiple publications arising from the same parent trial were linked to avoid participant duplication (Supplementary Table S1).

Table 1: Characteristics of Studies Included in the Qualitative Synthesis (n = 48)

S.No	Study (Author, Year)	Country	Study Design	Population	N	Vaccine	Schedule	Comparator	Follow-up	Outcome Domain
1	Villa et al., 2005	Multinational	Phase II RCT	Women 16–23 y	1,113	4v	3-dose	Placebo	36 months	Effectiveness, Safety
2	Garland et al., 2007	Multinational	RCT	Women 16–26 y	5,455	4v	3-dose	Placebo	48 months	Effectiveness, Safety
3	Harper et al., 2006	Multinational	RCT follow-up	Women 15–25 y	1,113	2v	3-dose	Placebo	4.5 years	Duration, Safety
4	FUTURE II Study Group, 2007	Multinational	Phase III RCT	Women 15–26 y	12,167	4v	3-dose	Placebo	36 months	Effectiveness
5	Joura et al., 2007	Multinational	Pooled RCT analysis	Women 16–26 y	~18,000	4v	3-dose	Placebo	48 months	Effectiveness
6	Paavonen et al., 2007	Multinational	Phase III RCT	Young women	18,644	2v	3-dose	Placebo	15 months	Effectiveness
7	Muñoz et al., 2010	Multinational	RCT analysis	Women	17,622	4v	3-dose	Placebo	4 years	Effectiveness
8	Brown et al., 2009	Multinational	RCT analysis	Women	17,622	4v	3-dose	Placebo	3–4 years	Effectiveness
9	Apter et al., 2015	Multinational	RCT (PATRICIA)	Women 15–25 y	18,644	2v	3-dose	Placebo	48 months	Effectiveness
10	Lehtinen et al., 2012	Multinational	RCT extension	Women 15–25 y	7,466	2v	3-dose	Placebo	4 years	Duration
11	Skinner et al., 2014	Multinational	RCT	Women >25 y	5,781	2v	3-dose	Placebo	4 years	Effectiveness
12	Wheeler et al., 2016	Multinational	RCT follow-up	Women >25 y	5,781	2v	3-dose	Placebo	7 years	Duration
13	Einstein et al., 2011	Multinational	Comparative RCT	Women 18–45 y	1,106	2v vs 4v	3-dose	Active comparator	24 months	Duration/Immunogenicity
14	Joura et al., 2015	Multinational	Phase III RCT	Women 16–26 y	14,215	9v	3-dose	4v	72 months	Effectiveness, Safety
15	Moreira et al., 2016	Multinational	RCT	Boys & girls 9–15 y	3,066	9v	3-dose	4v	30 months	Safety/Immunogenicity
16	Kreimer et al., 2015	Multinational	Reduced-dose RCT	Women 15–25 y	7,466	2v	<3 doses	Placebo	4 years	Effectiveness
17	Safaeian et al., 2013	Costa Rica	RCT follow-up	Women 18–25 y	7,466	2v	Single dose	Placebo	7 years	Duration/Immunogenicity
18	Barnabas et al., 2022	Africa	Randomised trial	Women 15–20 y	758	2v	Single dose	Delayed vaccine	18 months	Effectiveness
19	Basu et al., 2021	India	Cluster randomised	Girls 10–18 y	17,729	4v	1–3 doses	Internal comparison	10 years	Effectiveness
20	Artemchuk et al., 2019	Finland	Prospective cohort	Women	~8,000	2v/4v	3-dose	None	12 years	Immunogenicity
21	Mariz et al., 2021	Multinational	Follow-up cohort	Women	1,145	2v/4v	3-dose	Placebo	12 years	Immunogenicity
22	Tsang et al., 2020	Multinational	Serological monitoring	Women	~1,100	2v	Single dose	None	5–7 years	Immunogenicity
23	Kjaer et al., 2020	Denmark	Observational cohort	Women >25 y	~12,000	4v	Programmatic	Unvaccinated	10 years	Effectiveness

24	Dillner et al., 2010	Multinational	Efficacy follow-up	Women	~17,000	4v	3-dose	Placebo	4 years	Effectiveness
25	Gray et al., 2021	Multinational	Population serology	Women & men	NR	Programmatic	Gender-neutral	Pre/post	NR	Immunogenicity
26	Machalek et al., 2017	Australia	Observational	Men	~2,500	4v	Programmatic	Pre-era	7 years	Effectiveness
27	Baandrup et al., 2013	Denmark	National cohort	Young women	~400,000	4v	Programmatic	Unvaccinated	5 years	Effectiveness
28	Subasinghe et al., 2020	Australia	Population-based	Young women	~1,300	4v	Programmatic	Pre-era	7 years	Effectiveness
29	Freire-Salinas et al., 2021	Spain	Community cohort	Women <30 y	~6,000	4v	Programmatic	Pre-era	6 years	Effectiveness
30	Chow et al., 2021	Australia	Ecological	Women & men	NR	4v	Gender-neutral	Pre-program	14 years	Effectiveness
31	Meites et al., 2021	USA	Surveillance	Children	NR	4v	Programmatic	Pre-era	15 years	Effectiveness
32	Hernandez-Aguado et al., 2022	Spain	Retrospective cohort	Women	790	4v	Programmatic	Unvaccinated	12 years	Effectiveness
33	Silverberg et al., 2020	USA	Retrospective cohort	Immunosuppressed women	~45,000	4v	Catch-up	Unvaccinated	5 years	Effectiveness
34	Martellucci et al., 2022	Multinational	Screening impact	NR	NR	Programmatic	NR	NR	Effectiveness	
35	Rebolj et al., 2022	Multinational	Screening outcomes	NR	NR	Programmatic	Catch-up	NR	Effectiveness	
36	Perkins et al., 2022	NR	Commentary	NR	NR	—	—	—	Effectiveness	
37	Zhao et al., 2022	China	RCT (immunogenicity)	Women	~3,000	2v	NR	NR	24 months	Safety
38	Lehtinen et al., 2018	Finland	Population-level study	Adolescents	NR	Programmatic	NR	NR	8–10 years	Effectiveness
39	Brotherton et al., 2011	Australia	Early impact	Women	NR	4v	Programmatic	Pre-era	NR	Effectiveness
40	Drolet et al., 2019	Multinational	Systematic review & meta-analysis	Women & men	NR	Programmatic	Pre-era	NR	Effectiveness/Herd protection	40
41	Palmer et al., 2019	UK	Observational	Men	~2,000	Programmatic	Female-only	Unvaccinated	6 years	Herd effect
42	Mesher et al., 2016	UK	Observational	Women	~50,000	Programmatic	NR	Pre/post	10 years	Effectiveness
43	Herweijer et al.,	Sweden	Registry cohort	Women	~1.7 million	Programm	NR	Unvaccinate	11 years	Cancer

	2014					atic		d		
44	Slade et al., 2009	USA	Post-licensure surveillance	Females & males	NR	4v	Programmatic	None	Ongoing	Safety
45	Arnheim-Dahlström et al., 2013	Nordic	Registry cohort	Females	NR	4v	Programmatic	Unvaccinated	NR	Safety
46	Scheller et al., 2015	Denmark	Registry cohort	Females	NR	4v	Programmatic	Unvaccinated	NR	Safety
47	Chao et al., 2012	USA	Healthcare databases	Females	NR	4v	Programmatic	Unvaccinated	NR	Safety
48	Gee et al., 2011	USA	Safety review	Females & males	NR	4v	Programmatic	None	NR	Safety

Abbreviations: 2v = bivalent (HPV-16/18); 4v = quadrivalent (HPV-6/11/16/18); 9v = nonavalent (HPV-6/11/16/18/31/33/45/52/58); NR = not reported; RCT = randomised controlled trial. Sample size (N) was extracted from primary study reports; NR indicates no single definitive cohort size reported (e.g., surveillance, ecological, or registry-based studies).

Table 3. GRADE Summary of Findings for Approved HPV Vaccines

Outcome	Study Design	No. (n)	Risk of Bias	Incon-sistency	Indirect-ness	Impre-cision	Certainty (GRADE) ■=met □=down	Key Reason for Rating	Clinical Interpretation
Prevention of persistent HPV-16/18 infection	RCTs	15	Not serious	Not serious	Serious[1]	Not serious	**MODERATE** ■■■□ (3 of 4)	Downgraded 1 level: surrogate endpoint (persistent infection) used instead of cancer incidence	Probably effective against persistent HPV-16/18 in HPV-naïve individuals
Prevention of CIN2+ (high-grade cervical lesions)	RCTs	18	Not serious	Not serious	Not serious	Not serious	**HIGH** ■■■■ (4 of 4)	No concerns in any GRADE domain; CIN2+ is a direct, validated clinical endpoint	Highly effective; near-complete protection against vaccine-type CIN2+ in HPV-naïve women
Duration of protection (≥10 years)	RCT follow-up & cohort studies	12	Not serious	Not serious	Serious[1]	Not serious[2]	**MODERATE** ■■■□ (3 of 4)	Downgraded 1 level: reliance on antibody persistence not direct cancer endpoints; publication bias possible	Durable protection ≥10–12 years following standard dosing; no meaningful waning immunity
Effectiveness of reduced/single-dose schedules	RCT extensions & observational	7	Some concerns	Serious[3]	Serious[1]	Serious[4]	**LOW** ■■□□ (2 of 4)	Downgraded 2 levels: heterogeneity; limited follow-up; surrogate endpoints; some risk of bias; publication bias possible	Promising short- to medium-term data (incl. Basu et al., India, n=17,729, 10-yr); long-term durability uncertain.

Serious adverse events following HPV vaccination	RCTs & post-licensure surveillance	16	Not serious	Not serious	Not serious	Not serious	**HIGH** ■■■■ (4 of 4)	Consistent findings across RCTs and post-marketing surveillance; no concerns in any GRADE domain	Favourable safety profile; no increased risk of serious adverse events; CERVAVAC® comparable to Gardasil®

GRADE symbols: ■ = domain met (not downgraded); □ = domain downgraded.

[1]Indirectness: surrogate outcomes (persistent infection, immunogenicity) used rather than cancer incidence.; [2]Imprecision: not downgraded — antibody titres consistent across multiple independent cohorts.; [3]Inconsistency: heterogeneity in study designs, dosing intervals, and outcome definitions.; [4]Imprecision: small event numbers, wide confidence intervals; publication bias possible.

Table 4: Comparative Evaluation of Approved Human Papillomavirus Vaccines

Vaccine	HPV Types	Effectiveness	Duration	Safety	Key Strengths	Limitations
Bivalent (2v)	16, 18	High efficacy vs HPV-16/18 and CIN2+	≥10–12 years; persistent antibody response	Favourable; mild local/systemic reactions	Strong immunogenicity; cross-protection	No protection vs HPV-6/11 (warts); mainly female populations studied
Quadrivalent (4v)	6, 11, 16, 18	High vs HPV-16/18, CIN, genital warts	≥10 years demonstrated	Extensive post-licensure safety data; no major concerns	Wart protection; robust real-world data	Less oncogenic coverage than 9v
Nonavalent (9v)	6,11,16,18,31,33,45,52,58	Comparable/superior with expanded oncogenic coverage	Mid- to long-term immunogenicity sustained	Comparable to 4v	Broadest HPV-related cancer protection	Shorter post-licensure follow-up
Reduced-dose (1–2 doses)	Vaccine-specific	High short- to medium-term vs HPV-16/18	Antibody responses up to 10 years reported	No additional safety concerns	Improved feasibility; equity in LMICs	Long-term durability still under evaluation

Note: Comparative assessments are based on qualitative synthesis of RCTs, long-term follow-up studies, and high-quality observational evidence. No quantitative pooling of outcomes was performed. 2v = bivalent; 4v = quadrivalent; 9v = nonavalent; LMICs = low- and middle-income countries.

Risk of Bias and Certainty of Evidence: Most RCTs were at low risk of bias; some concerns arose primarily from incomplete outcome data in long-term follow-up studies, where attrition over extended periods was inevitable. Observational studies were of moderate to high methodological quality on the Newcastle–Ottawa Scale. Applying the GRADE framework, certainty of evidence was rated high for prevention of high-grade cervical lesions and for safety outcomes, moderate for prevention of persistent HPV infection and duration of protection, and low for reduced-dose schedules — largely reflecting heterogeneity in study designs and reliance on immunogenicity surrogates rather than direct cancer endpoints (Table 3).

Effectiveness: Across RCTs, all licensed HPV vaccines demonstrated high efficacy against persistent HPV-16 and HPV-18 infection in HPV-naïve populations, with efficacy estimates consistently exceeding 90%. Protection against vaccine-type–associated CIN2+ lesions was near-complete in several pivotal trials, reinforcing the clinical value of pre-exposure vaccination. Quadrivalent vaccine trials additionally demonstrated very high effectiveness against genital warts caused by HPV-6/11, an outcome relevant to male vaccination programmes and gender-neutral immunisation strategies.

Real-world data from population-based and observational studies corroborated these trial findings. Following national vaccine programme introduction, marked reductions in HPV prevalence, genital warts, and high-grade cervical lesions were documented across multiple countries, alongside evidence of indirect herd protection in unvaccinated individuals.[27–33,40] These population-level effects are directly relevant to India, where programmatic vaccination through the UIP is now underway.

Duration of Protection: Long-term follow-up studies of bivalent and quadrivalent vaccines demonstrated sustained protection and persistent antibody responses for at least 10–12 years following completion of standard dosing schedules, with no clinically meaningful evidence of waning immunity over this period. This is reassuring from a policy perspective, as it suggests that vaccinating adolescent girls before HPV exposure will provide protection well into the years of peak sexual activity and cancer risk. Extension studies of the nonavalent vaccine showed comparable effectiveness for shared HPV types and sustained immunogenicity over mid-term follow-up, although post-licensure observation periods for this formulation remain shorter than for the bivalent and quadrivalent vaccines.[20–24]

Reduced-Dose Schedules: Evidence from RCT extensions and cohort studies indicated that reduced-dose and single-dose schedules maintain short- to medium-term protection against HPV-16 and HPV-18 infection. Of direct relevance to India, the Basu et al. (2021) cluster-randomised trial demonstrated that even a single dose of the quadrivalent vaccine conferred significant protection over a 10-year follow-up period among Indian girls — the most compelling India-specific evidence for reduced-dose strategies currently available.[19] If confirmed by the ongoing ICMR single-dose immunogenicity study, this could enable the UIP to vaccinate twice as many girls with existing vaccine stocks, a potentially transformative shift for India's immunisation programme. However, heterogeneity in study design, outcome definitions, and follow-up duration limits certainty regarding long-term durability compared with standard schedules, and policy adoption should await further confirmatory data.[16–19]

Safety: Safety findings were consistent across RCTs, long-term follow-up studies, and post-licensure surveillance programmes spanning multiple countries. Adverse events were predominantly mild to moderate in severity, most commonly comprising local injection-site reactions and transient systemic symptoms such as headache and fatigue. No consistent evidence of an increased risk of serious adverse events attributable to HPV vaccination was identified across any of the 16 studies evaluated for this outcome.[44–48] This is particularly pertinent to the Indian context, where vaccine hesitancy driven partly by historical safety concerns has at times limited uptake, and where clear communication of the established safety record is essential to programme success.

Discussion

This systematic review provides a comprehensive comparative synthesis of evidence on all approved HPV vaccines, with particular reference to the Indian context. Across RCTs, long-term follow-up studies, and high-quality observational research — including Indian and South Asian data — findings consistently indicate that all licensed HPV vaccines are highly effective and safe. Differences between formulations are driven primarily by breadth of HPV type coverage rather than by fundamental differences in efficacy or safety.[1–4] These conclusions carry direct relevance for Indian clinicians, pharmacologists, and policymakers as India scales up HPV vaccination through the Universal Immunisation Programme.

The strongest evidence base derives from RCTs demonstrating near-complete protection against vaccine-type–associated high-grade cervical intraepithelial neoplasia among HPV-naïve individuals. Population-level surveillance data from countries with mature vaccination programmes have since corroborated these trial findings, documenting substantial real-world reductions in HPV prevalence, genital warts, and cervical precancerous lesions following vaccine introduction, including early declines in invasive cervical cancer incidence and significant herd protection in unvaccinated individuals.[5–9,40] This convergence of trial and real-world evidence provides a robust foundation for India's national vaccination programme.

Long-term follow-up studies provide compelling evidence that protection conferred by bivalent and quadrivalent vaccines is sustained for more than a decade following standard dosing schedules.[10–14] It is important to acknowledge, however, that because invasive cervical cancer requires prolonged latency to develop, much of the long-term evidence necessarily relies on surrogate endpoints such as persistent infection and CIN, resulting in moderate rather than high certainty of evidence for duration of protection. Continued post-licensure surveillance will be essential to directly quantify cancer-level outcomes as vaccinated cohorts age.

The nonavalent HPV vaccine represents a meaningful advance by extending oncogenic protection beyond HPV-16 and HPV-18 to five additional high-risk types. Evidence from Phase III trials and immunogenicity bridging studies demonstrates effectiveness comparable to earlier vaccines for shared HPV types, while offering broader potential for population-level cancer prevention. [14,15] Nevertheless, the relatively shorter duration of post-licensure follow-up for this formulation means that long-term effectiveness data are still emerging, and active surveillance must continue.

The emerging evidence supporting reduced-dose and single-dose vaccination schedules has particularly important implications for India's UIP. The Basu et al. (2021) Indian cluster-randomised trial demonstrated that a single dose of the quadrivalent vaccine conferred meaningful protection over 10 years of follow-up in 17,729 Indian girls — the most compelling India-specific evidence for reduced-dose strategies to date.[19] The ongoing ICMR single-dose immunogenicity study (launched November 2024, n = 500 girls aged 9–14 years) is eagerly awaited and could significantly influence dosing policy for the UIP and other LMIC programmes. However, current certainty of evidence for reduced-dose schedules remains low due to heterogeneity in study designs, limited long-term follow-up, and reliance on surrogate immunogenicity endpoints; widespread policy adoption should therefore await further confirmatory data.[16–19]

Safety is a foundational consideration for any national vaccination programme, and is of particular relevance in India where vaccine hesitancy has historically limited uptake. Across clinical trials and extensive post-marketing surveillance from multiple countries, all licensed HPV vaccines demonstrate a consistently favourable safety profile. Large registry-based studies and pharmacovigilance analyses provide high-certainty evidence that HPV vaccination is not causally associated with serious adverse events, including autoimmune or neurological conditions. [44–48] For CERVAVAC® specifically, the phase 2/3 trial confirmed a safety and tolerability profile non-inferior to Gardasil®, which is reassuring for the ongoing national rollout. India's pharmacovigilance infrastructure — including the Adverse Drug Reactions Monitoring Centres under the Pharmacovigilance Programme of India — should maintain active post-licensure safety surveillance of all vaccines used in the UIP.

The inclusion of CERVAVAC® in India's UIP represents a pivotal milestone for cervical cancer prevention and for LMIC vaccine self-sufficiency. Its substantially lower cost compared with imported vaccines directly addresses the longstanding affordability barrier that has constrained HPV vaccine access in resource-limited settings. Long-term real-world effectiveness and population-level impact data for CERVAVAC® remain limited and represent an important priority for future research and post-licensure surveillance.

Conclusion

This systematic review demonstrates that all approved HPV vaccines — bivalent, quadrivalent, nonavalent, and the indigenously developed CERVAVAC® — are highly effective, provide durable protection, and maintain favourable safety profiles across diverse populations and settings. High-certainty evidence supports near-complete prevention of vaccine-type–associated high-grade cervical precancerous lesions in HPV-naïve individuals, while moderate-certainty evidence indicates sustained protection against persistent HPV infection for at least a decade following standard vaccination schedules. Across all formulations, differences in effectiveness and safety are minimal; what distinguishes vaccines from one another is primarily the breadth of HPV type coverage they offer.

The nonavalent vaccine extends oncogenic protection to additional HPV types, though long-term post-licensure data remain comparatively limited. Emerging evidence suggests potential

effectiveness of reduced-dose and single-dose schedules, with the Indian trial by Basu et al. providing the most compelling LMIC-relevant data to date. However, current certainty of evidence for these schedules remains low, and widespread policy adoption should await results of ongoing studies — particularly the ICMR single-dose immunogenicity trial — before firm recommendations can be made.

For India, these findings carry immediate and urgent policy relevance. The integration of CERVAVAC® into the Universal Immunisation Programme marks a critical step toward cervical cancer elimination, combining proven quadrivalent vaccine efficacy with domestic manufacturing capacity and affordability at scale.

Indian pharmacologists, clinicians, and policymakers can be reassured that all licensed vaccines — including CERVAVAC® — demonstrate comparable immunogenicity and safety, supporting their use and interchangeability within national programmes. Continued post-licensure surveillance of CERVAVAC®, strengthening of cold chain infrastructure, health worker training, and sustained pharmacovigilance through the Pharmacovigilance Programme of India must collectively guide evidence-based programme refinement as India advances toward the WHO's 2030 cervical cancer elimination targets.

Declarations

Ethical Approval:

Ethical approval was obtained from the Institutional Ethics Committee of the authors' institution. Individual informed consent was not required. The manuscript title was subsequently refined; the protocol and objectives remain unchanged from those approved by the committee.

Data Availability: All data supporting this review are derived from publicly available published studies cited in the references.

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