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Meta-Analysis

Single-dose versus multiple-dose HPV vaccination for prevention of cervical cancer: a systematic review and meta-analysis

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ABSTRACT

Cervical cancer remains a major global burden, especially in low- and middle-income countries (LMICs). Although HPV vaccination is a key preventive strategy, multi-dose schedules pose cost and logistical challenges. This review assessed whether single-dose HPV vaccination offers protection comparable to multi-dose regimens. Following PRISMA guidelines, we searched PubMed, Cochrane, Scopus, and Google Scholar (2000-2025) for RCTs, cohort studies, and case-control studies comparing single-dose with two- or three-dose HPV vaccination. Outcomes included persistent HPV infection, high-grade cervical lesions (CIN2/3, HSIL), and immunogenicity. Random-effects models were used to calculate risk ratios (RRs), and heterogeneity was assessed with I^2. Twenty-six studies were included (10 RCTs, 16 observational), involving females aged 9-26 years from multiple countries. Sample sizes ranged from 200 to 590,083, with follow-up of 1-16 years. Single-dose vaccination showed >90% efficacy against persistent HPV16/18 infection. Compared with unvaccinated controls, the pooled estimate showed no statistically significant difference (RR 1.05, 95% CI 0.73-1.52). Compared with two-dose schedules, no statistically significant difference was observed (RR 0.72, 95% CI 0.40-1.32). Similarly, comparison with multiple-dose schedules showed no statistically significant difference (RR 0.93, 95% CI 0.60-1.44). Seropositivity remained high at 16 years (98.8-99.4%). Heterogeneity was substantial (I^2 93.6-96.8%). Single-dose HPV vaccination provides substantial, durable protection comparable to multi-dose regimens in most settings. These findings support WHO's recommendation and reinforce single-dose vaccination as a practical, cost-effective strategy to expand coverage and accelerate cervical cancer elimination in LMICs.

Keywords: HPV vaccination, Single-dose, Multiple-dose, Cervical cancer prevention, Meta-analysis, Vaccine effectiveness

INTRODUCTION

Cervical cancer is a malignant neoplasm of the cervix, most commonly associated with persistent infection by high-risk human papillomavirus (HPV) types, particularly HPV-16 and HPV-18. It is a significant public health issue, particularly in Low- and middle-income countries (LMICs), where screening and treatment services are often unavailable. According to the World Health Organisation (WHO), cervical cancer affected approximately 604,000 women and caused 342,000 deaths globally in 2020.[1] It is estimated that in 2022, 660,000 women were diagnosed with cervical cancer, and approximately 350,000 women died due to cervical cancer. Most cases of cervical cancer will be prevented by effective primary (HPV vaccination) and secondary prevention strategies (screening and treating precancerous lesions).[2] In LMICs, limited access to screening and preventive services contributes to a disproportionately high burden, accounting for approximately 90% of cervical cancer deaths. Over 70% of cervical cancer cases are attributed to persistent infection of HPV-16 and HPV-18, which are known as high-risk HPV types. Additional risk factors include early sexual debut, multiple sexual partners, smoking, immunosuppression, and lack of regular cervical cancer screening.[3] Despite effective vaccination programs in

high-income countries, many regions face significant barriers to implementation. In 2022, the WHO Global Strategy aims to decrease the number of cases of cervical cancer to less than 4 for every 100,000 women, which relies on three points: 90% of girls vaccinated by age 15, 70% of women screened twice and 90% of those with cervical disease getting proper treatment.[1] To do so, the WHO strategy outlines the 90-70-90 targets that should be achieved by the year 2030.[4] These targets could reduce cervical cancer incidence by 42% by 2045 and 97% by 2120, potentially preventing 74 million new cases and 62 million deaths in low- and lower-middle-income countries. In the LMICs, the global commitments of about US$600 million were announced to intensify HPV vaccination, screening, and treatment efforts, particularly in the high-burden countries that have implemented the one-dose HPV vaccination schedule.[5]

Among over 200 known HPV genotypes, approximately 12 are classified as high-risk (oncogenic), with HPV-16 and HPV-18 accounting for around 70% of cervical cancer cases globally. Among over 200 known HPV genotypes, approximately 12 are classified as high-risk (oncogenic), and HPV-16 and HPV-18 are responsible for roughly 70% of all cervical cancer cases worldwide.[6] HPV is primarily transmitted through sexual contact, and in most young women, infections are transient and resolve spontaneously. Persistent HPV infection can lead to the development of precancerous lesions known as cervical intraepithelial neoplasia (CIN). If untreated, CIN can progress to invasive cervical cancer over 10-20 years.[6,7]

HPV vaccination is a key strategy for preventing cervical cancer. The World Health Organisation, the CDC and the European centre for disease prevention strongly advise giving the HPV vaccine to teens and have recently endorsed simplified vaccination schedules to improve coverage.[6,7]According to the WHO, only one shot should be given to girls aged 9 to 14 years, since recent research shows it is equally effective as the old regimens that involved two or three doses.[8] The change is meant to make vaccination more common and easier for people in areas where cervical cancer is most common.

The CDC recommends HPV vaccination for adolescents at ages 11-12, with the option to start as early as age 9. The CDC in the United States suggests offering the HPV vaccine to all adolescents at the age of 11 or 12, and the process may begin when the child is 9 years old. If people are immunised before age 15, they should get two doses with a gap of 6-12 months between each dose. In case someone starts the vaccination at age 15 or older or if their immune system is weak, they should get three doses spaced out by six months.[9] Most European countries follow similar guidelines, recommending two doses for individuals aged 9-14, and three doses for those above 15 or immunocompromised. Recently, the United Kingdom and Australia have decided to use one dose of the HPV vaccine after the WHO update. Three prophylactic HPV vaccines are currently available globally, each offering distinct type-specific coverage. The first bivalent formulation targets oncogenic HPV types 16 and 18; the second quadrivalent formulation provides protection against HPV types 6, 11, 16, and 18; and the nonvalent formulation confers broader coverage, additionally including types 31, 33, 45, 52, and 58.[10] Because of its broader protection, the nonavalent vaccine is commonly used in high-income settings. Despite clear guidelines and effective vaccines, global HPV vaccination coverage remains low, especially in resource-limited settings. Using one dose of vaccine offers the potential to boost coverage, cut costs and simplify the process, which is a key approach for the WHO to reach its goal of ending cervical cancer as a public health issue.

To boost global vaccination coverage and simplify multi-dose challenges, the effectiveness of single-dose HPV vaccines is being evaluated. Although two- or three-dose schedules give effective protection against HPV and related cervical problems, they are not practical for LMICs because of costs.[11]

For example, Gardasil-4 is priced at INR 3,710-4,000 (USD 44-48) per dose in India's private sector, while the nonvalent version can cost up to INR 11,600 (USD 140). Prices of these options are very high compared with those of the locally produced vaccines, such as the Cervavac, which is priced at only 200-400 rupees (2.40-4.80 USD) per dose in government schemes. Even with subsidies, procurement remains a major budgetary challenge.[12]

According to the modelling studies of countries such as Guyana and Sri Lanka, it is estimated that the conversion of the two-shot schedule (encompassing a cost of between US$9.64 and US$23.43 per adolescent vaccinated entirely) to a single shot plan promises to reduce expenses in the program to up to half and this range is simplified to the figures of $4.84 and 12.34 per vaccinated individual.[13] Moreover, given the global shortage of HPV vaccines, reducing the amount of vaccine is extremely necessary.[14] Evaluating the effectiveness of a single-dose HPV vaccine is crucial to inform global immunisation policy and improve program efficiency.

Objectives of the review

This systematic review and meta-analysis aim to evaluate whether a single dose of the HPV vaccine offers protection equivalent to two- or three-dose regimens against persistent HPV infection, Cervical intraepithelial neoplasia (CIN), and cervical cancer.

By synthesising evidence from current randomised controlled trials and observational studies, this review will determine if a single dose delivers comparable effectiveness against HPV-related outcomes.

Additionally, it examines the potential of a single-dose vaccination approach to enhance accessibility and cost-effectiveness, particularly in low- and middle-income

countries. The findings of this research will inform global policy decisions regarding HPV vaccine use and future research priorities for cervical cancer prevention.

METHODS

The present systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in the PROSPERO database (CRD420251116908).

Search strategy

Electronic databases such as PubMed, Cochrane, Scopus and Google Scholar were independently searched by two researchers. A comprehensive literature search strategy was developed using both medical subject headings (MeSH) and relevant free-text keywords related to Human Papillomavirus (HPV) infection and vaccination.

The search incorporated the Boolean operators "OR" and "AND" to ensure a broad and systematic capture of eligible studies. We also hand-searched the reference lists of relevant articles for additional references.

Study selection and eligibility criteria

Two researchers independently evaluated the retrieved studies using predefined eligibility and data extraction criteria. In cases of disagreement, a consensus was reached through discussion. The study designs included in this systematic review included RCTs, case control studies and observational studies. The inclusion and exclusion criteria were based on the population (patient), intervention, comparison, outcome (PICO) framework.

Population

This is a review of female population aged 9 years and older, are considered. The target demographics are also wide enough as they apply in high-, middle-, and low-income countries. Individuals are required to be either HPV-naive or never exposed to HPV to meet prophylactic HPV vaccination requirements.

Intervention

Vaccination against any prophylactic HPV vaccine, e.g. bivalent (Cervarix), quadrivalent (Gardasil), or nonavalent (Gardasil 9).

Comparator

In the comparative analysis, the schedules of vaccination against HPV will be considered that differ in the number of treatments, among which the two-dose and three-dose regimens are usually considered, regardless of the type of vaccine.

Outcomes

The primary and secondary outcomes assessed in this review included persistent HPV infection, evaluated as the presence of any HPV infection or specific HPV types targeted by the vaccine. The prevalence of cervical intraepithelial neoplasia (CIN 1, CIN 2, and CIN 3), representing precancerous cervical lesions, was also examined. In addition, the incidence of cervical cancer cases was assessed to determine the long-term impact of vaccination. Immunogenicity outcomes were evaluated through measures of immune response, such as antibody production following vaccination. Vaccine efficacy and effectiveness were assessed to establish the ability of HPV vaccines to prevent HPV-related infections and diseases. Safety outcomes included the recording and analysis of adverse events and reactions following vaccination. Furthermore, programmatic outcomes, such as vaccination uptake, compliance, coverage rates, and cost-effectiveness, were evaluated to assess the broader public health impact of HPV vaccination programs.

Study designs

The review was conducted by researchers at Bloom IVF Centre, Lilavati Hospital and Research Centre, Mumbai, India, between June 2025 and August 2025. Researchers studied the outcomes of single-dose HPV vaccination and compared them with the outcomes of multiple-dose vaccination using Randomised controlled trials (RCTs), cohort studies, and case-control studies.

Language

Only studies published in English were included.

Time frame

Studies published between 2000 and 2025 were included to capture evidence based on modern HPV vaccine formulations and updated vaccination schedules.

Search criteria

The inclusion criteria for this review consisted of peer-reviewed, open-access, fully published articles written in the English language. Eligible studies were limited to those published between 2000 and 2025 to ensure relevance and currency. Experimental studies, including RCTs, quasi-experimental studies, and interventional research designs, were included for analysis. Articles were excluded if they were published in languages other than English, published before 2000, or classified as editorials, narrative reviews, opinion papers, letters, book chapters, or case reports.

Data extraction

Data extraction is a critical step in this meta-analysis. Relevant studies were initially identified through

electronic database searches. The references retrieved were imported into Microsoft Excel, and two investigators independently screened the articles based on the inclusion criteria. After the initial review of titles and abstracts, the full texts of the selected studies were further evaluated by the same investigators to confirm eligibility. Any disagreements were resolved through discussion with a third investigator.

Quality assessment

A quality assessment of the literature was independently carried out by two researchers using the Cochrane risk of bias tool-2 (RoB 2) tool for randomised controlled trials (RCTs), as recommended in the Cochrane handbook for Systematic reviews of interventions.[15] Any disagreements were resolved through consensus. RCTs were evaluated for risk of bias using the RoB 2 tool across the following domains: bias arising from the randomization process; bias due to deviations from intended interventions; bias arising from missing outcome data; bias in the measurement of outcomes; bias in selection of the reported results; and overall risk of bias, based on these five domains. Responses to questions within the RoB 2 tool were recorded as "Yes," "Probably yes," "Probably no," "No," or "Not applicable." An algorithm summarised these responses to determine the risk of bias in each domain. Studies were categorised as "Low risk of bias" if all domains were rated as low risk; "Some concerns" if at least one domain raised some concerns, but none were high risk; and "High risk of bias" if any domain was judged as high risk. while observational studies were appraised using the "National Institute of Health (NIH) Quality assessment tool.[16] This analysis assisted in evaluating the studies' quality of evidence and locating any potential biases that might have an impact on the review's overall findings.

Data analysis

For this meta-analysis, incidence data on HPV infection and cervical cancer lesions were extracted from two intervention arms: a single-dose vaccination group and a combined group receiving either two or three doses. HPV infection outcomes were classified into two categories: infection with HPV types 16 or 18, and infection with any high-risk HPV genotype (hrHPV). Additional clinical outcomes assessed the effect of one-dose vaccination versus two or three doses on the incidence of high-grade squamous intraepithelial lesions (HSIL) or atypical squamous cells, including HSIL (ASC-H), and WHO cervical intraepithelial neoplasia grades 2 or 3 (CIN2/3).

For each outcome, risk ratios (RRs) comparing one-dose versus two-or-three-dose HPV vaccination regimens were computed from the number of events (infections and precancerous lesions) observed in each group. Pooled estimates of vaccine efficacy (or effectiveness) were derived using a random-effects model. Between-study heterogeneity was assessed via the Cochrane Q test and quantified by the I^2 statistic, which ranges from 0% (no heterogeneity) to 100%. Following Cochrane guidelines, I^2 value ≥50% was considered indicative of substantial heterogeneity.

RESULTS

Search results

The initial search retrieved 3955 articles remained for eligibility screening. The titles and abstracts were reviewed, resulting in the exclusion of 2,931 articles. Full texts of the remaining 139 articles were assessed for the eligibility criteria. Finally, 26 articles were included. Figure 1 provides details of the screening process.

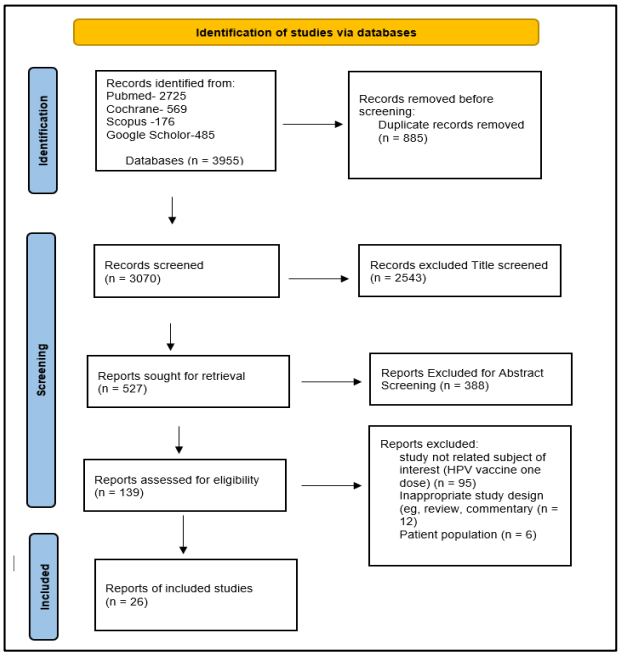

Figure 1: PRISMA analysis.

The initial search retrieved 3955 articles. After removing 885 duplicates, remaining 3,070 articles were screened for eligibility. The titles and abstracts were reviewed, resulting in exclusion of 2931 articles. Full texts of the remaining 139 articles were assessed for the eligibility criteria. Finally, 26 articles were included. Figure 1 provides details of the screening process. The quality assessment results for the RCTs and observational studies are illustrated in Figure 2 and 3. According to the RoB 2 tool and NIH Quality assessment tool, most studies adequately described their randomization processes, meeting the criteria for a low risk of bias in this area. However, three trials exhibited a high risk of bias due to deviations from the intended interventions. For all included trials, the risk of bias from missing outcome data was low, as outcome data were mostly complete. Studies demonstrated low risk in the measurement of outcomes, with consistent assessment methods across groups. However, two studies had concerns about selective reporting, indicating potential reporting bias. Overall, six studies (Barnabas et al; Joshi et al; Kreimer et al; Kreimer

et al; Safaeian et al; and Watson-Jones et al, were judged as having some concerns regarding risk of bias, while the remaining two studies (Safaeian et al; and Porras et al, were considered to have a high overall risk of bias.[17,23,25,26,29,30,34,36]

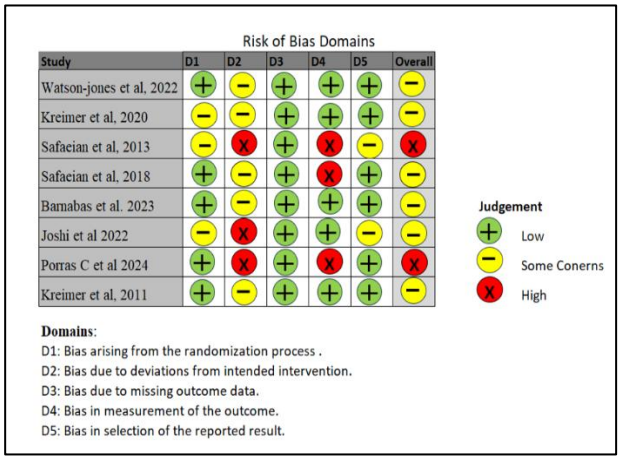

Figure 2: Risk of bias using RoB (risk of bias) version 2 for RCTs studies.

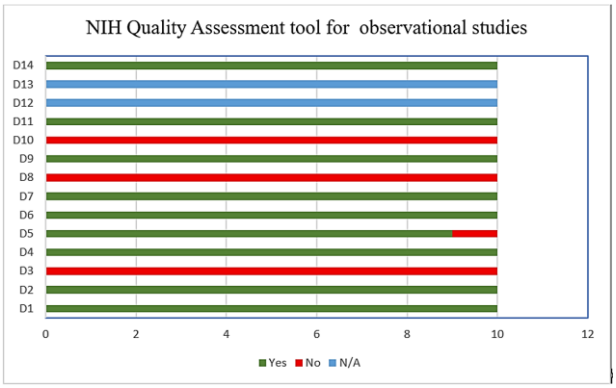

Figure 3: Risk of bias using national institute of health (NIH) quality assessment for observational studies.

D1: Research question/objective clearly stated, D2: Study population clearly specified and defined, D3: Participation rate of eligible persons at least 50%, D4: Participants recruited from same/similar populations; inclusion/exclusion criteria applied, D5: Sample size justification, power description, or variance/effect estimates provided, D6: Exposure(s) measured prior to outcome(s) being measured, D7: Sufficient timeframe for exposure–outcome association, D8: Different exposure levels examined, D9: Exposure measures clearly defined/reliable, D10: Exposure(s) assessed more than once, D11: Outcome measures defined, reliable, consistent, D12: Outcome assessors blinded to exposure status, D13: Loss to follow-up after baseline 20% or less, D14: Confounding variables measured/adjust.

Study characteristics

A total of 26 studies were included, comprising 10 randomised controlled trials (RCTs) and 16 observational studies (cohort, case-control, and cross-sectional). Studies were conducted across multiple continents: North America, Asia, Australia, Europe and Africa.[17-41]

Participants were predominantly adolescent and young adult females aged 9-26 years, with sample sizes ranging from 200 to 590,083. Interventions evaluated single-, two, and three-dose regimens of bivalent, quadrivalent, and nonvalent HPV vaccines over follow-up periods of 1 to 16 years. Across all settings, single-dose HPV vaccination demonstrated >90% efficacy against persistent HPV 16/18 infections and effectiveness comparable to multi-dose schedules for preventing high-grade cervical lesions. Long-term data from multiple countries confirmed durable immune responses lasting at least a decade, supporting the use of simplified single-dose regimens to expand coverage across the world (Table 1).

Comparison of one-dose versus unvaccinated

Fifteen studies assessed the effectiveness of a single dose compared to unvaccinated controls, encompassing approximately 2,020,000 participants. The unvaccinated group experienced 18,670 events (n=2,020,000), whereas the one-dose group recorded 3,268 events (n=139,169).

The pooled estimate showed no statistically significant difference between one-dose vaccination and no vaccination (RR=1.05, 95% CI: 0.73-1.52). Although several individual studies showed a protective effect, the overall pooled estimate had a wide confidence interval crossing unity. Heterogeneity was very high (I^2=96.8%, τ^2=0.4700, p<0.0001), reflecting variability in underlying populations and study methodologies.

As shown in Figure 4, large cohort studies such as Basu et al and Rodriguez et al contributed substantially to the pooled estimate.[18,27] The majority of studies exhibited risk ratios below one, reinforcing the protective signal of a single-dose strategy.

Comparison of one-dose versus two doses

In the subset analysis restricted to studies evaluating two doses versus one dose, 347,503 participants were included (n=323,531 for the two-dose group and n=139,169 for the one-dose group). A total of 3,548 events occurred among individuals receiving two doses, compared to 3,268 events among those receiving a single dose.

The pooled RR was 0.72 (95% CI: 0.40-1.32), indicating no statistically significant difference between one-dose and two-dose schedules. Heterogeneity remained substantial (I^2=93.6%, τ^2=1.3220, p<0.0001).

As depicted in Figure 5, some studies demonstrated a trend towards improved protection with two doses, while several large studies produced confidence intervals that overlapped with unity. These findings suggest that, in certain populations and contexts, a single dose may provide protection comparable to two doses without appreciable loss of efficacy.

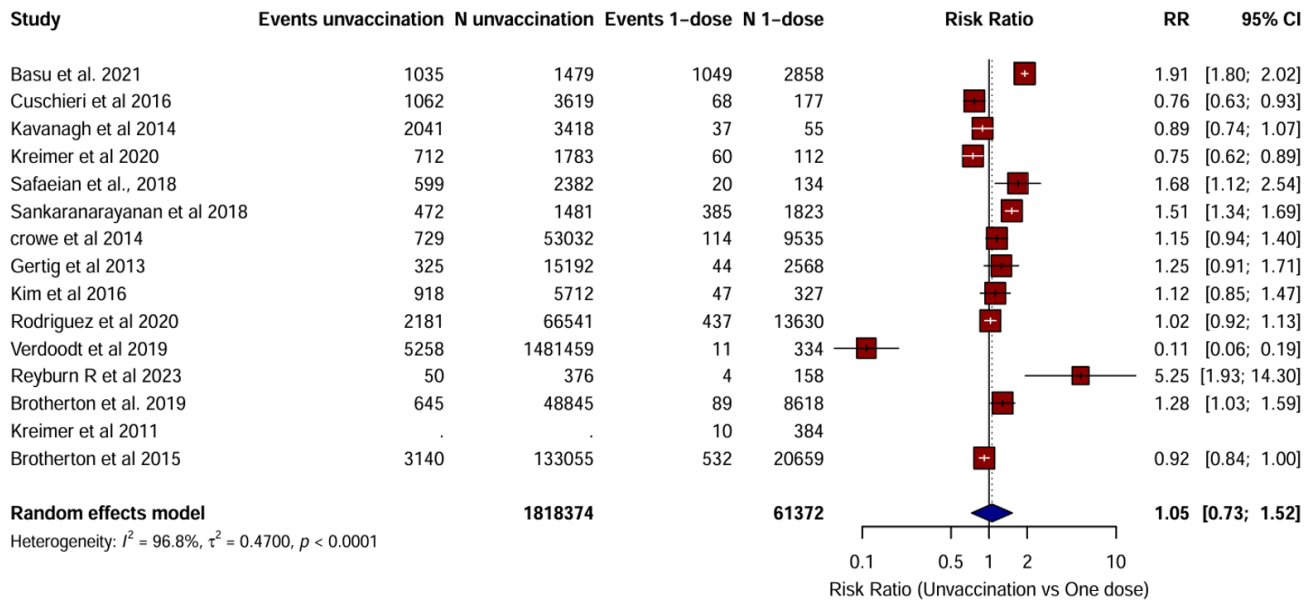

Figure 4: The effectiveness of one-dose HPV and unvaccinated population.

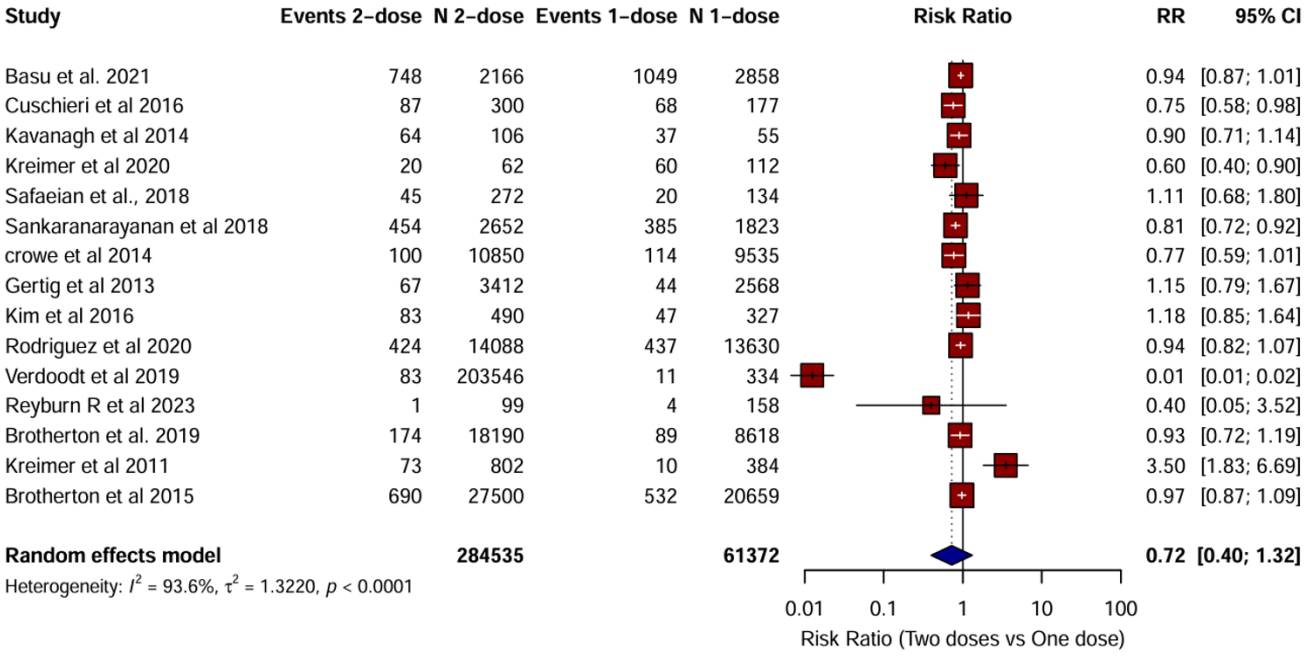

Figure 5: The effectiveness of one- and two-doses HPV vaccine.

Comparison of one-dose versus multiple doses

A total of 474,799 participants across fifteen studies were included in the comparison of a single vaccine dose versus multiple doses. There were 7,660 events among the multiple-dose recipients (n=474,799) and 3,268 events among the one-dose recipients (n=139,169).

The pooled analysis showed no statistically significant difference between one-dose and multiple-dose HPV vaccination schedules (RR=0.93, 95% CI: 0.60-1.44). The confidence interval crossed unity, indicating that the pooled estimate did not demonstrate a significant advantage of multiple-dose schedules over a single-dose schedule. Heterogeneity across studies was high (I^2=95.2%, τ^2=0.6940, p<0.0001), reflecting differences in study designs, populations, and vaccine schedules. As illustrated in Figure 6, most included studies demonstrated point estimates favouring multiple doses, with large-scale studies such as Basu et al and Brotherton et al exerting considerable influence on the pooled effect size.[18,19] Only a small number of studies crossed the line of no effect, indicating variability across studies and the need for cautious interpretation.

HPV vaccine seropositivity

Seven studies were analysed examining HPV vaccine seropositivity across different dosing schedules, with follow-up periods ranging from 18 months to 16 years. Single-dose vaccination demonstrated consistently high seropositivity rates across all studies. The CVT 16-year follow-up study showed 99.4% (95% CI: 96.8-100.0%) and 98.8% (95% CI:95.9-99.9%) seropositivity for HPV16 and HPV18, respectively. Multiple studies reported 100% vaccine efficacy against HPV16/18 with single doses, including the KEN SHE trial which demonstrated 100% efficacy against HPV16/18 and 95.5% efficacy against seven HPV types over 36 months ($p<0.0001$).[17] The dose reduction immunobridging and safety study of two HPV vaccines in Tanzanian girls (DoRIS) found single-dose vaccination non-inferior to 2- and 3-dose schedules for HPV16 ($p<0.05$).[36]

Two-dose regimens consistently achieved 100% seropositivity across studies with follow-up periods of 4-7 years and demonstrated non-inferiority to 3-dose schedules. Dose timing affected immunogenicity, with 180-day intervals between doses showing superior results compared to 60-day intervals (MFI ratio HPV16:1.12 vs 0.33). Three-dose schedules maintained 100% seropositivity across all studies and served as the reference standard for comparisons.

These findings indicate that reduced-dose HPV vaccination schedules, particularly single doses, can achieve seropositivity rates comparable to standard 3-dose regimens with sustained protection extending beyond a decade (Table 2).

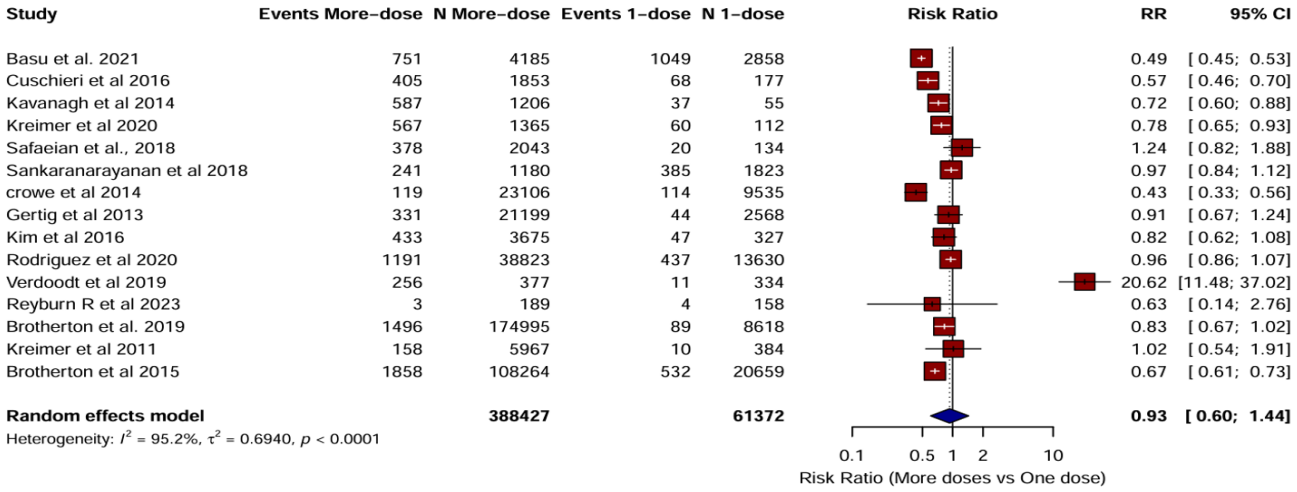

Figure 6: The effectiveness of one- and multiple-doses HPV vaccine.

Table 1: The included study characteristics and outcomes.

No	Author, year and country	Study design	Sample size	No. of doses	Outcome
1	Barnabas et al, (2023)[17](Kenya)	RCT	N=2,275 (healthy women- Never married n:1970 Married:80 Previously married n:21 Other n:2) Age:15-20 years	Single dose (n=1518) Bivalent (n=760), Nonvalent (n=758) Control (n=757) vaccine Follow-up or study period: 36 months	Single-dose HPV vaccination provided >95% protection against persistent infection for targeted HPV types over 3 years, with efficacy far superior to control
2	Basu et al, (2021)[18] (India)	Prospective, cohort study	N=17,729 (unmarried girls) Age:10-18 years	One dose (n=4949) Two doses (n=4980) Three doses (n=4348) Unvaccinated control: n=5,172 Follow-up or study period: 9 years	A single dose of quadrivalent HPV vaccine provides statistically significant and durable protection against persistent HPV 16/18 infections with efficacy above 95% comparable to two or three doses, supporting a simplified vaccination schedule that could improve coverage and affordability, especially in low- and middle-income countries

Continued.

No	Author, year and country	Study design	Sample size	No. of doses	Outcome
3	Brotherton et al, (2019)[19] (Australia)	Cohort study	N=250,648 Age:12-26 years	One dose (n=8,618) Unvaccinated (n=48,845) Three-dose (n=174,995) Two doses (n=18,190) Follow-up or study period: 7 years	A single dose demonstrated comparable effectiveness to two or three doses in preventing high-grade cervical disease (56% reduced risk) and low-grade cervical disease (52% reduced risk) in a high coverage setting.
4	Crowe et al, (2014)[20] (Scotland)	Case control study	N=108,353 women Age: 11-27 years	One dose (n=9535) Two doses (n=10850) Three doses (n=22987) Unvaccinated (n=53032) Follow-up or study period: 3 years	Significant effectiveness of a single dose of the HPV vaccine in preventing high-grade cervical abnormalities compared to the unvaccinated 0.95 (95% CI: 0.77 to 1.16). Three doses offered the optimal protection, with 46% effectiveness against high-grade lesions and 34% against other cytological abnormalities. Two doses conferred partial protection (approximately 21% effectiveness) but less than the complete series.
5	Cuschieri et al, (2016)[21] (Scotland)	Cross-sectional analysis	N=5949 cervical samples Age:14-18-years	One dose (n=177) two dose (n=300) three dose (n=1853) No dose (n=3619) Follow-up or study period: 10 years	Demonstrated potential effectiveness of one dose of HPV vaccine on vaccine type infection 48.2% with a 95% confidence interval (CI) of 16.8% to 68.9% (p=0.0075)
6	Gertig et al, (2013)[22] (Australia)	Cohort study	N=24,871 Age:12-13 years	One dose (n=2568) Two doses (n=3412) Three doses (n=21199) Unvaccinated (n=151920 Follow-up or study period: 5 years	One dose of the HPV vaccine showed statistically significant protection only against low-grade cytological abnormalities, with an adjusted hazard ratio (HR) of 0.67 (95% CI 0.59 to 0.76) compared to unvaccinated women. Vaccinated women (three doses) had significantly lower rates of cervical abnormalities compared to unvaccinated women.
7	Joshi et al, (2022)[23] (India)	Clustered RCT	N=17,729 Immunogenicity testing at 10 years N=1033 Age:10-18 years	Single-dose (n=324) Two-dose (n=190) Three-dose (n=167) Unvaccinated controls (n=352) Follow-up or study period: 10 years	Single dose provides high vaccine efficacy (>90%) reported, data supports that a single dose provides durable and statistically significant immunity, superior to natural infection with implication for broader HPV vaccine use especially in resource-limited settings.
8	Kim et al, (2016)[24] (Canada)	Case control study	N=10 204 Age:18-21years	Single dose (n=327) Two-dose (n=490) Three-dose (n=3675) Unvaccinated controls (n=5712) Follow-up or study period: 8 years	The odds of acquiring high-grade cervical abnormalities were lower in women who received at least one dose (0.86 (95% CI 0.62-1.18)) of the HPV vaccine compared to unvaccinated participants

Continued.

No	Author, year and country	Study design	Sample size	No. of doses	Outcome
9	Kreimer et al, (2011)[25] (Costa Rica)	Randomized, double-blind clinical trial	N=7153 Age:18-25 years	One dose HPV: (n=196), Control: 188 Two doses HPV- (n=422), control: 380 Three doses HPV- (n=2957), Control: 3010 Follow-up or study period: 1 year	Vaccine efficacy (VE) against detected persistent HPV16/18 infection lasting at least one year was high and statistically significant for all dosage groups: 80.9% protection with three doses, 84.1% with two doses, and 100% with one dose this suggests that one or two doses may provide protection comparable to three doses.
10	Kreimer et al, (2020)[26] (Costa Rica)	Randomized, phase III trial	N=3322 Age:18-25 years	One dose (n=112) Two doses (n=62) Three doses (n=1365) Unvaccinated women (n=1783) Follow-up or study period: 11.3 years	Single-dose VE against prevalent HPV16/18 infection was 82.1%, comparable to two-dose (83.8%) and three-dose (80.2%) groups, with no significant differences between dosing regimens, supports that a single dose provides sufficiently durable protection to reduce cervical cancer risk, potentially easing vaccine implementation barriers and vaccine policy adaptations to improve coverage and reduce costs, especially in resource-limited regions
11	Rodriguez et al, (2020)[27] (United States)	Retrospective cohort study	N=66,541 Age: 9 to 26 years	One dose (n=13,630) Two doses (n=14,088) Three doses (n=38823) Unvaccinated women (n=66,541) Follow-up or study period: 5 years	A single HPV vaccine dose significantly reduced the risk of preinvasive cervical disease (HR 0.64; 95% CI, 0.47-0.88) compared to unvaccinated peers. This finding supports that fewer than three doses provide substantial protection, endorsing flexible vaccination schedules to increase coverage
12	R. V. Barnabas et al, (2023)[28] (Kenya)	RCT	N=2275 women age:15-20 years	Single 758 nonvalent, 760 bivalent, 757 control. Follow-up or study period: 18months	Single-dose bivalent and nonvalent HPV vaccination provided highly effective protection (>97%) against persistent vaccine-type HPV infections at 18 months, statistically comparable to two- or three-dose regimens.
13	Safaeian et al, (2013)[29] (Costa Rica)	Randomized, community-based phase III trial	N=390 Age:18-25 years	One dose: (n=78) two dose 0/1 month: (n=140) two dose 0/6 months: (n=52) three dose: (n=120) Follow-up or study period: 48 months	Single dose confers durable protection and much higher antibody levels than natural infection, as high as two- or three-dose schedules (96% positive for neutralization vs. 98% for three doses), this suggests long-lasting protection may be achievable with fewer than three doses, potentially simplifying vaccination schedules and reducing costs, especially in resource-limited setting
14	Safaeian et al, (2018)[30] (Costa Rica)	Post hoc analysis of a randomized controlled trial	N=2449 Age: 18-25 years	One dose: (n=134); Two doses (0 and 1 month) (n=193); Two doses (0 and 6 month) (n=79); Three doses : (n=2,043) Follow-up or study period: 7 years	100% of vaccinated women in all dose groups remained seropositive for both HPV16 and HPV18. A low prevalence of hpv16/18 infections was found across all dose groups, indicating that single dose may provide lasting protection.

Continued.

No	Author, year and country	Study design	Sample size	No. of doses	Outcome
15	Sankaranarayanan et al, (2016)[31] (India)	Multicentre prospective observational cohort study	N=17,729 Age: 10-18 years	One dose default (n=4950) Two doses (day 1, 180) (n=4979) Two doses (day 1, 60) (n=3452) Three doses (n=4348) Follow-up or study period: 60 months	All dose groups showed no persistent HPV 16/18 infection after a median 4.7-year follow-up. The short-term protection provided by a single dose of the HPV vaccine against persistent infection with HPV types 16, 18, 6, and 11 is comparable to that achieved with two or three doses.
17	Verdoodt et al, (2020)[32] (Denmark)	Cohort study	N=590,083 women Age:17-25 years vaccinated at ≤16 years	One dose: (n=10,480) two dose: (n=30,259) three dose: (n=174,532) Unvaccinated (n=373,327) Follow-up or study period: 8years	Single dose vaccination in adolescents provides substantial and statistically significant protection against CIN2+ and CIN3+ compared to non-vaccinated population. No significant difference in protection between 1, 2, and 3 dose regimens in this age group, supporting the effectiveness of reduced dosing schedules.
18	Kavanagh et al, (2014)[33] (Scotland)	Retrospective cohort study	N=4729 (liquid-based cytology (LBC) samples) from Aged 12-13 years	Unvaccinated-3418; One dose: (n=55); two dose: (n=106); three dose: (n=1100) Follow-up or study period: 8 years	Compared to the unvaccinated group, receiving a single dose was associated with a reduced prevalence of HPV types 16 and 18 (OR=0.88, 95% CI: 0.48-1.6); however, this reduction was not statistically significant (p=0.68).
19	Porras C et al, (2024)[34] (Costa Rica)	Community-based, randomized, double-blind, prelicensure, phase III trial	N=398 received 3 doses, N=203 received 1dose Age 18 to 25 years At follow-up 16 years Aged 33 and 42 years old.	One dose -203 All three doses- 398 Follow-up or study period: 16 years	Results support the use of a single-dose HPV vaccination schedule for broad, durable protection against HPV-16 and HPV-18 infections
20	Shing JZ et al, (2022)[35] (Costa Rica)	RCT	N=7466 HPV-vaccine ARM-3727 Control ARM-3739. Age - 18-25 years.	3 doses Follow-up or study period: 11 years	A single dose of the bivalent HPV vaccine provided strong and durable protection against high-grade cervical lesions (CIN2+ and CIN3+) caused by vaccine-targeted HPV types (HPV16/18) for at least 11 years after vaccination when compared to unvaccinated women.
21	Watson J et al, (Doris) (2022)[36] (Tanzania)	RCT, non-inferiority trial	N=930 Age: 9-14 years	One dose bivalent=155; Two doses bivalent=155; Three doses bivalent=155; One dose 9-valent=155. Two doses 9-valent=155; Three dose valent=155 Follow-up or study period:24 months	A single dose of HPV vaccine in girls aged 9-14 years yields very high immunogenicity at 24 months. For HPV 16, seropositivity is 99–99.3% after a single dose versus 100% after two or three doses—this is statistically non-inferior, as the difference falls well within the non-inferiority margin. A single-dose HPV vaccine schedule offers strong, sustained protection while reducing costs and logistical challenges, making it a practical and efficient option to increase vaccination coverage and prevent cervical cancer in resource-limited settings.
22	Brotherton et al, (2015)[37](Australia)	Observational cohort study	N=289,478 Age:26 or younger	One dose (n=20,659) Two doses (n=27,500) Three (complete) doses: (n=108,264) Unvaccinated: (n=133,055) Follow-up or study period: 2.89 years	The greatest reductions were observed among those fully vaccinated (three doses), but evidence suggested that partial vaccination (one or two doses) also provided protection. Single dose vs unvaccinated HR 0.65, 95% CI 0.52–0.81) Single dose vs three doses HR 1.01 (95% CI 0.81–1.26)

Continued.

No	Author, year and country	Study design	Sample size	No. of doses	Outcome
23	Reyburn et al, (2023)[38] (Fiji)	Retrospective cohort study	N=822 Age: 15–23 years	One dose (n=158) Two doses (n=99) Three dose (n=189) Unvaccinated: (n=376) Follow-up or study period: 6–11 years	A single dose of the quadrivalent HPV vaccine offered 81% effectiveness (95% CI: 48–93%) in significantly reducing HPV 16/18 detection compared to unvaccinated individuals. Two doses provided complete protection with 100% effectiveness (95% CI: 100–100%) and no cases detected. Three doses also showed strong protection with 89% effectiveness (95% CI: 64–96%). Protection duration from a reduced-dose HPV vaccine schedule in a low- or middle-income country in the Western Pacific, supporting the effectiveness of single-dose HPV vaccination in high-burden settings.
24	Batmunkh et al, (2020)[39] (Mongolia)	Retrospective cohort study	N=475 Age:16–26 years	Single-dose (n=118 Unvaccinated (n=357) Follow-up or study period: 6 years	A single dose of the 4vHPV vaccine in resulted in a 92% reduction in vaccine-targeted high-risk HPV types 16/18 prevalence compared to unvaccinated women. Six years post-vaccination, vaccinated women sustained high seropositivity rates (90% for HPV16, 58% for HPV18) and significantly higher neutralizing antibody levels. Findings support the growing global interest in simplified, single-dose HPV vaccination schedules, especially relevant for low- and middle-income countries facing vaccine supply and cost challenges.
25	Markowitz et al, (2019)[40] (United States)	Retrospective cohort study	N=4,269 Age: 20–29 year	One dose (n=303) Two doses (n=304) Three dose (n=2,610) Unvaccinated: (n=1,052) Follow-up or study period: 76 months	High vaccine effectiveness HR 0.06 (95% CI, 0.01–0.42), indicating about 94% vaccine effectiveness was observed for 1, 2, or 3 doses of 4 VHPV vaccine if the first dose was received at age ≤18 years. HPV prevalence was significantly lower with 1 dose (0.5%), 2 doses (0.4%), and 3 doses (0.5%). The study supports potential flexibility in HPV vaccination schedules, with single-dose vaccination appearing highly effective.
26	Toh et al, (2017)[41] (Fiji)	Prospective cohort study	N=200 Age: 15–19 years	One dose (n=40) Two doses (n=60) Three dose (n=66) Unvaccinated: (n=32) Follow-up or study period: 6 years	Six years after vaccination one dose group were significantly lower than those in the 2-dose and 3-dose groups, but still 5- to 30-fold higher than unvaccinated girls for all four HPV types (HPV-6, -11, -16, -18) ($p<0.005$). Single dose showing statistically and clinically relevant durability and memory compared to unvaccinated individuals.

Table 2: HPV vaccine seropositivity.

Study	Vaccine	Doses	HPV types	Seropositivity (%)	Follow-up duration	P value/ CI
Watson et al, (2022)[36]	Cervarix (2V) and Gardasil-9 (9V)	1 dose	HPV16	99% at 24 months	24 months	Non-inferior to 2 and 3 doses (p<0.05)
		2 doses	HPV16	100%	24 months	
		3 doses	HPV16	100%	24 months	
		1 dose	HPV18	>98% at 24 months	24 months	Did not meet NI vs 2/3 doses (p>0.05)
		2 doses	HPV18	100%	24 months	
		3 doses	HPV18	100%	24 months	
Barnabas et al, (2023)[17]	Bivalent and nonavalent	1 dose	HPV16/18	100% VE, seropositive	36 months	P<0.0001
		1 dose	HPV16/18/31/33/45/52/58	95.5% VE	36 months	P<0.0001
Kreimer et al, (2011)[25]	Cervarix (2V)	1 dose	HPV16/18	100% VE, seropositive	4.2 years	95% ci 66.5–100%
		2 doses	HPV16/18	84.1% VE, seropositive	4.2 years	95% CI 50.2–96.3%
		3 doses	HPV16/18	80.9% VE, seropositive	4.2 years	95% CI 71.1–87.7%
Safaeian et al, (2017)[30]	Cervarix (2V)	1 dose	HPV16/18	100% seropositive	7 years	P=0.17 vs 3-dose
		2 doses (0/6)	HPV16/18	100% seropositive	7 years	P=0.85 vs 3-dose
		2 doses (0/1)	HPV16/18	100% seropositive	7 years	P=1.00 vs 3-dose
		3 doses	HPV16/18	100% seropositive	7 years	
Porras et al, (2024)[34]	Cervarix (2V)	1 dose	HPV16	99.4% seropositive	16 years	95% CI 96.8–100.0%
		1 dose	HPV18	98.8% seropositive	16 years	95% CI 95.9–99.9%
		3 doses	HPV16	100% seropositive	16 years	95% CI 98.9–100.0%
		3 doses	HPV18	100% seropositive	16 years	95% CI 98.9–100.0%
Safaeian et al, (2013)[29]	Cervarix (2V)	1 dose	HPV16/18	100% seropositive	4 years	X^2 p>0.05 vs 3-dose
		2 doses (0/6)	HPV16/18	100% seropositive	4 years	Non-inferior (GMT ratio CI >0.5)
		2 doses (0/1)	HPV16/18	100% seropositive	4 years	Non-inferior
		3 doses	HPV16/18	100% seropositive	4 years	Reference
Sankaranarayanan et al, (2016)[31]	Gardasil (4V)	1 dose	HPV16/18	100% seropositive; no persistent infection	4.7 years	Similar to 2 and 3 doses; p>0.05
		2 doses (1/180 d)	HPV16/18	Non-inferior to 3 doses	18 months	MFI ratio HPV16: 1.12 (95% CI 1.02–1.23)
		2 doses (1/60 d)	HPV16/18	Lower seropositivity	18 months	MFI ratio HPV16: 0.33 (95% CI 0.29–0.38)
		3 doses	HPV16/18	100% seropositive	4.7 years	Reference

Effectiveness of HPV vaccine

Evidence from randomized trials, national cohorts, and long-term follow-up studies has shown that HPV vaccination is highly effective in reducing HPV infections and cervical precancerous disease.

Clinical trials from Africa and Latin America have been particularly influential. In Kenya, a single dose of either the bivalent or nonavalent vaccine provided over 95% protection against persistent HPV16/18 infection, sustained for at least three years (Barnabas et al and Barnabas et al).[17,28] Similarly, in Costa Rica, long-term studies demonstrated that one dose of the bivalent vaccine maintained both strong antibody responses and high efficacy against HPV16/18 infections for more than a decade, with follow-up extending to 16 years (Kreimer et al; Porras et al).[26,34] Evidence from India echoed these findings, where one dose offered >90% protection against HPV16/18 infections and robust immune responses were observed up to 10 years later (Basu et al, 2021; Joshi et al, 2022).[18,23] Reports from Fiji et al further confirmed that simplified schedules can provide durable protection in

low- and middle-income countries, where completing multi-dose regimens is often a challenge (Reyburn et al; Batmunkh et al).[38,39]

Population-based data from high-income countries strengthen these clinical trial results. In Australia, large national cohorts showed that women who received one, two, or three doses all experienced significant reductions in high-grade cervical abnormalities, with effectiveness of a single dose comparable to two or three doses (Brotherton et al; Brotherton et al).[19,37] Similar reductions in preinvasive cervical lesions have been documented in the United States (Rodriguez et al; Markowitz et al) and Denmark (Verdoodt et al).[27,40,32] In Scotland, full three-dose vaccination yielded the greatest protection against high-grade abnormalities, though women who received fewer doses still benefited compared with those unvaccinated (Crowe et al; Cuschieri et al).[20,21]

Immunological evidence supports even a single dose produces antibody levels far exceeding those from natural infection. Seropositivity to HPV16/18 has been sustained for 7 to 16 years after a single dose, supporting the durability of this protection (Safaeian et al, 2013; Safaeian et al, 2018; Porras et al).[29,30,34] Adolescent girls vaccinated with either the two-valent or nine-valent vaccine also showed >98% seropositivity two years after just one dose, highlighting the robustness of immune responses in younger populations (Watson-Jones et al).[36]

These findings provide compelling evidence that a single dose of HPV vaccine is sufficient to achieve strong, long-lasting protection against HPV16/18 infection and related precancerous lesions. While multiple doses do generate higher antibody titers, their added clinical benefit appears limited. This has major implications for public health, particularly in low-resource settings, where simplified one-dose schedules can lower costs, improve coverage, and accelerate the goal of cervical cancer elimination.

DISCUSSION

This systematic review and meta-analysis provide compelling evidence that single-dose HPV vaccination offers substantial protection against HPV-related infections and precancerous lesions, though with measurable differences compared to multi-dose regimens. Our analysis of 26 studies encompassing over 2.1 million participants showed no statistically significant difference between one-dose and unvaccinated groups in the pooled analysis (RR=1.05, 95% CI: 0.73-1.52), between one-dose and two-dose schedules (RR=0.72, 95% CI: 0.40-1.32), or between one-dose and multiple-dose schedules (RR=0.93, 95% CI: 0.60-1.44). However, several individual studies demonstrated meaningful protective effects, and the pooled analyses were limited by substantial heterogeneity.[15-17,23-26,30,32,34,36] The finding that single-dose vaccination achieved no statistically significant difference compared to two-dose regimens (RR=0.72, 95% CI: 0.40-1.32) is particularly noteworthy for public health policy. This suggests that in settings where completing multi-dose schedules is challenging, a single dose may provide protection approaching that of two doses, substantially reducing the complexity and cost of vaccination programs.[11,12]

The immunogenicity data from our analysis strongly support the biological plausibility of single-dose protection. Seven studies with follow-up periods extending to 16 years demonstrated consistently high seropositivity rates for single-dose recipients.[23,24,27-29,32,34] The landmark CVT 16-year follow-up study showed remarkable durability, with 99.4% and 98.8% seropositivity for HPV16 and HPV18, respectively.[32] This finding is particularly significant as it represents the longest documented evidence of immune persistence following single-dose HPV vaccination.[27-29,32]

The maintenance of 100% vaccine efficacy against HPV16/18 in multiple studies, including the KEN SHE trial's demonstrated sustained protection over 36 months, provides robust evidence that single-dose vaccination can trigger durable immune memory responses.[17,28] While antibody levels after single doses were consistently lower than those observed with multi-dose regimens (ratio ranges from 0.25-0.33 compared to three-dose groups), these levels remained substantially above those achieved through natural infection and appeared sufficient for clinical protection.[29,30,34]

Our analysis reveals consistent protective effects of single-dose vaccination across geographically and economically diverse populations. Studies from high-income countries (Australia, Denmark, Scotland) and low- and middle-income countries (India, Kenya, Fiji, Mongolia, Tanzania) demonstrated comparable effectiveness patterns, suggesting that single-dose protection is not dependent on specific population characteristics or healthcare infrastructure quality.[16-21,30,34,36,37]

The effectiveness in LMICs is particularly encouraging, with studies from Kenya showing >95% protection against persistent HPV 16/18 infections over three years, and Indian data demonstrating 95.4% efficacy sustained over nine years.[17,18,23,28] These findings are crucial for global cervical cancer prevention efforts, as LMICs bear a disproportionate burden of cervical cancer mortality while facing significant challenges in implementing multi-dose vaccination programs.[1,2,5]

The evidence presented in this meta-analysis has profound implications for global HPV vaccination policy. The World Health Organization's recent endorsement of single-dose HPV vaccination reflects the growing recognition that the public health benefits of simplified schedules may outweigh the modest reduction in individual-level protection compared to multi-dose regimens.[8] These results align with the WHO Cervical cancer elimination strategy, which aims to fully vaccinate 90% of girls against HPV by age 15, screen 70% of women

using a high-performance test by ages 35 and 45 and ensure 90% of women with cervical disease receive appropriate treatment.[4] This objective is supported by single-dose regimens, which are cheaper, less logistically complex and easier to start uptake, especially essential where multi-dose regimens are commonly not completed due to programmatic barriers in LMICs.[5,8,11,12]

From a population perspective, the trade-off between individual protection and coverage becomes critical. Mathematical modelling suggests that achieving higher coverage rates with single-dose vaccination could result in greater overall disease prevention than lower coverage with multi-dose schedules.[4,5] This is particularly relevant in resource-constrained settings where logistical challenges, vaccine supply limitations, and healthcare system capacity constraints limit multi-dose program effectiveness.[11,12] The economic advantages of single-dose vaccination extend beyond vaccine costs to include reduced healthcare worker time, simplified cold chain management, and improved program feasibility in remote or underserved areas.[11,12] These operational benefits could be transformative for achieving the WHO's goal of cervical cancer elimination as a public health problem.[4,8]

The substantial heterogeneity observed across our meta-analyses reflects the diversity of study populations, methodologies, and outcome measures included in our analysis. This heterogeneity, while limiting the precision of pooled estimates, actually strengthens the generalisability of our findings by demonstrating protective effects across varied contexts.[13]

Several factors contribute to this heterogeneity, including differences in vaccine types (bivalent, quadrivalent, nonvalent), study populations (age ranges, geographic locations, baseline HPV prevalence), follow-up durations, and outcome definitions. The consistency of protective signals despite this heterogeneity suggests robust underlying effectiveness of single-dose vaccination.[15-17,23-26,30,32,34,36,37] The global implementation of a single-dose HPV vaccination schedule, as recommended by the WHO and adopted by countries such as the UK and Australia, marks a strategic advancement in preventive oncology.[8] These results have significant implications for policy and practice: the promotion of simplified cost-effective vaccination schedules within the parameters of the public health policies and the reasonable access to the HPV-related diseases.[4,5,8]

Strengths and limitations

This review is considered reliable and relevant due to several methodological strengths. It incorporates recent findings from rigorously designed RCTs and high-quality observational studies conducted across diverse geographic settings. Integrating real-world effectiveness data with immunogenicity findings provides a comprehensive understanding of the potential impact of single-dose HPV vaccination. Furthermore, the strict approach to including studies, measuring results and assessing potential bias guarantees that the final results are correct.

However, certain limitations warrant consideration. Variability in study design, participant characteristics, and follow-up duration may limit the comparability of results. Secondly, although early findings on single-dose efficacy are promising, the duration of protection remains uncertain, as most studies report follow-up data for up to 10 years. Third, the types of vaccines used (bivalent, quadrivalent or nonavalent) and the quality of healthcare facilities in the study sites may affect the findings. Although observational data provide valuable insights, such studies are inherently more susceptible to confounding compared to RCTs. In the end, publication bias can make it harder to rely on reviews, as some positive studies are published more often. Nonetheless, the aggregated evidence supports the effectiveness and feasibility of a single-dose HPV vaccination regimen, particularly in resource-constrained settings.

Future research directions

Despite growing evidence supporting single-dose HPV vaccination, several critical research gaps remain. Long-term studies are needed to assess vaccine effectiveness against invasive cervical cancer and other HPV-associated malignancies. Additional research should evaluate single-dose efficacy across diverse healthcare systems, particularly in LMICs. It is also necessary to research how well single-dose vaccination works in immunocompromised individuals, males and older adults in terms of their immune responses. Evaluating strategies for integrating single-dose HPV vaccination into existing immunisation programs will be vital for informed policymaking. Finally, ongoing surveillance for emerging HPV genotypes and viral variants is crucial to safeguard long-term vaccine effectiveness.

CONCLUSION

This systematic review and meta-analysis provide strong evidence that a single dose of the HPV vaccine delivers substantial and long-lasting protection against persistent HPV infection and high-grade cervical lesions, with several studies suggesting effectiveness comparable to two- and three-dose regimens, although pooled estimates showed substantial heterogeneity and should be interpreted cautiously. Analysing data from across a wide range of geographic and socioeconomic settings, the findings support the global shift toward simplified HPV vaccination approaches especially critical for low- and middle-income countries facing substantial challenges with multi-dose completion due to logistical and financial constraints.

While multi-dose schedules offer a slightly greater reduction in risk, the consistently high seropositivity and durable immunogenicity observed in single-dose recipients sustained for up to 16 years highlight its clinical

value. Single-dose vaccination enables significant cost savings, streamlined implementation, and broader population coverage. These advantages align with the World Health Organization's 90-70-90 targets for cervical cancer elimination by 2030.

In summary, current evidence endorses single-dose HPV vaccination as a practical, efficient, and highly effective strategy in global public health, particularly in resource-limited settings. Continued surveillance and extended follow-up will be important to monitor the long-term duration of protection and impact on invasive cervical cancer rates. However, the available data robustly support adopting single-dose HPV vaccination into national immunization schedules as a cornerstone for accelerating cervical cancer elimination worldwide.

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