Safety and effectiveness of human papillomavirus (HPV) vaccine: A systematic review and meta-analysis

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Abstract
Since the introduction of HPV vaccines, rates of HPV-related pre-cancers and cancers have declined significantly in the U.S. and other countries where the vaccine is used. We conducted a systematic review of studies assessing the safety, effectiveness, and immunogenicity of HPV vaccines available in the US that were published in the peer-reviewed literature from Sept 2024-Jan 2026. We combined our findings with two previously published Cochrane reviews of literature through Sept 2024 that met our inclusion criteria, integrating both newly identified and eligible Cochrane-included studies in meta-analysis where appropriate. The updated review synthesizes results from 274 studies across safety, effectiveness, and immunogenicity outcomes, encompassing randomized controlled trials, cohort studies, ecological studies, case-control studies, and immunogenicity analyses. Overall, findings are broadly consistent with prior Cochrane reviews. The totality of evidence—including randomized trials and observational studies—continues to show no association between HPV vaccination and serious adverse events (SAEs). Effectiveness data continue to reinforce substantial protection against cervical cancer, high-grade cervical lesions, and HPV infection. Increasing evidence suggests single-dose regimens may offer comparable protection to multidose schedules for key outcomes in females; further evidence is needed to assess effectiveness against non-cervical cancers and pre-cancers in males.

Introduction

Human papillomavirus (HPV) is responsible for 90% of cervical and anal cancers as well as over 50% of oropharyngeal, penile, vaginal, and vulvar cancers in the US (Jensen 2024). It is transmitted via skin-to-skin or skin-to-mucosa contact, and is the most common sexually transmitted infection in the world, with an estimated 80% of sexually active adults acquiring an infection at some point in their lives (Plotzker 2023, Chesson 2014). HPV is not one, but a diverse group of viruses that target and infect squamous epithelial cells. More than 170 genotypes of HPV have been identified, 12 of which are categorized as high-risk owing to their ability to cause cancer (Jensen 2024). Over time, tissue that is persistently infected with high-risk HPV genotypes can progress to pre-cancerous neoplasia (Yousaf 2024, Cosper 2021). Although most HPV infections are asymptomatic and resolve without intervention, the long-term impact of persistent, and often unrecognized, HPV infection is substantial. Direct medical costs of HPV disease screening and treatment are $9 billion annually in the US (Clay 2023).

To prevent acquisition, persistent infection, and long-term sequelae from HPV, the US Food and Drug Administration (FDA) approved the Recombinant Human Papillomavirus Quadrivalent Vaccine (4vHPV, Gardasil [Merck]) in 2006. This was followed by approval of the Recombinant Human Papillomavirus Bivalent Vaccine (2vHPV, Cervarix [GSK]) in 2009 and the Recombinant Human Papillomavirus 9-valent Vaccine (9vHPV, Gardasil 9 [Merck]) in 2014. 9vHPV is the only HPV vaccine currently used in the US (DeSieghardt 2025, CDC 2024a, FDA 2025). Since the introduction of HPV vaccines, rates of HPV-related pre-cancers and cancers have declined significantly in the U.S. and other countries where the vaccine is used (Palefsky 2011, Dorali 2024, Gargano 2025, Harper 2025). Long-term outcome data from different countries and study designs consistently report a reduction in the risk of pre-cancerous outcomes and the development of HPV-associated cancers (Henschke 2025, Bergman 2025).

HPV vaccines were first studied and licensed as a three-dose series. However, over time, studies indicated that reduced-dose HPV vaccination schedules may offer comparable immunogenicity and protection against disease end points (CDC 2024b). Post hoc analyses from a randomized trial of 2vHPV versus a control vaccine revealed that, despite incomplete uptake of the full three-dose regimen among participants, vaccine efficacy against HPV16/18 infection was consistent across one-, two-, and three-dose recipients. In addition, immunobridging studies comparing adolescents receiving two doses with young adult women receiving three doses demonstrated non-inferior seroconversion and antibody titers in the younger cohort. In light of accumulating evidence on reduced-dose HPV vaccine efficacy, the World Health Organization (WHO) in 2022 recommended a two-dose schedule for individuals aged 9 years and older and additionally recognized a single-dose regimen as an off-label option for those aged 9–20 years (WHO 2022). Today, questions still linger about whether a single dose is sufficient for longstanding protection.

Prior to January 2026, the Advisory Committee on Immunization Practices (ACIP) recommended routine HPV vaccination for adolescents at age 11 or 12 years, with the option to start at age 9 years (Petrosky 2015, Meites 2019, CDC 2024a). The recommended schedule was aligned with its FDA-approval: a two-dose series, with the second dose administered six to

12 months after the first. For older adolescents and young adults (ages 15-26), a three-dose series was still recommended. The optimal timing of vaccine initiation remains an active discussion; ACIP recently reviewed whether its guidance should explicitly recommend routine HPV vaccination for children ages 9–12 (CDC 2024c, CDC 2024d, CDC 2025a).

In the absence of any ACIP process or evidence review, in January 2026, the US Department of Health and Human Services (HHS) announced it was altering the childhood immunization schedule (CDC 2026) and reduced the HPV vaccine recommendation to a single dose at 11-12 years of age; thus, the HHS recommendations became inconsistent with formal FDA licensure of a two-dose schedule and with the FDA-approved package insert (CDC 2025b). We aimed to synthesize the available evidence on the safety, effectiveness, and immunogenicity of HPV vaccines. In particular, we evaluated evidence examining whether a single-dose regimen is comparable to the standard two-dose schedule with respect to safety, effectiveness, and immunogenicity. We also assessed whether any new safety signals have emerged that warrant further investigation.

Methods

Study overview

This systematic review and meta-analysis evaluated the safety, efficacy and effectiveness, and immunogenicity of HPV vaccines available in the US. The Cochrane Collaboration recently published two comprehensive reviews of HPV vaccine safety and efficacy through September 2024: the first (Bergman 2025) focused on randomized clinical trials, and the second (Henschke 2025) on observational studies. However, these reviews take a global perspective. This study begins by updating the evidence base through a comprehensive search of studies published from September 2024 to January 2026. Next, we limit both Cochrane reviews by applying US-specific eligibility criteria to identify the subset of Cochrane studies relevant to HPV vaccines available in the US. Finally, where appropriate, we synthesize the newer US-based studies with this subset of Cochrane studies, offering a comprehensive and up-to-date picture of the current evidence base. Throughout, we begin by presenting newly identified evidence from our updated search, followed by relevant findings from the Cochrane reviews that meet our inclusion criteria and, where appropriate, meta-analyses integrating both newly identified studies and eligible Cochrane-included studies.

Scientific contributors

This evidence review was conducted by researchers from the Center for Infectious Disease Research and Policy at the University of Minnesota, subject matter experts, and other specialists in relevant technical fields (Supplemental Material 1).

Study registration

We submitted and registered the protocol with the International Prospective Register of Systematic Reviews (PROSPERO) on February 5, 2026 (CRD420261300907).

Search methods

We replicated the previous Cochrane searches for randomized controlled trials (RCTs) and observational studies by searching PubMed/MEDLINE, Embase, Web of Science, and the Cochrane Library for peer-reviewed, English-language articles (Supplemental Material 3). Search windows began on the last date of the Cochrane HPV reviews: September 11, 2024, for observational studies and September 18, 2024, for clinical trials, and ended on January 27, 2026.

Study eligibility

In this updated review, we included RCTs and observational studies that addressed three domains: safety, vaccine efficacy (RCTs) or effectiveness (observational studies), and immunogenicity. Eligible vaccines included only US-licensed HPV vaccines: 4vHPV (FDA approved in June 2006, discontinued in US since 2017), 2vHPV (FDA approved in October 2009, discontinued in US since 2016), and 9vHPV (FDA approved in December 2014) (FDA 2025a, FDA 2019, FDA 2025b). Studies were included if they were published in English in a peer-reviewed journal.

We also examined data from the previous Cochrane reviews, limiting them to the same eligibility criteria (except the search window). Cochrane studies included RCTs and observational studies, irrespective of language or publication status, that evaluated WHO-prequalified HPV vaccines (2vHPV [Cervarix (GSK) and Cecolin (Innovax)], 4vHPV [Gardasil, Merck], 9vHPV [Gardasil, Merck]).

The current review integrated the subset of studies that evaluated the three vaccines that have been or currently are US-approved (2vHPV [Cervarix], 4vHPV, 9vHPV) and excluded those that assessed 2vHPV (Cecolin) only. Hereafter, 2vHPV will refer only to Cervarix.

Study screening and data extraction

Two reviewers independently screened the studies, first by title and abstract, followed by full-text review. Two reviewers then independently extracted data on study characteristics (including study design and population), vaccine product, comparator groups, follow-up time, descriptive findings, and effect measures using standardized forms. A third reviewer resolved any discrepancies between reviewers.

Outcomes

We examined outcomes in three domains. Safety outcomes included primary or SAEs, adverse pregnancy outcomes, and other specific adverse events: Guillain-Barré syndrome (GBS), postural orthostatic tachycardia syndrome (POTS), chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME), paralysis, complex regional pain syndrome (CRPS), premature ovarian failure, and infertility.

Primary vaccine effectiveness outcomes were HPV-related cancers comprising cervical, anal, penal, oropharyngeal, vaginal, and vulval cancers; high-grade intraepithelial neoplasia (i.e.,

cervical [CIN], anal [AIN], penile [PeIN], vaginal [VaIN], and vulval [VIN]); and incident HPV infection and persistent (>6 and >12 months) HPV infection with HPV16 and HPV18.

Immunogenicity outcomes included seroconversion and antibody neutralization titers; these outcomes were not reported in the Cochrane studies (hence, the data are limited to Sept 2024-Jan 2026) but are aligned with those prioritized for review by the ACIP HPV vaccine working group in their most recent discussions (CDC 2025c).

Quality of evidence

Risk of bias

Risk-of-bias (RoB) assessments evaluate how a study's design, conduct, and reporting may affect whether its estimated effect reflects the true effect. The updated review assessed the RoB for each domain presented in a study. We used the Cochrane Risk of Bias tool for Randomized Trials Version 2 (RoB 2) for RCTs and the Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I) for observational studies. Two reviewers independently assessed RoB, with discrepancies resolved by a third reviewer. The prior Cochrane reviews also reported RoB assessments for each included study.

Certainty of evidence

The previous Cochrane reviews also used a systematic GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) framework to assess the certainty and quality of evidence. Assessment of RoB constitutes a key component of the GRADE evaluation framework, which also incorporates additional criteria. GRADE is categorized into four levels (high, moderate, low, and very low) to indicate the degree of confidence that the estimated effect approximates the true effect. The previous Cochrane reports presented a full GRADE assessment for quality of evidence; the updated search (Sept 2024-Jan 2026) did not use a GRADE assessment.

Evidence synthesis and meta analysis

For safety and vaccine efficacy/effectiveness outcomes, we present tabular and narrative summaries of the recent evidence together with conclusions and certainty ratings from Cochrane reviews. We summarize immunogenicity findings separately in tabular and narrative form, as the Cochrane reviews did not address this topic.

Where we identified three or more comparable studies (i.e., study design, outcome), we quantitatively synthesized data from both this updated review and the US-relevant vaccine products from the previous Cochrane review. To prevent duplication, we verified study location, time period, and population across both the updated and Cochrane studies; in the case of duplicates, we included the study with the longest follow-up and lowest RoB. For comparable studies, we first calculated risk ratios and Wald 95% confidence intervals (CIs) for newly extracted studies, following the approach used by the Cochrane review of RCTs. We then conducted random-effects meta-analyses (DerSimonian–Laird) to generate pooled risk ratios (95% CI), evaluated heterogeneity with the I^2 statistic (range, 0% to 100%, with higher values indicating greater heterogeneity), and plotted effect estimates for included studies. We

estimated relative vaccine effectiveness (rVE) comparing two doses to one dose for outcomes reported by more than three studies of the same type and dose comparison (Lewis 2022) (Supplemental Material 4).

Use of artificial intelligence
No artificial intelligence tools or support were used in any part of the literature search, review of studies, or data extraction.

Results
Description of studies
The updated review found 121 studies comprising 25 studies presenting safety outcomes, 80 studies reporting vaccine effectiveness outcomes, and 31 with immunogenicity outcomes (Figure 1). The studies included 14 RCTs, five non-randomized clinical trials, 49 cohort studies, 19 ecological studies, 18 cross-sectional studies, eight case series, five case-control studies, two self-controlled case series, and one mechanistic immunogenicity studies. We assessed the RoB for 136 outcomes. RCTs in general had lower RoB than the other study types; over half of all observational studies had severe-to-critical RoB, whereas four RCTs had high RoB.

Adding to these studies extracted from the Sept 2024-Jan 2026 search, we combined a subset of data from the Cochrane reviews, limited to US-based vaccines aligned with our outcomes of interest. This subset included 153 studies of US-relevant vaccine products, for a total of 274 studies.

Safety
Serious adverse events (SAEs)
SAEs related to HPV vaccination were evaluated in four RCTs, one trial with both randomized and non-randomized arms, four case series, one self-controlled case series, and one prospective cohort study (Kreimer 2025, Watson-Jones 2025, El Hindi 2025, Xie 2025, Konopnicki 2025, Hu 2025, Meng 2025a, Su 2025, Yang 2025, Faksova 2024 Raethke 2025) (Table 1).

Five studies found that SAEs were rare following HPV vaccination (Hu 2025, Meng 2025a, Raethke 2025, Su 2025, Yang 2025) (RoB critical). An analysis of US-based Vaccine Adverse Reporting System (VAERS) data found that reports of death were less common following 2vHPV, 4vHPV, and 9vHPV vaccination compared to other vaccines (Su 2025, VAERS 2025) (RoB critical).

A self-controlled case series, using data from the Danish Vaccination Registry to assess adverse outcomes following 9vHPV vaccination among 10- to 17-year-olds, found no increased risk for thromboembolism and thrombocytopenia, venous thromboembolism, or arterial thromboembolism in the 28 days after vaccination (Faksova 2024) (RoB low, except for concerns about uncontrolled confounding).

These SAE findings are consistent with the previous Cochrane review, which did not identify an elevated risk of SAEs following 2vHPV, 4vHPV, or 9vHPV vaccination (Bergman 2025).

An RCT did not identify any difference in the risk of SAEs after 4vHPV vaccination compared to vaccination with Cecolin (a bivalent HPV vaccine not approved in the US) (Xie 2025) (RoB high). No increased risk of SAEs was identified in an RCT that evaluated severe systemic adverse events when administering 9vHPV alone and coadministered with live-attenuated dengue vaccine (El Hindi 2025) (RoB some concerns).

SAEs: One doses vs. two doses
Two RCTs (RoB low and some concerns), found a similar prevalence of SAEs in groups receiving one dose of 2vHPV or 9vHPV compared to two doses (Kreimer 2025, Watson-Jones 2025). These findings are consistent with the previous Cochrane review, which similarly did not identify differences in the risk of SAEs among one- versus two-dose recipients (Bergman 2025).

SAEs: Three doses vs two doses
We identified a trial with both randomized and non-randomized arms comparing three doses of 9vHPV to two doses of 9vHPV (Konopnicki 2025) (RoB serious). The study did not identify SAEs in the two- or three-dose groups in either arm. These findings are consistent with the Cochrane reviews, which did not identify differences in the risk of SAEs among those receiving two doses of 9vHPV compared to three doses (Bergman 2025).

Adverse pregnancy outcomes
We identified two RCTs, four cohort studies, and one case series assessing adverse pregnancy outcomes (Kreimer 2025, Watson-Jones 2025, Cortés 2025, Guo 2025, Hardalo 2025, Meng 2025[b], Boudova 2025) (Table 2). A peri-conception study found no increased risk of birth defects following 4vHPV or 9vHPV vaccination, and other observational studies did not suggest increased risks of adverse pregnancy outcomes (Guo 2025) (RoB serious). Other observational studies lacked sufficient data for effect-measure calculations, but did not suggest an elevated risk of adverse pregnancy outcomes, including misscarriage, stillbirth, birth defects, preterm birth, and maternal death, associated with vaccination (Cortés 2025, Hardalo 2025, Meng 2025[b], Boudova 2025) (RoB serious to critical). These findings are consistent with the Cochrane reviews, which similarly did not suggest a risk of adverse pregnancy outcomes associated with HPV vaccination (Bergman 2025, Henschke 2025).

Adverse pregnancy outcome: Two vs. one dose
Two RCTs found similar prevalence of adverse pregnancy outcomes or congenital abnormalities in those who received one compared to two doses of 2vHPV or 9vHPV (Kreimer 2025, Watson-Jones 2025) (RoB low and some concerns).

Postural orthostatic tachycardia syndrome (POTS)
We identified one self-controlled case series, one ecological study, and one case series that evaluated POTS after HPV vaccination (Margelyte 2024, Liu 2025, Wastila 2025) (Table 3). A self-controlled case series of commercially insured US girls and women (RoB low, except for

concerns about uncontrolled confounding) examined all US-approved HPV vaccinations. The study identified an increased risk of autonomic dysfunction (an umbrella term that includes POTS) after adjusting for age (adjusted incidence rate ratio [aIRR]: 1.23; 95% CI: 1.08-1.41), although the elevated risk was observed among 565 18- to 26-year-olds (aIRR: 1.40; 95% CI: 1.12-1.75) and not among 1,089 9- to 17-year-olds (aIRR: 1.14; 95% CI: 0.97-1.35) (Wastila 2025). The ecological study compared POTS cases in 10,881 UK girls eligible for 4vHPV vaccination to 10,972 ineligible for 4vHPV vaccination and found fewer than five cases of POTS in both groups, too few to detect a meaningful difference (Margelyte 2024) (RoB moderate). A case series found that reports of POTS were uncommon, but more common following vaccination with 9vHPV than with other vaccines in the VAERS database, with an odds ratio of 10.39 (95% CI: 7.75 to 13.93) among SAE reports (Liu 2025, VAERS 2025) (RoB critical).

The two smaller studies suggesting an increased risk of HPV-vaccine associated POTS are inconsistent with the largest available study and with prior Cochrane reviews, which is based on four randomized trials and two observational studies and found, with moderate certainty, no increased risk of POTS following HPV vaccination (Bergman 2025, Henschke 2025).

Chronic fatigue syndrome/myalgic encephalomyelitis/post viral fatigue syndrome (CFS/ME/PVFS)

The Margelyte 2024 UK ecological study identified fewer than five cases of CFS/ME in both the vaccine-eligible and vaccine-ineligible groups (RoB moderate). These results are consistent with the Cochrane reviews, which found, with moderate certainty, no increase in CFS/ME following HPV vaccination (Henschke 2025).

Complex regional pain syndrome (CRPS)

The Margelyte 2024 UK ecological study also identified fewer than five cases of CRPS in both the vaccine-eligible and vaccine-ineligible groups (RoB moderate). These results are consistent with the Cochrane reviews, which found no increase in CRPS risk following HPV vaccination, based on evidence rated as offering moderate certainty (Bergman 2025, Henschke 2025).

Guillain-Barre syndrome (GBS)

We identified one self-controlled case series assessing associations between 9vHPV and GBS among 10- to 17-year-olds using Danish Vaccination Registry data that found fewer than three cases of GBS in boys during the 28-day post-vaccination risk period and no cases in girls (Faksova 2024) (RoB low except for concerns about uncontrolled confounding). These results are consistent with the Cochrane reviews' findings of no increased risk of GBS following vaccination, based on evidence with low certainty (Henschke 2025).

Paralysis, premature ovarian failure, and infertility

We did not identify any new observational studies or RCTs that assessed paralysis, premature ovarian failure, or infertility. The Cochrane reviews of these outcomes found, with moderate certainty, that HPV vaccination did not increase the risk of these outcomes (Bergman 2025, Henschke 2025).

Overall, these findings regarding HPV vaccine safety are broadly reassuring and, with the exception of POTS, are consistent with the prior Cochrane reviews findings. With respect to POTS, the size and quality of the Cochrane studies, together with methodologic limitations in the study reporting an increased risk (see Discussion), support the conclusion that the risk of POTS associated with HPV vaccination is low.

Vaccine Effectiveness

Cancer Outcomes

Invasive cervical cancer

We identified four observational studies of cervical cancer outcomes (Table 4, Supplemental Table 1). Of three cohort studies, two reported lower risk of cervical cancer among fully or partially vaccinated compared to unvaccinated females (Van Lonkhuijzen 2026, Middeldorp 2025), and one reported no cases in groups vaccinated before diagnosis (Grieco 2025). A pre-post vaccine introduction study among US females showed lower cervical cancer incidence when comparing age vaccine-eligible cohorts to non-vaccine-eligible reference groups (Semprini 2025). In each of the four studies (all with serious to critical RoB), the effect estimates consistently indicated a protective trend, aligned with conclusions from the Cochrane review that HPV vaccination probably reduces the incidence of cervical cancer (moderate certainty) (Henschke 2025).

We conducted a meta-analysis of six cohort studies reporting cervical cancer outcomes, incorporating newly identified studies from our updated search alongside those included in the prior Cochrane review using US-approved HPV vaccine products. In follow-up periods exceeding five years after initial vaccination, vaccinated individuals showed a reduced risk of cervical cancer compared to unvaccinated individuals (relative risk [RR]: 0.34; 95% CI: 0.23–0.51) (Figure 2a). Greater protection was observed when vaccination was initiated at or before 16 years of age (RR: 0.20; 95% CI: 0.10–0.39) (Figure 2b).

Oropharyngeal cancer

We identified one cohort and one cross-sectional study of US females that demonstrated lower odds of oropharyngeal cancer among vaccinated compared to unvaccinated patients (Katz 2025), and a lower risk in vaccinated compared to unvaccinated females, with a greater risk reduction when vaccination was initiated at younger ages (Hung 2025) (RoB serious to critical) (Supplemental Table 2). The protective effect of HPV vaccination is consistent with the Cochrane review: that it may reduce oropharyngeal cancer incidence (low certainty) (Henschke 2025).

Vulval, vaginal, anal, or penile cancer

We did not identify any new studies that assessed the risk of vulval, vaginal, anal, or penile cancer by HPV vaccination status. The Cochrane review (Henschke 2025) noted that HPV vaccination may reduce vaginal and penile cancer incidence (low certainty), and that the effect of HPV vaccine on vulval and anal cancer incidence is unknown (very low certainty).

Cervical intraepithelial neoplasia grade 3+ (CIN3+)

We identified six cohort studies (Haas 2025, Lehtinen 2024, Palmer 2026, Eriksen 2026, Middeldorp 2025, Kjaer 2024), one case control study (Ikeda 2025), and one pre-post vaccine introduction study (Sorbye 2025) that reported outcomes of CIN3+ (RoB low, except for concerns about uncontrolled confounding, to critical) (Supplemental Table 3). The effect estimates consistently indicated a protective trend for CIN3+, aligned with conclusions from the Cochrane review that HPV vaccination probably reduces the risk of CIN3+ (moderate certainty) (Bergman 2025, Henschke 2025).

We conducted meta-analyses of studies reporting CIN3+ outcomes, combining studies identified in our search with those included in the prior Cochrane review—limited to US-available vaccines—and identified a protective effect of HPV vaccination for CIN3+ in both analyses. A pooled analysis of studies with follow-up periods exceeding five years after initial vaccination showed a reduced risk of CIN3+ among vaccinated compared with unvaccinated individuals (RR: 0.37; 95% CI: 0.30–0.46) (Figure 3a). Greater protection was observed when vaccination was initiated at or before 16 years of age (RR: 0.27; 95% CI: 0.18–0.42) (Figure 3b).

CIN3+: One doses vs. two or three doses

We conducted meta-analyses of cohort studies reporting CIN3+ outcomes in individuals who received one, two, or three doses of HPV vaccine, combining studies identified in our search with those included in the prior Cochrane review. Comparing meta-analytic estimates in relative vaccine effectiveness calculations suggests that two doses may prevent 4.7% of the residual disease that was not prevented by one dose, though 95% CIs overlap for the adjusted vaccine effectiveness meta-analytic estimates (Table 5).

Cervical intraepithelial neoplasia grade 2+ (CIN2+)

We identified two RCTs (Wen 2024, Wen 2025) (RoB low), two cohort studies that assessed outcomes of CIN2+ (Palmer 2026, Wu 2025a), and two cohort studies that assessed CIN2+ recurrence (Song 2025, Petras 2025) (RoB low, except for concerns about uncontrolled confounding, to serious) (Supplemental Table 4). The effect estimates consistently indicated a protective trend for CIN2+, aligned with conclusions from the Cochrane review that HPV vaccination probably reduces the risk of CIN2+ (moderate certainty) (Bergman 2025, Henschke 2025).

We conducted meta-analyses of studies reporting CIN2+ outcomes, combining studies identified in our search with those included in the prior Cochrane review—limited to US-available vaccines—and identified a protective effect of HPV vaccination for CIN2+ in six of seven analyses. A meta-analysis of six RCTs demonstrated a reduction in CIN2+ from vaccine-matched HPV types for females vaccinated at ages 15-25 years (RR: 0.39; 95% CI: 0.29-0.53) (Figure 4a). An analysis of five RCTs demonstrated a reduction in CIN2+ associated with HPV 16/18 comparing 2vHPV to control for females vaccinated at ages 15-25 years (RR: 0.27; 95% CI: 0.15-0.49) (Figure 4b). We found no difference in CIN2+ irrespective of HPV type in females vaccinated at 25 years or older (RR: 1.03; 95% CI: 0.83-1.28) (Figure 4c).

Meta-analysis of cohort studies demonstrate a reduced risk of CIN2+ in vaccinated individuals in both medium (<5 years) and long-term (≥5 years) follow-up periods (RR: 0.66; 95% CI: 0.49-0.88; RR: 0.54: 95% CI 0.46-0.63, respectively) (Figure 5a, 5b). The effect estimate was stronger when individuals were vaccinated at 16 years or younger (Figure 5c, 5d).

CIN2+: One dose vs. two or three doses

We conducted meta-analyses of cohort studies reporting CIN3+ outcomes in individuals who received one, two, or three doses of HPV vaccine, combining studies identified in our search with those included in the prior Cochrane review, limited to US-available vaccines. Comparing meta-analytic estimates in relative vaccine effectiveness calculations suggests that two doses may prevent 7.3% of the residual disease that was not prevented by one dose, though 95% CIs overlap for the adjusted vaccine effectiveness meta-analytic estimates (Figure 6c, 6d)(Table 5).

High-grade vulval or vaginal intraepithelial neoplasia (VIN, VaIN)

One cohort study found a lower incidence of high-grade vulvovaginal lesions among vaccinated compared to unvaccinated females in Sweden among those vaccinated at 10 to 16 years of age; there was no difference in the subset of those vaccinated at age 17 or older (Deng 2025) (RoB moderate) (Supplemental Table 5). This study is aligned with the Cochrane review's conclusion that HPV vaccination may reduce the incidence of high-grade VIN or VaIN from vaccine-matched HPV types (moderate certainty) (Bergman 2025), and based on observational studies, low-to-very-low certainty evidence that HPV vaccination may reduce high-grade VaIN incidence (Henschke 2025).

High-grade anal intraepithelial neoplasia (AIN)

We identified two cohort studies evaluating anal dysplasia among males and females with HIV (Sambo 2025, Mazzitelli 2025) (RoB critical) (Supplemental Table 6). Both studies reported a trend toward a protective effect against AIN, though both cohorts had a high prevalence of HPV infection at baseline. The Cochrane review identified low-certainty evidence based on two observational studies that HPV vaccination may reduce high-grade AIN incidence (Henschke 2025).

HPV 16/18 infection

We identified one RCT (Kreimer 2025) that found vaccine effectiveness for one or two doses of 9vHPV and 2vHPV greater than 97% against HPV 16 and HPV 18 (RoB low) (Supplemental Table 7). We identified one non-randomized clinical trial demonstrating a decrease in the number of participants anally infected with HPV16/18 following vaccination (Ron 2025) (RoB critical). Three cohort studies found zero or one case of incident HPV 16/18 in vaccinated groups (Kassam 2025, Lin 2026, Santos 2025). (RoB low, except for concerns about uncontrolled confounding, to critical). We also identified 14 observational studies that reported on prevalent HPV 16/18 infection comparing vaccinated to unvaccinated groups (RoB low, except for concerns about uncontrolled confounding, to critical). The effect estimates consistently indicated a protective trend for incident and persistent infection with HPV 16/18, aligned with conclusions from the Cochrane review that HPV vaccination probably reduces the risk of incident and persistent infection with HPV 16/18 (Bergman 2025, Henschke 2025).

We conducted meta-analyses of studies reporting HPV 16/18 persistent infection, combining studies identified in our search with those included in the prior Cochrane review, and identified a protective effect of HPV vaccination for HPV 16/18 persistent infection in both analyses. Meta-analysis of seven RCTs demonstrate an 84% reduction in HPV 16/18 persistent infection at six months among females 15 to 25 years at vaccination (RR 0.14, 95% CI 0.06-0.34) (Figure 6a). Meta-analysis of five RCTs demonstrate a 90% reduction at 12 months among females 15 to 25 years at vaccination (RR: 0.10; 95% CI: 0.03-0.32) (Figure 6b).

HPV 16/18 infection, one vs. multiple doses

One RCT reported no differences in rates of incident or persistent HPV16/18 infection in females between one- and two-dose schedules of 2vHPV and 9vHPV at five years of follow-up (Kreimer 2025) (RoB low). One cohort study identified no difference in vaccine effectiveness comparing one versus two or one versus three doses (Malvi 2024) (RoB moderate).

Immunogenicity

We identified 27 studies that presented immunogenicity outcomes following HPV vaccination (RoB low to critical) (Supplemental Table 8). Booster and recall studies supported durable immune memory up to 16 years after vaccination (Carter 2025, Guzun 2025, Moreira Dos Santos 2024, Sauvageau 2025, Day 2025, Porras 2024). Evidence for direct age comparisons was limited, but available studies suggest that vaccination earlier in adolescence elicited stronger and sometimes longer-lasting immune responses. Overall, immunogenicity was robust across age-groups, with greater magnitude and persistence in those vaccinated at younger ages (Steinberg 2025, Wen 2024, Cortes 2025).

Vaccine schedule and dosing

Among studies we identified, HPV vaccination produces robust antibody responses, with a consistent dose-response pattern, with two or three doses generating higher antibody concentrations than a single dose, despite one-dose schedules often inducing significant and sometimes durable responses (Giuliano 2025, Jiamsiri 2024, Kemp 2025, Porras 2024, Quang 2025, Watson-Jones 2025, Wiggins 2025). Antibody levels generally peak soon after series completion and then wane over time but remain above baseline or above post-dose-one levels during follow-up, supporting persistence (Kemp 2025, Porras 2024, Steinberg 2025, Watson-Jones 2025, Zhong 2025). Similar durability was seen after 4vHPV and 9vHPV schedules, including persistent long-term responses after one to three doses and higher sustained responses after delayed boosting when it was assessed (Quang 2025, Ron 2025, Sauvageau 2025).

In three studies, 2vHPV produced slightly stronger HPV16/18 responses than 4vHPV or 9vHPV comparators, particularly at later time points, although early responses were typically similar across products (Cortes 2025, Lehtinen 2024, Zha 2024) (RoB critical). Noninferiority results were mixed: two-dose 9vHPV was noninferior to three doses in women with HIV (Konopnicki 2025), whereas single-dose 2vHPV versus three-dose 4vHPV did not achieve overall noninferiority, as HPV16 criteria were not met, despite favorable HPV18 findings (Cortes 2025). Likewise, at 60 months, one-dose 2vHPV remained noninferior to two doses for HPV16

seropositivity but not for HPV18 seropositivity (Watson-Jones 2025). Regardless, seropositivity remained high across most regimens, including near-universal seropositivity after three-dose 9vHPV, persistent HPV16/18 seropositivity after one or three doses of 2vHPV, and durable detectable antibodies after two-dose or two-plus-one-dose 4vHPV schedules (El Hindi 2025, Guzun 2025, Kemp 2025, Porras 2024, Sauvageau 2025, Steinberg 2025, Wen 2024, Zhong 2025).

Discussion

Among the studies that evaluated HPV vaccine efficacy and effectiveness across multiple outcomes, our findings aligned well with the most recent Cochrane reviews when limited to US-approved HPV vaccines. While our review identified a host of new studies of variable quality, detailed examination of the updated evidence did not change the general perspective of the Cochrane review in either the safety or efficacy of HPV vaccines (Henschke 2025, Bergman 2025).

We assessed whether any new safety signals following HPV vaccination have emerged that merit further investigation. Across the 25 studies in our updated review on vaccine safety, we found no association between HPV vaccination and SAEs, adverse pregnancy outcomes, or other outcomes of interest (e.g., GBS, CFS/ME, CRPS). This conclusion is consistent with those of the recent Cochrane reviews.

The only outcome in which our findings diverged with the Cochrane reviews was in the assessment of POTS. While Cochrane did not identify a risk of POTS associated with HPV vaccination across seven randomized and observational studies, two of the three recently published studies reported a positive association. Of note, the Cochrane review did not include observational case series (e.g., data from VAERS) because these reports did not meet their inclusion criteria requiring comparative study designs (Henschke 2025). We identified one case series using unverified patient- and provider–reported VAERS data, that compared the reporting odds of POTS after HPV vaccination with those for other vaccines (e.g., the measles, mumps, and rubella vaccine). The vaccinations used in the control group included many of which are given at much younger ages (e.g., infancy), when POTS is exceptionally rare; this type of comparison therefore introduces substantial confounding. Indeed, given that POTS affects about 0.2% of the population, typically begins in adolescence or early adulthood, and is generally unrecognized among infants, any comparison that does not limit analysis to adolescence or later—for example, comparing 12-year-olds with 6-month-old infants—will likely capture age-related differences rather than a true vaccine effect (Sheldon 2015, Shaw 2019, ACOG 2020). The preponderance of evidence, including high-quality data from randomized trials, continues to indicate no association between HPV vaccination and POTS.

We also evaluated whether safety outcomes varied by dosing regimen. We found no differences in safety outcomes between one- and two-dose schedules or between two- and three-dose schedules.

We assessed the evidence of HPV vaccine effectiveness against cancer, pre-cancer, and infection outcomes. The previous Cochrane reviews concluded that HPV vaccination likely reduces cervical cancer incidence by about 80% in individuals vaccinated at or before age 16 years, with smaller reductions seen in those vaccinated at older ages (Henschke 2025). Our updated search similarly found consistent protective effects of HPV vaccination against cervical cancer and high-grade cervical intraepithelial neoplasia, particularly when vaccination occurred prior to HPV exposure, and our updated meta-analysis suggests this estimate remained stable after inclusion of updated studies. Protective effects were also consistently observed for VIN, VaIN, AIN, and both incident and persistent HPV-16/18 infections.

We also reviewed the evidence on effectiveness, focusing on whether a single-dose regimen is comparable to the standard two-dose schedule. Our meta-analysis of cohort studies found that incidences of CIN2+ and CIN3+ are comparable among those who received one-, two-, or three-doses of HPV vaccine. We also identified two studies that found no differences between one- and two-dose schedules on HPV16/18 infection in females up to five years following vaccination (Kreimer 2025, Malvi 2024). We also identified multiple immunogenicity studies that suggest a single dose of HPV vaccine produces noninferior antibody responses for HPV18 compared with two- or three-dose regimens, but that one-, two-, and three-dose HPV vaccination schedules all produce similarly high seropositivity rates for HPV16 and HPV18.

Current evidence on HPV vaccine effectiveness, particularly in relation to single- versus two-dose regimens, remains limited by important gaps. No studies have directly evaluated protection from one versus two doses at non-cervical sites, and no efficacy data are available comparing dosing schedules in males. We did not identify any studies that assessed HPV infection or cancer outcomes among males following one compared to two doses of HPV vaccine. One additional study, published outside our search window, found a protective effect of HPV vaccine against head and neck, esophageal, anal, and penile cancers in adolescent and young adult males (Kitano 2026).

Our narrative review and meta-analyses reflect the evidence available in the peer-reviewed literature, which is of varying quality and scope. In particular, many of the included studies, especially those addressing safety, were assessed as having serious to critical RoB, which is common for observational studies and may limit the robustness of pooled estimates and overall inferences. In addition, heterogeneity in study designs, populations, follow-up durations, and outcome definitions may have introduced variability that could not be fully accounted for.

Overall, the available evidence supports a strong and favorable safety and effectiveness profile for the US-approved HPV vaccines, with findings broadly consistent with prior Cochrane reviews. The totality of evidence—including randomized trials and observational studies—continues to show no association between HPV vaccination and SAEs. Of note, the US maintains multiple vaccine safety systems that are designed to detect rare events, and there is no evidence connecting the HPV vaccine, which has been in use in the US for more than 20 years, to the SAEs discussed above.

Robust evidence on the protective efficacy of these vaccines on non-cervical end points and male populations remain limited, underscoring the need for further long-term and sex-specific effectiveness studies. Effectiveness data continue to reinforce substantial protection against cervical cancer, high-grade cervical lesions, and HPV infection, with increasing evidence suggesting that single-dose regimens may offer comparable protection to multidose schedules for key outcomes in females.

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Table 1: Serious adverse events among new studies. May be aggregated or disaggregated data of one or more of the following outcomes: death, myocardial infarction, stroke, paralysis, other serious adverse event leading to hospitalization or life-threatening injury.

Study	Outcome	Study type	Population	Sample size	Findings (effect measure estimate included only when reported)	Risk of Bias
Cervarix (2vHPV, GSK Bivalent)						
Meng 2025[a]	Serious adverse events (any)	Case-series (CNIIS)	Female, 9 to 45 years	86 reports of bivalent adsorbed vaccine-related AEFIs in the database (1149 total HPV vaccine-related reports among all types of HPV vaccines available in China)	1 (1.16%) report was categorized as severe	Critical (case series)
Su 2025	Serious adverse events	Case-series (VAERS)	Male and Female, age not specified	5,004 reports of Cervarix vaccine-related AEs in the database (76,575 total HPV vaccine-related reports)	Death: ROR 0.43 (95% CI: 0.31 - 0.60)	Critical (case series)
Raethke 2025	Serious adverse events	Prospective cohort	Male, Female, and Non-Binary, 10 years	3063 participants received at least 1 dose of HPV vaccine	0 (0.0%) cases of serious AEFI among the study population. No difference observed between one- versus two-dose treatment	Critical
Hu 2025	Serious adverse events	Case-series (CNAEFIS)	Female, age not specified	668,412 doses of Cervarix administered (9,471,948 total doses administered)	0 (0.0%) reports following Cervarix were categorized as serious	Critical (case series)

Study	Outcome	Study type	Population	Sample size	Findings (effect measure estimate included only when reported)	Risk of Bias
Cervarix, 1 vs 2 doses						
Kreimer 2025	Serious adverse events	RCT	Female, 12 to 16 years	4880 assigned to one dose and 4880 assigned to two doses	287 (5.9%) participants in the single-dose group and 297 (6.1%) participants in the two-dose group reported any SAE during a five-year follow up period	Low
Watson-Jones 2025	Multiple serious adverse events	RCT	Female, 9 to 14 years	155 assigned to one dose and 155 assigned to two doses	0 (0%) in either group experienced death, life-threatening conditions, or persistent disability 10 (6.5%) in the single-dose group and and 3 (1.9%) in the two-dose group experienced hospitalization	Some concerns
Gardasil (4vHPV, Merck quadrivalent)						
Meng 2025[a]	Serious adverse events	Case-series (national immunization information system)	Female, 9 to 45 years	217 reports of vaccine-related AEFIs in the database following Gardasil-4 (1149 total HPV vaccine-related reports)	7 (3.23%) reports were categorized as severe	Critical (case series)
Su 2025	Serious adverse events	Case-series (VAERS)	Males and Females, ≥0 years	47,539 reports of Gardasil-4 vaccine-related AEs in the database (76,575 total HPV vaccine-related reports)	Death: ROR 0.70 (95% CI: 0.63 - 0.77)	Critical (case series)

Study	Outcome	Study type	Population	Sample size	Findings (effect measure estimate included only when reported)	Risk of Bias
Hu 2025	Serious adverse events	Case-series (CNAEFIS)	Female, ≥0 years	2,621,369 doses of Gardasil-4 administered (9,471,948 total doses administered)	0 (0.0%) reports were categorized as serious	Critical (case series)
Gardasil vs Cecolin (bivalent HPV vaccine not approved in US)						
Xie 2025	Serious adverse events	RCT	Female, 9 to 14 years	99 assigned to the Gardasil group and 99 assigned to the Cecolin group	1 (1.0%) participant in the Gardasil group and 1 (1.0%) participant in the Cecolin group self-reported any SAE during the 30 day follow up period	High
Gardasil-9 (9vHPV, Merck nonvalent)						
Meng 2025[a]	Serious adverse events	Case-series (national immunization information system)	Female, 9 to 45 years	505 reports of vaccine-related AEFIs in the database following Gardasil-9 (1149 total HPV vaccine-related reports)	5 (0.99%) reports were categorized as severe	Critical (case series)
Su 2025	Serious adverse events	Case-series (VAERS)	Males and Females, ≥0 years	24,032 reports of Gardasil-9 vaccine-related AEs in the database (76,575 total HPV vaccine-related reports)	Death: ROR 0.23 (95% CI: 0.17 - 0.31) Occurrence of neurological or autoimmune outcomes did not surpass the threshold for safety signal detection	Critical (case series)

Study	Outcome	Study type	Population	Sample size	Findings (effect measure estimate included only when reported)	Risk of Bias
Hu 2025	Serious adverse events	Case-series (CNAEFIS)	Sex not reported, ≥0 years	3,425,708 doses of Gardasil-9 administered (9,471,948 total doses administered)	2 (0.0%) reports of SAEs following a Gardasil-9 dose IR: 0.06 per 100,000 doses	Critical (case series)
Faksova 2024	Serious adverse events	Self-controlled case series	Males and Females, 10 to 17 years	3,354 individuals who received at least 1 dose and experienced at least one outcome	Thromboembolism/ thrombocytopenia - Boys IRR: 2.29 (95% CI: 0.66 - 7.93) - Girls IRR: 1.48 (95% CI: 0.42 - 5.19) Venous thromboembolism - Boys IRR 1.15 (0.14 - 9.20) - Girls IRR: 1.92 (0.54 - 6.86) Arterial thromboembolism - Boys IRR 4.05 (0.66 - 24.89) - Girls: No cases identified in risk period	Low risk of bias except for concerns about uncontrolled confounding
Gardasil-9, 1 vs 2 doses						
Kreimer 2025	Serious adverse events	RCT	Female, 12 to 16 years	4851 assigned to one dose and 4851 assigned to two doses	284 (5.9%) of participants in the one-dose group and 259 (5.3%) of the two-dose group reported any SAE during the five-year follow up period	Low
Watson-Jones	Multiple serious	RCT	Female, 9 to 14	155 assigned to	Death:	Some concerns

Study	Outcome	Study type	Population	Sample size	Findings (effect measure estimate included only when reported)	Risk of Bias
2025	adverse events		years	one dose and 155 assigned to two doses	- One-dose group: 0/155 (0.0%) - Two-dose group: 1/155 (0.6%) Hospitalization: - One-dose group: 7/155 (4.5%) - Two-dose group: 8/155 (5.2%) Life-threatening condition: - One-dose group: 0/155 (0.0%) - Two-dose group: 0/155 (0.0%) Persistent disability: - One-dose group: 0/155 (0.0%) - Two-dose group: 0/155 (0.0%)	
Gardasil-9, 2 vs 3 doses						
Konopnicki 2025	Serious adverse events	Non-randomized trial	Female, 15 to 40 years, HIV+	135 women who received 3 doses and 106 women who received 2-doses	No cases of serious adverse events reported	Serious
Gardasil-9 vs Gardasil-9 coadministered with TAK-003 (live-attenuated Dengue fever vaccine)						
El Hindi 2025	Severe systemic adverse events (excluding fever)	RCT	Male and Female, 9 to 14 years	307 assigned to Gardasil-9 only, 307 assigned to coadministration group	1 (0.3%) participant in the Gardasil-9–only group and 0 participants in the coadministration group reported severe systemic adverse events	Some concerns
All HPV-Vaccines (Cervarix, Gardasil, and Gardasil-9; not disaggregated)						

Study	Outcome	Study type	Population	Sample size	Findings (effect measure estimate included only when reported)	Risk of Bias
Yang 2025	Serious adverse events	Case series (VAERS)	Males and Females, ≥0 years	60,840 reports of HPV-related AEs in the database	Hospitalization: 6,893 (11.3%)	Critical (case series)

Abbreviations: HPV: Human papillomavirus; AEFI: adverse event following immunization; VAERS: Vaccine Adverse Events Reporting System; CNIIS: Chinese National Immunization Information System; CNAEFIS: Chinese National Adverse Events Following Immunization Information System; IR: incidence rate; IRR: incidence rate ratio; ROR: reporting adds ratio; CI: confidence interval;

[a] Serious adverse events include death, life-threatening conditions, hospitalization or prolonged hospitalization, persistent or significant disability, congenital anomalies or birth defects (if vaccination occurred during pregnancy), and other events that may lead to such outcomes without medical intervention. Typically, these cases require hospital treatment, including serious illnesses requiring clinical care. Examples include anaphylactic shock, laryngeal edema, Henoch–Schönlein purpura (HSP), Guillain–Barré syndrome (GBS), encephalopathy, and meningitis that are suspected to be related to the vaccine.

[b] Serious adverse events were defined according to the U.S. Food and Drug Administration (FDA) MedWatch criteria, including death, life-threatening illness, initial or prolonged hospitalization, permanent disability, or congenital anomaly.

Table 2: Pregnancy-related adverse events among new observational studies. May be aggregated or disaggregated data of one or more of the following outcomes: prematurity (<37 weeks), miscarriage/spontaneous abortion, stillbirth, congenital anomalies, pre-eclampsia, or other defined pregnancy-related outcomes.

Study	Outcome	Study type	Population	Sample size	Findings (effect measure estimate included only when reported)	Risk of Bias
Cervarix (2vHPV, GSK Bivalent)						
Cortés 2025	Multiple	Prospective Cohort	Female, 9 to 14 years[a]	620 girls were enrolled in the single-dose bivalent vaccine group[b]	Congenital abnormalities[c]: 0 (0.0%) girls reported congenital abnormalities 6 months after vaccine dose Obstetrics[c]: 0 (0.0%) girls reported obstetrics-related adverse events 6 months after vaccine dose	Serious
Cervarix, 1 vs 2 doses						
Kreimer 2025	Multiple	RCT	Female, 12 to 16 years	4880 assigned to one dose and 4880 assigned to two doses[b]	SAE - obstetrics: - One-dose group: 161/4880 (3.3%) - Two-dose group: 171/4880 (3.5%) Serious congenital abnormality: - One-dose group: 6/4880 (0.1%) - Two-dose group: 6/4880 (0.1%) Non-serious AE - obstetrics: - One-dose group: 39/4880 (0.8%) - Two-dose group: 29/4880 (0.6%) Non-serious congenital abnormality: - One-dose group: 0/4880 (0.0%) - Two-dose group: 1/4880 (0.0%)	Low
Watson-Jones 2025	Congenital abnormality	RCT	Female, 9 to 14 years	155 assigned to one dose and 155	0 (0.0%) participants in the one-dose group and 1 (0.6%) participant in the	Some concerns

Study	Outcome	Study type	Population	Sample size	Findings (effect measure estimate included only when reported)	Risk of Bias
				assigned to two doses[b]	two-dose group reported any congenital abnormalities in the five-year follow up period	
Gardasil (4vHPV, Merck quadrivalent)						
Cortés 2025	Multiple	Prospective Cohort	Female, 18 to 25 years[a]	620 women were enrolled in the three-dose quadrivalent vaccine group[b]	Congenital abnormalities[c]: 0 (0.0%) women reported congenital abnormalities 6 months after first vaccine dose Obstetrics[c]: 7 (1.1%) women reported obstetrics-related adverse events 6 months after vaccine dose	Serious
Meng 2025[b]	Multiple	Retrospective Cohort	Female, 20 to 45 years	168 pregnant individuals with maternal 4vHPV vaccine exposure	Stillbirth: 0 (0.0%) cases of stillbirth Congenital anomalies[d]: 5 cases (3.0%) of congenital heart disease diagnosed up to 3 months after birth	Critical
Guo 2025	Total birth defects	Retrospective Cohort	Female, pregnant	171 pregnant individuals with peri-conception 4vHPV vaccine exposure	Total birth defects: aRR: 0.99 (95% CI: 0.34 to 2.94) - Digestive: aRR: 3.98 (0.25-63.26) - Circulatory: aRR: 0.72 (0.16-3.23)	Serious
Gardasil-9 (9vHPV, Merck nonavalent)						

Study	Outcome	Study type	Population	Sample size	Findings (effect measure estimate included only when reported)	Risk of Bias
Boudova 2025	Multiple	Case series (VAERS)	Female, pregnant	273 reports of 9vHPV during pregnancy	Miscarriage[e]: 4 (1.5%) reports Stillbirth[f]: 0 (0.0%) reports Congenital anomalies: 2 (0.7%) reports Maternal death: 0 (0.0%) reports	Critical (case series)
Hardalo 2025	Multiple	Prospective cohort (Pregnancy Registry)	Female, pregnant, 12 to 38 years	180 prospectively enrolled cases with known exposure to 9vHPV in the US, 70 had known outcomes	Miscarriage/spontaneous abortion[e]: 3/70 (4.3%) reports Pre-term birth[g]: 1/70 (1.4%) report Congenital anomalies: 3/70 (4.3%) reports	Critical
Guo 2025	Total birth defects	Retrospective Cohort	Female, pregnant	80 pregnant individuals with peri-conception 9vHPV vaccine exposure	Total birth defects: aRR: 0.98 (95% CI: 0.11 to 8.69) - Circulatory: aRR: 1.97 (95% CI: 0.18-21.44)	Serious
Gardasil-9 (1 vs 2 doses)						
Kreimer 2025	Multiple	RCT	Female, 12 to 16 years	4851 assigned to one dose and 4851	SAE - obstetrics: - One-dose group: 135/4851	Low

Study	Outcome	Study type	Population	Sample size	Findings (effect measure estimate included only when reported)	Risk of Bias
				assigned to two doses[b]	(2.8%) - Two-dose group: 120/4851 (2.5%) Serious congenital abnormality: - One-dose group: 5/4851 (0.1%) - Two-dose group: 4/4851 (0.1%) Non-serious AE - obstetrics: - One-dose group: 30/4851 (0.6%) - Two-dose group: 31/4851 (0.6%) Non-serious congenital abnormality: - One-dose group: 0/4851 (0.0%) - Two-dose group: 0/4851 (0.0%)	
Watson-Jones 2025	Congenital abnormality	RCT	Female, 9 to 14 years	155 assigned to one dose and 155 assigned to two doses[b]	0 (0.0%) participants in either group reported any congenital abnormalities during the five-year follow up period	Some concerns

Abbreviations: HPV: Human papillomavirus; HR: hazard ratio; aHR: adjusted hazard ratio; OR: odds ratio; aOR: adjusted odds ratio; RR: risk ratio; aRR: adjusted risk ratio; CI: confidence interval;

[a] The first study group (n=620) of girls aged 9-14 received one dose of 2vHPV vaccine, while the second study group (n=620) of women aged 18-25 received three doses of 4vHPV vaccine

[b] Authors do not report how many individuals in each group were pregnant during the study

[c] Authors do not provide a definition for the outcome

[d] Major congenital anomalies included anencephaly, spina bifida, encephalocele, congenital hydrocephalus, cleft palate, cleft lip, cleft palate with cleft lip, microtia/ anotia, other malformations of outer ear, esophageal atresia or stenosis, rectoanal atresia or stenosis, hypospadias, exstrophy of urinary bladder, talipes equinovarus, polydactyly, syndactyly, limb reductions, congenital diaphragmatic hernia, exomphalos, gastroschisis, conjoined twins, down syndrome, and congenital heart diseases.

[e] Defined as occurring before 20-week gestational age.

[f] Defined as occurring at 20-week gestational age or later.

[g] Defined as birth at <37 weeks gestation

Table 3: Other adverse events among new observational studies. May be aggregated or disaggregated data of one or more of the following outcomes: postural orthostatic tachycardia syndrome (POTS), chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME), complex regional pain syndrome (CRPS), premature ovarian failure, infertility, Guillain-Barre syndrome

Study	Outcome	Study type	Population	Sample size	Findings (effect measure estimate included only when reported)	Risk of Bias
Gardasil (Merck quadrivalent)						
Margelyte 2024	Multiple	Pre-/post-vaccination	Female, Birth cohorts (2000-2005)	10,881 adolescent girls eligible for HPV vaccination compared to 10,972 ineligible for HPV vaccination (21,853 total)	<5 cases of CRPS, CFS/PVFS, and POTS/OI were identified in both the group ineligible for HPV vaccination and the group eligible for HPV for vaccination.	Moderate
Gardasil-9 (Merck nonavalent)						
Faksova 2024	Guillain-Barre Syndrome	Self-controlled case series (Danish Vaccination Registry)	Male and Female, 10 to 17 years	350,687 individuals who received ≥1 dose	Males: <3 cases identified during the risk period following vaccination Females: 0 cases identified during the risk period following vaccination	Low except for concerns about uncontrolled confounding
Liu 2025	Postural orthostatic tachycardia syndrome (POTS)	Case series (VAERS)	Male and Female, US	23,499 total reports related to 9vHPV vaccination (2015-2024)	ROR: 10.39 (95% CI: 7.75 - 13.93) among SAE reports	Critical (case series)
All HPV-Vaccines (Cervarix, Gardasil-4, and Gardasil-9; not disaggregated or specified)						

Study	Outcome	Study type	Population	Sample size	Findings (effect measure estimate included only when reported)	Risk of Bias
Wastila 2025	Multiple	Self-controlled case series	Female, 9 to 26 years	1,654 individuals in the autonomic dysfunction cohort	Autonomic dysfunction: All ages: - IRR: 1.33 (95% CI: 1.19 - 1.49) - aIRR: 1.23 (95% CI: 1.08 to 1.41) 9- to 17-year-old age group: - IRR: 1.29 (95% CI: 1.12 - 1.49) - aIRR: 1.14 (95% CI: 0.97 - 1.35) 18- to 26-year-old age group: - IRR: 1.44 (95% CI: 1.18 - 1.74) - aIRR: 1.40 (95% CI: 1.12- 1.75)	Low except for concerns about uncontrolled confounding

Abbreviations: aIRR: Adjusted Incidence Rate Ratio; CFS/PVFS: Chronic Fatigue Syndrome/Post-Viral Fatigue Syndrome; CRPS: Complex Regional Pain Syndrome; HPV: Human Papillomavirus; IRR: Incidence Rate Ratio; POTS/OI: Postural Orthostatic Tachycardia Syndrome/Orthostatic Intolerance; ROR: Reporting odds ratio; SAE: Serious Adverse Event; VAERS: Vaccine Adverse Event Reporting System;

Table 4: Summary of vaccine effectiveness against outcomes of interest, updated analysis and previous Cochrane reviews. General population of any age in any setting. Participants with the intervention of full or partial HPV vaccination series were compared to participants who were unvaccinated.

Analysis	Number of studies	Summary of effect	Certainty of evidence	Interpretation of findings
Outcome: Invasive cervical cancer				
Updated search (Sept 2024 to 27 Jan 2026)	Three cohort studies One pre-post vaccine introduction study	Of the three cohort studies, two reported a lower risk of cervical cancer among HPV vaccinated individuals. One did not report any cases of cervical cancer in the HPV vaccine group. The pre-post vaccine introduction study reported a reduction in cervical cancer incidence between the pre- and post-introduction periods.	Two studies had serious risk of bias; two studies had critical risk of bias.	Despite the serious-to-critical risk of bias in the studies, effect estimates consistently indicated a protective trend; HPV vaccination probably reduces the incidence of cervical cancer.
Cochrane (Bergman 2025)	Two RCTs (17,662 females)	Both RCTs comparing Gardasil with control reported zero cases of invasive cervical cancer in either group at 48 months.	n/a	n/a
Cochrane (Henschke 2025)	Six cohort studies (4,419,387 females plus 27,946 cases of cervical cancer) One case-control study (12,296 females) Three RCT extension studies (47,456 females) One cross-sectional study (1,392 females)	Of the six cohort studies, five reported a reduced risk of cervical cancer following HPV vaccination (RR 0.37, 95% CI 0.25 to 0.56). One cohort study did not report any cases of cervical cancer in the vaccine group. The case-control study, cross-sectional study and the three RCT extension studies all reported no cases of cervical cancer in the HPV vaccine groups. All nine pre-post vaccine introduction studies reported a reduction in cervical cancer incidence between the pre- and post-introduction periods.	Moderate	HPV vaccination probably reduces the incidence of cervical cancer.

Analysis	Number of studies	Summary of effect	Certainty of evidence	Interpretation of findings
	Nine pre-post vaccine introduction studies (> 1,030,882 cases)			
Outcome: Oropharyngeal cancer				
Updated search (Sept 2024 to 27 Jan 2026)	One cohort study One cross-sectional study	The cohort study reported a lower risk of oropharyngeal cancer among vaccinated females compared to unvaccinated females, with a greater risk reduction observed when vaccination was initiated at younger ages. The cross-sectional study reported lower odds of oropharyngeal cancer in vaccinated compared to unvaccinated patients.	One study had serious risk of bias; one study had critical risk of bias.	Despite the serious-to-critical risk of bias in the studies, effect estimates consistently indicated a protective trend; HPV vaccination may reduce head and neck cancer incidence.
Cochrane (Henschke 2025)	One cohort study (1,305,954 males and females) One RCT extension study (189,901 person-years) Three pre-post vaccine introduction studies (284,372 males and females plus 234,931 cases of oropharyngeal cancer)	In females and males, one cohort study reported a decreased risk of head and neck cancer following HPV vaccination. The RCT extension study did not identify any cases of head and neck cancer in vaccinated participants. Two pre-post vaccine introduction studies reported a reduction in head and neck cancer incidence between the pre- and post-introduction periods. One pre-post vaccine introduction study reported inconsistent results, with some ethnic groups seeing an increased incidence and others a decrease.	Low	HPV vaccination may reduce head and neck cancer incidence.

Analysis	Number of studies	Summary of effect	Certainty of evidence	Interpretation of findings
Cochrane (Bergman 2025)	n/a	n/a	n/a	n/a
Outcome: Vulval or vaginal cancer				
Updated search (Sept 2024 to 27 Jan 2026)	n/a	n/a	n/a	n/a
Cochrane (Bergman 2025)	One RCT (5,455 females)	No cases of invasive vulval or vaginal cancer positive for vaccine-type HPV reported.	n/a	n/a
Cochrane (Henschke 2025)	One RCT extension study (189,901 person-years) Four pre-post vaccine introduction studies (> 36,563 cases of vulval cancer)	The RCT extension study reported no cases of vulval cancer in vaccinated participants. Two pre-post-vaccine introduction studies reported a decrease in vulval cancer incidence between the pre- and post-introduction periods, while one reported an increase. The other study reported inconsistent results, with some ethnic groups seeing an increased incidence and others a decrease.	Very low	We do not know about the effect of HPV vaccination on vulval cancer incidence because the certainty of the evidence is very low.
Cochrane (Henschke 2025)	Three pre-post vaccine introduction studies (> 881 cases of vaginal cancer)	Three pre-post vaccine introduction studies reported a reduction in vaginal cancer incidence between the pre- and post-introduction periods.	Low	HPV vaccination may reduce vaginal cancer incidence.
Outcome: Anal cancer				

Analysis	Number of studies	Summary of effect	Certainty of evidence	Interpretation of findings
Updated search (Sept 2024 to 27 Jan 2026)	n/a	n/a	n/a	n/a
Cochrane (Bergman 2025)	One RCT (551 participants)	No cases of invasive anal cancer reported.	n/a	n/a
Cochrane (Henschke 2025)	Three pre-post vaccine introduction studies (> 42,127 cases of anal cancer)	In females and males, two pre-post vaccine introduction studies reported a decrease in anal cancer incidence between the pre- and post-introduction periods and one study reported an increase.	Very low	We do not know about the effect of HPV vaccine on anal cancer incidence because the certainty of the evidence is very low.
Outcome: Penile cancer				
Updated search (Sept 2024 to 27 Jan 2026)	n/a	n/a	n/a	n/a
Cochrane (Bergman 2025)	One RCT (3,880 males)	No cases of invasive penile cancer reported.	n/a	n/a
Cochrane (Henschke 2025)	Two pre-post vaccine introduction studies (> 15,804 cases of penile cancer)	Two pre-post vaccine introduction studies reported a decrease in penile cancer incidence between the pre- and post-introduction periods.	Low	HPV vaccination may reduce penile cancer incidence.
Outcome: Cervical intraepithelial neoplasia grade 3 or higher (CIN3+)				
Updated search (Sept 2024 to 27 Jan 2026)	Six cohort studies One case-control study One pre-post vaccine introduction study	Among the six cohort studies, meta-analysis of those with follow-up greater than five years demonstrated a lower risk of CIN3+ in vaccinated compared to unvaccinated individuals (RR 0.37, 95% CI 0.30 to 0.46), with a greater reduction when vaccination was initiated at 16 years of age or younger.	One study had low risk of bias; one study had moderate risk of bias; three studies had serious risk of bias; three studies had critical risk of bias.	Despite the serious-to-critical risk of bias in the studies, effect estimates consistently indicated a protective trend; HPV vaccination probably reduces the incidence of CIN3+.

Analysis	Number of studies	Summary of effect	Certainty of evidence	Interpretation of findings
		The case-control study reported reduced odds of CIN3+ among vaccinated participants. The pre-post vaccine introduction study reported a decrease in CIN3+ incidence between the pre- and post-introduction periods.		
Cochrane (Bergman 2025)	Four RCTs (35,655 females)	Four RCTs reported a reduced risk of CIN3+ positive for vaccine-matched HPV types in vaccinated females compared to unvaccinated females, with approximately 8 fewer cases per 1,000 participants at 48 months follow-up (RR 0.54, 95% CI 0.44 to 0.65).	Moderate	HPV vaccination probably reduces the incidence of CIN3+ from vaccine-matched HPV types.

Analysis	Number of studies	Summary of effect	Certainty of evidence	Interpretation of findings
Cochrane (Henschke 2025)	Twelve cohort studies (3,105,713 females) Three case-control studies (26,595 females) One RCT extension study (3,148 females) Five cross-sectional studies (219,953 females) Three pre-post vaccine introduction studies (116,139 females)	Of the 12 cohort studies, one did not report any cases of CIN3+. One study reported a reduction in the medium term (RR 0.43, 95% CI 0.35 to 0.53) and seven studies showed a reduction in the long term (RR 0.39, 95% CI 0.32 to 0.48). Three case-control studies reported a reduced risk of CIN3+ in vaccinated participants. The RCT extension study reported a decrease in CIN3+ incidence in vaccinated participants. Four cross-sectional studies reported a decreased risk of CIN3+ participants. One cross-sectional study reported no difference in risk of CIN3+ in vaccinated participants. Three pre-post vaccine introduction studies reported a decrease in CIN3+ incidence between the pre- and post-introduction periods.	Moderate	HPV vaccination probably reduces the incidence of CIN3+.
Outcome: Cervical intraepithelial neoplasia grade 2 or higher (CIN2+)				

Analysis	Number of studies	Summary of effect	Certainty of evidence	Interpretation of findings
Updated search (Sept 2024 to 27 Jan 2026)	One RCT Four cohort studies	One RCT reported high VE against CIN2+ associated with HPV16/18. VE against CIN2+ associated with other HPV subtypes analyzed in the study was not statistically significant. Among the four cohort studies, all reported a reduced risk of CIN2+ in vaccinated individuals compared to unvaccinated. The effect estimate was stronger when individuals were vaccinated at ≤16 years.	Two studies had low risk of bias; two studies had moderate risk of bias; one study had serious risk of bias.	Despite the moderate-to-critical risk of bias in the studies, effect estimates consistently indicated a protective trend; HPV vaccination probably reduces the incidence of CIN2+.
Cochrane (Bergman 2025)	Ten RCTs (59,717 females)	Ten RCTs reported a reduced risk of CIN2+ positive for vaccine-matched HPV types in vaccinated females compared to unvaccinated females, with approximately 13 fewer cases per 1,000 participants at 72 months follow-up (RR 0.50, 95% CI 0.39 to 0.65).	Moderate	HPV vaccination probably reduces the incidence of CIN2+ from vaccine-matched HPV types.
Cochrane (Henschke 2025)	Fourteen cohort studies (7,059,815 females) Three case-control studies (142,073 females) Two RCT extensions (11,675 females) Eleven cross-sectional studies (205,994 females) Seven pre-post vaccine introduction studies (4,914,524 females)	Twelve cohort studies reported a reduced risk of CIN2+ following HPV vaccination (RR 0.51, 95% CI 0.37 to 0.69) and one reported no difference in risk of CIN2+ between vaccinated and unvaccinated participants. One cohort study did not report any cases of CIN2+ in the HPV vaccine group. Three case-control studies all reported reduced odds of CIN2+ in vaccinated participants. One RCT extension study reported no cases of CIN2+ in the vaccinated participants and the other reported a decrease in CIN2+ with HPV vaccine.	Moderate	HPV vaccination probably reduces the incidence of CIN2+.

Analysis	Number of studies	Summary of effect	Certainty of evidence	Interpretation of findings
		Three cross-sectional studies reported a reduced risk of CIN2+ in vaccinated participants (RR 0.47, 95% CI 0.34 to 0.64). Five cross-sectional studies reported no difference in risk between vaccinated and unvaccinated participants. Three cross-sectional studies reported no cases of CIN2+ in the vaccinated participants. Six pre-post vaccine introduction studies reported a reduction in CIN2+ incidence between the pre- and post-introduction periods and one study reported an increased incidence.		
Outcome: High-grade VIN or VaIN				
Updated search (Sept 2024 to 27 Jan 2026)	One cohort study	One cohort study reported significantly lower incidence of high-grade vulvovaginal lesions in vaccinated females compared to unvaccinated females overall (aIRR 0.63, 95% CI 0.50 to 0.81) and among those vaccinated at 10 to 16 years of age (aIRR 0.45, 95% CI 0.32 to 0.65). There was no statistically significant difference in incidence among the subset of those vaccinated at age 17 or older (aIRR 0.80, 95% CI 0.61 to 1.06).	Moderate risk of bias.	Effect estimate indicates a protective trend; HPV vaccination may reduce the incidence of high-grade VIN and VaIN.
Cochrane (Bergman 2025)	Five RCTs (36,873 females)	Five RCTs reported a lower risk of high-grade VIN or VaIN positive for vaccine-matched HPV types in vaccinated females compared to unvaccinated females, with approximately 2 fewer cases per 1,000 participants at 48 months follow-up (RR 0.35, 95% CI 0.10 to 1.24).	Moderate	HPV vaccination may reduce the incidence of high-grade VIN or VaIN from vaccine-matched HPV types, but the result was not statistically significant.

Analysis	Number of studies	Summary of effect	Certainty of evidence	Interpretation of findings
Cochrane (Henschke 2025)	One pre-post vaccine introduction study (945 cases of VaIN)	One pre-post vaccine introduction study reported a reduction in VaIN incidence between the pre- and post-introduction periods.	Low	HPV vaccination may reduce the incidence of VaIN.
Cochrane (Henschke 2025)	Two pre-post vaccine introduction studies (6,128 cases of VIN)	One pre-post vaccine introduction study reported a reduction in VIN incidence between the pre- and post-introduction periods and the other reported an increase in VIN incidence.	Very low	We do not know about the effect of HPV vaccine on VIN incidence because the certainty of the evidence is very low.
Outcome: High-grade AIN				
Cochrane (Henschke 2025)	One cohort study (30 cases of AIN) One pre-post vaccine introduction study (2616 cases of AIN)	One cohort study reported a reduced risk of AIN following HPV vaccination. One pre-post vaccine introduction study reported an increase in AIN incidence in males and females between the pre- and post-introduction periods.	Low	HPV vaccination may reduce the incidence of AIN.
Updated search (Sept 2024 to 27 Jan 2026)	Two cohort studies	Among the two cohort studies of people living with HIV, one reported that HPV vaccination significantly reduced the risk of anal HSIL. The other found no significant difference in incident anal HSIL lesions between vaccinated and unvaccinated participants during follow-up.	Both studies had critical risk of bias.	Evidence from the updated search is limited to two small studies among people living with HIV, both at critical risk of bias, with inconsistent findings.
Outcome: Incident HPV16 and/or 18 infection				
Updated search (Sept 2024 to 27 Jan 2026)	One RCT One non-RCT Three cohort studies	One RCT demonstrated vaccine effectiveness for full and partial vaccination with Gardasil 9 and Cervarix >97% for HPV 16/18. No significant rate differences for incident or persistent HPV16/18 infection when comparing 1 vs 2 doses. One non-randomized clinical trial presented single arm data demonstrating a decrease in	One study with low risk of bias; two studies with moderate risk of bias; two studies with critical risk of bias.	Despite the serious-to-critical risk of bias in the studies, effect estimates consistently indicated a protective trend; HPV vaccination likely reduces the risk of incident infection with HPV16 and/or HPV18

Analysis	Number of studies	Summary of effect	Certainty of evidence	Interpretation of findings
		the number of participants anally infected with HPV16 or HPV18 following vaccination. Two cohort studies of HIV+ males found 0 cases of HPV16 in vaccinated groups; one study found 0 cases of HPV 18 in vaccinated groups; one study found HPV18 aHR 0.34 (0 to 1.38). One cohort study of females reported no incident cases of HPV 16/18 in the vaccinated group.		
Cochrane (Bergman 2025)	Six RCTs	Six RCTs including female participants 15-25 years old reported risk estimates for incident infection in vaccinated and unvaccinated groups. These data were meta-analyzed for a total effect estimate of 0.26 (0.22 to 0.31).	Certainty of evidence not evaluated for this outcome	HPV vaccine likely reduces the risk of incident infection with HPV16 and/or HPV18
Cochrane (Henschke 2025)	Two cohort studies Two RCT extension studies	In two cohort studies, vaccine effectiveness against incident HPV 16/18 infection ranged from 78.9 to 84%. Two RCT extension studies reported vaccine effectiveness for 1, 2, and 3 doses vs unvaccinated. Effectiveness estimates for 3 doses ranged from 66.4 to 84.9%. Vaccine effectiveness for partial schedules (i.e. one or two doses) ranged from 58.4% to 67.7% for two doses and 53.9% to 63.5% for one dose.	Certainty of evidence not evaluated for this outcome	HPV vaccine likely reduces the risk of incident infection with HPV16 and/or HPV18

Analysis	Number of studies	Summary of effect	Certainty of evidence	Interpretation of findings
Outcome: Persistent HPV16 and/or 18 infection				
Updated search (Sept 2024 to 27 Jan 2026)	One cohort study	In one cohort study, vaccine effectiveness of 1 to 3 doses (versus unvaccinated) ranged from 97.2 to 100% against persistent HPV16 and 80.8 to 85.0% against persistent HPV18 infection. There was no significant difference in VE comparing 1 vs 2 or 1 vs 3 doses.	Moderate risk of bias	HPV vaccine is likely very effective against persistent HPV16 infection, and moderately effective against persistent HPV18 infection. VE in the multidose vaccine series is comparable to a single dose.
Cochrane (Bergman 2025)	Six RCTs	*6-month persistence:* Six studies of female participants aged 15–25 years comparing Cervarix with control reported risk estimates for 6-month persistent HPV16/18 infection (meta-analysis: 0.13 [0.05 to 0.37]). One study among female participants aged >25 years reported a risk estimate of 0.41 (0.32 to 0.53). One study comparing Gardasil-9 with Cervarix reported no clear difference in 6-month persistent HPV16/18 infection (1.12 [0.71 to 1.76]).	Certainty of evidence not evaluated for this outcome	HPV vaccine reduces the risk of persistent (6- and 12-month) HPV16/18 infection among females. There is likely little difference in risk of outcome between Gardasil 9 and Cervarix.
		12-month persistence: Five studies of female participants aged 15–25 years comparing Cervarix with control reported risk estimates for 12-month persistent HPV16/18 infection (meta-analysis: 0.09 [0.02 to 0.38]). One study among female participants aged >25 years reported a risk estimate of 0.42 (0.30 to 0.58).		
Cochrane (Henschke 2025)	Two cohort studies (1,827)	In one cohort study, vaccine effectiveness was 97.7% (95% CI 83.5% to 99.7%), and in the	One study with moderate risk of bias;	HPV vaccine is effective at reducing the risk of persistent HPV16 and/or HPV18 infection.

Analysis	Number of studies	Summary of effect	Certainty of evidence	Interpretation of findings
	One RCT extension study	other the prevalence ratio was 1.37 (95% CI 1.08 to 1.74). Vaccine effectiveness was 93.3% (95% CI 77.5% to 99.7%) in the RCT extension study. The effectiveness of two doses (93.1%, 95% CI 77.3% to 99.8%) and one dose (95.4%, 95% CI 85.0% to 99.9%) were also reported by the RCT extension study.	two studies with critical risk of bias.	
Outcome: HPV16 and/or 18 infection (prevalence)				
Updated search (Sept 2024 to 27 Jan 2026)	Fourteen studies were included that reported on prevalent HPV16/18 infection following HPV vaccination: Three cohort studies One case-control study Nine cross-sectional studies One pre/post vaccination study	Two cohort studies observed fewer cases of HPV16 and HPV18 among vaccinated versus unvaccinated females. One cohort study reported prevalence ratios ranging from 0.2 to 0.3 for anal and cervical HPV16. One case-control study reported single arm data on vaccinated females; 1 of 403 participants had HPV16 infection. All nine cross-sectional studies reported lower prevalence of HPV16 and HPV18 among vaccinated versus unvaccinated individuals, with VE estimates consistently favoring vaccination and several estimates indicating complete or near-complete protection. HPV 16/18 combined adjusted effect estimates ranged from 0.06–0.55; HPV16 adjusted effect estimates ranged from 0.18–0.52, including several studies reporting no infections among vaccinated participants. HPV18 estimates ranged from 0.2–0.8, with multiple studies	Two studies with moderate risk of bias, five studies with serious risk of bias, seven studies with critical risk of bias.	Despite serious-to-critical risk of bias, HPV vaccination is consistently associated with substantially lower prevalence of HPV16 and HPV18 in vaccinated versus unvaccinated populations.

Analysis	Number of studies	Summary of effect	Certainty of evidence	Interpretation of findings
		reporting no infections among vaccinated participants. One pre/post study reported on the population-level prevalence reduction among females vaccinated before age 30. All age groups eligible for vaccination reported substantial reductions in prevalence of HPV 16/18 once the vaccine was approved in the US, with higher reductions among those vaccinated before age 20.		
Cochrane (Henschke 2025)	Forty-seven studies were included that reported on prevalent HPV 16/18 infection following HPV vaccination. Forty-two cross-sectional studies. One RCT extension study. Four pre-post vaccine introduction studies.	The type of effect estimate reported varied across studies, but almost all studies reported a reduction in HPV genital 16/18 infection with HPV vaccine. Three studies reported on oral HPV 16/18 infection. All three studies reported a reduction in prevalence following HPV vaccination but had confidence intervals that included no effect. One study reported a reduction of anal HPV 16/18 infection with a vaccine effectiveness of 89.9% (63.0% to 97.2%). Four studies reported on the effect of two doses or one dose of HPV vaccine on HPV 16/18 infection. The studies reported a reduction in HPV 16/18 infection following vaccination with two doses or one dose.	One study with moderate risk of bias; 29 studies with serious risk of bias; 17 studies with critical risk of bias.	
Cochrane (Bergman 2025)	n/a	n/a	n/a	n/a

Abbreviations: 95% CI: 95% Confidence Interval; AIN: Anal Intraepithelial Neoplasia; aHR: Adjusted Hazard Ratio; aIRR: Adjusted Incidence Rate Ratio; CIN: Cervical Intraepithelial Neoplasia; HPV: Human Papillomavirus; RCT: Randomized Controlled Trial; RR: Risk Ratio; VaIN: Vaginal Intraepithelial Neoplasia; VE: Vaccine Effectiveness; VIN: Vulvar Intraepithelial Neoplasia

[a]Certainty of evidence for the updated search is based on a risk of bias (RoB) assessment. Certainty of evidence for the two Cochrane reviews was conducted using the GRADE framework.

Table 5. Relative vaccine effectiveness (rVE) based on meta-analytic estimates, by outcome.

	Two-dose vaccine estimates		**One-dose vaccine estimates**		**rVE (exact calculation)[a]**
Outcome	**Meta-analytic RR**	**VE estimate**	**Meta-analytic RR**	**VE estimate**	
CIN2+	0.82 (0.57, 1.17)	18.3 (-16.7, 42.8)	0.88 (0.61, 1.27)	11.9 (-27.1, 38.9)	7.29
CIN3+	0.65 (0.53, 0.79)	35.1 (21.2, 46.5)	0.68 (0.55, 0.84)	31.9 (15.6, 45.0)	4.72

Abbreviations: CIN: Cervical Intraepithelial Neoplasia; RR: Relative Risk; VE: Vaccine effectiveness; rVE: relative vaccine effectiveness.

[a] rVE calculated as described in Supplemental Material 3.

Figure 1. PRISMA diagram, 2024-2026 updated analysis.

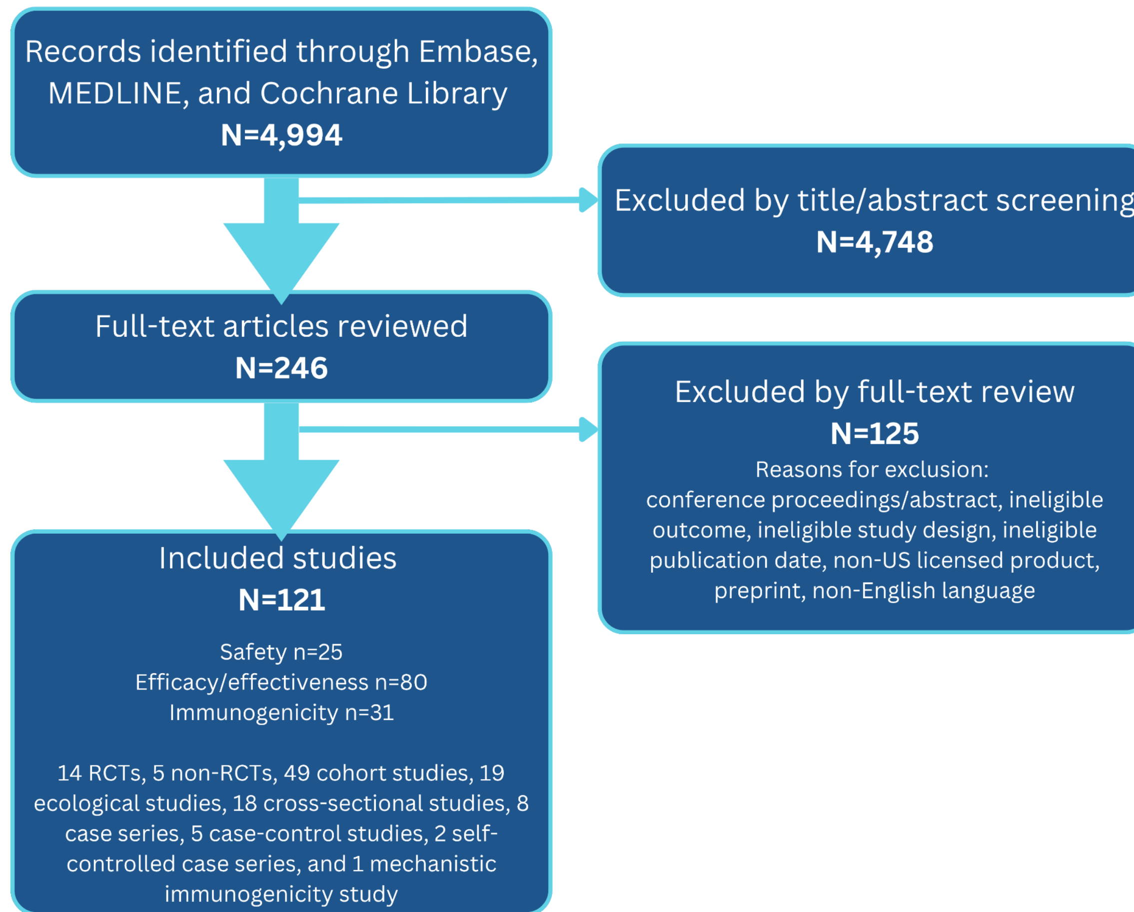
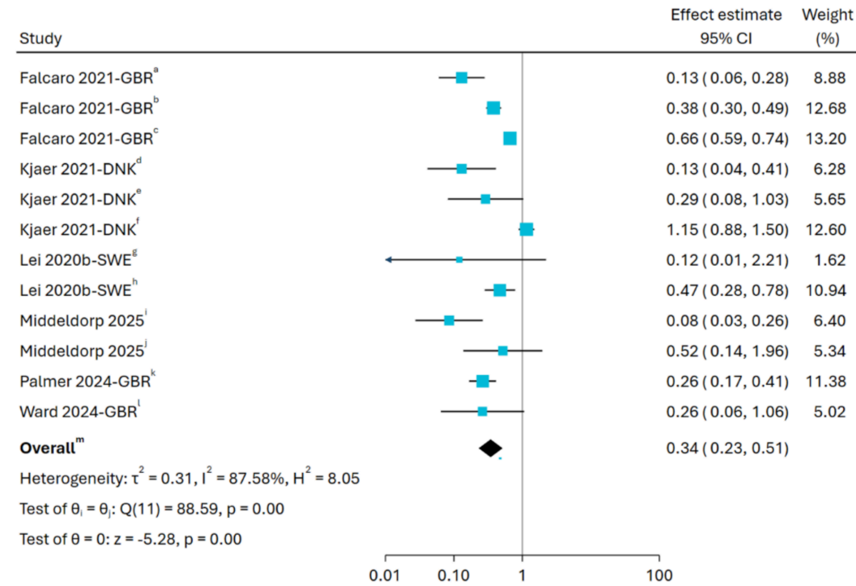
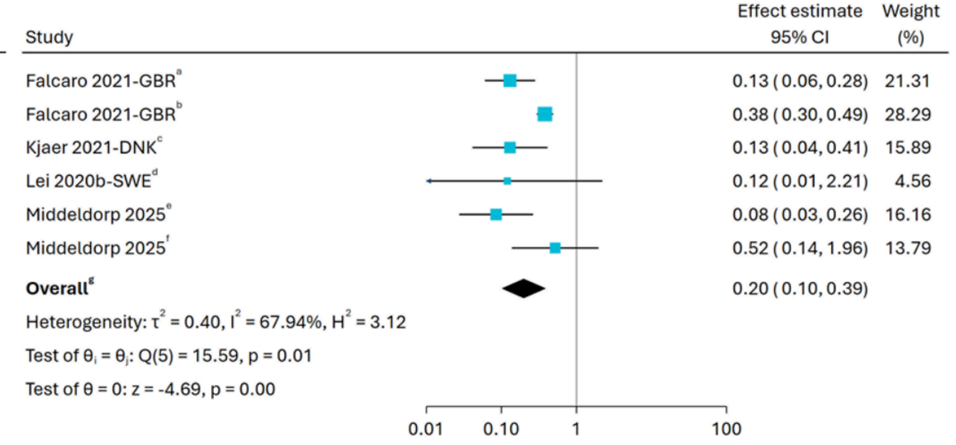


Figure 2. Forest plot and pooled analysis: Invasive cervical cancer, observational cohort studies, long-term follow-up.

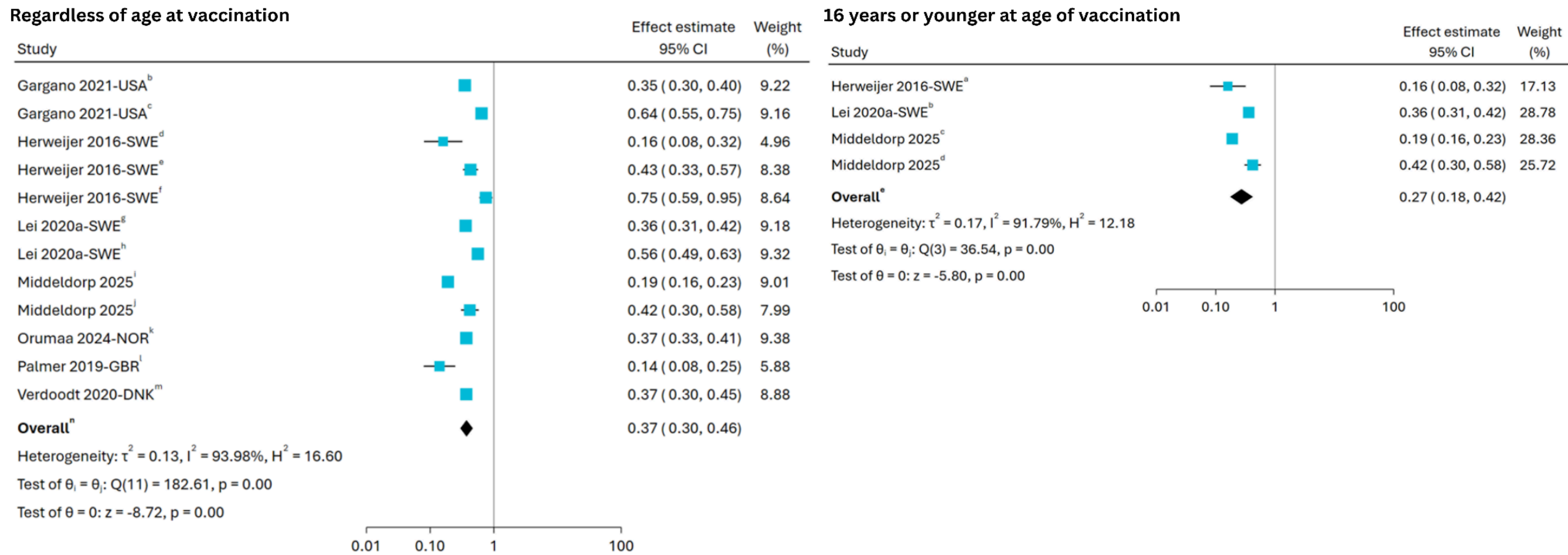




[a] 12 to 13 years at vaccination.
[b] 14 to 16 years at vaccination.
[c] 16 to 18 years at vaccination.
[d] ≤16 years at vaccination.
[e] 17 to 19 years at vaccination.
[f] 20 to 30 years at vaccination.
[g] 10 to 16 years at vaccination.
[h] 17 to 30 years at vaccination.
[i] 16 years at vaccination with 1-2 doses of Cervarix. Standardized cumulative risk ratio confidence interval recalculated.
[j] 16 years at vaccination with 3 doses of Cervarix. Standardized cumulative risk ratio confidence interval recalculated.
[k] ≥14 years at vaccination.
[l] 17 to 18 years at vaccination.
[m] Estimates generated using the DerSimonian and Laird method with Wald-type 95% CIs.

[a] 12 to 13 years at vaccination.
[b] 14 to 16 years at vaccination.
[c] ≤16 years at vaccination.
[d] 10 to 16 years at vaccination.
[e] 16 years at vaccination with 1-2 doses of Cervarix. Standardized cumulative risk ratio confidence interval recalculated.
[f] 16 years at vaccination with 3 doses of Cervarix. Standardized cumulative risk ratio confidence interval recalculated.
[g] Estimates generated using the DerSimonian and Laird method with Wald-type 95% CIs.

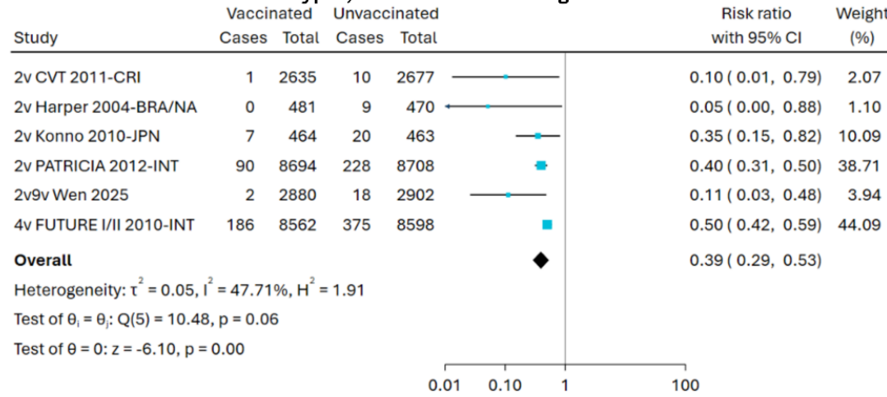
Figure 3. Forest plot and pooled analysis: CIN3+, observational cohort studies, long-term follow up.

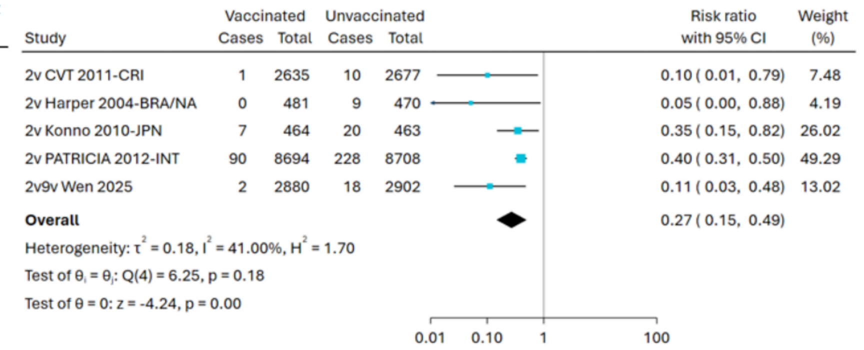


[a] The corresponding table in the Cochrane review includes estimates from one additional studies: Schurink van't Klooster 2023-NLD. The sole estimate from this study was removed from the current meta-analysis because of overlap with a newer publication, Middeldorp 2025.
[b] <20 years at vaccination.
[c] ≥20 years at vaccination.
[d] 11 to 16 years at vaccination.
[e] 17 to 19 years at vaccination.
[f] 20 to 29 years at vaccination.
[g] 10 to 16 years at vaccination.
[h] 17 to 22 years at vaccination.
[i] 16 years at vaccination with 3 doses of Cervarix.
[j] 16 years at vaccination with 1-2 doses of Cervarix.
[k] 16 to 30 years at vaccination.
[l] 12 to 18+ years at vaccination; odds ratio.
[m] < 16 years at vaccination.
[n] Estimates generated using the DerSimonian and Laird method with Wald-type 95% CIs.

[a] 11 to 16 years at vaccination.
[b] 10 to 16 years at vaccination.
[c] 16 years at vaccination with 3 doses of Cervarix.
[d] 16 years at vaccination with 1-2 doses of Cervarix.
[e] Estimates generated using the DerSimonian and Laird method with Wald-type 95% CIs.

Figure 4. Forest plot and pooled analysis: CIN2+ by HPV subtype, RCTs.





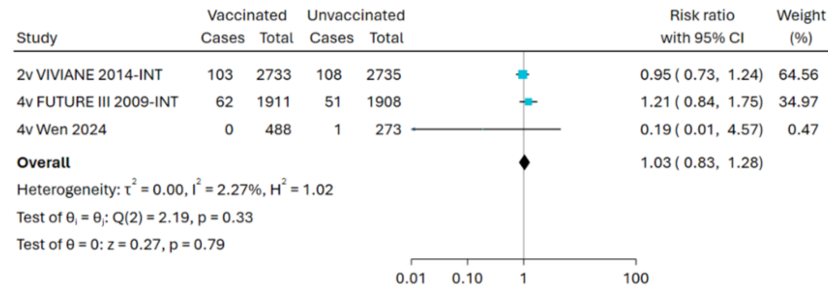
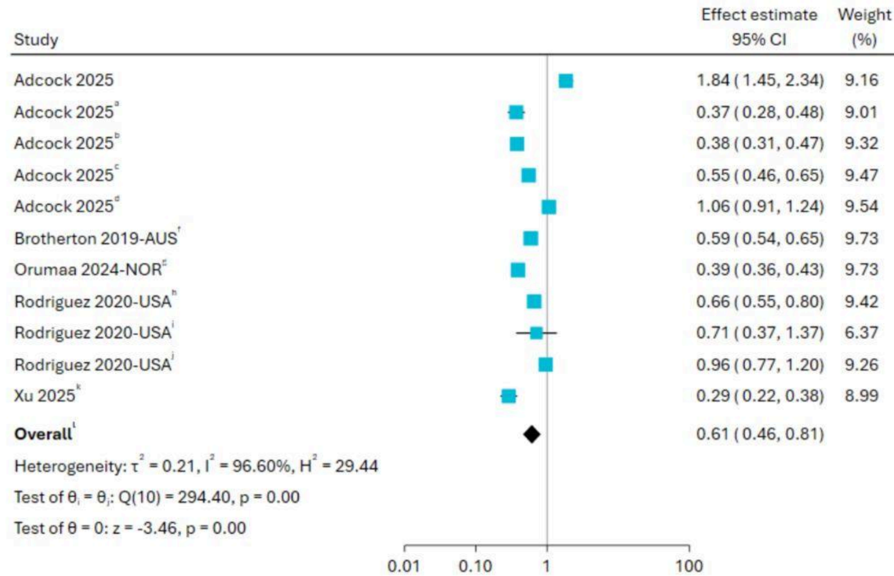
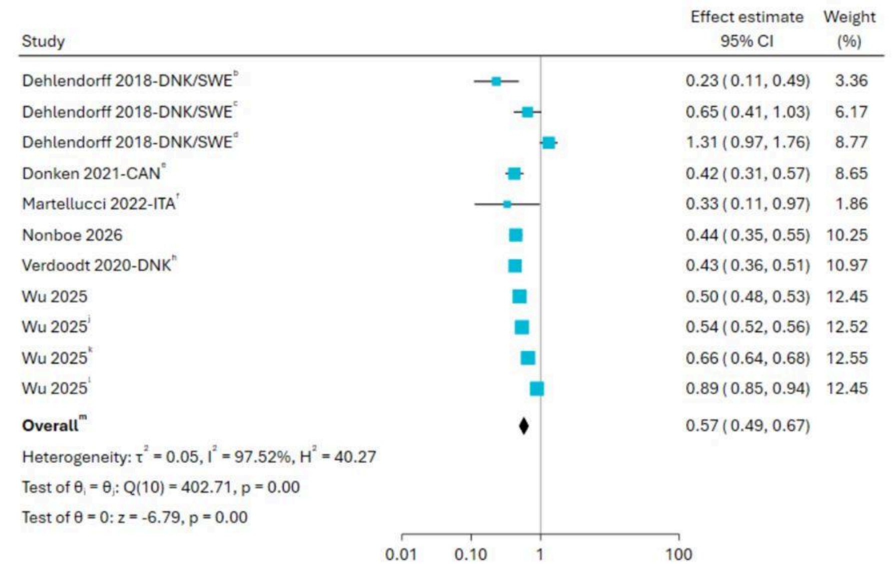


Figure 5. Forest plot and pooled analysis: CIN2+ by follow-up time and age, observational cohort studies.



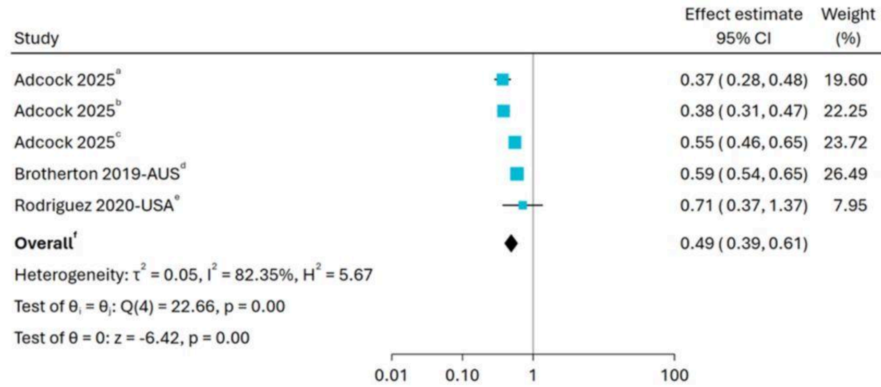


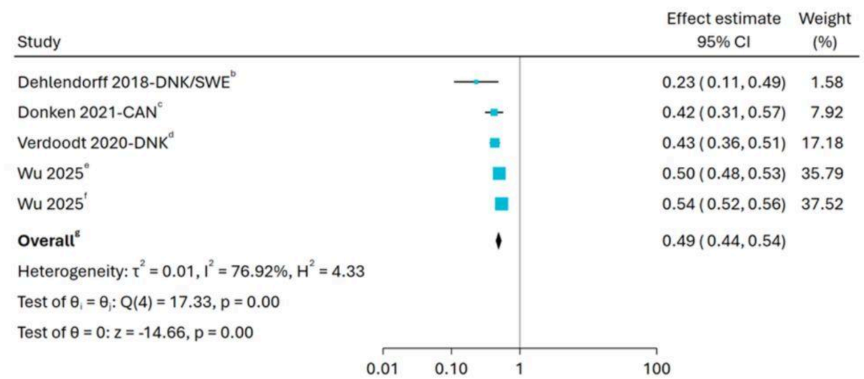
a.

[a] 9 to 12 years at vaccination.
[b] 13 to 14 years at vaccination.
[c] 15 to 16 years at vaccination.
[d] 17 to 18 years at vaccination.
[e] ≥19 years at vaccination.
[f] 12 to 15 years at vaccination.
[g] 16 to 30 years.
[h] 15 to 19 years at vaccination; hazard ratio.
[i] 9 to 14 years at vaccination; hazard ratio.
[j] > 20 years at vaccination; hazard ratio.
[k] Estimates generated using the DerSimonian and Laird method with Wald-type 95% CIs.

[a] The corresponding table in the Cochrane review includes estimates from two additional studies: Herweijer 2016SWE and Lei 2020a-SWE. A total of 5 estimates from these 2 studies (3 estimates from Herweijer 2016-SWE and 2 from Lei 2020a-SWE) were removed from the current meta-analysis because of overlap with a newer publication, Wu 2025.
[b] <16 years at vaccination.
[c] 17 to 19 years at vaccination.
[d] 20 to 29 years at vaccination.
[e] 9 to 14 years at vaccination.
[f] 25 to 30 years.
[g] ≥14 years at vaccination; hazard ratio. Standardized hazard ratio confidence interval recalculated.
[h] <16 years at vaccination.
[i] 10 to 14 years at vaccination with Gardasil.
[j] 15 to 16 years at vaccination with Gardasil.
[k] 17 to 20 years at vaccination with Gardasil.
[l] 21 to 35 years at vaccination with Gardasil.
[m] 12 to 18 years at vaccination.
[n] Estimates generated using the DerSimonian and Laird method with Wald-type

95% CIs.

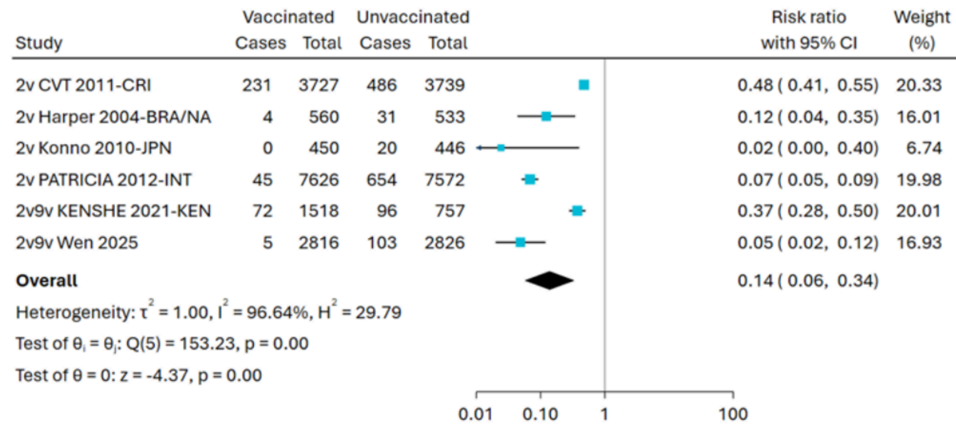


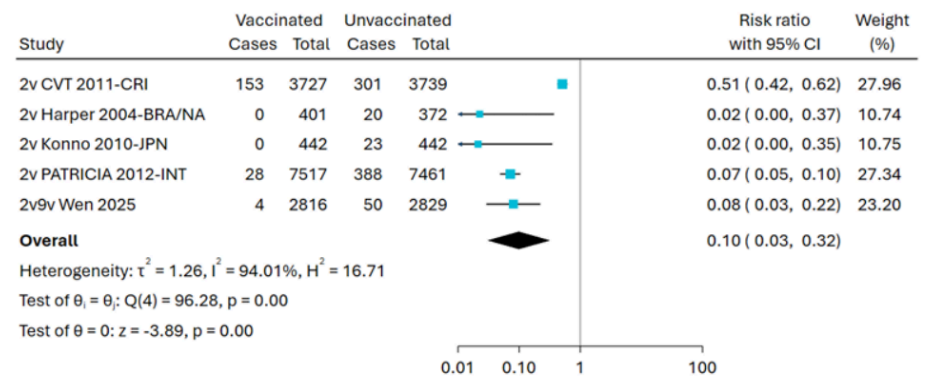


[a] 9 to 12 years at vaccination.
[b] 13 to 14 years at vaccination.
[c] 15 to 16 years at vaccination.
[d] 12 to 15 years at vaccination.
[e] 9 to 14 years at vaccination; hazard ratio.
[f] Estimates generated using the DerSimonian and Laird method with Wald-type 95% CIs.

[a] The corresponding table in the Cochrane review includes estimates from two additional studies: Herweijer 2016SWE and Lei 2020a-SWE. A total of 2 estimates from these 2 studies (1 from Herweijer 2016-SWE and 1 from Lei 2020a-SWE) were removed from the current meta-analysis because of overlap with a newer publication, Wu 2025.
[b] < 16 years at vaccination.
[c] 9 to 14 years at vaccination.
[d] < 16 years at vaccination.
[e] 10 to 14 years at vaccination with Gardasil.
[f] 15 to 16 years at vaccination with Gardasil.
[g] Estimates generated using the DerSimonian and Laird method with Wald-type 95% CIs.

Figure 6. Forest plot and pooled analysis: Persistent (6- and 12-months) HPV16/18 infections among females vaccinated at 15-25 years, RCTs.





Supplemental Materials

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Supplemental Material 2. Abbreviation list

2vHPV	Recombinant Human Papillomavirus Bivalent Vaccine
4vHPV	Recombinant Human Papillomavirus Quadrivalent Vaccine
9vHPV	Recombinant Human Papillomavirus 9-valent Vaccine
aIRR	Adjusted incidence rate ratio
ACIP	Advisory Committee on Immunization Practices
AIN	Anal intraepithelial neoplasia
CIDRAP	Center for Infectious Disease Research and Policy
CIN	Cervical intraepithelial neoplasia
CIN2+	Cervical intraepithelial neoplasia grade 2+
CIN3+	Cervical intraepithelial neoplasia grade 3+
CFS	Chronic fatigue syndrome
CRPS	Complex regional pain syndrome
CI	Confidence interval
FDA	US Food and Drug Administration
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
GBS	Guillain-Barré syndrome
HHS	US Department of Health and Human Services
HPV	Human papillomavirus
HPV16	Human papillomavirus type 16
HPV18	Human papillomavirus type 18
ME	Myalgic encephalomyelitis
PeIN	Penile intraepithelial neoplasia
POTS	Postural orthostatic tachycardia syndrome
PROSPERO	International Prospective Register of Systematic Reviews
RCTs	Randomized controlled trials
RoB	Risk of bias
RoB 2	Cochrane Risk of Bias tool for Randomized Trials Version 2
ROBINS-I	Risk Of Bias In Non-Randomized Studies - of Interventions
RR	Relative risk
SAEs	Serious adverse events
VAERS	Vaccine Adverse Reporting System
VaIN	Vaginal intraepithelial neoplasia
VIN	Vulval intraepithelial neoplasia
WHO	World Health Organization

Supplemental Material 3. Search strategy- Embase Ovid Search Terms

Observational studies

1 exp Human papilloma virus vaccine/
2 gardasil*.mp.
3 cervarix*.mp.
4 ((human papilloma virus* or human papiloma virus*) adj (vaccin* or immuni*)).tw. 5 ((human papillomavirus* or human papilomavirus*) adj (vaccin* or immuni*)).tw. 6 (HPV* adj3 (vaccin* or immuni*)).tw.
7 1 or 2 or 3 or 4 or 5 or 6
8 exp Papillomavirus Infection/
9 exp Papillomaviridae/
10 (HPV* or papilloma*).ti,ab.
11 uterine cervix carcinoma in situ/
12 Uterine Cervical Dysplasia/
13 (CIN* or adenocarcinoma in situ or AIS).ti,ab.
14 (cervi* adj5 (wart* or infection* or condyloma* or neoplas* or dysplas* or lesion* or cancer* or precancer* or "pre-cancer*" or "pre-invasive" or preinvasive or "intra-epithel*" or intraepithelial* or disease* or maligna*)).ti,ab.
15 ($genit* adj5 (wart* or infection* or condyloma* or neoplas* or dysplas* or lesion* or cancer* or precancer* or "pre-cancer*" or "pre-invasive" or preinvasive or "intra-epithel*" or intraepithelial* or disease* or maligna*)).ti,ab.
16 (vagina* adj5 (wart* or infection* or condyloma* or neoplas* or dysplas* or lesion* or cancer* or precancer* or "pre-cancer*" or "pre-invasive" or preinvasive or "intra-epithel*" or intraepithelial* or disease* or maligna*)).ti,ab.
17 (vulv* adj5 (wart* or infection* or condyloma* or neoplas* or dysplas* or lesion* or cancer* or precancer* or "pre-cancer*" or "pre-invasive" or preinvasive or "intra-epithel*" or intraepithelial* or disease* or maligna*)).ti,ab.
18 (anal* adj5 (wart* or infection* or condyloma* or neoplas* or dysplas* or lesion* or cancer* or precancer* or "pre-cancer*" or "pre-invasive" or preinvasive or "intra-epithel*" or intraepithelial* or disease* or maligna*)).ti,ab.
19 ((head or neck) adj5 (neoplas* or dysplas* or lesion* or cancer* or precancer* or "pre- cancer*" or "pre-invasive" or preinvasive or disease* or maligna*)).ti,ab.
20 (penile* adj5 (wart* or infection* or neoplas* or dysplas* or lesion* or cancer* or precancer* or "pre-cancer*" or "pre-invasive" or preinvasive or "intra-epithel*" or intraepithelial* or disease* or maligna*)).ti,ab.
21 Uterine Cervix Tumor/
22 exp Condylomata Acuminata/
23 vulva tumor/ or vagina tumor/ or anus tumor/ or anus disease/
24 "Head and Neck Neoplasms"/
25 penis tumor/ or penis disease/
26 Postural Orthostatic Tachycardia Syndrome/
27 (postural tachycardia syndrome* or postural orthostatic tachycardia syndrome* or POTS).mp.
28 Chronic Fatigue Syndrome/
29 chronic fatigue*.mp.
30 (myalgic encephalomyelitis or ME or chronic fatigue* or CFS).mp. 31
Paralysis/

32 paralys*.mp.
33 Complex Regional Pain Syndrome/
34 (complex regional pain syndrome or CRPS).mp.
35 premature ovarian failure/
36 ((premature ovar* or primary ovar*) adj2 (fail* or insufficien*)).mp. 37 Guillain Barre Syndrome/
38 (Guillain Barr* syndrome or GBS).mp.
39 Infertility/
40 infertil*.mp.
41 Sexual Behavior/
42 (earl* adj3 (sex* activity or sex* behaviour)).mp.
43 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42
44 ae.fs.
45 Adverse.ti,ab,kw,ox.
46 Safe*.ti,ab,kw.
47 Po.fs.
48 Co.fs.
49 exp adverse drug reaction/
50 Complication*.ti,ab,kw.
51 Drug safety/
52 To.fs.
53 Side effect*.ti,ab.
54 Risk.ti.
55 Tolerance.ti,ab.
56 Tolerated.ti,ab.
57 Harm.ti,ab.
58 Side reaction*.ti,ab.
59 drug withdrawal/
60 health risks.ti,ab.
61 potential risks.ti,ab.
62 toxic effects.ti,ab.
63 toxicity.ti,ab.
64 toxicities.ti,ab.
65 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64
66 43 or 65
67 7 and 66
68 limit 67 to dc=20240911-20260127

Clinical studies

1 exp Human papilloma virus vaccine/
2 gardasil*.mp.
3 cervarix*.mp.
4 ((human papilloma virus* or human papiloma virus*) adj (vaccin* or immuni*)).tw. 5 ((human papillomavirus* or human papilomavirus*) adj (vaccin* or immuni*)).tw. 6 (HPV* adj3 (vaccin* or immuni*)).tw.

7 or/1-6
8 crossover procedure/
9 double blind procedure/
10 randomized controlled trial/
11 single blind procedure/
12 random*.mp.
13 factorial*.mp.
14 (crossover* or cross over* or cross-over*).mp.
15 placebo*.mp.
16 (double* adj blind*).mp.
17 (singl* adj blind*).mp.
18 assign*.mp.
19 allocat*.mp.
20 volunteer*.mp.
21 or/8-20
22 7 and 21
23 limit 22 to dc=20240918-20260127

Supplemental Material 4. Calculation of meta-analytic estimates for cohort studies according to the number of HPV vaccine doses received.

We calculated study-specific estimates and 95% confidence intervals, as well as meta-analytic estimates, for cohort studies reporting vaccine effectiveness against HPV-related health outcomes (CIN2+ and CIN3+ disease), and according to the number of HPV vaccine doses received (1 or 2 doses).

Exact values of relative vaccine effectiveness (rVE) for 2 doses versus one dose are presented based on the following formula:

$$rVE_{2vs1} = \frac{aVE_{estimate2} - aVE_{estimate1}}{1 - aVE_{estimate1}}\ x\ 100\%$$

This formula is based on relative VE analyses described in the following publication:

Lewis NM, Chung JR, Uyeki TM, Grohskopf L, Ferdinands JM, Patel MM. Interpretation of relative efficacy and effectiveness for influenza vaccines. Clinical Infectious Diseases 2022:75(1):170-175.

However, because the original study values are based on adjusted risk estimates, 95% confidence intervals cannot be provided for rVE estimates.

In some cases, study-specific estimates from the original review or from new studies were found not to have symmetric 95% confidence intervals. In cases where the recalculation of the 95% confidence interval was necessary, this has been noted in footnotes to tables and plots.

All meta-analyses were obtained via random-effects models using the DerSimonian-Laird method.

Supplemental Table 1. Summary of studies reporting HPV vaccine efficacy/effectiveness against invasive cervical cancer.

Study	Study design	Vaccine Product	Study Population	Summary of Key Findings	Risk of Bias
Van Lonkhuijzen 2026	Cohort	Cervarix	*Demographics:* Females living in the Netherlands, born in 1993 or later. *Age at vaccination:* Not reported	*Follow-up:* Includes women born 1993 or later, diagnosed with cervical cancer before the age of 30, identified in the Netherlands Cancer Registry. *Results:* 135 cases; 71 unvaccinated, 13 vaccinated, 51 unknown vaccination status	Critical
Grieco 2025	Cohort	Gardasil Gardasil 9	*Demographics:* Females living in Italy *Age at vaccination:* 11 years or older	*Follow-up:* Identified women who had cervical cancer during 2003 - 2020, then retrospectively linked those cases to the vaccination registry. *Results:* 751 cases, all among unvaccinated VE = 99.2% (94.3 - 99.9)	Critical
Middeldorp 2025	Cohort	Cervarix	*Demographics:* Females living in the Netherlands *Age at vaccination:* Eligible for vaccination at age 16	*Follow-up:* 14 years *Results:* 5 cases/47,130 fully[a] vaccinated; 2 cases/5,096 partially[b] vaccinated Adjusted cumulative risk ratio (reference = unvaccinated): Fully vaccinated: 0.085 (0.025 - 0.24) Partially vaccinated: 0.52 (0.12 - 1.71)	Serious

Study	Study design	Vaccine Product	Study Population	Summary of Key Findings	Risk of Bias
Semprini 2025	Pre-post vaccine introduction	Cervarix Gardasil Gardasil 9	*Demographics:* Females living in the United States *Age at vaccination:* Eligible at age 9-13 years	*Follow-up:* Not applicable *Results:* 48% reduction in cervical cancer incidence comparing age vaccine-eligible cohorts (ages 25 - 29) to non-vaccine-eligible reference group (age 35 - 54) with incidence declining by 2.1 cases (-2.7 - -1.6) per 100,000 population (p-value: <0.001)	Critical

Abbreviations: HPV: human papillomavirus; VE: Vaccine efficacy/effectiveness

[a]Fully vaccinated = Three doses within an interval or two doses given at least 150 days apart.

[b]Partially vaccinated = One dose, or, if they received two or three doses, in a schedule that violated the criteria for being fully vaccinated.

Supplemental Table 2. Summary of studies reporting HPV vaccine efficacy/effectiveness against oropharyngeal cancer.
Abbreviations: aHR: adjusted hazard ratio; HPV: human papillomavirus

Study	Study design	Vaccine Product	Study Population	Summary of Key Findings	Risk of Bias
Hung 2025	Cohort	Gardasil 4, Gardasil 9, and multiple vaccines (not disaggregated)	*Demographics:* Females identified in the TriNetX Collaborative Network which is a multi-institutional EHR network *Age at vaccination:* 9 -14 and 15 - 26 years	*Follow-up:* 5 years *Results:* **Gardasil 4** Overall aHR: 0.064 (0.008 - 0.492) **Gardasil 9** Overall aHR: 0.262 (0.121 - 0.568) **Multiple vaccines** Overall aHR: 0.207 (0.092 - 0.468) Ages 9 - 14 aHR: 0.191 (0.065 - 0.560) Ages 15 - 26 aHR: 0.422 (0.109 - 1.631)	Critical
Katz 2025	Cross-sectional	Multiple vaccines (not disaggregated)	*Demographics:* Males and females who received care from the University of Florida, Gainesville Health Center *Age at vaccination:* Not reported	*Results:* Reference=unvaccinated Outcome: Oral and oropharyngeal cancer Overall odds ratio: 0.09 (0.04 - 0.18)	Serious

Supplemental Table 3. Summary of studies reporting HPV vaccine efficacy/effectiveness against cervical intraepithelial neoplasia grade 3 or higher (CIN3+).

Study	Study design	Vaccine Product	Study Population	Summary of Findings	Risk of Bias
Haas 2025	Cohort	Cervarix	*Demographics:* Females living in Costa Rica participating in an RCT. Participants were recruited to cohort due to elevated risk factors for anal disease. *Age at vaccination:* 18-25 years	*Follow-up:* N/A, results reported are from baseline (cross-sectional) *Results:* Baseline (cross-sectional) unadjusted prevalence ratios: 3 doses vs unvaccinated: 1.0 (0.8 - 1.3) 1 or 2 doses vs unvaccinated: 1.9 (1.3 - 2.7)	Critical
Lehtinen 2024	Cohort	Cervarix Gardasil	*Demographics:* Vaccinated females from two trials and females not eligible for trials who were unvaccinated living in Finland were recruited. *Age at vaccination:* 16-17 years	*Follow-up:* 15 years follow-up. Most participants received three doses. *Results:* Gardasil VE: 68.4% (24 - 87) Cervarix VE: 64.5% (41 - 79)	Moderate

Study	Study design	Vaccine Product	Study Population	Summary of Findings	Risk of Bias
Palmer 2026	Cohort	Cervarix	*Demographics:* Females identified from Scotland national cervical screening and immunization records *Age at vaccination (4 groups):* 12-13 years 14-16 years 17-18 years >18 years	*Follow-up:* Retrospectively collected data on all women in Scotland born on or after 1/1/1988 up to 6/6/2016 who were eligible for the national cervical cancer screening program. Linked with immunization records and schedules. *Results:* VE = (1-HR)*100, (95% CI) 12-13 years Incomplete[a] vaccination: 71 (-105.9 - 95.9) Complete[b] vaccination: 81.7 (76.2 - 85.9) 14-16 years Incomplete vaccination: 34.9 (17.0 - 48.9) Complete vaccination: 76.2 (73.2 - 78.9) 17-18 years Incomplete vaccination: 14.6 (-0.8 - 27.6) Complete vaccination: 44.1 (38.5 - 49.2) >18 years Incomplete vaccination: 12.6 (-32.8 - 42.5) Complete vaccination: 12.7 (-20.2 - 36.5)	Low risk of bias except for concerns about uncontrolled confounding
Eriksen 2026	Cohort	Product not specified but US licensed	*Demographics:* Females living in Denmark with CIN2 diagnosis and who were not vaccinated before CIN2 diagnosis. *Age at vaccination* (2 groups): 18-29 and 30-40	*Follow-up:* Historical cohort, data from 2007 - 2020 *Results:* Comparing incidence of CIN3+ progression of women who received HPV vaccine within 6 months of CIN2 diagnosis to those who did not receive the vaccine. 18 - 29 years Unadjusted HR: 1.43 (1.19 - 1.71) Adjusted HR (ages 18 - 29): 1.58 (1.32 - 1.89) 30-40 years Unadjusted HR: 1.13 (0.85 - 1.51) Adjusted HR: 1.19 (0.89 - 1.60)	Critical

Study	Study design	Vaccine Product	Study Population	Summary of Findings	Risk of Bias
				Overall Unadjusted HR: 1.22 (1.05 - 1.42) Adjusted HR: 1.45 (1.24 - 1.69)	
Middeldorp 2025	Cohort	Cervarix	*Demographics:* Females living in the Netherlands eligible for vaccination (born 1993 or later) *Age at vaccination:* 16+	*Follow-up:* Hisopathological results recorded until 4/1/2024 *Results:* Adjusted cumulative risk ratio (unvaccinated=reference): Fully[c] vaccinated: 0.19 (0.16 - 0.23) Partially[d] vaccinated: 0.42 (0.30 - 0.57) Comparing fully vaccinated to partially vaccinated: Fully vaccinated: 171 cases and 46,959 non-cases Partially vaccinated: 32 cases and 5,066 non-cases	Serious
Ikeda 2025	Case Control	Gardasil Cervarix (not disaggregated)	*Demographics:* Females living in Japan. Case: Control matched in a 1:5 ratio within the municipality by exact birth year and closest examination date. *Age at vaccination:* 12-16 years	*Follow-up:* Not applicable *Results:* Reference=unvaccinated Unadjusted OR: 0.14 (0.03 - 0.75) VE: 86% (1-OR)*100	Serious
Sorbye 2025	Pre-post vaccine introduction	Gardasil 4 and Cervarix (not disaggregated)	*Demographics:* Females living in Norwegian cities aged 25-29 years who had at least one cervical screening sample or cervical histology in a given calendar year *Age at vaccination:* Not reported	*Follow-up:* N/A *Results:* CIN3+ incidence fluctuated between 15 - 24 per 1000 screened women from 2010-2016, rose to 26.7 in 2017 and 27.8 in 2018, then declined steadily to 6.6 per 1000 in 2024 (17 cases). This was an approx 75% reduction from 2017 - 2024, with intermediate rates of 22.0 in 2020, 19.0 in 2021, 15.8 in 2022, and 11.7 in 2023.	Critical

Abbreviations: aHR: adjusted hazard ratio; CI: confidence interval; CIN2: cervical intraepithelial neoplasia grade 2; CIN3+: cervical intraepithelial neoplasia grade 3 or higher; HPV: human papillomavirus; HR: hazard ratio; N/A: not applicable; OR: odds ratio; RCT: randomized controlled trial; VE: vaccine efficacy/effectiveness

[a] Incomplete vaccination = One or two doses, one month apart.
[b] Complete vaccination = Two doses five months apart, or three doses.
[c] Fully vaccinated = Three doses within an interval or two doses given at least 150 days apart.
[d] Partially vaccinated = One dose, or, if they received two or three doses, in a schedule that violated the criteria for being fully vaccinated.

Supplemental Table 4. Summary of studies reporting HPV vaccine efficacy/effectiveness against cervical intraepithelial neoplasia grade 2 or higher (CIN2+).

Study	Study design	Vaccine Product	Study Population	Summary of Findings	Risk of Bias
Wen 2025	Randomized Control Trial	Cervarix	*Demographics:* Chinese females recruited from four sites in Jiangsu Province. *Age at vaccination:* 18-25 years	*Follow-up:* 10 years. Median follow-up of 9.4 years (IQR: 5.7- 9.9) *Results:* Vaccine effectiveness against CIN2+ with HPV 16/18: 87.67 (56.99 - 98.19) CIN2+ with HPV 31/33/45: 38.78 (-53.90 - 77.56) CIN2+ with HPV 35/52/58: 21.76 (-52.86 - 60.82) CIN2+ with HPV 39/51/56/59/66/68: -4.11 (-145.47 - 55.84)	Low
Palmer 2026	Cohort	Cervarix	*Demographics:* Females living in Scotland *Age at vaccination (4 groups):* 12-13 years 14-16 years 17-18 years >18 years	*Follow-up:* Retrospectively collected data on all women in Scotland born on or after 1/1/1988 up to 6/6/2016 who were eligible for the national cervical cancer screening program. Linked with immunization records and schedules. *Results:* VE = (1-HR)*100, (95% CI) 12-13 years Incomplete[a] vaccination: 48.4 (-60.2 - 83.3) Complete[b] vaccination: 72.6 (67.7 - 76.8) 14-16 years Incomplete vaccination: 20.5 (6.1 - 32.6) Complete vaccination: 63.2 (60.4 - 65.8) 17-18 years	Low risk of bias except for concerns about uncontrolled confounding

Study	Study design	Vaccine Product	Study Population	Summary of Findings	Risk of Bias
				Incomplete vaccination: 9.8 (-1.6 - 20.0) Complete vaccination: 35.4 (30.9 - 39.5) >18 years Incomplete vaccination: -5.5 (-39.8 - 20.3) Complete vaccination: 0.4 (-14.1 - 28.0)	
Song 2025	Cohort	Gardasil 9, Gardasil 4, and Cervarix. Not disaggregated	*Demographics:* Korean women aged 27 years or older with cytological findings of either atypical squamous cells of undetermined significance (ASCUS) or low-grade squamous intraepithelial lesions (LSILs), and who tested positive for HPV DNA. *Age at vaccination:* Not reported	*Follow-up:* Visits conducted from April 2010 - September 2021 with HPV DNA testing and cytology performed every 6 months. *Results:* Outcome of interest is progression to CIN2+. Reference group is unvaccinated. HR: 0.38 (0.18-0.80)	Moderate
Petras 2025	Cohort	Reports results both by overall vaccine status, including any Gardasil 9, Gardasil 4, and Cervarix (not disaggregated) . Also reports disaggregated results	*Demographics:* Females treated for CIN2+ recruited from one central lab in Czech Republic *Age at vaccination:* Not reported	*Follow-up:* Period from conization to the last histologically or cytologically confirmed negative finding in women without relapse during 15 years of follow-up *Results:* Outcome: Recurrence rate based on histologically confirmed CIN2+ from conization or a previous biopsy specimen. Two vaccination strategies: 1. Prophylactically vaccinated women (available through national program) 2. Post conization (recommended by medical society) VE = 100*(1-IRR). Reference=unvaccinated	Serious

Study	Study design	Vaccine Product	Study Population	Summary of Findings	Risk of Bias
				Vaccine type not disaggregated: Vaccinated irrespective of timing: 67 (53 - 77) Vaccinated post-excision: 74 (57 - 85) Vaccinated prophylactically: 54 (22 - 73) 2vHPV: Vaccinated post-excision: 56 (-18 - 84) Vaccinated prophylactically: 66 (-7 - 89) 4vHPV: Vaccinated post-excision: 64 (13 - 85) Vaccinated prophylactically: 42 (-6 - 68) 9vHPV: Vaccinated post-excision: 83 (61 - 92) Vaccinated prophylactically: 0 recurrences; therefore, unable to calculate VE	
Kjaer 2024	Cohort	Gardasil 9	*Demographics:* Females living in Denmark, Norway, or Sweden *Age at vaccination:* 16-26 years	*Follow-up:* Up to 14.1 years follow-up after first dose (median 10.9 years) and 13.6 years after dose 3 (median 10.4 years) *Results:* 0 cases /1,628 vaccinated	Serious
Wu 2025	Cohort	Gardasil (at least one dose)	*Demographics:* Females living in Sweden aged 10 35 years *Age at vaccination (4 groups):* 10-14 years 15-16 years 17-20 years 21-35 years	*Follow-up:* Retrospective cohort of females living in Sweden followed from 1/1/2006 or their 10th birthdays, whichever came later, until diagnosed with outcome, died, emigrated, lost to follow-up, received bivalent or nonavalent HPV vaccine, reached their 36th birthday or 12/31/2022, whichever came first. *Results:* Adjusted IRR (95% CI) (Ref: Unvaccinated historical reference): All ages	Moderate

Study	Study design	Vaccine Product	Study Population	Summary of Findings	Risk of Bias
				≥1 dose: 0.62 (0.60 - 0.63) 1 dose: 0.73 (0.69 - 0.78) 2 doses: 0.70 (0.66 - 0.74) 3 doses: 0.59 (0.58 - 0.61) 10-14 years ≥1 dose: 0.50 (0.47 - 0.52) 1 dose: 0.42 (0.33 - 0.52) 2 doses: 0.54 (0.47 - 0.63) 3 doses: 0.50 (0.47 - 0.53) 15-16 years ≥1 dose: 0.54 (0.52 - 0.56) 1 dose: 0.60 (0.52 - 0.70) 2 doses: 0.55 (0.49 - 0.62) 3 doses: 0.54 (0.52 - 0.56) 17-20 years ≥1 dose: 0.66 (0.64 - 0.68) 1 dose: 0.73 (0.66 - 0.81) 2 doses: 0.72 (0.66 - 0.79) 3 doses: 0.64 (0.61 - 0.66) 21-35 years ≥1 dose: 0.89 (0.85 - 0.94) 1 dose: 0.95 (0.85 - 1.05) 2 doses: 0.93 (0.84 - 1.02) 3 doses: 0.86 (0.80 - 0.92) Summary: Observed that girls who were vaccinated with one or two doses prior to age 17 and especially before 15, had comparable effectiveness against CIN2+ compared to girls receiving 3 doses. VE was lower among women who initiated vaccination after age 20.	

Abbreviations: 2vPHV: Recombinant Human Papillomavirus Bivalent Vaccine; 4vHPV: Recombinant Human Papillomavirus Quadrivalent Vaccine; 9vHPV: Recombinant Human Papillomavirus 9-valent Vaccine; ASCUS: atypical squamous cells of undetermined significance; CI: confidence interval; CIN2+: cervical intraepithelial neoplasia grade 2 or higher; DNA: deoxyribonucleic acid; HPV: human papillomavirus; HR: hazard ratio; IRR: incidence rate ratio; IQR: interquartile range; LSILs: low-grade squamous intraepithelial lesions; VE: vaccine efficacy/effectiveness

[a] Incomplete vaccination = One or two doses, one month apart.

[b] Complete vaccination = Two doses five months apart, or three doses.

Supplemental Table 5. Summary of studies reporting HPV vaccine efficacy/effectiveness against vaginal or vulval intraepithelial neoplasia (VaIN/VIN).

Study	Study design	Vaccine Product	Study Population	Summary of Findings	Risk of Bias
Deng 2025	Cohort	Gardasil	*Demographics:* Females living in Sweden *Age at vaccination:* 10-16 and ≥17 years	*Follow-up:* Retrospective cohort of females living in Sweden followed from 1/1/2006 or their 10th birthdays, whichever came later, until diagnosed with outcome, died, emigrated, lost to follow-up, received bivalent or nonavalent HPV vaccine, reached their 36th birthday or 12/31/2022, whichever came first. *Results:* Adjusted IRR (Ref = unvaccinated) Vulvar lesions Overall: 0.63 (0.44 - 0.89) 10-16 years: 0.43 (0.25 - 0.72) ≥17 years: 0.82 (0.55 - 1.22) Vaginal lesions Overall: 0.63 (0.46 - 0.87) 10-16 years: 0.47 (0.29 - 0.75) ≥17 years: 0.78 (0.54 - 1.13) High-grade vulvovaginal lesions Overall: 0.63 (0.50 - 0.81) 10-16 years: 0.45 (0.32 - 0.65) ≥17 years: 0.80 (0.61 - 1.06)	Moderate

Abbreviations: HPV: human papillomavirus; IRR: incidence rate ratio; VaIN: vaginal intraepithelial neoplasia; VIN: vulval intraepithelial neoplasia

Supplemental Table 6. Summary of studies reporting HPV vaccine efficacy/effectiveness against high-grade AIN.

Study	Study design	Vaccine Product	Study Population	Summary of Key Findings	Risk of Bias
Mazzitelli 2025	Cohort	Gardasil 9, Gardasil 4, and Cervarix, not disaggregated	*Demographics:* HIV+ females (age 18+) recruited from Padua University Hospital in northern Italy. All participants were receiving care at this clinic. *Age at vaccination:* Not reported	*Follow-up:* October 2022 - November 2024 *Results:* Partial vaccination (not defined) aOR: 4.83 (1.3 - 17.87) Complete vaccination (not defined) aOR: 2.25 (1.09 - 4.65)	Critical
Sambo 2025	Cohort	Gardasil 9	*Demographics:* HIV+ males and females, 18 years and older, living in Italy *Age at vaccination:* Not reported	*Follow-up:* Not reported *Results:* Anal HSIL lesions at baseline: 0 of 34 vaccinated with outcome, 2 of 76 unvaccinated with outcome Incident anal HSIL lesions during follow-up: 2 of 34 vaccinated with outcome, 4 of 76 unvaccinated with outcome	Critical

Abbreviations: AIN: anal intraepithelial neoplasia; aOR: adjusted odds ratio; HIV+: human immunodeficiency virus positive; HPV: human papillomavirus; HSIL: high-grade squamous intraepithelial lesion

Supplemental Table 7. Summary of studies reporting HPV vaccine efficacy/effectiveness against HPV 16 and/or 18.

Study	Study design	Vaccine Product	Study Population	Summary of Key Findings	Risk of Bias
Kreimer 2025	RCT	Gardasil 9, Cervarix	*Demographics:* Females living in Costa Rica *Age at vaccination:* 12-16 years	*Follow-up:* 5 years *Results:* incident and/or persistent infection for at least 6 months for HPV16, HPV18, and HPV 16/18 (not disaggregated). VE = (1-aOR)*100 **Gardasil 9** HPV16 2 vs 0 doses, VE: 99.2 (97.8 - 100) 1 vs 0 doses, VE: 97.2 (94.1 - 99.4) HPV18 2 vs 0 doses, VE: 97.6 (93.7 - 100) 1 vs 0 doses, VE: 97.1 (92.5 - 100) HPV16/18 1 vs 2 doses, rate difference: 0.21 (-0.09 - 0.51) 2 vs 0 doses, VE: 98.5 (96.7 - 99.7) 1 vs 0 doses, VE: 97.0 (94.3 - 99.1) **Cervarix** HPV16 2 vs 0 doses, VE: 98.4 (96.1 - 99.8) 1 vs 0 doses, VE: 97.7 (95.1 - 99.7) HPV18 2 vs 0 doses, VE: 97.1 (92.5 - 100) 1 vs 0 doses, VE: 99.3 (97.0 - 100) HPV16/18 1 vs 2 doses, rate difference: -0.13 (-0.45 - 0.15) 2 vs 0 doses, VE: 97.8 (95.6 - 99.3)	Low

Study	Study design	Vaccine Product	Study Population	Summary of Key Findings	Risk of Bias
				1 vs 0 doses, VE: 98.2 (96.1 - 99.6)	
Garcia 2023	Cross-sectional	Products not specified (but US licensed)	*Demographics:* Females living in Sweden aged 21-70 years. Recruited from a single center healthcare setting in Uppsala *Age at vaccination:* Not reported	*Follow-up:* Not applicable *Results:* PCR-confirmed infection with HPV16, HPV18, or at least 1 oncogenic subtype covered by bi- and tetravalent vaccines (HPV16, 18, 6 and 11) 1 of 17 vaccinated with outcome 22 of 65 unvaccinated with outcome HPV 16 1 of 16 vaccinated with outcome 18 of 62 unvaccinated with outcome HPV18 0 of 16 vaccinated with outcome 5 of 62 unvaccinated with outcome	Critical
Wen 2025	RCT	Cervarix	*Demographics:* Chinese females recruited from four sites in Jiangsu Province. *Age at vaccination:* 18-25 years	*Follow-up:* Median (IQR follow-up): 112.73 (68.41 - 119.03) months *Results:* VE = (1-RR)*100, (95% CI) HPV 16 & 18 (not disaggregated): 6-month persistent infection: 95.05 (89.06 - 98.27) 12-month persistent infection: 91.72 (79.69 - 97.55)	Low
Haas 2025	Cohort	Cervarix	*Demographics:* Sub-cohort of females participating in an RCT located in Costa Rica	*Follow-up:* N/A, results reported are from baseline (cross-sectional) *Results:*	Critical

Study	Study design	Vaccine Product	Study Population	Summary of Key Findings	Risk of Bias
			Age at vaccination: 18-25 years	Anal HPV16 or cervical HPV16 infection Anal HPV16 3 vs 0 doses PR: 0.3 (0.2 - 0.5) 1 or 2 vs 0 doses PR: 0.3 (0.1 - 0.8) Cervical HPV16 3 vs 0 doses PR: 0.2 (0.2 - 0.3) 1 or 2 vs 0 doses PR: 0.2 (0.1 - 0.4)	
Lin 2026	Cohort	Gardasil 9	*Demographics:* HIV+ males seeking care at the National Taiwan University Hospital *Age at vaccination:* 20-45 years	*Follow-up:* 12 months *Results:* Incident infection with HPV16 or HPV18 HPV 16 0 of 38 vaccinated with outcome 1 of 49 unvaccinated with outcome HPV18 0 of 38 vaccinated with outcome 0 of 49 unvaccinated with outcome	Critical
Kassam 2025	Cohort	Multiple vaccines (not disaggregated)	*Demographics:* HIV+ MSM living in Montreal recruited from a discontinued RCT *Age at vaccination:* Not reported	*Follow-up:* 12 months *Results:* Incident anal infection with HPV16 or HPV18 HPV16 0 of 54 vaccinated with outcome 4 of 149 unvaccinated with outcome HPV18 2 of 43 vaccinated with outcome 15 of 109 unvaccinated with outcome aHR: 0.34 (0 - 1.38)	Moderate

Study	Study design	Vaccine Product	Study Population	Summary of Key Findings	Risk of Bias
Louvanto 2024	Case control	Cervarix	*Demographics:* Vaccinated females living in Finland and participated in a previous trial. Controls matched in a 1:8 ratio based on place of residence and birth cohort *Age at vaccination:* 12-18 years	*Follow-up:* 15 years post vaccination *Results:* Infection with HPV16 HPV 16 1 of 403 vaccinated with outcome	Serious
Kusters 2024	Cross-sectional	Cervarix	*Demographics:* Females living in the Netherlands participating in the PApillomavirus Surveillance among Sti clinic YOungsters in the Netherlands (PASSYON) study *Age at vaccination:* Not reported	*Follow-up:* Not applicable *Results:* Positive DNA test result for HPV16 or HPV18 HPV16 Overall 1-aRR*100: 93.5 (89.8 - 95.9) HPV18 Overall VE: 89.5 (83.0 - 93.6) Routine (12 years) vaccinated VE: 86.8 (74.0 - 93.9) Catch-up (13-16 years) vaccinated VE: 92.2 (84.1 - 96.2)	Serious
Kops 2026	Cross-sectional	Multiple vaccines (Gardasil 4 and 9, not disaggregated)	*Demographics:* Brazilian MSM recruited from multiple centers nationwide *Age at vaccination:* Not reported	*Follow-up:* N/A *Results:* Positive test and genotype results for HPV16, HPV18, or HPV16/18 (anal) HPV 16 Adjusted prevalence among vaccinated: 8.3% (95% CI 2.6-13.9) Adjusted prevalence among unvaccinated: 17.9% (95% CI 11.5-24.4)	Critical

Study	Study design	Vaccine Product	Study Population	Summary of Key Findings	Risk of Bias
				aPR: 0.4637 HPV 18 Adjusted prevalence among vaccinated: 4.4 Adjusted prevalence among unvaccinated: 5.5 aPR: 0.8 HPV16/18 Adjusted prevalence among vaccinated: 12.1% (95% CI 5.1-19.2) Adjusted prevalence among unvaccinated: 21.9% (95% CI 15.3-28.6) aPR: 0.5525	
Garcia-Gil 2025	Cross-sectional	Products not specified (but US licensed)	*Demographics:* Females seeking care at outpatient care clinics "Salud Digna" in all 32 states of Mexico *Age at vaccination:* Not reported	*Follow-up:* Not applicable *Results:* Positive NAAT results for HPV16 or HPV18. Effect estimates reported here are for women under 25 years HPV 16 1 vs 0 doses aOR: 0.52 (0.44 - 0.61) 2 vs 0 doses aOR: 0.21 (0.17 - 0.26) 3 vs 0 doses aOR: 0.18 (0.11 - 0.26) HPV18 1 vs 0 doses aOR: 0.62 (0.49 - 0.78) 2 vs 0 doses aOR: 0.33 (0.24 - 0.44) 3 vs 0 doses aOR: 0.20 (0.10 - 0.36)	Serious
Ron 2025	Non-randomized, single arm clinical trial	Gardasil 9	*Demographics:* HIV+ MSM recruited from three hospitals in Madrid, Spain *Age at vaccination:* 16-35 years	*Follow-up:* Up to 96 weeks *Results:* Incident anal infection with HPV16 or HPV18 HPV16	Critical

Study	Study design	Vaccine Product	Study Population	Summary of Key Findings	Risk of Bias
				Follow up week 28: 13 of 106 vaccinated with outcome Follow up week 96: 8 of 93 vaccinated with outcome HPV18 Follow up week 28: 7 of 125 vaccinated with outcome Follow up week 96: 0 of 118 vaccinated with outcome	
Santos 2025	Cohort	Gardasil 4	*Demographics:* Females aged 18-24 years recruited from the Brazilian cities of Ouro Preto and Mariana *Age at vaccination:* Not reported	*Follow-up:* 18 months *Results:* Infection with HPV16 or 18 evaluated by PCR and genotyping HPV16 Baseline: 0 of 89 vaccinated with outcome, 5 of 160 unvaccinated with outcome During follow up: 0 vaccinated with outcome per 100 person-years, 2.42 unvaccinated with outcome per 100 person-years HPV18 Baseline: 0 of 89 vaccinated with outcome, 2 of 160 unvaccinated with outcome During follow up: 0 vaccinated with outcome per 100 person-years, 0 unvaccinated with outcome per 100 person-years	Moderate

Study	Study design	Vaccine Product	Study Population	Summary of Key Findings	Risk of Bias
Malvi 2024	Cohort	Gardasil 4	*Demographics:* Females recruited from 9 study sites across 7 states in India *Age at vaccination:* 10-18 years	*Follow-up:* Up to 5 years *Results:* Persistent HPV16 or HPV18 infection defined as DNA detection in two consecutive cervical samples collected ≥10 months apart. HPV16 1 vs 0 doses 1-PIR*100: 97.2 (93.2 - 98.8) 2 vs 0 doses 1-PIR*100: 100 3 vs 0 doses 1-PIR*100: 100 1 vs 2 doses: 1 of 3022 single dose participants with outcome, 0 of 2311 two-dose participants with outcome. Difference in VE: 2.8 (-6.5 - 8.5). 1 vs 3 doses: 1 of 3022 single dose participants with outcome, 0 of 2172 two-dose participants with outcome. Difference in VE: 2.8 (-6.0 - 8.3). HPV18 1 vs 0 doses 1-PIR*100: 80.8 (65.4 - 89.3) 2 vs 0 doses 1-PIR*100: 83.5 (67.2 - 91.6) 3 vs 0 doses 1-PIR*100: 85.0 (70.2 - 92.4) 1 vs 2 doses: 3 of 3022 single dose participants with outcome, 2 of 2311 two-dose participants with outcome. Difference in VE: 2.7 (-28.6 - 33.9). 1 vs 3 doses: 3 of 3022 single dose participants with outcome, 2 of 2172 two-dose participants with outcome. Difference in VE: 4.2 (-25.7 - 34.0).	Moderate

Study	Study design	Vaccine Product	Study Population	Summary of Key Findings	Risk of Bias
Lasic 2025	Cross-sectional	Multiple vaccines (Gardasil 4 and 9, not disaggregated)	*Demographics:* Females living in Slovenia *Age at vaccination:* 11-15 years	*Follow-up:* Not applicable *Results:* Cervical HPV infection with HPV16, HPV18, or HPV16/18 confirmed by assay HPV16 0 of 253 vaccinated with outcome, 8 of 379 unvaccinated with outcome. Overall RR: 0.09 (0.0 - 1.5) HPV 18 0 of 253 vaccinated with outcome, 4 of 379 unvaccinated with outcome Overall RR: 0.17 (0.0 - 3.1) HPV16/18 0 of 253 vaccinated with outcome, 12 of 379 unvaccinated with outcome Overall RR: 0.06 (0.0 - 1.0)	Critical
Harfouch 2024	Cross-sectional	Products not specified (but US licensed)	*Demographics:* Transgender people assigned male at birth recruited from a single center in Washington, DC *Age at vaccination:* Not reported	*Follow-up:* Not applicable *Results:* Anal infection with HPV16 HPV16 2 of 17 vaccinated with outcome, 13 of 45 unvaccinated with outcome. Overall OR: 0.33 (0.07 - 1.64)	Critical
Salman 2025	Cross-sectional	Products not specified (but US licensed)	*Demographics:* Females aged 18 or older with abnormal cervical cancer screening results,	*Follow-up:* Not applicable *Results:* HPV16 or HPV 18 infection	Critical

Study	Study design	Vaccine Product	Study Population	Summary of Key Findings	Risk of Bias
			recruited from a single center in Canada *Age at vaccination:* Not reported	HPV16 20 of 34 vaccinated with outcome, 48 of 79 unvaccinated with outcome HPV18 0 of 34 vaccinated with outcome, 4 of 79 unvaccinated with outcome	
Delaney-Moretlwe 2024	Cross-sectional	Cervarix	*Demographics:* Females recruited from 66 high-schools in one district of South Africa. Includes HIV+ females. Results adjust for HIV status. HIV+; Female, 15 - 16 years; South Africa; One district, 66 high schools *Age at vaccination:* 15-16 years	*Follow-up:* Not applicable *Results:* HPV infection with HPV16, HPV18, or HPV16/18 confirmed by PCR HPV16 aPR: 0.32 (0.13 - 0.78) HPV18 aPR: 0.38 (0.14 - 1.03) HPV16/18 aPR: 0.36 (0.19 - 0.70)	Serious
Wheeler 2025	Pre/post vaccination study	Products not specified (but US licensed)	*Demographics:* Population based cohorts of females attending routine cervical cancer screening in New Mexico, United States *Age at vaccination:* Not reported	*Follow-up:* Cohort 1: pre-vaccine licensure/introduction, participants who had attended screening between December 1, 2007, and April 30, 2009. Cohort 2: post-vaccine licensure/introduction, participants who attended screening between September 1, 2013, and September 30, 2016 *Results:* Infection with HPV16 or HPV18 confirmed with genotyping assay. Cohort 1 (assumed unvaccinated) was the reference group. HPV16	Moderate

Study	Study design	Vaccine Product	Study Population	Summary of Key Findings	Risk of Bias
				Ages 15-20, relative prevalence reduction: -74.3% (-80.3 - -68.3) Ages 21-25, relative prevalence reduction: -52.6% (-56.9 - -48.3) Ages 26-30, relative prevalence reduction: -11.7% (-20.9 - -2.5) HPV18 Ages 15-20, relative prevalence reduction: -79.0% (-88.5 - -69.5) Ages 21-25, relative prevalence reduction: -62.1% (-68.5 - -55.8) Ages 26-30, relative prevalence reduction: -19.5% (-34.3 - -4.7)	
Pereira 2025	Cohort	Gardasil 4	*Demographics:* HIV+ females treated at a canter in Rio de Janeiro, Brazil. *Age at vaccination:* 18-73 years	*Follow-up:* 4 years post vaccination *Results:* Infection with HPV 16 or HPV18 HPV16 0 of 42 vaccinated with outcome, 4 of 156 unvaccinated with outcome HPV18 0 of 42 vaccinated with outcome, 9 of 156 unvaccinated with outcome	Critical
Bennis 2024	Cross-sectional	Products not specified (but US licensed)	*Demographics:* MSM recruited from the Minneapolis/St. Paul area of Minnesota, United States *Age at vaccination:* Not reported	*Follow-up:* Not applicable *Results:* Detection of HPV16 or HPV 18 from DNA analysis of collected anorectal swabs HPV16	Serious

Study	Study design	Vaccine Product	Study Population	Summary of Key Findings	Risk of Bias
				0 of 29 vaccinated with outcome, 7 of 53 unvaccinated with outcome HPV18 0 of 29 vaccinated with outcome, 5 of 53 unvaccinated with outcome	

Abbreviations: aOR: adjusted odds ratio; aPR: adjusted prevalence ratio; aRR: adjusted relative risk; CI: confidence interval; DNA: deoxyribonucleic acid; HIV+: human immunodeficiency virus positive; HPV: human papillomavirus; HPV16: human papillomavirus type 16; HPV18: human papillomavirus type 18; IQR: interquartile range; MSM: men who have sex with men; N/A: not applicable; NAAT: nucleic acid amplification test; OR: odds ratio; PASSYON: PApillomavirus Surveillance among Sti clinic YOungsters in the Netherlands study; PCR: polymerase chain reaction; PIR: proportional index ratio; PR: prevalence ratio; RCT: randomized controlled trial; RR: relative risk; VE: vaccine efficacy/effectiveness

Supplemental Table 8. Immunogenicity of studies in updated analysis

Study	Vaccine Product(s)	Study Type	Population (sex; age at vaccination)	Special population included	Vaccine dose(s)	Comparator	Key findings	Risk of Bias
Bennis 2024	US licensed products, not-specified	Cross-sectional	Male; Mean age: (vaccinated= 28.0; unvaccinated =39.9)	MSM (all)	≥1 dose	Unvaccinated	**HPV16/18 L1 Ab levels**: Significantly higher in vaccinated vs unvaccinated. Serology patterns among vaccinated consistent with vaccine-induced immunity. **Seropositivity:** Vaccinated MSM had higher seropositivity for any high-risk HPV and for vaccine-type HPV than unvaccinated men. • Unlike unvaccinated men, vaccinated men had high HPV16/18 seropositivity without detectable HPV16/18 DNA.	Serious
Carter 2025	Prior 4vHPV or 9vHPV series, plus 9vHPV booster	Cohort	Male and Female; Age NR	N/A	Prior 2 vs 3 doses, then 1 booster 9vHPV dose	Prior 2-dose or 3-dose 4vHPV or 9vHPV	**HPV16/18 GMTs (1 month post-booster)**: 9vHPV booster dose produced strong anamnestic increases among those who completed the original series with either 2 or 3 doses **Plasmablast and memory B-cell responses:** Rose in parallel to GMTs.	Low
Cortes 2025	2vHPV vs 4vHPV	Cohort	Female; 9-14; 18-25	N/A	1 dose 2vHPV vs 3 doses 4vHPV	2vHPV (9-14 yo) vs 4vHPV (18-25 yo)	**HPV16 GMC (36 months after last dose)**: lower after 1-dose 2vHPV than after 3-dose 4vHPV. **HPV18 GMC (36 months after last dose)**: similar to slightly higher with 1-dose 2vHPV than after 3-dose 4vHPV. **Seropositivity**: HPV16 seropositivity was essentially identical between single-dose 2vHPV girls and 3-dose 4vHPV women. • HPV18 seropositivity was significantly higher in the single-dose 2vHPV group. **Noninferiority:** Single-dose 2vHPV vs 3-dose 4vHPV met NI for HPV18 GMC but not for HPV16 GMC. • Because both types were required, overall NI was not achieved.	Critical

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Day 2025	4vHPV	*In vitro* mechanistic	Female; Age NR	N/A	NR	Unvaccinated	**Neutralization titers:** Previously vaccinated HPV16-seropositive women had marked rises; unvaccinated seropositive women had little change or decline.	Critical
El Hindi 2025	9vHPV	RCT	Male and Female; 9-14	N/A	2 doses	None	**Total HPV IgG levels - all 9vHPV genotypes (1-month after last dose):** types ranged from 561 to 7823 mMU/mL **Seropositivity:** Seropositivity was over 99% against all 9 types	Low
Giuliano 2025	9vHPV	Cohort	Male and Female; 9-14; 9-15; 16-26	MSM	1 vs 2 vs 3 doses (w/age strata)	1 vs 2 vs 3 doses in adolescents; adults compared across heterosexual men, MSM, and women	**Adult GMTs - all 9vHPV genotypes (1 month after last dose:** In adults, MSM had lower GMTs than women for most types, while heterosexual men were often higher than women. **Adolescent GMTs - all 9vHPV genotypes (6 months after last dose):** boys had lower GMTs than girls after 1 dose; within sex, 2 doses produced significantly higher GMTs than 1 dose.	Moderate
Guzun 2025	4vHPV followed by 9vHPV booster	Cohort	Male and Female; 9-24	N/A	Single 4vHPV dose, then 1 dose 9vHPV booster 3-10 years later	Within person, Pre-booster	**HPV16/18 GMCs before 9vHPV boosting:** Before boosting, HPV16/18 GMCs were modest but persistent years after a single 4vHPV dose. **HPV16/18 GMCs one month after 9vHPV booster dose:** GMCs increased about 135-fold for HPV16 and 106-fold for HPV18. **Seropositivity**: Seropositivity remained high years after a single 4vHPV dose and increased to 100% for both types after 9vHPV boosting.	Critical
Henderson 2025	US licensed products, not-specified	Cohort	Female; ≥18	HIV+	NR	Unvaccinated	**HPV16/18 GMTs:** Vaccinated participants had significantly higher HPV16/18 GMTs than unvaccinated participants.	Critical

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							Seropositivity: Vaccinated participants had significantly higher HPV16/18 seropositivity than unvaccinated participants (HPV16 95% vs 47%; HPV18 77% vs 24%).	
Jiamsiri 2024	2vHPV	Cross-sectional	Female; 13-14	N/A	1 dose vs 2 doses	1 dose vs 2 doses	**HPV16/18 GMTs (2 and 4 years after last dose):** Both 1-dose and 2-dose 2vHPV markedly increased HPV16/18 GMTs over prevaccination levels. Titers were significantly higher after 2 doses than after 1 dose at both 2 and 4 years.	Serious
Kemp 2025	9vHPV	Cohort	Female: 9-14	N/A	1 dose vs 2 doses	1 dose vs 2 doses	**HPV GMCs - all 9vHPV genotypes (7, 12, 24, and 36 months after last dose):** GMCs were higher with 2 doses than with 1 dose at every timepoint. • One-dose GMCs plateaued by month 24 and stayed stable to month 36, while 2-dose responses peaked at month 7 and then declined. **Seropositivity:** At month 36, one-dose recipients remained universally seropositive for HPV16/31/58 and mostly seropositive for HPV11/18/33, but had lower rates for HPV6/45/52. • Two-dose recipients were essentially universally seropositive for all 9 types.	Low
Konopnicki 2025	9vHPV	Non-RCT clinical trial	Female; 15-40	HIV+ (all)	2 doses vs 3 doses	2 doses vs 3 doses	**HPV GMCs - all 9vHPV genotypes (7 months after last dose):** GMC rises after 2-dose 9vHPV were of similar magnitude to the 3-dose schedule. **Seropositivity:** 2-dose and 3-dose schedules produced virtually identical month-7 seroconversion across all 9 types. • Overall seroconversion was 97.7% with 2 doses vs 97.9% with 3 doses. **Noninferiority:** 2-dose 9vHPV was non-inferior to 3 doses for month-7 seroconversion across all 9 genotypes	Moderate

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							in women with HIV. • The prespecified risk-difference margin was met in the mITT analysis.	
Lehtinen 2024	2vHPV vs 4vHPV	Cohort	Female; 16-17	N/A	3-dose regimens for each	None	**Correlation of vaccine-induced HPV16 and HPV18 GMTs (2-12 years after last dose):** 2vHPV showed stronger coupling of HPV16 and HPV18 neutralizing responses than 4vHPV. • Among low-responders, both vaccines showed less-robust HPV18 responses.	Moderate
Miyaji 2024	4vHPV	Non-RCT clinical trial	Female; 18-45	SOT recipients	3 doses	Immunocompetent controls	**HPV GMCs - all 4vHPV genotypes (1 month after last dose): S**OT recipients had lower anti-HPV GMCs than immunocompetent controls. • Lower responses were associated with some transplant types (kidney, heart) and heavier immunosuppression. **Seropositivity:** SOT recipients had markedly lower seroconversion rates (57-72%) than immunocompetent controls (100% for all four types).	Critical
Moreira dos Santos 2024	4vHPV	Non-RCT clinical trial	Female; 18-45	Immunosuppressed (all)	Prior 3 doses, then 4th dose in poor responders	Within person, before and after booster	**HPV GMCs - all 4vHPV genotypes (1 month after last dose):** GMCs declined from post-dose 3 to pre-dose 4, then increased modestly after dose 4 for HPV6/16/18. • The largest post-dose-4 rise was for HPV16; HPV11 did not improve. **Seropositivity:** After a 4th dose in prior nonresponders, seroconversion was limited and variable, highest for HPV18 and lowest for HPV6/11/16.	Critical
Porras 2024	2vHPV	RCT	Female; 18-25	N/A	1 dose vs 3 doses	1 dose vs 3 doses	**HPV16/18 GMCs (11-, 14-, and 16-years after last d0se):** 3-dose recipients had persistently higher HPV16/18 GMCs than 1-dose	High

Study	Vaccine Product(s)	Study Type	Population (sex; age at vaccination)	Special population included	Vaccine dose(s)	Comparator	Key findings	Risk of Bias
							recipients through 16 years. • Both groups showed only modest waning, indicating durable long-term Ab persistence. **Seropositivity:** HPV16/18 seropositivity stayed ~99-100% in both 1-dose and 3-dose groups through 16 years.	
Quang 2025	4vHPV	Cohort	Female; 15-19	N/A	0 vs 1 vs 2 vs 3 prior doses	0 vs 1 vs 2 vs 3 prior doses	**HPV16/18 IgG and IgA1 (6 years after last dose):** 1 prior dose produced levels significantly higher than unvaccinated levels. • Responses after 1 dose were generally below 2- or 3-dose groups, although many differences were not statistically significant.	Serious
Ron 2025	9vHPV	Non-RCT clinical trial	Male; 16-35	HIV+ (all)	3 doses	None	**HPV GMCs - all 9vHPV genotypes (96 weeks after last dose):** GMCs rose sharply by week 28 for all 9 genotypes and remained above baseline at week 96. • HPV16 showed the strongest Ab response, while HPV18 responses were weaker. **Seropositivity:** Seroconversion was nearly 100% for all 9 genotypes at week 28 and remained above 85% for all types at week 96.	Critical
Sauvageau 2025	4vHPV	RCT	Female; 9-11 at primary series; 13-16 at booster/randomization	N/A	2 doses vs 2+1 booster (0,6 vs 0,6,60 months)	2 doses vs 2+1 booster	**HPV GMCs - all 4vHPV genotypes (5-10 years after last dose):** GMCs remained stable over time after the 2-dose series alone. • A delayed booster produced large and sustained GMC increases for HPV6/11/16/18 versus the 2-dose group. • Detectable antibodies to HPV6/11/16/18 remained 100% in both	Low

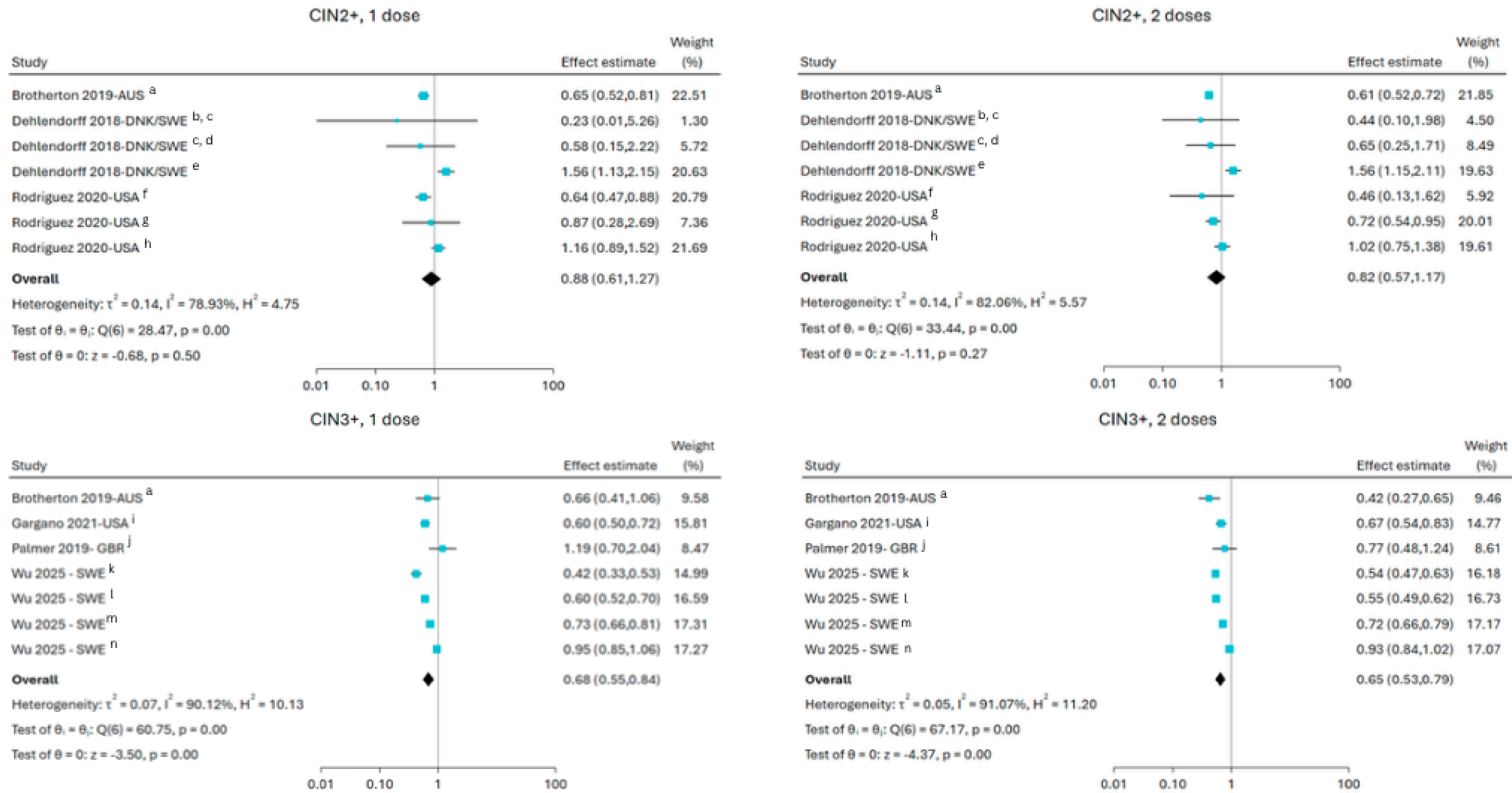
Study	Vaccine Product(s)	Study Type	Population (sex; age at vaccination)	Special population included	Vaccine dose(s)	Comparator	Key findings	Risk of Bias
							the 2-dose and 2+1-dose groups across 5, 7.5, and 10 years	
Steinberg 2025	9vHPV	Cohort	Sex NR; 9-14	N/A	2-dose series	None	**HPV16/18 IgG GMCs (1 month-3 years after last dose):** GMCs peaked after dose 2, then waned by 1 and 3 years but stayed above post-dose-1 levels. • Females and younger children tended to have higher long-term GMCs. **Seropositivity:** All participants were seropositive for all nine types after series completion, and 92% remained seropositive for all types at 3 years. • HPV18 and HPV45 had the lowest 3-year persistence.	Serious
Tortellini 2025	9vHPV	Cohort	Male and Female; >18	HIV+ (all)	3 doses	Stratified by prior HPV infection status and CD4 levels	• **Polyfunctional T-cell responses**: Increased in both prior-HPV-positive and prior-HPV-negative participants, with no significant between-group differences. • Participants with baseline CD4 >500 cells/μL showed stronger responding and polyfunctional T-cell responses than those with CD4 ≤500.	Serious
Watson-Jones 2025	2vHPV	RCT	Female; 9-14	N/A	1 dose vs 2 doses	1 dose vs 2 doses	**HPV16/18 GMCs (1-5 years after last dose):** GMCs remained lower after 1 dose than after 2 doses through month 60. • One-dose titers plateaued by ~month 12, whereas 2-dose titers peaked earlier and waned from higher levels. **Seropositivity:** At 5 years, HPV16 seropositivity after 1 dose remained above 99% and was non-inferior to 2 doses. • HPV18 seropositivity remained high at about 98% **Noninferiority:** At month 60, 1-dose 2vHPV was non-inferior to 2 doses for	Some concerns

Study	Vaccine Product(s)	Study Type	Population (sex; age at vaccination)	Special population included	Vaccine dose(s)	Comparator	Key findings	Risk of Bias
							HPV16 seropositivity. • HPV18 seropositivity remained high but did not meet the prespecified NI margin.	
Wen 2024	4vHPV	RCT	Female; 20-26; 27-45	N/A	NR	Placebo	**HPV GMTs - all 4vHPV genotypes (13 years after last dose):** GMTs were highest for HPV16 and lowest for HPV18 across vaccinated groups. **Seropositivity:** Seropositivity exceeded 80% across vaccinated groups; lowest for HPV18 and highest for HPV16.	Low
Wiek 2025	4vHPV	Case control	Female; 13-21	N/A	Primarily 3 doses	Breakthrough cases vs random control (HPV18/45-negative at baseline, regardless of vaccine doses)	**Total HPV18 Ab titers (6 months to 8 years after last dose):** Pre-infection anti-HPV18 titers were lowest in breakthrough cases and highest in high-risk controls. • Higher anti-HPV16/18 titers were associated with lower odds of breakthrough infection in pooled analyses (combined with HPV16 analysis in the same cohort).	Serious
Wiggins 2025	2vHPV and 9vHPV	RCT	Female; 9-14	N/A	1 vs 2 vs 3 doses	1 vs 2 vs 3 doses for both 2vHPV and 9vHPV	**Memory B-cell responses (1-36 months)**: Memory B-cell responses were similar across 1, 2, and 3 doses at month 1. • From months 7-36, responses ranked 3-dose highest, 2-dose intermediate, and 1-dose lowest.	Some concerns
Zha 2024	4vHPV, with comparison to 2vHPV and 9vHPV groups	Cross-sectional	Female; 15-45	N/A	NR	2vHPV vs 4vHPV vs 9vHPV	**HPV16/18 GMTs:** 4vHPV GMTs for HPV16/18 were lower than those seen with 2vHPV and 9vHPV groups. • 2vHPV had the highest HPV16/18 GMTs. **Seropositivity:** Seropositivity for HPV6/11/16/18 exceeded 88% after 4vHPV, but HPV16/18 seropositivity was slightly lower than in the other vaccine groups.	Critical

Study	Vaccine Product(s)	Study Type	Population (sex; age at vaccination)	Special population included	Vaccine dose(s)	Comparator	Key findings	Risk of Bias
Zhong 2025	9vHPV	Cohort	Female; 18-26	N/A	3 doses	None	**HPV GMTs - all 9vHPV genotypes (7 months-1 year after first dose):** Year-3 GMTs had fallen substantially from month 7 across all 9 types. • Despite waning, Ab responses persisted in a plateau phase. **Seropositivity:** Year-3 seropositivity remained high for all 9 types after 9vHPV, although it was lowest for HPV45.	Serious

Abbreviations: 2vHPV: Recombinant Human Papillomavirus Bivalent Vaccine; 4vHPV: Recombinant Human Papillomavirus Quadrivalent Vaccine; 9vHPV: Recombinant Human Papillomavirus 9-valent Vaccine; Ab: antibody; DNA: deoxyribonucleic acid; HPV: human papillomavirus; HPV6: human papillomavirus type 6; HPV11: human papillomavirus type 11; HPV16: human papillomavirus type 16; HPV18: human papillomavirus type 18; HPV45: human papillomavirus type 45; HIV+: human immunodeficiency virus positive; IgA: immunoglobulin A; IgG: immunoglobulin G; GMT: geometric mean titer; GMC: geometric mean concentration; MSM: men who have sex with men; N/A: not applicable; NI: Noninferiority; NR: not reported; RCT: randomized controlled trial; ROB: risk of bias; SOT: solid organ transplantation

Supplemental Figure 1. Forest plot and pooled analysis: CIN2+ and CIN3+ by doses (one or two) compared with no doses, cohort studies. HPV vaccination at various ages.



[a]Age at vaccination, 12-15 years
[b]Age at vaccination, <16 years
[c]Study upper bound recalculated manually to ensure symmetry of the 95% confidence interval around the effect estimate.
[d]Age at vaccination, 17-19 years
[e]Age at vaccination, 20-29 years
[f]Age at vaccination, 9-14 years
[g]Age at vaccination, 15-19 years
[h]Age at vaccination, >20 years
[i]Age at vaccination, 9-26 years
[j]Age at vaccination, 12-18+ years
[k]Age at vaccination, 10-14 years
[l]Age at vaccination, 15-16 years
[m]Age at vaccination, 17-20 years
[n]Age at vaccination, 21-35 years