

## **Executive Summary**

### **Safety and Effectiveness of Human Papillomavirus (HPV) Vaccine: A Systematic Review and Meta-analysis**

#### **Background**

Human papillomavirus (HPV) is the most common sexually transmitted infection globally and is responsible for approximately 90% of cervical and anal cancers and more than half of oropharyngeal, penile, vaginal, and vulvar cancers in the United States. Although most infections resolve spontaneously, persistent infection with high-risk HPV types can lead to precancerous lesions and invasive cancers, resulting in substantial human and economic costs. HPV-associated disease screening and treatment account for an estimated \$9 billion annually in direct medical costs in the U.S.

Since 2006, three HPV vaccines have been licensed in the U.S. – bivalent (2vHPV), quadrivalent (4vHPV), and 9-valent (9vHPV) – with 9vHPV (Gardasil 9) now the only HPV vaccine in use domestically. Following vaccine introduction, the incidence of HPV-associated precancers and cancers has declined substantially both in the US and globally. HPV vaccines were originally licensed as a three-dose series, but accumulating evidence over time has supported reduced-dose schedules. In January 2026, without discussion of the evidence, the US Department of Health and Human Services (HHS) announced a change to the childhood immunization schedule, recommending a single HPV vaccine dose for children ages 11–12, creating a divergence from FDA licensure, which continues to support a two-dose schedule. A federal judge subsequently struck down HHS’s immunization schedule.

This review was conducted to evaluate the evidence on HPV vaccine safety, effectiveness, and immunogenicity, with particular focus on whether a single-dose regimen provides protection comparable to the standard two-dose schedule.

## **Methods**

This systematic review and meta-analysis incorporated 121 new peer-reviewed studies published between September 2024 and January 2026 with 153 studies from two previously published comprehensive Cochrane reviews (2025) related to vaccines approved in the US that assessed our outcomes of interest. 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.

## **Results**

### *Safety*

The safety findings were broadly reassuring. Across 25 studies evaluating safety outcomes, there was no credible evidence of increased risk of serious adverse events, adverse pregnancy outcomes, Guillain-Barré syndrome, chronic fatigue syndrome/myalgic encephalomyelitis, complex regional pain syndrome, infertility, premature ovarian failure, or paralysis associated with HPV vaccination. Serious adverse events were rare and occurred at similar rates among vaccinated and comparator groups. Adverse pregnancy outcomes, including miscarriage, stillbirth, congenital abnormalities, and preterm birth, were also not increased following vaccination. These findings are consistent with prior Cochrane reviews and reinforce the strong safety profile of HPV vaccines.

The only area of divergence from prior reviews involved postural orthostatic tachycardia syndrome (POTS). Two smaller recent studies suggested a possible association, but these findings were inconsistent with larger studies and prior randomized and observational evidence. One study relied on VAERS reports and likely introduced substantial age-related confounding by comparing adolescents receiving HPV vaccine to much younger children receiving other vaccines. Overall, the preponderance of evidence continues to support the conclusion that HPV vaccination is not associated with an increased risk of POTS.

### *Vaccine Effectiveness and Efficacy*

The review found strong and consistent evidence of vaccine effectiveness against cervical cancer, precancerous lesions, and persistent HPV infection. Meta-analysis



showed that vaccinated individuals had a 65% lower risk of invasive cervical cancer, with even greater protection when vaccination was initiated at or before age 16. Vaccination was also associated with significant reductions in high-grade cervical lesions, including cervical intraepithelial neoplasia grades 2 and 3 (CIN 2+ and 3+) – moderate to severe pre-cancerous conditions typically caused by high-risk HPV, particularly when vaccination occurred before likely HPV exposure. Strong protective effects were also observed for persistent infection with the two most dangerous, high-risk strains of HPV (HPV 16/18), with randomized trials demonstrating 84–90% reductions in persistent infection. Emerging evidence also supports protection against oropharyngeal, vulvar, vaginal, and anal precancers and cancers, although long-term evidence for non-cervical cancers remains more limited.

Importantly, evidence comparing one-dose and multi-dose schedules was increasingly supportive of reduced-dose strategies. Randomized trials found no meaningful differences between one- and two-dose schedules for serious adverse events, pregnancy outcomes, or persistent HPV16/18 infection through five years of follow-up. Meta-analyses of cohort studies found comparable protection against CIN2+ and CIN3+ among individuals receiving one, two, or three doses. These findings suggest that a single dose may provide similar clinical protection for key outcomes in females, although evidence for long-term durability for males and non-cervical disease endpoints remain limited.

### *Immunogenicity*

Immunogenicity findings further support reduced-dose schedules while also showing some advantages for additional doses. One dose consistently generated strong and durable immune responses, often maintaining high seropositivity for HPV16 and HPV18 over time. While two- and three-dose schedules generally produced higher antibody concentrations and, in some studies, more durable responses, the clinical relevance to these higher concentrations is unclear. Vaccination earlier in adolescence was associated with stronger and longer-lasting immune responses. Evidence suggested that while one-dose schedules may not always meet formal noninferiority criteria for every HPV type – particularly HPV18 – the overall immune response remained robust across dosing schedules.



## **Conclusions**

Overall, the updated evidence continues to strongly support the safety and effectiveness of US-approved HPV vaccines and remains consistent with prior Cochrane reviews. The totality of evidence indicates no association between HPV vaccination and serious adverse events, while demonstrating substantial protection against cervical cancer, high-grade cervical lesions, and persistent HPV infection. Emerging evidence suggests that a single-dose schedule may offer protection comparable to two- and three-dose regimens for key outcomes in females, supporting ongoing policy discussions around dose reduction. However, important evidence gaps remain for male populations, non-cervical cancers, and long-term durability of single-dose protection, underscoring the need for continued surveillance and longer-term follow-up studies.