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Recommendations and guidance for human papillomavirus (HPV) vaccination for adults in Taiwan

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A B S T R A C T

Human papillomavirus (HPV) is the most prevalent viral infection globally, transmitted primarily through sexual or intimate skin-to-skin contact. Certain HPV types can cause anogenital warts and has the potential to cause cervical cancer, other anogenital, and oropharyngeal cancers. Adjuvanted, non-live, HPV recombinant

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vaccines, including the bivalent, quadrivalent, and 9-valent vaccines, are widely recommended for adolescents and young adults to prevent HPV infection and lower the incidence of HPV-related cancers. However, recommendations for adults aged 26 years or older have been lacking due to insufficient evidence until recently. The Working Group on Adult Immunization Practice of the Infectious Diseases Society of Taiwan (IDSTAIP working group) addressed this gap and drafted recommendations for HPV vaccination in adults using the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) system. These recommendations were then reviewed and revised by expert panels and endorsed by eight national medical societies. This document is positioned as a guidance to provide recommendations for HPV vaccination in adults, considering gender, age, immune status, and prior HPV vaccination history. Safety evaluations, dosing schedules, and special considerations regarding the occupational exposure of healthcare providers, based on potential modes of HPV transmission, are provided. In summary, a 3-dose HPV vaccination schedule is recommended for all adults through age 45 years, regardless of sex, to prevent genital warts, anogenital cancers, as well as oropharyngeal infections and cancers. This guidance serves to assist healthcare providers in facilitating shared decision-making but does not supersede clinical judgment in assessing individual risk and making specific recommendations.

1. Introduction

Human papilloma viruses (HPV) are non-enveloped, double-stranded DNA viruses, with over 200 identified types. They are epitheliotropic and primarily infect squamous epithelia, including the skin, as well as the anogenital and oropharyngeal mucosa. Sexual transmission is the primary route of anogenital HPV infection. The estimated global prevalence of cervical HPV in women with non-cancerous cytology was 11.7 % between 1995 and 2009, varying by region and country, immune status, co-infection with other sexually transmitted infections and sexual trends in men.[1] In Taiwan, the prevalence of HPV in women with normal cytology was 20.9 % in 2008.[2] The five most common HPV types found in women worldwide were HPV16 (3.2 %), HPV18 (1.4 %), HPV52 (0.9 %), HPV31 (0.8 %), and HPV58 (0.7 %).[1] The leading HPV types in Taiwan were similar, including HPV16 (5.8 %), HPV58 (5.3 %), HPV53 (4.1 %), HPV52 (3.8 %), and HPV18 (2.3 %).[2] High-risk mucosal HPV types, predominantly HPV types 16, 18, 31, 33 and 45, have been associated with the majority of cervical, penile, vulvar, vaginal, anal and oropharyngeal cancers and pre-cancers.[3]

Most HPV infections are asymptomatic and may clear spontaneously.[4,5] Certain HPV types can cause genital warts within 6–10 months after the initial infection, while cancers may develop after a minimum of 5–10 years, with an average of 20–25 years.[3,6] It is estimated that HPV is responsible for 91 % of cervical and anal cancers, 69 % of vaginal and 75 % of vulvar cancers, 63 % of penile cancer, and 70 % of oropharyngeal cancer.[5] Globally, HPV caused an estimated 620,000 cancer cases in women and 70,000 cancer cases in men in 2018.[7]

Currently, three adjuvanted recombinant HPV vaccines are approved for use in Taiwan: the bivalent (Cervarix, 2vHPV), quadrivalent (Gardasil, 4vHPV), and 9-valent (Gardasil 9, 9vHPV) vaccines (Table 1).[8–13] Prophylactic vaccination against HPV can prevent infection and significantly reduce the burden of HPV-related diseases.[14–16] The HPV types targeted by the 9vHPV vaccine account for approximately 90 % of HPV-attributable cancers worldwide.[17,18]

These vaccines are widely recommended for adolescents and young adults through age 26 years.[19] HPV vaccination programs primarily target adolescents, as the vaccine is most effective in HPV-naïve individuals when administered before the onset of sexual activity and potential HPV exposure.[5,20] Recommendations for adults aged 26 years or older are often lacking due to insufficient evidence, despite a large

Table 1
Comparison of three HPV adjuvanted recombinant vaccines.

Trade name	Cervarix[8]	Gardasil[9]	Gardasil 9[10]
Generic name	Bivalent vaccine (HPV types 16 and 18)	Quadrivalent vaccine (HPV types 6, 11, 16 and 18)	Human Papillomavirus 9-valent Vaccine, Recombinant (HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58)
Adjuvant[a]	500 μg *aluminum hydroxide,*50 μg 3-O-desacyl-4′-monophosphoryl lipid A	225 μg *amorphous aluminum hydroxyphosphate sulfate*	500 μg *amorphous aluminum hydroxyphosphate sulfate*
First approval year	2007	2006	2014
Manufacturer	GlaxoSmithKline	Merck	Merck
Dosage[b]	3 doses each of 0.5 ml at 0, 1, 6 months	3 doses each of 0.5 ml at 0, 2, 6 months	3 doses each of 0.5 ml at 0, 2, 6 months
Disease prevention	Premalignant genital lesions Cervical cancers	Genital warts Premalignant anogenital lesions Anogenital cancers	Genital warts Premalignant anogenital lesions Anogenital, oropharyngeal and other head and neck cancers
Approved indications in Taiwan	Prevention of premalignant genital lesions and cervical cancers causally related to certain oncogenic HPV types in women aged 9–25 years of age	Prevention of genital warts, premalignant anogenital lesions and anogenital cancers causally related to certain oncogenic HPV types in individuals aged 9–26 years of age and women aged 27–45 years of age	Prevention of genital warts, premalignant anogenital lesions, anogenital cancers, oropharyngeal and head and neck cancer, causally related to certain oncogenic HPV types in individuals aged 9–45 years of age
Contraindications[c]	Hypersensitivity to the active substances or to any of the excipients	Hypersensitivity, including severe allergic reactions to yeast (a vaccine component), or after a previous dose of Gardasil	Hypersensitivity, including severe allergic reactions to yeast (a vaccine component), or after a previous dose of Gardasil 9 or Gardasil
Costs per dose in Taiwan[d]	NT$3000–3500	NT$3000–3500	NT$5000–6500

Abbreviation: HPV, human papillomavirus.

[a] Aluminum salts, such as aluminum hydroxide and aluminum potassium sulfate, have been used safely in vaccines for more than 70 years. Adjuvants help the body to produce an antibody response strong enough to protect the person from the disease they are being vaccinated against. Adjuvanted vaccines can cause more local reactions (such as redness, swelling, and pain at the injection site) and more systemic reactions (such as fever, chills, and body aches) than non-adjuvanted vaccines.[11].

[b] All three HPV vaccines should be administered intramuscularly in the deltoid region of the upper arm or the anterolateral area of the thigh. The preferred site of administration is the deltoid region of the upper arm.[12].

[c] **Each vaccine was found to be safe and effective in clinical trials**. Cervarix was studied in clinical trials involving more than 30,000 females. Gardasil was studied in clinical trials involving more than 29,000 females and males. Gardasil 9 was studied in clinical trials involving more than 15,000 females and males. Since late 2016, Gardasil 9 has been the only HPV vaccine available for use in the United States.[13].

[d] Females born in 1994 or later are publicly funded (school-based program). Other vaccinee must pay out-of-pocket.

burden of disease in older adults. This guidance aims to provide recommendations for HPV vaccination in adults, taking into account factors such as gender, age, immune status, and previous HPV vaccination history.

2. Methods

2.1. Working group and expert panels

The Adult Immunization Practice of the Infectious Diseases Society of Taiwan (IDSTAIP) Working Group is committed to developing updated recommendations and guidance/guidelines for adult immunization, complementing those issued by the Taiwan Advisory Committee on Immunization Practices (ACIP). This working group is composed of 10 adult infectious diseases specialists, 9 pediatric infectious diseases specialists, and 1 pharmacist from 13 hospitals across Taiwan, all of whom were responsible for drafting the recommendations. The recommendations were subsequently reviewed and revised by expert panels during a series of consensus meetings. These panels included experts from the IDST and seven other national medical societies in Taiwan, including the Society of Colon and Rectal Surgeons, the Taiwan AIDS Society, the Taiwan Association of Family Medicine, the Taiwan Association of Gynecologic Oncologists, the Taiwanese Dermatological Association, the Taiwan Society of Otorhinolaryngology Head and Neck Surgery, and the Taiwan Urological Association.

2.2. Process of guidance development

From May to October 2023, the committee held six meetings to identify pertinent clinical questions using the population, intervention, comparison, outcome (PICO) framework, based on expert opinions and a literature review of HPV transmission modes and local epidemiology. The committee developed search strategies, conducted literature reviews for each PICO; assessed quality of evidence, determined the strength of recommendations, and synthesized draft recommendations. Two in-person meetings with internal and external expert review panels were held to provide feedback and conduct a critical evaluation of the draft recommendations. In November 2023, the final version of the recommendations was reviewed and endorsed by the IDST and 7 medical societies/associations. Prior to the initiation of the guidance development process and upon completion of the final draft of recommendations, all committee members disclosed potential conflicts of interest.

We conducted a comprehensive search of PubMed, Medline, Embase, the Cochrane Database, and Clinicaltrial.gov for systemic review, meta-analysis, randomized controlled trials and observational studies that compared HPV vaccination in adults to placebo or standard care, focusing on vaccine efficacy, effectiveness or immunogenicity. English-language articles published before May 31, 2023 were included. The full search strategies, search terms, and study eligibility criteria for the meta-analysis are available in Fig. 1.

The working group employed the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) system to assess both the quality of evidence and the strength of recommendations.[21] The GRADE system categorizes the quality of evidence as high, moderate, low, or very low, based on factors such as risk of bias, consistency of results, directness of evidence, precision, and publication bias in the included studies. These classifications reflect varying levels of confidence in the estimates of treatment effects.[22] While vaccine efficacy was considered a critical outcome, the lack of efficacy data in immunocompromised populations did not impact the directness of the evidence when rating its quality in the GRADE system. Given the limited evidence in this subgroup, expert consensus played a key role in guiding this decision. The strength of recommendations is categorized as either

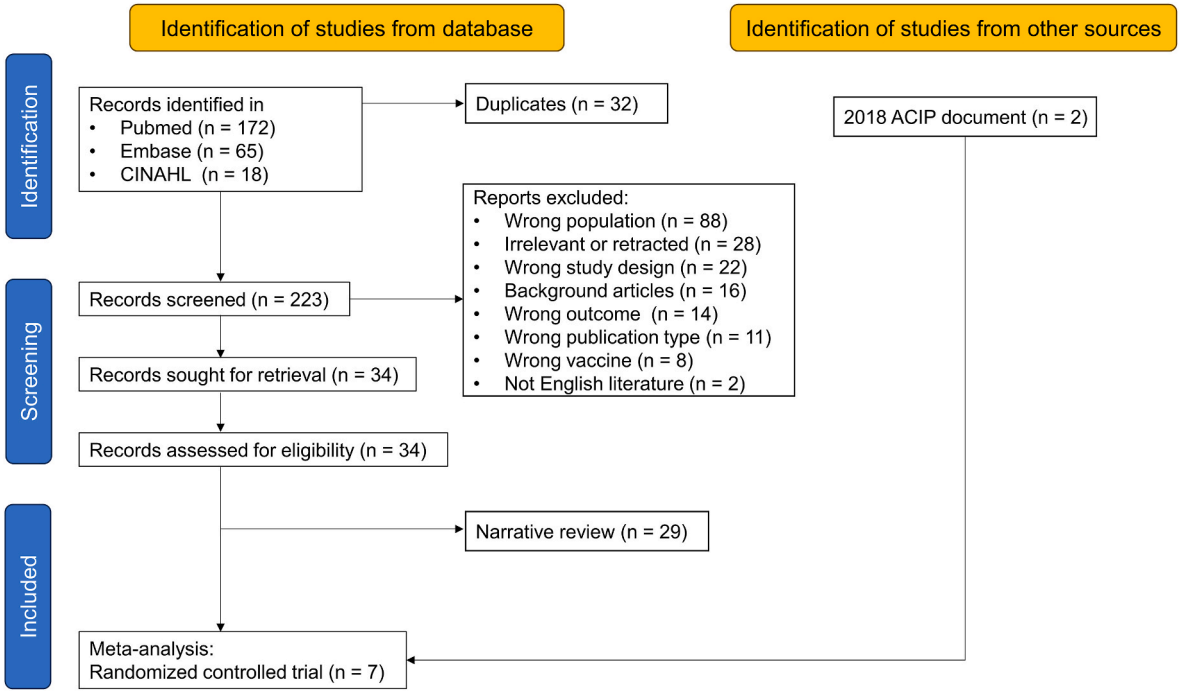


Fig. 1. PRISMA flowchart and search strategy[a] for a meta-analysis of HPV vaccine efficacy among adult women aged 27–45 years.
Fig. 1 footnotes.
Abbreviations: ACIP, Advisory Committee on Immunization Practices; HPV, human papillomavirus.
[a]A literature search was conducted spanning the period from the latest ACIP recommendation for the use of the HPV vaccine in adults aged 27 through 45 years, covering 2018 to 2023. The search utilized the following terms: (effectiveness OR efficacy OR immunogenicity OR safety) AND (adult women) AND (HPV vaccine) AND (nine-valent OR 9-valent OR nona-valent OR nonavalent OR 9vHPV OR 4-valent OR quadrivalent OR 4vHPV OR 2-valent OR bivalent OR 2vHPV), and included only the literature focusing on human subjects.

Table 2
Recommendations and guidance for HPV vaccination in Adults.

Risk group/Clinical Condition	Recommendations	GRADE Strength of Recommendation/Quality of Evidence	Comments
Genital warts, genital and anal cancers			
Adult women through age 26 years	HPV vaccination (primary series)	Strong/High (1 A)	HPV vaccination is recommended for all women through age 26 years who are not adequately vaccinated.
Adult women aged 27 through 45 years	Catch-up HPV vaccination through shared decision-making	Weak/Moderate (2 B)	• 9vHPV vaccine shows non-inferior immunogenicity to those administered to younger women. • 4vHPV vaccine prevents any cases of CIN or genital warts from vaccine-type virus for up to a decade post-vaccination. • 2vHPV vaccine exhibits 90.5 % efficacy in reducing persistent infection, any CIN, or external genital lesions. • All three vaccines are generally well-tolerated.
Adult men through age 26 years	HPV vaccination	Strong/High (1 A)	
Adult men aged 27 through 45 years	Catch-up HPV vaccination through shared decision-making	Weak/Very Low (2D)	No randomized controlled trial of HPV vaccination for adult males aged 27 through 45 years
Immunocompromised adults			
People with HIV	HPV vaccination	Strong/Moderate (1 B)	Deferring vaccination until receiving antiretroviral therapy and virologically suppressed with CD4 counts $\geq$200 cells/mm^3
Transplant recipients	HPV vaccination	Weak/Very low (2D)	Before transplantation or at least one year post-transplantation
Autoimmune inflammatory rheumatic diseases	HPV vaccination	Weak/Very low (2D)	
Oropharyngeal HPV infection			
Adults through age 45 years	HPV vaccination	Weak/Moderate (2 B)	The current recommendation relies on 2vHPV and 4vHPV vaccines for females aged 15–26 and people with HIV. Research is ongoing for the efficacy of 9vHPV against oral HPV infections.
Oropharyngeal cancer			
Adults through age 45 years	HPV vaccination	Weak/Very low (2D)	Limited evidence currently supports the use of HPV vaccination to reduce oropharyngeal cancer incidence. However, preventing oral HPV infection at specific sites, similar to the success in preventing cervical and anorectal cancers, can significantly impact oropharyngeal cancer prevention. For this reason, the panel recommends that individuals through 45 years receive HPV vaccination to prevent oropharyngeal cancer.
Dosing schedule			
All adults	3-dose schedule HPV vaccination at 0, 1–2, 6 months	Strong/High (1 A)	• The recommendation is derived from evidence obtained from randomized controlled trials. • Less frequent dosing schedules (1-dose and 2-dose) showed promising results in post-hoc analyses of previous trials, but real-world data showed discrepant results. • Investigation into the two-dose vaccination is ongoing.
Heterologous vaccination regimen	9vHPV vaccination	Expert opinion	
Adults who have completed 4vHPV or 2vHPV vaccination series	No recommendation for additional 9vHPV vaccination	Weak/Low (2C)	

Abbreviations: CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus.
*Strength of recommendations: 1, strong; 2, weak. Quality of evidence: A, high; B, moderate; C, low; D, very low.
The recommendations are stratified by gender and age as endpoints, and evidence of clinical trials and real-world data varies by gender and age group. Nevertheless, gender-neutral program of HPV vaccination for adults through age 26 years is strongly recommended, with high quality of evidence supporting this approach. The recommendation is limited to adults through age 45 years, as HPV vaccines are not licensed for use in adults aged >45 years, and only a limited amount of indirect evidence is available from extrapolation of real-world data.

strong or weak, based on an evaluation of the balance between benefits and harms, cost and resource implications, values and preferences, as well as feasibility and acceptability of the intervention.[23] The GRADEpro Guideline Development Tool was used to generate concise summary tables and streamline the guidance development process.[24] The final recommendations and guidance for HPV vaccination are outlined in Table 2.

3. Epidemiology

3.1. Cervical cancer

Cervical cancer is the most prevalent cancer associated with HPV infection.[7] A cross-sectional worldwide study identified HPV types 16, 18, 31, 33, 35, 45, 52, and 58, as the most common types attributing to cervical cancer, accounting for 91 % of cases. HPV16 and 18 were recognized as the most carcinogenic genotypes, responsible for 71 % of cases.[25] The distribution of HPV genotypes differs in older women, with an increasing prevalence of high-risk HPV types other than HPV16 and 18, as well as non-high-risk HPV types.[18,26,27] In Taiwan, in addition to HPV16, strains such as HPV31, 33, 52, and 58 were notable contributors to high-grade cervical neoplasia in 1992.[28] In the post-vaccine era, a 10-year molecular epidemiology study (2010–2020) demonstrated a significant shift in predominant HPV genotypes, with HPV16, 52, and 58 collectively accounting for over 70 % of high-risk HPV infections in women annually.[29,30] Vaccines targeting HPV16 and 18 infections may prevent approximately half of cervical cancer cases and high-grade precursor lesions in Taiwan, however, expanding coverage to include HPV31, 33, 52, and 58 may prevent up to an additional 40 %. The rising prevalence of HPV58 among women aged 30–50 years, highlights the importance of HPV vaccination for mid-adult women.

3.2. Anogenital HPV infection and cancer

The cumulative incidence of anogenital HPV infection is similar for both adult men and women who are sexually active, ranging from 29 % to 40 % over a 12-month period in the US.[31–33] The prevalence of anogenital HPV infections in women declines sharply with age, with rates of 17, 10, 7, 5, and 1.5 cases per 100 person-years in the 15–19, 20–24, 25–29, 30–54, and over 55 age groups, respectively. In men, the rates remain relatively constant with age, at 39, 41, and 33 cases per 100 person-years in the 18–30, 31–44, and 45–70 age groups, respectively.[33,34] While anal cancer is relatively uncommon in the general population, with an estimated incidence of 2 cases per 100,000 person-years, the risk is significantly higher among specific groups. The incidence of anal cancer was 85 cases per 100,000 person-years among HIV-positive men who had sex with men (MSM); 32 among HIV-positive, heterosexual men; 22 among HIV-positive women; and 19 among HIV-negative MSM.[35] Annually, approximately 70,000 cases of penile, anal, oropharyngeal, and other head and neck cancers, associated with HPV infection, are reported globally in men.[7] More than 80 % of these cancers are caused by HPV16 and 18, increasing to over 90 % when HPV16, 18, 31, 33, 45, 52, and 58 are included.[17] Therefore, addressing the prevention of HPV infection in men is crucial to meet this unmet need.

3.3. Oropharyngeal HPV infection and cancer

The prevalence of oropharyngeal HPV infection is generally lower than that of anogenital HPV infection. A higher prevalence of oropharyngeal HPV infection in men compared to women (10.1 % vs 3.6 %) reflects the gender distribution observed in HPV-associated oropharyngeal cancer.[36] In a U.S. population-based study (2011–2014), the prevalence of oral HPV infection, particularly HPV16, was significantly higher in men, especially those with a higher number of lifetime oral-sexual partners, concurrent genital HPV infections, and MSM.[37] Older age and intensity of current smoking are independent risk factors for oropharyngeal HPV infection and a high oral HPV viral load.[38] In Taiwan, the incidence rate of oropharyngeal cancer continues to rise despite declining prevalence of known risk factors such as betel quid chewing and cigarette smoking.[39] A nationwide study reported that the incidence rates of HPV-related head and neck cancer rose from 1.3 to 3.3 per 100,000 between 1995 and 2009, increasing more rapidly than HPV-negative cases.[40] A multicenter study further demonstrated that HPV-positive oropharyngeal cancer accounted for one-third of all oropharyngeal cancer cases, with a significant 181 % increase in incidence between the period of 1999–2002 to 2011–2014. Among patients with HPV-positive oropharyngeal cancer, the leading HPV subtypes were 16 and 58, accounting for 70 % and 12 %, respectively.[41]

4. What is the recommendation for HPV vaccination for adult women?

4.1. Recommendations

1. HPV vaccination is recommended for all women through 26 years of age who have not been adequately vaccinated. *(Strong recommendation, high quality of evidence) (1A)*
2. For adult women aged 27 through 45 years who were not adequately vaccinated before the age of 26, catch-up vaccination can be considered through shared clinical decision-making. *(Weak recommendation, moderate quality of evidence) (2B)*
3. For women over 45 years of age, HPV vaccination is not recommended due to limited supporting evidence. *(Weak recommendation, very low quality of evidence) (2D)*

4.2. Summary of the evidence

4.2.1. Women through age 26 years

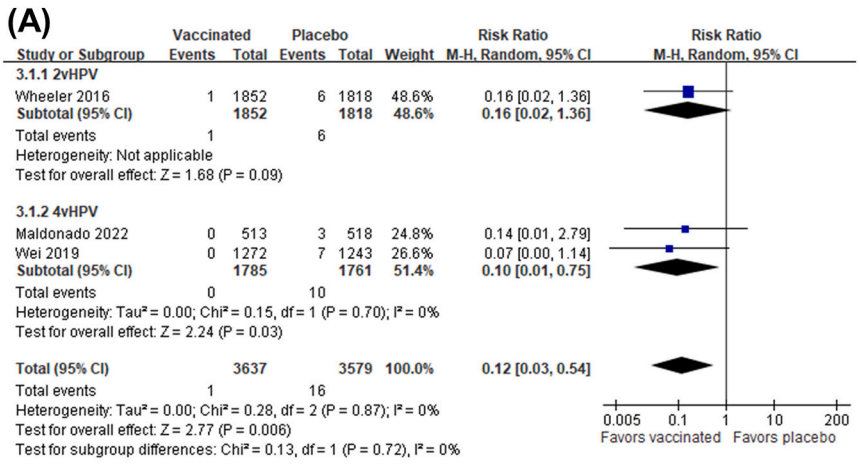
The HPV vaccine is most effective when administered to adolescents, especially those aged 9–14 years, as it elicits a particularly robust antibody responses in this age group, with vaccine effectiveness ranging from 74 to 93 %.[42] Although immunogenicity generally declines with age, two phase 3 studies of the 9vHPV vaccine in Chinese females and an international cohort showed consistent antibody responses across different age groups, demonstrating noninferiority in geometric mean titers (GMT) of antibodies for those aged 9–19 years and 27–45 years compared to those aged 16–26 years.[43,44]

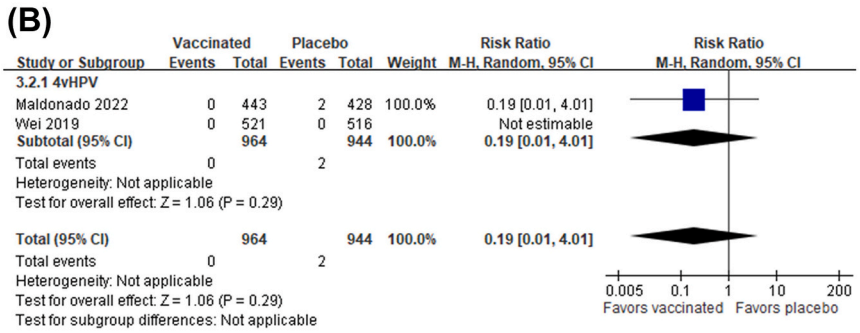
HPV vaccines effectively prevent infection by targeted HPV types. The 2vHPV vaccine demonstrated 82 % efficacy over 11 years against HPV16 and 18 incident infection in adult women aged 18–25 years,[45] indicating sustained protection for at least a decade. Based on antibody response data, there is potential for extended protection, possibly lasting lifelong.[46] The 4vHPV vaccine significantly reduced persistent HPV infection at 12 months post-vaccination by 97.5 % and demonstrated 100 % efficacy against both low-grade and high-grade cervical diseases associated with HPV 6, 11, 16, and 18 in adult women aged 20–45 years.[47] A randomized controlled trial (RCT) comparing the 9vHPV and 4vHPV vaccines in women aged 16–26 years demonstrated significant advantages of the 9vHPV vaccine.[48] It showed a 28.5 % improvement in efficacy against persistent infection for shared HPV types (6, 11, 16, and 18), and a remarkable 96.7 % efficacy for additional HPV types exclusive to the 9vHPV vaccine. Efficacy against low-grade cervical, vulvar, and vaginal diseases increased by 28.3 % for shared HPV types, rising to 98.0 % for types unique to the 9vHPV vaccine. Similarly, efficacy for high-grade cervical, vulvar, and vaginal diseases increased by 66.6 % for shared HPV types with a significant rise to 97.4 % for types exclusive to the 9vHPV vaccine.

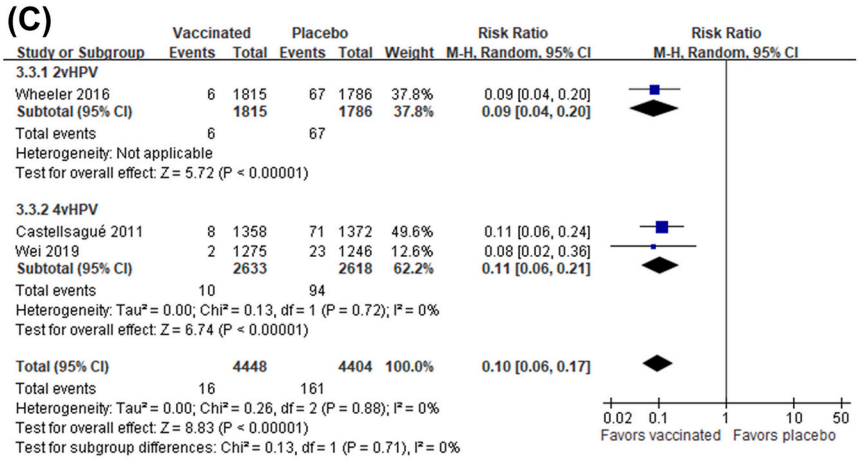
A meta-analysis of 65 studies across 14 high-income countries provided strong evidence that HPV vaccination significantly reduced HPV prevalence and associated diseases.[20] After 5–8 years of vaccination, HPV16 and 18 prevalence declined significantly by 83 % among girls aged 13–19 years and by 66 % among women aged 20–24 years. Additionally, HPV31, 33, and 45 prevalence decreased by 54 % among girls aged 13–19 years. After 5–9 years post-vaccination, the incidence of cervical intraepithelial neoplasia grade 2 or worse (CIN2+) declined by 51 % among screened girls aged 15–19 years and by 31 % among women aged 20–24 years. Although most clinical trials have focused on individuals without prior HPV infection, pre-existing conditions can vary widely in real-world settings. A literature review on the effectiveness of HPV vaccines in high-risk groups, including those with pre-existing cervical or anogenital diseases and recurrent respiratory papillomatosis, suggested that administering the 4vHPV or 9vHPV vaccines may potentially reduce the risk of recurrence in these patients.[49] Given the low incidence of vaginal and vulvar cancers, evidence concerning these conditions is limited. A systematic review evaluated the impact of the HPV vaccine on patients with pre-existing vaginal and vulvar lesions, reporting a reduction in lesion size, often accompanied by viral clearance and alleviation of symptoms.[50] However, HPV prophylactic vaccines do not have direct therapeutic effects on pre-existing lesions and peri-treatment conditions; the observed effects likely result from preventing new HPV infections of the same or different genotypes.[51] Given the demonstrated immunogenicity of HPV vaccines across various age groups and their promising efficacy in reducing persistent HPV infections and cervical diseases in women up to age 26, the panel recommends HPV vaccination for all women within this age group.

4.2.2. Women aged 27 through 45 years

In 2019, the US ACIP recommended catch-up HPV vaccination for adult women up to 26 years of age.[52] However, this recommendation was not extended to adults aged 27–45 years due to the available







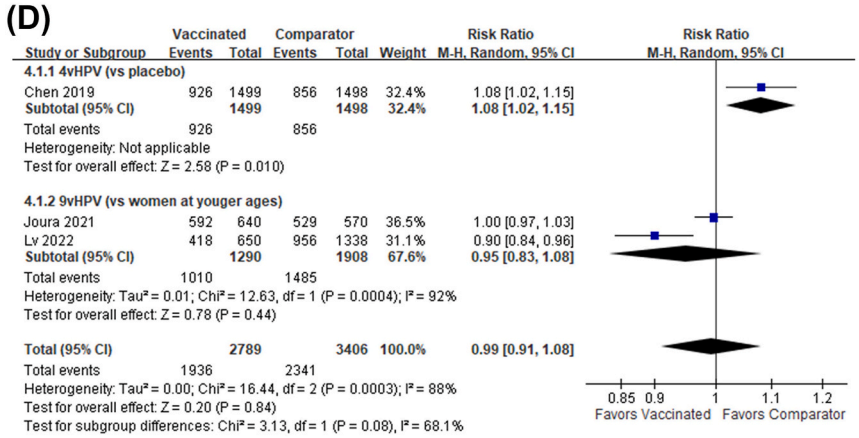


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Fig. 2. Meta-analysis of HPV vaccine efficacy against (A) precancerous lesions (CIN, VaIN, or AIN 2+), (B) external genital lesions (genital warts), and (C) persistent vaccine-type cervical HPV infection at 6 months, (D) harm of HPV vaccination compared to placebo or comparators.
Fig. 2 footnotes.
Abbreviations: 2vHPV, bivalent HPV vaccine; 4vHPV, quadrivalent HPV vaccine; AIN 2+, anal intraepithelial neoplasia grade 2 or worse; CIN, cervical intraepithelial neoplasia; CI, confidence interval; HPV, human papillomavirus; M − H, Mantel-Haenszel method; VaIN, vaginal intraepithelial neoplasia.

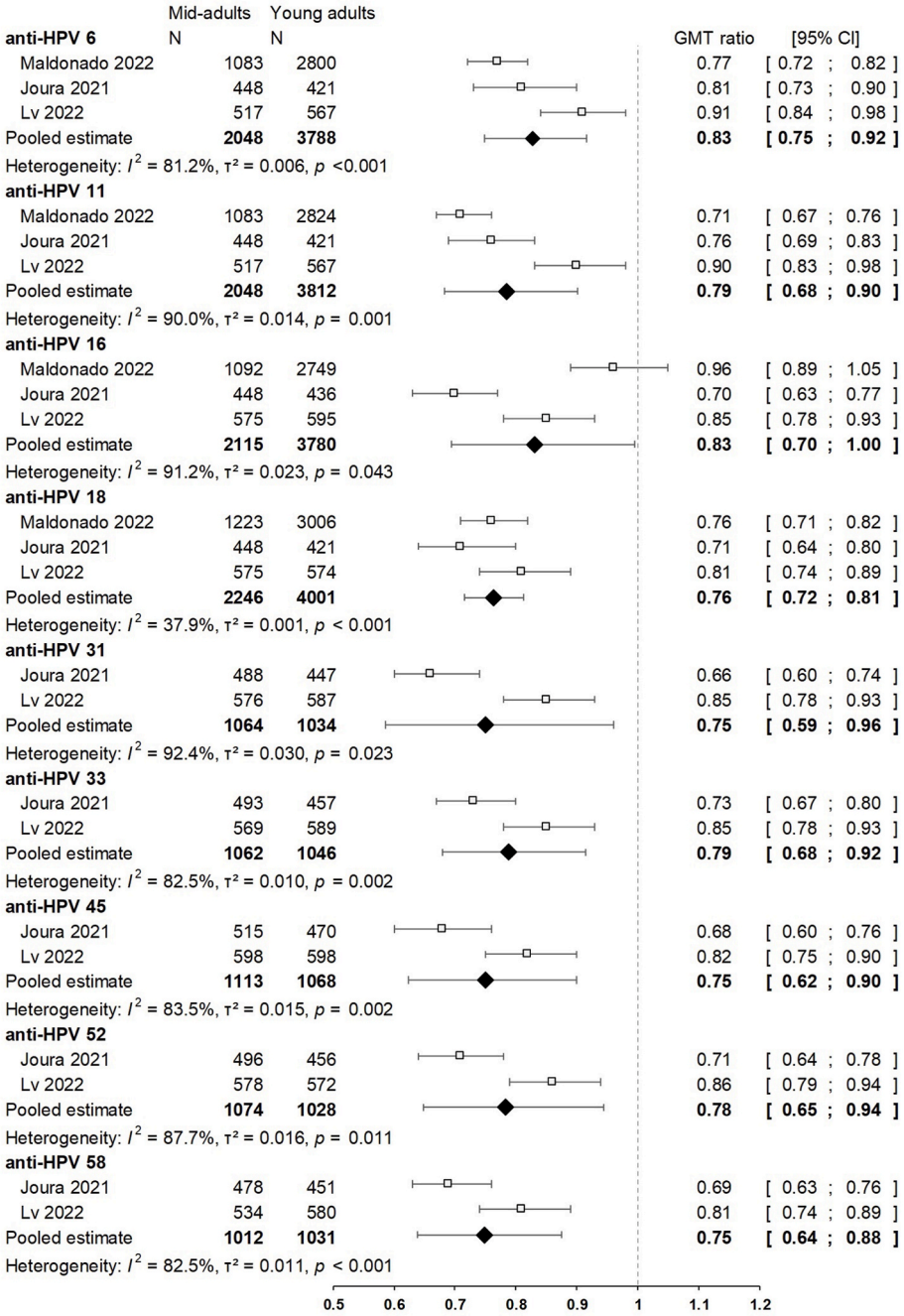

Fig. 3. Meta-analysis[a] of geometric mean titer (GMT) ratios comparing antibody responses between mid-adult (27–45 years) and young adult women (16–26 years[b]) at month 7 post-vaccination. Data included 4vHPV vaccine (Maldonado 2022) and 9vHPV vaccine (Joura 2021, Lv 2022) studies. Non-inferiority was demonstrated for all HPV serotypes (lower bound 95 % CI > 0.5).
Fig. 3 footnotes.
Abbreviation: 2vHPV, bivalent HPV vaccine; 4vHPV, quadrivalent HPV vaccine; CI, confidence interval; HPV, human papillomavirus.
[a]A random-effects meta-analysis was performed to calculate the pooled geometric mean titer (GMT) ratios comparing immunogenicity between mid-adults (27–45 years) and young adults (16–26 or 20–26 years) for each HPV type. The effect measure was expressed as GMT ratios with 95 % confidence intervals (CIs). Between-study heterogeneity was assessed using the I^2 statistic and tau-squared (τ^2) value, with I^2 values of 25 %, 50 %, and 75 % suggesting low, moderate, and high heterogeneity, respectively. All analyses were performed using the 'meta' package in R (version 4.4.1). Non-inferiority was defined as the lower bound of the 95 % CI exceeding 0.5 for the GMT ratio.
[b]20-26 years in Lv study.

evidence at the time. We conducted a meta-analysis to cover the period from 2018 to 2023, which included long-term follow-ups of clinical trials and meta-analyses (Fig. 1), and combined current evidence with that from the 2019 ACIP document.[43,44,47,53–56] However, not all included trials were specifically designed for the 27–45 age group.[47,54–56] The key outcomes were categorized as benefits and harms. Benefits included prevention of precancerous lesions, genital warts, persistent vaccine-type cervical HPV infection at 6 months, and immunogenicity assessment at 7 months. Pooled data from the 2vHPV and 4vHPV vaccines showed a significant reduction in the risk of CIN, vaginal intraepithelial neoplasia (VaIN), or anal intraepithelial neoplasia grade 2 or higher (AIN2+) (Fig. 2A), as well as a decrease in persistent vaccine-type cervical HPV infection at 6 months in women aged 27–45 years (Fig. 2C). The 4vHPV vaccine efficacy was 100 % in preventing CIN and genital warts caused by vaccine-type viruses for up to a decade post-vaccination in the intention-to-prevent analysis,[53] while the 2vHPV vaccine exhibited 90.5 % efficacy in reducing persistent infection or any CIN in the according-to-protocol analysis.[52] Similarly, the immunogenicity of 4vHPV and 9vHPV vaccines in women aged 27–45 years was found to be non-inferior to that in young adult women aged 16–26 years at 7 months (Fig. 3). However, the meta-analysis showed no significant effect of HPV vaccination in reducing the risk of genital warts (Fig. 2B). A lower incidence of genital warts in this age group may reduce the observed effectiveness of the vaccine.[1,57] Regarding harms, HPV vaccination showed no significant difference in adverse events compared to comparators (Fig. 2D).

Two cohort studies demonstrated the benefits of HPV vaccination in reducing HPV infection and cancer risk among women aged 27–45 years.[58,59] However, other cohort studies reported contrasting findings, showing no significant advantages.[60–62] This discrepancy may be attributed to factors such as ongoing risky behaviors, the absence of a gender-neutral vaccination program, and suboptimal dosing (only 1 or 2 doses administered). Due to the indirectness of included trials and limited supportive evidence from real-world data, the panel recommends that HPV vaccination for individuals aged through 27–45 years be considered through shared decision-making between individuals and their clinicians.

4.2.3. Women aged over 45 years

As women aged over 45 years were excluded from clinical trials, there is currently no evidence to support HPV vaccination for this age group. However, in specific patient populations such as people with HIV (PWH) or CIN2+ patients who have undergone surgical interventions like conization, the vaccine has demonstrated benefits in this older age group.[63–65] Additional real-world data is needed to inform recommendations for HPV vaccination in women aged over 45 years. Given that HPV vaccines are indicated for individuals up to 45 years of age, the panel does not recommend HPV vaccination for individuals older than 45 years.

5. What is the recommendation for HPV vaccination for adult men?

5.1. Recommendations

1. HPV vaccination is recommended for all men through 26 years of age who have not been adequately vaccinated. *(Strong recommendation, high quality of evidence) (1A)*
2. For adult men aged 27 through 45 years who were not adequately vaccinated before the age of 26, catch-up vaccination can be considered through shared clinical decision-making. *(Weak recommendation, very low quality of evidence) (2D)*

5.2. Summary of the evidence

5.2.1. Men through age 26 years

Three RCTs investigated the immunogenicity of the 4vHPV vaccine in male participants aged 16–26 years.[66–68] The seroconversion rates for HPV6, 11, 16, and 18 ranged from 97.1 % to 100 % among individuals who received the 4vHPV vaccine by month 7, 1 month after completion of 3 doses. Another RCT demonstrated that both the 9vHPV and 4vHPV vaccines elicited a similar antibody response, with seroconversion rates of 98.2–100 % for HPV6, 11, 16, and 18 in men aged 16–26 years.[69] Additionally, individuals receiving 3 doses of 9vHPV vaccine achieved 100 % seropositivity for antibodies against HPV31, 33, 45, 52, and 58. Another study found that seroconversion rates for all 9 vaccine serotypes were comparable among heterosexual men aged 16–26 years (99.6–100 %), men who have sex with men (MSM) (99.4–100 %), and women (99.5–100 %).[70]

Two RCTs demonstrated that the 4vHPV vaccine provided 100 % efficacy against penile, perianal, or perineal intraepithelial neoplasia (PIN) related to HPV 6, 11, 16, and 18 at month 36 in male participants aged 16–26 years.[67,71] Additionally, 3 RCTs showed high efficacy of the 4vHPV vaccine in preventing AIN and anal cancer among MSM, with efficacy rates ranging from 75.0 % to 89.6 %.[71–73] Furthermore, 4vHPV vaccine demonstrated an 89.4–90.4 % efficacy against anogenital warts.[67,72] For external genital lesions, including anogenital warts and neoplasia, the 4vHPV vaccine provided effective protection of 90.4–100 % for men aged 16–26 years.[66,67,71,72] Although the 9vHPV vaccine lacks clinical efficacy data from placebo-controlled RCTs in men, as the licensed 4vHPV vaccine has already demonstrated efficacy against external genital lesions and non-inferior antibody response for HPV 6, 11, 16, and 18. Due to the promising immunogenicity of HPV vaccines and their efficacy in reducing diseases associated with external genital lesions in men up to age 26, the panel recommends HPV vaccination for all men in this age group.

5.2.2. Men aged 27 through 45 years

No clinical trials have been conducted on the efficacy of the HPV vaccine in men aged 27–45 years. One observational study found non-inferior antibody responses to the 4vHPV vaccine in men between age groups 26–30, 31–35, 36–40, and 41–45 years, regardless of HPV type, with 100 % seroconversion. Significantly higher antibody responses were found at month 7 for those who were HPV seropositive at study entry.[74] During the development of this guidance, experts proposed that men aged 27–45 years may benefit from HPV vaccination due to proven protection against male external genital lesions observed in clinical practice. Therefore, the panel recommends that HPV vaccination should be considered for men aged 27–45 years after shared decision-making between individuals and their clinicians.

6. What is the recommendation for HPV vaccination to prevent anal cancer in the immunocompromised adults?

6.1. Recommendations

1. HPV vaccination is recommended for adult PWH. *(Strong recommendation, moderate quality of evidence) (1B)* Deferring vaccination until patients are receiving antiretroviral therapy and virologically suppressed with CD4 counts $\geq$200 cells/mm^3 may be considered to ensure a robust antibody response.
2. For adult transplant recipients, HPV vaccination is suggested before transplantation or at least one-year post-transplantation. *(Weak recommendation, very low quality of evidence) (2D)*
3. For immunocompromised adults with autoimmune inflammatory rheumatic diseases, HPV vaccination is suggested. *(Weak recommendation, very low quality of evidence) (2D)*

6.2. Summary of the evidence

6.2.1. Adult PWH

PWH are at a significantly higher risk of developing HPV-related cancers compared to the general population. Moreover, studies have demonstrated a correlation between lower CD4 counts and an increased risk of anal cancer in PWH.[75] HIV statu s does not affect the population impact of single-dose 2vHPV vaccination, as similar reductions were observed in both young women with and without HIV.[76] Two RCTs with small sample sizes indicated that both the 2vHPV and 4vHPV vaccines were immunogenic in adult PWH.[77,78] An RCT evaluated the immunogenicity and effectiveness of the 4vHPV vaccine among HIV-positive MSM aged over 26 years.[79,80] This trial demonstrated significantly higher antibody levels against 4vHPV vaccine genotypes in vaccinated individuals compared to unvaccinated controls at 48 months (87.2 % vs 30 %, respectively). However, no significant differences were observed between the vaccine and placebo groups in the rates of anal high-grade squamous intraepithelial lesions (HSILs) or external anogenital lesions, or in protection against infection by HPV vaccine genotypes during the 48-month follow-up, except for HPV6 at 12 months. Another RCT assessed the efficacy of 4vHPV vaccine among PWH aged 27 or older.[81] The seropositivity rates for HPV types 6, 11, 16, 18 at month 7 increased to 98.9 %, 100 %, 99.6 %, and 97.4 %, respectively. However, the vaccine demonstrated only 22 % efficacy in preventing persistent anal HPV infection and 0 % efficacy for improving HSIL outcomes. No serious adverse events associated with the vaccine were reported across these studies.[77–81]

While these studies enrolled PWH with relatively high CD4 count ($\geq$200 cells/mm^3), other studies have shown that PWH with a CD4 count <200 cells/mm^3 and those with HIV virological non-suppression tend to exhibit lower immunogenicity.[82,83] Based on the non-inferior antibody response seen in PWH, the panel recommends HPV vaccination in adult PWH. To ensure a robust antibody response, vaccination may be deferred until patients are on antiretroviral therapy, achieve virological suppression, and attain a CD4 count of $\geq$200 cells/mm^3.

6.2.2. Adult transplant recipients

Two prospective cohort studies evaluated the immunogenicity of the 4vHPV vaccine in adult solid organ transplant (SOT) recipients. At the month 7 following vaccination, antibody responses were observed at rates of 63.2 %, 68.4 %, 63.2 % and 52.6 % for HPV6, 11, 16 and 18, respectively. A non-significantly lower antibody response was observed in SOT recipients less than 1-year post-transplant.[84] Another study investigated the immunogenicity of the 9vHPV vaccine among SOT recipients, showing seroconversion rates ranging from 46 % to 72 %.[63] A small study investigated the immunogenicity of the 4vHPV vaccine in 64 adult hematopoietic stem cell transplantation (HSCT) recipients. Antibody responses to all 4vHPV vaccine types developed in 78.3 % of those receiving immunosuppressants, 95.2 % of those not on immunosuppressants, and 100 % of healthy volunteers.[85] No serious adverse events associated with the vaccine were reported in any of these studies.[63,84,85] Based on the limited available evidence from immunogenicity studies, the panel suggests that HPV vaccination may be considered for SOT recipients either before transplantation or at least one-year post--transplantation. The panel cautions that the optimal timing for vaccination post-transplantation remains uncertain.

6.2.3. Immunocompromised adults with autoimmune inflammatory rheumatic diseases

Two prospective cohort studies evaluated the immunogenicity of the HPV vaccine in adults with autoimmune diseases. In one study, 37 immunosuppressed female patients with inflammatory bowel disease, aged 9–26 years, showed 100 % seropositivity for HPV6, 11 and 16 and 96 % for HPV18 at month 7.[86] Another study which included 27 females aged 12–26 years with systemic lupus erythematosus, demonstrated seropositivity rates of 94.4 %, 100 %, 100 %, and 94.4 % for HPV6, 11, 16 and 18, respectively, at month 7.[87] The American College of Rheumatology (ACR) guidelines conditionally recommend continuing immunosuppressive medications during non-live attenuated vaccinations. For patients on rituximab, the ACR recommends administering the HPV vaccine when the next rituximab dose is due, followed by a 2-week delay before administering rituximab.[88] Based on the limited evidence from immunogenicity studies, the panel suggests HPV vaccination may be considered for adult patients with autoimmune inflammatory rheumatic diseases.

7. What is the recommendation for HPV vaccination to prevent oropharyngeal cancer and oral HPV infection in adults aged through 45 years?

7.1. Recommendations

1. For the prevention of oral HPV infection, HPV vaccination is suggested for adults aged through 45 years. *(weak recommendation, moderate quality evidence) (2B)*
2. For the prevention of HPV-related oropharyngeal cancer, HPV vaccination is suggested for adults aged through 45 years. *(weak recommendation, very low quality of evidence) (2D)*

7.2. Summary of the evidence

7.2.1. Oropharyngeal HPV infection

The efficacy of the HPV vaccine in reducing the risk of HPV infections in the oral cavity and oropharynx was evaluated in 4 RCTs.[81,89–91] The efficacy of 2vHPV vaccine against oral HPV infections was assessed in 7466 women aged 18–25,[89] and demonstrated an efficacy of 93.3 % against oral HPV16 and 18 infections, compared to 72 % against cervical infections, at 4 years post-vaccination. Another trial involving 4186 women aged 18–25 showed that the 2vHPV vaccine demonstrated an 83.5 % efficacy in preventing infections at cervical, anal, and oral sites among HPV-naïve women.[90] For women seropositive for HPV16 or 18 but with no detectable cervical DNA at vaccination, the vaccine's efficacy was 57.8 %. These findings highlight the substantial multisite vaccine effectiveness in women without prior exposure to HPV and the potential protective benefits for women previously infected with HPV16 or 18.

In a community-randomized trial, 38,631 Finnish adolescents (11,275 girls and 6129 boys) aged 13–15 years,[91] the 2vHPV vaccine was found to be 82.4 % effective in preventing oropharyngeal infections caused by HPV types 16 and 18 and 75.3 % effective against non-vaccine HPV types 31 and 45. This trial demonstrated that the 2vHPV vaccine is effective in preventing both vaccine-specific and several closely related non-vaccine HPV type oropharyngeal infections in adolescent females, with protection lasting up to 6 years after vaccination. Additionally, the efficacy of 4vHPV vaccine was assessed in 575 PW H aged 27 or older,[81] and demonstrated an 88 % efficacy in preventing persistent oral HPV infection. The reported efficacy for preventing persistent oral HPV infection at 6 months or detection at the final visit was 32 %. Although these trials demonstrated the effectiveness of HPV vaccination in preventing oropharyngeal HPV infections, the study populations were predominantly composed of women and PWH. Based on the available evidence, and with evidence supporting strong protection against other HPV-related cancers, the panel suggests HPV vaccination for all adults up to 45 years of age to prevent oropharyngeal HPV infections.

7.2.2. HPV-related oropharyngeal cancer

Studies have shown that oral HPV infection may be associated with HPV-positive oropharyngeal cancer. A case-control study conducted in the U.S. from 2000 to 2005 found that 72 % of newly diagnosed head and neck cancer patients were HPV-positive.[92] The presence of any type of oral HPV infection was associated with a 12.3-fold increased risk for head and neck cancer, with oral HPV16 infection having the highest risk

(odds ratio [OR] 14.6). Another nested case-control study enrolling 132 patients with newly developed head and neck squamous cell carcinoma showed that oral HPV16 detection was significantly associated with an increased risk of developing head and neck squamous cell carcinoma (OR, 7.1) and oropharyngeal squamous cell carcinoma (OR, 22.4).[93]

However, evidence supporting the use of HPV vaccination to reduce the risk of HPV-positive oropharyngeal cancer remains limited. A cross-sectional study that analyzed 1,310,034 patients from 2011 to 2020 showed that the risk of developing oropharyngeal cancer in unvaccinated individuals is 19 times higher than in the vaccinated group,[94] with unvaccinated men having a significantly higher risk than women (relative risk (RR), 23.8 versus 9.3, respectively). On the other hand, HPV vaccination has been proven to be effective in reducing oral HPV infection.[81,89–91,95] Considering the robust evidence of cervical cancer prevention by HPV vaccination, it is plausible that the prevention and reduction of oral HPV infection may also contribute to reducing HPV-positive oropharyngeal cancer. Based on the available evidence and the strong protection HPV vaccination provides against other HPV-positive cancers, as well as its existing recommendation for adults up to age 45 to prevent genital warts, genital, and anal cancers, the panel suggests that HPV vaccination should be considered for all adults up to 45 years of age to prevent HPV-related oropharyngeal cancer.

8. Is the 9vHPV vaccine safe?

8.1. Conclusion

9vHPV vaccine is safe for immunocompetent adults through age 26 years and aged 27 through 45 years.

8.2. Summary of the evidence

A meta-analysis comparing the safety of HPV vaccines in females who received either the vaccine or a placebo (vaccine adjuvants or another control vaccine) reported no increased risk of serious adverse effects among vaccine recipients of the 2vHPV or 4vHPV vaccine.[96] Due to the proven efficacy and safety of these vaccines, HPV vaccination has been widely recommended and implemented in many countries using either the 2vHPV or 4vHPV vaccines.

Most safety data on the 9vHPV vaccine are derived from comparisons with the 4vHPV vaccine, with limited data from placebo-controlled trials. One RCT compared the safety profiles of the 9vHPV and 4vHPV vaccines in women aged 16–26 years,[97] and found that the most common injection-site reactions in the 9vHPV group included pain and swelling, while headache and fever were the most frequently reported systemic events. Injection-site reactions were more frequent in the 9vHPV group than in the 4vHPV group, but vaccine-related systemic events were similar between the two groups. Two meta-analyses consistently demonstrated comparable safety outcomes between the 9vHPV and 4vHPV vaccines in RCTs involving women.[98,99] In contrast, the 2vHPV vaccine was associated with a significantly higher rate of systemic adverse events compared to both the 4vHPV and 9vHPV vaccines.[99] Vaccine-related serious adverse events were rare, and no deaths were attributable to the vaccine. A subgroup analysis within the RCT comparing the efficacy and safety of the 9vHPV and 4vHPV vaccines in Asian participants also demonstrated a similar safety profile.[100]

Two studies assessed the safety of 9vHPV vaccine in women aged 27–45 years and those aged 16–26 years.[44,97] The findings suggested that 9vHPV vaccination is safe for older women aged 27–45 years, with a consistent safety profile across both age groups. No increased risk of miscarriage or pregnancy termination was observed in women who received the 2vHPV or 4vHPV vaccines,[96] nor were there any adverse birth outcomes associated with 9vHPV vaccination.[97,101] However, there is limited safety data available on HPV vaccines in men. An RCT comparing the immunogenicity and safety of the 9vHPV and 4vHPV vaccines in men aged 16–26 years showed comparable safety profiles between groups, though there were slightly more reports of injection-site pain and swelling in those receiving the 9vHPV vaccine.[69] Additionally, a large cohort study including over 70,000 men found no new safety concerns associated with the 9vHPV vaccine.[102] Similarly, several post-licensure surveillance reports from various countries, including Taiwan, provided real-world data that did not raise any safety concerns.[103–107] In summary, data from clinical trials and post-licensure surveillance reports indicate that the 9vHPV vaccine has a favorable safety profile comparable to the 4vHPV vaccine, with a slightly higher incidence of injection-site swelling and pain. Based on this evidence, the panel concludes that the 9vHPV vaccine is safe for immunocompetent adults up to 45 years of age.

9. What is the recommended dosing schedule for HPV vaccination in adults?

9.1. Recommendations

1. A 3-dose schedule of HPV vaccination is recommended for all adults. *(Strong recommendation, high quality of evidence) (1A)*

9.2. Summary of the evidence

The 3-dose schedule of HPV vaccination was initially licensed based on trials conducted in adults. Subsequently, a 2-dose schedule for girls and boys aged 9–14 years was approved, supported by evidence demonstrating that this schedule was non-inferior to the 3-dose schedule for this age group.[108–110] One study showed that over 98 % of the girls and boys aged 9–14 years achieved seroconversion for all 9 vaccine types after receiving 2 doses of 9vHPV vaccination.[108] However, data on the reduced dosing schedule for adult women are limited.

Less frequent dosing schedules (1-dose and 2-dose) showed promising results in post-hoc analyses of prior trials, but real-world studies have shown inconsistent results. Several systematic reviews and meta-analyses have addressed the effectiveness of reduced-dose HPV vaccination in lowering HPV-related infections.[111–113] Post-hoc analyses of previous trials with follow-up durations of up to 7 years suggest that a single dose of the 2vHPV or 4vHPV can reduce the cumulative incidence of HPV infection compared to controls and induce higher antibody titers than those from natural infections.[112] Several RCTs have demonstrated that a single dose of the 2vHPV or 9vHPV vaccine is sufficiently immunogenic to provide similar protection as a multidose regimen against initial and persistent HPV infection in young females.[114–116] The protection provided by a single-dose HPV vaccination is durable and may last over 10 years, though the antibody titers elicited are lower than those in individuals who received 3 doses.[117–119] However, discrepant results were observed in real-world studies.[60,62,120,121]

While reduced dosing shows promise in offering similar benefits to the licensed 3-dose regimen, more evidence is needed to draw definitive conclusions, particularly regarding the 9vHPV vaccine. Until more robust evidence is available, the panel recommends that all adults should receive the full 3-dose HPV vaccine schedule, administered at 0, 1–2, and 6 months.

10. Is including the 9vHPV vaccine in a heterologous vaccination regimen effective?

10.1. Recommendations

The 9vHPV vaccine may be used to continue or complete a series for individuals who initiated their vaccination with 4vHPV or 2vHPV vaccines. *(expert opinion)*.

10.2. Summary of the evidence

Currently, no studies have specifically examined the effectiveness of

including the 9vHPV vaccine in a heterologous vaccination regimen. The panel provided a consensus recommendation based on CDC guidelines.[19]

11. What is the recommendation for administering 9vHPV vaccine in adults who have completed the 4vHPV or 2vHPV vaccination series?

11.1. Recommendations

No recommendation is given for administering additional doses of the 9vHPV vaccine to individuals who have already completed the 4vHPV or 2vHPV vaccination series. *(Weak recommendation, low quality of evidence) (2C)*.

11.2. Summary of the evidence

No studies have evaluated the effectiveness of including the 9vHPV vaccine into a heterologous vaccination regimen. However, according to CDC recommendations, if an individual was vaccinated with an unknown HPV vaccine product or if the previously used product is unavailable, women may receive any available HPV vaccine to continue or complete the series. Men may use either the 9vHPV or 4vHPV vaccines to continue or complete the series.[19]

A RCT investigated the safety and immunogenicity of additional 9vHPV doses in females aged 12–26 years who had previously completed the 4vHPV vaccination series.[122] The result showed that 98 % of the individuals who received an additional 3 doses of 9vHPV vaccine became seropositive for HPV types 31, 33, 45, 52 and 58, with a good safety profile. However, no current guidelines recommend initiating a new 3-dose 9vHPV vaccination series in individuals who have already completed the 2vHPV or 4vHPV vaccination series.

12. Special consideration: occupational exposure of healthcare providers

Some evidence indicates that HPV DNA may be present in the medical environment and surgical smoke, though there is no evidence of viable HPV transmission via these routes.[123,124] Studies have found no significant difference in the prevalence of HPV infection or HPV-related disease between medical personnel and the general population.[124] Nevertheless, concerns persist about the potential for HPV acquisition through medical procedures or environmental exposure. Currently, no guidelines recommend specific measures for preventing or monitoring HPV infection in medical settings. The panel emphasizes the importance of hand hygiene after the removal of gloves and adherence to established cleaning protocols. The American Society for Colposcopy and Cervical Pathology has advised medical providers, including obstetricians, gynecologists, dermatologists, and family physicians, to receive the HPV vaccination. Given the limited data on occupational HPV exposure, the panel suggests that clinicians frequently exposed to the virus, such as those in dermatology, otolaryngology, and genitourinary medicine, may consider HPV vaccination as a proactive self-protection measure.[125]

13. Conclusions

This HPV guidance is intended to provide recommendations and address relevant clinical questions and needs, even in areas where evidence may be limited. The panel acknowledges the limitations and challenges of giving recommendations when available evidence may be insufficient, and therefore, positions this document as a guidance rather than a formal guideline. A recommendation may thus be given despite a very low quality of evidence, strongly relying on expert opinion. For anogenital lesions, efficacy findings were primarily reported based on the per-protocol cohort, with additional support from efficacy data in the intention-to-treat cohort. However, the benefits of vaccination may be overestimated in adults, as the per-protocol analysis includes only individuals who are seronegative for specific HPV types, whereas many adults may have had prior HPV exposure. In the case of oropharyngeal cancers, the panel recommends HPV vaccination for prevention, considering the epidemiology and potential vaccine benefits inferred from an understanding of the disease mechanisms. The lack of evidence is attributed to the recent recognition of the association between HPV infection and these cancers, along with the unavailability of long-term efficacy data from RCTs, since premalignant precursor lesions of HPV-associated oropharyngeal cancer cannot be routinely identified. Important outcomes, such as cancer development, require long-term follow-up and results can only be expected in the future from well-designed studies with large sample sizes to achieve statistical significance. The panel believes it is reasonable to provide recommendations for potential vaccine benefits based on projections of long-term benefits derived from underlying mechanisms, but cautions that confirming these benefits will require future studies with sufficient long-term follow-up.

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare no potential conflicts of interest with regards to the research, authorship, or publication of this article.

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