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Vaccination Against Human Papillomavirus

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CLINICAL QUESTION Who should receive human papillomavirus (HPV) vaccination?

BOTTOM LINE Catch-up vaccination is now recommended for all persons through age 26 years. For persons aged 27 through 45 years, clinicians and patients should now jointly decide whether HPV vaccination is appropriate. Routine HPV vaccination at age 11 or 12 years (or as early as age 9 years) continues to be recommended.

Introduction

Human papillomavirus (HPV) infection is the most common sexually transmitted infection in the US, affecting at least 80% of women by age 50 years.[1] It is transmitted by mucocutaneous contact.[1] Vaccination can prevent vaccine-type HPV infection and HPV-associated diseases, including genital warts, cervical cancer, other anogenital cancers, and oropharyngeal cancers. Three HPV vaccines are licensed for use in the US: bivalent (2vHPV; types 16 and 18), quadrivalent (4vHPV; types 6, 11, 16, and 18), and nonavalent (9vHPV; types 6, 11, 16, 18, 31, 33, 45, 52, and 58). The 9vHPV vaccine is the only HPV vaccine currently available in the US.

The Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) issues recommendations for vaccination of the US civilian population. The ACIP previously recommended HPV vaccination of all persons aged 11 or 12 years (starting as early as age 9 years), with catch-up vaccination of all persons through age 21 years and of women, men who have sex with men, and immunocompromised persons through age 26 years.[2] Prior to the update, ACIP stated that other men "may be vaccinated" through age 26 years.[2] Herein we summarize ACIP's August 2019 update.[3]

Evidence Profile

No. of studies overall: 21

No. of randomized clinical trials: 14

No. of observational studies: 7

Study years: 2000-2019

No. of patients: 62 427

Sex: Male, 8%; Female, 92% (from 18 studies [57 104 participants]; sex not reported for 5 323 participants in 3 studies)

Race/ethnicity: Not reported in most studies

Age, range: 9-55 years (data available from 19 studies)

Settings: Not reported in most studies

Countries: Australia (n = 3), Austria (n = 2), Belgium (n = 3), Brazil (n = 6), Canada (n = 4), Chile (n = 1), China (n = 4), Colombia (n = 2), Costa Rica (n = 1), Croatia (n = 1), Czech Republic (n = 1), Denmark (n = 2), Finland (n = 5), France (n = 2), Germany (n = 5), Hong Kong (n = 1), India (n = 1), Italy (n = 2), Mexico (n = 5), Netherlands (n = 1), Norway (n = 4), Peru (n = 4), Philippines (n = 2), Poland (n = 3), Portugal (n = 1), Russia (n = 1), Singapore (n = 1), South Africa (n = 2), South Korea (n = 1), Spain (n = 5), Sweden (n = 4), Taiwan (n = 2), Thailand (n = 4), UK (n = 3), US (n = 12)

Comparisons (randomized clinical trials only): Intramuscular placebo (n = 10); different human papillomavirus virus (HPV) vaccines (n = 4, of which 1 was also placebo-controlled: 1 trial compared monovalent vaccine, quadrivalent vaccine, and placebo; another trial compared bivalent and quadrivalent vaccines; another trial compared quadrivalent and nonavalent vaccines; and another trial compared quadrivalent, low-dose nonavalent, mid-dose nonavalent, and high-dose nonavalent vaccines)

Primary outcome: Immunogenicity

Secondary outcomes:
- Persistent HPV infection (detection of the same HPV type[s] at 2 or more consecutive evaluations after enrollment)
- Incident HPV infection
- Anogenital warts
- Intraepithelial neoplasia of the anus, cervix, penis, perianal region, perineal region, vagina, or vulva
- Carcinoma of the anus, cervix, or vulva
- Adverse events

Summary of Findings

The ACIP reviewed HPV vaccination trials published from 2000 to 2019.[3] The ACIP recommendation focuses on vaccine efficacy and safety, HPV burden of disease and effect of vaccination, and health economic analyses.

Vaccine Efficacy and Safety

Efficacy centered on a combined end point, defined as absence of persistent vaccine-type HPV infections, anogenital warts, and cervical intraepithelial neoplasia grade 1 (low-grade lesions) or worse. Per-protocol efficacy of the 9vHPV vaccine against the combined end point among women aged 24 through 45 years was 88.7% (95% CI, 78.1%-94.8%). The 2vHPV and 4vHPV vaccines also showed statistically significant efficacy. Vaccine immunogenicity ranged from 93.6% to 100% at 7 months after administration of the first dose. Few serious adverse events and no vaccine-related deaths occurred.

HPV Burden of Disease and Effect of Vaccination

Approximately 33 700 HPV-caused cancers—mostly of the oropharynx, cervix, or anus—occur annually in the US. Although only 65.5% of adolescents in 2017 had received at least 1 HPV vaccine dose, vaccine-type infections and diseases had decreased among both vaccinated and unvaccinated persons.[4]

Box. Considerations for Shared Clinical Decision-making Regarding Human Papillomavirus (HPV) Vaccination of Adults Aged 27 Through 45 Years[a,b]

- HPV is a very common sexually transmitted infection. Most HPV infections are transient and asymptomatic and cause no clinical problems.
- Although new HPV infections are most commonly acquired in adolescence and young adulthood, some adults are at risk for acquiring new HPV infections. At any age, having a new sex partner is a risk factor for acquiring a new HPV infection.
- Persons who are in a long-term, mutually monogamous sexual partnership are not likely to acquire a new HPV infection.
- Most sexually active adults have been exposed to some HPV types, although not necessarily all of the HPV types targeted by vaccination.
- No clinical antibody test can determine whether a person is already immune or still susceptible to any given HPV type.
- HPV vaccine efficacy is high among persons who have not been exposed to vaccine-type HPV before vaccination.
- Vaccine effectiveness might be low among persons with risk factors for HPV infection or disease (eg, adults with multiple lifetime sex partners and likely previous infection with vaccine-type HPV), as well as among persons with certain immunocompromising conditions.
- HPV vaccines are prophylactic (ie, they prevent new HPV infections). They do not prevent progression of HPV infection to disease, decrease time to clearance of HPV infection, or treat HPV-related disease.

[a] Reprinted from the 2019 HPV vaccination recommendations from the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices.[3]

[b] Vaccination does not need to be discussed with most adults older than 26 years, according to the Advisory Committee on Immunization Practices.

Health Economic Analyses

Depending on the study, effects of HPV vaccination range from cost-saving to approximately $35 000 per quality-adjusted life-year gained. Recommending vaccination for all males through age 26 years, or for all adults through age 45 years, would result in minimal health benefits, less favorable cost-effectiveness estimates, and higher numbers needed to vaccinate to prevent vaccine-type disease.[4]

Discussion

The ACIP recommendation included 2 important changes. First, it recommends catch-up vaccination for all persons through age 26 years, explaining that a uniform HPV vaccination schedule, regardless of sex, would be simpler and more feasible. Second, ACIP endorses "shared clinical decision-making" (**Box**) between clinicians and patients to determine HPV vaccination appropriateness for persons ages 27 to 45 years, explaining that some persons in that age group might benefit. Importantly, under the Patient Protection and Affordable Care Act, private insurance plans must completely cover ACIP-recommended vaccinations (among other preventive health services).[5]

The update did not change several important recommendations. First, ACIP recommends routine vaccination at age 11 or 12 years (or as early as age 9 years) for all persons. Vaccines for HPV are safe and effective against vaccine-type HPV infections and HPV-associated diseases with which recipients are not infected at the time of vaccination. Therefore, according to ACIP, it is critical to vaccinate adolescents, who are less likely to have HPV infection and therefore stand to benefit the most from vaccination.[3]

Second, ACIP recommends HPV vaccination of age-appropriate persons regardless of prior or current HPV infection status. Prevaccination testing for HPV infection is not recommended.[2] Persons who are already infected with HPV might benefit from protection against not-yet-acquired HPV types.

Third, ACIP views HPV vaccination as preventing only vaccine-type HPV infections and diseases. It not only does not endorse HPV vaccination for treatment of HPV-associated disease, but it specifically recommends that clinicians counsel patients that HPV vaccination will not treat HPV infection or HPV-associated diseases.[2]

Fourth, ACIP makes no recommendation regarding 9vHPV vaccination for persons who have already received 2vHPV or 4vHPV vaccination. According to the Centers for Disease Control and Prevention, 9vHPV vaccination might confer additional protection against cervical precancers and cancers.[6]

Finally, ACIP continues to recommend age-based dosing schedules, with 2 doses for persons beginning HPV vaccination at ages 9 through 14 years and 3 doses for persons beginning after age 14 years or persons who are immunocompromised.[7]

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