Ten Years of Human Papillomavirus Vaccination in the United States

Lauri E. Markowitz, MD; Julianne Gee, MPH; Harrell Chesson, PhD; Shannon Stokley, DrPH

From the National Center for Immunization and Respiratory Diseases (Drs Markowitz and Stokley), Immunization Safety Office, National Center for Emerging and Zoonotic Infectious Diseases (Ms Gee), and National Center for HIV, Viral Hepatitis, STD and TB Prevention (Dr Chesson), Centers for Disease Control and Prevention, Atlanta, Ga
The authors have no conflicts of interest to disclose.
Address correspondence to Lauri E. Markowitz, MD, 1600 Clifton Rd NE, MS A34, Centers for Disease Control and Prevention, Atlanta, GA 30329 (e-mail: lem2@cdc.gov).
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ABSTRACT

Since human papillomavirus (HPV) vaccine was first introduced for females in the United States in 2006, vaccination policy has evolved as additional HPV vaccines were licensed and new data became available. The United States adopted a gender neutral routine HPV immunization policy in 2011, the first country to do so. Vaccination coverage is increasing, although it remains lower than for other vaccines recommended for adolescents. There are various reasons for low coverage, and efforts are ongoing to increase vaccine uptake. The safety profile of HPV vaccine has been well established from 10 years of postlicensure monitoring. Despite low coverage, the early effects of the HPV vaccination program have exceeded expectations.

KEYWORDS: human papillomavirus; human papillomavirus vaccine; immunization program

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DURING THE FIRST decade of the human papillomavirus (HPV) vaccination program in the United States, there have been policy, communication, implementation, and monitoring challenges. However, substantial progress has been made and advances in research have led to policy and program changes. In this review we summarize the first 10 years of the HPV vaccination program in the United States, including the evolution in vaccine policy, the vaccination program and coverage, as well as information obtained postlicensure on these safe and highly effective vaccines.

Infection with HPV, the most common sexually transmitted infection, can lead to a variety of HPV-associated cancers; approximately 31,500 cancers attributable to HPV occur annually in the United States.[1,2] Although most HPV infections are transient, persistent infection with oncogenic types can lead to precancerous lesions and cancer. Many HPV types can infect the anogenital area but HPV 16 and HPV 18 are responsible for approximately 50% of high-grade cervical dysplasias and 70% of cervical cancer cases. HPV 16 also is the cause of most other cancers attributable to HPV, including vaginal, vulvar, anal, penile, and oropharyngeal cancers.[1,3] Among HPV-attributable cancers, cervical cancers are the most common in women and oropharyngeal cancers are the most common in men. The total estimated number of HPV-attributable oropharyngeal cancers exceeds the number of cervical cancers in the United States.[2] Other conditions caused by HPV include genital warts and a rare but serious disease, recurrent respiratory papillomatosis, both due mainly to HPV 6 and 11, types not considered oncogenic. HPV vaccines were developed to target the most common types that cause cancer and large clinical trials showed high efficacy of the vaccines for prevention of cervical precancer lesions and other clinical end points.[4] Three HPV vaccines have been licensed for use in the United States.[5,6]

HPV VACCINATION POLICY AND RECOMMENDATIONS

In partnership with relevant professional organizations and following advice from the Advisory Committee on Immunization Practices (ACIP), the Centers for Disease Control and Prevention (CDC) makes vaccine policy in the United States. Recommendations are published in the *Morbidity and Mortality Weekly Report*. Since the first HPV vaccine was licensed in mid-2006, routine vaccination has been recommended for girls at age 11 or 12 years; the series can be started at age 9 years.[7] Vaccination has also been recommended through age 26 years for women not vaccinated previously. Age 11 or 12 years was recommended as the target age group because HPV vaccine should be administered before potential exposure to HPV and to facilitate administration, because 11 or 12 years is the age recommended for 2 other vaccines—tetanus-diphtheria-acellular pertussis vaccine and meningococcal conjugate vaccine.[5,8] Although age recommendations for girls

Table 1. Recommendations for HPV Vaccination in the United States, 2006 through 2016

Year*	Age and Sex Recommendations	Vaccines Recommended†	Number of Doses	Policy Publication
2006	Female: *Routine vaccination at age 11 or 12 years; series can be started at age 9 years. Vaccination recommended through age 26 years if not vaccinated previously*	4vHPV	3	Markowitz et al[7]
2009	Female: Recommendation as in 2006 Male: *May be vaccinated at age 9–26 years*	4vHPV, *2vHPV* *4vHPV*	3	CDC[9,10]
2011	Female: Recommendation as in 2006 Male: *Routine vaccination at age 11 or 12 years; series can be started at age 9 years. Vaccination recommended through age 21 years if not vaccinated previously. Vaccination recommended through age 26 years for men who have sex with men‡*	4vHPV, 2vHPV 4vHPV	3	CDC[11]
2015	Female: Recommendation as in 2006 Male: Recommendation as in 2011	4vHPV, 2vHPV, *9vHPV* 4vHPV, *9vHPV*	3	Petrosky et al[6]
2016	Female: Recommendation as in 2006 Male: Recommendation as in 2011	4vHPV, 2vHPV, 9vHPV 4vHPV, 9vHPV	*2 for immunocompetent persons starting series at age 9–14 years* 3 for persons starting series at older ages and for persons with immunocompromising conditions	Meites et al[12]

HPV indicates human papillomavirus; 2vHPV, bivalent HPV vaccine; 4vHPV, quadrivalent HPV vaccine; 9vHPV, 9-valent HPV vaccine; and CDC, Centers for Disease Control and Prevention.

Italics indicate changes in the recommendations that year.

*Year of vote by the Advisory Committee on Immunization Practices.

†The Advisory Committee on Immunization Practices did not preferentially recommend any HPV vaccine; after 2016 only 9vHPV has been available in the United States.

‡HPV vaccination is also recommended through age 26 years for immunocompromised persons, including those with HIV infection.

and women have not changed since 2006, there have been several modifications to recommendations over the past 10 years, after additional HPV vaccines were licensed and new data became available from clinical trials (Table 1).

The first HPV vaccine, quadrivalent HPV vaccine (Merck & Co, Kenilworth, NJ), targeting HPV 6, 11, 16, and 18, was licensed by the Food and Drug Administration (FDA) for use in a 3-dose schedule in females aged 9 through 26 years in 2006, and was recommended by ACIP that same year. A bivalent HPV vaccine (Glaxo-SmithKline, Rixensart, Belgium), targeting HPV 16 and 18, was licensed for use in a 3-dose schedule in 2009.[9] Because the initial vaccine trials were conducted only in women, it was not until 2009, after data were available from clinical trials in men, that quadrivalent HPV vaccine was licensed for males aged 9 through 26 years.[10] Policy deliberations were ongoing regarding burden of disease in men and cost-effectiveness, and data on efficacy against anal precancer end points in men were still pending from clinical trials.[13] After further consideration and availability of additional data from these trials, in 2011 routine HPV vaccination was recommended for boys aged 11 or 12 years and for those through 21 years not vaccinated previously.[11] The United States was the first country to recommend routine vaccination for boys and for several years was one of the few countries to do so.[14] Modeling the projected effect of vaccination provided important information to inform policy makers about policy decisions, including vaccination of boys.[15–17] The burden of disease among men, cost-effectiveness, and effect of male vaccination when there is low vaccination coverage levels in women, as in the United States in 2011, as well as equity considerations, informed the decision to include boys in the routine immunization program.[11]

In 2014, a 9-valent HPV vaccine (Merck & Co) was licensed by the FDA for use in a 3-dose schedule in females and males, and was recommended by ACIP in early 2015 as 1 of 3 vaccines that could be used for females and 1 of 2 vaccines for males.[6] The 9-valent HPV vaccine targets the same types as the quadrivalent HPV vaccine and 5 additional cancer-causing types, HPV 31, 33, 45, 52, and 58.[18]

The most recent recommendation change was in late 2016.[12] This was on the basis of data showing that a 2-dose series in persons aged 9 through 14 years produced noninferior antibody response compared with 3 doses in women aged 16 through 26 years, the age group and schedule for which efficacy was shown in clinical trials.[19] ACIP reviewed immunogenicity data as well as other evidence and recommended 2 doses, at a 0, 6 to 12 month schedule, for immunocompetent persons starting the series before their 15th birthday.[12,20]

Although all 3 HPV vaccines are licensed in the United States and ACIP did not preferentially recommend any vaccine, almost all vaccine used through 2015 was quadrivalent HPV vaccine. After the end of 2016, 9-valent HPV vaccine has been the only HPV vaccine sold in the United States.

The ACIP charter calls for consideration of health economic data in ACIP deliberations, although there is no