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Ten Years of Human Papillomavirus Vaccination in the United States

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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

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.

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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 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 official threshold for determining cost-effectiveness of vaccination in the United States. HPV vaccine recommendations published in the CDC's *Morbidity and Mortality Weekly Report* have consistently included information about cost-effectiveness (Table 2). Numerous modeling studies have indicated that routine HPV vaccination is an efficient use of public health resources and will yield substantial reductions in HPV-associated disease over time.[15,16,21–29]

HPV Vaccination Implementation

Almost all vaccinations are delivered by primary care providers in clinic-based settings in the United States. There is public as well as private financing for vaccines. The Vaccines for Children program supplies enrolled private and public health care providers with federally purchased vaccines for use among uninsured, Medicaid-eligible, and other entitled children through age 18 years.[30] Under the Patient Protection and Affordable Care Act of 2010, nongrandfathered private health plans must offer, at no cost to beneficiaries, vaccines that are recommended by ACIP. Similarly, qualified health plans on the health insurance exchanges that went into effect in 2014 must offer ACIP-recommended vaccines at no cost to beneficiaries.

In the first years of the HPV vaccination program, uptake of HPV vaccine among girls paralleled other recently recommended vaccines for adolescents; however, the increase in HPV vaccine coverage started to lag behind within 3 years after introduction.[31] Although HPV vaccine coverage, measured by the National Immunization Survey-Teen, continues to increase, it remains substantially lower than coverage of tetanus-diphtheria-acellular pertussis vaccine and meningococcal conjugate vaccine, recommended for the same age group (Figure). At least 1- and 3-dose HPV vaccine coverage in 2016 among adolescent girls aged 13 to 17 years was 65.1% and 43.0%, respectively. After the routine recommendation for boys in 2011, coverage in boys began to increase; in 2016, at least 1-dose and 3-dose coverage among adolescent boys aged 13 to 17 years reached 56.0% and 31.5%, respectively. There is striking variation according to state, with at least 1-dose coverage in 2016 ranging among adolescent girls from 47.8% to 90.1% and among adolescent boys from 36.9% to 87.8%. At least 1-dose coverage is significantly higher in Hispanic and non-Hispanic black compared with non-Hispanic white adolescents and among those living below compared with those living at or above the poverty level.[31]

Focusing specifically on receipt of the series at the recommended age, completion of the HPV vaccination series by age 13 years has been low. In 2013, a median of 12% and 19% of adolescent girls covered by commercial health plans and Medicaid plans, respectively, had completed the series by age 13.[32] However, National Immunization Survey-Teen data indicate that receipt of 3 doses of HPV vaccine by age 13 years has increased with each birth cohort from 11.3% among girls born in 1995 to 26.6% among girls born in 2000.[33]

Immunization requirements for school attendance, which are under the jurisdiction of states, have been effective in raising coverage for other childhood and adolescent vaccines. Soon after the HPV vaccine was introduced into the national program, school immunization requirements were advocated by a manufacturer; this raised a variety of philosophical, legal, and policy concerns and efforts were soon abandoned.[34,35] Subsequently, requirements for HPV vaccination were enacted in 2 jurisdictions, Virginia and Washington, DC. These differed from school requirements for other vaccinations, and had broad opt-out provisions, with little effect on coverage.[36] More recently, Rhode Island, a state that already had achieved high coverage, passed a school immunization requirement with a graduated integration of HPV vaccination over 3 years, beginning in 2015.[37]

Although experts in health care frequently cite a lack of adolescent preventive health care visits as a reason for low vaccination coverage, missed opportunities to administer HPV vaccine are common. Among girls born during 1999 to 2000 who had not received HPV vaccine before age 13 years, 80.1% had at least 1 missed opportunity to receive HPV vaccination.[33] Had HPV vaccine been administered during these encounters, first dose coverage would have reached 89% by age 13.

Multiple studies have examined reasons for the low HPV vaccine coverage and, more recently, practices that could improve uptake.[38,39] Lack of strong provider recommendation for vaccination at the recommended age has been identified by many studies and efforts to increase coverage have included providing education, tools, and communication messages for vaccine providers.[40,41] Parental attitudes toward HPV vaccination have also been

reported as an important factor contributing to low coverage, especially by health care providers.[39] Although parents have reported concerns over safety of the vaccine or that the vaccine was not necessary because their child was not sexually active,[39,42] one study suggested that parents view HPV vaccine as important as other vaccines recommended for adolescents and that health care providers might overestimate parental concerns about the HPV vaccine.[43] Reasons for low coverage are multifactorial and include factors at the parent and health system, in addition to provider levels, all of which are further explored in this special supplement.

Vaccine Safety

The safety profile of HPV vaccines has been well established from prelicensure trials as well as from 10 years of postlicensure monitoring and evaluation.[44] Prelicensure trials included >15,000 participants for each of the 3 HPV vaccines, all with favorable findings and the expected side effects of fever and injection site reactions.[45–48] Postlicensure data from the United States and other countries have provided a range of assessments of HPV safety through passive reporting and specific safety studies. The major systems used to monitor and evaluate vaccine safety in the United States include the Vaccine Adverse Event Reporting System (VAERS), the Clinical Immunization Safety Assessment Network, the Vaccine Safety Datalink (VSD), and the FDA Sentinel System. Postlicensure safety evaluations are also conducted through FDA postmarketing commitments by the manufacturer. The first postlicensure safety evaluations for any new vaccine are from VAERS. VAERS serves as an early warning system for potential safety concerns; however, it is a passive, spontaneous reporting system, and causal associations cannot be determined. Because mainly quadrivalent HPV vaccine was used in the United States through 2015, most data from the United States monitoring systems are available for this vaccine. Early data from VAERS showed disproportionate reporting for syncope and venous thromboembolic events; venous thromboembolic events were later found not to be associated with HPV vaccination in 5 large population-based studies.[44] Syncope is a known adverse event after any injectable vaccination and, although uncommon, has continued to be identified after HPV vaccination.[49] Through March 2016, 79 million doses of quadrivalent vaccine had been distributed in the United States.[50] Additional reviews of VAERS data during this time have revealed no new vaccine safety concerns.[50,51] Other large population-based evaluations of the general safety and death as well as multiple autoimmune and neurologic conditions examined in the VSD and in other studies have been reassuring with no other confirmed safety signals identified.[44] The CDC and FDA are continuously reviewing safety of HPV vaccines, as for all vaccines. VAERS conducts detailed review of all serious reports. Internationally, the World Health Organization Global Advisory Committee on Vaccine Safety has reviewed HPV vaccine multiple times, most recently in 2017.[52]

Despite the large amount of data available regarding safety and reviews by expert committees,[53] safety remains one of the top concerns among US parents whose children have not yet initiated HPV vaccination.[51] Traditional and social media have the ability to promote misleading HPV safety concerns. Several specific safety concerns about HPV vaccines have been raised over the past 10 years, including complex regional pain syndrome, postural orthostatic tachycardia syndrome, and primary ovarian insufficiency, but none have

been substantiated.[44] Communication and education about HPV vaccine safety and about ongoing safety monitoring for all vaccines in the United States are important components of the vaccination program.[41]

HPV Vaccine Controversies and Communications

The first decade of the HPV vaccine program was punctuated by various controversies, some mentioned earlier in this review, as well as media attention.[54] Although first hailed as a promising anticancer vaccine, this media theme was soon eclipsed by the push for school immunization requirements for HPV vaccination. In 2007, a governor's executive order for an HPV vaccination requirement for middle school attendance in 1 state, which was later reversed, pushed HPV vaccine into the political arena. This issue attracted media coverage again when it was discussed in national presidential primary debates in 2011 and in 2015.[54] Vaccine safety concerns, some of which have been raised by high visibility political, media, or medical figures, have also garnered media attention.[55] Widespread social media and online sources of information often have had negative content.[56] Among other controversies was the concern that the vaccine would promote risky sexual behavior; this has been examined and refuted by several studies.[57,58] Communication strategies have focused on providing correct information rather than responding to specific media episodes, and on providing assistance to providers so that they can deliver clear and strong messages about the safety and efficacy of HPV vaccines.[41]

Effect of HPV Vaccination

Prevention of HPV-associated cancer is the main goal of the HPV vaccination program; however, the effect on HPV-associated cancers might not be observed for decades. Although the United States has cancer registries in every state allowing trends in HPV-associated cancers to be monitored,[2] neither HPV infection nor other early outcomes of HPV are nationally reportable conditions. Therefore, projects were implemented to monitor the effect of HPV vaccination on HPV prevalence, genital warts, and cervical precancer lesions. Despite low coverage achieved in the United States, data from national surveys showed declines in HPV vaccine type prevalence among young women within the first 4 years of the HPV vaccination program—a 56% decrease in HPV vaccine types in cervical-vaginal samples from 14- to 19- year-olds.[59] Decreases among 20- to 24-year-olds were first observed within 6 years of vaccination introduction[60] and by 8 years after introduction, there was a 71% decrease in HPV vaccine type prevalence among 14- to 19-year-olds and a 61% reduction among 20- to 24-year-olds (Table 3).[61] The greater than expected effect observed with the low 3-dose coverage suggests high effectiveness with <3 doses and/or effect of herd protection. Clinic-based studies have also shown early effects of vaccination with HPV vaccine type prevalence decreases in vaccinated as well as unvaccinated women.[62–64] Other countries that have achieved high vaccine coverage with quadrivalent or bivalent HPV vaccines have reported rapid and larger declines in vaccine type HPV infection as well as evidence of herd effects.[70] There has been no consistent evidence of type replacement from HPV types not targeted by the vaccines.[71]

Declines in HPV-associated clinical outcomes have been observed in the United States as well. Decreases in genital warts were appreciated at the same time as the decrease in vaccine type HPV prevalence.[65,66] On the basis of claims data from US health plans, prevalence of anogenital warts per 1000 person-years declined from 2.9 in 2006 to 1.8 in 2010 among female adolescents aged 15 to 19 years.[65] Cervical cancer precursor lesions are more challenging to monitor because these are detected through cervical cancer screening and recommendations in the United States have changed to start screening at an older age and be done less frequently.[72,73] Therefore, cervical cancer precursors should ideally be monitored among screened women or be informed by changes in screening rates. Cervical cancer precursor lesions are being monitored through several efforts (Table 3). A 5-site project includes active population-based surveillance of cervical intraepithelial neoplasia (CIN) grades 2 and 3 and adenocarcinoma in situ (CIN2þ) and associated HPV types in women older than 18 years of age, as well as estimation of the annual rate of cervical cancer screening among the catchment area population.[74] Preliminary data indicate declines in estimated CIN2þ prevalence per 100,000 screened women age 18 to 20 and 21 to 24 years between 2008 through 2010 and 2013 through 2014.[67] Declines have also been observed in a population-based study in New Mexico, where estimates of screening prevalence as well as CIN are being obtained. When adjusting for changes in screening from 2007 to 2014, reductions in CIN 1, 2, and 3 incidence were observed among 15- to 19-year-olds and for CIN grade 2 among 20- to 24-year-olds.[68] Finally, on the basis of claims data restricted to women who received screening, CIN2 decreased significantly among 15- to 19- and 20-to 24-year-olds[69].

Summary

Since HPV vaccine was introduced 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. In 2016, a 2-dose schedule was recommended for persons starting vaccination at age 9 through 14 years. Postlicensure safety data show HPV vaccines are safe. However, concerns about safety continue to be raised, highlighting the need to communicate the robust safety monitoring systems and the available safety data from the United States and other countries. HPV vaccine coverage is increasing, although it remains lower than for other vaccines recommended for adolescents and has not reached the Healthy People target of 80% coverage for 13-to 15-year-olds.[75] Despite this, evidence of the early effect of the vaccination program has exceeded expectations.

As we move into the second decade of the HPV vaccination program, there is considerable room for improvement in vaccine uptake. The 2-dose schedule might facilitate vaccine initiation and make it easier to complete the series. Knowledge from substantial research over the past decade is being used to implement successful interventions for providers, parents, and health systems to improve coverage. In the coming years, further data on these highly effective vaccines can be expected from ongoing clinical research and monitoring efforts. Continued collaborations between public health, private providers, health systems, and other stakeholders will ensure that the United States can realize the full benefits of these vaccines.

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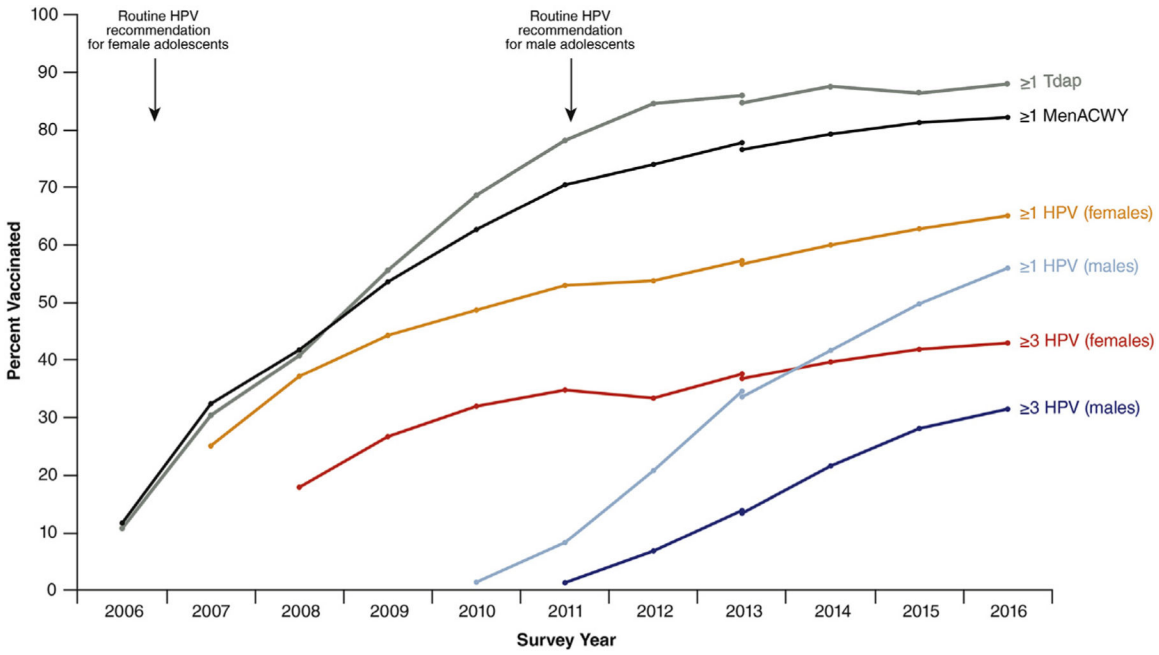

Figure.

Estimated vaccination coverage among adolescents aged 13 to 17 years, National Immunization Survey-Teen, United States, 2006 through 2016. Coverage on the basis of provider records; a revised definition of adequate provider data was used starting in 2013. HPV indicates human papillomavirus vaccine; Tdap, tetanus, diphtheria, and acellular pertussis vaccine; and MenACWY, meningococcal ACWY vaccine.

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	4vHPV, *2vHPV*	3	CDC[9,10]
	Male: *May be vaccinated at age 9–26 years*	*4vHPV*		
2011	Female: Recommendation as in 2006	4vHPV, 2vHPV	3	CDC[11]
	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		
2015	Female: Recommendation as in 2006	4vHPV, 2vHPV, *9vHPV*	3	Petrosky et al[6]
	Male: Recommendation as in 2011	4vHPV, *9vHPV*		
2016	Female: Recommendation as in 2006	4vHPV, 2vHPV, 9vHPV	*2 for immunocompetent persons starting series at age 9–14 years*	Meites et al[12]
	Male: Recommendation as in 2011	4vHPV, 9vHPV	3 for persons starting series at older ages and for persons with immunocompromising conditions	

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.

Table 2.

Cost-Effectiveness of HPV Vaccination in the United States

HPV Vaccination Strategy	Cost-Effectiveness Ratio Expressed as Cost Per QALY Gained	Policy Publication
Female (2vHPV or 4vHPV) *	$5000 to $30,000	Markowitz et al[7]
Male (4vHPV) †	$25,000–$45,000 (favorable scenario) $85,000 to >$250,000 (unfavorable scenario)	CDC[11]
MSM through age 26 years (4vHPV) ‡	<$50,000	CDC[11]
9vHPV versus 4vHPV (female and male) §	<$0 (cost-saving)	Petrosky et al[6]
2-dose versus 3-dose 9vHPV (female and male) ‖	< $0 (cost-saving)	Meites et al[12]

HPV indicates human papillomavirus; QALY, quality adjusted life year; MSM, men who have sex with men; 4vHPV, quadrivalent HPV vaccine; 2vHPV, bivalent HPV vaccine; 9vHPV, 9-valent HPV vaccine; ACIP, Advisory Committee on Immunization Practices; and CDC, Centers for Disease Control and Prevention.

The cost-effectiveness ratios listed are as provided in the *Morbidity and Mortality Weekly Report* ACIP statements or policy notes, adjusted to 2016 US dollars using the all-items component of the Consumer Price Index, and rounded to the nearest $5000.

* The cost-effectiveness of female adolescent vaccination was calculated compared with no vaccination. The cost-effectiveness ratios reported in the 2007 ACIP statement[7] were obtained from published studies.[21–24] In a subsequent ACIP statement,[5] additional cost-effectiveness studies were cited[25,26] and a wider range of cost-effectiveness ratios was listed ($5000–$45,000).

† The cost-effectiveness of male vaccination was calculated as compared with female-only vaccination. The cost-effectiveness ratios reported were obtained from 3 published studies.[15–17] The “favorable scenario” includes when female vaccination coverage is low (eg, 20%) and when all potential health benefits are included in the analysis. The “unfavorable scenario” includes when female vaccination coverage is high (eg, 75%) and when including only the health outcomes for which the vaccine is indicated.[5]

‡ The cost-effectiveness of MSM vaccination was calculated compared with no vaccination. The cost-effectiveness ratio reported in the 2011 ACIP recommendation was obtained from a single study.[27]

§ The cost-effectiveness of 9vHPV for both sexes was calculated as compared to 4vHPV for both sexes. The 2015 ACIP recommendation did not explicitly report a cost per QALY ratio, but instead noted that 9vHPV for both sexes was cost-saving compared to 4vHPV for both sexes, based on a single study.[28]

‖ The cost-effectiveness of 2-dose 9vHPV for both sexes was calculated as compared to 3-dose 9vHPV for both sexes. The 2016 ACIP recommendation did not explicitly report a cost per QALY ratio, but instead noted that 2-dose 9vHPV for both sexes was cost-saving compared to 3-dose 9vHPV for both sexes, based on a single study.[29]

Table 3.

Selected Postlicensure Monitoring: Evidence of Declines in HPV Prevalence and HPV-Associated Outcomes, United States

Outcome	Population	Comparison Years	Main Findings
HPV prevalence	Female participants; National Health and Nutrition Examination Surveys	2007–2010 with 2003–2006[59]	56% decrease in prevalence of 4vHPV types in cervical-vaginal samples among 14- to 19-year-olds (11.5%−5.1%)
		2009–2012 with 2003–2006[60]	64% decrease in prevalence of 4vHPV types in cervical-vaginal samples among 14- to 19-year-olds (11.5%−4.3%) and 34% decrease among 20- to 24-year-olds (18.5%−12.1%)
		2011–2014 with 2003–2006[61]	71% decrease in prevalence of 4vHPV types in cervical-vaginal samples among 14- to 19-year-olds (11.5%−3.3%) and 61% decrease among 20- to 24-year-olds (18.5%−7.2%)
	Female enrollees screened for cervical cancer in integrated health care plans, northwestern United States	2012–2013 with 2007[62]	42% decrease in prevalence of 4vHPV types among 20- to 29-year-olds (10.6%−6.2%)
	Female patients attending primary care and sexually transmitted disease clinics, Cincinnati, Ohio	2009–2010 with 2006–2007[63]	58% decrease in prevalence of 4vHPV types among 13- to 26-year-olds (31.7%−13.4%)
		2013–2014 with 2006–2007[64]	75% decrease in prevalence of 4vHPV types in cervical-vaginal samples among 13- to 26-year-olds (34.8%−8.7%)
Genital warts	Female and male enrollees; claims data from privately insured patients, nationwide database	2007–2010 with prevaccine era[65]	Decrease in anogenital wart prevalence among female enrollees aged 15–19 years, from 2.9/100,000 person-years in 2006 to 1.8/100,000 person-years in 2010
	Female and male enrollees; claims data from primary care clinics, Boston, Massachusetts area	2013 with 2004[66]	Decrease in rate of genital warts in 16- to 26-year-olds, from 3.5% to 1.5% among female and from 3.6% to 2.9% among male enrollees
Cervical cancer precursors	Population-based surveillance in 5 sites across the United States	2013–2014 with 2008–2010[67]	CIN2+ decrease in estimated screened women, from 690 to 207/100,000 among 18- to 20-year-olds and from 1107 to 732/100,000 among 21- to 24-year-olds
	Statewide surveillance, New Mexico	2014 with 2007[68]	CIN2 decrease in estimated screened women, from 896 to 415/100,000 among 15- to 19-year-olds and from 1028 to 627/100,000 among 20- to 24-year-olds
	Claims data from privately insured women, nationwide database	2014 with 2007[69]	CIN2+ decrease in screened women, from 14.8 to 4.9/1000 person-years among 15- to 19-year-olds and from 20.5 to 11.3/1000 person-years among 20- to 24-year-olds

HPV indicates human papillomavirus; 4vHPV, quadrivalent HPV vaccine; CIN2, cervical intraepithelial neoplasia, grade 2; and CIN2+, cervical intraepithelial neoplasia, grade 2 or worse or adenocarcinoma in situ.