

Human Papillomavirus Vaccination 2020 Guideline Update: American Cancer Society Guideline Adaptation

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Abstract: The American Cancer Society (ACS) presents an adaptation of the current Advisory Committee on Immunization Practices recommendations for human papillomavirus (HPV) vaccination. The ACS recommends routine HPV vaccination between ages 9 and 12 years to achieve higher on-time vaccination rates, which will lead to increased numbers of cancers prevented. Health care providers are encouraged to start offering the HPV vaccine series at age 9 or 10 years. Catch-up HPV vaccination is recommended for all persons through age 26 years who are not adequately vaccinated. Providers should inform individuals aged 22 to 26 years who have not been previously vaccinated or who have not completed the series that vaccination at older ages is less effective in lowering cancer risk. Catch-up HPV vaccination is not recommended for adults aged older than 26 years. The ACS does not endorse the 2019 Advisory Committee on Immunization Practices recommendation for shared clinical decision making for some adults aged 27 through 45 years who are not adequately vaccinated because of the low effectiveness and low cancer prevention potential of vaccination in this age group, the burden of decision making on patients and clinicians, and the lack of sufficient guidance on the selection of individuals who might benefit. *CA Cancer J Clin* 2020;70:274–280. © 2020 American Cancer Society.

Keywords: cancer prevention, human papillomavirus (HPV), immunization, vaccine

Introduction

The development and availability of a vaccine against the human papillomavirus (HPV) have presented an exceptional opportunity for cancer prevention. The Centers for Disease Control and Prevention estimates that, for the period from 2012 to 2016, an average of 34,800 cancers annually in the United States were attributable to HPV infection. Ninety-two percent of these cases (32,100) of cervical, oropharyngeal, anal, vaginal, vulvar, and penile cancers were attributable to the types targeted by the 9-valent HPV vaccine, the only vaccine formulation distributed in the United States since 2016.¹ The American Cancer Society (ACS) first issued a guideline for routine use of the vaccine in 2007,² with an update issued in 2016.³

Uptake of vaccination in the United States has been slower than in many other high-income countries.^{4,5} According to the National Immunization Survey-Teen, in 2018, 68.1% of adolescents (male and female) aged 13 to 17 years had received at least 1 dose of HPV vaccine, and 51.1% were up to date with the HPV vaccine series.⁶ Enhanced national efforts to reach high levels of vaccination coverage in the United States are directed toward increasing clinician awareness and education and partnering with health systems, federally qualified health centers, state health departments, and professional organizations to implement processes that will improve vaccination delivery.^{7–10}

TABLE 1. Advisory Committee on Immunization Practices Recommendations for Vaccination, 2019

	ACIP RECOMMENDATIONS
Children and adults aged 9-26 y	HPV vaccination is routinely recommended at age 11 or 12 y; vaccination can be given starting at age 9 y. Vaccination is recommended for all persons through age 26 y who are not adequately vaccinated.
Adults aged >26 y	Catch-up HPV vaccination is not recommended for all adults aged >26 y. Instead, shared clinical decision making regarding HPV vaccination is recommended for some adults aged 27-45 y who are not adequately vaccinated. HPV vaccines are not licensed for use in adults aged >45 y.
Administration	Dosing schedules, intervals, and definitions of persons considered adequately vaccinated have not changed. No prevaccination testing (eg, Pap or HPV testing) is recommended to establish the appropriateness of HPV vaccination.
Cervical cancer screening	Cervical cancer screening guidelines and recommendations should be followed.
Special populations and medical conditions	These recommendations for children and adults aged 9-26 y and for adults aged >26 y apply to all persons, regardless of behavioral or medical risk factors for HPV infection or disease. For persons who are pregnant, HPV vaccination should be delayed until after pregnancy; however, pregnancy testing is not needed before vaccination. Persons who are breastfeeding or lactating can receive HPV vaccine. Recommendations regarding HPV vaccination during pregnancy or lactation have not changed.

Abbreviations: ACIP, Advisory Committee on Immunization Practices; HPV, human papillomavirus; Pap, Papanicolaou.

Adapted from: Meites E, Szilagyi PG, Chesson HW, Unger ER, Romero JR, Markowitz LE. Human papillomavirus vaccination for adults: updated recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep*. 2019;68:698-702.¹²

Previous Advisory Committee on Immunization Practices and ACS Recommendations

The 2007 ACS guideline for HPV vaccine use to prevent cervical cancer and its precursors was developed in parallel with, but independent from, the Federal Advisory Committee on Immunization Practices (ACIP).^{2,11} In one respect, the ACS guideline differed from ACIP recommendations, concluding that there were insufficient data to recommend for or against the universal vaccination of females aged 19 to 26 years. The ACS offered supporting recommendations for continued cervical cancer screening, vaccine implementation and utilization, education, and research. In 2016, in updating its recommendations to address use of the vaccine in males and the newly available 9-valent vaccine formulation, the ACS issued an endorsement of the then-current ACIP recommendations.³ On the basis of a supplemental evidence review and a conclusion of reduced efficacy and effectiveness of vaccination in the late teens and early 20s compared with the preteens (a question not examined in the ACIP updates), the ACS 2016 guideline endorsement statement attached a qualifying statement to the recommendation for catch-up vaccination for individuals aged 22 to 26 years, emphasizing the reduced benefits of vaccination at older ages.³

ACIP 2019 Update

In 2019, the ACIP recommended catch-up HPV vaccination for all persons through age 26 years, to harmonize the age recommendation for males and females and to simplify the immunization schedule for the feasibility of implementation.¹² They also adopted a recommendation for shared clinical decision making for adults aged 27 through 45 years (following

US Food and Drug Administration approval for this population), “recognizing that some persons who are not adequately vaccinated might be at risk for new HPV infection and might benefit from vaccination in this age group.” In the publication presenting the updated ACIP recommendations, it was acknowledged that most adults aged 27 through 45 years would not benefit from vaccination; the authors emphasized that adolescents remain the most important focus of the HPV vaccination program.¹²

The ACIP provides additional guidance on dosing schedules, intervals, and definitions of persons considered adequately vaccinated, which have not changed (see Table 1).¹²

ACS Process

In 2016, the ACS issued an endorsement of the ACIP recommendations for HPV vaccine use, applying a process of guideline endorsement based on a model developed by the American Society of Clinical Oncology.^{3,13,14} In 2019 and 2020, a similar methodology was used, resulting in an *adaptation* of the updated ACIP recommendations for HPV vaccination¹² based on broad general agreement but some areas of difference between the ACIP recommendations and judgments of the ACS Guideline Development Group in the context of cancer prevention aims and nationwide efforts to increase vaccine utilization (see Table 2).³

Methodological review of the updated 2019 ACIP recommendations (specific to catch-up vaccination through age 26 years and vaccination of adults aged 27-45 years) was conducted using the Appraisal of Guidelines, Research, and Evaluation (AGREE II) instrument¹⁵ by 2 ACS staff members. The overall score of the ACIP 2019

TABLE 2. Summary of ACS Adapted Recommendations

The ACS adapts the ACIP HPV Vaccination Recommendations, as listed below, with **qualifying statements in bold italics**:

HPV vaccination is routinely recommended at age 11 or 12 y; vaccination can be given starting at age 9 y.

ACS Qualifying Statement: Routine HPV vaccination between ages 9-12 y is expected to achieve higher on-time vaccination rates, resulting in increased numbers of cancers prevented. Health care providers are encouraged to start offering the HPV vaccine at age 9 or 10 y.

Vaccination is recommended for all persons through age 26 y who are not adequately vaccinated.

ACS Qualifying Statement: Providers should inform individuals aged 22-26 y who have not been previously vaccinated or who have not completed the series that vaccination at older ages is less effective in lowering cancer risk. (Saslow 2016³).

Catch-up HPV vaccination is not recommended for all adults aged >26 y. Instead, shared clinical decision making regarding HPV vaccination is recommended for some adults aged 27-45 y who are not adequately vaccinated.

The ACS does not endorse the recommendation for shared clinical decision making for adults aged 27-45 y because of the low effectiveness and low cancer prevention potential of vaccination in this age group, the burden of decision making on patients and clinicians, and the lack of sufficient guidance on selection of individuals who might benefit.

Abbreviations: ACIP, Advisory Committee on Immunization Practices; ACS, American Cancer Society; HPV, human papillomavirus.

guideline on HPV vaccination using the AGREE II instrument was 75%. The Rigor of Development subscale, which is intended to evaluate the processes used in developing the guideline, evidence synthesis, and the methods used to formulate the recommendation statements, was given a slightly higher appraisal rating (78%). The reviewers noted that some domains of the instrument may not be suitable for evaluating a vaccine use guideline. The ACS reviewers concluded that the ACIP evidence review methods and findings were clearly presented, and the evidence regarding individual benefit and risk applied to recommendations formulation was well described. Supplemental materials provided with the 2019 publication by Meites et al¹² included Evidence to Recommendation Framework tables, addressing the key elements and judgments in the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework for recommendation development, adopted by the ACIP in 2011.¹⁶ The evidence and rationale for the recommended age for routine vaccination have not been revisited since the original ACIP publication in 2007, which was before ACIP adoption of GRADE.

Members of the ACS Guideline Development Group participated in content review of the 2 new 2019 ACIP recommendations¹² and proposed modification or adaptation of the recommendation for age at routine vaccination, deliberating on the adequacy and interpretation of the evidence evaluated by ACIP, recent studies, and considerations related

to implementation efforts to increase rates of population coverage and on-time vaccination.

ACIP Recommendations and ACS Adaptation and Rationale

1. ACIP: HPV Vaccination Is Routinely Recommended at Age 11 or 12 Years; Vaccination Can Be Given Starting at Age 9 Years

ACS Qualifying Statement: Routine HPV vaccination between ages 9 and 12 years is expected to achieve higher on-time vaccination rates, resulting in increased numbers of cancers prevented. Health care providers are encouraged to start offering the HPV vaccine series at age 9 or 10 years.

The original ACIP 2007 recommendation for the age to initiate routine vaccination in females, which was extended to males in 2011¹⁷ (a recommended age of 11 or 12 years, with a statement that the vaccine can be administered as young as age 9 years), was based on: 1) the age groups in clinical studies of immunogenicity and safety (with high antibody titers after vaccination at age 11 or 12 years); 2) HPV epidemiology and age of sexual debut in the United States; and 3) programmatic purposes (ie, the established young adolescent health care visit at age 11 or 12 years).¹¹

HPV vaccination has been shown to be more effective at younger ages.¹⁸⁻²⁰ The data available to date show that vaccinating at age 12 or 13 years is significantly more effective than vaccinating at age 14 or 15 years, which, in turn, is more effective than vaccinating later in adolescence and early adulthood.¹⁹⁻²¹ It is therefore expected that vaccinating at ages 9 to 11 years will be at least as effective in preventing infections with vaccine-type HPV, precancers, and cancers attributed to HPV as vaccinating at age 12 or 13 years and will likely result in a stronger immune response.²² Vaccination has shown no sign of protection waning over time, and thus earlier vaccination would still confer protection throughout adolescence and early adulthood.²³⁻²⁵

The ACIP recommendation for routine age of HPV vaccination has not been revisited since the original recommendation in 2007. Unfortunately, vaccination rates for HPV have lagged behind those of Tdap (diphtheria, tetanus, pertussis) and MenACWY (meningococcal groups A, C, W, and Y) and may have plateaued, at least for girls.⁶ It is not clear that the intended benefit of including HPV vaccination in the adolescent immunization platform has been achieved; there are reports of parental choices to defer HPV vaccination at the time other recommended vaccinations are administered and of providers making weaker recommendations for HPV compared with the Tdap and MenACWY vaccines.²⁶⁻²⁹ Furthermore, there are anecdotal reports of parents agreeing only to those

vaccines that are required for school entry (ie, usually the Tdap and MenACWY vaccines).

On the basis of these implementation factors and the need to increase vaccine uptake, the American Academy of Pediatrics (AAP) in 2018 recommended starting the HPV vaccination series between ages 9 and 12 years and, in 2019, published an article entitled *Why AAP recommends initiating HPV vaccination as early as age 9*.^{30,31} The AAP noted that earlier vaccination offers providers more flexibility, may be preferable to parents or adolescents, and offers more opportunities to complete the series. They further noted that there is no known downside and that some providers have found it easier to vaccinate earlier because there is less discussion about sexual behavior as a risk factor. The AAP cited studies showing higher completion rates and higher acceptance of HPV vaccination by parents.^{32,33}

Evidence is emerging that series completion rates and vaccine acceptance may be higher when vaccination is initiated at age 9 or 10 years compared with age 11 or 12 years. A quality improvement initiative demonstrated the feasibility of routine HPV vaccination at age 9 years. In a large primary care network, the percentage of patients initiating vaccination by age 11 years increased from 4.6% to 60.8% within 18 months, demonstrating the acceptability of initiating vaccination at an earlier age by parents and providers.³² Another study of a large population-based cohort showed that 97.5% of children who initiated HPV vaccination at age 9 or 10 years completed the series by age 13.5 years compared with 78.0% of children who initiated HPV vaccination at age 11 or 12 years.³³ A report of qualitative interviews of providers demonstrated high parental acceptance of earlier HPV vaccination. Parents preferred having their children receive fewer shots in a single visit and had fewer concerns related to sexual activity. Although providers were initially skeptical about initiating HPV vaccination earlier than age 11 years, including being concerned about unbundling the HPV vaccine from other preteen vaccines, no providers reported any negative reactions from parents. They found the ease of early initiation motivating and reported an increase in opportunities to complete as well as initiate the 2-dose series.³⁴

Earlier initiation of the vaccine has many potential benefits that are expected to lead to increased vaccination rates. Evidence is evolving of higher vaccine acceptance, increased ease of provider recommendation, and increased rates of vaccine series completion. Higher rates of vaccination will prevent more cancers, thus increasing vaccine effectiveness in the overall population.

The ACS adapted the ACIP recommendation for routine HPV vaccination at age 11 or 12 years, with a statement that routine HPV vaccination between ages 9 and 12 years is expected to achieve higher on-time vaccination rates, resulting in increased numbers of cancers prevented. Health care providers are encouraged to start offering the HPV vaccine

series at age 9 or 10 years. This provides an opportunity to increase vaccination uptake and completion of the vaccine series at the recommended age and, subsequently, to prevent cancers and deaths.

2. ACIP: Catch-Up HPV Vaccination Is Recommended for All Persons through Age 26 Years Who Are Not Adequately Vaccinated

ACS Qualifying Statement: Providers should inform individuals aged 22 to 26 years who have not been previously vaccinated or who have not completed the series that vaccination at older ages is less effective in lowering cancer risk.

Before the June 2019 ACIP update, the recommendation for men ages 22 to 26 years differed from that for women in this age group. Catch-up vaccination recommendations are now harmonized for all persons through age 26 years.¹² Having the same recommendation for men and women is simpler and more feasible for communicating and implementing vaccination efforts. The 2016 ACS qualifying statement about the reduced effectiveness of vaccination at older ages, based on 1) evidence of greater benefit for females vaccinated at ages 18 to 20 years compared with ages 21 to 26 years, 2) opportunities for young women and men to get vaccinated at college, and 3) opportunities for young women and men to access vaccination without parental consent, was reaffirmed (see Table 2).³

3. ACIP: Catch-Up HPV Vaccination Is Not Recommended for All Adults Aged >26 Years. Instead, Shared Clinical Decision Making Regarding HPV Vaccination Is Recommended for Some Adults Aged 27 through 45 Years Who Are Not Adequately Vaccinated. HPV Vaccines Are Not Licensed for Use in Adults Aged >45 Years

The ACS does not endorse the recommendation for shared clinical decision making for adults aged 27 through 45 years because of the low effectiveness and low cancer prevention potential of vaccination in this age group, the burden of decision making on patients and clinicians, and the lack of sufficient guidance on the selection of individuals who might benefit.

HPV vaccination is most effective in early adolescence, with effectiveness decreasing dramatically by age 18 years and minimal benefit noted by age 20 or 21 years.^{3,35} Although HPV vaccination is safe for adults aged 27 to 45 years, there would be limited public health benefits from vaccinating people in this age range.^{12,36,37} Compared with vaccination through age 26 years, vaccination of adults through age 45 years was estimated, using models that assumed low uptake of the vaccine by individuals in this age range, to prevent only an additional 0.5% cases of cancer, 0.4% cases of cervical precancer, and 0.3% cases of genital warts over the next 100 years.³⁸

Beyond general knowledge of HPV natural history, there is currently little evidence on which to base guidance about HPV vaccination as part of shared decision making for clinicians and adults.³⁹ Furthermore, these provider-patient discussions may interfere with efforts to increase vaccination at the recommended age. Soon after the introduction of HPV vaccination in the United States, public health experts began to urge that communication messages intended to increase provider recommendation and parent acceptance should focus on cancer prevention and not sexual transmission or sexual activity.^{40,41} Of the considerations for shared clinical decision making regarding HPV vaccination of adults aged 27 through 45 years included in the ACIP recommendations, more than one-half mention sexual transmission and/or behavior.¹² Given that many if not most parents of children aged between 9 and 12 years will themselves be in the age group for which shared decision making is now recommended, these same parents may hear from their own providers that vaccination decisions should be based on their past, present, and/or anticipated future sexual behavior while hearing from their children's providers that vaccination decisions should be based on cancer prevention and not sexual behavior. The new ACIP recommendation may have the unintended consequence of moving the focus of HPV vaccination from cancer prevention back to sexual behavior and stalling or even reversing the hard-earned progress made in this country to increase adolescent HPV vaccination rates.

HPV vaccination for adults aged 27 through 45 years is expected to provide minimal public health benefits. Anecdotal reports of providers recommending vaccination to all adults suggest that shared clinical decision making is not taking place and that adult vaccination is not focusing on individuals who might benefit. Adult vaccination is unlikely to prevent a significant number of cancers, precancers, or genital warts and, given the global shortage of HPV vaccine, which is expected to endure for the next several years,⁴² some have suggested that it is advisable to direct the available vaccine supply to individuals and populations for whom the burden is highest and the effectiveness is greatest.⁴³ The ACS chose not to endorse this ACIP recommendation and urges organizations, health systems, and health care providers to continue to focus HPV vaccination efforts on preteens, given that it continues to be challenging, even after more than 13 years since the first recommendation, to raise HPV vaccination rates to the level of other adolescent vaccines.

Discussion

This update of the ACS guideline addresses 3 key issues based on recent actions by the US Food and Drug

Administration, the ACIP, and the AAP, as well as new evidence. The ACS has adapted the ACIP recommendation for routine age for HPV vaccination to emphasize that vaccination may be routinely offered between ages 9 and 12 years. The ACS endorses harmonization of catch-up vaccination for all individuals through age 26 years, while continuing to include a qualifying statement about the reduced effectiveness of vaccination at older ages. The ACS does not endorse the recommendation for shared clinical decision making regarding vaccination for adults aged 27 to 45 years.

As noted above, evidence is emerging that series completion rates and vaccine acceptance may be higher when vaccination is initiated at age 9 or 10 years compared with age 11 or 12 years. Earlier initiation of HPV vaccination offers more time for completion of the series, increases the likelihood of vaccinating before first HPV exposure, and reduces concerns related to the discussion of sexual activity. The ACS is aware of a growing number of health systems that have set a goal of starting vaccinations at age 9 years to increase the likelihood that more parents will have completed the vaccination series by age 13 years. The qualifying statement for routine vaccination between ages 9 and 12 years is consistent with the original ACIP recommendation¹¹ and with the 2019 recommendation from the AAP.³¹

The ACS decision not to endorse shared clinical decision making for vaccination at ages 27 to 45 years was based primarily on the minimal cancer prevention benefit expected from the vaccination of individuals in this age range. In addition to the low effectiveness and low cancer prevention potential of vaccination in this age group, other considerations included the burden of decision making on patients and clinicians and the lack of sufficient guidance on the selection of individuals who might benefit.

Since its introduction in 2006, HPV vaccination has led to substantial population-wide decreases in genital warts,^{44,45} recurrent respiratory papillomatosis,⁴⁶ cervical precancers,^{20,47} and, most recently, cervical cancers.^{48,49} The Director-General of the World Health Organization has called for a global strategy to eliminate cervical cancer as a public health problem, which is to be achieved through a combination of vaccinating 90% of girls, screening 70% of women, and treating 90% of women identified as having precancerous cervical disease.⁵⁰ Yet rates of HPV vaccination in the United States continue to lag far behind rates in other high-income countries,⁴ as well as rates of other adolescent vaccines in this country.¹²

Forging a path to elimination will take sustained action by organizations and individuals in cancer control, immunization, and public health communities in the United States and around the world. The Centers for Disease Control and Prevention has provided funding to state public health

departments and to national organizations to prioritize HPV vaccination. This funding has supported 2 initiatives at the ACS. The ACS convenes and leads the National HPV Vaccination Roundtable, a national coalition of over 70 organizations working together to prevent HPV-associated cancers and precancers by increasing and sustaining US HPV vaccination.⁹ Through the Vaccinate Adolescents against Cancer (VACs) program, ACS staff across the country work with health systems to increase provider awareness and education and to improve system-wide processes that can increase HPV vaccination uptake, with a focus on integrated delivery systems, large hospital systems, federally qualified health centers, and state health coalitions.^{7,8} In 2018, the ACS launched *Mission: HPV Cancer Free*, a national public health campaign to reduce vaccine-preventable HPV cancers by increasing HPV vaccination rates. The campaign leverages high-impact public health partnerships with health care systems, clinicians, and other organizations to drive vaccination rate improvement and reduce barriers to vaccination.⁵¹

The combination of HPV vaccination and cervical cancer screening has the potential to prevent tens of thousands of cancers caused by HPV each year in this country and to eliminate cervical cancer as a public health problem in the coming decades. It is important that all individuals with a cervix, regardless of whether they have been vaccinated, get screened according to current guidelines. Vaccination of all children between ages 9 and 12 years will prevent >90% of the cervical, oropharyngeal, anal, vaginal, vulvar, and penile cancers that are caused by HPV and, combined with screening and the treatment of cervical precancers, can lead to the first elimination of a cancer in history. ■

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