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Human Papillomavirus Vaccination Guideline Update: American Cancer Society Guideline Endorsement

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Abstract

The American Cancer Society (ACS) reviewed and updated its guideline on human papillomavirus (HPV) vaccination based on a methodologic and content review of the Advisory Committee on Immunization Practices (ACIP) HPV vaccination recommendations. A literature review was performed to supplement the evidence considered by the ACIP and to address new vaccine formulations and recommendations as well as new data on population outcomes since publication of the 2007 ACS guideline. The ACS Guideline Development Group determined that the evidence

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Additional supporting information may be found in the online version of this article.

DISCLOSURES: The American Cancer Society (ACS) supported the development of the guideline through the use of general funds. Outside the submitted work, the ACS is the recipient of 2 cooperative agreements from the Centers for Disease Control and Prevention (CDC), Prevention and Public Health Fund, that seek to increase human papillomavirus (HPV) vaccination of girls and boys ages 11 to 12 years within the United States. Debbie Saslow reports being Principal Investigator of both of those cooperative agreements, and Marcie Fisher-Borne reports being co-Principal Investigator and receiving salary support through one of those cooperative agreements. All remaining authors report no conflicts of interest.

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supports ACS endorsement of the ACIP recommendations, with one qualifying statement related to late vaccination. The ACS recommends vaccination of all children at ages 11 and 12 years to protect against HPV infections that lead to several cancers and precancers. Late vaccination for those not vaccinated at the recommended ages should be completed as soon as possible, and individuals should be informed that vaccination may not be effective at older ages.

Keywords

American Cancer Society; Advisory Committee on Immunization Practices; guideline; human papillomavirus (HPV); vaccine; cancer prevention

Introduction

The burden of human papillomavirus (HPV)-related diseases, an understanding of the association of HPV infection with several cancer types, and the availability of vaccines together present an unprecedented opportunity for cancer prevention. Saraiya et al[1] performed a recent study in which archival tissue from patients with cancer in 7 population-based cancer registries was tested for the presence of high-risk HPV types. HPV infection was associated with 91% of cervical cancers, 69% of vulvar cancers, 75% of vaginal cancers, 63% of penile cancers, 89% of anal cancers in males, 93% of anal cancers in females, and 72% of oropharyngeal cancers in males and 63% of oropharyngeal cancers in females.[1] The Centers for Disease Control and Prevention (CDC) applied these proportions to the most recently available registry data on HPV-associated cancers to estimate the number of cancers caused by HPV. They estimated that around 30,700 cancers (based on 2008–2012 data) probably attributable to HPV are diagnosed in the United States each year: 19,200 in women and 11,600 in men.[2] The incidence rates of several of these cancers are increasing, with striking socioeconomic disparities for several HPV-associated cancers among both men and women.[3]

Three HPV vaccines (the Cervarix [GlaxoSmithKline, London, UK] bivalent vaccine [2vHPV] and the Gardasil [Merck & Company, Kenilworth, NJ] quadrivalent [4vHPV] and 9-valent [9vHPV] vaccines) are licensed in the United States and around the world (Table 1).[4–9] These vaccines protect against the HPV types that are responsible for most cases of HPV-associated cancers; the 4vHPV and 9vHPV vaccines also protect against nearly all cases of genital warts. The CDC, the American Cancer Society (ACS), and many provider groups recommend giving the 3-dose series of the HPV vaccine to children at ages 11 to 12 years (Table 1).[4–9]

2007 ACS Guideline for HPV Vaccine Use

The ACS first published a guideline for the use of prophylactic HPV vaccines for the prevention of cervical intraepithelial neoplasia (CIN) and cervical cancer in 2007,[10] recommending routine vaccination for females ages 11 to 12 years (with vaccination permitted in children as young as 9 years) and vaccination for females ages 13 to 18 years to catch up on a missed vaccine or to complete the vaccination series. The ACS concluded that there were insufficient data to recommend for or against routine universal vaccination of

females ages 19 to 26 years; instead, the ACS recommended informed decision making for vaccination in this population.[10]

The 2007 ACS guideline has been important in making clear the significance of the HPV vaccine as a cancer-prevention intervention. However, since publication of the guideline, there have been additional studies, new vaccine formulations licensed for use in the United States, and new immunization recommendations.[5–9] The 2007 ACS guideline does not address use of the vaccine in males or use of the most recently available 9-valent vaccine formulation; nor does it reflect recent evidence on the effectiveness of late vaccination, eg, at ages 19 to 26 years.

The ACS Consideration of Endorsement of Recommendations of the Advisory Committee on Immunization Practices

The recommendations for vaccines developed by the Advisory Committee on Immunization Practices (ACIP) serve as the principal source of guidance on US immunization policy; the ACS has been represented on the ACIP HPV Vaccine Work Group since 2005. The ACIP recommendations for HPV vaccination, as for other vaccines in children and adolescents, are harmonized with recommendations made by the American Academy of Pediatrics, the American Academy of Family Physicians, and the American College of Obstetricians and Gynecologists. Recognizing the need to update the ACS HPV vaccine use guideline and the value in consistency across organizations in HPV immunization efforts as a primary cancer-prevention strategy, the ACS chose to consider endorsement of the HPV vaccine recommendations of the ACIP.

HPV vaccination protects against infection with the targeted HPV types and subsequent related disease; however, it does not protect against disease resulting from previous exposure to these HPV types. The 2007 ACS guideline and the ACIP recommendations from 2006 through 2015 were primarily based on randomized controlled trial (RCT) evidence of vaccine efficacy, ie, the percentage reduction in disease incidence in a vaccinated group compared with the incidence in an unvaccinated control group under optimal conditions, and noninferior immunogenicity findings in females and males ages 9 to 15 years.[4–9] Thus, it is also important to consider observational data, such as results from ecological studies measuring vaccine effectiveness, ie, reduction in disease outcomes in a “real-world” setting. This is especially relevant when evaluating recommendations for vaccination among older females and males, who are more likely to have been sexually active and thus more likely to have had previous HPV exposure. Hence, the association between vaccine effectiveness and age and the implications for late vaccination recommendations were a major focus of this update.

ACIP Recommendations

The ACIP and the CDC first issued recommendations for routine HPV vaccination of females ages 11 to 12 years and catch-up vaccination for females ages 13 to 26 years with the quadrivalent HPV (4vHPV) vaccine in 2006.[4] An ACIP work group reviewed published and unpublished clinical trial data on vaccine efficacy against persistent HPV infections,

cervical disease, and external genital warts; immunogenicity; and safety and adverse events. Data on the epidemiology and natural history of HPV, vaccine acceptability, and cost effectiveness were also considered. The recommendation for catch-up vaccination of females who were not previously vaccinated was based in part on a review of data from efficacy clinical trials that included females ages 16 to 23 years or 16 to 26 years and the recognition that, when HPV vaccination was first introduced, females older than 12 years would not have had the opportunity to receive the vaccine. The ACIP report noted that overall vaccine effectiveness would be lower in a population of females who are sexually active; thus, effectiveness would decrease with increasing age, increasing number of sexual partners, and greater likelihood of HPV exposure. They concluded, however, that the majority of females in this age group would derive at least partial benefit from vaccination.[4]

In 2009, the ACIP updated its recommendation for females to include use of the bivalent (2vHPV) vaccine and provided guidance that 4vHPV may be given to males ages 9 through 26 years.[5,6] The ACIP recommended routine vaccination of males in 2011 based on a review of data on vaccine efficacy against anal cancer precursors and genital warts, vaccine safety, disease burden, cost effectiveness, and programmatic considerations.[7] For the recommendations on male vaccination, the ACIP adopted the Grading of Recommendation Assessment Development and Evaluation (GRADE) methodology to evaluate evidence and develop recommendations.[11] Routine vaccination of males ages 11 or 12 years was a category A recommendation, indicating that it applies to all persons in an age or risk-based group. Vaccination was also recommended for males ages 13 to 21 years who have not been vaccinated previously or who have not completed the 3-dose series. The ACIP stated that “males ages 22 through 26 years may be vaccinated.”[7]

In 2015, the ACIP updated their recommendations to include the 9-valent vaccine (9vHPV) based on data from 9vHPV prelicensure clinical trials as well as efficacy trials from the 4vHPV vaccine program.[9] The noninferior immunogenicity of 9vHPV compared with 4vHPV and in males compared with females was used to conclude its efficacy for HPV type 6 (HPV6), HPV11, HPV16, and HPV18. The safety of 9vHPV was evaluated based on 6 phase 3 studies in the clinical development program. All data came from RCTs conducted by the vaccine manufacturer.[9]

The current ACIP recommendations also address special populations, including men who have sex with men; persons who are immunocompromised because of transplantation, medications, or human immunodeficiency virus (HIV); and children with a history of sexual assault or abuse.[8,9]

Methods: ACS Guideline Endorsement

The ACS instituted a Guideline Development Group (GDG) (a volunteer group of clinicians, methodologists, and public health practitioners) in 2012.[12] To update the ACS recommendations for HPV vaccination, a guideline endorsement process was implemented similar to the American Society of Clinical Oncology (ASCO) model for endorsing another organization’s guidelines.[13] This model includes a methodologic review using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument,[14] a search for new

evidence published since completion of a guideline under consideration, and a content review.[13]

Following this approach, the ACS endorsement process for the HPV vaccine update included: 1) a methodologic assessment of the ACIP recommendations, 2) a supplemental evidence review, 3) a content review of the ACIP recommendations by the ACS GDG, 4) development and approval of endorsement statements, 5) a review of the evidence report and endorsement paper by expert advisors, and 6) approval of endorsement statements by the ACS Board of Directors.

The methodologic assessment of the ACIP recommendations for HPV vaccination was completed by 4 ACS guideline staff members working independently, using the AGREE II instrument.[14] A written summary of this assessment was provided to the ACS GDG.

A supplemental evidence review was conducted by ACS staff to identify any new data since the release of the ACIP recommendations (see online supporting information). The scope of the review also included male vaccination and the new vaccine formulation not covered in the 2007 ACS guideline, as well as continuing questions about the effectiveness of vaccination at older ages. This supplemental evidence review was designed to address 3 key questions:

1. Should HPV “catch-up” or “late” vaccination be recommended for females ages 19 to 26 years who have not been vaccinated previously?
2. Should HPV vaccination be recommended for males ages 9 to 26 years?
3. Should 9-valent HPV vaccination be recommended for males and females?

Methodologic details of the evidence review are described in the online supporting information. The evidence review report was reviewed by external advisors with expertise in epidemiology, HPV, HPV vaccines, cervical cancer screening, management and treatment, adolescent health, and gynecology. Reviewer comments, including those addressing interpretation of the literature, were incorporated into the final version.

The ACS GDG performed a content review of the ACIP HPV vaccination recommendations (consistent with its prior adoption of GRADE[15]) to assess: 1) whether the recommendations were adequately supported by the evidence, 2) whether there was confidence in the magnitude of estimates of effects on important outcomes, and 3) whether there was a favorable balance between desirable and undesirable outcomes. On the basis of the evidence considered by the ACIP, results of the ACS supplemental evidence review, and comments from expert advisors, the GDG voted on whether to endorse the ACIP recommendations either as stated or with commentary and qualifying statements when necessary for clarification or when the GDG judgments on the evidence and recommendations differed from those of the ACIP.

The draft endorsement statements were reviewed by the expert advisors and submitted with a draft supplemental evidence review report to the ACS Mission Outcomes Committee and Board of Directors for approval.

ACS Guidelines and Conflicts of Interest

All participants in the guideline development process were required to submit disclosures of all financial and nonfinancial (personal, intellectual, and practice-related) relationships and activities that might be perceived as posing a conflict of interest in development of the HPV vaccination guideline. The chairperson of the ACS GDG had the responsibility to ensure that balanced perspectives were taken into account in deliberations and decision making.

Results of the ACS Methodologic Assessment

The overall score (the average of the 4 reviewers) of the ACIP recommendations on HPV vaccination using the AGREE II instrument was 75%. Particular attention was given to the Rigour of Development subscale, which is designed to assess the quality of the processes used, evidence synthesis, and the methods used to formulate the guideline recommendation statements. A slightly lower appraisal rating (69%) was given on this subscale, although the reviewers noted that some domains of the AGREE II instrument may not be suitable for evaluating a vaccine use guideline.

The conclusion of the methodologic assessment was that, overall, ACIP recommendations are well written and presented, with suitable methods of development. Although extensive evidence to support the recommendation statements was presented and evidence tables were provided for the 2011 and 2015 updates, documentation was not provided that a systematic evidence review was performed for any of the ACIP guideline iterations, and data search strategies were not clearly described. There also was heavy reliance on data from RCTs sponsored by the vaccine manufacturers as well as unpublished data provided by the manufacturer. The possible limitations of such data were not clearly described or acknowledged in the recommendation statements.

Detailed epidemiologic, efficacy, harms, and vaccine safety information was presented with the ACIP recommendations. However, the recommendation statements did not address the benefit of specific catch-up ages (eg, ages 21–26 years) for females or provide a rationale for the difference in their recommended ages for males (ie, ages 13–21 years) and females (ages 13–26 years). Furthermore, while the ACIP has updated their recommendations several times and considered new data on efficacy and immunogenicity as well as adverse events, it is not clear what level of consideration was given to effectiveness data from countries with high vaccination rates or to evidence on vaccine effectiveness stratified by age.

Despite the aforementioned limitations, the ACIP recommendations are evidence based, with extensive summaries of the epidemiology of HPV and associated diseases as well as efficacy and immunogenicity findings for the vaccines presented. The licensed HPV vaccines are well described, and extensive updated information is provided on vaccine safety from clinical trials and postlicensure studies and monitoring.

ACS Supplemental Evidence Review

In addition to the methodological review, the ACS conducted a supplemental evidence review to identify relevant data published since the most recent ACIP recommendations

were released as well as relevant data that were not included by the ACIP. The report on this evidence review is provided online (see online supporting information).

A PubMed search updated through October 8, 2015, yielded 4091 articles, of which 338 were potentially relevant based on title; among these, 167 were selected for full review based on examination of the abstract and 29 articles were included in this review. The included articles address the critical outcomes of HPV vaccine effectiveness against the development of precancerous lesions and the important outcomes of HPV vaccine effectiveness against genital warts and persistent infection. There were 17 studies on late vaccination in females (ages 18–26 years), 6 on males (ages 9–26 years), and 6 that addressed use of the 9vHPV vaccine. Given the limited number and size of studies of efficacy for critical and important outcomes, the additional outcome of immunogenicity was considered for 9vHPV. The major findings of these studies are described in the online supporting information and summarized for each key question below.

Although not included in the search terms for this review, reported adverse events potentially associated with vaccination were included as outcomes of interest (see online supporting information). The CDC and the ACIP sponsor an extensive, ongoing surveillance and safety monitoring program related to vaccination, and updated results are publicly reported.[16] The CDC and ACIP regularly monitor postlicensure safety data through several systems in the United States as well as reports from other countries. Studies from the United States and Europe, for example, have shown no causal association of HPV vaccination and autoimmune disease, stroke, Guillain-Barre syndrome, venous thromboembolism, seizures, connective tissue disorders, or allergic disorders.[16] The World Health Organization also monitors vaccine safety through its Global Advisory Committee on Vaccine Safety, which has published 6 reports on HPV vaccines, with the most recent report released in December 2015.[17] Adverse events associated with the vaccination of males and with the 9vHPV vaccine were included when they were reported as outcomes in the studies included in the current supplemental review.

Results of the ACS Supplemental Evidence Review

1. Should HPV “late” vaccination be recommended for females ages 19 to 26 years who have not been vaccinated previously?—Although, in general, the data show efficacy across all age groups included in the RCTs, there is consistency in the findings from RCTs and observational studies that vaccine effectiveness is highest in preteens and early teens, lower in middle to late teen age groups, and lowest in young adult age groups (ie, ages 20 years and older) (see online supporting information). Results from a pooled analysis of 3 RCTs showed that estimates of benefits against high-grade cervical lesions are substantially reduced when vaccination occurs after age 21 years compared with vaccination before age 19 years.[18] The results from observational data (3 ecological studies and 1 case-control study using linked data) provide additional evidence of reduced vaccination effectiveness at older ages, with greater decline in high-grade cervical lesions among females younger than 19 years after the introduction of vaccination compared with older age groups.[19–22]

Estimates of the effectiveness of HPV vaccine by age must be regarded with caution. Most ecological studies did not specifically measure age at vaccination. The majority of these studies examined population outcomes after the introduction of vaccination and were not based on linked vaccination and screening data. Conclusions from the included observational studies are also limited by the time-frame since vaccine introduction and adoption.

2. Should HPV vaccination be recommended for males ages 9 to 26 years?— The manufacturer-sponsored RCTs have demonstrated vaccine efficacy, high levels of immunogenicity, and safety in males comparable to those in females. The evaluations of cancer precursor outcomes are limited by a small number of cases, particularly in heterosexual males.[23,24] Vaccine efficacy for the important outcomes of persistent infection and genital warts was demonstrated in all men included in the RCTs, and efficacy against anal intraepithelial neoplasia was demonstrated in men who have sex with men. Modeling studies also suggest reductions in critical and important outcomes and in HPV-associated cancer cases and deaths.[25,26] None of the studies reported outcomes stratified by age at vaccination.

3. Should 9vHPV vaccination be recommended for males and females?—The available data on the 9vHPV vaccine are limited but show efficacy, immunogenicity, and safety comparable to those demonstrated for the quadrivalent vaccine.

Although several RCTs reported on antibody response and seroconversion rates of the 9vHPV vaccine formulation,[27–31] only one reported data on our critical and important outcomes.[32] On the basis of an RCT with 4 years of follow-up, Joura et al found similar protection against cervical, vulvar, and vaginal lesions caused by the HPV types included in the 4vHPV vaccine and a lower overall rate of high-grade lesions in the 9vHPV group compared with the 4vHPV group.[32]

Given the limited direct evidence of efficacy of the recently approved 9vHPV vaccine formulation against disease outcomes, data on the endpoints of immunogenicity and noninferiority have been included, consistent with international recommendations on the use of surrogate trial endpoints.[33] Three RCTs found that the antibody response of the 9vHPV vaccine for HPV6, HPV11, HPV16, and HPV18 was noninferior to that of the 4vHPV vaccine, and both had similar safety profiles.[30–32]

ACS Content Review

The GDG conducted a content review of the ACIP HPV vaccine use recommendations as part of the ACS endorsement process. The objective of the content review was to assess the specific recommendations made and the extent to which the available evidence supports each recommendation.

In the evaluation of the content and evidence presented in the ACIP recommendations, the GDG members considered these questions:

- Were the results of the studies supporting these recommendations interpreted and applied according to the GDG's judgements about the data?
- Is the evidence presented in support of each recommendation sufficient?
- Are the recommendations in the guideline clear, and will they be easily understood by the intended audience?
- Is there agreement with the judgement of the balance of benefits and harms reflected in the recommendations, and is there confidence in the estimates of effects?
- Do the recommendations adequately take into consideration patient values and preferences?

Upon completion of the content review, the GDG selected among options of full endorsement, endorsement with qualifying statements or exceptions, or rejection for each ACIP recommendation (Table 2). The GDG determined that the benefits of HPV vaccination for prevention of cancer incidence, mortality, and morbidity in both males and females outweigh the limited, predominantly nonserious side effects. The available evidence strongly supports an update to the ACS recommendation for HPV vaccination related to the vaccination of males and the use of the 9vHPV vaccine formulation. The benefits are reduced at older ages at vaccination, supporting the recommendation for routine vaccination at ages 11 to 12 years or as soon thereafter as possible. 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.

The ACS Mission Outcomes Committee and Board of Directors then approved the endorsement and ACS guideline update as recommended by the GDG.

Discussion

Since release of the 2007 ACS guideline for HPV vaccine use to prevent cervical cancer and its precursors,[10] additional evidence has accumulated, and new immunization recommendations addressing additional populations and new vaccine formulations have been issued. The ACS conducted a supplemental evidence review and a methodologic assessment and content review of the current ACIP recommendations.[4–9] This update of the ACS guideline addresses changes since 2007 and endorses current ACIP recommendations for HPV vaccination, with the addition of one qualifying statement about decreased effectiveness of the vaccine in persons ages 22 years and older.

The original recommendations for routine vaccination at age 11 or 12 years were based on considerations of immunogenicity in this age group, including higher antibody titers compared with older age groups; data on age of initiation of sexual activity; and, for programmatic purposes, the established young adolescent health care visit at age 11 or 12 years.[4,10] This review did not revisit the age for routine vaccination (ie, at ages 11–12 years).

This update and endorsement process focused on 3 key questions. The 2007 ACS guideline agreed with the recommendations of the ACIP and other organizations in recommending

routine vaccination for females ages 11 to 12 years and catch-up vaccination for females ages 13 to 18 years but it differed in recommending informed decision making rather than routine vaccination for females ages 19 to 26 years. There was a lack of efficacy data for the prevention of HPV16/HPV18–related CIN2 or CIN3 in women who have had more than 4 lifetime sexual partners because of inclusion criteria for the clinical trials. National survey data showed that half of females over age 19 years had 4 or more lifetime sexual partners.[34] The ACS therefore selected a cutoff of age 18 years and recommended an informed discussion between a woman and her health care provider regarding her risk of previous HPV exposure and potential benefit from vaccination for women ages 19 to 26 years. An additional consideration supporting this cutoff was that the federally funded Vaccines for Children program provides free vaccination for uninsured and underinsured children, covering approximately one-half of the US population, through age 18 years.[35]

There is consistency in findings from the RCTs of greater efficacy among the per-protocol group (no evidence of current or past infection) compared with the intention-to-treat group (see online supporting information). The evidence for vaccine efficacy in preventing precancerous lesions is based primarily on data from RCTs that included women ages 15 to 26 years who had a limited number of lifetime sexual partners. Ecological studies examining trends in disease outcomes since the introduction of vaccination show either significantly reduced effectiveness or no effectiveness in older age groups.[20–22] These findings suggest that the “real-world” effectiveness of HPV vaccination in women (and men) older than age 21 years is likely to be lower than that in younger populations.

Two studies that were published after the completion of our supplemental evidence review provide individual-level data on outcomes by age. By using linkage data from Scotland measuring HPV prevalence in a population of women who had been eligible for the catch-up vaccination program and who presented for their first screening at age 20 or 21 years, Cameron et al[36] reported that the odds of testing positive for HPV16 or HPV18 were 7.7% for women who were vaccinated at age 15 or 16 years, 12.5% for those vaccinated at age 17 years, 16.6% for those vaccinated at age 18 years, and 30.3% for those vaccinated at ages 19 to 21 years, with an odds ratio of 5.31 when the age at vaccination was from 19 to 21 years compared with 15 to 16 years.[36] In a nationwide study that included the entire female population of Sweden ages 13 to 29 years,[37] Herweijer et al used national register-based data to measure the effectiveness of HPV vaccination stratified by age at vaccination. In their study, vaccine effectiveness against CIN2 or greater was 75% for individuals who were vaccinated before age 17 years, 46% for those vaccinated at ages 17 to 19 years, and 22% for those vaccinated at age 20 years or older. When the results were restricted to individuals in the organized cervical screening program (ie, women ages 23–29 years who had recently been screened), the authors found a strong protective effect of vaccination for women who were vaccinated before age 20 years and a much smaller level of protection that was not statistically significant for those vaccinated at age 20 years or older.[37]

Although some women (and, by inference, men) ages 22 to 26 years will benefit from HPV vaccination, and vaccination is both licensed and safe for this age group, the efficacy and effectiveness for preventing precancerous lesions are reduced compared with vaccination at a younger age (see online supporting information). In 2007, the ACIP report acknowledged

that, “although overall vaccine effectiveness would be lower when administered to a population of females who are sexually active, and would decrease with older age and likelihood of HPV exposure with increasing number of sex partners, the majority of females in this age group will derive at least partial benefit from vaccination.”[4] Similarly, the ACIP 2011 report on male vaccination reported that, “the population level benefits decrease with increasing age at vaccination, especially after age 21 years.”[7]

The supplemental evidence review included articles that stratified outcomes by age, with most studies reporting outcomes for females younger than 18 to 20 years compared with females older than 19 or 20 years. There are limited data on precise age distinctions. In considering endorsement, the ACS qualified the ACIP recommendation for late vaccination of individuals older than 21 years based on: 1) evidence of greater benefit for females vaccinated at ages 18 to 20 years compared with 21 to 26 years, 2) opportunities for young women and men to get vaccinated at college, 3) opportunities for young women and men to access vaccination without parental consent, and 4) consistency with the ACIP recommendation for males.

On the basis of the available evidence, the ACS endorses the ACIP recommendations for late vaccination with the caveat that 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. Adherence to routine vaccination at age 11 or 12 years should be emphasized, and vaccination should not be deferred with the expectation that later vaccination will be similarly effective.

The second key question addressed in this update is whether males as well as females should be vaccinated. The 2007 ACS guideline was developed before the availability of data from studies of male vaccination and before US Food and Drug Administration review and approval for this indication. Evidence published since 2007 has shown vaccine efficacy and immunogenicity in males and safety comparable to that in females. For average-risk men (excluding men who have sex with men and immunocompromised/HIV-positive men), there is no direct evidence of efficacy for cancer or precancer prevention because of the small number of disease outcomes. There is also no evidence for prevention of oropharyngeal cancers in males or females; however, there is limited evidence of prevention of oral HPV infection.[38] On the basis of data on immunogenicity and efficacy against persistent infections and anogenital warts in young males, as well as efficacy against precancers in men who have sex with men, it is possible to conclude that vaccination will be effective against cancer outcomes in the general male population, as has been shown for females.[23,24,39,40]

Modeling results suggest that vaccination of males, through herd immunity, may provide additional protection to females in addition to providing protection against HPV-associated cancers in males. Evidence from Australia has already demonstrated that HPV vaccination offers strong herd immunity, as shown by the 80% decrease in genital warts among adolescent boys before inclusion of males in the national vaccination program.[41,42]

On the basis of the available evidence, the ACS endorses the ACIP recommendation for vaccination of males. Furthermore, based on the high burden of HPV infection and HPV-related cancers among men who have sex with men, particularly anal cancer and precancers, as well as anogenital warts,[43] the ACS concurs with the recommendation for vaccination of men who have sex with men through age 26 years.

The third key question addresses vaccination with the 9vHPV vaccine. Although there are limited data available on the efficacy of the 9vHPV vaccine for the designated critical and important outcomes, results from one RCT showed noninferior immunogenicity for the types shared with the 4vHPV vaccine and efficacy for the 5 additional types.[30–32] Safety comparable to that of the 4vHPV vaccine was reported for the 9vHPV vaccine.

To supplement the ACIP recommendations, the CDC published additional guidance to answer questions and address issues that may arise during the transition from 4vHPV to 9vHPV.[44] In particular, individuals who start the vaccine series with 4vHPV may finish the series with 9vHPV, and there is no ACIP recommendation for routine additional 9vHPV vaccination of individuals who previously completed a 4vHPV or 2vHPV vaccination series.

The evidence reviewed by the ACIP and the additional studies examined in our supplemental review support national recommendations for HPV vaccination, particularly for early adolescents. The benefits of HPV vaccination for both males and females in terms of protection against multiple cancers as well as precancers and genital warts outweigh the limited, predominantly nonserious harms. The benefits are reduced at older ages at vaccination, supporting the recommendation to vaccinate at ages 11 to 12 years or as soon thereafter as possible.

Vaccination with 4vHPV or 2vHPV could prevent an estimated 24,600 cases of cancer in the U.S. annually; vaccination with 9vHPV could prevent an additional 3800 cases; in sum an estimated total of 28,500 cases could be prevented by the 9-valent vaccine.[2] Population-level decreases in cervical precancers have been observed in countries with high vaccination rates, including Denmark[45] and Australia,[46] and the prevalence of vaccine-type HPV has decreased by 64% among females ages 14 to 19 years in the United States.[47] Yet vaccination rates in the United States remain far lower than the rates of other vaccines given at the same age that were introduced at about the same time (ie, 2006–2007).[48] Many studies have identified key barriers to routine vaccination at the recommended ages.[49] Provider recommendation has been consistently identified as a factor of primary importance in HPV vaccine acceptance and utilization.[49] National efforts addressing barriers to vaccine uptake should focus on the recommendation for initiation of HPV vaccination at age 11 or 12 years. Clinicians and parents should not delay vaccination based on their speculation about the age at which the child is likely to become sexually active.

Given the importance as well as challenges of this public health priority, the ACS Board of Directors recently voted to make prevention of HPV-associated cancers through increased vaccination a nationwide priority for the organization. The ACS convened 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. 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 federally qualified health centers and state health systems. The ACS also continues to monitor data that will inform future changes to cervical cancer screening recommendations. It is important that all women, regardless of whether they have been vaccinated, get screened according to current guideline recommendations.[50]

HPV vaccination can potentially avert tens of thousands of cancers and hundreds of thousands of precancers each year with associated morbidity. It is critical that cancer prevention, immunization, health care provider, and other stakeholder organizations at the national, state, and local levels continue to prioritize HPV vaccination so that prevention of the vast majority of cervical, vaginal, vulvar, anal, penile, and oropharyngeal cancers can become a reality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Practical Implications for Continuing Education

- HPV causes most cervical, vulvar, vaginal, anal, and oropharyngeal cancers in females and most oropharyngeal, anal, and penile cancers in males. About 28,500 cancers could be prevented annually in the US by HPV vaccination.
- Clinicians should strongly recommend that all of their patients be vaccinated against HPV at age 11–12 years (bundled with the other routine adolescent vaccines, ie, Tdap and MCV4), with completion of the series by the 13th birthday for greatest effectiveness.
- Clinicians and their staff should be ready to answer FAQs accurately and succinctly. The CDC has scripts, tips, time-savers, and other free resources to help educate parents or guardians and answer their questions.

TABLE 1

Advisory Committee on Immunization Practices (ACIP) Recommendations for Vaccination, 2006 to 2015

YEAR OF RELEASE	ACIP RECOMMENDATIONS	LICENSED HPV VACCINES
2006 (Markowitz 2007[4])	Females: Routine vaccination with 3-dose series at age 11 or 12 y, starting as early as age 9 y, and through age 26 y if not vaccinated previously	Quadrivalent (4vHPV), females aged 9–26 y
2009 (CDC 2010[5,6])	Females: Either vaccine for routine vaccination with 3-dose series at age 11 or 12 y, starting as early as age 9 y, and through age 26 y if not vaccinated previously (Guidance) Males: aged 9–26 y may be vaccinated, but vaccination not routinely recommended for males (vaccination would be most effective when given before exposure to HPV through sexual contact)	4vHPV, females and males aged 9–26 y; bivalent (2vHPV), females aged 9–25 y
2011 (ACIP 2011[7])	Females: Either vaccine for routine vaccination with 3-dose series at age 11 or 12 y, starting as early as age 9 y, and through age 26 y if not vaccinated previously Males: Routine vaccination with 3-dose series at age 11 or 12 y and through age 21 y if not vaccinated previously; males aged 22–26 y may be vaccinated (vaccination recommended through age 26 y for men who have sex with men and men who are immunocompromised, including those with HIV infection)	4vHPV, females and males aged 9–26 y; 2vHPV, females aged 9–25 y
2014 (Markowitz 2014[8])	Females and males: Routine vaccination with 3-dose series at age 11 or 12 y (the vaccination series can be started beginning at age 9 y) Females aged 13–26 y and males aged 13–21 y who have not been vaccinated previously or who have not completed the 3-dose series Males aged 22–26 y may be vaccinated (vaccination recommended through age 26 y for men who have sex with men and persons who are immunocompromised, including those with HIV infection)	4vHPV, females and males aged 9–26 y; 2vHPV, females aged 9–25 y
2015 (Petrosky 2015[9])	Females and males: Routine vaccination with 3-dose series at age 11 or 12 y (the vaccination series can be started beginning at age 9 y) Vaccination recommended for females aged 13–26 y and for males aged 13–21 y who have not been vaccinated previously or who have not completed the 3-dose series Males aged 22–26 y may be vaccinated Vaccination recommended through age 26 y for men who have sex with men and for persons who are immunocompromised, including those with HIV infection	4vHPV, females and males aged 9–26 y; 2vHPV, females aged 9–25 y only; 9-valent (9vHPV), licensure in 2014 for females and males aged 9–26 y

CDC indicates Centers for Disease Control and Prevention; HIV, human immunodeficiency virus; HPV, human papillomavirus. Adapted from: Markowitz LE, Dunne EF, Saraiya M, et al. Human papillomavirus vaccination: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2014;63:1–30[8]; and Petrosky E, Bocchini JA Jr, Hariri S, et al. Use of 9-valent human papillomavirus (HPV) vaccine: updated HPV vaccination recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep*. 2015;64:300–304.[9]

TABLE 2

Summary of Recommendations

The American Cancer Society (ACS) endorses the Advisory Committee on Immunization Practices (ACIP) HPV vaccination recommendations, listed below, with one qualifying statement in **bold italics**

Routine recommendations

Routine HPV vaccination should be initiated at age 11 or 12 y. The vaccination series can be started beginning at age 9 y.

Vaccination of females is recommended with 2vHPV, 4vHPV (as long as these formulations remain available), or 9vHPV. Vaccination of males is recommended with 4vHPV (as long as this formulation remains available) or 9vHPV.

Recommendations for those not vaccinated at the routine age

Vaccination is also recommended for females aged 13–26 y and for males aged 13–21 y who have not been vaccinated previously or who have not completed the 3-dose series.

Males aged 22–26 y may be vaccinated.[a]

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.

Special populations

Vaccination is also recommended through age 26 y for men who have sex with men and for immunocompromised persons (including those with HIV infection) if not vaccinated previously.

2vHPV indicates bivalent human papillomavirus (HPV) vaccination; 4vHPV, quadrivalent HPV vaccination; 9vHPV, 9-valent HPV vaccination; HIV, human immunodeficiency virus.

[a]ACIP recommendation for individual clinical decision making.