Complete Summary

GUIDELINE TITLE

American Cancer Society guideline for human papillomavirus (HPV) vaccine use to prevent cervical cancer and its precursors.

BIBLIOGRAPHIC SOURCE(S)

Saslow D, Castle PE, Cox JT, Davey DD, Einstein MH, Ferris DG, Goldie SJ, Harper DM, Kinney W, Moscicki AB, Noller KL, Wheeler CM, Ades T, Andrews KS, Doroshenk MK, Kahn KG, Schmidt C, Shafey O, Smith RA, Partridge EE, Garcia F. American Cancer Society guideline for human papillomavirus (HPV) vaccine use to prevent cervical cancer and its precursors. CA Cancer J Clin 2007 Jan-Feb;57(1):7-28. [169 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

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SCOPE

DISEASE/CONDITION(S)

- Human papillomavirus (HPV) infection
- Sequelae to HPV infection, such as cervical cancer and genital warts

GUIDELINE CATEGORY

Prevention
Risk Assessment
Screening

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Nursing
Obstetrics and Gynecology
Pediatrics
Preventive Medicine

INTENDED USERS

Advanced Practice Nurses
Health Plans
Managed Care Organizations
Physician Assistants
Physicians
Public Health Departments

GUIDELINE OBJECTIVE(S)

- To address the use of prophylactic human papillomavirus (HPV) vaccines, including who should be vaccinated and at what age, as well as provide a summary of policy and implementation issues
- To attain the greatest impact on cervical cancer prevention

TARGET POPULATION

Females age 9 to 26 years

INTERVENTIONS AND PRACTICES CONSIDERED

1. Human papillomavirus (HPV) vaccination
2. Pap screening for cervical intraepithelial neoplasia and cancer before and after HPV vaccination
3. Education of patient and parents

MAJOR OUTCOMES CONSIDERED

- Rate of age-appropriate vaccine coverage
- Incidence of cervical intraepithelial neoplasia and cancer
- Persistent HPV-related infections
- Vaccine-related adverse events

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The panel reviewed published literature identified using PubMed (National Library of Medicine) and bibliographies of identified articles, as well as unpublished data.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The American Cancer Society (ACS) convened an expert panel to review the existing data on human papillomavirus (HPV) vaccines and develop recommendations specifically addressing the prevention of cervical cancer and precancerous lesions.

The evidence and recommendations were discussed during a series of conference calls before a July 2006 working meeting, and consensus was reached on the key issues within the Guideline recommendations. When evidence was insufficient or lacking, the final recommendations incorporated the expert opinion of the panel members.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

Currently, there are several published analyses addressing the potential impact of human papillomavirus (HPV) vaccines. In the absence of data on vaccine effect, duration, cost, and behavior of nontargeted HPV types over time, different assumptions were made for the base case analysis in each. While these model-based analyses differ in their objectives, and thus in their choice of model structure, the majority intended to be exploratory, aiming to provide qualitative insight while awaiting better data. The cost of the vaccine was unknown at the time these studies were conducted; the economic analyses were based on the assumption that the cost of the 3-dose vaccine series would be approximately $300, including administration (the cost of Gardasil is $360 for 3 doses; programmatic and administrative costs are likely to make the total cost higher). The models are based on cervical cancer direct medical costs only, and did not include genital warts, other HPV-related cancers or diseases, or nonhealth care costs. None of the published studies modeled a quadrivalent vaccine or catchup vaccination; each model assumed vaccination of females at age 12 years.

While a range of cost-effectiveness was found across different models, it is striking that the qualitative insights provided are complementary and fairly consistent. Several variables were identified that are likely to have the greatest impact on cost and benefits, including later onset of screening and less frequent screening, age of vaccination, duration of efficacy, and cost of vaccine. Female vaccination strategies costing less than $50,000 per quality adjusted life year saved (QALY) were identified by each model. The cost-effectiveness from prevention of all HPV6/11/16/18-associated diseases is highly dependent on the price of the vaccine, including administration and visit costs. When genital wart prevention is taken into account, cost-effectiveness ratios decline (i.e., become more attractive), although the magnitude of this is uncertain.

All models agree that a type-specific HPV vaccine will reduce, but not eliminate, the risk of cervical cancer. In the context of existing cervical cytology screening, a type-specific vaccine could reduce HPV16/18-associated CIN3 and cervical cancer, although the size of the incremental clinical benefits compared with screening alone will depend on the underlying effectiveness of the screening program. The cost effectiveness of vaccination will rely heavily on willingness to initiate screening at a later age, to conduct screening less frequently, and to adopt a conservative approach to the follow up of women with equivocal and mildly abnormal screening test results. It appears that, all else being equal, when vaccine coverage in women is high, vaccinating men in addition to women provides an incremental benefit that is relatively small compared with the incremental benefit of vaccinating women compared with no vaccination. In addition, vaccine benefit decreases as age at vaccination increases beyond sexual debut. The exploratory work thus far has elucidated several data priorities, including a better understanding of natural immunity following type-specific HPV infection, heterogeneity of vaccine response, duration of vaccine-induced immunity, and the effects of type-specific vaccination on other HPV types.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The American Cancer Society Gynecologic Cancer Advisory Group members and the National Board of Directors discussed and voted to approve the recommendations.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The table below summarizes the American Cancer Society (ACS) recommendations for human papillomavirus (HPV) vaccines.

Summary of ACS Recommendations for HPV Vaccine Use to Prevent Cervical Cancer and Its Precursors

- Routine HPV vaccination is recommended for females aged 11 to 12 years.
- Females as young as age 9 years may receive HPV vaccination.
- HPV vaccination is also recommended for females aged 13 to 18 years to catch up missed vaccine or complete the vaccination series.
- There are currently insufficient data* to recommend for or against universal vaccination of females aged 19 to 26 years in the general population. A decision about whether a woman aged 19 to 26 years should receive the vaccine should be based on an informed discussion between the woman and her health care provider regarding her risk of previous HPV exposure and potential benefit from vaccination. Ideally the vaccine should be administered prior to potential exposure to genital HPV through sexual intercourse because the potential benefit is likely to diminish with increasing number of lifetime sexual partners.
- HPV vaccination is not currently recommended for women over age 26 years or for males.
- Screening for cervical intraepithelial neoplasia and cancer should continue in both vaccinated and unvaccinated women according to current ACS early detection guidelines.

*Insufficient evidence of benefit in women aged 19 to 26 years refers to (1) clinical trial data in women with an average of 2, and not more than 4, lifetime sexual partners, indicating a limited reduction in the overall incidence of cervical intraepithelial neoplasia (CIN)2/3; (2) the absence of efficacy data for the prevention of HPV16/18-related CIN2/3 in women who have had more than 4 lifetime sexual partners; and (3) the lack of cost-effectiveness analyses for vaccination in this age group.

To attain the greatest impact on cervical cancer prevention, the ACS provides the following supporting recommendations:

Screening

- It is critical that women, whether vaccinated or not, continue screening according to current ACS early detection guidelines.

- A preventive health care visit in which vaccination is discussed or offered represents an appropriate opportunity to offer Pap screening to sexually active patients.
- HPV testing before initiating vaccination is not recommended.

Vaccine Implementation and Utilization

- Public health and policy efforts are needed to ensure access and encourage high HPV vaccine coverage for all racial, ethnic, and socioeconomic groups, particularly for females of color, immigrants, those living in rural areas, low-income and uninsured females, and others who have limited access to health care services.
- Strategies should be implemented to maximize adherence to vaccination recommendations, including coadministration with other recommended adolescent vaccines, once sufficient safety data are available.
- The use of noncomprehensive visits (e.g., minor illness visits, camp/sports physical visits) and alternative vaccination sites for adolescents unable to access comprehensive preventive care is encouraged.

Education

- There is a critical need for education of providers, policy-makers, parents, adolescents, and young women about cervical cancer prevention and early detection, including the need for regular screening even after vaccination.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is not specifically stated for each recommendation.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Appropriate use of human papillomavirus (HPV) vaccine to prevent HPV infection, cervical cancer precursor lesions, and genital warts
- There is potential for short-term benefit in reducing abnormal Pap test results, colposcopy referrals, and cervical biopsies. Use of procedures such as loop electrosurgical excision and cold knife conization can be reduced by preventing, through vaccination, cases of cervical intraepithelial neoplasia (CIN) likely to regress, thereby reducing obstetrical morbidity related to impaired cervical function in late pregnancy, including premature delivery, low birth weight, and premature rupture of membranes.

- The potential for HPV vaccination to reduce cervical cancer disparities is supported by cost-effectiveness data. A recent analysis found that HPV 16/18 vaccination, while having very small incremental benefits at the population level in comparison to current screening, may reduce disparities substantially in terms of cervical cancer mortality if widespread vaccine coverage could be achieved in underscreened populations.

POTENTIAL HARMS

Gardisil

- The most common injection site experiences were erythema, pain, and swelling, with severe intensity being reported more often in the vaccine recipients. The most common systemic adverse experiences, which were reported by a similar proportion of vaccine and placebo recipients (69%), were fever, headache, and nausea.
- Vaccine-related serious adverse experiences included one case of bronchospasm and one case of gastroenteritis (possibly related to a study procedure), one case of headache with hypertension (definitely related), one case of injection site pain with injection site joint movement impairment (probably related), and one case of vaginal hemorrhage (probably related).
- If prophylactic vaccine availability leads to declining participation in screening programs, then cancers will develop that may have been otherwise prevented. Benefits from HPV vaccines may be offset if vaccinated women acquire a false sense of protection that results in decreased compliance with recommended cervical cancer screening.
- Although the evidence does not support that introduction of HPV vaccination will lead to changes in sexual behavior, postmarketing monitoring will be important.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Limitations of Human Papillomavirus (HPV) Vaccine

- It will be important to conduct surveillance studies to assess safety and identify rare adverse events, including those in pregnant women, as human papillomavirus (HPV) vaccines are administered to large populations of girls and young women. Safety surveillance for coadministration of HPV vaccines with other adolescent vaccines is also needed. Monitoring rare events and pregnancy outcomes is challenging because it relies on education and commitment of providers to identify (usually during opportunistic observation) and voluntarily report such events.
- Limitations of current HPV vaccines include the following: (1) these vaccines do not protect against all carcinogenic HPV types; (2) the vaccines do not treat prevalent/existing HPV infections; (3) the duration of protection and the required length of protection to prevent cancer are unknown; (4) the cost of primary vaccination, and the possible need for additional booster vaccinations, will likely limit vaccine use among the medically underserved and the uninsured; and (5) a three-dose regimen for primary vaccination may

not be achievable in population where follow up is poor, such as uninsured and migrant populations or those living in underserved areas.
- There is currently insufficient evidence to recommend for or against universal vaccination of women aged 19 to 26 years in the general population.
- It is important to note that, when subjects entered these studies with evidence of current or past HPV infection, there was no clear evidence of protection from subsequent disease demonstrated by administration of the prophylactic quadrivalent vaccine.
- Actual efficacy may be even lower among the general population since the generalizability of the vaccine clinical trial data may be most applicable to women reporting on average 2 (and no more than 4) lifetime sexual partners at the time of vaccination.
- At this time efficacy is unknown for younger girls and for males.
- Even under the best of circumstances, it will be many decades before substantial reduction of cervical cancer risk could become a reality. Ultimately, cervical cancer rates will depend on (1) the degree of vaccination coverage of the at-risk population; (2) the number of carcinogenic HPV types targeted by the prophylactic vaccine; (3) the durability of protection; and (4) whether the medical community and the public continue to follow recommended screening guidelines.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Vaccine Implementation and Utilization

Adolescent Vaccination

Vaccinating any child or adult presents immense barriers. The most successful regimens are those required for infants. In adolescence and beyond, the ability to immunize is limited by access. Most adolescents do not receive annual health examinations. Hence, immunization opportunities occur during nonroutine visits. The experience with hepatitis B vaccines underscores the difficulty in immunizing adolescents. Clearly, a platform for adolescent immunization similar to that of infant immunizations is needed for the currently recommended vaccines. The Advisory Committee on Immunization Practices, American Medical Association, American Academy of Pediatrics, American Academy of Family Practice, and Society of Adolescent Medicine recommend an early adolescent health care visit at age 11 to 12 years. Vaccinations for tetanus/diphtheria/pertussis booster, hepatitis A, and meningococcal are recommended at this age, and other vaccines (hepatitis B, polio, varicella, measles/mumps/rubella, pneumococcal, influenza) are recommended as catch-up or for special risk groups. This adolescent platform may increase the likelihood of human papillomavirus (HPV) vaccination of girls aged 11 to 12 years. Other venues will be needed to get adequate coverage, including sport physicals, school programs, and acute care visits.

HPV Vaccine Acceptability

Several small studies on HPV vaccine acceptability among young women, parents of adolescents and providers have suggested that overall acceptability for a

prophylactic HPV vaccine is high. Multiple factors influenced attitudes. The most salient issues include high efficacy, safety, severity of infection, perceived risk, physician recommendation, and, for providers, professional society recommendation. Acceptability by parents and providers appears to be higher for older adolescents, although one study found that age was not a factor for parents of adolescent children. Some parents expressed concern that a vaccine would increase unsafe sexual behavior, while another study reported that sexual transmission did not affect parental attitudes.

Most parents, young women, and adolescents have minimal knowledge of HPV and its association with cervical cancer. Several studies indicate that vaccine acceptance is improved with increased knowledge. In one study of 575 parents of 10- to 15-year-old children, brief education significantly increased acceptance of an HPV vaccine, particularly for parents who were initially undecided. Results from a randomized intervention study designed to assess the impact of a brief HPV informational brochure (such as provided in doctors' offices) on parental acceptability of HPV vaccines for their 8- to 12-year-old children, however, showed that the observed increase in knowledge related to receipt of the brochure did not result in a significant increase in vaccine acceptability. Attitudes and life experiences appeared to be more important factors. Findings from these acceptability studies are limited by their small sample size and narrow population-based sampling. Many of the authors concluded that education of parents and providers should emphasize the risk of HPV infection in adolescents and the importance of vaccinating children before the onset of sexual activity. Acceptance also may be influenced by whether the vaccine is perceived as a vaccine to reduce the risk of cervical cancer or as a vaccine to prevent a sexually transmitted infection.

IMPLEMENTATION TOOLS

Patient Resources

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Saslow D, Castle PE, Cox JT, Davey DD, Einstein MH, Ferris DG, Goldie SJ, Harper DM, Kinney W, Moscicki AB, Noller KL, Wheeler CM, Ades T, Andrews KS, Doroshenk MK, Kahn KG, Schmidt C, Shafey O, Smith RA, Partridge EE, Garcia F. American Cancer Society guideline for human papillomavirus (HPV) vaccine use to prevent cervical cancer and its precursors. CA Cancer J Clin 2007 Jan-Feb;57(1):7-28. [169 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2007 Jan

GUIDELINE DEVELOPER(S)

American Cancer Society - Disease Specific Society

SOURCE(S) OF FUNDING

American Cancer Society

GUIDELINE COMMITTEE

American Cancer Society Guideline Panel

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Panel Members: Debbie Saslow, PhD; Philip E. Castle, PhD, MPH; J. Thomas Cox, MD; Diane D. Davey, MD; Mark H. Einstein, MD, MS; Daron G. Ferris, MD; Sue J. Goldie, MD, MPH; Diane M. Harper, MD, MPH, MS; Walter Kinney, MD; Anna-Barbara Moscicki, MD; Kenneth L. Noller, MD; Cosette M. Wheeler, PhD; Terri Ades, RN, MS, AOCN; Kimberly S. Andrews; Mary K. Doroshenk, MA; Kelly Green Kahn; Christy Schmidt; Omar Shafey, PhD, MPH; Robert A. Smith, PhD; Edward E. Partridge, MD (for the Gynecologic Cancer Advisory Group); Francisco Garcia, MD, MPH

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Workgroup members were asked to disclose relationships, including potential financial conflicts of interest, with vaccine manufacturers or trials. The following was disclosed: F. Garcia participated in an expert panel for GlaxoSmithKline (GSK) for an unrelated immune therapeutic class of agents; C. Cohen is a paid speaker for Merck; T. Cox is a paid member of the Merck Data Safety and Monitoring Committee and received an honorarium for serving on one management advisory board for GSK; D. Davey serves on the working group of the NCI-sponsored trial of GSK vaccine in Costa Rica; M. Einstein has received research support from GSK for a nonvaccine-related activity and serves on the speaker's bureau for Merck, but receives no salary support or honorarium; D. Ferris receives research support for vaccine trials from Merck and GSK and serves as a colposcopy quality control

consultant to both Merck and GSK and on the Merck medical advisory board; D. Harper serves on the study planning committee for Merck and GSK and is a clinical site PI for GSK; A. Moscicki serves on Merck's speaker's bureau and adolescent advisory board and is a local PI on the GSK vaccine trial; E. Partridge received an honorarium for a one-day advisory meeting for Merck and is a PI for a clinical study site for Merck; C. Wheeler receives research support for vaccine trials from Merck and GSK; D. Solomon is a medical monitor for the NCI-sponsored trial of GSK vaccine in Costa Rica.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available from the American Cancer Society Web site.

Print copies: Available from the American Cancer Society, 250 Williams St., Suite 600, Atlanta, GA 30303; Web site: www.cancer.org.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

The following are available:

- From the American Cancer Society: vaccines to prevent cervical cancer. CA Cancer J Clin 2007 Jan-Feb;57(1):29. Available from the CA A Cancer Journal for Clinicians Web site.
- Human papilloma virus (HPV). Cancer and HPV vaccines - frequently asked questions. Available from the American Cancer Society (ACS) Web site.

Also available by calling 1-800-ACS-2345.

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NGC STATUS

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