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American Cancer Society Guideline for Human Papillomavirus (HPV) Vaccine Use to Prevent Cervical Cancer and Its Precursors

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

ABSTRACT The American Cancer Society (ACS) has developed guidelines for the use of the prophylactic human papillomavirus (HPV) vaccine for the prevention of cervical intraepithelial neoplasia and cervical cancer. These recommendations are based on a formal review of the available evidence. They address the use of prophylactic HPV vaccines, including who should be vaccinated and at what age, as well as a summary of policy and implementation issues. Implications for screening are also discussed. (*CA Cancer J Clin 2007;57:7–28.*) *© American Cancer Society, Inc., 2007.*

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INTRODUCTION

Cervical cancer screening has successfully decreased squamous cell cervical cancer incidence and mortality. The American Cancer Society (ACS) Guideline for the Early Detection of Cervical Cancer was last reviewed and updated in 2002; for the first time, those recommendations incorporated options including liquid-based cytology and human papillomavirus (HPV) DNA testing.[1] Since that time, two vaccines against the most common cancer-causing HPV types have been developed and tested in clinical trials.[2–7] Numerous studies have been published on the efficacy of these vaccines, as well as issues related to policy and implementation.[8,9]

GUIDELINE DEVELOPMENT

The ACS convened an expert panel to review the existing data on HPV vaccines and develop recommendations specifically addressing the prevention of cervical

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Dr. Saslow is Director, Breast and Gynecologic Cancer, Cancer Control Science Department, American Cancer Society, Atlanta, GA.

Dr. Castle is Investigator, Hormonal and Reproductive Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Department of Health and Human Services, Rockville, MD.

Dr. Cox is Director, Colposcopy and Gynecologic Clinic, Health Services Department, University of California, Santa Barbara, CA.

Dr. Davey is Professor, Department of Pathology and Laboratory Medicine; and Director, Cytopathology, University of Kentucky Medical Center, Lexington, KY.

Dr. Einstein is Director, Clinical Research; and Attending Physician, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology and Women's Health, Montefiore Medical Center, Bronx, NY.

Dr. Ferris is Director, Gynecologic Cancer Prevention Center; and Professor, Departments of Family Medicine and Obstetrics and Gynecology, Medical College of Georgia, Augusta, GA.

Dr. Goldie is Professor of Health Policy and Decision Science; and Director of the Program in Health Decision Science, Department of Health Policy and Management, Harvard School of Public Health, Boston, MA.

Dr. Harper is Professor, Dartmouth Medical School; and Director, Gynecologic Cancer Prevention Research Group, Norris Cotton Cancer Center, Hanover, NH.

Dr. Kinney is Gynecologic Oncologist, Division of Gynecologic Oncology, The Permanente Medical Group, Inc., Sacramento, CA; and Associate Clinical Professor of Obstetrics and Gynecology, University of California, Davis, CA.

Dr. Moscicki is Professor of Pediatrics; and Associate Director, Division of Adolescent Medicine, University of California, San Francisco, CA.

Dr. Noller is Gynecologist-in-Chief, Tufts-New England Medical Center, Boston, MA.

Dr. Wheeler is Professor, Departments of Molecular Genetics and Microbiology and Obstetrics and Gynecology, University of New Mexico Health Sciences Center, Albuquerque, NM.

Ms. Ades is Director, Cancer Information, Health Promotions Department, American Cancer Society, Atlanta, GA.

Ms. Andrews is Research Associate, Cancer Control Science Department, American Cancer Society, Atlanta, GA.

Ms. Doroshenk is Manager, National Colorectal Cancer Roundtable, Cancer Control Science Department, American Cancer Society, Washington, DC.

Ms. Green Kahn is Senior Federal Relations Representative, National Government Relations Department, American Cancer Society, Washington, DC.

Ms. Schmidt is Senior Director, Policy, National Government Relations Department, American Cancer Society, Washington, DC.

Dr. Shafey is Director, International Programs and Research, International Affairs Department, American Cancer Society, Atlanta, GA.

Dr. Smith is Director, Cancer Screening, Cancer Control Science Department, American Cancer Society, Atlanta, GA.

Dr. Partridge is Acting Director of the Comprehensive Cancer Center; and Professor of Obstetrics and Gynecology, Division of Gynecologic Oncology, The University of Alabama at Birmingham, Birmingham, AL.

Dr. Garcia is Associate Professor of Obstetrics and Gynecology; and Director, University of Arizona National Center of Excellence in Women's Health and the Arizona Hispanic Center of Excellence, Tucson, AZ.

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cancer and precancerous lesions. The panel reviewed published literature identified using PubMed (National Library of Medicine) and bibliographies of identified articles, as well as unpublished data. 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. The ACS Gynecologic Cancer Advisory Group members and the National Board of Directors discussed and voted to approve the recommendations.

The ACS Guideline panel worked parallel to, but independent from, the Federal Advisory Committee on Immunization Practices (ACIP) and the ACIP working group on HPV. The ACIP develops written recommendations for the routine administration of vaccines with the goals of reducing the incidence of vaccine-preventable diseases and increasing the safe usage of vaccines. ACIP recommendations include the appropriate periodicity, dosage, and contraindications applicable to vaccines. The ACIP voted on recommendations for HPV vaccination in June 2006; a full report will be published in *Morbidity and Mortality Weekly Report* and available at http://www.cdc.gov/nip/publications/acip-list.htm.

RECOMMENDATIONS

Table 1 summarizes the ACS recommendations for HPV vaccines.

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 (eg, 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.

Research

- Ongoing research and surveillance should be conducted in diverse populations, including research on duration of protective immunity, population- and lesion-based changes in type-specific prevalence for the full spectrum of carcinogenic and noncarcinogenic genital HPV types, changes in Pap test performance characteristics, changes in screening practices and behaviors, comprehensive surveillance for reproductive toxicities, increasing vaccine coverage and acceptability, and impact on safe sexual behavior.
- Safety and efficacy of prophylactic HPV vaccine for the prevention of other anogenital

TABLE **1** Summary of American Cancer Society (ACS) Recommendations for Human Papillomavirus (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.

cancers and head and neck cancers in males, as well as females, should be evaluated.
- Research is needed regarding the design of sustainable vaccination programs in less developed countries.

BACKGROUND

HPV-related Disease Burden

In 2006, an estimated 9,710 cases of invasive cervical cancer will be diagnosed in the United States, and an estimated 3,700 women will die from this disease.[10] Globally, cervical cancer is the second most common cause of cancer death in women, with an estimated 510,000 newly diagnosed cervical cancer cases and 288,000 deaths.[11] In developing countries, cervical cancer is often the most common cancer in women.

Virtually all cervical cancers are causally related to infections by HPV.[12] Approximately 70% of cervical cancers are caused by HPV types 16 or 18.[13,14] About 500,000 precancerous lesions (cervical intraepithelial neoplasia [CIN] Grade 2 and 3 [CIN2 and CIN3]) are diagnosed each year in the United States, and about 50% to 60% are attributable to HPV16 and HPV18.[15] In contrast, CIN1 is caused by a variety of HPV types, about 25% by either HPV16 or HPV18,[16] and about 5% by HPV6 or HPV11.[17]

Anal cancer is diagnosed in about 4,000 people annually (620 deaths) in the United States, and approximately 80% to 90% of anal cancers are caused by either HPV16 or HPV18.[18,19] Vulvar cancers number about 3,870 annually (870 deaths), and at least 40% of these are HPV-related.[20,21] Variable proportions of penile,[22] vaginal,[23] urethral,[24] and head and neck cancers[25–27] have been found to contain carcinogenic HPV types.

Over 500,000 new cases of anogenital warts are diagnosed annually in the United States, and about 90% are caused by HPV types 6 or 11.[28] Approximately 10% of men and women will develop anogenital warts at some point in their lives.[29] Anogenital warts are benign growths that often recur within the first 6 months of initial diagnosis and therefore require repeated treatment sessions.[30] In rare instances anogenital warts become locally invasive and require extensive surgery for removal.[31]

Juvenile laryngeal papillomatosis occurs in about 1 in 200,000 children under age 18 years, most before age 4 years, and is characterized by recurrent benign tumors that may lead to respiratory obstruction. Because of the high recurrence rate, surgical removal often needs to be repeated multiple times.[32] In rare circumstances papillomas may transform to carcinoma; this has been reported to occur in the larynx, esophagus, and bronchi.[33,34] HPV types 6 and 11 are most

frequently demonstrated in respiratory papillomas, with some investigators finding HPV11 most often associated with progression to cancer.[35]

Screening

The most successful strategy for cervical cancer prevention has been the implementation of population-based organized and opportunistic screening programs utilizing exfoliative cervical cytology, the Pap test. The introduction of screening programs in unscreened populations has been shown to reduce cervical cancer rates by 60% to 90% within 3 years after implementation.[36] The purpose of cervical cancer screening is the early detection, diagnosis, and treatment of cancer precursor lesions and cancer.[1] US cervical cancer incidence rates decreased by 75% and mortality by 74% in the 50 years following the introduction of cervical cytology in 1949[37,38] and have continued to decrease in the current decade.

The success of cervical cytology as a public health intervention reflects (1) the generally slow progression from precancerous lesions to invasive cancer, providing ample opportunities for early detection; (2) the ability to identify associated cytologic abnormalities before invasive disease appears; (3) the availability of effective and minimally morbid therapy for premalignant disease; and (4) a strategy that includes frequent repetition of the test.[39] All these factors contribute to making invasive squamous cell carcinoma of the uterine cervix an almost entirely preventable disease. Despite this success, the imperfect sensitivity of cytology testing is estimated to be responsible for 30% of all cervical cancers; and provider error in follow up of abnormal results accounts for another 10%.[40] Cytologic screening suffers from suboptimal single-test sensitivity,[41] limited reproducibility,[42] and many equivocal results. Consequently, several organizations, including the ACS, have recommended HPV DNA testing in conjunction with cytology as a screening option for women aged 30 years and older.[1,43] It has been suggested that, even under the best screening circumstances, an incidence rate of 2 to 3 per 100,000 women can be expected.[40]

Beyond the limitations of the test itself, the failure of some at-risk women to receive regular screening tests also contributes to the burden of cervical cancer. Half of all women who develop cervical cancer in the United States have never been screened, and an additional 10% will have not been screened within 5 years of their diagnosis.[40,44,45] Nonparticipation in cervical cancer screening is a complex multifactorial phenomenon. Failure to undergo a cytologic screening examination is due to a variety of sometimes inter-related reasons including personal factors (fear, embarrassment, anxiety, inadequate knowledge, lack of time, misperception of risk), cultural factors (provider gender, lack of acculturation, age, religious beliefs), and systemic factors (lack of insurance, poverty, legal migratory status, geographic isolation, lack of providers).[46–49] According to the 2002 Behavioral Risk Factor Surveillance System (BRFSS) survey, after adjustment for individual-level factors, area poverty rate was independently associated with never having been screened for breast and colorectal cancer, but not cervical cancer. Factors other than economic ones are often at play in lack of participation in cervical cancer screening, whereas poverty is commonly the inhibitor to obtaining evaluation and treatment after cytologic detection of an abnormality.[50]

Disparities in Cervical Cancer Incidence and Mortality

The greatest burden of cervical cancer is found in underserved, resource-poor populations of women in whom at least 80% of all incident cervical cancer and related mortality occurs.[51] The highest rates of cervical cancer have been observed in regions of Africa, Central and South America, and Micronesia, where age-standardized incidence rates exceeding 50 cases per 100,000 women per year have been observed.

While rates of cervical cancer incidence and related mortality in the United States have fallen following successful implementation of cervical cytology and colposcopy programs, significant racial and ethnic disparities exist with regard to incidence, mortality, and survival associated with the diagnosis of cervical cancer in this country.[52–54] The disparities in incidence and mortality between non-Hispanic white women and other racial/ethnic groups increase with age.[55] Although disparities in incidence and mortality have decreased in recent years, cervical cancer

incidence remains about 60% higher among black women (10.5/100,000) compared with white women (6.6/100,000), and cervical cancer mortality among black women is the highest (4.7/100,000) of any racial or ethnic group.[38] Rates are particularly high among those African Americans living in the rural South (eg, the Mississippi Delta) and also in some urban areas (eg, Washington, DC)[56] (Figure 1). Other US racial/ethnic/geographic groups experience cervical cancer incidence and mortality higher than the population average. These include (1) Hispanics living along the US-Mexico border areas[58]; (2) White (non-Hispanic) women living in Appalachia, rural New York State, and Northern New England[49]; (3) American Indian women living in the Northern Plains and Alaskan Natives[59]; and (4) Vietnamese Americans[54] (Figure 1). Cervical cancer incidence remains high among these groups because of limited resources and poor access to health care, which is further exacerbated by social and cultural barriers.[60]

Natural History of Cervical Cancer

Studies of the natural history of cervical cancer have shown that infection with carcinogenic HPV types may lead to low-grade or high-grade intraepithelial lesions. High-grade lesions may progress to cervical carcinoma if not treated. HPV16 accounts for about 50% to 60% of invasive squamous cell carcinoma worldwide, and HPV18 accounts for an additional 10% to 15%.[61] For adenocarcinoma, global evaluations have shown that HPV16 again accounts for the majority of cases (about 40%), although HPV18 is more commonly detected (about 30%) than in squamous cell carcinomas.[62] This histologic tumor type is relatively rare, but is becoming increasingly important in the United States[55,63] and in some European countries.[64]

Over 40 types of HPV infect the genital epithelium, and it is now widely accepted that cervical infections by approximately 15 carcinogenic types cause virtually all cervical cancer worldwide.[13] Most HPV infections, even by carcinogenic HPV types, are typically transient and resolve or become undetectable within a year or two, sometimes causing mild cytopathologic changes, including atypical squamous cells (ASC), low-grade squamous intraepithelial lesions (LSIL), and histopathologic cervical intraepithelial neoplasia Grade 1 (CIN1) changes.[65–70] Some infections persist, and women with persistent carcinogenic HPV infections are at the greatest risk of developing precancerous lesions and then cancer.[71,72] HPV16 is unique in that it is the most prevalent type in cervical intraepithelial neoplasia Grade 3 or worse (CIN3+), is most likely to persist, and has the highest probability of incident CIN3+ given persistence.[73] However, not all persistent infections progress to precancerous (high-grade) lesions, and not all high-grade lesions develop into cancer. Approximately 75% of low-grade lesions in adults and 90% of low-grade lesions in adolescents resolve without treatment.[68] The longer an HPV infection persists, the less likely a patient is to clear her infection.[66,73]

The stepwise development of invasive cancer (HPV acquisition, HPV persistence, development of cancer precursors, and invasion) takes 20 years on average, with the longest amount of time from high-grade lesions to invasive cancer, although there are cases that develop more rapidly.[74] This reflects, in part, the time needed for random genetic events (eg, accumulation of host gene mutations, which can include HPV integration events). HPV E6 and HPV E7 proteins disrupt the host cell regulatory machinery, thereby allowing infected cells to replicate in a compromised fashion, and in the case of persistent HPV infection, without consistent repair or elimination of chromosomes with DNA damage.[75,76] The relatively slow development of cancer from the time of initial infection has contributed to the success of cytology/colposcopy-based programs.

Transmission of HPV

The sexual transmission of HPV is an important factor in considerations for vaccination strategies, including the optimal age of vaccination. Genital HPV is usually transmitted via vaginal (or anal) intercourse. Infection is common within a few years after onset of intercourse. For example, more than 50% of college-age women acquired an HPV infection within 4 years of first intercourse.[77] Transmission by nonpenetrative genital contact is rare, but infection has been reported in women who did not have a history of penetrative intercourse.[77,78] Oral-genital and hand to genital transmission of some genital

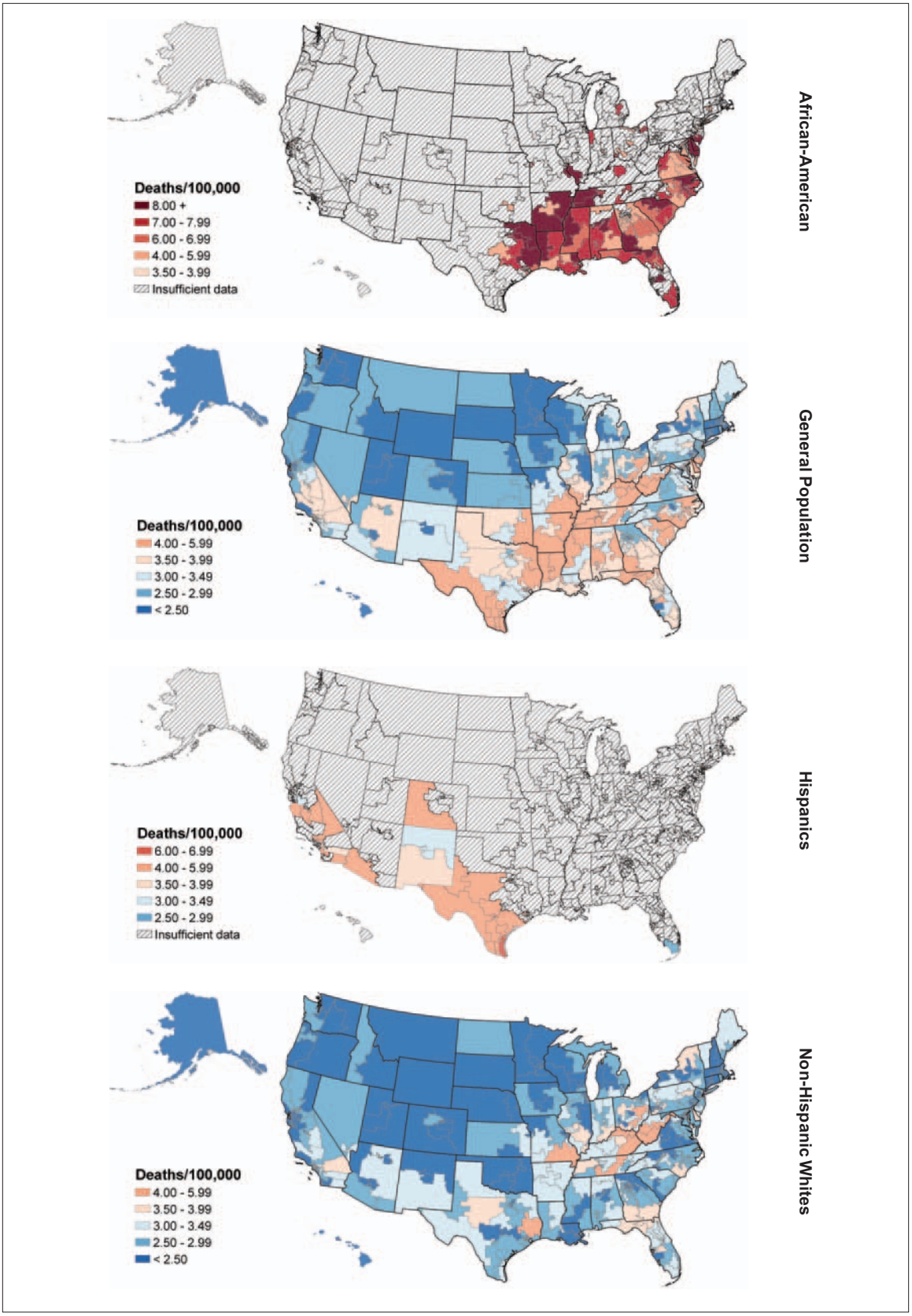

FIGURE **1** Cervical Cancer Mortality Rates per 100,000, Year by Congressional District (Age-adjusted to the 2000 US Standard Population), and Race/Ethnicity, 1990–2001.[57]

HPV types is a plausible phenomenon that has been reported anecdotally, but remains to be proven.[77] Although vertical transmission from mother to newborn is relatively uncommon, it can lead to significant morbidity in the form of respiratory papillomatosis.[79]

Incidence and Prevalence of HPV

Globally, HPV is typically the most common sexually transmitted infection, although there is significant regional variability in the prevalence of HPV even in regions of close proximity and common ancestry,[80] which may be due to differences in sexual and cultural norms. In the United States, each year it is estimated that over 6 million people are infected with genital HPV.[81] An estimated 20 million people in the United States, approximately 15% of the population, are currently infected as detected by HPV DNA assays.[82,83] Almost half of the infections are in those aged 15 to 25 years. Point prevalence estimates for young women range from 27% to 46%.[66,84–86] At least half of all sexually active men and women acquire HPV at some point in their lifetime, and modeling studies suggest that up to 80% of sexually active women will have become infected by age 50.[87] Approximately 1.4 million people in the United States currently have genital warts.[88]

RATIONALE AND EVIDENCE FOR HPV VACCINATION

The burden of HPV-related diseases, recent scientific discoveries of viral etiology of several anogenital cancer types, and the development of prophylactic vaccines together present an unprecedented opportunity for global cervical cancer prevention.

Two prophylactic HPV vaccines have been developed. Both vaccines are based on the recombinant expression and self-assembly of the major capsid protein, L1, into virus-like particles (VLPs) that resemble the outer capsid of the whole virus. The HPV VLPs contain no DNA and are not live/attenuated viruses. Injection of the HPV VLPs elicits a strong and sustained type-specific response.[89,90] One of the vaccines, Gardasil (Merck & Co., Inc.), protects against HPV types 6, 11, 16, and 18 (quadrivalent), and the other, Cervarix (GlaxoSmithKline), protects against types 16 and 18 (bivalent). The goal of prophylactic vaccination is to reduce the incidence of HPV-related genital disease, including cervical, penile, vulvar, vaginal, and anal cancer, and precancerous lesions. Additionally, reduction in the incidence of genital warts is expected for those receiving the quadrivalent vaccine, and reduction in laryngeal papillomatosis is expected among their children.

Efficacy and safety data for these two vaccines are available. Because only one of these vaccines is currently licensed by the FDA, the recommendations and evidence in this guideline focus primarily on Gardasil. The ACS and others will continue to monitor data from studies using Cervarix, as well as Gardasil, and will update the guidelines as new prophylactic vaccine products are licensed and available in the United States.

Efficacy

The prolonged time interval from HPV infection to cervical cancer, low incidence of cervical cancer in developed countries, extensive screening data showing that detection and treatment of cervical intraepithelial neoplasia Grade 2/3 (CIN2/3) reduces cervical cancer incidence and mortality, and ethical considerations have required the designation of CIN2/3 as an accepted intermediate disease endpoint for cervical cancer, and therefore for determination of vaccine efficacy. Several randomized placebo-controlled trials have shown that prophylactic vaccines for HPV types 16[5,6,90,91]; 16 and 18[3,4]; and 6, 11, 16, and 18[7] prevented persistent HPV16 and HPV18 infections and HPV16- and HPV18-related CIN2/3.[5–7] Enrollment criteria for these trials restricted the lifetime number of sex partners and past histories of cervical abnormalities. The studies demonstrated 100% efficacy in the prevention of persistent type-specific HPV infections and CIN2/3, with follow-up data available for up to 4 to 5 years, among subjects who were strictly adherent to the study protocol. Gardasil also protected against HPV6-, HPV11-, HPV16-, and HPV18-related external genital lesions, including genital warts and vulvar and vaginal neoplasia (VIN and VaIN, respectively). Among women with normal Pap tests and without infection by any of 14 carcinogenic HPV types within 90

days of study enrollment, Cervarix reduced the rate of HPV16/18-associated abnormal cytologic results by 93%.

The Phase III efficacy studies for Gardasil were conducted as two main substudies with the following reported results:

Gardasil FUTURE II

Among women aged 15 to 26 years who completed the vaccination regimen, did not violate the protocol, and had no virological evidence of infection with the respective HPV vaccine type at study entry through 1 month following the third vaccine dose (vaccine=5,301 versus placebo=5,258), vaccine efficacy was 100% (97.96% confidence interval [CI], 76% to 100%) for preventing HPV16- or HPV18-related CIN2/3 and adenocarcinoma in situ (AIS). Fifteen of the 21 placebo cases had CIN3.

Gardasil FUTURE I

Among women aged 16 to 23 years who completed the vaccination regimen, did not violate the protocol, and who had no virological evidence of infection with the respective HPV vaccine type at study entry through 1 month following the third vaccine dose (vaccine=2,261 versus placebo=2,279), vaccine efficacy was 100% (97.5% CI, 88% to 100%) for preventing HPV6/11/16/18-related external genital warts or vulvar/vaginal intraepithelial neoplasia (VIN/VaIN) of any grade. In this population (vaccine=2,240 versus placebo=2,258), the vaccine prevented 100% of HPV6/11/16/18-related cervical lesions of any grade. The average follow-up time was approximately 1.5 years following completion of the 3-dose vaccine schedule.

Gardasil ITT

Intention-to-treat (ITT) analyses were also conducted to evaluate the overall impact of Gardasil with respect to HPV6-, HPV11-, HPV16-, and HPV18-related cervical and other genital disease in all women who were randomized into the trials and received one dose of vaccine. No other restrictions were applied. Thus the overall vaccine impact was estimated among women regardless of baseline HPV6-, HPV11-, HPV16-, or HPV18-PCR status (ie, evidence of current infection) and sero-status (ie, evidence of prior infection). The analyses included events arising from HPV infections with vaccine HPV types that were present at the start of vaccination, as well as events that arose from those infections that were acquired after the start of vaccination. Impact was measured starting 1 month post dose 1. The mean follow-up period for Gardasil available to date was approximately 1.5 years post dose 3 of the vaccine. Protocol violations did not influence efficacy findings, including variations in dosing intervals of up to 1 year. The majority of CIN and genital warts, VIN, and VaIN detected in the group that received Gardasil occurred as a consequence of HPV infection with the relevant HPV type that was already present at study enrollment. The percent reduction of HPV16/18-related CIN2/3 or AIS was estimated at 39% (95% CI, 23% to 52%). The percent reduction in HPV6/11/16/18-related CIN or AIS was 46% (95% CI, 35% to 56%). The percent reduction of HPV16- or HPV18-related VIN 2/3 and VaIN 2/3 was 69% (95% CI, 30% to 88%). The percent reduction of HPV6/11/16/18-related genital warts was 69% (95% CI, 58% to 77%). In addition, an interim analysis of combined Phase II and III Gardasil studies (median follow-up of 1.9 years) demonstrated a percent reduction for CIN2/3 of only 12.2% (95% CI, -3.2% to 25.3%) compared with placebo when extended to include all CIN2/3 regardless of HPV type.[92] Actual efficacy may be even lower among the general population since the generalizability of these 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.

It is important to note that, when subjects entered these studies with evidence of current or past HPV infection (ie, PCR- or serology-positive for HPV vaccine types), there was no clear evidence of protection from subsequent disease demonstrated by administration of the prophylactic quadrivalent vaccine.[92] Limited longer-term efficacy data will be available for study participants from northern European countries with comprehensive registration of cervical cancer and precancer. Cases of infection and even failed/recurring CIN may be identified as longer-term follow-up data become available. At this time efficacy is unknown for younger girls and for males.

Cervarix

Among women aged 15 to 25 years who completed the 3-dose vaccination regimen and participated in an extended follow-up study (vaccine=393 versus placebo=383), vaccine efficacy was 100% (95% CI, 42.4% to 100%) for preventing HPV16- or HPV18-related CIN. Five HPV16 or HPV18-related placebo cases had CIN2, and 3 had CIN1. The follow-up period was up to 4.5 years (44 to 53 months).[4]

Safety

Both Gardasil and Cervarix have had few safety issues during any of the trials. Injection site adverse experiences were reported in 83% of the Gardasil recipients and in 73.4% of the placebo recipients who participated in the Phase IIb randomized controlled trial.[7] 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. Overall, 11.4% of the vaccine recipients and 9.6% of the placebo recipients had a temperature of ≥100° F (≥37.8° C). Higher temperatures of ≥102° F (≥38.9° C) were recorded in only 1.5% of the vaccine and in 1.1% of the placebo recipients. There were no deaths in the trial considered to be secondary to vaccine or procedure. Five vaccine and two placebo recipients had serious vaccine-related experiences. 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). The placebo serious adverse experiences included one case of hypersensitivity and one case of chills with headache and fever. Only 0.2% of the subjects discontinued due to an adverse experience in both vaccine and placebo groups.[7]

Women determined to be pregnant by a sensitive human chorionic gonadotropin (HCG) test on the day of expected vaccination were excluded from receiving the vaccine. However, some women became pregnant during the few weeks or months following the receipt of a vaccine or placebo injection. Overall, 10.7% of the Gardasil and 12.6% of the placebo recipients became pregnant. Pregnancy outcomes were evaluated with respect for time from the injection to the onset of pregnancy. Sixty-two percent of the vaccine and 60% of the placebo recipients who became pregnant had a live birth. Fifty-six women receiving Gardasil and 58 women receiving placebo became pregnant within 30 days of the injection, and 512 Gardasil and 509 placebo recipients became pregnant beyond 30 days from the injection. Spontaneous pregnancy loss occurred in 26.1% of pregnant women in both groups. Among women becoming pregnant within 30 days of vaccination, 5 delivered infants with congenital anomalies, in contrast to none of the women receiving the placebo. The anomalies were unrelated in type (one pyloric stenosis with ankyloglossia, one congenital megacolon, one hydronephrosis, one hip dysphasia, and one club foot) and were judged by expert review not likely related to the vaccine. Congenital anomalies affect 2% to 4% of all US live-born infants. Therefore, it would be expected that up to 2.4 women who became pregnant within 30 days in both the vaccine and placebo groups would have congenital anomalies, or a total of five for both groups combined. For women becoming pregnant beyond 30 days after vaccination, 10 Gardasil and 16 placebo recipients had pregnancies with congenital anomalies.[93] A pregnancy registry postmarketing of the vaccine has been proposed, and will be crucial, to further evaluate reproductive toxicities and pregnancy outcomes associated with vaccine exposures.

For Cervarix, detailed safety data for the Phase IIb randomized controlled trial were collected by daily diary for 7 days and by interview 30 days after each injection. Information on serious adverse events and pregnancy outcomes was collected throughout the duration of each trial. Overall, the vaccine appeared to be generally safe and well-tolerated. Injection site adverse events, including pain, redness, or swelling, were reported more often among vaccine recipients than among placebo recipients (94% versus 88%). Systemic adverse events, including headaches, fatigue, and gastrointestinal symptoms, were reported by a similar proportion of vaccine and

placebo recipients (86%). Most adverse events were recorded as mild or moderate in intensity. Overall, 16.6% of the vaccine recipients and 13.6% of the placebo recipients had a temperature of ≥100° F (≥37.5° C). Only 0.2% (n=1) of the vaccine recipients and zero placebo recipients discontinued due to a serious adverse experience. There were no deaths in the trial considered to be secondary to vaccine or procedure. Pregnancy and congenital anomaly data for this vaccine have not yet been published.[3,4]

It will be important to conduct surveillance studies to assess safety and identify rare adverse events, including those in pregnant women, as 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.

Duration of Protection

There is little information currently available on duration of HPV vaccine-induced immunity. There is no available immune correlate of vaccine-induced immunity (eg, postvaccine peak or current antibody titers). During naturally occurring HPV infections, many women do not develop detectable HPV antibodies. In the case of HPV16, the available serologic assays detect type-specific antibodies in only 54% to 60% of women who are infected.[67,94,95] Thus longer-term follow up in Phase III and Phase IV postlicensure studies cannot rely on serologic measurement of HPV vaccine-induced antibody titers. Further, because the currently available HPV vaccines do not protect against all carcinogenic HPV types, longer-term surveillance will need to assess genital HPV type-specific infections in vaccine recipients to adequately measure duration of vaccine efficacy against HPV vaccine types. These evaluations will be critical to identifying potential waning immunity and evaluating any requirements for booster immunizations. In addition, Northern European cohorts that were immunized at least 3 years before the vaccines became commercially available in the United States will be monitored for break-through lesions to determine when and if a booster is needed. These cohorts are relatively small, however, and may not have statistical power to adequately address issues related to duration of vaccine immunity.

Age to Vaccinate

There are three important factors to take into account when recommending age to vaccinate: duration of protection, age for optimal efficacy, and feasible plans for distribution. As previously noted, duration data are limited since Phase II studies have data up to only 3.5 to 5 years.

It is important to vaccinate patients before the age at which exposure is likely to occur. The lower age limit is bound by the age of study participants, the youngest being aged 9 years. These studies, however, only evaluated safety and immunogenicity. The lower age limit for vaccine efficacy studies of Gardasil is 16 years and for Cervarix is 15 years. As the vaccine is prophylactic, it is important to consider risk of prior infection, which is best estimated by prior sexual activity. In the United States, according to national survey data, 24% of females report being sexually active by age 15 years, 40% by age 16 years, and 70% by age 18 years.[96] Seven percent of high school students (male and female) reported having initiated intercourse before aged 13 years, and 10% of sexually active ninth graders reported having had 4 or more lifetime sex partners.[97] HPV acquisition often occurs soon after sexual debut; in one study, 39% of college-aged women acquired HPV within 24 months of onset of sexual activity.[77] In a study of adolescents and young women aged 13 to 21 years, 70% had evidence of HPV infection within 5 to 7 years of onset of sexual intercourse.[98] However, it is important to recognize that epidemiologic studies can only underestimate the true exposure to HPV infections since the infections of very short duration will likely go undetected. In addition, HPV infections are further underestimated as a result of test and sampling errors that have been demonstrated in studies using weekly repeated HPV measurements.[99] From a public health perspective, routine vaccination before sexual debut or

shortly thereafter is important to achieve optimal effectiveness.

While HPV-related cervical disease remains an important health issue for girls and women of all ages, the efficacy and potential benefit of HPV vaccines for females aged 19 years and older in the general population are less clear than for girls younger than age 19 years. Females aged 19 years and older who have not yet engaged in sexual intercourse would derive full benefit from HPV vaccination. Because many females aged 19 to 26 years may not have been exposed to all of the vaccine HPV types, there could be some benefit from vaccination if they have not received the full 3-dose vaccination series. However, many currently or previously sexually active females will have been exposed to HPV16 and/or HPV18. For example, Brown et al[100] tested sexually active adolescent girls (median number of sex partners of 2) every 2 months and found the cumulative prevalence of HPV16 to be 31.3% at 2.2 years, and 20.0% for HPV18. The risk of exposure to carcinogenic and noncarcinogenic HPV types increases with number of lifetime sex partners.[66,67,77,101] National survey data have shown that approximately 50% of females over age 19 years have had 4 or more sexual partners,[102] with a median number of 4.[103] The generalizability of Gardasil vaccine trial results to general population impact is thus questionable given study inclusion/exclusion criteria which limited the maximum number of lifetime sex partners and past history of genital abnormalities. Specifically only about a quarter of the Gardasil study participants between age 16 and 26 years had 4 lifetime sex partners and the remainder had 3 or fewer; the mean number was only 2.

There is currently insufficient evidence to recommend for or against universal vaccination of women aged 19 to 26 years in the general population. In the Gardasil clinical trials, there was no clear evidence of protection from disease caused by HPV types for which study participants were PCR-positive and/or seropositive at the time they entered the trial, ie, females with a current or prior HPV16 or HPV18 infection that could be detected.[104] Because HPV is highly prevalent in the sexually active population, and the median number of lifetime sexual partners for women aged 19 to 26 years is 3-4,[102,103] the likelihood of prior HPV exposure to at least one of the high-risk vaccine types is substantial. The potential population benefit of universal prophylactic HPV vaccination in women aged 19 to 26 years, therefore, is diminished. A woman in this age group who has been sexually active may choose whether to receive the vaccine based upon her personal sexual history; an understanding of the likely diminished benefit with increasing likelihood of previous HPV exposure; and her values, preferences, and competing health care needs.

While vaccine trial data have not demonstrated equivalent efficacy for already-exposed women (ie, women receiving HPV vaccine who have evidence of past or current HPV infection with HPV vaccine types), equivalent safety has been demonstrated. HPV testing before initiating vaccination, however, is *not* recommended because there are no good measures of past exposure; additionally current clinically available testing reflects only current viral shedding.

Vaccination of Males

Only trials of the Gardasil vaccine have included male participants: 9- to 15-year-old boys were included in the safety and immunogenicity study (Protocol 018). Efficacy trials in young men are ongoing, with results expected in 2007. If efficacy among males is shown, vaccination may be recommended in the future for the purpose of preventing (1) anogenital warts in males and, indirectly, infection and anogenital neoplasia and warts in female and male partners; (2) a subset of anal, penile, oral, and head and neck cancers; and (3) juvenile respiratory papillomatosis in their children. Mathematical modeling has shown that, if vaccine coverage is high, vaccination of males in addition to females will offer little additive benefit in preventing HPV-related cervical disease. Available data from mathematical modeling suggest that male vaccination may not be cost-effective for the prevention of cervical cancer in women.[105,106] If vaccine coverage is high, a female-only vaccination program is likely to protect males (who have sex with female partners) against HPV6/11/16/18 through herd immunity. If coverage is low, as may occur in certain low resource countries,

modeling suggests that vaccination of both males and females may be more effective in preventing HPV-related cervical disease.[107]

ANTICIPATED IMPACT OF HPV VACCINATION

Impact on Screening Recommendations

The reduction of cervical cancer risk by 70% or more becomes a theoretic possibility depending on the number of carcinogenic HPV types eventually included in a future HPV prophylactic vaccine and on the percent of the population vaccinated. However, even under the best of circumstances, it will be many decades before this could become a reality. Vaccinating young girls will not have a substantial impact on cervical cancer rates until they attain the median age of cervical cancer diagnosis, 48 years.[38] 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. If immune protection wanes with time, booster HPV vaccine shots may theoretically provide ongoing protection, but population protection will depend on the percent of the population obtaining the booster and the efficacy of that booster. If prophylactic vaccine availability leads to declining participation in screening programs, then cancers will develop that may have been otherwise prevented. VLP vaccines for all the important carcinogenic HPV types may, theoretically, be produced. But until long after HPV vaccines are available, women will continue to require screening to prevent cancers that occur from the other carcinogenic HPV types not in the present vaccines. Screening will also need to continue to protect women who will not get the vaccine and who are already infected prevaccination. These realities caution against scaling back cervical cancer screening, as premature relaxation of cervical cancer control measures already in place could potentially cause cervical cancer rates to increase.[8] Cervical screening will continue to be necessary for the foreseeable future.

While vaccination will provide protection against HPV16- and HPV18-associated invasive cervical cancer in the long-term, there is potential for short-term benefit in reducing abnormal Pap test results, colposcopy referrals, cervical biopsies, and genital warts since HPV6, HPV11, HPV16, and HPV18 are associated with approximately 40% of histologically-confirmed CIN. Use of procedures such as loop electrosurgical excision and cold knife conization can be reduced by preventing, through vaccination, cases of CIN likely to regress (eg, CIN1 at all ages and CIN2 in younger women), thereby reducing obstetrical morbidity related to impaired cervical function in late pregnancy, including premature delivery, low birth weight, and premature rupture of membranes.[108] This is especially germane for young women early in their reproductive lives who may require multiple excisional procedures for recurrent or persistent high-grade disease.

Because screening tests are not perfect, lowering the prevalence of a disease (such as CIN2/3+) in the population virtually always causes the positive predictive value (PPV) of a screening test for that disease to decrease and the negative predictive value (NPV) to increase. Thus, when widespread HPV vaccination is achieved, it is anticipated that the PPV of a screening Pap test for detection of CIN2/3+ will decrease and the NPV will increase. Similar changes may be expected for carcinogenic HPV testing, as the risk of precancer and cancer over 10 years among carcinogenic HPV-positive women who test negative for HPV16 and HPV18 at a single time point is surprisingly low.[109] The implication of this effect is that a smaller percentage of women with an abnormal Pap test result will have CIN2/3+ detected during a colposcopically-directed biopsy procedure (ie, the percentage with a false positive Pap test will increase). On the other hand, a smaller percentage of women with a negative screening test result will have a missed CIN2/3+ lesion (ie, the percentage of women with a false negative Pap test will decrease). It will be important to monitor changes in Pap test performance characteristics and evaluate the impact on screening and screening guidelines.

At this time there is insufficient evidence to alter screening recommendations; women who

receive HPV vaccine should follow current guidelines. 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.

Recent reports have shown that type-specific detection of HPV16 and HPV18 may have clinical utility.[109,110] The expected commercial availability of HPV16 and HPV18 type-specific tests in the coming years is likely to significantly alter screening and follow-up recommendations for vaccinated as well as unvaccinated women.

Impact on Disparities

Cytology screening programs have proved relatively ineffective in resource-poor regions throughout the world and in underserved populations in the United States.[49,57,111] The underlying causes for failures of cytology programs to reach underserved populations are varied and complex. In addition to the personal, cultural, and systemic factors noted earlier in this article, additional reasons include the following: (1) a single cytologic test is insensitive, and thus a negative test does not provide long-lasting reassurance against cancer risk, and multiple rounds of screening are required; and (2) the multiple-visit model for diagnosis and treatment may be unrealistic among resource-poor and hard to reach populations. Effective cytology-based screening programs often cannot be maintained in resource-limited countries and in underserved populations in wealthy countries, primarily because of high cost and loss to follow up.

Further substantial improvements in cytology programs are unlikely to be cost-effective and are unlikely to reduce existing racial, ethnic, and socioeconomic disparities in participation in screening, cervical cancer incidence, or mortality. Thus, more efficient prevention strategies that target the causal factor, HPV infection, could ultimately expand protection to the underserved, resulting in improved health outcomes. In particular, provision of free HPV vaccines under the federal Vaccine for Children Program[112,113] to all eligible girls through age 18 years is expected to reach many medically underserved individuals who are least likely to receive regular screening as they get older. Similar racial and ethnic disparities in acute hepatitis B infections among children under age 19 years were virtually eliminated in this country between 1990 and 2004 following recommendation for universal hepatitis B vaccination.[114] Of major concern, however, is the challenge of vaccinating young immigrants, such as those in border states who are ineligible for many public health programs. More than half of cervical cancer deaths in the United States have been reported to occur in foreign-born women.[115]

The potential for HPV vaccination to reduce cervical cancer disparities is also supported by cost-effectiveness data. Most published cost-effectiveness analyses of vaccination have thus far been in settings with existing screening. In a recent analysis integrating data on screening patterns by race in the United States, S. J. Goldie, MD, MPH, and colleagues (written communication, August 9, 2006) found that HPV16/18 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.

Impact on Sexual Behavior

There have been some concerns that the perception of safety resulting from introduction of a prophylactic HPV vaccine will lead to an increase in unsafe behaviors and premature sexual activity among adolescents ("behavioral disinhibition"). Some organizations have expressed their support for universal availability of HPV vaccines while emphasizing that vaccination should not be a substitute for sexual abstinence until marriage and fidelity after marriage.[116,117] Media coverage has cited such concerns as a potential barrier to vaccine acceptance and implementation, and several small studies also have cited this as a barrier to parental and provider acceptability.[118,119] Historically, similar concerns have been raised with regard to penicillin for syphilis, condom availability programs, and emergency contraception.

Concerns about behavioral disinhibition are based on assumptions that perceptions of HPV risk protect adolescents from exposure to HPV and that fear of HPV is a motivation for safer sex and/or abstinence. While data are limited,

several examples cited below may provide some insight into the potential impact of HPV vaccination on behavior. National Survey of Family Growth data[96] show that only 10% of male and 7% of female adolescents who have never had sex cite "don't want STD" as the main reason for not having sex. Knowledge of HPV as an STD is extremely limited in both male and female adolescent and adult populations.[120,121] Studies of emergency contraception and condom availability programs addressing similar concerns also showed no differences in unprotected intercourse, frequency of intercourse, number of sex partners, or sexually transmitted infections.[122,123] Although the evidence does not support that the introduction of HPV vaccination will lead to changes in sexual behavior, postmarketing monitoring will be important.

VACCINE IMPLEMENTATION AND ADMINISTRATION

Adolescent Vaccination

Vaccinating any child or adult presents immense barriers.[124] The most successful regimens are those required for infants.[125–127] In adolescence and beyond, the ability to immunize is limited by access.[128,129] Most adolescents do not receive annual health examinations.[130] Hence, immunization opportunities occur during nonroutine visits. The experience with hepatitis B vaccines underscores the difficulty in immunizing adolescents.[131] 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.[132,133] 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.[133] This adolescent platform may increase the likelihood of 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,[134–136] parents of adolescents,[118,119,137,138] and providers[139,140] 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[138] found that age was not a factor for parents of adolescent children. Some parents expressed concern that a vaccine would increase unsafe sexual behavior,[118,119] while another study reported that sexual transmission did not affect parental attitudes.[138]

Most parents, young women, and adolescents have minimal knowledge of HPV and its association with cervical cancer.[120,121] Several studies indicate that vaccine acceptance is improved with increased knowledge.[119,135,141,142] 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.[119] 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.[143] 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.

Cost-effectiveness Analyses

Because of the extended length of time involved in the progression from HPV infection to cervical cancer, it will be many years before a reduction in cancer incidence and mortality rates would be possible to observe within a vaccinated population. Since no single empirical study can address all policy questions involving vaccination and screening, mathematical models that simulate the natural history of disease and that integrate the best available clinical and economic data can be used to estimate the potential cost-effectiveness of different strategies. While different kinds of models may be used, in all of them there are important factors that influence the probabilities of acquiring and clearing infection, progression and regression of CIN, and incidence of cancer. While in a simulation model of a single cohort the probability of HPV acquisition is governed by the current age, age of sexual debut, HPV type, exposure to screening, and whether there is type-specific immunity to natural infection, in a transmission model the probability of an individual acquiring an infection is also dependent on the sexual contact patterns between individuals and the distribution of the infection within the population at that specific time. While cohort models have advantages related to representing complex interaction between vaccination and screening, transmission models that can estimate herd immunity effects are needed for consideration of male vaccination.

Currently, there are several published analyses addressing the potential impact of HPV vaccines.[105,106,144–150] 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 catch-up 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.[106,147,149] 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 (ie, 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.

Education Needs

Various studies have assessed awareness and knowledge of HPV among adolescents,[120,151,152] university students,[153–157] and young adults,[121,152] including women with past experience with abnormal Pap results and colposcopy[158–160] and with HPV testing,[161] and the majority have indicated that such knowledge is very limited. For example, in one study of over 1000 women attending a well woman clinic, only 30% had heard of HPV, and even those women had poor knowledge about HPV.[121] In another survey of over 500 inner city high school students, 87% had not heard of HPV. Eighty-five percent of these students had visited a doctor or clinic within the past year, but only 29% had talked about sexual health.[120] One study concluded that a brief educational intervention was effective at increasing knowledge about HPV, at least in the short term.[155] Studies that assessed knowledge of other common sexually transmitted infections found that knowledge of HPV was the lowest or one of the lowest.[120,151,157]

Two qualitative studies collected data about women's informational needs. The most frequently asked questions to the American Social Health Association National HPV and Cervical Cancer Prevention Resource Center include questions about HPV transmission, effect on pregnancy, source of infection, prevention, treatment options, and duration of infection.[162] A series of focus groups with lower income women led to similar findings, with the recommendations that effective education about HPV must include (1) information about transmission, prevention, treatment, and cancer risk; (2) messages tailored to different age and risk groups; (3) clarification of carcinogenic and noncarcinogenic HPV types and their consequences; and (4) reassurance, eg, that even though HPV infection is very common, cancer risk is very low with screening.[163] Additional research on HPV awareness and knowledge will be needed to assess the effects of media coverage of the introduction of vaccines, as well as marketing efforts of the manufacturers.

Knowledge of HPV also varies among health care providers. Pediatricians and primary care providers may have limited familiarity with and understanding of HPV, whereas gynecologists may have greater understanding of HPV infection, regression, persistence, and progression to cervical cancer precursors. One national survey reported that 90% of family physicians were knowledgeable about how common HPV infections are and the relationship between HPV, cervical cancer, and genital warts, while only 47% agreed that the HPV types associated with genital warts differ from the types associated with cervical cancer, and only 33% agreed that most HPV infections clear without intervention.[164] In comparison, 98% of surveyed obstetricians/gynecologists were aware of the prevalence of HPV infections, 97% were knowledgeable about the connection between HPV and cervical cancer, 70% agreed that HPV types associated with genital warts differ from carcinogenic HPV types, and 67% knew that most HPV infections clear spontaneously.[165] Professional education should be tailored to the level of understanding of individual providers. For example, pediatricians are more likely to benefit from an overview of the HPV natural history, epidemiology, and molecular biology, whereas gynecologists are most likely to need training on vaccine administration and logistical issues such as storage and reimbursement. A modular education and training curriculum, including scripts and talking points, may be helpful in preparing providers to implement HPV vaccination.

International Challenges

Cervical cancer poses a significant global cancer burden. About 510,000 cases of cervical cancer are reported annually: 68,000 in Africa, 77,000 in Latin America, and 245,000 in Asia.[11] Successful global implementation of an effective HPV vaccine offers an unprecedented opportunity to prevent millions of deaths and dramatically reduce the world's cancer burden.

Ensuring widespread coverage by HPV vaccination programs will depend on vaccine affordability, HPV epidemiology, socio-cultural environment, and the logistical capacity and commitment of national and international health organizations. Historically, there has been limited success in overcoming the initial logistic and economic challenges of integrating new vaccines into the health care systems of developing countries. Each country will have to decide whether HPV vaccination programs are appropriate for their population given the national burden of cervical cancer, the cost and effectiveness of vaccination, and the relative importance of HPV vaccination compared with other health care system priorities.[166] It may require many years or even decades to implement effective, affordable, and acceptable vaccination programs for cervical cancer prevention in developing countries.[167] Vaccine manufacturers are acutely aware of the issue of affordability and, in partnership with global vaccine distribution and financing agencies, an effort is under way to develop strategies for making HPV vaccines available globally at an affordable price.[168]

RECOMMENDATIONS FOR ADDITIONAL RESEARCH

As promising as the current HPV VLP vaccines appear to be, it is important to recognize the limitations of currently available vaccines and the available data. 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 a population where follow up is poor, such as uninsured and migrant populations or those living in underserved areas.

Only limited and short-term data are available to assess the benefit of HPV vaccination in females aged 19 to 26 years, and no data are available for populations of women with more than an average of 2 lifetime sex partners. This is an important area of research given the recommendation by ACIP and many provider groups for catch-up vaccination of all females aged 13 to 26 years, the manufacturers' emphasis on vaccinating this age group, the cost of vaccinating such a large cohort, and the limited public funding available for vaccination of uninsured and underinsured adults. It will be important to review data (beyond the 2-year data currently available) from the vaccine trials to assess the impact on overall number of abnormal cytology results and follow-up procedures, as well as the impact on the general population of young women that will have had more than an average of 2 lifetime sex partners. Cost-effectiveness analyses of catch-up vaccination strategies, and in particular the age range of the catch-up program, are also critically needed. In addition, tools to assist women and providers in making informed decisions about vaccination need to be developed and evaluated.

It will also be important to evaluate alternative vaccine schedules that reduce the cost and expand the coverage of vaccination. Certainly, one of the questions is the level of protection offered by 2 or even 1 immunization with the current vaccines. A second question is whether 2 vaccinations administered within a 12-month interval might achieve better compliance (eg, particularly in populations who migrate according to seasonal patterns) with sufficient efficacy. Further, there is a need for program research and evaluation, including (1) long-term data on duration of vaccine-induced immunity; (2) vaccine safety data, including reproductive toxicities and coadministration with other adolescent vaccines; (3) registry and other tracking data to assess vaccine coverage; (4) surveillance data to assess population-based vaccine effectiveness in reduction of targeted disease outcomes; (5) data for population- and lesion-based changes in type-specific prevalence for the full spectrum of carcinogenic and noncarcinogenic genital HPV types; and (6) qualitative and quantitative data on vaccine acceptability and impact on sexual behaviors and, just as importantly, screening behavior.

It will be important to evaluate the impact of the HPV VLP vaccines on other genital and

nongenital HPV-associated tumors. HPV vaccination might be helpful for individuals at high risk of anal cancer (eg, men who have sex with men), if vaccination of men achieves similar protective immune responses as those seen in women.

HIV-infected patients have a higher prevalence and persistence of HPV infection, which increases their risk of developing anogenital (cervical and anal) precancer and cancer. It is unknown what the impact of patients' HIV status (eg, viral load and CD4 count) has on developing protective immune responses to HPV VLP vaccination. HIV-infected individuals, especially those with well-controlled HIV infections, could significantly benefit from HPV VLP vaccination, but safety, immunogenicity, and efficacy need to be established in clinical trials before any recommendations can be proposed.

A critical need in the United States and other countries with cervical screening is to understand the integration of vaccination with, and likely impact on, screening. This includes measuring the impact on cytology and carcinogenic HPV testing performance characteristics, such as the positive and negative predictive values, as well as the impact on women's screening behavior and provider behavior, such as in recommending screening to patients.

Finally, much research is needed to ensure the introduction and success of HPV vaccination programs in developing countries. Evidence to justify the allocation of financial and other resources to HPV vaccines, as well as to support efficient and cost-effective implementation, will be required to obtain agreement from ministries of health in these countries. Vaccination in younger women and low-cost HPV DNA screening in older women could significantly reduce the global burden of cervical cancer with a few lifetime patient visits, but such an approach requires a demonstration project for widespread adoption.[169]

CONCLUSION

If duration of immunity is substantial or can be extended adequately through booster vaccinations, the high vaccine efficacy observed in Phase II and III studies suggests that female populations receiving prophylactic immunization will experience a reduction in the morbidity and mortality associated with HPV-related anogenital diseases. The promise of prophylactic vaccines from a broad public health perspective, however, can be realized only if vaccination can be achieved for those groups of women for whom access to cervical cancer screening services is most problematic. The protective effect of vaccination that is successfully provided to adolescent and young women who are unlikely to undergo regular Pap screening will be of greater magnitude than that provided to women who will undergo regular screening regardless. Even as HPV vaccination for the prevention of cervical cancer is introduced and promoted, it remains critical that women undergo regular screening regardless of whether they have been vaccinated.

GYNECOLOGIC CANCER ADVISORY GROUP

Members: Carmel J. Cohen, MD; Professor of Clinical Obstetrics and Gynecology, Division of Gynecologic Oncology, Columbia University Medical Center, New York, NY; **Francisco Garcia, MD, MPH**; Associate Professor of Obstetrics and Gynecology; and Director, University of Arizona National Center of Excellence in Women's Health and the Arizona Hispanic Center of Excellence, Tucson, AZ; **Diane M. Harper, MD, MPH, MS**; Professor, Dartmouth Medical School; and Director, Gynecologic Cancer Prevention Research Group, Norris Cotton Cancer Center, Hanover, NH; **Joan G. Jones, MD**; Professor of Clinical Pathology and Laboratory Medicine, Weill Cornell Medical College; and Director of Anatomic Pathology, New York Presbyterian Hospital, New York, NY; **William P. McGuire, MD**; Director, Franklin Square Hospital Cancer Center, Baltimore, MD; **Edward E. Partridge, MD**; Acting Director of the Comprehensive Cancer Center; and Professor of Obstetrics and Gynecology, Division of Gynecologic Oncology, The University of Alabama at Birmingham, Birmingham, AL; **Carolyn D. Runowicz, MD**; Professor of Obstetrics and Gynecology; NEU Chair in Experimental Oncology; and Director

of the Neag Comprehensive Cancer Center, University of Connecticut Health Center, Farmington, CT; **Debbie Saslow, PhD**; Director, Breast and Gynecologic Cancer, Cancer Control Science Department, American Cancer Society, Atlanta, GA; **Diane Solomon, MD**; Senior Investigator, Division of Cancer Prevention, National Cancer Institute, Rockville, MD

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