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Quadrivalent Human Papillomavirus Vaccine

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

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Quadrivalent Human Papillomavirus Vaccine

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Prepared by
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Summary

These recommendations represent the first statement by the Advisory Committee on Immunization Practices (ACIP) on the use of a quadrivalent human papillomavirus (HPV) vaccine licensed by the U.S. Food and Drug Administration on June 8, 2006. This report summarizes the epidemiology of HPV and associated diseases, describes the licensed HPV vaccine, and provides recommendations for its use for vaccination among females aged 9–26 years in the United States.

Genital HPV is the most common sexually transmitted infection in the United States; an estimated 6.2 million persons are newly infected every year. Although the majority of infections cause no clinical symptoms and are self-limited, persistent infection with oncogenic types can cause cervical cancer in women. HPV infection also is the cause of genital warts and is associated with other anogenital cancers. Cervical cancer rates have decreased in the United States because of widespread use of Papanicolaou testing, which can detect precancerous lesions of the cervix before they develop into cancer; nevertheless, during 2007, an estimated 11,100 new cases will be diagnosed and approximately 3,700 women will die from cervical cancer. In certain countries where cervical cancer screening is not routine, cervical cancer is a common cancer in women.

The licensed HPV vaccine is composed of the HPV L1 protein, the major capsid protein of HPV. Expression of the L1 protein in yeast using recombinant DNA technology produces noninfectious virus-like particles (VLP) that resemble HPV virions. The quadrivalent HPV vaccine is a mixture of four HPV type-specific VLPs prepared from the L1 proteins of HPV 6, 11, 16, and 18 combined with an aluminum adjuvant. Clinical trials indicate that the vaccine has high efficacy in preventing persistent HPV infection, cervical cancer precursor lesions, vaginal and vulvar cancer precursor lesions, and genital warts caused by HPV types 6, 11, 16, or 18 among females who have not already been infected with the respective HPV type. No evidence exists of protection against disease caused by HPV types with which females are infected at the time of vaccination. However, females infected with one or more vaccine HPV types before vaccination would be protected against disease caused by the other vaccine HPV types.

The vaccine is administered by intramuscular injection, and the recommended schedule is a 3-dose series with the second and third doses administered 2 and 6 months after the first dose. The recommended age for vaccination of females is 11–12 years. Vaccine can be administered as young as age 9 years. Catch-up vaccination is recommended for females aged 13–26 years who have not been previously vaccinated. Vaccination is not a substitute for routine cervical cancer screening, and vaccinated females should have cervical cancer screening as recommended.

Introduction

Genital human papillomavirus (HPV) is the most common sexually transmitted infection in the United States; an estimated 6.2 million persons are newly infected every year (*1*). Although the majority of infections cause no symptoms and are self-limited, persistent genital HPV infection can cause cervical cancer in women and other types of anogenital cancers and genital warts in both men and women.

Approximately 100 HPV types have been identified, over 40 of which infect the genital area (*2*). Genital HPV types are categorized according to their epidemiologic association with cervical cancer. Infections with low-risk types (e.g., types 6 and 11) can cause benign or low-grade cervical cell changes, genital warts, and recurrent respiratory papillomatosis. High-risk HPV types act as carcinogens in the development of cervical cancer and other anogenital cancers (*3,4*). High-risk types, including types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 69, 73, and 82, can cause low-grade cervical cell

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abnormalities, high-grade cervical cell abnormalities that are precursors to cancer, and anogenital cancers (*5*). High-risk HPV types are detected in 99% of cervical cancers (*6*); approximately 70% of cervical cancers worldwide are caused by types 16 and 18 (*7*). Although infection with high-risk types is considered necessary for the development of cervical cancer, it is not sufficient because the majority of women with high-risk HPV infection do not develop cancer (*3,4*).

In addition to cervical cancer, HPV infection also is associated with anogenital cancers such as cancer of the vulva, vagina, penis, and anus (Table 1) (*8,9*). Each of these is less common than cervical cancer (*10–14*). The association of genital types of HPV with nongenital cancer is less well established, but studies support a role in a subset of oral cavity and pharyngeal cancers (*15*).

In June 2006, the quadrivalent HPV vaccine types 6,11,16,18 (GARDASIL™, manufactured by Merck and Co., Inc., Whitehouse Station, New Jersey) was licensed for use among females aged 9–26 years* for prevention of vaccine HPV-type–related cervical cancer, cervical cancer precursors, vaginal and vulvar cancer precursors, and anogenital warts. Efficacy studies are ongoing in men.

In the United States, cervical cancer prevention and control programs have reduced the number of cervical cancer cases and deaths through cervical cytology screening, which can detect precancerous lesions. The quadrivalent HPV vaccine will not eliminate the need for cervical cancer screening in the United States because not all HPV types that cause cervical cancer are included in the vaccine.

* The en dash in numeric ranges is used to represent inclusive years, hours, days, ages, dosages, or a sequence of numbered items.

TABLE 1. Cancers associated with human papillomavirus (HPV) and percentage attributable to oncogenic HPV — United States, 2003

Cancer	Cases*	% Attributable to oncogenic HPV†
Cervix§	11,820	100
Anus¶	4,187	90
Vulva¶	3,507	40
Vagina¶	1,070	40
Penis¶	1,059	40
Oral cavity and pharynx¶	29,627	≤12

* **Source:** U.S. Cancer Statistics Working Group. United States cancer statistics: 2003. Incidence and motality. Atlanta, GA: US Department of Health and Human Services, CDC, and the National Cancer Institute; 2006. Available at http://www.cdc.gov/uscs.

† **Source:** Parkin M. The global health burden of infection-associated cancers in the year 2002. Int J Cancer 2006;118:3030–44.

§ A total of 70% attributed are HPV types 16 or 18.

¶ Majority of these cancers attributable to HPV type 16.

Methods

The Advisory Committee on Immunization Practices (ACIP) HPV vaccine workgroup first met in February 2004 to begin reviewing data related to the quadrivalent HPV vaccine. The workgroup held monthly teleconferences and meetings three times a year to review published and unpublished data from the HPV vaccine clinical trials, including data on safety, immunogenicity, and efficacy. Data on epidemiology and natural history of HPV, vaccine acceptability, and sexual behavior in the United States also were reviewed. Several economic and cost effectiveness analyses were considered. Presentations on these topics were made to ACIP during meetings in June 2005, October 2005, and February 2006. Recommendation options were developed and discussed by the ACIP HPV vaccine workgroup. When evidence was lacking, the recommendations incorporated expert opinion of the workgroup members. Options being considered by the workgroup were presented to ACIP in February 2006. The final recommendations were presented to ACIP at the June 2006 ACIP meeting. After discussions, minor modifications were made and the recommendations were approved at the June 2006 meeting. Modifications were made to the ACIP statement during the subsequent review process at CDC to update and clarify wording in the document.

The quadrivalent HPV vaccine is a new vaccine; additional data will be available in the near future from clinical trials. These data and any new information on epidemiology of HPV will be reviewed by ACIP as they become available, and recommendations will be updated as needed.

Background

Biology of HPV

HPVs are nonenveloped, double-stranded DNA viruses in the family *Papillomaviridae.* Isolates of HPV are classified as "types," and numbers are assigned in order of their discovery (*16*). Types are designated on the basis of the nucleotide sequence of specific regions of the genome. All HPVs have an 8 kb circular genome enclosed in a capsid shell composed of the major and minor capsid proteins L1 and L2, respectively. Purified L1 protein will self-assemble to form empty shells that resemble a virus, called virus-like particles (VLPs). In addition to the structural genes (L1 and L2), the genome encodes several early genes (E1, E2, E4, E5, E6, and E7) that enable viral transcription and replication and interact with the host genome. Immortalization and transformation functions are associated with the E6 and E7 genes of high-risk HPV. E6 and E7 proteins from high-risk types are the pri-

mary oncoproteins; they manipulate cell cycle regulators, induce chromosomal abnormalities, and block apoptosis (*17*).

Papillomaviruses initiate infection in the basal layer of the epithelium, and viral genome amplification occurs in differentiating cells using the cellular replication machinery. After infection, differentiating epithelial cells that are normally nondividing remain in an active cell cycle. This can result in a thickened, sometimes exophytic, epithelial lesion. The virus is released as cells exfoliate from the epithelium. With neoplastic progression, the virus might integrate into the host chromosomes, and little virion production will occur.

Immunology of HPV

HPV infections are largely shielded from the host immune response because they are restricted to the epithelium (*18*). Humoral and cellular immune responses have been documented, but correlates of immunity have not been established. Serum antibodies against many different viral products have been demonstrated. The best characterized and most type-specific antibodies are those directed against conformational epitopes of the L1 capsid protein assembled as VLPs. Not all infected persons have antibodies; in one study, 54%–69% of women with incident HPV 16, 6, or 18 infections had antibodies (*19*). Among newly infected women, the median time to seroconversion is approximately 8 months (*20,21*).

Laboratory Testing for HPV

HPV cannot be cultured. Detecting HPV requires identification of HPV genetic information (DNA in the majority of assay formats). Assays differ considerably in their sensitivity and type specificity. The anatomic region sampled and the method of specimen collection will impact detection.

Only the Digene Hybrid Capture® 2 (HC2) High-Risk HPV DNA Test is approved by the U.S. Food and Drug Administration (FDA) for clinical use. The HC2 High Risk test uses liquid nucleic acid hybridization and detects 13 high-risk types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68). Results are reported as positive or negative and are not type-specific. The HC2 High Risk test is approved for triage of women with equivocal Papanicolaou (Pap) test results (atypical squamous cells of undetermined significance [ASC-US]) and in combination with the Pap test for cervical cancer screening in women aged >30 years. The test is not clinically indicated nor approved for use in men.

Epidemiology and basic research studies of HPV typically use nucleic acid amplification methods that generate type-specific and, in certain formats, quantitative results. Polymerase chain reaction (PCR) assays used most commonly in epidemiologic studies target genetically conserved regions of the L1 gene. These consensus assays are designed to amplify HPV, and types are then determined by type specific hybridization, restriction enzyme digestion, or sequencing. In the trials of quadrivalent HPV vaccine, multiplex assays were used that specifically detect the L1, E6, and E7 gene for each HPV type.

The most frequently used HPV serologic assays are VLP-based enzyme immunoassays, designed to detect antibodies to the L1 viral protein. The type-specificity of the assay depends on preparation of conformationally intact VLPs in recombinant baculovirus or other eukaryotic expression systems (*22*). Serologic assays are available only in research settings. Key laboratory reagents are not standardized, and no gold standards exist for setting a threshold for a positive result (*23*). In trials of the quadrivalent HPV vaccine, a competitive radioimmunoassay or a quadriplex competitive immunoassay was used, both of which measure neutralizing antibodies in serum (*24,25*).

Epidemiology of HPV Infection

Transmission and Risk Factors

Genital HPV infection is primarily transmitted by genital contact, usually through sexual intercourse (*2,26*). In virtually all studies of HPV prevalence and incidence, the most consistent predictors of infection have been measures of sexual activity, most importantly the number of sex partners (lifetime and recent) (*27–34*). For example, one study indicated that 14.3% of women aged 18–25 years with one lifetime sex partner, 22.3% with two lifetime sex partners, and 31.5% with more than three lifetime partners (*33*) had HPV infection. Transmission of HPV through other types of genital contact in the absence of penetrative intercourse (i.e., oral-genital, manual-genital, and genital-genital contact) has been described, but is less common than through sexual intercourse (*26,35,36*). Additional risk factors primarily identified for females include partner sexual behavior (*26*) and immune status (*37,38*). Genital HPV infection also can be transmitted by nonsexual routes, but this is uncommon. Nonsexual routes of genital HPV transmission include transmission from a mother to a newborn baby (*39,40*).

Because HPV is transmitted by sexual activity, understanding the epidemiology of HPV requires data on sexual behavior. The 2002 National Survey of Family Growth (http://www.cdc.gov/nchs/nsfg) indicated that 24% of females in the United States were sexually active by age 15 years (*41*). This percentage increased to 40% by age 16 years and to 70% by age 18 years. Among sexually active females aged 15–19 years and 20–24 years, the median number of lifetime male sex partners was 1.4 and 2.8, respectively (*42*). The 2005 Youth Behavioral Risk Survey (http://www.cdc.gov/mmwr/preview/

mmwrhtml/SS5505a1.htm) indicated that that 3.7% of female students had been sexually active before age 13 years (*43*). Of those sexually active, 5.7% of 9th-grade females and 20.2% of 12th-grade females had had four or more sex partners.

Natural History of HPV Infection

The majority of HPV infections are transient and asymptomatic and cause no clinical problems; 70% of new HPV infections clear within 1 year, and approximately 90% clear within 2 years (*27,44–46*). The median duration of new infections is 8 months (*27,45*). Persistent infection with high-risk types of HPV is the most important risk factor for cervical cancer precursors and invasive cervical cancer (*45,47–50*). The risk for persistence and progression to precancerous lesions varies by HPV type, with HPV 16 being more oncogenic than other high-risk HPV types (*51,52*). Factors associated with cervical cancer in epidemiologic studies include cigarette smoking, increased parity, increased age, other sexually transmitted infections, immune suppression, long-term oral contraceptive use, and other host factors (*53–55*). The time between initial HPV infection and development of cervical cancer is usually decades. Many aspects of the natural history of HPV are poorly understood, including the role and duration of naturally acquired immunity after HPV infection.

HPV Prevalence and Incidence in the United States

Overall in the United States, an estimated 6.2 million new HPV infections occur every year among persons aged 14–44 years (*1*). Of these, 74% occur among those aged 15–24 years. Modeling estimates suggest that >80% of sexually active women will have acquired genital HPV by age 50 years (*56*).

Routine reporting of HPV does not exist in the United States. Information on prevalence and incidence has been obtained primarily from clinic-based populations, such as family planning and sexually transmitted disease or university health clinic patients. These evaluations have documented prevalence of HPV DNA ranging from 14% to 90% (*57*). Prevalence was highest among sexually active females aged <25 years and decreased with increasing age (*31,32,58,59*). Data from a multisite, clinic-based study of sexually active women in the United States indicated that prevalence was highest among those aged 14–19 years (*60*).

Two studies have reported prevalence in representative, population-based samples. In a study of sexually active women aged 18–25 years, prevalence of any HPV was 26.9% (*33*). Prevalence of types 6 or 11 was 2.2%, and prevalence of types 16 or 18 was 7.8%. In a study of females aged 14–59 years during 2003–2004, the prevalence of any HPV was 26.8% (*61*). Prevalence was highest among women aged 20–24 years (44.8%). Overall, prevalence of types 6, 11, 16, and 18 was 1.3%, 0.1%, 1.5%, and 0.8%, respectively.

Few data exist on cumulative risk for HPV infection. Detection of HPV DNA indicates infection and does not provide information on women who were infected but cleared the HPV. Seroprevalence data can provide a better estimate of cumulative risk but will also be an underestimate, because not all persons with natural HPV infection have detectable antibodies. In a representative sample of women aged 20–29 years in the United States, HPV 16 seroprevalence was 25% (*62*). Because as few as 60% of those infected with HPV have detectable antibodies, the seroprevalence is an underestimate, and true exposure to HPV 16 could be as high as 41% among women in that age group. Data also are available from the quadrivalent HPV vaccine phase III trials, in which both HPV PCR assays on cervical specimens and serologic tests were performed at enrollment. Participation was restricted to sexually active women who had no more than four lifetime partners or were planning sexual debut. Among 5,996 North American females aged 16–24 years, 92% were sexually active, and the median number of lifetime sex partners was two; 24% had evidence of previous or current infection with HPV 6,11,16, or 18 on the basis of serology and/or PCR at the time of enrollment; four (0.1%) had evidence of infection with all four vaccine types (Merck and Co., unpublished data, 2006).

Studies of incident HPV infection that have evaluated HPV DNA detection over time demonstrate that acquisition occurs soon after sexual debut. In a prospective study of college women in the United States, the cumulative probability of incident infection was 38.9% by 24 months after first sexual intercourse. Of all HPV types, HPV 16 acquisition was highest (10.4%); 5.6% had acquired HPV 18 (*26*).

HPV infection also is common among men (*63–67*). Among heterosexual men in clinic-based studies, prevalence of genital HPV infection often is >20% and is highly dependent on the anatomic sites sampled and method of specimen collection (*64,66,67*).

Clinical Sequelae of HPV Infection

Clinical sequelae of HPV infection include cervical cancer and cervical cancer precursors, other anogenital cancers and their precursor lesions, anogenital warts, and recurrent respiratory papillomatosis.

Cervical Cancer and Precursor Lesions

HPV is a necessary but not sufficient cause of all cervical cancers. Approximately three fourths of all cervical cancers in the United States are squamous cell; the remaining are adenocarcinomas. HPV 16 and 18 account for approximately 68% of squamous cell cancers and 83% of adenocarcinomas (*7*).

Although HPV infection usually is asymptomatic, cervical infection can result in histologic changes that are classified as cervical intraepithelial neoplasias (CIN) grades 1, 2, or 3 on the basis of increasing degree of abnormality in the cervical epithelium or adenocarcinoma in situ (AIS). Spontaneous clearance or progression to cancer in the absence of treatment varies for CIN 1 and CIN 2, and CIN 3. CIN 1 usually clears spontaneously (60% of cases) and rarely progresses to cancer (1%); a lower percentage of CIN 2 and 3 spontaneously clears (30%–40%), and a higher percentage progresses to cancer if not treated (>12%) (*68*). Cervical cancer screening with the Pap test can detect cytologic changes that reflect the underlying tissue changes. However, cytologic abnormalities detected by the Pap test can be ambiguous or equivocal. Abnormalities include ASC-US, atypical glandular cells, low- and high-grade squamous intraepithelial lesions (LSIL and HSIL), and AIS. HPV types 16 and 18 are more commonly found in association with higher-grade lesions. In one study, the prevalence of HPV 16 was 13.3% among ASC-US, 23.6% among LSIL, and 60.7% among HSIL Pap tests (*69*).

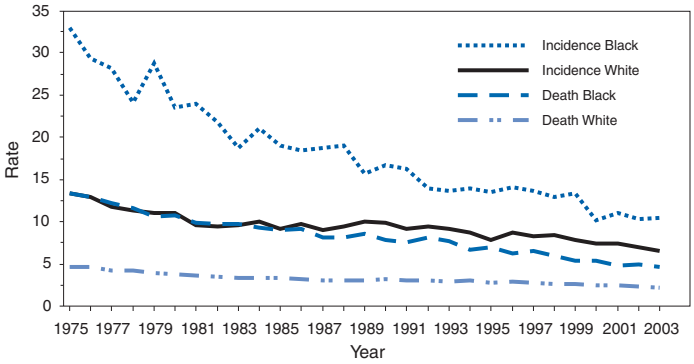
No routine reporting or registry exists for abnormal Pap tests or cervical cancer precursor lesions in the United States; however, data are available from managed-care organizations and administrative data sets (*70,71*). Each year, approximately 50 million women undergo Pap testing; approximately 3.5–5.0 million of these Pap tests will require some follow-up, including 2–3 million ASC-US, 1.25 million LSIL, and 300,000 HSIL Pap tests (*72–74*).

In the United States, cases of cervical cancer are routinely reported to cancer registries such as the National Cancer Institute Surveillance, Epidemiology, and End Results program, and CDC-administered National Program of Cancer Registries that cover approximately 96% of the U.S. population in 2003. Cervical cancer incidence rates have decreased approximately 75% and death rates approximately 70% since the 1950s, largely because of the introduction of Pap testing (*74,75*). However, the decrease in incidence is observed primarily in squamous cell carcinomas; the incidence of adenocarcinomas has not changed appreciably (*76*). Adenocarcinomas are more difficult to detect because they are found in the endocervix; they account for approximately 20% of cervical cancer cases in the United States (*77,78*). In 2003, cervical cancer incidence in the United States was 8.1 per 100,000 women, with approximately 11,820 new cases reported (*79*). The median age of diagnosis for cervical cancer was 47 years.

Substantial differences exist in the cervical cancer incidence and mortality by racial/ethnic group in the United States (*78*). The incidence for black women was approximately 1.5 times higher than that for white women (Figure 1). Incidence for Hispanic women also was higher than that for white women (*78*). Death rates for black women were twice that for white women. Although incidence for Asian women overall is similar to that for white women (*78*), certain Asian subgroups, especially Vietnamese and Korean women, have higher rates of cervical cancer (*80*).

Geographic differences exist in incidence and mortality, with notably higher incidence and mortality in Southern states (Figures 2 and 3) and Appalachia (*78,81*). Mortality rates are

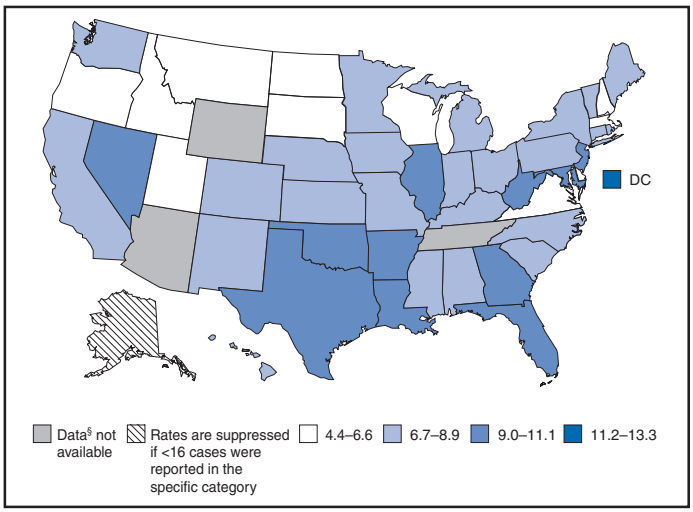
FIGURE 1. Cervical cancer (invasive) SEER incidence* and death rates, by race and year — United States, 1975–2003



Source: National Cancer Institute. SEER Cancer Statistics Review, 1975–2003. Bethesda, MD: National Cancer Institute; 2004.

* Per 100,000 persons and age-adjusted to the 2000 U.S. standard population.

FIGURE 2. Cervical cancer* incidence† — United States, 2003



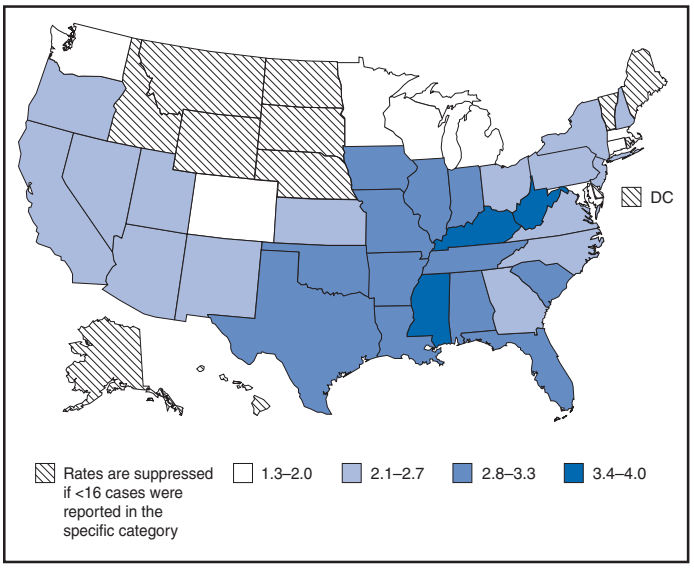
Source: U.S. Cancer Statistics Working Group. United States cancer statistics: 2003 Incidence and mortality. Atlanta, GA: US Department of Health and Human Services, CDC, and National Cancer Institute; 2006. Available at http://www.cdc.gov/uscs.

* Invasive cancers only.

† Per 100,000 persons and age-adjusted to the 2000 U.S. standard population (19 age groups — Census P25-1130).

§ Data are from selected statewide and metropolitan area cancer registries that meet the data quality criteria for all invasive cancer sites combined. Incidence covers approximately 96% of the U.S. population.

FIGURE 3. Cervical cancer death rates* — United States, 2003†



Source: U.S. Cancer Statistics Working Group. United States cancer statistics: 2003 incidence and mortality. Atlanta, GA: US Department of Health and Human Services, CDC, and National Cancer Institute; 2006. Available at http://www.cdc.gov/uscs.

* Per 100,000 persons and age-adjusted to the 2000 U.S. standard population (19 age groups — Census P25-1130).

† Data are from the National Vital Statistics System (NVSS).

higher among specific groups, including Hispanic women living on the Texas-Mexico border; white women in Appalachia, rural New York State, and the northern part of the northeast United States; and among American Indians in the Northern Plains and Alaska Native women (*82*).

Vaginal and Vulvar Cancer and Precursor Lesions

HPV is associated with vaginal and vulvar cancer and vaginal and vulvar intraepithelial neoplasias; however, unlike cervical cancer, not all vaginal and vulvar cancers are associated with HPV. The natural history of vaginal and vulvar neoplasia is incompletely understood (*83,84*). No routine screening exists for vaginal or vulvar cancer in the United States.

The majority of vaginal cancers and vaginal intraepithelial neoplasias III (VaIN III) are positive for HPV (*85*); HPV 16 is the most common type (*86,87*). Approximately one third of women with VaIN or vaginal cancer had been treated previously for an anogenital cancer, usually cervical cancer (*86*). Vaginal cancer is rare, and incidence has decreased by 20% during the preceding two decades. In the United States in 2003, a total of 1,070 cases of invasive vaginal cancer (age-adjusted incidence rate: 0.7 per 100,000 females) and 391 deaths (death rate: 0.2 per 100,000 females) occurred (*79*). The median age for diagnosis of vaginal cancer was 69 years.

HPV is associated with approximately half of vulvar squamous cell cancers, the most common type of vulvar cancer. HPV-associated vulvar cancer tends to occur in younger women and might be preceded by vulvar intraepithelial neoplasia (VIN). In a recent study, HPV types 16 or 18 were detected in 76% of the VIN 2/3 and 42% of vulvar carcinoma samples (*87*). In 2003, a total of 3,507 cases of vulvar cancer (age-adjusted incidence rate: 2.2 per 100,000) and 775 deaths (death rate: 0.4 per 100,000 females) occurred in the United States (*79*). During 1973–2000, the incidence of in situ vulvar cancer increased by 400%, and the rate of invasive vulvar cancer increased by 20%. Changes in detection or reporting of in situ cancers might be responsible for the increased rate of in situ cancers (*88*).

Anal Cancer

HPV is associated with approximately 90% of anal squamous cell cancers. Anal intraepithelial neoplasia (AIN) is recognized as a precursor of anal cancer, although the natural history of these lesions (i.e., rate of progression and regression) is less clear than for CIN (*50*). Anal cancer is more common in women (2,516 new cases in 2003 [rate: 1.6 per 100,000 women]) than in men (1,671 new cases [rate: 1.3 per 100,000 men]) (*79*). During the preceding three decades, the incidence of anal cancer in the United States has increased, especially among men (*89*). Women at high risk for anal cancer include those with high-grade cervical lesions and cervical and vulvar cancers. Men who have sex with men and persons who have human immunodeficiency virus (HIV) infection also are at high risk for anal cancer (*90*). No national recommendations exist for cytologic screening to prevent anal cancers.

Genital Warts

All anogenital warts (condyloma) are caused by HPV, and approximately 90% are associated with HPV types 6 and 11 (*91*). The average time to development of new anogenital warts after infection with HPV types 6 or 11 is approximately 2–3 months (*92*). However, not all persons infected with HPV types 6 or 11 acquire genital warts. Anogenital warts can be treated, although many warts (20%–30%) regress spontaneously. Recurrence of anogenital warts is common (approximately 30%), whether clearance occurs spontaneously or following treatment (*93*). Anogenital warts are not routinely reported in the United States. The prevalence of genital warts has been examined using health-care claims data (*94*). An estimated 1% of sexually active adolescents and adults in the United States have clinically apparent genital warts (*29*).

Recurrent Respiratory Papillomatosis

Infection with low-risk HPV types, primarily types 6 or 11, rarely results in recurrent respiratory papillomatosis (RRP), a disease that is characterized by recurrent warts or papillo-

mas in the upper respiratory tract, particularly the larynx. On the basis of age of onset, RRP is divided into juvenile onset (JORRP) and adult onset forms. JORRP, generally defined as onset before age 18 years, is better characterized than the adult form. JORRP is believed to result from vertical transmission of HPV from mother to baby during delivery, although the median age of diagnosis is 4 years. A multicenter registry of JORRP in the United States that collected data during 1999–2003 (*95*) demonstrated that although the clinical course of JORRP was variable, it is associated with extensive morbidity, requiring a median of 13 lifetime surgeries to remove warts and maintain an open airway. Estimates of the incidence of JORRP are relatively imprecise but range from 0.12 to 2.1 cases per 100,000 children aged <18 years in two cities in the United States (*96*). The prevalence, incidence, and disease course of the adult form of RRP are less clear.

Treatment of HPV Infection

HPV infections are not treated; treatment is directed at the HPV-associated lesions. Treatment options for genital warts and cervical, vaginal, and vulvar cancer precursors include various local approaches that remove the lesion (e.g., cryotherapy, electrocautery, laser therapy, and surgical excision). Genital warts also are treated with topical pharmacologic agents (*97*). On the basis of limited existing data, available therapies for HPV-related lesions might reduce but probably do not eliminate infectiousness.

Prevention

HPV Infection

Condom use might reduce the risk for HPV and HPV-associated diseases (e.g., genital warts and cervical cancer). A limited number of prospective studies have demonstrated a protective effect of condoms on acquisition of genital HPV. A study among newly sexually active college women demonstrated a 70% reduction in HPV infection when their partners used condoms consistently and correctly (*98*). Abstaining from sexual activity (i.e., refraining from any genital contact with another persons) is the surest way to prevent genital HPV infection. For those who choose to be sexually active, a monogamous relationship with an uninfected partner is the strategy most likely to prevent future genital HPV infections.

Neither routine surveillance for HPV infection nor partner notification is useful for HPV prevention (*97*). Genital HPV infection is so prevalent that the majority of partners of persons found to have HPV infection are infected already; no prevention or treatment strategies have been recommended for partners.

Cervical Cancer Screening

The majority of cervical cancer cases and deaths can be prevented through detection of pre-cancerous changes in the cervix by cytology using the Pap test. Pap test screening includes a conventional Pap or a liquid-based cytology (*99*). CDC does not issue recommendations for cervical cancer screening, but certain professional groups have published recommendations (Table 2).

TABLE 2. Cervical cancer screening guidelines — United States

Guidelines	American Cancer Society*	U.S. Preventive Services Task Force†	American College of Obstetricians and Gynecologists§
When to start	Approximately 3 years after onset of vaginal intercourse, but no later than age 21 years	Within 3 years of onset of sexual activity or age 21 years, whichever comes first	Approximately 3 years after onset of sexual intercourse, but no later than age 21 years
Intervals			
Conventional Pap test	Annually; every 2–3 years for women aged ≥30 years with three negative cytology tests¶	At least every 3 years	Annually; every 2–3 years for women aged ≥30 years with three negative cytology tests¶
If liquid-based cytology used	Every 2 years; every 2–3 years for women aged ≥30 years with three negative cytology tests¶	Insufficient evidence	Annually; every 2–3 years for women aged ≥30 years with three negative cytology tests¶
If human papillomavirus (HPV) testing used as an adjunct to cytology	Every 3 years if HPV negative, cytology negative	Insufficient evidence	Every 3 years if HPV negative, cytology negative

* **Source:** Saslow D, Runowicz CD, Solomon D, et al. American Cancer Society guideline for the early detection of cervical neoplasia and cancer. CA Cancer J Clin 2002;52:342–62.
† **Source:** U.S.Preventive Services Task Force. Screening for cervical cancer: recommendations and rationale. Available at http://www.ahrq.gov.
§ **Source:** ACOG Practice Bulletin. Clinical management guidelines for obstetrician-gynecologists: cervical cytology screening. Obstet Gynecol 2003;102:417–27.
¶ Certain exemptions apply (e.g., women who are immunocompromised, infected with human immunodeficiency virus, or have history of prenatal exposure to diethylstilbesterol in utero). See guidelines for details.

The American College of Obstetricians and Gynecologists (ACOG), the American Cancer Society (ACS), and the U.S. Preventive Services Task Force (USPSTF) guidelines state that all women should have a Pap test for cervical cancer screening within 3 years of beginning sexual activity or by age 21 years, whichever occurs first (Table 2) (*74,100,101*). USPSTF recommends a conventional Pap test at least every 3 years, regardless of age. ACOG recommends annual screening of women aged <30 years; ACS recommends annual or biennial screening in this age group, depending on use of conventional or liquid-based cytology. According to these national organizations, women aged ≥30 years with three normal consecutive Pap tests should be screened every 2–3 years.

ACS and ACOG also recommend use of the HC2 High Risk test as an adjunct to regular Pap screening of women aged ≥30 years. If both tests are negative, women should be rescreened no more frequently than every 3 years. In addition, ACOG and the American Society of Colposcopy and Cervical Pathology (ASCCP) recommend that HPV DNA testing be used to triage women with equivocal, ASC-US Pap test results (*102*). USPSTF concluded that evidence is insufficient to recommend for or against routine use of HPV tests (*100*).

An estimated 82% of women in the United States have had a Pap test during the preceding 3 years (*103*). Pap test rates for all age and ethnic populations have increased during the preceding two decades. However, certain groups continue to have lower screening rates. These include women with less than a high school education (77%); foreign-born women, especially women who have been in the United States for <10 years (61%); women without health insurance (62%); and certain racial/ethnic populations such as Hispanics (77%) and Asians (71%). Approximately half of women who had cervical cancer diagnosed in the United States had not had a Pap test in the 3 years before diagnosis (*104*).

Quadrivalent Human Papillomavirus Vaccine

Composition

The licensed vaccine is a quadrivalent HPV vaccine (GARDASIL™, produced by Merck and Co, Inc.). The L1 major capsid protein of HPV is the antigen used for HPV vaccination (*105*). Using recombinant DNA technology, the L1 protein is expressed in *Saccharomyces cerevisiae* (yeast), and the proteins self-assemble into conformationally intact, noninfectious VLPs. Each 0.5-mL dose contains 20 μg HPV 6 L1 protein, 40 μg HPV 11 L1 protein, 40 μg HPV 16 L1 protein, and 20 μg HPV 18 L1 protein. VLPs are adsorbed on an aluminum-containing adjuvant. Each 0.5-mL dose contains 225 μg amorphous aluminum hydroxyphosphate sulfate. The formulation also includes sodium chloride, L-histidine, polysorbate 80, sodium borate, and water for injection. The quadrivalent HPV vaccine contains no thimerosal or antibiotics.

The vaccine should be stored at 2°C–8°C (36°F–46°F) and not frozen.

Dose and Administration

Quadrivalent HPV vaccine is administered intramuscularly as three separate 0.5-mL doses. The second dose should be administered 2 months after the first dose and the third dose 6 months after the first dose. The vaccine is available as a sterile suspension for injection in a single-dose vial or a prefilled syringe.

Efficacy

One clinical study evaluated efficacy of monovalent HPV 16 vaccine, and three studies evaluated efficacy of quadrivalent HPV vaccine: a phase II study of a monovalent HPV 16 vaccine (protocol 005) (*106,107*), a phase II study of quadrivalent HPV vaccine (protocol 007) (*108–110*), both among females aged 16–23 years, and two phase III studies of quadrivalent HPV vaccine (protocols 013 and 015) among females aged 16–23 and 16–26 years, respectively. All were randomized, double-blind, placebo-controlled studies.

The studies used prespecified endpoints to evaluate the impact of the quadrivalent vaccine in preventing HPV-related infection and disease. Phase II studies were primarily proof-of-concept studies that evaluated the efficacy of vaccine using a persistent infection endpoint. Phase III studies evaluated the efficacy of vaccine on clinical lesions. Predefined combinations of phase II and III studies were used to improve the precision of the efficacy findings. Various endpoints were assessed in the different studies, including vaccine type-related persistent HPV infection, CIN, VIN and VaIN, and genital warts. The primary endpoint and the basis for licensure was the combined incidence of HPV 16- and 18-related CIN 2/3 or AIS. These endpoints served as surrogate markers for cervical cancer. Studies using an invasive cervical cancer endpoint were not feasible because the standard of care is to screen for and treat CIN 2/3 and AIS lesions to prevent invasive cervical cancer. Furthermore, the time from acquisition of infection to the development of cancer can exceed 20 years. The two phase III efficacy studies of quadrivalent HPV vaccine (protocols 013 and 015) were international studies, which included persons from North America, South America, Europe, Australia, and Asia. Data on efficacy against CIN end-

points also are available from the phase II study (protocol 007) (*108,110*) and of monovalent HPV-16 vaccine (protocol 005) (*107*).

The quadrivalent HPV vaccine has a high efficacy for prevention of vaccine HPV type HPV 6-, 11-, 16-, and 18-related persistent infection, vaccine type-related CIN, CIN 2/3, and external genital lesions (genital warts, VIN and VaIN) when analyses were restricted to participants who received all 3 doses of vaccine, had no protocol violations, and no evidence of infection with the relevant vaccine HPV type (seronegative and HPV PCR-negative through 1 month after dose 3) (Tables 3 and 4) (*111*). No evidence exists of protection against disease caused by vaccine types for which participants were PCR positive at baseline. Participants infected with

TABLE 3. Summary of quadrivalent human papillomavirus (HPV) vaccine efficacy studies in the per protocol populations*

	Quadrivalent vaccine		Placebo			
Outcome and protocol	**No.†**	**Cases**	**No.**	**Cases**	**% Efficacy**	**(95% CI§)**
HPV 16- or 18- related CIN 2/3 or AIS¶						
Protocol 005**	755	0	750	12	100.0	(65.1–100.0)
Protocol 007	231	0	230	1	100.0	(-3734.9–100.0)
Protocol 013	2,200	0	2,222	19	100.0	(78.5–100.0)
Protocol 015	5,301	0	5,258	21	100.0††	(80.9–100.0)
Combined protocols§§	8,487	0	8,460	53	100.0††	(92.9–100.0)
HPV 6-, 11-, 16-, 18- related CIN (CIN 1, CIN 2/3) or AIS						
Protocol 007	235	0	233	3	100.0	(-137.8–100.0)
Protocol 013	2,240	0	2,258	37	100.0††	(89.5–100.0)
Protocol 015	5,383	4	5,370	43	90.7	(74.4–97.6)
Combined protocols§§	7,858	4	7,861	83	95.2	(87.2–98.7)
HPV 6-, 11-, 16-, 18- related genital warts						
Protocol 007	235	0	233	3	100.0	(-139.5–100.0)
Protocol 013	2,261	0	2,279	29	100.0	(86.4–100.0)
Protocol 015	5,401	1	5,387	59	98.3	(90.2–100.0)
Combined protocols§§	**7,897**	**1**	**7,899**	**91**	**98.9**	**(93.7–100.0)**

Source: Adapted from Food and Drug Administration. Product approval information—licensing action, package insert: GARDASIL (quadrivalent human papillomavirus types 6, 11, 16, and 18), Merck & Co. Whitehouse Station, NJ: Food and Drug Administration; 2006. Available at http://www.fda.gov/cber/label/HPVmer060806LB.pdf.

* Populations consisted of persons who received all three vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, and were naïve (polymerase chain reaction–negative and seronegative) to the relevant HPV type(s) (types 6, 11, 16, and 18) before dose 1 and through 1 month post dose 3 (month 7). Median follow-up time for protocols 007, 013, and 015 was 1.9 years; median follow-up time for protocol 005 was 3.9 years.

† Number of persons with at least one follow-up visit after month 7.

§ Confidence interval.

¶ CIN: cervical intraepithelial neoplasis; AIS: adenocarcinoma in situ.

** Evaluated only the HPV 16 L1 VLP vaccine component of GARDASIL.

†† P-values were computed for pre-specified primary hypothesis tests. All p-values were <0.001, supporting the following conclusions: efficacy against HPV 16/18-related CIN 2/3 is >0 (protocol 015); efficacy against HPV 16/18-related CIN 2/3 is >25% (combined protocols); and efficacy against HPV 6/11/16/18-related CIN is >20% (protocol 013).

§§ Analyses of the combined trials were prospectively planned and included the use of similar study entry criteria.

Note: Point estimates and confidence intervals are adjusted for person-time of follow-up.

TABLE 4. Efficacy of quadrivalent human papillomavirus (HPV) vaccine against HPV 16- or 18-related condyloma, VIN 1 or VaIN 1* and VIN 2/3 or VaIN 2/3 in the per protocol populations† (protocols 007, 013, and 015)

	Vaccine		Placebo		Efficacy	
Endpoint	**No.§**	**Cases**	**No.**	**Cases**	**%**	**(95% CI¶)**
Condyloma, VIN 1 or VaIN 1	7,769	0	7,741	24	100.0	(83.4–100.0)
VIN 2/3 or VaIN 2/3	7,769	0	7,741	10	100.0	(55.5–100.0)

Source: Food and Drug Administration. Vaccines and Related Biological Products Advisory Committee, May 18, 2006: FDA GARDASIL briefing information. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration; 2006. Available at http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4222s-index.htm.

* VIN: vulvar intraepithelial neoplasia; VaIN: vaginal intraepithelial neoplasia.

† Includes all persons who were not general protocol violators, received all three vaccinations within acceptable day ranges, and were seronegative at day 1 and polymerase chain reaction–negative day 1 through month 7 for the relevant HPV type.

§ Number of persons with at least one follow-up visit after month 7.

¶ Confidence interval.

one or more vaccine HPV types before vaccination were protected against disease caused by the other vaccine HPV types. No evidence exists that the vaccine protects against disease caused by nonvaccine HPV types.

Persistent HPV Infection

Two phase II studies evaluated persistent infection, defined as a vaccine HPV type detected by PCR at two or more consecutive visits 4 months apart or at a single visit if it was the last visit of record. In the phase II quadrivalent vaccine study (protocol 007), 276 women received the 20/40/40/20 μg dose formulation of vaccine, and 275 received a placebo. The efficacy for prevention of persistent HPV 6, 11, 16, or 18 infection or disease at the end of study (approximately 2.5 years after dose 3) was 89.5% (95% confidence interval [CI] = 70.7%–97.3%). Of the vaccinated persons with persistent infection endpoints, three had HPV 16 detected at the last visit (without observed persistence), and one had persistent infection with HPV 18 (detected at both 12 and 18 months) but not at months 24, 30, or 36 (*108*). In the phase II study of a monovalent HPV 16 vaccine (protocol 005), the efficacy against persistent HPV 16 infection was 100% at a midpoint analysis (*106*) and 94.3% (CI = 87.8%–97.7%) at the end of the study (*107*). All seven cases in the vaccine group had HPV 16 DNA detected on the person's last study visit (without observed persistence).

Cervical Disease

Two phase III trials evaluated efficacy against cervical disease. Protocol 015 included 12,157 women aged 16–26 years. Participants had a Pap test, cervicovaginal sampling for HPV DNA testing, and detailed genital inspection at day 1 and months 7, 12, 24, 36, and 48, and were referred to colposcopy using a protocol specified algorithm based on Pap test results. The primary study endpoint was incidence of HPV 16- or 18-related CIN 2, CIN 3, AIS, or cervical cancer. In a per protocol analysis, the vaccine efficacy was 100% (CI = 80.9%–100%) for prevention of HPV 16 or 18 related CIN 2/3 or AIS (Table 3).

Protocol 013 included 5,442 females aged 16–23 years. Participants had a Pap test at day 1 and at months 7, 12, 18, 24, 30, 36, and 48 and were referred to colposcopy according to protocol. In addition, participants had detailed genital inspection, with biopsy of abnormalities and cervicovaginal sampling for HPV DNA sampling. The study had two primary efficacy endpoints: 1) external genital lesions related to HPV 6, 11, 16, or 18, including genital warts, VIN, VaIN, vulvar cancer, or vaginal cancer; and 2) cervical endpoints related to HPV 6, 11, 16, or 18, including CIN, AIS, or cervical cancer. In a per protocol analysis, the vaccine efficacy was 100% (CI = 89.5%–100%) for prevention of any grade CIN related to vaccine types (Table 3).

In a planned combined efficacy analysis, including data from four clinical studies (protocol 005, 007, 013, and 015), protection against HPV 16- or 18-related CIN 2/3 or AIS was 100% (CI = 92.9%–100%) (*111*). In a planned combined analysis, including data from three studies (protocol 007, 013, and 015), protection against any CIN attributed to HPV 6, 11, 16, or 18, the efficacy was 95.2% (CI = 87.2%–98.7%). Four cases of CIN occurred in the vaccine group; all were CIN 1.

External Genital Lesions

Data from three studies (protocol 007, 013, and 015) provide data on efficacy against external genital lesions. In a combined analysis, the efficacy of quadrivalent HPV vaccine against HPV 6-, 11-, 16-, or 18-related external genital warts was 98.9% (CI = 93.7%–100%) in a per protocol analysis (Table 3). Efficacy against HPV 16- or 18-related VIN 2/3 or VaIN 2/3 was 100% (CI = 55.5–100.0) (Table 4).

Efficacy in Females with Current or Previous Vaccine HPV-Type Infection

Because participants were enrolled into the clinical trials even if they were HPV DNA or antibody positive, evaluating efficacy in females infected with a vaccine HPV type at the time of vaccination was possible. Overall, 27% of the study population had evidence of previous exposure to or infection with a vaccine HPV type. Among these participants, 74% were positive to only one vaccine HPV type and did not have evidence of infection with the other three types. Among participants positive to one or more vaccine HPV types, the vaccine had high efficacy for prevention of disease caused by the remaining vaccine HPV types (*112*).

The vaccine's impact on the course of infection present at the time of infection was evaluated using data from four clinical studies (protocols 005, 007, 013, and 015). Three different groups were analyzed on the basis of antibody and HPV DNA detection at the time of vaccination (Table 5). Among persons seropositive to the relevant HPV type but HPV DNA negative, efficacy against CIN 2/3 or AIS caused by that type was 100% (CI = -63.6%–100%). Among women who were HPV DNA positive but seronegative, efficacy was 31.2% (CI = -4.5–54.9). Among women who were both seropostive and HPV DNA positive, efficacy against CIN 2/3 caused by that type was -25.8% (CI = -76.4%–10.1%). Because of the small numbers and wide confidence intervals around efficacy estimates, limited conclusions can be drawn from these estimates.

Efficacy in the Intent-to-Treat Population

Analyses among all women who received at least 1 dose of vaccine and had any follow-up 1 month after the first dose, regardless of initial PCR or serology, provide information on

TABLE 5. Efficacy of quadrivalent human papillomavirus (HPV) vaccine against HPV 16- or 18-related CIN 2/3 or AIS* caused by the HPV type with which the participant was or had been infected at the time of vaccination (protocols 005, 007, 013, and 015)

	Quadrivalent HPV vaccine		Placebo		Efficacy	
Baseline characteristics	No.	Cases	No.	Cases	%	(95% CI†)
HPV DNA negative, HPV seropositive	853	0	910	4	100.0	(-63.6–100.0)
HPV DNA positive, HPV seronegative	661	42	626	57	31.2	(-4.5–54.9)
HPV DNA positive, HPV seropositive	473	79	499	69	-25.8	(-76.4–10.1)

Source: Food and Drug Administration. Vaccines and Related Biological Products Advisory Committee. FDA GARDASIL briefing information. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration; 2006. Available at http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4222s-index.htm.

* CIN: cervical intraepithelial neoplasia; AIS: adenocarcinoma in situ.

† Confidence interval.

efficacy that would be seen in the total study population. At baseline, 27% of clinical trial participants had evidence of previous or current infection with a vaccine type HPV. In a combined analysis of protocols 005, 007, 013, and 015, the efficacy for prevention of HPV 16- or 18-related CIN 2/3 or AIS was 39.0% (CI = 23.3%–51.7%). In a combined analysis of protocols 007, 013 and 015, efficacy for prevention of any vaccine-type–related CIN was 46.4% (CI = 35.2%–55.7%), for prevention of vaccine-type–related VIN 2/3 and VaIN 2/3 was 69.1% (CI = 29.8%–87.9%), and for prevention of vaccine- type–related genital warts was 68.5% (CI = 57.5%–77.0%). The lower efficacy in these analyses compared with the per protocol population indicates that certain women were infected with vaccine types before vaccination. A 12.2% (CI = -3.2%–25.3%) reduction occurred in any CIN 2/3 in the vaccinated group compared with the placebo group at a median follow-up time of 1.9 years (*111*).

Duration of Protection

A subset of participants (n = 241) in the phase II quadrivalent HPV vaccine study (protocol 007) is being followed for 60 months after dose one. In a combined analysis of all participants through year 3 and a subset through 60 months, the efficacy against vaccine HPV type persistent infection or disease was 95.8% (CI = 83.8%–99.5%) and efficacy against vaccine-type–related CIN or external genital lesions was 100% (CI = 12.4%–100%) (*110*).

Follow-up studies are planned by Merck and Co., Inc. to determine duration of protection among women enrolled in the phase III studies through 3 years after dose 3. Additional data on duration of protection will be available from follow-up of approximately 5,500 women enrolled in one of the phase III quadrivalent HPV vaccine studies in the Nordic countries. These women will be followed for at least 14 years; serologic testing will be conducted 5 and 10 years after vaccination; and Pap testing results will be linked to data from vaccine registries to monitor outcomes.

Immunogenicity

Immunogenicity in Persons Aged 9–26 Years

The immunogenicity of the quadrivalent HPV vaccine has been measured by detection of IgG antibody to the HPV L1 by a type-specific competitive Luminex-based immunoassay (cLIA) in the majority of the studies (*24,25*). This assay measures antibodies against neutralizing epitopes for each HPV type. The units (milliMerck units) are internally consistent but cannot be directly compared across HPV types or with results from other HPV antibody assays. The height of the antibody titers (geometric mean titers [GMTs]) for the different types cannot be directly compared.

Data on immunogenicity are available from Phase II (*109*) and Phase III double-blind, randomized, placebo-controlled trials conducted among females aged 16–26 years and immunogenicity studies conducted among males and females aged 9–15 years (*113*). In all studies conducted to date, ≥99% of study participants had an antibody response to all four HPV types in the vaccine 1 month after completing the 3-dose series (*109,113*). High seropositivity rates were observed after vaccination regardless of sex, ethnicity, country of origin, smoking status, or body mass index.

Vaccination produced antibody titers higher than those after natural infection. Among females aged 16–23 years, anti-HPV 6, 11, 16, and 18 GMTs 1 month after the third dose of vaccine were higher than those observed in participants who were HPV seropositive and PCR negative at enrollment in the placebo group (*109*).

Vaccination of females who were seropositive to a specific vaccine HPV type at enrollment resulted in higher antibody titers to that type, particularly after the first dose, compared with those seronegative at enrollment (*109*), suggesting a boosting of naturally acquired antibody by vaccination. In studies among females aged 16–26 years, the interval between the first and second dose of vaccine ranged from 6 to 12 weeks.

Variation in the interval did not diminish the GMTs post-vaccination. Likewise, little impact of intervals was observed between the second and third dose ranging from 12 to 23 weeks.

A serologic correlative of immunity has not been identified and no known minimal titer determined to be protective. The high efficacy found in the clinical trials to date has precluded identification of a minimum protective antibody titer. Further follow-up of vaccinated cohorts might allow determination of serologic correlates of immunity.

Immunogenicity Bridge to Efficacy Among Females

Immunogenicity studies provide data, allowing comparison of seropositivity and GMTs among females aged 9–15 years with those among females aged 16–26 years who were in the efficacy studies (Table 6) (*111*). Seropositivity rates in all age groups were approximately 99% for HPV 6, 11, 16, and 18. Anti-HPV responses 1 month post dose 3 among females aged 9–15 years were noninferior to those aged 16–26 years. At month 18, anti-HPV GMTs in females aged 9–15 years remained two to three fold higher than those observed at the same time point in females aged 16–26 years in the vaccine efficacy trials.

Duration of Antibody

The longest follow-up to date is 60 months in the phase II trial of quadrivalent HPV vaccine (*110*). Antibody titers decline over time after the third dose but plateau by 24 months. At 36 months, anti-HPV 16 GMT among vaccinees remained higher than those in participants in the placebo group who were seropositive at baseline, and anti-HPV 6, 11, and 18 titers were similar to those seropositive in the placebo group (*109*). At 36 months, seropositivity rates were 94%, 96%, 100%, and 76% to HPV 6, 11, 16, and 18, respectively. No evidence exists of waning efficacy among participants who become seronegative during follow-up (*110*). Data from a revaccination study in which vaccinated women were given a challenge dose 5 years after enrollment into the study demonstrated an augmented rise in antibody titer consistent with immune memory (*114*).

Concomitant Administration of HPV Vaccine with Other Vaccines

GMTs after concomitant administration of quadrivalent HPV vaccine and hepatitis B vaccine at all 3 doses were noninferior to GMTs after administration at separate visits. Studies are planned to evaluate concomitant administration with meningococcal conjugate vaccine and with the adolescent/adult formulation of tetanus, diphtheria and acellular pertussis (Tdap) vaccine.

Safety and Adverse Events

The quadrivalent HPV vaccine was evaluated for injection-site and systemic adverse events, new medical conditions reported during the follow-up period, and safety during pregnancy and lactation. Safety data on quadrivalent HPV vaccine are available from seven clinical trials and include 11,778 persons aged 9–26 years who received quadrivalent vaccine and 9,686 who received placebo. Detailed data were collected using vaccination report cards for 14 days following each injection of study vaccine on a subset of participants aged 9–23 years. The population with detailed safety data included 5,088 females who received quadrivalent HPV vaccine and 3,790 who received placebo (Tables 7–9) (*111*).

Local Adverse Events

In the study population with detailed safety data, a larger proportion of persons reported injection-site adverse events

TABLE 6. Immunogenicity bridging between females aged 9–15 years in the immunogenicity studies to females aged 16–26 years in the quadrivalent human papillomavirus (HPV) vaccine efficacy studies (per-protocol immunogenicity population*)

	Females aged 9–15 years in immunogenicity studies			Females aged 16–26 years in efficacy studies		
Assay (cLIA†)	No.	GMT§ (mMU/mL)	(95% CI¶)	No.	GMT (mMU/mL)	(95% CI)
Anti-HPV 6	915	928.7	(874.0–986.8)	2,631	542.6	(526.2–559.6)
Anti-HPV 11	915	1,303.0	(1,223.1–1,388.0)	2,655	761.5	(735.3–788.6)
Anti-HPV 16	913	4,909.2	(4,547.6–5,299.5)	2,570	2,293.9	(2,185.0–2,408.2)
Anti-HPV 18	920	1,039.8	(954.9–1,120.4)	2,796	461.6	(444.0–480.0)

Source: Food and Drug Administration. Product approval information—licensing action, package insert: GARDASIL (quadrivalent human papillomavirus types 6, 11, 16, and 18), Merck & Co. Whitehouse Station, NJ: Food and Drug Administration; 2006. Available at http://www.fda.gov/cber/label/HPVmer013007LB.pdf.

* Includes all persons who were not general protocol violators, received all three vaccinations within acceptable day ranges, were seronegative at day 1 and (for all persons except those aged <16 years in the immunogenicity studies who were not tested) polymerase chain reaction–negative day 1 through month 7 for the relevant HPV type(s), and had a month 7 serum sample collected within an acceptable day range.

† Competitive luminex immunoassay.

§ Geometric mean titer; mMU: milli-Merck units.

¶ Confidence interval.

TABLE 7. Injection-site adverse events among female participants aged 9–23 years in the detailed safety data, days 1–5 after any vaccination with quadrivalent human papillomavirus (HPV) vaccine

Adverse event	Quadrivalent HPV vaccine (% Occurrence)	Aluminum-containing placebo (% Occurrence)	Saline placebo (% Occurrence)
Pain	83.9	75.4	48.6
Mild/Moderate	81.1	74.1	48.0
Severe	2.8	1.3	0.6
Swelling*	25.4	15.8	7.3
Mild/Moderate	23.3	15.2	7.3
Severe	2.0	0.6	0
Erythema*	24.7	18.4	12.1
Mild/Moderate	23.7	18.0	12.1
Severe	0.9	0.4	0

Source: Food and Drug Administration. Product approval information—licensing action, package insert: GARDASIL (quadrivalent human papillomavirus types 6, 11, 16, and 18), Merck & Co. Whitehouse Station, NJ: Food and Drug Administration; 2006. Available at http://www.fda.gov/cber/label/HPVmer060806LB.pdf.

* Intensity of swelling and erythema was measured by size (inches): mild: 0 to ≤1; moderate: >1 to ≤2; and severe: >2.

TABLE 8. Systemic clinical adverse events among female participants aged 9–23 years in the population with detailed safety data, days 1–15 after vaccination with quadrivalent human papillomavirus (HPV) vaccine

Adverse event (1–15 days postvaccination)	Quadrivalent HPV vaccine (N = 5,088)	Placebo (N = 3,790)
Pyrexia	13.0%	11.2%
Nausea	6.7%	6.6%
Nasopharyngitis	6.4%	6.4%
Dizziness	4.0%	3.7%
Diarrhea	3.6%	3.5%
Vomiting	2.4%	1.9%
Myalgia	2.0%	2.0%
Cough	2.0%	1.5%
Toothache	1.5%	1.4%
Upper respiratory tract infection	1.5%	1.5%
Malaise	1.4%	1.2%
Arthralgia	1.2%	0.9%
Insomnia	1.2%	0.9%
Nasal congestion	1.1%	0.9%

Source: Food and Drug Administration. Product approval information—licensing action, package insert: GARDASIL (quadrivalent human papillomavirus types 6, 11, 16, and 18), Merck & Co. Whitehouse Station, NJ: Food and Drug Administration; 2006. Available at http://www.fda.gov/cber/label/HPVmer060806LB.pdf.

in the group that received quadrivalent HPV vaccine compared with aluminum-containing or saline placebo groups (Table 7). Pain was the most common injection site adverse event, reported by 83.9% of vaccinees, 75.4% of those who received aluminum-containing placebo, and 48.6% of those who received saline placebo. Swelling and erythema were the next most common reactions in the vaccine and placebo groups. The majority of injection-site adverse experiences reported among recipients of quadrivalent HPV vaccine were mild to moderate in intensity; only 2.8%, 2.0%, and 0.9% of vaccinees reported severe pain, swelling, or erythema, respectively.

Systemic Adverse Events

Systemic clinical adverse events were reported by a similar proportion of vaccine and placebo recipients in the population with detailed safety data (Table 8). In both quadrivalent HPV vaccine and placebo groups, more persons reported a systemic clinical adverse experience in the 15 days after dose 1 compared with after dose 2 and after dose 3. For the majority of persons, the maximum intensity rating of systemic clinical adverse events was mild or moderate. Overall, 4.0%–4.9% of females who received quadrivalent HPV vaccine reported

TABLE 9. Percentage of females aged 9–23 years with fever in the population with detailed safety data who had fever, days 1–5 after any vaccination with quadrivalent human papillomavirus (HPV) vaccine

	Quadrivalent HPV vaccine (% Occurrence)			Placebo (% Occurrence)		
Temperature (°F)*	Post dose 1	Post dose 2	Post dose 3	Post dose 1	Post dose 2	Post dose 3
≥100° to <102°	3.7	4.1	4.4	3.1	3.8	3.6
≥102°	0.3	0.5	0.5	0.3	0.4	0.6

Source: Food and Drug Administration. Product approval information—licensing action, package insert: GARDASIL (quadrivalent human papillomavirus types 6, 11, 16, and 18), Merck & Co. Whitehouse Station, NJ: Food and Drug Administration; 2006. Available at http://www.fda.gov/cber/label/HPVmer060806LB.pdf.

* Oral or oral equivalent temperature.

a temperature of ≥100°F (≥38°C) after dose one, two, or three (Table 9).

Serious Adverse Events in All Safety Studies

Vaccine-related serious adverse events occurred in <0.1% of persons. The proportions of persons reporting a serious adverse event were similar in the vaccine and placebo groups, as were the types of serious adverse events reported. Seven persons had events that were determined to be possibly, probably, or definitely related to the vaccine or placebo. Five events occurred among quadrivalent HPV vaccine recipients and two among placebo recipients. The five in the quadrivalent HPV vaccine group included bronchospasm, gastroenteritis, headache/hypertension, vaginal hemorrhage, and injection site pain/movement impairment.

In the overall safety evaluation, 10 persons in the group that received quadrivalent HPV vaccine and seven persons in the placebo group died during the course of the trials. None of the deaths was considered to be vaccine related. Two deaths in the vaccine group and one death in the placebo group occurred within 15 days following vaccination. Seven deaths were attributed to motor-vehicle accidents (four in vaccine group and three in placebo group), three were caused by intentional overdose (nonstudy medications) or suicide (one in vaccine group and two in placebo group), two were attributed to pulmonary embolus or deep venous thrombosis (one each in vaccine and placebo group), two were attributed to sepsis, one case each attributed to cancer and arrhythmia (in vaccine group), and one case caused by asphyxia (placebo group).

New Medical History

Information was collected on new medical conditions that occurred in up to 4 years of follow-up. Overall, nine (0.08%) participants in the vaccine group and three (0.03%) participants in the placebo group had conditions potentially indicative of autoimmune disorders, including various arthritis diagnoses (nine in vaccine group and two in placebo group) and systemic lupus erythematosis (none in vaccine group and one in placebo group) (*111*). No statistically significant differences exist between vaccine and placebo recipients for the incidence of these conditions.

Vaccination During Pregnancy

The quadrivalent clinical trial protocols excluded women who were pregnant. Human beta gonadotropin testing was conducted before administration of each vaccine dose, and if women were found to be pregnant, vaccination was delayed until completion of pregnancy. Nevertheless, among clinical trial participants, 1,244 pregnancies occurred in the vaccine group and 1,272 occurred in the placebo group (Table 10) (*111*). Among those with known outcomes (996 and 1,018), the percentage with spontaneous loss was similar in both groups (25%). A total of 15 and 16 congenital abnormalities occurred in the vaccine and placebo groups, respectively, including five in the vaccine group and none in the placebo group among infants born to women who received vaccine or placebo within 30 days of estimated onset of pregnancy. The five congenital abnormalities were determined by an expert panel to be unrelated (one pyloric stenosis with ankyloglossia, one congenital hydronephrosis, one congenital megacolon, one club foot, and one hip dysplasia). Rates of congenital abnormalities in the study were consistent with those in surveillance registries. Quadrivalent HPV vaccine has been classified as Category B on the basis of animal studies in rats showing no evidence of impaired fertility or harm to the fetus.

Vaccination During Lactation

In the clinical trials, 995 women in the evaluated population (500 and 495 persons in the group that received quadrivalent HPV vaccine or placebo, respectively) were breast feeding during the vaccination period. A total of 17 (3.4%) and nine (1.8%) infants of women who breastfed who received quadrivalent HPV vaccine or placebo, respectively, experienced a serious adverse event. Of the 23 experiences among the 17 infants of women who received vaccine, 12 were respiratory infections, five were gastroenteritis or diarrhea, and the remaining included various other single events. None was considered vaccine related.

TABLE 10. Pregnancy outcomes in the quadrivalent human papillomavirus (HPV) vaccine phase III database

	Quadrivalent HPV vaccine		Placebo	
Outcome	**No.**	**(%)**	**No.**	**(%)**
Women with pregnancies	1,115	(10.7)	1,151	(12.6)
No. of pregnancies	1,244		1,272	
Infants/fetuses with known outcomes	996		1,018	
Live births*	621	(62.3)	611	(60.0)
Spontaneous miscarriage*	249	(25.0)	257	(25.2)
Late fetal deaths*	11	(1.1)	8	(0.8)
Congenital anomalies*	15	(1.5)	16	(1.6)

Source: Food and Drug Administration. Vaccines and Related Biological Products Advisory Committee, May 18, 2006: FDA GARDASIL briefing information. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration; 2006. Available at http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4222s-index.htm.

* Percentage of those with known outcomes.

Impact of Vaccination and Cost Effectiveness

Economic Burden of HPV

The prevention and treatment of anogenital warts and cervical HPV-related disease imposes an estimated burden of $4 billion or more (2004 dollars) in direct costs in the United States each year (*70,71,115*). Of this, approximately $200 million is attributable to the management of genital warts; approximately $300–$400 million to invasive cervical cancer; and the remainder to routine cervical cancer screening, the follow-up of abnormal Pap tests, and pre-invasive cervical cancer (*71,115*). The estimated economic burden associated with HPV would be more substantial if the cost of other HPV-related diseases (e.g., vaginal and anal cancer and RRP) were included.

Expected Impact of Vaccination

Various different models have been developed to evaluate the impact of HPV vaccine (*116*). Markov models have suggested that vaccination of an entire cohort of females aged 12 years could reduce the lifetime risk for cervical cancer by 20%–66% (*117,118*) in that cohort, depending on the efficacy of the vaccine and the duration of vaccine protection. Models also project decreases in Pap test abnormalities and cervical cancer precursor lesions as a result of vaccination. For example, incidence of low-grade Pap test abnormalities would decrease by 21% over the life of a vaccinated cohort of females aged 12 years (*117*). Models that incorporate HPV transmission dynamics suggest an even greater potential impact of HPV vaccination on cervical cancer and cervical cancer precursors (*119–121*). Decreases in cervical cancer incidence and precursor lesions would occur more quickly with catch-up vaccination according to models that evaluated catch-up for females aged 12–24 years (*121,122*).

Cost Effectiveness of HPV Vaccine

Since 2003, four studies have estimated the potential cost effectiveness of HPV vaccination in the context of cervical cancer screening practices in the United States (*117–119,121*). Two of these studies applied Markov models to estimate the cost per quality-adjusted life year (QALY), focusing on the costs and impact of HPV vaccination for a given cohort, without considering the effect of vaccination on HPV transmission in the population (herd immunity). The other studies applied dynamic transmission models to incorporate the benefits of herd immunity in estimating the cost effectiveness of HPV vaccination.

The two studies based on Markov models of the natural history of HPV infection examined the cost effectiveness of vaccinating females aged 12 years. One study assumed 100% vaccine coverage, 90% vaccine efficacy against HPV 16/18, lifetime duration of protection, and a cost of $377 per vaccine series (*118*). Under these assumptions, an estimated 58% reduction was achieved in the lifetime risk for cervical cancer for the vaccinated cohort at a cost of $24,300 (2002 dollars) per QALY compared with no vaccination. A second study assumed 70% vaccine coverage, 75% efficacy against all high-risk HPV types, 10 years duration of protection plus 10 additional years of protection with a booster, and a cost of $300 per vaccine series plus $100 per booster (*117*). Under these assumptions, an estimated 20% reduction in cervical cancer incidence was achieved in the vaccinated cohort at a cost of $22,800 per QALY (2001 dollars) compared with no vaccination.

The two cost effectiveness analyses based on dynamic transmission models examined the cost effectiveness of vaccinating females. One study assumed vaccination at age 12 years with 70% vaccine coverage. The vaccine cost $300 per series plus $100 per booster and targeted HPV 16/18 with 90% efficacy and 10-year duration of protection plus 10 additional years with a booster (*119*). Under these assumptions, the lifetime risk for cervical cancer among vaccinated females would be reduced by 62% at a cost per QALY of $14,600 (2001 dollars) compared with no vaccination. A second study assumed vaccination at or before age 12 years with 70% vaccine coverage (*121*). The vaccine cost $360 per series and targeted HPV types 6, 11, 16, and 18, with 90% efficacy against infection and 100% efficacy against HPV-related diseases attributable to these HPV types, with lifelong duration of protection. Under these assumptions, over the long term, a reduction of approximately 75% was achieved in the cervical cancer incidence rate attributable to HPV 16 and 18 at a cost of $3,000 per QALY in 2005 dollars compared with no vaccination. This model also suggested that a catch-up program for females aged 12–24 years would cost $4,700 per QALY compared with vaccination of females aged 12 years only.

The cost per QALY gained by routine vaccination of females at age 12 years in the published studies ranged from $3,000 to $24,300. The results summarized are calculated using base-case scenarios, which vary across studies. In the sensitivity analyses, when base-case assumptions were modified, the estimated cost effectiveness ratios changed substantially. For example, factors such as duration of vaccine-induced protection, duration of natural immunity, frequency of cervical cancer screening, vaccine coverage, and vaccine cost impacted the estimated cost effectiveness of HPV vaccination (*116–119,121,123*).

Summary of Rationale for Quadrivalent HPV Vaccine Recommendations

The availability of a quadrivalent HPV vaccine offers an opportunity to decrease the burden of HPV infection and its sequelae, including cervical cancer precursors, cervical cancer, other anogenital cancers, and genital warts in the United States. Quadrivalent HPV vaccine is licensed for use among females aged 9–26 years. In this age group, clinical trials indicate that the vaccine is safe and immunogenic. Trials among females aged 16–26 years indicated the vaccine to be effective against HPV types 6-, 11-, 16-, and 18-related cervical, vaginal and vulvar cancer precursor and dysplastic lesions, and genital warts. HPV 16 and 18 are the cause of approximately 70% of cervical cancers; HPV 6 and 11 are the cause of approximately 90% of genital warts. Because HPV is sexually transmitted and often acquired soon after onset of sexual activity, vaccination should ideally occur before sexual debut. The recommended age for vaccination is 11–12 years; vaccine can be administered to females as young as age 9 years. At the beginning of a vaccination program, females aged >12 years will exist who did not have the opportunity to receive vaccine at age 11–12 years. Catch-up vaccination is recommended for females aged 13–26 years who have not yet been vaccinated.

The recommendation for routine vaccination of females aged 11–12 years is based on several considerations, including studies suggesting that quadrivalent HPV vaccine among adolescents will be safe and effective; high antibody titers achieved after vaccination at age 11–12 years; data on HPV epidemiology and age of sexual debut in the United States; and the high probability of HPV acquisition within several years of sexual debut. Ideally, HPV vaccine should be administered before sexual debut, and duration of protection should extend for many years, providing protection when exposure through sexual activity might occur. The vaccine has been demonstrated to provide protection for at least 5 years without evidence of waning protection. Long-term follow-up studies are underway to determine duration of protection. The recommendation also considered cost effectiveness evaluations and the established young adolescent health-care visit at age 11–12 years recommended by several professional organizations, when other vaccines are also recommended.

Although routine vaccination is recommended at age 11–12 years, the majority of females aged 13–26 years also can benefit from vaccination. Females not yet sexually active can be expected to receive the full benefit of vaccination. Although sexually active females in this age group might have been infected with one or more vaccine HPV types, type-specific prevalence studies in the United States suggest that a small percentage of sexually active females have been infected with all four of the HPV vaccine types. These data, available from North American females aged 16–24 years who participated in the quadrivalent vaccine trials, are from women who were more likely to have ever had sex than similar aged females in the general U.S. population. Among those sexually active females, the median number of lifetime sex partners (two) was similar in trial participants and females in the general U.S. population. The vaccine does not appear to protect against persistent infection, cervical cancer precursor lesions, or genital warts caused by an HPV type that females are infected with at the time of vaccination. However, females already infected with one or more vaccine HPV types before vaccination would be protected against disease caused by the other vaccine HPV types. Therefore, although overall vaccine effectiveness would be lower when administered to a population of females who are sexually active, and would decrease with older age and likelihood of HPV exposure with increasing number of sex partners, the majority of females in this age group will derive at least partial benefit from vaccination.

Recommendations for Use of HPV Vaccine

Recommendations for Routine Use and Catch-Up

Routine Vaccination of Females Aged 11–12 Years

ACIP recommends routine vaccination of females aged 11–12 years with 3 doses of quadrivalent HPV vaccine. The vaccination series can be started as young as age 9 years.

Catch-Up Vaccination of Females Aged 13–26 Years

Vaccination also is recommended for females aged 13–26 years who have not been previously vaccinated or who have not completed the full series. Ideally, vaccine should be administered before potential exposure to HPV through sexual contact; however, females who might have already been exposed to HPV should be vaccinated. Sexually active females who have not been infected with any of the HPV vaccine types would receive full benefit from vaccination. Vaccination would provide less benefit to females if they have already been infected with one or more of the four vaccine HPV types. However, it is not possible for a clinician to assess the extent to which sexually active persons would benefit from vaccination, and the risk for HPV infection might continue as long as persons are sexually active. Pap testing and screening for

HPV DNA or HPV antibody are not needed before vaccination at any age.

Dosage and Administration

The vaccine should be shaken well before administration. The dose of quadrivalent HPV vaccine is 0.5 mL, administered intramuscularly (IM), preferably in the deltoid muscle.

Recommended Schedule

Quadrivalent HPV vaccine is administered in a 3-dose schedule. The second and third doses should be administered 2 and 6 months after the first dose.

Minimum Dosing Intervals and Management of Persons Who Were Incorrectly Vaccinated

The minimum interval between the first and second doses of vaccine is 4 weeks. The minimum recommended interval between the second and third doses of vaccine is 12 weeks. Inadequate doses of quadrivalent HPV vaccine or vaccine doses received after a shorter-than-recommended dosing interval should be readministered.

Interrupted Vaccine Schedules

If the quadrivalent HPV vaccine schedule is interrupted, the vaccine series does not need to be restarted. If the series is interrupted after the first dose, the second dose should be administered as soon as possible, and the second and third doses should be separated by an interval of at least 12 weeks. If only the third dose is delayed, it should be administered as soon as possible.

Simultaneous Administration with Other Vaccines

Although no data exist on administration of quadrivalent HPV vaccine with vaccines other than hepatitis B vaccine, quadrivalent HPV vaccine is not a live vaccine and has no components that adversely impact safety or efficacy of other vaccinations. Quadrivalent HPV vaccine can be administered at the same visit as other age appropriate vaccines, such as the Tdap and quadrivalent meningococcal conjugate (MCV4) vaccines. Administering all indicated vaccines together at a single visit increases the likelihood that adolescents and young adults will receive each of the vaccines on schedule. Each vaccine should be administered using a separate syringe at a different anatomic site.

Cervical Cancer Screening Among Vaccinated Females

Cervical cancer screening recommendations have not changed for females who receive HPV vaccine (Table 2). HPV types in the vaccine are responsible for approximately 70% of cervical cancers; females who are vaccinated could subsequently be infected with a carcinogenic HPV type for which the quadrivalent vaccine does not provide protection. Furthermore, those who were sexually active before vaccination could have been infected with a vaccine type HPV before vaccination. Health-care providers administering quadrivalent HPV vaccine should educate women about the importance of cervical cancer screening.

Groups for Which Vaccine is Not Licensed

Vaccination of Females Aged <9 Years and >26 Years

Quadrivalent HPV vaccine is not licensed for use among females aged <9 years or those aged >26 years. Studies are ongoing among females aged >26 years. No studies are under way among children aged <9 years.

Vaccination of Males

Quadrivalent HPV vaccine is not licensed for use among males. Although data on immunogenicity and safety are available for males aged 9–15 years, no data exist on efficacy in males at any age. Efficacy studies in males are under way.

Special Situations Among Females Aged 9–26 Years

Equivocal or Abnormal Pap Test or Known HPV Infection

Females who have an equivocal or abnormal Pap test could be infected with any of approximately 40 high-risk or low-risk genital HPV types. Such females are unlikely to be infected with all four HPV vaccine types, and they might not be infected with any HPV vaccine type. Vaccination would provide protection against infection with HPV vaccine types not already acquired. With increasing severity of Pap test findings, the likelihood of infection with HPV 16 or 18 increases and the benefit of vaccination would decrease. Women should be advised that results from clinical trials do not indicate the vaccine will have any therapeutic effect on existing HPV infection or cervical lesions.

Females who have a positive HC2 High-Risk test conducted in conjunction with a Pap test could have infection with any of 13 high-risk types. This assay does not identify specific HPV types, and testing for specific HPV types is not conducted routinely in clinical practice. Women with a positive HC2 High-Risk test might not have been infected with any

of the four HPV vaccine types. Vaccination would provide protection against infection with HPV vaccine types not already acquired. However, women should be advised that results from clinical trials do not indicate the vaccine will have any therapeutic effect on existing HPV infection or cervical lesions.

Genital Warts

A history of genital warts or clinically evident genital warts indicates infection with HPV, most often type 6 or 11. However, these females might not have infection with both HPV 6 and 11 or infection with HPV 16 or 18. Vaccination would provide protection against infection with HPV vaccine types not already acquired. However, females should be advised that results from clinical trials do not indicate the vaccine will have any therapeutic effect on existing HPV infection or genital warts.

Lactating Women

Lactating women can receive HPV vaccine.

Immunocompromised Persons

Because quadrivalent HPV vaccine is a noninfectious vaccine, it can be administered to females who are immunosuppressed as a result of disease or medications. However, the immune response and vaccine efficacy might be less than that in persons who are immunocompetent.

Vaccination During Pregnancy

Quadrivalent HPV vaccine is not recommended for use in pregnancy. The vaccine has not been causally associated with adverse outcomes of pregnancy or adverse events in the developing fetus. However, data on vaccination during pregnancy are limited. Until additional information is available, initiation of the vaccine series should be delayed until after completion of the pregnancy. If a woman is found to be pregnant after initiating the vaccination series, the remainder of the 3-dose regimen should be delayed until after completion of the pregnancy. If a vaccine dose has been administered during pregnancy, no intervention is needed. A vaccine in pregnancy registry has been established; patients and health-care providers should report any exposure to quadrivalent HPV vaccine during pregnancy (telephone: 800-986-8999).

Precautions and Contraindications

Acute Illnesses

Quadrivalent HPV vaccine can be administered to persons with minor acute illnesses (e.g., diarrhea or mild upper respiratory tract infections with or without fever). Vaccination of persons with moderate or severe acute illnesses should be deferred until after the patient improves (*124*).

Hypersensitivity or Allergy to Vaccine Components

Quadrivalent HPV vaccine is contraindicated for persons with a history of immediate hypersensitivity to yeast or to any vaccine component. Data from passive surveillance in Vaccine Adverse Event Reporting System (VAERS) indicates that recombinent yeast derived vaccines pose a minimal risk for anaphylaxic reactions in persons with a history of allergic reactions to *Saccharomyces cerevisiae* (baker's yeast) (*125*).

Preventing Syncope After Vaccination

Syncope (i.e., vasovagal or vasodepressor reaction) can occur after vaccination, most commonly among adolescents and young adults (*124*). Among reports to VAERS for any vaccine that were coded as syncope during 1990–2004, a total of 35% of these episodes were reported among persons aged 10–18 years. Through January 2007, the second most common report to VAERS following receipt of HPV vaccine was syncope (CDC, unpublished data, 2007). Vaccine providers should consider observing patients for 15 minutes after they receive HPV vaccine.

Reporting of Adverse Events After Vaccination

As with any newly licensed vaccine, surveillance for rare adverse events associated with administration of quadrivalent HPV vaccine is important for assessing its safety in widespread use. All clinically significant adverse events should be reported to VAERS at http://vaers.hhs.gov, even if causal relation to vaccination is not certain. VAERS reporting forms and information are available electronically at http://www.vaers.hhs.gov or by telephone (800-822-7967). Web-based reporting is available and providers are encouraged to report electronically at https://secure.vaers.org/VaersDataEntryintro.htm to promote better timeliness and quality of safety data.

Safety surveillance for adolescent quadrivalent HPV vaccine, Tdap, MCV4, and other vaccines is being conducted on an ongoing basis in cooperation with FDA. A vaccine in pregnancy registry has been established by Merck and Co., Inc.; patients and health-care providers should report any exposure to quadrivalent HPV vaccine during pregnancy (telephone: 800-986-8999).

Areas for Research and Program Activity Related to HPV Vaccine

With licensure and introduction of quadrivalent HPV vaccine for females, monitoring impact of vaccination and vaccine safety will be needed. Research in several areas is ongoing, and research in other areas is needed.

Duration of Protection from the Quadrivalent Vaccine: Long-term data on duration of antibody response and clinical protection will be obtained through studies conducted in the Nordic countries through the Nordic cancer registries and through other studies in the United States (*111*). Follow up of vaccine trial participants aged 9–15 years will continue for up to 10 years after dose 3. This will include evaluation of antibody titers and, in participants who reach their 16th birthday, evaluation of vaccine effectiveness.

Surveillance for HPV-Related Outcomes: Although it will take years to realize the impact of vaccination on cervical cancer, decreases in cervical cancer precursors and genital warts should be realized sooner. Studies are planned to monitor these lesions and other HPV-related outcomes in the United States.

Virologic Surveillance: Prevalence and incidence of HPV types in the vaccine are expected to decrease as a result of vaccination. Studies are planned to monitor HPV types in various populations and specimens.

Safety of Vaccination: Postlicensure studies to evaluate general safety and pregnancy outcomes will be conducted by the manufacturer and independently by CDC. Monitoring will be accomplished through VAERS and CDC's Vaccine Safety Datalink, which will include surveillance of cohorts of recently vaccinated females and evaluation of outcomes of pregnancy among those pregnant at the time of vaccination. The manufacturer will be monitoring long-term safety as part of the Nordic Cancer Registry Program (*111*).

Simultaneous Vaccination: Safety and immunogenicity studies of simultaneous administration of quadrivalent HPV vaccine with Tdap and MCV4 are ongoing.

Efficacy of HPV Vaccine in Men: Studies are needed to define the efficacy of HPV vaccination in preventing genital warts and anogenital intraepithelial neoplasia in men. Studies of the effectiveness of HPV vaccination of men in preventing transmission to both female and male sex partners are also needed.

Cervical Cancer Screening: Recommendations for cervical cancer screening guidelines have not changed. Evaluation of the impact of HPV vaccination on cervical cancer screening provider practices and women's screening behavior is needed as well as further economic analyses.

Vaccine Delivery and Implementation: Administration of 3 doses of vaccine in adolescents will be challenging. Programmatic research is needed to determine optimal strategies to reach this age group.

Vaccines for Children Program

The Vaccines for Children (VFC) program supplies vaccines to all states, territories, and the District of Columbia for use by participating providers. These vaccines are to be administered to eligible children without cost to the patients or the provider. All routine childhood vaccines recommended by ACIP are available through this program. The program saves patients and providers out-of-pocket expenses for vaccine purchases and provides cost savings to states through CDC vaccine contracts. The program results in lower vaccine prices and ensures that all states pay the same contract prices. Detailed information about the VFC program is available at http://www.cdc.gov/nip/vfc/default.htm.

Additional Information About HPV and HPV Vaccine

Additional information about HPV and HPV vaccine is available from several sources, and new information will be available in the future. Updated information about HPV, cervical cancer, and HPV vaccine is available at the following websites: http://www.cdc.gov/nip/vaccine/hpv; http://www.cdc.gov/cancer; http://www.cdc.gov/std/hpv; http://www.cancer.gov/cancertopics/hpv-vaccines; http://www.cancer.org; and http://www.ashastd.org/hpv.

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