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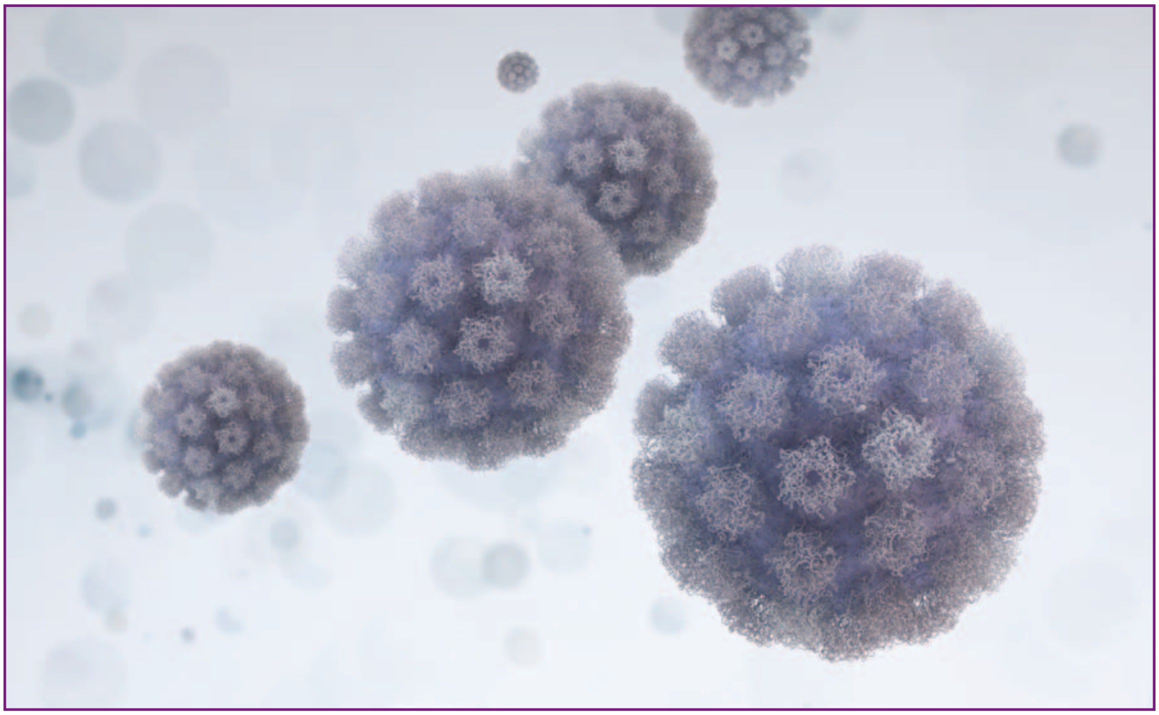
Human Papillomavirus Vaccination

Recommendations of the Advisory Committee on Immunization Practices (ACIP)



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U.S. Department of Health and Human Services
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CDC Adoption of ACIP Recommendation

Recommendations for routine use of vaccines in children, adolescents and adults are developed by the Advisory Committee on Immunization Practices (ACIP). ACIP is chartered as a federal advisory committee to provide expert external advice and guidance to the Director of CDC on use of vaccines and related agents for the control of vaccine-preventable diseases in the civilian population of the United States. Recommendations for routine use of vaccines in children and adolescents are harmonized to the greatest extent possible with recommendations made by the American Academy of Pediatrics (AAP), the American Academy of Family Physicians (AAFP), and the American College of Obstetrics and Gynecology (ACOG). Recommendations for routine use of vaccines in adults are harmonized with recommendations of AAFP, ACOG, and the American College of Physicians (ACP). ACIP recommendations adopted by the CDC Director become agency guidelines on the date published in *MMWR*. Additional information regarding ACIP is available at http://www.cdc.gov/vaccines/acip.

Disclosure of Relationship

The developers of these guidelines wish to disclose that they have no financial interests or competing interests with the manufacturers of commercial products or suppliers of commercial services related to human papillomavirus (HPV) vaccines. Content will not include any discussion of the unlabeled use of a product or a product under investigational use, with the following exceptions:

- Bivalent HPV vaccine can be administered through age 26 years to females.
- HPV vaccines can be administrated beyond age 27 years to complete the vaccination series if started when younger.

Front cover photo: An illustration of human papillomavirus (HPV) virions constructed with 3D animation software, using Protein Data Bank entry 1L0T.

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Recommendations of the Advisory Committee on Immunization Practices (ACIP)

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Summary

This report summarizes the epidemiology of human papillomavirus (HPV) and associated diseases, describes the licensed HPV vaccines, provides updated data from clinical trials and postlicensure safety studies, and compiles recommendations from CDC's Advisory Committee on Immunization Practices (ACIP) for use of HPV vaccines.

Persistent infection with oncogenic HPV types can cause cervical cancer in women as well as other anogenital and oropharyngeal cancers in women and men. HPV also causes genital warts. Two HPV vaccines are licensed in the United States. Both are composed of type-specific HPV L1 protein, the major capsid protein of HPV. Expression of the L1 protein using recombinant DNA technology produces noninfectious virus-like particles (VLPs). Quadrivalent HPV vaccine (HPV4) contains four HPV type-specific VLPs prepared from the L1 proteins of HPV 6, 11, 16, and 18. Bivalent HPV vaccine (HPV2) contains two HPV type-specific VLPs prepared from the L1 proteins of HPV 16 and 18. Both vaccines are administered in a 3-dose series.

ACIP recommends routine vaccination with HPV4 or HPV2 for females aged 11 or 12 years and with HPV4 for males aged 11 or 12 years. Vaccination also is recommended for females aged 13 through 26 years and for males aged 13 through 21 years who were not vaccinated previously. Males aged 22 through 26 years may be vaccinated. ACIP recommends vaccination of men who have sex with men and immunocompromised persons (including those with HIV infection) through age 26 years if not previously vaccinated.

As a compendium of all current recommendations for use of HPV vaccines, information in this report is intended for use by clinicians, vaccination providers, public health officials, and immunization program personnel as a resource. ACIP recommendations are reviewed periodically and are revised as indicated when new information and data become available.

Introduction

Genital human papillomavirus (HPV) is the most common sexually transmitted infection in the United States; an estimated 14 million persons are newly infected every year (*1*). Although most infections cause no symptoms and are self-limited, persistent HPV infection can cause cervical cancer in women as well as other anogenital cancers, oropharyngeal cancer, and genital warts in men and women.

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More than 150 HPV types have been identified, including approximately 40 that infect the genital area (*2*,*3*). Genital HPV types are categorized according to their epidemiologic association with cervical cancer. High-risk types have the potential to act as carcinogens. Low-risk types (e.g., types 6 and 11) can cause benign or low-grade cervical cell changes, genital warts, and recurrent respiratory papillomatosis (*4*). High-risk types (e.g., types 16 and 18) can cause low-grade cervical cell abnormalities, high-grade cervical cell abnormalities that are precursors to cancer, and cancers (*5*–*7*). Essentially all cervical cancers are attributable to high-risk HPV types (*8*), and approximately 70% of cervical cancer cases worldwide are caused by types 16 and 18 (*9*). In addition to cervical cancer, HPV infection also is the cause of some other anogenital cancers such as cancer of the vulva, vagina, penis, and anus, as well as cancer of the oropharynx (*6*).

Two HPV vaccines, bivalent HPV vaccine (HPV2) and quadrivalent HPV vaccine (HPV4) are licensed for use in the United States (*10*,*11*). Both vaccines protect against HPV types 16 and 18, which cause 70% of cervical cancers. HPV type 16 also causes the majority of other cancers attributable to HPV. HPV4 also protects against HPV types 6 and 11, which cause >90% of genital warts and recurrent respiratory papillomatosis (*4*). This report summarizes the epidemiology of HPV and associated diseases, describes the licensed HPV vaccines, provides updated information on vaccines from clinical trials and postlicensure safety studies and monitoring, and compiles recommendations from CDC's Advisory Committee on Immunization Practices (ACIP) for use of HPV vaccines (*12*–*15*).

Methods

The Advisory Committee on Immunization Practices (ACIP) HPV Vaccine Work Group* first met in February 2004 to begin reviewing data related to HPV4. Since February 2004, the Work Group has held multiple teleconferences and periodic meetings to review published and unpublished data from HPV2 and HPV4 clinical trials including data on safety, immunogenicity, and efficacy (*12*–*15*). Data on epidemiology and natural history of HPV, sexual behavior, vaccine acceptability, and cost-effectiveness of HPV vaccination also were considered. Presentations were made to ACIP during multiple meetings before ACIP votes (*16*). The first vote for routine use of HPV4 in females was held in June 2006 (Table 1). The second vote occurred in October 2009 after HPV2 was licensed for use in females; ACIP updated the recommendation to state that either vaccine could be used in females (*13*). At the same meeting, ACIP provided guidance that HPV4 may be given to males aged 9 through 26 years, but vaccination of males was not included in the routine schedule (*14*). In October 2011, ACIP recommended routine vaccination of males (*15*). Grading of Recommendations, Assessment, Development and Evaluation (GRADE) was adopted by ACIP in 2011 (*14*) and the routine recommendation for males was considered using GRADE (*15*). Factors considered in determining the recommendation for males included benefits and harms, evidence type, values and preferences, and health economic analysis (*17*). The Work Group continues to review data as they become available and considers any needed policy changes.

*A list of the members of the Work Group appears on page 30.

Background

Biology and Immunology of HPV

HPVs are nonenveloped, double-stranded DNA viruses in the family *Papillomaviridae.* Isolates of HPV are classified as "types" in most commonly used nomenclature, with International Committee on Taxonomy of Viruses (ICTV) proposing use of "strains." The types (or strains) are assigned numbers in order of their discovery (*2*). 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 comprising 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 types. E6 and E7 proteins from high-risk types are the primary oncoproteins; they manipulate cell cycle regulators, induce chromosomal abnormalities, and block apoptosis (*3*).

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.

HPV infections are largely shielded from the host immune response because they are nonlytic and restricted to the epithelium (*3*,*18*). Humoral and cellular immune responses have been documented, but correlates of immunity have not been established (*18*). Serum antibodies against many different viral products have been demonstrated. The best characterized antibodies are those directed against conformational epitopes of the L1 capsid protein assembled as VLPs. Not all infected persons develop detectable antibody; in one study, 54%–69% of women with incident HPV 6, 16, or 18 infections had type-specific antibody (*19*). Among newly infected men, 4%–36% developed type-specific antibody to one of seven types (*20*). Only 13% developed antibody after infection with HPV 16.

TABLE 1. Human papillomavirus vaccines licensed in the United States and ACIP recommendations for vaccination, 2006–2014

Characteristic	Quadrivalent HPV vaccine (HPV4)	Bivalent HPV vaccine (HPV2)
Manufacturer	Merck and Co, Inc.	GlaxoSmithKline
HPV types	HPV 6, 11, 16, 18	HPV 16, 18
Year of licensure (age range)	Females: 2006 (9–26 years)	Females: 2009 (9–25 years)
	Males: 2009 (9–26 years)	Not licensed for use in males
ACIP recommendations, 2006*	Females: routine vaccination with 3-dose series at age 11 or 12 years[†,§] and through age 26 years if not vaccinated previously	
ACIP recommendations, 2009[¶]	Females: either vaccine for routine vaccination with 3-dose series at age 11 or 12 years[†,§] and through age 26 years if not vaccinated previously	
	Males aged 9–26 years may be vaccinated, but vaccination not routinely recommended for males	
ACIP recommendations, 2011**	Females: either vaccine for routine vaccination with 3-dose series at age 11 or 12 years[†,§] and through age 26 years if not vaccinated previously	
	Males: routine vaccination with 3-dose series at age 11 or 12 years[†,§] and through age 21 years if not vaccinated previously[††] Vaccination recommended through age 26 years for men who have sex with men and men who are immunocompromised (including those with HIV infection)	

Abbreviations: ACIP = Advisory Committee on Immunization Practices; HIV = human immunodeficiency virus; HPV = human papillomavirus.

* **Source:** CDC. Quadrivalent human papillomavirus vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2007;56(No. RR-2).

† 3-dose series at interval of 0, 1–2, and 6 months.

§ Vaccination series can be started at age 9 years.

¶ **Sources:** CDC. FDA licensure of bivalent human papillomavirus vaccine (HPV2, Cervarix) for use in females and updated HPV vaccination recommendations from the Advisory Committee on Immunization Practices (ACIP). MMWR 2010;59:626–9. CDC. FDA licensure of quadrivalent human papillomavirus vaccine (HPV4, Gardasil) for use in males and guidance from the Advisory Committee on Immunization Practices (ACIP). MMWR 2010;59:630–2.

** **Source:** CDC. Recommendations on the use of quadrivalent human papillomavirus vaccine in males—Advisory Committee on Immunization Practices (ACIP), 2011. MMWR 2011;60:1705–8.

†† Males aged 22–26 years may be vaccinated.

Laboratory Testing for HPV

Because HPV infections are not treated, the clinical indications for HPV testing are to identify women at risk for HPV-associated cervical disease and to guide follow-up decisions for those with disease. HPV cannot be cultured directly from patient specimens, so tests require detecting HPV genetic information. Most commercially available assays detect DNA. Because HPV is cell-associated, cellular samples are required. The Food and Drug Administration (FDA) has approved clinical HPV tests for detecting clinically significant levels of any of 14 high-risk HPV types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) from cervical specimens (see Cervical Cancer Screening). HPV tests are approved either for use with the Papanicolaou (Pap) test for routine screening in women aged >30 years or for following up certain abnormal Pap test results. One HPV test has been approved for primary cervical cancer screening but is not currently part of national recommendations (*21*). There are no other approved indications for clinical HPV testing. HPV tests are not recommended or approved for use in men or adolescents, for detection of HPV in partners, or at anatomic sites other than the cervix.

Epidemiologic 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 targeting genetically conserved regions of the L1 gene are designed to amplify essentially all HPV, and types are then determined by type-specific hybridization. However, a wide variety of HPV detection and typing methods exist (*22*).

Although HPV DNA tests detect current HPV infection at specific sites, HPV serology can be used as a measure of current or past infection (or vaccination) in research settings. As noted previously, the host immune response to HPV infection is weak, and not all infected persons develop detectable antibody. Nonetheless, in unvaccinated populations, the age-specific seroprevalence reflects the overall age of first exposure, and seroprevalence data were used to help guide the ages targeted for preventive HPV vaccines. Serologic testing was conducted in the HPV vaccine clinical trials (see Evaluation of Serologic Response to Vaccination). The most frequently used HPV serologic assays are VLP-based enzyme-linked immunoassays, which are 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 (*23*). Serologic assays have no clinical use and are available only in research settings. Key laboratory reagents are not standardized, and no gold standard exists for setting a threshold for a positive antibody result.

HPV Prevalence and Incidence

Genital HPV infection is common. Overall in the United States, an estimated 79 million persons are infected, and an estimated 14 million new HPV infections occur every year among persons aged 15–59 years (*1*). Approximately half of new infections occur among persons aged 15–24 years.

Population-based prevalence data among U.S. females are available. Since 2002, HPV prevalence has been determined from self-collected cervicovaginal swabs in the National Health and Nutrition Examination Survey (NHANES). During 2003–2006, the prevalence of any HPV was 42.5% among females aged 14–59 years (*24*). Prevalence of HPV was highest among those aged 20–24 years (53.8%). In this age group, prevalence of HPV types 6, 11, 16, or 18 was 18.5% (*25*). Other information on HPV prevalence among females and males has been obtained primarily from clinic-based populations (e.g., family planning and sexually transmitted disease or university health clinic patients). These evaluations found prevalence of HPV ranging from 14% to 90%, with similar peak prevalence in young adults (*26*,*27*). Although most information on HPV epidemiology is derived from studies of cervical infection in women, there are also studies on anogenital HPV infection in males (*28*,*29*). A study among men aged 18–70 years seeking information about sexually transmitted disease testing from Brazil, Mexico, and the United States determined that genital HPV prevalence ranged from 52% to 69% by country, with no consistent variation by age (*28*).

Studies of incident infections demonstrate that first HPV infection occurs within a few years of becoming sexually active. In a prospective study of women attending university in the United States, the cumulative probability of incident infection was 38.9% by 24 months after first sexual intercourse (*30*). Of all HPV types, new detection of HPV 16 was highest (10.4%); new detection of HPV 18 was 4.1% (*30*). Detection of HPV DNA is the best indication of infection but does not provide information on persons who were infected but cleared the HPV infection. Seroprevalence data provide an estimate of cumulative exposure but also will be an underestimate because not all persons with natural HPV infection develop or maintain detectable antibodies. NHANES 2003–2004 data indicate that seroprevalence of HPV 6, 11, 16, or 18 among females reached 42% by age 30–39 years (*31*). The cumulative incidence of HPV infection among men also is high. In a prospective study of men attending university in the United States, the cumulative probability of incident infection at 24 months after study enrollment was 62.4% (*32*). In contrast to women, for whom the risk for HPV acquisition increases with age through the early 20s and then decreases, studies have demonstrated that incidence among men is relatively constant over a wide age range (*33*).

Transmission and Natural History

Genital HPV infection is transmitted primarily by genital contact, usually through sexual intercourse but also through other intimate contact (e.g., oral-genital or genital-genital) (*30*,*34*–*37*). Nonsexual routes of genital HPV transmission are less common and can include intrapartum transmission from mother to infant (*38*).

Most data on natural history of HPV are obtained from studies of cervical infection. 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) (*39*–*44*). However, even persons with one lifetime sex partner are at risk for infection. One study found that HPV prevalence among women aged 18–25 years was 14.3% for those with one lifetime sex partner, 22.3% for those with two lifetime partners, and 31.5% for those with three or more lifetime partners (*44*). Additional risk factors include sexual behavior of the partner (*30*) and immune status (*45*,*46*). Transmission is very common between sex partners, and likely more frequent from females to males than from males to females (*36*).

Most HPV infections are transient and asymptomatic and cause no clinical problems; 70% of persons with new cervical HPV infection will clear the infection within 1 year, and approximately 90% within 2 years (*39*,*47*–*49*). The median duration of new infections is about 8 months for genital infection among both females and males (*33*,*39*,*48*,*50*–*52*). Oral HPV infection is much less common than genital infection (*53*), but time to clearance appears to be similar (*54*). Immunocompromised persons, such as those with human immunodeficiency virus (HIV), have higher rates of HPV acquisition and progression to disease (*55*).

The risk for persistence and progression to cancer precursor lesions varies by HPV type as well as host factors. HPV 16 is more likely to persist and progress to cancer than other high-risk HPV types (*52*,*56*). The usual time between initial HPV infection and development of cervical cancer is decades but more rapid progression has occurred. Many aspects of the natural history of HPV are poorly understood, including the role and duration of naturally acquired immunity after HPV infection.

Clinical Sequelae of HPV Infection

Cancers Associated with HPV

Persistent infection with oncogenic HPV types has a causal role in nearly all cervical cancers and in many vulvar, vaginal, penile, anal, and oropharyngeal cancers (*57*). On the basis of data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program and CDC's National Program of Cancer Registries (NPCR), the burden of HPV-associated cancers in the United States has been estimated (*58*).

Because cancer registries typically do not capture information on HPV, the number of HPV-attributable cancers was estimated by multiplying the number of cancers at each body site (HPV-associated) by the percentage attributable to HPV, based on genotyping studies (*59*–*64*). From 2006 to 2010, on average, 33,160 HPV-associated cancers were diagnosed in the United States, including 20,589 (62%) among females and 12,571 (38%) among males. Approximately 26,900 new cancers at these body sites were attributable to HPV, including 17,600 (65%) among females and 9,300 (35%) among males. Cervical and oropharyngeal cancers were the most common with an estimated 10,400 cervical cancers and 9,000 oropharyngeal cancers (7,200 [80%] among men and 1,800 [20%] among women). Among these six cancers, approximately 17,500 were attributable to HPV16/18 (5,900 [34%] among men and 11,600 [66%] among women) (Table 2).

Data from nine cancer registries in the SEER program have been analyzed to obtain long-term trends of invasive HPV-associated cancers and their precursors from 1978 through 2007 (*65*), and data from 42 NPCR/SEER cancer registries that cover a larger percentage of the U.S. population have been analyzed to obtain trends of invasive HPV-associated cancers from 2000 through 2009 (*66*).

Cervical Precancers and Cancer

The only HPV-associated cancer for which screening is recommended is cervical cancer (*67*,*68*). Cervical cancer screening is based on exfoliated cytology (Pap test) with clinical HPV testing in appropriate settings (see Cervical Cancer Screening). Abnormalities detected in screening require follow-up, and diagnosis is based on histology of the tissue sample. Terminology for histologic outcomes of squamous precursor lesions is changing from grades 1–3 of cervical intraepithelial neoplasia (CIN) to the same terminology that is used for cytological abnormalities: low- or high-grade squamous intraepithelial lesions (LSIL and HSIL, respectively) (*69*). HSIL is considered a cancer precursor that requires treatment whereas LSIL generally clears without treatment. Precursors of glandular or adenocarcinomas are designated adenocarcinoma in situ (AIS). These lesions are detected less readily by Pap test because of their endocervical location. AIS also is considered a cancer precursor that requires treatment. The CIN terminology continues to be used widely and conveys the spectrum of changes from those that are clearly low grade (CIN1) to those that are clearly high grade (CIN3). The CIN2 lesions represent an intermediate group that includes lesions that could be grouped into either low- or high-grade lesions (*69*). Most LSIL, HSIL, and AIS lesions are HPV-associated, but the type distribution changes with severity of the abnormality; high-risk types, particularly HPV 16, increase in frequency with severity of lesion. In meta-analyses, HPV prevalence was 12% (HPV 16 accounting for 20%) in women with normal cytology, 52% (HPV 16 accounting for 23%) in those with equivocal cytology, and 76% and 85%, respectively, in those with LSIL and HSIL cytology. Among histological specimens, HPV prevalence increased from 73% among CIN1 lesions to 93% among CIN3 lesions (*70*).

On the basis of a combination of natural history studies and HPV molecular analyses, essentially all cervical cancers are thought to be attributable to HPV (*57*). A 2011 meta-analysis of studies using sensitive PCR methods reported HPV detection in 90% of cervical cancers worldwide (*71*). HPV 16 and 18 were the most common types, detected in approximately 70% of cervical cancers (*9*,*71*). The prevalence of other types varies somewhat worldwide, but the next-most-frequent types detected were HPV 31, 33, 45, 52, and 58. A U.S. study found that HPV was detected in 91% of cervical cancers (51% HPV 16, 16% HPV 18, and 24% other oncogenic and rare types) (*62*).

Beyond high-risk HPV persistence, additional independent risk factors for cervical precancer and cancer include cigarette smoking, oral contraceptive use, and higher parity (*72*–*74*). In the United States, cervical cancer cases and deaths have decreased substantially since the 1950s (*75*). Racial/ethnic and geographic disparities remain, with non-Hispanic black and Hispanic women having higher cervical cancer incidence and mortality; rates of cervical cancer also are higher in the southern states. Most disparities are thought to be attributable to differential access to both screening and follow-up after an abnormal cervical cancer screening result (*76*).

Vulvar and Vaginal Precancers and Cancer

Worldwide studies report detection of HPV in 85% of vulvar intraepithelial neoplasia grade 2 or 3 (VIN2/3), and 40% of invasive vulvar cancer (*77*). HPV 16 is the most frequent type detected. In the United States, HPV was detected in 69% of invasive vulvar cancer and 97% of VIN3, with HPV 16 detected in 49% of invasive cancers and 81% of VIN3 (*61*). Since the 1970s, the incidence of pre-invasive vulvar cancer in the United States has increased at a faster rate than has invasive vulvar cancer (*65*). Recent data indicate that rates of invasive vulvar cancer are increasing among both white and black women (*66*).

Worldwide, 90% of vaginal intraepithelial neoplasia grade 2 or 3 (VaIN2/3) and 70% of invasive vaginal cancers have been

TABLE 2. Average annual number and percentage of cancer cases attributable to human papillomavirus and to HPV 16 and HPV 18, by anatomic site and sex — United States, 2006–2010.

	Average no. of cancers per year in sites where HPV is often found (HPV-associated cancers)*			Cancers attributable to any HPV				Cancers attributable to HPV 16/18			
					Average no.†				Average no.†		
Anatomic site	Male	Female	Both sexes	%	Male	Female	Both sexes	%	Male	Female	Both sexes
Cervix	0	11,422	11,422	91§	0	10,400	10,400	67	0	7,000	7,000
Anus	1,549	2,821	4,370	91	1,400	2,600	4,000	80	1,100	2,100	3,200
Oropharynx	9,974	2,443	12,417	72	7,200	1,800	9,000	63	4,500	1,100	5,600
Penis	1,048	0	1,048	63	700	0	700	48	300	0	300
Vagina	0	735	735	75	0	600	600	55	0	300	300
Vulva	0	3,168	3,168	69	0	2,200	2,200	49	0	1,100	1,100
Total	**12,571**	**20,589**	**33,160**		**9,300**	**17,600**	**26,900**		**5,900**	**11,600**	**17,500**

Abbreviation: HPV = human papillomavirus.

* **Sources:** Data come from population-based cancer registries that participate in the National Program of Cancer Registries and/or the Surveillance, Epidemiology, and End Results Program, and meet criteria for high data quality. Cancer Registry Data are from all states meeting USCS publication criteria (http://www.cdc.gov/cancer/npcr/uscs/technical_notes/criteria.htm) for all years 2006–2010 and cover approximately 94.8% of the US population. In order to determine those cancers most likely to be HPV-associated, the following additional criteria were applied to the NPCR/SEER data: all cancers were microscopically confirmed. Cervical cancers were limited by histology to carcinomas only (ICD-O-3 histology codes 8010–8671, 8940–8941). All other cancer sites were limited by histology to squamous cell carcinomas only (ICD-O-3 histology codes 8050–8084,8120-8131). Oropharyngeal cancers were defined as having the following ICD-O-3 site codes: 19, 24, 28, 90–91, 98–99, 102, 108–109, 140, 142, and 148.

† The estimated number of HPV-attributable or HPV 16/18-attributable cancers was calculated by multiplying the HPV-associated cancer counts by the percentage of each cancer attributable to HPV or HPV16/18. Estimates rounded to the nearest 100.

§ Although HPV is accepted to be a necessary factor in the causal pathway to invasive cervical cancer, HPV is not always detected in tumor specimens from women who receive a diagnosis of invasive cervical cancer due to a variety of reasons: including misclassification of tissue specimens as cervix, quality of tissue specimens, assay sensitivity, and a small proportion of HPV-negative, cervical cancers.

demonstrated to be HPV DNA-positive (*77*). In a U.S. study, 75% of invasive vaginal cancer cases were positive for HPV; HPV 16 was the most common type detected (55%) (*64*). The incidence of vaginal cancer has remained stable in the United States. Vaginal cancer rates have been highest among non-Hispanic black women; the most recent data show the rate declining among this group (*65*,*66*).

Anal Precancers and Cancer

Anal intraepithelial neoplasia (AIN) grade 2/3 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 cervical disease (*51*). Worldwide, a meta-analysis reported HPV in 84% of anal cancers, but HPV prevalence was higher in AIN2/3 (94%) (*77*). In the United States, 91% of anal cancers have been found to be positive for HPV, with HPV 16 being the most common type detected (77%) (*59*).

Men who have sex with men (MSM) and persons who have HIV infection are at higher risk for anal precancer and cancer (*29*,*78*,*79*). Although the burden of anal cancer and precancers is substantial, data are insufficient to recommend routine anal cancer screening with anal cytology in HIV-infected persons or HIV-negative MSM (*29*,*80*). More evidence is needed concerning the natural history of anal intraepithelial neoplasia, the best screening methods and target populations, and safety and response to treatments before routine screening can be recommended (*80*). Some clinical centers perform anal cytology to screen for anal cancer among high-risk populations (e.g., HIV-infected persons and MSM), followed by high-resolution anoscopy for those with abnormal cytologic results. Rates of AIN3 have risen more rapidly among men than among women (*65*). This increase could be attributable to true increases or more aggressive screening among MSM in certain areas of the country, facilitating diagnosis (*81*). Both long- and short-term trends indicate that invasive anal cancer has increased at a steady rate among both males and females and among persons in almost every racial/ethnic group (*65*,*66*).

Oropharyngeal Cancer

Some oropharyngeal cancers are attributable to HPV. Although tobacco smoking, tobacco chewing, and alcohol are strongly associated with cancers of the oropharynx, substantial evidence indicates a causal association between HPV infection and oropharyngeal cancers (*57*,*82*). Previous studies reported that worldwide, HPV DNA detection in oropharyngeal cancers varies substantially (range: 13%–56%) (*57*,*83*). HPV 16 is detected in the majority of HPV-attributable cancers (*57*,*83*). A recent U.S. study reported that approximately 72% of oropharyngeal cancers were positive for HPV; 61% had HPV 16 (*63*). By anatomic oropharyngeal location, 80% of tonsillar and 70% of base of tongue cancers were positive for one of 14 high-risk HPV types. Prevalence of HPV 16/18 in these cancers was higher in males than females, and lower in non-Hispanic blacks than in other racial/ethnic groups. Trends for oropharyngeal cancer are limited to invasive cancer because no pre-invasive lesion has been established for oropharyngeal cancer. In the United States, oropharyngeal cancer rates have increased for males since the 1970s (*65*) and for females from 2000 through 2009 (*66*).

Penile Cancer

Penile cancer is extremely rare. Worldwide, HPV has been associated with 40%–50% of penile squamous cell cancers (*57*,*84*). Among HPV-positive penile cancers, HPV 16 has been detected in a large portion (*57*,*84*). A U.S. study reported HPV prevalence of 63%, with HPV 16 detected in 46% of all cases (*60*). Differences in detection found among studies have been attributed to geographic variations or differences in sampling and testing (*84*). Besides HPV, independent risk factors for penile cancer include cigarette smoking and lack of circumcision (*85*). In the United States, rates of invasive penile cancer have declined since the late 1970s (*85*) with stable rates from 2000 through 2009 (*66*).

Anogenital Warts

All anogenital warts are caused by HPV, and >90% are associated with HPV 6 and 11 (*4*,*86*). The average time to development of new anogenital warts following HPV infection has ranged in studies from a few months to years (*86*–*89*). Anogenital warts might regress, grow larger, or remain the same. Recurrence of anogenital warts is common (approximately 30%), whether clearance occurs spontaneously or following treatment (*90*). Genital warts occurring among HIV-infected persons often require longer courses of treatment (*80*).

Anogenital warts are not reported routinely in the United States. On the basis of 2004 health claims data in the United States, the annual incidence of genital warts was 1.2/1000 females and 1.1/1000 males, and highest in females aged 20–24 years and males aged 25–29 years (*91*). Anogenital warts are associated with psychosocial reactions, including increased anxiety and depression, and can have a substantial negative impact on personal relationships (*92*,*93*).

Recurrent Respiratory Papillomatosis

Infection with low-risk HPV types, primarily types 6 or 11, can cause recurrent respiratory papillomatosis, a rare disease that is characterized by recurrent warts or papillomas in the upper respiratory tract, particularly the larynx. Recurrent respiratory papillomavirus (RRP) is divided into juvenile onset (JORRP) and adult onset forms based on age at presentation. JORRP, generally defined as onset before age 18 years, is believed to result from vertical transmission of HPV from mother to infant during delivery, although the median age of diagnosis is 3.1 years (*94*). A multicenter registry of JORRP in the United States, including 22 centers, collected data during 1996–2002 and demonstrated that although the clinical course of JORRP is variable, it is associated with extensive morbidity, requiring a median of 4.3 annual surgeries to remove warts and maintain an open airway (*94*). Estimates of the incidence of JORRP are relatively imprecise but range from 0.12–2.1 cases per 100,000 children aged <18 years in two U.S. cities (*95*). The prevalence, incidence, and disease course of adult onset RRP are less clear.

Prevention (Other Than Vaccine), Cervical Cancer Screening, and Treatment

Prevention of Sexual Transmission

Abstaining from sexual activity (i.e., refraining from any genital contact with another person) is the surest way to prevent genital HPV infection. Persons also can lower their chances of becoming infected with HPV by being in a monogamous relationship with one partner, limiting their number of sex partners, and choosing a partner who has had no or few previous sex partners. However, even persons with only one lifetime sex partner can be infected with HPV. Consistent and correct condom use can reduce the risk for HPV and HPV-associated diseases (e.g., genital warts and cervical cancer). A limited number of prospective studies have been conducted evaluating male condom use and HPV; one prospective study among newly sexually active women attending university demonstrated a 70% reduction in HPV infection when their partners used condoms consistently and correctly (*96*). Randomized clinical trials of male circumcision demonstrate a lower risk of HPV infection among circumcised males as well as among their female partners (*97*–*99*). Neither routine surveillance for HPV infection nor partner notification is useful for HPV prevention. Genital HPV infection is so prevalent that most partners of HPV-infected persons have already acquired HPV themselves (*80*).

Cervical Cancer Screening

Cervical cancer screening does not prevent HPV infection, but can secondarily prevent most cervical cancer cases and deaths if women with abnormal screening results receive appropriate follow-up and treatment. In the United States, cervical cancer screening recommendations were revised in 2012 after the U.S. Preventive Services Task Force (USPSTF) and a multidisciplinary group that included representatives of the American Cancer Society (ACS), American Society for Colposcopy and Cervical Pathology (ASCCP), American Society for Clinical Pathology (ASCP), and the American College of Obstetrics and Gynecology (ACOG) reviewed new evidence (*67*,*68*,*100*). Since 2012, all of these organizations recommend that screening with cervical cytology (Pap test; conventional or liquid-based) should begin at age 21 years. Women aged 21–65 years should be screened with a Pap test every 3 years. For women aged 30–65 years who want to lengthen the screening interval, screening can be performed with a combination of cytology and HPV testing ("co-testing") every 5 years. "Co-testing" in this age group every 5 years is preferred by ACS, ASCCP, and ASCP. In 2014, FDA approved one clinical HPV test for primary screening, but there are no national recommendations for use of this test for primary screening (*21*).

In the United States, cervical cancer screening programs have reduced the number of cervical cancer cases and deaths (*67*,*68*,*75*). The availability and use of HPV4 and HPV2 does not eliminate the need for cervical cancer screening in the United States because not all HPV types that cause cervical cancer are prevented by either vaccine. Screening strategies in the United States will continue to be reviewed and evaluated as vaccination coverage increases and further postlicensure monitoring data become available (*67*).

Treatment

There is no treatment for HPV infections. Only HPV-associated lesions including genital warts, RRP, precancers, and cancers are treated (*101–103*). Recommended treatments vary depending on the diagnosis, size, and location of the lesion. Local treatment of lesions might not eradicate all HPV containing cells fully; whether available therapies for HPV-associated lesions reduce infectiousness is unclear.

Health-Care and Research Laboratory Workers

For this report, data were reviewed on potential risks to health-care and research laboratory workers. Some HPV-associated conditions (including anogenital and oral warts, anogenital intraepithelial neoplasias [e.g., CIN], and recurrent respiratory papillomatosis) are treated with laser or electrosurgical procedures. These procedures should be performed in an appropriately ventilated room using standard precautions (*104*) and local exhaust ventilation (e.g., smoke evacuator) (*105*). Workers in HPV research laboratories handling wild-type virus or "quasi virions" might be at risk of acquiring HPV from occupational exposures (*106*). In the laboratory setting, proper infection control should be instituted including, at minimum, biosafety level 2 (BSL-2). Whether HPV vaccination would be of benefit in these settings is unclear because no data exist on transmission risk or vaccine efficacy.

HPV Vaccines and Evaluation

HPV Vaccine Composition

Two HPV vaccines are licensed for use in the United States (*10*,*11*) (Table 3). Quadrivalent HPV vaccine (Gardasil, produced by Merck and Co, Inc., Whitehouse Station, New Jersey) is licensed for use in females and males aged 9 through 26 years. Bivalent HPV vaccine (Cervarix, produced by GlaxoSmithKline, Rixensart, Belgium) is licensed for use in females aged 9 through 25 years. Both vaccines are composed of type-specific HPV L1 protein, the major capsid protein of HPV. Expression of the L1 protein using recombinant DNA technology produces VLPs. The vaccines are noninfectious.

Quadrivalent vaccine (HPV4) contains HPV 6, 11, 16, and 18 L1 VLPs. The L1 protein is expressed in *Saccharomyces cerevisiae* (baker's yeast) and self-assembles 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 (AAHS).

Bivalent vaccine (HPV2) contains HPV 16 and 18 L1 VLPs. The L1 protein is expressed in *Trichoplusia ni* Hi-5 insect cells and self-assembles into conformationally intact, noninfectious VLPs. Each 0.5-mL dose contains 20 μg HPV 16 L1 protein and 20 μg HPV 18 L1 protein. The AS04 adjuvant contains 500 μg aluminum hydroxide and 50 μg 3-O-desacyl-4' monophosphoryl lipid A (MPL).

Evaluation of Efficacy of HPV Vaccines

The efficacy of HPV vaccines has been evaluated by using a variety of endpoints; these include HPV-associated disease and persistent infection. The primary endpoint in the phase III trials, and the basis for licensure in females for both vaccines, was incident HPV 16- and 18-related CIN2/3 or AIS (CIN2+) (*10*,*11*). These endpoints served as a surrogate marker for cervical cancer. Studies using invasive cervical cancer as an endpoint are not feasible because the standard of care is to screen for and treat CIN2+ lesions to prevent invasive cervical cancer. Furthermore, the time from acquisition of infection to the development of cancer can exceed 20 years. VaIN2/3, VIN2/3 and AIN2/3 were used as endpoints and surrogate markers in some trials for vaginal, vulvar and anal cancers.

In the phase III efficacy trials, participants were enrolled without regard to HPV DNA or antibody status (*10*,*11*). Participants were tested for HPV DNA by PCR to determine current infection and for antibody to vaccine types to evaluate past infection but were not excluded from the trials. Several

TABLE 3. Characteristics of quadrivalent and bivalent human papillomavirus (HPV) vaccines

Characteristic	Quadrivalent (HPV4)*	Bivalent (HPV2)†
Vaccine composition	20 μg HPV 6 40 μg HPV 11 40 μg HPV 16 20 μg HPV 18	20 μg HPV 16 20 μg HPV 18
Manufacturing	*Saccharomyces cerevisiae* (Baker's yeast) - expressing L1§	*Trichoplusia ni* insect cell line infected with L1 encoding recombinant baculovirus
Adjuvant	AAHS: 225 μg amorphous aluminum hydroxyphosphate sulfate	AS04: 500 μg aluminum hydroxide 50 μg 3-O-desacyl-4′ monophosphoryl lipid A
Preservatives	None	None
Volume per dose	0.5 ml	0.5 ml
Other content	Sodium chloride, L-histidine, polysorbate 80, sodium borate, and water for injection	Sodium chloride and sodium dihydrogen phosphate dihydrate, and water for injection
Storage	Store refrigerated at 2° to 8°C (35° to 46°F).¶ Do not freeze.	Store refrigerated at 2° to 8°C (35° to 46°F).¶ Do not freeze.
Administration	Intramuscular	Intramuscular

* Package insert available at http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM111263.pdf
† Package insert available at http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM186981.pdf.
§ The major capsid protein of HPV.
¶ **Source:** CDC. General recommendations on immunization—recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2011;60(No. RR-2).

different analyses have been conducted. The main analyses were restricted to participants who received all 3 doses, had no evidence of current or past infection with the relevant vaccine HPV type through 1 month after the third dose (month 7), and did not deviate from protocol. In these according-to-protocol (ATP) or per-protocol analyses, cases were counted starting 1 month after the third dose. The intention-to-treat population (ITT) or total vaccinated cohort (TVC) included all participants regardless of baseline HPV status, and cases were counted starting 1 day after the first dose. Efficacy was lower in the ITT compared with the ATP or per-protocol analyses because some participants had prevalent infection with a vaccine type HPV at the time of study enrollment and the vaccines do not prevent progression of infection to disease among those already infected. Other populations analyzed included the unrestricted susceptible population (or total vaccinated-naive population) which included only participants who were negative to all HPV types evaluated and received at least 1 dose.

Protection against oncogenic types other than HPV 16 and 18 (cross protection) also has been evaluated in post hoc analyses (*107–109*). Types evaluated include those related to HPV 16 (types in the alpha 9 species) and HPV 18 (types in the alpha 7 species). Both infection and disease endpoints have been assessed. Evaluation of cross-protection against disease endpoints is complicated because more than one type can be detected in a lesion, making it difficult to determine the causal HPV type.

Evaluation of Serologic Response to Vaccination

Serologic assays used in the HPV4 and HPV2 vaccine trials differed. The competitive Luminex immunoassay (cLIA) was used in the HPV4 trials, and an enzyme linked immunosorbant assay (ELISA) was used in the HPV2 trials (*107*,*110*,*111*). These assays measure different subsets of antibody induced by vaccination, making comparison across vaccine trials difficult. The cLIA measures all antibody classes but detects antibodies against a single neutralizing epitope for each HPV type. The ELISA measures only IgG but detects antibodies against all conformational epitopes for each HPV type. Antibody titers cannot be compared directly between assays, or across HPV types for a given assay. Some studies that compared the two vaccines directly by using the same serologic assay found higher HPV 16 and 18 antibody titers among vaccinees who received HPV2 compared with HPV4 (*112*). There is no known serologic correlative of immunity or minimum titer determined to be protective. The high efficacy found in the clinical trials to date has precluded identification of a minimum protective antibody titer.

Quadrivalent HPV Vaccine (HPV4)

HPV4 Efficacy

Females Aged 16–26 years

Three randomized, double-blind, placebo-controlled clinical trials evaluated the efficacy of HPV4 for prevention of HPV-associated disease: a phase II trial (protocol 007) among females aged 16–23 years (*113*) and two phase III trials (protocols 013 and 015) among females aged 16–24 and 15–26 years, respectively (*114*,*115*). Data from these trials and data from a randomized, placebo-controlled phase II trial of monovalent HPV 16 vaccine (*116*,*117*) were included in the FDA Biologics

License Application (*11*). More than 20,000 females were enrolled in these four studies and received either vaccine or placebo. Interim analysis of the phase III trials showed high efficacy (*114*,*115*). In the end-of-study per-protocol analysis (median follow-up time of 42 months after the first dose), including data from phase II (protocol 007) and phase III trials (protocols 013 and 015), efficacy against HPV 6-, 11-, 16-, and 18-related CIN2+ was 98.2% (Table 4) (*118*). Statistically significant efficacy was demonstrated individually against HPV 16- and HPV 18-related lesions. Per-protocol efficacy for prevention of vaccine type-related VIN2/3 or VaIN2/3 was 100%. In the phase III trials, per-protocol efficacy against HPV 6- and 11-related genital warts was 98.9% (*119*). In the ITT analyses, efficacy against HPV 6-, 11-, 16-, and 18-related CIN2+ was 51.5% (95% confidence interval [CI] = 40.6–60.6), against HPV 6-, 11-, 16-, and 18-related VIN2/3 or VaIN2/3 was 79.0% (95% CI = 56.4–91.0) (*118*), and against HPV 6- and 11-related genital warts was 79.3% (95% CI = 72.7–84.5) (*119*).

Efficacy for prevention of persistent infection was evaluated in phase II efficacy trials. HPV 16 persistent infection was the primary endpoint for the phase II monovalent HPV vaccine trial; efficacy for prevention of persistent infection (defined as a vaccine type detected by PCR at 2 or more visits at least 4 months apart) was 100% (*116*,*117*). In the phase II HPV4 trial, efficacy for prevention of persistent HPV 6, 11, 16, and 18 infection was 89% (95% CI = 70–97); three of four cases in the vaccine group were detected at last study visit with no documented persistence (*113*).

In the phase III trials, among females aged 16–26 years who had HPV vaccine type DNA detected at study enrollment (either seropositive or seronegative), there was no efficacy against progression to disease or impact on clearance of infection of that type (*114*,*120*). However, HPV4 had 100% efficacy for prevention of CIN2+ attributable to types not already acquired (*120*). Among persons seropositive to the relevant HPV type but HPV DNA-negative, too few cases were detected to evaluate efficacy, but disease incidence was low and all cases occurred in the placebo group.

Males Aged 16–26 Years

Efficacy of HPV4 among males was evaluated in one phase III trial, including 4,065 males aged 16–26 years (*121*). In the end-of-study analysis (median follow-up time of 35 months after the first dose), per-protocol efficacy for prevention of HPV 6-, 11-, 16-, and 18-related genital warts was 89.4% (Table 5). In the ITT analysis, efficacy was 67.2% (95% CI = 47.3–80.3). As in females, no efficacy was observed among males who were infected with the respective HPV type

TABLE 4. Per-protocol efficacy for prevention of human papillomavirus vaccine-type disease outcomes among females in trials of the bivalent and quadrivalent human papillomavirus vaccines, end-of-study analyses

Vaccine/Endpoint related type	Vaccine		Control		Vaccine efficacy	
	No.	Cases	No.	Cases	%	(95% CI)
Quadrivalent vaccine*						
CIN2/3 or AIS†						
HPV 6, 11, 16, 18	7,864	2	7,865	110	98.2	(93.3–99.8)
HPV 16	6,647	2	6,455	81	97.6	(91.1–99.7)
HPV 18	7,382	0	7,316	29	100.0	(86.6–100.0)
VIN/VaIN2/3†						
HPV 6, 11, 16, 18	7,900	0	7,902	23	100.0	(82.6–100.0)
HPV 16	6,654	0	6,467	17	100.0	(76.5–100.0)
HPV 18	7,414	0	7,343	2	100.0	(<0–100.0)
Genital warts§						
HPV 6 and/or 11	6,718	2	6,647	186	98.9	(96.1–99.9)
Bivalent vaccine¶						
CIN2/3 or AIS						
HPV 16 and/or 18	7,338	5	7,305	97	94.9	(87.7–98.4)
HPV 16	6,296	2	6,160	81	97.6	(91.0–99.7)
HPV 18	6,789	3	6,739	23	87.1	(57.2–97.5)

Abbreviations: AIS = adenocarcinoma in situ; CI = confidence interval; CIN = cervical intraepithelial neoplasia; HPV = human papillomavirus; VIN = vulvar intraepithelial neoplasia; VaIN = vaginal intraepithelial neoplasia.

* Quadrivalent HPV vaccine: combined analysis of three Phase II and Phase III trials. Per-protocol efficacy population included females aged 16–26 years, HPV DNA negative for the respective HPV type at day 1 and month 6, seronegative at day 1, with case counting started day 1 after third dose.

† **Source:** Kjær SK, Sigurdsson K, Iversen OE, et al. A pooled analysis of continued prophylactic efficacy of quadrivalent human papillomavirus (Types 6/11/16/18) vaccine against high-grade cervical and external genital lesions. Cancer Prev Res 2009;2:868–78.

§ **Source:** Dillner J, Kjær SK, Wheeler CM, et al. Four year efficacy of prophylactic human papillomavirus quadrivalent vaccine against low grade cervical, vulvar, and vaginal intraepithelial neoplasia and anogenital warts: randomised controlled trial. BMJ 2010;341:c3493.

¶ Bivalent HPV vaccine: phase III trial. According to protocol, efficacy population included females aged 15–25 years, HPV DNA negative for the respective HPV type at day 1 and month 6, seronegative for the respective type at day 1 and had normal or low grade cytology, with case counting started day 1 after third dose. **Source:** Lehtinen M, Paavonen J, Wheeler CM, et al. Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. Lancet Oncol 2012;13:89–99;Suppl Appendix, Table 3.

TABLE 5. Per-protocol efficacy of quadrivalent human papillomavirus vaccine for prevention of HPV 6-, 11-, 16-, and 18-related disease among males aged 16–26 years*

	Vaccine		Control		Vaccine efficacy	
Endpoint	No.	Cases	No.	Cases	%	(95% CI)
Genital warts[†]	1,397	3	1,408	28	89.4	(65.5–97.9)
PIN[†]	1,397	0	1,408	3	100.0	(-141.2–100.0)
AIN 1/2/3[§]	194	5	208	24	77.5	(39.6–93.3)
AIN2/3[§]	194	3	208	13	74.9	(8.8–95.4)

Abbreviations: AIN = anal intraepithelial neoplasia; CI = confidence interval; HPV = human papillomavirus; PIN = penile/perineal/perianal intraepithelial neoplasias.

* Per-protocol population included males who received all 3 vaccine doses, were seronegative at day 1 and DNA negative at day 1 through month 7 to the respective HPV type, with case counting started after month 7. Median duration of follow-up was 2.9 years.

[†] **Source:** Giuliano A, Palefsky JM, Goldstone S, et al. Efficacy of quadrivalent HPV vaccine against HPV infection and disease in males. N Engl J Med 2011;364:401–11.

[§] Efficacy for AIN studied in men who have sex with men. **Source:** Palefsky J, Giuliano AR, Goldstone S, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. N Engl J Med 2011;365:1576–85.

at baseline. Although grade 1, 2, and 3 penile/perineal/perianal intraepithelial neoplasias were evaluated, too few cases were observed to evaluate efficacy.

A substudy of the phase III efficacy trial included 602 MSM; outcomes were AIN grades 1, 2, or 3 (AIN1/2/3), AIN2/3 and anal warts (Table 5) (*122*). Per-protocol efficacy for prevention of HPV 6-, 11-, 16-, and 18-related AIN2/3 was 74.9% (95% CI = 8.8–95.4) and for prevention of HPV 6-, 11-, 16-, and 18-related anal warts was 100% (95% CI = 8.2–100). In the ITT analyses, efficacy for prevention of vaccine type AIN2/3 was 54.2% (95% CI = 18.0–75.3) and for anal warts was 57.2% (95% CI = 15.9–79.5).

Efficacy for prevention of 6-month persistent HPV 6, 11, 16, or 18 infection was a prespecified secondary endpoint for the phase III trials among males and for the substudy in MSM. Per-protocol efficacy for prevention of 6-month persistent vaccine type genital or perianal HPV infection was 85.6% (97.5% CI = 73.4–92.9). In the MSM substudy, per-protocol efficacy for prevention of anal 6-month persistent vaccine type HPV infection was 94.9% (95% CI = 80.4–99.4).

Duration of Protection

In the phase III trials, females aged 16–26 years were followed for a mean of 42 months after dose one (*118*). The longest follow-up for HPV4 is from the phase II trial (protocol 007): a subset of participants (n = 241) were followed for 60 months after dose one. Efficacy against vaccine type persistent infection or disease was 95.8% (95% CI = 83.8–99.5) and efficacy against vaccine type-related CIN or external genital lesions was 100% (95% CI = 12.4–100) (*123*). Follow-up through 8.5 years in the monovalent HPV 16 vaccine trial showed high efficacy and no decline in protection (*124*).

Additional data on duration of protection will be available from follow-up of approximately 5,500 females enrolled in one of the phase III HPV4 trials in the Nordic countries. Half of the females had received vaccine while the other half had received placebo in the randomized clinical trial and were then vaccinated after the first 4 years of the study. These females will be followed for at least 10–14 years after vaccination; serologic testing will be conducted 9 and 14 years after vaccination among the original group of vaccine recipients, and Pap testing results will be linked to pathology specimens for sectioning and HPV DNA testing by PCR. Data from follow-up through 7 to 8 years showed no evidence of waning protection (*125*). Males in the phase III trial will be followed for 10 years after vaccination. In addition, adolescent girls and boys who were vaccinated at age 10–15 years in an immunogenicity study (see HPV4 Immunogenicity) are being followed as they become sexually active. Through 8 years of follow-up, no cases of disease in females or infection in males related to HPV 6, 11, 16, or 18 were observed (*126*). This study will continue to follow participants through at least 10 years after vaccination.

Evaluation of Protection Against Nonvaccine Types

Protection against infection and CIN2+ attributable to nonvaccine types was evaluated for HPV4. In prespecified analyses among females without evidence of current or previous infection with 14 HPV types at baseline in the phase III trials (protocols 013 and 015), efficacy against CIN2+ associated with any of five nonvaccine types in the alpha 9 species (HPV 31, 33, 35, 52, and 58) was 35.4% (95% CI = 4.4–56.8). Efficacy against 6-month persistent infection with HPV 31 (46.2%; 95% CI = 15.3–66.4) and HPV 31-related CIN2+ (70.0%; 95% CI = 32.1, 88.2) were observed (*109*). No protection was demonstrated against any other individual nonvaccine HPV type. Analyses did not exclude lesions in which HPV 16 or 18 were also detected, making results difficult to interpret (*107*,*109*). Among males, no efficacy was observed against external genital lesions or AIN associated with any of the 10 nonvaccine types evaluated (*127*).

HPV4 Immunogenicity

Females and Males Aged 9–26 Years

Data on immunogenicity in females are available from phase II and III efficacy trials conducted among females aged 16–26 years and immunogenicity trials conducted among children and adolescents aged 9–15 years. In all studies conducted to date, more than 99% of females had an antibody response to all four HPV vaccine types 1 month after the third dose (*123*,*128*). High seropositivity rates were observed after vaccination regardless of sex, race/ethnicity, country of origin, smoking status, or body mass index (*129*). Vaccination produced antibody titers higher than those after natural infection: among females aged 16–23 years, anti-HPV 6, 11, 16, and 18 geometric mean titers (GMTs) 1 month after the third dose were higher than those observed in participants who were HPV seropositive and PCR negative at enrollment in the placebo group (*123*). Antibody titers declined over time after the third dose but plateaued by 24 months. At 36 months, HPV 16 GMTs among vaccinees remained higher than those in participants in the placebo group who were seropositive at baseline; HPV 6, 11, and 18 GMTs were similar to those seropositive in the placebo group (*113*). At 36 months, seropositivity rates in vaccinees were 94%, 96%, 100%, and 76% to HPV 6, 11, 16, and 18, respectively (*113*). In the follow-up of females in the phase II or phase III efficacy trials, there was no evidence of waning efficacy among participants who became seronegative (*130*). This suggests that loss of detectable antibody by the cLIA, seen particularly for HPV 18, is not associated with loss of protection. Data from a revaccination study in which vaccinated females were given a challenge dose of vaccine 5 years after enrollment demonstrated an augmented rise in antibody titer, consistent with immune memory (*131*).

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, suggesting a boosting of naturally acquired antibody by vaccination (*131*).

Data on immunogenicity among males are available from the phase III trial in males aged 16–26 years and immunogenicity trials among males aged 9–15 years (*128*,*132*). Among males in the efficacy trial, seroconversion rates were 97%–99% 1 month after the third dose (*132*). High seropositivity rates were observed after vaccination regardless of demographic group, but blacks had higher GMTs than whites, and heterosexual males had higher GMTs than MSM. By month 36, 89%, 94%, 98%, and 57% of males remained seropositive to HPV 6, 11, 16, and 18, respectively (*132*).

Immunogenicity trials allowed comparison of seroconversion rates and GMTs among females and males aged 9–15 years with participants in the efficacy trials (*11*,*128*). Seroconversion rates for both females and males aged 9–15 years exceeded 99% for all four vaccine types (Table 6). Among those vaccinated at age 9–15 years, GMTs 1 month after the third dose were noninferior (and 1.7- to 2.7-fold higher) to those vaccinated at age 16–26 years. At 24–36 months after vaccination, GMTs among those vaccinated at 9–15 years remained higher than among those vaccinated at age 16–26 years (*11*).

Spacing of Vaccine Doses

In prelicensure trials among females aged 16–26 years, vaccine was administered according to a 0-, 2-, and 6-month schedule. The interval between the first and second dose ranged from 6–12 weeks and the interval between the second and third dose ranged from 12–23 weeks. Variation in the interval did not diminish GMTs postvaccination. Postlicensure studies have also evaluated GMTs after longer intervals between doses including: 0, 2, and 12 months; 0, 3, and 9 months; 0, 6, and 12 months; and 0, 12, and 24 months (*133*,*134*). GMTs in schedules with longer intervals between doses were noninferior and for some schedules were higher than with the standard schedule (0, 2, 6 months).

Concomitant Administration with Other Vaccines

Seroconversion rates and GMTs after concomitant administration of HPV4 with other vaccines (including meningococcal conjugate vaccine, tetanus, diphtheria, and acellular pertussis vaccine; inactivated polio vaccine; and hepatitis B vaccine) have been evaluated (*135*). In all studies conducted to date, HPV GMTs in the co-administered group were noninferior to GMTs after administration of HPV vaccine alone. Rates of solicited and unsolicited symptoms and adverse events were similar in all study groups.

HIV-Infected Persons

Several immunogenicity studies of HPV4 in HIV-infected persons have been published, and others are ongoing (*46*). A randomized clinical trial of HPV4 found the vaccine to be safe and immunogenic in 126 HIV-infected children aged 7–12 years. Antibody titers were lower for HPV 6 and 18 compared with historic age-matched immunocompetent controls (*136*). At 18 months after the third dose, 94%–99% had antibody to HPV 6, 11 and 16; 76% had antibody to HPV 18. After a fourth dose, all children demonstrated an anamnestic response for all HPV vaccine types (*137*). A study in 109 HIV-infected males and another in 99 HIV-infected females found the vaccine to be immunogenic and well tolerated (*138*,*139*). GMTs were higher among persons on antiretroviral therapy compared with those not receiving therapy.

Efficacy and Immunogenicity Among Persons Aged >26 years

HPV4 is not licensed in the United States for use in persons aged >26 years. One randomized, double-blind, placebo-controlled trial of HPV4 was conducted in 3,819 females aged 24–45 years (*140*). In the end-of-study analysis, per-protocol efficacy against HPV 6, 11, 16, and 18 persistent infection, related CIN, or external genital lesions was 88.7% (95% CI = 78.1–94.8) (*141*). There were few CIN2+ events

TABLE 6. Geometric mean antibody titers after quadrivalent HPV vaccine among females and males aged 9–15 and 16–26 years, one month after third dose (per-protocol immunogenicity population)*

	Females aged 9–15 years				Females aged 16–26 years			
Assay (cLIA)	No.	GMT (mMU/mL)	(95% CI)	Seropositivity %	No.	GMT (mMU/mL)	(95% CI)	Seropositivity %
Anti-HPV 6	917	929	(875–987)	99.9	3,329	545	(530–560)	99.8
Anti-HPV 11	917	1,305	(1,225–1,390)	99.9	3,353	749	(726–773)	99.8
Anti-HPV 16	915	4,919	(4,557–5,309)	99.9	3,249	2,409	(2,309–2,514)	99.8
Anti-HPV 18	922	1,043	(968–1,123)	99.8	3,566	475	(459–492)	99.4
	Males aged 9–15 years				Males aged 16–26 years			
Assay (cLIA)	No.	GMT (mMU/mL)	(95% CI)	Seropositivity %	No.	GMT (mMU/mL)	(95% CI)	Seropositivity %
Anti-HPV 6	884	1,038	(963–1,117)	99.9	1,093	448	(419–479)	98.9
Anti-HPV 11	885	1,387	(1,298–1,481)	99.9	1,093	624	(588–662)	99.2
Anti-HPV 16	882	6,056	(5,601–6,549)	99.8	1,136	2,403	(2,243–2,575)	98.8
Anti-HPV 18	887	1,357	(1,249–1,475)	99.8	1,175	403	(375–433)	97.4

Abbreviations: CI = confidence interval; cLIA = competitive Luminex immunoassay; GMT = geometric mean titer; HPV = human papillomavirus; mMU, milli-Merck units.
Source: Adapted from: Food and Drug Administration. Product approval-prescribing information [Package insert]. Gardasil [human papillomavirus quadrivalent (types 6, 11, 16, and 18) vaccine, recombinant], Merck & Co, Inc. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2014. Available at http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM111263.pdf.
* The per-protocol immunogenicity population included all subjects who were not general protocol violators, received all three vaccinations within acceptable day ranges, were seronegative at day 1 and (for all subjects except those aged <16 years in the immunogenicity studies who were not tested) DNA 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.

(one case in the vaccine arm and six cases in the placebo arm of the trial). In the ITT analysis, efficacy against vaccine type-related persistent infection or disease was 47.2% (95% CI = 33.5–58.2), but efficacy was not demonstrated against CIN2+: 22.4% (95% CI = -42.5–58.3). One month after the third dose, seropositivity to HPV 6, 11, 16 and 18 was 98%, 98%, 99%, and 97%, respectively. At month 48, seropositivity was 92%, 92%, 97%, and 48%, respectively. GMTs were lower than those among females aged 16–23 years. There are no data from efficacy trials in males aged >26 years.

HPV4 Safety

Prelicensure Trials

In prelicensure trials, HPV4 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 HPV4 are available from seven clinical trials and included 18,083 persons who received HPV4, aluminum-containing control (AAHS), or saline placebo (*11*). In both the female and male study populations aged 9–26 years with detailed safety data, a larger proportion reported injection-site adverse events in the group that received HPV4 compared with AAHS control or saline placebo groups. In all three groups, pain was the most common injection site adverse event (Table 7).

Systemic clinical adverse events were reported by a similar proportion of vaccine and control/placebo groups among both females and males. Headache was most common, reported by 28.2% of females who received HPV4 and 28.4% of those who received AAHS or saline placebo; among males, 12.3% of those who received HPV4 and 11.2% of those who received AAHS or saline placebo reported headache. Overall, 4.0%–4.9% of females and 2.8%–3.0% of males who received HPV4 reported a temperature ≥100°F (≥38°C) after the first, second, or third dose. The proportions of persons reporting a serious adverse event were similar in the vaccine and placebo groups, as were the types of serious adverse event reported. Vaccine-related serious adverse events occurred in <0.1% of persons. Across all clinical studies (29,323 participants), during the course of the trials, 21 deaths (0.1%) occurred among persons in HPV4 groups and 19 (0.1%) among persons in the control or placebo groups. None of the deaths was considered to be vaccine related (*11*).

Information was collected on new medical conditions that occurred during follow-up of up to 4 years for females and 3 years for males. Overall, among females aged 9–26 years, 2.3% in the HPV4 group and 2.3% in the AAHS control or placebo groups had conditions potentially indicative of autoimmune disorders. Among males aged 9–26 years, 1.5% in the HPV4 group and 1.5% in the AAHS control or placebo groups had conditions potentially indicative of autoimmune disorders. No statistically significant differences were found between vaccine and AAHS control/placebo recipients for the incidence of the conditions (*11*).

Although HPV4 is not licensed by FDA for use among persons aged >26 years, studies among females aged 27–45 years indicate that the adverse events profile is comparable to the profile observed in those aged 9–26 years (*11*).

TABLE 7. Injection-site reactions within 5 days after receipt of quadrivalent human papillomavirus vaccine in females and males aged 9–26 years

Adverse event	Quadrivalent vaccine %	AAHS control %	Saline control %
Females	N = 5,088	N = 3,470	N = 320
Pain	83.9	75.4	48.6
Swelling	25.4	15.8	7.3
Erythema	24.7	18.4	12.1
Males	N = 3,093	N = 2,029	N = 274
Pain	61.4	50.8	41.6
Swelling	13.9	9.6	8.2
Erythema	16.7	14.1	14.5

Abbreviation: AAHS = Amorphous aluminum hydroxyphosphate sulfate.
Source: Food and Drug Administration. Product approval-prescribing information [Package insert]. Gardasil [human papillomavirus quadrivalent (types 6, 11, 16, and 18) vaccine, recombinant], Merck & Co, Inc. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2014. Available at http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM111263.pdf.

Pregnancy

The HPV4 trial protocols excluded women who were pregnant; however, 3,819 females in the trials reported at least one pregnancy (*11*). Adverse outcomes (defined as the combined numbers of spontaneous abortions, late fetal deaths, and congenital anomaly cases out of the total number of known pregnancy outcomes, excluding elective terminations), were 22.6% (446/1973) in the HPV4 group and 23.1% (460/1994) in the AAHS control or saline placebo group. A total of 45 cases of congenital anomaly in pregnancies occurred in females who received HPV4, and 34 cases occurred in females who received AAHS control or saline placebo. For pregnancies with estimated onset within 30 days of vaccination, five anomalies (all different) occurred in the vaccine group, and one occurred in the placebo group. In pregnancies with onset >30 days following vaccination, 40 cases of congenital anomaly were observed in the group that received HPV4 and 33 cases in the group that received AAHS control or saline placebo. Rates of congenital anomalies were consistent with those in surveillance registries. HPV4 has been classified as Pregnancy Category B on the basis of studies in rats showing no evidence of impaired fertility or harm to the fetus (*11*).

A registry for females inadvertently vaccinated during pregnancy was established by the manufacturer as part of its postlicensure commitment to FDA (*142*,*143*). More than 2,800 females who received vaccine within 1 month before their last menstrual period or anytime during pregnancy were enrolled in the registry (*144*). Rates of spontaneous abortions and major birth defects were not greater than those of a comparison unexposed population. The registry was terminated at the end of December 2012 with concurrence from FDA and other regulatory agencies. However, the manufacturer is still collecting information on persons inadvertently vaccinated during pregnancy. CDC will continue to monitor pregnancy outcomes through reports to the Vaccine Adverse Event Reporting System (VAERS) and through studies in the Vaccine Safety Datalink (VSD) (see Postlicensure Safety Data).

Postlicensure Safety Data

In the United States, federal agencies and vaccine manufacturers conduct independent postlicensure vaccine safety and monitoring activities. CDC monitors vaccine safety through several systems, including VAERS and VSD (*145*).

CDC and FDA established VAERS in 1990 (*146*). VAERS is a national spontaneous reporting system that accepts reports from providers and the public regarding adverse events that occur after vaccination. The system is not designed to determine whether a reported adverse event was caused by vaccination, but it does identify signals or trends that warrant further study. From June 2006 through March 2014, approximately 67 million doses of HPV4 were distributed in the United States. VAERS received a total of 25,063 adverse event reports (22,867 in females and 2,196 males) after receipt of HPV4 (*147*). Reporting among females peaked in 2008 and decreased each year thereafter (*148*). The proportion of reports to VAERS that were classified as serious (i.e., those resulting in permanent disability, hospitalization, life-threatening illnesses, or death) peaked in 2009 at 12.8% and then decreased to 7.4% in 2013 (the last full year of reporting).† Of the total HPV4 reports, 92.4% were classified as nonserious. Among the nonserious adverse events, the most commonly reported generalized symptoms in females were syncope (fainting), dizziness, nausea, headache, and fever; in males, the most commonly reported generalized symptoms were dizziness, syncope, pallor, headache, and loss of consciousness. Overall, the most commonly reported local symptoms were injection-site pain and redness. Among the 7.6% of total reports classified as serious, headache, nausea, vomiting, and fever were the most frequently reported symptoms for both males and females (CDC, unpublished data, 2014). Overall reporting of adverse events to VAERS is consistent with prelicensure clinical trial data and with the 2009 published summary of the first 2.5 years of postlicensure reporting to VAERS (*147*,*149*).

During the postlicensure period from June 2006 to March 2014, a total of 96 reports of death after receiving HPV4 were submitted to VAERS. CDC and FDA review all available information on reports of death following any vaccine, including HPV4. Among the 96 reports of death, 47 deaths were considered confirmed in that the reports included a certificate of death, autopsy report, or other medical documentation of death (*150*). Causes of the confirmed death reports included

† Additional information is available at http://www.fda.gov/safety/medwatch/howtoreport/ucm053087.htm.

bacterial meningitis, viral myocarditis, pulmonary embolism, diabetic ketoacidosis, and seizure disorder. Detailed review of every report of death following HPV4 alone or in combination with other vaccines by medical officers from CDC and FDA identified no pattern of occurrence of death with respect to time after vaccination, vaccine dose number, combination of vaccines administered, or diagnosis at death that would suggest a causal association with HPV4.

VSD is a collaboration between CDC and nine integrated health-care organizations that allows for active surveillance and research. VSD conducts evaluations of specific events that might be associated with vaccination (*151*). Data were analyzed after 600,558 doses of HPV4 had been administered to females. No statistically significant increased risks were observed for any of the prespecified endpoints including Guillain-Barré syndrome (GBS), stroke, venous thromboembolism, appendicitis, seizures, syncope, allergic reactions, and anaphylaxis (*151*) (Table 8). Studies in males are ongoing. Postlicensure studies also have been conducted by the manufacturer (*152,153*). In a general safety assessment evaluating outcomes diagnosed in emergency departments visits and hospitalizations among 189,000 females receiving at least 1 dose of HPV4, same-day syncope and skin infections in the 2 weeks after vaccination were found to be associated with HPV4. No other safety concerns were identified (*152*). In another study, rates of 16 autoimmune disorders in the vaccinated population were not increased compared with a matched population of nonvaccinated females (*153*). Postlicensure safety data for HPV4 available from other countries show a good safety profile (*154–156*). A large population-based cohort study conducted in Denmark and Sweden analyzed data on >696,000 doses of HPV4 among females. No consistent evidence supporting causal associations between exposure to HPV4 and autoimmune, neurologic conditions, and venous thromboembolism was observed (*155*). In France, a case-control study was conducted to evaluate autoimmune disorders following HPV4. Among 211 cases and 875 controls, no increased risk was observed for idiopathic thrombocytopenic purpura, central demyelination/multiple sclerosis, GBS, connective tissue disorders (including systemic lupus erythematosus, rheumatoid arthritis/juvenile arthritis), type 1 diabetes mellitus, and autoimmune thyroiditis after receipt of HPV4 (*156*).

Bivalent HPV Vaccine (HPV2)

HPV2 Efficacy

Females Aged 15–25 Years

HPV2 efficacy against CIN2+ was evaluated in two randomized, double-blind, controlled clinical trials in females aged 15–25 years, including a phase II study and a phase III trial (*157,158*). The phase III trial included 18,644 females (*158,159*). Interim analysis of the phase III trial showed high efficacy (*158*). In the end-of-study ATP analysis, efficacy against HPV 16- and 18-related CIN2+ was 94.9% (95% CI = 87.7–98.4) (Table 4) (*160*). Statistically significant efficacy was demonstrated individually against HPV 16- and HPV 18-related lesions. In the ITT analysis, efficacy against HPV 16- and 18-related CIN2+ was 60.7% (95% CI = 49.6–69.5). The end-of-study analysis also found high efficacy against CIN3 regardless of HPV type in the TVC-naïve population (*160*).

HPV2 efficacy against persistent HPV infection was evaluated. In the phase III trial, efficacy against 6-month and 12-month persistent HPV 16 or HPV 18 cervical infection in the ATP cohort was 94.3% (96.1% CI = 91.5–96.3) and 91.4% (96.1% CI = 86.1–95.0), respectively (*159*). Data on persistent infection endpoints are also available from a trial conducted in Costa Rica (*161*), a randomized, double-blind, controlled trial in 7,466 women aged 18–25 years. (Efficacy data from the Costa Rica trial were not included in the FDA Biologics License Application.) The primary endpoint was 12-month persistent HPV 16 or HPV 18 cervical infection (*161*). In the ATP analysis, efficacy against HPV 16 or HPV 18 persistent infection was 90.9% (95% CI = 82.0–95.9) and in the ITT analysis was 49.0% (95% CI = 38.1–58.1).

Among women who were HPV 16 or 18 DNA positive at enrollment into the clinical trials, either seropositive or seronegative, the vaccine had no efficacy against progression of infection to disease (*159*) or impact on clearance of infection of that HPV type (*162*). However, among participants DNA positive to one vaccine HPV type, HPV2 was found to have high efficacy (90%) for prevention of CIN2+ associated with the type for which a female was DNA negative at enrollment (*163*). Among persons seropositive to the relevant HPV type but HPV DNA negative, there were fewer cases, but efficacy was observed against CIN1 or higher grade lesions (*163*).

Efficacy against prevalent anal and oral HPV infection was evaluated in the Costa Rica trial. Although this trial was not designed to assess efficacy against oral or anal infection, and baseline infection at these anatomic sites was not determined, prevalent infection was determined at the 4-year exit study visit. There were 15 prevalent HPV 16 or 18 oral infections among the 2,924 females in the control group and one among the 2,910 females in the vaccine group; estimated efficacy was 93.3% (95% CI = 62.5–99.7) (*164*). Among females who were HPV 16/18 seronegative and DNA negative at the cervix at the time of enrollment, efficacy against anal HPV 16 or HPV 18 prevalent infection was 83.6% (95% CI = 66.7–92.8) (*165*).

TABLE 8. Observational, population-based, postlicensure quadrivalent human papillomavirus vaccine safety studies among females aged 9–26 years — United States and three other countries

System or review and country	No. of doses evaluated	Description	Methods	Findings
Vaccine Safety Datalink* USA	600,558	Large data base used for active surveillance and research; safety assessment of seven prespecified health outcomes among females vaccine recipients†	Cohort design with weekly sequential analyses of electronic medical data§	No statistically significant increase in risk for the outcomes monitored
Postmarketing commitment (to FDA)¶ USA	346,972	General assessment of safety following routine administration of HPV4 at two large managed care organizations	Self-controlled risk interval design supplemented with medical record review	HPV4 associated with syncope on the day of vaccination and skin infections in the two weeks after vaccination;** no other vaccine safety signals detected
Postmarketing commitment (to FDA)†† USA	346,972	Assessment of 16 pre-specified autoimmune conditions following routine use of HPV4 at two large managed care organizations	Retrospective cohort using electronic medical data, supplemented with medical record review§§	No confirmed safety signals for monitored conditions
Register-based cohort study¶¶ Denmark and Sweden	696,420	Assessment of 23 different autoimmune, five neurologic conditions, and VTE following HPV4 among females aged 10–17 years	Retrospective cohort using national patient registers	No consistent evidence of causal associations between HPV4 and the events monitored***
Pharmacoepidemiologic General Research Extension††† France	NA	Assessment of 6 different autoimmune outcomes among 211 cases and 875 controls aged 14–26 years§§§	Case-control study with recruitment of cases and controls through registries	No increased risk for combined endpoint of six autoimmune disorders

Abbreviations: FDA = Food and Drug Administration; GBS = Guillain-Barré syndrome; HPV = human papillomavirus; HPV4 = quadrivalent HPV vaccine; NA = not applicable; VTE = venous thromboembolism.

* **Source:** Gee J, Naleway A, Shui I, et al. Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the Vaccine Safety Datalink. Vaccine 2011;29:8270–84.

† Prespecified outcomes included GBS, stroke, appendicitis, seizures, allergic reactions, anaphylaxis, syncope, and venous thromboembolism (VTE).

§ Comparison groups included historic background rates for GBS, stroke, appendicitis, VTE, anaphylaxis; concurrent preventive health visits for seizures; or, among adolescents, vaccination visits associated with report of syncope and/or allergic reactions.

¶ **Source:** Klein NP, Hansen J, Chao C, et al. Safety of quadrivalent human papillomavirus vaccine administered routinely to females. Arch Pediatr Adolesc Med 2012;166:1140–8.

** Medical record review suggested some cases might have been local injection site reactions.

†† **Source:** Chao C, Klein NP, Velicer CM, et al. Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine. J Intern Med 2012;271:193–203.

§§ Comparison group included background incidence rates.

¶¶ **Source**: Arnheim-Dahlström L, Pasternak B, Svanström H, Sparén P, Hviid A. Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study. BMJ 2013;347:f5906.

*** For three separate autoimmune events (Behcet's syndrome, Raynaud's disease, and type 1 diabetes), statistically significant increased risks were observed. Further assessment concluded that no consistent evidence existed for causal association for these outcomes and HPV4 exposure.

††† **Source**: Grimaldi-Bensouda L, Guillemot D, Godeau B, et al. Autoimmune disorders and quadrivalent human papillomavirus vaccination of young female subjects. J Intern Med 2014;275:398–408.

§§§ Idiopathic thrombocytopenic purpura, connective tissue disorders, central demyelination and multiple sclerosis, GBS, type 1 diabetes mellitus, and autoimmune thyroid disorders.

Duration of Protection

In the phase III efficacy trial, females were followed for a median of 47 months after the first vaccine dose (*160*). The longest follow-up from the HPV2 clinical trials is from the phase II trial; a subset of participants has been followed for up to 9.4 years after the first dose (*166*). Among the 437 participants evaluated, efficacy for prevention of HPV 16/18 12-month persistent infection was 100% (95% CI = 61.4–100). Further data on duration of protection will be available from follow-up of females in the phase III trial. In addition, adolescents who were vaccinated at age 10–15 years in an immunogenicity trial (see HPV2 Immunogenicity) are being followed as they become sexually active.

Evaluation of Protection Against Nonvaccine Types

Protection against persistent infection and CIN2+ endpoints attributable to nonvaccine types was evaluated using a variety of different analytic populations (*107*,*108*). The most consistent findings were for HPV 31, 33, and 45. In ATP analyses of the phase III trial, protection was found against 6-month persistent cervical infection with HPV 31 (76.8%; 95% CI = 69.0–82.9), HPV 33 (44.8%; 95% CI = 24.6–59.9), and HPV 45 (73.6%; 95% CI = 58.1–83.9). In an analysis of lesions with or without HPV 16 or 18 co-infection, efficacy was 46.8% (95% CI = 30.7–59.4) against CIN2+ associated with any of 12 nonvaccine types (HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) (*108*). Efficacy against HPV 31-related CIN2+ was 87.5% (95% CI = 68.3–96.1) and against HPV 33-related CIN2+ was 68.3% (95% CI = 39.7–84.4) (*108*). In an analysis limited to lesions without HPV 16 or HPV 18 co-infection, efficacy against HPV 31-related CIN2+ was 84.3% (95% CI = 59.5–95.2) and against HPV 33-related CIN2+ was 59·4% (95% CI = 20.5–80.4). In the Costa Rica trial, ATP efficacy against 12-month persistent infection with any of 3 types (HPV 31, 33, or 45) was 44.5% (95% CI = 17.5–63.1); for individual types, efficacy was found for HPV 31 (45.7%; 95% CI = 8.2–68.6) (*161*).

HPV2 Immunogenicity

Females Aged 9–25 Years

Data on immunogenicity are available from the phase II and phase efficacy III trials conducted in females aged 15–25 years and immunogenicity trials conducted in females aged 9–14 years (*10*,*158*,*167*). In all trials, >99% of study participants developed antibody to both HPV 16 and HPV 18 1 month after completing the 3-dose series. Among females aged 15–25 years, antibody titers were more than 100-fold higher than those after natural infection (*158*).

Follow-up data from females who received HPV2 at ages 15–25 years are available through 9.4 years (*166*). Peak GMTs occur at 1 month after the third dose and then plateau about 2 years later. At 9.4 years after vaccination, all females had detectable antibody; GMTs were at least 10-fold higher by ELISA and fourfold higher by a neutralizing assay than GMTs after clearance of natural infection.

Immunogenicity trials including 1,275 females aged 9–14 years provided data allowing comparison of seroconversion and GMTs with those in females aged 15–25 years who were enrolled in the phase III efficacy trial (*10*). A direct comparison between females aged 10–14 years and 15–25 years was made in one study (Table 9) (*167*). In all trials, seropositivity 1 month after the third dose among females aged 10–14 years was 100% for HPV 16 and HPV 18; GMTs were noninferior (and approximately twofold higher) to those vaccinated at age 15–25 years. At month 48, GMTs in females vaccinated at ages 10–14 years remained twofold higher than those in females vaccinated at ages 15–25 years (*168*).

Spacing of Vaccine Doses

In prelicensure efficacy and immunogenicity trials, HPV2 was administered according to a 0, 1, and 6 month schedule. Postlicensure trials have evaluated GMTs after longer intervals between doses, including 6 months between the first and second dose and 12 months between the first and third dose (*169*,*170*). GMTs after schedules with longer intervals between doses were noninferior to those after the standard dosing schedule.

Concomitant Administration with Other Vaccines

Seroconversion rates and GMTs after concomitant administration of HPV2 with other vaccines, including meningococcal conjugate vaccine, tetanus, diphtheria and acellular pertussis vaccine, inactivated poliovirus vaccine, hepatitis B vaccine, and combined hepatitis A and B vaccine have been evaluated (*135*). GMTs were noninferior in the co-administered group compared with GMTs after administration of HPV2 alone in all studies. Rates of solicited and unsolicited symptoms and events were similar in all study groups.

HIV-Infected Persons

One HPV2 immunogenicity study has been conducted comparing antibody response in HIV-infected and uninfected females aged 18–25 years. All subjects seroconverted to HPV 16 and HPV 18 and the vaccine was well tolerated; GMTs were lower in the HIV-infected females compared with those not infected (*171*). However, HPV 16 and HPV 18 GMTs in HIV-infected females 1 month after the third dose were 124- and 90-fold higher, respectively than those reported in healthy females aged 15–25 years after natural infection.

Immunogenicity in Females Aged >25 Years

HPV2 is not licensed in the United States for use among females aged >25 years. No published data are available on HPV2 efficacy in females aged >25 years. One trial compared HPV2 immunogenicity among females aged 26–55 years and those aged 15–25 years (*172*). All participants were seropositive to HPV 16 and HPV 18 at 1 month after the third dose, and >99% were seropositive at month 48 (*173*). GMTs were lower than those among females aged 15–25 years and decreased with increasing age. However, even in the oldest age group (age 46–55 years), GMTs 1 month after the third dose were 57- and 84- fold higher than GMTs after natural infection for HPV 16 and HPV 18 (*172*).

HPV2 Safety

In prelicensure trials, HPV2 vaccinees were evaluated for injection-site and systemic adverse events, medically significant conditions, new onset autoimmune disorders, new onset

TABLE 9. Geometric mean antibody titers after bivalent human papillomavirus vaccine among females aged 10–14 years and 15–25 years, 1 month after third dose (according to protocol immunogenicity population*)

Antibody assay (ELISA)	Females aged 10–14 years				Females aged 15–25 years			
	No.	GMT (EL.U./mL)	(95% CI)	Seropositivity[†] %	No.	GMT (EL.U./mL)	(95% CI)	Seropositivity[†] %
Anti-HPV 16	143	17,273	(15,118–19,734)	100	118	7,439	(6,325–8,750)	100
Anti-HPV 18	141	6,864	(5,976–7,883)	100	116	3,070	(2,600–3,625)	100

Abbreviations: CI = confidence interval; ELISA = enzyme linked immunosorbent assay; EL.U./mL = ELISA unit per ml; GMT = geometric mean titer; HPV = human papillomavirus.
Source: Food and Drug Administration. Product approval-prescribing information [Package insert]. Cervarix [human papillomavirus bivalent (types 16, 18) vaccine, recombinant], Glaxo Smith Kline. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2014. Available at http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM186981.pdf.
* According-to-protocol immunogenicity population includes all subjects who were not general protocol violators, received all three vaccinations within acceptable day ranges, were seronegative at day 1, and had least one postvaccination antibody measurement.
† Seropositive for anti-HPV 16 ≥8 EL.U./mL; Seropositive for anti-HPV 18 ≥7 EL.U./mL.

chronic diseases, deaths, serious adverse events, and pregnancy outcomes. Safety was evaluated by pooling data from 11 clinical trials of HPV2 in females aged 9 through 25 years and by a meta-analysis of safety databases of HPV2 as well as other vaccines that have the same adjuvant (*10*,*174*,*175*).

The pooled safety analysis included 23,952 females aged 9–25 years; approximately 13,000 females received at least 1 dose of HPV2 (*10*). In an analysis of local and systemic adverse events, a larger proportion of persons reported at least one injection-site symptom in the HPV2 group compared with controls (who received hepatitis A vaccine). In the HPV2 group, 92% reported injection-site pain, 48% redness, and 44% swelling compared with 64%–87%, 24%–28%, and 17%–21%, respectively, in the control groups (Table 10). Fatigue, headache, and myalgia were the most common systemic symptoms. No differences were observed in unsolicited symptoms within 30 days of vaccination between the vaccine group and control groups.

Serious adverse events were evaluated in a pooled safety analysis that included 30,192 females aged 9–72 years (16,381 received HPV2). Proportions of persons reporting a serious adverse event were similar in vaccine and control groups (5.3% and 5.9%, respectively), as were the types of serious adverse events reported (*10*). In the pooled safety analysis, including 12,772 females who received HPV2 and 10,730 in the control groups, incidence of potential new autoimmune disorders did not differ (0.8% in both groups). Overall, among completed and ongoing studies that enrolled 57,323 females aged 9–72 years, 37 deaths were reported during 7.4 years of follow-up: 20 among those who received bivalent vaccine (0.06%) and 17 among those in the control groups (0.07%). None of the deaths was considered to be vaccine-related.

Vaccination During Pregnancy

Clinical protocols excluded females who were pregnant, and participants were instructed to avoid pregnancy until 2 months after the last vaccination. However, 3,696 pregnancies occurred in the HPV2 group and 3,580 in the pooled control groups (*10*). Overall, no differences were observed in rates of any specific pregnancy outcomes between groups. Among 761 pregnancies around the time of vaccination (defined as last menstrual period 30 days before to 45 days after vaccination), 13.6% of pregnancies ended in spontaneous abortion in the HPV2 group compared with 9.6% in the control group. Abnormal infant outcomes (other than congenital anomalies) were reported in 5.1% of the HPV2 group and 4.7% of the control group. Other outcomes (congenital anomalies, still birth, ectopic pregnancy, and therapeutic abortion) were reported in 0.3% to 1.8% of the HPV2 group and 0.3% to 1.4% of the control group. HPV2 has been classified as Pregnancy Category B on the basis of animal studies that revealed no evidence of impaired fertility or harm to the fetus (*10*). A registry for females inadvertently vaccinated during pregnancy was established by the manufacturer as part of its postlicensure commitment to FDA. To date, the rate of major congenital anomalies and spontaneous abortions has been within the reported background rates (*176*). In addition, a postmarketing required study is being conducted to assess the risk of spontaneous abortions in females who receive HPV2 during pregnancy in an observational database cohort study in the United Kingdom (*177*). No data are available on use of HPV2 in lactating females.

Postlicensure Safety Data

From October 2009 through March 2014, approximately 719,000 doses of HPV2 were distributed in the United States. Because of the smaller number of doses distributed compared with HPV4, formal evaluations of the passive surveillance data from VAERS or data from VSD have not been conducted. During this time period, VAERS has received a total of 113 adverse event reports occurring in females after receipt of HPV2; 93.8% were classified as nonserious (CDC, unpublished data, 2014). Among nonserious adverse events, the most commonly reported generalized symptoms were nausea, dizziness, headache, and urticaria; the most commonly

TABLE 10. Rates of solicited local adverse reactions and general adverse events in females aged 9–25 years, within 7 days of vaccination with bivalent human papillomavirus vaccine*

Adverse event	Bivalent HPV vaccine (9–25 yrs) %	HAV 720 (15–25 yrs) %	HAV 360 (10–14 yrs) %	$Al(OH)_3$ control (15–25 yrs) %
Local	N = 6,669	N = 3,079	N = 1,027	N = 549
Pain	91.9	78.0	64.2	87.2
Redness	48.4	27.6	25.2	24.4
Swelling	44.3	19.8	17.3	21.3
General	N = 6,670	N = 3,079	N = 1,027	N = 549
Fatigue	54.6	53.7	42.3	53.6
Headache	53.4	51.3	45.2	61.4
GI†	27.9	27.3	24.6	32.8
Fever (≥99.5°F)	12.9	10.9	16.0	13.5
Rash	9.5	8.4	6.7	10.0
Myalgia§	48.8	44.9	33.1	—
Arthralgia§	20.7	17.9	19.9	—
Urticaria§	7.2	7.9	5.4	—

Abbreviations: $Al(OH)_3$ = aluminium hydroxide; $Al(OH)_3$ control = control containing 500 mcg $Al(OH)_3$; GI = gastrointestinal; HAV 360 = hepatitis A vaccine control group (360 EL.U. of antigen and 250 mcg of $Al(OH)_3$); HAV 720 = hepatitis A vaccine control group (720 EL.U. of antigen and 500 mcg $Al(OH)_3$); HPV = human papillomavirus.

Source: Food and Drug Administration. Product approval-prescribing information [Package insert]. Cervarix [human papillomavirus bivalent (types 16, 18) vaccine, recombinant], Glaxo Smith Kline. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2014. Available at http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM186981.pdf.

* Included subjects with at least 1 documented dose.

† GI symptoms, including nausea, vomiting, diarrhea, and/or abdominal pain.

§ Adverse events solicited in a subset of subjects in the bivalent HPV vaccine group (N = 6,119).

reported local symptoms were injection-site redness, swelling, and induration. Postlicensure safety data are available from other countries that have implemented vaccination programs using HPV2 (*154*,*176*). In a review of passive reports from countries that have implemented HPV2 vaccination programs, the distribution of adverse events was consistent with prelicensure trials. Passive reports revealed no concerns about potentially immune mediated diseases (*176*). In addition, a postmarketing observational database cohort study will assess the risk of autoimmune diseases in adolescent and young adult women who received HPV2 in the United Kingdom (*177*).

Economic Burden of HPV and Cost-Effectiveness of Vaccination in the United States

Before HPV vaccine introduction, the prevention and treatment of HPV-related disease imposed an estimated burden of $8 billion or more in direct costs in the United States each year (*178*). Of this, approximately $1 billion was for treatment of cancer, including $400 million for invasive cervical cancer and $300 million for oropharyngeal cancer. Approximately $200 million was for treatment of recurrent respiratory papillomatosis and $300 million was for treatment of genital warts. The remainder ($6.6 billion) was for cervical cancer screening and follow-up.

Modeling studies have shown consistently that the routine vaccination of 12-year-old girls with either HPV2 or HPV4 is a cost-effective use of public health resources, as long as vaccine duration of protection is sufficient (e.g., 30 years) (*179*,*180*). Estimates of the incremental cost per quality-adjusted life year (QALY) gained by adding HPV vaccination of girls aged 12 years to existing cervical cancer screening programs vary (approximate range: $3,000–$45,000) (*181–186*).

Although cost-effectiveness estimates for vaccination of girls aged 12 years are quite consistent across published models, cost-effectiveness estimates for vaccination of females aged >12 years and for vaccination of males are more uncertain and less precise. The published models generally suggest that the cost-effectiveness of vaccination of females becomes less favorable as the age at vaccination increases beyond the early teenage years. However, there is no consensus on the exact age at which catch-up vaccination of females might no longer be considered cost-effective. Models suggest that catch-up vaccination of females could be cost-effective through the mid-20s, particularly if all potential benefits of vaccination are included (*185*,*187*).

Numerous published models have found that the cost-effectiveness of adding males to a female-only vaccination program depends on the vaccination coverage in females and the cost of vaccine (*180*). As vaccination coverage of females increases, the health burden of HPV can be reduced in both females and males (through herd immunity), thereby reducing the potential benefits of male vaccination. Male vaccination at age 12 years, when added to a female-only vaccination program, costs about $20,000 to $40,000 per QALY gained in the most favorable scenarios for male vaccination and about $75,000 to more than $250,000 per QALY gained in the least favorable scenarios (*187–189*). Scenarios for male vaccination are more favorable when female vaccination coverage is low (e.g., 20%) and when all potential health benefits are included in the analysis (*179*,*188*). Scenarios for male vaccination are less favorable when female vaccination coverage is high (e.g., 75%), when including only the health outcomes for which evidence of vaccine efficacy is available, if vaccinated males have mostly vaccinated female sex partners, and when male vaccination is compared with an alternative strategy of increased vaccination coverage among females (*179*,*188*). Vaccination of adult males becomes less cost-effective as age at vaccination increases, particularly for age >21 years (*15*). Vaccination of MSM through age 26 years potentially could be cost-effective across many scenarios, according to the only study available of the cost-effectiveness of HPV vaccination of MSM in the United States (*190*).

HPV Vaccination Program in the United States

Recommendations for HPV vaccination have evolved since HPV4 was first licensed in 2006. In June 2006, HPV4 was licensed for use in females and recommended for routine vaccination of females aged 11 or 12 years and for those aged 13 through 26 years not previously vaccinated (*12*). In 2009, HPV2 was licensed for use in females and ACIP updated recommendations to state that either HPV vaccine is recommended for females (*13*). In 2009, HPV4 was licensed for use in males (*14*) and in late 2011, HPV4 was recommended for routine vaccination of males aged 11 or 12 years and for those aged 13 through 21 years not previously vaccinated (*15*). The recommendations for females and males state that the vaccination series can be started beginning at age 9 years.

Most HPV vaccine administered in the United States has been HPV4 (*147*). Almost all HPV vaccinations are delivered by primary care providers or health clinics (*191*). In the United States, there is both public and private financing for vaccines. The Vaccines for Children Program (VFC) supplies enrolled private and public health-care providers with federally purchased vaccines for use among uninsured, Medicaid-eligible and other entitled children through age 18 years (*192,193*). Under the Patient Protection and Affordable Care Act of 2010, nongrandfathered private health plans must offer, at no cost to beneficiaries, vaccines that are recommended by ACIP. Similarly, qualified health plans on the new health insurance exchanges that went into effect starting in 2014 must offer ACIP-recommended vaccines at no cost to beneficiaries (*194*).

HPV vaccination coverage with at least 1 dose among girls aged 13–17 years increased from 25.1% in 2007 to 53.0% in 2011 (*148*). However, the annual increase lagged behind that of other vaccines recommended for adolescents, and in 2012 there was no increase. In 2013, at least 1 dose coverage and 3 dose coverage increased slightly; among girls aged 13–17 years 57.3% had received at least 1 dose and 37.6% had received all 3 doses (*147*). Variation by state remains wide, with at least 1 dose vaccine coverage ranging from 39.9% to 76.6% (*195*). The main reasons parents reported for not intending or being unsure about vaccinating their daughters in the next 12 months were a lack of knowledge, a belief that the vaccine was not needed, concerns about vaccine safety or side effects, and the vaccine not being recommended by their provider (*147*). These responses indicate gaps in understanding, including the reasons vaccination is recommended at age 11 or 12 years and the need to strengthen provider recommendations. Updated educational materials that address these issues are available from CDC at http://www.cdc.gov/vaccines/who/teens/index.html. Data from 2012 were the first since the October 2011 ACIP recommendation for routine vaccination of males. At least 1 dose coverage among boys aged 13–17 years increased from 8.3% in 2011 to 20.8% in 2012 and further increased to 34.6% in 2013 (*147*).

Summary of Rationale for HPV Vaccination Recommendations

The availability of HPV vaccines provides an opportunity to decrease the burden of cervical cancer precursors, cervical cancer, other anogenital cancer precursors and cancers, and genital warts in the United States (*10,11*). Although data on efficacy against oropharyngeal disease endpoints are not available from clinical trials, HPV vaccination is also likely to be effective for prevention of HPV-attributable oropharyngeal cancer (*63,164*). Two vaccines are licensed for use in females in the United States; HPV4 (directed against HPV 6, 11, 16, and 18) and HPV2 (directed against HPV 16 and 18). One vaccine (HPV4) is licensed for use in males in the United States. HPV 16 and 18 are the cause of approximately 70% of cervical cancers and most other HPV-attributable cancers; HPV 6 and 11 are the cause of approximately 90% of genital warts.

HPV vaccines are most effective when administered before exposure to HPV (*107,118,160*). The recommendation for routine vaccination at age 11 or 12 years is based on several considerations including studies indicating that HPV vaccines are safe and immunogenic in this age group, the higher antibody titers achieved after vaccination at age 11 or 12 years compared with older age groups, data on HPV epidemiology, and age of sexual debut in the United States (*128,167,196*). The recommendation also considered cost-effectiveness evaluations and the established young adolescent health-care visit at age 11 or 12 years recommended by several professional organizations, when receipt of other vaccines also is recommended (*197*). Data suggest that protection after vaccination will be long lasting (*124–126,166*); long-term follow-up studies are underway to determine the duration of protection.

Although routine vaccination is recommended at age 11 or 12 years, older adolescents and young adults through the recommended ages can benefit from vaccination. Adolescents and young adults who are not yet sexually active can be expected to receive the full benefit of vaccination. Although sexually active persons in this age group might have been infected with one or more vaccine HPV types, studies suggest that only a small percentage have been infected with both HPV

16 and 18 or all four vaccine types (*31,198*). The vaccines can protect against types not already acquired. Neither vaccine protects against persistent infection, precancer lesions, or anogenital warts caused by an HPV type that persons are infected with at the time of vaccination. Although vaccine effectiveness would be lower when administered to those who are sexually active, and would decrease with older age and likelihood of previous HPV exposure, the majority of persons in the recommended age groups will derive at least partial benefit from vaccination.

HPV vaccines are not licensed in the United States for use in persons aged >26 years. Among women, the expected population-level impact of HPV vaccination in this age group is lower than that for younger women because of the higher likelihood that women have already had vaccine type infection, because fewer would have incident infection that could be prevented and the risk for development of disease from incident infection is less (*199*).

Recommendations for Use of HPV Vaccines

Routine Recommendations

ACIP recommends routine vaccination at age 11 or 12 years with HPV4 or HPV2 for females and with HPV4 for males (male GRADE recommendation category: A, evidence type: 2 [*15,17*]). The vaccination series can be started beginning at age 9 years.

HPV4 and HPV2 are each administered in a 3-dose schedule. The second dose should be administered 1–2 months after the first dose and the third dose 6 months after the first dose.

Recommendations for Those Not Vaccinated at the Routine Age

Vaccination also is recommended for females aged 13 through 26 years and for males aged 13 through 21 years, who have not been vaccinated previously or who have not completed the 3-dose series. Males aged 22 through 26 years may be vaccinated.

If females or males reach age 27 years before the vaccination series is complete, the second and/or third doses of vaccine can be administered after age 26 years to complete the vaccination series.

Prevaccination assessments (e.g., Pap testing or screening for high-risk HPV DNA, type-specific HPV DNA tests, or HPV antibody tests) to establish the appropriateness of HPV vaccination are not recommended.

Administration

HPV vaccine (either HPV4 or HPV2) should be shaken well before administration. The dose for either vaccine is 0.5 ml, administered intramuscularly (IM), preferably in the deltoid muscle.

Minimum Dosing Intervals and Interrupted Schedules

The minimum interval between the first and second doses of HPV vaccine (either HPV4 or HPV2) is 4 weeks. The minimum recommended interval between the second and third dose of vaccine is 12 weeks. The minimum interval between the first and third dose is 24 weeks. Inadequate doses or vaccine doses received after a shorter-than-recommended dosing interval should be re-administered. If the vaccine schedule is interrupted for either HPV4 or HPV2, the vaccine series does not need to be restarted. If the series is interrupted after the first dose, the second dose should be administered, and the second and third doses should be separated by an interval of at least 12 weeks.

Concomitant Administration with Other Vaccines

HPV vaccine (either HPV4 or HPV2) can be administered at the same visit as other age-appropriate vaccines, such as tetanus, diphtheria, and acellular pertussis and quadrivalent meningococcal conjugate vaccines. Administering all indicated vaccines together at a single visit increases the likelihood that adolescents will receive each of the vaccines on schedule. Each vaccine should be administered by using a separate syringe at a different anatomic site.

Interchangeability of HPV Vaccine Products

ACIP recommends that the HPV vaccination series for females be completed with the same HPV vaccine product, whenever possible. However, if vaccination providers do not know or have available the HPV vaccine product previously administered, either HPV vaccine product may be used to continue or complete the series for females to provide protection against HPV 16 and HPV 18. Only HPV4 is licensed for use in males.

No studies address the interchangeability of the two HPV vaccines. However, there is no theoretic reason to expect that the risk for adverse events would be increased if the series included more than one product. The effectiveness of a series that contained both products might be reduced compared with a complete series with one product for protection against HPV 16/18-related cancers and precancers. A series with <3 doses of HPV4 might provide less protection against genital warts than a complete 3-dose series of HPV4.

Special Populations

Abnormal Pap Test, Known HPV Infection, Anogenital Warts, or HPV-Associated Lesions

HPV vaccination can provide protection against infection with HPV vaccine types not already acquired. Therefore, vaccination is recommended through the recommended age for females regardless of whether they have an abnormal Pap test result, and for females or males regardless of known HPV infection, HPV-associated precancer lesions, or anogenital warts. Females who have abnormalities on cervical cancer screening are likely to be infected with one or more genital HPV types. With increasing severity of Pap test findings, the likelihood of infection with HPV 16 or HPV 18 increases (*70*), and the expected benefit of vaccination decreases. Females who have had HPV testing as part of cervical cancer screening might have information about their HPV status. Males or females with AIN are likely infected with HPV. The presence of anogenital warts or a history of anogenital warts indicates present or past infection with HPV, most often HPV 6 or HPV 11. Although vaccination is still recommended, patients should be advised that vaccination will not have any therapeutic effect on an existing HPV infection, HPV-associated precancer lesion, cancer, or anogenital warts.

Immunocompromised Persons

Persons who are immunocompromised because of transplant, medications, or HIV have a higher burden of HPV-associated disease and cancer (*46*). Although studies have found the vaccines to be well tolerated and immunogenic in HIV-infected persons, some studies found that GMTs were lower among HIV-infected persons compared with those who are uninfected (*136–139*,*171*). Whether there will be any differences in HPV vaccine efficacy between immunocompromised and immunocompetent persons is unclear. ACIP recommends routine vaccination at age 11 or 12 years with HPV2 or HPV4 for females and with HPV4 for males. Vaccination is recommended through age 26 years for immunocompromised persons who have not been vaccinated previously or who have not completed the 3-dose series.

Men Who Have Sex with Men

MSM are at high risk for infection with HPV and associated conditions, including anogenital warts and anal cancer (*29*). For MSM, ACIP recommends routine vaccination with HPV4, as for all males, and vaccination through age 26 years for those who have not been vaccinated previously or who have not completed the 3-dose series.

Lactating Women

Lactating women can receive HPV vaccine.

History of Sexual Abuse or Assault

Health-care providers who evaluate and treat children and youth who are suspected or confirmed victims of sexual abuse or assault should be aware of the need for HPV vaccination. Sexual abuse and assault raise the risk of HPV infection attributable to the abuse itself, potential future victimization, and subsequent engagement in at-risk behaviors. Children who are victims of sexual abuse or assault are recognized to be more likely to engage in subsequent unsafe and unprotected intercourse and to engage in these behaviors at an earlier age than nonabused children (*200*). Although HPV vaccination will not promote viral clearance or protect against disease progression attributable to types already acquired, vaccination would protect against vaccine-preventable types not yet acquired. ACIP recommends HPV vaccination beginning at age 9 years for children and youth with any history of sexual abuse or assault who have not initiated or completed the 3-dose series. Females and males who are victims of sexual abuse or assault should receive HPV vaccine through the recommended ages if they have not already been vaccinated.

Precautions and Contraindications

Hypersensitivity or Allergy to Vaccine Components

HPV vaccines are contraindicated for persons with a history of immediate hypersensitivity to any vaccine component. HPV4 is produced in *Saccharomyces cerevisiae* (baker's yeast) and is contraindicated for persons with a history of immediate hypersensitivity to yeast. The tip cap of prefilled syringes of HPV2 might contain latex. HPV2 should not be used in persons with anaphylactic allergy to latex.

Acute Illnesses

HPV vaccines 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.

Preventing Syncope After Vaccination

Syncope (vasovagal or vasodepressor reaction) can occur after vaccination, most commonly among adolescents and young adults (*201*). One of the most frequent reports to VAERS for HPV4 since licensure has been syncope (*148*). Although syncopal episodes are uncommon, vaccine providers should consider observing patients (with patients seated or lying down to decrease the risk for injury should they faint) for 15 minutes after they receive any vaccine, including HPV vaccine (*202*).

Vaccination During Pregnancy

HPV vaccines are not recommended for use in pregnant women. The vaccines have not been associated causally with adverse outcomes of pregnancy or adverse events in the developing fetus. However, if a woman is found to be pregnant after initiating the vaccination series, the remainder of the 3-dose series should be delayed until completion of pregnancy. Pregnancy testing is not needed before vaccination. If a vaccine dose has been administered during pregnancy, no intervention is needed.

Patients and health-care providers can report an exposure to HPV vaccine during pregnancy to VAERS. FDA considered Merck's regulatory commitment for a pregnancy registry fulfilled in April 2013 and the registry was terminated (see HPV4 Safety). Although the registry has been terminated, HPV4 exposure during pregnancy can continue to be reported to Merck at telephone 1-877-888-4231. HPV2 exposure during pregnancy should be reported to the GlaxoSmithKline Pregnancy Registry at telephone 1-888-452-9622.

Monitoring Impact of HPV Vaccination in the United States

Most cancers that could be prevented by HPV vaccine occur years after infection; therefore, it might be decades before an impact of vaccination is observed on these outcomes. The United States has cancer registries that monitor the incidence of cervical and other HPV-associated cancers (*203*). To determine earlier impact of vaccination, several more proximal outcomes are being monitored, including HPV prevalence, genital warts, and cervical precancers (*204–208*). Challenges to establishing a unified monitoring system for precancer outcomes as well as other outcomes include incomplete immunization information systems, lack of unique identifiers to link medical records, and lack of population-based cervical cancer screening registries. Despite 3-dose coverage in 2010 of only 32% in girls aged 13–17 years (*148*), data obtained within 4 years of introduction of HPV vaccination in the United States show a reduction of HPV vaccine type prevalence and genital warts in adolescent girls. In a national survey, HPV 6, 11, 16, and 18 type prevalence among girls aged 14–19 years decreased from 11.5% in 2003–2006 to 5.1% in 2007–2010 (*207*). An analysis of health claims data found that genital warts decreased among girls aged 15–19 years from a prevalence per 1,000 person-years of 2.9 in 2006 to 1.8 in 2010 (*208*). Data from other studies in the United States also show vaccine impact (*209*). Dramatic decreases in genital warts and vaccine type prevalence have been demonstrated in countries that have achieved high coverage (*209,210*).

Areas of Ongoing Research and Future Priority Activities

Since HPV vaccine was first introduced in the United States, substantial additional data have been provided by clinical trials and postlicensure evaluations. Ongoing research and other activities will provide additional data in the future.

- *Efficacy and duration of protection:* Available data show no loss of protection through 8 to 10 years (*124,125,166*). Ongoing evaluations will continue to provide information on duration of protection for both vaccines.
- *Reduced dose schedules:* There is broad interest in reduced dose schedules; immunogenicity trials show noninferior antibody response after 2 doses in females aged 9–14 years compared with 3 doses in females aged 15–26 years (*170,211,212*). Available data as well as data from ongoing studies will provide important information for policy considerations (*170,212,213*).
- *Safety:* Multiple studies have provided evidence supporting HPV4 vaccine safety. Postlicensure monitoring and evaluation by CDC and FDA continue.
- *Monitoring HPV-associated outcomes*: Although it will take years to realize the impact of vaccination on cervical and other HPV-associated cancers, a variety of investigations already have shown early impact on prevalence of HPV vaccine types and genital warts in the United States and other countries (*208*). Evaluations are ongoing. To date, there is no indication replacement with nonvaccine HPV types is occurring.
- *Second generation vaccines*: An investigational 9-valent HPV vaccine that targets high-risk types HPV 16 and 18 and five additional high-risk types as well as HPV 6 and 11 is under review by FDA, and ACIP consideration of this vaccine is forthcoming (*214*).
- *Cervical cancer screening*: As vaccine coverage increases, recommendations for cervical cancer screening will need to be re-assessed. Evaluation of the impact of HPV vaccination on provider and patient cervical cancer screening practices is needed.
- *Vaccine delivery and implementation*: Increasing coverage of HPV vaccine in the United States has been challenging. A variety of needed efforts have been identified including: educating parents, providers and patients, increasing consistency and strength of HPV vaccination recommendations by providers, and eliminating missed opportunities for vaccination (*147*).

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