

Chapter 5: Human Papillomavirus

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I. Background

Genital human papillomavirus (HPV) is the most common sexually transmitted infection in the United States.^{1,2} An estimated 14 million persons newly infected every year, resulting in approximately \$1.7 billion (estimates range from \$800 million to \$2.9 billion) in direct medical costs.³ Although the vast majority of HPV 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.¹

More than 200 HPV types have been identified, including approximately 40 that preferentially infect the genital mucosa.^{4–6} Genital HPV types are categorized according to their epidemiologic association with cancer.⁷ 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 to cancers.^{7–9} Nearly all cervical cancers are attributable to high-risk HPV types,¹⁰ and approximately 70% of cervical cancer cases worldwide are caused by types 16 and 18.¹¹ HPV 16 infection is also responsible for most cases of other anogenital cancers such as cancers of the vulva, vagina, penis, and anus, as well as cancers arising in some oropharynx subsites.⁷ According to the International Agency for Research on Cancer (IARC), ten additional HPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) have sufficient evidence of carcinogenicity in humans based on their association with cervical cancer, and several types are classified as probably or possibly carcinogenic.⁷ Other types, including types 6 and 11, can cause genital warts, benign or low-grade cervical cell changes, and recurrent respiratory papillomatosis (RRP).¹²

Among the cancer-related outcomes of HPV infection, invasive cervical cancer has been considered the most important worldwide, with over 500,000 new cases and 265,000 attributable deaths in 2012.¹³ Though the vast majority of women with high-risk HPV infection do not develop cancer, persistent infection with high-risk HPV types is widely recognized as the primary causative factor for development of cervical cancer.^{14–16}

II. Disease Description

Most HPV infections are transient and asymptomatic, causing no symptoms. More than 90% of new HPV infections, including those caused by high-risk HPV types, clear or become undetectable within 2 years, and clearance usually occurs in the first 6 months after infection.^{16–18} Persistent infection with high-risk HPV is the most important risk factor for HPV-related diseases including cancer precursors and invasive cervical cancer.^{6, 18–21}

Many aspects of the natural history of HPV are poorly understood, including the role and duration of naturally acquired immunity after HPV infection. The risk for persistence and progression to cancer precursor lesions varies by HPV type as well as host factors.¹ HPV 16 is more likely to persist and progress to cancer than other high-risk HPV types.^{22, 23} The usual time between initial HPV infection and development of cervical cancer is decades, but more rapid progression has occurred. The median age at diagnosis for cervical cancer in the United States is 49 years.²⁴

In the United States, cervical cancer incidence rates have decreased approximately 75% and mortality rates approximately 70% since the 1950s, largely due to increased use of cytology screening (i.e., Papanicolaou [Pap] smears) and effective treatment of precancerous lesions.^{25, 26} In 2009–2013, invasive cervical cancer incidence in the United States was 7.2 per 100,000 women, with over 11,000 new cases reported annually.^{24, 27, 28}



This number does not include incidence of cervical precancers, for which surveillance data are not collected nationally. However, abnormal lesions and precancers related to HPV are extremely common, with varied rates depending on data collection methods and geographic area.^{29–31} Treatment for cervical precancers may affect pregnancy outcomes and thus is an important aspect of preventable disease burden.^{32, 33}

In the United States, in samples collected from several cancer registries prior to vaccine implementation, HPV was detected in about 90% of cervical cancers (See Appendix A).³⁴ From the same study, HPV was detected in varying proportions of HPV-associated cancers occurring at non-cervical sites. Those with the largest proportion attributable to HPV were anal cancers (about 90%), followed by vaginal cancers (about 75%), oropharyngeal cancers (about 70%), vulvar cancers (about 70%), and penile cancers (about 60%).³⁴ Among HPV-attributable cancers, oropharyngeal squamous cell carcinomas (SCC) were the most common; from 2009–2013, there were an estimated 9,600 among males and 2,000 among females annually.^{24, 27} Rates of oropharyngeal SCC were higher among males (7.6%) than females (1.7%). Rates of anal SCC were higher among females (1.8%) than males (1.1%).²⁷

Anogenital warts typically develop approximately 2–3 months after HPV infection (almost all caused by types 6 or 11); however, not all persons infected with HPV types 6 and 11 develop genital warts.^{35, 36} Anogenital warts should be assessed by a clinician and can be treated, although many warts (20–30%) regress spontaneously.³⁷ Recurrence of anogenital warts within 3 months is common (approximately 30%), whether clearance occurs spontaneously or following treatment.³⁸

Non-high-risk HPV types (primarily types 6 or 11) can also cause RRP, a rare disease that is characterized by recurrent warts or papillomas in the upper respiratory tract.¹² RRP is usually diagnosed by a specialist based upon clinical and pathologic evaluation. RRP is divided into juvenile onset (JORRP) and adult onset (AORRP) forms based on age at symptom onset. JORRP is believed to result from vertical transmission of HPV from a mother to her baby at the time of delivery; the age of diagnosis is usually under 5 years of age.³⁹ A multicenter registry including patients with JORRP from 22 U.S. clinical centers demonstrated that the clinical course of JORRP is highly variable and associated with extensive morbidity, requiring a median of 4.3 annual surgeries to remove papillomas, preserve vocal quality, and maintain an open airway.³⁹

III. Screening and Treatment

No treatment is required for asymptomatic HPV infections; instead, treatment is directed at the HPV-associated conditions.³⁷ Current treatment options for intraepithelial neoplasias (precancerous lesions), cancers, and anogenital warts vary by the severity of disease and the anatomical location as described below. Routine screening for early detection of cervical cancer and precancerous lesions is recommended. Screening is not recommended for other HPV-associated cancers, although some specialized clinics conduct anoscopy to identify precancerous anal lesions in men who have sex with men.³⁷

Anogenital warts

Anogenital warts are usually diagnosed by visual inspection, although biopsy may be helpful in some cases. The primary objective of treatment is removal of the wart and amelioration of symptoms, if present.³⁷ The appearance of warts also can result in substantial psychosocial distress, and removal can relieve cosmetic concerns. In most patients, treatment results in resolution of the wart(s). Untreated, anogenital warts can resolve spontaneously, remain unchanged, or increase in size or number. Because warts might spontaneously resolve, an acceptable approach for some persons is to forego treatment and monitor for spontaneous resolution within 1 year. Available therapies for anogenital warts might reduce, but probably do not eradicate, HPV infectivity. Whether the reduction in HPV viral DNA resulting from treatment reduces future transmission remains unknown. Detailed treatment guidelines have been published.³⁷ Treatment of anogenital warts may be guided by considerations such as wart size, number, and anatomic site; patient preference; cost of treatment; convenience; adverse effects; and clinician experience.

Recommended treatment regimens for external anogenital warts can be classified as either patient-applied or provider-administered. Patient-applied therapies for warts include imiquimod 3.75% or 5% cream; podoflox 0.5% solution or gel; and sinecatechins 15% ointment.³⁷ Provider-administered therapies include cryotherapy with liquid nitrogen or cryoprobe; surgical removal either by tangential scissor excision,

tangential shave excision, curettage, laser, or electrosurgery; or application of trichloroacetic acid (TCA) or bichloroacetic acid (BCA) 80%–90% solution.³⁷ No definitive evidence suggests that any specific recommended treatment is superior to another, and no single treatment is ideal for all patients or all warts.

Cervical precancer

Persistent HPV infection can result in precancerous cervical lesions as well as invasive cervical cancer. With regular cervical cancer screening and appropriate follow-up, most cervical cancer precursors can be identified and treated in time to prevent progression to invasive disease. Precancerous cervical lesions and invasive cancers are diagnosed based on the histology of tissues obtained with biopsy or excision, and these specimens guide further treatment decisions.

Recommendations for cervical cancer screening in the United States are based on systematic reviews of evidence and are largely consistent across the major medical organizations, including the American Cancer Society (ACS), American Congress of Obstetricians and Gynecologists (ACOG), and the U.S. Preventative Services Task Force (USPSTF).^{37,40–42} For women in the United States, routine cervical screening should be performed starting at 21 years of age and continue through 65 years of age. Screening can be performed using either conventional or liquid-based cytologic tests (i.e., Pap tests). The Pap test is a screening test, not a diagnostic test.

Pap testing is recommended every 3 years from 21–29 years of age. From 30–65 years of age, women should either receive a Pap test every 3 years or a Pap test plus HPV test (co-test) every 5 years; co-testing can be done by either collecting one swab for the Pap test and another for the HPV test or by using the remaining liquid cytology material for the HPV test. Because of the high negative predictive value of these 2 tests, women with normal results for both HPV and Pap tests do not need to be screened again for 5 years. Cervical screening recommendations do not currently differ for unvaccinated women and those who have received HPV vaccination. ACS, ACOG, and USPSTF concur that no Pap testing is recommended before 21 years of age, and that women with a history of negative tests can cease screening after 65 years of age. In 2015, prompted by FDA approval of one test for the indication of primary screening for high-risk HPV types, several organizations, the ACS, the American Society for Colposcopy and Cervical Pathology, and the American Society for Clinical Pathology released interim guidance for primary screening with high-risk HPV testing every 3 years in women ≥ 25 years of age.⁴³

For cytopathologic and high-risk-HPV testing, clinics should use Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories using acceptable terminology (Bethesda 2001 or Lower Anogenital Squamous Terminology [LAST] terminology).^{37,44} Screening for non–high-risk HPV infection is not recommended by any clinical or medical organization.⁴⁵ Abnormal screening results require further evaluation with colposcopic examination of the cervix (i.e., under magnification). During colposcopy, cervical biopsies may be taken for histologic examination to diagnose the presence and severity of lesions.

The suggested nomenclature for precancerous squamous lesions in the anogenital tract has shifted from intraepithelial neoplasia (IN terminology, graded 1, 2, or 3) to intraepithelial lesions (graded as low or high grade).⁴⁴ In this LAST, high-grade squamous intraepithelial lesions (HSIL) include those formerly called cervical intraepithelial neoplasia CIN 3 and those called CIN 2 that have p16, an immunohistochemical marker of disease. Precancerous cervical lesions include HSIL and adenocarcinoma in situ (AIS).

For cervical biopsy results of low-grade squamous intraepithelial lesions (LSIL, also called CIN1), the preferred management may be to follow-up with repeat cytology to detect persistence or progression of the lesion. For HSIL or AIS, there are several treatment options including removal of the area of abnormality (via laser, loop electrosurgical excisional procedure [LEEP], or cold knife conization) or destruction of the area of abnormality (via cryotherapy or laser vaporization).⁴⁶ Each approach has its indications, advantages and disadvantages, but, importantly, cure rates are comparable. Since 2012, observation has been recommended over treatment for HSIL in young women 21 through 24 years of age or in pregnant women, to avoid reproductive harms.⁴⁵

Treatment of cervical and other HPV-associated cancers

For invasive cervical and other HPV-associated cancers, several treatment options are available including surgery, radiation therapy, and chemotherapy, alone or in combination depending on stage of disease. For cervical cancer, depending on the stage of disease at diagnosis, a woman may have the option to preserve her fertility or keep her ovaries. The survival rate 5 years after diagnosis of cervical cancer varies depending upon the stage of cervical cancer, ranging from 93% among those diagnosed at the earliest invasive state to only about 15% of those diagnosed at the latest stages.⁴⁷

IV. Laboratory testing

Specimen collection

The Centers for Disease Control and Prevention (CDC) conducts HPV testing only for certain special studies and surveillance programs. Jurisdictions should not send specimens to CDC except as part of an existing project or study.

HPV testing

HPV cannot be detected through culture methods. HPV infection of epithelial cells is associated with characteristic morphologic changes, and the presence of HPV may be suggested on the basis of pathologic findings. However, definitive detection of HPV requires molecular testing.

HPV testing can be used in cervical cancer screening.³⁷ Only clinically validated tests, i.e., those approved by the U.S. Food and Drug Administration (FDA) should be used. Currently approved tests detect 14 high-risk types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) and report results for detection of any of these types. Some tests also provide separate results for HPV 16 or 18. Clinical tests use a variety of technical approaches, including signal and target amplifications, and have been validated against clinical outcomes, i.e. HSIL/AIS or higher-grade-lesions. None of the HPV tests are approved for use in men, adolescents, or detection of infection in partners.

For epidemiologic and research questions using detection of HPV DNA as an endpoint, type-specific HPV research tests yield important information. There are many different formats, and results are dependent on the nature of the assay and the type of sample. The most common approach is to use a polymerase chain reaction (PCR) that amplifies all mucosal HPV types (consensus PCR) with type(s) being determined by subsequent hybridization and/or sequencing of the products. Research tests have not been validated for disease detection and should not be used clinically: their high analytic sensitivity detects low levels of HPV that is not predictive of disease requiring treatment.

Research tests such as serologic testing for HPV antibodies may be useful to monitor population exposure to HPV. As HPV infection is confined to the epithelium and infected cells are shed before cell death, natural HPV infection results in minimal host immune response and not all those infected have detectable antibodies. Serologic assays are currently available only in research settings.

V. HPV Vaccines

Three HPV vaccines are licensed in the United States: a quadrivalent vaccine (4vHPV; Gardasil, Merck and Co, Inc.); a bivalent vaccine (2vHPV; Cervarix, GlaxoSmithKline); and a 9-valent vaccine (9vHPV; Gardasil 9, Merck and Co, Inc.).⁴⁸ (See Table 1). None are live vaccines; all the vaccines are composed of virus-like particles (VLPs) prepared from recombinant L1 capsid protein of the targeted HPV types. Although all 3 vaccines are still licensed in the United States, only 9vHPV was being distributed in the United States as of late 2016.

2vHPV is directed against 2 oncogenic types (HPV 16 and 18). 4vHPV is directed against 2 oncogenic types (HPV 16 and 18) and 2 non-oncogenic types (HPV 6 and 11). 9vHPV is directed against all 4vHPV types plus 5 additional oncogenic types (31, 33, 45, 52, 58). The vaccines are prophylactic and have no therapeutic effect on HPV-related disease, nor on risk of progression to disease in persons already infected with vaccine-type HPV-related disease, nor on risk of progression to disease in persons already infected with vaccine-type HPV at the time of vaccination. 4vHPV (Gardasil) is licensed by the FDA for use in females and males 9 through 26 years of age. 2vHPV (Cervarix) is licensed for use in females 9 through 25

years of age.^{48,49} 9vHPV is licensed for use in females and males 9–26 years of age.⁴⁸ Information on vaccine efficacy, safety, and contraindications is reviewed and updated as needed by the Advisory Committee on Immunization Practices (ACIP), which provides national recommendations for vaccine use.^{1,50,51}

TABLE 1. Characteristics of the three human papillomavirus (HPV) vaccines licensed for use in the United States

Characteristic	Bivalent (2vHPV)*	Quadrivalent (4vHPV)†	9-valent (9vHPV)‡
Brand name	Cervarix	Gardasil	Gardasil 9
Virus-like particles	16, 18	6, 11, 16, 18	6, 11, 16, 18, 31, 33, 45, 52, 58
Manufacturer	GlaxoSmithKline	Merck and Co., Inc.	Merck and Co., Inc.
First FDA licensure	2009	2006	2014
Manufacturing	<i>Trichoplusia ni</i> insect cell line infected with L1 encoding recombinant baculovirus	<i>Saccharomyces cerevisiae</i> (Baker's yeast), expressing L1	<i>Saccharomyces cerevisiae</i> (Baker's yeast), expressing L1
Adjuvant	500 µg aluminum hydroxide	225 µg amorphous aluminum hydroxyphosphate sulfate	500 µg amorphous aluminum hydroxyphosphate sulfate
Volume per dose	50 µg 3-O-desacyl-4' monophosphoryl lipid A	0.5 ml	0.5 ml
Administration	Intramuscular	Intramuscular	Intramuscular

Adapted from [51].

Abbreviation: L1 = the HPV major capsid protein.

* Only licensed for use in females in the United States. Package insert available at <http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM186981.pdf>.

† 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/UCM426457.pdf>.

Recommendations for use of HPV vaccines

National recommendations for use of HPV vaccines are developed by ACIP and harmonized with other professional organizations.^{1,49–51}

Routine and catch-up age groups

ACIP recommends routine HPV vaccination for U.S. girls and boys at 11 or 12 years of age.

Vaccination can be given starting at 9 years of age. ACIP also recommends vaccination for females through 26 years of age and for males through 21 years of age who were not adequately vaccinated previously. Males 22 through 26 years of age may be vaccinated.¹ (See also: Special populations, Medical conditions.)

Dosing schedules

During 2006–2016, a 3-dose vaccination schedule was recommended for all vaccinees. In October 2016 ACIP voted to recommend a 2-dose schedule for persons initiating vaccination at age 9–14 years.⁵⁰

Current recommendations are for 2 doses of HPV vaccine for persons initiating vaccination before their 15th birthday. The second dose should be administered 6–12 months after the first dose (0, 6–12 month schedule,[†] https://www.cdc.gov/mmwr/volumes/65/wr/mm6549a5.htm#T1_down).

For persons initiating vaccination on or after their 15th birthday, the recommended immunization schedule is 3 doses of HPV vaccine. The second dose should be administered 1–2 months after the first dose, and the third dose should be administered 6 months after the first dose (0, 1–2, 6 month schedule,[‡] https://www.cdc.gov/mmwr/volumes/65/wr/mm6549a5.htm#T1_down).

Persons vaccinated previously

Persons who initiated vaccination with 9vHPV, 4vHPV, or 2vHPV before their 15th birthday, and received 2 doses of any HPV vaccine at the recommended dosing schedule (0, 6–12 months), or 3 doses of any HPV vaccine at the recommended dosing schedule (0, 1–2, 6 months), are considered adequately vaccinated.

Persons who initiated vaccination with 9vHPV, 4vHPV, or 2vHPV on or after their 15th birthday, and received 3 doses of any HPV vaccine at the recommended dosing schedule, are considered adequately vaccinated.

9vHPV may be used to continue or complete a vaccination series started with 4vHPV or 2vHPV.

For persons who have been adequately vaccinated with 2vHPV or 4vHPV, there is no ACIP recommendation regarding additional vaccination with 9vHPV.

Interrupted schedules

If the vaccination schedule is interrupted, the series does not need to be restarted. The number of recommended doses is based on age at administration of the first dose.

Special populations

For children with a history of sexual abuse or assault, ACIP recommends routine HPV vaccination beginning at 9 years of age.

For men who have sex with men, including men who identify as gay or bisexual, or who intend to have sex with men, ACIP recommends routine HPV vaccination as for all males, and vaccination through 26 years of age for those who were not adequately vaccinated previously.

For transgender persons, ACIP recommends routine HPV vaccination as for all adolescents and vaccination through 26 years of age for those who were not adequately vaccinated previously.

Medical conditions

ACIP recommends vaccination with 3 doses of HPV vaccine (0, 1–2, 6 months) for females and males 9 through 26 years of age with primary or secondary immunocompromising conditions that might reduce cell-mediated or humoral immunity, such as B-lymphocyte antibody deficiencies, T-lymphocyte complete or partial defects, HIV infection, malignant neoplasms, transplantation, autoimmune disease, or immunosuppressive therapy, because immune response to vaccination might be attenuated.⁵² (See Appendix B.)

Contraindications and precautions

HPV vaccines are contraindicated for persons with a history of immediate hypersensitivity to any vaccine component. 4vHPV and 9vHPV are contraindicated for persons with a history of immediate hypersensitivity to yeast. HPV vaccines can be administered to persons with minor acute illnesses. Vaccination of persons with moderate or severe illnesses should be deferred until after the patient improves. Syncope can occur after vaccination, most commonly among adolescents and young adults. Although syncopal episodes are uncommon, vaccine providers should consider observing patients (with patients seated or lying down) for 15 minutes after they receive any vaccine, including HPV vaccine.¹

HPV vaccines are not recommended for use in pregnant women. If a woman is found to be pregnant after initiating the vaccination series, the remainder of the series should be delayed until she is no longer pregnant. If a vaccine dose has been administered during pregnancy, no intervention is needed. A new pregnancy registry has been established for 9vHPV. Inadvertent exposure during pregnancy can be reported to the vaccine manufacturer or to the Vaccine Adverse Event Reporting System (VAERS).

Adverse events occurring after administration of any vaccine should be reported to VAERS. Reports can be submitted to VAERS online, by fax, or by mail. Additional information about VAERS is available by telephone (1-800-822-7967) or online (<https://vaers.hhs.gov>).

VI. Importance of Surveillance.

HPV infections are not nationally notifiable (see section on reporting, below).⁵³ This is because (1) most sexually active individuals will acquire at least 1 type of HPV infection at some point in their lives and infections usually clear or become undetectable, and (2) most infections will not have any associated clinical disease. However, special studies to monitor HPV infection and HPV-associated diseases can help determine the impact of HPV vaccines. Existing and new systems are in place to monitor coverage and impact of HPV vaccine on short-, medium-, and long-term HPV-related outcomes in the United States (see Enhanced Surveillance section).

VII. Disease Reduction Goals

After the quadrivalent HPV vaccine was licensed in 2006, *Healthy People 2020* stated an objective of 80% coverage with 3 doses of HPV vaccine for females by age 13 to 15 years.⁴⁷ It also stated objectives to “Reduce the death rate from cancer of the uterine cervix below a target of 2.2 deaths/100,000 females (from a baseline of 2.4 per 100,000 in 2007)” and “Reduce invasive uterine cancer to 7.2 new cases per 100,000 females.⁵⁵ There is also a stated goal to “increase the proportion of women who receive a cervical cancer screening based on the most recent guidelines” with a target of 90% of women 21 to 65 years of age receiving screening (from a baseline of 84.5% in 2008).⁵⁵ There are currently no stated goals for reduction of anogenital warts, RRP, or non-cervical HPV-associated cancers.

Another *Healthy People 2020* objective addresses surveillance to “increase the number of central, population-based registries from the 50 States and the District of Columbia which captures case information on at least 95 percent of the expected number of reportable cancers”.⁵⁵

VIII. Case Definitions

HPV infections and most HPV-associated conditions are not nationally notifiable. However, invasive cancers and in situ cancers (including cancers and precancers caused by HPV) are reportable to central cancer registries, with the exception of in situ cervical cancer and any intraepithelial neoplasia. The explanations provided below are intended to describe classification of HPV-associated endpoints where surveillance is possible.

HPV infection

No national case-reporting system for HPV infections exists. Routine testing for HPV infection is not recommended; screening for high-risk types is clinically indicated in specific situations. For information on clinical indications for high-risk HPV testing, see Section III. Screening and Treatment. For information on laboratory tests that can be used to detect HPV infections, see Section IV. Laboratory Testing.

Abnormal Pap tests and precancerous anogenital lesions

Pap tests assess cells collected by scraping or brushing the surface of the cervix (exfoliated cytology). Abnormal Pap test categories are listed by increasing grade of severity for squamous lesions: atypical squamous cells (ASC)-US; ASC cannot rule out high-grade squamous intraepithelial lesion (ASC-H); low-grade intraepithelial lesions (LSIL); and high-grade intraepithelial lesions (HSIL). Categories for glandular lesions include atypical glandular cells (AGC) and adenocarcinoma in situ (AIS). An abnormal cervical cancer screening test (Pap test and/or clinical HPV test) should prompt follow-up colposcopy and biopsy as indicated. Histologic evaluation of the biopsy determines clinical management. Terminology introduced in 2012 for precancerous cervical and other anogenital histologic lesions (vulvar, vaginal, anal) also uses HSIL terminology instead of intraepithelial neoplasia (IN Grade 2 or Grade 3).⁴⁴

Anogenital and oropharyngeal cancers

The primary site and pathologic diagnosis of the cancers are coded using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3).

Anogenital warts

A diagnosis of anogenital warts is made based on visual inspection of the lesion(s). Although anogenital warts are not nationally notifiable at this time, a 1996 case definition was published based on a clinical description and laboratory criteria.⁵³

Recurrent respiratory papillomatosis

A diagnosis of recurrent respiratory papillomatosis is made based on the presence of wart-like lesions in any upper aerodigestive tract site, and histopathology demonstrating papillomas.

IX. Reporting and Case Notification

Case reporting within a jurisdiction

In the United States, the impact from cervical disease and other HPV-related cancers are measured by population-based cancer registries participating in the CDC's National Program of Cancer Registries (NPCR) and/or the Surveillance Epidemiology and End Results (SEER) program. Data are collected and analyzed at the state (central cancer registries) as well national (NPCR/SEER) levels (see Appendix C).

Case notification to CDC

HPV infection and other HPV-associated clinical conditions are not nationally reportable or required by CDC. However, some states or jurisdictions have made certain HPV-associated conditions reportable. Contact your state health department for reporting requirements in your area.

X. Enhancing Surveillance

The primary goal of HPV vaccination is to prevent cervical cancers, other HPV-associated cancers, and genital warts associated with vaccine-targeted HPV infections. The primary purpose of surveillance for HPV infections and associated conditions is to monitor potential impacts of the vaccination program. Such surveillance poses many challenges: infection with HPV is relatively common, a high proportion of infections are asymptomatic and resolve spontaneously, and some associated disease may not develop until many years after initial infection.

Surveillance data on HPV-associated cancers, including cervical cancer, are collected in 2 population-based central cancer registries—NPCR and SEER—which together collect data on cancers diagnosed in 100% of the U.S. population. Data from the registries have been used to assess the pre-vaccine burden of HPV-associated cancers and will be the basis for monitoring relevant cancers post-vaccine introduction. However, the impact of vaccine on preventing invasive cancers is not expected until several decades after widespread adoption of the vaccine.

Early measures of vaccine impact include outcomes such as incidence of HPV infections, anogenital warts, and cervical cancer precursors. A variety of activities have been established to monitor these endpoints in the United States as described below.

Efforts to monitor HPV vaccine impact on high-grade HPV-associated cervical lesions are on-going. A geographically varied 5-site sentinel population cervical precancer monitoring program has measured the incidence of HPV type-specific CIN grades 2 and 3 (now designated HSIL) and AIS since 2008 and has demonstrated vaccine effectiveness and impact.^{56–58} A statewide project in New Mexico has monitored the incidence of cases of CIN1, CIN2, and CIN3 since 2007; this system, which also conducts typing on lesions, and maintains a Pap registry to monitor changes in screening practices, has documented declines in precancer in screened women.²⁹ Another study collects surveillance data on high-grade cervical cancer precursors (CIN3) from 4 central cancer registries (3 entire states and 1 large metropolitan area).⁵⁹ Finally, a pilot study was conducted in 5 cancer registries in areas with a high burden of cervical cancer to evaluate baseline type-specific HPV prevalence in cervical and other relevant cancers.³⁴

Methods for monitoring genital warts in the United States include surveillance in a network of STD clinics and clinical claims data.

The National Health and Examination Survey (NHANES), is used to monitor the impact of vaccination on HPV prevalence; type-specific HPV prevalence is being monitored in genital specimens in United States females and males; monitoring was conducted in oral specimens in 2009–2016.^{60–64} HPV prevalence is also monitored in women undergoing cervical cancer screening at selected managed care organizations⁶⁵ and among men who have sex with men through clinic-based studies.⁶⁶ A project has also been established to monitor trends in recurrent respiratory papillomatosis.

Additional ongoing efforts include analysis of data from administrative claims and managed care organizations to monitor HPV-associated conditions and determine the impact of HPV vaccine on health care costs related to detection and treatment of these conditions.^{65,67,68}

Although CDC does not recommend collection of routine surveillance data on HPV-associated conditions other than cancer, such data may be useful in sentinel projects within specific states or jurisdictions with sufficient resources to collect data and where standardized protocols are used. Within these settings, making conditions reportable, such as CIN2/3 (HSIL) and AIS, has been initiated in some jurisdictions and has facilitated complete case ascertainment.

Appendix A.

Table A1. Number of HPV-associated and HPV-attributable cancer cases per year, United States, 2009–2013

Cancer site	Average number of cancers per year in sites where HPV is often found (HPV-associated cancers)	Percentage probably caused by any HPV type*	Number probably caused by any HPV type*	Percentage probably caused by HPV types 16/18†	Number probably caused by HPV types 16/18†	Percentage probably caused by HPV types 31/33/45/52/58‡	Number probably caused by HPV types 31/33/45/52/58‡
Cervix	11,693	91%	10,600	66%	7,700	15%	1,700
Vagina	819	75%	600	55%	500	18%	100
Vulva	3,671	69%	2,500	49%	1,800	14%	500
Penis	1,181	63%	700	48%	600	9%	100
Anus	5,229	91%	4,800	79%	4,200	8%	400
female	3,416	93%	3,200	80%	2,700	11%	400
male	1,813	89%	1,600	79%	1,400	4%	100
Rectum	772	91%	4,800	79%	600	8%	100
female	528	93%	3,200	80%	400	11%	100
male	244	89%	1,600	79%	200	4%	<100
Oropharynx	16,479	70%	11,600	60%	9,900	6%	900
female	3,203	63%	2,000	51%	1,600	10%	300
male	13,279	72%	9,600	63%	8,400	4%	600
Total	39,844	79%	31,500	63%	25,300	10%	3,800
female	23,330	83%	19,400	63%	14,700	13%	3,100
male	16,514	73%	12,100	64%	10,600	4%	700

Adapted from [24].

* HPV types detected in genotyping study; most were high risk HPV types known to cause cancer.³⁴

† HPV types 16/18 can be prevented by the bivalent, quadrivalent, and 9-valent HPV vaccines.

‡ HPV types 31/33/45/52/58 can be prevented by the 9-valent HPV vaccine.

Appendix B.

Table B2. ACIP-recommended number of doses and intervals for human papillomavirus (HPV) vaccine, by age at series initiation and medical conditions—United States, 2016

Population	Recommended number of HPV vaccine doses	Recommended interval between doses
Persons initiating HPV vaccination at ages 9 through 14 years,* except immunocompromised persons†	2	0, 6–12 months‡
Persons initiating HPV vaccination at ages 15 through 26 years§ and immunocompromised persons† initiating HPV vaccination at ages 9 through 26 years	3	0, 1–2, 6 months**

Adapted from [50].

* ACIP recommends routine HPV vaccination for adolescents at age 11 or 12 years; vaccination may be given starting at age 9 years.

† Persons with primary or secondary immunocompromising conditions that might reduce cell-mediated or humoral immunity (see also: Medical conditions).

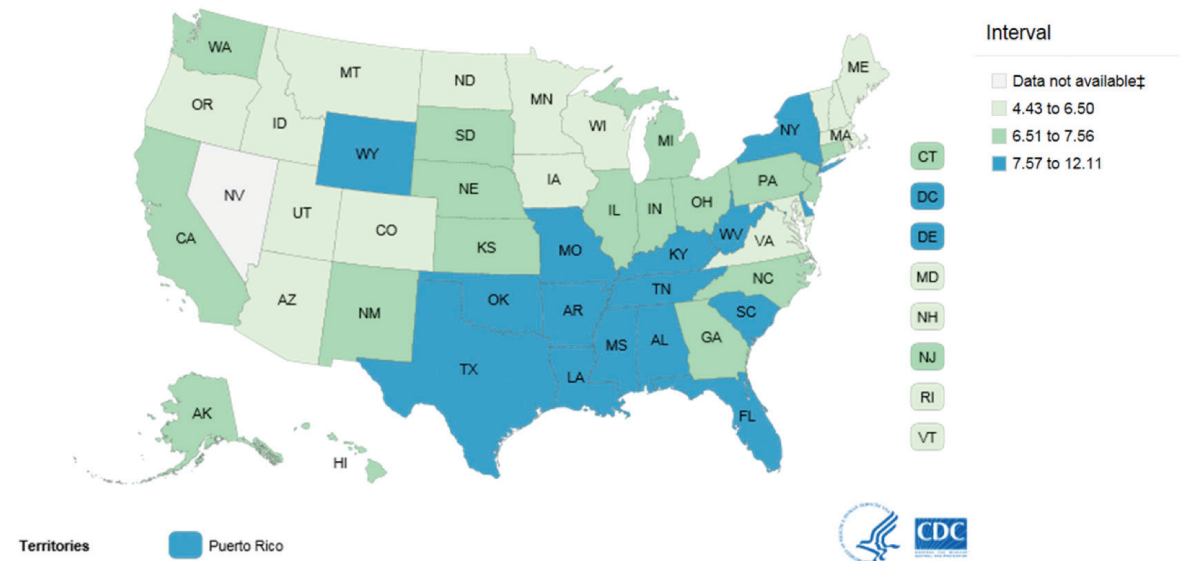
‡ In a 2-dose schedule of HPV vaccine, the minimum interval between the first and second doses is 5 months.

§ For persons who were not adequately vaccinated previously, ACIP recommends vaccination for females through age 26 years and for males through age 21 years; males ages 22 through 26 years may be vaccinated. Vaccination is recommended for some persons aged 22 through 26 years; see Medical conditions and Special populations.

** In a 3-dose schedule of HPV vaccine, the minimum intervals are 4 weeks between the first and second doses, 12 weeks between the second and third doses, and 5 months between the first and third doses.

Appendix C.

Figure C1. HPV-Associated Cervical Cancer Rates by State, United States, 2009–2013



Rates are per 100,000 and age-adjusted to the 2000 U.S. Standard Population (19 age groups—Census P25–1130).

Data are from population-based cancer registries participating in the CDC National Program of Cancer Registries and/or the NCI Surveillance, Epidemiology and End Results Program, meeting criteria for high data quality for all years 2009–2013, and covering about 99% of the US population.

HPV-associated cancers were defined as cancers at specific anatomic sites with specific cellular types in which HPV DNA frequently is found. All cancers were confirmed histologically. Cervical cancers (ICD-O-3 site codes C53.0–C53.9) were limited to carcinomas (ICD-O-3 histology codes 8010–8671, 8940–8941).

Rates were suppressed if the data did not meet criteria for high data quality or if there were fewer than 16 cases.

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