

## 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, with an estimated 6.2 million persons becoming newly infected every year.<sup>1</sup> More than 100 HPV types have been identified, over 40 of which can infect the genital area. HPV types are classified by their association with cancer.<sup>2</sup> Non-oncogenic, or low-risk HPV types, such as HPV 6 or 11, can cause (1) benign or low-grade abnormalities of the cervix, (2) anogenital warts, and (3) a disease of the respiratory tract called recurrent respiratory papillomatosis (RRP).<sup>3</sup> Oncogenic, or high-risk HPV types, including types 16 and 18, can cause intraepithelial neoplasia of the anogenital region, including cervical, vulvar, vaginal, penile, and anal cancers as well as some oropharyngeal cancers.<sup>4-6</sup>

Among the cancer-related outcomes of HPV infection, cervical cancer is the most important outcome, with over 500,000 new cases and 275,000 attributable deaths world-wide in 2008.<sup>4,7</sup> High-risk HPV types are detected in almost all cervical cancers; approximately 70% of cervical cancers worldwide are due to types 16 and 18.<sup>8</sup> While persistent infection with high-risk types is considered necessary for the development of cervical cancer, it is not sufficient because the vast majority of women with high-risk HPV infection do not develop cancer.<sup>9-11</sup>

In addition to its association with cervical cancer, high-risk HPV infection is associated with cancer of the vulva, vagina, penis and anus<sup>5</sup> (see Appendix A). Each of these cancers is less common than cervical cancer and, unlike cervical cancer, not all cases of these less common anogenital cancers are related to HPV infection.<sup>4,12-16</sup> High-risk types of HPV also play a role in the development of some oropharyngeal cancers.<sup>5,6</sup>

Genital HPV infection is primarily transmitted by genital contact, usually (but not necessarily) through sexual intercourse.<sup>17</sup> Most HPV infections are transient and asymptomatic, causing no clinical manifestations. Studies have shown that more than 90% of new HPV infections, including those with high-risk types, clear or become undetectable within two years, and clearance usually occurs in the first 6 months after infection.<sup>11,18-20</sup> Persistent infection with high-risk HPV is the most important risk factor for cervical cancer precursors and invasive cervical cancer.<sup>11,20-23</sup>

Noncancer-related outcomes of HPV infection include anogenital warts and RRP. Almost all anogenital warts are due to infection with low-risk HPV types; approximately 90% are associated with two low-risk HPV types, types 6 and 11.<sup>3</sup> The prevalence of genital warts has been examined using nationally representative surveys and health-care claims data.<sup>24,25</sup> An estimated 1% of sexually active adolescents and adults in the United States have clinically apparent genital warts at any given time.<sup>26</sup> In one national survey, 5.6% of males and females aged 14-59 reported having been diagnosed with genital warts in their lifetime.<sup>25</sup> RRP is a rare condition characterized by recurrent warts or papillomas in the upper respiratory tract, particularly the larynx. There are juvenile onset and adult onset forms. The juvenile onset (JORRP) form is believed to result from HPV infection transmitted perinatally from a mother to her baby during delivery. Estimates of the incidence of JORRP are relatively imprecise but range from 0.12 to 2.1 cases per 100,000 children aged <18 years.<sup>27</sup> Even less is known about the incidence of the adult form of RRP.

### II. Disease Description

Most instances of HPV infection are asymptomatic (no clinical manifestations). However, even asymptomatic cervical infection can result in cervical changes that can be detected as a result of cervical cancer screening with cytology (Pap test). Cervical cytology can detect changes in cervical epithelial cells (epithelial cells found on the external surface of the cervix are squamous and those in the endocervical canal are glandular).

Abnormal Pap test results are classified by increasing grade of abnormality. Since 2003, molecular tests that detect oncogenic HPV DNA have provided another screening method that may be used in conjunction with Pap tests for certain age groups or situations. Each year, approximately 50 million women in the United States undergo cervical cancer screening. Approximately 3.5–5 million will require further evaluation: 2–3 million atypical squamous cells of unknown significance (ASC-US), 1.25 million low-grade squamous intraepithelial lesions (LSIL) and 300,000 high-grade intraepithelial lesions (HSIL) Pap tests.<sup>29–31</sup> HPV types 16 and 18 are more commonly found in higher grade lesions than lower grade lesions. In one study, the prevalence of HPV 16 was 29.8% among women with LSIL compared to 57.8% among those with HSIL Pap tests.<sup>28</sup>

Regular screening for cervical cancer with the Pap test can detect cancer precursor lesions early. Abnormal Pap test results (repeated ASC-US, ASC-US with positive HPV test, or more severe abnormality) require the woman to be evaluated further with colposcopic examination of the cervix (i.e. under magnification). During colposcopy, a biopsy of the cervix may be taken for histologic examination to diagnose precancerous or invasive (either squamous cell carcinoma or adenocarcinoma) cancer lesions. Precancerous lesions include cervical intraepithelial neoplasias (CIN) grades 2 and 3 and adenocarcinoma in situ (AIS).

Cervical screening recommendations in the US differ by organization;<sup>29</sup> however, all recommendations state that screening should begin by age 21 years. Cervical cancer incidence rates have decreased approximately 75% and mortality rates approximately 70% since the 1950's, largely due to Pap testing.<sup>30,31</sup> In 2007, cervical cancer incidence in the United States was 7.9 per 100,000 women<sup>32</sup>, with approximately 12,200 new cases reported.<sup>33</sup> The median age at diagnosis for cervical cancer was 48 years.<sup>34</sup>

Anogenital warts typically develop approximately 2–3 months after HPV infection (typically types 6 and 11). However, not all persons infected with HPV types 6 and 11 develop genital warts. Anogenital warts can be treated, although many warts (20–30%) regress spontaneously. Recurrence of anogenital warts is common (approximately 30%), whether clearance occurs spontaneously or following treatment.<sup>35</sup> Juvenile-onset recurrent respiratory papillomatosis (JORRP), believed to be from vertical transmission of HPV from mother to infant during delivery, has a median age at diagnosis of 4 years. A multicenter registry of JORRP in the US collecting data between 1997 to 2002,<sup>36</sup> demonstrated that the clinical course of JORRP was associated with extensive morbidity, requiring a median of 13 lifetime surgeries to remove warts and maintain an open airway.

### III. Treatment of HPV-Associated Diseases

HPV infections are not treated; instead treatment is directed at the HPV-associated conditions. Current treatment options for anogenital warts and intraepithelial neoplasias vary by the severity of disease and the anatomical location as described below.

#### *Anogenital warts*

The primary goal of treating visible anogenital warts is wart removal. In the majority of patients, treatment can induce wart-free periods. If left untreated, visible anogenital warts might resolve on their own, remain unchanged, or increase in size or number. It is unknown if treatment of anogenital warts affects genital transmission of HPV. No evidence indicates that the presence of genital warts or their treatment is associated with the development of cervical cancer. No single treatment is ideal for all patients. Most patients require a course of therapy rather than a single treatment.

Treatment regimens are classified into patient-applied and provider-applied modalities. Patient-applied modalities include: Podoflox solution or gel 0.5%, Imiquimod cream 5%, or sinecatechins ointment 15%; provider-administered modalities include cryotherapy, podophyllin resin 10%–25%, trichloroacetic acid (TCA) or bichloroacetic acid 80%–90%, or surgical removal. Other regimens include intralesional interferon or laser surgery.<sup>37</sup>

### *Cervical Cancer and 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 to interrupt progression to invasive disease. Precancerous cervical lesions and invasive cancer are diagnosed based on the histology of tissues obtained with biopsy or excision, and these samples guide further treatment decisions. Cervical cytology (Pap test) is a screening, not a diagnostic, test.

For low-grade precancerous cervical biopsy results (CIN 1), the recommended management may be to follow-up with further screening to detect persistence or progression of the lesion. For moderate to high grade precancerous cervical lesions CIN 2, CIN 3, or AIS, a woman has several treatment options including removal of the area of abnormality (laser, loop electrosurgical excisional procedure or LEEP, cold knife conization) or destruction of the area of abnormality (cryotherapy, laser vaporization).<sup>38</sup> Each of those have their indications, advantages and disadvantages, but, importantly, cure rates are comparable. More recently, observation is recommended over treatment for CIN 2 lesions in women of reproductive age.<sup>38</sup>

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 five years after diagnosis of cervical cancer varies depending upon the stage of cervical cancer. The risk of survival decreases with higher stages of disease.

## **IV. Laboratory testing**

HPV cannot be detected through culture methods. HPV detection requires molecular testing. As noted in the treatment section, HPV infection per se is not treated, rather treatment is directed at clinically detectable lesions associated with the infections. HPV testing has a clinical role in identifying individuals with an increased risk of an HPV-associated cervical precancer or cancer. Three tests are currently approved by the Food and Drug Administration (FDA) for detecting clinically significant levels of any of 13–14 high-risk HPV types: (1) the Digene HC2 High-Risk HPV DNA test (Qiagen, Gaithersburg, MD, <http://www.qiagen.com/products/digenehpvtsthc2.aspx>), (2) the Cervista™ HPV HR test (Hologics, Bedford, MA, <http://www.cervistahpv.com>), and (3) the cobas 4800 HPV test (Roche Molecular Systems, Pleasanton, CA, <https://www.cobas-roche.co.uk>). Cervista™ High-Risk and HC2 High-Risk tests indicate the presence of one or more of the high risk types but does not indicate a specific type. The cobas test also provides individual detection of HPV 16 and 18, as does another test, the Cervista™ 16/18 HPV test (Hologics, Bedford, MA, <http://www.cervistahpv.com>). None of the HPV tests are approved for use in men, adolescents, or detection of infection in partners.

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 is not used for screening of HPV associated lesions in anatomic sites other than the cervix, and it is not useful in diagnosis or clinical management of cancer, cancer precursors, or warts.

For epidemiologic and research questions using HPV as an endpoint, type-specific HPV tests have many advantages. 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 PCR that amplifies all mucosal HPV types (consensus PCR) with type(s) being determined by subsequent hybridization and/or sequencing of the products. These PCR tests are not useful clinically because 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 Vaccine

Two HPV vaccines are licensed in the US: a quadrivalent vaccine (HPV4; Gardasil, Merck and Co, Inc.) and a bivalent vaccine (HPV2; Cervarix, GlaxoSmithKline).<sup>39</sup> Neither vaccine is a live vaccine; both vaccines are composed of virus-like particles (VLPs) prepared from recombinant L1 capsid protein of the targeted HPV types. HPV2 is directed against two oncogenic types (HPV 16 and 18). HPV4 is directed against two oncogenic types (HPV 16 and 18) and two non-oncogenic types (HPV 6 and 11). The vaccines are prophylactic and have no therapeutic effect on HPV-related disease, or on risk of progression to disease in persons who have HPV infection at the time of vaccination. HPV4 (Gardasil) was licensed by the Food and Drug Administration (FDA) in 2006 for use in females aged 9 through 26 years and in 2009 for use in males aged 9 through 26 years. HPV2 (Cervarix) was licensed by the FDA in 2009 for use in females aged 10 through 25 years.<sup>40,41</sup>

Clinical trials in >18,000 females aged 15–25 years for HPV2 and >20,000 females aged 16–26 for HPV4 have demonstrated high levels of efficacy for both vaccines in preventing cervical precancers (CIN 2/3 and AIS) caused by the targeted HPV types in females naïve to vaccine type infection at the time of vaccination.<sup>42,43</sup> HPV4 also has demonstrated high efficacy against HPV 6 and HPV 11-related genital warts (males and females), HPV 16 and 18-related vaginal and vulvar precancer lesions, and HPV 16 and 18 related anal precancers (males).<sup>42</sup> In post hoc analyses, HPV2 demonstrated partial efficacy against incident cervical precancers related to non-vaccine HPV types 31 and 45 and HPV4 showed partial efficacy against HPV 31.<sup>43</sup>

Immunogenicity and safety studies were conducted in females aged 9 to 15 (quadrivalent vaccine)<sup>44</sup> and females aged 10–14 years (bivalent vaccine)<sup>45</sup> of age to bridge the antibody titers to females in the efficacy trials. For both vaccines, over 99% of study participants developed antibodies after vaccination; titers were higher for young girls than for older females participating in the efficacy trials.

Data from clinical trials demonstrated high efficacy of the quadrivalent vaccine against HPV vaccine type-related genital warts and anal HPV vaccine type-related precancers among males aged 9–26 years.<sup>46</sup> These data supported FDA licensure of the quadrivalent vaccine for prevention of genital warts and anal cancers among males aged 9–26 years.

Each 0.5-mL dose of HPV4 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. The VLPs are adsorbed on 225 µg amorphous aluminum hydroxyphosphate sulfate adjuvant (alum). Each 0.5-mL dose of HPV2 contains 20 µg HPV 16 L1 protein and 20 µg HPV 18 L1 protein. The VLPs are adsorbed on 500 µg aluminum hydroxide and 50 µg 3-O-desacyl-4' monophosphoryl lipid A adjuvant.

## VI. Recommendations for Use of HPV vaccines.<sup>40, 46</sup> (see Appendix B)

Both HPV vaccines are administered intramuscularly as 3 separate 0.5 ml doses. The second dose should be administered 1–2 months after the first dose, and the third dose is administered 6 months after the first dose.

### *Female vaccination*

The Advisory Committee on Immunization Practices (ACIP) recommends vaccination with HPV2 or HPV4 vaccine for prevention of cervical cancers and precancers. Both vaccines may also provide protection against other HPV-related cancers in addition to cervical cancer. HPV4 vaccine is also recommended for prevention of genital warts in females.

ACIP recommends routine vaccination of females 11 or 12 years of age with three doses of either HPV2 or HPV4 vaccine. The vaccination series can be started as young as 9 years of age. Catch up vaccination with either vaccine is also recommended for females 13 through 26 years of age who have not been previously vaccinated or who have not completed the full series. Sexually active females who have not been infected with any of the HPV vaccine types would receive full benefit from vaccination. However, the great majority of females who may have

already been exposed to one or more of the HPV vaccine types can benefit from vaccination, even though benefit would be less. Pap testing, screening for HPV DNA or HPV antibody are not needed prior to vaccination at any age.

Whenever feasible, the same HPV vaccine should be used for the complete vaccination series. However, in the absence of information on previous doses, either vaccine can be used to complete the series for protection against HPV types 16 and 18. A vaccination series with less than 3 doses of HPV4 may provide less protection against HPV 6 or 11-related genital warts.

#### *Male vaccination*

ACIP provides guidance that HPV4 may be given to males aged 9 through 26 years; however, vaccine for males is not part of the routine immunization schedule.

#### *Cervical cancer screening among vaccinated females*

At present, cervical cancer screening recommendations have not changed for females who receive HPV vaccine. Health care providers administering HPV vaccine should educate women about the importance of cervical cancer screening as recommended by national organizations.

#### *Immunocompromised persons*

Because HPV2 and HPV4 vaccines are non infectious vaccines, they can be administered to females who are immunosuppressed as a result of disease or medications; however, the immune response and vaccine efficacy might be less than that in persons who are immunocompetent.

#### *Vaccination during Pregnancy*

HPV2 and HPV4 vaccines are not recommended for use in pregnancy. If a woman is found to be pregnant after initiating the vaccination series, the remainder of the 3-dose regimen should be delayed until after completion of the pregnancy. If a vaccine dose has been administered during pregnancy, there is no indication for any intervention.

#### *Precautions and Contraindications*

##### **1) Acute Illnesses**

HPV2 and HPV4 vaccines can be administered to persons with minor acute illnesses (e.g., diarrhea or mild upper respiratory track infections, with or without fever).

Vaccination of persons with moderate or severe acute illnesses should be deferred until after the illness improves.

##### **2) Hypersensitivity or allergy to vaccine components**

HPV2 is contraindicated for persons with a history of immediate hypersensitivity to any vaccine component. The prefilled syringes of HPV2 should not be used in persons with anaphylactic latex allergy because syringes have latex in the rubber stopper. HPV2 single dose vials contain no latex. HPV4 is contraindicated for persons with a history of immediate hypersensitivity to yeast or to any vaccine component.

## **VII. Importance of Surveillance**

Identification of every instance of HPV infection is not necessary. This is because (1) most sexually active individuals will acquire 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, especially cervical cancer, 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 outcomes in the US (see Enhanced Surveillance section).

## **VIII. Disease Reduction Goals**

Since the quadrivalent HPV vaccine was licensed in 2006, Healthy People 2020 states a goal of 80% coverage of 3 doses of HPV vaccines for females by age 13 to 15 years.<sup>47</sup> It also states a goal 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).” 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 aged 21 to 65 years receiving screening (from a baseline of 84.5 percent in 2008). 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 that capture case information on at least 95 percent of the expected number of reportable cancers”.

## IX. Case Definitions

There are currently no case definitions approved by the Council of State and Territorial Epidemiologists (CSTE) for the National Notifiable Diseases Surveillance System for HPV infection or any HPV-associated conditions including anogenital warts, RRP, precancerous lesions, or invasive cancers. However, explanations provided below are intended to describe classification of HPV-associated endpoints where surveillance is possible:

**HPV Infection:** Routine testing for HPV infection is not recommended. Testing for high risk types is clinically indicated in two specific clinical situations: (1) in order to triage women with ASC-US Pap tests for further evaluation, and (2) as an adjunct to Pap testing for women age 30 years and older. Tests for low risk HPV infection are not recommended by any clinical or medical organization.

**Abnormal Pap tests and precancerous anogenital lesions:** Pap tests are based on the cytology of the cells and are collected by scraping or brushing cells from the surface of the cervix (exfoliated cytology). Abnormal Pap test categories are listed by increasing grade of severity for squamous lesions: ASC-US; atypical squamous cells-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). Precancerous lesions (CIN 2/3 and AIS) are diagnosed by pathologists on specimens from cervical biopsy prompted by an abnormal Pap tests. Precancerous lesions are also defined for grade 2 or 3 vaginal intraepithelial neoplasias (VAIN 2/3), vulvar intraepithelial neoplasias (VIN 2/3), and anal intraepithelial neoplasia (AIN 2/3) These are defined and used for clinical diagnostics and management.

**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). There are no case definitions for anogenital warts used for surveillance purposes.

**Recurrent Respiratory Papillomatosis:** RRP is diagnosed by a specialist based upon clinical evaluation. No case definitions for RRP are currently in use for surveillance purposes.

## X. Reporting

In the US, disease burden from cervical and other HPV-related cancers are measured by population-based cancer registries participating in the Centers for Disease Control and Prevention’s (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).

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

## XI. Enhancing Surveillance

The goal of HPV vaccination is to prevent clinical conditions associated with infection with vaccine HPV types, with the primary goal being prevention of cervical cancers. However, monitoring the impact of a vaccination program poses many challenges because infection with HPV is relatively common, a high proportion of infections are asymptomatic and the consequences are not seen for many years.

Cervical cancer surveillance data (as well as data on other HPV-associated cancers) are collected by the NPCR and SEER population-based cancer registries which cover over 99% of the US 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 invasive cancers is not expected until several decades after widespread adoption of the vaccine.

The proximal measures of vaccine impact include outcomes such as cervical cancer precursors, anogenital warts, and HPV infection. Although these outcomes are not nationally notifiable, a variety of activities have been established to monitor these endpoints in the US<sup>48</sup> as described below.

Projects have been initiated to determine the feasibility of monitoring HPV vaccine impact on high grade HPV-associated cervical lesions and include state wide or sentinel population monitoring of cervical precancers as well as HPV type specific CIN2/3 and AIS.

Methods for monitoring genital warts in the US include surveillance in a network of STD clinics and through self report of ever being diagnosed with genital warts in the National Health and Examination Survey (NHANES), a nationally representative survey of the US population. NHANES data are also used to monitor the prevalence of type specific HPV infection in US females.

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. Finally, a pilot study was initiated in 5 cancer registries in areas with a high burden of cervical cancer to evaluate baseline HPV types in cervical and other relevant cancers, and typing may be repeated in similar special projects in the future.

Although CDC does not recommend collection of routine surveillance data with respect to HPV-associated conditions other than cancer, these data may be useful in sentinel projects with resources to collect data and where rigorous methods are utilized within specific states and jurisdictions. Within these settings, making conditions reportable, such as CIN2/3, may facilitate complete collection of data and has been initiated in some states/jurisdictions.

## Appendix A.

### Cancers Attributable to High-Risk Human Papillomavirus Infection, US, 2004-2007

Anatomic Area	Average annual number of cases*	HPV associated*	HPV 16/18 associated*
Cervix	11,845	11,370	9,000
Vagina	714	460	400
Vulva	3062	1,560	1,350
Anus & rectum (W)	2977	2,770	2,590
Oropharynx (W)	2306	1,450	1,380
<b>Total (Females)</b>	<b>20,903</b>	<b>17,610</b>	<b>14,720</b>
Penis	1,000	360	310
Anus & Rectum (M)	1,618	1,500	1,410
Oropharynx (M)	8,936	5,630	5,360
<b>Total (Males)</b>	<b>11,553</b>	<b>7,490</b>	<b>7,080</b>

\* Watson M et al. Cancer 2008

\* Gillison ML et al. Cancer 2008

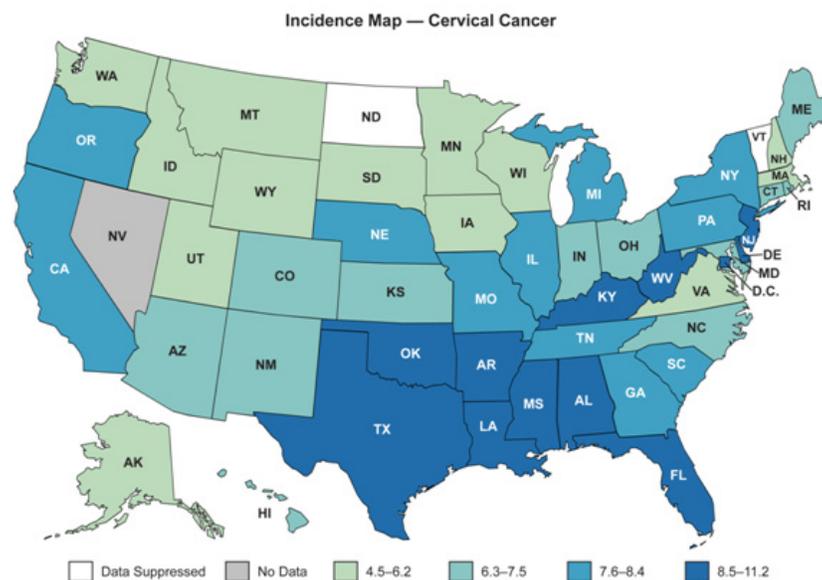
## Appendix B.

### ACIP Recommended Age Groups, Schedule, Dosages and Route of Administration for HPV vaccines

Target population	ACIP Recommendation	Vaccine	Schedule	Dosage, Route
Females	Routine at ages 11 or 12 years and catch up through age 26 years	Quadrivalent or Bivalent vaccine	0, 1-2, 6 months	0.5 ml, Intramuscular injection
Males	May be given to males age 9 through 26 years	Quadrivalent		

## Appendix C.

### United States Cervical Cancer\* Incidence Rates by State, 2007†



\* Rates are per 100,000 and are age-adjusted to the 2000 US standard population.

† Source: US Cancer Statistics Working Group. United States Cancer Statistics: 2003 Incidence and Mortality (preliminary data). Atlanta (GA): US Department of Health and Human Services, Centers for Disease Control and Prevention, and National Cancer Institute; 2006.

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