HPV-Related Cancers and Diseases and How to Increase HPV Vaccination Rates

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Objectives

- Discuss the prevalence of HPV in the United states
- Review and discuss specific HPV-related cancers and diseases in both males and females
- Common questions and answers concerning the switch from HPV4 to HPV9 addressed.
- Review and discuss current ACIP recommendations as they pertain to HPV vaccination for both males and females
- Discuss evidence based action steps to increase HPV vaccination rates in both males and females

Human Papillomavirus (HPV)

- >100 types identified
- 15-20 oncogenic types including 16, 18, 31, 33, 35, 39, 45, 51, 52, 56
- HPV 16 and HPV 18 account for the majority of worldwide cervical cancers
- Nononcogenic types include: 6, 11, 40, 42, 43, 44, 54
- HPV 6 and 11 are most often associated with external anogenital warts

References:
HPV Is Widespread

- Approximately 79 million people in the US are currently infected with HPV.
  - ~39,000 new HPV infections occur every day
  - ~14 million new HPV infections occur each year in the United States.
- Most HPV infections clear on their own; however, persistence of certain HPV types can lead to clinically significant diseases.
- For HPV-associated cervical disease, it cannot be reliably predicted which patients with infection or abnormal cytology will progress to clinically significant disease versus spontaneously regress.


Estimated Prevalence of HPV Infection, Including in the Younger Population


- Estimates include all HPV types, not just HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58.
- Prevalence of HPV DNA was determined from 4,150 study participants (aged 14–59) who provided self collected cervicovaginal swab samples.

Prevalence of High risk/oncogenic HPV and Low risk/non-oncogenic HPV by age.

HPV Transmission

Sexual Routes
- Skin-to-skin contact of genital areas
  - Genital-genital, manual-genital, oral-genital contact
  - Nonpenetrating sexual contact; rare
- Through sexual intercourse

Nonsexual Routes
- Self-inoculation from an infected site to a previously uninjected site
- Mother to newborn: vertical transmission; rare
- Fomites (eg, undergarments, surgical gloves, biopsy forceps)
- Hypothesized, but not well documented
**HPV Is Easily Acquired and Transmitted Even Without Sexual Intercourse**

- Adolescence can be a time of experimentation.
  - Many adolescents report engaging in sexual activities other than intercourse.\(^1\,\(^6\)
  - ~46% of adolescents do not consider other forms of sexual contact besides intercourse to be a “big deal.”\(^1\,\(^6\)
- HPV is easily transmitted through experimentation that involves genital contact of any kind—intercourse is not necessary.
  - It may take only 1 encounter to be infected with HPV.\(^2\)
- Though most infections clear on their own, persistence of certain HPV types can lead to clinically significant disease.\(^2\)

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**HPV Is Associated With Many Anogenital Conditions**

- Genital Warts
- Vaginal Intraepithelial Neoplasia
- Anal Intraepithelial Neoplasia
- Cervical Cancer
- Cervical Adenocarcinoma
- In Situ
- Vulvar Intraepithelial Neoplasia
- Vaginal Intraepithelial Neoplasia
- Penile Intraepithelial Neoplasia
- Cervical Intraepithelial Neoplasia

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**HPV and Cancer: A Broader Picture**

<table>
<thead>
<tr>
<th>Cancer</th>
<th>% Associated With Certain HPV Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical*</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>Vaginal*</td>
<td>~75%</td>
</tr>
<tr>
<td>Vulva*</td>
<td>~70%</td>
</tr>
<tr>
<td>Perineal</td>
<td>~70%</td>
</tr>
<tr>
<td>Anal</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Oropharyngeal</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>Nonmelanoma skin/cutaneous squamous cell</td>
<td>90%*</td>
</tr>
</tbody>
</table>

*Includes cancer and intraepithelial neoplasia.
Annual US HPV-related Cancer and Disease Cases Caused by certain HPV Types

According to estimates for males and females:

- **Cervical cancer**
  - 11,124 cases

- **Anal cancer**
  - 5,386 cases

- **Vulvar and vaginal cancers**
  - 3,263 cases

- **Low-grade cervical lesions**
  - 488,750 cases

- **High-grade cervical precancers**
  - 216,000 cases

- **Genital warts**
  - 324,000 cases

Cervical cancer 1,2
11,124 cases

- **Anal cancer**
  - 5,386 cases

- **Vulvar and vaginal cancers**
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- **Low-grade cervical lesions**
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11. Cervical cancer: 11,124 cases
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Cervical cancer
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CIN and Cervical Adenocarcinoma

Estimated ~12,200 new cases of cervical cancer in the US in 2012.

- >75% of cases of cervical cancer are caused by HPV types 16 and 18.

CIN and Cervical Adenocarcinoma

HPV and Anogenital Warts

- HPV 6 and 11 responsible for >90% of anogenital warts
- Infectivity >75%
- Up to 30% spontaneously regress within 4 months in women
- Treatment can be painful and embarrassing
- Topical and surgical therapies are available for genital warts
- Recurrence rates vary greatly
  - As low as 5% with podofilox or laser treatment
  - As high as 65% with other treatments

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**Recurrent Respiratory Papillomatosis**

- Caused by HPV types 6 and 11
- ~20,000 active cases in the United States with fewer than 2,000 children developing RRP each year
- RRP in children results from vertical transmission of HPV from mother to child during vaginal delivery particularly in mothers with active condyloma
- Characterized by growth of tumors (papillomas) in the larynx, trachea, and bronchi
- Surgery is the primary method of removing the tumors but they have a tendency to return unpredictably
- HPV vaccines do not have an indication for RRP

**Recurrent Respiratory Papillomatosis**

**HPV-Related Oropharyngeal Cancers**

- >12,000 cases in the US each year of which ~9,000 are attributable to HPV
- HPV type 16 is responsible for the majority of HPV-related oropharyngeal cancers
- Males account for 80% of the cases
- Primarily occurs in the posterior regions of the pharynx such as the base of the tongue, back of the throat, the tonsils, the tonsillar crypts, and the tonsillar pillars
- Treatment may include surgery, radiotherapy, and chemotherapy
- HPV vaccines do not have an indication for OP cancers
HPV-Related Oropharyngeal Cancers

HPV Vaccines

• Quadrivalent HPV vaccine (licensed 2006)
  — Protects against HPV serotypes 6, 11, 16, 18
  — Indicated for females and males
• Bivalent HPV vaccine (licensed 2009)
  — Protects against serotypes 16 and 18
  — Only indicated for females
• Nine-valent HPV vaccine (licensed 2014)
  — Protects against serotypes 6, 11, 16, 18, 31, 33, 45, 52, and 58
  — Indicated for females and males

9-Valent Human Papillomavirus Vaccine

• Approved by the FDA in December 2014
• Covers HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58
• Currently approved for females 9 – 26 years of age for the prevention of cervical, vaginal, vulvar, and anal cancers as well as pre-cancerous or dysplastic lesions and genital warts caused by the 9 HPV types
• Currently approved for males 9 – 26 years of age for the prevention of anal cancer and precancerous or dysplastic lesions and genital warts caused by the 9 HPV types
• Given in a 3 dose series at 0, 2, and 6 months
### Worldwide Burden of HPV Disease

<table>
<thead>
<tr>
<th>Estimated type contribution for certain HPV-related cancer and disease cases</th>
<th>4 HPV types cause: (6, 11, 16, and 18)</th>
<th>9 HPV types cause a total of: (6, 11, 16, 18, 31, 33, 45, 52, and 58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical cancer cases</td>
<td>70%</td>
<td>90%</td>
</tr>
<tr>
<td>Vulvar cancer cases</td>
<td>75%</td>
<td>90%</td>
</tr>
<tr>
<td>Vaginal cancer cases</td>
<td>65%</td>
<td>85%</td>
</tr>
<tr>
<td>Anal cancer cases</td>
<td>85%</td>
<td>90%–95%</td>
</tr>
<tr>
<td>High-grade cervical precancer</td>
<td>50%</td>
<td>80%</td>
</tr>
<tr>
<td>Low-grade cervical lesion</td>
<td>25%</td>
<td>50%</td>
</tr>
<tr>
<td>Genital warts cases</td>
<td>90%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Not all cervical precancers and lesions, and vulvar, vaginal, and anal cancer cases are caused by HPV. Approximately 90% of high-grade cervical precancers, 75% of low-grade cervical lesions, 30% of vulvar cancer cases, 75% to 75% of vaginal cancer cases, and 85% to 90% of anal cancer cases are HPV related.

High-grade cervical precancers defined as CIN 2/3.

### US Pediatric Experience When Shifting From HPV4 to HPV9

- After the ACIP and AAP recommended routine use of HPV9 in males and females it took ~3-6 months for most (not all) public and private insurance carriers to cover HPV9.
- Some Pediatricians believed that if a patient began the series with HPV4 then they should finish with HPV4 so they delayed ordering and using HPV9 until late 2015.
- Most Pediatricians immediately made the shift to HPV9 for both series initiation as well as completion.
- A small percentage of Pediatricians ordered both vaccines and gave HPV9 to female patients but continued using HPV4 for their male patients.
- Now in 2016 the majority of US Pediatricians use only HPV9 for both their male and female patients.

### Common Questions And Answers (From the US-ACIP) Concerning The Shift From HPV4 To HPV9

- **If a series was started with HPV4 or HPV2 can it be completed using HPV9?**
  - Yes

- **Are additional HPV9 doses recommended for a person who started a series with HPV4 or HPV2 but completed the series with 1 or 2 doses of HPV9?**
  - No

- **Is additional vaccination (revaccination) with HPV9 recommended for persons who have already completed a 3 dose series with HPV4 or HPV2?**
  - No, the ACIP has not recommended routine revaccination but there are data to indicate it is safe.
Common Questions And Answers (From the US-ACIP) Concerning The Shift From HPV4 To HPV9 (Continued)

• What adverse events can be expected from vaccination with HPV9 compared to HPV4?
  — There is an increase in local reactions such as injection site pain, redness, and swelling (most likely because of the larger amount of aluminum adjuvant in HPV9) but systemic reactions are essentially the same
  — Overall safety profile for HPV9 vaccine is acceptable
• Can HPV9 be administered with other vaccines?
  — Yes, the HPV vaccine is not live
• Does the HPV9 schedule remain the same as HPV4?
  — Yes, with doses given at 0, 1-2, and 6 month intervals
  — A 2-dose schedule (0, 6-12 mos.) is under investigation

Common Questions And Answers (From the US-ACIP) Concerning The Shift From HPV4 To HPV9 (Continued)

• What percentage of HPV-associated cancers in females and males are caused by the 5 additional types in the HPV9 vaccine?
  — About 14% in females (~2800 US cases annually)
  — About 4% in males (~550 US cases annually)
• Would pap smears still be necessary for women who have completed the 3-dose HPV9 vaccine series?
  — Yes, HPV9 covers 90% of the HPV types that cause cervical cancer but not all of the HPV types
• Is switching to HPV9 cost-effective?
  — Yes, models have estimated that routine HPV9 use in the US would be cost-saving compared to HPV4 use

Question

• The CDC’s ACIP recommends routine vaccination with HPV vaccine for which age groups?
  A. 11 - 12 year old girls and boys
  B. 9 - 26 year old males and females
  C. 9 - 15 year old males and females
ACIP Recommendation: Routine HPV Vaccination

**Males: HPV Vaccination with HPV4 or HPV9**
Routine: 11- or 12-year-olds

**Females: HPV Vaccination with HPV2, HPV4, or HPV9**
Routine: 11- or 12-year-olds

- Males and females: Vaccination series can be started at age 9 years

ACIP=Advisory Committee on Immunization Practices; HPV=human papillomavirus; HPV2=bivalent HPV vaccine; HPV4=quadrivalent vaccine; HPV9=9-valent HPV vaccine.

For complete ACIP recommendations on HPV vaccination, please see the MMWR.

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A Rationale For Making HPV Vaccination Routine For 11 – 12 Years and Younger

- The immune response to the HPV vaccine has been well demonstrated to be more robust (significantly higher post-vaccination antibody titers) in 9-15 year olds compared to 16-26 year olds
- Preventive care visits decline significantly after age 14 making series completion of the HPV vaccine far more difficult compared to 11-12 year olds who come in for recommended preventive healthcare visits
- Data suggests minimal exposure to HPV at 11-12 years of age and younger
  - The most effective time to vaccinate is prior to exposure


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A Rationale for Making Vaccination Routine For 11- or 12-Year Olds

- The National Survey of Family Growth interviewed 6346 individuals 15–44 years of age in the United States between 2006–2010. These data reflect participants 15–24 years of age who reported an initial sexual intercourse encounter.

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Question

- Are you recommending HPV, Tdap, and MCV4 vaccines to all 11–12 year old males and females at the same visit?

Well-Child Visits are Underutilized for Administration of HPV Vaccine

Although ACIP recommends that eligible preteens ages 11 or 12 years receive recommended adolescent vaccines at a single visit, only 10% received Tdap, MCV4, and HPV during a single visit, based on Commercial Claims database.
Estimated US Vaccine Coverage Among Adolescents 13-17 Years

Helping to Improve HPV Vaccination Rates

How to get the vaccine out of the refrigerator and into the patient!

HPV Vaccine Coverage Rates Remain Low

- The CDC has stated that the number of girls and boys who have received HPV vaccine remains low

“It is frustrating to report almost the same HPV vaccination coverage levels among girls for another year … Preteens need HPV vaccine today to be protected from HPV cancers tomorrow.”

—Anne Schuchat
Assistant Surgeon General and Director of CDC’s National Center for Immunization and Respiratory Diseases

Increased HPV Vaccination Coverage Is Possible

According to the Centers for Disease Control and Prevention:

“High HPV vaccination coverage with existing infrastructure and health-care utilization is possible in the United States. Taking advantage of every health-care encounter, to assess every adolescent’s vaccination status can help minimize missed opportunities.”

According to the Centers for Disease Control and Prevention:

HPV=human papillomavirus.


A missed opportunity was defined as a health care encounter occurring on or after a girl’s 11th birthday but before the 13th birthday and on or after March 23, 2007 (publication date of Advisory Committee on Immunization Practices quadrivalent HPV vaccine recommendation) during which a girl received at least 1 vaccine but did not receive the first dose of HPV vaccine.

CDC=Centers for Disease Control and Prevention; HPV=human papillomavirus; NIS=National Immunization Survey.


Top 5 Reasons Why Primary Care Physicians Do Not Discuss HPV Vaccination

• I know the patient is not yet sexually active
• I don’t have enough time to discuss it
• I think the patient is too young
• The patient is already getting other vaccines at that visit
• I expect the parents to refuse

Analysis limited to parents reporting that they were not likely to seek HPV vaccination for their teen in the next 12 months or were unsure of their HPV vaccination plans.

NIS=National Immunization Survey; HPV=human papillomavirus.


2013 NIS-Teen: Top 5 Parental Reasons For Not Vaccinating Adolescents With HPV Vaccine

*Top 5 reasons for not vaccinating adolescents with HPV vaccine, NIS-Teen 2013*

- Not recommended by HCP or clinician
- Not needed or necessary
- Lack of knowledge
- Not sexually active
- Safety concern/side effects


CDC Recommended Strategies to Increase HPV Vaccine Coverage

- Using vaccination prompts available through electronic health records
- Checking local and state immunization information systems to assess vaccination needs at every encounter
- Scheduling appointments for second and third doses before patients leave office after receiving first dose
- Automated reminder-recall systems

Role of the Health Care Provider

- 86% of adults cite their health care provider as a source of health information.1
- 88% of parents say that they generally do what their doctor recommends regarding vaccines for their children.2

United States Strategies To Help Improve HPV Vaccination Rates

- Provide clear same-day recommendations
- Follow the ACIP recommendations to routinely vaccinate 11- or 12-year old males and females, may start as young as 9 years
- Consider appropriate opportunities to vaccinate
  - eg, well-child visits, sports physicals
- Make use of reminder systems to help ensure series completion


Summary

- HPV can be transmitted through genital contact of any kind and may occur with just 1 encounter.
- Persistence of certain HPV types can lead to clinically significant diseases and cancers.
- The ACIP recommends routine HPV vaccination for 11- or 12-year old males and females, may start as young as 9 years
- Your clear recommendation is important.

WEB SITES FOR ACCURATE VACCINE INFORMATION

- www.cdc.gov/vaccines The CDC’s National Immunization Program
- www.immunize.org The Immunization Action Coalition
- www.aap.org The American Academy of Pediatrics
- www.vaccine.chop.edu The Children’s Hospital of Philadelphia Vaccine Education Center
- www.aafp.org The American Academy of Family Physicians
- www.nih.gov The National Institute of Health