Human Papilloma Virus (HPV): Associated Diseases and Vaccine Recommendations

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Disclosures

• None
Objectives

• Describe the epidemiology of genital and oral HPV
• Discuss the pathogenesis of HPV
• Review the clinical manifestations of HPV
• Discuss indications for HPV vaccine
• Controversies re: HPV vaccine
Human Papilloma Virus (HPV)

• Most common sexually transmitted disease in US
  – Estimated 14.1 million persons are newly infected each year (incidence)
  – Estimated 100% of sexually active men and women acquire genital HPV at some point in their lives (prevalence)
  – ~79 million females aged 14–59 years are infected with some type of HPV; highest prevalence 20-24yr
  – ~33,000 cases of HPV associated cancers are diagnosed annually
• Invades squamous epithelium
• 1981 zurHouser, et al. defined link between HPV and cervical cancer (won Nobel prize)
• 1983 Syrjanen(s) et al. discovered link between HPV and oropharyngeal cancer
Human Papilloma Virus (HPV)

- > 100 types
- HPV types are divided into two groups based on their association with cancer (CA)
  - Low-risk types (nononcogenic) associated with genital warts/condylomases and mild Pap test abnormalities
  - High-risk types (oncogenic) associated with moderate to severe Pap test abnormalities, cervical CA, other anogenital CAs and oral CA (base of tongue, tonsillar)
- Most genital HPV infections are transient, asymptomatic, and have no clinical consequences
Low Risk HPV (Nononcogenic Types)

- Keratinized skin, mucocutaneous lesions (papillomas, condylomas)
- Most common HPV 6, 11, 1, 2, 4
- **Not** implicated in neoplasms transformation
- Viral genome is packaged as an episome and segregated from host genome
  - **NOT** highly integrated into host genome as do high risk HPVs
- Gene types / products: E1, E2, L1, L2
  - (e = early, l= late gene products)

Episome = extrachromosomal DNA
High Risk HPV (Oncogenic Types)

- Mucocutaneous (oropharyngeal / anogenital) squamous epithelium
- Trigger malignant growths
- Gene types / products: E5, E6, E7
  - Viral genome highly integrated into host genome → immortalization of host cell
  - E5: stimulates EGFR
  - E6, E7: suppress tumor suppressors
- HPV 16, 18 (as well as ~14 others)
  - 70% cervical, vaginal, anal cancers
  - 40-50% vulva, penis
  - Oropharyngeal cancers are increasing: 90% due to HPV 16
- Most women with high-risk HPV infxn have normal Pap test results and never develop cellular changes or cervical CA
Risk Factors for Transmission of Genital HPV

- Predominantly associated with sexual activity
  - genital contact; vaginal intercourse is **NOT** required
- Number of partners; partner(s) number of partners; **New partners increase risk**
- Young age
- Smoking: 4x RR
- Persistence of high risk HPV; increases risk of SIL
- Immunosuppression (HIV+, RA, cancer, txp)
  - HPV more likely to be detected in immune-suppressed women
Risk Factors for Transmission of Genital HPV

• Can occur from asymptomatic and subclinical patients
• Condoms may reduce risk; not very good
• Spermicide nanoxynol 9 is not protective
• Males: Being uncircumcised increases risk
• Infectivity after treatment of genital warts or cervical cellular abnormalities is unknown
Natural History of HPV

• Most genital HPV infections are transient, asymptomatic (subclinical), and have no clinical consequences in immunocompetent persons

• Time to development of clinical manifestations is variable

• Median duration of new cervical infections is 8 months, but varies
  – 70% of infections clear within 1 year
  – 90% of infections clear within 2 years
  – Gradual development of an effective immune response is the likely mechanism for HPV DNA clearance
Natural History of HPV

- Persistent HPV infection (e.g. HPV 16)
  - Not cleared by the immune system
  - Characterized by persistently detectable type-specific HPV DNA
  - Persistent oncogenic HPV infection is most important risk factor for precancerous cervical cellular changes and cervical cancer
  - Persistent infection with a high-risk HPV type is necessary, but not sufficient, for the development of cervical cancer
HPV 16 Life Cycle
Castillo, A, Carcinogenesis 2013
Age at Peak Prevalence for Each Stage in Cervical Carcinogenesis
Clinical Manifestations and Sequelae

• In most cases, genital HPV infection is transient and has no clinical manifestations or sequelae.

• Clinical manifestations of genital HPV infection include
  – Genital warts,*
  – Cervical cellular abnormalities detected by Pap tests,*
  – Some anogenital squamous cell cancers,
  – Some oropharyngeal cancers, and
  – Recurrent respiratory papillomatosis

*Two most common clinically significant manifestations of genital HPV infection
Vulvar Warts
Cervical Warts

www.cdc.gov
Cervical Cancer
Perineal Warts

www.cdc.gov

https://cdn.std.uw.edu/doc/426-1/perineal-warts.jpg
Perianal Warts

*Source:* Seattle STD/HIV Prevention Training Center at the University of Washington/UW HSCER Slide Bank
Penile Warts
2015 STD Treatment Guidelines: External Anogenital Warts

• Patient Applied Therapy
  – Podofilox 0.5% solution or gel
  – Imiquimod 3.75% or 5% cream
  – Sinecatechins 15% ointment

• Provider Applied Therapy
  – Cryotherapy with liquid nitrogen or cryoprobe
  – Surgical removal by tangential excision or shave
  – Trichloroacetic acid (TCA) or Bichloroacetic acid (BCA)

Internal warts require provider applied therapy

**Recurrences after treatment are common**
Cervical Cancer Screening Recommendations

• Routine cervical screening should be performed starting at age 21 yrs and continue through age 65 yrs

• Annual cervical cancer screening is no longer recommended for all women.
  – Ages 21-29 yrs: Pap testing is recommended every 3 years
  – Ages 30–65 yrs: Pap test every 3 years or a Pap test plus HPV test (co-test) every 5 years.
    • If both tests are negative, repeat screening in 5 years (high negative predictive value)

• Although the prevalence of oncogenic HPV types is high in females < 21y, the oncogenic HPV and squamous intraepithelial lesions caused by HPV in adolescent girls are more likely to regress in younger women than in older women. (No pap test)
Oral HPV Involving Tonsil

Papilloma
HPV Related Oropharyngeal Cancer (OPC)

- 650,000 cases head/neck squamous cell carcinoma (HNSCC) diagnosed worldwide, yearly
- 350,000 deaths
- US incidence: 11.9/100,000 persons
  - 3 male / 1 female
  - Increase in tonsillar and tongue base lesions
  - 90% oropharyngeal cancers are HPV related
  - Cofactors include smoking and alcohol
- In countries with high tobacco use, <20% of OPC are HPV related
- HPV 16: accounts for ~99% OPC

HPV Related Oropharyngeal Cancer (OPC)


- Tonsillar cancers are the most prevalent HPV+ OPC
- Invade less keratinized cells of the tonsillar crypts
- Increasing prevalence, particularly in young adults
- Contributing variables include:
  - Earlier initiation of sexual activity
  - Higher number of sexual partners
  - Oral sex practices
- > 50% of school aged youth report practicing oral sex
  - 2/3 had multiple partners
**Differentiation Between HPV+ vs. HPV- Oropharyngeal CA**


<table>
<thead>
<tr>
<th></th>
<th>HPV+</th>
<th>HPV-</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Younger (30-50)</td>
<td>Older (50-70)</td>
</tr>
<tr>
<td><strong>Risk Factor</strong></td>
<td>Oral sex, multiple sex partners, h/o STD</td>
<td>Long h/o tobacco +/- ETOH</td>
</tr>
<tr>
<td><strong>Incidence</strong></td>
<td>Increasing</td>
<td>Decreasing</td>
</tr>
<tr>
<td><strong>Localization</strong></td>
<td>Tongue base, tonsils</td>
<td>Oral mucosa</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td>Poorly differentiated</td>
<td>Well differentiated</td>
</tr>
<tr>
<td><strong>Metastasis</strong></td>
<td>Low</td>
<td>Frequent</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>Good; sensitive to XRT and chemo</td>
<td>Poor</td>
</tr>
<tr>
<td><strong>5 year survival</strong></td>
<td>60-90%</td>
<td>20-70%</td>
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</table>
Oral HPV Infection: Differences in Prevalence Between Sexes and Concordance with Genital HPV Infection, NHANES 2011-2014

- Oral HPV is common in men with bimodal age distribution (35-39y, 50-54y)
- Overall prevalence of oral HPV infection was 11.5% in men (11 million) and 3.2% in women (3.2 million) nationwide
- High risk oral HPV infection was more prevalent in men (7.3%) than in women (1.4%)
- HPV 16: 6x more common in men (1.8%) than in women (0.3%)
- Same sex partners:
  - Prevalence of high risk HPV infxn: 12.7% men; 3.6% women
- Oral HPV prevalence among men with concurrent genital infection was 4x greater (19.3%) than those without it (4.4%)
- Predicted probability of high risk HPV infection was greatest in blacks, smoke > 20 cigarettes/day; current marijuana use; report 16+ lifetime vaginal or oral sex partners

## Cancers Caused by HPV per Year, U.S., 2010–2014

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Percentage probably caused by any HPV type</th>
<th>Number probably caused by any HPV type</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Cervix</td>
<td>91%</td>
<td>10,600</td>
<td>0</td>
</tr>
<tr>
<td>Vagina</td>
<td>75%</td>
<td>600</td>
<td>0</td>
</tr>
<tr>
<td>Vulva</td>
<td>69%</td>
<td>2,600</td>
<td>0</td>
</tr>
<tr>
<td>Penis</td>
<td>63%</td>
<td>0</td>
<td>800</td>
</tr>
<tr>
<td>Anus*</td>
<td>91%</td>
<td>3,800</td>
<td>1,900</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>70%</td>
<td>2,100</td>
<td>10,100</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td><strong>19,700</strong></td>
<td><strong>12,800</strong></td>
</tr>
</tbody>
</table>

*Includes anal and rectal squamous cell carcinomas

HPV Vaccines
HPV Prophylactic Vaccines

HPV Vaccines

- Recombinant L1 capsid proteins that form “virus-like” particles (VLP)
- Non-infectious and non-oncogenic
- Produce higher levels of neutralizing antibody than natural infection
- Safe to give to immunocompromised patients
HPV Vaccine Production: Virus Like Particles

- Human Papillomavirus
  - DNA
  - L1 Coding Region
  - Plasmid DNA
- Yeast
  - L1 Molecule
- Self Assembly of L1 Proteins
  - L1 Penton
  - Viral-Like Particle (VLP)

www.cdc.gov
HPV Vaccine

• Vaccine is **most effective** if administered **before** the individual begins engaging in sexual activity
  • vaccine not active against HPV strains acquired before vaccination
• Children mount the most robust antibody responses to the vaccine between 9-15yo
• Serologic testing or HPV DNA testing is **not** required prior to immunization at any age
• Sexually active women and women with previous abnormal cervical cytology can receive the HPV vaccine
# Available HPV Vaccines

<table>
<thead>
<tr>
<th></th>
<th>Bivalent (Ceravix®)</th>
<th>Quadrivalent (Gardasil®)</th>
<th>9-valent (Gardasil®9)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Manufacturer</strong></td>
<td>Glaxo Smith Kline</td>
<td>Merck</td>
<td>Merck</td>
</tr>
</tbody>
</table>
| **L1 VLP types**    | 16,18               | 6,11,16,18               | 6,11,16,18  
|                     |                     |                          | 31,33,45,52,58       |
| **Manufacturing**   | *Trichoplusia ni* insect line infected with L1 encoding recombinant baculovirus | *Saccharomyces cerevisiae* (Brewer’s yeast) expressing L1 | *Saccharomyces cerevisiae* (Brewer’s yeast) expressing L1 |
| **Licensed**        | Females 9-25yo      | Females 9-26yo           | Females 9-26yo        
|                     |                     | Males 9-26yo             | Males 9-21yo         |

Randomized Control Trial: Efficacy of 9vHPV Vaccine Against HPV Types 31/33/45/52/58 in Women 16-26YO

Per Protocol Population

<table>
<thead>
<tr>
<th>End Point</th>
<th>9vHPV Cases/Total</th>
<th>4vHPV Cases/Total</th>
<th>Risk Reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High grade cervical, vulvar or vaginal disease</td>
<td>1/6016</td>
<td>30/6017</td>
<td>96.7 (80.9-99.8)</td>
</tr>
<tr>
<td>High grade CIN, AIS* and cervical cancer</td>
<td>1/5948</td>
<td>27/5943</td>
<td>96.3 (79.5-99.8)</td>
</tr>
<tr>
<td>Persistent infection (&gt; 6 months)</td>
<td>35/5939</td>
<td>810/5939</td>
<td>96.0 (94.4-97.2)</td>
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</tbody>
</table>

*AIS = adenocarcinoma in situ

# HPV9 Vaccine Administrative Schedule

<table>
<thead>
<tr>
<th>AGE</th>
<th>DOSES</th>
<th>SCHEDULE</th>
</tr>
</thead>
</table>
| 9–14 years| 2* DOSES| 1st shot: Today  
2nd shot: 6–12 months after the first shot                                  |
| or 15–26 years** | 3† DOSES | 1st shot: Today  
2nd shot: 2 months after first shot  
3rd shot: 6 months after the first shot                                       |

**Boys: 13-21yo; 22-26 MSM or immunocompromised  
www.merck.com
Missed Doses of Vaccine

• If series is interrupted for any length of time, it can be resumed without restarting the series
• Same formulation should be used to complete the series if possible
Duration of Protection of Vaccine

• Studies suggest that vaccine protection is long-lasting

• No evidence of waning protection
  ▪ Available evidence indicates protection for at least 10 years
  ▪ Multiple studies are in progress to monitor

• Precise antibody level needed for protection against infection is unknown

Over 10 Years of HPV Vaccine Safety Data

• HPV vaccines are safe

• Reactions after vaccination may include:
  ▪ Injection site reactions: pain, redness, and/or swelling in the arm where the shot was given
  ▪ Systemic: fever, headaches

• HPV vaccines should not be given to anyone who has had a previous allergic reaction to the HPV vaccine or who has an allergy to yeast

• Brief fainting spells (syncope) and related symptoms (such as jerking movements) can happen soon after any injection, including HPV vaccine

• Patients should be seated (or lying down) during vaccination and remain in that position for 15 minutes

Vaccination: Pregnancy and Lactation

• Use of the vaccine in pregnancy is not recommended, although no teratogenic effect by vaccine has been reported
  – No evidence that HPV vaccine adversely affects fertility, pregnancy or infant outcome
  – Women planning to conceive:
    • defer vaccination until after delivery
  – Women who become pregnant before completion of vaccination series:
    • Defer remaining dose until after pregnancy
    • Do NOT need to terminate pregnancy

• Lactating women can receive the HPV vaccine and continue to breastfeed because the vaccine does NOT contain live viral DNA
HPV Vaccine Shown to Also Protect Against Oral HPV Infection: NCI Costa Rica Vaccine Trial

- First attempt to assess vaccine efficacy for prevention of oropharyngeal cancer
- Randomized clinical trial-- 4 years duration
- N=5,834 females completed the study
- Treatment group received bivalent vaccine at 0, 1 and 6 mo
- Control group received HAV vaccine
- Annual exams for cervical HPV
- Single oral exam at 4 years (15 second rinse with 15 ml Scope®)
- 1 oropharyngeal cancer in vaccine group compared to 15 oropharyngeal cancer in control group
- Estimated vaccine efficacy for prevention of oral HPV was 93%; efficacy against cervical HPV infection was 72%

Herrero, R, et al. 2013 DOI:10.1371/journal.pone.0068329
Efficacy: Impact of HPV Vaccine on Cervicovaginal HPV Prevalence (6, 11, 16, 18)

Only 14.7% received vaccine
Impact of Eliminating Missed Opportunities by Age 13 Years in Girls Born in 2000

Missed opportunity: Healthcare encounter when some, but not all ACIP-recommended vaccines are given. HPV-1: Receipt of at least one dose of HPV. MMWR. 63(29):620-4.
HPV Vaccine Controversies
My child is NOT (and NEVER will be) sexually active!!
HPV Vaccine: Correcting Myths and Misinformation

• Recommendations from health care providers play an important role in assisting pre-adolescents in deciding to receive HPV vaccine.

• Two surveys of groups who did not elect to receive HPV vaccine found that the lack of health care provider recommendation was identified as a major reason for non-vaccination.

Parents of Unvaccinated Girls – Top Reasons for Not Starting HPV Vaccine Series: 2013 NIS Teen Study

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

Lack of knowledge: 15%

Stokley et al. MMWR. 2014
Vaccination Safety Controversy: Debunking Vaccination Risks

• Providers need to be educated about the HPV vaccine
• Providers need to educate adolescents and parents about the need to receive the vaccine, and discuss risk of not getting vaccine
Conclusions

- HPV is the most common sexually transmitted infection
- Low-risk HPV types 6 and 11 cause approximately 90% of genital warts
- High-risk HPV types 16 account for ~50% of cervical cancers, and 90% oropharyngeal cancers
- Vaccine is highly effective and safe in both males and females
- Health care providers need to be proactive about HPV concerns:
  - Warn patients about high risk of exposure to HPV
  - Discuss pros and cons of vaccination
  - Vaccinate patients— it’s not about the STDs—it’s about the cancer!
Bibliography

- Wu, X et al. MMWR 2012; 61:41-5.
- Bauch, CT and Galvani, AP. Science 2013; 342, 47-9.
- Markowitz, L. Infectious Disease News Feb 28, 2014
- Uptodate.com
- [www.cdc.gov](http://www.cdc.gov)
- Petrosky, E etal. MMWR 2015 Mar27;64(11)300-4