HPV: Protecting Your Patient from Harm
Clinical Advances in Pediatrics
Children’s Mercy Health Network
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Cynthia Holland-Hall, MD, MPH
Associate Professor of Clinical Pediatrics
The Ohio State University College of Medicine
Physician, Section of Adolescent Health
Nationwide Children’s Hospital
Columbus, Ohio

Disclosure
I have no actual or potential conflict of interest in relation to this program.

Objectives
At the end of this activity, the participant will be able to…
• …state the current guidelines for cervical cancer screening in adolescents.
• …have a basic understanding of the natural history of HPV infection in adolescent females.
• …counsel patient and parents about the available HPV vaccines.

Human Papillomavirus (HPV)
• Double-stranded DNA virus
• 30–40 anogenital
• Oncogenic (“high risk”) types include: 16, 18, 31, 45…
  — About 70% of cervical cancers caused by types 16 and 18
• Nononcogenic (“low risk”) types include: 6, 11, 40, 42, 43…
  — 90% of genital warts caused by types 6 and 11
  — Also associated with recurrent respiratory papillomatosis

Estimated Annual Burden of HPV-Related Diagnoses in the United States, 2006

Prevalence of STIs
14–19 year-old U.S. females (n=838)

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Sexually Experienced</th>
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</thead>
<tbody>
<tr>
<td>HPV (HR/6/11)</td>
<td>18.3%</td>
<td>29.5%</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>3.9%</td>
<td>7.1%</td>
</tr>
<tr>
<td>Trichomonas</td>
<td>2.5%</td>
<td>3.6%</td>
</tr>
<tr>
<td>HSV-2</td>
<td>1.9%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td>1.3%</td>
<td>2.5%</td>
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<tr>
<td>“Any STI”</td>
<td>24.1%</td>
<td>37.7%</td>
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Forhan SE, Pediatrics, 2009
Infection from Time of First Intercourse, Female College Students (N=603)

Risk of Acquiring HPV After First Intercourse: Female Adolescents with Only 1 Sexual Partner

Risk of Cervical Lesions and Cancer in Women Exposed to HPV at a Young Age

Cervical Ectropion

The Cervical Transformation Zone

- Area of immature metaplasia between the original and current squamocolumnar junction (SCJ)
- ~99% of cervical cancers arise within the transformation zone
- Target zone for Pap smears

Low grade HPV Lesions
**High grade HPV lesions**

![High grade HPV lesions diagram]

**HPV and Anogenital Warts**

- HPV 6 and 11 responsible for >90% of anogenital warts
- Topical therapies
  - Patient-applied
  - Clinician-applied
- Surgical therapies
- Numerous follow-up visits
- Psychological morbidity
- Recurrence is common

**Cervical Intraepithelial Neoplasia**

- CIN 1
- CIN 2
- CIN 3

**Low Grade Squamous Intraepithelial Lesions (LSIL)**

- Associated with viral replication
- Mild basal cell proliferation and nuclear enlargement
- Corresponds histologic diagnoses of CIN 1
- Most common among adolescents
- Prevalence 2-14%
- Over 90% resolve spontaneously

**High Grade Squamous Intraepithelial Lesion (HSIL)**

- Chromosomal abnormalities and aneuploidy
- Corresponds to histologic diagnoses of CIN 2 or CIN 3
- Prevalence similar to older adults (0.7%)
- Risk factors:
  - Persistent HPV infection
  - Smoking
  - Prolonged oral contraceptive use
- About 15% chance of progression to cervical cancer if left untreated

**Treatment of Cervical Dysplasia**

- **Mild/LSIL**
  - Repeat Pap smears
    - Q 3-4 months
    - Q 6 months
    - Annually
  - Colposcopy (multiple?)
  - Biopsy (multiple?)
  - Excisional Procedures
    - Some association with premature labor, LBW

- **Severe/HSIL**
Cervical Cancer in Adolescents

- Incidence of 0.1 per 100,000
  - 1990-2006 SEER data
  - Similar to reported rates in 1973-1977
- Rates declining the LEAST in 15-24 yo (Barnholtz-Sloan, 2009)
- U.K.: Screening 20-24 yo women has no detectable impact on cancer rates (Sasieni, 2009)
- No convincing evidence that screening decreases cancer rates in this age group

U.S. Screening Recommendations

- Begin screening all women at 21 years of age, using Pap smear
  - ASCCP, CDC, ACOG; others adopting
- Immunocompromised women: begin screening with onset of sexual activity
- No role for HPV DNA testing in adolescents
- Conservative management of most abnormal Paps
- More aggressive screening regimens were not evidence based

PREVENTION = VACCINATION

Quadrivalent HPV Vaccine (HPV-4)

- Gardasil (Merck & Co.) approved June 2006
- HPV types 6, 11, 16, 18
- Non-infectious L1 virus-like particle (VLP)
- Adjuvant: amorphous aluminum hydroxyphosphate sulfate
- Approved for females and males 9-26 yo
- Protection demonstrated for 42 months
- Schedule: 0, 2, 6 months

Bivalent HPV Vaccine (HPV-2)

- Cervarix (GlaxoSmithKline) approved October 2009
- HPV types 16, 18
- Non-infectious L1 virus-like particle (VLP)
- Adjuvant: aluminum hydroxide and monophosphoryl lipid A (MPL)
- Approved for females 10-25 yo
- Protection demonstrated to 6.4 years
- Schedule: 0, 1, 6 months

Natural History of HPV Infection and Potential Progression to Cervical Cancer

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<th>1-20 Years</th>
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<td>Continuing Infection</td>
<td>CIN 2/3 AIS</td>
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<td>CIN 1</td>
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Invasive Cervical Cancer

Cleared HPV Infection

HPV Vaccines

- Highly efficacious against included serotypes
- Per-protocol studies demonstrate nearly 100% efficacy
  - Naïve to all types
  - Received all doses on time
- Efficacy greatly reduced in intention-to-treat group
  - Already exposed to one or more types
  - Pooled analysis showed efficacy inversely related to age of subject (Kjaer, 2009)
- Antibody decay models suggest decades of protection (Fraser, 2007)

Adverse Experiences

- Injection-site reactions
- Headache
- Fever
- Nausea
- Dizziness
- Syncope
  - May result in falling with injury
  - Observe for 15 minutes after administration

Neutralizing Antibodies by Age at Enrollment

Neutralizing anti-HPV 6 GMTs at Month 7

Monitoring Vaccine Safety: Post-marketing Safety Surveillance

- Vaccine Adverse Event Reporting System (VAERS)
  - CDC and FDA
  - Passive reporting system
  - Phone # or online reporting
  - No need to prove the vaccine caused the event
- Vaccine Safety Datalink Project (VSD)
  - CDC and eight managed care organizations
- Clinical Immunization Safety Assessment Network (CISA)
  - CDC and six academic centers in the U.S.

Reports to VAERS Following HPV Vaccination

- Difficult to compare two vaccines at this time
- As of May 2010:
  - 29,500,000 doses of Gardasil distributed in the U.S.
  - 16,140 VAERS reports of adverse events
- Non-serious AE reports (92%)
  - Injection site complaints; fainting; HA; nausea; fever
- Serious AE reports (8%)
  - No common pattern identified
**Selected Serious AE Reports**

- Guillain-Barré Syndrome
  - No increased rate over rate expected in general population
- Blood clots
  - Most had other risk factors
- Deaths
  - 29 confirmed among vaccine recipients
  - No pattern/clustering identified

**ACIP Recommendations**

- Routine vaccination of females 11-12 yo
  - May begin as young as 9 yo
- Catch-up vaccination of females 13-26 yo
- May give at same visit as Tdap, MCV4, Hepatitis B vaccine
- No change in cervical cancer screening recommendations
- Okay to give with minor, acute illnesses

**What About the Boys?**

- Gardasil approved for males October 2009
- 9-26 yo
- For prevention of genital warts
- ACIP granted permissive recommendation
- Covered by VFC and increasing numbers of private payors

**Why Early Vaccination?**

- Important to reach younger adolescents prior to exposure
- Adolescent females may have increased susceptibility to HPV infection.
- Timing opportunity: young children (9 to 12 years old) have more frequent contact with healthcare provider (pediatrician) than older adolescents (>13 years old).

**Common Questions…**

- Accelerated dosing for HPV-4
  - At least 4 weeks between dose #1 and #2
  - At least 12 weeks between dose #2 and #3, AND at least 6 months between dose #1 and #3
- No need to restart series for missed doses
- Give even if history of abnormal Pap or genital warts
  - Very few are (+) for all types
- Avoid if known to be pregnant (but category B)

**Talking to Parents**

- May be easiest at younger ages!
- “Giving permission” to have sex?
  - Seatbelt analogy
  - Clarify parents’ feelings about sex
  - More to sexual decision-making than a shot
  - Fear of cervical cancer rarely the reason for choosing abstinence!
- Distinguishing features of HPV vs. other STIs
- Harder to get in at later ages
Further Reading


Thank You!!