Primary Prevention of HPV-Related Cancers: HPV Vaccine

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Financial Disclosure

During the past 12 months, I have not had a significant financial interest or other relationship with the manufacturers of the products or providers of the services that will be discussed in this presentation.

Objectives

• Briefly discuss the epidemiology and outcomes of HPV infection
• Discuss HPV-related cancers
• Discuss the newly licensed 9vHPV vaccine
• Review available data on HPV vaccine safety and effectiveness
• Discuss ACIP/AAP recommendations for use of HPV vaccines
Human Papillomavirus

- Most common sexually transmitted pathogen in males and females
- Highest prevalence in sexually active adolescents and young adults
- First infection occurs soon after onset of sexual activity
- Lifetime risk ~80%

Human papillomavirus

- ~ 40 types infect genital tract
- High-risk types ~ 12
  - Responsible for:
    - Nearly all cervical cancer
    - 50-70% of other anogenital cancers in women and men
    - > 50% of oropharyngeal cancers
- Low-risk types
  - Genital warts
  - Juvenile recurrent respiratory papillomatosis

HPV Burden in Adolescents and Young Adults

- Most infections are asymptomatic and undetectable
  - Resolve: 70% over 1 year, 90% over 2 years
- Clinical manifestations
  - Genital warts ~ 360,000 cases/yr
  - Juvenile recurrent respiratory papillomatosis
  - Intraepithelial lesions of increasing abnormality (cervical, vaginal, vulvar, anal)
  - Persistent infection can lead to cancer outcome
Average Number of New Cancers Probably Caused by HPV, by Sex, United States 2006-2010

Women (n = 17,600)
- Cervix: 10,400 (59%)
- Oropharynx: 2,000 (11%)
- Vagina: 1,800 (10%)
- Vulva: 1,200 (7%)

Men (n = 9,300)
- Anus: 1,400 (15%)
- Oropharynx: 7,200 (77%)
- Penis: 700 (8%)

HPV-associated cancers
- Types 16, 18
  - US ~ 62% of HPV-associated cancers
  - ~ 50% of ≥ CIN2
- Types 31, 33, 45, 52, 58
  - Worldwide ~ 20% of invasive cervical cancer
  - US:
    - ~ 14% of HPV-related cancers in women
    - ~ 15% of invasive cervical cancer
    - ~ 25% of ≥ CIN2
    - ~ 5% in men

Assessment of HPV types in cancers: US
- 7 US population-based cancer registries
- Archival tissues for cancers diagnosed 1993-2005
- HPV DNA testing on 2670 cases, representative of population
HPV-Related Cancer Trends in the US

- **Cervical cancer**
  - Rates decreasing due to screening and treatment of precancerous lesions
  - Over 10,000 new cases and 4,000 deaths in 2011

- **Anal cancer rates**
  - Increasing in both men and women (~2.7%/year)
  - Doubled from 1975 to 2009

- **Oropharyngeal cancer rates** are increasing in men and women
  - 1-4.9% for men and women in different racial/ethnic groups.

HPV VLP Vaccines

- HPV L1 major capsid protein of the virus is antigen used for immunization
- Expression of L1 protein uses recombinant DNA technology
- L1 protein self-assembles into noninfectious virus-like particles (VLP) which resemble HPV virions
- Produce high levels of antibody
- Protection lasts at least 10 years (ongoing studies)

Available HPV vaccines

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Bivalent (Cervarix)</th>
<th>Quadrivalent (Gardasil)</th>
<th>9-valent (Gardasil 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1 VLP types</td>
<td>16, 18</td>
<td>6, 11, 16, 18</td>
<td>6, 11, 16, 18, 31, 33, 45, 52, 58</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>AS04: 500 µg aluminum hydroxide + 50 µg 3'-O-desacyl-4'-(aminoalkyl)-1,3,2'-dioxapentadecanoic acid</td>
<td>AAS01B: 250 µg aluminum hydroxide + 2.5 µg monophosphoryl lipid A</td>
<td>AAHS: 500 µg amorphous aluminum hydroxyphosphate sulfate</td>
</tr>
<tr>
<td>Licensed</td>
<td>Females 9-25 years</td>
<td>Females 9-26 years</td>
<td>Females 9-26 years</td>
</tr>
</tbody>
</table>

9-valent HPV vaccine (9vHPV)

- Licensed by FDA December 10, 2014
  - Three dose schedule
- L1 Viral-like-particle vaccine, similar to quadrivalent HPV vaccine
- Targets 5 additional high-risk types
  - 6,11,16,18,31,33,45,52,58
- Males 16-26 years – data submitted to FDA
  - Safety and immunogenicity data already presented to ACIP
Results of selected clinical trials on HPV vaccine efficacy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Vaccine</th>
<th>Sex</th>
<th>Vaccine efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical precancer</td>
<td>Bivalent and quadrivalent</td>
<td>Females</td>
<td>≥93%</td>
</tr>
<tr>
<td>Vaginal/vulvar precancer</td>
<td>Quadrivalent</td>
<td>Females</td>
<td>100%</td>
</tr>
<tr>
<td>Anal precancer</td>
<td>Quadrivalent</td>
<td>Males</td>
<td>75%</td>
</tr>
<tr>
<td>Anogenital warts</td>
<td>Quadrivalent</td>
<td>Females</td>
<td>99%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Males</td>
<td>98%</td>
</tr>
</tbody>
</table>

Table from MMWR 2014;63(04):69-72

9vHPV vaccine: Summary of pivotal study results

- **Immunogenicity**
  - Non-inferior anti-HPV 6,11,16,18 response vs. 4vHPV
  - ≥97% seroresponse rate to all types
  - Immunobridging: 6/11/16/18/31/33/45/52/58
    - Higher GMTs in young adolescents

- **Safety**
  - Well tolerated, AE profile similar to 4vHPV
  - Increase in mild to moderate injection site AEs


Luxembourg: Presentation of Merck data to ACIP, February 27, 2014

Efficacy Against HPV 31/33/45/52/56

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>9vHPV Vaccine No. of cases</th>
<th>6vHPV Vaccine No. of cases</th>
<th>Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2CIN2, VIN2a, VaIN2a</td>
<td>1 / 5016</td>
<td>30 / 5017</td>
<td>96.7% (90.5, 99.8)</td>
</tr>
<tr>
<td>All CIN, VIN, VaIN</td>
<td>3 / 6016</td>
<td>103 / 6017</td>
<td>97.1% (91.8, 99.2)</td>
</tr>
<tr>
<td>6-month persistent infection</td>
<td>35 / 5030</td>
<td>810 / 5053</td>
<td>96.0% (94.4, 97.3)</td>
</tr>
</tbody>
</table>

Luxembourg: Presentation of Merck data to ACOI: February 27, 2014
Post-licensure safety monitoring

- >100 million doses of quadrivalent vaccine distributed in US
- Vaccine Adverse Events Reporting System (VAERS) – June 2006 – March 2013
  - 21,194 reports:
    - 92.1% nonserious
    - Generalized symptoms: syncope, dizziness, nausea, headache, fever, urticaria
    - Local: injection-site pain, redness, swelling
    - 7.9% serious
    - Headache, nausea, vomiting, fatigue, dizziness, syncope, generalized weakness

Post-licensure safety monitoring

- Vaccine Safety Datalink (VSD)
  - Over 600,000 doses of 4vHPV – no significant risk for any pre-specified adverse events
    - Guillain-Barré Syndrome, seizures, stroke, venous thromboembolism (VTE), appendicitis, anaphylaxis, other allergic reactions
- Pregnancy registry for 4vHPV – no safety concerns identified
  - CDC, FDA, Merck and GSK continue to monitor
ACIP/AAP Recommendations for Use of HPV Vaccines

- Routine vaccination at age 11 or 12 years
  - Can start at age 9 years
- Vaccination for females 13 through 26 years and males 13 through 21 years of age* who have not completed the series

*Recommendation for males ≥ 16 years is off label for 9vHPV

ACIP/AAP Recommendations for Use of HPV Vaccines

- Males 22 through 26 years of age* may be vaccinated
- Males 22 through 26 years of age* who are immunocompromised and men who have sex with men should receive HPV vaccine

*Recommendation for males ≥ 16 years is off label for 9vHPV

ACIP/AAP Recommendations for Use of HPV Vaccines

- Females: 2vHPV, 4vHPV (as long as available), or 9vHPV can be used
- Males: 4vHPV (as long as available), or 9vHPV can be used
- 3-dose schedule
  - 2nd at least 1 mo after 1st and 3rd at least 6 mos after 1st
- Complete series with same HPV product whenever possible
  - 9vHPV can be used to complete 4vHPV series
ACIP/AAP Recommendations for Use of HPV Vaccines

- Consider observing for 15 minutes for syncopal symptoms
- Not recommended for pregnant women
  - Pregnancy testing is not needed before vaccination
  - If found to be pregnant after initiation of series
    - No intervention needed
    - Delay remainder of doses until completion of pregnancy
    - Registry has been established for 9vHPV

Rationale for Recommendation for Immunization of 11-12 Year Olds

- Modeling shows greater impact if given universally before onset of sexual activity
  - “targeting” risk groups not possible
- Antibody response in 11-15 year olds is greater than 16-26 year olds
  - Antibody titers have persisted for > 8 years
- Vaccine is well tolerated in this age group
- Implementation advantage: visit at age 11-12 already scheduled as immunization visit

MMWR 2015;64(29):784-792
**HPV vaccination coverage, adolescents, 13-17 years, US, 2013 and 2014**

<table>
<thead>
<tr>
<th></th>
<th>2013</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females, ≥1 dose</td>
<td>56.7%</td>
<td>60.0%</td>
</tr>
<tr>
<td>Females, 3 doses</td>
<td>36.8%</td>
<td>39.7%</td>
</tr>
<tr>
<td>Males, ≥1 dose</td>
<td>33.6%</td>
<td>41.7%</td>
</tr>
<tr>
<td>Males, 3 doses</td>
<td>13.4%</td>
<td>21.6%</td>
</tr>
</tbody>
</table>

**Estimated vaccination coverage with ≥1 dose of HPV vaccine, 13-17 year olds, National Immunization Survey-Teen, 2014**

Females

Males

**HPV Vaccine Series Initiation**

Girls 13-17 Years, by State, 2013
HPV vaccination coverage, adolescents, 13-17 yrs: US and Nevada, 2014

<table>
<thead>
<tr>
<th>US</th>
<th>Nevada</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females, &gt;1 dose</td>
<td>60.0%</td>
</tr>
<tr>
<td>Females, 3 doses</td>
<td>39.7%</td>
</tr>
<tr>
<td>Males, &gt;1 dose</td>
<td>41.7%</td>
</tr>
<tr>
<td>Males, 3 doses</td>
<td>21.6%</td>
</tr>
</tbody>
</table>

Impact of Eliminating Missed Opportunities by Age 13 Years in Girls Born in 2000

Impact: Healthcare encounter when some, but not all ACIP-recommended vaccines are given. HPV-1: Receipt of at least one dose of HPV.

Nevada 87.6% 86.8% 54.2% 53.4%
US National 87.6% 66.5% 60.0% 41.7%
Evidence-Based Messages

- Parents should
  - Realize HPV vaccine is cancer prevention
  - Understand it is best to give HPV vaccine at 11-12 years old
  - Recognize importance of getting all 3 doses

- Providers should
  - Be familiar with HPV epidemiology, outcomes of infection and indications for vaccine
  - Make a strong recommendation

Monitoring impact of HPV vaccine programs: HPV-associated outcomes

<table>
<thead>
<tr>
<th></th>
<th>2003-6</th>
<th>2007-10</th>
<th>Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Types 6/11/16/18</td>
<td>11.5%</td>
<td>5.1%</td>
<td>56%</td>
</tr>
<tr>
<td>Types 16/18</td>
<td>7.2%</td>
<td>3.6%</td>
<td>50%</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>12.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccinated (&gt;1 dose)</td>
<td>3.1%</td>
<td></td>
<td>VE: 82%</td>
</tr>
</tbody>
</table>

No change in prevalence in any other age group
No evidence of type replacement

Providers should
Be familiar with HPV epidemiology, outcomes of infection and indications for vaccine
Make a strong recommendation

Prevalence: HPV types 6/11/16/18: females, 14-19 y/o
Prevalence

Types 6/11/16/18: females, 14-19 y/o
Prevalence

Types 16/18: females, 14-19 y/o
Prevalence

Unvaccinated females, 14-19 y/o
Prevalence

Vaccinated females, 14-19 y/o
Prevalence

No change in prevalence in any other age group
No evidence of type replacement
4vHPV vaccine available free to Australian-born girls at age 12-13 since mid-2007; with catch-up through 26 years during 2007-9
- Uptake of ~70%
- Analysis of new patients attending Melbourne Sexual Health Centre from July, 2004 – June, 2014 (n=41,776)
- Genital warts in <21 y/o women decreased from 18.4% in 2004/5 to 1.1% in 2013/4 (p<0.001)

ENDNOTES

1HPV types 6 and 11 which are associated with genital warts.
2No previously demonstrated that these procedures were not effective in the treatment of HPV-associated genital warts.

Decline in genital warts, Melbourne Sexual Health Center, by age
HPV genotype prevalence, Australia

Cross-sectional analysis of women 18-24 years undergoing PAP screening during 2005-7 and 2010-11 in Sydney, Melbourne and Perth.

Tabrizi, et al. JID 2012;206;1645-51

- Kaiser Permanente Northwest, comparing HPV genotypes in 2007 and 2012-13 in women undergoing liquid cytology cervical specimens
- Results: 40% reduction in vaccine type prevalence in 20-29 y/o women

Journal of Infectious Diseases Advance Access published July 14, 2015


Kaiser Permanente Northwest

- Results: 40% reduction in vaccine type prevalence in 20-29 y/o women

Table 1. Prevalence of Type-Specific (90% Area Under Women's Receiver Operating Characteristic Curve) HPV in Women Undergoing Cervical Screening, Kaiser Permanente Northwest, 2015-2016

Table 2. Services Analyzed as Characterized Associated With HPV in Women Undergoing Cervical Screening, Kaiser Permanente Northwest, 2015-2016

J Infect Dis 2015 June 29 pii:jiv342. [Epub ahead of print]
Impact of HPV vaccination on HPV16/18-related prevalence in precancerous lesions

- HPV-IMPACT project: monitoring women undergoing PAP testing for findings of CIN2+ (CIN2, CIN2/3, CIN3, AIS/AIS+CIN)
  - Block sent for HPV DNA typing
- Outcome: women with CIN2+
  - Women 18-31 y/o who started HPV vaccine series >24 months before PAP
    - aPR = .67, 95% CI: .48-.94 for HPV16/18 related lesions


9vHPV: Remaining questions

- Revaccination of girls who have completed the 4vHPV series?
  - Prelicensure trial showed safety and immunogenicity against 5 additional high-risk types
  - To be discussed at October ACIP meeting
- Immunogenicity of 2 versus 3 dose series of 9vHPV?
  - Study underway

Additional ACIP guidance for use of 9vHPV vaccine

Thank You!