HPV Vaccines: What’s new?

Teresa M. Darragh, MD
UCSF
Departments of Pathology and Obstetrics, Gynecology & Reproductive Sciences
Faculty Disclosures:
Teresa M. Darragh, MD

• Hologic: Research supplies for anal cytology
• Roche-Ventana: (October 2016)
  – Honorarium
  – Travel expenses
Objectives

- In brief, burden of HPV-associated disease
  - Worldwide
  - US
  - Mexico
- HPV Prophylactic Vaccines

- The future?
  - Therapeutic vaccines
  - L2 vaccines
Cervical Cancer: Global Burden, 2012

- 4th most frequent cancer in women
- Approximately 530,000 new cases
- 2nd most common cancer in women living in less developed regions
  - 445,000 new cases in 2012
  - 84% of the new cases worldwide
- Approximately 270,000 women died
  - More than 85% of these deaths occurring in low- and middle-income countries.
- 7.5% of all female cancer deaths.

http://www.who.int/mediacentre/factsheets/fs380/en/

## Burden of cervical cancer

<table>
<thead>
<tr>
<th></th>
<th>United States</th>
<th>Mexico</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incidence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New cases per year</td>
<td>12,966</td>
<td>13,960</td>
</tr>
<tr>
<td>Age-standardized rate</td>
<td>6.6</td>
<td>23.3</td>
</tr>
<tr>
<td>Ranking of cervical cancer (15-44 years)</td>
<td>4th</td>
<td>1st</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6605</td>
<td>4769</td>
</tr>
<tr>
<td>Age-standardized rate</td>
<td>2.7</td>
<td>8.0</td>
</tr>
</tbody>
</table>

2016 Estimates | www.hpvcentre.net
HPV-associated Cancers by Type

Average number of new HPV-related cancers, by sex, United States, 2006-2010

Women (n = 17,600)
- Cervix: 59%
- Oropharynx: 10%
- Vulva: 13%
- Anus: 15%
- Vagina: 3%

Men (n = 9,300)
- Oropharynx: 77%
- Anus: 15%
- Penis: 8%

Total
- Oropharynx: 77%
- Anus: 15%
- Vulva: 13%
- Vagina: 3%
- Cervix: 59%
Oropharyngeal Cancer

- 11,000 cases annually; 7,000 in men
- Will be more common than cervical cancer by 2020
- Rise in incidence and changing patient demographics due to HPV

Courtesy of Bechara Ghorayeb, MD
http://www.ghorayeb.com/OropharyngealCarcinoma.html
## HPV-associated Cancers in U.S.

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Average # Cancers Per Year at Site (a)</th>
<th>Percent Probably Caused by HPV (a)</th>
<th>Number Probably Caused by HPV (a)</th>
<th>Percent HPV Cancers Probably Caused by HPV16 or 18 (b)</th>
<th>Number of Cancers Per Year Probably Caused by HPV16 or 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anus</td>
<td>4,767</td>
<td>93</td>
<td>4,500</td>
<td>93</td>
<td>4,200</td>
</tr>
<tr>
<td>Cervix</td>
<td>11,967</td>
<td>96</td>
<td>11,500</td>
<td>76</td>
<td>8,700</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>11,726</td>
<td>63</td>
<td>7,400</td>
<td>95</td>
<td>7,000</td>
</tr>
<tr>
<td>Penis</td>
<td>1,046</td>
<td>36</td>
<td>400</td>
<td>87</td>
<td>300</td>
</tr>
<tr>
<td>Vagina</td>
<td>729</td>
<td>64</td>
<td>500</td>
<td>88</td>
<td>400</td>
</tr>
<tr>
<td>Vulva</td>
<td>3,136</td>
<td>51</td>
<td>1,600</td>
<td>86</td>
<td>1,400</td>
</tr>
<tr>
<td>TOTAL</td>
<td>33,371</td>
<td></td>
<td>25,900</td>
<td></td>
<td>22,000</td>
</tr>
</tbody>
</table>

Gillison ML et al. HPV prophylactic vaccines and the potential prevention of noncervical cancers in both men and women. Cancer 2008;113(10 Suppl):3036-46
President’s Cancer Panel Annual Report 2012-2013*
What HPV Types Cause Cervical Cancer?

International

<table>
<thead>
<tr>
<th>HPV Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV 16</td>
<td>61%</td>
</tr>
<tr>
<td>HPV 18</td>
<td>71%</td>
</tr>
<tr>
<td>HPV 45</td>
<td>77%</td>
</tr>
<tr>
<td>HPV 31</td>
<td>81%</td>
</tr>
<tr>
<td>HPV 33</td>
<td>85%</td>
</tr>
<tr>
<td>HPV 52</td>
<td>88%</td>
</tr>
<tr>
<td>HPV 58</td>
<td>90%</td>
</tr>
</tbody>
</table>

Mexico: HPV types in HSIL and Cancer

### High-grade lesions (7, 8)

- HPV 16: 31.2%
- HPV 58: 9.7%
- HPV 33: 7.1%
- HPV 31: 6.5%
- HPV 82: 6.5%
- HPV 51: 2.9%
- HPV 45: 2.0%
- HPV 45: 1.5%
- HPV 73: 1.5%
- HPV 70: 1.1%

**Worldwide:**

HPV 16 + 18 → ~50% HSIL

### Cervical Cancer (1, 2)

- HPV 16: 52.8%
- HPV 18: 10.2%
- HPV 31: 5.2%
- HPV 45: 4.7%
- HPV 58: 3.2%
- HPV 39: 2.9%
- HPV 33: 1.8%
- HPV 35: 1.1%
- HPV 52: 1.0%
- HPV 59: 1.0%

**Worldwide:**

HPV 16 + 18 → ~70% cancers

[www.hpvcentre.net](http://www.hpvcentre.net)
Mexico: HPV types in Cervical Cancer

Squamous cell carcinoma
- HPV type 16: 54.8%
- HPV type 18: 9.5%
- HPV type 45: 4.2%
- HPV type 31: 3.9%
- HPV type 58: 3.1%
- HPV type 39: 3.0%
- HPV type 52: 1.5%
- HPV type 33: 1.4%
- HPV type 68: 1.0%
- HPV type 35: 1.0%

Adenocarcinoma
- HPV type 16: 42.2%
- HPV type 45: 12.5%
- HPV type 18: 10.9%
- HPV type 31: 4.7%
- HPV type 39: 3.1%
- HPV type 59: 1.6%
- HPV type 33: 1.6%
- HPV type 58: 1.6%
- HPV type 68: 1.6%
- HPV type 10th*: 1.6%

www.hpvcentre.net
Cervical Cancer Prevention

• Primary prevention
  – HPV vaccination
  – Prophylactic vaccination

• Secondary prevention
  – Screening, detection & treatment
    • Precancer
    • (Early) cancer
HPV Prophylactic Vaccines

- Recombinant L1 capsid proteins that form virus-like particles (VLPs)
- Noninfectious, nononcogenic
- Produce higher levels of neutralizing antibody than natural infection

Cocktails of L1 VLPs from 2, 4, or 9 HPV types
## Current FDA-approved HPV vaccines

<table>
<thead>
<tr>
<th></th>
<th>Bivalent (2vHPV)</th>
<th>Quadrivalent (4vHPV)</th>
<th>Nonovalent (9vHPV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacture</td>
<td>GlaxoSmithKline</td>
<td>Merck</td>
<td>Merck</td>
</tr>
<tr>
<td>L1,VLP</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>ASO4</td>
<td>AAHS</td>
<td>AAHS</td>
</tr>
<tr>
<td>Age groups</td>
<td>Females 9-25 years (2009)</td>
<td>Females 9-26 years (2004)</td>
<td>Females 9-26 years and Males 9-18 years (2014) Catch period for boys to 26 that are gay, bisexual or who have not completed series</td>
</tr>
<tr>
<td>ACIP meeting 2015</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Relative Contribution of HPV Types in 9vHPV Vaccine to Cervical Disease

<table>
<thead>
<tr>
<th>Type of lesion</th>
<th>6/11/16/18 Contribution</th>
<th>31/33/45/52/58 Contribution</th>
<th>Overall 9V Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical cancer</td>
<td>70%</td>
<td>20%</td>
<td>90%</td>
</tr>
<tr>
<td>CIN2/3**</td>
<td>50%</td>
<td>30%</td>
<td>75-85%</td>
</tr>
<tr>
<td>CIN1**</td>
<td>30-35%</td>
<td>25%</td>
<td>50-60%</td>
</tr>
</tbody>
</table>

**Based on the placebo cohort in the GARDASIL® clinical program & several meta analyses http://www.cdc.gov/vaccines/acip/meetings/downloads//slides-oct-2013/03-HPV-Luxembourg.pdf**

Mexico: HPV types in Cervical Cancer

- HPV type 16: 52.8%
- HPV type 18: 10.2%
- HPV type 31: 5.2%
- HPV type 45: 4.7%
- HPV type 58: 3.2%
- HPV type 39: 2.9%
- HPV type 33: 1.8%
- HPV type 52: 1.4%
- HPV type 35: 1.1%
- HPV type 59: 1.0%

2v and 4v Vaccines ~63%
9v Vaccine ~79.3%
HPV Vaccination in U.S.

**Recommendations**

**Female & Male**
Initiate at 11-12 years
Can start at 9 years
Females – catch up 13-26
Males – catch up 13-21 & up 26*

**Administration**
2vHPV, 4vHPV, & 9vHPV

3-dose schedule:
0, 2, 6 months (4vHPV & 9VHPV)
0, 1, 6 months (2vHPV)
Series does *not* need to be restarted if the schedule is interrupted.

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6411a3.htm
HPV Vaccination rates in U.S.

- Received at least one dose of HPV vaccine
  - Six out of 10 teen girls (63 percent)
  - Five out of 10 teen boys (50 percent)

Mexico: HPV Vaccination Program

- **Start Date:** 2008
- **National program – now school-based**
- **Target age:** 9-12 years old girls
- **Extended dosing schedule:** 0, 6, 60 months
- **Full course HPV vaccination coverage for routine immunization:** 67% (2010)
1 or 2 or 3 doses?

• 2014 WHO endorsed 2 doses: 2v and 4v
  – Young adolescents, girls up to age 15
  – At least 6 months apart
  – Reduce costs
  – Improve coverage

• Costa Rica Vaccine Trial
  – Efficacy of 1 dose
  – 2v-vaccine
  – 3-4 years follow-up

• 9v-vaccine: Dose studies in progress

HPV Vaccination Uptake

Differences in Adolescent Vaccine Delivery Systems

<table>
<thead>
<tr>
<th>Country</th>
<th>System</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>Doctors offices, Private and public insurance</td>
</tr>
<tr>
<td>Canada</td>
<td>School-based, National immunization programs</td>
</tr>
<tr>
<td>Australia</td>
<td>School-based, National immunization programs</td>
</tr>
<tr>
<td>England</td>
<td>School-based, National immunization programs</td>
</tr>
</tbody>
</table>

It’s More than Just Attitudes and Access

- Vaccine Availability
- Cost
- Social Norms and Values
- HC recommendation and provision
- Parent attitudes
- Parent Consent
- Patient’s attitudes
- Patient’s Consent

Who should NOT have HPV vaccines?

- Anyone allergic to the components in the vaccine
- 2vHPV (Bivalent vaccine)
  - Latex allergy
- 4vHPV or 9vHPV (Quadrivalent or Nonovalent)
  - Yeast allergies
Monitoring the Impact of HPV Vaccination

Outcomes of interest

• Short-term (months)
  – HPV prevalence
  – Incidence of genital warts

• Intermediate-term (years)
  – Incidence of high-grade cervical lesions
  – Juvenile onset recurrence respiratory papillomatosis

• Long-term (decades)
  – Incidence of and mortality from HPV-related cancers

Proportion of Australian-born females with Genital Warts, by age group, 2004–2011

qHPV vaccine introduced

- <21 Years (n=9,405)
- 21–30 Years (n=15,228)
- >30 Years (n=10,246)

Percent

Year

2004 2005 2006 2007 2008 2009 2010 2011

P_trend=0.89
P_trend=0.23
P_trend=0.07
P_trend<0.001
P_trend<0.001
P_trend<0.001

-72.6%
-92.6%

Proportion of Australian-born heterosexual males with Genital Warts by age group, 2004–2011

Herd immunity when there is adequate vaccine coverage

Reduction of High-grade disease after HPV vaccination (U.S.)

HPV Vaccine Safety

- Studied worldwide
  - No serious safety concerns
- June 2006 to March 2013:
  - ~56 million doses 4vHPV distributed in U.S.
- VAERS: 21,194 adverse event reports during this period.
  - 92% “Non-Serious”: e.g. Injection site soreness
  - 7.9% “Serious”
    - Syncope- Observe seated or prone for 15 minutes
    - Headache, nausea, fatigue, generalized weakness

http://www.cdc.gov/std/hpv/STDFact-HPV-vaccine-hcp.htm
http://www.clinicaltherapeutics.com/article/S0149-2918(13)00102-8/fulltext
“...allegations of harm from vaccination based on weak evidence can lead to real harm when, as a result, safe and effective vaccines cease to be used.”

WHO’s Global Advisory Committee on Vaccine Safety
March 12, 2014
HPV Genome

Early region:
Viral replication

Late region:
Viral capsid

Prophylactic vaccines

Therapeutic vaccines

L1: Major capsid protein
L2
L1
URR
E6
E7 binds Rb
E6 binds p53
E1
E2 / E4
E5

HPV: Circular DNA ~8000 base pairs
Therapeutic HPV Vaccines

- Preventive vaccines: Generate neutralizing antibodies to prevent HPV infection
- Therapeutic vaccines: Aimed at generating cell-mediated immunity
- Targets for therapeutic vaccines:
  - HPV-encoded early proteins
  - Oncoproteins E6 and E7:
    • Consistently expressed in HPV-associated malignancies and precancerous lesions
    • Play crucial roles in the generation and maintenance of HPV-associated disease.
L2 HPV Vaccines

- L2 – minor capsid protein
- More conserved among all HPV types
  - Anogenital mucosal types: Alpha
  - Cutaneous types: beta, gamma, mu, and nu
- L2 is subdominant to L1
  - Mostly buried below the capsid surface except during infection
  - Relatively weak immunogenicity
- Possible therapeutic potential

Galloway D. The Lancet Infectious Diseases 2003 3, 469-475
HPV vaccine will save lives.

If there were a vaccine against cancer, wouldn’t you get it for your kids?

HPV vaccine is cancer prevention. Talk to the doctor about vaccinating your 11–12 year old sons and daughters against HPV.