HPV

Your Semi-Annual Update

Women’s Health Symposium
Audrey P. Garrett, MD, MPH
September, 25, 2015
HPV
Disclosures

• Speaker Bureau, Merck
  – Gardasil, Gardasil 9

• Speaker Bureau, Hologic
  – Cervista and Aptima

• Speaker Bureau, Roche
  – Cobas
Disclosures-2

Gynecologic Oncologist

Parent

Vaccine Enthusiast
Objectives

• Review HPV statistics
• Review Gardasil utilization
• Introduce Gardasil 9
• Review HPV testing
• Review Cervical Cancer Screening
• Discuss HPV only screening
HPV causes more than cervical cancer

- Cervical Cancer \(^1,3\) (100%)
- Penile Cancer \(^3\) (45%)
- Head & Neck Cancer \(^3\) (12-70%)
- Vulvar Cancer \(^1\) (40%)
- Vaginal Cancer \(^1\) (60-90%)
- Anal Cancer \(^1-3\) (80%+)
- Genital Warts \(^1,3\) (~100%)

Percentages represent cases attributable to HPV infection

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# Annual US HPV-related Cancer and Disease Cases Caused by 9 HPV Types

According to estimates for males and females:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical cancer</td>
<td>11,124 cases</td>
</tr>
<tr>
<td>Anal cancer</td>
<td>5,386 cases</td>
</tr>
<tr>
<td>Vulvar and vaginal cancers</td>
<td>3,263 cases</td>
</tr>
<tr>
<td>Low-grade cervical lesions</td>
<td>468,750 cases</td>
</tr>
<tr>
<td>High-grade cervical precancers</td>
<td>216,000 cases</td>
</tr>
<tr>
<td>Genital warts</td>
<td>324,000 cases</td>
</tr>
</tbody>
</table>

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HPV Facts: Most common STD in the U.S.

Approximately 20 million Americans are currently infected.¹

- Estimated incidence of new cases 6 million per year¹
- 80% sexually active adults in U.S. infected w/ at least one HPV type by age 50¹
- Peak prevalence during adolescence and young adulthood
  - Among sexually active 15-24 year olds:
    - 74% new infections occur in this age group²
    - ~9.2 million currently infected²

¹ Centers for Disease Control & Prevention, Rockville MD: CDC National Prevention Information Network; 2009
Could YOU have HPV?
YES... if you have...

- a cervix
- a vagina
- a penis
- tonsils
- a throat
- an anus
- ever had sex
HPV is associated with many anogenital conditions.

HPV = human papillomavirus. Image © Scott Camazine / Phototake.


HPV causes more than cervical cancer

- Cervical Cancer\(^1,^3\) ~100%
- Penile Cancer\(^3\) 45%
- Vulvar Cancer\(^1\) ~40%
- Head & Neck Cancer\(^3\) 12-70%
- Vaginal Cancer\(^1\) 60-90%
- Genital Warts\(^1,^3\) ~100%
- Anal Cancer\(^1-^3\) 80%+

Percentages represent cases attributable to HPV infection

HPV is Ubiquitous

- SNL
- Amy Schumer
- Republican Debates
- Doctor’s offices?
- Schools?
Established Efficacy for HPV Types 6, 11, 16, and 18—Results From Clinical Trials for GARDASIL

In clinical studies of young men and women 16 to 26 years of age naïve to HPV Type 6, 11, 16, or 18, efficacy of GARDASIL® [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant] was:

<table>
<thead>
<tr>
<th>Disease</th>
<th>Efficacy Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CERVICAL CANCER</strong></td>
<td>HPV 16- and 18-related CIN 2/3 or AIS</td>
</tr>
<tr>
<td></td>
<td>98% efficacy</td>
</tr>
<tr>
<td><strong>VULVAR/VAGINAL CANCER</strong></td>
<td>HPV 16- and 18-related VIN 2/3 or VaIN 2/3</td>
</tr>
<tr>
<td></td>
<td>100% efficacy</td>
</tr>
<tr>
<td><strong>ANAL CANCER</strong></td>
<td>HPV 6-, 11-, 16-, and 18-related AIN 2/3</td>
</tr>
<tr>
<td></td>
<td>75% efficacy</td>
</tr>
<tr>
<td><strong>GENITAL WARTS</strong></td>
<td>HPV 6- and 11-related</td>
</tr>
<tr>
<td></td>
<td>89% efficacy in males</td>
</tr>
<tr>
<td></td>
<td>99% efficacy in females</td>
</tr>
</tbody>
</table>

**Study results for data above**

**Cervical:** 2 CIN 2/3 or AIS cases in the group receiving GARDASIL (n=8,493) vs 112 cases in the group receiving placebo (n=8,464) [95% CI, 93.5–99.8].

**Vulvar/Vaginal:** No VIN 2/3 or VaIN 2/3 cases in either group receiving GARDASIL (n=7,772) vs 10 cases in the VIN 2/3 group receiving placebo (n=7,744) [95% CI, 55.5–100.0], and 9 cases in the VaIN 2/3 group receiving placebo (n=7,744) [95% CI, 49.5–100.0].

**Anal:** 3 AIN 2/3 cases in the male group receiving GARDASIL (n=194) vs 13 cases in the male group receiving placebo (n=208) [95% CI, 8.8–95.4].

**Genital Warts:** 3 genital warts cases in the male group receiving GARDASIL (n=1,394) vs 28 cases in the male group receiving placebo (n=1,404) [95% CI, 65.3–97.9] and 2 genital warts cases in the female group receiving GARDASIL (n=6,932) vs 189 cases in the female group receiving placebo (n=6,856) [95% CI, 96.2–99.9].
Population Efficacy

• Australia: 70% completed series
  – 77% decrease in HPV infection
  – 90% decrease in condyloma
  – significant decrease in CIN3

• US: 32% completion rates
  – 11.5% HPV prevalence down to 5.1% (CDC)
  – 2.9/1000 to 1.8/1000 warts (2006-2010)
Figure 3a: HPV vaccine effectiveness for cervical histological outcome, by age in completed vaccine course

- Any high-grade histology
- CIN3/AIS
- CIN2
- CIN1

Age groups: ≤14, 15, 16, 17, All ages
Figure 3a: HPV vaccine effectiveness for cervical histological outcome, by age in 2007, for completed vaccine course.

Figure 3b: HPV vaccine effectiveness for cervical histological outcome, by age in 2007, for any vaccine dose.

Footnotes: All high grade histology defined as CIN2, CIN3, AIS, and mixed CIN3/AIS. Vaccine effectiveness defined as (1- adjusted hazard rate) x 100. Age in 2007 years.
HPV VACCINATION IS THE BEST WAY TO PREVENT MANY TYPES OF CANCER. MANY ADOLESCENTS HAVEN'T STARTED THE HPV VACCINE SERIES.

NATIONWIDE
4 OUT OF 10 GIRLS ARE UNVACCINATED

National coverage is 60% Coverage by state:
- 49% or less
- 50-59%
- 60-69%
- 70% or greater

NATIONWIDE
6 OUT OF 10 BOYS ARE UNVACCINATED

National coverage is 42% Coverage by state:
- 29% or less
- 30-39%
- 40-49%
- 50% or greater

IMPROVING HPV VACCINATION RATES WILL HELP SAVE LIVES. A high national Tdap vaccination rate of 88% shows that it is possible to achieve high HPV vaccination coverage.

Percentage of adolescent girls who have received one or more doses of HPV vaccine*

Percentage of adolescent boys who have received one or more doses of HPV vaccine*

*Estimated coverage with ≥1 dose of Human Papillomavirus (HPV) vaccine, either quadrivalent or bivalent, among adolescents aged 13-17 years, National Immunization Survey-Teen (NIS-Teen), United States, 2014
Source: MMWR July 31, 2015

www.cdc.gov/hpv
Figure 3
HPV Vaccination Rates of Adolescent Girls ages 13-17, by State

Completion of 3 dose HPV vaccine series among females ages 13-17, 2014

2014 U.S. average = 39.7%

Estimated vaccine coverage for females ages 13-17
- <30% (7 states)
- 30 – 39.7% (14 states)
- 39.8 – 44.9% (19 states)
- ≥45% (7 states + DC)

NOTES: Share of females ages 13-17 who have received all 3 doses of the HPV vaccine series. *Statistically significant (p<.05) percentage point change from 2013.
Figure 2

Estimated HPV Vaccination Coverage Among Female Adolescents in the US

Share that have received 3-doses of HPV Vaccine, 2014

<table>
<thead>
<tr>
<th>Total</th>
<th>Race/ Ethnicity</th>
<th>Poverty Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>40%</td>
<td>38% 39% 47% 36%</td>
<td>45% 38%</td>
</tr>
</tbody>
</table>

NOTE: Among female adolescents ages 13-17.
Figure 4

HPV Vaccination Policies- Mandates, Education, and Funding

State laws requiring HPV vaccinations for school entry, providing funding to cover the cost of the vaccine, or requiring public education (including for school children and parents)

NOTES: *States may have other laws relating to the HPV vaccine, such as insurance coverage mandates and research initiatives.
ACIP Recommendation: Routine HPV Vaccination\(^1,\)\(^a\)

**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

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

\(^a\)For complete ACIP recommendations on HPV vaccination, please see the *MMWR*.

• 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.

HPV Vaccine Coverage Rates Remained Low in 2013\textsuperscript{1,2}

- 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

CDC=Centers for Disease Control and Prevention; HPV=human papillomavirus.

Well-Child Visits are Underutilized for Administration of HPV Vaccine$^{1–3,a}$

Although ACIP recommends that eligible preteens ages 11 or 12 years receive recommended adolescent vaccines at a single visit,$^{1,2}$ only 10% received Tdap, MCV4, and HPV during a single visit, based on Commercial Claims database$^3$

HPV=human papillomavirus; ACIP=Advisory Committee on Immunization Practices; MCV4=Meningococcal Conjugate Vaccine; Tdap=Tetanus, Diphtheria and Pertussis vaccine.

$^a$Study of 1,245,336 eligible preteens aged 11–12 years who were continuously enrolled in Truven Health® MarketScan® Commercial Claims and Encounters Database between January 2010 and December 2014 who had at least 1 vaccination visit for any of the 3 recommended vaccines during the study period.$^3$

Introducing Gardasil 9

- Gardasil: June, 2006
  - approved for boys 2009
- Cervarix: October, 2009
- Gardasil 9: December, 2014
  - Product Launch: April, 2015
  - available in Oregon: May, 2015
GARDASIL®9 (Human Papillomavirus 9-valent Vaccine, Recombinant)

GARDASIL®
[Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant]

AAHS = 225μg

GARDASIL®9

AAHS = 500μg

AAHS = Amorphous Aluminum Hydroxyphosphate Sulfate; HPV = human papillomavirus; qHPV = quadrivalent HPV vaccine.
## 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%(^1)</td>
<td>90%(^1)</td>
</tr>
<tr>
<td>Vulvar cancer cases(^a)</td>
<td>75%(^2)</td>
<td>90%(^2)</td>
</tr>
<tr>
<td>Vaginal cancer cases(^a)</td>
<td>65%(^3)</td>
<td>85%(^3)</td>
</tr>
<tr>
<td>Anal cancer cases(^a)</td>
<td>85%(^4)</td>
<td>90%–95%(^4)</td>
</tr>
<tr>
<td>High-grade cervical precancer(^a, b)</td>
<td>50%(^5)</td>
<td>80%(^5)</td>
</tr>
<tr>
<td>Low-grade cervical lesion(^a)</td>
<td>25%(^5)</td>
<td>50%(^5)</td>
</tr>
<tr>
<td>Genital warts cases</td>
<td>90%(^6)</td>
<td>90%(^6)</td>
</tr>
</tbody>
</table>

\(^a\)Not all cervical precancers and lesions, and vulvar, vaginal, and anal cancer cases are caused by HPV. Approximately 90% of high-grade cervical precancers,\(^7\) 75% of low-grade cervical lesions,\(^7\) 30% of vulvar cancer cases,\(^2\) 70% to 75% of vaginal cancer cases,\(^3\) and 85% to 90% of anal cancer cases\(^4\) are HPV related.

\(^b\)High-grade cervical precancers defined as CIN 2/3.

Primary Objective of Efficacy Evaluation for GARDASIL® 9 (Human Papillomavirus 9-valent Vaccine, Recombinant)¹

GARDASIL® [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant]

Demonstrate non-inferior immunogenicity

Demonstrate efficacy

GARDASIL®9

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Girls and women 9–26 years of age</th>
<th>Boys 9–15 years of age</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cancers caused by HPV Types 16, 18, 31, 33, 45, 52, and 58</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cervical</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>• Vulvar</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>• Vaginal</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>• Anal</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Precancerous or dysplastic lesions caused by HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• CIN grade 2/3 and AIS</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>• CIN grade 1</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>• VIN grades 2 and 3</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>• VaIN grades 2 and 3</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>• AIN grades 1, 2, and 3</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Genital warts caused by HPV Types 6 and 11</strong></td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

CIN=cervical intraepithelial neoplasia; AIS=cervical adenocarcinoma in situ; VIN=vulvar intraepithelial neoplasia; VaIN=vaginal intraepithelial neoplasia; AIN=anal intraepithelial neoplasia.
### Efficacy of GARDASIL 9 for Combined Disease Endpoint in the PPE Population, 16 to 26 Year Old Girls and Women

<table>
<thead>
<tr>
<th>Combined Disease Endpoint</th>
<th>GARDASIL 9 N=7099</th>
<th>GARDASIL N=7105</th>
<th>GARDASIL 9 Efficacy % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Number of cases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV 31-, 33-, 45-, 52-, 58-related:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- CIN 2/3</td>
<td>6016</td>
<td>1</td>
<td>96.7 (80.9, 99.8)</td>
</tr>
<tr>
<td>- AIS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Cervical Cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- VIN 2/3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- VaIN 2/3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Vulvar Cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Vaginal Cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Study Design:** Efficacy of GARDASIL 9 in 16- to 26-year-old women was assessed in an active comparator-controlled, double-blind, randomized clinical study that included a total of 14,204 women (GARDASIL 9 =7,099; GARDASIL® [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant] =7,105). Subjects were followed up with a median duration of 40 months (range 0 to 64 months) after last vaccination and efficacy was measured starting after the Month 7 visit. Efficacy was evaluated in the PPE population which consisted of subjects who received all 3 vaccinations within 1 year of enrollment, had no major deviations from the study protocol, were naïve to the relevant HPV type(s) prior to dose 1, and remained PCR negative to the relevant HPV type(s) through 1 month postdose 3 (Month 7).

CIN=cervical intraepithelial neoplasia; AIS=adenocarcinoma in situ; VaIN=vaginal intraepithelial neoplasia; VIN=vulvar intraepithelial neoplasia; HPV=human papillomavirus; CI=confidence interval.
GARDASIL ®9 (Human Papillomavirus 9-valent Vaccine, Recombinant)—Data for Other Clinical Endpoints

### Efficacy of GARDASIL 9 for Other Clinical Endpoints in the PPEa Population, 16 to 26 Year Old Girls and Women

<table>
<thead>
<tr>
<th>Disease Endpoint</th>
<th>GARDASIL 9 N=7099</th>
<th>GARDASIL N=7105</th>
<th>GARDASIL 9 Efficacy % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Number of cases</td>
<td>n</td>
</tr>
<tr>
<td>HPV 31-, 33-, 45-, 52-, 58-related ASC-US HR-HPV Positive or Worse Pap Abnormality</td>
<td>5881</td>
<td>35</td>
<td>5882</td>
</tr>
<tr>
<td>HPV 31-, 33-, 45-, 52-, 58-related Biopsy</td>
<td>6016</td>
<td>7</td>
<td>6017</td>
</tr>
<tr>
<td>HPV 31-, 33-, 45-, 52-, 58-related Definitive Therapyb</td>
<td>6012</td>
<td>4</td>
<td>6014</td>
</tr>
</tbody>
</table>

*aStudy Design: Efficacy of GARDASIL 9 in 16- to 26-year-old women was assessed in an active comparator-controlled, double-blind, randomized clinical study that included a total of 14,204 women (GARDASIL 9=7,099; GARDASIL 7,105). Subjects were followed up with a median duration of 40 months (range 0 to 64 months) after last vaccination and efficacy was measured starting after the Month 7 visit. Efficacy was evaluated in the PPE population which consisted of subjects who received all 3 vaccinations within 1 year of enrollment, had no major deviations from the study protocol, were naïve to the relevant HPV type(s) prior to dose 1, and remained PCR negative to the relevant HPV type(s) through 1 month postdose 3 (Month 7);
*bIncluding loop electrosurgical excision procedure (LEEP) and conization.
ASC-US=atypical squamous cells of undetermined significance; CI=confidence interval; HR=high-risk; Pap=Papanicolaou test.
HPV and Cervical Cancer Screening

- Digene testing 1998
- ALTS trial
- Reflex testing
- Co-testing
- Genotyping
  - cervista
- HPV primary
  - Cobas
Objectives of Screening

• Prevent morbidity and mortality from CACX
• Prevent overzealous management of precursor lesions which would likely resolve or for which management would likely cause more risk than benefit
• “finding the lesion” is not the end all be all
  – we don’t know which lesions will progress
  – need to focus on persistent HPV
  – CIN 3 (no margin for error)
  – CIN2 in older women
  – persistent CIN2/3 in younger women
Reality of CACX Screening

• Preventing 100% of cacx is unrealistic
• ASCCP assumption that developing a risk strategy equivalent to the risk of cytology alone at a 2-3 y interval is appropriate
• Women at similar risk of cancer should be managed similarly
• Several different strategies may be acceptable
Reality of CACX Screening

- sensitivity of single pap 50-70%
- cancer risk 18 mo after 3 neg paps 1.5/100,000
- cancer risk 36 mo after 3 neg paps 4.7/100,000
- 99,997 women screened to help 3
- risk of HSIL up to 3 yrs after neg pap is not statistically significantly higher than after 1 yr

Justification for longer intervals

• Screening harms: lifetime risk of colpo
  – screening annually: 2000 colpos/1000 women
  – screening q 2 yr: 1080 colpo/1000 women
  – screening q 3 yr: 760 colpo/1000 women

Cotesting at 5yr interval: PREFERRED

- Increased detection of CIN3
- Decreased detection of CIN3 in subsequent screening rounds
- Increased reproducibility
- Enhances detection of AIS/Adenoca
- Cancer risk equivalent to q3 yr cytology
- Minimizes the increase in colpo (reduces harm)
Q: How many women will be infected with HPV at some point in their lives?

Over 75% of women will be infected by HPV. 50% of all surveyed knew the correct answer is >75%.

Q: Identify risks and impact associated with HPV genotypes 16 and 18.

89% of all surveyed knew that genotypes 16 & 18 are responsible for about 70% of all cancer cases.

Normal cytology does not always mean cancer free.

Regarding the new Cervical Cancer Screening Guidelines for women 30-65 years old:

- 66% are aware of new guidelines for HPV co-testing
- BUT - 14% still use Pap alone

Approximately 50% of cervical pre-cancer can be missed by Pap cytology alone.

Only 1 in 5 know the limitations of using Pap cytology alone.
Risk Stratification with HPV Types 16 and 18 in Women ≥ 30 Years of Age with Negative Cytology

In women ≥ 30 years of age, 10-year cumulative incidence of ≥ CIN 3 was 20% and 18% for HPV 16 and 18, respectively.
Changing Epidemiology
CONTROVERSY

• ABOG article
• Increased Cervical Cancer Risk Associated with Screening at Longer Intervals
  • Kinney, et al. (OB/GYN, 125:311-5, Feb 2015)
• questions establishing the “acceptable risk” as that of q3 yr cytology
• proposes annual cytology as benchmark
• suggests that additional burden of disease
  – 1/369 women diagnosed, 1/1,639 dying of disease
HPV PRIMARY

- Roche Cobas test
- ATHENA trial
- Consensus opinions of ASCCP, SGO, ACOG
There are more than twenty STDs affecting thirteen million men and women in this country. These include Chlamydia, Herpes, HPV, Gonorrhea, and I miss Cooties. You would.
KEEP CALM
we will have
Gardasil 9
FAQs

• Do I start the series over again?
• Revaccinate kids?
• Why is it not approved for boys over 15?