Cervical Cancer Prevention with GARDASIL®

NNSAHC Annual Meeting
Tucson, AZ

Gregg C. Sylvester, MD, MPH
Senior Medical Director
Merck Vaccine Division
There are over 100 types of HPV. Each type is given a number (e.g., HPV type 16). Each type of HPV generally grows on a specific part of the body:

- Common warts on the hands
- Plantar warts on the feet
- Genital warts on the genitals

HPV (Human Papillomavirus)

• 30-40 types infect the genital area\(^1,2\)
  - 15-20 of these types are *oncogenic* (*cancer-causing*)\(^1,2\) including 16, 18, 31, 33, 35, 39, 45, 51, 52, 58\(^3\)
    - HPV 16 (54%) and HPV 18 (13%) account for the majority of worldwide cervical cancers.\(^4\)
    - These are called *high-risk* types
  - The remainder are *non-oncogenic*. These include types 6, 11, 40, 42, 43, 44, 54\(^3\)
    - HPV 6 and 11 are most often associated with external genital warts.\(^2\)
    - These are thought of as *low-risk* types

By 50 years of age, at least 80\% of women will have acquired genital HPV infection.\(^1\)

Estimated new infections per year: 6.2 million\(^1\)

Estimated active infections (prevalence): 20 million\(^2\)

In sexually active individuals 15–24 years of age, ~9.2 million are currently infected.\(^3\)

---

Definitions

- CIN
  - Cervical intraepithelial neoplasia
    - Abnormal changes in the tissue of the cervix (*dysplasia*)
    - Level of abnormality tells us how serious it is
      - CIN 1: Mild dysplasia & genital warts
      - CIN 2: Moderate dysplasia
      - CIN 3: Severe dysplasia
        » CIN 2/3 are *precancers* that can develop into invasive cervical cancer

CIN1 ➔ CIN2 ➔ CIN3

Less serious ➔ More serious
Definitions

- **Dysplasia**
  - Another way of saying cervical tissue abnormality

- **AIS**
  - Adenocarcinoma in situ
    - Another type of noninvasive cervical cancer

- **VIN**
  - Vulvar intraepithelial neoplasia
  - Graded 1-3 similar to CIN

- **VaIN**
  - Vaginal intraepithelial neoplasia
  - Graded 1-3 similar to CIN
Estimated Annual Burden of HPV-Related Conditions in the US

- 1 million new cases of genital warts
- 1.4 million new cases of low-grade cervical dysplasia (CIN 1)
- 330,000 new cases of high-grade cervical dysplasia (CIN 2/3)
- 9,710 new cases of cervical cancer

CIN = Cervical Intraepithelial Neoplasia.


3,700 deaths estimated in 2006
HPV Is a Necessary Cause of Invasive Cervical Cancer

• First ever identified *necessary* cause of cancer.¹

• Persistent cervical infection with certain HPV types is single most important cervical cancer risk factor

• World Health Organization (WHO) recognizes cervical cancer as first cancer virtually 100% attributable to infection²

---

Most Common HPV Types in Cervical Cancer & Number of Cervical Cancer Cases in Europe and North America

Estimated total number of cases in women >15 years of age: 79,772

<table>
<thead>
<tr>
<th>Types</th>
<th>Cumulative Percentages</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>65.4</td>
<td>52,199</td>
</tr>
<tr>
<td>+ 18</td>
<td>71.5</td>
<td>57,005</td>
</tr>
<tr>
<td>+ 33</td>
<td>77.1</td>
<td>61,530</td>
</tr>
<tr>
<td>+ 31</td>
<td>81.2</td>
<td>64,793</td>
</tr>
<tr>
<td>+ 45</td>
<td>84.1</td>
<td>67,108</td>
</tr>
<tr>
<td>+ 56</td>
<td>85.6</td>
<td>68,266</td>
</tr>
<tr>
<td>+ 35</td>
<td>86.8</td>
<td>69,213</td>
</tr>
<tr>
<td>+ 52</td>
<td>87.8</td>
<td>70,055</td>
</tr>
</tbody>
</table>

Natural History of High-Risk HPV Infection and Potential Progression to Cervical Cancer\textsuperscript{1,2}

- **Transient Infection**: 1-12 Months
- **Cleared HPV Infection**: 90% clear their HPV infection within 2 years
- **Persistent Infection**: 1-5 Years
  - Over 2 Years
  - ~1 Year
  - 10% develop persistent infection
- **Low-Grade Dysplasia CIN 1**: 1-5 Years
- **High-Grade Dysplasia CIN 2/3**: 9–15 Years
- **Invasive Cancer**: 9–15 Years

HPV and Anogenital Warts

• HPV 6 and 11 is responsible for >90% of anogenital warts\(^1\)
  – (raised warts)
• Treatment can be painful and embarrassing.\(^2\)
• Capable of recurring even after treatment.\(^3\)

Images top left and top right: Reprinted with permission from NZ DermNet (www.dermnetnz.org)

GARDASIL®: The First Cervical Cancer Vaccine in the US

- Quadrivalent HPV 6/11/16/18 L1 virus-like particle (VLP) vaccine
- Preventive vaccine
  - Does not treat infection, dysplasia or cancer
- 3 dose regimen
  - Given at 0, 2, & 6 months
- Recommended for girls 11-12, with “catch up” of those 13-26
  - May be given to girls as young as 9
Approximate Disease Burden

<table>
<thead>
<tr>
<th>HPV Type</th>
<th>16 and 18</th>
<th>6, 11, 16, and 18</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• 70% of cervical cancer, AIS, CIN 3, VIN 2/3, and VaIN 2/3 cases</td>
<td>• 35%–50% of all CIN 1, VIN 1, and VaIN 1 cases</td>
</tr>
<tr>
<td></td>
<td>• 50% of CIN 2 cases</td>
<td>• 90% of genital warts cases</td>
</tr>
</tbody>
</table>

AIS = Adenocarcinoma in situ  
CIN = Cervical Intraepithelial Neoplasia  
VaIN = Vaginal Intraepithelial Neoplasia  
VIN = Vulvar Intraepithelial Neoplasia
Effectiveness of GARDASIL® in women naïve to vaccine HPV types

• Per Protocol Population Enrollment Criteria
  – Young woman aged 16-26 enrolled from North America, Latin America, Asia/Pacific, & Europe
  – Tested negative for HPV 6,11,16 or 18 at Day 1
  – Remain uninfected during course of vaccination through 1 month after dose 3
  – Lifetime history of 5 or fewer sexual partners
• No protocol violations
• Received all 3 doses
• Case counting starting 1 month after dose 3
### GARDASIL® (Quadrivalent Human Papillomavirus [HPV Types 6, 11, 16, 18] Recombinant Vaccine)

#### Efficacy: 100% Efficacious Against HPV 16- and 18-Related Cervical Cancer Precursors in Per Protocol Group

<table>
<thead>
<tr>
<th>End Point: HPV 16/18-related</th>
<th>n</th>
<th>GARDASIL® or HPV 16 L1 VLP Cases*</th>
<th>n</th>
<th>Placebo Cases</th>
<th>Vaccine Efficacy</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN 2/3 or AIS</td>
<td>8,487</td>
<td>0</td>
<td>8,460</td>
<td>53</td>
<td>100%</td>
<td>93–100</td>
</tr>
<tr>
<td>CIN 3 or AIS†‡</td>
<td>8,487</td>
<td>0</td>
<td>8,460</td>
<td>32</td>
<td>100%</td>
<td>88–100</td>
</tr>
</tbody>
</table>

AIS = Adenocarcinoma in situ; CIN = Cervical Intraepithelial Neoplasia

*Analysis of CIN 2/3 and AIS end points included protocol 005.

†Defined by FIGO as Stage 0 cervical cancers; FIGO = International Federation of Gynecology and Obstetrics.

‡CIN 3 or AIS analysis was a secondary end point.
### Efficacy: 100% Efficacious Against HPV 16- and 18-Related VIN 2/3 and VaIN 2/3 in Per-Protocol Group

<table>
<thead>
<tr>
<th>HPV 16/18-related VIN 2/3 or VaIN 2/3</th>
<th>GARDASIL®</th>
<th>Placebo</th>
<th>Vaccine Efficacy</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=7,769</td>
<td>n=7,741</td>
<td>0</td>
<td>10</td>
<td>100%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HPV 6/11/16/18-related VIN 1 or VaIN 1</th>
<th>GARDASIL</th>
<th>Placebo</th>
<th>Vaccine Efficacy</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=7,897</td>
<td>n=7,899</td>
<td>0</td>
<td>17</td>
<td>100%</td>
</tr>
</tbody>
</table>

VaIN = vaginal intraepithelial neoplasia.  
VIN = vulvar intraepithelial neoplasia.

Data available on request from Merck & Co., Inc., Professional Services-DAP, WP1-27, PO Box 4, West Point, PA 19486-0004. Please specify information package 20651717(3)-GRD.
**Efficacy: 99% Efficacious Against HPV 6/11/16/18 Genital Warts in Per Protocol Group**

<table>
<thead>
<tr>
<th>HPV 6/11/16/18-related Genital warts</th>
<th>GARDASIL®</th>
<th>Placebo</th>
<th>Vaccine Efficacy</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=7,897</td>
<td>n=7,899</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>91</td>
<td>99%</td>
<td>94–100</td>
<td></td>
</tr>
</tbody>
</table>
Effectiveness of GARDASIL® in the General Population

• GARDASIL® is effective when given to young women before they come in contact with the HPV types targeted by the vaccine

• So if we vaccinate all appropriate young women between 11 and 26, some will already have been infected with vaccine HPV types

• Will GARDASIL® help these young women?
27% of subjects had evidence of prior exposure to or ongoing infection with at least 1 of the 4 vaccine HPV types.

• 73% of subjects were naïve to all 4 vaccine HPV types
• Among subjects who were positive to a vaccine HPV type, most were positive to only 1 type
• Exclusion criteria: 6 or more sexual partners
Efficacy of GARDASIL® in the General Population

• Including those already infected with a vaccine HPV type, GARDASIL®:
  – Reduced the population risk of developing precancerous lesions caused by HPV types 18 & 18 by **39%** after 2-4 years
  – Reduced the population risk of developing genital warts caused by HPV types 6/11/16/18 by **69%** after 2-4 years

• There was no clear evidence of protection from disease caused by HPV types for which subjects were PCR positive and/or seropositive at baseline

• GARDASIL® has not been shown to protect against diseases due to non-vaccine HPV types
The Most Effective Time to Vaccinate Is Before Exposure

Behavior reported in an independent study

<table>
<thead>
<tr>
<th>Age at first intercourse</th>
<th>Suggests minimal exposure to HPV at 9 to 11 years of age</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;11 years old</td>
<td></td>
</tr>
<tr>
<td>12–13 years old</td>
<td></td>
</tr>
<tr>
<td>14–15 years old</td>
<td></td>
</tr>
<tr>
<td>16–17 years old</td>
<td></td>
</tr>
</tbody>
</table>

These data suggest minimal risk of exposure to HPV in 9- to 11-year-olds.

In an analysis of 1,552 adolescents and young adults, the subset (n=1,014) featured in this chart reported having engaged in sexual intercourse.

Bridging Gardasil Effectiveness to Younger Girls

• Our efficacy study was done in young women aged 16-24. Such a study in younger adolescents is not feasible.
  – Such studies require evaluation of sexual activity

• It is possible to compare immunogenicity and safety in younger girls with that seen in 16-24 year old young women
  – Safety and immunogenicity of girls 9-15 years of age was evaluated

• By comparing their immune responses, we were able to bridge vaccine efficacy in young women to younger female adolescents

Bridging Study Results
Neutralizing anti-HPV 6 GMTs at Month 7

Per-protocol immunogenicity population (ages 9–26)*

Titers in younger girls 9-15

Titers in older girls & young women 16-26

*Inclusive of 5 study protocols; all GMTs measured using cLIA.
Selected Information About GARDASIL®

- Indicated in girls and women 9 to 26 years of age for the prevention of cervical cancer, precancerous or dysplastic lesions, and genital warts caused by HPV Types 6, 11, 16, and 18.

- Contraindicated in individuals who are hypersensitive to the active substances or to any of the excipients of the vaccine.

- Vaccination with GARDASIL does not substitute for routine cervical cancer screening, and women who receive GARDASIL should continue to undergo screening per standard of care.
Selected Information About GARDASIL® (cont.)

• Vaccination with GARDASIL may not result in protection in all vaccine recipients.

• GARDASIL is not intended to be used for treatment of active genital warts; cervical cancer; CIN, VIN, or VaIN.

• GARDASIL has not been shown to protect against diseases due to non-vaccine HPV types.

• The vaccine-related adverse experiences that were observed among recipients of GARDASIL at a frequency of at least 1.0% and also at a greater frequency than that observed among placebo recipients were pain, swelling, erythema, fever, nausea, pruritus, and dizziness.
# Safety & Side Effects

The vaccine-related adverse experiences that were observed among recipients of GARDASIL were at a frequency of at least 1.0% and also at a greater frequency than that observed among placebo recipients.

## Injection Site (1 to 5 days Postvaccination)

<table>
<thead>
<tr>
<th></th>
<th>GARDASIL® (N=5,088)</th>
<th>Placebo (Aluminum) (N=3,470)</th>
<th>Placebo (Saline) (N=320)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>83.9%</td>
<td>75.4%</td>
<td>48.6%</td>
</tr>
<tr>
<td>Swelling</td>
<td>25.4%</td>
<td>15.8%</td>
<td>7.3%</td>
</tr>
<tr>
<td>Erythema</td>
<td>24.6%</td>
<td>18.4%</td>
<td>12.1%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3.1%</td>
<td>2.8%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

## Systemic AEs (1 to 15 days Postvaccination)

<table>
<thead>
<tr>
<th></th>
<th>GARDASIL (N=5,088)</th>
<th>Placebo (N=3,790)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>10.3%</td>
<td>8.6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>4.2%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2.8%</td>
<td>2.6%</td>
</tr>
</tbody>
</table>

- Few subjects (0.1%) discontinued due to AEs.
### Organization Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>ACIP¹</th>
<th>ACOG ²</th>
<th>AAFP ³</th>
<th>ACHA ⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine vaccination in 11- to 12-year-old females and catch-up vaccination in 13- to 26-year-olds</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Females 9–10 years old can be vaccinated</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>N/A</td>
</tr>
<tr>
<td>Vaccinate regardless of previous HPV infection or abnormal Pap test results</td>
<td>✓</td>
<td>✓</td>
<td>N/A</td>
<td>✓</td>
</tr>
<tr>
<td>Continue Pap testing after vaccination</td>
<td>✓</td>
<td>✓</td>
<td>N/A</td>
<td>✓</td>
</tr>
</tbody>
</table>

# Organization Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>ACIP¹</th>
<th>AAFP²</th>
<th>SAM³</th>
<th>ACHA⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine vaccination in 11- to 12-year-olds and catch-up vaccination in 13- to 26-year-olds</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Females 9–10 years old can be vaccinated</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>N/A</td>
</tr>
<tr>
<td>Vaccinate regardless of previous HPV infection or abnormal Pap test results</td>
<td>✓</td>
<td>N/A</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Continue Pap testing after vaccination</td>
<td>✓</td>
<td>N/A</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Overall Conclusions for GARDASIL®

- Highly effective in preventing cervical cancer, CIN 2/3, AIS, and other anogenital diseases including genital warts caused by HPV 6, 11, 16, and 18 in 16- to 26-year-old women naïve to the relevant HPV types
- Successful immunogenicity bridge between female adolescents and young adult women
  - Antibody response in 10- to 15-year-old females is higher, compared with response observed in young adult women (16–26 years old)
- Duration of efficacy is demonstrated between 2 and 4 years
- Favorable tolerability profile
- Before administering GARDASIL®, please read the Prescribing Information

AIS = Adenocarcinoma in situ; CIN = Cervical Intraepithelial Neoplasia
HPV Vote – Routine Vaccination

- ACIP recommends routine vaccination for females 11-12 years of age with three doses of quadrivalent HPV vaccine

- The vaccination series can be started as young as 9 years of age at the discretion of the provider

UNANIMOUS – IN FAVOR!
HPV Vote – Vaccination of Females 13-26

• Vaccination is recommended for females 13-26 years of age who have not been previously vaccinated

• Ideally vaccine should be administered before sexual activity, but females who are sexually active should still be vaccinated

UNANIMOUS – IN FAVOR!
HPV Other Recommendations and Wording

– Cervical cancer screening – no change
  • Vaccinated females could subsequently be infected with non-vaccines HPV types
  • Sexually active females could have been infected prior to vaccination

– Decision to vaccinate should not be based on Pap testing, HPV DNA or HPV serologic testing
Equivocal or Abnormal Pap Test

• Vaccination recommended; however
  – Could already have been infected with a vaccine HPV type
  – Data do not indicate vaccine will have therapeutic effect on existing cervical lesions or HPV infection

Positive HPV test

• Vaccination recommended; however
  – Could already have been infected with a vaccine HPV type
  – Data do not indicate vaccine will have therapeutic effect on existing cervical lesions or HPV infection
Genital Warts
- Vaccination recommended; however
  - Data do not indicate vaccine will have therapeutic effect on existing genital warts or HPV infection

Immunosuppression
- Can be vaccinated
  - Not a live vaccine
  - Immune response and vaccine efficacy might be less than in immunocompetent persons

Lactating women
- Lactating women can receive vaccines
**HPV Vaccination During Pregnancy Moved to Special Situations from Precautions and Contraindications**

**Pregnancy***

- Initiation of the vaccine series should be delayed until after completion of the pregnancy.
- If a woman is found to be pregnant after initiating the vaccination series, completion should be delayed until after the pregnancy.
- If a vaccine dose has been administered during pregnancy, there is no indication for intervention.

*ACIP is creating working group to address vaccination during pregnancy specifically for all new vaccines.*
HPV Vote – Special Situations

- Special Situations
  - Equivocal or abnormal Pap test
  - Positive HPV test
  - Genital warts
  - Immunosuppression
  - Lactating women
  - Vaccination during pregnancy

UNANIMOUS – IN FAVOR!
HPV Vote – Precautions and Contraindications

- Moderate or severe acute illnesses (precaution)

- History of ‘immediate’ hypersensitivity or severe allergic reaction to yeast or to any vaccine component (contraindication)

UNANIMOUS – IN FAVOR!
Classification of Histological Findings: CIN

- Cervical Intraepithelial Neoplasia (CIN)\(^1\)
  - CIN 1: Mild dysplasia; includes condyloma (anogenital warts)
  - CIN 2: Moderate dysplasia
  - CIN 3: Severe dysplasia; includes carcinoma in situ (CIS)

<table>
<thead>
<tr>
<th>CIN(^1)</th>
<th>Normal</th>
<th>CIN 1 (condyloma)</th>
<th>CIN 1 (mild dysplasia)</th>
<th>CIN 2 (moderate dysplasia)</th>
<th>CIN 3 (severe dysplasia/CIS)</th>
<th>Invasive Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology of squamous cervical epithelium(^1)</td>
<td>![Histology Image]</td>
<td>![Histology Image]</td>
<td>![Histology Image]</td>
<td>![Histology Image]</td>
<td>![Histology Image]</td>
<td>![Histology Image]</td>
</tr>
</tbody>
</table>

- CIN caused by HPV can clear without treatment; however, rates of regression are dependent on grade of CIN.\(^2\)

Cervical Cancer Rates By Race/Ethnicity
United States, 1997 – 2001

Cervical Cancer Incidence

Source: American Cancer Society. Cancer Facts & Figures 2005
Cervical Cancer Rates By Race/Ethnicity
United States, 1997 – 2001

Deaths per 100,000 women

Cervical Cancer Mortality

Source: American Cancer Society. Cancer Facts & Figures 2005