Human Papillomavirus (HPV) Disease and Prevention

**Human Papillomavirus (HPV)**

Nonenveloped encapsulated double-stranded small DNA virus

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**Human Papillomavirus**

- >100 types
  - Mucosal/genital (~40 types)
  - Nonmucosal/cutaneous (~60 types)

- High-risk types
  - 16, 18, 31, 45
  - Low grade cervical abnormalities
  - Cancers precursors
  - Genital cancers

- Low-risk types
  - Skin warts (hands/feet)
  - Nonpenetrative sexual contact

**HPV Transmission**

**Sexual Contact**
- Through sexual intercourse
- Genital-genital, manual-genital, oral-genital
- Genital HPV infection in virgins is rare, but may result from nonpenetrative sexual contact
- Condom use may help reduce risk, but does not fully protect

**Nonsexual Routes**
- Mother to newborn (vertical transmission, rare)
- Fomites (e.g., undergarments, surgical gloves, biopsy forceps)
  - Hypothesized, but not well documented
Genital HPV Prevalence and Incidence in U.S.A.

- Lifetime risk for sexually active men and women is > 50%
- By 50 years of age > 80% of women will have acquired genital HPV infection
- Estimated annual incidence: ~6 million
- Estimated prevalence: ~20 million
- In sexually active individuals 15–24 years of age ~9 million are currently infected

Genital HPV Infection Risk Factors

<table>
<thead>
<tr>
<th>RISK FACTOR</th>
<th>WOMEN</th>
<th>MEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young age (20-29 years)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Number of sexual partners (lifetime)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Uncircumcised (man/male partner)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Early age of sexual début</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Partner sexual behavior</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Oral contraceptive use</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

Biological Factors That May Increase Susceptibility of Female Adolescents to HPV Infection

- Inadequate production of cervical mucus, which may act as a barrier against infection
- Immature columnar and metaplastic cells in the transformation zone of the cervix are especially susceptible to HPV
- Incomplete local immunity against certain infections
- Increased susceptibility to minor trauma during sexual intercourse

Risk of Acquiring HPV After First Intercourse in Female Adolescents

- 60% infected by 5-years
- 35% infected by 18-months

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Why Are We Concerned About HPV?

Because HPV is...

...a necessary causative agent in cervical cancer

One of the most common sexually transmitted infections (STI) in the United States today


Most Common HPV Types in Cervical Cancer: Cumulative Prevalence (Squamous Cell Carcinoma)

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

Relative risks for CIN and invasive cancer increase with decreasing age of first sexual intercourse.

- **Age at First Intercourse (Years)**
  - ~6-FOLD INCREASE
  - ~3-FOLD INCREASE

### Table of Relative Risk Estimates

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Relative Risk CIN</th>
<th>Relative Risk Invasive Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥23 or Never</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤17</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Relative risks for CIN and invasive cancer increase with decreasing age of first sexual intercourse.*

### Additional Notes

- Cervical adenocarcinoma:
  - Becoming more common in women born in the late 20th and early 21st century.
  - Developing from the mucus-producing gland cells of the endocervix.

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**Cervical Intraepithelial Neoplasia (CIN)**

- CIN 1
- CIN 2: Moderate dysplasia
- CIN 3: Severe dysplasia, includes carcinoma in situ (CIS)

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**Natural History of High-Risk HPV Infection and Potential Progression to Cervical Cancer**

- Transient infection
- Persistent infection
- Low-grade dysplasia
- High-grade dysplasia
- Invasive cancer

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**Cervical Adenocarcinoma**

- Developing from the mucus-producing gland cells of the endocervix.

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**References**

Percentage Cervical Cancer Mortality in the US and Prevalence of High-Risk HPV

Prevalence of High-Risk HPV

Peak HPV infection occurs in young adults
Cervical cancer deaths peak in midlife

1. Adapted from Dunne EF et al. JAMA. 2007;297:813–819.

Age distribution of all cervical cancer deaths between 1935 and 2000 in the United States.

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

3,700 estimated deaths
9,710 new cases of cervical cancer
330,000 new cases of high-grade cervical dysplasia
1 million new cases of genital warts
1.4 million new cases of low-grade cervical dysplasia (CIN 1)

CIN = cervical intraepithelial neoplasia.


Symptoms and Treatment of VIN

HPV 16 and 18 contribute to 89% of VIN 1 and 79% to 86% of VIN 2/3 lesions.
Frequent symptoms are pruritus, vulvar pain or discomfort, and vaginal discharge.
Symptoms may be present for a long time prior to diagnosis (median of 1 year).
Recommended treatment is surgery, including vulvectomy or wide local excision.
— Recurrence is likely when lesions are not completely excised.
— Laser ablation techniques have had variable outcomes and can be associated with painful healing.

VIN = vulvar intraepithelial neoplasia.

Why Are We Concerned About HPV?

Because HPV is...

A necessary causative agent in cervical cancer¹

...one of the most common sexually transmitted infections (STI) in the United States today²

Estimated number of new cases per year in the United States¹: 1 million

Estimated number of sexually active adults with clinically visible genital warts³: 1 in 100

Estimated number of people who will develop genital warts in their lifetime³: 1 in 10

Genital Warts: An Important Healthcare Issue

Estimated number of new cases per year in the United States¹: 1 million

Estimated number of sexually active adults with clinically visible genital warts³: 1 in 100

Estimated number of people who will develop genital warts in their lifetime³: 1 in 10

Incidence of New Claims for Genital Warts in Young Adults

HPV 6 and 11 are responsible for >50% of anogenital warts.

Anogenital warts are common and highly contagious.

Peak prevalence: Women 20-24 years of age (6,171,000 persons/year)

Clinically apparent in ~1% of sexually active US adult population.⁴
**Anogenital Warts and HPV**

- While most HPV infections clear on their own, this year alone, it is estimated that 1 million people in the United States will develop genital warts.
- 99% of anogenital warts contain HPV 6 and HPV 11.
- Anogenital warts are common and highly contagious.
  - About two-thirds of sexual partners develop warts when exposed.
- Symptoms include:
  - Itching, burning, and tenderness at the wart site.
- Quite resolve without treatment, but for those that require treatment, warts recur in at least 25% of cases.

**ACIP Recommendations**

1. Routine immunization of girls 11-12 years old
2. Catch-up vaccination for un-/incompletely immunized females 13-26 years old
3. Second dose 2-months and third dose 6-months following first dose
4. Concomitant immunizations at same visit
5. No change in current cervical cancer screening recommendations
6. Can immunize women with: abnormal Pap smear; lactation; immunodeficiency

**Cervical Cancer Mortality in the US and Prevalence of High-Risk HPV**

- Age distribution of all cervical cancer deaths between 1935 and 2000 in the United States.

**ACIP Provisional Recommendations**

- Vaccination with either the bivalent HPV vaccine or the quadrivalent vaccine for prevention of cervical cancers and precancers
- Vaccination with the quadrivalent HPV vaccine for prevention of cervical cancers and precancers, and genital warts
- The quadrivalent vaccine has also been demonstrated to protect against vulvar and vaginal cancers and precancers
- The 3-dose series of quadrivalent HPV vaccine may be given to males aged 9 through 26 years to reduce their likelihood of acquiring genital warts
- Ideally, vaccine should be administered before potential exposure to HPV through sexual contact
**GARDASIL® (Quadrivalent Human Papillomavirus [HPV Types 6, 11, 16, 18] Recombinant Vaccine)**

**GARDASIL®: The First Cervical Cancer Vaccine in the United States**

- Quadrivalent human papillomavirus 6/11/16/18 L1 virus-like particle (VLP) vaccine
- VLPs are produced in Saccharomyces cerevisiae
  - The L1 proteins self-assemble into VLPs.
  - Purified VLPs are adsorbed on aluminium-containing adjuvant.
  - The adjuvant is amorphous aluminum hydroxyphosphate sulfate (225 µg per dose).
- Each 0.5-mL dose contains HPV Types 6/11/16/18 (20/40/40/20 µg L1 protein, respectively)

**GARDASIL® Maintained Type-Specific, Neutralizing Antibody Responses**

<table>
<thead>
<tr>
<th>Months Since Enrollment</th>
<th>Serum cRIA GMT, mMU/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>680</td>
</tr>
<tr>
<td>7</td>
<td>680</td>
</tr>
<tr>
<td>12</td>
<td>661</td>
</tr>
<tr>
<td>18</td>
<td>638</td>
</tr>
<tr>
<td>30</td>
<td>604</td>
</tr>
<tr>
<td>42</td>
<td>532</td>
</tr>
<tr>
<td>48</td>
<td>489</td>
</tr>
</tbody>
</table>

Number of Subjects

- 984
- 984
- 984
- 984
- 984
- 984
- 984

*Evaluated only the HPV 16 L1 VLP vaccine component of GARDASIL.

- GMT = Geometric mean titer; cRIA = Competitive radioimmunoassay.

**Populations Used to Evaluate GARDASIL®**

<table>
<thead>
<tr>
<th>Subject age: 16-26 years old</th>
<th>PPE Population</th>
<th>General Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sero (+) and/or PCR (+) to the relevant vaccine HPV type at day 1</td>
<td>Excluded</td>
<td>Included</td>
</tr>
<tr>
<td>PCR (+) to the relevant vaccine HPV type during the vaccination phase</td>
<td>Excluded</td>
<td>Included</td>
</tr>
<tr>
<td>Protocol violators</td>
<td>Excluded</td>
<td>Included</td>
</tr>
<tr>
<td>&lt;3 Doses</td>
<td>Excluded</td>
<td>Included</td>
</tr>
<tr>
<td>Case counting</td>
<td>1 month Postdose</td>
<td>3 month Postdose</td>
</tr>
</tbody>
</table>

**General Populations [MITT] Used to Evaluate GARDASIL®**

<table>
<thead>
<tr>
<th>MITT-2 [Naïve]</th>
<th>MITT-3 [All]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sero (+) and/or PCR (+) to the Relevant Vaccine HPV Type at Day 1</td>
<td>Included</td>
</tr>
<tr>
<td>Sero (+) and/or PCR (+) to the Relevant Vaccine HPV Type at Day 1</td>
<td>EXCLUDED</td>
</tr>
<tr>
<td>PCR (+) to the Relevant Vaccine HPV Type During the Vaccination Phase</td>
<td>Included</td>
</tr>
<tr>
<td>Day 1 (+) to non-vaccine HPV type</td>
<td>Included</td>
</tr>
<tr>
<td>Day 1 Pap ≥ASCUS</td>
<td>Included</td>
</tr>
<tr>
<td>Protocol Violators&gt;3 doses</td>
<td>Included</td>
</tr>
<tr>
<td>Case Counting</td>
<td>After Day 30</td>
</tr>
</tbody>
</table>

ASCUS = Atypical squamous cells of undetermined significance; those who had a normal Pap at baseline were considered part of a restricted cohort of MITT-3 called R-MITT-3.

1. Data on file, MSD.

**Abbreviations**
PPE = Per-protocol efficacy
### EFFICACY: HPV 16/18

<table>
<thead>
<tr>
<th>Clinical Condition</th>
<th>Protective Efficacy [PPE]</th>
<th>General Population Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate/Severe Cervical Intraepithelial Neoplasia (CIN 2/3) and Adenocarcinoma in situ (AIS)</td>
<td>98%</td>
<td>97% (naïve) 52% (all)</td>
</tr>
<tr>
<td>Moderate/Severe Vulvar and Vaginal Intraepithelial Neoplasia (VIN 2/3 and VaIN 2/3)</td>
<td>100%</td>
<td>97% (naïve) 76% (all)</td>
</tr>
</tbody>
</table>

### EFFICACY: HPV 6/11/16/18

<table>
<thead>
<tr>
<th>Clinical Condition</th>
<th>Protective Efficacy [PPE]</th>
<th>General Population Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild/Moderate/Severe Cervical Intraepithelial Neoplasia (CIN1/2/3) and Adenocarcinoma in situ (AIS)</td>
<td>96%</td>
<td>95% (naïve) 61% (all)</td>
</tr>
<tr>
<td>Genital Warts</td>
<td>99%</td>
<td>96% (naïve) 80% (all)</td>
</tr>
</tbody>
</table>

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### GARDASIL® Demonstrated Protection Through 5 Years in Phase 2 Extension Study

<table>
<thead>
<tr>
<th>HPV 6, 11, 16, or 18-Related</th>
<th>GARDASIL (N = 233)</th>
<th>Placebo (N = 229)</th>
<th>Efficacy (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent Infection</td>
<td>5%</td>
<td>45</td>
<td>96</td>
<td>(63.3–100)</td>
</tr>
<tr>
<td>Disease</td>
<td>0</td>
<td>6</td>
<td>100</td>
<td>(12–100)</td>
</tr>
<tr>
<td>Genital Warts</td>
<td>0</td>
<td>3</td>
<td>100</td>
<td>(&lt;6–100)</td>
</tr>
<tr>
<td>CIN 1, 2, or 3</td>
<td>0</td>
<td>3</td>
<td>100</td>
<td>(&lt;6–100)</td>
</tr>
</tbody>
</table>

A total of 241 subjects were entered into the 5-year extension phase of Merck’s phase 2 trial US15-007.

*One case of confirmed persistent infection: HPV 10 DNA detected at months 12 and 18 only, no cases in the 5-year extension phase. One case of HPV 18 DNA detected at the last visit (month 36). CI=confidence interval; CIN=cervical intraepithelial neoplasia; PPE=protected population efficacy.

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### Bridging the Efficacy of GARDASIL® From Young Adult Women to Adolescent Girls

**Adolescent Girls**
- 9 to 15 years of age
- N = 1,121

**Young Adult Women**
- 16 to 26 years of age
- N = 4,229

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*GMT = Geometric mean titer in mMU/mL (mMU = milli-Merck units).*
CERVARIX®
[HPV Bivalent (Types 16 and 18) Vaccine]

- Recombinant AS04-adjuvanted vaccine that contains recombinant L1 protein of oncogenic HPV types 16 and 18
- Administered as three doses (0.5-mL each) by intramuscular injection according to the following schedule: 0, 1, and 6 months
- Most common local adverse reactions in ≥20% of subjects were pain, redness, and swelling at the injection site.
- Most common general adverse events in ≥20% of subjects were fatigue, headache, myalgia, gastrointestinal symptoms, and arthralgia.

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**CERVARIX® IMMUNOGENICITY**

- **ELISA**
  - Ant-HPV 16: 9.269 (8.967, 9.542) N=318
  - Ant-HPV 18: 4.744 (4.454, 5.039) N=769

- **PRxNA**
  - Ant-HPV 16: 9.053 (8.551, 9.605) N=44

**EFFICACY: HPV 16/18**

<table>
<thead>
<tr>
<th>Clinical Condition</th>
<th>Protective Efficacy</th>
<th>General Population Impact</th>
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<td>93%</td>
<td>98% (naïve) 53% (all)</td>
</tr>
<tr>
<td>Mild/Moderate/Severe Cervical Intraepithelial Neoplasia (CIN 1/2/3) and Adenocarcinoma in situ (AIS)</td>
<td>92%</td>
<td>97% (naïve) 56% (all)</td>
</tr>
</tbody>
</table>

- Ant: antibody
- GMT: geometric mean titre
- PPE: post-vaccination enco
d- ELISA: enzyme-linked immunosorbent assay
- PRxNA: pseudo-reverse neutralization assay
Bridging the Efficacy of Cervarix® From Young Adult Women to Adolescent Girls

<table>
<thead>
<tr>
<th>Antibody</th>
<th>10-14 Years of Age</th>
<th>15-19 Years of Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CMV ELISA titer (95% CI)</td>
<td>Seropositivity Rate (%)</td>
</tr>
<tr>
<td>Anti-HPV-16</td>
<td>143</td>
<td>17.275 (5.817, 19.174)</td>
</tr>
<tr>
<td>Anti-HPV-18</td>
<td>143</td>
<td>6.040 (3.734, 8.329)</td>
</tr>
</tbody>
</table>

1. Subjects who received 3 doses of vaccine for whom assay results were available for at least one post-vaccination antibody measurement (N).
2. Non-inferiority based on the upper limit of the 2-sided 95% CI for the GEET ratio (10-14 year olds/10-14 year olds) was >2.
3. Non-inferiority based on the upper limit of the 2-sided 95% CI for the difference between the seropositivity rates for 10-14 year olds and 15-23 year olds was >10%.

Indications and Usage (cont): Limitations of Use and Effectiveness

**GARDELIX®** Human papillomavirus (HPV) vaccine, recombinant
- GARDELIX does not alleviate the necessity for women to continue to undergo recommended cervical cancer screening.
- GARDELIX has not been demonstrated to protect against disease from a full spectrum of HPV types for which it is licensed.
- GARDELIX is not indicated for use in the treatment of external anal or genital warts or other sexually transmitted infections.
- GARDELIX has not been demonstrated to protect against anal cancers due to HPV types not contained in the vaccine.
- Not all anal and genital cancers are caused by HPV, and GARDELIX protects only against those HPV types known to cause anal cancers.
- GARDELIX does not protect against genital warts not caused by HPV.
- Vaccination with GARDELIX may not result in protection in all vaccine responders.

**GARDASIL®** Human papillomavirus (HPV) vaccine, recombinant
- GARDASIL is contraindicated for use in patients with a history of anaphylaxis or other serious allergic reaction following a previous dose of the vaccine or to any component of the vaccine.
- GARDASIL is not indicated for use in the treatment of external anal or genital warts or other sexually transmitted infections.
- Not all anal and genital cancers are caused by HPV, and GARDASIL protects only against those HPV types known to cause anal cancers.
- GARDASIL does not protect against genital warts not caused by HPV.
- Vaccination with GARDASIL may not result in protection in all vaccine responders.

**CERVIX®** Human papillomavirus (HPV) vaccine, recombinant
- CERVIX does not provide protection against disease due to all HPV types.
- CERVIX has not been demonstrated to protect against disease from a full spectrum of HPV types for which it is licensed.
- CERVIX is not indicated for use in the treatment of external anal or genital warts or other sexually transmitted infections.
- Not all anal and genital cancers are caused by HPV, and CERVIX protects only against those HPV types known to cause anal cancers.
- CERVIX does not protect against genital warts not caused by HPV.
- Vaccination with CERVIX may not result in protection in all vaccine responders.

Dosage and Administration

**GARDASIL®**
- GARDASIL should be administered intramuscularly, as a 0.5 ml dose at each of the following schedules: 0, 2 months, 6 months.
- GARDASIL should be administered in the deltoid region of the upper arm or in the high interscapular area of the upper back.
- Intramuscularly, GARDASIL consists of 3 doses of 0.5 ml each, by intramuscular injection at the deltoid region of the upper arm.
- Do not administer the product intravenously, subcutaneously, or by direct injection into a vein.

**Dosage Forms and Strengths**
- 0.5 ml, suspension for intramuscular injection in a single-dose vial and prefilled syringe.

**CERVIX®**
- Intramuscularly, CERVIX consists of 3 doses of 0.5 ml each, by intramuscular injection at the deltoid region of the upper arm.
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Summary

- HPV infection is common in both the United States and worldwide
- HPV is easily transmitted and often asymptomatic
- Genital HPV is responsible for low-grade and high-grade cervical dysplastic lesions and anogenital warts
- Virtually all cases of cervical cancer are linked to high-risk genital HPV types