Human Papillomavirus (HPV): Understanding the Burden of Disease in Adults
Approximately 79 million people in the United States are currently infected with HPV.\textsuperscript{1, a}

~14 million people become newly infected with HPV each year in the US.\textsuperscript{1, 2, a}

~50% of these new infections occur in adults over the age of 25.\textsuperscript{1, 2}

For most people, HPV clears on its own. But, for others who don’t clear the virus, it could cause certain HPV-related cancers and diseases.\textsuperscript{1}

It cannot be reliably predicted which individuals with infection or precancerous lesions will progress to clinically significant disease.\textsuperscript{1, 3, 4}

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\textsuperscript{a}Estimates are for 2008 and reflect persons with detectable infection with any of 37 different HPV types, not just Types 6, 11, 16, 18, 31, 33, 45, 52, and 58.\textsuperscript{2}

HPV=human papillomavirus.

<table>
<thead>
<tr>
<th>Disease Type</th>
<th>Estimated Annual Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vulvar and vaginal cancers</td>
<td>~4,700 (^6–8,b)</td>
</tr>
<tr>
<td>Anal cancer</td>
<td>~6,800 (^1,4,b)</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>~11,800 (^1,5)</td>
</tr>
<tr>
<td>Genital warts</td>
<td>~320,000 (^9,10)</td>
</tr>
<tr>
<td>High-grade cervical precancers</td>
<td>~216,000 (^6–8,b)</td>
</tr>
<tr>
<td>Low-grade cervical lesions</td>
<td>~468,700 (^6–8,b)</td>
</tr>
</tbody>
</table>

**EACH DAY:**

- **WOMEN** are diagnosed with cervical cancer \(^1,5,a\)
- **MEN AND WOMEN** are diagnosed with anal cancer \(^1,4,a\)

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\(^a\)HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58. \(^b\)Estimated cases not limited to adults. \(^c\)Not all cervical precancers and lesions, and vulvar, vaginal, and anal cancer cases are caused by HPV. Approximately 90% of high-grade cervical precancers, 75% of low-grade cervical lesions, 30% of vulvar cancer cases, 70% to 75% of vaginal cancer cases, and 85% to 90% of anal cancer cases are HPV related.

HPV=human papillomavirus.

Over 35% of women and over 45% of men in the US aged 25–49 years had an infection with any of the 37 HPV types.

HPV DNA prevalence from self-collected cervicovaginal and penile swabs from 3,251 sexually experienced people.

Overall analysis conducted in sexually experienced participants aged 14–59 years who had adequate HPV DNA typing results. Weighted estimates using the examination sample weights account for unequal probability of selection and nonresponse.

Any HPV includes positivity to any of the 37 HPV types; high-risk HPV includes positivity to any of 14 types considered high risk.

HPV=human papillomavirus; NHANES=National Health and Nutrition Examination Survey.

GARDASIL® [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant] and GARDASIL ®9 (Human Papillomavirus 9-valent Vaccine, Recombinant)

**Indication**

- GARDASIL 9 is a vaccine indicated in females 9 through 45 years of age. GARDASIL is a vaccine indicated in females 9 through 26 years of age. GARDASIL 9 prevents cervical, vulvar, vaginal, and anal cancers caused by human papillomavirus (HPV) Types 16, 18, 31, 33, 45, 52, and 58; and precancerous or dysplastic lesions caused by HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58. GARDASIL prevents cervical, vulvar, vaginal, and anal cancers, and precancerous or dysplastic lesions caused by HPV Types 6, 11, 16, and 18. Both prevent genital warts caused by HPV Types 6 and 11.

- GARDASIL 9 is indicated in males 9 through 45 years of age. GARDASIL is indicated in males 9 through 26 years of age. GARDASIL 9 prevents anal cancer caused by HPV Types 16, 18, 31, 33, 45, 52, and 58; and precancerous or dysplastic lesions caused by HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58. GARDASIL prevents anal cancer caused by HPV Types 16 and 18, and precancerous or dysplastic lesions caused by HPV Types 6, 11, 16, and 18. Both prevent genital warts caused by HPV Types 6 and 11.
Select Safety Information

• GARDASIL 9 and GARDASIL are contraindicated in individuals with hypersensitivity, including severe allergic reactions to yeast, or after a previous dose of GARDASIL 9 or GARDASIL.

• Because vaccinees may develop syncope, sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended. Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following HPV vaccination. When syncope is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion.
A study simulated the natural history of cervical cancer in women in the absence of screening or HPV vaccination.¹

- Projections were generated by an individual-based cervical cancer natural history model that integrated empirical data from the largest prospective and clinical studies of HPV-induced cervical carcinogenesis into a single analytic framework.

- The model simulated a cohort of women without screening or HPV vaccine use to project the cumulative number of causal infections by age and HPV type (HPV Type 16 vs non-HPV 16) in this cohort of women.

The study estimated that approximately half of all HPV-related cervical cancers are caused by HPV infections acquired in adulthood.¹

~50% are caused by HPV infections acquired after the age of 20 years

~25% are caused by HPV infections acquired after the age of 30 years

HPV=human papillomavirus.
Select Safety Information (continued)

- Safety and effectiveness of GARDASIL 9 and GARDASIL have not been established in pregnant women.

- For GARDASIL 9, the most common (≥10%) local and systemic adverse reactions in females were: injection-site pain, swelling, erythema, and headache. The most common (≥10%) local and systemic reactions in males were injection-site pain, swelling, and erythema. For GARDASIL, the most common (≥1.0%) adverse reactions were headache, fever, nausea, dizziness; and injection-site pain, swelling, erythema, pruritus, and bruising.

- The duration of immunity of GARDASIL 9 or GARDASIL has not been established.
Risk for CIN After Persistent Infection With Same HPV Type Similar for Young and Adult Women

Post hoc Analysis from the placebo arm of 2vHPV vaccine trials\(^1,a\)

 Analyzed the risk for progression from detection of an HPV infection to detection of a CIN lesion associated with the same HPV type or natural clearance of infection.

15–25 years (solid line), \(N=3,363\); >25 years (dotted line, arrow), \(N=708\)

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**CIN1+**

Log-rank p-value = 0.0632

9.1% of adult women aged over 25 years with 6MPI (\(N=528\)) progressed to CIN1+ within 48 months (\(n=48\))

**CIN2+**

Log-rank p-value = 0.1880

4.2% of adult women aged over 25 years with 6MPI (\(N=528\)) progressed to CIN2+ within 48 months (\(n=22\))

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\(^a\)Analysis in women >25 years of age tested for HPV Types 16, 18, 31, 33, 45 and other oncogenic and non-oncogenic types.\(^1\) Analysis in women 15–25 years of age tested for HPV Types 16, 18, 31, 35 and other oncogenic and non-oncogenic types.\(^2\)

2vHPV=2-valent HPV vaccine; 6MPI=6-month persistent infection; CIN=cervical intraepithelial neoplasia; HPV=human papillomavirus.

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Females 9–45 years of age</th>
<th>Males 9–45 years of age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancers caused by HPV Types 16, 18, 31, 33, 45, 52, and 58</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>Precancerous or dysplastic lesions caused by HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58</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>Genital warts caused by HPV Types 6 and 11</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

AIN=anal intraepithelial neoplasia; AIS=cervical adenocarcinoma in situ; CIN=cervical intraepithelial neoplasia; HPV=human papillomavirus; VaIN=vaginal intraepithelial neoplasia; VIN=vulvar intraepithelial neoplasia.
GARDASIL® [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant] and GARDASIL®9 (Human Papillomavirus 9-valent Vaccine, Recombinant)

**Limitations of Use**

- GARDASIL 9 and GARDASIL do not eliminate the necessity for women to continue to undergo recommended cervical cancer screening.

- Recipients of GARDASIL 9 or GARDASIL should not discontinue anal cancer screening if it has been recommended by a health care professional.

- GARDASIL 9 and GARDASIL have not been demonstrated to provide protection against diseases from vaccine HPV types to which a person has previously been exposed through sexual activity.
Limitations of Use (continued)

• GARDASIL 9 and GARDASIL are not a treatment for external genital lesions; cervical, vulvar, vaginal, and anal cancers; or cervical intraepithelial neoplasia (CIN), vulvar intraepithelial neoplasia (VIN), vaginal intraepithelial neoplasia (VaIN), or anal intraepithelial neoplasia (AIN).

• Not all vulvar, vaginal, and anal cancers are caused by HPV, and GARDASIL 9 and GARDASIL protect only against those vulvar, vaginal, and anal cancers caused by HPV types contained in the vaccines.

• Vaccination with GARDASIL 9 or GARDASIL may not result in protection in all vaccine recipients.
10-Year HPV Vaccine Study in Women Aged 27–45 Years: Study Design of Base and Extension Phases\textsuperscript{1,2a}

The overall study was conducted in women aged 24–45 years at enrollment (N=3,819),\textsuperscript{2} but the analyses presented forthwith are in women aged 27–45 years at enrollment (N=3,253).\textsuperscript{1 b} Participants were randomized 1:1 to received either GARDASIL® [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant] or AAHS control. The per-protocol efficacy population received all 3 vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, were naive (PCR negative and seronegative) to the relevant HPV Types(s) (Types 6, 11, 16, 18) prior to dose 1 and remained PCR negative to the relevant HPV types(s) through 1 month post-dose 3 (Month 7). Median follow-up of 3.5 years post-dose 3.

HPV=human papillomavirus; Mo=month; PCR=polymerase chain reaction.

\textsuperscript{a}The overall study was conducted in women aged 24–45 years at enrollment (N=3,819),\textsuperscript{2} but the analyses presented forthwith are in women aged 27–45 years at enrollment (N=3,253).\textsuperscript{1 b}Participants were randomized 1:1 to received either GARDASIL® [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant] or AAHS control. The per-protocol efficacy population received all 3 vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, were naive (PCR negative and seronegative) to the relevant HPV Types(s) (Types 6, 11, 16, 18) prior to dose 1 and remained PCR negative to the relevant HPV types(s) through 1 month post-dose 3 (Month 7). Median follow-up of 3.5 years post-dose 3.

HPV=human papillomavirus; Mo=month; PCR=polymerase chain reaction.

## BASE STUDY

### Combined incidence of HPV 6-, 11-, 16-, and 18-related

<table>
<thead>
<tr>
<th>Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent infection, genital warts, VIN, VaIN, vulvar cancer, vaginal cancer, cervical dysplasia (any grade CIN), AIS, and cervical cancer *The efficacy estimate for the combined end point was driven primarily by prevention of persistent infections.</td>
</tr>
<tr>
<td>Cervical dysplasia or genital warts</td>
</tr>
</tbody>
</table>

While no statistically significant efficacy was demonstrated for GARDASIL® [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant] in the base study for the prevention of CIN 2/3, AIS, or cervical cancer related to HPV Types 16 and 18, there was 1 case of CIN2/3 observed in the group receiving GARDASIL and 5 cases in the placebo group. The CIN 2 case in the group receiving GARDASIL tested positive by PCR for HPV 16 and HPV 51.

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*a* The overall study was conducted in women aged 24–45 years at enrollment (N=3,819), but the analyses presented here are in women aged 27–45 years at enrollment (N=3,253).

*b* Median follow-up post-dose 3 was 3.5 years.

AIS=adenocarcinoma *in situ*; CI=confidence interval; CIN=cervical intraepithelial neoplasia; HPV=human papillomavirus; PCR=polymerase chain reaction; PPE=per protocol efficacy; VaIN=vaginal intraepithelial neoplasia; VIN=vulvar intraepithelial neoplasia.

Sustained Efficacy and Long-term Effectiveness Against HPV-related Cancers and Diseases in Women Aged 27–45 Years

**No cases** of HPV 6-, 11-, 16-, or 18-related CIN (any grade) or genital warts were observed during the long-term extension in the PPE population.1

In an analysis of 10 high-risk HPV types not covered by the HPV vaccine, cumulative incidence of CIN or condyloma related to nonvaccine HPV Types1:

- 3 cases from Year 4 to Year 8.
- 4 cases from Year 6 to Year 10.

Sustained immunogenicity for vaccine-HPV Types 6, 11, 16, and 18 through 10 years postvaccination onset.1,2

Efficacy, effectiveness, and safety of GARDASIL are relevant to GARDASIL 9 because the vaccines are manufactured similarly and contain 4 of the same HPV L1 virus-like particles (HPV Types 6, 11, 16, and 18). The FDA approval for people ages 27 to 45 is supported by data from clinical trials for GARDASIL and through bridging results across age and gender in clinical trials that demonstrated consistent safety, efficacy, and immunogenicity between GARDASIL and GARDASIL 9.

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**STUDY EXTENSION, Colombian Cohort (N=600)1,2,b**


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1. Median follow-up post-dose 3 was 8.9 years.

CIN=cervical intraepithelial neoplasia; GMT=geometric mean titers; HPV=human papillomavirus; PPE=per protocol efficacy.
Effectiveness and Immunogenicity in Men Aged 27–45 Years

- Effectiveness of GARDASIL® [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant] in men 27 through 45 years of age is inferred from efficacy data in women 27 through 45 years of age and supported by immunogenicity data from a clinical trial in which 150 men 27 through 45 years of age received a 3-dose regimen of GARDASIL (0, 2, 6 months).

- A cross-study analysis of PPI populations compared Month 7:
  - **Study A**: Men aged 27–45 years from the immunogenicity study (n=150).
  - **Study B**: Males aged 16–26 years in whom efficacy of GARDASIL has been established.

### GMT Ratio (Study A/Study B)

<table>
<thead>
<tr>
<th>HPV Type</th>
<th>95% CI</th>
<th>95% CI</th>
<th>95% CI</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 6</td>
<td>0.82 (0.65, 1.03)</td>
<td>0.79 (0.66, 0.93)</td>
<td>0.91 (0.72, 1.13)</td>
<td>0.74 (0.59, 0.92)</td>
</tr>
<tr>
<td>Type 11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 16</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 18</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GMT=geometric mean titer; HPV=human papillomavirus; PPI=per-protocol immunogenicity.
GARDASIL 9 should be administered intramuscularly in the deltoid region of the upper arm or in the higher anterolateral area of the thigh.

2-dose and 3-dose regimens use the same formulation of GARDASIL 9.

Studies using a mixed regimen of HPV vaccines to assess interchangeability were not performed for GARDASIL 9.

### Dosage and Administration for GARDASIL®9 (Human Papillomavirus 9-valent Vaccine, Recombinant)

<table>
<thead>
<tr>
<th>Age</th>
<th>Regimen</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 through 14 years</td>
<td>2-dose</td>
<td>0, 6 to 12 months&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>9 through 14 years</td>
<td>3-dose</td>
<td>0, 2, 6 months</td>
</tr>
<tr>
<td>15 through 45 years</td>
<td>3-dose</td>
<td>0, 2, 6 months</td>
</tr>
</tbody>
</table>

<sup>a</sup> If the second dose is administered earlier than 5 months after the first dose, administer a third dose at least 4 months after the second dose.

- GARDASIL 9 should be administered intramuscularly in the deltoid region of the upper arm or in the higher anterolateral area of the thigh.
- 2-dose and 3-dose regimens use the same formulation of GARDASIL 9.
- Studies using a mixed regimen of HPV vaccines to assess interchangeability were not performed for GARDASIL 9.
Dosage and Administration

• Administer either GARDASIL 9 or GARDASIL intramuscularly in the deltoid region of the upper arm or in the higher anterolateral area of the thigh.

• For GARDASIL 9, a complete vaccination regimen consists of:
  – For individuals 9 through 14 years of age, GARDASIL 9 can be administered using a 2-dose or 3-dose schedule. For the 2-dose schedule, the second dose should be administered 6–12 months after the first dose. If the second dose is administered less than 5 months after the first dose, a third dose should be given at least 4 months after the second dose. For the 3-dose schedule, GARDASIL 9 should be administered at 0, 2 months, and 6 months.
  – For individuals 15 through 45 years of age, GARDASIL 9 is administered using a 3-dose schedule at 0, 2 months, and 6 months.

• For GARDASIL, a complete vaccination regimen for individuals 9 through 26 years of age consists of 3 doses at the following schedule: 0, 2 months, 6 months.
Safety Profile for GARDASIL®9 (Human Papillomavirus 9-valent Vaccine, Recombinant)

Solicited and Unsolicited Injection-site and Systemic Adverse Reactions Post any Dose in Persons 9 through 26 Years of Age at a Frequency of ≥10%

<table>
<thead>
<tr>
<th>Population (n)</th>
<th>Injection-site, % (1 to 5 days post-vaccination)</th>
<th>Systemic, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pain</td>
<td>Swelling</td>
</tr>
<tr>
<td>Females aged 9–15 y (n=299)</td>
<td>89.3</td>
<td>47.8</td>
</tr>
<tr>
<td>Females aged 16–26 y (n=7,071)</td>
<td>89.9</td>
<td>40.0</td>
</tr>
<tr>
<td>Males aged 9–15 y (n=639)</td>
<td>71.5</td>
<td>26.9</td>
</tr>
<tr>
<td>Males aged 16–26 y (n=1,394)</td>
<td>63.4</td>
<td>20.2</td>
</tr>
</tbody>
</table>

- Safety of GARDASIL 9 in individuals 27 through 45 years of age is inferred from the safety data of GARDASIL in individuals 9 through 45 years of age and GARDASIL 9 in individuals 9 through 26 years of age.

**Study Design:** Safety of GARDASIL 9 was evaluated in 7 clinical studies that included 15,703 individuals who received at least 1 dose of GARDASIL 9 and 7,378 individuals who received at least 1 dose of GARDASIL® [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant] as a control; both groups had safety follow-up. The vaccines were administered on the day of enrollment and the subsequent doses administered approximately 2 and 6 months thereafter. Safety was evaluated using vaccination report card (VRC)-aided surveillance for 14 days after each injection of GARDASIL 9 or GARDASIL. Injection-site reactions (pain, swelling, and erythema) and oral temperature were solicited using VRC-aided surveillance for 5 days after each injection of GARDASIL 9 during the clinical studies.

**For subjects reporting temperature data:** females 16 through 26 years of age N=7,022; boys 9 through 15 years of age N=637; boys and men 16 through 26 years of age N=1,386; y=years.
Strategies for Improving Vaccine Uptake

1. **Provide counseling**
   - Discuss any concerns about the efficacy and safety of the vaccine.
   - Individualize counseling approaches to the patient.
   - Provide independent information, such as CDC Vaccine Information Statements.

2. **Maximize opportunities for vaccinations**
   - Use any patient encounter as an opportunity to discuss vaccinations.
   - Implement patient notifications via patient reminder letters and texts.

3. **Improve vaccine accessibility**
   - Services such as walk-in clinics and alternative venues for vaccinations have been shown to provide high quality of care, reach new patients, and contain costs.

4. **Maintaining electronic medical records (EMR)**
   - EMR systems can be used to prompt providers to determine their patients’ vaccination needs and recommend appropriate vaccinations.

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HPV is prevalent in adult men and women in the United States; ~50% of new infections occur in adults aged 25–59 years.\textsuperscript{1,2}

The risk for progression to cancer/precancerous lesions is similar between females aged 15–25 years and over 25 years.\textsuperscript{3}

In women without screening or HPV vaccination, ~50% of all HPV-related cervical cancers were estimated to be caused by HPV infections acquired after 20 years of age, and ~25% caused by HPV infections acquired after age of 30 years.\textsuperscript{4}

Data from clinical trials demonstrate the long-term effectiveness of the HPV vaccine in adults aged 27–45 years.\textsuperscript{5}

Implement strategies for improving vaccine uptake, including providing education, maximizing opportunities for vaccination, and improving access through venues such as walk-in clinics and retail pharmacies.\textsuperscript{6}
Before administering
GARDASIL®9 (Human Papillomavirus 9-valent Vaccine, Recombinant) please read the Prescribing Information.
The Patient Information also is available.