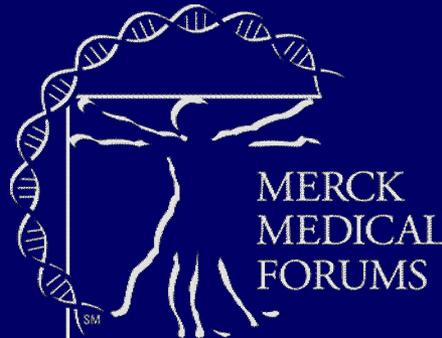


# Latest Developments in HPV-related Diseases and Cervical Cancer

**GARDASIL®**

**[Quadrivalent Human Papillomavirus (HPV Types 6, 11, 16, 18) Recombinant Vaccine]**



Advancing Medical Education  
and Practice

# Impact of Cervical Cancer

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- United States:
  - Annual incidence: ~10,000
  - ~10 women die each day of cervical cancer
- Worldwide:
  - Annual incidence: ~500,000
  - Second most common cause of cancer death in women
  - ~240,000 deaths each year

# GARDASIL: The First Cervical Cancer Vaccine in the United States

- Quadrivalent human papillomavirus (HPV) 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 aluminum-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).

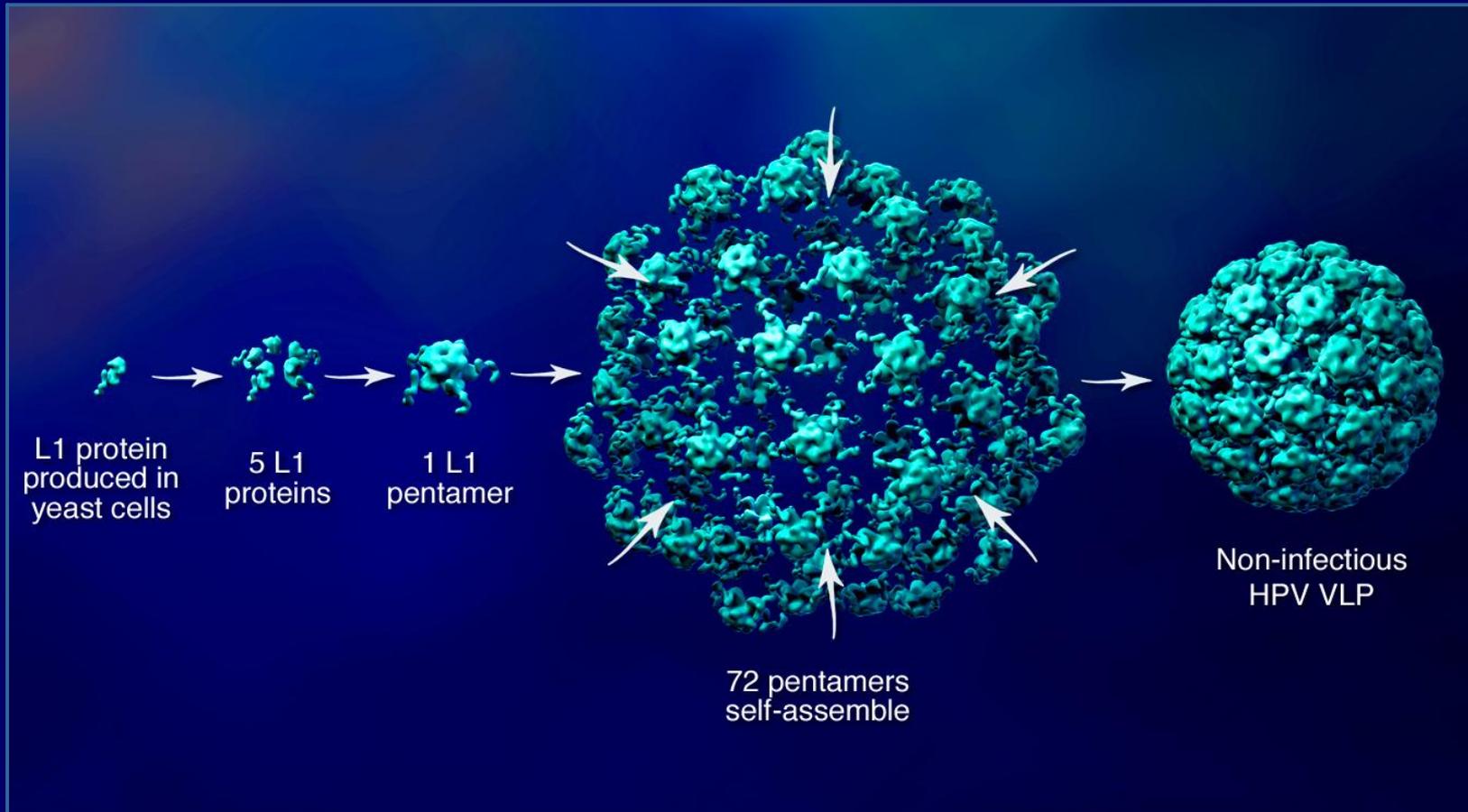


# Disease Burden From HPV Types 6, 11, 16, and 18

HPV Type	Approximate Disease Burden
16 and 18	<ul style="list-style-type: none"><li>• 70% of cervical cancer, AIS, CIN 3, VIN 2/3, and VaIN 2/3 cases</li><li>• 50% of CIN 2 cases</li></ul>
6, 11, 16, and 18	<ul style="list-style-type: none"><li>• 35%–50% of all CIN 1, VIN 1, and VaIN 1 cases</li><li>• 90% of genital warts cases</li></ul>

AIS = adenocarcinoma *in situ*; CIN = cervical intraepithelial neoplasia; VIN = vulvar intraepithelial neoplasia; VaIN = vaginal intraepithelial neoplasia.

## Assembly of VLPs<sup>1-3</sup>



1. Berzofsky JA et al. *J Clin Invest.* 2004;114:450–462.
2. Kirnbauer R et al. *Proc Natl Acad Sci USA.* 1992;89:12180–12184.
3. Modis Y et al. *EMBO J.* 2002;21:4754–4762.

# Humoral Immune Response Is Protective Against HPV Infection

- HPV only infects humans, but animal studies with analogous (animal, not human) papillomaviruses suggest that

— The efficacy of L1 VLP vaccines is mediated by the development of humoral immune responses.

# Clinical Efficacy Studies for GARDASIL: Study Characteristics

Study Design	Protocol 005*	Protocol 007	FUTURE I	FUTURE II
N	2,391	551	5,442	12,157
Age (years)	16 to 26			
Median duration of follow-up (years)	4.0	3.0	2.4	2.0
Vaccination schedule	Subjects received GARDASIL or placebo on the day of enrollment, and 2 and 6 months thereafter.			

FUTURE = Females United To Unilaterally Reduce Endo/Ectocervical Disease.

\*Protocol 005 evaluated only the HPV 16 component of GARDASIL.

# Clinical Program for GARDASIL: Selection of Trial End Points<sup>1</sup>

Necessary Criteria	End Points		
	HPV Infection	CIN 1	CIN 2/3
Immediate precursor for cervical cancer	√	—	√
Prompts secondary prevention measures	—	—	√
Detection and removal have been shown to prevent cancer	—	—	√

# Populations Used to Evaluate GARDASIL

	<b>PPE Population</b>	<b>General Population Impact</b>
Sero (+) and/or PCR (+) to the relevant vaccine HPV type at day 1	<b>Excluded</b>	<b>Included</b>
PCR (+) to the relevant vaccine HPV type during the vaccination phase	<b>Excluded</b>	<b>Included</b>
Protocol violators	<b>Excluded</b>	<b>Included</b>
<3 Doses	<b>Excluded</b>	<b>Included</b>
Case counting	<b>1 month Postdose 3</b>	<b>1 month Postdose 1</b>

## Clinical Studies for GARDASIL: Analysis in Per-Protocol Efficacy (PPE) Population

- Primary analysis of efficacy conducted in PPE population:
  - Received all 3 vaccinations within 1 year of enrollment
  - Did not have major deviations from the study protocol
  - Were naïve to the relevant HPV type(s) prior to Dose 1 and through 1 month Postdose 3 (Month 7)
- Efficacy measurements started after Month 7 visit.

## **Prophylactic Efficacy: GARDASIL Was 100% Efficacious Against HPV 16- and 18-related CIN 2/3 or AIS**

<b>Population</b>	<b>n</b>	<b>GARDASIL Cases</b>	<b>n</b>	<b>Placebo Cases</b>	<b>Efficacy</b>	<b>95% CI</b>
Protocol 005*	755	0	750	12	<b>100%</b>	65.1–100
Protocol 007	231	0	230	1	<b>100%</b>	-3734.9–100
FUTURE I	2,200	0	2,222	19	<b>100%</b>	78.5–100
FUTURE II	5,301	0	5,258	21	<b>100%†</b>	80.9–100
<b>Combined protocols</b>	<b>8,487</b>	<b>0</b>	<b>8,460</b>	<b>53</b>	<b>100%†</b>	<b>92.9–100</b>

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

†P-values were computed for the prespecified primary hypothesis tests. All p-values were <0.001, supporting the following conclusions: efficacy against HPV 16/18-related CIN 2/3 is >0% (FUTURE II); and efficacy against HPV 16/18-related CIN 2/3 is >25% (combined protocols).

## **Prophylactic Efficacy: GARDASIL Was Efficacious Against HPV 6-, 11-, 16-, and 18-related CIN (CIN 1, CIN 2/3) or AIS**

<b>Population</b>	<b>n</b>	<b>GARDASIL Cases</b>	<b>n</b>	<b>Placebo Cases</b>	<b>Efficacy</b>	<b>95% CI</b>
Protocol 007	235	0	233	3	<b>100%</b>	-137.8–100
FUTURE I	2,240	0	2,258	37	<b>100%*</b>	89.5–100
FUTURE II	5,383	4	5,370	43	<b>90.7%</b>	74.4–97.6
<b>Combined protocols</b>	<b>7,858</b>	<b>4</b>	<b>7,861</b>	<b>83</b>	<b>95.2%</b>	<b>87.2–98.7</b>

\*P-values were computed for the prespecified primary hypothesis tests. All p-values were <0.001, supporting the following conclusions: efficacy against HPV 6/11/16/18-related CIN is >20% (FUTURE I).

## Prophylactic Efficacy: GARDASIL Was Efficacious Against HPV 6-, 11-, 16-, and 18-related Genital Warts

Population	n	GARDASIL Cases	n	Placebo Cases	Efficacy	95% CI
Protocol 007	235	0	233	3	100%	-139.5–100
FUTURE I	2,261	0	2,279	29	100%	86.4–100
FUTURE II	5,401	1	5,387	59	98.3%	90.2–100
<b>Combined protocols</b>	<b>7,897</b>	<b>1</b>	<b>7,899</b>	<b>91</b>	<b>98.9%</b>	<b>93.7–100</b>

- The efficacy of GARDASIL against HPV 6-, 11-, 16-, and 18-related VIN 1 or VaIN 1 was 100%.

# Populations Used to Evaluate GARDASIL

	<b>PPE Population</b>	<b>General Population Impact</b>
Sero (+) and/or PCR (+) to the relevant vaccine HPV type at day 1	<b>Excluded</b>	<b>Included</b>
PCR (+) to the relevant vaccine HPV type during the vaccination phase	<b>Excluded</b>	<b>Included</b>
Protocol violators	<b>Excluded</b>	<b>Included</b>
<3 Doses	<b>Excluded</b>	<b>Included</b>
Case counting	<b>1 month Postdose 3</b>	<b>1 month Postdose 1</b>

# Impact of GARDASIL in the General Population

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- GARDASIL is a prophylactic vaccine.
- There was no clear evidence of protection from disease caused by HPV types for which subjects were PCR positive and/or seropositive at baseline.
- Individuals who were already infected with 1 or more vaccine-related HPV types prior to vaccination were protected from clinical disease caused by the remaining vaccine HPV types.

# General Population Impact: GARDASIL Reduced HPV 16- and 18-related CIN 2/3 or AIS

HPV 16- or 18-Related CIN 2/3 or AIS	N	GARDASIL or HPV 16 L1 VLP Cases	N	Placebo Cases	% Reduction	95% CI
Prophylactic Efficacy*	9,342	1	9,400	81	98.8%	93–100
HPV 16 and/or HPV 18 Positive at Day 1	--	121	--	120	--	--
General Population Impact†	9,831	122	9,896	201	39.0%	23–52

\*Includes all subjects who received at least 1 vaccination and who were naïve [PCR (-) and sero (-)] to HPV 6, 11, 16, and/or 18 at Day 1. Case counting started at 1 month Postdose 1.

†Includes all subjects who received at least 1 vaccination (regardless of baseline HPV status at Day 1). Case counting started at 1 month Postdose 1.

**Note: Table does not include disease due to nonvaccine HPV types.**

## General Population Impact: GARDASIL Reduced HPV 16- and 18-related VIN 2/3 or VaIN 2/3

HPV 16- or 18-Related VIN 2/3 and VaIN 2/3	N	GARDASIL or HPV 16 L1 VLP Cases	N	Placebo Cases	% Reduction	95% CI
Prophylactic Efficacy*	8,641	0	8,667	24	100%	83–100
HPV 16 and/or HPV 18 Positive at Day 1	--	8	--	2	--	--
General Population Impact†	8,954	8	8,962	26	69.1%	30–88

\*Includes all subjects who received at least 1 vaccination and who were naïve [PCR (-) and sero (-)] to HPV 6, 11, 16, and/or 18 at Day 1. Case counting started at 1 month Postdose 1.

†Includes all subjects who received at least 1 vaccination (regardless of baseline HPV status at Day 1). Case counting started at 1 month Postdose 1.

Note: Table does not include disease due to nonvaccine HPV types.

## General Population Impact: GARDASIL Reduced HPV 6-, 11-, 16- and 18-related CIN (CIN 1, CIN 2/3) or AIS

HPV 6-, 11-, 16-, 18-Related CIN (CIN 1, CIN 2/3) or AIS	N	GARDASIL or HPV 16 L1 VLP Cases	N	Placebo Cases	% Reduction	95% CI
Prophylactic Efficacy*	8,625	9	8,673	143	<b>93.7%</b>	88–97
HPV 6, 11, 16 and/or HPV 18 Positive at Day 1	--	161 <sup>†</sup>	--	174 <sup>†</sup>	--	--
General Population Impact <sup>‡</sup>	8,814	170	8,846	317	<b>46.4%</b>	35–56

\*Includes all subjects who received at least 1 vaccination and who were naïve [PCR (-) and sero (-)] to HPV 6, 11, 16, and/or 18 at Day 1. Case counting started at 1 month Postdose 1.

<sup>†</sup>Includes 2 subjects (1 in each vaccination group) who underwent colposcopy for reasons other than an abnormal Pap and 1 placebo subject with missing serology/PCR data at Day 1.

<sup>‡</sup>Includes all subjects who received at least 1 vaccination (regardless of baseline HPV status at Day 1). Case counting started at 1 month Postdose 1.

**Note: Table does not include disease due to nonvaccine HPV types.**

# General Population Impact: GARDASIL Reduced HPV 6-, 11-, 16- and 18-related Genital Warts

HPV 6-, 11-, 16-,18-Related Genital Warts	N	GARDASIL or HPV 16 L1 VLP Cases	N	Placebo Cases	% Reduction	95% CI
Prophylactic Efficacy*	8,760	9	8,786	136	<b>93.4%</b>	87–97
HPV 6, 11, 16 and/or HPV 18 Positive at Day 1	--	49	--	48†	--	--
General Population Impact‡	8,954	58	8,962	184	<b>68.5%</b>	57–77

\*Includes all subjects who received at least 1 vaccination and who were naïve [PCR (-) and sero (-)] to HPV 6, 11, 16, and/or 18 at Day 1. Case counting started at 1 month Postdose 1.

†Includes 1 subject with missing serology/PCR data at Day 1.

‡Includes all subjects who received at least 1 vaccination (regardless of baseline HPV status at Day 1). Case counting started at 1 month Postdose 1.

**Note: Table does not include disease due to nonvaccine HPV types.**

# Immunogenicity

- Because there were few disease cases in subjects naïve (PCR negative and seronegative) to vaccine HPV types at baseline in the group that received GARDASIL, it has not been possible to establish minimum anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 antibody levels that protect against clinical disease caused by HPV 6, 11, 16, and/or 18.
- Type-specific competitive immunoassays with type-specific standards were used to assess immunogenicity to each vaccine HPV type. These assays measured antibodies against neutralizing epitopes for each HPV type. The scales for these assays are unique to each HPV type; thus, comparisons across types and to other assays are not appropriate.

# Immune Response to GARDASIL

- Assessed in:
  - Women 18 to 26 years of age (GARDASIL N=4,666; placebo N=4,249)
  - Female adolescents 9 to 17 years of age (GARDASIL N=1,471; placebo N=583)
- Individuals who were seronegative and PCR negative to the HPV Types 6, 11, 16, and 18 at enrollment remained HPV PCR negative to the relevant HPV type(s) through 1 month Postdose 3 (Month 7), received all 3 vaccinations, and did not deviate from the study protocol in ways that could interfere with the effects of the vaccine.
- At least 99.5% of girls and women across all age groups tested, who received GARDASIL became anti-HPV 6-, 11-, 16-, and 18-seropositive by 1 month Postdose 3.

# Immune Response to GARDASIL: PPI Population

Study Time	GARDASIL (N* = 276)		Aluminum-Containing Placebo (N = 275)	
	n**	GMT (95% CI) mMU/mL†	n	GMT (95% CI) mMU/mL
<b>Anti-HPV 6</b>				
Month 07	208	582.2 (527.2, 642.8)	198	4.6 (4.3, 4.8)
Month 24	192	93.7 (82.2, 106.9)	188	4.6 (4.3, 5.0)
Month 36	183	93.8 (81.0, 108.6)	184	5.1 (4.7, 5.6)
<b>Anti-HPV 11</b>				
Month 07	208	696.5 (617.8, 785.2)	198	4.1 (4.0, 4.2)
Month 24	190	97.1 (84.2, 112.0)	188	4.2 (4.0, 4.3)
Month 36	174	91.7 (78.3, 107.3)	180	4.4 (4.1, 4.7)
<b>Anti-HPV 16</b>				
Month 07	193	3889.0 (3318.7, 4557.4)	185	6.5 (6.2, 6.9)
Month 24	174	393.0 (335.7, 460.1)	175	6.8 (6.3, 7.4)
Month 36	176	507.3 (434.6, 592.0)	170	7.7 (6.8, 8.8)
<b>Anti-HPV 18</b>				
Month 07	219	801.2 (693.8, 925.4)	209	4.6 (4.3, 5.0)
Month 24	204	59.9 (49.7, 72.2)	199	4.6 (4.3, 5.0)
Month 36	196	59.7 (48.5, 73.5)	193	4.8 (4.4, 5.2)

\*Number of subjects randomized to the respective vaccination group who received at least 1 injection.

\*\*Number of subjects in the per-protocol analysis with data at the specified study time point.

†mMU = milli-Merck units.

Note: These data are from Protocol 007.

# Dosing Regimen Data

Dosing Regimen	Anti HPV 6		Anti- HPV 11		Anti-HPV 16		Anti-HPV 18	
	N	GMT (95% CI)	N	GMT (95% CI)	N	GMT (95% CI)	N	GMT (95% CI)
<b>Dose 2*</b>								
Early	883	570.9 (542.2, 601.2)	888	824.6 (776.7, 875.5)	854	2625.3 (2415.1, 2853.9)	926	517.7 (482.9, 555.0)
On Time	1767	552.3 (532.3, 573.1)	1785	739.7 (709.3, 771.5)	1737	2400.0 (2263.9, 2544.3)	1894	473.9 (451.8, 497.1)
Late	313	447.4 (405.3, 493.8)	312	613.9 (550.8, 684.2)	285	1889.7 (1624.4, 2198.5)	334	388.5 (348.3, 433.3)
<b>Dose 3**</b>								
Early	495	493.1 (460.8, 527.8)	501	658.9 (609.5, 712.2)	487	2176.6 (1953.4, 2425.3)	521	423.4 (388.8, 461.2)
On Time	2081	549.6 (531.1, 568.8)	2093	752.8 (723.8, 782.9)	2015	2415.0 (2286.3, 2550.9)	2214	486.0 (464.7, 508.2)
Late	335	589.0 (537.0, 645.9)	339	865.3 (782.6, 956.7)	326	2765.9 (2408.7, 3176.2)	361	498.5 (446.2, 557.0)

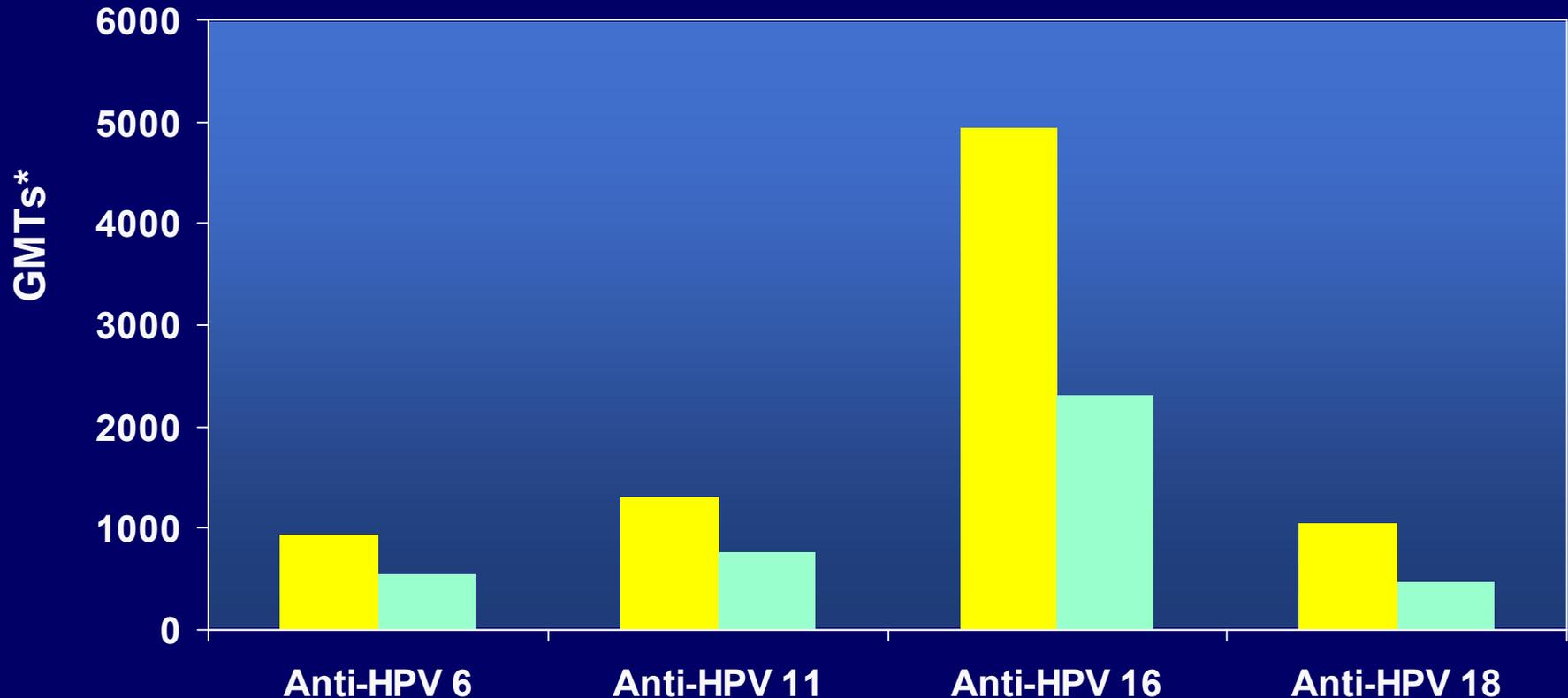
\*Dose 2 (Postdose 1): Early = 36–50 days Postdose 1; On-Time = 51–70 days Postdose 1; Late = 71–84 days Postdose 1.

\*\*Dose 3 (Postdose 2): Early = 80–105 days Postdose 2; On-Time = 106–137 days Postdose 2; Late = 138–160 days Postdose 2.

# 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



\*GMT = geometric mean titer in mMU/mL (mMU = milli-Merck units).

# Indications and Usage for GARDASIL

- GARDASIL is a vaccine indicated in girls and women 9 to 26 years of age for the prevention of the following diseases caused by HPV Types 6, 11, 16, and 18:
  - Cervical cancer
  - Genital warts (condyloma acuminata)and the following precancerous or dysplastic lesions:
  - Cervical AIS
  - CIN grades 2 and 3
  - VIN grades 2 and 3
  - VaIN grades 2 and 3
  - CIN grade 1

## Contraindications for GARDASIL

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- Hypersensitivity to the active substances or to any of the excipients of the vaccine
- Individuals who develop symptoms indicative of hypersensitivity after receiving a dose of GARDASIL should not receive further doses.

## Precautions: General

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- As for any vaccine, vaccination with GARDASIL may not result in protection in all vaccine recipients.
- Not intended to be used for treatment of active genital warts; cervical cancer; CIN, VIN, or VaIN
- Will not protect against diseases not caused by HPV
- Has not been shown to protect against diseases due to nonvaccine HPV types
- As with all injectable vaccines, appropriate medical treatment should always be readily available in case of rare anaphylactic reactions following the administration.

## Precautions: General (*cont*)

- The decision to administer or delay vaccination because of a current or recent febrile illness depends largely on the severity of the symptoms and their etiology.
  - Low-grade fever and mild upper respiratory tract infection are generally not contraindications to vaccination.
- Individuals with impaired immune responsiveness may have reduced antibody response to active immunization.
- As with other intramuscular injections, this vaccine should not be given to individuals with bleeding disorders such as hemophilia or thrombocytopenia, or to persons on anticoagulant therapy unless the potential benefits clearly outweigh the risk of administration.
  - If the decision is made to administer the vaccine to such persons, it should be given with steps to avoid the risk of hematoma following the injection.

## Precautions: Information for the Patient, Parent, or Guardian

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- Vaccination does not substitute for routine cervical cancer screening.
  - Women should continue to undergo cervical cancer screening per standard of care.
- GARDASIL is not recommended for use in pregnant women. (Pregnancy Category B)
- It is not known whether vaccine antigens or antibodies induced by the vaccine are excreted in human milk.
- Completion of the immunization series is important unless contraindicated.

## Precautions: Studies With Other Vaccines

- Coadministration\* of GARDASIL with recombinant hepatitis B vaccine
  - Safety and immunogenicity evaluated in randomized study of 1,871 women aged 16 to 24 years.
  - Immune response to both vaccines was noninferior whether administered at same visit or at different visit.
  - Frequency of systemic or injection-site adverse events similar to that with GARDASIL or hepatitis B vaccine administered alone.
- Coadministration of GARDASIL with other vaccines has not been studied.

\*Same visit, injections at separate sites.

# Precautions: Drug Interactions in PPE Population

- Use with Hormonal Contraceptives
  - Use of hormonal contraceptives or lack of use of hormonal contraceptives among study participants did not alter vaccine efficacy.
- Use with Systemic Immunosuppressive Medications
  - Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune responses to vaccines.

# Vaccine-Related Experiences

<b>Injection site (1 to 5 days postvaccination)</b>			
	<b>GARDASIL (N=5,088)</b>	<b>Placebo (Aluminum) (N=3,470)</b>	<b>Placebo (Saline) (N=320)</b>
Pain	83.9%	75.4%	48.6%
Swelling	25.4%	15.8%	7.3%
Erythema	24.6%	18.4%	12.1%
Pruritus	3.1%	2.8%	0.6%
<b>Systemic Adverse Event (1 to 15 days postvaccination)</b>			
	<b>GARDASIL (N=5,088)</b>	<b>Placebo (N=3,790)</b>	
Fever	10.3%	8.6%	

- Few subjects (0.1%) discontinued due to adverse experiences.

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.

# All-Cause Common Systemic Adverse Experiences\*

Adverse Experience (1 to 15 days postvaccination)	GARDASIL (N = 5,088) %	Placebo (N = 3,790) %
Pyrexia	13.0	11.2
Nausea	6.7	6.6
Nasopharyngitis	6.4	6.4
Dizziness	4.0	3.7
Diarrhea	3.6	3.5
Vomiting	2.4	1.9
Myalgia	2.0	2.0
Cough	2.0	1.5
Toothache	1.5	1.4
Upper respiratory tract infection	1.5	1.5
Malaise	1.4	1.2
Arthralgia	1.2	0.9
Insomnia	1.2	0.9
Nasal congestion	1.1	0.9

\*Greater than or equal to 1% frequency and greater than or equal to the incidence in the placebo group.

# Postdose Evaluation of Injection-Site Adverse Experiences

Adverse Experience	Vaccine (% occurrence)				Aluminum-Containing Placebo (% occurrence)				Saline Placebo (% occurrence)			
	Post-dose 1	Post-dose 2	Post-dose 3	Post Any Dose	Post-dose 1	Post-dose 2	Post-dose 3	Post Any Dose	Post-dose 1	Post-dose 2	Post-dose 3	Post Any Dose
<b>Pain</b>	63.4	60.7	62.7	83.9	57.0	47.8	49.5	75.4	33.7	20.3	27.3	48.6
Mild/Moderate	62.5	59.7	61.2	81.1	56.6	47.3	48.9	74.1	33.3	20.3	27.0	48.0
Severe	0.9	1.0	1.5	2.8	0.4	0.5	0.6	1.3	0.3	0.0	0.3	0.6
<b>Swelling*</b>	10.2	12.8	15.1	25.4	8.2	7.5	7.6	15.8	4.4	3.0	3.3	7.3
Mild/Moderate	9.6	11.9	14.3	23.3	8.0	7.2	7.3	15.2	4.4	3.0	3.3	7.3
Severe	0.6	0.8	0.8	2.0	0.2	0.3	0.2	0.6	0.0	0.0	0.0	0.0
<b>Erythema*</b>	9.2	12.1	14.7	24.7	9.8	8.4	8.9	18.4	7.3	5.3	5.7	12.1
Mild/Moderate	9.0	11.7	14.3	23.7	9.5	8.3	8.8	18.0	7.3	5.3	5.7	12.1
Severe	0.2	0.3	0.4	0.9	0.3	0.1	0.1	0.4	0.0	0.0	0.0	0.0

\*Intensity of swelling and erythema was measured by size (inches): Mild = 0 to ≤1; Moderate = >1 to ≤2; Severe = >2.

# Postdose Evaluation of Fever

Temperature (°F)	Vaccine (% occurrence)			Placebo (% occurrence)		
	Postdose 1	Postdose 2	Postdose 3	Postdose 1	Postdose 2	Postdose 3
≥100 to <102	3.7	4.1	4.4	3.1	3.8	3.6
≥102	0.3	0.5	0.5	0.3	0.4	0.6

# All-Cause Serious Adverse Experiences\*

<b>Adverse Experience (1 to 15 days postvaccination)</b>	<b>GARDASIL %</b>	<b>Placebo %</b>
Headache	0.03	0.02
Gastroenteritis	0.03	0.01
Appendicitis	0.02	0.01
Pelvic inflammatory disease	0.02	0.01

One case of bronchospasm and 2 cases of asthma were reported as serious adverse experiences that occurred during Days 1 through 15 of any vaccination visit.

\*Most frequently reported.

## All-Cause Related Mortality

Cause of Death	GARDASIL N	Placebo N
Motor vehicle accident	4	3
Overdose/suicide	1	2
Pulmonary embolus/DVT	1	1
Sepsis	2	0
Pancreatic cancer	1	0
Arrhythmia	1	0
Asphyxia	0	1

The events reported were consistent with events expected in healthy adolescent and adult populations.

# New Medical Conditions After Enrollment\*

Potential Autoimmune Disorder	GARDASIL (N = 11,813)	Placebo (N = 9,701)
<b>Specific Terms</b>	<b>3 (0.025%)</b>	<b>1 (0.010%)</b>
Juvenile arthritis	1	0
Rheumatoid arthritis	2	0
Systemic lupus erythematosus	0	1
<b>Other Terms</b>	<b>6 (0.051%)</b>	<b>2 (0.021%)</b>
Arthritis	5	2
Reactive arthritis	1	0
N = number of subjects enrolled.		

\*Potentially indicative of a systemic immune disorder.

# Dosage and Administration of GARDASIL

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- GARDASIL should be administered intramuscularly as 3 separate 0.5-mL doses according to the following schedule:
  - First dose: at elected date
  - Second dose: 2 months after the first dose
  - Third dose: 6 months after the first dose

## Dosage and Administration of GARDASIL (*cont*)

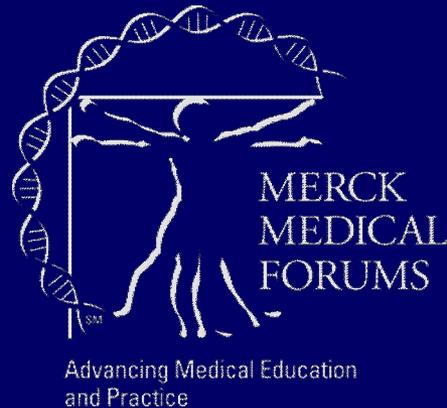
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- Administer intramuscularly.
  - In deltoid region of upper arm or in higher anterolateral area of the thigh.
- Do not inject intravascularly.
- Subcutaneous and intradermal administrations have not been studied.
  - Therefore they are not recommended.
- Use as supplied.
  - No dilution or reconstitution is necessary.

## Summary for GARDASIL

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- First and only quadrivalent HPV vaccine that is effective in preventing cervical cancer and genital warts, as well as AIS, CIN 1–3, VIN 2/3, and VaIN 2/3 caused by HPV 6, 11, 16, and 18 in 9- to 26-year-old women
- On the basis of immunogenicity bridging, the efficacy of GARDASIL in 9- to 15-year-old girls is inferred.



**Before administering GARDASIL® [Quadrivalent Human Papillomavirus (HPV Types 6, 11, 16, 18) Recombinant Vaccine], please read the Prescribing Information available at this presentation.**



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