



Demystifying the HPV vaccine: Is it really safe and effective?

Rita Singhal, MD, MPH
Medical Director, Office of Women's Health
Los Angeles County Dept of Public Health

3rd Annual CORICA Symposium
Los Angeles, CA
May 22, 2007

What is HPV?

- **H**uman **P**apillomav**v**irus – DNA virus with protein shell; infect skin and mucous membranes
- How many people have genital HPV?
 - >20 million people currently infected
 - 6.2 million new infections every year
- Who gets genital HPV?
 - Young people – rates decrease with increasing age
 - Associated with sexual behaviors – early onset, number of partners
- Persistent infection with high risk HPV types leads to cervical cancer

> 100 HPV Types

Genital HPVs
sexual contact
(>40 types)

Dermal HPVs
nonsexual contact
(>50 types)

**"High-risk"
types**

16,18,
31,33,35,39,
45,51,52,56,58

- low grade cervical abnormalities
- genital pre-cancers
- genital cancers

**"Low-risk"
types**

6,11,40,42,43,44
54,61,72,73,81

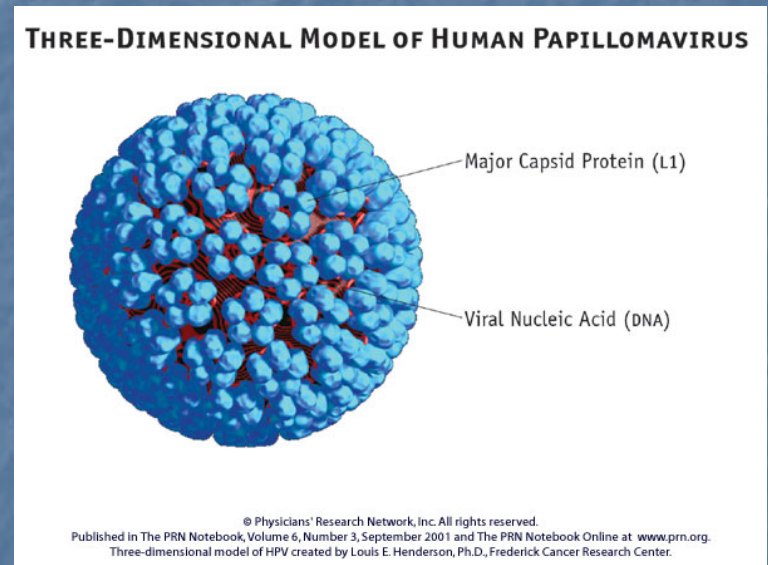
- low grade cervical abnormalities
- genital warts
- respiratory papillomatosis

**"Common"
warts**

(e.g., hands/feet)

HPV Vaccine Structure

- Recombinant vaccine
- HPV L1 proteins self assemble into virus-like particles (VLP)
- L1 protein serves as antigen
- No live virus
- No thimerosal or mercury



Licensed & Candidate Prophylactic HPV Vaccines

<u>Vaccine/ Manufacturer</u>	<u>HPV Types</u>	<u>Doses</u>	<u>Adjuvant</u>	<u>Diseases Prevented</u>
Quadrivalent Merck	6/11/16/ 18	0, 2, 6 months	Alum	Cervical Cancer Genital Warts
Bivalent GlaxoSmithKline	16/18	0, 1, 6 months	Alum and MPL	Cervical Cancer

Current Status of Prophylactic HPV Vaccines

<u>Vaccine/ Manufacturer</u>	<u>FDA Application</u>	<u>FDA Status</u>	<u>US Licensure</u>
Quadrivalent Merck	Filed Dec 2005 Females 9-26 years and males 9-15 years	Approved for females 9- 26 years	Approved June 8, 2006
Bivalent GlaxoSmithKline	Filed March 2007	Pending approval	Pending approval

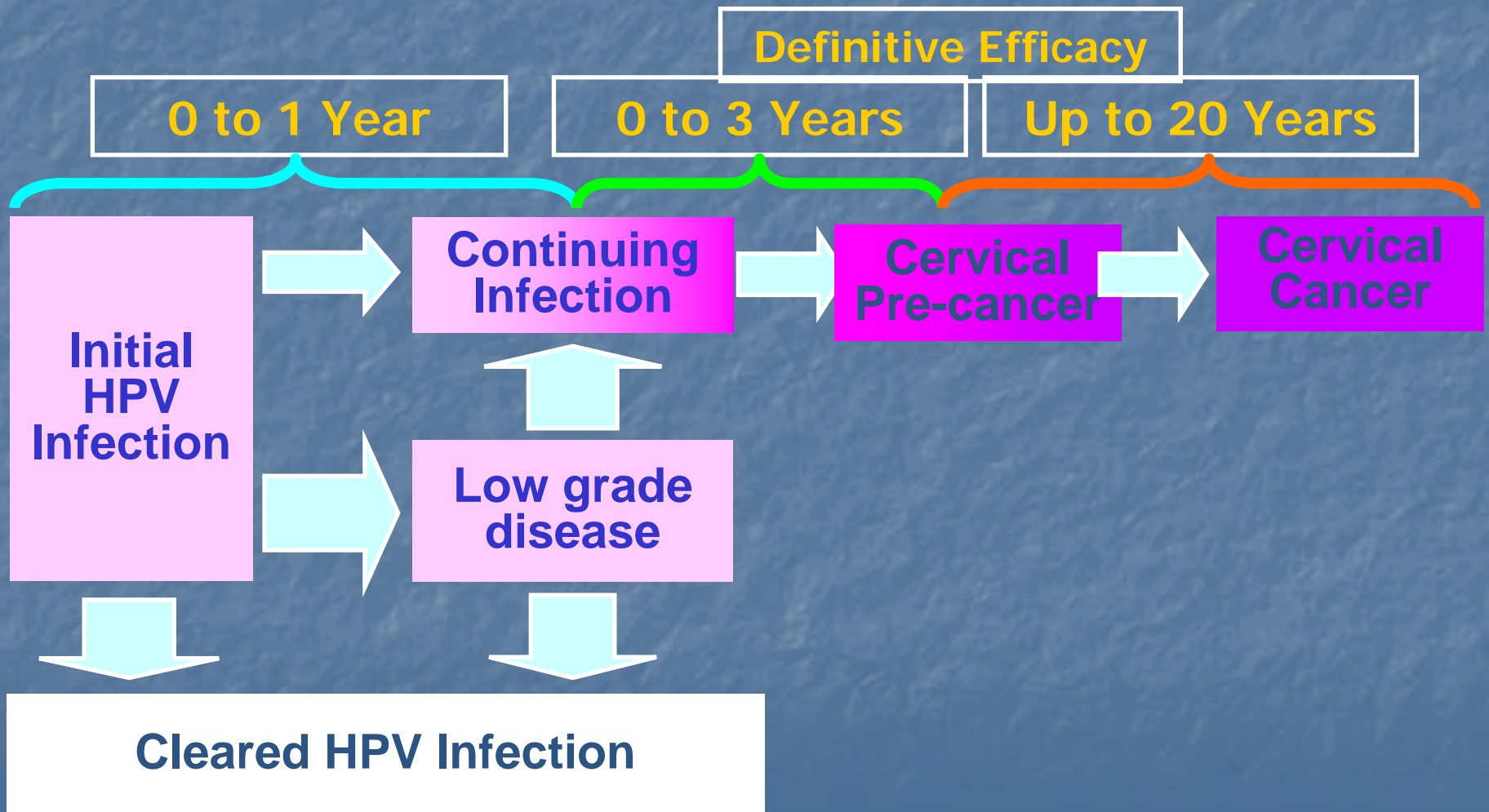
Quadrivalent HPV Vaccine

- FDA approved June 8, 2006
- Noninfectious, recombinant, quadrivalent vaccine
- HPV types 6/11/16/18
- Approved for use in females 9-26 years of age
- Prevention of the following disease:
 - Cervical cancer
 - Cervical, vaginal and vulvar pre-cancer
 - Genital warts

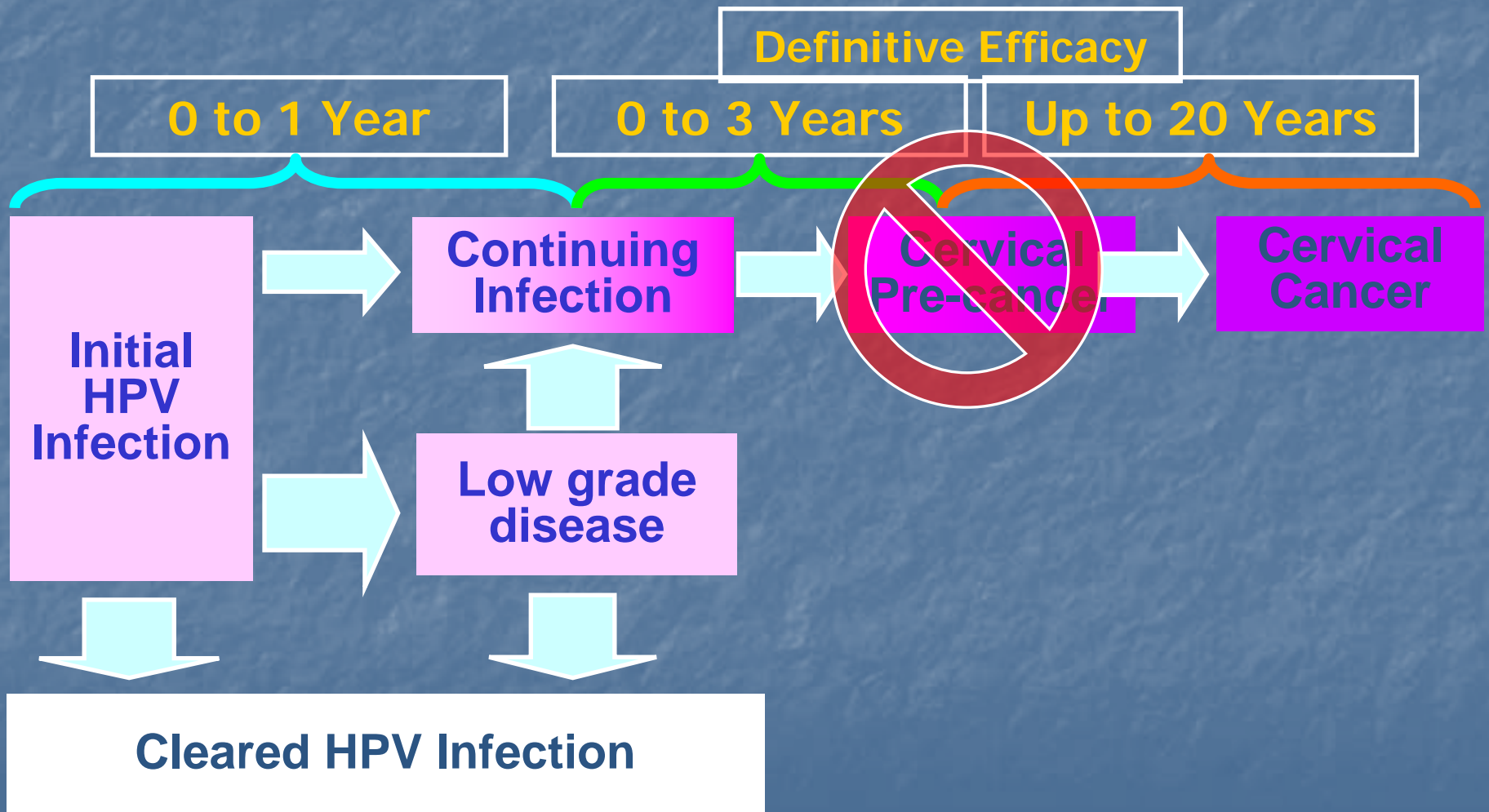
Quadrivalent HPV Vaccine Clinical Development Program

- Efficacy studies in females 16-26 years
- Safety and immunogenicity studies in 9-15 year olds
- Clinical endpoints
 - Cervical cancer
 - Cervical pre-cancer/High grade cervical lesions
 - Vaginal and vulvar pre-cancers
 - External genital lesions/warts

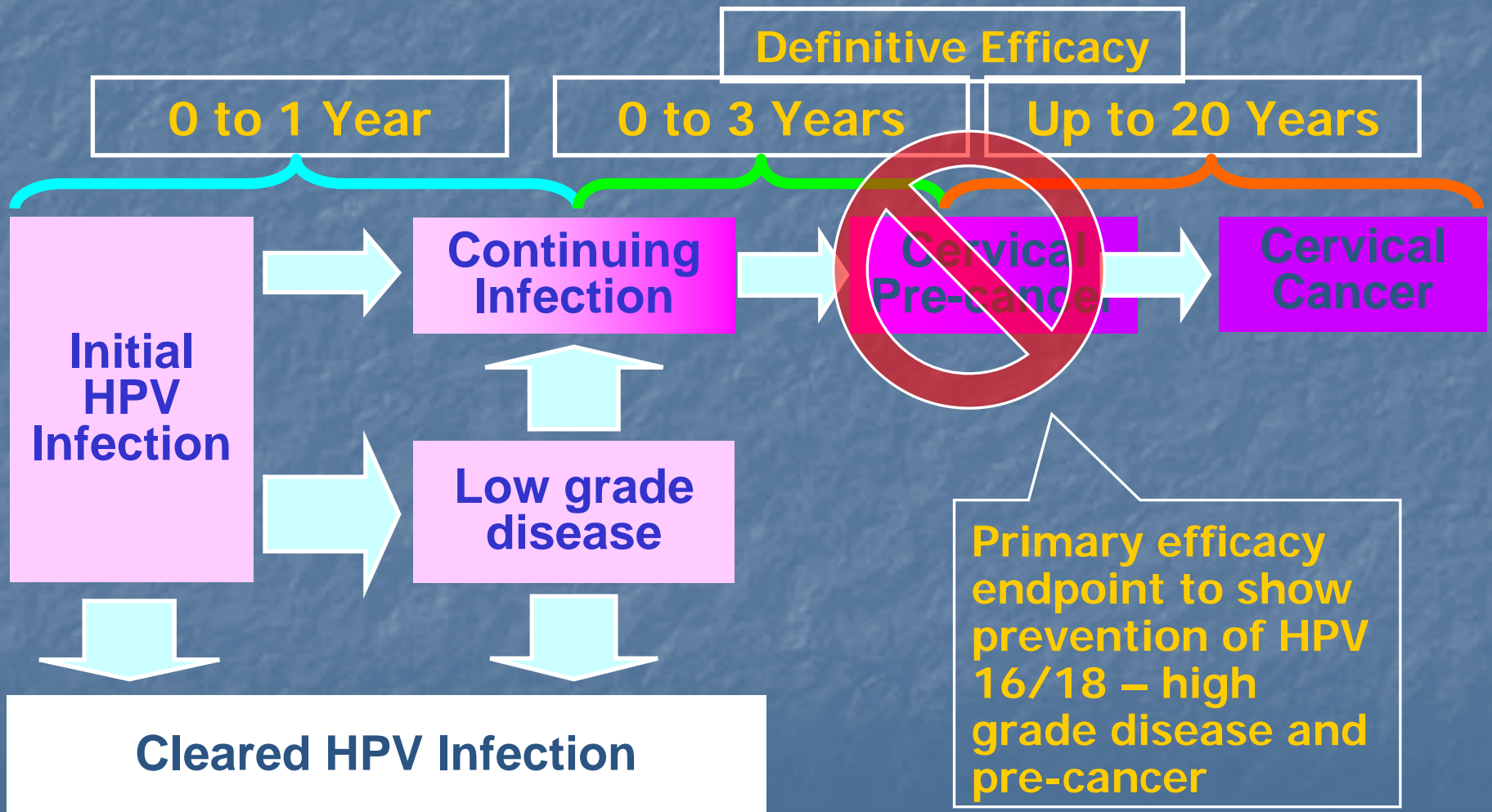
Endpoints for Clinical Trials



Endpoints for Clinical Trials



Endpoints for Clinical Trials



Quadrivalent HPV Vaccine Efficacy Clinical Trials

- Total: 20,541 subjects
- 4 clinical trials
 - Protocol 005 – 2,391 women, 4 ½ years follow-up – HPV 16 component only
 - Protocol 007 – 551 women, 3 ½ years
 - **FUTURE I (protocol 013)** – 5,455 women, 3 years follow-up, 62 study sites in 16 countries
 - **FUTURE II (protocol 015)** – 12,167 women, 2 ½ years follow-up, 90 study sites in 13 countries

Clinical Trials Efficacy Analyses

- Per-protocol Efficacy
 - Was vaccine effective in reducing HPV 6/11/16/18 related disease in those who have not been exposed
- Intent-to-treat Efficacy
 - What was impact in reducing disease from HPV 6/11/16/18 in all subjects
- General Population Impact
 - What was impact in reducing all disease (regardless of HPV type) in all subjects

Per-protocol Efficacy of Quadrivalent Vaccine

<u>Endpoint</u>	<u>Vaccine</u>		<u>Placebo</u>		<u>Efficacy</u>	<u>95% CI</u>
	<u>N</u>	<u>Cases</u>	<u>N</u>	<u>Cases</u>		
HPV 16/18 related high grade disease and pre-cancer*	5305	1	5260	42	98%	(86,100)
HPV 6/11/16/18 related genital warts and vaginal lesions**	2261	0	2279	60	100%	(94,100)

Source: NEJM May 2007;356:1915-27 and 1928-43, * FUTURE II, ** FUTURE I

Intent-to-treat Efficacy of Quadrivalent Vaccine

<u>Endpoint</u>	<u>Vaccine</u>		<u>Placebo</u>		<u>% Reduced</u>	<u>95% CI</u>
	<u>N</u>	<u>Cases</u>	<u>N</u>	<u>Cases</u>		
HPV 16/18 related high grade disease and pre-cancer*	6087	83	6080	148	44	(26, 58)
HPV 6/11/16/18 related genital warts and vaginal lesions**	2723	28	2732	102	73	(58, 83)

Source: NEJM May 2007;356:1915-27 and 1928-43, * FUTURE II, ** FUTURE I

General Population Impact of Quadrivalent Vaccine

<u>Endpoint</u>	<u>Vaccine</u>		<u>Placebo</u>		<u>% Reduced</u>	<u>95% CI</u>
	<u>N</u>	<u>Cases</u>	<u>N</u>	<u>Cases</u>		
High grade disease and pre-cancer from any HPV type*	6087	219	6080	266	17	(1,31)
Genital warts and vaginal lesions from any HPV type**	2723	104	2732	157	34	(15,49)

Source: NEJM May 2007;356:1915-27 and 1928-43, * FUTURE II, ** FUTURE I

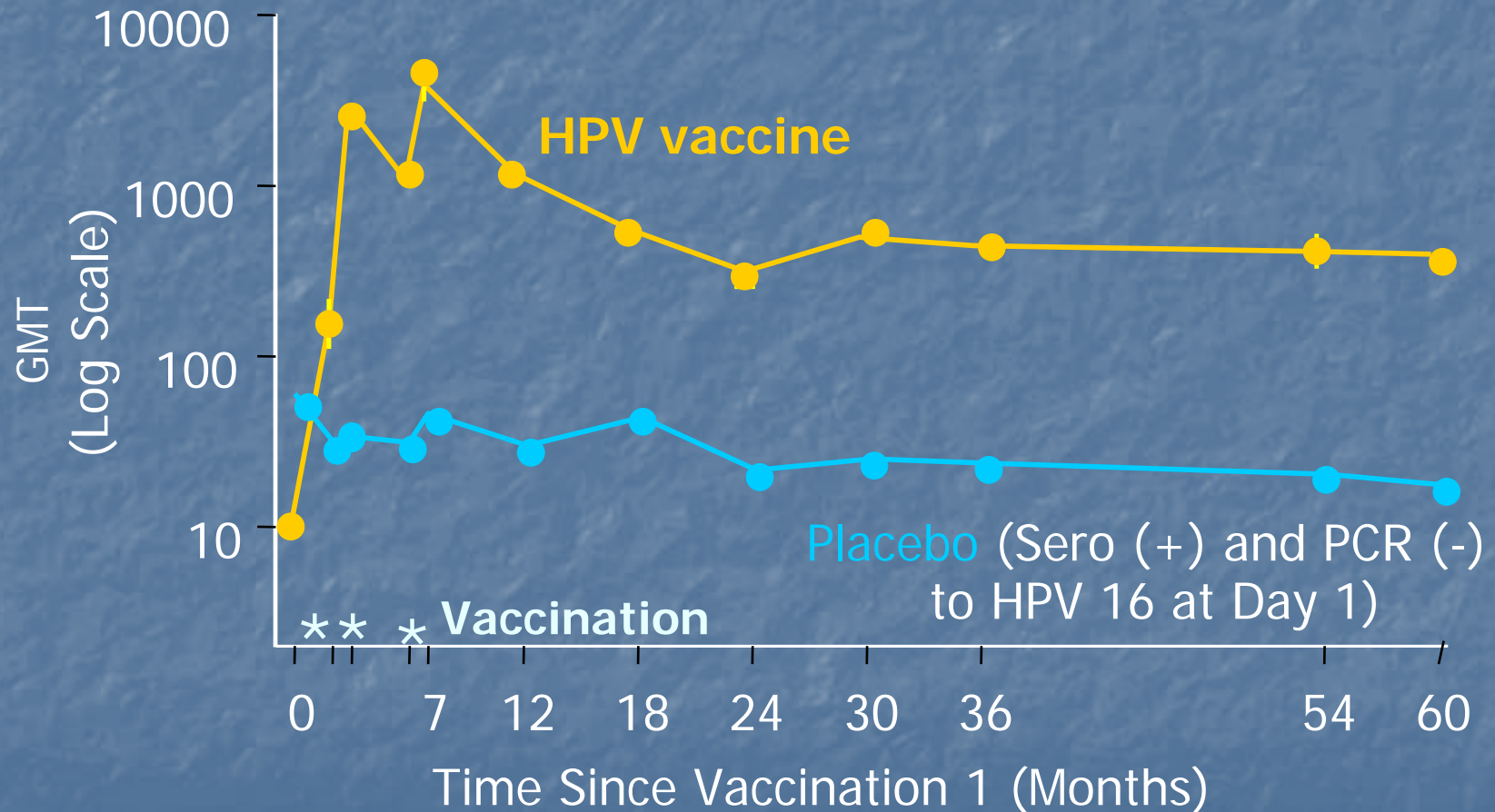
Clinical Trials Efficacy Analyses Summary

- Highly efficacious in those not previously exposed
- Significant impact on reducing disease related to vaccine HPV types
- Modest impact on overall disease reduction
- Full benefit of vaccine remains to be seen

Quadrivalent HPV Vaccine Immunogenicity Data

- Duration of Immune Response
 - Followed levels of antibodies in 8,915 women and girls
- Bridging Efficacy to 9-15 year old girls
 - Clinical endpoints could not be measured in young girls
 - Antibody levels used as surrogate for efficacy in this age group

Immune Response to Quadrivalent Vaccine through 5 Years

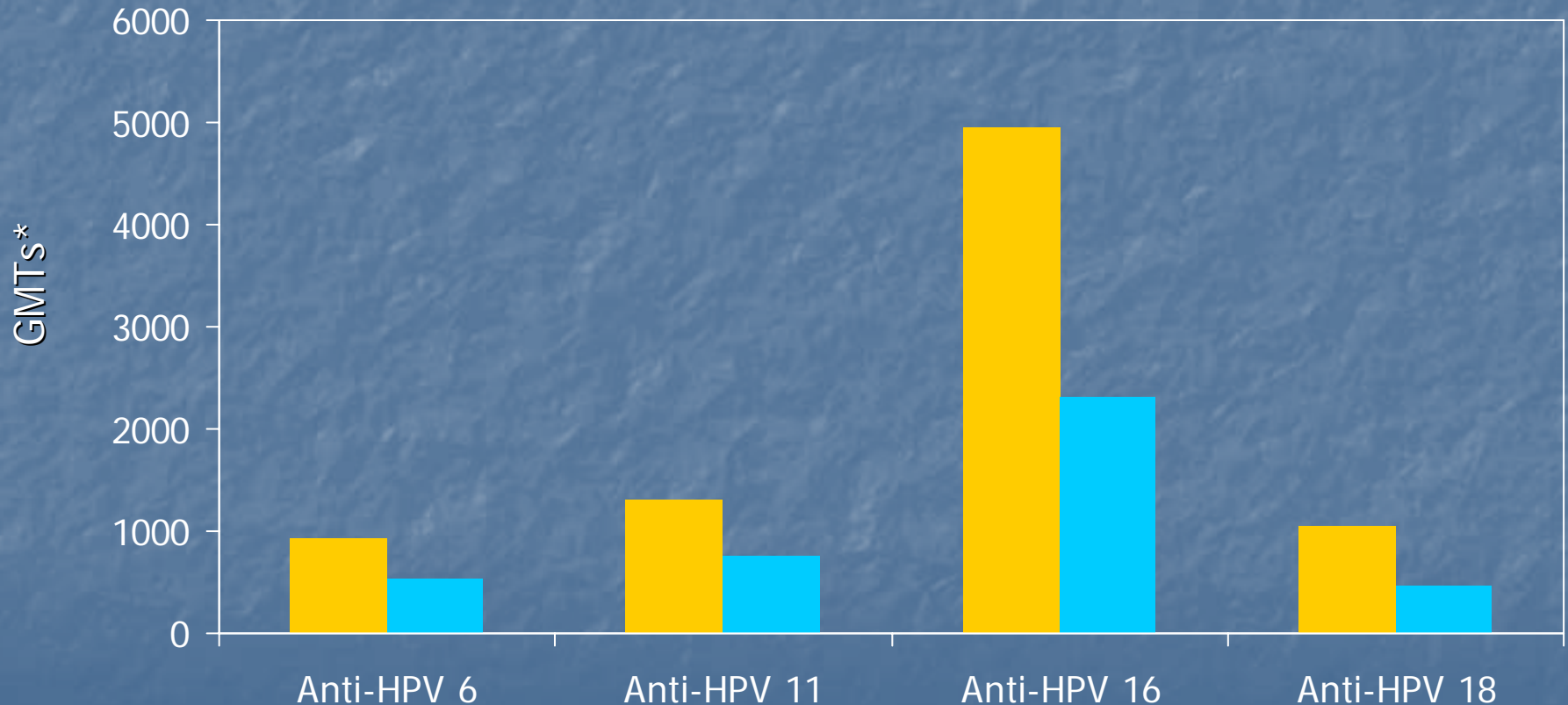


*GMT = Geometric mean titer in mMU/mL (mMU = milli-Merck units).
Merck, unpublished data, Presented at ACIP meeting, June 2006

Bridging Efficacy of the Quadrivalent Vaccine to 9-15 year old 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).

Source: <http://www.fda.gov/cber/label/hpvmer013007LB.pdf>

Local and Systemic Adverse Events

Local Adverse Event (1 to 5 Days after vaccination)	HPV Vaccine (n=5088) %	Alum Placebo (n=3470) %	Saline Placebo (n=320) %
Pain	83.9	75.4	48.6
Swelling	25.4	15.8	7.3
Erythema	24.6	18.4	12.1
Pruritis	3.1	2.8	0.6

Systemic Adverse Event (1 to 15 Days after vaccination)	HPV Vaccine (n=5088) %	Placebo (n=3790) %
Fever	10.3	8.6
Nausea	4.2	4.1
Dizziness	2.8	2.6

VAERS Data for Quadrivalent HPV Vaccine

- Vaccine Adverse Event Reporting System
- Updated data - Feb 2007
- 5 most frequently reported symptoms (total = 542)
 - Injection site pain 18%
 - Dizziness 11%
 - Syncope 11%
 - Fever 9%
 - Nausea 9%

Quadrivalent HPV Vaccine during Pregnancy and Lactation

- Pregnancy
 - Adverse events similar in vaccine and placebo groups
 - Currently not recommended
 - Further study required – Pregnancy Registry
- Lactation
 - No adverse events related to vaccine
 - Ok to get vaccine during lactation

Quadrivalent HPV Vaccine Summary

- Highly efficacious in those not exposed
- Immune response sustained for 5 years
- Superior immune response in younger girls; no efficacy data
- Safe vaccine



Remaining Unanswered Questions

- Long term safety
- Extent of immunity
- Cross protection vs. type replacement
- Pre/post sexual debut
- Male vaccination
- Impact on cervical cancer deaths will not be apparent for long time
- Comparison to other HPV vaccines



COUNTY OF LOS ANGELES

Public Health



Rita Singhal, MD, MPH

Medical Director

Office of Women's Health

LAC Department of Public Health

risinghal@ph.lacounty.gov

626-569-3816

