HPV Vaccines
Overview of Data from Clinical Trials

Advisory Committee on Immunization Practices

October 25, 2007

Lauri Markowitz, MD

NCHHSTP

Centers for Disease Control and Prevention

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

Overview

- Background
- Efficacy
- Immunogenicity
- Ongoing and planned studies

Background: HPV

- More than 100 different types
  - >40 types are mucosal
  - "High risk", oncogenic types (**16, 18**, 31, 33, 35, 39, 45, 51, 52, 56, 58….)
    - ~ 70% of cervical cancers due to types 16 or 18
  - "Low risk", nononcogenic types (**6, 11**, 42, 43, 44…)
    - >90% of genital warts, recurrent respiratory papillomatosis caused by types 6 or 11

Munoz. NEJM 2003;348

CDC
Centers for Disease Control and Prevention

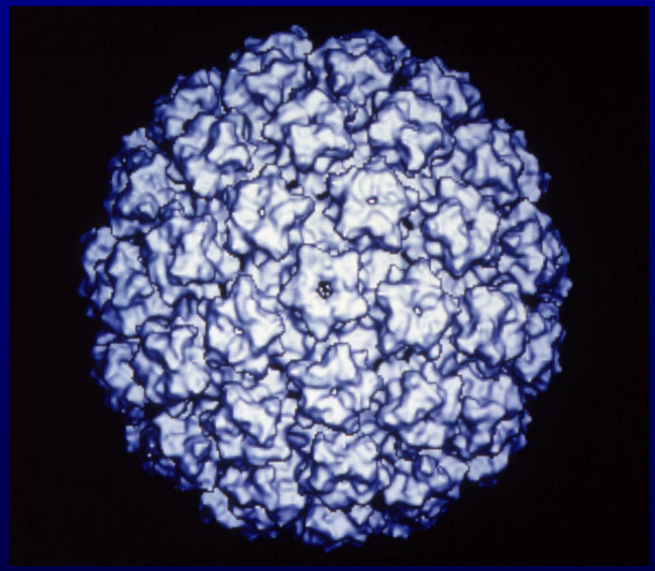
HPV-Related Cancers United States, 2003

Anatomic site	Total Cancers	% due to HPV
Cervix	11,820	100
Anus	4,187	85
Vaginal/vulvar	4,577	40
Penis	1,059	40
Oral/Pharyngeal	29,627	15

HPV L1 VLP Vaccines

- HPV L1 major capsid protein of the virus is antigen used for immunization
- Expression of L1 protein using recombinant technology
- L1 proteins self-assemble into virus-like particles (VLP)

HPV VLP



Prophylactic HPV L1 VLP Vaccines

	Quadrivalent (Merck)	Bivalent (GSK)
Vaccine Type	HPV 6/11/16/18	HPV 16/18
Manufacturing	Yeast - S. *cerevisiae*	Baculovirus
Composition	20 µg HPV 6 40 µg HPV 11 40 µg HPV 16 20 µg HPV 18	20 µg HPV 16 20 µg HPV 18
Schedule	0,2,6 months	0,1,6 months
Adjuvant	Alum: 225 µg Aluminum Hydroxyphosphate Sulfate	AS04: 500 µg Aluminum Hydroxide 50 µg 3-deacylated Monophosphoryl Lipid A
Availability in US	Licensed in June 2006	Application submitted to FDA in March 2007

HPV Vaccines: Selected Aspects of Clinical Development Programs

Vaccine/ Manufacturer	Phase II Efficacy Trials*	Phase III Efficacy Trials+	Adolescent Immunogenicity Safety Trials
Quadrivalent	females	females	9-15 yrs
Merck	16-23 yrs	16-26 yrs	
Bivalent	females	females	10-14 yrs
GSK	15-25 yrs	15-25 yrs	

*powered to detected incident and persistent infection endpoints
+powered to detect CIN 2/3 or AIS endpoints

HPV Vaccines: Selected Aspects of Clinical Development Programs

Vaccine/ Manufacturer	Phase II Efficacy Trials*	Phase III Efficacy Trials+	Adolescent Immunogenicity Safety Trials	Immunogenicity and Efficacy in females > 25 years
Quadrivalent *Merck*	females 16-23 yrs	females 16-26 yrs	9-15 yrs	24-45 yrs
Bivalent *GSK*	females 15-25 yrs	females 15-25 yrs	10-14 yrs	26-55 yrs

*powered to detected incident and persistent infection endpoints
+powered to detect CIN 2/3 or AIS endpoints

Quadrivalent HPV Vaccine Efficacy Trials by Protocol and Region

	Phase II		Phase III		
Region	Protocol 005	Protocol 007	Protocol 013 Future I	Protocol 015 Future II	Total Subjects
North America	X	X	X	X	5475
Latin America		X	X	X	5780
Europe		X	X	X	9232
Asia-Pacific			X	X	702
Total Subjects	2409	1158	5455	12,167	21,189

Protocol 005 studied monovalent HPV 16 vaccine
Protocols 007, 013, and 015 studied quadrivalent HPV vaccine

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

Bivalent HPV Vaccine Efficacy Trials by Protocol and Region

	Phase II		Phase III	
Region	Protocol 001	Protocol 007	Protocol 008 PATRICIA	Total subjects
North America	X	X*	X	3679
Latin America	X	X*	X	3280
Europe			X	6445
Asia-Pacific			X	6353
Total Subjects	1113	776*	18,644	19,757

* HPV-007 subjects were enrolled in HPV-001 and are not counted in totals

Efficacy

- Bivalent and quadrivalent HPV vaccine trials
  - similar endpoints – such as persistent infection or CIN2/3
  - slightly different protocols for detecting HPV, screening and management of abnormal cytology results

Efficacy Analysis Populations

In phase III trials, most females were sexually active and were enrolled without regard to PCR or antibody status

Per Protocol Population for Efficacy
- Naïve to relevant vaccine HPV type through month 7
- Received all 3 vaccinations
- No Protocol deviation
- Cases counted after dose 3

Unrestricted susceptible populations (or total vaccinated)
- Naïve to relevant vaccine HPV type
- Received at least 1 vaccination
- Cases counted day one after dose 1

Intent-to-Treat Population
- All subjects regardless of baseline status
- Received at least 1 vaccination
- Cases counted day one after dose 1

HPV Vaccine Efficacy

Prevention of HPV 16/18-related CIN 2/3 or AIS

Vaccine/Analysis	Vaccine N	Vaccine cases	Control N	Control cases	Efficacy	(CI)
Quadrivalent						
Per protocol	5305	1	5260	42	98	(86-100)
Unrestricted	5865	3	5863	62	95	(85-99)
Bivalent						
Unrestricted	7788	2	7838	21	90	(53-99)

CIN – cervical intraepithelial neoplasia; AIS – adenocarcinoma in situ

The Future II Study Group. NEJM 2007;356. 16-26 year old females; mean follow-up 3 years
Paavonen, et al. Lancet 2007;369 15-25 year old females; mean follow-up 15 months

CDC
Centers for Disease Control and Prevention

HPV Vaccine Efficacy

Prevention of HPV 16/18-related CIN 2/3 or AIS

Vaccine/Analysis	Vaccine N	Vaccine cases	Control N	Control cases	Efficacy	(CI)
Quadrivalent						
Per protocol	5305	1	5260	42	98	(86-100)
Bivalent						
Unrestricted	7788	2	7838	21	90	(53-99)

- For both quadrivalent and bivalent vaccines, cases in vaccine group had a non vaccine oncogenic type detected in preceding specimen (s) and also in the CIN2/3 lesion
- Analyses using lesions believed causally associated with vaccine types showed even higher (100%) efficacy (Paavonen, et al. Lancet 2007;369)

HPV Vaccine Efficacy

Prevention of HPV 16/18-related CIN 2/3 or AIS

	Vaccine		Control			
Vaccine/HPV type	N	Cases	N	Cases	Efficacy	(CI)
Quadrivalent						
HPV 16	5054	3	5043	51	94	(82-99)
HPV 18	5602	0	5602	16	100	(74-100)
Bivalent						
HPV 16	6701	1	6717	15	93	(47-100)
HPV 18	7221	1	7258	6	83	(-78-100)

Unrestricted susceptible or total vaccinated populations

The Future II Study Group. NEJM 2007;356. 16-26 year old females; mean follow-up 3 years
Paavonen, et al. Lancet 2007;369 15-25 year old females; mean follow-up 15 months

CDC
Centers for Disease Control and Prevention

Quadrivalent Vaccine Efficacy

Prevention of HPV 6,11,16,18 related External Anogenital & Vaginal Disease

	Vaccine		Placebo			
Endpoint	**N**	**cases**	**N**	**cases**	**Efficacy**	**(95% CI)**
Condyloma	2261	0	2279	48	100	(92, 100)
VIN or VaIN 2/3	7811	0	7785	15	100	(72-100)

Per Protocol Population

VIN – vulvar intraepithelial neoplasia; VaIN – vaginal intraepithelial neoplasia

Garland, et al. NEJM 2007;356
Joura, et al. Lancet 2007;369

Efficacy for Prevention of HPV Disease, by Baseline Status Quadrivalent HPV Vaccine Trials

	Seronegative	Seropositive
PCR (-)	Prophylactic efficacy	*Few cases* *100% efficacy*
PCR (+)	*No evidence of efficacy against respective type*	*No evidence of efficacy against respective type*

Quadrivalent Vaccine

Prevention of HPV 16/18 Related CIN 2/3 or AIS by Baseline HPV Status

	Vaccine		Placebo			
Baseline Status	**N**	**cases**	**N**	**cases**	**Efficacy**	**(95% CI)**
PCR + Sero -	423	33	402	35	10.0%	(<0-46)
PCR + Sero +	298	47	332	52	1.2%	(<0-100)
PCR - Sero +	498	0	524	4	100%	(<0-35)

At baseline, 16% sero or PCR positive to HPV 16; 7% sero or PCR positive to HPV 18

The Future II Study Group. NEJM 2007;356 – supplementary appendix

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

Bivalent Vaccine
Viral Clearance for HPV 16/18

	Vaccine		Control			
Endpoint	**N**	**cleared**	**N**	**cleared**	**Efficacy**	**(95% CI)**
6 months	241	81	288	93	2.6%	(−10.1 to 13.8)
12 months	149	98	196	98	-7%	(−31.7 to 13.0)

Hildesheim, et al. JAMA 2007

Quadrivalent Vaccine
Intent-to-Treat Analysis
Vaccine Type-Related Outcomes

Protocols 007, 013, 015

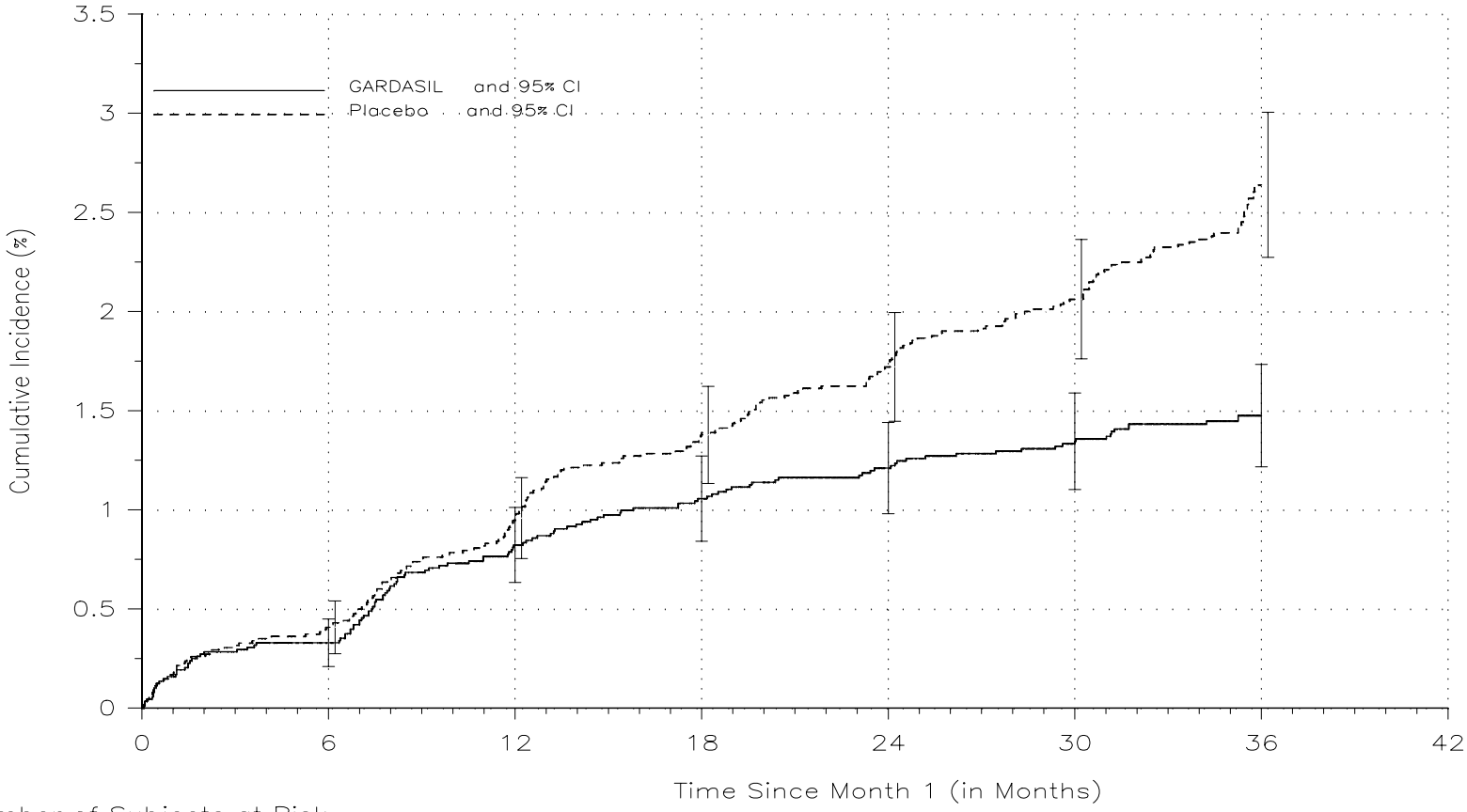
Endpoint	Vaccine cases	Placebo cases	Efficacy	(95% CI)
CIN2/3 or AIS	137	232	41	(27, 53)
VIN or VaIN 2/3	9	31	71	(37, 88)
Vulvar and vaginal lesions (including genital warts)	72	319	78	(71, 83)

Barr, Presented at ACIP – February 2007; mean follow up 2.8 years

CDC
Centers for Disease Control and Prevention

Quadrivalent HPV Vaccine

Time to HPV 16/18-Related CIN 2/3 or AIS



Number of Subjects at Risk

GARDASIL	8,817	8,728	8,537	8,419	8,154	7,934	2,544
Placebo	8,847	8,750	8,545	8,398	8,139	7,887	2,575

Intent to treat populations – protocols 07, 013, 015

Duration of Protection

Mean Follow-up Time in Clinical Trials

Trial	Quadrivalent	Bivalent
Phase III	3 years	15 months
Phase II	5 years	5.5 years

Published or presented

Quadrivalent Vaccine – Phase II Study

HPV 6,11,16,18 related endpoints

Efficacy through 5 years

Endpoint	Vaccine N	Vaccine cases	Placebo N	Placebo cases	Efficacy	(95% CI)
Persistent infection	235	2	233	45	95.6	(83.3-99.5)
CIN 1-3	235	0	233	3	100	(<0-100)
Condyloma	235	0	233	3	100	(<0-100)

Per protocol analysis
Persistent infection - HPV detected at two visits 4 months apart

Villa, et al. Br J CA 2006

Bivalent Vaccine - Phase II Study

HPV-001/007: HPV-16/18 endpoints

Efficacy through 5.5 yrs

Endpoints	Vaccine (Cases)	Control (Cases)	Efficacy	(95% CI)
Incident Infection	3	66	96	(88,99)
12 Month Persistence	0	14	100	(72,100)
CIN lesions	0	11	100	(33, 100)

Per protocol analysis for virologic endpoints

ITT analysis for cytologic and CIN endpoints

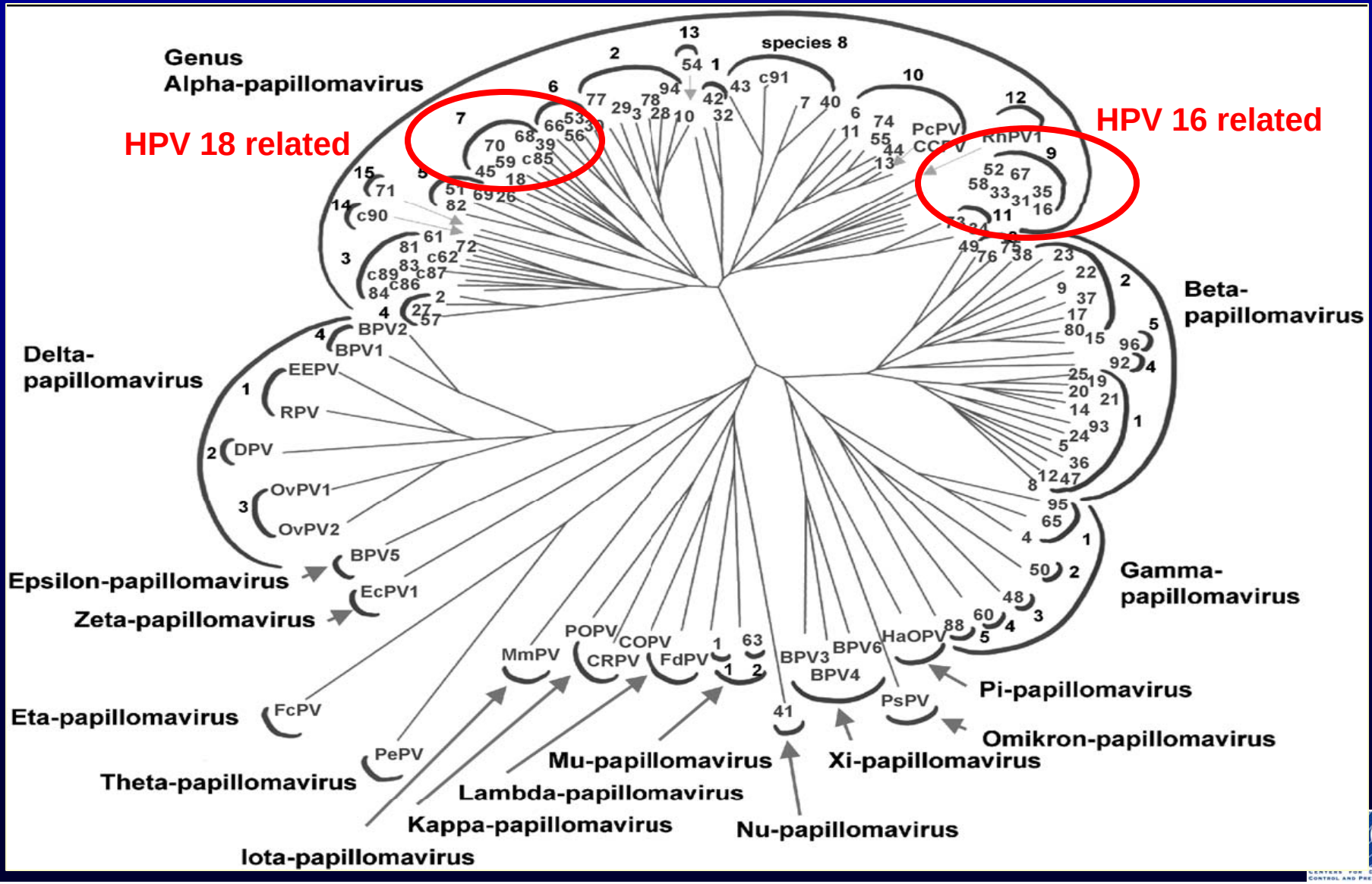
Gall, et al. Presented AACR 2007. Abstract 4900

CDC
Centers for Disease Control and Prevention

Cross Protection

Do the HPV vaccines provide protection against related HPV types?

Phylogenetic Characterization of Oncogenic HPV Types



Cross-protection: Bivalent Vaccine

6 month Persistent Infection

Causal HPV Type	Vaccine N	Vaccine cases	Placebo N	Placebo cases	Efficacy	(97.9% CI)
Type 45*	6734	10	6747	25	59.9	(2.6 - 85.2)
Type 31+	6615	47	6667	74	36.1	(.5 - 59.5)
Type 33+	6702	31	6736	49	36.5	(-9.9 - 64.0)
Type 52+	6532	79	6573	116	31.6	(3.5 - 51.9)
Type 58+	6688	43	6734	33	-31.4	(-132 – 24.7)

* HPV 18 related; +HPV 16 related

- Significant protection against combination of (12) non-vaccine oncogenic types using 12 mos persistent infection: VE = 27%; CI: 0.5-47%

Paavonen, et al. Lancet 2007;369

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

Cross Protection: Quadrivalent Vaccine

CIN 2/3 and AIS

Causal HPV Types	Vaccine N=4616	Placebo N=4675	Efficacy	(95% CI)
A9 Species (16 related) HPV 31, 33, 35, 52, 58	**26**	**48**	**45%**	**(10, 68)**
A7 Species (18 related) HPV 39, 45, 59	**8**	**15**	**46%**	**(-35, 80)**

Among generally HPV-naïve Population

Villa, et al. Presented at Eurogin 2007

Immunogenicity

- Main basis of protection is neutralizing antibody
- Minimum protective antibody threshold is not known
- Serologic tests for HPV antibody not standardized
  - Merck - competitive Luminex immunoassay (cLIA)
  - GSK - type specific ELISA
- Differences in methods of antibody detection preclude direct comparison of type specific antibody within studies and between two vaccines

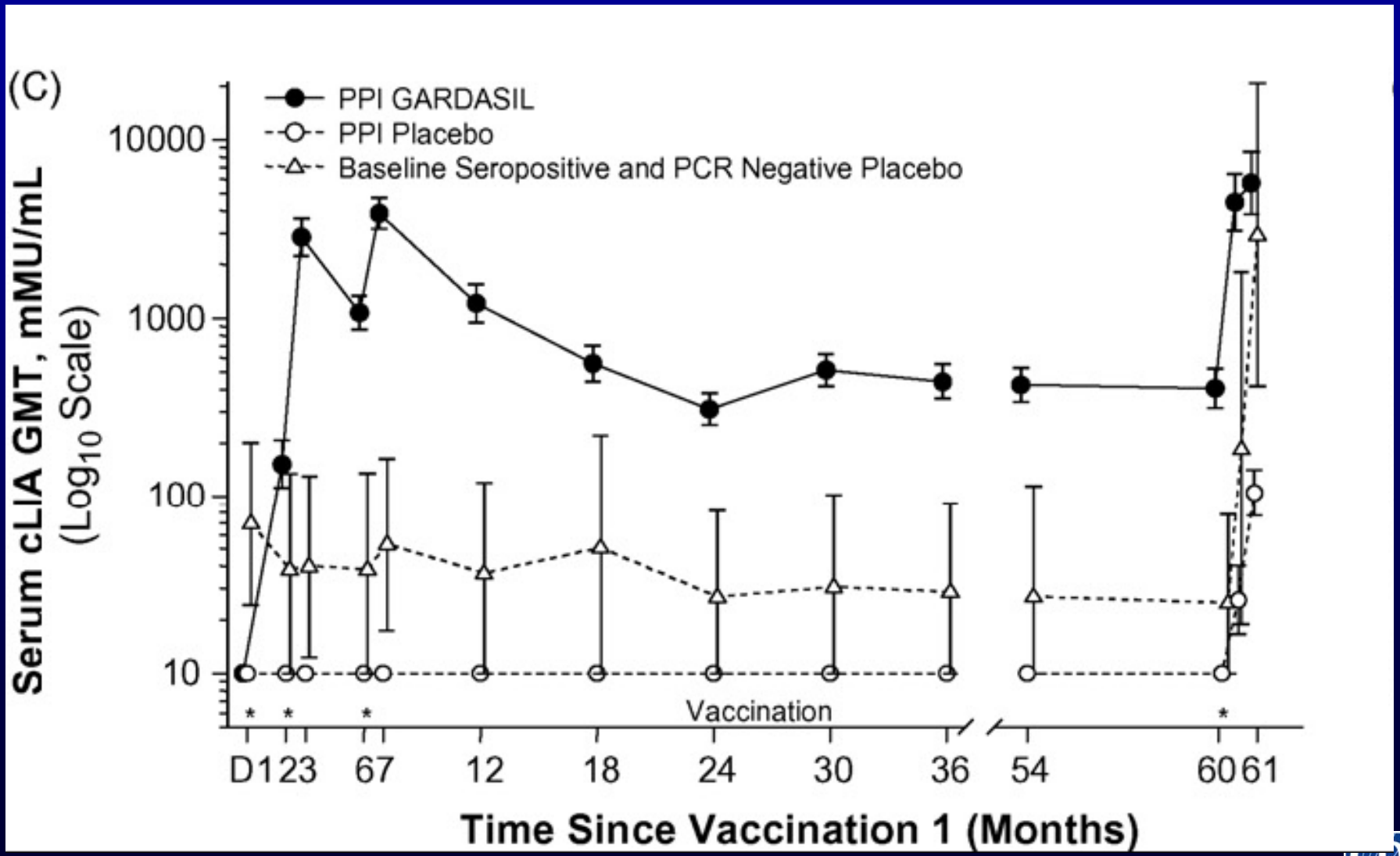
Seropositivity at Months 7 and 36 Post Vaccination

Vaccine/ HPV type	Month 7	Month 36
Quadrivalent*		
Anti-HPV 6	100%	96%
Anti-HPV 11	100%	98%
Anti-HPV 16	100%	99%
Anti-HPV 18	100%	74%
Bivalent+		
Anti-HPV 16	100%	99%
Anti-HPV 18	100%	99%

* Villa, et al. Vaccine 2006 - competitive Luminex immunoassay (cLIA)
+ Harper, et al. Lancet 2006 - type specific ELISA

Quadrivalent Vaccine

HPV 16 GMTs and Response to Dose 4



Olsson, et al. Vaccine 2007

Adolescent Bridging Immunogenicity Data

Immunogenicity non-inferior to older females in phase III efficacy trials for both vaccines

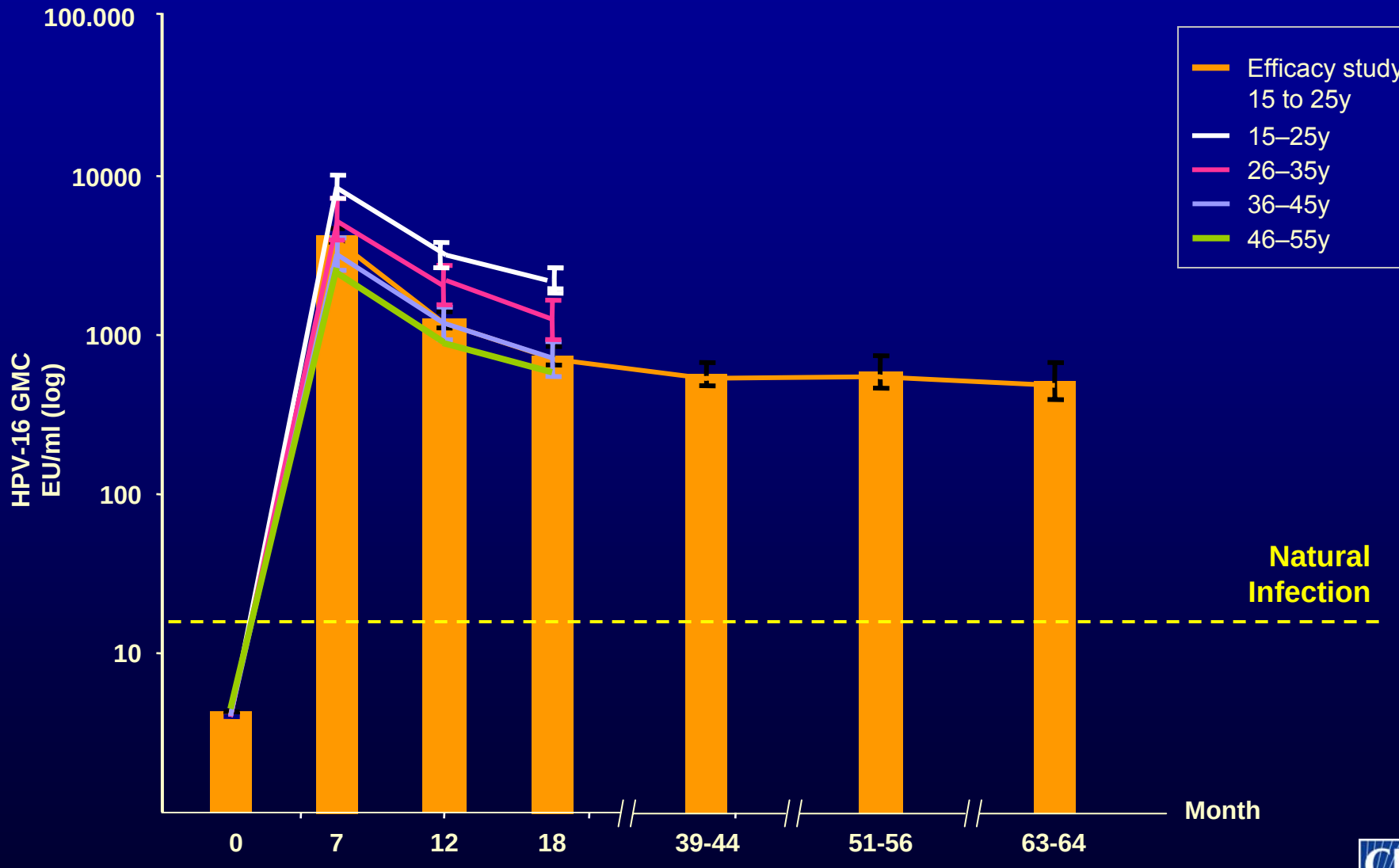
- Seropositivity similar (>99%)
- GMTs 2- fold higher

Immunogenicity Data in Women >25 Years

- Bivalent HPV vaccine: 26-55 year-old women
  - 100% seropositivity after 3 doses
  - Age-related differences in peak GMTs
- Quadrivalent HPV vaccine
  - Available in near future

Bivalent HPV Vaccine

HPV 16 Antibody in Women >25 Years



Harper, et al. Lancet 2006; 367: 1247–55; Presentation Schwarz, ASCO 2006

Safety

- Multiple safety outcomes evaluated in clinical trials including:
  - Injection site reactions
  - Serious adverse events
  - New onset chronic diseases including new onset of autoimmune diseases
  - Pregnancy and pregnancy related outcomes

Safety

- Injection site events occur more often in vaccine than control recipients
- No significant increase in serious adverse events or new onset chronic diseases
- No difference in overall pregnancy outcomes in vaccine or control groups

Summary: Efficacy

- High efficacy against vaccine HPV type related virologic and CIN endpoints among females naïve to the relevant vaccine type for both vaccines
- High efficacy against vaccine HPV type related genital warts, VIN and VaIN (Quadrivalent)
- Efficacy data available from Phase II trials through ~60 months show sustained high efficacy
- Some cross protection against non vaccine types (virologic endpoints for Bivalent; histologic for Quadrivalent)
- No evidence of therapeutic efficacy

Summary: Immune Response

- Serum antibodies induced in all vaccinees
- Vaccine induced antibody levels are higher than those seen after natural infection
- Duration of antibody through ~5 years. Loss of detectable antibody to HPV 18 not associated with loss of protection (Quadrivalent)
- Challenge produces anamnestic response (Quadrivalent)
- Antibody titers are non inferior in young adolescents (9 or 10-15 years) compared with women in efficacy trials
- Age related decreases in GMTs in women >25 yrs, but GMTs substantially higher than after natural infection (Bivalent)

CDC
Centers for Disease Control and Prevention

Ongoing or Planned Studies

	Quadrivalent	Bivalent
Follow-up phase II and III trials	x	x
Immuno/efficacy in females >25 yrs	x	x
Efficacy trials in men 16-26 yrs	x	
Simultaneous administration	x	x
Comparative immunogenicity		x
Safety & immunogenicity in HIV+ women (and men - Quadrivalent)	x	x
Phase 4: long term follow-up	x	x

Acknowledgments

Eliav Barr
Gary Dubin
Elizabeth Unger
Eileen Dunne