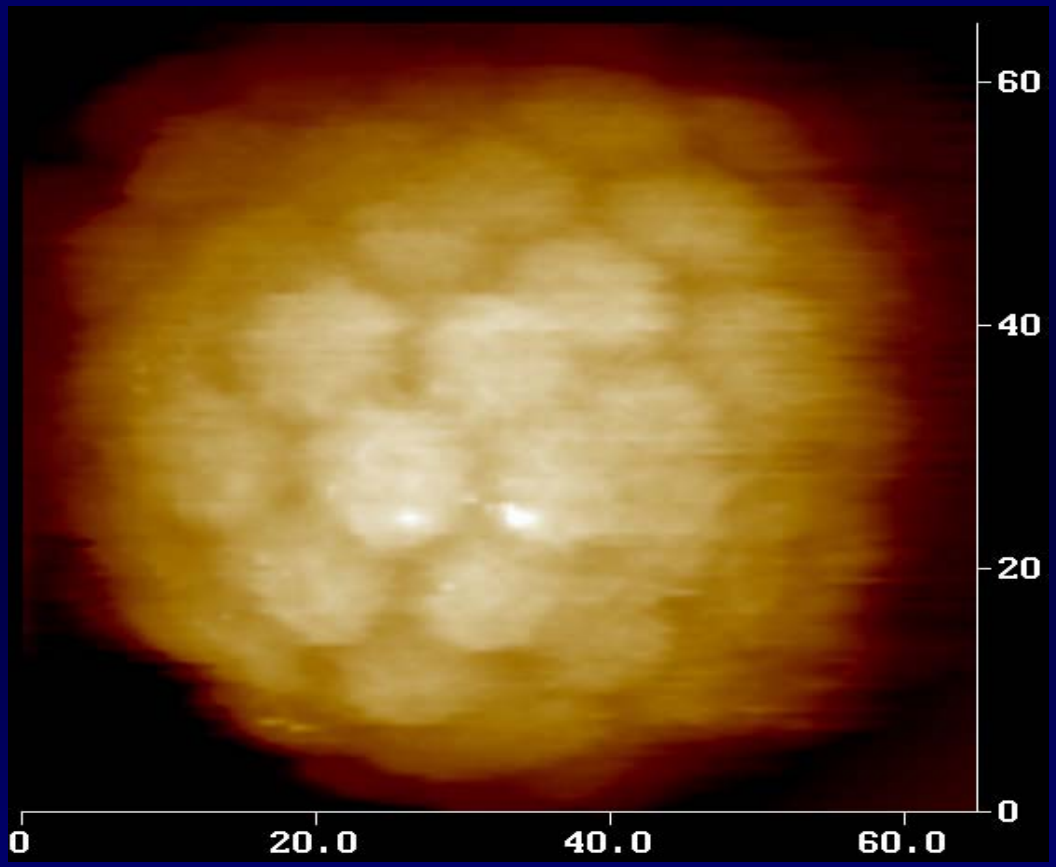
Current Research on HPV Vaccine

Punnee Pititsuttithum MBBS,DTM&H,FRCPT

Faculty of Tropical Medicine, Mahidol U

National Cancer Meeting, Bangkok 13/12/07

HPV L1 Virus-Like Particle (protein from the L1 gene of HPV)



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

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	>25 yrs

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

Efficacy Trials

Bivalent HPV Vaccine Efficacy Trials by Protocol and Region

	Phase II		Phase III		
Region	Protocol 001	Protocol 007	Protocol 008	Protocol 009	Total subjects
North America	X	X*	X		3679
Latin America	X	X*	X	X	10746
Europe			X		6445
Asia-Pacific			X		6353
Total Subjects	1113	776*	18,644	7466	27,223

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

Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women

- 17,106 (92%) women received full three-dose vaccination schedule (18,644 enrolled)
- 3753 (20%) women had cervical oncogenic HPV DNA at baseline
- The mean follow-up time (this analysis) was about 14.8 (SD 14.9) M

an interim analysis of a phase III double-blind,randomized controlled trial

Paavonen J, et al. Lancet 2007,369,2135-37

Efficacy against CIN2+ associated with HPV16 or HPV18 in the total vaccinated cohort for efficacy

	Group	N	n	Vaccine efficacy	p
CIN2+					
Based on HPV16 or HPV18 DNA in the lesion (prespecified)					
Type 16/18	Vaccine	7788	2	90.4%(53.4 to 99.3)	<0.0001
	Control	7838	21		
Type 16	Vaccine	6701	1	93.3%(47.0 to 99.9)	0.0005
	Control	6717	15		
Type 18	Vaccine	7221	1	83.3% (-78.8 to 99.9)	0.1249
	Control	7258	6		

Quadrivalent Vaccine
Selected Efficacy & Immunogenicty Protocols

005: Phase II "Proof of Concept" Efficacy (HPV 16)
007: Phase II Quadrivalent Dose-Ranging and Efficacy

013: Phase III CIN/Warts Efficacy Study (FUTURE I)
015: Phase III CIN 2/3 Efficacy Study (FUTURE II)

Adolescent/Adult Bridging Study
Adolescent Immunogenicity and Safety Study
Mid Adult Women Study

Quadrivalent HPV Vaccine Efficacy Trials by Protocol and Region

	Phase II		Phase III		
Region	Protocol 005	Protocol 007	Protocol 013	Protocol 015	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 L1 VLP vaccine; Protocols 007, 013, and 015 studied quadrivalent HPV L1 VLP vaccine.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 10, 2007 VOL. 356 NO. 19

Quadrivalent Vaccine against Human Papillomavirus to Prevent High-Grade Cervical Lesions

The FUTURE II Study Group*

ABSTRACT

CONCLUSIONS

In young women who had not been previously infected with HPV-16 or HPV-18, those in the vaccine group had a significantly lower occurrence of high-grade cervical intraepithelial neoplasia related to HPV-16 or HPV-18 than did those in the placebo group. (ClinicalTrials.gov number, NCT00092534.)

Table 3. Vaccine Efficacy against Cervical Intraepithelial Neoplasia Grade 2 or 3 or Adenocarcinoma In Situ Associated with HPV-16 or HPV-18 or Any HPV Type.*

End Point	Vaccine Group (N=6087)			Placebo Group (N=6080)			Vaccine Efficacy
	Total Subjects	No. of Cases	Rate†	Total Subjects	No. of Cases	Rate†	% (95% CI)‡
Lesions associated with HPV-16 or HPV-18							
Subjects in per-protocol susceptible population	5305	1	<0.1	5260	42§	0.3	98 (86–100)¶
Lesion type							
Cervical intraepithelial neoplasia grade 2	5305	0	0	5260	28	0.2	100 (86–100)
Cervical intraepithelial neoplasia grade 3	5305	1	<0.1	5260	29	0.2	97 (79–100)
Adenocarcinoma in situ	5305	0	0	5260	1	<0.1	100 (<0–100)
HPV type							
HPV-16	4559	1	<0.1	4408	35	0.3	97 (84–100)
HPV-18	5055	0	0	4970	11	0.1	100 (61–100)
Subjects in unrestricted susceptible population‖	5865	3	<0.1	5863	62**	0.4	95 (85–99)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Quadrivalent Vaccine against Human Papillomavirus to Prevent Anogenital Diseases

Suzanne M. Garland, M.D., Mauricio Hernandez-Avila, M.D., Cosette M. Wheeler, Ph.D., Gonzalo Perez, M.D., Diane M. Harper, M.D., M.P.H., Sepp Leodolter, M.D., Grace W.K. Tang, M.D., Daron G. Ferris, M.D., Marc Steben, M.D., Janine Bryan, Ph.D., Frank J. Taddeo, Ph.D., Radha Railkar, Ph.D., Mark T. Esser, Ph.D., Heather L. Sings, Ph.D., Micki Nelson, B.S., John Boslego, M.D., Carlos Sattler, M.D., Eliav Barr, M.D., and Laura A. Koutsky, Ph.D., for the Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) I Investigators

ABSTRACT

CONCLUSIONS

The quadrivalent vaccine significantly reduced the incidence of HPV-associated anogenital diseases in young women. (ClinicalTrials.gov number, NCT00092521.)

Table 3. Vaccine Efficacy against External Anogenital, Vaginal, and Cervical Lesions Associated with HPV-6, HPV-11, HPV-16, or HPV-18 or Regardless of HPV Type.*

End Point	Vaccine Group (N = 2723)			Placebo Group (N = 2732)			Efficacy
	No. of Subjects	No. of Cases	Rate per 100 Person-Years at Risk	No. of Subjects	No. of Cases	Rate per 100 Person-Years at Risk	
							% (95% CI)
Lesions associated with vaccine-type HPV							
Per-protocol susceptible population†							
External anogenital and vaginal lesions	2261	0	0	2279	60	1.1	100 (94–100)
According to type of lesion							
Condyloma	2261	0	0	2279	48	0.9	100 (92–100)
Vulvar condyloma	2261	0	0	2279	47	0.8	100 (92–100)
Vaginal condyloma	2261	0	0	2279	6	0.1	100 (14–100)
VIN grade 1 or VaIN grade 1	2261	0	0	2279	9	0.2	100 (49–100)
VIN grade 2 or 3 or VaIN grade 2 or 3	2261	0	0	2279	9	0.2	100 (49–100)
According to vaccine-type HPV							
HPV-6	1978	0	0	1991	41	0.8	100 (91–100)
HPV-11	1978	0	0	1991	12	0.2	100 (64–100)
HPV-16	1890	0	0	1855	12	0.3	100 (65–100)
HPV-18	2120	0	0	2136	3	0.1	100 (<0–100)
Cervical lesions	2241	0	0	2258	65‡	1.2	100 (94–100)
According to grade of lesion							
CIN grade 1	2241	0	0	2258	49	0.9	100 (92–100)
CIN grade 2	2241	0	0	2258	21	0.4	100 (81–100)
CIN grade 3	2241	0	0	2258	17	0.3	100 (76–100)
Adenocarcinoma in situ	2241	0	0	2258	6	0.1	100 (15–100)

Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of CIN 2/3 and adenocarcinoma in situ: a combined analysis of four randomized clinical trials

- N = 20583, n = 17129 per protocol
- Vaccine efficacy was 99% for the primary endpoint
- In an intention-to-treat analysis of all randomised women (including those who were HPV16/18 naïve or HPV16/18-infected at day 1). The efficacy was 44% (95% CI 31-55

The Future II study group. Lancet 2007,369:1861-8

Efficacy of a quadrivalent vaccine against high-grade vulval and vaginal lesions: a combined analysis of three randomized clinical trials

	Vaccine (n=9087)			Placebo (n=9087)			Efficacy (95% CI)
	Number in given population	Cases	Rate (cases per 100 person-years at risk)	Number in given population	Cases	Rate (cases per 100 person-years at risk)	
Per-protocol susceptible population*							
HPV16-related or HPV18-related VIN2/3 or VaIN2/3	7811	0	0·00	7785	15†	0·08	100% (72 to 100)
HPV16-related VIN2/3 or VaIN2/3	6687	0	0·00	6500	13	0·08	100% (68 to 100)
HPV18-related VIN2/3 or VaIN2/3	7450	0	0·00	7381	2	0·01	100% (-427 to 100)
By lesion type							
HPV16-related or HPV18-related VIN2/3	7811	0	0·00	7785	8	0·04	100% (42 to 100)
HPV16-related VIN2/3	6687	0	0·00	6500	7	0·04	100% (33 to 100)
HPV18-related VIN2/3	7450	0	0·00	7381	1	0·01	100% (<-999 to 100)
HPV16-related or HPV18-related VaIN2/3	7811	0	0·00	7785	7	0·04	100% (31 to 100)
HPV16-related VaIN2/3	6687	0	0·00	6500	6	0·04	100% (18 to 100)
HPV18-related VaIN2/3	7450	0	0·00	7381	1	0·01	100% (<-999 to 100)

Joura E et al Lancet 2007,369:1693-702

Immunogenicity Data

The main basis of protection is neutralizing antibody

The minimum protective antibody threshold is not known

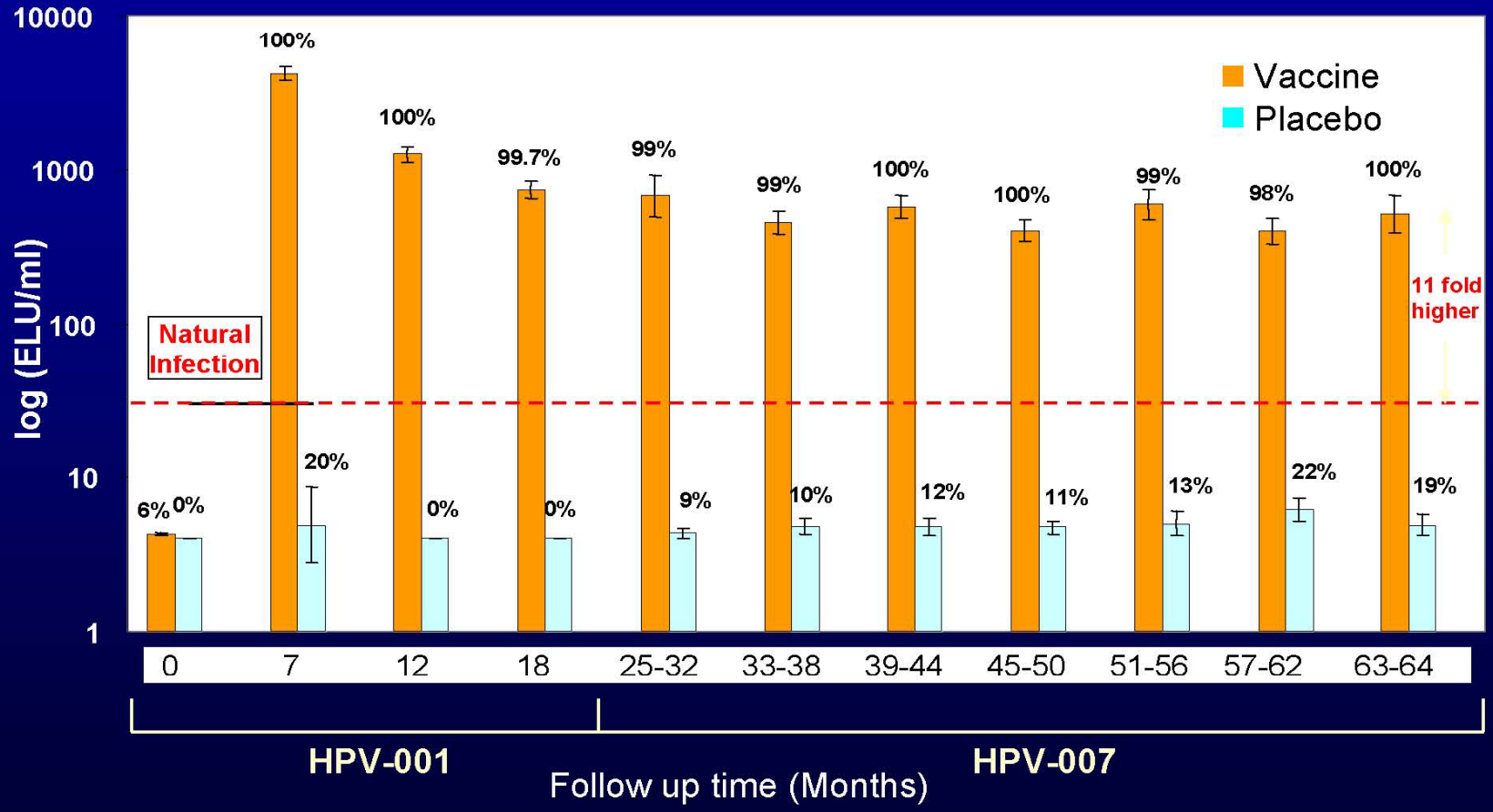
Serologic tests for HPV antibody not standardized

- 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

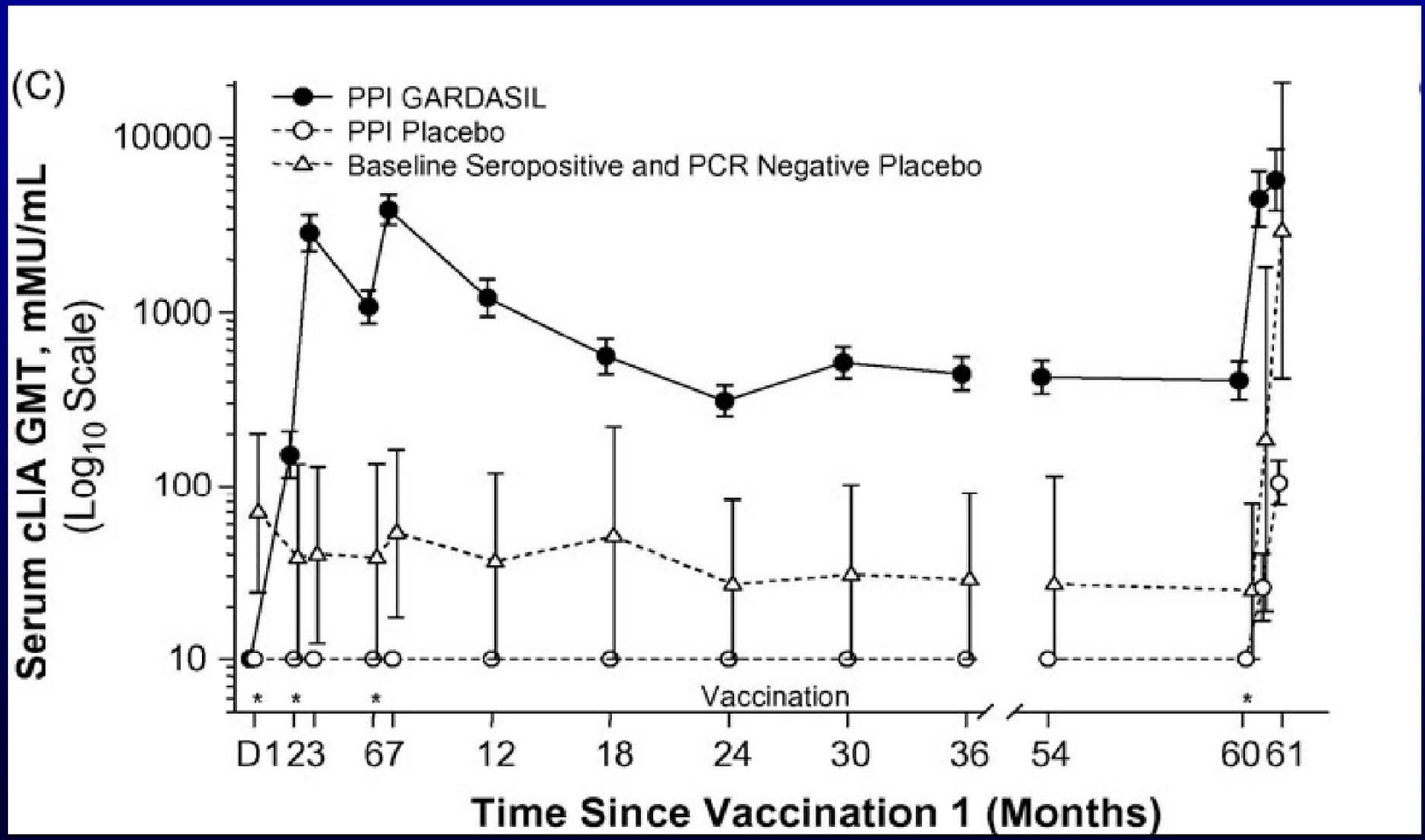
Bivalent HPV Vaccine

HPV 16 Seropositivity and GMTs through 5 Years



Dubin, presented at ACIP meeting, Feb 2007

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

- Seroconversion rates similar (>99%)
- GMTs 2- fold higher

Quadrivalent HPV Vaccine Immunogenicity Bridging

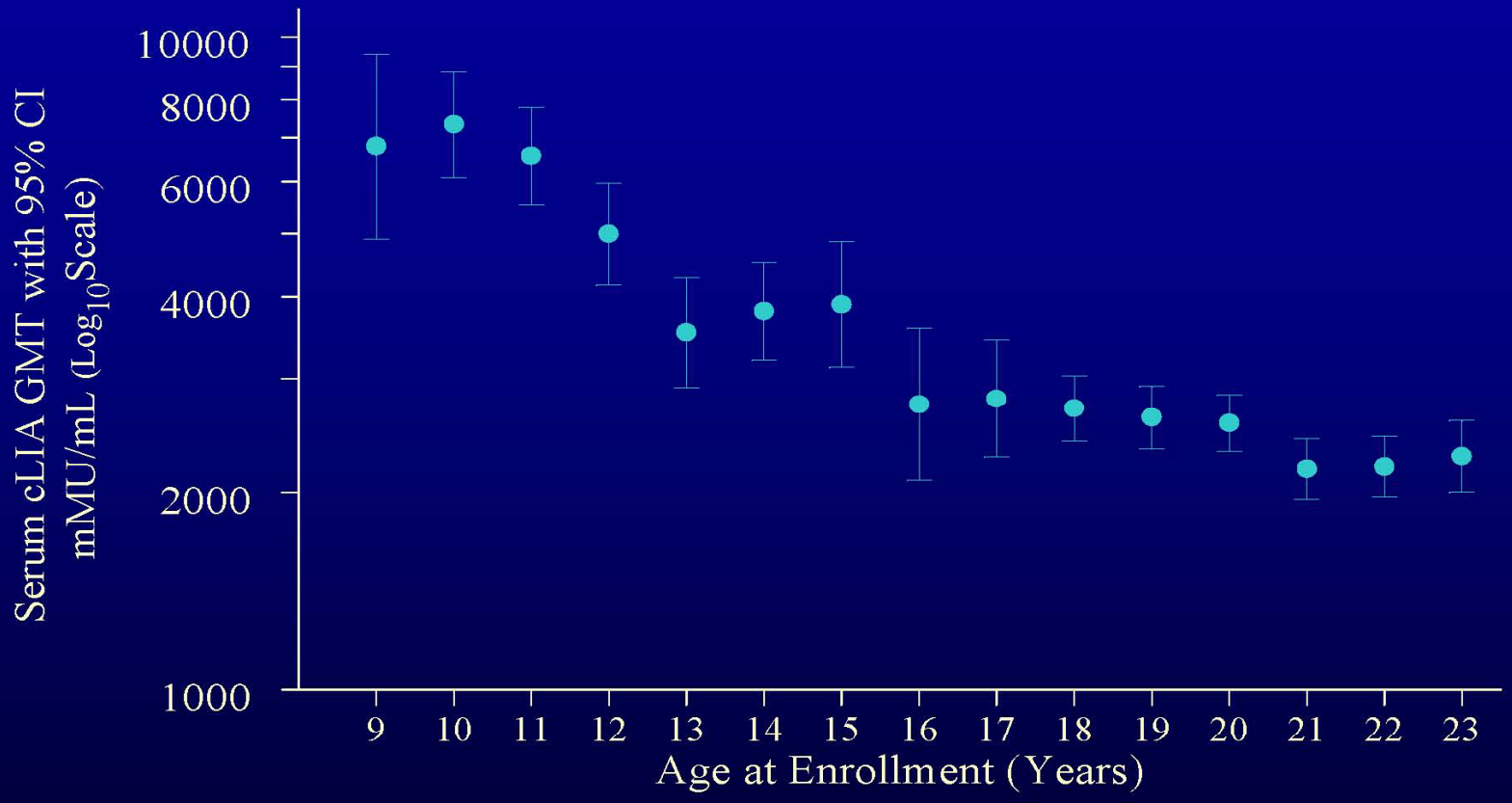
10-15 year-olds, 16-23 year-old Females

	Girls 10-15 years		Boys 10-15 years		Women 16-23 years	
Assay (cLIA)	N	GMT* mMU/mL	N	GMT mMU/mL	N	GMT mMU/mL
Anti-HPV 6	423	959	428	1041	320	575
Anti-HPV 11	423	1220	428	1318	320	706
Anti-HPV 16	424	4697	427	5638	306	2548
Anti-HPV 18	426	916	429	1212	340	453

Block *et al.* Pediatrics 2006:118

Geometric mean titers one month after dose 3; mMU: milli-Merck units

Anti-HPV 16 Antibody Titers after 3 Doses by Age at Enrollment, Quadrivalent HPV vaccine



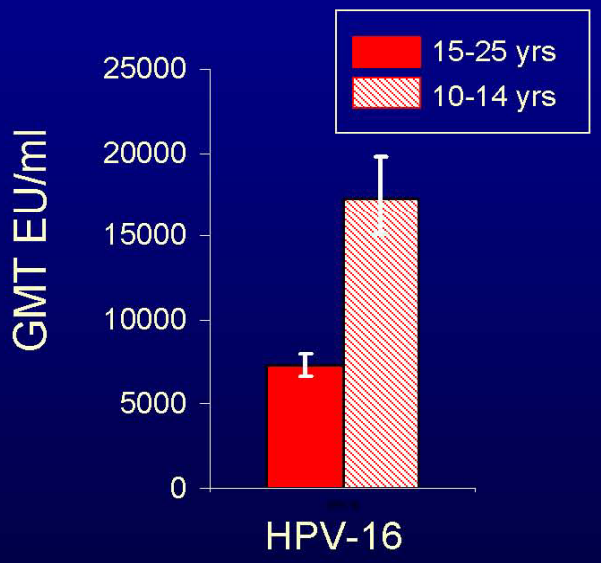
Number of Subjects Evauable (n)

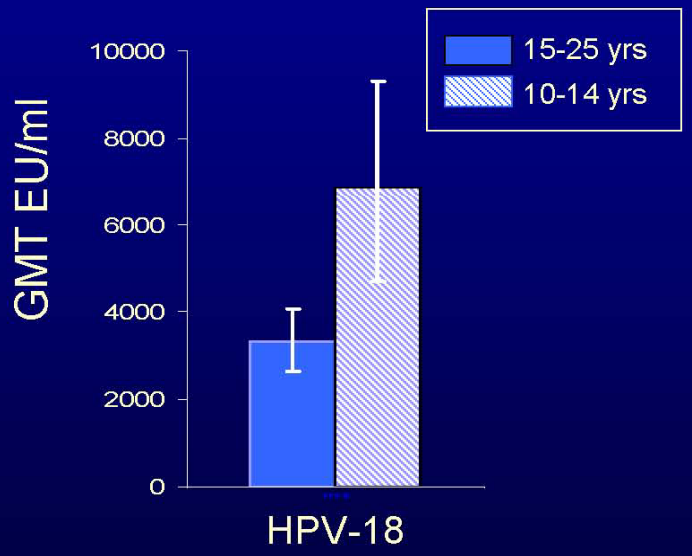
9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
67	131	165	142	165	150	109	80	135	423	506	595	550	527	375

Bivalent HPV Vaccine Immunogenicity Bridging

10-14 year-old and 15-25 year-old Females

Geometric mean titers one month after dose 3





Dubin *et al*, ICAAC 2005

Safety of a Quadrivalent HPV Vaccine in Preadolescents and Adolescents

TABLE 5. Adverse Experience Summary Days 1–15 Postdose 1, 2 and 3 and Across All Vaccinations

	Postdose 1		Postdose 2		Postdose 3		Across All Vaccinations	
	Vaccine	Non-Aluminum Placebo	Vaccine	Non-Aluminum Placebo	Vaccine	Non-Aluminum Placebo	Vaccine	Non-Aluminum Placebo
Subjects with follow-up	1165	584	1139	564	1120	559	1165	584
No. (%)* of subjects								
With 1 or more AE	779 (66.9)	312 (53.4)	627 (55.0)	200 (35.5)	577 (51.5)	191 (34.2)	963 (82.7)	392 (67.1)
Injection-site AE	663 (56.9)	198 (33.9)	555 (48.7)	131 (23.2)	517 (46.2)	137 (24.5)	877 (75.3)	292 (50.0)
Erythema†	91 (7.8)	42 (7.2)	105 (9.2)	31 (5.5)	123 (11.0)	30 (5.4)	237 (20.3)	77 (13.2)‡
Pain†	623 (53.5)	180 (30.8)	532 (46.7)	114 (20.2)	494 (44.1)	124 (22.2)	853 (73.2)	265 (45.4)‡
Swelling†	91 (7.8)	27 (4.6)	106 (9.3)	13 (2.3)	135 (12.1)	19 (3.4)	241 (20.7)	45 (7.7)‡
Systemic AE	377 (32.4)	199 (34.1)	202 (17.7)	97 (17.2)	168 (15.0)	84 (15.0)	541 (46.4)	260 (44.5)
With serious AE	2 (0.2)	0 (0.0)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.4)	0 (0.0)
With serious vaccine-related AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fever								
Subjects with follow-up	1153	574	1121	554	1105	552	1157	579
<100° F or normal†	1122 (97.3)	557 (97.0)	1092 (97.4)	540 (97.5)	1075 (97.3)	538 (97.5)	1074 (92.8)	541 (93.4)
≥100° F†	31 (2.7)	17 (3.0)	29 (2.6)	14 (2.5)	30 (2.7)	14 (2.5)	83 (7.2)	38 (6.6)§

*Percentages are calculated based on the number of subjects with follow-up.

†Adverse experiences reported days 1 to 5 following any vaccination visit.

‡$P < 0.001$, for comparison of vaccination groups across all vaccination visits.

§$P = 0.638$, for comparison of vaccination groups across all vaccination visits.

AE indicates adverse experience.

Reisenger KS,et al. Ped Inf Dis J, 2007,26:1-8

Table 8. Systemic clinical adverse events among female participants aged 9-23 years in the population with detailed safety data, days 1-15 after vaccination with quadrivalent human papillomavirus (HPV) vaccine

Adverse event (1-15 days postvaccination)	Quadrivalent HPV vaccine (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 infectior	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	%

Source: Food and Drug Administration. Product approval information-licensing action, package insert: GARDASIL (quarivalent human papillomavirus types 6, 11, 16, and 18), Merck & Co. Whitehouse Station, NJ: Food and Drug Administration; 2006. Available at http://www.fda.gov/cber/label/HPVmer060806LB.pdf.

High sustained efficacy of a prophylactic quadri-valent human papillomavirus types 6/11/16/18 LI virus-like particle vaccine through 5 years of follow-up

Villa LL, *et al*. British Journal of Cancer,2006 ,1-8

Bivalent vaccine efficacy (IIb) in extended follow up on cytological end point

ANCET
T ARTICLE

Links

Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle
vaccine against human papillomavirus types 16 and 18: follow-up from a randomized control trial.

Harper DM, *et al*

Lancet. 2006 Apr 15;367(9518):1247-55.

MMWR™
Morbidity and Mortality Weekly Report
Recommendations and Reports
March 23, 2007 / Vol. 56 / RR-2

Quadrivalent Human Papillomavirus Vaccine

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

"The primary endpoint and the basis for licensure was the combined incidence of HPV 16 and 18 related CIN 2/3 or AIS.These endpoints served as surrogate markersfor cervical cancer."

ACOG

Committee on Adolescent Health Care and The ACOG Working Group on Immunization

This information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

The College wishes to thank

Committee Opinion

Number 344, September 2006

Human Papillomavirus Vaccination

"Studies of the quadrivalent HPV vaccine have shown that in subjects naive to the vaccine genotypes who followed protocol, the vaccine was 100% effective in preventing cervical intraepithelial neoplasia CIN2, CIN3 and condylomatous vulvar disease related to the HPV genotypes covered by the vaccine"

: ACOG, Number 344, September 2006

Recommendations for Routine Use and Catch-Up:

- Routine Vaccination of Females Aged 11-12 years.

  - ACIP recommends routine vaccination of females aged 11-12 years with 3 doses of quadrivalent HPV vaccine.

  - The vaccination series can be started as young as age 9 years.

- Catch-Up Vaccination of Females Aged 13-26 Years.

SAFETY, EFFICACY, AND IMMUNOGENICITY OF QUADRIVALENT HPV VACCINE (GARDASIL™) IN WOMEN AGED 24-45

AFFILIATIONS:

1. *Instituto Nacional de Cancerología, Bogotá, Colombia*
2. *Merck & Co., Inc., West Point PA, USA*

Joaquin Luna[1], Alfred Saah[2], Sara Hood[2], Oliver Bautista[2], and Eliav Barr[2] for the FUTURE III Investigators

24th International Papillomavirus Congress

November 3-9, 2007

Beijing, China

Presentation #PA1-04

METHODS

PROTOCOL 019 (FUTURE III) : STUDY DESCRIPTION

- Multi-center, international study
- Randomization (1:1 ratio) to GARDASIL or placebo (1:1 stratification to 24 to 34 or 35 to 45 year-olds)
- In 3,817 24- to 45-year-old women
  - No history of LEEP or hysterectomy
  - No history of biopsy-diagnosed cervical HPV disease in past 5 years
  - No history of genital warts
  - Lifetime sexual partner number not an inclusion criterion
- Pap testing and cervicovaginal sampling at ~6 month intervals for a total of 48 months
  - Colposcopy for ≥ASC-US

PROTOCOL 019: EFFICACY DEMONSTRATION ENDPOINTS

- Primary analysis: per-protocol efficacy population
- Co-Primary endpoints
  - First co-primary: Combined incidence of persistent infection, CIN, or external genital lesions (EGLs) caused by HPV 6, 11, 16, or 18
  - Second co-primary: Combined incidence of persistent infection, CIN or EGLs caused by HPV 16 or 18
- Secondary endpoint
  - Combined incidence of persistent infection, CIN, or EGLs caused by HPV 6 or 11

PROTOCOL 019: EFFICACY ANALYSIS POPULATION

- Per-protocol efficacy population
  - Received all three vaccinations
  - Seronegative at day 1 and PCR negative at day 1 and month 7 to the appropriate HPV types
  - Did not deviate from the protocol
  - Endpoints were counted starting at month 7

OBJECTIVE

To evaluate the tolerability, efficacy and immunogenicity of quadrivalent HPV vaccine in women 24-45 years of age.

Baseline Demographics

	24-34 Year Strata (N =1907)	35-45 Year Strata (N = 1906)	Total (N = 3813)
Mean age (years)	29	40	34
Region			
Asia-Pacific	566 (29.7%)	616 (32.3%)	1182 (31.0%)
Europe	287 (15.0%)	194 (10.2%)	481 (12.6%)
Latin America	766 (40.2%)	842 (44.2%)	1608 (42.2%)
North America	288 (15.1%)	254 (13.3%)	542 (14.2%)

Enrollment by Country and by stratum

Country	24-34 Year Strata	35-45 Year Strata	Total
Colombia	766	842	1608
France	62	44	106
Germany	194	116	310
Philippines	201	199	400
Spain	31	34	65
Thailand	365	417	782
United States	288	254	542
All Countries	1907	1906	3813

Baseline Demographics

Day 1 Parameter	Global Total N=3816		Asia Pacific N=1181		Europe N=481		Latin America N=1610		North America N=544	
	24-34 1911	35-45 1905	24-34 566	35-45 615	24-34 288	35-45 193	24-34 767	35-45 843	24-34 290	35-45 254
Mean Age	29	40	29	40	28	40	29	40	28	40
Mean Age at Sexual Debut	18	20	20	22	18	18	18	19	17	17

Baseline Demographics

Day 1 Parameter	Global Total N=3816		Asia Pacific N=1181		Europe N=481		Latin America N=1610		North America N=544	
	24-34 N=1911	35-45 N=1905	24-34 N=566	35-45 N=615	24-34 N=288	35-45 N=193	24-34 N=767	35-45 N=843	24-34 N=290	35-45 N=254
Past Pregnancy	37.5 %	62.5 %	15.5 %	21.5 %	1.6%	4.5%	14.6 %	28.5%	5.8%	7.9%
% Using Hormonal Contraception	21.0 %	9.9%	6.7%	4.3%	5.2%	1.8%	5.3%	1.9%	4.0%	1.8%
Chlamydia (From Pap)	2.1%	1.0%	0.9%	0.3%	0.1%	0 .0%	0.9%	0.7%	0.2%	0.0%

Day 1 Pap Results by Country

Country	Colombia	France	Germany	Philippines	Spain	Thailand	USA
Normal	90.0%	78.8%	88.4%	94.0%	88.2%	92.1%	88.7%
AGC	0.0%	1.8%	0.0%	0.0%	1.5%	0.0%	0.2%
ASC-H	0.1%	0.9%	0.3%	1.0%	0.0%	0.1%	1.1%
ASC-US	2.9%	6.2%	4.4%	1.8%	1.5%	2.4%	3.6%
ASC-US, HPV-	1.6%	2.7%	2.2%	1.6%	1.5%	2.1%	2.3%
ASC-US, Retest	0.1%	0.0%	0.3%	0.0%	0.0%	0.1%	0.0%
ASC-US HPV+	1.2%	3.5%	1.9%	0.3%	0.0%	0.3%	1.1%
LSIL	3.5%	5.3%	1.9%	1.3%	7.4%	2.2%	2.9%
HSIL	0.4%	0.9%	0.6%	0.0%	0.0%	0.8%	0.2%
Cancer	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

RESULTS

PROTOCOL 019: BASELINE CHARACTERISTICS

Parameter	Vaccine (N = 1,911)	Placebo (N = 1,908)
Ethnicity		
Asian	31%	31%
Black	5%	4%
Hispanic	43%	43%
White	20%	21%
Other	1%	1%
Country of Origin		
Colombia	804	806
Thailand	391	391
USA	271	274
Philippines	200	200
Germany	156	155
France	56	50
Spain	33	31

PROTOCOL 019: SEXUAL HISTORY/MARITAL STATUS DATA

Parameter	Vaccine (N = 1,911)	Placebo (N = 1,908)
% Non-Virgins	100%	100%
Median (Range) Age at Sexual Debut (Years)	18 (5 to 39)	18 (4 to 39)
Lifetime Number of Partners		
0 to 2	58%	58%
2 to 4	19%	19%
>4	23%	23%
Marital Status		
Never Married	18%	18%
Separated/Divorced	8%	7%
Widowed	1%	1%
Permanent Relationship	28%	27%
Married – 1st marriage	40%	42%
Married – 2nd or higher marriage	5%	6%

PRIMARY EFFICACY RESULTS

Combined incidence of disease related to HPV 6/11/16/18

Population	Vaccine	Placebo	Efficacy	95% CI	P-value
P019 Mid-Adult Women†	4	41	91%	74, 98	<0.001
P007 Young-Adult Women‡	1	26	96%	78, 100	<0.001

†P019: 24- to 45-Year-Old Women; mean of 1.65 years' follow-up
‡P007: 16- to 23-Year-Old Women; mean of 2.33 years' follow-up

PRIMARY EFFICACY RESULTS (CONT)

Combined incidence of disease related to HPV 6/11/16/18

Population	Vaccine		Placebo		% Reduction	95% CI	P-value
	Cases	PYR	Cases	PYR			
All Subjects	**4**	**2,721**	**41**	**2,654**	**91%**	**74, 98**	**<0.001**
24- to 34-Year-Olds	2	1,329	24	1,301	92%	67, 99	<0.001
35- to 45-Year-Olds	2	1,393	17	1,353	89%	52, 99	<0.001

PYR = person years at risk.

Combined incidence of disease (primary and secondary endpoints)

Endpoint	Vaccine		Placebo		% Reduction	95% CI	P-value
	Cases	PYR	Cases	PYR			
HPV6/11/16/18	**4**	**2,721**	**41**	**2,654**	**91%**	**74, 98**	**<0.001**
HPV16/18	4	2,700	23	2,621	83%	51, 96	<0.001
HPV6/11	0	2,243	19	2,204	100%	79, 100	<0.001

PYR = person years at risk.

HPV16/18-RELATED ABNORMAL PAP TESTS

Endpoint	Vaccine	Placebo	% Reduction	95% CI
ASC-US(HR+) or Worse	**1**	**17**	**94%**	**63, 100**
ASC-US HR(+)	1	7	86%	-10, 100
LSIL or Worse	0	11	100%	61, 100
LSIL	0	10	100%	56, 100
ASC-H	0	1	100%	–
HSIL	0	0	–	–

ASC-US = atypical squamous cells of undetermined significance; HR = high-risk; LSIL = low-grade squamous intraepithelial neoplasia; HSIL = high-grade squamous intraepithelial neoplasia; ASC-H = atypical squamous cells, cannot rule out HSIL.

PROTOCOL 019: SAFETY PROFILE – PRESPECIFIED ENDPOINTS

Parameter	Vaccine		Placebo		Risk Difference (G-P)	95% CI	P-Value†
	n	%	n	%			
Subjects With Follow-up	1,889		1,886				
SAEs	3	0.2	7	0.4	-0.2	(-0.6, 0.1)	0.204
VR-SAEs	0	0.0	0	0.0	0.0	(-0.2, 0.2)	1.000
Injection Site AEs	1,443	76.4	1,210	64.2	12.2	(9.3, 15.1)	
Erythema	273	14.5	200	10.6	3.8	(1.7, 6.0)	<0.001
Pain	1,423	75.3	1,170	62.0	13.3	(10.3, 16.2)	<0.001
Pruritus	31	1.6	25	1.3	0.3	(-0.5, 1.1)	
Swelling	353	18.7	214	11.3	7.3	(5.1, 9.6)	<0.001
Warmth	18	1.0	14	0.7	0.2	(-0.4, 0.8)	
Systemic AEs							
Fever (≥100°F)	203	10.8	213	11.3	-0.6	(-2.6, 1.4)	0.575

† Unadjusted for multiple comparisons; SAE = Serious Adverse Experience; R-SAEs = Vaccine-related SAEs

Conclusion

- HPV vaccine (Quadrivalent) is safe and is approved for use to prevent cervical, vulva,vagina cancer and genital wart lesions in an HPV niave women(16-26 yrs) and boys and girls (9-17 yrs)
- First demonstration efficacy of quadri-valent HPV vaccine in age >26
- Bivalent HPV vaccine is efficacious agaist cervical cancer in HPV niave women (15-25 years,and 10-14 years)
- Prevention of cervical cancer require both screening and vaccination
- Introduction of this vaccine into developing countries remains a challenge

Ongoing or Planned Studies Quadrivalent HPV Vaccine

- Efficacy trials
  - Women 24-45 yrs (N ~ 3800)
  - Men 16-26 yrs (N ~ 4000)
  - Follow-up of adolescent trials (N~1500)
- Local registration trials
- Phase IV program
  - Long term follow-up of phase III Nordic cancer registry
  - Demonstrate population impact of mass vaccination programs on overall rates of disease - General population of Norway
  - Post marketing surveillance in US (N ~ 44,000)
- Alternative dosing schedules

Ongoing or Planned Studies Bivalent HPV Vaccine

- Efficacy trials
  - Women >25 yrs of age (N ~ 5700)
  - Women 18-25 yrs Costa Rica (NCI sponsored; N~7500)
- Local registration trials
- Phase IV program
  - Long term pre-cancer/cancer surveillance in Finland of phase III cohort
  - Community randomized trial to evaluate herd immunity 60-70,000) – start in fall 2007
  - Other phase IV studies under development
- Comparative Immunogenicity
  - Bivalent vs quadrivalent (N~ 1000)

Ongoing or Planned Studies Safety and Immunogenicity in HIV infected and other Populations

Quadrivalent

- HIV+ men (N =100)
- HIV+ women (N = 396)
- HIV+ children 7-11 years (N=120)
- Solid organ transplant (N= 200)

Bivalent

- HIV+ women

Ongoing or Planned Studies

	Quadrivalent	Bivalent
Followup phase III trials	x	x
Efficacy in females >25 yrs	x	x
Efficacy trials in men 16-26 yrs	x	
Concomitant administration	x	x
Comparative immunogenicity studies		x
Safety & immunogenicity in HIV+ women (and men)	x	x
Phase 4: long term follow-up	x	x

What next? WHO-UNFPA program and policy guidance on HPV vaccines (March 2006)

- Access to HPV vaccines is critical public health need for all women particular less developed countries
- Affordability, feasibility and acceptability issue are the some of the major challenges
- Sexual and reproductive program will need to develop new strategies for counseling adolescents and women
- Advocacy, information and communication- could be unawareness or high expectation on part of the community etc.

2006

The Bill & Melinda Gates Foundation announced a $27.8 million grant to PATH (Program for Appropriate Technology in Health)

to

oversee pilot HPV vaccine introduction projects in India, Peru, Uganda and Vietnam.

Target population and delivery strategies

- Girls
- Age 9-13
- School based Program
- Child health day
- Community outreach
- Health facility based

PATH's formative research

	India (n~1,650)	Peru (n~770)	Uganda (n~850)	Vietnam (n~830)
Individual recipients	Girls 10–14	Children 9–12, adolescents 13–16	5th grade girls and boys; out-of-school girls 10–12	Girls 11–14
Interpersonal influencers	Parents, teachers	Parents, teachers	Parents, teachers	Parents, teachers
Community	NGOs, religious leaders, local healers, media	Community leaders, religious groups, NGOs, media	Community leaders, religious groups	People's Committees, Women's Union, Youth Union
Institution (health, education)	Govt. health and educ. officials; health workers	Govt. health and educ. officials; health worker	District HOs and EOs; school principals and head teachers	Provincial and district hlth. and educ. officials
Policy	State and federal officials	National and regional officials	National officials and multilaterals	National and provincial officials
Data collection	**Began July 07**	**Completed February 07**	**Completed July 07**	**Began July 07**

Vivien Tsu ,PATH, Geneva,2007

Challenges of introducing HPV vaccine in developing countries (1)

- Burden of disease and care (Medical cost) in the country are mostly unknown
- Which target population should be the first to focused
- Acceptability issue for parent and adolescents need to be assessed which depends on culture and norms as well

Challenges of introducing HPV vaccine in developing countries (2)

- Introductory issues: Health care delivery system
  - school based vaccination program, comprehensive package with counseling
  - Logistic-cold chain,
- Cost, cost effectiveness of the vaccine over time
- Competing with national pap screening or other programs in the country

Vaccine introduction requires