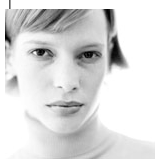
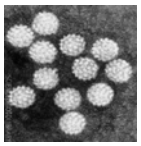
Licensing a vaccine to prevent cancer: Clinical trials of Human papillomavirus vaccines



Shelly McNeil, MD, FRCPC
Associate Professor of Medicine
Clinical Research Scholar
Canadian Centre for Vaccinology
Dalhousie University

Objectives

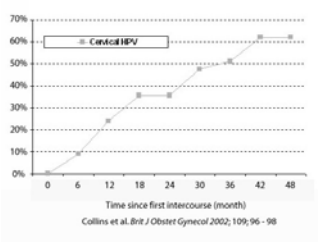
- To discuss the epidemiology of HPV infection and its associated spectrum of disease
- To review the clinical trials evidence of safety, immunogenicity, efficacy and potential impact of HPV vaccines for primary cervical cancer prevention
- To discuss the outstanding issues/questions mandating Phase IV post-marketing studies



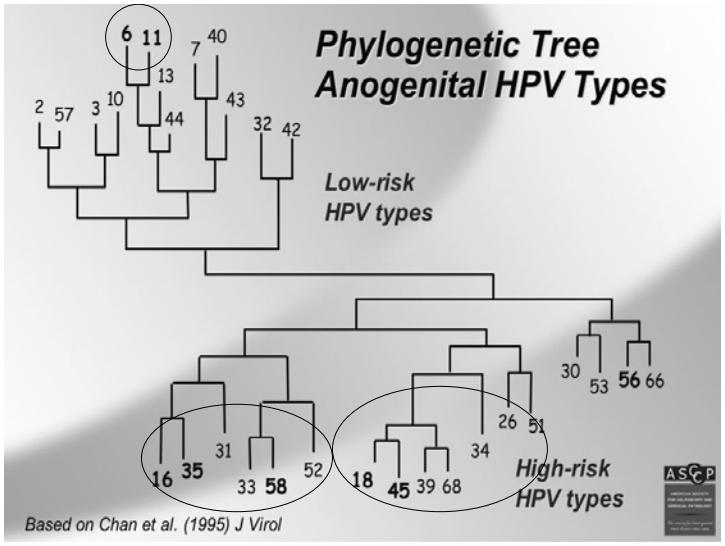
Human papillomavirus (HPV)

- **non-enveloped, dsDNA virus**
- **> 100 types; 30-40 infect human genital tract**
- **The most common STI**
- **~75% of adults infected over lifetime**

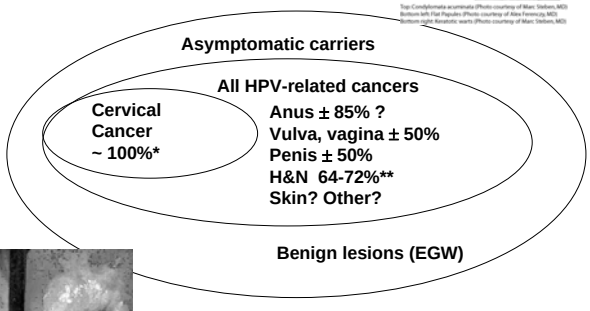
De Villiers et al. (2004) Virology

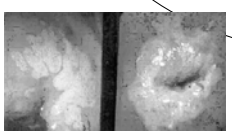


Acquisition of HPV following sexual debut

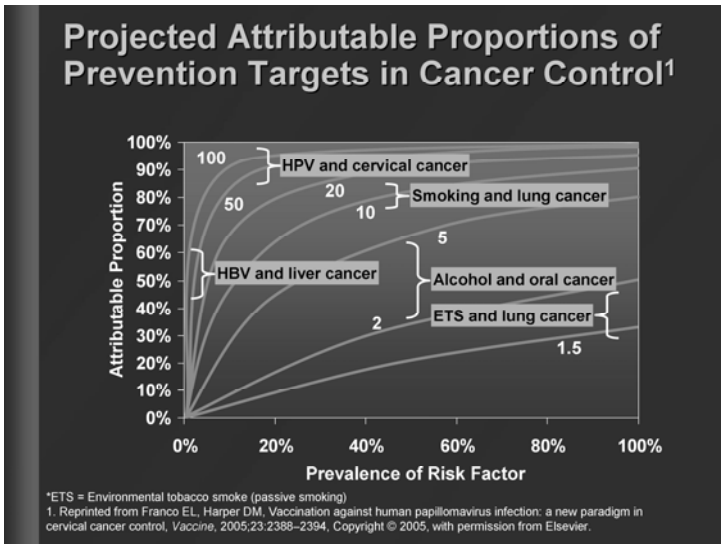


Spectrum of HPV-related Disease

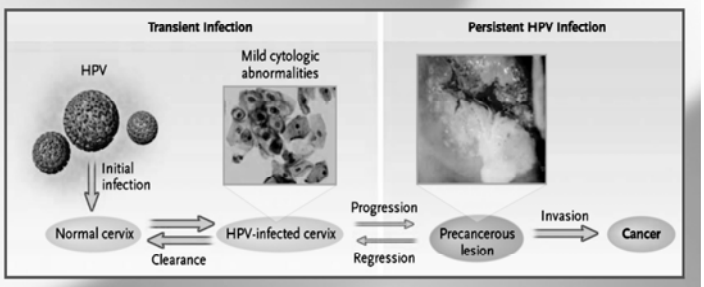




*Walboomers et al. J Pathol 1999;189:12-19
**D'Souza et al. NEJM 2007;356:1944-56



Natural History of HPV Infections



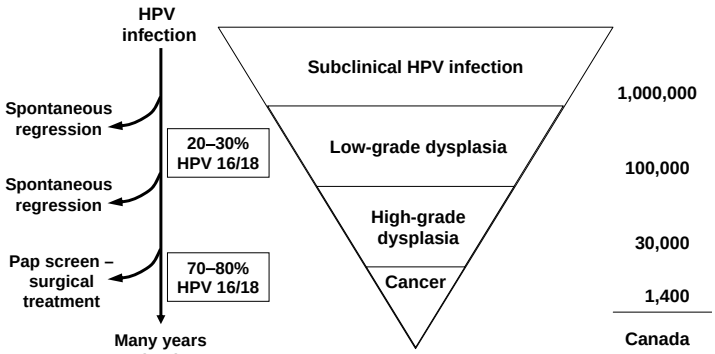
Wright and Schiffman (2003) NEJM

Persistence of HPV Infections

% persistent over time

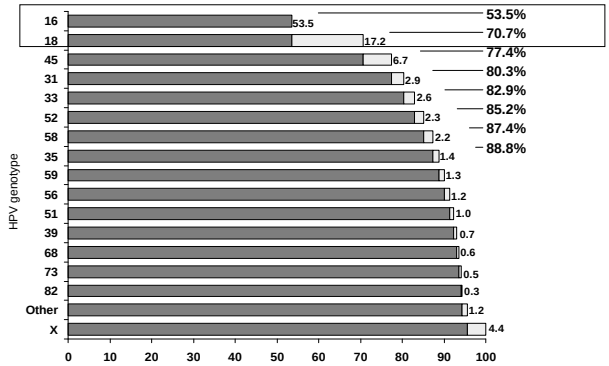
Author	Age	Type Inf'n	6 mos	12 mos	24 mos
Woodman	20	I	24	4	<1
Moscicki	20	P	50	30	10
Ho	20	I		30	9
Sun	34	I/P	50	35	18
Ahdieh	32	I/P	47	36	19
Richardson	23	I		62	

The Path to Cervical Cancer



Ref: Health Canada, *Cervical Cancer Screening in Canada: 1998 Surveillance report*; Canadian Cancer Society/National Cancer Institute of Canada: *Canadian Cancer Statistics 2005;* PHAC, *Women's Health Surveillance Report: cancer of the uterine cervix, 2003*

HPV 16 and 18 account for 70.7% of cervical cancer cases worldwide

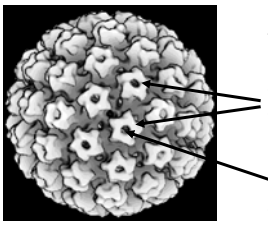


Cervical cancer cases attributed to the most frequent HPV genotypes (%)

Munoz N *et al. Int J Cancer* 2004; 111: 278–85.

The Virus Particle

The virus shell or coat has 2 proteins L1 and L2



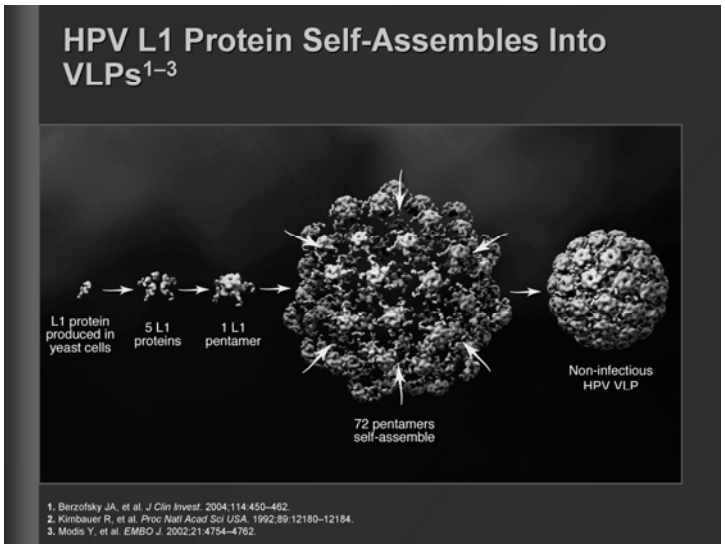
The virus shell consists of 72 pentamers each of 5 molecules of L1 that stud the surface of the particle

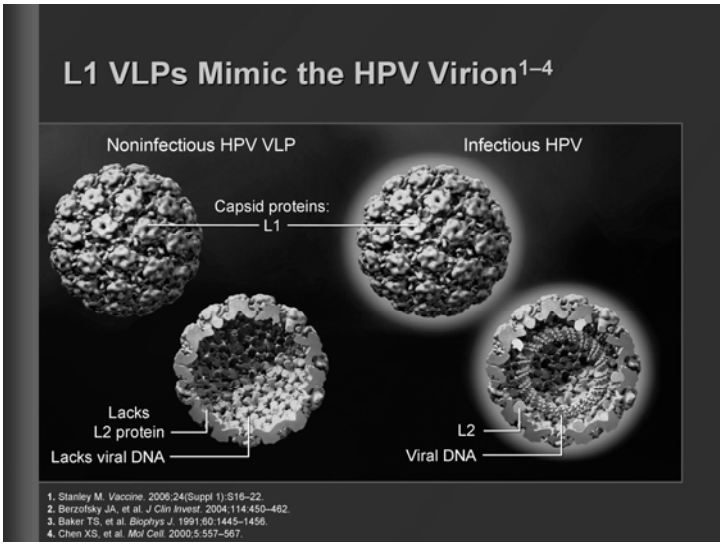
L2 sits deep in the dimple in the centre of the rosette

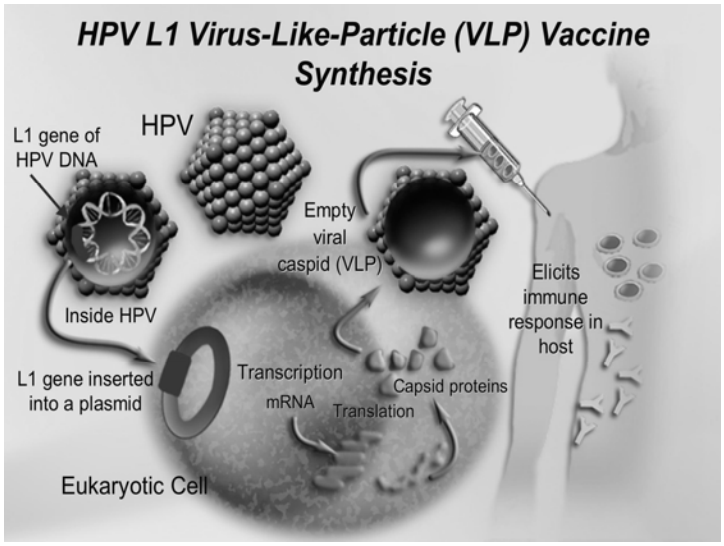
Virus neutralising antibodies recognise conformational epitopes* in L1

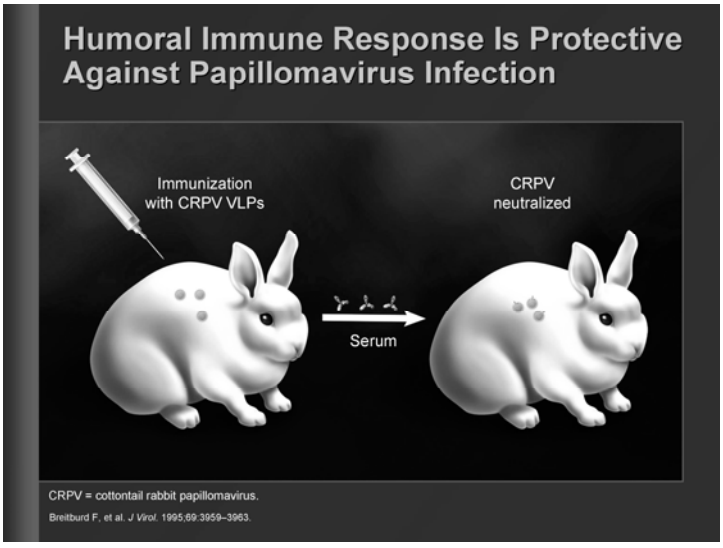
Neutralising antibodies to L2 are not made in natural infections

*Epitopes = antigenic determinants





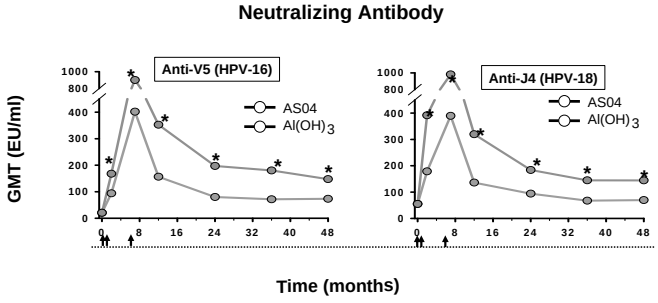




HPV Vaccines

	Bivalent	Quadrivalent
Reference	Harper DM et al., Lancet, 2004 Harper DM et al., Lancet, 2006	Villa LL et al., Lancet Onc ,2005 Villa LL et al., Vaccine, 2006 FUTURE I and II NEJM 2007;356:1915
Vaccine Type	Bivalent HPV-16 and HPV-18 VLP L1 capsid component	Quadrivalent HPV-6/11/16/18 VLP L1 capsid component
Expression system	Hi-5 Baculovirus	Yeast
Concentration	20 µg HPV 16 20 µg HPV 18	20 µg HPV 6 40 µg HPV 11 40 µg HPV 16 20 µg HPV 18
Adjuvant	AS04 : 500 µg Aluminum Hydroxide 50 µg 3-deacylated Monophosphoryl Lipid A	Alum: 225 µg Aluminum Hydroxyphosphate Sulfate
Placebo	Alum	Alum

AS04 versus Aluminum



Enhanced and Sustained Immunogenicity Over 4 Years

*** Statistically significant**

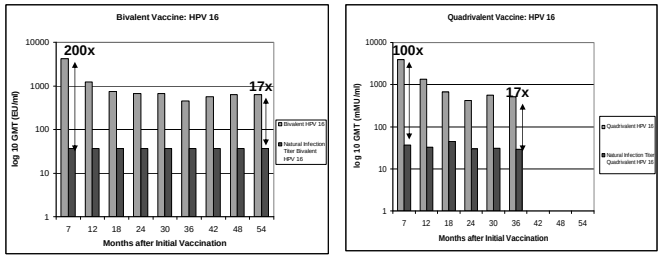
Giannini SL et al. Vaccine 2006

Safety: Comparison of Vaccine to Control Groups

	Bivalent Vaccine	Quadrivalent Vaccine
Injection Site Pain, Erythema, Edema	Increased Acceptable	Increased Acceptable
General adverse events	NS	NS
New Onset Chronic Diseases > 4 years	NS	NS
Serious Adverse Events	NS	NS

NS – not significantly different from controls

Immunogenicity – HPV 16



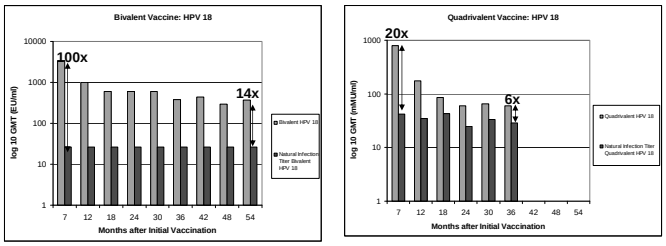
Bivalent Vaccine **Quadrivalent Vaccine**

- ☐ Vaccine Recipients
- ☐ Type Specific Natural Infection Titers

Harper DM et al., Lancet, 2004
Harper DM et al., Lancet, 2006
Villa LL et al, Lancet Onc 2005
Villa LL et al, Vaccine 2006

Slide provided courtesy of Dr. Diane Harper

Immunogenicity – HPV 18



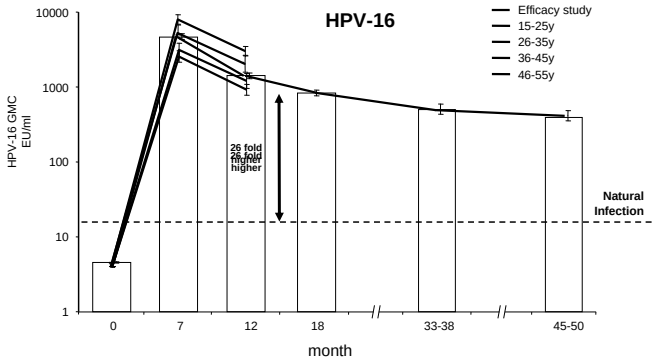
Bivalent Vaccine **Quadrivalent Vaccine**

- ☐ Vaccine Recipients
- ☐ Type Specific Natural Infection Titers

Harper DM et al., Lancet, 2004
Harper DM et al., Lancet, 2006
Villa LL et al, Lancet Onc 2005
Villa LL et al, Vaccine 2006

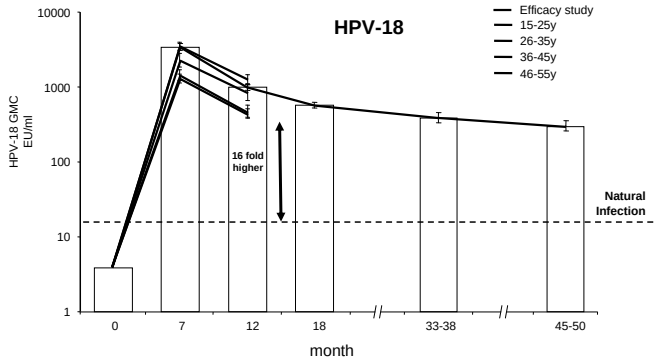
Slide provided courtesy of Dr. Diane Harper

Bivalent Immunogenicity – HPV 16 26 – 55-year-old female (OLDER)



Harper, et al. Lancet 2006; 367:1247-55.

Bivalent Immunogenicity – HPV 18 26 – 55-year-old female (OLDER)



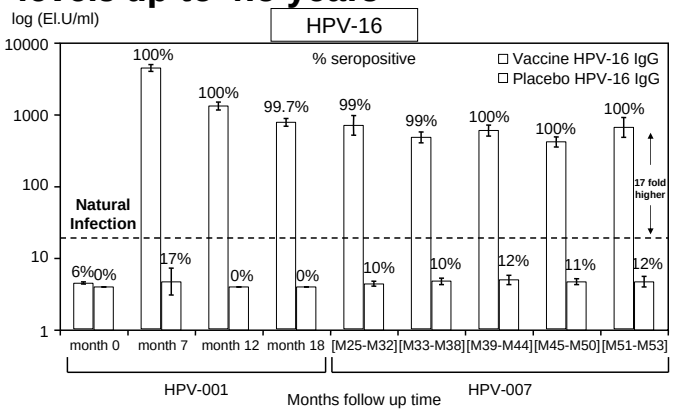
Harper, et al. Lancet 2006; 367:1247-55.

Immunogenicity Bridging

- **9–15-year-old females (both vaccines)**
- **9–15-year-old boys (quadrivalent)**
- **In general, higher GMT for children than for adolescents**
  - **No comparison group for natural infection titer reported for either vaccine**

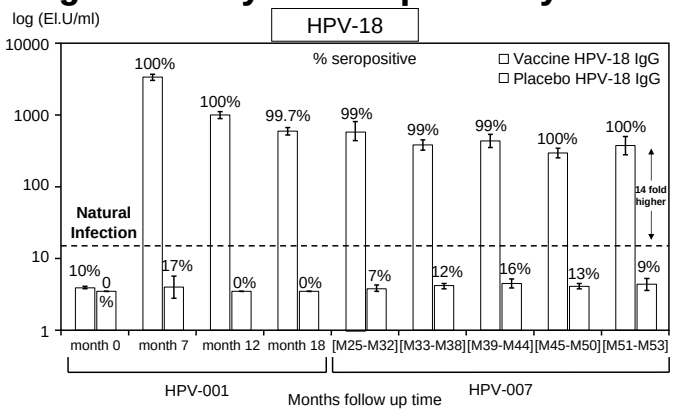
How long do the antibodies last?

GSK studies 001 & 007:Sustained seropositivity and High antibody levels up to 4.5 years



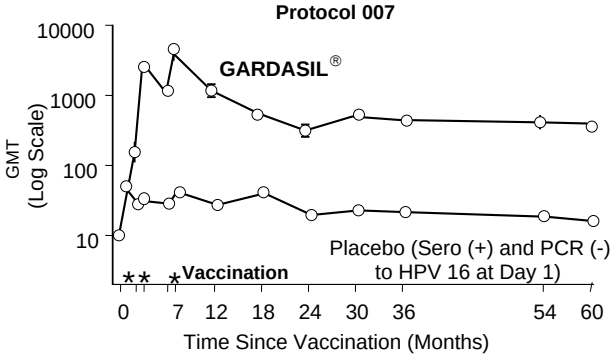
Harper *et al.* Lancet 2006; 367: 1247-55

GSK studies 001 & 007: Sustained seropositivity and High antibody levels up to 4.5 years

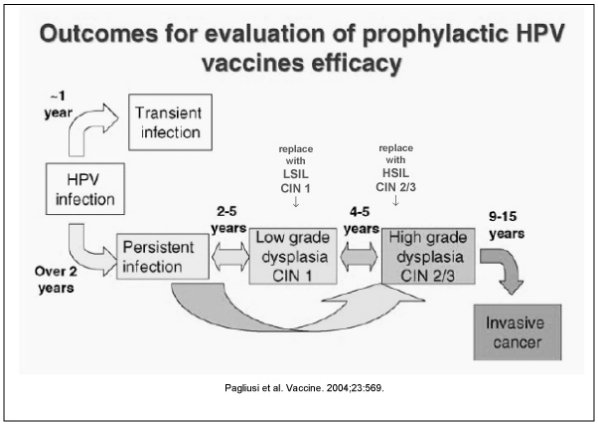


Harper *et al.* Lancet 2006; 367: 1247-55

Anti-HPV 16 GMTs Through 5 Years



Merck, unpublished data, Presented at ACIP meeting, June 2006



Pagliusi et al. Vaccine. 2004;23:569.

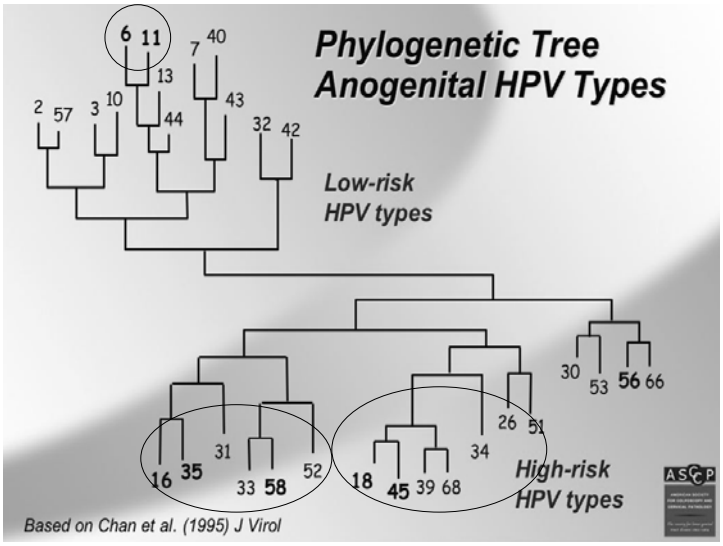
HPV Vaccines Efficacy Summary

	Bivalent Vaccine 4.5 yr Phase II Follow Up (N=776)	Quadrivalent Vaccine Phase III (N=5305)
Efficacy for type specific associated cytologic abnormalities	96% (95% CI: 84-100) P/V: 44/2 events	Not Reported
Efficacy in preventing vaccine specific type associated CIN 1	100% (95% CI: <0 – 100) P/V: 8/0 events	100% (95% CI: 84-100) P/V: 25/0 events
Efficacy in preventing vaccine specific type associated CIN 2/3	100% (95% CI: <0 – 100) P/V: 5/0 events	98% (95% CI: 86-100) P/V: 42/1 events
Efficacy in preventing EGW	Not a study aim	100% (95% CI: 94-100) P/V: 60/0 events

Harper DM et al., Lancet, 2004
Harper DM et al., Lancet, 2006
FUTURE I & II NEJM 2007

Slide provided courtesy of Dr. Diane Harper

Will these vaccines provide cross-protection against non-vaccine HPV types?



Are There Cross-Reactive and Cross-Neutralising Epitopes?

YES

6 and 11

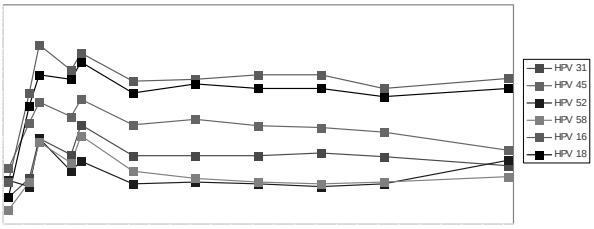
31 and 33

16 and 31

18 and 45

The cross-reactive epitopes are not the dominant neutralising epitopes and they may not be generated in all vaccinated individuals

Evidence of Cross-Reacting Antibodies Gardasil™



J. Clin Oncol 2006;24(185):1508

GSK studies 001 & 007 up to 4.5 years: first evidence of broader protection

- **Independent of HPV DNA status**

Endpoint	Vaccine		Placebo		Vaccine efficacy (%) (95% CI)	p-values *	Estimated prevalence of HPV-16/18
	N	**n**	N	**n**			
≥ASCUS	505	**90**	497	**138**	39.8 (20.9-54.4)	<0.001	20-30% [1]
≥LSIL	505	**41**	497	**70**	44.6 (17.4-63.3)	0.003	25-30% [1]
CIN1+	481	**12**	470	**24**	51.5 (-0.9-77.9)	0.042	25-30% [1]
CIN2+	481	**3**	470	**11**	73.3 (-1.0-95.2)	0.033	50% [2]

Harper *et al.* Lancet 2006; 367: 1247-55
ITT analysis, Conditional Exact method
* p-values not used for inferential purposes

[1]Clifford *et al.* Cancer Epidemiol Biomarkers Prev 2005; 14(5):1157-64 [2]Muñoz *et al.* N Engl J Med 2003; 348:518-27

GSK studies 001 & 007 up to 4.5 years: First evidence of cross protection types 45 & 31

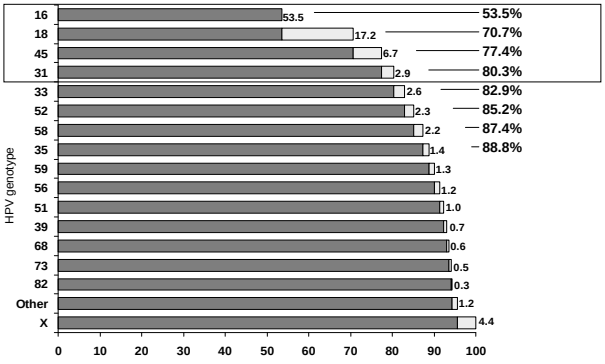
Incident infection with most common oncogenic types beyond 16 & 18

HPV Type	Vaccine			Placebo			Vaccine Efficacy (%) (95% CI)
			Event rate (rate per 100) (95% CI)			Event rate (rate per 100) (95% CI)	
	N	n	Rate	N	n	Rate	
HPV-45	528	1	0.1 (0.0-0.4)	518	17	1.2 (0.7-1.9)	94.2 (63.3-99.9)
HPV-31	528	14	0.9 (0.5-1.6)	516	30	2.1 (1.4-3.0)	54.5 (11.5-77.7)
HPV-33	529	12	0.8 (0.4-1.4)	519	13	0.9 (0.5-1.5)	8.6 (-117.3-61.9)
HPV-52	524	40	2.8 (2.0-3.8)	515	48	3.5 (2.6-4.6)	18.6 (-26.5-47.8)
HPV-58	529	14	0.9 (0.5-1.6)	517	16	1.1 (0.6-1.8)	14.0 (-87.9-61.1)

Study not powered to evaluate cross protection against all individual types

Harper *et al.* Lancet 2006; 367: 1247-55
Combined initial efficacy and extended follow up studies

HPV 16, 18, 45 and 31 account for 80.3% of cervical cancer cases worldwide



Cervical cancer cases attributed to the most frequent HPV genotypes (%)

Munoz N *et al. Int J Cancer* 2004; 111: 278–85.

Key Remaining Issues/Priorities

- Duration of protection (?need for booster)
- Cross-protection
- HPV type replacement
- Long-term safety (novel adjuvant)

PHASE IV

- Efficacy in boys/men
- Efficacy in older women- ? Therapeutic effect vs new infection
- Special populations- ie HIV
- Screening recommendations in vaccinated women
  - ?start screening later
  - ?screen less frequently
  - ?role of HPV DNA testing
  - ?linked vaccine registries

How will HPV vaccination impact on current cervical cancer screening programs?

Cervical Cancer Screening

- **Cervical cancer screening – no change**
  - 30% of cervical cancers caused by HPV types not prevented by the quadrivalent HPV vaccine
  - Vaccinated females could subsequently be infected with non-vaccine HPV types
  - Sexually active females could have been infected prior to vaccination
- Providers should educate women about the importance of cervical cancer screening
- Decision to vaccinate should not be based on Pap testing, HPV DNA testing or HPV serologic testing

Questions?