


Leading the way for the prevention of cervical cancer and beyond



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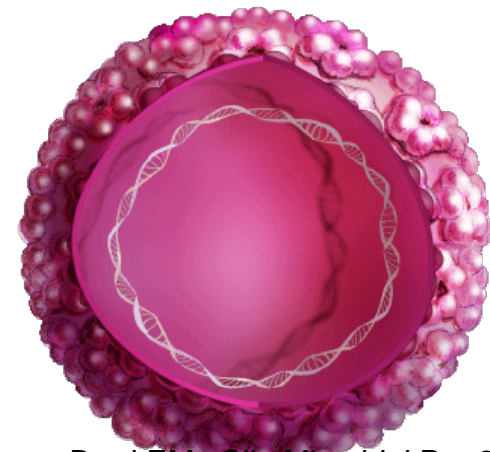
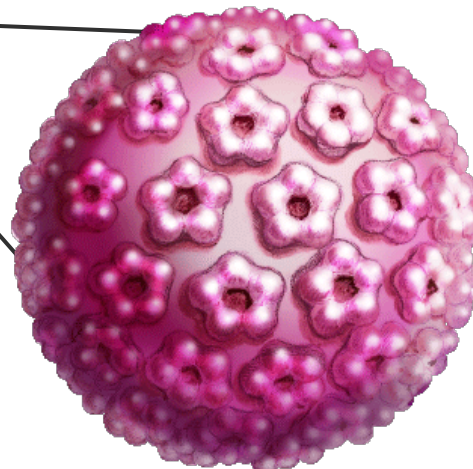
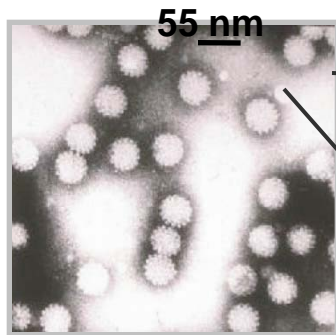
Points to be covered

- HPV: Epidemiology and burden
- Impact of HPV on disease progression and outcomes
- Vaccines and the public health challenge of primary prevention
- Recommendations

- DISCLOSURE

1. Human papillomavirus

- HPV is a relatively small virus containing circular double-stranded DNA within a spherical shell (capsid)
- HPVs infect cutaneous epithelium (skin) and mucosal epithelium (e.g. cervical and other anogenital mucosae)



HPV infections of the genital tract

- ❑ The **most common genital infection** worldwide^{1,2}
- ❑ Sexually transmitted (non-sexual transmission is less frequent)¹
- ❑ Mostly clinically **silent and self-limiting**¹
- ❑ Some women remain **persistent carriers** of the viral infection and become at high risk of progression to precancer and cancer of the cervix, vulva, vagina and anal canal^{1,3}
- ❑ May cause cancers in the penis and anal canal³
- ❑ Cancers at other sites³

1. Trottier H & Franco EL. *Am J Manag Care* 2006; **12**:S462–472;
2. Schiffman M & Krüger Kjaer S. *J NCI Monographs* 2003; 31:14–19;
3. Parkin DM & Bray F. *Vaccine* 2006; **24**(Suppl 3):S11.

HPV DNA PREVALENCE IN WOMEN WITH NORMAL CYTOLOGY ADJUSTED MODEL (N=139,777)

Global	10.4% (10.2-10.7)
Africa	22.1% (20.9-23.4)
Central and South America & The Caribbean	13.0% (12.4-13.5)
Europe	8.1% (7.8-8.4)
Asia	7.9% (7.5-8.4)

Source of data: De Sanjosé S et al. *Lancet Infect Dis* 2007;7(7):453-459.

2. Burden of the oncogenic and low-risk HPV types

- At least **30** HPV types target the genital mucosa¹
- At least **15** HPV types are classified as **oncogenic** (high risk)¹
 - Globally, HPV types **16** and **18** together account for > 70% of cervical cancer cases^{1,2}
 - The next most common oncogenic HPV types are **45, 31 and 33***^{1,2}

* In descending order of global prevalence in cervical cancer tissue.

1. Munoz N, *et al. N Engl J Med* 2003; **348**:518–527;
2. Bosch FX *et al. Vaccine*. 2008; **26S**:K1–K16;
3. Greer CE, *et al. J Clin Microbiol* 1995; **33**:2058;
4. Brown DR, *et al. J Clin Microbiol* 1999; **37**:3316–3322.

Low risk HPV and burden of genital warts

- ❑ Non-oncogenic or 'low-risk' HPV types can cause benign *condylomata acuminata*, i.e. genital warts¹
- ❑ 'Low-risk' HPV types are rarely associated with severe cervical dysplasia or cervical carcinoma and commonly manifest as external genital warts¹
- ❑ Two low-risk HPV types, **6 and 11**, are found in more than 90% of genital warts^{1,2}



1. Hillemanns P, *et al. BMC Infect Dis* 2008; **8**:76–85; 2. Gall S. *Infect Dis Obstet Gynecol* 2001; **9**:149–154;

Oncogenic HPV and burden of cervical cancer

- **500,000** women diagnosed per year¹
- Worldwide, every 2 minutes a woman dies of cervical cancer¹
 - **270,000** deaths (data from GLOBOCAN 2002)¹
 - In less-developed regions, cervical cancer remains the leading cause of cancer deaths in women
 - Projections indicate > 1 million new cases of cervical cancer each year by 2050²
- Despite the impact of screening in a large number of countries, women continue to be at risk³

1. Ferlay J, *et al.* *GLOBOCAN 2002 Cancer Incidence, Mortality and Prevalence Worldwide*. IARC CancerBase; Lyon, 2004;

2. Parkin DM, *et al.* *Eur J Cancer* 2001; **37**(Suppl 8):S4–S66;

3. Kitchener HC, *et al.* *Vaccine* 2006; **24**(Suppl 3):S63–S70.

3. Risk behavior



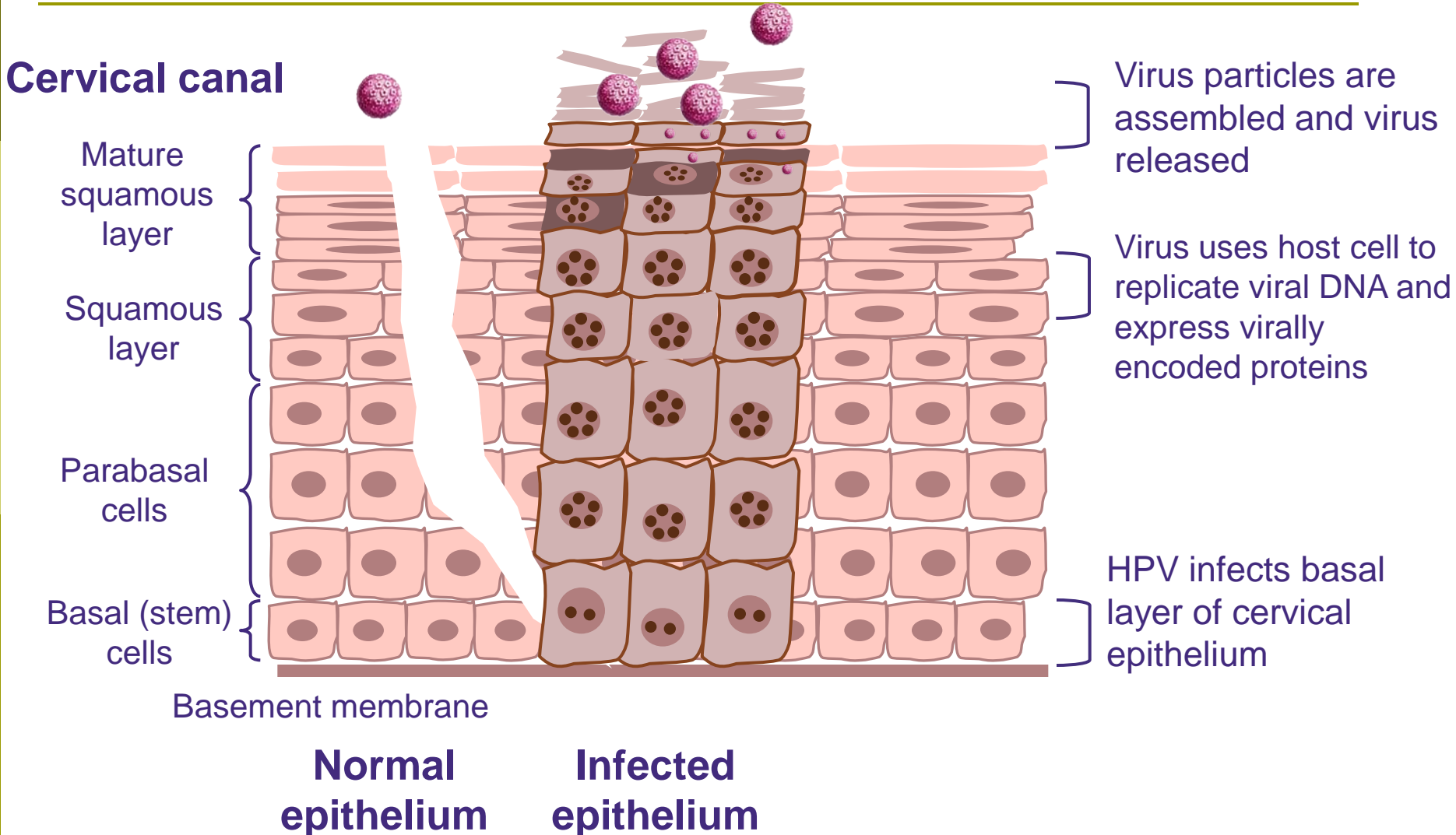
Determinants of risk of HPV infection

- ❑ HPV infections are very common
- ❑ The cumulative risk of acquiring cervical HPV infection in women with only one sexual partner is **46%** (3 years after first sexual encounter)¹
- ❑ The risk of oncogenic HPV infection is high even after first intercourse and **continues throughout** a woman's sexually active lifetime²⁻⁴

4. Impact on disease progression



HPV lifecycle in the cervix



Disease progression

- For every **1 million** women infected with HPV¹:
 - **100,000** will develop precancerous changes (cervical dysplasia)*
 - **8,000** will develop carcinoma in situ (CIS)*
 - **1,600** will develop invasive cervical cancer if dysplasia and CIS are not detected or treated*
- Cervical cancer is a **relatively rare** outcome of a common oncogenic HPV infection²
- **Over 80%** of HPV infections are transient, asymptomatic and resolve spontaneously³⁻⁶

* Highest estimate based on model without screening.

1. McIntosh N. Jhpiego strategy paper 8. May 2000. Available at

http://www.jhpiego.jhu.edu/scripts/pubs/category_detail.asp?category_id=4 (accessed September 2009);

2. Bosch FX, *et al. J Clin Pathol* 2002; **55**:244–265;

3. Ho GY, *et al. N Engl J Med* 1998; **338**:423–428; 4. Moscicki AB, *et al. J Pediatr* 1998; **132**:277–284;

5. Giuliano AR, *et al. J Infect Dis* 2002; **186**:462–469; 6. Franco EL, *et al. J Infect Dis* 1999; **180**:1415–1423.

5. Leading the way to primary prevention?

□ Vaccinate?

OR

□ Screen?

OR

□ Vaccinate and screen?

Characteristics of Current HPV Vaccines

	Quadrivalent	Bivalent
Description	Quadrivalent recombinant vaccine prepared from HPV L1 protein VLPs	Bivalent recombinant vaccine prepared from HPV L1 protein VLPs
HPV types	6, 11, 16, 18	16, 18
Concentrations per dose (mcg)	20/40/40/20	20/20
VLP preparation	Yeast Proprietary assembly/reassembly process increasing stability	Insect cell substrate
Adjuvant	AAHS Amorphous aluminum hydroxyphosphate sulfate (Merck and Co., Inc.)	AS04 Aluminum hydroxide + 3-O-desacyl-4'- monophosphoryl lipid A (MPL, Corixa/GSK)
Adjuvant dose <small>VLP = virus-like particle.</small>	225 mcg	500 mcg/50 mcg

1. Worldwide Product Circular. GARDASIL™ [Quadrivalent human papillomavirus Types 6, 11, 16, 18) recombinant vaccine]; WPC-GRD-I-122008. 2. Cervarix [package insert]. Rixensart, Belgium: GlaxoSmithKline Biologicals; 2007.

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- QV: Cervical precancers and cancers, anogenital warts, vulvar and vaginal precancers and cancers
 - 0, 2, 6 IM injections

- BV: Cervical precancers and cancers
- 0, 1, 6 IM injections

The quadrivalent HPV vaccine has shown efficacy against HPV 6/11/16/18- related CIN and AIS (Phase III)

□ Per-protocol population (protocols 007, 013 and 015):

Endpoint*	Quadrivalent HPV vaccine cases (n = 9,075)	Placebo cases (n = 9,075)	Vaccine efficacy, %	95% CI
HPV 6-/11-/16-/18-related CIN or AIS	9	225	96	92–98
By type				
HPV 6-related	0	47	100	92–100
HPV 11-related	0	12	100	65–100
HPV 16-related	8	137	94	89–98
HPV 18-related	1	61	98	91–100
By disease	AIS = adenocarcinoma <i>in situ</i> .			
CIN1	7	170	96	91–98
CIN2/3	2 [†]	110	98	93–100
AIS	0	7	100	31–100

Quadrivalent HPV vaccine efficacy (per-protocol susceptible population): Phase III trial (3.6 years)

Endpoint	Vaccine efficacy, % (95% CI)
HPV 16/18 CIN2/3 or AIS	98.2 (93.5–99.8)
HPV 16/18 CIN3	96.9 (88.4–99.6)
HPV 16/18 AIS	100 (30.6–100.0)

Per-protocol susceptible population: women with no virological evidence of infection with HPV 16 or HPV 18 through 1 month after the third dose (Month 7), case counting started 30 days after third dose.

n = 8,493 (vaccine group); 8,464 (placebo).

Quadrivalent HPV vaccine Protocol 019:

24–45-year-old women (2.2 years' mean follow-up)

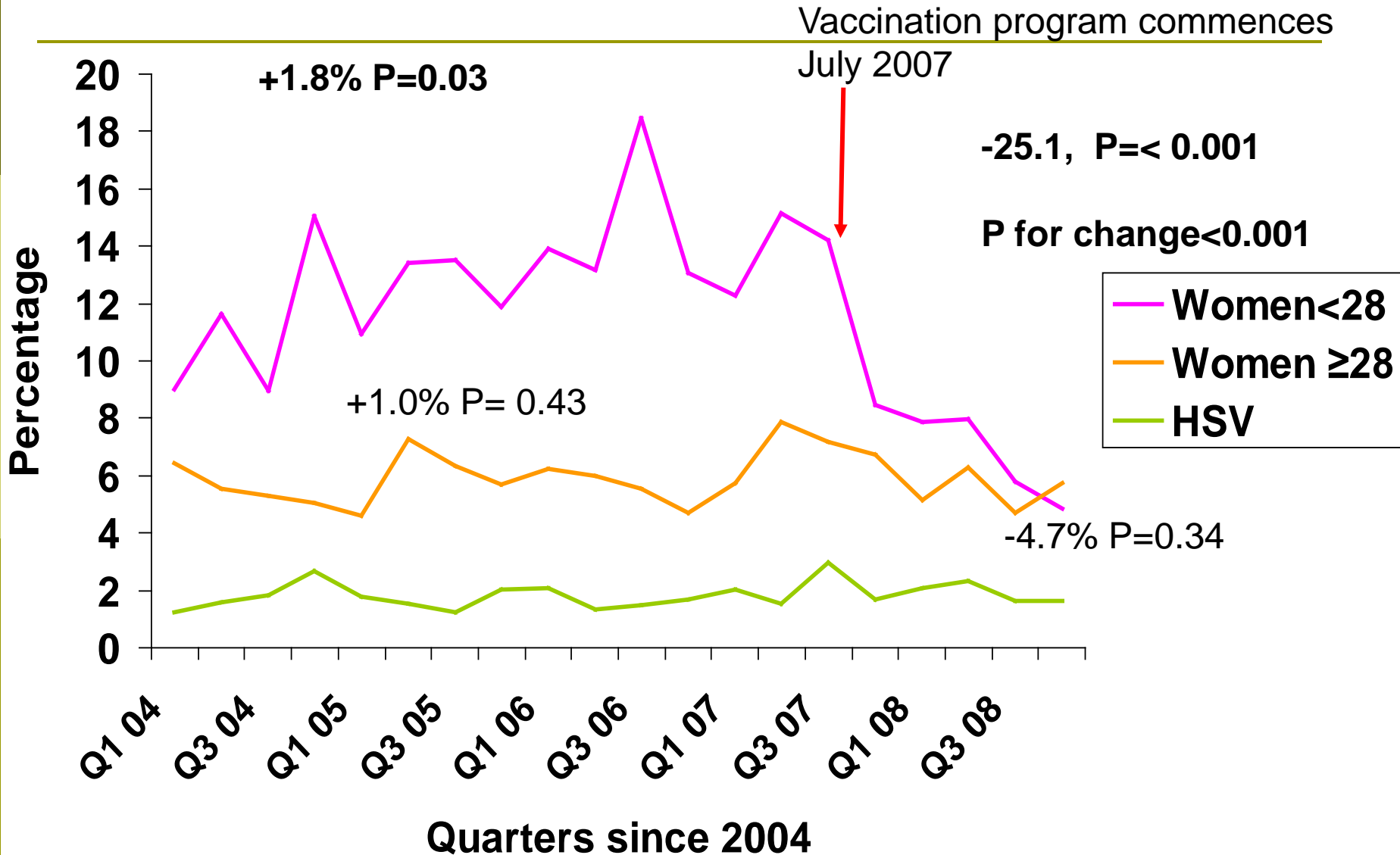
- Combined incidence of infection (≥ 6 months) and disease (including CIN, VIN, VaIN; cervical, vulvar and vaginal cancer and genital warts)

PPE population *	Quadrivalent HPV vaccine		Placebo		Vaccine efficacy		
	n	Cases	n	Cases	%	95% CI	p-value
HPV 16/18/6/11	1,615	4	1,607	41	90.5	73.7–97.5	< 0.0001
HPV 16/18	1,601	4	1,579	23	83.1	50.6–95.8	0.0001
HPV 6/11	1,329	0	1,323	19	100	79.0–100	< 0.0001

* Per-protocol susceptible population: women with no virological evidence of infection with HPV 16 or HPV 18 through 1 month after the third dose (Month 7), case counting started 30 days after third dose.

VaIN = vaginal intraepithelial neoplasia; VIN = vulvar intraepithelial neoplasia.

Proportion of new clients with Warts per quarter change



QV efficacy

- Combined analysis of phase II trial of the QV vaccine, 1 phase II trial of a monovalent HPV- 16 vaccine and the 2 phase III trials of the QV vaccine → an efficacy of 99% (95% CI, 93–100%) for the composite end-point of CIN2 or CIN3 or AIS after 3 years of FU among women naive to the relevant type at baseline who had received all 3 doses

(Ault, Lancet, 07)

Bivalent HPV vaccine: high efficacy confirmed up to 6.4 years against HPV 16/18 CIN2+ (Phase IIb, women aged 15–25 years)

	HPV 16/18-related CIN2+	Bivalent HPV vaccine	Control	Vaccine efficacy	
		n	n	%	95% CI
Initial efficacy study	2.3 years¹	0	3	NA*	NA*
Combined analysis of initial efficacy study and extended follow-up	4.5 years²	0	5	100	–7.7–100
	5.5 years³	0	7	100	32.7–100
	6.4 years^{4,5}	0	9	100	51.3–100

* The initial efficacy study was not powered to calculate vaccine efficacy against histopathologically confirmed CIN.

n = number of subjects reporting at least one event in each group
ITT analysis.

1. Harper D, *et al. Lancet* 2004; **364**:1757–1765;

2. Harper D, *et al. Lancet* 2006; **367**:1247–1255;

3. Gall S, *et al. AACR* 2007; Abstract;

4. Harper D, *et al. SGO* 2008; Abstract; 5. Romanowski B, *et al. Lancet* 2009, in press.

Bivalent HPV vaccine efficacy in TVC-naïve: final analysis of Phase III trial (39.4 months)

Primary analysis (TVC-naïve)

Endpoint	Group	N	n	Vaccine Efficacy (96.1%CI)			
				%	LL	UL	p-value
CIN2+ HPV-16/18	HPV	5,449	1	98.4	90.4	100	< 0.0001
	Control	5,436	63				
Endpoint	Group	N	n	Vaccine Efficacy (96.1%CI)			
				%	LL	UL	p-value
CIN3+ HPV-16/18	HPV	5,449	0	100	64.7	100	< 0.0001
	Control	5,436	13				

The TVC-naïve cohort approximates adolescent girls pre-exposure

vaccine cross-protection

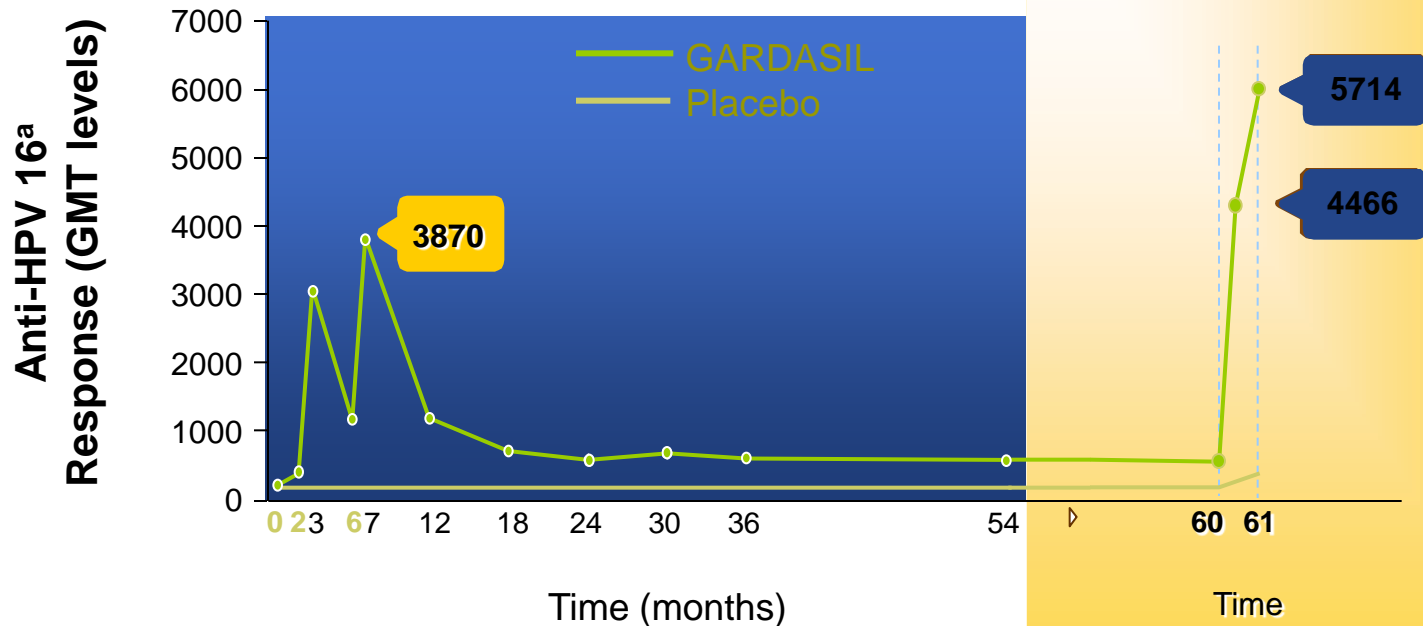
- **BV**: High vaccine efficacy against combined non-vaccine HPV types substantiated by cross-protection against 31, 33 and 45 individually (TVC)
- 100% cross-protective efficacy against CIN2+ caused by non-vaccine HPV types 31/45 (TVC-naïve)

QV

- Cross-protection against CIN2+ or adenocarcinoma in situ:
 - naïve to 14 oncogenic HPV types
 - 70.0% cross-protective efficacy against HPV 31
- Overall efficacy was 42.7% against CIN2+ and 82.8% against genital warts irrespective of HPV type (RMITT-2 cohort)
- Clinical implication???

Duration: QV& immune memory¹

Rapid and Strong Anamnestic Response to Antigen Challenge



Antigen challenge
Reexposure to
antigen at month 60

GMT = geometric mean titer.

^aSimilar response with the other 3 types of HPV within vaccine.

1. Olsson SE et al. *Vaccine*. 2007;25:4931–4939.

Safety: Vaccine Adverse Event Reporting System (VAERS)

- As of December 31, 2008
 - >23 million doses of QV distributed in the United States
 - 11,916 VAERS reports of adverse events following vaccination in the US
 - 94% were reports of events considered to be nonserious

- Bivalent vaccine had a clinically acceptable safety profile similar to that of other vaccines licensed and in general use

HPV = Human Papillomavirus; CDC=Centers for Disease Control and Prevention; FDA=Food and Drug Administration.

Centers for Disease Control and Prevention. Reports of Health Concerns Following HPV Vaccination.

<http://www.cdc.gov/vaccinesafety/vaers/gardasil.htm>. Accessed March 31, 2009.

Screening prevention of cervical cancer

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- ❑ Screening programmes vary widely between countries
 - ❑ HPV DNA testing may be used to detect existing HPV infection
 - ❑ BUT...Neither method offers 1ry prevention; HPV infection and cervical disease can still occur
 - Deaths from cervical cancer still occur in countries with established screening programmes²
 - ❑ Vaccination offers an important new management option in the primary prevention of cervical cancer

1. Sankaranarayanan R, *et al. Int J Gynaecol Obstet* 2005; **89**(Suppl 2):S4–S12;
2. WHO/ICO Information Centre on Human Papilloma Virus (HPV) and Cervical Cancer.
Available at: <http://www.who.int/hpvcentre/statistics> (accessed September 2009).

Is there a case for Lebanon?

- ❑ Screening: Opportunistic
- ❑ Burden is HPV: Sexual activity, Adolescents into adults
- ❑ Very good vaccine campaigns
- ❑ Utilization of services of RA women
- ❑ Quality and type of screening?
- ❑ Cost- effectiveness: Naïve, 70%, > 10 years

Country	Screening modality (1960s–1990s)	Decrease in cervical cancer mortality, 1960s–1990s*, %
Finland	Organized	82
Sweden	Organized	65
Norway	Opportunistic	41

Lebanese recommendations

- Pre- adolescent 11- adult females 26
- Joint tasks (Intersociety + Government support)
- Two vaccines options
- Routine screening continues
- Clinic- based-→ school- based

The way to primary prevention?

□ Vaccinate?

OR

□ Screen?

OR

□ Vaccinate and screen?