Updates on Cervical Cancer Vaccines

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Declaration of Interest

- Advisor to GSK and MSD cervical cancer control and prevention
- PI of HPV vaccines clinical trials GSK and MSD
- Received sponsorships or honoraria from GSK and MSD as speaker, expert consultant and member of Advisory Board

Vaccines

- Antibodies
- Efficacy
- Background
- Safety
- Who Benefit
- Screening

HPV types associated with the development of cervical cancer

- The five most common HPV types associated with squamous cell carcinoma by region (ICO survey 2007, preliminary results)

World (n = 7,733)		Africa (n = 616)		Asia (n = 1,130)		Europe* (n = 2,618)		L. America† (n = 3,236)		Oceania (n = 133)	
HPV	%	HPV	%	HPV	%	HPV	%	HPV	%	HPV	%
HPV 16	61.6	HPV 16	46.8	HPV 16	66.6	HPV 16	63.9	HPV 16	60.1	HPV 16	64.8
HPV 18	8.2	HPV 18	18.9	HPV 18	7.2	HPV 18	6.7	HPV 18	7.5	HPV 18	14.1
HPV 45	5.5	HPV 45	10.8	HPV 58	4.7	HPV 33	5.7	HPV 45	6.0	HPV 45	5.5
HPV 31	4.5	HPV 35	5.3	HPV 33	4.5	HPV 45	4.7	HPV 31	5.8	HPV 33	3.1
HPV 33	4.3	HPV 52	4.4	HPV 52	3.1	HPV 31	4.0	HPV 33	3.7	HPV 35	2.3

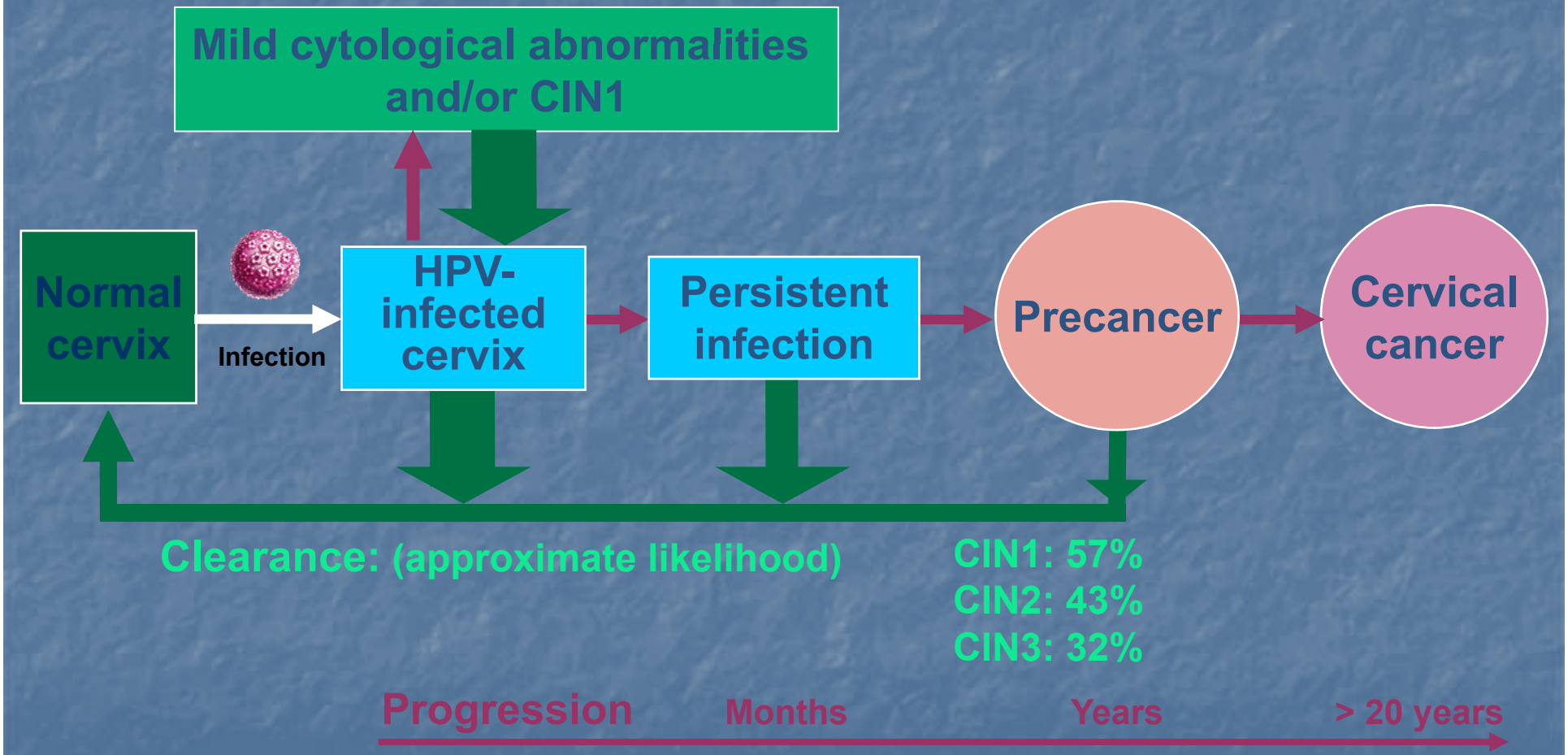
* Europe + North America.

† Latin America: Central and South America.

Multiple infections are proportionally distributed by the number of types infected.

Data updated July 2007.
Professor Xavier Bosch.

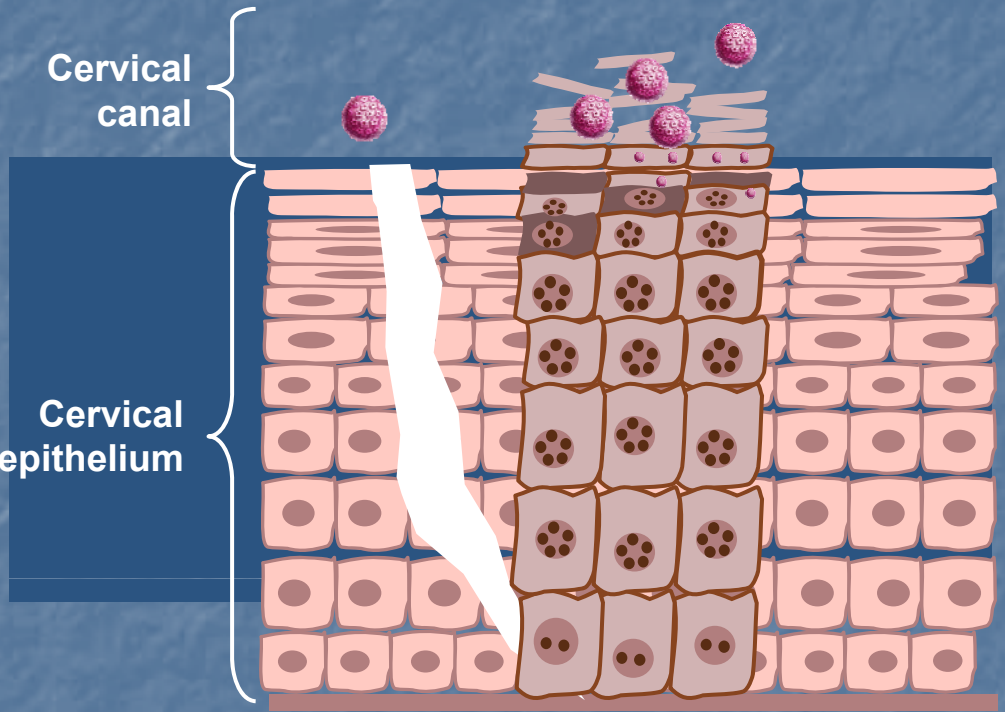
Progression of cervical carcinogenesis



CIN = cervical intraepithelial neoplasia.
Precancer is equivalent to CIN2/3.

Adapted from Schiffman M & Kruger Kjaer S. *J Natl Cancer Inst Monogr* 2003; **31:**14–19.

HPV lifecycle and immune evasion



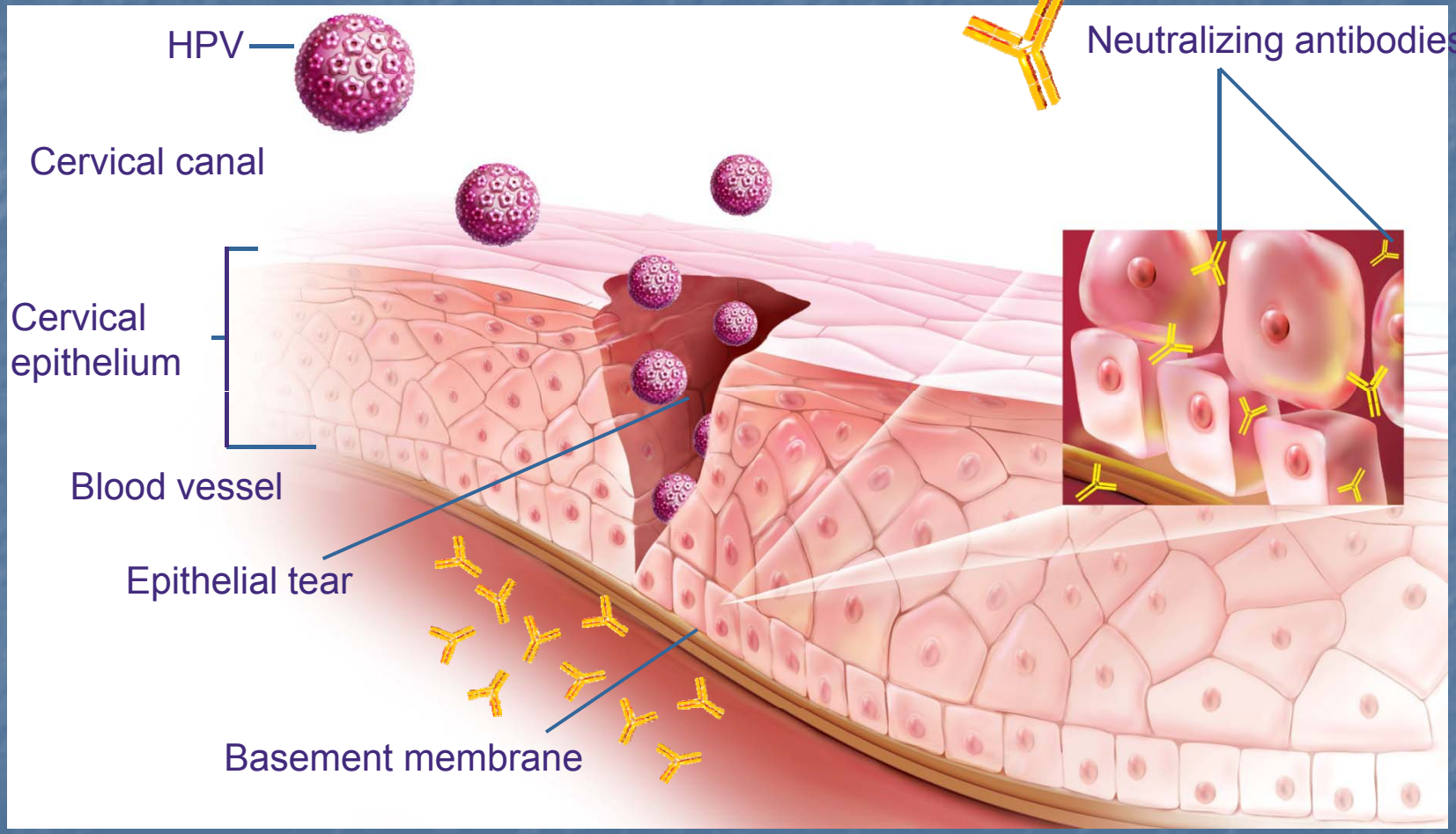
HPV has many immune evasion mechanisms:[1]

- Viral lifecycle occurs entirely within epithelium
- No viraemia
- No cell death
- No inflammation
- Local immunosuppression caused by viral proteins

- HPV 'stealth' and immune evasive mechanisms enable infection to persist[1]
- Persistent infection is a prerequisite, but may not be sufficient alone for progression to cervical cancer[2]

1. Stanley M, *et al. Vaccine* 2006; **24S1:**S1/16–S1/22;
2. Trottier H & Franco EL. *Am J Manag Care* 2006; **12:**S462–S472.

Active protection via vaccination is mediated by neutralizing antibodies at the cervix

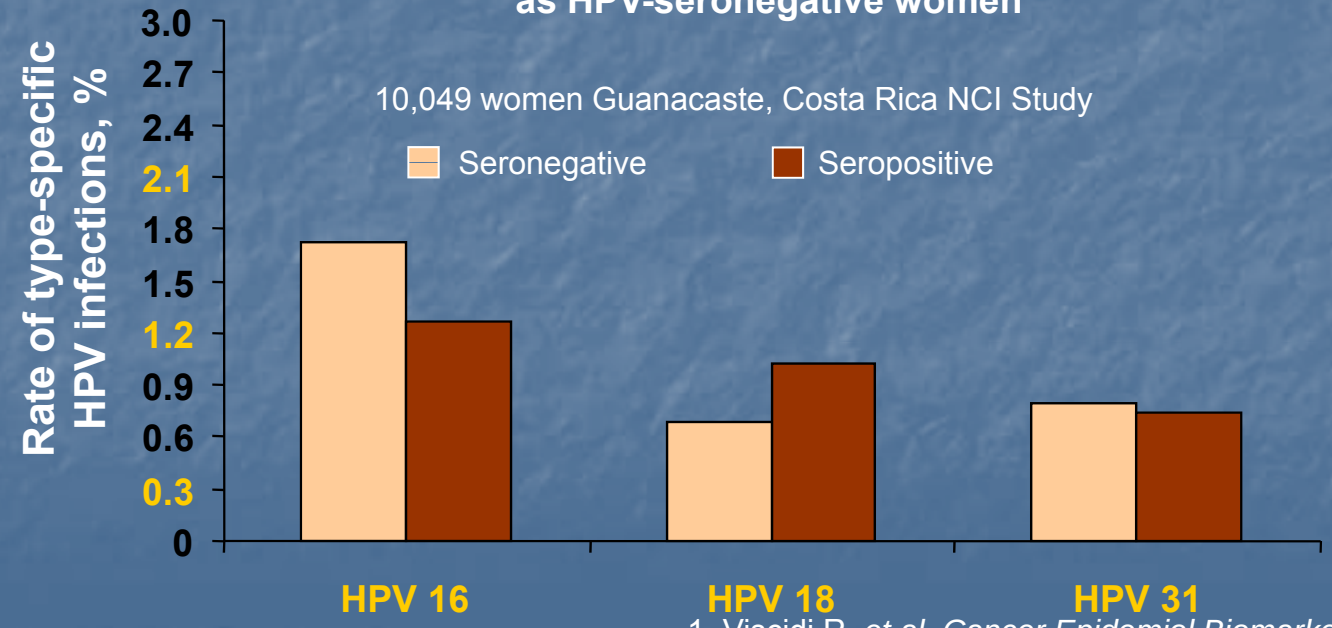


Stanley M. *Vaccine* 2006; **24:**S16–S22;
Giannini S, *et al. Vaccine* 2006; **24:**5937–5949;
Nardelli-Haefliger D, *et al. J Natl Cancer Inst* 2003; **95:**1128–1137;
Poncelet S, *et al. IPvC* 2007; Abstract.

Antibody response following natural infection

- **~ 50 % of women develop no measurable antibody response following HPV infection[1,2]**
- **In women who have detectable antibody levels following natural infection, levels of antibodies are low*[1]**
- **Low antibody levels may not protect against re-infection or reactivation[1]**

HPV-seropositive women have similar rates of HPV infections as HPV-seronegative women[1]



* In comparison to post-vaccination levels.

1. Viscidi R, *et al. Cancer Epidemiol Biomarkers Prev* 2004; **13:**324–327;
2. Carter J, *et al. J Infect Dis* 2000; **181:**1911–1919.

Composition of the bivalent HPV vaccine and the quadrivalent HPV vaccine

Bivalent HPV vaccine

Antigens

+

AS04 adjuvant

Aluminium salt ($Al(OH)_3$) + **MPL** Immunostimulant

AS04-containing vaccine

Quadrivalent HPV vaccine

Antigens

+

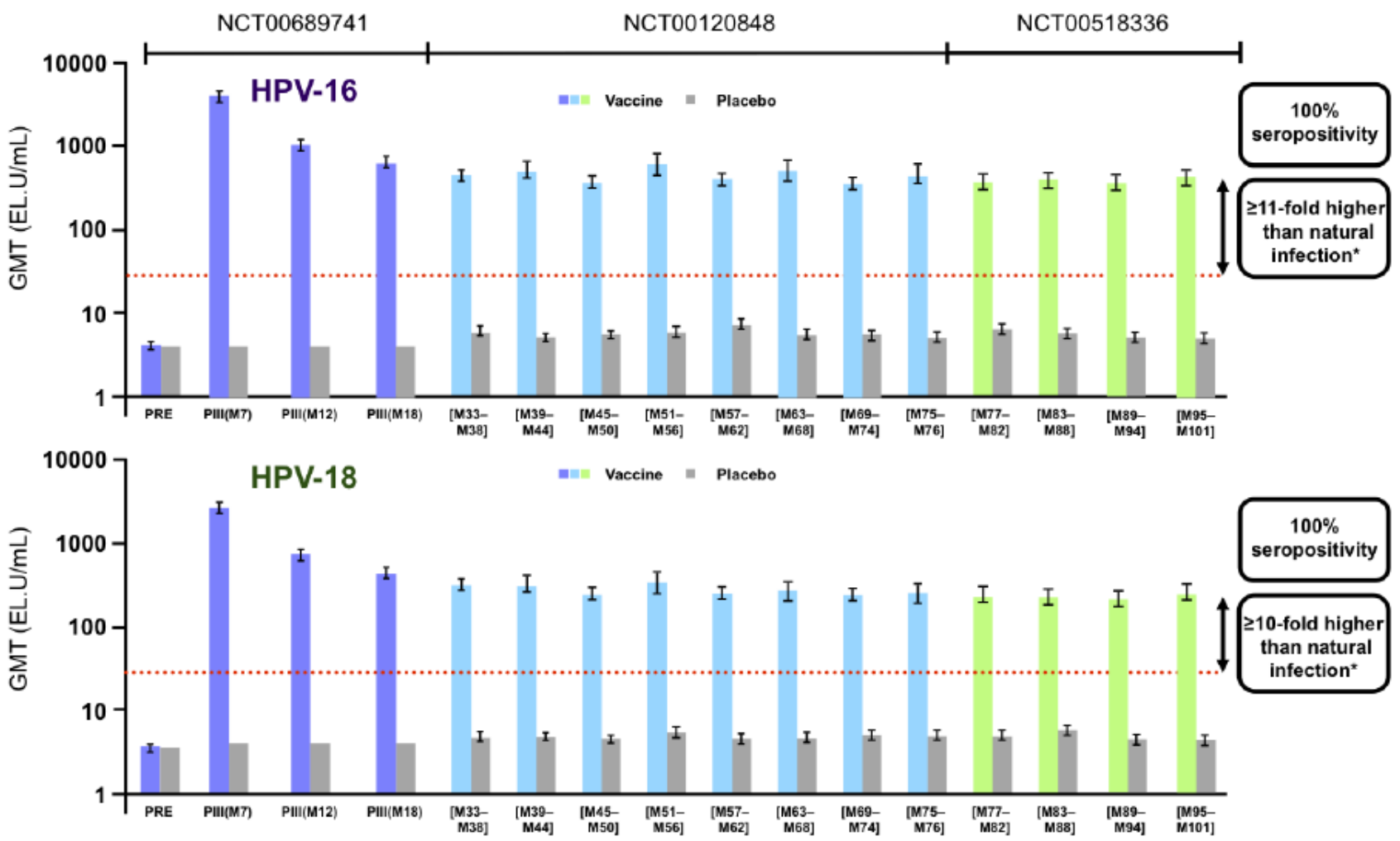
Adjuvant

Aluminium salt (amorphous aluminium hydroxyphosphate sulphate [AAHS])

AAHS-containing vaccine

MPL = monophosphoryl lipid A.

Sustained Anti-HPV-16/18 Antibody Levels up to 8.4 Years



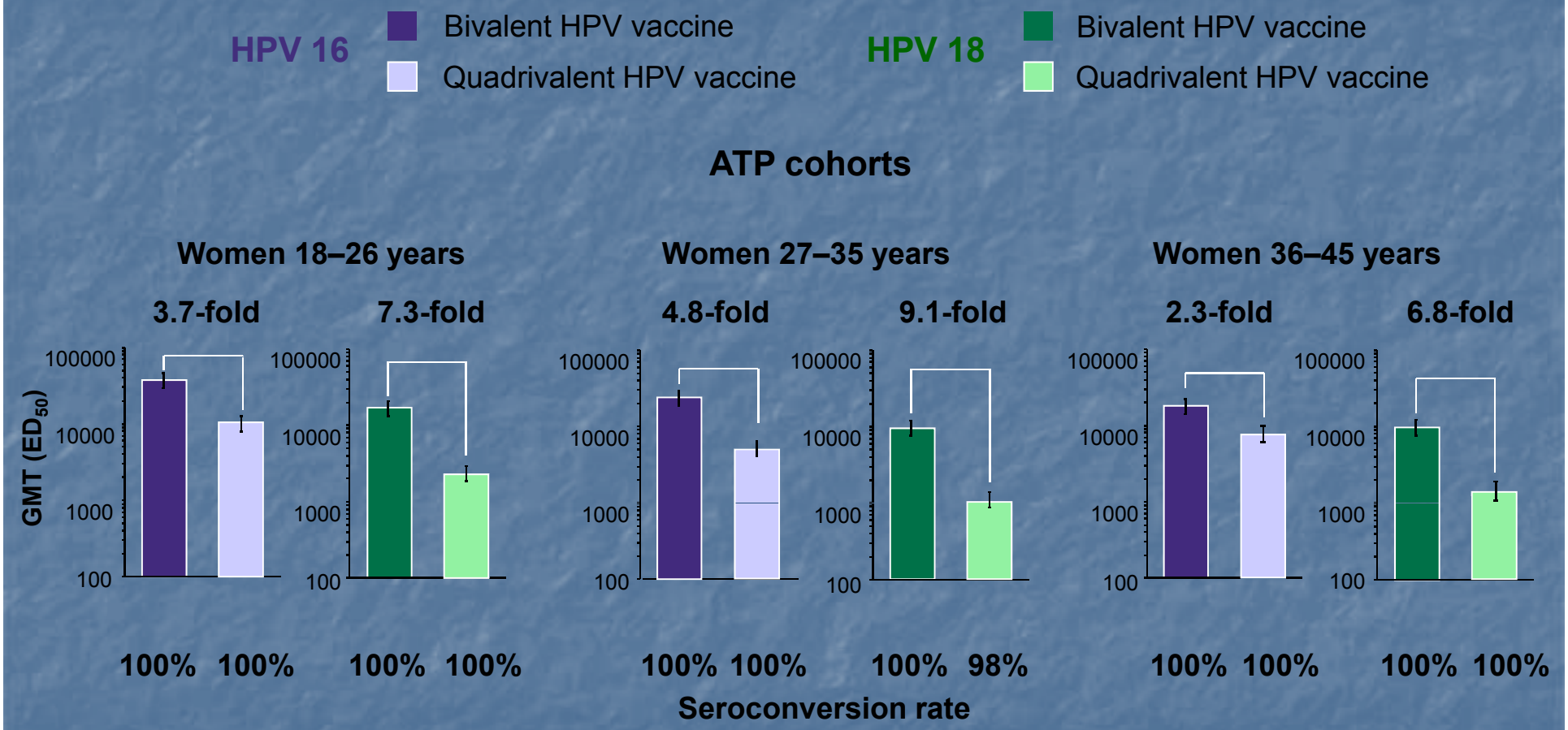
*Antibody levels in women from a phase III study who cleared a natural infection before enrolment[7]
ATP = according-to-protocol

Adapted from Roteli-Martins CM, et al. ESPID 2010; oral presentation

Comparison of the immunogenicity and safety of the prophylactic bivalent HPV vaccine and quadrivalent HPV vaccine in healthy women aged 18–45 years

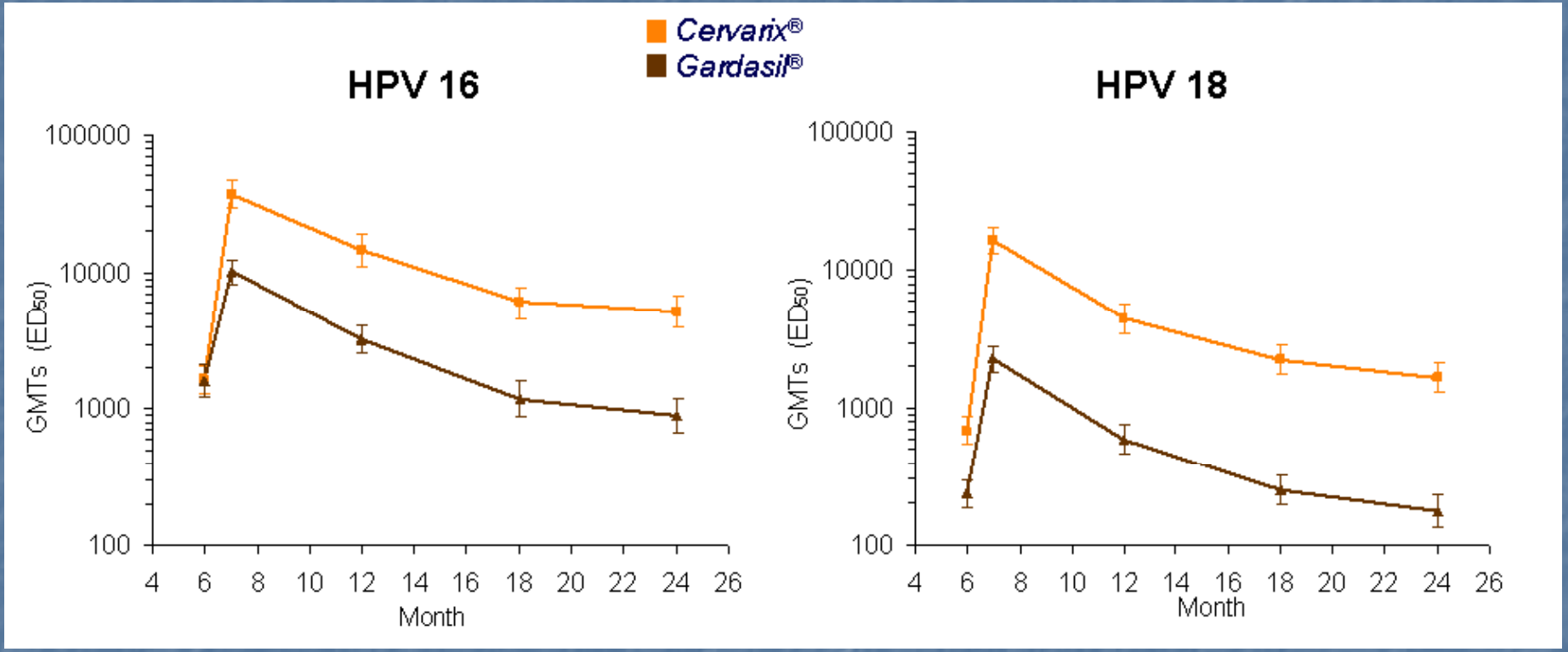
Using same assay methodology - **Pseudovirion-based neutralization assay (PBNA)**

HPV 16 and 18 neutralizing antibody responses: geometric mean titre, geometric mean titre ratio and seroconversion rate



Einstein MH, et al. *Human Vaccines* 2009; **5:**[Epub ahead of print].

Comparative study: Anti-HPV-16/18 level of HPV vaccines through Month 24 (women aged 18-26)



GMT = geometric mean titre;
PBNA = pseudovirion based neutralisation

- Since there is no breakthrough CIN 2+ in both vaccine cohort, do not have a immune-correlation on what antibody level is considered inadequate for protection
- Mathematical modeling suggest sustained antibodies level for more than 20 years
- Study demonstrated high antibodies response on giving booster
- Need to wait before we know if booster is needed

Efficacy

- Both vaccines showed similar efficacy in preventing HPV 16 and 18 CIN2+ in Phase III trials
- : 93-98%
- Total population cohort showed decreased in colposcopy referral (20-26%) and procedures related to CIN treatment (42-69%)
- Direct comparison between trials not possible because of differences in recruitment, baseline prevalence of HPV or abnormal cervical lesions and assessment
- However all trials have control for comparison and hence given similar population or prevalence mix, provide an insight of possible impact
- Additional benefit observed led to study on cross-infection which is not originally part of the endpoint of the trials

Summary: bivalent HPV vaccine cross-protection

The bivalent HPV vaccine has demonstrated (HPV-008 trial):

- High vaccine efficacy against combined non-vaccine HPV types substantiated by cross-protection against 31 (68%), 33 (50%) and 45 (100%) individually (TVC)
- 100% cross-protective efficacy against CIN2+ caused by
  non-vaccine HPV types 31/45 (TVC-naïve)
- Substantial overall efficacy against CIN2+ and CIN3+ irrespective of HPV type, (70% and 87% respectively, TVC-naïve)

Summary: quadrivalent HPV vaccine cross-protection

The quadrivalent HPV vaccine has demonstrated (FUTURE I/II subjects):

- Cross-protection against CIN or adenocarcinoma in situ:
  - ITT cohort
    - 26.0% cross-protective efficacy against HPV 31
    - 28.1% cross-protective efficacy against HPV 58
    - 37.6% cross-protective efficacy against HPV 59
  - naïve to 14 oncogenic HPV types
    - 56.9% cross-protective efficacy against HPV 31
- 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)

Precautions in extrapolating cross-infection data

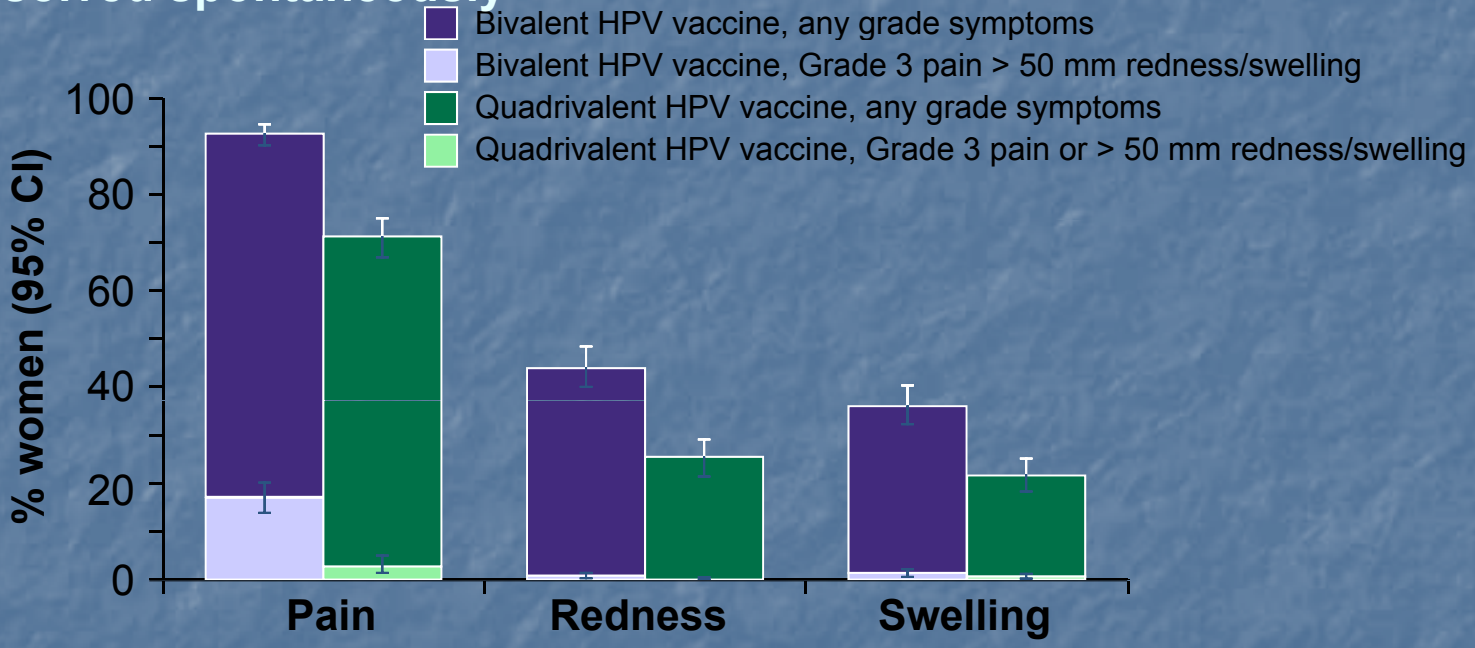
- The trial was not designed or powered for the study of efficacy of these other HPV types
- Efficacy is not 100% and the exact percentage of protection is difficult to determine because of the low prevalence of these HPV types
- How long this protection last is not known?
- Again, direct comparison between the 2 vaccines not advisable because of differences in design and base-line population characteristics

Safety

- Both vaccines showed no increase in serious adverse event compared to control in clinical trials
- Both are safe

Reactogenicity*: solicited local symptoms

- **Higher percentage of women reported solicited local symptoms within 7 days after any dose in the bivalent HPV vaccine group**
  - **All symptoms were transient (mean duration ≤ 3.3 days) and resolved spontaneously**



- High compliance with the three-dose vaccination course for both vaccines (≥ 84%)

* TVC.
Grade 3 symptoms defined as preventing normal activity.

Einstein MH, *et al. Human Vaccines* 2009; **5:**[Epub ahead of print].

Hong Kong study on the immunogenecity and safety of Cervarix

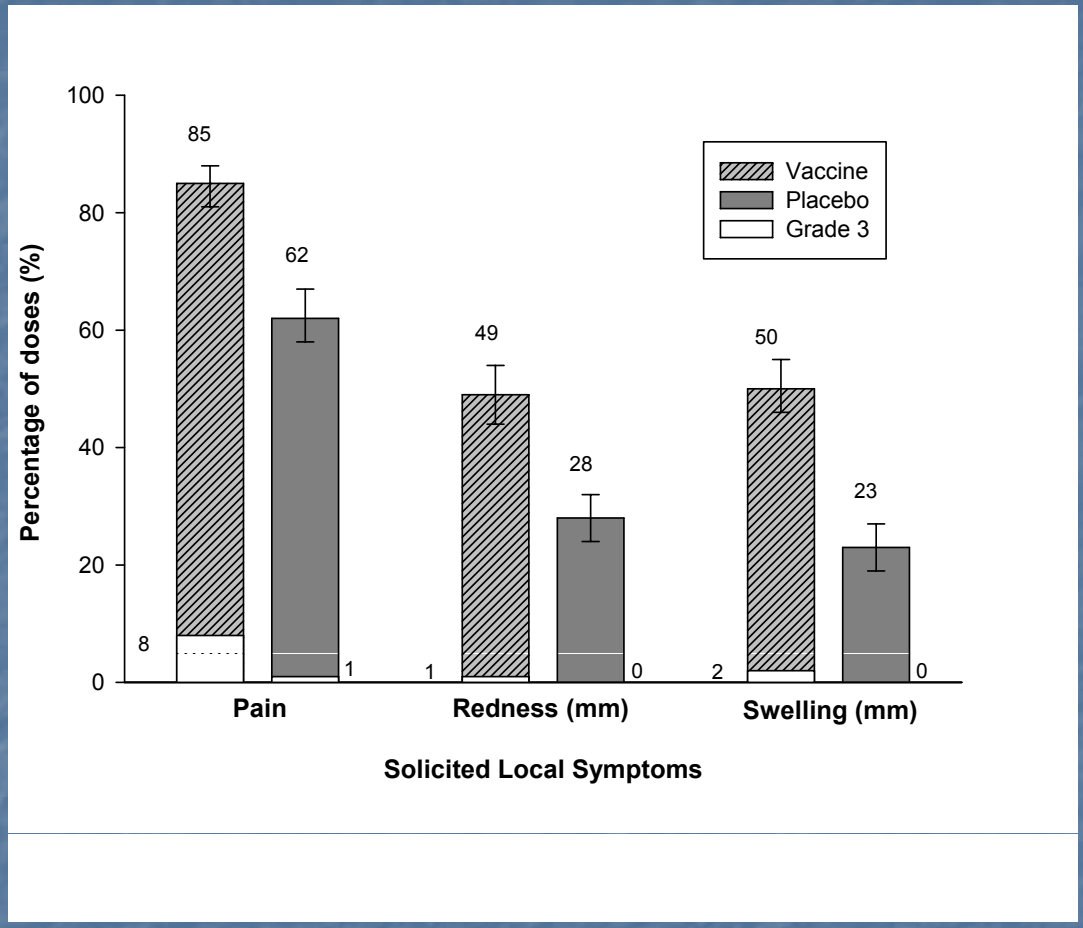
- Objective
  - To assess the immunogenicity and safety of human papillomavirus–16/18 AS04-adjuvanted cervical cancer vaccine in Chinese women aged 18 to 35 years enrolled from Hong Kong.

- Design
  - Double-blind, randomised controlled trial with vaccine and placebo groups.
  - Three hundred women enrolled (150 per group) between March 2006 and June 2007.

- Results
  - Cervarix was shown to be highly immunogenic (all initially sero-ve subjects are seroconverted)
  - Immune responses induced were comparable to global studies
  - High compliance rate (99%) and well tolerated

Ngan HYS, et al. Hong Kong Med J. 2010; 16(3): 171-179

Overall frequency of solicited local symptoms during days 0-6 post-vaccination (total vaccinated cohort)



- The AS04-adjuvanted cervical cancer vaccine is generally well tolerated in Chinese women from Hong Kong and the compliance was high (99%) in both groups.

Ngan HYS, et al. Hong Kong Med J. 2010; 16(3): 171-179

Requirement for pharmacovigilance/ post-marketing surveillance

- Information sources used for pharmacovigilance
  - Spontaneous adverse drug reaction reporting schemes (e.g. VAERS, Yellow Card Scheme run by MHRA and CSM)
  - Clinical and epidemiological studies
  - Worldwide published medical literature
  - Information from pharmaceutical companies
  - Information from worldwide regulatory authorities
  - Morbidity and mortality databases
- Findings from these sources can lead to:
  - restrictions in use
  - changes in the dose of medicine
  - introduction of specific warnings of side-effects in product information

VAERS = Vaccine adverse event reporting system.
MHRA = UK Medicines and Healthcare Products Regulatory Agency.
CSM = Committee on Safety of Medicines.

pharmacovigilance/ post-marketing surveillance

- Major limitations
  - Under- or over-reporting
  - Impossibility to calculate frequency of AE
  - Impossibility to determine causality between reported AE and vaccine
  - Inconsistent quality of data

Who benefits from the vaccines

- Best protection in girls or women never exposed to HPV 16 and 18
- Before sexual exposure
- For population vaccination, logistic in maximizing coverage ties in with school based vaccination of 10-12 girls
- Catch-up programme is offered in many countries up to 18 or 26
- Efficacy among these women is variable depending on their sexual life

High Efficacy Demonstrated for the Co-Primary Endpoint

HPV 6/11/16/18-Related Persistent Infection, CIN, or EGL

Per Protocol Efficacy Population

Endpoints	Gardasil (N=1910)	Placebo (N=1907)	Observed Efficacy (%)	95% CI
Persistent Infection, CIN, or EGL	**10**	**86**	**88.7**	**78, 95**
Persistent Infection	9	85	89.6	79, 95
CIN (any grade)	1	17	94.1	63, 100
CIN 2/3 or worse	1	6	83.3	-38, 100
EGL	0	7	100	31, 100
Condyloma	0	7	100	31, 100
VIN 2/3 or VaIN 2/3	0	0	NA	NA

Vaccine Efficacy in Women Previously Infected with HPV 16 or 18 (ATP-E of HPV-008 study)

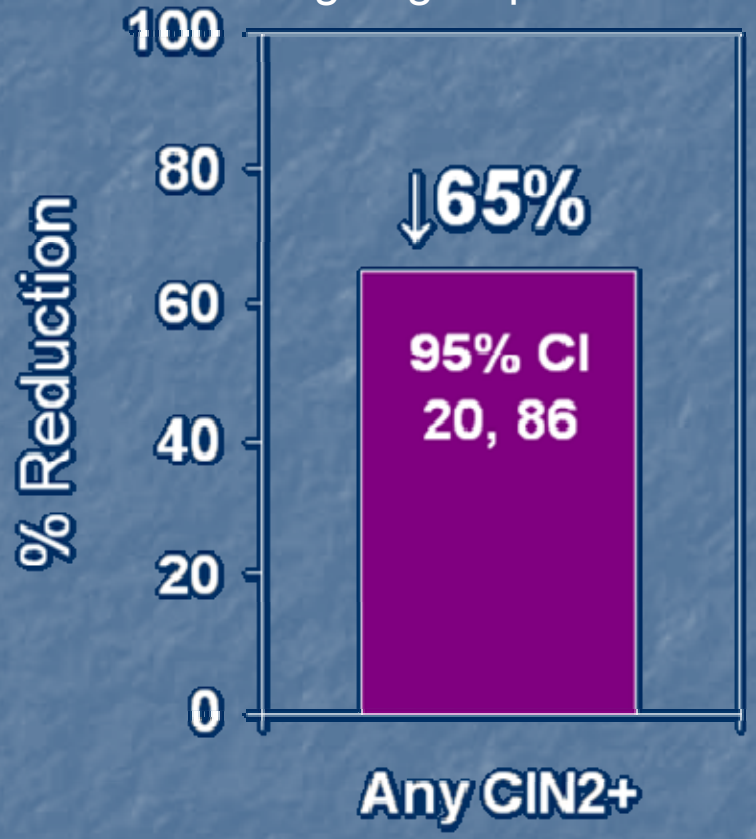
HPV 16/18 sero status/ DNA status	HPV 16/18 endpoint	Vaccine cases (N)	Control cases (N)	Efficacy %	96.1% CI
Sero+/DNA-	6-month PI	9 (1,462)	47 (1,496)	80.6[1]	58.6 - 92.0
	12-month PI	2 (1,427)	24 (1,461)	91.5[1]	64.0 - 99.2
	CIN2+	2 (1,510)	6 (1,547)	65.8[1]	-105.7 - 97.1
	CIN2+ TAA	0 (1,510)	5 (1,547)	100.0[1]	-22.9 - 100

TAA = HPV type-assignment algorithm. Persistent Infection (PI)
According-to-protocol cohort for efficacy (ATP-E)

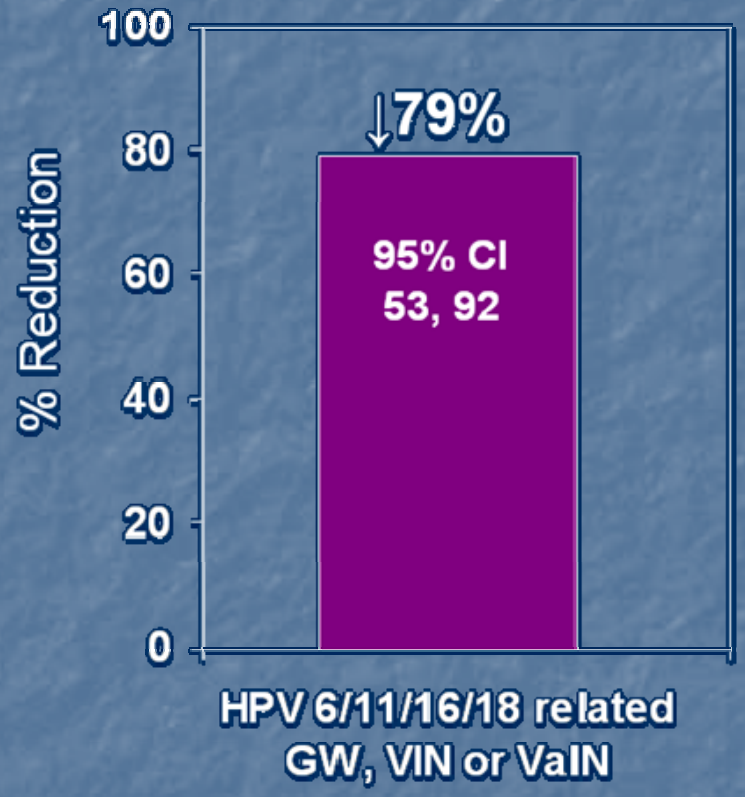
1. FDA. *CervarixTMVaccines and Related Biological Products Advisory Committee (VRBPAC) Briefing Document. Available at:* http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeeting/BloodVaccinesanOtherBiologics/VaccinesandRelatedBiolOgicalProductsAdvisoryCommittee/UCM181371.pdf. Accessed June 25, 2010.

Impact of GARDASIL on the incidence of "new" CIN / EGL after treatment*

*Case counting begins post-treatment



Vaccine group N=587
Placebo group N=763
2 year FU



Vaccine group N=222
Placebo group N=306
1.6 year FU

CIN= cervical intraepithelial neoplasia; EGL=external genital lesion

*Elmar A. Joura, 2009 ESGO presentation # 366

Is it safe in adult women?

- Both vaccines in adult women trials were shown to be safe

What benefit an adult women get out of vaccination?

- Assuming the women has not have sex and HPV exposure before, efficacy should be high
- If a woman is already sexually active, no test is reliable to be sure that she has never been infected or being infected but with a low viral titre. Thus no point in performing HPV testing
- Women with abnormal cytology or even CIN can be vaccinated though vaccines has no effect in reversing the abnormality. Potential benefit in preventing infection against re-infection or new infection
- Overall, we are not certain of how much benefit but it seems that it is likely that there will be some benefit

Cervical cancer screening

- MUST continue irrespective whether vaccinating before or after sexual exposure
- High protection is only to the vaccines types hence about 30% cervical cancer cannot be protected, need screening to pick them up
- Efficacy variable for those started sexual exposure, screening is needed to pick up pre-existing lesion or lesion caused by non-vaccine types
- Whether HPV testing should replace cytology for screening need further study

Conclusions

- Cervical Cancer Vaccines are effective especially before sexual exposure and are safe
- No data to show either vaccine is loosing effectiveness, hence, do not know if need booster
- Direct comparison between results of the 2 vaccines should be avoided as design, population characteristic and assessments were different
- Cross protection and some efficacy in previously infected women were sub-set analysis and should be interpreted with caution
- Post-marketing surveillance is important but do not jump into conclusion on any causal effect before review by expert panel
- Screening should be continued or initiated

Asia-Oceania Research Organisation in Genital Infection and Neoplasia

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