Giornate di Pediatria Preventiva e Sociale
Capri, 10 ottobre 2009

Protezione dal carcinoma della cervice uterina: i criteri di scelta del vaccino

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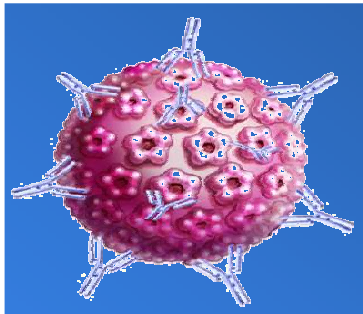
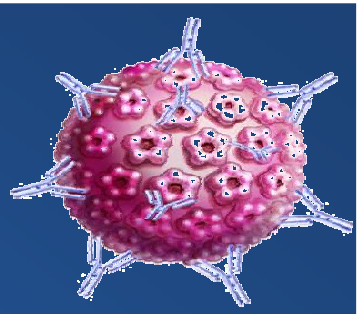
Università degli Studi di Genova



Characteristics of the current available HPV vaccines



	Quadrivalent [*Gardasil*]	Bivalent [*Cervarix*]
VLPs of genotype	6, 11, 16, 18	16, 18
Dose of L1 protein	20/40/40/20 mg	20/20 mg
Substrate	Yeast [S. Cerevisiae]	Baculovirus expression system [trichoplusia insect cell line infected with L1 recombinant virus]
Adjuvant	Amorphous aluminium hydroxyphosphate sulphate (**AAHS**), 225 mg	**AS04 system**: Aluminium hydroxyde, 225 mg AND Monophosphoryl lipid A (detoxified LPS from Salm. Minnesota), 50mg
Schedule used in trials	T0-T2-T6 months	T0-T1-T6 months
Way of administration	Intramuscular	Intramuscular

Current available HPV vaccines: two different products

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Clinical evaluation: main endpoints

- **Safety and tolerability profile**
- **Immunogenicity**
- **Efficacy against HPV 16-18 and cross-protection against NV-types**

Acquired knowledge, open issues and future perspectives on current available prophylactic HPV vaccines

Up date on the:

- **Safety and tolerability profile**
- **Immunogenicity**
- **Efficacy against HPV 16-18 and cross-protection against NV-types**

Safety profile of VLP vaccines

- VLPs are non-live and non-infectious protein subunit vaccines: safety profile expected similar to other protein subunit vaccines, i.e., tetanus or hepatitis B
- Safety data from the large phase III trials and early post-marketing surveillance supported this conjecture
- Very few dropouts due to vaccine-related symptoms (good compliance to the 3-dose schedule)
- No AE increased with each subsequent dose
- AE were not more severe in woman with evidence of prior exposure

HPV-vaccines WHO Position Paper, WER 2009
WHO Meeting Report, Biologicals 2009

Tolerability profile of VLP vaccines

- In clinical trials, most common reactions were mild or moderate i.e., pain, swelling and erythema at the site of injection
- Mild and transient local reactions at the site of injection (erythema, pain or swelling) were 10-20% more frequent among those who received the current HPV vaccines than in their respective control groups, but no systemic adverse reactions assessed to be causally associated with the HPV immunization have been reported
- Control vaccines in the trials: HAV vaccine for Cervarix – Aluminum based adjuvant alone for Gardasil

Study	N. of subjects	A.E.	Gardasil % vaccinees vs controls	Cervarix % vaccinee vs controls
Future I	2,241/2,258	Local pain	85.3 vs 75.4	
		Fever in 5d	14.8 vs 11.5	
Patricia	6,344/6,402	Local pain		90.5 vs 78
		Fever in 7d		12.4 vs 10.9

HPV-vaccines WHO Position Paper, WER 2009
WHO Meeting Report, Biologicals 2009
Garland et al., NEJM 2007
Paavonen et al, Lancet 2007
Einstein MH. Human Vaccines 2009

Human Vaccines 5:10 702-716; October; © 2009 Landes Bioscience

Comparison of the immunogenicity and safety of *Cervarix*™ and *Gardasil*® human papillomavirus (HPV) cervical cancer vaccines in healthy women aged 18–45 years

Mark H. Einstein,[1,*] Mira Baron,[2] Myron J. Levin,[3] Archana Chatterjee,[4] Robert P. Edwards,[5] Fred Zepp,[6] Isabelle Carletti,[7] Francis J. Dessy,[7] Andrew F. Trofa,[8] Anne Schuind,[8] and Gary Dubin,[8] on behalf of the HPV-010 Study Group

[1] Montefiore Medical Center, Albert Einstein College of Medicine, Department of Obstetrics & Gynecology and Women's Health, Division of Gynecologic Oncology, Bronx, NY USA; [2] Rapid Medical Research, Cleveland, OH USA; [3] University of Colorado Denver and Health Sciences Center, Aurora, CO USA; [4] Creighton University School of Medicine, Omaha, NE USA; [5] Ovarian Cancer Center of Excellence/Sciences University of Pittsburgh School of Medicine, Pittsburgh, PA USA; [6] University of Mainz, Mainz, Germany; [7] GlaxoSmithKline Biologicals, Rixensart, Belgium; [8] GlaxoSmithKline Biologicals, King of Prussia, PA USA

- Both vaccines were generally well tolerated.
- The percent of women in each group receiving all 3 doses was similar between the groups (84.6% Cervarix; 84.4% Gardasil): good compliance.
- The % of women reporting at least one solicited local (including grade 3) or general symptom within 7 days following vaccination was higher in those who received Cervarix than in those who received Gardasil (95.1% vs. 85.1%).
- All local solicited symptoms were transient (mean duration ≤3.3 days) and resolved spontaneously.

Safety profile of VLP vaccines in particular conditions and situations

- Data on the safety in pregnancy are limited: vaccination should be avoided!
- Little information do not suggest any concern in people who are immunocompromised due to medications or diseases (i.e., infected with HIV): evident benefit…
- Data on the quadrivalent vaccine do not indicate any safety concern following administration to lactating females (administrable)
- Data not available concerning the interchangeably of the two marketed vaccines. However, if the vaccine used for prior doses is unknown or unavailable, either of the marketed HPV vaccines can be administered to complete the schedule
- Co-administration with other non-live vaccines (HBV, DTaP-IPV) possible. Studies with other vaccines are ongoing……

HPV-vaccines WHO Position Paper, WER 2009
WHO Meeting Report, Biologicals 2009

Cervarix®: pooled safety analysis

Pooled HPV Vaccine Safety Analysis: 11 studies with same vaccination schedule and similar methodology of safety assessment

- Controls include placebo (Alum – $Al(OH)_3$) and the Hepatitis A vaccine, *Havrix*™ (360µg and 720µg), that does not contain MPL components

Robust methodology for collection of standard safety data with additional prospective collection of data on pregnancy outcomes and autoimmune diseases

Safety outcomes	HPV	Pooled control groups
Women reporting at least one SAE	**2.8%**	3.1%
Medically significant conditions	**19.4%**	21.4%
New onset chronic disease	**1.7%**	1.7%
New onset autoimmune disease	**0.4%**	0.3%

Descamps *et al.* Human Vaccines 2009

Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women

J Paavonen, P Naud, J Salmerón, C M Wheeler, S-N Chow, D Apter, H Kitchener, X Castellsague, J C Teixeira, S R Skinner, J Hedrick, U Jaisa
G Limson, S Garland, A Szarewski, B Romanowski, F Y Aoki, T F Schwarz, W A J Poppe, F X Bosch, D Jenkins, K Hardt, T Zahaf, D Descamy
M Lehtinen, G Dubin, for the HPV PATRICIA Study Group

Lancet 2009; 374: 301–14
Published Online
July 7, 2009
DOI:10.1016/S0140-6736(09)61248-4

	Vaccine	Control
Safety outcomes		
Women assessed (n)	9319	9325
Serious adverse event	701 (8%)	699 (8%)
Vaccine-related serious adverse events	11 (<1%)	6 (<1%)
Medically significant condition*	2960 (32%)	3025 (32%)
New-onset chronic disease†	251 (3%)	268 (3%)
New-onset autoimmune disease	78 (<1%)	77 (<1%)
Deaths‡	9 (<1%)	8 (<1%)
Pregnancy and pregnancy outcomes§		
Pregnancies (n)	1804	1802
Ongoing pregnancies	204 (11%)	212 (12%)
Normal infant	1124 (62%)	1136 (63%)
Abnormal infant		
Congenital anomaly¶	12 (<1%)	9 (<1%)
Medically significant condition‖	9 (<1%)	10 (<1%)
Spontaneous abortion	164 (9%)	156 (9%)
Elective termination	185 (10%)	194 (11%)

Data are number (%) of women reporting an event, unless otherwise indicated. *Medically significant conditions were defined as adverse events (prompting visits to the emergency department or to the physician) that are not routine or related to common diseases, or serious adverse events that are not related to common diseases. †A predefined list of potential new-onset chronic diseases (NOCDs) was reviewed by the Independent Data Monitoring Committee (IDMC). On the basis of this prespecified list, the clinical database was searched for all potential NOCDs and reviewed in a blinded manner by a physician from GlaxoSmithKline before data analysis was done. An event was thought to be a potential NOCD if it had not been recorded in the previous medical history of the individual (ie, new onset) or if symptoms were characteristic of a NOCD, or both. A separate list, restricted to potential autoimmune events, was also reviewed by the IDMC and was used by the GlaxoSmithKline safety physician to identify new-onset autoimmune diseases. ‡No deaths were thought to be possibly related to vaccination in either group. §Some less frequent pregnancy outcomes are not listed. ¶Defined as structural, morphological, chromosomal, and genetic anomalies. ‖Defined as all other reports of abnormal outcomes considered to be medically significant (eg, congenital infectious conditions, neonatal death).

Table 5: **Safety and pregnancy outcomes in the total vaccine cohort during the entire study**

Human papillomavirus vaccines
WHO position paper

In June 2007, WHO's Global Advisory Committee on Vaccine Safety (GACVS) concluded that both vaccines had good safety profiles.[22] In December 2008, GACVS reviewed data on early post-marketing surveillance of the quadrivalent HPV vaccine. No reports raised sufficient concern to change previous advice given by GACVS.[23]

WEEKLY EPIDEMIOLOGICAL RECORD, NO. 15, 10 APRIL 2009

Acquired knowledge, open issues and future perspectives on current available prophylactic HPV vaccines

Up date on the:

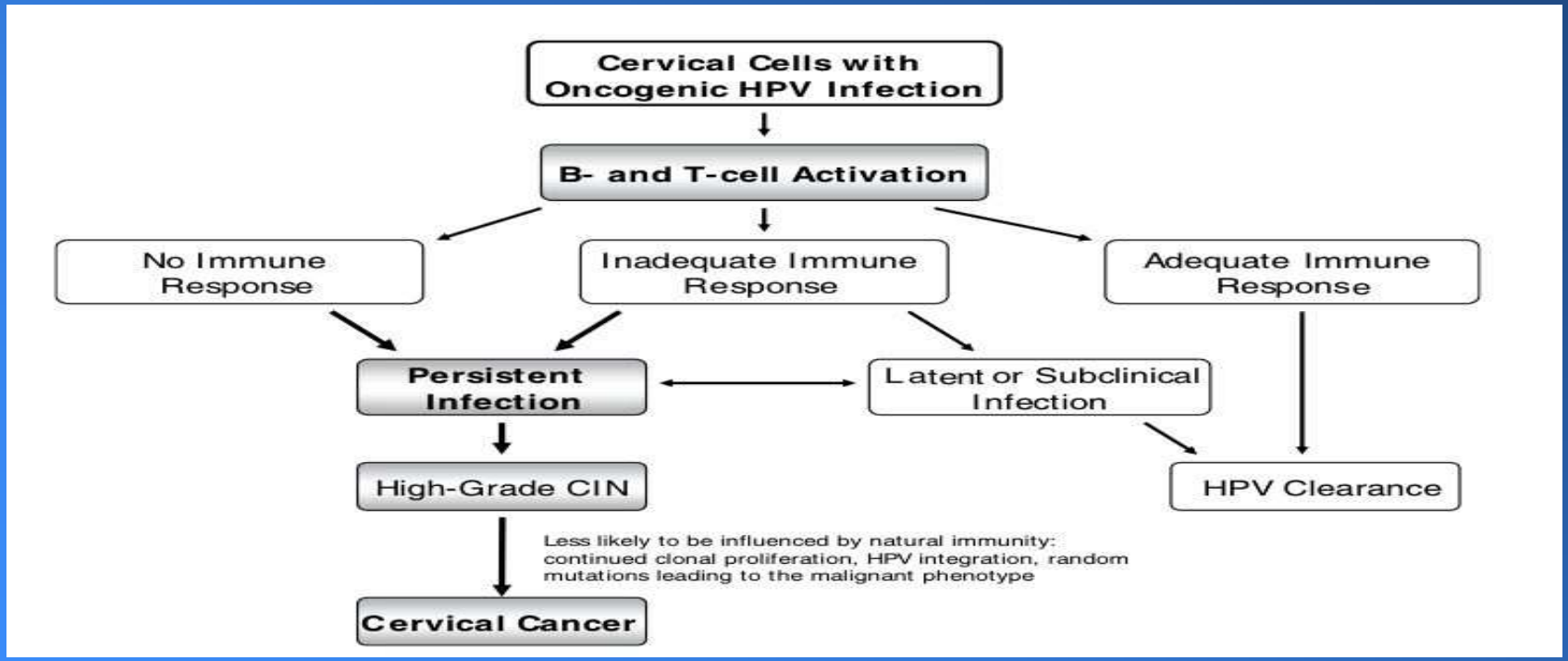
- **Safety and tolerability profile**
- **Immunogenicity**
- **Efficacy against HPV 16-18 and cross-protection against NV-types**

Cancer Immunol Immunother (2008) 57:443–451
DOI 10.1007/s00262-007-0440-y

REVIEW

Acquired immune response to oncogenic human papillomavirus associated with prophylactic cervical cancer vaccines

Mark H. Einstein



The mechanisms by which these vaccines induce protection have not been fully defined but **active protection from infection is thought to be mediated by both cellular immunity and neutralizing Ig G antibodies at the cervix.**

Stanley M, *et al. Vaccine* 2006;
WHO Position Paper 2009

No Immune Correlate of Protection for HPV vaccines exists to date….

2009, 84, 117–132 No. 15

World Health Organization

Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

10 APRIL 2009, 84th YEAR / 10 AVRIL 2009, 84e ANNÉE
No. 15, 2009, 84, 117–132
http://www.who.int/wer

Gardasil® Summary of Product Characteristics

No minimum antibody level associated with protection has been identified for HPV vaccines.

Cervarix® Summary of Product Characteristics

Immunogenicity

No minimal antibody level associated with protection against CIN of grade 2 or 3 or against persistent infection associated with vaccine HPV types has been identified for HPV vaccines.

Available online at www.sciencedirect.com
ScienceDirect
Vaccine 24S3 (2006) S3/187–S3/192
Vaccine
www.elsevier.com/locate/vaccine

Chapter 22: Assuring the quality, safety and efficacy of HPV vaccines: The scientific basis of regulatory expectations pre- and post-licensure

David Wood [a,*,1], Jin-ho Shin [a,1], Bernard Duval [b], Heinz-Joe Schmitt [c]

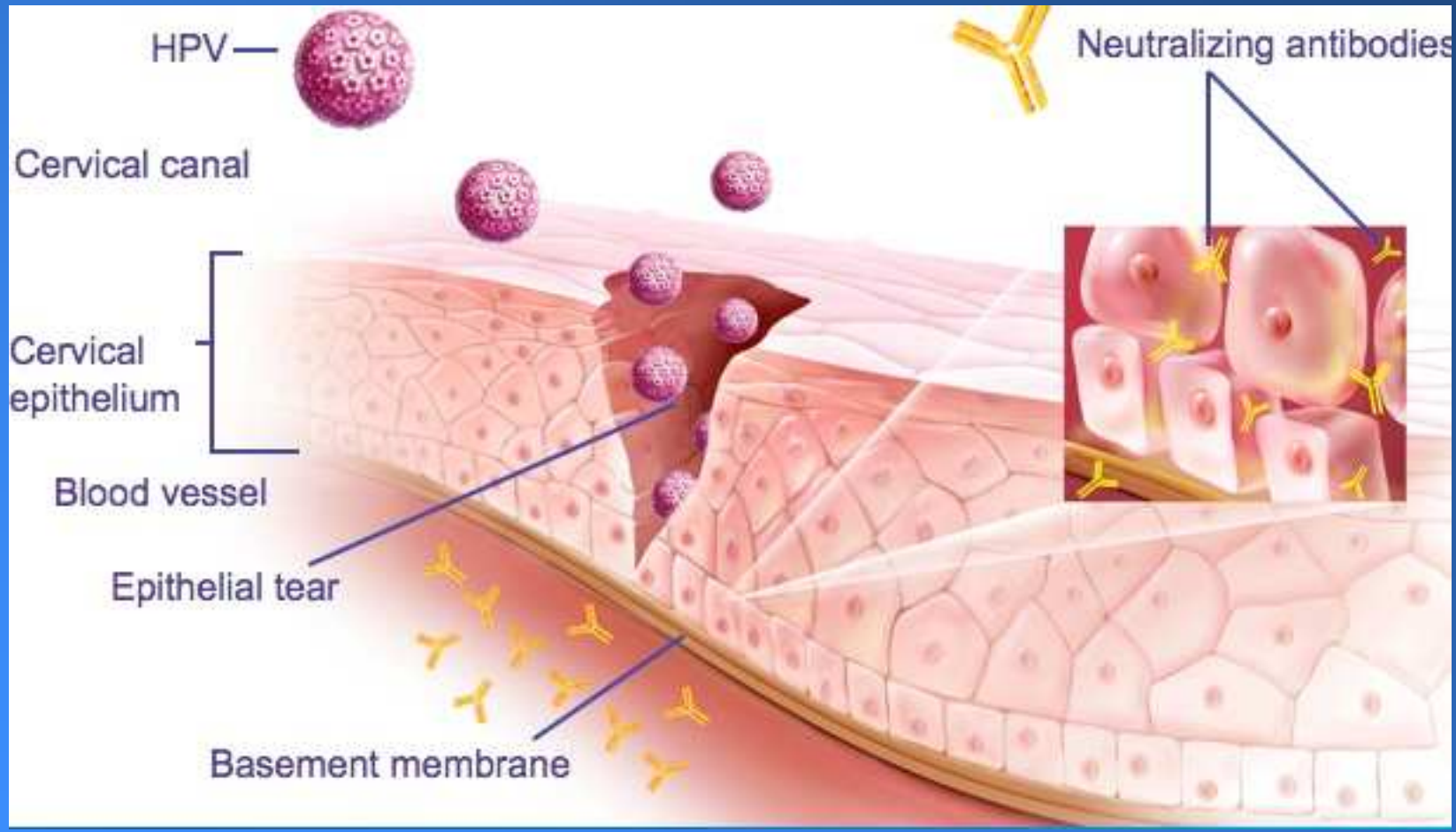
[a] *World Health Organization, Immunizations, Vaccines and Biological, Avenue Appia, CH 1211 Geneva, Switzerland*
[b] *Groupe scientifique en immunisation, Institut national de santé publique du Québec, Québec, Canada G1E 7G9*
[c] *Department of Paediatrics and Center for Clinical Trials, Johannes Gutenberg Universitat, Mainz, Germany*

Received 18 April 2006; accepted 15 May 2006

"…….Even if correlation cannot be established, Ab titres will be used as surrogate of protection…"

Wood D, Vaccine 2006

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

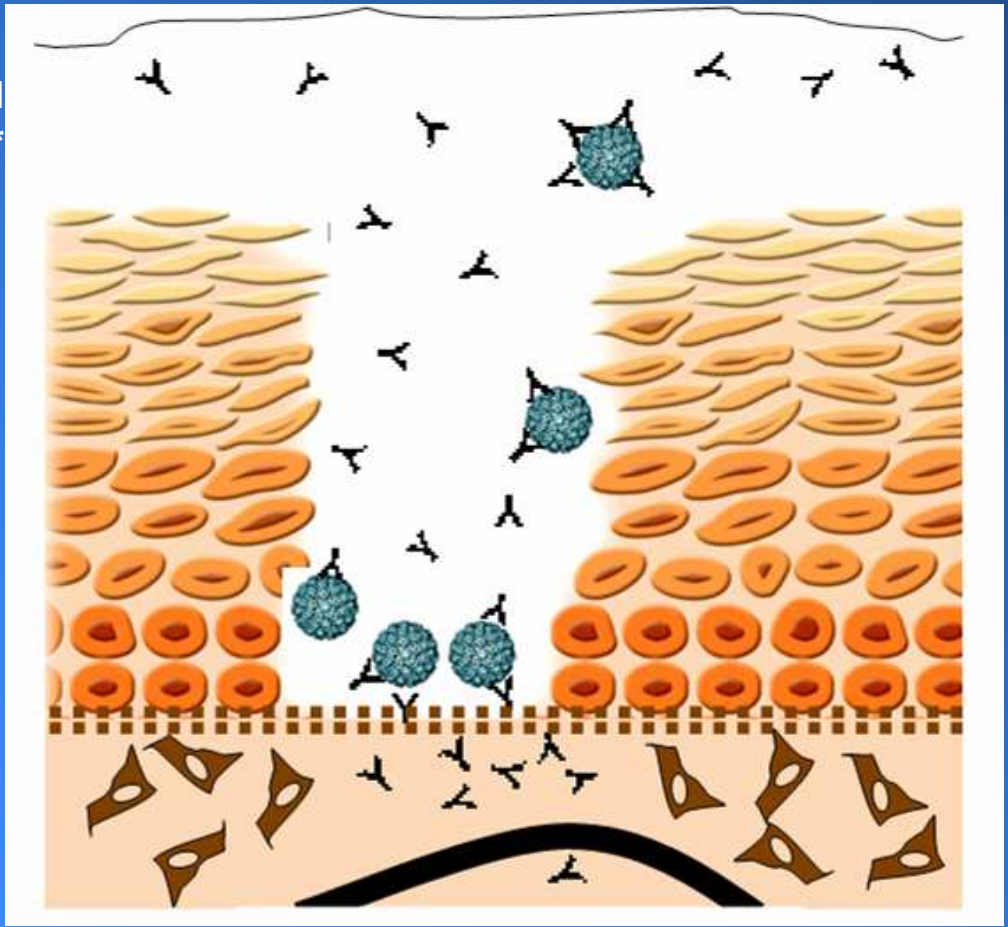


1. Stanley M. *Vaccine* 2006; **24:**S16–S22;
2. Giannini S, *et al. Vaccine* 2006; **24:**5937–5949;
3. Nardelli-Haefliger D, *et al. J Natl Cancer Inst* 2003; **95:**1128–1137;
4. Poncelet S, *et al.* IPC 2007(poster).

How could IM injection of a VLP vaccine prevent mucosal infection at the cervix?

Transudated Abs in mucus*

Exudated Abs at sites of trauma



Cervical mucus

Cervical epithelium

Basement membrane

Submucosa

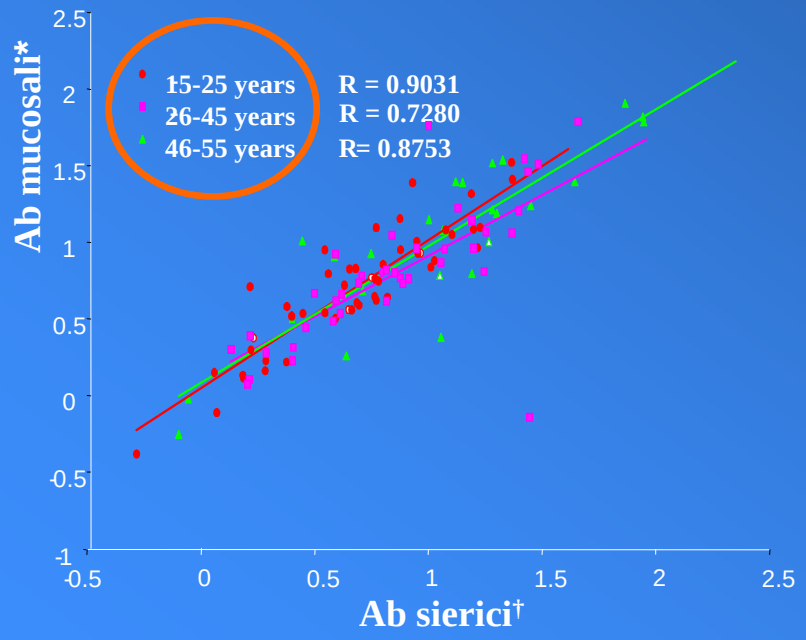
* VLP-specific IgG in cervical mucus ~10-fold lower than in the serum after intramuscular (IM) vaccination.[2]

1. Munoz N, *et al.* Chapter 1: HPV in the etiology of human cancer. *Vaccine* 2006; 24(Suppl 3)**:**S1–S10;
2. Nardelli-Haefliger D. *et al. J Natl Cancer Inst.* 2003; **95:**1128–1137; 3. Giannini S, *et al. Vaccine* 2006; **24:**5937–5949;
4. Poncelet S. *et al.* Abstract. Annual Meeting of the European Society for Pediatric Infectious Diseases. May 2–4, Porto, Portugal. 2007.

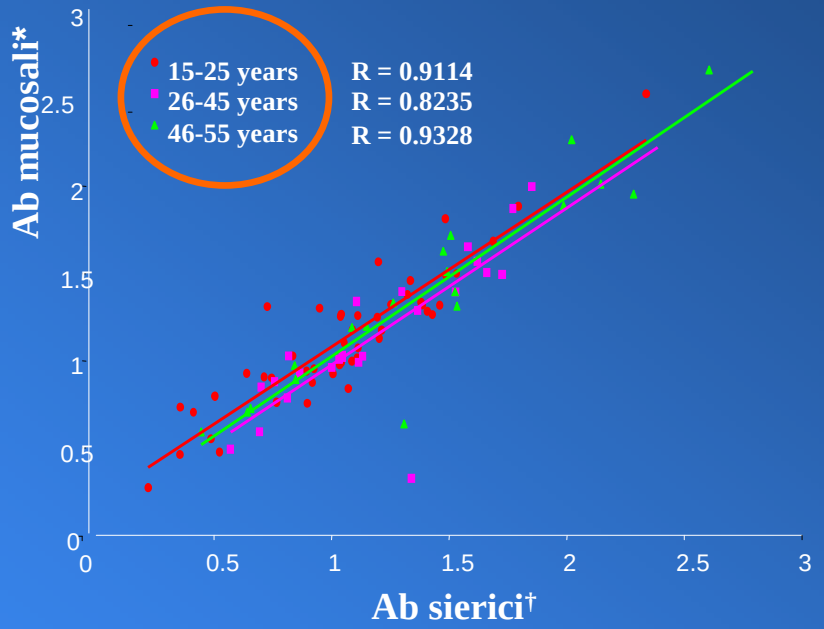
Significato di un elevato livello di Ab a livello della cervice

Elevata correlazione tra livelli anticorpali sierici e mucosali in soggetti 15-55aa di età, misurati in ELISA

Anti-HPV 16



Anti-HPV 18



*** Log titolo di CVS/totali IgG**

†Log titolo di Siero/totali IgG. I titoli Ab mucosali sono approssimativamente 1/10° di quelli presenti nel siero.

Poncelet S et al. 24th International Papillomavirus Conference 2007;Abstract PS19-25.

Immunogenicity of HPV vaccines

Both vaccines were shown to be highly immunogenic in clinical trials, resulting in essentially 100% seroconversion.

Stanley M, Vaccine 2008

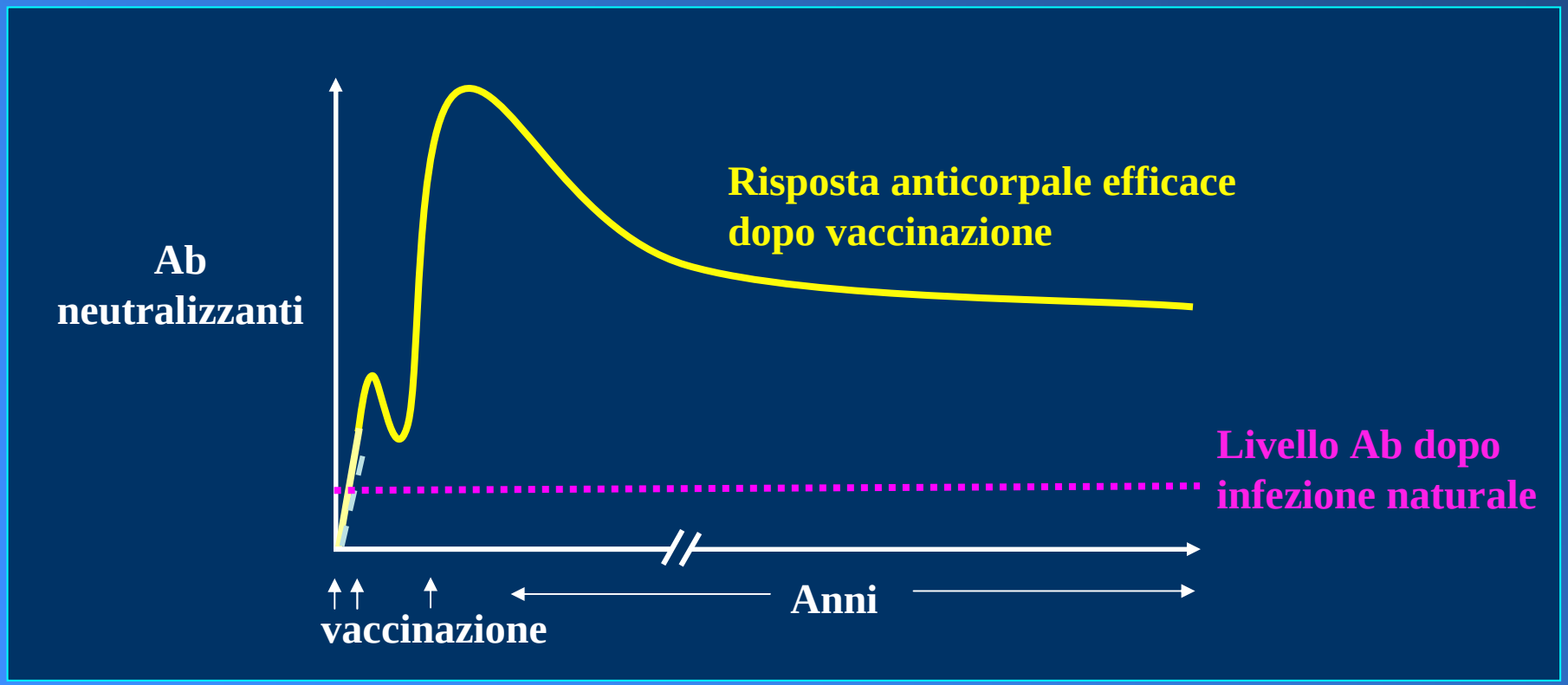
Peak geometric mean antibody titers (GMTs) were approximately 10- to 100-fold higher than the GMTs generated after natural infection.

Harper DM Lancet 2004

Garland SM, CVI 2007

Risposta immune dopo infezione naturale e dopo vaccinazione

- La vaccinazione dovrebbe prevenire l'infezione da HPV inducendo la produzione di Ab neutralizzanti, ad elevato titolo e di lunga durata, in tutti i soggetti immunizzati[1,2]
- L'immunità che segue all'infezione naturale non ha queste caratteristiche[3–5]



Viscidi RP et al. Clin Diag Lab Immunol 1997;4:122–126; Carter JJ et al. J Infect Dis 2000;181:1911–1919; Ho GY et al. Cancer Epidemiol Biomarkers Prev 2004;13:110-116.; Stanley M et al. Vaccine 2006;24 Suppl 3:S106–S113; 2. WHO Department of Immunization, Vaccines and Biologicals 2007.

Available online at www.sciencedirect.com
ScienceDirect
Gynecologic Oncology 110 (2008) S1–S10
Gynecologic Oncology
www.elsevier.com/locate/ygyno

Immune response to human papillomavirus after prophylactic vaccination with AS04-adjuvanted HPV-16/18 vaccine: Improving upon nature

Tino F. Schwarz [a,*], Oberdan Leo [b,1]

As a result of the asymptomatic pattern of HPV infection in women and their life-long risk of being infected, the first goal of a prophylactic vaccine is:

- to improve on natural immunity, inducing a first line of immunological defense by eliciting high level of Abs able to prevent the virus from entering the cells just at the site of infection

- to ensure long-term protection

The immune system: key players

Innate immunity

- Not antigen specific
- Recognize '**danger signals**' from stressed or dying cells
- Leads to inflammation
- Involves activation of **antigen-presenting cells (APCs)**
- No 'recall' or immune memory

Leads to activation of

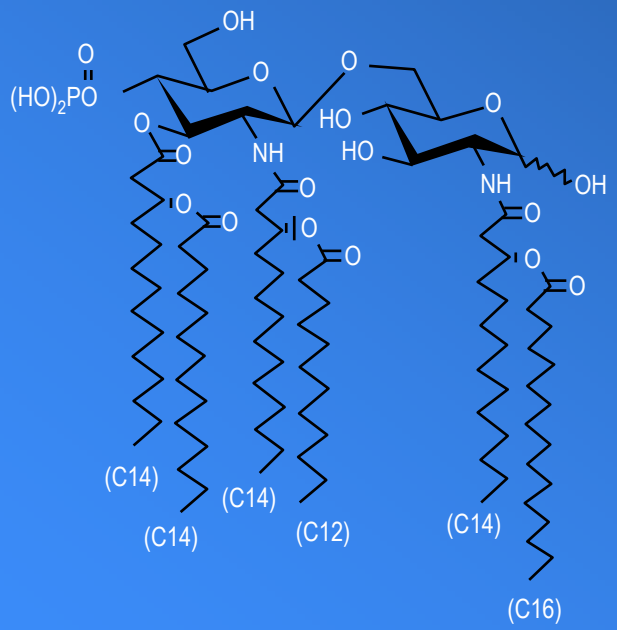
Adaptive immunity

- Antigen specific
- **APCs** are critical for activation of effector cells
- Two main effector cell types:
  - **B cells** produce antibodies
  - **T cells** (cell-mediated immunity)
    - T helper cells: 'help' B cells to make antibodies
    - Cytotoxic T cells (CTL): kill virally infected cells
- Generates **immune memory**

Seya T, *et al. Evid Based Complement Alternat Med* 2006; **3:**31–38.
Pulendran B & Ahmed R. *Cell* 2006; **124:**849–863.

Monophosphoryl lipid A: detoxified LPS

Obtained from
Salmonella minnesota

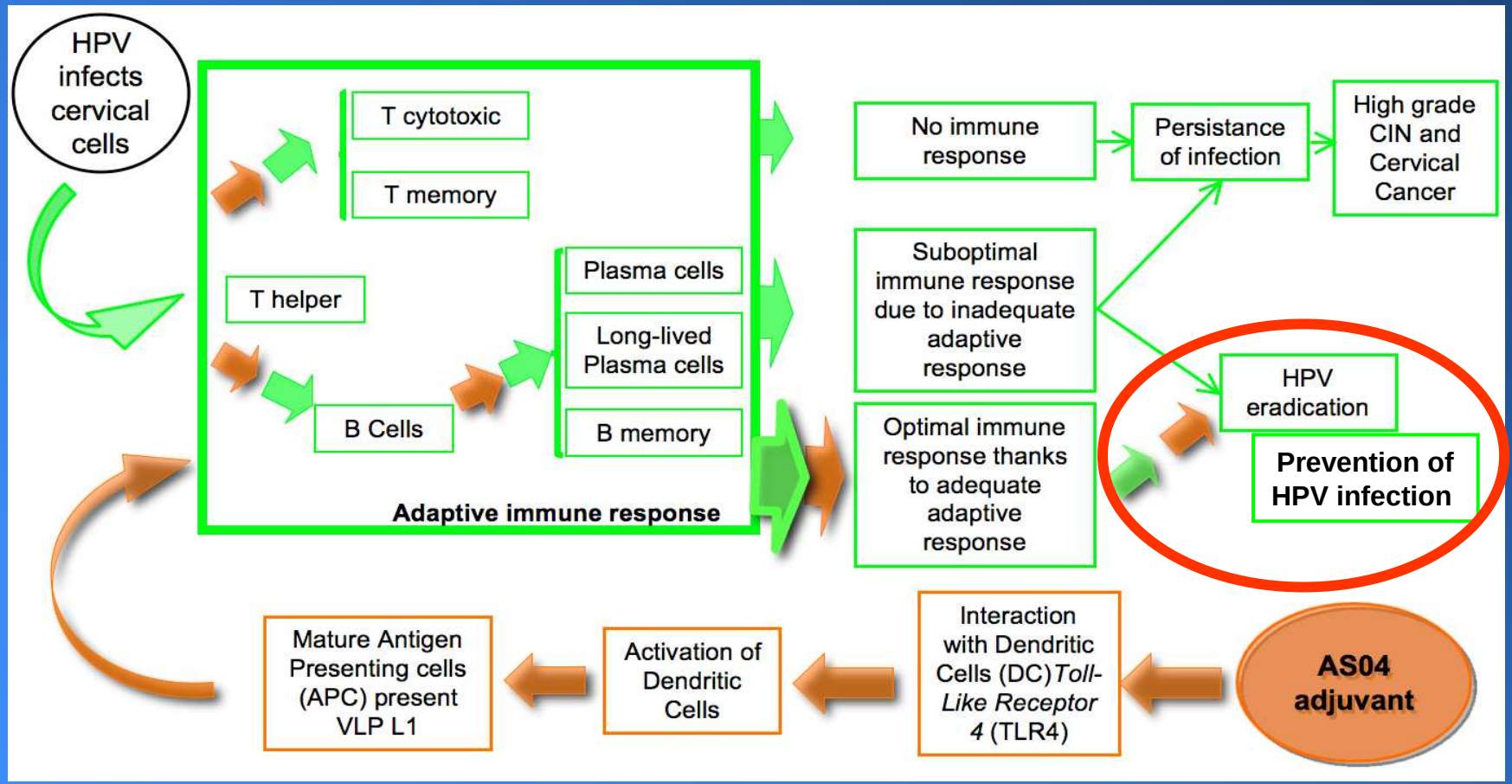


MPL adsorbed onto $Al(OH)_3$= AS04, a GSK proprietary adjuvant system

MPL, the novel immunostimulant within AS04, is derived by chemical modification of lipopolysaccharide (LPS)[1,2]
LPS is present in bacteria and ubiquitous in the environment
Humans are regularly exposed to LPS[1]
AS04 has shown to be well tolerated in numerous clinical trials[1]
Individual clinical trials may not have the power to monitor and evaluate the occurrence and impact of vaccination on rare adverse events (AEs)[1]
Verstraeten *et al.* evaluated the safety of AS04 adjuvanted vaccines with regard to rates of AEs of potential autoimmune aetiology[1]

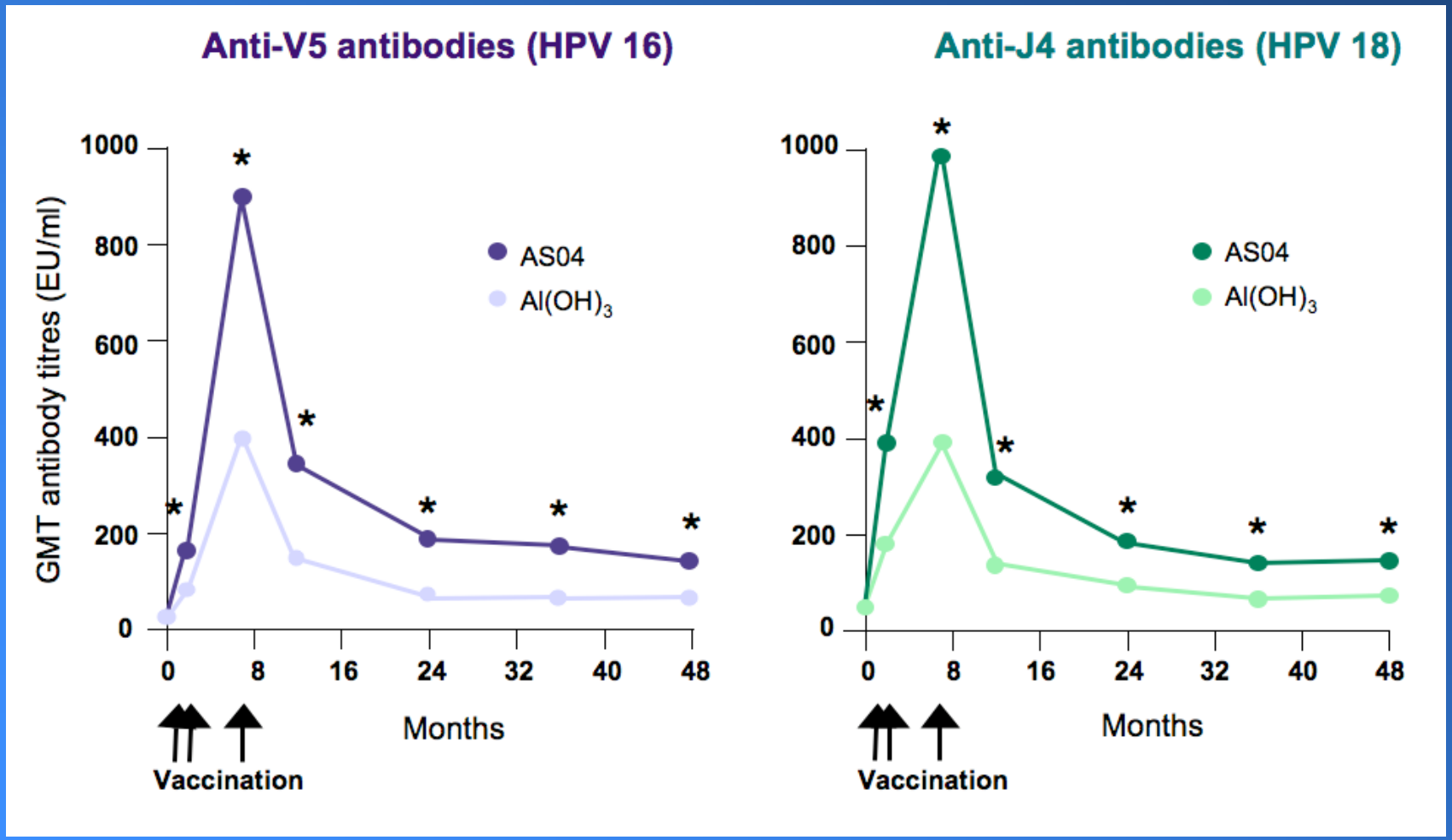
1,Verstraeten M, *et al. Vaccine*. 2008
2, Garcon N. In: *Immunopotentiators in modern vaccines*, 2006; pp. 161–178

Role of the immune system in response to HPV natural infection: key players, clinical outcomes and triggering effect of the AS04 adjuvant on the activation of the immune response



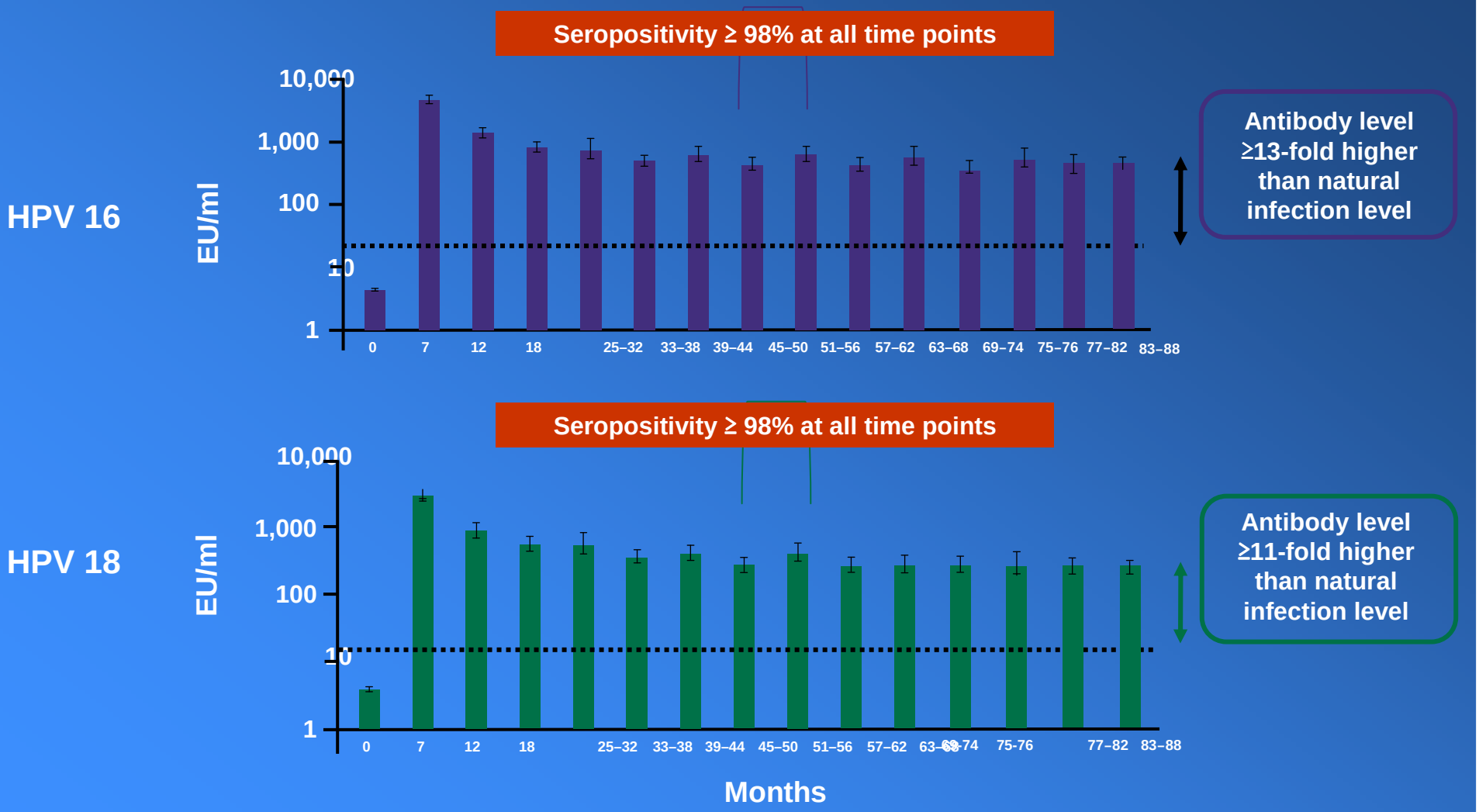
Seya T, *Evid Based Complement Alternat Med* 2006
Pulendran B & Ahmed R. *Cell* 2006
Stanley M, Vaccine 2006
Schwarz TF, Gynecol Oncol 2008
Stanley M, Vaccine 2008

Cervarix® with AS04 induces antibody levels that are sustained at higher levels than the same antigens adjuvanted with $Al(OH)_3$ in humans



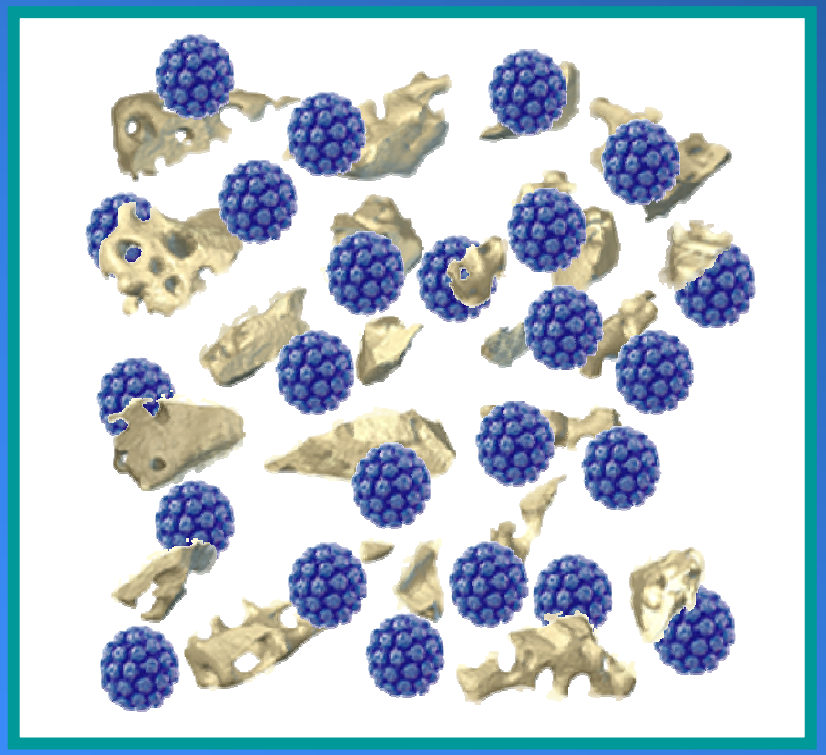
Giannini SL, Vaccine 2006

Cervarix® Phase IIb study: high and sustained antibody levels up to 7.3 years (ELISA antibodies)

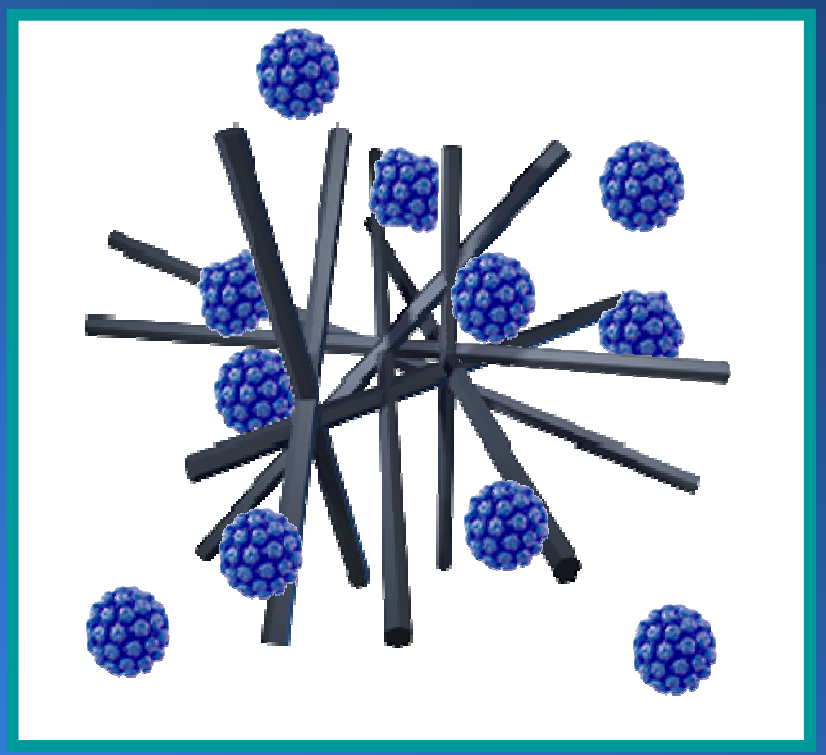


Adapted from De Carvalho, N *et al.* 25th International Papillomavirus Conference (Abstract P-29.15), 2009.

Confronto tra Idrossido di Alluminio ed il nuovo Idrossifosfato Solfato amorfo di Alluminio



con AAHS*



con $Al(OH)_3$**

Gli adiuvanti aiutano a presentare le particelle vaccinali al sistema immune. La "presentazione" è un aspetto importante e AAHS* permette un uptake migliore da parte del sistema immune rispetto all' $Al(OH)_3$**

* Idrossifosfato Solfato amorfo di Alluminio

** Idrossido di Alluminio

Lindblad E. *Vaccine* 2004;22:3658–68.
Morefield G et al. *Vaccine* 2005;23:1588-95.

Gardasil®: confronto tra alluminio idrossido cristallino e alluminio idrossi fosfato solfato amorfo (AAHS)

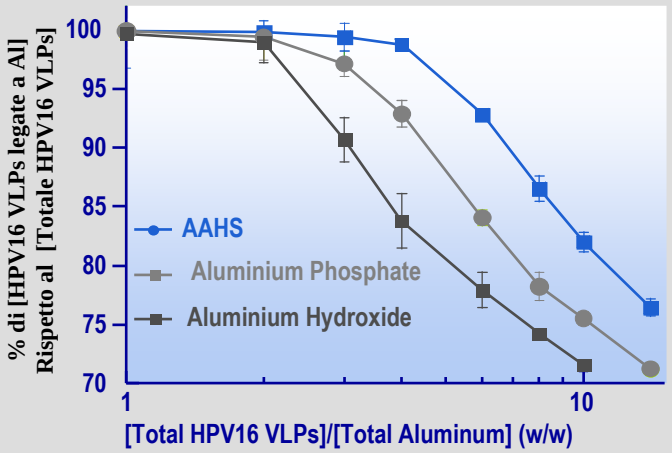
[Human Vaccines 3:4, 139-146, July/August 2007]; ©2007 Landes Bioscience

Research Paper

Effect of Alternative Aluminum Adjuvants on the Absorption and Immunogenicity of HPV16 L1 VLPs in Mice

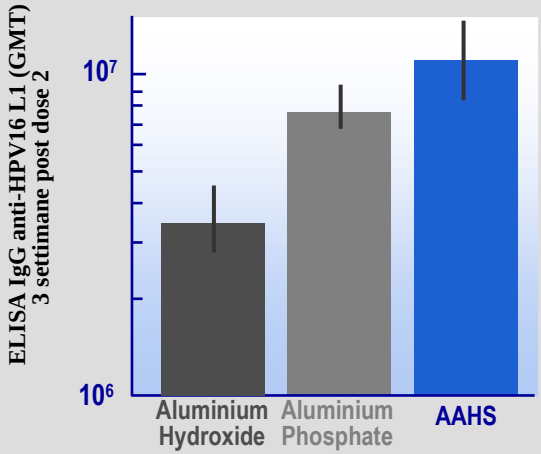
Michael J. Caulfield[1,*]
Li Shi[2]
Su Wang[1]
Bei Wang[2]
Timothy W. Tobery[1,†]
Henryck Mach[2]
Patrick L. Ahl[2]
Jayme L. Cannon[2]
James C. Cook[1]
Jon H. Heinrichs[1]
Robert D. Sitrin[3]

AAHS lega più VLP rispetto agli altri adiuvanti con alluminio**



Capacità di legame ad HPV 16 VLP dei differenti adiuvanti

AAHS ottimizza l'immunogenicità delle VLPs

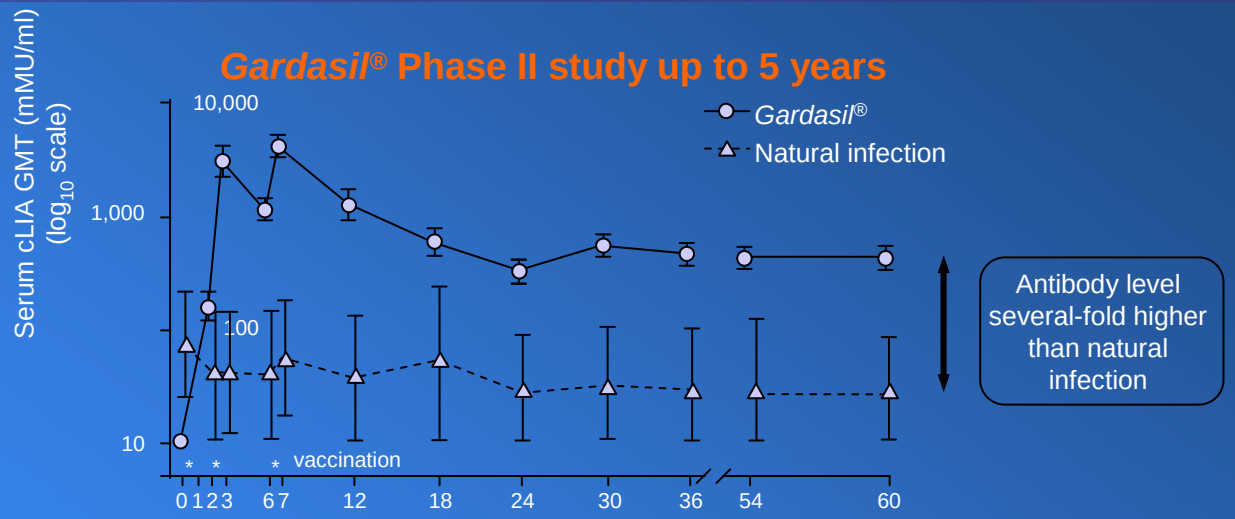


Risposta anticorpale verso HPV 16 VLP con i diversi adiuvanti misurata in vivo in topi Balb c

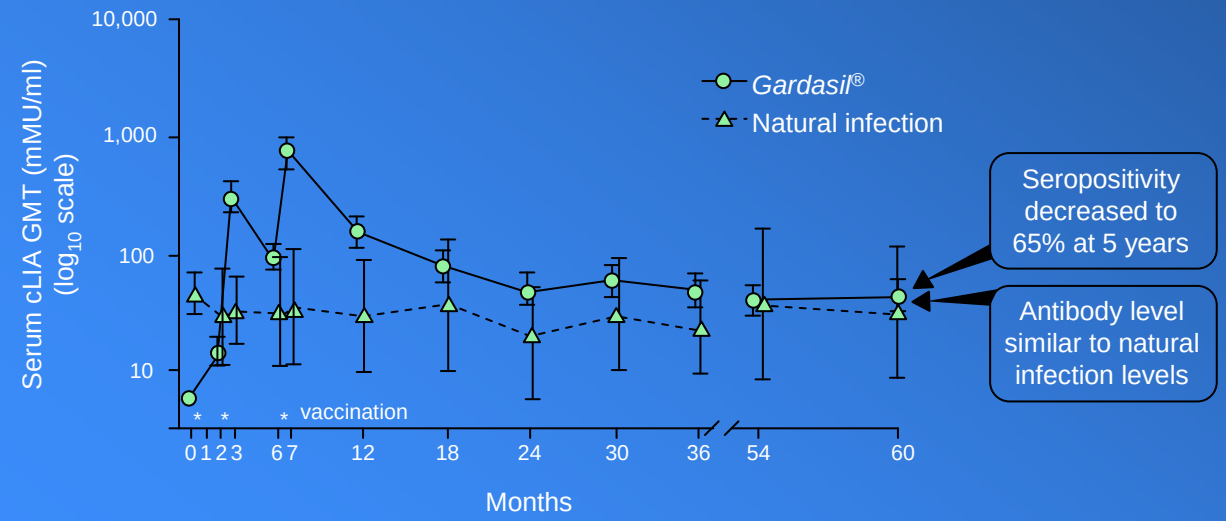
Antibody levels with *Gardasil*® compared with those following natural infection (up to 5 yrs)

*** Antibody levels reported here are measured by different methods and in separate studies for *Cervarix*™ and *Gardasil*® and therefore cannot be directly compared**

HPV 16

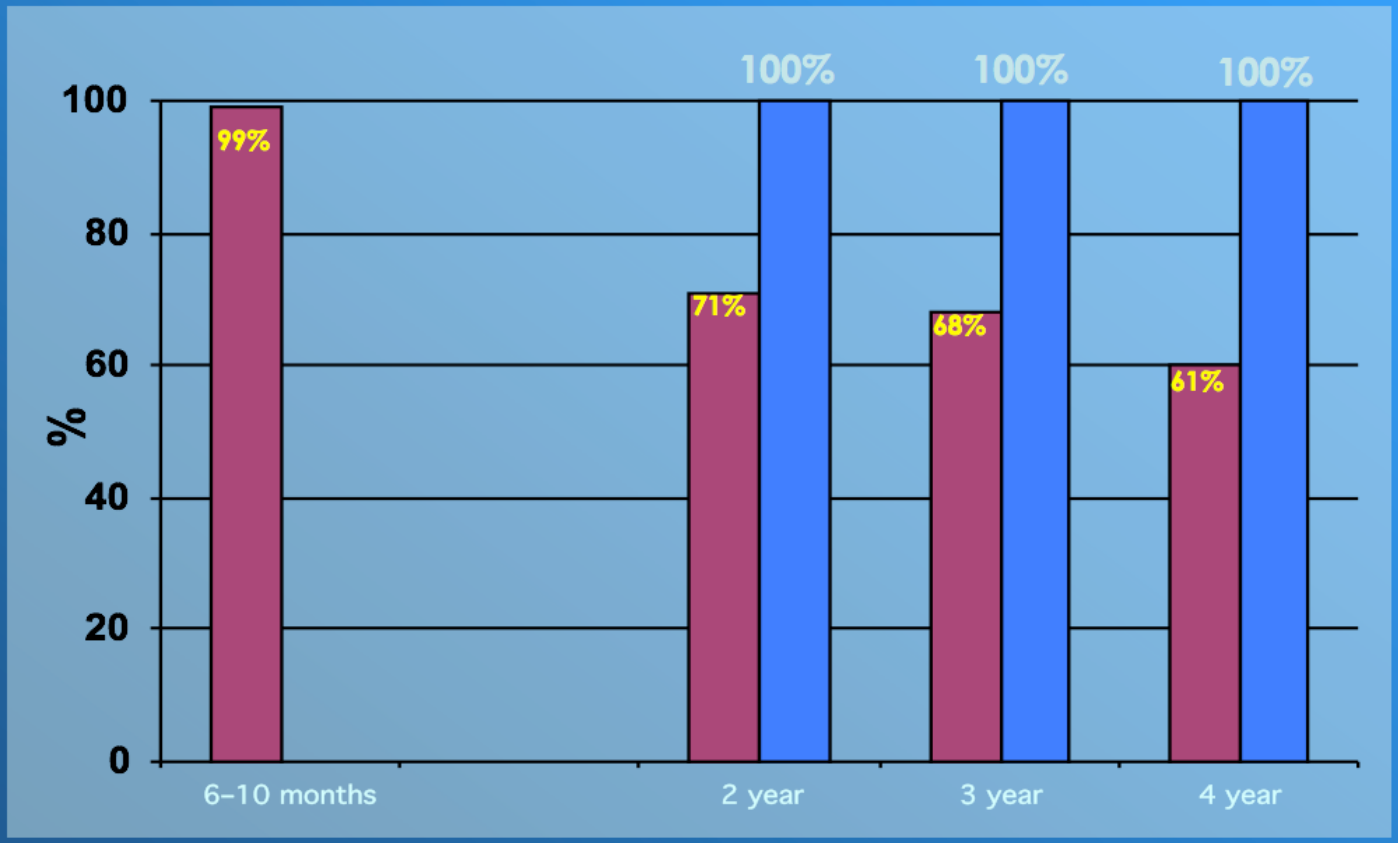


HPV 18



Adapted from Olsson SE, *et al. Vaccine* 2007; **25:**4931–4939; Villa LL, *et al. Vaccine* 2006; **24:**5571–5583.

Seropositivity and Efficacy of Gardasil® against HPV 18 related CIN2/3 or AIS in Women 16–26 years



*Seropositivity to HPV 18 neutralizing antibodies to a single neutralizing epitope measured by cLIA

Joura E, Vaccine 2008

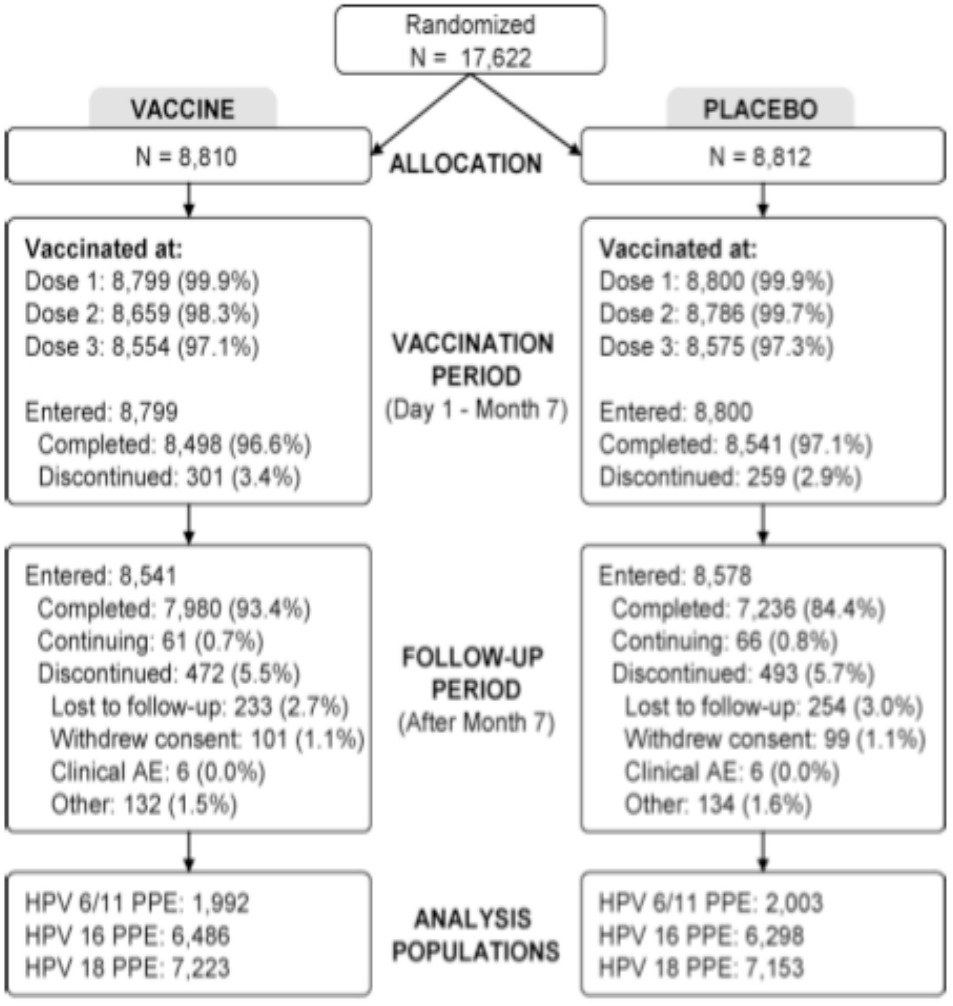
Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

HPV antibody levels and clinical efficacy following administration of a prophylactic quadrivalent HPV vaccine

Elmar A. Joura[a,*], Susanne K. Kjaer[b], Cosette M. Wheeler[c], Kristján Sigurdsson[d], Ole-Erik Iversen[e],



AE = adverse experience; PPE = per-protocol efficacy.

Although 40% of vaccine subjects were anti-HPV 18 seronegative at end-of-study, efficacy against HPV 18-related disease remained high (98.4%; 95% CI: 90.5-100.0) despite high attack rates in the placebo group.

These results suggest vaccine-induced protection via immune memory, or lower than detectable HPV 18 antibody titers.

Vaccine xxx (2009) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Letter to the Editor

HPV 18 antibody levels, clinical efficacy and induced immune memory: A trio?

The follow-up time simply does not allow the detection of breakthrough infections. The study will never answer this question because it has been stopped and all participant of the placebo arm have been offered the vaccine. The only possible way breakthrough infection of HPV 18 can be detected is by the follow-up of the Nordic registries and registration trials. The question of immune memory remains unanswered until then.

Marc R. De Ridder
Institut de Pharmacie, Campus de la Plaine,
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ELSEVIER

Gynecologic Oncology 110 (2008) S1 – S10

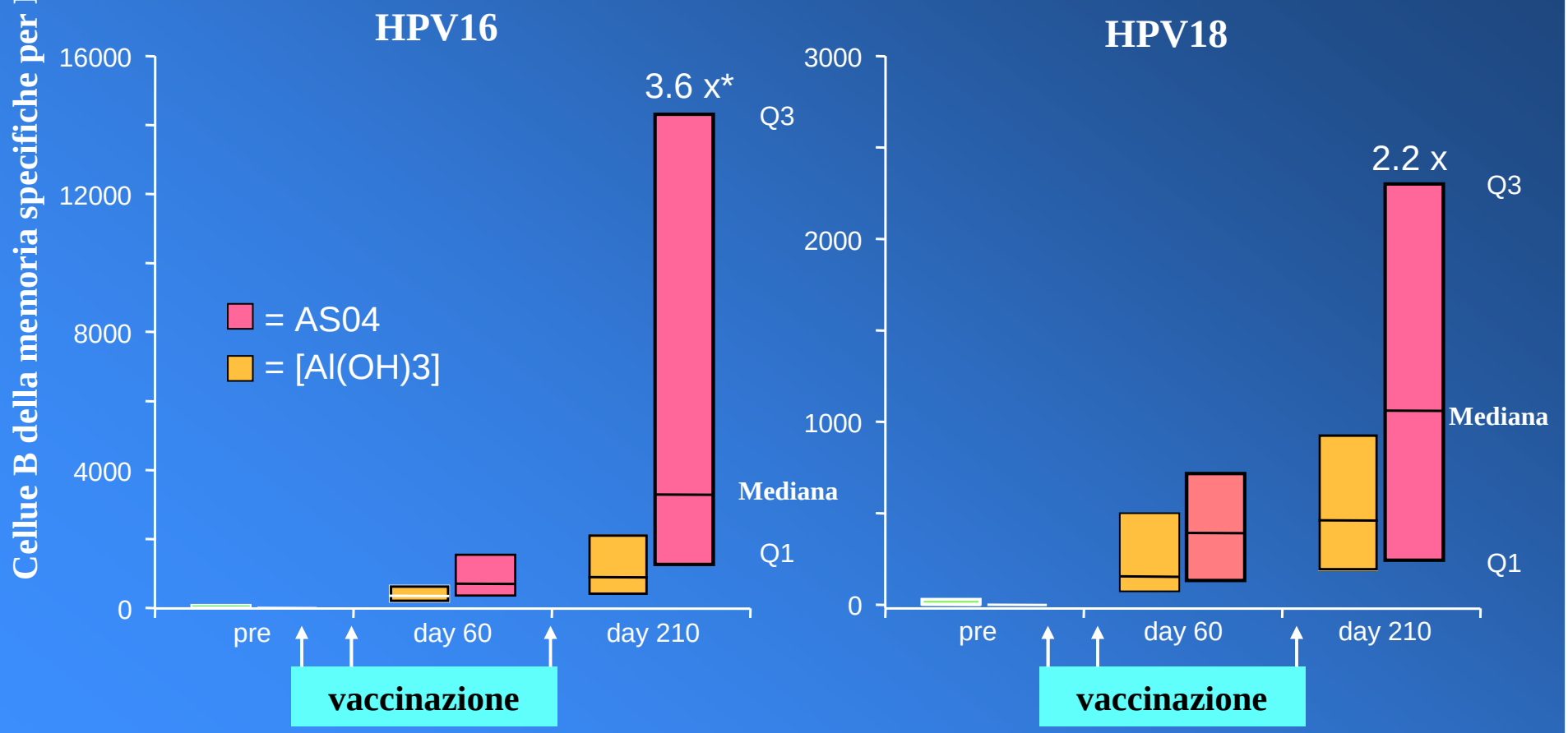
www.elsevier.com/locate/ygyno

Immune response to human papillomavirus after prophylactic vaccination with AS04-adjuvanted HPV-16/18 vaccine: Improving upon nature

Tino F. Schwarz [a,*], Oberdan Leo [b,1]

Traditionally, the induction of memory B cells is considered a crucial factor for the long-term efficacy of vaccine-induced protection . Indeed, a sustained specific antibody production does not only reflect the generation of long-lived plasma cells but also the induction of memory B cells able to regenerate the pool of antibody-secreting cells.

Effetti del sistema adiuvante AS04 di *Cervarix* e di $Al(OH)_3$ sulle cellule B della memoria nell'uomo a confronto



* Statisticamente significativo (p <0.05, Wilcoxon's test)

Giannini SL, Vaccine 2006

Available online at www.sciencedirect.com
ScienceDirect
Vaccine 25 (2007) 4931–4939
Vaccine
www.elsevier.com/locate/vaccine

Induction of immune memory following administration of a prophylactic quadrivalent human papillomavirus (HPV) types 6/11/16/18 L1 virus-like particle (VLP) vaccine

Sven-Eric Olsson [a,*], Luisa L. Villa [b], Ronaldo L.R. Costa [c], Carlos A. Petta [d], Rosires P. Andrade [e], Christian Malm [f], Ole-Erik Iversen [g], John Høye [h], Margareta Steinwall [i], Grete Riis-Johannessen [j], Agneta Andersson-Ellstrom [k], Kristina Elfgren [l], Geo von Krogh [m], Matti Lehtinen [n], Jorma Paavonen [o], Gretchen M. Tamms [p], Katherine Giacoletti [p], Lisa Lupinacci [p], Mark T. Esser [p], Scott C. Vuocolo [p], Alfred J. Saah [p], Eliav Barr [p]

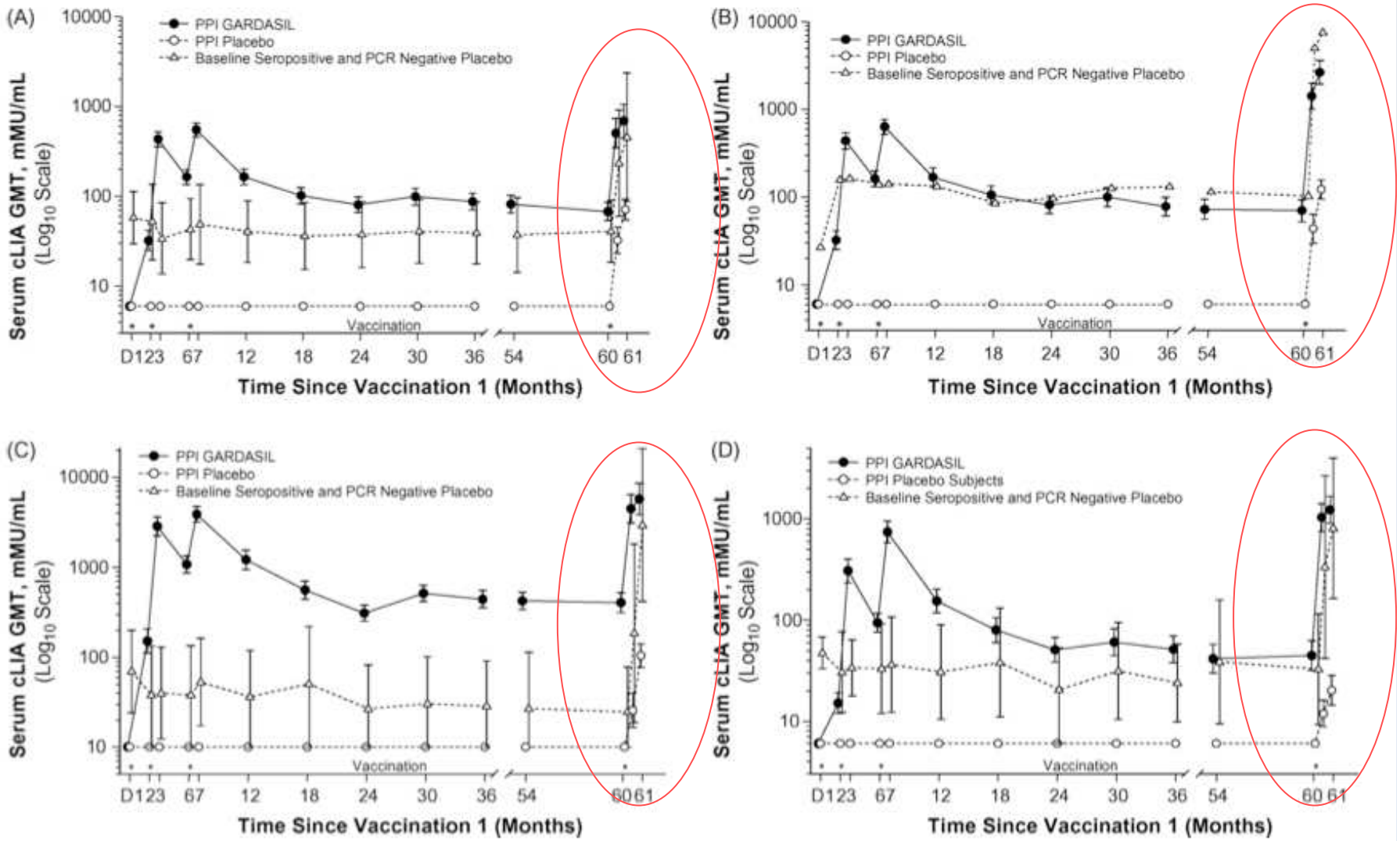
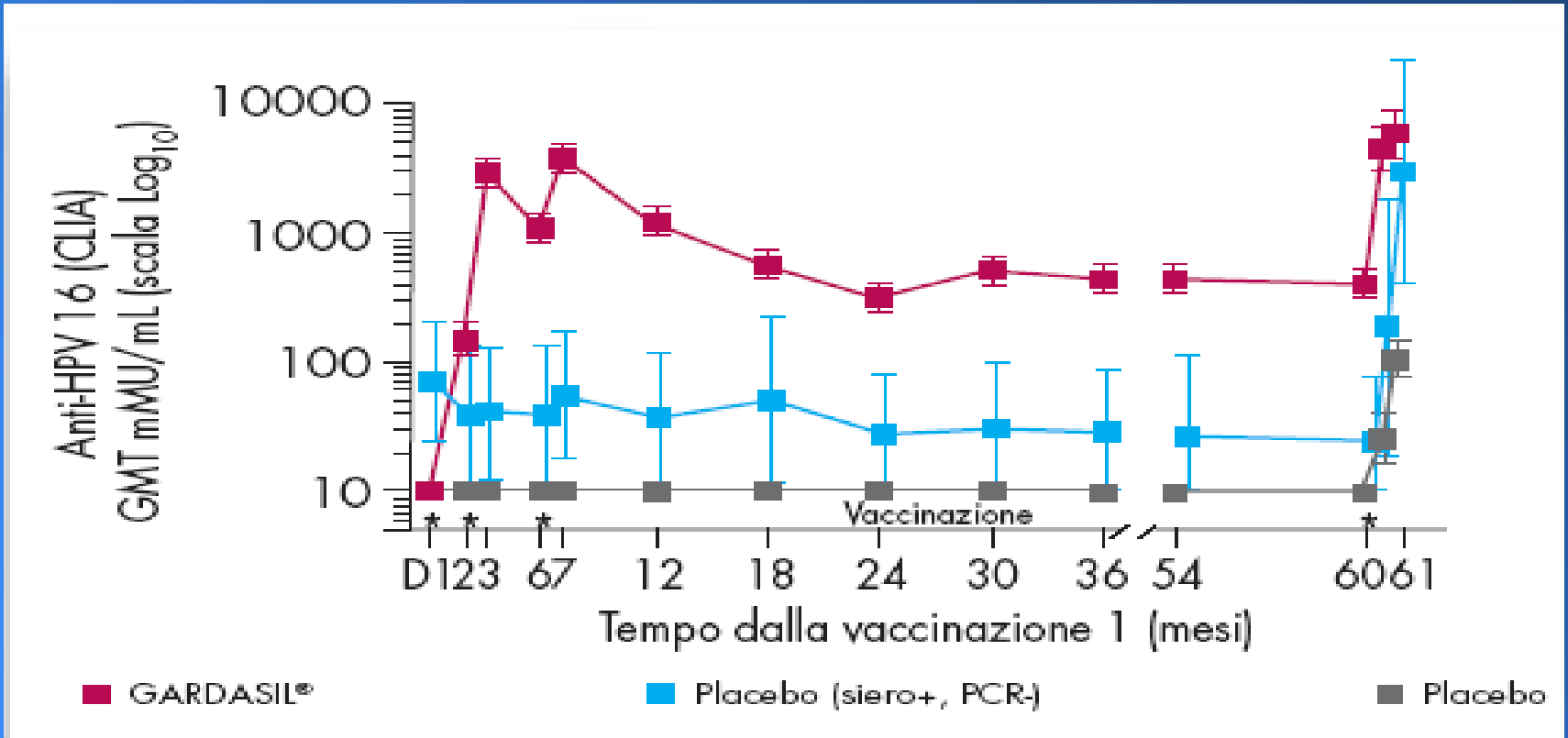


Fig. 2. Persistence of anti-HPV responses following a three-dose regimen of quadrivalent HPV vaccine or placebo. Data are shown for subjects in the extension per-protocol immunogenicity population who received quadrivalent HPV vaccine in the original study, subjects in the extension per-protocol immunogenicity population who received placebo in the original study, and subjects who were seropositive and PCR negative to vaccine HPV types who received placebo in the original study. Anti-HPV 6, 11, 16, and 18 cLIA results are in panels (A–D), respectively. Error bars represent 95% confidence intervals.

Gardasil:
memoria immunologica post *challenge* vaccinale

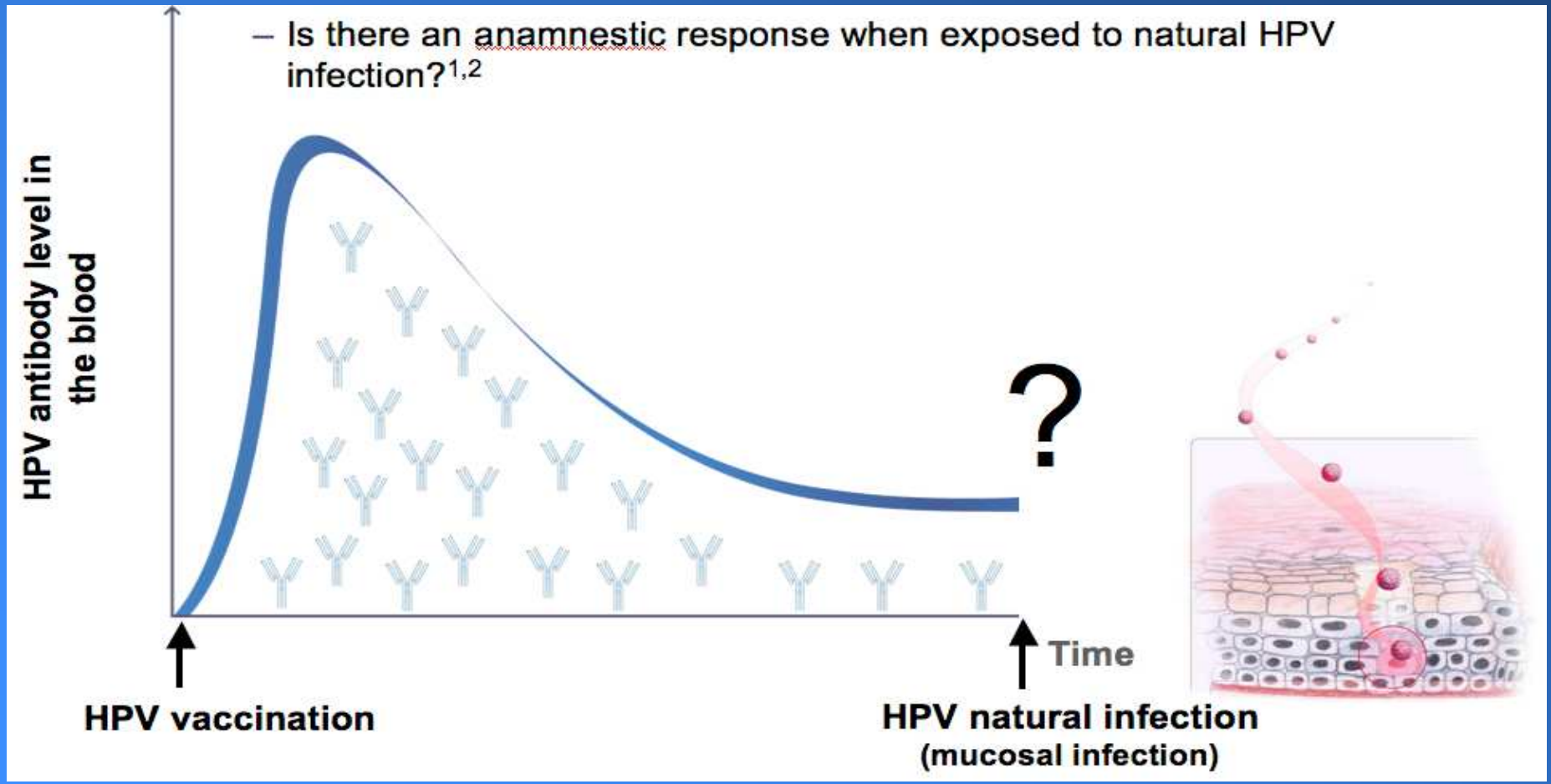


"……Immune memory is the hallmark of vaccines that induce long-term protection.

The vaccine exhibited excellent immune memory as evidenced by the rapid and robust increase in vaccine-type specific antibodies in response to challenge…"

Olsson SE, Vaccine 2007

HPV vaccination: what will happen when antibody levels are waning?



Human papillomavirus vaccines
WHO position paper

"….A need for booster doses has not been established."

WEEKLY EPIDEMIOLOGICAL RECORD, NO. 15, 10 APRIL 2009

Published Online
July 7, 2009
DOI:10.1016/S0140-6736(09)61247-2

HPV vaccine for all

…Life-long immunity is unlikely, making the need for a booster dose probable…..

Michels BE, Hausen H, The Lancet 2009

Human Vaccines 5:10 702-716; October; © 2009 Landes Bioscience

Comparison of the immunogenicity and safety of *Cervarix*™ and *Gardasil*® human papillomavirus (HPV) cervical cancer vaccines in healthy women aged 18–45 years

Mark H. Einstein,[1,*] Mira Baron,[2] Myron J. Levin,[3] Archana Chatterjee,[4] Robert P. Edwards,[5] Fred Zepp,[6] Isabelle Carletti,[7] Francis J. Dessy,[7] Andrew F. Trofa,[8] Anne Schuind,[9] and Gary Dubin,[8] on behalf of the HPV-010 Study Group

[1] Montefiore Medical Center, Albert Einstein College of Medicine, Department of Obstetrics & Gynecology and Women's Health, Division of Gynecologic Oncology, Bronx, NY USA; [2] Rapid Medical Research, Cleveland, OH USA; [3] University of Colorado Denver and Health Sciences Center, Aurora, CO USA; [4] Creighton University School of Medicine, Omaha, NE USA; [5] Ovarian Cancer Center of Excellence/Sciences University of Pittsburgh School of Medicine, Pittsburgh, PA USA; [6] University of Mainz, Mainz, Germany; [7] GlaxoSmithKline Biologicals, Rixensart, Belgium; [8] GlaxoSmithKline Biologicals, King of Prussia, PA USA

Good compliance of the study population with the vaccine-schedules: in the TVC cohort, ≥ 84% of women received all 3 doses of *Cervarix*® or *Gardasil*®

Study design and admnistration schedule

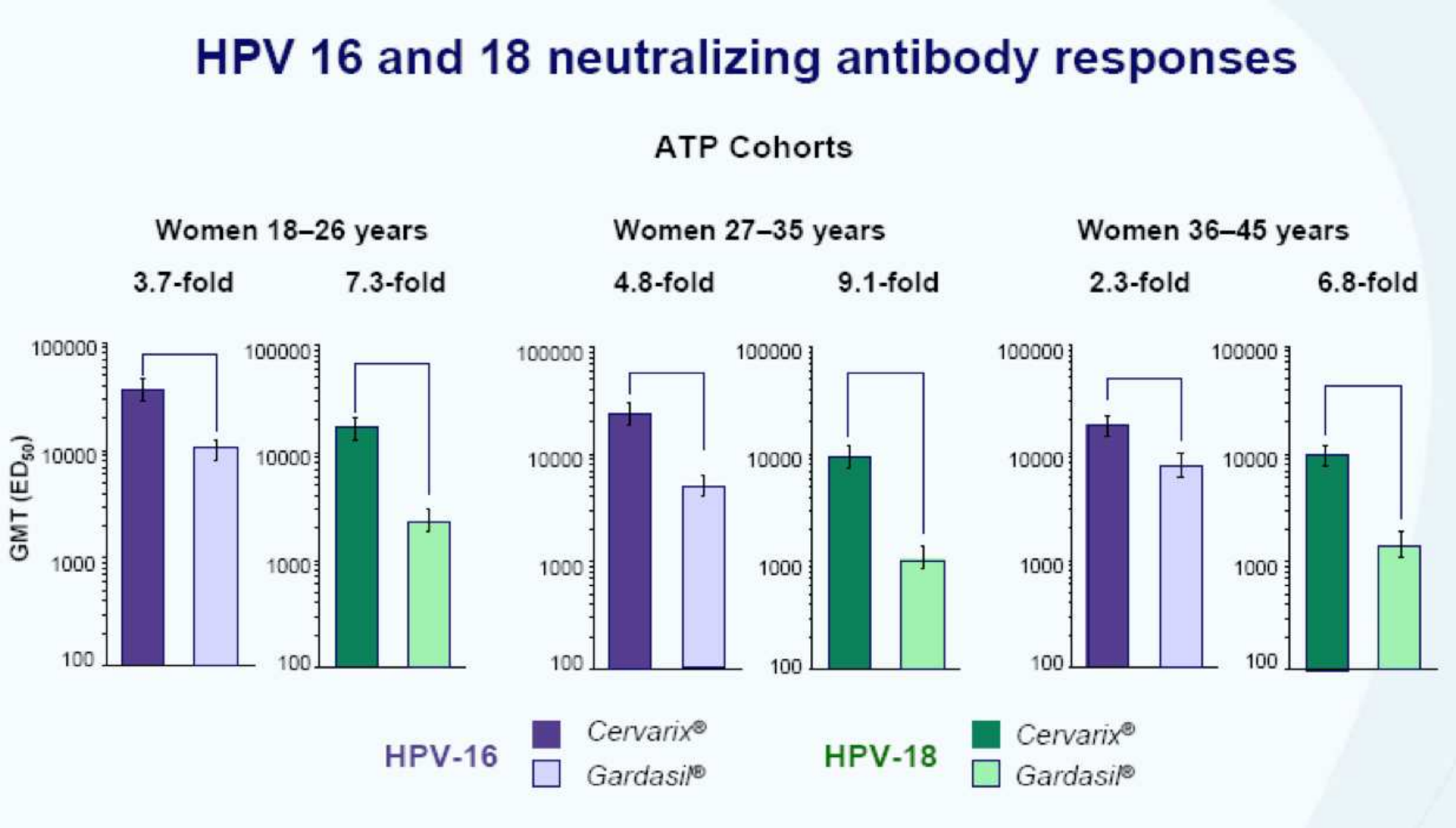
- Phase IIIb:
  - Blinded, randomized (1:1) study
- Study population:
  - Healthy women 18–45 years
  - N = 1106
  - Stratified: 18–26 years / 27–35 years / 36–45 years
- Two treatment groups:
  - *Cervarix*® (HPV 16/18 L1 AS04 adjuvanted vaccine)
  - *Gardasil*® (HPV 6,11,16,18 L1 AAHS adjuvanted vaccine)
- Vaccination:
  - 3 doses according to the respective vaccination schedules
- Evaluation of immunogenicity and safety:
  - 1 month after the completion of the 3 dose schedule
  - Safety was monitored throughout

	Cervarix™	*Gardasil*®
Antigens	20 µg HPV-16 VLP 20 µg HPV-18 VLP	40 µg HPV-16 VLP 20 µg HPV-18 VLP 20 µg HPV-6 VLP 40 µg HPV-11 VLP
Expression system	Baculovirus expression vector system in *Trichoplusia ni* Rix4446 cell substrate	*Saccharomyces cerevisiae* yeast
Adjuvant	AS04 [50 µg MPL and 500 µg Al(OH)3]	225 µg amorphous aluminum hydroxyphosphate sulfate
Administration schedule		
Month 0	Cervarix™	Gardasil®
Month 1	Cervarix™	Placebo [500 µg Al(OH)3]
Month 2	Placebo [500 µg $Al(OH)_3$]	Gardasil®
Month 6	Cervarix™	Gardasil®

Einstein MH, on behalf of the HPV-010 study group. 25th International Papillomavirus Conference (Abstract O-01.02), 2009
Einstein MH, Human Vaccines 5:10 702-716; 2009

Head-to-head study (HPV-010): immunogenicity of Cervarix vs Gardasil

Seroconversion rate: Cervarix: 100% vs Gardasil: 98%



Einstein MH, on behalf of the HPV-010 study group. 25th International Papillomavirus Conference (Abstract O-01.02), 2009

Cervicovaginal secretion antibody titers: positivity rates at Month 7 for anti-HPV-16 and anti-HPV-18 antibodies measured by (A) pseudovirion-based neutralization assay (PBNA) and (B) enzyme-linked immunosorbent assay (ELISA)

[ATP cohort for immunogenicity, irrespective of HPV serostatus and HPV DNA status prior to vaccination]

A PBNA

			Cervarix™			*Gardasil®*	
Antigen	Timing	N	n	% P [95% CI]	N	n	% P [95% CI]
HPV-16	Baseline	24	3	12.5 [2.7, 32.4]	36	5	13.9 [4.7, 29.5]
	Month 7	48	39	81.3 [67.4, 91.1]	57	29	50.9 [37.3, 64.4]
HPV-18	Baseline	24	1	4.2 [0.1, 21.1]	36	2	5.6 [0.7, 18.7]
	Month 7	48	16	33.3 [20.4, 48.4]	57	5	8.8 [2.9, 19.3]

B ELISA

			Cervarix™			*Gardasil®*	
Antigen	Timing	N	n	% P [95% CI]	N	n	% P [95% CI]
HPV-16	Baseline	24	0	0.0 [0.0, 14.2]	36	0	0.0 [0.0, 9.7]
	Month 7	48	46	95.8 [85.7, 99.5]	57	51	89.5 [78.5, 96.0]
HPV-18	Baseline	24	1	4.2 [0.1, 21.1]	36	3	8.3 [1.8, 22.5]
	Month 7	48	43	89.6 [77.3, 96.5]	57	40	70.2 [56.6, 81.6]

Einstein MH, Human Vaccines 5:10 702-716; 2009

Human Vaccines 5:10 702-716; October; © 2009 Landes Bioscience

Comparison of the immunogenicity and safety of *Cervarix*™ and *Gardasil*® human papillomavirus (HPV) cervical cancer vaccines in healthy women aged 18–45 years

Mark H. Einstein,[1,*] Mira Baron,[2] Myron J. Levin,[3] Archana Chatterjee,[4] Robert P. Edwards,[5] Fred Zepp,[6] Isabelle Carletti,[7] Francis J. Dessy,[7] Andrew F. Trofa,[8] Anne Schuind,[8] and Gary Dubin,[8] on behalf of the HPV-010 Study Group

[1] Montefiore Medical Center, Albert Einstein College of Medicine, Department of Obstetrics & Gynecology and Women's Health, Division of Gynecologic Oncology, Bronx, NY USA; [2] Rapid Medical Research, Cleveland, OH USA; [3] University of Colorado Denver and Health Sciences Center, Aurora, CO USA; [4] Creighton University School of Medicine, Omaha, NE USA; [5] Ovarian Cancer Center of Excellence/Sciences University of Pittsburgh School of Medicine, Pittsburgh, PA USA; [6] University of Mainz, Mainz, Germany; [7] GlaxoSmithKline Biologicals, Rixensart, Belgium; [8] GlaxoSmithKline Biologicals, King of Prussia, PA USA

This suggests that the higher levels of serum antibodies induced by *Cervarix*™ result in more antibodies transudating to the CVS and therefore more HPV-specific antibodies at the site of infection.

Frequency of HPV 16- and HPV 18-specific memory B cells in responders

Circulating HPV 16/18-specific memory B-cell frequencies were higher for *Cervarix*® compared with *Gardasil*®

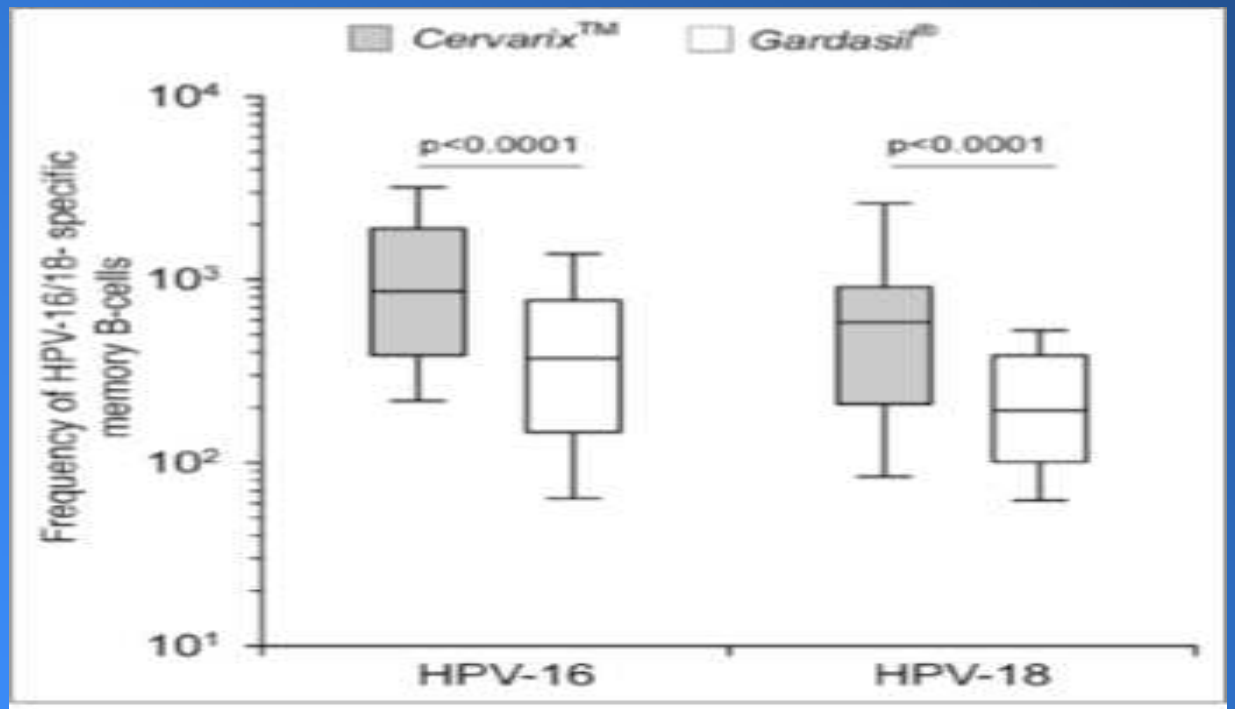


Figure 4. Frequency of HPV-16 and HPV-18 specific memory B-cells per million memory B-cells at Month 7 in responders (i.e., women with no detectable HPV type-specific B-cells prior to vaccination but with detectable HPV type-specific B-cells at Month 7) on a logarithmic scale (ATP cohort for immunogenicity). Whiskers represent 10th and 90th percentiles; p<0.0001 for *Cervarix*™ versus *Gardasil*® for both antigens.

Einstein MH, Human Vaccines 5:10 702-716; 2009

Conclusions

- The vaccine tolerability and safety profile was consistent with previous studies:
  - Incidence of solicited symptoms was higher with Cervarix
  - Compliance was similar

- At month 7 after vaccination Serum Neutralizing Antibodies were higher with Cervarix than Gardasil

- **Long term follow up studies evaluating duration of antibodies response and EFFICACY in disease prevention will be necessary to determine the clinical relevance of the observed differences in the present study….**

Einstein MH, Human Vaccines 5:10 702-716; 2009

Acquired knowledge, open issues and future perspectives on current available prophylactic HPV vaccines

Up date on the:

- **Safety and tolerability profile**
- **Immunogenicity (innate and adaptive response)**
- **Efficacy against HPV 16-18 and cross-protection against NV-types**

Outline of HPV vaccine efficacy phase II and III trials in young women

Characteristic	GSK 001/007	Merck 007	PATRICIA	FUTURE I	FUTURE II
Vaccine	Cervarix™	Gardasil®	Cervarix™	Gardasil®	Gardasil®
Study phase	II	II	III	III	III
Control	500 μg aluminum hydroxide	225 μg aluminum hydroxy-phosphate sulfate	Hepatitis A vaccine	225 μg aluminum hydroxy-phosphate sulfate	225 μg aluminum hydroxy-phosphate sulfate
# Participants	1,113	552	18,644	5,455	12,167
Mean age (years) (range)	20 (15–25)	20 (16–23)	20 (15–25)	20 (16–24)	20 (15–26)
Lifetime no. of sex partners	≤6	≤4	≤6	≤4	≤4
Screening frequency	6 months	6 months	12 months	6 months	12 months
Mean duration of follow up	48 months	60 months	15 months[a]	36 months[a]	36 months[a]
Primary efficacy endpoint	Incident -16/18 infection	-6/11/16/18 persistent infection and cervical or external genital disease	-16/18 CIN2+	-6/11/16/18 CIN1+ and external genital lesions	-16/18 CIN2+
Secondary endpoints	Persistent infection, CIN1+, adverse events	Adverse events	Persistent infection or CIN1+ by any type; Adverse events	Adverse events	Adverse events

CIN: cervical intraepithelial neoplasia; CIN1+: CIN grade 1 or worse; CIN2+: CIN grade 2 or worse; FUTURE: Females united to unilaterally reduce endo/ectocervical disease; GSK: GlaxoSmithKline; PATRICIA: Papilloma trial against cancer in young adults [6–10].

[a] Interim analysis of projected four year follow-up trial.

J.T. Schiller et al. / Vaccine 26S (2008) K53–K61

Efficacy of VLP vaccines against infection and lesions related to vaccine targeted HPV types

J.T. Schiller et al. / Vaccine 26S (2008) K53–K61

Prophylactic efficacy of VLP vaccines against infection and lesions related to vaccine targeted HPV types

Vaccine	Study	Number of subjects		Endpoints	Vaccine efficacy (95% CI)[a]		
		Vaccine group	Placebo group		ATP	MITT	ITT
Gardasil®	Merck 007	235	233	HPV persistence (4 months)	96 (83–100)	94 (83–98)	NR
	Merck 007	235	233	External genital lesions	100 (<0–100)	100 (<0–100)	NR
	Merck 007	235	233	CIN1+, AIS	100 (<0–100)	100 (31–100)	NR
	FUTURE I	2,241	2,258	CIN1+, AIS	100 (94–100)	98 (92–100)	55 (40–66)
	FUTURE I	2,261	2,279	External genital lesions	100 (94–100)	95 (87–99)	73 (58–83)
	FUTURE II	6,087	6,080	CIN2+, AIS	98 (86–100)	95 (85–99)	44 (26–58)
Cervarix™	GSK 001/007	414	385	HPV persistence (6 months)	96 (75–100)	94 (78–99)	NR
	GSK 001/007	414	385	HPV persistence (12 months)	100 (52–100)	94 (61–100)	NR
	GSK 001/007	481	470	CIN1+	NR	100 (42–100)	NR
	GSK 001/007	481	470	CIN2+	NR	100 (−8–100)	NR
	PATRICIA	6,344	6,402	HPV persistence (6 months)	NR	80 (70–87)	NR
	PATRICIA	3,386	3,437	HPV persistence (12 months)	NR	76 (48–90)	NR
	PATRICIA	7,788	7,838	CIN1+	NR	89 (59–99)	NR
	PATRICIA	7,788	7,838	CIN2+	NR**100 (74.2-100)**	90 (53–99)[b]	NR

AIS: adenocarcinoma in situ; ATP: according to protocol; CIN: cervical intraepithelial neoplasia; CIN1+: CIN grade 1 or worse; CIN2+: CIN grade 2 or worse; FUTURE: Females united to unilaterally reduce endo/ectocervical disease; GSK: GlaxoSmithKline Biologicals, Rixensart, Belgium; ITT: intention to treat; Merck: Merck & Co., Inc., Whitehouse Station, NJ USA; MITT: modified intention to treat; NR: not reported; PATRICIA: Papilloma trial against cancer in young adults, CI: confidence interval.

[a] 95% confidence intervals, except 97.9% confidence intervals used in PATRICIA.

[b] A post-hoc analyses of PATRICIA including HPV -specific causal attribution in 3 CIN 2/3 cases with multiple HPV types generated efficacy estimates of 100% (97.9%CI: 74.2–100) [9].

World Health Organization

Organisation mondiale de la Santé

Human papillomavirus vaccines

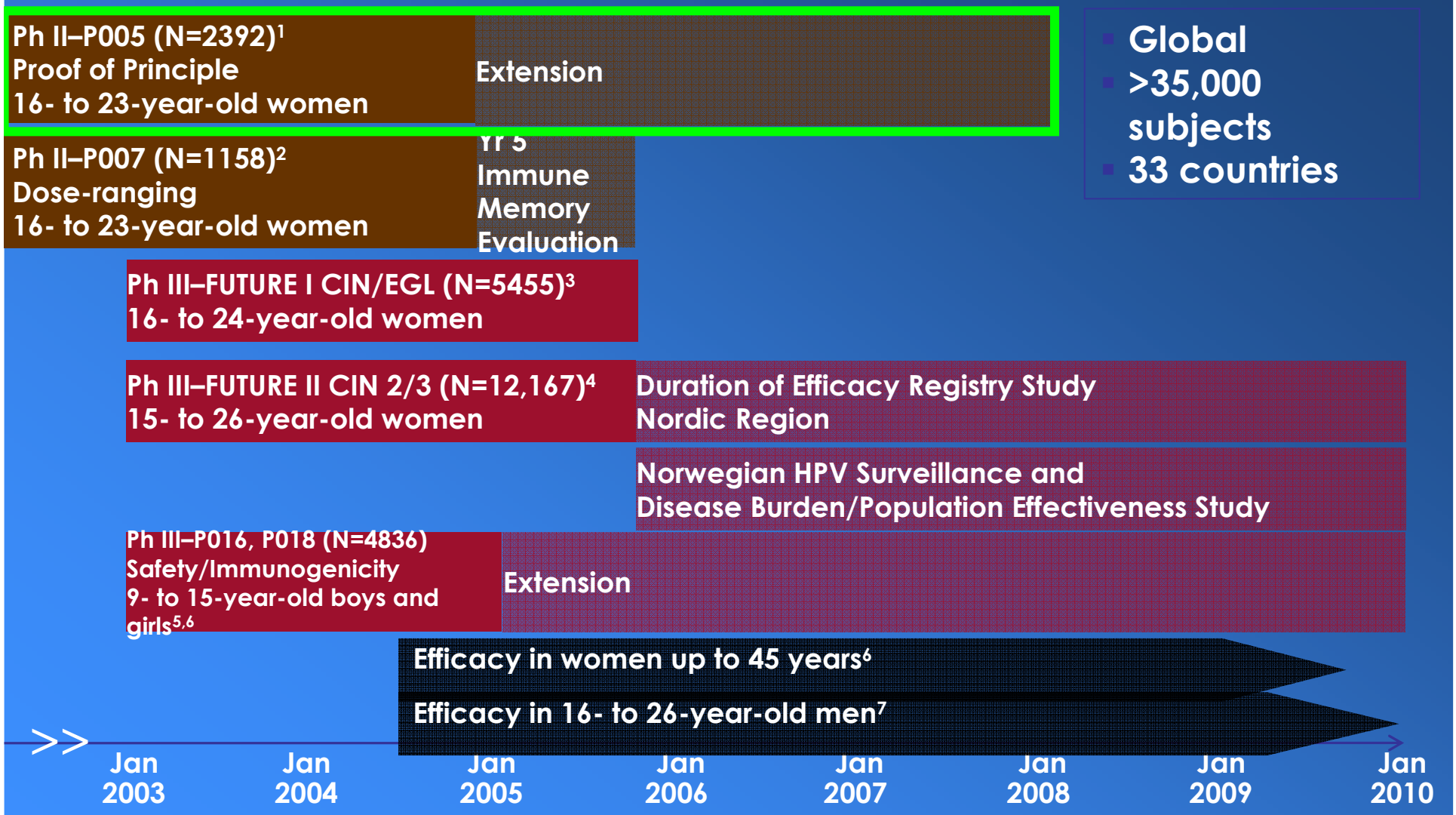
WHO position paper

April 2009

The protective efficacy of the 2 vaccines has been maintained throughout their respective observation periods, currently extending to 6.4 years (bivalent vaccine) [1] and 5 years (quadrivalent vaccine). [2]

1. Harper Dm, Gynecologic Oncol 2008
2. Villa LL, Br J Cancer 2006

Clinical Development Program for GARDASIL®



- Global
- >35,000 subjects
- 33 countries

EGL = external genital lesions.

1. Koutsky LA, Ault KA, Wheeler CM et al. *N Engl J Med.* 2002;347:1645–1651. 2. Villa LL, Costa RLR, Petta CA, et al. *Lancet Oncol.* 2005;6:271–278. 3. Garland SM, Hernandez-Avila M, Wheeler CM, et al. NEJM 2007 4. FUTURE II study group. NEJM 2007 5. Block SL, Nolan T, Sattler C, et al. Pediatric 2006. 6. Munoz 2009 Lancet in press 7. Palefsky/Giuliano IPV 2009 abstracts

Longer term efficacy of a prophylactic monovalent human papillomavirus type 16 vaccine

Ali Rowhani-Rahbar[a,*], Constance Mao[b], James P. Hughes[c], Frances B. Alvarez[d], Janine T. Bryan[d], Stephen E. Hawes[a], Noel S. Weiss[a], Laura A. Koutsky[a]

[a] Department of Epidemiology, University of Washington, Seattle, WA, USA
[b] Department of Obstetrics and Gynecology, University of Washington, Seattle, WA, USA
[c] Department of Biostatistics, University of Washington, Seattle, WA, USA
[d] Merck Research Laboratories, West Point, PA, USA

Vaccine 27 (2009) 5612–5619

Endpoint	Vaccine group				Placebo group				Efficacy[b], %
	No. of subjects	No. of cases	Woman-years	Rate[a]	No. of Subjects	No. of Cases	Woman-years	Rate[a]	(95% CI)
Extended follow-up period									
HPV-16 infection									
Per-protocol	113	0	516.9	0	103	6	454.0	1.3	100 (29–100)
Unrestricted	123	0	584.9	0	106	6	470.9	1.3	100 (33–100)
HPV-16-related cervical lesions									
Per-protocol									
CIN-1 or worse	113	0	516.9	0	103	3	457.8	0.7	100 (<0–100)
CIN-2 or worse	113	0	516.9	0	103	3	457.8	0.7	100 (<0–100)
Unrestricted									
CIN-1 or worse	123	0	584.9	0	106	3	474.6	0.6	100 (<0–100)
CIN-2 or worse	123	0	584.9	0	106	3	474.6	0.6	100 (<0–100)
Intention-to-treat									
CIN-1 or worse	134	0	634.8	0	113	3	507.5	0.6	100 (<0–100)
CIN-2 or worse	134	0	634.8	0	113	3	507.5	0.6	100 (<0–100)
Entire project period									
HPV-16 infection									
Per-protocol	114	1	902.5	0.1	118	21	832.2	2.5	96 (27–100)
Unrestricted	126	3	1053.9	0.3	127	27	929.3	2.9	90 (31–99)
HPV-16-related cervical lesions									
Per-protocol									
CIN-1 or worse	114	0	909.8	0	118	8	884.1	0.9	100 (41–100)
CIN-2 or worse	114	0	909.8	0	118	7	891.0	0.8	100 (29–100)
Unrestricted									
CIN-1 or worse	126	0	1078.0	0	127	9	1014.2	0.9	100 (50–100)
CIN-2 or worse	126	0	1078.0	0	127	8	1021.1	0.8	100 (41–100)
Intention-to-treat									
CIN-1 or worse	148	4	1240.5	0.3	142	10	1142.6	0.9	64 (−27–92)
CIN-2 or worse	148	3	1246.8	0.2	142	8	1156.5	0.7	64 (−51–94)
All cervical lesions regardless of HPV type									
Intention-to-treat									
CIN-1 or worse	148	20	1169.8	1.7	142	22	1086.7	2.0	15 (−68–56)
CIN-2 or worse	148	8	1225.8	0.7	142	12	1137.8	1.1	33 (−79–77)

HPV: human papillomavirus; CI: confidence interval; CIN: cervical intraepithelial neoplasia.

[a] Per 100 woman-years.

[b] Adjusted for age and race.

Some comments…..

The *monovalent* HPV 16 vaccine demonstrated 100% efficacy against HPV 16-associated infection and CIN endpoints over the entire follow up period, after a mean of 8.5 years: these data are relevant in view of the required long-term effectiveness of the vaccination programs targeted to young women in pre-adolescent age.

However, no direct transposition of these results can be done for the HPV 6, 11, 16, 18 quadrivalent vaccine : in fact, each vaccine formulation has his own different characteristics both in terms of immunogenicity and efficacy…..

The Impact of Quadrivalent Human Papillomavirus (HPV; Types 6, 11, 16, and 18) L1 Virus-Like Particle Vaccine on Infection and Disease Due to Oncogenic Nonvaccine HPV Types in Generally HPV-Naive Women Aged 16–26 Years

Darron R. Brown, Susanne K. Kjaer, Kristján Sigurdsson, Ole-Erik Iversen, Mauricio Hernandez-Avila, Cosette M. Wheeler, Gonzalo Perez, Laura A. Koutsky, Eng Hseon Tay, Patricia Garcia, Kevin A. Ault, Suzanne M. Garland, Sepp Leodolter, Sven-Eric Olsson, Grace W. K. Tang, Daron G. Ferris, Jorma Paavonen, Marc Steben, F. Xavier Bosch, Joakim Dillner, Elmar A. Joura, Robert J. Kurman, Slawomir Majewski, Nubia Muñoz, Evan R. Myers, Luisa L. Villa, Frank J. Taddeo, Christine Roberts, Amha Tadesse, Janine Bryan, Lisa C. Lupinacci, Katherine E. D. Giacoletti, Heather L. Sings, Margaret James, Teresa M. Hesley, and Eliav Barr*

Methods

17,622 women aged 16 - 26 years, negative for 14 HPV types on day 1, receiving ≥ 1 dose of vaccine.

All underwent cervicovaginal sampling and Pap testing at regular intervals for up to 4 years.

HPV genotying was performed for biopsy samples, and histological diagnoses were determined by a pathology panel.

Prespecified analyses included infection of ≥ 6 months' duration and CIN1 - 3/AIS due to the 2 and 5 most common HPV types in cervical cancer after HPV types 16 and 18, as well as all tested nonvaccine types.

The Journal of Infectious Diseases 2009; 199:926–35

Cross-protection against CIN 1-3 or adenocarcinoma in situ (AIS) due to HPV types other than 16 and 18 in the efficacy population that was negative for 14 HPV types (prespecified analyses)

(Naive subjects negative for the 4 HPV vaccine types and 10 non-vaccine types on Day 1)

Category	Vaccine (n = 4616)		Placebo (n = 4680)		Efficacy (95% CI), %
	Cases	Rate[a]	Cases	Rate[a]	
HPV-31 or -45	34	0.2	61	0.4	43.6 (12.9 to 64.1)
HPV-31, -33, -45, -52, or -58	103	0.6	147	0.9	29.2 (8.3 to 45.5)
HPV-31, -33, -35, -39, -45, -51, -52, -56, -58, or -59	205	1.3	270	1.6	23.4 (7.8 to 36.4)
Nonvaccine A9 species (HPV-31, -33, -35, -52, or -58)[b]	101	0.6	150	0.9	31.9 (11.8 to 47.6)
HPV-31	23	0.1	54	0.3	56.9 (28.6 to 74.8)
HPV-33	18	0.1	30	0.2	39.2 (−12.6 to 68.1)
HPV-35	11	0.1	14	0.1	20.4 (−88.8 to 67.3)
HPV-52	35	0.2	51	0.3	30.6 (−8.9 to 56.2)
HPV-58	36	0.2	44	0.3	17.1 (−31.7 to 48.2)
Nonvaccine A7 species (HPV-39, -45, or -59)[b]	54	0.3	75	0.5	27.3 (−4.6 to 49.7)
HPV-39	28	0.2	42	0.3	32.6 (−11.4 to 59.8)
HPV-45	11	0.1	10	0.1	−11.3 (−192.2 to 57.1
HPV-59	20	0.1	26	0.2	22.3 (−44.7 to 58.9)
HPV-51[b]	66	0.4	64	0.4	−4.3 (−49.5 to 27.2)
HPV-56[b]	58	0.4	81	0.5	27.6 (−2.6 to 49.3)

NOTE. This population was restricted to subjects who received ≥1 vaccination and, at enrollment, were seronegative and DNA negative for each of the quadrivalent HPV vaccine types (6, 11, 16, and 18); were DNA negative for each of 10 nonvaccine types (31, 33, 35, 39, 45, 51, 52, 56, 58, and 59); and had a normal Pap test result. Disease was defined as the diagnosis of a tissue sample as CIN, AIS, or cervical cancer by a pathology panel with DNA detected in tissue from the same lesion. A subject is counted only once within each applicable row. CI, confidence interval.

[a] Cases per 100 person-years at risk.

The Journal of Infectious Diseases 2009; 199:926–35

The Impact of Quadrivalent Human Papillomavirus (HPV; Types 6, 11, 16, and 18) L1 Virus-Like Particle Vaccine on Infection and Disease Due to Oncogenic Nonvaccine HPV Types in Sexually Active Women Aged 16–26 Years

Cosette M. Wheeler, Susanne K. Kjaer, Kristján Sigurdsson, Ole-Erik Iversen, Mauricio Hernandez-Avila, Gonzalo Perez, Darron R. Brown, Laura A. Koutsky, Eng Hseon Tay, Patricia García, Kevin A. Ault, Suzanne M. Garland, Sepp Leodolter, Sven-Eric Olsson, Grace W. K. Tang, Daron G. Ferris, Jorma Paavonen, Marc Steben, F. Xavier Bosch, Joakim Dillner, Elmar A. Joura, Robert J. Kurman, Slawomir Majewski, Nubia Muñoz, Evan R. Myers, Luisa L. Villa, Frank J. Taddeo, Christine Roberts, Amha Tadesse, Janine Bryan, Lisa C. Lupinacci, Katherine E. D. Giacoletti, Margaret James, Scott Vuocolo, Teresa M. Hesley, and Eliav Barr[a]

Methods

17,622 women aged 16-26 years, with preexisting HPV infection and/or HPV-related disease, receiving ≥ 1 dose of vaccine.

Subjects underwent cervicovaginal sampling and Pap testing on day 1 and then at 6 -12-month intervals for up to 4 years.

HPV typing was performed on samples from enrollment and follow-up visits, including samples obtained for diagnosis or treatment of HPV-related disease.

All subjects who returned for follow-up were included.

The Journal of Infectious Diseases 2009; 199:936–44

Cross-protection for CIN 1-3 or adenocarcinoma in situ (AIS) in the intention to-treat (ITT) population due to HPV types other than 16 and 18

(ITT cohort: all subjects who received ≥1 vaccine dose, regardless of HPV status)

	Vaccine (n = 8562[a])			Placebo (n = 8598[a])			
HPV type	Cases	PYR	Rate[b]	Cases	PYR	Rate[b]	Efficacy, % (95% CI)
HPV-31, -33, -35, -39, -45, -51, -52, -56, -58, or -59	696	29,113.2	2.4	818	29,063.4	2.8	15.1 (6.0 to 23.4)
Nonvaccine A9 species (HPV-31, -33, -35, -52, and -58)	420	29,400.7	1.4	519	29,381.7	1.8	19.2 (7.9 to 29.1)
Nonvaccine A7 species (HPV-39, -45, and -59)	182	29,568.4	0.6	213	29,546.8	0.7	14.7 (−4.4 to 30.4)
HPV-31	131	29,604.1	0.4	177	29,616.2	0.6	26.0 (6.7 to 41.4)
HPV-33	74	29,676.6	0.2	95	29,688.7	0.3	22.0 (−6.8 to 43.3)
HPV-35	46	29,690.5	0.2	52	29,711.1	0.2	11.5 (−34.2 to 41.8)
HPV-39	113	29,613.9	0.4	115	29,639.3	0.4	1.7 (−28.5 to 24.9)
HPV-45	40	29,692.8	0.1	49	29,690.2	0.2	18.4 (−26.5 to 47.6)
HPV-51	168	29,590.4	0.6	183	29,604.0	0.6	8.2 (−13.8 to 26.0)
HPV-52	148	29,604.0	0.5	172	29,619.3	0.6	13.9 (−7.9 to 31.4)
HPV-56	165	29,595.5	0.6	198	29,585.6	0.7	16.7 (−2.9 to 32.7)
HPV-58	92	29,656.9	0.3	128	29,663.4	0.4	28.1 (5.3 to 45.6)
HPV-59	40	29,693.3	0.1	64	29,682.4	0.2	37.6 (6.0 to 59.1)

NOTE. Disease was defined as diagnosis in a tissue sample of a composite end point of CIN1–3, AIS, or cervical cancer by a 4-member pathology panel with type-specific HPV DNA detected in tissue from the same lesion. A subject is counted only once within each applicable row. The ITT population was composed of all subjects who received ≥1 injection of quadrivalent HPV vaccine or placebo and returned for follow-up, regardless of the presence of HPV infection or HPV-related disease at enrollment. Follow-up for end-point ascertainment started after day 1. CI, confidence interval; PYR, person-years at risk.

[a] No. of subjects who received ≥1 dose of vaccine or placebo and returned for least 1 follow-up visit.

[b] Cases per 100 PYR.

Vaccination reduced the rate of HPV-31/33/45/52/58 cervical intraepithelial neoplasia (CIN) 1-3 or adenocarcinoma in situ (AIS) by 18.8% (95% CI, 7.4% to 28.9%)

The Impact of Quadrivalent Human Papillomavirus (HPV; Types 6, 11, 16, and 18) L1 Virus-Like Particle Vaccine on Infection and Disease Due to Oncogenic Nonvaccine HPV Types in Sexually Active Women Aged 16–26 Years

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Conclusions

These cross-protection results complement the vaccine's prophylactic efficacy against disease associated with HPV-6, -11, -16, and -18.

Long-term monitoring of vaccinated populations are needed to fully ascertain the population-based impact and public health significance of these findings.

The Journal of Infectious Diseases 2009; 199:936–44

Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women

J Paavonen, P Naud, J Salmerón, C M Wheeler, S-N Chow, D Apter, H Kitchener, X Castellsague, J C Teixeira, S R Skinner, J Hedrick, U Jaisamrarn, G Limson, S Garland, A Szarewski, B Romanowski, F Y Aoki, T F Schwarz, W A J Poppe, F X Bosch, D Jenkins, K Hardt, T Zahaf, D Descamps, F Struyf, M Lehtinen, G Dubin, for the HPV PATRICIA Study Group

Lancet 2009; 374: 301–14

PATRICIA trial: study design

- Randomized 1:1; double blind, controlled Phase III trial involving 18,644 young women aged 15–25 years (Total Vaccinated Cohort)
- Subjects received *Cervarix*® (n = 9319) or Hep A control vaccine (n = 9325) at 0, 1 and 6 months
- Procedures:
  - Gynaecological examination and routine cervical cytological sampling (every 12 months)
  - Cytological sampling for HPV DNA testing (every 6 months)
  - Serum samples for assessment of immunogenicity
- Interim analysis previously reported at mean follow-up of 14.8 months (Paavonen et al 2007)
- Final analysis conducted at mean follow-up of 34.9 months

Paavonen J *et al*. *Lancet* 2007; **369**: 2161–2170.
Paavonen J *et al*. 25th International Papillomavirus Conference (Abstract O-29.06), 2009
Paavonen J et al:, The Lancet 2009

PATRICIA trial: main objectives

- **Primary objective**
  - Vaccine efficacy against CIN2+ associated with HPV-16/18

- **Other objectives included:**
  - Vaccine efficacy against CIN2+ and CIN3+ irrespective of HPV type in the lesion
  - Vaccine efficacy against CIN2+ associated with non-vaccine oncogenic types
  - Reduction of colposcopy referrals and cervical excision procedures*
  - Safety

Paavonen J *et al*. *Lancet* 2007; **369**: 2161–2170.
Paavonen J *et al*. 25th International Papillomavirus Conference (Abstract O-29.06), 2009
Paavonen J et al:, The Lancet 2009

*LEEP, Laser, Knife or cone biopsy

Definitions of e□cacy and safety cohorts

TVC
N=18 644
- All women who were given at least one dose of study vaccine (17 106 [92%] were given three doses)
- Data available for efficacy endpoints*
- Case counting began the day after first vaccination

TVC-naive
N=11 641 (62% of TVC)
- All women who were given at least one dose of study vaccine (10 750 [92%] were given three doses)
- Data available for efficacy endpoints*
- Normal cytology at month 0
- HPV DNA negative for all 14 oncogenic types at month 0
- Seronegative for HPV-16 and HPV-18 at month 0
- Case counting began the day after first vaccination

TVC-E
N=18 525 (99% of TVC)
- Received at least one dose of study vaccine
- Data available for efficacy endpoints*
- Normal or low-grade cytology at month 0
- Case counting began the day after first vaccination

ATP-E
N=16 162 (87% of TVC)
- Met eligibility criteria and complied with protocol
- Received three doses of study vaccine
- Data available for efficacy endpoints*
- Normal or low-grade cytology at month 0
- Case counting began the day after third vaccination

Primary Endpoint:
Cervarix® efficacy against HPV-16/18 CIN2+
(Mean follow-up after 3rd dose= 34.9 months, SD= 6.4)

According to Protocol Cohort for Efficacy (ATP-E)

Pre-specified analysis

Endpoint	Vaccine efficacy	
	%	96.1% CI
CIN2+ HPV-16/18	92.9	79.9–98.3

Analysis for causality

Endpoint	Vaccine efficacy	
	%	96.1% CI
CIN2+ HPV-16/18	98.1	88.4–100.0

Paavonen J et al. The Lancet 2009; 374:301-14

Primary Endpoint:
Cervarix® efficacy against HPV-16/18 CIN3
(Mean follow-up after 3rd dose= 34.9 months, SD= 6.4)

	N	HPV-16 or HPV-18 DNA in lesion				HPV-16 or HPV-18 DNA in lesion and in preceding cytology samples (HPV type assignment algorithm)*			
		n	Event rate (96·1% CI)†	Vaccine efficacy (96·1% CI)	p value	n	Event rate (96·1% CI)†	Vaccine efficacy (96·1% CI)	p value
ATP-E									
CIN3+									
HPV-16/18‡									
Vaccine	7344	2	0·01 (0·00 to 0·04)	80·0% (0·3 to 98·1)	0·0221	0	0·00 (0·00 to 0·02)	100% (36·4 to 100)	0·0038
Control	7312	10	0·06 (0·03 to 0·11)	..	..	8	0·05 (0·02 to 0·09)	..	..
HPV-16									
Vaccine	6303	2	0·01 (0·00 to 0·05)	67·2% (−97·1 to 97·2)	0·1749	0	0·00 (0·00 to 0·03)	100% (8·8 to 100)	0·0146
Control	6165	6	0·04 (0·01 to 0·09)	..	..	6	0·04 (0·01 to 0·09)	..	..
HPV-18									
Vaccine	6794	0	0·00 (0·00 to 0·02)	100% (−19·3 to 100)	0·0307	0	0·00 (0·00 to 0·02)	100% (−170·5 to 100)	0·1236
Control	6746	5	0·03 (0·01 to 0·07)	..	..	3	0·02 (0·00 to 0·06)	..	..

Cervarix® efficacy against CIN2+ associated with non-vaccine oncogenic HPV types: significant cross-protection by single type

ATP-E	N	n	Vaccine efficacy (96·1% CI)	p value
CIN2+				
HPV-31				
Vaccine	7583	2	92·0% (66·0 to 99·2)	<0·0001
Control	7599	25	--	--
HPV-33				
Vaccine	7720	12	51·9% (−2·9 to 78·9)	0·0332
Control	7706	25	--	--
HPV-45‡				
Vaccine	7782	0	100% (67·8 to 100)	0·0619
Control	7745	4	--	--
Vaccine	7461	12	14·3% (−108·1 to 65·4)	0·7000
Control	7414	14	--	--
HPV-58				
Vaccine	7709	6	64·5% (1·5 to 89·2)	0·0225
Control	7702	17	--	--
HPV-31/33/45/52/58				
Vaccine	7862	30	53·0% (24·7 to 71·3)	0·0004
Control	7853	64	--	--

Although efficacy against persistent infection with HPV-45 was highly significant, data for CIN2+ were limited by the small number of cases.
Vaccine efficacy of 100% against HPV-45 was noted in the broadest cohort TVC in women negative for HPV-45 DNA at baseline…

Paavonen J et al. The Lancet 2009; 374:301-14

Cervarix® efficacy against CIN2+ associated with 12 non-vaccine oncogenic HPV types and associated with any oncogenic type: significant cross-protection

According to Protocol Cohort for Efficacy (ATP-E)

Endpoint	Vaccine efficacy	
	%	96.1% CI
CIN2+ by any of the 12 oncogenic type, except HPV-16/18	54.0	34.0–68.4

Endpoint	Vaccine efficacy	
	%	96.1% CI
CIN2+ by any oncogenic type	61.9	46.7–73.2

Thus, our analyses suggest that cross-protection of the vaccine could represent 11-16% additional protection against cervical cancer, greater than that afforded by efficacy against HPV16-18…..

Paavonen J et al. The Lancet 2009; 374:301-14

Cervarix®: overall efficacy against CIN2+ irrespective of HPV type in lesion

Endpoint	Cohort	VE %	96.1% CI
CIN2+ irrespective of HPV type in lesion, irrespective of baseline HPV DNA status	TVC	**30.4**	**16.4–42.1**
CIN2+ irrespective of HPV type in lesion, DNA negative for all high-risk HPV types at baseline	TVC naïve	**70.2**	**54.7–80.9**

The overall effect of the vaccine was also assessed in two study cohorts: TVC and TVC-naive

TVC: included women both with and without oncogenic HPV infections and lesions at baseline (GENERAL POPULATION OF SEXUALLY ACTIVE WOMEN, TARGET FOR CATCH-UP VACCINATION STRATEGY)

TVC-naive: no evidence of exposure to any of the 14 oncogenic HPV types at baseline (ADOLESCENT GIRLS BEFORE SEXUAL DEBUT)

Paavonen J et al. The Lancet 2009; 374:301-14

Reduction in Colposcopy Referrals and Cervical Excision Procedures

		Vaccine n	Control n	Reduction % (96.1% CI)	P-value
TVC- naïve	Colposcopy Referrals	354	476	**26.3** (14.7-36.4)	<0.0001
	Cervical Excision Procedures*	26	83	**68.8** (50.0-81.2)	<0.0001
TVC	Colposcopy Referrals	1107	1235	**10.4** (2.3-17.8)	0.0055
	Cervical Excision Procedures*	180	240	**24.7** (7.4-38.9)	0.0035

TVC-naïve; Vaccine N = 5,449; Control N = 5,436
TVC; Vaccine N = 8,667; Control N = 8,682

*LEEP, Laser, Knife or cone biopsy

Paavonen J et al. The Lancet 2009; 374:301-14

Cervarix® : up-dated summary

- *Cervarix*® demonstrated:
  - 98% efficacy against HPV-16/18 CIN2+ (ATP cohort, post-hoc analysis)
  - substantial efficacy against CIN2+ irrespective of HPV type (70%, TVC naïve cohort)
  - 100% cross-protective efficacy against CIN2+ caused by non-vaccine HPV types 31/45
  - an acceptable safety profile

Paavonen J *et al.* 25th International Papillomavirus Conference (Abstract O-29.06), 2009.
Skinner SR *et al.* 25th International Papillomavirus Conference (Abstract O-29.01), 2009.

"…HPV vaccination has the potential to substantially reduce the incidence of cervical cancer and precancer, and the numbers of colposcopy referrals and cervical excision procedures."

Paavonen J et al. The Lancet 2009; 374:301-14

Available online at www.sciencedirect.com
ScienceDirect
Gynecologic Oncology 111 (2008) 1–2
Gynecologic Oncology
www.elsevier.com/locate/ygyno

Editorial

Human papillomavirus vaccine efficacy: Aligning expectations with reality

The actual effectiveness of vaccination against cervical cancer will be determined over the next several decades through surveillance and longitudinal population studies such as the Nordic cohort, which will provide information about rates of CIN 3 and cancer in vaccinated and unvaccinated women beginning in the year 2020 [8].

Phase III trials of the quadrivalent vaccine enrolled women 15–26 years of age with a very small proportion of virgins; interim results from these trials indicate that *overall* reduction of CIN lesions (regardless of associated HPV type or HPV exposure status) is 17% for CIN 2,3/AIS lesions [6] and 22% for CIN 1–3/AIS lesions [7], clearly far less than the 100% efficacy observed for HPV 16 and 18-associated disease in women naïve to those types.

Large-Scale-Community based HPV efficacy trials

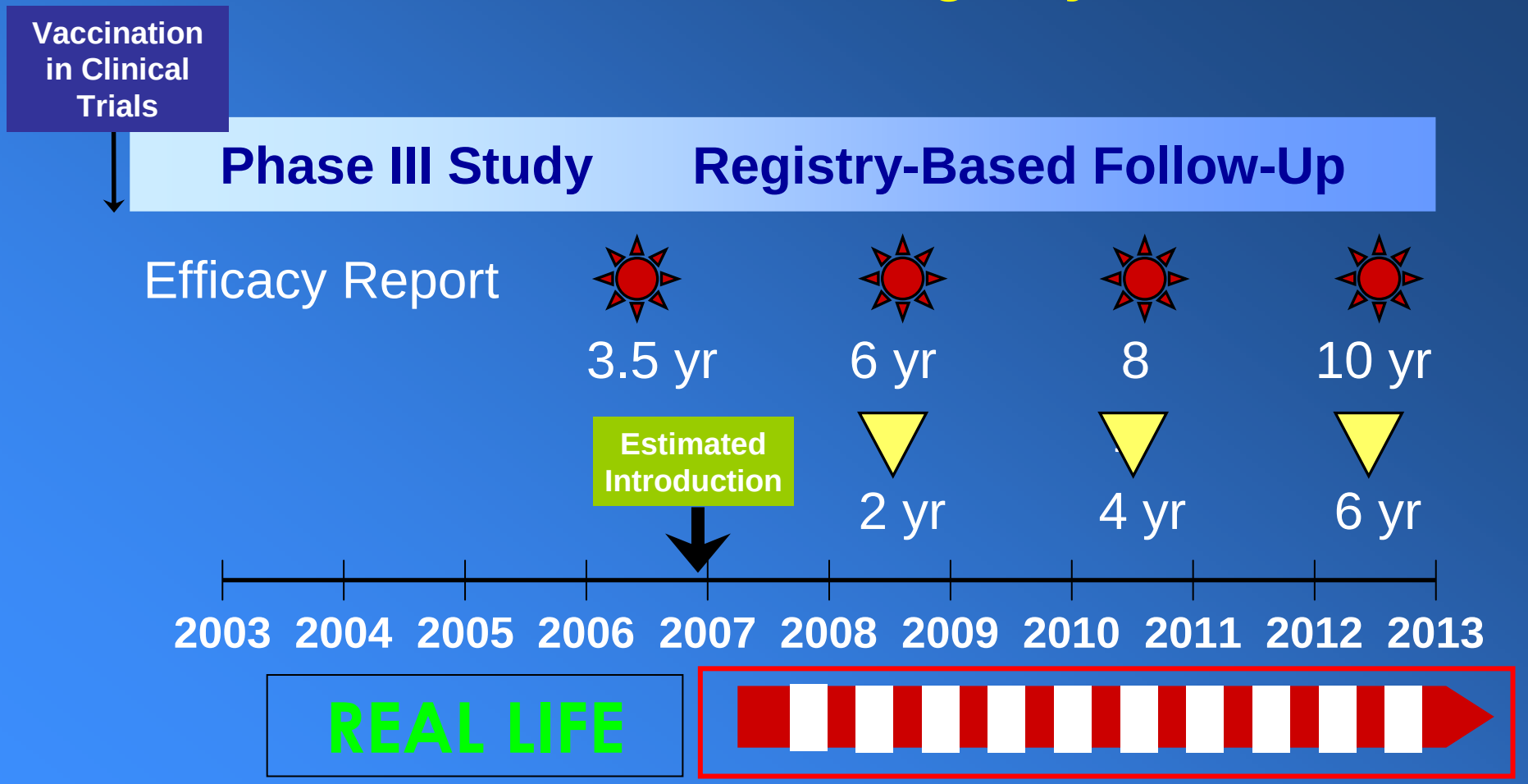
Vaccine sponsor	HPV genotypes	Adjuvant	Trial sites
National Cancer Institute	HPV16, HPV18	AS04	Costa Rica
GlaxoSmithKline	HPV16, HPV18	AS04	Usa, South America, Europe
Merck	HPV16, HPV18 HPV6, HPV11	Alum	Usa, South America, Europe

Thousands of young women will be followed for several years.

Endpoints: CIN (Cervical intraepitelial neoplasia) 2-3-4-5 years follow-up; persistent HPV DNA, 2-3 years follow-up.

Delivering on the promise: HPV vaccines and cervical cancer – JT. Schiller and P. Davies- Nat. Rev. 2004

Development Program for GARDASIL in the "real life": the Nordic Cancer Registry Extension



Follow-up through Nordic Registries provides a Sentinel Cohort with a 4 year head start

Longer-term community based phase III-IV efficacy studies in the Nordic Countries and the extended follow-up planned for the Costa Rica trial

These studies will evaluate long term vaccine safety, impact and protection vs cervical cancer and CIN 3, using active and cancer-registry-based follow up…..

……giving further informations on the potential overall benefit of vaccination in general use, **useful for public health policy makers to make decisions on how best to implement the vaccines**….

Programmi Vaccinali Anti-HPV a Livello Regionale.

Regione	Coorti Rimborsate Offerta Attiva e Gratuita	Offerta Gratuita non Attiva (13enni)	Classi di età in Pagamento Agevolato	Delibere Regionali
Abruzzo	12enni		12-26 anni	DGR n.1359 del 27/12/2007
Basilicata	12, 15, 18 e 25enni		12-26 anni	DGR n.838 dell'11/06/2007
Bolzano	12enni		13-26 anni	DGR n. 4699 del28/12/2007
Calabria	12enni	Si		Nota regionale del 13/11/2007
Campania	12enni			Circolare Regionale del 02/08/2007
Emilia R.	12enni	Si	12-17 anni	DGR n. 236 del 25/02/2008
Friuli V.G.	12 e 16enni		16-17 anni	DGR n.856 del 15/05/2008
Lazio	12enni	Si	12-26 anni	DGR n.133 del 29/02/08
Liguria	12enni	Si [2]	12-26 anni	DGR n. 54 del 25/01/08 Nota integrativa Prot. n. PG/2008/173464 del 30/12/2008
Lombardia	12enni			DGR n.VIII/006683 del 27/02/08
Marche	12enni	Si	12-17 anni	DGR n.433 del 26/03/2008
Molise	12enni	Si	12-26 anni	DGR n.368 dell'8/4/2008
Piemonte	12 e 16enni			DGR n.8-8167 dell'11/02/2008
Puglia	12enni			DGR n.245 del 26/2/2008
Sardegna	12enni [1]		12-17 anni	Deliberazione 32/12 del 4/6/2008
Sicilia	12enni [2]	Si (attiva) [2]	12-26 anni [3]	Decreto Assessoriale del 29/02/2008
Toscana	12 e 16enni	Si (13, 14 e 15enni)		DGR n.1020 del 27/12/2007 e DGR n. 856 del 27/10/2008
Trento	12enni		12-26 anni	Comunicato nr. 2336 del 22/08/08
Umbria	12enni	Si	12-17 anni	DGR n.84 del 04/02/2008
Valle d'Aosta	12 e 16enni	Si		DGR n. 2371 del 31/08/2007
Veneto	12enni [4]	Si	13-26 anni	DGR n.411 del 26/2/2008. Protocollo Generale 07/58302 del 18/06/07

1 Diritto alla gratuità della vaccinazione anche in caso di adesione della ragazza negli anni successivi a quello in cui il diritto è maturato, fermo il limite dei 18 anni di età per l'inizio del ciclo vaccinale.

2 Per le coorti di nascita 1996 & 1997 il diritto ad accedere gratuitamente alla vaccinazione anti-HPV permane nel tempo, anche al superamento dell'età di 12 anni.

3 Nelle 17enni e nelle 25enni la vaccinazione dovrà essere offerta attivamente (ma non gratuitamente).

4 La coorte del 1997 potrà essere oggetto di convocazione anche nell'anno successivo (gratuitamente).

Editoriale Vaccinare Oggi (*in press*, 2009)

I programmi regionali di vaccinazione anti-HPV in Italia: stato attuale e prospettive future

*Paolo Bonanni, °Paolo Durando, *Angela Bechini, ∞Roberto Carloni

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° Dipartimento di Scienze della Salute - Università degli Studi di Genova
∞ Agenzia Sanitaria Regionale - Regione Liguria

Considerazioni conclusive e prospettive future dei vaccini attualmente disponibili

In generale, dalla valutazione dei dati preliminari disponibili, le coperture vaccinali ottenute nelle coorti target dell'intervento possono essere ritenute soddisfacienti ad un anno dall'avvio, su scala nazionale, del programma d'immunizzazione contro il cancro della cervice uterina.
Tuttavia, il quadro dell'applicazione della vaccinazione in Italia è ancora piuttosto composito e tuttora in continua evoluzione.

Vale comunque la pena sottolineare che il nostro Paese, per il fatto di disporre di una rete capillare di servizi di vaccinazione diffusi su tutto il territorio nonchè per la possibilità di registrare sistematicamente tutte le informazioni riguardanti le ragazze e donne immunizzate, si pone in Europa tra le aree in cui sarà possibile monitorare meglio l'andamento complessivo della campagna vaccinale, requisito essenziale per poter valutare criticamente, nel medio-lungo termine, sia i dati epidemiologici raccolti dai registri tumori e da altre banche dati sanitarie, sia eventuali risultati di studi di sorveglianza attiva della popolazione, al fine di stimare il reale impatto della vaccinazione nei confronti delle patologie correlate all'infezione da HPV.

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Editorial

Vaccination against the Human Papillomavirus: The lessons we have not learned

We have a vaccine, we have safety and efficacy studies, we have proven causative correlations between the vaccine-susceptible virus and multiple forms of cancer, but most importantly, we have an opportunity to learn from our lessons and to make a difference in the fight against cancer.

Brianna Hoffner, Vaccine 2008

GRAZIE !!!