Infezione da HPV, storia naturale, vaccinazione e risposta immunitaria

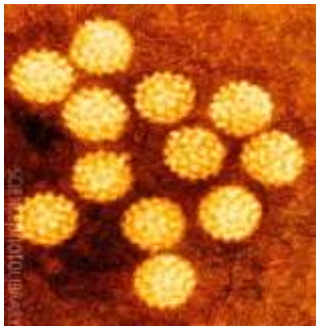
G. Gabutti

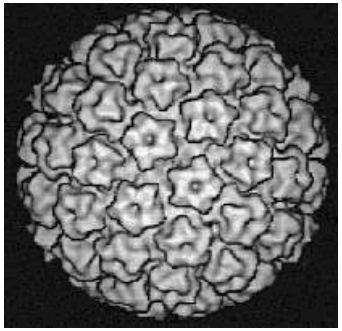
Direttore S.C. Igiene e Sanità Pubblica

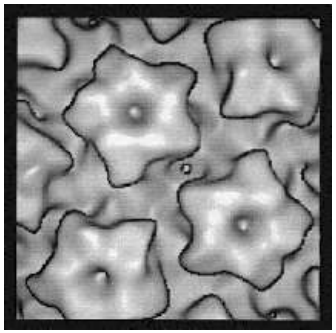
ASL4 Chiavarese – Regione Liguria

HPV

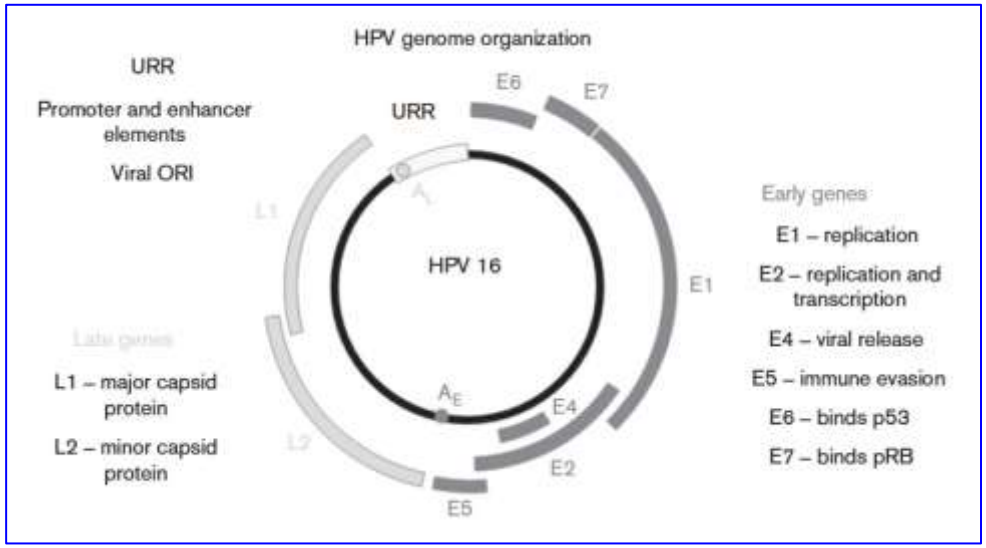
- **100 - 200 genotipi differenti**
- **Capside senza involucro esterno consistente di 72 capsomeri a pentagono**
- **Genoma circolare a doppia elica di DNA (7,000–8,000 paia di basi)**







- **L1. Immunogeno**
- **L2. Immunogeno**
- **E1.Replicazione**
- **E2. Sito di integrazione**
- **E 3 / 4 / 5. Funzioni virali**
- **E6. Oncogene (p53)**
- **E7. Oncogene (Rb)**
- **LCR. Regolatorio**



Syrjänen and Syrjänen. Papillomavirus infections in human pathology. Wiley & Sons 2000, Chichester: 11–46
Stanley M, 2012

Ciclo di vita dell'HPV nell'epitelio squamoso della cervice

Canale cervicale

Strato squamoso maturo

Strato squamoso

Cellule parabasali

Cellule basali (staminali)

Membrana basale

Epitelio normale

Epitelio infetto

Settimana 6-12

Desquamazione delle cellule epiteliali "ripiene" di virus

Assemblaggio virale (L1 e L2)

Replicazione del DNA virale (E6 e E7)

DNA virale episomale nel nucleo cellulare (E1 e E2, E6 e E7)

Infezione delle cellule basali (E1 e E2)

Settimana 0

No viremia, No citolisi o morte, Ciclo infettivo lungo

1. Frazer IH. Nat Rev Immunol 2004; 4: 46–54; 2

Gynecologic Oncology 118 (2010) 312–317

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Review

Current understanding of the mechanism of HPV infection

John T. Schiller *, Patricia M. Day, Rhonda C. Kines

Laboratory of Cellular Oncology, National Cancer Institute, Bethesda, MD 20892, USA

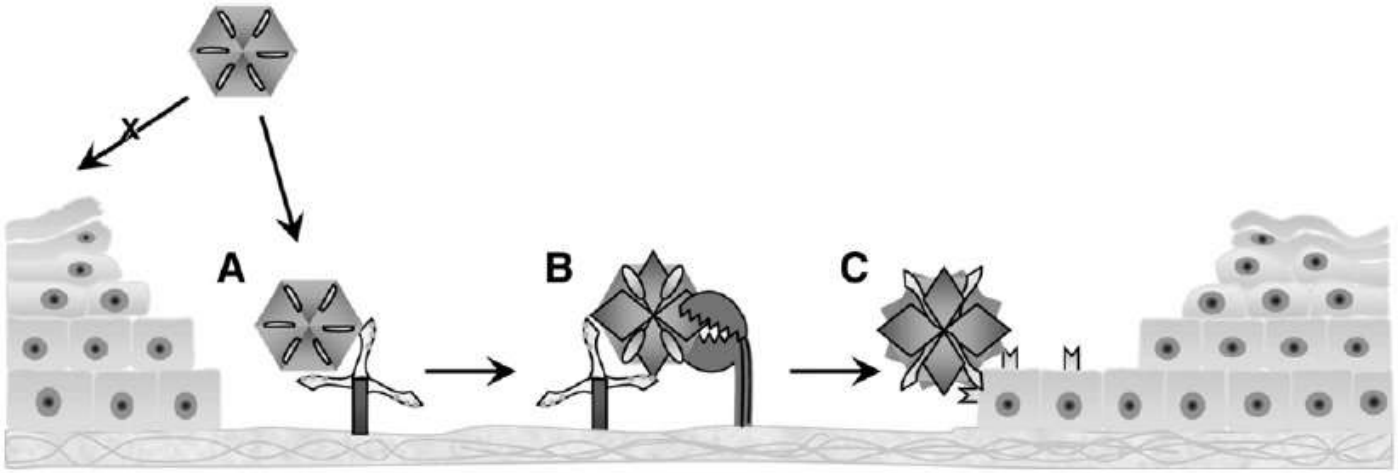


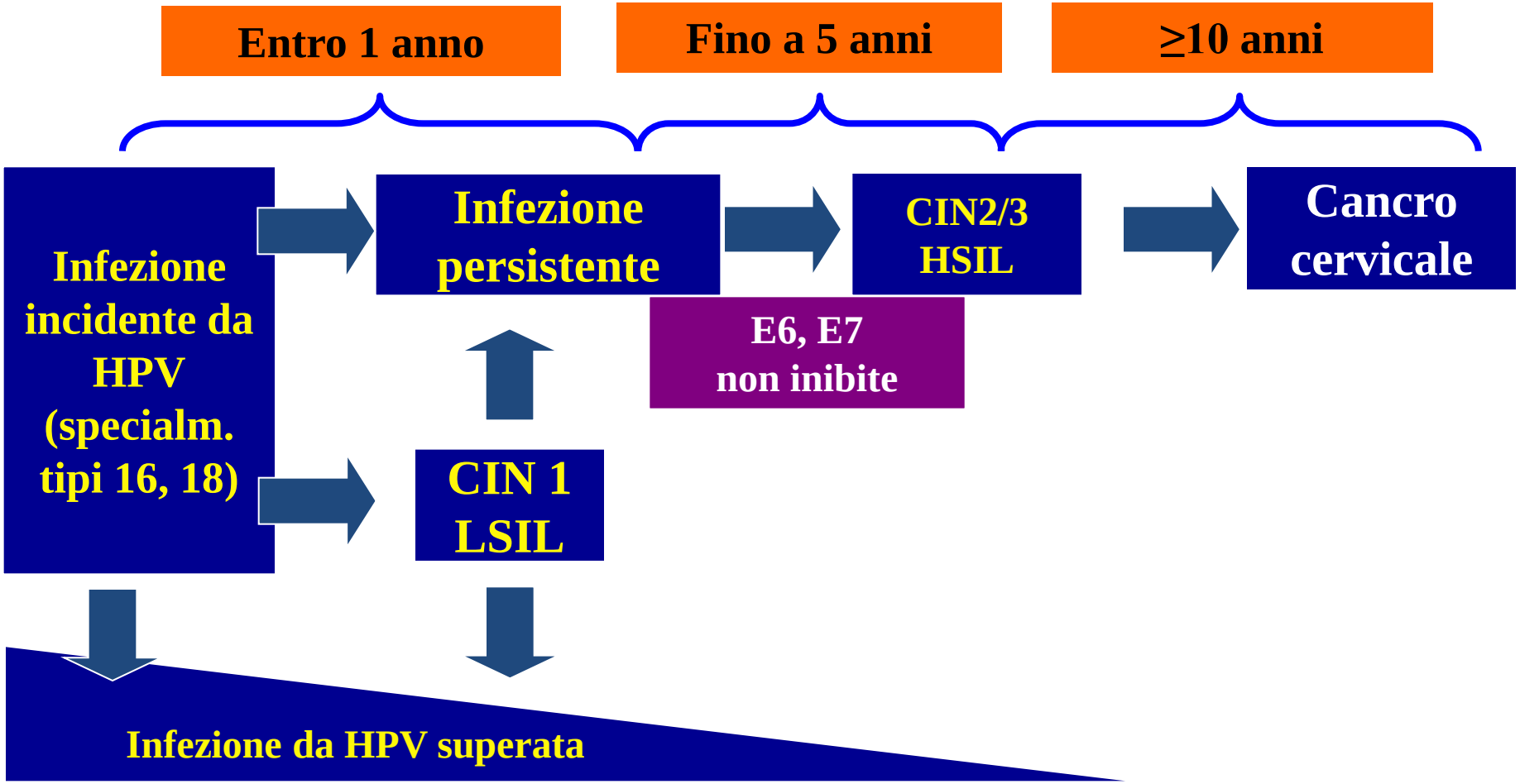
Fig. 1. The virion first binds to HSPGs on the BM exposed after disruption (A). This induces a conformational change exposing a site on L2 susceptible to proprotein convertase (furin or PC 5/6) cleavage (B). After L2 cleavage, an L2 neutralizing epitope is exposed and a previously unexposed region of L1 binds to an unidentified secondary receptor on the invading edge of the epithelial cells (C). BM = basement membrane; HSPG = heparan sulfate proteoglycan.

L'esposizione prolungata di target specifici per gli Ab neutralizzanti durante il processo infettivo costituisce il "tallone di Achille" degli HPV contribuendo all'eccezionale efficacia dei vaccini profilattici basati su L1

Interazioni virus-cellula

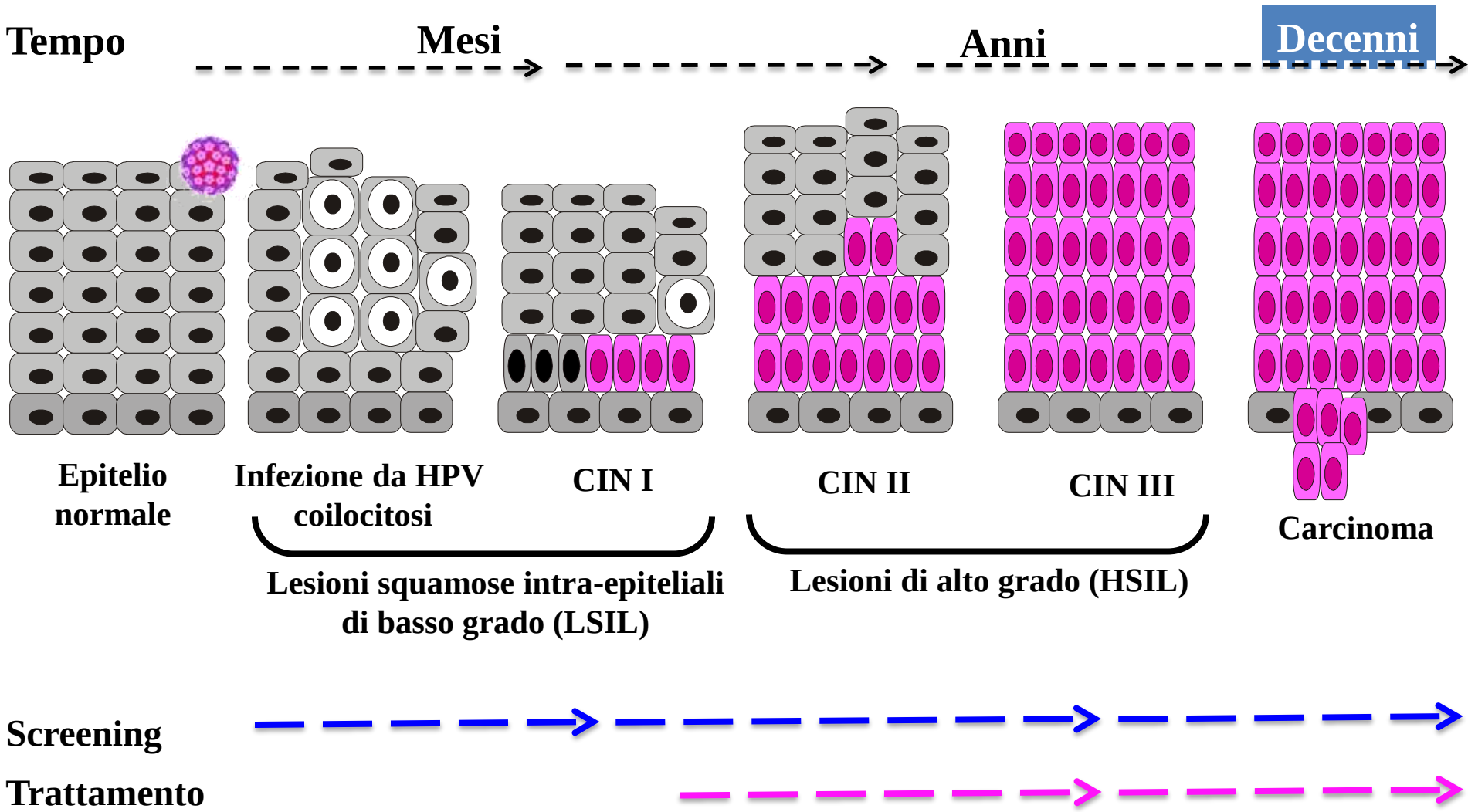
- ✓ **I ceppi ad elevato potenziale oncogeno hanno una spiccata tendenza ad integrarsi nel genoma cellulare**
- ✓ **Il processo di integrazione determina l'interruzione del gene E2 e la conseguente perdita della sua funzione di controllo sull'espressione di E6 ed E7**
- ✓ **I prodotti di E6 ed E7 interagiscono con proteine regolatorie del ciclo cellulare (p53 e pRB) inibendone la funzione**

HPV: storia naturale del cancro della cervice uterina

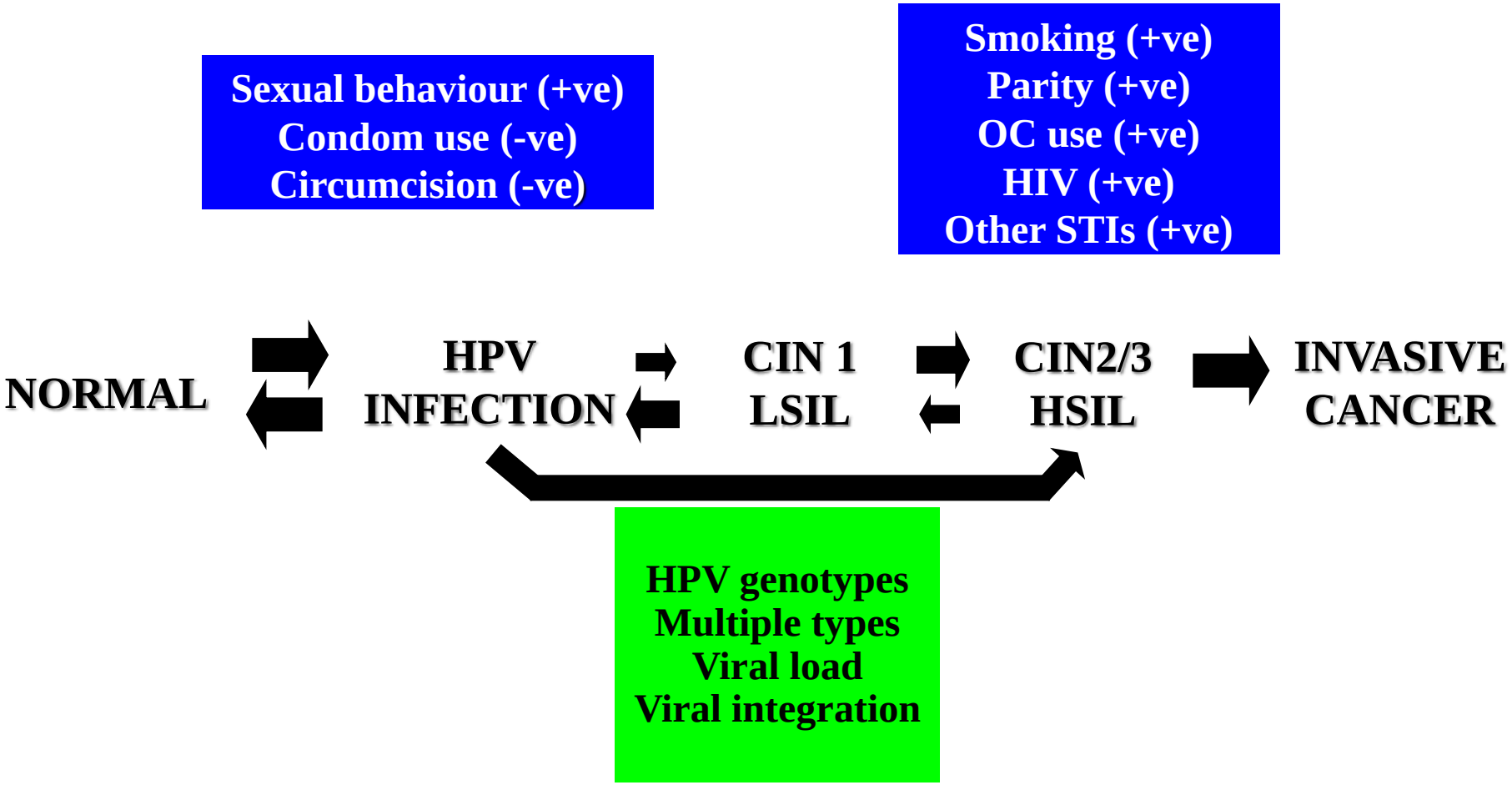


1. Koutsky L. Am J Med 1997; 102 (5A): 3–8; 2. Feoli-Fonseca et al. J Med Virol 2001; 63: 284-292; 3. Liaw et al. JNCI 1999; 4. Clifford et al. Int Papillomvius Conference 2004; 5. Globocan 2002. 6.Sawaya et al. NEJM 2003

Progressione della malattia

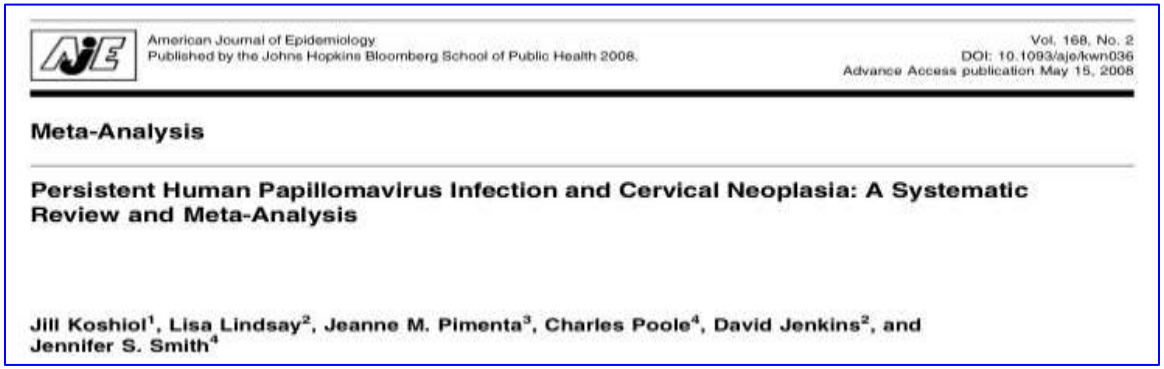


Ruolo dei co-fattori nello sviluppo del cancro cervicale



HIV = human immunodeficiency virus; OC = oral contraceptive; STI = sexually transmitted infection.

1. Castellsague X et al. J Natl Cancer Inst Monogr. 2003; 31: 20–28; 2. Castellsague X et al. Virus Res. 2002; 89: 191–199; 3. Castellsague X et al. N Engl J Med. 2002; 346: 1105–1112



American Journal of Epidemiology
Published by the Johns Hopkins Bloomberg School of Public Health 2008.

Vol. 168, No. 2
DOI: 10.1093/aje/kwn036
Advance Access publication May 15, 2008

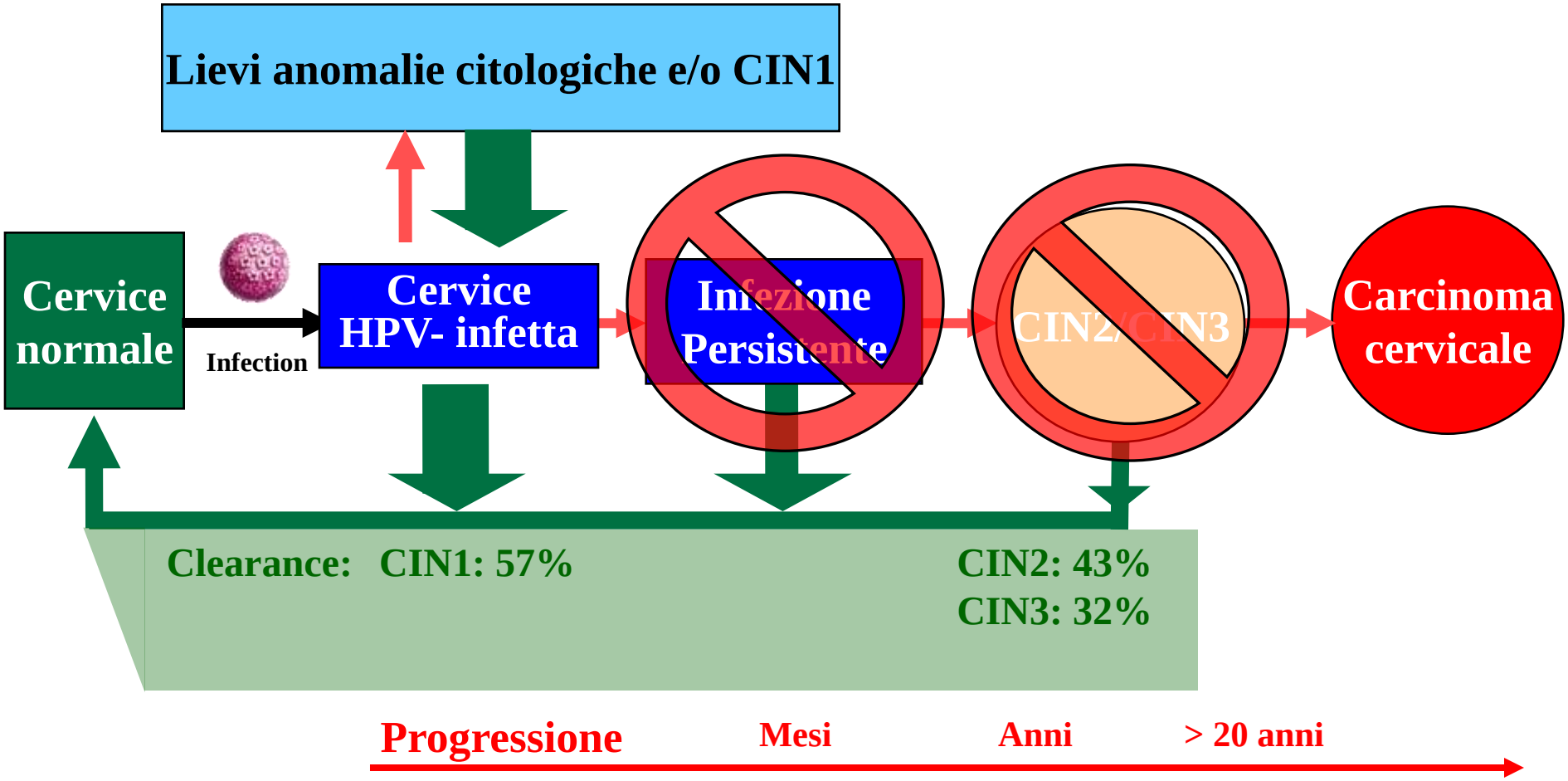
Meta-Analysis

Persistent Human Papillomavirus Infection and Cervical Neoplasia: A Systematic Review and Meta-Analysis

Jill Koshiol[1], Lisa Lindsay[2], Jeanne M. Pimenta[3], Charles Poole[4], David Jenkins[2], and Jennifer S. Smith[4]

- ✓ **L'infezione persistente svolge un ruolo importante nella progressione da neoplasia cervicale a carcinoma invasivo**
- ✓ **La continuata espressione degli oncogeni è fondamentale per il mantenimento e la progressione della neoplasia cervicale**
- ✓ **Il rilevamento ripetuto dello stesso genotipo oncogeno è particolarmente importante per il processo carcinogenetico**
- ✓ **L'infezione persistente è fortemente associata con la comparsa di CIN2-3/HSIL+**
- ✓ **L'infezione persistente rappresenta sia un marker clinico che un endpoint per i trial clinici**

Scelta degli endpoint - Punti chiave



CIN = cervical intraepithelial neoplasia; CIN1 = CIN grado 1

Modificato da Schiffman M, Kruger Kjaer S. J Natl Cancer Inst Monogr 2003; 31: 14–19

Gynecologic Oncology 117 (2010) S15–S19

Contents lists available at ScienceDirect

Gynecologic Oncology

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

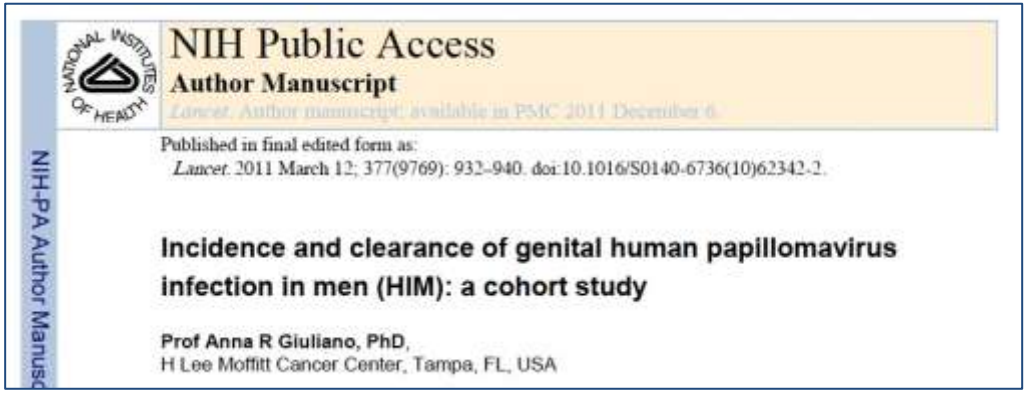
Review

Epidemiology and pathology of HPV disease in males

Anna R. Giuliano *, Gabriella Anic, Alan G. Nyitray

Key points

- Men have a significant role in the transmission of the human papillomavirus (HPV) to women.
- There is a knowledge gap with regard to the natural history of HPV infection and progression to disease in men.
- In males, HPV infection commonly presents as genital warts, and nearly all cases are caused by low-risk HPV types 6, 11 or 6/11.
- HPV types 6 and 11 are implicated in the majority of cases of a rare condition known as recurrent respiratory papillomatosis.
- HPV has been identified in the majority of anal carcinomas and in approximately 50% of penile cancers.
- A subset of head and neck carcinomas appear to be linked to HPV infection, and there is a strong causal association between these cancers and high-risk HPV types, such as HPV 16.
- In a multinational study, HPV DNA was present in 65.2% of asymptomatic males aged 18–70 years.
- Lifetime number of sexual partners was the most significant risk factor for the acquisition of HPV infection ($P<0.05$).
- Genital HPV infections may be less likely to persist in men than in women; in men, the median time to clearance of any HPV infection was 5.9 months, with 75% of infections clearing within 12 months.
- Preliminary data from Australia show that vaccination of girls leads to a decrease of genital warts in men, demonstrating that herd immunity occurs with HPV vaccination.
- Low awareness of HPV in males may be a barrier to the prevention of HPV infection through vaccination.



Published in final edited form as:
Lancet. 2011 March 12; 377(9769): 932–940. doi:10.1016/S0140-6736(10)62342-2.

Incidence and clearance of genital human papillomavirus infection in men (HIM): a cohort study

Prof Anna R Giuliano, PhD,
H Lee Moffitt Cancer Center, Tampa, FL, USA

Findings—In 1159 men, the incidence of a new genital HPV infection was 38·4 per 1000 person months (95% CI 34·3–43·0). Oncogenic HPV infection was significantly associated with having a high number of lifetime female sexual partners (hazard ratio 2·40, 1·38–4·18, for at least 50 partners *vs* not more than one partner), and number of male anal-sexual partners (2·57, 1·46–4·49, for at least three male partners *vs* no recent partners). Median duration of HPV infection was 7·52 months (6·80–8·61) for any HPV and 12·19 months (7·16–18·17) for HPV 16. Clearance of oncogenic HPV infection decreased in men with a high number of lifetime female partners (0·49, 0·31–0·76, for at least 50 female partners *vs* not more than one partner), and in men in Brazil (0·71, 0·56–0·91) and Mexico (0·73, 0·57–0·94) compared with the USA. Clearance of oncogenic HPV was more rapid with increasing age (1·02, 1·01–1·03).

HPV - Elusione della risposta immunitaria dell'ospite

- **Il Virus non è citolitico** (Gonçalves: 2004 – Stanley 2005)
  - Non lisa le cellule dell'ospite per liberare i virioni
  - Infetta i cheratinociti: cellule con morte programmata (apoptosis)
  - Riduzione di efficacia vs attivazione del Sistema Immune
- **Non provoca infiammazione** (Stanley 2005)
  - No "danger signal" che attiva la risposta immune
- **Elude il riconoscimento degli Ag capsidici da parte delle cell. di Langerhans** (Schiller: 2003)
  - Altera il normale processo di presentazione dell'Ag (APC)
  - Altera il processo di attivazione dei linfociti T
  - Risposta cellulo-mediata difettosa
  - Evita l'attacco dei linfociti T comunque attivati
- **Inibisce gli Interferoni tipo I (alpha e beta)** (Schiller: 2003)
  - Alta tendenza all' integrazione genomica
  - Infezione persistente
  - progressione maligna (genotipi HR)

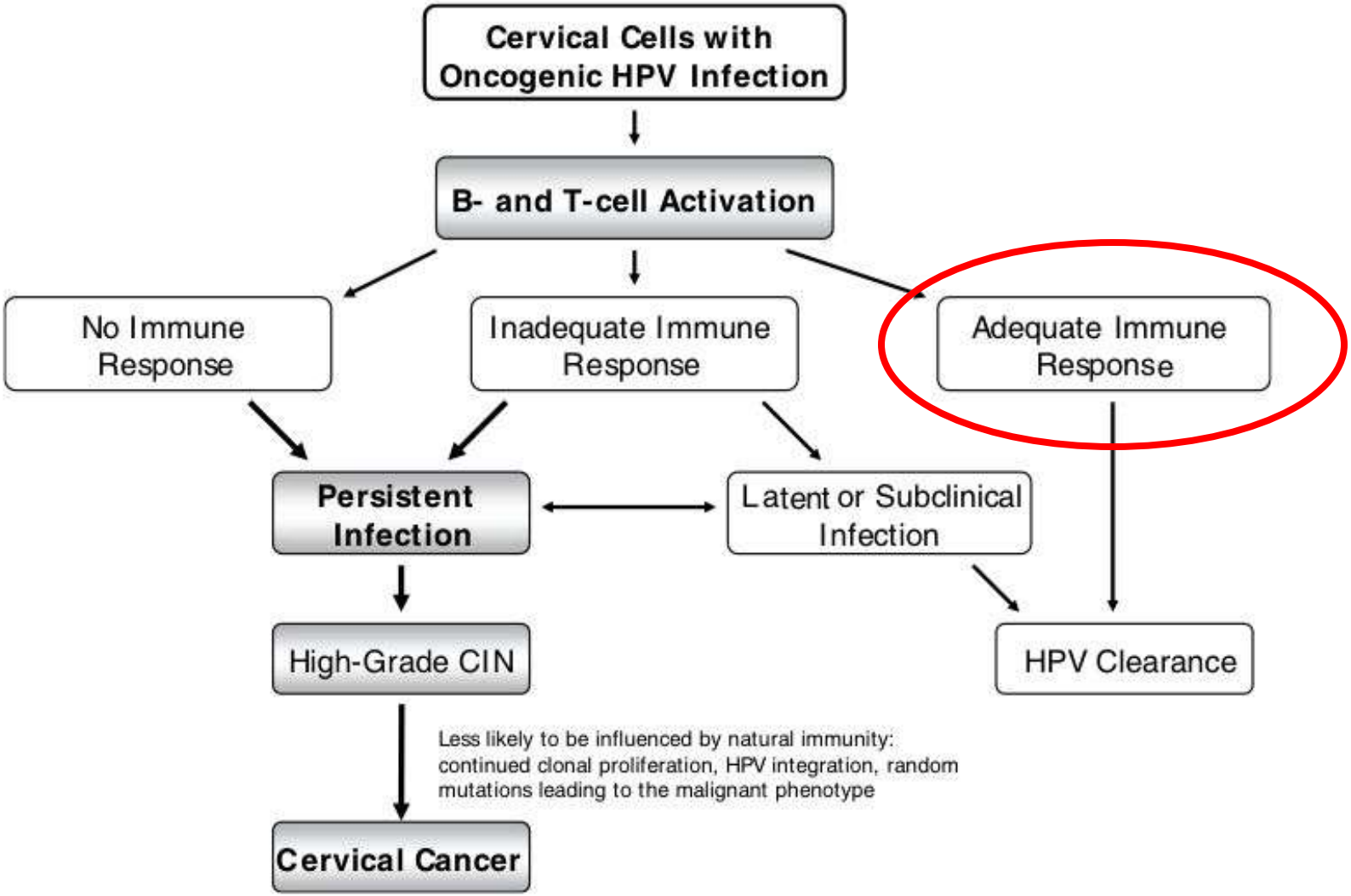
Stanley M et al. Vaccine 2006; 24 (Suppl 1): S16–S22

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

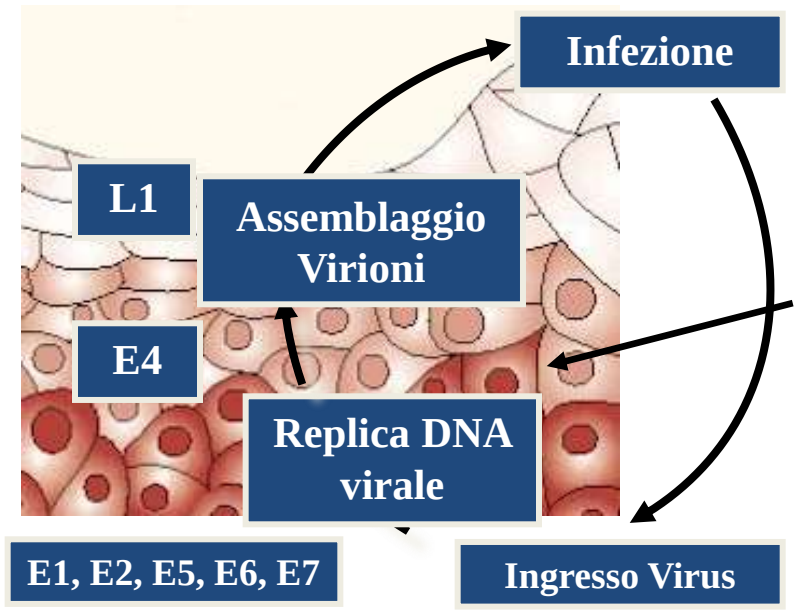
REVIEW

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

Mark H. Einstein



Risposta immune ai Papilloma Virus



Immunità umorale

- **Principalmente diretta contro L1**
- **Previene l'ancoraggio del virus e la sua entrata**

Immunità cellulo-mediata

Capace di eliminare la maggior parte delle infezioni da HPV

Tuttavia:

✓I tipi HPV oncogeni stimolano fattori cellulari che inibiscono la risposta immune locale

✓Infezioni pregresse da HPV oncogeni non necessariamente inducono immunità verso infezioni successive poichè:

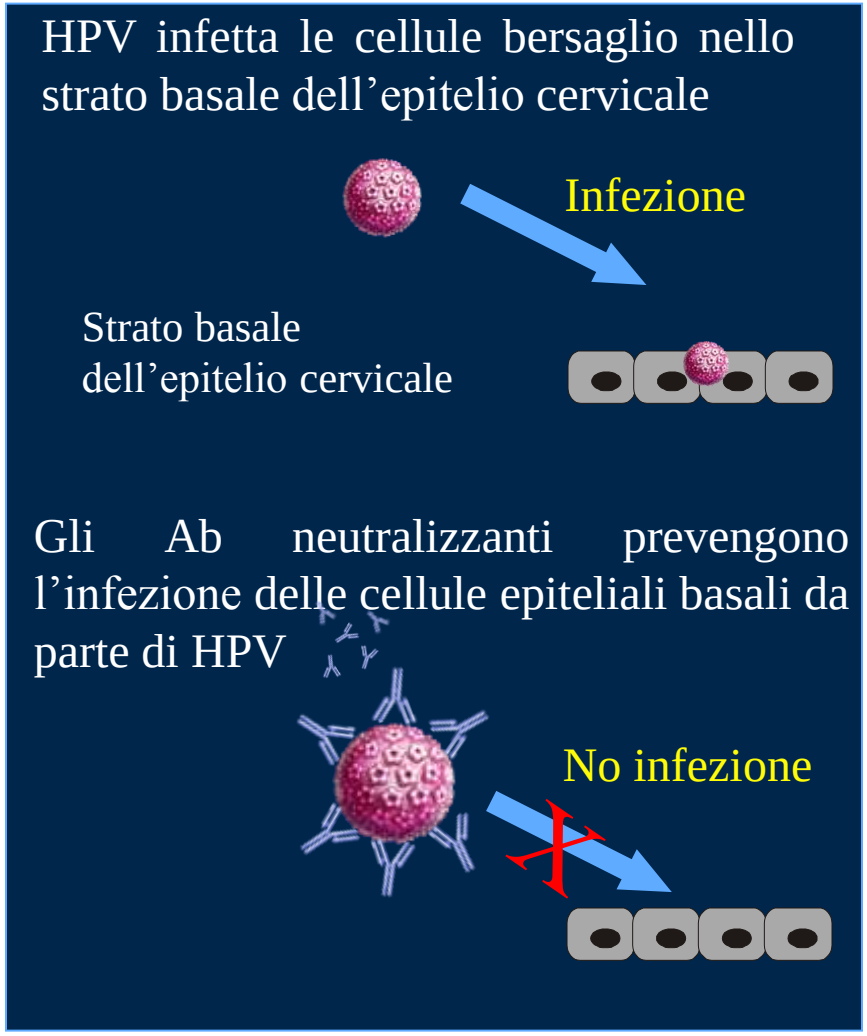
- Il livello di protezione conferito dall'infezione naturale è variabile
- Sono possibili le reinfezioni o nuove infezioni

✓A seguito dell'infezione naturale, solo il 50% delle donne presenta anticorpi misurabili

Handsfield HH. Am J Med 1997; 102: 16–20; Stern et al. J Clin Virol 2000; 19: 57–66; Bosch FX et al. J Clin Pathol 2001; 54: 163–175; Roden R et al. Rev Vaccines 2003; 2: 495–516; Viscidi R et al. Cancer Epidemiol Biomarkers Prev. 2004;13:324-27;

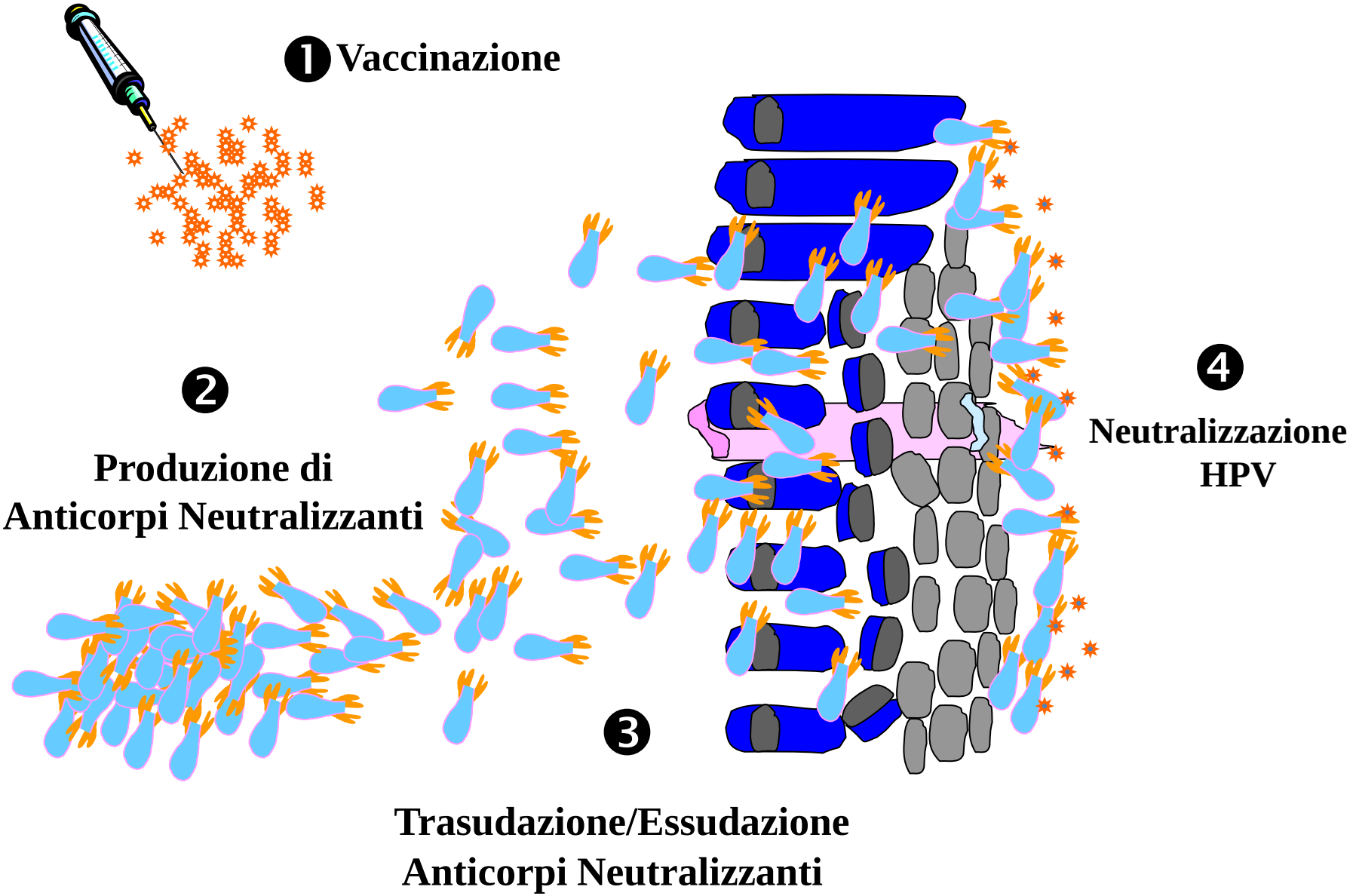
Vaccino HPV
Il ruolo degli Ab neutralizzanti

Il principale meccanismo di protezione della vaccinazione nei confronti dell'infezione è rappresentato dagli Ab neutralizzanti (WHO 2007)



Stanley M et al. Vaccine 2006; 24 Suppl 3: S106–S113;
WHO Department of Immunization, Vaccines and Biologicals 2007

Meccanismo di protezione del vaccino HPV



Immunologia - Punti chiave

- ✓ **Gli Ab neutralizzanti sono fondamentali per la protezione post-vaccinale nei confronti dell'infezione da HPV**

- ✓ **Non esiste un correlato immunitario di protezione né a breve termine nè a lungo termine**

- ✓ **La tecnologia vaccinologica moderna permette di controllare qualità e quantità della risposta immune Ag-specifica**

Virology 414 (2011) 153–163

Contents lists available at ScienceDirect

Virology

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

Persistence of viral DNA in the epithelial basal layer suggests a model for papillomavirus latency following immune regression

Gareth Adam Maglennon, Pauline McIntosh, John Doorbar *

Division of Virology, MRC National Institute for Medical Research, The Ridgeway, Mill Hill, London, NW7 1AA, UK

Review series

The known unknowns of HPV natural history

Patti E. Gravitt[1,2]

[1]Perdana University Graduate School of Medicine, Serdang, Malaysia. [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA.

The Journal of Clinical Investigation http://www.jci.org Volume 121 Number 12 December 2011

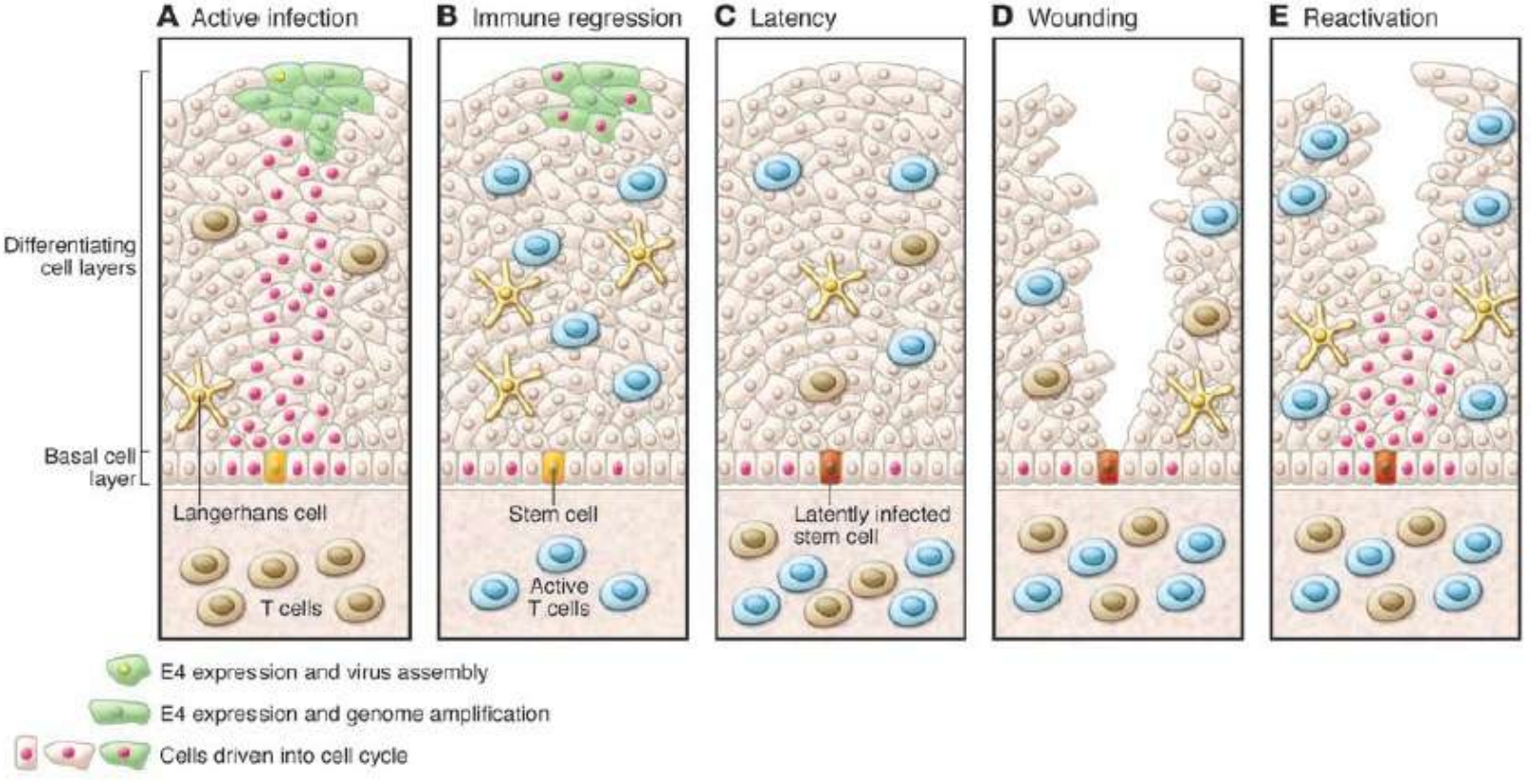
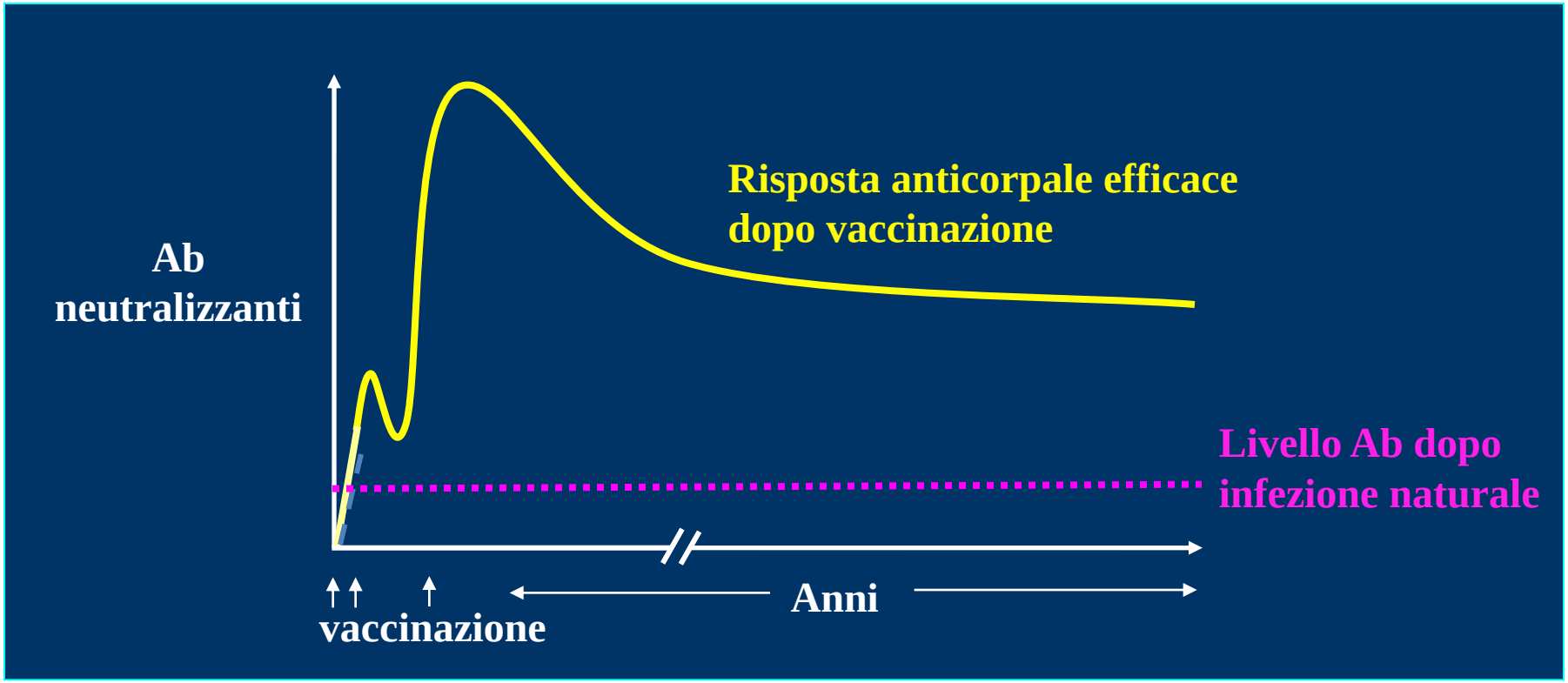


Figure 5

Model for cervical HPV latency and reactivation. (**A**) Active infection drives cells in the basal layer and above into cell cycle, allowing genome amplification and new virion production. (**B**) Triggering of an effective immune response leads to immune regression, accompanied by infiltration of predominantly T cells. (**C**) Viral latency may ensue, with viral genomes restricted to stem cells in the basal layer of the epithelium. (**D** and **E**) Wounding may stimulate latently infected basal cells to divide and trigger reactivation and stimulation of tissue-resident memory T cells. Adapted with permission from *Virology* (63).

Risposta immune dopo infezione naturale e dopo vaccinazione

- **La vaccinazione permette di 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.

Vaccine 27 (2009) 581–587

Contents lists available at ScienceDirect

Vaccine

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

Immunogenicity and tolerability of an HPV-16/18 AS04-adjuvanted prophylactic cervical cancer vaccine in women aged 15–55 years

Tino F. Schwarz[a,*], Marek Spaczynski[b], Achim Schneider[c,d], Jacek Wysocki[e], Andrzej Galaj[f], Pamela Perona[g], Sylviane Poncelet[h], Toufik Zahaf[h], Karin Hardt[h], Dominique Descamps[h], Gary Dubin[i], on behalf of the HPV Study Group for Adult Women

[a] Stiftung Juliusspital Würzburg, Zentrallabor, Juliuspromenade 19, D-97070 Würzburg, Germany
[b] Katedra Ginekologii Polaznictwa Klinika Onkologi, Poznań, Poland
[c] Charité Universitätsmedizin Berlin, Campus Benjamin Franklin, D-12200 Berlin, Germany
[d] Campus Mitte, Department of Gynaecology, Berlin, Germany
[e] Department of Preventive Medicine, University School of Medical Sciences, Poznań, Poland
[f] Vitamed Bydgoszcz, Bydgoszcz, Poland
[g] Department of Tropical Medicine and Infectious Diseases, Ludwig Maximilians Universität, Leopoldstrasse 5, 80802, Munich, Germany
[h] GlaxoSmithKline Biologicals, B-1330 Rixensart, Belgium
[i] GlaxoSmithKline Biologicals, King of Prussia, PA 19406, USA

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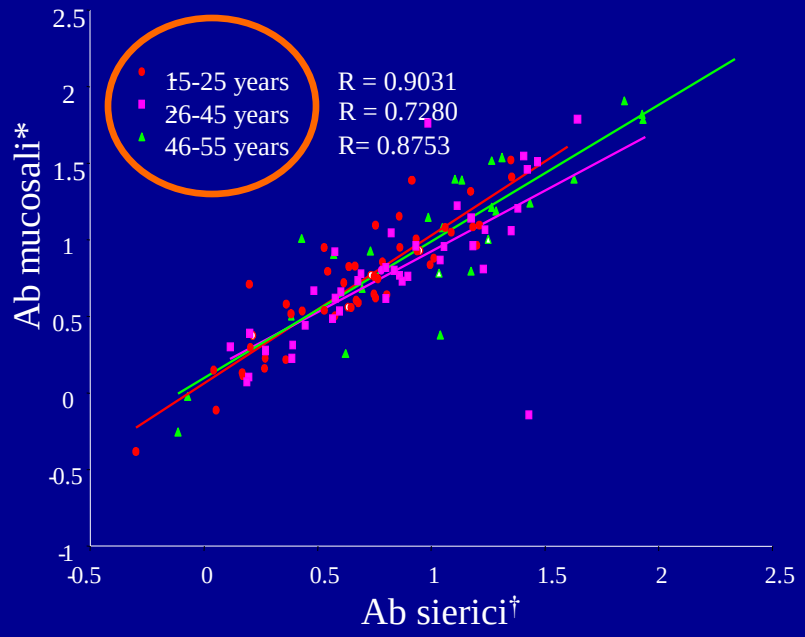
ABSTRACT

The immunogenicity and safety of an HPV-16/18 AS04-adjuvanted vaccine were assessed in women aged 26–55 years and compared with women aged 15–25 years in a Phase III, non-randomised, open-label, age-stratified study. Overall the vaccine was well tolerated and 100% seropositivity was achieved 1 month after the third dose in all age groups. There was a high correlation between HPV-16 and HPV-18 antibody levels (IgG) in cervicovaginal secretions and sera, regardless of age. The HPV-16/18 AS04-adjuvanted vaccine induces a robust and persistent immune response in women >26 years of age and generates antibodies that transudate through the cervix epithelium.

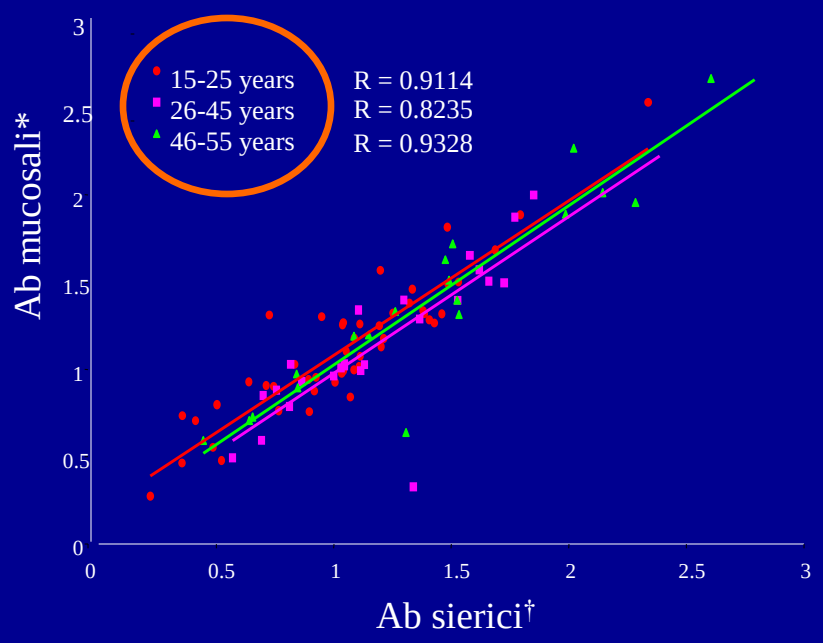
Elevato livello di Ab a livello della cervice

- **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; Schwarz TF et al,. Vaccine 2009: 581-587

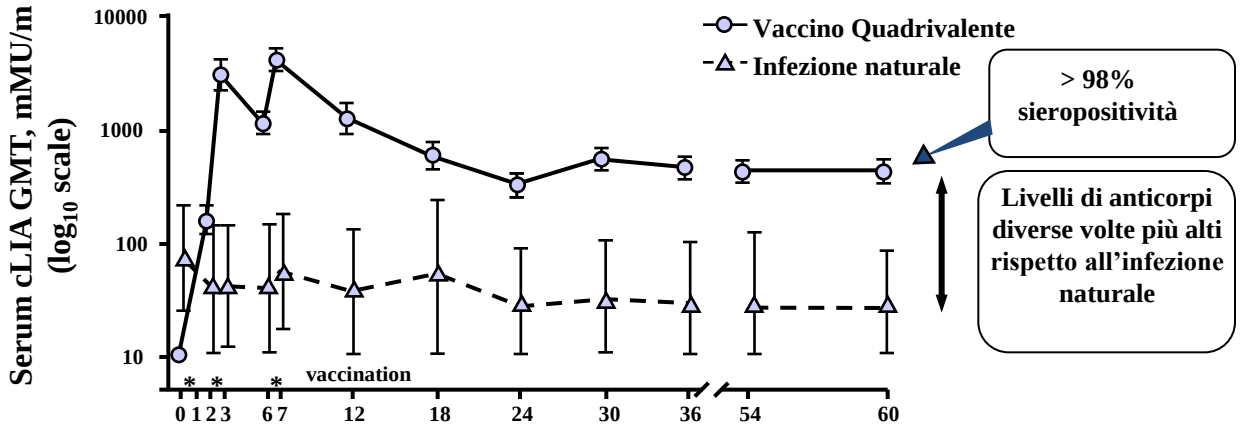
Vaccino anti-HPV : i requisiti essenziali

- ✓**Elevati titoli di Anticorpi Neutralizzanti**
- ✓**Lunga durata della protezione**
- ✓**Efficacia verso i tipi di HPV oncogeni più rilevanti nel Cancro Cervicale (HPV 16 e 18)**
- ✓**Sicurezza e tollerabilità**

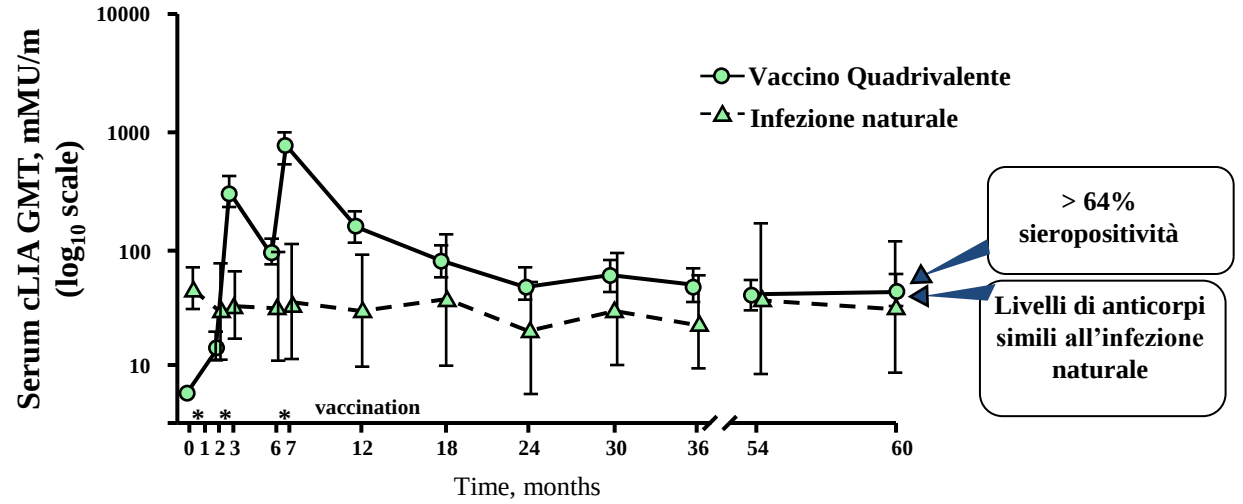
Poncelet S et al. 24th International Papillomavirus Conference 2007: Abstract PS19-25;
Stanley M et al. Vaccine 2006;2 4 Suppl 3: S106–S113; Banatvala J. Vaccine 2001; 19: 877–885

Vaccino quadrivalente: Immunogenicità a 5 anni

HPV 16



HPV 18



Adattato da Olsson SE et al. Vaccine 2007; 25: 4931–4939; Villa LL et al. Vaccine 2006; 24: 5571–558

Vaccino bivalente
ultimo follow-up: durata della protezione a 9.4 anni

- **>430 donne** (sottogruppo brasiliano)
- testata la presenza di anticorpi sia con il metodo ELISA che con il PBNA
- **sieropositività mantenuta per ambedue i ceppi HPV16 e HPV18**
- EV 100% verso le CIN2+

O-18.04

HPV-16/18 VACCINE: SUSTAINED IMMUNOGENICITY AND EFFICACY UP TO 9.4 YEARS

P Naud, Federal University of Rio Grande do Sul, Porto Alegre, BRAZIL, C M Roteli - Martins, Hospital Leonor Mendes de Barros- Secretaria da Saúde de São Paulo, São Paulo, BRAZIL, N De Carvalho, Federal University of Parana, Parana, BRAZIL, J Teixeira, State University of Campinas - UNICAMP, Campinas, BRAZIL, P Borba, Ceara Cancer Prevention Institute, Ceara State, BRAZIL, N Sanchez, GlaxoSmithKline Biologicals, Rio de Janeiro, BRAZIL, T Zahaf, GlaxoSmithKline Biologicals, Wavre, BELGIUM, B Geeraerts, GlaxoSmithKline Biologicals, Wavre, BELGIUM, D Descamps, GlaxoSmithKline Biologicals, Wavre, BELGIUM

Naud P. Oral Comunication O-18.04 IPV, Berlino 2011

- **Nello studio 023 (sottogruppo dello studio 001/007 che include donne da 15 a 25 aa al momento della vaccinazione) la risposta immunitaria è stata valutata fino a 113 mesi**

- **Nel gruppo vaccino, i dati di immunogenicità nel range 107-113 mesi indicano il 100% di sieropositività per HPV16 e HPV18 (IC95%: 96,1-100)**

Vaccino quadrivalente – RCP*

Efficacia protettiva verso le lesioni CIN (donne naïve ai tipi di HPV contenuti nel vaccino)

	% efficacia a 2 aa (CI 95%)	% efficacia al termine dello studio (CI 95%)
CIN 2/3 o AIS correlati ad HPV 16/18	**100 (92,9-100)**	**98,2 (93,5-99,8)**
CIN 3 correlate ad HPV 16/18	**100 (86,5-100)**	**96,9 (88,4-99,6)**
AIS correlati ad HPV 16/18	**100 (14,8-100)**	**100 (30,6-100)**

*** Vaccino quadricvalente - RCP vers. aggiornata 19 Dicembre 2011**

Vaccino bivalente – RCP*

Efficacia protettiva verso le lesioni CIN (donne naïve ai tipi di HPV contenuti nel vaccino)

	% efficacia (CI 96,1%)	% efficacia analisi post-hoc (CI 96,1%)
CIN 2/3 o AIS correlati ad HPV 16/18	**92,9 (79,9-98,3)**	**98,1 (88,4-100)**
CIN 3 o AIS correlati ad HPV 16/18	**80 (0,3-98,1)**	**100 (36,4-100)**

*** Vaccino bivalente - RCP vers. Aggiornata 5 Dicembre 2011**

Vaccino bivalente

Efficacia verso CIN2+, CIN3+ e AIS indipendentemente dal tipo HPV

TVC–naïve

Endpoint	Vaccino		Controlli		Efficacia, % (95% CI)
	N	Cases	N	Cases	
CIN2+	5,466	61	5,452	172	**64.9** (52.7–74.2)
CIN3+	5,466	3	5,452	44	**93.2** (78.9–98.7)
AIS	5,466	0	5,452	7	**100** (31.0–100)

simile in tutte le fasce di età

TVC

Endpoint	Vaccino		Controlli		Efficacia, % (95% CI)
	N	Cases	N	Cases	
CIN2+	8,694	287	8,708	428	**33.1** (22.2–42.6)
CIN3+	8,694	86	8,708	158	**45.6** (28.8–58.7)
AIS	8,694	3	8,708	13	**76.9** (16.0–95.8)

più alta nelle 15–17enni e decresce con l'età

Lehtinen M et al. Lancet Oncol 2012; 13: 89-99

Cross-protezione verso CIN2+
da tipi oncogeni diversi da HPV16 e 18

L'efficacia dei due vaccini non deriva da uno studio di confronto diretto

	Quadrivalente		Bivalente	
Tipi correlati al virus HPV-16 (specie A9)	**% Efficacia[1]**	**95% IC**	**% Efficacia[2]**	**95% IC**
HPV 31	**55,6 %**	**26,2 - 74,1**	**87,5%**	**68,3 - 96,1**
HPV 33	19,1%	< 0 - 52,1	**68,3%**	**39,7 - 84,4**
Tipi correlati al virus HPV-18 (specie A7)				
HPV 39	37,5%	< 0 - 69,5	**74,9%**	**22,3 - 93,9**
HPV 45	0,0%	< 0 - 60,7	**81,9%**	**17,0 – 98,1**
Altri Tipi				
HPV 51	16,3%	< 0 – 48,5	**54,4%**	**22,0– 74,2**

1.Quadrivalente - RCP vers. aggiornata Dicembre 2011
2. Bivalente - RCP vers. aggiornata 5 Dicembre 2011

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Vaccine

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

Monitoring the safety of quadrivalent human papillomavirus vaccine: Findings from the Vaccine Safety Datalink☆

Julianne Gee[a,*], Allison Naleway[b], Irene Shui[c], James Baggs[a], Ruihua Yin[c], Rong Li[c], Martin Kulldorff[c], Edwin Lewis[d], Bruce Fireman[d], Matthew F. Daley[e], Nicola P. Klein[d], Eric S. Weintraub[a]

International Scholarly Research Network
ISRN Obstetrics and Gynecology
Volume 2011, Article ID 457204, 20 pages
doi:10.5402/2011/457204

Review Article

Next Generation Cancer Protection: The Bivalent HPV Vaccine for Females

Diane M. Harper and Stephen L. Vierthaler

Profilo di sicurezza favorevole

“Ultimi aggiornamenti”

- ✓ **Potenziale dei cancri prevenibili è in funzione dell’età della vaccinazione**
- ✓ **Efficacia nelle donne adulte**
- ✓ **Analisi farmaco-economiche**
- ✓ **Co-somministrabilità**
- ✓ **Potenziale impatto della vaccinazione**

Potenziale impatto della vaccinazione

- ✓ **70% riduzione di tutti i CCU***
- ✓ **85% riduzione dei casi di adenoK***
- ✓ **Riduzione del numero di colposcopie e conizzazioni[1] (e nascite pretermine associate[2-3])**
- ✓ **Riduzione di esami, stress emotivo e ansietà correlati con un referto di Pap test anormale[4]**

***** *Estimated worldwide prevalence of HPV16/18: +70%all invasive cervical cancer, + 80% cervical adenocarcinoma[5].*

Assumption: efficacy of HPV 16/18 vaccine against cervical cancer is 100%; vaccine coverageis 100%

1. Paavonen J et al. Lancet 2009; 2. Arbyn M et al. BMJ 2008; 3. Kyrgiou M et al. Lancet 2006; 4. Hellsten C et al. Eur J Obstet Gynecol Reprod Biol 2009; 5. Bosch FX et al. Vaccine 2008

DOI: 10.1093/jnci/djr319
Advance Access publication on September 9, 2011.

ARTICLE

Proof-of-Principle Evaluation of the Efficacy of Fewer Than Three Doses of a Bivalent HPV16/18 Vaccine

Aimée R. Kreimer, Ana Cecilia Rodriguez, Allan Hildesheim, Rolando Herrero, Carolina Porras, Mark Schiffman, Paula González, Diane Solomon, Silvia Jiménez, John T. Schiller, Douglas R. Lowy, Wim Quint, Mark E. Sherman, John Schussler, Sholom Wacholder; for the CVT Vaccine Group

Manuscript received January 11, 2011; revised July 21, 2011; accepted July 22, 2011.

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Background Three-dose regimens for human papillomavirus (HPV) vaccines are expensive and difficult to complete, especially in settings where the need for cervical cancer prevention is greatest.

Methods We evaluated the vaccine efficacy of fewer than three doses of the HPV16/18 vaccine Cervarix in our Costa Rica Vaccine Trial. Women were randomly assigned to receive three doses of the HPV16/18 vaccine or to a control vaccine and were followed for incident HPV16 or HPV18 infection that persisted in visits that were 10 or more months apart (median follow-up 4.2 years). After excluding women who had no follow-up or who were HPV16 and HPV18 DNA positive at enrollment, 5967 women received three vaccine doses (2957 HPV vaccine vs 3010 control vaccine), 802 received two doses (422 HPV vs 380 control), and 384 received one dose (196 HPV vs 188 control). Reasons for receiving fewer doses and other pre- and post-randomization characteristics were balanced within each dosage group between women receiving the HPV and control vaccines.

Results Incident HPV16 or HPV18 infections that persisted for 1 year were unrelated to dosage of the control vaccine. Vaccine efficacy was 80.9% for three doses of the HPV vaccine (95% confidence interval [CI] = 71.1% to 87.7%; 25 and 133 events in the HPV and control arms, respectively), 84.1% for two doses (95% CI = 50.2% to 96.3%; 3 and 17 events), and 100% for one dose (95% CI = 66.5% to 100%; 0 and 10 events).

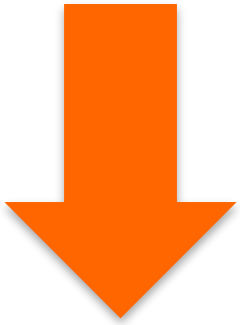
Conclusion Four years after vaccination of women who appeared to be uninfected, this nonrandomized analysis suggests that two doses of the HPV16/18 vaccine, and maybe even one dose, are as protective as three doses.

J Natl Cancer Inst 2011;103:1444–1451

J Formos Med Assoc. 2010 January ; 109(1): 4–24.

Perspectives for Preventive and Therapeutic HPV Vaccines

Ken Lin[1,*], Kimberley Doolan[2,*], Chien-Fu Hung[3,6], and T-C Wu[3,4,5,6,†]

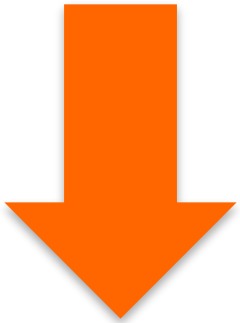


✓**Vaccini preventivi**

✓**Vaccini terapeutici**

Vaccini preventivi

- ✓ **Abbattere i costi**
- ✓ **Massimizzare la protezione verso le patologie tumorali HPV-correlate**



- ✓ **Uso di L1 capsomeri prodotti in *E.coli* e somministrati per via transdermica o per inalazione nasale**
- ✓ **Uso di L2 vaccini adiuvati**
- ✓ **Vaccini L1 polivalenti**

Considerazioni conclusive

- ✓ **Molti aspetti dell'infezione da HPV, della storia naturale e della risposta immunitaria sono consolidati**
- ✓ **Sono disponibili molti dati sugli aspetti immunologici conseguenti alla vaccinazione**
- ✓ **I vaccini disponibili hanno un elevato profilo di immunogenicità ed efficacia protettiva**
- ✓ **Il profilo di sicurezza e tollerabilità è eccellente**
- ✓ **Per la Sanità pubblica è essenziale che vaccinazione e prevenzione secondaria siano integrati**