Università degli Studi di Padova
Dipartimento di Scienze Ginecologiche e della Riproduzione Umana
Scuola di Specializzazione in Ginecologia e Ostetricia
Direttore Prof. Giovanni Battista Nardelli

Portio, precancerous lesion screening and managment updates

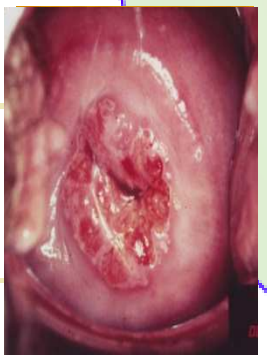
Dott. Simone Fagherazzi

HPV, history

460 BC
Genital warts defined as Condyloma[1]

1930s
Proof of warts viral cause

1940s
Nuns often die of breast cancer. Married women & prostitute of cervical cancer[4]



1975
Hypothesis: HPV can cause cervical cancer[1]

1983
HPV 16 isolated from cervical cancer[1]

1984
HPV 18 extracted from cervical cancer[2]

1992
Making of vaccine antigen

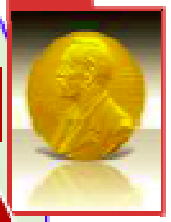
Early 1990s
Gardasil® development starts

1997
Clinical studies start

1999
HPV in 99.7% of all cervical cancer [3]

2006
Licencure for Gardasil®, the first HPV vaccine

2008

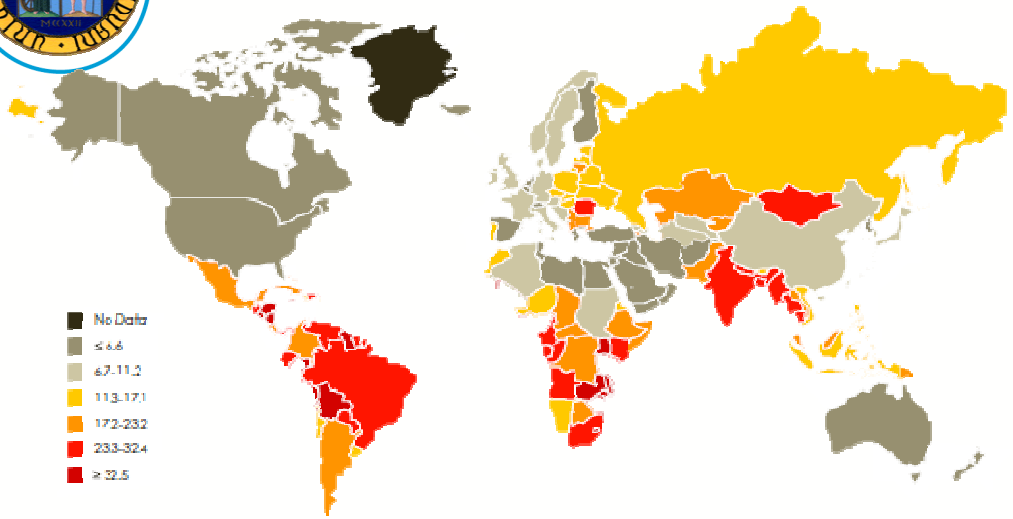


2008
2008 Gardasil® wins International Galien Prize

HPV = Human Papillomavirus; VLP = Virus-like particles

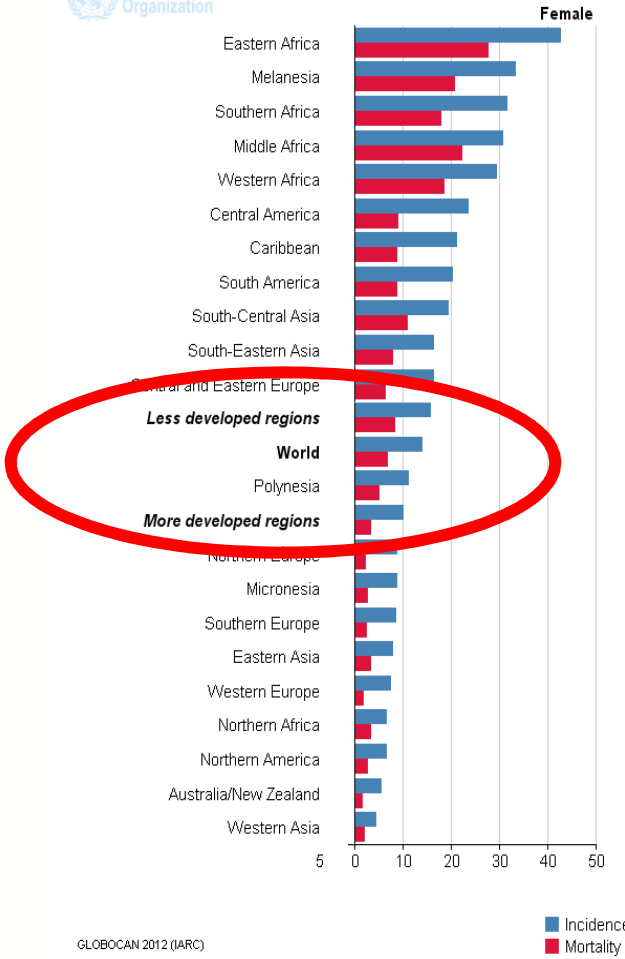
1. Syrjänen and Syrjänen, Wiley & Sons, Chichester; 2000. p.1–10;
2. Zur Hausen H. Nat Rev Cancer 2002;2:342–350
3. Walboomers J et al. J Pathol 1999; 189: 12-19.
4. Rigoni-Stern A. *Gior Servire Progr Pathol Terap.* 1842;2:507-517.

HPV, epidemiology

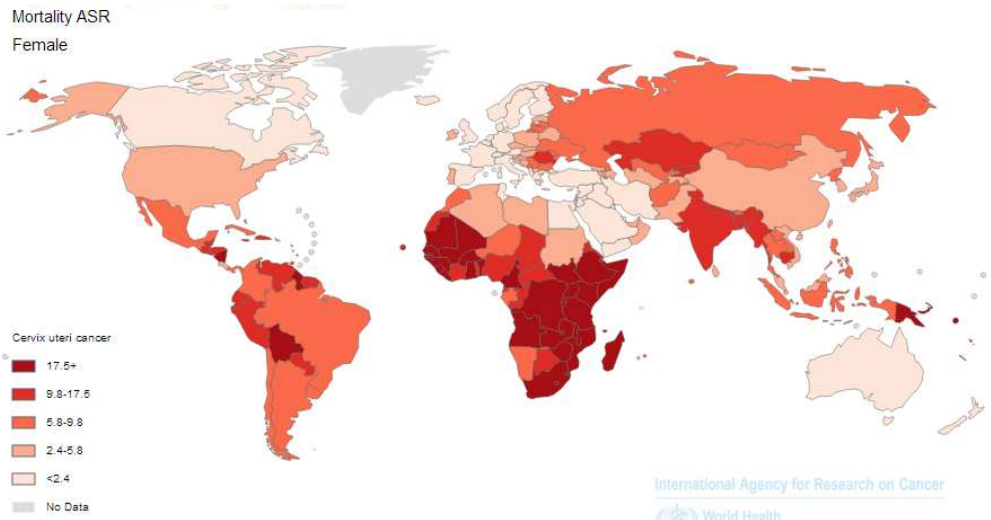


HPV infection worldwide incidence

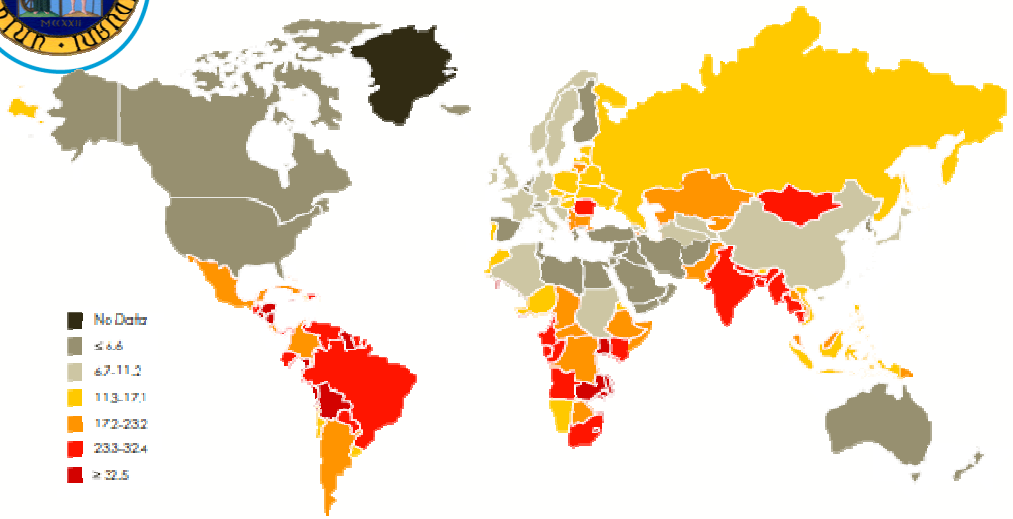
World Health Organization



HPV worldwide mortality

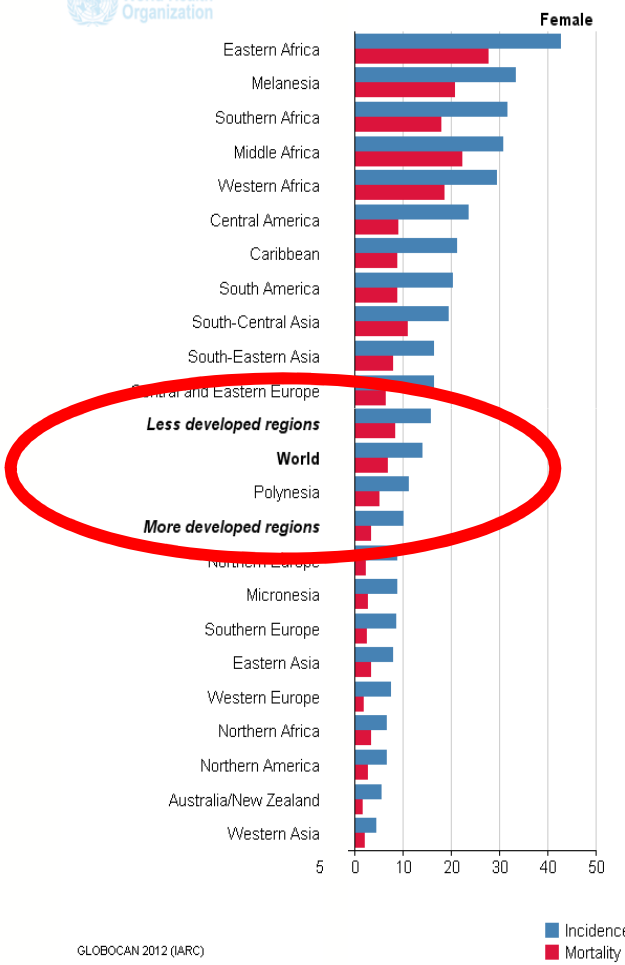


HPV, epidemiology



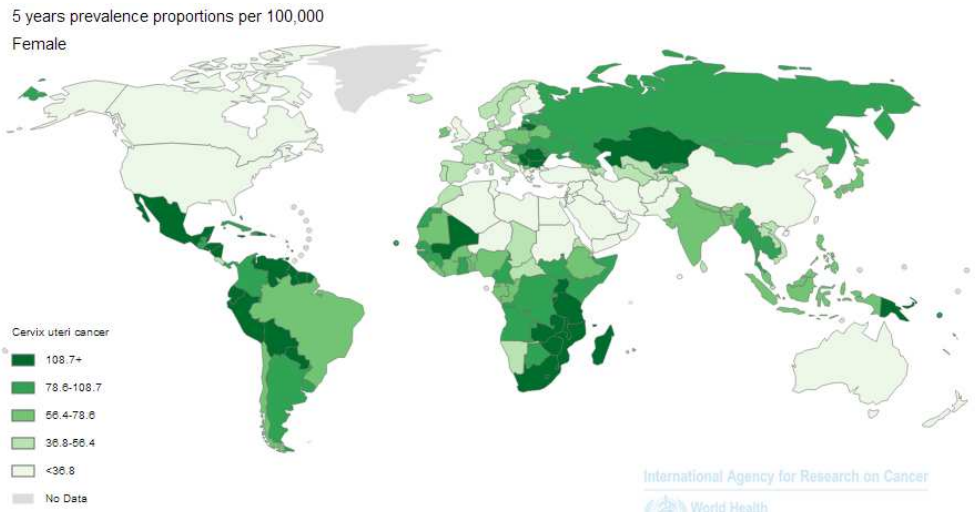
HPV infection worldwide incidence

World Health Organization



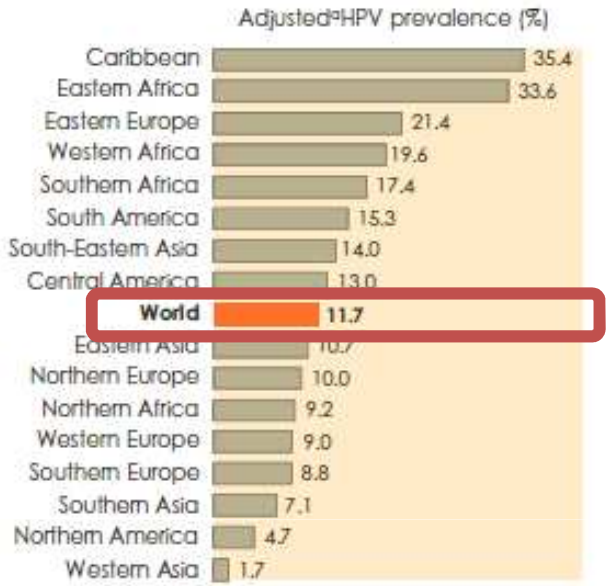
GLOBOCAN 2012 (IARC)

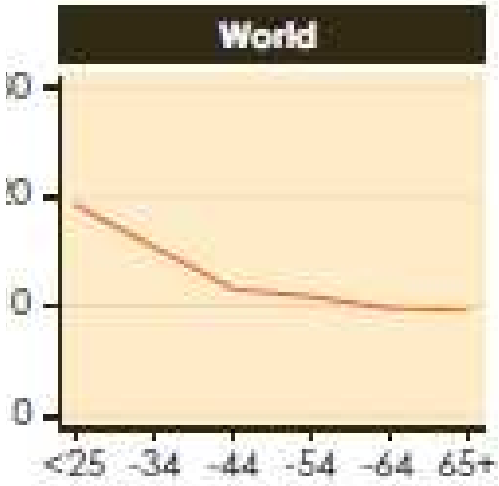
HPV worldwide prevalence

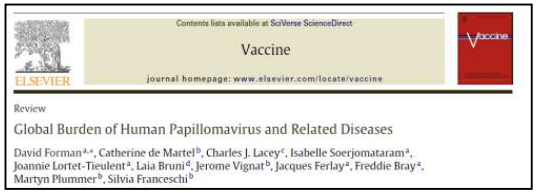


International Agency for Research on Cancer
World Health Organization

HPV, epidemiology






Contents lists available at SciVerse ScienceDirect

Vaccine

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

Review

Global Burden of Human Papillomavirus and Related Diseases

David Forman[a,*], Catherine de Martel[b], Charles J. Lacey[c], Isabelle Soerjomataram[a], Joannie Lortet-Tieulent[a], Laia Bruni[d], Jerome Vignat[b], Jacques Ferlay[a], Freddie Bray[a], Martyn Plummer[b], Silvia Franceschi[b]

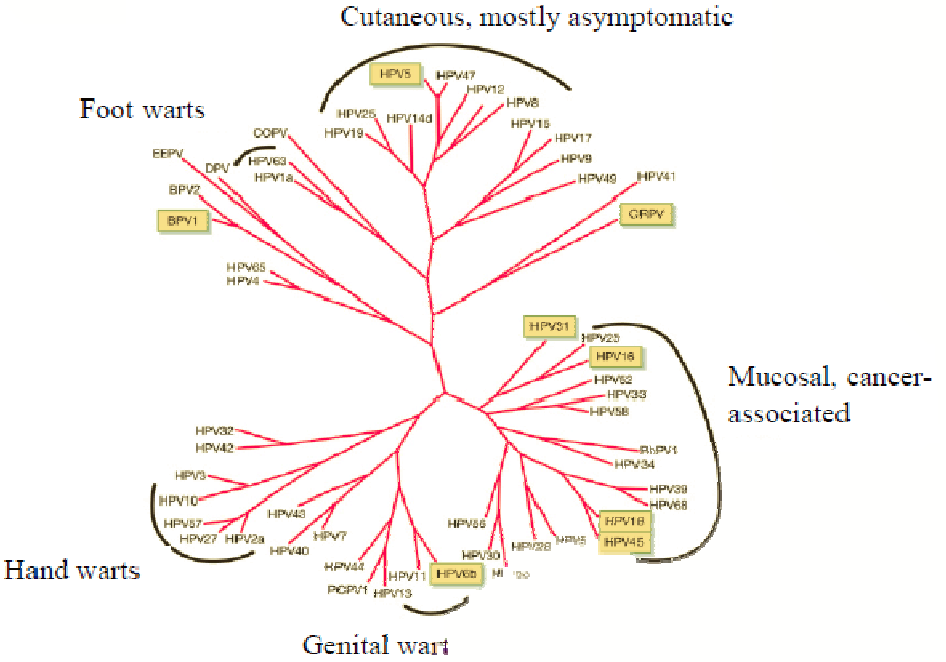
CIN 3 patients are in 93% of cases HPV positive and 58% among them present an HPV16 infection

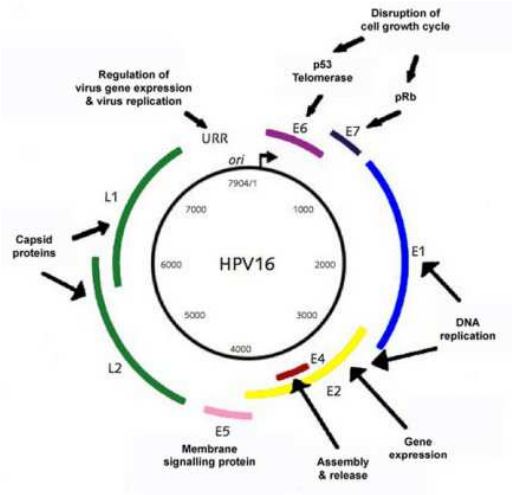
Table 1
Results from meta-analysis showing number of women tested for HPV and HPV16, number and pe positive by cervical dise e grade.

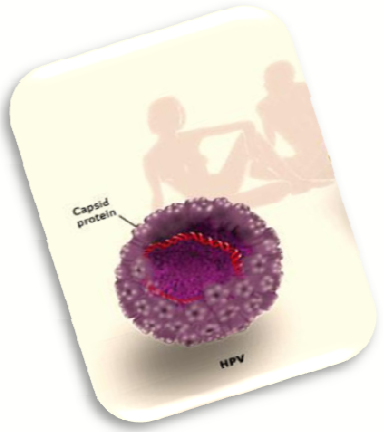
Grade of cervical disease	Number of women tested	Number of women HPV-positive	Percentage HPV-positive	Percentage HPV16-positive[a]
Normal cytology	266611	33154	12	20
ASCUS	12983	6810	52	23
LSIL	17805	13480	76	25
HSIL	7743	6616	85	48
CIN1	11043	8108	73	28
CIN2	4754	4068	86	40
CIN3	11618	10753	93	58
ICC	40679	36374	89	63

[a] Among HPV-positives.
ASCUS: Atypical squamous cells of undetermined significance (cytology based); CIN1: Cervical intraepithel lesion (patholo based); CIN2/3: Cervical intraepithelial neoplasia grade 2 or 3; HSIL: High-grade squamous intraepithelial lesion (cytology based); ICC: Invasive cervical (pathology based); LSIL: Low-grade squamous intraepithelial lesion (cytology based).
Based on Guan P et al. [3].

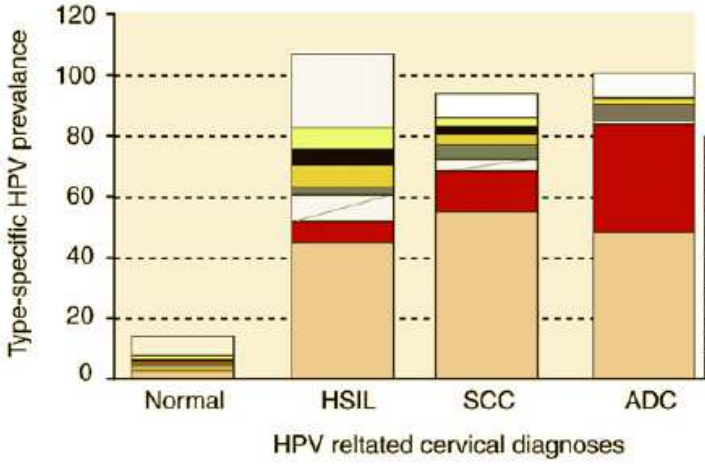
HPV, pathogenic sierotipes





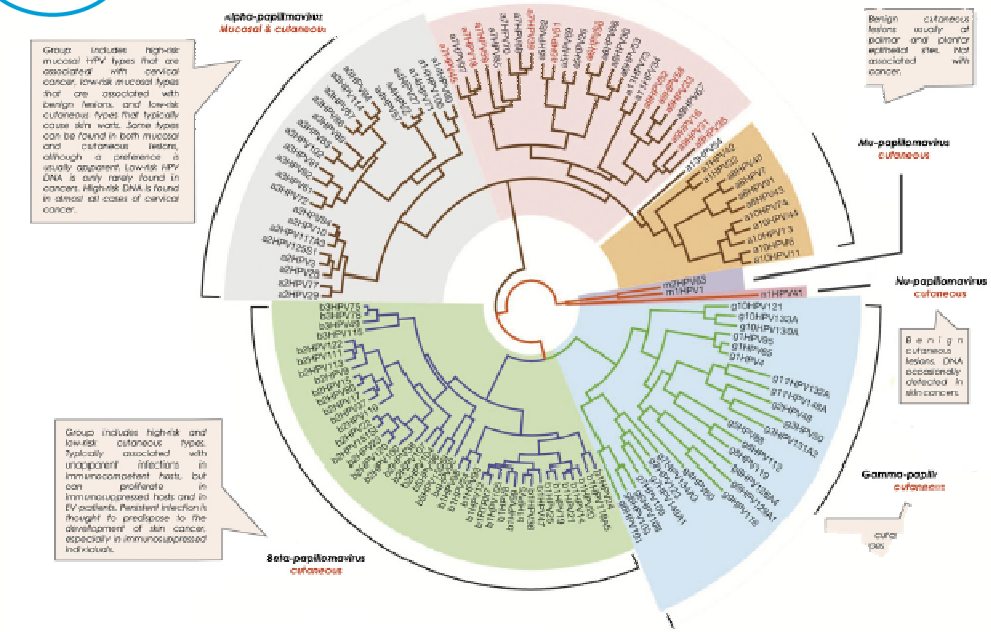


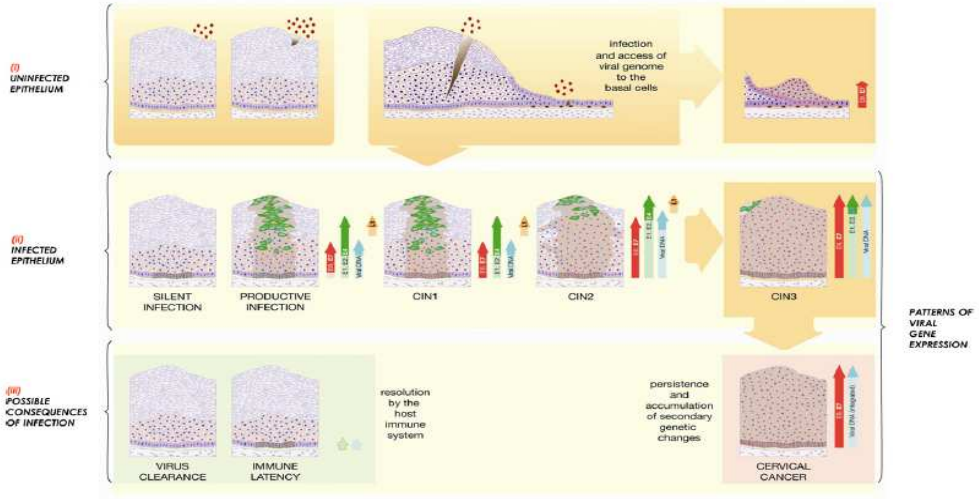
HPV serotipe and citologicala bnormalities



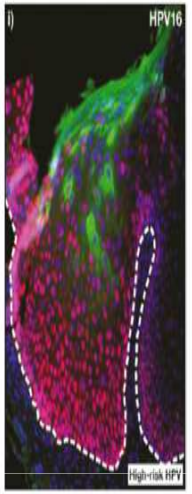
	Normal	HSIL	SCC	ADC
HVP-16	2.6	45.3	55.2	48.4
HPV-18	0.9	6.9	12.8	36.3
HPV-31	0.6	8.6	3.8	0.7
HPV-45	0.4	2.3	4.6	5.8
HPV-33	0.5	7.3	3.7	2.0
HPV-52	0.9	5.1	2.9	0
HPV-58	0.9	7.0	2.8	0.7
Others	6.8	23.9	7.6	7.7

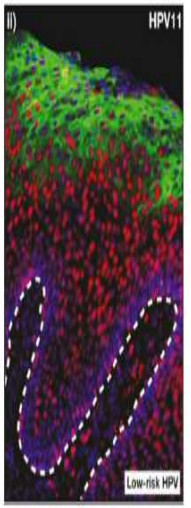
HPV, pathogenic sierotipes



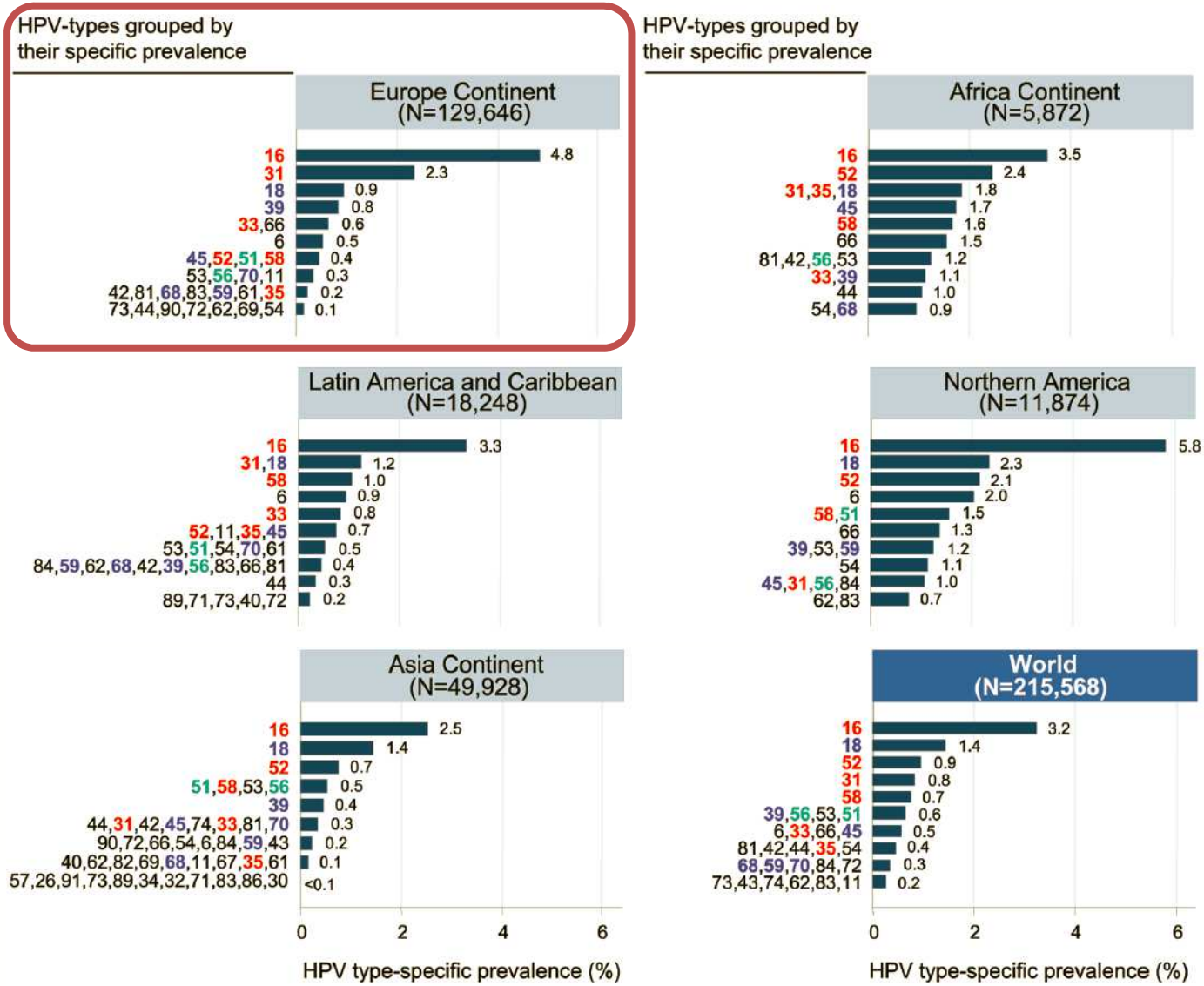


	High-Risk Alpha	Low-Risk Alpha
E6	encodes E6* products	no E6* products
	binding and degradation of... •p53 •specific PDZ-domain proteins (e.g. Dlg, MAGI-1, Scribble)	weaker binding (no degradation) of... •p53 •no binding of PDZ-domain proteins
	interact with the E6AP ubiquitin ligase inhibition of p53 transactivation and acetylation	
	inhibition of apoptosis	unknown
	bypass of growth arrest following DNA damage	normal growth arrest following DNA damage
	inhibition of keratinocyte differentiation	unknown
	inhibition of interferon response	weaker inhibition of interferon response
	activation of signaling pathways... •Akt •Wnt •Notch •mTORC1	unknown
	telomerase activation	no activation
	c-myc activation	no activation
E7	binding and degradation of... •pRb •p107 •p130	weaker binding (no degradation) of... •pRb •p107 •E2F1
	binding (no degradation) of... •E2F1 •Cullin2 •HDAC	binding of... •p130
	binding of regulatory proteins including E2F6, p600, HAT, PP2A induction of cell cycle entry and DNA synthesis role in genome amplification	
	induction of genome instability	no stimulation of instability
	suppression of STAT-1 function	no suppression
	immortalization and transformation functions	no such functions
	activation of signaling pathways... •Akt	unknown

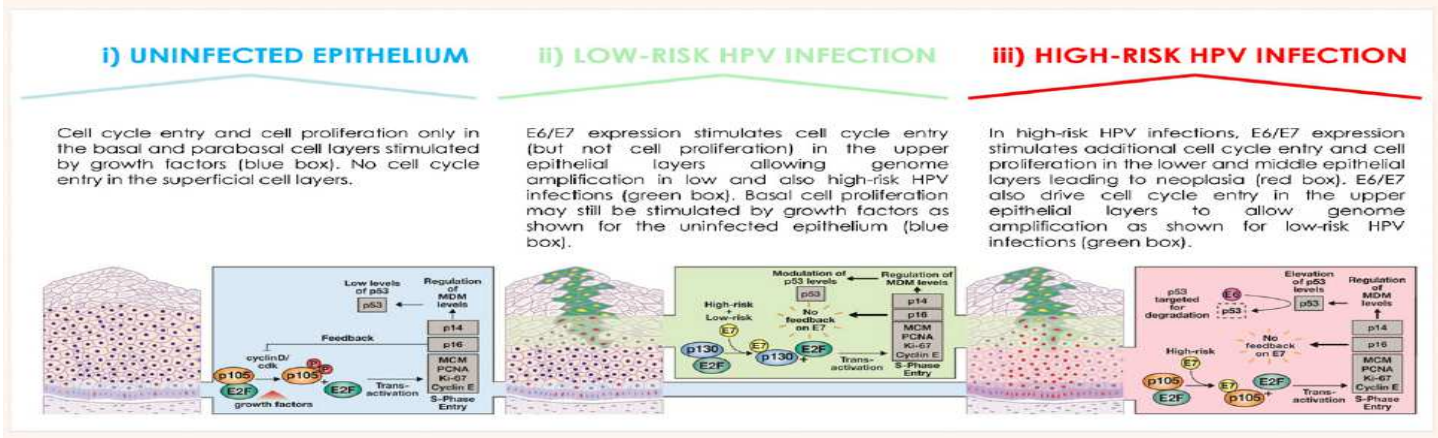


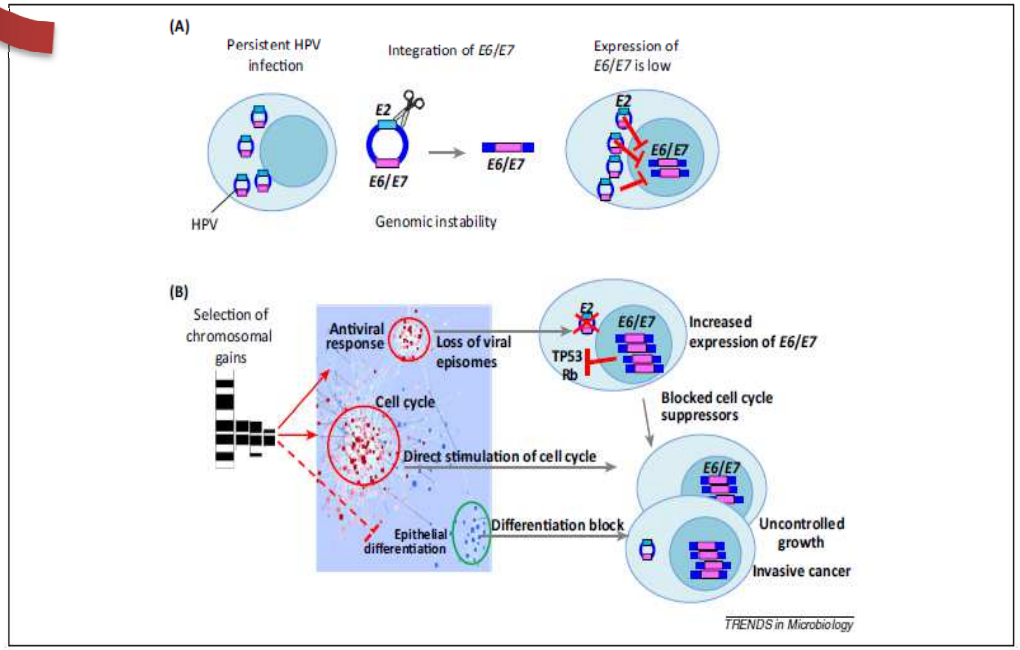


HPV, epidemiology



Life Cycle of Hr-Risk HPVs in Cervical Epithelium





E6/E7 mediate proliferation of the basal and para-basal cells, facilitating lesion growth

Initial viral replication in the basal cells requires **E1** and **E2** proteins.

Deregulation of **E6/E7** expression is critical in determining neoplastic grade

Integration of the viral genome into the cell genome occurs in many high-grade lesions, although cancer can arise from cells exclusively containing **episomes**

HPV, poor immunitary response

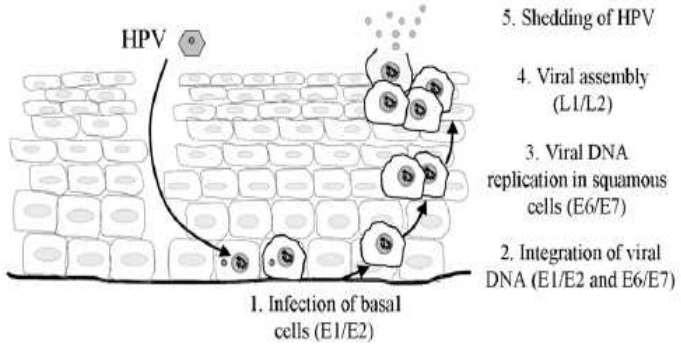


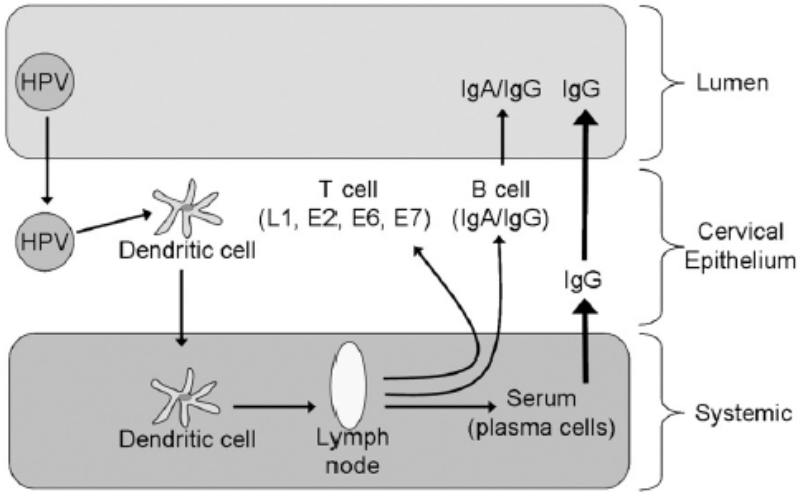
Fig. 1. Life cycle of human papillomavirus.

Available online at www.sciencedirect.com
ScienceDirect
Gynecologic Oncology 109 (2008) S15–S21
Gynecologic Oncology
www.elsevier.com/locate/ygyno

Immunobiology of HPV and HPV vaccines

Margaret Stanley *
Department of Pathology, Tennis Court Road, University of Cambridge, CB2 1QP UK

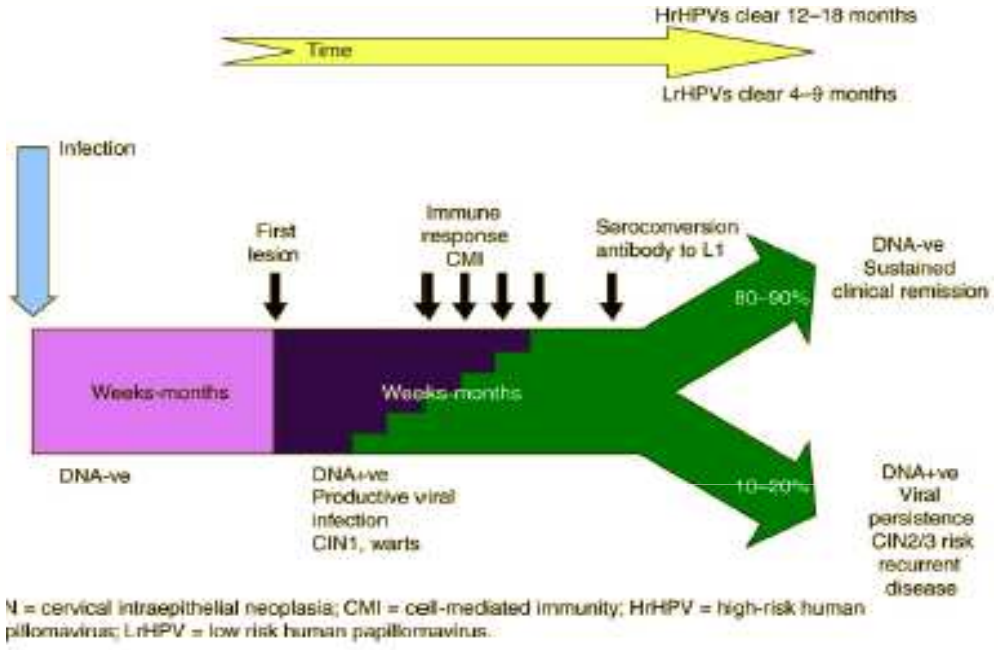
Received 7 February 2008



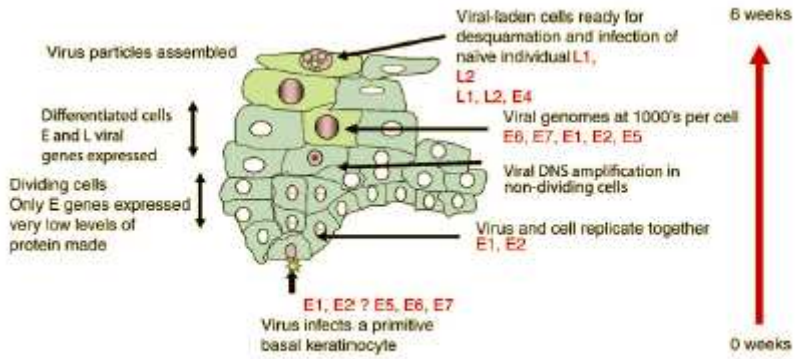
- No inflammation response
- Effective Interferon I escape mechanism
- No spread of virions before a massive development of mature virus
- Low antibodies levels after primary infection that make reinfection by same serotipe a little harder but not possible.

HPV, cancer raise from precancerous lesions

Timeline Progression

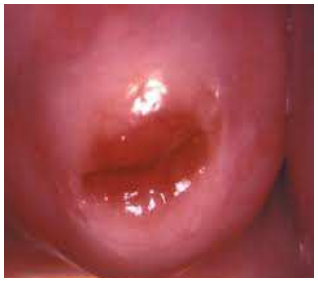


N = cervical intraepithelial neoplasia; CMI = cell-mediated immunity; HrHPV = high-risk human papillomavirus; LrHPV = low risk human papillomavirus.

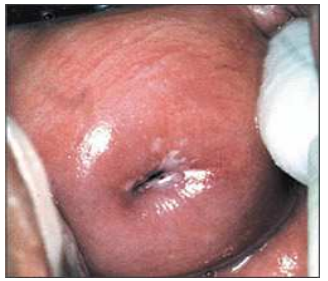


Exclusively intraepithelial infectious cycle no cytolysis or death, no viraemia, long infectious cycle

Clinical findings

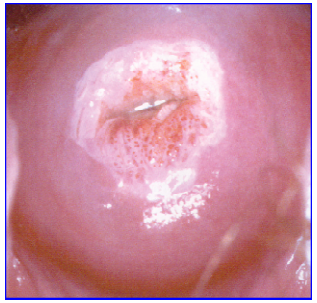


Normal cervix

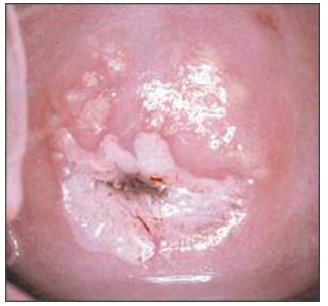


CIN I

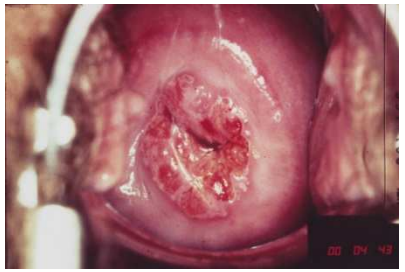
CIN II



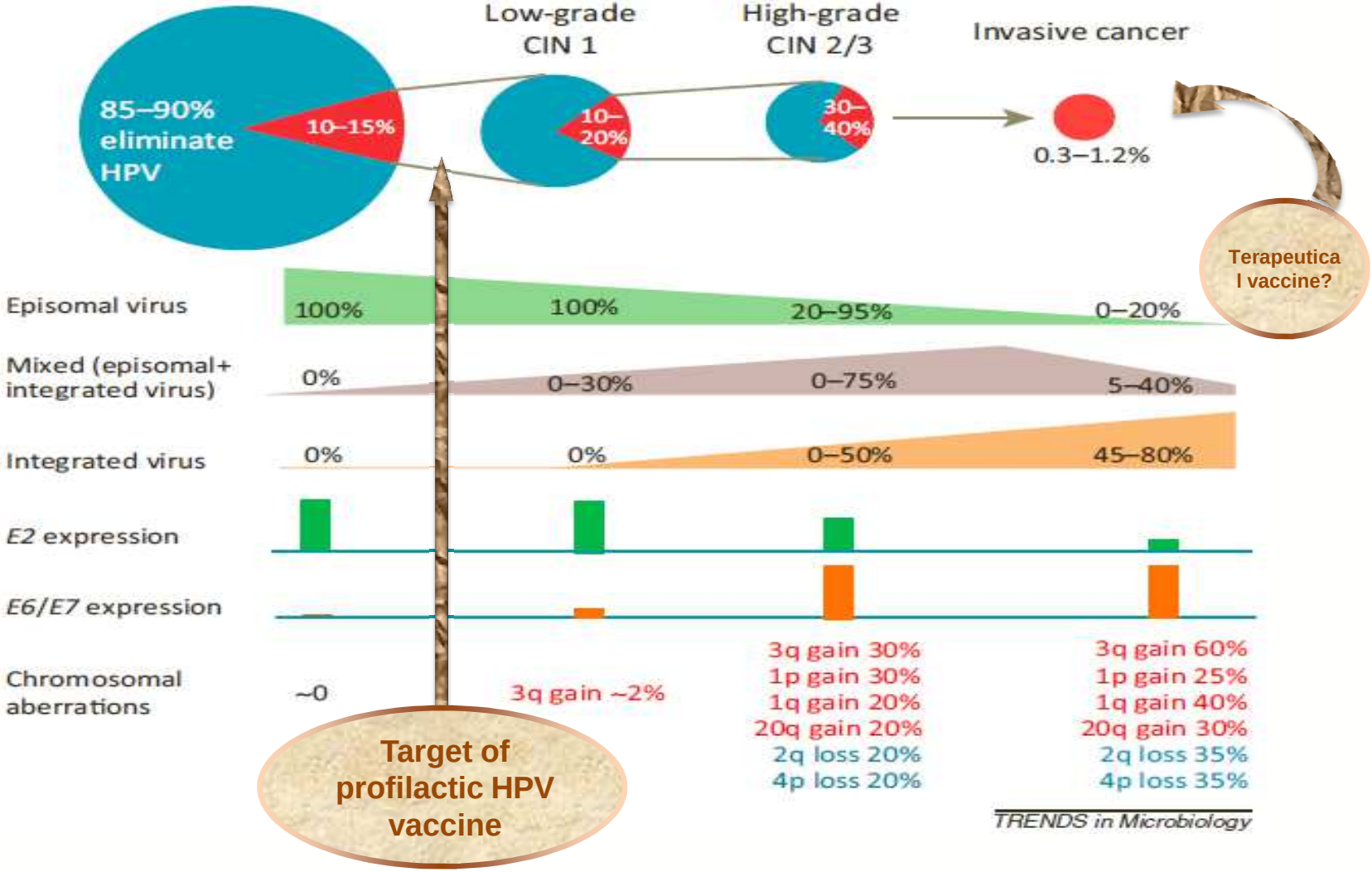
CIN III



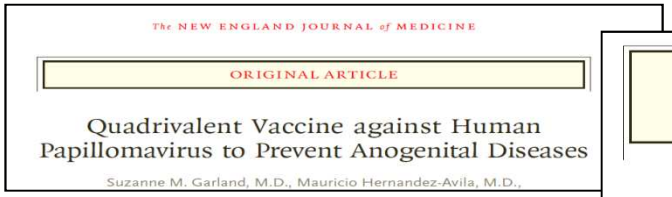
Cervical Cancer



HPV, rate of progression



HPV, rate of progression


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Quadrivalent Vaccine against Human Papillomavirus to Prevent Anogenital Diseases

Suzanne M. Garland, M.D., Mauricio Hernandez-Avila, M.D.,

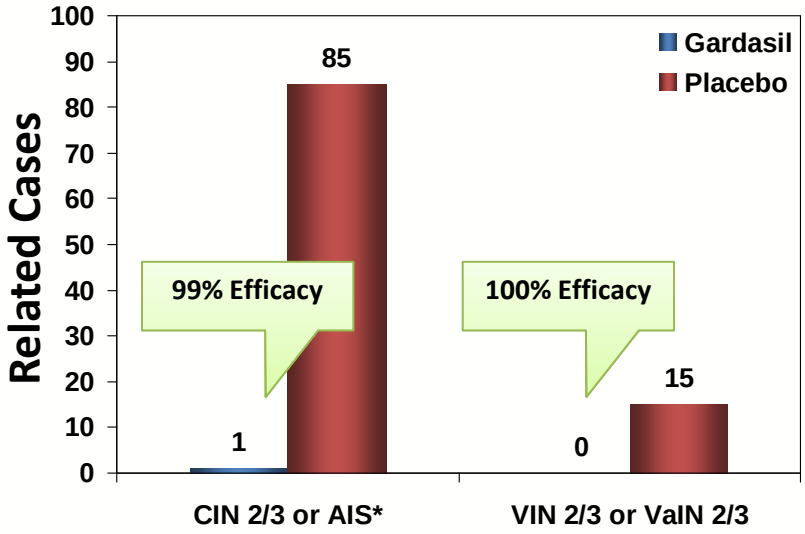

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 10, 2007 VOL. 356 NO. 19

Quadrivalent Vaccine against Human Papillomavirus to Prevent High-Grade Cervical Lesions

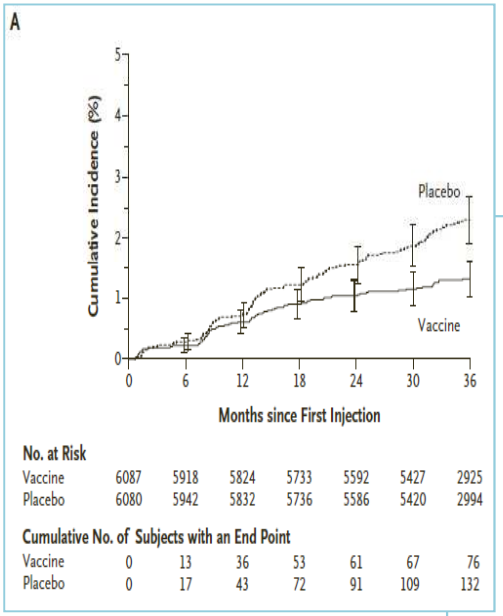
The FUTURE II Study Group*

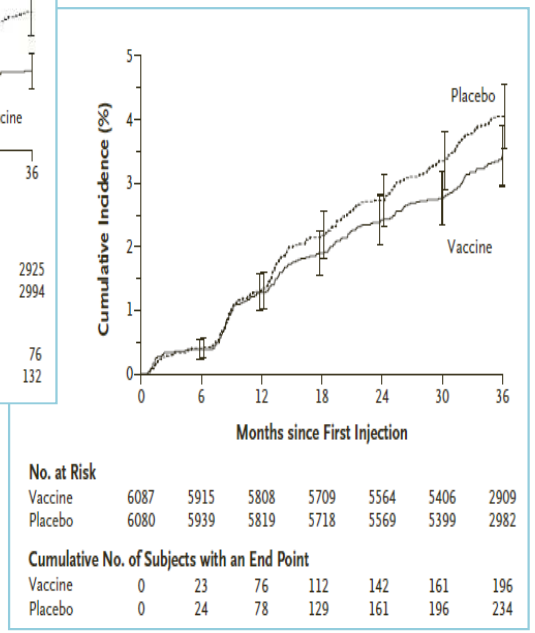
Gardasil is Efficacious Against HPV 16 and 18-Related Disease



Analysis of CIN 2/3 and AIS end points included protocol 005.

GARDASIL Worldwide Product Circular. Merck & Co., Inc., Whitehouse Station, NJ, USA.





HPV, rate of progression

TABLE 1

Major trials of HPV vaccine

YEAR	CLINICAL TRIAL	STUDY POPULATION	HPV VACCINE	KEY CONCLUSIONS
2007	FUTURE I[54]	5,455 women from Latin America or North America, age 16–24	Quadrivalent	The vaccine was 100% effective in preventing HPV-related anogenital disease in women not previously infected with HPV The vaccine was also 100% effective in preventing cervical intraepithelial neoplasia (CIN) grades I, II, and III and carcinoma in situ
2007	FUTURE II[28]	12,000 women from Europe and Latin America, age 15–26	Quadrivalent	The vaccine was effective for the prevention of HPV 16- or 18-related CIN grades II and III and carcinoma in situ
2009	PATRICIA[29]	18,000 women from Europe or Asia Pacific, age 15–25	Bivalent	The vaccine was 92.9% effective for the prevention of CIN grades II and III, carcinoma in situ, or cancer
2011	Giuliano et al[55]	4,065 men, age 16–26	Quadrivalent	The vaccine was 90.4% effective in preventing external genital lesions associated with HPV types 6, 11, 16, and 18 in men not previously infected with HPV
2011	Palefsky et al[23]	598 men who have sex with men, age 16–26	Quadrivalent	The vaccine was 77.5% effective against anal intraepithelial neoplasia associated with HPV 6,11, 16, or 18 in men not previously infected with HPV

FUTURE – Females United to Unilaterally Reduce Endo/ectocervical Disease; PATRICIA – Papilloma Trial Against Cancer in Young Adults

REVIEW

EDUCATIONAL OBJECTIVE: Readers will recommend vaccination against human papillomavirus according to current guidelines

XIAN WEN JIN, MD, PhD, FACP
LAURA LIPOLD, MD
ANDREA SIKON, MD
ELLEN ROME, MD, MPH

Human papillomavirus vaccine: Safe, effective, underused

Composition of Gardasil.

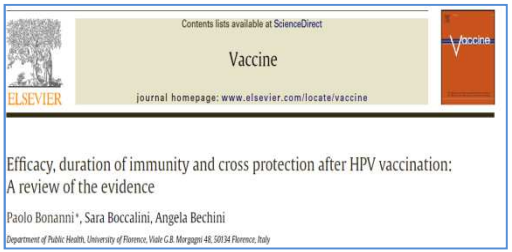
Material*	Amount
HPV Type 6 L1 protein	20 µg
HPV Type 11 L1 protein	40 µg
HPV Type 16 L1 protein	40 µg
HPV Type 18 L1 protein	20 µg
Aluminum hydroxyphosphate sulfate adjuvant	225 µg
Sodium chloride	9.56 mg
Sodium borate	35 µg
L-histidine	0.78 mg
Polysorbate 80	50 µg
Yeast protein	<7 µg

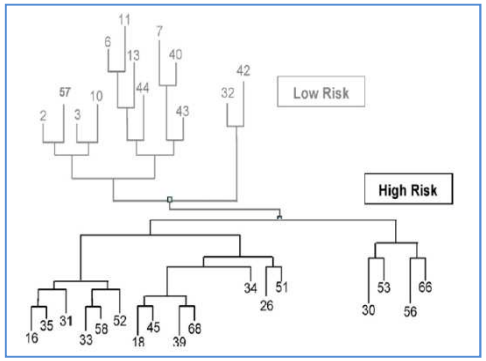
*Vaccine is **raccomended in a population of young female** aged less than thirteen that haven't started their sexual life yet.*

*Vaccine is suggested in women with **previous infection to aid the immune system and to prevent re-infections***

Xian Wen Jin et al «*Human papillomavirus vaccine: Safe, effective, underused*» *Cleveland J. of M. 2013*

HPV, cross-protection



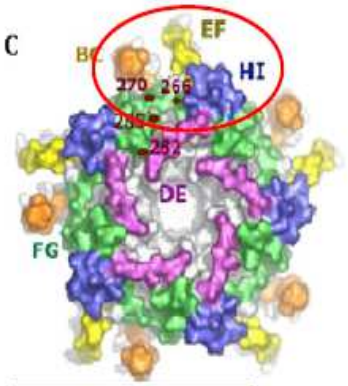


Endpoint	6-month persistent infection with HPV-16/18					12 month persistent infection with HPV-16/18			
DNA negative and seronegative at study entry	Group	*N*	*n*	Vaccine efficacy (97.9% CI)	*P*-value	*N*	*n*	Vaccine Efficacy (97.9% CI)	*P*-value
Type 16/18	HPV	6344	38	80.4%	<0.0001	3386	11	75.9%	<0.0001
	Control	6402	193	(70.4 to 87.4)		3437	46	(47.7 to 90.2)	
Type 16	HPV	5493	23	84.1%	<0.0001	2945	7	79.9%	<0.0001
	Control	5520	144	(73.5 to 91.1)		2972	35	(48.3 to 93.8)	
Type 18	HPV	5896	15	74.0%	<0.0001	3143	4	66.2%	0.0766
	Controls	5939	58	(49.1 to 8.8)		3190	12	(−32.6 to 94.0)	
Endpoint	6-month persistent infection with oncogenic HPV types					12-month persistent infection with oncogenic HPV types			
Type specific DNA negative at study entry	Group	*N*	*n*	Vaccine efficacy (97.9% CI)	*P*-value	*N*	*n*	Vaccine Efficacy (97.9% CI)	*P*-value
Type 45	HPV	6724	10	59.9%	0.0165	3584	3	62.3%	0.2262
	Control	6747	25	(2.6 to 85.2)		3601	8	(−93.2 to 95.4)	
Type 31	HPV	6615	47	36.1%	0.0173	3527	15	10.8%	0.8598
	Control	6667	74	(0.5 to 59.5)		3568	17	(−115.2 to 63.6)	
Type 33	HPV	6702	31	36.5%	0.0560	3574	6	45.1%	0.3318
	Control	6736	49	(−9.9 to 64.0)		3603	11	(−91.8 to 86.5)	
Type 52	HPV	6532	79	31.6%	0.0093	3489	16	46.5%	0.0533
	Control	6573	116	(3.5 to 51.9)		3508	30	(−12.3 to 75.8)	
Type 58	HPV	6688	43	−31.4%	0.2515	3563	6	−1.1%	1.000
	Control	6734	33	(−132.1 to 24.7)		3601	6	(−372.0 to 78.4)	
Oncogenic HPV other than vaccine types	HPV	6773	505	9.0%	0.1410	3611	100	27.1%	0.0174
	Control	6804	554	(−5.1 to 21.2)		3632	137	(0.5 to 46.8)	
Oncogenic HPV	HPV	6773	545	21.9%	<0.0001	3611	112	38.2%	<0.0001
	Control	6804	691	(10.7 to 31.7)		3632	180	(18.0 to 53.7)	

CIN 2/3 or AIS due to	Quadrivalent vaccine *N* = 4616	Placebo *N* = 4675	Efficacy	95% CI
HPV-31/45	8	21	62%	(10, 85)
HPV-31/33/45/52/58	27	48	43%	(7, 66)
10 oncogenic HPV types (non-vaccine types) 31, 33, 35, 39, 45, 51, 52, 56, 58, 59	38	62	38%	(6, 60)

Data strongly suggest that both vaccines can have a variable level of cross protection against HPV types genetically and antigenically-closely related to vaccine types. Demonstration of cross protection against combined endpoints (CIN2/3 and AIS) for combined HPV types, and, as a single type, for HPV-31, has been reached for the quadrivalent vaccine, and there is evidence of cross protection against HPV 31 and 45 persistent infections (as single types) for the bivalent vaccine.

HPV, cross-protection



HPV 16
Species A9

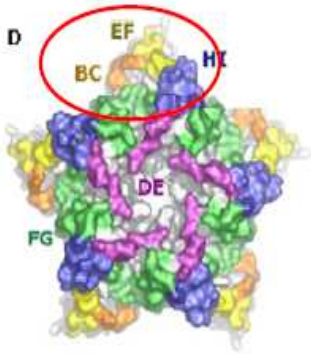
Gynecologic Oncology 130 (2013) 642–651
Contents lists available at SciVerse ScienceDirect
Gynecologic Oncology
journal homepage: www.elsevier.com/locate/ygyno

Review

HPV vaccine cross-protection: Highlights on additional clinical benefit

Rosa De Vincenzo *, Caterina Ricci, Carmine Conte, Giovanni Scambia
Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Catholic University of the Sacred Heart, L.go A. Gemelli 8, 00168, Rome, Italy

The opportunity of **cross-protection** against other non-vaccine HPVtypes **is an extremely important key factor of interest,** because it could increase the fraction of cervical cancers prevented.



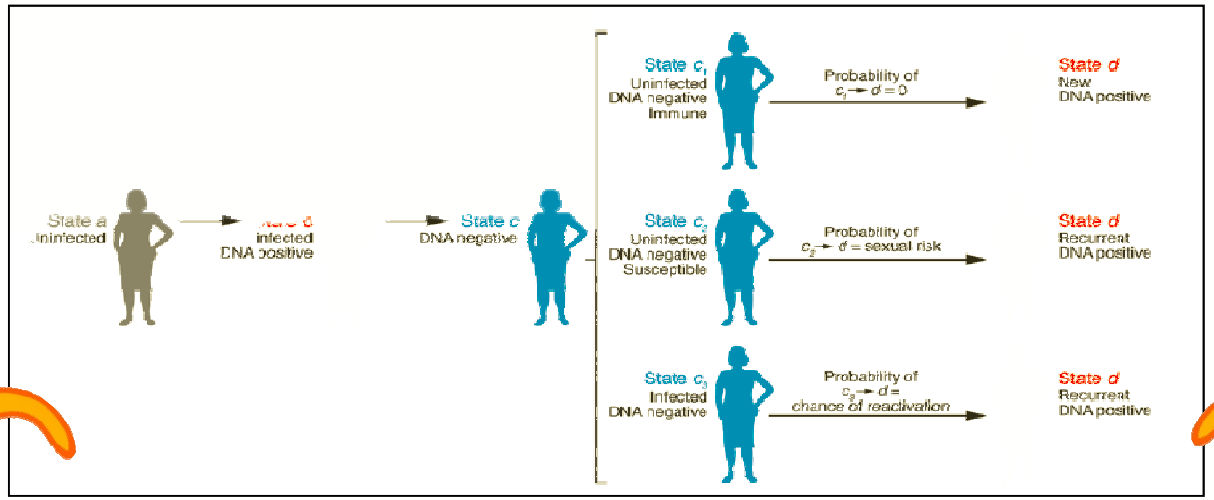
HPV 18
Species A7

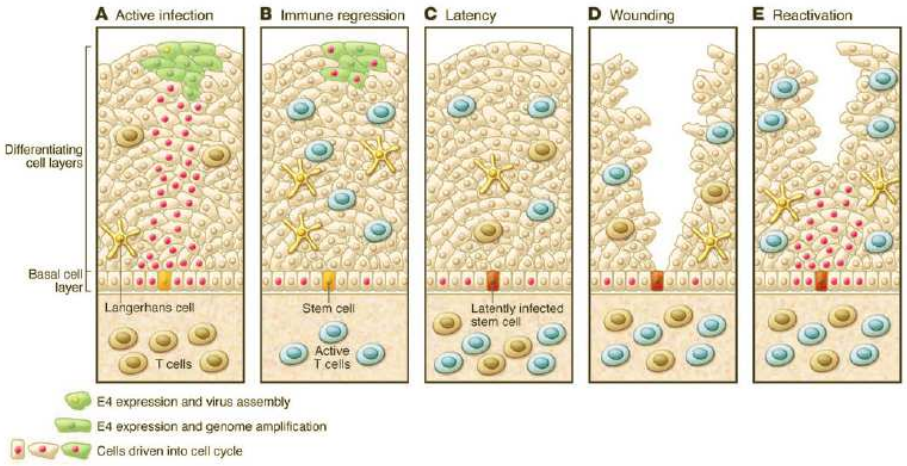
HPV Type	Species	L1 homology
HPV 16	A9	
HPV 45	*A7*	*67%*
HPV 31	A9	83%
HPV 33	A9	81%
HPV 52	A9	80%
HPV 58	A9	80%
HPV 35	A9	82%
HPV 59	*A7*	*65%*
HPV 39	*A7*	*64%*

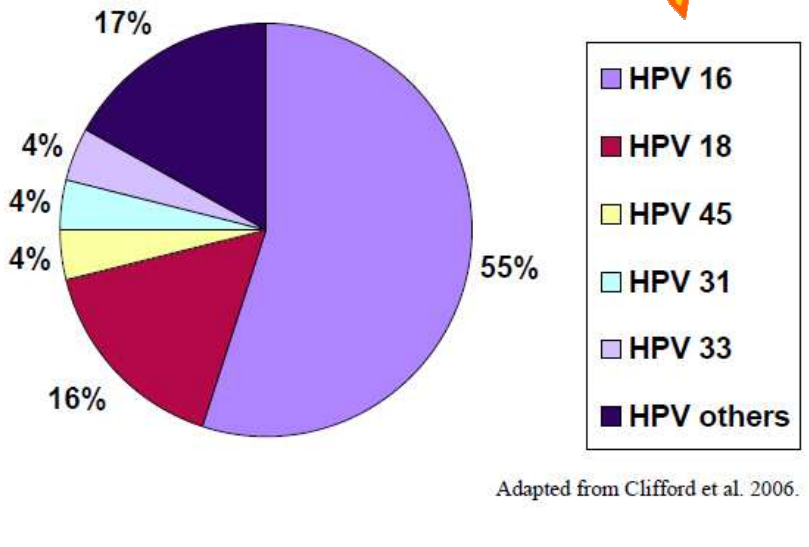
Evidence of cross-protection against either infection or disease by non-vaccine type comes from trials of both Bivalent and Quadrivalent vaccines.

HPV Type	Species	L1 homology
HPV 18	A7	
HPV 45	A7	88%
HPV 31	*A9*	*66%*
HPV 33	*A9*	*66%*
HPV 52	*A9*	*66%*
HPV 58	*A9*	*66%*
HPV 35	*A9*	*65%*
HPV 59	A7	78%
HPV 39	A7	77%

HPV, re-activation and re-infection







Adapted from Clifford et al. 2006.

HPV, vaccine as intention to treat

Letter

Cell PRESS

Gardasil administration to hr-HPV-positive women and their partners

Salvatore Gizzo, Marco Noventa, and Giovanni Battista Nardelli

Department of Woman and Child Health, University of Padua, Giustiniani, 3, 35128 Padua, Italy

The rationale for proposing the use of Gardasil in an intention-to-treat basis should have two aims: (i) strengthening of the immunological response to the hr-HPV genotype already detected; and (ii) prevention of *de novo* co-infection and superinfection by a different hr-HPV genotype to that already detected in non-naïve women.

The public health costs of non-naïve mass vaccination programs currently seem to be higher than second-level treatment and follow up of this cohort of patients [8], so a short-term cost–benefit analysis does not recommend universal vaccination. However, similar to the international effort to eradicate smallpox, hr-HPV herd immunity can only be achieved when 100% of the naïve population is immune. According to long-term cost–benefit analysis, vaccination of male and non-naïve women would reduce the time necessary to obtain herd immunity and could represent a real way to eradicate an infection responsible for a significant number of worldwide cancer deaths. In our opinion, a long-term pilot study of approximately 10 years (a reasonable interval necessary for cancer onset after hr-HPV infection) should be conducted in developed countries to evaluate the health and economic benefits of non-naïve HPV vaccination programs.

HPV, vaccine as intention to treat

Matherials and Methods

We enroll Patients who underwent a routinary or follow up pap test at Gynecological and Obstetrical Clinic, University of Padua. Were suggested to vaccination in

- Women founded with a positive citology.

- Women with a latest negative citology but previous evidence of either HPV DNA TEST positivity or cervical pathology.

HPV, vaccine as intention to treat

Data collection form

Pazienti sottoposte a Vaccinazione HPV quadrivalente Gardasil

Medico | ID paziente (Nuovo)

Cognome | Nome | Nata il

Tel | Mail | Femmina | Maschio

Indirizzo | CF

peso | altezza | Partner Stabile

Pap-Test | Esito | Data

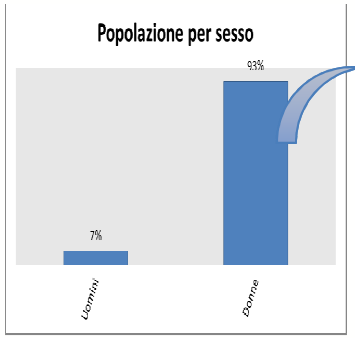
Colposcopia | Esito | Data

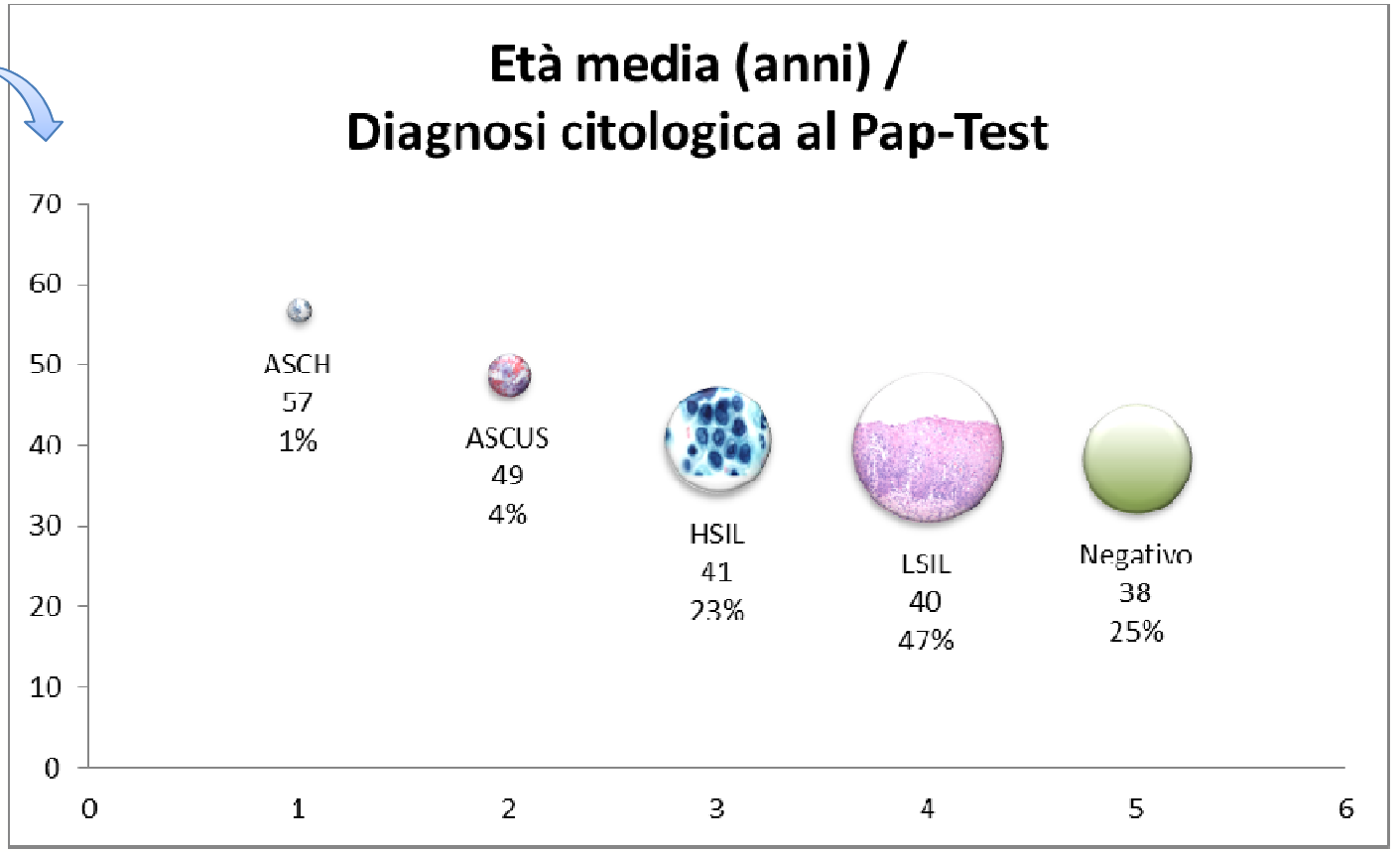
dna | HR | Data

Data Vaccino | Note

HPV, vaccine as intention to treat

Preliminary Results





Several HPV serotipes like ***58, 51, 31, 35, 63*** were founded alone or as HPV 16 coinfection

HPV, ASCCP guidelines

Triple A Guideline: ACS, ASCCP, American Society for Clinical Pathology

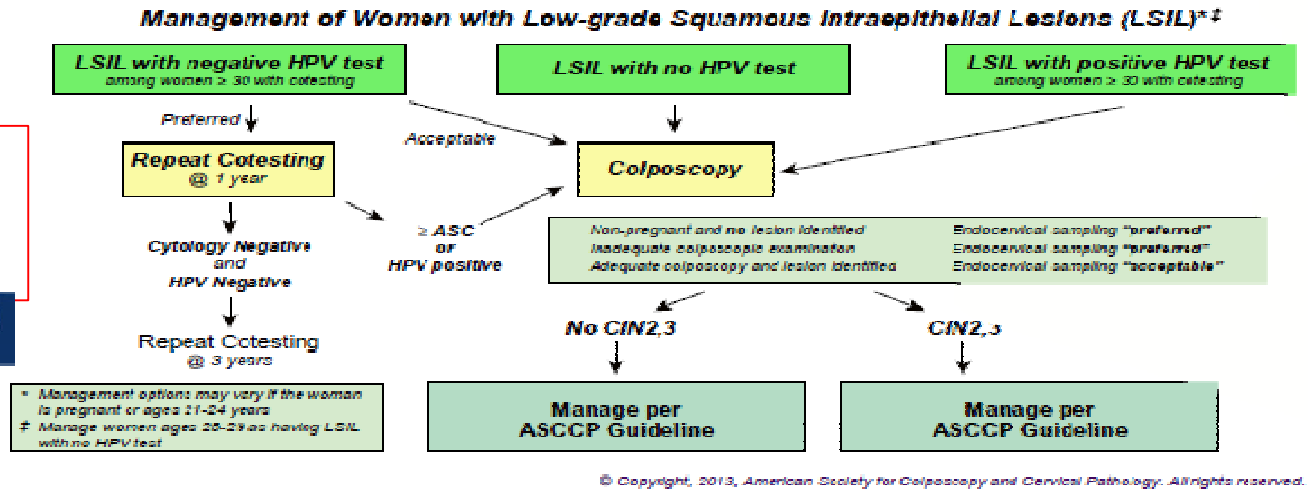
Cancer J CLIN March 2012

Age	Screening
< 21	No Screening
21-29	Cytology alone every 3 years
30-65	Preferred: Cytology + HPV every 5 years* OR
	Acceptable: Cytology alone every 3 years*
> 65	No screening, following adequate neg prior screens
After total hysterectomy	No screening, if no history of CIN2+ in the past 20 years of cervical cancer ever

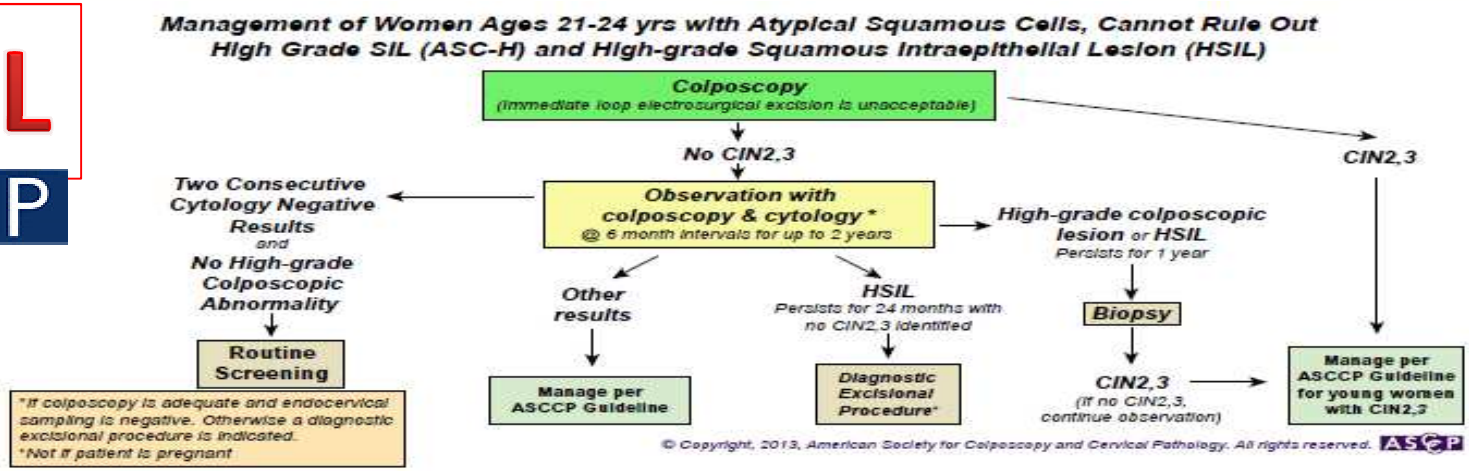
*If cytology result is negative or ASCUS + HPV negative

HPV, ASCCP guidelines

L-SIL



H-SIL

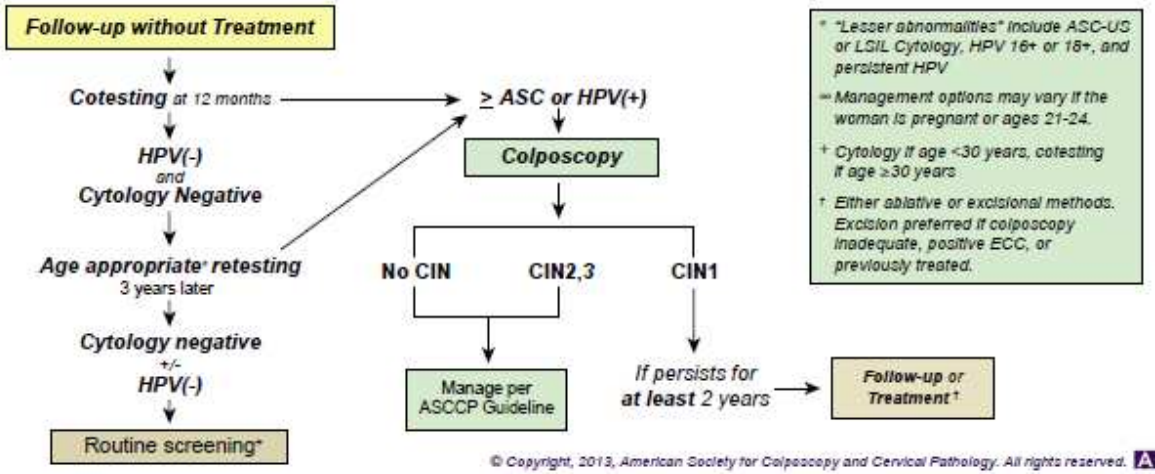


HPV, ASCCP guidelines

CIN1

ASCCP

Management of Women with No Lesion or Biopsy-confirmed Cervical Intraepithelial Neoplasia — Grade 1 (CIN1) Preceded by "Lesser Abnormalities"[*] [∞]

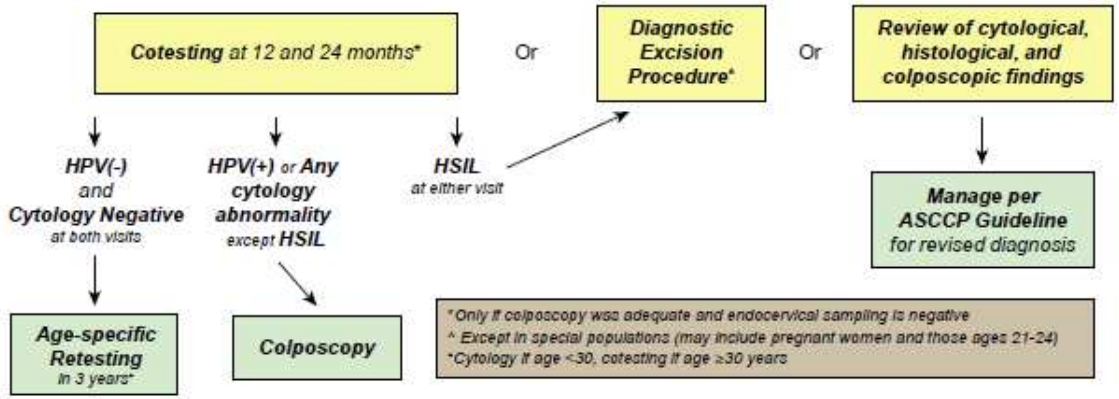


CIN1

(with previous –HSIL)

ASCCP

Management of Women with No Lesion or Biopsy-confirmed Cervical Intraepithelial Neoplasia — Grade 1 (CIN1) Preceded by ASC-H or HSIL Cytology



HPV vaccine, new perspectives

Cancer Immunol Immunother (2004) 53: 642–650
DOI 10.1007/s00262-004-0501-4

ORIGINAL ARTICLE

Sophie Hallez · Philippe Simon · Frédéric Maudoux
Jean Doyen · Jean-Christophe Noël · Aude Beliard
Xavier Capelle · Frédéric Buxant · Isabelle Fayt
Anne-Cécile Lagrost · Pascale Hubert · Colette Gerday
Arsène Burny · Jacques Boniver · Jean-Michel Foidart
Philippe Delvenne · Nathalie Jacobs

Phase I/II trial of immunogenicity of a human papillomavirus (HPV) type 16 E7 protein–based vaccine in women with oncogenic HPV-positive cervical intraepithelial neoplasia

E7- and PD-specific IgG. Conclusions: The encouraging results obtained from this study performed on a limited number of subjects justify further analysis of the efficacy of the PD-E7/AS02B vaccine in CIN patients.

HPV, scientific litterature debate

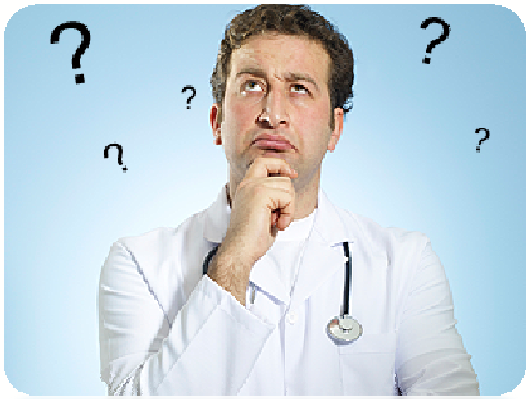
OPEN ACCESS Freely available online

PLOS ONE

Systematic Review and Meta-Analysis of L1-VLP-Based Human Papillomavirus Vaccine Efficacy against Anogenital Pre-Cancer in Women with Evidence of Prior HPV Exposure

Ada Miltz*, **Huw Price, Maryam Shahmanesh, Andrew Copas, Richard Gilson**

Centre for Sexual Health and HIV Research, Research Department of Infection and Population Health, Mortimer Market Centre, University College London, London, United Kingdom



Discussion

There was no evidence from this analysis that HPV vaccines given to women with evidence of prior HPV infection can prevent vaccine-type HPV-associated CIN3+ and VIN2-3 or VaIN2-3. However, there are several limitations to this review. The trials

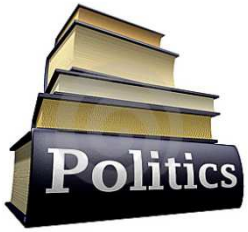
Conclusions: There was no evidence that HPV vaccines are effective in preventing vaccine-type HPV associated pre-cancer in women with evidence of prior HPV exposure. Small effects of vaccination however cannot be excluded and a longer-term benefit in preventing re-infection remains possible.

HPV, political debate

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

DECEMBER 7, 2006



The Ethics and Politics of Compulsory HPV Vaccination

James Colgrove, Ph.D., M.P.H.

Too Fast or Not Too Fast:
The FDA's Approval of Merck's HPV Vaccine Gardasil

Lucija Tomljenovic and Christopher A. Shaw