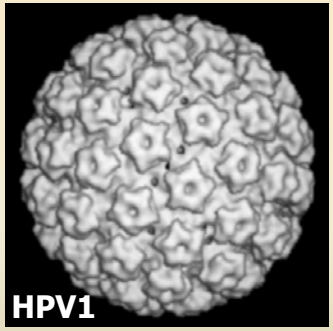
ΜΕΤΑΠΤΥΧΙΑΚΟ ΔΙΠΛΩΜΑ ΕΙΔΙΚΕΥΣΗΣ
ΕΦΑΡΜΟΓΕΣ ΤΗΣ ΒΙΟΛΟΓΙΑΣ ΣΤΗΝ ΙΑΤΡΙΚΗ

Μάθημα: Μικροβιολογία και Δημόσια Υγεία

Ο Ρόλος του Ιού HPV στη Δημόσια Υγεία



Μιχάλης Αραμπατζής

Πρώτη Πανεπιστημιακή Κλινική Δερματολογίας-Αφροδισιολογίας, Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης

2022

Καρκινογόνοι Ιοί

- Human papillomavirus
- Hepatitis B and C viruses
- Epstein-Barr virus
- Merkel Cell Polyomavirus
- Human herpesvirus type 8
- Human T-cell lymphotropic virus type 1
- HIV

Αριθμός καρκίνων ανά 100.000

Table 1.2. Infectious Agents and Associated Cancers Canada, 1995–2004

Infectious Agent	*Main Associated Cancers*	*Males*	*Females*
Human papillomavirus (HPV)	Cervix	—	8.36
	Anus	1.27	1.29
	Vulva/Vagina	—	3.20*
	Penis	0.82	—
	Oropharyngeal	0.51	0.16
	Larynx	6.19	1.16
	Esophageal	5.94	1.79
	Non-melanoma Skin	1.16	0.85
Hepatitis B/C virus (HBV, HCV)	Liver	4.75	1.40
Helicobacter pylori	Stomach	12.23	5.36
Epstein-Barr virus (EBV)	Hodgkin's disease	3.04	2.44
	Nasopharyngeal carcinoma	0.91	0.38
	Burkitt lymphoma	rare	rare
Human herpesvirus type 8 (HHV-8)	Kaposi sarcoma	0.65	0.06
HumanT cell lymphotrophic virus type I (HTLV-1)	Adult T cell leukemia/lymphoma	rare	rare

1 Introduction—Infection and Cancer: An Expanding Paradigm 3
2 Human Papillomavirus: Structure, Transmission, and Occurrence 21
3 Human Papillomavirus: Infection, Natural History, and Carcinogenesis 57
4 Human Papillomavirus: Associations with Cervical Cancer 79
5 Human Papillomavirus: Associations with Noncervical Cancer 129
6 Human Papillomavirus: Detection of Infection and Disease 213
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10 Epstein-Barr Virus 385
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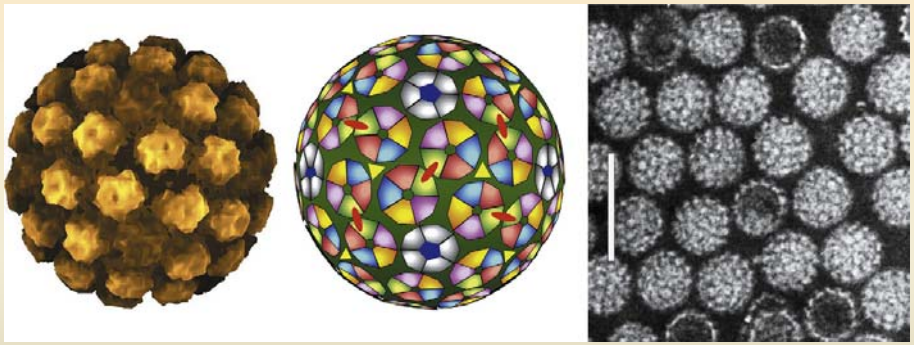
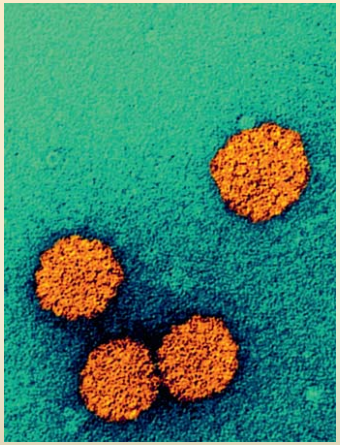
12 Human T-cell Lymphotropic Virus Type 1 471
13 Conclusion—Infection and Cancer: A Paradigm Shift 505
Index 537

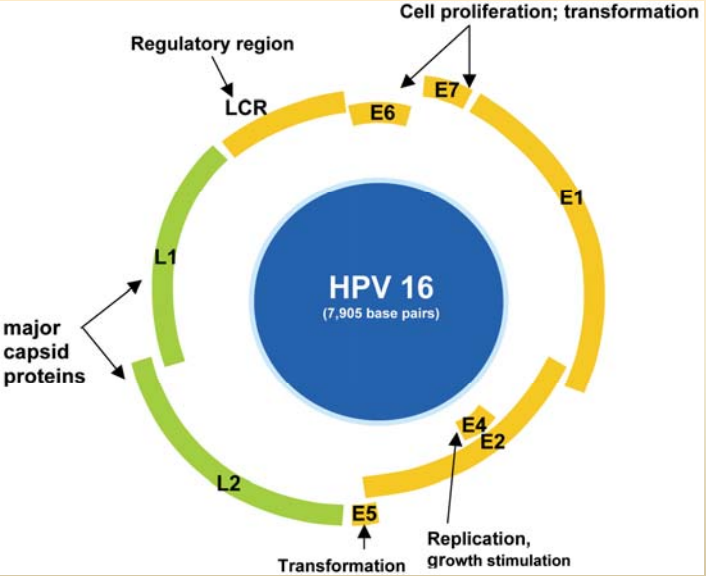
- *275.000 θάνατοι παγκοσμίως από καρκίνο του τραχήλου της μήτρας (HPV) κατ΄ έτος*
- *296 εκατομμύρια γυναίκες έχουν HPV σε κάθε στιγμή*

Βιολογία του HPV





Γονιδίωμα



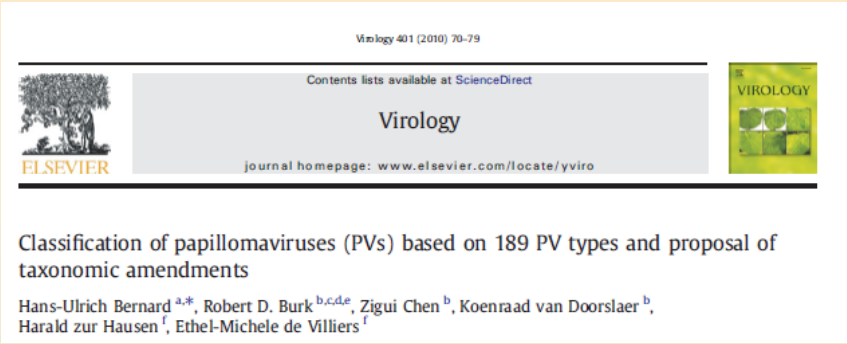
Τύποι, Υπότυποι, Ποικιλίες

Τύπος HPV (Type) 10% διαφορές στο L1

Υπότυπος HPV (Subtype) 2-10% διαφορές στο L1
HPV-68a/b HPV-34/64 HPV-44/55 HPV20/46 και -38a/b

Ποικιλία HPV (Variant) <2% διαφορές στο L1

Ταξινόμηση


Virology 401 (2010) 70–79

Contents lists available at ScienceDirect

Virology

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

Classification of papillomaviruses (PVs) based on 189 PV types and proposal of taxonomic amendments

Hans-Ulrich Bernard [a,*], Robert D. Burk [b,c,d,e], Zigui Chen [b], Koenraad van Doorslaer [b], Harald zur Hausen [f], Ethel-Michele de Villiers [f]

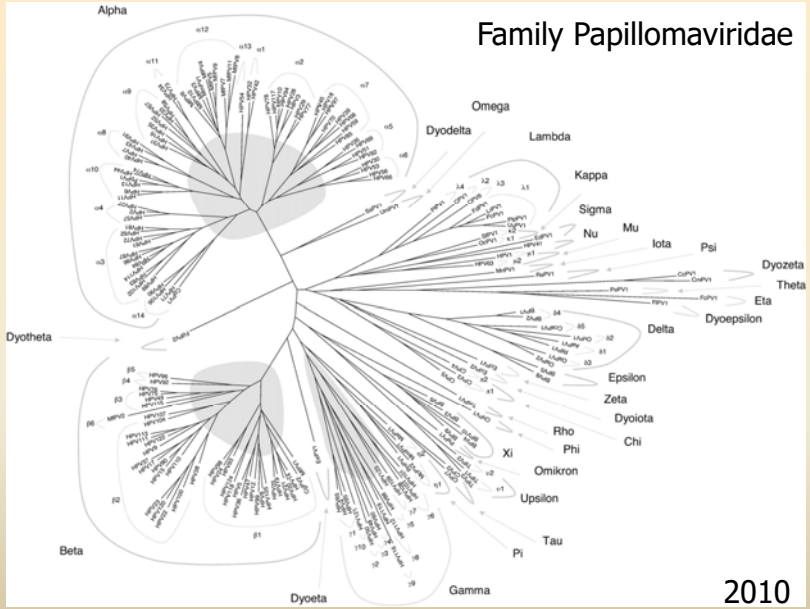
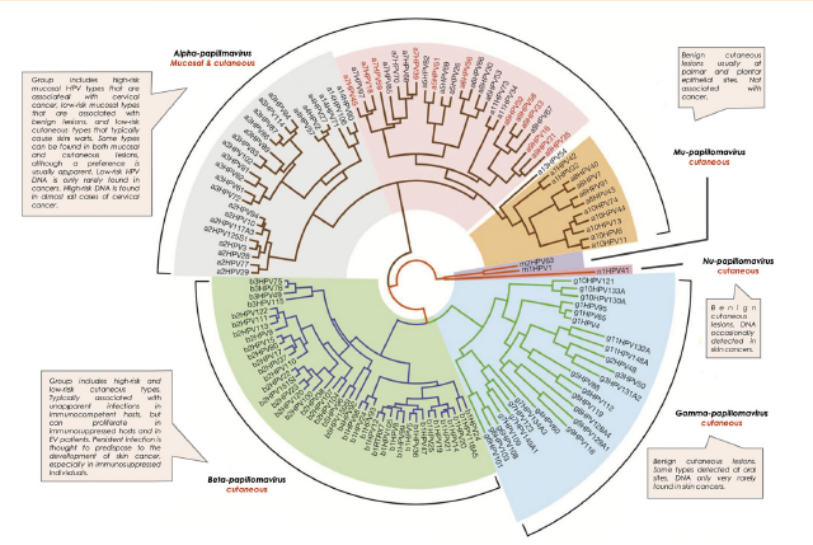


Table 4
Human papillomaviruses characterized since 2004.

HPV type	PV genus	PV species (common use)	PV species (ICTV)	GenBank No.	Reference
HPV 97	*Alphapapillomavirus*	Alpha-7	*Human Papillomavirus 18*	DQ080080	Chen et al. (2007a)
HPV 98	*Betapapillomavirus*	Beta-1	*Human Papillomavirus 5*	FM955837	de Villiers and Gunst (2009)
HPV 99	*Betapapillomavirus*	Beta-1	*Human Papillomavirus 5*	FM955838	de Villiers and Gunst (2009)
HPV 100	*Betapapillomavirus*	Beta-2	*Human Papillomavirus 9*	FM955839	de Villiers and Gunst (2009)
HPV 101	*Gammapapillomavirus*	Gamma-6	*Human Papillomavirus 101*	NC_008189	Chen et al. (2007c)
HPV 102	*Alphapapillomavirus*	Alpha-3	*Human Papillomavirus 61*	DQ080083	Chen et al. (2007b)
HPV 103	*Gammapapillomavirus*	Gamma-6	*Human Papillomavirus 101*	NC_008188	Chen et al. (2007c)
HPV 104	*Betapapillomavirus*	Beta-2	*Human Papillomavirus 9*	FM955840	de Villiers and Gunst (2009)
HPV 105	*Betapapillomavirus*	Beta-1	*Human Papillomavirus 5*	FM955841	de Villiers and Gunst (2009)
HPV 106	*Alphapapillomavirus*	Alpha-14	*Human Papillomavirus 90*	DQ080082	Chen et al. (2007b)
HPV 107	*Betapapillomavirus*	Beta-2	*Human Papillomavirus 9*	EF422221	Vasiljevic et al. (2008)
HPV 108	*Gammapapillomavirus*	Gamma-6	*Human Papillomavirus 101*	NC_012213	Nobre et al. (2009)
HPV 109	*Gammapapillomavirus*	Gamma-7	*Human Papillomavirus 109*	NC_012485	Ekstrom et al. (in press)
HPV 110	*Betapapillomavirus*	Beta-2	*Human Papillomavirus 9*	EU410348	Vasiljevic et al. (2008)
HPV 111	*Betapapillomavirus*	Beta-2	*Human Papillomavirus 9*	EU410349	Vasiljevic et al. (2008)
HPV 112	*Gammapapillomavirus*	Gamma-8	*Human Papillomavirus 112*	EU541442	Ekstrom et al. (in press)
HPV 113	*Betapapillomavirus*	Beta-2	*Human Papillomavirus 9*	FM955842	de Villiers and Gunst (2009)
HPV 114	*Alphapapillomavirus*	Alpha-3	*Human Papillomavirus 61*	GQ244463	Ekstrom et al. (in press)
HPV 115	*Betapapillomavirus*	Beta-3	*Human Papillomavirus 49*	HQ947080	Chouhy et al. (2010)
HPV 116	*Gammapapillomavirus*	Gamma-9	*Human Papillomavirus 116*	HQ804072	Li et al. (2009)
HPV 117	*Alphapapillomavirus*	Alpha-2	*Human Papillomavirus 10*	GQ246950	Köhler et al. (in press)
HPV 118	*Betapapillomavirus*	Beta-1	*Human Papillomavirus 5*	GQ246951	Nindl et al., unpubl.
HPV 119	*Gammapapillomavirus*	Gamma-8	*Human Papillomavirus 112*	GQ845441	Chen et al., unpubl.
HPV 120	*Betapapillomavirus*	Beta-2	*Human Papillomavirus 9*	GQ845442	Chen et al., unpubl.
HPV 121	*Gammapapillomavirus*	Gamma-10	*Human Papillomavirus 121*	GQ845443	Chen et al., unpubl.
HPV 122	*Betapapillomavirus*	Beta-2	*Human Papillomavirus 9*	GQ845444	Chen et al., unpubl.
HPV 123	*Gammapapillomavirus*	Gamma-7	*Human Papillomavirus 109*	GQ845445	Chen et al., unpubl.
HPV 124	*Betapapillomavirus*	Beta-1	*Human Papillomavirus 5*	GQ845446	Chen et al., unpubl.



Μετάδοση

Δέρμα με δέρμα

Ο πρωκτογεννητικός HPV μεταδίδεται εύκολα με σεξουαλική επαφή

Στοματογεννητική επαφή
Στόμα με στόμα
Γεννητική περιοχή-δάκτυλο στόμα

Κάθετη μετάδοση

? Έμμεσα (αντικείμενα, εργαλεία, κ.α)
? Καθημερινή επαφή

Μετάδοση στην προεφηβεία

Κοινές μυρμηκίες στην ηλικία 1 μήνας - 4 έτη 50-70%
Κονδυλώματα πρωκτογεννητικής περιοχής προεφηβικής ηλικίας 3-35% (HPV6, 11, 1, 2)

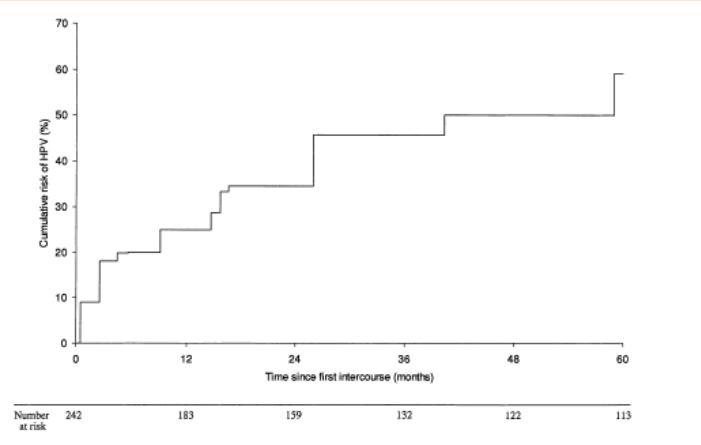
Table 2.7. HPV Detection in Finnish Children

	HPV DNA *Prevalence* (%)	
Sample Subset/Age	*Genital*	*Oral*
Parents	13–25	8–34
Children/birth	15	10
Children/6 months	18	21
Children/24 months	10	10

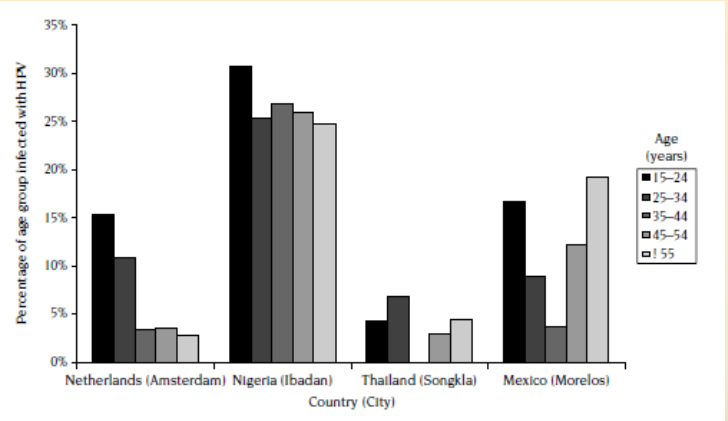
Source: Rintala et al., *Journal of Clinical Microbiology*, 2005.

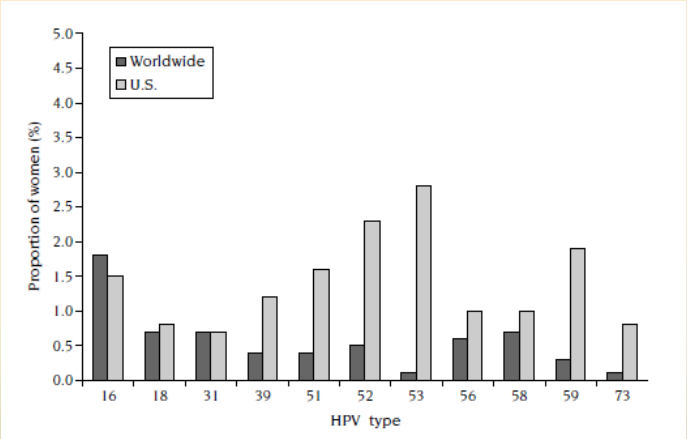
Επιδημιολογία

Επιπολασμός HPV κατά την πρώτη σεξουαλική σχέση σε γυναίκες

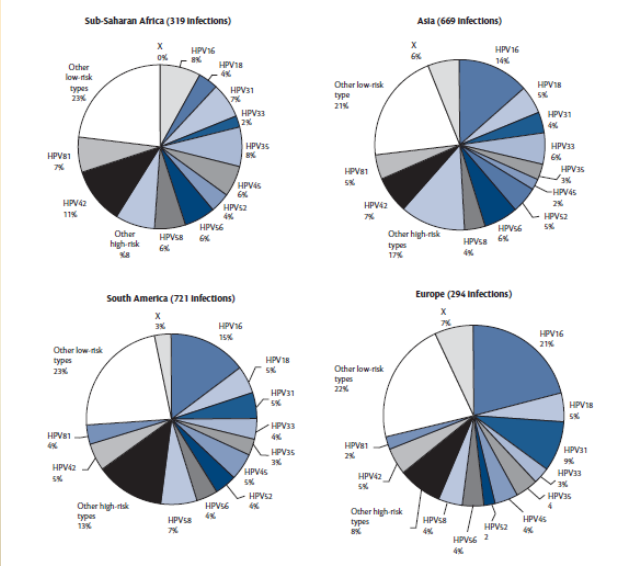


Collins et al. Brit J Obstet Gynecol 200,109: 96-98



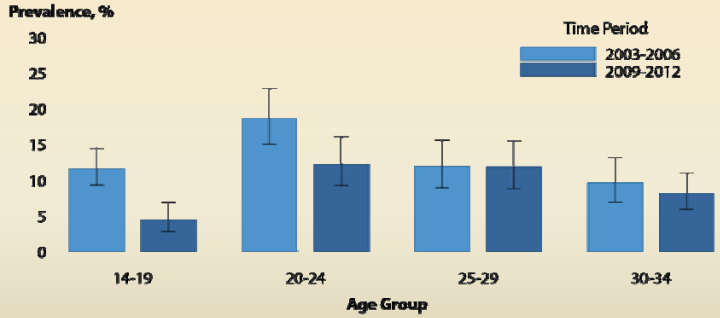


Τύποι ιού HPV από τράχηλο ανά γεωγραφική περιοχή



Clifford, G.M. et al., The Lancet, 366, 9490, 991–998

Human Papillomavirus — Cervicovaginal Prevalence of Types 6, 11, 16 and 18 Among Females Aged 14–34 Years by Age Group and Time Period, National Health and Nutrition Examination Survey (NHANES), 2003–2006 and 2009–2012



NOTE: Error bars indicate 95% confidence interval.
SOURCE: Markowitz LE, Liu G, Hariri S, et al. Prevalence of HPV After Introduction of the Vaccination Program in the United States. Pediatrics 2016; 137(3):e20151968.

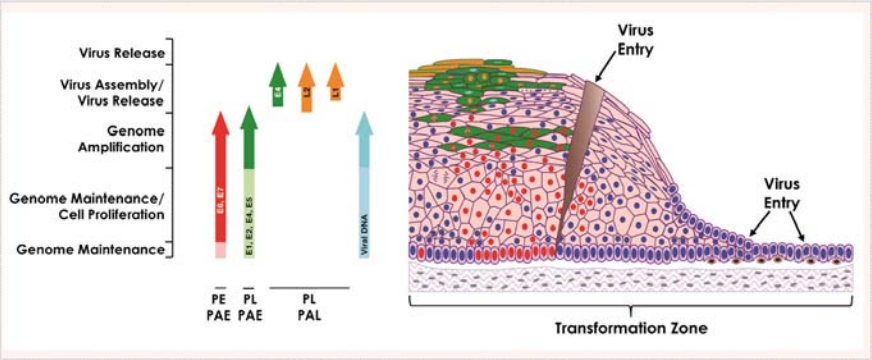
Ιστοί Στόχοι

Table 3.1. Categories of Stratified Squamous Epithelia

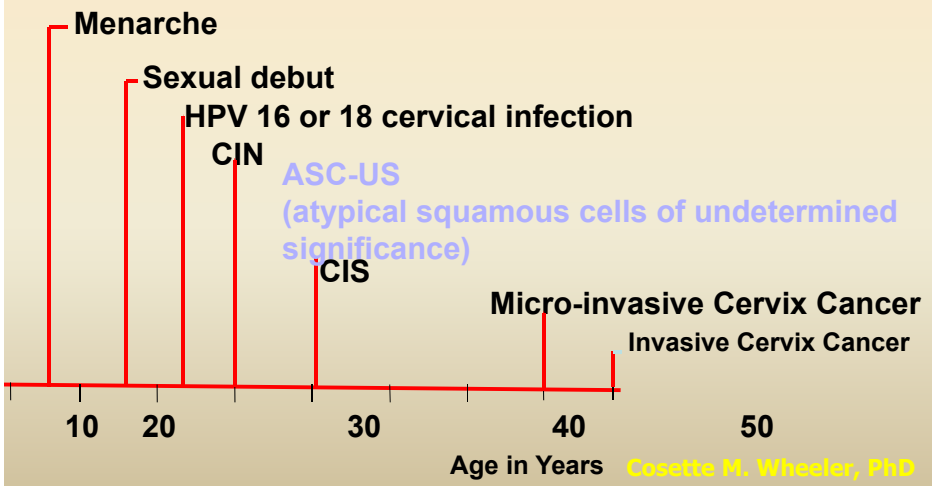
Feature	*Site*
More keratinized	Skin
	Tongue (dorsal)
	Hard palate
	Gums
	Anal margin
	Labia majora
Special susceptibility to mucosal HPV	Oral cavity
	Tonsil (crypt)
	Vocal folds
	Esophagus
	Anus (distal)
	Labia minora
	Vagina
	Ectocervix
	Glans penis (uncircumcized)
	Foreskin
	Cornea

Ζώνη μετάπτωσης!!!

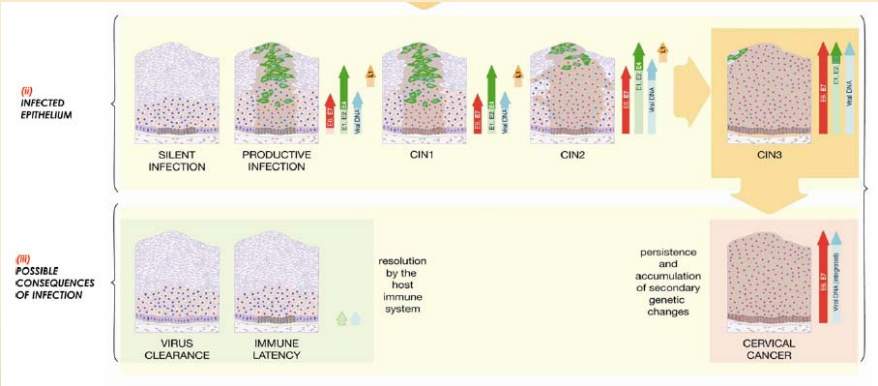
Κύκλος ζωής



Natural History of HPV 16/18-Related Cervical Neoplasia: Estimated Median Age of Events



Cosette M. Wheeler, PhD

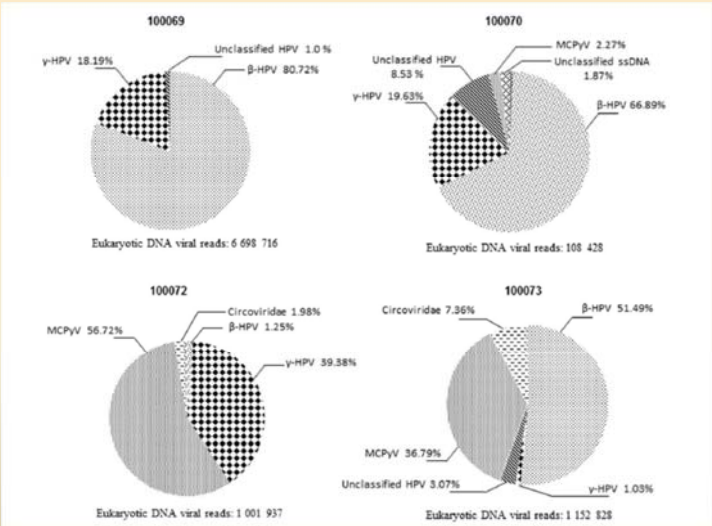


Καλοήθεις Νόσοι που προκαλούνται από τον HPV

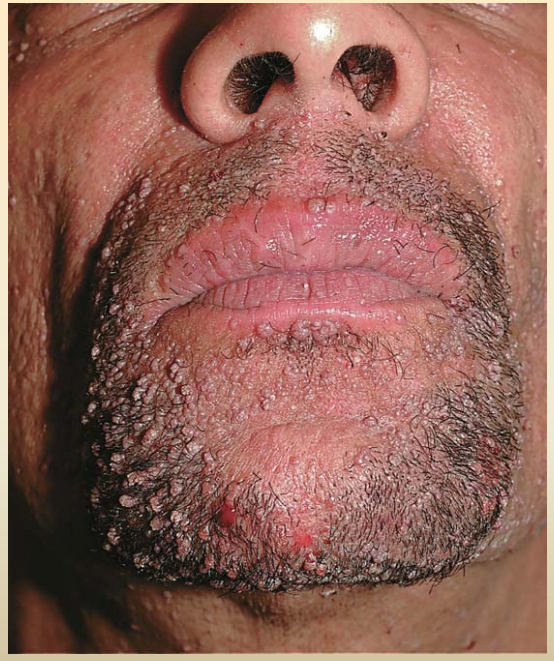
Κοινές μυρμηκίες παλαμών HPV-1 και -60
Κοινές μυρμηκίες πελμάτων HPV-1 και -60
Επίπεδες μυρμηκίες HPV-3, -10, -28, -94
Μυρμηκίες του χασάπη HPV-7
Καλοήθεις βλάβες έξω ακουστικού πόρου HPV-6

Epidermodysplasia verruciformis HPV-5, -8

Κονδυλώματα (Γεννητικές μυρμηκίες) HPV-6 και -11



Επίπεδες βλάβες στο πέος των ογκογόνων τύπων



Epidermodysplasia verucciformis

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Καρκίνος και HPV

THE NOBEL PRIZE

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Medicine | The Nobel Prize in Physiology or Medicine 2008 | Harald zur Hausen - Facts

The Nobel Prize in Physiology or Medicine 2008

Harald zur Hausen
Françoise Barré-Sinoussi
Luc Montagnier

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Harald zur Hausen
Facts

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Harald zur Hausen
The Nobel Prize in Physiology or Medicine 2008

Born: 11 March 1936, Gelsenkirchen, Germany

Affiliation at the time of the award: German Cancer Research Center, Heidelberg, Germany

Prize motivation: "for his discovery of human papilloma viruses causing cervical cancer"

Prize share: 1/2

Table 2.1. Known Clinical Burden of HPV Infection

	Proportion of Cases Due to HPV Infection	Proportion of HPV-Related Cases by HPV Type			
		16	18	6	11
Cancers					
Cancer of the cervix	100%	55%	13%		
Ano-genital cancers					
Cancer of the vulva	44%	67%	9%		
Cancer of the vagina	57%	51%	8%		
Cancer of the penis	47%	68%	3%	7%	
Cancer of the anus	78%	78%	6%	1%	1%
Head and neck cancers					
Cancer of the larynx	25%	65%	19%		
Oral cancers	30%	73%	28%		
Cancer of the tonsils	41%	87%	2%		
Sinonasal cancers	22%	100%	0%		
Cancer of the ocular surface	78%	50%	50%		
Total—Cancers	58%	62%	11%	<1%	<1%
Nonmalignant Diseases					
Genital warts	100%			90%	
Recurrent respiratory papillomatosis	76%			60%	40%
Sinonasal papilloma	33%			Primary	
Conjunctival papilloma	92%			85%	
Total—Nonmalignant diseases	100%	0%	0%	>90%	

High-risk types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82

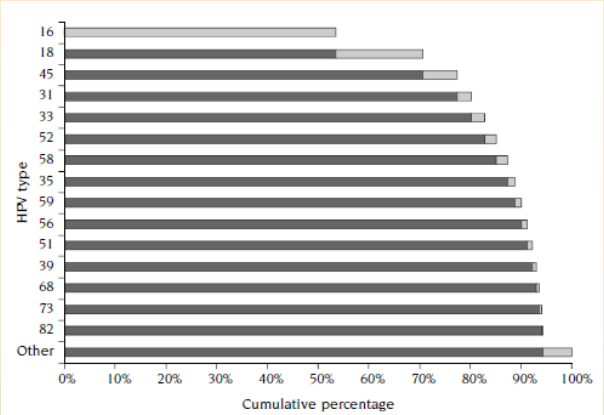
Low-risk types: 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, CP6108

Potentially high-risk types: 26, 53, 66

Συσχέτιση τύπου ιού και καρκίνου -IARC

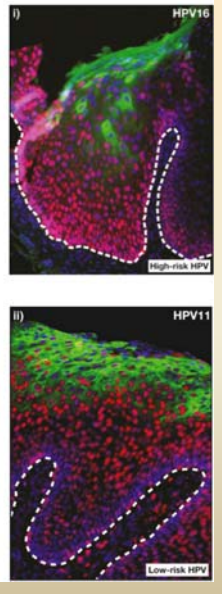
Human papilloma virus type 16	S	Cervix, vulva, vagina, penis, anus, oral cavity, tonsil, pharynx, (larynx)	64, 90, 100B
Human papilloma virus type 18	S	Cervix, (oral cavity), (penis), (anus), (vulva)	64, 90, 100B
Human papilloma virus types 31, 35, 39, 45, 51, 52, 56, 58, 59	S	Cervix	64, 90, 100B
Human papilloma virus type 33	S	Cervix, (anus), (vulva)	64, 90, 100B
Human papilloma virus types 6, 11	I	(Larynx)	90, 100B
Human papilloma virus types 26, 53, 66, 67, 68, 70, 73, 82	L	(Cervix)	100B
Human papilloma virus types 30, 34, 69, 85, 97	I		100B
Human papilloma virus, genus-beta types (except 5 and 8) and gamma types	I	(Skin)	90, 100B
Human papillomavirus types 5, 8 (in patients with epidermodysplasia verruciformis)	L	(Skin)	100B

Attributable factor HPV:
100 % καρκίνος τραχήλου
55,7 % για πρωκτογεννητικό καρκίνο
4,4 % για στόμα και στοματοφάρυγγα

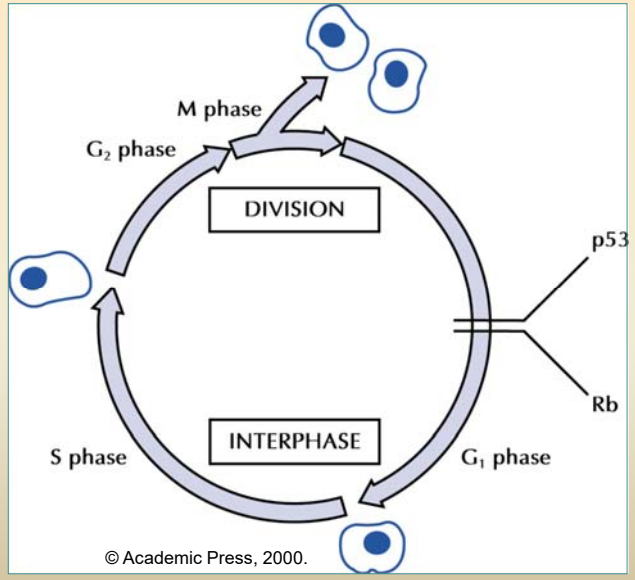


Καρκινογένεση

	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



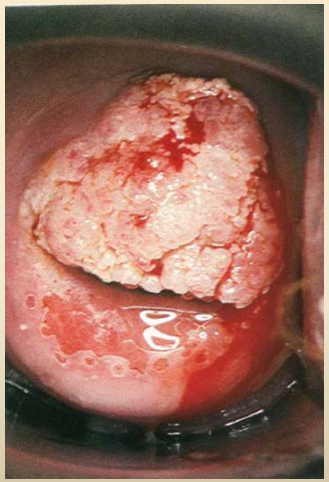
The Cell Cycle



© Academic Press, 2000.

Ο HPV είναι αναγκαίος αλλά όχι ικανός αιτιολογικός παράγοντας του καρκίνου του τραχήλου

Άλλοι παράγοντες:
Κάπνισμα
Άλλες λοιμώξεις
HIV
Γενετική ευαισθησία
Χρήση ΟΣ



Καρκίνος του τραχήλου της μήτρας

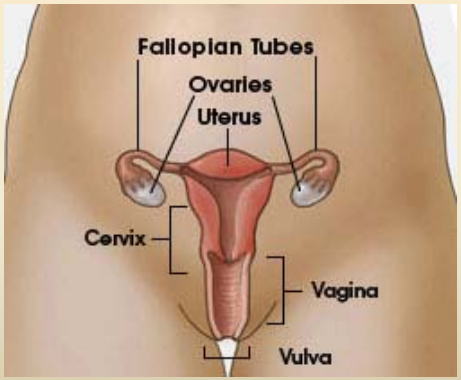
Ο πλέον συχνός καρκίνος στις γυναίκες στις αναπτυσσόμενες χώρες

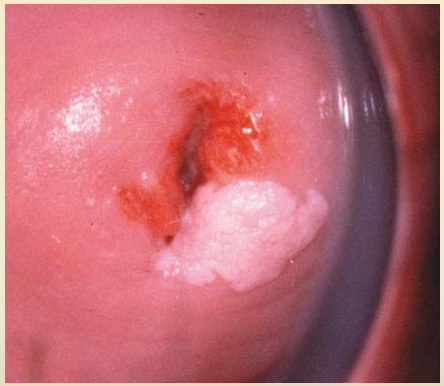
HPV16 ο συχνότερος τύπος στα επιδερμοειδή

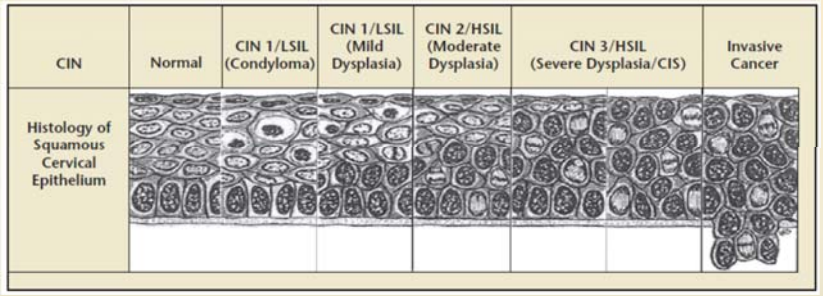
HPV18 ο συχνότερος τύπος στα αδενοκαρκινώματα

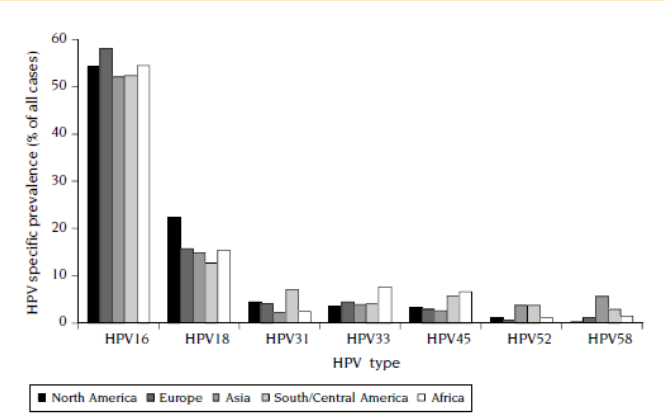
HPV31, 33, 35, 39, 45, 51, 52, 56, 58, 59, και 66 στα επιδερμοειδή

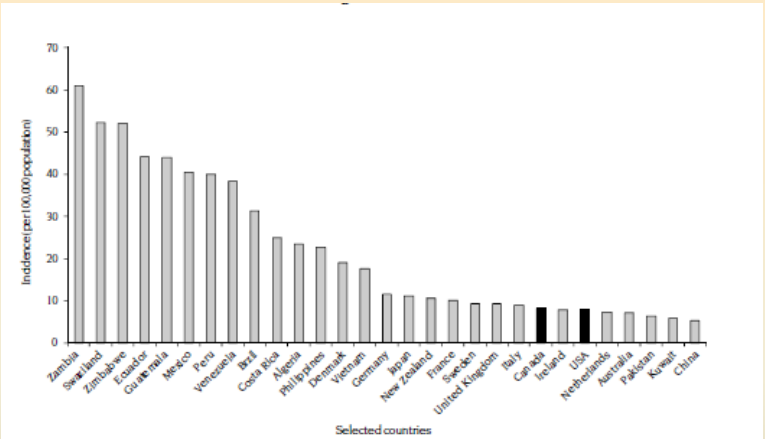
Καρκίνος του τραχήλου της μήτρας



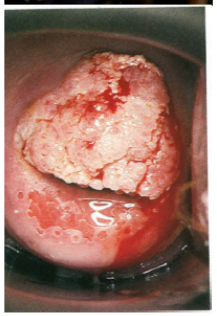








Cervical Cancer & HPV



- DNA of high-risk HPVs can be found in 99.7% of cervical cancers (932 specimens from women in 22 countries).

Walboomers JM, Jacobs MV, Manos MM, et al. *J. Pathol. 1999;189:12-19*

CervixCheck
CancerCare Manitoba

ARTICLE

US Assessment of HPV Types in Cancers: Implications for Current and 9-Valent HPV Vaccines

Mona Saraiya, Elizabeth R. Unger, Trevor D. Thompson, Charles F. Lynch, Brenda Y. Hernandez, Christopher W. Lyu, Martin Steinau, Meg Watson, Edward J. Wilkinson, Claudia Hopenhayn, Glenn Copeland, Wendy Cozen, Edward S. Peters, Youjie Huang, Maria Sibug Saber, Sean Altekruse, Marc T. Goodman*; HPV Typing of Cancers Workgroup

2670 Ασθενείς με καρκίνο

Ο HPV ανιχνεύεται στο 90,6% περιπτώσεων τραχηλικών καρκίνων, 91,1% πρωκτικών, 75,0% of κολπικών, 70,1% στοματοφαρυγγικών, 68,8% αιδοιικών, 63,3% του πέους, 32,0% στοματικής κοιλότητας, 20,9% λαρυγγικών, 98,8% of τραχηλικών καρκίνων in situ (CCIS).

JNCI J Natl Cancer Inst (2015) 107(6): djv086

Ελλάς

Οκτώβριο 2005 - Ιανουάριο 2011
HPV DNA σε δείγμα τραχηλικού επιχρίσματος από 5379 Ελληνίδες από διαφορετικές περιοχές της χώρας.

Ο επιπολασμός της HPV λοίμωξης με ογκογόνους (υψηλού κινδύνου) τύπους HPV ήταν 5,8%.

Ο συχνότερος τύπος HPV ήταν ο 16 (24,8% των γυναικών με HPV λοίμωξη, 1,4% στον συνολικό πληθυσμό της μελέτης).
Ακολουθούσαν κατά φθίνουσα σειρά οι τύποι 31, 35, 53, 18, 51, 56, 58, 52, 39, 66, 45, 33, 59 και 68

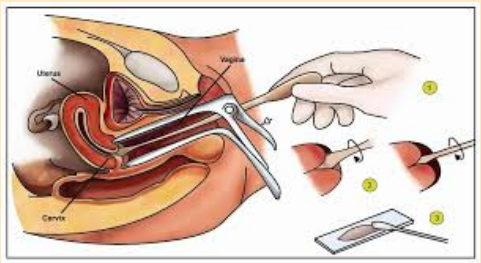
Agorastos T et al. *Eur J Cancer Prev.* 2014;23: 425-431.

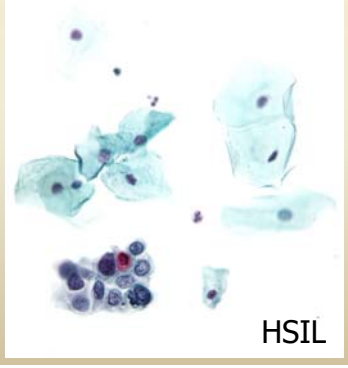
Ανίχνευση του καρκίνου του τραχήλου

***Screening (Pap test** 5–30% ψευδώς αρνητικά)*

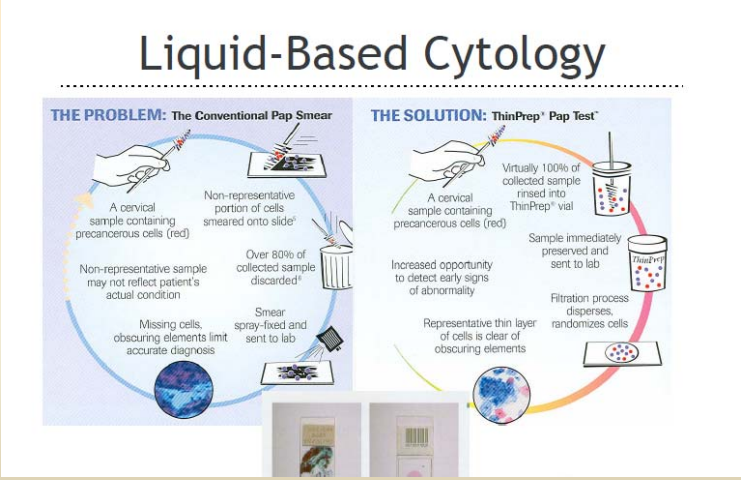
Liquid based cytology
HPV screening (υψηλό κόστος, ψευδώς θετικά)
100.000 γυναίκες γλύτωσαν πρόωρο θάνατο στην Αγγλία 1951-1970
Stop σε επιδημία που θα σκότωνε 1 στις 65 γυναίκες

Ιστοπαθολογία





Κάθε 3 έτη από 21/25 μέχρι 65 ετών

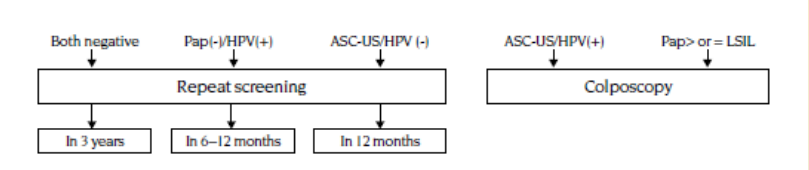


Ανίχνευση του HPV

Nucleic Acid Hybridization
PCR
Multiplex HPV Genotyping
HPV RNA Detection

Αντισώματα
Επιδημιολογική αξία, Ηλικία εμβολιασμού, αμυγδαλές

Biomarkers
p16
p53
E6
E7
κ.α.



Changes planned for May 1, 2017, will transform cervical screening in Australia.

What will change?

Tests and funding: The high-risk HPV test, also known as the oncogenic HPV test, will become the Medicare-funded cervical screening test. Pap smears will not be funded after May 1, 2017.
Screening age and interval: Asymptomatic women between the ages of 25 and 74 with a negative HPV test will be screened every five years.
Regions: The HPV test result will assign women to different risk categories – low, higher or intermediate risk (see discussion below).
Sample collected: The sample will need to be collected into a liquid-based lab. ThinPrep vial. See overleaf.

Why the change?

Australia's school-based HPV vaccination program has been very successful and, in 2017, most women under the age of 25 will be vaccinated. As more women are vaccinated, the rates of cervical disease will fall, so the Australian Government has accepted recommendations to change the way cervical screening will be undertaken for all women, vaccinated or unvaccinated, in the future.

What do you need to do now?

Continue to screen under the current guidelines until May 1, 2017.

What will the results tell me?

Unlike the current Pap test, results from the new screening program will assign patients to different levels of risk for cervical abnormality.

Cervical screening results will be reported as:

LOW RISK

No evidence of oncogenic HPV types in the sample. This places the patient in the low risk category for cervical cancer. If the patient is asymptomatic with a negative screening history, she will be advised to have another screening HPV test in five years.

HIGHER RISK

The presence of either or both HPV types 16 and 18 places the patient in the higher risk category because of the strong association between these particular HPV types and cervical abnormalities. The same sample will be further tested with a reflex liquid-based cytology (LBC) being prepared. A combined HPV/LBC report will be issued with a recommendation that the patient be referred for colposcopy.

INTERMEDIATE RISK

If the sample tests negative for types 16/18 but positive for one of the other oncogenic HPV types (reported as a group), the patient falls into the intermediate risk category. The same sample will be further tested with a reflex LBC being prepared. A combined HPV/LBC report will be issued. If the LBC result is negative or low-grade, the patient will be asked to return for a repeat HPV test in 12 months. If the LBC result shows a high-grade, possible high-grade or glandular abnormality, the risk category will be upgraded to Higher Risk and the patient referred for colposcopy.

HPV και άλλοι καρκίνοι:
Πρωκτογεννητικοί καρκίνοι

HPV16 κύριος τύπος

Καρκίνος αιδοίου 2 τύποι VIN, 20-80% HPV (16, 18, 33), 60% 2006

Καρκίνος κόλπου 83% HPV VaIN 1997, 82% in situ και 64% διηθητικοί καρκίνοι, diethylstibestrol

Καρκίνος πέους HPV 75-100% σε PIN, Ινδία Βραζιλία, καρκίνος εκτός PIN HPV 15% με 82%, περιτομή?, HPV 16, -18 , -6, -11, HPV-8 Queyrat

Καρκίνος πρωκτού Πιο συχνός από τους άνωθεν, Επιδημία σε ομάδες, HIV , αντιρετροϊκά όχι χρήσιμα, 3-15% γυναίκες, >50% MSM, HPV-16 73-93%

MAJOR ARTICLE

Long-Term Outcomes of Adding HPV Vaccine to the Anal Intraepithelial Neoplasia Treatment Regimen in HIV-Positive Men Who Have Sex With Men

Ashish A. Deshmukh,[1,2] Jagpreet Chhatwal,[6,7] Elizabeth Y. Chiao,[5] Alan G. Nyitray,[4] Prajnan Das,[3] and Scott B. Cantor[1]

HPV και άλλοι καρκίνοι: *Κεφαλή και Τράχηλος*

HPV16 κύριος τύπος, HPV18, HPV6

Κακή πρόγνωση, καλύτερη σε HPV+, κάπνισμα, αλκοόλ

HPV 3.9% σε 766 καρκίνους στόματος, 18.3% σε 142 όγκους στοματοφάρυγγα

Μικρή συσχέτιση με MSM και HIV

Καρκίνος στόματος

Καρκίνος στοματοφάρυγγα 25% του συνόλου, βάση γλώσσας και αμυγδαλές (ισχυρότερη συσχέτιση), καλύτερη πρόγνωση, HPV-16

Καρκίνος λάρυγγα HPV σε 20%, HPV 6, -11 σε 100% των θηλωμάτων

Καρκίνος κόλπων κρανίου 22%

Καρκίνος οισοφάγου ? 0-67% HPV 16, -11 *Καρκίνος ρινοφάρυγγα, Καρκίνος πνεύμονα*

HPV και άλλοι καρκίνοι: *Καρκίνος δέρματος*

Ο πλέον συχνός τύπος καρκίνου στους καυκάσιους 100-150 ανά 100.000 άτομα

UV ως παράγων καρκινογένεσης

UV-induced immunosuppression

EV τύποι HPV

Δερματικοί τύποι HPV

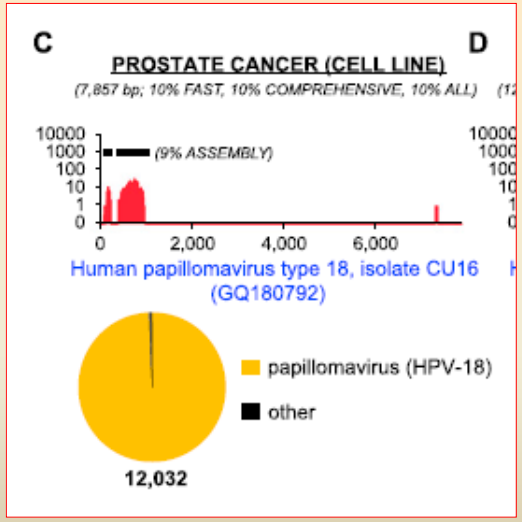
Βλενογονικοί τύποι HPV

Genus	Species	Prototype	Other types →											
α papillomavirus	1													
	2	HPV-10	HPV-3	HPV-28	HPV-29	HPV-78	HPV-94							
	3													
	4	HPV-2	HPV-27	HPV-57										
	5													
	6													
	7													
	8	HPV-7	HPV-40											
	9													
	10													
	11													
	13													
	14													
	15													
β papillomavirus	1	HPV-5	HPV-8	HPV-12	HPV-14	HPV-19	HPV-20	HPV-21	HPV-24	HPV-25	HPV-36	HPV-47	HPV-93	
	2	HPV-9	HPV-15	HPV-17	HPV-22	HPV-23	HPV-37	HPV-38	HPV-80					
	3	HPV-49	HPV-75	HPV-76										
	4	HPV-92												
	5	HPV-96												
γ papillomavirus	1	HPV-4	HPV-65	HPV-95										
	2	HPV-48												
	3	HPV-50												
	4	HPV-60												
	5	HPV-88												
μ-papillomavirus	1	HPV-1												
	2	HPV-63												
ν papillomavirus	1	HPV-41												

Legend

Skin cancer or precursor: HPV type

Other skin lesions: HPV type



Πρόληψη

Εκπαιδευτικά Κοινωνικά Συμπεριφορικά μέτρα

Ασφαλείς σεξουαλικές συμπεριφορές για την πρόληψη της μετάδοσης του HPV

Προφυλακτικά κ.α.

HPV & Αντισηπτικά

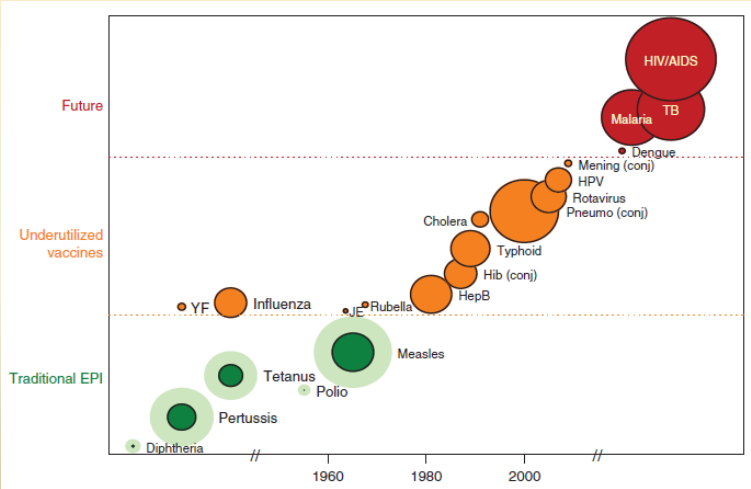
Table 1. Effectiveness of clinical disinfectants on HPV virions

Disinfectant	Native virion (log_{10} reduction)	±SD	Quasivirion (log_{10} reduction)	±SD
70% Ethanol	−0.789	0.106	0.197	0.530
95% Ethanol	−0.076	0.481	0.307	0.123
70% Isopropanol	−0.770	0.186	4.675	0.415
95% Isopropanol	−0.272	0.023	4.435	0.196
2.4% GTA	−0.856	0.179	−0.041	0.014
3.4% GTA	−0.306	0.232	−0.145	0.232
0.55% OPA	0.017	0.200	0.109	0.180
Phenol	−0.319	0.380	4.218	0.144
0.25% PAA-silver	−0.857	0.195	1.359	0.408
1.2% PAA-silver	5.150	0.971	4.946	0.548
0.525% Hypochlorite	4.862	0.623	5.087	0.413

All tests were performed at least five times and the averages are shown.

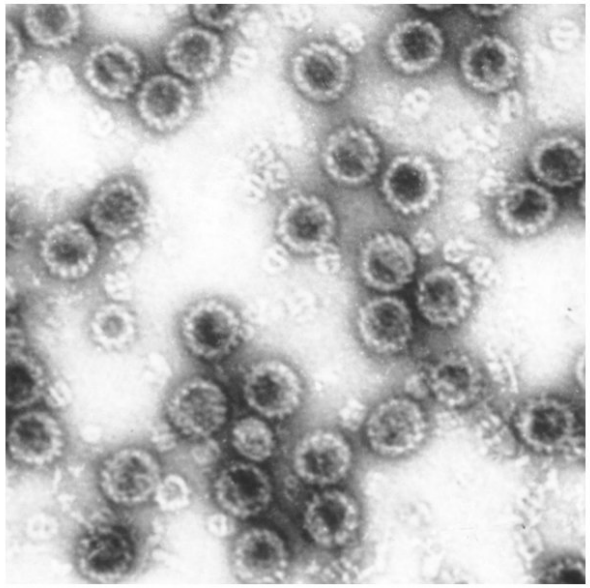
J Meyers et al, J Antimicrob Chemother 2014; 69: 1546–1550

Εμβόλια έναντι του HPV

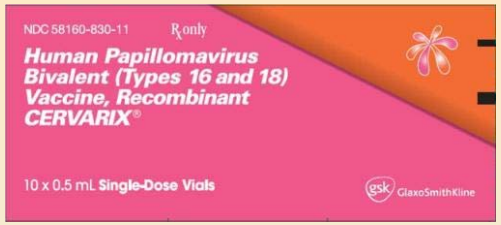


"A vaccine targeting HPV 16/18 potentially prevents the majority of invasive cervical (66.2%), anal (79.4%), oropharyngeal (60.2%) and vaginal (55.1%) cancers, as well as many penile (47.9%), vulvar (48.6%) cancers: 24 858 cases annually.

The 9-valent vaccine also targeting HPV 31/33/45/52/58 may prevent an additional 4.2% to 18.3% of cancers: 3944 cases Annually"



VLP L1



2006

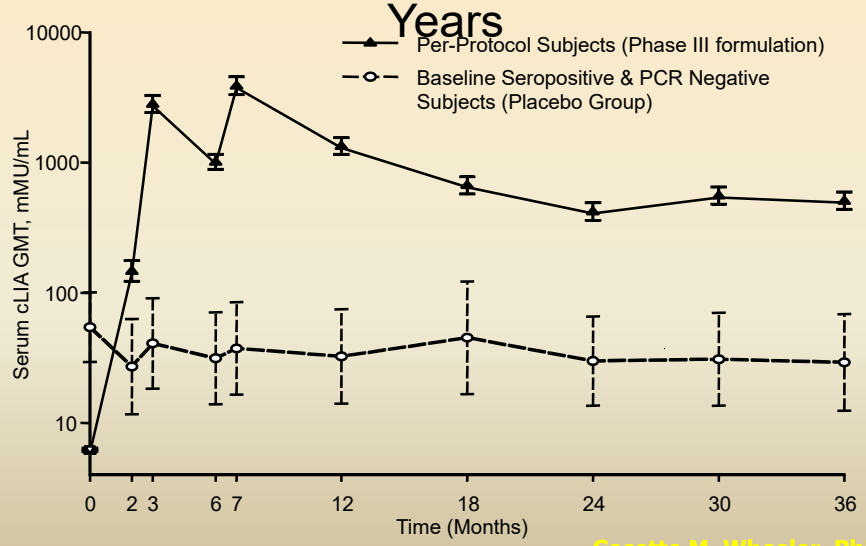
2-δύναμο εμβόλιο (L1)
HPV 16 HPV 18

0-1-6 μήνες

2006

4-δύναμο εμβόλιο (L1)
HPV 16 HPV 18 (66% καρκίνος τραχήλου
25-50% in situ καρκινώματα
HPV 6 HPV 11 (90% κονδυλωμάτων)

Quadrivalent HPV Vaccine Study: Anti-HPV 16 Immunogenicity Over 3.0 Years



Cosette M. Wheeler, PhD

Table 6.6.1 Incremental costs and QALY gains from vaccination

	Non-vaccinated	Vaccinated	Difference
Total cost (Can$)	476	739	263
Total QALYs	30.5015	30.5098	0.0083

Source: data from Anonychuk et al., A cost-utility analysis of cervical cancer vaccination in preadolescent Canadian females, *BMC Public Health*, Volume 9, Issue 1, pp. 401, Copyright © 2009 Anonychuk et al. licensee BioMed Central Ltd. Reproduced under the Creative Commons Attribution License 2.0.

Για κάθε 100.000 εμβολιασθείσες 390-633 Περιπτώσεις καρκίνου του τραχήλου και 168-175 θάνατοι θα προλαμβάνονταν, (herd immunity and διασταυρούμενη προστασία). QALY (Quality-adjusted life year) gains 0,0083 με 0,0095 ανά άτομο εφ' όρου ζωής. Κόστος Can$256 με Can$263 ανά άτομο.

Anonychuk et al., BMC Public Health 2009, 9:401

Κλινική αποτελεσματικότητα

Table 6: Analysis of Efficacy of GARDASIL in the PPE* Population for Vaccine HPV Types

Disease Endpoints	GARDASIL N	GARDASIL Number of cases	AAHS Control N	AAHS Control Number of cases	% Efficacy (95% CI)
16- through 26-Year-Old Girls and Women†					
HPV 16- or 18-related CIN 2/3 or AIS	8493	2	8464	112	98.2 (93.5, 99.8)
HPV 16- or 18-related VIN 2/3	7772	0	7744	10	100.0 (55.5, 100.0)
HPV 16- or 18-related VaIN 2/3	7772	0	7744	9	100.0 (49.5, 100.0)
HPV 6-, 11-, 16-, or 18-related CIN (CIN 1, CIN 2/3) or AIS	7864	9	7865	225	96.0 (92.3, 98.2)
HPV 6-, 11-, 16-, or 18-related Genital Warts	7900	2	7902	193	99.0 (96.2, 99.9)
HPV 6- and 11-related Genital Warts	6932	2	6856	189	99.0 (96.2, 99.9)
16- through 26-Year-Old Boys and Men					
External Genital Lesions HPV 6-, 11-, 16-, or 18-related					
External Genital Lesions	1394	3	1404	32	90.6 (70.1, 98.2)
Condyloma	1394	3	1404	28	89.3 (65.3, 97.9)
PIN 1/2/3	1394	0	1404	4	100.0 (-52.1, 100.0)
HPV 6-, 11-, 16-, or 18-related Endpoint					
AIN 1/2/3	194	5	208	24	77.5 (39.6, 93.3)
AIN 2/3	194	3	208	13	74.9 (8.8, 95.4)
AIN 1	194	4	208	16	73.0 (16.3, 93.4)
Condyloma Acuminatum	194	0	208	6	100.0 (8.2, 100.0)
Non-acuminate	194	4	208	11	60.4 (-33.5, 90.8)

2014

GARDASIL.9
Human Papillomavirus
9-valent Vaccine, Recombinant

9-δύναμο εμβόλιο (L1) **ΣΥΝ**

HPV 16 HPV 18
HPV 6 HPV 11 **HPV 31/33/45/52/58**

ΕΝΔΕΙΞΗ: Κορίτσια/Γυναίκες & Αγόρια/Άνδρες 9-26 ετών

Age	Regimen	Schedule
9 through 14 years	2-dose	0, 6 to 12 months*
	3-dose	0, 2, 6 months
15 through 26 years	3-dose	0, 2, 6 months

Σύσταση εμβολιασμού στις ΗΠΑ (CDC)

HPV2/ HPV4/HPV9

2006 Κορίτσια 11-12 ετών 2 ή τρεις δόσεις
Κορίτσια/Γυναίκες > 15-26 ετών τρεις δόσεις

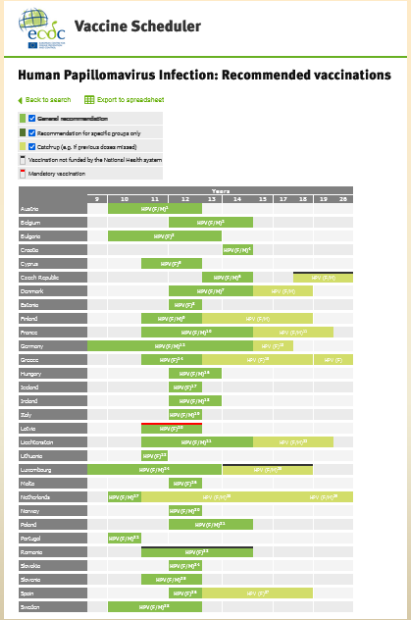
2011 Αγόρια 11-12 ετών 2 ή τρεις δόσεις
Αγόρια /Άντρες μέχρι 21 ετών

MSM μέχρι 26 ετών και ανοσοκατεσταλμένοι μέχρι 26 ετών

Τι ισχύει στην Ελλάδα (ΕΘΝΙΚΗ ΕΠΙΤΡΟΠΗ ΕΜΒΟΛΙΑΣΜΩΝ);

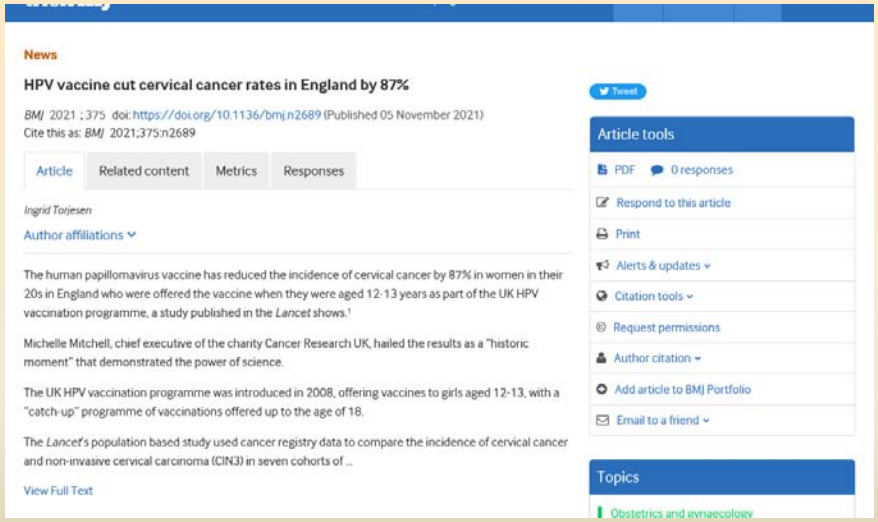
HPV9
2014 Κορίτσια 11-15 ετών 2 δόσεις
Κορίτσια/Γυναίκες > 15-26 ετών τρεις δόσεις
Αποζημιώνεται στα Κορίτσια/Γυναίκες από 11 μέχρι και 18 ετών και στους ομοφυλόφιλους άντρες < 26 ετών

2022 Κορίτσια/Αγόρια 9-11 ετών 2 δόσεις
Αναπλήρωση 15-18 ετών
Αποζημιώνεται από 11 μέχρι και 18 ετών (15-18 ετών 31/12/2023) και στους ομοφυλόφιλους άντρες < 26 ετών

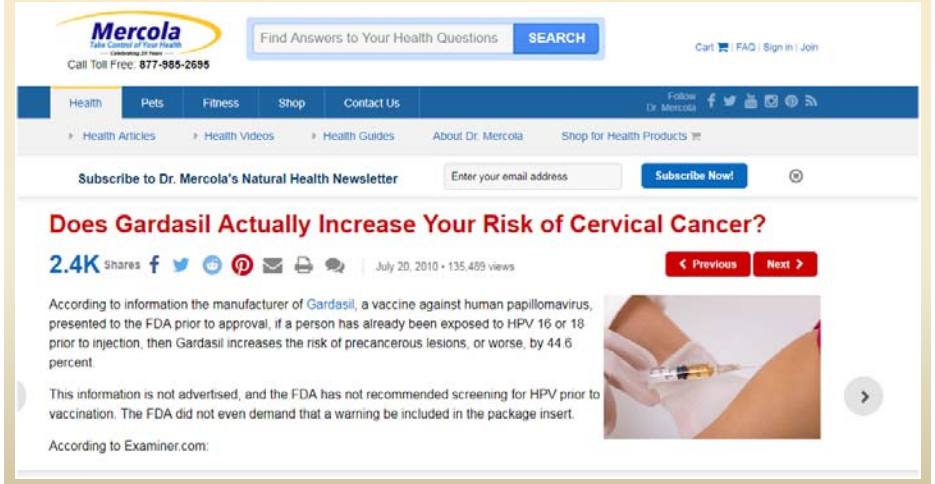


17 χώρες EU κορίτσια & αγόρια

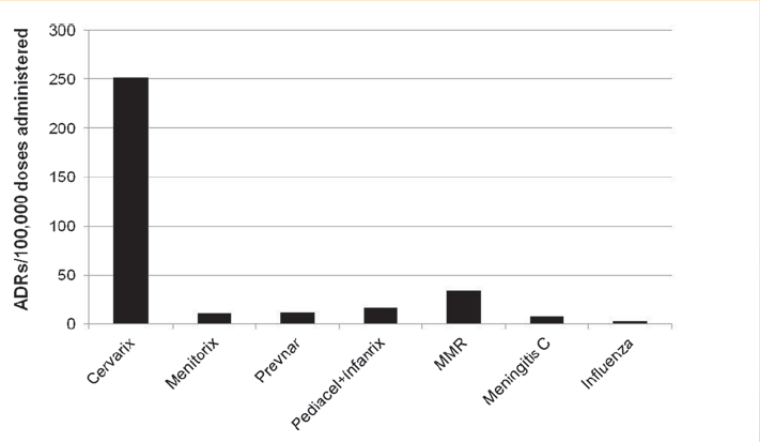
13 χώρες EU μόνο κορίτσια

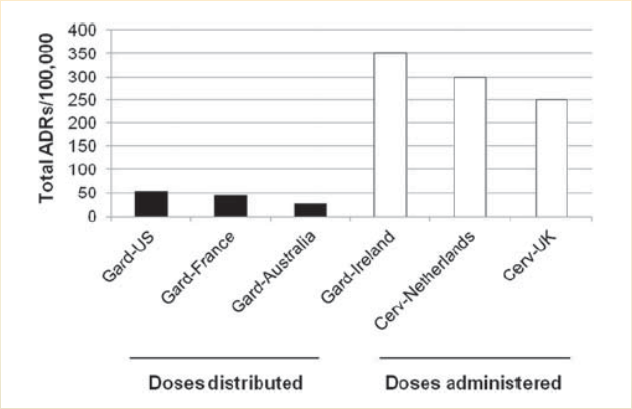


Παρενέργειες?
ΝΑΙ



Παρενέργειες?
ΟΧΙ





	GARDASIL 9				GARDASIL			
	Post-dose 1	Post-dose 2	Post-dose 3	Post any dose	Post-dose 1	Post-dose 2	Post-dose 3	Post any dose
Girls and Women 16 through 26 Years of Age								
Injection-Site Adverse Reactions	**N=7069**	**N=6997**	**N=6909**	**N=7071**	**N=7076**	**N=6992**	**N=6909**	**N=7078**
Pain, Any	70.7	73.5	71.6	89.9	58.2	62.2	62.6	83.5
Pain, Severe	0.7	1.7	2.6	4.3	0.4	1.0	1.7	2.6
Swelling, Any	12.5	23.3	28.3	40.0	9.3	14.6	18.7	28.8
Swelling, Severe	0.6	1.5	2.5	3.8	0.3	0.5	1.0	1.5
Erythema, Any	10.6	18.0	22.6	34.0	8.1	12.9	15.6	25.6
Erythema, Severe	0.2	0.5	1.1	1.6	0.2	0.2	0.4	0.8
Systemic Adverse Reactions	**n=6995**	**n=6913**	**n=6743**	**n=7022**	**n=7003**	**n=6914**	**n=6725**	**n=7024**
Temperature ≥100°F	1.7	2.6	2.7	6.0	1.7	2.4	2.5	5.9
Temperature ≥102°F	0.3	0.3	0.4	1.0	0.2	0.3	0.3	0.8
Girls 9 through 15 Years of Age								
Injection-Site Adverse Reactions	**N=300**	**N=297**	**N=296**	**N=299**	**N=299**	**N=299**	**N=294**	**N=300**
Pain, Any	71.7	71.0	74.3	89.3	66.2	66.2	69.4	88.3
Pain, Severe	0.7	2.0	3.0	5.7	0.7	1.3	1.7	3.3
Swelling, Any	14.0	23.9	36.1	47.8	10.4	17.7	25.2	36.0
Swelling, Severe	0.3	2.4	3.7	6.0	0.7	2.7	4.1	6.3
Erythema, Any	7.0	15.5	21.3	34.1	9.7	14.4	18.4	29.3
Erythema, Severe	0	0.3	1.4	1.7	0	0.3	1.7	2.0
Systemic Adverse Reactions	**n=300**	**n=294**	**n=295**	**n=299**	**n=299**	**n=297**	**n=291**	**n=300**
Temperature ≥100°F	2.3	1.7	3.0	6.7	1.7	1.7	0	3.3
Temperature ≥102°F	0	0.3	1.0	1.3	0.3	0.3	0	0.7

ASIA: 'Autoimmune (Auto-inflammatory) Syndrome induced by Adjuvants'

Table 2 Prevalence of relevant clinical findings in the ASIA registry cohort

Clinical findings	Frequency	Prevalence (%)
Arthralgia	184	61
Chronic fatigue	178	59
Myalgia	147	49
Sleep disturbances	112	37
Fever	101	34
General weakness	100	33
Arthritis	88	29
Neurological manifestations	78	26
Cognitive impairment	63	21
Sicca symptoms	55	18
Raynaud's phenomenon	48	16
Chronic rash	47	16
Lymphadenopathy	43	14
Photosensitivity	33	11
Mouth ulcers	18	6
Postural orthostatic tachycardia syndrome	13	4
Myositis	7	2

- **Συστηματικός Ερυθηματώδης Λύκος**

❖ Molecular mimicry of peptides (συμπλήρωμα, υποδοχείς των NK)

❖ Σύγκριση 48 816 περιστατικών SLE με 21 998 controls έδειξε στατιστικά σημαντική υπεροχή αυτών που είχαν λάβει εμβόλιο HPV

❖ Εμφάνιση 3-37 μέρες μετά τον εμβολιασμό

- **Σύνδρομο ορθοστατικής υπότασης ταχυκαρδίας**

❖ Small fiber neuropathy leading to autonomic dysfunction

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Research

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Could the human papillomavirus vaccines drive virulence evolution?

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CALIFORNIA LEGISLATURE—2011–12 REGULAR SESSION

ASSEMBLY BILL **No. 499**

Introduced by Assembly Member Atkins
(Principal coauthor: Assembly Member Ma)

February 15, 2011

An act to amend Section 6926 of the Family Code, relating to minors.

LEGISLATIVE COUNSEL'S DIGEST

AB 499, as introduced, Atkins. Minors: medical care: consent.

Existing law allows minors to consent to specified forms of medical or dental treatment.

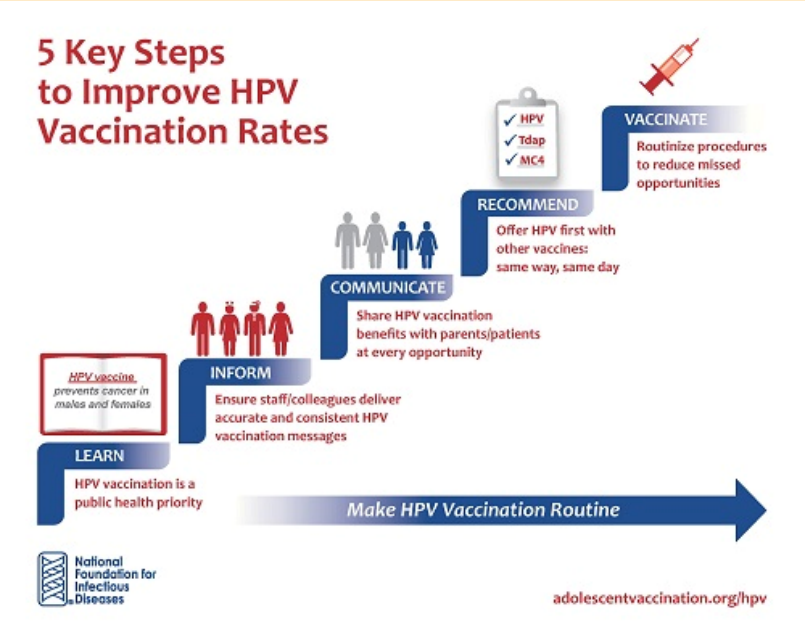
This bill would, in addition, allow a minor who is 12 years of age or older to consent to medical care related to the prevention of a sexually transmitted disease.

Vote: majority. Appropriation: no. Fiscal committee: no. State-mandated local program: no.

The people of the State of California do enact as follows:

SECTION 1. Section 6926 of the Family Code is amended to read:

6926. (a) A minor who is 12 years of age or older and who may have come into contact with an infectious, contagious, or communicable disease may consent to medical care related to the diagnosis or treatment of the disease, if the disease or condition is one that is required by law or regulation adopted pursuant to law to be reported to the local health officer, or is a related sexually transmitted disease, as may be determined by the State ~~Director of Health Services~~ *Public Health Officer*.



Ευχαριστώ!