Cepljenje proti HPV

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Človeški papilomavirusi (HPV) so zelo heterogena skupina virusov, ki jih povezujemo z nastankom številnih benignih in malignih novotvorb ploščatoceličnega epitelija. Dvanajst onkogenih genotipov HPV (najpomembnejša sta genotipa HPV-16 in HPV-18) je odgovornih za nastanek več kot 99 % raka materničnega vratu, 84 % raka zadnjika, 70 % raka nožnice, 47 % raka penisa, 40 % raka ženskega zunanjega spolovila (vulve) ter 28 % raka ustnega dela žrela. Nasprotno je 12 neonkogenih genotipov HPV (najpomembnejša sta genotipa HPV-6 in HPV-11) odgovornih za nastanek več kot 95 % genitalnih bradavic in ploščatoceličnih papilomov grla.

V zadnjih nekaj letih sta razvoj in uspešna uvedba profilaktičnih cepiv proti HPV omogočila pomemben napredek v učinkovitemu preprečevanju okužbe s HPV. Trenutno sta na evropskem tržišču dve profilaktični cepivi proti HPV: štirivalentno in dvovalentno. Profilaktični cepivi temeljita na uporabi t. i. virusom podobnih delcev (ang. *viral-like particles*), ki predstavljajo umetno narejene kapside HPV, sestavljene iz rekombinantnih virusnih beljakovin L1. Virusom podobni delci ne vsebujejo virusne DNA, ne morejo okužiti človeških celic, niti se v njih razmnoževati ali povzročati bolezni.

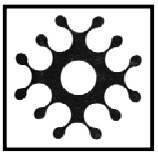
Štirivalentno cepivo vsebuje virusom podobne delce genotipov HPV-6, HPV-11, HPV-16 in HPV-18 in je v EU od septembra 2006 odobreno za preprečevanje nastanka raka materničnega vratu, predrakavih sprememb materničnega vratu, ženskega zunanjega spolovila in nožnice ter anogenitalnih bradavic. Učinkovitost štirivalentnega cepiva je bila v začetnih indikacijah v EU omejena le na HPV-6, HPV-11, HPV-16 in HPV-18, od avgusta 2010 je postavljena nekoliko širše in ni več omejena samo na zaščito pred cepilnimi genotipi HPV. Znotraj indikacij v EU s štirivalentnim cepivom lahko cepimo osebe ženskega spola od 9. leta starosti dalje, brez zgornje omejitve starosti. Ameriška FDA je štirivalentno cepivo odobrila za oba spola: pri ženskah v starosti 9-26 let za preprečevanje štirih rakov: raka materničnega vratu, raka ženskega zunanjega spolovila, raka nožnice

in raka zadnjika, predrakavih sprememb navedenih rakov (CIN1-3, adenokarcinom in situ, VIN2-3, VaIN2-3, AIN1-3) in anogenitalnih bradavic ter pri moških v starosti 9-26 let za preprečevanje raka zadnjika, predrakavih sprememb zadnjika (AIN1-3) ter anogenitalnih bradavic. Ameriška FDA omejuje učinkovitost štirivalentnega cepiva pri obeh spolih na HPV-6, HPV-11, HPV-16 in HPV-18. Osnovno cepljenje s štirivalentnim cepivom se izvaja s tremi posameznimi odmerki cepiva po shemi 0., 2., 6. mesec.

Dvovalentno cepivo vsebuje virusom podobne delce genotipov HPV-16 in HPV-18 in je v EU od septembra 2007 odobreno za preprečevanje raka materničnega vratu in predrakavih sprememb materničnega vratu (CIN1-3, adenokarcinom in situ). Učinkovitost dvovalentnega cepiva je bila v EU v začetnih indikacijah omejena le na HPV-16 in HPV-18, od avgusta 2010 je postavljena nekoliko širše in ni več omejena samo na zaščito pred cepilnimi genotipi HPV. Znotraj indikacije v EU lahko cepimo osebe ženskega spola v starosti od 10 do 25 let. Ameriška FDA je odobrila enake indikacije za dvovalentno cepivo kot EMA, vendar omejuje učinkovitost cepiva na HPV-16 in HPV-18. Osnovno cepljenje z dvovalentnim cepivom se izvaja s tremi posameznimi odmerki cepiva po shemi 0., 1., 6. mesec.

Do marca 2011 je bilo z obema HPV-cepivoma cepljenih več kot 50 milijonov ljudi. Idealni čas cepljenja proti HPV je obdobje pred prvimi spolnimi odnosi in ni neposredno vezan na starost. Glede na to, da cepljenje ščiti predvsem pred boleznimi, ki jih povzročajo genotipi virusa, vključeni v cepivo, je pri cepljenih ženskah zaenkrat treba izvajati presejalne preglede za odkrivanje predrakavih sprememb materničnega vratu v enakem obsegu in na enak način kot pri necepljenih. Cepivi proti HPV nimata nobenega merljivega terapevtskega učinka in zato nista indicirani za zdravljenje raka materničnega vratu in drugih s HPV povezanih rakov ali za zdravljenje in preprečevanje napredovanja predrakavih sprememb materničnega vratu, ženskega zunanjega spolovila, nožnice in zadnjika. Razvoj profilaktičnih cepiv proti HPV druge generacije temelji na vključevanju večjega nabora genotipov HPV, nižanju njihove cene, večanju temperaturne obstojnosti cepiva ter enostavnejši aplikaciji (npr. transdermalna ali intranazalna aplikacija).

Cepljenje proti HPV



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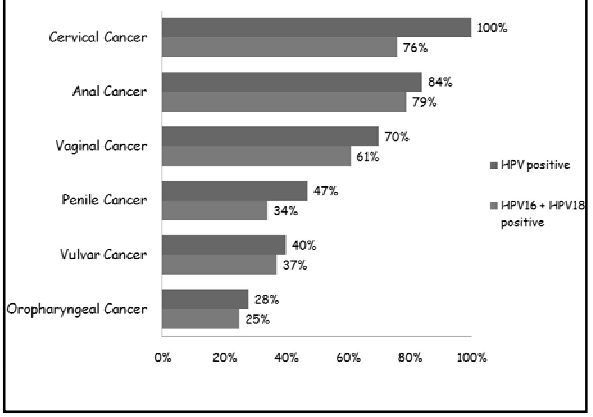
high-risk HPV genotypes (12)

16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59

Bouvard V et al.
A review of human carcinogens - Part B: biological agents.
Lancet Oncol. 2009;10:321-2.



low-risk HPV genotypes (12)

6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, CP6108

	MSD Silgard™, Gardasil™ Quadrivalent vaccine HPV-6, HPV-11, HPV-16, HPV-18	GSK Cervarix™ Bivalent vaccine HPV-16, HPV-18
Expression system	Yeast (*Saccharomyces cerevisiae*)	Insect cells (baculovirus)
Composition (quant.)	20 µg HPV-6 L1 protein 40 µg HPV-11 L1 protein 40 µg HPV-16 L1 protein 20 µg HPV-18 L1 protein	20 µg HPV 16 L1 protein 20 µg HPV 18 L1 protein
Adjuvant	Aluminum hydroxyphosphate sulfate	AS04
Dose and administration	0.5 ml, intramuscular	0.5 ml, intramuscular
Schedule	0, 2, and 6 months	0, 1, and 6 months

EMA

Gardasil is a vaccine for use from the age of 9 years for the prevention of:
- premalignant genital lesions (cervical, vulvar and vaginal) and cervical cancer causally related to certain oncogenic Human Papillomavirus (HPV) types
- external genital warts (condyloma acuminata) causally related to specific HPV types.

See sections 4.4 and 5.1 for important information on the data that support this indication.

FDA

GARDASIL is a vaccine indicated in girls and women 9 through 26 years of age for the prevention of the following diseases caused by Human Papillomavirus (HPV) types included in the vaccine:
- cervical, vulvar, vaginal, and anal cancer caused by HPV types 16 and 18
- genital warts (condyloma acuminata) caused by HPV types 6 and 11

and the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, and 18:
- cervical intraepithelial neoplasia (CIN) grade 2/3 and cervical adenocarcinoma *in situ* (AIS)
- cervical intraepithelial neoplasia (CIN) grade 1
- vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
- vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3
- anal intraepithelial neoplasia (AIN) grades 1, 2, and 3

Status: 02 April 2011

EMA

FDA

GARDASIL is indicated in boys and men 9 through 26 years of age for the prevention of the following diseases caused by HPV types included in the vaccine:

- anal cancer caused by HPV types 16 and 18
- genital warts (condyloma acuminata) caused by HPV types 6 and 11

and the following precancerous or dysplastic lesions caused by types 6, 11, 16, and 18:

- nal intraepithelial neoplasia (AIN) grades 1, 2, and 3.

Status: 02 April 2011

	MSD Silgard™, Gardasil™ Quadrivalent vaccine HPV-6, HPV-11, HPV-16, HPV-18	GSK Cervarix™ Bivalent vaccine HPV-16, HPV-18
Expression system	Yeast (*Saccharomyces cerevisiae*)	Insect cells (baculovirus)
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Adjuvant	Aluminum hydroxyphosphate sulfate	AS04
Dose and administration	0.5 ml, intramuscular	0.5 ml, intramuscular
Schedule	0, 2, and 6 months	0, 1, and 6 months

EMA

Cervarix is a vaccine for the prevention of

- premalignant cervical lesions and cervical cancer

causally related to certain oncogenic Human Papillomavirus (HPV) types.
See sections 4.4 and 5.1 for important information on the data that support this indication.
The indication is based on the demonstration of efficacy in women aged 15-25 years following vaccination with Cervarix and on immunogenicity of the vaccine in girls and women aged 10-25 years.

FDA

CERVARIX is a vaccine indicated for the prevention of the following diseases caused by oncogenic human papillomavirus (HPV) types 16 and 18:

- cervical cancer
- cervical intraepithelial neoplasia (CIN) grade 2 or worse and adenocarcinoma *in situ*
- cervical intraepithelial neoplasia (CIN) grade 1.

CERVARIX is approved for use in females 10 through 25 years of age.

Status: 02 April 2011

Lu et al. BMC Infectious Diseases 2011, 11:13
http://www.biomedcentral.com/1471-2334/11/13

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Efficacy and Safety of Prophylactic Vaccines against Cervical HPV Infection and Diseases among Women: A Systematic Review & Meta-Analysis

Beibei Lu[1], Ambuj Kumar[2], Xavier Castellsagué[2], Anna R Giuliano[1*]

Conclusion:

Prophylactic HPV vaccines are safe, well tolerated, and highly efficacious in preventing persistent infections and cervical diseases associated with vaccine-HPV types among young females.

CSIRO PUBLISHING Review
www.publish.csiro.au/journals/sh Sexual Health, 2010, 7, 320–324

Human papillomavirus vaccine safety in Australia: experience to date and issues for surveillance

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Abstract. Australia was one of the first countries to licence a quadrivalent human papillomavirus (HPV) vaccine, rapidly followed by a federally funded program of universal vaccination of a broad age group of females through schools (12 to 18 years) and primary care (19 to 26 years). As of August 2009, more than 5.8 million doses of Gardasil® (quadrivalent; Merck, New Jersey, USA) have been distributed in Australia and a total of 1394 suspected adverse events following immunisation (AEFI) have been reported to the passive surveillance system. Most reports are of common and expected reactions. Case series of more uncommon and serious AEFI, both known to be potentially vaccine related (anaphylaxis, conversion disorders and lipoatrophy) and otherwise (multiple sclerosis and pancreatitis) have been published.

Postlicensure Safety Surveillance for Quadrivalent Human Papillomavirus Recombinant Vaccine

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Laura Leidel, RN, FNP-C, MPH
Claudia Vellozzi, MD, MPH
Emily Jane Woo, MD, MPH
Wei Hua, MD, PhD
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Nancy Miller, MD
M. Miles Braun, MD, MPH
Lauri E. Markowitz, MD
John Iskander, MD

Context In June 2006, the Food and Drug Administration licensed the quadrivalent human papillomavirus (types 6, 11, 16, and 18) recombinant vaccine (qHPV) in the United States for use in females aged 9 to 26 years; the Advisory Committee on Immunization Practices then recommended qHPV for routine vaccination of girls aged 11 to 12 years.

Objective To summarize reports to the Vaccine Adverse Event Reporting System (VAERS) following receipt of qHPV.

Design, Setting, and Participants Review and describe adverse events following immunization (AEFIs) reported to VAERS, a national, voluntary, passive surveillance system, from June 1, 2006, through December 31, 2008. Additional analyses were performed for some AEFIs in prelicensure trials, those of unusual severity, or those that had received public attention. Statistical data mining, including proportional reporting ratios (PRRs) and empirical Bayesian geometric mean methods, were used to detect disproportionality in reporting.

Main Outcome Measures Numbers of reported AEFIs, reporting rates (reports per 100 000 doses of distributed vaccine or per person-years at risk), and comparisons with expected background rates.

Results VAERS received 12 424 reports of AEFIs following qHPV distribution, a rate of 53.9 reports per 100 000 doses distributed. A total of 772 reports (6.2% of all reported) described serious AEFIs, including 32 reports of death. The reporting rates per 100 000 qHPV doses distributed were 8.2 for syncope; 7.5 for local-site reactions; 6.8 for dizziness; 5.0 for nausea; 4.1 for headache; 3.1 for hypersensitivity reactions; 2.6 for urticaria; 0.2 for venous thromboembolic events, autoimmune disorders, and Guillain-Barré syndrome; 0.1 for anaphylaxis and death; 0.04 for transverse myelitis and pancreatitis; and 0.009 for motor neuron disease. Disproportional reporting of syncope and venous thromboembolic events was noted with data mining methods.

Conclusions Most of the AEFI rates were not greater than the background rates expected with other vaccines, but there was disproportional reporting of syncope and venous thromboembolic events. The significance of these findings must be tempered with the limitations (possible underreporting) of a passive reporting system.

JAMA. 2009;302(7):750-757 www.jama.com

MHRA PUBLIC ASSESSMENT REPORT

Cervarix (HPV vaccine): Update on UK safety covering the first two years of the HPV immunisation programme

October 2010

4703 case reports of suspected ADRs for Cervarix between 14/4/2008-28/7/2010, out of at least 4.5 million doses given across the UK (around 1 report per 1000 doses)

- 17% injection-site reactions
- 11% allergic reactions
- 37% side effects listed in the product information (dizziness, headache and nausea)
- 21% psychogenic' reactions, due to the injection process rather than the vaccine itself

no serious new risks identified during the extensive use of Cervarix in the UK over 2 years

balance of Cervarix benefits and risks remains positive

TABLE 1

Vaccination policy and target population (routine immunisation) in Europe, 2010 VENICE 2 human papillomavirus vaccination survey

Countries (N=28)[a]	Gender	Target age group	Coverage (3 doses, %)	Date of start
Austria	Female / Male	Girls/Women - Boys/Men before sexual debut	-	November 2006
Belgium	Female	12-18	-	November 2007
Denmark	Female	17	58 (2010)	January 2009
France	Female	14	24 (2008)	July 2007
Germany	Female	12-17	-	March 2007
Greece	Female	12-15	-	January 2008
Ireland	Female	12-13	-	May 2010
Italy	Female	11	56 (2009)	July 2007 – November 2008[b]
Latvia	Female	12	-	September 2010
Luxemburg	Female	17	17 (2009)	March 2008
Netherlands	Female	12	-	April 2010
Norway	Female	12	30 (2010)	August 2009
Portugal	Female	13	81 (2009)	October 2008
Romania	Female	12	-	November 2009
Slovenia	Female	11-12	-	September 2009
Spain	Female	11-14	-	January 2008
Sweden	Female	10-12	-	January 2010
United Kingdom	Female	12	80 (2009)	September 2008

[a] The 28 countries that have human papillomavirus in the national immunisation schedule.
[b] Depending on the region.

Dorleans F, Giambi C, Dematte L, et al.
The current state of introduction of human papillomavirus vaccination into national immunisation schedules in Europe: first results of the VENICE2 2010 survey.
Euro Surveill. 2010;15(47):pii=19730.

TABLE 2

Vaccination policy and target population (catch-up programme) in Europe, 2010 VENICE 2 human papillomavirus vaccination survey

Countries (N=9)[a]	Gender	Target age group	Coverage (3 doses, %)	Date of start
Belgium	Female	13-18	-	May 2008
Denmark	Female	15, 16, 17	73 (2010)	October 2008
France	Female	15-23	30 (2008)	July 2007
Italy	Female	11/13/16/13/24[b]	-	July 2007- January 2010[b]
Luxemburg	Female	13-18	29 (2009)	March 2008
Netherlands	Female	13-16	65 (2009)	March 2009
Portugal	Female	17	56 (2009)	January 2009
Romania	Female	17-24		January 2010
United Kingdom	Female	13-17	32 (2009)	September 2008

[a] The nine countries that have catch-up immunisation programme.
[b] Depending on the region.

Dorleans F, Giambi C, Dematte L, et al.
The current state of introduction of human papillomavirus vaccination into national immunisation schedules in Europe: first results of the VENICE2 2010 survey.
Euro Surveill. 2010;15(47):pii=19730.

Quadrivalent human papillomavirus vaccination and trends in genital warts in Australia: analysis of national sentinel surveillance data

Lancet Infect Dis 2011; 11: 39–44

Basil Donovan, Neil Franklin, Rebecca Guy, Andrew E Grulich, David G Regan, Hammad Ali, Handan Wand, Christopher K Fairley

Summary

Background Quadrivalent human papillomavirus (HPV) vaccine has high efficacy in clinical trials but no reports describe its effects at a population level. From July, 2007, Australia was the first country to fund a vaccination programme for all women aged 12–26 years. We established a national surveillance network in Australia and aimed to identify trends in diagnoses of genital warts in 2004–09.

Methods We obtained standardised data for demographic factors, frequency of genital warts, HPV vaccination status, and sexual behaviour for new patients attending eight sexual health services in Australia between January, 2004, and December, 2009. We used χ^2 analysis to identify significant trends in proportions of patients diagnosed with warts in periods before and after vaccination began. Our primary group of interest was female Australian residents who were eligible for free vaccination, although data were assessed for patients ineligible for free vaccination, including women older than 26 years of age, non-resident women, and men.

Findings Among 112 083 new patients attending sexual health services, we identified 9867 (9%) cases of genital warts. Before the vaccine programme started, there was no change in proportion of women or heterosexual men diagnosed with genital warts. After vaccination began, a decline in number of diagnoses of genital warts was noted for young female residents (59%, $p_{trend}<0·0001$). No significant decline was noted in female non-residents, women older than 26 years in July, 2007, or in men who have sex with men. However, proportionally fewer heterosexual men were diagnosed with genital warts during the vaccine period (28%, $p_{trend}<0·0001$), and this effect was more pronounced in young men. By 2009, 65·1% of female Australian residents who were eligible for free vaccine reported receipt of quadrivalent or unknown HPV vaccine.

Interpretation The decrease in frequency of genital warts in young Australian women resulting from the high coverage of HPV vaccination might provide protective effects in heterosexual men through herd immunity.

Prophylactic HPV vaccines- Unresolved issues I

What fraction of cervical cancer overall will be prevented ?

Cross-protection ?

Will booster vaccinations be necessary, and if so, when ?

TIME WILL TELL

Prophylactic HPV vaccines- Unresolved issues II

Which vaccine is better ?

- considerable marketing efforts have been made to compare the two vaccines in relation to the HPV 16 and HPV 18 components
- markedly different populations/subpopulations were used in each of the vaccine trials
- direct comparison of trials' results impossible

Prophylactic HPV vaccines – unresolved issues III

Completion of the HPV vaccine schedule & small coverage

- at least 80% of pre-adolescent girls need to be vaccinated against HPV to achieve a major reduction in cervical cancer rates in women aged 20–29 years by 2025

- great majority of countries are struggling to achieve high coverage and/or to reach the level of coverage that will have the most impact on cancer rates

Prophylactic HPV vaccines – unresolved issues IV

Improving girls'/parents/medical workers understanding of HPV infection & vaccination

Prophylactic HPV vaccines – unresolved issues V

HPV vaccination of women aged 26 years & above

HPV vaccination of males

- until there is high HPV vaccine coverage among targeted groups, broadening the population eligible for (free) vaccination should be approached with caution

- it is important to maintain clarity about the primary purpose of HPV vaccination and to ensure that information, delivery systems and finances are in place to achieve that purpose

- vaccination of men or older women could offer individual benefit but this may confuse the public, which is already unclear about age selection

Prophylactic HPV vaccines – unresolved issues VI

Monitoring of long-term safety and vaccine disease efficacy

- given the likely absence of further large Phase III clinical trials, it is extremely important that countries with national vaccination programs comprehensively evaluate long-term safety and any breakthrough infections of HPV vaccine types over the short and longer term

- linkage of vaccination history and cervical screening history is necessary

Prophylactic HPV vaccines – unresolved issues VII

Integration of primary & secondary cervical cancer prevention

- a clear strategy for integrating primary (HPV vaccination) and secondary prevention (cervical screening/HPV testing) must emerge ASAP

- cervical screening guidelines have to be reviewed in the next 5-10 years

- there is an increasing acceptance that screening based on HPV testing would be better than continuing with cytology as the primary screen

Prophylactic HPV vaccines – unresolved issues VIII

The price of HPV vaccine MUST go down substantially !

it would NOT be a satisfactory outcome if HPV vaccines are proven to be safe and effective

but

are not made available to the women of the world who are most in need of them

HPV Prophylactic Vaccines – second generation

- polyvalent VLP L1 vaccines
- L1 capsomers (pentameric subunit of VLP)
- VLP L2 vaccines
- new adjuvants-based vaccines