Väestöliitto

Efficacy of HPV vaccination in males

Dan Apter
dan.apter@vaestoliitto.fi
Chief Physician & Director
The Sexual Health Clinic
Väestöliitto, Family Federation of Finland

Disclosure

- I have as an employee of Väestöliitto participated as the principal investigator in research projects of GSK, Bayer-Schering, Merck/Organon, Wyeth, WHO, and Population Council during the last 5 years. Väestöliitto has been paid for conducting the research.
- I have given lectures at educational occasions organized by health care and medical companies, participated in various meetings paid by these (Merck, GSK, Bayer-Schering, Organon, Wyeth, WHO, and Population Council)
- Member of the working group of HPV prevention 2008-11, National Public Health Institute.

Content

- HPV disease burden in men
- Other means of limiting HPV epidemy
  - Sexuality education
  - Condom use
  - Circumcision
- Efficacy of HPV vaccination in phase III
- Immunology
- International recommendations

Estimated proportions of HPV-positive cancers (Parkin & Bray, Vaccine monograph, 2006):

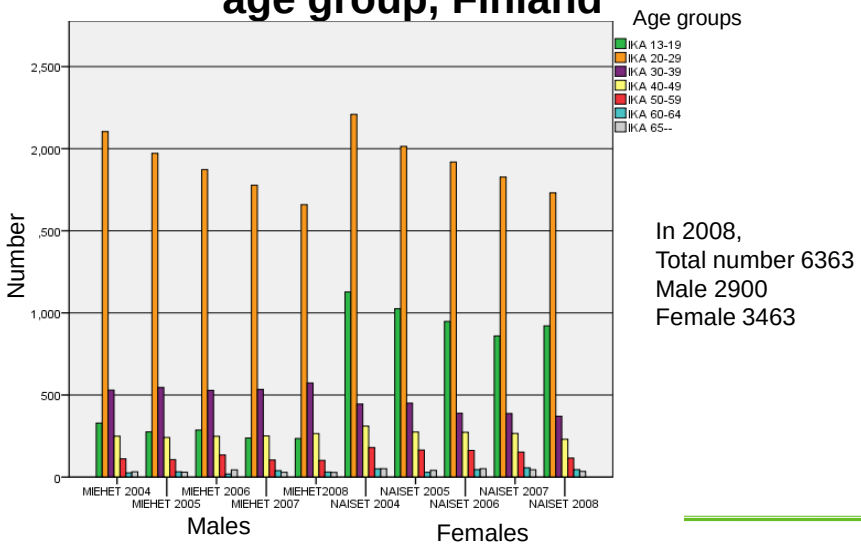
Primary site	HPV positive	HPV16/18 –positive
Cervix [f]	1.00	0.70
Vulva [f]	0.40	0.32
Vagina [f]	0.40	0.32
Penis [m]	0.40	0.25
Anus[B] [f+m]	0.90	0.83
Mouth [f+m]	0.03	0.03
Oropharynx [f+m][B]	0.12	0.11
Tonsil f+m	0.45	0.40
Tonsil f+m, <40 years	0.90	0.65

Number of new HPV-related cancers and cases of death in Finland. Based on Finnish Cancer register February 2011

Primary site	New cases, annual average 2004-2008			Cancer deaths, annual average 2004-2008		
	All ages	0-39 y	40+ y	All ages	0-39 y	40+ y
Cervix (f)	151	43	109	56	4	52
Vulva (f)	88	2	78	27	<0,5	27
Vagina (f)	21	<0,5	21	13	0	13
Penis (m)	24	1	23	7	0	7
Anus (f)	23	1	22	9	<0,5	9
Anus (m)	15	<0,5	15	5	<0,5	5
Oropharynx (f)	3	<0,5	3	1	0	1
Oropharynx (m)	9	<0,5	9	3	0	3
Tonsil (f)	13	1	12	4	<0,5	3
Tonsil (m)	35	1	34	12	0	12

THL Report 28/2011 (Papilloomavirustautien torjuntatyöryhmän selvitys)

Estimated number of condyloma cases among men and women 2004-2008 per age group, Finland



In 2008,
Total number 6363
Male 2900
Female 3463

THL Report 28/2011 (Papilloomavirustautien torjuntatyöryhmän selvitys)

Epidemiology and pathology of HPV disease in males

- More than 90% of genital warts are caused by non-oncogenic HPV types 6 and 11.
- Genital HPV infection is very common in men with estimated prevalence of 65% in males 18-70 years. Lifetime number of sexual partners was the most significant risk factor for HPV infection, and circumcision has been associated with reduced risk.
- HPV infection may be less likely to persist in men than in women. In men, median time to clearance was 5,9 months, with 75% of infections clearing within 12 months

Giuliano et al, Gynecologic Oncology 2010

Sex and HIV Education Programs: Their Impact on Sexual Behaviors of Young People Throughout the World

- Douglas B. Kirby, B.A. Laris, Lori A. Rolleri
- Journal of Adolescent Health 2007, 40: 206–217
- reviews 83 studies that measure the impact of curriculum-based sexuality education programs on sexual behavior and mediating factors < 25 years anywhere in the world.

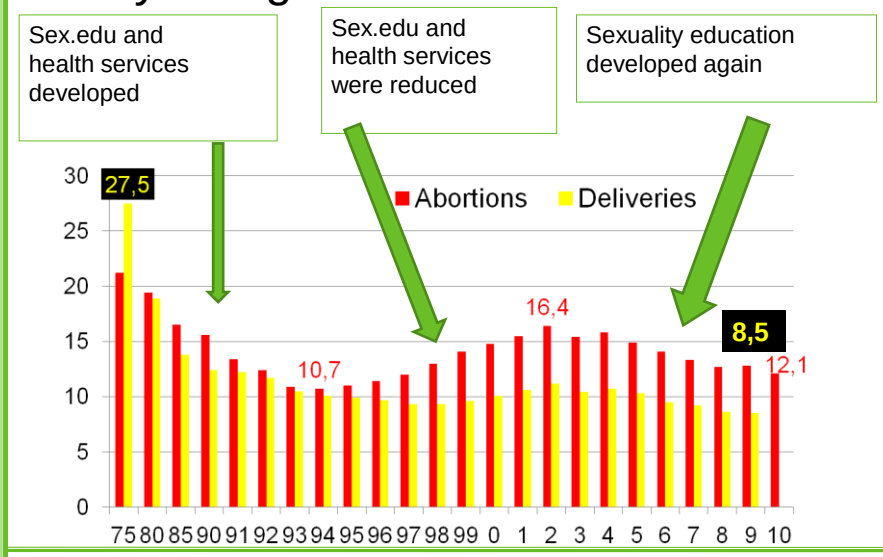
Sexuality education works !

- Two thirds of the programs significantly improved one or more aspects of sexual behavior.
- The evidence is strong that programs do not hasten or increase sexual behavior but, instead, some programs delay or decrease sexual behaviors or increase condom or contraceptive use.
- Programs were effective across a wide variety of countries, cultures, and groups of youth.
- Of the 54 studies measuring program impact on condom use, almost half (48%) showed increased condom use; none found decreased condom use.

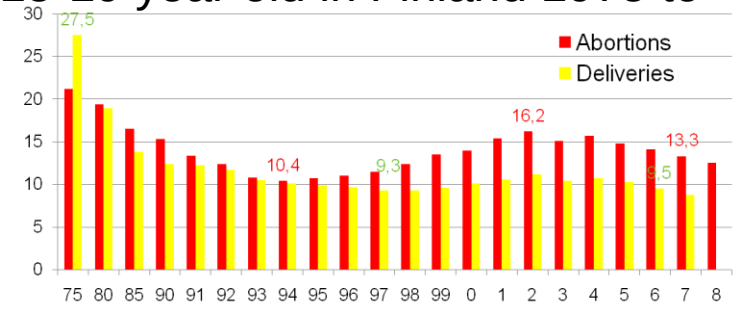
Sexual abstinence only programmes to prevent HIV infection in high income countries: systemic review Underhill et al BMJ 2007

- 13 trials enrolling 16 000 US youths identified, all outcomes were self reported
- No program affected incidence of unprotected sex, number of partners, condom use, or sexual initiation

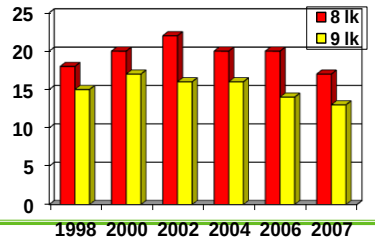
Abortions and deliveries (per 1000) in 15-19 yr old girls in Finland 1975 - 2010



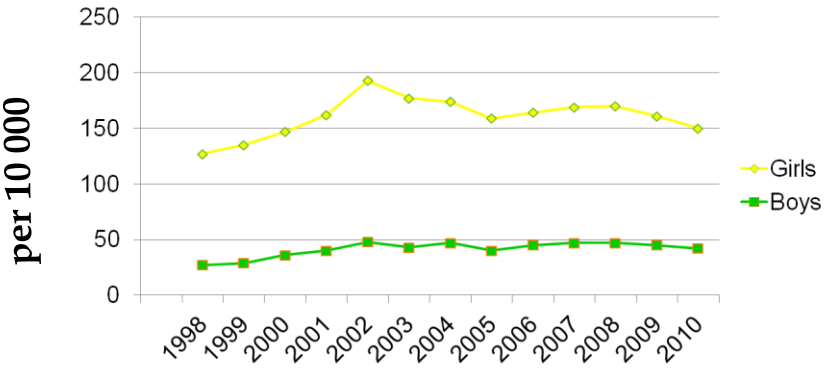
Abortions and deliveries per 1000 girls 15-19 year old in Finland 1975 to - 2008



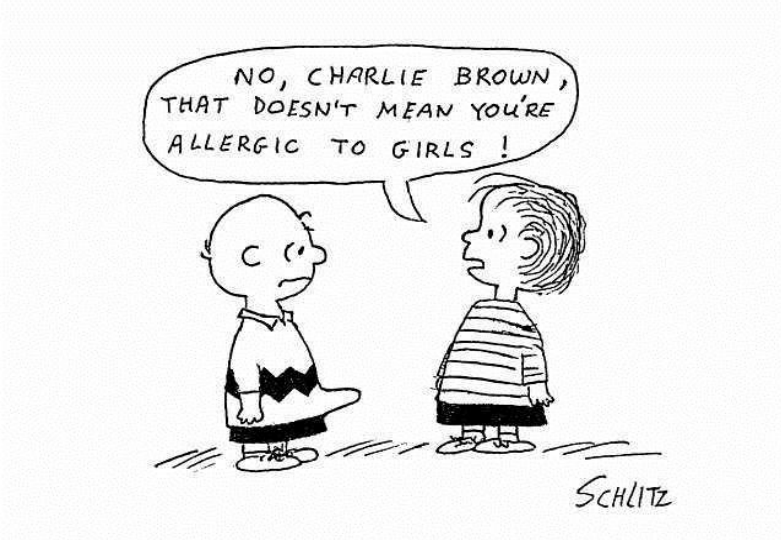
%-girls who did not use contraception at last intercourse



Reported number of chlamydia among 15-19 yr old girls and boys in Finland 1988-2010



Boys lack adequate knowledge



Circumcision reduces HPV and HIV infections

- Giuliano AR et al. Circumcision and sexual behavior: factors independently associated with human papillomavirus detection among men in the HIM study. Int J Cancer 124:1251-7, 2009
- Tobian AA et al. Male circumcision for the prevention of HSV-2 and HPV infections and syphilis. New Engl J Med 360:1298-309, 2009
- Wawer et al. Effect of circumcision of HIV-negative men on transmission of human papillomavirys to HIV-negative women: a randomised trial in Rakai, Uganda. Lancet 2011

Condom use reduce HPV infections

But exact evaluation very difficult

- Hernandez BY ym. Transmission of human papillomavirus in heterosexual couples. Emerg Inf Dis 14:888-94, 2008
- Nielson CM ym. Consistent condom use is associated with lower prevalence of human papillomavirus infection in men. J Infect Dis 202:445-51, 2010
- Winer RL ym. Condom use and the risk of genital human papillomavirus infection in young women. New Engl J Med 354:2645-54, 2006

Efficacy of Quadrivalent HPV Vaccine against HPV Infection and Disease in Males; Giuliano et al NEJM 2011

- Randomized, placebo-controlled, double-blind trial, 4065 healthy males 16 to 26 years of age, with 1-5 partners.
- Primary efficacy objective was to show that the quadrivalent HPV vaccine reduced the incidence of external genital lesions related to HPV-6, 11, 16, or 18.
- Efficacy analyses were conducted in a per-protocol population, in which subjects received all three vaccinations and were negative for relevant HPV types at enrollment, and in an intention-to-treat population, in which subjects received vaccine or placebo, regardless of baseline HPV status.

Efficacy of Quadrivalent Vaccine against the Development of External Genital Lesions in the Intention-to-Treat Population

	Cases of EGL	Rate no./100 person-yr at risk	Cases of EGL	Rate no./100 person-yr at risk	**Observed efficacy % (95% CL)**
HPV type					
Any type	36	0,80	89	2,00	60,2 (40,8 to 73,8)
Type 6, 11, 16 or 18	27	0,58	77	1,69	**65,5** (45,8 to 78,6)
Sexual orientation					
Heterosexual males	21	0,51	57	1,39	63,7 (39,3 to 79,1)
Males who had sex with male partners	6	1,27	20	4,26	70,2 (23,0 to 90,2)
Lesion type					
Condyloma acuminatum	24	0,52	72	1,58	67,2 (47,3 to 80,3)
All PIN lesions	6	0,13	5	0,11	-19,2 (-393 to 69,7)

Giuliano et al NEJM 2011

Efficacy of Quadrivalent Vaccine Efficacy against External Genital Lesions in the Per-Protocol Population

Variable	Quadrivalent HPV Vaccine		Placebo		Observed Efficacy
	Cases of EGL	Rate no./100 person-yr at risk	Cases of EGL	Rate no./100 person-yr at risk	% (95% CI)
HPV type					
Any type	6	0.20	36	1.20	83.8 (61.2 to 94.4)
Type 6, 11, 16 or 18	3	0.11	31	1.10	**90.4** (69.2 to 98.1)
Type 6	3	0.12	19	0.74	84.3 (46.5 to 97.0)
Type 11	1	0.04	11	0.43	90.9 (37.7 to 99.8)
Type 16	0	0.00	2	0.08	100 (-420.8 to 100)
Type 18	0	0.00	1	0.04	100 (-3804 to 100)

Giuliano et al NEJM 2011

Efficacy of Quadrivalent Vaccine Efficacy against External Genital Lesions in the Per-Protocol Population

Variable	Quadrivalent HPV Vaccine		Placebo		Observed Efficacy
	Cases of EGL	Rate no./100 person-yr at risk	Cases of EGL	Rate no./100 person-yr at risk	% (95% CI)
Lesion type					
Condyloma acuminatum	3	0.11	28	1.00	89.4 (65.5 to 97.9)
All PIN lesions	0	0.00	3	0.11	100 (-141.2 to 100)

Giuliano et al NEJM 2011

Efficacy against Persistent Infection with HPV type 6, 11, 16, 18 in the Intention-to-Treat Population

Variable	Quadrivalent HPV Vaccine (N=1817)		Placebo (N= 1815)		Observed Efficacy
Persistent infection	Cases	Rate no./100 person-yr at risk	Cases	Rate no./100 person-yr at risk	% (95% CI)
HPV type					
Type 6, 11, 16 or 18	148	3.61	273	6.92	47.8 (36.0 to 57.6)
Type 6	63	1.50	112	2.71	44.7 (24.1 to 60.1)
Type 11	16	0.37	39	0.92	59.4 (25.7 to 78.8)
Type 16	71	1.69	131	3.19	46.9 (28.6 to 60.8)
Type 18	25	0.59	56	1.33	56.0 (28.2 to 73.7)
Sexual orientation					
Heterosexual males	96	2.58	187	5.20	50.4 (36.2 to 61.1)
Males who had sex with male partners	52	14.03	274	24.87	43.6 (19.5 to 60.8)

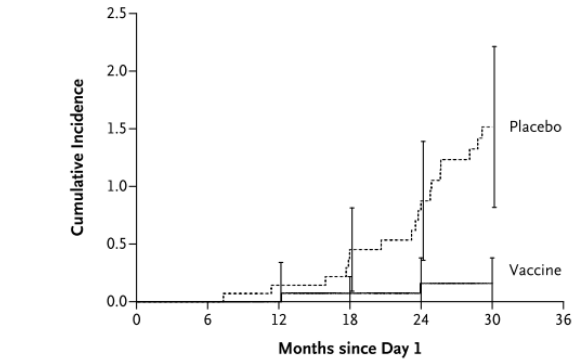
Giuliano et al NEJM 2011

Summary of Adverse Events

Adverse Events, entire study period	Quadrivalent HPV Vaccine	Placebo	P Value
No of subjects with follow-up data	1945	1950	
No event	599 (30.8)	698 (35.8)	
One or more events	1346 (69.2)	1252 (64.2)	<0.001
Injection site	1169 (60.1)	1047 (53.7)	<0.001
Systemic	616 (31.7)	622 (31.9)	0.88
Vaccine related events	1242 (63.9)	1134 (58.2)	<0.001
Injection site	1169 (60.1)	1046 (53.6)	<0.001
Systemic	274 (14.1)	284 (14.6)	0.67
Serious events	8 (0.4)	11 (0.6)	0.49
Serious vaccine-related events	0	0	1.00
Death	3 (0.2)	10 (0.5)	0.052

Giuliano et al NEJM 2011

External genital lesions related to types 6,11, 16 and 18 in the per protocol population



No. at Risk						
Vaccine	1397	1397	1367	1267	1166	983
Placebo	1408	1408	1374	1267	1149	949

Giuliano et al NEJM 2011

THE IMMUNOGENICITY OF QUADRIVALENT HPV (TYPES 6/11/16/18) VACCINE IN MALES AGED 16-26

- Serum samples were collected prior to vaccination at day 1, and at months 7, 24 and 36 post vaccination in 3,463 heterosexual men and 602 men who had sex with men.
- Immunogenicity was evaluated with a multiplex, competitive Luminex Immunoassay.
- Almost all subjects (97.4-99.2%) seroconverted for vaccine HPV types by month 7. At month 36, 89%, 94%, 98% and 57% of subjects were still seropositive for HPV 6, 11, 16 and 18. GMT lower than in women

Hillman et al, Clin. Vaccine Immunol 2011

Immunogenicity and Safety of HPV-16/18 AS04-Adjuvanted Vaccine in Healthy Boys Aged 10–18 Years

- Healthy males aged 10 to 18 years were randomized (2:1 ratio) to receive HPV-16/18 AS04-adjuvanted vaccine (Cervarix) (181) or hepatitis B virus (HBV) control vaccine (89) at 0, 1, and 6 months, and were followed for 7 months.
- All initially seronegative subjects in the HPV-16/18 group seroconverted for HPV-16 and 18 (ELISA) at month 2. At month 7, all subjects were seropositive, and the HPV-16 and -18 antibody levels were, respectively, four- and twofold higher than at month 2.
- The anti-HPV-16 and -18 antibody responses for males aged 10 to 18 years and 10 to 14 years, respectively, were higher than those reported for females aged 15 to 25 years and 10 to 14 years, respectively, in a previous study

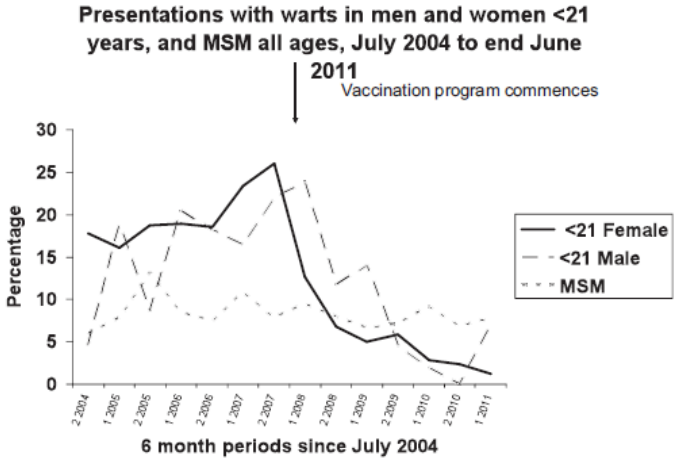
Petäjä et al, Journal of Adolescent Health 44 (2009) 33–40

The near disappearance of genital warts in young women 4 years after commencing a national HPV vaccination programme

- Australia introduced free quadrivalent HPV vaccine for 12-13 year-old girls mid-2007; with catch-up for women aged <26 years until the end of 2009.
- From 2004 to 2011, 52 454 new patients were seen at Melbourne Sexual Health Centre and 5021 (9.6%) were diagnosed with GW. From 2004 to 2007, the proportions with GW did not change.
- Comparing the two 12-month periods of 2007/2008 and 2010/2011, GW declined in women <21 years from 18.6% to 1.9% and in heterosexual men <21 years from 22.9% to 2.9%.

Read et al, Sex Transm Infect 2011

Proportion of patients aged <21 diagnosed as having genital warts at Melbourne Sexual Health Centre



Read et al, Sex Transm Infect 2011

Australian recommendation

- The PBAC recommended extension of the National Immunisation Program listing of quadrivalent human papillomavirus to include ongoing administration to males approximately 12-13 years of age in a school-based program
- and for two catch-up cohorts for all males in the two year groups above the ongoing cohort, delivered over two years, on the basis of acceptable cost effectiveness compared with female-only vaccination.

Summary

- Immunogenicity of HPV vaccines seem similar in males and females, good response
- No safety concerns
- Quadrivalent HPV vaccine seems to have high efficacy against EGL in males
- Herb immunity works with high coverage as example from Australia indicates.
- Phase IV population based trial of vaccinating girls/boys in Finland
- Recommendations of vaccinating also boys in improving sexual health coming?

Reported number of STI:s in Finland

	Chlamydia	Gc	Syfilis	HIV
1990	12567	2326	32	89
1991	11245	1426	37	57
1992	11462	993	33	93
1993	9883	781	48	62
1994	8289	493	63	69
1995	9317*	331	122	72
1996	9438	182	148	69
1997	10175	218	172	71
1998	10654	269	187	81
1999	10660	243	116	143
2000	11731	287	212	144
2001	12142	247	159	127
2002	13661	235	128	131
2003	12862	189	132	131
2004	13365	252	109	130
2005	12697	240	144	140
2006	13850	236	129	193
2007	13973	194	188	187
2008	13873	200	216	148
2009	13246	239	202	178
2010	12 825	256	208	187

Chlamydia reprting system changed in 1995

KTL

- **Quadrivalent HPV vaccine indications**
- •Females and males, 9 through 26 years
- •Prevention of the following diseases caused by HPV types 6, 11, 16, 18
- -Cervical cancer
- -Vulvar cancer
- -Vaginal cancer
- -Anal cancer*
- -Genital warts*
- -Cervical adenocarcinoma in situ (AIS)
- -Cervical intraepithelial neoplasia (CIN) grades 1 – 3
- -Vulvar intraepithelial neoplasia (VIN) grades 2 and 3
- -Vaginal intraepithelial neoplasia (VaIN) grades 2 and 3
- •No data from vaccine trials on efficacy against oropharyngeal cancer, penile cancer, RRP
- *males and females
- http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM094042

How good is the evidence for effect of sexuality education on different outcomes?

▪ Improved knowledge	Strong
▪ Improved skills	Good
▪ Less risk behaviour	Good
▪ Contraceptive use	Mixed
▪ Pregnancy reduction	Weak
▪ STI prevention	Weak

Judith Stephenson
Margaret Pyke Professor of Sexual Health, UK

Summary of Adverse Events

Adverse Events, in first 15 days after injection	Quadrivalent HPV Vaccine	Placebo no (%)	P Value
No event	600 (30.8)	706 (36.2)	
One or more events	1345 (69.2)	1244 (63.8)	<0.001
Injection site	1169 (60.1)	1047 (53.7)	<0.001
Systemic	615 (31.6)	613 (31.4)	0.90
Vaccine-related events	1242 (63.9)	1134 (58.2)	<0.001
Injection site	1169 (60.1)	1046 (53.6)	<0.001
Systemic	247 (14.1)	248 (14.6)	0.67
Serious events	5 (0.3)	1 (0.1)	0.10
Serious vaccine-related events	0	0	1.00
Death	0	0	1.00

Giuliano et al NEJM 2011

Clamydia in the Nordic countries 2002-2008