NATIONAL INSTITUTE FOR HEALTH AND WELFARE

No type-replacement following papillomavirus vaccination

The National Medicine 2012 Convention

12 January 2012

Introduction (1)

•We cannot predict whether HPV mass vaccination will change the distribution of high-risk HPV types in the population because the population biology and the potential risk for competition between HPV types are not well understood.

•Overall, 20-30% of women with cervical HPV infections haver more than one HPV type regardless of lesion degree. (Moscicki et al. J Infect Dis 2004:190, 37-45)

•The presence of cervicovaginal HPV infections increase the risk of acquisition of new HPV types. (references)

•These observations favor co-infection rather than super infection which implies that HPV type-replacement is unlikely.

Introduction (2)

Table 3. Adjusted IRR with 95% CI for HPV6, 11, 16, 18, 31, 33 and 45 in initially HPV16 or HPV18 seropositive women compared to initially seronegative women using Poisson regression main effect models ($N = 3183$, an FMC-serum bank subsample of 123,773 women <29 years of age with a minimum of two pregnancies between 1995 and 2003)

	Follow-up					
Baseline	**HPV6**	**HPV11**	**HPV16/HPV18**	**HPV31**	**HPV33**	**HPV45**
Seronegative						
IRR	1.0	1.0	1.0/1.0	1.0	1.0	1.0
Seropositive						
HPV16						
IRR	0.3 (0.1–0.9)	1.2 (0.5–2.7)	n.a./2.6 (1.1–6.0)	0.9 (0.4–1.9)	3.2 (2.0–5.2)	2.4 (1.6–7.1)
HPV16 only						
IRR	0.2 (0.1–1.0)	0.0 (0.0–∞)	n.a./3.0 (1.1–8.2)	0.3 (0.0–1.9)	2.9 (1.6–5.4)	1.2 (0.3–5.4)
HPV18						
IRR	0.4 (0.1–1.3)	1.9 (0.8–4.3)	1.4 (0.6–3.2)/n.a.	1.9 (1.0–3.7)	3.6 (2.1–5.9)	6.4 (3.0–14)
HPV18 only						
IRR	0.5 (0.1–3.3)	2.3 (0.7–7.8)	1.2 (0.4–4.0)/n.a.	1.8 (0.6–5.9)	2.5 (1.1–6.0)	2.9 (0.6–13)

n.a.: not applicable.

Merikukka et al. Int. J. Cancer 2011:128, 1114-1119

Introduction (3)

•Less common hrHPV types may fill the ecological niche following HPV16/18 vaccination.

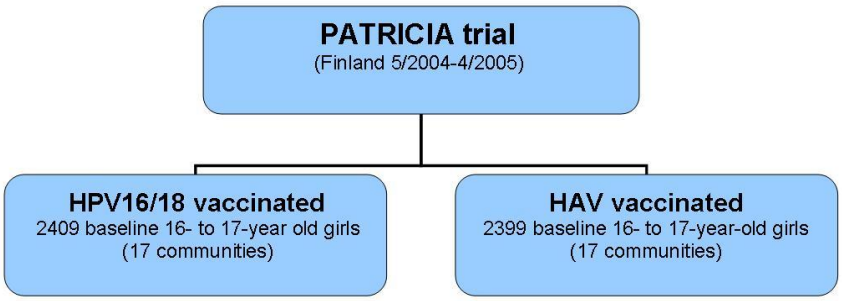
•To explore type-replacement related to HPV mass vaccination using a prophylactic HPV16/18 virus-like particle vaccine (Cervarix™, GlaxoSmithKline Biologicals) with documented cross-protective efficacy against HPV types 31 and 45, we studied occurence of HPV types in adolescent females participating a population based phase III trial PATRICIA

•PATRICIA= PApilloma TRIal against Cancer In young Adults)

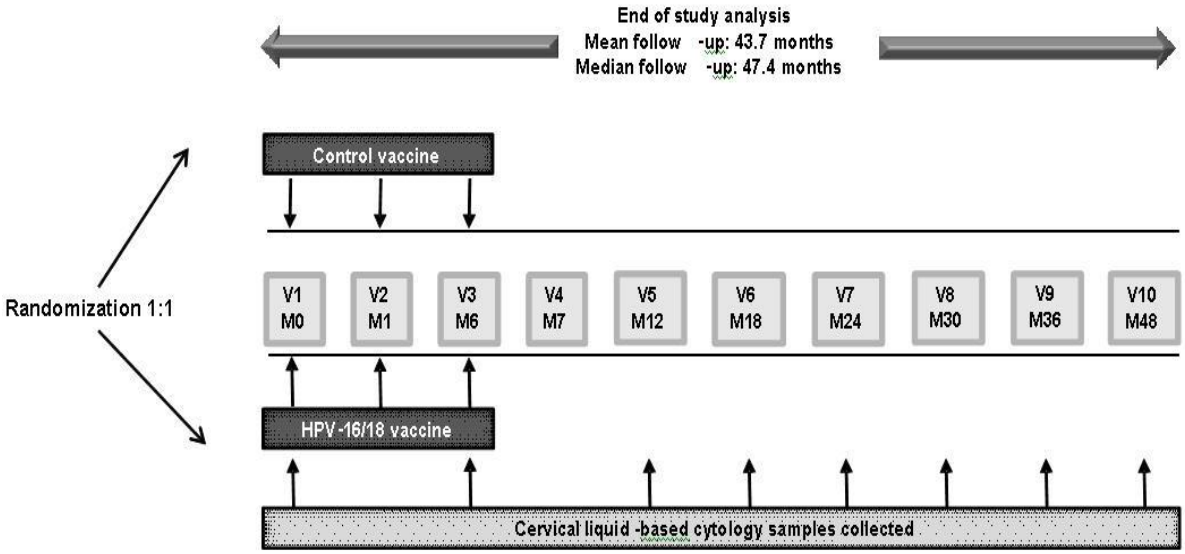
Methods (1) - Participants

•All 24 046 healthy Finnish women aged 16-17 years from 17 Finnish study site communities were eligible and invited into an PATRICIA by two personal invitation letters between May 2004 and April 2005

•They were eligible regardless of their baseline HPV DNA status, HPV serostatus or cytology. No exclusion criteria based on the lifetime number of sexual pertners were used.



Methods (2) - Prosedures



Statistical methods (1)

•Time elapsed between withdrawals of the consecutive and two consecutive positive samples varied from 6 moths and 6 to 48 months, respectively.

•Hence we used person-time based statistical approach to evaluate if a cervical infection by HPV16 or HPV18 PCR positivity was associated with an incident cervical HPV type 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 or 68/73 infection identified by PCR at one or more of the consecutive study visits.

•We calculated incidence rates (IR) per 1000 person years, and used a Poisson regression model to calculate incidence rate ratios (IRR) 95% confidence intervals (CI) for estimating the risk of infection with different HPV types after initial infection indicated by PCR for at least one HPV type (HPV16 or HPV18) compared to those negative for these HPV types.

Statistical methods (2)

•A deviance test was used to evaluate the fit of the main effect Poisson models

•The Poisson regression models were fitted to adjust for confounding factors, i.e., vaccination coverage and risk-taking sexual behaviour

•*Chlamydia trachomatis* PCR screening was performed annually, and positive result was used as a surrogate marker for risk taking behaviour)

•All the statistical analyses were done using PASW 18.0 (SPSS Inc., Chicago, IL) and the Genmod procedure SAS 9.1 (SAS Institute INC., Cary, NC)

Results – species A5, A7, A9 and A10

Table 1. Risk of acquiring human papillomavirus (HPV) species A5, A7, A9 or A10 in baseline HPV16 or HPV18 positive individuals compared to baseline HPV16/18 negative individuals among HPV16/18 or hepatitis A (HAV) vaccinated Finnish PATRICIA participants (N = 2409 and 2399, respectively) followed-up by cervical sampling every 6 months for 4 years (crude/adjusted incidence rate ratios (IRR) with 95% confidence interval)

Baseline status	Follow-up findings							
	HPVA5 Pos¶ IRR (95% CI)	Adjusted§ HPVA5 Pos¶ IRR (95% CI)	HPVA7 Pos¶ IRR (95%CI)	Adjusted§ HPVA7 Pos¶ IRR (95% CI)	HPVA9 Pos¶ IRR (95% CI)	Adjusted§ HPVA9 Pos¶ IRR (95% CI)	HPVA10 Pos¶ IRR (95% CI)	Adjusted§ HPVA10 Pos¶ IRR (95% CI)
HPV16/18 vaccinated								
HPV16/18 neg (n=165)	(65) 1.0	1.0	(68) 1.0	1.0	(76) 1.0	1.0	(50) 1.0	1.0
HPV16 pos# (n=53)	(21) 0.9 (0.6,1.5)	1.0 (0.6,1.6)	(20) 0.9 (0.5,1.4)	0.9 (0.5-1.4)	(27) 1.2 (0.7,1.8)	1.2 (0.8,1.9)	(7) 0.4 (0.2,0.9)	1.0 (0.6,1.7)
HPV18 pos# (n=24)	(9) 1.2 (0.6,2.3)	1.1 (0.5,2.2)	(8) 0.9 (0.4,1.8)	0.9 (0.4-1.8)	(8) 0.8 (0.4,1.7)	0.9 (0.4,1.8)	(7) 1.3 (0.6,2.9)	1.2 (0.6-2.7)
HAV vaccinated								
HPV16/18 neg (n=168)	(54) 1.0	1.0	(75) 1.0	1.0	(107) 1.0	1.0	(38) 1.0	1.0
HPV16 pos# (n=56)	(21) 1.2 (0.7,1.9)	0.9 (0.5,1.6)	(32) 1.3 (0.9,1.9)	1.3 (0.8,1.9)	(35) 0.9 (0.6,1.3)	0.9 (0.6,1.3)	(21) 1.7 (1.0°,2.9)	1.7 (1.0°,2.8)
HPV18 pos# (n=26)	(11) 1.3 (0.7,2.6)	1.0 (0.4,2.2)	(15) 1.7 (1.0°,2.9)	1.8 (1.0°,3.1)	(15) 1.0 (0.6,1.6)	0.9 (0.5,1.6)	(6) 1.0 (0.4,2.4)	1.1(0.5,2.6)

* > 1.0, ° < 1.0, # baseline positives for HPV16 or HPV18 only, §Poisson regression analysis: adjusted for *Chlamydia trachomatis* and community vaccination coverage, ¶ number ( ) of positives for A5 = HPV51, or A7 = any of HPV39/45/59/68, or A9 = any of HPV31/33/35/52/58, or A10 = any of HPV6/11

Results – at least partially covered by the HPV16/18 vaccine

Table 2. Risk of acquiring human papillomavirus (HPV) types at least partially covered by the HPV16/18 vaccine in baseline HPV16 or HPV18 positive individuals compared to baseline HPV16/18 negative individuals among HPV16/18 or hepatitis A (HAV) vaccinated Finnish PATRICIA participants (N = 2409 and 2399, respectively) followed-up by cervical sampling every 6 months for 4 years (crude/adjusted incidence rate ratios (IRR) with 95% confidence interval).

Baseline status	Follow-up findings							
	HPV16/18/31/ 33/45/51¶ IRR (95% CI)	Adjusted§ HPV16/18/31/ 33/45/51 IRR (95% CI)	HPV31/33/45/51¶ IRR (95% CI)	Adjusted§ HPV31/33/45/51 IRR (95% CI)	HPV31/33¶ IRR (95% CI)	Adjusted§ HPV31/33 IRR (95% CI)	HPV45¶ IRR (95% CI)	Adjusted§ HPV45 IRR (95% CI)
HPV16/18 vaccinated								
HPV16/18 neg (n=165)	(96) 1.0	1.0	(87) 1.0	1.0	(67) 1.0	1.0	(7) 1.0	1.0
HPV16 pos# (n=53)	(30) 0.9 (0.6,1.4)	1.0 (0.6,1.4)	(26) 0.9 (0.6,1.4)	0.9 (0.6,1.4)	(11) 0.5 (0.3,1.0°)	1.0 (0.5,2.1)	(0) 0.0 (0.0,)	0.0 (0.0,)
HPV18 pos# (n=24)	(17) 1.5 (0.9,2.6)	1.6 (0.9,2.7)	(11) 1.0 (0.5,1.9)	1.0 (0.5,1.8)	(3) 0.3 (0.1,1.1)	0.8 (0.2,2.5)	(0) 0.0 (0.0,)	0.0 (0.0,)
HAV vaccinated								
HPV16/18 neg (n=168)	(118) 1.0	1.0	(100) 1.0	1.0	(67) 1.0	1.0	(16) 1.0	1.0
HPV16 pos# (n=56)	(38) 0.9 (0.6,1.3)	0.9 (0.6,1.3)	(34) 1.0 (0.7,1.4)	1.0 (0.7,1.5)	(26) 1.1 (0.7,1.7)	1.1 (0.7,1.7)	(1) 0.2 (0.0,1.2)	0.2 (0.0,1.3)
HPV18 pos# (n=26)	(20) 1.4 (0.9,2.3)	1.4 (0.9,2.3)	(18) 1.4 (0.9,2.3)	1.4 (0.9,2.4)	(11) 1.1 (0.6,2.2)	1.1 (0.6,2.2)	(6) 2.5 (1.0°,6.3)	2.5 (1.0°,6.4)

° < 1.0, # baseline positives for HPV16 or HPV18 only, §Poisson regression analysis: adjusted for *Chlamydia trachomatis* and community vaccination coverage, ¶number ( ) of positives for HPV16/18/31/33/45/51, or HPV31/33/45/51, or HPV31/33, or HPV45

Results – species A5, A7, A9 and A10

Table 3. Risk of acquiring human papillomavirus (HPV) types not covered by the HPV16/18 vaccine in baseline HPV16 or HPV18 positive individuals compared to baseline HPV16/18 negative individuals among HPV16/18 or hepatitis A (HAV) vaccinated Finnish PATRICIA participants (N = 2409 and 2399, respectively) followed-up by cervical sampling every 6 months for 4 years (crude/adjusted incidence rate ratios (IRR) with 95% confidence interval).

	Follow-up findings					
Baseline status	HPV39/59/68¶ IRR (95% CI)	Adjusted§ HPV39/59/68 IRR (95% CI)	HPV35/39/52/58¶ IRR (95% CI)	Adjusted§ HPV35/39/52/58 IRR (95% CI)	HPV35/39/52/58/59/68¶ IRR (95% CI)	Adjusted§ HPV35/39/52/58/59/68 IRR (95% CI)
HPV16/18 vaccinated						
HPV16/18 neg (n=165)	(64) 1.0	1.0	(72) 1.0	1.0	(96) 1.0	1.0
HPV16 pos# (n=53)	(20) 0.9 (0.6-1.6)	1.0 (0.6,1.6)	(26) 1.1 (0.7,1.7)	1.1 (0.7,1.8)	(35) 1.2 (0.8,1.7)	1.2 (0.8,1.8)
HPV18 pos# (n=24)	(8) 1.0 (0.5-2.0)	0.9 (0.5,2.0)	(10) 1.2 (0.6,2.3)	1.2 (0.6,2.4)	(11) 0.9 (0.5,1.7)	0.9 (0.5,1.8)
HAV vaccinated						
HPV16/18 neg (n=168)	(70) 1.0	1.0	(84) 1.0	1.0	(104) 1.0	1.0
HPV16 pos# (n=56)	(31) 1.4 (0.9-2.1)	1.4 (0.9,2.1)	(33) 1.3 (0.9,1.9)	1.3 (0.9,2.0)	(40) 1.2 (0.9,1.8)	1.3 (0.9,1.8)
HPV18 pos# (n=26)	(12) 1.3 (0.7-2.3)	1.3 (0.7,2.5)	(11) 0.8 (0.4,1.6)	0.9 (0.5,1.6)	(15) 1.0 (0.6,1.7)	1.0 (0.6-1.8)

#baseline positives for HPV16 or HPV18 only, §Poisson regression analysis: adjusted for *Chlamydia trachomatis* and community vaccination coverage, ¶number ( ) of positives for A5 = HPV51, or A7 = any of HPV39/45/59/68, or A9 = any of HPV31/33/35/52/58, or A10 = any of HPV6/11

Conclusion

•In conclusion, our study suggests that HPV type-replacement does not take place following mass vaccination.

•However, surveillance of community randomized trial cohorts and other populations in countries which have implemented HPV vaccination programs immediately after licensure of the vaccines, with special focus on vaccination coverage rates are warranted.

Discussion

•The strenghts of our study:
>population based nature of cohorts
>low drop-out rate
>long active follow-up with repeat cytological sampling and
>use of sensitive SPF10-PCR methodology

•The limitations of our study:
>the vaccination coverage

References

Acknowledgement

Johanna Palmroth University of Kuopio Hospital, Kuopio, Finland

Jorma Paavonen University of Helsinki, Helsinki, Finland

Dan Apter Family Federation of Finland, Helsinki, Finland

Tiina Eriksson University of Tampere, Tampere, Finland

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