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Characteristics of a cluster-randomized phase IV human papillomavirus vaccination effectiveness trial

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ABSTRACT

High-risk human papillomaviruses (hrHPV) cause anogenital and oropharyngeal cancers. HPV-16/18 virus-like particle vaccine formulated with an AS04 adjuvant is very efficacious against hrHPV associated precancers but the herd effects of different vaccination scenarios are not known. Our cluster randomized trial (NCT00534638) assesses the overall and herd effects of vaccinating girls vs. girls and boys. In two school-years (2007–2008 and 2008–2009) we invited 80,272 1992–1995 born early adolescents to a CRT in 33 communities a priori stratified by low, intermediate and high HPV-16/18 seroprevalence. In 11 Arm A communities 90% of participating girls and boys were assigned to receive HPV-16/18 vaccine, in 11 Arm B communities 90% of girls were assigned to receive HPV-16/18 vaccine – boys were assigned to receive hepatitis B-virus (HBV) vaccine, and in 11 Arm C communities all were assigned to receive HBV-vaccine. Prevalence of HPV in vaccinated and unvaccinated girls is studied at age 18.5 years. Recruitment resulted in equal enrolment of four birth cohorts (born 1992–1995) comprising altogether 32,175 (40% response) early adolescents: 20,514 girls (50.5–53.0% response by arm) and 11,661 boys (21.9–31.6%% response by arm). At the age of 15 years, 79.3% of the vaccinees completed a questionnaire. Among them >98% were living at, and during the week-ends 1.3–1.6% stayed outside, the study site communities. Smoking habit and alcohol consumption were similar in the different trial arms, also mean-age of menarche (12.4 years) and 1st ejaculation (12.6 years), and sexual behaviour (among those <25%, who had had sexual debut) did not differ by arm: mean-age at the sexual debut 14.3 and 14.4 in girls and boys, and proportions of those with multiple (≥5) life-time sexual partners (6.5–7.5%) at the age of 15 years. Uniform residential, life-style and sexual behaviour characteristics indicate successful randomization/enrolment of the CRT. Our CRT will verify modelled predictions on up to 31% herd effect of vaccinating both girls and boys with moderate vaccine coverage – quantifying overall effectiveness of different strategies which will soon guide how to implement HPV vaccination.

1. Introduction

Virus-like particle (VLP) vaccines against high-risk human papillomavirus (hrHPV) types 16 and 18 (Gardasil® and Cervarix®) have been licensed for females in most countries [1–4]. Moderate or very high vaccine efficacies (VE) against overall cervical intraepithelial neoplasia grade 3 (CIN3), that is, the cervical precancer, irrespectively of HPV type, have been reported [5], and ongoing Nordic long-term follow-up trials involving more than 22,000 young women [6,7] will help to definitively determine whether the two vaccines are efficacious against invasive cervical cancer. The two vaccines have also been highly immunogenic [8,9] and/or

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efficacious in males [9] leading to implementation of male vaccination by a few health authorities [10,11].

Female HPV vaccination programmes have been launched in many countries [12,13] but even if highly efficacious at the individual level low vaccination coverage threatens herd effect and the desired public health impact [12–14]. In the US and continental Europe devoid of school-based vaccination programmes, free indirect protection due to herd effect will probably remain low since the coverage of HPV vaccination in the females has mostly been between 30% and 50%, with moderate compliance in receiving three doses [12,15,16] Coverage of even the best school-based HPV vaccination programmes among girls has been in the range of 70–90% [13,17–19] leaving a proportion of (marginalized) girls without protection [20]. Modelling suggest increased effectiveness by gender neutral vaccination programmes which are gaining attention [21,22].

Our cluster randomized trial (CRT:ClinicalTrials.gov reg.number NCT00534638) aims to identify the most effective HPV vaccination programme among various modelled programmes for 12–15 year old early adolescents by assessing overall and indirect effectiveness and safety of the two major HPV vaccination strategies; that is, to vaccinate early adolescents girls only, or to vaccinate early adolescent girls and boys. We present here the key characteristics of our CRT.

2. Methods

2.1. Stratified randomization of study site communities

There are 57 communities in Finland, outside the Helsinki metropolitan area, with more than 35,000 inhabitants. The number of eligible communities was 34 based on a 50 km distance cut-off (25 km in southern Finland) between communities. To control variation of background HPV exposure rates in the 33 communities (one was excluded) we determined HPV-16/18 seroprevalence rates in 50 per community under age 23 years in 1983–2003 [23,24] and 2006 using serum samples from the population-based Finnish Maternity Cohort (FMC). The serum bank stores first trimester serum samples from 98% of pregnant Finnish women, all of whom have given informed consent for medical research [22]. Before randomization into the three study arms the 33 communities were stratified into three groups according to low (<20.5%), intermediate (20.5–24%) and high (>24%) of HPV-16/18 seroprevalence (Fig. 1), which resulted in a low coefficient of variation (CV) of 0.13 across communities, and ample power for the study with a conservative CV estimate of 0.15 and reasonable sample size, i.e. numbers of communities per study arm for the overall effectiveness assessment (Table 1).

2.2. Enrolment and follow-up

Ethical clearance for this investigator initiated [25,26] trial was obtained in June 2007 from the Ethical Review Board of the Pirkanmaa Hospital District (Eudra-CT number 2007-001731-55). Identification of residents 1992–1995 born and their parents or legal guardians in the 33 communities was based on personal identity codes (PIC) and the Population Register Centre of Finland. Informed consent based linkages of the Registry of Vaccinated Individuals (RVI) and two population-based health registries: the Hospital Discharge Registry (HILMO [27]) and the Finnish Cancer Registry (FCR [28]) will utilize this unique PIC (Finnish National Institute for Health & Welfare permission, Dnro 33/5.05.00/2009).

All the 80,272 Finnish or Swedish speaking boys and girls in the 1992–1995 birth cohorts were invited during two school years

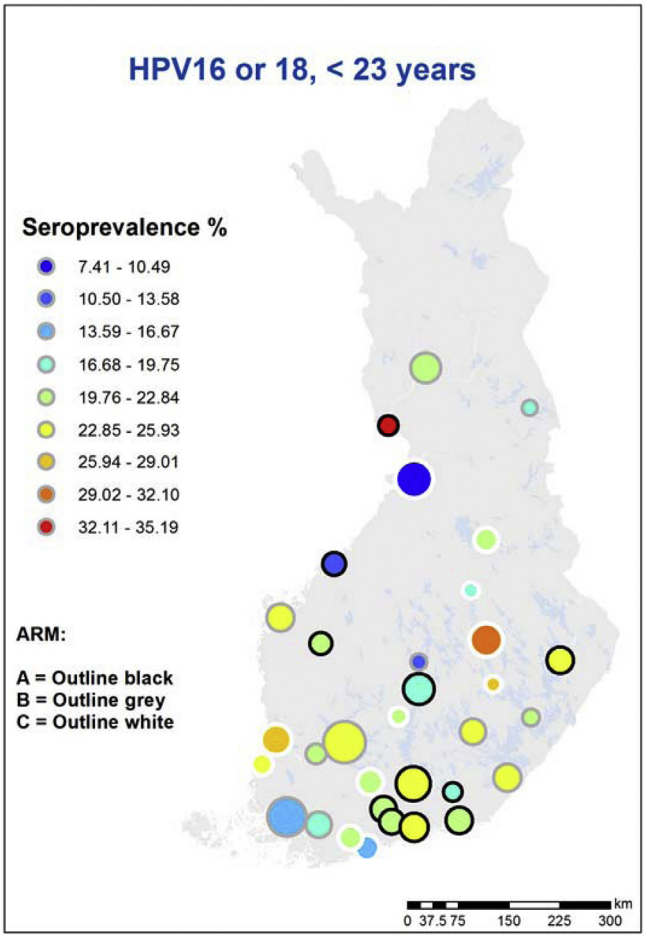

Fig. 1. Human papillomavirus (HPV) type-16/18 seroprevalence (%) among <23 year old Finnish women in 2006/7 (study site communities are circled by vaccination strategy: (A) HPV vaccination of boys and girls, black circle. (B) HPV vaccination of girls only, boys were assigned to receive hepatitis B-virus (HBV) vaccine, grey circle. (C) HBV vaccination of boys and girls, white circle.

(2007–2008 and 2008–2009) by letters sent to their parents or legal guardians (preferably mother) living in the same household. The letters included pertinent study information, consent form and a prepaid envelope for the consent. Six thousand 1992–1995 born immigrants whose native language was neither Finnish nor Swedish were also eligible to participate in the study (translation provided when needed) although not invited by letters

After receiving the parental informed consent, the study nurses arranged the first appointment at school health care facilities of the 250 municipal junior high schools the students were attending. Following informed consent 90% of the participating girls and boys were assigned to receive Cervarix® (referred hereafter as HPV-16/18) -vaccine and 10% were assigned to receive Engerix™ B (referred hereafter as hepatitis B-virus, HBV) -vaccine in 11 Arm A communities, 90% of the girls were assigned to receive Cervarix®-vaccine, 10% of girls were assigned to receive HBV-vaccine and all boys received HBV-vaccine in 11 Arm B communities, and all participants were assigned to receive HBV-vaccine in 11 Arm C communities. The next two vaccine doses (at months 1 and 6) were given at schools by the same study nurses. Blinding was maintained for all subjects in arm A and for girls in arm B. During the immunization phase serious adverse effects (SAE) were surveyed and reported for 12 months.

At the age of 15 years both girls and boys received a questionnaire on living conditions, life habits and sexual behaviour. In addition, all female study participants and all Finnish or Swedish

Table 1
Number of communities needed to have at least 90% of power at final analysis for the co-primary objectives (testing at age 18.5, community size 1000) assuming a 0.15 co-efficient of variation in background HPV16/18 exposure by community, and no change in sexual activity in Arms A (90% of boys and girls assigned to receive HPV vaccination, B (90% of girls assigned to receive HPV vaccination, boys assigned to receive hepatitis B-virus, HBV vaccination, and C (both boys and girls assigned to receive HBV vaccination) during the trial.

Coverage	Comparison	Number of communities
55%	A vs. C	3.8 (3.1–5.1)*
	B vs. C	5.3 (3.7–9.9)*
50%	A vs. C	4.1 (3.3–6.0)*
	B vs. C	6.0 (4.0–13.3)*
45%	A vs. C	4.7 (3.5–7.5)*
	B vs. C	7.1 (4.2–19.2)*
40%	A vs. C	5.3 (3.7–10.0)*
	B vs. C	8.4 (4.5–31.0)*
35%	A vs. C	6.3 (4.0–14.7)*
	B vs. C	10.4 (4.9–60.4)*
30%	A vs. C	7.8 (4.4–25.3)*
	B vs. C	13.5 (5.4–170.3)*

* Number of communities needed when the effect of the trial is increased or decreased by 20% (20% more or 20% fewer cases prevented by HPV vaccination than the model predicts).

speaking female residents of the study site communities born between 1992 and 1995 were invited at the age of 18.5 years to attend a follow-up visit to obtain a cervical sample (and for the 1994 and 1995 birth cohorts an oral gargle sample) taken by a study nurse, and a self-collected cervico-vaginal sample for HPV and/or *Chlamydia trachomatis* PCR analyses. In addition, the female study participants were offered the vaccine (either HBV-vaccine or HPV-16/18 -vaccine) they had not received at the junior high-school.

2.3. Statistical analyses

Descriptive statistics of the participants by arm were performed for the 1992–1995 born study participants living in the study site communities and answering the questionnaire at the age of 15 years.

Two separate dynamic transmission models [21,22,29] calibrated to Finnish data were used for the estimation of herd effect (the relative reduction of HPV prevalence among unvaccinated girls compared to no-HPV-16/18 vaccination scenario, Arm C) by the CRT-specific HPV-16/18 vaccine coverages among girls in Arm B and girls and boys in Arm A assuming 95% vaccine efficacy against HPV-16/18 infection, and 4.6% or 8.3% prevalence rate of HPV-16/18 infection in unvaccinated 18.5-year old females.

3. Results

3.1. Enrolment

During 2007–2009 two invitation letters were sent to the parents of 39,420 girls and 40,852 boys. The median numbers of invited girls and boys by community were: 1018 (range 482–3809), and 1110 (range 496–3920), respectively. Invitation letters to those born 1992–1993 were sent starting in October 2007, to those born 1994 in August 2008 and to those born 1995 in October 2008. Thereafter, study nurses in the 33 study site communities gave oral presentations at 250 junior high-schools involving the 9th and 8th grade classes (15- to 13-year olds, school year 2007–2008) and the 8th and 7th grade classes (14- to 12-year olds, school year 2008–2009), as well as at parents' evenings organized by the schools. The numbers of volunteers and vaccinated individuals increased rapidly during both school years in Autumn 2007 and 2008, reaching a plateau by the end of April 2008 and 2009 (Fig. 2).

Overall, the numbers of enrolled subjects and the proportions of the invited subjects (11,661, 28.5% of boys and 20,514, 52.0% of girls) were equally distributed between the study arms (Table 2). The proportions of vaccinated boys, however, increased in all study arms by approximately 5 percentage points during the enrolment phase (20.5%, 1992 vs. 24.8%, 1995, Arm A, and 29.8% and 27.5%, 1992 vs. 33.6% and 34.6%, 1995, Arms B and C, respectively). The female participation rates were materially equal in all the study arms: Arm A) 52.8%, Arm B) 50.5%, and Arm C) 53.0% (Table 2). The proportions of HPV-16/18 vaccinated girls were not remarkably different in arms A and B (approximately 47.5% vs. 45.5%). In Arms A and B there were no outlier communities having more than a 15 per cent difference from the average vaccine coverage. In Arm C, two communities had over 70% vaccine coverage in girls.

3.2. Residential history and life-style characteristics

At the age of 1598.5%, 98.2% and 98.3% of the study participants were living at the A, B and C study site communities (Table 3). During the week-ends 1.4%, 1.2% and 1.4% of the study participants stayed usually outside the A, B and C communities, respectively. Also smoking habit and alcohol consumption were similar in the trial arms, and there were no major differences between male and female study participants: neither for never smokers (range 66.4–70.2%) vs. current smokers (range 16.7–19.0%), nor for never consumers (range 45.2–51.8%) vs. once or twice a week alcohol consumers (range 1.7–2.4%) (Table 4). However, heavy smoking was twice as common in boys than in girls.

3.3. Sexual behaviour characteristics

The characteristics of sexual development (menarche, mean-age 12.4 years/1st ejaculation, mean-age 12.6 years) did not differ by trial arm (Table 5). Also sexual behaviour, mean age at sexual debut (among those approximately 21% and 24% of boys and girls, who had had their 1st sexual intercourse) were similar; that is, mean-age 14.4. years (boys) and mean-age 14.3 years (girls) (Table 4). Among those who had had their 1st sexual intercourse by 15 years, the numbers of (multiple $\geq$5) life-time sexual partners were similar by study arm and gender (range 6.5–7.5%) (Table 5).

3.4. Predicted herd effects

Finally, two established dynamic transmission models were used to predict herd effect for the different HPV vaccination strategies using the vaccine coverage rates observed. While in the Arm B (girls only) communities the predicted herd effects were low, in the Arm A (girls and boys) communities with approximately 47.5% and 19.8% HPV-16/18 vaccine coverage rates, respectively, the predicted herd effects on HPV-16 prevalence ranged between 14% and 31% among the 1994-born and 1995-born unvaccinated 18.5 year-old girls (Table 6).

4. Discussion

We enrolled early adolescent girls and boys to a population-based, cluster randomized trial on the effectiveness of different HPV vaccination strategies with on average 45.5–47.5% HPV-16/18 vaccine coverage in the females, and 19.8% coverage in the males. According to established dynamic transmission models [21,22] this will yield eventually up to 17–31% herd effect. Randomization of the study site communities was successful in yielding

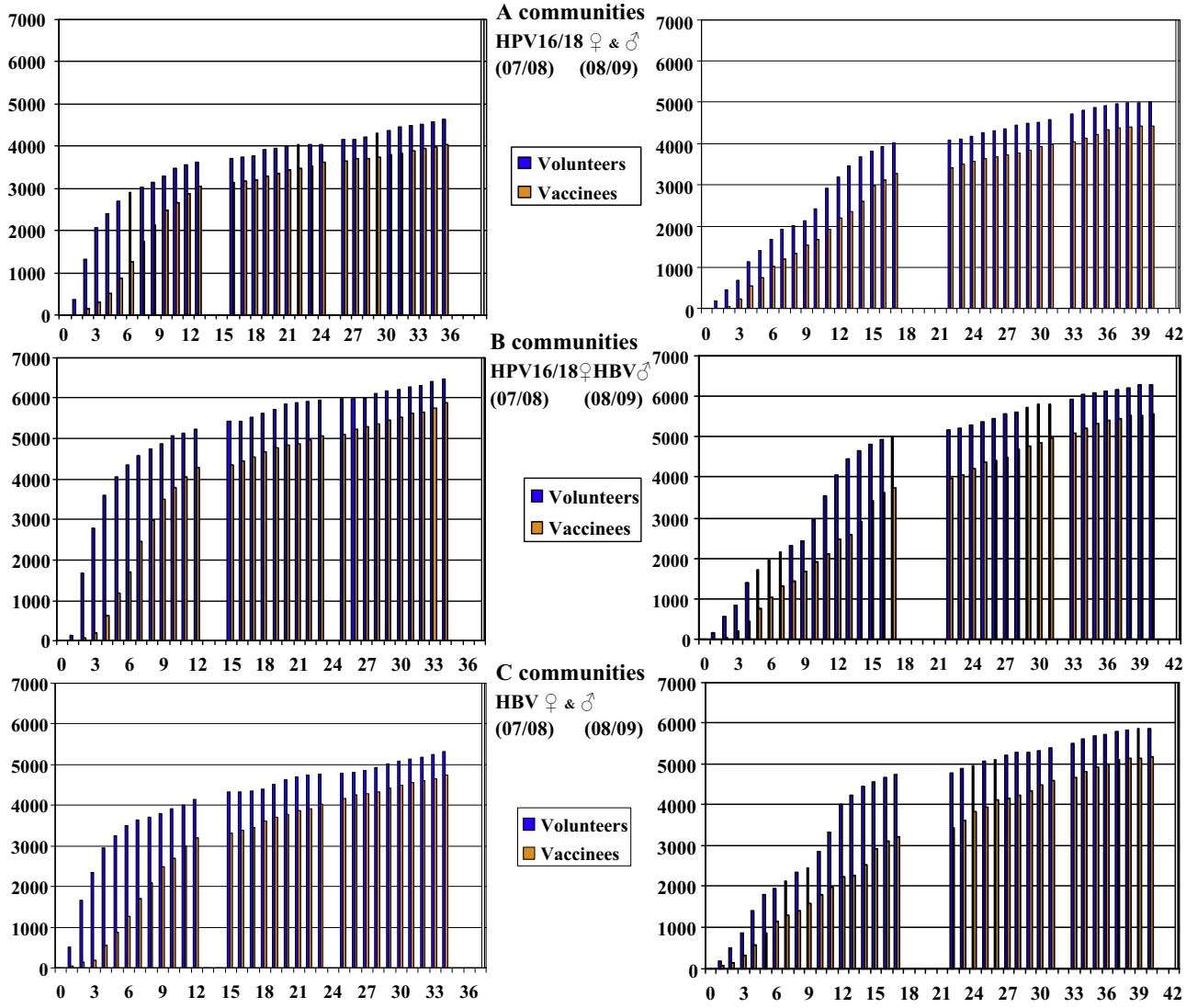

Fig. 2. Cumulative numbers of HPV-16/18 vaccinated and non-HPV-16/18 vaccinated 1992–1995 born adolescents attending the trial in two school years 2007–2008 (1992–1993 born) and 2008–2009 (1994–1995 born) at the 33 study sites. The *x*-axis indicates school weeks starting from October 2007 to May 2008, and August 2008 to May 2009 (the *y*-axis indicates the number of volunteers (blue columns) and vaccinees (orange column).

uniform residential, demographic, life-style and sexual behaviour participant characteristics for the trial arms.

The enrolment took place over two school years with constant pace the 1992–1993 and 1994–1995 birth cohorts attending during the first halves of two consecutive school-years 2007–2008 and 2008–2009, respectively. We had only a few outlier communities. Two Arm C communities had over 70% vaccination coverage but this does not have an effect on the herd effect estimates, since only HBV vaccine was used in these communities. There was only a small difference in the participation rate of adolescent girls between Arm

Table 2
Number (%) recruited/invited (80,272) 1992–1995 born girls and boys by vaccine arm* and birth cohort in 2007–2008 and 2008–2009(10)#.

Arm		1992			1993			1994			1995			1992–1995		
		N	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%
A	Girls	3143	1545	49.2	3191	1621	50.8	3063	1772	57.9	2846	1530	53.8	12,243	6468	52.8
	Boys	3246	666	20.5	3230	617	19.1	3066	726	23.7	2921	725	24.8	12,463	2734	21.9
B	Girls	3844	1940	50.5	3746	1846	49.3	3572	1853	51.9	3408	1725	50.6	14,570	7364	50.5
	Boys	4132	1232	29.8	3934	1237	31.4	3756	1194	31.8	3638	1222	33.6	15,460	4885	31.6
C	Girls	3398	1752	51.6	3142	1553	49.4	3040	1734	57.0	3027	1643	54.3	12,607	6682	53.0
	Boys	3349	922	27.5	3286	946	28.8	3118	1075	34.5	3176	1099	34.6	12,929	4042	31.3
Total	Girls	10,385	5237	50.4	10,079	5020	49.8	9675	5359	55.4	9281	4898	52.8	39,420	20,514	52.0
	Boys	10,727	2820	26.3	10,450	2800	26.8	9940	2995	30.1	9735	3046	31.3	40,852	11,661	28.5

N = Number of invited subjects; *n* = Number of recruited subjects; % = *n*/*N*.

* (A) 90% of girls and boys received human papillomavirus (HPV)-16/18 vaccine, 10% girls and boys received hepatitis B-virus (HBV) vaccine. (B) 90% of girls received the HPV-16/18 vaccine, 10% of girls and 100% boys received the HBV vaccine. (C) 100% of girls and boys received the HBV vaccine.

Q1/2010, for the 1995 birth cohort

Table 3
Residential (upper part) and week-end (lower part) histories of the HPV vaccine trial participants at junior high school at the age of 15 years by gender and trial arm.

Category	Arm A		Arm B		Arm C	
	Boys *N* = 2059 *n* (%)	Girls *N* = 5154 *n* (%)	Boys *N* = 3751 *n* (%)	Girls *N* = 6017 *n* (%)	Boys *N* = 3089 *n* (%)	Girls *N* = 5459 *n* (%)
Lived in the same community where attending school	2019(98.3)	5076(98.7)	3667(98.2)	5893(98.1)	3027(98.4)	5344(98.2)
Lived in another community at baseline	35(1.7)	68(1.3)	68(1.8)	114(1.9)	49(1.6)	97(1.8)
Missing	5(−)	10(−)	16(−)	10(−)	13(−)	18(−.)
Stayed in the community where was living	1378(67.5)	3408(66.7)	2561(68.6)	4109(68.8)	2071(67.5)	3666(67.6)
Stayed occasionally in another community	637(31.2)	1631(31.9)	1121(30.0)	1794(30.1)	949(30.9)	1687(31.1)
Stays usually in another community	27(1.3)	70(1.4)	49(1.3)	67(1.1)	50(1.6)	69(1.3)
Missing	17(−)	45(−)	20(−)	47(−)	19(−)	37(−)

N = number of subjects; *n* (%) = number (percentage) of subjects in a given category.

Table 4
Smoking and drinking habits of the HPV vaccine trial participants at junior high school at the age of 15 years by gender and trial arm.

Category	Arm A		Arm B		Arm C	
	Boys *N* = 2059 *n* (%)	Girls *N* = 5154 *n* (%)	Boys *N* = 3751 *n* (%)	Girls *N* = 6017 *n* (%)	Boys *N* = 3089 *n* (%)	Girls *N* = 5459 *n* (%)
Never smoked	1339(69.3)	3196(66.4)	2441(69.7)	3919(70.0)	2071(70.2)	3458(68.2)
Quitted smoking	264(13.7)	705(14.6)	477(13.6)	750(13.4)	372(12.6)	739(14.6)
Current smokers	330(17.1)	914(19.0)	583(16.7)	933(16.7)	509(17.2)	873(17.2)
Missing	126(−)	339(−)	250(−)	415(−)	137(−)	389(−)
≤One pack a month	173(33.9)	540(37.4)	313(33.6)	598(40.2)	243(31.3)	618(43.7)
Two packs a month	45(8.8)	173(12.0)	110(11.8)	208(14.0)	89(11.5)	163(11.5)
One pack a week	73(14.3)	247(17.1)	126(13.5)	276(18.6)	119(15.3)	219(15.5)
Two packs a week	68(13.3)	233(16.2)	132(14.2)	185(12.4)	112(14.4)	178(12.6)
Half a pack a day	123(24.1)	213(14.8)	207(22.2)	178(12.0)	157(20.2)	199(14.1)
≥One pack a day	28(5.5)	36(2.5)	43(4.6)	41(2.8)	57(7.3)	36(2.5)
Missing	1549(−)	3712(−)	2820(−)	4531(−)	2312(−)	4046(−)
Did not consume	956(49.6)	2169(45.2)	1778(50.7)	2607(46.7)	1530(51.8)	2399(47.6)
≤once a month	667(34.6)	1812(37.7)	1189(33.9)	2065(37.0)	958(32.4)	1852(36.8)
2–4 times a month	253(13.1)	715(14.9)	467(13.3)	777(13.9)	395(13.4)	696(13.8)
1–2 times a week	46(2.4)	103(2.1)	68(1.9)	128(2.3)	64(2.2)	88(1.7)
≥3 times a week	6(0.3)	4(0.1)	4(0.1)	3(0.1)	6(0.2)	3(0.1)
Missing	131(−)	351(−)	245(−)	437(−)	136(−)	421(−)

A and Arm B which resulted in a negligible (two percent) difference in the HPV-16/18 vaccine coverage rates in girls between the two arms.

The trial enrolment of early adolescent boys was not particularly successful in the Arm A communities, where the HPV-16/18 vaccine was offered also to boys, probably due to the fact that parental and minor informed consents were both required. Active recruitment and the information package provided at the junior high schools increased the participation in the Arm A communities from 19.1% (1993-born) to 24.8% (1995-born) during the two school years. Such

Table 5
Sexual development and sexual behaviour of the HPV vaccine trial participants at junior high school at the age of 15 years by gender and trial arm.

Category		Arm A		Arm B		Arm C	
		Boys *N* = 2059 *n* (age or %)	Girls *N* = 5154 *n* (age or %)	Boys *N* = 3751 *n* (age or %)	Girls *N* = 6017 *n* (age or %)	Boys *N* = 3089 *n* (age or %)	Girls *N* = 5459 *n* (age or %)
Mean age (years) at 1st ejaculation/menarche		1492(12.6)	4418(12.4)	2657(12.6)	5176(12.5)	2237(12.6)	4685(12.4)
Missing		567	736	1094	841	852	774
Sexual debut by 15 years of age		435(21.8%)	1283(25.3%)	732(20.1%)	1419(24.0%)	605(20.2%)	1262(23.5%)
Mean age (years) at sexual debut		410(14.4)	1202(14.3)	687(14.3)	1315(14.3)	577(14.4)	1162(14.3)
Number of sex partners* by 15 years of age	1	255(58.9%)	707(55.1%)	414(56.9%)	766(54.1%)	344(57.0%)	684(54.3%)
	2	90(20.8%)	276(21.5%)	160(22.0%)	294(20.8%)	142(23.5%)	276(21.9%)
	3–4	59(13.6%)	212(16.5%)	107(14.7%)	256(18.1%)	76(12.6%)	204(16.2%)
	≥5	29(6.7%)	88(6.9%)	47(6.5%)	99(7.0%)	41(6.8%)	95(7.5%)
Missing		1626	3871	3023	4602	2486	4200

* Calculated for those study participants who had had the first sexual intercourse by age of 15 years.

Table 6
Modelled* reduction of HPV16 prevalence in unvaccinated 18.5-year old females following vaccination of 1992–1995 –born birth cohorts (BC) in 2007–2010 (at 12 to 15 years of age) by different vaccination strategies and vaccine coverages.

Birth cohort/Calendar year	ICL/IARC model[a]				THL/UTA model[b]			
	BC-92/2011	BC-93/2012	BC-94/2013	BC-95/2014	BC-92/2011	BC-93/2012	BC-94/2013	BC-95/2014
Vaccine coverage								
♀ 45.5% (Arm B)								
Prevalence	n.a.	4.0%	3.6%	3.5%	8.2%	8.0%	7.9%	7.7%
Reduction	n.a.	15%	22%	24%	1.8%	3.5%	5.5%	7.4%
♀ 47.5%/♂ 19.8% (Arm A)								
Prevalence	n.a.	3.7%	3.2%	3.2%	7.8%	7.5%	7.2%	6.9%
Reduction	n.a.	22%	30%	31%	6.5%	10%	14%	17%

n.a. = not available.
* Dynamic transmission model [21,22] predicted herd-effect to be verified with data from the community randomize trial, assumed baseline prevalence in unvaccinated women: 4.6%[a] and 8.3%[b].

phenomenon was also seen in the Arm B and C communities. Mathematical models suggest that HPV vaccination of both boys and girls provides a strong herd effect [21,22,29] and can substitute for low HPV vaccine coverage in the females [21]. In the upcoming analyses it will be useful to assess the effectiveness estimates by birth cohort since both the absolute numbers and proportions of vaccinated males are the highest in the youngest birth cohorts, which have on top 2–3 vaccinated birth cohorts, predicted to translate into stronger herd effects.

Strengths of our study are uniform enrolment of the early adolescents by school year and birth cohort and community. There was no confounding by opportunistic or national HPV vaccination. Notably homogeneous participation of both vaccinated and unvaccinated 18.5 year-old girls (approximately 3000 by birth cohorts 1992–1995, data not shown) to cervical sampling at the follow-up phase is important for the assessment of the overall effectiveness and the herd effect. No differences existed in the sexual risk behaviour characteristics by study community or arm. It is also noteworthy, that the recently (November 2013) launched national HPV vaccination programme in Finland involving 1998-born and younger girls will not interfere with the herd effect estimation even in the last birth cohort (born 1995).

At the baseline there was very little daily/weekly mobility outside the study site communities. The demographics, life-style and sexual behaviour characteristics of the study participants indicate that both the randomization and study enrolment were successful. A similar more detailed questionnaire to be fulfilled at the end of the study by the 18.5 year-old girls and boys will provide further assurance on the comparability of the study site communities. The Finnish population is genetically homogeneous although some differences in the distribution of cervical cancer associated HLA genes (DR2 and B15) have been reported [30]. There, however, are equal numbers of Swedish speaking participants in one community included in each of the arms A, B and C.

Finally, the overall vaccination coverages among females meets or exceeds many of the national vaccination programmes in the US and Europe and over some Australian counties in which only the school-based system has provided more than 70% coverage rates [12,13,15–18]. With the more than 12,000 vaccinated and unvaccinated 18.5 year-old girls now sampled, the amply powered overall effectiveness data, and the unique randomized-trial based herd effect data by different vaccination strategies provided by our CRT will be critical for evidence-based decision making especially in poor resource countries. Also comparison of the study arms A and B in relation to the direct assessment of overall effectiveness of vaccinating girls only or girls and boys will be important. This data is needed to overcome the emergence of new HPV associated cancer epidemics in both males and females [31,32] which low coverage in girls only probably cannot tackle. Extensive cross-protection by the current HPV-16/18 vaccine [33] and the new multivalent HPV vaccines further emphasize the need to identify the HPV vaccination strategy needed for elimination(eradication) of the major hrHPV types [5].

In conclusion the randomization and enrolment in our community-randomized effectiveness trial have been successful. We will have a sound basis for estimating the overall effectiveness and indirect herd effect of the different HPV vaccination strategies to reduce cervical HPV prevalence in adolescent women. Evidence-based decision making will follow.

Notes

Cervarix is a registered trademark of the GSK group of companies. Engerix-B is a trademark of the GSK group of companies. *Gardasil* is a trademark of Merck & Co., Inc.

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Conflict of interest statement

ML, DA and JP have received grants form Merck & Co. Inc., and from the GSK group of companies for their HPV vaccination studies through their employers: University of Tampere, Family Federation of Finland and University of Helsinki, respectively. DB, SKD, MPD, GD and FS are employees of the GSK group of companies. DB, SKD, MPD, GD, and FS receive stock options/restricted shares from the GSK group of companies. GD has previously received patent royalties from Wyeth Vaccines.

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References

[1] EMA. European public assessment report; 2006 http://www.ema.europa.eu/PDFs/EPAR/gardasil/

[2] EUROPA. European public assessment report; 2007 http://www.europa.eu/PDFs/EPAR/cervarix/
[3] Markowitz L, Dunne EF, Saraiya M, Lawson HW, Chesson H, Unger ER. Quadrivalent human papillomavirus vaccine. Recommendations of the Advisory Committee on Immunization Practices. MMWR 2007;56:1–24.
[4] FDA. FDA approves new vaccine for prevention of cervical cancer; 2009 www.fda.gov/
[5] Lehtinen M, Dillner J. Clinical HPV vaccine trials and beyond. Nat Rev Clin Oncol 2013;10:400–10.
[6] Lehtinen M, Herrero R, Mayaud P, Barnabas R, Dillner J, Paavonen J, et al. Studies to assess long-term efficacy and effectiveness of HPV vaccination in developed and developing countries. Vaccine 2006;24S:233–41.
[7] Rana M, Huhtala H, Apter D, Eriksson T, Luostarinen T, Natunen K, et al. Understanding of long-term protection of human papillomavirus vaccination against cervical carcinoma. Int J Cancer 2013;132:2833–8.
[8] Petaja T, Keränen H, Karppa T, Kawa A, Lantela S, Siitari-Mattila M, et al. Immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04 adjuvanted vaccine in healthy boys aged 10–18 years. J Adolesc Health 2009;44:33–41.
[9] Palefsky JM, Giuliano AR, Goldstone S, Moreira Jr ED, Aranda C, Jessen H, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. N Engl J Med 2011;365:1576–85.
[10] Stanley M. Vaccinate boys too. Nature 2012;488:S10.
[11] www.hpvvaccine.org.au
[12] European Cervical Cancer Association. HPV vaccination across Europe; 2011 http://www.ecca.info/en/ecca-publications.html
[13] Markowitz LE, Tsu V, Deeks SL, Cubie H, Wang SA, Vicari AS, et al. Human papillomavirus vaccine introduction – the first five years. Vaccine 2012;30:F139–48.
[14] Brotherton J, Fridman JM, May CL, Chappell G, Saville AM, Gertig DM. Early effect of HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study. Lancet 2011;377:2085–92.
[15] Taylor R, Hariri S, Sternberg M, Dunne EF, Markowitz L. Human papillomavirus vaccine coverage in the United States: National Health and Nutrition Examination Survey, 2007–2008. Prev Med 2011;52:398–400.
[16] Dorell CG, Stokley S, Yankey D, Markowitz LE. Compliance with recommended dosing intervals for HPV vaccination among females, 13–17 years, National Immunization Survey-Teen, 2008–2009. Vaccine 2011;30:503–5.
[17] Brabin L, Roberts SA, Stretch R, Baxter D, Chambers G, Kitchener H, et al. Uptake of the first two doses of human papillomavirus vaccine by adolescent schoolgirls in Manchester: prospective cohort study. BMJ 2008;336:1056–8.
[18] Gertig DM, Brotherton JM, Saville M. Measuring human papillomavirus (HPV) vaccination coverage and the role of the National HPV Vaccination Program Register, Australia. Sex Health 2011;8:171–8.
[19] Kavanagh K, Pollock KG, Potts A, Love J, Cuschieri K, Cubie H, et al. Introduction and sustained high coverage of the HPV bivalent vaccine leads to a reduction in prevalence of HPV 16/18 and closely related HPV types. Br J Cancer 2014;110:2804–11.
[20] Malmqvist E, Natunen K, Lehtinen M, Helgesson G. Just implemention of human papillomavirus vaccination. J Med Ethics 2012;38:247–9.
[21] Vänskä S, Auranen K, Leino T, Salo H, Nieminen P, Kilpi T, et al. Impact of vaccination on 14 high-risk HPV type infections: a mathematical modelling approach. PLoS ONE 2013;8:e72088.
[22] Baussano I, Elfström KM, Lazzarato F, Gillio-Tos A, De Marco L, Carozzi F, et al. Type-specific human papillomavirus biological features: validated model-based estimates. PLoS ONE 2013;8:e81171.
[23] Lehtinen M, Kaasila M, Pasanen K, Patama T, Palmroth J, Laukkanen P, et al. Seroprevalence ATLAS of HPV infections in Finland. Int J Cancer 2006;120:2612–9.
[24] Kaasila M, Koskela P, Kirnbauer R, Pukkala E, Surcel H-M, Lehtinen M. Population dynamics of serologically identified coinfections with human papillomavirus types 11, 16, 18 and 31 in fertile-aged Finnish women. Int J Cancer 2009;125:2166–72.
[25] Lehtinen M, Paavonen J. Effectiveness of preventive HPV vaccination. Int J STD & AIDS 2003;14:787–92.
[26] Lehtinen M, French K, Dillner J, Paavonen J, Garnett G. Sound implementation of HPV vaccination. Future Med 2008;5:289–94.
[27] HILMO. Sosiaalihuollon-ja terveydenhuollon hoitoilmoitus. Ohjeita ja luokituksia. Stakes 2006;2.
[28] Pukkala E, Andersen A, Berglund G, Gislefoss R, Gudnason V, Hallmans G, et al. Nordic biological specimen banks as basis for studies of cancer causes and control – 25 million person-years and 100,000 prospective cancers. Acta Oncol 2007;46:286–307.
[29] Barnabas R, Laukkanen P, Koskela P, Kontula O, Lehtinen M, Garnett GP. The epidemiology of HPV16 and cervical cancer in Finland and the potential of vaccination. PLoS Med 2006;3:e138.
[30] Castro F, Haimila K, Pasanen K, Kaasila M, Patama T, Partanen J, et al. Geographic distribution of cervical cancer associated HLA antigens and cervical cancer incidence in fertile-aged Finnish women. Int J STD & AIDS 2007;18:672–9.
[31] Ramqvist T, Dalianis T. Oropharyngeal cancer epidemic and human papillomavirus. Emerg Infect Dis 2010;11:1671–7.
[32] Azvolinsky A. Concerned about HPV-related cancer rise, researchers advocate boosting HPV vaccination rates. J Natl Cancer Inst 2013;105:1335–6.
[33] Wheeler CM, Castellsague X, Garland S, Szarewski A, Paavonen J, Naud P, et al. Cross-protective efficacy of HPV-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by non-vaccine oncogenic HPV types: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. Lancet Oncol 2012;13:100–10.