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Ten-year follow-up of human papillomavirus vaccine efficacy against the most stringent cervical neoplasia end-point—registry-based follow-up of *three cohorts from randomized trials*

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ABSTRACT

Objective Due to long lag time between infection/cancer diagnoses human papillomavirus (HPV) vaccination programs will deliver vaccine efficacy (VE) estimates against cancer end-points late. Cancer registry follow-up of population-based, randomised trial cohorts of vaccinated and unvaccinated women was undertaken for the estimation of VE against cervical intraepithelial neoplasia grade three and invasive cancer (CIN3+).

Methods We report interim results with 98 561 person years of Finnish Cancer Registry -based follow-up of individually and/or cluster randomised cohorts of HPV-16/18 vaccinated and unvaccinated adolescent women enrolled in June 2003/2005, and between May 2004 and April 2005, respectively. The cohorts comprised 15 627 18- to 19-year-old unvaccinated women (NCT01393470), and 2 401 and 64 16- to 17-year-old HPV-16/18 vaccinated women participating the PATRICIA (NCT00122681) and HPV-012 (NCT00169494) trials, respectively. The age-aligned passive follow-up started 6 months after the clinical trials' end.

Results During the follow-up of 4.5 to 10 years post enrolment we identified 75 cases of cervical intraepithelial neoplasia grade 3 (CIN3) and 4 cases of invasive cervical cancer (ICC) in the unvaccinated cohort, and 4 CIN3 cases in the HPV-16/18 vaccinated women. Diagnostic blocks were available for HPV typing from 87% of the cases. CIN3+ lesions were detectable in 54 cases. HPV16 was found in 26 of 50 unvaccinated CIN3+ cases, and in 3 CIN3+ cases in the HPV-16/18 vaccinated women. The latter were all baseline positive for cervical HPV16 DNA. Baseline data was not available for the unvaccinated women. Intention-to-treat VE against any CIN3+ was 66% (95% CI 8, 88).

Conclusions Ten years post vaccination the AS04-adjuvanted HPV-16/18 vaccine shows continued efficacy against CIN3+ irrespectively of HPV type. Vaccine efficacy was not observed in baseline HPV16 DNA positive subjects.

Trial registration number NCT01393470.

Strengths and limitations of this study

- ► Country-wide cancer registry follow-up of sizeable randomised cohorts of HPV vaccinated and unvaccinated women for 100.000 person years (up to10 years post vaccination) provides most reliable vaccine efficacy estimates against cancerous end-points.
- ► Retrieval of most diagnostic histopathological blocks and state-of-science identification of the causal HPV type in the lesion enable identification of HPV type-specific vaccine efficacy estimates.
- ► The per protocol defined interim analysis has limited statistical power.

INTRODUCTION

High-risk (hr) human papillomaviruses (HPVs) cause up to 9% and 1% of cancers in females and males.[1] Bivalent, quadrivalent and nonavalent vaccines against HPV types 16/18, 6/11/16/18, and 6/11/16/18/31/33/45/52/58, respectively, have an acceptable safety profile and are highly efficacious against a number of infections with hrHPVs and associated precancers.[2–6] Proof of vaccine efficacy (VE) against HPV-associated cancers is, however, not easy to reach due to the long lag time between exposure to the virus and diagnosis of the associated cancer. This phenomenon is not uncommon, and has for instance hindered the determination of VE against hepatitis B virus (HBV) associated hepatocellular carcinoma, since the time lag between virus exposure and diagnosis of carcinoma is 15 to 25.[7 8]

Proving the concept of vaccine induced protection against (one of) the major

HPV-associated cancers, i.e., in situ and invasive cervical carcinoma is not only of conceptual but also of practical importance. It would guarantee the impact of primary cancer prevention via prophylactic HPV vaccination, guide targeting this prophylaxis, and provide the scientific basis for understanding how and when such proof will be available for other HPV-associated cancers such as non-cervical anogenital cancers, and head and neck cancers.

Our objective is to determine VE against cervical cancer. To accomplish this we identify invasive cervical cancer (ICC) and intraepithelial neoplasia grade 3 (CIN3+) incidence in passive, population-based cancer registry follow-up of a randomised clinical HPV vaccine trial cohort (PATRICIA),[4] and a cluster-randomised control cohort enrolled in 2003-2005.[9–11] The follow-up of originally adolescent females has previously proven to be feasible.[12] With the observed CIN3+ incidence of 93.4/100 000 in the control cohort,[12] which equals that of the Finnish female population of similar age 99.5/100 000,[12] it is well powered to verify 65% VE against CIN3+ and ICC, 10 and 15 years post vaccination, respectively.[9–12] We report interim results on the efficacy of the bivalent HPV16/18 vaccine against overall and HPV type-specific CIN3+ end-points.

METHODS

Study design and Ethics Our cluster-randomised follow-up study involves separate birth cohorts of clinical trial participants[4 12 13] aged 16–17 years and unvaccinated non-participants[9 10] aged 18–19 years assigned according to the start of PATRICIA[14] trial in May 2004 by ML (the principal investigator for phase III HPV vaccination trials in Finland). The former were also individually randomised.[13] The trials, establishing the unvaccinated control cohort and their Finnish Cancer Registry (FCR) –based follow-up were approved by the Finnish National Ethical Review Board (TUKIJA: 1174/2004 and 1153/2003), respectively

The study involved consecutive recruitment of adjacent, partially overlapping birth cohorts subjected to i) HPV vaccination and 4 years of clinical follow-up including cervical cytological sampling (birth cohorts Q2/1986 to Q1/1988), or ii) 4 years of clinical follow-up including cervical cytological sampling (birth cohorts Q2/1986 to Q1/1988), and iii) unvaccinated and no intervention (birth cohorts Q3/1984 to Q2/1985, and birth cohorts Q3/1985 to Q2/1987). The intervention measured was vaccination with the AS04-adjuvanted HPV-16/18 vaccine against no vaccination with the end-point: cervical intraepithelial neoplasia grade three or invasive cervical cancer (CIN3+). The end-points were histopathologically diagnosed 0–4 years post vaccination (during the active follow-up), 4–4.5 years post vaccination (during the intermittent period between the active follow-up and the passive follow-up), or 4.5–10 years post vaccination (during the passive follow-up).

Patient involvement Patients (with cervical neoplasia / condyloma) were not involved in the design of this study in 2000. A study on the feasibility of population-based enrolment was done in 1998.[14]

Enrolment Starting in May 2004 originally all 24 046 (Q2/1986-Q1/1988 born) 16–17 year old Finnish females resident in 17 trial communities were sent invitations to participate to the PATRICIA trial (HPV-008, NCT00122681) on the immunogenicity, safety and efficacy of the AS04-adjuvanted HPV-16/18 vaccine against HPV16/18 positive CIN2+ (figure 1). By June 2005 a total of 4 808 women participated. They were randomly assigned to HPV-16/18 or hepatitis A-virus (HAV) vaccination in 1:1 ratio to receive three doses of the HPV-16/18 vaccine or the HAV vaccine at months 0, 1 and 6, followed by seven active follow-up visits with 6 month interval up to 4 years.[4 13] In addition, 64 16–17 year olds received 3 doses of the HPV-16/18 vaccine by May 2005 in a concomitant HPV-012 trial which ended 4 years later.[15]

Following the end of the active follow-up in May 2009, approximately 50% of the HAV-vaccine recipients chose HPV-16/18 cross-vaccination during 2009–2010. HrHPV DNA positives at the last PATRICIA trial visit (215 from the HPV-16/18 cohort and 318 from the HAV cohort) continued active clinical follow-up (HPV-052 study protocol) for approximately 1.9 years after the end of the PATRICIA trial. They had annual HPV testing cytology until HPV DNA negative or exit colposcopy after 4 years.

An unvaccinated control cohort from entire adjacent birth cohorts of 18–19 year olds was recruited inviting 30 947 and 58 996 in May/June 2003/5 by the Finnish Population Register Centre as described (NCT01393470).[9–11] All PATRICIA[4 13] and earlier Future[12] trial participants were excluded from the control cohort. There were no healthcare interventions targeted to the control cohort.

Follow-up Both the vaccinated and unvaccinated control cohorts responded at the age of 22–23 years to a questionnaire on life habits with special emphasis on sexual health, that is, at the beginning of the passive registry-based follow-up.[16 17] Opportunistic vaccination by Gardasil or Cervarix vaccines after their licensures in 2006 and 2007 was considered based on questionnaires in 2007 and 2009, and among the vaccinated PATRICIA and HPV-012 trial cohorts in 2010. In addition, vital status and emigration were updated until the end of 2014.

Invitations to cervical screening were sent to all study participants at the age of 25 years, also in communities which organise the screening from age 30 onwards. With over-lapping time-windows of 5.5 years we age-aligned the passive follow-up for the different birth cohorts.[12]

The study outcomes were CIN3+ lesions diagnosed during the passive follow-up. According to local standard of care, women with cytological abnormalities were referred to colposcopy biopsy for histopathological diagnosis within a 6 month period following cytology.[18] Thus, the passive, Finnish Cancer Registry (FCR) -based follow-up was started 6 months after the end of active clinical follow-up of the PATRICIA (and 052) trial and

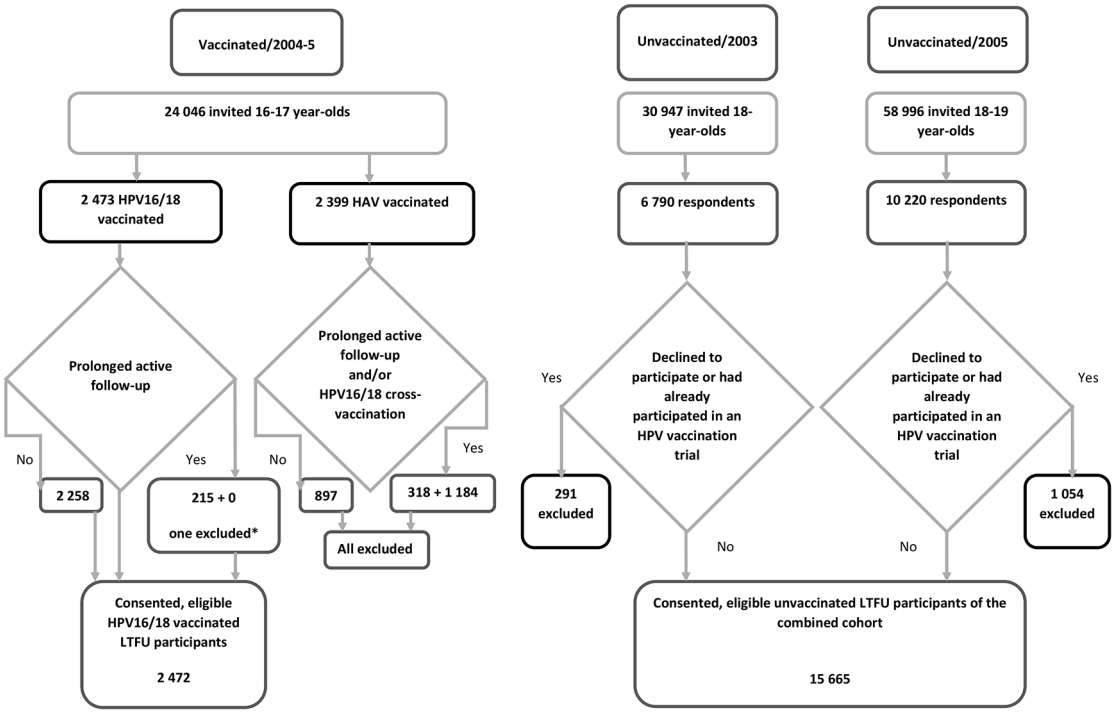

Figure 1 Consort diagram with relevant invitation, enrolment and exclusion criteria/steps.*Due to migration not eligible to Finnish Cancer Registry follow-up.

012 trials. For the control cohort the passive follow-up was age-aligned by a comparable time-period.[12] Based on age-specific incidence of CIN3+ in the Finnish female population (www.cancer.fi) the enrolled cohorts of HPV-16/18 vaccinated women and control women exceed the numbers required for at least 80% power to identify statistically significant 65% vaccine efficacy against CIN3+.[9 10] An interim analysis for CIN3+ was planned to take place after 5 years of passive follow-up, and the final analysis for ICC after 10 years of passive follow-up.

The FCR is population-based and receives cancer notifications from the entire country with 100% coverage, and 80% coverage for CIN3 (www.cancer.fi). Individually, the passive follow-up of the different cohorts extended until 10 years post vaccination or from the receipt of informed consent (unvaccinated women) up to the end of 2014.

Table 1 Sample size and power calculations for a registry-based follow-up study on the efficacy of human papillomavirus (HPV) type 16/18 vaccine against cervical intraepithelial neoplasia grade three and invasive cancer (CIN3+). (A) Required sample sizes for the cancer-registry follow-up phase III trial cohorts assuming 90% vaccine efficacy against CIN3+ (statistical power: 1-β=80%, α=0.05) and 10 years of follow-up. (B) Statistical power with actuarial*† sample sizes for the cancer-registry follow-up of phase III trial cohorts assuming 50%, 70% and 90% HPV vaccine efficacy (VE) against CIN3+

Cumulative incidence %	Category	Design 1:3		Design 1:4
0.2	HPV vaccinated/unvaccinated	3 990/11 970		3 880/15 520
0.4	HPV vaccinated/unvaccinated	1 773/5 319		1 685/6 740
0.6	HPV vaccinated/unvaccinated	936/2 808		889/3 556
0.8	HPV vaccinated/unvaccinated	795/2 385		755/3 220
1.2	HPV vaccinated/unvaccinated	495/1 485		470/1 880
Cumulative incidence %	**Category**	**VE 50%**	**VE 70%**	**VE 90%**
0.3	HPV vaccinated*/unvaccinated†	0.203	0.441	0.825
0.6	HPV vaccinated*/unvaccinated†	0.447	0.847	0.998
0.9	HPV vaccinated*/unvaccinated†	0.657	0.973	1.000
1.2	HPV vaccinated*/unvaccinated†	0.805	0.996	1.0000

*2465 HPV-16/18 vaccinated and †15 627 unvaccinated women followed up for up to 10 years post vaccination by a population-based cancer registry

Table 2 Demographic characteristics of the cohorts subjected to Finnish Cancer Registry follow-up.

Category	HPV-16/18 vaccinated (n = 2 472)	HAV-vaccinated (n=2 399)	Unvaccinated (n=15 627)
Age at enrolment	16–17 years	16–17 years	18–19 years
Age at passive follow-up	22–28 years	22–28 years	22–28 years
Response rate*	1 107 (46.5%)	1 010 (42.1%)	7 118 (45.5%)
Sexual debut (mean age)	15.8 years	16.0 years	16.4 years
No. of life-time partners			
0	37 (3.3%)	32 (3.2%)	400 (5.6%)
1	143 (12.9%)	146 (14.5%)	1 335 (18.8%)
2	131 (11.8%)	114 (11.3%)	750 (10.5%)
3–9	511 (46.2%)	458 (45.3%)	3 023 (42.4%)
10 or more	284 (25.7%)	257 (25.4%)	1 588 (22.3%)
No. of partners in the past 12 months			
0	531 (49.8%)	507 (50.2%)	3 848 (54.1%)
1	237 (21.4%)	230 (22.8%)	1 365 (19.2%)
2	111 (10.1%)	92 (9.1%)	580 (8.1%)
three or more	170 (15.4%)	145 (14.4%)	914 (12.8%)
Use of contraception			
BCP (ever)	1 028 (92.9%)	920 (91.1%)	6 017 (84.5%)
Condom†			
use	298 (26.9%)	261 (25.8%)	2 004 (28.2%)
no use	787 (71.1%)	728 (72.1%)	4 977 (69.5%)
No contraception	1 (0.1%)	5 (0.5%)	56 (0.8%)

*returned questionnaires at the age of 22–23 years when the passive follow-up was started
†last year

Following Finnish national ethical committee clearances in 2003 and 2004, registers of HPV-16/18 vaccinated and unvaccinated cohorts were established and have since been maintained at the University of Tampere.[9 10] Permission to link these registers with the FCR for the identification new cancer cases until 2024 was obtained from the Finnish Institute for Health & Welfare in 2004.

For the interim analysis the age-aligned HPV-16/18 vaccine (n=2 465) and the unvaccinated control cohort (n=15 627) were linked using personal identifiers with the FCR to determine the incidence (per 100 000 person years) of CIN3 and ICC (CIN3+) during the overlapping 5.5 year follow-up periods of passive follow-up.

Table 3 Incidence rate (/100 000 women years) of cervical intraepithelial neoplasia grade three and invasive cancer (CIN3+) in cluster-randomised cohorts of 16- to 17-year-old HPV-16/18 vaccine recipients, and unvaccinated originally 18- to 19 year old women. Passive follow- up was by the population-based Finnish Cancer Registry up to 10 years post vaccination.

End point of the follow-up	Vaccine				Control			
	N	Person yrs	n	Rate*	N	Person yrs	n	Rate*
FCR registered CIN3+ diagnoses								
Active	2472	10 199	–	–	15 665	62 628	–	–
Intermittent	2 466	1 232	1	81	15 634	7 815	–	–
Passive	2 465	12 561	4	32	15 627	85 328	79	93
KI re-reviewed CIN3+ diagnoses								
Intermittent	2 466	1 232	1	81	15 634	7 815	–	–
Passive	2 465	12 561	3	24	15 627	85 328	50	59

Active (0–4 years), Intermittent (4–4.5 years), Passive (4.5–10 years)
*incidence/100 000 women years

Table 4 Characteristics of 5 CIN3 cases identified among the 2 466 recipients of the HPV-16/18 vaccine in the Finnish Cancer Registry –based passive long-term follow-up of the clinical trial participants between 4.5 and 10 years post vaccination.

Age at enrolment	Baseline cervical HPV DNA status	Number of doses received in 2004-20	Date of diagnosis	d-point (CIN3) HPV DNA status	HPV-052 participant
16 years	HPV16	three doses	Sep 2010	HPV16	no
17 years	HPV16	three doses	May 2012	HPV16	no
17 years	HPV16	three doses	Mar 2013	HPV16	no
16 years	HPV31	three doses	Apr 2013	n.a.	yes*
17 years	HPV16	three doses	Mar 2012	HPV16	yes†

*One HPV DNA test after the end of the PATRICIA trial 3.5 years before the CIN3+ diagnosis
†CIN3+ diagnosis made before start of the passive follow-up

Histopathological block retrieval and re-analysis Diagnostic, formalin-fixed histopathological blocks were identified by the permission of Valvira, a department of the Finnish Ministry of Health and Social Welfare. An experienced pathologist confirmed that the retrieved archival diagnostic block contained a CIN3+ lesion. All eligible blocks were sectioned according to a PCR-proof manner as described.[19] Extraction, amplification and typing of the lesional HPV DNA was performed as previously described.[19]

Statistic analysis Vaccine efficacy (VE) was calculated as 1 - incidence rate in vaccinated / incidence rate in unvacctinated following the intention-to-treat (ITT) principle including all individuals regardless of baseline HPV status receiving at least one HPV-16/18 vaccine dose in the arm of HPV vaccinated using statistical software SAS 9.4 software (SAS Institute, Cary, NC, USA) according to Ewell[20] and Chan.[21] The 95% confidence intervals were based on exact binomial distribution of number of vaccinated cases conditional on total number of cases.[20 21]

RESULTS

Between May 2004 and June 2005 a total of 4 808 16–17 year-old Finnish women participated the PATRICIA (HPV-008) trial (figure 1). Concomitantly, 64 16–17 year old Finnish females received the AS04-adjuvanted HPV-16/18 vaccine in an HPV-012 immunogenicity trial. In May to June 2003 and 2005 respectively 6 790 and 10 220 18–19 year old non-HPV vaccinated women responded to a health questionnaire and consented to the passive registry-based follow-up. Only the 15 627 women who were willing to participate in an HPV vaccination trial provided that they were of appropriate age, and retained their consent for 10 years were eligible to the control cohort of unvaccinated women (figure 1). The actuarial numbers of vaccinated and unvaccinated study participants followed up for 10 years yielded sufficient statistical power for the main study outcome: VE against overall CIN3+ (table 1).

The demographics of the HPV-16/18 vaccine and control cohorts did not differ except for the birth cohort (table 2). The proportions of ever users of oral contraceptives and the number of sexual partners were slightly higher, and the time of sexual debut was slightly lower in the vaccinated women as compared with the unvaccinated women. The sizeable cohorts of unvaccinated and HPV-16/18 vaccinated women for ITT-analysis resulted in 98 561 years of follow-up. Mixture of cross-vaccination and continuation of active follow-up in the HAV vaccine arm precluded it from the passive long-term follow-up.

Re-review of all the 84 CIN3+ cases was performed in 87 percent of the cases. The presence of CIN3+ was confirmed in 74 percent of the diagnostic blocks available (table 3). Three of the 4 CIN3 cases identified during the passive follow-up among the HPV-16/18 vaccinated individuals could be confirmed in the re-review. All were baseline (pre-vaccination) positive for cervical HPV16 DNA, and HPV16 DNA was identified also in the diagnostic blocks containing the CIN3 lesion (table 4). The fourth CIN3 case was baseline HPV31 DNA positive but no diagnostic block was available. One CIN3 case was diagnosed during the prolonged follow-up in the 052 study.

All the CIN3+ cases were found in the FCR follow-up between 4.5 to 10 years post vaccination. Identification of 4 and 79 cases yielded overall CIN3+ incidence rates of 32/100 000 and 93/100 000 women years in the HPV-16/18 vaccinated cohort and the unvaccinated cohort, respectively. This resulted in 66% (95%CI 8, 88) overall VE against CIN3+, irrespectively of HPV type (table 4). For the re-reviewed material the corresponding overall VE against CIN3+ was 59% (95%CI −26, 85).

In the two cohorts, HPV16 was found in all the three HPV-16/18 vaccinated CIN3 cases and in 52% (26) of the unvaccinated CIN3+ cases that were available and eligible for HPV DNA typing (table 5). VEs against HPV16 or HPV16/18 associated CIN3+ were low (table 5). The VE estimate against other than HPV16 clade A9 HPV type, including 31/33/52/58, associated CIN3+ increased from 53% to 100% when CIN3+ lesions with HPV16 co-infection were excluded from the analysis (table 5). Numbers for clade A7 or other non clade A9 HPV types were small.

There were no healthcare interventions targeted to the control cohort, and the cancer-registry follow-up was passive. No harm was caused in this study.

Table 5 Vaccine efficacy (VE, 95% CI) against cervical intraepithelial neoplasia grade three and invasive cancer (CIN3+) associated with vaccine and/or non-vaccine HPV types in women vaccinated in 2004/2005 with the HPV-16/18 vaccine between ages 16- to 17 years and in an age-aligned control cohort of originally 18- to 19-year-old women passively followed via Finnish Cancer Registry for up to 10 years post vaccination.

	Vaccine				Control					
End-point (CIN3+)	**N**	**Person yrs**	**n**	**Rate#**	**N**	**Person yrs**	**n**	**Rate#**	**VE**	**(95% CI)**
HPV16	2 465	12 561	3	24	15 627	85 328	26	30	22	–160 to 73
HPV18	2 465	12 561	–	–	15 627	85 328	3	3.5	100	–1500 to 100
HPV16/18	2 465	12 561	3	24	15 627	85 328	28	33	27	–140 to 74
HPVA9	2 465	12 561	3	24	15 627	85 328	43	50	53	–48 to 83
HPVA9*	2 465	12 561	–	–	15 627	85 328	17	20	100	–65 to 100
HPVA9/A7†	2 465	12 561	–	–	15 627	85 328	18	21	100	–55 to 100
HPV31/33/45	2 465	12 561	–	–	15 627	85 328	13	15	100	–120 to 100
All protected HPV types‡	2 465	12 561	3	24	15 627	85 328	41	48	50	–60 to 82
All protected HPV types§	2 465	12 561	–	–	15 627	85 328	13	15	100	–120 to 100
All non-protected HPVs¶	2 465	12 561	–	–	15 627	85 328	6	7.0	100	-480 to 100
All detected HPV types	2 465	12 561	3	24	15 627	85 328	46	54	56	–38 to 84
All detected HPV types**†	2 465	12 561	–	–	15 627	85 328	18	21	100	–55 to 100
Total††	2 465	12 561	3	24	15 627	85 328	50	56	59	–26 to 85
Total all§§	2 465	12 561	4	32	15 627	85 328	79	66	66	8.4 to 88

A9=HPV16/31/33/35/52/58, A7=HPV18/39/45/59/68,
All vaccine protected HPV types: 6/11/16/18/31/33/45/51/74,
All non-vaccine protected HPV types: 34/35/39/40/42/43/44/52/53/54/56/58/59/66,/68/73 and 70
*(excluding co-infections with 16)
†(excluding co-infections with 16/18)
‡HPV6/11/16/18/31/33/45/51/74
§HPV6/11/31/33/45/51/74 (excluding co-infections with 16/18)
¶HPV34/35/39/40/42/43/44/52/53/54/56/58/59/66/68/70/73 (excluding co-infections with 16/18),
**HPV positive and HPV negative
††original FCR registered CIN3+ diagnoses
§§incidence/100 000 women years

DISCUSSION

Ten years post vaccination we found statistically significant VE of 66% for the HPV-16/18 vaccine against any CIN3+ in passive cancer registry -based follow-up of our population-based cohorts comprising more than 18 000 originally 16- to 19year old women.

Our interim ITT estimates of VE against any CIN3+ are in line with what we reported about the 4year follow-up of the total vaccinated cohort (TVC) from the PATRICIA trial: VE was 45.3%.[4] With the close to 100.000 follow-up years and FCR –based follow-up, our 80% power, 0.6% cumulative CIN3+ incidence and 70% VE assumptions[9 10] were conservative. Retrieval and review of the histopathological blocks were important quality control steps for the HPV typing which, even if informative, was not always possible. It also diversified the end-points yielding very wide confidence intervals. However, even with the reduced number of HPV typed cases the overall CIN3+ VE estimate of 59% (CI included 0) was comparable with the above Finnish Cancer Registry information-based estimate. Unfortunately, the lack of baseline data for the unvaccinated cohort precluded the TVC-naive (ie, baseline HPV negative) type of analyses which earlier demonstrated a very high (93.2%) VE against any CIN3, irrespectively of HPV type in the PATRICIA trial 4 years post vaccination.[4]

One limitation was that some HPV-16/18 vaccinated women (8.3%) also participated in the HPV-052 study, the effects of which may have been contradictory. In one of these women annual HPV DNA screening may have led to an earlier detection of the CIN3 lesions, identified in the FCR follow-up, due to the high sensitivity of HPV DNA screening compared with conventional opportunistic cytology.[22] On the other hand, removal of an earlier CIN lesion in an HPV-052 participant could theoretically have led to excision of a lesion that might have surfaced as CIN3+ in the FCR follow-up. ITT analysis of the entire cohorts of HPV-16/18 vaccinated and unvaccinated women participating in the passive follow-up does not allow distinguishing between these two alternatives but is a conservative approach. Most importantly for the validity of the ongoing long-term follow-up, all our vaccinated and unvaccinated study subjects were invited to organised cytological screening visits at the age of 25 years. Moreover, opportunistic HPV vaccination among the unvaccinated controls following the licensure of the quadrivalent Gardasil and bivalent Cervarix HPV vaccines in 2006 and 2007, respectively has been negligible (data not shown).

We found only a relatively low long-term vaccine efficacy against HPV-16/18 positive CIN3+. This was because several baseline, pre-vaccination HPV16 positive vaccine recipients, developed HPV16 positive CIN3 during the 10 years of post vaccination follow-up. The HPV-16/18 AS04-adjuvanted vaccine,[6] does not protect against the HPV16 positive CIN3+ if viral infection already exists and persistent HPV16 infection has been established. The low efficacy observed in the PATRICIA trial among baseline positives already pointed to this direction.[23] Vaccination of adult women[24] of whom up to 30+% already have been exposed to hrHPV infection *may not be the most* effective HPV vaccination strategy.

In conclusion, ten years post vaccination the AS04-adjuvanted HPV-16/18 vaccine shows continued efficacy against CIN3+ irrespectively of HPV type. Our results also suggest that the wide cross-protective efficacy of the HPV-16/18 vaccine reported in clinical trials against HPV types 31/33/45[4 5] is true for the associated CIN3+ end-point in the long-term context. It is warranted to continue the long-term follow-up of the HPV vaccination trial cohorts to more accurate HPV type-specific CIN3+ end-points and all HPV-associated invasive cancer end-points.

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Contributors Contributors ML, GD, JPaa, EP and FS designed the study. ML and EP participated in planning the statistical analysis. TL did the statistical analyses. DA, MK, JPa, TP and MS-M conducted the study as study doctors, and TE and KN coordinated the study. KH, TE and EP were responsible for the registry linkages. CL, PN, and JD were responsible for the lab analyses. ML and JPaa wrote the first draft of the manuscript, all the co-authors contributed to the writing in important intellectual content by revisions and comments.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Full dataset and statistical code available from the lead author at Ilmale@uta.fi. Consent was not obtained but the presented data are anonymised and risk of identification is low.

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