Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial

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Summary

Background Cervical intraepithelial neoplasia grade 2 or greater (CIN2+) is the surrogate endpoint used in licensure trials of human papillomavirus (HPV) vaccines. Vaccine efficacy against CIN3+, the immediate precursor to invasive cervical cancer, is more difficult to measure because of its lower incidence, but provides the most stringent evidence of potential cancer prevention. We report vaccine efficacy against CIN3+ and adenocarcinoma in situ (AIS) in the end-of-study analysis of PATRICIA (PApilloma TRIal against Cancer In young Adults).

Methods Healthy women aged 15–25 years with no more than six lifetime sexual partners were included in PATRICIA, irrespective of their baseline HPV DNA status, HPV-16 or HPV-18 serostatus, or cytology. Women were randomly assigned (1:1) to receive an HPV-16/18 AS04-adjuvanted vaccine or a control hepatitis A vaccine via an internet-based central randomisation system using a minimisation algorithm to account for age ranges and study sites. The patients and study investigators were masked to allocated vaccine. The primary endpoint of PATRICIA has been reported previously. In the present end-of-study analysis, we focus on CIN3+ and AIS in the populations of most clinical interest, the total vaccinated cohort (TVC) and the TVC-naive. The TVC comprised all women who received at least one vaccine dose, approximating catch-up populations and including sexually active women (vaccine n=9319; control=9325). The TVC-naive comprised women with no evidence of oncogenic HPV infection at baseline, approximating early adolescent HPV exposure (vaccine n=5824; control=5820). This study is registered with ClinicalTrials.gov, number NCT00122681.

Findings Vaccine efficacy against CIN3+ associated with HPV-16/18 was 100% (95% CI 85·5–100) in the TVC-naive and 45·7% (22·9–62·2) in the TVC. Vaccine efficacy against all CIN3+ (irrespective of HPV type in the lesion and including lesions with no HPV DNA detected) was 93·2% (78·9–98·7) in the TVC-naive and 45·6% (28·8–58·7) in the TVC. In the TVC-naive, vaccine efficacy against all CIN3+ was higher than 90% in all age groups. In the TVC, vaccine efficacy against all CIN3+ and CIN3+ associated with HPV-16/18 was highest in the 15–17 year age group and progressively decreased in the 18–20 year and 21–25 year age groups. Vaccine efficacy against all AIS was 100% (31·0–100) and 76·9% (16·0–95·8) in the TVC-naive and TVC, respectively. Serious adverse events occurred in 835 (9·0%) and 829 (8·9%) women in the vaccine and control groups, respectively; only ten events (0·1%) and five events (0·1%), respectively, were considered to be related to vaccination.

Interpretation PATRICIA end-of-study results show excellent vaccine efficacy against CIN3+ and AIS irrespective of HPV DNA in the lesion. Population-based vaccination that incorporates the HPV-16/18 vaccine and high coverage of early adolescents might have the potential to substantially reduce the incidence of cervical cancer.

Funding GlaxoSmithKline Biologicals.

Introduction

Nearly a decade ago, a proof-of-principle report[1] on the high efficacy of a prophylactic monovalent human papillomavirus (HPV) vaccine against HPV-16 was heralded as the possible "beginning of the end" for cervical cancer,[2] the major disease associated with oncogenic HPV infection. Comprehensive reports describing excellent vaccine efficacy against precursors of cervical cancer were subsequently published for the HPV-16/18 AS04-adjuvanted vaccine (Cervarix, GlaxoSmithKline Biologicals)[3–5] and the HPV-6/-11/-16/-18 vaccine (Gardasil, Merck),[6–8] which are now licensed in many countries.

Licensure studies focused primarily on prevention of cervical intraepithelial neoplasia grade 2 or greater (CIN2+; defined as CIN2, CIN3, adenocarcinoma in situ [AIS], or invasive cervical cancer [ICC]) as the primary endpoint, since regulatory agencies considered CIN2+ to be an

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acceptable surrogate endpoint for ICC. However, it was recognised at the time that CIN2+ had limitations, including potential lack of reproducibility[9] and the fact that a large proportion of CIN2 cases spontaneously regress.[10] CIN3 is the immediate precursor of ICC,[11] and CIN3+ is generally considered to be a more predictive endpoint than CIN2+. Moreover, the prevalence of different HPV types in CIN3 lesions is more similar to that in ICC than in CIN2 lesions.[12] However, the lower incidence of CIN3+ means that its use as an endpoint requires a large sample size with a long follow-up period to ensure sufficient statistical power to make firm conclusions regarding efficacy.

The PApilloma TRIal against Cancer In young Adults (PATRICIA) is the largest trial of HPV-16/18 vaccine efficacy so far. Results from event-driven analyses showed high vaccine efficacy against CIN2+ lesions associated with HPV-16 and HPV-18 infections, and protection against non-vaccine HPV types (HPV-31, HPV-33, and HPV-45).[3,4] However, information on CIN3+ endpoints was limited because of the follow-up time accrued. Here, we report end-of-study results at month 48 with roughly 68 000 person-years of follow-up, most notably vaccine efficacy against all CIN3+ and AIS lesions irrespective of HPV DNA.

Methods

Detailed methods of the double-blind, randomised, controlled PATRICIA trial, including full inclusion and exclusion criteria, trial locations, and dates, has been reported previously.[3,4] Briefly, healthy women aged 15–25 years, from 14 countries in Asia Pacific, Europe, Latin America, and North America, and with no more than six lifetime sexual partners were included in the trial irrespective of their baseline HPV DNA status, HPV-16/18 serostatus, or cytology. The exclusion criterion of no more than six lifetime sexual partners was not applied in Finland, in accordance with local regulatory and ethical requirements,[13] so women with more than six lifetime sexual partners enrolled in Finland were included in the trial. Written informed consent was obtained from all adult participants. For minors, written informed assent was obtained from the participant and written informed consent from their parents. The trial was approved by independent ethics committees or institutional review boards at each location.

Procedures

Women received either the HPV-16/18 AS04-adjuvanted vaccine (Cervarix, GlaxoSmithKline Biologicals) or a control hepatitis A vaccine (GlaxoSmithKline Biologicals) in a 1:1 ratio at 0, 1, and 6 months (figure 1).[3,4] The study protocol prescribed that both groups were to be unmasked after the month 48 visit and offered the crossover vaccine. Long-term follow-up of women enrolled in Finland is ongoing; these women are participating in registry-based follow-up as part of a separate study (NCT01393470).[13] Cervical liquid-based cytology samples were obtained every 6 months. HPV DNA typing was done on these samples every 6 months and cytological examination using the Bethesda system was done every 12 months. A prespecified clinical management algorithm for abnormal cytology results and colposcopy referral was used (webappendix p 6, 7). Broad spectrum PCR SPF_{10}-$LiPA_{25}$ (version 1 based on licensed Innogenetics SPF10 technology; Labo Biomedical Products, Rijswijk, Netherlands) and type-specific PCR for HPV-16 and HPV-18 DNA were used to

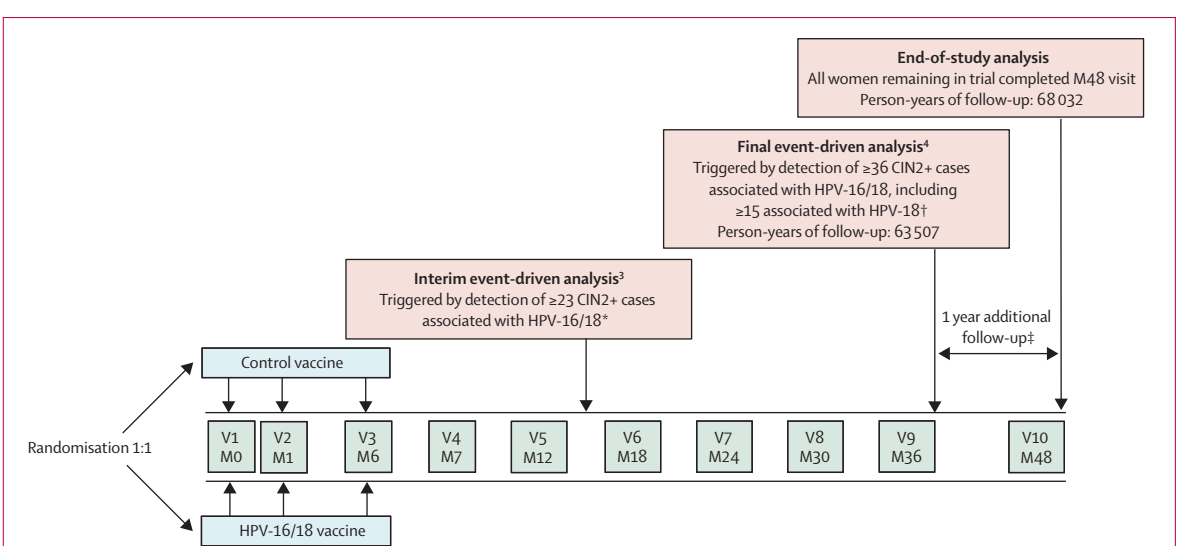

Figure 1: **Study design**
Person-years of follow-up shown are for the total vaccinated cohort. V=visit. M=month. CIN=cervical intraepithelial neoplasia. HPV=human papillomavirus. *In the total vaccinated cohort for efficacy. †In the according-to-protocol cohort for efficacy. ‡End-of-study dataset contains an additional year of follow-up for most women, versus the final event-driven analysis dataset.

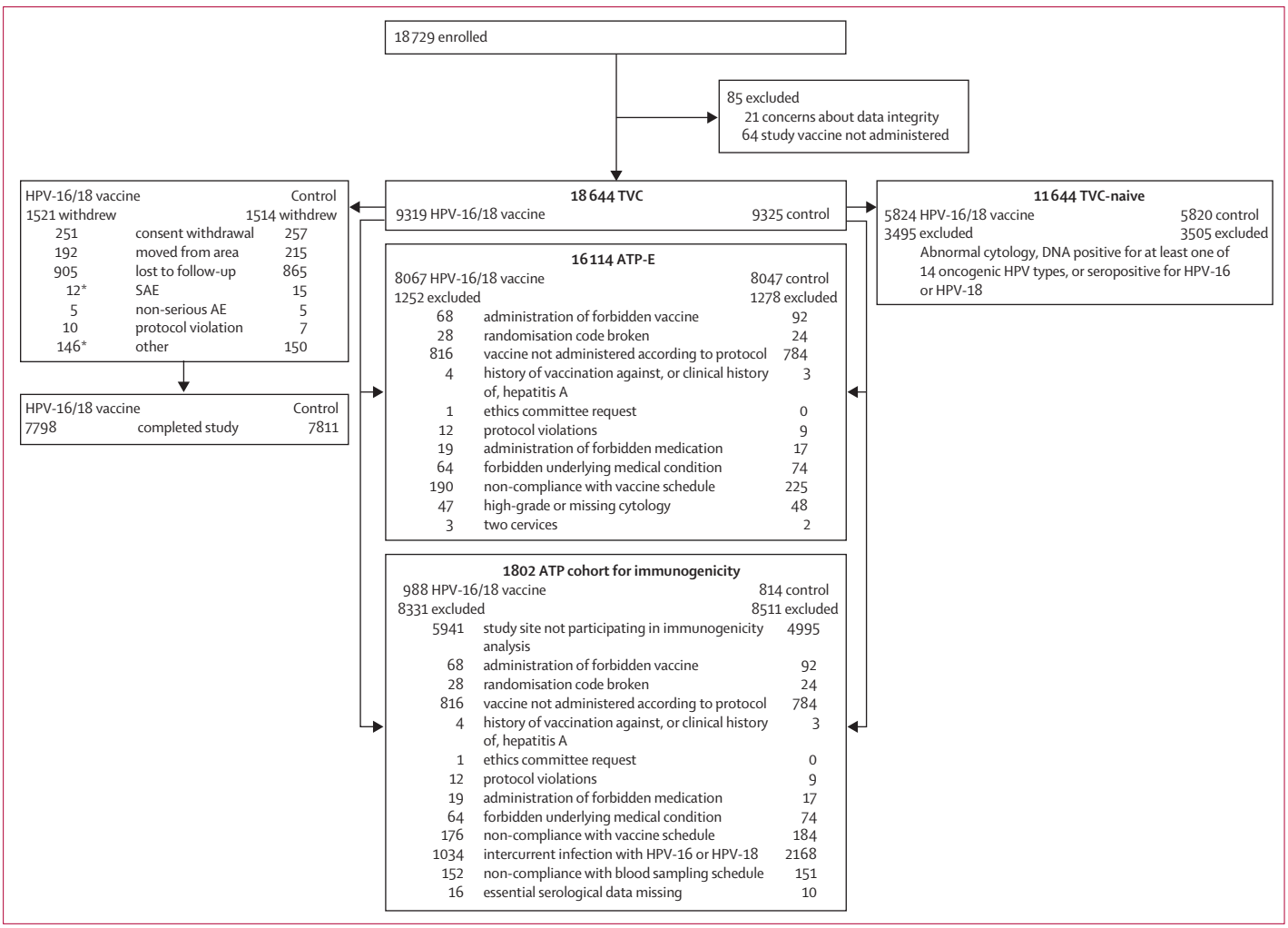

Figure 2: **Participant disposition**
HPV=human papillomavirus. TVC=total vaccinated cohort. TVC-naive=total vaccinated cohort of HPV-naive women. ATP-E=according-to-protocol cohort for efficacy. *One woman in the vaccine group was classified as having withdrawn for an "other" reason, but had in fact died. This should have been classified as a serious adverse event and is therefore now shown as such.

test cervical samples and biopsy material for HPV DNA from 14 HPV oncogenic types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68).[3,14]

Vaccine efficacy was assessed against 6-month and 12-month persistent infection, CIN1+, CIN2+, CIN3+, and AIS associated with the following: HPV-16; HPV-18; HPV-16 or HPV-18, or HPV-16 and HPV-18 (HPV-16/18). Efficacy against CIN and AIS was also assessed irrespective of HPV DNA (this includes all lesions sampled and analysed, irrespective of the HPV type identified in the lesion, plus lesions in which no HPV DNA was detected). Vaccine efficacy against abnormal cytology (atypical squamous cells of undetermined significance [ASC-US], low-grade squamous intraepithelial lesions [LSIL], high-grade intraepithelial lesions [HSIL], ASC cannot exclude HSIL [ASC-H]), colposcopy referrals, and cervical excision procedures was also assessed. Additional categories of cytological abnormalities were defined as ASC-US positive for high-risk (oncogenic) HPV types (ASC-US HR+) and ASC-US HR+ or greater, which included ASC-US HR+, LSIL, ASC-H, HSIL, and atypical glandular cells. Persistent infection was defined as detection of the same HPV type in consecutive samples over a minimum of 5 months (6-month definition) and 10 months (12-month definition). CIN1+ was defined as CIN1, CIN2, CIN3, AIS, or ICC; CIN2+ excluded CIN1, and CIN3+ excluded CIN1 and CIN2. All CIN cases were reviewed by a panel of three pathologists who were masked to vaccine allocation, using a majority rule, and an endpoint committee made final case assignments.[3]

Antibodies against HPV-16 and HPV-18 were assessed by ELISA. Seropositivity was defined as an antibody titre greater than or equal to the assay cut off: 8 EU/mL for HPV-16 and 7 EU/mL for HPV-18. Safety assessments included serious adverse events, new-onset chronic

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	Vaccine			Control			Efficacy (95% CI)
	N	Cases	Rate	N	Cases	Rate	
TVC-naive							
CIN1+							
All	5466	5	0·02	5452	141	0·69	96·5% (91·6 to 98·9)
15–17 years	1997	2	0·03	2022	79	1·01	97·4% (90·5 to 99·7)
18–25 years	3459	3	0·02	3425	62	0·49	95·3% (85·5 to 99·1)
18–20 years	1096	0	0·00	1144	35	0·83	100% (88·6 to 100)
21–25 years	2363	3	0·03	2281	27	0·32	89·4% (65·5 to 97·9)
CIN2+							
All	5466	1	0·00	5452	97	0·47	99·0% (94·2 to 100)
15–17 years	1997	1	0·01	2022	53	0·68	98·1% (88·9 to 100)
18–25 years	3459	0	0·00	3425	44	0·35	100% (91·4 to 100)
18–20 years	1096	0	0·00	1144	27	0·64	100% (85·0 to 100)
21–25 years	2363	0	0·00	2281	17	0·20	100% (76·8 to 100)
CIN3+							
All	5466	0	0·00	5452	27	0·13	100% (85·5 to 100)
15–17 years	1997	0	0·00	2022	14	0·18	100% (69·4 to 100)
18–25 years	3459	0	0·00	3425	13	0·10	100% (67·8 to 100)
18–20 years	1096	0	0·00	1144	8	0·19	100% (39·5 to 100)
21–25 years	2363	0	0·00	2281	5	0·06	100% (−4·6 to 100)
AIS							
All	5466	0	0·00	5452	6	0·03	100% (15·5 to 100)
TVC							
CIN1+							
All	8694	121	0·37	8708	324	1·01	62·9% (54·1 to 70·1)
15–17 years	2882	31	0·28	2892	155	1·47	80·1% (70·6 to 80·7)
18–25 years	5800	90	0·42	5806	169	0·80	47·0% (31·2 to 59·4)
18–20 years	1871	32	0·47	1908	83	1·21	61·3% (41·1 to 75·1)
21–25 years	3929	58	0·40	3898	86	0·60	33·2% (5·7 to 53·0)
CIN2+							
All	8694	90	0·28	8708	228	0·71	60·7% (49·6 to 69·5)
15–17 years	2882	21	0·19	2892	100	0·90	79·1% (66·2 to 87·6)
18–25 years	5800	69	0·32	5806	128	0·60	46·3% (27·5 to 60·5)
18–20 years	1871	23	0·34	1908	66	0·96	65·0% (43·0 to 79·2)
21–25 years	3929	46	0·32	3898	62	0·43	26·4% (−9·6 to 50·9)
CIN3+							
All	8694	51	0·16	8708	94	0·29	45·7% (22·9 to 62·2)
15–17 years	2882	7	0·06	2892	36	0·32	80·5% (55·6 to 92·7)
18–25 years	5800	44	0·21	5806	58	0·27	24·2% (−14·1 to 50·0)
18–20 years	1871	13	0·19	1908	30	0·43	56·3% (13·6 to 79·1)
21–25 years	3929	31	0·21	3898	28	0·20	−10·1% (−90·5 to 36·1)
AIS							
All	8694	3	0·01	8708	10	0·03	70·0% (−16·6 to 94·7)

Women were infected with at least one of types HPV-16 and HPV-18, and may have been infected with both types. Women included in the analysis of the TVC-naive cohort were HPV DNA negative for all 14 oncogenic HPV types tested for, seronegative for HPV-16 and HPV-18, and had negative cytology at month 0. Women were included in the analysis of the TVC regardless of their HPV DNA or serostatus at month 0. Oncogenic HPV types tested for were HPV-16, HPV-18, HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, HPV-56, HPV-58, HPV-59, HPV-66, and HPV-68. CIN1+ was defined histologically as CIN1, CIN2, CIN3, AIS, or invasive carcinoma; CIN2+ did not include CIN1, and CIN3+ did not include CIN1 or CIN2. Numbers of patients for the age categories do not add up to the total in the All category, because 26 patients age 14 years or 26–33 years were enrolled in the study and included in the All category. CIN=cervical intraepithelial neoplasia. AIS=adenocarcinoma in situ. HPV=human papillomavirus. TVC-naive=total vaccinated HPV-naive cohort. TVC=total vaccinated cohort. N=number of evaluable women in each group. Cases=number of evaluable women reporting at least one event. Rate=number of cases divided by sum of follow-up period (per 100 woman years); follow-up period started on the day after the first vaccine dose.

Table 1: **Vaccine efficacy against CIN1+, CIN2+, CIN3+, and AIS associated with HPV-16/18 stratified by age (TVC-naive and TVC)**

diseases (including new-onset autoimmune diseases), medically significant conditions, and pregnancy outcomes.

Statistical analysis

Here, we primarily report data from the total vaccinated cohort (TVC) and total vaccinated cohort of HPV-naive women (TVC-naive). The TVC included all women who received at least one vaccine dose and were evaluable for efficacy, irrespective of baseline HPV DNA, cytological status, and serostatus (webappendix p 8). The TVC-naive included women who received at least one vaccine dose, were evaluable for efficacy, and at baseline were HPV DNA negative for all 14 HPV types tested for, seronegative for HPV-16 and HPV-18, and had negative cytology (webappendix p 8). Data from the according-to-protocol cohort for efficacy (ATP-E) are shown in the webappendix p 5.

In the previously published analyses of PATRICIA,[3,4] which were event-driven, the ATP-E was the primary cohort. Licensure of the vaccine was based on these analyses, therefore the ATP-E was the key cohort to fully describe the vaccine's profile. However, the TVC and the TVC-naive are more relevant from a public health perspective, so we focused on these cohorts for the end-of-study analysis.

The end-of-study analysis was intended to expand and confirm the efficacy results of the previous event-driven analysis.[4] All end-of-study analyses were descriptive. Vaccine efficacy and 95% CIs were calculated using a conditional exact method (actual 95% CIs were calculated for the end-of-study analysis, whereas 97·9% and 96·1% CIs were used for the interim and final event-driven analyses, respectively[3,4]). Results were considered to confirm the statistically significant vaccine efficacy observed in the final event-driven analysis if end-of-study estimates of vaccine efficacy and their 95% CIs were higher than zero. All analyses were prespecified apart from the following, which were exploratory post-hoc analyses and must therefore be interpreted with caution: age-stratification of CIN1+, CIN3+, and AIS by 15–17 year and 18–25 year age groups; all analyses stratified by 18–20 year and 21–25 year age groups; colposcopy referrals; number of cases prevented; and reduction in cytological abnormalities (number of events for all abnormalities and number of cases and vaccine efficacy for ASC-US HR+ or greater, ASC-US HR+, and ASC-H).

Event rates were calculated as the number of cases divided by the total follow-up in years and were expressed per 100 woman years. Follow-up for the TVC and TVC-naive started the day after the first vaccine dose and ended for each outcome at the time the outcome occurred, or at the last sample (up to month 48). Statistical analyses were done with SAS version 9.1 and Proc StatXact-7 on Windows XP. The trial is registered with ClinicalTrials.gov, number NCT00122681.

	Vaccine			Control			Efficacy (95% CI)	Number of cases prevented (95% CI)*
	N	Cases	Rate	N	Cases	Rate		
TVC-naive								
CIN1+								
All	5466	174	0·85	5452	346	1·71	50·3% (40·2 to 58·8)	860 (640 to 1080)
15–17 years	1997	87	1·14	2022	190	2·47	53·8% (40·2 to 64·6)	1330 (910 to 1760)
18–25 years	3459	87	0·68	3425	156	1·24	45·5% (28·7 to 58·6)	560 (330 to 810)
18–20 years	1096	38	0·94	1144	68	1·64	42·6% (13·4 to 62·5)	700 (210 to 1200)
21–25 years	2363	49	0·56	2281	88	1·05	46·9% (23·8 to 63·3)	490 (230 to 770)
CIN2+								
All	5466	61	0·30	5452	172	0·84	64·9% (52·7 to 74·2)	540 (400 to 700)
15–17 years	1997	34	0·44	2022	101	1·30	65·9% (49·3 to 77·6)	860 (570 to 1160)
18–25 years	3459	27	0·21	3425	71	0·56	62·8% (41·3 to 77·0)	350 (200 to 510)
18–20 years	1096	10	0·25	1144	38	0·91	73·0% (44·8 to 88·0)	660 (350 to 1020)
21–25 years	2363	17	0·19	2281	33	0·39	50·7% (8·9 to 74·2)	200 (40 to 370)
CIN3+								
All	5466	3	0·01	5452	44	0·21	93·2% (78·9 to 98·7)	200 (140 to 270)
15–17 years	1997	2	0·03	2022	24	0·31	91·5% (65·9 to 99·0)	280 (170 to 430)
18–25 years	3459	1	0·01	3425	20	0·16	95·1% (69·3 to 99·9)	150 (90 to 240)
18–20 years	1096	1	0·02	1144	11	0·26	90·6% (35·5 to 99·8)	240 (90 to 440)
21–25 years	2363	0	0·00	2281	9	0·11	100% (51·4 to 100)	110 (60 to 200)
AIS								
All	5466	0	0·00	5452	7	0·03	100% (31·0 to 100)	30 (20 to 70)
TVC								
CIN1+								
All	8694	579	1·83	8708	798	2·54	27·7% (19·5 to 35·2)	710 (480 to 930)
15–17 years	2882	243	2·27	2892	368	3·43	33·9% (22·1 to 44·0)	1210 (720 to 1610)
18–25 years	5800	336	1·61	5806	430	2·08	22·3% (10·2 to 32·8)	470 (200 to 720)
18–20 years	1871	139	2·09	1908	184	2·75	24·0% (4·7 to 39·5)	660 (140 to 1190)
21–25 years	3929	197	1·39	3898	246	1·76	20·8% (4·1 to 34·7)	370 (80 to 660)
CIN2+								
All	8694	287	0·90	8708	428	1·34	33·1% (22·2 to 42·6)	440 (280 to 610)
15–17 years	2882	112	1·02	2892	200	1·83	44·0% (29·1 to 56·0)	810 (490 to 1120)
18–25 years	5800	175	0·83	5806	228	1·09	23·5% (6·5 to 37·6)	260 (70 to 440)
18–20 years	1871	62	0·91	1908	105	1·54	40·6% (18·0 to 57·3)	630 (260 to 1010)
21–25 years	3929	113	0·79	3898	123	0·87	8·9% (−18·6 to 30·0)	80 (−130 to 290)
CIN3+								
All	8694	86	0·27	8708	158	0·49	45·6% (28·8 to 58·7)	220 (130 to 320)
15–17 years	2882	21	0·19	2892	61	0·55	65·5% (42·5 to 80·0)	360 (200 to 530)
18–25 years	5800	65	0·31	5806	97	0·46	33·1% (7·5 to 51·9)	150 (30 to 270)
18–20 years	1871	22	0·32	1908	44	0·64	49·5% (13·9 to 71·2)	320 (90 to 560)
21–25 years	3929	43	0·30	3898	53	0·37	19·5% (−22·7 to 47·4)	70 (−60 to 210)
AIS								
All	8694	3	0·01	8708	13	0·04	76·9% (16·0 to 95·8)	30 (10 to 60)

Women included in the analysis of the TVC-naive cohort were HPV DNA negative for all 14 oncogenic HPV types tested for, seronegative for HPV-16 and HPV-18, and had negative cytology at month 0. Women were included in the analysis of the TVC regardless of their HPV DNA or serostatus at month 0. Oncogenic HPV types tested for were HPV-16, HPV-18, HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, HPV-56, HPV-58, HPV-59, HPV-66, and HPV-68. CIN1+ was defined histologically as CIN1, CIN2, CIN3, AIS, or invasive carcinoma; CIN2+ did not include CIN1, and CIN3+ did not include CIN1 or CIN2. Numbers of patients for the age categories do not add up to the total in the All category, because 26 patients age 14 years or 26–33 years were enrolled in the study and included in the All category. CIN=cervical intraepithelial neoplasia. AIS=adenocarcinoma in situ. HPV=human papillomavirus. TVC-naive=total vaccinated HPV-naive cohort. TVC=total vaccinated cohort. N=number of evaluable women in each group. Cases=number of evaluable women reporting at least one event. Rate=number of cases divided by sum of follow-up period (per 100 woman years); follow-up period started on the day after the first vaccine dose. *Number of cases prevented per 100 000 woman years of follow-up

Table 2: **Vaccine efficacy and number of cases prevented for CIN1+, CIN2+, CIN3+, and AIS, irrespective of HPV DNA in the lesion, stratified by age (TVC-naive and TVC)**

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See **Online** for webappendix

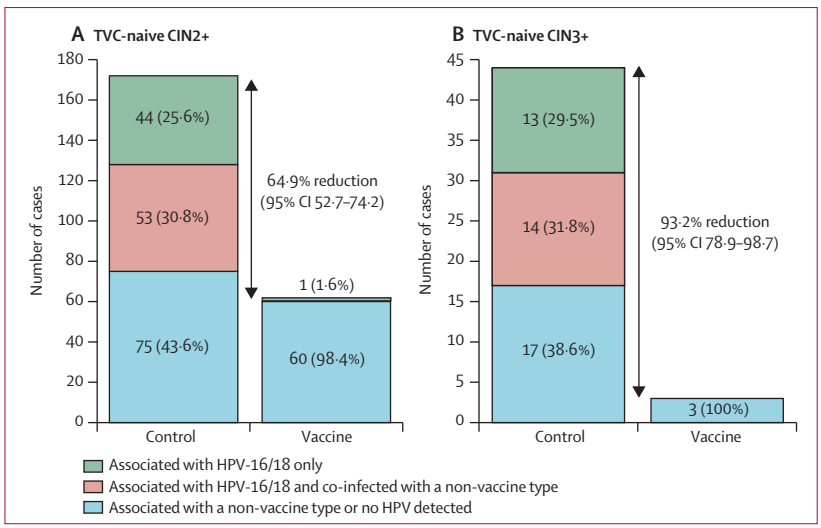


Figure 3: **Number of cases of CIN2+ and CIN3+ associated with vaccine and non-vaccine HPV types, in the TVC-naive**

Number of cases is shown inside or above the bars. Women included in the analysis of the TVC-naive cohort were HPV DNA negative for all 14 oncogenic HPV types tested for, seronegative for HPV-16 and HPV-18, and had negative cytology at month 0. Oncogenic HPV types tested for were HPV-16, HPV-18, HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, HPV-56, HPV-58, HPV-59, HPV-66, and HPV-68. Follow-up period started on the day after the first vaccine dose. CIN2+ was defined histologically as CIN2, CIN3, adenocarcinoma in situ, or invasive carcinoma; CIN3+ did not include CIN2. The percentage reduction was calculated using the conditional exact method taking into account follow-up time. CIN=cervical intraepithelial neoplasia. HPV=human papillomavirus. TVC-naive=total vaccinated cohort of HPV-naive women.

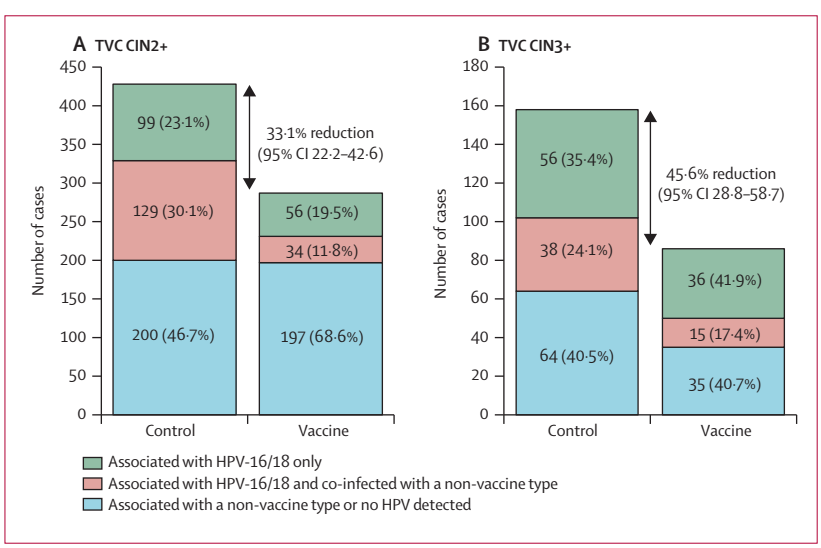


Figure 4: **Number of cases of CIN2+ and CIN3+ associated with vaccine and non-vaccine HPV types, in the TVC**

Number of cases is shown inside the bars. Women were included in the analysis of the TVC regardless of their HPV DNA or serostatus at month 0. Oncogenic HPV types tested for were HPV-16, HPV-18, HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, HPV-56, HPV-58, HPV-59, HPV-66, and HPV-68. Follow-up period started on the day after the first vaccine dose. CIN2+ was defined histologically as CIN2, CIN3, adenocarcinoma in situ, or invasive carcinoma; CIN3+ did not include CIN2. The percentage reduction was calculated using the conditional exact method taking into account follow-up time. CIN=cervical intraepithelial neoplasia. HPV=human papillomavirus. TVC=total vaccinated cohort.

Role of the funding source

The trial was funded by GlaxoSmithKline Biologicals, who designed the study in collaboration with investigators and coordinated collection, analysis, and interpretation of data. Investigators from the HPV PATRICIA Study Group collected data for the trial and cared for the participants. All authors had full access to all the trial data and had final responsibility for the decision to submit for publication.

Results

The first study participant was enrolled in May, 2004, and the last study visit took place in November, 2009. Participant disposition is shown in figure 2. In the TVC, mean and median follow-up times were 43·7 months (SD 11·7) and 47·4 months (range 0–62; 3·6 and 4·0 years), respectively. The number of person-years of follow-up was 42 942 in the TVC-naive, and 68 032 in the TVC. Demographic and baseline data are shown in the webappendix p 2.

The vaccine had efficacy against 6-month and 12-month persistent infection with HPV-16/18, with higher point estimates in the TVC-naive than in the TVC (webappendix p 3, 4). In the TVC-naive, very high vaccine efficacy was noted against CIN1+, CIN2+, CIN3+, and AIS associated with HPV-16/18; estimates were similar in all age strata (table 1). Estimates of vaccine efficacy for women in the ATP-E cohort who were DNA negative for the corresponding HPV type at baseline and month 6 were similar to those in the TVC-naive (webappendix p 5). In the TVC, efficacy against these endpoints was highest in the 15–17 year age group and progressively decreased in the 18–20 year and 21–25 year age strata (trend test p<0·0001 for CIN1+, p=0·0002 for CIN2+, and p=0·0013 for CIN3+; table 1). Indeed, the lower limit of the 95% CI of the vaccine efficacy estimate was below zero for CIN2+ and CIN3+ in the 21–25 year age group.

Vaccine efficacy irrespective of HPV DNA in the lesion progressively increased with higher lesion severity in the TVC-naive as follows: 50·3% (95% CI 40·2–58·8) for CIN1+, 64·9% (52·7–74·2) for CIN2+, and 93·2% (78·9–98·7) for CIN3+ (trend test p=0·038; table 2). A more gradual increase was observed in the TVC: 27·7% (19·5–35·2), 33·1% (22·2–42·6), and 45·6% (28·8–58·7), respectively (trend test p<0·0001; table 2). Vaccine efficacy against AIS was particularly high in the TVC-naive, at 100% (31·0–100), and was also substantial in the TVC, at 76·9% (16·0–95·8; table 2). As seen for endpoints associated with HPV-16/18, vaccine efficacy for CIN2+ and CIN3+ irrespective of HPV DNA in the lesion was highest in the 15–17 year age group and progressively decreased in the 18–20 year and 21–25 year age strata in the TVC (trend test p=0·017 for CIN2+ and p=0·0375 for CIN3+; table 2). The trend was not statistically significant for CIN1+. Again, in the 21–25 year age group, the lower limit of the 95% CI of the vaccine efficacy estimate was below zero for CIN2+ and CIN3+. Estimates were similar in all age strata in the TVC-naive.

In the TVC-naive, only three CIN3+ cases were found in the vaccine group compared with 44 in the control group, representing a 93·2% reduction (95% CI

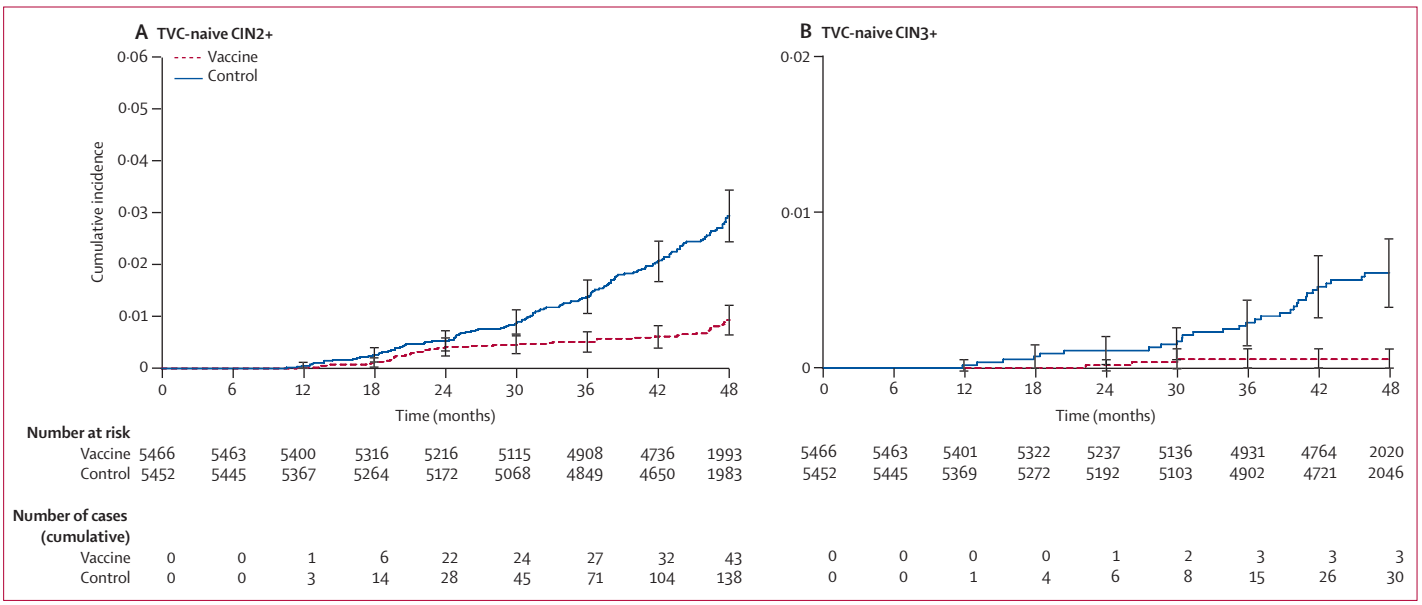


Figure 5: **Cumulative incidence of CIN2+ (A) and CIN3+ (B) irrespective of HPV DNA in the lesion, in the TVC-naive**
Women included in the analysis of the TVC-naive cohort were HPV DNA negative for all 14 oncogenic HPV types tested for, seronegative for HPV-16 and HPV-18, and had negative cytology at month 0. Oncogenic HPV types tested for were HPV-16, HPV-18, HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, HPV-56, HPV-58, HPV-59, HPV-66, and HPV-68. Follow-up period started on the day after the first vaccine dose. CIN2+ was defined histologically as CIN2, CIN3, adenocarcinoma in situ, or invasive carcinoma; CIN3+ did not include CIN2. CIN=cervical intraepithelial neoplasia. HPV=human papillomavirus. TVC-naive=total vaccinated cohort of HPV-naive women.

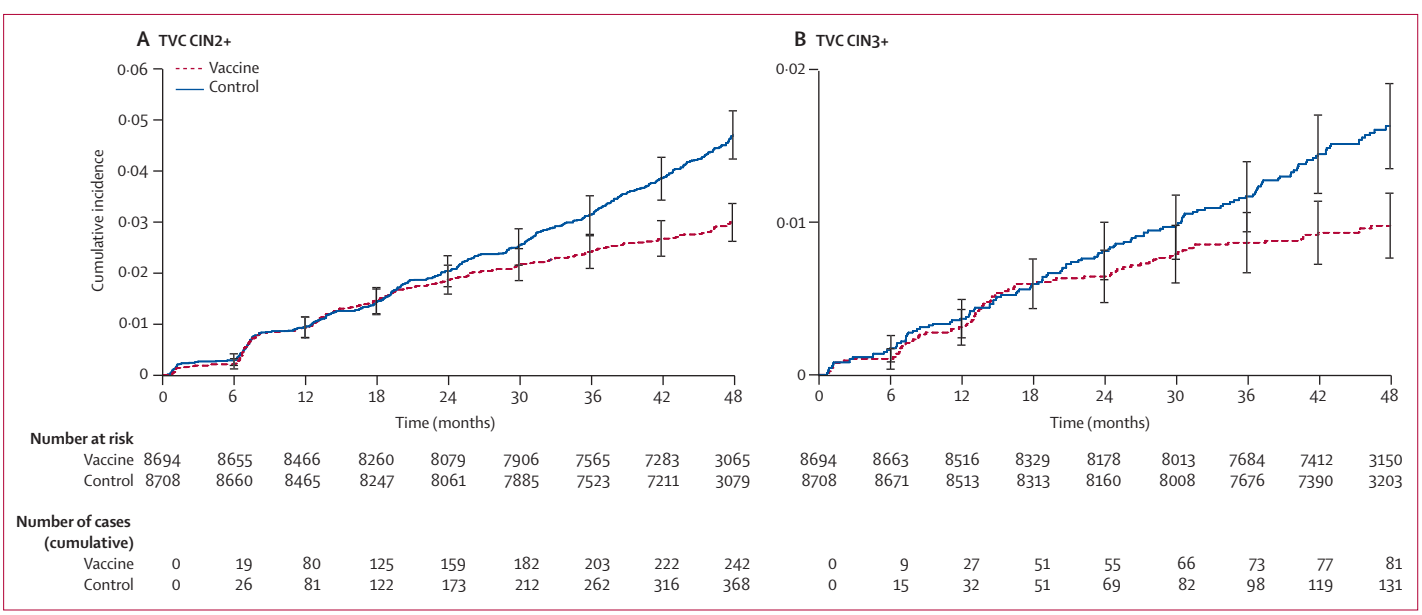
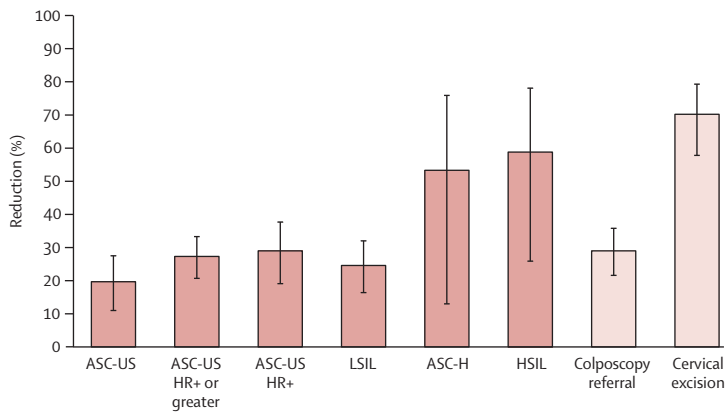


Figure 6: **Cumulative incidence of CIN2+ (A) and CIN3+ (B) irrespective of HPV DNA in the lesion, in the TVC**
Women were included in the analysis of the TVC regardless of their HPV DNA or serostatus at month 0. Oncogenic HPV types tested for were HPV-16, HPV-18, HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, HPV-56, HPV-58, HPV-59, HPV-66, and HPV-68. Follow-up period started on the day after the first vaccine dose. CIN2+ was defined histologically as CIN2, CIN3, adenocarcinoma in situ, or invasive carcinoma; CIN3+ did not include CIN2. CIN=cervical intraepithelial neoplasia. HPV=human papillomavirus. TVC=total vaccinated cohort.

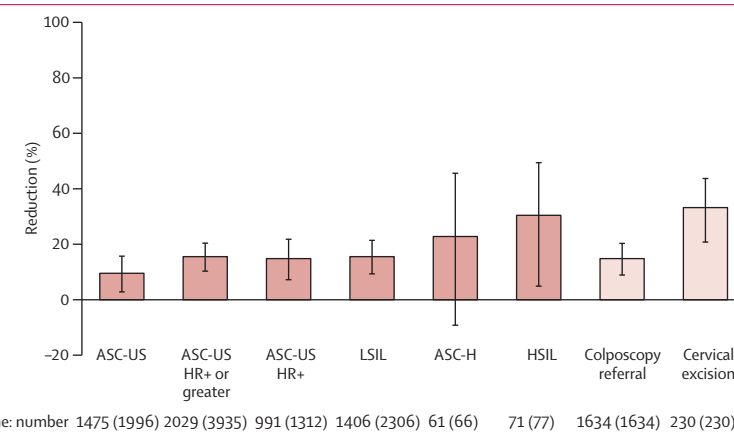
78·9–98·7); none of the three cases in the vaccine group were associated with a vaccine type (figure 3). The percentage reduction in CIN2+ cases was lower (64·9% [52·7–74·2]), with 61 cases of CIN2+ in the vaccine group and 172 in the control group. Notably, however, only one of the 61 cases in the vaccine group (1·6%) was associated with HPV-16/18 (figure 3). In the TVC, the percentage reductions in CIN3+ and CIN2+ cases were lower than in the TVC-naive (45·6% [28·8–58·7] and 33·1% [22·2–42·6], respectively; figure 4). In the control group, 40·5% of CIN3+ cases were associated with a non-vaccine type or no HPV DNA, 24·1% were associated with



	ASC-US	ASC-US HR+ or greater	ASC-US HR+	LSIL	ASC-H	HSIL	Colposcopy referral	Cervical excision
Vaccine: number of cases (events)	679 (791)	907 (1428)	400 (465)	650 (926)	16 (16)	17 (17)	672 (672)	43 (43)
Control: number of cases (events)	831 (1005)	1215 (1999)	554 (663)	847 (1248)	34 (34)	41 (42)	933 (933)	143 (143)
Vaccine efficacy	19·7%	27·3%	29·0%	24·6%	53·3%	58·8%	29·0%	70·2%
95% CI	11·0–27·5	20·7–33·3	19·1–37·7	16·4–32·0	13·0–75·9	25·9–78·1	21·6–35·8	57·8–79·3

***Figure 7*: Reduction in cytological abnormalities, colposcopy referrals, and cervical excision procedures, in the TVC-naive**

Bars show percent reduction and 95% CIs. Women included in the analysis of the TVC-naive cohort were DNA negative for all 14 oncogenic HPV types tested for, seronegative for HPV-16 and HPV-16, and had negative cytology at month 0. Oncogenic HPV types tested for were HPV-16, HPV-18, HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, HPV-56, HPV-58, HPV-59, HPV-66, and HPV-68. Follow-up period started on the day after the first vaccine dose. ASC-US, LSIL, ASC-H, HSIL, colposcopy referrals, and cervical excision procedures are irrespective of HPV DNA. TVC-naive=total vaccinated cohort of HPV-naive women. HPV=human papillomavirus. ASC-US=atypical squamous cells of undetermined significance. ASC-US HR+=ASC-US which were positive for high-risk (oncogenic) HPV DNA by Hybrid Capture II test. ASC-US HR+ or greater=ASC-US HR+, LSIL, ASC-H, HSIL, and atypical glandular cells. LSIL=low-grade squamous intraepithelial lesions. ASC-H=atypical squamous cells, cannot exclude HSIL. HSIL=high-grade intraepithelial lesions.



	ASC-US	ASC-US HR+ or greater	ASC-US HR+	LSIL	ASC-H	HSIL	Colposcopy referral	Cervical excision
Vaccine: number of cases (events)	1475 (1996)	2029 (3935)	991 (1312)	1406 (2306)	61 (66)	71 (77)	1634 (1634)	230 (230)
Control: number of cases (events)	1622 (2150)	2368 (4557)	1155 (1499)	1650 (2693)	79 (82)	102 (107)	1908 (1908)	344 (344)
Vaccine efficacy	9·5%	15·5%	14·8%	15·5%	22·8%	30·4%	14·8%	33·2%
95% CI	2·8–15·7	10·3–20·4	7·2–21·8	9·3–21·4	–9·2 to 45·6	4·9–49·4	8·9–20·3	20·8–43·7

***Figure 8*: Reduction in cytological abnormalities, colposcopy referrals, and cervical excision procedures, in the TVC**

Bars show percent reduction and 95% CIs. Women were included in the analysis of the TVC regardless of their HPV DNA or serostatus at month 0. Oncogenic HPV types tested for were HPV-16, HPV-18, HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, HPV-56, HPV-58, HPV-59, HPV-66, and HPV-68. Follow-up period started on the day after the first vaccine dose. ASC-US, LSIL, ASC-H, HSIL, colposcopy referrals and cervical excision procedures are irrespective of HPV DNA. TVC=total vaccinated cohort. HPV=human papillomavirus. ASC-US=atypical squamous cells of undetermined significance. ASC-US HR+=ASC-US which were positive for high-risk (oncogenic) HPV DNA by Hybrid Capture II test. ASC-US HR+ or greater=ASC-US HR+, LSIL, ASC-H, HSIL, and atypical glandular cells. LSIL=low-grade squamous intraepithelial lesions. ASC-H=atypical squamous cells, cannot exclude HSIL. HSIL=high-grade intraepithelial lesions.

HPV-16/18 and were co-infected with a non-vaccine type, and 35·4% were associated with HPV-16/18 only (figure 4).

Finally, for CIN3+ and CIN2+ irrespective of HPV DNA in the lesion, the cumulative incidence curves seemed to start to separate for the vaccine and control groups at around 12 months post-vaccination in the TVC-naive and around 18 months post-vaccination in the TVC (figures 5 and 6). Vaccine efficacy was also observed against cytological abnormalities in both the TVC-naive and TVC (figures 7, 8). Reductions in colposcopy referrals (29·0% [95% CI 21·6–35·8] and 14·8% [8·9–20·3]) and cervical excision procedures (70·2% [57·8–79·3] and 33·2% [20·8–43·7]) were observed in the TVC-naive and TVC, respectively (figures 7, 8).

A similar proportion of women in the vaccine and control groups experienced serious adverse events, new-onset chronic diseases, new-onset autoimmune diseases, and medically significant conditions. Pregnancy outcomes were also similar in both groups (table 3). Anti-HPV-16 and anti-HPV-18 antibody concentrations were sustained throughout 48 months of follow-up (webappendix p 9,10).

Discussion

The most important finding of the PATRICIA end-of-study analysis reported here was the high vaccine efficacy for HPV-16/18 vaccine against CIN3+ and AIS irrespective of HPV DNA in the lesion in women who were HPV naive at baseline. This represents the estimate of efficacy against the most stringent ICC precursor lesions in a cohort that approximates adolescents before sexual debut. The overall effect of the vaccine against CIN3+ is derived from protection against lesions associated with vaccine types (HPV-16/18) and protection against lesions associated with related non-vaccine oncogenic types.

The attributable proportion of HPV-16/18 increases with increasing lesion severity. Additionally, the prevalence of non-vaccine oncogenic HPV types belonging to the A7 and A9 HPV species (for which HPV-18 and HPV-16, respectively, are the prototype viruses) is increased in more severe lesions, whereas the prevalence of several other HPV types declines.[12] In fact, our observation of increasing vaccine efficacy in increasingly severe lesions is partly a result of the cross-protective vaccine efficacy consistently observed against the non-vaccine types HPV-31 and HPV-33 (both A9 species), and also apparent against HPV-45 (A7 species) and HPV-51 (A5 species). Details of the evaluation of this cross-protection are provided in a companion article.[15] The significantly higher vaccine efficacy against CIN3+ irrespective of HPV DNA compared with the corresponding CIN2+ endpoint is particularly important, because CIN3 is a more reproducible and stringent diagnostic endpoint than CIN2 and frequently progresses to ICC.[9–11] The very high vaccine efficacy against AIS irrespective of HPV DNA is also

noteworthy. Roughly 50% of adenocarcinoma is caused by HPV-16, 32% by HPV-18, and 12% by HPV-45.[16] Incidence and mortality from adenocarcinoma, which is more difficult to detect than squamous cell carcinoma,[17] are rising in many countries,[18] and adenocarcinoma might comprise up to 25% of ICC.[16]

Vaccine efficacy in the overall study population (ie, the TVC) was substantially less than that observed in the TVC-naive. Similar findings have been reported in the FUTURE trials of HPV-6/-11/-16/-18 vaccine.[8] This is not surprising, since the overall populations enrolled in these studies include women with pre-existing infections or lesions that are not affected by prophylactic vaccines.[4,8,19] The observation of progressively decreasing vaccine efficacy in the 15–17, 18–20, and 21–25 year age groups in the TVC is most likely due to the higher exposure to HPV at baseline among older women in PATRICIA, as has been reported elsewhere;[20] in PATRICIA, around 80% of women in the TVC aged 15–17 years were HPV-16/18 DNA-negative and seronegative compared with around 70% of those aged 18–25 years. This difference in efficacy by age group was absent in the TVC-naive, in which vaccine efficacy against CIN3+ irrespective of HPV DNA exceeded 90% for all age groups.

Estimates of the numbers of CIN1+, CIN2+, and CIN3+ lesions prevented in the youngest age group (15–17 years) were considerably higher than in the older age group (18–25 years and when further stratified as 18–20 and 21–25 years) in both cohorts. This observation probably reflects the higher rate of new infections in the younger age group compared with the older age group in both cohorts. Overall, the number of lesions prevented was similar in both cohorts, as has been reported for the HPV-6/11/16/18 vaccine.[8] The TVC-naive is a selected subset of the TVC, identified on the basis of being HPV-16 and HPV-18 seronegative and having no prevalent infection at baseline. This selection might introduce bias for comparisons of case prevention between the two cohorts, because of potential differences with regard to epidemiological factors that affect the rate of infection and lesion development during follow-up. Indeed, our data show that the lesion attack rate is higher in the TVC than in the TVC-naive. This might explain why the number of lesions prevented is similar in both cohorts, despite higher vaccine efficacy in the TVC-naive.

Overall, our results support the notion that maximum population benefit from immunisation of women will most likely be achieved if girls in early adolescence are vaccinated before sexual debut, since the risk of HPV infection starts from sexual debut and infection is high in adolescents.[21,22] Additionally, the HPV-16/18 vaccine produces the highest immune response, sustained over the long-term, in adolescent girls compared with young adult women,[23] further supporting immunisation of young adolescents. Our data also suggest that catch-up vaccination programmes that include sexually active women aged 15–20 years will provide a benefit against high-grade cervical lesions, albeit reduced benefit compared with vaccination of early adolescents. Although the age-stratified results we report here must be considered with caution, they are consistent with analyses suggesting reduced effectiveness and cost-effectiveness of vaccination programmes in women aged 18 or 21 years and older.[24,25] Indeed, recent data from Australia show that the introduction of the HPV vaccination programme was followed by a decrease in incidence of high-grade cervical lesions in women younger than 18 years but not in older age groups.[26] Construction of a risk model to assess whether or not there is a subgroup of women aged 21–25 years who could benefit from catch-up vaccination might be possible, but is beyond the scope of this report.

The distribution of women from different countries across the different cohorts might weaken the generalisability of our study. For example, Finland enrolled only women aged 16 or 17 years, who made up a large proportion of the TVC-naive. The exclusion of women with more than six lifetime sexual partners also weakens the generalisability of the findings, especially in the 21–25 year age group in the TVC, where some of the excluded women most likely had multiple HPV

	Vaccine	Control
Safety outcomes		
Number of women assessed	9319	9325
Serious adverse event	835 (9·0%)	829 (8·9%)
Vaccine-related serious adverse event	10 (0·1%)	5 (0·1%)
Medically significant condition*	3298 (35·4%)	3378 (36·2%)
New-onset chronic disease†	285 (3·1%)	307 (3·3%)
New-onset autoimmune disease	99 (1·1%)	95 (1·0%)
Deaths‡	10 (0·1%)	13 (0·1%)
Pregnancy and pregnancy outcomes§		
Number of pregnancies	2257	2257
Ongoing pregnancies	12 (0·5%)	11 (0·5%)
Normal infant	1642 (72·8%)	1671 (74·0%)
Abnormal infant	26 (1·2%)	22 (1·0%)
Congenital anomaly¶	18 (0·8%)	13 (0·6%)
Medically significant condition‖	8 (0·4%)	9 (0·4%)
Spontaneous abortion	205 (9·1%)	195 (8·6%)
Elective termination	212 (9·4%)	228 (10·1%)

Data are number (%) of women reporting event. TVC=total vaccinated cohort. *Medically significant conditions were defined as adverse events prompting emergency room visits, physician visits that are not routine or related to common diseases, or serious adverse events that are not related to common diseases. †A predefined list of potential new-onset chronic diseases (NOCDs) was reviewed by the Independent Data Monitoring Committee (IDMC). Based on this list, the clinical database was searched for all potential NOCDs and reviewed in a masked manner by a GlaxoSmithKline (GSK) physician before data analysis. An event was considered to be a potential NOCD if it had not been recorded in the participant's previous medical history or if symptoms were characteristic of an NOCD. A separate list, restricted to potential autoimmune events, was also reviewed by the IDMC and was used by the GSK safety physician to identify new-onset autoimmune diseases. ‡No deaths were considered possibly related to vaccination in either the vaccine group or control group. §Some less frequent pregnancy outcomes are not listed. ¶Congenital anomalies were defined as structural-morphological, chromosomal, and genetic anomalies. ‖Medically significant conditions in the infant were defined as all other reports of abnormal outcomes considered to be medically significant (eg, congenital infectious conditions, neonatal death).

Table 3: **Safety and pregnancy outcomes throughout the study (TVC)**

***Panel:* Research in context**

Systematic review

The present study is part of a development programme for prophylactic HPV vaccine. Studies were done to achieve licensure of the vaccine and to examine how the vaccine might be best used in real-world settings, and were developed in conjunction with leading experts in HPV vaccine research and with regulatory bodies. Literature related to HPV vaccination studies was systematically followed before the start of the study, during the trial, and during the development of the publication (1997 to June, 2011). The volume of literature has now increased, and we used our knowledge and expertise to select trials we thought were most relevant for the present report.

Interpretation

The primary target population for HPV vaccination is adolescent girls before sexual debut, and the most stringent endpoints currently measurable in HPV vaccine trials are CIN3+ and AIS, irrespective of HPV DNA in the lesion. Here, the end-of-study analysis of PATRICIA reports for the first time the efficacy of the HPV-16/18 vaccine against these endpoints in a population that approximates adolescents before sexual debut. Very high vaccine efficacy was shown in this population, supporting the notion that vaccination of girls in early adolescence will probably achieve maximum population benefit. We also noted substantial vaccine efficacy in a population approximating a general population of sexually active women, suggesting that catch-up vaccination will also provide some benefit. The study provides data to substantiate the benefits of HPV vaccination programmes, and health-care professionals should be encouraged to aim for a high vaccine uptake. Moving forward, if protection from HPV vaccines is shown to be durable, and high vaccination coverage can be achieved, public health bodies might want to consider whether cervical cancer screening programmes can be modified when conducted alongside vaccination strategies.

infections. Unfortunately, we do not have country-specific data on the relative proportions of the excluded women.

The main strengths of our 4-year end-of-study analysis were the size and diversity of the study population and the study duration, which resulted in roughly 68 000 person-years of follow-up and a considerably higher number of lesion cases than were available at the final event-driven analysis reported previously.[4] At the time of the final event-driven analysis, only around 3000 women had completed the month 48 visit, whereas at the end-of-study analysis, 15 600 women had completed this visit. Thus, the present end-of-study dataset contains an extra year of follow-up for most women. Furthermore, the colposcopy algorithm led to a much higher referral rate in the later part of the study, most notably in the HPV-naive population, whose first possible colposcopy would have occurred after the month 12 or month 18 visit. Thus, even though the study was powered to assess vaccine efficacy against CIN2+ associated with HPV-16/18, the large number of cases in the end-of-study analysis enabled us to verify vaccine efficacy against CIN3+ irrespective of HPV DNA, and expand our observations to AIS. Safety, immunogenicity, and efficacy against persistent HPV-16/18 infections were in line with our previous observations.[4]

The high efficacy of the vaccine against CIN3+ irrespective of HPV type in the lesion in HPV-naive women suggests that the target population for vaccination might benefit from substantial protection against cervical cancer. If the broad protection offered by HPV vaccination is durable in ongoing long term follow-up[13] and high population coverage can be achieved, modifications of cervical cancer screening programmes might be possible (panel). Screening programmes have been very effective in reducing cervical cancer,[27] but are dependent on attendance rates.[28] For developed and developing countries choosing whether to direct resources towards comprehensive screening, opportunistic forms of screening, or HPV vaccination, the present data provide important information for health economic analyses.

In conclusion, provided that organised vaccination programmes achieve high coverage in early adolescents before sexual debut, HPV vaccination has the potential to substantially reduce the incidence of cervical cancer, perhaps allowing modification of screening programmes. Appropriate effectiveness and implementation studies assessing the combination of vaccination and new screening strategies are warranted.

Contributors

ML, JP, CMW, UJ, SMG, XC, SRS, DA, M-PD, DD, FS, and GD formed the core writing team for the manuscript. All authors reviewed and commented on a draft of the manuscript and gave final approval to submit for publication. All authors contributed to the study design, acquisition of data or statistical analyses, and interpretation of data. See webappendix p 11 for the HPV PATRICIA Study Group.

Conflicts of interest

DD, GD, FS, and M-PD are employees of GlaxoSmithKline Biologicals. DD, GD, and FS own stock in GlaxoSmithKline Biologicals, and GD holds a relevant patent. All investigators at study clinical sites were funded through their institutions to do the study protocol. CMW, DA, JP, PN, HK, PDS, FYA, FXB, JH, SRS, SMG, ML, TFS, AS, XC, JCT, and BR have received funding through their institutions to do HPV vaccine studies for GlaxoSmithKline Biologicals or Merck Sharp & Dohme (Sanofi Pasteur MSD). JP received a research grant through the Helsinki University Hospital Research Institute to conduct clinical trials on HPV vaccination. SRS has also received funding through her institution from CSL to do research on school-based adolescent HPV vaccination. Through the University of New Mexico, CMW has received equipment and reagents for HPV genotyping from Roche Molecular Systems and funding for HPV vaccine studies from GlaxoSmithKline (in addition to the present study) and Merck & Co. FXB is an editor of the international newsletter (HPV TODAY) and guest editor of the journal *Vaccine* to prepare international reviews on topics related to HPV. WAJP, NSDC, FXB, XC, SMG, PN, BR, TFS, and AS have received consulting fees. SMG, SRS, FYA, PN, and TFS have received honoraria; TFS, BR, and FXB have been paid for expert testimony; BR, FYA, SRS, JCT, NSDC, PDS, and WAJP have received payment for board membership; JCT, FYA, NSDC, XC, PDS, PN, FXB, BR, and TFS have received payment for lectures, including service on speakers bureau; AS, FYA, NSDC, PDS, FXB, and BR have received payment for development of educational presentations; and NSDC, JS, WAJP, JCT, SRS, PN, XC, FXB, UJ, FYA, JH, SMG, AM, AS, and CMW have received travel reimbursements from GlaxoSmithKline Biologicals or Merck Sharp & Dohme (Sanofi Pasteur MSD), or both. DA has received support for travel from Väestöliitto. S-NC, KP, MJVG, and GL declare that they have no conflicts of interest.

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