Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women

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Summary

Background The human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine was immunogenic, generally well tolerated, and effective against HPV-16 or HPV-18 infections, and associated precancerous lesions in an event-triggered interim analysis of the phase III randomised, double-blind, controlled PApilloma TRIal against Cancer In young Adults (PATRICIA). We now assess the vaccine efficacy in the final event-driven analysis.

Methods Women (15–25 years) were vaccinated at months 0, 1, and 6. Analyses were done in the according-to-protocol cohort for efficacy (ATP-E; vaccine, n=8093; control, n=8069), total vaccinated cohort (TVC, included all women receiving at least one vaccine dose, regardless of their baseline HPV status; represents the general population, including those who are sexually active; vaccine, n=9319; control, n=9325), and TVC-naive (no evidence of oncogenic HPV infection at baseline; represents women before sexual debut; vaccine, n=5822; control, n=5819). The primary endpoint was to assess vaccine efficacy against cervical intraepithelial neoplasia 2+ (CIN2+) that was associated with HPV-16 or HPV-18 in women who were seronegative at baseline, and DNA negative at baseline and month 6 for the corresponding type (ATP-E). This trial is registered with ClinicalTrials.gov, number NCT00122681.

Findings Mean follow-up was 34·9 months (SD 6·4) after the third dose. Vaccine efficacy against CIN2+ associated with HPV-16/18 was 92·9% (96·1% CI 79·9–98·3) in the primary analysis and 98·1% (88·4–100) in an analysis in which probable causality to HPV type was assigned in lesions infected with multiple oncogenic types (ATP-E cohort). Vaccine efficacy against CIN2+ irrespective of HPV DNA in lesions was 30·4% (16·4–42·1) in the TVC and 70·2% (54·7–80·9) in the TVC-naive. Corresponding values against CIN3+ were 33·4% (9·1–51·5) in the TVC and 87·0% (54·9–97·7) in the TVC-naive. Vaccine efficacy against CIN2+ associated with 12 non-vaccine oncogenic types was 54·0% (34·0–68·4; ATP-E). Individual cross-protection against CIN2+ associated with HPV-31, HPV-33, and HPV-45 was seen in the TVC.

Interpretation The HPV-16/18 AS04-adjuvanted vaccine showed high efficacy against CIN2+ associated with HPV-16/18 and non-vaccine oncogenic HPV types and substantial overall effect in cohorts that are relevant to universal mass vaccination and catch-up programmes.

Funding GlaxoSmithKline Biologicals.

Introduction

Human papillomavirus (HPV) vaccines are now licensed in more than 100 countries. National and regional immunisation programmes aimed at young adolescent girls have been widely implemented, and include catch-up programmes in some countries up to the age of 18 years or older.[1] The HPV-16/18 vaccine is adjuvanted with AS04 (consisting of aluminium hydroxide and 3-O-desacyl-4'-monophosphoryl lipid A), shown to enhance the vaccine's immunogenicity.[2] This adjuvanted vaccine has been shown to be highly immunogenic, generally well tolerated, and effective against HPV-16 or HPV-18 infections and associated precancerous lesions, in an event-triggered interim analysis in our phase III randomised, double-blind, controlled PApilloma TRIal against Cancer In young Adults (PATRICIA),[3] and other trials.[4–7] Additionally, the vaccine has been shown to protect not only against HPV-16 and HPV-18 but also against other non-vaccine oncogenic HPV types.[3,5,8]

We now present the final event-driven analysis, which includes cases accrued over a follow-up of about 3 years. As well as a further assessment of the vaccine efficacy against persistent infection and cervical intraepithelial neoplasia grade 2+ (CIN2+) associated with HPV-16/18 that was already noted in the interim analysis, we also assessed the efficacy of the vaccine against CIN3+ lesions,

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and infections and lesions caused by non-vaccine oncogenic HPV types in the final event-driven analysis. To further explore the potential public health effect of the HPV-16/18 AS04-adjuvanted vaccine, we did efficacy analyses in a broad population of sexually active young women that included a large proportion with evidence of current or previous HPV infection at the start of the trial. Additionally, we did analyses in a population with no evidence of exposure to 14 oncogenic HPV types that represents young adolescent girls before sexual debut (the primary target population for current public health vaccination programmes).

Methods

Participants

Healthy women aged 15–25 years at the time of first vaccination were enrolled in the trial between May, 2004, and June 2005, at 135 centres in 14 countries in Asia Pacific, Europe, Latin America, and North America. Women who reported no more than six lifetime sexual partners before study enrolment, agreed to using adequate contraception over the vaccination period, and had an intact cervix were eligible for inclusion. Women were excluded if they had a history of colposcopy, were pregnant or breastfeeding, or had chronic or autoimmune disease or immunodeficiency.[3] Women were enrolled irrespective of their HPV DNA status, HPV serostatus, or cytology at baseline.

Written informed consent or assent was obtained from all participants or their parents, or both. The protocol and other materials were approved by independent ethics committees or institutional review boards.

Procedures

This final analysis in PATRICIA was initiated when a defined number of primary endpoint cases was confirmed. The trial remains double-blinded and will continue until all individuals have completed 48 months of follow-up after the first immunisation. We randomly assigned participants in a 1:1 ratio, using an internet-based centralised randomisation system, to receive HPV-16/18 AS04-adjuvanted vaccine (Cervarix, GlaxoSmithKline Biologicals, Rixensart, Belgium) or a control hepatitis A vaccine (GlaxoSmithKline Biologicals) at 0, 1, and 6 months as previously described.[3] Both vaccines were identical in appearance and were presented in indistinguishable prefilled syringes.

The primary objective was to assess the efficacy of the adjuvanted vaccine against CIN2+ associated with HPV-16 or HPV-18 in women who were seronegative at baseline, and DNA negative at baseline and month 6 for the corresponding type. This analysis was selected to provide an estimate of prophylactic vaccine efficacy in women uninfected with the vaccine type considered. Additional secondary and exploratory objectives included assessment of efficacy against 6-month and 12-month persistent infections with HPV-16, HPV-18, or other oncogenic HPV types; efficacy against CIN associated with HPV-16, HPV-18, or other oncogenic HPV types; efficacy against CIN irrespective of HPV DNA in the lesion; and reduction of colposcopy referrals and cervical excision procedures. Immunogenicity and safety were also assessed.

Cervical samples were gathered from all women every 6 months for HPV DNA typing. Gynaecological and cytopathological examinations were done every 12 months.[3] Paavonen and colleagues have described in detail the gathering of cytology, biopsy, and excisional treatment specimens, and also the prespecified clinical management algorithm for abnormal cytology and colposcopy referral.[3] A broad spectrum PCR SPF_{10} HPV $LiPA_{25}$ version 1 and SPF_{10} HPV DEIA (manufactured by Labo Biomedical Products, Rijswijk, Netherlands, based on licensed INNOGENETICS SPF_{10} technology) was used to test cervical and biopsy samples for the presence of DNA from 14 oncogenic HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68).[3,9] In prespecified analyses, detection of HPV DNA in the tissue biopsies was regarded as associated with the CIN lesion. We did an additional analysis, using the HPV type assignment algorithm, to attribute a likely causal association between a lesion and the HPV type. If more than one HPV type was found in a lesion, causality was attributed on the basis of detection of the same HPV type in the preceding cytological samples.[3] The endpoints of CIN2+ and CIN3+ irrespective of HPV DNA in the lesion included all cases of histopathologically confirmed CIN2+ and CIN3+ regardless of whether a HPV type was detected in the lesion. CIN2+ was defined histologically as CIN2, CIN3, adenocarcinoma in situ, or invasive carcinoma. CIN3+ was defined histologically as CIN3, adenocarcinoma in situ, or invasive carcinoma. All CIN cases were reviewed by an endpoint committee.

Blood samples for assessment of HPV-16/18 antibody responses were gathered from all women at months 0, 7, and 24; additional samples were gathered at months 6, 12, 36, and 48 for a subset of women from selected study sites. HPV-16 and HPV-18 antibodies were measured with HPV type-specific ELISA.[10]

Reports of serious adverse events, new-onset chronic diseases (including new-onset autoimmune diseases), medically significant conditions, and pregnancy and pregnancy outcomes were gathered. Immediate post-vaccination adverse events have been described previously.[3]

Statistical analysis

Figure 1 shows the descriptions of the analysis cohorts. The total vaccinated cohort (TVC) included all women who were given at least one vaccine dose and were evaluable for efficacy (ie, had a baseline PCR or cytology sample and one further sample available) irrespective of other criteria, and was intended to represent the general population of young women, including those who are sexually active. These women were a diverse population, including those with evidence of current or previous HPV infection and with

abnormal low-grade or high-grade cytology. The total vaccinated cohort for efficacy (TVC-E) included all women who were given at least one vaccine dose, had normal or low-grade cytology at baseline (ie, negative, atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesion), and were evaluable for efficacy. The according-to-protocol cohort for efficacy (ATP-E) included all evaluable women (ie, those meeting all eligibility criteria, complying with the protocol procedures, without any protocol violations) who were given three vaccine doses, had normal or low-grade cytology at baseline, and were evaluable for efficacy. The total vaccinated naive cohort (TVC-naive) included women who were given at least one vaccine dose, were evaluable for efficacy, and at baseline had normal cytology, were DNA negative for all 14 oncogenic HPV types investigated, and were seronegative for HPV-16 and HPV-18. This cohort was representative of young girls before their sexual debut. The HPV-16/18 type-specific analyses in the ATP-E, TVC-E, and TVC cohorts were stratified by serostatus at month 0. HPV type-specific analyses were done in women who were HPV DNA negative for the corresponding type at month 0 (and month 6 for the ATP-E cohort). Some analyses were also done irrespective of the initial HPV DNA status.

The final event-driven analysis was initiated when at least 36 cases of CIN2+ associated with HPV-16/18 (including at least 15 cases of CIN2+ associated with HPV-18) were confirmed in the ATP-E cohort. The enrolment of an estimated target of 18 000 unscreened women would provide 17 100 women who were DNA negative for HPV-16 or HPV-18 at months 0 and 6. At final analysis, assuming a dropout rate no greater than 35%, an estimated 11 114 women would be available for assessment of the primary endpoint. If a CIN2+ incidence rate of 0·55% per year and vaccine efficacy against CIN2+ of 85% are assumed, the final efficacy analysis would provide 94% power to achieve the primary objective.

Vaccine efficacy for all histopathological and virological endpoints was calculated with a conditional exact method. For the final analysis, we defined significance when the lower limit of the 96·1% CI for vaccine efficacy was greater than 30·0% for CIN2+ associated with HPV-16/18, and greater than zero for all other endpoints. The overall α of 0·05 was divided into 0·021 for the interim analysis (97·9% CI) and 0·039 for the final analysis (96·1% CI). Fisher's exact test was used to calculate p values for the comparison of the proportion of events between the vaccine and control groups. However, the p values did not determine significance because the comparison of the proportions did not take follow-up time into account. All secondary and exploratory endpoints were prespecified, except efficacy against colposcopy referrals. The HPV type assignment algorithm was prespecified for the final analysis. Statistical analyses were done with Statistical Analysis System (SAS) 9·2 and Proc StatXact-7.

Event rates were calculated as the number of cases divided by the total follow-up in years for each group and were expressed per 100 woman-years. The follow-up for each woman started the day after the third vaccination for analyses that were done in the ATP-E cohort, and the day after the first vaccination for analyses that were done in the TVC, TVC-E, and TVC-naive. Follow-up ended at the time of an event (eg, detection of CIN2+ or start of persistent infection). For women who did not have an event, follow-up ended at month 48 for those who completed the study, or the date of the last visit for which a biopsy, cytology, or PCR sample was available for those who were active in the study.

Immunogenicity analyses were done in the ATP cohort for immunogenicity (figure 1). Seropositivity rates and geometric mean titres with 95% CI were calculated, as described previously.[3] Safety analyses were done in the TVC.

This trial is registered with ClinicalTrials.gov, number NCT00122681.

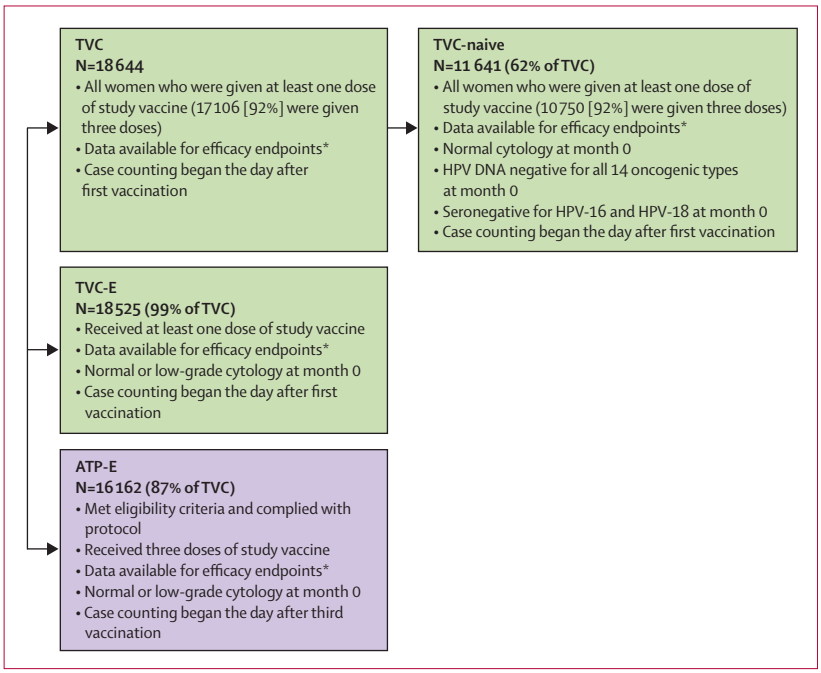

Figure 1: **Definitions of efficacy and safety cohorts**
The according-to-protocol (ATP) for immunogenicity cohort (not shown) consisted of women who met eligibility criteria and complied with the protocol, were given all three doses of the study vaccine, and for who at least one blood sample was available for at least one vaccine antigen. Immunogenicity was assessed in a subset of women from selected study sites, including at least 2000 women with at least 500 per region. A different subset of women was included in each endpoint analysis depending on the HPV type(s) found—eg, a woman with HPV-52 but no other oncogenic HPV type at baseline was excluded from the analysis of HPV-52-related endpoints, but included in all other analyses. TVC=total vaccinated cohort. TVC-naive=total vaccinated naive cohort. TVC-E=total vaccinated cohort for efficacy. ATP-E=according-to-protocol cohort for efficacy. *Baseline PCR or cytology sample and one further sample were available (does not apply to safety analysis in the TVC).

Role of the funding source

The study sponsor designed the study in collaboration with investigators, and coordinated gathering, analysis, and interpretation of data, and writing of the report. The analysis was done by an independent statistician to maintain the trial blinding. Investigators from the HPV

PATRICIA Study Group gathered data for the trial and cared for the women. The authors had access to the trial data. The corresponding author and the core writing team had full access to all the trial data and had final responsibility for the decision to submit for publication.

Results

A total of 18 644 women were included in the TVC. Figure 2 shows the distribution of the participants. A total of 17 106 women (92%) completed the full vaccination schedule. Table 1 shows the demographic and baseline

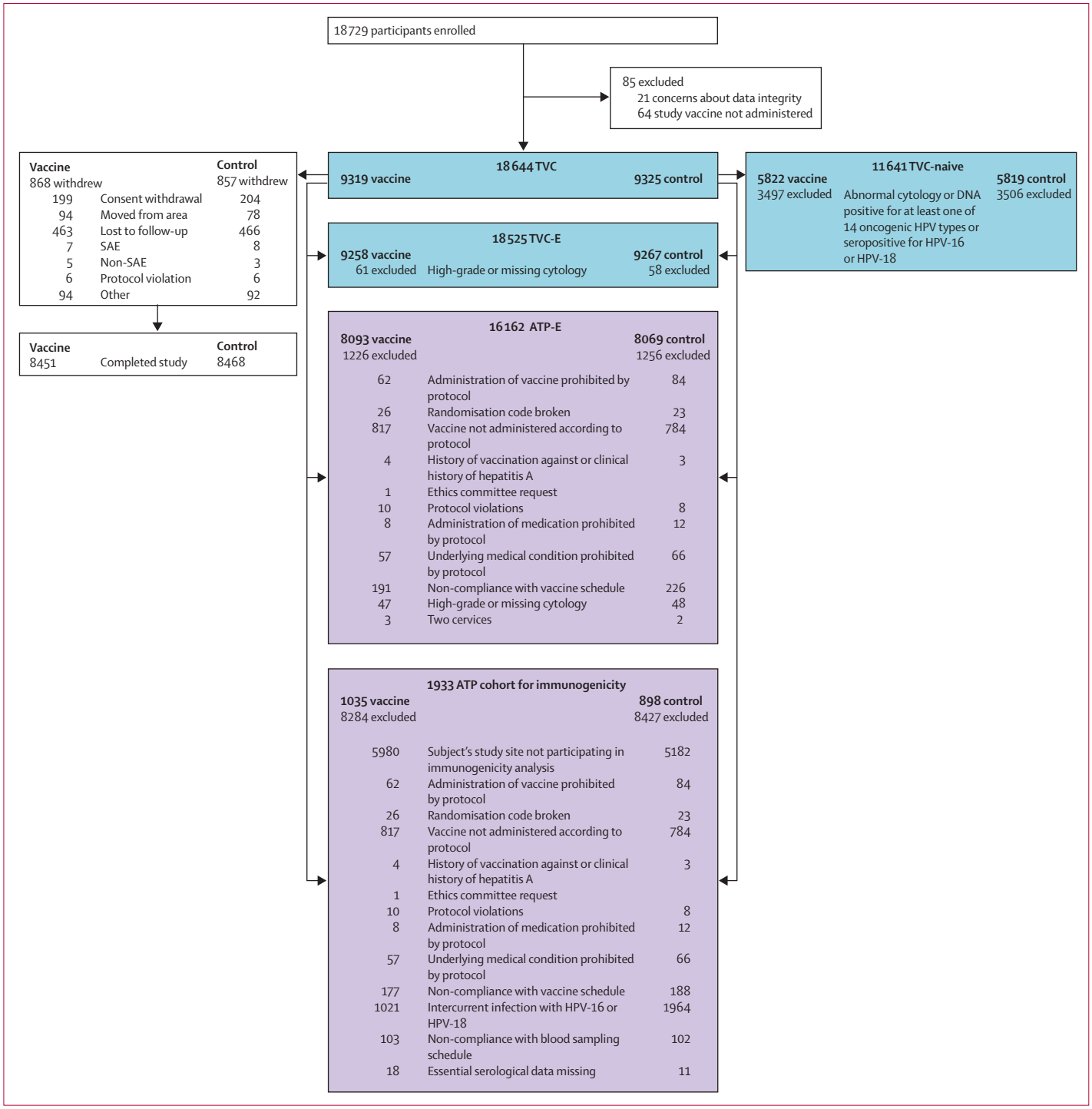

***Figure 2*: Participant disposition**

TVC=total vaccinated cohort. TVC-naive=total vaccinated naive cohort. SAE=serious adverse event. TVC-E=total vaccinated cohort for efficacy. ATP-E=according-to-protocol cohort for efficacy.

characteristics of the three cohorts. The characteristics of women in the TVC-E and ATP cohort for immunogenicity were similar (data not shown). A substantial proportion of women (n=4828, 26%) had evidence of past or current infection with HPV-16/18 at baseline (table 1), but only 98 (<1%) were DNA positive for both HPV-16 and HPV-18. The mean duration of follow-up at the time of the final event-driven analysis was 34·9 months (SD 6·4) for the ATP-E cohort, and 39·4 months (9·5) for the TVC-E.

The primary endpoint analysis was done in the ATP-E cohort in women who were seronegative at month 0 and HPV DNA negative at months 0 and 6 for the HPV type considered in the analysis. All results presented here are from this population unless otherwise stated. At the final analysis, a total of 60 cases of CIN2+ were confirmed (table 2), of which 33 (55%) contained DNA from non-vaccine oncogenic HPV types in addition to HPV-16 or HPV-18.

High efficacy was noted against CIN2+ associated with HPV-16/18 in the ATP-E cohort when the two HPV types were considered as a composite endpoint or when they were considered separately. Similary, high vaccine efficacy against CIN2+ was noted in the TVC-E (table 2).

In the analysis with the HPV type assignment algorithm, vaccine efficacy was 98·1% (96·1% CI 88·4–100; p<0·0001) against HPV-16/18, 100% (91·0–100; p<0·0001) against HPV-16, and 92·3% (45·7–99·9; p=0·0009) against HPV-18. Results in the TVC-E were similar. In the one case of CIN2+ lesion associated with HPV-16/18 in the vaccine group (ATP-E), the CIN2 lesion was detected at month 42 with HPV-18 and HPV-52 DNA. The woman was DNA positive for HPV-52 at baseline and throughout the study; HPV-18 infection was detected in the month 36 cervical sample, 6 months before detection of CIN2, and in the cytological specimen taken before the month 42 biopsy.

12 CIN3+ lesions containing HPV-16/18 DNA (including three cases of adenocarcinoma in situ but no cases of invasive cervical cancer) were detected among the 60 cases of CIN2+, two in the vaccine group, and ten in the control group (table 2). With the HPV type assignment algorithm,

	ATP-E		TVC		TVC-naive	
	Vaccine (N=8093)	Control (N=8069)	Vaccine (N=9319)	Control (N=9325)	Vaccine (N=5822)	Control (N=5819)
Age (years, SD)	19·9 (3·1)	19·9 (3·1)	20·0 (3·1)	20·0 (3·1)	19·9 (3·2)	19·8 (3·1)
Region						
Asia Pacific	2658 (33%)	2651 (33%)	3175 (34%)	3177 (34%)	2203 (38%)	2134 (37%)
Europe	3032 (37%)	3037 (38%)	3224 (35%)	3224 (35%)	2173 (37%)	2209 (38%)
North America	1202 (15%)	1197 (15%)	1532 (16%)	1538 (16%)	772 (13%)	786 (14%)
Latin America	1201 (15%)	1184 (15%)	1388 (15%)	1386 (15%)	674 (12%)	690 (12%)
Number of sexual partners in past year						
0	250 (4%)	256 (4%)	294 (4%)	292 (4%)	210 (5%)	208 (4%)
1	5148 (74%)	5136 (74%)	5862 (74%)	5869 (74%)	3665 (79%)	3655 (78%)
2	990 (14%)	1033 (15%)	1114 (14%)	1161 (15%)	530 (11%)	552 (12%)
≥3	577 (8%)	532 (8%)	636 (8%)	595 (8%)	238 (5%)	245 (5%)
No data	1128	1112	1413	1408	1179	1159
HPV-16 infection status						
DNA negative and seronegative	6512 (81%)	6485 (81%)	7448 (81%)	7430 (81%)	5822 (100%)	5819 (100%)
DNA negative and seropositive	1078 (13%)	1106 (14%)	1258 (14%)	1302 (14%)	0	0
DNA positive and seronegative	200 (2%)	184 (2%)	230 (2%)	228 (2%)	0	0
DNA positive and seropositive	232 (3%)	210 (3%)	286 (3%)	250 (3%)	0	0
No data	71	84	97	115	0	0
HPV-18 infection status						
DNA negative and seronegative	7014 (87%)	7005 (87%)	8035 (87%)	8057 (87%)	5822 (100%)	5819 (100%)
DNA negative and seropositive	840 (10%)	829 (10%)	988 (11%)	968 (10%)	0	0
DNA positive and seronegative	102 (1%)	94 (1%)	127 (1%)	114 (1%)	0	0
DNA positive and seropositive	78 (<1%)	82 (1%)	88 (<1%)	102 (1%)	0	0
No data	59	59	81	84	0	0
HPV-16/18 infection status						
No evidence of infection	5965 (74%)	5936 (74%)	6802 (74%)	6788 (74%)	5822 (100%)	5819 (100%)
Evidence of current or past infection	2050 (26%)	2045 (26%)	2409 (26%)	2419 (26%)	0	0
No data	78	88	108	118	0	0

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	ATP-E		TVC		TVC-naive	
	Vaccine (N=8093)	Control (N=8069)	Vaccine (N=9319)	Control (N=9325)	Vaccine (N=5822)	Control (N=5819)
(Continued from previous page)						
Chlamydia trachomatis						
Negative	7128 (95%)	7138 (95%)	8155 (94%)	8188 (94%)	5225 (96%)	5224 (96%)
Positive	387 (5%)	381 (5%)	478 (6%)	475 (5%)	191 (4%)	191 (4%)
No data	578	550	686	662	406	404
Contraceptive use*						
Hormonal	4855 (60%)	4914 (61%)	5544 (59%)	5662 (61%)	3107 (53%)	3236 (56%)
Intrauterine device	403 (5%)	352 (4%)	501 (5%)	472 (5%)	311 (5%)	259 (4%)
Sterilised	84 (1%)	80 (<1%)	105 (1%)	96 (1%)	59 (1%)	48 (<1%)
Condom use						
Always	1700 (31%)	1695 (31%)	1891 (31%)	1859 (30%)	1220 (35%)	1145 (32%)
Sometimes/never	3801 (69%)	3782 (69%)	4287 (69%)	4298 (70%)	2304 (65%)	2424 (68%)
No data	2592	2592	3141	3168	2298	2250
Smoking status						
Never smoked or smoked for ≤6 months	5707 (71%)	5683 (70%)	6401 (70%)	6388 (70%)	4253 (75%)	4221 (74%)
Smoker for ≥6 months (current or past)	2385 (29%)	2381 (30%)	2706 (30%)	2726 (30%)	1422 (25%)	1472 (26%)
No data	1	5	212	211	147	126

Data are n (%), unless otherwise indicated. When data were missing, percentages were calculated with available data. ATP-E=according-to-protocol cohort for efficacy. TVC=total vaccinated cohort. TVC-naive=total vaccinated naive cohort. *Women might have used more than one method of contraception, or a method that is not listed.

Table 1: **Participant demographics and baseline characteristics**

	N	HPV-16 or HPV-18 DNA in lesion				HPV-16 or HPV-18 DNA in lesion and in preceding cytology samples (HPV type assignment algorithm)*			
		n	Event rate (96·1% CI)†	Vaccine efficacy (96·1% CI)	p value	n	Event rate (96·1% CI)†	Vaccine efficacy (96·1% CI)	p value
ATP-E									
CIN2+									
HPV-16/18‡									
Vaccine	7344	4	0·02 (0·01 to 0·06)	92·9% (79·9 to 98·3)	<0·0001	1	0·01 (0·00 to 0·03)	98·1% (88·4 to 100)	<0·0001
Control	7312	56	0·32 (0·24 to 0·42)	..	..	53	0·30 (0·22 to 0·40)	..	..
HPV-16									
Vaccine	6303	2	0·01 (0·00 to 0·05)	95·7% (82·9 to 99·6)	<0·0001	0	0·00 (0·00 to 0·03)	100% (91·0 to 100)	<0·0001
Control	6165	46	0·31 (0·22 to 0·42)	..	..	45	0·30 (0·22 to 0·41)	..	..
HPV-18									
Vaccine	6794	2	0·01 (0·00 to 0·05)	86·7% (39·7 to 98·7)	0·0013	1	0·01 (0·00 to 0·04)	92·3% (45·7 to 99·9)	0·0009
Control	6746	15	0·09 (0·05 to 0·16)	..	..	13	0·08 (0·04 to 0·14)	..	..
CIN3+									
HPV-16/18‡									
Vaccine	7344	2	0·01 (0·00 to 0·04)	80·0% (0·3 to 98·1)	0·0221	0	0·00 (0·00 to 0·02)	100% (36·4 to 100)	0·0038
Control	7312	10	0·06 (0·03 to 0·11)	..	..	8	0·05 (0·02 to 0·09)	..	..
HPV-16									
Vaccine	6303	2	0·01 (0·00 to 0·05)	67·2% (–97·1 to 97·2)	0·1749	0	0·00 (0·00 to 0·03)	100% (8·8 to 100)	0·0146
Control	6165	6	0·04 (0·01 to 0·09)	..	..	6	0·04 (0·01 to 0·09)	..	..
HPV-18									
Vaccine	6794	0	0·00 (0·00 to 0·02)	100% (–19·3 to 100)	0·0307	0	0·00 (0·00 to 0·02)	100% (–170·5 to 100)	0·1236
Control	6746	5	0·03 (0·01 to 0·07)	..	..	3	0·02 (0·00 to 0·06)	..	..

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	N	HPV-16 or HPV-18 DNA in lesion			HPV-16 or HPV-18 DNA in lesion and in preceding cytology samples (HPV type assignment algorithm)*			
		n	Event rate (96·1% CI)†	Vaccine efficacy (96·1% CI)	p value	n	Event rate (96·1% CI)†	Vaccine efficacy (96·1% CI)	p value
(Continued from previous page)									
TVC-E									
CIN2+									
HPV-16/18‡									
Vaccine	8040	5	0·02 (0·01 to 0·05)	94·5% (86·2 to 98·4)	<0·0001	2	0·01 (0·00 to 0·03)	97·7% (91·0 to 99·8)	<0·0001
Control	8080	91	0·39 (0·31 to 0·48)	..	..	87	0·37 (0·30 to 0·47)	..	..
HPV-16									
Vaccine	6921	3	0·01 (0·00 to 0·05)	95·9% (87·0 to 99·3)	<0·0001	1	0·00 (0·00 to 0·03)	98·6% (91·5 to 100)	<0·0001
Control	6923	73	0·37 (0·28 to 0·46)	..	..	71	0·36 (0·27 to 0·45)	..	..
HPV-18									
Vaccine	7455	2	0·01 (0·00 to 0·04)	91·6% (64·6 to 99·2)	<0·0001	1	0·00 (0·00 to 0·03)	95·4% (70·1 to 99·9)	<0·0001
Control	7480	24	0·11 (0·07 to 0·17)	..	..	22	0·10 (0·06 to 0·16)	..	..
CIN3+									
HPV-16/18‡									
Vaccine	8040	2	0·01 (0·00 to 0·03)	90·9% (60·8 to 99·1)	<0·0001	0	0·00 (0·00 to 0·02)	100% (78·1 to 100)	<0·0001
Control	8080	22	0·09 (0·06 to 0·15)	..	..	20	0·09 (0·05 to 0·13)	..	..
HPV-16									
Vaccine	6921	2	0·01 (0·00 to 0·04)	87·5% (43·8 to 98·8)	0·0013	0	0·00 (0·00 to 0·02)	100% (72·1 to 100)	<0·0001
Control	6923	16	0·08 (0·04 to 0·13)	..	..	16	0·08 (0·04 to 0·13)	..	..
HPV-18									
Vaccine	7455	0	0·00 (0·00 to 0·02)	100% (24·2 to 100)	0·0156	0	0·00 (0·00 to 0·02)	100% (–20·3 to 100)	0·0625
Control	7480	7	0·03 (0·01 to 0·07)	..	..	5	0·02 (0·01 to 0·06)	..	..

N=number of evaluable women in each group. n=number of evaluable women reporting at least one event in each group. ATP-E=according-to-protocol cohort for efficacy. TVC-E=total vaccinated cohort for efficacy. *In cases with several HPV types, the lesion was assigned to the HPV types found in the lesion if the same types were found in at least one of the two preceding cytology samples. †Number of cases divided by sum of follow-up period (per 100 woman years); follow-up period started on day after third vaccine dose for the ATP-E cohort and day after first vaccine dose for the TVC-E. ‡Women were infected with one or both HPV types (thus, number of women with a HPV-16-associated lesion and number with a HPV-18-associated lesion might not equal number of women with a HPV-16/18-associated lesion).

Table 2: **Vaccine efficacy against cervical intraepithelial neoplasia grade 2 or more (CIN2+) and grade 3 or more (CIN3+) associated with human papillomavirus (HPV)-16/18 in women who were DNA negative and seronegative at baseline for the corresponding HPV type**

no cases of CIN3+ associated with HPV-16/18 were identified in the vaccine group compared with eight in the control group, and vaccine efficacy was 100% (table 2). Results in the TVC-E were similar (table 2).

A high level of protection was noted against persistent infections with HPV-16/18 in the ATP-E cohort: vaccine efficacy was 93·8% (96·1% CI 91·0–95·9; p<0·0001) against 6-month persistence, and 91·2% (85·9–94·8; p<0·0001) against 12-month persistence (webappendix p 1).

Vaccine efficacy against CIN2+ associated with HPV-16/18 in women in the TVC who were DNA positive at baseline, irrespective of initial serostatus, was 5·8% (96·1% CI –34·3 to 33·9; p=0·7251; webappendix p 2). Vaccine efficacy in women who were DNA positive and seronegative at study entry was 35·2% (–22·2 to 66·3; p=0·1374; webappendix p 2). In women who were HPV-16/18 DNA positive and seropositive at study entry, the number of cases of CIN2+ was non-significantly higher in the vaccine group than in the control group (53 of 333 [15·9%] *vs* 44 of 307 [14·3%]; vaccine efficacy –13·8% [–77·6 to 26·7; p=0·5835]). This outcome could possibly be

	N	n	Vaccine efficacy (96·1% CI)	p value
6-month persistent infection				
HPV-31				
Vaccine	7394	46	78·7% (70·2 to 85·2)	<0·0001
Control	7398	215	..	..
HPV-33				
Vaccine	7527	67	45·7% (25·1 to 60·9)	<0·0001
Control	7496	123	..	..
HPV-45				
Vaccine	7587	23	75·7% (60·4 to 85·7)	<0·0001
Control	7540	94	..	..
HPV-52				
Vaccine	7280	314	7·8% (–8·7 to 21·8)	0·2796
Control	7221	339	..	..
HPV-58				
Vaccine	7512	144	1·8% (–26·0 to 23·4)	0·8592
Control	7494	147	..	..

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See **Online** for webappendix

	N	n	Vaccine efficacy (96·1% CI)	p value
(Continued from previous column)				
HPV-31/33/45/52/58				
Vaccine	7664	534	30·2% (21·5 to 38·1)	<0·0001
Control	7640	755	..	..
Any oncogenic type except HPV-16/18*				
Vaccine	7665	1247	12·1% (4·7 to 19·0)	0·0005
Control	7640	1406	..	..
Any oncogenic type				
Vaccine	7665	1271	25·0% (18·9 to 30·6)	<0·0001
Control	7640	1647	..	..
12-month persistent infection†				
HPV-31				
Vaccine	7248	21	79·4% (66·1 to 88·1)	<0·0001
Control	7252	102	..	..
HPV-33				
Vaccine	7375	31	38·0% (–1·4 to 62·6)	0·0344
Control	7347	50	..	..
HPV-45				
Vaccine	7435	10	63·0% (18·4 to 84·7)	0·0049
Control	7388	27	..	..
HPV-52				
Vaccine	7134	150	–4·7% (–34·3 to 18·3)	0·7679
Control	7078	143	..	..
HPV-58				
Vaccine	7361	64	–14·9% (–70·7 to 22·5)	0·5213
Control	7346	56	..	..
HPV-31/33/45/52/58				
Vaccine	7508	255	24·4% (10·0 to 36·5)	0·0007
Control	7488	336	..	..
Any oncogenic type except HPV-16/18*				
Vaccine	7509	567	12·1% (0·9 to 22·1)	0·0209
Control	7488	643	..	..
Any oncogenic type				
Vaccine	7509	585	28·4% (19·8 to 36·1)	<0·0001
Control	7488	803	..	..
(Continues in next column)				

	N	n	Vaccine efficacy (96·1% CI)	p value
(Continued from previous column)				
CIN2+				
HPV-31				
Vaccine	7583	2	92·0% (66·0 to 99·2)	<0·0001
Control	7599	25	..	..
HPV-33				
Vaccine	7720	12	51·9% (–2·9 to 78·9)	0·0332
Control	7706	25	..	..
HPV-45‡				
Vaccine	7782	0	100% (–67·8 to 100)	0·0619
Control	7745	4	..	..
HPV-52				
Vaccine	7461	12	14·3% (–108·1 to 65·4)	0·7000
Control	7414	14	..	..
HPV-58				
Vaccine	7709	6	64·5% (1·5 to 89·2)	0·0225
Control	7702	17	..	..
HPV-31/33/45/52/58				
Vaccine	7862	30	53·0% (24·7 to 71·3)	0·0004
Control	7853	64	..	..
Any oncogenic type except HPV-16/18*				
Vaccine	7863	50	54·0% (34·0 to 68·4)	<0·0001
Control	7853	109	..	..
Any oncogenic type				
Vaccine	7863	54	61·9% (46·7 to 73·2)	<0·0001
Control	7853	142	..	..

For combined HPV types, women included in the analysis were DNA negative for at least one HPV type at months 0 and 6 (i.e. women were included in the analysis of at least one single type). Women were included regardless of their serostatus at month 0. N=number of evaluable women in each group. n=number of evaluable women reporting at least one event in each group. *A non-vaccine oncogenic HPV type (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, or 68) had to be present; for CIN2+, lesions might be co-infected with HPV-16/18. †Women with a 12-month persistent infection were also counted in the analysis of 6-month persistent infection. ‡In the analysis of the total vaccinated cohort, there were no cases associated with HPV-45 in the vaccine group and six cases in the control group, corresponding to a vaccine efficacy of 100% (96·1% CI 7·0–100; p=0·0312).

Table 3: **Vaccine efficacy against persistent infection and cervical intraepithelial neoplasia grade 2 or more (CIN2+) associated with oncogenic human papillomavirus (HPV) types in women who were DNA negative at baseline for corresponding HPV type (according-to-protocol cohort for efficacy)**

attributed to an imbalance in the baseline cytology diagnoses in this subgroup (155 women in the vaccine group had baseline cytological abnormalities *vs* 131 in the control group). A potential increased risk of CIN2+ in HPV vaccine recipients who were HPV-16/18 DNA positive and seropositive at study entry has been suggested for the licensed quadrivalent HPV vaccine; however, this finding was also not significant.[11]

Cross-protection against individual HPV types was assessed for both persistent infection and CIN2+. Women were included in these analyses if they were HPV DNA negative at month 0 (and month 6 for ATP-E cohort) for the HPV type, irrespective of the initial serostatus.

Significant vaccine efficacy against HPV-31 was noted for 6-month persistent infection, 12-month persistent infection, and CIN2+ in all three cohorts (ATP-E, TVC-E and TVC; table 3; webappendix pp 3–6). For HPV-45, cross-protection was noted for 6-month and 12-month persistent infections in all three cohorts (table 3; webappendix pp 3–6). In the ATP-E cohort, the vaccine group did not have any cases of CIN2+ with HPV-45 DNA in the lesions; however, because only four cases were noted in the control group, vaccine efficacy did not reach significance in this cohort. In the broadest cohort (TVC), additional cases of CIN2+ associated with HPV-45 were reported in the control group; vaccine efficacy was 100% (96·1% CI 7·0–100; p=0·0312). Vaccine efficacy was also

seen against HPV-33 for 6-month persistent infection (all three cohorts; table 3; webappendix pp 3–6), 12-month persistent infection (TVC-E and TVC; webappendix pp 3–6), and CIN2+ (TVC-E and TVC; webappendix pp 3–6).

Vaccine efficacy against CIN2+ with a composite endpoint of the five most prevalent non-vaccine oncogenic HPV types (ie, 31, 33, 45, 52, and 58) in invasive cervical cancer was greater than 50% in the ATP-E cohort (table 3). Vaccine efficacy against CIN2+ that was associated with all 14 oncogenic HPV types combined was greater than 60% (table 3). For the analysis including all 12 non-vaccine oncogenic types, vaccine efficacy was more than 50% (table 3). Results in the TVC-E and TVC were similar to the ATP-E cohort (webappendix pp 3–6). Since several lesions were co-infected with HPV-16/18, we also did a post-hoc analysis excluding these lesions. In this analysis (figure 3), 48 cases in the vaccine group and 77 in the control group remained, giving a vaccine efficacy of more than 37% (figure 3).

The potential public health effect of the vaccine was assessed in the TVC and TVC-naive. Figure 4 shows the cumulative incidence of CIN2+ associated with HPV-16/18 and irrespective of HPV DNA in the lesion for the TVC (irrespective of serostatus or HPV DNA status at baseline). Vaccine efficacy was highest against CIN2+ that was associated with HPV-16/18, and that against all CIN2+ irrespective of the HPV type detected was slightly less than the vaccine efficacy against the composite endpoint of CIN2+ associated with HPV-31/33/45/52/58 (table 4). Vaccine efficacy against CIN3+ associated with HPV-16/18 infection was similar to CIN3+ irrespective of the HPV type detected (table 4). Results in the TVC-E were in agreement with those in the TVC (TVC-E data, webappendix p 7). In the TVC-naive, high efficacy was noted against CIN2+ associated with HPV-16/18. Vaccine efficacy against CIN2+ associated with HPV-31/33/45/52/58 was over 68%, and vaccine efficacy against CIN2+ irrespective of the type detected was over 70%. Vaccine efficacy against CIN3+ was 100% for HPV-16/18 and 87% for lesions irrespective of HPV type detected.

The vaccine substantially reduced the number of colposcopy referrals and cervical excision procedures in both the TVC and TVC-naive (table 4).

The proportions of women with serious adverse events, medically significant conditions, new-onset chronic diseases, and new-onset autoimmune diseases were similar in the HPV 16/18 vaccine and control groups, and so were the number of pregnancies and pregnancy outcomes (table 5).

In the ATP cohort for immunogenicity, 99·5% of women who were initially seronegative for the corresponding vaccine type seroconverted for HPV-16 and HPV-18 at month 7 (857 of 861 for HPV-16, 919 of 924 for HPV-18), and 100% of those assessed at month 36 had seroconverted for both vaccine types (webappendix p 8). Anti-HPV-16 and anti-HPV-18 antibody levels peaked at month 7 and reached a plateau between months 12 and 24 after vaccination (webappendix p 8).

Discussion

The final event-triggered analysis of our trial confirmed the high efficacy of the HPV-16/18 AS04-adjuvanted vaccine in the prevention of CIN2+ lesions associated

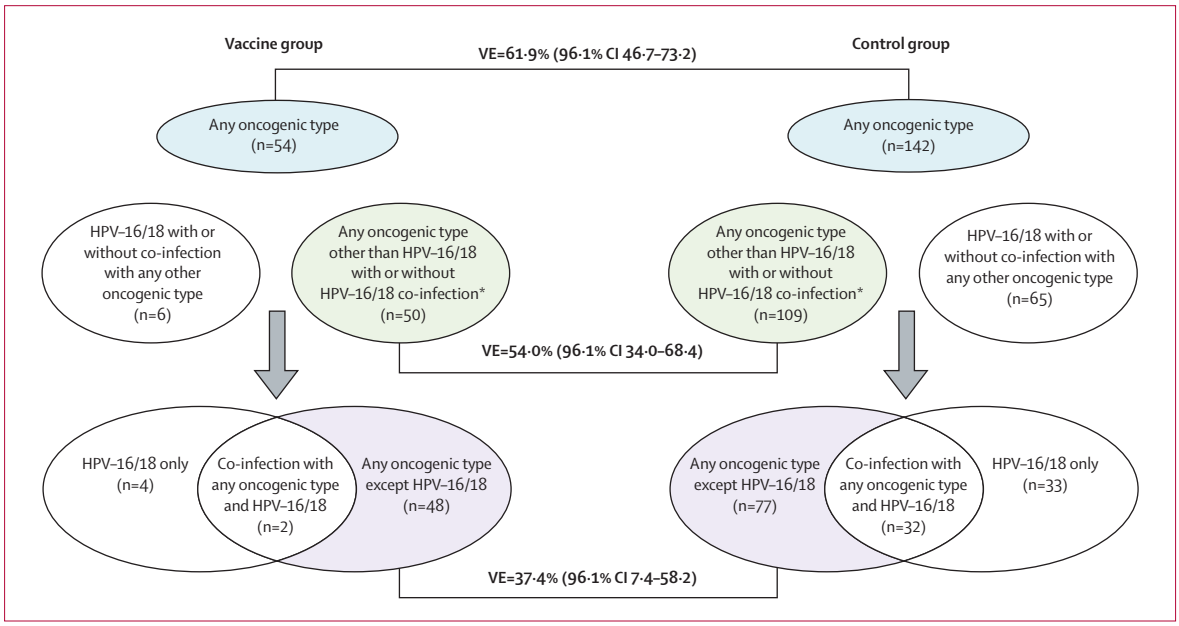

Figure 3: **Vaccine efficacy against cervical intraepithelial neoplasia grade 2 or more (CIN2+) associated with non-vaccine oncogenic human papillomavirus (HPV) types, accounting for co-infections with several types (according-to-protocol cohort for efficacy, regardless of initial serostatus)**
VE=vaccine efficacy. *An oncogenic HPV type, other than HPV-16/18, had to be present.

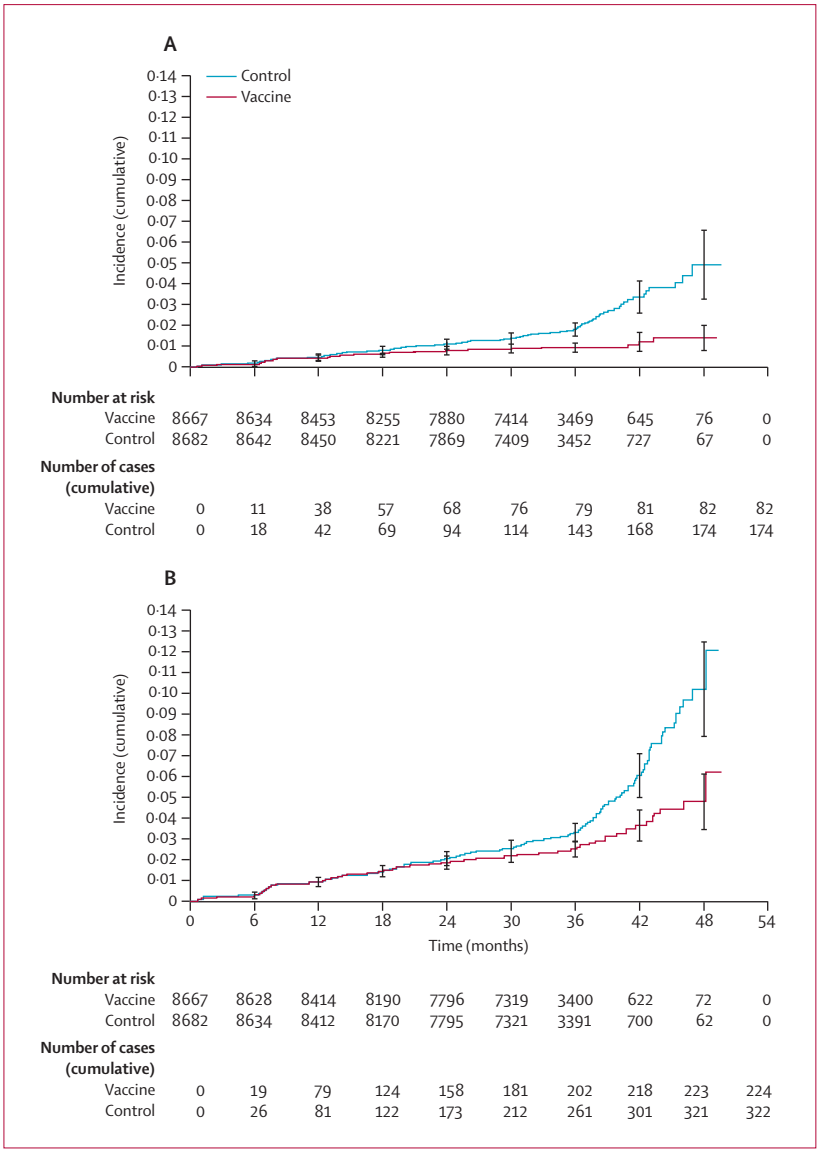

Figure 4: **Cumulative incidence of cervical intraepithelial neoplasia grade 2 or more (CIN2+) regardless of human papillomavirus (HPV) DNA status or serostatus at baseline (total vaccinated cohort) (A) associated with HPV-16/18 and (B) irrespective of HPV DNA in the lesion**

with HPV-16/18. The present analysis adds important information about the prevention of CIN2+ associated with HPV-16 and HPV-18 individually, and also the prevention of CIN3+, the immediate precursor of invasive cervical cancer (ATP-E cohort analysis). We were also able to confirm and add to our previous findings of cross-protection against non-vaccine oncogenic HPV types using both infection and lesion endpoints. The long follow-up allowed an analysis of cohorts that was relevant to public health outcomes.

The overall effect of this vaccine was assessed in two study cohorts—TVC and TVC-naive. The TVC included women both with and without oncogenic HPV infections and lesions at baseline. It represented the general population of young women, including those who were sexually active, and is therefore relevant to populations that are targeted for catchup vaccination. By contrast, the TVC-naive included only women with no evidence of exposure to any of 14 oncogenic HPV types at baseline and is closest to the population targeted by universal mass HPV vaccination (ie, young girls before sexual debut).

Vaccine efficacy against CIN2+ irrespective of HPV DNA in the lesion was about 30% (table 3) in the TVC. The effect on CIN2+ lesions resulting from newly acquired infections was only apparent with long follow-up since the vaccine would not be expected to change CIN2+ lesions derived from prevalent infections or low-grade lesions.[12] This finding was supported by the delayed separation of the Kaplan-Meier curves for the cumulative incidences of CIN2+ in this population (figure 4). Vaccine efficacy against CIN3+ irrespective of the HPV DNA in the lesion was about 33%. The efficacy in the TVC, which included women with evidence of previous or current HPV infection at entry, was indicative of the expected effect of the vaccine when used in catchup programmes.

In the TVC-naive, vaccine efficacy irrespective of HPV DNA in the lesion was about 70% (table 4) against CIN2+. The higher level of efficacy in this analysis than in the TVC resulted from the exclusion of women with prevalent infections and lesions. Vaccine efficacy against CIN3+ was higher than against CIN2+ (table 4), indicating the larger contribution of HPV-16/18 to precancerous lesions of increasing severity. The high level of overall protection suggests that the cross-protection against infection with non-vaccine oncogenic HPV types described by Paavonen and colleagues[3] applies to CIN2+ lesions.

As in the interim analysis,[3] we noted a high proportion of lesions infected with several HPV types. In more than half those women with a CIN2+ lesion associated with HPV-16/18, the lesion also contained DNA from non-vaccine oncogenic HPV types. This finding complicates the analysis of how protection against each individual HPV type contributes to overall protection since no conventional method exists to assign causality when several HPV types are detected. We therefore did an additional analysis (the HPV type assignment algorithm[3]) because of a consistent association between persistent infection and increased risk of cervical precancer and cancer.[13,14] With this approach, vaccine efficacy against HPV-16/18-associated lesions was high (table 2). DNA from HPV-18 and HPV-52 was detected in one woman with a CIN2 lesion in the vaccine group. Although our HPV type assignment algorithm helped to clarify possible causality, definite causality to HPV-52 or HPV-18 could not be assigned in this case.

Vaccine efficacy against HPV-16/18 is clearly the most important contributor to the overall reduction in cervical precancers in vaccinees; however, protection against lesions associated with non-vaccine types also contributes

	N	n	Vaccine efficacy (96·1% CI)	p value
TVC				
CIN2+				
HPV-16/18 DNA in lesion				
Vaccine	8667	82	52·8% (37·5 to 64·7)	<0·0001
Control	8682	174	..	..
HPV-31/33/45/52/58				
Vaccine	8667	95	31·5% (9·1 to 48·5)	0·0046
Control	8682	139	..	..
Irrespective of HPV DNA in lesion				
Vaccine	8667	224	30·4% (16·4 to 42·1)	<0·0001
Control	8682	322	..	..
CIN3+				
HPV-16/18 DNA in lesion				
Vaccine	8667	43	33·6% (-1·1 to 56·9)	0·0422
Control	8682	65	..	..
Irrespective of HPV DNA in lesion				
Vaccine	8667	77	33·4% (9·1 to 51·5)	0·0058
Control	8682	116	..	..
Reduction in number of colposcopy referrals*				
Vaccine	8667	1107	10·4% (2·3 to 17·8)	0·0055
Control	8682	1235	..	..
Reduction in number of cervical excision procedures				
Vaccine	8667	180	24·7% (7·4 to 38·9)	0·0035
Control	8682	240	..	..
TVC-naive				
CIN2+				
HPV-16/18 DNA in lesion				
Vaccine	5449	1	98·4% (90·4 to 100)	<0·0001
Control	5436	63	..	..
HPV-31/33/45/52/58				
Vaccine	5449	15	68·2% (40·5 to 84·1)	<0·0001
Control	5436	47	..	..
Irrespective of HPV DNA in lesion				
Vaccine	5449	33	70·2% (54·7 to 80·9)	<0·0001
Control	5436	110	..	..
CIN3+				
HPV-16/18 DNA in lesion				
Vaccine	5449	0	100% (64·7 to 100)	<0·0001
Control	5436	13	..	..
Irrespective of HPV DNA in lesion				
Vaccine	5449	3	87·0% (54·9 to 97·7)	<0·0001
Control	5436	23	..	..
Reduction in number of colposcopy referrals†				
Vaccine	5449	354	26·3% (14·7 to 36·4)	<0·0001
Control	5436	476	..	..
Reduction in number of cervical excision procedures				
Vaccine	5449	26	68·8% (50·0 to 81·2)	<0·0001
Control	5436	83	..	..

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N=number of evaluable women in each group. n=number of evaluable women reporting at least one event in each group. *In the total vaccinated cohort (TVC), 1107 women were referred for 2458 colposcopies in the vaccine group and 1235 were referred for 2723 colposcopies in the control group. †In the total vaccinated naive cohort (TVC-naive), 354 women were referred for 656 colposcopies in the vaccine group and 476 were referred for 916 colposcopies in the control group. In the TVC analysis, women were included regardless of their HPV DNA or serostatus at month 0.

Table 4: **Vaccine efficacy against cervical intraepithelial neoplasia grade 2 or more (CIN2+), or grade 3 or more (CIN3+), colposcopy referrals, and cervical excision procedures associated with human papillomavirus (HPV)-16/18, five non-vaccine oncogenic types, and irrespective of HPV DNA in lesion**

to efficacy. Vaccine efficacy against CIN2+ lesions associated with 12 non-vaccine oncogenic types was more than 50% in the ATP-E cohort (table 3). To address the complexity of co-infection with several HPV types, we did a conservative post-hoc analysis that excluded all CIN2+ lesions associated with non-vaccine types in which HPV-16/18 was also detected. Vaccine efficacy was about 37% against CIN2+ lesions associated exclusively with non-vaccine types (figure 3).

The results from these two analyses suggest that the true vaccine efficacy against CIN2+ associated with non-vaccine oncogenic HPV types is between 37% and 54%. Globally, 70% of cervical cancer is estimated to be caused by HPV-16 or HPV-18,[15] with the remaining 30% caused by other oncogenic HPV types. Thus, our analyses suggest that cross-protective efficacy of the vaccine could represent 11–16% additional protection against cervical cancer that is greater than the protection afforded by efficacy against HPV-16/18.

We also noted significant type-specific cross-protection for several non-vaccine oncogenic HPV types using both virological and lesion endpoints. Unlike lesion endpoints (eg, CIN2+) which might be complicated by the presence of several HPV types, virological endpoints (eg, persistent infection) directly measure an effect related to an individual HPV type and have been proposed as valuable clinical markers for vaccine trials when used in conjunction with lesion endpoints.[8,13] The highest level of protection against individual HPV types consistently noted in all cohorts was against HPV-31 (most closely related to HPV-16) and HPV-45 (most closely related to HPV-18). For HPV-31, data were consistent for CIN2+ and persistent infection. Although vaccine efficacy against persistent infection with HPV-45 was highly significant, data for CIN2+ associated with HPV-45 were limited by the small number of cases. Like HPV-18, HPV-45 is under-represented in cervical precancer compared with cervical cancer.[15,16] However, significant vaccine efficacy of 100% was noted in the broadest cohort (TVC) in women who were negative for HPV-45 DNA at baseline. Additionally, vaccine efficacy against CIN1+ associated with HPV-45 was significant (data not shown). HPV-45 infection plays a greater part in the development

	Vaccine	Control
Safety outcomes		
Women assessed (n)	9319	9325
Serious adverse event	701 (8%)	699 (8%)
Vaccine-related serious adverse events	11 (<1%)	6 (<1%)
Medically significant condition*	2960 (32%)	3025 (32%)
New-onset chronic disease†	251 (3%)	268 (3%)
New-onset autoimmune disease	78 (<1%)	77 (<1%)
Deaths‡	9 (<1%)	8 (<1%)
Pregnancy and pregnancy outcomes§		
Pregnancies (n)	1804	1802
Ongoing pregnancies	204 (11%)	212 (12%)
Normal infant	1124 (62%)	1136 (63%)
Abnormal infant		
Congenital anomaly¶	12 (<1%)	9 (<1%)
Medically significant condition||	9 (<1%)	10 (<1%)
Spontaneous abortion	164 (9%)	156 (9%)
Elective termination	185 (10%)	194 (11%)

Data are number (%) of women reporting an event, unless otherwise indicated. *Medically significant conditions were defined as adverse events (prompting visits to the emergency department or to the physician) 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). On the basis of this prespecified list, the clinical database was searched for all potential NOCDs and reviewed in a blinded manner by a physician from GlaxoSmithKline before data analysis was done. An event was thought to be a potential NOCD if it had not been recorded in the previous medical history of the individual (ie, new onset) or if symptoms were characteristic of a NOCD, or both. A separate list, restricted to potential autoimmune events, was also reviewed by the IDMC and was used by the GlaxoSmithKline safety physician to identify new-onset autoimmune diseases. ‡No deaths were thought to be possibly related to vaccination in either group. §Some less frequent pregnancy outcomes are not listed. ¶Defined as structural, morphological, chromosomal, and genetic anomalies. ||Defined as all other reports of abnormal outcomes considered to be medically significant (eg, congenital infectious conditions, neonatal death).

Table 5: **Safety and pregnancy outcomes in the total vaccine cohort during the entire study**

of adenocarcinoma than in the development of squamous cell carcinoma.[15] Incidence of adenocarcinoma is rising in some countries, possibly because the current cytological screening programmes have not been successful for the detection of adenocarcinoma precursor lesions.[17,18] Indeed, developed countries with screening programmes tend to report that adenocarcinoma now accounts for up to 20% of all cervical cancers.[15,19,20] Evidence suggests that the HPV-16/18 AS04-adjuvanted vaccine also protects against HPV-33-associated endpoints, although this protection did not reach significance in some analyses (ATP-E, table 3; TVC and TVC-E, webappendix pp 3–6). The use of both virological and lesion endpoints in our study supports the robustness of cross-protection against HPV types 31, 33, and 45.

In previous studies in which cross-protection associated with another HPV vaccine was investigated, a composite endpoint of the five non-vaccine HPV types (ie, 31, 33, 45, 52, and 58) most commonly associated with invasive cervical cancer has been reported.[21,22] In our vaccine trial, vaccine efficacy was significant with this composite endpoint in all cohorts that were assessed.

The reduction in the number of lesions in the TVC and TVC-naive was accompanied by a significant proportional reduction in the numbers of colposcopy referrals and cervical excision procedures. Reduction in the number of cervical excision procedures might be accompanied by a reduction in the numbers of preterm births and other adverse pregnancy outcomes because these outcomes have been shown to be associated with the treatment of CIN.[23,24]

Our trial had some limitations but also several important strengths. Key strengths of the trial were its duration and size. These enabled demonstration in the TVC-naive of protection against CIN3+, which is thought to be a more reliable endpoint than is CIN2+.[25] Future assessment of the duration of clinical protection cannot be done in this trial because women in the control group are offered the HPV-16/18 vaccine after 4 years of follow-up. However, long-term follow-up of many of the women in TVC-naive will continue in Finland[26] and in phase IV trials.

Another strength of this trial is that a broadly representative group of women from four global regions (North America, Latin America, Europe, and Asia-Pacific) with up to six lifetime sexual partners, who might have had abnormal cytology at entry or previous or current HPV infections, were enrolled. This population is one of the most diverse populations of young women in HPV vaccine efficacy studies reported so far. The vaccine immune response in this population was uniformly high, supporting potential broad generalisability of the results. However, despite the widespread geographical recruitment, some regions, including Africa, were not included. Since 2004, several trials of the vaccine have started in Africa and other countries that did not participate in our PATRICIA trial.

The results in the TVC-naive give a good indication of the potential benefit of vaccinating presexually active adolescents—ie, the population being targeted for universal mass vaccination. However, serological status is an imperfect marker of previous infection, and therefore the TVC-naive might not be fully representative of the target population. Similarly, the TVC is not fully representative of the general population, as some exclusion criteria were applied to enrolment. Generalisability of the results might also be limited by the high proportion of women (92%) who received the full immunisation series, which might not be achievable in practice.

An unavoidable limitation of our trial is that the high efficacy of the vaccine against HPV-16 and HPV-18 meant that more women in the control group than in the vaccine group were referred for colposcopy. This difference might have resulted in a bias of case ascertainment for detection of lesions associated with non-vaccine types.[27] However, data for persistent infection are not confounded by this bias and also indicate type-specific protection against

important non-vaccine oncogenic HPV types. Noteworthy, true CIN2+ incidence rate associated with non-vaccine HPV types could have been underestimated during this trial because infection with oncogenic HPV types other than HPV-16 and HPV-18 results in an overall slower progression to detectable CIN2+.[28,29] High levels of cross-protection against non-vaccine types will be crucial in the consideration of modifications to the screening protocols for cervical cancer.

The safety profile of the HPV-16/18 AS04-adjuvanted vaccine was generally similar to that of the control vaccine. In a pooled analysis of data from almost 30 000 girls and women participating in phase II and III trials (including our trial), the vaccine was shown to be generally well tolerated, with a favourable safety profile in women of all ages.[7] No evidence existed of an increase in the relative risk of autoimmune disorders associated with AS04-adjuvanted vaccines in an integrated analysis of more than 68 000 participants who were given vaccines (HPV-16/18, hepatitis B, and herpes simplex vaccines) adjuvanted with AS04 compared with control vaccine.[30] The findings of our study showed that the kinetics of antibody titres to HPV-16 and HPV-18 induced by vaccination were similar to the profile reported previously.[4,5] A good correlation between the results of the ELISA used in this trial and an assay for measurement of the biologically relevant neutralising antibodies has already been shown.[10]

In conclusion, the HPV-16/18 AS04-adjuvanted vaccine provided protection against CIN2+ lesions that were associated with HPV-16 and HPV-18 as well as lesions that were associated with non-vaccine types HPV-31, HPV-33, and HPV-45; together, these five types are responsible for about 82% of all cervical cancers.[15] Although the importance of continued tests for pap or HPV in vaccinated and unvaccinated women must be emphasised, HPV vaccination has the potential to substantially reduce the incidence of cervical cancer and precancer, and the numbers of colposcopy referrals and cervical excision procedures.

Contributors

JP, CMW, SRS, AS, FXB, DJ, DD, FS, ML, and GD formed the core writing team for the report. XC, S-NC, DD, GD, DJ, ML, FS, JT, CMW, and TZ contributed to study conception and design. All authors reviewed and commented on a draft of the report and gave final approval to submit for publication. FA, DA, FXB, XC, S-NC, DD, GD, SG, HK, JH, UJ, DJ, HK, ML, GL, PN, WAJP, BR, JS, TFS, SRS, FS, AS, JCT, CMW, TZ, and JP participated in acquisition of data, statistical analyses, or interpretation of data.

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Conflicts of interest

DD, GD, FS, KH, and TZ are employees of GlaxoSmithKline Biologicals. DD, GD, FS, and KH 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. FYA, SG, ML, TFS, CMW, and BR have received funding through their institutions to do other HPV vaccine studies for GlaxoSmithKline Biologicals or Merck, or both. CMW has also received funding through her institution from Roche Molecular Systems to do HPV genotyping studies. FXB, XC, SG, DJ, PN, WAJP, BR, JS, TFS, AS, and JCT have received consulting fees in the past 3 years. DA, FXB, XC, HK, PN, JP, BR, TFS, SRS, AS, and JCT have received honoraria, paid expert testimony, or travel grants from GlaxoSmithKline Biologicals. S-NC, JH, UJ, GL declare that they have no conflicts of interest.

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