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Efficacy of Human Papillomavirus 16 and 18 (HPV-16/18) AS04-Adjuvanted Vaccine against Cervical Infection and Precancer in Young Women: Final Event-Driven Analysis of the Randomized, Double-Blind PATRICIA Trial

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We report final event-driven analysis data on the immunogenicity and efficacy of the human papillomavirus 16 and 18 ((HPV-16/18) AS04-adjuvanted vaccine in young women aged 15 to 25 years from the PApilloma TRIal against Cancer In young Adults (PATRICIA). The total vaccinated cohort (TVC) included all randomized participants who received at least one vaccine dose (vaccine, *n* = 9,319; control, *n* = 9,325) at months 0, 1, and/or 6. The TVC-naive (vaccine, *n* = 5,822; control, *n* = 5,819) had no evidence of high-risk HPV infection at baseline, approximating adolescent girls targeted by most HPV vaccination programs. Mean follow-up was approximately 39 months after the first vaccine dose in each cohort. At baseline, 26% of women in the TVC had evidence of past and/or current HPV-16/18 infection. HPV-16 and HPV-18 antibody titers postvaccination tended to be higher among 15- to 17-year-olds than among 18- to 25-year-olds. In the TVC, vaccine efficacy (VE) against cervical intraepithelial neoplasia grade 1 or greater (CIN1+), CIN2+, and CIN3+ associated with HPV-16/18 was 55.5% (96.1% confidence interval [CI], 43.2, 65.3), 52.8% (37.5, 64.7), and 33.6% (−1.1, 56.9). VE against CIN1+, CIN2+, and CIN3+ irrespective of HPV DNA was 21.7% (10.7, 31.4), 30.4% (16.4, 42.1), and 33.4% (9.1, 51.5) and was consistently significant only in 15- to 17-year-old women (27.4% [10.8, 40.9], 41.8% [22.3, 56.7], and 55.8% [19.2, 76.9]). In the TVC-naive, VE against CIN1+, CIN2+, and CIN3+ associated with HPV-16/18 was 96.5% (89.0, 99.4), 98.4% (90.4, 100), and 100% (64.7, 100), and irrespective of HPV DNA it was 50.1% (35.9, 61.4), 70.2% (54.7, 80.9), and 87.0% (54.9, 97.7). VE against 12-month persistent infection with HPV-16/18 was 89.9% (84.0, 94.0), and that against HPV-31/33/45/51 was 49.0% (34.7, 60.3). In conclusion, vaccinating adolescents before sexual debut has a substantial impact on the overall incidence of high-grade cervical abnormalities, and catch-up vaccination up to 18 years of age is most likely effective. (This study has been registered at ClinicalTrials.gov under registration no. NCT001226810.)

Cervical cancer is the fourth most common cancer among women, with estimates from 2012 indicating that there are 528,000 new cases and 266,000 deaths each year worldwide (1). It is now established that persistent infection (PI) with human papillomavirus (HPV) is a prerequisite for cervical cancer (2). Approximately 70% of cervical cancer cases are attributable to high-risk (hr) HPV-16 and -18, with HPV-31, -33, -35, -45, -51, -52, and -58 contributing to an additional 20% of cases (3).

The GSK group of companies have developed a prophylactic vaccine against HPV types 16 and 18, formulated with the AS04 adjuvant system (containing aluminum hydroxide and 3-*O*-desacyl-4′ monophosphoryl lipid A). This vaccine is immunogenic and efficacious and has a clinically acceptable safety profile (4–11). In the end-of-study analysis of the according-to-protocol cohort from a large randomized, double-blind, controlled study (the PApilloma TRIal against Cancer In young Adults [PATRICIA]; registration no. NCT001226810), high vaccine efficacy (VE) was shown against PIs and high-grade cervical intraepithelial neopla-

sia (CIN) associated with HPV-16 and/or HPV-18 (12). Cross-protective efficacy was also shown against some phylogenetically related and nonrelated nonvaccine hr HPV types (13).

The risk of HPV infection starts from the onset of sexual activity, and the rate of acquisition of infection is highest in adolescents (14, 15). Therefore, the target population for current organized public health vaccination programs is adolescent girls before sexual debut, although a number of countries have also initiated catch-up vaccination programs up to 26 years of age (16–19). In this article, we provide data on the impact of the HPV-16/18 AS04-adjuvanted vaccine in a cohort of adolescent girls and young women from PATRICIA (8), who at baseline had no DNA detected for 14 hr HPV types, were seronegative for HPV-16 and HPV-18, and who had normal cytology results. This total vaccinated, HPV-naive cohort (TVC-naive) immunologically and virologically approximates the target population of current vaccination programs in terms of exposure to and acquisition of HPV types. To approximate the potential impact of catch-up vaccination, we also report results for the total vaccinated cohort (TVC), which includes all women who received at least one vaccine dose irrespective of their baseline cytological, serological, or HPV DNA status and approximates the population of women targeted by catch-up HPV vaccination programs.

The data summarized here are from the final event-driven analysis of PATRICIA and include approximately 39 months of follow-up. Data from a prespecified, descriptive end-of-study analysis, which include follow-up to month 48, have been published previously (12, 13). However, the final event-driven data from the prespecified conclusive analysis, for which type I error was controlled, are included in the vaccine prescribing information in many countries and help to illustrate the high overall efficacy of the HPV-16/18 AS04-adjuvanted vaccine. Here, we report age-stratified VE against all grades of CIN associated with HPV-16 and/or -18 and irrespective of HPV type in the lesion, VE against PIs with hr HPV types, and immunogenicity.

MATERIALS AND METHODS

Data are derived from the final event-driven analysis of PATRICIA, which was a phase III, randomized, double-blind, controlled efficacy study (8, 12). The design of PATRICIA has been reported previously, and the event-driven analysis was the prespecified primary analysis (8).

Participants. Healthy women aged 15 to 25 years at the time of first vaccination who reported no more than six lifetime sexual partners before study enrollment (this criterion was not applied to subjects aged 15 to 17 years in Finland) were enrolled regardless of their HPV DNA status, HPV serostatus, or cytology at baseline. Since women were not asked to specify the precise number of total lifetime sexual partners, this overall HPV exposure variable was not ascertained. Written informed consent/assent was obtained from all participants and/or their parents. The protocol and other materials were approved by independent ethics committees or institutional review boards.

Procedures. Women were randomized in a 1:1 ratio to receive either the HPV-16/18 AS04-adjuvanted vaccine (Cervarix; GSK group of companies) or a control hepatitis A vaccine at 0, 1, and 6 months (8, 12). The study protocol prescribed that both groups were to be unblinded following the month 48 visit and offered the crossover vaccine. Further follow-up of subjects enrolled in Finland is ongoing (20). Cervical sample collection, HPV DNA testing, gynecological and cytopathological examinations, assessment of cytology, and testing of cervical and biopsy samples for the presence of DNA from 14 hr HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68), using the broad-spectrum PCR SPF_{10} $LiPA_{25}$ system (version 1 based on licensed Innogenetics SPF_{10} technology; Labo Biomedical Products, Rijswijk, Netherlands), and type-specific PCR for HPV-16 and HPV-18 were performed as described previously (8, 12, 21). HPV DNA detected in the tissue biopsy specimens was regarded as associated with the lesion.

Antibodies against HPV-16 and HPV-18 were assessed by enzyme-linked immunosorbent assay (ELISA) in a subset of women from selected study sites (22). Seropositivity was defined as an antibody titer greater than or equal to the assay cutoff: 8 ELISA units (EU)/ml for HPV-16 and 7 EU/ml for HPV-18.

Management of abnormal cytology results and colposcopy referral. A prespecified clinical management algorithm for abnormal cytology results and colposcopy referral was employed. The colposcopy referral algorithm was designed to capture the most clinically relevant lesions, i.e., those that were most likely to persist. Subjects with a normal Pap smear underwent yearly scheduled cytological examinations. For a single observation of abnormal low-grade cytology, such as atypical squamous cells of undetermined significance (ASC-US) with HPV DNA Hybrid Capture II (HCII)-positive results (referred to as high-risk HPV probe positive or HR+) or low-grade squamous cell intraepithelial lesion (LSIL), the cytology was to be repeated at the next scheduled study visit (6 months later). Two observations (consecutive or intermittent) of low-grade cytology led to a referral for colposcopy. Subjects with a single observation of high-grade abnormal cytology (atypical squamous cells in which high-grade squamous intraepithelial lesions could not be excluded [ASC-H], atypical glandular cells of undetermined significance [AGC-US], or high-grade squamous intraepithelial lesion [HSIL] or greater) were referred for immediate colposcopy with cervical biopsy and, if appropriate, endocervical specimen collection and further medical follow-up. In a protocol amendment, the algorithm was updated to adapt to the evolution of standard medical practices (23) to allow for women with ASC-US (HR+ or with testing not performed) or LSIL to be immediately referred for colposcopic evaluation at the discretion of the investigator.

Prespecified colposcopy management algorithms were employed in which cytology and/or colposcopy had to be repeated for some outcomes at the next scheduled study visit (6 months later). If the biopsy or endocervical specimen results were negative or ≤CIN grade 1 (CIN1) or if the cytology result were ≤LSIL, the cytology and colposcopy were to be repeated at 6 months. If the biopsy or the endocervical specimen result was CIN grade 2 or greater ([CIN2+], defined as CIN grade 2 [CIN2], CIN grade 3 [CIN3], adenocarcinoma *in situ* [AIS], or invasive carcinoma) or the cytology result was ≥HSIL, a loop electrosurgical excision procedure

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TABLE 1 Demographic and baseline characteristics

Cohort and parameter[a]	Value[b] for group							
	Total cohort[c]		15–17 yr		18–20 yr		21–25 yr	
	Vaccine	Control	Vaccine	Control	Vaccine	Control	Vaccine	Control
TVC-naive								
No. of subjects	5,822	5,819	2,063	2,081	1,206	1,257	2,543	2,476
Mean age (SD), yr	19.9 (3.2)	19.8 (3.1)	16.4 (0.6)	16.4 (0.6)	19.1 (0.8)	19.1 (0.8)	23.0 (1.4)	23.0 (1.4)
Region								
Asia Pacific	2,203 (37.8)	2,134 (36.7)	121 (5.9)	115 (5.5)	486 (40.3)	516 (41.1)	1,588 (62.4)	1,498 (60.5)
Europe	2,173 (37.3)	2,209 (38.0)	1,719 (83.3)	1,738 (83.5)	184 (15.3)	195 (15.5)	269 (10.6)	276 (11.1)
North America	772 (13.3)	786 (13.5)	132 (6.4)	129 (6.2)	340 (28.2)	356 (28.3)	299 (11.8)	301 (12.2)
Latin America	674 (11.6)	690 (11.9)	91 (4.4)	99 (4.8)	196 (16.3)	190 (15.1)	387 (15.2)	401 (16.2)
Ever had sexual intercourse								
Yes	4,655 (82.0)	4,674 (82.1)	1,352 (66.0)	1,357 (65.6)	996 (85.6)	1,056 (86.2)	2,298 (93.6)	2,256 (94.2)
No	1,020 (18.0)	1,017 (17.9)	695 (34.0)	711 (34.4)	167 (14.4)	168 (13.7)	157 (6.4)	138 (5.8)
No data	147	128	16	13	43	33	88	82
No. of sexual partners in last year								
0	210 (4.5)	208 (4.5)	57 (4.2)	50 (3.7)	48 (4.8)	53 (5.0)	105 (4.6)	105 (4.7)
1	3,665 (78.9)	3,655 (78.4)	898 (66.6)	915 (67.6)	767 (77.2)	800 (76.2)	1,993 (87.0)	1,935 (85.9)
2	530 (11.4)	552 (11.8)	257 (19.1)	248 (18.3)	121 (12.2)	145 (13.8)	150 (6.5)	159 (7.1)
≥3	238 (5.1)	245 (5.3)	137 (10.2)	140 (10.3)	57 (5.7)	52 (5.0)	44 (1.9)	53 (2.4)
Not applicable[d]	1,020	1,017	695	711	167	168	157	138
No data	159	142	19	17	46	39	94	86
Chlamydia trachomatis[e]								
Negative	5,225 (96.5)	5,224 (96.5)	1,943 (98.7)	1,955 (98.8)	1,046 (94.8)	1,124 (95.5)	2,230 (95.4)	2,140 (94.9)
Positive	191 (3.5)	191 (3.5)	25 (1.3)	24 (1.2)	57 (5.2)	53 (4.5)	107 (4.6)	114 (5.1)
No data	406	404	95	102	103	80	206	222
Contraceptive use[f]								
Hormonal	3,107 (53.4)	3,236 (55.6)	862 (41.8)	895 (43.0)	723 (60.0)	792 (63.0)	1,515 (59.6)	1,547 (62.5)
Intrauterine device	311 (5.3)	259 (4.5)	5 (0.2)	4 (0.2)	47 (3.9)	43 (3.4)	259 (10.2)	211 (8.5)
Sterilized	59 (1.0)	48 (0.8)	1 (<0.1)	1 (<0.1)	5 (0.4)	3 (0.2)	52 (2.0)	44 (1.8)
Smoking status								
Never smoked or smoked for ≤6 mo	4,253 (74.9)	4,221 (74.1)	1,395 (68.1)	1,403 (67.8)	900 (77.4)	935 (76.3)	1,950 (79.4)	1,880 (78.5)
Smoker for ≥6 mo (current or past)	1,422 (25.1)	1,472 (25.9)	652 (31.9)	666 (32.2)	263 (22.6)	290 (23.7)	505 (20.6)	514 (21.5)
No data	147	126	16	12	43	32	88	82
TVC								
No. of subjects	9,319	9,325	2,973	2,984	2,065	2,095	4,269	4,236
Mean age (SD), yr	20.0 (3.1)	20.0 (3.1)	16.4 (0.6)	16.4 (0.6)	19.1 (0.8)	19.1 (0.8)	23.0 (1.4)	23.0 (1.4)
Region								
Asia Pacific	3,175 (34.1)	3,177 (34.1)	164 (5.5)	179 (6.0)	743 (36.0)	760 (36.3)	2,258 (52.9)	2,229 (52.6)
Europe	3,224 (34.6)	3,224 (34.6)	2,448 (82.3)	2,451 (82.1)	310 (15.0)	309 (14.7)	465 (10.9)	464 (11.0)
North America	1,532 (16.4)	1,538 (16.5)	201 (6.8)	196 (6.6)	617 (29·9)	646 (30.8)	713 (16·7)	695 (16.4)
Latin America	1,388 (14.9)	1,386 (14.9)	160 (5.4)	158 (5.3)	395 (19.1)	380 (18.1)	833 (19.5)	848 (20.0)
Ever had sexual intercourse								
Yes	7,924 (87.0)	7,936 (87.1)	2,152 (72.9)	2,142 (72.3)	1,810 (90.3)	1,835 (90.2)	3,951 (95.5)	3,949 (96.2)
No	1,183 (13.0)	1,176 (12.9)	800 (27.1)	820 (27.7)	194 (9.7)	198 (9.7)	188 (4.5)	158 (3.8)
No data	212	213	21	22	61	62	130	129
No. of sexual partners in last year								
0	294 (3.7)	292 (3.7)	73 (3.4)	59 (2.8)	68 (3.8)	73 (4.0)	153 (3.9)	160 (4.1)
1	5,862 (74.1)	5,869 (74.1)	1,291 (60.1)	1,288 (60.2)	1,300 (72.0)	1,324 (72.5)	3,262 (82.8)	3,248 (82.4)
2	1,114 (14.1)	1,161 (14.7)	433 (20.1)	462 (21.6)	285 (15.8)	302 (16.5)	394 (10.0)	397 (10.1)
≥3	636 (8.0)	595 (7.5)	352 (16.4)	329 (15.4)	153 (8.5)	128 (7.0)	131 (3.3)	137 (3.5)
Not applicable[d]	1,183	1,176	800	820	194	198	188	158
No data	230	232	24	26	65	70	141	136
Chlamydia trachomatis[e]								
Negative	8,155 (94.5)	8,188 (94.5)	2,748 (97.3)	2,758 (97.4)	1,740 (91.7)	1,817 (92.9)	3,659 (93.8)	3,604 (93.3)
Positive	478 (5.5)	475 (5.5)	76 (2.7)	75 (2.6)	157 (8.3)	139 (7.1)	243 (6.2)	260 (6.7)
No data	686	662	149	151	168	139	367	372
Contraceptive use[f]								
Hormonal	5,544 (59.5)	5,662 (60.7)	1,416 (47.6)	1,452 (48.7)	1,357 (65.7)	1,410 (67.3)	2,763 (64.7)	2,795 (66.0)
Intrauterine device	501 (5.4)	472 (5.1)	7 (0.2)	6 (0.2)	83 (4.0)	86 (4.1)	411 (9.6)	379 (8.9)
Sterilized	105 (1.1)	96 (1.0)	1 (0.0)	2 (0.1)	6 (0.3)	4 (0.2)	96 (2.2)	90 (2.1)

(Continued on following page)

TABLE 1 (Continued)

Cohort and parameter[a]	Value[b] for group							
	Total cohort[c]		15–17 yr		18–20 yr		21–25 yr	
	Vaccine	Control	Vaccine	Control	Vaccine	Control	Vaccine	Control
Smoking status								
Never smoked or smoked for ≤6 mo	6,401 (70.3)	6,388 (70.1)	1,840 (62.3)	1,867 (63.0)	1,471 (73.4)	1,469 (72.2)	3,080 (74.4)	3,405 (74.1)
Smoker for ≥6 mo (current or past)	2,706 (29.7)	2,726 (29.9)	1,112 (37.7)	1,096 (37.0)	533 (26.6)	565 (27.8)	1,059 (25.6)	1,062 (25.9)
No data	212	211	21	21	61	61	130	129

[a] TVC, total vaccinated cohort. TVC-naive, total vaccinated cohort of women who at baseline had no DNA detected for 14 high-risk HPV types, were seronegative for HPV-16 and HPV-18, and had normal cytology results.
[b] Data are number of subjects (percentage) unless indicated otherwise. Where data were missing, percentages were calculated from data available.
[c] Twenty-two subjects in the TVC and 15 subjects in the TVC-naive were aged <15 years or >25 years at time of first vaccination and are not included in an age stratum.
[d] Responded "no" to the question, "Have you ever had sexual intercourse?"
[e] *Chlamydia trachomatis* detected in cervical samples by PCR (Cobas Amplicor, Roche).
[f] Women may have used more than one method of contraception or a method that is not listed.

or cone biopsy was to be performed. Further management was performed according to local medical practice.

Statistical analysis. This was an event-driven analysis study with a fixed sample size. The final analysis was triggered when a prespecified number of endpoints was reached (at least 36 cases of CIN2+ associated with HPV-16/18, including at least 15 cases of CIN2+ associated with HPV-18) in the according-to-protocol cohort for efficacy, as defined previously (8). The TVC included all women who received at least one vaccine dose and were evaluable for efficacy (i.e., had a baseline PCR or cytology sample and one further sample available). The TVC-naive included women who received at least one vaccine dose, were DNA negative for all 14 hr HPV types investigated and seronegative for HPV-16 and HPV-18, and had normal cytology at baseline. Women infected with low-risk HPV types only were not excluded. Follow-up for each woman started on the day after administration of the first dose of study vaccine. Any lesions diagnosed as a result of abnormal cytology or any infections detected at the first visit were included in the outcome analysis. Follow-up time for each analysis ended (i) at the time of an event (e.g., detection of CIN2+ or start of PI), (ii) for those who did not have an event and who completed the study, at 48 months after administration of the first vaccine dose, or (iii) for those who did not have an event and who were active in the study at the time this present final event-driven analysis was performed, at the date of the last visit for which a biopsy, cytology, or PCR sample was available.

Histopathological and virological efficacy outcomes were evaluated as described previously (8, 12). We evaluated VE against CIN1+, CIN2+, and CIN3+ associated with HPV-16 or HPV-18 DNA in the lesion and against CIN1+, CIN2+, and CIN3+ irrespective of HPV DNA (this included all lesions regardless of whether an HPV type was detected). We also evaluated VE against 6-month and 12-month PIs associated with vaccine HPV types (HPV-16/18), common nonvaccine hr HPV types (HPV-31/33/45/51), and any hr HPV type (HPV-16/18/31/33/35/39/45/51/52/56/58/59/66/68). Additionally, we stratified efficacy analyses by age (15 to 17, 18 to 20, or 21 to 25 years). Analyses were prespecified, except for cross-protective efficacy against PIs with the combination of nonvaccine HPV types 31/33/45/51, against which consistent cross-protection against virological and clinical endpoints was shown in the 4-year end-of-study analysis (12, 13).

VE was calculated with a conditional exact method (see the supplemental material for details). For all endpoints, the overall alpha of 0.05 was divided into 0.021 for the interim analysis (97.9% confidence interval [CI]) and 0.039 for the final analysis (96.1% CI). The 96.1% CIs presented could be interpreted as 95% CIs to limit the overall type one error to 5%. For the final analysis, significance was defined when the lower limit of the 96.1% CI for VE was greater than 30.0% for CIN2+ associated with HPV-16/18 and greater than zero for all other endpoints. Event rates were calculated as the number of cases divided by the sum of the follow-up period in years for each group and are expressed per 100 woman-years.

HPV-16 and HPV-18 geometric mean antibody titers (GMTs) with 95% CI were calculated for the vaccine group. In an exploratory *post hoc* analysis, we stratified GMT data by age (15 to 17 or 18 to 25 years) and by number of reported sexual partners in the year prior to study (0, 1 or 2, or ≥3 partners). For the GMT calculations, seronegative women were assigned a value of half the assay cutoff level.

For VE against 6-month and 12-month PI, we performed an additional exploratory analysis which excluded those women in the TVC-naive at baseline. This cohort (TVC baseline positive), represents women who had evidence of past and/or current HPV infection or lesions at baseline.

Statistical analyses were done with Statistical Analysis System (SAS) 9.2 and Proc StatXact-7.

RESULTS

Study population. Totals of 11,641 and 18,644 women were included in the TVC-naive and TVC, respectively. Demographic and baseline characteristics for these cohorts are shown in Table 1, together with characteristics by age strata (36% and 32% were aged 15 to 17 years, 21% and 22% aged 18 to 20 years, and 43% and 46% aged 21 to 25 years in the TVC-naive and TVC, respectively). The mean ages at first vaccination were 19.8 years (TVC-naive) and 20.0 years (TVC). Compliance with completion of the three-dose vaccination schedule was high (92% in each group). Approximately 8% and 10% of subjects were withdrawn from the TVC-naive and TVC, respectively, at the time of the final event-triggered analysis. The numbers of subjects who did not complete the study were balanced between the vaccine and control groups. At the time of the final event-driven analysis, the mean durations of follow-up for the TVC-naive and TVC were 39.5 (standard deviation [SD], 9.0) and 39.4 (SD, 9.7) months, respectively.

Overall, subjects were predominantly from Europe and Asia Pacific (35% and 34%, respectively, in the TVC), with some differences among the age groups in the geographical distribution of participants. Most notably, 80% of 15- to 17-year-olds were from Finland. Finnish participants were recruited exclusively at schools, as described previously (20). Thirty-six percent of all 18- to 20-year-olds and 53% of all 21- to 25-year-olds were from Asia Pacific.

At baseline, the overall study population (TVC) was predominantly sexually active, and only 13% reported that they had never had sexual intercourse (defined as penetrative or genital-to-genital sexual contact) (Table 1). Only 4% of those who reported prior sexual activity indicated no sexual partner in the year prior to the study, while 74% indicated one sexual partner. More 15- to 17-

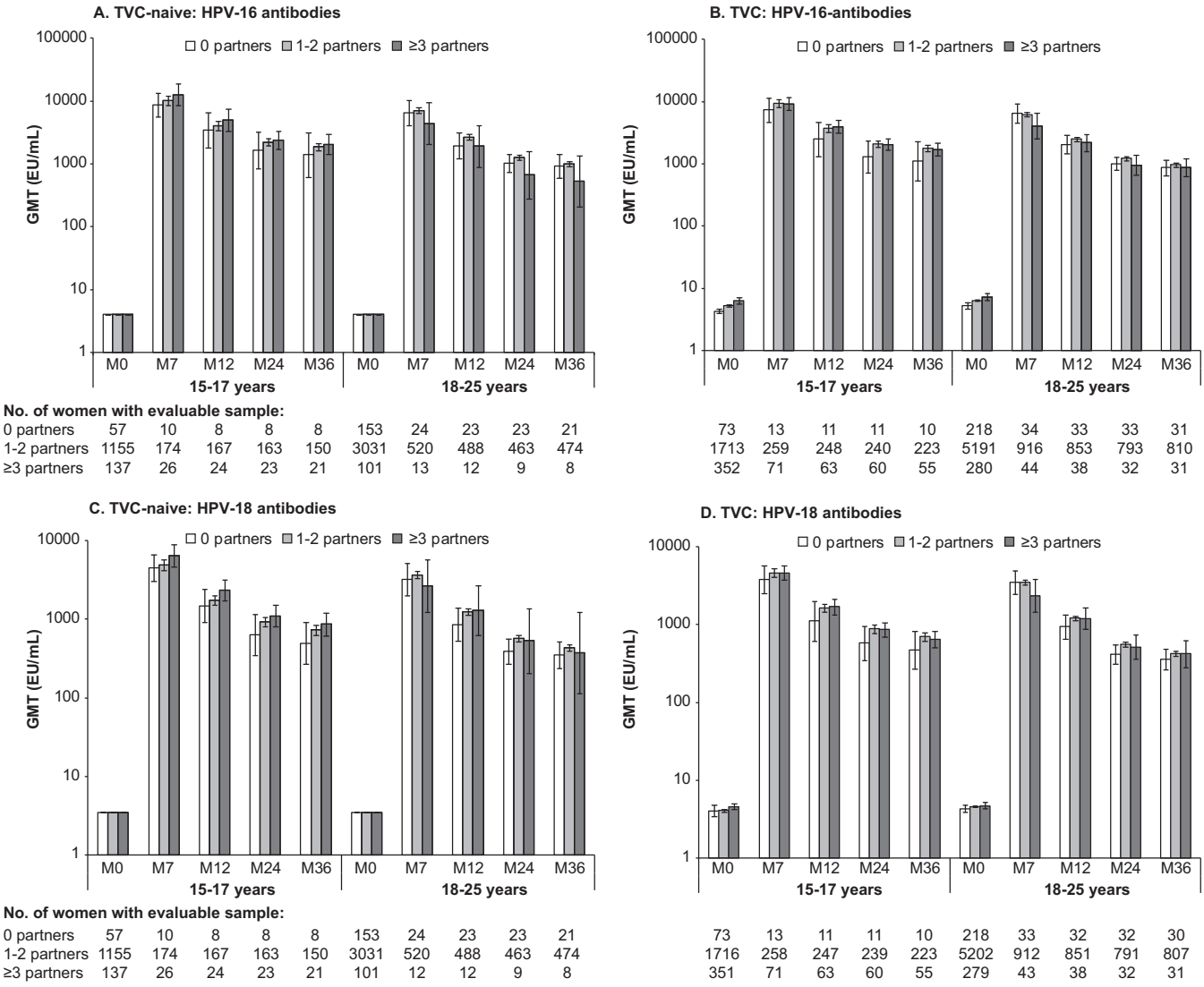

FIG 1 Geometric mean antibody titers measured by ELISA in the vaccine group, according to age and reported number of sexual partners in the year prior to study, against HPV-16 and HPV-18 in the TVC-naive (A and C, respectively) and the TVC (B and D, respectively). Bars show $\log_{10}$ geometric mean antibody titer (GMT) and 95% confidence interval. For the GMT calculation, seronegative women were assigned a value of half the assay cutoff level. M, month.

year-olds (27%) than 18- to 20-year-olds (10%) or 21- to 25-year-olds (4%) reported that they had never had sexual intercourse, but a greater proportion of the 15- to 17-year-olds who did report sexual intercourse had more than one partner in the year prior to the study, compared to 18- to 20-year-olds or 21- to 25-year-olds (21%, 16%, and 10% for two partners and 16%, 8%, and 3% for three partners, respectively). In the TVC-naive, a larger proportion of 15- to 17-year-olds than of 18- to 20- or 21- to 25-year-olds reported that they had never had sexual intercourse (34%, 14%, and 6%, respectively). Of those baseline negative women with reported data regarding sexual intercourse, a larger proportion of 15- to 17-year-olds than of 18- to 20- or 21- to 25-year-olds reported at least three sexual partners in the last year (10%, 5%, and 2%, respectively), and a smaller proportion reported only one sexual partner (67%, 77%, and 86%, respectively).

In both cohorts, a smaller proportion of 15- to 17-year-olds than of 18- to 20- or 21- to 25-year-olds reported that they had never smoked or had smoked for ≤6 months. *Chlamydia trachomatis* positivity was approximately 2 to 4 times higher in the older age groups than in the 15- to 17-year-olds.

Approximately one-quarter of women in the TVC (26%) had evidence of past and/or current HPV-16 and/or -18 infection (seropositive and/or HPV DNA positive for at least one of the vaccine HPV types) at baseline (see Table S1 in the supplemental material). When stratified by age, a higher proportion of 18- to 20-year-olds (27%) and 21- to 25-year-olds (30%) had evidence of past and/or current HPV-16/18 infection compared with 15- to 17-year-olds (20%). Approximately 5% of these women were HPV-16 DNA positive and approximately 2% were HPV-18 DNA positive at baseline, with fewer than 1% positive for both HPV types (data not shown). Approximately 20% of women were DNA positive for at least one hr HPV type at baseline. Baseline seropositivity was 17% for HPV-16 and 12% for HPV-18. At baseline, over 90% of the women had normal cytology, 9% had ASC-US

TABLE 2 Efficacy against 6-month and 12-month persistent infections stratified by age[a]

				TVC-naive				TVC-baseline positive				TVC			
Age stratum	Endpoint	HPV type	Group	*n*	No. of cases	Rate	Efficacy (96.1% CI)	*n*	No. of cases	Rate	Efficacy (96.1% CI)	*n*	No. of cases	Rate	Efficacy (96.1% CI)
All	6 mo	HPV-16/18	Vaccine	5,406	32	0.20	93.0 (89.7, 95.3)	3,450	466	5.74	31.7 (22.5, 39.8)	8,856	498	2.08	56.4 (51.3, 61.1)
			Control	5,375	435	2.87		3,484	668	8.40		8,859	1,103	4.77	
		HPV-31/33/45/51	Vaccine	5,406	287	1.85	42.5 (32.9, 50.9)	3,450	612	7.71	8.1 (−3.3, 18.2)	8,856	899	3.84	23.5 (16.1, 30.3)
			Control	5,375	487	3.22		3,484	673	8.39		8,859	1,160	5.02	
		Any hr HPV	Vaccine	5,406	809	5.51	33.5 (26.9, 39.6)	3,450	1,561	28.47	2.9 (−4.6, 9.8)	8,856	2,370	11.75	17.5 (12.6, 22.2)
			Control	5,375	1,163	8.29		3,484	1,627	29.31		8,859	2,790	14.25	
	12 mo	HPV-16/18	Vaccine	5,331	22	0.14	89.9 (84.0, 94.0)	3,294	305	3.58	23.3 (10.0, 34.7)	8,625	327	1.35	47.3 (39.2, 54.4)
			Control	5,291	212	1.38		3,357	398	4.67		8,648	610	2.55	
		HPV-31/33/45/51	Vaccine	5,331	110	0.70	49.0 (34.7, 60.3)	3,294	344	4.05	7.7 (−7.9, 21.1)	8,625	454	1.88	23.5 (12.8, 32.9)
			Control	5,291	212	1.38		3,357	378	4.39		8,648	590	2.46	
		Any hr HPV	Vaccine	5,331	383	2.53	36.7 (27.4, 44.9)	3,294	1,002	14.77	4.6 (−4.6, 13.0)	8,625	1,385	6.32	17.4 (10.9, 23.4)
			Control	5,291	587	3.99		3,357	1,060	15.48		8,648	1,647	7.65	
15–17 yr	6 mo	HPV-16/18	Vaccine	1,988	12	0.20	95.4 (91.6, 97.7)	928	150	6.57	50.0 (38.1, 59.8)	2,916	162	1.94	70.5 (64.5, 75.7)
			Control	2,020	249	4.29		899	268	13.15		2,919	517	6.59	
		HPV-31/33/45/51	Vaccine	1,988	170	2.92	42.0 (29.0, 52.8)	928	230	10.62	19.4 (2.7, 33.3)	2,916	400	5.01	30.2 (20.0, 39.2)
			Control	2,020	290	5.04		899	271	13.17		2,919	561	7.18	
		Any hr HPV	Vaccine	1,988	421	7.75	32.2 (22.5, 40.7)	928	492	33.54	12.9 (0.6, 23.7)	2,916	913	13.24	22.0 (14.4, 29.0)
			Control	2,020	600	11.43		899	521	38.50		2,919	1,121	16.98	
	12 mo	HPV-16/18	Vaccine	1,971	6	0.10	95.4 (89.4, 98.5)	906	99	4.07	46.0 (29.6, 58.9)	2,877	105	1.24	66.1 (57.0, 73.4)
			Control	2,002	129	2.17		888	170	7.55		2,890	299	3.65	
		HPV-31/33/45/51	Vaccine	1,971	65	1.09	49.1 (29.8, 63.4)	906	124	5.16	14.3 (−11.2, 34.1)	2,877	189	2.26	30.1 (14.7, 42.9)
			Control	2,002	128	2.15		888	141	6.02		2,890	269	3.24	
		Any hr HPV	Vaccine	1,971	200	3.50	38.3 (25.5, 49.1)	906	320	16.94	8.6 (−7.7, 22.4)	2,877	520	6.84	22.5 (12.4, 31.5)
			Control	2,002	319	5.68		888	338	18.52		2,890	657	8.83	
18–20 yr	6 mo	HPV-16/18	Vaccine	1,084	8	0.26	91.6 (82.2, 96.7)	838	134	7.22	18.2 (−4.7, 36.2)	1,922	142	2.87	45.1 (31.6, 56.1)
			Control	1,114	95	3.08		844	162	8.83		1,958	257	5.22	
		HPV-31/33/45/51	Vaccine	1,084	57	1.89	32.2 (2.4, 53.2)	838	160	8.71	4.5 (−20.6, 24.5)	1,922	217	4.47	13.3 (−5.4, 28.7)
			Control	1,114	86	2.78		844	168	9.12		1,958	254	5.15	
		Any hr HPV	Vaccine	1,084	165	5.81	31.3 (15.1, 44.6)	838	399	32.54	3.6 (−11.7, 16.8)	1,922	564	13.88	13.6 (2.5, 23.4)
			Control	1,114	241	8.47		844	412	33.75		1,958	653	16.06	
	12 mo	HPV-16/18	Vaccine	1,061	6	0.20	86.1 (66.2, 95.5)	790	92	4.70	−4.1 (−43.1, 24.3)	1,851	98	1.95	25.4 (1.1, 43.9)
			Control	1,093	44	1.41		795	89	4.51		1,888	133	2.61	
		HPV-31/33/45/51	Vaccine	1,061	23	0.76	28.0 (−29.9, 60.8)	790	84	4.23	10.2 (−23.9, 35.0)	1,851	107	2.13	13.6 (−14.3, 34.8)
			Control	1,093	33	1.05		795	93	4.71		1,888	126	2.47	
		Any hr HPV	Vaccine	1,061	68	2.31	37.7 (13.7, 55.4)	790	247	15.85	10.3 (−8.0, 25.5)	1,851	315	6.99	16.9 (2.5, 29.2)
			Control	1,093	111	3.70		795	269	17.67		1,888	380	8.41	

21–25 yr	6 mo	HPV-16/18	Vaccine	2,327	12	0.18	87.6 (76.7, 94.1)	1,681	182	4.58	21.8 (3.8, 36.5)	4,008	194	1.82	42.8 (30.8, 52.8)
			Control	2,237	91	1.45		1,736	238	5.85		3,973	329	3.18	
		HPV-31/33/45/51	Vaccine	2,327	60	0.90	49.1 (28.6, 64.1)	1,681	222	5.66	0.7 (−21.0, 18.6)	4,008	282	2.67	19.9 (5.1, 32.3)
			Control	2,237	111	1.78		1,736	234	5.70		3,973	345	3.33	
		Any hr HPV	Vaccine	2,327	222	3.47	36.1 (23.3, 46.9)	1,681	670	24.07	−3.0 (−15.3, 8.1)	4,008	892	9.72	14.9 (6.3, 22.7)
			Control	2,237	322	5.44		1,736	693	23.37		3,973	1,015	11.42	
	12 mo	HPV-16/18	Vaccine	2,292	10	0.15	75.7 (48.9, 89.7)	1,596	114	2.77	14.8 (−11.4, 34.9)	3,888	124	1.15	31.6 (12.4, 46.7)
			Control	2,192	39	0.62		1,669	139	3.25		3,861	178	1.68	
		HPV-31/33/45/51	Vaccine	2,292	22	0.33	59.2 (29.8, 77.1)	1,596	136	3.32	1.3 (−27.2, 23.5)	3,888	158	1.47	20.3 (0.1, 36.5)
			Control	2,192	51	0.81		1,669	144	3.36		3,861	195	1.85	
		Any hr HPV	Vaccine	2,292	115	1.78	31.2 (10.8, 47.1)	1,596	435	13.06	−0.5 (−15.7, 12.7)	3,888	550	5.62	12.0 (0.5, 22.2)
			Control	2,192	157	2.59		1,669	453	13.00		3,861	610	6.38	

[a] Any hr HPV, any high-risk HPV (HPV-16/18/31/33/35/39/45/51/52/56/58/59/66/68); *n*, number of evaluable women in each group; no. of cases, number of evaluable women reporting at least one event; rate, number of cases divided by sum of follow-up period (per 100 person-years), where follow-up period started on the day after the first vaccine dose; TVC, total vaccinated cohort; TVC-naive, total vaccinated cohort of women who at baseline had no DNA detected for 14 high-risk HPV types, were seronegative for HPV-16 and HPV-18, and had normal cytology results. The TVC-baseline-positive population excluded those women in the TVC who were HPV naive at baseline (i.e., women who were DNA negative for all 14 high-risk HPV types, were seronegative for HPV-16 and HPV-18, and had normal cytology at baseline).

(regardless of HCII result) or LSIL and 0.5% had high-grade cytology (HSIL, ASC-H AGC) (see Table S2 in the supplemental material). Baseline cytology status was similar in each stratum. A total of 7,003 (38%) women had evidence of past and/or current HPV infection or lesions at baseline (i.e., DNA positive for at least one of the 14 hr HPV types, seropositive for HPV-16 and/or HPV-18, or abnormal cytology at baseline).

Immunogenicity. In both cohorts, following an initial peak at month 7, HPV-16 and HPV-18 GMTs were sustained throughout 36 months of follow-up (Fig. 1). In the TVC-naive for women aged 15 to 17 years, HPV-16 and HPV-18 peak GMTs at month 7 tended to increase by number of sexual partners in the year prior to study at all postvaccination time points, although 95% CIs for GMTs overlapped for all groups. In contrast, in the TVC, among adult women aged 18 to 25 years, peak HPV-16 and -18 GMTs at month 7 tended to be the lowest in individuals with higher numbers of sexual partners in the year prior to vaccination. However, the 95% CIs overlapped for all groups, and these tendencies were not statistically significant even in the population of TVC women who had evidence of past and/or current HPV infection at baseline (HPV DNA positive and/or seropositive for HPV-16 or HPV-18 and/or abnormal cytology at baseline) (data not shown).

Efficacy against PI. VE against persistent infection (PI) with vaccine HPV-16/18 was higher than that against nonvaccine hr HPV types (Table 2). However, in the TVC-naive we still observed statistically significant cross-protective VE against persistent 6-month and 12-month infections, both with a combination of nonvaccine HPV-31/33/45/51 (42.5% [96.1% CI, 32.9 to 50.9] and 49.0% [34.7 to 60.3], respectively) and with any hr HPV type (33.5% [26.9 to 39.6] and 36.7% [27.4 to 44.9], respectively). With the exception of VE against 12-month PI with HPV-31/33/45/51 in 18- to 20-year-old women, this was true for all age groups in the TVC-naive, albeit at a lower level than corresponding VE against PIs with HPV-16/18.

In the TVC, VE against 6-month and 12-month PIs with vaccine or nonvaccine hr HPV types was highest for women aged 15 to 17 years (Table 2). In women aged 18 to 20 years and 21 to 25 years, statistically significant VE was shown against PIs with HPV-16/18 and with any hr HPV type but was not consistently shown for PIs with nonvaccine HPV-31/33/45/51. In the baseline positive subset of women in the TVC, who had evidence of past and/or current HPV infection, no cross-protective VE was observed against 6-month or 12-month PIs with HPV-31/33/45/51 or any hr HPV type in women aged 18 to 25 years (Table 2).

Efficacy against cervical intraepithelial neoplasia. In the TVC-naive, a total of 88 CIN1+ cases associated with HPV-16 and/or HPV-18 were identified (including 64 CIN2+ and 13 CIN3+, of which 3 were adenocarcinoma *in situ* [AIS]) during the follow-up period (Table 3). VE against CIN1+, CIN2+, and CIN3+ associated with HPV-16 and/or -18 was 96.5% (89.0 to 99.4), 98.4% (90.4 to 100), and 100% (64.7 to 100), respectively. In the TVC, a total of 347 CIN1+ cases associated with HPV-16 and/or HPV-18 were identified (including 256 CIN2+ and 108 CIN3+, of which 5 were AIS [all in the control group]) (Table 3). The majority of the CIN2+ lesions were associated with HPV-16 (227/256, 87%). In 28.6% of the 256 CIN2+ cases associated with HPV-16 and/or HPV-18, DNA from nonvaccine hr HPV types was also detected. VE against CIN1+, CIN2+, and CIN3+ associated with HPV-16 and/or -18 was 55.5% (43.2 to 65.3), 52.8% (37.5 to 64.7), and 33.6% (−1.1 to 56.9), respectively.

TABLE 3 Efficacy against CIN1+, CIN2+, and CIN3+ associated with HPV-16 and/or -18, stratified by age[a]

				TVC-naive				TVC			
Age stratum	Endpoint	HPV type[b]	Group	*n*	No. of cases	Rate	Efficacy (96.1% CI)	*n*	No. of cases	Rate	Efficacy (96.1% CI)
All	CIN1+	HPV-16/18	Vaccine	5,449	3	0.02	96.5 (89.0, 99.4)	8,667	107	0.43	55.5 (43.2, 65.3)
			Control	5,436	85	0.54		8,682	240	0.97	
		HPV-16	Vaccine	5,449	2	0.01	97.3 (89.3, 99.7)	8,667	90	0.36	54.5 (40.6, 65.4)
			Control	5,436	73	0.46		8,682	198	0.80	
		HPV-18	Vaccine	5,449	1	0.01	94.5 (62.8, 99.9)	8,667	18	0.07	70.4 (48.0, 84.1)
			Control	5,436	18	0.11		8,682	61	0.24	
	CIN2+	HPV-16/18	Vaccine	5,449	1[c]	0.01	98.4 (90.4, 100)	8,667	82	0.33	52.8 (37.5, 64.7)
			Control	5,436	63	0.40		8,682	174	0.70	
		HPV-16	Vaccine	5,449	1[c]	0.01	98.2 (89.1, 100)	8,667	75	0.30	50.6 (33.5, 63.6)
			Control	5,436	56	0.36		8,682	152	0.61	
		HPV-18	Vaccine	5,449	0	0.00	100 (61.3, 100)	8,667	8	0.03	75.7 (44.4, 90.8)
			Control	5,436	12	0.08		8,682	33	0.13	
	CIN3+	HPV-16/18	Vaccine	5,449	0	0.00	100 (64.7, 100)	8,667	43	0.17	33.6 (−1.1, 56.9)
			Control	5,436	13	0.08		8,682	65	0.26	
		HPV-16	Vaccine	5,449	0	0.00	100 (57.1, 100)	8,667	41	0.16	31.4 (−5.9, 56.0)
			Control	5,436	11	0.07		8,682	60	0.24	
		HPV-18	Vaccine	5,449	0	0.00	100 (−170.8, 100)	8,667	2	0.01	77.7 (−14.7, 98.0)
			Control	5,436	3	0.02		8,682	9	0.04	
15–17 yr	CIN1+	HPV-16/18	Vaccine	1,996	1	0.02	97.6 (85.0, 100)	2,880	28	0.32	73.6 (58.8, 83.7)
			Control	2,022	42	0.68		2,891	106	1.22	
		HPV-16	Vaccine	1,996	1	0.02	97.0 (81.2, 99.9)	2,880	25	0.29	71.2 (53.7, 82.8)
			Control	2,022	34	0.55		2,891	87	1.00	
		HPV-18	Vaccine	1,996	0	0.00	100 (64.1, 100)	2,880	4	0.05	87.5 (63.1, 97.0)
			Control	2,022	13	0.21		2,891	32	0.36	
	CIN2+	HPV-16/18	Vaccine	1,996	1[c]	0.02	96.6 (78.5, 99.9)	2,880	19	0.22	72.8 (53.2, 85.0)
			Control	2,022	30	0.49		2,891	70	0.80	
		HPV-16	Vaccine	1,996	1[c]	0.02	95.8 (72.5, 99.9)	2,880	18	0.21	69.9 (47.0, 83.8)
			Control	2,022	24	0.39		2,891	60	0.69	
		HPV-18	Vaccine	1,996	0	0.00	100 (51.0, 100)	2,880	2	0.02	87.4 (43.5, 98.8)
			Control	2,022	10	0.16		2,891	16	0.18	
	CIN3+	HPV-16/18	Vaccine	1,996	0	0.00	100 (23.2, 100)	2,880	6	0.07	74.9 (34.3, 92.1)
			Control	2,022	7	0.11		2,891	24	0.27	
		HPV-16	Vaccine	1,996	0	0.00	100 (5.7, 100)	2,880	6	0.07	72.6 (27.3, 91.4)
			Control	2,022	6	0.10		2,891	22	0.25	
		HPV-18	Vaccine	1,996	0	0.00	100 (−527.0, 100)	2,880	0	0.00	100 (−68.8, 100)
			Control	2,022	2	0.03		2,891	4	0.05	
18–20 yr	CIN1+	HPV-16/18	Vaccine	1,090	0	0.00	100 (83.0, 100)	1,862	30	0.58	55.7 (29.6, 72.8)
			Control	1,139	26	0.81		1,902	69	1.31	
		HPV-16	Vaccine	1,090	0	0.00	100 (81.5, 100)	1,862	23	0.44	60.3 (33.1, 77.2)
			Control	1,139	24	0.75		1,902	59	1.12	
		HPV-18	Vaccine	1,090	0	0.00	100 (−183.7, 100)	1,862	7	0.13	52.3 (−29.8, 84.5)
			Control	1,139	3	0.09		1,902	15	0.28	
	CIN2+	HPV-16/18	Vaccine	1,090	0	0.00	100 (78.5, 100)	1,862	21	0.40	61.9 (34.4, 78.7)
			Control	1,139	21	0.66		1,902	56	1.06	
		HPV-16	Vaccine	1,090	0	0.00	100 (77.3, 100)	1,862	18	0.35	63.3 (34.3, 80.5)
			Control	1,139	20	0.63		1,902	50	0.94	
		HPV-18	Vaccine	1,090	0	0.00	100 (−544.0, 100)	1,862	3	0.06	69.4 (−26.1, 95.1)
			Control	1,139	2	0.06		1,902	10	0.19	
	CIN3+	HPV-16/18	Vaccine	1,090	0	0.00	100 (−75.1, 100)	1,862	10	0.19	51.4 (−11.9, 80.5)
			Control	1,139	4	0.12		1,902	21	0.40	
		HPV-16	Vaccine	1,090	0	0.00	100 (−183.7, 100)	1,862	9	0.17	51.7 (−16.6, 81.7)
			Control	1,139	3	0.09		1,902	19	0.36	
		HPV-18	Vaccine	1,090	0	0.00	100 (−5,157.1, 100)	1,862	1	0.02	65.9 (−372.9, 99.5)
			Control	1,139	1	0.03		1,902	3	0.06	
21–25 yr	CIN1+	HPV-16/18	Vaccine	2,356	2	0.03	88.8 (50.0, 98.9)	3,916	49	0.45	25.3 (−12.0, 50.6)
			Control	2,271	17	0.27		3,880	65	0.60	

(Continued on following page)

TABLE 3 (Continued)

Age stratum	Endpoint	HPV type[b]	Group	TVC-naive				TVC			
				n	No. of cases	Rate	Efficacy (96.1% CI)	*n*	No. of cases	Rate	Efficacy (96.1% CI)
		HPV-16	Vaccine	2,356	1	0.02	93.6 (55.9, 99.9)	3,916	42	0.39	19.9 (−25.3, 49.1)
			Control	2,271	15	0.24		3,880	52	0.48	
		HPV-18	Vaccine	2,356	1	0.02	52.1 (−959.2, 99.4)	3,916	7	0.06	50.5 (−37.2, 84.0)
			Control	2,271	2	0.03		3,880	14	0.13	
	CIN2+	HPV-16/18	Vaccine	2,356	0	0.00	100 (62.9, 100)	3,916	42	0.39	13.2 (−37.1, 45.3)
			Control	2,271	12	0.19		3,880	48	0.44	
		HPV-16	Vaccine	2,356	0	0.00	100 (62.9, 100)	3,916	39	0.36	7.9 (−49.4, 43.3)
			Control	2,271	12	0.19		3,880	42	0.39	
		HPV-18	Vaccine	2,356	0	0.00		3,916	3	0.03	57.5 (−98.7, 93.6)
			Control	2,271	0	0.00		3,880	7	0.06	
	CIN3+	HPV-16/18	Vaccine	2,536	0	0.00	100 (−490.4, 100)	3,916	27	0.25	−34.1 (−160.6, 29.7)
			Control	2,271	2	0.12		3,880	20	0.18	
		HPV-16	Vaccine	2,536	0	0.00	100 (−490.4, 100)	3,916	26	0.24	−35.9 (−168.6, 29.8)
			Control	2,271	2	0.12		3,880	19	0.17	
		HPV-18	Vaccine	2,536	0	0.00		3,916	1	0.01	50.4 (−996.4, 99.4)
			Control	2,271	0	0.00		3,880	2	0.02	

[a] *n*, number of evaluable women in each group; no. of cases, number of evaluable women reporting at least one event; rate, number of cases divided by sum of follow-up period (per 100 person-years), where follow-up period started on the day after the first vaccine dose; TVC, total vaccinated cohort; TVC-naive, total vaccinated cohort of women who at baseline had no DNA detected for 14 high-risk HPV types, were seronegative for HPV-16 and HPV-18, and had normal cytology results.

[b] Women were infected with one or both HPV types (thus, the number of women with an HPV-16-associated lesion and the number with an HPV-18-associated lesion might not equal number with an HPV-16/18-associated lesion).

[c] This young woman acquired the HPV-16 responsible for development of the lesion prior to completion of the full three-dose series (HPV-16 DNA was detected at months 6, 12, and 18; the CIN2 lesion was detected at month 21, and HPV-16 DNA was the only type in the lesion).

In age-stratified analyses for baseline negative women (TVC-naive), VE against HPV-16/18-associated CIN2+ was 96.6% (78.5 to 99.9) for women aged 15 to 17 years, 100% (78.5 to 100) for women aged 18 to 20 years, and 100% (62.9 to 100) for women aged 21 to 25 years (Table 3). In the TVC, VE against HPV-16/18-associated CIN2+ was 72.8% (53.2 to 85.0) for women aged 15 to 17 years and 61.9% (34.4 to 78.7) for women aged 18 to 20 years but was negligible for women aged 21 to 25 years (13.2% [−37.1 to 45.3]).

To assess the potential public health benefit of the vaccine, we also evaluated efficacy against CIN, irrespective of HPV DNA type in the lesion (Table 4). In the TVC-naive, a total of 317 CIN1+ cases, irrespective of HPV DNA, were identified (including 143 CIN2+ and 26 CIN3+, of which 3 were AIS). VE increased with increasing lesion severity: 50.1% (35.9 to 61.4) for CIN1+, 70.2% (54.7 to 80.9) for CIN2+, and 87.0% (54.9 to 97.7) for CIN3+. In the age-stratified analysis, estimates of VE were similar in the three age strata and statistically significant against all grades of CIN in women aged 15 to 17 years. Cases of CIN were limited in numbers in the older age groups, and statistically significant VE was not attained against CIN3+ in women aged 18 to 20 years or against CIN2+ or CIN3+ in women aged 21 to 25 years, although point estimates of vaccine efficacy ranged from 57 to 100% (Table 4).

In the TVC a total of 1028 CIN1+ cases irrespective of HPV DNA in the lesion were identified (including 546 CIN2+ and 193 CIN3+, of which 9 were AIS [2 in the vaccine group and 7 in the control group]) (Table 4). VE irrespective of HPV DNA in the lesion was 30.4% (16.4 to 42.1) against CIN2+ and 33.4% (9.1 to 51.5) against CIN3+. As previously noted for HPV-16/18-associated lesions, low or negligible efficacy was shown in women aged 21 to 25 years against CIN2+ (−0.2% [−37.0 to 26.7]) or CIN3+ (3.2% [−57.1 to 40.4]) irrespective of DNA in the lesion.

DISCUSSION

We examined the impact of the HPV-16/18 AS04-adjuvanted vaccine on women aged 15 to 25 years from PATRICIA, either those who at baseline had no evidence of hr HPV infection (TVC-naive), approximating the population of adolescent girls targeted by HPV vaccination programs, or all vaccinated women in the study (TVC). We build on previously published findings (7, 8, 12, 13) by reporting data from the final, prespecified event-driven analysis regarding age-stratified immunogenicity and efficacy against persistent hr HPV infections and all grades of CIN associated with HPV-16 and/or -18 and also irrespective of HPV type.

In the TVC-naive, we confirmed the high efficacy of the HPV-16/18 AS04-adjuvanted vaccine in preventing lesions associated with HPV-16 and/or HPV-18. Efficacy was 96.5% against CIN1+, 98.4% against CIN2+, and 100% against the immediate precursor of invasive cervical cancer, CIN3+. These results are generally in line with published data regarding efficacy due to vaccine types for the licensed quadrivalent HPV-6/11/16/18 vaccine in a similar cohort of women, despite there being differences in methodologies between these studies (24, 25).

In the TVC, the vaccine prevented approximately 56% and 53% of CIN1+ and CIN2+ associated with vaccine types HPV-16 and/or -18, respectively, compared with the control. Although direct comparison of studies with differences in methodology and populations can be subject to a variety of issues, the estimate against CIN2+ is within the same range as previously reported in studies with the licensed quadrivalent HPV vaccine in an equivalent population (24, 26–28). Efficacy against CIN3+ associated with HPV-16 and/or -18 was 34% across all ages but was not significant. Uniform, statistically significant VE against HPV-16/18-associated CIN1+, CIN2+, and CIN3+ was observed in the

TABLE 4 Efficacy against CIN1+, CIN2+, and CIN3+, stratified by age, irrespective of HPV type in the lesion[a]

Age stratum	Endpoint	Group	TVC-naive				TVC			
			n	No. of cases	Rate	Efficacy (96.1% CI)	*n*	No. of cases	Rate	Efficacy (96.1% CI)
All	CIN1+	Vaccine	5,449	106	0.67	50.1 (35.9, 61.4)	8,667	451	1.85	21.7 (10.7, 31.4)
		Control	5,436	211	1.35		8,682	577	2.37	
	CIN2+	Vaccine	5,449	33	0.21	70.2 (54.7, 80.9)	8,667	224	0.91	30.4 (16.4, 42.1)
		Control	5,436	110	0.70		8,682	322	1.31	
	CIN3+	Vaccine	5,449	3[b]	0.02	87.0 (54.9, 97.7)	8,667	77	0.31	33.4 (9.1, 51.5)
		Control	5,436	23	0.15		8,682	116	0.47	
15–17 yr	CIN1+	Vaccine	1,996	51	0.85	52.2 (31.5, 67.0)	2,880	182	2.15	27.4 (10.8, 40.9)
		Control	2,022	108	1.77		2,891	252	2.96	
	CIN2+	Vaccine	1,996	20	0.33	67.8 (44.7, 82.1)	2,880	84	0.98	41.8 (22.3, 56.7)
		Control	2,022	63	1.03		2,891	145	1.68	
	CIN3+	Vaccine	1,996	2	0.03	85.5 (33.1, 98.6)	2,880	18	0.21	55.8 (19.2, 76.9)
		Control	2,022	14	0.23		2,891	41	0.47	
18–20 yr	CIN1+	Vaccine	1,090	25	0.82	46.9 (10.2, 69.4)	1,862	110	2.17	23.6 (0.2, 41.6)
		Control	1,139	49	1.55		1,902	147	2.84	
	CIN2+	Vaccine	1,090	5	0.16	82.1 (51.2, 94.9)	1,862	46	0.89	44.2 (17.7, 62.7)
		Control	1,139	29	0.91		1,902	84	1.60	
	CIN3+	Vaccine	1,090	1	0.03	82.6 (−55.0, 99.7)	1,862	19	0.21	43.0 (−5.8, 70.3)
		Control	1,139	6	0.19		1,902	34	0.44	
21–25 yr	CIN1+	Vaccine	2,356	30	0.45	46.9 (13.6, 68.0)	3,916	159	1.48	11.7 (−11.3, 30.0)
		Control	2,271	54	0.85		3,880	178	1.67	
	CIN2+	Vaccine	2,536	8	0.12	57.5 (−7.1, 84.8)	3,916	94	0.87	−0.2 (−37.0, 26.7)
		Control	2,271	18	0.28		3,880	93	0.87	
	CIN3+	Vaccine	2,356	0	0.00	100 (−160.1, 100)	3,916	40	0.37	3.2 (−57.1, 40.4)
		Control	2,271	3	0.05		3,880	41	0.38	

[a] *n*, number of evaluable women in each group; no. of cases, number of evaluable women reporting at least one event; rate, number of cases divided by sum of follow-up period (per 100 person-years), where follow-up period started on day after first vaccine dose; TVC, total vaccinated cohort; TVC-naive, total vaccinated cohort of women who at baseline had no DNA detected for 14 high-risk HPV types, were seronegative for HPV-16 and HPV-18, and had normal cytology results.

[b] Two CIN3 cases were associated with HPV-33, and one subject had a CIN3 lesion which could not be associated with a high-risk HPV type according to the rules prespecified by the Endpoint Committee. This subject had a 6-month persistent infection with HPV-58 and a CIN2 lesion associated with HPV-58 preceding the CIN3 diagnosis, suggesting that HPV-58 might have been involved in the development of the lesion.

15- to 17-year-old stratum only (74%, 73%, and 75%, respectively).

An important public health aspect of our analysis was to evaluate overall efficacy of the HPV-16/18 AS04-adjuvanted vaccine against clinical lesions without taking into consideration HPV DNA testing results, as nonvaccine hr HPV types also contribute to at least 20% of the burden of cervical disease (3). The overall VE in the TVC-naive, irrespective of HPV DNA results, was 50%, 70%, and 87% against CIN1+, CIN2+, and CIN3+, respectively. In the TVC, irrespective of HPV DNA in the lesion, the vaccine prevented 30% and 33% of high-grade cervical lesions (CIN2+ and CIN3+), respectively. Reductions of 42% and 44% were observed in 15- to 17-year-olds and in 18- to 20-year-olds, respectively, but none was observed for 21- to 25-year-olds. The lower efficacy in the oldest age group could be due to a larger proportion of women in this group with prevalent infections at baseline, which the vaccine does not impact (29). The higher efficacy estimates in CIN2+ and CIN3+ reflect the increasing relative prevalence of HPV-16 and -18 compared to some other hr HPV types with increasing lesion severity (30–32) but also the consistent cross-protective efficacy of the HPV-16/18 AS04-adjuvanted vaccine against HPV-31, -33, -45, and -51 (8, 13), which may extend even further (33, 34).

To obtain the greatest benefit from prophylaxis, most HPV vaccination programs target young adolescents with the aim of immunizing before HPV exposure through sexual contact (15–17). As there are no clinical efficacy studies with HPV vaccines in the target population, the TVC-naive cohort from PATRICIA was used as an approximation of HPV-naive adolescents, by including only study participants who at baseline had no evidence of exposure to any of 14 hr HPV types detected by PCR, seronegativity to HPV-16/18, and no evidence of cytological abnormalities. We chose the age strata to reflect the variability in currently implemented HPV vaccination programs, some of which (assuming high compliance to the three-dose schedule) recommend catch-up vaccination to 17 years of age and others through 25 to 26 years of age. In modeling and cost-benefit analyses, 18 years is generally considered to be the upper age limit at which HPV vaccines are considered to be cost-effective (35, 36). The incidences of CIN lesions associated with HPV-16/18, or irrespective of HPV DNA, were consistently higher in women 15 to 17 years than in women 21 to 25 years, but observed estimates of VE against CIN and persistent hr HPV infections were similar in each age group.

At present, no conventional method exists to assign lesion causality when several HPV types are detected. The complexities of evaluating cross-protective efficacy against CIN lesions are ad-

dressed in more detail in an article by Wheeler and colleagues (13). Virological endpoints have the advantage of not being complicated by infection with multiple HPV types. In young women aged 15 to 17 years, VE against 6-month and 12-month PIs with HPV-16 and/or -18 was 71% and 66%, respectively, which reflects the 73% to 75% efficacy observed against CIN1+, CIN2+, and CIN3+ associated with HPV-16 and/or -18 in this age group in the TVC. We also observed some cross-protection in 15- to 17-year-olds against PIs with the combination of nonvaccine hr types HPV-31/33/45/51. No cross-protection was observed in older age groups with evidence of past and/or current HPV infection at baseline (baseline positive cohort).

Multiple infections were commonly associated with CIN2+ lesions in the control group of the TVC-naive. Estimates of the proportion of lesions associated with HPV-16/18 in unvaccinated women ranged from 31.6% (lesions with only HPV-16 and/or -18 present) to 64.3% (lesions with HPV-16 and/or -18 plus at least one additional HPV type) for CIN2+ and 31.6% to 73.7% for CIN3+. Yet, in the baseline negative subjects, the vaccine provided high and very high efficacy against both CIN2+ and CIN3+ lesions, irrespective of HPV type.

Approximating a sexually naive population has several limitations. HPV serology is not a perfect marker of prior exposure to HPV infection. Previous studies have shown that approximately 30 to 40% of women with incident HPV-16 infection never have detectable antibodies (37, 38). Furthermore, serological testing was not performed for cross-neutralizing antibodies (39). Thus, cross-protective immunogenicity and prior exposure to nonvaccine HPV types were unknown. Similarly, although the PCR used in this study detected 14 of the most relevant hr HPV types, women in the TVC-naive could have been infected with other high-risk types not detected by the specific PCR-based HPV DNA assays. Therefore, the TVC-naive may have included some young women who were not truly HPV naive, which would result in an underestimation of the expected vaccine impact in naive young adolescents. On the other hand, even among the target population of young adolescents, some might already be infected with HPV, for example, through sexual abuse. Other factors which may limit the extrapolation of the study results were the enrollment of 80% of 15- to 17-year-olds from a single country (Finland) and the enrollment of approximately half of the older age groups from Asia Pacific, although recent data from Scotland have shown the impact of the HPV-16/18 AS04-adjuvanted vaccine in other populations in a real-world setting (40). Additionally, compliance with the three-dose vaccination schedule was >90% in this study, which is higher than that achieved in most catch-up campaigns, particularly for older cohorts (19, 41, 42).

In conclusion, this study confirms the widely held view that targeting young adolescent girls before sexual debut for prophylactic HPV vaccination could have a substantial impact on the incidence of high-grade cervical abnormalities. Modeling data predict that anti-HPV-16 and -18 antibodies elicited by the HPV-16/18 AS04-adjuvanted vaccine will persist for many years after vaccination, suggesting that vaccinated young girls may be protected for the most of their sexually active lives (43). Inconsistent or negligible efficacy was observed for women aged 21 to 25 years, likely due to a higher proportion of women with prevalent infections at baseline. This is in line with analyses suggesting reduced or negligible cost-effectiveness of vaccination programs in women aged 21 years and above (36, 44). For women aged 18 to 25 years, unfortunately neither the models nor our data are conclusive. There may, however, be individual benefit for vaccination of HPV-negative women aged 18 years and older.

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