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ARTICLE

Efficacy of the AS04-Adjuvanted HPV16/18 Vaccine: Pooled Analysis of the Costa Rica Vaccine and PATRICIA Randomized Controlled Trials

Joseph E. Tota*, Frank Struyf*, Joshua N. Sampson, Paula Gonzalez, Martin Ryser, Rolando Herrero, John Schussler, Naveen Karkada, Ana Cecilia Rodriguez, Nicolas Folschweiller (1), Carolina Porras, Mark Schiffman, John T. Schiller, Wim Quint, Aimée R. Kreimer, Cosette M. Wheeler*, Allan Hildesheim (1) *, for the Costa Rica Vaccine Trial and PATRICIA Study

See the Notes section for the full list of authors' affiliations.

Correspondence to: Joseph E. Tota, PhD, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 9609 Medical Center Dr, Room 6E220, Rockville, MD 20850 (e-mail: joseph.tota@nih.gov).

*Authors contributed equally to this work.

Abstract

Background: The AS04-adjuvanted HPV16/18 (AS04-HPV16/18) vaccine provides excellent protection against targeted human papillomavirus (HPV) types and a variable degree of cross-protection against others, including types 6/11/31/33/45. High efficacy against any cervical intraepithelial neoplasia grade 3 or greater (CIN3+; >90%) suggests that lower levels of protection may exist for a wide range of oncogenic HPV types, which is difficult to quantify in individual trials. Pooling individual-level data from two randomized controlled trials, we aimed to evaluate AS04-HPV16/18 vaccine efficacy against incident HPV infections and cervical abnormalities .

Methods: Data were available from the Costa Rica Vaccine Trial (NCT00128661) and Papilloma Trial Against Cancer in Young Adults trial (NCT00122681), two large-scale, double-blind randomized controlled trials of the AS04-HPV16/18 vaccine. Primary analyses focused on disease-free women with no detectable cervicovaginal HPV at baseline.

Results: A total of 12 550 women were included in our primary analyses (HPV arm = 6271, control arm = 6279). Incidence of 6-month persistent oncogenic and nononcogenic infections, excluding known and accepted protected types 6/11/16/18/31/33/45 (focusing on 34/35/39/40/42/43/44/51/52/53/54/56/58/59/66/68/73/70/74), was statistically significantly lower in the HPV arm than in the control arm (efficacy = 9.9%, 95% confidence interval [CI] = 1.7% to 17.4%). Statistically significant efficacy (P < .05) was observed for individual oncogenic types 16/18/31/33/45/52 and nononcogenic types 6/11/53/74. Efficacy against cervical abnormalities (all types) increased with severity, ranging from 27.7% (95% CI = 21.7% to 33.3%) to 58.7% (95% CI = 34.1% to 74.7%) for cytologic outcomes (low-grade squamous intraepithelial neoplasia lesion or greater, and high-grade squamous intraepithelial neoplasia lesion or greater, respectively) and 66.0% (95% CI = 54.4% to 74.9%) to 87.8% (95% CI = 71.1% to 95.7%) for histologic outcomes (CIN2+ and CIN3+, respectively). Comparing Costa Rica Vaccine Trial and Papilloma Trial Against Cancer in Young Adults results, there was no evidence of heterogeneity, except for type 51 (efficacy = -28.6% and 20.7%, respectively; two-sided P = .03).

Conclusions: The AS04-HPV16/18 vaccine provides some additional cross-protection beyond established protected types, which partially explains the high efficacy against CIN3+.

Human papillomavirus (HPV) infection is a necessary cause of cervical cancer, which remains a leading cause of female cancer mortality worldwide (1). Infection with oncogenic HPV types 16/ 18 is responsible for approximately 60-70% of cervical cancer cases globally (2). These HPV types are targeted by all commercially available prophylactic vaccines, including Cervarix (AS04adjuvanted HPV16/18 [AS04-HPV16/18] vaccine; GSK, Brentford, UK), Gardasil and Gardasil 9 (4vHPV and 9vHPV vaccines, respectively; Merck & Co., Whitehouse Station, NJ). Both 4vHPV and 9vHPV vaccines also target nononcogenic HPV types 6/11 for prevention of genital warts, whereas only 9vHPV vaccine specifically targets oncogenic HPV types 31/33/45/52/58, responsible for approximately 20% of cervical cancer cases globally (2,3). Among females (younger than 25 years) not infected with the respective target types, the three available vaccines provide excellent protection against infection with their respective target types. Additionally, among first-generation vaccines (AS04-HPV16/18 and 4vHPV) there is a variable degree of crossprotection against other HPV types (4-8).

In addition to valency, another important difference in vaccine composition is that the AS04-HPV16/18 vaccine contains an adjuvant system (AS04) formulated with 50 µg 3-O-deacyl-4'monophosphoryl lipid A (produced by GSK) adsorbed on 500 μg aluminum salt (Al³⁺) for enhanced immunogenicity that is possibly responsible for the relatively high level of cross-protection (6,7,9). In the GSK-sponsored Papilloma Trial Against Cancer in Young Adults (PATRICIA) trial (10)—the largest completed randomized controlled trial of the AS04-HPV16/18 vaccine—investigators reported, in the cohort of baseline HPV-negative women, statistically significant cross-protection against oncogenic types 31/33 from the alpha-9 species (same as HPV16), type 45 from the alpha-7 species (same as HPV18), and type 51 from the alpha-5 species (5). In PATRICIA, statistically significant crossprotection (approximately 35%) against 6-month persistent infection (6 M-PI) was also observed against nononcogenic types 6 and 11 (11). Efficacy against oncogenic HPV31, -33, -45, and -51 6 M-PI in PATRICIA was estimated at 77%, 45%, 74%, and 17% (5), and these types account for approximately 3.8%, 4.6%, 4.5%, and 1% of global cervical cancer cases, respectively (2). Additionally, results from the National Cancer Institute (NCI)-sponsored Costa Rica AS04-HPV16/18 vaccine trial (CVT) confirmed crossprotection against oncogenic HPV types 31/33/45 (4).

Based on protection estimates in PATRICIA and the proportion of cervical cancer cases linked to each oncogenic HPV type worldwide, additional cross-protective efficacy of approximately 8.5% was expected (2,5). Therefore, assuming near complete protection against target types 16/18 and accounting for documented cross-protection (2), the AS04-HPV16/18 vaccine was expected to provide approximately 70-80% total protection against cervical cancer. However, greater than 90% efficacy against cervical intraepithelial neoplasia grade 3 or greater (CIN3+) was reported in PATRICIA irrespective of the HPV type found in the lesion (12). This high level of protection against CIN3+ irrespective of HPV type has been confirmed in Scotland, the Netherlands, and Finland (13-16). The underlying biological reason for the high degree of protection against CIN3+ afforded by the AS04-HPV16/18 vaccine is not fully understood. Protection mechanisms that have been proposed to explain the very high degree of protection (ie, beyond vaccine types) invoke cross-neutralization (of closely related types) and nonneutralization mechanisms, including impact of nonneutralizing binding antibodies on local inflammation and clearance of infections as well as cross-reactive T cells on clearance and progression of lesions attributable to nonvaccine infections (17).

One possibility that has yet to be evaluated is that the AS04-HPV16/18 vaccine affords low-level protection against a broader set of HPV types beyond HPV types 6/11/16/18/31/ 33/45. The GSK-sponsored PATRICIA trial and the NCIsponsored CVT trial are the only two completed large-scale, double-blind randomized controlled trials of the AS04-HPV16/18 vaccine with similar design and methodology (4,18). To better understand the effects of the AS04-HPV16/18 vaccine against HPV infections and more precisely quantitate reductions in cervical abnormalities, we pooled PATRICIA and CVT data and compared rates of incident 6 M-PI and disease outcomes across arms.

Methods

Study Design and Laboratory Procedures

The methods of this study (GSK study no. 205206) are similar to other pooled analyses using the same trial populations (19,20). Briefly, women from PATRICIA (NCT00122681, n = 18729) (10) and CVT (NCT00128661, n = 7466) (4,18) who were randomly assigned to receive the AS04-HPV16/18 vaccine or hepatitis A vaccine were considered for inclusion. PATRICIA participants (aged 15-25 years) were from Europe, Latin America, North America, and the Asia-Pacific region, whereas all CVT participants (aged 18-25 years) were from Costa Rica. Recruitment in both trials took place from 2004 to 2005 with 4year follow-up.

PATRICIA and CVT protocols were closely harmonized at the design phase. For example, vaccines were administered on the same schedule (enrollment, 1 month, 6 months), HPV DNA and serology assays were consistent with testing done in the same laboratories, and referral procedures for additional workup (cvtological testing and colposcopy) were similar. The main difference is that PATRICIA participants were seen every 6 months, whereas in CVT, unless a participant had abnormal cytology, women were observed annually.

At each clinic visit, broad-spectrum polymerase chain reaction (PCR)-based HPV DNA testing (DDL Diagnostic Laboratory) was performed on all collected samples. The assay used is based on amplification and probe hybridization with the SPF10 HPV DNA enzyme immunoassay system followed by typing (6/ 11/16/18/31/33/34/35/39/40/42/43/44/45/51/52/53/54/56/58/59/ 66,[68/73],70/74) with the LiPA25 version 1 method (Labo Biomedical Products, Rijswijk, the Netherlands) (21,22). In the list above, HPV 68 and -73 are contained in square brackets to indicate that the assay used could not distinguish between infection with these types. In both studies, all specimens positive for HPV DNA (by DNA enzyme immunoassay) but negative for types 16/18 (by LiPA25) were retested with type-specific primers and probes for HPV16 and HPV18 DNA. In PATRICIA, additional type-specific primers and probes were available for oncogenic HPV types 31/33/35/45/52/58/59. For consistency in our primary analyses, results from retesting of negative samples with type-specific primers and probes were excluded but considered in study-specific sensitivity analyses. Using a virus-like, particle-based, direct enzyme-linked immunosorbent assay (GSK), serology status for HPVs 16/18 was assessed at baseline using standard cutoff values (23).

Clinical protocols and other study material were approved by independent ethics committees or institutional review boards, and all participants provided written informed consent before enrollment.

Statistical Analysis

The primary endpoints included incident cervical HPV infection with any of the grouped types (6/11/16/18/31/33/34/35/39/40/42, 43/44/45/51/52/53/54/56/58/59/66,[68/73],70/74, any except 6/11/ 16,18/31/33/45), any of the grouped oncogenic types (16/18/31/ 33/35,39/45/51/52/56/58/59, any except 16/18/31/33/45, 16/18 only, 31/33/45 only), and the grouped nononcogenic types (6/11/ 34/40/42/43/44/53/54/66,[68/73],70/74, any except 6/11, 6/11 only) as well as incident cervical cytological abnormalities (low-grade squamous intraepithelial lesion or greater, high-grade squamous intraepithelial lesion or greater [HSIL+]) and histological abnormalities (CIN2+, CIN3+). Patients with HSIL+ were further stratified into two groups: one including atypical glandular cells (AGC) and atypical squamous cells, cannot exclude HSIL (ASC-H), and another excluding these lesions. Secondary endpoints included incident infection with individual oncogenic and nononcogenic HPV types. The proportion of cervical abnormalities associated with different HPV infection categories (16/18 only, 31/33/45 only, etc) was also calculated. All oncogenic HPV types detected at the most recent clinic visit (time of or immediately preceding lesion diagnosis) and at least one other visit before diagnosis were considered to be associated with the lesion. If no oncogenic HPV types met this criteria, then the following algorithm was applied: oncogenic types present at the most recent visit, nononcogenic HPV types detected at the most recent visit and at least one other visit before diagnosis, nononcogenic types present at the most recent visit, unknown HPV type(s) if overall PCR test was positive (uncharacterized) at most recent visit, or no HPV if the overall PCR test was negative at the most recent visit.

Women who received the study vaccine according to their random assignment, received all three vaccine doses (or two doses separated by 6 months), and had follow-up of at least 1 year were considered for inclusion. We decided to include women who received two doses separated by 6 months based on similar efficacy (compared with three doses) against incident infection with HPV target types 16/18 and cross-protected types 31/33/45 (19). Our primary analyses focused on the pooled total vaccinated cohort, Naive (TVC-Naive), including women who were baseline HPV DNA negative and seronegative for HPV16/ 18, had normal baseline cytology, and were not referred for colposcopy before their 12-month visit. Additional analyses were conducted using a less stringent TVC-Naive cohort definition, that is, excluding women with "oncogenic" HPV types rather than "any" HPV type (TVC-Oncogenic Naive). In our primary analyses, 6 M-PI was considered as the outcome (defined as \geq 2 type-specific positive tests >150 days apart with no intervening negatives); however, we also considered single-time HPV detection and 12 M-PI (defined as \geq 2 detections of the same infection type >300 days apart with no intervening negatives). Additional analyses were performed comparing results in each trial, restricted to PATRICIA and incorporating results with typespecific primers and probes for additional HPV types and evaluating cytological and histological outcomes stratified by year of participant follow-up.

Incidence rates and associated 95% confidence intervals (CIs) were calculated for virologic and disease outcomes. Incidence rates for individual HPV types and disease outcomes were based on total follow-up time at risk for each type and disease category separately, and rates were expressed per 1000 person-years. Grouped rates (infections) were expressed per 1000 infection-years as the ratio of number events to the total combined follow-up time for each HPV type that a woman was

at risk of acquiring in the respective groups. Outcome assessment began at the 12-month visit, that is, the first visit attended by a woman after receiving her third vaccine dose or second vaccine dose if separated by 6 months. For each individual HPV type, counting of time (infection-years) began at enrollment and ended at either detection of the specific HPV type of interest, or last negative HPV test or follow-up visit.

Efficacy was evaluated by comparing cumulative rates of HPV infection and cervical abnormalities between the two arms. Efficacy estimates represent the percentage change in the outcome of interest calculated as one minus the rate ratio. The 95% confidence intervals for vaccine efficacy were calculated using a two-step approach: first, an exact 95% confidence interval was calculated for the proportion of vaccinated cases, π , conditioning on the number of cases and using the mid-p correction, and second, letting (π L, π U) denote this confidence interval and letting NV and NU denote the number of vaccinated and unvaccinated participants, respectively; 95% confidence intervals for vaccine efficacy were calculated by $(1-\pi UNU)$ [NV(1- π U]), 1- π LNU /(NV[1- π L]) (24). Positive estimates were interpreted as evidence of efficacy if the 95% confidence interval excluded zero. For virologic outcomes, this analysis was conducted at the infection level rather than the woman level to increase power (ie, same individual could acquire infection with multiple unique HPV types at different time points during follow-up). To account for lack of independence between infections occurring within the same individual, generalized estimating equation methods were used (25). Heterogeneity in vaccine efficacy between the two trials was evaluated using a Poisson regression model with an interaction term for vaccination group by trial. Main statistical tests were two-sided with an alpha level of 0.05; however, we also applied Bonferroni correction to account for multiple comparisons for individual oncogenic and nononcogenic HPV types (25 total) with an alpha level of 0.002. Other objectives of this study will be reported in subsequent publications. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

The CONSORT diagram, which includes information for the to-(n = 26 195)and individual trial populations (PATRICIA = 18729, CVT = 7466), is presented for the TVC-Naive cohort (Figure 1). After applying restrictions, 12550 women remained in the TVC-Naive cohort and 13386 women remained in the TVC-Oncogenic Naive cohort, with balance across arms. There was also balance across arms for baseline characteristics (age, sexual history) and follow-up characteristics (total followup time, number of clinic visits; Table 1).

The incidence of oncogenic and nononcogenic HPV infections that persisted for 6 months, excluding known protected types 6/11/16/18/31/33/45 (focusing on 34/35/39/40/42/43/44/51/ 52/53/54/56/58/59/66,[68/73],70/74), was statistically significantly lower in the HPV arm than in the control arm (efficacy = 9.9%, 95% CI = 1.7% to 17.4%) (Table 2). Similarly, the incidence of 6month persistent oncogenic HPV infections, excluding known protected types 16,18,31,33,45 (focusing on 35/39/51/52/56/58/ 59), was lower in the HPV arm; however, the difference was smaller and not statistically significant (efficacy = 9.4%, 95% CI = -0.4% to 18.2%). Individual oncogenic types for which statistically significant vaccine efficacy was observed include targeted types 16 and 18 (95.5% and 92.9%, respectively); known cross-protected types 31 (77.9%), 33 (36.2%), and 45 (79.8%); and

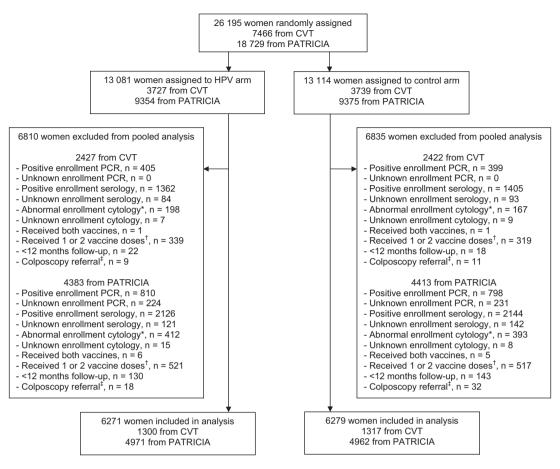


Figure 1. Consort diagram for this Costa Rica Vaccine Trial (CVT; NCT0012861) and Papilloma Trial Against Cancer in Young Adults (PATRICIA; NCT00122681) pooled analysis. *Women with low-grade squamous intraepithelial lesion or worse cytology results were excluded from this analysis. HPV = human papillomavirus; PCR = polymerase chain reaction. †Women receiving two vaccine doses separated by 6 months (at enrollment and 6 months) were not excluded from this analysis. ‡Women referred for colposcopy before one year were excluded from this analysis. Note: In the PATRICIA trial, 21 patients from one study site were excluded from prior analyses because of concerns about data integrity. Those patients did not contribute any data or outcomes to the current pooled analysis because they were excluded for the various reasons included in the consort diagram and/or no cases of cervical intraepithelial neoplasia, incident, or persistent infection were detected.

type 52 (15.8%). Focusing on nononcogenic HPV infections (6/11/ 34/40/42/43/44/53/54/66,[68/73],70/74), the overall incidence was statistically significantly lower in the HPV arm (efficacy = 14.1%, 95% CI = 4.1% to 23.1%); however, after excluding types 6/11, the was no longer statistically (efficacy = 10.6%, 95% CI = -0.4% to 20.4%) (Table 2). Statistically significant vaccine efficacy was observed for individual nononcogenic types 6 (30.1%), 11 (59.9%), 53 (22.9%), and 74 (44.7%), whereas a statistically significant deleterious effect was observed for type 42 (-145.6%). Correcting for multiple comparisons using the Bonferroni method, efficacy against individual oncogenic types 33 and 52 and nononcogenic types 6/11/53/74 no longer remained statistically significant.

Statistically significant vaccine efficacy was observed for all cytological and histological outcomes, with greater efficacy associated with higher grade: 27.7% for low-grade squamous intraepithelial lesion or greater, 44.3% for HSIL+ (including AGC and ASC-H), 58.7% for HSIL+ (excluding AGC and ASC-H), 66.0% for CIN2+, and 87.8% for CIN3+ (Table 3). A higher proportion of lesions among women in the control arm was associated with HPVs 16/18 (38.6% vs 4.9% for HSIL+ and 55.9% vs 3.4% for CIN2+; total percentage detected alone or with other types) as well as known cross-protected types 31/33/45 (22.8% vs 12.3% for HSIL+ and 32.4% vs 15.5% for CIN2+), whereas the

detection of other oncogenic types (35/39/51/52/56/58/59) was less common in lesions among women in the control arm (44.1% vs 58.0% for HSIL+ and 47.6% vs 74.1% for CIN2+) (Table 4).

Efficacy against incident HPV 6M-PI infections, excluding known protected HPV types 6/11/16/18/31/33/45 (focusing on 34,35/39/40/42/43/44/51/52/53/54/56/58/59/66,[68/73],70/74), tended to be higher in PATRICIA than in CVT (12.4% vs -2.1%); however, the difference (assessed by including an interaction term in the model) was not statistically significant (test for heterogeneity, P=.24, TVC-Naive cohort; Table 5). In our study-specific analyses focusing on individual HPV types, we found no evidence of heterogeneity (P > .05) apart from type 51 (efficacy = 20.7% in PATRICIA vs -28.6% in CVT, P = .03; Table 5). Similarly, efficacy against cervical abnormalities was similar across trials for all cytological and histological endpoints except CIN3+ and also tended to be higher in PATRICIA compared with CVT (91.9% vs 49.1%, P=.23), albeit with only six observed cases in CVT (TVC-Naive cohort; Table 6).

Focusing on grouped infection outcomes, results in the TVC-Oncogenic Naive cohort were similar to results in the TVC-Naive cohort (Supplementary Table 1, available online). PATRICIA results incorporating additional type-specific PCR

Table 1. Baseline age, sexual history, and follow-up characteristics of PATRICIA and CVT trial participants (pooled)

	-	
	HPV arm	Control arm
Characteristic	(n = 6271)	(n = 6279)
Age, y		
Mean (SD)	19.9 (3.0)	19.9 (3.0)
Median (IQR)	20.0 (17.0-23.0)	20.0 (17.0-23.0)
Lifetime sexual partners*, no. (%)		
0	507 (39.0)	550 (41.8)
1	452 (34.8)	488 (37.1)
2	200 (15.4)	170 (12.9)
3	90 (6.9)	55 (4.2)
≥4	50 (3.8)	53 (4.0)
Missing	1 (0.1)	1 (0.1)
Sexual partners in last		
12 mo†, no. (%)		
0	1140 (22.9)	1139 (23.0)
1	3192 (64.2)	3169 (63.9)
2	434 (8.7)	446 (9.0)
3	142 (2.9)	132 (2.7)
\geq 4	51 (1.0)	57 (1.1)
Missing	12 (0.2)	19 (0.4)
Follow-up characteristics		
Mean total follow-up time per woman, mo	47.2	47.2
Mean total clinic visits per woman, no.	6.3	6.4

*Data only available from CVT (NCT00128661). CVT = Costa Rica AS04-HPV16/18 vaccine trial; HPV = human papillomavirus; IQR = interquartile range; PATRICIA = PApilloma TRIal against Cancer In young Adults.

†Data only available from PATRICIA (NCT00122681).

information (TVC-Naive and TVC-Oncogenic Naive cohorts) were also similar to PATRICIA results excluding this information (Supplementary Tables 2 and 3, available online). Efficacy estimates in both naive cohorts, applying singletime detection outcome definition (Supplementary Tables 4 and 5, available online) and 1-year persistence definition (Supplementary Tables 6 and 7, available online), were also generally similar. Finally, although no major difference was observed in our analysis of cytological and histological abnormalities in the TVC-Oncogenic Naive cohort (efficacy and attribution of types, Supplementary Tables 8 and 9, available online, respectively), in our analyses stratified by year of participant follow-up, efficacy was generally higher in later follow-up years (Supplementary Tables 10 and 11, available

Discussion

Among HPV-negative women at enrollment, the cohort that approximates adolescents before sexual debut, our findings reveal that the ASO4-HPV16/18 vaccine confers an additional low level of protection (9.9%) against the composite of 19 HPV types that excludes vaccine target types (HPVs 16/18) and others for which strong evidence of efficacy and crossprotection already exists (HPVs 6/11/31/33/45). When we evaluated individual HPV types, in addition to confirming moderate to high cross-protection against HPV types 6/11/31/33/45, we also observed modest protection against oncogenic type 52 (alpha-9 species, same as HPV16) as well as nononcogenic types 53 and 74.

The immune mechanisms responsible for vaccineinduced cross-protection are not fully understood, and several alternative biological mechanisms have been proposed, including cross-neutralization of HPV types phylogenetically related to vaccine types, impact of nonneutralizing, binding antibodies on local inflammation and clearance of nonvaccine or related infections, and possible impact of crossreactive T cells on clearance and progression of lesions caused by nontargeted and protected HPV types (17). Regardless of mechanism, whether protection beyond that against HPV16/18-induced infections will be long-lasting remains an open question (26).

Unlike previous results, which suggest that cross-protection may extend outside the alpha-9/alpha-7 species (5), statistically significant protection against HPV51 (alpha-5 species) was not observed in our primary analysis. Presumably, HPV epitopes that differ by either L1 amino acid sequence or structure confer type-specific neutralization. Yet HPV types that are phylogenetically related to vaccine types, with perhaps only minor differences in amino acid sequences or conformation, share epitopes that elicit partial cross-reactive immune responses (27–31). Indeed, with HPV31 sharing 83% L1 homology with HPV16, and HPV45 sharing 88% L1 homology with HPV18 (32), we observed a high level of cross-protection.

Despite modest cross-protection beyond types 31/33/45, efficacy against CIN3+, the immediate precursor to invasive cancer, was nearly 90%. This estimate corresponds to the expected level of protection against CIN3+ from the 9vHPV vaccine, which targets five additional oncogenic HPV types (2,3). Reduced efficacy against CIN2+ (<70%) may be due to lower attributable fraction of protected types in CIN2 or early evidence of unmasking, that is, increased progression of other HPV types in vaccinated women caused by reduced excisional treatment of lesions coinfected with targeted and other HPV types (33).

Although measurement of histologically confirmed disease endpoints, especially CIN3+, is more accurate for estimation of efficacy against invasive cancer, we also evaluated impact on cytological abnormalities because of the high clinical burden associated with management of these lesions. The relatively high proportion of lesions associated with other oncogenic HPV types (non-targeted or non-cross-protected types) in the vaccine arm suggests that these types will cause most cervical precancer and cancer cases in vaccinated cohorts.

Results from our sensitivity analyses were generally consistent, intended to provide either greater power (analyses focusing on the oncogenic HPV naive cohort and applying single-time detection outcome definition) or improved accuracy (analyses including additional typing information, and applying 1-year persistence outcome definition). Increased efficacy associated with time since vaccination is likely due to waning influence of false-negative baseline HPV results, supported by higher efficacy against virologic outcomes in our analyses incorporating additional type-specific PCR results, which more effectively excludes positive individuals.

A limitation of evaluating vaccine efficacy against numerous individual HPV types is that chance findings may have occurred. Applying a much more conservative threshold for statistical significance (using Bonferroni correction), efficacy against individual types 6/11/33/52/53/74 no longer remained statistically significant; however, this approach increases the type-2 error probability. Also, although CVT and PATRICIA protocols were not identical (ie, frequency of regular follow-up was different), it

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Table 2. Efficacy of the AS04-HPV16/18 vaccine against incident (6-month persistent) HPV infections among women without detectable HPV infection at enrollment, pooled analysis of PATRICIA and CVT trials

		HPV (1	n = 6271		Control	Control (n = 6279)	
HPV type	Cases	Person-years	Rate per 1000 person-years* (95% CI)	Cases	Person-years	Rate per 1000 person-years* (95% CI)	Efficacy % (95% CI)
All HPV types							
Any type†	1836	598491.5	3.1 (2.9 to 3.3)	2805	597 709.3	4.7 (4.4 to 5.0)	34.6 (29.1 to 39.7)
All except 6/11/16/18/31/33/45‡	1625	429549.4	3.8 (3.6 to 4.0)	1807	430428.6	4.2 (4.0 to 4.5)	9.9 (1.7 to 17.4)
Oncogenic HPV types							
Any type§	1094	287 147.3	3.8 (3.5 to 4.1)	1939	285736.9	6.8 (6.4 to 7.2)	43.9 (38.4 to 48.9)
All except 16/18/31/33/45	958	166209.0	5.8 (5.3 to 6.2)	1059	166489.6	6.4 (5.9 to 6.8)	9.4 (-0.4 to 18.2)
HPV16/18	30	48890.13	0.6 (0.4 to 0.9)	554	47 554.95	11.6 (10.7 to 12.7)	94.7 (92.4 to 96.4)
HPV31/33/45	106	72 048.22	1.5 (1.2 to 1.8)	326	71692.31	4.5 (4.1 to 5.1)	67.6 (59.6 to 74.1)
HPV16	18	24437.75	0.7 (0.5 to 1.1)	387	23525.05	16.5 (14.9 to 18.2)	95.5 (93.0 to 97.3)
HPV18	12	24452.38	0.5 (0.3 to 0.8)	167	24029.90	6.9 (5.9 to 8.1)	92.9 (87.7 to 96.2)
HPV31	40	23 985.24	1.7 (1.2 to 2.2)	179	23723.76	7.5 (6.5 to 8.7)	77.9 (69.1 to 84.5)
HPV33	53	23 982.49	2.2 (1.7 to 2.9)	83	23970.92	3.5 (2.8 to 4.3)	36.2 (10.1 to 55.0)
HPV35	32	24035.16	1.3 (0.9 to 1.9)	31	24074.55	1.3 (0.9 to 1.8)	-3.4 (-70.3 to 37.2)
HPV39	117	23 799.30	4.9 (4.1 to 5.9)	132	23842.52	5.5 (4.7 to 6.5)	11.2 (-13.9 to 30.8)
HPV45	13	24080.49	0.5 (0.3 to 0.9)	64	23997.63	2.7 (2.1 to 3.4)	79.8 (64.1 to 89.3)
HPV51	276	23340.72	11.8 (10.5 to 13.3)	321	23350.74	13.7 (12.3 to 15.3)	14.0 (-1.0 to 26.8)
HPV52	244	23 492.40	10.4 (9.1 to 11.8)	289	23417.61	12.3 (11.0 to 13.8)	15.8 (0.2 to 29.1)
HPV56	139	23731.40	5.9 (4.9 to 6.9)	150	23797.68	6.3 (5.3 to 7.4)	7.1 (-17.1 to 26.3)
HPV58	100	23862.22	4.2 (3.4 to 5.1)	88	23 973.99	3.7 (3.0 to 4.5)	-14.2 (-52.3 to 14.3)
HPV59	20	23 947.79	2.1 (1.6 to 2.7)	48	24032.52	2.0 (1.5 to 2.6)	-4.5 (-55.8 to 29.8)
Nononcogenic HPV types							
Any type¶	742	311344.2	2.4 (2.2 to 2.6)	998	311972.4	2.8 (2.6 to 3.0)	14.1 (4.1 to 23.1)
All except 6/11#	299	263340.4	2.5 (2.3 to 2.8)	748	263939.0	2.8 (2.6 to 3.1)	10.6 (-0.4 to 20.4)
HPV6/11	75	48003.72	1.6 (1.2 to 2.0)	118	48033.48	2.5 (2.0 to 2.9)	36.4 (14.9 to 52.5)
HPV6	65	23 928.71	2.7 (2.1 to 3.4)	93	23926.09	3.9 (3.2 to 4.7)	30.1 (4.2 to 49.3)
HPV11	10	24075.01	0.4 (0.2 to 0.7)	25	24107.38	1.0 (0.7 to 1.5)	59.9 (17.9 to 81.6)
HPV34	6	24079.50	0.4 (0.2 to 0.7)	13	24150.11	0.5 (0.3 to 0.9)	30.6 (-63.3 to 71.5)
HPV40	14	24062.39	0.6 (0.3 to 1.0)	13	24116.25	0.5 (0.3 to 0.9)	-7.9 (-134.0 to 49.9)
HPV42	22	24047.25	0.9 (0.6 to 1.4)	თ	24161.71	0.4 (0.2 to 0.7)	-145.6 (-461.2 to -14.9)
HPV43	28	24020.97	1.2 (0.8 to 1.7)	24	24107.17	1.0 (0.7 to 1.5)	-17.1 (-103.8 to 32.3)
HPV44	35	24003.91	1.5 (1.0 to 2.0)	38	24080.91	1.6 (1.1 to 2.1)	7.6 (-46.6 to 41.9)
HPV53	149	23721.70	6.3 (5.3 to 7.4)	193	23675.57	8.2 (7.0 to 9.4)	22.9 (4.6 to 37.8)
HPV54	81	23 894.74	3.4 (2.7 to 4.2)	89	23986.84	2.8 (2.2 to 3.6)	-19.6 (-65.5 to 13.4)
HPV66	143	23718.44	6.0 (5.1 to 7.1)	154	23772.28	6.5 (5.5 to 7.6)	6.9 (-16.9 to 25.9)
HPV68/73	110	23 784.87	4.6 (3.8 to 5.6)	113	23854.19	4.7 (3.9 to 5.7)	2.4 (-27.0 to 25.0)
HPV70	39	24017.79	1.6 (1.2 to 2.2)	26	24029.83	2.3 (1.8 to 3.0)	30.3 (-4.7 to 54.0)
HPV74	37	23 988.89	1.5 (1.1 to 2.1)	29	24004.11	2.8 (2.2 to 3.5)	44.7 (17.7 to 63.3)

*For grouped HPV endpoints, analyses focus on infection-years (rather than person-years) as the total combined follow-up time for each HPV type that a woman was at risk of acquiring in the respective groups. CI = confidence interval; CVT = Costa Rica AS04-HPV16/18 vaccine trial; HPV = human papillomavirus; n = number of women in the analyzed cohort; PATRICIA = PApilloma TRIal against Cancer In young Adults.

†Grouped oncogenic and nononcogenic types include HPVs 6/11/16/18/31/33/34/35/38/45/58/58/58/66/68/73/70/74.

#Includes oncogenic and nononcogenic types (HPVs 34/35/39/40/42/43/44/51/52/53/54/56/58/59/66/68/73/70/74) for which vaccine efficacy has not been established. §Grouped oncogenic types include HPVs 16/18/31/33/35/39/45/51/52/56/58/59.

||Includes oncogenic types 35/39/51/52/56/58/59. ||Grouped nononcogenic types include HPVs 6/11/34/40/42/43/44/53/54/66/68/73/70/74.

#Includes nononcogenic types 34/40/42/43/44/53/54/66/68/73/70/74.

Table 3. Overall efficacy of the AS04-HPV16/18 vaccine against incident cytological and histological cervical abnormalities among women without detectable HPV infection at enrolment, pooled analysis of PATRICIA and CVT trials

		HPV (n	= 6271)		Control (n = 6279)	
Cervical abnormality	Cases	Person-years	Rate per 1000 person-years (95% CI)	Cases	Person-years	Rate per 1000 person-years (95% CI)	Efficacy %, (95% CI)
Cytology-based diagno	sis						
LSIL+	1046	22 960.45	45.6 (42.8 to 48.4)	1414	22 441.08	63.0 (59.8 to 66.4)	27.7 (21.7 to 33.3)
HSIL+*	81	24 409.69	3.3 (2.7 to 4.1)	145	24 321.96	6.0 (5.0 to 7.0)	44.3 (27.1 to 57.7)
HSIL+†	24	24 514.99	1.0 (0.6 to 1.4)	58	24 460.35	2.4 (1.8 to 3.0)	58.7 (34.1 to 74.7)
Histology-based diagn	osis						
CIN2+	58	24 507.04	2.4 (1.8 to 3.0)	170	24 419.35	7.0 (6.0 to 8.1)	66.0 (54.4 to 74.9)
CIN3+	5	24 565.07	0.2 (0.1 to 0.5)	41	24 545.23	1.7 (1.2 to 2.2)	87.8 (71.1 to 95.7)

*HSIL+ definition includes both AGC and ASC-H cases. AGC = atypical glandular cells; ASC-H = atypical squamous cells, cannot exclude HSIL; CI = confidence interval; CIN2+ = cervical intraepithelial neoplasia of grade 2 or greater; CIN3+ = cervical intraepithelial neoplasia of grade 3 or greater; HSIL+ = high-grade squamous intraepithelial neoplasia of grade 3 or greater; HSIL+ = high-grade squamous intraepithelial neoplasia of grade 3 or greater; HSIL+ = high-grade squamous intraepithelial neoplasia of grade 3 or greater; HSIL+ = high-grade squamous intraepithelial neoplasia of grade 3 or greater; HSIL+ = high-grade squamous intraepithelial neoplasia of grade 3 or greater; HSIL+ = high-grade squamous intraepithelial neoplasia of grade 3 or greater; HSIL+ = high-grade squamous intraepithelial neoplasia of grade 3 or greater; HSIL+ = high-grade squamous intraepithelial neoplasia of grade 3 or greater; HSIL+ = high-grade squamous intraepithelial neoplasia of grade 3 or greater; HSIL+ = high-grade squamous intraepithelial neoplasia of grade 3 or greater; HSIL+ = high-grade squamous intraepithelial neoplasia of grade 3 or greater; HSIL+ = high-grade squamous intraepithelial neoplasia of grade 3 or greater; HSIL+ = high-grade squamous intraepithelial neoplasia of grade 3 or grade 3 o $the lial lesion \ or \ greater; \ HPV = human \ papillo mavirus; \ LSIL + = low-grade \ squamous \ in traepithe lial lesion \ or \ greater; \ n = number \ of \ women \ in \ the \ analyzed \ cohort.$ †HSIL+ definition excludes both AGC and ASC-H cases.

Table 4. Number and proportion of lesions associated with targeted, cross-protected, or other oncogenic HPV infections among women without detectable HPV infection at enrolment according to study arm, pooled analysis of PATRICIA and CVT trials

		Cytology cla	ssification]	Histology cla	assification	1
	LS	IL+	HS	SIL+	CIN	12+	CII	N3+
	HPV No. (%)	Control No. (%)						
HPV infection status	(n = 1046)	(n = 1414)	(n = 81)	(n = 145)	(n = 58)	(n = 170)	(n=5)	(n=41)
16/18 only	12 (1.2)	190 (13.4)	2 (2.5)	32 (22.1)	1 (1.7)	50 (29.4)	0 (0.0)	13 (31.7)
31/33/45 only	23 (2.2)	86 (6.1)	5 (6.2)	15 (10.3)	8 (13.8)	22 (12.9)	2 (40.0)	4 (9.8)
Other oncogenic type(s) only*	662 (63.3)	435 (30.8)	41 (50.6)	31 (21.4)	41 (70.7)	34 (20.0)	3 (60.0)	7 (17.1)
16/18 and 31/33/45†	0 (0.0)	28 (2.0)	0 (0.0)	2 (1.4)	0 (0.0)	10 (5.9)	0 (0.0)	2 (4.9)
16/18 and other oncogenic types‡	11 (1.1)	184 (13.0)	1 (1.2)	17 (11.7)	1 (1.7)	24 (14.1)	0 (0.0)	5 (12.2)
31/33/45 and other oncogenic types§	40 (3.8)	124 (8.8)	4 (4.9)	11 (7.6)	1 (1.7)	12 (7.1)	0 (0.0)	5 (12.2)
16/18 and 31/33/45 and other oncogenic types	6 (0.6)	81 (5.7)	1 (1.2)	5 (3.5)	0 (0.0)	11 (6.5)	0 (0.0)	4 (9.8)
No oncogenic types	292 (27.9)	286 (20.2)	27 (33.3)	32 (22.1)	6 (10.3)	7 (4.1)	0 (0.0)	1 (2.4)

*Includes cases that were negative for HPV types 16/18/31/33/45. CIN2+ = cervical intraepithelial neoplasia of grade 2 or greater: CIN3+ = cervical intraepithelial neoplasia of grade 3 or greater; CVT = Costa Rica AS04-HPV16/18 vaccine trial; HSIL+ = high-grade squamous intraepithelial lesion or greater; HPV = human papillomavi $rus; LSIL += low-grade\ squamous\ intraepithelial\ lesion\ or\ greater; PATRICIA = PApilloma\ TRIal\ against\ Cancer\ In\ young\ Adults.$

†Includes coinfection cases where HPV16 and/or HPV18 was present with other cross-protected types (HPV31, -33, and/or -45) but no other oncogenic types.

‡Includes co-infection cases where HPV16 and/or HPV18 and other oncogenic HPV types (excluding HPV31, -33, and -45) were present.

SIR = 100 SIncludes co-infection cases where HPV31, -33, and/or -45 and other oncogenic HPV types (excluding HPV16 and -18) were present.

||Includes co-infection cases where HPV16 and/or HPV18 and HPV31, -33, and/or -45 were present, along with other oncogenic types.

is not expected that this had any major impact on our results given that women in the HPV and control arms had the same total follow-up and number of visits.

In Scotland, the AS04-HPV16/18 vaccine was introduced in 2008, and more than 90% of targeted girls (aged 12-13 years, 1995 birth-cohort) were fully vaccinated in 2008-2009. With cervical screening initiated at age 20 years among this and preceding (unvaccinated) birth-cohorts, investigators evaluated vaccine effectiveness among girls in the target age range. Compared with the 1988 birth-cohort, they found that prevalence of targeted and cross-protected types, measured 7 years postvaccination, was lower in the 1995 birth-cohort: 16/18 fell by 89%, and types 31/33/45 fell by 94%, 79%, and 83%, respectively (13). In a similar analysis, CIN3+ prevalence declined by 89% in vaccinated 1995 and 1996 birth-cohorts compared with the unvaccinated 1988 birth-cohort (14). These results are consistent with our observation of additional protection

against HPV types for which protection was previously not reported.

As the most comprehensive analysis of the AS04-HPV16/18 vaccine to date, to our knowledge, our results provide evidence for low additional cross-protection beyond known and accepted types as a group and, at the individual type level, support for protection against HPVs 6/11/31/33/45/52/53/74. Additional population studies and/or trials with longer follow-up could help address questions related to duration of protection.

Funding

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ARTICLE

Table 5. Efficacy of the HPV16/18 vaccine against incident (6-month persistent) HPV infections among women without detectable HPV infection at enrollment evaluated separately in CVT (NCT00128661) and the PATRICIA (NCT00122681) trial

HPV type				P/	PATRICIA trial					CVT		
Rate per		HF	ν (n = 4971)	Coı			出	^{1}V $(n = 1300)$	Con	trol (n = 1317)		
313(310.35) 2347 52(490.55) 365(305041.9) 335 24(210.27) 468 32(280.36) 258(1050.384) 41(380.43) 151 46(43.64.9) 12.4(360.20.4) 28 24(210.27) 46(400.53) 258(1050.384) 54 41(380.44) 1622 75/700.80 45.4(350.20.4) 29 29.25.50.33 29 25.60.33 27.1(248.016.5) 56 62(570.67) 367 10.6(310.20.4) 317 46(400.83) 36.5(110.48.8) 56 62(570.67) 367 10.6(310.20.4) 317 46(400.83) 36.5(110.48.8) 56 26 37 26 37 46(400.83) 36.5(110.48.8)	HPV type	Cases	Rate per 1000 person- years* (95% CI)	Cases	Rate per 1000 person- years* (95% CI)	Efficacy % (95% CI)	Cases	Rate per 1000 person- years* (95% CI)	Cases	Rate per 1000 person- years* (95% CI)	Efficacy % (95% CI)	Heterogeneity P**
56 4.1(380.44) 1622 7.5 (7.00.8.0) 45.4(3550.50.7) 199 2.9 (25.03.4) 317 4.6(4.00.5.3) 36.5 (2.110.48.8) 56 6.2(5.70.6.7) 887 7.0 (6.50.76) 117 (1.10.21.2) 172 4.3 (3.70.5.3) 173 (2.50.5.1) 117 (1.10.21.2) 172 4.3 (2.70.5.3) 11.5 (2.20.2.1) 11.	All HPV types Any type† All except 6/11,	1501	3.3 (3.1 to 3.5) 4.1 (3.8 to 4.3)	2347	5.2 (4.9 to 5.5) 4.6 (4.3 to 4.9)	36.5 (30.5 to 41.9) 12.4 (3.6 to 20.4)	335	2.4 (2.1 to 2.7) 2.9 (2.5 to 3.3)	458	3.2 (2.8 to 3.6) 2.9 (2.5 to 3.3)	25.8 (10.5 to 38.4) -2.1 (-24.8 to 16.5)	.32
55 4.1(38 to 44) 152. 7.5(70 to 80) 4.5(45 to 5.3) 35.5(21 to 4.8) 35.5(2	16/18/31/33/45‡ Oncogenic HPV types		•							•	•	
25 0.6 (0.4 to 0.9) 471 1.30 (11.9 to 14.3) 95.3 (9.2 k to 9.6) 7 0.6 (0.3 to 1.3) 83 7.3 (5.8 to 9.1) 91.6 (8.18 to 9.2.) 86 1.6 (1.3 to 1.9) 264 4.9 (4.3 to 2.5) 67.7 (\$28 to 9.4.) 5 0.9 (2.0 to 0.1.) 5 0.4 (8 to 1.3.4) 91.6 (8.0 to 9.2.) 92.7 (\$28 to 9.4.) 5 0.9 (2.0 to 0.1.) 92.4 (\$6.0 to 9.2.) 92.2 (\$28 to 9.4.) 9.0 (\$6.3 to 9.2.) 9.0 (\$6.3 to 9.2.) 9.0 (\$6.0 to 9.2.)	Any type§ All except 16/18, 31/33/45	895	4.1 (3.8 to 4.4) 6.2 (5.7 to 6.7)	1622	7.5 (7.0 to 8.0) 7.0 (6.5 to 7.6)	45.4 (39.5 to 50.7) 11.7 (1.1 to 21.2)	199	2.9 (2.5 to 3.4) 4.3 (3.7 to 5.2)	317	4.6 (4.0 to 5.3) 4.3 (3.6 to 5.1)	36.5 (21.1 to 48.8) -1.8 (-29.6 to 20.1)	.41 .35
56 16 (13 to 19) 264 49 (43 to 5.5) 677 (58.7 to 74.8) 20 12 (08 to 18) 62 3 6 (28 to 4.6) 677 (46 to 10.8) 12 12 (08 to 12.9) 12 12 (08 to 12.9) 12 12 (08 to 12.9) 12 12 (14.4 to 20.8) 12 12 (14.4 to 20.8) 13 12 (14.4 to 20.8) 13 13 (14.4 to 20.8) 14 <td>HPV16/18</td> <td>23</td> <td>0.6 (0.4 to 0.9)</td> <td>471</td> <td>13.0 (11.9 to 14.3)</td> <td>95.3 (92.8 to 96.9)</td> <td>7</td> <td>0.6 (0.3 to 1.3)</td> <td>83</td> <td>7.3 (5.8 to 9.1)</td> <td>91.6 (81.8 to 96.1)</td> <td>.28</td>	HPV16/18	23	0.6 (0.4 to 0.9)	471	13.0 (11.9 to 14.3)	95.3 (92.8 to 96.9)	7	0.6 (0.3 to 1.3)	83	7.3 (5.8 to 9.1)	91.6 (81.8 to 96.1)	.28
13 0.7 (0.4 to 1.2) 328 18.4 (16.4 to 20.5) 9.5 (0.93 to 1.9) 5.09 (0.3 to 1.9) 5.09 (0.3 to 1.9) 9.4 (0.3 to 1.2) 9.4 (0.6 to 2.7) 9.6 (0.3 to 1.2) 9.4 (0.6 to 2.7) 9.6 (0.8 to 2.9) 9.4 (0.6 to 2.7) 9.4 (0.7 to 0.7) 9.4 (0.7 to 0.7) 9.4 (0.6 to 2.7) 9.4 (0.6 to 2.7) 9.4 (0.6 to 0.7) 9.4	HPV 31/33/45	98	1.6 (1.3 to 1.9)	264	4.9 (4.3 to 5.5)	67.7 (58.7 to 74.8)	20	1.2 (0.8 to 1.8)	62	3.6 (2.8 to 4.6)	67.4 (46.0 to 80.3)	66:
11 17(12.02.4) 143 7.8 (6.00 9.2) 39.2 (8.5 to 9.6.6) 2 0.3 (0.1101.2) 24 4.2 (2.7 to 6.1) 916 (9.5 to 9.8.7) 11 1.7 (1.2 to 2.4) 148 8.7 (8.6 to 9.2) 39.0 (9.3 to 8.8.7) 149 1.7 (1.2 to 2.4) 148 8.7 (1.4 to 8.6.0) 149 2.5 (1.2 to 2.4) 150	HPV16	13	0.7 (0.4 to 1.2)	328	18.4 (16.4 to 20.5)	96.2 (93.6 to 97.9)	5 0	0.9 (0.3 to 1.9)	59	10.4 (8.0 to 13.4)	91.6 (80.5 to 97.0)	.24
2.5 (1812) 3.1 (18	HPV18 HPV31	10	0.5 (0.3 to 1.0)	143	7.8 (6.6 to 9.2) 8 1 (6.8 to 9.5)	93.2 (87.5 to 96.6)	о 7	0.3 (0.1 to 1.2)	24 34	4.2 (2.7 to 6.1) 5 9 (4.2 to 8.2)	91.6 (69.7 to 98.7) 73.4 (46.1 to 88.0)	.81
29 1.6 (1.10 c.2) 23 1.3 (0.8 to 1.9) -25.8 (-1197 to 27.3) 3 0.5 (0.11 to 1.4) 8 1.4 (0.6 to 2.6) 620 (-390 to 91.8) 21 5.0 (4.10 to 6.1) 46 2.5 (1.40 to 4.3) 2.6 (4.10 to 6.4) 3 3.2 (2.0 to 5.0) 3.3 (2.0 to 5.0) 3.99 (-1564 to 22.6) 21 5.0 (4.10 to 6.1) 46 2.5 (1.40 to 3.3) 7.4 (5.84 to 8.2) 3 3.1 (1.54 to 4.8) 3.3 (2.10 to 9.6) 3 3.2 (2.10 to 9.6) 3.3 (2.10 to 9.6) </td <td>HPV33</td> <td>45</td> <td>2.5 (1.8 to 3.3)</td> <td>73</td> <td>4.0 (3.2 to 5.0)</td> <td>38.7 (11.4 to 58.0)</td> <td>າ ∞</td> <td>1.4 (0.6 to 2.7)</td> <td>10</td> <td>3.3 (₹.2 to 8.2) 1.7 (0.9 to 3.1)</td> <td>18.6 (-109.8 to 69.3)</td> <td>59.</td>	HPV33	45	2.5 (1.8 to 3.3)	73	4.0 (3.2 to 5.0)	38.7 (11.4 to 58.0)	າ ∞	1.4 (0.6 to 2.7)	10	3.3 (₹.2 to 8.2) 1.7 (0.9 to 3.1)	18.6 (-109.8 to 69.3)	59.
91 50 (4.1 b 6.1) 113 6.3 (5.2 to 7.5) 198 (-5.6 to 39.3) 26 46 (311 to 6.6) 19 3.3 (2.0 to 5.0) -399 (-1564 to 22.6) 10 0.5 (0.3 to 1.0) 46 2.5 (1.9 to 3.3) 784 (584 to 89.7) 3 0.5 (0.1 to 1.4) 18 3.1 (1.9 to 4.8) 83.2 (47.7 to 6.0) 12 1.2 (10.9 to 14.2) 2.7 1.4 (1.7 to 15.2) 1.4 (-3.0 to 29.2) 40 7.1 (5.2 to 9.4) 22 2.6 (5.5 to 10.1) 2.28 (1.3 to 8.0) 33.2 (1.3 to 8.0) 2.2 (2.5 to 10.1) 2.28 (1.3 to 8.0) 3.2 (1.5 to 2.8) 3.2 (2.5 to 5.4) 3.2 (1.5 to 2.9) 3.2 (2.5 to 5.4) 3.2 (1.5 to 2.9) 3.2 (2.5 to 5.4) 3.2 (1.5 to 2.9) 3.2 (2.5 to 5.4) 3.3 (1.5 to 2.8) 3.2 (1.5 to 2.8) 3.3 (1.5 to 2.8)	HPV35	29	1.6 (1.1 to 2.2)	23	1.3 (0.8 to 1.9)	-25.8 (-119.7 to 27.3)	3	0.5 (0.1 to 1.4)	∞	1.4 (0.6 to 2.6)	62.0 (-39.0 to 91.8)	60:
10 0.5 (0.3 to 1.0) 46 2.5 (1.3 to 0.3.3) 784 (584 to 89.7) 3 0.5 (0.1 to 1.4) 18 3.1 (1.9 to 4.8) 832 (477 to 96.0) 2.2 (1.25 (10.9 to 14.2) 2.78 (1.25 to 3.6) 2.5 (1.3 to 12.3) 2.7 (5.4 to 12.6) 43 7.6 (5.5 to 10.1) -28.6 (-92.8 to 13.9) 2.4 (1.5 to 2.9) 2.7 (1.5 to 2.8) 7.9 (-1.8.2 to 2.8) 7.9 (-1.8.2 to 2.8) 2.7 (1.5 to 2.9) 3.1 (-1.5 to 4.8) 3.1 (-1.5 to 4.8) 3.1 (-1.5 to 4.8) 3.1 (-1.5 to 4.8) 3.1 (-1.5 to 2.8) 3.1 (-1.5 to 2.8) <td>HPV39</td> <td>91</td> <td>5.0 (4.1 to 6.1)</td> <td>113</td> <td>6.3 (5.2 to 7.5)</td> <td>19.8 (-5.6 to 39.3)</td> <td>56</td> <td>4.6 (3.1 to 6.6)</td> <td>19</td> <td>3.3 (2.0 to 5.0)</td> <td>-39.9 (-156.4 to 22.6)</td> <td>.10</td>	HPV39	91	5.0 (4.1 to 6.1)	113	6.3 (5.2 to 7.5)	19.8 (-5.6 to 39.3)	56	4.6 (3.1 to 6.6)	19	3.3 (2.0 to 5.0)	-39.9 (-156.4 to 22.6)	.10
22 12.5 (10.9 to 14.2) 278 15.7 (13.9 to 17.7) 20.7 (5.4 to 12.6) 43 7.6 (5.5 to 10.1) -22.8 (-22.8 to 13.9) 24 11.4 (9.9 to 13.1) 278 15.7 (13.9 to 17.7) 20.7 (5.4 to 29.2) 40 7.1 (5.2 to 9.6) 52 9.2 (6.9 to 11.9) 22.3 (-17.3 to 48.8) 24 11.4 (9.9 to 13.1) 27 1.4 (-3.0 to 29.2) 20 3.5 (2.2 to 5.4) 18 3.1 (-9.4 to 8.8) 3.1 (-9.0 to 4.8) 3.1 (-9.4 to 4.8) 3.2 (-9.4 to 4.1) 3.2 (-9.4 to 4.1) <	HPV45	10	0.5 (0.3 to 1.0)	46	2.5 (1.9 to 3.3)	78.4 (58.4 to 89.7)	က	0.5 (0.1 to 1.4)	18	3.1 (1.9 to 4.8)	83.2 (47.7 to 96.0)	.72
12. (1.5 to 2.9) 12.9 12.9 (1.5 to 2.8) 12.9 (1.5 to 2.9) 12.9 12.9 (1.5 to 2.8) 12.9 (1.5 to 2.9) 12.9 (1.5 to 2.8) 12.1 (1.5 to 2.9) 12.2 (1.5 to 2.4) 12.5 (1.5 to 2.4) <	HPV51	222	12.5 (10.9 to 14.2)	278	15.7 (13.9 to 17.7)	20.7 (5.4 to 33.6)	4, 6	9.7 (7.4 to 12.6)	43	7.6 (5.5 to 10.1)	-28.6 (-92.8 to 13.9)	.03
32 45 (3.6 to 5.6) 70 3.8 (3.0 to 4.8) -17.2 (-6.16 to 14.8) 18 3.2 (1.9 to 4.8) -1.8 (-977 to 47.6) 39 2.1 (1.5 to 2.9) 37 2.0 (1.5 to 2.8) -5.3 (-6.5.7 to 33.1) 11 1.9 (1.0 to 3.4) 11 1.9 (1.0 to 3.3) -1.9 (-140.3 to 56.8) 56 2.6 (2.3 to 2.8) 725 3.1 (2.8 to 3.4) 13.4 (1.5 to 2.2) 141 1.9 (1.6 to 2.2) 1.9 (-140.3 to 56.8) 141 2.7 (2.5 to 3.0) 623 3.1 (2.8 to 3.4) 13.4 (1.5 to 2.3) 126 2.0 (1.7 to 2.4) 125 2.0 (1.6 to 2.4) -2.5 (-34.2 to 2.16) 55 1.8 (14 to 2.3) 102 2.8 (2.3 to 3.4) 3.6 (13.2 to 5.3) 1.0 0.9 (0.5 to 1.6) 1.2 2.0 (1.6 to 2.4) -2.5 (-34.2 to 2.16) 55 1.8 (14 to 2.3) 102 2.8 (2.3 to 7.8) 0.0 (0.0 to 0.5) 1.2 2.0 (1.6 to 2.4) -2.5 (-34.2 to 2.16) 56 2.0 (2.3 to 2.3) 1.1 (0.7 to 1.7) 3.2.5 (0.1 to 2.3) 1.0 1.8 (0.9 to 3.1) 1.2 2.1 (1.1 to 3.5) 1.1 (1.1 to 2.2) 1.2 2.0 (1.6 to 2.2) <td< td=""><td>HPV56</td><td>119</td><td>6.6 (5.5 to 7.9)</td><td>129</td><td>7.2 (6.0 to 8.5)</td><td>7.9 $(-18.2 \text{ to } 28.3)$</td><td>8</td><td>3.5 (2.2 to 5.4)</td><td>32 21</td><td>3.6 (2.3 to 5.5)</td><td>3.1 (-80.0 to 48.0)</td><td>oo. 88.</td></td<>	HPV56	119	6.6 (5.5 to 7.9)	129	7.2 (6.0 to 8.5)	7.9 $(-18.2 \text{ to } 28.3)$	8	3.5 (2.2 to 5.4)	32 21	3.6 (2.3 to 5.5)	3.1 (-80.0 to 48.0)	oo. 88.
39 2.1(1.5 to 2.9) 37 2.0(1.5 to 2.8) -5.3(-65.7 to 33.1) 11 1.9(1.0 to 3.4) 11 1.9(1.0 to 3.3) -1.9(-140.3 to 5.8) 26 2.6(2.3 to 2.8) 725 3.1(2.8 to 3.3) 16.6(5.8 to 26.2) 136 1.8(1.5 to 2.2) 141 1.9(1.6 to 2.2) 1.9(-26.8 to 24.1) 27 2.5 to 3.0 623 3.1(2.9 to 3.4) 13.4(1.5 to 23.8) 126 2.0(1.7 to 2.4) 125 2.0(1.6 to 2.4) -2.5(-34.2 to 21.6) 25 1.8(1.4 to 2.3) 102 2.8(2.3 to 3.4) 36.6(13.2 to 53.6) 10 0.9(0.5 to 1.6) 16 1.4(0.8 to 2.2) 36.4(-39.7 to 71.1) 25 3.0(2.3 to 3.9) 81 4.5(3.6 to 5.5) 32.5(5.1 to 52.3) 10 1.8(0.9 to 3.1) 12 2.1(1.1 to 3.5) 15.1(-99.2 to 6.4) 10 0.5(0.3 to 1.0) 2.0 1.8(0.9 to 3.1) 1.2 2.1(1.1 to 3.5) 15.1(-99.2 to 6.4) 10 0.5(0.3 to 1.0) 2.0 1.8(0.9 to 3.1) 1.2 2.1(1.1 to 3.5) 1.2 2.1(1.1 to 3.5) 1.2 2.1(1.1 to 3.5) 1.2 <td< td=""><td>HPV58</td><td>82</td><td>4.5 (3.6 to 5.6)</td><td>70</td><td>3.8 (3.0 to 4.8)</td><td>-17.2 (-61.6 to 14.8)</td><td>18</td><td>3.2 (1.9 to 4.9)</td><td>18</td><td>3.1 (1.9 to 4.8)</td><td>-1.8 (-97.7 to 47.6)</td><td>.70</td></td<>	HPV58	82	4.5 (3.6 to 5.6)	70	3.8 (3.0 to 4.8)	-17.2 (-61.6 to 14.8)	18	3.2 (1.9 to 4.9)	18	3.1 (1.9 to 4.8)	-1.8 (-97.7 to 47.6)	.70
26 (2.3 to 2.8) 725 3.1 (2.8 to 3.3) 16.6 (5.8 to 26.2) 136 1.8 (1.5 to 2.2) 141 1.9 (1.6 to 2.4) -2.5 (-34.2 to 21.6) 151 2.7 (2.5 to 3.0) 623 3.1 (2.9 to 3.4) 13.4 (1.5 to 2.38) 126 2.0 (1.7 to 2.4) 125 2.0 (1.6 to 2.4) -2.5 (-34.2 to 21.6) 15 18 (1.4 to 2.3) 102 2.8 (2.3 to 3.4) 36.6 (13.2 to 53.6) 10 0.9 (0.5 to 1.6) 16 1.4 (0.8 to 2.2) 36.4 (-39.7 to 7.1.1) 10.2 (2.8 (2.3 to 3.4) 32.5 (5.1 to 52.3) 10 1.8 (0.9 to 3.1) 12 2.1 (1.1 to 3.5) 15.1 (-99.2 to 64.4) 12.5 (0.3 to 1.0) 12 1.1 (0.7 to 1.7) 52.5 (0.3 to 7.8 6) 0 0.0 (0.0 to 0.5) 1 0.2 (0.0 to 0.8) 10.0 (-133.4.5 to 10.0) 12 0.7 (0.4 to 1.1) 25.1 (-794 to 69.7) 0 0.0 (0.0 to 0.5) 1 0.2 (0.0 to 0.8) 10.0 (-1334.5 to 10.0) 13 0.7 (0.4 to 1.2) 10 0.5 (0.3 to 1.0) 10 0.5 (0.3 to 1.0) 10 0.5 (0.3 to 1.0) 10 0.5 (0.3 to 1.2) 10 0.5 (0.3 to 1.	HPV59	39	2.1 (1.5 to 2.9)	37	2.0 (1.5 to 2.8)	-5.3 (-65.7 to 33.1)	11	1.9 (1.0 to 3.4)	11	1.9 (1.0 to 3.3)	$-1.9\ (-140.3\ { m to}\ 56.8)$.95
peff 606 2.6 (2.3 to 2.8) 725 3.1 (2.8 to 3.3) 16.6 (5.8 to 26.2) 136 18 (1.5 to 2.2) 141 1.9 (1.6 to 2.2) 1.9 (-26.8 to 24.1) ept 6/11# 541 2.7 (2.5 to 3.0) 623 3.1 (2.9 to 3.4) 134 (1.5 to 23.8) 126 2.0 (1.7 to 2.4) 125 2.0 (1.6 to 2.4) -2.5 (-34.2 to 21.6) 1.0 12 2.8 (2.3 to 3.4) 36.6 (13.2 to 5.3.6) 10 0.9 (0.5 to 1.6) 16 1.4 (0.8 to 2.2) 3.6 4 (-39.7 to 7.1.1) 1.0 10.5 (0.3 to 1.0) 2.1 1.1 (0.7 to 1.7) 52.5 (0.3 to 7.8.6) 0 0.0 (0.0 to 0.5) 4 0.7 (0.2 to 1.7) 100.0 (-132 to 100.0) 1.0 0.5 (0.3 to 1.0) 1.1 (0.7 to 1.1) 25.1 (-79.4 to 69.7) 0 0.0 (0.0 to 0.5) 1 0.2 (0.0 to 0.8) 100.0 (-133.4 to 100.0) 1.2 0.7 (0.4 to 1.1) 25.1 (-79.4 to 69.7) 0 0.0 (0.0 to 0.5) 1 0.2 (0.0 to 0.8) 100.0 (-133.4 to 100.0) 1.3 0.7 (0.4 to 1.2) 1.0 0.5 (0.3 to 1.0) 1.0 -2.9 (-205.9 to 43.6) 1 0.2 (0.0 to 0.9) 3 0.5 (0.1 to 1.4) 66.2 (-217.3 to 98.7) 1.0 (0.6 to 1.5) 2.0 1.1 (0.7 to 1.7) 10.1 (-71.1 to 53.0) 10 1.8 (0.9 to 3.1) 1.0 0.2 (0.0 to 0.8) 1.0 (0.6 to 1.5) 1.0 (0.6 to 1.5) 2.0 1.1 (0.7 to 1.7) 10.1 (-71.1 to 53.0) 10 1.8 (0.9 to 3.1) 1.1 (0.9 to 3.1) 1.1 (0.7 to 1.7) 10.1 (-71.1 to 53.0) 1.1 (1.7 (0.9 to 3.1) 1.1 (0.9 to 3.1) 1.1 (0.7 to 1.2) 1.1 (0.7 t	Nononcogenic HPV ty	bes										
ppt 6/11# 541 2.7 (2.5 to 3.0) 623 3.1 (2.9 to 3.4) 13.4 (1.5 to 2.3.8) 126 2.0 (1.7 to 2.4) 125 2.0 (1.6 to 2.4) -2.5 (-34.2 to 21.6) 1.0 (1.5 to 2.3.9) 623 3.1 (2.9 to 3.4) 13.4 (1.5 to 2.3.8) 126 2.0 (1.7 to 2.4) 125 2.0 (1.6 to 2.4) -2.5 (-34.2 to 21.6) 1.0 (1.6 to 2.4) 1.2 (1.1 to 2.3) 10.2 (2.3 to 3.4) 36.6 (13.2 to 5.3.6) 10.0 (0.0 to 0.5) 12 2.1 (1.1 to 3.5) 15.1 (-99.2 to 64.4) 10.5 (0.3 to 1.0) 2.1 (1.0 7 to 1.7) 52.5 (0.3 to 7.8.6) 0.0 (0.0 to 0.5) 4.0 7 (0.2 to 1.7) 100.0 (-13.2 to 100.0) 1.3 (0.5 to 2.0) 1.0 (0.5 (0.3 to 1.0) 1.0 (Any type¶	909	2.6 (2.3 to 2.8)	725	3.1 (2.8 to 3.3)	16.6 (5.8 to 26.2)	136	1.8 (1.5 to 2.2)	141	1.9 (1.6 to 2.2)	1.9 (-26.8 to 24.1)	.24
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	All except 6/11#	541	2.7 (2.5 to 3.0)	623	3.1 (2.9 to 3.4)	13.4 (1.5 to 23.8)	126 40	2.0 (1.7 to 2.4)	125	2.0 (1.6 to 2.4)	-2.5 (-34.2 to 21.6)	97.
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	HPV6/11	00 7.	3.0 (2.3 to 3.9)	102	2.8 (2.3 t0 3.4) 4 5 (3 6 to 5 5)	30.6 (13.2 to 33.6)	10	18 (09 to 3.1)	12	1.4 (0.8 t0 2.2) 2 1 (1 1 to 3 5)	36.4 (-39.7 to 7 1.1) 15 1 (-99 2 to 64 4)	
9 $0.5 (0.2 \text{to}. 0.9)$ 12 $0.7 (0.4 \text{to}. 1.1)$ 25.1 $(-79.4 \text{to}. 69.7)$ 0 $0.0 (0.0 \text{to}. 0.5)$ 1 $0.2 (0.0 \text{to}. 0.8)$ 100.0 $(-1834.5 \text{to}. 100.0)$ 13 $0.7 (0.4 \text{to}. 1.2)$ 10 $0.5 (0.3 \text{to}. 1.0)$ $-29.8 (-205.9 \text{to}. 43.6)$ 1 $0.2 (0.0 \text{to}. 0.9)$ 3 $0.5 (0.1 \text{to}. 1.4)$ 66.2 $(-217.3 \text{to}. 98.7)$ 20 $1.1 (0.7 \text{to}. 1.7)$ 8 $0.4 (0.2 \text{to}. 0.8)$ $-150.1 (-502.3 \text{to}- 12.2)$ 2 $0.3 (0.1 \text{to}. 1.2)$ 1 $0.2 (0.0 \text{to}. 0.8)$ $-103.8 (-591.8 \text{to}. 44.5)$ 10 $1.8 (0.9 \text{to}. 3.1)$ 4 $0.7 (0.2 \text{to}. 1.7)$ $-154.9 (-837.7 \text{to}. 18.1)$ 12 $1.5 (1.0 \text{to}. 2.1)$ 12 $1.5 (1.0 \text{to}. 2.7)$ 10 $1.7 (0.9 \text{to}. 3.1)$ 18.6 $(-110.0 \text{to}. 69.2)$ 12 $1.5 (1.0 \text{to}. 2.8)$ 2.4 $(-110.0 \text{to}. 69.2)$ 2.5 $(-110.0 \text{to}. 69.2)$ 2.7 $(-11.1 \text{to}. 3.6)$ 2.7 $(-11.1 $	HPV11	10	0.5 (0.3 to 1.0)	21	1.1 (0.7 to 1.7)	52.5 (0.3 to 78.6)	0	0.0 (0.0 to 0.5)	4	0.7 (0.2 to 1.7)	100.0 (-13.2 to 100.0)	N/E
13 0.7 (0.4 to 1.2) 10 0.5 (0.3 to 1.0) -29.8 (-205.9 to 43.6) 1 0.2 (0.0 to 0.9) 3 0.5 (0.1 to 1.4) 66.2 (-217.3 to 98.7) 20 1.1 (0.7 to 1.7) 8 0.4 (0.2 to 0.8) -150.1 (-502.3 to -12.2) 2 0.3 (0.1 to 1.2) 1 0.2 (0.0 to 0.8) -103.8 (-591.8 to 84.5) 18 1.0 (0.6 to 1.5) 20 1.1 (0.7 to 1.7) 10.1 (-71.1 to 53.0) 10 1.8 (0.9 to 3.1) 4 0.7 (0.2 to 1.7) -154.9 (-837.7 to 18.1) 27 1.5 (1.0 to 2.1) 28 1.5 (1.0 to 2.2) 3.7 (-64.2 to 43.6) 8 1.4 (0.7 to 2.7) 10 1.7 (0.9 to 3.1) 18.6 (-110.0 to 69.2) 19 12 5 (9.5 s to 8.2) 168 9.4 (8.0 to 10.9) 26.2 (7.0 to 41.5) 12 2.1 (1.1 to 3.6) 9 1.6 (0.8 to 2.8) -35.9 (-235.3 to 43.3)	HPV34	6	0.5 (0.2 to 0.9)	12	0.7 (0.4 to 1.1)	25.1 (-79.4 to 69.7)	0	0.0 (0.0 to 0.5)	⊣	0.2 (0.0 to 0.8)	100.0 (-1834.5 to 100.0)	N/E
20 1.1 (0.7 to 1.7) 8 0.4 (0.2 to 0.8) -150.1 (-502.3 to -12.2) 2 0.3 (0.1 to 1.2) 1 0.2 (0.0 to 0.8) -103.8 (-5911.8 to 84.5) 18 1.0 (0.6 to 1.5) 20 1.1 (0.7 to 1.7) 10.1 (-71.1 to 53.0) 10 1.8 (0.9 to 3.1) 4 0.7 (0.2 to 1.7) -154.9 (-837.7 to 18.1) 27 1.5 (1.0 to 2.1) 28 1.5 (1.0 to 2.2) 3.7 (-64.2 to 43.6) 8 1.4 (0.7 to 2.7) 10 1.7 (0.9 to 3.1) 18.6 (-110.0 to 69.2) 125 6.9 (5.8 to 8.2) 168 9.4 (8.0 to 10.9) 26.2 (7.0 to 41.5) 24 4.2 (2.8 to 6.2) 25 4.3 (2.9 to 6.3) 2.4 (-71.8 to 44.7) 69 3.8 (3.0 to 4.8) 59 3.2 (2.5 to 4.2) -16.8 (-65.8 to 17.5) 12 2.1 (1.1 to 3.6) 9 1.6 (0.8 to 2.8) -35.9 (-235.3 to 43.3)	HPV40	13	0.7 (0.4 to 1.2)	10	0.5 (0.3 to 1.0)	-29.8 (-205.9 to 43.6)	₽	0.2 (0.0 to 0.9)	3	0.5 (0.1 to 1.4)	66.2 (-217.3 to 98.7)	.26
18 1.0 (0.6 to 1.5) 20 1.1 (0.7 to 1.7) 10.1 (-71.1 to 53.0) 10 1.8 (0.9 to 3.1) 4 0.7 (0.2 to 1.7) -154.9 (-837.7 to 18.1) 27 1.5 (1.0 to 2.1) 28 1.5 (1.0 to 2.2) 3.7 (-64.2 to 43.6) 8 1.4 (0.7 to 2.7) 10 1.7 (0.9 to 3.1) 18.6 (-110.0 to 69.2) 125 6.9 (5.8 to 8.2) 168 9.4 (8.0 to 10.9) 26.2 (7.0 to 41.5) 24 4.2 (2.8 to 6.2) 25 4.3 (2.9 to 6.3) 2.4 (-71.8 to 44.7) 69 3.8 (3.0 to 4.8) 59 3.2 (2.5 to 4.2) -16.8 (-65.8 to 17.5) 12 2.1 (1.1 to 3.6) 9 1.6 (0.8 to 2.8) -35.9 (-235.3 to 43.3)	HPV42	20	1.1 (0.7 to 1.7)	∞	0.4 (0.2 to 0.8)	-150.1 (-502.3 to -12.2)	2	0.3 (0.1 to 1.2)	1	0.2 (0.0 to 0.8)		<u>%</u>
27 1.5 (1.0 to 2.1) 28 1.5 (1.0 to 2.2) 3.7 (-64.2 to 43.6) 8 1.4 (0.7 to 2.7) 10 1.7 (0.9 to 3.1) 18.6 (-110.0 to 69.2) 125 6.9 (5.8 to 8.2) 168 9.4 (8.0 to 10.9) 26.2 (7.0 to 41.5) 24 4.2 (2.8 to 6.2) 25 4.3 (2.9 to 6.3) 2.4 (-71.8 to 44.7) 26 3.8 (3.0 to 4.8) 59 3.2 (2.5 to 4.2) -16.8 (-65.8 to 17.5) 12 2.1 (1.1 to 3.6) 9 1.6 (0.8 to 2.8) -35.9 (-235.3 to 43.3)	HPV43	18	1.0 (0.6 to 1.5)	20	1.1 (0.7 to 1.7)	10.1 (-71.1 to 53.0)	10	1.8 (0.9 to 3.1)	4	0.7 (0.2 to 1.7)	-154.9 (-837.7 to 18.1)	.11
125 6.9 (5.8 to 8.2) 168 9.4 (8.0 to 10.9) 26.2 (7.0 to 41.5) 24 4.2 (2.8 to 6.2) 25 4.3 (2.9 to 6.3) 2.4 (-71.8 to 44.7) 69 3.8 (3.0 to 4.8) 59 3.2 (2.5 to 4.2) -16.8 (-65.8 to 17.5) 12 2.1 (1.1 to 3.6) 9 1.6 (0.8 to 2.8) -35.9 (-235.3 to 43.3)	HPV44	27	1.5 (1.0 to 2.1)	28	1.5 (1.0 to 2.2)	3.7 (-64.2 to 43.6)	∞	1.4 (0.7 to 2.7)	10	1.7 (0.9 to 3.1)	18.6 (-110.0 to 69.2)	.76
69 $3.8 (3.0 \text{ to } 4.8)$ 59 $3.2 (2.5 \text{ to } 4.2)$ $-16.8 (-65.8 \text{ to } 17.5)$ 12 $2.1 (1.1 \text{ to } 3.6)$ 9 $1.6 (0.8 \text{ to } 2.8)$ $-35.9 (-235.3 \text{ to } 43.3)$	HPV53	125	6.9 (5.8 to 8.2)	168	9.4 (8.0 to 10.9)	26.2 (7.0 to 41.5)	24	4.2 (2.8 to 6.2)	25	4.3 (2.9 to 6.3)	2.4 (-71.8 to 44.7)	.37
	HPV54	69	3.8 (3.0 to 4.8)	29	3.2 (2.5 to 4.2)	-16.8 (-65.8 to 17.5)	12	2.1 (1.1 to 3.6)	6	1.6 (0.8 to 2.8)	-35.9 (-235.3 to 43.3)	.75

Table 5. (continued)

			P,	PATRICIA trial					CVT		
	H	HPV $(n = 4971)$	COI	Control (n = 4962)		HP	HPV (n = 1300)	Cont	Control (n = 1317)		
		Rate per 1000 person- vears*		Rate per 1000 person- vears*	Efficacy		Rate per 1000 person- vears*		Rate per 1000 person- vears*	Efficacy	Heterogeneity
HPV type	Cases	(95% CI)	Cases	(65% CI)	% (95% CI)	Cases	(io %56)	Cases	(95% CI)	% (95% CI)	D**
HPV66	115	6.4 (5.3 to 7.6)	122	6.8 (5.6 to 8.0)	5.9 (-21.5 to 27.1)	28	5.0 (3.4 to 7.1)	32	5.6 (3.9 to 7.8)	11.2 (-47.8 to 46.9)	.84
HPV68/73	91	5.0 (4.1 to 6.1)	66	5.5 (4.5 to 6.6)	8.3 (-22.0 to 31.1)	19	3.3 (2.1 to 5.1)	14	2.4 (1.4 to 4.0)	-38.3 (-182.0 to 30.8)	.28
HPV70	25	1.4 (0.9 to 2.0)	42	2.3 (1.7 to 3.1)	40.7 (3.1 to 64.3)	14	2.5 (1.4 to 4.0)	14	2.4 (1.4 to 4.0)	-1.6 (-116.4 to 52.3)	.24
HPV74	29	1.6 (1.1 to 2.2)	52	3.0 (2.3 to 3.9)	47.5 (18.0 to 66.9)	∞	1.4 (0.7 to 2.7)	12	2.1 (1.1 to 3.5)	32.4 (-66.3 to 73.7)	.63

For grouped HPV endpoints, analyses focus on infection-years (rather than person-years) as the total combined follow-up time for each HPV type that a woman was at risk of acquiring in the respective groups. CI = confidence interval; CVT = Costa Rica AS04-HPV16/18 vaccine trial; HPV = human papillomavirus; n = number of women in the analyzed cohort; N/E = not able to estimate; PATRICIA = PApilloma TRIal against Cancer In young Adults. +Grouped oncogenic and nononcogenic types include HPVs 6/11/16/18/31/33/34/35/39/40/42/43/44/45/51/52/53/54/56/58/59/66/68/73/70/74.

‡Includes oncogenic and nononcogenic types (HPVs 34/35/39/40/42/43/44/51/52/53/54/56/58/59/66/68/73/70/74) for which vaccine efficacy has not been established

SGrouped oncogenic types include HPVs 16/18/31/33/35/39/45/51/52/56/58/59. |Includes oncogenic types 35/39/51/52/56/58/59.

||Incruaces oncogenic types 33/37/13/14/34/40/42/43/44/53/54/66/68/73/70/74. ||Grouped nononcogenic types include HPVs 6/11/34/40/42/43/44/53/54/66/68/73/70/74.

#Includes nononcogenic types 34/40/42/43/44/53/54/66/68/73/70/74.

"Heterogeneity was tested with a Wald statistic for the vaccine × study interaction term in the Poisson model (2-sided P value).

Table 6. Overall efficacy of the HPV16/18 vaccine against incident cytological and histological cervical abnormalities among women without detectable HPV infection at enrollment evaluated separately in CVT (NCT00128661) and the PATRICIA (NCT00122681) trial

		Efficacy Heter	70 (95% C1) P‡	% (50 % LI)	% (95% CJ) 23.2 (9.8 to 34.7)	76 (95% CJ) 23.2 (9.8 to 34.7) 33.7 (4.0 to 54.6)	76 (95% CJ) 23.2 (9.8 to 34.7) 33.7 (4.0 to 54.6) 58.3 (1.4 to 83.9)	78.3 (1.4 to 83.9)	76 (95% CJ) 23.2 (9.8 to 34.7) 33.7 (4.0 to 54.6) 58.3 (1.4 to 83.9) 76.1 (32.8 to 93.1)
CVT	Control (n = 1317)	Rate per 1000 person-years (95% CI)			336 65.2 (58.5 to 72.6)				
	HPV (n = 1300)	Rate per 1000 person-years (95% CI)			50.1 (44.2 to 56.6)	50.1 (44.2 to 56.6) 8.2 (6.1 to 10.8)	50.1 (44.2 to 56.6) 8.2 (6.1 to 10.8) 1.2 (0.5 to 2.4)	50.1 (44.2 to 56.6) 8.2 (6.1 to 10.8) 1.2 (0.5 to 2.4)	50.1 (44.2 to 56.6) 8.2 (6.1 to 10.8) 1.2 (0.5 to 2.4) 0.7 (0.2 to 1.7)
		Cases) 261				
		Efficacy % (95% CI)			29.1 (22.2 to 35.3)				
PATRICIA trial	Control (n = 4962)	Rate per 1000 person-years (95% CI)			62.3 (58.7 to 66.2)	62.3	62.3 4.0 2.2	62.3 4.0 2.2	62.3 4.0 2.2 8.2
PATR	S	Cases			1078				
	HPV (n = 4971)	Rate per 1000 person- years (95% CI)			44.2 (41.2 to 47.4)	44.2 (41.2 to 47.4) 1.9 (1.3 to 2.6)	44.2 (41.2 to 47.4) 1.9 (1.3 to 2.6) 0.9 (0.5 to 1.4)	44.2 (41.2 to 47.4) 1.9 (1.3 to 2.6) 0.9 (0.5 to 1.4)	44.2 (41.2 to 47.4) 1.9 (1.3 to 2.6) 0.9 (0.5 to 1.4) 2.9 (2.2 to 3.7)
	田	Cases		osis	osis 785	osis 785 35	osis 785 35 17	osis 785 35 17 100sis	osis 785 35 17 nosis 54
		Cervical abnormality Cases		Cytology-based diagnosis	Cytology-based diagn LSIL+	Cytology-based diagn LSIL+ HSIL+*	Cytology-based diagn LSIL+ HSIL+* HSIL+†	Cytology-based diagnosis LSIL+ HSIL+* HSIL+† HSIL+† Histology-based diagnosis	Cytology-based diagn L.SIL.+ H.SIL.+* HISIL.+† Histology-based diagn CIN2.+

HSIL+ definition includes both AGC and ASC-H cases. AGC = atypical glandular cells; ASC-H = atypical squamous cells, cannot exclude HSIL; CI = confidence interval; CIN2+ = cervical intraepithelial neoplasia of grade 2 or greater; CIN3+=cervical intraepithelial neoplasia of grade 3 or greater; CVT=Costa Rica ASO4-HPV16/18 vaccine trial; HSIL+=high- grade squamous intraepithelial lesion or greater; HPV=human papillomavirus; LSIL+=low-grade squamous intraepithelial lesion or greater; n=number of women in the analyzed cohort; PATRICIA=PApilloma TRIal against Cancer In young Adults. †HSIL+ definition excludes both AGC and ASC-H cases.

#Heterogeneity was tested with a Wald statistic for the vaccine × study interaction term in the Poisson model (two-sided P value).

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Notes

Affiliations of authors: Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD (JET, JNS, MS, ARK, AH); GSK, Wavre, Belgium (FS, MR, NK, NF); Proyecto Epidemiológico Guanacaste, Fundación INCIENSA, Guanacaste, Costa Rica (PG); Section of Early Detection and Prevention, International Agency for Research on Cancer, Lyon, France (RH); Information Management Services, Rockville, MD (JS); Provecto Epidemiológico Guanacaste, Fundación INCIENSA, San José, Costa Rica (ACR, CP); Center for Cancer Research, National Cancer Institute, Bethesda, MD (JTS); DDL Diagnostic Laboratory, Rijswijk, the Netherlands (WQ); Department of Pathology and Obstetrics and Gynecology, University of New Mexico Cancer Center, Albuquerque, NM (CMW).

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All authors qualify for authorship in adherence with the ICMJE guidelines. All authors were involved in the interpretation of results, commented on a draft, and approved the final version of the report. JET, FS, JNS, MR, JS, NK, ACR, MS, ARK, CMW, and AH were involved in the conception and/or the design of the analysis; JET, PG, RH, JS, ACR, CP, MS, WQ, ARK, CMW, and AH participated in the collection and/or generation of the study data; JET, FS, JNS, JS, ARK, CMW, and AH performed the analysis. The NCI and Costa Rica investigators are responsible for the design and conduct of CVT. GSK and the PATRICIA investigators are responsible for the design and conduct of the PATRICIA trial. The NCI pooled the CVT and PATRICIA data. The NCI conducted the analysis of the pooled data in parallel with GSK. The NCI interpreted the results and prepared the manuscript in conjunction with GSK and the authors. JET wrote the manuscript.

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