MAJOR ARTICLE

Efficacy of the HPV-16/18 AS04-Adjuvanted Vaccine Against Low-Risk HPV Types (PATRICIA Randomized Trial): An Unexpected Observation

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(See the major article by Howell-Jones et al on pages 1397–403.)

Background. Public Health England has reported a decrease of up to 20.8% in new diagnoses of external genital warts (GWs) among women aged <19 years since the national vaccination program with the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine began in 2008. A post hoc analysis of the phase III PATRICIA (PApilloma TRIal against Cancer In young Adults) trial (NCT00122681) was performed to ascertain whether protection against low-risk HPV types was apparent.

Methods. Vaccine efficacy (VE) at 48 months was assessed against 6-month persistent infection (6MPI) with low-risk HPV types in the total vaccinated cohort (TVC) and in the TVC naive (for 25 HPV types tested) populations.

Results. In the TVC naive cohort, VE against 6MPI (95% confidence interval) was 34.5% (11.3 to 51.8) for HPV-6/11, 34.9% (9.1 to 53.7) for HPV-6, 30.3% (−45.0 to 67.5) for HPV-11, and 49.5% (21.0 to 68.3) for HPV-74.

Conclusions. The HPV-16/18 AS04-adjuvanted vaccine appears to have moderate efficacy against persistent infections with a number of low-risk HPV types (HPV-6/11/74), which are responsible for the majority of external GWs, and recently, antibody and cell-mediated immune response to HPV-6/11 have been observed. These findings may help to explain the decrease in external GW diagnoses seen in England.

Keywords. human papillomavirus; HPV; HPV vaccine; genital warts.

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The human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine (*Cervarix*®; GlaxoSmithKline Vaccines) has been demonstrated to have high efficacy against infection and both low- and high-grade cervical intraepithelial neoplasia (CIN; caused by oncogenic HPV types 16 and 18, with substantial cross protection against other high-risk HPV types 31, 33, 45, and 51 [1, 2]. Low-risk HPV types are found in approximately 12% of low-grade CIN, although there is likely to be coinfection with high-risk types [3]. While immunogenicity has been demonstrated in boys [4], the HPV-16/18 AS04-adjuvanted vaccine is not currently licensed for use in boys.

Genital warts (GWs) are the most common viral sexually transmitted infection in the Western world, and a 30% increase in new diagnoses was seen in the United Kingdom between 2000 and 2009 [5]. Treatment has a significant morbidity and can be frustrating, and recurrences are common. This causes psychosocial distress to patients and results in substantial financial costs [6, 7]. GWs result from persistent infection with low-risk HPV genotypes, predominantly 6 and 11, although other low-risk types were not evaluated in the former study [8, 9]. It has been suggested that a small proportion of GWs may be caused by HPV types 16 and 18; [10, 11] if true, limited efficacy against warts could occur with a vaccine directed against these types [10, 11].

The HPV-16/18 AS04-adjuvanted vaccine was chosen for the UK national vaccination program, which commenced in September 2008 and has achieved >84% uptake in 12- to 15-year-old girls for all 3 doses. A catch-up program to the age of 18 years achieved between 50% and 70% uptake for all 3 doses [12].

Public Health England (formerly the Health Protection Agency), which monitors rates of sexually transmitted infections in England, has reported a decrease in new diagnoses of GWs in genitourinary medicine clinics among young women since 2008 [13]. By 2011, the overall reduction was 13.3% among 16- to 19-year-olds, with the greatest decline (20.8%) in 17-year-olds, for whom HPV-16/18 AS04-adjuvanted vaccine coverage in 2011 was estimated at 64%. By contrast, rates in the older age groups were generally either static or increasing [14]. Among the potential reasons for this decrease, as discussed by Howell-Jones et al [14], is the possibility of an effect of the HPV-16/18 ASO4-adjuvanted vaccine on low-risk HPV types. A post hoc analysis of the PATRICIA (PApilloma TRIal against Cancer In young Adults) trial was therefore performed to ascertain whether any protection against low-risk HPV types was apparent.

METHODS

PATRICIA (HPV-008 PATRICIA, NCT00122681) is a phase III, multicenter, randomized, double-blind trial of the HPV-16/18 AS04-adjuvanted vaccine vs a hepatitis A vaccine as control (1:1 randomization). The study design and methodology have been fully described elsewhere [1, 15]. It should be noted that neither a history of GWs nor current GWs were exclusion criteria and that no systematic collection of GW data was done. Written informed consent/assent was obtained from all participants and/or their parents, and the study was approved by independent ethics committees or institutional review boards.

The primary objective of the trial was to assess the efficacy of the HPV-16/18 AS04-adjuvanted vaccine against CIN2+ associated with HPV-16 or HPV-18 in women who were seronegative at baseline and DNA negative at baseline and month 6 for the corresponding type [15]. The objectives of this post hoc analysis, with the end-of-study data at month 48, were to assess vaccine efficacy (VE) against 6-month persistent infection (6MPI) with HPV types 6, 11 and other low-risk (non-oncogenic) HPV types in the total vaccinated cohort (TVC) and in the TVC naive population (see below).

Cervical samples were obtained from all women every 6 months for HPV DNA typing. A broad-spectrum polymerase chain reaction (PCR) SPF10 HPV LiPA25 version 1 and SPF10 HPV DEIA (Labo Biomedical Products, Rijswijk, Netherlands; based on licensed INNOGENETICS SPF10 technology) were used to test the cervical and biopsy samples for the presence of DNA from 14 oncogenic HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) and 11 non-oncogenic HPV types (6, 11, 34, 40, 42, 43, 44, 53, 54, 70, and 74) [16]. Because the PCR assay used in this study generated data for 11 low-risk types in addition to 14 high-risk types, we were able to perform these post hoc analyses.

Gynecological and cytological examinations were carried out every 12 months, and women were referred for colposcopy and appropriate treatment, as per the protocol-specified clinical management algorithm. Clinical data on the presence of GWs/condylomata acuminata were not systematically collected.

The TVC included all women (n = 18 644) who received at least 1 dose and included women regardless of their baseline cytological, serological, or HPV DNA status. Case counting began the day after the first dose.

The TVC naive (for all 25 HPV types tested) is a subset of this group (n = 11 286), comprising women who had received at least 1 dose and at baseline had normal cytology and were DNA negative for 14 oncogenic and 11 low-risk HPV types. In addition, they were seronegative at baseline for HPV types 16 and 18. However, their serological status for low-risk HPV types was not ascertained.

Persistent cervical HPV infection (6-month definition) was defined as the detection of the same HPV type (by PCR) in cervical samples at 2 consecutive evaluations over approximately a 6-month interval.

Vaccine efficacy and 95% confidence intervals (CIs) were calculated using a conditional exact method. Event rates were calculated as the number of cases divided by the total follow-up in years and were expressed per 100 woman-years.

The analyses presented here are all post hoc exploratory analyses and should be interpreted with this limitation.

Table 1. Incidence Rates and Vaccine Efficacy Against 6-Month Persistent Infections With All Low-Risk Human Papillomavirus Types (Total Vaccinated Cohort [TVC] and TVC Naive for All Types)

	6-Month Persistent Infection				
	Vaccine		Control		
Efficacy (95% CI)	Cases	Rate	Cases	Rate	Efficacy (95% confidence interval)
TVC	N = 8863		N = 8870		
HPV-6/11	232	0.72	260	0.81	10.9% (–6.8 to 25.6)
HPV-6	182	0.56	208	0.65	12.6% (–7.2 to 28.8)
HPV-11	53	0.16	56	0.17	5.3% (–40.4 to 36.2)
HPV-34	24	0.07	27	0.08	11.1 (–60.1 to 50.9)
HPV-40	35	0.11	34	0.10	–2.9 (–70.1 to 37.7)
HPV-42	48	0.15	39	0.12	–23.2 (–93.1 to 20.9)
HPV-43	65	0.20	54	0.17	–20.6 (–76.3 to 17.3)
HPV-44	102	0.31	104	0.32	1.9 (–30.2 to 26.1)
HPV-53	439	1.39	450	1.42	2.5 (–11.5 to 14.7)
HPV-54	194	0.60	172	0.53	–13.0 (–39.5 to 8.5)
HPV-70	107	0.33	139	0.43	**23.2 (0.5 to 40.9)**
HPV-74	116	0.36	148	0.46	21.7 (–0.5 to 39.2)
TVC naive	N = 5259		N = 5249		
HPV-6/11	74	0.37	112	0.57	**34.5% (11.3 to 51.8)**
HPV-6	61	0.31	93	0.47	**34.9% (9.1 to 53.7)**
HPV-11	14	0.07	20	0.10	30.3% (–45.0 to 67.5)
HPV-34	9	0.04	13	0.07	31.1% (–74.2 to 74.0)
HPV-40	14	0.07	12	0.06	–16.1% (–174.9 to 50.2)
HPV-42	20	0.10	12	0.06	–66.1% (–272.6 to 22.7)
HPV-43	22	0.11	22	0.11	0.4% (–88.5 to 47.4)
HPV-44	30	0.15	31	0.81	3.7% (–64.5 to 43.7)
HPV-53	137	0.69	185	0.25	**26.7% (8.1 to 41.7)**
HPV-54	76	0.38	65	0.33	–16.5% (–64.8 to 17.5)
HPV-70	34	0.17	46	0.23	26.5% (–17.0 to 54.3)
HPV-74	31	0.16	61	0.31	**49.5% (21.0 to 68.3)**

N is the number of evaluable women in each group. Cases is the number of evaluable women reporting at least 1 event. Rate is the number of cases divided by sum of the follow-up period (per 100 woman-years); follow-up period started on the day after the first vaccine dose. Women were included in the analysis of the TVC regardless of their HPV DNA or serostatus at month 0. Women included in the analysis of the TVC naïve for all types cohort were HPV DNA negative for all 14 oncogenic and 11 non-oncogenic HPV types tested for, were seronegative for HPV-16 and HPV-18, and had negative cytology at month 0. Types tested for HPV DNA were HPV-6, HPV-11, HPV-16, HPV-18, HPV-31, HPV-33, HPV-34, HPV-35, HPV-39, HPV-40, HPV-42, HPV-43, HPV-44, HPV-45, HPV-51, HPV-52, HPV-53, HPV-54, HPV-56, HPV-58, HPV-59, HPV-66, HPV-68, HPV-70, and HPV-74.

Abbreviations: HPV, human papillomavirus; TVC, total vaccinated cohort.

Statistical analyses were performed using Statistical Analysis System (SAS) 9.1 and Proc StatXact-7 on Windows XP.

RESULTS

The trial was carried out between May 2004 and November 2009. In the TVC, mean and median follow-up times were 43.7 months (standard deviation, 11.7) and 47.4 months (range, 0–62; 3.6 and 4.0 years), respectively. There were no significant demographic differences between the HPV vaccine group and the controls; in particular, there was no difference in the reported number of sexual partners in the last year or reported sexually transmitted infections (data not shown).

Since women were not specifically screened, diagnosed, or treated for the presence of GWs, efficacy against clinical disease cannot be evaluated; however, results of vaccine efficacy against 6MPI infection with low-risk HPV types may be presented. In the TVC, no efficacy was seen for 6MPI with either HPV-6 or HPV-11 (Table 1). However, VE of 23.2% (95% CI, 0.5 to 40.9) was seen for HPV-70. In the TVC naïve (for all 25 HPV types tested) cohort, VE against 6MPI was 34.5% (95% CI, 11.3 to 51.8) for HPV-6/11 combined, 34.9% (95% CI, 9.1 to 53.7) for HPV-6, 49.5% (95% CI, 21.0 to 68.3) for HPV-74, and 26.7% (95% CI, 8.1 to 41.7) for HPV-53. VE against 6MPI with HPV-11 was comparable at 30.3% (Table 1), but the 95% CIs included 0.

DISCUSSION

The finding that the HPV-16/18 AS04-adjuvanted vaccine demonstrates efficacy against 6-month persistent infection with low-risk HPV types is unexpected, as the low-risk types are phylogenetically not closely related to the oncogenic types [17]. However, in the last few years, cell-mediated immune responses to HPV-6 and HPV-11 in women vaccinated with the HPV-16/18 AS04-adjuvanted vaccine have been observed. A study comparing L1-specific T helper cell responses induced by the HPV-6/11/16/18 vaccine and the HPV-16/18 AS04-adjuvanted vaccine showed that the latter induced cross-reactive T-cell responses to HPV-31 and HPV-45, which was to be expected from the efficacy data. In addition, HPV-6 and HPV-11 L1-reactive T cells were induced after administration of the HPV-16/18 AS04-adjuvanted vaccine at frequencies comparable to those in HPV-6/11/16/18 vaccine recipients [18].

A comparative trial showed that both HPV vaccines induced circulating antigen-specific CD4+ T cells to HPV-31 and HPV-45 [19, 20]. At month 24, the proportion of T-cell responders was overall significantly higher in the HPV-16/18 AS04-adjuvanted vaccine group than in the HPV-6/11/16/18 vaccine group for HPV-31 (86.7% vs 43.3%; $P = .0009$) and for HPV-45 (62.5% vs 37.5%; $P = .0793$) [20]. A follow-up study 4 to 6 years post vaccination showed that frequencies of L1-specific CD4+/CD154+/interferon-gamma/interleukin-2+ T cells in women vaccinated with the HPV-6/11/16/18 vaccine and the HPV-16/18 AS04-adjuvanted vaccine were similar for HPV types 6 and 11 (HPV-6: 0.045% vs 0.045%; HPV-11: 0.051% vs 0.033%, respectively) [10, 21]. Cross-reactivity at the T helper cell (CD4 receptor) level is a plausible mechanism for the vaccine-induced cross protection observed. The cross-reactivity between vaccine and non-vaccine HPV types may be explained by homology and/or structural similarities, which are conserved due to a cross-linking function within the L1 virus-like particle (VLP) [10].

Antibodies to HPV-6 and HPV-11 can also be measured in women vaccinated with the HPV-16/18 AS04-adjuvanted vaccine [10]. To what extent these antibodies are directed against the monoclonal antibody identified epitope(s) in the conformationally identical FG loop of the HPV-6/11, HPV-16, and HPV-18 L1 protein remains to be defined [22]. Using VLP–enzyme-linked immunosorbent assay, the HPV-6/11 titers induced by the HPV-16/18 AS04-adjuvanted vaccine were significantly lower compared with those induced by the HPV-6/11/16/18 vaccine [10]. To date there is no known immune correlate of protection, and the finding that only minimal concentrations of neutralizing antibodies are sufficient to prevent HPV infection could help to explain the observed vaccine efficacy against non-vaccine low-risk types [23].

In this study, efficacy against 6MPI rather than GWs was assessed; ideally, a clinical trial should be conducted to determine the VE of the HPV-16/18 AS04-adjuvanted vaccine against GWs before definitive conclusions can be drawn. However, if the findings of Howell–Jones et al [14] are borne out in further ecological or clinical studies, the additional protection afforded against GWs could be included in cost–benefit analyses, and may assist governments in deciding which vaccine should receive public funding.

In conclusion, results from this post hoc analysis suggest that in the TVC naive (negative for all 25 HPV types tested) cohort, a population that approximates young women before sexual debut (the target population for public health vaccination programs), the HPV-16/18 AS04-adjuvanted vaccine appears to have moderate efficacy against persistent infections with a number of low-risk HPV types (including HPV-6/11, HPV-74), which together are responsible for the majority of external GWs. However, the clinical significance of these observations remains unclear. Some protection against low-risk HPV types afforded by the HPV-16/18 AS04-adjuvanted vaccine may help to explain the decrease in GWs diagnoses seen in the cohort of adolescent females who were offered the HPV-16/18 AS04-adjuvanted vaccine in England in recent years, contrary to expectation [24].

Notes

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