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ORIGINAL REPORT

Pooled analysis of large and long-term safety data from the human papillomavirus-16/18-AS04-adjuvanted vaccine clinical trial programme

Maria-Genalin Angelo[1]*, Marie-Pierre David[1], Julia Zima[1], Laurence Baril[1], Gary Dubin[2], Felix Arellano[1] and Frank Struyf[1]

[1] *GlaxoSmithKline Vaccines, Wavre, Belgium*
[2] *GlaxoSmithKline Vaccines, King of Prussia, PA, USA*

ABSTRACT

Purpose The purpose of this study is to further evaluate the safety of the human papillomavirus (HPV)-16/18-AS04-adjuvanted vaccine (HPV-16/18-vaccine *Cervarix*®, GlaxoSmithKline, Belgium) through a pooled analysis of data from 42 completed/ongoing clinical studies.
Methods Unsolicited adverse events (AEs) were reported for 30 days after each dose. Medically significant conditions, serious AEs (SAEs), potential immune-mediated diseases (pIMDs) and pregnancy outcomes were captured until study completion. Events leading to subject withdrawal were reviewed. Relative risks compared incidences of spontaneous abortion and pIMDs in controlled studies.
Results Thirty one thousand one hundred seventy-three adolescent girls/women received HPV-16/18-vaccine alone (HPV group), 2166 received HPV-16/18-vaccine coadministered with another vaccine and 24 241 were controls. Mean follow-up was 39 months (range 0–113.3). Incidences of unsolicited AEs reported within 30 days after any dose were similar between HPV and Control groups (30.8%/29.7%). During the entire study period, reports of medically significant conditions (25.0%/28.3%) and SAEs (7.9%/9.3%) were also similarly distributed between groups. Deaths were rare: HPV (alone/coadministered) $n = 25$, controls $n = 20$ ($n = 18$ in blinded groups). pIMDs within 1 year were reported by 0.2% of HPV-16/18 vaccinees and controls. For each pIMD event category, no increased relative risks were reported for HPV-16/18 vaccinees versus controls. Coadministration did not change the overall safety profile. Pregnancy outcomes and withdrawal rates were similar between groups.
Conclusions Analysis of safety data arising from 57 580 subjects and 96 704 HPV-16/18-vaccine doses shows that the incidences and distribution of AEs were similar among HPV-16/18-vaccine recipients and controls. No new safety signals were identified. The data confirm previous findings that HPV-16/18-vaccine has an acceptable benefit-risk profile in adolescent girls and adult women. © 2014 GlaxoSmithKline. *Pharmacoepidemiology and Drug Safety* published by John Wiley & Sons, Ltd.

KEY WORDS—human papillomavirus vaccine; safety; adverse drug reactions; pregnancy; autoimmune disease; AS04; pharmacoepidemiology

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INTRODUCTION

Cervical infection with oncogenic human papillomavirus (HPV) strains is a necessary prerequisite for the development of cervical cancers.[1] Therefore, prevention of HPV infection by prophylactic vaccination has the potential to substantially reduce the disease burden. The HPV-16/18-AS04-adjuvanted cervical cancer vaccine, *Cervarix*® (HPV-16/18-vaccine, GlaxoSmithKline, Belgium) contains HPV-16 and 18 virus-like particles formulated with the AS04 immunostimulatory adjuvant. AS04 contains aluminium salt and monophosphoryl lipid A, a purified, detoxified derivative of the lipopolysaccharide molecule from the bacterial wall of *Salmonella minnesota*. AS04 induces direct but temporary immunostimulatory effects on the innate immune response at the injection site.[2] HPV-16/18-vaccine prevents incident and persistent HPV-16/18 infection and induces cross-protection against other important oncogenic types including HPV-31, HPV-33, HPV-45 and HPV-51.[3–6] Very high efficacy has been demonstrated in preventing the development of HPV-16/18-associated precancerous cervical lesions irrespective of HPV type, and efficacy has been

*Correspondence to: M.-G. Angelo, Safety Evaluation and Risk Management, Biologicals Clinical Safety & Pharmacovigilance, GlaxoSmithKline Vaccines, Wavre, Belgium. E-mail: gena.angelo@gsk.com

observed lasting up to 8.4 years after vaccination.[3–5,7–9] HPV-16/18-vaccine was first approved for use in 2007 and is licensed in at least 129 countries.

GlaxoSmithKline Vaccines has a systematic process for identification of potential safety signals that is applied to all marketed products. One aspect of this process is the review of spontaneous adverse events (AEs) in the post-marketing setting.[10] Another aspect is the ongoing review of clinical trial data. A first pooled analysis conducted with clinical trial safety data available (11 studies) until November 2006[11] showed no clinically relevant differences between groups of women vaccinated with HPV-16/18-vaccine or with control vaccines in terms of the rate of occurrence of serious AEs (SAEs, defined in Descamps *et al*[11]), medically significant conditions (MSCs, defined in Descamps *et al*[11]), new onset of chronic diseases, new onset of autoimmune diseases or pregnancy outcomes. Additional clinical trial data have since become available, and we present an updated pooled analysis of safety. This analysis includes 32 additional studies compared with the previous analysis, with follow-up data now available until approximately 8.4 years post-vaccination (previously 5.5 years), totalling 95 546.1 women-years of follow-up after vaccination with HPV-16/18-vaccine alone, and including safety data from 33 339 girls and women from 9 years of age who received the licensed formulation of HPV-16/18-vaccine (compared with 13 262 subjects in the previous analysis).

METHODS

Design of studies

Forty-two completed or ongoing controlled and uncontrolled studies conducted in 40 countries were included in this pooled analysis of safety (Table 1). The data lock point was 30 April 2011, and the number of subjects/doses in this analysis included the subjects enrolled/doses administered on or before this date. In contrast with the previous safety analysis, studies where HPV-16/18-vaccine was coadministered (for at least one dose) with another vaccine were included in the present analysis (Table 1). For ongoing blinded studies, all personnel involved in the conduct of the study as well as personnel directly involved in the current analyses remained blinded at the individual subject level in order to preserve study integrity as described in individual study protocols. In all studies, safety outcomes were actively followed up. Blinding was maintained for ongoing studies to avoid unintentional unblinding of individual cases.

Data collection

All studies evaluated the occurrence of AEs following vaccination. All 'unsolicited' symptoms reported within 30 days (day 0–29) after each dose were recorded. In most studies, MSCs, SAEs, potentially immune-mediated diseases (pIMDs) and deaths were captured until study completion. pIMDs were events either reported as such in some studies, or detected in the database by a search of Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms related to immune-mediated diseases. A predefined list of pIMDs[10] included autoimmune diseases and other inflammatory disorders of interest, which may or may not have an autoimmune aetiology, including new onset of pIMD or exacerbations of pre-existing pIMDs. The list of pIMDs is thus broad, potentially including events previously classified as 'new onset of autoimmune disease' in the HPV clinical development programme.

Adverse events leading to the withdrawal of a subject from a study were reviewed. All pregnancy outcomes were evaluated. Potential causal associations between vaccination and each AE were evaluated by the investigator by using standard guidelines provided in the study protocols.

Statistical analysis

Adverse events were classified according to MedDRA codes. Incidences of AEs in each category, and for age subcategories (9–14, 15–25 and >26 years), were calculated with exact 95% confidence intervals (95%CIs) for subjects who received HPV-16/18-vaccine alone (HPV group), HPV-16/18-vaccine coadministered with another vaccine (Coad group) and for subjects in Control groups. The reporting periods for MSCs, SAEs (including deaths) and pIMDs included events with onset within 30 days after any dose, and events with onset at any time throughout the entire study period. According to a recent proposal,[12] for pIMDs, we additionally considered events with onset within 12 months after any dose.

Information on pregnancy outcomes was calculated for two risk windows (Figure 1): (1) pregnancies with onset 'around vaccination' defined as occurring in women that reported the date of onset of their last menstrual period as during the risk period between 30 days before and 45 days after each vaccination; (2) pregnancies with exposure at any time defined as exposures occurring from 60 days before pregnancy

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Table 1. Summary of studies included in the pooled analysis of safety and contribution to safety endpoints

	Study	www.clinicaltrials.gov	Blinding	Status at data lock (30 April 2011)	Groups (Total vaccinated cohort)			Unsolicited	SAEs (including deaths)	pIMDs	MSC	Pregnancies	
					HPV	Coad**	Control‡	Day 0–29	Entire study period§			Subcategory	Overall
Studies included in previous pooling[11]	HPV-001*†[5]	NCT00689741/ NCT00518336/	DB	Completed	560	0	553	x	x	x		x	x
	HPV-003†	580299/003	DB	Completed	31	0	30		x	x		x	x
	HPV-004†	NCT00693615	DB	Completed	20	0	0		x	x		x	x
	HPV-005†	NCT00693966	DB	Completed	63	0	0		x	x		x	x
	HPV-008†[3,23]	NCT00122681	DB	Completed	9319	0	9325	x	x	x	x	x	x
	HPV-012*†[24,25]	NCT00169494/ NCT00337818/	DB	Completed	770	0	0	x	x	x	x	x	x
	HPV-013*†[26]	NCT00196924/ NCT00316706/ NCT00877877	DB	Completed	1035	0	1032	x	x	x	x	x	x
	HPV-014*†[27–29]	NCT00196937/ NCT00947115	O	Completed	666	0	0	x	x	x	x	x	x
	HPV-016*†	NCT00250276	DB	Completed	798	0	0	x	x	x	x	x	x
	HPV-015†φ	NCT00294047	DB	Ongoing	2881	0	2871	x	x	x	x	x	x
New studies added in the new pooling	HPV-NG-001	NCT00478621	SB	Completed	90	0	0	x	x	x	x	x	x
	HPV-009[30–32]κ	580299/009	DB	Completed	3728	0	3737		x			x	x
	HPV-021	NCT00481767	DB	Completed	450	0	226	x	x	x	x	x	x
	HPV-024	NCT00546078	O	Completed	115	0	0	x	x	x	x	x	x
	HPV-031[33]	NCT00344032	DB	Completed	176	0	178	x	x	x	x	x	x
	HPV-033[34]	NCT00290277	DB	Completed	160	0	161	x	x	x	x	x	x
	HPV-034	NCT00549900	O	Completed	30	0	0	x	x	x	x	x	x
	HPV-035[35]	NCT00306241	DB	Completed	150	0	150	x	x	x	x	x	x
	HPV-036	NCT00345878	DB	Completed	135	0	136	x	x	x	x	x	x
	HPV-038[34]	NCT00485732	DB	Completed	149	0	76	x	x	x	x	x	x
	HPV-044	NCT00552279	O	Completed	804	0	0	x	x	x	x	x	x
	HPV-046	NCT00492544	O	Completed	100	0	0	x	x	x	x	x	x
	HPV-TETRA-051*	NCT00231413	DB	Completed	88	0	0	x	x	x	x	x	x
	HPV-100	NCT00730847	O	Completed	457	0	0	x	x	x	x	x	x
	HPV-018*[36]	NCT00369824	O	Completed	215	1068	0	x	x	x	x	x	x
	HPV-026[37]	NCT00637195	O	Completed	0	76	76	x	x	x	x	x	x
	HPV-029[38]	NCT00578227	O	Completed	270	272	271	x	x	x	x	x	x
	HPV-030[39]	NCT00652938	O	Completed	247	247	247	x	x	x	x	x	x
	HPV-042[40]	NCT00426361	O	Completed	248	503	0	x	x	x	x	x	x
	HPV-010[41–43]	NCT00423046	DB	Ongoing	553	0	553	x	x	x	x	x	x
	HPV-019	NCT01031069	DB	Ongoing	30	0	31	x	x	x	x	x	x
	HPV-020	NCT00586339	DB	Ongoing	91	0	59	x	x	x	x	x	x
	HPV-032[8]	NCT00316693/ NCT00929526	DB	Ongoing	519	0	521	x	x	x	x	x	x
	HPV-039	NCT00779766	DB	Ongoing	3027	0	3026	x	x	x	x	x	x
	HPV-048[44]	NCT00541970	SB	Ongoing	479	0	0	x	x	x	x	x	x
	HPV-055	NCT00849381	O	Ongoing	1203	0	0		x	x	x	x	x
	HPV-056	NCT00811798	O	Ongoing	92	0	0		x			x	x
	HPV-057	NCT00799825	O	Ongoing	338	0	0		x	x	x	x	x

(*Continues*)

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Table 1. (Continued)

Study	www.clinicaltrials.gov	Blinding	Status at data lock (30 April 2011)	Groups (Total vaccinated cohort)			Unsolicited	SAEs (including deaths)	pIMDs	MSC	Pregnancies	
				HPV	Coad**	Control‡	Day 0–29	Entire study period§			Subcategory	Overall
HPV-058	NCT00996125	DB	Ongoing	374	0	376	x	x	x	x	x	x
HPV-059	NCT01101542	O	Ongoing	105	0	0	x	x	x	x	x	x
HPV-067	NCT01190189	O	Ongoing	1	0	0		x	x	x	x	x
HPV-069	NCT01277042	DB	Ongoing	606	0	606	x	x	x	x	x	x

O, Open label; DB, double blind, SB, single blind; pIMD, potential immune-mediated disease; MSC, medically significant conditions; SAE, serious adverse events; pIMD, potential immune-mediated diseases; HPV, human papillomavirus

*including follow-up, which for some studies went until year nine

[†]included in previous analysis[11]

[K], study HPV-009 was funded by the National Cancer institute, which was responsible for the design, implementation and analysis of the study

[φ]From Month 48 onwards safety follow-up was limited to SAEs related to vaccination, fatal SAEs and adverse events leading to study withdrawal

**HPV 16/18-AS04 was coadministered with *Menactra*® (Sanofi Pasteur)) or *Boostrix*™ (GSK Vaccines) in study HPV-018, *Twinrix*™ Paediatric (GSK Vaccines) in HPV-029, *Engerix* B™ (GSK Vaccines) in HPV-026 and HPV-030, and *Boostrix*™ Polio (GSK Vaccines) in HPV-042

[‡]Controls included placebo (Al(OH)3), *Havrix*™ (GSK Vaccines), *Aimmugen*™ (hepatitis A vaccine, Kaketsuken, Japan), Gardasil® (Merck & Co.), *Menactra*®, *Boostrix*,™ *Boostrix*™ Polio, *Engerix* B™ or *Twinrix*™ Paediatric

[§]Entire study period refers to the time from study start until study completion. For ongoing studies, the time from study start until the data lock point (30 April 2011)

MSC, any adverse event prompting emergency room or physician visits that was not related to common diseases or routine visits for physical examination or vaccination, or SAEs that were not related to common diseases

SAE, any untoward medical occurrence resulting in death that was life-threatening, resulted in persistent or significant disability/incapacity, required hospitalisation or prolongation of existing hospitalisation. Important medical events that may have jeopardised the subject or may have required intervention to prevent one of the other outcomes listed earlier were also considered serious

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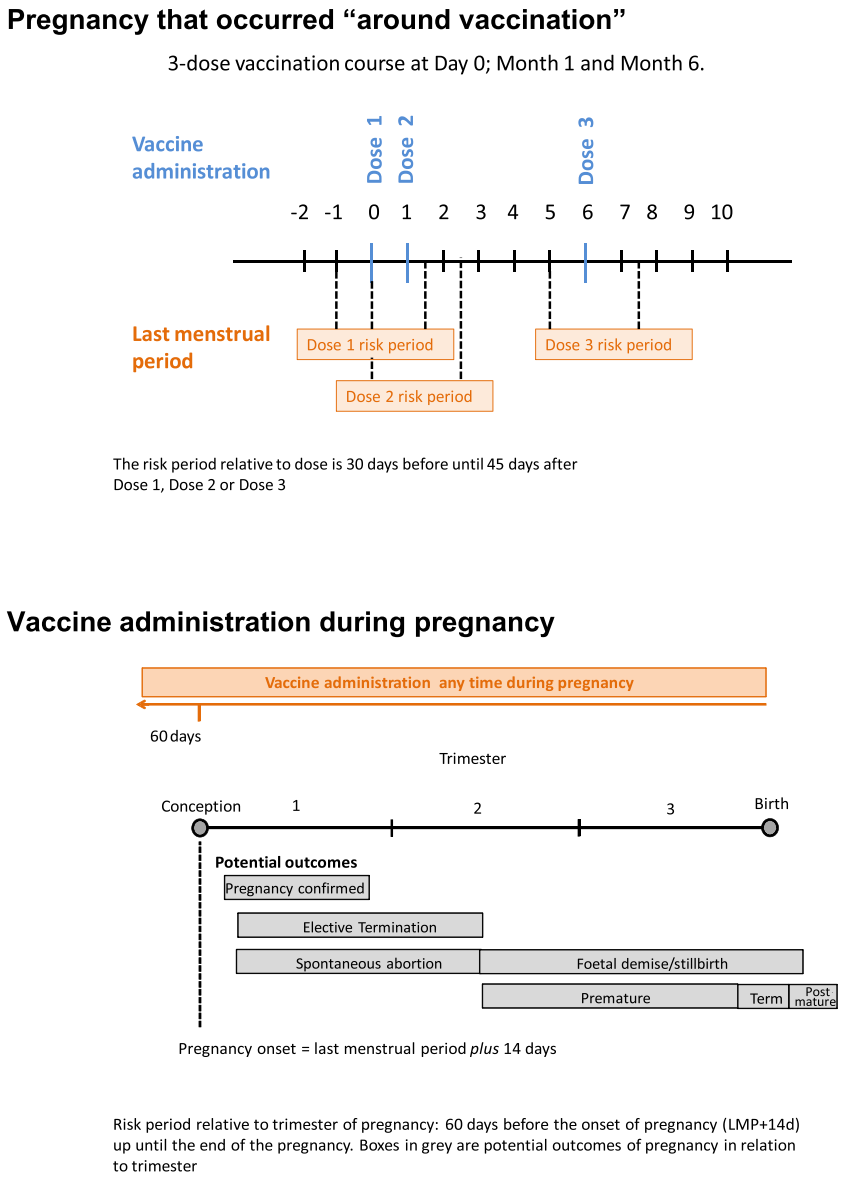

Figure 1. Risk windows defined for the analysis of pregnancy outcomes around vaccination

onset (defined as the date of onset of the last menstrual period + 14 days) until the end of pregnancy.

Relative risks (RR) with 95%CI were estimated for the incidence of spontaneous abortion and for the incidence of pIMDs between study groups for controlled studies. This exploratory analysis was not corrected for multiple comparisons and so should be interpreted with caution.

RESULTS

Study population

There were 31 173 adolescent girls and adult women in the HPV group, 2166 in the Coad group and 24 241 subjects in Control groups. Safety data represent a total of 96 704 HPV-16/18-vaccine doses. The median age of subjects was 22.0 years (range 9–72 years) in the HPV group, 13.0 years (9–25) in the Coad group and 22.0 years (8–68) in the pooled Control group. At the time of data base lock, the mean duration of individual follow-up after first vaccination was 39.0 months (range 0–113.3 months) in the HPV group, 11.8 months (0–17.6 months) in the Coad group, and 42.0 months (0–112.7 months) in the Control group. The total duration of the safety follow-up across all studies was 95 546.1 women-years in the HPV group, 2116.0 women-years in the Coad group and 84 696.6 women-years in the pooled Control group.

Unsolicited symptoms

Symptoms were reported within 30 days after each dose by 30.8% (95%CI 30.2–31.3) of subjects in the HPV group, 29.7% (29.1–30.3) of controls and 48.1% (45.9–50.2) in the Coad group (Figure 2). The most frequently reported Preferred Terms in each group were upper respiratory tract infection, nasopharyngitis and headache.

Infections (gynaecological chlamydia infection in the HPV and Control groups and nasopharyngitis in the Coad group) were the most frequent unsolicited symptoms reported during the entire study period.

Medically significant conditions

The percentage of women reporting MSCs within 30 days after each dose was 9.6% (95%CI 9.3–10.0) in the HPV group, 10.4% (10.0–10.8) in controls and 15.8% (14.3–17.4) in the Coad group (Figure 2). The most frequently reported MSCs in the HPV and Control groups were gynaecological chlamydia infection and gonococcal infection, related to screening undertaken in study HPV-008, followed by bronchitis and headache in the HPV group and influenza and headache in the Control group. Bronchitis, followed by ear pain, was the most frequent MSC in the Coad group. During the entire study period, gynaecological Chlamydia infection and depression were the most frequently reported MSCs in the HPV and Control groups.

Serious adverse events

Serious adverse events within 30 days of each dose were reported by 167 women in the HPV group (0.5%), 135 controls (0.6%) and by 11 women (0.5%) in the Coad group. The most frequently reported SAE during the 30-day follow-up period was appendicitis with similar reporting rates in the HPV and Control groups (0.1% in both groups). SAEs within the 30-day follow-up period considered to be related to vaccination were reported by 12 subjects (<0.1%) in the HPV group, 14 controls (0.1%) and by 2 subjects in the Coad group (0.1%). Among causally related SAEs, only two Preferred Terms were reported more than once (anaphylactic reaction in three subjects whose group allocation remains blinded and spontaneous complete abortion [four subjects]).

Serious adverse events during the entire study period were reported by 2448 women (7.9%) in the HPV group, 2244 controls (9.3%) and by 29 in the Coad group (1.3%). The most frequently reported events in the HPV and Control groups were those that related to spontaneous abortion, followed by appendicitis (105 in the HPV group [0.3%]), 111 in controls (0.5%) and 5 in the Coad group (0.2%).

Potential immune-mediated disease

The percentage of subjects reporting pIMDs within 30 days of any vaccine dose, and within the entire study period, was similar in each group (Figure 2). Within 1 year of any dose, pIMDs were reported with equal frequencies in the three study groups (0.2%). Of five subjects who reported two pIMDs, three reported exacerbations of the disease (Crohn's disease, rheumatoid arthritis, ulcerative colitis). The most frequently reported events within 1 year of any dose were cranial nerve disorders (6/27 353 subjects in

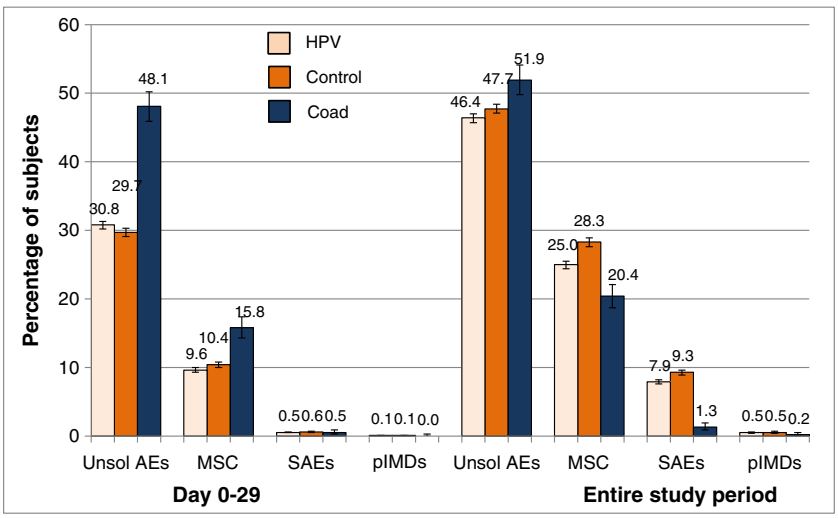

Figure 2. Percentage (95%CIs) of all women reporting all unsolicited adverse symptoms, medically significant conditions, potential immune-mediated diseases and serious adverse events after vaccination (Total vaccinated cohort): 30-day and entire study follow-up periods

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the HPV group and 6/20 504 controls), psoriasis (seven and five cases, respectively), Grave's disease (seven and three cases, respectively), autoimmune thyroiditis and vasculitis (four cases of each in the HPV group and controls), rheumatoid arthropathies (five and three cases, respectively) and neuritis (three and five cases, respectively). No clustering of events in terms of the time-to-onset was evident in the year following any dose (Figure 3).

The RR for each event category estimated from controlled studies showed no increased risk in women vaccinated with HPV alone compared with controls either for each individual pIMD Preferred Term ($p > 0.2$ for all comparisons, data not shown) or for each pIMD category, for either follow-up period (Table 2).

Deaths

There were 63 deaths: 25 in HPV recipients (alone or coadministered), 20 in controls and 18 in groups that remain blinded (none of the blinded cases was considered vaccine-related). The most common causes of death were suicide (13 cases), malignancy (12 cases) and infections and road traffic accidents (eight cases each). One death was considered by the investigator to be possibly vaccine-related: A 25-year-old woman died from Crohn's disease approximately 17 months after the second dose of HPV-16/18-vaccine. Autoimmune investigations carried out on pre-vaccination and post-vaccination blood samples were negative. The subject developed constipation 44 days post-dose 2, diarrhoea around 1 month later and was treated surgically for a giant ovarian teratoma around 14 months after vaccination. Crohn's disease was diagnosed after she developed anaemia and a rectovaginal fistula. Death was because of post-operative acute peritonitis and septic shock after total colectomy. No family history was available and it is not possible to exclude disease pre-dating vaccination.

Withdrawals

The proportion of women withdrawing from the study because of AEs or SAEs was low and did not differ between HPV and the Control groups.

Pregnancy outcomes

Study participants were required to have a negative pregnancy test prior to each vaccine dose and were to use contraception from 30 days before the first dose until two months after completion of the vaccination series.

A total of 10 476 pregnancies were reported during clinical trials (including long-term follow-up studies) of which 141 (1.35%) were ongoing and 98 (0.9%) were lost-to-follow-up at the time of analysis. The majority of pregnancies were reported in the 15–25 year age group ($n = 9521$). There were 875 pregnancies reported in the 26+ year age group and 79 in the 9–14 year age group. The most frequently reported pregnancy outcomes were delivery of live healthy infants (73.9%) followed by spontaneous abortion (11.2%) and elective termination (6.5%), all of which were classified with no congenital anomalies.

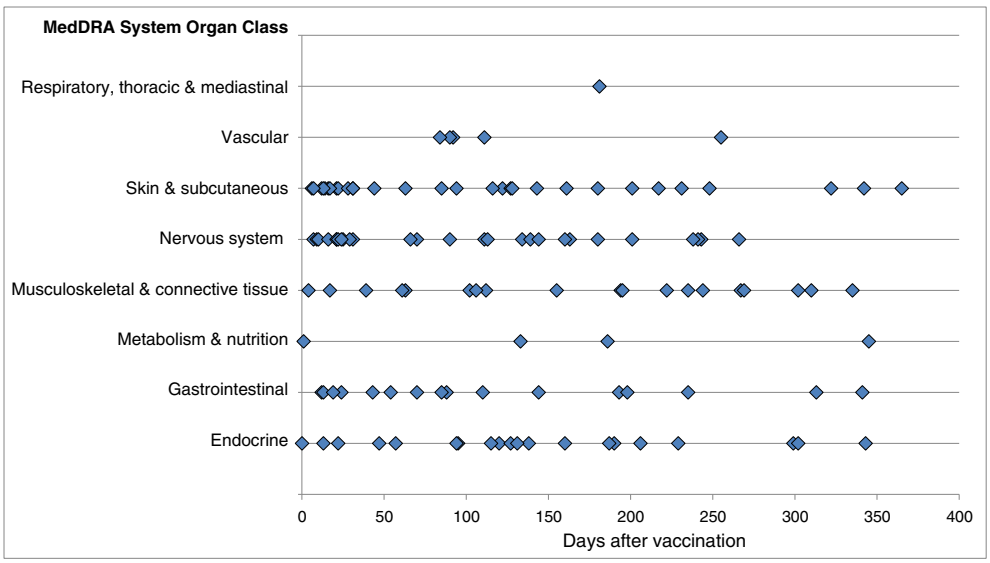

Figure 3. Day to onset of 122 potential immune-mediated diseases by MedDRA System Organ Class with onset within 1 year or after any dose of HPV-16/18 vaccine (all study groups (HPV group $N = 27\,353$, Coad group $N = 2166$, Controls $N = 20\,504$ doses)

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Table 2. Percentage of subjects reporting the occurrence of potential immune-mediated diseases symptoms within 1 year of any dose, classified by Immune-mediated disorder. Estimated Relative Risks for controlled studies (Total vaccinated cohort)

	Total	HPV $N = 21\,358$		Control $N = 20\,504$		
Immune-mediated disorder	*n*	*n*	%	*n*	%	RR (95% CI*)
At least one symptom	97	47	0.2	50	0.2	0.90 (0.59-1.37)
Gastrointestinal disorders	11	4	0.0	7	0.0	0.55 (0.12-2.16)
Celiac disease	4	—	—	—	—	0.96 (0.07-13.24)
Crohn's disease	3	—	—	—	—	—
Ulcerative colitis	3	—	—	—	—	0.48 (0.01-9.22)
Ulcerative proctitis	1	—	—	—	—	—
Metabolic disorders	19	9	0.0	10	0.0	0.86 (0.31-2.37)
Addison's disease	1	—	—	—	—	—
Autoimmune/ Hashimoto's thyroiditis	6	—	—	—	—	0.48 (0.04-3.35)
Diabetes mellitus type I	3	—	—	—	—	0.48 (0.01-9.22)
Grave's disease	9	—	—	—	—	1.92 (0.41-11.86)
Musculoskeletal disorders	16	10	0.0	6	0.0	1.60 (0.53-5.36)
Polymyalgia rheumatica	1	—	—	—	—	—
Psoriatic arthropathy	1	—	—	—	—	—
Reactive arthritis	3	—	—	—	—	—
Rheumatoid arthropathies	8	—	—	—	—	1.60 (0.31-10.30)
Systemic lupus erythematosus	3	—	—	—	—	1.92 (0.10-113.27)
Neuroinflammatory disorders	22	9	0.0	13	0.1	0.66 (0.25-1.68)
Cranial nerve disorders	11	—	—	—	—	0.80 (0.19-3.15)
Multiple sclerosis	1	—	—	—	—	—
Narcolepsy	2	—	—	—	—	0.96 (0.01-75.36)
Neuritis	8	—	—	—	—	0.58 (0.09-2.96)
Other	1	*1*	—	*1*	—	1.00
Stevens-Johnson syndrome	1	—	—	—	—	—
Skin disorders	21	11	0.1	10	0.0	1.06 (0.41-2.77)
Alopecia areata	2	—	—	—	—	0.96 (0.01-75.36)
Cutaneous lupus erythematosus	1	—	—	—	—	—
Erythema nodosum	1	—	—	—	—	—
Lichen planus	2	—	—	—	—	—
Psoriasis	11	—	—	—	—	1.15 (0.29-4.77)
Raynaud's phenomenon	2	—	—	—	—	—
Vitiligo	2	—	—	—	—	0.96 (0.01-75.36)
Vasculitides	8	4	0.0	4	0.0	0.96 (0.18-5.15)
Vasculitis & vasculitides	8	—	—	—	—	0.96 (0.18-5.15)

HPV, human papillomavirus
At least one symptom = at least one symptom experienced
N = number of subjects with at least one administered dose in controlled studies
n/% = number/percentage of subjects reporting the symptom at least once (not provided by group for subcategories of pIMDs to avoid unblinding)
RR, relative risk (group HPV over Control), not provided when all events are observed in one group to avoid unblinding
95% CI* = 95% confidence interval for relative risk (exact conditional to total number of cases)
1 refers to cases that appear in one of the groups with no cases in the other groups if studies are still blinded

Outcomes of a total of 871 completed pregnancies that occurred 'around vaccination' (defined in Figure 1) were distributed similarly between the HPV group and controls (Table 3).

Of 935 pregnancies that were exposed to vaccination within 60 days prior to pregnancy onset through the entire pregnancy duration (Figure 1), congenital abnormalities were reported in 12 cases (2.5%) in the HPV group and in 11 controls (2.5%). No particular pattern of anomalies suggestive of a teratogenic effect was observed, although data remain blinded (Table 4). Live infants from mothers in the HPV and Control groups were similar in terms of mean birth weight (3.16 kg versus 3.13 kg, respectively) and gestational age at delivery (93.8% ≥37 weeks versus 92.9%, respectively). In controlled studies, the percentage of spontaneous abortions following exposure to vaccination during pregnancy in the HPV group was 15.3% compared with 11.1% for controls (Table 5). The rates and RR for spontaneous abortion in women who were vaccinated within 60 days prior to pregnancy onset were 15.1% versus 9.5% for controls; RR 1.60 95% CI 0.99–2.61, and for those who had pregnancy onset around the second dose were 14.7% versus 8.0%; RR 1.85 95%CI 0.87–4.20.

Adverse events in age subgroups

The incidences of each AE category were similar across each age group (Table 6). Fewer SAEs over

Table 3. Pregnancy outcomes over the total number of pregnancies with date of onset of last menstrual period around vaccination (−30 to +45 days after vaccination) or after exposure at any time 60 days before to the end of the pregnancy

	Risk period −30 to +45 days post-vaccination						Exposure during −60 days to the end of the pregnancy *					
	HPV		Coad		Control		HPV		Coad		Control	
	N = 473		*N* = 6		*N* = 414		*N* = 509		*N* = 7		*N* = 449	
Outcome	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Live infant *no* apparent congenital anomaly	295	62.4	2	33.3	274	66.2	311	61.1	2	28.6	294	65.5
Live infant congenital anomaly	8	1.7	0	0.0	9	2.2	8	1.6	0	0.0	9	2.0
Premature live infant *no* apparent congenital anomaly	18	3.8	1	16.7	20	4.8	18	3.5	1	14.3	23	5.1
Premature live infant congenital anomaly	3	0.6	0	0.0	0	0.0	*3*	—	*3*	—	*3*	—
Elective termination *no* apparent congenital anomaly	68	14.4	1	16.7	55	13.3	74	14.5	2	28.6	60	13.4
Elective termination congenital anomaly	*1*	—	*1*	—	*1*	—	*1*	—	*1*	—	*1*	—
Therapeutic abortion	*1*	—	*1*	—	*1*	—	*1*	—	*1*	—	*1*	—
Ectopic pregnancy	3	0.7	0	0.0	2	0.5	3	0.6	0	0.0	2	0.5
Spontaneous abortion *no* apparent congenital anomaly	61	12.9	1	16.7	42	10.1	72	14.2	1	14.3	49	10.9
Spontaneous abortion congenital anomaly	*1*	—	*1*	—	*1*	—	*1*	—	*1*	—	*1*	—
Stillbirth *no* apparent congenital anomaly	1	0.2	0	0.0	3	0.7	2	0.4	0	0.0	3	0.7
Stillbirth congenital anomaly	*1*	—	*1*	—	*1*	—	*1*	—	*1*	—	*1*	—
Lost to follow-up	6	1.3	1	16.7	7	1.7	8	1.6	1	14.3	7	1.6
Molar pregnancy	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Ongoing pregnancies	*8*	—	*8*	—	*8*	—	*8*	—	*8*	—	*8*	—

*There were 669 pregnancies with exposure reported prior to pregnancy, 274 with exposure reported during the first trimester, 18 in the second and 4 exposure reported in the third trimester
1 refers to cases that appear in one of the groups with no cases in the other groups if studies are still blinded.
Congenital anomalies include congenital abnormalities, foetopathies, genetic diseases with early onset, developmental delay and others. See [10] for additional details on the classification of congenital abnormalities.

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Table 4. Pregnancy outcomes observed at birth that were classified with congenital anomalies

Description of anomaly	Classification of defect
Live infant	
Congenital deafness	Non-structural
Congenital talipes equinovarus	Non-structural
Gastroschisis	Structural
Cleft lip	Structural
Intrauterine growth retardation, congenital strabismus, club foot	Multiple non-structural
Congenital left kidney malformation and congenital malformations of female genitalia	Structural
Bilateral strabismus	Non-structural
Congenital hemangioma	Non-structural
Congenital deafness	Non-structural
Hypertrophy of the clitoris	Non-structural
Intraventricular septal defect, macrosomia, patent ductus arteriosus	Structural and non-structural
Apert syndrome	Non-structural
Anencephaly	Structural
Patent ductus arteriosus	Non-structural
Laryngothracheomalacia	Non-structural
Congenital myopia	Non-structural
Congenital hip dysplasia	Structural
Congenital deafness	Non-structural
Congenital talipes equinovarus	Non-structural
Gastroschisis	Structural
Premature live infant	
Congenital ocular toxoplasmosis, intrauterine growth retardation, right eye strabismus	Multiple non-structural
Right pre-auricular fistula	Structural
Multiple congenital anomalies, cleft lip, cleft palate, congenital diaphragmatic hernia, cryptorchidism, hypertelorism, preauricular appendices	Multiple structural
Elective termination	
Trisomia 21	Non-structural
Spontaneous abortion	
Trisomia 21 in first twin and anencephaly in the second twin	Non-structural in first twin and structural in second twin
Stillbirth	
Multiple congenital anomalies, hydrops fetalis	Multiple structural and non-structural

*pregnancy onset defined as the date of onset of the last menstrual period + 14 days
Cases remain blinded because some studies are ongoing.

the entire study period tended to be reported in 9–14 year olds, reflecting the lower number of pregnancy-related events in this age group.

DISCUSSION

This is the largest review of HPV-16/18-vaccine safety data yet reported, reinforcing the previous review published in 2009 with inclusion of over 20 000 additional subjects and strengthening the safety evaluation of the licensed formulation in the clinical trial setting. The incidence and distribution of AEs was similar to the previous pooled analysis,[11] which points to the validity of the previous and current analysis and supports the currently recognised safety profile of the HPV-16/18-vaccine.

We observed a difference in the distribution of unsolicited events in the HPV and Control groups compared with the Coad groups, which not only reflects the impact of a single large study (HPV-008, $N = 18\,000$) without a Coad group, in which regular screening for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* was undertaken, but also the different age distribution of the two groups. The percentage of subjects who experienced MSCs was similar between HPV and Control groups.

As to be expected in this healthy female patient population, there were few SAEs (including deaths) with similar frequencies of SAEs observed in all study groups. Furthermore, HPV-16/18-vaccine had an acceptable safety profile when coadministered with other vaccines, such as *Boostrix*™/*Boostrix*™ Polio (GlaxoSmithKline, Belgium) and *Twinrix*™ Paediatric/*Engerix* B™ (GlaxoSmithKline, Belgium), recommended for the same age groups.

Potentiation or activation of previously unrecognised autoimmune disease in susceptible individuals is a theoretical concern related to the immune-stimulatory effects of new adjuvants. Immune-mediated diseases encompass a diverse range of conditions with aetiologies that may have genetic or infective triggers.[13–15] In our analysis, pIMDs occurred in a similar percentage of HPV-16/18 vaccinees and controls, and there were no patterns in disease syndromes or time-to-onset. We observed no statistical evidence for an increased risk of any pIMD, or of any specific syndrome after HPV-16/18 vaccination compared with other vaccines used as controls. These results are consistent with a previous analysis of safety in that they showed no increased risk of pIMDs after vaccination with an AS04-containing vaccine,[16] and with reports of no increase in risk in presumed autoimmune disease among populations vaccinated with aluminium-adjuvanted HPV vaccine.[17] Thus, currently available evidence from a range of data sources continues to support the acceptable benefit-risk profile of AS04-adjuvanted vaccines, including HPV-16/18-vaccine, with respect to the onset of pIMDs after vaccination. GlaxoSmithKline Vaccines continues to monitor the occurrence of pIMDs in the post-marketing setting.[10]

The distribution of pregnancy outcomes was similar between HPV and controls for those exposures, which occurred during the risk period as defined for this analysis. The majority of pregnancies resulted in live births with no congenital anomalies. Stillbirth was infrequent in all groups and congenital anomalies were rarely reported, with no unexpected patterns. The overall incidence rates of spontaneous abortion

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Table 5. Percentage of spontaneous abortions with the estimated relative risks following exposure to vaccination during pregnancy for controlled studies—by dose, and following exposure before the onset of pregnancy and during the first trimester of pregnancy (Total vaccinated cohort)

Nearest dose to pregnancy onset	HPV			Control			Relative Risk (groups HPV over Control)
	N	*n*	% (95% CI)	*N*	*n*	% (95% CI)	RR (95% CI*)
Total*	465	71	15.3 (12.1–18.9)	449	50	11.1 (8.4–14.4)	1.37 (0.94–2.01)
Dose 1	122	18	14.8 (9.0–22.3)	130	20	15.4 (9.7–22.8)	0.96 (0.48–1.91)
Dose 2	156	23	14.7 (9.6–21.3)	138	11	8.0 (4.0–13.8)	1.85 (0.87–4.20)
Dose 3	184	30	16.3 (11.3–22.5)	178	18	10.1 (6.1–15.5)	1.61 (0.87–3.07)
Exposure*							
Vaccination before pregnancy	317	48	15.1 (11.4–19.6)	316	30	9.5 (6.5–13.3)	1.60 (0.99–2.61)
Vaccination during the first trimester	137	16	11.7 (6.8–18.3)	124	17	13.7 (8.2–21.0)	0.85 (0.40–1.79)
Vaccination during the third trimester	9	5	55.6 (21.2–86.3)	7	1	14.3 (0.4–57.9)	3.89 (0.44–183.93)

HPV, human papillomavirus
N = number of exposed pregnancies in controlled studies
n/% = number/percentage of spontaneous abortions
95% CI = exact 95% confidence interval
95% CI* = 95% confidence interval for relative risk (exact conditional to total number of cases)
1 refers to cases that appear in one of the groups with no cases in the other groups if studies are still blinded
*There were too few women (2) in each group with exposure during the third trimester, and too few who received a fourth vaccine dose (3 across groups), to allow meaningful comparisons for these exposures

(15.1% in HPV recipients and 11.1% in control recipients in controlled studies), although showing a tendency to occur more frequently versus control vaccine around the administration of the first and second doses, are within the published range in the general population in the UK and the US (up to 15% across all ages).[18–21] The results are also in line with the previous pooled analysis,[11] and with an analysis conducted by the National Cancer Institute comparing miscarriage rates after HPV-16/18-vaccine and controls, that concluded there was no overall effect of HPV-16/18 vaccination on the risk of miscarriage,[22] although the authors stated that they 'could not completely rule out the possibility of an increased risk among pregnancies conceived within 3 months of vaccination in the study'. Theoretically, the results are also compatible with a protective effect of the control vaccine (mostly hepatitis A vaccine) or could be because of chance. Pregnancy outcomes continue to be closely monitored in post-marketing settings.[10]

The strengths of this study include the large size of the safety database in terms of the number of vaccinated subjects in clinical trials; the duration of follow-up (up to 8.4 years compared with 5.5 years in the previous analysis);[11] the availability of Control groups; the prospective nature of the data collection in clinical trial settings; and the generally consistent methodology of safety assessment employed in all studies. Potential limitations include different study designs, different vaccines administered in the Control and Coad groups, differing inclusion criteria between individual studies, and that a limited proportion of the data remain blinded. Furthermore, clinical trial populations that may be defined by strict inclusion and exclusion criteria might not reflect the characteristics of the general vaccinated population when the vaccine is in routine use. Unlike the other safety outcomes, the analysis of pregnancy outcomes was also potentially limited by the non-randomised nature of the events. Our analysis did not attempt to examine heterogeneity between studies or assess outlier studies. Finally, this analysis included subjects already part of a previous pooled analysis.

Although safety outcomes are rigorously explored in clinical trials, such studies are usually too small to detect potentially rare AEs that may occur after vaccination. Because of their much larger sample size, pooled analyses have an increased ability to detect rare events post-vaccination. Analysis of safety data arising from 57 580 subjects and 96 704 HPV-16/18-vaccine doses show that the incidences and distribution of AEs were similar among HPV-16/18-vaccine recipients and controls. No new safety signals were identified and no changes to the product label have been made on the basis of this analysis. The data confirm previous findings that the HPV-16/18-vaccine has an acceptable benefit-risk profile in adolescent girls and adult women.

TRADEMARKS

Cervarix is a registered trademark of the GlaxoSmithKline group of companies. Boostrix, Twinrix, Engerix and Havrix are trademarks of the GlaxoSmithKline group of companies. Menactra is a trademark of Sanofi Pasteur. Aimmugen is a trademark of Kaketsuken, Japan. Gardasil is a trademark of Merck & Co.

Table 6. Percentage of women reporting unsolicited symptoms, medically significant conditions, potential immune-mediated diseases and serious adverse events in each age subgroup (Total vaccinated cohort)

Outcome	9–14 years						15–25 years						26+ years			
	HPV		Coad		Control		HPV		Coad		Control		HPV		Control	
	n	% (95% CI)	*N*	% (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)
Unsolicited symptoms																
N	*2793*		*1501*		*1990*		*17836*		*654*		*14353*		*5017*		*4131*	
Day 0–29	1104	39.5 (37.7–41.4)	712	47.4 (44.9–50.0)	759	38.1 (36.0–40.3)	5252	29.4 (28.8–30.1)	326	49.8 (45.9–53.7)	3887	27.1 (26.4–27.8)	1543	30.8 (29.5–32.1)	1436	34.8 (33.3–36.2)
Overall	1411	50.5 (48.6–52.4)	764	50.9 (48.3–53.5)	917	46.1 (43.9–48.3)	8210	46.0 (45.3–46.8)	358	54.7 (50.8–58.6)	6756	47.1 (46.3–47.9)	2288	45.6 (44.2–47.0)	2103	50.9 (49.4–52.4)
MSCs																
N	*2793*		*1501*		*1990*		*17471*		*654*		*13803*		*6364*		*4128*	
Day 0–29	354	12.7 (11.5–14.0)	213	14.2 (12.5–16.1)	250	12.6 (11.1–14.1)	1674	9.6 (9.1–10.0)	129	19.7 (16.7–23.0)	1351	9.8 (9.3–10.3)	537	8.4 (7.8–9.1)	472	11.4 (10.5–12.4)
Overall	660	23.6 (22.1–25.3)	274	18.3 (16.3–20.3)	388	19.5 (17.8–21.3)	4486	25.7 (25.0–26.3)	165	25.2 (21.9–28.7)	3914	28.4 (27.6–29.1)	1512	23.8 (22.7–24.8)	1328	32.2 (30.7–33.6)
SAEs																
N	*2793*		*1501*		*1990*		*21837*		*654*		*18118*		*6492*		*4133*	
Day 0–29	13	0.5 (0.2–0.8)	5	0.3 (0.1–0.8)	10	0.5 (0.2–0.9)	125	0.6 (0.5–0.7)	5	0.8 (0.2–1.8)	95	0.5 (0.4–0.6)	29	0.4 (0.3–0.6)	30	0.7 (0.5–1.0)
Overall	105	3.8 (3.1–4.5)	15	1.0 (0.6–1.6)	41	2.1 (1.5–2.8)	2000	9.2 (8.8–9.5)	12	1.8 (1.0–3.2)	1906	10.5 (10.1-11.0)	343	5.3 (4.8–5.9)	297	7.2 (6.4–8.0)
pIMDs																
N	*2793*		*1501*		*1990*		*18105*		*654*		*14381*		*6404*		*4133*	
Day 0–29	1	0.0 (0.0–0.2)	1	0.1 (0.0–0.4)	1	0.1 (0.0–0.3)	10	0.1 (0.0–0.1)	0	0.0 (0.0–0.6)	6	0.0 (0.0–0.1)	5	0.1 (0.0–0.2)	6	0.1 (0.1–0.3)
Overall	17	0.6 (0.4–1.0)	2	0.1 (0.0–0.5)	7	0.4 (0.1–0.7)	96	0.5 (0.4–0.6)	2	0.3 (0.0–1.1)	64	0.4 (0.3–0.6)	30	0.5 (0.3–0.7)	41	1.0 (0.7–1.3)

MSC, medically significant conditions; SAE, serious adverse events; pIMD, potential immune-mediated disease

MSC, any adverse event prompting emergency room or physician visits that was not related to common diseases or routine visits for physical examination or vaccination, or SAEs that were not related to common diseases

SAE, any untoward medical occurrence resulting in death, that was life-threatening, resulted in persistent or significant disability/incapacity, required hospitalisation or prolongation of existing hospitalisation. Important medical events that may have jeopardised the subject or may have required intervention to prevent one of the other outcomes

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CONFLICT OF INTEREST

Maria-Genalin Angelo, Marie-Pierre David, Laurence Baril, Frank Struyf, Julia Zima, Felix Arellano and Gary Dubin are all employed by GlaxoSmithKline Vaccines. Maria-Genalin Angelo, Laurence Baril, Frank Struyf, Julia Zima, Felix Arellano and Gary Dubin all hold shares in the company as part of their employee remuneration. Gary Dubin holds several relevant patents and has previously received royalty payments from Wyeth Vaccines.

KEY POINTS

- Building on a previous report, a new analysis of clinical trial data evaluated an even larger sample size and longer safety follow-up; including 32 additional studies, 95 546.1 women-years of follow-up (mean 39 months, range 0-113.3 months), and safety data from 33 339 girls and women from 9 years of age who received the licensed formulation of HPV-16/18-vaccine.
- Ongoing systematic review of safety data from any source is undertaken by GlaxoSmithKline Vaccines to detect and investigate potential safety signals. For marketed products with ongoing clinical activities, clinical trial data serve as a reference to support evaluation of signals detected in the post-marketing setting.
- Incidences of unsolicited events, MSCs, SAEs and pIMDs as well as the distributions of MedDRA Preferred Terms across each of these categories of events were similar between HPV-16/18 vaccinees and controls. Rates of study withdrawal were similar between groups.
- Pregnancy outcomes were similar between HPV-16/18 vaccinees and controls, notably for those exposures that are believed to have occurred during a specified risk period.
- No new safety signals were identified and no further changes to the prescribing information were made based on the results of this analysis. The data confirm previous findings that HPV-16/18-vaccine has a positive benefit-risk profile in women of all ages.

ETHICS STATEMENT

For all clinical studies included in this pooled analysis, written informed consent or assent was obtained from all participants or their parents, or both. The protocol of each study and other materials were approved by independent ethics committees or institutional review boards.

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