Vaccine 26 (2008) 6630–6638

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Analysis of adverse events of potential autoimmune aetiology in a large integrated safety database of AS04 adjuvanted vaccines

Thomas Verstraeten[a,*], Dominique Descamps[a], Marie-Pierre David[a], Toufik Zahaf[a], Karin Hardt[a], Patricia Izurieta[a], Gary Dubin[b], Thomas Breuer[a]

[a] GlaxoSmithKline Biologicals, Rixensart, Belgium
[b] GlaxoSmithKline Biologicals, King of Prussia, Pennsylvania, USA

ARTICLE INFO

Article history:
Received 19 July 2008
Accepted 12 September 2008
Available online 7 October 2008

Keywords:
Adjuvant system
Autoimmune
Safety

ABSTRACT

Newly licensed vaccines against human papillomavirus (HPV) and hepatitis B (HBV), and several vaccines in development, including a vaccine against genital herpes simplex virus (HSV), contain a novel Adjuvant System, AS04, composed of 3-O-desacyl-4′ monophosphoryl lipid A and aluminium salts. Given the background incidence of autoimmune disorders in some of the groups targeted for immunisation with these vaccines, it is likely that autoimmune events will be reported in temporal association with vaccination, even in the absence of a causal relationship. The objective of this integrated analysis was to assess safety of AS04 adjuvanted vaccines with regard to adverse events (AEs) of potential autoimmune aetiology, particularly in adolescents and young adults. All randomised, controlled trials of HPV-16/18, HSV and HBV vaccines were analysed in an integrated analysis of individual data ($N = 68{,}512$). A separate analysis of the HPV-16/18 vaccine trials alone was also undertaken ($N = 39{,}160$). All data were collected prospectively during the vaccine development programmes (mean follow-up of 21.4 months), and included in the analysis up to a pre-defined data lock point. Reporting rates of overall autoimmune events were around 0.5% and did not differ between the AS04 and control groups. The relative risk (AS04/control) of experiencing any autoimmune event was 0.98 (95% confidence intervals 0.80, 1.21) in the integrated analysis and 0.92 (0.70, 1.22) in the HPV-16/18 vaccine analysis. Relative risks calculated overall, for disease category or for individual events were close to 1, and all confidence intervals around the relative risk included 1, indicating no statistically significant difference in event rates between the AS04 and control groups. This integrated analysis of over 68,000 participants who received AS04 adjuvanted vaccines or controls demonstrated a low rate of autoimmune disorders, without evidence of an increase in relative risk associated with AS04 adjuvanted vaccines.

1. Introduction

Vaccination is recognised as one of the most successful and cost-effective public health strategies, and has had a major impact worldwide on the burden of many infectious diseases [1]. As a consequence of this success and in the absence of visible burden of disease, attention has shifted over time to adverse events (AEs) temporally associated with vaccination rather than to the actual diseases prevented. The past few decades have seen considerable discussion in the medical literature and lay press as to whether vaccination may be a cause or trigger of autoimmune disorders. Probably the best known example is the intense debate on a possible link between hepatitis B (HBV) vaccination and multiple sclerosis, for which all epidemiological studies showed no association, except one [2–9]. Although there are numerous case reports of a temporal association between administration of various vaccines and development of other autoimmune disorders, these do not provide sufficient evidence for a causal link. In addition controlled studies have consistently failed to show such a link [10].

Despite this reassuring evidence, it is essential that public health bodies and vaccine manufacturers continue to monitor vaccine safety carefully, with particular attention to disorders with an unknown origin. A recent cohort study has shown that autoimmune disorders are not rare in adolescent and young adult female populations [11]. This study, which was performed in a large health management organisation in the United States, found that immune-mediated conditions were the third most frequent rea-

* Corresponding author at: GlaxoSmithKline Biologicals, Rue de l'Institut 89, B-1330 Rixensart, Belgium. Tel.: +32 2 6568828; fax: +32 2 6568009.
E-mail addresses: thomas.verstraeten@gskbio.com (T. Verstraeten), dominique.descamps@gskbio.com (D. Descamps), marie-pierre.david@gskbio.com (M.-P. David), zahaf.toufik@gskbio.com (T. Zahaf), karin.hardt@gskbio.com (K. Hardt), patricia.izurieta@gskbio.com (P. Izurieta), gary.o.dubin@gsk.com (G. Dubin), thomas.breuer@gskbio.com (T. Breuer).

0264-410X/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.vaccine.2008.09.049

son for emergency room visits (10.3% visits) by adolescent girls, and the annual hospitalisation rate for such conditions in the same population was 53 per 100,000. The hospitalisation rate for autoimmune conditions was even higher among young women (19–30 y), reaching 389 per 100,000.

The need to augment the immediate immune response to therapeutic and prophylactic vaccines as well as to improve their long-term protection has led to the development of Adjuvant Systems (AS) [12]. Adjuvant Systems are unique combinations of traditional adjuvants such as aluminium salts, oil/water emulsion and liposomes with immunomodulatory molecules such as QS21, a saponin fraction of a tree bark, and 3-O-desacyl-4′ monophosphoryl lipid A (MPL), which is derived from chemical modification of the potent immunomodulator lipopolysaccharide (LPS) [12,13]. Like QS21, LPS has its origin in nature since it is present in bacteria and thus ubiquitous in the environment [13]. Humans are regularly exposed to LPS by natural exposure to bacteria, many of which contain LPS as a major component of the bacterial cell wall [13]. The appropriate AS is selected based on the target disease/pathogen and population, the antigen, the route of administration and the desired immune response and duration of immunity, with the aim of achieving optimally modulated innate and adaptive immune responses [12]. The human papillomavirus-16/18 (HPV-16/18) vaccine from GlaxoSmithKline (GSK) Biologicals (*Cervarix*™) contains the Adjuvant System AS04, a combination of aluminium salt and MPL [12,13]. This AS is also used in GSK's licensed vaccine against HBV (*Fendrix*™) and in an investigational herpes simplex 2 virus (HSV) vaccine currently in phase III clinical development.

Although human exposure to different components of adjuvants by natural means is therefore common, the safety of AS has been evaluated carefully as is required for any new technology. The AS04 adjuvanted vaccines have shown excellent tolerability in numerous clinical trials [14–21]. However, individual clinical trials may not have the power to monitor and evaluate the occurrence and impact of vaccination on some rare AEs as this may require a very large sample size. The purpose of the present analysis was to evaluate the occurrence of disorders of potential autoimmune aetiology in a large safety database of AEs prospectively collected throughout the development programme of the HPV-16/18, HBV and HSV AS04 adjuvanted vaccines from studies with an overall mean follow-up period of 21.4 months.

Cervarix and *Fendrix* are trademarks of the GlaxoSmithKline group of companies.

2. Materials and methods

The primary objective of this integrated analysis was to evaluate the safety of AS04 adjuvanted vaccines with regard to rates of AEs of potential autoimmune aetiology.

2.1. Studies included in the analysis

All completed or ongoing controlled, randomised studies of AS04 adjuvanted HPV-16/18, HSV and HBV vaccines conducted by GSK Biologicals or collaborators were included in the analysis, with the exception of one small study of a new investigational HPV vaccine in an early development phase, for which only limited safety data were available (Table 1). Our search of the literature found no studies conducted by independent sources on this subject. For all ongoing studies, a data lock point of June 30, 2007 was used, with the exception of two HPV studies. For study HPV-009, conducted in collaboration with the US National Cancer Institute, safety data were only available up to 31 March 2007 at the time of this analysis. For study HPV-008, which is the largest phase III study in the analysis, the most recently available data (up to 31 July 2007) were used. Study participants were included in the analysis if they had received at least one dose of AS04 containing study vaccine or control. The mean follow-up period of the studies was 1.8 y (21.4 months). It is important to note that none of these studies were set up primarily to study autoimmune disorders.

All studies were conducted in accordance with the 1996 version of the Declaration of Helsinki and with International Conference on Harmonisation (ICH) Good Clinical Practice Guidelines. Study protocols were approved by the Institutional Review Board of the institutions taking part and/or local ethics committees, and all participants provided written, informed consent.

2.2. Collection and description of adverse event data

Adverse event data were collected prospectively. Besides a study-specific list of local or general events that were solicited during a brief period following vaccination, four categories of unsolicited AEs were distinguished: non-serious AEs, serious AEs (SAEs), medically significant events and new onset of chronic disease. The method of collection varied slightly depending upon the study, but, in general, unsolicited AEs were reported to investigators at a study visit. Non-serious AEs were collected for 30 days after each vaccine dose. Data on SAEs were collected throughout the studies; these events were defined according to ICH criteria as: resulted in death, life-threatening, required hospitalisation, a congenital abnormality or birth defect in the offspring of a study participant or considered as medically significant. In some studies, mainly phase III studies of the HPV-16/18 and HSV vaccines, data on medically significant events and new onset of chronic disease were also collected throughout the study. A medically significant event was generally defined as (1) a condition prompting an emergency room visit, (2) a physician visit that was not related to a common disease or was not a routine visit for physical examination or vaccination or (3) a SAE not related to a common disease. Finally, the classification of an AE as a new onset of chronic disease was determined by the investigator. Records of all AEs were maintained by GSK Biologicals, with separate databases for non-serious AEs and SAEs. The information collected for SAEs was comprehensive, while that for non-serious AEs was generally limited to a brief description, start and end date, severity, outcome and causality assessment.

Medical Dictionary for Regulatory Activities (MedDRA) preferred terms were used to search the non-serious AE and SAE databases, and events were categorised as follows: neuroinflammatory, gastrointestinal, musculoskeletal, skin disorders, thyroid disease and others (Table 2). Although an evaluation of the diagnostic validity of the events reported by the investigator was undertaken by GSK Biologicals or external experts for a number of events, this evaluation was not taken into account in the analysis presented here which included all reported events. Given the relatively limited information on the non-serious AEs, no distinction was made between new onset of disorders and pre-existing conditions.

2.3. Analysis

Participants who received AS04 adjuvanted vaccines (HPV-16/18, HSV or HBV) were included in the AS04 group; participants who received a non-adjuvanted control vaccine, aluminium-adjuvanted vaccines or aluminium hydroxide alone were included in the control group. Event rates were estimated by treatment group by dividing the number of participants reporting at least one event of potential autoimmune aetiology by the total number of participants receiving at least one dose of vaccine.

Common relative risks across studies and their 95% confidence intervals (CI) were estimated on the exact conditional likelihood approach adjusted for study effect (Proc StatXact 5.0 User Man-

Table 1
Overview of studies included in the analysis.

Vaccine and study	NCT/e-track number	Population included in studies	Mean follow-up period (months)	No. of participants (AS04 group)	No. of participants (control group)
HPV-003	NCT00263744, 580299_003	Females 18–30 y	10.7	31	30
HPV-004	NCT00693615, 580299_004	Females 18–30 y	11.2	20	40
HPV-005	NCT00693966, 580299_005	Females 18–30 y	10.9	182	27
HPV-001/007	NCT00689741, 580299_001 NCT00120848, 580299_007	Females 15–26 y	52.8	560	553
HPV-008	NCT00122681, 580299_008	Females 14–33 y	29.3	9319	9325
HPV-009	NCT00128661, 580299_009	Females 18–25 y	16.2	3750	3750
HPV-010	NCT00423046, 108933	Females 18–45 y	3.8	551	552
HPV-011	NCT00309166, 580299_011	Males 10–18 y	13.4	181	89
HPV-013	NCT00196924/NCT00316706, 580299_013	Females 10–15 y	32.3	1035	1032
HPV-015	NCT00294047, 104820	Females 25–72 y	13.7	2881	2871
HPV-031	NCT00344032, 104479	Females 18–35 y	6.9	149	148
HPV-032	NCT00316693, 104798	Females 20–25 y	9.6	519	521
HPV-033	NCT00290277, 104951	Females 10–14 y	7.5	160	161
HPV-035	NCT00306241, 106001	Females 18–35 y	11.6	150	150
HPV-036	NCT00345878, 105926	Females 18–35 y	6.0	135	136
HPV-038	NCT00485732, 107291	Females 15–25 y	0.3	100	52
HSV-001	NCT00698893, 208141_001	Males and females 21–41 y	1.5	8	8
HSV-002	NCT00697567, 208141_002	Males and females 19–40 y	45.6	40	40
HSV-015	NCT00698490, 208141_015	Males and females 18–44 y	11.7	100	30
HSV-016	NCT00698568, 208141_016	Males and females 18–87 y	15.2	4968	2492
HSV-017	NCT00699764, 208141_017	Males and females 18–59 y	16.7	1255	1236
HSV-039	NCT00057330, 208141_039	Females 18–30 y	22.2	4329	3481
HSV-040	NCT00224484, 208141_040	Females 10–17 y	29.8	2977	2978
HBV MPL 001	NCT00699231, 208129_002	Males and females 22–86 y	35.5	15	15
HBV MPL 003	NCT00697229, 208129_004	Males and females 18–40 y	33.3	24	25
HBV MPL 004	NCT00697125, 208129_005	Males and females 18–40 y	11.6	20	40
HBV MPL 005	NCT00697970, 208129_006	Males and females 18–40 y	12.0	216	105
HBV MPL 009	NCT00697242, 208129_009	Males and females 49–70 y	11.6	146	215
HBV MPL 016	NCT00698087, 208129_016	Males and females 18–40 y	11.0	36	19
HBV MPL 019	NCT00697840, 208129_019	Males and females 18–40 y	6.4	50	100
HBV MPL 021	NCT00697931, 208129_021	Males and females 18+ y	7.2	56	54
HBV MPL 022	NCT00696891, 208129_022	Males and females 49–70 y	11.7	190	190
HBV MPL 025-026	NCT00698555/NCT00698906, 208129_025-026	Males and females 18–39 y	9.4	270	54
HBV MPL 027	NCT00697216, 208129_027	Males and females 16–40 y	11.4	168	169
HBV MPL 028	NCT00697775, 208129_028	Males and females 11–15 y	7.0	100	50
HBV MPL 030	NCT00697853, 208129_030	Males and females 15–49 y	6.5	160	40
HBV MPL 031	NCT00696917, 208129_031	Males and females 15–76 y	6.8	870	433
HBV MPL 032/042	NCT00383227/NCT00383383, 208129_032-042	Males and females 15–86 y	29.3	82	83
HBV MPL 033/038	NCT00698061, 208129_033-038	Males and females 19–64 y	12.3	72	73
HBV MPL 034	NCT00697749, 208129_034	Males and females 15–50 y	6.7	109	121
HBV MPL 036	NCT00697554, 208129_036	Males and females 19–72 y	9.0	47	42
HBV MPL 037	NCT00697866, 208129_037	Males and females 13–60 y	3.0	713	238
Total				36,744	31,768

Participants were included in the analysis if they had received at least one dose of study vaccine. Study HPV-NG-001 (e-track 109836) was not included because at the time the analysis was performed, only a few participants had been enrolled, only 18 had received AS04 adjuvanted vaccine, and no autoimmune disorders had been reported.
HPV: human papillomavirus; HSV: herpes simplex 2 virus; HBV: hepatitis B.
For ongoing studies, data lock point was June 30, 2007; except for HPV-009 March 31, 2007 and for HPV-008 July 31, 2007.

ual). Homogeneity testing of the relative risk across studies was conducted using the Breslow–Day method (Proc StatXact 5.0 User Manual). In these analyses, a *p*-value of less than 5% may be indicative of heterogeneity.

Given the recent introduction of the HPV-16/18 vaccine and the fact that the bulk of the data came from the HPV-16/18 vaccine trials, a separate analysis of these trials was also undertaken. In total, 42 studies and 68,512 participants were included in the HPV-16/18, HSV and HBV vaccine analysis, and 16 studies and 39,160 participants were included in the separate HPV-16/18 vaccine analysis (Table 1).

3. Results

3.1. HPV-16/18, HSV and HBV vaccine analysis

A total of 362 participants reported at least one autoimmune event, with an event rate of 0.52% (95% CI: 0.45, 0.60) in the AS04 group and 0.54% (0.46, 0.63) in the control group (Table 3). The disease category with the most events was thyroid disease, with 81 (0.22%) and 78 (0.25%) participants in the AS04 and control groups reporting an event, respectively (Table 3). Hypothyroidism was the most common individual event, with a total of 38 participants reporting an event in the AS04 group (0.10%) and 40 in the control group (0.13%) (Table 3). The next most frequent category was musculoskeletal disorders, reported by 45 (0.12%) and 34 (0.11%) participants in the AS04 and control groups, respectively (Table 3). Five participants in the AS04 group and 4 participants in the control group reported 7 and 4 neuroinflammatory events, respectively. In the AS04 group, there was 1 case of Guillain-Barré syndrome, 2 cases of optic neuritis, 2 cases of multiple sclerosis, and 1 case each of encephalitis and myasthenia gravis in the same participant (in fact, these were alternate diagnoses as a specific diagnosis could not be made; however, they were included as separate events for the purpose of this analysis). One participant reported both multiple sclerosis and optic neuritis. In the control group, there was 1 case of Guillain-Barré syndrome, 2 cases of optic neuritis, and 1 case of multiple sclerosis.

Table 2
Adverse events of potential autoimmune aetiology used to search the safety databases (Medical Dictionary for Regulatory Activities preferred terms).

Disease category	MedDRA preferred term	
Neuroinflammatory	Optic neuritis	Myelitis
	Optic neuritis retrobulbar	Leukoencephalomyelitis
	Multiple sclerosis	Encephalitis
	Demyelination	Encephalitis post immunisation
	Myasthenia gravis	Guillain-Barré syndrome
	Myelitis transverse	
Gastrointestinal	Inflammatory bowel disease	Proctitis ulcerative
	Crohn's disease	Coeliac disease
	Ulcerative colitis	
Musculoskeletal	Systemic lupus erythematosus	Juvenile arthritis
	Systemic lupus erythematosus rash	Arthritis
	Sjogren's syndrome	Arthritis reactive
	Rheumatoid arthritis	Scleroderma
Skin disorders	Dermatomyositis	Psoriasis
	Vitiligo	Psoriatic arthropathy
	Erythema nodosum	Stevens-Johnson syndrome
	Cutaneous lupus erythematosus	Raynaud's phenomenon
Thyroid disease	Basedow's disease	Hyperthyroidism
	Autoimmune thyroiditis	Hypothyroidism
	Thyroiditis	Goiter
	Thyroiditis acute	Hypothyroidic goiter
	Thyroiditis subacute	
Other	Anaemia haemolytic autoimmune	Autoimmune hepatitis
	Cold type haemolytic anaemia	Nephritis
	Coombs positive haemolytic anaemia	Nephritis autoimmune
	Haemolytic anaemia	Lupus nephritis
	Warm type haemolytic anaemia	Glomerulonephritis
	Antiphospholipid syndrome	Uveitis
	Diabetes mellitus[a]	Sarcoidosis
	Diabetes mellitus insulin-dependent	Addison's disease
	Idiopathic thrombocytopenic purpura	Leukocytoclastic vasculitis
	Autoimmune thrombocytopenia	Vasculitis
	Thrombocytopenia[a]	Behcet's syndrome

[a] Additional terms used to search the serious adverse event database, but not used in the non-serious adverse event database search.

The overall relative risk for developing an autoimmune disease was 0.98 (95% CI: 0.80, 1.21) (Table 4 and Fig. 1). Relative risks calculated for each disease category or for any individual event were mostly close to 1 (Table 4) and all 95% CIs included 1, indicating that there was no evidence of a statistically significant difference in relative risk in the AS04 group compared with the control group. The highest relative risk for an individual event occurred for idiopathic thrombocytopenic purpura (3.74 [0.37, 184.54]), corresponding to 4 and 1 cases in the AS04 and control groups, respectively. The lowest relative risk occurred for Raynaud's phenomenon (0.39 [0.01, 7.81]), corresponding to 1 and 2 cases in the AS04 and control groups, respectively. Homogeneity testing did not reveal any heterogeneity of the relative risk across studies.

3.2. HPV-16/18 vaccine analysis

There were no apparent differences in the pattern of autoimmune events between the HPV-16/18 vaccine analysis and the HPV-16/18, HSV and HBV vaccine analysis (all events in the HPV-16/18 vaccine analysis were also included in the combined analysis of the three vaccines). Overall, 96 (0.49% [95% CI: 0.39, 0.59]) participants in the AS04 group and 104 (0.54% [0.44, 0.65]) participants in the control group reported an autoimmune event (Table 5). Again, thyroid disease was the most common disease category (0.24% and 0.29% of participants in the AS04 and control groups, respectively), with musculoskeletal being the second most common (0.10% and 0.08%); hypothyroidism was the most frequent individual event (0.10% and 0.14%) (Table 5). Six neuroinflammatory events were reported by 5 participants (2 participants in the AS04 group and 3 in the control group): 1 case of multiple sclerosis in each group and 2 cases of optic neuritis in each group.

For each disease category or for any individual event, most relative risks were close to 1 and all the 95% CIs included 1 (Table 4 and Fig. 1). The overall relative risk was 0.92 (95% CI: 0.70, 1.22). The highest relative risk for an individual event was 2.39 (0.25, 30.86) for systemic lupus erythematosus (corresponding to 3 cases in the AS04 group and 1 case in the control group) and the lowest were 0.53 (0.01, 7.32) for diabetes mellitus and 0.53 (0.01, 7.31) for nephritis (both corresponding to 1 case in the AS04 group and 2 in the control group). As seen in the combined analysis of the three vaccines, the 95%CIs of the relative risk for these events all included 1, suggesting no significantly increased or decreased risk following receipt of the AS04 adjuvant system in the HPV-16/18 vaccine. Again, homogeneity testing showed no heterogeneity of the relative risk across studies.

4. Discussion

Bearing in mind the background incidence of autoimmune disorders in the adolescent and young adult population, it seems likely that, with broader use of HPV vaccines or other vaccines targeting this age group, autoimmune disorders will be reported in temporal association with vaccine administration even in the absence of a causal relationship [11]. While controlled clinical trials provide key vaccine safety data, individual trials may be too small to allow a complete assessment of rare events. The integrated analysis described in this article uses methodology that allows safety data from many studies to be considered in aggregate. It provides data from more than 68,500 participants of controlled trials in which subjects received either AS04 adjuvanted vaccines or control vaccines. Among these, 19,723 subjects received GSK's HPV-16/18 vaccine and 17,021 subjects received another AS04 adjuvanted vaccine. Data on AEs from the trials included in the analysis reported here were prospectively captured for a mean follow-up period of 21.4 months. The size of this database potentially allows identification of even very rare events, and is a key strength of the present analysis.

Both the combined HPV-16/18, HSV and HBV vaccine analysis and the separate HPV-16/18 vaccine analysis did not show evidence of an overall increase in relative risks for autoimmune disorders in participants receiving vaccines containing AS04 compared with controls (relative risk of 0.98 for the HPV-16/18, HSV and HBV analysis and 0.92 for the HPV-16/18 analysis). There were also no significant imbalances between groups with respect to individual events or categories of autoimmune disorders, including neuroinflammatory disorders (relative risk of 1.00 for the HPV-16/18, HSV and HBV vaccine analysis, and 0.67 for the HPV-16/18 vaccine analysis). As can be expected in such an analysis, in which multiple comparisons ($n = 52$) were performed, a few numerical imbalances were observed. It is reassuring to note that all confidence intervals around the relative risk included 1, indicating no evidence of a statistically significant difference between groups, that imbalances

Table 3
Participants in controlled studies of HPV-16/18, HSV and HBV vaccines reporting an autoimmune event classified according to Medical Dictionary for Regulatory Activity preferred term.

MedDRA preferred term	AS04 (*N* = 36,744)				Control (*N* = 31,768)			
	n	%	95% CI		*n*	%	95% CI	
			LL	UL			LL	UL
At least one AE	191	0.52	0.45	0.60	171	0.54	0.46	0.63
Neuroinflammatory								
Overall	5	0.01	0.00	0.03	4	0.01	0.00	0.03
Encephalitis[a]	1	0.00	0.00	0.02	0	0.00	0.00	0.01
Guillain-Barré syndrome	1	0.00	0.00	0.02	1	0.00	0.00	0.02
Multiple sclerosis	2	0.01	0.00	0.02	1	0.00	0.00	0.02
Myasthenia gravis	1	0.00	0.00	0.02	0	0.00	0.00	0.01
Optic neuritis[b]	2	0.01	0.00	0.02	2	0.01	0.00	0.02
Gastrointestinal								
Overall	16	0.04	0.02	0.07	17	0.05	0.03	0.09
Coeliac disease	3	0.01	0.00	0.02	5	0.02	0.01	0.04
Crohn's disease	4	0.01	0.00	0.03	5	0.02	0.01	0.04
Inflammatory bowel disease	2	0.01	0.00	0.02	2	0.01	0.00	0.02
Proctitis ulcerative	1	0.00	0.00	0.02	0	0.00	0.00	0.01
Ulcerative colitis	6	0.02	0.01	0.04	5	0.02	0.01	0.04
Musculoskeletal								
Overall	45	0.12	0.09	0.16	34	0.11	0.07	0.15
Arthritis	25	0.07	0.04	0.10	24	0.08	0.05	0.11
Arthritis reactive	3	0.01	0.00	0.02	0	0.00	0.00	0.01
Rheumatoid arthritis	12	0.03	0.02	0.06	9	0.03	0.01	0.05
Scleroderma	1	0.00	0.00	0.02	0	0.00	0.00	0.01
Systemic lupus erythematosus[c]	4	0.01	0.00	0.03	1	0.00	0.00	0.02
Skin disorders								
Overall	27	0.07	0.05	0.11	22	0.07	0.04	0.10
Cutaneous lupus erythematosus	0	0.00	0.00	0.01	1	0.00	0.00	0.02
Dermatomyositis	0	0.00	0.00	0.01	1	0.00	0.00	0.02
Erythema nodosum	3	0.01	0.00	0.02	1	0.00	0.00	0.02
Psoriasis	21	0.06	0.04	0.09	15	0.05	0.03	0.08
Psoriatic arthropathy	0	0.00	0.00	0.01	1	0.00	0.00	0.02
Raynaud's phenomenon	1	0.00	0.00	0.02	2	0.01	0.00	0.02
Stevens-Johnson syndrome	1	0.00	0.00	0.02	0	0.00	0.00	0.01
Vitiligo	1	0.00	0.00	0.02	1	0.00	0.00	0.02
Thyroid disease								
Overall	81	0.22	0.18	0.27	78	0.25	0.19	0.31
Goiter[d]	24	0.07	0.04	0.10	18	0.06	0.03	0.09
Basedow's disease	6	0.02	0.01	0.04	4	0.01	0.00	0.03
Hyperthyroidism	8	0.02	0.01	0.04	10	0.03	0.02	0.06
Hypothyroidism	38	0.10	0.07	0.14	40	0.13	0.09	0.17
Thyroiditis[e]	12	0.03	0.02	0.06	6	0.02	0.01	0.04
Other								
Overall	19	0.05	0.03	0.08	17	0.05	0.03	0.09
Addison's disease	0	0.00	0.00	0.01	1	0.00	0.00	0.02
Anaemia haemolytic autoimmune	1	0.00	0.00	0.02	0	0.00	0.00	0.01
Diabetes mellitus[f]	3	0.01	0.00	0.02	4	0.01	0.00	0.03
Idiopathic thrombocytopenic purpura[g]	4	0.01	0.00	0.03	1	0.00	0.00	0.02
Nephritis[h]	4	0.01	0.00	0.03	8	0.03	0.01	0.05
Sarcoidosis	1	0.00	0.00	0.02	0	0.00	0.00	0.01
Uveitis	2	0.01	0.00	0.02	0	0.00	0.00	0.01
Vasculitis[i]	4	0.01	0.00	0.03	3	0.01	0.00	0.03

CI: confidence interval; LL: lower limit of 95% CI; UL: upper limit of 95% CI. Exact 95% CI is shown. MedDRA: Medical Dictionary for Regulatory Activity; HPV: human papillomavirus; HSV: herpes simplex 2 virus; HBV: hepatitis B.

[a] Includes encephalitis and encephalitis post immunisation.

[b] Includes optic neuritis and optic neuritis retrobulbar.

[c] Includes systemic lupus erythematosus (SLE) and SLE rash.

[d] Includes goiter and hypothyroidic goiter.

[e] Includes autoimmune thyroiditis, thyroiditis, thyroiditis acute, thyroiditis subacute.

[f] Includes diabetes mellitus and diabetes mellitus insulin-dependent (the term diabetes mellitus was used to search only the serious adverse event database, not the non-serious adverse event database).

[g] Includes idiopathic thrombocytopenic purpura, autoimmune thrombocytopenia and thrombocytopenia (the term thrombocytopenia was used to search only the serious adverse event database, not the non-serious adverse event database).

[h] Includes nephritis, nephritis autoimmune and lupus nephritis.

[i] Includes leukocytoclastic vasculitis, vasculitis and Behcet's syndrome.

Table 4
Relative risk (AS04/control) of autoimmune events in controlled studies of HPV-16/18, HSV and HBV vaccines (pooled analysis of HPV-16/18, HSV and HBV vaccines and separate analysis of HPV-16/18 vaccine).

MedDRA preferred term	Pooled HPV-16/18, HSV, HBV (*N* = 68,512)			HPV-16/18 (*N* = 39,160)		
	RR	95% CI LL	UL	RR	95% CI LL	UL
At least one AE	0.98	0.80	1.21	0.92	0.70	1.22
Neuroinflammatory						
Overall	1.00	0.21	5.13	0.67	0.06	5.82
Encephalitis[a]	INF	0.01	INF	ND	ND	ND
Guillain-Barré syndrome	0.50	0.01	39.38	ND	ND	ND
Multiple sclerosis	1.99	0.10	117.50	1.00	0.01	78.59
Myasthenia gravis	INF	0.01	INF	ND	ND	ND
Optic neuritis[b]	1.00	0.07	13.80	1.00	0.07	13.80
Gastrointestinal						
Overall	0.85	0.41	1.75	0.97	0.37	2.43
Coeliac disease	0.57	0.09	2.92	0.66	0.06	5.80
Crohn's disease	0.63	0.12	2.84	0.60	0.05	4.61
Inflammatory bowel disease	1.00	0.08	7.49	1.00	0.08	7.49
Proctitis ulcerative	INF	0.03	INF	INF	0.03	INF
Ulcerative colitis	1.10	0.28	4.28	1.43	0.18	11.41
Musculoskeletal						
Overall	1.16	0.73	1.85	1.24	0.62	2.47
Arthritis	0.88	0.48	1.64	0.87	0.27	2.76
Arthritis reactive	INF	0.41	INF	INF	0.41	INF
Rheumatoid arthritis	1.17	0.47	2.86	1.00	0.29	3.08
Scleroderma	INF	0.02	INF	ND	ND	ND
Systemic lupus erythematosus[c]	3.00	0.40	35.41	2.39	0.25	30.86
Skin disorders						
Overall	1.07	0.59	1.98	0.92	0.37	2.24
Cutaneous lupus erythematosus	0.00	0.00	39.03	0.00	0.00	39.03
Dermatomyositis	0.00	0.00	31.36	ND	ND	ND
Erythema nodosum	2.02	0.19	27.84	1.73	0.11	26.18
Psoriasis	1.23	0.60	2.58	1.17	0.34	4.20
Psoriatic arthropathy	0.00	0.00	39.03	0.00	0.00	39.03
Raynaud's phenomenon	0.39	0.01	7.81	0.00	0.00	5.32
Stevens-Johnson syndrome	INF	0.03	INF	INF	0.03	INF
Vitiligo	1.00	0.01	78.41	1.00	0.01	78.41
Thyroid disease						
Overall	0.92	0.67	1.26	0.85	0.57	1.25
Goiter[d]	1.15	0.62	2.10	0.85	0.40	1.70
Basedow's disease	1.27	0.31	5.56	2.24	0.41	15.15
Hyperthyroidism	0.78	0.27	2.10	0.74	0.19	2.46
Hypothyroidism	0.83	0.52	1.33	0.74	0.39	1.37
Thyroiditis[e]	1.64	0.56	5.36	1.75	0.44	8.14
Other						
Overall	0.98	0.48	2.00	0.88	0.28	2.64
Addison's disease	0.00	0.00	38.86	0.00	0.00	38.86
Anaemia haemolytic autoimmune	INF	0.03	INF	ND	ND	ND
Diabetes mellitus[f]	0.66	0.10	3.64	0.53	0.01	7.32
Idiopathic thrombocytopenic purpura[g]	3.74	0.37	184.54	INF	0.19	INF
Nephritis[h]	0.42	0.09	1.63	0.53	0.01	7.31
Sarcoidosis	INF	0.01	INF	ND	ND	ND
Uveitis	INF	0.12	INF	ND	ND	ND
Vasculitis[i]	1.29	0.22	8.84	1.00	0.13	7.47

RR: estimated relative risk as AS04/control adjusted by study effect. 95% CI: 95% confidence interval for relative risk (Exact Stratified Conditional to total number of cases); LL: lower limit of 95% CI; UL: upper limit of 95% CI. INF: infinity, no cases reported in control group. ND: not done (relative risk not calculated unless an event occurred in one group). MedDRA: Medical Dictionary for Regulatory Activity; HPV: human papillomavirus; HSV: herpes simplex 2 virus; HBV: hepatitis B.

[a] Includes encephalitis and encephalitis post immunisation.

[b] Includes optic neuritis and optic neuritis retrobulbar.

[c] Includes systemic lupus erythematosus (SLE) and SLE rash.

[d] Includes goiter and hypothyroidic goiter.

[e] Includes autoimmune thyroiditis, thyroiditis, thyroiditis acute, thyroiditis subacute.

[f] Includes diabetes mellitus and diabetes mellitus insulin-dependent (the term diabetes mellitus was used to search only the serious adverse event database, not the non-serious adverse event database).

[g] Includes idiopathic thrombocytopenic purpura, autoimmune thrombocytopenia and thrombocytopenia (the term thrombocytopenia was used to search only the serious adverse event database, not the non-serious adverse event database).

[h] Includes nephritis, nephritis autoimmune and lupus nephritis.

[i] Includes leukocytoclastic vasculitis, vasculitis and Behcet's syndrome.

Table 5
Participants in controlled studies of HPV-16/18 vaccine reporting an autoimmune event classified according to Medical Dictionary for Regulatory Activity preferred term.

MedDRA preferred term	AS04 (*N* = 19,723)				Control (*N* = 19,437)			
	n	%	95% CI		*n*	%	95% CI	
			LL	UL			LL	UL
At least one AE	96	0.49	0.39	0.59	104	0.54	0.44	0.65
Neuroinflammatory								
Overall	2	0.01	0.00	0.04	3	0.02	0.00	0.05
Multiple sclerosis	1	0.01	0.00	0.03	1	0.01	0.00	0.03
Optic neuritis[a]	2	0.01	0.00	0.04	2	0.01	0.00	0.04
Gastrointestinal								
Overall	10	0.05	0.02	0.09	10	0.05	0.02	0.09
Coeliac disease	2	0.01	0.00	0.04	3	0.02	0.00	0.05
Crohn's disease	2	0.01	0.00	0.04	3	0.02	0.00	0.05
Inflammatory bowel disease	2	0.01	0.00	0.04	2	0.01	0.00	0.04
Proctitis ulcerative	1	0.01	0.00	0.03	0	0.00	0.00	0.02
Ulcerative colitis	3	0.02	0.00	0.04	2	0.01	0.00	0.04
Musculoskeletal								
Overall	19	0.10	0.06	0.15	15	0.08	0.04	0.13
Arthritis	7	0.04	0.01	0.07	8	0.04	0.02	0.08
Arthritis reactive	3	0.02	0.00	0.04	0	0.00	0.00	0.02
Rheumatoid arthritis	6	0.03	0.01	0.07	6	0.03	0.01	0.07
Systemic lupus erythematosus[b]	3	0.02	0.00	0.04	1	0.01	0.00	0.03
Skin disorders								
Overall	11	0.06	0.03	0.10	12	0.06	0.03	0.11
Cutaneous lupus erythematosus	0	0.00	0.00	0.02	1	0.01	0.00	0.03
Erythema nodosum	2	0.01	0.00	0.04	1	0.01	0.00	0.03
Psoriasis	7	0.04	0.01	0.07	6	0.03	0.01	0.07
Psoriatic arthropathy	0	0.00	0.00	0.02	1	0.01	0.00	0.03
Raynaud's phenomenon	0	0.00	0.00	0.02	2	0.01	0.00	0.04
Stevens-Johnson syndrome	1	0.01	0.00	0.03	0	0.00	0.00	0.02
Vitiligo	1	0.01	0.00	0.03	1	0.01	0.00	0.03
Thyroid disease								
Overall	48	0.24	0.18	0.32	57	0.29	0.22	0.38
Goiter[c]	14	0.07	0.04	0.12	17	0.09	0.05	0.14
Basedow's disease	5	0.03	0.01	0.06	2	0.01	0.00	0.04
Hyperthyroidism	5	0.03	0.01	0.06	7	0.04	0.01	0.07
Hypothyroidism	20	0.10	0.06	0.16	27	0.14	0.09	0.20
Thyroiditis[d]	7	0.04	0.01	0.07	4	0.02	0.01	0.05
Other								
Overall	7	0.04	0.01	0.07	8	0.04	0.02	0.08
Addison's disease	0	0.00	0.00	0.02	1	0.01	0.00	0.03
Diabetes mellitus[e]	1	0.01	0.00	0.03	2	0.01	0.00	0.04
Idiopathic thrombocytopenic purpura[f]	2	0.01	0.00	0.04	0	0.00	0.00	0.02
Nephritis[g]	1	0.01	0.00	0.03	2	0.01	0.00	0.04
Vasculitis[h]	3	0.02	0.00	0.04	3	0.02	0.00	0.05

CI: confidence interval; LL: lower limit of 95% CI; UL: upper limit of 95% CI. Exact 95% CI is shown. MedDRA: Medical Dictionary for Regulatory Activity; HPV: human papillomavirus.

[a] Includes optic neuritis and optic neuritis retrobulbar.

[b] Includes systemic lupus erythematosus (SLE) and SLE rash.

[c] Includes goiter and hypothyroidic goiter.

[d] Includes autoimmune thyroiditis, thyroiditis, thyroiditis acute, thyroiditis subacute.

[e] Includes diabetes mellitus and diabetes mellitus insulin-dependent (the term diabetes mellitus was used to search only the serious adverse event database, not the non-serious adverse event database).

[f] Includes idiopathic thrombocytopenic purpura, autoimmune thrombocytopenia and thrombocytopenia (the term thrombocytopenia was used to search only the serious adverse event database, not the non-serious adverse event database).

[g] Includes nephritis, nephritis autoimmune and lupus nephritis.

[h] Includes leukocytoclastic vasculitis, vasculitis and Behcet's syndrome.

occurred both in favour of the vaccine and of the control, and that no such imbalances were seen among the events for which a more significant number of cases were reported.

Overall, the reporting rate of autoimmune disorders was low, with an event rate of approximately 0.5% in participants receiving AS04 containing vaccines. Although there were differences in the methods used to capture events, this rate is comparable to that found in the recent analysis by Siegrist et al. [11]. The distribution of the reports by category did not suggest unusual patterns of autoimmune disorder. As expected, the most frequently occurring autoimmune disorders were diseases of the thyroid, followed by musculoskeletal disorders. This is broadly in line with natural history studies of autoimmune disorders reported in the literature. In Siegrist et al. cohort study in adolescent and young adult women, thyroid disorders were the most common reason for emergency room visits and hospitalisation, followed by systemic lupus erythematosus [11]. These disorders were also among the most commonly identified in an analytical review of the epidemiology of selected autoimmune disorders in the United States, which reported highest prevalence rates for Graves'/hyperthyroidism, insulin-dependent

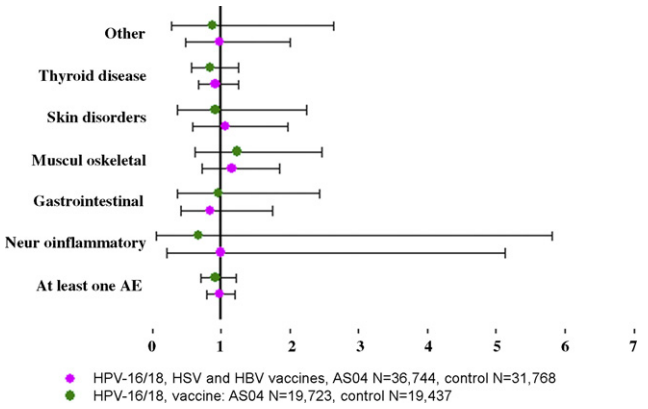

Fig. 1. Relative risk (AS04/control) of experiencing an autoimmune event according to event category (95% CI).
Relative risk = estimated relative risk as AS04/control adjusted by study effect 95% CI = 95% confidence interval for relative risk (Exact Stratified Conditional to total number of cases).

diabetes mellitus, pernicious anaemia, rheumatoid arthritis, thyroiditis/hypothyroidism and vitiligo [22].

The main strength of the integrated analysis reported in this article was the large sample size and the relatively long duration of follow-up which allowed analysis of AEs too rare to be studied in individual trials. In addition, individual studies were conducted according to a similar, robust methodology which allowed pooling of the data. With regard to the statistical methodology, we performed an integrated analysis adjusting for study effect, which is known to be one of the most efficient approaches to reliably summarise safety data from several clinical trials because it focuses on studies rather than treatment groups, and therefore maintains the validity of the comparisons.

The main limitations of the analysis include lack of validation of each diagnosis, which relied on investigator reports, and variability between studies in the collection of AE data. The first limitation is related to the fact that these studies were not set up primarily to study autoimmune disorders, but mainly to evaluate the general safety profile of the vaccines, as well as their immunogenicity and/or efficacy. However, given the randomised and controlled nature of all these studies, there is no reason to expect that the validity of the diagnoses would differ between the AS04 and control groups. The inclusion of some unvalidated diagnoses in the analysis is therefore unlikely to result in biased results. The variability of data collection across the different studies is mostly related to regulatory requirements that have changed during the period in which these studies were conducted. The main change is related to the collection of medically significant events and new onset of chronic disease. These changes were primarily introduced in the HPV trials. Since the analyses adjust for a potential study effect, however, it is not expected that this variability in AE collection would affect the overall results. The similarity in the results considering all three vaccines compared with the HPV-16/18 vaccine only supports this assessment. In the absence of more detailed knowledge of pre-existing conditions among the non-serious AEs, we may have included some events that existed before vaccination. However, since most autoimmune disorders would qualify as an exclusion criterion in the trials, we expect these to be few in number and to be balanced across groups as a result of randomisation.

In summary, the results of these analyses do not suggest any causal association between AS04 adjuvanted vaccines and development of autoimmune disorders. This supports other reports in the literature concluding that there is no evidence for a causal association between autoimmune disorders and most vaccines [8,10]. Billions of classically adjuvanted vaccine doses have been distributed worldwide over the past decades, with the body of evidence indicating no causal association between autoimmune disorders and vaccination. The present analysis suggests that this is also the case for vaccines using the new AS04 adjuvant system. As is appropriate with the introduction of any new vaccine, careful monitoring for autoimmune disease events will continue.

Acknowledgements

The authors would like to thank all investigators who contributed data to the studies included in the analysis and all members of independent safety monitoring committees for their invaluable contribution to overseeing safety in individual studies. We also acknowledge Katherine Ward (GSK Biologicals) for assistance in preparing the original report, Mary Greenacre Ph.D. for assistance in preparing the manuscript and Slavka Baronikova Ph.D. (GSK Biologicals) for editorial assistance and coordination of manuscript development.

Contributors: T Breuer, T Verstraeten, G Dubin, D Descamps, M P David and T Zahaf contributed to the design of the integrated safety analysis. Each author made a significant contribution to the interpretation of the data, development of this manuscript and approved the final submitted version. All authors had full access to safety data included in the integrated analysis.

Conflict of interest statement: All authors are employees of GSK Biologicals. They have no other conflict of interest to declare.

Funding statement: All studies included in this analysis were funded by GSK Biologicals, as was the analysis itself. GSK Biologicals was involved in the study design, data collection, interpretation and analysis, preparation of the manuscript and decision to publish.

References

[1] Chabot I, Goetghebeur MM, Grégoire JP. The societal value of universal childhood vaccination. Vaccine 2004;22(15–16):1992–2005.
[2] Ascherio A, Zhang SM, Hernán MA, Olek MJ, Coplan PM, Brodovicz K, et al. Hepatitis B vaccination and the risk of multiple sclerosis. N Engl J Med 2001;344(5):327–32.
[3] Confavreux C, Suissa S, Saddier P, Bourdès V, Vukusic S. Vaccines in Multiple Sclerosis Study Group. Vaccinations and the risk of relapse in multiple sclerosis. New Engl J Med 2001;344(5):319–26.
[4] Hernán MA, Jick SS, Olek MJ, Jick H. Recombinant hepatitis B vaccine and the risk of multiple sclerosis: a prospective study. Neurology 2004;63(5):838–42.
[5] Hernán MA, Jick SS. Hepatitis B vaccination and multiple sclerosis: the jury is still out. Pharmacoepidemiol Drug Saf 2006;15(9):653–5.
[6] Destefano F, Weintraub ES, Chen RT. Recombinant hepatitis B vaccine and the risk of multiple sclerosis: a prospective study (letter). Neurology 2005;64(7):1317.
[7] Destefano F, Weintraub ES, Chen RT. Hepatitis B vaccine and risk of multiple sclerosis. Pharmacoepidemiol Drug Saf 2007;16(6):705–7.
[8] Wraith DC, Goldman M, Lambert P-H. Vaccination and autoimmune disease: what is the evidence? Lancet 2003;362(9396):1659–66.
[9] Zuckerman JN. Protective efficacy, immunotherapeutic potential, and safety of hepatitis B vaccines. J Med Virol 2006;78(2):169–77.
[10] Schattner A. Consequence or coincidence? The occurrence, pathogenesis and significance of autoimmune manifestations after viral vaccines. Vaccine 2005;23(30):3876–86.
[11] Siegrist C-A, Lewis EM, Eskola J, Evans SJW, Black SB. Human papilloma virus immunization in adolescent and young adults. A cohort study to illustrate what events might be mistaken for adverse reactions. Pediatr Infect Dis J 2007;26(11):979–84.
[12] Garçon N, Chomez P, Van Mechelen M. GlaxoSmithKline Adjuvant Systems in vaccines: concepts, achievements and perspectives. Expert Rev Vaccines 2007;6(5):723–39.
[13] Beutler B, Rietschel RT. Innate immune sensing and its roots: the story of endotoxin. Nat Rev Immunol 2003;3(2):169–76.
[14] Harper DM, Franco EL, Wheeler C, Ferris DG, Jenkins D, Schuind A, et al. GlaxoSmithKline HPV Vaccine Study Group. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. Lancet 2004;364(9447):1757–65.
[15] Harper DM, Franco EL, Wheeler CM, Moscicki AB, Romanowski B, Roteli-Martins CM, et al. HPV Vaccine Study group. Sustained efficacy up to 4.5

years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. Lancet 2006;367(9518):1247–55.
[16] Paavonen J, Jenkins D, Bosch FX, Naud P, Salmerón J, Wheeler CM, et al. HPV PATRICIA study group. Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial. Lancet 2007;369(9580):2161–70.
[17] Crosbie EJ, Kitchener HC. Cervarix—a bivalent L1 virus-like particle vaccine for prevention of human papillomavirus type 16- and 18-associated cervical cancer. Expert Opin Biol Ther 2007;7(3):391–6.
[18] Schwarz TF. Human papillomavirus-16/18 candidate vaccine adjuvanted with AS04 and its impact on the incidence of cervical cancer. Expert Rev Obstet Gynecol 2007;2(3):293–303.
[19] Tong NK, Beran J, Kee SA, Miguel JL, Sánchez C, Bayas JM, et al. Immunogenicity and safety of an adjuvanted hepatitis B vaccine in pre-hemodialysis and hemodialysis patients. Kidney Int 2005;68(5):2298–303.
[20] Kundi M. New hepatitis B vaccine formulated with an improved adjuvant system. Expert Rev Vaccines 2007;6(2):133–40.
[21] Stanberry LR, Spruance SL, Cunningham AL, Bernstein DI, Mindel A, Sacks S, et al. GlaxoSmithKline Herpes Vaccine Efficacy Study Group. Glycoprotein-D-adjuvant vaccine to prevent genital herpes. N Engl J Med 2002;347(21):1652–61.
[22] Jacobsen DL, Gange SJ, Rose NR, Graham NMH. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. Clin Immunol Immunopathol 1997;84(3):223–43.