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Autoimmune disorders and quadrivalent human papillomavirus vaccination of young female subjects

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Abstract. Grimaldi-Bensouda L, Guillemot D, Godeau B, Bénichou J, Lebrun-Frenay C, Papeix C, Labauge P, Berquin P, Penfornis A, Benhamou P-Y, Nicolino M, Simon A, Viallard J-F, Costedoat-Chalumeau N, Courcoux M-F, Pondarré C, Hilliquin P, Chatelus E, Foltz V, Guillaume S, Rossignol M, Abenhaim L for the PGRx-AID Study Group (LA-SER, Paris; Conservatoire National des Arts et Métiers (CNAM), Paris; Institut Pasteur, Paris; INSERM U657, Paris; University of Paris-Ile de France Ouest, Paris; Henri Mondor University Hospital, Créteil; University Paris Est Créteil, Créteil; University Hospital of Rouen, Rouen; INSERM U657, Rouen; Centre Hospitalier Universitaire (CHU) de Nice, Nice; AP-HP, Paris; CHU de Nîmes, Nîmes; CHU d'Amiens-Picardie, Amiens; University of Franche-Comté, Besançon; CHRU Besançon, Besançon; CHU de Grenoble, Grenoble; CHU de Lyon, Lyon; Versailles Hospital, Versailles; CHU de Bordeaux, Bordeaux; University René Descartes, Paris; AP-HP, Paris; AP-HP, Paris; University Lyon I, Lyon; Referral Centre for Thalassemia, Marseille-Lyon; Centre Hospitalier Sud-Francilien, Corbeil-Essonnes; CHRU Strasbourg, Strasbourg; AH-HP, Paris; AP-HP, Le Kremlin Bicêtre, France; McGill University, Montreal; LA-SER Center for Risk Research, Montreal, QC, Canada; London School of Hygiene & Tropical Medicine, London; LA-SER Europe Limited, London, UK). Autoimmune disorders and quadrivalent human papillomavirus vaccination of young female subjects. *J Intern Med* 2014; **275**: 398–408.

Objectives. The aim of this study was to investigate whether the quadrivalent human papillomavirus (HPV) vaccine Gardasil is associated with a change in the risk of autoimmune disorders (ADs) in young female subjects.

Design. Systematic case–control study of incident ADs associated with quadrivalent HPV vaccination in young women across France.

Participants and setting. A total of 113 specialised centres recruited (from December 2007 to April 2011) females aged 14–26 years with incident cases of six types of ADs: idiopathic thrombocytopenic purpura (ITP), central demyelination/multiple sclerosis (MS), Guillain–Barré syndrome, connective tissue disorders (systemic lupus erythematosus, rheumatoid arthritis/juvenile arthritis), type 1 diabetes mellitus and autoimmune thyroiditis. Control subjects matched to cases were recruited from general practice.

Analysis. Multivariate conditional logistic regression analysis; factors included age, geographical origin,

[†]Contributing members of the PGRx-AID Study Group are in Appendix 1.

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smoking, alcohol consumption, use of oral contraceptive(s) or vaccine(s) other than Gardasil received within 24 months before the index date and personal/family history of ADs.

Results. Overall, 211 definite cases of ADs were matched to 875 controls. The adjusted odds ratio (OR) for any quadrivalent HPV vaccine use was 0.9 [95% confidence interval (CI) 0.5–1.5]. The individual ORs were 1.0 (95% CI 0.4–2.6) for ITP, 0.3 (95% CI 0.1–0.9) for MS, 0.8 (95% CI 0.3–2.4) for connective disorders and 1.2 (95% CI 0.4–3.6) for type 1 diabetes. No exposure to HPV vaccine was observed in cases with either Guillain–Barré syndrome or thyroiditis.

Conclusions. No evidence of an increase in the risk of the studied ADs was observable following vaccination with Gardasil within the time periods studied. There was insufficient statistical power to allow conclusions to be drawn regarding individual ADs.

Keywords: autoimmune disorders, human papillomavirus, human papillomavirus vaccine, systematic case–control study, vaccination, vaccine safety.

Introduction

Human papillomavirus (HPV) types 16 and 18 are responsible for about 70% of all cervical cancers. Vaccines have been developed to protect against these HPV types and are used worldwide [1]. The quadrivalent vaccine protects against HPV types 6 and 11, which are the most common causes of genital warts, in addition to types 16 and 18. Extensive vaccination campaigns have been conducted in Europe and North America following the introduction of the HPV vaccines, resulting in large fractions of the young female population being exposed. Alleged associations between mass vaccinations and autoimmune disorders (ADs) have been previously reported to be controversial in both Europe and North America [2–4]. The mechanism most frequently proposed for putative associations is molecular mimicry [5, 6]; however, associations were not confirmed in other studies [5, 7]. In this case–control study, we investigated whether the quadrivalent HPV vaccine was associated with ADs. This study was planned initially as part of the risk management plan for the vaccine in France, which was then extended across Europe.

Methods

Study population

The Pharmacoepidemiologic General Research Extension (PGRx) programme is an ongoing research platform recruiting (i) cases of ADs prospectively to clinical registries in France through networks of centres interested in research on ADs [8], and (ii) representative pools of patients from general practice for the selection of controls. Cases and controls drawn from these registries were female, aged 14–26 years, and living in France; all subjects were able to read and respond to a telephone interview (parents could be interviewed for participants under 18 years of age). This age group was initially recommended for vaccination by health authorities in 2006.

Cases

The risk management plan targeted surveillance for the following six types of ADs: idiopathic thrombocytopenic purpura (ITP), connective tissue disorders (undifferentiated connective tissue disorder, lupus erythematosus, rheumatoid arthritis/juvenile arthritis, myositis and dermatomyositis), central demyelination and multiple sclerosis (MS), Guillain–Barré syndrome, type 1 diabetes mellitus and autoimmune thyroid disorders (ATDs) including Grave–Basedow and Hashimoto diseases.

Cases with incident ADs were recruited through a network of specialist centres (internal medicine, neurology, rheumatology, paediatric, endocrinology and dermatology departments), at university and general hospitals across France, participating in the PGRx programme [8]. An on-site audit of recruitment and data quality was performed in three of four centres (randomly selected) over a 2-month period.

Recruitment to the registries was exhaustive during the study period (identifying all potentially eligible cases), regardless of any exposure history, including individuals of all ages and both sexes. Amongst the female patients aged 14–26 years included in this study, the first symptoms of AD appeared between 1 December 2006, the date when the quadrivalent HPV vaccine Gardasil was first marketed nationally, and 31 December 2010 (inclusive) for central demyelination or 30 April 2011 (inclusive) for all other ADs.

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Case definitions were based on internationally accepted classifications for each disorder [2, 9–15]. Diagnoses for cases were classified as 'definite', 'possible' or 'rejected', allowing for the recruitment of cases at the early stages of disease in young patients. Some unclassified cases were reviewed by two independent experts blind to vaccination status. When necessary to confirm diagnosis, cases were followed for up to 1 year.

Controls

A population termed 'referents' was recruited by a network of general practitioners (GPs) who regularly recruit representative samples of patients treated in general practice for a pharmacoepidemiologic general research programme. Controls were randomly selected from the pool of referents for matching to cases according to age (best match available within ±1, ±2, ±6 or ±12 months for cases under 18 years of age and within ±12 or ±24 months for cases aged 18 years or older), region of residence (northern or southern France) and recruitment consultation date (best match available within ±3 or ±9 months). For each AD case, only referents with no history of that particular type of AD were selected as potential controls. On average, four controls were matched to each case. The selection of controls was carried out separately for the study of each AD and then repeated for the combined study of all ADs.

Assessment of HPV vaccination and other potential risk factors for ADs

Human papillomavirus vaccination history was assessed using prescription records received from cases and referents, as well as directly from GPs and during the telephone interviews. Using this method, a high level of agreement (95.9%) between medical records and patients' reports of HPV vaccination was demonstrated in a validation study [16]. HPV vaccination reported in the telephone interview was considered to be confirmed in this study when at least one of the following was available: vaccine batch number, vaccine prescription, vaccination certificate or other confirmatory document.

Cases and referents underwent a standardised telephone interview including questions concerning socio-demographic, medical and lifestyle factors, as well as all use of medicines (prescription or over the counter) and vaccines within 24 months before the recruitment consultation date. Interviews were conducted within 45 days of recruitment by trained interviewers blind to case/referent status. An interview guide was provided to patients prior to the interview.

Time windows for defining exposure to Gardasil vaccine

The index date was the date of the first clinical sign or symptom suggestive of the AD in the case, reported by the recruiting specialist. The same date was taken as the index date for each matched control. Only factors reported for the period on or before the index date were included in the analysis.

Exposure to the Gardasil vaccine was defined according to predefined time windows before the index date. The primary time windows considered were ≤6 months before the index date for ITP, ≤2 months for Guillain–Barré syndrome and ≤24 months for the other ADs. Other time windows were used in sensitivity analyses. If a patient was vaccinated at least once within a time window, she was considered to be exposed for that analysis.

Statistical methods

Potential confounders for the relation between HPV vaccination and ADs considered for the statistical models included age, geographical origin (see footnote to Table 1 for definition), smoking, alcohol consumption and use of oral contraceptive(s) or vaccine(s) other than Gardasil received within 24 months before the index date. A multivariate risk score (MRS) was derived from a conditional logistic regression model incorporating all these variables. A score was constructed for each individual as the sum of the relevant values of the regression equation parameters for all variables in the model. Personal or family hx (PFAD) was found to be associated with an increased risk of AD; therefore, all analyses of associations between Gardasil vaccination and ADs were either adjusted for or stratified by PFAD.

Cases and controls were compared with regard to exposure to the quadrivalent HPV vaccine. Comparisons were based on crude odds ratios (ORs) from unconditional logistic regression and adjusted ORs from conditional logistic regression (adjusted for the MRS and a PFAD). The analysis was repeated after stratification according to PFAD, using unconditional logistic regression for both crude and adjusted ORs. Stratified adjusted ORs were controlled for the matching factors in

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Table 1 *Description of cases and controls for the six types of ADs combined (including cases of ATDs)*

Characteristics[a]	Definite and possible cases (n = 269) (%)	Controls[b] (n = 1096) (%)	P-value
Age, years			
14–17	24.2	25.5	NA
18–26	75.8	74.5	
Mean (standard deviation)	21.4 (3.8)	21.2 (3.8)	
Region of residence in France			
North	57.2	57.2	NA
South	42.8	42.8	
Geographical origin[c]			
Northern Europe and North America	83.6	90.9	<0.001
Other	11.2	3.4	
Missing	5.2	5.7	
Smoking			
Smoker	36.8	33.7	0.61
Former smoker (stopped smoking for ≥1 year)	5.2	4.9	
Never smoked	58.0	61.4	
Alcohol consumption			
Daily or almost daily	0.4	0.0	0.71
A few times per week	8.9	8.5	
Occasionally or never	90.7	91.5	
Number of medicines (any) taken within 24 months before recruitment date			
0–6	27.5	27.1	0.57
7+	72.5	72.9	
Use of oral contraceptive(s) within 24 months before index date			
Yes	49.4	58.6	0.01
Vaccine(s) other than Gardasil received within 24 months before index date			
Yes	31.2	38.2	0.05
At least one chronic comorbidity[d]			
Yes	12.6	15.4	0.32
Personal history of previous AD[e]			
Yes	4.5	0.6	0.001
No	95.5	99.4	
Family history of AD[f]			
Yes	10.4	5.0	0.02
No	64.3	70.3	
Unknown or missing	25.3	24.6	
Previous personal history or familial history of AD			
Yes	14.1	5.6	<0.001
No	61.0	70.1	
Unknown or missing	24.9	24.4	

AD, autoimmune disorder; ATD, autoimmune thyroid disorder; NA, not applicable.
[a]All information obtained from the patient interview. [b]Proportions weighted by the number of matched controls per case. [c]Global geographical origin was defined as follows: Region of birth of the patient was categorized as 'N' (within Northern Europe or North America), 'other' (outside N) or 'missing'. Region of birth of the patient's parents was also categorized as 'N', 'other' or 'missing': if the region of birth for one parent was 'N' and for the second parent was 'other', the parents' region of birth was classified as 'other'; if one or both parents had a missing region of birth, overall parents' region of birth was classified as 'missing'. Next, (i) if either the patient's or both parents' region of birth was 'N', then the geographical origin was classified as 'N', (ii) if the patient's and both parents' region of birth was 'other', then the geographical origin was classified as 'other', and (iii) if the patient's and/or both parents' region of birth was 'missing' and condition (i) did not apply, then the geographical origin was classified as 'missing'. [d]At least one of the following comorbidities: diabetes, obesity, Crohn's disease, ulcerative colitis, cirrhosis, cancer, epilepsy, multiple sclerosis, migraine, rheumatoid arthritis, chronic renal failure, asthma and chronic obstructive pulmonary disease. [e]Not including the AD of the case, includes the following: multiple sclerosis, lupus, rheumatoid arthritis, Crohn's disease, ulcerative colitis and autoimmune thyroiditis. [f]Includes the above ADs (listed in e) in first-degree relatives; only available for patients interviewed after 11 September 2008.

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addition to the MRS. Three analyses were performed, first for all studied ADs except ATDs (i.e. ITP, connective tissue disorders, central demyelination and MS, Guillain-Barré syndrome and type 1 diabetes mellitus) combined and then for each of the five ADs separately, if the sample size allowed. Cases of ATDs were included in the descriptive analyses, but not in the case–control analysis because of uncertainty regarding the date of first symptoms in many cases, which led to doubts concerning their definition as incident diagnoses. First, only definite cases and their matched controls were compared for confirmed exposure to the vaccine during the primary time window. Secondly, these analyses were repeated using different time windows. Thirdly, sensitivity analyses were performed by also including possible cases and their matched controls and unconfirmed vaccine exposure during the primary time window. All analyses were performed using SAS software version 9.2 (SAS Institute, Cary, NC, USA).

Ethical considerations

The study protocol was approved by the Ethics Review Committee of Paris-Ile de France III (*Comité de Protection des Personnes Ile de France III*) and approved by the French Data Protection Authority (Commission Nationale de l'Informatique et des Libertés). All participants or their parents provided written informed consent. Participating physicians were compensated for inviting and recruiting patients, but patients were offered no financial reward for their participation.

Results

Overall, 219 specialist centres were part of the networks recruiting for AD registries (adult and paediatric), 113 (51.6%) of which recruited at least one female case aged 14–26 years included in this study (33 internal medicine, 32 neurology, seven rheumatology, 11 paediatric, 28 endocrinology and two dermatology departments). Amongst 387 general practices participating in the PGRx networks, 253 (65.4%) recruited referents eligible for this study. Figure 1 shows the recruitment of cases and controls. Of the 321 recruited cases, 248 (77.3%) were definite, 21 (6.5%) were possible, 13 (4.1%) were rejected and 39 (12.2%) were eligible but not included (see Fig. 1). An audit of recruitment and data quality was carried out in 87 of the 113 (77.0%) specialist centres over a 2-month period. During the audit, it was found that 47 female AD cases eligible for the study and aged 14–26 years had been seen at these centres during a 2-month period and that 43 (91.5%) of these patients had been invited to participate in the study.

A total of 1389 eligible referents were interviewed. Of these, 474 reported receiving an HPV vaccine at some time and 469 (33.8%) the quadrivalent HPV vaccine. This proportion was similar to that expected from national health insurance data (32% coverage, almost all the quadrivalent vaccine). Amongst the 502 quadrivalent HPV vaccinations reported in the study population (by 285 cases and 1389 referents), 489 (97.4%) were confirmed by one of the objective sources (see Methods).

Table 1 shows the definite and possible cases of the six types of ADs and their matched controls. Cases were not statistically different from controls with regard to all variables shown except for PFAD, which was more frequently observed in cases [crude OR 2.9, 95% confidence interval (CI) 1.9–4.5]. PFAD was not associated with quadrivalent HPV vaccination in the reference population (data not shown).

The relation between Gardasil vaccination and five types of ADs (excluding ATDs) combined is shown in Table 2. None of the cases of Guillain–Barré syndrome was exposed to HPV vaccine. In the main analysis, the adjusted OR for quadrivalent HPV vaccination in these AD cases and their matched controls was 0.9 (95% CI 0.5–1.5) in the primary time windows defined in the Methods. In sensitivity analyses, the time windows were ≤2 months for ITP and ≤6 months for the other groups of ADs; the adjusted OR for quadrivalent HPV vaccination in these analyses was 0.8 (95% CI 0.4–1.6). In a further sensitivity analysis including definite and possible cases and confirmed and unconfirmed quadrivalent HPV vaccinations, the adjusted OR was 0.9 (95% CI 0.6–1.5).

When the ADs were investigated individually, cases of central demyelination/MS were less likely to have been vaccinated with the quadrivalent HPV vaccine than controls (adjusted OR 0.3, 95% CI 0.1–0.9). For the other ADs, we found no evidence of an association between this vaccine and disease in adjusted analyses, either in primary analyses (Table 2), stratified by PFAD, or in secondary and sensitivity analyses (data not shown). The analyses of individual ADs had limited statistical power due to the small numbers of cases.

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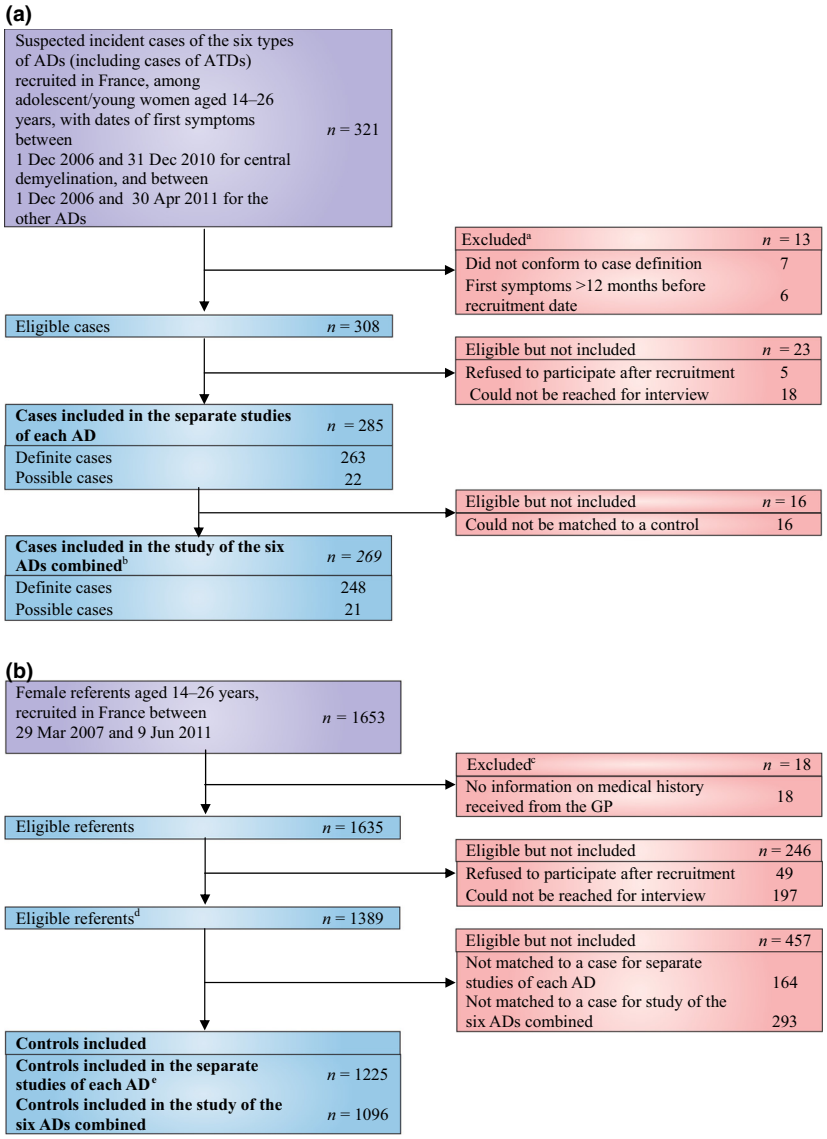

Fig. 1 *Flow charts describing the recruitment of cases (a) and control subjects (b). AD, autoimmune disorder; ATD, autoimmune thyroid disorder; GP, general practitioner.* [a]*Vaccination with Gardasil in excluded cases: of the seven not conforming to the case definition, none was vaccinated; of the six not included with first symptoms > 12 months before recruitment, one was vaccinated; of the 23 not interviewed, medical records were obtained for 15 (four were vaccinated); of the 16 not matched to a control, none was vaccinated.* [b]*The study of the ADs combined included fewer cases than the separate studies of each AD. Each control could only be matched to one case for the combined study, so 16 cases could not be matched. For the separate studies of each AD, a control could be matched to more than one case if the cases had different ADs.* [c]*Vaccination with Gardasil in excluded referents: of the 18 excluded with no information on medical history, 10 were interviewed (four were vaccinated); of the 197 not reached for the interview, medical records were obtained for 187 (31 were vaccinated).* [d]*The pool of eligible referents included patients with a history of AD. For each AD case, only referents with no history of that AD were selected as potential controls. In referents, a history of AD was defined as ADs reported by the recruiting GP or a treatment consistent with AD reported by the patient (list of treatments available upon request).* [e]*For the separate studies of each AD, a control could be matched to more than one case if the cases had different ADs. Thus, some controls were included for several ADs.*

Table 2 *Associations between Gardasil vaccination and ADs (excluding ATDs)*

Analysis (*n* cases/*n* controls)	Cases exposed *n* (%)	Controls exposed *n* (%)	Crude OR[b] (95% CI)	Adjusted OR[b] (95% CI)
For definite cases and confirmed Gardasil vaccinations in primary time window[a]:				
All ADs combined				
211 of 875	25 (11.8)	192 (21.9)	0.5 (0.3–0.7)[c]	0.9 (0.5–1.5)[c]
With personal or family history of AD: 20 of 55	3 (15.0)	15 (27.3)	0.5 (0.1–1.9)[d]	1.1 (0.2–5.9)[d]
Without personal or family history of AD: 137 of 602	19 (13.9)	139 (23.1)	0.5 (0.3–0.9)[d]	0.8 (0.5–1.5)[d]
ADs separately				
Idiopathic thrombocytopenic purpura: 40 of 183	6 (15.0)	33 (18.0)	0.8 (0.3–2.2)[c]	1.0 (0.4–2.6)[c]
Connective tissue disorders: 49 of 200	6 (12.2)	37 (18.5)	0.6 (0.2–1.5)[c]	0.8 (0.3–2.4)[c]
Central demyelination: 83 of 290	4 (4.8)	48 (16.6)	0.3 (0.1–0.7)[c]	0.3 (0.1–0.9)[c]
Guillain–Barré syndrome: 15 of 91	0 (0.0)	7 (7.7)	–	–
Type 1 diabetes: 38 of 202	9 (23.7)	41 (20.3)	1.2 (0.5–2.9)[c]	1.2 (0.4–3.6)[c]

AD, autoimmune disorder; ATD, autoimmune thyroid disorder; OR, odds ratio; CI, confidence interval.
[a]Primary time window A was ≤6 months before the index date for ITP, ≤2 months for Guillain–Barré syndrome and ≤24 months for the other ADs. For each case–control set, the relevant time window was used according to the AD. [b]ORs were calculated whenever there were three or more patients in each cell considered. [c]Crude ORs were calculated using unconditional logistic regression; adjusted ORs were calculated using conditional logistic regression and controlled for the multivariate risk score and a personal or family history of AD. [d]Crude and adjusted ORs were calculated using unconditional logistic regression; adjusted ORs controlled for the multivariate risk score and matching factors.

Assuming 95% confidence and 80% power, the minimum detectable ORs for the numbers of definite and possible cases were 1.6 for the five ADs (excluding ATDs) combined (229 cases) and between 2.2 and 2.8 for the ADs individually except for Guillain–Barré syndrome. For the latter, no exposed case was reported, thus suggesting no risk; however, the study had limited statistical power, so that a definite conclusion could not be drawn regarding this syndrome.

Discussion

There was no evidence of an increase in the risk of the studied ADs following vaccination with Gardasil within the time windows set *a priori* for each of the ADs in this age group. Using different time windows in sensitivity analyses did not affect the main results. From a monitoring viewpoint, no unusual patterns of accrual of incident cases of any of the ADs were observed in a large series of AD specialist centres, at a time when one-third of the girls/young women in the survey were being vaccinated against HPV, mainly with Gardasil.

Considering the rarity of ADs in this group, this was a relatively large and possibly the largest case–control study of HPV vaccines and ADs in young women. Nevertheless, the sample size was small for individual ADs and resulted in relatively large confidence intervals. Point estimates were all close to or below unity, which represents a robust and consistent finding. Further studies and meta-analyses are needed to confirm the safety of the Gardasil vaccine.

In this study, we focused exclusively on the quadrivalent HPV vaccine Gardasil because it was used in 99% of HPV vaccinations in the studied population. Vaccination stimulates the immune system to produce antigen-specific immunity. Because ADs also involve stimulation of the immune system, it has been suggested that vaccination may trigger ADs. The mechanism most frequently proposed is molecular mimicry, in which antigens of the host are recognized as being similar to antigens of the vaccine, thus provoking the development of autoantibodies [5, 6]. Putative associations were reported between A/New Jersey influenza vaccination and Guillain–Barré syndrome in 1979 [2] and later between hepatitis B immunization and multiple sclerosis [3]. Other ADs possibly linked to vaccinations include ITP [17, 18] and lupus [19, 20]. The majority of these studies were case reports

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or case series demonstrating temporal associations between vaccination and ADs in a small number of patients. In general, epidemiological investigations at the population level adjusting for confounders have not confirmed an association between vaccination and risk of AD [5, 7, 8].

In the present study, we found no evidence following vaccination with Gardasil of an increase in the risk of the studied ADs, analysed either individually or together, except for a lower OR for central demyelination/MS. However, the statistical power to obtain a significant result was low for individual diseases due to the rarity of AD cases. For demyelination/MS, the observed association may be due to chance, a true decreased risk or unexpected confounders. It is possible that prodromal illnesses, comorbidities or family history may have prevented vaccination in susceptible individuals. The latter explanation could be partly supported by the fact that a PFAD was more likely in cases of central demyelination (11.4%), compared with the corresponding controls (7.4%), and vaccination was less common in this group. The ORs for ATDs and HPV vaccination could not be studied due to lack of precision in determining the date of first symptoms, but the absence of vaccination in any case at any time before disease onset (up to 2 years) was noted.

All of the potential confounders shown in Table 1 were adjusted for in the multivariate analyses. For most of the ADs considered, there are few, if any, known risk factors for onset at a young age, and it is possible that unknown confounders may have been overlooked. In addition, some factors may have acted as potential confounders for some ADs, but not for others. Furthermore, our findings were consistent with previous reports of clusters of ADs within families [21].

All methods for recruitment of cases and controls and collection data were standardized and validated to reduce the potential for bias [22]. Any selection or diagnostic bias was likely to be minimal; cases and referents were recruited for prospective registries (PGRx); and therefore, recruiters were unlikely to be biased with regard to specific hypotheses. Recruited cases and controls not included were no more likely to be vaccinated with the quadrivalent HPV vaccine than patients who were included in the study (see footnotes to Fig. 1). Vaccination coverage by year of birth was consistent with estimates from national prescription data: 33.5% vs. 32% expected according to the age of the study population. The pools of referents recruited in PGRx have been shown to be similar (results available upon request) to the general population according to the national data from general practice [23].

Our findings are consistent with the favourable safety profile described in early postmarketing studies [24–27]. Using the case–control approach, the reporting of bias and diagnostic uncertainty (which are common problems in surveillance systems that often result in a lack of cases compared with the rate expected in the background population) were avoided [27]. Advantages of the method also include consideration of a PFAD and other known risk factors. We are confident that the ascertainment of vaccination status in cases and controls had a high validity, as information was obtained from both patient reports and medical records. The high level of agreement between information provided by study subjects and physicians may be explained by the relative novelty of the HPV vaccine and the publicity that targeted young women.

In conclusion, no evidence of an increase in the risk of the studied ADs was observed following vaccination with Gardasil within the time windows investigated. There was insufficient power to allow conclusions to be drawn for individual ADs. Further research should address the potential effects of vaccination on other ADs not investigated in the present study, such as neuritis and autoimmune hepatitis type 2, which have been associated with HPV vaccines in case reports [28–30].

Conflict of interest statement

LG-B was the recipient of a research fellowship from INSERM (French National Institute of Health and Medical Research) at the time of the study and is currently employed by the Conservatoire National des Arts et Métiers and LA-SER, the company conducting the study. DG has received a consulting fee/honorarium from LA-SER within the framework of the present study and, in the last 3 years, has been a member of the board for Axa and Welcome Trust, has been a consultant for LA-SER (outside the present work) and BioMérieux and has received grants from the Principality of Monaco, the French Government and the European Union; he is currently employed by the University of Versailles Saint-Quentin and the

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consortium Assistance Publique-Hôpitaux de Paris. BG has received a consulting fee/honorarium from Sanofi Pasteur MSD. In addition, he (or his institution) has been paid for consultancy work for Roche, the Laboratoire Français du Fractionnement et des Biotechnologies, Amgen and GlaxoSmithKline; his institution has also received grant support for research from Roche. JB is a consultant to LA-SER. CL-F has received consultancy fees from Allergan, Almirall, Biogen Idec, Genzyme, Bayer, Merck Serono SA, Novartis, Sanofi and Teva Pharmaceutical Industries Ltd, as well as travel grants from Biogen Idec, Bayer, Merck, Teva Pharmaceutical Industries Ltd, Sanofi and Novartis. CPa is a member of the board for Bayer Schering Pharma, Novartis, Roche, Teva Pharmaceutical Industries Ltd and Sanofi-Genzyme BioVentures; she has also received payment for lectures and participation in speakers' bureaus from Bayer Schering Pharma, Novartis, Teva Pharmaceutical Industries Ltd, Merck Serono SA, Biogen Idec and Genzyme. AP received a consultancy fee/honorarium from Interunec. P-YB received a consultancy fee/honorarium from the University Hospital of Grenoble; during the 3 years prior to submission of this manuscript, he was also a member of the board for Sanofi-France, a consultant for LifeScan Inc. and Medotronic, and received payment for lectures and participation in speakers' bureaus from Abbott and Lilly France. MN is a board member for Novo Nordisk, Merck Serono SA and Roche. AS received support for travel relevant to the present study and for other purposes from Novo Nordisk (ESPE 2012) and Lilly France (Endocrine 2012). SG received a consultancy fee/honorarium for work related to the present study from LA-SER, payment for the development of educational presentations from Bristol-Myers Squibb (BMS) and Pfizer and additional travel/accommodation/meeting expenses from BMS, Pfizer, Novartis and Roche. MRo is currently employed by LA-SER and an Associate Professor of the Department of Epidemiology, Biostatistics & Occupational Health at McGill University (Canada), but declares no other conflict of interest. LA is a stock owner and chairman of LA-SER, an independent research organisation that owns and develops the PGRx database. LA-SER has no commercial interests in any of the products investigated in this study. For use of the data from PGRx or other sources, LA-SER receives funds and/or other support from regulatory agencies, public sources, academic institutions, private groups and the pharmaceutical industry (in the past 3 years, the donor companies have included, amongst others: AstraZeneca, Boiron, Expanscience, Genevrier, GlaxoSmithKline, Janssen-Cilag, Merck/Schering-Plough, Negma/Wokhardt, Novartis, Pfizer and several divisions of Sanofi). All other authors (PL, J-FV, NC-C, M-FC, CPo, PH, EC, VF and PB) have no conflict of interests to declare.

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Authors' contributions

The work presented here was carried out with the involvement of all authors. Additionally, all authors were involved in formulating the research topic and designing the methods, analysing the data and interpreting the results. LG-B was in charge of the study in France and together with MR and LA drafted and revised the manuscript. LG-B is the guarantor for the study. All authors have contributed to, read and approved the final manuscript. All authors, external and internal, had full access to all study data (including statistical reports and tables) and take responsibility for the integrity of the data and accuracy of the data analysis.

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APPENDIX 1

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