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Human papillomavirus vaccination and risk of autoimmune diseases: A large cohort study of over 2 million young girls in France

Sara Miranda [a,1], Christophe Chaignot [b,1], Cédric Collin [a], Rosemary Dray-Spira [a], Alain Weill [b], Mahmoud Zureik [a,*]

[a] Agence Nationale de Sécurité des Médicaments et des Produits de Santé (ANSM) [French National Agency for Medicines and Health Products Safety], Saint-Denis, France
[b] Caisse Nationale de l'Assurance Maladie des Travailleurs Salariés (CNAMTS) [French National Health Insurance Fund for Salaried Workers], Paris, France

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ABSTRACT

Background: Whether human papillomavirus (HPV) vaccination could induce or trigger autoimmune diseases (AID) has been questioned, and potentially contributes to low immunization coverage in France. This study evaluated the association between HPV vaccination and the risk of AID using routinely collected data sources.

Methods: All girls aged 13–16 years between 2008 and 2012, covered by the general health insurance scheme and without history of HPV vaccination or AID, were included and followed using French nationwide databases. Fourteen neurological, rheumatological, haematological, gastrointestinal or endocrine AID, were identified from ICD-10 codes allocated to hospital stays and long-term illnesses or by marker drugs. Their incidence was compared between girls exposed and non-exposed to HPV vaccination, using a Cox model adjusted for inclusion year, geographic area, socio-economic indicators, healthcare use level and other immunizations.

Results: Among 2,252,716 girls, 37% received HPV vaccine and 4,096 AID occurred during a mean follow-up time of 33 months. The incidence of AID was not increased after exposure to HPV vaccination, except for Guillain-Barré syndrome (GBS) (incidence rate of 1.4 among exposed [20 cases] versus 0.4 per 100,000 PY among unexposed [23 cases]; adjusted HR: 3.78 [1.79–7.98]). This association persisted across numerous sensitivity analyses and was particularly marked in the first months following vaccination. Under the hypothesis of a causal relationship, this would result in 1–2 GBS cases attributable to HPV vaccine per 100,000 girls vaccinated.

Conclusions: Our study provides reassuring results regarding the risk of AID after HPV vaccination, but an apparently increased risk of GBS was detected. Further studies are warranted to confirm this finding.

1. Background

Human papillomavirus (HPV) infection is a common sexually transmitted infection affecting the general population. Certain HPV types are associated with cancer development, most strongly types 16 and 18.

Two HPV vaccines were available at the time of this study for the prevention of precancerous genital lesions, cervical cancer and genital warts: Gardasil®, quadrivalent vaccine (HPV types 6, 11, 16 and 18) and Cervarix®, bivalent vaccine (HPV types 16 and 18). Target population, indications and immunization schedules have evolved over the years in line with marketing authorizations and specific national recommendations. By end-2015, over 80 million girls worldwide were vaccinated against HPV (more than 63 million with quadrivalent and more than 19 million with bivalent vaccine) [1].

The introduction of new large-scale vaccinations often raises apprehension among population, specifically concerning post-vaccination autoimmune diseases (AID). Following the Guillain-Barré syndrome (GBS) safety signal during the A/New Jersey/H1N1 vaccination campaign in 1976, more recent concerns have fuelled controversy about the role of vaccination, such as the alleged risk of multiple sclerosis following Hepatitis B vaccines or the risk of GBS or narcolepsy after A(H1N1)pdm09 vaccination [2,3].

Available data from passive surveillance systems or epidemiological studies, including three population-based cohort studies

* Corresponding author at: Agence Nationale de Sécurité des Médicaments et des Produits de Santé, 143-147 boulevard Anatole France, 93285 Saint-Denis Cedex, France.
E-mail address: mahmoud.zureik@ansm.sante.fr (M. Zureik).
[1] Equal contribution.

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in the United States [4] and Northern Europe [5,6] and a French case-control study [7], do not support the hypothesis that HPV vaccination is associated with an increased risk of AID. However, epidemiological studies focusing specifically on AID risk have remained few and their power to detect any increase in rare events was limited.

In France, nationwide healthcare databases covering over 65 million people, are a powerful and useful tool for conducting large epidemiological studies. Therefore to complement the existing knowledge, a pharmaco-epidemiological study using these databases, conducted jointly by the French national agency for medicines and health products safety (ANSM) and the national health insurance fund for salaried workers (CNAMTS), aimed to evaluate the risk of AID after exposure to HPV vaccines using routinely collected health data.

2. Methods

2.1. Study design

We carried out a longitudinal observational study based on national healthcare administrative databases, comparing the incidence of selected AID between young girls exposed and not exposed to HPV vaccines, between January 1, 2008 and December 31, 2013.

Two French nationwide datasets linked by a unique individual identifier were used. The SNIIRAM, French national health insurance anonymised claim database, has been available since 2006 and contains demographic data, including age, gender, vital status and all reimbursements for patient health expenditure, including drugs and outpatient medical or nursing care [8]. This system covers the entire French population, with different schemes based on employment situation. The status regarding coverage by the complementary Universal Health Insurance (CMU-c), free health care coverage for low-income residents, provides information on the individual's socioeconomic level. As for the SNIIRAM, while it does not specify the medical indication for each outpatient reimbursement, it provides the patient's status with respect to full reimbursement of care related to a severe and costly long-term illness (LTI), defined using the International Classification of Diseases, 10th edition (ICD-10). The SNIIRAM database is fully available and accurate for individuals covered by the general scheme, which covers employees in the industry, business, and service sectors, and some categories of workers considered as employees, representing around 77% of the French general population. This database was linked to the national hospital discharge database (PMSI) which provides individual medical information for all hospital admissions in France, including discharge diagnoses coded in ICD-10 and medical procedures performed during hospital stay. This linkage has previously been used for large epidemiological studies [9–18], and its use in this study was approved by the French data protection authority (CNIL).

2.2. Study population

During study period, HPV vaccination was recommended for girls aged 14 years old since July 2007 and July 2008 (quadrivalent and bivalent vaccines, respectively) coupled with a catch-up campaign targeting girls aged 15–23 years old. Vaccination was provided through the private sector and reimbursed by the national insurance scheme, remaining partially at the expense of the vaccinees (or their private insurance). All girls aged 13–16 years old between January 1, 2008 and December 31, 2012 and covered by the general insurance scheme were considered in the study, unless they had a history of HPV vaccination or any of the AID of interest prior to entry to the cohort. History of autoimmune diseases was defined as the presence of an ICD-10 diagnosis code or reimbursements for immunosuppressant or immunomodulator drugs in the 2 years prior to inclusion (cf Supplementary Table 1). Girls were included in the cohort on January 1, 2008 or on their thirteenth birthday, whichever occurred latest.

2.3. Follow-up and exposure

Girls were followed up from their inclusion until December 31, 2013, or until the date of the event of interest, their seventeenth birthday (since changes in health insurance scheme are common after the age of 17), change in health insurance scheme or death, whichever occurred first. Exposure was defined by reimbursement of at least one dose of a HPV vaccine. Therefore, all girls were considered as non-exposed at inclusion and as exposed from the first vaccine dose until the end of follow-up. Since actual date of injection is not recorded, the dispensing date was considered the date of exposure.

2.4. Outcomes of interest

Fourteen outcomes likely to be due to an auto-immune process were pre-selected, based on plausibility criteria and availability of specific disease codes or marker drugs, including neurological (central nervous system demyelinating diseases and GBS), rheumatological (localized or systemic lupus, localized or systemic scleroderma, vasculitis, rheumatoid or juvenile arthritis, myositis or dermatomyositis, Sjögren's syndrome), hematological (idiopathic thrombocytopenic purpura), endocrine (type 1 diabetes, thyroiditis, pancreatitis) and gastro-intestinal disorders (inflammatory bowel disease, coeliac disease).

For each outcome of interest, the index date corresponded to the date of diagnosis as identified based on dates of hospitalisations, long-term illness reimbursement records and reimbursement of marker drugs if appropriate (see supplementary Table 1 for case definition details).

2.5. Covariates

Sociodemographic characteristics included year of inclusion, socioeconomic level and geographic area of residence at inclusion. Covariates also included healthcare use indicators, including all-causes hospitalizations and outpatient primary care (ie, general practitioner, paediatrician, gynaecologist or dentist) and specialist visits. Hospitalizations were considered in the model as a time-dependent binary variable, indicating if at least one hospitalisation ocurred over the 12-month period running from 15 months to 3 months prior to each time point. Outpatient visits were considered as time-fixed variables: binary variables indicating the occurrence during the year prior inclusion, and quantitative variables indicating the mean annual frequency of visits during follow-up (ratio of the total number of visits after inclusion until 3 months before the event or censoring). All other vaccines, other than HPV, as long as giving rise to a reimbursement by the national insurance, were considered as time-fixed binary variable indicating whether vaccines occured during the two years prior to inclusion, and as a time-dependent binary variable indicating whether or not girls were exposed to these vaccines, after inclusion.

2.6. Statistical analyses

The incidence rate of each event of interest was calculated for the overall cohort and according to HPV vaccine exposure status. The incidence rates for non-exposed girls were standardized on the age of vaccinated girls after exposure.

Cox proportional hazard models were used to estimate the associations between HPV vaccination and the events of interest, considering age as time scale and HPV exposure as time-dependent variable. Crude and adjusted hazard ratios (HR and $_{a}$HR) were calculated for the fourteen events of interest considered as separated and independent analyses. All time-fixed and time-dependent covariates were included in adjusted models: vaccinations other than HPV, hospitalisations, health-care seeking behaviour indicators, year of inclusion, geographic area of residence and socioeconomic level.

The analytical strategy included an initial approach using models common to all study outcomes and several sensitivity analyses. These included subgroup analyses on HPV vaccine product reimbursed (bivalent or quadrivalent); censoring observations at the first of any other vaccinations during follow-up; analyses by risk-windows, and models excluding health-care seeking indicators after inclusion. Further specific analysis were conducted for outcomes significantly associated with HPV exposure, using alternative case definition and including, when appropriate, a Self-Control Case Series (SCCS) alternative design, additional adjustment for season and calendar year as time-dependent variables, and different sub-events definition according to history of recent infections (defined as reimbursement of medicines suggestive of gastrointestinal or respiratory tract infections in the three months preceding diagnosis, cf. Supplementary Table 4) or specific medications consumption.

All statistical analyses were performed using SAS Enterprise Guide 4.3 and SAS 9.3 software (SAS Institute, North Carolina, USA).

3. Results

3.1. Study population

The study cohort was composed of 2,252,716 girls aged 13.5 years at inclusion who were followed 33 months in mean. Girls vaccinated against HPV during follow-up had higher socioeconomic level, higher level of health care use and received more often vaccinations other than HPV, both at baseline and during follow-up, than unvaccinated girls (Table 1).

3.2. HPV vaccination

Overall, 842,120 girls (37%) were vaccinated against HPV during follow-up, mainly with the quadrivalent vaccine (93%). In means, these were vaccinated at 15 years old (±0.84) and followed 20 months (±11) after vaccination. A three-dose schedule was supplied to around 64% of vaccinated girls, and median intervals between the first and second doses and the second and third doses were approximately 2 and 4 months, respectively (Table 2). Regional variations for HPV vaccination were observed, girls living North-East and North-West regions being more represented among vaccinated.

3.3. Incidence of autoimmune diseases

Overall, 4,096 incident cases of AID were identified during follow-up. Crude incidence rates varied across AID, ranging from

Table 1
Descriptive characteristics of girls included in the cohort.

Characteristics	Total cohort N = 2,252,716		Not vaccinated during follow-up N = 1,410,596 (63%)		Vaccinated during follow-up N = 842,120 (37%)	
Year of inclusion						
2008	1,096,378	49%	599,103	42%	497,275	59%
2009	290,252	13%	164,581	12%	125,671	15%
2010	285,188	13%	185,269	13%	99,919	12%
2011	289,457	13%	214,265	15%	75,192	9%
2012	291,441	13%	247,378	18%	44,063	5%
Age at inclusion, mean (SD)	13.5 (0.87)		13.5 (0.87)		13.6 (0.87)	
Geographical area						
DOM (overseas departments)	90,975	4%	72,080	5%	18,895	2%
Paris region	431,475	19%	296,901	21%	134,574	16%
North-East	515,964	23%	287,731	20%	228,233	27%
North-West	432,591	19%	248,102	18%	184,489	22%
South-East	522,359	23%	348,064	25%	174,295	21%
South-West	259,352	12%	157,718	11%	101,634	12%
Low socioeconomic level[a]	479,228	21%	340,186	24%	139,042	17%
History of health system use during the year prior to inclusion						
At least 1 primary-care visit[b]	2,012,455	89%	1,219,528	86%	792,927	94%
At least 1 specialist visit	1,558,306	69%	919,273	65%	639,033	76%
Mean frequency of outpatient visits after inclusion[c]						
Tertile 1	751,523	33%	623,900	44%	127,623	15%
Tertile 2	749,376	33%	438,756	31%	310,620	37%
Tertile 3	751,817	33%	347,940	25%	403,877	48%
Hospitalisation during study period[d]	483,530	21%	281,738	20%	201,792	24%
Other vaccines						
During the 2 years prior to inclusion	1,182,643	52%	710,511	50%	472,132	56%
During follow-up	900,860	40%	426,657	30%	474,203	56%

[a] Missing index for 97,632 girls, including all girls from DOM-TOM.
[b] General practitioner, paediatrician, gynaecologist or dentist.
[c] Tertile 1: ≤1.9 per year, Tertile 2:]1.9–4 [per year, Tertile 3: ≥4 per year.
[d] At least one hospitalisation from 15 months before inclusion up to 3 months before end of follow-up.

Table 2
Descriptive characteristics of HPV vaccination in the cohort.

Girls vaccinated during follow-up (N)	842,120	
Total number of doses of vaccine	2,076,753	
Follow-up, person-years	1,392,877	
Age at vaccination		
Mean age (SD)	15.0	(0.84)
13 years	53,469	6%
14 years	406,407	48%
15 years	250,131	30%
16 years	132,113	16%
Number of doses per girl vaccinated		
1 dose	148,523	18%
2 doses	152,561	18%
3 doses	541,036	64%
Median interval between doses, in months [IQR]		
1st and 2nd doses	2.3 [1.8–3.4]	
2nd and 3rd doses	4.1 [3.4–5.4]	
Type of vaccine (first dose)		
Gardasil	786,575	93%
Cervarix	55,545	7%
Year of vaccination (first dose)		
2008	211,408	25%
2009	165,499	20%
2010	154,499	18%
2011	108,063	13%
2012	90,849	11%
2013	111,802	13%

0.3 per 100,000 person-years for Sjögren's syndrome, to 15.3 per 100,000 person-years for inflammatory bowel disease (IBD). As shown in Table 3, AID incidence differed according to HPV vaccine exposure for GBS (incidence rate of 1.36 among exposed [20 cases] versus 0.37 per 100,000 PY among unexposed [23 cases], $p < 0.001$) and for IBD (21.04 per 100,000 PY among the exposed [293 cases] vs. 16.90 per 100,000 PY among the unexposed [647 cases]; $p < 0.05$). All the co-factors available for analysis were associated with the risk of autoimmune diseases: vaccinations other than HPV, hospitalisations, health-care seeking behaviour indicators, year of inclusion, geographic area of residence and socioeconomic level.

3.4. Associations between exposure to HPV vaccines and AID

In multivariate analyses, for 12 out of the 14 studied outcomes no association was found with HPV vaccination, with $_a$HRs ranging from 0.70 to 1.07 and non-significantly different from 1. In contrast, HPV vaccination was associated with significantly increased risks of GBS and IBD: $_a$HR of 3.78 [95% CI: 1.79–7.98] ($p < 0.001$) and 1.18 [95% CI: 1.01–1.38] ($p = 0.032$), respectively (Fig. 1). Sensitivity analysis excluding healthcare seeking indicators after inclusion from the model provided similar results (data not shown).

3.4.1. Guillain-Barré syndrome

Among the 43 GBS cases, 40 had required ≥6 days of inpatient hospital stay or two different hospital stays (19 exposed/21 unexposed), and were thus retained for further analysis. Among the 19 exposed GBS cases, 15 (78.9%) had received at least 2 doses of HPV vaccine and 10 (52.6%) had received 3 doses. The median time from exposure to GBS onset was 4.6 months [IQR: 0.9–11.3]. Supplementary figure provides visual distribution of HPV vaccinations and GBS cases over follow-up.

As shown in Table 4, the association between HPV vaccination and GBS was particularly marked in the first 2 months following vaccination and then tended to decrease for longer exposure windows, reaching non-significancy beyond 12 months after vaccination. Consistent results were obtained with an alternative approach using SCCS method (see Table 5). This association did not differ with the type of HPV vaccine or whether or not GBS was preceded by a recent history of gastrointestinal or respiratory tract infection, and remained consistent when the analysis censored observations at the first of any other vaccination during the follow-up (Table 4). Further adjustment for seasonality and calendar year yielded similar results: $_a$HR of 3.94 [95% CI: 1.82–8.56] and 4.05 [95% CI: 1.86–8.80], respectively.

Assuming a causal relationship, and based on our estimated $_a$HR of 3.96, 15 of the 19 exposed cases of GBS in our study would be attributable to HPV vaccination, thus leading to an estimated attributable number of cases of 1.8 per 100,000 girls vaccinated (95% CI [1.1–2.0]).

The median length of hospital stay for GBS in our cohort was 16 days [IQR: 10–21] among vaccinated girls and 12 days [IQR: 8–25] among unvaccinated girls. During hospitalisation, nutritional and life support techniques were equally as frequent among vaccinated and unvaccinated girls (supplementary Table 2). None of the 40 cases died as of Dec 31, 2013.

3.4.2. Inflammatory bowel disease

The association between HPV vaccination and IBD was significant but weak: $_a$HR 1.18 [95% CI: 1.01–1.38]. This association

Table 3
Incidence rates and unadjusted hazard ratios for the association between exposure to HPV vaccination and each event of interest.

	Unvaccinated			After vaccination			Unadjusted HR[c] (95% CI)	
	Person-years	Number of events	Incidence rate[a]	Person-years	Number of events	Incidence rate[b]		
Demyelinating diseases of the CNS	4,746,499	219	5.81	1,393,138	82	5.89	0.98	(0.75–1.29)
Guillain-Barré syndrome	4,746,753	23	0.37	1,393,228	20	1.36	3.62	(1.73–7.59)
Cutaneous or systemic lupus erythematosus	4,746,593	139	3.42	1,393,167	45	3.23	0.97	(0.67–1.39)
Localized or systemic scleroderma	4,746,727	44	1.12	1,393,233	11	0.79	0.70	(0.35–1.39)
Vasculitis	4,746,453	220	4.78	1,393,103	69	4.95	1.07	(0.80–1.44)
Rheumatoid arthritis or juvenile arthritis	4,746,340	308	6.70	1,393,064	99	7.11	1.07	(0.84–1.37)
Myositis or Polymyositis or Dermatomyositis	4,746,739	36	1.07	1,393,232	15	1.08	1.04	(0.55–1.96)
Sjögren's syndrome	4,746,765	13	0.34	1,393,249	5	0.36	1.08	(0.35–3.27)
Idiopathic thrombocytopenic purpura	4,746,505	168	3.67	1,393,203	37	2.66	0.68	(0.46–0.99)
Inflammatory bowel disease	4,745,920	647	16.90	1,392,760	293	21.04	1.27	(1.09–1.47)
Coeliac disease	4,746,575	148	3.19	1,393,157	40	2.87	0.97	(0.66–1.42)
Type 1 diabetes	4,745,780	652	11.53	1,392,826	149	10.70	0.95	(0.79–1.16)
Thyroiditis	4,746,401	272	5.84	1,393,060	87	6.25	1.08	(0.83–1.40)
Pancreatitis	4,746,524	190	4.82	1,393,153	68	4.88	0.96	(0.71–1.29)

[a] Standardized incidence rate (Events/100,000 Person-Years), standardization on the age structure of exposed girls (after vaccination).
[b] Crude Incidence rate (Events/100,000 Person-Years).
[c] Cox regression (age time scale).

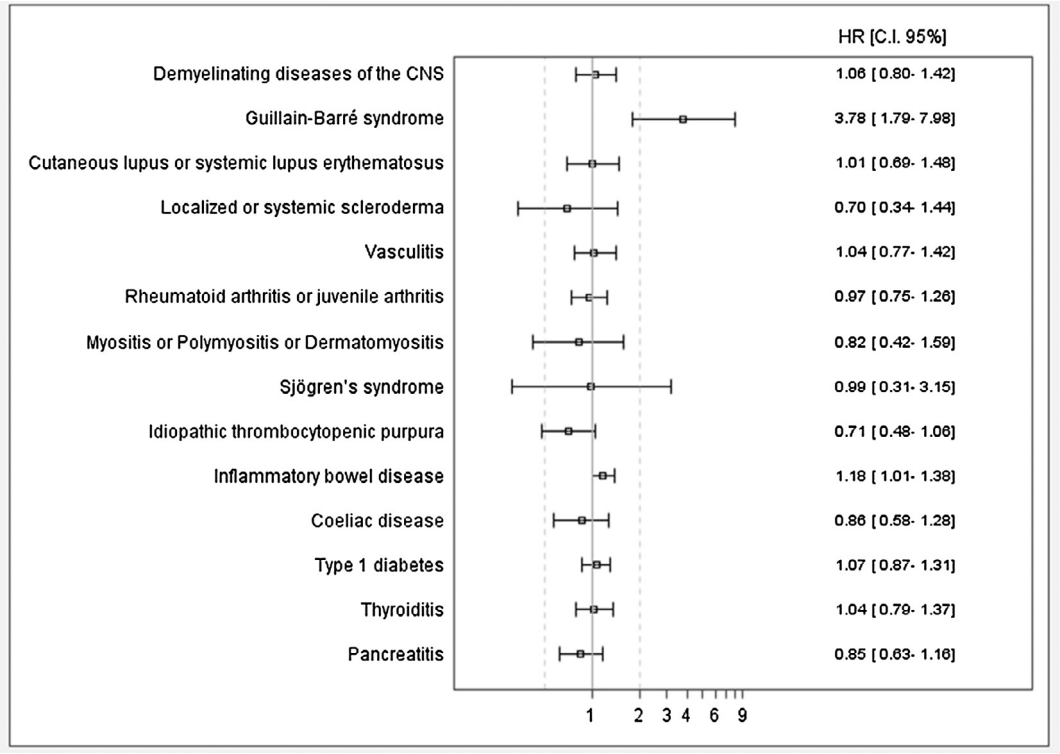

Fig. 1. Association between exposure to HPV vaccination and each event of interest. Hazard ratios are adjusted for age (time scale), year of inclusion, geographical zone, CMUc, history of use of health care and other vaccinations, use of health care and other vaccinations after inclusion.

Table 4
Sensitivity analysis for association between exposure to HPV vaccination and Guillain-Barré Syndrome, under revised case definition (n = 40 GBS cases).

	Unvaccinated			After vaccination			Adjusted HR (95% CI)[c]	
	Person-years	Number of events	Incidence rate[a]	Person-years	Number of events	Incidence rate[b]		
Analysis by risk-windows								
0–2 months	4,746,753	21	0.41	320,890	6	1.87	5.35	(2.01–14.27)
2–12 months	4,746,753	21	0.39	678,765	9	1.33	3.94	(1.58–9.78)
>12 months	4,746,753	21	0.31	393,573	4	1.02	2.43	(0.69–8.54)
Analysis by type of vaccine								
Gardasil	4,746,753	21	0.37	1,323,942	17	1.28	3.78	(1.70–8.41)
Cervarix	4,746,753	21	0.37	69,286	2	2.89	8.08	(1.69–38.61)
Analysis censoring follow-up at other vaccinations[d]	4,127,100	18	0.41	866,8109	12	1.38	4.55	(1.88–11.02)
Analysis according to recent history of gastrointestinal or respiratory tract infections[e]								
GBS preceded by infection	4,746,775	10	0.19	1,393,237	10	0.72	4.52	(1.45–14.03)
GBS not preceded by infection	4,746,766	11	0.18	1,393,240	9	0.65	3.60	(1.24–10.48)

[a] Standardized incidence rate (Events/100,000 Person-Years), standardization on the age structure of exposed girls (after vaccination).
[b] Crude Incidence rate (Events/100,000 Person-Years).
[c] Cox regression (age time scale) adjusted for: year of inclusion, geographical zone, CMUc, history of use of health care and other vaccinations, use of health care and other vaccinations after inclusion.
[d] Analysis censoring observations at the first of any other vaccinations during follow-up.
[e] History of infection defined by the reimbursement of at least one drug suggestive of gastrointestinal or respiratory tract infection in the 3 months prior to GBS diagnosis.

Table 5
Relative incidence of GBS in risk periods following any dose of HPV vaccine (SCCS method).

Risk window	Nr. periods analysed	Control periods			Risk periods			Crude IRR (95% CI)	Adjusted IRR[a] (95% CI)
		Person-Years	Nr. events	Incidence (/100 PY)	Person-Years	Nr. events	Incidence (/100 PY)		
42 days	506	134.3	37	27.6	5.6	6	107.1	3.87 (1,69–8.82)	3.83 (1.67–8.75)
2 months	503	132.0	37	28.0	7.9	6	75.9	2.70 (1.17–6,20)	2.65 (1.12–6,30)
6 months	486	122.6	32	26.1	17.3	11	63.7	2.44 (1.29–4.63)	2.39 (1.21–4.72)

[a] Adjusted for age, A(H1N1) pandemics period (September–December 2009) and winter season known for gastroenteritis/influenza-like epidemics in France (December–March, each year).

was strongest in the first 3 months after vaccination and tended to decrease during subsequent risk-windows (0–3 months: $_a$HR 1.31 [95% CI: 1.04–1.65]; 3–12 months: $_a$HR 1.15 [95% CI: 0.93–1.42]; over 12 months: $_a$HR 1.13 [95% CI: 0.88–1.45]).

3.4.3. Sensitivity analyses

The associations between exposure to HPV vaccines and each of the 14 study outcomes generally did not differ according to the type of HPV vaccine (supplementary Table 3), except for thyroiditis for which a significant increased risk was found after exposure to the bivalent vaccine ($_a$HR: 2.40; IC 95%: [1.25–4.59]) but not after the quadrivalent vaccine ($_a$HR: 0.96; IC 95%: [0.72–1.28]).

Results remained unchanged when observations were censored at the first of any other vaccination during follow-up (data not shown).

4. Discussion

Overall, in this large population-based study cohort including more than 2.2 million young girls, exposure to HPV vaccination was not associated with the occurrence of 12 out of 14 AID of interest. A strong and robust association was found between HPV vaccination and GBS, which was particularly marked in the first months following vaccination. A significant but weak association with IBD was found.

To our knowledge, this is the largest study evaluating the risk of AID after HPV vaccination, thus allowing the assessment of rare diseases risks not investigated previously. Various safety signals regarding HPV vaccines have arisen from clinical case reports or safety reviews [19–22] and from analyses of pharmacovigilance systems as VAERS in the US [23,24], although inconsistently. However, the few pharmacoepidemiological studies conducted to date, based on population-based registries in Northern-Europe [5,6], health care network databases in California [4], or clinical settings in France [7], have failed to confirm these signals. Our results confirm these previous findings for 12 of the 14 studied AID.

As regard to GBS, isolated cases have been reported following HPV vaccination and successive studies based on analysis of reporting rates to VAERS led to inconsistent results [24–26]. Our study is the first population-based epidemiological study suggesting an increased risk of GBS after HPV vaccination. However, most previous epidemiological studies had limited power to study rare events like GBS. Considering these differences in statistical power, our results are not inconsistent with most previous findings, excluding those from a recent case-only study which did not show any increased risk of GBS in England, when analysing over one hundred incident GBS cases in girls aged 11–20 years old [27]. More generally, studies focusing on the risk of GBS associated with all vaccinations [28,29] or with specific vaccines other than HPV [30–34] have provided evidence of an increased risk of GBS following influenza vaccines, either seasonal or pandemic (H1N1), with relative risks of GBS ranging from 1.5 to 4.4 [31–34].

No excess risk of Crohn's disease or ulcerative colitis has been reported in previous studies on HPV vaccines safety. Studies have also failed to show an association with tuberculosis or smallpox vaccines [35], or H1N1 influenza vaccines [36]. However, an increased risk of IBD has been reported following poliomyelitis and pertussis vaccinations [37,38].

Lastly, a post-licensure study conducted at European authorities' request using CPRD database (UK) has recently reported an almost four-fold higher risk of thyroiditis associated with the bivalent vaccine (RR: 3.75 [95% CI: 1.25–11.31]) [39]. Our results from sensitivity analyses, even if based on few exposed cases, are in line with this finding.

Since it was not possible to refer back to patients' medical records due to the anonymous nature of the databases used, GBS cases validity cannot be ensured, but is deemed relatively reliable. First, we applied a more specific case definition for GBS, only retaining cases which required at least 6 days of inpatient stay or 2 different hospital stays, as usually necessary for such a morbid condition. Second, according to this definition, the observed GBS incidence rate among unvaccinated girls (0.4/100,000 person-years) is consistent with previous epidemiological studies [40–43]. Third, the excess risk of GBS we found was stronger during the first months following vaccination consistently with the risk window generally considered as plausible for post-infectious or post-vaccination GBS occurrence [28,34,44,45]. The association tended to decrease after that, but remained statistically significant up to 12 months. This could be due to unmeasurable gaps between the dispensation dates recorded in databases and actual vaccine administration. However, this hypothesis is not supported by other studies having assessed the gap between vaccines dispensation and administration dates [5,46]. Moreover, the very low number of cases in each risk-window require cautious interpretation. We could not measure exposure to A(H1N1) vaccination, which was administrated free of charge during 2009 mass campaign, thus not recorded in our reimbursement databases. Nevertheless, the association remained unchanged in a sensitivity analysis limited to the period prior pandemics, suggesting that A(H1N1) vaccination was not a confounder of the observed association ($_a$HR: 4.05 [IC95%: [1.16–14.16]).

Overall, the strong association found between HPV vaccination and GBS remained very robust across several sensitivity analyses and alternative SCCS design, notably when adjusting for calendar year or seasonality, or when considering the history of recent gastrointestinal or respiratory infections, when censoring when other vaccines occurred, or when limiting analysis to a period prior pandemics vaccination. This suggests that our results are unlikely to be explained by classical confounders in GBS studies, such as 2009–2010 A(H1N1) influenza virus or vaccination, seasonal variations and/or previous respiratory tract infections. However, sensitivity and specificity of our definition of history of recent infections is likely limited, imposing cautious interpretation of results from these sub-group analyses.

As in any observational study, the interpretation of our results in terms of causality should remain cautious. Furthermore, we cannot exclude the possibility of a chance finding. Though, the association remained statistically significant when considering an alpha risk of 0.35% (5% divided by 14) to account for multiple testing. Anyway, even if causal, the increased risk of GBS associated with HPV vaccination is likely to have a limited public health impact. Indeed, given the rarity of the disease, the number of cases attributable to HPV vaccination would be low, i.e. with one to two additional cases per 100,000 vaccinated girls. Moreover, the natural history and prognosis of GBS in children is generally more favourable than in adults [47], associated with high sequelae-free recovery rates [48,49]. Accordingly, in our study no death was recorded after GBS.

Several months are often needed for an IBD diagnosis to be established, notably due to fairly unspecific and non-severe symptoms [45]. It is therefore possible that cases of IBD diagnosed early after vaccination were indeed prevalent cases, erroneously categorized as exposed. Actually, the association between HPV vaccine and the risk of IBD decreased in magnitude over time and was no longer significant neither when censuring the first three months after vaccination ($_a$HR: 1.14 [95% CI: 0.97–1.35]), nor when accounting for multiple testing. Thus, our results do not support a causal association between HPV vaccination and IBD. They may rather reflect a higher level of vaccination uptake among girls that have repeated contact with the health care system due to their

early symptoms of, as yet undiagnosed IBD, resulting in a reverse causality phenomenon.

Because our study is based on comprehensive databases covering the whole French population, among whom approximately 77% are covered by the general insurance scheme, our results are inherently representative and generalizable to the female population aged 13–16 years. Indeed, the associations studied are not expected to vary according to the health insurance scheme. In addition, data are prospectively and independently recorded, avoiding information bias for both exposure and outcomes.

Our study has several limitations though, notably related to the administrative nature of the healthcare data. Firstly, cases validation was not possible among the irreversibly anonymised databases used. In this context, broader ICD-codes including non-autoimmune disorders, was used for the analysis of certain outcomes as thyroiditis or pancreatitis, in order to capture events possibly not properly coded. This less specific definition may have resulted in underestimated HRs. Furthermore, study was mostly limited to more severe or chronic cases which warranted hospitalisation or attribution of a long term illness status. Also, exposure and outcomes dates are inherently inaccurate, since approximated by dispensing dates rather than actual administration ones, and diagnosis date rather than date of disease onset, respectively. Nevertheless, the lag between onset and diagnosis is not expected to strongly bias study results, especially for events with sudden and severe symptoms such as GBS, quickly requiring hospital care. In addition, HPV-vaccinated girls in our cohort had higher levels of healthcare use than those unvaccinated. This may have resulted in a differential surveillance and detection of AID, and thus could have biased our results towards an overestimation of the association between HPV exposure and AID. However, adjustment for healthcare use indicators probably allowed mitigating this potential bias. Finally, residual confounding by unmeasured characteristics, as personal or familiar history of AID that might influence the propensity to HPV vaccination, cannot be excluded, but might have had limited impact. Indeed, overall rate of autoimmune diseases among girls ever vaccinated compared to those never vaccinated was quite similar, suggesting no difference in the underlying risk of those who chose to be vaccinated against HPV. Such confounder could have biased associations towards the null, except for IBD, given vaccination recommendations in this population at higher risk of cervical cancer [50].

Lastly, we chose a standard analysis approach for quite heterogeneous outcomes, without consideration of different epidemiological and clinical characteristics, notably plausible risk windows. In order to mitigate this limitation, more specific analysis were undertaken for every significant association raised by the initial screening.

In conclusion, our study provides reassuring results with respect to the risk of AID after HPV vaccination, confirming the results of previous epidemiological studies. An increased risk of GBS after HPV vaccination is possible, but further studies are warranted to confirm this finding.

Conflict of interest

None.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2017.06.030.

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