PGRX

Pharmacoepidemiologic General Research eXtension

REPORT

ANALYSIS OF CERVARIX® & AUTOIMMUNE DISORDERS USING THE PGRx INFORMATION SYSTEM

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Validation of the report by the scientific committee

I certify that I have validated independently the following report version xxx, xxx 2015, in the context of the Scientific Committee "Cervarix® and autoimmune diseases use the PGRx information system".

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Disclosure

This study was conducted by using the database accrued by the PGRx Information System. This system collects cases of diseases and a reference pool of controls independently of any exposure to drugs. The system and the data collected belong to LA-SER, a private corporation. Interested parties, such as pharmaceutical companies or other organisations, obtain copies of the database (with aggregated data) by a system of subscription. Several parties can subscribe to the same data, for similar or for different purposes. The reference pool is subscribed by all users. This was the case for the study presented here, where cases were subscribed by GSK, which commercialises Cervarix®. Several pharmaceutical companies have subscribed to the system for other studies, including several using part of the cases used in this study and all using the same reference pool (in all or in part).

LA-SER is a private organisation conducting studies or consultancies sponsored by virtually all health product companies internationally and some by regulatory agencies. LA-SER can be mandated to also perform the analysis of the studies conducted with the PGRx Data, and thus to develop the protocols, the SAP and the reporting of the study. This was the case for this study here, under the auspices of two scientific committees: The PGRx scientific Board and the Cervarix® scientific Committee commissioned by GSK and proposed to the French Authorities. The work was conducted totally independently. GSK had no impact on the protocol, the SAP, the analysis or the reporting.

The study followed the code of conduct of the ENCePP, a network to which LA-SER, and notably PGRx are members

Summary of the report

1. Context

A surveillance program of the vaccination of young women against human papillomavirus (HPV) vaccine was requested by French health authorities (DGS, ANSM & HAS) in agreement with GSK since the marketing authorisation of Cervarix®:

- From 2008 to April 2013, Cervarix® targeted population by the CT covered girls aged 14 to 17 years-old and young women up to 25.
- Since April 2013, Cervarix® was recommended by the HCSP also to girls aged 11 to 14 years-old

A large widespread vaccination program was expected at that time in the considered specific age group, corresponding to the incidence of a number of autoimmune disorders (AIDs). The need to distinguish the fortuitous occurrence of an AID from any outbreak of AID associated with HPV vaccination was mandatory to French health authorities. GlaxoSmithKline (GSK) subscribed to the PGRx system to obtain the data used in this study. GSK asked the LA-SER research team to propose study protocols for each outcome under study and statistical analytical plans, and to conduct these analyses and write the related reports.

2. Objectives

The study had two objectives:

- To conduct a 'Surveillance Study' consisting in the identification of all consecutive cases of AID in patients between 11 and 25 y.o. in a large sentinel network of PGRx–AID centres, from April 2008 to September 2014 ;
- To conduct a 'Risk Study' to assess the risk of HPV vaccination and Cervarix® in AID occurrence.

3. Methods

Design

- Surveillance Study: Monitoring of a large number of centres specialised in the considered autoimmune diseases, including referral centres in the country, for the occurrence of AID and their exposure to HPV vaccine and Cervarix®.
- Risk Study: Systematic case-referent study for the assessment of risk of AID occurrence associated with the use of an HPV vaccine and Cervarix®, using the PGRx (Pharmacoepidemiological General Research eXtension) methodology.

Case-patients

The diseases considered for this study cases are the following:

- Central demyelination/ Multiple sclerosis (CD/MS)
- Guillain-Barré syndrome (GBS)
- Inflammatory arthritis, lupus erythematosus and myositis and dermatomyositis – Grouped as Connective Tissue Diseases (CTD)
- Type 1 diabetes (T1D)
- Autoimmune thyroiditis and Graves' disease (AIT)
- Idiopathic thrombocytopenic purpura (ITP)

All consecutive cases of studied AIDs were identified by board-certified specialists. Cases were classified as 'definite cases' and 'possible cases'.

Among all autoimmune disorders cases recruited by specialists participating in the PGRx System, case patients eligible for the Cervarix® study fulfilled the following inclusion criteria:

- Female, aged from 14 to 25 years-old from 01/04/2008 to 14/04/2013; Age 11 to 25 years-old from 15/04/2013

Exclusion criteria for cases:

- Any history of the relevant autoimmune disease with evidence
- Patient not able, or their proxy not able to, to read and answer a phone interview in French
- Refusal to participate in the study

Control-patients

Controls were defined as patients who reside in the same regions as cases and seen by a participating general practitioner (GP) with no restriction as to the reasons for consultation.

Control patients fulfilled the following *general inclusion criteria*:

- Female, aged 11 to 25 years old (inclusive)
- Resident in France

Controls did not meet the following *general exclusion criteria*:

- Patient is not able to, or their proxy not able to, read and answer a phone interview in French
- Refusal to participate in the study

In addition, for each autoimmune disease under consideration, patients who had a history of such disease in the pool of referents were excluded as potential controls for the cases of this disease.

Eligible controls meeting all inclusion and exclusion criteria were matched with the cases. A maximum of 10 controls are matched to each case on the following factors:

- Date of first symptom for cases and date of recruitment in the study for controls.
- Age
- Place of residence

Exposure assessment

- Guided interview of patients or proxies using the PGRx System interview tools, questionnaires and method (progressive backward active recall)
- Copies of vaccination booklets, prescriptions, physicians certificate and other objective information on vaccine use were collected to conduct validation studies on interviews
- Validation studies showed 100% agreement for Cervarix® and 98% agreement for HPV vaccines.

Risk factors

Risk factors to investigate:

- Smoking
- Alcohol consumption
- Geographical origin (Northern Europe or North America, Southern Europe or Africa or others, Mixed or Missing)
- Personal or familial history of AID (Yes, No, Don't know / Missing)
- Vaccines received except HPV in the 2 years before index date (Yes, without date / Index date, No)
- Any use of estroprogestatives/contraceptives before index date (Yes, No)

Apart from smoking and alcohol, all the other risk factors have been taken into account in the analysis (modelling and stratification).

Data collection

Physicians entered information on consenting patients using a detailed e-CRF (eCRF for each AID and eCRF for general practice patients were provided)

Centres were all audited to check the consecutive recruitment of each centre and to perform source data verification.

Patients were interviewed by trained centres monitored by research team.

Sample size

- Target N cases: 624 cases.
- Target N controls: 2496.

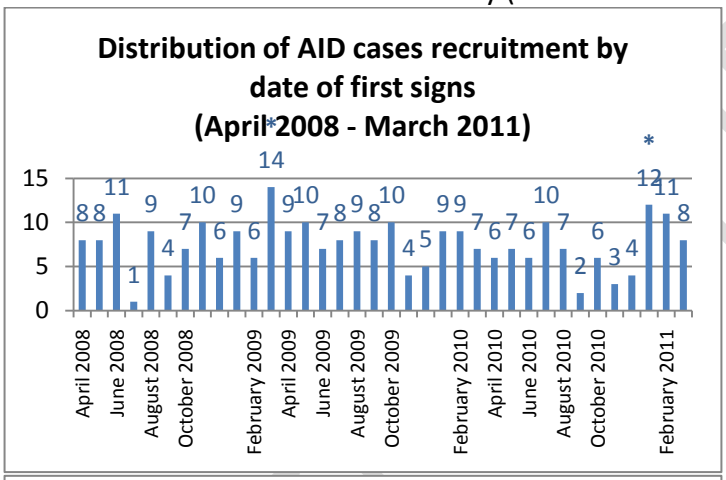
Analysis

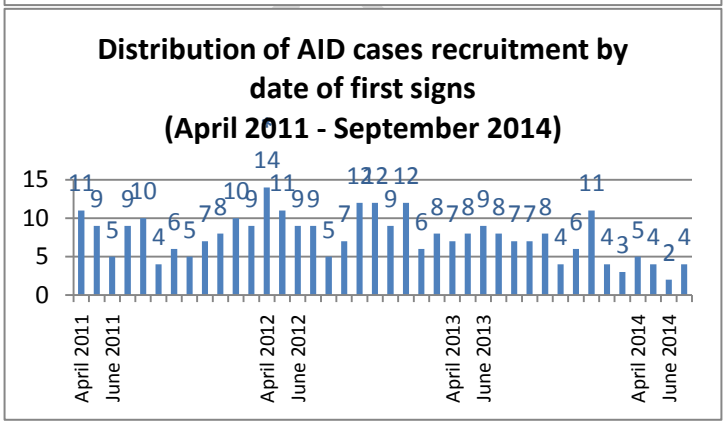
- Descriptive analysis of cases, referents, centres,
- Crude matched odds ratios estimated through conditional logistic regression. Multivariate analysis adjusted on geographical origin, personal or familial history of AID, vaccines received except HPV in the 2 years before index date, any use of estroprogestatives/contraceptives before index date.
- To further investigate potential confounding, stratified analyses on geographical origin in the one hand and personal or familial history of AID on the other hand were also conducted.

4. Results

Surveillance Study

The monitoring of 299 centres identified 3131 cases of which 705 were females aged 11 to 25 yo, of which 574 were initially eligible for the study. The monthly distribution of these 574 cases showed variations but annual stability (around 95 cases per year).





Two population-density methodologies identified peaks of AID occurrence significantly departing from expectations. Both methods concurred to identify significant variations over time in the number of cases of AID occurring over more than 6 years of surveillance. None of the peaks was attributable to HPV vaccine or Cervarix® use.

Risk Study

1953 controls could be matched to 510 fully documented eligible cases; out of these, 418 cases were definite and had 1869 controls matched.

In the General analysis, using the definite and possible cases (n= 510) which could be matched to controls (n=1953) and considering any use of HPV vaccine before index date, the adjusted odds ratio was 0.64 (95% CI 0.49, 0.83). The same General analysis applied to any use of Cervarix®, the crude odds ratio was 0.30 (95% CI 0.07, 1.27).

Table below presents the Main analysis, using definite cases (n= 478) matched to 1869 controls and considering HPV vaccine exposure in the primary time-windows at risk.

Table. HPV vaccine exposure (at risk TW/past TW/Not exposed) in the primary time-window at risk for definite cases of AID (individually and all combined) and their matched controls and corresponding odds ratios

Exposure	Cases n (%)	Controls n (%)	Matched Crude OR 95% CI	Matched Adjusted* OR 95% CI
At risk time-window – DEFINITE CASES				
HPV vaccines				
CD/MS (113/863)	7 (6.2%)	173 (20.0%)	0.28 [0.12 - 0.64]	0.31 [0.13 - 0.73]
CTD (92/769)	14 (15.2%)	147 (19.1%)	0.78 [0.40 - 1.52]	0.84 [0.41 - 1.73]
GBS (13/130)	0 (0.0%)	2 (1.5%)	-	-
T1D (86/804)	14 (16.3%)	189 (23.5%)	0.56 [0.30 - 1.06]	0.61 [0.32 - 1.17]
AIT (97/802)	6 (6.2%)	126 (15.7%)	0.28 [0.11 - 0.74]	0.35 [0.13 - 0.92]
ITP (77/698)	11 (14.3%)	87 (12.5%)	1.18 [0.58 - 2.42]	1.17 [0.56 - 2.41]
ALL (478/1869)	**52 (10.9%)**	**421 (22.5%)**	**0.54 [0.38 - 0.75]**	**0.58 [0.41 - 0.83]**

CD/MS: central demyelination/multiple sclerosis; CTD: Connective tissue disease; GBS: Guillain-Barre Syndrom; AIT: autoimmune thyroiditis; T1D: Type 1 diabetes; ITP : immune thrombocytopenic purpura ; ALL : All AID combined.

*: Conditional logistic regression on matched case-control sets adjusted for age, fphaid, geographic origin, any use of estroprogestatives/contraceptives before index date, number of vaccines other than HPV received within two years before the index date

In the Main analysis, using all definite cases (n= 478) which could be matched to controls (n-1869) and considering Cervarix® exposure in the primary time-windows at risk, the crude odds ratio was 0.50 (95% CI 0.12, 2.19). Odds ratios for each individual AID could not be calculated due to a very low use of Cervarix®.

5. Discussion

- Largest study of autoimmune disorders in young females, with clinical recruitment and confirmation of diagnosis
- None of the associations showed a statistically significant increase of risk
- Variable results were observed for the association between individual autoimmune disorders and vaccination by HPV
- A statistically significant lower odds ratio was observed for multiple sclerosis and autoimmune thyroiditis and HPV vaccination, which is discussed further below.
- Overall, a statistically significant lower odds ratio was observed for all studied AID and HPV vaccination, which is discussed further below.
- Results for Cervarix® alone did not seem to differ from those observed for all HPV vaccination; however the exposure of cases was small (only 2 AID cases exposed).

Cases

- Recruitment targets were achieved globally (705 vs an objective of 624 for the 2 periods).
- Recruitments were variable according to the disease:

    - Targets achieved for CD/MS, T1D, AIT and ITP
    - Targets were not achieved for CTD and GBS
- Diagnostic certainty was highly specific with only 0.9% rejected cases.
    - Validation of cases showed that specialists ensured a high clinical quality of cases all over the study recruitment.
    - Possible cases are likely to be confirmed with follow-up as they are recruited on first symptoms and classified as AID based on specialists' opinion.

Referents & Controls

- Recruitment targets of referents and controls were achieved globally, PGRx referents providing a sufficient number of matched controls, above targets.
- Appropriate matching occurred for all individual disorders and for all AID combined, with an average of matched controls per cases close to target (4 expected).
- Cases and control series were very similar on factors of interest except for variable potentially associated with risk (eg: history of autoimmune disorders, exposure to vaccines).

Risk factors

- A personal or familial history of autoimmune disorder was a strong risk factor for all AID combined (OR= 1.86 [95%CI: 1.33 - 2.60], however it showed variations between individual AID.
- Southern origin (both parents) was associated with a higher risk of AID (OR=3.68 [95%CI: 2.76 – 4.89]).
- Smoking and alcohol use were not associated with the risk of AID.

Exposure

- Average exposure of referents is consistent with sales figures globally with a 5% difference; Differences with sales figures may be underreporting by patients, overestimation of actual use by sales figures due to non-adherence to prescription; if true, this difference would be artificially inflating the estimation of the risk.
- Curves and dynamic of exposure by birth cohort were close to expectations.
- The exposure of referents to Cervarix® was low over the whole period (1.5%), although increasing proportionally recently (3.1% in the phase II of the study).
- Propensity of use of an HPV vaccine was not significantly different in patients with a personal or familial history of autoimmune disorder than in patients without such an history or not knowing about this history (OR= 1.18, – 95%CI: 0.83-1.68).
- Propensity of use an HPV vaccine was significantly lower in persons with a geographical origin from Southern countries (OR= 0.53 [95%CI: 0.36 - 0.76]).
- Use of other vaccines was significantly associated with the propensity to use HPV vaccines (OR= 1.32 [95%CI: 1.09 - 1.59]).
- The use of an oral contraceptive was associated with the probability to be exposed to HPV vaccination (OR= 1.73 [95%CI: 1.39 - 2.14])

Confounding

- A higher probability of exposure to HPV vaccine may exist in patients with a higher risk of autoimmune disorder due to personal or familial history of AID.
- Conversely, patients from Southern origin, who show a higher risk of certain AID, may also be less likely to use HPV vaccines.
- Other markers of potential confounding are other vaccination and use of oral contraceptives.
- Analyses stratified by geographical origin and by history of AID did not display significantly different estimates than the multivariate analyses adjusted for all potential confounders

- Remaining, unmeasured, confounding cannot be excluded to explain the lower risk observed for HPV vaccines and certain AID.

6. Conclusion

- No increased risk of autoimmune disorder was observable as associated with HPV vaccination.
- The results observed with the lower used vaccine (Cervarix®) were in accordance with observations in the overall sample.
- The apparent lower risk observed with the occurrence of multiple sclerosis/central demyelination and autoimmune thyroiditis has to be further explored as it could be due to remaining unmeasured confounding, chance or, protection conferred by the vaccination itself.

List of abbreviations used in the reports

AAb – auto antibodies
Ab - antibody
ACR – American College of Rheumatology
Ag – antigen
AID – autoimmune disorder
AITD – autoimmune thyroid disorders
Anti-IA2 – antibody to tyrosine phosphatase ICA 512
Anti-DNA – antibody to deoxyribonucleic acid antigen
Anti-dsDNA – antibody to double-stranded deoxyribonucleic acid antigen
Anti-ECT – (Extrait de cellule thymique) (Soluble nuclear antigen antibodies)
Anti-GAD – antibody to glutamic acid decarboxylase
Anti-RNP - antibody to ribonucleoprotein
Anti-Sm – anti-Smith antibody
Anti-TG – anti-thyroglobulin
Anti-TPO – anti-peroxydase
CD – central demyelination
CDC – Centers for Disease Control and Prevention
CDMS – central demyelination/multiple sclerosis
CHU – centre hospitalier universitaire
CI – confidence interval
CMV – cytomegalovirus
CNS – central nervous system
CPK – creatine phosphokinase
CSF – cerebrospinal fluid
CT – Commission de Transparence
CTD – connective rissue diseases (or disorders)
DREES - Direction de la Recherche, des Etudes, de l'Evaluation et des Statistiques
EBV – Epstein-Barr virus
EMA – European Medicines Agency
EMG – electromyography
ENCePP - European Network of Centres in Pharmacovigilance and Pharmacoepidemiology
fhaid – family history of autoimmune disorder
f/pHAID – family or personal history of autoimmune disorder
GBS – Guillain Barré Syndrome
GP – general practice
GSK - GlaxoSmithKline
HBS – hepatitis B serology
HCSP – Haut Conseil de Santé Publique
HCV – hepatitis C virus
HIV – human immunodeficiency virus
HLA – human leukocyte antigen
HPV – human papillomavirus
IA – inflammatory arthritis
ICA – islet-cell antibodies

ICD – International Classification of Diseases
ICSA – islet-cell surface antibodies
IdF – Ile de France
IgG – immunoglobulin G
ITP – idiopathic thrombocytopenic purpura
K – kappa statistic
MCV – mean corpuscular volume
Mo – month
MRI – magnetic resonance imaging
MRS – multivariate risk score
MS – multiple sclerosis
NA – not applicable
NC – not calculated
OC – oral contraceptive
OR – odds ratio
p/fhaid – personal or family history of autoimmune disorder
PDS – Pharmacoepidemiology and Drug Safety
PedIA – pediatric inflammatory arthritis
PGRx – Pharmacoepidemiologic General Research Extension
RA – rheumatoid arthritis
SD – standard deviation
STEMI/NSTEMI – ST-elevation myocardial infarction and non-ST-elevation myocardial infarction
T1D – Type 1 diabetes
T1DM – Type 1 diabetes mellitus
TSH – thyroid-stimulating hormone
UC – undifferentiated connectivitis
UK – United Kingdom
US – United States
y.o. – years-old

SECTION 1. GENERAL METHODS

PGRx- International Scientific Committee

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Cervarix® & autoimmune disorders - Scientific committee

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1. Study background and objectives

1.1 Background

A surveillance program of the vaccination of young women against human papillomavirus (HPV) vaccine was requested by French health authorities (DGS, ANSM & HAS) in agreement with GSK since the marketing authorisation of Cervarix®

- From 2008 to April 2013, Cervarix® targeted population by the CT covered girls aged 14 to 17 years-old and young women up to 25.
- Since April 2013, Cervarix® was recommended by the HCSP also to girls aged 11 to 14 years-old

A large widespread vaccination program was expected at that time in the considered specific age group, corresponding to the incidence of a number of autoimmune disorders. The need to distinguish the fortuitous occurrence of an AID from any outbreak of AID associated with HPV vaccination was mandatory to French health authorities

The PGRx system recruits cases and referents of diseases independently of sponsoring, under the auspices of an International scientific board and with funding by the LA-SER Group. Several subscribers use the system and the data are multipurpose.
GlaxoSmithKline (GSK) subscribed to the PGRx system to obtain the data used in this study.
GSK asked the LA-SER research team to propose study protocols for each outcome under study and statistical analytical plans, and to conduct these analyses and write the related reports. Finally, GSK organised a scientific committee to supervise this study.

1.2 Background documents

The methodology presented here is a summary of the methods applied in the conduct of the study program. Eight protcols are appended to this report, corresponding to the methods used for the study of each of the autoimmune disorders considered in this study. These protocols provide a very detailed methodology for each study. In addition, the statistical analyses are detailed further below. Departures from these protocols were minimal and applied only when made necessary by the actual conditions of the study and of its recruitment; they are identified in this document.

1.3 Objectives of the research program

The research program monitored a large number of specialty centres in France for the occurrence of the following autoimmune disorders in females 11-25 years old: central demyelination / multiple sclerosis, Guillain-Barré Syndrome, lupus, rheumatoid arthritis, undifferentiated connectivitis, myositis and dermatomyositis, type 1 diabetes, auto-immune thyroiditis (Grave-Basedow and Hashimoto diseases), immune thrombocytopenic purpura.

1.3.1 General objectives

The study had two general objectives:

(i) To conduct a 'Surveillance Study' consisting in the identification of all consecutive cases of AID in patients between 11 and 25 y.o. in a large sentinel network of PGRx–AID centres, from April 2008 to September 2014 ;

(ii) To conduct a 'Risk Study' to assess the risk of HPV vaccination and Cervarix® in AID occurrence.

1.3.2 Specific objectives

The specific objectives of the 'Surveillance study' were:

(i) To monitor a large number of centres (target 200+) recruiting patients with defined AID in France and identify all cases of eligible AID observed in these centres since April 1st, 2008 and for more than 6 years thereafter.

(ii) In case of presence of a peak of AID occurrence during recruitment, the proportion of HPV vaccine and specifically Cervarix® use were assessed in order to see if there is an abnormal proportion compared to the months where no peak had occurred.

The specific objectives of the 'Risk study' were:

(i) To assess whether the use of Cervarix® and HPV vaccination is associated with a modified risk of autoimmune disease

(ii) To assess whether the use of Cervarix® and HPV vaccination is associated with a modified risk for each individual AID:

- Central demyelination/ Multiple sclerosis (CD/MS)
- Guillain-Barré syndrome (GBS)
- Inflammatory arthritis, lupus erythematosus and myositis and dermatomyositis – Grouped as Connective Tissue Diseases (CTD)
- Type 1 diabetes (T1D)
- Autoimmune thyroiditis and Graves' disease (AIT)
- Idiopathic thrombocytopenic purpura (ITP)

(iii) To assess the contribution of known risk factors for AID.

2. Summary of the PGRx system

The system and method has been described in detail in the study protocols appended and in recent publications (Grimaldi et al, Arthritis Rheumatol. 2014; Grimaldi et al, Ann Rheum Dis. 2014; Grimaldi et al, J Intern Med. 2014 ; Grimaldi et al, Int J Cardiol. 2013 ; Grimaldi et al, Blood. 2012 ; Grimaldi et al, American Journal of Epidemiology, 2011).

PGRx is a system collecting data independently of any sponsorship (except that of LA-SER) and employing systematic case-control methodology. It was developed to study disorders and events which are potentially associated with medicines, and which are infrequent and/or of delayed onset. It was developed in response to the paucity of databases and information systems available to study such events with sufficient specificity and power. PGRx has been operating since late 2006, is currently available in France, Canada, the UK, Germany, Italy and Spain for different diseases.

The system prospectively and routinely collects incident autoimmune disorders cases among other disorders[1], from more than 200 specialised referral centres. Case patients are recruited

[1] The following diseases are currently routinely surveyed: myocardial infarction (STEMI & NSTEMI), multiple sclerosis (first central demyelination), Guillain-Barré syndrome, lupus erythematosus, myositis and dermatomyositis,

systematically among the patients referred to these participating centres, whether they are referred for diagnosis, disease management or hospitalisation. Investigators are instructed to propose participation to all consecutive patients presenting during defined calendar periods of time to their centres and who comply with the inclusion and exclusion criteria for the disease at hand.

A stratified sample of patients representative from general practices (the 'Reference Pool') is also recruited each year. It serves as a source of potential controls. For that purpose, controls are selected from this pool and matched to cases of diseases under study.

Cases and referents are documented on their medical conditions and history by their recruiting physicians, using specially designed web-based forms. Selection biases are minimised through a large series of procedures. At least 250 of the most commonly used and/or newly marketed drugs (including vaccines) are documented through: (i) guided telephone interviews and (ii) medical prescription records and/or other objective confirmation of exposure. Almost all vaccines are documented routinely; Cervarix® was among studied vaccines. (See Exhibit 1A for list of drugs and vaccines studied by dates).

A series of behavioural, medical and family risk factors are also ascertained routinely for all cases and referents.

Cases and controls, selected from the pools of cases and referents can be compared with respect to their exposure to one or more drugs, while taking account of known risk factors for the condition under study, to investigate any potential associations between the drug(s) and the condition.

Several PGRx Pathology Specific Scientific Committees determine the elements of data and the research methodology recommended for the study of each autoimmune disease. These committees are composed of experts in the contemplated disorder and work independently from any sponsor (lists are provided with each disease studied in this report).

All data are collected independently from sponsors and are shared widely through subscriptions and/or for academic purposes. The collection of data used for this study was thus totally independent from GSK or any other pharmaceutical group. Moreover, the analysis was also conducted totally independently from GSK or any pharmaceutical group, following the rules and code of conduct of the ENCePP (European Medicine Agency European Network of Centres in Pharmacovigilance and Pharmacoepidemiology).

PGRx/LA-SER is a member of the EMA ENCePP network and applies its code of conduct to all studies. PGRx is also a participating member of EMA's PROTECT program.

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inflammatory arthritis, unspecified connectivitis, type I diabetes, thyroiditis (Basedow and Hashimoto), thrombocytopenia, suicide attempts, major depression, long QT & torsade de pointes, breast cancer, acute liver injuries, atrial fibrillation and stroke.

3. Autoimmune disorder cases

3.1 The PGRx Network for recruitment of AID cases

The PGRx Network for autoimmune diseases comprises University Health Centres; General Hospitals and private clinics that have a specialised unit or a health care network for the management of autoimmune disease.
The PGRx Network for the recruitment of autoimmune diseases cases allows observing a potential unusual accrual of the studied diseases during the study period (closed in 26 September 2014) in young females (monitoring goal viewpoint).

3.2 Source population for the cases

Case patients meeting the inclusion and exclusion criteria retained for this study (see below) were identified amongst all AID cases recruited. These individuals may have been referred to these participating centres for diagnosis, disease management or hospitalisation. Investigators were instructed to propose participation to all incident cases consecutively, during a given time period, presenting to these centres who complied with the inclusion and exclusion criteria for the study.

Centres participating in the PGRx Network are contacted at least once per month by research assistants or by project manager (with either a site visit or a telephone call or an e-mail), to foster the completeness of the recruitment during the periods of recruitment of the centres. An audit of recruitment and data quality was performed for recruiting centres; a period of two months was randomly selected for this audit.

The recruiting physician completed a medical data form for each case patient recruited. Each case patient also nominated his or her treating physician. This physician was approached by the research team and asked to complete the following information: chronic diseases and comorbidities, medical risk factors, and prescriptions for the previous two years.

3.3 Eligibility criteria for cases

For autoimmune disorders cases, the following eligibility criteria have been applied during recruitment by specialists participating in the PGRx System:

- Female and male
- Age 0 to 79 years old (inclusive) - Age 0 to 49 years old for T1D and autoimmune thyroiditis
- Incident case with diagnosis consistent with case definition
- Resident in France

Among recruited cases, case patients eligible for the Cervarix® study fulfilled the following additional inclusion criteria:

- Female, aged from 14 to 25 years-old from 01/04/2008 to 14/04/2013; Age 11 to 25 years-old from 15/04/2013

NB: the inclusion criteria changed in April 2013 with the change of HPV vaccination recommendations from the HCSP

Exclusion criteria for cases:

- Any history of the relevant autoimmune disease with evidence

- Patient not able, or their proxy not able to, to read and answer a phone interview in French
- Refusal to participate in the study

Also excluded were patients with missing information on any of the above inclusion or exclusion criteria, as well as patients without any medical information recorded.

3.4 Levels of diagnostic certainty

The diagnostic certainty was adapted from internationally accepted definitions for each disorder to allow for the recruitment of cases at the early stages of the disease and to account for the age groups concerned. Levels of diagnostic certainty were assigned for each disease through clinical algorithms defined by the Cervarix® scientific committee.

Using these criteria, each case was defined (automatically or by a clinician) and independently from vaccine use, as a:

- Definite diagnosis
- Possible diagnosis, reflecting either:
    - Incomplete information or
    - Symptoms which may or may not evolve into a definite diagnosis
- Rejected diagnosis

Those cases who could not be classified directly in these categories were reviewed with the recruiting specialist and if needed by two independent experts blind to the medications and vaccinations status of each case. They were then classified as definite, possible or rejected.

PGRx centres were contacted to assess the potential evolution of the diagnoses, up to one year after each case was reported. Any change in the diagnosis of a case until the database was locked was recorded and the case was reclassified as a definite diagnosis, a possible diagnosis, or was rejected.

3.5 Monitoring and audit of the centres for recruitment of cases

The audit focused on centres that had recruited at least one female aged between 11 and 25 years old. These centres were visited by a PGRx research assistant for the control of quality.

The objectives of the audits were:

1. To check that the recruitment of cases had been done consecutively through the audit of a randomly defined time period of two months within the period of recruitment of the centres.
2. To control the quality of the data entered for cases recruited during this same randomly defined period

During the study, participating physicians were asked to invite all eligible case patients to participate to the study; patients who had not been included in the study for a reason other than one of the exclusion criteria had to be registered in the registry of eligible, non-included cases. This registry included patient's age, gender, some clinical items and reason for non-inclusion.

A research assistant was sent to each sampled centre to conduct the audit. For audit objective 1, the research assistant checked whether all incident patients seen in the centre during the audited

period were either recorded in the registry of non-participants by the physician or included in the study.

For the second audit objective, the medical data form of the cases included during the audited period was compared with source data.

4. Controls

Controls used for the study were selected from a reference pool routinely assembled in PGRx.

4.1 Reference pool

Each year, a network of general practitioners (GPs) and paediatricians recruits a pool of patients in the PGRx system. These GPs were contacted after being randomly selected from the French national list of GPs. They practice in the same regions as the specialty centres participating in the PGRx Network for autoimmune diseases. A stratified representation of their practice was sought by the recruitment during a defined period each, of the first male and the first female who presented to their practice and accepted to take part in the study, within the following age categories:

- 14-17, 18-34, 35-49, 50-64, and 65-79 years-old;
- 11-13, 14-15, 16-17, 18-19, 20-21, 22-23 and 24-25 years-old;
- 0-2, 3-6, 7-10, 11-13 and 14-17 years-old.

The patients were recruited without reference to reasons for consulting a GP, and independent of morbidities or exposures. Recruitment rotated among different general practices throughout the year. This registry of patients constituted the Pool of Referents (or 'Reference Pool') from which controls matched to cases were selected.

The GP physician completed an electronic data form for each recruited patient including the following information: chronic diseases and comorbidities, medical risk factors, biological data, and prescriptions for the previous two years.

4.2 Selection of controls

4.2.1. Eligibility

Controls were defined as patients who reside in the same regions as cases and seen by a participating general practitioner (GP) with no restriction as to the reasons for consultation.

Control patients fulfilled the following *general inclusion criteria*:

- Female
- Age 11 to 25 years old (inclusive)
- Resident in France

Controls fulfilled the following *general exclusion criteria*:

- Patient is not able to, or their proxy not able to, read and answer a phone interview in French
- Refusal to participate in the study

In addition, for each autoimmune disease under consideration, patients who had a history of such disease in the pool of referents were excluded as potential controls for the cases of this disease.

Also excluded were patients with missing information on any of the above inclusion or exclusion criteria, as well as patients without any medical information recorded.

For controls, eligibility criteria and matching rules have been applied during the draw of study controls from the pool of referents.

4.2.2 Selection of controls for the analysis

Reference pool

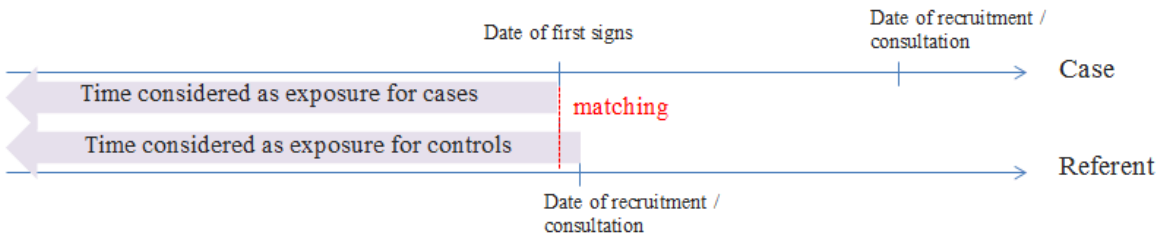
Patients from the PGRx reference pool meeting the general eligibility criteria constituted the reference pool for this study. Controls were drawn from this pool to be matched to cases. First, a set of controls was drawn from the reference pool for the sample of all cases of autoimmune disorders combined. After these patients were reintroduced in the reference pool, a set of controls was drawn from the pool for each indicidual autoimmune disease studied. Controls for each of the samples of autoimmune disorders were taken separately (central demyelination, connective tissue diseases, Guillain Barré, T1 diabetes mellitus, autoimmune thyroid disorders, thrombocytopenia). Thus, the same person could serve as referent to different cases of autoimmune disorders as long as they were studied separately, while when all AIDs were considered together, each referent considered could be matched to only one case.

Matching

Eligible controls meeting all inclusion and exclusion criteria were matched with the cases. A maximum of 10 controls are matched to each case to reach an average of 4 matched controls per case, on the following factors:

1) Date of first symptom for cases and date of recruitment in the study for controls. Controls are chosen from the same trimester as the case, or from the two subsequent trimesters. Controls are preferentially chosen from the closest trimester to the case.

Matching on the date of the first symptom for cases and the date of recruitment for controls, the 'index date' being the date of the first symptom for cases and date of recruitment for controls.



The rational was a trade between minimizing potential information bias (especially recall bias), and having a comparable length of observation time-window for both the case and her matched controls. Indeed, as the interview is performed after recruitment, the time between index date and interview could for instance be longer for cases than controls which could lead to a diiferential recall of drugs use; however this is deemed to be unlikely to occur as the exposure of interest is a

vaccination with a shot at a point in time and as vaccinations dates are confirmed through an objective source.

2) Age:

- For cases aged ≤ 17 years, controls were chosen aged ± 1 month, ± 3 months, ±6 months, or ±1 year from the case's age.
- For cases aged ≥ 18 years, controls were chosen aged ±1 year, or ±2 years from the case's age.

Controls were preferentially chosen with ages closest to the case's age.

3) Place of residence: North and South (defined by telephon regions) cases were matched to referents of the same region, if necessary matching were performed with referents from contiguous regions; if necessary, referents from all France were considered.

For each drawing of a given case-control set, eligible controls were identified at random from the pool of referents. Selected referents were then individually matched to cases using an iterative matching process. Controls were dropped from the pool after matching for the considered set. In each set, cases for which no controls could be matched were not used in the main analysis but were retained for descriptive purposes.

5. Clinical data collection for case and control patients

5.1 Medical data form for the cases

Clinical data collection for the eligible patients with first autoimmune disorders was done by specialists and contained information on whether patient was included or not in the study and the reason for non-inclusion.

For included patients with a signed consent form, the following information was recorded on the PGRx secured website by the specialists or their team:

- Consent form dated and signed by the patient with consent on every step of the study and more particularly on permission to contact the treating physician
- gender and age, date of birth
- Patient's contact information and preferred time for phone interview
- Contact information of treating physician
- Inclusion and non-inclusion criteria
- Date of first episode evocative of an autoimmune disorders (at least month and year)
- Symptomatic description of the event
- Results of the clinical examination
- Results of imaging, if applicable
- Results of laboratory tests, if applicable
- Medical history
- History of autoimmune disease in first degree relatives (CNS demyelination only)
- List of comorbidities

5.2 Medical data form for the referents

Data collection for the included referents was done by participating GPs and contained:

- Contact information of the participating GP (name, gender, place of practice)
- Gender and age
- Date of birth
- Patient's contact information and preferred time for phone interview
- Date of consultation (day, month, year)
- Reason for consultation
- Prescriptions during two years preceding the date of consultation (extract of the electronic medical file of the physician)
- List of comorbidities (including autoimmune disorders)

6. Risk factors

The risk factors studied are described in Table 1 below.

Table 1. Potential Risk factors studied

Risk Factors	Definition
Socio-Demographic Risk Factors	
Age (matching variable)	11-17 years, 18-25 years, mean, median, interquartile range, range
Region of residence (matching variable)	North/South, telephon regions ("01", "02" and "03" were considered as North and "04" and "05" were considered as South; for patients who provided only mobile phone number the post code was considered)
Geographical origin	Region of birth of patient's parents defined in 3 categorises : Northern Europe or North America (both parents) Southern Europe or Africa or others (both parents) Mixed or Missing
Social status	Lives alone / Lives with at least one person
Professional status	Employed, Unemployed, Students
Medical Risk Factors	
Family history of autoimmune disorder	Yes, no, don't know. Including the following in first degree relatives: multiple sclerosis, lupus, rheumatoid arthritis, Crohn's disease, ulcerative colitis, autoimmune thyroiditis
Personal history of autoimmune disorder	Yes/no. Including the following AIDs : central demyelination/multiple sclerosis (CD/MS), Guillain-Barré syndrome (GBS), inflammatory arthritis/rheumatoid arthritis, lupus, myositis, type 1 diabetes (T1D), autoimmune thyroiditis, immune thrombocytopenia
Any use of estroprogestatives /contraceptives before index date	Yes/no ATC codes considered G03A, G03C, G03F, G03HB01 and G02BB
Use of a vaccine other than HPV vaccine in the two years before the index date	Yes/no
Behavioural Risk Factors	
Smoking	Smoker, former smoker (has stopped smoking for ≥ 1 year), never smoked
Alcohol consumption	Occasionally or never / daily or almost daily /a few times a week

Season of first symptoms occurrence is described in cases.

The variables "recent or prevalent infections", "recent pregnancy'' and "recent surgery'' that were envisioned in the protocols to be studied for certain disorders could not be used in this report as it was not possible to always determine if they occurred before or after the index date.

7. Index date

The index date is the date before which vaccine use could be considered as a potential exposure for autoimmune disorders (according to time windows, defined later), and after which vaccine use was not considered as an exposure.

The index date was the date of the first symptom evocative of the autoimmune disorder considered for the case. It was reported by the recruiting physician in the case's medical form. The index date of matched controls was the date of consultation date leading to the recruitment in the PGRx information system.

8. Ascertainment of exposure to drugs, vaccines and risk factors

8.1 General telephone interview (PGRx methodology)

Cases and controls underwent a structured standardised telephone interview according to "Progressive-Assisted Backward Active Recall" (PABAR) method used and validated previously (Grimaldi-Bensouda et al, PDS 2010, PDS 2012, PDS 2013).

This questionnaire was developed to include the categories of variables and exposure that were most likely to be required as controlling factors for all "PGRx" studies (including those not about autoimmune diseases).

The guided phone interviews were conducted on average 20 days after patient's recruitment by trained interviewers (cases and referents) and covered the following information (collected data):

- Date of interview and patient identification
- A systematic review of organ systems (15 systems) to identify the comorbidities from which patients could suffer
- Drug use during 2 years preceding the 'index date' these were searched within each organ system disorders. Three iterative methods were used:
    - A list of most common drugs for each of the organ system, with their pictures for the most common ones among them
    - Elicitation of spontaneous recall of any drug use by the patient
    - Lists of vaccines
- Medical history and hospital admissions in the year preceding the index date
- History of autoimmune diseases in first degree relatives
- Number of visits to a doctor in the year preceding the index date (not used in this study)
- Health insurance coverage
- Occupation
- Smoking
- Alcohol consumption
- Physical activity (not used in this study)

Interviews were taped for quality control (in accordance with the patient). A quality control on 10% interview performed and taped was done on a regular basis by project managers since November 2013 to ensure the quality and consistency of data registered and flow of interview.

8.2 Ascertaining HPV vaccine and Cervarix® use

Ascertainment of HPV vaccination was done with a series of sources:

- Telephone interviews
- Objective documentation of vaccination
- Physicianreports
- Pharmacist reports

8.2.1. Guided interview on vaccine

A guide was provided to patients for use during the interview, which contained a list of all marketed vaccines in France with photographs of vaccine packages for easy identification. During the interview, patients were asked to identify any vaccinations that they had received. Patients were specifically asked if they underwent a vaccination against HPV, among 56 other named vaccinations.

8.2.2. Confirmation of HPV vaccine and Cervarix®

HPV vaccine and Cervarix® use was considered as 'confirmed' when one of the following was received from either the patient or her usual general practitioner (for the cases) or the GPs who identified the referents chosen as controls:

- Vaccine batch number (from the drug package or patient's health record)
- A copy of the vaccination notebook, vaccine prescription, health record, medical chart or other document confirming the prescription of HPV vaccine and Cervarix®, including physician's report or a pharmacist report.
- Certificate of vaccination against HPV

In the absence of any of these objective documentations of vaccination, the vaccination by HPV vaccine and Cervarix® was considered 'unconfirmed'.

8.2.3. Information collected on HPV vaccine and Cervarix® use

From these reports, the following information was recorded:

- Name of the vaccine
- Number of vaccine shots
- Dates for vaccine shots

In case of discrepancy between dates reported by the patients and dates in the objective confirmation, the latter was used.

In case of absence of date within the objective confirmation of vaccination (some such as batch number or packages may not have a date attached), the date reported by the patient was used.

8.2.4. Management of confirmation and processes in discrepancies

A vaccine use confirmation was performed for cases and referents following the process displayed in the table below:

Table 2. Agreement between patient self-report and physician's records

		HPV vaccine reported in the physician's records	
		Yes	**No**
HPV vaccine self-reported by the patient	**Yes**	Confirmed use	Unconfirmed use
	No	Written confirmation requested from the patient or the physician to confirm vaccine use or non-use	Confirmed non-use

8.3 Time windows and exposure definition

8.3.1. Time windows defining exposure for different autoimmune disorders

Exposure to HPV vaccine and Cervarix® was defined with reference to the use of HPV vaccine or Cervarix® (at least one shot) within the considered time windows before the index date (Table 3). These time windows were defined according to a priori assumptions regarding the potential time to development of autoimmune disorders following vaccination. They were chosen for each disorder by consensus within the Cervarix Scientific Committee, in the absence of definitive biological or epidemiological data.

Three time windows were planned to be studied for each autoimmune disorder in the initial protocols:

- a primary time window
- a secondary time window
- an exploratory time window

They were determined a priori for each disease, and announced in the protocols.

The analyses performed for this study were done using:

- any use before index date
- the primary time window at risk

Table 3. Time windows defining exposure for different autoimmune disorders

	Primary time-window before index date	**Secondary time window before index date**	**Exploratory time window before index date**
Central demyelination	≤ 24 months[a]	≤ 6months[b]	≤ 2months[c]
Connective tissue diseases (Lupus, rheumatoid arthritis, myositis)	≤ 24 months[a]	≤ 6 months[b]	≤ 2 months[c]
Type 1 diabeted mellitus	≤ 24 months [a]	≤6 months[b]	≤2 months[c]
Autoimmune thyroiditis	≤ 24 months [a]	≤6 months[b]	≤2 months[c]
Guillain Barré syndrome	≤42 days[d]	≤ 6 months[b]	none
Idiopathic thrombocytopenic purpura	≤6 months[b]	≤ 2 months[c]	≤ 24 months[a]

[a] The 730 days before the index date;

[b] The 183 calendar days before the index date;

[c] The 61 calendar days before the index date.

[d] The 42 calendar days before the index date.

8.3.2. HPV vaccines exposure categories

For each contemplated time-window, exposure to HPV vaccine and Cervarix® was measured using the patients self-reports during the interview and described using the following categories (Table 4).

Table 4. Detailed categories defining exposure to HPV vaccine and Cervarix®

Categories for defining exposure in a considered time-window	
Confirmed	Exposed in the considered time-window with an objective source of vaccine use
Unconfirmed	Exposed in the considered time-window without an objective source of vaccine use
Without Date	Exposed but no date available during the interview and on the objective source (batch number, vaccine box)
Index date	The first shot received on Index date with or without an objective source of information
Past	Exposed any day before the considered time-window with or without an objective source of vaccine use
Not exposed	No vaccine use or vaccine use any day after the Index date

8.3.3. Definition of exposure in the analyses

For each at risk time window, the ''Exposure'' variable was categorised as follows:

- **At risk time-window**: Confirmed and unconfirmed in the considered TW at-risk and on index date use
- **Past time-window**: Past use and without date use
- **No exposure**

Sensitivity and validity analyses were performed using:

- Any use of HPV vaccine and Cervarix® before index date (yes/no)
- Confirmed exposure in the considered time-window (3 categories : confirmed / unconfirmed or without date or index date or past / Not exposed)

9. Methodology of the validation studies conducted

A series of analyses were performed to asseses the validity of the methods used in this study.

9.1. Validity studies on cases

In addition to centres audits described above, a follow up of cases, at least one year after their recruitement, was performed to check if the diagnosis suspected or made at the early stage of the disease was confirmed, notably for borderline cases. Analyses were done using both definite and possible cases on the one hand and only definite cases on the other hand. Rejected cases were described for their exposure to HPV vaccine and Cervarix®.

9.2. Validity studies on the sample of controls and their HPV vaccine and Cervarix®coverage

9.2.1. Representativeness of the PGRx reference pool as compared to the French general practice

To assess the validity of the reference pool, the motives of consultation of the PGRx reference pool (as a whole) were compared with published statistics from the French Ministry of Health (Direction de la Recherche, des Etudes, de l'Evaluation et des Statistiques (DREES)) on patients in general practice in France.

9.2.2. Expected vs. observed coverage by HPV vaccination

HPV vaccination coverage by age and year of birth observed in the reference pool of this study was compared to the same data available from the ''Haut Conseil de Santé Publique" July 2014 report.

9.3. Validity studies on the ascertainment of exposure to Cervarix®

9.3.1. Agreement between patients and their physicians on HPV vaccine and Cervarix® use

In addition to the fact that all HPV vaccine and Cervarix® use reported by the patients (or their parents) had to be confirmed by an objective information (see Section 1, 8.2 above), a specific study was performed to compare the agreement between patients self reports and their treating physician report (general practitioner). This was done in the sample of cases and controls where both sources of information were available.

To be able to conduct this agreement analysis, a series of activities were conducted:

- Cases were asked to provide the name of their usual general practitioner (GP) and permission to the research team to contact him or her and obtain copies of their medical charts, or at least reports on their vaccination. A big effort was made to contact these GPs, reach them and offer a compensation to provide this information. It was successful in 47.3 % of cases.
- Controls were documented on these prescriptions of vaccination by their recruiting general practioner contributing to the PGRx reference pool.

9.3.2. Studies of exposure recall

Whenever a physician reported a prescription of an HPV vaccine that was not reported in the patient interview, the patient and/or the physician were called to find out the origin of the discrepancy. The latter was corrected in the database each time a final validated answer regarding the HPV vaccine use was reached. Otherwise, the primary source of vaccine use for the analysis was the patients interview.

We also compared the prevalence of Cervarix® use derived from prescription reports with the one derived from patients' interviews.

10. Methods and statistical analyses for the 'Surveillance study'

The statistical analysis was conducted using SAS software (SAS Institute, North Carolina, USA, version 9.3).

The objective of the Surveillance study was to monitor a large number of centres recruiting incident cases of AID and to identify if any unexpected peaks of AID occurred. If any occurred, the proportion of patients exposed to HPV vaccine and Cervarix® was examined.

Therefore, the total number of eligible young (11-25 y-o) female patients attending the study recruitment centres and diagnosed with AID during the study period (after the reimbursement of Cervarix® April 2008 to September 2014) were reported.

For this Surveillance study, we used 2 methods to analyse the monitoring of cases:

a) An event density methodology based on Poisson model of time to event where the time unit was the month (N event per month) and the moving time window was over 3 months. The number of events each month was compared to the event density over the 3 preceding months. (Model 1)

b) An event density methodology based on Poisson model where the time unit was the month (N event per month) and the comparator time window was the total months that preceeded the observed month. (Model 2)

The results of the surveillance study were provided using figures presenting number of cases identified by month of first symptoms. The analysis for all AID combined is presented below, and the analysis for each individual AIDs are appended.

11. Methods and statistical analyses for the 'Risk study'

The statistical analysis was conducted using SAS software (SAS Institute, North Carolina, USA, version 9.3).

Statistical analyses were carried out for all the AIDs combined as well as separately. The combined analysis was performed in order to provide results for autoimmunity in general, whilst maximising power for the analysis.

11.1 Method of description of case/control samples

The description of the case/control samples included cases with definite and possible diagnoses and their matched controls.

All AID combined cases and their matched controls were described in terms of socio-demographic factors, medical factors and behavioural risk factors described in Table 1.

A descriptive analysis was also carried out for rejected cases, and for cases which could not be matched to any control.

11.2. Method of description of HPV vaccine and Cervarix® vaccine use

Cases and controls were described for:

a) Any reported use (confirmed or not) of HPV vaccine and Cervarix® before the index date
b) Detailed categories defining exposure within a considered time-window

11.3 Method of comparison of case-controls sets for general risk factors

11.3.1. Methods of description of risk factors

The characterisation of the samples was based on all cases with definite and possible diagnoses and their matched controls prepared for the combined analysis. The prevalence of the risk factor in cases and in controls was reported. The adjusted odds ratios association between each a priori defined risk factor and the disease were estimated from conditional logistic regression controlling for all risk factors.

11.3.2. Propensity to use HPV vaccine

The propensity to use HPV vaccine according to the presence of the potential risk factors listed above was assessed in an attempt to identify potential confounders for a potential association of these vaccines with the occurrence of AIDs. Confounding occurs when an external factor gives rise to a spurious association between an exposure and an outcome in a statistical model. For a factor to be a confounder, it must be associated with the exposure -here, exposure to HPV vaccine and the outcome.

This was done on the eligible documented referents recruited within the PGRx information system. The propensity was estimated using an unconditional logistic regression model where the use of HPV vaccine (any time before index date *vs.* no use) was the (dichotomous) outcome.

After these initial analyses, it was decided that risk factors associated either with the outcome or the exposure would be used in the multivariate model; and that the risk factors not associated with neither the disease nor the exposure, would not be included in the multivariate model for assessment of HPV exposure regarding case-control status. The analyses would be stratified for risk factors associated with both the exposure and the disease.

11.4 Methods of analysis of the relation between HPV vaccine and Cervarix® use and autoimmune disorders

For all AID combined and each individual AID considered, the following analyses were performed:

a) The general analysis compared definite and possible cases and their matched controls for use of HPV vaccine and Cervarix® before index date. This analysis was performed for all AID combined and for each individual AID. The crude odds ratios were calculated using conditional logistic regression on exposure status. The adjusted odds ratios for the association between HPV vaccine and Cervarix®, and AIDs were estimated from conditional logistic regression controlling for a priori defined risk factors and age.

b) The main analysis compared definite cases and their matched controls for exposure using the variable in 3 categories (at risk time-window, past time-window, not exposed; as defined in section 8.3.3) in the contemplated primary time windows of HPV vaccine and Cervarix® before index date. This analysis was performed for All AID combined and for each individual AID. The crude odds ratios were calculated using conditional logistic regression on exposure status. The adjusted odds ratios for the association between HPV vaccine and Cervarix®, and AIDs were estimated from conditional logistic regression controlling for a priori defined risk factors and age.

c) A secondary analysis compared definite and possible cases and their matched controls for exposure using the variable in 3 categories (at risk time-window, past time-window, not exposed; as defined in section 8.3.3) in the contemplated primary time windows of HPV vaccine and Cervarix® before index date. This analysis was performed for All AID combined and for each individual AID. The adjusted odds ratios for the association between HPV vaccine and Cervarix®, and AIDs were estimated from conditional logistic regression controlling for a priori defined risk factors and age. The crude odds ratios were calculated using conditional logistic regression on exposure status.

d) To further explore confounding that could be linked with familial/personal history of AID (f/phaid) and with geographical origin (that can approach the the ethnicity and the cultural perception of this vaccination), stratified analyses on f/phaid (two categories "Yes" and "No or don't know") and geographical origin (two categories "Northern Europe or North America" and "Southern Europe or Africa or others or mixed origin") using definite and possible cases and their controls, were carried out in each of the four sub-populations as follows :
    a. Northern Europe or North America and with f/phaid
    b. Northern Europe or North America and without or unknown f/phaid
    c. Southern Europe or Africa or others and with f/phaid
    d. Southern Europe or Africa or others and without or unknown f/phaid

    These analyses were performed using unconditional logistic regression with adjustement for the matching criteria (age).

Adjusted ORs were estimated with multivariable modelling whenever there were at least 3 subjects in each numerator. Odds ratios are presented with 95% confidence intervals.

11.5 Assumptions regarding the hazard function

The analysis rested on the assumptions that the risk of developing an autoimmune disorder did not vary according to the number of vaccine shots received or the rank of the vaccine shot. The hazard was considered as constant for each vaccine shot.

11.6. Sensitivity analysis performed

The study explored the impact of using different case definitions and different definitions of exposure, including primary time windows and any use of HPV vaccine before index date (see above). This was done for each AID separately and for all AIDs combined.

For all AIDs combined, the following analyses were performed:

a) The general analysis was repeated with the removal of autoimmune thyroiditis cases and with the removal of GBS cases.

For all AIDs combined and each individual AID considered, the following analyses were performed:

a) The general analysis was repeated stepping-back the index date of 1 year.

b) The general analysis was repeated separately in each recruitment phase (date of first symptoms of cases from April 2008 to April 2011 and from May 2011 to September 2014).