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Risk of autoimmune diseases and human papilloma virus (HPV) vaccines: Six years of case-referent surveillance

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ABSTRACT

Background: Safety of HPV vaccines is still in question due to reports of autoimmune diseases (ADs) following HPV immunization.
Objectives: To assess the risk of ADs associated with HPV vaccination of female adolescents/young adults in France.

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Methods: Systematic prospective case-referent study conducted to assess the risks associated with real-life use of HPV vaccines. Cases were female 11–25 years old with incident ADs [central demyelination/multiple sclerosis (CD/MS), connective tissue disease (CTD), Guillain-Barré syndrome (GBS), type-1 diabetes (T1D), autoimmune thyroiditis (AT), and idiopathic thrombocytopenic purpura (ITP)]. Cases were consecutively and prospectively identified at specialized centers across France (2008–2014) and individually matched by age and place of residence to referents recruited in general practice. Risk was computed using multivariate conditional logistic regression models adjusted for family history of ADs, living in France (north/south), co-medications and co-vaccinations.

Results: With a total of 478 definite cases matched to 1869 referents, all ADs combined were negatively associated to HPV vaccination with an adjusted odds ratio of 0.58 (95% confidence interval: 0.41–0.83). Similar results were obtained for CD/MS, AT, CT, and T1D, the last two not reaching statistical significance. No association was found for ITP and GBS. Sensitivity analyses combining definite and possible cases with secondary time window showed similar results.

Conclusion: Exposure to HPV vaccines was not associated with an increased risk of ADs within the time period studied. Results were robust to case definitions and time windows of exposure. Continued active surveillance is needed to confirm this finding for individual ADs.

1. Introduction

Human papilloma virus (HPV) is one of the most common sexually transmitted infections worldwide [1]. The two HPV vaccines available at the time of the study, the HPV-6/11/16/18 vaccine (*Gardasil*®, Merck & Co., Inc) and the HPV-16/18 AS04-adjuvanted vaccine (*Cervarix*®, GSK Vaccines), protect against HPV types 6, 11, 16, and 18 and HPV types 16 and 18, respectively. HPV types 16 and 18 are known to cause cervical lesions and are responsible for up to 80% of all cervical cancers, the third most frequent type of female cancer [2] while non-oncogenic HPV types 6 and 11 are responsible for more than 90% of genital warts [3]. The HPV-6/11/16/18 vaccine is the most widely used vaccine in France [4].

While proven effective, the safety of HPV vaccines is in doubt on the basis of reported adverse effects associated to autoimmune events [5] hypothetically connected to molecular mimicry mechanism [6]. However, several studies conducted to date have not been able to provide robust evidence to support these safety concerns [7], which have been reported as barriers to preventive HPV vaccination but justify continued surveillance of autoimmune diseases (ADs) following exposure to HPV vaccines [8].

The Pharmacoepidemiologic General Research eXtension (PGRx) is an ongoing information system developed to assess risks of rare or delayed health events associated with real-life use of medicines and vaccines. The PGRx-Autoimmune Disease (PGRx-AD) registry systematically collects incident cases of autoimmune diseases (ADs) through a network of board-certified specialists and a pool of referents (controls) consulting General Practitioners (GP), from which cases can be matched to referents, allowing for case-referent analyses. The system has also been used to assess the risk of ADs with the quadrivalent HPV-6/11/16/18 vaccine [9]. The objective of this follow-up study was to assess the risk of ADs following exposure to HPV vaccines for over 6.5 years across France as requested by the French health authorities (*Haute Autorité de Santé*).

2. Methods

2.1. Study population

Cases and referents were recruited prospectively using the PGRx information system between April 2008 and October 2014 (NCT01498627). Cases were recruited consecutively in a network of 168 specialized centers (internal medicine, neurology, rheumatology, pediatric, endocrinology, and dermatology) from university and general hospitals participating in the PGRx-AD registry across metropolitan France [10]. Recruiting centers were randomly audited during the recruitment period to ensure exhaustive inclusion of cases. Referent-patients were recruited by a network of 236 GPs and pediatricians, all from across metropolitan France, participating in the "PGR-GP" registry. Patients were offered participation regardless of their reason for consulting a physician.

Eligibility criteria for participating in the present study were similar in cases and referent-patients: (1) female gender; (2) aged 11–25 years; (3) living in France; (4) able to undergo a telephone interview in French (the participant herself or her parents); and (5) consenting to participate to the study (parental consent for minor participants).

2.2. Case definition and ascertainment

Cases were defined as patients with a first incident clinical manifestation in their lifetime compatible with one of the six following ADs: (1) central demyelination and multiple sclerosis (CD/MS), (2) connective tissue diseases (CTD) – including lupus, chronic inflammatory arthritis, juvenile idiopathic arthritis, rheumatoid arthritis, myositis, and undetermined connective tissue disease – (3) Guillain-Barré syndrome (GBS), (4) type 1 diabetes (T1D), (5) autoimmune thyroiditis (AT), and (6) idiopathic thrombocytopenic purpura (ITP). Each AD was defined according to international conventions [11–17]. Patients with a lifetime history of the AD suspected at inclusion were excluded.

Then, cases were classified as definite, possible or rejected by physicians on the basis of their evolution over the twelve months following diagnosis. When concerns of uncertainty were raised for cases, two physicians, blinded to the vaccination status were requested to independently review the cases.

2.3. Referents and matching

Referents were defined as patients meeting the eligibility criteria above, but with no lifetime history of any of the ADs under study. An average of four referents were matched to each case by: (1) age (best match available within a maximum range of 2 years as follows: cases $\leq$17 years-old: age of referent $\pm$1 month, $\pm$3 months, $\pm$6 months, $\pm$1 year from age of case; and cases $\geq$18 years-old: age of referent $\pm$1 year, $\pm$2 years from age of case), (2) place of residence (North vs. South of France) and (3) index date (defined for cases as